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Ru- and Rh-catalyzed [2+2+2] cycloadditions: an access to fluorenone, 2-aminopyridine, and 1,3-dihydroisobenzofuran derivatives

Fei Ye

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Université Pierre et Marie Curie

Ecole Doctorale de Chimie Moléculaire de Paris-Centre

Institut de Recherche de Chimie Paris / Equipe CSB2D

Ru- and Rh-catalyzed [2+2+2] cycloadditions: an access to fluorenone, 2-aminopyridine, and 1,3- dihydroisobenzofuran derivatives

Par Fei YE

Thèse de doctorat de Chimie Organique

Dirigée par les Drs. Véronique MICHELET et Virginie VIDAL

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« If we knew what we were doing, it wouldn't be called research, would it? »

Albert Einstein

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Abbreviations

A	Ac	Acetyl
	Ar	Aryl
	atm	Atmosphere
B	Boc	<i>tert</i> -Butyloxycarbonyl
	BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
	Bn	Benzyl
	Bu	Butyl
C	cat.	Catalyst
	°C	Degree Celsius
	cod	1,5-Cyclooctadiene
	Conv.	Conversion
	cot	Cyclooctatetraene
	Cp	Cyclopentadienyl
	Cp*	Pentamethylcyclopentadienyl
	CsPiv	Cesium pivalate
D	dba	Dibenzylideneacetone
	DCM	Dichloromethane
	DCE	Dichloroethane
	DFT	Density functional theory
	DMA	Dimethylacetamide
	DMAP	4-Dimethylaminopyridine
	DMF	Dimethylformamide
	dmfu	Dimethyl fumarate
	DMSO	Dimethyl sulfoxide
	dmpe	1,2-Bis(dimethylphosphino)ethane
	dppe	1,2-Bis(diphenylphosphino)ethane
	dppf	1,1'-Bis(diphenylphosphino)ferrocene
	dppp	1,3-Bis(diphenylphosphino)propane
	DRX	Diffraction des rayons X
	δ	Chemical shift (units: ppm)
	E	ee
Eq.		Equation
equiv		Equivalent
équiv		Équivalent

Abbreviations

	Et	Ethyl
F	FDA fdppe	Food and Drug Administration 1,2-Bis(dipentafluorophenylphosphino)ethane
G	g	Gramme
H	h Het HFIP HIV HRMS	Hour(s) or heure Heterocycle Hexafluoroisopropanol Human immunodeficiency virus High Resolution Mass Spectrometry
I	<i>i</i> Pr	<i>iso</i> -Propyl
L	LEDs L*	Light-emitting diodes Chiral ligand
M	M Me min μ W mL mol MS m.p. MRS m/z	Mole/Liter Methyl Minute(s) Microwave Milliliter Mole Mass Spectrometry Melting point Methicillin-resistant staphylococci Mass to charge ratio
N	NBS <i>n</i> Bu nd NIS NHCs NMI NMP NMR NOESY nr	<i>N</i> -bromosuccinimide <i>n</i> -Butyl Not detected <i>N</i> -iodosuccinimide <i>N</i> -heterocyclic carbenes <i>N</i> -methylimidazole <i>N</i> -methyl-2-pyrrolidone Nuclear magnetic resonance Nuclear Overhauser effect spectroscopy No reaction
O	<i>o</i> - oct	<i>ortho</i> - Octyl

	OLEDs	Organic light-emitting diodes
P	<i>p</i> - <i>p</i> -cymene pbq pent	<i>para</i> - 4-Isopropyltoluene 1,4-Benzoquinone Pentyl
Q	quant.	Quantitative
R	rac Rdt ref R _f RMN rt	Racemic Rendement Reference Retention factor Résonance magnétique nucléaire Room temperature
S	SFC	Supercritical fluid chromatography
T	<i>T</i> <i>t</i> t.a. TBAF TBDPS <i>t</i> Bu TFA THF TMS Ts	Temperature Time Température ambiante Tetrabutylammonium fluoride <i>tert</i> -Butyldiphenylsilyl <i>tert</i> -Butyl Trifluoroacetic acid Tetrahydrofuran Trimethylsilyl Tosyl
V	<i>v</i>	Volume

Abbreviations

Résumé

Résumé

Ce manuscrit présente le développement de nouveaux systèmes catalytiques à base de ruthénium et de rhodium pour des réactions de cyclisation [2+2+2].

Chapitre 1. Réactions de cycloaddition [2+2+2]: bibliographie

Au cours de ce chapitre nous examinerons les différents types de cycloaddition en fonction de la nature des fonctions alcynes impliquées dans la cycloaddition (Schéma R1).

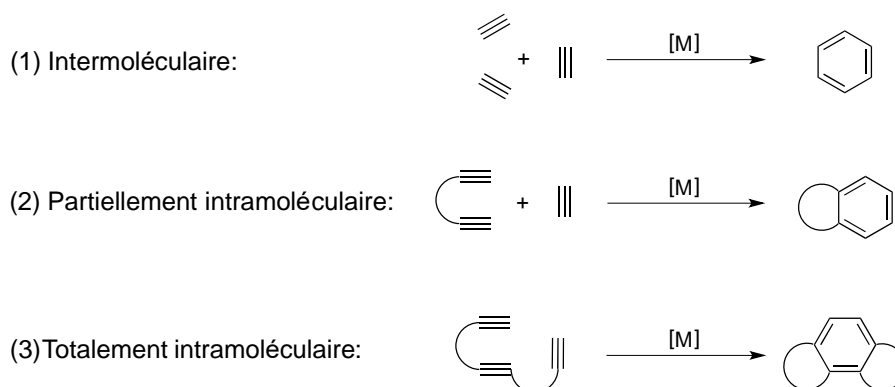


Schéma R1

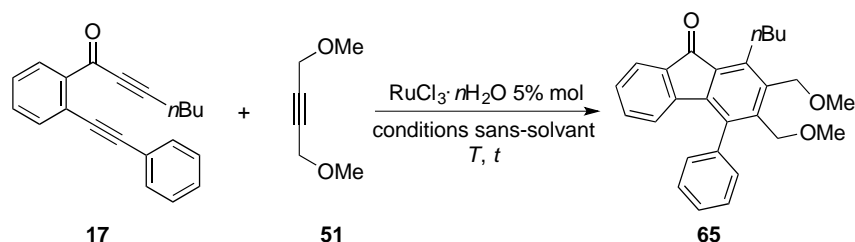
Pour chaque cas, des exemples seront donnés afin d'illustrer les résultats de la littérature.

Dans une seconde partie, nous détaillerons les différents métaux de transition utilisés pour mettre en œuvre les réactions. Parmi les complexes de métaux de transition, on verra que ceux qui sont le plus couramment utilisés sont des complexes au cobalt avec le complexe $\text{CpCo}(\text{CO})_2$; au rhodium (par exemple le complexe de Wilkinson $\text{RhCl}(\text{PPh}_3)_3$ ou encore au rhodium sous forme cationique tel $\text{Rh}(\text{cod})_2\text{BF}_4$ associé à un ligand phosphine type BINAP); le nickel a aussi été utilisé sous forme $\text{Ni}(\text{dppe})\text{Br}_2$ par exemple ou bien $\text{Ni}(\text{CO})_2(\text{PPh}_3)_2$; ensuite on peut citer l'iridium dont le complexe dimère $[\text{Ir}(\text{cod})\text{Cl}]_2$ a été souvent employé; pour finir nous citerons le ruthénium, dont le complexe le plus connu est le catalyseur de Grubbs de 1ère génération.

Chapitre 2. Vers un nouvel accès aux dérivés fluorénones via une cycloaddition [2+2+2] catalysée par le trichlorure de ruthenium hydraté.

Au cours de notre étude sur la synthèse de carbocycles et d'hétérocycles, catalysée par les métaux de transition, nous avons mis en évidence la possibilité d'accéder relativement facilement à des fluorénones substituées ainsi qu'à des analogues, à partir de diynes-1,6 pontés et d'alcyne, en présence de $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ comme catalyseur. Nous avons étudié la cycloaddition [2+2+2] catalysée par le complexe $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$, en utilisant le diyne **17**, qui contient un pont benzoyle, avec le 1,4-diméthoxy-but-2-yne **51** comme substrat modèle. Nous avons examiné différents paramètres en vue d'optimiser les conditions de la réaction. Nous avons ainsi fait varier la température, le nombre d'équivalents d'alcyne, le pourcentage de $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ et enfin le temps de réaction. Nous avons ainsi pu établir que les meilleures conditions étaient d'opérer avec 2 équivalents d'alcyne, 5% molaire de $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$, à 50 °C pour une durée de deux heures. Dans ces conditions réactionnelles, le dérivé **65** a été isolé avec 72% de rendement.

Table R1. Optimisation des conditions de la réaction



Entrée	17/51	T (°C)	t (h)	Conv. (%) ^b	Rdt (%) ^c
1	1:6	110	18	> 99	86
2	1:4	80	18	> 99	74
3	1:3	80	18	> 99	73
4 ^a	1:3	80	18	60	40
5	1:3	50	18	> 99	75
6	1:2	50	18	> 99	72
7	1:2	50	4	> 99	73
8	1:2	50	2	> 99	72
9 ^b	1:2	50	18	40	nd

^a 2% mol $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (0.007 mmol) utilisés. ^b Sous atmosphère d'air.

Ayant établi les conditions optimales de la réaction, nous nous sommes intéressés à la généralisation, en particulier l'effet du substituant en position C7. Il ressort ainsi qu'un phényle

augmente la réactivité par rapport à un groupe alkyle (*n*-butyle). L'introduction de groupements donneur ou accepteur conduit à peu de changement, les rendements restant du même ordre. Un groupement silyle à la place du groupe phényle apporte peu de modifications, et conduit aussi au produit attendu (Schéma R2). Ce résultat est intéressant car il permet d'envisager une post-fonctionnalisation. Le groupement protecteur des alcools a aussi été examiné et les groupes benzyle ou *tert*-butyle sont compatibles avec les conditions réactionnelles, et conduisent ainsi aux produits **76** et **77** (80 et 81%). La structure de la fluorénone **77** a pu être établie sans ambiguïté par une analyse de diffraction des rayons X (Schéma R3).

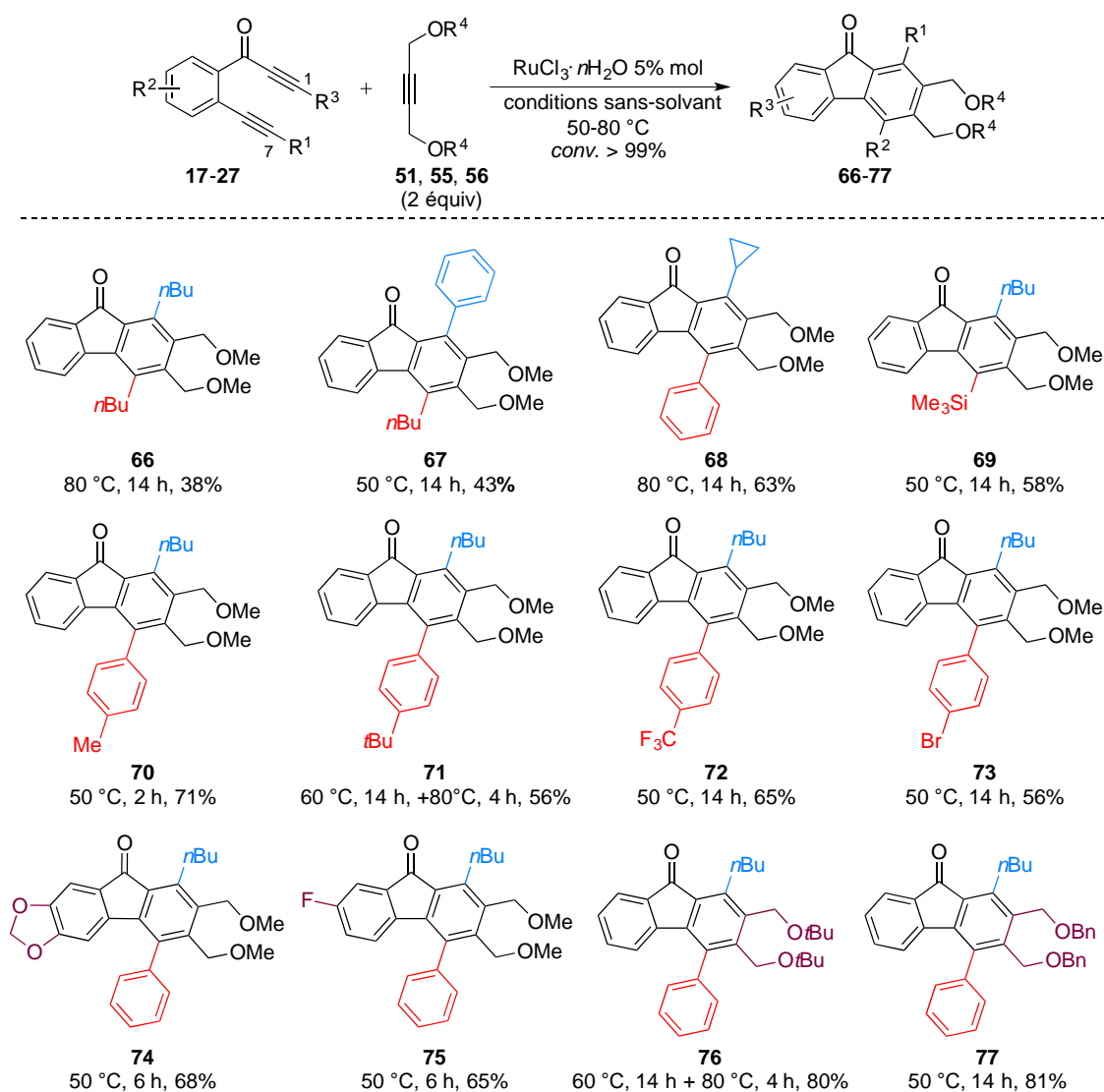


Schéma R2

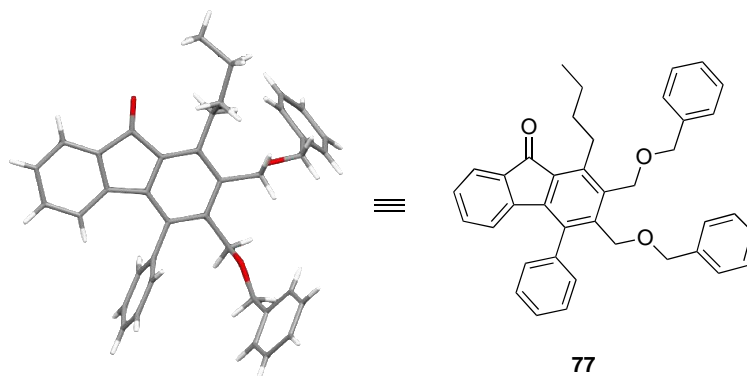


Schéma R3

Le pont reliant les deux fonctions diynes a ensuite été modifié: le groupe phényle a ainsi été remplacé par un hétérocycle (furanyle, thiényle, cycle azoté); la cycloaddition se fait également pour conduire à des hétéro-fluorénones variées **83-87**, **89** et **90** avec des rendements allant de 30 à 78 % (Schéma R4).

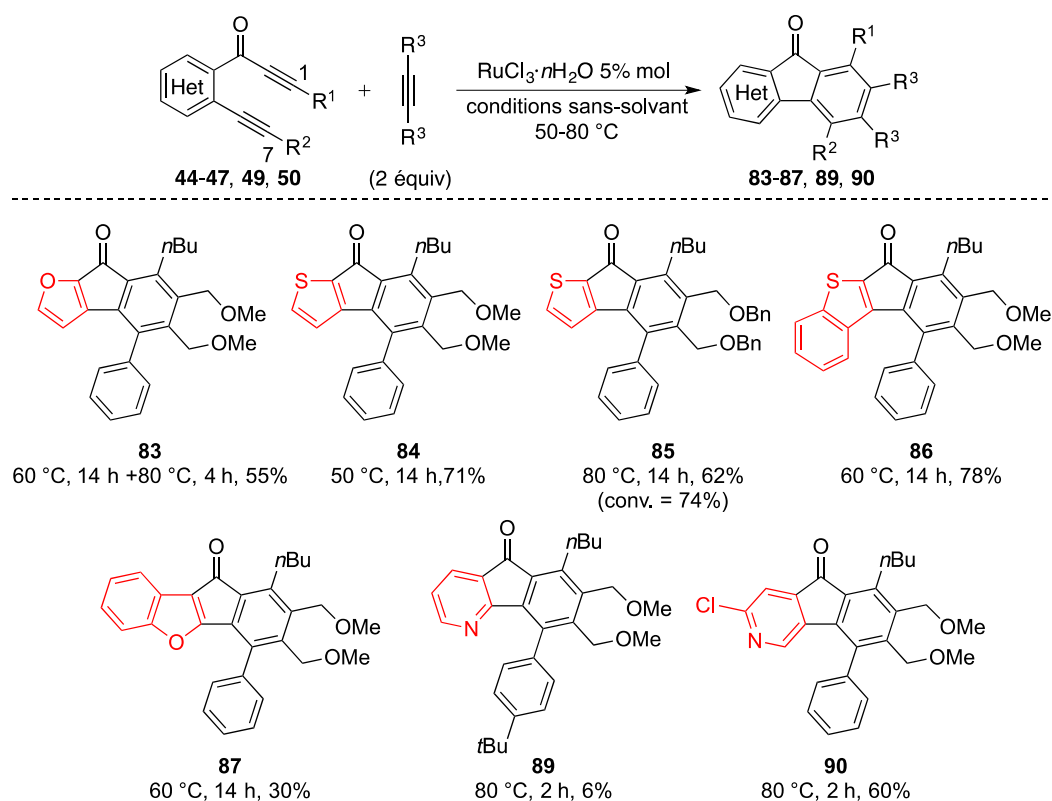
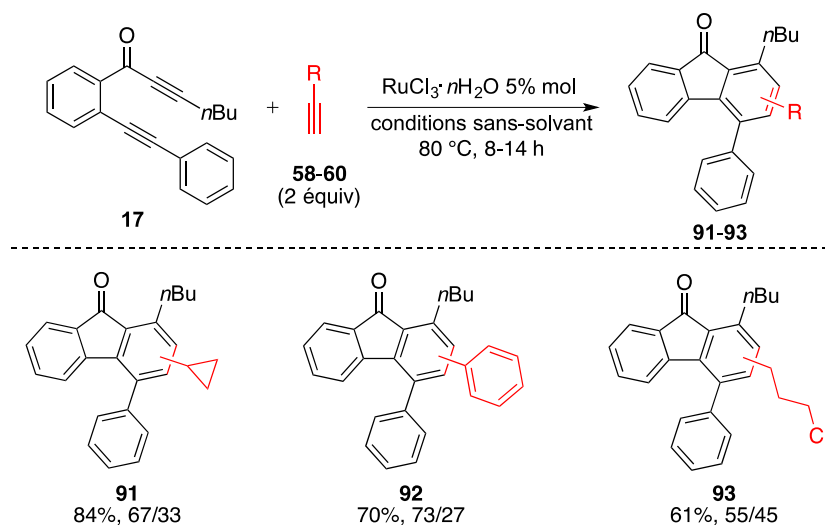


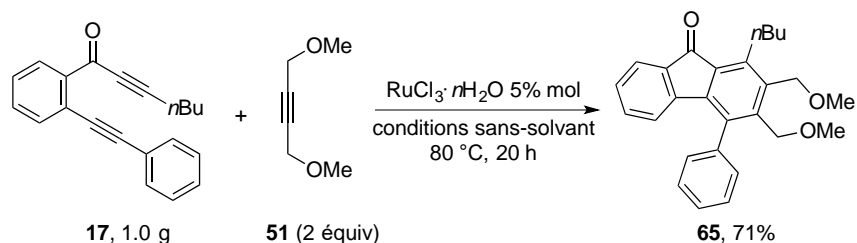
Schéma R4

Cette réaction de cycloaddition ne se limite pas aux diynes symétriques internes, puisqu'une série de diynes terminaux a été utilisée. La réaction de ces derniers avec le diène **17**

est détaillée dans le Schéma R5. La faible régiosélectivité peut s'expliquer par un encombrement stérique proche des substituants présents.



Pour valider l'intérêt synthétique de cette méthode catalytique, la réaction a été conduite sur une échelle d'un gramme dans les conditions pré-établies. La fluorénone **65** a pu être isolée avec un rendement de 71% (Schéma R6).



Après avoir synthétisé une gamme de dérivés fluorénones, nous nous sommes tournés vers l'étude de la post-fonctionnalisation des composés **65**, **69** et **76**. En utilisant des protocoles décrits dans la littérature, nous avons pu accéder aux composés dihydrobenzo[*b*]furan **94**, au diol **95**, et au polycycle dibromé **96** avec de bons rendements (Schéma R7).

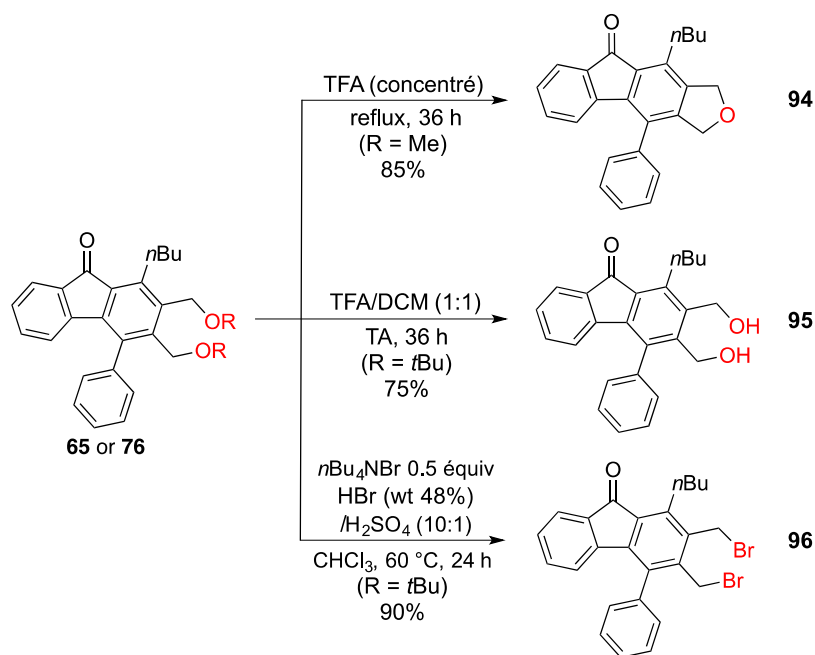


Schéma R7

La fluorénone silylée **69** s'est également avérée un bon intermédiaire pour accéder, après iodation au composé **97**, lui même précurseur de dérivés fonctionnalisés par un alcyne ou un ester boronique par des réactions de couplage de Sonogashira ou Suzuki-Miyaura (Schéma R8).

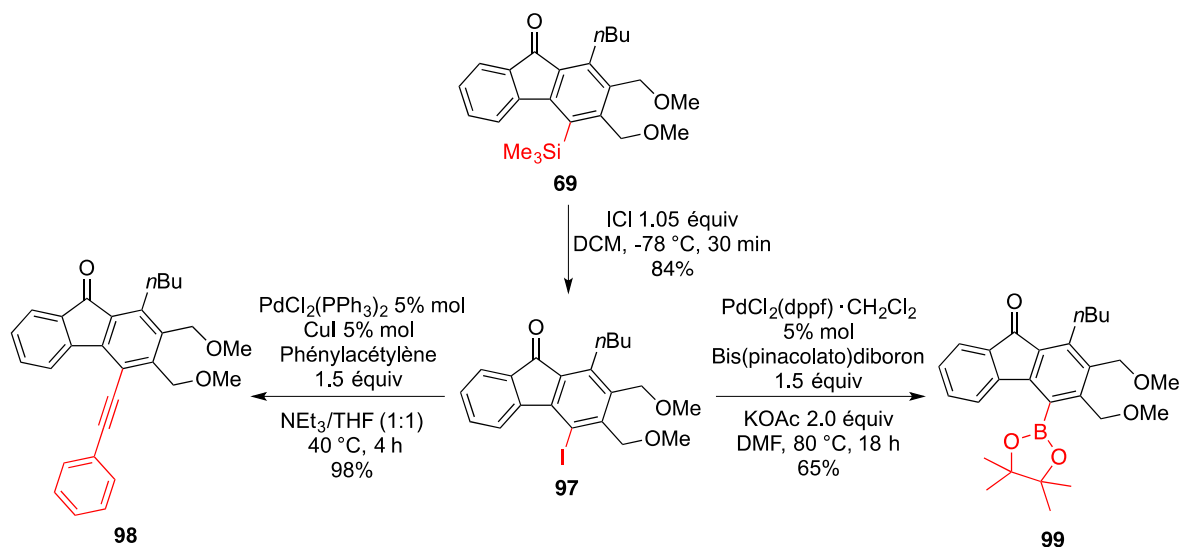


Schéma R8

La fluorénone bromée **73** s'est également révélée un bon adduit, puisque après couplage de Suzuki-Miyaura, elle a été transformée en ester boronique **100** avec un rendement de 85% (Schéma R9).

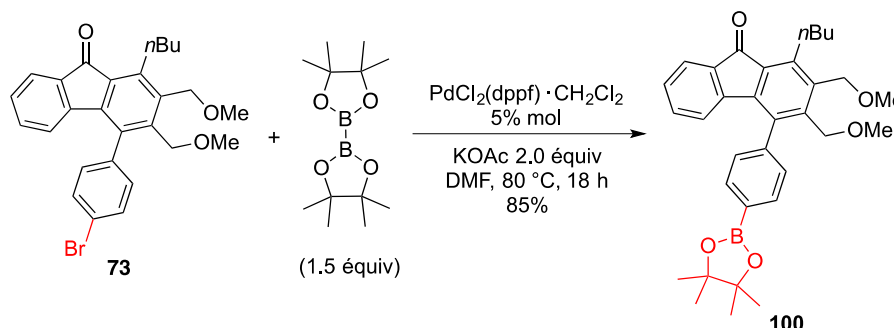


Schéma R9

Une nouvelle approche directe et éco-compatible vers la synthèse de fluorénones hautement substituées ainsi que des analogues a été mise au point. Cette méthode fait intervenir une cycloaddition [2+2+2] semi-intramoléculaire de cétones possédant un motif 1,6-diyne avec un alcyne, initié par le complexe $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$. Ce procédé économique est conduit sans solvant, ni aucun ligand ou additif, et ce dans des conditions douces. Cette réaction a permis l'obtention de fluorénones polycycliques complexes, d'aza-fluorénones, des benzo[*b*]furanones et également des thiophénones polycycliques, avec de bons rendements. Des études ultérieures ont montré que les fluorénones ainsi obtenues pouvaient être converties en molécules plus complexes.

Chapitre 3. Utilisation de la catalyse au ruthénium pour des cycloadditions [2+2+2] de diynes avec des cyanamides électroniquement enrichis: un accès facile aux dérivés 2-aminopyridines

Dans la continuité de notre précédent travail relatif aux cycloadditions [2+2+2] catalysées par un métal de transition, nous avons décidé d'explorer, la réaction de cycloaddition [2+2+2] de α,ω -diynes et cyanamides dans le but de synthétiser des dérivés 2-aminopyridines.

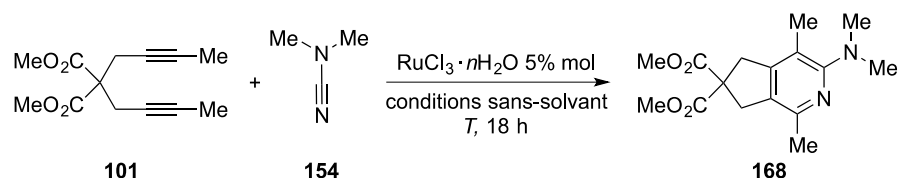
a. Cycloaddition [2+2+2] d' α,ω -diynes avec des cyanamides catalysée par $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$

Différent diynes et cyanamides ont été efficacement préparés. La diyne **101** et le diméthyl cyanamide **154** ont été choisis comme substrats modèles pour optimiser les conditions

Résumé

réactionnelles. Nous avons commencé l'étude avec 5% molaire de $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$, dans des conditions sans solvant. Un examen plus approfondi a montré qu'il fallait opérer à 110 °C pour une durée de 18 heures.

Table R2. Optimisation des conditions de la réaction



Entrée	101/154	T (°C)	Conv. (%) ^b	Rdt (%) ^c
1	1:6	110	>99	75
2	1:3	110	>99	76
3 ^{a,b}	1:3	110	50	nd
4	1:3	80	90	72
5	1:3	50	nr	nd
6	1:2	80	30	nd
7 ^b	1:2	90	70	nd
8 ^b	1:2	100	93	70
9	1:2	110	>99	74

^a 0.02 mmol of $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (2% mol) utilisés. ^b 24 heures de réaction.

Après avoir mis au point les conditions pour réactionnelles, nous avons évalué la réactivité de divers diynes et cyanamides. Les résultats sont regroupés dans le Schéma R10. Une série de cyanamides obtenus à partir d'amines secondaires ont été soumis à la réaction de cycloaddition pour conduire aux 2-aminopyridines correspondantes avec de bons rendements. Par exemple, des diynes symétriques portant diverses fonctions telles que des esters, cétones ou amides sont compatibles.

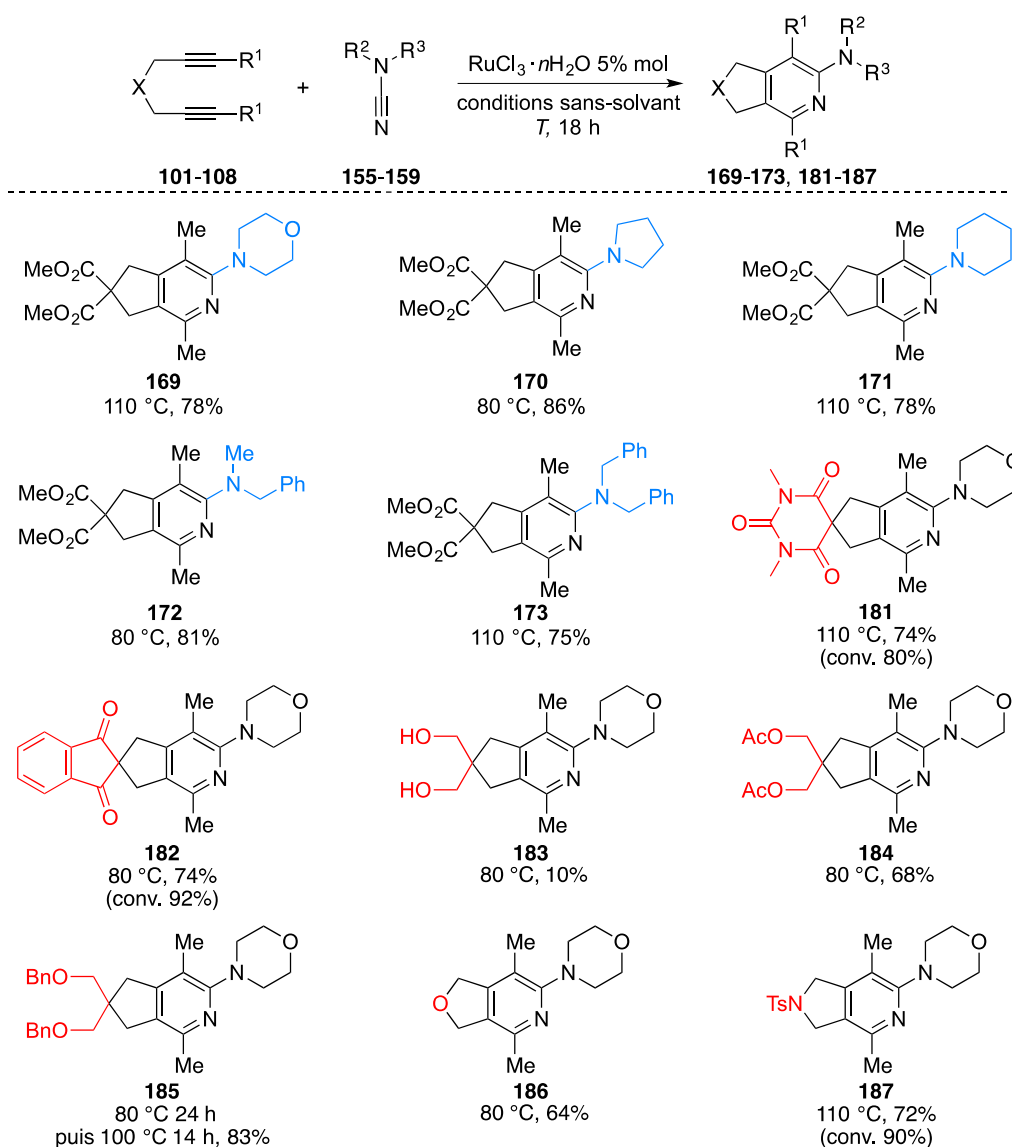


Schéma R10

La régiosélectivité de la réaction de cycloaddition de diynes-1,6 non symétriques a aussi été étudiée, comme indiqué dans le Schéma R11. Les diynes-1,6 portant un substituant méthyle ou phényle ont été mis en réaction avec la 4-carbonitrile morpholine et ont conduit à 2 régioisomères avec une sélectivité réduite et un rendement global plus faible. Le ratio des deux régioisomères a été déterminé par analyse RMN ^1H du brut réactionnel.

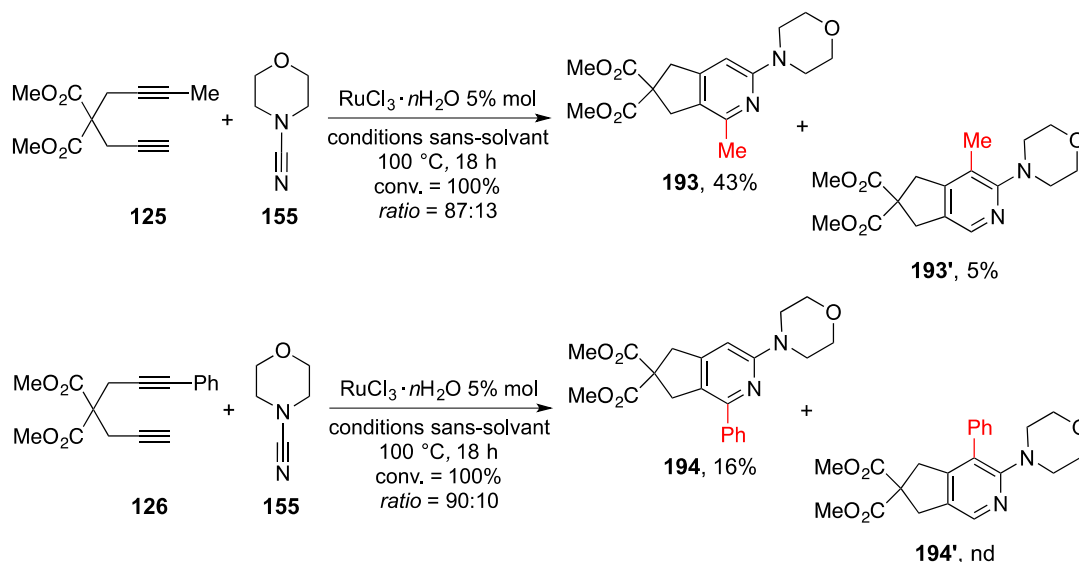


Schéma R11

Un exemple de nitrile électro-déficient a également été considéré, plus précisément le malononitrile qui a été soumis à la cycloaddition avec le diyne **108** comportant un pont azoté, dans les conditions usuelles de 110°C en présence de $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$. Dans ce cas, le cycloadduit **195** est obtenu avec une conversion de 22%, malgré un taux de catalyseur de 10% molaire (Schéma R12). Ce résultat est nettement inférieur à ceux obtenus avec des nitriles enrichis.

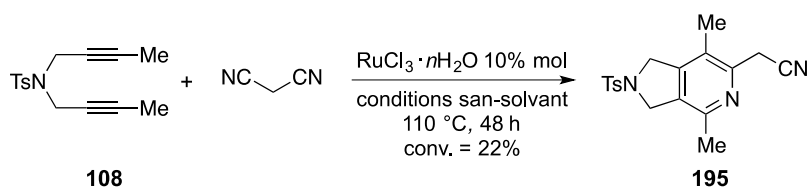


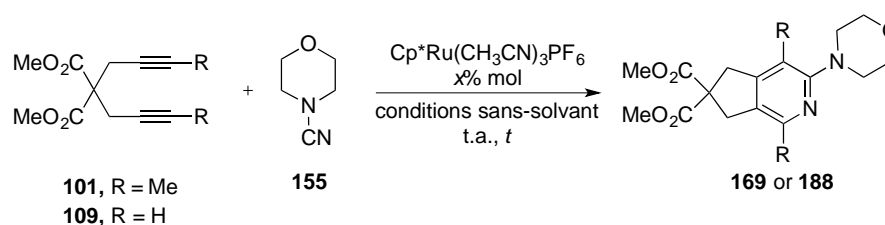
Schéma R12

b. Cycloadditions [2+2+2] d' α,ω -diynes avec des cyanamides catalysés par le complexe $\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$

Au cours du travail précédent faisant intervenir le ruthénium sous forme neutre ($\text{RuCl}_3 \cdot n\text{H}_2\text{O}$) pour la mise en œuvre de cycloaddition [2+2+2] d' α,ω -diynes et cyanamides, nous avons démontré que le ruthénium sous forme cationique était également très efficace pour cette réaction. Les essais initiaux ont porté sur l'utilisation du diyne **101** et du cyanamide **155**, dans des conditions sans solvant à température ambiante. La réaction a été optimisée en faisant varier différents paramètres. Nous avons ainsi montré que la réaction pouvait être conduite

efficacement avec 2% molaire du complexe pentaméthylcyclopentadiényle (Cp*) Cp*Ru(CH₃CN)₃PF₆ pour fournir la 2-aminopyridine **169** avec un excellent rendement et un temps de réaction de 5 min. Par ailleurs, nous avons également découvert que lorsque la réaction était réalisée avec un petit volume de dichlorométhane, avec le diyne **109** comme modèle, il était possible de réduire à la fois le taux catalytique à 1% molaire et le nombre d'équivalents de cyanamide à 1.2 équivalents (entrée 8). L'utilité de cette méthode a été démontrée en conduisant la réaction sur une échelle d'un gramme, avec le diyne **109** comme modèle. La 2-aminopyridine **188** a ainsi été obtenue avec 82% de rendement (entrée 10).

Table R3. Optimisation des conditions de la réaction



Entrée	Diyne	Catalyst (x% mol)	t	Produit	Conv. (%)	Rdt (%)
1	101	Ru(PPh ₃) ₃ Cl ₂ (5)	8 h	169	nr	nd
2	101	[Ru(<i>p</i> -cymene)Cl ₂] ₂ (2.5)	8 h	169	nr	nd
3	101	Cp*Ru(cod)Cl (2)	5 min	169	>99	85
4	101	Cp*Ru(CH ₃ CN) ₃ PF ₆ (5)	5 min	169	>99	93
5	101	Cp*Ru(CH ₃ CN) ₃ PF ₆ (2)	5 min	169	>99	91
6	101	Cp*Ru(CH ₃ CN) ₃ PF ₆ (1)	60 min	169	80	nd
7	109	Cp*Ru(CH ₃ CN) ₃ PF ₆ (2)	3 min	188	>99	94
8 ^a	109	Cp*Ru(CH ₃ CN) ₃ PF ₆ (1)	2 min	188	>99	95
9 ^a	109	Cp*Ru(CH ₃ CN) ₃ PF ₆ (0.5)	18 h	188	90	82
10 ^b	109	Cp*Ru(CH ₃ CN) ₃ PF ₆ (2)	5 min	188	>99	82

^a 0.6 mmol de cyanamide **155** et 0.5 mL de dichlorométhane utilisés. ^b échelle d'un gramme

Dans un second temps et comme précédemment, ayant établi les conditions optimales de la réaction, nous nous sommes intéressés à la généralisation de cette réaction en faisant intervenir divers diynes substitués et le cyanamide **155** comme partenaire (Schéma R13). Une grande variété de diynes symétriques, pontés avec un carbone quaternaire, un oxygène ou encore un azote protégé ont été soumis au cyanamide **155** pour donner les 2-aminopyridines correspondantes. L'introduction de groupements volumineux tels que le groupe *tert*-butyle ou *iso*-propyle conduit également à d'excellents rendements. De même, des groupes fonctionnels portés par le carbone quaternaire, tels que des diols, des nitriles, des diones ont également été

Résumé

utilisés avec succès. La formation des composés **186** et **187** montre aussi que la réaction est compatible avec des diynes internes (Schéma R13).

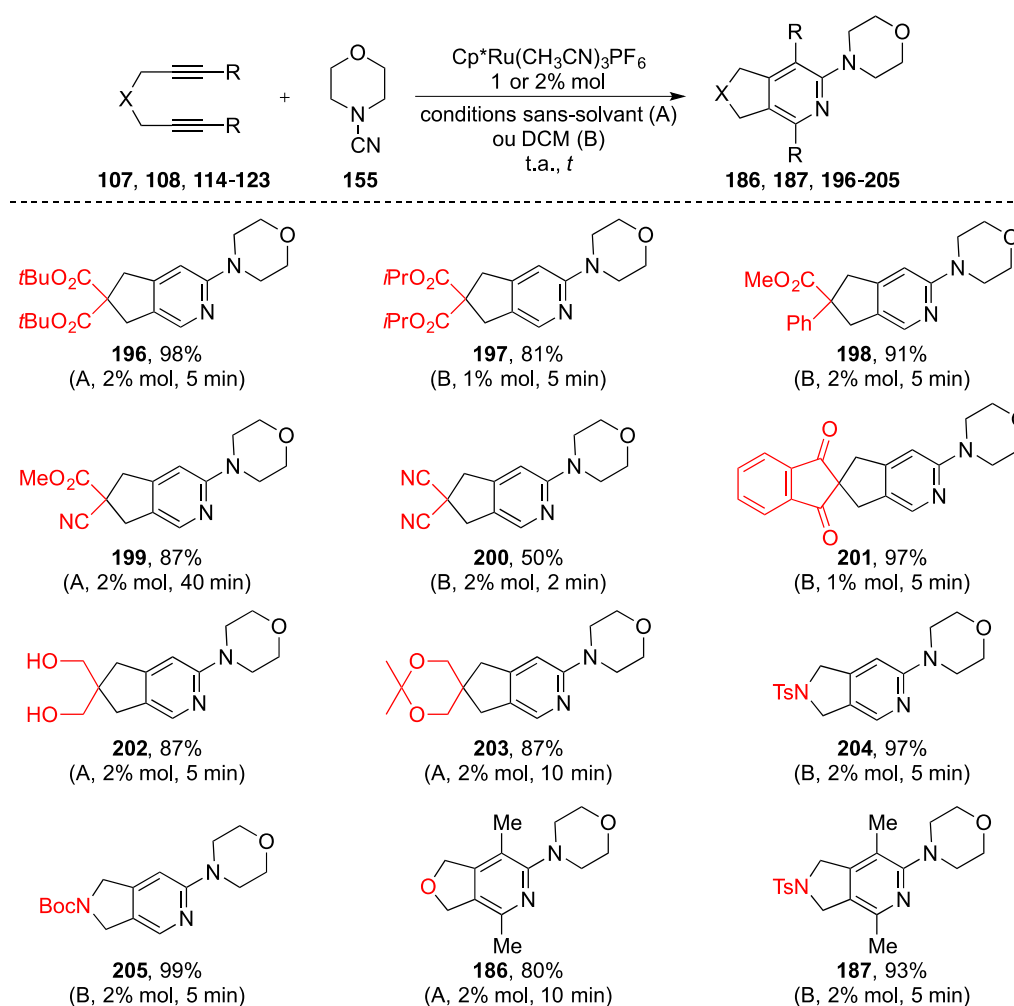


Schéma R13

Par la suite, dans le but d'examiner les limites de la réaction, un certain nombre d'amines secondaires portées sur le cyanamide a été testé. Comme indiqué dans le Schéma R14, les résultats se sont avérés très probants avec l'obtention d'un grand nombre de 2-aminopyridines.

Résumé

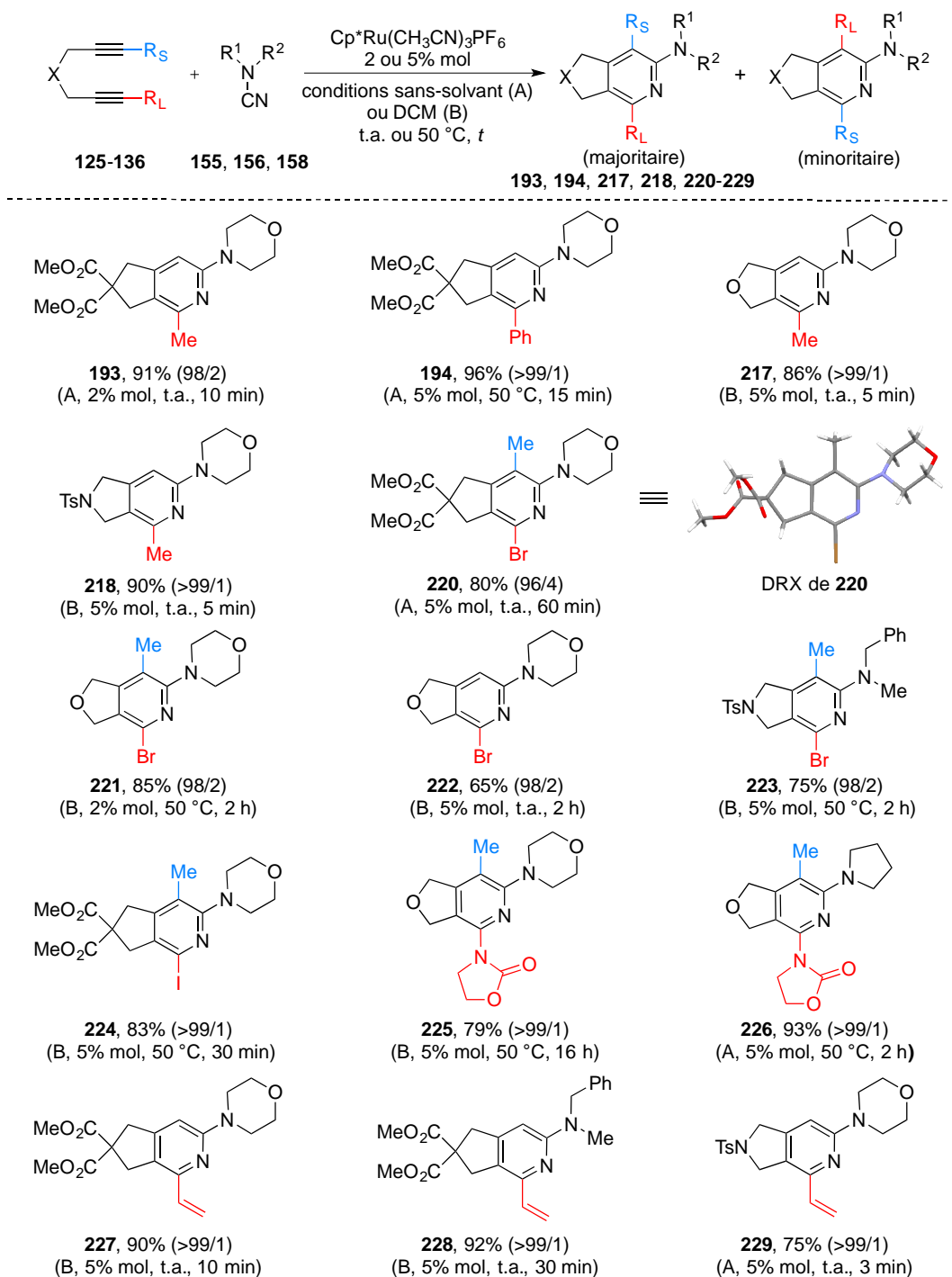


Schéma R15

Une étude ultérieure a par ailleurs montré que la réaction était possible avec les diynes-1,7 **138** (lien oxygéné) et **139** (lien azoté). En présence de 5% molaire de $\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$, ils conduisent aux pyridines bicycliques à 6 chaînons **230-233** avec des rendements de 34 à 86% et une excellente régiosélectivité (Schéma R16).

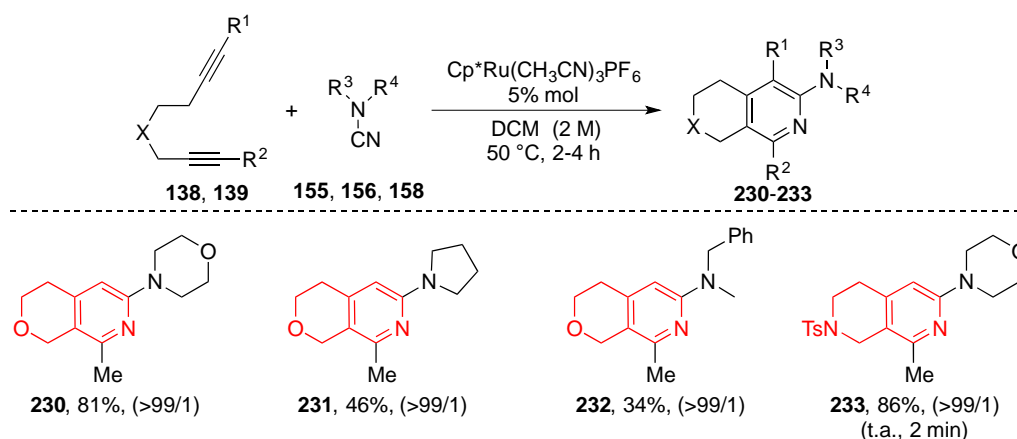


Schéma R16

Le composé spirocyclique **237** a été isolé à partir d'un dérivé du mestranol avec 58% de rendement et une haute régiosélectivité. La structure de ce dernier a été précisément établie par diffraction des rayons X (Schéma R17).

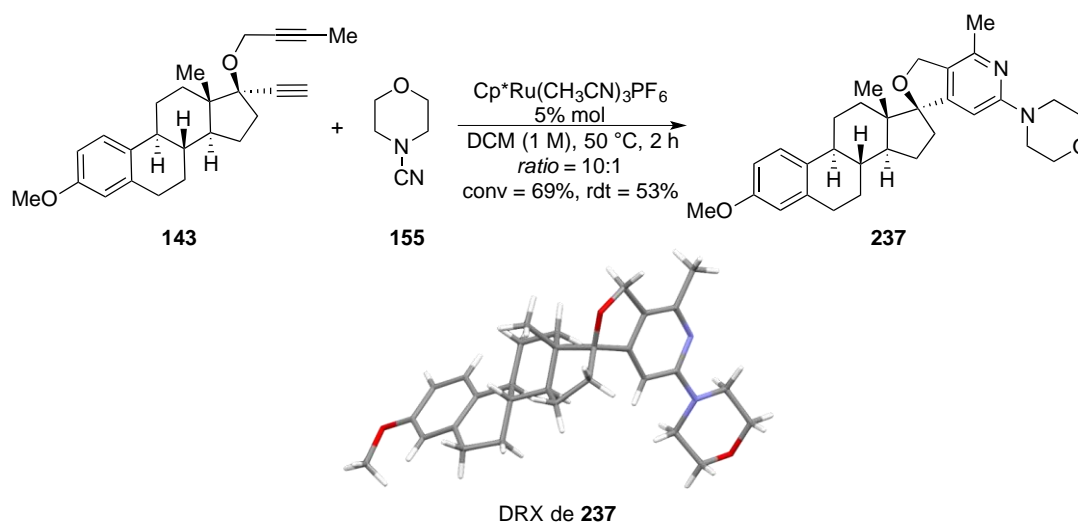


Schéma R17

c. Obtention d'aza-fluorénols et aza-fluorénones par cycloaddition [2+2+2] catalysée par le complexe $\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$

En utilisant cette méthode catalytique et éco-compatible, une famille d'aza-fluorénols et aza-fluorénones a été préparée. Le choix de la position du substituant sur le diyne permet de contrôler la régiosélectivité du substituant sur le cycle pyridine. La structure de l'azafluorénone **248** a été formellement établie par diffraction des rayons X (Schéma R18).

Résumé

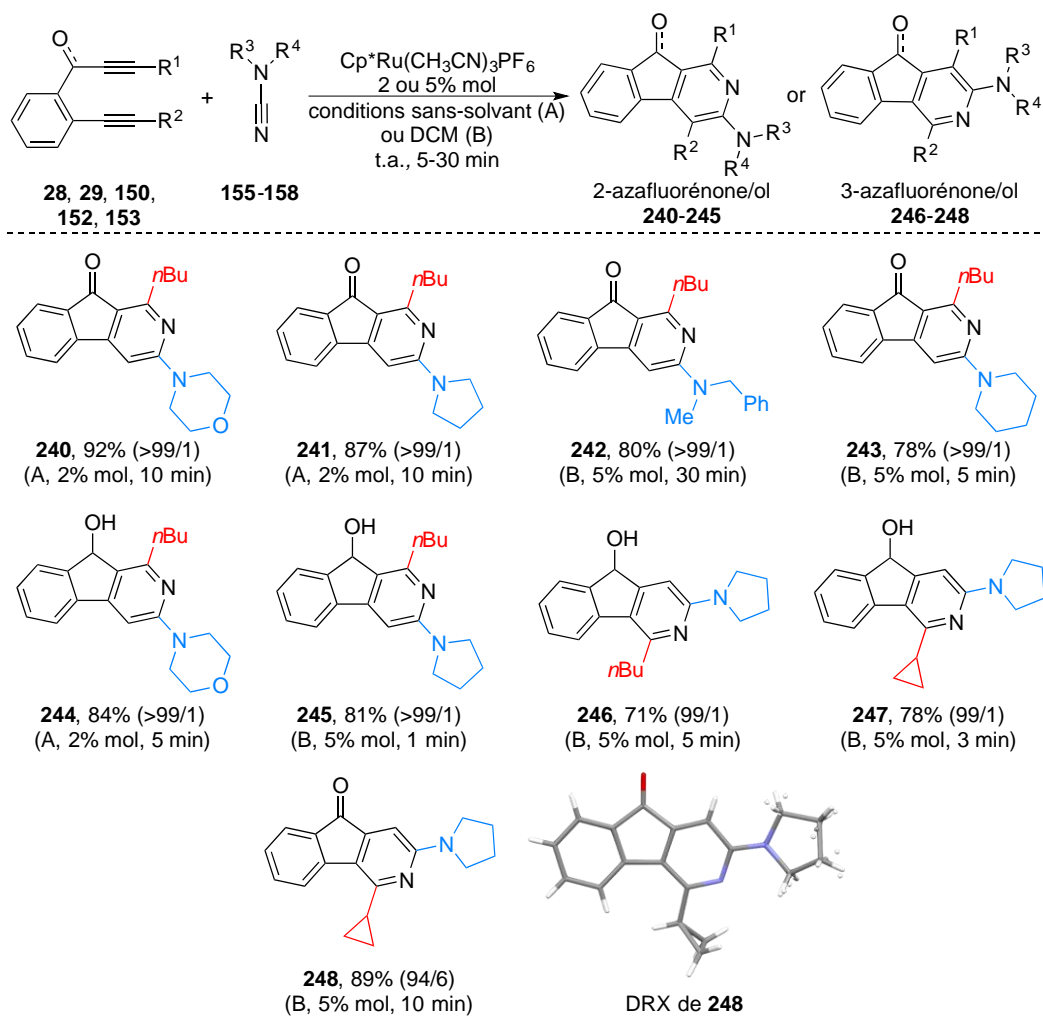


Schéma R18

En se basant sur les résultats obtenus, ainsi que sur ceux décrits dans la littérature, nous proposons le mécanisme ci-dessous afin d'expliquer la régiosélectivité observée (Schéma R19). La réaction passerait par un intermédiaire ruthénacyclopentadiène Ru-**II**, dont la formation serait suivie par l'insertion du cyanamide et l'élimination de l'espèce ruthénium, conduisant majoritairement à la pyridine *ortho*-substituée la moins encombrée.

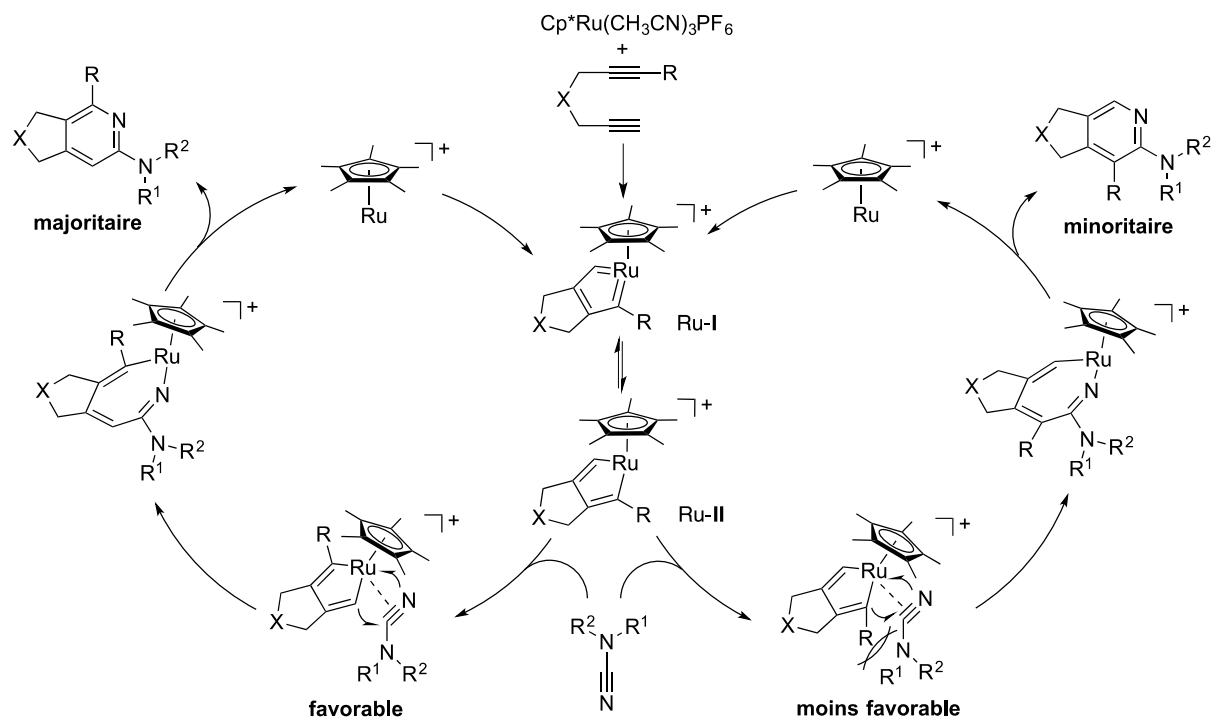


Schéma R19

La synthèse de composés à motif 2-aminopyridine hautement substitués par cycloaddition [2+2+2] de α,ω -diynes avec des cyanamides via une catalyse en présence de complexes de ruthénium aussi bien sous forme neutre ($\text{RuCl}_3 \cdot n\text{H}_2\text{O}$) que cationique ($\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$), a donc été réalisée. Le complexe $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ peu onéreux s'est révélé très efficace en tant que catalyseur pour la préparation de 2-aminopyridines substituées. La réaction se déroule en présence de 5% molaire de $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ sans l'ajout de ligand ou autre additif, et en l'absence de solvant. Le ruthénium complexe cationique ($\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$) s'est avéré très efficace pour ce type de cycloaddition aussi bien dans le cas des diynes-1,6 ou -1,7, en présence de cyanamides et dans des conditions douces. Diverses diynes, terminaux ou internes possédant des groupes fonctionnels variés se sont révélés compatibles avec ce système catalytique. Une excellente régiosélectivité a été obtenue dans le cas de diynes dissymétriques. L'utilité de ce protocole a ensuite été démontrée avec la synthèse de molécules à haute valeur ajoutée telles que des halopyridines, des diaminopyridines ou encore des vinylpyridines en une seule étape. Cette réaction a pu conduire à des pyridines polycycliques incluant des hétéroatomes, à partir de diynes-1,7 et cyanamides. La fonctionnalisation du mestranol, molécule biologiquement active, a pu aussi valider le potentiel de cette méthodologie. Une famille d'aza-fluorénones et aza-fluorénols a également été préparée efficacement selon cette méthode éco-compatible et directe.

Chapitre 4. Synthèse asymétrique de 1,3-dihydroisobenzofuranes 1,1-disubstitués à partir de triynes prochiraux et des alcynes internes catalysée par des complexes de rhodium

Les 1,3-dihydroisobenzofuranes sont une classe de composés hétérocycliques oxygénés très présents dans les composés naturels biologiquement actifs¹⁷² ainsi que dans un certain nombre de médicaments.¹⁷³ Plusieurs méthodes permettent d'accéder à ces structures, parmi lesquelles on peut citer la cyclotrimérisation [2+2+2] d'alcynes,⁷ les réactions de Diels-Alder,¹⁷⁵ ou encore la transformation de phthalides¹⁷⁶. Parmi ces méthodes, la cycloaddition [2+2+2] catalysée par les métaux de transition constitue l'une des plus efficaces comme indiqué dans le chapitre I.

Concernant la préparation de 1,3-dihydroisobenzofuranes contenant un centre chiral en position α , peu d'exemples ont été rapportés, c'est pourquoi leur accès constitue un défi.¹⁷⁷

La réaction de désymétrisation de composés prochiraux constitue un moyen efficace pour accéder à des molécules complexes possédant un centre stéréogène. C'est pourquoi nous avons envisagé que la construction de 1,3-dihydroisobenzofuranes optiquement actifs pouvait être accomplie via une cycloaddition [2+2+2] de triynes oxygénés avec un alcyne interne catalysée par un métal de transition comme indiqué dans le Schéma R20.

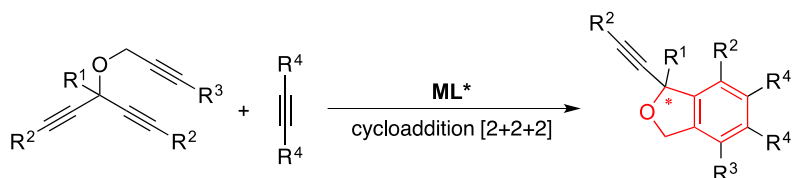


Schéma R20

Les triynes de départ peuvent être facilement obtenus à partir de produits commerciaux selon la rétrosynthèse décrite dans le schéma R21.

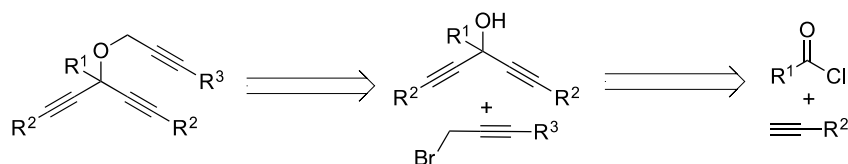


Schéma R21

Résumé

Ayant établi les conditions optimales pour mener la réaction de cycloaddition, nous avons examiné l'influence de différentes phosphines, comme le (*R*)-Xylyl-BINAP, le (*R*)-Difluorphos ou encore le (*R*)-MeOBiphep. Nous n'avons pas noté d'amélioration significative. De même, plusieurs solvants ont été testés, parmi lesquels le THF, le dichloroéthane, ou le xylène. Le toluène s'est avéré un bon candidat puisque il a donné un *ee* identique à celui obtenu avec le DCM, et avec un rendement supérieur (70%); toutefois cela nécessite d'opérer à une température de 100 °C.

c. Influence de l'alcyne interne symétrique

Par la suite, nous avons examiné l'influence de différents groupes protecteurs sur les fonctions alcools en utilisant les conditions mises au point, à savoir des groupements donneurs ou électroattracteurs. De même, les fonctions alcools ont été remplacées par des groupes alkyles ou esters. Il est à noter qu'aucune réaction n'a lieu avec deux groupements phényles (composé **272** voir Schéma R22). Les rendements varient entre 20% et 79%, tandis que les *ee* restent modérés à faibles (21-50%).

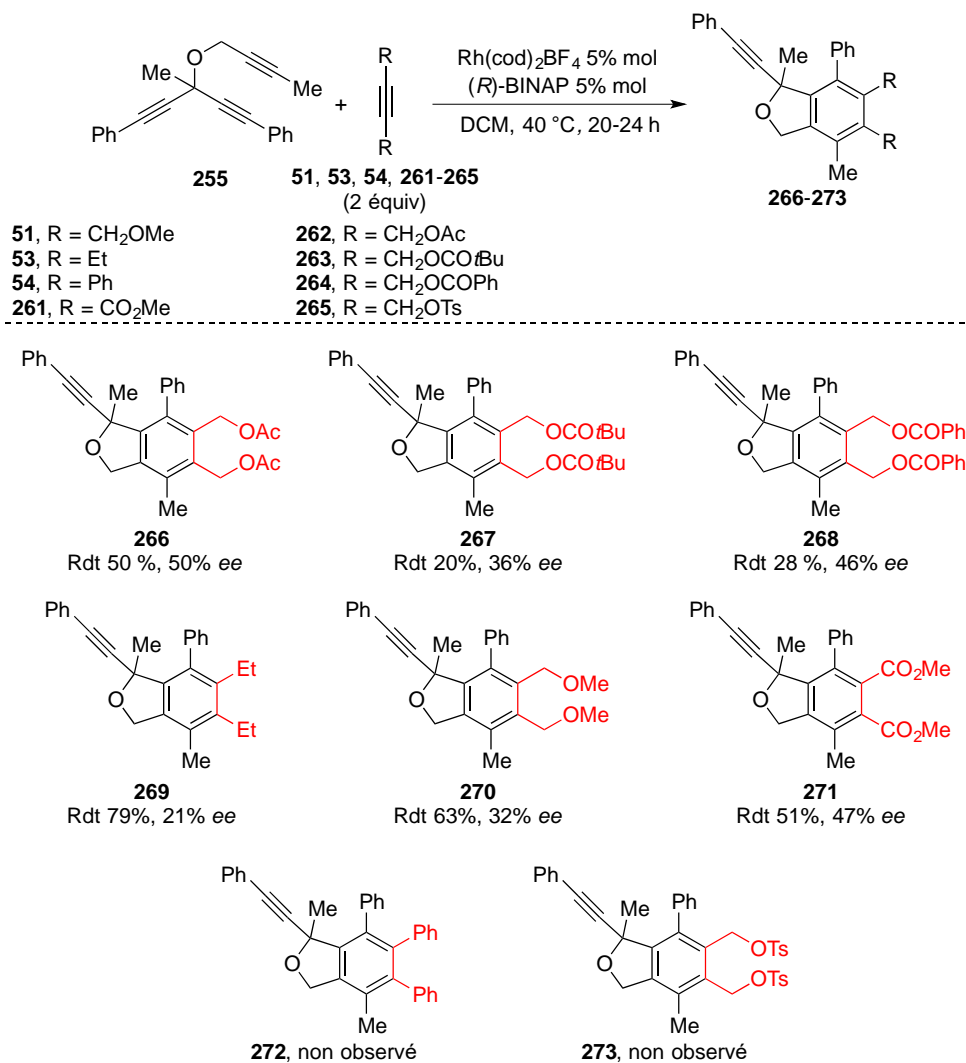


Schéma R22

d. Influence du substituant porté par le carbone quaternaire du triyne

Pour compléter cette étude, nous nous sommes intéressés à l'influence stérique engendrée sur les triynes, en remplaçant le groupe méthyle par un groupement plus volumineux, comme le *n*-propyle ou *tert*-butyle ou encore un phényle. L'augmentation de l'encombrement stérique en position R' ne conduit pas à une amélioration du rendement ni de l'excès énantiomérique (Schéma R23).

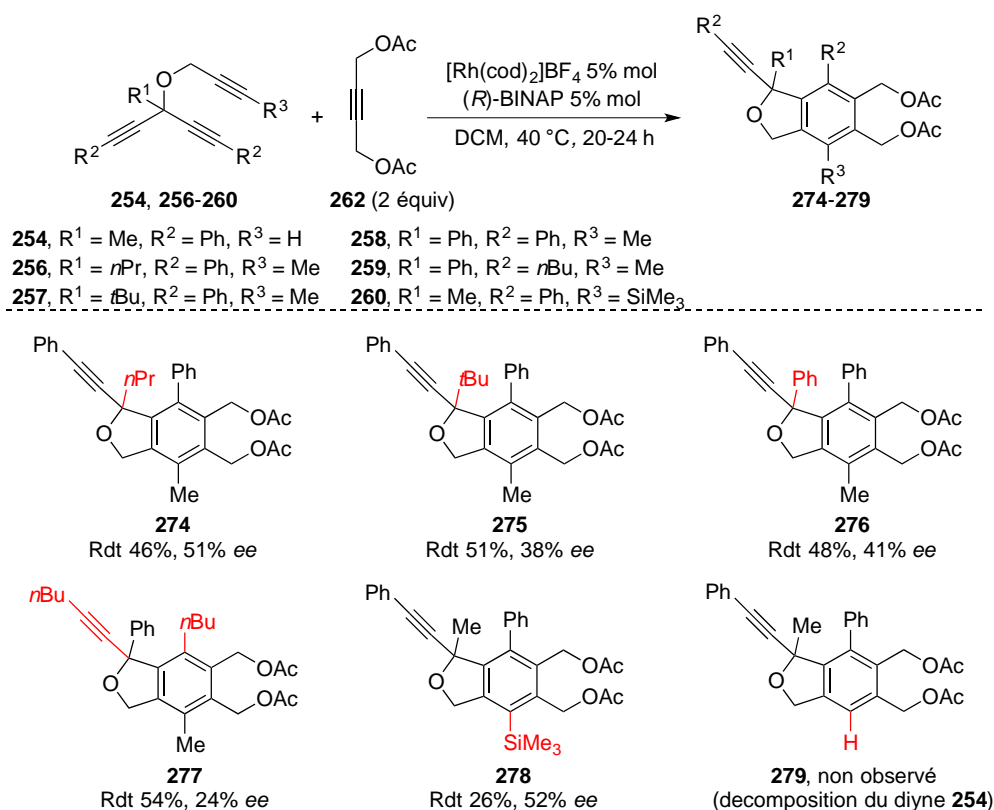


Schéma R23

e. Mécanisme proposé

Afin de rendre compte de la stéréosélectivité observée, nous nous sommes intéressés au cycle catalytique de la réaction. Un des mécanismes possible est développé dans le Schéma R24.

La réaction pourrait débuter par le couplage oxydatif de deux fonctions alcynes issues du triyne et de l'alcyne avec l'espèce rhodium pour conduire à l'intermédiaire rhodacyclopentadiène Rh-**I**. Une coordination intramoléculaire ultérieure avec l'une des fonctions alcynes portée par le carbone quaternaire fournirait l'intermédiaire Rh-**II**. Ceci pourrait être considéré comme l'étape stéréo déterminante pour expliquer l'énantiosélectivité observée en raison de la gêne stérique entre le groupe alcyne et le ligand chiral. L'insertion intramoléculaire de l'alcyne sur le rhodium de Rh-**II** délivrerait alors l'intermédiaire à 7 chaînons Rh-**III**, qui subirait une élimination réductrice pour donner le 1,3-dihydroisobenzofurane avec un excès énantiomérique (Schéma R24).

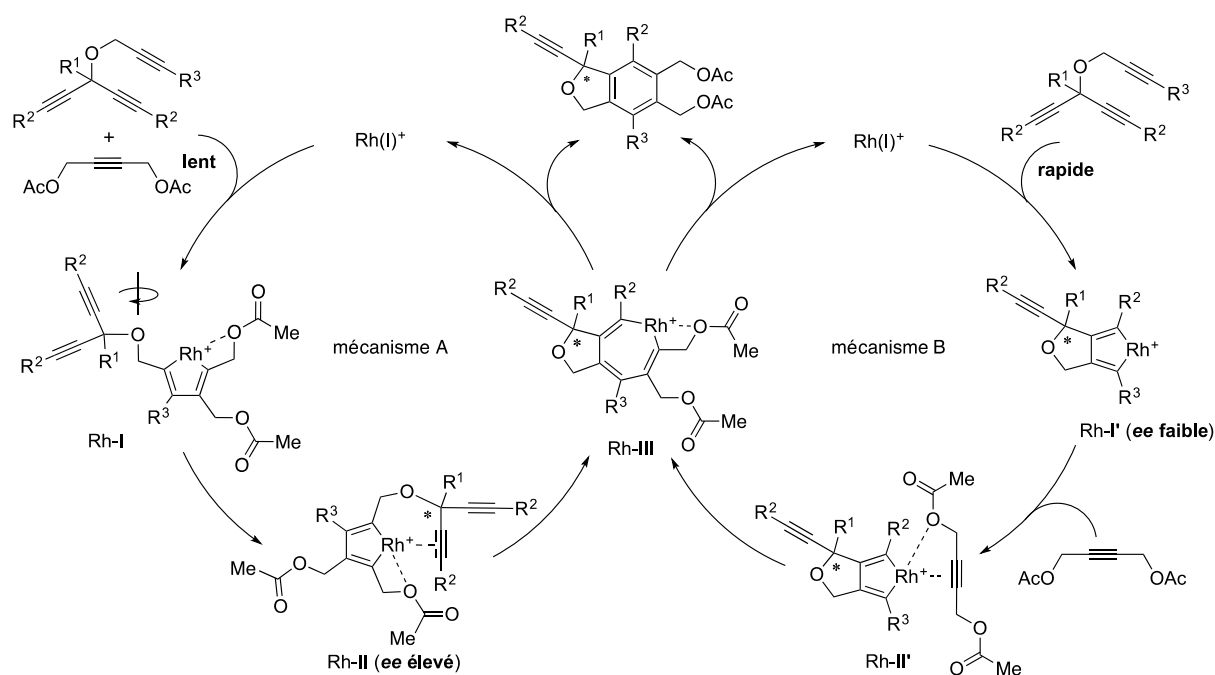


Schéma R24

Dans ce chapitre, nous avons donc démontré que la cycloaddition [2+2+2] conduite en présence d'un catalyseur au rhodium $\text{Rh}(\text{cod})_2\text{BF}_4$, en présence d'une phosphine chirale, était un moyen d'accès rapide vers les 1,3-dihydroisobenzofuranes énantiomériquement enrichis. Bien que les rendements et l'énantiosélectivité restent à améliorer, cette méthode est prometteuse.

General introduction

General introduction

Heterocycles represent by far the largest of classical divisions in organic chemistry and are of great importance biologically and industrially. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic while several additives and modifiers used in industrial applications in the field of cosmetics, reprography, information storage and plastics are heterocyclic in nature. Over the past century, heterocycles have constituted one of the largest areas of research in organic chemistry. They have contributed to the development of humanity from a biological and industrial point of view as well as to the understanding of life processes and to the improvement of the quality of life.

In this context in the field of chemistry, efficient clean methods to access functionalized heterocycles are highly suitable. One of the key principles of “Green Chemistry”¹ (Figure 1) is to limit the use of organic solvents in industrial processes. Indeed, these solvents are often toxic, expensive and generate difficulties in disposal and reprocessing. A major research effort in recent years is to develop new more environmentally friendly synthetic methods. Even if water seems to be the best choice because of its abundance and non-toxicity,² the development of solvent-free processes during the reaction and purification, is undeniably the ideal solution.³ A solvent-free system is not only environmentally friendly but also provides effective, safer and more economical solutions for industrial partners (temperature and reaction time decreased, reducing the size of the reactors, process intensification, no extra costs incurred relating to the purchase and processing of solvents).

¹ Anastas, P.T.; Warner, J. C. *Green chemistry: Theory and Practice*, Oxford University Press, New York, **1998**, 30.

² Reviews: (a) Li, C. J. *Chem. Rev.* **2005**, *105*, 3095. (b) Pinault, N.; Bruce, D.W. *Coord. Chem. Rev.* **2003**, *241*, 1. (c) Lindström, U, M. *Chem. Rev.* **2002**, *102*, 2751. (d) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023. (e) Li, C.-J.; Chan, T.H. *Tetrahedron* **1999**, *55*, 11149.

³ a) Tanaka, K. *Solvent-Free Organic Synthesis*, Wiley-VCH, Weinheim, Germany, **2003**. (b) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025. (c) Metzger, J. O. *Angew. Chem., Int. Ed.* **1998**, *37*, 2975. (d) Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Chem. Comm.* **2001**, 2159. (e) Walsh, P. J.; Li H.; de Parrodi, C. A. *Chem. Rev.* **2007**, *107*, 2503. (f) Marvaniya, H. M.; Modi, K. N.; Sen, D. J. *Greener reactions under solvent free conditions*, Int J. Drug Dev. & Res. April-June **2011**, *3*, 34. (g) Varma, R. S. *Green Chem.* **1999**, *1*, 43. (h) Capello, C.; Fischer, U.; Hungerbühler, K. *Green Chem.* **2007**, *9*, 927. (i) Keith, L. H.; Gron, L. U.; Young, J. L.; *Chem. Rev.* **2007**, *107*, 2695.

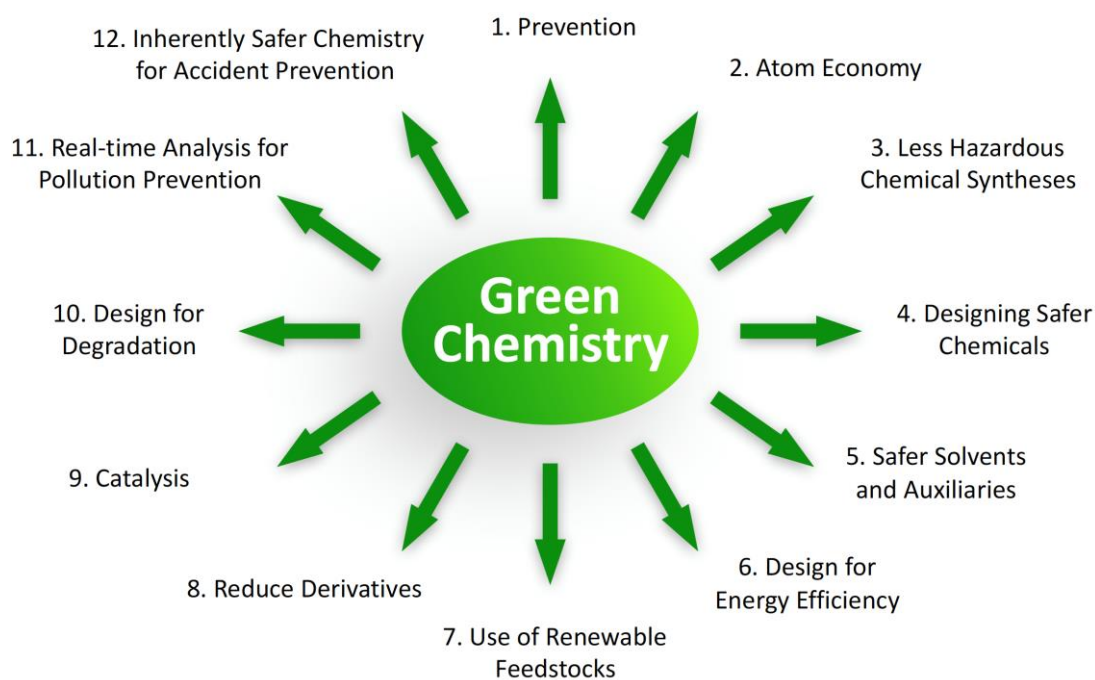


Figure 1

Functionalization of aromatic or heteroaromatic compounds has been a major topic of study among organic chemists, and has been used both in industrial⁴ and academic laboratories. One of the best known and traditional methods to functionalize aromatic rings involves the stepwise addition of electrophilic substituents, using Friedel-Crafts alkylation⁵ or acylation⁶. This method is very useful for the synthesis of polysubstituted benzene derivatives, but may cause problems in terms of regioselectivity (and therefore yield), which requires special attention in the choice of reagents and synthesis plan of the target compound (Scheme 1). Another method, transition-metal-catalyzed [2+2+2] cycloaddition reactions,⁷ involves the

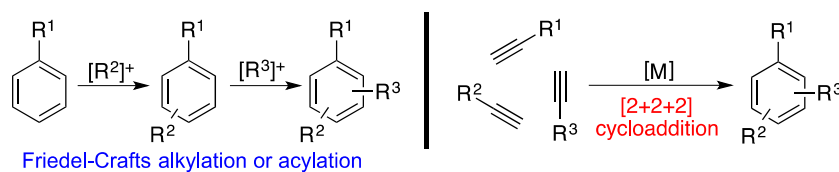
⁴ Elango, V.; Murphy, M. A.; Smith, B. L.; Davenport, K. G.; Mott, G. N.; Moss, G. L. US Patent 4981995, **1991**.

⁵ Groves, J. K. *Chem. Soc. Rev.* **1972**, *1*, 73.

⁶ Price, C. C. *Org. React.* **1946**, *3*, 1.

⁷ For selected recent reviews and chapters, see: (a) Peter, K.; Vollhardt, C. *Angew. Chem. Int. Ed.* **1984**, *23*, 539. (b) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787. (c) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, *2005*, 4741. (d) Gandon, V.; Aubert, C.; Malacria, M. *Curr. Org. Chem.* **2005**, *9*, 1699. (e) Gandon, V.; Aubert, C.; Malacria, M. *Chem. Commun.* **2006**, *21*, 2209. (f) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307. (g) Heller, B.; Hapke, M. *Chem. Soc. Rev.* **2007**, *36*, 1085. (h) Tanaka, K. *Synlett* **2007**, 1977. (i) Varela, J. A.; Saa, C. *Synlett* **2008**, 2571. (j) Tanaka, K. *Chem. - Asian J.* **2009**, *4*, 508. (k) Leboeuf, D.; Gandon, V.; Malacria, M. in: *Handbook of Cyclization Reactions*, Vol. 1, (Ed.: S. Ma), Wiley-VCH, Weinheim, **2009**, pp 367. (l) Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2011**, *40*, 3430. (m) Hua, R.; Abrenica, V. A.; Wang, P.; others. *Curr. Org. Chem.* **2011**, *15*, 712. (n) Shaaban, M. R.; El-Sayed, R.; Elwahy, A. H. M. *Tetrahedron* **2011**, *67*, 6095. (o) Weding, N.; Hapke, M. *Chem. Soc. Rev.* **2011**, *40*, 4525. (p) Broere, D. L.; Ruijter, E. *Synthesis* **2012**, *44*, 2639. (q) Okamoto, S. *Heterocycles* **2012**, *85*, 1579. (r) Tanaka, K. *Heterocycles* **2012**, *85*, 1017. (s) Wang, C.; Wan, B. *Chin. Sci. Bull.* **2012**, *57*, 2338. (t) Okamoto, S.; Sugiyama, Y. *Synlett* **2013**, *24*, 1044. (u)

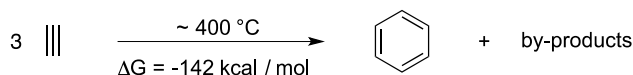
construction of aromatic rings in a single step, thereby obtaining highly functionalized aromatic rings in a one pot reaction (Scheme 1).



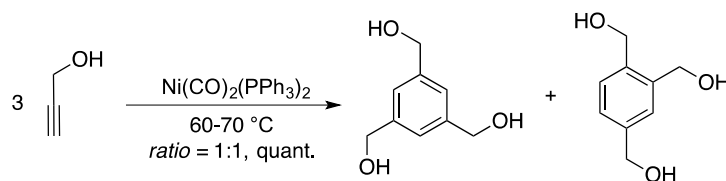
Scheme 1

Since Berthelot's pioneering thermal cyclization of three acetylene leading to benzene formation discovered in 1866,⁸ many advances have been reported in this field. The first metal-catalyzed [2+2+2] cycloaddition reaction was reported in 1948 by Reppe and Schweckendiek and involved Ni(CO)₂(PPh₃)₂ complex. This cyclotrimerization of monoalkynes occurred at 60-70 °C to provide 1,3,4- and 1,3,5-trisubstituted benzene derivatives in quantitative yield with no regioselectivity (Scheme 2).⁹ After this pioneering work, extensive studies have been conducted using cobalt, rhodium, nickel, ruthenium, and iridium.

First thermal [2+2+2] cyclotrimerization:



First metal-catalyzed [2+2+2] cyclotrimerization:



Scheme 2

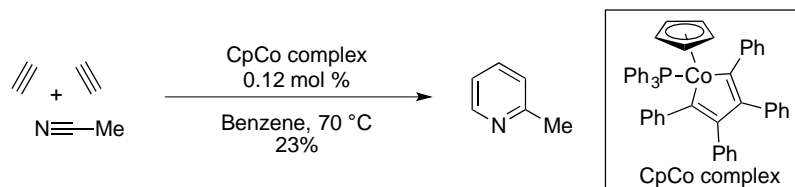
Yamamoto, Y. *Heterocycles* **2013**, 87, 2459. (v) Kumar, P.; Louie, J. Nickel-Mediated [2 + 2 + 2] Cycloaddition, In *Transition-Metal-Mediated Aromatic Ring Construction*; Tanaka, K., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2013. (w) Yamamoto, Y. Ruthenium-Mediated [2 + 2 + 2] Cycloaddition, In *Transition-Metal-Mediated Aromatic Ring Construction*; Tanaka, K., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2013. (x) Amatore, M.; Aubert, C. *Eur. J. Org. Chem.* **2015**, 265. (y) Satoh, Y.; Obara, Y. *Eur. J. Org. Chem.* **2015**, 2015, 5041. (z) Jungk, P.; Täufer, T.; Thiel, I.; Hapke, M. *Synthesis* **2016**, 48, 2026.

⁸ Berthelot, M. *Ann. Chim.* **1866**, 9, 445.

⁹ Reppe, W.; Schweckendiek, W. J. *Justus Liebigs Ann. Chem.* **1948**, 560, 104.

General introduction

In 1973, Yamazaki and Wakatsuki discovered that the substituted pyridines can be stepwise assembled from two acetylenes and one nitrile by using a catalytic amount of π -cyclopentadienyl(triphenylphosphine)cobalt complex (Scheme 3).^{10,11}

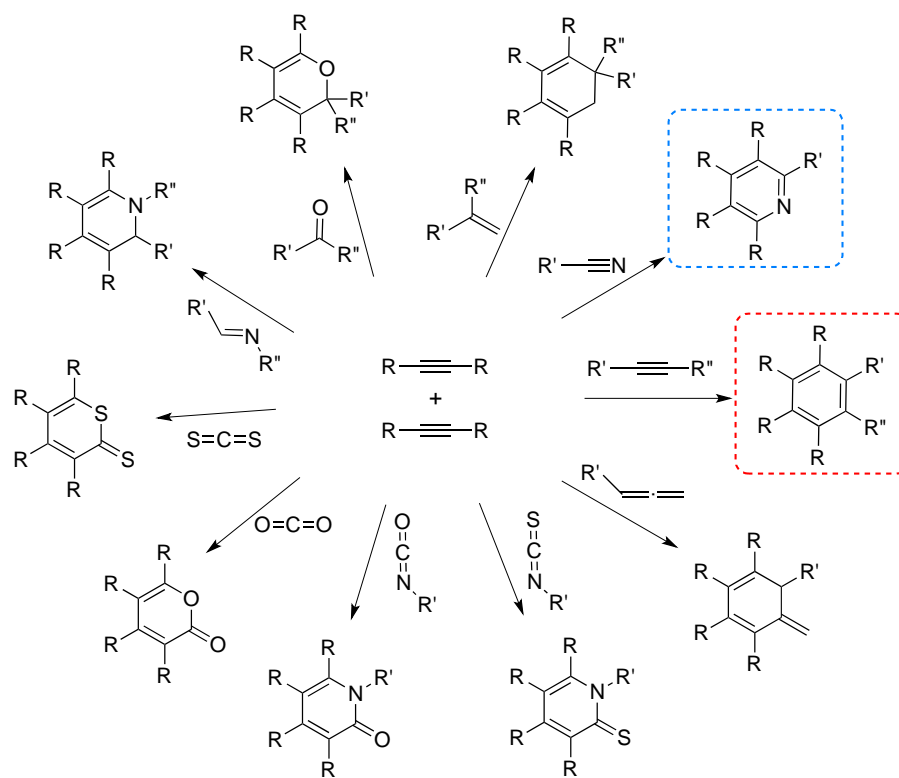


Scheme 3

Apart from the synthesis of benzenes and pyridines via cyclotrimerization of three alkynes or two alkynes with one nitrile, other unsaturated carbocyclic and heterocyclic compounds such as 1,3-cyclohexadienes, 1,2-dihydropyridines, thioxothiopyranes, 2-pyrones, 2-pyridones, and thiopyridones were also synthesized reacting two alkynes with the corresponding unsaturated alkenes, allenes, carbonyl compounds, imines, carbon disulfide, carbon dioxide, isocyanates, and thiocyanates (Scheme 4). The most commonly studied work is the synthesis of multiple substituted benzene and pyridine derivatives, which is the topic of this work.

¹⁰ Wakatsuki, Y.; Yamazaki, H. *J. Chem. Soc. Chem. Commun.* **1973**, 280.

¹¹ Wakatsuki, Y.; Yamazaki, H. *Tetrahedron. Lett.* **1973**, 3383.

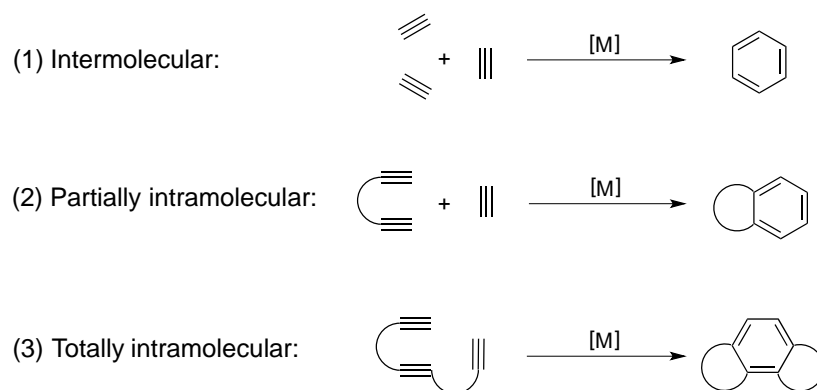


Scheme 4

Chapter I: Bibliography

Chapter I: Bibliography

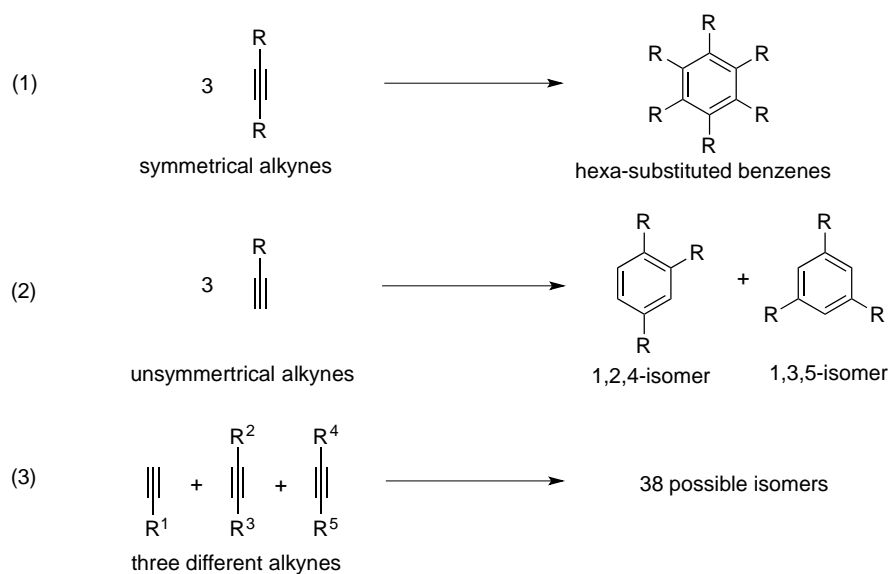
The first chapter will present selected literature data concerning the formation of benzene via transition-metal-catalyzed [2+2+2] cycloaddition reactions. In each section, we will deliver the works based on three types of cycloaddition reactions (intermolecular, partially intramolecular, and totally intramolecular, Scheme 5). Practical and general catalyst, construction of novel scaffolds, recent advances in mechanistic insight, regioselectivity and chemoselectivity issues will also be described.



Scheme 5

1. Intermolecular reactions

The intermolecular [2+2+2] alkyne cyclotrimerization is considered as one of the most efficient synthetic method to access benzene skeleton. Various types of transition metal complexes have been used for this transformation. However, the reaction is limited because of the low chemo- and regioselectivity. For example, as shown in Scheme 6, the homocyclotrimerization of a single symmetrical alkyne gives hexa-substituted benzenes (Eq. 1), the cycloaddition of unsymmetrical alkynes produces two regioisomers (Eq. 2), and the combination of two or three different alkynes leads to the formation of complex mixtures (Eq. 3).

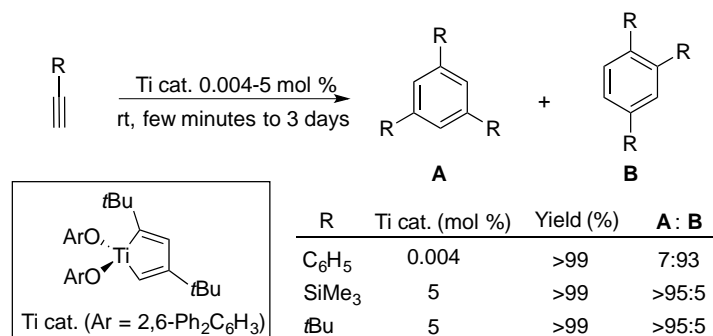


Scheme 6

1.1. Cyclotrimerization of one alkyne

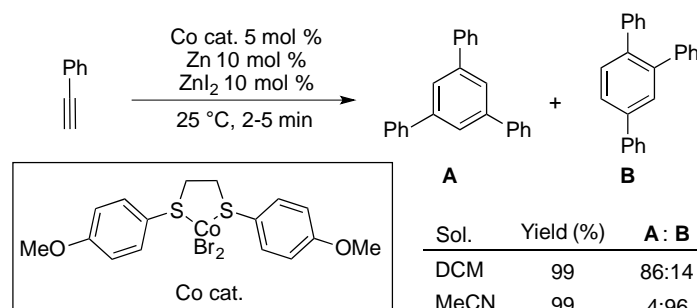
In 1993, Rothwell and co-workers reported the first regioselective transition-metal-catalyzed [2+2+2] cycloaddition reactions, which selectively produced the symmetrical 1,3,5- and unsymmetrical 1,2,4-substituted benzene derivatives using a catalytic amount of titanium complex.¹² It was demonstrated that the steric effects controlled the regioselectivity. For instance, in the presence of 0.004 mol % titanium catalyst, cyclotrimerization of phenylacetylene led to trisubstituted benzenes in quantitative yield, with 1,2,4-substituted regioisomer as the major product (ratio = 7:93). The more sterically hindered alkynes, such as trimethylsilyl acetylene and *tert*-butyl acetylene, afforded the 1,3,5-substituted products in high yields (ratio > 95:5), albeit with higher catalyst loading and prolonged reaction time (Scheme 7).

¹² Hill, J. E.; Balaich, G.; Fanwick, P. E.; Rothwell, I. P. *Organometallics* **1993**, *12*, 2911.



Scheme 7

After this pioneering work, many late transition metals have been used for the regioselective synthesis of benzene derivatives. The most common employed metals were cobalt, rhodium, ruthenium, iridium, nickel, and iron. An interesting example was reported by Hess and co-workers, who described a solvent-dependent regioselective [2+2+2] cyclotrimerization of phenylacetylene using a cobalt complex catalyst containing a disulfide ligand (Scheme 8).¹³ Optimization of different disulfide ligands in various solvents was also studied in this reaction. The result indicates that the coordination ability of the solvent greatly influenced the regioselectivity of the cyclotrimerizations.



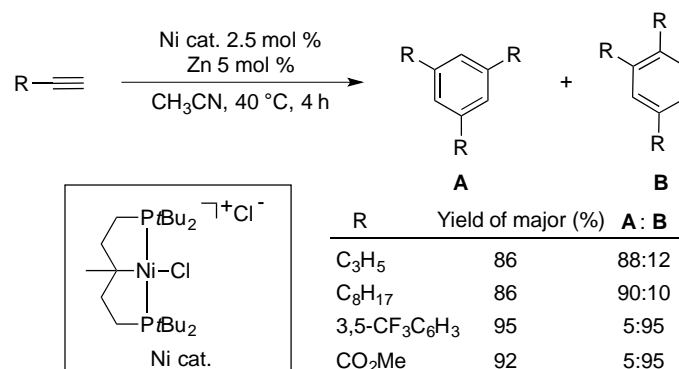
Scheme 8

Sivasankar and co-workers reported a series of highly efficient pincer ligands stabilized Ni(II) complexes as catalyst to promote the regioselective [2+2+2] cyclotrimerization of various alkynes. The complex bearing di-*tert*-butyl groups on the phosphine ligand acts as the best catalyst in this reaction.¹⁴ They observed that the selectivity correlated well with the electronic feature of the alkynes, the electron-rich alkynes were trimerized to give 1,3,5-

¹³ Hilt, G.; Hengst, C.; Hess, W. *Eur. J. Org. Chem.* **2008**, 2293.

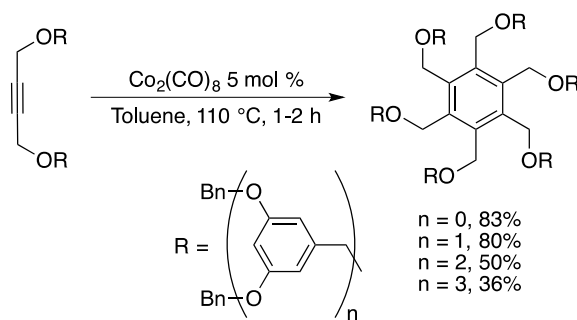
¹⁴ Tamizmani, M.; Sivasankar, C. *J. Organomet. Chem.* **2017**, DOI: 10.1016/j.jorganchem.2017.02.039.

substituted benzenes as the major products, whereas the electron-deficient alkynes afforded the 1,2,4-substituted benzenes as the major products (Scheme 9).



Scheme 9

Transition-metal-catalyzed [2+2+2] cyclotrimerization of disubstituted acetylene is considered as an elegant and efficient method to access hexa-substituted benzene derivatives in a single synthetic operation. Many groups have reported such reactions, including Fréchet and co-workers for the convergent synthesis of dendrimers using a cobalt-catalyzed [2+2+2] cyclotrimerization of bisdendritic alkynes, affording the corresponding benzene-cored dendrimers in 36-83% yields (Scheme 10).¹⁵



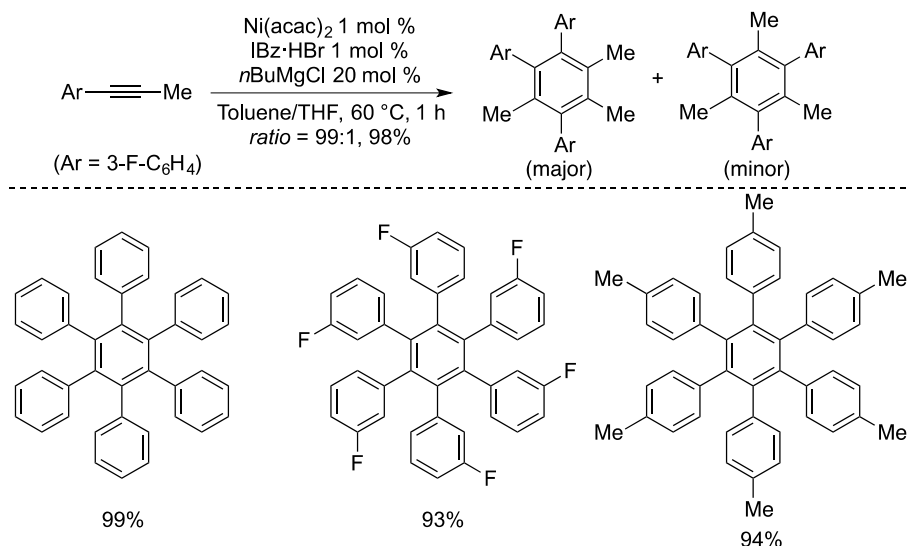
Scheme 10

Zhao and co-workers reported a facile and efficient method for the regioselective synthesis of polysubstituted benzenes via nickel-catalyzed [2+2+2] cyclotrimerization of simple unactivated alkyl(aryl)acetylenes and diarylacetylenes (Scheme 11).¹⁶ They found that the combination of Ni(acac)₂, imidazonium salt (IBz·HBr) and Grignard reagent (*n*BuMgCl) at

¹⁵ Hecht, S.; Fréchet, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 4084.

¹⁶ Xue, F.; Loh, Y. K.; Song, X.; Teo, W. J.; Chua, J. Y. D. Zhao, J.; Hor, T. S. A. *Chem. Asian J.* **2017**, *12*, 168.

60 °C led exclusively to the formation of 1,2,4-substituted isomer in up to 98% yield. This method was also utilized to access hexa-substituted benzenes by using IBz·HCl as the imidazolium salt partner providing a convenient synthetic route to various π -conjugated systems.

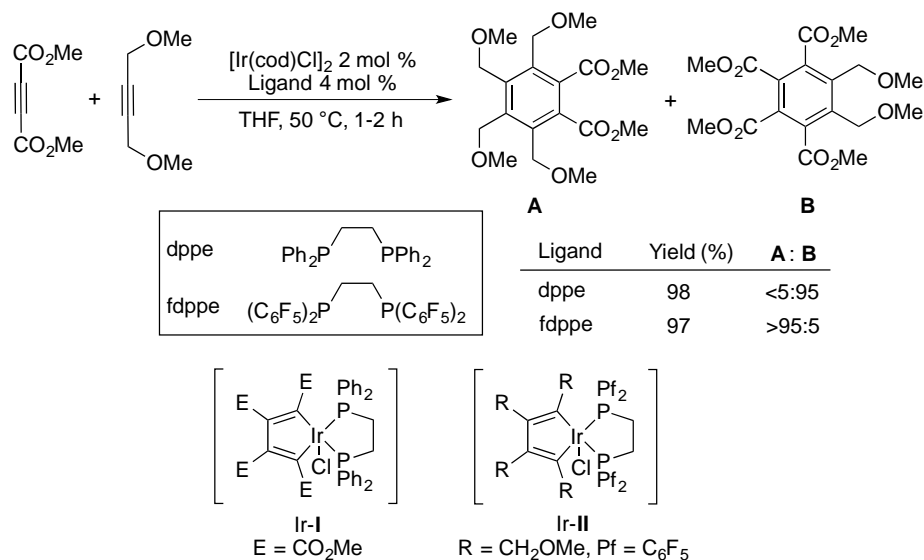


Scheme 11

1.2. Cycloaddition between two different alkynes.

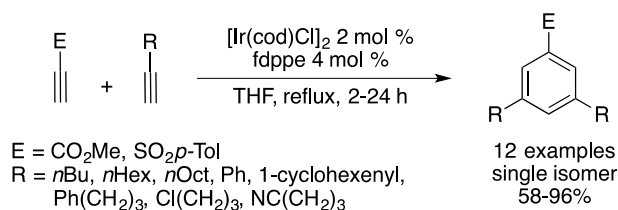
Takeuchi and Nakaya¹⁷ described the chemoselective iridium-catalyzed [2+2+2] cyclotrimerization of electron-deficient alkynes with electron-rich internal alkynes (Scheme 12). It was demonstrated that the chemoselectivity was controlled by the nature of the phosphine ligands. When 1,2-bis(diphenylphosphino)ethane (dppe) was used as a ligand, the electron-rich iridium/dppe complex coordinates with two electron-deficient alkynes to form iridacyclopentadiene Ir-**I** which undergoes coordination and insertion of another electron-rich alkyne to furnish the dicarbomethoxyl-substituted product as a major product. On the other hand, when electron-deficient 1,2-bis(dipentafluorophenylphosphino)ethane (fdppe) was employed, the reaction proceeded via iridacyclopentadiene Ir-**II** as the intermediate, affording the tetracarbomethoxyl-substituted compound as a major product. This reaction provided a useful and practical method for the synthesis of polycyclic substituted benzene derivatives.

¹⁷ Takeuchi, R.; Nakaya, Y. *Org. Lett.* **2003**, *5*, 3659.



Scheme 12

The same group also described in 2008 an iridium-catalyzed chemo- and regioselective synthesis of 1,3,5-substituted benzene derivatives via [2+2+2] cyclotrimerization of two different terminal alkynes.¹⁸ In the presence of Ir/fdppe catalyst system, a variety of 1,3,5-substituted benzenes was obtained as a single regioisomer in 58-96% yields. However, this strategy required the combination of one strong electron-deficient alkyne and one electron-rich alkyne (Scheme 13).



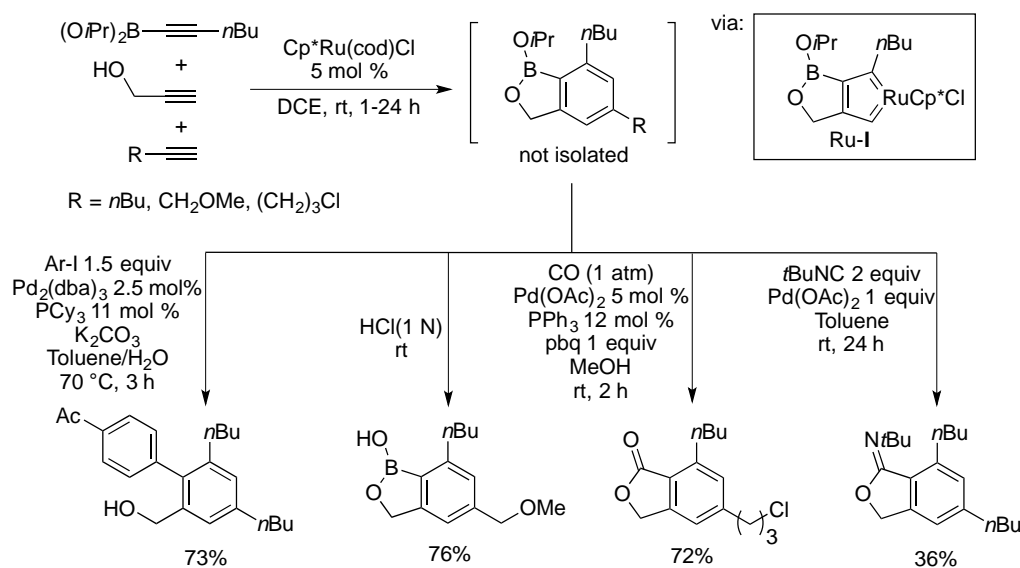
Scheme 13

¹⁸ Onodera, G.; Matsuzawa, M.; Aizawa, T.; Kitahara, T.; Shimizu, Y.; Kezuka, S.; Takeuchi, R. *Synlett* **2008**, 755.

1.3. Cycloaddition of three different alkynes

The intermolecular [2+2+2] cyclotrimerization of three different alkynes is difficult to control. Early transition metals such as zirconium¹⁹ and titanium²⁰ were used for such transformation. However, the use of stoichiometric catalyst and harsh reaction conditions were required in some cases.

In 2004, Yamamoto and co-workers developed a chemo- and regioselective intermolecular cyclotrimerization of three different unsymmetrical alkynes using Cp*Ru(cod)Cl as the catalyst.²¹ The reaction is initiated by the oxidative cyclization of an alkynylboronate and a propargyl alcohol to form the key ruthenacycle intermediate Ru-I, which undergoes insertion of the third alkyne to afford the intermediate arylboronate. The subsequent one-pot functionalization of these arylboronates could further be converted into several substituted aromatic compounds such as biaryls, boraphthalides, phthalides, and imidates (Scheme 14).



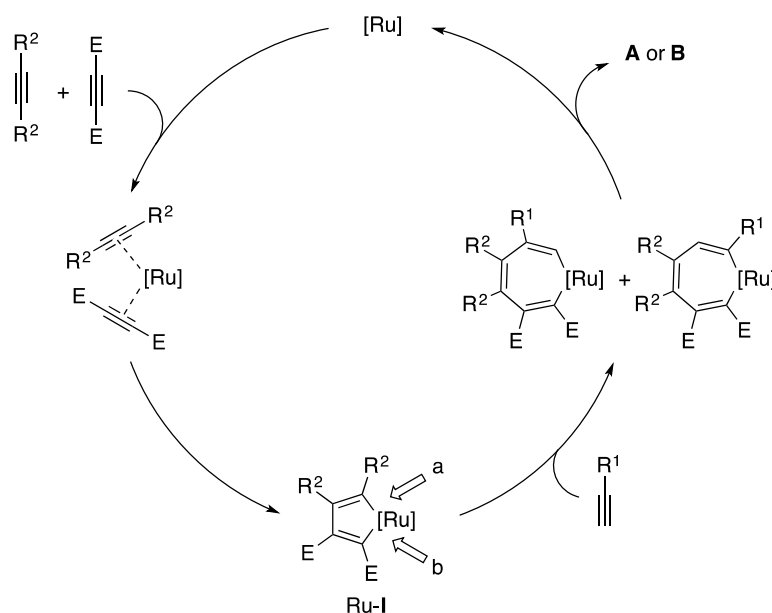
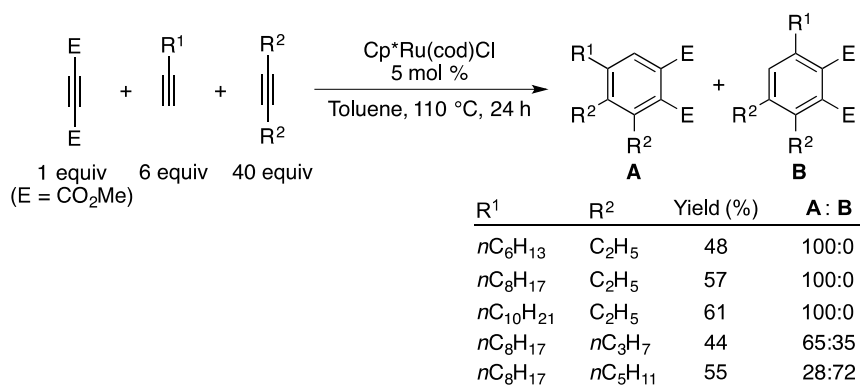
Scheme 14

¹⁹ (a) Takahashi, T.; Kotora, M.; Xi, Z. *J. Chem. Soc. Chem. Commun.* **1995**, 361. (b) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **1999**, *121*, 11093.

²⁰ (a) Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2001**, *123*, 7925. (b) Tanaka, R.; Nakano, Y.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2002**, *124*, 9682.

²¹ (a) Yamamoto, Y.; Ishii, J.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2004**, *126*, 3712. (b) Yamamoto, Y.; Ishii, J.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 9625.

In 2005, Mitsudo and co-workers developed a ruthenium-catalyzed chemoselective [2+2+2] cycloaddition to form polysubstituted *o*-phthalates (Scheme 15).²² It was demonstrated that a high chemoselectivity and regioselectivity could be attained by controlling the molar ratio of the three substrates. The reaction is also influenced by the bulkiness of the two substituents on the internal and terminal alkynes. Mitsudo's group proposed a plausible mechanism for the [2+2+2] cycloaddition. At the first step, the internal alkyne and DMAD react with the ruthenium to form the ruthenacyclopentadiene Ru-I intermediate, followed by an insertion of the terminal alkyne into the formed ruthenacycle. A subsequent reductive elimination would afford the final regioisomers and regenerate the ruthenium catalytic species. However, a large excess of internal alkyne was required to avoid the formation of side-products.

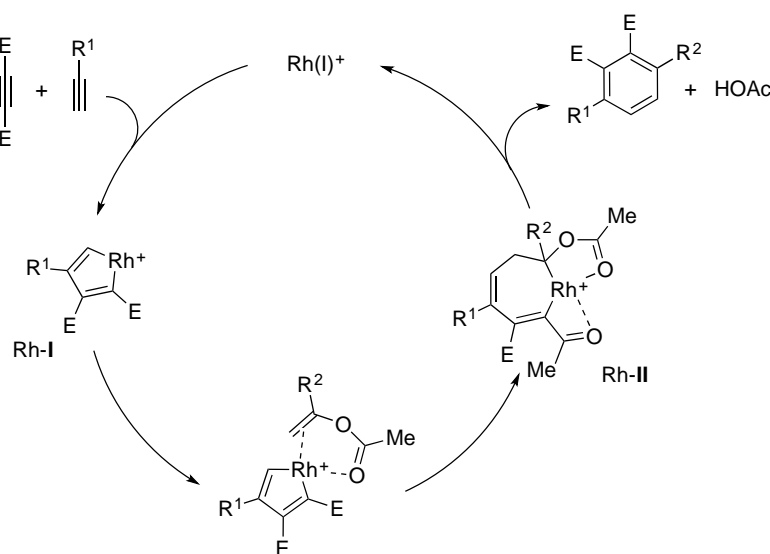
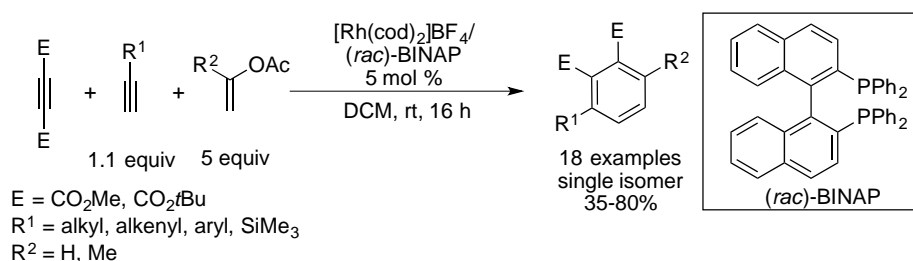


Scheme 15

²² Ura, Y.; Sato, Y.; Tsujita, H.; Kondo, T.; Imachi, M.; Mitsudo, T. *J. Mol. Catal. Chem.* **2005**, 239, 166.

1.4. Cyclotrimerization of two alkynes with another unsaturated substrate

Tanaka and co-workers described a cationic rhodium-catalyzed intermolecular [2+2+2] cycloaddition reaction of a terminal alkyne, a dialkyl acetylenedicarboxylate, and an enol ester.²³ A variety of tri- and tetra-substituted benzenes was obtained in 35-80% yields with complete regioselectivity. The proposed mechanism features the regioselective formation of the rhodacyclopentadiene **Rh-I** followed by the regioselective insertion of an enol acetate leading to the intermediate **Rh-II**, which is stabilized by the coordination of the carbonyl group with the cationic rhodium through a five-membered chelation. Finally, a subsequent reductive elimination affords the corresponding substituted benzenes and one equivalent of acetic acid (Scheme 16).



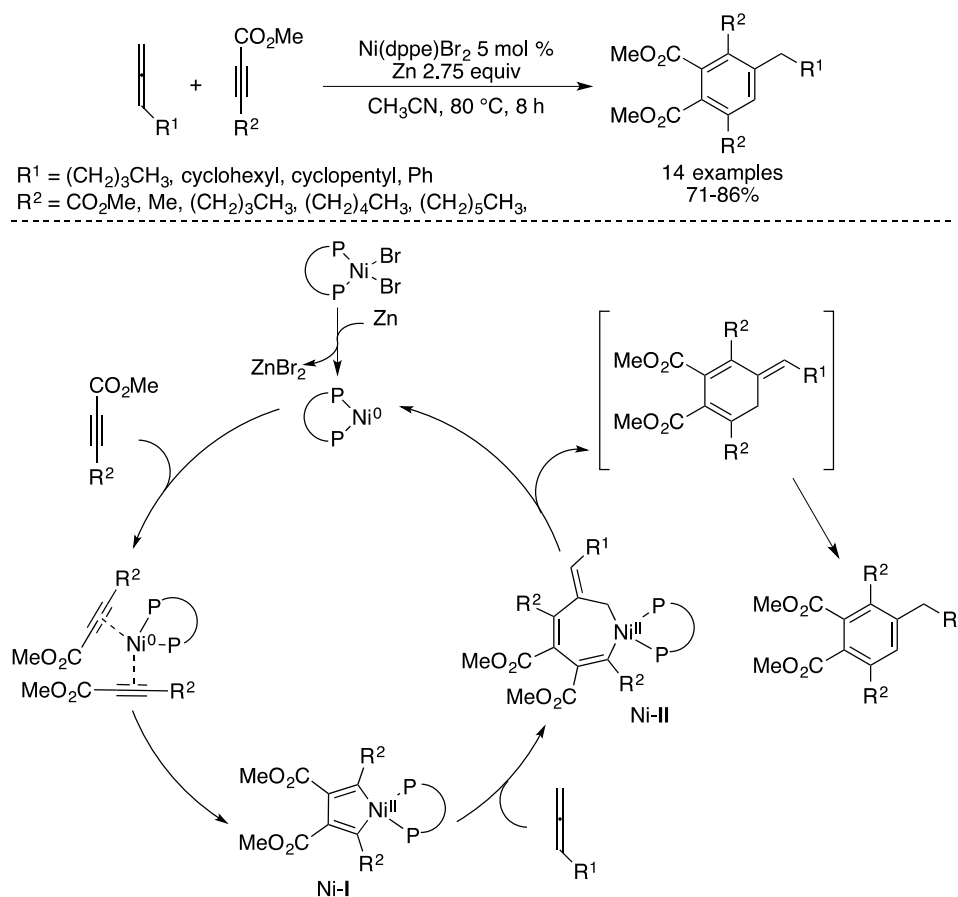
Scheme 16

Cheng and co-workers described a new and efficient Ni(dppe)Br₂/Zn catalytic system for the cross intermolecular [2+2+2] cyclotrimerization of two alkynes with an allene.²⁴ A

²³ (a) Hara, H.; Hirano, M.; Tanaka, K. *Org. Lett.* **2008**, *10*, 2537. (b) Hara, H.; Hirano, M.; Tanaka, K. *Tetrahedron* **2009**, *65*, 5093.

²⁴ Shanmugasundaram, M.; Wu, M.-S.; Cheng, C.-H. *Org. Lett.* **2001**, *3*, 4233.

variety of polysubstituted benzene derivatives was obtained in complete regioselectivity and high chemoselectivity. According to the proposed mechanism, at the first step, two molecules of propiolate are consumed in the presence of the catalytic Ni(0) species to form the nickellacyclopentadiene intermediate Ni-I, coordination and subsequent insertion of allene into a Ni(II)-carbon bond gives nickellacyclopentadiene intermediate Ni-II. Subsequent reductive elimination and isomerization provide the aromatic product and regenerate the Ni(0) catalyst. Notably, the results indicated that the presence of a strong electron-withdrawing ester group in the alkyne moiety was necessary to ensure the success of the reactions. (Scheme 17)



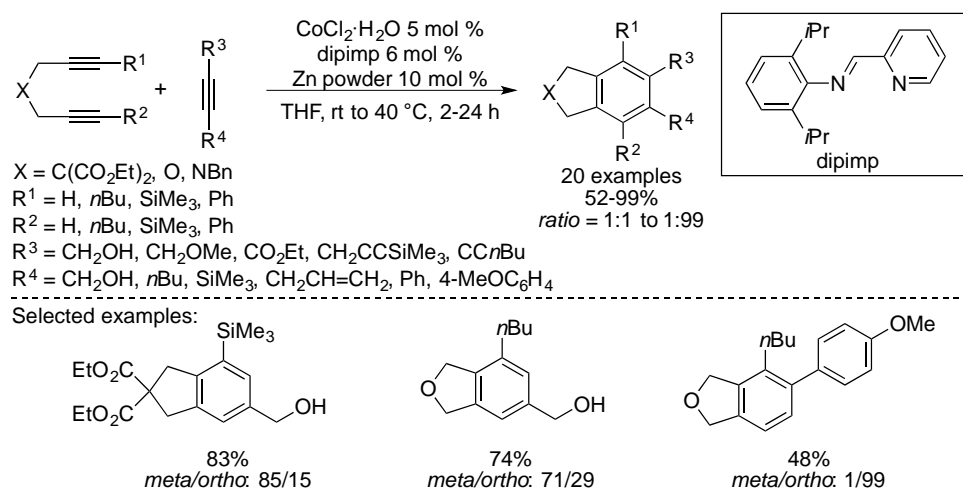
Scheme 17

2. Partially intramolecular reactions

2.1. Cobalt-catalyzed partially intramolecular [2+2+2] cycloadditions

In 2006, Okamoto and co-workers reported the first partially intramolecular cobalt-catalyzed [2+2+2] cycloaddition reaction of α,ω -diynes with alkynes by using a catalytic

system based on the combination of 2-(2,6-diisopropylphenyl)iminomethylpyridine (dipimp), $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, and Zn powder.²⁵ This method is efficient with a variety of functional terminal or internal alkynes, such as alcohols, esters, alkenes and silyl-substituted alkynes (Scheme 18). The use of Zn powder was required to promote the catalytic cycles, and the reaction was incompatible with aryl bromides, iodides, and nitro compounds because of the interaction with zinc and/or cobalt. Okamoto's team also demonstrated that the addition of a silver salt, such as silver triflate (AgOTf) or silver hexafluoroantimonate (AgSbF_6), could accelerate the reaction to furnish sterically demanding benzene derivatives starting from unactivated simple internal alkynes.²⁶



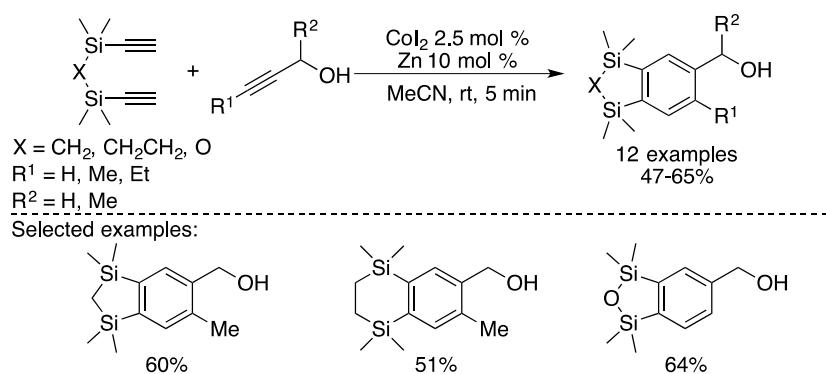
Scheme 18

Doszczak and Tacke accomplished a one-step synthesis of hydroxyalkyl-substituted 1,3-disilaindanes, 1,4-disilatetralines, and 1,3-disila-1,3-dihydroisobenzofuranes via Co/Zn-catalyzed [2+2+2] cycloaddition of silicon-containing diynes and unprotected propargyl alcohols under mild conditions (Scheme 19).²⁷

²⁵ Saino, N.; Amemiya, F.; Tanabe, E.; Kase, K.; Okamoto, S. *Org. Lett.* **2006**, 8, 1439.

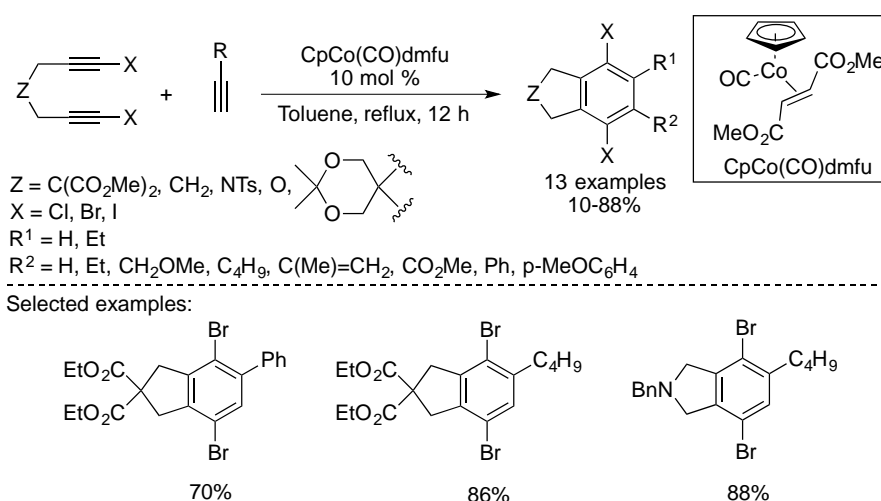
²⁶ Goswami, A.; Ito, T.; Okamoto, S. *Adv. Synth. Catal.* **2007**, 349, 2368.

²⁷ Doszczak, L.; Tacke, R. *Organometallics* **2007**, 26, 5722.



Scheme 19

In 2011, Aubert, Gandon, and Malacria engaged a series of halogenated diynes with alkynes in the presence of $\text{CpCo}(\text{CO})(\text{dimethylfumarate})$ and $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$ catalyst via [2+2+2] cycloaddition reactions.²⁸ The studies confirmed that the ruthenium complex remains the best choice for the cycloaddition of all kind of alkynyl halides. The air-stable $\text{CpCo}(\text{CO})(\text{dmfu})$ complex proved to be efficient with alkynyl bromides (Scheme 20).



Scheme 20

2.2. Rhodium-catalyzed partially intramolecular [2+2+2] cycloadditions

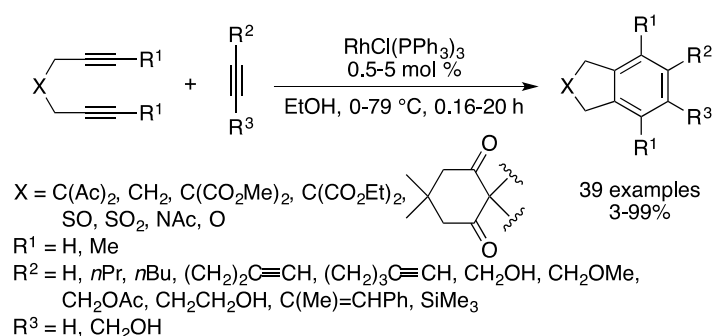
Since the first examples of partially intramolecular [2+2+2] cycloadditions of α,ω -diynes and alkynes using a stoichiometric amount of Wilkinson's catalyst ($\text{RhCl}(\text{PPh}_3)_3$)

²⁸ Iannazzo, L.; Kotera, N.; Malacria, M.; Aubert, C.; Gandon, V. *J. Organomet. Chem.* **2011**, 696, 3906.

reported by Müller in 1974,²⁹ the rhodium-catalyzed [2+2+2] cycloaddition of diynes and alkynes has been well studied over the past few decades. The most efficient and widely used rhodium catalysts were neutral $\text{RhCl}(\text{PPh}_3)_3$ complex and cationic rhodium(I)/biaryl bisphosphine complex catalysts.

Wilkinson's catalyst:

Grigg and co-workers described the first catalytic [2+2+2] cycloaddition of 1,6-diynes with alkynes under mild conditions in the presence of a catalytic amount of $\text{RhCl}(\text{PPh}_3)_3$ catalyst.³⁰ Various tethered diynes and monoalkynes could be employed under these reaction conditions to afford the cycloadducts in 3-99% yields (Scheme 21).³¹



Scheme 21

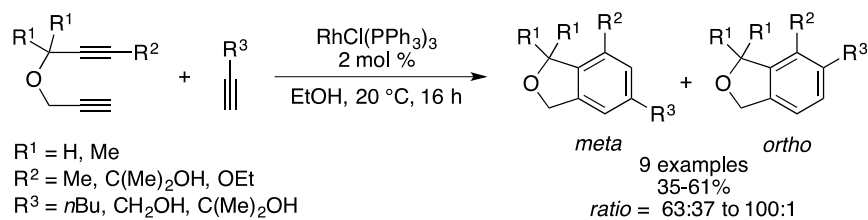
The Wilkinson's catalyst could also be used in the regioselective cycloaddition of unsymmetrical diynes with alkynes. In 1995, McDonald and co-workers reported the $\text{RhCl}(\text{PPh}_3)_3$ -catalyzed [2+2+2] cycloaddition of different substituted diynes with simple monosubstituted alkynes to afford functionalized dihydroisobenzofuran products in 35-61% yields.³² In most cases, the *meta*-substituted aromatic products were formed as major products because of the steric hindrance of the alkyne substituents (Scheme 22).

²⁹ Müller, E. *Synthesis* **1974**, 761.

³⁰ Grigg, R.; Scott, R.; Stevenson, P. *Tetrahedron Lett.* **1982**, 23, 2691.

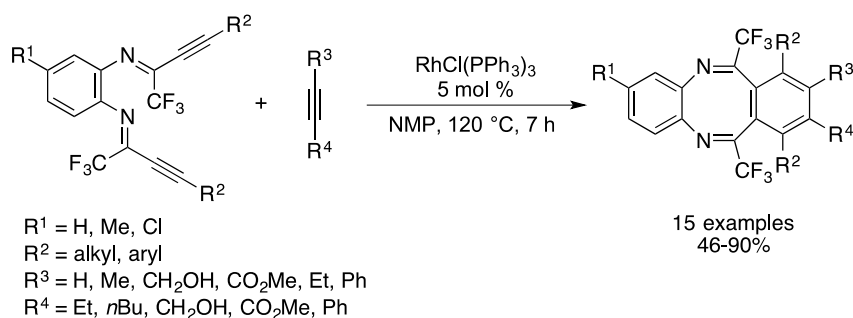
³¹ Grigg, R.; Scott, R.; Stevenson, P. *J. Chem. Soc. Perkin 1* **1988**, 1357.

³² McDonald, F. E.; Zhu, H. Y.; Holmquist, C. R. *J. Am. Chem. Soc.* **1995**, 117, 6605.



Scheme 22

In contrast to the formation of five or six-membered bicyclic benzene derivatives, the [2+2+2] cycloadditions to form medium-sized ring systems remain a challenge. Wu and co-workers developed a Rh-catalyzed [2+2+2] cycloaddition reaction for the preparation of trifluoromethylated benzo-fused eight-membered rings. The Wilkinson's catalyst was chosen for the reaction to deliver the expected products in 46-90% yields with good functional group tolerance (Scheme 23).³³



Scheme 23

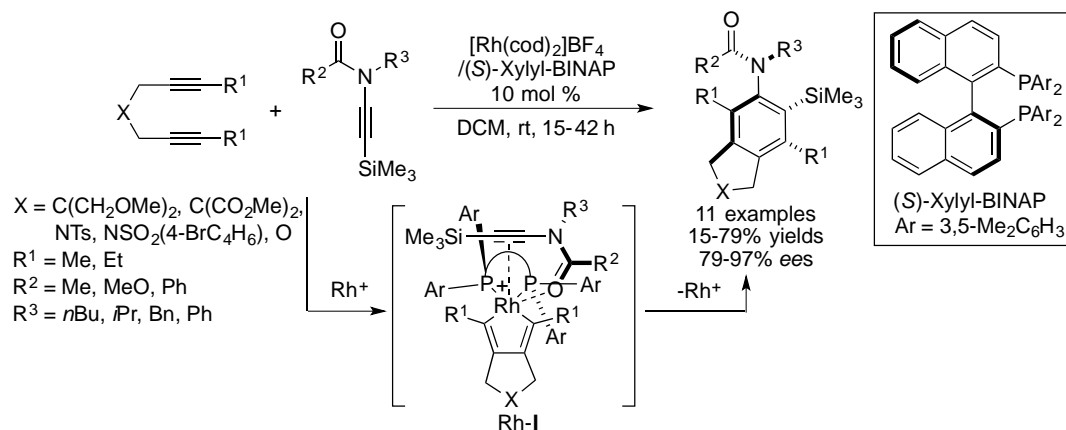
Cationic Rh(I)-biaryl bisphosphine complexes:

The cationic rhodium/biaryl bisphosphine catalysts are the most efficient catalysts and have been widely studied in partially intramolecular [2+2+2] cycloaddition reactions. In 2006, Tanaka and co-workers successfully employed a $\text{Rh}(\text{cod})_2\text{BF}_4/(\text{S})\text{-Xylyl-BINAP}$ complex for the enantioselective [2+2+2] cycloaddition of α,ω -diynes with trimethylsilylynamides to furnish axially chiral anilides.³⁴ The authors demonstrated that the substituted groups on the ynamides greatly influenced the yield of anilides. Indeed, the phenyl- and methoxycarbonyl-substituted trimethylsilylynamides showed high reactivity. According to the mechanism, the high enantioselectivity of the anilides could be explained by the formation of the key

³³ Zhang, L.; Li, Y.; Zhang, L.; Wu, Y. *Org. Biomol. Chem.* **2014**, *12*, 1040.

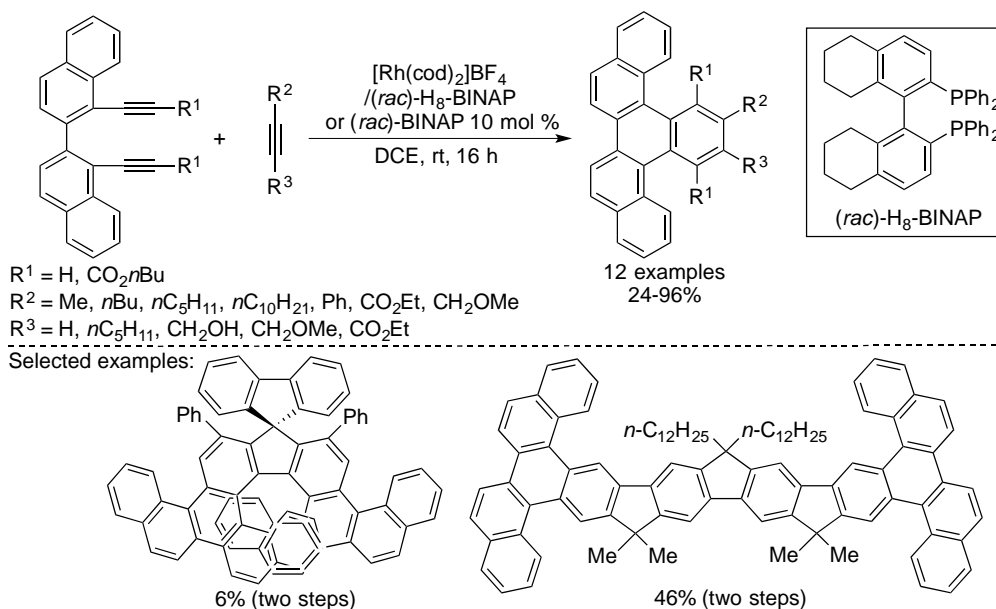
³⁴ Tanaka, K.; Takeishi, K.; Noguchi, K. *J. Am. Chem. Soc.* **2006**, *128*, 4586.

intermediate **Rh-I**, in which the rhodium center is coordinated to the carbonyl group of trimethylsilylynamide and the bulky PAR_2 group of (*S*)-Xylyl-BINAP which sterically interacts with the R^3 of the trimethylsilylynamide (Scheme 24).



Scheme 24

The same group applied the cationic rhodium(I)/ $\text{H}_8\text{-BINAP}$ catalyst for the synthesis of substituted benzopicycenes via [2+2+2] cycloaddition of binaphthyl-linked diynes with alkynes (Scheme 25).³⁵ This method was further applied for the benzopicycene-based long ladder and helical molecules synthesis.



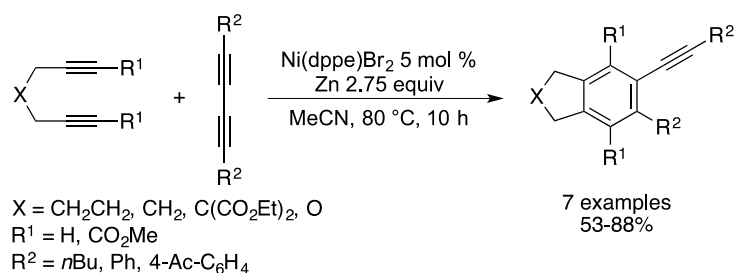
Scheme 25

³⁵ Murayama, K.; Shibata, Y.; Sugiyama, H.; Uekusa, H.; Tanaka, K. *J. Org. Chem.* **2017**, *82*, 1136.

2.3. Nickel-catalyzed partially intramolecular [2+2+2] cycloadditions

Since the first examples of cyclotrimerization of alkynes to form benzene derivatives reported by Reppe,⁹ the nickel-catalyzed [2+2+2] cycloaddition reactions have been well studied because of several advantages such as a high reactivity, a broad functional groups tolerance, relatively cheaper price compared to other late transition metals.

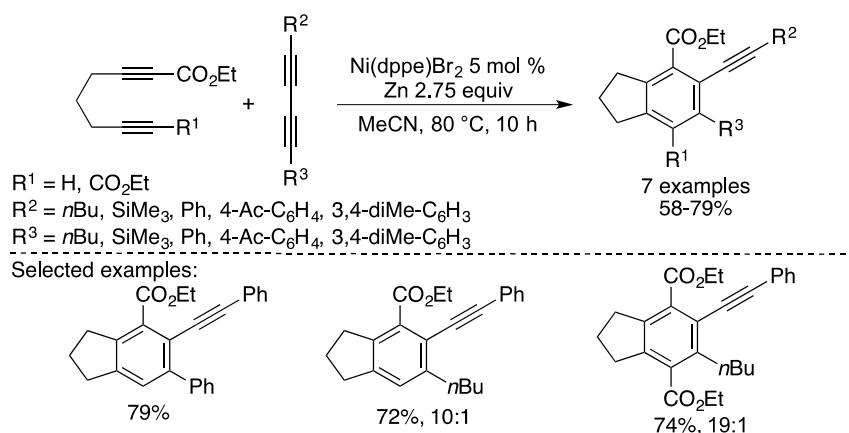
Cheng and co-workers developed an efficient protocol for the synthesis of polysubstituted arylalkynes based on the nickel-catalyzed [2+2+2] cycloaddition of non-conjugated diynes with 1,3-diynes in a single transformation (Scheme 26).³⁶ The results showed that the electron-withdrawing ester groups substituted diynes are more reactive compared to the terminal diynes.



Scheme 26

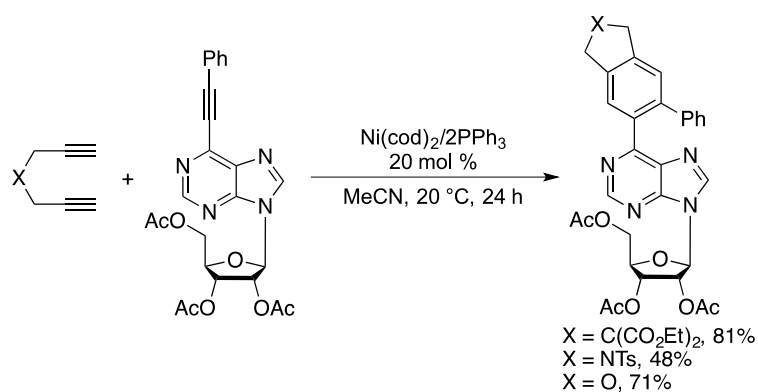
Under the optimized conditions, the reaction of unsymmetrical 1,6-diynes with symmetrical 1,3-diynes afforded the products in 58-79% yields with excellent chemo- and regioselectivity. Phenyl-, *n*-butyl-, and trimethylsilyl-substituted 1,3-diynes reacted with 1,6-diynes to afford highly functionalized arylalkynes. Interestingly, unsymmetrical 1,3-diynes reacted with di-ester-substituted symmetrical diynes at room temperature to give the cycloadduct with high regioselectivity (ratio = 19:1). The cycloaddition mainly occurred with the triple bond adjacent to the *n*-butyl group of the 1,3-diyne (Scheme 27).

³⁶ Jeevanandam, A.; Korivi, R. P.; Huang, I.; Cheng, C.-H. *Org. Lett.* **2002**, *4*, 807.



Scheme 27

Kotora and co-workers reported a nickel-catalyzed [2+2+2] cycloaddition of 6-alkynylpurines with α,ω -diynes to access biologically active 6-arylpurines.³⁷ A variety of terminal diynes and substituted 6-alkynylpurines was examined to afford various functionalized 6-arylpurines. Several catalysts have been evaluated in this reaction, such as $\text{CoBr}(\text{PPh}_3)_3$, $\text{RhCl}(\text{PPh}_3)_3$, $\text{NiBr}_2(\text{dppe})/\text{Zn}$, $\text{NiI}_2(\text{PPh}_3)/\text{Zn}$, and $\text{Ni}(\text{cod})_2/\text{PPh}_3$. The results showed that Ni/phosphine complexes were the best catalysts for the cyclotrimerization of alkynes. For example, in the presence of 20 mol % of $\text{Ni}(\text{cod})_2/2\text{PPh}_3$, different 1,6-diyne smoothly reacted with 6-alkynylpurine nucleosides at 20 °C to deliver the 6-arylpurine nucleosides in 48-81% yields (Scheme 28).³⁸

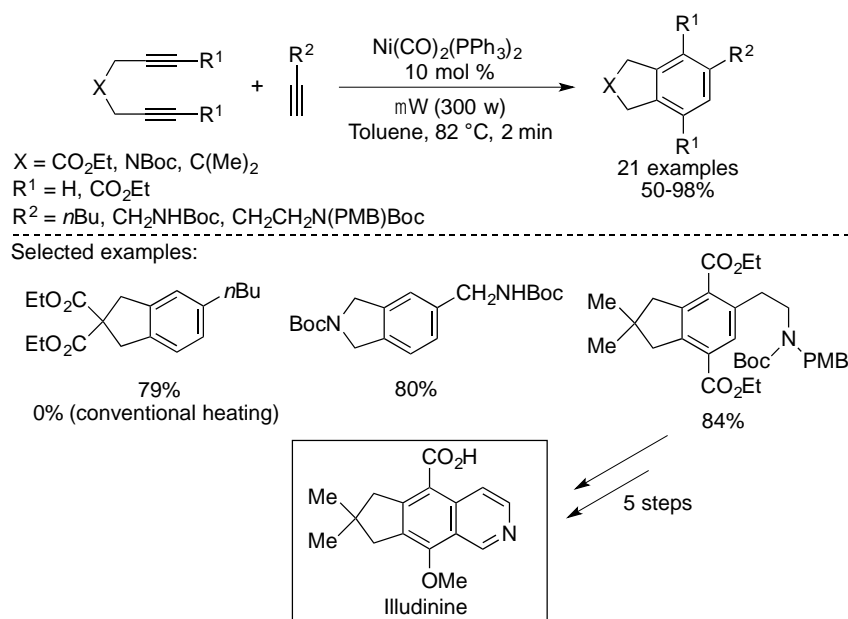


Scheme 28

³⁷ Turek, P.; Kotora, M.; Hocek, M.; Císařová, I. *Tetrahedron Lett.* **2003**, *44*, 785

³⁸ (a) Turek, P.; Kotora, M.; Tišlerová, I.; Hocek, M.; Votruba, I.; Císařová, I. *J. Org. Chem.* **2004**, *69*, 9224. (b) Turek, P.; Novak, P.; Pohl, R.; Hocek, M.; Kotora, M. *J. Org. Chem.* **2006**, *71*, 8978.

Deiters and co-workers described the microwave irradiation assisted nickel-catalyzed [2+2+2] cyclotrimerization reactions to quickly access highly substituted aromatic compounds.³⁹ The application of microwave irradiation highly enhanced the reactivity of Ni(CO)₂(PPh₃)₂ catalyst, and enabled the reaction to produce highly substituted benzene derivatives in a short reaction time. A variety of diynes and alkynes were tolerated to afford various substituted indanes, isoindolines, and tetraline core structures in 50-98% yields. Notably, the developed protocols were used as a key step for the total synthesis of natural product Illudinine (Scheme 29).



Scheme 29

2.4. Iridium-catalyzed partially intramolecular [2+2+2] cycloadditions

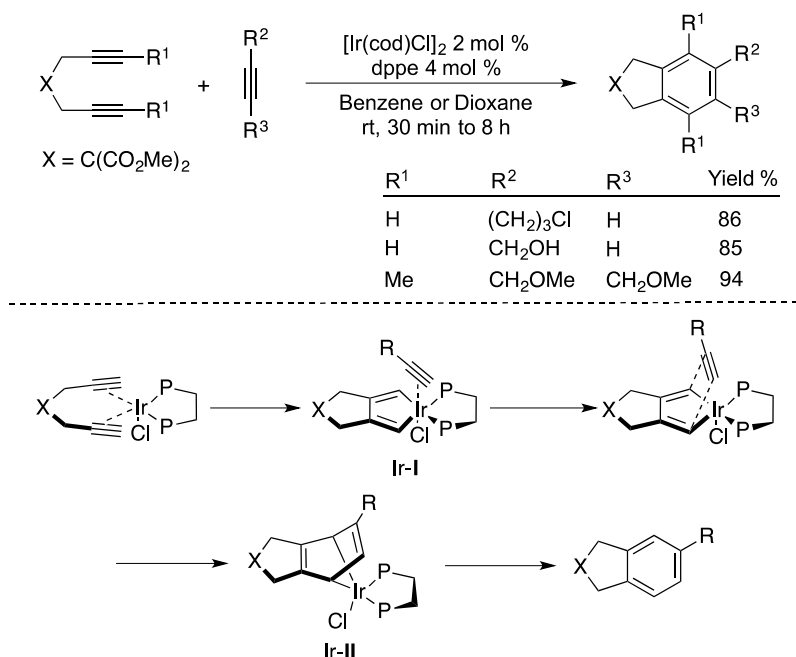
In 2001, Takeuchi and co-workers described a simple and convenient protocol for the synthesis of polysubstituted benzene derivatives by using [Ir(cod)Cl]₂/dppe complex as a catalyst.⁴⁰ A broad range of functional groups such as alcohols, amines, alkenes, ethers, halogens, and nitriles were tolerated to give various functionalized benzene derivatives.⁴¹ It was proposed that the reaction formed an iridacyclopentadiene intermediate Ir-I by the oxidative cyclization of α,ω -diynes. The coordination of a monoynone would facilitate a Diels-Alder type

³⁹ Teske, J. A.; Deiters, A. *J. Org. Chem.* **2008**, *73*, 342.

⁴⁰ Takeuchi, R.; Tanaka, S.; Nakaya, Y. *Tetrahedron Lett.* **2001**, *42*, 2991.

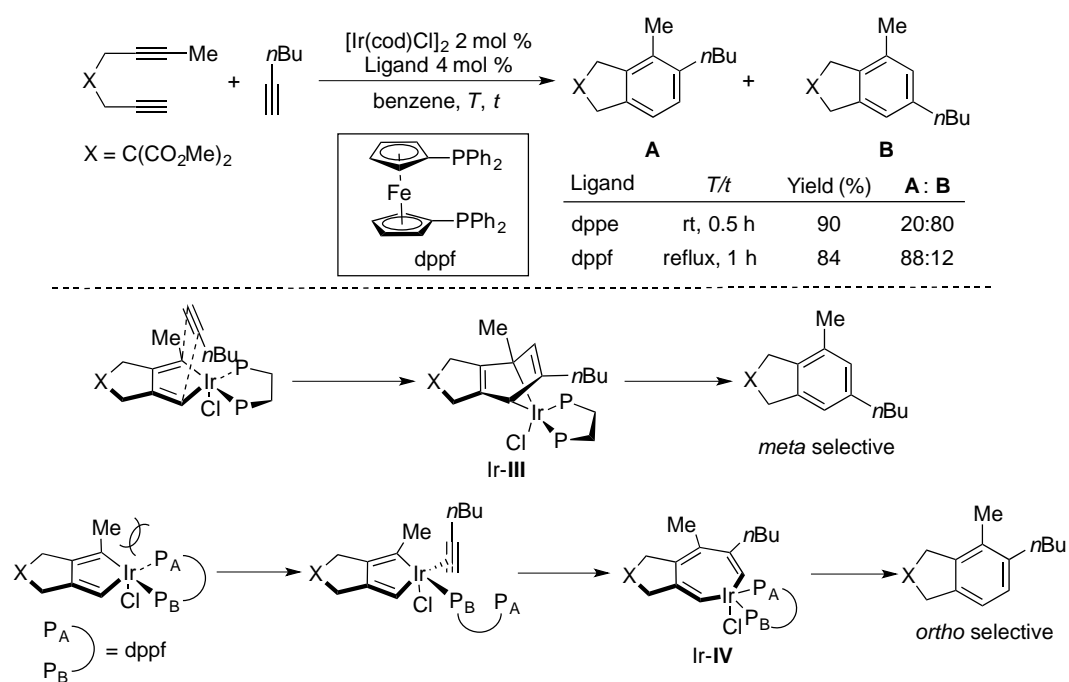
⁴¹ Kezuka, S.; Tanaka, S.; Ohe, T.; Nakaya, Y.; Takeuchi, R. *J. Org. Chem.* **2006**, *71*, 543.

process to form an intermediate **Ir-II**, followed by reductive elimination to deliver the cycloadduct (Scheme 30).



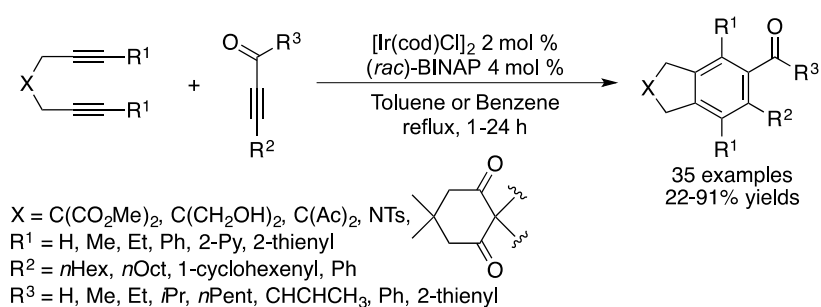
Scheme 30

The authors also studied the regioselective cycloaddition of unsymmetrical diynes with terminal alkynes. The regioselectivity was controlled by the ligands. A plausible mechanism was shown in Scheme 31. When dppe is employed as the ligand, the reaction goes through a [4+2] Diels-Alder type mechanism forming intermediate **Ir-III**, and affords *meta* selective product as the major product. When dppf is used as ligand, the reaction proceeds via an insertion mechanism forming intermediate **Ir-IV** and provides selectively the *ortho* product as the major product.



Scheme 31

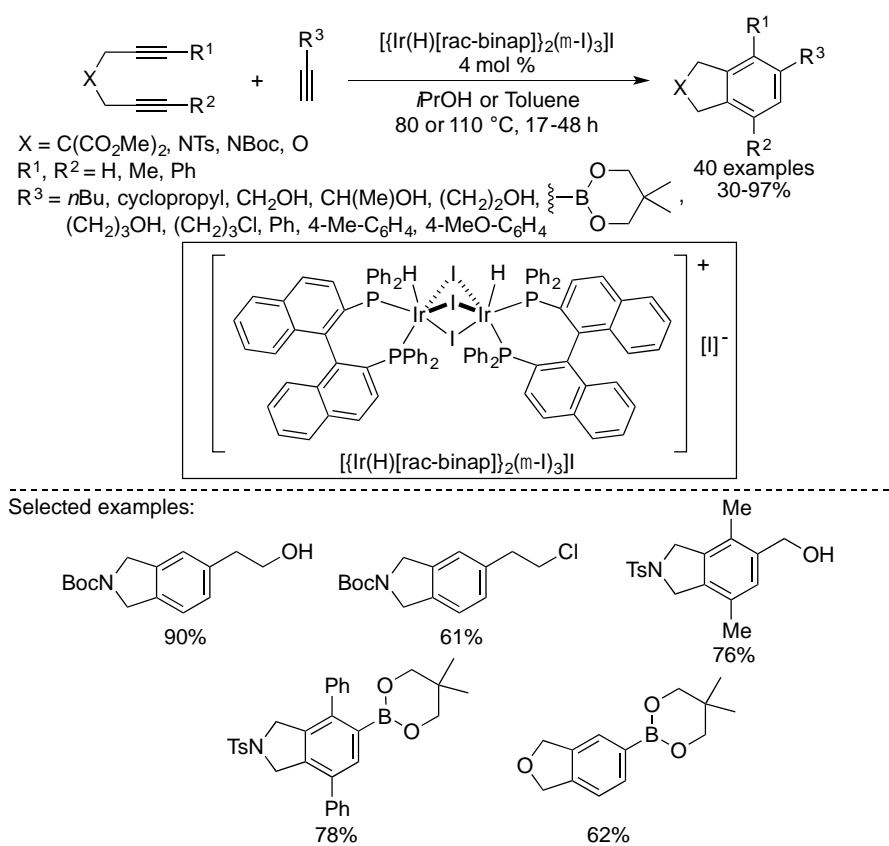
In 2014, Takeuchi's group expanded the scope of this reaction to the synthesis of carbonyl group functionalized benzene derivatives. Upon screening several iridium complexes and ligands, they found that the $[\text{Ir}(\text{cod})\text{Cl}]_2/(\text{rac})\text{-BINAP}$ was the best catalytic system for the reaction.⁴² A broad range of 2,7-diyne reacted with alkynyl ketones and alkynyl esters in the presence of $[\text{Ir}(\text{cod})\text{Cl}]_2/(\text{rac})\text{-BINAP}$ catalyst to provide the corresponding functionalized benzenes in 22-91% yields (Scheme 32).



Scheme 32

⁴² Hashimoto, T.; Okabe, A.; Mizuno, T.; Izawa, M.; Takeuchi, R. *Tetrahedron* **2014**, *70*, 8681.

Taking advantage of the triply iodo-bridged iridium(III) complexes, $[\{\text{Ir}(\text{H})[\text{rac-binap}]\}_2(\mu\text{-I})_3]\text{I}$,⁴³ our group developed in 2012 a convenient and efficient protocol for the preparation of fused arenes. Isoindolines, indanes, and dihydroisobenzofurans bearing a wide range of substitution groups could be achieved through an iridium(III)-catalyzed [2+2+2] cycloaddition of α,ω -diynes with alkynes. The reaction proceeds with symmetrical and unsymmetrical diynes, which affords highly substituted benzene derivatives in up to 97% yields. This methodology can be applied to alkynylboronates, which is a convenient means to generate the challenging, highly functionalized borylated fused arenes that present great potential for further elaboration. Notably, these processes are extremely robust and simple to perform. The catalyst system is compatible with commercial grade non-degassed solvents, whereas the alkynes herein do not necessitate purification before use (Scheme 33).⁴⁴

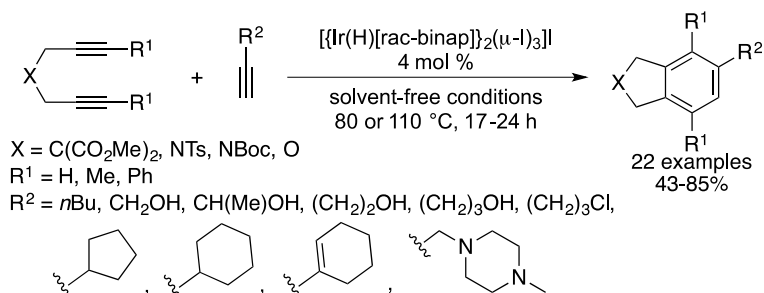


Scheme 33

⁴³ Yamagata, T.; Tadaoka, H.; Nagata, M.; Hirao, Y.; Kataoka, Y.; Ratovelomanana-Vidal, V.; Genet, J.-P.; Mashima, K. *Organometallics* **2006**, *25*, 2505.

⁴⁴ (a) Auvinet, A.-L.; Ez-Zoubir, M.; Vitale, M. R.; Brown, J. A.; Michelet, V.; Ratovelomanana-Vidal, V. *ChemSusChem* **2012**, *5*, 1888. (b) Auvinet, A.-L.; Ez-Zoubir, M.; Bompard, S.; Vitale, M. R.; Brown, J. A.; Michelet, V.; Ratovelomanana-Vidal, V. *ChemCatChem* **2013**, *5*, 2389.

In 2003, this atom-economical process has also been successfully performed under solvent-free conditions to access various fused arenes in 43-85% yields (Scheme 34).⁴⁵

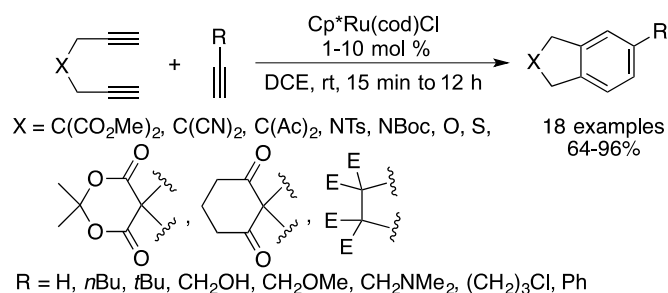


Scheme 34

2.5. Ruthenium-catalyzed partially intramolecular [2+2+2] cycloadditions

Cp**Ru*(cod)Cl catalyst:

In 2000, Itoh and Yamamoto described the first example of ruthenium-catalyzed [2+2+2] cycloaddition of α,ω -diynes with monoalkynes using Cp**Ru*(cod)Cl catalyst.⁴⁶ Later, they extended the scope of this reaction, and found that a variety of tethered diynes including heteroatom tethered diynes, such as nitrogen, oxygen, sulfur, was compatible with these reaction conditions leading to the formation of the corresponding benzene derivatives in 64-96% yields. A self-dimerization or trimerization of diynes product have been detected in some cases as a competitive process (Scheme 35).⁴⁷



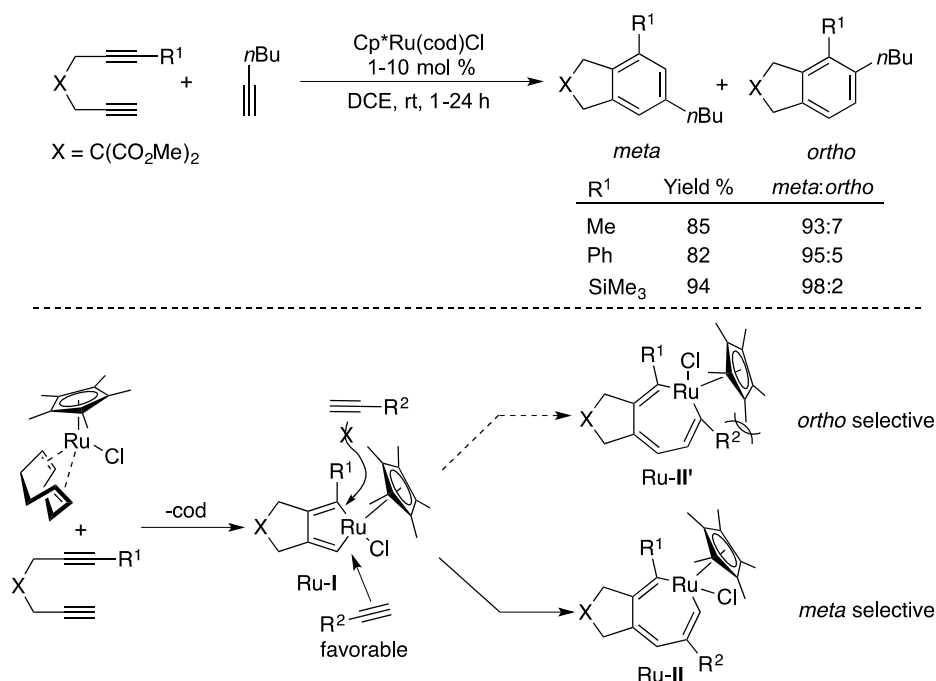
Scheme 35

⁴⁵ Auvinet, A.-L.; Michelet, V.; Ratovelomanana-Vidal, V. *Synthesis* **2013**, 45, 2003.

⁴⁶ Yamamoto, Y.; Ogawa, R.; Itoh, K. *Chem. Commun.* **2000**, 549.

⁴⁷ Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, 125, 12143.

The regioselectivity of the ruthenium-catalyzed cycloadditions was also studied by using unsymmetrical monosubstituted diynes. Treatment of the unsymmetrical diynes, bearing methyl, phenyl, and trimethylsilyl terminal substituents, with the Cp*Ru(cod)Cl catalyst, gave the corresponding cycloadducts in high yields with high regioselectivities, the *meta* selective product being formed as the major product. According to the mechanism, the coordination and oxidative coupling of diyne with ruthenium complex led to the ruthenacyclopentadiene intermediate Ru-I, followed by the selective insertion of the monoalkyne into the less substituted Ru–C single bond leading to the formation of the ruthenacycloheptatriene intermediates Ru-II or Ru-II'. The reductive elimination from Ru-II afforded *meta*-selective product, whereas Ru-II' furnished *ortho*-selective isomer (Scheme 36).

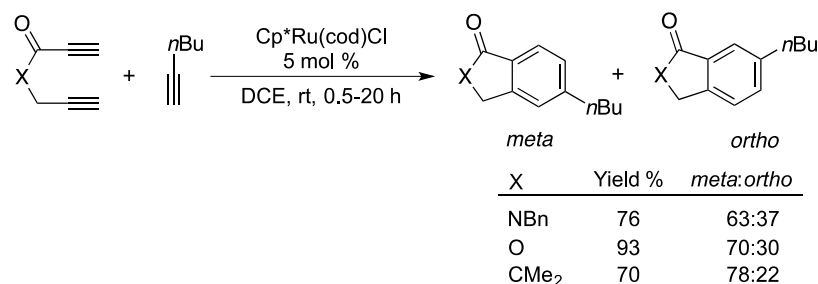


Scheme 36

In 2004, Yamamoto's group described the cycloaddition of unsymmetrical terminal diynes bearing amide, ester and ketone carbonyl tethered groups with terminal alkynes to afford the corresponding cycloadducts with unexpected regioselectivities.⁴⁸ The observed results showed that the regioselectivity was directed by the electron effects of the internal conjugated carbonyl groups, and increased in the order of amide tether (X = NBn) \approx ester tether (X = O)

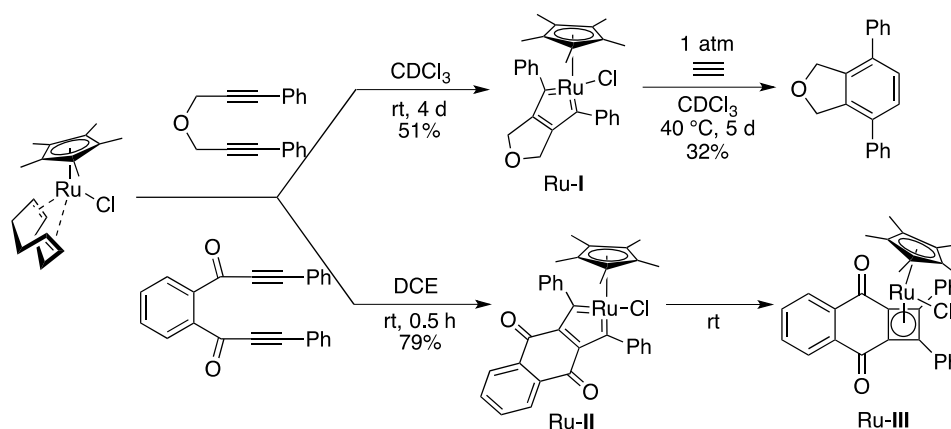
⁴⁸ Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Nishiyama H.; Itoh, K. *Org. Biomol. Chem.* **2004**, *2*, 1287.

< ketone ($X = \text{CH}_2$). The stronger electron-withdrawing ability of the carbonyl group allowed the highest regioselectivity (Scheme 37).



Scheme 37

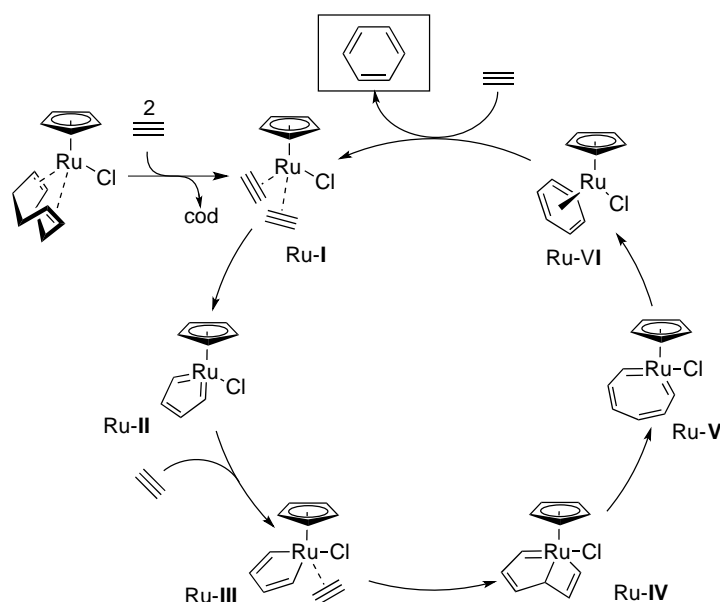
During the investigation of partially intramolecular [2+2+2] cycloaddition reactions, a bicyclic ruthenacyclopentatriene complex **Ru-I** was isolated by Yamamoto's group.⁴⁷ The internal diene bearing two phenyl substituents slowly reacts with $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$ complex in CDCl_3 at room temperature to give the bis-carbene ruthenium complex in 51% yield, which could react in a stoichiometric way with acetylene to afford [2+2+2] cycloadduct. Another example of naphthoquinone-fused ruthenacyclopentatriene complex **Ru-II** was prepared from 1,2-bis(phenylpropiolyl)benzene and $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$ complex by the same group.⁴⁹ The **Ru-II** complex could be isomerized to form cyclobutadiene complex **Ru-III** at room temperature in solution (Scheme 38).



Scheme 38

⁴⁹ (a) Yamamoto, Y.; Hata, K.; Arakawa, T.; Itoh, K. *Chem. Commun.* **2003**, 1290. (b) Yamamoto, Y.; Arakawa, T.; Itoh, K. *Organometallics* **2004**, 23, 3610.

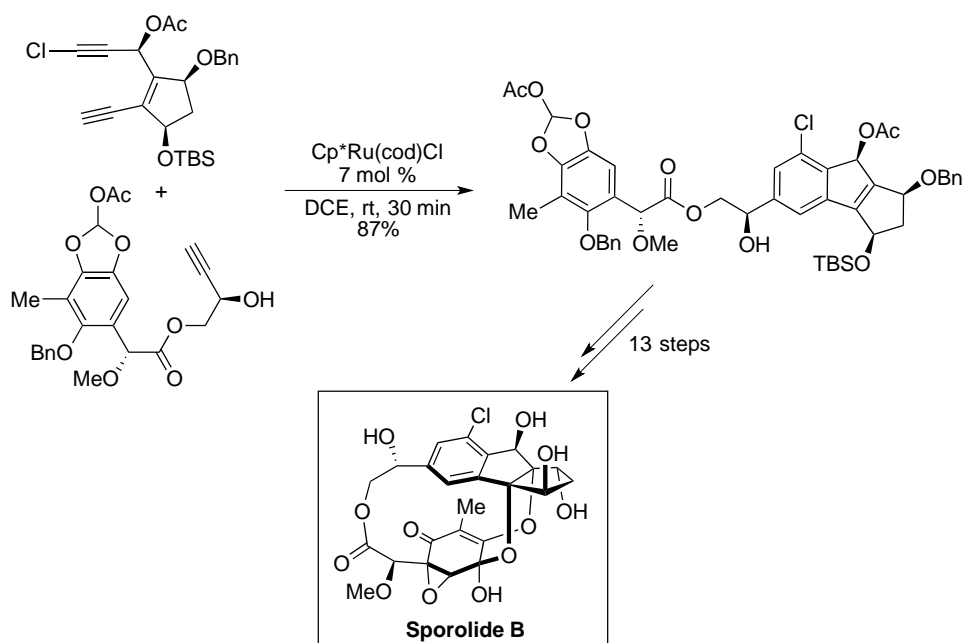
Based on the observed results and DFT calculations, Yamamoto's group proposed a mechanism for the cycloaddition of acetylene to form benzene on a CpRuCl fragment, as shown in Scheme 39. The coordination of two alkynes to the ruthenium center exchanges with the diene ligand to form species Ru-I, which undergoes oxidative cycloaddition to give ruthenacyclopentatriene Ru-II. Coordination of a third alkyne to the ruthenium center followed by a subsequent [2+2] cycloaddition between the Ru-C double bond with alkyne produces metallobicyclo[3.2.0]heptatriene Ru-IV, this intermediate rapidly undergoes ring-opening process resulting in the formation of ruthenacycloheptatetraene Ru-V. Finally, a ring-closing step occurs with the seven-membered ruthenacycle Ru-V via a carbene-carbene coupling delivering an η^2 -arene complex Ru-VI. A rapid exchange between arene and acetylene produces the cycloadduct and regenerates the starting ruthenium complex Ru-I.



Scheme 39

Taking advantage of this efficient catalyst, Nicolaou's group accomplished the total synthesis of the highly oxygenated, marine-derived, natural product Sporolide B. The key intermediate indene structural motif was prepared by the partially intramolecular [2+2+2] cycloaddition of chloroacetylenic cyclopentyne and propargylic alcohol in the presence of 7 mol % Cp*Ru(cod)Cl in dichloroethane at room temperature. The reaction provided the key

building block as a single regioisomer in 87% yield, which was finally converted to Sporolide B over 13 steps (Scheme 40).⁵⁰



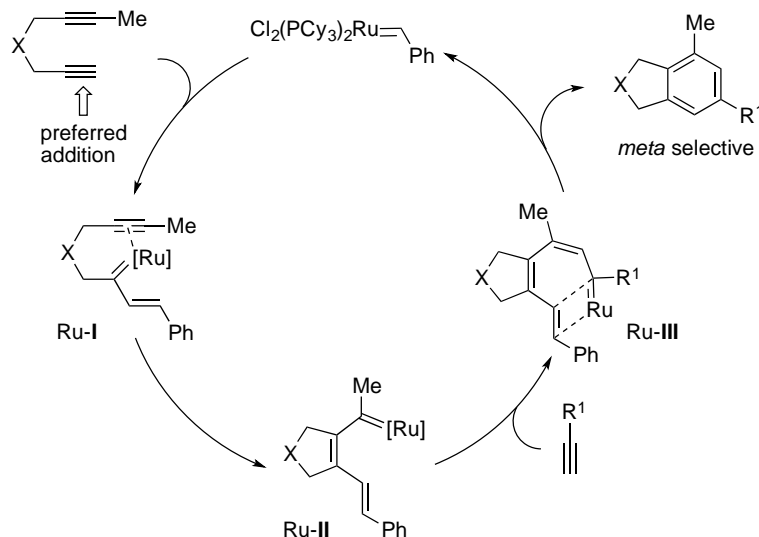
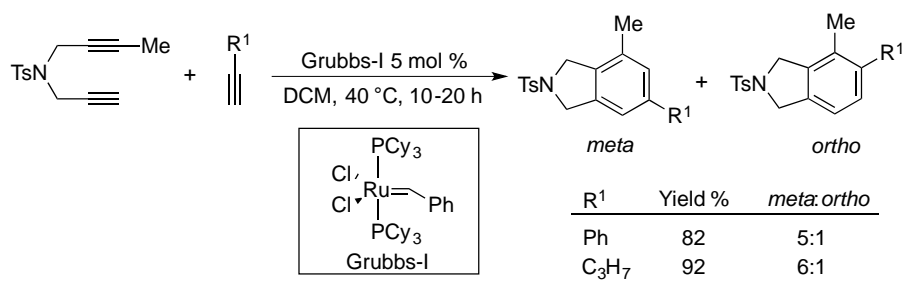
Scheme 40

Grubbs catalyst:

Grubbs catalyst has also been used in partially intramolecular [2+2+2] cycloaddition reactions. In 2000, Witulski and co-workers employed Grubbs **I** ($[\text{RuCl}_2(\text{NCHPh})(\text{PCy}_3)_2]$) for the regioselective synthesis of 4,6-substituted indolines.⁵¹ The reaction probably proceeds via a cascade metathesis mechanism to give the high regioselective formation of 2,4-substituted product. The catalytic cycle was shown in Scheme 41. The Grubbs **I** complex initially adds to the least substituted alkyne moiety of the 1,6-diyne leading to the formation of vinyl carbene complex **Ru-I**, which undergoes an intramolecular metathesis reaction to give the five-membered carbo- or heterocycle **Ru-II**. The coordination of another monoalkyne followed by an intermolecular metathesis insertion affords the highly conjugated carbene complex **Ru-III**, which undergoes the final ring-closing olefin metathesis step resulting in the regeneration of the ruthenium benzylidene catalyst and in the preferred formation of the corresponding *meta*-isomer (Scheme 41).

⁵⁰ Nicolaou, K. C.; Tang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 3449.

⁵¹ Witulski, B.; Stengel, T.; Fernández-Hernández, J. M. *Chem. Commun.* **2000**, 1965.



Scheme 41

3. Totally intramolecular reactions

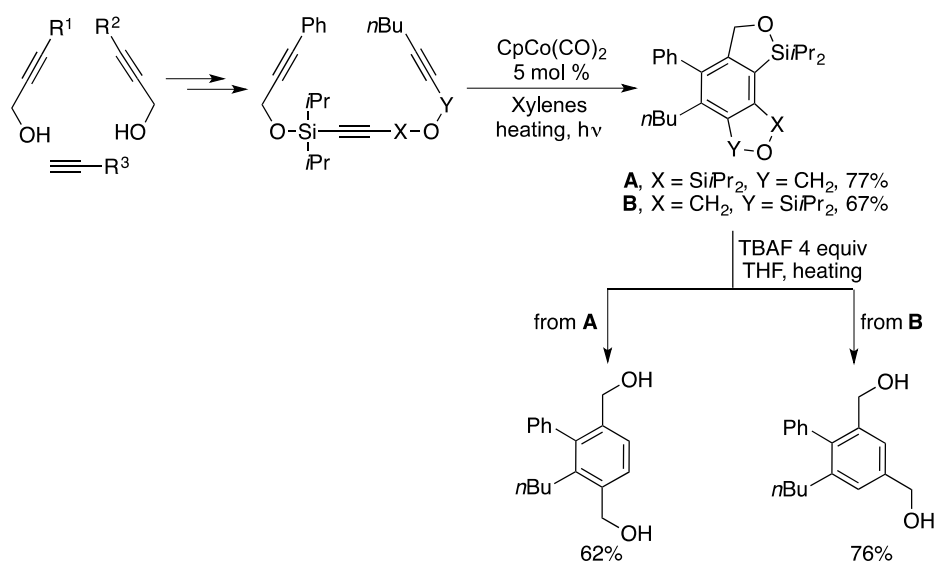
Totally intramolecular cycloaddition reactions are considered as the most efficient method to solve the problem of the control of the chemo- and regioselectivity to access highly substituted benzenes. Three alkynes linked with two or three carbo- or hetero-tethers form a triyne which can be assembled via a cyclotrimerization to give a polycyclic aromatic compound with complete selectivity.

Malacria and Aubert reported in 2004 the first totally chemo- and regioselective formal intermolecular [2+2+2] cycloaddition of three different alkynes by using the CpCo(CO)₂ catalyst.⁵² A series of easily prepared silicon-tethered triynes⁵³ successfully reacted with cobalt catalyst to furnish various benzene derivatives. Selective deprotection of the silylated group,

⁵² Chouraqui, G.; Petit, M.; Aubert, C.; Malacria, M. *Org. Lett.* **2004**, *6*, 1519.

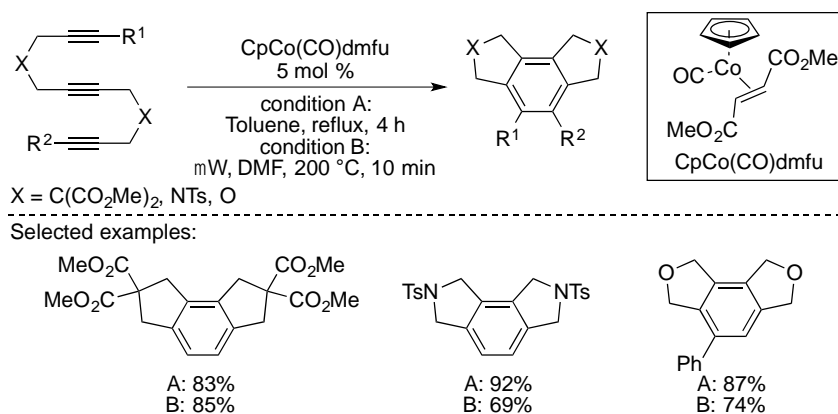
⁵³ Petit, M.; Chouraqui, G.; Aubert, C.; Malacria, M. *Org. Lett.* **2003**, *5*, 2037.

resulted in the formation of functionalized arenes. This synthetically useful method avoided the formation of unexpected regioisomers in such cycloaddition reactions (Scheme 42).



Scheme 42

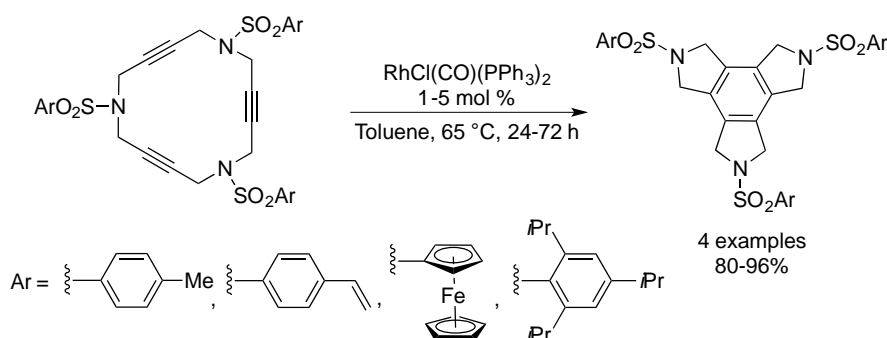
In 2009, Aubert, Gandon, and Malacria applied the new designed and synthesized CpCo(CO)dmfu catalyst for totally intramolecular [2+2+2] cycloaddition reactions.⁵⁴ The air-stable cobalt catalyst efficiently catalyzed the cyclotrimerization of carbo- and hetero-tethered triynes, forming a variety of fused tricyclic benzenes in 69-92% yields (Scheme 43). Notably, these reactions can be performed under both conventional heating and microwave irradiation heating conditions.



⁵⁴ Geny, A.; Agenet, N.; Iannazzo, L.; Malacria, M.; Aubert, C.; Gandon, V. *Angew. Chem. Int. Ed.* **2009**, *48*, 1810.

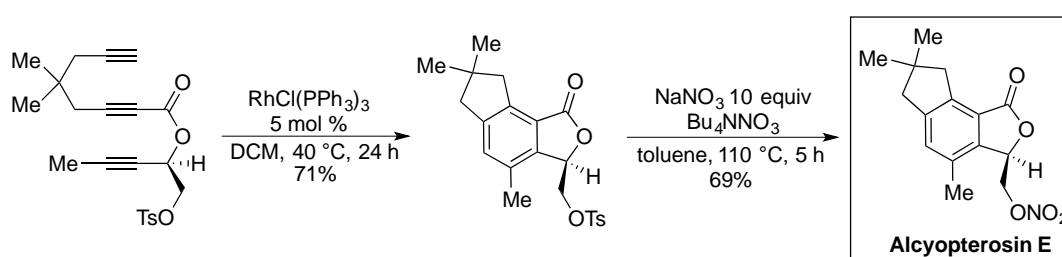
Scheme 43

In contrast to the linear triynes, the macrocyclic triynes can also be employed in [2+2+2] cycloaddition reactions. In 2004, Roglans and co-workers reported a totally intramolecular rhodium-catalyzed [2+2+2] cycloaddition reaction of nitrogen-containing 15-membered triacetylenic macrocycles.⁵⁵ The nitrogen-tethered macrocyclic triynes smoothly reacted with 1-5 mol % of $\text{RhCl}(\text{CO})(\text{PPh}_3)_2$ in toluene to afford various multiple ring compounds in 80-96% yields (Scheme 44). Notably, this was the first example of [2+2+2] cycloaddition reactions of macrocyclic triynes.



Scheme 44

Taking advantage of this strategy, Witulski and co-workers reported the first total synthesis of the sesquiterpenoid alcyopterosin E from simple starting materials. In this multi-step synthesis, the formation of the key precursor indeno[4,5-*c*]furan was achieved through a totally intramolecular cycloaddition of an enantiomerically pure triyne by using Wilkinson's catalyst in dichloromethane at 40 °C. Subsequent transformation of the tosylate into a nitrate group completed the total synthesis (Scheme 45).⁵⁶



⁵⁵ Torrent, A.; González, I.; Pla-Quintana, A.; Roglans, A.; Moreno-Mañas, M.; Parella, T.; Benet-Buchholz, J. J. *Org. Chem.* **2005**, *70*, 2033.

⁵⁶ Witulski, B.; Zimmermann, A.; Gowans, N. D. *Chem. Commun.* **2002**, 2984.

Scheme 45

Chapter II: Access toward
fluorenone derivatives through
solvent-free ruthenium trichloride
mediated [2+2+2] cycloadditions

Chapter II: Access toward fluorenone derivatives through solvent-free ruthenium trichloride mediated [2+2+2] cycloadditions

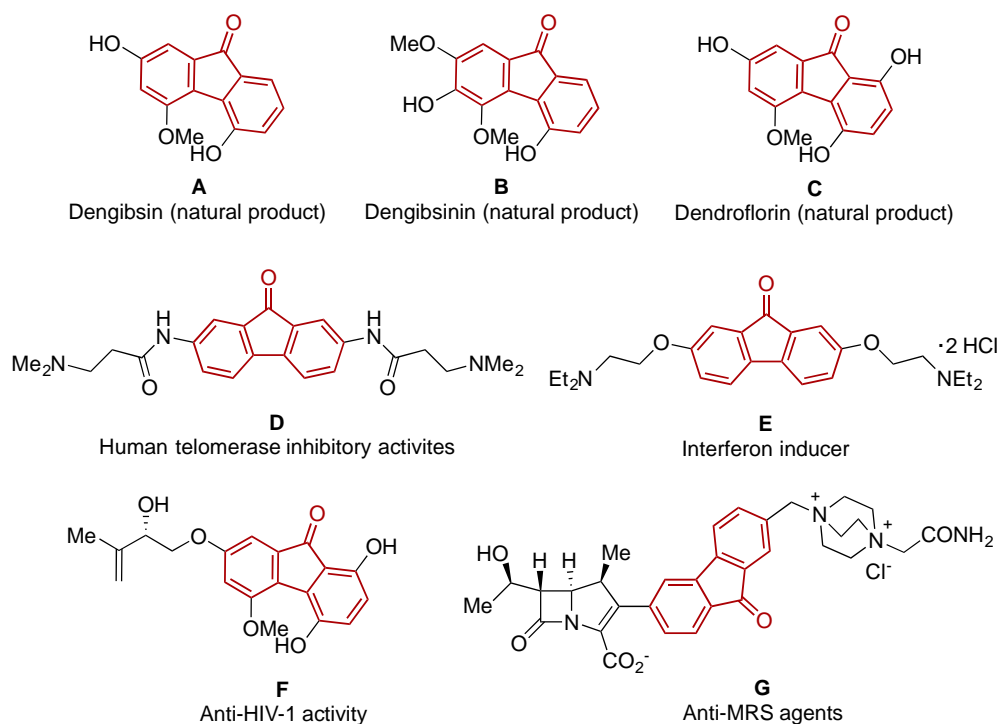
1. Interest of fluorenones

Over the past few years, fluoren-9-one and its derivatives have attracted much attention from academia and industry regarding their frequent application in various fields.⁵⁷

The fluorenone scaffolds and related chemicals are important structural moiety that constitute the central core of a variety of compounds, which are found in many natural products and bioactive molecules encompassing a wide range of biological properties (Scheme 46).⁵⁸ For example, Dengibsin **A** and Dengibsinin **B** were the first natural fluorenone derivatives isolated from the Indian orchid *Dendrobium gibsonii* Lindl.,^{58a} 2,7-disubstituted amidofluorenone derivatives **D** exhibited a range of human telomerase inhibitory activities,^{58d} tilorone dihydrochloride **E** has great potential for inducing interferon against pathogenic infection,^{58e} indenone **F** showed anti-HIV-1 activity,^{58f} dicationic 2-fluorenonylcarbapenems **G** were potent anti-MRS agents.^{58g}

⁵⁷ For selected reviews, see: (a) Prostackov, N. S.; Soldatenkov, A. T.; Kolyadina, N. M.; Obynochnyi, A. A. *Russ. Chem. Rev.* **1997**, *66*, 121. (b) Zhou, A.-H.; Pan, F.; Zhu, C.-Y.; Ye, L.-W. *Chem. Eur. J.* **2015**, *21*, 10278. (c) Shi, Y.-B.; Gao, S.-H. *Tetrahedron* **2016**, *72*, 1717.

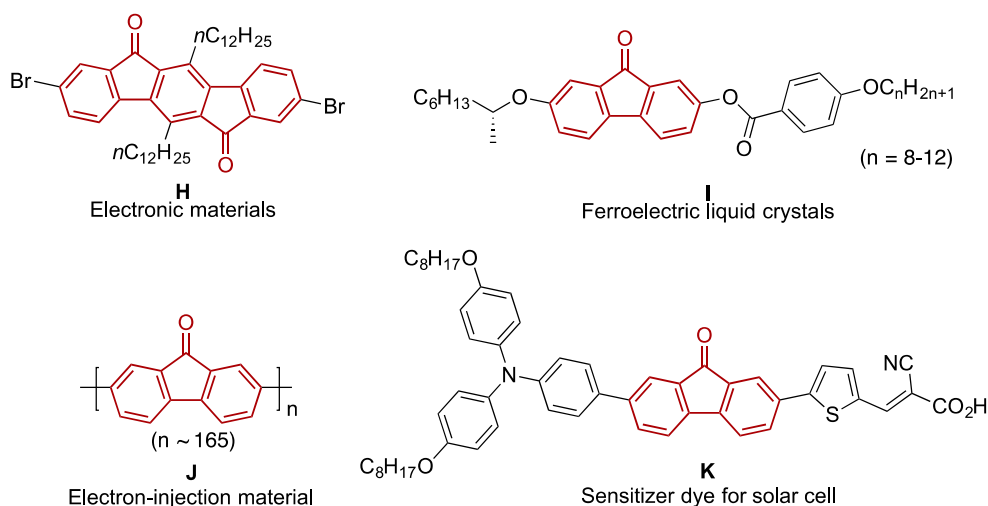
⁵⁸ For selected examples, see: (a) Talapatra, S. K.; Bose, S.; Malik, A. K.; Talapatra, B. *Tetrahedron* **1985**, *41*, 2765. (b) Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2553. (c) Jones Jr., W. D.; Ciske, F. L. *J. Org. Chem.* **1996**, *61*, 3920. (d) Perry, P. J.; Read, M. A.; Davies, R. T.; Gowan, S. M.; Reszka, A. P.; Wood, A. A.; Kelland, L. R.; Neidle, S. *J. Med. Chem.* **1999**, *42*, 2679. (e) Zhang, J.-R.; Yao, Q.-Z.; Liu, Z.-L. *Molecules* **2015**, *20*, 21458. (f) Hu, Q.-F.; Zhou, B.; Huang, J.-M.; Gao, X.-M.; Shu, L.-D.; Yang, G.-Y.; Che, C.-T. *J. Nat. Prod.* **2013**, *76*, 292. (g) Greenlee, M. L.; Laub, J. B.; Rouen, G. P.; DiNinno, F.; Hammond, M. L.; Huber, J. L.; Sundelof, J. G.; Hammond, G. G. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3225. (h) Niu, D.-Y.; Han, J.-M.; Kong, W.-S.; Cui, Z.-W.; Hu, Q.-F.; Gao, X.-M. *Asian J. Chem.* **2013**, *25*, 9514.



Scheme 46

Additionally, because of their attractive luminescent properties, fluorenones could also be employed as organic and polymer light-emitting diodes, bulk heterojunction solar cells and photochemical sensitizers (Scheme 47).⁵⁹ For examples, bisindenofluorene **H** represented a novel building block class for n-type electronic materials,^{59a} compounds **I** formed ferroelectric liquid crystals,^{59b} 2,7-poly(9-fluorenone) **J** was a suitable candidate as an electron-injection material in multilayer LEDs,⁵⁹ⁱ and compound **K** was a stable fluorenone-based sensitizer dye for solar cell.^{59j}

⁵⁹ For selected examples, see: (a) Usta, H.; Facchetti, A.; Marks, T. J. *Org. Lett.* **2008**, *10*, 1385. (b) McCubbin, J. A.; Tong, X.; Wang, R.-Y.; Zhao, Y.; Snieckus, V.; Lemieux, R. P. *J. Am. Chem. Soc.* **2004**, *126*, 1161. (c) Estrada, L. A.; Yarnell, J. E.; Neckers, D. C. *J. Phys. Chem. A* **2011**, *115*, 6366. (d) Yao, W.; Liu, Q.-C.; Shi, Y.-B.; Tang, J. *Heterocycles* **2012**, *85*, 1077. (e) Xia, J.-B.; Zhu, C.; Chen, C. *J. Am. Chem. Soc.* **2013**, *135*, 17494. (f) Li, C.; Mao, Z.-P.; Chen, H.-J.; Zheng, L.-P.; Huang, J.-Y.; Zhao, B.; Tan, S.-T.; Yu, G. *Macromolecules* **2015**, *48*, 2444. (g) Capodilupo, A. L.; Vergaro, V.; Fabiano, E.; Giorgi, M. D.; Baldassarre, F.; Cardone, A.; Maggiore, A.; Maiorano, V.; Sanvitto, D.; Gigli, G.; Ciccarella, G. *J. Mater. Chem. B*, **2015**, *3*, 3315; (h) Gong, X.; Moses, D.; Heeger, A. J. *J. Phys. Chem. B*, **2004**, *108*, 8601. (i) Uckert, F.; Tak, Y.-H.; Müllen, K.; Bäessler, H. *Adv. Mater.* **2000**, *12*, 905. (j) Qin, C. Islam, A. Han, L. *J. Mater. Chem.* **2012**, *22*, 19236.



Scheme 47

2. Preparation methods in the literature

2.1 Traditional methods for the preparation of fluorenones

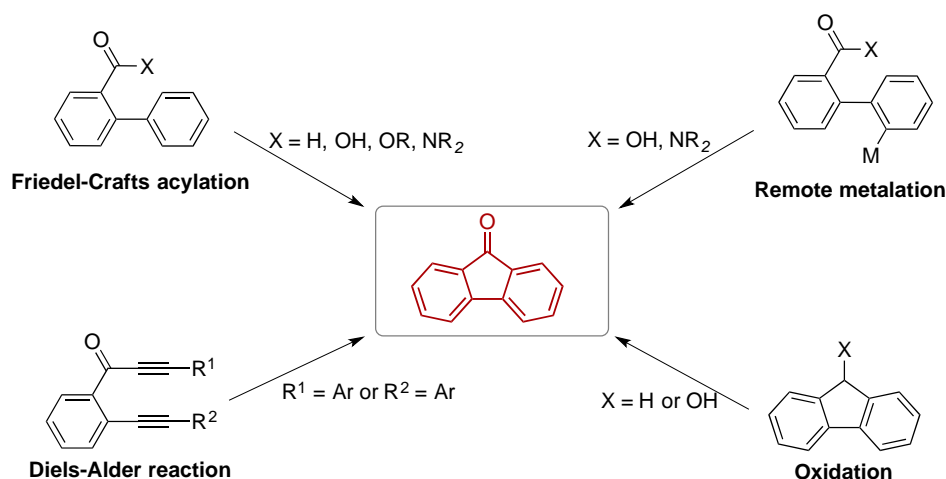
Numerous synthetic methods have been developed for the synthesis of fluorenones. Traditional synthetic methods include Friedel-Crafts acylation,⁶⁰ remote metalation,⁶¹ Diels-Alder reaction,⁶² and oxidation of fluorenes or fluorenols.⁶³ (Scheme 48)

⁶⁰ (a) Barluenga, J.; Trincado, M.; Rubio, E.; González, J. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 3140. (b) Reim, S.; Lau, M.; Langer, P. *Tetrahedron Lett.* **2006**, *47*, 6903. (c) Chinnagolla, R. K.; Jeganmohan, M. *Org. Lett.* **2012**, *14*, 5246. (d) Tilly, D.; Samanta, S. S.; Faigl, F.; Mortier, J. *Tetrahedron Lett.* **2002**, *43*, 8347. (e) F. Pünner, J. Schieven, G. Hilt, *Org. Lett.* **2013**, *15*, 4888. (f) Olah, G. A.; Mathew, T.; Farnia, M.; Prakash, G. K. S. *Synlett* **1999**, *7*, 1067.

⁶¹ (a) Tilly, D.; Samanta, S. S.; De, A.; Castanet, A.-S.; Mortier, J. *Org. Lett.* **2005**, *7*, 827. (b) Tilly, D.; Samanta, S. S.; Castanet, A.-S.; De, A.; Mortier, J. *Eur. J. Org. Chem.* **2006**, 174. (c) Alessi, M.; Larkin, A. L.; Ogilvie, K. A.; Green, L. A.; Lai, S.; Lopez, S.; Snieckus, V. *J. Org. Chem.* **2007**, *72*, 1588. (d) Tilly, D.; Fu, J.-M.; Zhao, B.-P.; Alessi, M.; Castanet, A.-S.; Snieckus, V.; Mortier, J. *Org. Lett.* **2010**, *12*, 68. (e) Ciske, F. L.; W. D. Jones, *Synthesis* **1998**, 1195.

⁶² (a) Rodríguez, D.; Navarro, A.; Castedo, L.; Domínguez, D.; Saá, C. *Org. Lett.* **2000**, *2*, 1497. (b) C. Atienza, C. Mateo, O. de Frutos, A. M. Echavarren, *Org. Lett.* **2001**, *3*, 153. (c) D. Rodríguez, M. F. M. Esperon, V. A. Navarro, L. Castedo, D. Domínguez, C. Saá, *J. Org. Chem.* **2004**, *69*, 3842.

⁶³ (a) Bei, X.; Hagemeyer, A.; Volpe, A.; Saxton, R.; Turner, H.; Guram, A. S. *J. Org. Chem.* **2004**, *69*, 8626. (b) Yang, G.; Zhang, Q.; Miao, H.; Tong, X.; Xu, J. *Org. Lett.* **2005**, *7*, 263. (c) Catino, A. J.; Nichols, J. M.; Choi, H.; Gottipamula, S.; Doyle, M. P. *Org. Lett.* **2005**, *7*, 5167. (d) Kaiser, R. P.; Hessler, F.; Mosinger, J.; Císařová, I.; Kotora, M. *Chem. - Eur. J.* **2015**, *21*, 13577.



2.2 Transition-metal-catalyzed synthesis of fluorenones

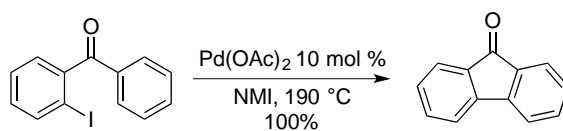
Over recent years, transition-metal-catalyzed functionalization has been recognized as a novel and efficient method to synthesize complex fluorenone derivatives that are not accessible by conventional methods. Palladium, rhodium, silver and copper complexes have been reported as catalysts to access fluorenones and derivatives. Synthetic methods for the preparation of fluorenone derivatives are summarized below and classified according to the metal.

2.2.1 Palladium-catalyzed synthesis of fluorenones

2.2.1.1 C-H functionalization of 2-haloarylketones

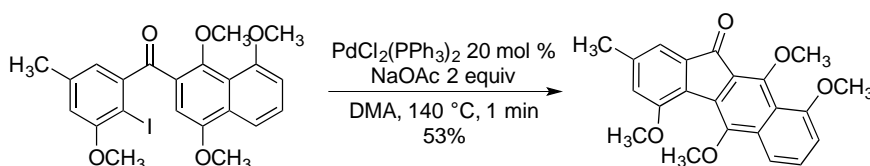
In 1984, Ames and Opalko disclosed a novel palladium-catalyzed dehydrohalogenation of 2-iodobenzophenone to provide fluorenone (Scheme 49).⁶⁴ Various bases and solvents employed with Pd(OAc)₂ have been used in this reaction. When 2-iodobenzophenone was heated in *N*-methylimidazole in the presence of Pd(OAc)₂ at 190 °C, fluorenone product was obtained in 100% yield.

⁶⁴ Ames, D. E.; Opalko, A. *Tetrahedron* **1984**, *40*, 1919.



Scheme 49

Based on the previous results reported by Ames and Opalko, Jones and co-workers further optimized the reaction conditions, involving high-temperature with $\text{PdCl}_2(\text{PPh}_3)_2$ and sodium acetate in dimethylacetamide (DMA) under microwave irradiation (Scheme 50).⁶⁵ They successfully synthesized benzo[*b*]fluorenone in 53% yield, this derivative being considered as a key intermediate to access the natural products stealthin C⁶⁶ and prekinamycin⁶⁷.



Scheme 50

2.2.1.2 Directing-group-assisted C-H activation

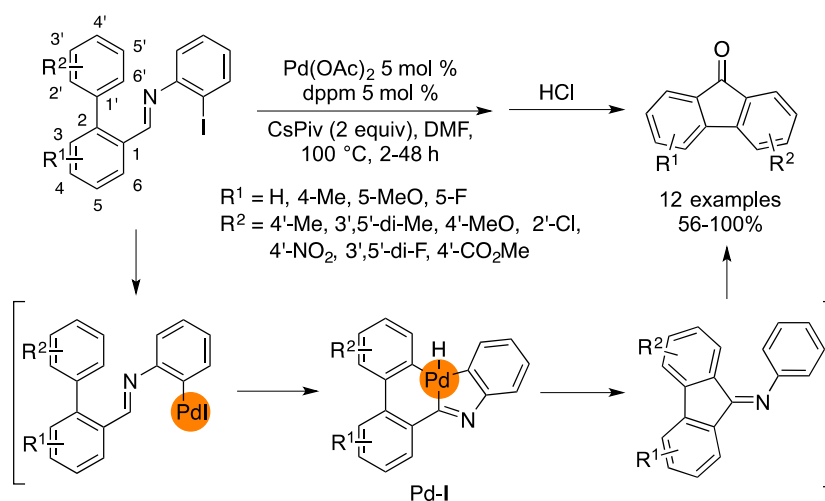
In 2007, Larock's research group reported an efficient synthesis of fluorenones using a Pd-catalyzed intramolecular C-H activation strategy involving an aryl to imidoyl palladium migration process (Scheme 51).⁶⁸ Treatment of imines with 5 mol % of $\text{Pd}(\text{OAc})_2$, 5 mol % of bis(diphenylphosphino)methane (dppm), and 2 equivalents of $\text{CsO}_2\text{CCMe}_3$ (CsPiv) in DMF at 100 °C, followed by hydrolysis using aqueous HCl, afforded the desired fluorenones in 56-100% yields. Subsequent deuterium labeling experiments showed that the reaction involved both a palladium migration and a C-H activation process through an unprecedented organopalladium hydride intermediate Pd-I.

⁶⁵ Qabaja, G.; Jones, G. B. *J. Org. Chem.* **2000**, *65*, 7187.

⁶⁶ Koyama, H.; Kamikawa, T. *Tetrahedron. Lett.* **1997**, *38*, 3973.

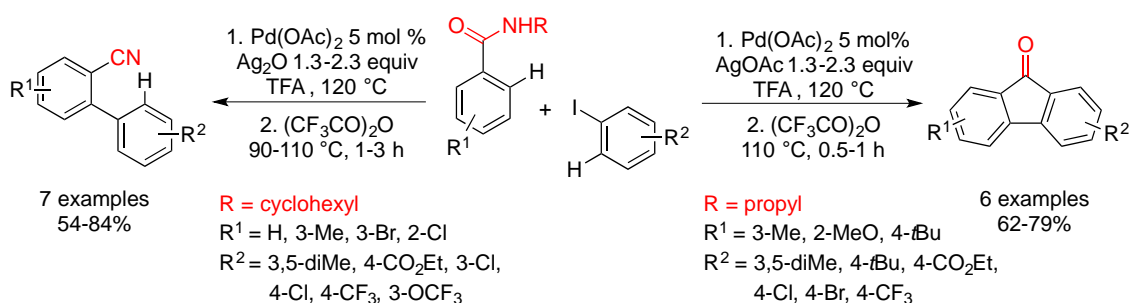
⁶⁷ Gore, M. P.; Gould, S. J.; Weller, D. D. *J. Org. Chem.* **1992**, *57*, 2774.

⁶⁸ Zhao, J.; Yue, D.-W.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2007**, *129*, 5288.



Scheme 51

In 2008, Daugulis and co-workers reported a one-pot synthetic method for *ortho*-benzonitriles and fluorenone derivatives formation by the palladium-catalyzed C-H bond functionalization of simple benzamide and aryl halides (Scheme 52).⁶⁹ Notably, the reaction could afford various desired products by tuning the alkyl substituent on the amide group. *N*-cyclohexyl benzamides led to the formation of benzonitrile derivatives, whereas *N*-propyl benzamides can be converted to fluorenones.



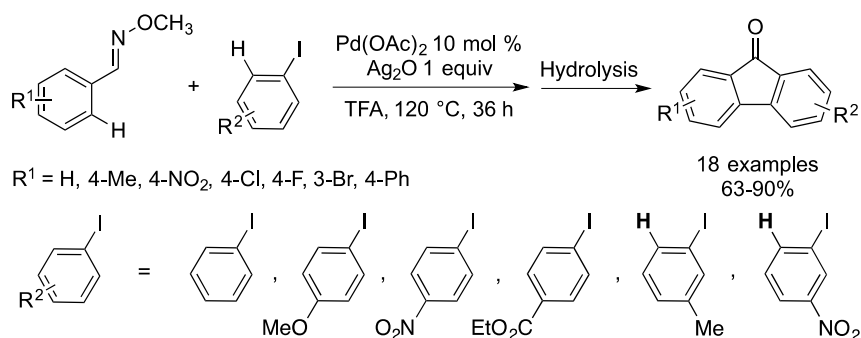
Scheme 52

Beside imines, oximes can be also considered as directing groups in Pd-catalyzed C-H activation to synthesize fluorenone derivatives. In 2008, Cheng and co-workers reported a Pd-catalyzed synthesis of fluorenones from substituted aromatic aldoxime ethers and aryl iodides through a dual C-H activation and oxidative Heck cyclization (Scheme 53).⁷⁰ A series of control

⁶⁹ Shabashov, D.; Maldonado, J. R. M.; Daugulis, O. *J. Org. Chem.* **2008**, *73*, 7818.

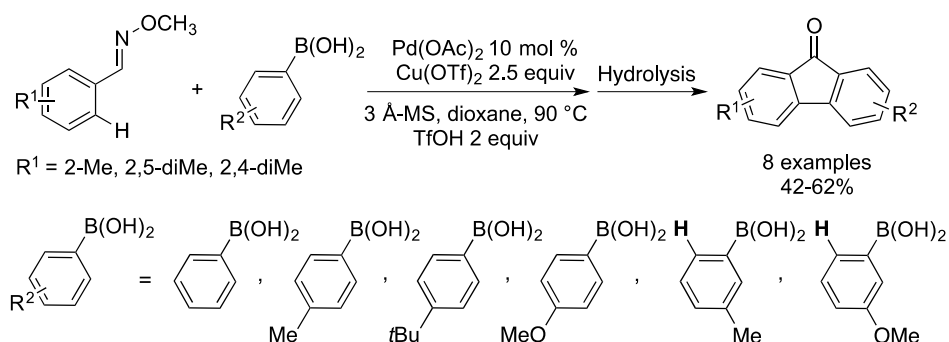
⁷⁰ Thirunavukkarasu, V. S.; Parthasarathy, K.; Cheng, C.-H. *Angew. Chem. Int. Ed.* **2008**, *47*, 9462.

experiments suggested that both palladium acetate and silver oxide are required for this transformation, allowing the facile synthesis of the desired fluorenones in 63-90% yields.



Scheme 53

Shi and co-workers described in 2010 a one-pot Pd-catalyzed *ortho*-directed C-H arylation of aromatic aldoxime ether and arylboronic acids for the synthesis of fluorenone derivatives (Scheme 54).⁷¹

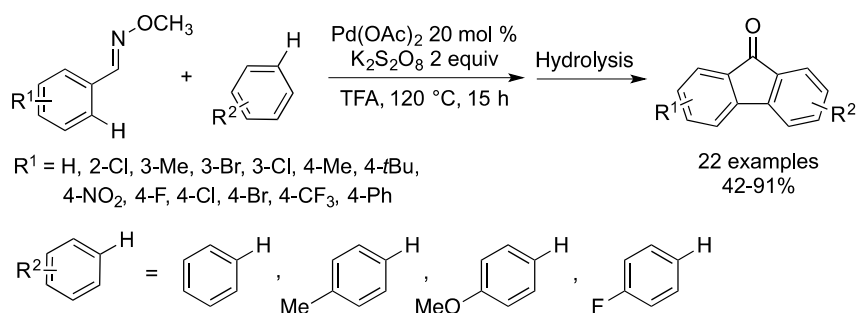


Scheme 54

In 2011, the continuous work in Cheng's group demonstrated that a Pd-catalyzed *ortho*-directed multiple C-H activation of aromatic aldoxime ether with arenes could proceed smoothly to give the corresponding substituted fluorenone derivatives in 42-91% yields (Scheme 55).⁷² Notably, this synthetic method for the preparation of fluorenones showed a significant improvement since it avoided the use of aryl halides, aryl boronic acids, and expensive metal oxidants.

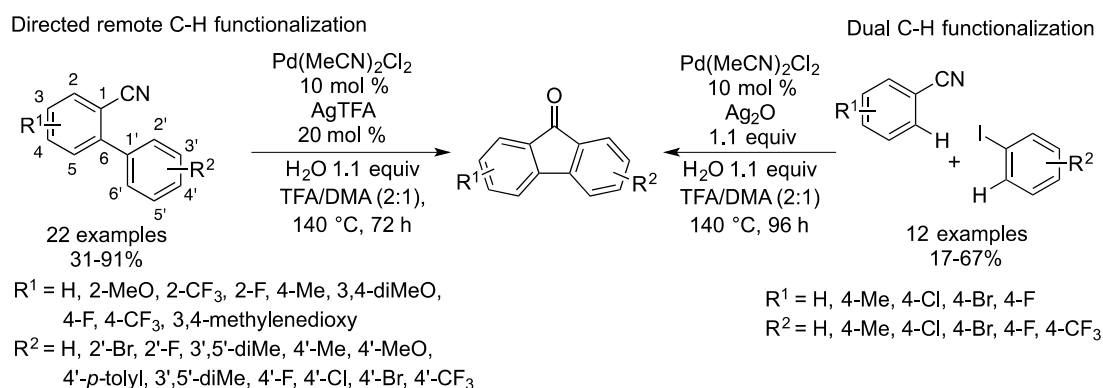
⁷¹ Sun, C.-L.; Liu, N.; Li, B.-J.; Yu, D.-G.; Wang, Y.; Shi, Z.-J. *Org. Lett.* **2010**, *12*, 184.

⁷² Thirunavukkarasu, V. S.; Cheng, C.-H. *Chem. Eur. J.* **2011**, *17*, 14723.



Scheme 55

Hsieh and co-workers developed in 2013 a method for the preparation of polysubstituted fluorenones via a Pd-catalyzed nitrile directed remote C-H and dual C-H bond activation with intramolecular 1,2-insertion of nitrile (Scheme 56).⁷³ A wide range of functional groups were tolerated under the reaction conditions, providing various fluorenones in 17-91% yields.

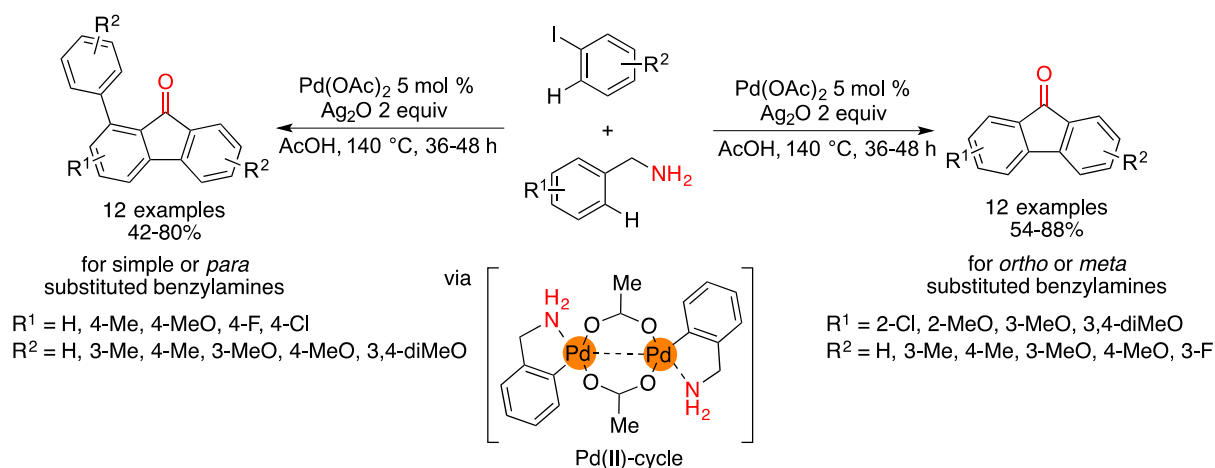


Scheme 56

In addition, a Pd-catalyzed *ortho* C-H activation of benzylamines with iodo arenes to provide fluorenone derivatives has been explored. Satyanarayana and co-workers reported a one-pot domino Pd-catalyzed reaction proceeding through the formation of a five-membered Pd(II)-cycle and subsequent *ortho* C-H activation with iodoarenes to give fluorenones in 42-88% yields with high regioselectivities (Scheme 57).⁷⁴ Notably, the reaction could further activate C(sp³)-H and C(sp²)-H bonds to afford the fused fluorenone derivatives.

⁷³ Wan, J.-C.; Huang, J.-M.; Jhan, Y.-H.; Hsieh, J.-C. *Org. Lett.* **2013**, *15*, 2742.

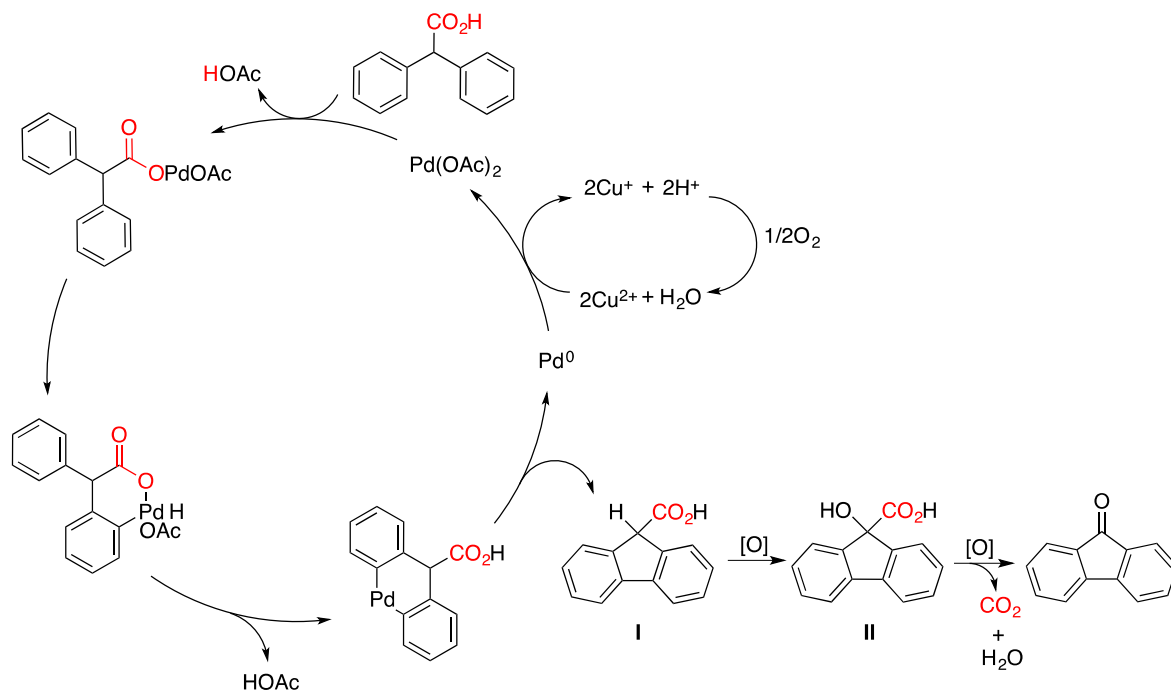
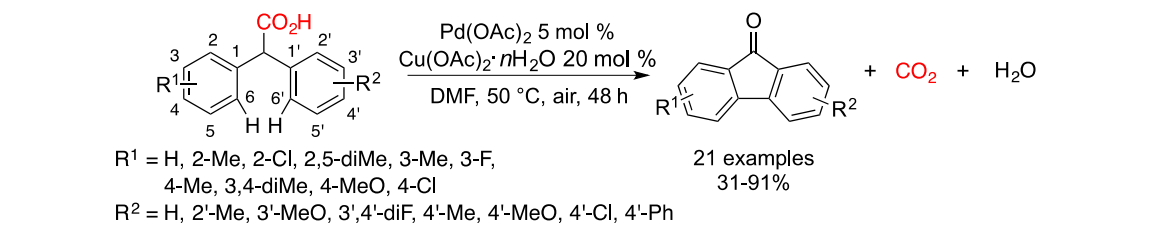
⁷⁴ Kumar, D. R.; Satyanarayana, G. *Org. Lett.* **2015**, *17*, 5894.



Scheme 57

In 2014, Wang's group described a Pd-catalyzed intramolecular C-C coupling reaction through a dual C-H bond activation directed by a removable carboxylate group.⁷⁵ The reaction proceeds in the presence of Pd(OAc)_2 and $\text{Cu(OAc)}_2 \cdot n\text{H}_2\text{O}$ under air atmosphere, to provide various substituted fluorenones in 31-91% yields. According to the proposed mechanism, the intramolecular carboxylate-directed dual C-H activation generates a 9*H*-fluorene-9-carboxylic acid (I) intermediate, a subsequent oxidative decarboxylation by the oxygen from the air in the presence of Pd(OAc)_2 and Cu(OAc)_2 and furnishes the cyclized product along with eliminating carbon dioxide and water (Scheme 58).

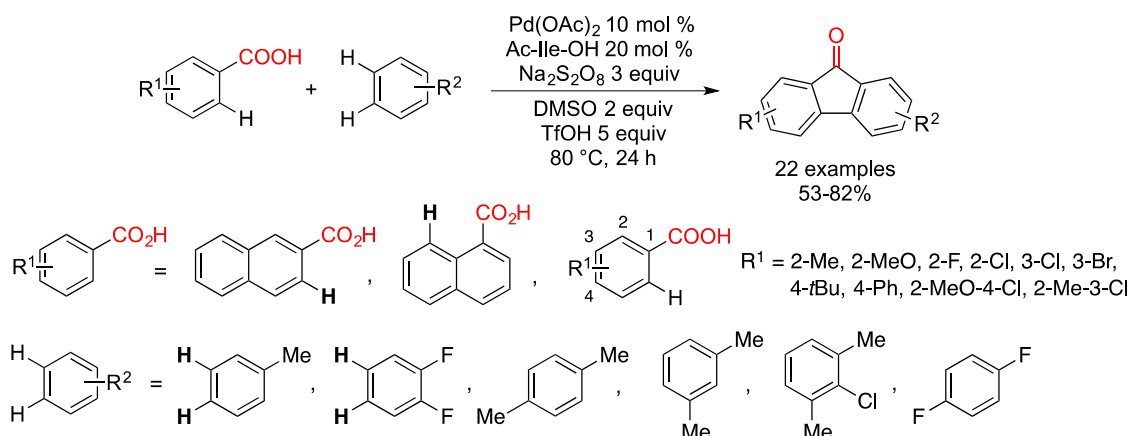
⁷⁵ Liu, L.; Wang, F.; Li, Z.-H.; Wang, J.-H. *Asian J. Org. Chem.* **2014**, 3, 695.



Scheme 58

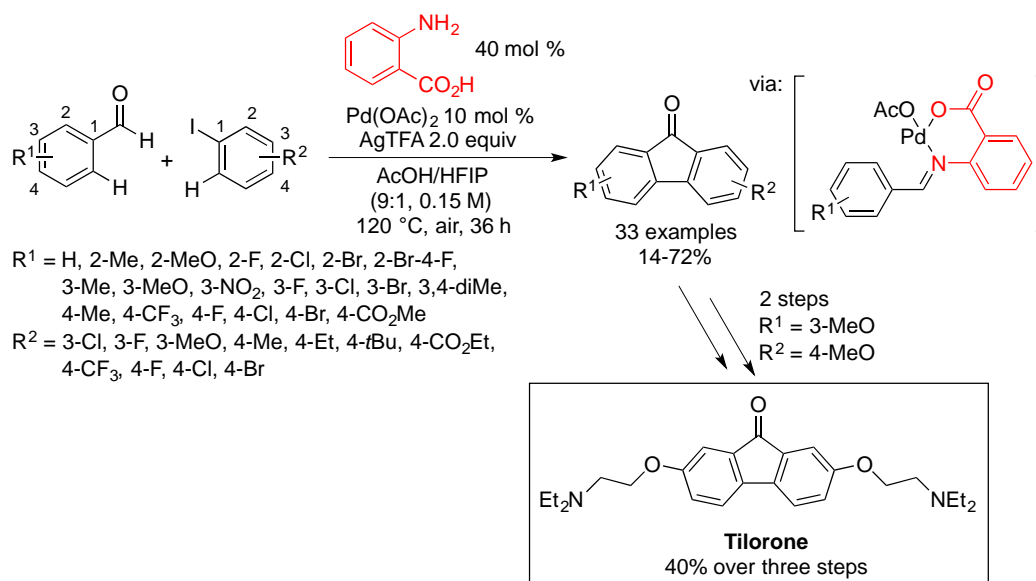
Another interesting example involving Pd-catalyzed carboxylic acid directed *ortho*-selective oxidative C-H/C-H cross-coupling of aromatic carboxylic acids with arenes followed by subsequent intramolecular Friedel-Crafts acylation for the construction of poly-substituted fluorenones was reported by You and co-workers. (Scheme 59).⁷⁶ By following this strategy, a variety of commercially available aromatic carboxylic acids and arenes were successfully converted to substituted fluorenones in 53-82% yields.

⁷⁶ Sun, D.-N.; Li, B.-J.; Lan, J.-B.; Huang, Q.; You, J.-S. *Chem. Commun.* **2016**, 52, 3635.



Scheme 59

Sorensen's group reported in 2017 Pd-catalyzed C(sp²)-H functionalization cascade reactions for the preparation of fluorenones from readily available benzaldehydes and aryl iodides using anthranilic acid as transient directing group.⁷⁷ It is worthy to mention that the antiviral drug Tilorone was synthesized in 40% yield over three steps (Scheme 60).



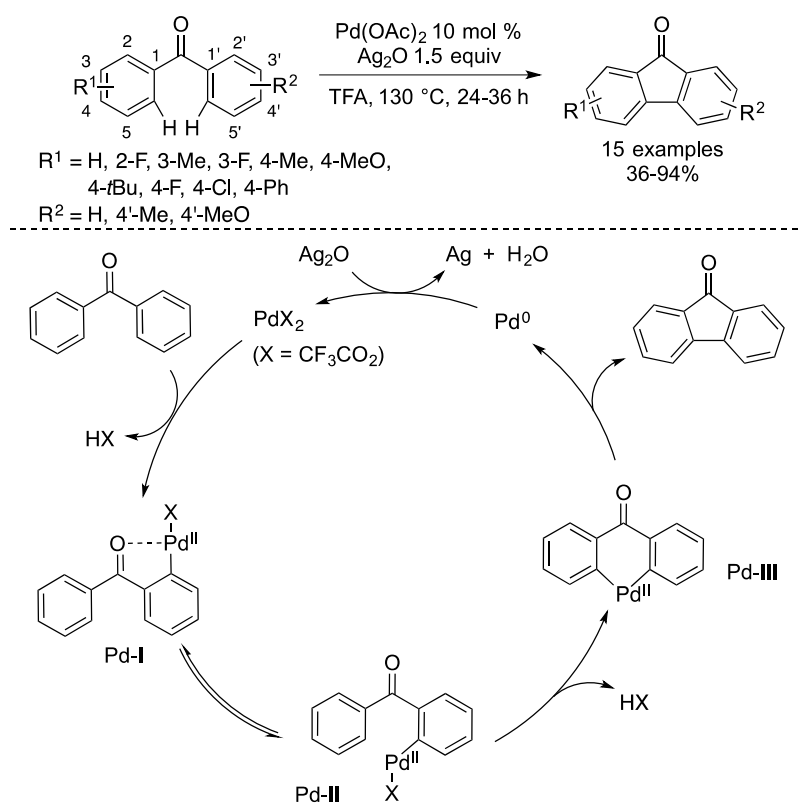
Scheme 60

2.2.1.3 Dehydrogenative cyclization

In 2012, Cheng's group disclosed a novel synthetic method involving a dual C-H activation of diarylketones to form fluorenones by Pd-catalyzed oxidative dehydrogenative

⁷⁷ Chen, X.-Y.; Ozturk, S.; Sorensen, E. J. *Org. Lett.* **2017**, *19*, 1140.

cyclization of benzophenones.⁷⁸ This process provided a wide range of fluorenones in 36-94% yields (Scheme 61). A mechanistic study demonstrated that the first step was the coordination between the ketone group and Pd(II) followed by the consecutive *ortho*-C-H activation to form a palladacycle Pd-I, which was expected to be in equilibrium with its palladium aryl σ -complex Pd-II. Then the palladium complex Pd-II underwent the second C-H activation, lead to the six-membered palladium complex Pd-III and subsequent reductive elimination to produce the fluorenone product and Pd(0) species. Independently, Shi's group reported similar conditions to access fluorenone derivatives through palladium-catalyzed dehydrogenative cyclization reactions.⁷⁹



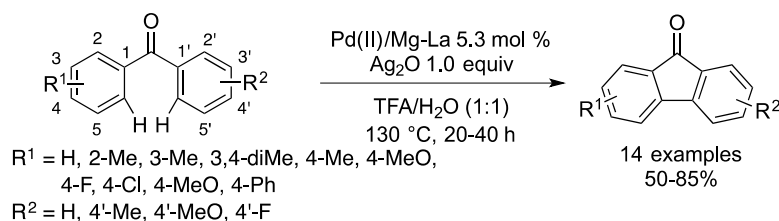
Scheme 61

Kantam and co-workers reported in 2015 an efficient method for the synthesis of fluorenones by dehydrogenative cyclization of benzophenones using a palladium(II)/magnesium-lanthanum mixed oxide catalyst in TFA/H₂O solution system

⁷⁸ Gandeepan, P.; Hung, C.-H.; Cheng, C.-H. *Chem. Commun.* **2012**, 48, 9379.

⁷⁹ Li, H.; Zhu, R.-Y.; Shi, W.-J.; He, K.-H.; Shi, Z.-J. *Org. Lett.* **2012**, 14, 4850.

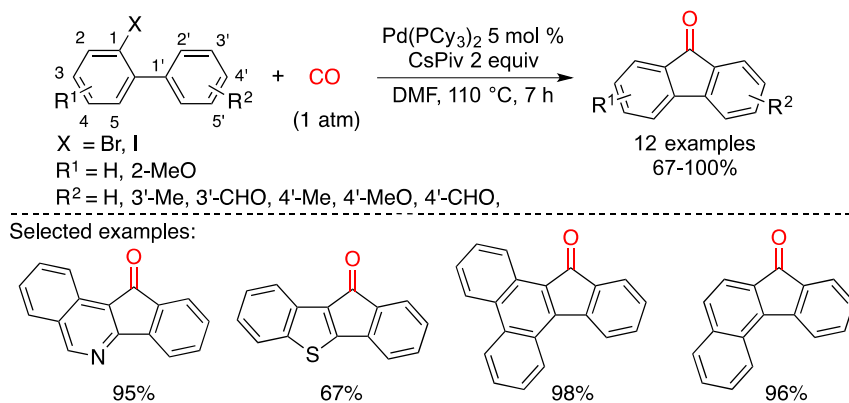
(Scheme 62).⁸⁰ Fluorenones were formed in 50-85% yields in the presence of reusable Pd(II)/Mg-La catalyst under heterogeneous reaction conditions.



Scheme 62

2.2.1.4 Cyclocarbonylation

The first practical method for the Pd-catalyzed cyclocarbonylation of *ortho*-halobiaryls to substituted fluorenone derivatives was developed by Larock's group in 2000.⁸¹ Treatment of the *ortho*-halobiaryls with 5 mol % of Pd(PCy₃)₂ and 2 equivalents of anhydrous cesium pivalate in DMF solution under 1 atm of carbon monoxide atmosphere provided the expected fluorenones in 67-100% yield. This method has been successfully employed for the preparation of polycyclic and heterocyclic fluorenones (Scheme 63).



Scheme 63

A related study published in 2015 by Xie and co-workers⁸² demonstrated that the Pd-catalyzed carbonylative cross-coupling of aryl dihalides with arylboronic acids proceeded

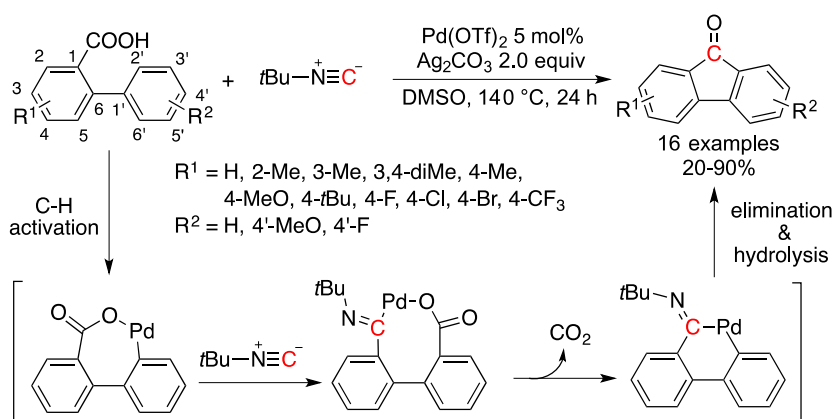
⁸⁰ Kishore, R.; Priya, S. S.; Sudhakar, M.; Venu, B.; Venugopal, A.; Yadav, J.; Kantam, M. L. *Catal. Sci. Technol.* **2015**, *5*, 3363.

⁸¹ Campo, M. A.; Larock, R. C. *Org. Lett.* **2000**, *2*, 3675.

⁸² Song, J.; Wei, F.-L.; Sun, W.; Li, K.; Tian, Y.-N.; Liu, C.; Li, Y.-L.; Xie, L.-H. *Org. Lett.* **2015**, *17*, 2106.

2.2.1.5 Decarboxylative cyclization

With respect to carbonyl sources, several methods involving different carbonyl sources, such as carboxylic acids, nitriles, aldoximes, aldehydes, have been reported for the preparation of fluorenones. Jin and co-workers reported in 2016 a one-pot palladium-catalyzed decarboxylative cyclization of 2-phenylbenzoic acid to synthesize fluorenones by using *tert*-butyl isocyanide as a new carbonyl source (Scheme 66).⁸⁴ Subsequent C-H activation and decarboxylation insertion of the isocyanide into 2-phenylbenzoic acid provided a six-membered intermediate that underwent elimination and hydrolysis to generate the cyclized product.



Scheme 66

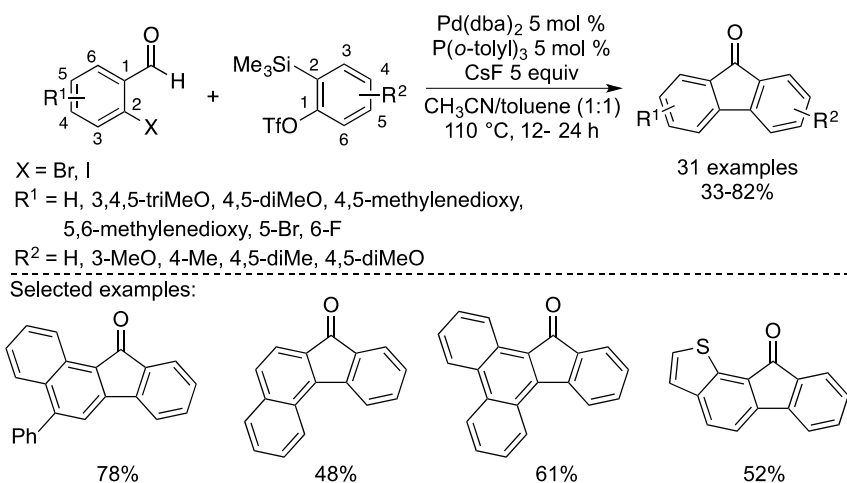
2.2.1.6 Other methods for the preparation of fluorenones

In 2005, Larock's group reported the synthesis of fluorenone derivatives via a palladium-catalyzed annulation of arynes with *o*-halobenzaldehydes.⁸⁵ Later, they extended the scope of functionalized *o*-halobenzaldehydes and arynes.⁸⁶ A variety of *o*-halobenzaldehydes and arynes has been examined, affording the substituted fluorenones in 33-82% yields (Scheme 67).

⁸⁴ Cai, Z.-Q.; Hou, X.; Hou, L.; Hu, Z.-Q.; Zhang, B.; Jin, Z.-S. *Synlett* **2016**, 27, 395.

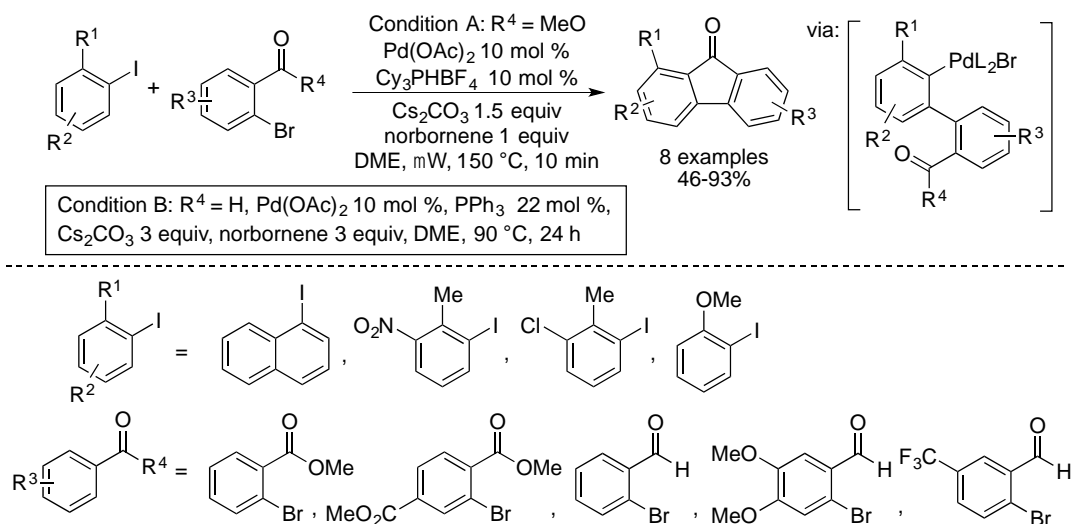
⁸⁵ Zhang, X.-X.; Larock, R. C. *Org. Lett.* **2005**, 7, 3973.

⁸⁶ Waldo, J. P.; Zhang, X.-X.; Shi, F.; Larock, R. C. *J. Org. Chem.* **2008**, 73, 6679.



Scheme 67

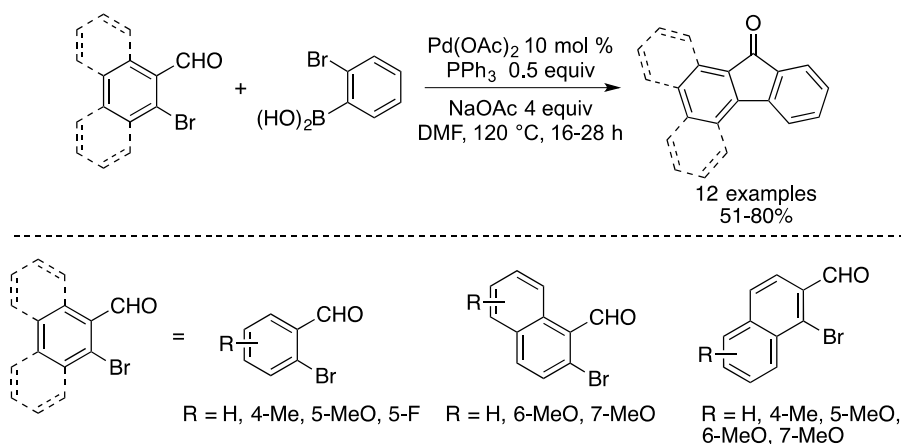
A rapid approach to access fluorenone derivatives via domino reactions using microwave as heating source has been reported by Lautens and co-workers.⁸⁷ The aryl-palladium intermediate generated by a sequence of norbornene mediated C-H activation and subsequent *ortho*-arylation, underwent ester addition providing the corresponding fluorenone in 46-93% yields (Scheme 68). Several aldehydes were also subjected to this method affording the 9*H*-fluoren-9-one products in good yields. In the case of aldehydes, the reaction proceeded with triphenylphosphine as ligand under conventional heating at 90 °C for 24 h.



Scheme 68

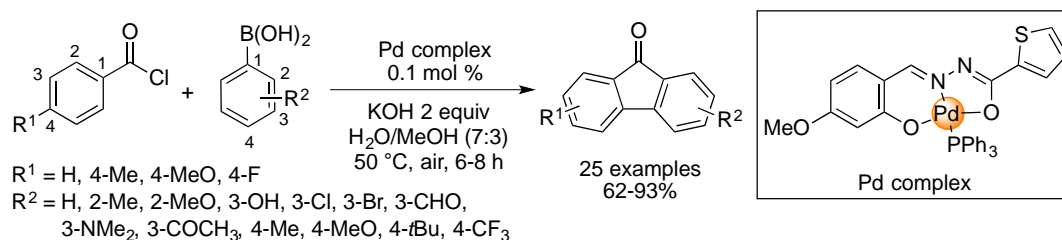
⁸⁷ Zhao, Y.-B.; Mariampillai, B.; Candito, D. A.; Laleu, B.; Li, M.; Lautens, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 1849.

In 2010, Ray and co-workers disclosed an efficient method for the preparation of fluorenones through a palladium-catalyzed one-pot Suzuki-Miyaura coupling reaction followed by an intramolecular arylpalladation of 2-bromophenyl boronic acid with 2-bromocarboxaldehyde (Scheme 69).⁸⁸ Various fluorenones and condensed fluorenone derivatives have been synthesized in 51-80% yields from readily available starting materials.



Scheme 69

The Dharmaraj's group described in 2016 an efficient palladium-catalyzed domino reaction of benzoyl chloride with arylboronic acid to synthesize substituted fluorenones (Scheme 70).⁸⁹ A newly synthesized ONO pincer-type Pd^{II} complex has been used in this reaction and exhibited high catalytic efficiency (0.1 mol % catalyst-loading). Compared to other systems the catalyst could be reused over six consecutive runs.



Scheme 70

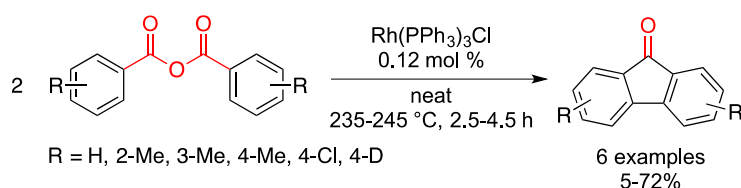
⁸⁸ Paul, S.; Samanta, S.; Ray, J. K. *Tetrahedron Lett.* **2010**, *51*, 5604.

⁸⁹ Vignesh, A.; Kaminsky, W.; Dharmaraj, N. *ChemCatChem* **2016**, *8*, 3207.

2.2.2 Rhodium-catalyzed synthesis of fluorenones

2.2.2.1 Conversion of benzoic anhydrides into fluorenones

Blum and co-workers reported in 1969 the first example of Rh-catalyzed transformation of benzoic anhydrides to fluorenones. Treatment of benzoic anhydride derivatives with chlorotris(triphenylphosphine)rhodium at high temperature led to the corresponding fluorenones in 5-72% yields. (Scheme 71).⁹⁰



Scheme 71

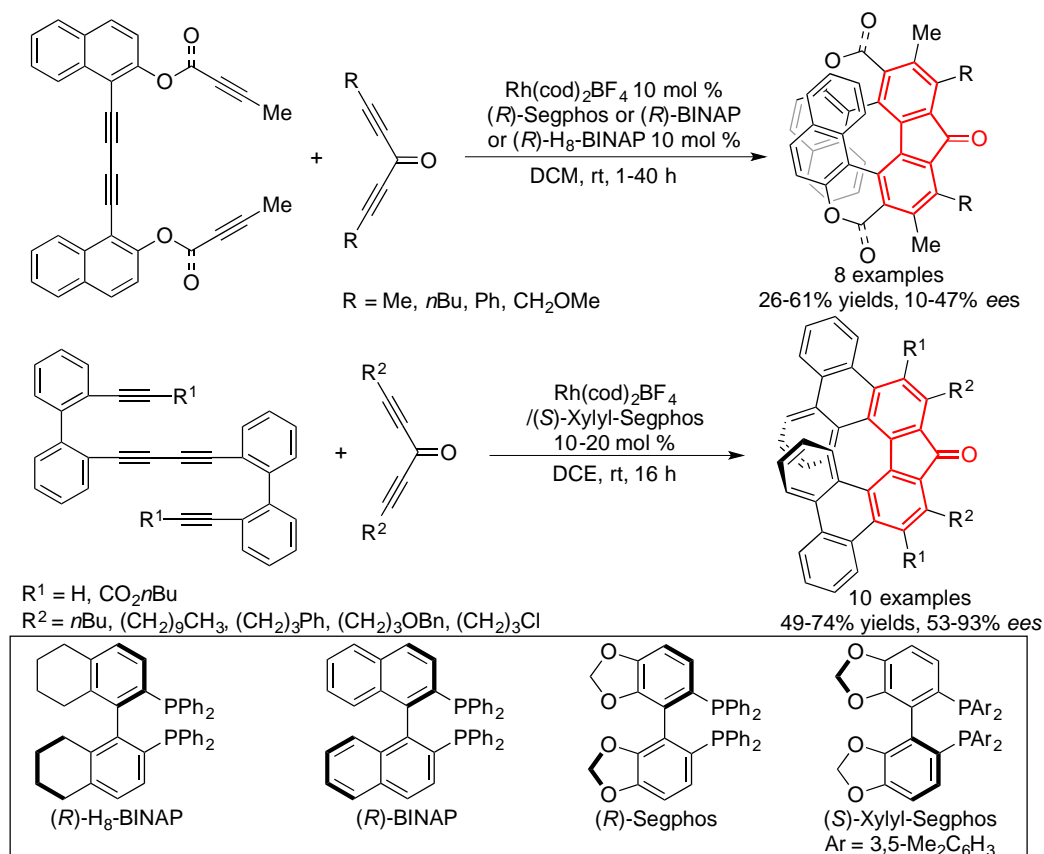
2.2.2.2 Partially intramolecular [2+2+2] cycloadditions

Considering the potential applications of optical and electronic functional materials, Tanaka and co-workers developed an efficient rhodium-catalyzed partially intramolecular double [2+2+2] cycloaddition to synthesize enantioenriched fluorenone-containing [9]-helicene-like derivatives and 1,1'-bistriphenylenes (Scheme 72).^{91,92}

⁹⁰ (a) Blum, J.; Lipshes, Z. *J. Org. Chem.* **1969**, *34*, 3076. (b) Blum, J.; Milstein, D.; Sasson, Y. *J. Org. Chem.* **1970**, *35*, 3233.

⁹¹ Tanaka, K.; Fukawa, N.; Suda, T.; Noguchi, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 5470.

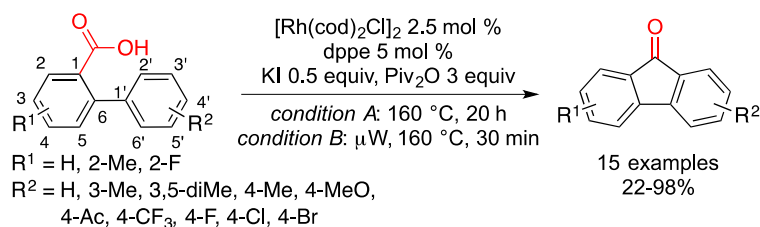
⁹² Sawada, Y.; Furumi, S.; Takai, A.; Takeuchi, M.; Noguchi, K.; Tanaka, K. *J. Am. Chem. Soc.* **2012**, *134*, 4080.



Scheme 72

2.2.2.3 Intramolecular acylation

Ryu and co-workers disclosed in 2014 the first catalytic preparation of fluorenone derivatives through Rh-catalyzed intramolecular acylation of biarylcarboxylic acids (Scheme 73).⁹³ Screening of several reaction conditions led to the selection of [Rh(cod)Cl]₂/dppe system and potassium iodide/pivalic anhydride as catalyst and additives. Notably, the microwave irradiation promoted the reaction in a shorter reaction time.



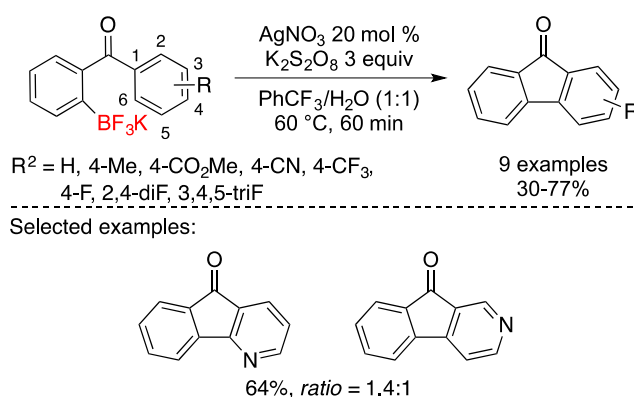
Scheme 73

⁹³ Fukuyama, T.; Maetani, S.; Miyagawa, K. Ryu, I. *Org. Lett.* **2014**, *16*, 3216.

2.2.3 Silver-catalyzed synthesis of fluorenones

2.2.3.1 Intramolecular radical cyclization

In 2011, Baran and co-workers developed a silver-catalyzed intramolecular radical cyclization of arylboronic acids and potassium aryltrifluoroborates, in the presence of silver nitrate and potassium persulfate, to access fluorenones through a ‘borono-Pschorr’ process (Scheme 74).⁹⁴ The reaction was carried out under mild conditions and tolerated various functional groups, such as CO₂Me, CN, CF₃. The aza-fluorenones were synthesized as a mixture with moderate regioselectivity.



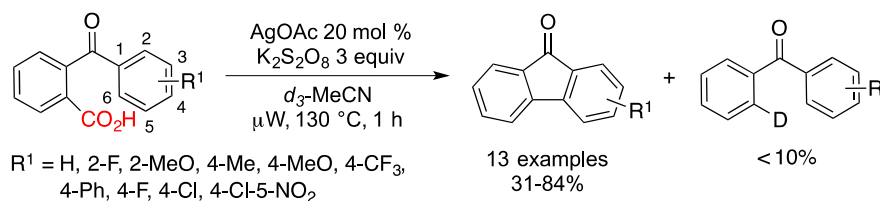
Scheme 74

2.2.3.2 Decarboxylative radical cyclization

Greaney and co-workers reported in 2012 a similar study which involved Ag-catalyzed decarboxylative radical cyclization of arylbenzoic acids to afford fluorenones (Scheme 75).⁹⁵ Notably, CD₃CN was unconventionally chosen as solvent, because of the stronger C-D bond that decreased hydrogen atom abstraction from the solvent. In addition, deuterated decarboxylation product was obtained as a side product which confirmed that the solvent was acting as a hydrogen atom donor.

⁹⁴ Lockner, J. W.; Dixon, D. D.; Risgaard, R.; Baran, P. S. *Org. Lett.* **2011**, *13*, 5628.

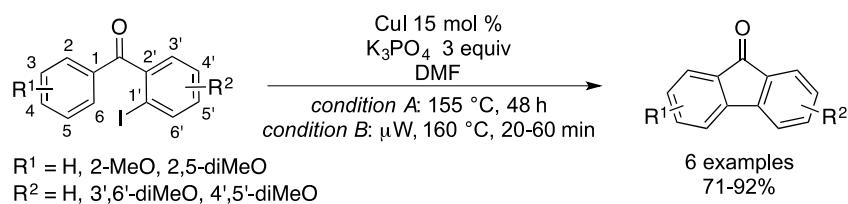
⁹⁵ Seo, S.; Slater, M.; Greaney, M. F. *Org. Lett.* **2012**, *14*, 2650.



Scheme 75

2.2.4 Copper-catalyzed synthesis of fluorenones

A Cu-catalyzed simple construction of methoxy-substituted fluorenones from substituted 2-iodobenzophenones was reported by Haggam (Scheme 76).⁹⁶ This study demonstrated that the intramolecular Cu-catalyzed cyclization of 2-iodobenzophenones afforded the corresponding fluorenones in 71-92% yields under conventional heating or under microwave conditions in a shorter reaction time.

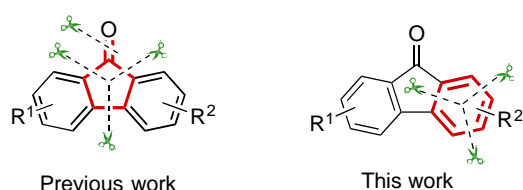


Scheme 76

⁹⁶ Haggam, R. A. *Tetrahedron* **2013**, *69*, 6488.

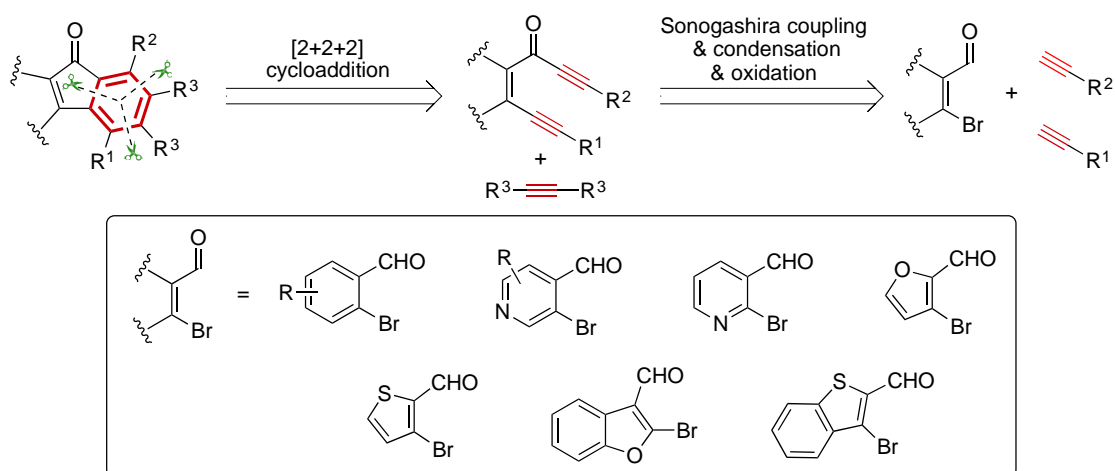
3. Objectives

As we detailed above, various fluorenones have been synthesized through transition-metal-catalyzed reactions. However, there are still important challenges to solve considering current limitations of these methods. Because of special structural features, the construction of the three single C-C bonds between the two six-membered rings has been generally privileged (Scheme 77). In contrast, only few examples focused on the construction of one of the two six-membered rings.



Scheme 77

Considering the results described in the literature, we envisioned that highly substituted fluorenones and related derivatives, such as azafluorenones, indenothiophenones, and benzo[*b*]furanones, could be successfully accessed using [2+2+2] cycloaddition of suitably substituted arylcarbamoyl bridged α,ω -diynes and monoalkynes. The retrosynthetic analysis is shown in Scheme 78.



Scheme 78

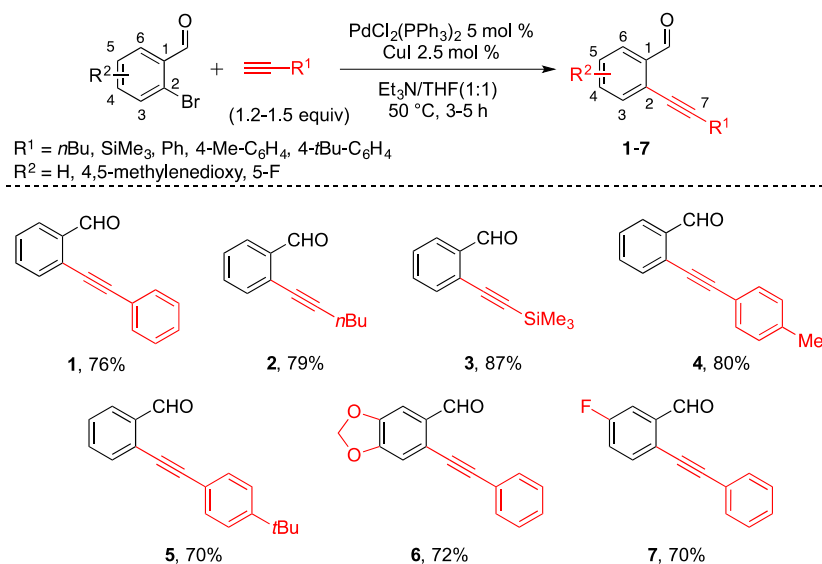
4. Results and discussion

4.1 Synthesis of starting materials: arylcarbamoyl bridged α,ω -diynes and internal alkynes

4.1.1. Synthesis of benzoyl bridged α,ω -diynes

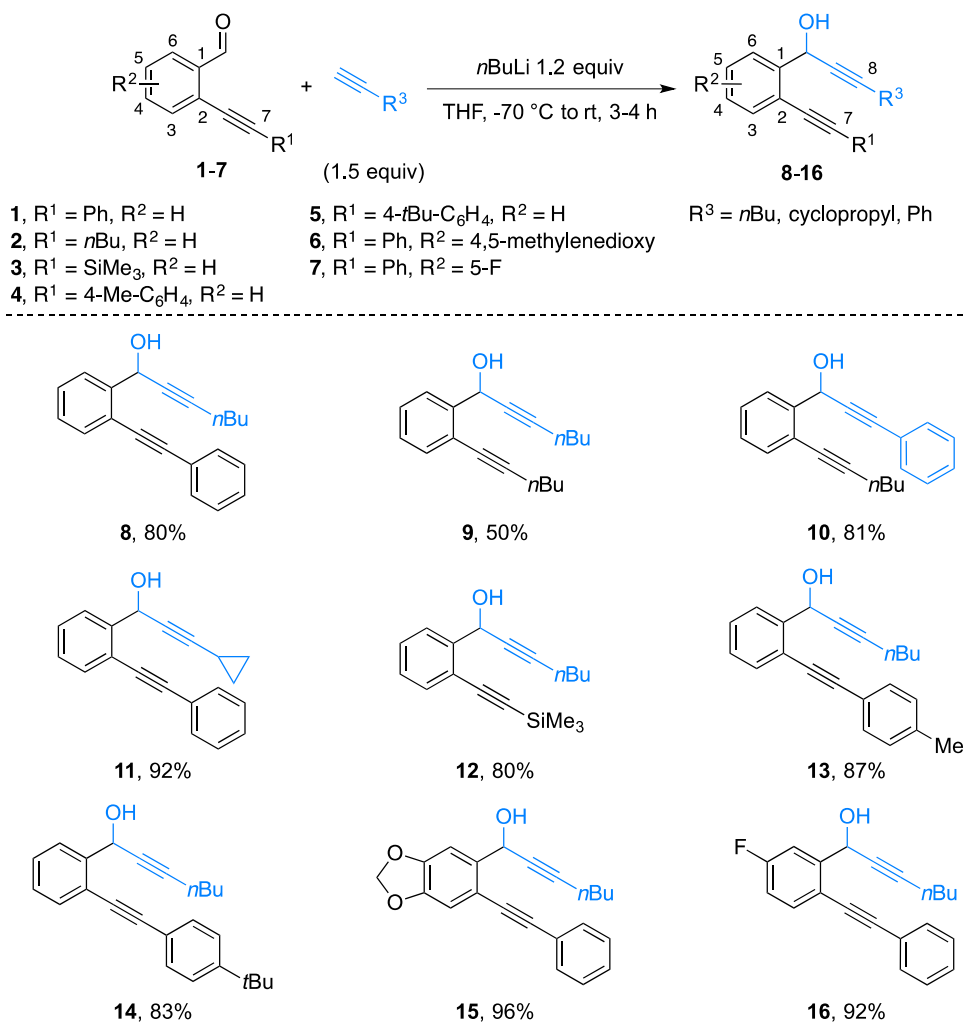
The synthesis of benzoyl bridged diynes could be accessed from the commercially available 2-bromobenzaldehydes via Sonogashira cross-coupling followed by condensation of the corresponding alkyl or phenyl substituted terminal alkyne to the carbonyl group, and final oxidation of the resulting secondary alcohol to ketone.

First, the substituted monoalkyne benzaldehyde derivatives **1-7** were prepared by a Sonogashira cross-coupling reaction. Under classical conditions, the reactions were conducted with 1.2 to 1.5 equivalents of the corresponding terminal alkynes and 2-bromobenzaldehyde in the presence of 5 mol % $\text{PdCl}_2(\text{PPh}_3)_2$ and 2.5 mol % CuI in a mixture of triethylamine and tetrahydrofuran (5.0 M, $v/v = 1/1$) at 50 °C. As shown in Scheme 79, various commercial substituted acetylenes were used, such as phenylacetylene, 1-hexyne, and trimethylsilylacetylene. In order to study the influence of the substituents on the phenyl ring at C7 position, electron-donating groups such as methyl (**4**) or *tert*-butyl (**5**) were introduced by using 4-ethynyltoluene or 4-(*tert*-butyl)phenylacetylene. In order to evaluate the effect on the tethered phenyl ring, the 2-bromoarylaldehydes having both electron-donating and electron-withdrawing substituents, such as methylenedioxy (**6**) and fluoride (**7**), were used for the cross-coupling reaction. All the desired compounds **1-7** were obtained in 70-87% yields (Scheme 79).



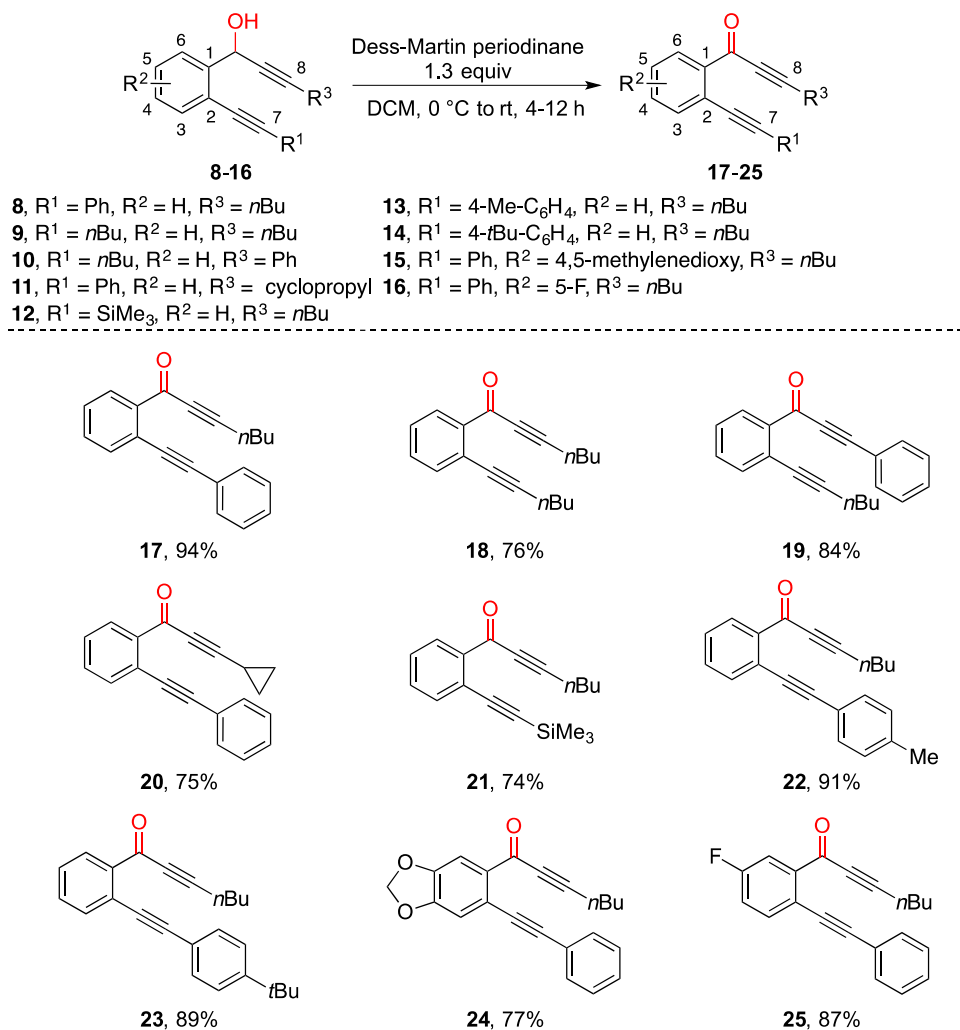
Scheme 79

In the second step, derivatives **8-16** were synthesized by a lithium mediated nucleophilic addition of terminal alkynes with benzaldehyde derivatives **1-7**, as shown in Scheme 80. The anion of terminal alkynes was formed by reacting *n*-butyl lithium with terminal alkyne at low temperature and was followed by the addition of the previously synthesized alkynyl benzaldehyde derivatives **1-7** in THF, allowing the preparation of substituted diynes **8-16** in 50-96% yields. To maximize the yield of the reaction, 1.2 equivalents of *n*-butyllithium and 1.5 equivalents of terminal alkynes were used. Different functionalities at C8 position, such as *n*-butyl, cyclopropyl and phenyl, were introduced to study the influence of the substituents.



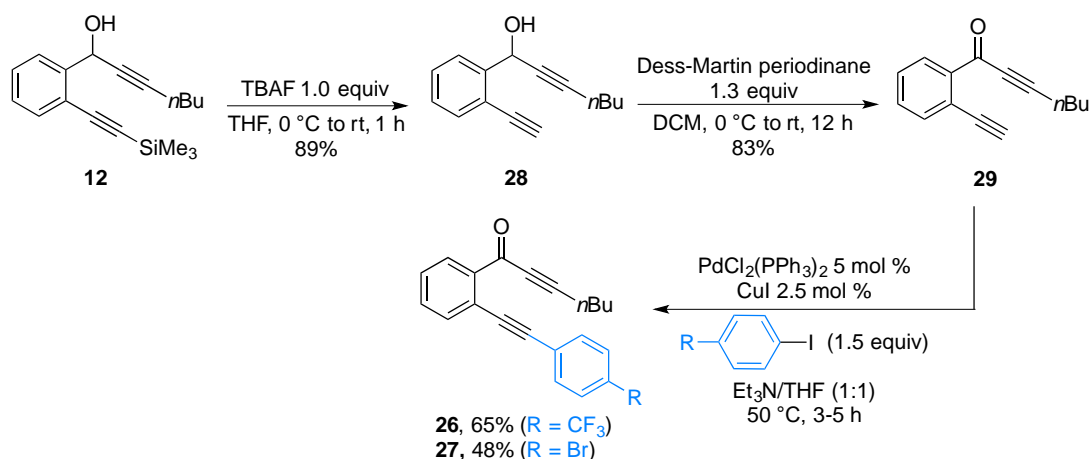
Scheme 80

Compounds **8-16** were next converted to the corresponding benzoyl bridged α,ω -diynes **17-25** via oxidation reaction using Dess-Martin periodinane reagent (1.3 equivalents) (Scheme 81). After transformation of the secondary alcohols into ketones, symmetrically and unsymmetrically benzoyl bridged α,ω -diynes **17-25** were isolated in 74-94% yields.



Scheme 81

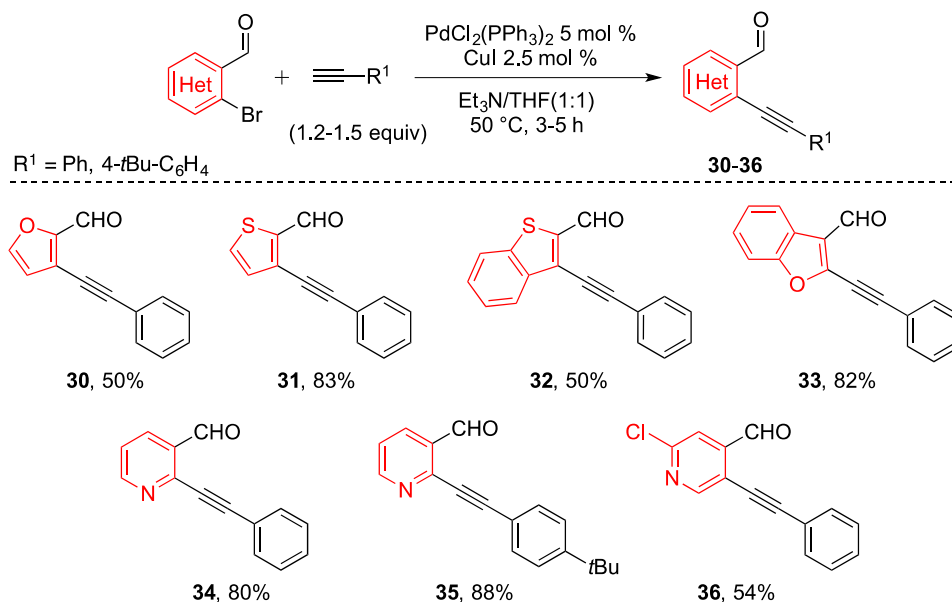
Having in hand diyne **12**, a standard deprotection with TBAF and oxidation reaction with Dess-Martin periodinane afforded substituted terminal phenylacetylene **29**. The Sonogashira cross-coupling reaction was next envisaged for the preparation of electron-withdrawing group substituted diynes **26** and **27**. Compound **29** reacted with a 1.5 equivalents of 4-iodobenzotrifluoride or 1-bromo-4-iodobenzene in the presence of 5 mol % of PdCl₂(PPh₃)₂ and 2.5 mol % of CuI in tetrahydrofuran/triethylamine at 50 °C. The reaction provided the desired products **26** and **27** in 65% and 48% yields, respectively (Scheme 82).



Scheme 82

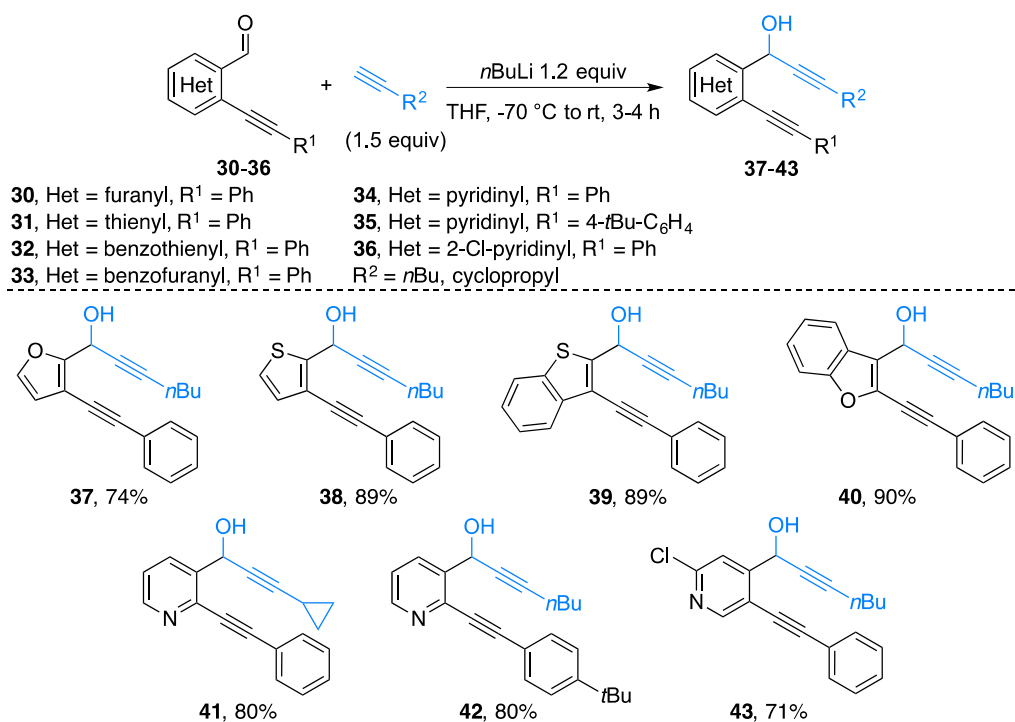
4.1.2. Synthesis of heteroaromatic bridged α,ω -diynes

Heteroaromatic compounds **30-36** were prepared following the same strategy by Sonogashira cross-coupling of the corresponding 2-bromo-heteroarylaldehydes with phenylacetylene. As shown in scheme 83, the coupling products **30-36** were obtained in 50-88% yields under the same conditions.



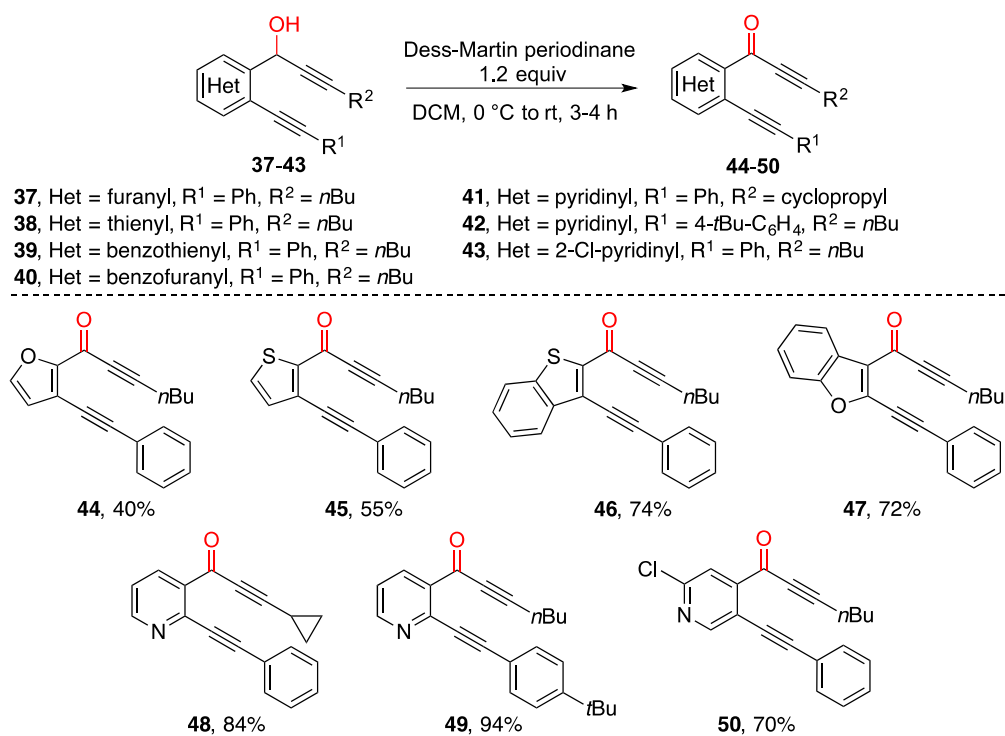
Scheme 83

Next, aldehydes **30-36** reacted with terminal alkynes in the presence of *n*BuLi to provide the corresponding diynes **37-43** in yields ranging from 71% to 90% (Scheme 84).



Scheme 84

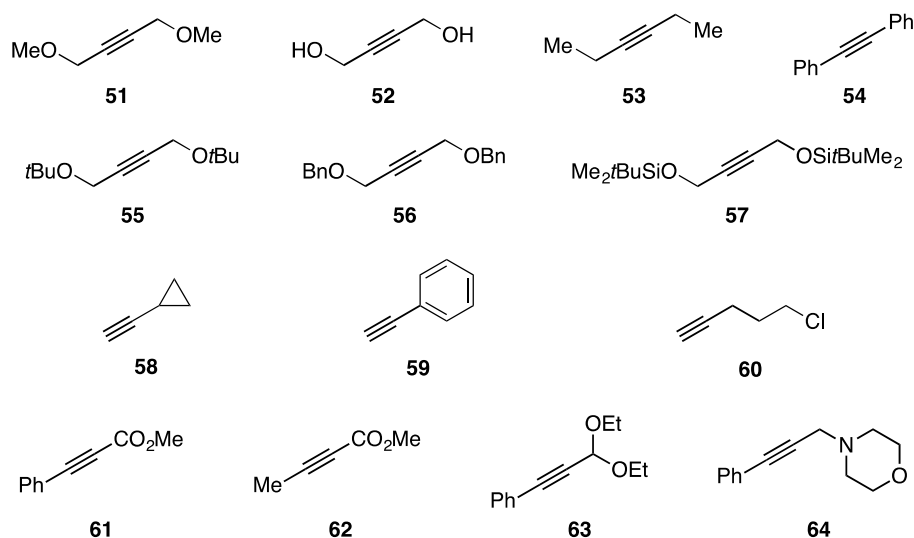
Finally, oxidation of diynes **37-43** with Dess-Martin periodinane furnished the hetero-aromatic carbonyl bridged diynes **44-50** in 40-94% yields. (Scheme 85).



Scheme 85

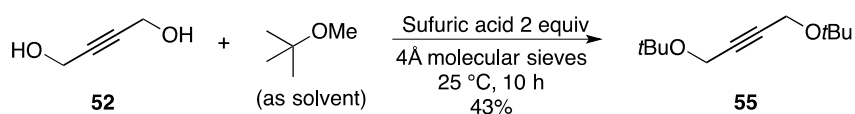
4.1.3. Synthesis of internal alkynes

Alkynes **51-64** that were used in this chapter are shown in Scheme 86. Symmetrical alkynes **51-54** and unsymmetrical alkynes **58-64** were purchased, while ether-substituted monoalkynes **55**,⁹⁷ **56**,⁹⁸ and **57**⁹⁹ were synthesized in agreement with the methods described in the literature.



Scheme 86

Alkyne **55** was prepared by reacting 2-butyne-1,4-diol **52** with a large excess of *tert*-butyl methyl ether (as solvent). The reaction was performed in the presence of two equivalents of sulfuric acid and molecular sieves at room temperature, providing 1,4-di-*tert*-butoxy-2-butyne **55** in 43% yield (Scheme 87).



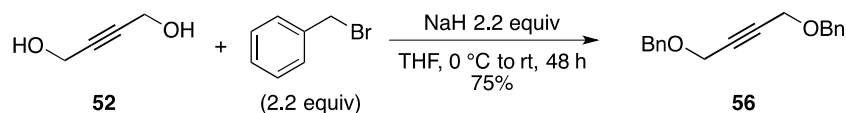
Scheme 87

⁹⁷ Mallesha, N.; Prahlada Rao, S.; Suhas, R.; Channe Gowda, D. *Tetrahedron Lett.* **2012**, 53, 641.

⁹⁸ Arai, A.; Irchikizaki, I. *Bull. Chem. Soc. Jpn.* **1961**, 34, 1571.

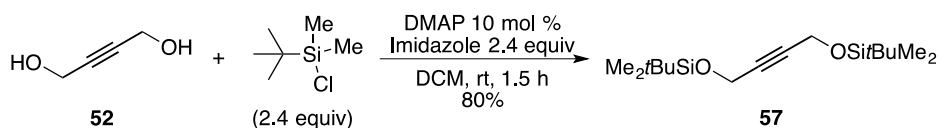
⁹⁹ Schlama, T.; Baati, R.; Gouverneur, V.; Valleix, A.; Falck, J. R.; Mioskowski C. *Angew. Chem. Int. Ed.* **1998**, 37, 2085.

The nucleophilic substitution of 2-butyne-1,4-diol **52** with 2.2 equivalents of benzyl bromide in the presence of sodium hydride, afforded 1,4-dibenzyloxy-2-butyne **56** in 75% isolated yield (Scheme 88).



Scheme 88

Internal alkyne **57** was synthesized through the nucleophilic substitution of 2-butyne-1,4-diol **52** with 2.4 equivalents of *tert*-butyldimethylsilyl chloride at room temperature, using 2.4 equivalents of imidazole and a catalytic amount of DMAP, leading to 1,4-bis-*tert*-butyldimethylsilyloxy-2-butyne **57** in 80% yield (Scheme 89).



Scheme 89

4.2 Interest of $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ complex

Since we synthesized a series of benzoyl bridged α,ω -diynes and internal alkynes, we therefore attempted to find a suitable catalytic system for the [2+2+2] cycloaddition reactions.

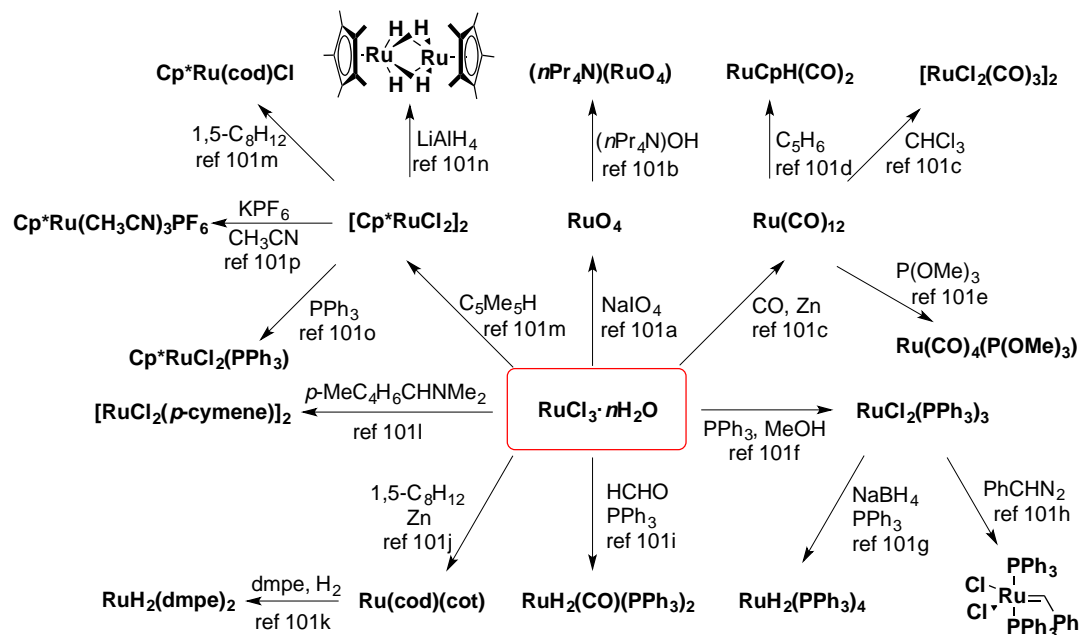
In this context, ruthenium trichloride is a stable salt which can be easily oxidized or reduced, and most commonly used in hydrated form ($\text{RuCl}_3 \cdot n\text{H}_2\text{O}$). As shown in Scheme 90, anhydrous ruthenium(III) chloride is usually prepared by heating powdered ruthenium metal with chlorine.¹⁰⁰



Scheme 90

¹⁰⁰ Fletcher, J. M.; Gardner, W. E.; Fox, A. C.; Topping, G. *J. Chem. Soc. (A)* **1967**, 1038.

As the most commonly available ruthenium source, ruthenium trichloride was reported to be the best starting material for the synthesis of various ruthenium complexes (Scheme 91),¹⁰¹ with a wide range of oxidation states present in these complexes (Ru VIII to Ru II).



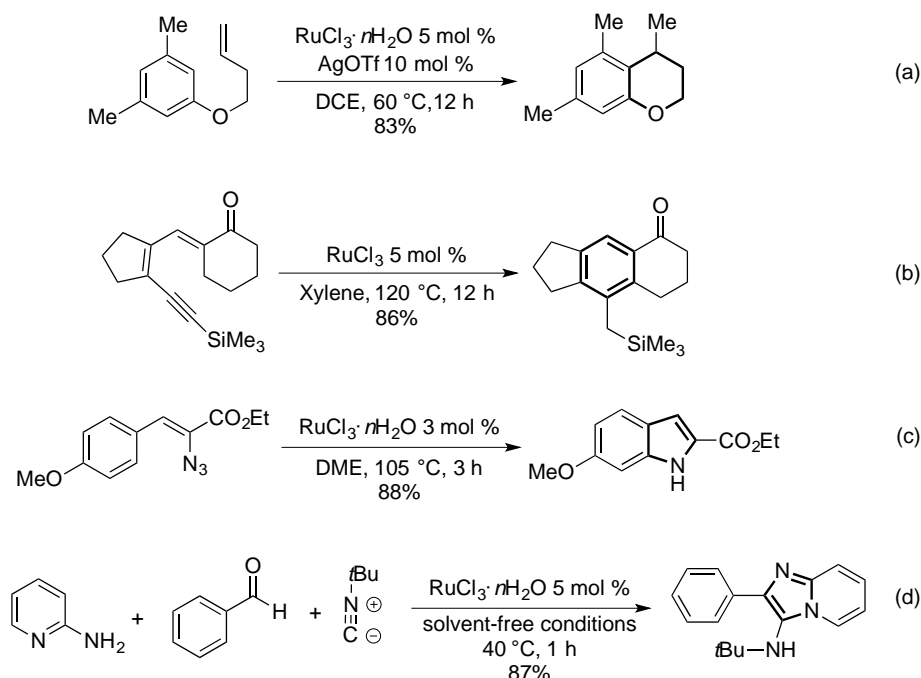
Scheme 91

Ruthenium trichloride was also reported as an efficient catalyst to promote C-C, C-H, C-O and C-N bond formations.¹⁰² Notable examples include many types of cyclization

¹⁰¹ (a) Caputo, J. A.; Fuchs, R. *Tetrahedron Lett.* **1967**, *47*, 4729. (b) Ley, S. M.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639. (c) Teulon, P.; Roziere, J. *J. Organomet. Chem.* **1981**, *214*, 391. (d) Humphries, A. P.; Knox, S. A. R. *J. Chem. Soc. Dalton*, **1975**, 1710. (e) Cobbleck, R. E.; Einstein, F. W. B.; Pomeroy, R. K.; Spetch, E. R. *J. Organomet. Chem.* **1980**, *195*, 77. (f) Hallman, P. S.; Stephenson, T. A.; Wilkinson, G. *Inorg. Synth.* **1970**, *12*, 237. (g) Munk, M. E.; Nelson, D. B.; Antosz, F. J.; Herald, Jr. D. L.; Haskell, T. H. *J. Am. Chem. Soc.* **1968**, *90*, 1089. (h) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100. (i) Ahmad, N.; Levison, J. J.; Robinson, S. D.; Uttley, M. F.; Wonchoba, E. R.; Parshall, G. W. *Inorg. Synth.* **1974**, *15*, 45. (j) Pertici, P. Vitulli, G. *J. Chem. Soc. Dalton*, **1980**, 1961. (k) Chaudret, B.; Commenges, G.; Poilblanc, R. *J. Chem. Soc. Chem. Comm.* **1982**, 1388. (l) Bennett, M. A.; Smith, A. K. *J. Chem. Soc. Dalton*, **1974**, 233. (m) Oshima, N.; Suzuki, H.; Moro-oka, Y. *Chem. Lett.* **1984**, 1161. (n) Suzuki, H.; Omori, H.; Lee, D. H.; Yoshida, Y.; Moro-oka, Y. *Organometallics* **1988**, *7*, 2243. (o) Oshima, N.; Suzuki, H.; Moro-oka, Y. *J. Organomet. Chem.* **1986**, *314*, C46. (p) Mbaye, M. D.; Demerseman, B.; Renaud, J.-L.; Toupet, L.; Bruneau, C. *Adv. Synth. Catal.* **2004**, *346*, 835.

¹⁰² (a) Madec, J.; Pfister, X.; Phansavath, P.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Tetrahedron* **2001**, *57*, 2563. (b) Li, C.-J.; Wei, C. *Chem. Commun.* **2002**, *38*, 268. (c) Youn, S. W.; Pastine, S. J.; Sames, D. *Org. Lett.* **2004**, *6*, 581. (d) Lian, J.-J.; Lin, C.-C.; Chang, H.-K.; Chen, P.-C.; Liu, R.-S. *J. Am. Chem. Soc.* **2006**, *128*, 9661. (e) Bonfield, E. R.; Li, C.-J. *Org. Biomol. Chem.* **2007**, *5*, 435. (f) Labeeuw, O.; Roche, C.; Phansavath, P.; Genêt, J.-P. *Org. Lett.* **2007**, *9*, 105. (g) Ackermann, L.; Althammer, A.; Born, R. *Synlett* **2007**, 2833. (h) Cheng, K.; Yao, B.; Zhao, J.; Zhang, Y. *Org. Lett.* **2008**, *10*, 5309. (i) Goossen, L. J.; Arndt, M.; Blanchot, M.; Rudolphi, F.; Menges, F.; Niedner-Schatteburg, G. *Adv. Synth. Catal.* **2008**, *350*, 2701. (j) Ackermann, L.; Althammer, A.; Born, R. *Tetrahedron* **2008**, *64*, 6115. (k) Denmark, S.; Nguyen, S. T. *Org. Lett.* **2009**, *11*, 781. (l) Shou, G. E.; Li, J.; Guo, T.; Lin, Z.; Jia, G. *Organometallics* **2009**, *28*, 6847. (m) Simon, M.-O.; Genêt, J.-P.; Darses, S. *Org. Lett.* **2010**, *12*, 3038. (n) Luo, N.; Yu, Z. *Chem. Eur. J.* **2010**, *16*, 787. (o) Simon, M.-O.; Ung, G.; Darses, S. *Adv. Synth.*

reactions. For example, as shown in Scheme 92, Sames and co-workers demonstrated that $\text{RuCl}_3/\text{AgOTf}$ was a mild and efficient catalyst for the intramolecular hydroarylation cyclization of a range of arene-ene substrates (Eq. a).^{102c} Liu and co-workers reported that the thermal cyclization of various 3,5-dien-1-yne can be greatly enhanced by using RuCl_3 as catalyst (Eq. b).^{102d} The group of Jia developed a series of RuCl_3 -catalyzed intramolecular C-H amination reactions of organic azides, affording the corresponding indoles (Eq. c).^{102l} Rostamnia and co-workers described a RuCl_3 -catalyzed solvent-free Ugi-type Groebke–Blackburn condensations of aldehydes and 2-aminopyridines with isocyanides in the presence of 5 mol % $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ without any ligand or additive leading to the formation of aminoimidazole heterocycles (Eq. d).^{102t}

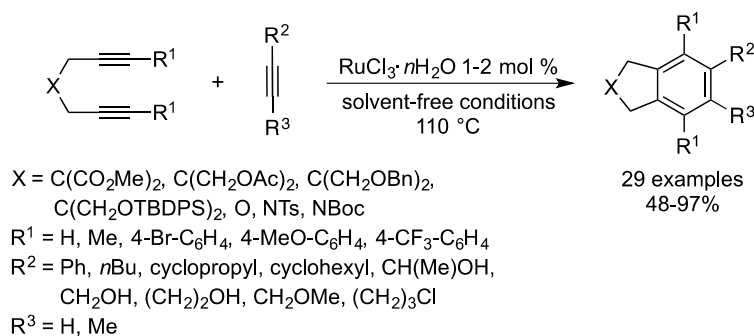


Scheme 92

In the context of RuCl_3 -catalyzed cycloaddition reactions, our group previously reported the first $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ -promoted [2+2+2] cycloaddition reaction of α,ω -diynes and alkynes to

Catal. **2011**, 353, 1045. (p) Kawatsura, M.; Uchida, K.; Terasaki, S.; Tsuji, H.; Minakawa, M.; Itoh, T. *Org. Lett.* **2014**, 16, 1470. (q) Seki, M. *ACS Catal.* **2011**, 1, 607. (r) Thirunavukkarasu V. S.; Ackermann, L. *Org. Lett.* **2012**, 14, 6206. (s) Adrio, L. A.; Gimeno, J.; Vicent, C. *Chem. Commun.* **2013**, 49, 8320. (t) Rostamnia, S.; Hassankhani, A. *RSC Adv.* **2013**, 3, 18626. (u) Singh, M. K.; Akula, H. K.; Satishkumar, S.; Stahl, L.; Lakshman, M. K. *ACS Catal.* **2016**, 6, 1921. (v) Tan, D.-W.; Li, H.-X.; Young, D. J.; Lang, J.-P. *Tetrahedron* **2016**, 72, 4169. (w) Baruah, P. K.; Deb, M. L.; Borpatra, P. J.; Saikia, P. J. *Org. Biomol. Chem.* **2017**, 15, 1435.

access highly substituted benzene derivatives (Scheme 93).¹⁰³ We demonstrated that the cost-effectively available $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ was an efficient catalyst to promote the cycloaddition reaction under solvent-free conditions affording fused functionalized arenes including dihydrobenzofurans, isoindolines, and indanes in 48-97% yields. Notably, this practical method used neither additional ligand nor additive.



Scheme 93

Encouraged by these results, we assumed that the $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ complex might also be an efficient catalyst for solvent-free [2+2+2] cycloaddition of arylcarbamoyl bridged α,ω -diynes and monoalkynes to access fluorenone derivatives.

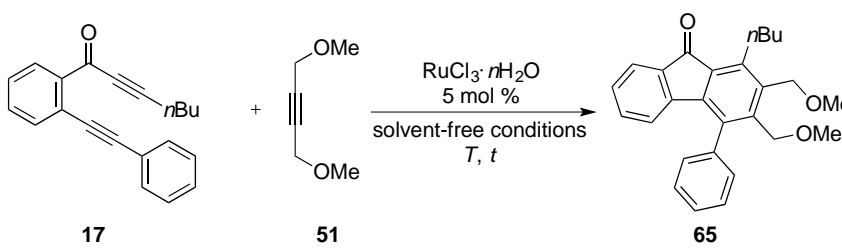
4.3 $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ -mediated [2+2+2] cycloaddition of benzoyl bridged α,ω -diynes with symmetrical internal alkynes

With a series of diynes and alkynes in hand, we began our study by investigating the reaction of arylcarbamoyl bridged diyne **17** with 1,4-dimethoxy-2-butyne **51** which has often been reported as a good partner in transition-metal-catalyzed [2+2+2] cycloaddition reactions. The reaction was therefore initially performed in the presence of 5 mol % $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ at 110 °C under previously described solvent-free conditions.¹⁰³ Fortunately, the reaction gave the corresponding fluorenone **65** in complete conversion and isolated yield up to 86% (Entry 1, Table 1). It is noteworthy that the desired product could be isolated on silica column chromatography without any treatment after complete conversion (determined by TLC and crude ^1H NMR). This result confirmed that $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ is an efficient catalyst in [2+2+2] cycloaddition of α,ω -diynes with alkynes under solvent-free conditions. Based on such

¹⁰³ Jacquet, J.; Auvinet, A.-L.; Mandadapu, A. K.; Haddad, M.; Ratovelomanana-Vidal, V.; Michelet, V. *Adv. Synth. Catal.* **2015**, 357, 1387.

encouraging result, we further optimized the reaction conditions. First, we studied the consumption of the monoalkyne **51**, we were pleased to observe that when the amount of alkyne **51** was decreased from 6 to 2 equivalents, the reaction still provided the desired product **65** in satisfactory yields (Entries 2-6). In addition, decreasing the reaction temperature to 50 °C provided the cycloadduct in a similar yield (Entry 3, 73% and Entry 5, 75%, respectively). Lowering the catalyst loading from 5 to 2 mol %, led to a decrease of the conversion and isolated yield was observed in 18 hours at 80 °C (Entry 4, 60% conv. and 40% yield, respectively). Furthermore, we found that the reaction could be accomplished in 2 hours at 50 °C affording the desired cycloadduct **65** in satisfactory yield of 72% (Entries 6-8). When the reaction was placed under open-air condition, the conversion decreased significantly (Entry 9).

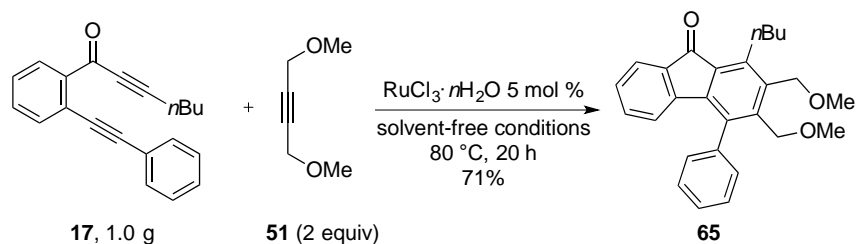
Table 1 Optimization of the reaction conditions



Entry ^a	17/51	T (°C)	t (h)	Conv. (%) ^b	Yield (%) ^c
1	1:6	110	18	> 99	86
2	1:4	80	18	> 99	74
3	1:3	80	18	> 99	73
4 ^d	1:3	80	18	60	40
5	1:3	50	18	> 99	75
6	1:2	50	18	> 99	72
7	1:2	50	4	> 99	73
8	1:2	50	2	> 99	72
9 ^e	1:2	50	18	40	nd

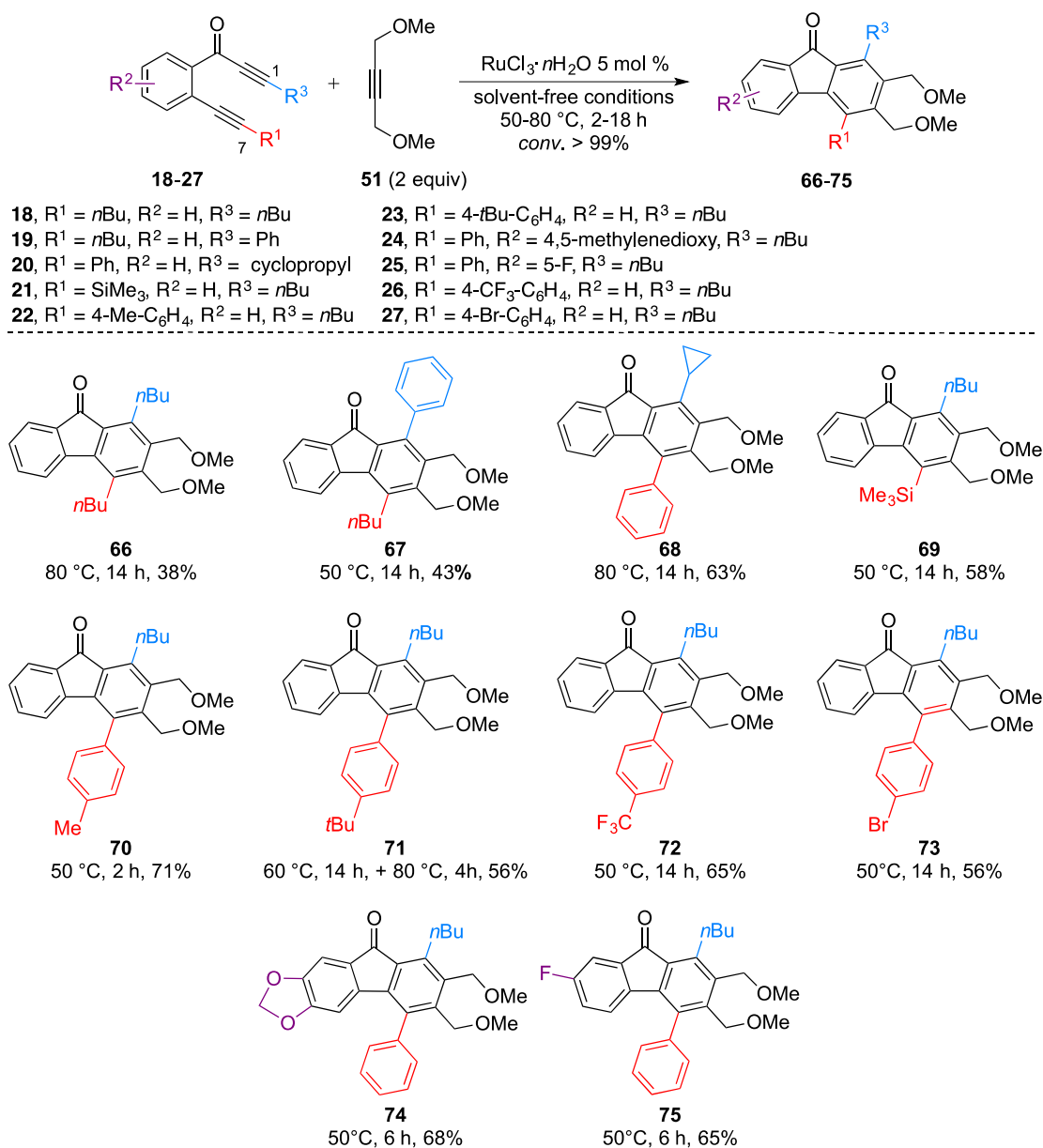
^a Reaction conditions: RuCl₃·nH₂O (0.0175 mmol), diyne **17** (0.35 mmol), alkyne **51** (0.7 mmol) were heated in a screw-capped tube under free-solvent conditions and argon atmosphere. ^b Determined by ¹H NMR. ^c Isolated yields. ^d 2 mol % RuCl₃·nH₂O (0.007 mmol) was used. ^e Under air atmosphere.

To investigate the synthetic utility of this catalytic method, the reaction was performed on one gram-scale under optimized conditions. Fluorenone **65** was efficiently isolated in 71% yield (Scheme 94).



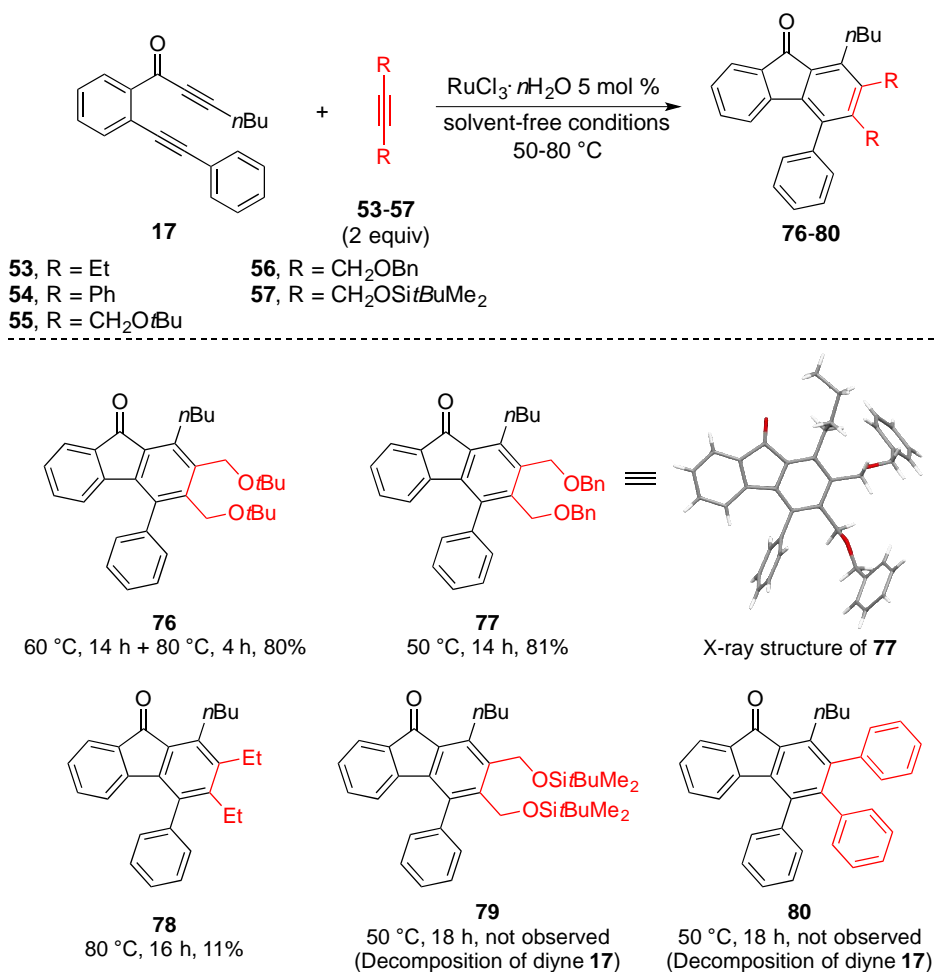
Scheme 94

Having established a set of optimal conditions, we examined the scope and limitations of the solvent-free $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ -catalyzed [2+2+2] cycloaddition between diynes **18-27** and alkyne **51**, as shown in Scheme 95. Initially, we observed that diyne **18** having two identical alkyl substituents at the C1 and C7 positions was less reactive compared to the unsymmetrical substituted diynes having a phenyl group at C7 position, the corresponding product **66** was obtained in 38% yield. The use of diyne **19** gave the desired product **67** in 43% yield. This result suggested that the unsymmetrical substituted diynes having a phenyl group at C7 positions was necessary. On the other hand, the reaction of diyne **20** with a cyclopropyl moiety delivered the cyclic product **68** in 63% yield. Interestingly, the cyclization of silyl-substituted diyne **21** with alkyne **51** provided the desired compounds **69** with 58% yield, which was used for further functionalization. Further experiments showed that diynes **22**, **23**, **26** and **27**, having electron-donating or electron-withdrawing substituent on *para* position of phenyl ring at C7 could be successfully used in this reaction, leading to the targeted products **70-73** in 56-71% yields. To evaluate the influence of the tethered phenyl group, cycloaddition using diynes **24** and **25**, bearing electron-donating or electron-withdrawing group, were accomplished smoothly to yield the desired products **74** and **75** in similar yields (68% and 65%, respectively). It is worth mentioning that these reactions were based on complete conversion even at elevated temperatures or prolonged reaction times.



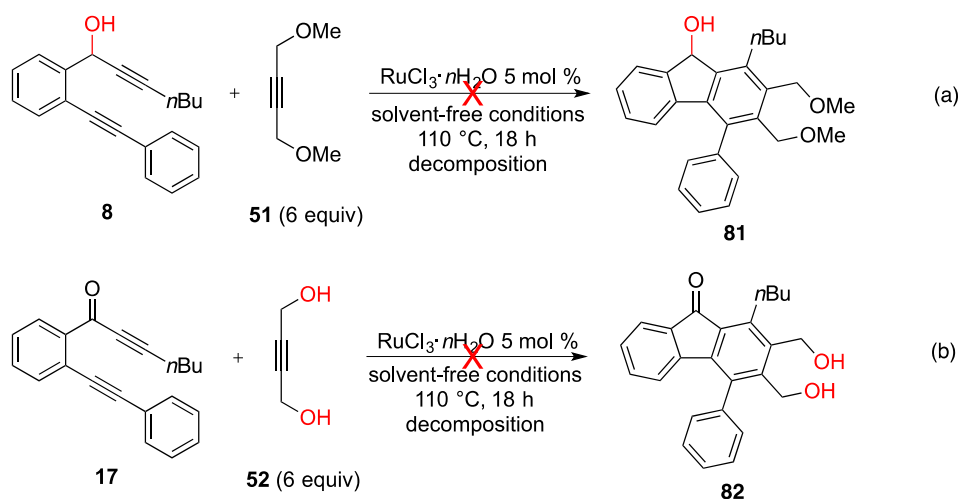
Scheme 95

To further investigate the generality of the [2+2+2] cyclization, the reactivity of various alkynes was examined (Scheme 96). Switching the methyl group to a bulkier group, such as *tert*-butyl and benzyl, allowed to access the corresponding functionalized fluorenones **76** and **77** in 80% and 81% yields, respectively. The structure of fluorenone **77** was unambiguously confirmed by single crystal X-ray diffraction as shown in Scheme 96. Furthermore, when the cycloaddition of diyne **17** with 3-hexyne **53** was carried out under the same conditions, cycloadduct **78** was obtained in 11% isolated yield. However, we did not observe the cyclized products **79** and **80** when the alkynes **54** and **57** were used in the reactions, these results could be explained by the steric effects and poor reactivity of these alkynes.



Scheme 96

During our ongoing investigation on the scope of different substituted diynes and alkynes, we found that the reaction of diyne **8** with alkyne **51** did not afford cyclic product **81**, most of starting material being decomposed under the reaction conditions (Eq. a, Scheme 97). To further evaluate the influence of free hydroxyl substituent, the reaction of diyne **17** with 2-butyn-1,4-diol **51** was studied. Unfortunately, we did not observe any desired product **82** (Eq. b, Scheme 97). This result suggested that free hydroxyl groups from both diyne or monoalkyne would greatly influence the formation of cycloadduct in this reaction.

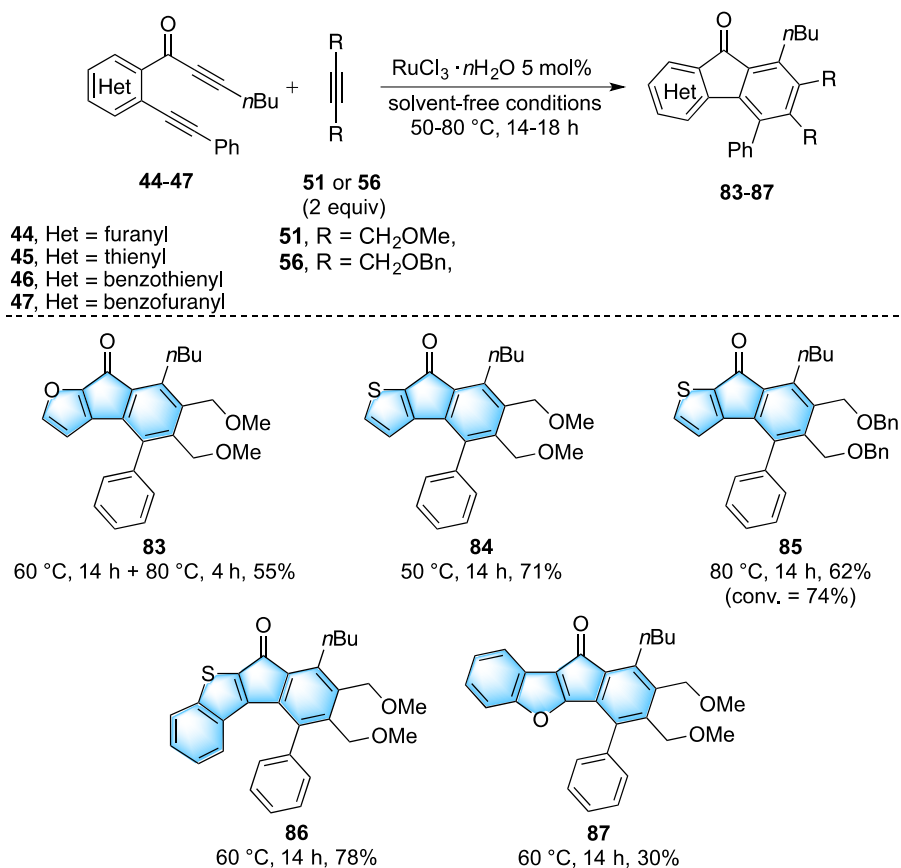


Scheme 97

4.4 $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ -mediated [2+2+2] cycloaddition of heteroaromatic carbonyl bridged α,ω -diynes with internal alkynes

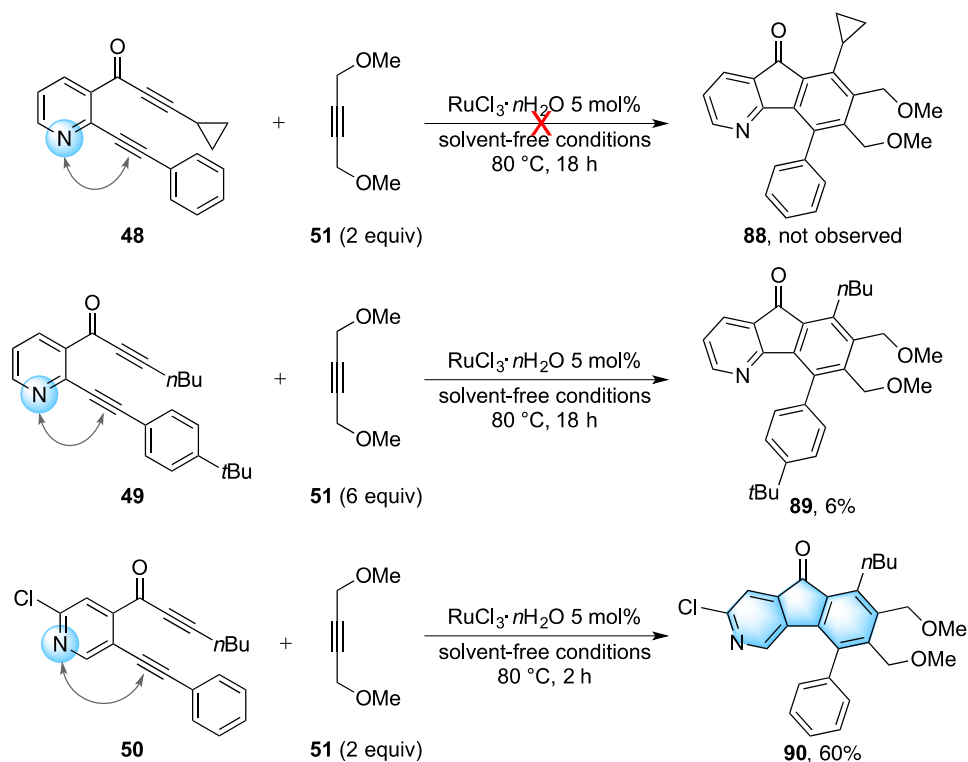
Once the heteroaromatic carbonyl bridged diynes **44-50** were obtained, we examined their partially intramolecular [2+2+2] cycloaddition to provide the corresponding hetero-based fluorenones. A series of hetero-aromatic tethered diynes has been studied.

First, the cycloaddition of furan-bridged diyne **44** with alkyne **51** in the presence of $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ under the optimal conditions delivered the corresponding benzo[*b*]furanones **83** in 55% yield. Then, the thienyl-based fluorenones **84** and **85** were obtained in 71% and 62% isolated yields, respectively. Moreover, the cyclization of diyne **46**, having a benzo[*b*]thiophene moiety as tether, produced the expected fused fluorenone **86** in 78% yield. When diyne **47** was used in the cycloaddition, the corresponding cyclic product **87** was obtained in 30% yield (Scheme 98).



Scheme 98

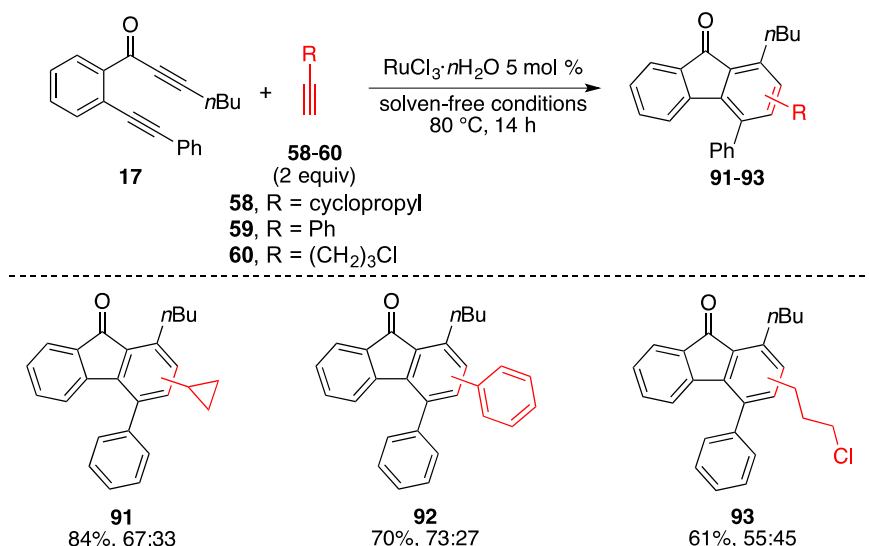
On the other hand, it was found that the use of diyne **49** only gave the corresponding cycloadduct **89** in 6% yield, while cyclization of diyne **48** with alkyne **51** did not provide cyclized product **88**. To explain these results, we speculate that the position of the nitrogen atom in pyridine would influence the course of the reaction toward the formation of an unactivated intermediate where the ruthenium is coordinated to the nitrogen atom. This could be confirmed by the preparation of aza-fluorenone **90**, starting from the pyridine tethered diynes **50** and alkyne **51**, 60% yield was obtained and a chlorine atom was compatible with this reaction. (Scheme 99).



Scheme 99

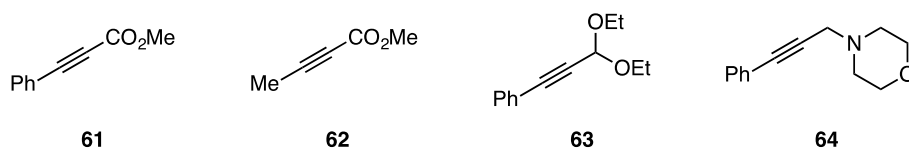
4.5 Regioselective $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ -mediated [2+2+2] cycloaddition of benzoyl bridged α,ω -diynes with unsymmetrical terminal and internal alkynes

The cycloaddition reaction was not limited to symmetrical internal alkynes, since a series of unsymmetrical terminal alkynes, such as cyclopropylacetylene **58**, phenylacetylene **59**, and 5-chloro-1-pentyne **60**, were successfully reacted with phenylcarbamoyl bridged diyne **17** under optimized reaction conditions. The [2+2+2] cycloaddition reactions led to unseparable mixtures of regioisomers **91**, **92**, and **93** in 61–84% yields with regioselectivities from 55:45 to 73:27 ratio (Scheme 100).



Scheme 100

Next, we turned our attention to the examination of unsymmetrical internal alkynes. Unfortunately, cycloaddition of methyl 3-phenylpropiolate **61**, methyl 2-butynoate **62**, phenylpropargyl aldehyde diethyl acetal **63**, and 4-(3-phenylprop-2-yn-1-yl)morpholine **64** failed to afford the desired fluorenone products (Scheme 101). Only degradation of starting diynes was observed. The control of the regioselectivity is therefore still a challenge for $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ -catalyzed [2+2+2] cycloaddition of diynes with unsymmetrical alkynes.



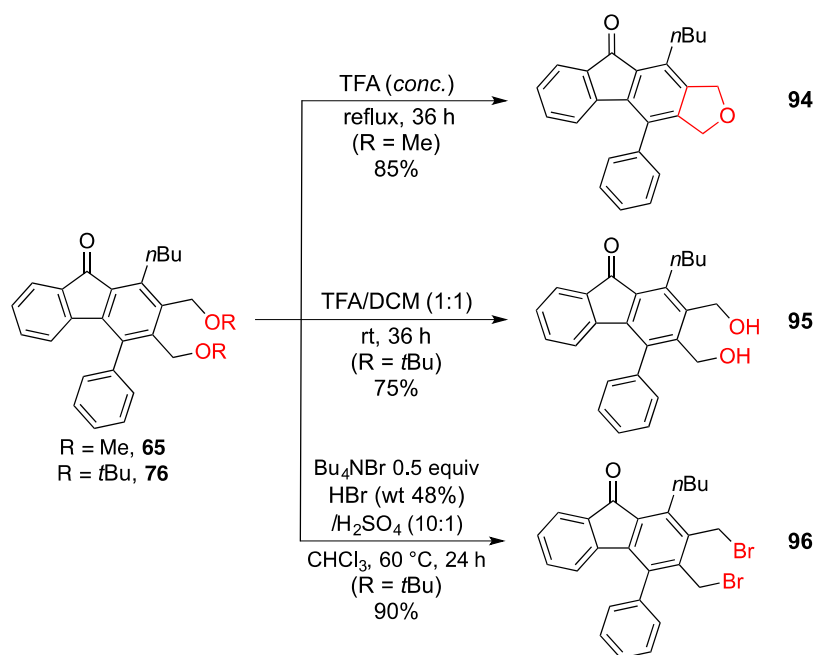
Scheme 101

4.6 Post-functionalization of fluorenone derivatives

With a set of substituted fluorenone derivatives in hand, we then turned our attention toward the investigation of post-functionalization reactions of fluorenone derivatives, including compounds **65** and **76**, silylated derivative **69** and bromo-functionalized adduct **73**.

First, we focused on the functionalization of cycloadducts **65** and **76**, as shown in Scheme 102. When the dimethyl ether substituted fluorenone **65** was refluxed in the presence of concentrated trifluoroacetic acid, the reaction did not lead to the expected deprotected diol

95: the substituted cyclized product dihydrobenzo[*b*]furan **94** was isolated as the main product in 85% yield. To achieve the deprotection of di-*tert*-butyl ether substituted fluorenone **76**, the latter was subjected to classical deprotection conditions, yielding 75% of diol **95**. On the other hand, the direct dibromination of compound **76** in the presence of refluxing mixture of HBr and Bu₄NBr in chloroform provided the dibrominated **96** in 90% yield. The diol and dibrominated products were reported as key building blocks for the synthesis of OLEDs materials.^{59d}



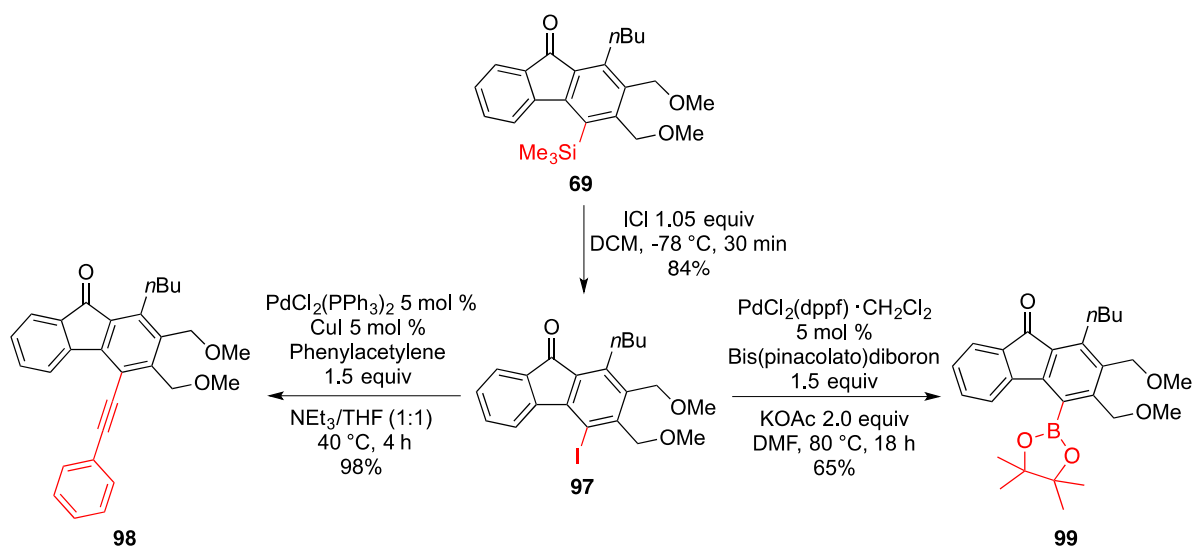
Scheme 102

The silyl-based fluorenone adduct **69** has been considered as a suitable substrate, since the reactivity of the substituted silyl group is expected to enable functionalization reactions, such as iodination reaction.¹⁰⁴ The iodinated product could further allow the introduction of a variety of substituents using metal-catalyzed cross-coupling reactions.¹⁰⁵ Starting from compound **69**, the iodination by means of iodine monochloride afforded the iodinated product **97** in 84% yield. Consequently, a single Sonogashira cross-coupling reaction of compound **97** with phenylacetylene led to the desired alkyne **98** in 98% yield. Additionally, adduct **97** was

¹⁰⁴ Durka, K.; Górká, J.; Kurach, P.; Luliński, S.; Serwatowski, J. *J. Organomet. Chem.* **2010**, 695, 2635.

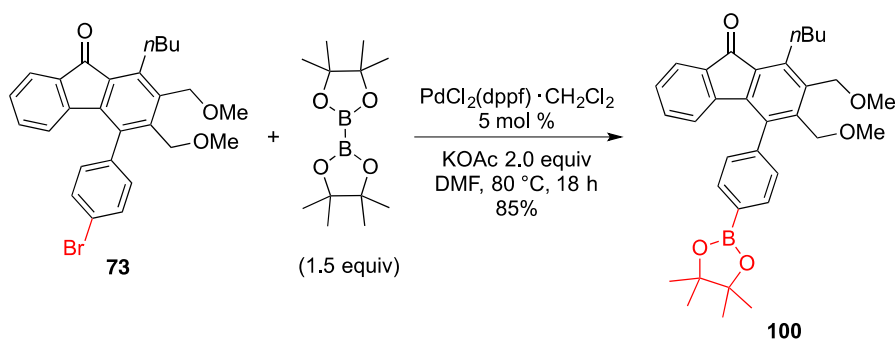
¹⁰⁵ (a) Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, 107, 874. (b) Doucet, H.; Hierso, J.-C. *Angew. Chem. Int. Ed.* **2007**, 46, 834. (c) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, 51, 5062. (d) Palladium-Catalyzed Coupling Reactions: Practical Aspects and Future Developments, (Ed.: A. Molnar), Wiley-VCH, Weinheim, **2013**.

subjected to Suzuki-Miyaura cross-coupling reaction, leading to boronic ester **99** in 65% yield (scheme 103).



Scheme 103

To extend the applications of the functionalized fluorenones, additional Suzuki-Miyaura cross-coupling reaction was performed with bromo-substituted fluorenone **73**. Boronic ester derivative **100** was obtained in 85% yield (Scheme 104).



Scheme 104

5. Conclusion

In summary, we have developed a novel and eco-friendly straightforward access to highly substituted fluorenones and related analogues using $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ -promoted partially intramolecular [2+2+2] cycloaddition of carbonyl bridged α,ω -diynes with alkynes. This economical process was performed without solvent, additional ligands or additives, and allowed the construction of complex polycyclic fluorenones, aza-fluorenones, benzo[*b*]furanones and indenothiophenones. This protocol offers several advantages: i) the stability and cost-effective $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ used as catalyst, ii) prevention of pollution with no elimination of toxic or volatile solvents, iii) practical protocol without work up to access the targeted products.

A wide range of carbonyl bridged α,ω -diynes and alkynes containing different substituents was evaluated in this reaction. Unsymmetrical diynes bearing alkyl and phenyl substituents proved to be more active in the ruthenium-catalyzed [2+2+2] cycloaddition reaction. Both electron-donating and electron-withdrawing substituents on the phenyl ring and tether phenyl ring were tolerated in this reaction. Furthermore, heteroarene tethered carbonyl diynes, such as furanyl-, thienyl- and aza-based moieties, have been shown to be active in this cyclization and their cycloaddition proceeded efficiently to give the expected cycloadducts in 30-78% yields. With regards to the scope of the alkynes, a wide range of substituted alkynes has been used for the [2+2+2] cycloaddition. It was found that symmetrical dialkoxy-substituted alkynes, such as methoxy, benzyloxy and *tert*-butoxy, could be engaged in the cyclization to deliver the desired product in 6-81% yields. Unsymmetrical terminal alkynes also converted well to the expected cycloadducts, although 55:45 to 73:27 regioselectivities were obtained.

Chapter III: Ruthenium-catalyzed
[2+2+2] cycloaddition of diynes with
electron-rich cyanamides: an easy
access to 2-aminopyridine derivatives

Chapter III: Ruthenium-catalyzed [2+2+2] cycloaddition of diynes with electron-rich cyanamides: an easy access to 2-aminopyridine derivatives

1. Interest of 2-Aminopyridines

A recent report demonstrated that pyridine is the second most commonly used nitrogen heterocycle among all U.S. FDA approved pharmaceuticals (Figure 2).¹⁰⁶ As analogues of pyridines, 2-aminopyridines represent one of the most important skeleton motifs which are widely present in many biologically active molecules as well as pharmaceuticals.

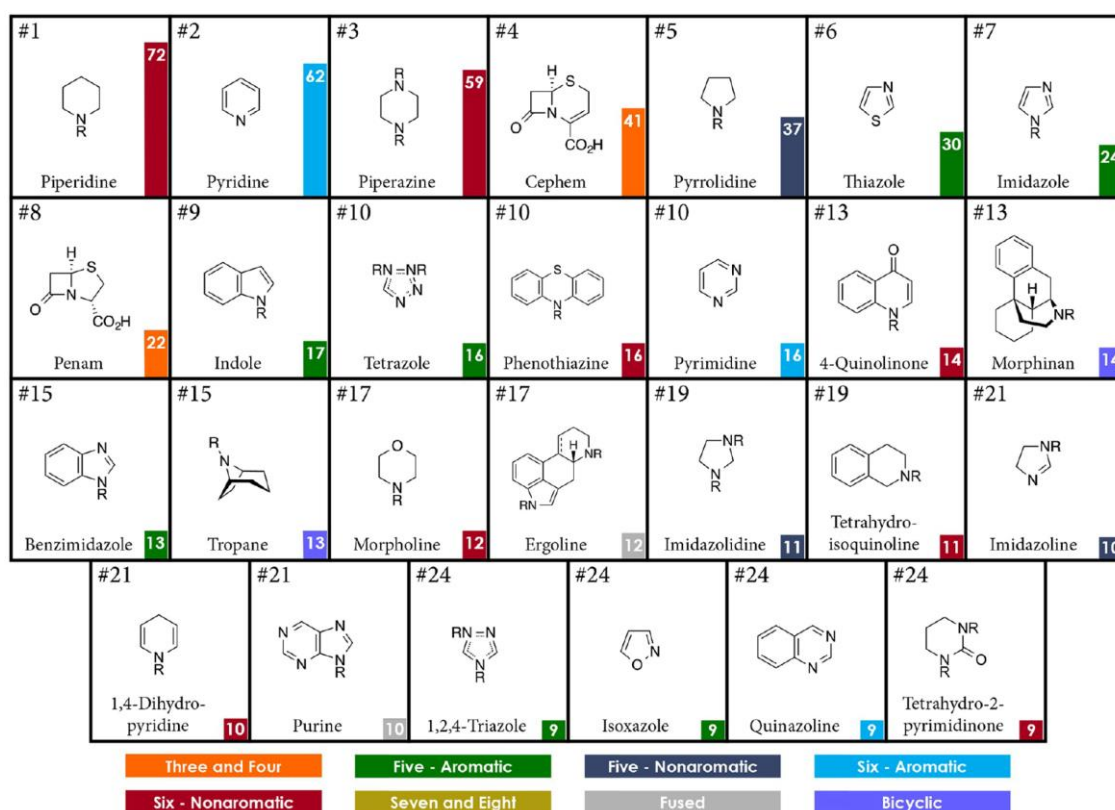


Figure 2¹⁰⁶

¹⁰⁶ Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257.

Compounds containing 2-aminopyridine ring scaffold exhibit an array of pharmacological properties such as antimicrobial,¹⁰⁷ anti-inflammatory,¹⁰⁸ anti-prion,¹⁰⁹ anti-HBV,¹¹⁰ antithrombotic,¹¹¹ antineoplastic,¹¹² and antitumoral.¹¹³ Particularly, morpholine derived pyranopyridines (MBX2319) **A** is active against Gram-negative bacteria;¹⁰⁷ piperazine derived pyranopyridine **B** is used as IDH1 mutants inhibitor for the treatment of cancer;^{113d} ethyl 6-aminonicotinate acyl sulfonamide **C** is potent antagonist of the P2Y₁₂ receptor;¹¹¹ heterocycle **D** which exhibits potent γ -secretase modulator activity is expected for the treatment of Alzheimer's disease;¹¹⁴ Crizotinib **E** is a commercially available anti-cancer drug, which has been approved for the treatment of lung cancer;^{113a-113c} α -carboline derivative (TAK-901) **F** is potent Aurora B kinase inhibitor with antineoplastic activity^{112a} (Scheme 105).

In addition to bioactive compounds, 2-aminopyridines are also synthetically useful compounds present in organometallic and material chemistry. The *L*-amino acid containing a 2-aminopyridine moiety **G** was used as highly efficient bidentate ligand for direct asymmetric

¹⁰⁷ (a) Opperman, T. J.; Kwasny, S. M.; Kim, H. S.; Nguyen, S. T.; Houseweart, C.; D'Souza, S.; Walker, G. C.; Peet, N. P.; Nikaido, H.; Bowlin, T. L. *Antimicrob. Agents Chemother.* **2014**, *58*, 722. (b) Nguyen, S. T.; Kwasny, S. M.; Ding, X.; Cardinale, S. C.; McCarthy, C. T.; Kim, H. S.; Nikaido, H.; Peet, N. P.; Williams, J. D.; Bowlin, T. L.; Opperman, T. J. *Bioorganic Med. Chem.* **2015**, *23*, 2024.

¹⁰⁸ Mannal, F.; Chimentil, F.; Bolascol, A.; Palla, A.; Filippelli, W.; Lampa, E.; Mercantini, R.; Filippelli, A. *Eur. J. Med. Chem.* **1992**, *27*, 627.

¹⁰⁹ (a) Reddy, T. R. K.; Mutter, R.; Heal, W.; Guo, K.; Gillet, V. J.; Pratt, S.; Chen, B. *J. Med. Chem.* **2006**, *49*, 607. (b) May, B. C. H.; Zorn, J. A.; Witkop, J.; Sherrill, J.; Wallace, A. C.; Legname, G.; Prusiner, S. B.; Cohen, F. E. *J. Med. Chem.* **2007**, *50*, 65.

¹¹⁰ Chen, H.; Zhang, W.; Tam, R.; Raney, A. K. *PCT Int. Appl.* WO 2005058315 A1 20050630, **2005**.

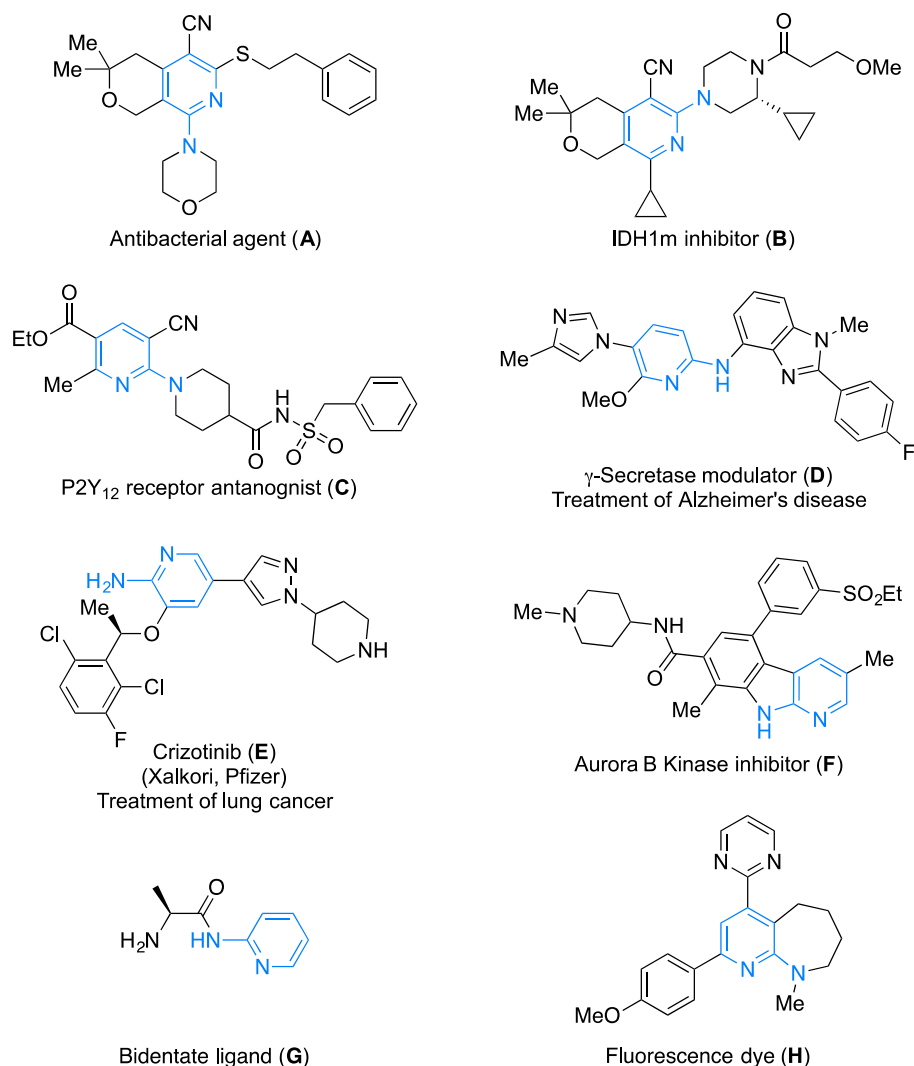
¹¹¹ Bach, P.; Antonsson, T.; Bylund, R.; Björkman, J. A.; Österlund, K.; Giordanetto, F.; Van Giezen, J. J. J.; Andersen, S. M.; Zachrisson, H.; Zetterberg, F. *J. Med. Chem.* **2013**, *56*, 7015.

¹¹² (a) Farrell, P.; Shi, L.; Matuszkiewicz, J.; Balakrishna, D.; Hoshino, T.; Zhang, L.; Elliott, S.; Fabrey, R.; Lee, B.; Halkowycz, P.; Sang, B.; Ishino, S.; Nomura, T.; Teratani, M.; Ohta, Y.; Grimshaw, C.; Paraselli, B.; Satou, T.; de Jong, R. *Mol. Cancer Ther.* **2013**, *12*, 460. (b) Mineno, M.; Sera, M.; Ueda, T.; Mizufune, H.; Zanka, A.; Obryan, C.; Brown, J.; Scoria, N. *J. Org. Chem.* **2015**, *80*, 1564.

¹¹³ (a) Christensen, J. G.; Zou, H. Y.; Arango, M. E.; Li, Q.; Lee, J. H.; McDonnell, S. R.; Yamazaki, S.; Alton, G. R.; Mroczkowski, B.; Los, G. *Mol. Cancer Ther.* **2007**, *6*, 3314. (b) Zou, H. Y.; Li, Q.; Lee, J. H.; Arango, M. E.; McDonnell, S. R.; Yamazaki, S.; Koudriakova, T. B.; Alton, G.; Cui, J. J.; Kung, P. P.; Nambu, M. D.; Los, G.; Bender, S. L.; Mroczkowski, B.; Christensen, J. G. *Cancer Res.* **2007**, *67*, 4408. (c) Cui, J. J.; Tran-Dubé, M.; Shen, H.; Nambu, M.; Kung, P.; Pairish, M.; Jia, L.; Meng, J.; Funk, L.; Botrous, I.; McTigue, M.; Grodsky, N.; Ryan, K.; Padriue, E.; Alton, G.; Timofeevski, S.; Yamazaki, S.; Li, Q.; Zou, H.; Christensen, J.; Mroczkowski, B.; Bender, S.; Kania, R. S.; Edwards, M. P. *J. Med. Chem.* **2011**, *54*, 6342. (d) Cao, S.; Popovici-Muller, J.; Salituro, F. G.; Saunders, J.; Tan, X.; Travins, J. Yan, S.; Ye, Z. *PCT Int. Appl.* WO 2012171506 A1 20121220, **2012**. (e) Cocco, M. T.; Congiu, C.; Lilliu, V.; Onnis, V. *Eur. J. Med. Chem.* **2005**, *40*, 1365.

¹¹⁴ Bischoff, F.; Berthelot, D.; De Cleyn, M.; Macdonald, G.; Minne, G.; Oehlrich, D.; Pieters, S.; Surkyn, M.; Trabanco, A. A.; Tresadern, G.; Van Brandt, S.; Velter, I.; Zaja, M.; Borghys, H.; Masungi, C.; Mercken, M.; Gijssen, H. J. M. *J. Med. Chem.* **2012**, *55*, 9089.

aldol reaction.¹¹⁵ Pyrido[2,3-*b*]azepine **H**, a pH sensitive fluorescence dye, can be an ideal candidate for fluorescence label¹¹⁶ (Scheme 105).



Scheme 105

Amino-aza-fluorenones, containing 2-aminopyridine structural motif, have received increasing interest in recent years. Many of the synthetic and natural amino-aza-fluorenones displayed interesting properties and are present in a variety of pharmacophores¹¹⁷ and chromophores.¹¹⁸ As depicted in Scheme 106, 2-azafluorenone **I** is an antagonist of the

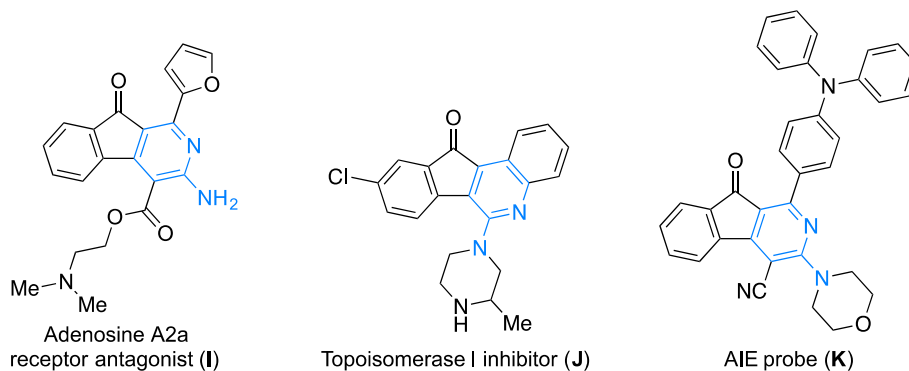
¹¹⁵ Daka, P.; Xu, Z.; Alexa, A.; Wang, H. *Chem. Commun.* **2011**, 47, 224.

¹¹⁶ Schramm, O. G.; Dediu, N.; Oeser, T.; Müller, T. J. J. *J. Org. Chem.* **2006**, 71, 3494.

¹¹⁷ (a) Heintzelman, G. R.; Bullington, J. L.; Rupert, K. C. *PCT Int. Appl. WO 2005042500 A1 20050512*, **2005**. (b) Chen, T.-C.; Yu, D.-S.; Chen, S.-J.; Chen, C.-L.; Lee, C.-C.; Hsieh, Y.-Y.; Chang, L.-C.; Guh, J.-H.; Lin, J.-J.; Huang, H.-S. *Arab. J. Chem.* **2016**. DOI: 10.1016/j.arabjc.2016.06.014.

¹¹⁸ (a) Landmesser, T.; Linden, A.; Hansen, H.-J. *Helv. Chim. Acta* **2008**, 91, 265. (b) Gao, M.; Su, H.; Lin, Y.; Ling, X.; Li, S.; Qin, A.; Tang, B. Z. *Chem. Sci.* **2017**, 8, 1763.

Adenosine A2a receptor;^{117a} piperazinyl derived compound **J** which exhibits inhibitory effect on topoisomerase I would be a potent anti-breast cancer candidate;^{117b} 2-azafluorenone **K** with typical aggregation-induced emission (AIE) properties can be used for lipid droplet-specific live cell imaging.^{118b}



Scheme 106

2. Synthetic methods for the preparation of 2-aminopyridines

2.1 Traditional methods

The preparation of 2-aminopyridines has been reported with numerous strategies. For example, Chichibabin reactions start from pyridine and sodium amide,¹¹⁹ Buchwald-Hartwig amination¹²⁰ and Ullmann coupling reactions¹²¹ of halopyridines with primary or secondary amines, one-pot three-component cascade reaction¹¹⁶ using *N*-tosyl propargyl amines, aryl halides, and *N,S*-ketene acetals, formal [2+2+1+1] cycloaddition reaction¹²² of aldehydes with ketones, and malononitrile (Scheme 107). However, these methods were efficient to access simple 2-aminopyridines, but for more complex substitution patterns, additional synthetic

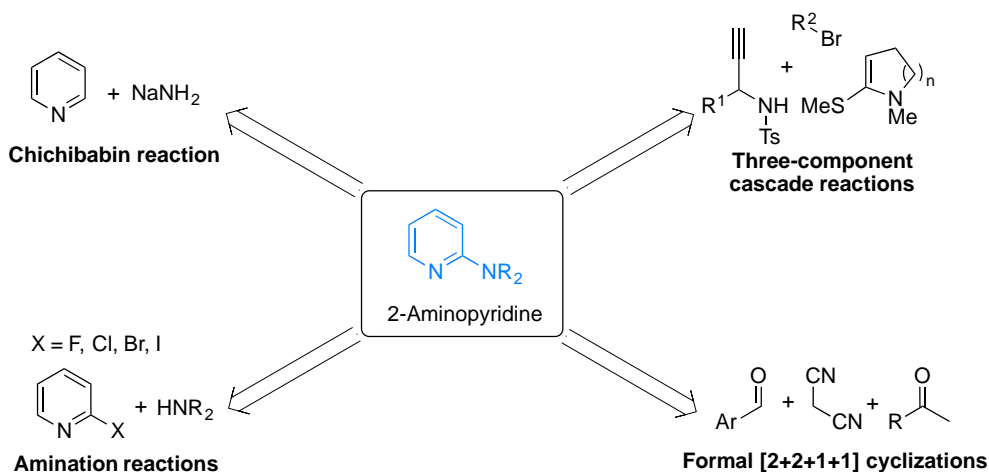
¹¹⁹ (a) Chichibabin, A. E.; Zeide, O. A. *J. Russ. Phys. Chem. Soc.* **1914**, *46*, 1216. (b) Chichibabin, A. E.; Zeide, O. A. *Ber. Dtsch. Chem. Ges.* **1923**, *56B*, 1879.

¹²⁰ (a) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240. (b) Patriciu, O. I.; Finaru, A. L.; Massip, S.; Léger, J. M.; Jarry, C.; Guillaumet, G. *Eur. J. Org. Chem.* **2009**, *22*, 3753. (c) Shen, Q.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 4109. (d) Lorimer, A. V.; O'Connor, P. D.; Brimble, M. A. *Synthesis* **2008**, 2764.

¹²¹ (a) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742. (b) Liu, Z.; Vors, J.; Gesing, E. R. F.; Bolm, C. *Adv. Synth. Catal.* **2010**, *352*, 3158.

¹²² (a) Teague, S. J. *J. Org. Chem.* **2008**, *73*, 9765. (b) Ranu, B. C.; Jana, R.; Sowmiah, S. *J. Org. Chem.* **2007**, *72*, 3152.

manipulations were required. In addition, these reactions suffered more or less from some shortcomings such as harsh reaction conditions, multistep procedures, limited functionalities tolerance, etc.



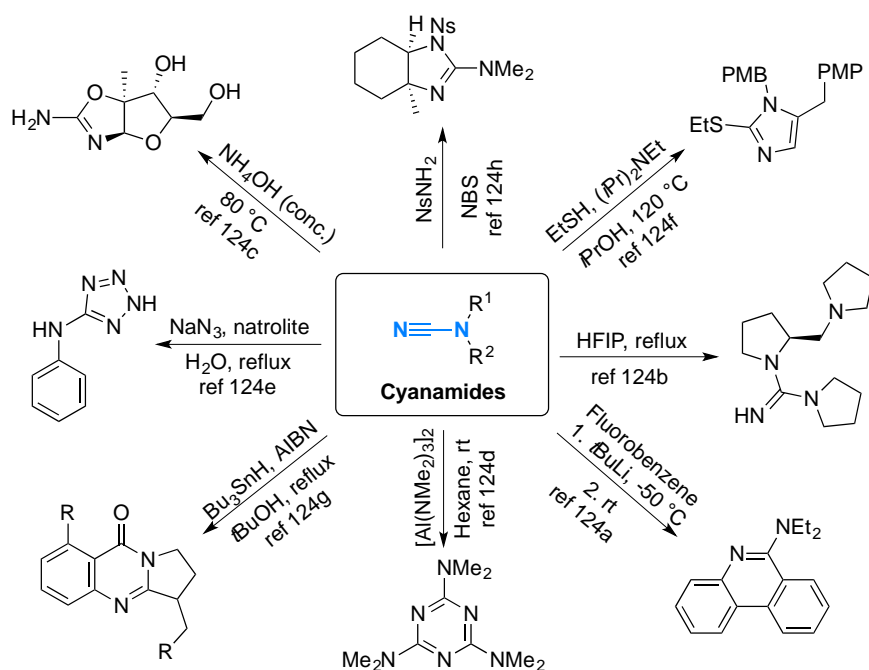
Scheme 107

2.2 Transition-metal-catalyzed [2+2+2] cycloadditions of alkynes with cyanamides

Cyanamide derivatives moiety are widely present in pharmaceutical molecules and bioactive compounds.¹²³ Owing to the high reactivity of the electron-rich nitrile triple bonds, bearing an amine group at the α -position of nitrile (R_2N-CN), these privileged structures serve as versatile building blocks and have been widely used for the synthesis of various nitrogen-containing heterocycles,¹²⁴ as shown in Scheme 108.

¹²³ (a) Kumar, R.; Rai, D.; Sharma, S. K.; Saffran, H. A.; Blush, R.; Tyrrell, D. L. *J. Med. Chem.* **2001**, *44*, 3531. (b) Larraufie, M.-H.; Maestri, G.; Malacria, M.; Ollivier, C.; Fensterbank, L.; Lacôte, E. *Synthesis* **2012**, *44*, 1279. (c) Carta, F.; Akdemir, A.; Scozzafava, A.; Masini, E.; Supuran, C. T. *J. Med. Chem.* **2013**, *56*, 4691. (d) Yu, J.-T.; Teng, F.; Cheng, J. *Adv. Synth. Catal.* **2017**, *359*, 26.

¹²⁴ (a) Pawlas, J.; Begtrup, M. *Org. Lett.* **2002**, *4*, 2687. (b) Köhn, U.; Klopffleisch, M.; Görls, H.; Anders, E. *Tetrahedron Asymmetry* **2006**, *17*, 811. (c) Jenkinson, S. F.; Jones, N. A.; Moussa, A.; Stewart, A. J.; Heinz, T.; Fleet, G. W. *J. Tetrahedron Lett.* **2007**, *48*, 4441. (d) Dornan, P.; Rowley, C. N.; Priem, J.; Barry, S. T.; Burchell, T. J.; Woo, T. K.; Richeson, D. S. *Chem. Commun.* **2008**, *31*, 3645. (e) Nasrollahzadeh, M.; Habibi, D.; Shahkarami, Z.; Bayat, Y. *Tetrahedron* **2009**, *65*, 10715. (f) Giles, R. L.; Nkansah, R. A.; Looper, R. E. *J. Org. Chem.* **2010**, *75*, 261. (g) Larraufie, M.-H.; Courillon, C.; Ollivier, C.; Lacôte, E.; Malacria, M.; Fensterbank, L. *J. Am. Chem. Soc.* **2010**, *132*, 4381. (h) Zhou, L.; Chen, J.; Zhou, J.; Yeung, Y.-Y. *Org. Lett.* **2011**, *13*, 5804.

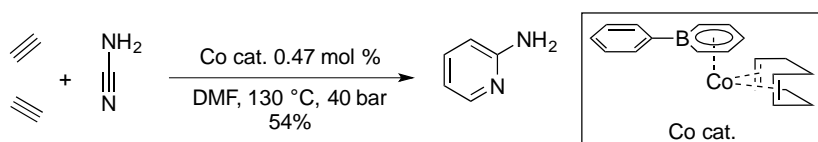


Scheme 108

Particularly, cyanamides also proved to be good partners for the transition-metal-catalyzed [2+2+2] cycloaddition which has been reported as a powerful and atom-economical method for the construction of highly substituted 2-aminopyridines. The following discussion will focus on the [2+2+2] cycloaddition reactions involving the most common used cobalt, rhodium, nickel, iron, iridium and ruthenium complexes.

2.2.1. Cobalt-catalyzed [2+2+2] cycloadditions

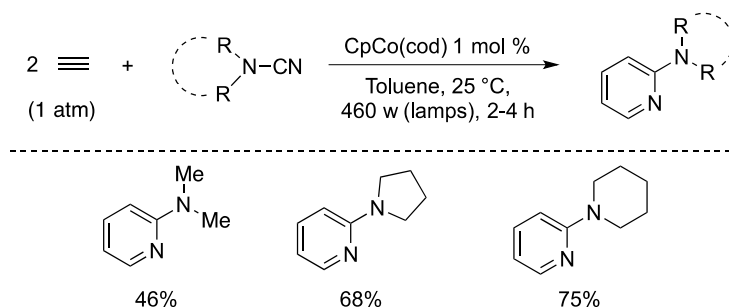
In 1984, Bönnemann and co-workers disclosed the first cobalt-catalyzed [2+2+2] cycloaddition of acetylene and cyanamide to form 2-aminopyridine containing a free amino group using (η^6 -boranato)cobalt as catalyst. The reaction was successfully performed at 130 °C under 40 bar to afford 2-aminopyridine in 54% yield (Scheme 109).¹²⁵



Scheme 109

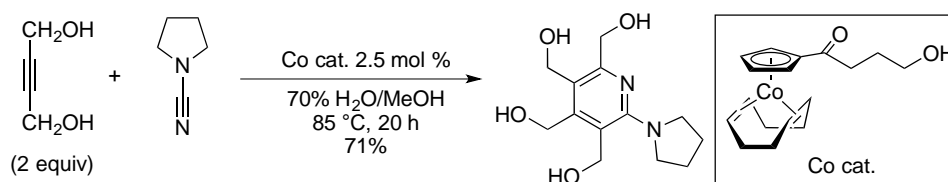
¹²⁵ Bönnemann, H.; Brijoux, W.; Brinkmann, R.; Meurers, W. *Helv. Chim. Acta* **1984**, *67*, 1616.

After the pioneer work reported by Bönemann, Heller and co-workers described the co-trimerization of acetylene with dimethyl-, pyrrolidinyl-, piperidinyl-substituted cyanamides in the presence of CpCo(cod) catalyst under photo-irradiation conditions at room temperature (Scheme 110).¹²⁶ The reaction afforded the corresponding 2-aminopyridines respectively in 46%, 68%, and 75% yields. Notably, in this case, the acetylene gas was delivered at constant normal pressure.



Scheme 110

In 2000, Eaton and co-workers reported one example of cyclotrimerization of 2-butyne-1,4-diol with *N*-cyanopyrrolidine to afford a highly functionalized pyridine in 71% yield.¹²⁷ This reaction presented many advantages including the use of a water-soluble cobalt(I) complex as catalyst, without the need of photochemical activation, only a stoichiometric amount of nitrile (alkyne:nitrile = 2:1) was required (Scheme 111).



Scheme 111

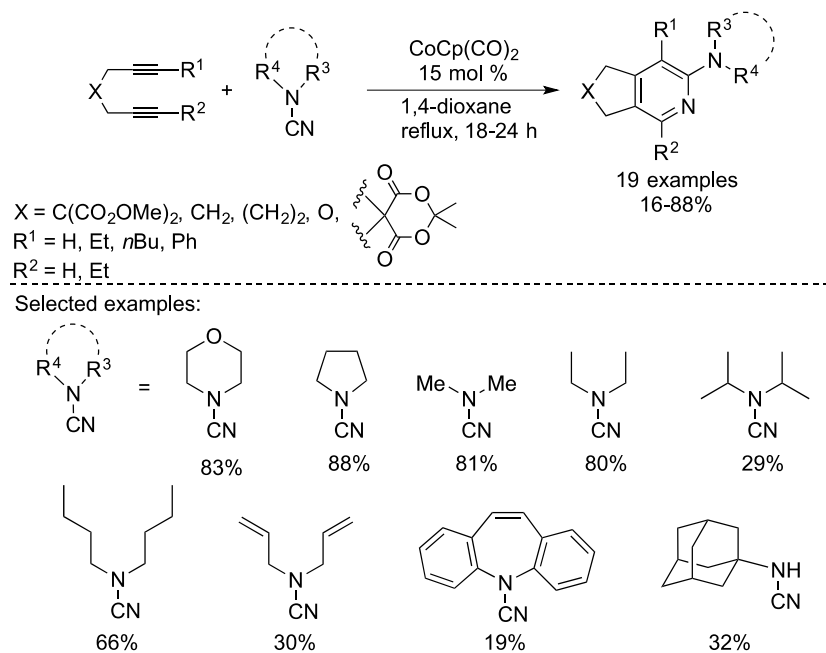
In 2004, Maryanoff's group described the preparation of bicyclic 2-aminopyridine derivatives starting from α,ω -diynes and cyanamides.¹²⁸ A variety of diynes and *N*-substituted cyanamides underwent cycloadditions in the presence of 15 mol % of CpCo(CO)₂ catalyst in

¹²⁶ (a) Heller, B.; Reihsig, J.; Schulz, W.; Oehme, G. *Appl. Organomet. Chem.* **1993**, 7, 641. (b) Heller, B.; Sundermann, B.; Buschmann, H.; Drexler, H.-J.; You, J.; Holzgrabe, U.; Heller, E.; Oehme, G. *J. Org. Chem.* **2002**, 67, 4414.

¹²⁷ Fatland, A. W.; Eaton, B. E. *Org. Lett.* **2000**, 2, 3131.

¹²⁸ Boñaga, L. V. R.; Zhang, H.-C.; Maryanoff, B. E. *Chem. Commun.* **2004**, 2394.

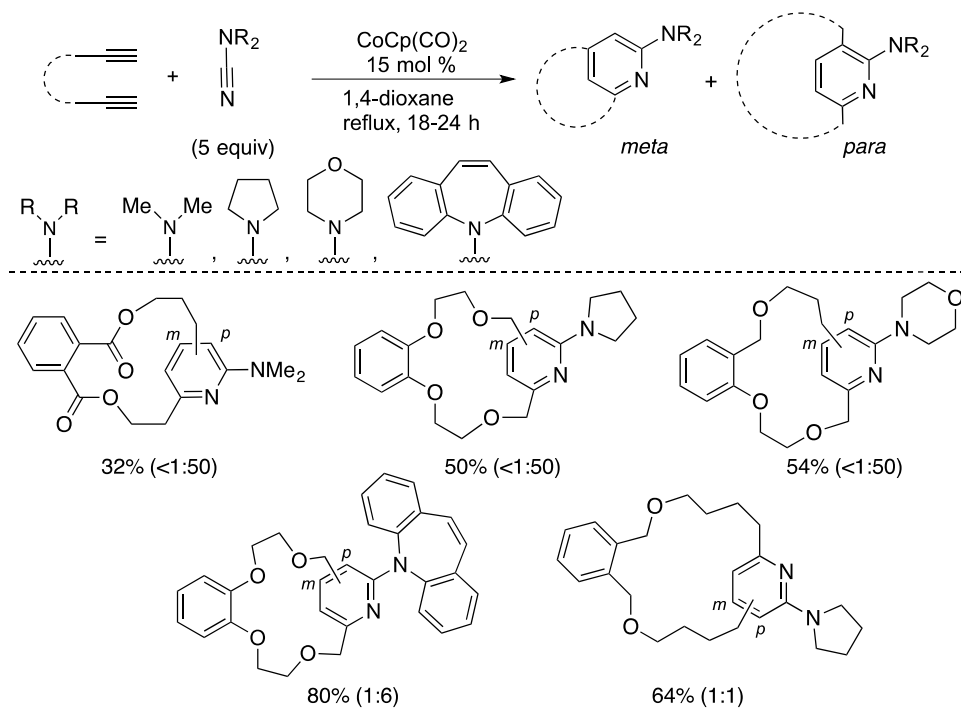
refluxing dioxane, providing the corresponding bicyclic 2-aminopyridines in a range of 16% to 88% yield. Cyanamides disubstituted with alkyl, allyl, and aryl groups furnished the annulated compounds in 19-88% yields. The cyanamides possessing a large dibenzazepinyl group showed lower reactivity, and gave the cycloadduct in 19% yield. The cycloaddition of a bulky adamantyl-substituted cyanamide led to the corresponding 2-aminopyridine with a secondary amine group in 32% yield (Scheme 112).



Scheme 112

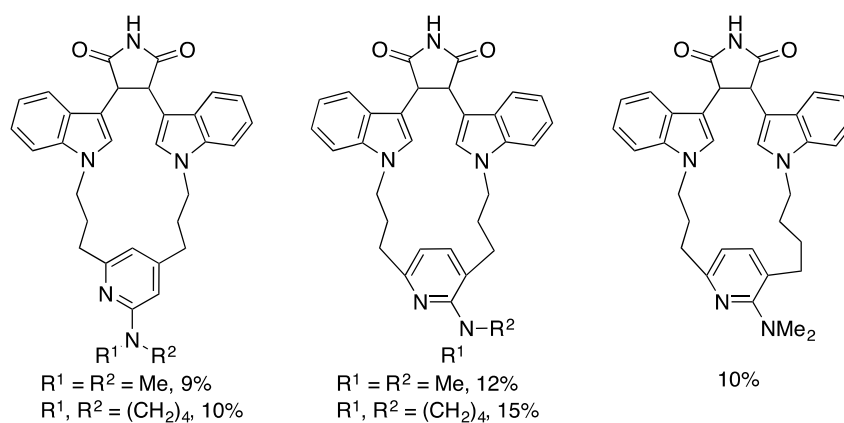
The same group also investigated in 2005 the formation of macrocycles from long-chain diynes and cyanamides in cobalt-mediated [2+2+2] cycloaddition reactions.¹²⁹ The reaction of 1,15-diynes with cyanamides provided mainly the corresponding 16-membered *para*-pyridinophanes in 32-80% yields, whereas the reaction of 1,17-diyne furnished a mixture of both 17-membered *meta*- and 18-membered *para*-pyridinophanes in 64% yield. These results indicated that the regioselectivity of the reactions was affected by the length and the type of linker unit between the alkyne groups (Scheme 113).

¹²⁹ Boñaga, L. V. R.; Zhang, H.-C.; Moretto, A. F.; Ye, H.; Gauthier, D. A.; Li, J.; Leo, G. C.; Maryanoff, B. E. *J. Am. Chem. Soc.* **2005**, *127*, 3473.



Scheme 113

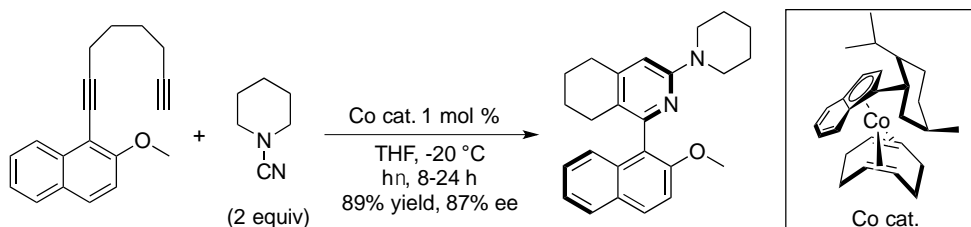
In 2007, Maryanoff and co-workers applied this method employing CpCo(CO)₂ catalyst system for the synthesis of macrocyclic (17-20 members) bis(indolyl)maleimide pyridinophanes, although lower isolated yields (9-15%) were observed (Scheme 114). The biological results indicated that these macrocyclic heterophanes were potent and selective inhibitors of glycogen synthase kinase-3 β .¹³⁰



Scheme 114

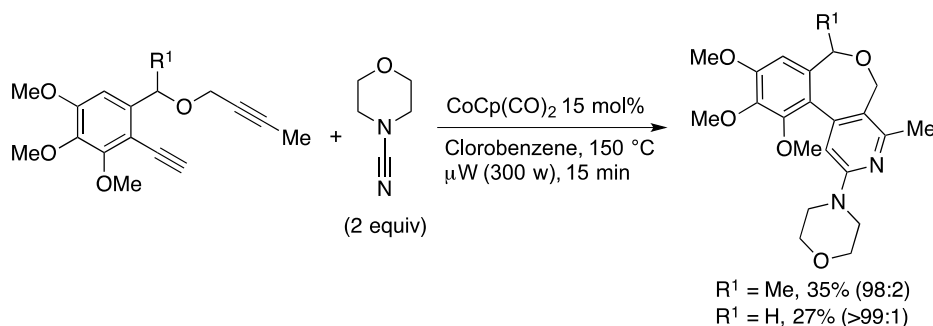
¹³⁰ Zhang, H.-C.; Boñaga, L. V. R.; Ye, H.; Derian, C. K.; Damiano, B. P.; Maryanoff, B. E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2863.

One example of the synthesis of axially chiral biaryl containing 2-aminopyridine moiety was achieved.¹³¹ The use of chiral cobalt(I) catalyst for the enantioselective [2+2+2] cycloaddition of naphthyl-substituted 1,7-diyne with *N*-cyanopiperidine gave the expected biaryl cycloadduct in 89% yield with 87% enantioselectivity (Scheme 115).



Scheme 115

A quick access to allocolchicine analogues was developed by Schmalz and Nicolaus.¹³² In the presence of 20 mol % $\text{CpCo}(\text{CO})_2$ under microwave conditions at 150 °C, the 3,4,5-trimethoxybenzaldehyde and 3,4,5-trimethoxyacetophenone derived diynes reacted with morpholine-4-carbonitrile to generate the desired products in a short reaction time with 27% and 35% yields, and regioselectivities up to >99:1 were obtained (Scheme 116).



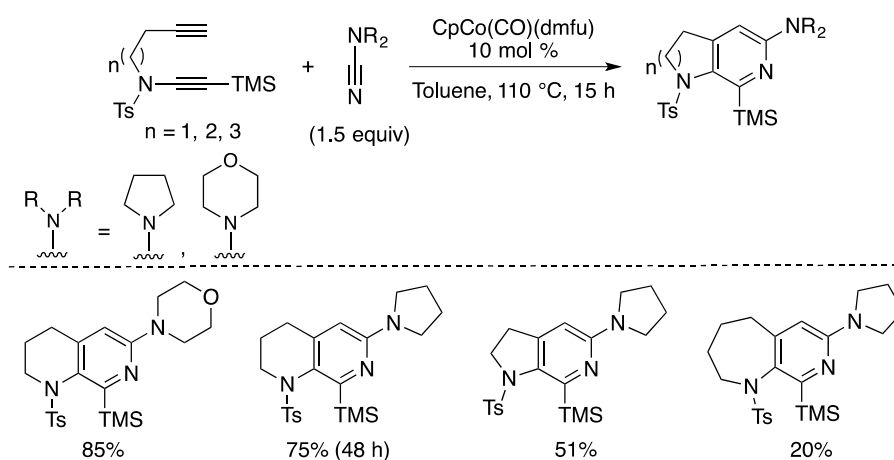
Scheme 116

Malacria, Aubert, Gandon and co-workers reported the $\text{CpCo}(\text{CO})(\text{dmfu})$ complex-catalyzed [2+2+2] cycloaddition of yne-ynamides with cyanamides to provide 2,5-

¹³¹ Hapke, M.; Kral, K.; Fischer, C.; Spannenberg, A.; Gutnov, A.; Redkin, D.; Heller, B. *J. Org. Chem.* **2010**, *75*, 3993.

¹³² Nicolaus, N.; Schmalz, H.-G. *Synlett* **2010**, 2071.

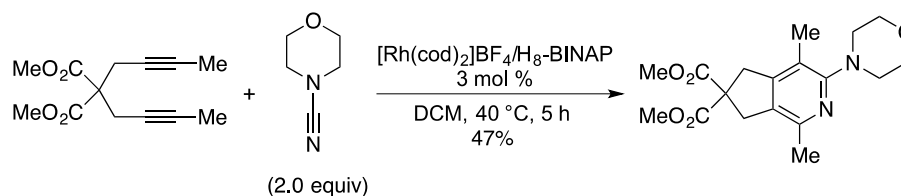
diaminopyridine derivatives.¹³³ Five-, six-, and seven-membered bicyclic compounds were synthesized in 20-85% yields with perfect regioselectivities (Scheme 117).



Scheme 117

2.2.2. Rhodium-catalyzed [2+2+2] cycloadditions

As described in the first chapter, the cationic rhodium/bisphosphine complex is an efficient catalyst for [2+2+2] cycloaddition reactions (Schemes 24 and 25). However, only a single example was described for the synthesis of annulated 2-aminopyridine via a Rh(I)/H₈-BINAP-catalyzed [2+2+2] cycloaddition of malonate-tethered diyne with morpholine-4-carbonitrile. The corresponding cycloadduct was obtained in 47% yield (Scheme 118).¹³⁴



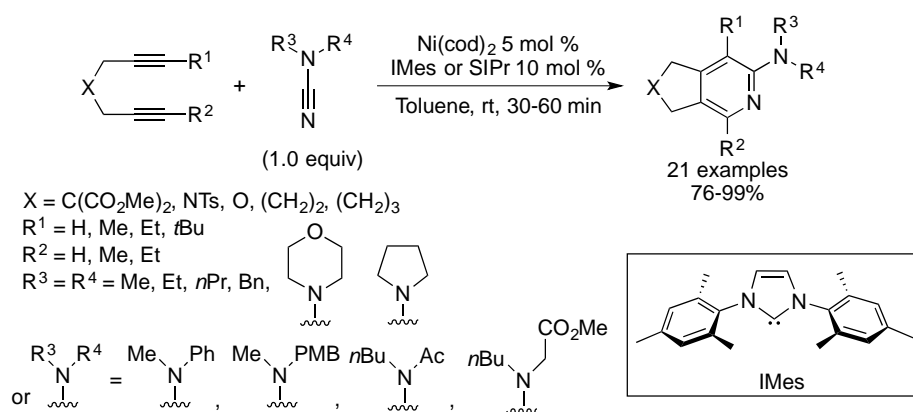
Scheme 118

¹³³ (a) Garcia, P.; Evanno, Y.; George, P.; Sevrin, M.; Ricci, G.; Malacria, M.; Aubert, C.; Gandon, V. *Org. Lett.* **2011**, *13*, 2030. (b) Garcia, P.; Evanno, Y.; George, P.; Sevrin, M.; Ricci, G.; Malacria, M.; Aubert, C.; Gandon, V. *Chem. - Eur. J.* **2012**, *18*, 4337.

¹³⁴ Tanaka, K.; Suzuki, N.; Nishida, G. *Eur. J. Org. Chem.* **2006**, 3917.

2.2.3. Nickel-catalyzed [2+2+2] cycloadditions

Louie and co-workers reported the nickel-catalyzed [2+2+2] cycloaddition of α,ω -diynes with cyanamides to form 2-aminopyridines.¹³⁵ A variety of diynes reacted with different substituted cyanamides in the presence of Ni(cod)₂ catalyst in combination with a *N*-heterocyclic carbene (NHC) at room temperature. Various 2-aminopyridines were successfully obtained in 76-99% yields (Scheme 119). However, the nickel catalyst and NHC ligands required a pre-treatment in a glove box for at least 4 hours before introducing the two reactants.

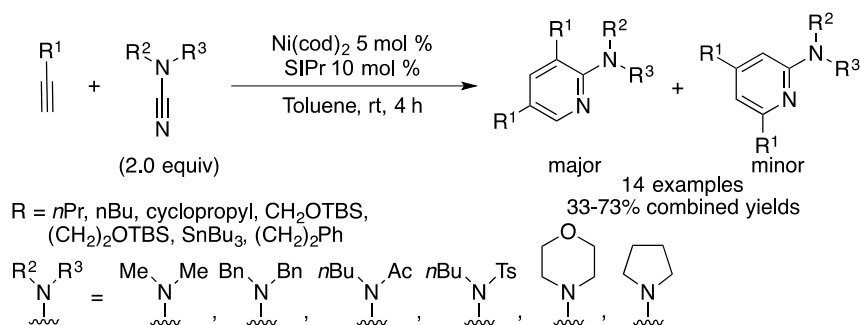


Scheme 119

This Ni/NHC catalytic system was also applied for the totally intermolecular cyclotrimerization of two alkynes with cyanamides.¹³⁶ Treatment of terminal alkynes and cyanamides with Ni(cod)₂/SIPr (1:2) complex catalyst in toluene at room temperature for 4 h, provided the 3,5-disubstituted-2-aminopyridines as the major products (Scheme 120). However, this protocol was limited to the use of alkyl-alkynes, whereas the reaction of aryl-, ester-, or chloride-substituted alkynes failed to afford the desired 2-aminopyridines.

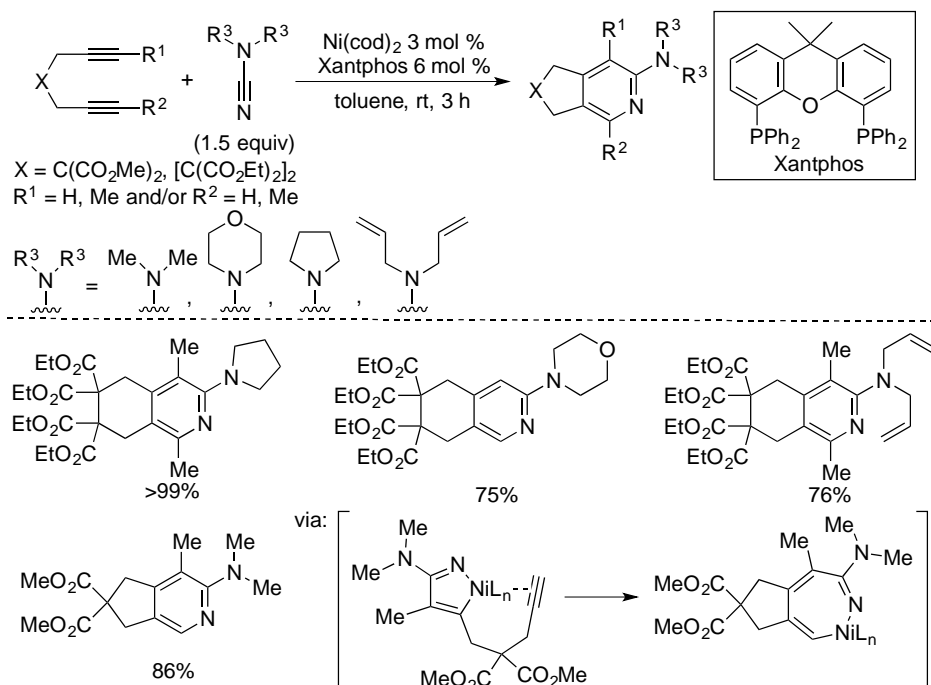
¹³⁵ (a) Stolley, R. M.; Maczka, M. T.; Louie, J. *Eur. J. Org. Chem.* **2011**, 3815. (b) Stolley, R. M.; Duong, H. A.; Louie, J. *Organometallics* **2013**, 32, 4952.

¹³⁶ Zhong, Y.; Spahn, N. A.; Stolley, R. M.; Nguyen, M. H.; Louie, J. *Synlett* **2015**, 26, 307.



Scheme 120

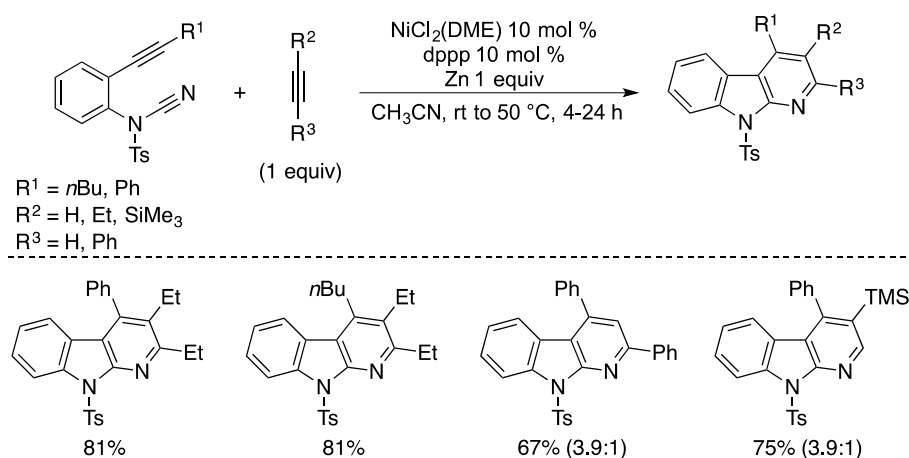
The same group also disclosed in 2011 the Ni/Xantphos-mediated cycloaddition of 1,6- and 2,7-diyne with *N*-cyanopyrrolidine, *N*-cyanomorpholine, *N,N*-diallylcyanamide at room temperature to access 6,6-fused cycloadducts in >99%, 75%, and 76% yields.¹³⁷ Interestingly, unsymmetrical 1,6-diyne reacted with *N,N*-dimethylcyanamide leading to the formation of *meta*-substituted product as a single regioisomer. This result could be explained as follow: the reaction proceeded via the initial regioselective oxidative coupling to form azametallacycle followed by the intramolecular insertion of the less-sterically demanding terminal alkyne (Scheme 121).



Scheme 121

¹³⁷ Kumar, P.; Prescher, S.; Louie, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 10694.

Liu and co-workers successfully developed in 2017 the synthesis of α -carbolines via nickel-catalyzed [2+2+2] cycloaddition of functionalized alkyne-cyanamides with alkynes.¹³⁸ Both internal and terminal alkynes successfully reacted with aryl- or alkyl substituted alkyne-cyanamides in the presence of NiCl₂(DME)/dppp/Zn catalytic system to provide α -carboline derivatives in 67-81% yields with moderate regioselectivities (Scheme 122). Interestingly, when phenyl- and TMS-substituted acetylenes were employed as the alkyne partners, the reaction resulted in the opposite regioselective formation of the cycloadduct, probably because of the difference of electronic effects between the two terminal alkynes.



Scheme 122

2.2.4. Iron-catalyzed [2+2+2] cycloadditions

Iron, the earth abundant and low cost metal, has rarely been used for the pyridines synthesis via [2+2+2] cycloadditions.¹³⁹ Louie's group described in 2012 the iron-catalyzed [2+2+2] cycloaddition of diynes with electron-rich cyanamides to form highly substituted 2-aminopyridines.¹⁴⁰ The reaction proceeded in the presence of 5 mol % FeCl₂ in combination with 10 mol % ^{Mes}PDAI and Zn dust in benzene at 70 °C, various 2-aminopyridines were synthesized in 35-97% yields. The group of Wan reported in 2013 a similar work by using FeI₂/dppp/Zn catalytic system.¹⁴¹ Several examples have been described in 40-99% yields.

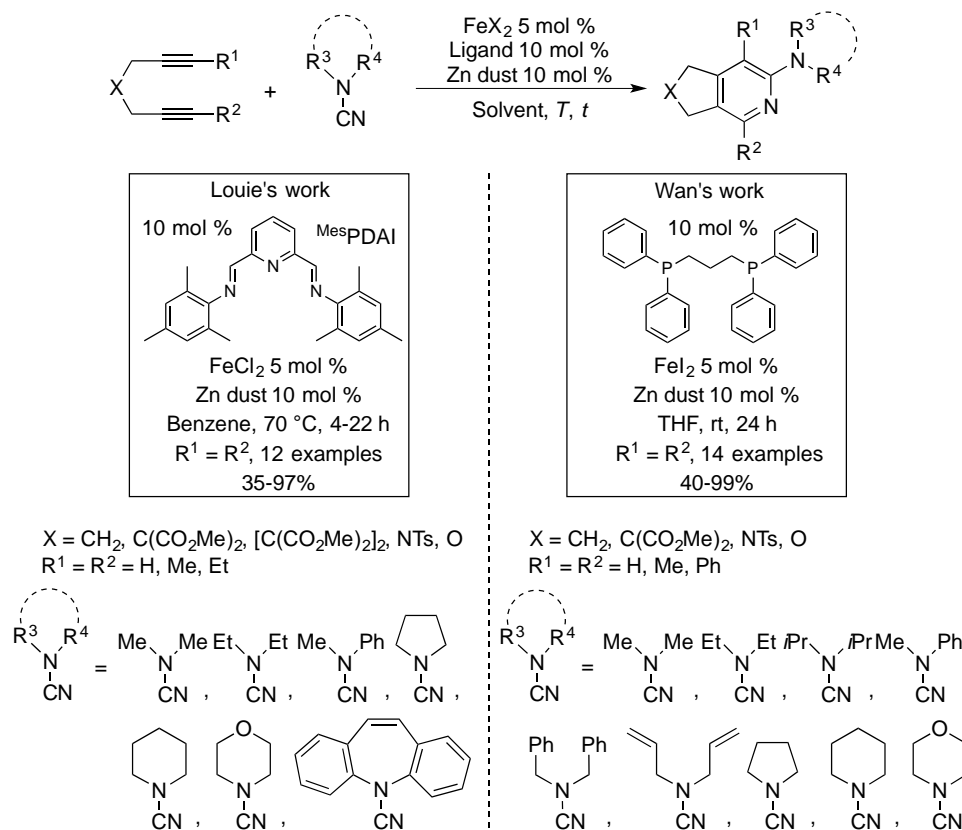
¹³⁸ Wang, G.; You, X.; Gan, Y.; Liu, Y. *Org. Lett.* **2017**, *19*, 110.

¹³⁹ (a) D' Souza, B. R.; Lane, T. K.; Louie, J. *Org. Lett.* **2011**, *13*, 2936. (b) Wang, C.; Li, X.; Wu, F.; Wan, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 7162. (c) Richard, V.; Ipouck, M.; Mérel, D. S.; Gaillard, S.; Whitby, R. J.; Witulski, B.; Renaud, J.-L. *Chem. Commun* **2014**, *50*, 593. (d) Casitas, A.; Krause, H.; Goddard, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2015**, *54*, 1521.

¹⁴⁰ Lane, T. K.; D'Souza, B. R.; Louie, J. *J. Org. Chem.* **2012**, *77*, 7555.

¹⁴¹ Wang, C.; Wang, D.; Xu, F.; Pan, B.; Wan, B. *J. Org. Chem.* **2013**, *78*, 3065.

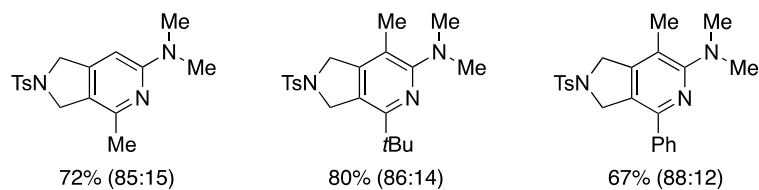
When comparing these works, Wan's group used less toxic THF as solvent instead of benzene, and lower reaction temperature (Scheme 123). However, both conditions suffered from the moisture-sensitive iron salts as well as a slow-addition technique which was required in Louie's work.



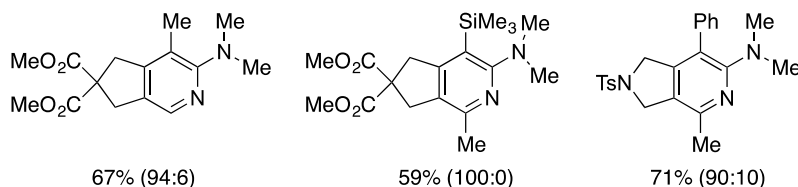
Scheme 123

With regard to the regioselectivity, the two reactions gave rise to an opposite selectivity of the regioisomers. In the case of Louie's conditions, the reaction provided the sterically less demanding compound as the major product whereas the small substituent was placed in *ortho* to the nitrile substituent. In the case of Wan's conditions, the regioselectivity trends led to the 2-aminopyridines with the small substituent placed in *ortho* to the nitrogen atom in the pyridine ring (Scheme 124). These two iron systems suggested that the regioselectivity may be controlled by the choice of the ligand.

Louie's work:

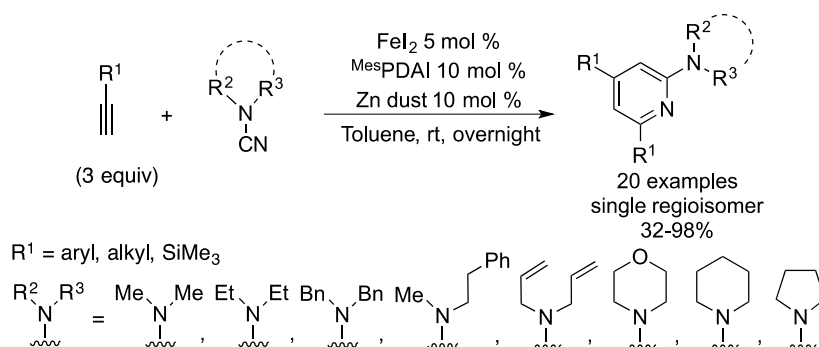


Wan's work:



Scheme 124

Furthermore, Louie and co-workers also reported the totally intermolecular iron-catalyzed [2+2+2] cycloaddition of two alkynes with cyanamides.¹⁴² In contrast to the Ni(cod)₂/SIPr system (Scheme 120), in this case, the 2,4-disubstituted-2-aminopyridines were formed as major products with complete regioselectivity (Scheme 125).



Scheme 125

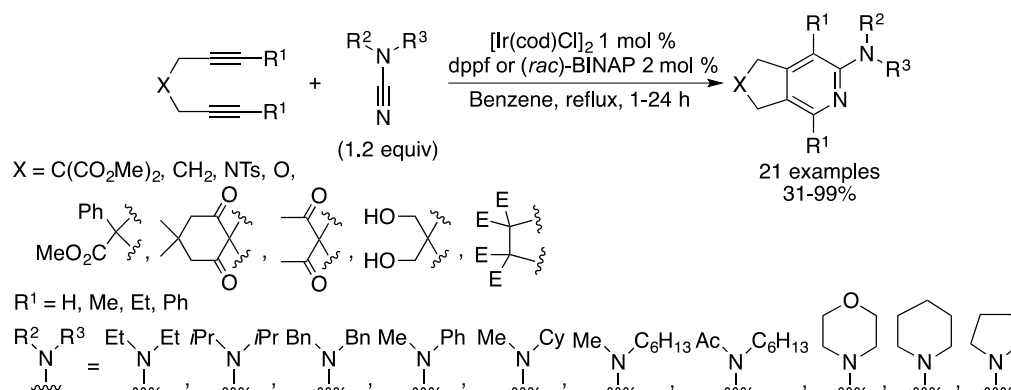
2.2.5. Iridium-catalyzed [2+2+2] cycloadditions

In 2015, Takeuchi and co-workers developed an efficient [Ir(cod)Cl]₂/dppf or BINAP catalyst system that was able to promote the [2+2+2] cycloaddition of α,ω -diynes and cyanamides in refluxing benzene.¹⁴³ A wide range of secondary amines derived cyanamides was tolerated under these reaction conditions. Several examples have been studied by using

¹⁴² Spahn, N. A.; Nguyen, M. H.; Renner, J.; Lane, T. K.; Louie, J. *J. Org. Chem.* **2017**, *82*, 234.

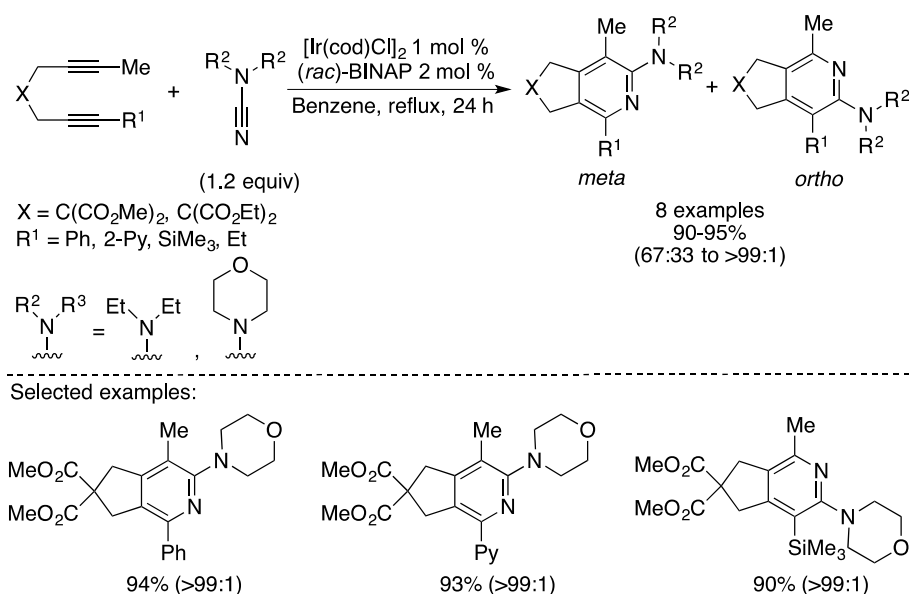
¹⁴³ Hashimoto, T.; Ishii, S.; Yano, R.; Miura, H.; Sakata, K.; Takeuchi, R. *Adv. Synth. Catal.* **2015**, *357*, 3901.

symmetrical diynes with cyanamides to provide various 2-aminopyridines in 31-99% yields (Scheme 126). However, toxic and refluxing benzene was used as solvent.



Scheme 126

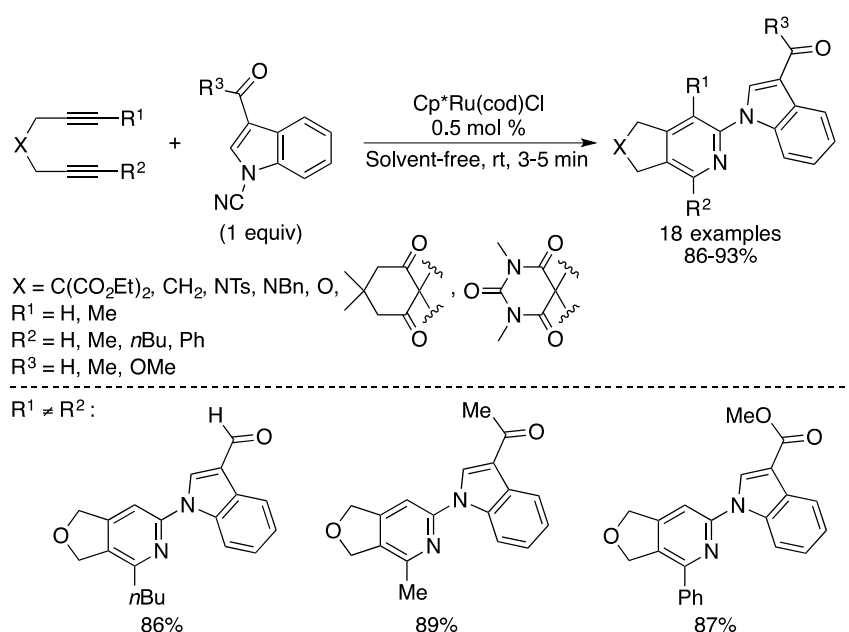
For the regioselectivity, as shown in Scheme 127, the methyl-/phenyl- or methyl-/2-pyridyl-substituted diynes reacted with *N*-cyanomorpholine, leading to the formation of less hindered product as a single product in which the phenyl and pyridyl groups were substituted at the α -position. Interestingly, the methyl/TMS-substituted diyne underwent cycloaddition reaction and gave exclusively the more sterically hindered product in which the TMS group was substituted at the β -position. The authors therefore demonstrated that the regioselectivity was mainly controlled by the electronic effect of the substituent on the terminus of alkynes.



Scheme 127

2.2.6. Ruthenium-catalyzed [2+2+2] cycloadditions

During the publication process of our work, Goswami's group reported a ruthenium-catalyzed [2+2+2] cycloaddition of *N*-cyanoindoles with α,ω -diynes to provide 1-(2-pyridyl)indole derivatives.¹⁴⁴ In this work, the reaction was performed under solvent-free or with small amount of EtOH conditions with Cp*Ru(cod)Cl catalyst for a short reaction time, providing the desired product in 86-93% yields. Three examples have been studied using monosubstituted unsymmetrical oxygen tethered diynes to evaluate the regioselectivity. The less sterically hindered products were obtained as a single regioisomer in 86-89% yields (Scheme 128). However, the scope of diynes and cyanamides were limited to eight diynes and three 3-carbonyl indoles derived cyanamides.



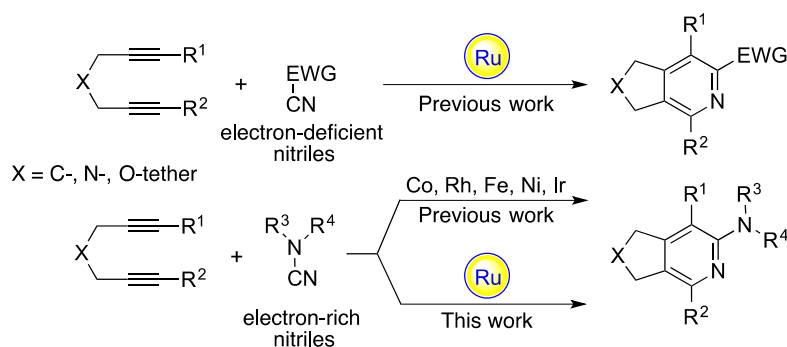
Scheme 128

3. Objectives

Ruthenium complexes have been reported as highly efficient catalysts for the cycloaddition of α,ω -diynes with activated nitriles,^{7u,7w} such as electron-deficient nitriles, dicyanides, and α -halogen nitriles. However, there was no ruthenium-catalyzed synthesis of

¹⁴⁴ Chowdhury, H.; Goswami, A. *Adv. Synth. Catal.* **2017**, 359, 314.

functionalized pyridines with electron-rich nitriles such as cyanamides that have been reported when we started this project (Scheme 129).



Scheme 129

Considering the rare reports on the transition-metal-catalyzed [2+2+2] cycloadditions of alkynes with cyanamides to access 2-aminopyridines, as well as the limitations of current methodologies, we decided to investigate the ruthenium-catalyzed [2+2+2] cycloaddition reaction to access highly substituted 2-aminopyridines and its derivatives.

4. Results and discussion

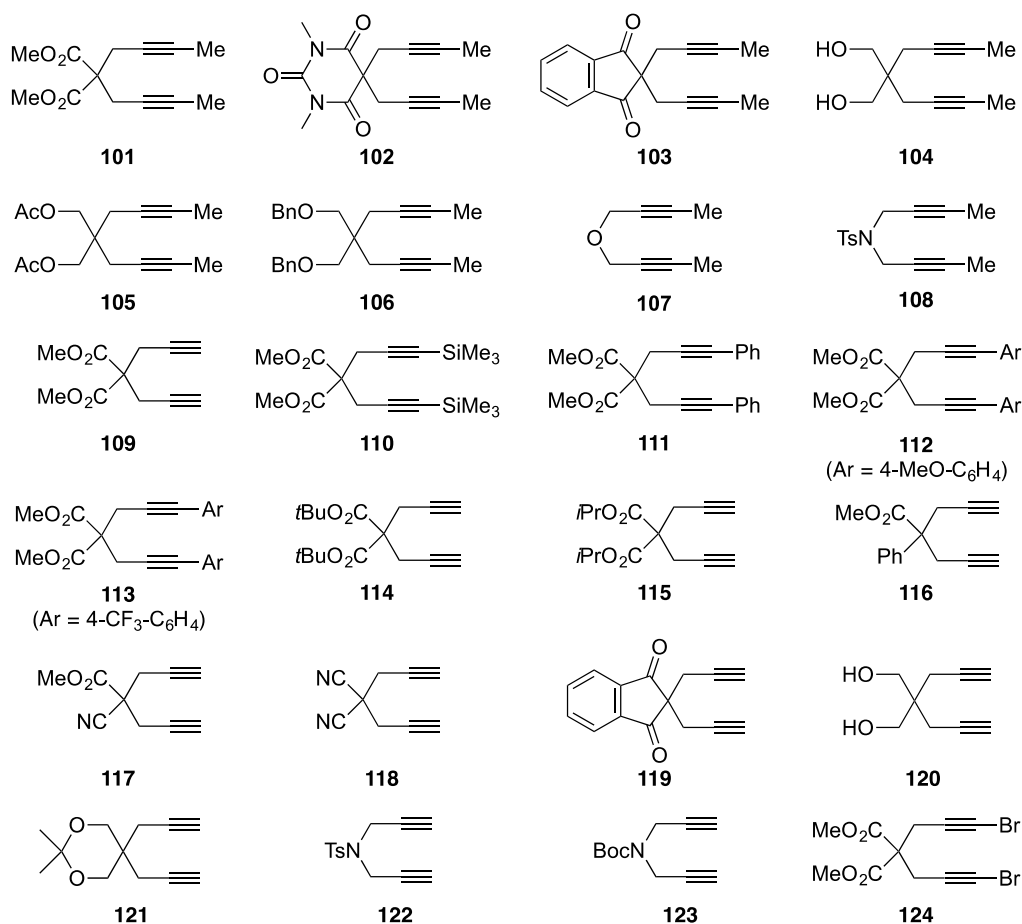
4.1 Synthesis of starting materials: diynes and cyanamides

We first decided to study the partially intramolecular [2+2+2] cycloadditions to access 2-aminopyridine derivatives using α,ω -diynes and cyanamides. Most of the starting diynes and cyanamides were not commercially available and were synthesized.

4.1.1. Synthesis of symmetrical diynes

Firstly, a series of symmetrical internal and terminal α,ω -diynes were prepared, as shown in Scheme 130. The diynes **101-110** and **121-124** were synthesized in accordance with the literature.¹⁴⁵ Diynes **111-120** were produced based on laboratory's work.

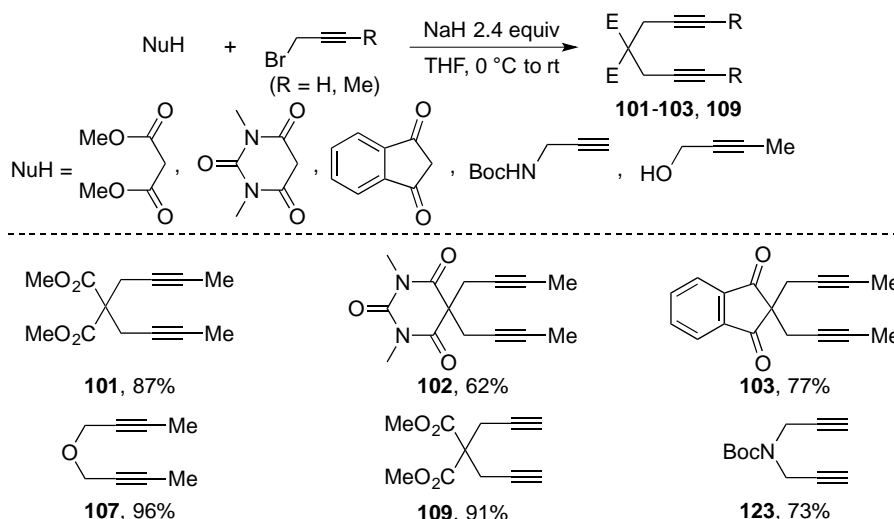
¹⁴⁵ (a) For diyne **110**, see: Ishizaki, M.; Hoshino, O. *Tetrahedron* **2000**, *56*, 8813. (b) For diynes **105** and **106**, see: Liu, C.; Widenhofer, R. A. *Organometallics* **2002**, *21*, 5666. (c) For diyne **102**, see: Genin, E.; Toullec, P. Y.; Marie, P.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. *Arkivoc* **2007**, *67*. (d) For diyne **108**, see: Sylvester, K. T.; Chirik, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 8772. (e) For diyne **103**, see: Kumar, P.; Zhang, K.; Louie, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 8602. (f) For diyne **101**, **107** and **109**, see ref 154. (g) For diyne **121**,



Scheme 130

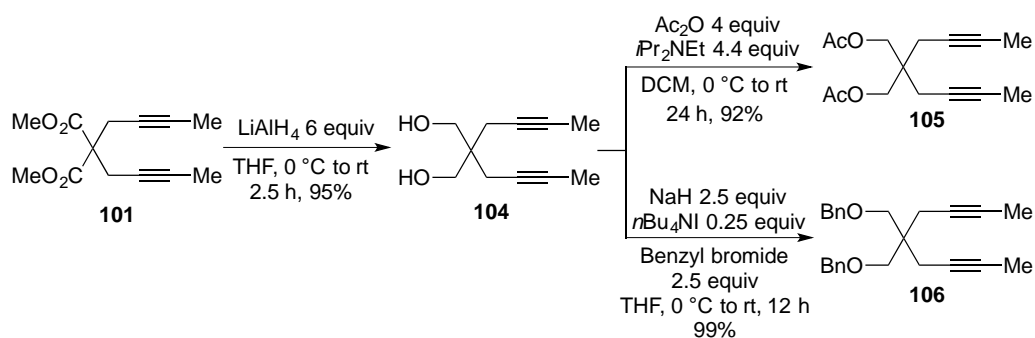
Diyne **101-103**, **107**, **109** and **123** were prepared through the nucleophilic substitution reaction of commercially available dimethyl malonate, 1,3-dimethylbarbituric acid, 2-butyn-1-ol, indene dione, and *N*-Boc-protected propargyl amine with 1.2-2.4 equivalents of propargyl bromide or 1-bromo-2-butyne in THF. The reaction used 1.5-2.4 equivalents of sodium hydride as base to afford the desired diynes in a range of 62-96% yields (Scheme 131). Notably, 1,3-dimethylbarbituric acid derived diyne **102** was a new substrate.

see: Wilking, M.; Mück-Lichtenfeld, C.; Daniliuc C. G.; Hennecke, U. *J. Am. Chem. Soc.* **2013**, *135*, 8133. (h) For diyne **104**, see ref 34. (i) For diyne **121**, see: Llerena, D.; Buisine, O.; Aubert, C.; Malacria, M. *Tetrahedron* **1998**, *54*, 9373. (j) For diyne **122**, see: Oppolzer, W.; Pimm, A.; Stammen, B.; Hume, W. E. *Helv. Chim. Acta* **1997**, *80*, 623. (k) For diyne **123**, see: Boger, D. L.; Lee, J. K.; Goldberg, J.; Jin, Q. *J. Org. Chem.* **2000**, *65*, 1467. (l) For diyne **124**, see: Bednářová, E.; Colacino, E.; Lamaty, F.; Kotora, M. *Adv. Synth. Catal.* **2016**, *358*, 1916.



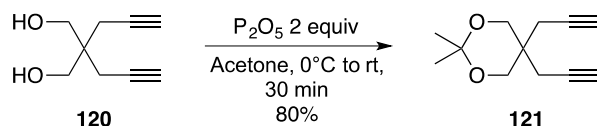
Scheme 131

Treatment of diyne **101** with 6 equivalents of LiAlH_4 in THF solution afforded the diol-diyne **104** in 95% yield. The two hydroxyl groups of diyne **104** could be easily protected with acetyl and benzyl groups under basic conditions. In the presence of 4.4 equivalents of diisopropylethylamine in DCM, diyne **104** reacted with acetic anhydride to afford diacetyl-functionalized diyne **105** in 92% yield. The nucleophilic substitution of diol **105** with benzyl bromide using 2.5 equivalents of sodium hydride as base with 25 mol % *n*-tetrabutylammonium iodide as additive, gave dibenzyl protected diyne **106** in quantitative yield (Scheme 132).



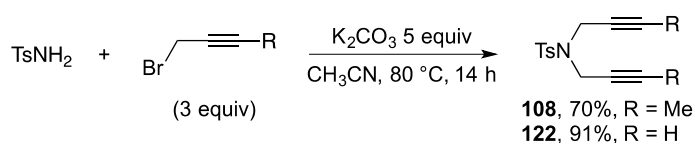
Scheme 132

The reaction of diol **120**, in the presence of 2 equivalents of phosphorus pentoxide in dry acetone at room temperature, allowed a rapid access to diyne **121** in 80% isolated yield (Scheme 133).



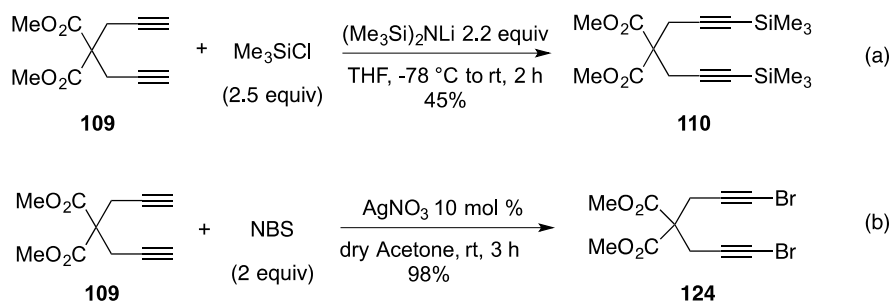
Scheme 133

The synthesis of nitrogen-tethered diynes **108** and **122** was based on the nucleophilic substitution of *p*-toluenesulfonamide with 1-bromo-2-butyne or propargyl bromide using 5 equivalents of potassium carbonate as base. The desired products could be easily synthesized in 70% and 91% yields, respectively (Scheme 134).



Scheme 134

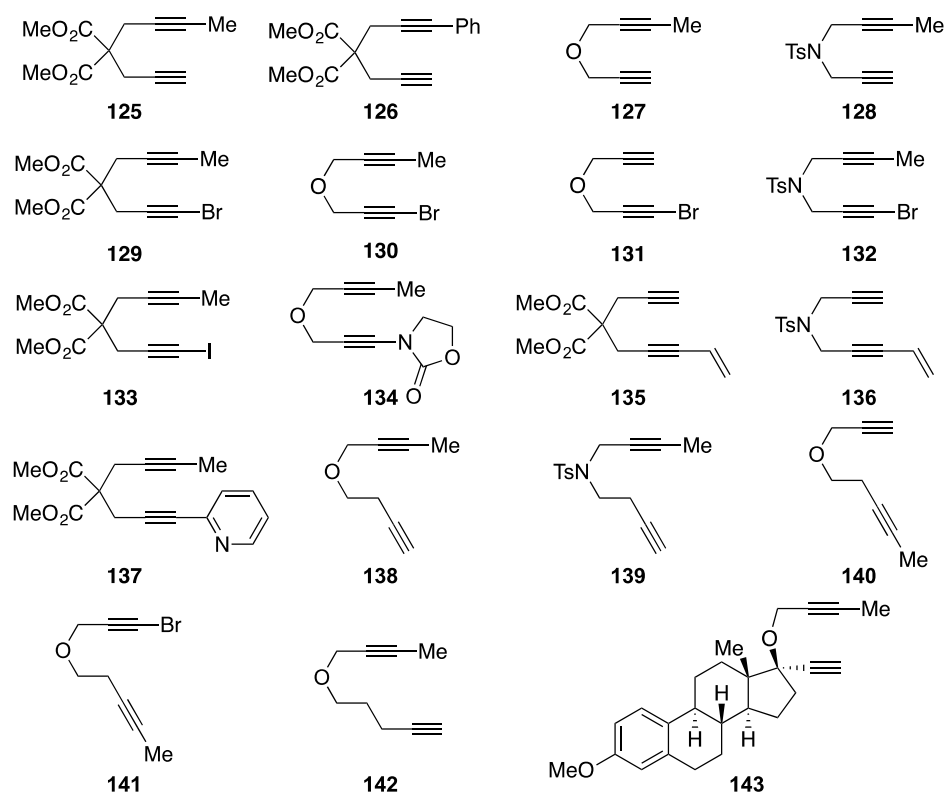
The malonate derived diynes **110** and **124**, bearing two functional groups on the terminal position of α,ω -diyne, have been synthesized (Scheme 135). Diyne **109** was treated with 2.2 equivalents of lithium bis(trimethylsilyl)amide in anhydrous THF at -78°C , followed by the addition of an excess of trimethylsilyl chloride at the same temperature. After stirring for additional 1 h at room temperature, the reaction provided the disubstituted internal alkyne **110** in 45% yield (Eq. a). The low yield could be explained by the low reactivity of the terminal position of the alkyne as well as the formation of the monosubstituted side product. Dibromo-substituted diyne **124** was prepared through a classical bromination reaction using diyne **109** and NBS, in 98% yield (Eq. b).



Scheme 135

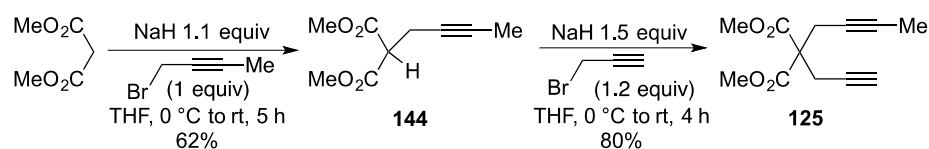
4.1.2. Synthesis of unsymmetrical diynes

To study the regioselective [2+2+2] cycloaddition reactions, we synthesized several unsymmetrical 1,6-, 1,7- and 1,8-diynes, as depicted in Scheme 136.



Scheme 136

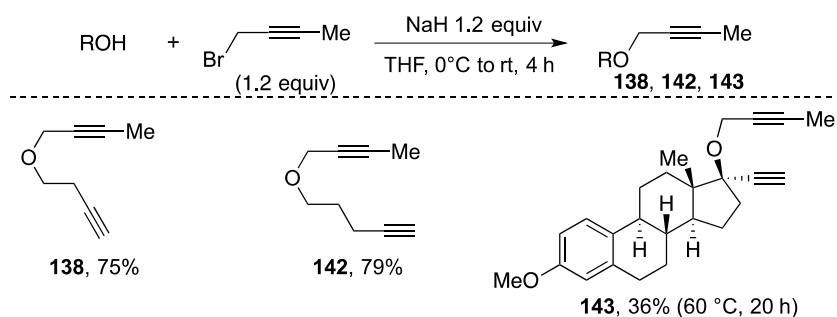
The preparation of monosubstituted unsymmetrical diyne **125** started from malonate by stepwise alkylation reactions to introduce the internal and terminal alkyne motifs. Finally, the desired product was successfully isolated in 50% yield over two steps (Scheme 137).



Scheme 137

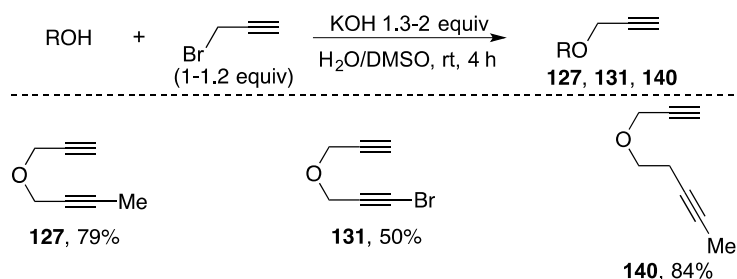
Compounds **138**, **142**, and **143** were prepared *via* nucleophilic substitution reactions. Starting from commercially available alcohols 3-butyn-1-ol, 4-pentyn-1-ol and Mestranol, the

oxygen tethered 1,6- **143**, 1,7- **138** and 1,8-diynes **142** were respectively synthesized in 36%, 75%, and 79% yields (Scheme 138).



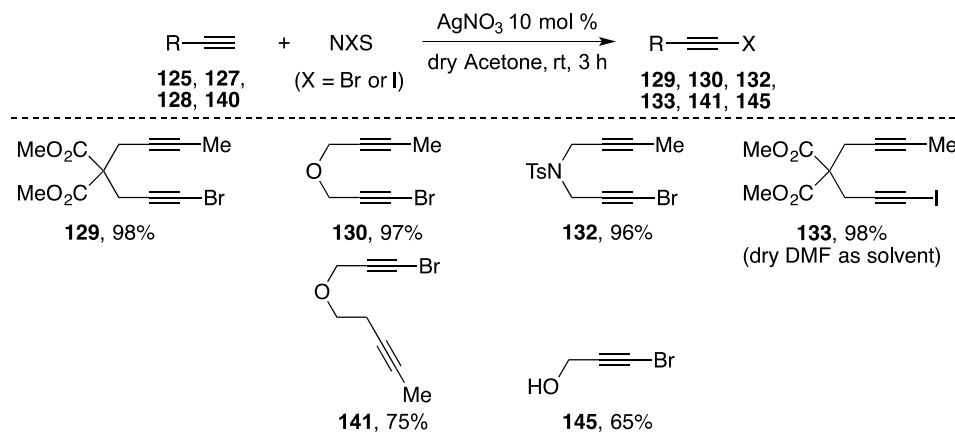
Scheme 138

To prepare the unsymmetrical oxygen tethered diynes **127**, **131** and **140** containing a propargyl motif, the nucleophilic substitution reaction was performed using potassium hydroxide as the base in a mixed solution of water and DMSO, affording **127**, **131** and **140** in respectively 79%, 50%, and 84% yields (Scheme 139).



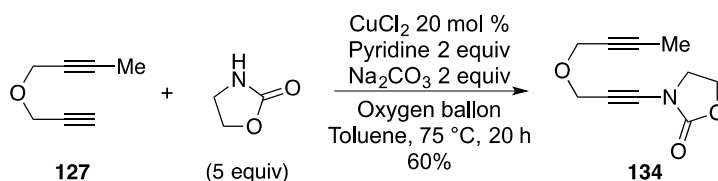
Scheme 139

Upon treatment with *N*-bromosuccinimide (NBS) in the presence of 10 mol % AgNO_3 in dry acetone at room temperature, the corresponding terminal alkynes were converted to bromo-substituted diynes **129**, **130**, **132** and **141** in 65-98% yields. The iodo-substituted diyne **133** was prepared via the silver-catalyzed *C*_{sp}-H halogenation reaction using 10 mol % AgNO_3 in *N,N*-dimethylformamide (DMF), with 98% yield. In addition, starting from propargyl alcohol, the useful intermediate bromo-substituted propargyl alcohol **145** was prepared in 65% yield (Scheme 140).



Scheme 140

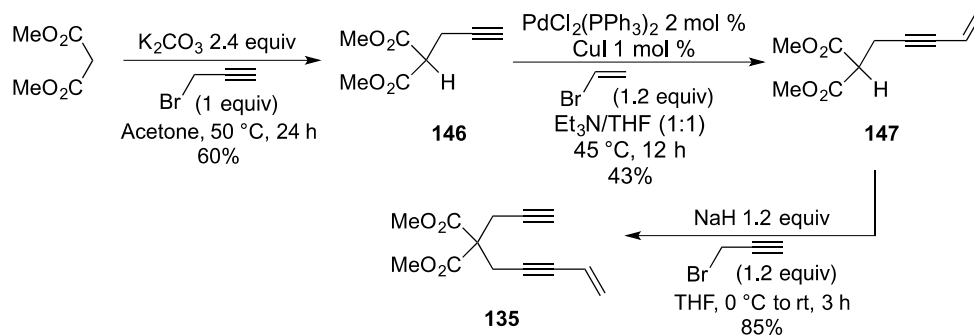
The diyne **134** containing an ynamide moiety was obtained using a copper-catalyzed aerobic oxidative coupling reaction¹⁴⁶ of terminal alkyne **127** with 2-oxazolidinone. The reaction proceeded efficiently in the presence of 20 mol % CuCl_2 and 2 equivalents of Na_2CO_3 and pyridine under 1 atm of O_2 , providing the corresponding ynamide in 60% yield (Scheme 141).



Scheme 141

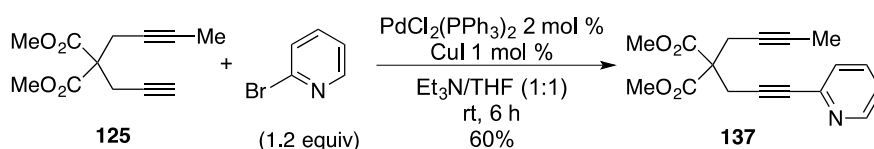
To study the tolerance ability of the [2+2+2] cycloaddition reactions, other examples were evaluated. For this purpose, the synthesis of diyne **135** containing a vinyl group was envisaged. Starting from dimethyl malonate, a mono-alkylation with 0.85 equivalents of propargyl bromide followed by a Sonogashira cross-coupling reaction with 1.2 equivalents vinyl bromide provided the malonate-derived enyne **147**. Subsequent nucleophilic substitution of the latter with 1.2 equivalents propargyl bromide in the presence of sodium hydride afforded the desired diyne **135** (Scheme 142).

¹⁴⁶ Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833.



Scheme 142

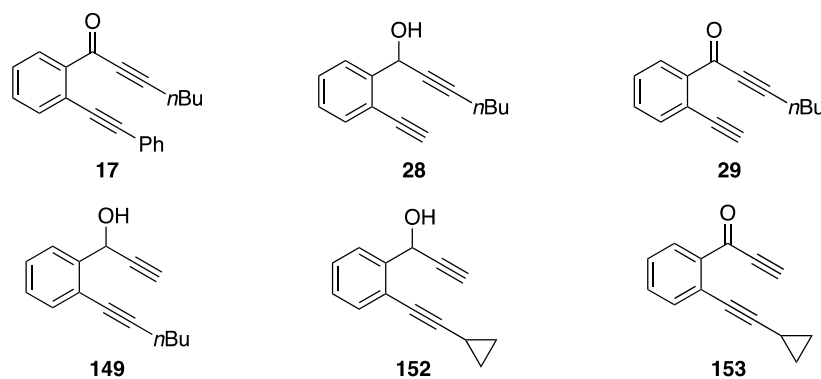
The unsymmetrical diyne **137** was prepared through a Sonogashira reaction of diyne **125** with 1.2 equivalents of 2-bromopyridine using 2 mol % $\text{PdCl}_2(\text{PPh}_3)_2$ and 1 mol % CuI , and was obtained in 60% yield (Scheme 143).



Scheme 143

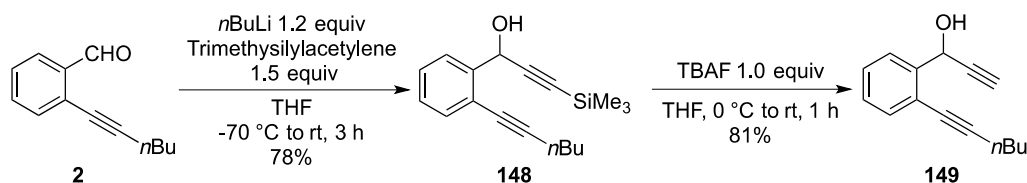
4.1.3. Synthesis of benzoyl bridged α,ω -diynes

With the aim to synthesize amino-aza-fluorenones, the preparation of benzoyl or benzyl bridged α,ω -diynes **17**, **28**, **29**, **149**, **152**, and **153** were envisaged, as shown in Scheme 144. The synthesis of diynes **17**, **28**, and **29** has been described in chapter II. Diynes **149**, **152**, and **153** were synthesized in accordance with the previously described protocols for diyne **29**.



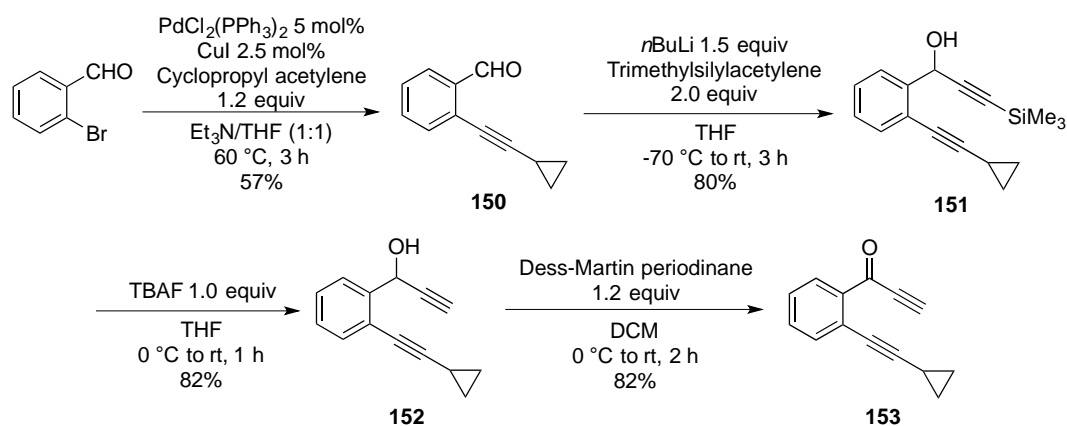
Scheme 144

The preparation of diyne **149** followed a two-steps procedure. The previously prepared monoalkyne **2** was treated with a lithium TMS-acetylide, which was prepared *in situ* from trimethylsilylacetylene and *n*-butyllithium, affording the product **148** in 78% yield. The resulting silylated alcohol **148** was subjected to deprotection using 1 equivalent of TBAF. The desired compound **149** was isolated in 81% yield (Scheme 145).



Scheme 145

The synthetic methods for preparation of **2**, **148**, and **149** were used for the preparation of compounds **150-152**, as shown in Scheme 146. Finally, treatment of the resulting diyne **152** with 1.2 equivalents of Dess-martin periodinane in dichloromethane solution, furnished the terminal diyne **153** in 82% yield.

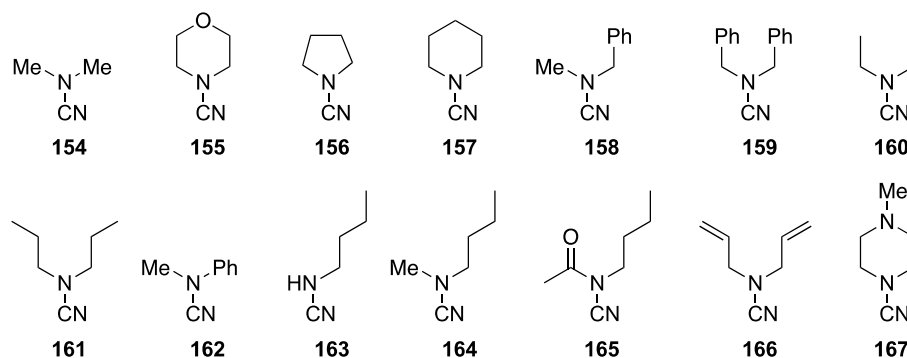


Scheme 146

4.1.4. Synthesis of cyanamides

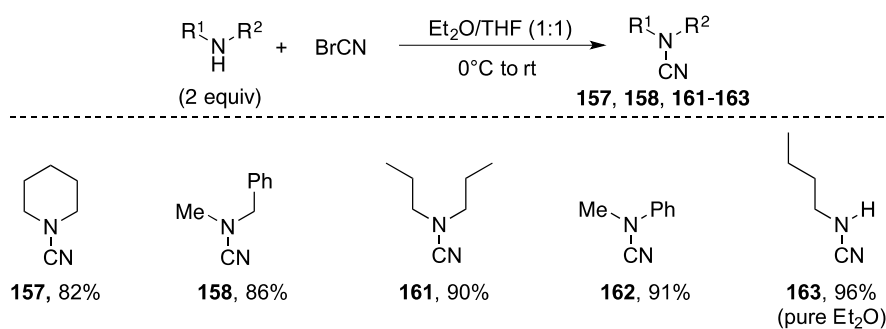
Cyanamides **154-167** that were used in this chapter are depicted in Scheme 147. The cyanamides **154-156** and **160** were commercially available. The other different *N*-substituted

cyanamides **157-159** and **161-167** were prepared according previously reported procedures,¹⁴⁷ most commonly via the electrophilic *N*-cyanation of amines using cyanogen bromide.



Scheme 147

The synthesis of cyanamides **157**, **158**, and **161-163** was achieved by the *N*-cyanation of piperidine, *N*-methylbenzylamine, *N*-methylaniline, and *n*-butylamine with cyanogen bromide in a mixture solution of diethyl ether and THF (1:1) at 0 °C. Two equivalents of amines were required to promote the reaction furnishing the desired compounds in 82-96% yields. In the case of *n*-butylamine, pure diethyl ether was used as solvent, the reaction was complete in 1 hour (Scheme 148).

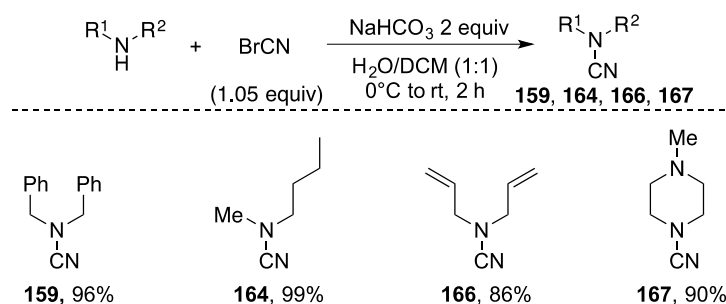


Scheme 148

Another similar protocol was used for the preparation of cyanamides **159**, **164**, **166**, and **167**. Dibenzylamine, diallylamine, *N*-methylpiperazine and *N*-methylbutylamine were treated with cyanogen bromide in a mixture solution of water and dichloromethane (1:1) at 0 °C. In this case, 2 equivalents of sodium bicarbonate were used as the base, with 1.05 equivalents of

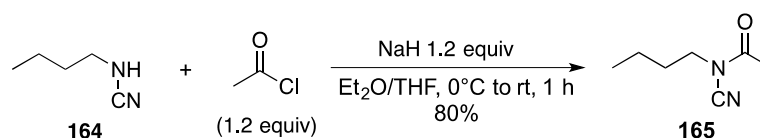
¹⁴⁷ (a) For cyanamide **161-165**, see: ref 130a. (b) For cyanamide **159**, see: Goldberg, K.; Clarke, D. S.; Scott, J. S. *Tetrahedron Lett.* **2014**, *55*, 4433.

cyanogen bromide. After 3 hours stirring at room temperature, the reaction afforded the desired products in 86-99% yields. (Scheme 149).



Scheme 149

The cyanamide **164** containing a secondary amine group could easily undergo the acetylation by using 1.2 equivalents of sodium hydride and acetyl chloride to give the acetyl-protected cyanamide **165** in 80% yield (Scheme 150).



Scheme 150

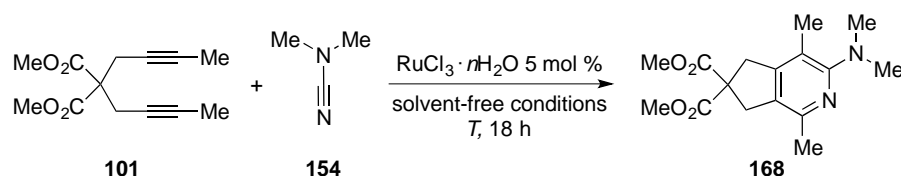
4.2 RuCl₃·nH₂O-mediated [2+2+2] cycloaddition of α,ω-diyne with cyanamides

With a series of α,ω-diyne and cyanamides in hand, we evaluated the RuCl₃·nH₂O-mediated [2+2+2] cycloaddition reactions. Based on the previous work, we used 5 mol % RuCl₃·nH₂O as catalyst to conduct the reaction under solvent-free conditions. Diyne **101** and dimethyl cyanamide **154** were chosen as model substrates to optimize the reaction conditions.

Firstly, we examined the reaction of diyne **101** with a large excess of cyanamide **154** (6 equivalents) in the presence of 5 mol % RuCl₃·nH₂O at 110 °C affording the highly substituted 2-aminopyridine **168** in 75% yield (Entry 1, Table 2). Subsequently, we decreased the amount of cyanamide from 6 to 3 equivalents. To our delight, the reaction gave almost the same isolated yield of product **168** (Entry 2). Attempt to decrease the catalyst loading to 2 mol % caused a significant decrease of the conversion (50%, Entry 3). We also evaluated the temperature effect

on the reaction. Incomplete conversion of the benzannulation was observed when the reaction was carried out at 80 °C, 50 °C, 90 °C, 100 °C (Entries 4-8). Finally, we found that the diyne **101** was fully converted to pyridine **168** in 74% yield when the amount of cyanamide **154** was further reduced to 2 equivalents (Entry 9).

Table 2 Optimization of reaction conditions



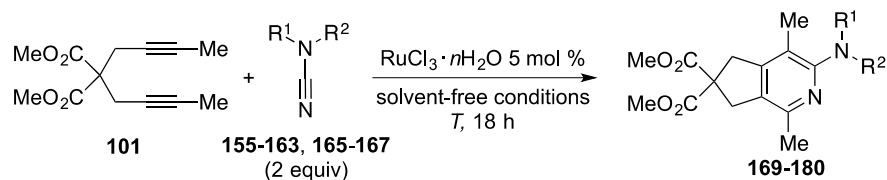
Entry	101/154	T (°C)	Conv. (%) ^b	Yield (%) ^c
1	1:6	110	>99	75
2	1:3	110	>99	76
3 ^{d,e}	1:3	110	50	nd
4	1:3	80	90	72
5	1:3	50	nr	nd
6	1:2	80	30	nd
7 ^e	1:2	90	70	nd
8 ^e	1:2	100	93	70
9	1:2	110	>99	74

^a Reaction conditions: RuCl₃ · nH₂O (0.05 mmol), diyne **101** (1.0 mmol), cyanamides **154** (2.0 mmol) were heated in a screw-capped tube under free-solvent conditions and an argon atmosphere. ^b Determined by crude ¹H NMR, nr = no reaction. ^c Isolated yields, nd = not detected. ^d 0.02 mmol of RuCl₃ · nH₂O (2 mol %) was used. ^e The reaction was stirred for 24 hours.

With a set of optimized reaction conditions in hand, we next evaluated the reactivity of various secondary or primary amines derived cyanamides **155-163** and **165-167** with diyne **101**, as shown in Table 3. We found that the [2+2+2] cycloaddition of diyne **101** with morpholine-functionalized cyanamide **155** furnished the desired pyridine **169** in excellent 95% yield, the reaction being carried out at 80 °C under solvent-free conditions (Entry 1). However, attempts to further decrease the reaction temperature to 70 °C and 60 °C, led to a decreased conversion or no reaction (Entries 2 and 3). Cyclic cyanamides *N*-cyanopyrrolidine **156** and *N*-cyanopiperidine **157** successfully reacted with diyne **101** to give the targeted heterocycles **170** and **171** in 86% and 78% yields, respectively (Entries 4 and 5). The *N*-methylbenzylcyanamide **158** reacted with diyne **101** at 80 °C to provide 2-aminopyridine **172** in 81% yield (Entry 6),

whereas the dibenzyl-substituted cyanamides **159** showed less reactivity than cyanamide **158**, despite higher temperature, furnishing the corresponding product **173** in 90% conversion and 75% isolated yield (Entry 7).

Table 3 Scope of different substituted cyanamides

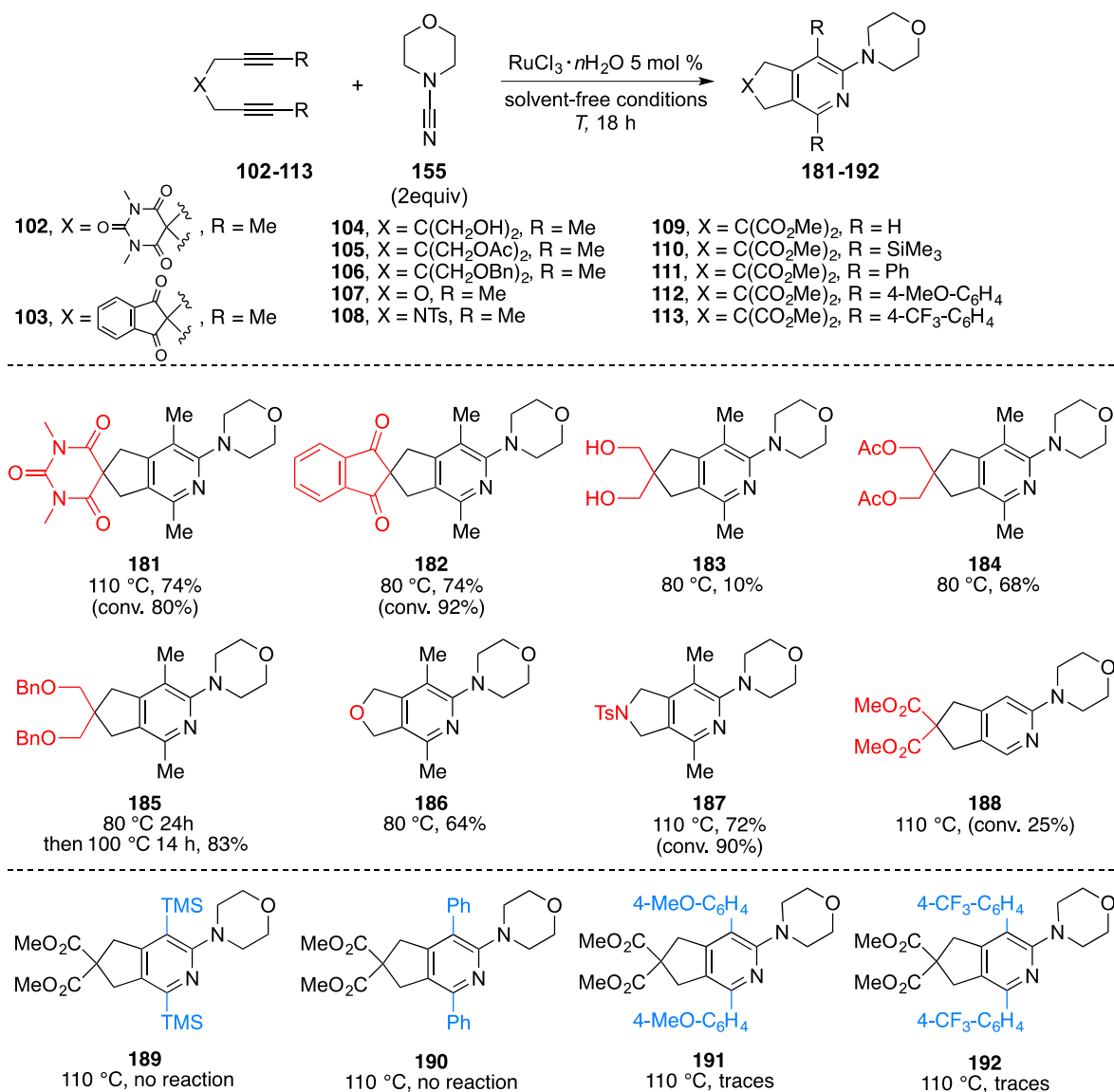


Entry	Cyanamides	T ($^{\circ}\text{C}$)	Product	Conv. (%) ^b	Yield (%) ^c
1		80	169	>99	95
2	155	70	169	95	88
3		60	169	nr	nd
4	156	80	170	96	86
5	157	110	171	>99	78
6	158	80	172	>99	81
7	159	110	173	90	75
8	160	80	174	26	nd
9	161	110	175	20	nd
10	162	80	176	22	nd
11	163	110	177	nr	nd
12	165	110	178	nr	nd
13	166	110	179	decomposed	nd
14	167	110	180	nr	nd

^a Reaction conditions: $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (0.05 mmol), diyne **101** (1.0 mmol), cyanamides **155-163** and **165-167** (2.0 mmol) were heated in a screw-capped tube under free-solvent conditions and an argon atmosphere. ^b Determined by crude ^1H NMR, nr = no reaction. ^c Isolated yields, nd = not detected.

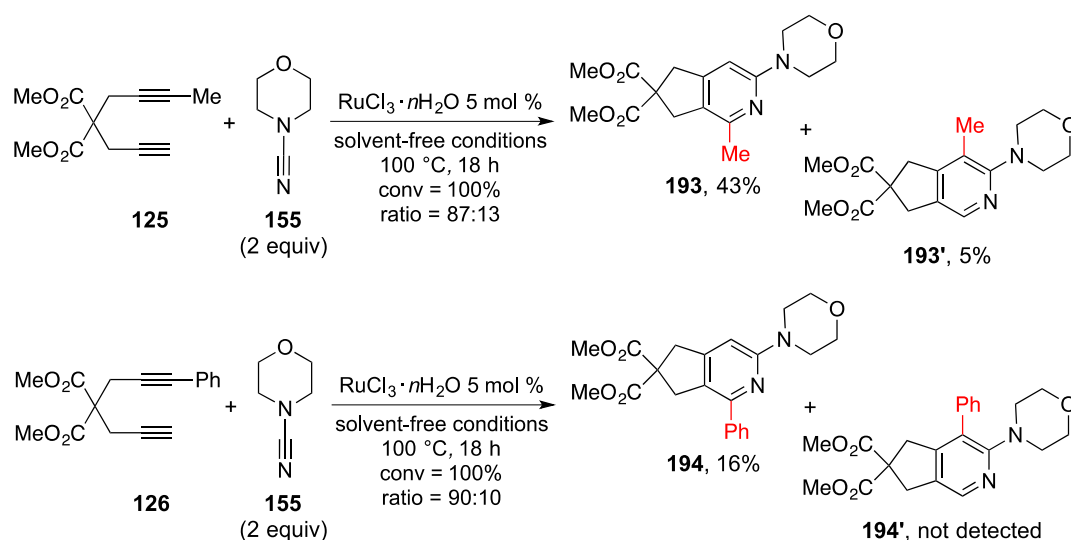
The cyanamides **160-163** and **165-167** seemed incompatible with the $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ -mediated [2+2+2] cycloaddition reaction, despite a higher temperature in some cases. Low conversion of cycloadducts was observed in the case of *N,N*-diethylcyanamide **160**, *N,N*-dipropylcyanamide **161**, and *N*-methyl-*N*-phenylcyanamide **162**, because of the lower reactivity of the alkyl substituted cyanamides (Entries 8-10, Table 3). The reaction did not occur with both unprotected *N*-butylcyanamide **163** and acetyl-protected *N*-butyl-*N*-cyanoacetamide **165** (Entries 11 and 12). *N,N*-diallylcyanamide **166**, containing two alkenes, was also evaluated and gave decomposed reaction mixtures (Entry 13), which could be explained by the competitive reaction between the activated alkenes and alkynes. *N*-methylpiperazine-derived cyanamide **167** was also employed but no reaction took place in these conditions (Entry 14).

Having evaluated the reactivity of several cyanamides, we then turned our attention to explore the scope and limitations of the reaction conditions by using the prepared symmetrical diynes **102-113** (Scheme 151), the highest reactive morpholine-4-carbonitrile **155** was chosen as the nitrile partner. The 1,3-dimethylbarbituric acid-derived diyne **102** and indene-1,3-dione-derived diyne **103** were successfully reacted with cyanamide **155** to access functionalized 2-aminopyridines **181** and **182** in good yields. The diyne **104** containing two hydroxyl groups was employed in the reaction, however, only 10% of the expected product **183** was isolated from the crude reaction mixture. Interestingly, the reaction of acetyl- (**105**) and benzyl-functionalized diynes **106** with cyanamide **155** furnished at 80 °C the corresponding 2-aminopyridines **184** and **185** in respectively 68% and 83% yields. The reaction was not limited to a quaternary-carbon tethered diyne since both oxygen- and nitrogen-tethered diynes were successfully used. The oxygen-tethered diyne **107** was converted to the corresponding oxygen fused bicyclic pyridines **186** in 64% yield. The cycloaddition of *N*-tosyl-tethered diyne **108** performed at 110 °C provided the heterocycle **187** in 72% yield. Meanwhile, we observed that the reaction was not feasible with terminal or TMS- and phenyl-substituted diynes **109-111**, despite a higher reaction temperature. The diynes **112** and **113** bearing electron-donating or electron-withdrawing aryl moieties were also unreactive under these reaction conditions, afforded only traces of **191** and **192**.



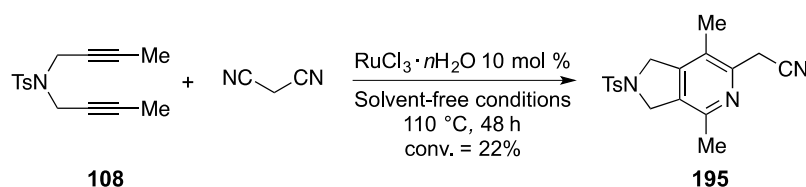
Scheme 151

Next, the regioselective of the RuCl₃·*n*H₂O-mediated [2+2+2] cycloaddition using unsymmetrical 1,6-diynes was examined. As shown in Scheme 152, the reaction of methyl-substituted unsymmetrical 1,6-diyne **125** proceeded to give **193** (major, 43%) and **193'** (minor, 5%) in 48% combined yield with 87:13 regioselectivity. The reaction of phenyl-substituted unsymmetrical 1,6-diyne **126** with cyanamide **155** also proceeded under the same conditions. However, only the major isomer **194** was isolated in 16% yield, despite a 90:10 ratio of the two regioisomers detected by crude ¹H NMR.



Scheme 152

Compared to electron-rich cyanamides, the reaction of symmetrical diyne **108** with electron-deficient nitrile such as malononitrile was also performed in the presence of $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ catalyst at 110°C to afford cycloadduct **195** with 22% conversion, although with increased catalyst loading and prolonged reaction time (Scheme 153). This result indicated that the electron-rich nitriles are more suitable with the $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ complex catalytic system.



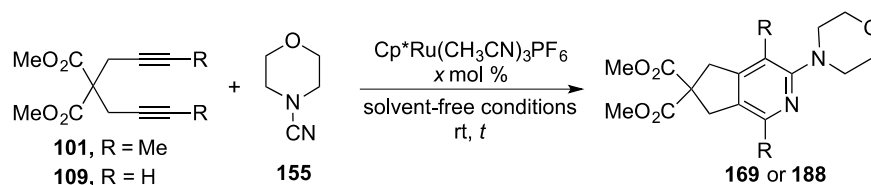
Scheme 153

The neutral $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ has therefore been successfully used for the synthesis of highly substituted 2-aminopyridine derivatives via [2+2+2] cycloaddition of α,ω -diynes with electron-rich cyanamides. A range of 2-aminopyridines has been successfully synthesized in 10-95% yields. However, the regioselective synthesis of 2-aminopyridines still remains a challenge. To address this issue, encouraged by our results with $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$, we decided to investigate the ruthenium-catalyzed [2+2+2] cycloadditions by using cationic ruthenium complex as catalyst.

4.3 Cp*Ru(CH₃CN)₃PF₆-catalyzed [2+2+2] cycloaddition of α,ω -diynes with cyanamides

Encouraged by the results obtained using the neutral RuCl₃·*n*H₂O complex for the [2+2+2] cycloaddition reaction of α,ω -diynes with cyanamides, and since the cationic ruthenium complex is known to be an efficient catalyst for [2+2+2] cycloaddition reactions,⁴⁶⁻⁵⁰ we anticipated that the cationic ruthenium complex would be a good alternative for conducting this reaction.

Initial studies were focused on the ruthenium-catalyzed [2+2+2] cycloaddition reactions between dimethyl substituted internal diyne **101** and cyanamide **155** using ruthenium complex catalyst under solvent-free conditions at room temperature. The reaction was optimized with respect to the different type of ruthenium complexes and catalyst loading, as shown in Table 4. Several ruthenium complexes were evaluated. When Ru(PPh₃)₃Cl₂ and [Ru(*p*-cymene)Cl₂]₂ were used as catalyst, no desired products were observed (Entries 1 and 2). We found that the presence of both pentamethylcyclopentadienyl (Cp*) complexes Cp*Ru(cod)Cl and Cp*Ru(CH₃CN)₃PF₆, allowed to access the desired 2-aminopyridine **169** in respectively 85% and 93% yields in a short reaction time of 5 min (Entries 3 and 4). The catalyst loading could be efficiently reduced to 2 mol % when using Cp*Ru(CH₃CN)₃PF₆ as catalyst. The reaction effectively provided the cycloadduct in 91% yield within 5 min (Entry 5). We showed that the conversion of the benzannulation was significantly diminished by lowering the catalyst loading to 1 mol % (Entry 6). In addition to the internal diyne, terminal 1,6-diyne **109** was examined under these reaction conditions. Treatment of diyne **109** with cyanamide **155** in the presence of 2 mol % Cp*Ru(CH₃CN)₃PF₆ under solvent-free conditions at room temperature provided the cycloadduct **188** in 94% yield (Entry 7). Interestingly, we found that when the reaction was conducted with a small amount of dichloromethane as solvent, the catalyst loading (1 mol %) and consumption of cyanamide (1.2 equivalents) were further reduced (Entries 7 and 8). However, lowering the catalyst loading to 0.5 mol % led to lower conversion and yield, despite longer reaction time (Entry 9). Finally, to demonstrate the applicability of our method, we performed the Ru-catalyzed cycloaddition on one-gram of 1,6-diyne **109** (Entry 10). Under the optimized solvent-free conditions in the presence of 2 mol % of Cp*Ru(CH₃CN)₃PF₆ catalyst, the corresponding 2-aminopyridine **188** was isolated in 82% yield.

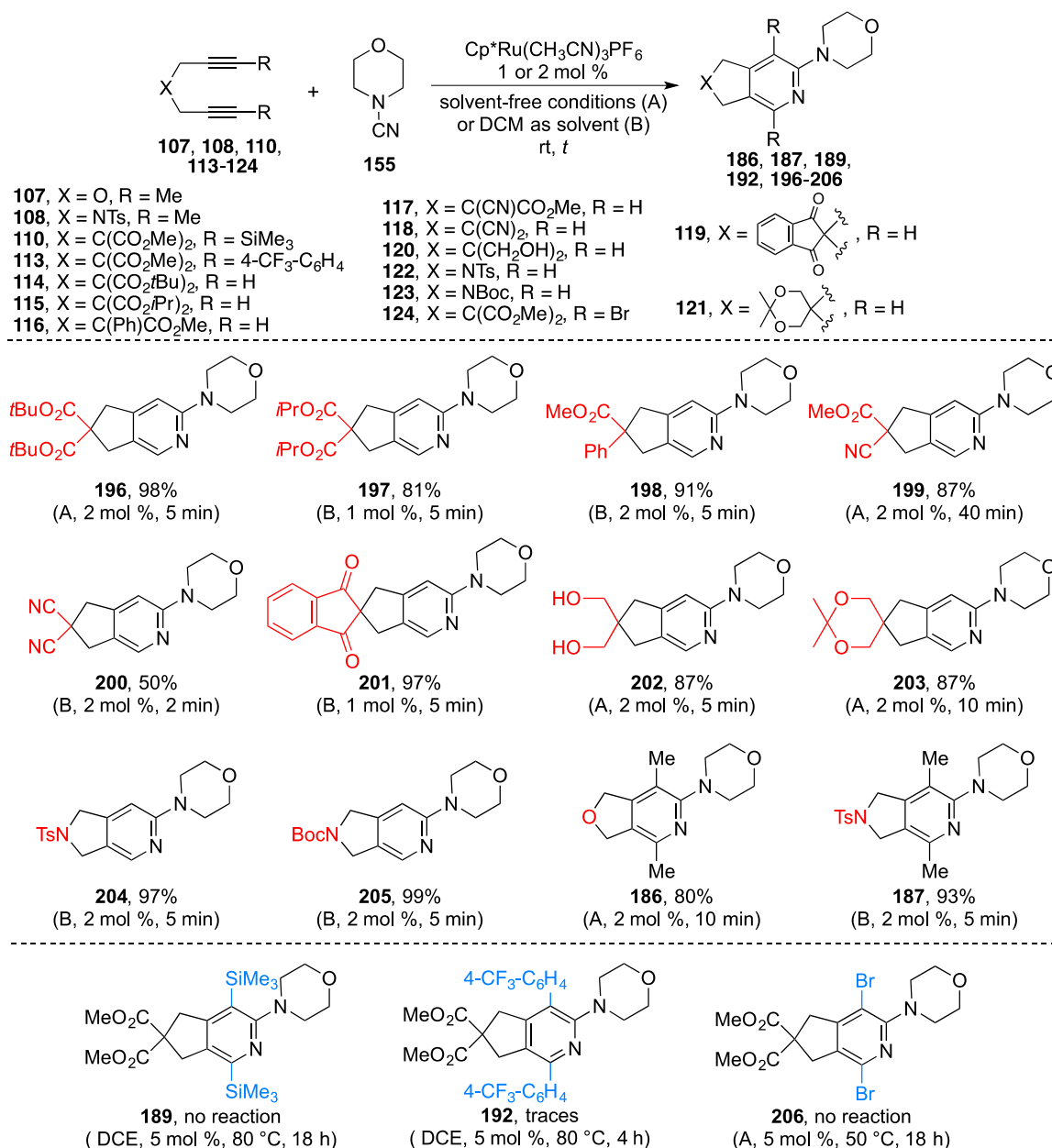
Table 4 Optimization of reaction conditions

Entry	Diyne	Catalyst ($x \text{ mol } \%$)	t	Product	Conv. (%) ^b	Yield (%) ^c
1	101	$\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$ (5)	8 h	169	nr	nd
2	101	$[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (2.5)	8 h	169	nr	nd
3	101	$\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$ (2)	5 min	169	>99	85
4	101	$\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ (5)	5 min	169	>99	93
5	101	$\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ (2)	5 min	169	>99	91
6	101	$\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ (1)	60 min	169	80	nd
7	109	$\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ (2)	3 min	188	>99	94
8 ^d	109	$\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ (1)	2 min	188	>99	95
9 ^d	109	$\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ (0.5)	18 h	188	90	82
10 ^e	109	$\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ (2)	5 min	188	>99	82

^a Reaction conditions: Ru complex (0.5-5 mol %), diyne **101** or **109** (0.5 mmol), cyanamides **155** (1.0 mmol) were stirred in a screw-capped tube under solvent-free conditions and an argon atmosphere. ^b Determined by crude ¹H NMR, nr = no reaction. ^c Isolated yields, nd = not detected. ^d With 0.6 mmol of cyanamide **155** was used and 0.5 mL of dichloromethane as solvent. ^e One gram-scale.

With a set of optimal conditions in hand, we investigated the scope and limitations of the cycloaddition using different substituted diynes and cyanamide **155** as partner (Scheme 154). A variety of symmetrical diynes with a quaternary-carbon tether reacted with cyanamide **155** to give various 2-aminopyridines in high yields. The 2-aminopyridine cycloadducts **196-199** bearing bulkier *tert*-butyl, isopropyl, and methyl ester moieties were obtained in 81-98% yields from the corresponding diynes. Notably, a nitrile group substituted on the quaternary-carbon of diyne **117** was compatible with the reaction conditions. However, the malononitrile-derived diyne **118** provided the desired product **200** in relatively lower yield (50%), because the competitive reaction of the activated nitrile substituents. The spirocyclic derivative **201** was synthesized in 97% yield, starting from the indene-1,3-dione-derived diyne **119**. Interestingly, diyne **120** possessing two hydroxyl groups reacted nicely with cyanamide **155** under solvent-free conditions at room temperature to give the diol-derived 2-aminopyridine **202** in 87% yield. The diyne **121** containing a ketal moiety was also reactive to afford the corresponding product **203** in 87% yield. The reaction was not limited to a quaternary-carbon tethered diyne since the heteroatom-tethered diynes were successfully used, leading to the formation of various

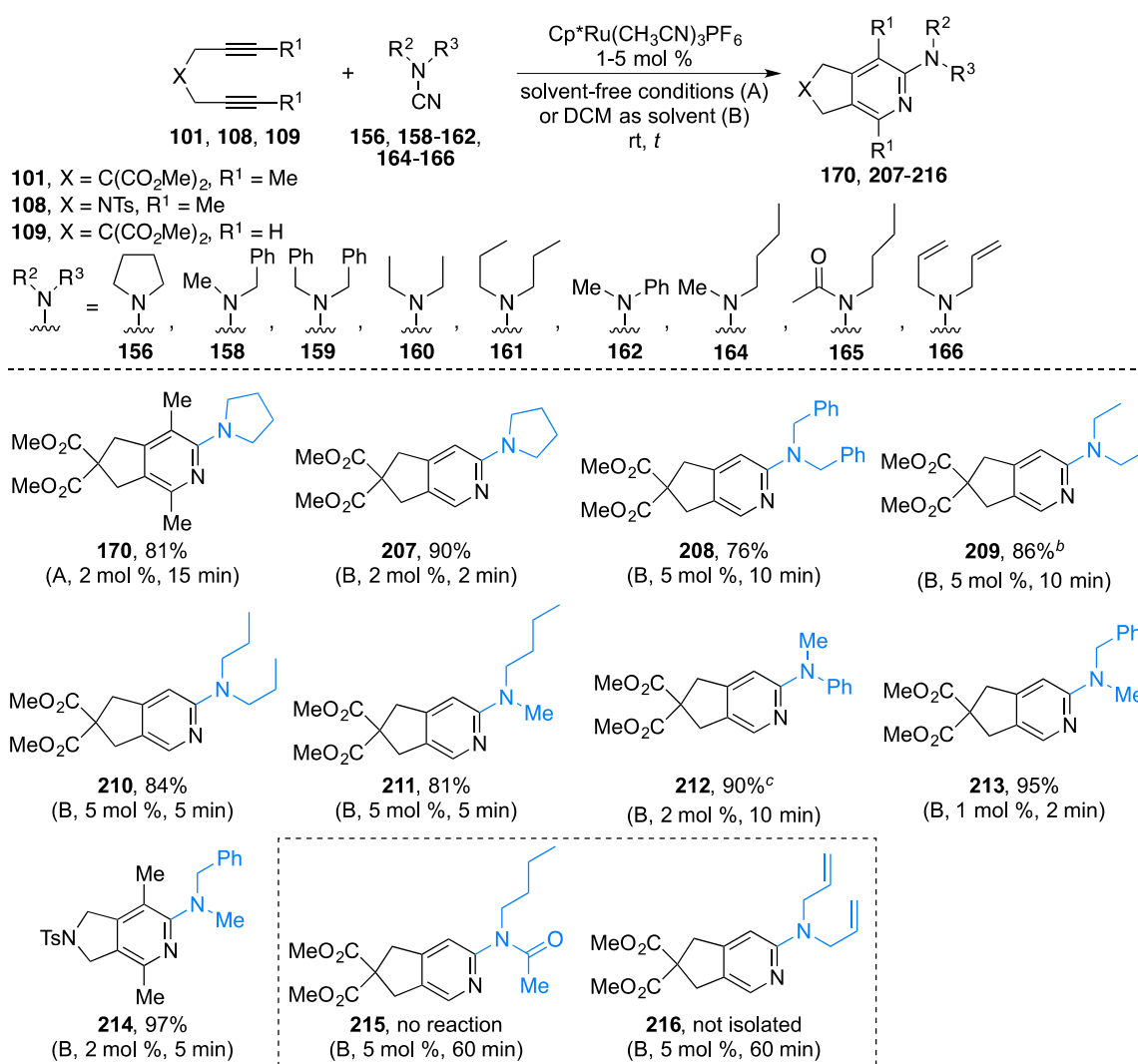
pyridine-based fused heterocycles (**186**, **187**, **204**, and **205**) within a range of 80-99% yields. The formation of compounds **186** and **187** demonstrated that the cycloaddition was not limited to terminal diynes but also worked well with internal diynes. However, more sterically hindered internal diynes, such as di-TMS, diaryl, and dibromo-substituted diynes (**110**, **113** and **124**) did not afford the desired cycloadducts, despite increased reaction temperature (Scheme 154).



Scheme 154

Next, an evaluation of the reactivity of the cyanamide substrates was examined. As shown in Scheme 155, various secondary amine derived cyanamides smoothly underwent the cycloaddition reactions to produce the corresponding 2-aminopyridines in 76-97% yields. The

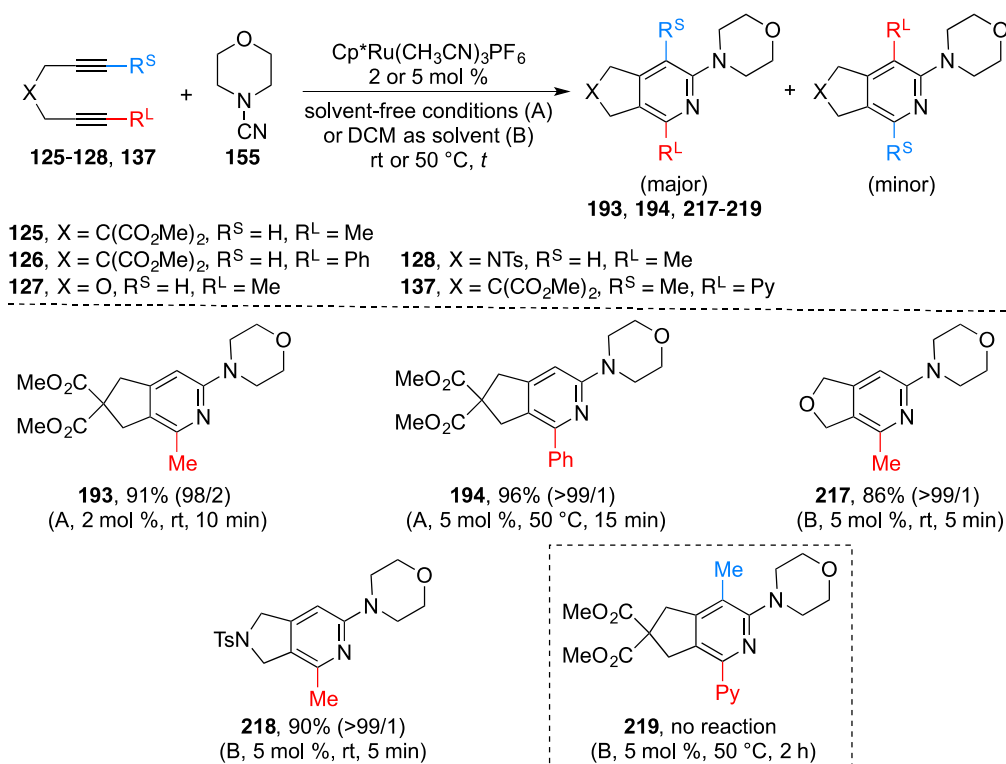
reaction of *N*-cyanopyrrolidine **156** with diynes **101** and **109** delivered the cycloadducts **170** and **207** in 81% and 90% yields, respectively. The cyanamides **159-161** and **164**, bearing dibenzyl, diethyl, di-*n*-propyl, and methyl/*n*-butyl groups, were engaged in the cycloaddition to provide the 2-aminopyridines **208-211** in 76%-86% yields, albeit with increased catalyst loading. High yields (90-97%) were obtained for 2-aminopyridines bearing a phenyl group (**212**) and a monobenzyl group (**213** and **214**) in the presence of 1-2 mol % ruthenium catalyst. Similarly, as previously observed, no desired products **215** and **216** were obtained by using *N*-butyl-*N*-cyanoacetamide **165** and *N,N*-diallylcyanamide **166**.



Scheme 155

With respect to the regioselectivity, we previously studied the reaction of unsymmetrical diynes **125** with cyanamides **155** in the presence of neutral RuCl₃·*n*H₂O catalyst. However, moderate yield and regioselectivity (48%, 88:12) were obtained. In contrast, when the reaction

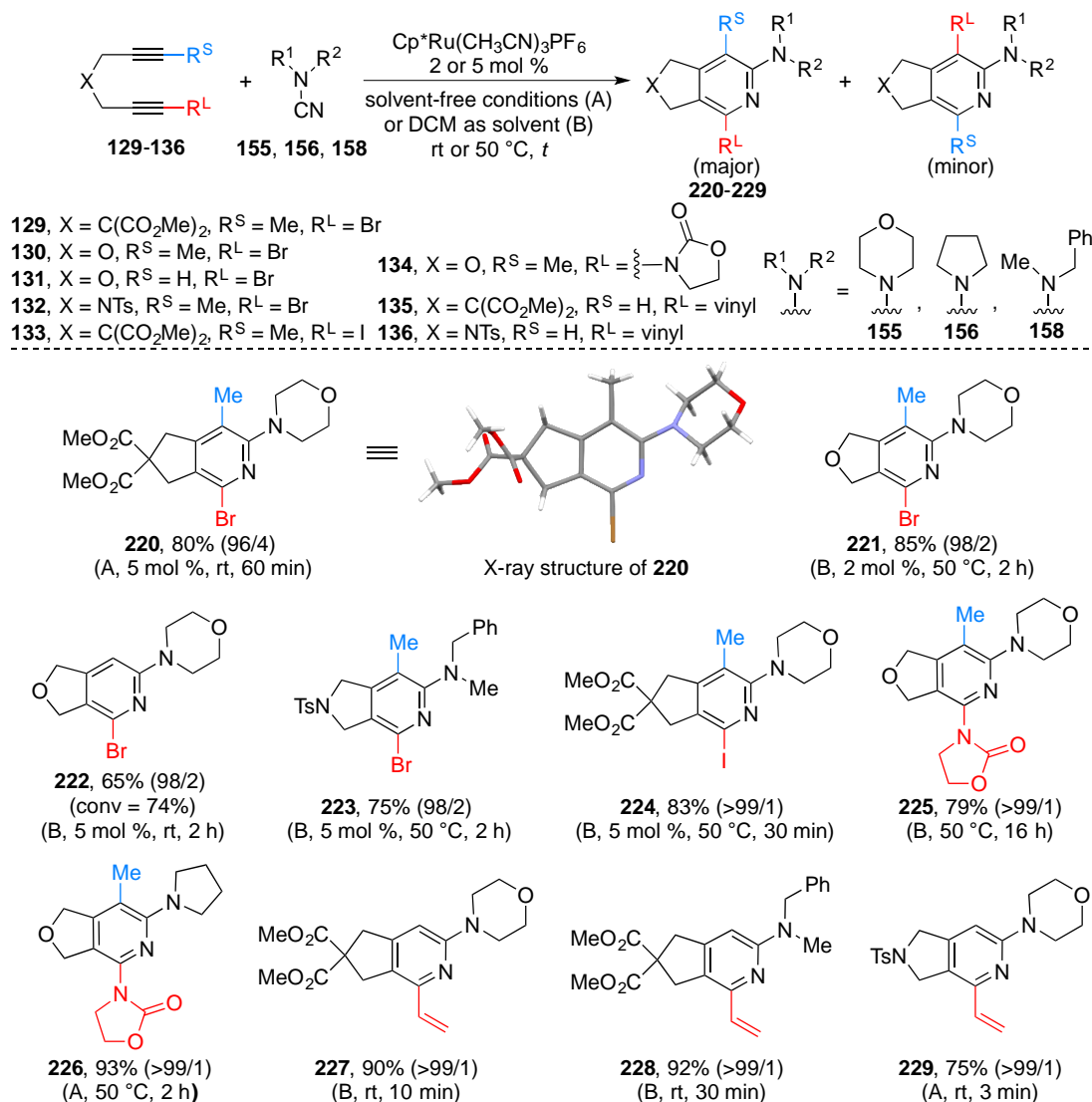
was run using the cationic ruthenium complex, $\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$, the yield and regioselectivity were significantly increased (91%, 98:2) and the *ortho*-substituted regioisomer **193** was formed as the major product (Scheme 156). In addition, other unsymmetrical diynes were employed to explore the regioselectivity of the cycloaddition reactions. The reaction of phenyl-substituted diyne **126** exclusively furnished the biaryl compound **194** in excellent 96% yield. Unsymmetrical 1,6-diynes tethered by either oxygen or nitrogen atom, possessing a terminal alkyne and a methyl internal alkyne moieties, were compatible with the cycloadditions and afforded the corresponding bicyclic compounds **217** and **218** as a single regioisomer, in 86% and 90% yields. However, the methyl/2-pyridyl-substituted diyne **137** did not undergo the cycloaddition to give the bipyridine **219**, although the reaction was heated at 50 °C for 2 hours.



Scheme 156

Encouraged by these promising results, we extended this study to develop a feasible synthetic route for the preparation of pyridine derivatives possessing various functional groups. To our delight, the challenging halogen-substituted diynes were all tolerated to deliver the synthetic useful halopyridines in 65-85% yields with up to 99:1 regioselectivities (Scheme 157). Treatment of malonate-derived bromodiyne **129** and cyanamide **155** under the standard solvent-free conditions at room temperature, generated the less sterically hindered *ortho*-bromopyridine

as the major product, in 80% yield and high regioselectivity (96:4). The structure of the product **220** was unambiguously determined by the basis of 2D-NMR analysis and X-ray crystallographic analysis. Bromodiynes **130-132** reacted nicely with cyanamide **155** to provide the corresponding bromopyridines **221-223** in 65-85% yields with 98:2 regioselectivities. The iodo-substituted 2-amimopyridine **224** was isolated as a single regioisomer in 83% yield.

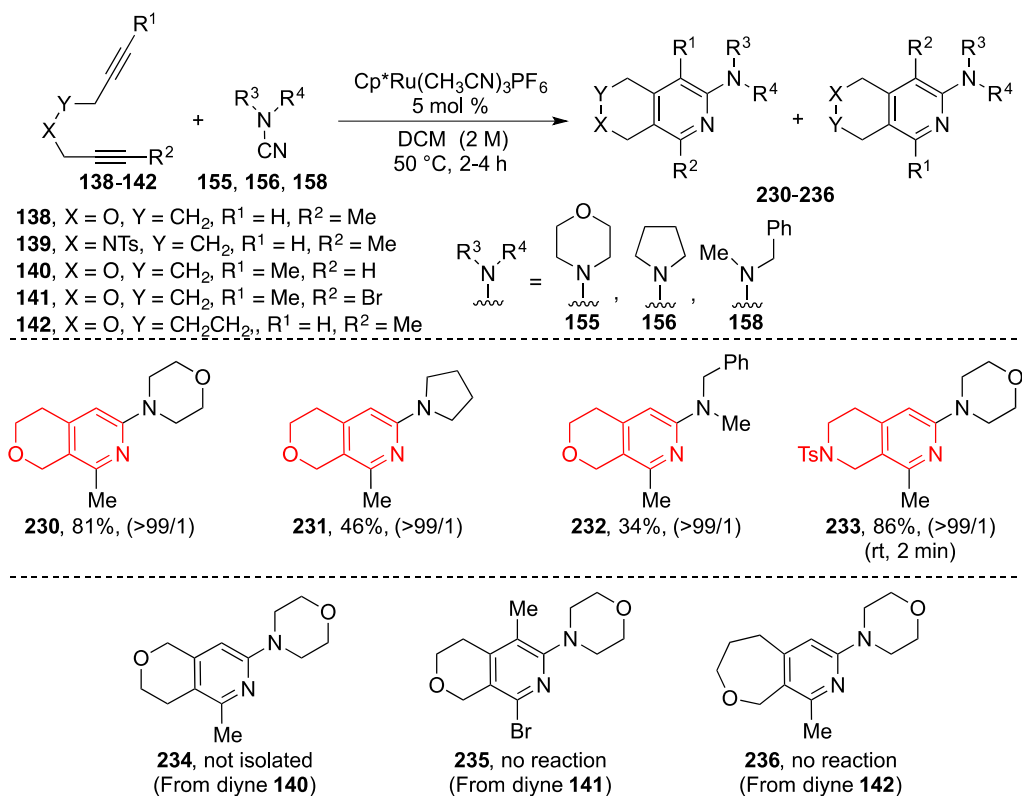


Inspired by the success of halogen substituted diynes to yield the halopyridines, we next examined whether the ynamide and enyne, could be suitable for the synthesis of the corresponding functionalized pyridines under the same conditions (Scheme 157). Gratifyingly, the cycloaddition of ynamide **134** with cyclic cyanamides **155** and **156** gave rise to pyridines **225** and **226** with excellent regioselectivities, in 79% and 93% yields, respectively.

Additionally, the regioselectivity was still controlled by the steric effect of the substituents, affording less sterically hindered *ortho*-substituted pyridines as the major product. More interestingly, we successfully employed enyne **135** with 1.2 equivalents of cyanamides **155** and **158** in the presence of 5 mol % Cp*Ru(CH₃CN)₃PF₆ combined with dichloromethane as solvent to afford the malonate-derived vinylpyridines **227** and **228** in 90% and 92% yields with complete regioselectivities. The *N*-tosyl-tethered enyne **136** was also subjected to standard solvent-free conditions, the corresponding vinylpyridine **229** was obtained as a single regioisomer in 75% yield. It is worthwhile to mention that the cycloaddition exclusively took place at the triple bond to form pyridines, no side-product from the double bond reactivity was detected.

To further demonstrate the synthetic utility of this method, the reaction of the challenging linear 1,7-diynes and 1,8-diynes was examined (Scheme 158). Oxygen-tethered 1,7-diyne **138** and cyanamide **155** were treated with 5 mol % Cp*Ru(CH₃CN)₃PF₆ in dichloromethane at 50 °C, affording the six-membered bicyclic pyridine **230** in 81% yield with excellent regioselectivity. Cyanamides **156** and **158**, containing pyrrolidyl and methyl/benzyl moieties, provided 2-aminopyridines **231** and **232** in diminished yields (46% and 34%, respectively), despite with a total regioselectivity. Replacing the oxygen tether by a *N*-tosyl tether, the diyne **139** allowed rapidly an access to nitrogen-fused pyridine **233** in 86% yield with complete regioselectivity. Notably, compounds containing the pyrano-pyridine and piperidine-pyridine moieties are known to exhibit interesting pharmacological properties such as antibacterial and anticancer activities.^{107,113d} Moreover, further studies showed that diynes **140-142** were not compatible with the reaction conditions. Diyne **140** having a propargyl motif failed to deliver the desired product. No reaction took place with both bromo-substituted 1,7-diyne **141** and terminal 1,8-diyne **142**, probably because of the lack of a Thorpe-Ingold effect¹⁴⁸.

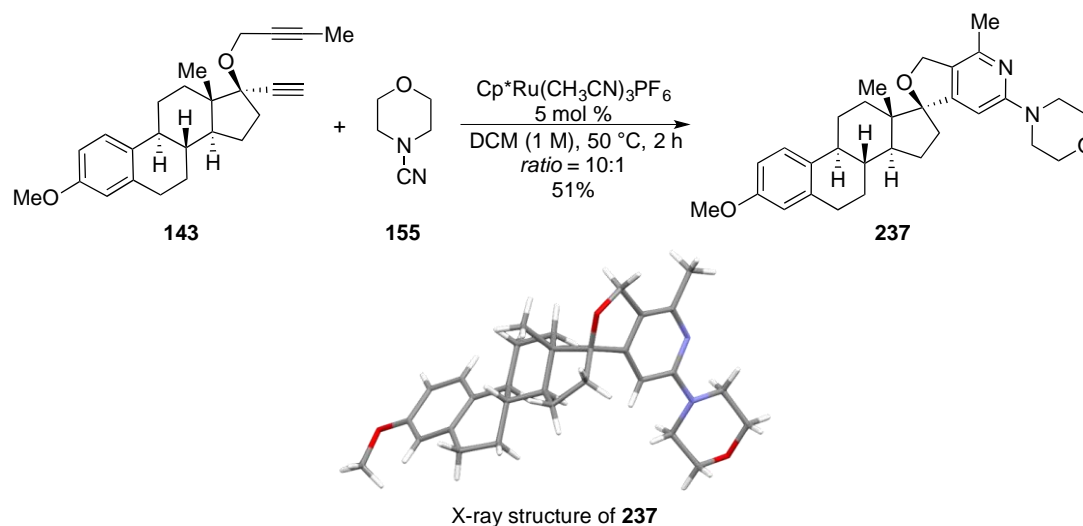
¹⁴⁸ Jung, M. J.; Piizi, G. *Chem. Rev.* **2005**, *105*, 1735.



Scheme 158

Finally, we consider the feasibility of the late-stage functionalization of potential drug or bioactive compounds. As an example, the diyne **143**, derived from biologically active compounds mestranol¹⁴⁹ was employed to deliver the spirocyclic framework having a 2-aminopyridine moiety **237** in 51% isolated yield with 10:1 regioselectivity. The structure of the polycyclic product **237** was unambiguously confirmed by single crystal X-ray diffraction (Scheme 159).

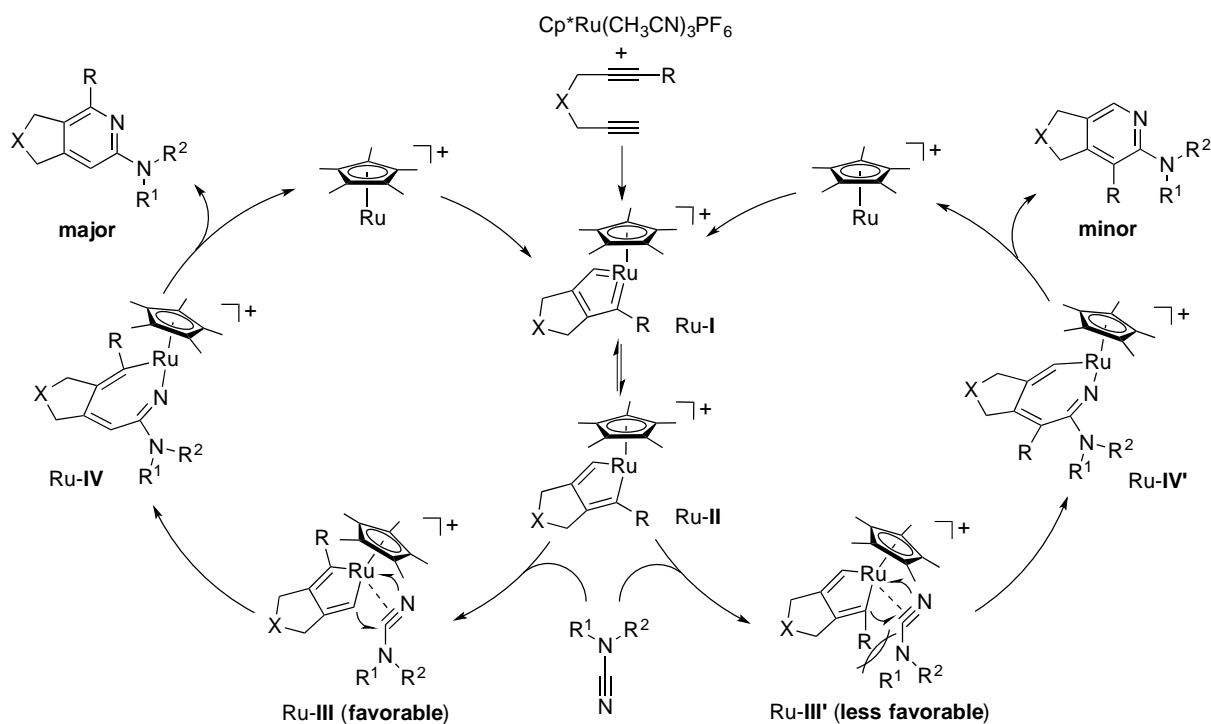
¹⁴⁹ (a) Sierra, M. A.; Torres, M. R.; De Torre, C.; Elsa, A. *J. Org. Chem.* **2007**, 72, 4213. (b) Hanson, J. R. *Nat. Prod. Rep.* **2010**, 27, 887. (c) Sedláček, D.; Novák, P.; Kotora, M.; Bartuněk, P. *J. Med. Chem.* **2010**, 53, 4290. (d) Kotora, M.; Hessler, F.; Eignerová, B. *Eur. J. Org. Chem.* **2012**, 29.



Scheme 159

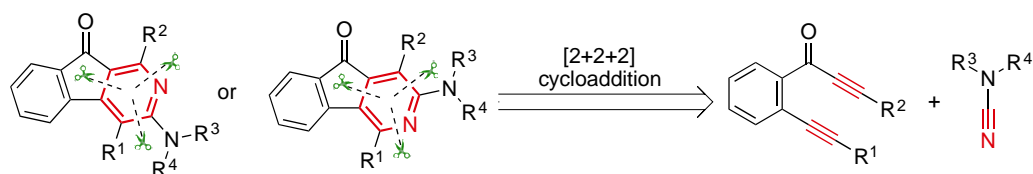
Mechanistically, the metal-catalyzed [2+2+2] cycloaddition has been thoroughly studied in the presence of several metals.⁷ Nevertheless, as described in Scheme 160, one important feature concerns the regioselectivity of the ruthenium-catalyzed process, *e.g.*, the formation of the major isomer versus the minor isomer. Following *in situ* ligand decoordination and coordination of 1,6-diyne, the oxidative coupling of the two alkyne units leads to a ruthenacyclopentadiene **Ru-II** in equilibrium with the bis-carbenic intermediate **Ru-I**.^{47,49,150} The next elemental step determines the regioselectivity of the reaction. Indeed, coordination of cyanamide gives intermediates **Ru-III** or **Ru-III'**. The origin of the observed regiochemistry can be reasonably explained by the steric hindrance of the amino part of the cyanamide leading to the favourable formation of **Ru-III**. Insertion of cyanamide gives rise to azaruthenacyclopentadiene intermediate **Ru-IV**, which upon reductive elimination subsequently affords the *ortho*-substituted product. When the 1,6-diyne is substituted by two very hindered groups (dienes **110** and **124**), no reaction is observed. A hydrogen atom and/or methyl group as substituent of the alkynes are fully compatible with the cycloaddition process and favor the formation of the major intermediate **Ru-III**. This mechanism is therefore in agreement with the experimental data.

¹⁵⁰ (a) Albers, M. O.; De Waal, D. J. A.; Liles, D. C.; Robinson, D. J.; Singleton, E.; Wiege, M. B. *J. Chem. Soc. Chem. Commun.* **1986**, 1680. (b) J. Le Paih, F. Monnier, S. Dérien, P. H. Dixneuf, E. Clot, O. Eisenstein, *J. Am. Chem. Soc.* **2003**, *125*, 11964.



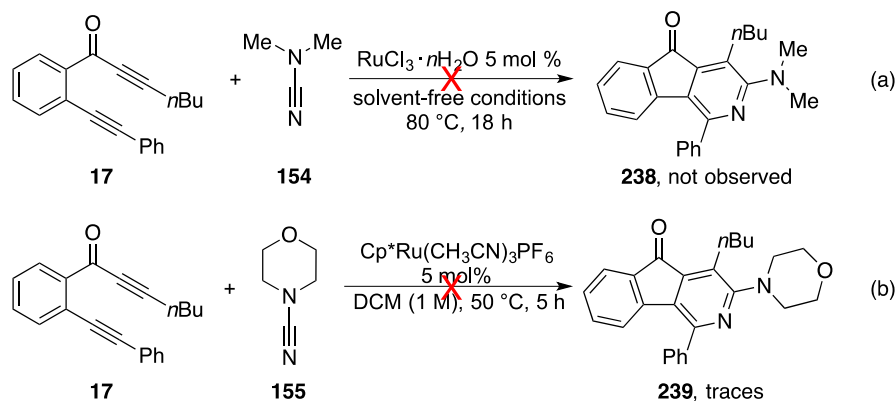
4.4 Cp^{*}Ru(CH₃CN)₃PF₆-catalyzed [2+2+2] cycloadditions to access aza-fluorenols and aza-fluorenones

Aza-fluorenones represent a privileged scaffold in material and medicinal chemistry. We hypothesized that by using benzoyl bridged α,ω -diynes and cyanamides, it should be possible to access amino-aza-fluorenones via the regioselective ruthenium-catalyzed [2+2+2] cycloaddition reaction. A retrosynthesis was proposed in Scheme 161.



Therefore, the benzoyl bridged internal diyne **17** was reacted with dimethylcyanamide **154** under the optimized conditions using 5 mol % RuCl₃·*n*H₂O under solvent-free conditions at 80 °C. Unfortunately, no desired product **238** was obtained and only decomposition of diyne **17** was detected (Eq. a, Scheme 162). The same result was also observed by using

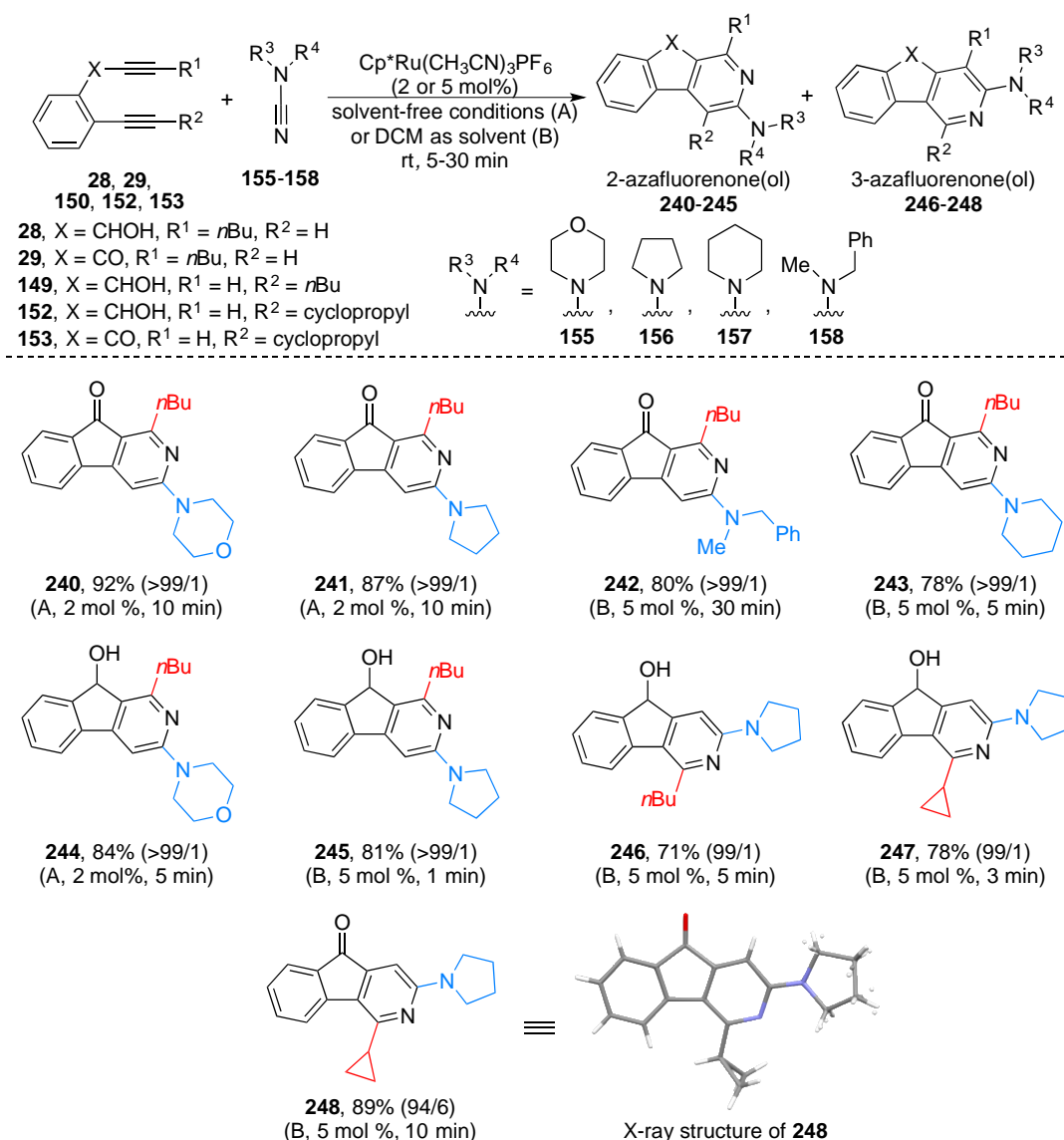
$\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ as catalyst for the cycloaddition of diyne **17** and cyanamide **155** (Eq. b, Scheme 162). The results could be explained by the lower reactivity of the diyne which bears both phenyl and *n*-butyl groups on the terminal positions.



Scheme 162

To address this issue, we reasoned that a less sterically demanding diynes possessing a terminal alkyne moiety would be more reactive in the presence of $\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ catalytic system. Indeed, as shown in Scheme 163, when the benzoyl bridged diyne **29** was reacted with morpholine-4-carbonitrile **155** in the presence of 2 mol % $\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ at room temperature under solvent-free conditions, the 2-azafluorenone **240** was formed as a single regioisomer in 92% yield. Different cyanamides were next screened, such as *N*-cyanopyrrolidine **156**, *N*-cyanopiperidine **157** and *N,N*-methylbenzyl cyanamide **158**, and the desired 2-azafluorenones **241-243** were synthesized as a single isomer in 78-87% yields. In addition, the reaction of benzyl-bridged diyne **28** bearing an unprotected hydroxyl group could also be performed smoothly and exclusively to give rise to 2-azafluorenols **244** and **245** in 84% and 81% yields, respectively. Interestingly, in parallel to the synthesis of 2-azafluorenone **245**, exchanging the terminal position of the starting diyne, allowed the formation of the 3-azafluorenone **247** in 71% yield with 99:1 regioselectivity. Moreover, switching to a cyclopropyl group instead of *n*-butyl group promoted the formation of 3-azafluorenone **247** in 78% yield with the same regioselectivity. The cycloaddition of benzoyl bridged diyne **153** was performed under the optimized reaction conditions, 3-azafluorenone **248** was formed as the major product in 89% isolated yield, with a decreased regioselectivity (94:6). The structure of **248** was unambiguously confirmed by single crystal X-ray diffraction (Scheme 163). These results illustrated that the regioselectivity allows the formation of less sterically hindered regioisomer.

It is important to highlight that all the reactions occurred in a short reaction time using traces of dichloromethane or solvent-free conditions.



Scheme 163

5. Conclusion

To conclude, we have demonstrated that highly substituted 2-aminopyridine derivatives can be efficiently synthesized by ruthenium-catalyzed [2+2+2] cycloaddition of 1,6-diyne and 1,7-diyne with cyanamides using both neutral $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ and cationic $\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ complex as catalyst.

Firstly, the easy to handle and cost-effective $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ complex has been successfully employed for the synthesis of highly substituted 2-aminopyridines. The reaction proceeded in the presence of 5 mol % $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$, with neither additional ligands nor additives under solvent-free conditions, affording a range of different 2-aminopyridines in 10-95% yields.

Secondly, we established that a cationic $\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ complex is a highly efficient catalyst for the cycloaddition of both 1,6- and 1,7-diynes with cyanamides under mild conditions. Various symmetrical terminal or internal diynes possessing different functional groups were compatible with the catalytic system. High regioselectivity was obtained when unsymmetrical diynes were employed. The practicability and utility of this protocol were demonstrated with the preparation of high valuable halopyridines, diaminopyridines, and vinylpyridines in one-step synthesis. The reaction also provided synthetic useful six-membered heteroatom-fused pyridines starting from unsymmetrical 1,7-diynes and cyanamides. The late-stage functionalization of biologically active mestranol further improved the facile and usefulness of the present method.

Finally, a family of aza-fluorenones and aza-fluorenols were synthesized via eco-friendly and straightforward approaches. Controlling the terminal position of the benzoyl- or benzyl-bridged diyne allowed the synthesis of 2- or 3-azafluorenone(ol) with high regioselectivities.

Chapter IV: Rhodium-catalyzed
asymmetric synthesis of 1,1-
disubstituted 1,3-dihydroisobenzofurans
from prochiral triynes and internal
alkynes

Chapter IV: Rhodium-catalyzed asymmetric synthesis of 1,1-disubstituted 1,3-dihydroisobenzofurans from prochiral triynes and internal alkynes

The transition-metal-catalyzed enantioselective [2+2+2] cycloaddition reactions are extremely important tools in modern synthetic organic chemistry, because they serve as a powerful and atom-economical straightforward approach for the rapid construction of chiral polycyclic carbocycles and heterocycles in a single step.^{7h,7j,7x} Since the first example of enantioselective [2+2+2] cycloaddition discovered in 1994 with the work of Sato, Mori, and Nishimata,¹⁵¹ catalytic asymmetric [2+2+2] cycloaddition reactions using a transition metal catalyst, such as rhodium, cobalt, nickel, and iridium, in the presence of a chiral ligand have been widely reported for the construction of various chiral molecules associated with central, axial, planar, helical chirality (Figure 3).

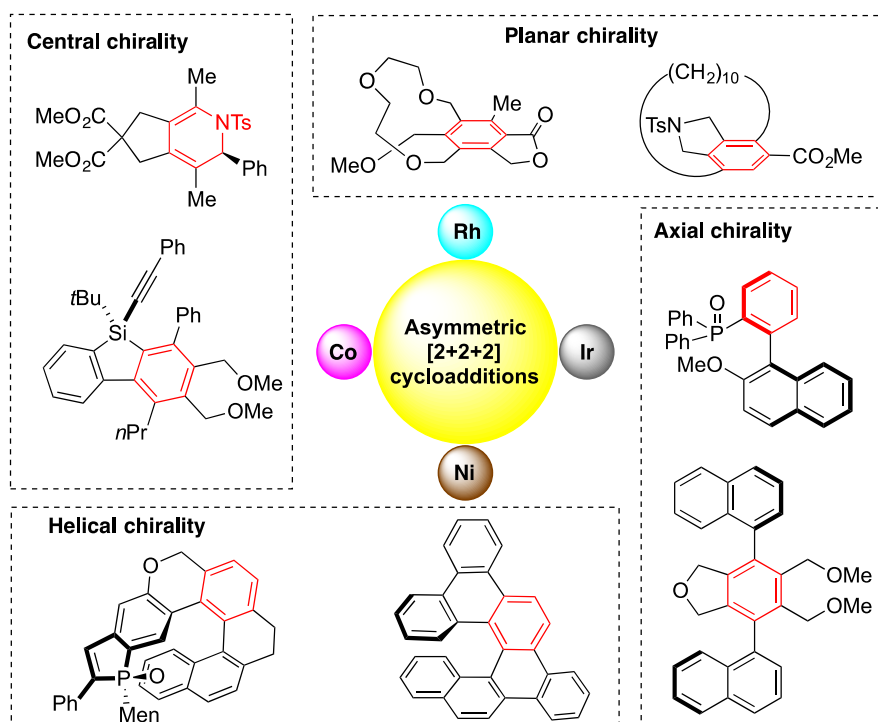


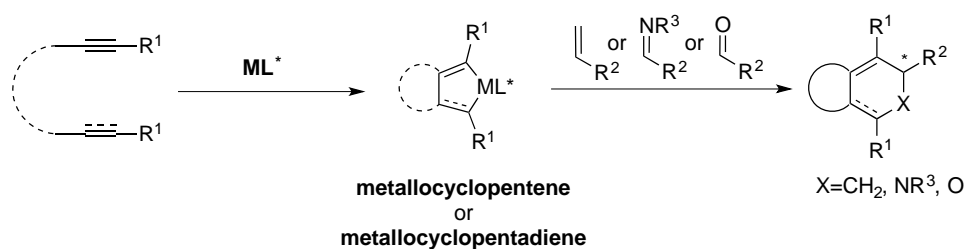
Figure 3

¹⁵¹ Sato, Y.; Nishimata, T.; Mori, M. *J. Org. Chem.* **1994**, *59*, 6133.

1. Enantioselective [2+2+2] cycloaddition reactions

1.1. Construction of central chirality

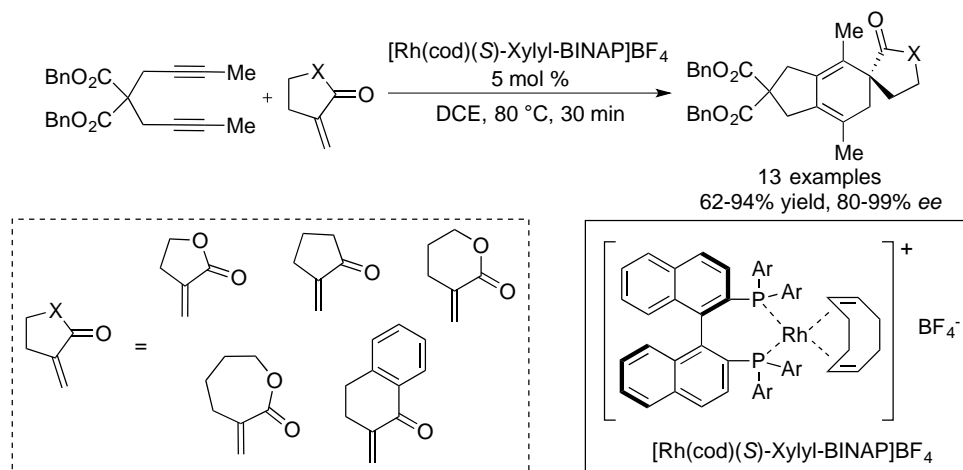
The transition-metal-catalyzed [2+2+2] cycloadditions of alkynes with unsaturated partners, such as olefins, imines, aldehydes, are of great interest given that they allow the construction of a six-membered ring containing one or more chiral carbon center. These processes proceed via a widely known reactive metallacyclopentene or metallacyclopentadiene intermediate, which is generated from the oxidative coupling of two unsaturated carbon-carbon bonds to the chiral metal catalytic species. The insertion and reductive elimination steps then provide the cyclic compound with chiral carbon center(s) on the six-membered ring (Scheme 164).



Scheme 164

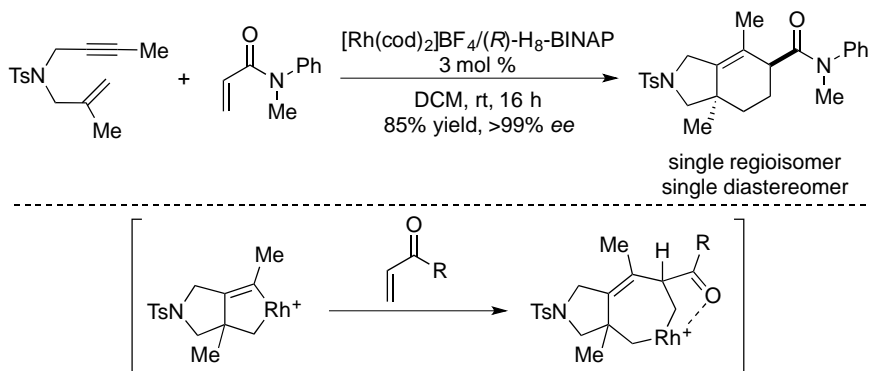
In 2006, Shibata reported the first rhodium-catalyzed enantioselective [2+2+2] cycloaddition of diynes and alkenes.¹⁵² In the presence of a preliminary isolated chiral rhodium(I) complex, various *exo*-methylene cyclic lactones and ketones could undergo the cycloaddition with 1,6-diynes to give a family of chiral spirocyclic compounds possessing a quaternary carbon stereocenter, with 62-94% yields and 80-99% enantioselectivities (Scheme 165).

¹⁵² Tsuchikama, K.; Kuwata, Y.; Shibata, T. *J. Am. Chem. Soc.* **2006**, *128*, 13686.



Scheme 165

The enantioselective [2+2+2] cycloaddition involving two alkene units allowed to introduce two new stereogenic centers in a single step in the resulting cycloadduct. The first report was described by Tanaka and co-workers in 2012.¹⁵³ They demonstrated that the successful construction of annulated cyclohexene relies on the use of reactive acrylamides as alkene partners (Scheme 166). The high regioselective and diastereoselective formation of the cycloadduct could be explained by the regioselective insertion of the acrylamide into a rhodacyclopentene intermediate.



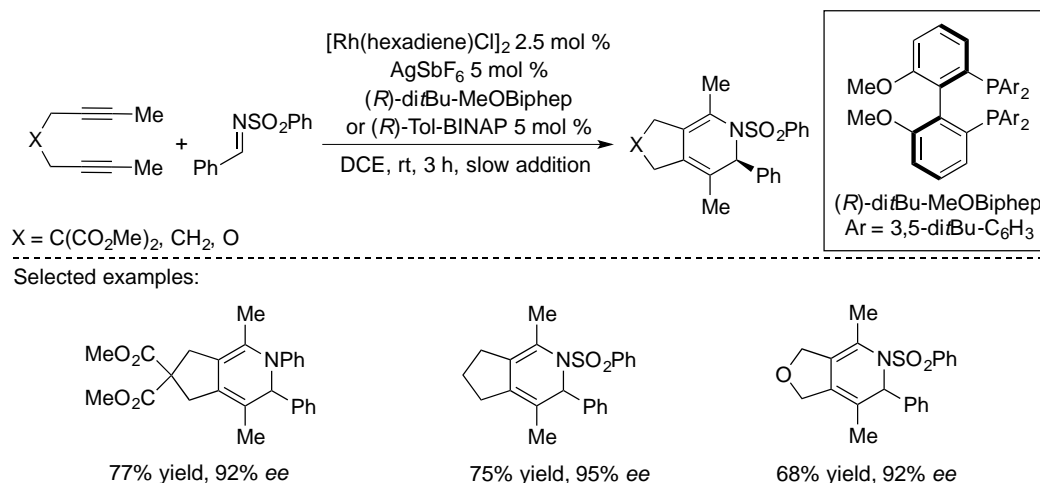
Scheme 166

The unsaturated imine was also a good partner for these cycloadditions. The first asymmetric transition-metal-catalyzed [2+2+2] cycloaddition of diynes with sulfonimines was reported by Aubert, Gandon, Malacria and co-workers,¹⁵⁴ and provided a new and efficient

¹⁵³ Masutomi, K.; Sakiyama, N.; Noguchi, K.; Tanaka, K. *Angew. Chem. Int. Ed.* **2012**, *51* (52), 13031.

¹⁵⁴ Amatore, M.; Lebœuf, D.; Malacria, M.; Gandon, V.; Aubert, C. *J. Am. Chem. Soc.* **2013**, *135*, 4576.

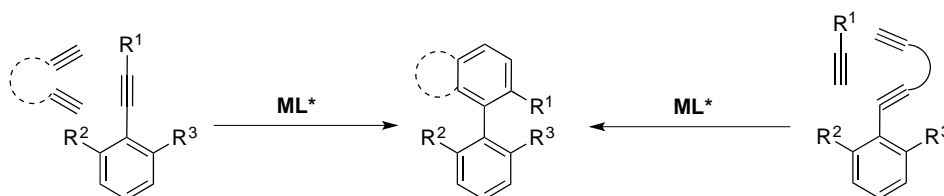
method for the synthesis of enantioenriched 1,2-dihydropyridines. The combination of $[\text{Rh}(\text{hexadiene})\text{Cl}]_2/\text{AgSbF}_6/(R)\text{-di}t\text{Bu-MeOBiphep}$ (or $(R)\text{-Tol-BINAP}$) was found to be the best catalytic system to promote the access to various heterocycles with good enantioselectivities (Scheme 167).



Scheme 167

1.2. Construction of axial chirality

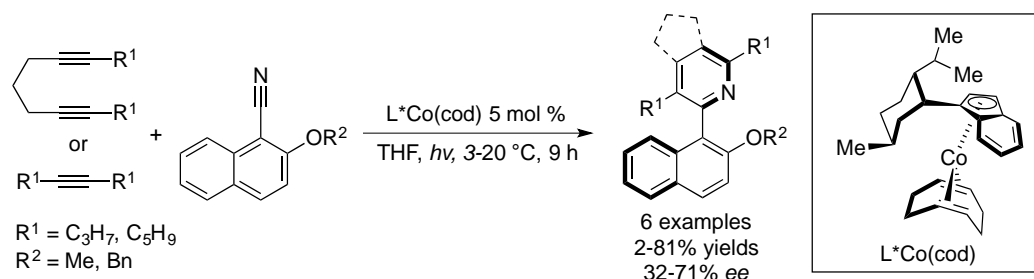
Axially chiral biaryl compounds are widely found as a key structural motif in many chiral ligands, catalysts as well as biologically active compounds.¹⁵⁵ The catalytic enantioselective synthesis of axially chiral biaryls via transition-metal-catalyzed [2+2+2] cycloadditions have been proved to be a straightforward and efficient method. The sterically demanding prochiral substrates and a chiral catalyst were commonly used for the formation of chiral biaryl compounds (Scheme 168).



Scheme 168

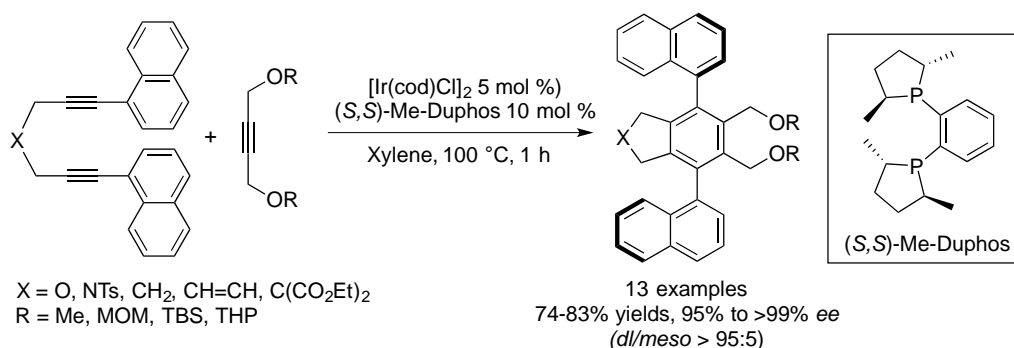
¹⁵⁵ (a) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 5384. (b) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. *Chem. Rev.* **2011**, *111*, 563.

In 2004, Gutnov, Heller and co-workers reported the first example of direct synthesis of enantioenriched axially biaryls via a chiral cobalt(I) complex-catalyzed [2+2+2] cycloaddition of alkynes with nitriles.¹⁵⁶ The reaction was performed under mild conditions using visible light or sunlight as the energy source (Scheme 169).



Scheme 169

Shibata and co-workers reported the first example of iridium-catalyzed [2+2+2] cycloaddition of α,ω -diynes with alkynes.¹⁵⁷ The combination of $[Ir(cod)Cl]_2$ and (*S,S*)-Me-Duphos promoted the high enantio- and diastereoselective synthesis of axially chiral 1,4-teraryls (Scheme 170).



Scheme 170

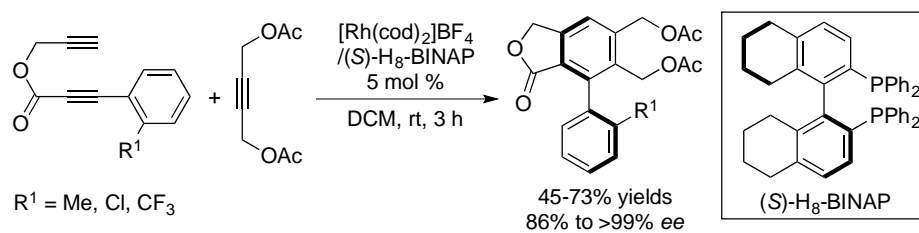
Tanaka and co-workers also employed the cationic rhodium(I)/bisphosphine catalytic system to the asymmetric synthesis of axially chiral biaryls.¹⁵⁸ In the presence of cationic rhodium(I)/(*S*)-H₈-BINAP complex, various unsymmetrical diynes and internal alkynes were

¹⁵⁶ Gutnov, A.; Heller, B.; Fischer, C.; Drexler, H. J.; Spannenberg, A.; Sundermann, B.; Sundermann, C. *Angew. Chem. Int. Ed.* **2004**, *43*, 3795.

¹⁵⁷ Shibata, T.; Fujimoto, T.; Yokota, K.; Takagi, K. *J. Am. Chem. Soc.* **2004**, *126*, 8382.

¹⁵⁸ Tanaka, K.; Nishida, G.; Wada, A.; Noguchi, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 6510.

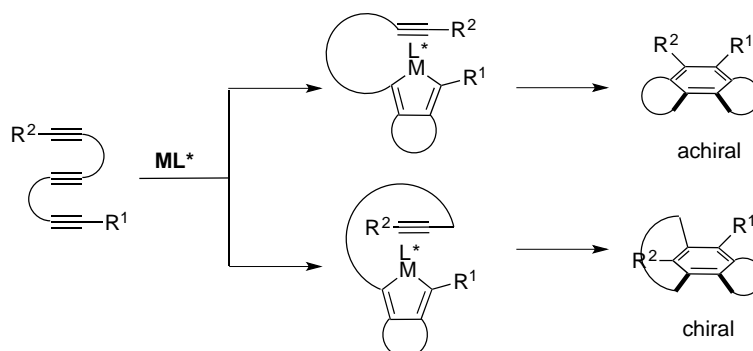
converted to axially chiral phthalides. Functional groups, such as trifluoromethyl and chloride were tolerated using these conditions (Scheme 171).



Scheme 171

1.3. Construction of planar chirality

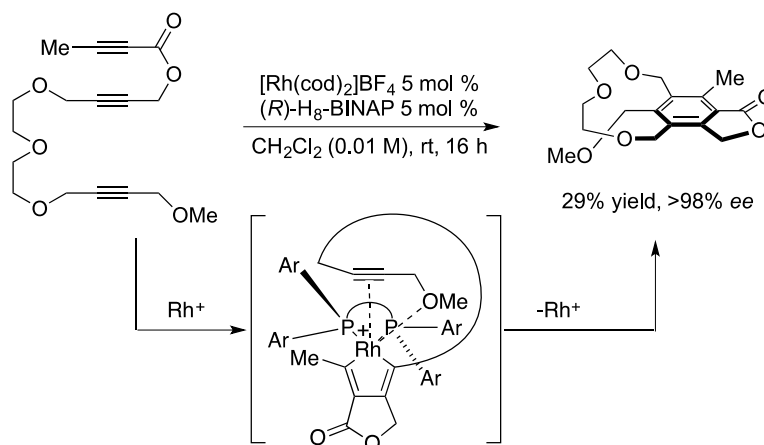
The transition-metal-catalyzed intramolecular [2+2+2] cycloaddition of triynes, possessing a short ansa chain, could be possible to form a planar chirality cyclophanes in which the ansa chain cannot flip around the benzene ring (Scheme 172).



Scheme 172

In 2007, the group of Tanaka first reported that the planar-chiral metacyclophanes could be synthesized by transition-metal-catalyzed [2+2+2] cycloaddition reactions.¹⁵⁹ The intramolecular cyclotrimerization of linear triynes, bearing ester or ether-linked 1,6-diyne moieties, proceeded in the presence of rhodium(I)/(*R*)-H₈-BINAP complex furnishing the [7]-[10]metacyclophanes with high enantioselectivities (Scheme 173). This method opened a new way to synthesize these compounds.

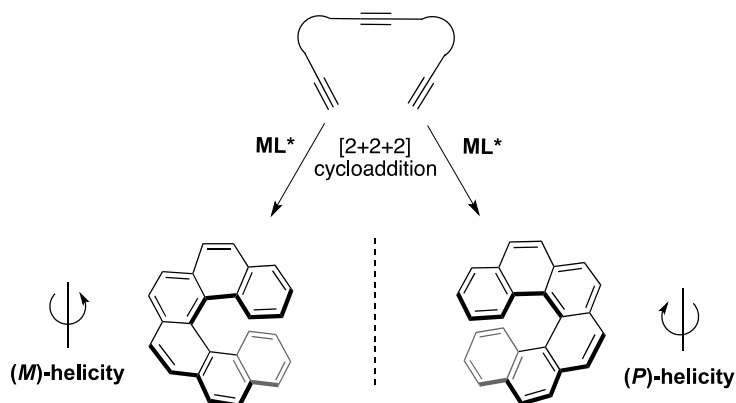
¹⁵⁹ Tanaka, K.; Sagae, H.; Toyoda, K.; Noguchi, K.; Hirano, M. *J. Am. Chem. Soc.* **2007**, *129*, 1522.



Scheme 173

1.4. Construction of helical chirality

The combination of transition metals with chiral ligands to catalyze [2+2+2] cyclotrimerization of alkynes is considered as one of the most efficient methods for the synthesis of helically chiral π -electron systems, although most examples are diastereoselective cycloadditions (Scheme 174).

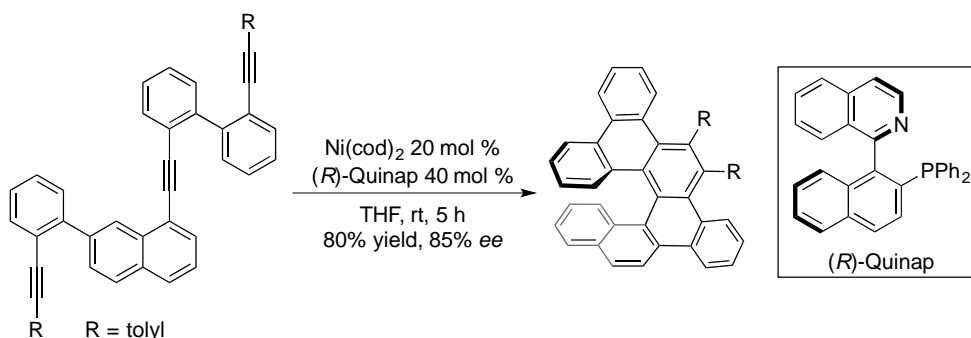


Scheme 174

Stará, Starý and co-workers reported a rapid approach for the synthesis of dibenzohelicenes based on a nickel-catalyzed cycloaddition reaction.¹⁶⁰ A series of *ortho*-phenylene-tethered triynes were employed under the $\text{Ni}(\text{cod})_2/(R)\text{-Quinap}$ catalytic system and

¹⁶⁰ Jančařík, A.; Rybáček, J.; Cocq, K.; Chocholoušová, J. V.; Vacek, J.; Pohl, R.; Bednárová, L.; Fiedler, P.; Císařová, I.; Stará, I. G.; Starý, I. *Angew. Chem. Int. Ed.* **2013**, 52, 9970.

gave rise to various dibenzo[5]-, dibenzo[6]-, and dibenzo[7]helicenes. Notably, a high catalyst loading (20 mol %) was required to give a higher enantioselectivity (Scheme 175).



Scheme 175

2. Desymmetric transition-metal-catalyzed [2+2+2] cycloaddition reactions

Although many methods have been developed on enantioselective transition-metal-catalyzed [2+2+2] cycloadditions for the synthesis of useful chiral compounds, new strategies to access challenging targets are still desirable.

The construction of all-carbon quaternary stereogenic centers via catalytic enantioselective desymmetrization¹⁶¹ of prochiral substrate is an ideal method which exhibits many advantages over conventional strategies (Figure 4). For example, the quaternary carbon stereocenter is formed, no matter what kind of reaction occurred at one of the two identical functional groups attached to the quaternary carbon; the functional groups could previously be introduced to the quaternary carbon; the theoretical yield of the desymmetrization reaction is 100%, while the yield of the kinetic resolution reaction cannot exceed 50%.

¹⁶¹ Zeng, X. P.; Cao, Z. Y.; Wang, Y. H.; Zhou, F.; Zhou, J. *Chem. Rev.* **2016**, *116*, 7330.

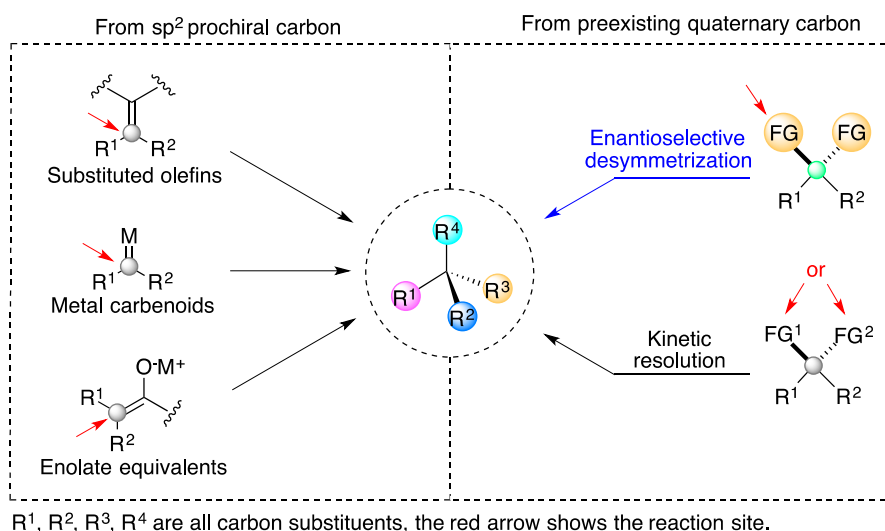
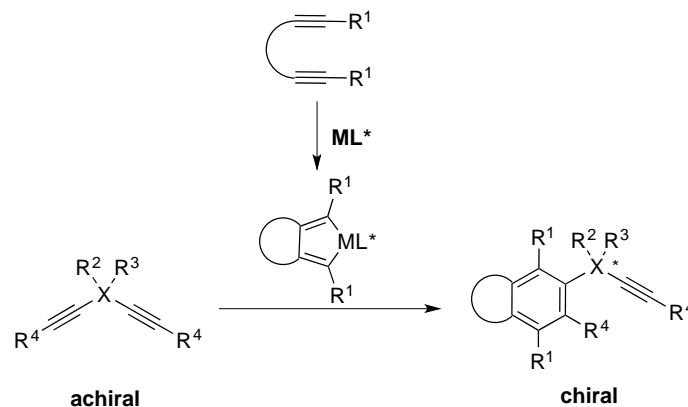


Figure 4

Taking advantage of the powerful and practical transition-metal-catalyzed [2+2+2] cycloadditions, and based on the principles of desymmetrization reactions, the synthesis of chiral compounds in term of desymmetric enantioselective [2+2+2] cycloaddition reactions were designed but scarcely reported (Scheme 176).

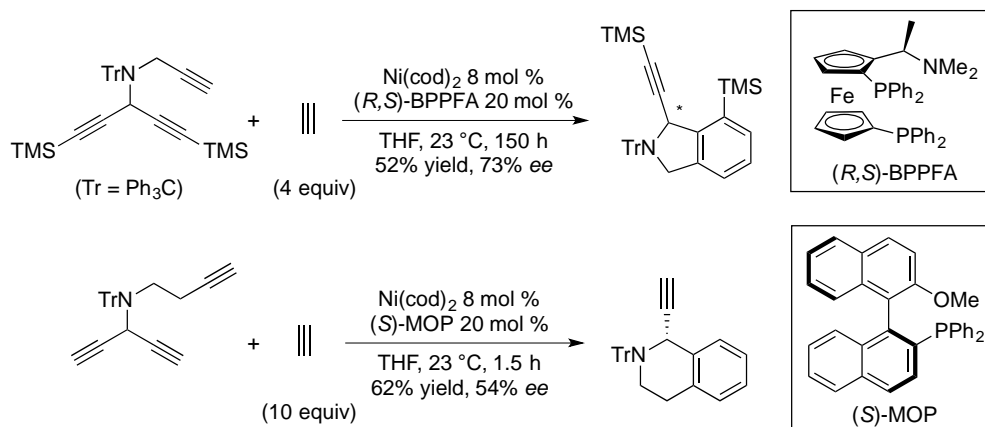


Scheme 176

The first example was reported by Sato, Mori and Nishimata using a nickel(0)-catalyzed enantioselective [2+2+2] cycloaddition of prochiral triynes with gaseous acetylene in the presence of chiral phosphine ligands under mild conditions (Scheme 177).^{151, 162} The combination of Ni(cod)₂ and (*R,S*)-BPPFA promoted the reaction of prochiral triynes with acetylene affording the isoindoline derivatives in 52% yield and 73% enantioselectivity,

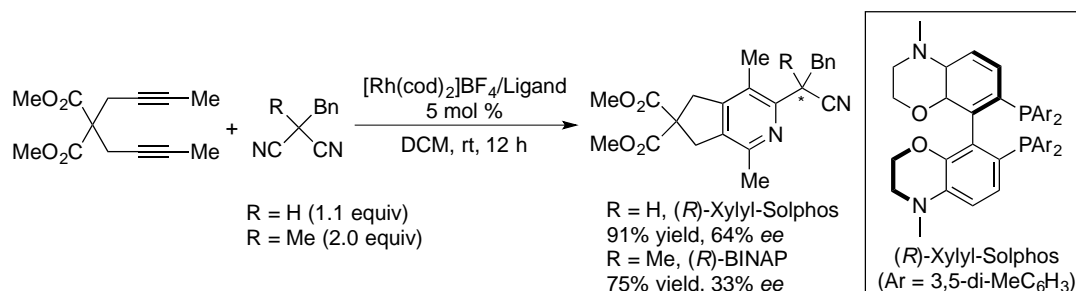
¹⁶² Sato, Y.; Nishimata, T.; Mori, M. *Heterocycles* **1997**, *44*, 443.

whereas the cycloaddition of 1,7-diynes and acetylene by using (*S*)-MOP as ligand led to isoquinoline in 62% yield and 54% enantioselectivity. Notably, this new method opened a novel route for the construction of benzylic chiral carbon centers, although the enantioselectivities were moderate.



Scheme 177

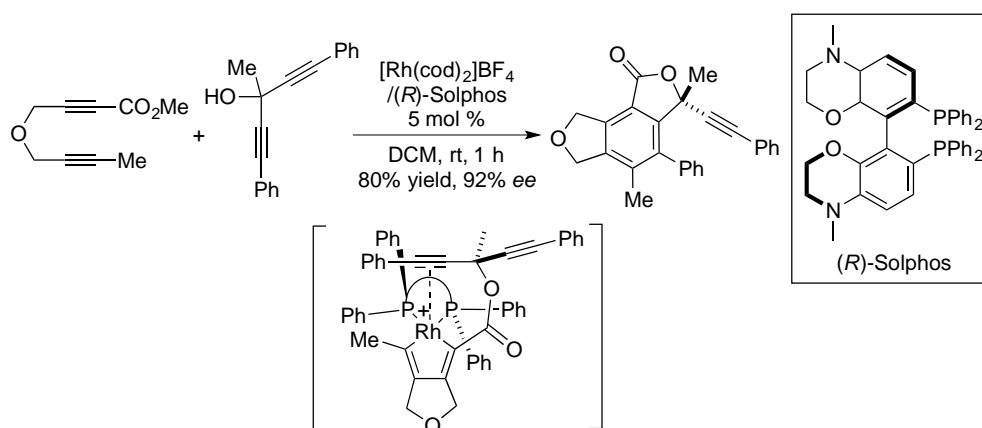
Since this pioneering work, the desymmetric [2+2+2] cycloadditions of prochiral substrates received more attention. Taking advantage of cationic rhodium(I)/phosphine catalytic systems, the group of Tanaka reported several examples by using these strategies. In 2006, they described two examples of enantioselective desymmetrization of substituted malononitriles.¹⁶³ Using cationic $[\text{Rh}(\text{cod})_2]\text{BF}_4/(\textit{R})\text{-Xylyl-Solphos}$ (or (*R*)-BINAP) complex catalyst, the reaction afforded enantioenriched bicyclic pyridines in 75-91% yields with moderate enantioselectivities (33% and 64%, respectively, Scheme 178).



Scheme 178

¹⁶³ Tanaka, K.; Suzuki, N.; Nishida, G. *Eur. J. Org. Chem.* **2006**, 3917.

In 2007, the same group described the synthesis of enantioenriched tricyclic 3,3-disubstituted phthalides involving a cationic rhodium-catalyzed desymmetric [2+2+2] cycloaddition reaction.¹⁶⁴ The reaction proceeded via an initial oxidative coupling of 1,6-diyne bearing a carbomethoxy group and simultaneously a transesterification with a symmetrical bispropargylic alcohol to form the rhodacyclopentadiene reactive species, followed by desymmetric insertion of one of the two alkynes to give the phthalide derivatives, which bear a chiral quaternary carbon center at the benzylic position (Scheme 179). The high regio- and enantioselectivity strongly relied on the presence of both methoxycarbonyl group and propargylic hydroxyl group.

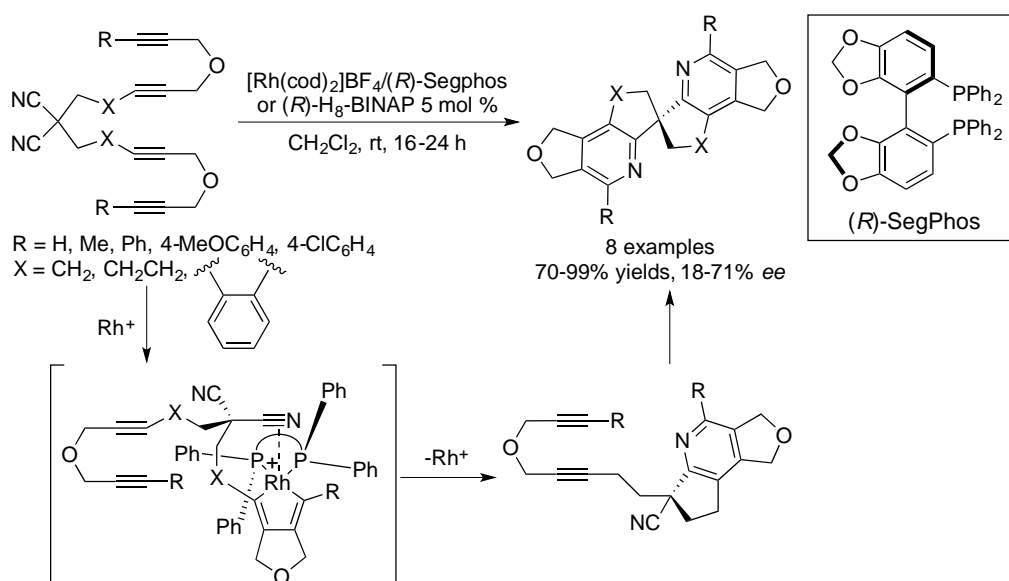


Scheme 179

The C_2 -symmetric spirobipyridine structures were also prepared via the rhodium/bisphosphine-catalyzed enantioselective intramolecular double [2+2+2] cycloadditions of bis-diyne nitriles.¹⁶⁵ A wide range of substrates were examined to produce various C_2 -symmetric spirobipyridine ligands in 70-99% yields with 18-71% enantioselectivities (Scheme 180).

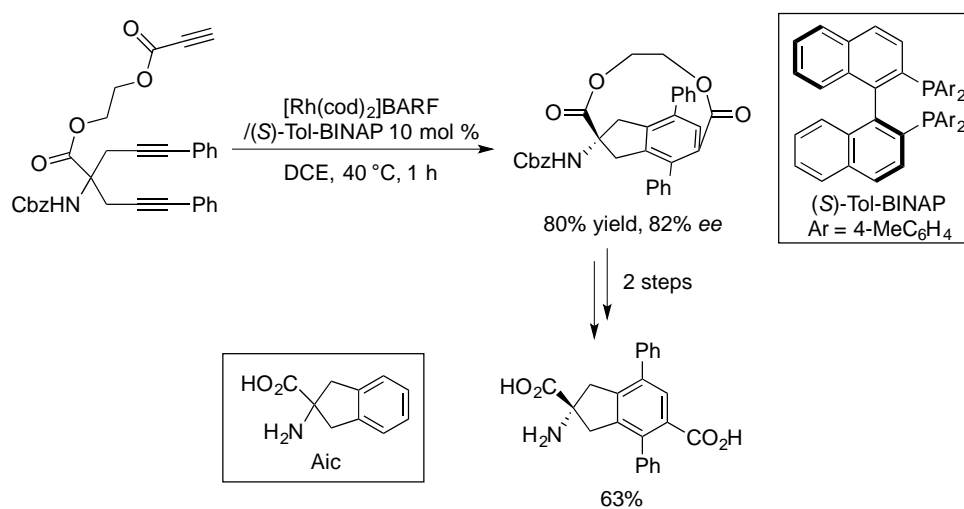
¹⁶⁴ Tanaka, K.; Osaka, T.; Noguchi, K.; Hirano, M. *Org. Lett.* **2007**, *9*, 1307.

¹⁶⁵ Wada, A.; Noguchi, K.; Hirano, M.; Tanaka, K. *Org. Lett.* **2007**, *9*, 1295.



Scheme 180

The aromatics containing a chiral center at β -position are more challenging to synthesize. Thus, Shibata and co-workers recently developed a rhodium-catalyzed intramolecular enantioselective [2+2+2] cycloaddition of amino-acid-tethered triynes for the preparation of the chiral center of tethered Aic derivatives (Scheme 181).¹⁶⁶

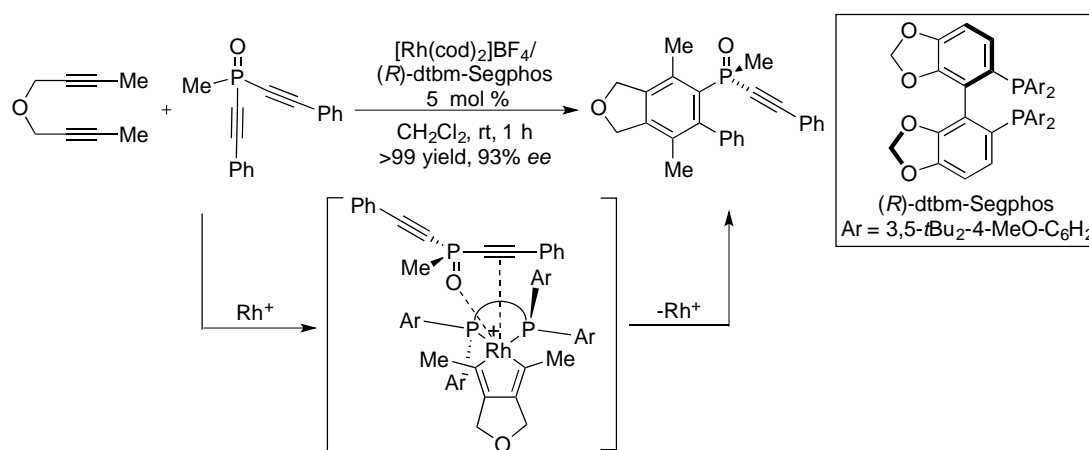


Scheme 181

¹⁶⁶ Tahara, Y. K.; Obinata, S.; Kanyiva, K. S.; Shibata, T.; Mándi, A.; Taniguchi, T.; Monde, K. *Eur. J. Org. Chem.* **2016**, 1405.

Not only quaternary-carbon-stereogenic centers but also other hetero-stereogenic centers, such as phosphorus and silicon, can be constructed through desymmetric enantioselective [2+2+2] cycloaddition reactions.

In 2008, Tanaka and co-workers successfully synthesized a family of phosphorus-stereogenic alkynylphosphine oxides by using cationic rhodium(I)/bisphosphine complex-catalyzed [2+2+2] cycloadditions of symmetrical dialkynylphosphine oxides with 1,6-diynes.¹⁶⁷ The desymmetric formation of a phosphorus-stereogenic center could be explained by the steric effect between the coordinated dialkynylphosphine oxide and the chiral phosphine ligand in the formed rhodium intermediate (Scheme 182).



Scheme 182

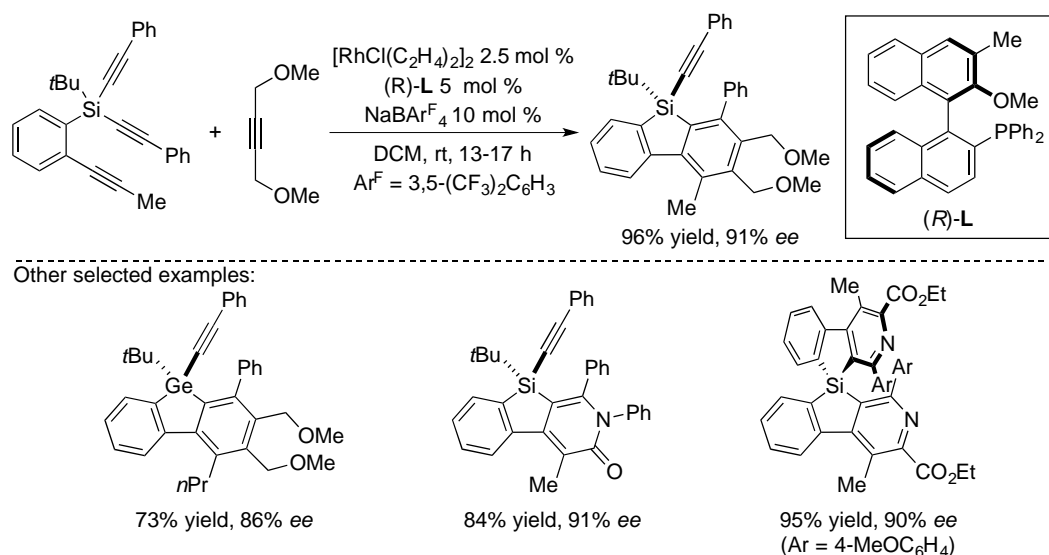
Nozaki and co-workers reported in 2015 a facile and efficient method for the preparation of silicon-stereogenic dibenzosiloles through enantioselective rhodium-catalyzed [2+2+2] cycloaddition of silicon-containing prochiral triynes with internal alkynes.¹⁶⁸ In the presence of $[\text{RhCl}(\text{C}_2\text{H}_4)_2]_2/\text{monophosphine}$ catalytic system, by exchange of the different tethers and unsaturated partners, enantioenriched germanium-stereogenic dibenzogermoles, silicon-stereogenic silicon-bridged arylpyridinones¹⁶⁹ and arylpyridines¹⁷⁰ were successfully obtained with good to high chemo-, regio- and enantioselectivities (Scheme 183). A drawback of this method was the difficult multiple-step synthesis of starting prochiral triynes.

¹⁶⁷ Nishida, G.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 3410.

¹⁶⁸ Shintani, R.; Takagi, C.; Ito, T.; Naito, M.; Nozaki, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 1616.

¹⁶⁹ Shintani, R.; Takano, R.; Nozaki, K. *Chem. Sci.* **2016**, *7*, 1205.

¹⁷⁰ Shintani, R.; Misawa, N.; Takano, R.; Nozaki, K. *Chem. Eur. J.* **2017**, *23*, 2660.



Scheme 183

3. Interest and synthesis of 1,3-dihydroisobenzofurans

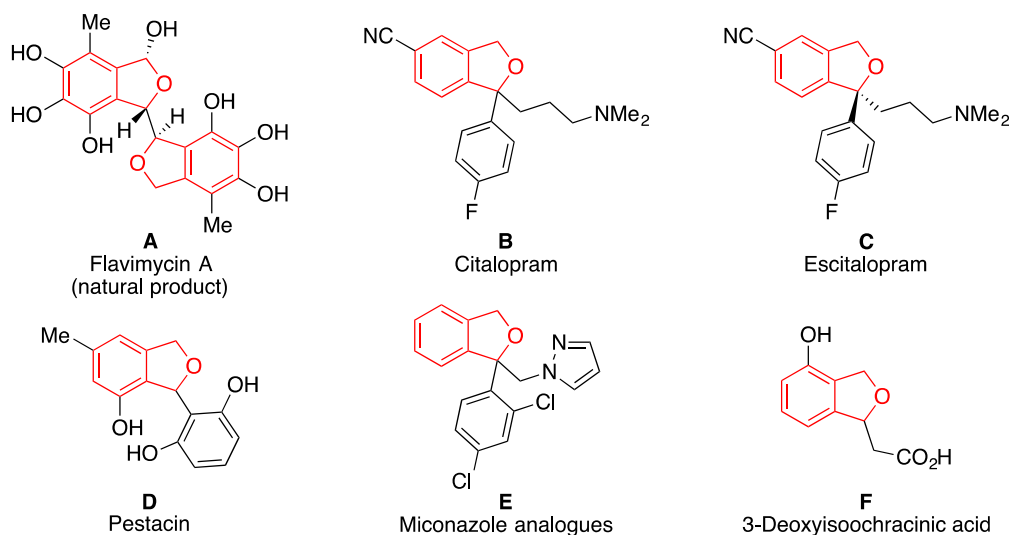
1,3-dihydroisobenzofurans (phthalanes)¹⁷¹ constitute an important class of oxygenated heterocycles, which are widely present in many bioactive natural products¹⁷² and pharmaceuticals¹⁷³. For examples, as shown in Scheme 184, Flavimycin A (**A**) was isolated as inhibitor of peptide deformylase from cultures of *Aspergillus flavipes*.^{172b} Citalopram (**B**) is a widely used antidepressant drug for the treatment of major depressive and general anxiety disorders in adults.^{173a-c} Further investigation indicated that the pharmaceutical activity of citalopram almost resided in the (*S*)-enantiomer, Escitalopram (**C**).^{173d} Pestacin (**D**) isolated from microorganism *Pestalotiopsis microspora* exhibits antifungal, antimycotic, and potent

¹⁷¹ Karmakar, R.; Pahari, P.; Mal, D. *Chem. Rev.* **2014**, *114*, 6213.

¹⁷² (a) Xu, X.; Song, F.; Wang, S.; Li, S.; Xiao, F.; Zhao, J.; Yang, Y.; Shang, S.; Yang, L.; Shi, J. *J. Nat. Prod.* **2004**, *67*, 1661. (b) Kwon, Y. J.; Sohn, M. J.; Kim, C. J.; Koshino, H.; Kim, W. G. *J. Nat. Prod.* **2012**, *75*, 271.

¹⁷³ (a) Eildal, J. N. N.; Andersen, J.; Kristensen, A. S.; Jørgensen, A. M.; Bang-Andersen, B.; Jørgensen, M.; Strømgaard, K. *J. Med. Chem.* **2008**, *51*, 3045. (b) Andersen, J.; Stühr-Hansen, N.; Zachariassen, L.; Toubro, S.; Hansen, S. M. R.; Eildal, J. N. N.; Bond, A. D.; Bøgesø, K. P.; Bang-Andersen, B.; Kristensen, A. S.; Strømgaard, K. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 12137. (c) Tu, H. M.; Wang, Q.; Zhu, J. *Chem. Commun.* **2016**, *4*, 11100. (d) Hyttel, J.; Bøgesø, K. P.; Perregaard, J.; Sanchez, C. *J. Neural Transm.* **1992**, *88*, 157. (e) Harper, J. K.; Arif, A. M.; Ford, E. J.; Strobel, G. A.; Porco, J. A.; Tomer, D. P.; Oneill, K. L.; Heider, E. M.; Grant, D. M. *Tetrahedron* **2003**, *59*, 2471. (f) Lovey, R. G.; Elliott, A. J.; Kaminski, J. J.; Loebenberg, D.; Parmegiani, R. M.; Rane, D. F.; Girijavallabhan, V. M.; Pike, Guzik, R. E.; Antonacci, H.; B.; Tomaine, T. Y. *J. Med. Chem.* **1992**, *35*, 4221. (g) Höller, U.; Gloer, J. B.; Wicklow, D. T. *J. Nat. Prod.* **2002**, *65*, 876. (h) Ewing, D. F.; Len, C.; Mackenzie, G.; Ronco, G.; Villa, P. *Tetrahedron Asymmetry* **2000**, *11*, 4995. (i) Egron, D.; Périgaud, C.; Gosselin, G.; Aubertin, A. M.; Faraj, A.; Sélouane, M.; Postel, D.; Len, C. *Bioorganic Med. Chem. Lett.* **2003**, *13*, 4473. (j) Goetzler, B.; Goetzler, T.; Shamma, M. *Tetrahedron* **1983**, *39*, 577. (b) Jing, L.; Wenzao, L.; Guoshi, T. *Planta Med.* **1994**, *60*, 486.

antioxidant activities.^{173e} Conformationally constrained miconazole analogues (**E**) containing a 1,3-dihydroisobenzofuran motif have improved antifungal potency compared to miconazole.^{173f} 3-Deoxyisoochracinic acid (**F**), the most abundant polyketide-derived metabolites of *Cladosporium sp*, showed antibacterial activity and inhibits the growth of *B. subtilis*.^{173g}



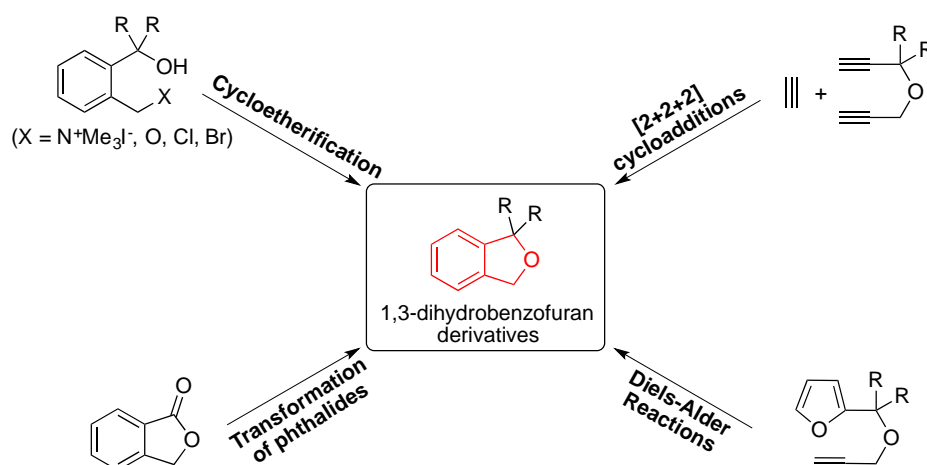
Scheme 184

Many synthetic approaches have been reported in the literature for the synthesis of these structurally diverse 1,3-dihydroisobenzofurans including cycloetherification of the *ortho*-substituted aromatics,¹⁷⁴ [2+2+2] cyclotrimerization of alkynes,⁷ Diels–Alder reaction,¹⁷⁵ and transformation of phthalides¹⁷⁶ (Scheme 185). Among them, the preparation of this scaffold by transition-metal-catalyzed [2+2+2] cycloaddition reaction may be considered as one of the most efficient method, as described in chapter I.

¹⁷⁴ (a) Yus, M.; Foubelo, F.; Ferrandez, J. V. *Tetrahedron* **2003**, *59*, 2083. (b) Kobayashi, K.; Shikata, K.; Fukamachi, S.; Konishi, H. *Heterocycles* **2008**, *75*, 599. (c) Capriati, V.; Florio, S.; Luisi, R.; Perna, F. M.; Salomone, A. *J. Org. Chem.* **2006**, *71*, 3984. (d) Dem'yanovich, V. M.; Shishkina, I. N.; Kuznetsova, A. A.; Potekhin, K. A.; Chesnova, A. V. *Russ. J. Org. Chem.* **2006**, *42*, 986.

¹⁷⁵ (a) Wu, H.-J.; Yen, C.-H.; Chuang, C. T. *J. Org. Chem.* **1998**, *63*, 5064. (b) Martín-Matute, B.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2003**, *125*, 5757. (c) Subrahmanyam, A. V.; Palanichamy, K.; Kaliappan, K. P. *Chem. Eur. J.* **2010**, *16*, 8545.

¹⁷⁶ (a) Meegalla, S. K.; Rodrigo, R. *Synthesis* **1989**, *12*, 942. (b) Verdaguer, X.; Berk, S. C.; Buchwald, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 12641. (c) Aggarwal, S.; Ghosh, N. N.; Aneja, R.; Joshi, H.; Chandra, R. *Helv. Chim. Acta.* **2002**, *85*, 2458. (d) Cox, C.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 3493.

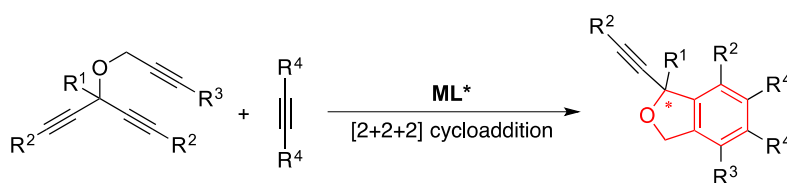


Scheme 185

4. Objectives

Considering the literature, the enantioselective synthesis of 1,3-dihydroisobenzofurans containing a stereogenic center at the α -position has rarely been reported and remains a challenge.¹⁷⁷

Desymmetrization of prochiral compounds serves as an efficient method to prepare complex molecules with a stereogenic chiral center. Therefore, we anticipated that the construction of 1,3-dihydroisobenzofurans could be achieved via the transition-metal-catalyzed [2+2+2] cycloaddition of prochiral oxygen-tethered triynes with internal alkynes. The proposed synthetic route is shown in Scheme 186.



Scheme 186

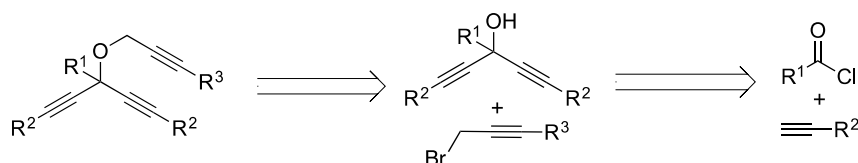
¹⁷⁷ Tomooka, K.; Wang, L.-F.; Okazaki, F.; Nakai, T. *Tetrahedron Lett.* **2000**, *41*, 6121. (b) Solares, L. F.; Brieva, R.; Quirós, M.; Llorente, I.; Bayodb, M.; Gotor, V. *Tetrahedron: Asymmetry* **2004**, *15*, 341. (c) Yuen, T.-Y.; Yang, S.-H.; Brimble, M. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8350. (d) Chai, Z.; Xie, Z.-F.; Liu, X.-Y.; Zhao, G.; Wang, J.-D. *J. Org. Chem.* **2008**, *73*, 2947.

5. Results and discussion

5.1 Synthesis of starting materials: prochiral triynes and internal alkynes

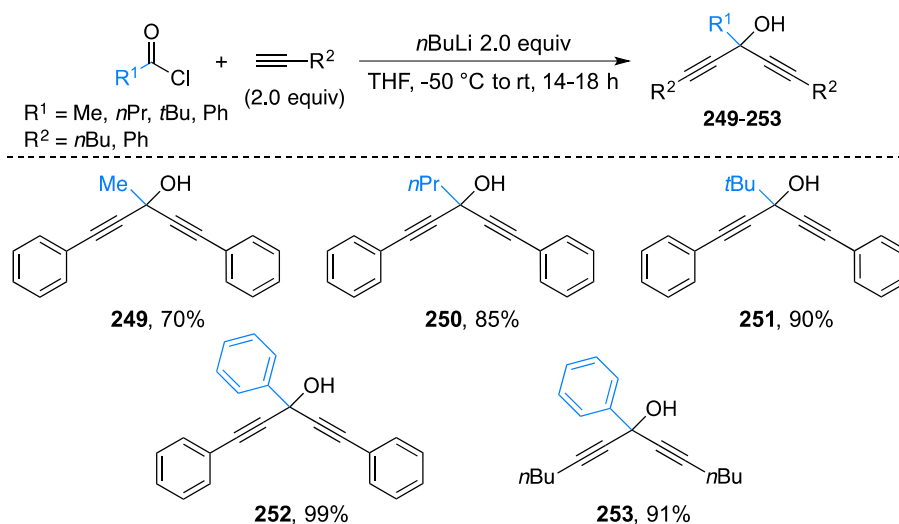
5.1.1. Synthesis of prochiral triynes

The prochiral oxygen-tethered triynes having an α,ω -diyne motif could be prepared from commercially available reagents, the retrosynthetic route is depicted in Scheme 187.



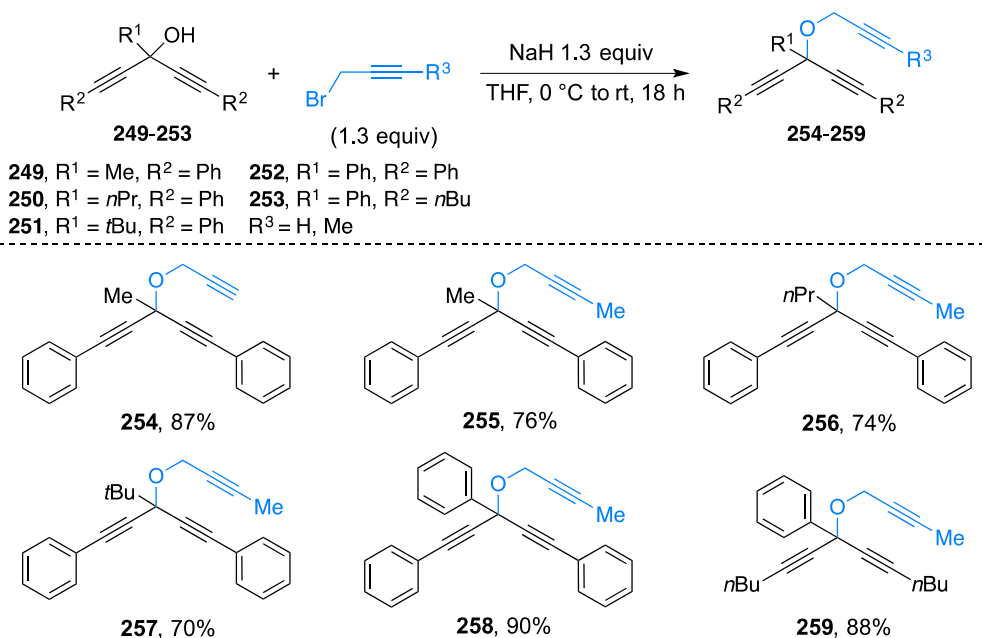
Scheme 187

The symmetrical bispropargylic alcohols **249-253** were prepared through the lithium mediated nucleophilic addition of terminal alkynes with acyl chlorides. As shown in Scheme 188, a series of acyl chlorides reacted with 2 equivalents of lithium acetylide, prepared *in situ* from the corresponding alkynes and *n*-butyllithium, affording the bispropargylic alcohols **249-253** in 70-99% yields. Both aryl and alkyl groups could be introduced to the quaternary carbon atom by using different acyl chlorides.



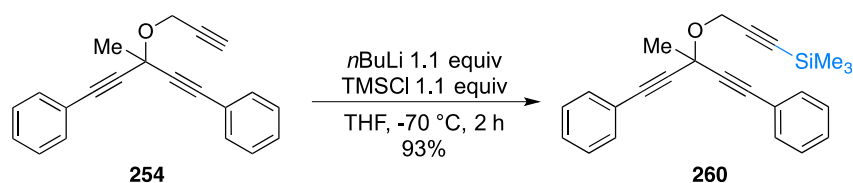
Scheme 188

The oxygen-tethered triynes **254-259** were successfully synthesized via the nucleophilic substitution of the alcohols **249-253** with 1.3 equivalents of propargyl bromide or 1-bromo-but-2-yne. The reaction was performed in the presence 1.3 equivalents of sodium hydride in THF, and afforded the desired triynes **254-259** in 70-90% yields (Scheme 189).



Scheme 189

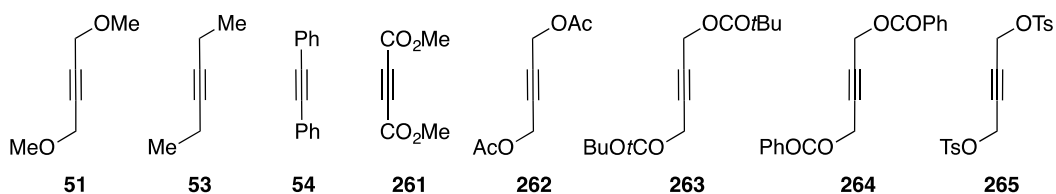
Treatment of terminal triyne **254** with 1.1 equivalents of *n*butyllithium in THF at -70 °C, followed by subsequent silylation with 1.1 equivalents of trimethylsilyl chloride, delivered the TMS-substituted triyne **260** in 93% yield (Scheme 190).



Scheme 190

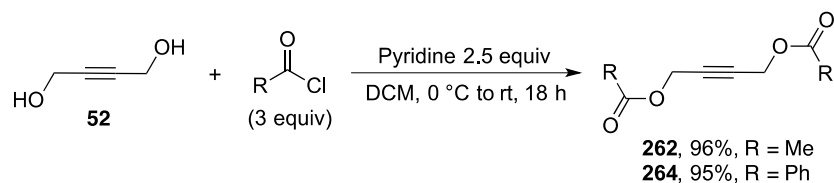
5.1.2. Synthesis of internal monoalkynes

To study the steric influence of the alkynes, different internal alkynes were prepared (Scheme 191). Dienes **51**, **53**, **54** and **261** were purchased from commercial sources, diynes **262-265** were prepared in the laboratory following the procedures described in the literature.¹⁷⁸



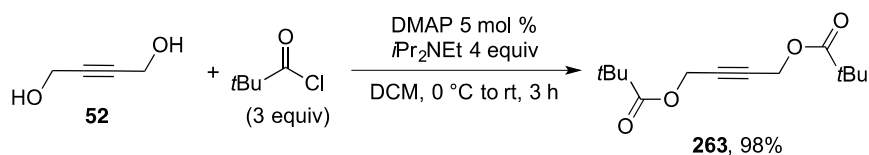
Scheme 191

The reaction of 2-butyl-1,4-diol **52** with 3 equivalents of acyl chlorides, such as acetyl chloride and benzoyl chloride, in the presence of 2.5 equivalents of pyridine provided the corresponding alkynes **262** and **264** in 96% and 95% yields, respectively (Scheme 192).



Scheme 192

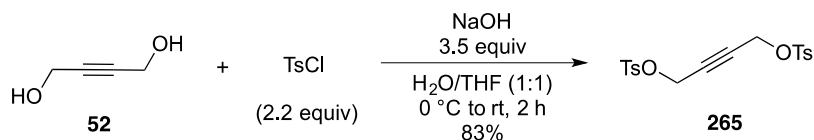
Alkyne **263** could be prepared by the reaction of 2-butyl-1,4-diol **52** with 3 equivalents of pivaloyl chloride using 5 mol % DMAP as catalyst and 4 equivalents of ethyldiisopropylamine as base, 98% of the desired product was obtained (Scheme 193).



Scheme 193

¹⁷⁸ (a) Muchow, G.; Brunel, J. M.; Maffei, M.; Buono, G. *J. Org. Chem.* **1995**, *60*, 852. (b) Hudiono, Y. C.; Miller, A. L.; Gibson, P. W.; LaFrate, A. L.; Noble, R. D.; Gin, D. L. *Ind. Eng. Chem. Res.* **2012**, *51*, 7453.

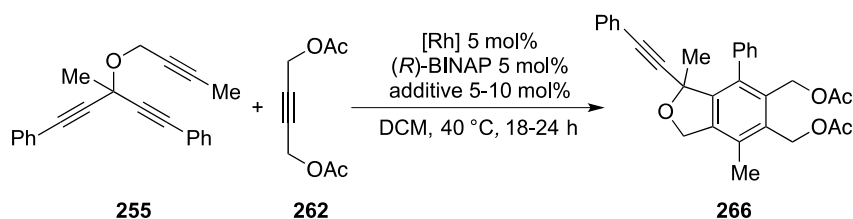
Treatment of the 2-butyl-1,4-diol **52** with 3.5 equivalents of sodium hydroxide in a mixture solution of water and THF at 0 °C with 2.2 equivalents of tosyl chloride furnished the tosyl protected internal alkyne **265** in 83% yield (Scheme 194).



Scheme 194

5.2 Rhodium-catalyzed desymmetric [2+2+2] cycloaddition of prochiral triynes with internal alkynes

With a series of alkynes in hand, we then attempted to synthesize 1,3-dihydroisobenzofuran **266** from prochiral triyne **255** and 1,4-diacetoxy-2-butyne **262** through an enantioselective rhodium-catalyzed [2+2+2] cycloaddition reaction. As shown in Table 5, we began our studies by investigating the reactivity of different cationic rhodium catalysts, such as $\text{Rh}(\text{cod})_2\text{BF}_4$,¹⁶³⁻¹⁶⁷ $[\text{Rh}(\text{hexadiene})\text{Cl}]_2/\text{AgSbF}_6$,¹⁵⁴ $[\text{Rh}(\text{ethylene})\text{Cl}]_2/\text{NaBAR}_4^{\text{F}}$,¹⁶⁸⁻¹⁷⁰ which proved to be efficient catalysts in related enantioselective [2+2+2] cycloadditions (Entries 1-3). The results showed that the use of $\text{Rh}(\text{cod})_2\text{BF}_4$ in combination with (*R*)-BINAP was the best choice for the transformation. Using 5 mol % of cationic $\text{Rh}(\text{cod})_2\text{BF}_4/(\text{R})\text{-BINAP}$ complex in dichloromethane at 40 °C lead to 50% yield and 50% *ee* of the desired product **266** by using 1:2 ratio of triyne **255** and alkyne **262** (Entry 1). Further evaluation of the ratio of [Rh]/ligand showed that an increase of the amount of (*R*)-BINAP (10 mol %, Entry 4) gave no improvement (yield and enantioselectivity). The reaction did not take place in the absence of phosphine ligand (Entry 5). Hydrogenation of the rhodium complex under 1 atm H_2 for 1 hour to remove the cod ligand allowed the formation of cycloadduct **266** in 66% isolated yield, but with a lower enantiomeric excess of 43% (Entry 6). Moreover, slow-addition technique was used to introduce triyne **255** in 3 h to a DCM solution of alkyne **262** and $\text{Rh}(\text{cod})_2\text{BF}_4/(\text{R})\text{-BINAP}$ complex using a syringe pump (Entry 7). However, the formation of unclear side products was observed, due to the homo-cyclization of triyne and totally intramolecular cycloaddition of triyne with alkyne.

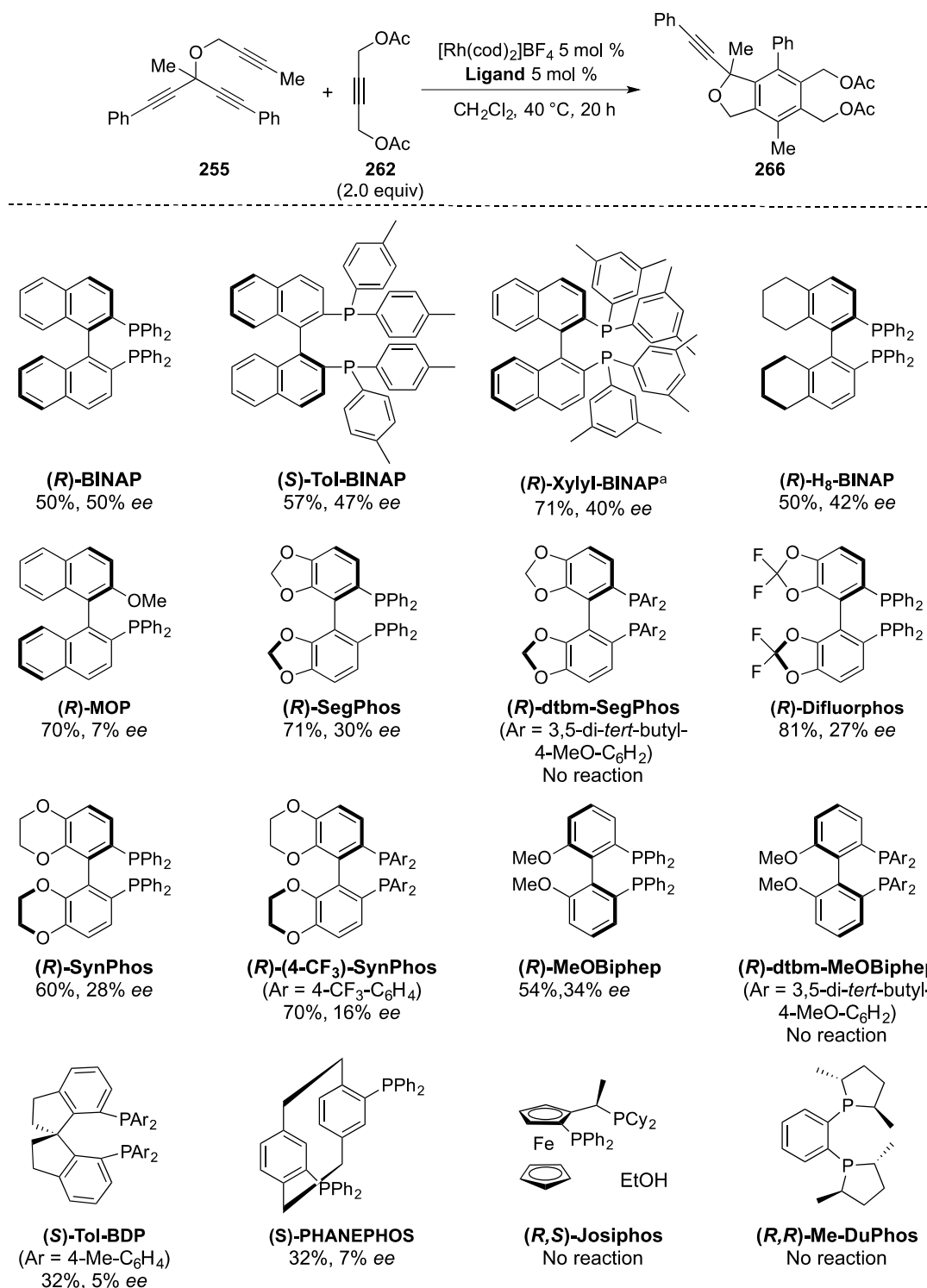
Table 5 Optimization of reaction conditions

Entry ^a	[Rh] catalyst	Additive (mol %)	Yield (%) ^b	<i>ee</i> (%) ^c
1	Rh(cod)₂BF₄	/	50	50
2	[Rh(hexadiene)Cl] ₂	AgSbF ₆ (5)	74	20
3 ^d	[Rh(ethylene)Cl] ₂	NaBAr ^F ₄ (10)	72	49
4 ^e	Rh(cod) ₂ BF ₄	/	50	50
5 ^f	Rh(cod) ₂ BF ₄	/	nr	/
6 ^g	Rh(cod) ₂ BF ₄	/	66	43
7 ^h	Rh(cod) ₂ BF ₄	/	50	50

^a Reaction conditions: [Rh] catalyst (5 mol %), (*R*)-BINAP (5 mol %), triyne **255** (0.3 mmol), alkyne **262** (0.6 mmol) were heated at 40 °C in a sealed Schlenk tube in DCM (3 mL) under an argon atmosphere for 20-24 h. ^b Isolated yield, nr = no reaction. ^c Determined by SFC analysis. ^d Ar^F = 3,5-(CF₃)₂C₆H₃. ^e 10 mol % of (*R*)-BINAP was used. ^f No ligand. ^g [Rh]/(*R*)-BINAP complex with previous hydrogenation (H₂, 1 atm, rt, 1 h). ^h Slow addition of triyne **255** in 3 hours using a syringe pump.

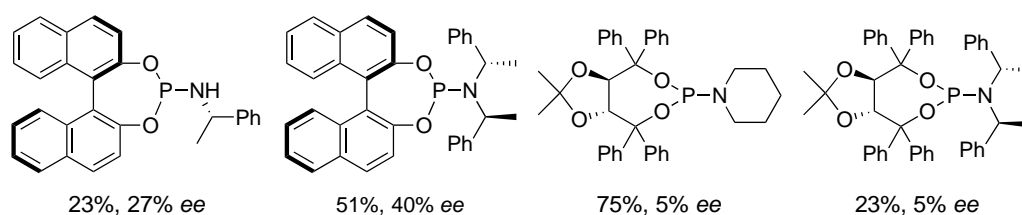
To further optimize the reaction conditions, a variety of bisphosphine and monophosphine ligands has been examined (Table 6). The influence of the chiral ligand was explored, (*S*)-Tol-BINAP, (*R*)-Xylyl-BINAP and (*R*)-H₈-BINAP gave slight decreased enantiomeric excesses. The combination of Rh(cod)₂BF₄ with axially chiral monophosphine (*R*)-MOP, which previously demonstrated high reactivity and selectivity for the desymmetrization of silicon-containing prochiral triynes with internal alkynes,¹⁶⁸⁻¹⁷⁰ afforded the cycloadduct in 70% yield with 7% *ee*. Oxygen fused electron-rich and electron-poor bidentate ligands, such as (*R*)-SegPhos, (*R*)-DifluorPhos, (*R*)-SynPhos and (*R*)-(4-CF₃)-SynPhos, showed higher reactivity to access compound **266** (60-81% yields), but lower enantioselectivities were obtained (16-30% *ee*). Phosphine ligands bearing sterically hindered PAr₂ moiety, such as (*R*)-dtbm-SegPhos and (*R*)-dtbm-MeOBiphep, did not provide the desired product. In contrast to the axially chiral phosphine ligands, (*S*)-Tol-BDP, (*S*)-PHANEPHOS, (*R,S*)-JosiPhos and (*R,R*)-Me-DuPhos, showed poor enantioselectivities and low reactivities under these reaction conditions.

Table 6 Screening of chiral phosphine ligands



^a Toluene was used as solvent.

We also evaluated a series of monodentate phosphoramidite ligands.¹⁷⁹ However, no improvement of enantioselectivity of compound **267** was obtained (5-40%, Scheme 195).

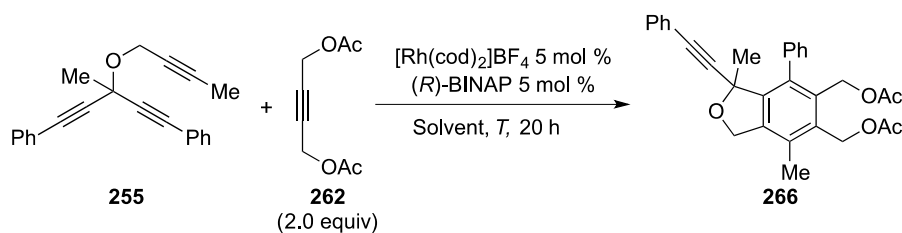


Scheme 195

These results demonstrated that the chiral phosphine ligands play an important role to promote the desymmetric [2+2+2] cycloadditions, although moderate enantioselectivities were obtained. In this context, the $\text{Rh}(\text{cod})_2\text{BF}_4/(\text{R})\text{-BINAP}$ complex was selected for the [2+2+2] cycloaddition reactions.

To improve the yield and enantiomeric excess, we next screened different organic solvents (Table 7). First, polar solvents were examined. The reaction was carried out in dichloroethane and tetrahydrofuran at 40 °C, in the presence of 5 mol % $\text{Rh}(\text{cod})_2\text{BF}_4/(\text{R})\text{-BINAP}$ complex to deliver the desired 1,3-dihydroisobenzofuran **266** in 61% and 72% yields, respectively, with 37% and 47% ee, respectively (Entries 2 and 3). The non-polar solvents such as toluene, xylene, chlorobenzene have also been evaluated (Entries 4-6). Slight increased yields of cycloadducts were observed, with moderate enantioselectivity. Performing the cycloaddition in toluene at 100 °C did not significantly improve the course of the cycloaddition (70% yield, 50% ee, Entry 4). The reaction was performed in the presence of 5 mol % $\text{Rh}(\text{cod})_2\text{BF}_4/(\text{R})\text{-BINAP}$ complex in 3 mL dichloromethane at 40 °C to evaluate the scope of the [2+2+2] cycloaddition.

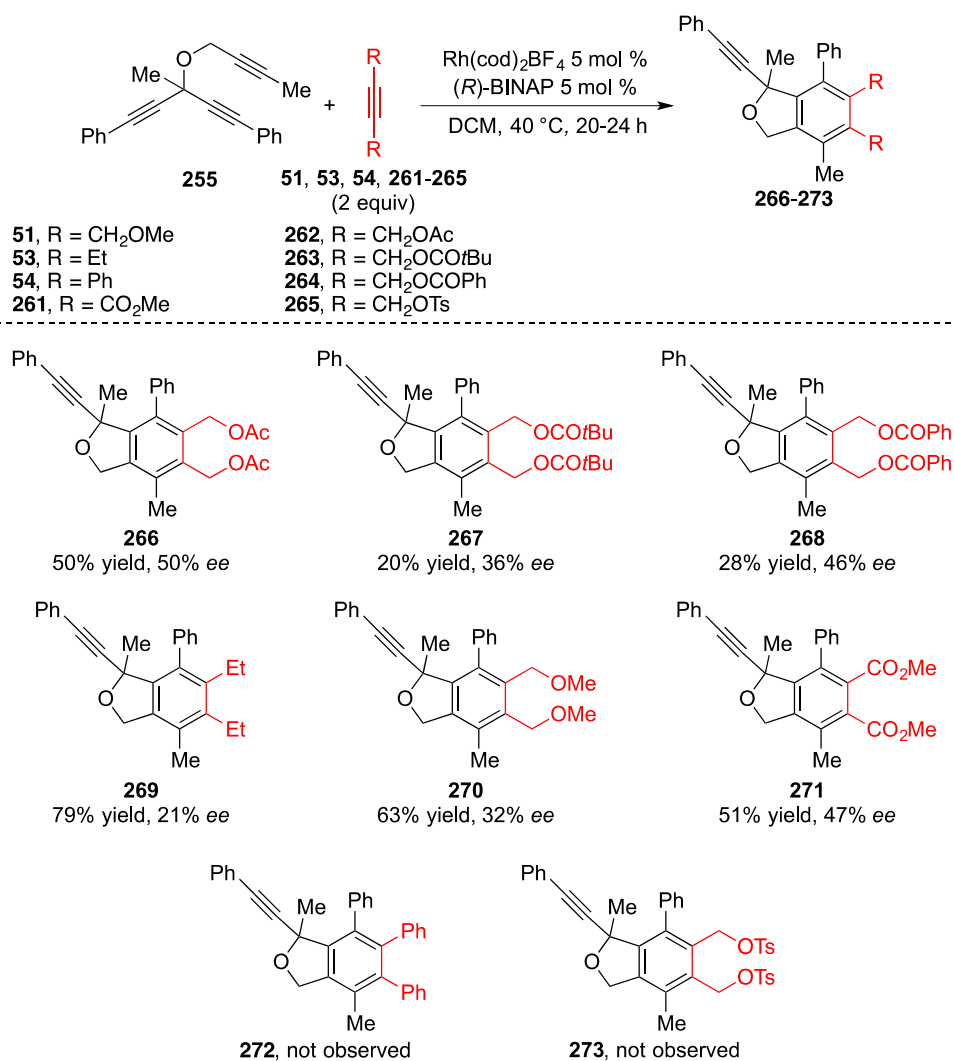
¹⁷⁹ Grandclaude C. (2016) *Réactions d'halocarbo-cyclisation par activation électrophile de fonctions carbonées insaturées (alcènes, alcynes, allènes). Etude des versions racémiques et chirales catalysées par des bases de Lewis* (Doctoral dissertation). Retrieved from <https://www.theses.fr/en/2016PA066228>

Table 7 The effect of solvent

Entry	Solvent	T ($^{\circ}\text{C}$)	Yield (%) ^b	ee (%) ^c
1	DCM	40	50	50
2	DCE	40	61	37
3	THF	40	72	47
4	Toluene	100	70	50
5	Xylene	100	60	46
6	Chlorobenzene	100	54	42

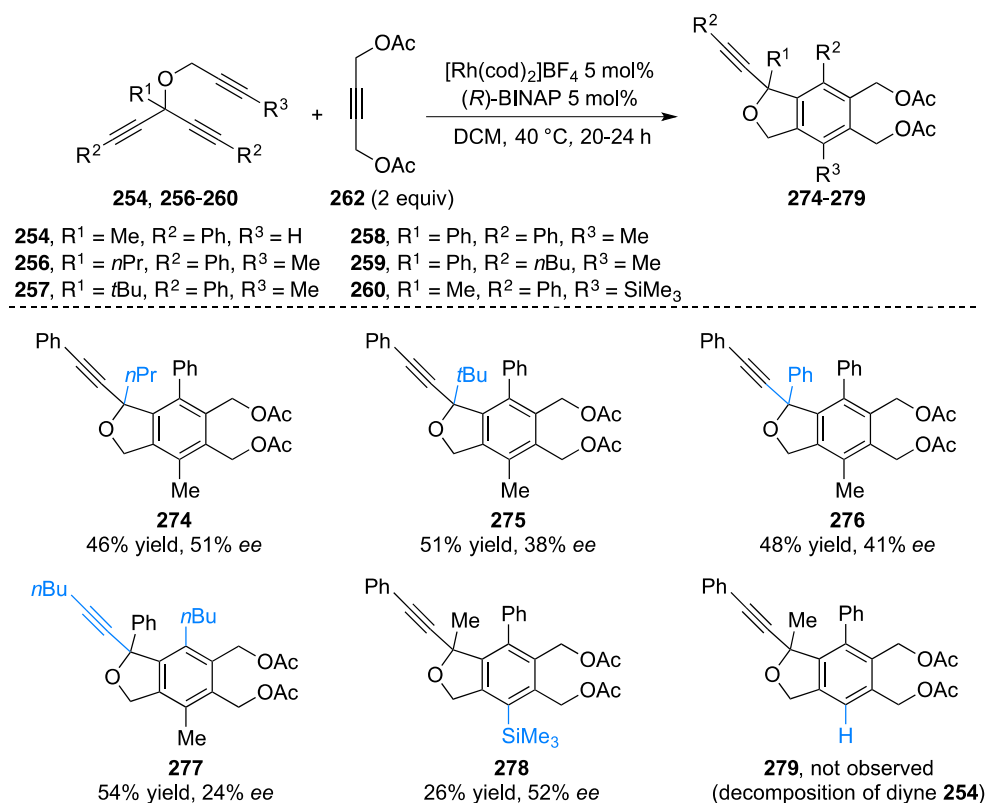
^a Reaction conditions: $\text{Rh}(\text{cod})_2\text{BF}_4$ (5 mol %), $(R)\text{-BINAP}$ (5 mol %), triyne **255** (0.3 mmol), alkyne **262** (0.6 mmol) were heated at 40 $^{\circ}\text{C}$ or 100 $^{\circ}\text{C}$ in a sealed Schlenk tube under an argon atmosphere for 20 h. ^b Isolated yield. ^c Determined by SFC analysis.

With the optimized reaction conditions in hand, we then investigated the generality and limitations of the synthetic protocol. A series of symmetrical internal alkynes with different substituents were engaged with triyne **255** under the optimized reaction conditions (Scheme 196). Switching to the more sterically hindered 2,2-dimethylpropanoate **263** and benzoate **264** allowed to promote the reaction to form cycloadducts **267** and **268** in respective 20% and 28% yields, and 36% and 46% ee . The use of 3-hexyne **53** gave the desired product **269** in 79% yield and 21% ee . The reaction of more electron-rich alkyne such as 1,4-dimethoxy-2-butyne **51** with triyne **255** afforded the cycloadduct **270** in 63% yield with 32% ee . In addition, the electron-deficient alkyne dimethyl acetylenedicarboxylate **261** can also be employed to provide the corresponding cyclized product **271** in 51% yield and 47% ee . On the other hand, we observed that the reaction was not compatible with diphenylacetylene **54**, probably because of the steric effect of the two phenyl groups. It was also found that no reaction occurred with the tosyl group protected 2-butyne **265**.



Scheme 196

With respect to the prochiral triynes, different substituents on the triynes were evaluated (Scheme 197). Replacement of methyl group on the quaternary carbon atom by *n*-propyl group provided the corresponding product **274** with similar 46% yield and 51% enantiomeric excess. The reaction of sterically demanding *tert*-butyl- and phenyl-substituted triynes **257** and **258** with internal alkyne **262** were inefficient for the enhancement of the enantioselectivity, leading to cycloadducts **275** and **276** with slightly lower 38% and 41% *ee*. The reaction also proceeded smoothly with the prochiral triyne **259** affording the cycloadduct **277** in 54% yield with 24% *ee*. The reaction was also applicable to the trimethylsilyl-substituted triyne **260**, which successfully reacted with alkyne **262** to deliver the corresponding product **278** with 52% enantioselectivity in 26% yield. Finally, the reactivity of the triyne **254** having a terminal alkyne moiety was examined. However, no desired product **279** was formed under these reaction conditions, only the decomposition of the starting triyne was observed.

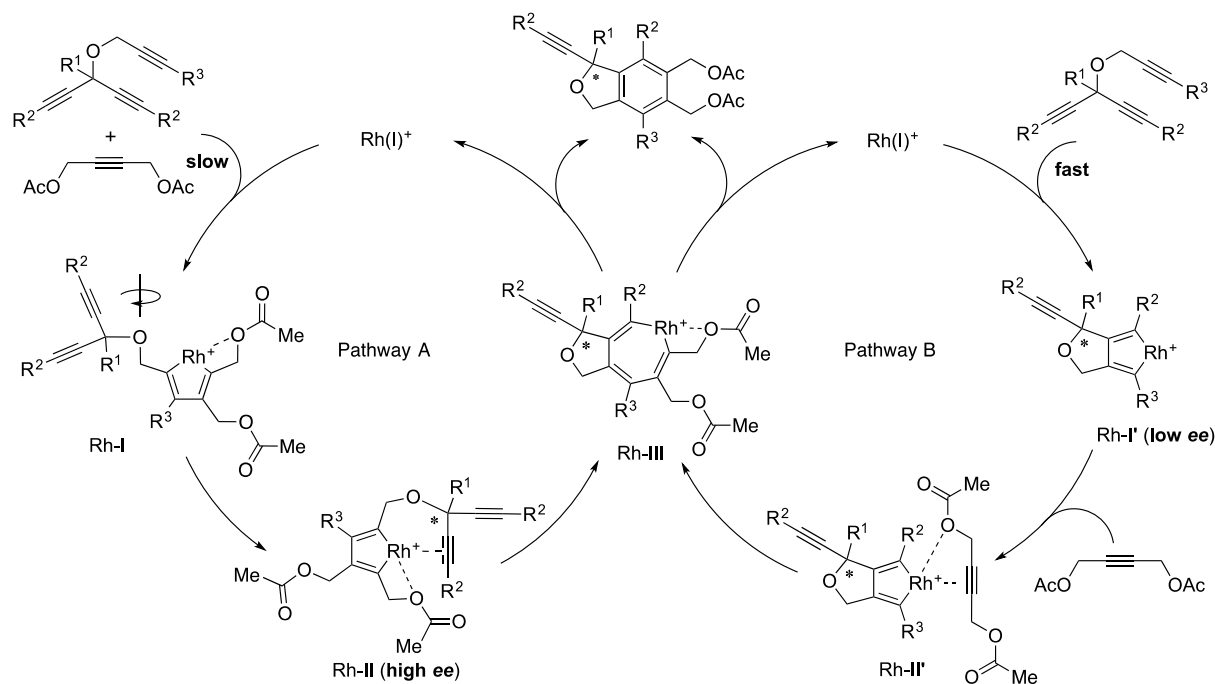


Scheme 197

To rationalize the moderate enantioselectivities, two plausible reaction pathways for the formation of chiral 1,3-dihydroisobenzofurans could be considered, A and B (Scheme 198). Reaction pathway A would comply a catalytic cycle starting from the intermolecular oxidative coupling of two alkyne motifs from both triyne and alkyne with rhodium species to afford the rhodacyclopentadiene intermediate Rh-I. Subsequent intramolecular selective coordination of one of the two alkynes substituted on the quaternary carbon atom to rhodium would lead to the intermediate Rh-II. This step could be considered as the enantioselective determining step affording higher enantioselective excess because of the steric interaction between the uncoordinated alkynyl group and the chiral ligand. The intramolecular insertion of the alkyne to the rhodium-carbon bond of Rh-II would deliver the seven-membered rhodacycle intermediate Rh-III, and the final reductive elimination would provide the 1,3-dihydroisobenzofuran with high *ee*.

On the other hand, pathway B would involve the rhodacyclopentadiene intermediate Rh-I' initially formed by the fast intramolecular oxidative coupling of the triyne with rhodium species. The low enantioselectivities would be explained by the position of the quaternary center located "far" from the metal center. Coordination and insertion of the monoalkyne would

also lead to the rhodacycle intermediate **Rh-III**. Reductive elimination would regenerate the rhodium species, and deliver the cycloadduct with lower *ee*. Considering the moderate enantioselectivities observed, we hypothesized that these two reaction pathways would occur at the same time.



Scheme 198

6. Conclusion

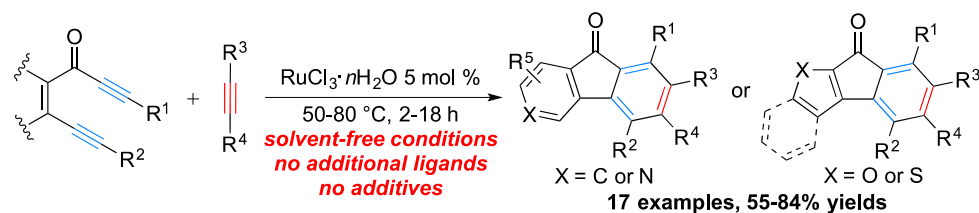
In summary, we have developed a new route for the synthesis of enantioenriched 1,3-dihydroisobenzofuran derivatives via an enantioselective rhodium-catalyzed [2+2+2] cycloaddition of prochiral triynes and monoalkynes. The reaction proceeded in the presence of a cationic $\text{Rh}(\text{cod})_2\text{BF}_4/(\text{R})\text{-BINAP}$ complex in DCM. This desymmetrization strategy allowed the formation of 1,1-disubstituted 1,3-dihydroisobenzofurans containing a quaternary carbon stereocenter in up to 79% yield and up to 52% *ee*. Two plausible reaction pathways were proposed to rationalize the moderate enantioselectivities.

General conclusion

General conclusion

With the aim of the PhD project to develop environmentally friendly and atom-economical processes to access biologically interesting polycyclic and heterocyclic aromatic compounds via transition-metal-catalyzed [2+2+2] cycloaddition reactions, we successfully accessed relevant building blocks including fluorenones, 2-aminopyridines and enantioenriched 1,3-dihydroisobenzofurans.

This work was first dedicated to the development of an efficient and practical route for the preparation of highly substituted fluorenones and analogues via solvent-free $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ -mediated [2+2+2] cycloaddition of α,ω -diynes and alkynes.¹⁸⁰ This green approach involves a solvent-free and atom-economical catalytic process to generate densely functionalized fluorenones and related derivatives of high synthetic utility (Scheme 199).



Scheme 199

We also developed a convenient access to functionalized 2-aminopyridines via a solvent-free $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ -promoted [2+2+2] cycloaddition reaction of α,ω -diynes and cyanamides.¹⁸¹ This transformation efficiently proceeds in the presence of a stable, easy to handle, and cost-effective $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ complex, leading to various 2-aminopyridines in moderate to high yields following an eco-friendly straightforward approach. During the course of the studies, we found that the cationic ruthenium complex, $\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$, could also be an efficient catalyst to promote the [2+2+2] cycloadditions of 1,6- and 1,7-diynes with cyanamides to prepare 2-aminopyridines.¹⁸² Mild reaction conditions were developed for this transformation. Notably, this atom-economical catalytic process demonstrated remarkable

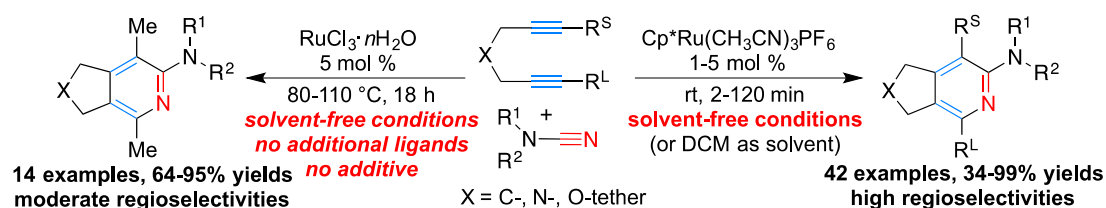
¹⁸⁰ Ye, F.; Haddad, M.; Michelet, V.; Ratovelomanana-Vidal, V. *Org. Lett.* **2016**, *18*, 5612.

¹⁸¹ Ye, F.; Haddad, M.; Michelet, V.; Ratovelomanana-Vidal, V. *Org Chem Front* **2017**, *4*, 1063.

¹⁸² Ye, F.; Haddad, M.; Ratovelomanana-Vidal, V.; Michelet, V. *Org. Lett.* **2017**, *19*, 1104.

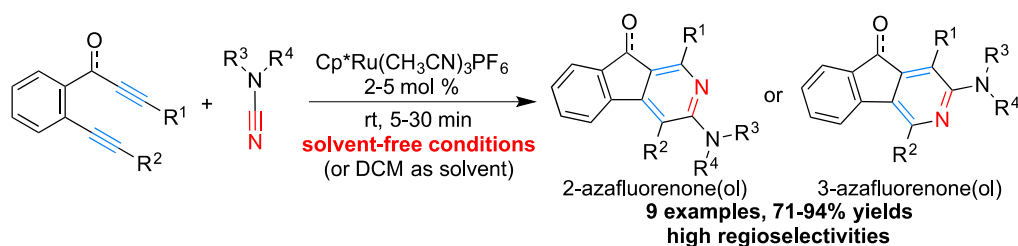
General conclusion

regioselectivities to access highly substituted pyridine derivatives of high synthetic utility (Scheme 200).



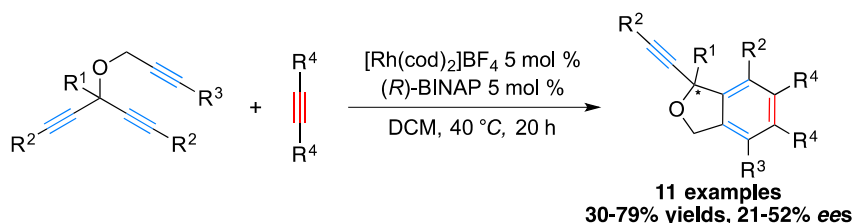
Scheme 200

Taking advantage of the cationic $\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ catalytic system, we also synthesized a family of aza-fluorenones and aza-fluorenols with high regioselectivities (Scheme 201).



Scheme 201

Finally, we focused on the enantioselective synthesis of substituted 1,3-dihydroisobenzofurans, containing a quaternary carbon stereogenic center, through a [2+2+2] cycloaddition of prochiral triynes with internal alkynes using a cationic rhodium complex incorporating BINAP ligand. Moderate yields and enantioselectivities were obtained (Scheme 202). Further investigations of this method are underway in the laboratory.



Scheme 202

Experimental part

Experimental part

1. General informations

1.1. Analysis

^1H NMR and ^{13}C NMR were recorded on Bruker AV300 or AV400 instruments. All signals are expressed as ppm (δ) and are referenced to the non-deuterated solvent peak CHCl_3 (7.26 ppm for ^1H and 77.16 ppm for ^{13}C) or Methanol- D_4 (3.31 ppm for ^1H and 49.00 ppm for ^{13}C). Coupling constants (J) are given in Hz and refer to apparent peak multiplicities. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

Melting points were determined with a Kofler Heizbank 7841 apparatus and are uncorrected.

Enantiomeric excesses were determined by SFC using stationary phase columns: Daicel Chiralpak OD-H.

Mass spectrometry analyses (direct introduction by chemical ionization with ammoniac or electrospray) were performed at the Ecole Nationale Supérieure de Chimie de Paris (ENSCP). High resolution mass spectra were performed at the University Pierre and Marie Curie (Paris).

X-ray diffraction was made at Pierre et Marie Curie University (UPMC).

1.2. Chromatography

Sigma-Aldrich Silica gel (high-purity grade, pore size 60 Å, 230-400 mesh particle size, 40-63 μm particle size) was employed for flash column chromatography. Analytical thin layer chromatography (TLC) was carried out using commercial silica-gel plates (Merck 60 F254), spots were detected with UV light (254 nm) and revealed with a KMnO_4 or *para*-anisaldehyde stain solution.

Experimental part

1.3. Purification of solvents and reagents

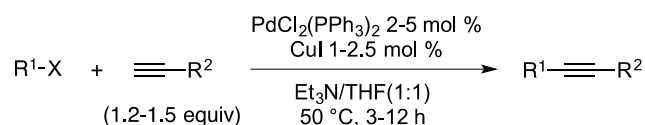
All reactions were performed under an atmosphere of argon. Toluene, THF, CH₂H₂, DMF, Et₂O were dried over alumina columns in an Innovative Technologies apparatus. Acetone was distilled over K₂CO₃, and water was distilled. All the solvents for catalysis were degassed prior to use.

All reagents were used as received from commercial sources, unless specified otherwise, or prepared as described in the literature. Every reagent was either purified following the methods described in the literature or used without further purification.

2. Formation of fluorenone and related derivatives

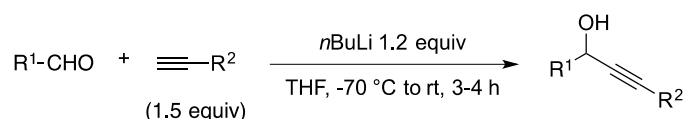
2.1. Synthesis of benzoyl bridged α,ω -diynes

General procedure A:



PdCl₂(PPh₃)₂ (2-5 mol %) and CuI (1-2.5 mol %) were added to a NEt₃/THF (1:1, 5.0 M) solution containing aryl halide (1.0 equiv), alkyne (1.2-1.5 equiv). The mixture was stirred at 50 °C for 3-5 h. When the reaction was complete (TLC monitoring), the mixture was cooled to room temperature. A saturated aqueous solution of ammonium chloride was added and the mixture was stirred for 5 minutes. The organic layer was extracted with ethyl acetate (×3), washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the desire compound.

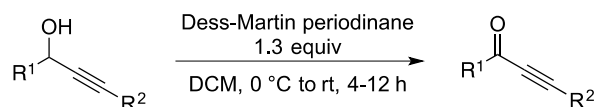
General procedure B:



To a THF solution of alkyne (1.2 equiv, 5.0 M) was added *n*BuLi (1.3 equiv) at -70 °C. The mixture was warmed to 0 °C and stirred for 1 h. The resulting mixture was then cooled to

-70 °C again and a solution of aldehyde (1.0 equiv) in THF was added over 10 min. Then the mixture was warmed to room temperature and stirred for 2-3 h before addition of a saturated aqueous ammonium chloride solution. The organic layer was extracted with ethyl acetate (×3), washed with water and brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the desired compound.

General procedure C:



Dess-Martin periodinane (1.3 equiv) was added to a solution of corresponding alcohol (1 equiv) in anhydrous CH₂Cl₂ (5 M) at 0 °C and the resulting mixture was stirred at room temperature for 4-12 h. When the reaction was complete (TLC monitoring), the reaction mixture was filtered through a pad of celite. A saturated aqueous solution of NaHCO₃ was added to the organic layer and stirred for 20 minutes. The organic layer was washed with water and brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the desired compound.

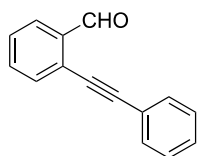
General procedure D:



TBAF (1 M in THF, 1.0 equiv) was added to a solution of TMS-protected product (1 equiv) in THF (5 M) at 0 °C and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with water and the product was extracted with DCM (×3). The organic layer was washed with saturated aqueous solution of NaHCO₃, water and brine, dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography to afford the desired product.

2-(Phenylethynyl)benzaldehyde (1)

Experimental part



Chemical Formula: C₁₅H₁₀O
Exact Mass: 206.0732

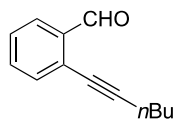
This compound was prepared using procedure **A**. Starting from 2-bromobenzaldehyde (1.0 g, 5.4 mmol) and phenylacetylene (0.71 mL, 6.5 mmol, 1.2 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 100/0 to 98/2) afforded **1** (0.85 g, 76%) as an orange oil. The analytical data were identical to the literature.¹⁸³

R_f = **0.6** (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃), δ 10.66 (d, J = 0.8 Hz, 1H), 7.97 – 7.94 (m, 1H), 7.66 – 7.54 (m, 4H), 7.47 – 7.37 (m, 4H).

¹³C NMR (75 MHz, CDCl₃), δ 191.8, 135.9, 133.9, 133.3, 131.8, 129.2, 128.7, 128.6, 127.4, 127.0, 122.4, 96.4, 85.0.

2-(Hex-1-yn-1-yl)-benzaldehyde (**2**)



Chemical Formula: C₁₃H₁₄O
Exact Mass: 186.1045

This compound was prepared using procedure **A**. Starting from 2-bromobenzaldehyde (2.5 g, 13.5 mmol) and 1-hexyne (2.0 mL, 17.5 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 99/1 to 95/5) afforded **2** (1.95 g, 79%) as a brown oil. The analytical data were identical to the literature.¹⁸³

R_f = **0.8** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

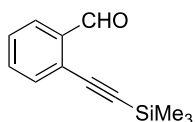
¹H NMR (300 MHz, CDCl₃) δ 10.53 (d, J = 0.7 Hz, 1H), 7.87 (dd, J = 4.8, 4.0 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.41 – 7.30 (m, 1H), 2.48 (t, J = 7.0 Hz, 2H), 1.68 – 1.55 (m, 2H), 1.55 – 1.40 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H).

¹⁸³ Sakamoto, T.; Kondo, Y.; Miura, N.; Hayashi, K.; Yamanaka, H. *Heterocycles* **1986**, *24*, 2311.

^{13}C NMR (75 MHz, CDCl_3) δ 192.3, 136.2, 133.8, 133.4, 128.1, 128.0, 127.0, 98.3, 76.5, 30.7, 22.2, 19.4, 13.7.

MS (CI, NH_3): $m/z = 187$ $[\text{M} + \text{H}]^+$.

2-((Trimethylsilyl)ethynyl)benzaldehyde (3)



Chemical Formula: $\text{C}_{12}\text{H}_{14}\text{OSi}$
Exact Mass: 202.0814

This compound was prepared using procedure **A**. Starting from 2-bromobenzaldehyde (3.68 g, 20.0 mmol) and trimethylsilylacetylene (3.3 mL, 24.0 mmol, 1.2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 98/2 to 90/10) afforded **3** (3.5 g, 87%) as a white solid. m.p. 56 – 58 °C.

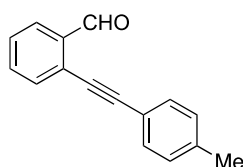
$R_f = 0.62$ (Cyclohexane/Ethyl acetate; 95/5, KMnO_4 , UV).

^1H NMR (300 MHz, CDCl_3) δ 10.37 (d, $J = 0.8$ Hz, 1H), 7.74 – 7.68 (m, 1H), 7.41 – 7.29 (m, 2H), 7.26-7.19 (m, 1H), 0.10 (s, 9H).

^{13}C NMR (75 MHz, CDCl_3) δ 191.8, 136.3, 133.7, 133.6, 128.9, 127.0, 126.9, 102.5, 100.2, -0.1.

MS (CI, NH_3): $m/z = 203$ $[\text{M} + \text{H}]^+$.

2-(*p*-Tolylethynyl)benzaldehyde (4)



Chemical Formula: $\text{C}_{16}\text{H}_{12}\text{O}$
Exact Mass: 220.0888

This compound was prepared using procedure **A**. Starting from 2-bromobenzaldehyde (2.5 g, 13.5 mmol) and 4-ethynyltoluene (1.88 mL, 16.2 mmol, 1.2 equiv). Purification on silica gel

Experimental part

(Cyclohexane/Ethyl acetate gradient from 99/1 to 98/2) afforded **4** (2.3 g, 80%) as a white solid. m.p. 32 – 34 °C. The analytical data were identical to the literature.¹⁸⁴

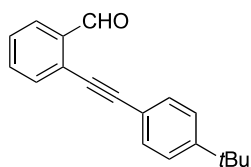
R_f = **0.62** (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃), δ 10.66 (d, *J* = 0.9 Hz, 1H), 7.97 – 7.92 (m, 1H), 7.68 – 7.53 (m, 2H), 7.49 – 7.41 (m, 3H), 7.23– 7.16 (m, 2H), 2.39 (s, 3H).

¹³C NMR (75 MHz, CDCl₃), δ 191.9, 139.5, 136.0, 133.9, 133.3, 131.7, 129.4, 128.5, 127.4, 119.4, 96.8, 84.5, 21.7.

MS (CI, NH₃): *m/z* = 221 [M + H]⁺.

2-((4-(*tert*-Butyl)phenyl)-ethynyl)-benzaldehyde (**5**)



Chemical Formula: C₁₉H₁₈O
Exact Mass: 262.1358

This compound was prepared using procedure **A**. Starting from 2-bromobenzaldehyde (2.5 g, 13.5 mmol) and 4-(*tert*-butyl)phenylacetylene (2.56 g, 16.2 mmol, 1.2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 99/1 to 98/2) afforded **5** (2.4 g, 70%) as a brown solid. m.p. 50 – 52 °C. The analytical data were identical to the literature.¹⁸⁵

R_f = **0.7** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

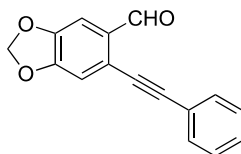
¹H NMR (300 MHz, CDCl₃) δ 10.66 (s, 1H), 7.95 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.68 – 7.54 (m, 2H), 7.54 – 7.35 (m, 5H), 1.34 (s, 9H).

¹³C NMR (75 MHz, CDCl₃) δ 192.0, 152.7, 136.0, 133.9, 133.3, 131.6, 130.2, 128.6, 127.3, 125.7, 119.5, 96.8, 84.5, 35.1, 31.3.

6-(Phenylethynyl)benzo[*d*][1,3]dioxole-5-carbaldehyde (**6**)

¹⁸⁴ Alfonsi, M.; Dell'Acqua, M.; Facoetti, D.; Arcadi, A.; Abbiati G.; Rossi, E. *Eur. J. Org. Chem.* **2009**, 2852.

¹⁸⁵ K. K. Wang, H.-R. Zhang and J. L. Petersen, *J. Org. Chem.*, 1999, **64**, 1650.



Chemical Formula: C₁₆H₁₀O₃
Exact Mass: 250.0630

This compound was prepared using procedure **A**. Starting from 2-bromo-4,5-methylenedioxybenzaldehyde (2.3 g, 10.0 mmol) and phenylacetylene (1.2 mL, 11.2 mmol, 1.1 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 99/1 to 98/2) afforded **6** (1.8 g, 72%) as a white solid. m.p. 118 – 120 °C. The analytical data were identical to the literature.¹⁸⁶

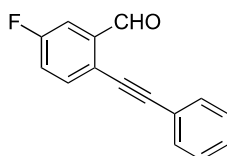
R_f = **0.6** (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 10.49 (s, 1H), 7.58-7.49 (m, 2H), 7.41-7.34 (m, 4H), 7.03 (s, 1H), 6.09 (s, 2H).

¹³C NMR (75 MHz, CDCl₃) δ 190.1, 152.5, 148.9, 132.3, 131.7, 129.1, 128.7, 123.8, 122.5, 112.2, 106.3, 102.5, 95.3, 84.9.

MS (CI, NH₃): m/z = 251 [M + H]⁺.

5-Fluoro-2-(phenylethynyl)benzaldehyde (**7**)



Chemical Formula: C₁₅H₉FO
Exact Mass: 224.0637

This compound was prepared using procedure **A**. Starting from 2-bromo-5-fluorobenzaldehyde (2.0 g, 10.0 mmol) and phenylacetylene (1.23 g, 12.0 mmol, 1.2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) afforded **7** (1.55 g, 70%) as a pale yellow solid. m.p. 54 – 56 °C. The analytical data were identical to the literature.¹⁸⁷

¹⁸⁶ Huang, Q.-H.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437.

¹⁸⁷ Obika, S.; Kono, H.; Yasui, Y.; Yanada, R.; Takemoto, Y. *J. Org. Chem.* **2007**, *72*, 4462.

Experimental part

R_f = **0.62** (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

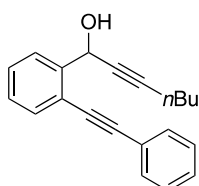
¹H NMR (300 MHz, CDCl₃) δ 10.60 (d, *J* = 3.0 Hz, 1H), 7.68-7.59 (m, 2H), 7.58-7.52 (m, 2H), 7.43-7.36 (m, 3H), 7.34-7.26 (m, 1H).

¹³C NMR (75 MHz, CDCl₃) δ 190.5, 162.6 (d, *J* = 215.6 Hz), 138.0 (d, *J* = 6.6 Hz), 135.4 (d, *J* = 7.7 Hz), 131.8, 129.3, 128.7, 123.1 (d, *J* = 3.3 Hz), 122.3, 121.5 (d, *J* = 22.6 Hz), 113.9 (d, *J* = 22.6 Hz), 96.2, 84.0.

¹⁹F NMR (282 MHz, (CDCl₃): -109.94 (t, *J* = 2.8 Hz).

MS (CI, NH₃): *m/z* = 242 [M + NH₄]⁺.

1-(2-(Phenylethynyl)phenyl)hept-2-yn-1-ol (**8**)



Chemical Formula: C₂₁H₂₀O
Exact Mass: 288.1514

This compound was prepared using procedure **B**. Starting from 2-(phenylethynyl)benzaldehyde **1** (2.6 g, 12.6 mmol) and 1-hexyne (2.16 mL, 18.0 mmol, 1.5 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded **8** (3.3 g, 92%) as a pale orange oil. The analytical data were identical to the literature.¹⁸⁸

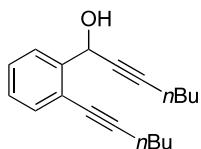
R_f = **0.34** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃), δ 7.74 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.58 – 7.54 (m, 3H), 7.42 – 7.28 (m, 5H), 5.96 (s, 1H), 2.70 (s, 1H), 2.30 – 2.25 (m, 2H), 1.51 – 1.39 (m, 4H), 0.88 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃), δ 143.0, 132.5, 131.7, 128.9, 128.7, 128.5, 128.2, 126.7, 123.0, 121.4, 94.9, 87.7, 86.8, 79.4, 63.5, 30.7, 22.1, 18.7, 13.7.

1-(2-(Hex-1-yn-1-yl)-phenyl)hept-2-yn-1-ol (**9**)

¹⁸⁸ Chen, Y.-F.; Chen, M.; Liu, Y.-H. *Angew. Chem. Int. Ed.* **2012**, *51*, 6181.



Chemical Formula: C₁₉H₂₄O
Exact Mass: 268.1827

This compound was prepared using procedure **B**. Starting from 2-(hex-1-yn-1-yl)benzaldehyde **2** (0.91 g, 4.9 mmol) and 1-hexyne (0.73 mL, 6.4 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate 95/5) afforded **9** (0.68 g, 50%) as a pale orange oil.

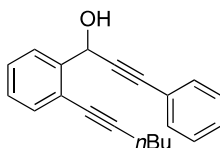
R_f = **0.38** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.66 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.41 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.34 – 7.20 (m, 2H), 5.88 – 5.79 (m, 1H), 2.64 (d, *J* = 5.5 Hz, 1H), 2.46 (t, *J* = 7.0 Hz, 2H), 2.28 (t, *J* = 7.0 Hz, 2H), 1.65 – 1.52 (m, 4H), 1.49 – 1.37 (m, 4H), 0.96 (t, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 142.9, 132.6, 128.2, 128.1, 126.7, 122.3, 96.3, 87.6, 79.4, 78.1, 63.7, 30.9, 30.8, 22.2, 22.1, 19.4, 18.7, 13.7.

MS (CI, NH₃): *m/z* = 251 [M + H - H₂O]⁺.

1-(2-(Hex-1-yn-1-yl)phenyl)-3-phenylprop-2-yn-1-ol (**10**)



Chemical Formula: C₂₁H₂₀O
Exact Mass: 288.1514

This compound was prepared using procedure **B**. Starting from 2-(hex-1-yn-1-yl)benzaldehyde **2** (1 g, 5.4 mmol) and phenylacetylene (0.77 mL, 7.0 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded **10** (1.25 g, 81%) as a pale yellow oil.

R_f = **0.4** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

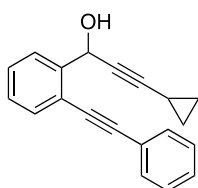
Experimental part

¹H NMR (300 MHz, CDCl₃) δ 7.73 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.52 – 7.41 (m, 3H), 7.37 – 7.23 (m, 5H), 6.06 (s, 1H), 2.80 (br, 1H), 2.49 (t, $J = 7.0$ Hz, 2H), 1.69 – 1.56 (m, 2H), 1.56 – 1.44 (m, 2H), 0.94 (t, $J = 7.3$ Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 142.3, 132.7, 131.9, 128.6, 128.4, 128.3, 128.3, 126.8, 122.8, 122.4, 96.7, 88.5, 86.6, 78.1, 64.1, 30.9, 22.2, 19.5, 13.8.

MS (CI, NH₃): $m/z = 271$ [M + H - H₂O]⁺.

3-Cyclopropyl-1-(2-(phenylethynyl)phenyl)prop-2-yn-1-ol (11)



Chemical Formula: C₂₀H₁₆O
Exact Mass: 272.1201

This compound was prepared using procedure **B**. Starting from 2-(phenylethynyl)benzaldehyde **1** (1.1 g, 5.3 mmol) and cyclopropylacetylene (0.58 mL, 7.0 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded **11** (1.2 g, 92%) as a pale yellow oil. The analytical data were identical to the literature.¹⁸⁸

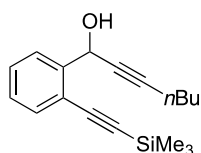
R_f = **0.38** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.70 (dd, $J = 7.6, 1.4$ Hz, 1H), 7.60 – 7.51 (m, 3H), 7.42 – 7.34 (m, 4H), 7.34 – 7.30 (m, 1H), 5.90 (dd, $J = 5.5, 1.6$ Hz, 1H), 2.62 (d, $J = 5.6$ Hz, 1H), 1.38 – 1.23 (m, 1H), 0.79 – 0.69 (m, 4H).

¹³C NMR (75 MHz, CDCl₃) δ 142.9, 132.5, 131.7, 129.0, 128.7, 128.5, 128.2, 126.8, 123.0, 121.4, 94.9, 90.7, 86.8, 74.7, 63.6, 8.4, -0.3.

MS (CI, NH₃): $m/z = 255$ [M + H - H₂O]⁺.

1-(2-((Trimethylsilyl)ethynyl)phenyl)hept-2-yn-1-ol (12)



Chemical Formula: $C_{18}H_{24}OSi$
Exact Mass: 284.1596

This compound was prepared using procedure **B**. Starting from 2-((trimethylsilyl)ethynyl)benzaldehyde **3** (1.5 g, 7.4 mmol) and 1-hexyne (1.1 mL, 9.6 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **12** (1.7 g, 80%) as a colorless oil. The analytical data were identical to the literature.¹⁸⁹

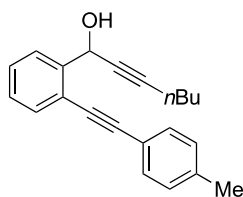
R_f = **0.44** (Cyclohexane/Ethyl acetate; 90/10, $KMnO_4$, UV).

¹H NMR (300 MHz, $CDCl_3$) δ 7.71 – 7.63 (m, 1H), 7.47 (dd, $J = 7.6, 1.2$ Hz, 1H), 7.35 (td, $J = 7.6, 1.4$ Hz, 1H), 7.28 – 7.21 (m, 1H), 5.87 – 5.80 (m, 1H), 2.77 (d, $J = 5.4$ Hz, 1H), 2.27 (td, $J = 7.0, 2.0$ Hz, 2H), 1.59 – 1.35 (m, 4H), 0.91 (t, $J = 7.2$ Hz, 3H), 0.28 (s, 9H).

¹³C NMR (75 MHz, $CDCl_3$) δ 143.7, 132.9, 129.2, 128.1, 126.7, 121.3, 102.6, 100.5, 87.8, 79.2, 63.6, 30.8, 22.1, 18.7, 13.7, -0.02.

MS (CI, NH_3): $m/z = 267$ $[M + H - H_2O]^+$.

1-(2-(*p*-Tolyethynyl)phenyl)hept-2-yn-1-ol (**13**)



Chemical Formula: $C_{22}H_{22}O$
Exact Mass: 302.1671

This compound was prepared using procedure **B**. Starting from 2-(*p*-tolylethynyl)benzaldehyde **4** (1.0 g, 4.6 mmol) and 1-hexyne (0.68 mL, 5.9 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **13** (1.19 g, 87%) as a pale oil. The analytical data were identical to the literature.¹⁹⁰

¹⁸⁹ Schmittl, M.; Strittmatter, M.; Mahajan, A. A.; Vavilala, C.; Cinar, M. E.; Maywald, M. *Arkivoc* **2007**, 66.

¹⁹⁰ Schmittl, M.; Keller, M.; Kiau, S.; Strittmatter, M. *Chem. Eur. J.* **1997**, *3*, 807.

Experimental part

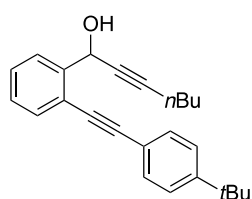
R_f = **0.43** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.78-7.70 (m, 1H), 7.58-7.51 (m, 1H), 7.51-7.43 (m, 2H), 7.41-7.27 (m, 2H), 7.22-7.14 (m, 2H), 5.96 (s, 1H), 2.81 (d, J = 4.8 Hz, 1H), 2.38 (s, 3H), 2.33-2.24 (m, 2H), 1.59-1.35 (m, 4H), 0.90 (t, J = 7.2 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 143.0, 138.8, 132.3, 131.5, 129.2, 128.7, 128.1, 126.6, 121.6, 119.9, 95.1, 87.5, 86.2, 79.5, 63.5, 30.7, 22.0, 21.6, 18.6, 13.6.

MS (CI, NH₃): m/z = 285 [M + H - H₂O]⁺.

1-(2-((4-(*tert*-Butyl)phenyl)ethynyl)-phenyl)-hept-2-yn-1-ol (**14**)



Chemical Formula: C₂₅H₂₈O
Exact Mass: 344.2140

This compound was prepared using procedure **B**. Starting from 2-((4-(*tert*-butyl)-phenyl)-ethynyl)-benzaldehyde **5** (0.92 g, 3.5 mmol) and 1-hexyne (0.52 mL, 4.5 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **14** (1.0 g, 83%) as a pale oil.

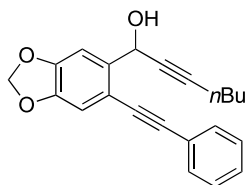
R_f = **0.42** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.72 (dd, J = 7.6, 1.4 Hz, 1H), 7.54 (dd, J = 7.5, 1.3 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.43 – 7.34 (m, 3H), 7.30 (td, J = 7.5, 1.5 Hz, 1H), 5.91 – 5.96 (m, 1H), 2.48 (br, 1H), 2.28 (td, J = 7.0, 2.0 Hz, 2H), 1.56 – 1.35 (m, 4H), 1.33 (s, 9H), 0.88 (t, J = 7.2 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 152.1, 143.0, 132.5, 131.5, 128.8, 128.2, 126.8, 125.6, 121.8, 120.0, 95.2, 87.8, 86.2, 79.5, 63.7, 35.0, 31.3, 30.8, 22.1, 18.7, 13.7.

MS (CI, NH₃): m/z = 327 [M + H - H₂O]⁺.

1-(6-(Phenylethynyl)benzo[*d*][1,3]dioxol-5-yl)hept-2-yn-1-ol (**15**)



Chemical Formula: C₂₂H₂₀O₃
Exact Mass: 332.1412

This compound was prepared using procedure **B**. Starting from 6-(phenylethynyl)benzo[*d*][1,3]dioxole-5-carbaldehyde **6** (1.0 g, 4.0 mmol) and 1-hexyne (0.6 mL, 5.2 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **15** (1.27 g, 96%) as a colorless oil.

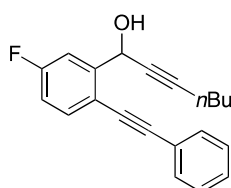
R_f = **0.27** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.58 – 7.47 (m, 2H), 7.40 – 7.29 (m, 3H), 7.24 (s, 1H), 6.96 (s, 1H), 6.01 (s, 2H), 5.92 (d, *J* = 2.0 Hz, 1H), 2.46 (d, *J* = 4.6 Hz, 1H), 2.27 (td, *J* = 7.0, 2.0 Hz, 2H), 1.55 – 1.33 (m, 4H), 0.89 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 148.5, 147.4, 138.6, 131.6, 128.5, 123.2, 114.9, 111.7, 107.6, 101.8, 93.4, 87.7, 86.8, 79.5, 63.2, 30.8, 22.1, 18.7, 13.7.

MS (CI, NH₃): *m/z* = 315 [M + H - H₂O]⁺.

1-(5-Fluoro-2-(phenylethynyl)phenyl)hept-2-yn-1-ol (**16**)



Chemical Formula: C₂₁H₁₉FO
Exact Mass: 306.1420

This compound was prepared using procedure **B**. Starting from 5-fluoro-2-(phenylethynyl)benzaldehyde **7** (0.9 g, 4.1 mmol) and 1-hexyne (0.6 mL, 5.2 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **16** (1.16 g, 92%) as a colorless oil.

R_f = **0.35** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

Experimental part

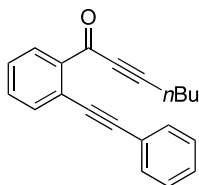
¹H NMR (300 MHz, CDCl₃) δ 7.58 – 7.49 (m, 3H), 7.46 (dd, $J = 9.5, 2.6$ Hz, 1H), 7.40 – 7.32 (m, 3H), 7.01 (td, $J = 8.3, 2.7$ Hz, 1H), 5.91 (s, 1H), 2.56 (d, $J = 4.9$ Hz, 1H), 2.27 (td, $J = 7.0, 1.9$ Hz, 2H), 1.54 – 1.34 (m, 4H), 0.88 (t, $J = 7.2$ Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 162.8 (d, $J = 247.5$ Hz), 145.8 (d, $J = 7.1$ Hz), 134.4 (d, $J = 8.2$ Hz), 131.7, 128.8, 128.6, 123.0, 117.5 (d, $J = 3.3$ Hz), 115.4 (d, $J = 22.0$ Hz), 114.2 (d, $J = 23.6$ Hz), 94.6, 88.2, 85.9, 79.0, 63.1, 30.7, 22.1, 18.7, 13.7.

¹⁹F NMR (282 MHz, (CDCl₃) δ -110.5 (dd, $J = 14.1, 8.5$ Hz).

MS (CI, NH₃): $m/z = 289$ [M + H - H₂O]⁺.

1-(2-(phenylethynyl)phenyl)hept-2-yn-1-one (17)



Chemical Formula: C₂₁H₁₈O
Exact Mass: 286.1358

This compound was prepared using procedure C. Starting from 1-(2-(phenylethynyl)phenyl)hept-2-yn-1-ol **8** (1.7 g, 5.9 mmol) and Dess-Martin periodinane (3.25 g, 7.6 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 100/0 to 98/2) afforded **17** (1.6 g, 94%) as a pale yellow oil. The analytical data were identical to the literature.¹⁹¹

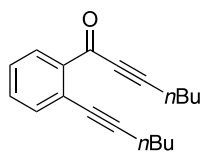
R_f = **0.42** (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.11 (dd, $J = 7.8, 1.3$ Hz, 1H), 7.65 – 7.59 (m, 3H), 7.51 (td, $J = 7.5, 1.4$ Hz, 1H), 7.42 (td, $J = 7.6, 1.4$ Hz, 1H), 7.37 – 7.32 (m, 3H), 2.43 (t, $J = 7.1$ Hz, 2H), 1.61 – 1.56 (m, 2H), 1.47 – 1.42 (m, 2H), 0.90 (t, $J = 7.3$ Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 177.8, 138.4, 134.3, 132.4, 132.0, 131.8, 128.7, 128.4, 127.9, 123.4, 122.9, 97.2, 95.2, 88.4, 80.8, 29.9, 22.2, 19.1, 13.6.

¹⁹¹ Tang, J.-M.; Liu, T.-A.; Liu, R.-S. *J. Org. Chem.* **2008**, *73*, 8479.

1-(2-(hex-1-yn-1-yl)phenyl)-hept-2-yn-1-one (18)



Chemical Formula: C₁₉H₂₂O
Exact Mass: 266.1671

This compound was prepared using procedure **C**. Starting from 1-(2-(hex-1-yn-1-yl)phenyl)-hept-2-yn-1-ol **9** (0.68 g, 2.5 mmol) and Dess-Martin periodinane (1.39 g, 3.3 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/ Ethyl acetate gradient from 100/0 to 98/2) afforded **18** (0.52 g, 76%) as a pale oil.

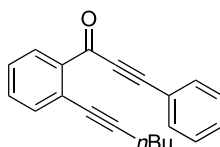
R_f = **0.4** (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.04 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.54 – 7.40 (m, 2H), 7.35 (td, *J* = 7.5, 1.5 Hz, 1H), 2.54 – 2.40 (m, 4H), 1.70 – 1.56 (m, 4H), 1.56 – 1.40 (m, 4H), 0.95 (t, *J* = 7.2 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 178.1, 138.6, 134.7, 132.2, 131.7, 127.2, 123.8, 97.0, 96.7, 81.0, 79.3, 30.8, 30.0, 22.2, 19.8, 19.1, 13.8, 13.7.

MS (ESI, NH₃): *m/z* = 267 [M + H]⁺.

1-(2-(Hex-1-yn-1-yl)phenyl)-3-phenylprop-2-yn-1-one (19)



Chemical Formula: C₂₁H₁₈O
Exact Mass: 286.1358

This compound was prepared using procedure **C**. Starting from 1-(2-(hex-1-yn-1-yl)phenyl)-3-phenylprop-2-yn-1-ol **11** (1.25 g, 4.37 mmol) and Dess-Martin periodinane (2.4 g, 5.7 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **19** (1.05 g, 84%) as an orange oil.

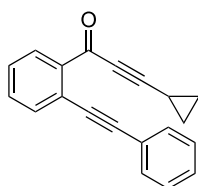
R_f = **0.62** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

Experimental part

¹H NMR (300 MHz, CDCl₃) δ 8.14 – 8.03 (m, 1H), 7.65 (dd, J = 8.1, 1.4 Hz, 2H), 7.57 – 7.34 (m, 6H), 2.43 (t, J = 7.0 Hz, 2H), 1.65 – 1.52 (m, 2H), 1.52 – 1.40 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 178.0, 138.7, 134.7, 133.2, 132.4, 131.3, 130.8, 128.7, 127.3, 124.1, 120.6, 97.6, 93.2, 88.4, 79.2, 30.8, 22.2, 19.8, 13.7.

3-cyclopropyl-1-(2-(phenylethynyl)phenyl)prop-2-yn-1-one (20)



Chemical Formula: C₂₀H₁₄O
Exact Mass: 270.1045

This compound was prepared using procedure **C**. Starting from 3-cyclopropyl-1-(2-(phenylethynyl)phenyl)prop-2-yn-1-ol **11** (1.1 g, 4.0 mmol) and Dess-Martin periodinane (2.2 g, 5.2 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 99/1 to 98/2) afforded **20** (0.82 g, 75%) as a pale yellow oil.

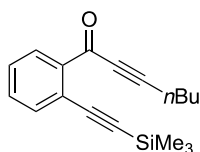
R_f = **0.55** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃), δ 8.07 – 8.02 (m, 1H), 7.66 – 7.58 (m, 3H), 7.51 (td, J = 7.5, 1.5 Hz, 1H), 7.41 (td, J = 7.5, 1.5 Hz, 1H), 7.38 – 7.33 (m, 3H), 1.49 – 1.41 (m, 1H), 0.99 – 0.93 (m, 4H).

¹³C NMR (75 MHz, CDCl₃), δ 177.6, 138.8, 134.3, 132.2, 132.0, 131.5, 128.7, 128.4, 128.0, 123.5, 122.9, 101.6, 95.3, 88.4, 10.0, 0.3.

MS (ESI, NH₃): m/z = 271 [M + H]⁺.

1-(2-((Trimethylsilyl)ethynyl)phenyl)hept-2-yn-1-one (21)



Chemical Formula: C₁₈H₂₂OSi
Exact Mass: 282.1440

This compound was prepared using procedure C. Starting from 1-(2-((trimethylsilyl)ethynyl)phenyl)hept-2-yn-1-ol **12** (2.06 g, 10.0 mmol) and Dess-Martin periodinane (5.1 g, 12.0 mmol, 1.2 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **21** (2.06 g, 74%) as a pale yellow oil.

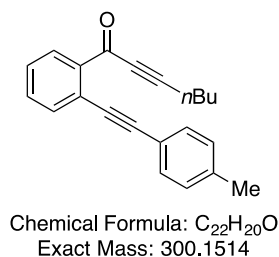
R_f = **0.58** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.10 – 7.96 (m, 1H), 7.61 – 7.51 (m, 1H), 7.48 – 7.41 (m, 1H), 7.41 – 7.35 (m, 1H), 2.45 (t, *J* = 7.1 Hz, 2H), 1.68 – 1.54 (m, 2H), 1.38 – 1.52 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H), 0.27 (s, 9H).

¹³C NMR (75 MHz, CDCl₃) δ 177.5, 139.0, 135.1, 132.1, 131.7, 128.2, 122.6, 103.3, 100.9, 96.8, 80.7, 29.9, 22.2, 19.1, 13.6, -0.1.

MS (ESI, NH₃): *m/z* = 283 [M + H]⁺.

1-(2-(*p*-Tolylethynyl)phenyl)hept-2-yn-1-one (**22**)



This compound was prepared using procedure C. Starting from 1-(2-(*p*-tolylethynyl)phenyl)hept-2-yn-1-ol **13** (1.1 g, 3.64 mmol) and Dess-Martin periodinane (2.0 g, 4.73 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **22** (1.0 g, 91%) as a pale yellow solid. m.p. 35 – 37 °C.

R_f = **0.6** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

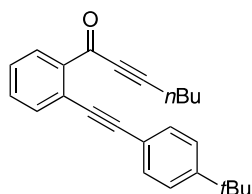
¹H NMR (300 MHz, CDCl₃) δ 8.14 – 8.06 (m, 1H), 7.68 – 7.58 (m, 1H), 7.56 – 7.46 (m, 3H), 7.45 – 7.37 (m, 1H), 7.20 – 7.13 (m, 2H), 2.43 (t, *J* = 7.2 Hz, 2H), 2.37 (s, 3H), 1.62 – 1.52 (m, 2H), 1.50 – 1.38 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 177.9, 138.9, 138.5, 134.3, 132.3, 132.0, 131.8, 129.2, 127.8, 123.3, 120.4, 97.2, 95.6, 87.9, 81.0, 29.9, 22.2, 21.7, 19.2, 13.6.

Experimental part

MS (ESI, NH₃): $m/z = 301 [M + H]^+$.

1-(2-((4-(*tert*-Butyl)phenyl)ethynyl)-phenyl)-hept-2-yn-1-one (23)



Chemical Formula: C₂₅H₂₆O
Exact Mass: 342.1984

This compound was prepared using procedure C. Starting from 1-(2-((4-(*tert*-butyl)phenyl)ethynyl)-phenyl)-hept-2-yn-1-ol (0.36 g, 1.05 mmol) **14** and Dess-Martin periodinane (0.53 g, 1.25 mmol, 1.2 equiv). Purification on silica gel (Petroleum ether/ Ethyl acetate gradient from 99/1 to 98/2) afforded **23** (0.32 g, 89%) as a pale yellow oil.

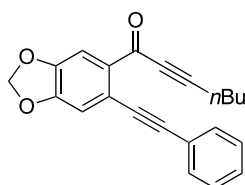
R_f = 0.55 (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.16 – 8.06 (m, 1H), 7.65 – 7.58 (m, 1H), 7.59 – 7.52 (m, 2H), 7.47 (td, *J* = 7.5, 0.8 Hz, 1H), 7.42 – 7.36 (m, 3H), 2.41 (t, *J* = 7.1 Hz, 2H), 1.61 – 1.50 (m, 2H), 1.46 – 1.38 (m, 2H), 1.31 (s, 9H), 0.88 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 177.5, 151.9, 138.3, 134.1, 132.2, 131.6, 131.6, 127.6, 125.3, 123.1, 120.3, 96.9, 95.5, 87.8, 80.8, 34.8, 31.1, 29.8, 22.0, 19.0, 13.5.

MS (ESI, NH₃): $m/z = 343 [M + H]^+$.

1-(6-(Phenylethynyl)benzo[*d*][1,3]dioxol-5-yl)hept-2-yn-1-one (24)



Chemical Formula: C₂₂H₁₈O₃
Exact Mass: 330.1256

This compound was prepared using procedure C. Starting from 1-(6-(phenylethynyl)benzo[*d*][1,3]dioxol-5-yl)hept-2-yn-1-ol **15** (1.25 g, 3.8 mmol) and Dess-

Martin periodinane (2.07 g, 4.9 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded **24** (0.9 g, 77%) as a pale yellow oil.

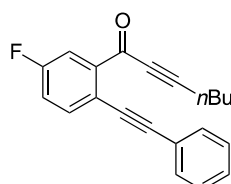
R_f = **0.31** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.61 – 7.56 (m, 3H), 7.36 – 7.31 (m, 3H), 7.05 (s, 1H), 6.09 (s, 2H), 2.43 (t, *J* = 7.1 Hz, 2H), 1.63 – 1.53 (m, 2H), 1.46 – 1.37 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 176.0, 151.1, 147.8, 133.9, 132.0, 128.6, 128.4, 123.6, 119.0, 113.6, 111.4, 102.5, 96.8, 94.3, 88.6, 80.8, 30.0, 22.2, 19.2, 13.6.

MS (ESI, NH₃): *m/z* = 331 [M + H]⁺.

1-(5-Fluoro-2-(phenylethynyl)phenyl)hept-2-yn-1-one (25)



Chemical Formula: C₂₁H₁₇FO
Exact Mass: 304.1263

This compound was prepared using procedure **C**. Starting from 1-(5-fluoro-2-(phenylethynyl)phenyl)hept-2-yn-1-ol **16** (1.1 g, 3.6 mmol) and Dess-Martin periodinane (1.98 g, 4.7 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **25** (0.95 g, 87%) as an orange oil.

R_f = **0.62** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.79 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.66 – 7.54 (m, 3H), 7.39 – 7.32 (m, 3H), 7.27 – 7.19 (m, 1H), 2.44 (t, *J* = 7.1 Hz, 2H), 1.66 – 1.51 (m, 2H), 1.50 – 1.36 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H).

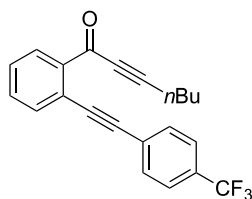
¹³C NMR (75 MHz, CDCl₃) δ 176.4, 161.8 (d, *J* = 249.8 Hz), 140.4 (d, *J* = 6.8 Hz), 136.2 (d, *J* = 7.5 Hz), 132.0, 128.8, 128.5, 123.3, 119.8 (d, *J* = 21.8 Hz), 119.1, 118.4 (d, *J* = 23.3 Hz), 98.2, 95.0, 87.4, 80.6, 29.9, 22.2, 19.2, 13.6.

¹⁹F NMR (282 MHz, CDCl₃) δ -111.4 (dd, *J* = 14.1, 8.5 Hz).

Experimental part

MS (ESI, NH₃): $m/z = 305 [M + H]^+$.

1-(2-((4-(Trifluoromethyl)phenyl)ethynyl)phenyl)hept-2-yn-1-one (26)



Chemical Formula: C₂₂H₁₇F₃O
Exact Mass: 354.1231

This compound was prepared using procedure **A**. Starting from 1-(2-ethynylphenyl)hept-2-yn-1-one **29** (0.5 g, 2.38 mmol) and 4-iodobenzotrifluoride (0.71 g, 2.62 mmol, 1.1 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 99/1 to 98/2) afforded **26** (0.55 g, 65%) as a brown solid. m.p. 35 – 37 °C.

R_f = **0.6** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

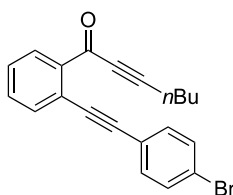
¹H NMR (300 MHz, CDCl₃) δ 8.21 – 8.11 (m, 1H), 7.75 – 7.68 (m, 2H), 7.68 – 7.58 (m, 3H), 7.58 – 7.52 (m, 1H), 7.51 – 7.44 (m, 1H), 2.46 (t, $J = 7.1$ Hz, 2H), 1.67 – 1.55 (m, 2H), 1.52 – 1.38 (m, 2H), 0.92 (t, $J = 7.3$ Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 177.5, 138.7, 134.5, 132.5, 132.2, 132.2, 150.33 (d, $J_{C-F} = 32.3$ Hz), 128.6, 127.3, 125.9, 125.4, 125.4, 122.3, 122.2, 97.3, 93.3, 90.8, 80.7, 29.9, 22.2, 19.1, 13.6.

¹⁹F NMR (282 MHz, CDCl₃) δ -63.8 (s).

MS (ESI, NH₃): $m/z = 355 [M + H]^+$.

1-(2-((4-Bromophenyl)ethynyl)phenyl)-hept-2-yn-1-one (27)



Chemical Formula: C₂₁H₁₇BrO
Exact Mass: 364.0463

This compound was prepared using procedure **A**. Starting from 1-(2-ethynylphenyl)-hept-2-yn-1-one **29** (0.3 g, 1.42 mmol) and 1-Bromo-4-iodobenzene (0.48 g, 1.7 mmol, 1.2 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **27** (0.25g, 48%) as a brown oil.

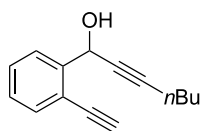
R_f = **0.4** (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.14 (dd, J = 7.7, 1.1 Hz, 1H), 7.65 – 7.60 (m, 1H), 7.56 – 7.41 (m, 6H), 2.45 (t, J = 7.0 Hz, 2H), 1.65 – 1.55 (m, 2H), 1.52 – 1.38 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 177.6, 138.5, 134.3, 133.5, 132.4, 132.1, 131.8, 128.2, 123.1, 122.6, 122.5, 97.2, 93.9, 89.6, 80.8, 29.9, 22.2, 19.1, 13.6.

MS (CI, NH₃): m/z = 365 [M + H]⁺.

1-(2-Ethynylphenyl)hept-2-yn-1-ol (**28**)



Chemical Formula: C₁₅H₁₆O
Exact Mass: 212.1201

This compound was prepared using procedure **D**. Starting from 1-(2-((trimethylsilyl)ethynyl)phenyl)-hept-2-yn-1-ol **12** (1.7 g, 6 mmol) and TBAF (6 mL, 1.0 M in THF). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **28** (1.13 g, 89%) as a pale yellow oil.

R_f = **0.2** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

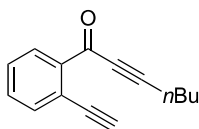
¹H NMR (300 MHz, CDCl₃) δ 7.72 (dd, J = 7.8, 1.2 Hz, 1H), 7.51 (dd, J = 7.6, 1.2 Hz, 1H), 7.40 (td, J = 7.6, 1.4 Hz, 1H), 7.28 (dt, J = 7.5, 1.3 Hz, 1H), 5.92 – 5.80 (m, 1H), 3.37 (s, 1H), 2.50 (d, J = 4.5 Hz, 1H), 2.27 (td, J = 7.0, 2.0 Hz, 2H), 1.61 – 1.37 (m, 4H), 0.91 (t, J = 7.2 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 143.7, 133.3, 129.5, 128.2, 126.9, 120.5, 88.0, 82.6, 81.3, 79.3, 63.3, 30.8, 22.1, 18.7, 13.7.

Experimental part

MS (CI, NH₃): $m/z = 212$ [M + NH₄ - H₂O]⁺.

1-(2-ethynylphenyl)hept-2-yn-1-one (29)



Chemical Formula: C₁₅H₁₄O
Exact Mass: 210.1045

This compound was prepared using procedure **C**. Starting from 1-(2-ethynylphenyl)hept-2-yn-1-ol **28** (1.0 g, 4.7 mmol) and Dess-Martin periodinane (2.59 g, 6.1 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded **29** (0.82 g, 83%) as a colorless oil.

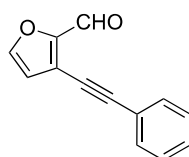
R_f = **0.65** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.15 – 8.06 (m, 1H), 7.66 – 7.56 (m, 1H), 7.54 – 7.41 (m, 2H), 3.39 (s, 1H), 2.47 (t, $J = 7.0$ Hz, 2H), 1.68 – 1.58 (m, 2H), 1.48 (m, 2H), 0.95 (t, $J = 7.3$ Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 177.5, 139.2, 135.5, 132.3, 131.8, 128.6, 121.7, 97.4, 82.9, 82.1, 80.8, 29.9, 22.2, 19.1, 13.6.

MS (CI, NH₃): $m/z = 211$ [M + H]⁺.

3-(Phenylethynyl)furan-2-carbaldehyde (30)



Chemical Formula: C₁₃H₈O₂
Exact Mass: 196.0524

This compound was prepared using procedure **A**. Starting from 3-bromofuran-2-carbaldehyde (0.59 g, 3.4 mmol) and phenylacetylene (0.41 g, 4 mmol, 1.2 equiv). Purification on silica gel

(Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) afforded **30** (0.4 g, 50%) as an orange oil. The analytical data were identical to the literature.¹⁹²

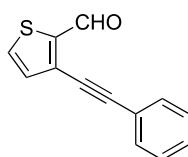
R_f = **0.6** (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 9.87 (s, 1H), 7.65 (dd, J = 1.7, 0.8 Hz, 1H), 7.60 – 7.47 (m, 2H), 7.45 – 7.33 (m, 3H), 6.68 (d, J = 1.8 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 176.3, 152.9, 147.7, 131.9, 129.6, 128.7, 122.0, 119.8, 115.3, 97.6, 78.4.

MS (ESI, NH₃): m/z = 197 [M + H]⁺.

3-(Phenylethynyl)thiophene-2-carbaldehyde (**31**)



Chemical Formula: C₁₃H₈OS
Exact Mass: 212.0296

This compound was prepared using procedure **A**. Starting from 3-bromothiophene-2-carbaldehyde (1.0 g, 5.23 mmol) and phenylacetylene (0.64 g, 6.28 mmol, 1.2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) afforded **31** (0.92 g, 83%) as a brown oil. The analytical data were identical to the literature.¹⁹³

R_f = **0.4** (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 10.24 (d, J = 1.3 Hz, 1H), 7.70 (dd, J = 5.0, 1.3 Hz, 1H), 7.58 – 7.53 (m, 2H), 7.45 – 7.30 (m, 3H), 7.27 – 7.23 (m, 1H).

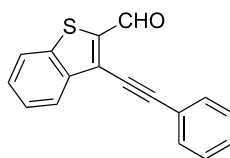
¹³C NMR (75 MHz, CDCl₃) δ 183.1, 143.7, 134.0, 131.9, 131.7, 131.1, 129.4, 128.7, 122.2, 96.2, 81.7.

MS (CI, NH₃): m/z = 213 [M + H]⁺.

¹⁹² Sagar, P.; Fröhlich, R.; Würthwein, E.-U. *Angew. Chem. Int. Ed.* **2004**, *43*, 5694.

¹⁹³ Okamoto, N.; Sakurai, K.; Ishikura, M.; Takeda, K.; Yanada, R. *Tetrahedron Lett.* **2009**, *50*, 4167.

3-(Phenylethynyl)benzo[*b*]-thiophene-2-carbaldehyde (32)



Chemical Formula: C₁₇H₁₀OS
Exact Mass: 262.0452

This compound was prepared using procedure **A**. Starting from 3-bromobenzo[*b*]thiophene-2-carbaldehyde (0.72 g, 3.0 mmol) and phenylacetylene (0.37 g, 3.6 mmol, 1.2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 99/1 to 98/2) afforded **32** (0.4 g, 50%) as a yellow solid. m.p. 114 – 116 °C. The analytical data were identical to the literature.¹⁹⁴

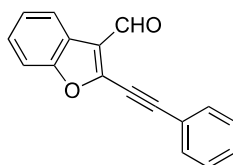
R_f = **0.4** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 10.48 (s, 1H), 8.16 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.93 – 7.82 (m, 1H), 7.70 – 7.60 (m, 2H), 7.60 – 7.48 (m, 2H), 7.47 – 7.38 (m, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 184.6, 143.6, 141.3, 139.6, 132.1, 129.7, 129.0, 128.8, 127.9, 125.8, 125.2, 123.5, 122.1, 99.2, 80.7.

MS (ESI, NH₃): *m/z* = 263 [M + H]⁺.

2-(Phenylethynyl)benzofuran-3-carbaldehyde (33)



Chemical Formula: C₁₇H₁₀O₂
Exact Mass: 246.0681

This compound was prepared using procedure **A**. Starting from 2-chlorobenzofuran-3-carbaldehyde (0.9 g, 5 mmol), phenylacetylene (0.61 g, 6 mmol, 1.2 equiv), PdCl₂(PPh₃)₃ (140 mg, 0.2 mmol, 4 mol %) and CuI (19 mg, 0.1 mmol, 2 mol %). Purification on silica gel

¹⁹⁴ Lyaskovskyy, V.; Fröhlich R.; Würthwein, E.-U. *Synthesis* **2007**, *14*, 2135.

(Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) afforded **33** (1.3 g, 82%) as a yellow solid. The analytical data were identical to the literature.¹⁹⁵

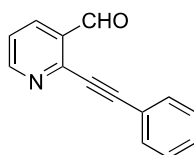
R_f = **0.4** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 10.37 (s, 1H), 8.24 – 8.16 (m, 1H), 7.70 – 7.61 (m, 2H), 7.55 – 7.38 (m, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 185.7, 154.8, 148.2, 132.3, 130.5, 128.9, 127.3, 125.4, 124.0, 123.5, 122.6, 120.6, 111.4, 101.1.

MS (ESI, NH₃): m/z = 247 [M + H]⁺.

2-(Phenylethynyl)nicotinaldehyde (**34**)



Chemical Formula: C₁₄H₉NO
Exact Mass: 207.0684

This compound was prepared using procedure **A**. Starting from 2-bromonicotinaldehyde (2 g, 10.8 mmol) and phenylacetylene (1.15 g, 11.2 mmol, 1.05 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **34** (1.8 g, 80%) as a yellow solid. The analytical data were identical to the literature.¹⁹⁶

R_f = **0.26** (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 10.66 (d, J = 0.6 Hz, 1H), 8.81 (dd, J = 1.8, 4.8 Hz, 1H), 8.20 (dd, J = 1.8, 7.9 Hz, 1H), 7.66-7.59 (m, 2H), 7.43-7.37 (m, 4H).

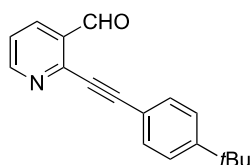
¹³C NMR (75 MHz, CDCl₃) δ 190.9, 154.6, 146.1, 134.9, 132.3, 131.9, 130.0, 128.7, 123.3, 121.3, 96.2, 84.7.

MS (CI, NH₃): m/z = 208 [M + H]⁺.

¹⁹⁵ Tiano, M.; Belmont, P. *J. Org. Chem.* **2008**, *73*, 4101.

¹⁹⁶ Verma, A. K.; Rustagi, V.; Aggarwal, T.; Singh, A. P. *J. Org. Chem.* **2010**, *75*, 7691.

2-((4-(tert-Butyl)phenyl)ethynyl)nicotinaldehyde (35)



Chemical Formula: C₁₈H₁₇NO
Exact Mass: 263.1310

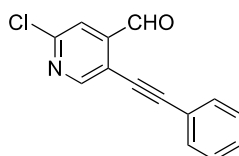
This compound was prepared using procedure **A**. Starting from 2-bromonicotinaldehyde (2 g, 10.8 mmol) and 4-*tert*-Butylphenylacetylene (1.8 g, 11.2 mmol, 1.05 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **35** (2.5 g, 88%) as a white solid.

R_f = **0.32** (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 10.66 (d, *J* = 0.4 Hz, 1H), 8.80 (dd, *J* = 1.8, 4.8 Hz, 1H), 8.19 (dd, *J* = 1.8, 7.9 Hz, 1H), 7.58-7.56 (m, 2H), 7.42-7.35 (m, 3H), 1.32 (s, 9H).

¹³C NMR (75 MHz, CDCl₃) δ 191.0, 154.6, 153.5, 146.4, 134.9, 132.1, 131.8, 125.7, 123.1, 118.3, 96.7, 84.3, 35.1, 31.2.

2-Chloro-5-(phenylethynyl)isonicotinaldehyde (36)



Chemical Formula: C₁₄H₈ClNO
Exact Mass: 241.0294

This compound was prepared using procedure **A**. Starting from 5-bromo-2-chloroisonicotinaldehyde (0.44 g, 2.0 mmol) and phenylacetylene (0.21 g, 2.1 mmol, 1.05 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) afforded **36** (0.26 g, 54%) as a yellow solid. m.p. 69 – 71 °C.

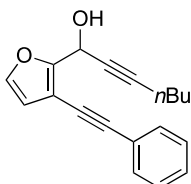
R_f = **0.4** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 10.55 (s, 1H), 8.74 (s, 1H), 7.75 (s, 1H), 7.63 – 7.52 (m, 2H), 7.47 – 7.36 (m, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ 189.4, 154.6, 151.6, 142.8, 132.0, 130.0, 128.8, 121.5, 120.8, 120.4, 100.1, 81.1.

MS (CI, NH_3): $m/z = 242$ $[\text{M} + \text{H}]^+$.

1-(3-(Phenylethynyl)furan-2-yl)hept-2-yn-1-ol (37)



Chemical Formula: $\text{C}_{19}\text{H}_{18}\text{O}_2$
Exact Mass: 278.1307

This compound was prepared using procedure **B**. Starting from 3-(phenylethynyl)furan-2-carbaldehyde **30** (0.43 g, 2.2 mmol) and 1-hexyne (0.37 mL, 3.3 mmol, 1.5 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **37** (0.45 g, 74%) as a yellow oil.

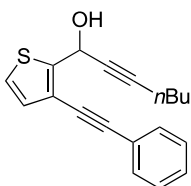
$R_f = 0.28$ (Cyclohexane/Ethyl acetate; 90/10, KMnO_4 , UV).

^1H NMR (300 MHz, CDCl_3) δ 7.50 (dd, $J = 6.6, 3.0$ Hz, 2H), 7.37 (d, $J = 1.8$ Hz, 1H), 7.37 – 7.29 (m, 3H), 6.48 (d, $J = 1.8$ Hz, 1H), 5.72 – 5.65 (m, 1H), 2.38 (d, $J = 6.9$ Hz, 1H), 2.25 (td, $J = 7.0, 2.0$ Hz, 2H), 1.56 – 1.44 (m, 2H), 1.44 – 1.32 (m, 2H), 0.88 (t, $J = 7.2$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ 155.3, 142.3, 131.6, 128.5, 123.2, 113.4, 105.0, 93.6, 87.9, 79.9, 57.2, 30.6, 22.1, 18.7, 13.7.

MS (ESI, NH_3): $m/z = 261$ $[\text{M} + \text{H} - \text{H}_2\text{O}]^+$.

1-(3-(Phenylethynyl)thiophen-2-yl)hept-2-yn-1-ol (38)



Chemical Formula: $\text{C}_{19}\text{H}_{18}\text{OS}$
Exact Mass: 294.1078

Experimental part

This compound was prepared using procedure **B**. Starting from 3-(phenylethynyl)thiophene-2-carbaldehyde **31** (0.92 g, 4.33 mmol) and 1-Hexyne (0.65 mL, 5.6 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **38** (1.13 g, 89%) as a yellow oil.

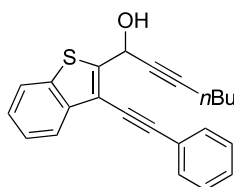
R_f = **0.28** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.59 – 7.46 (m, 2H), 7.35 (dd, *J* = 6.5, 2.7 Hz, 3H), 7.23 (d, *J* = 5.2 Hz, 1H), 7.08 (d, *J* = 5.2 Hz, 1H), 6.05 – 5.88 (m, 1H), 2.48 (d, *J* = 5.1 Hz, 1H), 2.28 (td, *J* = 6.9, 2.0 Hz, 2H), 1.47 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 148.4, 131.7, 130.1, 128.6, 128.5, 124.7, 123.1, 120.2, 93.5, 87.6, 82.8, 79.2, 59.4, 30.6, 22.1, 18.6, 13.7.

MS (CI, NH₃): *m/z* = 277 [M + H - H₂O]⁺.

1-(3-(Phenylethynyl)benzo[*b*]thiophen-2-yl)hept-2-yn-1-ol (**39**)



Chemical Formula: C₂₃H₂₀OS
Exact Mass: 344.1235

This compound was prepared using procedure **B**. Starting from 3-(phenylethynyl)benzo[*b*]thiophene-2-carbaldehyde **32** (0.4 g, 1.5 mmol) and 1-hexyne (0.26 mL, 2.25 mmol, 1.5 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **39** (0.46 g, 89%) as a yellow oil.

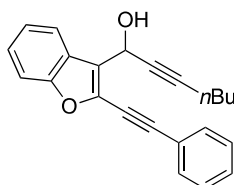
R_f = **0.3** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.02 – 7.91 (m, 1H), 7.87 – 7.79 (m, 1H), 7.65 – 7.55 (m, 2H), 7.49 – 7.33 (m, 5H), 6.25 – 6.14 (m, 1H), 2.54 (d, *J* = 5.1 Hz, 1H), 2.29 (td, *J* = 7.0, 2.0 Hz, 2H), 1.52 – 1.36 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 149.3, 139.6, 138.1, 131.8, 128.8, 128.6, 125.6, 125.0, 123.4, 123.0, 122.8, 115.9, 96.4, 88.3, 81.4, 78.8, 60.1, 30.6, 22.1, 18.7, 13.7.

MS (ESI, NH₃): m/z = 327 [M + H - H₂O]⁺.

1-(2-(Phenylethynyl)benzofuran-3-yl)hept-2-yn-1-ol (40)



Chemical Formula: C₂₃H₂₀O₂
Exact Mass: 328.1463

This compound was prepared using procedure **B**. Starting from 2-(phenylethynyl)benzofuran-3-carbaldehyde **33** (0.52 g, 2.1 mmol) and 1-hexyne (0.37 mL, 3.2 mmol, 1.5 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **40** (0.62 g, 90%) as a yellow solid.

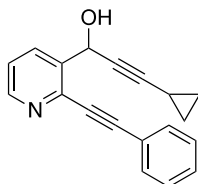
R_f = **0.35** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.98 – 7.88 (m, 1H), 7.64 – 7.52 (m, 2H), 7.50 – 7.43 (m, 1H), 7.43 – 7.34 (m, 4H), 7.34 – 7.25 (m, 1H), 5.92 – 5.80 (m, 1H), 2.31 – 2.20 (m, 3H), 1.59 – 1.31 (m, 4H), 0.88 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 155.0, 136.2, 131.9, 129.5, 128.7, 126.2, 125.7, 124.8, 123.4, 121.7, 121.3, 111.5, 98.7, 87.6, 78.6, 78.1, 57.5, 30.6, 22.1, 18.7, 13.7.

MS (ESI, NH₃): m/z = 311 [M + H - H₂O]⁺.

3-Cyclopropyl-1-(2-(phenylethynyl)pyridin-3-yl)prop-2-yn-1-ol (41)



Chemical Formula: C₁₉H₁₅NO
Exact Mass: 273.1154

This compound was prepared using procedure **B**. Starting from 2-(phenylethynyl)nicotinaldehyde **34** (1.8 g, 8.7 mmol) and cyclopropylacetylene (0.95 mL, 11.3

Experimental part

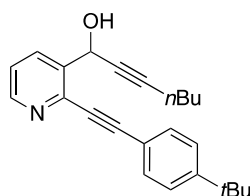
mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 60/40) afforded **41** (1.9 g, 80%) as a gray oil.

R_f = **0.12** (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.49 (d, *J* = 3.0 Hz, 1H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.59-7.55 (m, 2H), 7.38-7.29 (m, 3H), 7.25-7.20 (m, 1H), 5.92 (d, *J* = 0.8 Hz, 1H), 3.61 (br, 1H), 1.28-1.20 (m, 1H), 0.74-0.71 (m, 2H), 0.66-0.63 (m, 2H).

¹³C NMR (75 MHz, CDCl₃) δ 149.2, 141.2, 139.6, 134.5, 132.1, 129.3, 128.5, 123.3, 122.1, 94.7, 90.8, 86.2, 74.3, 62.0, 8.6, 8.4, -0.4.

1-(2-((4-(*tert*-Butyl)phenyl)ethynyl)pyridin-3-yl)hept-2-yn-1-ol (**42**)



Chemical Formula: C₂₄H₂₇NO
Exact Mass: 345.2093

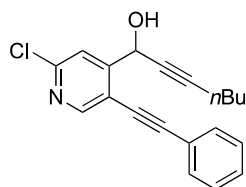
This compound was prepared using procedure **B**. Starting from 2-((4-(*tert*-butyl)phenyl)ethynyl)nicotinaldehyde **35** (2.13 g, 8.09 mmol) and 1-hexyne (1.21 mL, 10.5 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 70/30) afforded **42** (2.23 g, 80%) as a pale yellow oil.

R_f = **0.23** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.55 (dd, *J* = 1.7, 4.8 Hz, 1H), 8.07 (dd, *J* = 1.6, 7.9 Hz, 1H), 7.58-7.54 (m, 2H), 7.41-7.38 (m, 2H), 7.30-7.26 (m, 1H), 5.98 (t, *J* = 2.0 Hz, 1H), 3.20 (br, 1H), 2.26 (td, *J* = 2.0, 7.0 Hz, 2H), 1.49-1.37 (m, 4H), 1.34 (s, 9H), 0.86 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 152.8, 149.3, 141.5, 139.4, 134.5, 131.9, 125.5, 123.1, 119.0, 95.0, 88.1, 85.7, 78.9, 62.2, 35.0, 31.2, 30.6, 22.1, 18.6, 13.7.

1-(2-Chloro-5-(phenylethynyl)pyridin-4-yl)hept-2-yn-1-ol (**43**)



Chemical Formula: C₂₀H₁₈ClNO
Exact Mass: 323.1077

This compound was prepared using procedure **B**. Starting from 2-chloro-5-(phenylethynyl)isonicotinaldehyde **36** (0.25 g, 1.04 mmol) and 1-hexyne (0.15 mL, 1.3 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **43** (0.24 g, 71%) as a yellow oil.

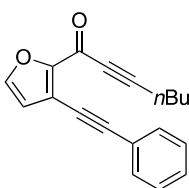
R_f = **0.2** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.51 (s, 1H), 7.67 (s, 1H), 7.59 – 7.49 (m, 2H), 7.44 – 7.33 (m, 3H), 5.82 – 5.75 (m, 1H), 2.66 (d, *J* = 5.1 Hz, 1H), 2.36 – 2.18 (m, 2H), 1.53 – 1.32 (m, 4H), 0.85 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 153.8, 152.5, 151.3, 131.8, 129.4, 128.7, 122.3, 121.3, 117.4, 98.9, 89.0, 82.7, 62.2, 30.5, 22.1, 18.6, 13.6.

MS (CI, NH₃): *m/z* = 324 [M + H]⁺.

1-(3-(Phenylethynyl)furan-2-yl)hept-2-yn-1-one (44)



Chemical Formula: C₁₉H₁₆O₂
Exact Mass: 276.1150

This compound was prepared using procedure **C**. Starting from 1-(3-(phenylethynyl)furan-2-yl)hept-2-yn-1-ol **37** (0.45 g, 1.6 mmol) and Dess-Martin periodinane (0.89 g, 2.1 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient 98/2 to 95/5) afforded **44** (0.18 g, 40%) as an orange oil.

R_f = **0.4** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

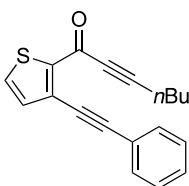
Experimental part

¹H NMR (300 MHz, CDCl₃) δ 7.62 – 7.50 (m, 3H), 7.41 – 7.31 (m, 3H), 6.67 (d, J = 1.6 Hz, 1H), 2.37 (t, J = 7.2 Hz, 2H), 1.59 – 1.42 (m, 2H), 1.40 – 1.26 (m, 2H), 0.83 (t, J = 7.3 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 164.1, 152.7, 146.4, 131.9, 129.2, 128.6, 122.7, 116.4, 116.3, 98.0, 97.8, 80.8, 79.7, 29.8, 22.2, 19.2, 13.6.

MS (ESI, NH₃): m/z = 277 [M + H]⁺.

1-(3-(Phenylethynyl)thiophen-2-yl)hept-2-yn-1-one (45)



Chemical Formula: C₁₉H₁₆OS
Exact Mass: 292.0922

This compound was prepared using procedure C. Starting from 1-(3-(phenylethynyl)thiophen-2-yl)hept-2-yn-1-ol **38** (1.12 g, 3.8 mmol) and Dess-Martin periodinane (2.1 g, 4.9 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient 99/1 to 98/2) afforded **45** (0.6 g, 55%) as a yellow solid. m.p. 33 – 35 °C.

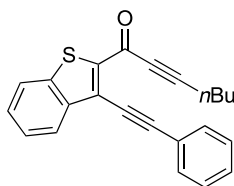
R_f = **0.33** (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.63 – 7.52 (m, 3H), 7.42 – 7.31 (m, 3H), 7.28 – 7.19 (m, 1H), 2.36 (t, J = 7.1 Hz, 2H), 1.52 – 1.45 (m, 2H), 1.41 – 1.28 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 169.0, 144.3, 133.3, 132.5, 131.9, 129.1, 128.6, 126.9, 123.0, 97.5, 96.3, 84.4, 80.3, 29.9, 22.2, 19.2, 13.6.

MS (CI, NH₃): m/z = 293 [M + H]⁺.

1-(3-(Phenylethynyl)benzo[*b*]thiophen-2-yl)hept-2-yn-1-one (46)



Chemical Formula: C₂₃H₁₈OS
Exact Mass: 342.1078

This compound was prepared using procedure C. Starting from 1-(3-(phenylethynyl)benzo[*b*]thiophen-2-yl)hept-2-yn-1-ol **39** (0.46 g, 1.34 mmol) and Dess-Martin periodinane (0.74 g, 1.7 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient 98/2 to 95/5) afforded **46** (0.34 g, 74%) as a yellow solid. m.p. 90 – 92 °C.

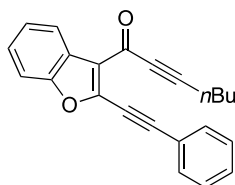
R_f = **0.62** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.19 – 8.09 (m, 1H), 7.88 – 7.62 (m, 1H), 7.72 – 7.62 (m, 2H), 7.58 – 7.45 (m, 2H), 7.45 – 7.34 (m, 3H), 2.41 (t, *J* = 7.2 Hz, 2H), 1.62 – 1.48 (m, 2H), 1.45 – 1.29 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 170.5, 144.3, 140.7, 140.5, 132.0, 129.3, 128.7, 128.6, 125.6, 123.3, 122.9, 99.7, 98.8, 83.1, 80.6, 77.5, 77.2, 76.8, 29.9, 22.2, 19.4, 13.6.

MS (ESI, NH₃): *m/z* = 343 [M + H]⁺.

1-(2-(Phenylethynyl)benzofuran-3-yl)hept-2-yn-1-one (**47**)



Chemical Formula: C₂₃H₁₈O₂
Exact Mass: 326.1307

This compound was prepared using procedure C. Starting from 1-(2-(phenylethynyl)benzofuran-3-yl)hept-2-yn-1-ol **40** (0.62 g, 1.9 mmol) and Dess-Martin periodinane (1.04 g, 2.4 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient 98/2 to 95/5) afforded **47** (0.45 g, 72%) as a yellow solid.

R_f = **0.5** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

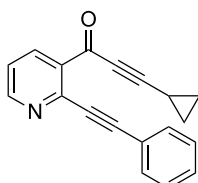
¹H NMR (300 MHz, CDCl₃) δ 8.35 – 8.22 (m, 1H), 7.71 – 7.60 (m, 2H), 7.55 – 7.32 (m, 6H), 2.39 (t, *J* = 7.2 Hz, 2H), 1.61 – 1.46 (m, 2H), 1.44 – 1.28 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 171.7, 154.3, 144.3, 132.2, 130.2, 128.8, 127.0, 125.0, 124.9, 124.0, 123.1, 121.4, 111.2, 101.2, 96.4, 81.1, 79.6, 30.0, 22.2, 19.2, 13.6.

Experimental part

MS (ESI, NH₃): $m/z = 327 [M + H]^+$.

3-Cyclopropyl-1-(2-(phenylethynyl)pyridin-3-yl)prop-2-yn-1-one (48)



Chemical Formula: C₁₉H₁₃NO
Exact Mass: 271.0997

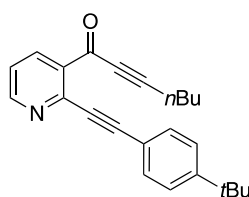
This compound was prepared using procedure **C**. Starting from 3-cyclopropyl-1-(2-(phenylethynyl)pyridin-3-yl)prop-2-yn-1-ol **41** (1.9 g, 7 mmol) and Dess-Martin periodinane (3.83 g, 9 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient 80/20 to 70/30) afforded **48** (1.6 g, 84%) as a brown oil.

R_f = **0.57** (Cyclohexane/Ethyl acetate; 70/30, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.72 (dd, $J = 1.7, 4.7$ Hz, 1H), 8.26 (dd, $J = 1.8, 8.0$ Hz, 1H), 7.70-7.64 (m, 2H), 7.38-7.32 (m, 4H), 1.48-1.29 (m, 1H), 0.97-0.92 (m, 4H).

¹³C NMR (75 MHz, CDCl₃) δ 175.4, 151.7, 140.8, 137.5, 134.0, 131.5, 128.5, 127.4, 121.3, 102.4, 94.2, 87.0, 9.2, -0.73.

1-(2-((4-(*tert*-Butyl)phenyl)ethynyl)pyridin-3-yl)hept-2-yn-1-one (49)



Chemical Formula: C₂₄H₂₅NO
Exact Mass: 343.1936

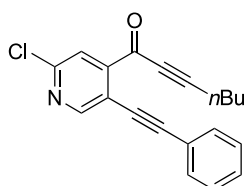
This compound was prepared using procedure **C**. Starting from 1-(2-((4-(*tert*-butyl)phenyl)ethynyl)pyridin-3-yl)hept-2-yn-1-ol **42** (2.3 g, 6.7 mmol) and Dess-Martin periodinane (3.67 g, 8.7 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient 95/5 to 80/20) afforded **49** (2.14 g, 94%) as a brown oil.

R_f = **0.35** (Cyclohexane/Ethyl acetate; 85/15, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.73 (dd, $J = 1.7, 4.8$ Hz, 1H), 8.31 (dd, $J = 1.8, 8.0$ Hz, 1H), 7.63-7.59 (m, 2H), 7.40-7.32 (m, 3H), 2.42 (t, $J = 7.1$ Hz, 2H), 1.58-1.53 (m, 2H), 1.40-1.38 (m, 2H), 1.31 (s, 9H), 0.87 (t, $J = 7.3$ Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 177.8, 138.4, 134.3, 132.4, 132.0, 131.8, 128.7, 128.4, 127.9, 123.4, 122.9, 97.2, 95.2, 88.4, 80.8, 29.8, 22.2, 19.1, 13.6.

1-(2-chloro-5-(phenylethynyl)pyridin-4-yl)hept-2-yn-1-one (50)



Chemical Formula: C₂₀H₁₆ClNO
Exact Mass: 321.0920

This compound was prepared using procedure C. Starting from 1-(2-chloro-5-(phenylethynyl)pyridin-4-yl)hept-2-yn-1-ol **43** (0.23 g, 0.71 mmol) and Dess-Martin periodinane (0.39 g, 0.92 mmol, 1.3 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient 98/2) afforded **50** (0.16 g, 70%) as a yellow solid. m.p. 34 – 36 °C.

R_f = 0.5 (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.66 (d, $J = 0.6$ Hz, 1H), 7.85 (d, $J = 0.6$ Hz, 1H), 7.63 – 7.55 (m, 2H), 7.42 – 7.33 (m, 3H), 2.46 (t, $J = 7.1$ Hz, 2H), 1.63 – 1.54 (m, 2H), 1.50 – 1.35 (m, 2H), 0.91 (t, $J = 7.3$ Hz, 3H).

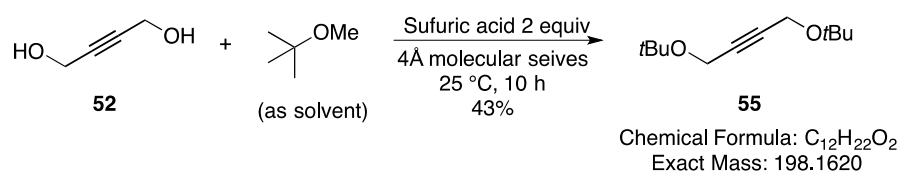
¹³C NMR (75 MHz, CDCl₃) δ 175.2, 154.7, 150.8, 146.4, 132.1, 129.5, 128.6, 124.3, 122.5, 117.2, 100.5, 98.9, 84.1, 80.2, 29.7, 22.2, 19.3, 13.6.

MS (CI, NH₃): $m/z = 322$ [M + H]⁺.

2.2. Preparation of internal alkynes

1,4-Di-*tert*-butoxybut-2-yne (55)

Experimental part



1,4-Diol-2-butyne **52** (1.72 g, 20 mmol), 4Å molecular sieves (4 g) and MTBE (20 mL) were introduced in a 50 mL round bottom flask fitted with septum and cooled to 25 °C. To this solution sulfuric acid (3.7 mL, 40 mmol, 2 equiv) was added dropwise using a syringe. The reaction was carried out at 25 °C for 10 h. The resulting mixture was slowly quenched into a saturated aqueous sodium bicarbonate solution (20 mL). The organic layer was separated and washed with water and brine, dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) to afford compound **55** (1.7 g, 43%) as a colorless oil. The analytical data were identical to the literature.⁹⁷

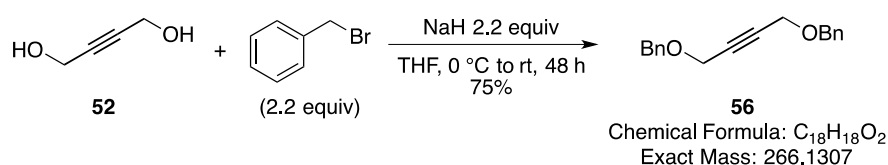
R_f = **0.45** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV)

¹H NMR (300 MHz, CDCl₃) δ 4.06 (s, 4H), 1.18 (s, 18H).

¹³C NMR (75 MHz, CDCl₃) δ 82.5, 74.2, 50.8, 27.5.

MS (CI, NH₃): m/z = 216 [M + NH₄]⁺.

1,4-Bis(benzyloxy)but-2-yne (**56**)



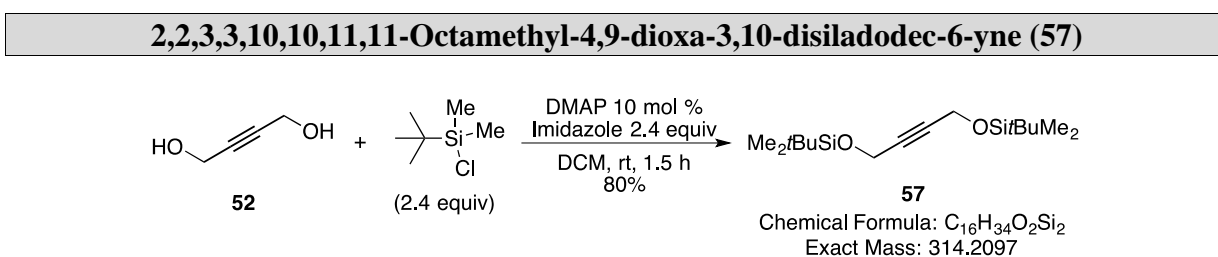
In an oven-dried argon-filled round bottom flask, sodium hydride (0.88 g, 22 mmol, 2.2 equiv) was dissolved in dry THF (20 mL). A THF solution (10 mL) of 2-butyne-1,4-diol **52** (0.86 g, 1.0 equiv) was added dropwise at 0 °C. The mixture was stirred at room temperature for 1 h. The solution was cooled to 0 °C and benzyl bromide (2.6 mL, 2.2 equiv) was added. The resulting mixture was allowed to warm to room temperature for 48 h. When the reaction was complete (TLC monitoring), water (20 mL) was added and the residue was extracted with diethyl ether (2 × 40 mL). The organic layer was separated and washed with water and brine, dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue

was purified by flash chromatography (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) to afford compound **56** (2.0 g, 75%) as a colorless oil. The analytical data were identical to the literature.⁹⁸

$R_f = 0.52$ (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV)

¹H NMR (300 MHz, CDCl₃) δ 7.49 – 7.24 (m, 10H), 4.62 (s, 4H), 4.26 (s, 4H).

¹³C NMR (75 MHz, CDCl₃) δ 137.6, 128.6, 128.2, 128.0, 82.7, 71.8, 57.6.



2-Butyn-1,4-diol **52** (2.0 g, 23.2 mmol), imidazole (3.8 g, 55.8 mmol), and *N,N*-4-dimethylaminopyridine (0.28 g, 2.32 mmol) were introduced in an oven-dried 250 mL round-bottom flask with a stir bar containing dichloromethane (200 mL). Recrystallized chloro-tert-butylchlorodimethylsilane (8.4 g, 55.8 mmol) was added. The resulting solution was stirred at room temperature for 3 h. Then the reaction mixture was poured into 40 mL 10% aqueous potassium carbonate. The resulting aqueous fraction was extracted with diethyl ether (2 × 40 mL). The combined organic fractions were washed with water and brine, dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) to afford compound **57** (5.85 g, 80%) as a colorless oil. The analytical data were identical to the literature.⁹⁹

$R_f = 0.5$ (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

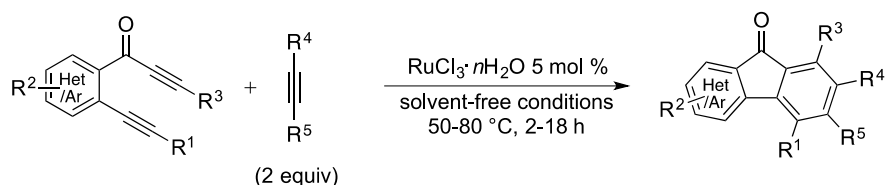
¹H NMR (300 MHz, CDCl₃) δ 4.34 (s, 4H), 0.90 (s, 18H), 0.11 (s, 12H).

¹³C NMR (75 MHz, CDCl₃) δ 83.5, 52.0, 26.0, 18.5, -5.0.

2.3. RuCl₃·*n*H₂O-catalyzed [2+2+2] cycloadditions for the formation of fluorenone and related derivatives

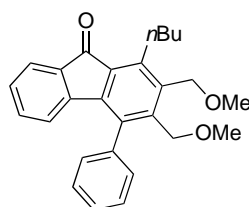
General procedure E:

Experimental part



A sealed tube was equipped with $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (5 mol%) and diyne (1 equiv), followed by the addition of alkyne (2 equiv) under argon atmosphere. The tube was sealed and the reaction mixture was stirred for the required time at 50-80 °C. When the reaction was complete (TLC monitoring), the crude reaction mixture was directly purified by flash chromatography over silica gel to afford cycloadducts.

1-Butyl-2,3-bis(methoxymethyl)-4-phenyl-9H-fluoren-9-one (**65**)



Chemical Formula: $\text{C}_{27}\text{H}_{28}\text{O}_3$
Exact Mass: 400.2038

This compound was obtained following the general procedure **E**. Starting from diyne **17** (100 mg, 0.35 mmol), 1,4-dimethoxy-2-butene **51** (80 mg, 0.7 mmol, 2 equiv) and $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 50 °C for 2 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) afforded **65** (101 mg, 72%) as a yellow solid. m.p. 88 – 90 °C.

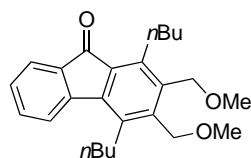
$R_f = 0.34$ (Cyclohexane/Ethyl acetate; 95/5, KMnO_4 , UV).

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.60 – 7.57 (m, 1H), 7.54 – 7.46 (m, 3H), 7.36 – 7.28 (m, 2H), 7.13 (td, $J = 7.5, 0.9$ Hz, 1H), 7.04 (td, $J = 7.5, 1.2$ Hz, 1H), 5.94 (d, $J = 7.5$ Hz, 1H), 4.57 (s, 2H), 4.19 (s, 2H), 3.51 (s, 3H), 3.29 – 3.20 (m, 2H), 3.18 (s, 3H), 1.67 – 1.49 (m, 4H), 1.02 (t, $J = 6.9$ Hz, 3H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 194.6, 144.8, 143.6, 142.9, 142.4, 138.3, 137.6, 137.0, 135.2, 134.1, 130.8, 129.6, 128.9, 128.5, 128.1, 123.6, 123.2, 68.5, 67.4, 58.9, 58.6, 33.6, 27.3, 23.5, 14.1.

HRMS (ESI⁺): calcd. for C₂₇H₂₈O₃Na [M+Na]⁺: 423.1931, found 423.1928.

1,4-Dibutyl-2,3-bis(methoxymethyl)-9H-fluoren-9-one (66)



Chemical Formula: C₂₅H₃₂O₃
Exact Mass: 380.2351

This compound was obtained following the general procedure **E**. Starting from diyne **18** (93 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne **51** (80 mg, 0.7 mmol, 2.0 equiv) and RuCl₃·*n*H₂O (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 80 °C for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **66** (50 mg, 38%) as a yellow solid. m.p. 76 – 78 °C.

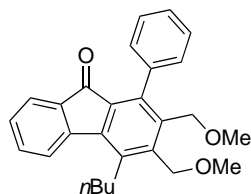
R_f = **0.33** (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.68 – 7.62 (m, 1H), 7.62 – 7.56 (m, 1H), 7.47 (td, *J* = 7.5, 1.2 Hz, 1H), 7.27 (td, *J* = 7.5, 1.2 Hz, 1H), 4.52 (s, 2H), 4.48 (s, 2H), 3.51 (s, 3H), 3.49 (s, 3H), 3.22 – 3.12 (m, 2H), 3.01 – 2.91 (m, 2H), 1.68 – 1.56 (m, 4H), 1.55 – 1.46 (m, 4H), 1.03 (t, *J* = 6.9 Hz, 3H), 0.98 (t, *J* = 6.9 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 194.9, 144.0, 143.1, 142.9, 142.8, 137.8, 137.5, 135.4, 134.6, 131.3, 128.4, 124.0, 123.5, 68.1, 67.5, 59.0, 58.8, 33.6, 32.3, 29.2, 27.2, 23.4, 14.1.

MS (CI, NH₃): *m/z* = 349 [M + H - MeOH]⁺.

4-Butyl-2,3-bis(methoxymethyl)-1-phenyl-9H-fluoren-9-one (67)



Chemical Formula: C₂₇H₂₈O₃
Exact Mass: 400.2038

This compound was obtained following the general procedure **E**. Starting from diyne **19** (100 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne **51** (80 mg, 0.7 mmol, 2.0 equiv) and RuCl₃·*n*H₂O

Experimental part

(3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 50 °C for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 99/1 to 98/2) afforded **67** (60 mg, 43%) as a yellow oil.

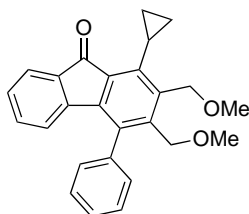
$R_f = 0.38$ (Cyclohexane/Ethyl acetate; 95/5, $KMnO_4$, UV).

1H NMR (300 MHz, $CDCl_3$) δ 7.67 (dt, $J = 7.7, 0.9$ Hz, 1H), 7.59 – 7.48 (m, 2H), 7.49 – 7.42 (m, 3H), 7.32 – 7.24 (m, 3H), 4.64 (s, 2H), 4.18 (s, 2H), 3.55 (s, 3H), 3.22 (s, 3H), 3.13 – 3.02 (m, 2H), 1.80 – 1.57 (m, 4H), 1.09 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 192.9, 143.9, 142.9, 142.8, 140.6, 139.4, 137.6, 136.9, 135.2, 134.6, 131.3, 129.2, 128.6, 127.8, 127.6, 124.1, 123.6, 68.2, 68.1, 59.1, 58.4, 32.2, 29.3, 23.5, 14.1.

MS (CI, NH_3): $m/z = 401$ $[M + H]^+$.

1-Cyclopropyl-2,3-bis(methoxymethyl)-4-phenyl-9H-fluoren-9-one (68)



Chemical Formula: $C_{26}H_{24}O_3$
Exact Mass: 384.1725

This compound was obtained following the general procedure **E**. Starting from diyne **20** (100 mg, 0.37 mmol), 1,4-dimethoxy-2-butyne **51** (85 mg, 0.74 mmol, 2.0 equiv) and $RuCl_3 \cdot nH_2O$ (3.8 mg, 0.0185 mmol). The reaction mixture was stirred at 80 °C for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **68** (90 mg, 63%) as a yellow solid. m.p. 166 – 168 °C.

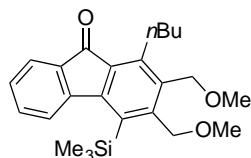
$R_f = 0.31$ (Cyclohexane/Ethyl acetate; 95/5, $KMnO_4$, UV).

1H NMR (300 MHz, $CDCl_3$) δ 7.61 – 7.55 (m, 1H), 7.53 – 7.46 (m, 3H), 7.35 – 7.29 (m, 2H), 7.13 (t, $J = 7.2$ Hz, 1H), 7.04 (td, $J = 7.5, 1.2$ Hz, 1H), 5.92 (d, $J = 7.5$ Hz, 1H), 4.81 (s, 2H), 4.20 (s, 2H, CH), 3.51 (s, 3H), 3.17 (s, 3H), 2.11 – 1.99 (m, 1H), 1.26 – 1.17 (m, 2H), 0.71 – 0.68 (m, 2H).

^{13}C NMR (75 MHz, CDCl_3) δ 193.4, 143.8, 143.4, 142.9, 142.6, 139.5, 138.1, 137.8, 135.1, 134.0, 133.2, 129.5, 128.8, 128.5, 128.1, 123.6, 123.1, 68.4, 68.2, 59.0, 58.7, 10.9, 8.4.

HRMS (ESI⁺): calcd. for $\text{C}_{26}\text{H}_{24}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 407.1618, found 407.1623.

1-Butyl-2,3-bis(methoxymethyl)-4-(trimethylsilyl)-9H-fluoren-9-one (69)



Chemical Formula: $\text{C}_{24}\text{H}_{32}\text{O}_3\text{Si}$
Exact Mass: 396.2121

This compound was obtained following the general procedure **E**. Starting from diyne **21** (99.0 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne **51** (80 mg, 0.7 mmol, 2.0 equiv) and $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 50 °C for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **69** (81 mg, 58%) as a yellow oil.

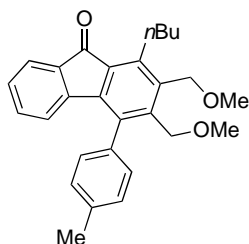
$R_f = 0.46$ (Cyclohexane/Ethyl acetate; 90/10, KMnO_4 , UV).

^1H NMR (300 MHz, CDCl_3) δ 7.62 (t, $J = 7.5$ Hz, 2H), 7.42 (td, $J = 7.5, 1.2$ Hz, 1H), 7.30 – 7.20 (m, 1H), 4.59 (s, 2H), 4.47 (s, 2H), 3.44 (s, 3H), 3.34 (s, 3H), 3.26 – 3.15 (m, 2H), 1.58 – 1.44 (m, 4H), 0.98 (t, $J = 6.6$ Hz, 3H), 0.46 (s, 9H).

^{13}C NMR (75 MHz, CDCl_3) δ 195.0, 152.9, 151.9, 145.5, 144.6, 135.4, 135.3, 133.2, 130.7, 128.5, 125.9, 123.5, 71.9, 67.3, 58.5, 57.7, 33.5, 27.0, 23.4, 14.1, 2.8.

HRMS (ESI⁺): calcd. for $\text{C}_{24}\text{H}_{32}\text{O}_3\text{SiNa}$ $[\text{M}+\text{Na}]^+$: 419.2013, found 419.2008.

1-Butyl-2,3-bis(methoxymethyl)-4-(*p*-tolyl)-9H-fluoren-9-one (70)



Chemical Formula: $\text{C}_{28}\text{H}_{30}\text{O}_3$
Exact Mass: 414.2195

Experimental part

This compound was obtained following the general procedure **E**. Starting from diyne **22** (102 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne **51** (80 mg, 0.7 mmol, 2.0 equiv) and $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 50 °C for 2 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **70** (101 mg, 71%) as a yellow solid. m.p. 86 – 88 °C.

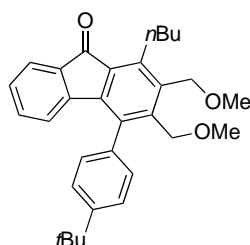
$R_f = 0.4$ (Cyclohexane/Ethyl acetate; 90/10, KMnO_4 , UV).

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.56 (d, $J = 7.5$ Hz, 1H), 7.35 – 7.27 (m, 2H), 7.24 – 7.17 (m, 2H), 7.17 – 7.02 (m, 2H), 6.02 (d, $J = 7.5$ Hz, 1H), 4.57 (s, 2H), 4.19 (s, 2H), 3.51 (s, 3H), 3.28 – 3.18 (m, 2H), 3.20 (s, 3H), 2.49 (s, 3H), 1.66 – 1.51 (m, 4H), 1.02 (t, $J = 7.2$ Hz, 3H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 194.7, 144.6, 143.8, 143.0, 142.6, 137.8, 137.6, 137.1, 135.1, 134.1, 130.7, 129.6, 129.4, 128.4, 123.6, 123.3, 68.5, 67.4, 58.9, 58.5, 33.6, 27.3, 23.5, 21.5, 14.1.

HRMS (ESI⁺): calcd. for $\text{C}_{28}\text{H}_{30}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 437.2087, found 437.2087.

1-Butyl-4-(4-(*tert*-butyl)-phenyl)-2,3-bis(methoxymethyl)-9H-fluoren-9-one (**71**)



Chemical Formula: $\text{C}_{31}\text{H}_{36}\text{O}_3$
Exact Mass: 456.2664

This compound was obtained following the general procedure **E**. Starting from diyne **23** (120 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne **51** (80 mg, 0.7 mmol, 2.0 equiv) and $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 60 °C for 14 h, then at 80 °C for 4 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **71** (90 mg, 56%) as a yellow oil.

$R_f = 0.52$ (Cyclohexane/Ethyl acetate; 90/10, KMnO_4 , UV).

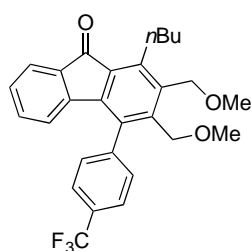
$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.60 – 7.48 (m, 3H), 7.25 – 7.20 (m, 2H), 7.12 (td, $J = 7.5, 0.9$ Hz, 1H), 7.03 (td, $J = 7.5, 1.2$ Hz, 1H), 5.91 (d, $J = 7.5$ Hz, 1H), 4.57 (s, 2H), 4.20 (s, 2H), 3.51

(s, 3H), 3.29 – 3.21 (m, 2H), 3.19 (s, 3H), 1.64 – 1.52 (m, 4H), 1.43 (s, 9H), 1.02 (t, $J = 6.9$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ 194.7, 151.3, 144.7, 143.8, 143.1, 142.6, 137.6, 137.1, 135.2, 134.1, 130.7, 129.2, 128.4, 125.7, 123.6, 123.2, 68.6, 67.5, 58.9, 58.6, 34.9, 33.7, 31.6, 27.3, 23.5, 14.1.

HRMS (ESI⁺): calcd. for $\text{C}_{31}\text{H}_{36}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 479.2557, found 479.2557.

1-Butyl-2,3-bis(methoxymethyl)-4-(4-(trifluoromethyl)-phenyl)-9H-fluoren-9-one (72)



Chemical Formula: $\text{C}_{28}\text{H}_{27}\text{F}_3\text{O}_3$
Exact Mass: 468.1912

This compound was obtained following the general procedure **E**. Starting from diyne **26** (100.0 mg, 0.28 mmol), 1,4-dimethoxy-2-butyne **51** (80 mg, 0.56 mmol, 2.0 equiv) and $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (2.9 mg, 0.014 mmol). The reaction mixture was stirred at 50 °C for 14 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) afforded **72** (85 mg, 65%) as a brown solid. m.p. 113 – 115 °C.

$R_f = 0.53$ (Cyclohexane/Ethyl acetate; 95/5, KMnO_4 , UV).

^1H NMR (300 MHz, CDCl_3) δ 7.79 (d, $J = 8.0$ Hz, 2H), 7.59 (dd, $J = 7.3, 0.6$ Hz, 1H), 7.49 (d, $J = 7.9$ Hz, 2H), 7.17 (td, $J = 7.5, 1.0$ Hz, 1H), 7.08 (td, $J = 7.6, 1.3$ Hz, 1H), 5.91 (d, $J = 7.5$ Hz, 1H), 4.55 (s, 2H), 4.11 (s, 2H), 3.51 (s, 3H), 3.30 – 3.20 (m, 2H), 3.17 (s, 3H), 1.64 – 1.50 (m, 4H), 1.02 (t, $J = 7.0$ Hz, 3H).

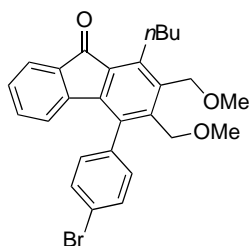
^{13}C NMR (75 MHz, CDCl_3) δ 194.3, 145.4, 143.2, 142.7, 142.3, 142.1, 137.9, 135.5, 135.2, 134.3, 130.9, 130.3, 128.9, 125.8, 125.8, 124.0, 122.9, 68.4, 67.3, 59.0, 58.7, 33.7, 27.4, 23.5, 14.1.

^{19}F NMR (282 MHz, CDCl_3) δ -63.4 (s).

Experimental part

HRMS (ESI⁺): calcd. for C₂₈H₂₇F₃O₃Na [M+Na]⁺: 491.1805, found 491.1803.

4-(4-Bromophenyl)-1-butyl-2,3-bis(methoxymethyl)-9H-fluoren-9-one (73)



Chemical Formula: C₂₇H₂₇BrO₃
Exact Mass: 478.1144

This compound was obtained following the general procedure **E**. Starting from diyne **27** (127.0 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne **51** (80 mg, 0.7 mmol, 2.0 equiv) and RuCl₃·*n*H₂O (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 50 °C for 14 h. Purification on silica gel (Petroleum ether/ Ethyl acetate gradient from 98/2 to 95/5) afforded **73** (94 mg, 56%) as a yellow oil.

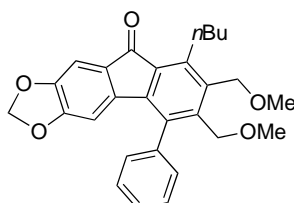
R_f = **0.43** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.71 – 7.61 (m, 2H), 7.61 – 7.54 (m, 1H), 7.25 – 7.20 (m, 2H), 7.20 – 7.07 (m, 2H), 6.04 (d, *J* = 7.5 Hz, 1H), 4.54 (s, 2H), 4.13 (s, 2H), 3.50 (s, 3H), 3.28 – 3.18 (m, 2H), 3.20 (s, 3H), 1.64 – 1.51 (m, 4H), 1.01 (t, *J* = 6.9 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 194.4, 145.2, 143.3, 142.8, 142.3, 137.8, 137.2, 135.6, 135.1, 134.3, 132.1, 131.5, 130.9, 128.8, 123.9, 123.1, 122.4, 68.5, 67.4, 59.0, 58.7, 33.7, 27.3, 23.5, 14.1.

HRMS (ESI⁺): calcd. for C₂₇H₂₇BrO₃Na [M+Na]⁺: 501.1036, found 501.1036.

8-Butyl-6,7-bis(methoxymethyl)-5-phenyl-9H-fluoreno[2,3-d][1,3]dioxol-9-one (74)



Chemical Formula: C₂₈H₂₈O₅
Exact Mass: 444.1937

This compound was obtained following the general procedure **E**. Starting from diyne **24** (115.5 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne **51** (80 mg, 0.7 mmol, 2.0 equiv) and $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 50 °C for 6 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **74** (105 mg, 68%) as a yellow oil.

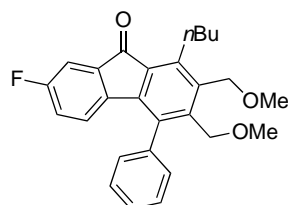
$R_f = 0.25$ (Cyclohexane/Ethyl acetate; 90/10, KMnO_4 , UV).

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.52 – 7.46 (m, 3H), 7.33 – 7.27 (m, 2H), 6.99 (s, 1H), 5.88 (s, 2H), 5.32 (s, 1H), 4.53 (s, 2H), 4.14 (s, 2H), 3.49 (s, 3H), 3.22 – 3.15 (m, 2H), 3.16 (s, 3H), 1.61 – 1.49 (m, 4H), 1.00 (t, $J = 6.9$ Hz, 3H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 193.0, 152.4, 147.9, 144.2, 142.0, 140.6, 138.0, 137.0, 136.0, 131.2, 130.1, 129.6, 128.9, 128.2, 104.6, 104.5, 101.9, 68.5, 67.4, 58.9, 58.6, 33.7, 27.2, 23.5, 14.1.

HRMS (ESI⁺): calcd. for $\text{C}_{28}\text{H}_{28}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$: 467.1829, found 467.1830.

1-Butyl-7-fluoro-2,3-bis(methoxymethyl)-4-phenyl-9H-fluoren-9-one (75)



Chemical Formula: $\text{C}_{27}\text{H}_{27}\text{FO}_3$
Exact Mass: 418.1944

This compound was obtained following the general procedure **E**. Starting from diyne **25** (106 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne **51** (80 mg, 0.7 mmol, 2.0 equiv) and $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 50 °C for 6 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **75** (98 mg, 65%) as a yellow oil.

$R_f = 0.36$ (Cyclohexane/Ethyl acetate; 95/5, KMnO_4 , UV).

Experimental part

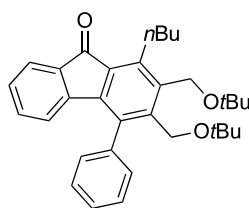
¹H NMR (300 MHz, CDCl₃) δ 7.54 – 7.47 (m, 3H), 7.35 – 7.27 (m, 2H), 7.22 (dd, $J = 7.2, 2.4$ Hz, 1H), 6.72 (td, $J = 8.7, 2.4$ Hz, 1H), 5.86 (dd, $J = 8.1, 4.5$ Hz, 1H), 4.56 (s, 2H), 4.17 (s, 2H), 3.50 (s, 3H), 3.26 – 3.18 (m, 2H), 3.18 (s, 3H), 1.66 – 1.51 (m, 4H), 1.01 (t, $J = 6.9$ Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 193.1, 163.2 (d, $J = 247.5$ Hz), 145.2, 142.8, 142.4, 139.4 (d, $J = 2.8$ Hz), 138.1, 137.5, 137.4, 136.7, 131.0 (d, $J = 1.6$ Hz), 129.5, 129.0, 128.3, 124.6 (d, $J = 7.7$ Hz), 120.2 (d, $J = 22.5$ Hz), 111.1 (d, $J = 23.6$ Hz), 68.5, 67.4, 59.0, 58.6, 33.6, 27.4, 23.5, 14.1.

¹⁹F NMR (282 MHz, CDCl₃) δ -113.6 (dd, $J = 11.3, 8.5$ Hz).

HRMS (ESI⁺): calcd. for C₂₇H₂₇FO₃Na [M+Na]⁺: 441.1836, found 441.1837.

2,3-Bis(*tert*-butoxymethyl)-1-butyl-4-phenyl-9H-fluoren-9-one (76)



Chemical Formula: C₃₃H₄₀O₃
Exact Mass: 484.2977

This compound was obtained following the general procedure **E**. Starting from diyne **17** (100 mg, 0.35 mmol), 1,4-di-*tert*-butoxybut-2-yne **55** (139 mg, 0.7 mmol, 2.0 equiv) and RuCl₃·*n*H₂O (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 60 °C for 14 h, then at 80 °C for 4 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 99/1 to 98/2) afforded **76** (140 mg, 83%) as a yellow solid. m.p. 158 – 160 °C.

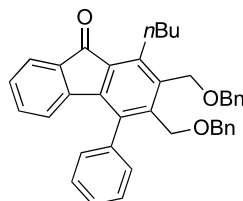
R_f = **0.46** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃), δ 7.58 – 7.52 (m, 1H), 7.56 – 7.44 (m, 3H), 7.39 – 7.29 (m, 2H), 7.11 (td, $J = 7.5, 0.9$ Hz, 1H), 7.02 (td, $J = 7.5, 1.2$ Hz, 1H), 5.89 (d, $J = 7.5$ Hz, 1H), 4.55 (s, 2H), 4.19 (s, 2H), 3.28 – 3.15 (m, 2H), 1.72 – 1.51 (m, 4H), 1.36 (s, 9H), 1.03 (t, $J = 6.9$ Hz, 3H), 1.01 (s, 9H).

^{13}C NMR (75 MHz, CDCl_3), δ 194.8, 145.1, 143.9, 143.3, 142.8, 138.4, 138.3, 137.3, 135.2, 134.0, 130.7, 129.9, 128.7, 128.3, 128.0, 123.5, 123.1, 73.7, 73.6, 57.9, 56.8, 33.7, 27.9, 27.6, 27.5, 23.7, 14.1.

HRMS (ESI⁺): calculated for $\text{C}_{39}\text{H}_{36}\text{O}_3\text{Na}^+$ [$\text{M}+\text{Na}^+$]: 575.2557, found 575.2551.

2,3-Bis((benzyloxy)-methyl)-1-butyl-4-phenyl-9H-fluoren-9-one (77)



Chemical Formula: $\text{C}_{39}\text{H}_{36}\text{O}_3$
Exact Mass: 552.2664

This compound was obtained following the general procedure **E**. Starting from diyne **17** (100 mg, 0.35 mmol), 1,4-bis(benzyloxy)but-2-yne **56** (186 mg, 0.7 mmol, 2.0 equiv) and $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 50 °C for 14 h. The excess of alkyne was removed by bulb to bulb distillation (condition: 3.0×10^{-3} mbar, 175 °C for 20 minutes). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **77** (156 mg, 81%) as a yellow solid. m.p. 145 – 147 °C.

$R_f = 0.25$ (Cyclohexane/Ethyl acetate; 95/5, KMnO_4 , UV).

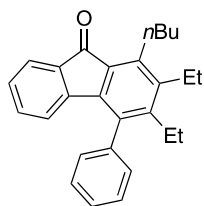
^1H NMR (300 MHz, CDCl_3), δ 7.58 – 7.53 (m, 1H), 7.53 – 7.46 (m, 3H), 7.40 – 7.27 (m, 10H), 7.22 – 7.17 (m, 2H), 7.13 (td, $J = 7.5, 0.9$ Hz, 1H), 7.04 (td, $J = 7.5, 1.2$ Hz, 1H), 5.93 (d, $J = 7.5$ Hz, 1H), 4.53 (s, 2H), 4.50 (s, 2H), 4.16 (s, 2H), 4.15 (s, 2H), 3.23 – 3.12 (m, 2H), 1.57 – 1.41 (m, 4H), 0.97 (t, $J = 6.9$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3), δ 194.7, 144.9, 143.7, 143.0, 142.6, 138.2, 138.0, 137.7, 137.1, 135.2, 134.1, 130.8, 129.7, 128.9, 128.7, 128.6, 128.5, 128.3, 128.1, 127.9, 123.7, 123.2, 73.6, 73.3, 66.2, 64.7, 33.7, 27.4, 23.5, 14.1

HRMS (ESI⁺): calculated for $\text{C}_{33}\text{H}_{40}\text{O}_3\text{Na}^+$ [$\text{M}+\text{Na}^+$]: 507.2870, found 507.2867.

1-Butyl-2,3-diethyl-4-phenyl-9H-fluoren-9-one (78)

Experimental part



Chemical Formula: C₂₇H₂₈O
Exact Mass: 368.2140

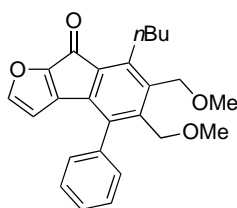
This compound was obtained following the general procedure **E**. Starting from diyne **17** (100 mg, 0.35 mmol), 3-hexyne **53** (86.3 mg, 1.05 mmol, 3.0 equiv) and RuCl₃·*n*H₂O (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 80 °C for 16 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 100/0 to 99/1) afforded **78** (pure, 14 mg, 11%) as a sticky oil.

R_f = **0.8** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.57 – 7.41 (m, 4H), 7.38 – 7.27 (m, 2H), 7.12 – 7.03 (m, 1H), 7.03 – 6.92 (m, 1H), 5.73 (d, *J* = 7.5 Hz, 1H), 3.23 – 3.05 (m, 2H), 2.73 (q, *J* = 7.5 Hz, 2H), 2.48 (q, *J* = 7.5 Hz, 2H), 1.66 – 1.49 (m, 4H), 1.23 (t, *J* = 7.7 Hz, 3H), 1.10 – 0.89 (m, 6H).

¹³C NMR (75 MHz, CDCl₃) δ 195.1, 147.8, 144.2, 143.2, 142.8, 140.8, 139.6, 136.0, 135.3, 133.8, 129.5, 129.0, 128.9, 127.9, 127.8, 123.4, 122.6, 33.6, 27.6, 23.7, 23.6, 21.5, 15.8, 15.5, 14.1.

7-Butyl-5,6-bis(methoxymethyl)-4-phenyl-8H-indeno[2,1-b]furan-8-one (**83**)



Chemical Formula: C₂₅H₂₆O₄
Exact Mass: 390.1831

This compound was obtained following the general procedure **E**. Starting from diyne **44** (97 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne **51** (80 mg, 0.7 mmol, 2.0 equiv) and RuCl₃·*n*H₂O (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 60 °C for 14 h, then at 80 °C for 4 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **83** (75 mg, 55 %) as a yellow oil.

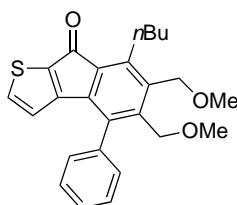
R_f = 0.32 (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.52 – 7.38 (m, 3H), 7.35 – 7.27 (m, 3H), 5.40 (d, *J* = 1.7 Hz, 1H), 4.49 (s, 2H), 4.16 (s, 2H), 3.48 (s, 3H), 3.23 (s, 3H), 3.13 – 3.02 (m, 2H), 1.60 – 1.46 (m, 4H), 0.99 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 179.6, 154.6, 151.3, 145.0, 144.6, 140.9, 138.2, 137.7, 135.1, 134.8, 131.6, 129.7, 128.4, 128.0, 108.0, 68.8, 67.4, 58.9, 58.5, 33.7, 26.7, 23.4, 14.1.

HRMS (ESI⁺): calculated for C₂₅H₂₆O₄Na⁺ [*M*+Na⁺]: 413.1723, found 413.1723.

7-Butyl-5,6-bis(methoxymethyl)-4-phenyl-8*H*-indeno[2,1-*b*]thiophen-8-one (84)



Chemical Formula: C₂₅H₂₆O₃S
Exact Mass: 406.1603

This compound was obtained following the general procedure **E**. Starting from diyne **45** (102 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne **51** (80 mg, 0.7 mmol, 2.0 equiv) and RuCl₃·*n*H₂O (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 50 °C for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **84** (101 mg, 71%) as a yellow oil.

R_f = 0.4 (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

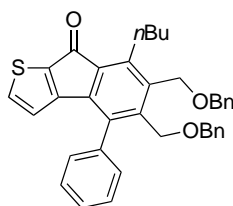
¹H NMR (300 MHz, CDCl₃) δ 7.49 – 7.43 (m, 3H), 7.34 (d, *J* = 4.5 Hz, 1H), 7.33 – 7.27 (m, 2H), 5.62 (d, *J* = 4.8 Hz, 1H), 4.51 (s, 2H), 4.16 (s, 2H), 3.49 (s, 3H), 3.19 (s, 3H), 3.17 – 3.07 (m, 2H), 1.62 – 1.47 (m, 4H), 1.00 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 186.6, 157.2, 144.6, 141.2, 139.3, 138.5, 138.1, 137.3, 134.8, 133.7, 129.8, 128.5, 128.0, 122.3, 68.8, 67.4, 58.9, 58.5, 33.7, 26.9, 23.5, 14.1.

HRMS (ESI⁺): calcd. for C₂₅H₂₆O₃SNa [*M*+Na]⁺: 429.1495, found 429.1494.

5,6-Bis((benzyloxy)-methyl)-7-butyl-4-phenyl-8*H*-indeno[2,1-*b*]thiophen-8-one (85)

Experimental part



Chemical Formula: C₃₇H₃₄O₃S
Exact Mass: 558.2229

This compound was obtained following the general procedure **E**. Starting from diyne **45** (102 mg, 0.35 mmol), 1,4-bis(benzyloxy)-but-2-yne **56** (186 mg, 0.7 mmol, 2.0 equiv) and RuCl₃·*n*H₂O (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 80 °C for 14 h. The excess of alkyne was removed by bulb to bulb distillation (condition: 3.0x10⁻³ mbar, 175 °C for 20 minutes). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **85** (121 mg, 62%) as a yellow solid. m.p. 124 – 126 °C.

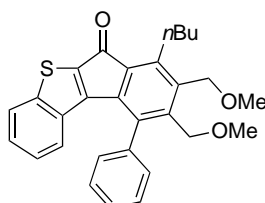
R_f = **0.34** (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃), δ 7.48 – 7.42 (m, 3H), 7.38 – 7.27 (m, 11H), 7.22 – 7.17 (m, 2H), 5.62 (d, *J* = 4.8 Hz, 1H), 4.49 (s, 2H), 4.48 (s, 2H), 4.17 (s, 2H), 4.15 (s, 2H), 3.13 – 3.03 (m, 2H), 1.52 – 1.38 (m, 4H), 0.95 (t, *J* = 6.9 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃), δ 186.6, 157.2, 144.6, 141.5, 139.3, 138.5, 138.0, 137.4, 137.3, 134.9, 133.7, 129.8, 128.6, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 122.3, 73.5, 73.2, 66.4, 64.7, 33.7, 26.9, 23.4, 14.0.

HRMS (ESI⁺): calculated for C₃₇H₃₄O₃SNa⁺ [*M*+Na⁺]: 581.2121, found 581.2115.

7-Butyl-8,9-bis(methoxymethyl)-10-phenyl-6H-benzo[b]indeno[1,2-d]thiophen-6-one (**86**)



Chemical Formula: C₂₉H₂₈O₃S
Exact Mass: 456.1759

This compound was obtained following the general procedure **E**. Starting from diyne **46** (120 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne **51** (80 mg, 0.7 mmol, 2.0 equiv) and $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 60 °C for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **86** (124 mg, 78 %) as a red solid. m.p. 135 – 137 °C.

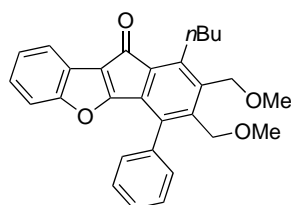
$R_f = 0.32$ (Cyclohexane/Ethyl acetate; 90/10, KMnO_4 , UV).

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.68 (d, $J = 8.2$ Hz, 1H), 7.51 – 7.40 (m, 5H), 7.20 – 7.10 (m, 1H), 6.83 – 6.72 (m, 1H), 5.19 (d, $J = 8.6$ Hz, 1H), 4.52 (s, 2H), 4.10 (s, 2H), 3.51 (s, 3H), 3.24 – 3.11 (m, 2H), 3.19 (s, 3H), 1.69 – 1.52 (m, 4H), 1.03 (t, $J = 7.0$ Hz, 3H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 188.4, 151.6, 147.4, 144.6, 142.1, 141.3, 140.2, 139.9, 137.4, 135.0, 133.2, 132.6, 131.2, 128.7, 128.4, 126.6, 126.3, 125.1, 124.0, 68.9, 67.4, 59.0, 58.6, 33.6, 27.0, 23.5, 14.0.

HRMS (ESI⁺): calcd. for $\text{C}_{29}\text{H}_{28}\text{O}_3\text{SNa}$ $[\text{M}+\text{Na}]^+$: 479.1651, found 479.1650.

1-Butyl-2,3-bis(methoxymethyl)-4-phenyl-10H-indeno[1,2-b]benzofuran-10-one (87)



Chemical Formula: $\text{C}_{29}\text{H}_{28}\text{O}_4$
Exact Mass: 440.1988

This compound was obtained following the general procedure **E**. Starting from diyne **47** (114.1 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne **51** (80 mg, 0.7 mmol, 2.0 equiv) and $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 60 °C for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **87** (42 mg, 30 %) as a yellow oil.

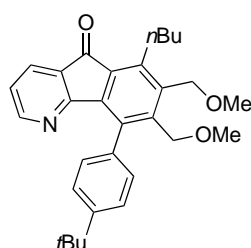
$R_f = 0.32$ (Cyclohexane/Ethyl acetate; 90/10, KMnO_4 , UV).

Experimental part

¹H NMR (300 MHz, CDCl₃) δ 7.71 – 7.63 (m, 1H), 7.55 – 7.46 (m, 3H), 7.46 – 7.37 (m, 2H), 7.26 – 7.11 (m, 3H), 4.54 (s, 2H), 4.18 (s, 2H), 3.51 (s, 3H), 3.26 (s, 3H), 3.17 (t, $J = 7.8$ Hz, 2H), 1.68 – 1.51 (m, 4H), 1.02 (t, $J = 6.9$ Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 186.3, 177.5, 160.7, 144.3, 140.8, 140.3, 136.7, 134.2, 133.0, 129.8, 128.2, 128.1, 125.1, 124.8, 122.2, 120.7, 119.6, 112.7, 68.5, 67.4, 59.0, 58.5, 33.7, 27.0, 23.5, 14.1.

6-Butyl-9-(4-(*tert*-butyl)phenyl)-7,8-bis(methoxymethyl)-5*H*-indeno[1,2-*b*]pyridin-5-one (89)



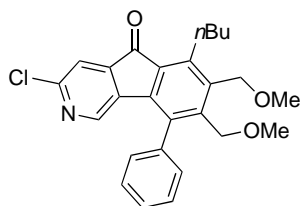
Chemical Formula: C₃₀H₃₅NO₃
Exact Mass: 457.2617

This compound was obtained following the general procedure **E**. Starting from diyne **49** (100 mg, 0.29 mmol), 1,4-dimethoxy-2-butyne **51** (200 mg, 1.75 mmol, 6.0 equiv) and RuCl₃·*n*H₂O (3.0 mg, 0.0146 mmol). The reaction mixture was stirred at 80 °C for 18 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **89** (8 mg, 6%) as a brown oil.

R_f = **0.65**(Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.23 (dd, $J = 5.0, 1.7$ Hz, 1H), 7.76 (dd, $J = 7.4, 1.7$ Hz, 1H), 7.45 (d, $J = 8.4$ Hz, 2H), 7.23 (d, $J = 8.3$ Hz, 2H), 6.99 (dd, $J = 7.5, 5.1$ Hz, 1H), 4.59 (s, 2H), 4.18 (s, 2H), 3.51 (s, 3H), 3.27 – 3.18 (m, 2H), 3.20 (s, 3H), 1.62 – 1.54 (m, 2H), 1.41 (s, 9H), 1.37 – 1.32 (m, 2H), 1.01 (t, $J = 6.9$ Hz, 3H).

6-Butyl-3-chloro-7,8-bis(methoxymethyl)-9-phenyl-5*H*-indeno[1,2-*c*]pyridin-5-one (90)



Chemical Formula: $C_{26}H_{26}ClNO_3$
Exact Mass: 435.1601

This compound was obtained following the general procedure **E**. Starting from diyne **50** (112 mg, 0.35 mmol), 1,4-dimethoxy-2-butyne **51** (80 mg, 0.7 mmol, 2.0 equiv) and $RuCl_3 \cdot nH_2O$ (3.6 mg, 0.0175 mmol). The reaction mixture was stirred at 80 °C for 2 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **90** (91 mg, 60%) as a yellow solid. m.p. 94 – 96 °C.

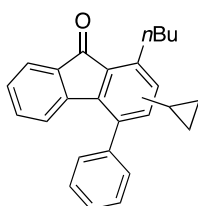
$R_f = 0.31$ (Cyclohexane/Ethyl acetate; 90/10, $KMnO_4$, UV).

1H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.48 (m, 3H), 7.40 (d, $J = 0.9$ Hz, 1H), 7.32 – 7.27 (m, 2H), 6.90 (d, $J = 1.2$ Hz, 1H), 4.57 (s, 2H), 4.22 (s, 2H), 3.51 (s, 3H), 3.24 – 3.15 (m, 2H), 3.20 (s, 3H), 1.60 – 1.52 (m, 4H), 1.01 (t, $J = 6.9$ Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 191.9, 151.7, 146.4, 144.2, 143.7, 141.5, 138.8, 137.8, 137.6, 136.0, 130.3, 129.4, 129.1, 128.9, 128.8, 118.1, 67.3, 59.1, 58.7, 33.5, 27.6, 23.5, 14.0.

HRMS (ESI⁺): calcd. for $C_{26}H_{26}ClNO_3Na$ $[M+Na]^+$: 458.1493, found 458.1494.

1-Butyl-3-cyclopropyl-4-phenyl-9H-fluoren-9-one and 1-butyl-3-cyclopropyl-4-phenyl-9H-fluoren-9-one (91)



Chemical Formula: $C_{26}H_{24}O$
Exact Mass: 352.1827

These compounds were obtained following the general procedure **E**. Starting from diyne **17** (200 mg, 0.7 mmol), cyclopropyl acetylene **58** (93 mg, 1.4 mmol, 2.0 equiv) and $RuCl_3 \cdot nH_2O$ (7.2 mg, 0.035 mmol). The reaction mixture was stirred at 80 °C for 14 h. Purification on silica

Experimental part

gel (Petroleum ether/Ethyl acetate 99/1) afforded the title regioisomers **91** (208 mg, 84%) in the ratio of 67/33 as an orange oil.

R_f = **0.6** (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

Major product: **¹H NMR** (300 MHz, CDCl₃) δ 7.60 – 7.45 (m, 4H), 7.39 – 7.33 (m, 2H), 7.15 – 7.08 (m, 2H), 6.56 (s, 1H), 6.04 – 5.98 (m, 1H), 3.05 (t, *J* = 7.8 Hz, 2H), 1.68 – 1.55 (m, 3H), 1.51 – 1.40 (m, 2H), 0.98 (t, *J* = 7.2 Hz, 3H), 0.86 – 0.74 (m, 2H), 0.75 – 0.64 (m, 2H).

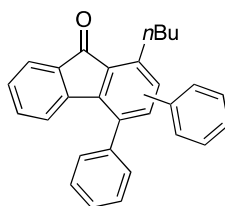
¹³C NMR (75 MHz, CDCl₃) δ 194.5, 149.6, 144.2, 144.1, 142.6, 138.9, 136.0, 133.8, 129.7, 129.1, 128.3, 127.9, 125.3, 123.5, 123.1, 33.1, 31.5, 22.9, 14.1, 12.5, 10.2.

Minor product: **¹H NMR** (300 MHz, CDCl₃) δ 7.60 – 7.45 (m, 4H), 7.43 – 7.39 (m, 2H), 7.04 (td, *J* = 7.5, 1.4 Hz, 2H), 6.88 (s, 1H), 6.64 – 6.60 (m, 1H), 3.35 (t, *J* = 7.8 Hz, 2H), 2.05 – 1.97 (m, 1H), 1.68 – 1.50 (m, 4H), 1.02 (t, *J* = 7.8 Hz, 3H), 0.86 – 0.74 (m, 2H), 0.75 – 0.64 (m, 2H).

¹³C NMR (75 MHz, CDCl₃) δ 195.2, 143.9, 143.4, 140.2, 139.4, 135.8, 135.2, 134.0, 133.3, 131.1, 129.1, 128.8, 128.6, 128.2, 128.0, 123.7, 122.7, 32.6, 27.0, 23.5, 14.0, 12.5, 7.8.

HRMS (ESI⁺): calculated for C₂₆H₂₄O⁺ [M+H⁺]: 353.1900, found 353.1900.

1-Butyl-3,4-diphenyl-9H-fluoren-9-one and 1-butyl-2,4-diphenyl-9H-fluoren-9-one (**92**)



Chemical Formula: C₂₉H₂₄O
Exact Mass: 388.1827

These compounds were obtained following the general procedure **E**. Starting from diyne **17** (200 mg, 0.7 mmol), phenyl acetylene **59** (93 mg, 1.4 mmol, 2.0 equiv) and RuCl₃·*n*H₂O (7.2 mg, 0.035 mmol). The reaction mixture was stirred at 80 °C for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate 99/1) afforded the title regioisomers **92** (191 mg, 70%) in the ratio of 73/27 as an orange solid.

R_f = **0.45** (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

Major product: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.66-7.58 (m, 1H), 7.34-7.30 (m, 3H), 7.20-7.05 (m, 10H), 6.22 – 6.13 (m, 1H), 3.15 (t, $J = 7.8$ Hz, 2H), 1.75-1.65 (m, 2H), 1.55-1.46 (m, 2H), 0.99 (t, $J = 7.2$ Hz, 3H).

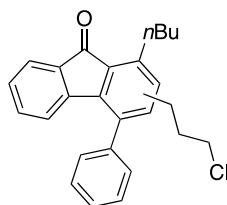
$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 194.7, 148.0, 144.1, 143.8, 143.1, 140.4, 138.3, 135.3, 134.6, 134.1, 132.8, 130.4, 130.0, 129.6, 128.6, 128.5, 127.8, 127.7, 127.1, 123.6, 123.3, 33.1, 31.2, 23.0, 14.1.

Minor product: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.66-7.58 (m, 1H), 7.50-7.33 (m, 10H), 7.22-7.05 (m, 3H), 6.77-6.72 (m, 1H), 3.08-3.03 (m, 1H), 1.55-1.46 (m, 2H), 1.37-1.30 (m, 2H), 0.82 (t, $J = 7.2$ Hz, 3H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 194.9, 144.2, 143.7, 142.2, 141.2, 140.4, 139.7, 137.9, 135.7, 135.1, 134.1, 131.4, 129.4, 129.1, 129.0, 128.8, 128.3, 128.1, 127.4, 123.8, 123.0, 33.3, 27.7, 23.1, 13.8.

HRMS (ESI⁺): calculated for $\text{C}_{29}\text{H}_{24}\text{ONa}^+$ [$\text{M}+\text{Na}^+$]: 411.1719, found 411.1722.

1-Butyl-3-(3-chloropropyl)-4-phenyl-9H-fluoren-9-one and 1-butyl-2-(3-chloropropyl)-4-phenyl-9H-fluoren-9-one (93)



Chemical Formula: $\text{C}_{26}\text{H}_{25}\text{ClO}$
Exact Mass: 388.1594

This compound was obtained following the general procedure **E**. Starting from diyne **17** (200 mg, 0.7 mmol), 5-chloro-1-pentyne **60** (143 mg, 1.4 mmol, 2.0 equiv) and $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (7.2 mg, 0.035 mmol). The reaction mixture was stirred at 80 °C for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate 99/1) afforded the title regioisomers **93** (165 mg, 61%) in the ratio of 55/45 as an orange oil.

$R_f = 0.5$ (Cyclohexane/Ethyl acetate; 95/5, KMnO_4 , UV).

Experimental part

Major product: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.57-7.50 (m, 4H), 7.30-7.27 (m, 2H), 7.19 - 7.11 (m, 1H), 7.05 (dd, $J = 7.5, 1.4$ Hz, 1H), 7.01 (s, 1H), 5.95-5.92 (m, 1H), 3.40 (t, $J = 6.6$ Hz, 2H), 3.08 (t, $J = 7.7$ Hz, 2H), 2.57-2.52 (m, 2H), 1.91-1.86 (m, 2H), 1.68-1.64 (m, 2H), 1.52-1.46 (m, 2H), 0.99 (t, $J = 7.7$ Hz, 3H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 194.7, 146.3, 144.1, 144.0, 143.1, 138.2, 135.4, 135.2, 134.0, 131.6, 129.4, 129.3, 129.0, 128.4, 128.2, 123.6, 123.0, 44.4, 33.6, 33.1, 31.2, 30.6, 22.9, 14.1.

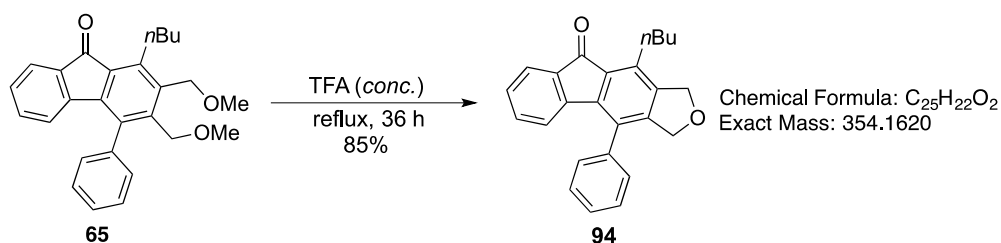
Minor product $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.59-7.57 (m, 1H), 7.49-7.49 (m, 2H), 7.45-7.40 (m, 3H), 7.16 -7.11 (m, 3H), 6.67-6.63 (m, 1H), 3.62 (t, $J = 6.3$ Hz, 2H), 3.20-3.12 (m, 2H), 2.88-2.78 (m, 2H), 2.12-2.04 (m, 2H), 1.59-1.53 (m, 4H), 1.09 (t, $J = 7.7$ Hz, 3H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 195.0, 143.8, 142.6, 140.9, 140.3, 139.9, 137.2, 136.0, 135.0, 134.7, 134.1, 131.5, 129.1, 128.8, 128.1, 123.8, 122.8, 44.6, 34.0, 33.3, 29.1, 26.9, 23.5, 14.1.

HRMS (ESI⁺): calculated for $\text{C}_{26}\text{H}_{25}\text{ClONa}^+$ [$\text{M}+\text{Na}^+$]: 411.1486, found 411.1490.

2.4. Post-functionalization of [2+2+2] cycloadducts

10-Butyl-4-phenyl-1*H*-fluoreno[2,3-*c*]furan-9(3*H*)-one (**94**)



A solution of **65** (400 mg, 1.0 mmol) in trifluoroacetic acid (3 mL) was refluxed for 36 h. Evaporation of the excess of trifluoroacetic acid under reduced pressure gave a residue which was purified by column chromatography on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) to afford compound **94** (300 mg, 85%) as a yellow solid. m.p. 109 – 111 °C.

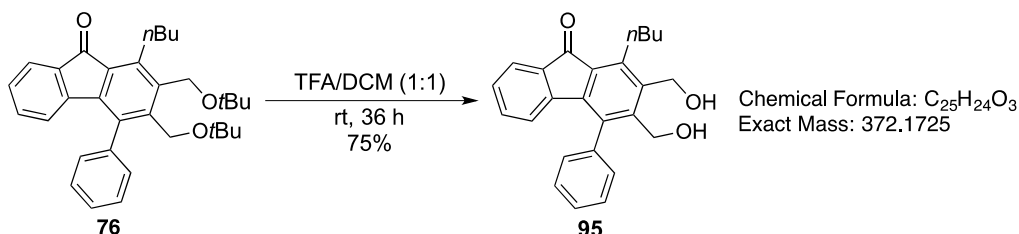
R_f = **0.28** (Cyclohexane/Ethyl acetate; 90/10, KMnO_4 , UV).

$^1\text{H NMR}$ (300 MHz, CDCl_3), δ 7.60 – 7.55 (m, 1H), 7.53 – 7.47 (m, 3H), 7.37 – 7.32 (m, 2H), 7.18 – 7.05 (m, 2H), 6.38 (d, $J = 7.2$ Hz, 1H), 5.17 (s, 1H), 4.86 (s, 1H), 2.97 (t, $J = 7.5$ Hz, 2H), 1.68 – 1.54 (m, 2H), 1.52 – 1.40 (m, 2H), 0.97 (t, $J = 7.2$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3), δ 194.3, 145.4, 143.6, 142.7, 139.9, 137.8, 137.5, 135.4, 134.1, 131.2, 129.8, 129.3, 128.5, 123.8, 122.8, 73.9, 73.3, 32.2, 29.0, 23.2, 14.1.

HRMS (ESI⁺): calculated for $\text{C}_{25}\text{H}_{22}\text{O}_2\text{Na}^+$ [$\text{M}+\text{Na}^+$]: 377.1512, found 377.1515.

1-Butyl-2,3-bis(hydroxymethyl)-4-phenyl-9H-fluoren-9-one (95).



To a solution of **76** (100 mg, 0.21 mmol) in CH_2Cl_2 (1 mL) was added trifluoroacetic acid (1 mL, large excess amount). The reaction mixture was stirred at room temperature for 36 h. When the reaction was complete (TLC monitoring), CH_2Cl_2 and the excess of trifluoroacetic acid were evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) to afford compound **95** (60 mg, 75%) as a yellow solid. m.p. 166 – 168 °C.

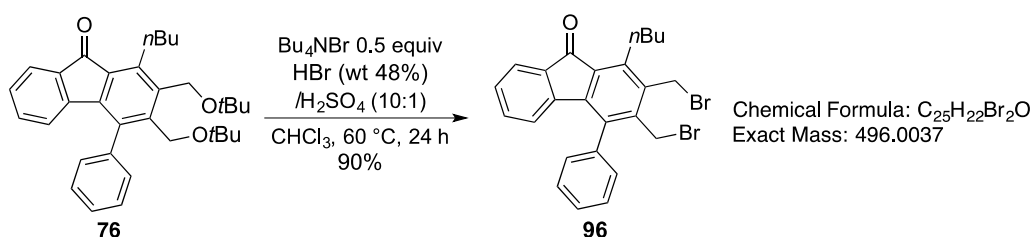
R_f = 0.28 (Cyclohexane/Ethyl acetate; 90/10, KMnO_4 , UV).

^1H NMR (300 MHz, CDCl_3), δ 7.66 – 7.60 (m, 1H), 7.58 – 7.51 (m, 3H), 7.34 – 7.27 (m, 2H), 7.22 (td, J = 7.5, 0.9 Hz, 1H), 7.11 (td, J = 7.5, 1.2 Hz, 1H), 5.96 (d, J = 7.5 Hz, 1H), 5.57 (s, 2H), 5.22 (s, 2H), 3.33 – 3.22 (m, 2H), 1.63 – 1.52 (m, 4H), 1.01 (t, J = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3), δ 193.7, 145.4, 144.9, 142.7, 138.2, 138.0, 136.5, 134.9, 134.7, 133.1, 132.1, 129.6, 129.6, 129.2, 124.2, 123.6, 63.7, 62.7, 33.8, 27.4, 23.4, 13.9.

HRMS (ESI⁺): calculated for $\text{C}_{25}\text{H}_{24}\text{O}_3\text{Na}^+$ [$\text{M}+\text{Na}^+$]: 395.1618, found 395.1619.

2,3-Bis(bromomethyl)-1-butyl-4-phenyl-9H-fluoren-9-one (96)



Experimental part

To a solution of **76** (480 mg, 1.0 mmol) in CHCl_3 (10 mL) were added $n\text{Bu}_4\text{NBr}$ (0.16 g, 0.5 mmol), aq. HBr (48% in water, 3 mL) and *conc.* H_2SO_4 (0.3 mL). The resulting mixture was heated at $60\text{ }^\circ\text{C}$ for 24 h. At the end of the reaction (TLC monitoring), the reaction mixture was poured into water (50 mL). The product was extracted with CH_2Cl_2 (3×30 mL) and the combined organic layers were dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Petroleum ether/Dichloromethane = 2/1) to afford compound **96** (444 mg, 90%) as a yellow solid. m.p. $132 - 133\text{ }^\circ\text{C}$.

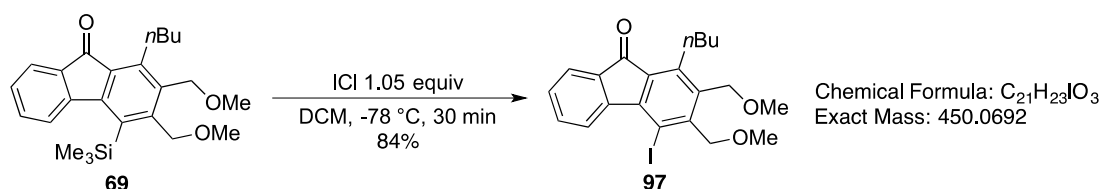
$R_f = 0.52$ (Cyclohexane/Ethyl acetate; 90/10, KMnO_4 , UV).

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.62 – 7.50 (m, 4H), 7.48 – 7.35 (m, 2H), 7.17 (td, $J = 7.5, 0.9$ Hz, 1H), 7.07 (td, $J = 7.6, 1.3$ Hz, 1H), 5.88 (d, $J = 7.5$ Hz, 1H), 4.79 (s, 2H), 4.42 (s, 2H), 3.37 – 3.13 (m, 2H), 1.75 – 1.50 (m, 4H), 1.04 (t, $J = 7.0$ Hz, 3H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 194.0, 144.5, 143.8, 143.1, 142.1, 137.0, 136.9, 136.8, 135.0, 134.4, 131.2, 129.4, 129.3, 129.1, 128.9, 123.9, 123.4, 33.3, 27.5, 27.3, 26.3, 23.5, 14.0.

HRMS (ESI⁺): calcd. for $\text{C}_{25}\text{H}_{22}\text{Br}_2\text{OH}$ $[\text{M}+\text{H}]^+$: 497.0110, found 497.0109.

1-Butyl-4-iodo-2,3-bis(methoxymethyl)-9H-fluoren-9-one (**97**)



To a solution of **69** (0.56 g, 1.41 mmol) in CH_2Cl_2 (10 mL) was added a solution of iodine monochloride (240 mg, 1.5 mmol) in DCM (2 mL) at $-78\text{ }^\circ\text{C}$ and the mixture was allowed to warm to room temperature and stirred for additional 30 minutes. The reaction was quenched with aqueous saturated $\text{Na}_2\text{S}_2\text{O}_3$ and extracted with CH_2Cl_2 (3×30 mL). The organic layer was washed with brine and dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) to afford compound **97** (0.53 g, 84%) as a yellow solid. m.p. $93 - 95\text{ }^\circ\text{C}$.

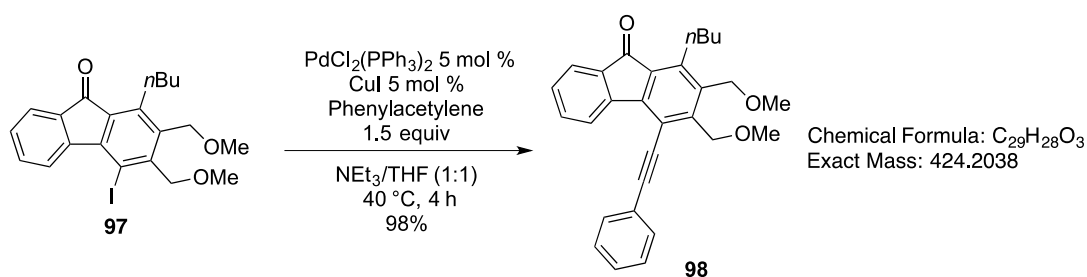
$R_f = 0.3$ (Cyclohexane/Ethyl acetate; 90/10, KMnO_4 , UV).

¹H NMR (300 MHz, CDCl₃) δ 8.98 – 8.87 (m, 1H), 7.67 (dd, *J* = 7.3, 0.6 Hz, 1H), 7.56 (td, *J* = 7.7, 1.3 Hz, 1H), 7.35 (td, *J* = 7.4, 0.8 Hz, 1H), 4.74 (s, 2H), 4.55 (s, 2H), 3.54 (s, 3H), 3.48 (s, 3H), 3.18 (t, *J* = 7.5 Hz, 2H), 1.55 – 1.44 (m, 4H), 0.98 (t, *J* = 6.8 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 193.3, 147.8, 146.5, 145.3, 144.2, 138.9, 135.1, 133.8, 133.1, 129.6, 124.1, 122.9, 95.8, 75.2, 67.8, 59.0, 58.9, 33.5, 27.0, 23.4, 14.0.

HRMS (ESI⁺): calcd. for C₂₁H₂₃IO₃Na [M+Na]⁺: 473.0584, found 473.0580.

1-Butyl-2,3-bis(methoxymethyl)-4-(phenylethynyl)-9H-fluoren-9-one (98)



PdCl₂(PPh₃)₂ (5 mol%, 19.6 mg) and CuI (5 mol%, 2.7 mg) were added to a NEt₃/THF (1:1, 2 mL) solution containing iodo-substituted fluorenone **97** (250 mg, 0.56 mmol), phenylacetylene (86 mg, 0.84 mmol, 1.5 equiv). The mixture was stirred at 40 °C for 4 h under argon. When the reaction was complete (TLC monitoring), a saturated aqueous solution of ammonium chloride was added and the mixture was stirred for 5 minutes. The organic layer was extracted with ethyl acetate (3×20 mL), washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) to afford compound **98** (232 mg, 98%) as a yellow solid. m.p. 124 – 126 °C.

R_f = **0.28** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

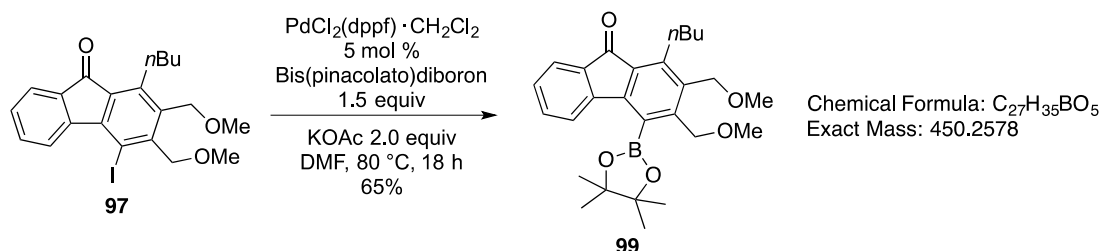
¹H NMR (300 MHz, CDCl₃) δ 8.43 (d, *J* = 7.6 Hz, 1H), 7.72 – 7.57 (m, 3H), 7.55 – 7.39 (m, 4H), 7.36 – 7.29 (m, 1H), 4.86 (s, 2H), 4.57 (s, 2H), 3.52 (s, 3H), 3.48 (s, 3H), 3.21 (t, *J* = 7.5 Hz, 2H), 1.68 – 1.40 (m, 4H), 0.99 (t, *J* = 6.9 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 193.9, 145.9, 145.3, 143.3, 138.1, 134.9, 134.7, 131.6, 131.0, 129.4, 129.1, 128.8, 123.9, 123.2, 123.1, 116.9, 97.8, 86.2, 69.5, 67.1, 59.0, 58.8, 33.6, 27.4, 23.5, 14.1.

Experimental part

HRMS (ESI⁺): calcd. for C₂₉H₂₈O₃Na [M+Na]⁺: 447.1931, found 447.1930.

1-Butyl-2,3-bis(methoxymethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9H-fluoren-9-one (**99**)



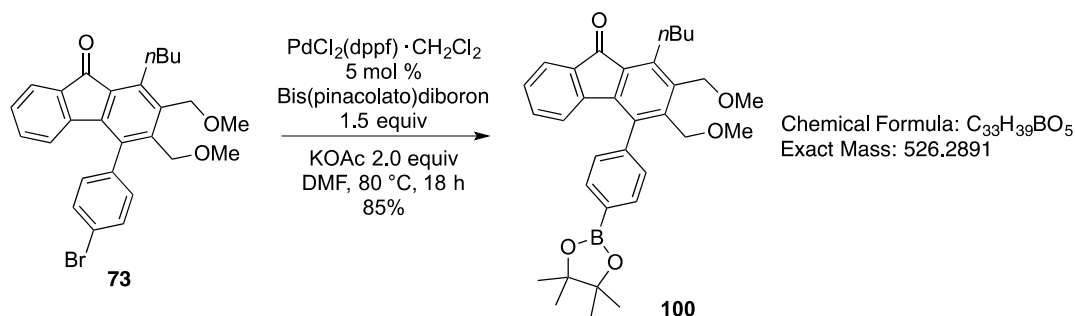
To a dry DMF solution (1 mL) of **97** (135 mg, 0.3 mmol) were added bis(pinacolato)diboron (114 mg, 0.45 mmol), PdCl₂(dppf)·CH₂Cl₂ (11 mg, 0.015 mmol), and KOAc (60 mg, 0.6 mmol). The mixture was stirred at 80 °C for 18 h. After cooling, the DMF was removed under vacuum, and CH₂Cl₂ and water were added. The resulting mixture was extracted with dichloromethane (2×30 mL), and the organic layer was washed with water and brine, dried over anhydrous MgSO₄. The organic solvent was concentrated in vacuo to yield a dark-black oil. The excess bis(pinacolato)diboron was removed under reduced pressure with heating. The residue was purified by flash chromatography on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded **99** (88 mg, 65%) as a yellow oil.

R_f = **0.23** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.07 (d, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 7.2 Hz, 1H), 7.42 (td, *J* = 7.6, 1.3 Hz, 1H), 7.30 – 7.19 (m, 1H), 4.70 (s, 2H), 4.42 (s, 2H), 3.39 (s, 3H), 3.27 (s, 3H), 3.24 – 3.13 (m, 2H), 1.47 (s, 16H), 1.01 – 0.90 (m, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 194.9, 150.5, 148.7, 145.2, 144.9, 135.2, 135.0, 134.0, 129.8, 128.8, 123.7, 122.7, 84.1, 71.2, 66.7, 58.3, 57.5, 33.6, 27.0, 25.9, 23.3, 14.1.

1-Butyl-2,3-bis(methoxymethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-9H-fluoren-9-one (**100**)



To a dry DMF solution (1 mL) of **73** (150 mg, 0.313 mmol) were added bis(pinacolato)diboron (120 mg, 0.47 mmol), $PdCl_2(dppf) \cdot CH_2Cl_2$ (11.4 mg, 0.0156 mmol), and KOAc (61 mg, 0.626 mmol). The mixture was stirred at 80 °C for 18 h. After the solution was cooled, the DMF was removed under vacuum, and CH_2Cl_2 and water were added. The resulting mixture was extracted with dichloromethane (2×30 mL), and the organic layer was washed with water and brine, dried over anhydrous $MgSO_4$. The solvent was concentrated in vacuo to yield a dark-black oil. The excess bis(pinacolato)diboron was removed under reduced pressure with heating. The residue was purified by flash chromatography on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded **100** (140 mg, 85%) as a yellow oil.

$R_f = 0.2$ (Cyclohexane/Ethyl acetate; 90/10, $KMnO_4$, UV).

1H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, $J = 7.7$ Hz, 2H), 7.56 (d, $J = 7.0$ Hz, 1H), 7.34 (d, $J = 7.7$ Hz, 2H), 7.09 (dt, $J = 23.8, 7.2$ Hz, 2H), 6.00 (d, $J = 7.4$ Hz, 1H), 4.55 (s, 2H), 4.14 (s, 2H), 3.49 (s, 3H), 3.31 – 3.18 (m, 2H), 3.17 (s, 3H), 1.66 – 1.45 (m, 4H), 1.42 (s, 12H), 1.01 (t, $J = 6.6$ Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.6, 144.9, 143.5, 142.7, 142.2, 141.3, 137.7, 136.9, 135.2, 135.1, 134.3, 130.8, 129.0, 128.5, 123.6, 123.4, 84.2, 68.5, 67.4, 58.9, 58.6, 33.6, 27.3, 25.1, 23.5, 14.1.

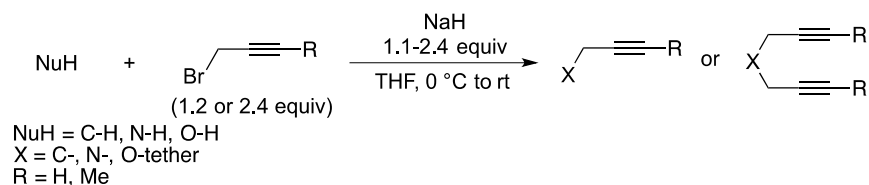
MS (ESI, NH_3): $m/z = 549$ $[M + Na]^+$.

3. Formation of 2-aminopyridine and related derivatives

3.1. Synthesis of symmetrical diynes

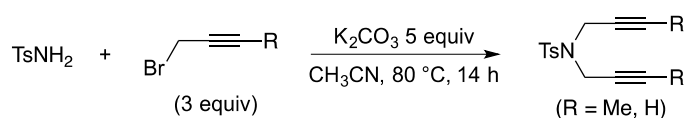
General procedure F:

Experimental part



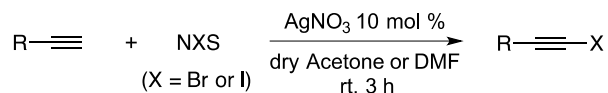
To a suspension of NaH (60% in mineral oil, 1.1-2.4 equiv) in THF was added dropwise a solution of nucleophile (1.0 equiv) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. A solution of 1-bromo-2-butyne or propargyl bromide (1.2 or 2.4 equiv) in THF was added to the mixture. The reaction was allowed to warm up to room temperature and stirred until completion. The mixture was finally quenched with saturated ammonium chloride and extracted with diethyl ether (×3). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography or distillation under vacuum to afford the desired product.

General procedure G:



To a round bottom flask *p*-toluenesulfonamide (1 equiv), 1-bromo-2-butyne or propargyl bromide (3.0 equiv), potassium carbonate (5 equiv) and acetonitrile (5 M) were employed. The resulting mixture was stirred at 80 °C for 14 h. When the reaction was complete (TLC monitoring), the reaction mixture was filtered, and the organic layer was concentrated under reduced pressure. The residue was purified by column chromatography to afford the desired product.

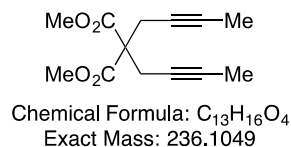
General procedure H:



Silver nitrate (10 mol%) and *N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS) (1.2-2 equiv) were added to a solution of terminal alkyne (1 equiv) in dry acetone or DMF, and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with Et₂O and washed with water. The aqueous phase was extracted with Et₂O (×3), the combined organic fractions were washed with water, saturated Na₂S₂O₃ aqueous solution and

brine. The solvent was dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the desired compound.

Dimethyl 2,2-di(but-2-yn-1-yl)malonate (101)



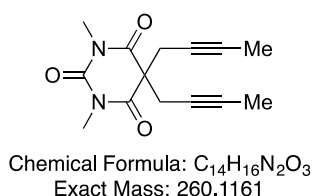
This compound was obtained following the general procedure **F**. Starting from dimethyl malonate (4.01 g, 30 mmol), 1-bromo-2-butyne (5.84 mL, 66 mmol, 2.2 equiv) and NaH (2.64 g, 66 mmol). The reaction mixture was stirred at room temperature for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded **101** (6.15 g, 87 %) as a white solid. The analytical data were identical to the literature.¹⁵⁴

$R_f = 0.51$ (Cyclohexane/Ethyl acetate; 90/10, KMnO_4 , UV).

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 3.73 (s, 6H), 2.88 (q, $J = 2.7$ Hz, 4H), 2.05 (t, $J = 2.7$ Hz, 6H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 169.8, 79.1, 73.2, 57.1, 53.0, 23.1, 3.6.

5,5-Di(but-2-yn-1-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (102)



This compound was obtained following the general procedure **F**. Starting from 1,3-dimethylbarbituric acid (0.94 g, 6 mmol), 1-bromo-2-butyne (1.26 mL, 14.4 mmol, 2.4 equiv) and NaH (0.58 g, 14.4 mmol, 2.4 equiv). The reaction mixture was stirred at room temperature for 12 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 85/15) afforded **102** (0.96 g, 62 %) as a white solid. m.p. 118-120 °C.

$R_f = 0.62$ (Cyclohexane/Ethyl acetate; 80/20, KMnO_4 , UV).

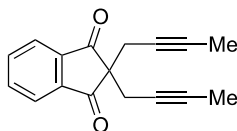
$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 3.40 – 3.24 (m, 6H), 2.78 – 2.51 (m, 4H), 1.75 – 1.50 (m, 6H).

Experimental part

^{13}C NMR (75 MHz, CDCl_3) δ 170.3, 151.4, 80.0, 72.4, 56.6, 28.8, 28.3, 3.4.

MS (CI, NH_3): $m/z = 261$ $[\text{M} + \text{H}]^+$.

2,2-Di(but-2-yn-1-yl)-1H-indene-1,3(2H)-dione (103)



Chemical Formula: $\text{C}_{17}\text{H}_{14}\text{O}_2$
Exact Mass: 250.0994

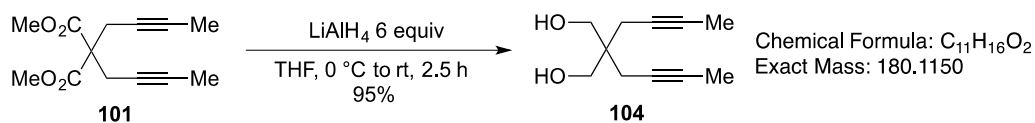
This compound was obtained following the general procedure **F**. Starting from indene dione (0.84 g, 6 mmol), 1-bromo-2-butyne (1.26 mL, 14.4 mmol, 2.4 equiv) and NaH (0.58 g, 14.4 mmol, 2.4 equiv). The reaction mixture was stirred at room temperature for 3 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded **103** (1.15 g, 77 %) as a yellow solid. m.p. 97-99 °C. The analytical data were identical to the literature.^{145e}

$R_f = 0.28$ (Cyclohexane/Ethyl acetate; 90/10, KMnO_4 , UV).

^1H NMR (300 MHz, CDCl_3) δ 8.06 – 7.93 (m, 2H), 7.92 – 7.76 (m, 2H), 2.63 – 2.46 (m, 4H), 1.39 (s, 6H).

^{13}C NMR (75 MHz, CDCl_3) δ 201.9, 142.8, 135.6, 123.2, 79.5, 73.1, 56.6, 23.5, 3.2.

2,2-Di(but-2-yn-1-yl)propane-1,3-diol (104)



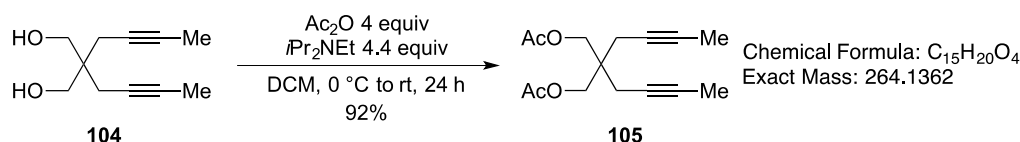
To a stirred mixture of LiAlH_4 (2.89 g, 76.2 mmol, 6 equiv) in dry THF (50 mL) at 0 °C was added dropwise a solution of dimethyl 2,2-di(but-2-ynyl)malonate **101** (3.0 g, 12.7 mmol, 1 equiv) in THF (20 mL). The resulting mixture was stirred at room temperature for 1 h. The reaction was quenched carefully with water (2.9 mL), followed by stirring at 0 °C for 10 min. Then a solution of NaOH (15%, 2.9 mL) was added and stirred for additional 10 min, followed by addition of water (8.7 mL) and stirred for additional 1 h. The resulting solution was dried over MgSO_4 , filtered through Celite, and concentrated to give the diol **104** (2.05 g, 95%) as a white solid. m.p. 85-87 °C. The analytical data were identical to the literature.³⁴

$R_f = 0.1$ (Cyclohexane/Ethyl acetate; 90/10, KMnO_4 , UV).

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 3.68 (s, 4H), 2.46 (br, 2H), 2.24 (q, $J = 2.4$ Hz, 4H), 1.78 (s, 6H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 78.5, 75.2, 67.1, 42.5, 22.5, 3.6.

2,2-Di(but-2-yn-1-yl)propane-1,3-diyl diacetate (105)



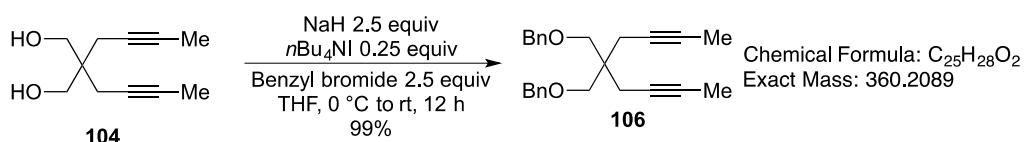
To a solution of diol **104** (0.72 g, 4 mmol) in DCM (20 mL) at 0 °C was added dropwise acetic anhydride (1.63 g, 16 mmol, 4 equiv) and diisopropylethylamine (2.27 g, 17.6 mmol, 4.4 equiv). The reaction mixture was stirred at room temperature for 24 h and then quenched with water. The aqueous layer was extracted with Et_2O (2×50 mL), and the combined organic layers were washed with brine, dried with MgSO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded **105** (0.98 g, 92%) as a colorless oil. The analytical data were identical to the literature.^{145b}

$R_f = 0.48$ (Cyclohexane/Ethyl acetate; 90/10, KMnO_4 , UV).

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 4.07 (s, 4H), 2.30 (q, $J = 2.6$ Hz, 4H), 2.05 (s, 6H), 1.76 (t, $J = 2.6$ Hz, 6H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 170.9, 78.8, 73.8, 65.6, 40.4, 22.6, 21.0, 3.7.

(((2,2-Di(but-2-yn-1-yl)propane-1,3-diyl)bis(oxy))bis(methylene))dibenzene (106)



To a suspension of NaH (60% in mineral oil, 2.5 equiv, 2.14 g) in THF (20 mL) was added dropwise diol **104** (0.9 g, 5 mmol) in THF (5 mL). The reaction mixture was stirred at 0 °C for 30 minutes before a solution of benzyl bromide (2.14 g, 12.5 mmol, 2.5 equiv) was added

Experimental part

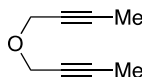
dropwise. The reaction mixture was stirred at room temperature for 12 h and then quenched with water. The aqueous layer was extracted with Et₂O (2 × 50 mL), and the combined organic layers were washed with brine, dried with MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded **106** (1.8 g, 99%) as a colorless oil. The analytical data were identical to the literature.^{145b}

R_f = 0.45 (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.41 – 7.22 (m, 10H), 4.53 (s, 4H), 3.47 (s, 4H), 2.41 – 2.23 (m, 4H), 1.75 (s, 6H).

¹³C NMR (75 MHz, CDCl₃) δ 139.0, 128.3, 127.5, 127.4, 75.6, 73.4, 71.7, 42.6, 22.5, 3.7.

1-(But-2-yn-1-yloxy)but-2-yne (107)



Chemical Formula: C₈H₁₀O
Exact Mass: 122.0732

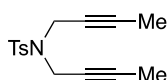
This compound was obtained following the general procedure **F**. Starting from 2-butyne-1-ol (1.05 g, 15 mmol), 1-bromo-2-butyne (1.6 mL, 18 mmol, 1.2 equiv) and NaH (1.32 g, 33 mmol, 2.2 equiv). The reaction mixture was stirred at room temperature for 4 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 99/1 to 80/20) afforded **107** (1.75 g, 96 %) as a colorless oil. The analytical data were identical to the literature.¹⁵⁴

R_f = 0.5 (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 4.18 (q, *J* = 2.3 Hz, 4H), 1.85 (t, *J* = 2.3 Hz, 6H).

¹³C NMR (75 MHz, CDCl₃) δ 83.0, 74.7, 57.1, 3.7.

N,N-di(but-2-yn-1-yl)-4-methylbenzenesulfonamide (108)



Chemical Formula: C₁₅H₁₇NO₂S
Exact Mass: 275.0980

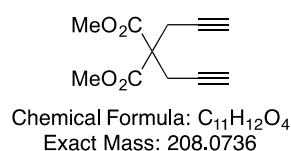
This compound was obtained following the general procedure **G**. Starting from *p*-toluenesulfonamide (2 g, 11.7 mmol), 1-bromo-2-butyne (4.66 g, 35.1 mmol, 3 equiv) and K_2CO_3 (8 g, 58.5 mmol, 5 equiv). The reaction mixture was stirred at 80 °C for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate; 90/10) afforded **108** (2.8 g, 70 %) as a white solid. The analytical data were identical to the literature.^{145d}

$R_f = 0.76$ (Cyclohexane/Ethyl acetate; 70/30, KMnO_4 , UV).

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.71 (d, $J = 8.4$ Hz, 2H), 7.32 – 7.20 (m, 2H), 4.07 (q, $J = 2.2$ Hz, 4H), 2.41 (s, 3H), 1.64 (t, $J = 2.2$ Hz, 6H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 150.4, 143.3, 129.2, 128.0, 81.7, 71.8, 36.8, 21.6, 3.5.

Dimethyl 2,2-di(prop-2-yn-1-yl)malonate (**109**)



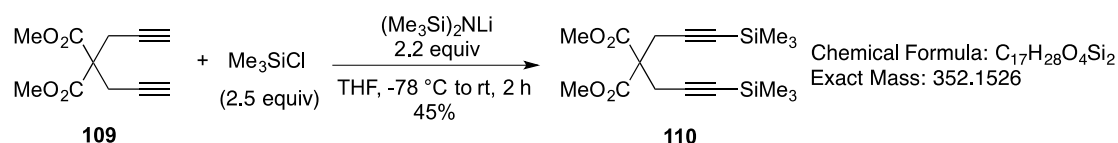
This compound was obtained following the general procedure **F**. Starting from dimethyl malonate (4.01 g, 30 mmol), propargyl bromide (7.12 mL, 67.5 mmol, 2.2 equiv) and NaH (2.64 g, 66 mmol). The reaction mixture was stirred at room temperature for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded **109** (5.7 g, 91 %) as a white solid. The analytical data were identical to the literature.⁴¹

$R_f = 0.3$ (Cyclohexane/Ethyl acetate; 85/15, KMnO_4 , UV).

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 3.75 (s, 6H), 2.98 (d, $J = 2.7$ Hz, 4H), 2.03 (t, $J = 2.6$ Hz, 2H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 169.0, 78.3, 71.8, 56.4, 53.2, 22.6.

Dimethyl 2,2-bis(3-(trimethylsilyl)prop-2-yn-1-yl)malonate (**110**)



Experimental part

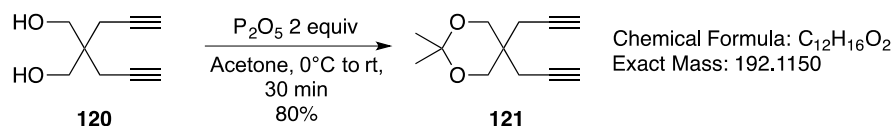
To a solution of dimethyl 2,2-di(prop-2-yn-1-yl)malonate **109** (1.04 g, 5 mmol) in THF (40 mL) was slowly added lithium hexamethyldisilazide (11 mmol, 11 mL, 1 M in THF) at -78 °C, and the solution was stirred at the same temperature for 1 h. To the resulting mixture was added chlorotrimethylsilane (1.08 mL, 12.5 mmol, 2.5 equiv) at -78 °C, and the reaction mixture was allowed to warm to room temperature and stirred for additional 1 h. The reaction was quenched with water (10 mL). The aqueous layer was extracted with Et₂O (2 × 30 mL), and the combined organic layer was washed with brine, dried with MgSO₄, filtered and concentrated under reduced pressure. The residues was purified by flash chromatography on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **110** (0.8 g, 45%) as a colorless sticky oil. The analytical data were identical to the literature.^{145a}

R_f = **0.65** (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 3.74 (s, 6H), 2.97 (s, 4H), 0.12 (s, 18H).

¹³C NMR (75 MHz, CDCl₃) δ 169.2, 101.1, 88.5, 57.4, 53.0, 24.2, 0.1.

2,2-Dimethyl-5,5-di(prop-2-yn-1-yl)-1,3-dioxane (**121**)



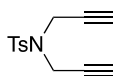
To a solution of diol **120** (0.6 g, 4.0 mmol) in dry acetone (20 mL) was added phosphorus pentoxide (1.14 g, 8.0 mmol, 2 equiv) by one portion and the reaction mixture was stirred at room temperature for 20 mins. Then the resulting mixture was poured into a mixture of NaOH (2 g) and ice (30 g), and extracted with diethyl ether (3 × 30 mL). The combined organic fractions were washed with saturated aqueous NaHCO₃ and brine, dried with MgSO₄, filtered and concentrated under reduced pressure. The residues was purified by flash chromatography on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded **121** (0.61 g, 80%) as a slight yellow oil. The analytical data were identical to the literature.¹⁴⁵ⁱ

R_f = **0.65** (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 3.77 (s, 4H), 2.43 (d, *J* = 2.7 Hz, 4H), 2.05 (t, *J* = 2.7 Hz, 2H), 1.42 (s, 6H).

^{13}C NMR (75 MHz, CDCl_3) δ 98.4, 79.9, 71.5, 66.0, 35.2, 23.9, 22.8.

4-Methyl-*N,N*-di(prop-2-yn-1-yl)benzenesulfonamide (122)



Chemical Formula: $\text{C}_{13}\text{H}_{13}\text{NO}_2\text{S}$
Exact Mass: 247.0667

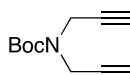
This compound was obtained following the general procedure **G**. Starting from *p*-toluenesulfonamide (6.84 g, 40 mmol), propargyl bromide (11.4 mL, 120 mmol, 3 equiv) and K_2CO_3 (27.2 g, 200 mmol, 5 equiv). The reaction mixture was stirred at 80 °C for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate; 85/15) afforded **122** (9.2 g, 91 %) as a white solid. The analytical data were identical to the literature.^{145j}

R_f = 0.3 (Cyclohexane/Ethyl acetate; 85/15, KMnO_4 , UV).

^1H NMR (300 MHz, CDCl_3) δ 7.71 (d, J = 7.8 Hz, 2H), 7.30 (d, J = 7.8 Hz, 2H), 4.16 (d, J = 2.7 Hz, 4H), 2.42 (s, 3H), 2.14 (t, J = 2.7 Hz, 2H).

^{13}C NMR (CDCl_3 , 75 MHz): δ 144.2, 136.9, 129.2, 128.2, 76.2, 74.4, 36.2, 21.6.

***tert*-Butyl di(prop-2-yn-1-yl)carbamate (123)**



Chemical Formula: $\text{C}_{11}\text{H}_{15}\text{NO}_2$
Exact Mass: 193.1103

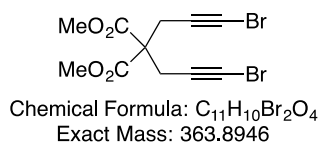
This compound was obtained following the general procedure **F**. Starting from Boc-protected propargylamine (3.45 g, 22.3 mmol), propargyl bromide (3.5 mL, 33.4 mmol, 1.5 equiv) and NaH (1.34 g, 33.4 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 14 h. Purification on silica gel (Petroleum ether/Ethyl acetate; 90/10) afforded **123** (3.13 g, 73%) as pale yellow oil. The analytical data were identical to the literature.^{145k}

R_f = 0.57 (Cyclohexane/Ethyl acetate; 90/10, KMnO_4 , UV).

^1H NMR (300 MHz, CDCl_3) δ 4.16 (br, 4H), 2.22 (t, J = 2.5 Hz, 2H), 1.47 (s, 9H).

^{13}C NMR (CDCl_3 , 75 MHz): δ 154.4, 81.3, 79.0, 72.0, 35.3, 28.4.

Dimethyl 2,2-bis(3-bromoprop-2-yn-1-yl)malonate (124)



This compound was obtained following the general procedure **H**. Starting from dimethyl 2,2-di(prop-2-yn-1-yl)malonate **109** (1.04 g, 5 mmol), NBS (1.78 g, 10 mmol, 2 equiv) and silver nitrate (85 mg, 0.5 mmol). The reaction mixture was stirred at room temperature for 3 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded **124** (5.7 g, 98 %) as a slight yellow solid. m.p. 60-62 °C. The analytical data were identical to the literature.¹⁴⁵¹

R_f = **0.38** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

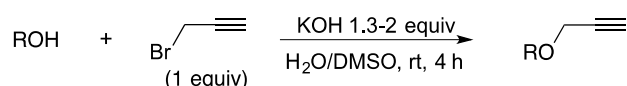
¹H NMR (300 MHz, CDCl₃) δ 3.76 (s, 6H), 2.99 (s, 4H).

¹³C NMR (75 MHz, CDCl₃) δ 169.0, 74.4, 56.5, 53.4, 42.3, 24.2.

MS (CI, NH₃): m/z = 384 [M + NH₄]⁺.

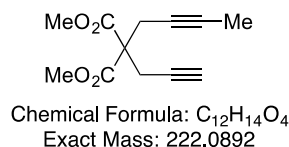
3.2. Synthesis of unsymmetrical diynes

General procedure I:



To a solution of alcohol (1.0 equiv) in DMSO (1 M) was slowly added an aqueous solution of potassium hydroxide (1 M, 1.3 equiv) at 0 °C. After 10 mins, a solution of propargyl bromide (1.0 equiv) was added dropwise. The reaction mixture was stirred at room temperature for 4 h. The reaction was quenched with water, and the aqueous layer was extracted with Et₂O (×3). The combined organic layers were washed with water and brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the desired compound.

Dimethyl 2-(but-2-yn-1-yl)-2-(prop-2-yn-1-yl)malonate (125)



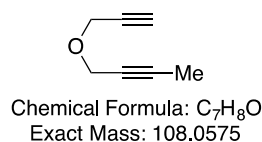
This compound was obtained following the general procedure **F**. Starting from dimethyl 2-(but-2-yn-1-yl)malonate **144** (3.3 g, 18 mmol), propargyl bromide (2.4 mL, 21.6 mmol, 1.2 equiv) and NaH (1.08 g, 27 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 4 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **125** (3.2 g, 80%) as a pale yellow solid. The analytical data were identical to the literature.¹⁴⁵¹

R_f = **0.35** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 3.75 (s, 6H), 2.97 (d, *J* = 2.6 Hz, 2H), 2.93 (q, *J* = 2.5 Hz, 2H), 2.02 (t, *J* = 2.7 Hz, 1H), 1.75 (t, *J* = 2.6 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 169.5, 79.4, 78.8, 73.0, 71.6, 57.0, 53.1, 23.2, 22.9, 3.6.

1-(Prop-2-yn-1-yloxy)but-2-yne (**127**)



This compound was obtained following the general procedure **I**. Starting from 2-butyne-1-ol (2.8 g, 40 mmol), propargyl bromide (4.3 mL, 40 mmol, 1 equiv) and KOH (2.92 g, 52 mmol, 1.3 equiv). The reaction mixture was stirred at room temperature for 4 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded **127** (3.4 g, 79%) as a pale yellow oil. The analytical data were identical to the literature.¹⁹⁷

R_f = **0.5** (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

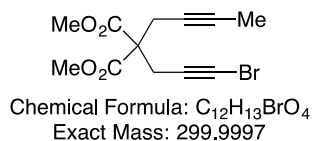
¹H NMR (300 MHz, CDCl₃) δ 4.23 (d, *J* = 2.4 Hz, 2H), 4.20 (q, *J* = 2.3 Hz, 2H), 2.46 – 2.38 (m, 1H), 1.85 (t, *J* = 2.4 Hz, 3H).

¹⁹⁷ For diyne **127**, see: Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2005**, *127*, 4763.

Experimental part

^{13}C NMR (75 MHz, CDCl_3) δ 83.3, 79.3, 74.8, 74.3, 57.3, 56.4, 3.7.

Dimethyl 2-(3-bromoprop-2-yn-1-yl)-2-(but-2-yn-1-yl)malonate (**129**)



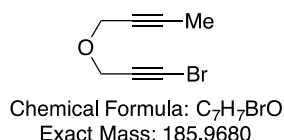
This compound was obtained following the general procedure **H**. Starting from dimethyl 2-(but-2-yn-1-yl)-2-(prop-2-yn-1-yl)malonate **125** (0.89 g, 4 mmol), NBS (1 g, 5.5 mmol, 1.4 equiv) and silver nitrate (0.1 g, 0.6 mmol). The reaction mixture was stirred at room temperature for 3 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded **129** (1.17 g, 98 %) as a white solid. m.p. 65-67 °C. The analytical data were identical to the literature.¹⁴⁵¹

R_f = 0.44 (Cyclohexane/Ethyl acetate; 90/10, KMnO_4 , UV).

^1H NMR (300 MHz, CDCl_3) δ 3.74 (s, 6H), 2.98 (s, 2H), 2.89 (q, J = 2.5 Hz, 2H), 1.74 (t, J = 2.6 Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ 169.4, 79.5, 74.8, 72.9, 56.9, 53.2, 41.7, 24.1, 23.3, 3.6.

1-((3-Bromoprop-2-yn-1-yl)oxy)but-2-yne (**130**)



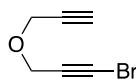
This compound was obtained following the general procedure **H**. Starting from 1-(prop-2-yn-1-yloxy)but-2-yne **127** (1.08 g, 10 mmol), NBS (1.96 g, 11 mmol, 1.1 equiv) and silver nitrate (0.17 g, 1 mmol). The reaction mixture was stirred at room temperature for 3 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **130** (1.8 g, 97 %) as a pale yellow oil. The analytical data were identical to the literature.¹⁴⁵¹

R_f = 0.4 (Cyclohexane/Ethyl acetate; 95/5, KMnO_4 , UV).

^1H NMR (300 MHz, CDCl_3) δ 4.26 (s, 2H), 4.20 (q, J = 2.3 Hz, 2H), 1.86 (t, J = 2.3 Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ 83.5, 75.9, 74.3, 57.5, 57.4, 46.4, 3.7.

1-Bromo-3-(prop-2-yn-1-yloxy)prop-1-yne (131)



Chemical Formula: $\text{C}_6\text{H}_5\text{BrO}$
Exact Mass: 171.9524

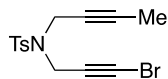
This compound was obtained following the general procedure **I**. Starting from 3-bromoprop-2-yn-1-ol **145** (1.6 g, 12 mmol), propargyl bromide (1.55 mL, 14.4 mmol, 1.2 equiv) and KOH (0.87 g, 15.6 mmol, 1.3 equiv). The reaction mixture was stirred at room temperature for 4 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded **131** (1 g, 50%) as a pale yellow oil. The analytical data were identical to the literature.¹⁴⁵¹

$R_f = 0.66$ (Cyclohexane/Ethyl acetate; 80/20, KMnO_4 , UV).

^1H NMR (300 MHz, CDCl_3) δ 4.29 (s, 2H), 4.25 (d, $J = 2.4$ Hz, 2H), 2.46 (t, $J = 2.4$ Hz, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ 78.8, 75.5, 75.3, 57.6, 56.8, 46.9.

***N*-(3-bromoprop-2-yn-1-yl)-*N*-(but-2-yn-1-yl)-4-methylbenzenesulfonamide (132)**



Chemical Formula: $\text{C}_{14}\text{H}_{14}\text{BrNO}_2\text{S}$
Exact Mass: 338.9929

This compound was obtained following the general procedure **H**. Starting from *N*-(but-2-yn-1-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide **128** (0.51 g, 2 mmol), NBS (0.43 g, 2.4 mmol, 1.2 equiv) and silver nitrate (0.034 g, 0.2 mmol). The reaction mixture was stirred at room temperature for 3 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 90/10 to 80/20) afforded **132** (0.65 g, 96 %) as a white solid. m.p. 86 – 88°C.

$R_f = 0.5$ (Cyclohexane/Ethyl acetate; 80/20, KMnO_4 , UV).

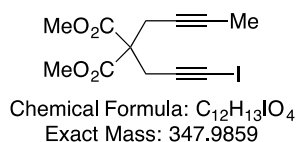
^1H NMR (300 MHz, CDCl_3) δ 7.73 – 7.68 (m, 2H), 7.39 – 7.30 (m, 2H), 4.16 (s, 2H), 4.10 – 4.00 (m, 2H), 2.41 (s, 3H), 1.72 – 1.59 (m, 3H).

Experimental part

^{13}C NMR (75 MHz, CDCl_3) δ 143.9, 135.3, 129.6, 128.1, 82.3, 73.0, 71.5, 45.2, 37.4, 37.2, 21.7, 3.5.

MS (CI, NH_3): $m/z = 339$ $[\text{M} + \text{H}]^+$.

Dimethyl 2-(but-2-yn-1-yl)-2-(3-iodoprop-2-yn-1-yl)malonate (133)



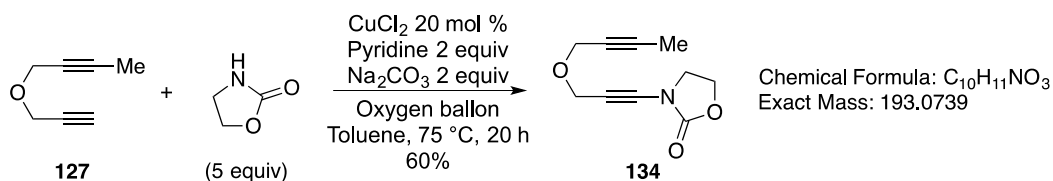
This compound was obtained following the general procedure **H**. Starting from dimethyl 2-(but-2-yn-1-yl)-2-(prop-2-yn-1-yl)malonate **125** (0.67 g, 3 mmol), NIS (0.87 g, 3.6 mmol, 1.2 equiv) and silver nitrate (0.05 g, 0.3 mmol). The reaction mixture was stirred at room temperature for 3 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 90/10 to 80/20) afforded **133** (1.02 g, 99 %) as a yellow solid. m.p. 68-70 °C. The analytical data were identical to the literature.¹⁴⁵¹

$R_f = 0.34$ (Cyclohexane/Ethyl acetate; 90/10, KMnO_4 , UV).

^1H NMR (300 MHz, CDCl_3) δ 3.75 (s, 6H), 3.13 (s, 2H), 2.90 (q, $J = 2.5$ Hz, 2H), 1.75 (t, $J = 2.5$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ 169.4, 88.9, 79.5, 77.4, 72.9, 57.2, 53.2, 25.1, 23.3, 3.6.

3-(3-(But-2-yn-1-yloxy)prop-1-yn-1-yl)oxazolidin-2-one (134)



To a 250 mL flask were added CuCl_2 (0.26 g, 2 mmol, 0.2 equiv), 2-Oxazolidone (4.35 g, 50.0 mmol, 5 equiv) and sodium carbonate (2.12 g, 20 mmol, 2.0 equiv). The reaction flask was purged with oxygen for 15 min. A solution of pyridine (1.58 g, 20.0 mmol, 2.0 equiv) in dry toluene (40 mL) was added. A balloon filled with oxygen was connected to the reaction flask via a needle. The flask was placed in an oil-bath and heated at 70 °C. After 15 min, a solution of 1-(prop-2-yn-1-yloxy)but-2-yne **127** (1.08 g, 10.0 mmol, 1 equiv) in dry toluene (40

mL) was added over 4 h using syringe pump. After this addition, the mixture was allowed to stir at 70 °C for additional 16 h and was then cooled to room temperature. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (Cyclohexane/Ethyl acetate gradient from 60/40 to 50/50) to afford **134** (1.15 g, 60%) as a slight yellow solid. m.p. 63 – 65 °C.

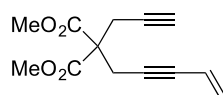
R_f = **0.11** (Cyclohexane/Ethyl acetate; 70/30, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 4.49 – 4.38 (m, 2H), 4.36 (s, 2H), 4.16 (q, *J* = 2.3 Hz, 2H), 3.95 – 3.85 (m, 2H), 1.84 (t, *J* = 2.3 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 156.2, 83.2, 76.5, 74.4, 67.6, 63.2, 57.2, 56.8, 46.8, 3.7.

MS (CI, NH₃): *m/z* = 194 [M + H]⁺.

Dimethyl 2-(pent-4-en-2-yn-1-yl)-2-(prop-2-yn-1-yl)malonate (135)



Chemical Formula: C₁₃H₁₄O₄
Exact Mass: 234.0892

This compound was obtained following the general procedure **F**. Starting from dimethyl 2-(pent-4-en-2-yn-1-yl)malonate **147** (0.35 g, 1.8 mmol), propargyl bromide (0.32 g, 2.1 mmol, 1.2 equiv) and NaH (0.84 g, 2.1 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 2 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **135** (0.36 g, 85%) as a colorless oil.

R_f = **0.27** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

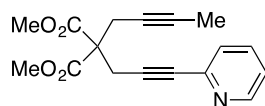
¹H NMR (300 MHz, CDCl₃) δ 5.78 – 5.65 (m, 1H), 5.60 – 5.50 (m, 1H), 5.45 – 5.37 (m, 1H), 3.75 (s, 6H), 3.12 – 3.07 (m, 2H), 2.99 – 2.94 (m, 2H), 2.03 (t, *J* = 2.7 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ 169.3, 127.1, 117.0, 84.3, 82.6, 78.6, 71.8, 56.9, 53.2, 23.7, 22.9.

MS (CI, NH₃): *m/z* = 235 [M + H]⁺.

Dimethyl 2-(but-2-yn-1-yl)-2-(3-(pyridin-2-yl)prop-2-yn-1-yl)malonate (137)

Experimental part



Chemical Formula: C₁₇H₁₇NO₄
Exact Mass: 299.1158

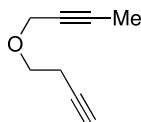
This compound was obtained following the general procedure **A**. Starting from dimethyl 2-(but-2-yn-1-yl)-2-(prop-2-yn-1-yl)malonate **125** (1.1 g, 5 mmol), 2-bromo pyridine (0.57 mL, 6 mmol, 1.2 equiv), PdCl₂(PPh₃)₂ (70 mg, 2 mol %) and CuI (9.5 mg, 1 mol %). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 70/30) afforded **137** (0.9 g, 60%) as a pale yellow oil. The analytical data were identical to the literature.¹⁹⁸

R_f = **0.2** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.53 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 7.60 (td, *J* = 7.7, 1.8 Hz, 1H), 7.34 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.19 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H), 3.77 (s, 6H), 3.23 (s, 2H), 3.04 – 2.94 (m, 2H), 1.75 (t, *J* = 2.4 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 169.6, 150.0, 136.1, 127.4, 122.8, 84.8, 83.3, 79.6, 73.0, 57.1, 53.2, 23.7, 23.5, 3.6.

4-(But-2-yn-1-yloxy)but-1-yne (138)



Chemical Formula: C₈H₁₀O
Exact Mass: 122.0732

This compound was obtained following the general procedure **F**. Starting from 3-butyn-1-ol (0.84 g, 12 mmol, 1.2 equiv), 1-brom-2-butyne (1.33 g, 10 mmol, 1.0 equiv) and NaH (0.48 g, 12 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 1 h. Purification on silica gel (pure dichloromethane) afforded **138** (0.92 g, 75%) as a pale yellow oil.

R_f = **0.52** (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

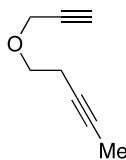
¹H NMR (300 MHz, CDCl₃) δ 4.17 – 4.09 (m, 2H), 3.63 (t, *J* = 7.0 Hz, 2H), 2.49 (td, *J* = 7.0, 2.7 Hz, 2H), 1.99 (t, *J* = 2.7 Hz, 1H), 1.85 (t, *J* = 2.4 Hz, 3H).

¹⁹⁸ Sperger, C.; Strand, L. H. S.; Fiksdahl, A. *Tetrahedron* **2010**, *66*, 7749.

^{13}C NMR (75 MHz, CDCl_3) δ 82.8, 81.2, 74.9, 69.5, 67.8, 58.9, 19.8, 3.7.

MS (CI, NH_3): $m/z = 140$ [$\text{M} + \text{NH}_4$] $^+$.

5-(Prop-2-yn-1-yloxy)pent-2-yne (140)



Chemical Formula: $\text{C}_8\text{H}_{10}\text{O}$
Exact Mass: 122.0732

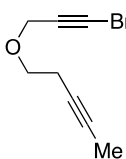
This compound was obtained following the general procedure **I**. Starting from pent-3-yn-1-ol (1.68 g, 20 mmol), propargyl bromide (2.2 mL, 20 mmol, 1 equiv) and KOH (2.26 g, 40 mmol, 2 equiv). The reaction mixture was stirred at room temperature for 4 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **140** (2.05 g, 84%) as a pale yellow oil. The analytical data were identical to the literature.¹⁹⁹

$R_f = 0.67$ (Cyclohexane/Ethyl acetate; 90/10, KMnO_4 , UV).

^1H NMR (300 MHz, CDCl_3) δ 4.18 (d, $J = 2.4$ Hz, 2H), 3.61 (t, $J = 7.0$ Hz, 2H), 2.50 – 2.38 (m, 3H), 1.78 (t, $J = 2.6$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ 79.7, 77.0, 75.7, 74.6, 68.7, 58.3, 20.1, 3.6.

5-((3-Bromoprop-2-yn-1-yl)oxy)pent-2-yne (141)



Chemical Formula: $\text{C}_8\text{H}_9\text{BrO}$
Exact Mass: 199.9837

This compound was obtained following the general procedure **H**. Starting from 5-(prop-2-yn-1-yloxy)pent-2-yne **140** (0.61 g, 5 mmol), NBS (1.06 g, 6 mmol, 1.2 equiv) and silver nitrate (0.085 g, 0.5 mmol). The reaction mixture was stirred at room temperature for 3 h. Purification

¹⁹⁹ Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2006**, *128*, 6044.

Experimental part

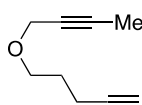
on silica gel (Petroleum ether/Ethyl acetate gradient from 98/2 to 95/5) afforded **141** (0.75 g, 75 %) as a pale yellow oil.

R_f = **0.44** (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 4.19 (s, 2H), 3.57 (t, J = 6.9 Hz, 2H), 2.41 (ddt, J = 6.9, 4.4, 2.5 Hz, 2H), 1.76 (t, J = 2.6 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 77.0, 76.2, 75.6, 68.8, 59.2, 46.2, 20.0, 3.6.

5-(But-2-yn-1-yloxy)pent-1-yne (142)



Chemical Formula: C₉H₁₂O
Exact Mass: 136.0888

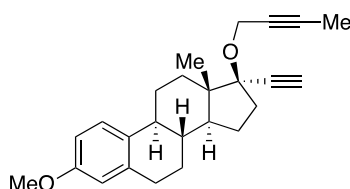
This compound was obtained following the general procedure **F**. Starting from 4-pentyn-1-ol (0.84 g, 10 mmol), 1-bromo-2-butyne (1.6 g, 12 mmol, 1.2 equiv) and NaH (0.48 g, 12 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 5 h. Purification on silica gel (Pentane/diethyl ether; 95/5) afforded **142** (1.07 g, 79%) as a colorless oil.

R_f = **0.51** (Cyclohexane/Ethyl acetate; 85/15, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 4.10 – 4.02 (m, 2H), 3.55 (t, J = 6.2 Hz, 2H), 2.27 (td, J = 7.1, 2.7 Hz, 2H), 1.95 – 1.89 (m, 1H), 1.83 (t, J = 2.4 Hz, 3H), 1.82 – 1.74 (m, 2H).

¹³C NMR (75 MHz, CDCl₃) δ 84.0, 82.4, 75.3, 68.5, 68.4, 58.8, 28.6, 15.4, 3.7.

(8*R*,9*S*,13*S*,14*S*,17*R*)-17-(But-2-yn-1-yloxy)-17-ethynyl-3-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene (143)



Chemical Formula: C₂₅H₃₀O₂
Exact Mass: 362.2246

This compound was obtained following the general procedure **F**. Starting from Mestranol (0.31 g, 1 mmol), 1-bromo-2-butyne (0.16 g, 1.2 mmol, 1.2 equiv) and NaH (48 mg, 1.2 mmol, 1.2 equiv). The reaction mixture was stirred at 60 °C for 20 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded **143** (0.13 g, 36%) as a white solid. m.p. 138-140 °C.

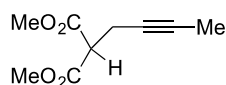
R_f = **0.4** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.20 (d, *J* = 8.6 Hz, 1H), 6.71 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.63 (d, *J* = 2.7 Hz, 1H), 4.33 – 4.20 (m, 2H), 3.78 (s, 3H), 2.90 – 2.76 (m, 2H), 2.65 (s, 1H), 2.39 – 1.92 (m, 5H), 1.91 – 1.66 (m, 7H), 1.53 – 1.27 (m, 4H), 0.92 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 157.6, 138.1, 132.7, 126.5, 113.9, 111.6, 85.9, 84.35, 81.76, 76.6, 76.1, 55.4, 54.5, 49.7, 47.8, 43.6, 39.4, 37.4, 34.3, 30.0, 27.4, 26.7, 22.9, 13.0, 3.9.

MS (CI, NH₃): *m/z* = 380 [M + NH₄]⁺.

Dimethyl 2-(but-2-yn-1-yl)malonate (**144**)



Chemical Formula: C₉H₁₂O₄
Exact Mass: 184.0736

This compound was obtained following the general procedure **F**. Starting from dimethyl malonate (11.6 g, 87.5 mmol, 2.3 equiv), 1-bromo-2-butyne (3.3 mL, 37.5 mmol, 1 equiv) and NaH (1.65 g, 41.3 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 5 h. The residue was purified by distillation under vacuum (80 °C, 1.5 torr) to afford **144** (4.3 g, 62%) as a colorless oil. The analytical data were identical to the literature.²⁰⁰

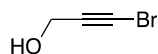
R_f = **0.29** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 3.76 (s, 6H), 3.55 (t, *J* = 7.7 Hz, 1H), 2.76– 2.70 (m, 2H), 1.74 (t, *J* = 2.5 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 168.7, 78.1, 74.7, 52.8, 51.6, 19.0, 3.6.

²⁰⁰ Zhao, L.-G.; Lu, X.-Y.; Xu, W. *J. Org. Chem.* **2005**, *70*, 4059.

3-Bromoprop-2-yn-1-ol (145)



Chemical Formula: C₃H₃BrO
Exact Mass: 133.9367

This compound was obtained following the general procedure **H**. Starting from propargyl alcohol (2.8 g, 50 mmol), NBS (10 g, 55 mmol, 1.1 equiv) and silver nitrate (0.43 g, 5 mmol). The reaction mixture was stirred at room temperature for 3 h. Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 90/10 to 80/20) afforded **145** (4.35 g, 65 %) as a colorless oil. The analytical data were identical to the literature.²⁰¹

R_f = **0.38** (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 4.28 (s, 2H), 3.40 (br, 1H).

¹³C NMR (75 MHz, CDCl₃) δ 78.4, 52.1, 46.1.

Dimethyl 2-(prop-2-yn-1-yl)malonate (146)



In a round bottom flask, dimethyl malonate (4.76 g, 36 mmol, 1.2 equiv), propargyl bromide (3.34 mL, 30 mmol, 1 equiv), potassium carbonate (9.95 g, 72 mmol, 2.4 equiv) and acetone (60 mL) were placed. The resulting mixture was stirred at 50 °C for 24 h. After the reaction was complete, the reaction mixture was filtered, and the organic layers were concentrated under reduced pressure. The residue was purified by distillation under vacuum (70 °C, 1.5 torr) to afford **146** (3.1 g, 60%) as a colorless oil. The analytical data were identical to the literature.²⁰²

R_f = **0.25** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

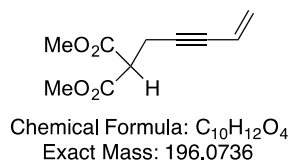
²⁰¹ Karmakar, R.; Yun, S. Y.; Chen, J.; Xia, Y.; Lee, D. *Angew. Chem. Int. Ed.* **2015**, *54*, 6582.

²⁰² Iafe, R. G.; Kuo, J. L.; Hochstatter, D. G.; Saga, T.; Turner, J. W.; Merlic, C. A. *Org. Lett.* **2013**, *15*, 582.

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 3.77 (s, 6H), 3.61 (t, $J = 7.7$ Hz, 1H), 2.79 (dd, $J = 7.7, 2.7$ Hz, 2H), 2.02 (t, $J = 2.7$ Hz, 1H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 168.6, 80.1, 70.8, 53.2, 51.2, 18.8.

Dimethyl 2-(pent-4-en-2-yn-1-yl)malonate (147)



This compound was obtained following the general procedure **A**. Starting from dimethyl 2-(prop-2-yn-1-yl)malonate (1.02 g, 6 mmol), vinyl bromide (7.2 mL, 7.2 mmol, 1.2 equiv), $\text{PdCl}_2(\text{PPh}_3)_2$ (84 mg, 2 mol %) and CuI (11 mg, 1 mol %). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **147** (0.5 g, 43%) as a colorless oil.

$R_f = 0.2$ (Cyclohexane/Ethyl acetate; 90/10, KMnO_4 , UV).

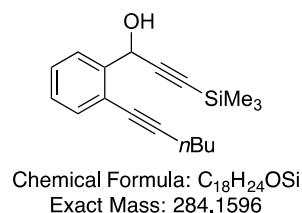
$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 5.79 – 5.65 (m, 1H), 5.62 – 5.50 (m, 1H), 5.48 – 5.38 (m, 1H), 3.77 (s, 6H), 3.61 (t, $J = 7.7$ Hz, 1H), 2.95 – 2.84 (m, 2H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 168.5, 126.8, 117.1, 86.0, 81.3, 52.9, 51.2, 19.5.

MS (CI, NH_3): $m/z = 214$ [$\text{M} + \text{NH}_4$] $^+$.

3.3. Synthesis of benzoyl or benzyl bridged α,ω -diynes

1-(2-(Hex-1-yn-1-yl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-ol (148)



This compound was obtained following the general procedure **B**. Starting from 2-(hex-1-yn-1-yl)benzaldehyde **2** (1.0 g, 5.4 mmol), trimethylsilylacetylene (1.14 mL, 8 mmol, 1.5 equiv) and $n\text{-BuLi}$ (3.5 mL, 1.85 M in hexane, 6.5 mmol, 1.2 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 95/5 to 90/10) afforded **148** (1.2 g, 78%) as a pale yellow oil.

Experimental part

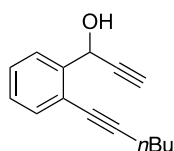
R_f = 0.33 (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.70 – 7.63 (m, 1H), 7.44 – 7.38 (m, 1H), 7.36 – 7.21 (m, 2H), 5.84 (d, *J* = 5.7 Hz, 1H), 2.69 (dd, *J* = 5.7, 0.4 Hz, 1H), 2.46 (t, *J* = 7.0 Hz, 2H), 1.68 – 1.56 (m, 2H), 1.54 – 1.43 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H), 0.20 (s, 9H).

¹³C NMR (75 MHz, CDCl₃) δ 141.9, 132.6, 128.3, 128.2, 126.8, 122.6, 104.5, 96.5, 91.5, 78.0, 63.9, 30.9, 22.2, 19.4, 13.8, 0.0.

MS (CI, NH₃): *m/z* = 267 [M + H – H₂O]⁺.

1-(2-(Hex-1-yn-1-yl)phenyl)prop-2-yn-1-ol (149).



Chemical Formula: C₁₅H₁₆O
Exact Mass: 212.1201

This compound was obtained following the general procedure **D**. Starting from 1-(2-(Hex-1-yn-1-yl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-ol **148** (1.2 g, 4.2 mmol) and TBAF (4.2 mL, 1.0 M in THF). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 85/15) afforded **149** (0.72 g, 81%) as a pale yellow oil.

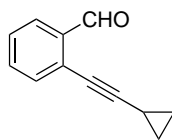
R_f = 0.4 (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (400 MHz, CDCl₃) δ 7.67 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.43 (dd, *J* = 7.1, 1.9 Hz, 1H), 7.45 – 7.30 (m, 2H), 5.85 (d, *J* = 2.3 Hz, 1H), 2.64 (s, 1H), 2.64 (s, 1H), 2.48 (t, *J* = 7.0 Hz, 2H), 1.70 – 1.57 (m, 2H), 1.57 – 1.41 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 141.6, 132.7, 128.4, 128.3, 126.6, 122.4, 96.7, 83.1, 77.9, 74.6, 63.3, 30.9, 22.2, 19.4, 13.7.

MS (CI, NH₃): *m/z* = 212 [M + NH₄ – H₂O]⁺.

2-(Cyclopropylethynyl)benzaldehyde (150)



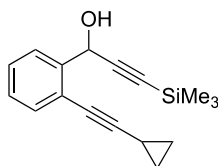
Chemical Formula: C₁₂H₁₀O
Exact Mass: 170.0732

This compound was obtained following the general procedure **A**. Starting from 2-bromobenzaldehyde (4.0 g, 21.7 mmol), cyclopropylacetylene (1.7 g, 26 mmol, 1.2 equiv), PdCl₂(PPh₃)₂ (0.75 mg, 1.09 mmol, 5 mol %) and CuI (0.1 g, 0.55 mmol, 2.5 mol %). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) afforded **150** (2.1 g, 57%) as an orange oil.

¹H NMR (300 MHz, CDCl₃) δ 10.48 (d, *J* = 0.6 Hz, 1H), 7.89 – 7.82 (m, 1H), 7.53 – 7.43 (m, 2H), 7.39 – 7.30 (m, 1H), 1.57 – 1.45 (m, 1H), 0.98 – 0.85 (m, 4H).

¹³C NMR (75 MHz, CDCl₃) δ 192.2, 136.2, 133.8, 133.4, 128.0, 127.9, 127.1, 101.4, 71.6, 9.0, 0.5.

1-(2-(Cyclopropylethynyl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-ol (**151**).



Chemical Formula: C₁₇H₂₀OSi
Exact Mass: 268.1283

This compound was obtained following the general procedure **B**. Starting from 2-(cyclopropylethynyl)benzaldehyde **150** (2.0 g, 11.8 mmol), trimethylsilylacetylene (3.25 mL, 23.5 mmol, 2 equiv) and *n*-BuLi (8.8 mL, 2.0 M in hexane, 17.6 mmol, 1.5 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **151** (2.5 g, 80%) as a pale yellow oil.

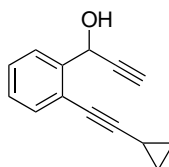
¹H NMR (300 MHz, CDCl₃) δ 7.70 – 7.55 (m, 1H), 7.43 – 7.35 (m, 1H), 7.35 – 7.18 (m, 2H), 5.79 (d, *J* = 5.5 Hz, 1H), 2.70 (d, *J* = 5.7 Hz, 1H), 1.54 – 1.40 (m, 1H), 0.94 – 0.76 (m, 4H), 0.20 (s, 9H).

¹³C NMR (75 MHz, CDCl₃) δ 142.1, 132.6, 128.3, 128.2, 126.8, 122.4, 104.5, 99.6, 91.4, 73.1, 63.9, 9.0, 8.9, 0.5, -0.01.

Experimental part

MS (CI, NH₃): $m/z = 267 [M + H - H_2O]^+$.

1-(2-(Cyclopropylethynyl)phenyl)prop-2-yn-1-ol (152)



Chemical Formula: C₁₄H₁₂O
Exact Mass: 196.0888

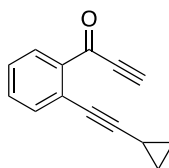
This compound was obtained following the general procedure **D**. Starting from 1-(2-(cyclopropylethynyl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-ol **151** (2.5 g, 9.3 mmol) and TBAF (9.3 mL, 1.0 M in THF). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **152** (1.5 g, 82%) as a pale yellow solid. m.p. 45 – 48 °C.

¹H NMR (300 MHz, CDCl₃) δ 7.71 – 7.56 (m, 1H), 7.44 – 7.36 (m, 1H), 7.36 – 7.20 (m, 2H), 5.80 (s, 1H), 2.72 (s, 1H, OH), 2.63 (d, $J = 2.3$ Hz, 1H), 1.56 – 1.42 (m, 1H), 0.98 – 0.80 (m, 4H).

¹³C NMR (75 MHz, CDCl₃) δ 141.8, 132.7, 128.4, 128.2, 126.6, 122.2, 99.8, 83.1, 74.6, 73.0, 63.3, 9.0, 0.5.

MS (CI, NH₃): $m/z = 196 [M + NH_4 - H_2O]^+$.

1-(2-(Cyclopropylethynyl)phenyl)prop-2-yn-1-one (153).



Chemical Formula: C₁₄H₁₀O
Exact Mass: 194.0732

This compound was obtained following the general procedure **C**. Starting from 1-(2-(cyclopropylethynyl)phenyl)prop-2-yn-1-ol **152** (0.92 g, 4.7 mmol) and Dess-Martin periodinane (2.4 g, 5.6 mmol, 1.2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **153** (0.75 g, 82%) as yellow solid. m.p. 181 – 183 °C.

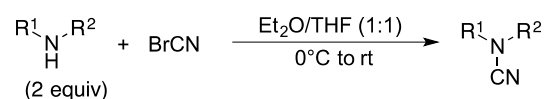
¹H NMR (300 MHz, CDCl₃) δ 8.20 – 8.05 (m, 1H), 7.52 – 7.42 (m, 2H), 7.41 – 7.30 (m, 1H), 3.41 (d, *J* = 0.3 Hz, 1H), 1.58 – 1.42 (m, *J* = 6.6 Hz, 1H), 0.91 (d, *J* = 6.6 Hz, 4H).

¹³C NMR (75 MHz, CDCl₃) δ 175.7, 136.3, 133.6, 131.9, 131.2, 126.2, 123.2, 99.9, 80.3, 79.6, 73.6, 8.0, -0.1.

MS (CI, NH₃): *m/z* = 195 [M + H]⁺.

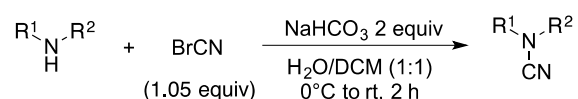
3.4. Synthesis of cyanamides

General procedure J:



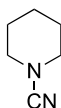
N-substituted amine (2 equiv) was added to a solution of cyanogen bromide (1 equiv) in Et₂O/THF (1:1, 5 M) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. Hexane (5 mL) was added, and the mixture was stirred for an additional 10 min. It was then filtered through a pad of Celite, and the filtrate was washed with water (×3) and brine (×3). The solution was dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the desired product.

General procedure K:



A solution of sodium hydrogen carbonate (2 equiv) in H₂O (2 M) was slowly added to a solution of *N*-substituted amine (1 equiv) in DCM (1 M) at 0 °C. Then, a solution of cyanogen bromide (1.05 equiv) in DCM (1 M) was added to the reaction mixture at 0 °C. The mixture was stirred at the same temperature for 30 min, and then allowed to warm to room temperature for an additional 2 h. The organic layers were separated and washed with saturated sodium hydrogen carbonate solution (×3) and brine (×3), dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the desired product.

Piperidine-1-carbonitrile (157)



Chemical Formula: C₆H₁₀N₂
Exact Mass: 110.0844

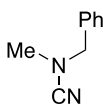
This compound was obtained following the general procedure **J**. Starting from piperidine (1.83 mL, 20.0 mmol, 2 equiv) and cyanogen bromide (1.06 g, 10 mmol, 1 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate from 90/10 to 85/15) afforded **157** (0.9 g, 82%) as a colorless oil. The analytical data were identical to the literature.²⁰³

R_f = **0.35** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 3.23 – 3.01 (m, 4H), 1.72 – 1.49 (m, 6H).

¹³C NMR (75 MHz, CDCl₃) δ 118.7, 50.3, 24.7, 23.1.

N-Benzyl-N-methylcyanamide (158)



Chemical Formula: C₉H₁₀N₂
Exact Mass: 146.0844

This compound was obtained following the general procedure **J**. Starting from *N*-methylbenzylamine (1.45 g, 12 mmol, 2 equiv) and cyanogen bromide (0.64 g, 6 mmol, 1 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 70/30) afforded compound **158** (0.75 g, 86 %) as a colorless oil. The analytical data were identical to the literature.²⁰⁴

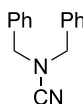
R_f = **0.52** (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.30 – 7.47 (m, 5H), 4.15 (s, 2 H), 2.77 (s, 3 H).

¹³C NMR (75 MHz, CDCl₃) δ 134.5, 129.1, 128.8, 128.5, 119.0, 57.3, 37.9.

²⁰³ Teng, F.; Yu, J.-T.; Jiang, Y.; Yang, H.; Cheng, J. *Chem. Commun.* **2014**, 50, 8412.

²⁰⁴ Bakunov, S. A.; Rukavishnikov, A. V.; Tkachev, A. V. *Synthesis*, **2000**, 1148.

***N,N*-Dibenzylcyanamide (159)**

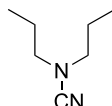
Chemical Formula: C₁₅H₁₄N₂
Exact Mass: 222.1157

This compound was obtained following the general procedure **K**. Starting from dibenzylamine (2.96 g, 15 mmol, 1 equiv), cyanogen bromide (1.69 g, 16 mmol, 1.05 equiv) and sodium hydrogen carbonate (2.5 g, 30 mmol, 2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded compound **159** (3.2 g, 96 %) as a white solid. The analytical data were identical to the literature.^{147b}

R_f = **0.31** (Cyclohexane/Ethyl acetate; 85/15, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.48 – 7.27 (m, 10H), 4.12 (s, 4 H).

¹³C NMR (75 MHz, CDCl₃) δ 134.5, 129.0, 128.8, 128.7, 118.4, 54.4.

***N,N*-Dipropylcyanamide (161)**

Chemical Formula: C₇H₁₄N₂
Exact Mass: 126.1157

This compound was obtained following the general procedure **J**. Starting from dipropylamine (3 mL, 20 mmol, 2 equiv) and cyanogen bromide (1.06 g, 10 mmol, 1 equiv). The reaction provided the compound **161** (1.13 g, 90 %) as a colorless oil, pure enough to be used without purification. The analytical data were identical to the literature.^{135a}

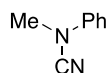
R_f = **0.6** (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 2.91 (t, *J* = 7.2 Hz, 4H), 1.69 – 1.53 (m, 4H), 0.93 (t, *J* = 7.4 Hz, 6H).

¹³C NMR (75 MHz, CDCl₃) δ 117.9, 53.3, 21.1, 11.1.

***N*-Methyl-*N*-phenylcyanamide (162)**

Experimental part



Chemical Formula: $C_8H_9N_2$
Exact Mass: 132.0687

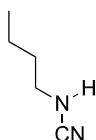
This compound was obtained following the general procedure **J**. Starting from *N*-methylaniline (2.16 mL, 20.0 mmol, 2 equiv) and cyanogen bromide (1.06 g, 10 mmol, 1 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 80/20 to 50/50) afforded compound **162** (1.2 g, 91 %) as a white solid. The analytical data were identical to the literature.^{135a}

R_f = **0.45** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.47 – 7.32 (m, 2H), 7.16 – 7.01 (m, 3H), 3.34 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 140.5, 129.7, 123.5, 115.0, 114.2, 36.9.

***N*-Butylcyanamide (163)**



Chemical Formula: $C_5H_{10}N_2$
Exact Mass: 98.0844

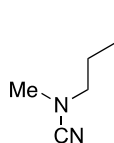
This compound was obtained following the general procedure **J**. Starting from *N*-butylamine (2.93 g, 40.0 mmol, 2 equiv) and cyanogen bromide (2.12 g, 20 mmol, 1 equiv). The reaction provided the compound **163** (1.9 g, 96 %) as a colorless oil, pure enough to be used without purification. The analytical data were identical to the literature.²⁰⁵

R_f = **0.2** (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 3.36 (br, 1H), 3.07 (t, J = 7.0 Hz, 2H), 1.67 – 1.50 (m, 2H), 1.47 – 1.25 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 116.4, 46.1, 31.8, 19.6, 13.7.

²⁰⁵ Ayres, J. N.; Ashford, M. W.; Stöckl, Y.; Prudhomme, V.; Ling, K. B.; Platts, J. A.; Morrill, L. C. *Org. Lett.* **2017**, *19*, 3835.

***N*-butyl-*N*-methylcyanamide (164)**

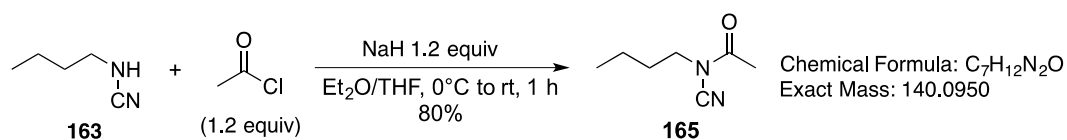
Chemical Formula: C₆H₁₂N₂
Exact Mass: 112.1000

This compound was obtained following the general procedure **K**. Starting from *N*-methylbutylamine (1.74 g, 20 mmol, 1 equiv), cyanogen bromide (2.22 g, 21 mmol, 1.05 equiv) and sodium hydrogen carbonate (3.3 g, 40 mmol, 2 equiv). The reaction provided the compound **164** (2.23 g, 99 %) as a pale yellow oil, pure enough to be used without purification.

R_f = **0.3** (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 2.96 (t, *J* = 7.2 Hz, 2H), 2.84 (s, 3H), 1.67 – 1.57 (m, 2H), 1.45 – 1.33 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 118.8, 52.8, 38.9, 29.4, 19.8, 13.7.

***N*-butyl-*N*-cyanoacetamide (165)**

To a suspension of NaH (0.77 g, 19.2 mmol, 1.2 equiv) in THF (30 mL) was added *N*-butylcyanamide (1.6 g, 16 mmol) in Et₂O (10 mL) at 0 °C. The mixture was warmed to room temperature, and acetyl chloride (1.36 mL, 19.2 mmol, 1.2 equiv) was added. The reaction mixture was stirred at room temperature for 1 h, and quenched with H₂O (1 mL). The crude reaction mixture was extracted with Et₂O (3 × 15 mL), washed with water and brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (Petroleum ether/Ethyl acetate gradient from 90/10 to 80/20) to afford compound **165** (1.8 g, 80 %) as a colorless oil. The analytical data were identical to the literature.^{135a}

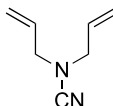
R_f = **0.45** (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).

Experimental part

¹H NMR (300 MHz, CDCl₃) δ 3.60 – 3.50 (m, 2H), 2.39 (s, 3H), 1.77 – 1.53 (m, 2H), 1.45 – 1.29 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 169.4, 111.1, 46.1, 29.7, 22.3, 19.6, 13.6.

***N,N*-diallylcyanamide (166)**



Chemical Formula: C₇H₁₀N₂
Exact Mass: 122.0844

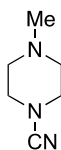
This compound was obtained following the general procedure **K**. Starting from diallylamine (1.46 g, 15 mmol, 1 equiv), cyanogen bromide (1.69 g, 16 mmol, 1.05 equiv) and sodium hydrogen carbonate (2.5 g, 30 mmol, 2 equiv). Purification on silica gel (Petroleum ether/Ethyl acetate gradient from 80/20 to 70/30) afforded compound **166** (1.7 g, 93 %) as a pale yellow oil. The analytical data were identical to the literature.²⁰³

R_f = **0.36** (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 5.90 – 5.75 (m, 2H), 5.41 – 5.32 (m, 2H), 5.32 – 5.24 (m, 2H), 3.65 – 3.54 (m, 4H).

¹³C NMR (75 MHz, CDCl₃) δ 131.1, 120.6, 117.7, 53.5.

4-Methylpiperazine-1-carbonitrile (167)



Chemical Formula: C₆H₁₁N₃
Exact Mass: 125.0953

This compound was obtained following the general procedure **K**. Starting from *N*-methyl piperazine (2 g, 20 mmol, 1 equiv), cyanogen bromide (2.22 g, 21 mmol, 1.05 equiv) and sodium hydrogen carbonate (3.3 g, 4 mmol, 2 equiv). The reaction provided the compound **167** (1.45 g, 58 %) as a pale yellow oil, pure enough to be used without purification.

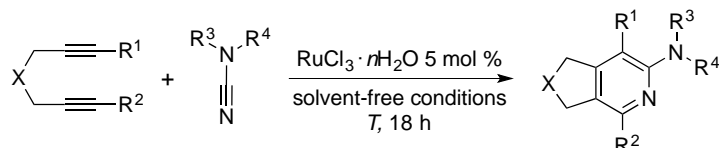
R_f = **0.24** (EA, KMnO₄, UV).

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 3.29 – 3.19 (m, 4H), 2.50 – 2.39 (m, 4H), 2.30 (s, 3H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 117.9, 53.7, 49.2, 46.4.

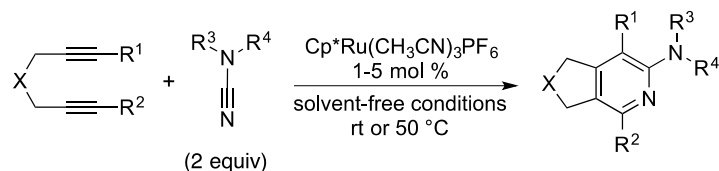
3.5. Ruthenium-catalyzed [2+2+2] cycloaddition of α,ω -diynes with cyanamides

General procedure L:



A sealed tube was equipped with $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (5 mol %) and α,ω -diyne (1 mmol, 1 equiv), followed by the addition of cyanamide (2.0 mmol, 2.0 equiv) under argon atmosphere. The tube was sealed and the reaction mixture was stirred vigorously at 80 °C or 110 °C. When the reaction was complete (TLC monitoring), the crude reaction mixture was directly purified by flash chromatography over silica gel to afford cycloadduct. In some cases, the excess of cyanamide was removed by bulb to bulb distillation.

General procedure M:



A sealed tube was equipped with $\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ (1-5 mol %) and diyne (1 equiv), followed by the addition of cyanamide (2 equiv) under argon atmosphere. The reaction mixture was stirred vigorously at room temperature or 50 °C. When the reaction was complete (TLC monitoring), the crude mixture was directly purified by flash chromatography over silica gel to afford cycloadduct. In some cases, the excess of cyanamide was removed by bulb to bulb distillation.

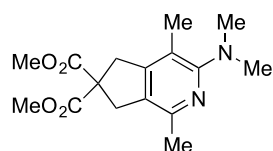
General procedure N:

Experimental part



A sealed tube was equipped with Cp*Ru(CH₃CN)₃PF₆ (1-5 mol %) and cyanamide (1.2 or 2.0 equiv), a solution of diyne (1 equiv) in DCM (1 or 2 M) was added under argon atmosphere. The reaction mixture was stirred vigorously at room temperature or 50 °C. When the reaction was complete (TLC monitoring), the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography over silica gel to afford cycloadduct. In some cases, the excess of cyanamide was removed by bulb to bulb distillation.

Dimethyl 3-(dimethylamino)-1,4-dimethyl-5,7-dihydro-6H-cyclopenta[*c*]pyridine-6,6-dicarboxylate (**168**)



Chemical Formula: C₁₆H₂₂N₂O₄
Exact Mass: 306.1580

This compound was obtained following the general procedure **L**. Starting from diyne **101** (236 mg, 1.0 mmol), *N,N*-dimethylcyanamide **154** (140 mg, 2.0 mmol, 2.0 equiv) and RuCl₃·*n*H₂O (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 110 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 70/30) afforded **168** (225 mg, 74%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 70 °C for 10 minutes). The analytical data were identical to the literature.^{135a}

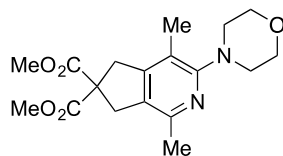
R_f = **0.34** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 3.74 (s, 6H), 3.48 (s, 2H), 3.47 (s, 2H), 2.75 (s, 6H), 2.31 (s, 3H), 2.14 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 172.2, 161.6, 150.3, 147.9, 127.2, 117.1, 59.9, 53.2, 42.5, 40.1, 38.7, 21.8, 14.9.

MS (CI, NH₃): *m/z* = 307 [M + H]⁺.

Dimethyl 1,4-dimethyl-3-morpholino-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (169)



Chemical Formula: C₁₈H₂₄N₂O₅
Exact Mass: 348.1685

a) This compound was obtained following the general procedure **L**. Starting from diyne **101** (236 mg, 1.0 mmol), 4-cyanomorpholine **155** (224 mg, 2.0 mmol, 2.0 equiv) and RuCl₃·*n*H₂O (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 80 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **169** (330 mg, 95%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes). The analytical data were identical to the literature.^{135a}

b) This compound was obtained following the general procedure **M**. Starting from diyne **101** (118 mg, 0.5 mmol), 4-cyanomorpholine **155** (112 mg, 1.0 mmol, 2.0 equiv) and Cp*Ru(CH₃CN)₃PF₆ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 2 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **169** (158 mg, 91%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes).

R_f = **0.24** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

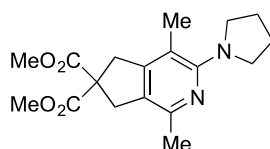
¹H NMR (300 MHz, CDCl₃) δ 3.86 – 3.78 (m, 4H), 3.76 (s, 6H), 3.50 (s, 2H), 3.48 (s, 2H), 3.12 – 2.99 (m, 4H), 2.33 (s, 3H), 2.14 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 172.1, 160.2, 150.5, 148.5, 128.3, 117.9, 67.4, 59.9, 53.2, 50.8, 40.0, 38.7, 21.7, 14.4.

MS (CI, NH₃): *m/z* = 349 [M + H]⁺.

Dimethyl 1,4-dimethyl-3-(pyrrolidin-1-yl)-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (170)

Experimental part



Chemical Formula: $C_{18}H_{24}N_2O_4$
Exact Mass: 332.1736

a) This compound was obtained following the general procedure **L**. Starting from diyne **101** (236 mg, 1.0 mmol), pyrrolidine-1-carbonitrile **156** (192 mg, 2.0 mmol, 2.0 equiv) and $RuCl_3 \cdot nH_2O$ (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 80 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 70/30) afforded **170** (285 mg, 86%) as a pale yellow solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0×10^{-3} mbar, 80 °C for 10 minutes).

b) This compound was obtained following the general procedure **M**. Starting from diyne **101** (118 mg, 0.5 mmol), pyrrolidine-1-carbonitrile **156** (96 mg, 1.0 mmol, 2.0 equiv) and $Cp^*Ru(CH_3CN)_3PF_6$ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 15 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 70/30) afforded **170** (134 mg, 81%) as a pale yellow solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0×10^{-3} mbar, 80 °C for 10 minutes).

The analytical data were identical to the literature.^{135a}

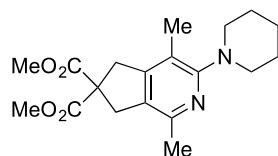
$R_f = 0.35$ (Petroleum ether/Ethyl acetate; 80/20, $KMnO_4$, UV).

1H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 6H), 3.44 (m, 8H), 2.29 (s, 3H), 2.15 (s, 3H), 1.87 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 158.9, 150.3, 147.4, 124.6, 113.5, 60.0, 53.1, 50.3, 40.1, 38.6, 25.6, 21.7, 15.8.

MS (CI, NH_3): $m/z = 333$ $[M + H]^+$.

Dimethyl 1,4-dimethyl-3-(piperidin-1-yl)-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (171)



Chemical Formula: $C_{19}H_{26}N_2O_4$
Exact Mass: 346.1893

This compound was obtained following the general procedure **L**. Starting from diyne **101** (236 mg, 1.0 mmol), piperidine-1-carbonitrile **157** (220 mg, 2.0 mmol, 2.0 equiv) and $RuCl_3 \cdot nH_2O$ (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 110 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **171** (251 mg, 73%) as a colorless oil. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0×10^{-3} mbar, 80 °C for 10 minutes). The analytical data were identical to the literature.¹⁴³

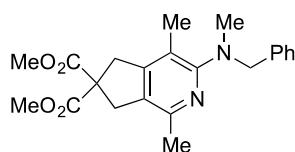
R_f = **0.33** (Petroleum ether/Ethyl acetate; 90/10, $KMnO_4$, UV).

¹H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 6H), 3.49 (s, 2H), 3.47 (s, 2H), 3.06 – 2.91 (m, 4H), 2.32 (s, 3H), 2.13 (s, 3H), 1.73 – 1.61 (m, 4H), 1.61 – 1.50 (m, 2H).

¹³C NMR (75 MHz, $CDCl_3$) δ 172.2, 161.7, 150.1, 148.1, 127.5, 118.1, 59.8, 53.2, 51.6, 40.01, 38.7, 26.5, 24.8, 21.7, 14.4.

MS (CI, NH_3): m/z = 347 [M + H]⁺.

Dimethyl 3-(benzyl(methyl)amino)-1,4-dimethyl-5,7-dihydro-6H-cyclopenta[*c*]pyridine-6,6-dicarboxylate (172)



Chemical Formula: $C_{22}H_{26}N_2O_4$
Exact Mass: 382.1893

This compound was obtained following the general procedure **L**. Starting from diyne **101** (236 mg, 1.0 mmol), *N*-benzyl-*N*-methylcyanamide **158** (292 mg, 2.0 mmol, 2.0 equiv) and $RuCl_3 \cdot nH_2O$ (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 80 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 85/15) afforded **172** (306 mg, 81%) as a colorless oil. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0×10^{-3} mbar, 120 °C for 10 minutes).

Experimental part

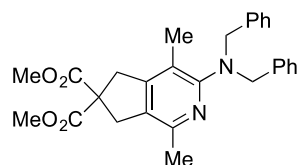
R_f = **0.26** (Petroleum ether/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.45 – 7.38 (m, 2H), 7.32 (t, *J* = 7.3 Hz, 2H), 7.28 – 7.16 (m, 1H), 4.26 (s, 2H), 3.77 (s, 6H), 3.55 – 3.45 (m, 4H), 2.67 (s, 3H), 2.35 (s, 3H), 2.20 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 172.2, 161.4, 150.4, 148.1, 140.0, 128.4, 128.2, 127.7, 126.8, 117.8, 59.9, 58.4, 53.2, 40.1, 39.8, 38.8, 21.7, 14.8.

MS (CI, NH₃): *m/z* = 383 [M + H]⁺.

Dimethyl 3-(dibenzylamino)-1,4-dimethyl-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (**173**)



Chemical Formula: C₂₈H₃₀N₂O₄
Exact Mass: 458.2206

This compound was obtained following the general procedure **L**. Starting from diyne **101** (236 mg, 1.0 mmol), dibenzylcyanamide **159** (444 mg, 2.0 mmol, 2.0 equiv) and RuCl₃·*n*H₂O (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 110 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **173** (344 mg, 75%) as a sticky yellow oil. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 180 °C for 20 minutes).

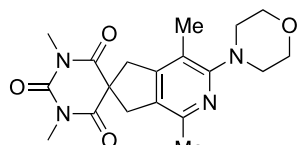
R_f = **0.17** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.39 – 7.13 (m, 10H), 4.25 (s, 4H), 3.76 (s, 6H), 3.49 (s, 4H), 2.29 (s, 3H), 2.24 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 172.2, 159.9, 150.4, 148.2, 139.9, 128.6, 128.3, 128.2, 126.7, 118.9, 59.7, 55.4, 53.2, 40.1, 38.8, 21.6, 14.5.

MS (CI, NH₃): *m/z* = 459 [M + H]⁺.

1,1',3',4'-Tetramethyl-3-morpholino-5,7-dihydro-2'*H*-spiro[cyclopenta[*c*]pyridine-6,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione (**181**)



Chemical Formula: $C_{19}H_{24}N_4O_4$
Exact Mass: 372.1798

This compound was obtained following the general procedure **L**. Starting from diyne **102** (260 mg, 1.0 mmol), 4-cyanomorpholine **155** (224 mg, 2.0 mmol, 2.0 equiv) and $RuCl_3 \cdot nH_2O$ (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 110 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 50/50) afforded **181** (275 mg, 74%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0×10^{-3} mbar, 90 °C for 10 minutes). m.p. 175 – 178 °C.

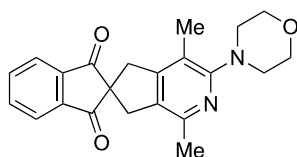
$R_f = 0.12$ (Petroleum ether/Ethyl acetate; 80/20, $KMnO_4$, UV).

1H NMR (300 MHz, $CDCl_3$) δ 3.90 – 3.76 (m, 4H), 3.49 (s, 2H), 3.45 (s, 2H), 3.34 (s, 6H), 3.17 – 2.94 (m, 4H), 2.30 (s, 3H), 2.15 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 160.7, 151.4, 150.6, 148.3, 127.3, 117.8, 67.4, 55.8, 50.8, 44.0, 42.6, 29.3, 21.8, 14.5.

MS (CI, NH_3): $m/z = 373$ $[M + H]^+$.

1,4-Dimethyl-3-morpholino-5,7-dihydrospiro[cyclopenta[*c*]pyridine-6,2'-indene]-1',3'-dione (182)



Chemical Formula: $C_{22}H_{22}N_2O_3$
Exact Mass: 362.1630

This compound was obtained following the general procedure **L**. Starting from diyne **103** (250 mg, 1.0 mmol), 4-cyanomorpholine **155** (224 mg, 2.0 mmol, 2.0 equiv) and $RuCl_3 \cdot nH_2O$ (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 80 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **182** (268 mg, 74%) as a yellow solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0×10^{-3} mbar, 90 °C for 10 minutes). m.p. 206 – 209 °C.

Experimental part

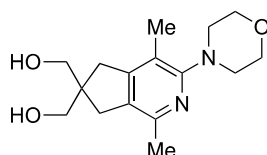
R_f = **0.21** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.08 – 7.98 (m, 2H), 7.93 – 7.85 (m, 2H), 3.89 – 3.73 (m, 4H), 3.23 (s, 2H), 3.22 (s, 2H), 3.14 – 3.01 (m, 4H), 2.31 (s, 3H), 2.13 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 202.9, 160.6, 151.3, 148.4, 141.7, 136.2, 128.9, 123.9, 118.0, 67.4, 58.5, 50.8, 39.6, 21.8, 14.5.

MS (CI, NH₃): m/z = 363 [M + H]⁺.

(1,4-Dimethyl-3-morpholino-6,7-dihydro-5H-cyclopenta[*c*]pyridine-6,6-diyl)dimethanol (183)



Chemical Formula: C₁₆H₂₄N₂O₃
Exact Mass: 292.1787

This compound was obtained following the general procedure **L**. Starting from diyne **104** (180 mg, 1.0 mmol), 4-cyanomorpholine **155** (224 mg, 2.0 mmol, 2.0 equiv) and RuCl₃·*n*H₂O (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 80 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate 80/20) afforded **183** (30 mg, 10%) as a pale yellow solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes). The analytical data were identical to the literature.¹⁴³

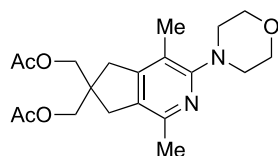
R_f = **0.2** (Petroleum ether/Ethyl acetate; 2/1, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 3.86– 3.81 (m, 4H), 3.81 – 3.67 (m, 4H), 3.13 – 2.99 (m, 4H), 2.72 – 2.60 (m, 4H), 2.31 (s, 3H), 2.12 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 159.8, 152.4, 149.1, 130.0, 118.6, 69.5, 67.4, 50.8, 48.7, 37.9, 36.6, 21.7, 14.4.

MS (CI, NH₃): m/z = 293 [M + H]⁺.

(1,4-Dimethyl-3-morpholino-6,7-dihydro-5H-cyclopenta[*c*]pyridine-6,6-diyl)bis (methylene) diacetate (184)



Chemical Formula: $C_{20}H_{28}N_2O_5$
Exact Mass: 376.1998

This compound was obtained following the general procedure **L**. Starting from diyne **105** (264 mg, 1.0 mmol), 4-cyanomorpholine **155** (224 mg, 2.0 mmol, 2.0 equiv) and $RuCl_3 \cdot nH_2O$ (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 80 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **184** (255 mg, 68%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0×10^{-3} mbar, 90 °C for 10 minutes). m.p. 102 – 104 °C.

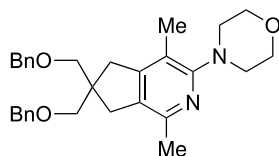
$R_f = 0.3$ (Cyclohexane/Ethyl acetate; 80/20, $KMnO_4$, UV).

1H NMR (300 MHz, $CDCl_3$) δ 4.08 (s, 4H), 3.89 – 3.73 (m, 4H), 3.16 – 2.92 (m, 4H), 2.78 – 2.70 (m, 4H), 2.31 (s, 3H), 2.12 (s, 3H), 2.07 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 160.1, 151.4, 149.1, 129.2, 118.4, 67.4, 66.9, 50.8, 46.2, 38.1, 36.8, 21.7, 21.0, 14.4.

MS (CI, NH_3): $m/z = 377$ [M + H] $^+$.

4-(6,6-Bis((benzyloxy)methyl)-1,4-dimethyl-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)morpholine (185)



Chemical Formula: $C_{30}H_{36}N_2O_3$
Exact Mass: 472.2726

This compound was obtained following the general procedure **L**. Starting from diyne **106** (360 mg, 1.0 mmol), 4-cyanomorpholine **155** (224 mg, 2.0 mmol, 2.0 equiv) and $RuCl_3 \cdot nH_2O$ (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 80 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate 80/20) afforded **185** (390 mg, 83%) as a pale yellow oil. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0×10^{-3} mbar, 90 °C for 10 minutes).

Experimental part

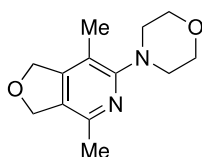
R_f = **0.38** (Petroleum ether/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.40 – 7.18 (m, 10H), 4.53 (s, 4H), 3.96 – 3.72 (m, 4H), 3.50 (s, 4H), 3.16 – 2.94 (m, 4H), 2.79 – 2.70 (m, 4H), 2.31 (s, 3H), 2.11 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 159.7, 152.9, 148.9, 138.8, 130.7, 128.5, 127.6, 118.5, 73.7, 73.4, 67.5, 50.9, 48.1, 38.5, 37.1, 21.7, 14.4.

MS (CI, NH₃): m/z = 473 [M + H]⁺.

4,7-Dimethyl-6-morpholino-1,3-dihydrofuro[3,4-c]pyridine (186)



Chemical Formula: C₁₃H₁₈N₂O₂
Exact Mass: 234.1368

a) This compound was obtained following the general procedure **L**. Starting from diyne **107** (122 mg, 1.0 mmol), 4-cyanomorpholine **155** (224 mg, 2.0 mmol, 2.0 equiv) and RuCl₃·*n*H₂O (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 80 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **186** (150 mg, 64%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes).

b) This compound was obtained following the general procedure **M**. Starting from diyne **107** (61 mg, 0.5 mmol), 4-cyanomorpholine **155** (112 mg, 1.0 mmol, 2.0 equiv) and Cp*Ru(CH₃CN)₃PF₆ (5.0 mg, 0.01 mmol). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **186** (94 mg, 80%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes).

The analytical data were identical to the literature.¹⁴³

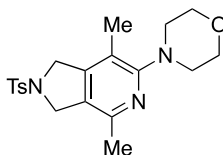
R_f = **0.13** (Petroleum ether/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 5.05 (s, 2H), 5.00 (s, 2H), 3.86 – 3.81 (m, 4H), 3.12 – 3.07 (m, 4H), 2.32 (s, 3H), 2.12 (s, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ 160.5, 150.1, 146.2, 127.6, 115.1, 73.2, 72.7, 67.3, 50.7, 21.9, 14.6.

MS (CI, NH_3): $m/z = 235$ $[\text{M} + \text{H}]^+$.

4-(4,7-Dimethyl-2-tosyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-yl)morpholine (187)



Chemical Formula: $\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}_3\text{S}$
Exact Mass: 387.1617

a) This compound was obtained following the general procedure **L**. Starting from diyne **108** (275 mg, 1.0 mmol), 4-cyanomorpholine **155** (224 mg, 2.0 mmol, 2.0 equiv) and $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 110 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **187** (280 mg, 72%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0×10^{-3} mbar, 90 °C for 10 minutes).

b) This compound was obtained following the general procedure **N**. Starting from diyne **108** (137.5 mg, 0.5 mmol), 4-cyanomorpholine **155** (67 mg, 0.6 mmol, 1.2 equiv) and $\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **187** (180 mg, 93%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0×10^{-3} mbar, 90 °C for 10 minutes).

The analytical data were identical to the literature.¹⁴³

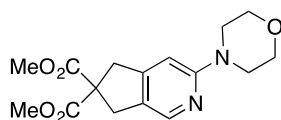
$R_f = 0.15$ (Petroleum ether/Ethyl acetate; 80/20, KMnO_4 , UV).

^1H NMR (300 MHz, CDCl_3) δ 7.78 (d, $J = 8.3$ Hz, 2H), 7.33 (d, $J = 8.0$ Hz, 2H), 4.52 – 4.40 (m, 4H), 3.85 – 3.75 (m, 4H), 3.10 – 3.00 (m, 4H), 2.41 (s, 3H), 2.27 (s, 3H), 2.08 (s, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ 160.8, 147.7, 146.8, 144.0, 134.1, 130.1, 127.8, 124.8, 116.4, 67.3, 53.5, 52.6, 50.69, 21.7, 14.5.

MS (CI, NH_3): $m/z = 388$ $[\text{M} + \text{H}]^+$.

Dimethyl 3-morpholino-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (188)



Chemical Formula: C₁₆H₂₀N₂O₅
Exact Mass: 320.1372

This compound was obtained following the general procedure **N**. Starting from diyne **109** (104 mg, 0.5 mmol), 4-cyanomorpholine **155** (67 mg, 0.6 mmol, 1.2 equiv) and Cp**Ru*(CH₃CN)₃PF₆ (2.5 mg, 0.005 mmol). The reaction mixture was stirred at room temperature for 2 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 60/40) afforded **188** (152 mg, 95%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes). The analytical data were identical to the literature.¹²⁸

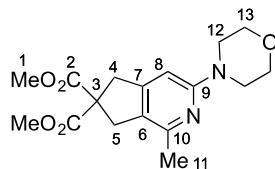
R_f = **0.1** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.02 (s, 1H), 6.52 (s, 1H), 3.88 – 3.77 (m, 4H), 3.74 (s, 6H), 3.50 (s, 4H), 3.47 – 3.37 (m, 4H).

¹³C NMR (75 MHz, CDCl₃) δ 171.8, 159.4, 151.7, 143.1, 126.3, 102.8, 66.9, 60.7, 53.2, 46.3, 40.6, 37.6.

MS (CI, NH₃): *m/z* = 321 [M + H]⁺.

Dimethyl 1-methyl-3-morpholino-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (193)



Chemical Formula: C₁₇H₂₂N₂O₅
Exact Mass: 334.1529

a) This compound was obtained following the general procedure **L**. Starting from diyne **125** (222 mg, 1.0 mmol), 4-cyanomorpholine **155** (224 mg, 2.0 mmol, 2.0 equiv) and RuCl₃·*n*H₂O (10.4 mg, 0.05 mmol). The reaction mixture was stirred at 100 °C for 18 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **193** (71 mg, 43%, ratio

= 87:13) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0×10^{-3} mbar, 90 °C for 10 minutes).

b) This compound was obtained following the general procedure **M**. Starting from diyne **125** (111 mg, 0.5 mmol), 4-cyanomorpholine **155** (112 mg, 1.0 mmol, 2.0 equiv) and $\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 10 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **193** (148 mg, 89%, ratio = 98:2) as a slight yellow solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0×10^{-3} mbar, 90 °C for 10 minutes). m.p. 110 – 112 °C.

$R_f = 0.17$ (Cyclohexane/Ethyl acetate; 85/15, KMnO_4 , UV).

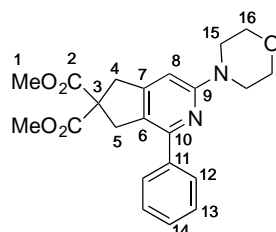
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.33 (s, 1H, H_8), 3.83 – 3.78 (m, 4H, H_{13}), 3.75 (s, 6H, H_1), 3.49 (s, 2H, H_4), 3.47 – 3.41 (m, 6H, $\text{H}_{5,12}$), 2.32 (s, 3H, H_{11})

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 172.0 (C_2), 159.3 (C_7), 151.7 (C_9), 151.5 (C_{10}), 124.3 (C_6), 100.1 (C_8), 67.0 (C_{13}), 60.0 (C_3), 53.2 (C_1), 46.4 (C_{12}), 40.8 (C_4), 38.0 (C_5), 22.2 (C_{11}).

NOESY (400 MHz, CDCl_3) H_8 (6.33 ppm) correlates to H_{12} (3.47 – 3.41 ppm), H_5 (3.47 – 3.41 ppm) correlates to H_{11} (2.32 ppm).

HRMS (ESI^+): calcd. for $\text{C}_{17}\text{H}_{23}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$: 335.1601, found 335.1603.

Dimethyl 3-morpholino-1-phenyl-5,7-dihydro-6H-cyclopenta[*c*]pyridine-6,6-dicarboxylate (194)



Chemical Formula: $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_5$
Exact Mass: 396.1685

a) This compound was obtained following the general procedure **L**. Starting from diyne **126** (142 mg, 0.5 mmol), 4-cyanomorpholine **155** (112 mg, 1.0 mmol, 2.0 equiv) and $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (5.2 mg, 0.025 mmol). The reaction mixture was stirred at 100 °C for 18 h. Purification on silica

Experimental part

gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **194** (32 mg, 16%, ratio = 90:10) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0×10^{-3} mbar, 90 °C for 10 minutes).

b) This compound was obtained following the general procedure **M**. Starting from diyne **126** (142 mg, 0.5 mmol), 4-cyanomorpholine **155** (112 mg, 1.0 mmol, 2.0 equiv) and $\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at 50 °C for 15 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 70/30) afforded **194** (190mg, 96%, ratio > 99:1) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0×10^{-3} mbar, 90 °C for 10 minutes). m.p. 166 – 168 °C.

$R_f = 0.2$ (Petroleum ether/Ethyl acetate; 85/15, KMnO_4 , UV).

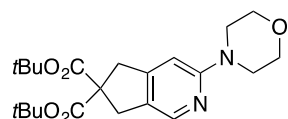
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.81 – 7.78 (m, 2H, H_{12}), 7.47 – 7.41 (m, 2H, H_{13}), 7.39 – 7.35 (m, 1H, H_{14}), 6.52 (s, 1H, H_8), 3.86 – 3.80 (m, 4H, H_{16}), 3.73 (s, 6H, H_{11}), 3.72 (s, 2H, H_5), 3.60 – 3.41 (m, 4H, H_{15}), 3.54 (s, 2H, H_4).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 171.8 (C_2), 159.0 (C_9), 153.1 (C_6), 151.2 (C_{10}), 139.9 (C_{11}), 128.4 (C_{12}), 128.3 (C_{13}), 128.3 (C_{14}), 123.2 (C_7), 101.5 (C_8), 67.0 (C_{16}), 60.5 (C_3), 53.2 (C_1), 46.0 (C_{15}), 40.5 (C_4), 39.6 (C_5).

NOESY (400 MHz, CDCl_3) H_{12} (7.81 – 7.78 ppm) correlates to H_5 (3.72 ppm), H_8 (6.52 ppm) correlate to H_{15} (3.60 – 3.41 ppm) and H_4 (3.54 ppm).

HRMS (ESI^+): calcd. for $\text{C}_{22}\text{H}_{25}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$: 397.1758, found 397.1756.

Di-*tert*-butyl 3-morpholino-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (196)



Chemical Formula: $\text{C}_{22}\text{H}_{32}\text{N}_2\text{O}_5$
Exact Mass: 404.2311

This compound was obtained following the general procedure **M**. Starting from diyne **114** (146 mg, 0.5 mmol), 4-cyanomorpholine **155** (112 mg, 1.0 mmol, 2.0 equiv) and

Cp*Ru(CH₃CN)₃PF₆ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate 80/20) afforded **196** (198 mg, 98%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes). m.p. 135 – 137 °C.

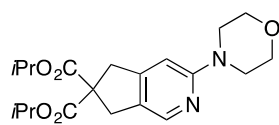
R_f = **0.23** (Petroleum ether/Ethyl acetate; 85/15, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.00 (s, 1H), 6.51 (s, 1H), 3.89 – 3.72 (m, 4H), 3.50 – 3.40 (m, 4H), 3.38 (s, 4H), 1.44 (s, 18H).

¹³C NMR (75 MHz, CDCl₃) δ 170.7, 159.4, 152.3, 143.0, 127.0, 102.8, 81.8, 67.0, 61.8, 46.4, 40.3, 37.3, 28.0.

HRMS (ESI⁺): calcd. for C₂₂H₃₃N₂O₅ [M+H]⁺:405.2384, found 405.2385.

Diisopropyl 3-morpholino-5,7-dihydro-6H-cyclopenta[*c*]pyridine-6,6-dicarboxylate (**197**)



Chemical Formula: C₂₀H₂₉N₂O₅
Exact Mass: 376.1998

This compound was obtained following the general procedure **N**. Starting from diyne **115** (132 mg, 0.5 mmol), 4-cyanomorpholine **155** (67 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH₃CN)₃PF₆ (2.5 mg, 0.005 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 70/30) afforded **197** (152 mg, 81%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes). m.p. 115 – 117 °C.

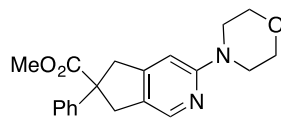
R_f = **0.11** (Petroleum ether/Ethyl acetate; 85/15, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.01 (s, 1H), 6.51 (s, 1H), 5.03 (dt, *J* = 12.5, 6.3 Hz, 2H), 3.86 – 3.74 (m, 4H), 3.50 – 3.38 (m, 8H), 1.23 (d, *J* = 6.3 Hz, 12H).

¹³C NMR (75 MHz, CDCl₃) δ 170.9, 159.4, 152.0, 143.1, 126.7, 102.8, 69.4, 67.0, 60.8, 46.3, 40.4, 37.4, 21.6.

HRMS (ESI⁺): calcd. for C₂₀H₂₉N₂O₅ [M+H]⁺: 377.2071, found 377.2071.

**Methyl 3-morpholino-6-phenyl-6,7-dihydro-5H-cyclopenta[*c*]pyridine-6-carboxylate
(198)**



Chemical Formula: C₂₀H₂₂N₂O₃
Exact Mass: 338.1630

This compound was obtained following the general procedure **N**. Starting from diyne **116** (113 mg, 0.5 mmol), 4-cyanomorpholine **155** (67 mg, 0.6 mmol, 1.2 equiv) and Cp**Ru*(CH₃CN)₃PF₆ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 70/30) afforded **198** (154 mg, 91%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes). m.p. 178 – 180 °C.

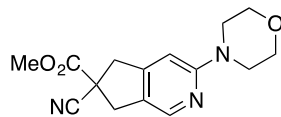
R_f = **0.1** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.07 (s, 1H), 7.45 – 7.22 (m, 5H), 6.59 (s, 1H), 4.00 – 3.74 (m, 6H), 3.60 (s, 3H), 3.50 – 3.33 (m, 4H), 3.23 (dd, *J* = 19.8, 15.7 Hz, 2H).

¹³C NMR (75 MHz, CDCl₃) δ 175.6, 159.4, 152.9, 142.9, 142.2, 128.7, 127.6, 127.4, 126.7, 103.1, 67.0, 60.0, 52.9, 46.3, 42.9, 39.5.

HRMS (ESI⁺): calcd. for C₂₀H₂₃N₂O₃ [M+H]⁺: 339.1703, found 339.1704.

**Methyl 6-cyano-3-morpholino-6,7-dihydro-5H-cyclopenta[*c*]pyridine-6-carboxylate
(199)**



Chemical Formula: C₁₅H₁₇N₃O₃
Exact Mass: 287.1270

This compound was obtained following the general procedure **M**. Starting from diyne **117** (87.5 mg, 0.5 mmol), 4-cyanomorpholine **155** (112 mg, 1.0 mmol, 2.0 equiv) and Cp**Ru*(CH₃CN)₃PF₆ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 40 min. Purification on silica gel (Cyclohexane/Ethyl acetate 80/20) afforded **199** (125 mg, 87%) as a pale yellow oil.

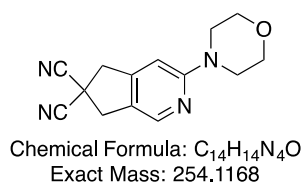
R_f = **0.1** (Petroleum ether/Ethyl acetate; 85/15, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.05 (s, 1H), 6.53 (s, 1H), 3.85 (s, 3H), 3.83 – 3.74 (m, 4H), 3.65 – 3.39 (m, 8H).

¹³C NMR (75 MHz, CDCl₃) δ 168.7, 159.7, 149.9, 143.5, 124.0, 120.1, 102.6, 66.8, 54.1, 47.6, 46.0, 42.9, 40.6.

HRMS (ESI⁺): calcd. for C₁₅H₁₈N₃O₃ [M+H]⁺: 288.1343, found 288.1343.

3-Morpholino-5,7-dihydro-6H-cyclopenta[*c*]pyridine-6,6-dicarbonitrile (**200**)



This compound was obtained following the general procedure **N**. Starting from diyne **118** (71 mg, 0.5 mmol), morpholine-4-carbonitrile **155** (67 mg, 0.6 mmol, 1.2 equiv) and Cp^{*}Ru(CH₃CN)₃PF₆ (5 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 2 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 50/50) afforded **200** (64 mg, 50%) as a white solid. m.p. 176 – 178 °C.

R_f = **0.4** (Petroleum ether/Ethyl acetate; 50/50, KMnO₄, UV).

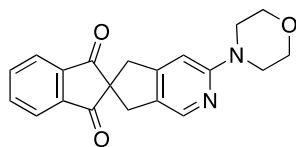
¹H NMR (400 MHz, CDCl₃) δ 8.12 (s, 1H), 6.56 (s, 1H), 3.85 – 3.76 (m, 4H), 3.65 (s, 2H), 3.61 (s, 2H), 3.55 – 3.40 (m, 4H).

¹³C NMR (75 MHz, CDCl₃) δ 159.9, 147.7, 144.0, 121.8, 116.0, 102.6, 66.7, 45.9, 44.6, 42.0, 34.0.

MS (CI, NH₃): m/z = 255 [M + H]⁺.

3-Morpholino-5,7-dihydrospiro[cyclopenta[*c*]pyridine-6,2'-indene]-1',3'-dione (**201**)

Experimental part



Chemical Formula: $C_{20}H_{18}N_2O_3$
Exact Mass: 334.1317

This compound was obtained following the general procedure **N**. Starting from diyne **119** (111 mg, 0.5 mmol), 4-cyanomorpholine **155** (67 mg, 0.6 mmol, 1.2 equiv) and $Cp^*Ru(CH_3CN)_3PF_6$ (2.5 mg, 0.005 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 50/50) afforded **201** (162 mg, 97%) as a pale yellow solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0×10^{-3} mbar, 90 °C for 10 minutes). m.p. 194 – 196 °C.

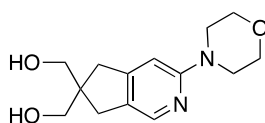
R_f = **0.1** (Petroleum ether/Ethyl acetate; 80/20, $KMnO_4$, UV).

¹H NMR (300 MHz, $CDCl_3$) δ 8.08 – 7.95 (m, 3H), 7.93 – 7.81 (m, 2H), 6.54 (s, 1H), 3.89 – 3.72 (m, 4H), 3.54 – 3.37 (m, 4H), 3.24 (s, 2H), 3.23 (s, 2H).

¹³C NMR (75 MHz, $CDCl_3$) δ 202.5, 159.6, 152.5, 143.0, 141.5, 136.1, 126.7, 123.8, 102.7, 66.9, 59.1, 46.3, 39.7, 38.4.

HRMS (ESI⁺): calcd. for $C_{20}H_{19}N_2O_3$ [M+H]⁺: 335.1390, found 335.1392.

(3-Morpholino-6,7-dihydro-5H-cyclopenta[c]pyridine-6,6-diyl)dimethanol (**202**)



Chemical Formula: $C_{14}H_{20}N_2O_3$
Exact Mass: 264.1474

This compound was obtained following the general procedure **M**. Starting from diyne **120** (76 mg, 0.5 mmol), 4-cyanomorpholine **155** (112 mg, 1.0 mmol, 2.0 equiv) and $Cp^*Ru(CH_3CN)_3PF_6$ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Pure ethyl acetate followed by DCM/MeOH 9/1) afforded **202** (115 mg, 87%) as a white solid. m.p. 158 – 160 °C.

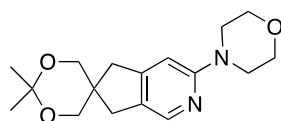
R_f = **0.2** (Pure ethyl acetate, $KMnO_4$, UV).

¹H NMR (300 MHz, MeOD) δ 7.89 (s, 1H), 6.71 (s, 1H), 4.89 (s, 2H, OH), 3.83 – 3.74 (m, 4H), 3.54 (s, 4H), 3.41 – 3.33 (m, 4H), 2.77 (s, 2H), 2.71 (s, 2H).

¹³C NMR (75 MHz, MeOD) δ 160.7, 156.5, 143.8, 130.6, 105.7, 67.8, 66.2, 51.6, 47.9, 38.8, 35.3.

HRMS (ESI⁺): calcd. for C₁₄H₂₁N₂O₃ [M+H]⁺: 265.1547, found 265.1546.

2',2'-Dimethyl-3-morpholino-5,7-dihydrospiro[cyclopenta[*c*]pyridine-6,5'-[1,3]dioxane] (203)



Chemical Formula: C₁₇H₂₄N₂O₃
Exact Mass: 304.1787

This compound was obtained following the general procedure **M**. Starting from diyne **121** (96 mg, 0.5 mmol), 4-cyanomorpholine **156** (112 mg, 1.0 mmol, 2.0 equiv) and Cp*Ru(CH₃CN)₃PF₆ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 10 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 60/40) afforded **203** (132 mg, 87%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes). m.p. 125 – 127 °C.

R_f = **0.1** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

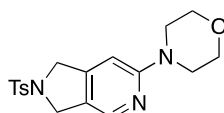
¹H NMR (300 MHz, CDCl₃) δ 8.00 (s, 1H), 6.51 (s, 1H), 3.84 – 3.77 (m, 4H), 3.70 (tt, *J* = 11.3, 5.8 Hz, 4H), 3.46 – 3.35 (m, 4H), 2.83 (s, 2H), 2.72 (s, 2H), 1.45 (d, *J* = 2.8 Hz, 6H).

¹³C NMR (75 MHz, CDCl₃) δ 159.3, 153.3, 143.8, 127.8, 103.7, 98.2, 68.7, 66.9, 46.4, 42.8, 40.2, 36.4, 24.7, 23.2.

HRMS (ESI⁺): calcd. for C₁₇H₂₅N₂O₃ [M+H]⁺: 305.1860, found 305.1861.

4-(2-Tosyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-yl)morpholine (204)

Experimental part



Chemical Formula: C₁₈H₂₁N₃O₃S
Exact Mass: 359.1304

This compound was obtained following the general procedure N. Starting from diyne **122** (123.5 mg, 0.5 mmol), 4-cyanomorpholine **155** (67 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH₃CN)₃PF₆ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 2/1 to 0/1) afforded **204** (174 mg, 97%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes). m.p. 202 – 204 °C

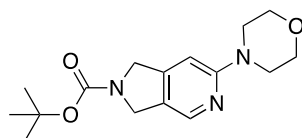
R_f = **0.1** (Petroleum ether/Ethyl acetate; 70/30, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.01 (s, 1H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.43 (s, 1H), 4.52 (s, 4H), 3.87 – 3.67 (m, 4H), 3.50 – 3.30 (m, 4H), 2.41 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 159.5, 147.8, 144.0, 142.1, 133.8, 130.0, 127.7, 122.5, 100.5, 66.8, 53.5, 51.4, 46.0, 21.7.

HRMS (ESI⁺): calcd. for C₁₈H₂₂N₃O₃S [M+H]⁺: 360.1376, found 360.1378.

tert-Butyl 6-morpholino-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridine-2-carboxylate (**205**)



Chemical Formula: C₁₆H₂₃N₃O₃
Exact Mass: 305.1739

This compound was obtained following the general procedure N. Starting from diyne **123** (96.5 mg, 0.5 mmol), 4-cyanomorpholine **155** (67 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH₃CN)₃PF₆ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 7/3 to 0/1) afforded **205** (151 mg, 99%) as a white solid. m.p. 195 – 197 °C.

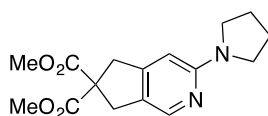
R_f = **0.1** (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (400 MHz, CDCl₃, 55 °C) δ 8.09 (s, 1H), 6.51 (s, 1H), 4.57 (s, 4H), 3.89 – 3.68 (m, 4H), 3.53 – 3.35 (m, 4H), 1.51 (s, 9H).

¹³C NMR (101 MHz, CDCl₃, 55 °C) δ 159.6, 154.6, 148.7, 142.2, 124.1, 100.8, 80.1, 66.9, 52.0, 49.8, 46.4, 28.7.

HRMS (ESI⁺): calcd. for C₁₆H₂₄N₃O₃ [M+H]⁺: 306.1812, found 306.1814.

**Dimethyl 3-(pyrrolidin-1-yl)-5,7-dihydro-6H-cyclopenta[*c*]pyridine-6,6-dicarboxylate
(207)**



Chemical Formula: C₁₆H₂₀N₂O₄
Exact Mass: 304.1423

This compound was obtained following the general procedure **N**. Starting from diyne **109** (104 mg, 0.5 mmol), pyrrolidine-1-carbonitrile **156** (57 mg, 0.6 mmol, 1.2 equiv) and Cp^{*}Ru(CH₃CN)₃PF₆ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 2 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 70/30) afforded **207** (144 mg, 90%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 3.0x10⁻³ mbar, 80 °C for 10 minutes). The analytical data were identical to the literature.¹²⁸

R_f = **0.42** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

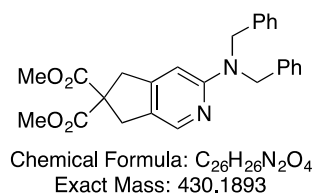
¹H NMR (300 MHz, CDCl₃) δ 7.96 (s, 1H), 6.22 (s, 1H), 3.74 (s, 6H), 3.47 (s, 4H), 3.44 – 3.30 (m, 4H), 2.07 – 1.87 (m, 4H).

¹³C NMR (75 MHz, CDCl₃) δ 172.0, 157.1, 151.0, 143.3, 123.3, 101.8, 60.8, 53.1, 47.0, 40.5, 37.6, 25.7.

MS (CI, NH₃): m/z = 305 [M + H]⁺.

**Dimethyl 3-(dibenzylamino)-5,7-dihydro-6H-cyclopenta[*c*]pyridine-6,6-dicarboxylate
(208)**

Experimental part



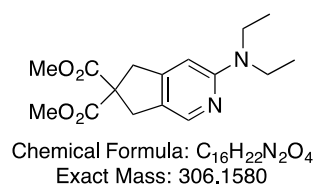
This compound was obtained following the general procedure **N**. Starting from diyne **109** (104 mg, 0.5 mmol), *N,N*-dibenzylcyanamide **159** (133 mg, 0.6 mmol, 1.2 equiv) and $Cp^*Ru(CH_3CN)_3PF_6$ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 10 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **208** (163 mg, 76%) as a pale yellow oil. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 5×10^{-3} mbar, 150 °C for 30 minutes).

$R_f = 0.37$ (Petroleum ether/Ethyl acetate; 85/15, $KMnO_4$, UV).

1H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.35 – 7.14 (m, 10H), 6.33 (s, 1H), 4.76 (s, 4H), 3.74 (s, 6H), 3.50 (s, 2H), 3.42 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 158.4, 151.6, 143.1, 138.7, 128.7, 127.2, 127.0, 124.6, 101.2, 60.6, 53.1, 51.3, 40.6, 37.6.

Dimethyl 3-(diethylamino)-5,7-dihydro-6H-cyclopenta[*c*]pyridine-6,6-dicarboxylate (209)



This compound was obtained following the general procedure **N**. Starting from diyne **109** (104 mg, 0.5 mmol), *N,N*-diethylcyanamide **160** (59 mg, 0.6 mmol, 1.2 equiv) and $Cp^*Ru(CH_3CN)_3PF_6$ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 10 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **209** (132 mg, 86%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0×10^{-3} mbar, 80 °C for 10 minutes). The analytical data were identical to the literature.¹²⁸

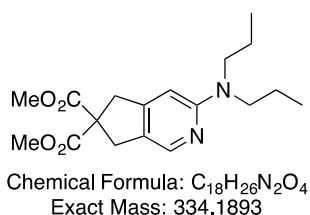
$R_f = 0.22$ (Petroleum ether/Ethyl acetate; 80/20, $KMnO_4$, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.95 (s, 1H), 6.32 (s, 1H), 3.74 (s, 6H), 3.54 – 3.40 (m, 8H), 1.15 (t, J = 7.0 Hz, 6H).

¹³C NMR (75 MHz, CDCl₃) δ 172.1, 157.3, 151.1, 143.2, 123.0, 100.8, 60.7, 53.1, 42.8, 40.6, 37.6, 13.1.

MS (CI, NH₃): m/z = 307 [M + H]⁺

Dimethyl 3-(dipropylamino)-5,7-dihydro-6H-cyclopenta[*c*]pyridine-6,6-dicarboxylate (210)



This compound was obtained following the general procedure **N**. Starting from diyne **109** (104 mg, 0.5 mmol), *N,N*-dipropylcyanamide **161** (76 mg, 0.6 mmol, 1.2 equiv) and Cp**Ru*(CH₃CN)₃PF₆ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **210** (140 mg, 84%) as a pale yellow oil. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 5x10⁻³ mbar, 100 °C for 10 minutes).

R_f = **0.23** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

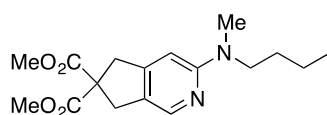
¹H NMR (300 MHz, CDCl₃) δ 7.94 (s, 1H), 6.27 (s, 1H), 3.74 (s, 6H), 3.51 – 3.40 (m, 4H), 3.40 – 3.28 (m, 4H), 1.68 – 1.47 (m, 4H), 0.91 (t, J = 7.4 Hz, 6H).

¹³C NMR (75 MHz, CDCl₃) δ 172.1, 157.8, 151.0, 143.1, 122.9, 100.8, 60.7, 53.1, 51.0, 40.6, 37.6, 20.9, 11.6.

HRMS (ESI⁺): calcd. for C₁₈H₂₇N₂O₄ [M+H]⁺: 335.1965, found 335.1967.

Dimethyl 3-(butyl(methyl)amino)-5,7-dihydro-6H-cyclopenta[*c*]pyridine-6,6-dicarboxylate (211)

Experimental part



Chemical Formula: $C_{17}H_{24}N_2O_4$
Exact Mass: 320.1736

This compound was obtained following the general procedure **N**. Starting from diyne **109** (104 mg, 0.5 mmol), *N*-butyl-*N*-methylcyanamide **164** (67 mg, 0.6 mmol, 1.2 equiv) and $Cp^*Ru(CH_3CN)_3PF_6$ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 70/30) afforded **211** (130 mg, 81%) as a colorless oil. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0×10^{-3} mbar, 90 °C for 10 minutes).

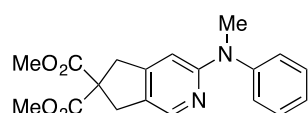
$R_f = 0.24$ (Petroleum ether/Ethyl acetate; 80/20, $KMnO_4$, UV).

1H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 6.33 (s, 1H), 3.74 (s, 6H), 3.52 – 3.38 (m, 6H), 3.00 (s, 3H), 1.59 – 1.48 (m, 2H), 1.42 – 1.30 (m, 2H), 0.93 (t, $J = 7.3$ Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 158.4, 151.2, 143.0, 123.3, 101.0, 60.8, 53.1, 50.4, 40.6, 37.5, 36.7, 29.6, 20.4, 14.2.

HRMS (ESI⁺): calcd. for $C_{17}H_{25}N_2O_4$ $[M+H]^+$: 321.1809, found 321.1810.

Dimethyl 3-(methyl(phenyl)amino)-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (**212**)



Chemical Formula: $C_{19}H_{20}N_2O_4$
Exact Mass: 340.1423

This compound was obtained following the general procedure **N**. Starting from diyne **109** (104 mg, 0.5 mmol), *N*-methyl-*N*-phenylcyanamide **162** (79 mg, 0.6 mmol, 1.2 equiv) and $Cp^*Ru(CH_3CN)_3PF_6$ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 10 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **212** (153mg, 90%) as a pale yellow solid. The analytical data were identical to the literature.^{135a}

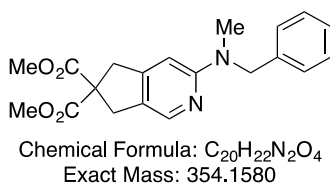
$R_f = 0.24$ (Petroleum ether/Ethyl acetate; 80/20, $KMnO_4$, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.04 (s, 1H), 7.51 – 7.32 (m, 2H), 7.31 – 7.13 (m, 3H), 6.40 (s, 1H), 3.73 (s, 6H), 3.49 (s, 2H), 3.44 (s, 3H), 3.37 (s, 2H).

¹³C NMR (75 MHz, CDCl₃) δ 171.9, 158.5, 150.8, 147.3, 142.8, 129.8, 126.3, 125.7, 125.3, 104.8, 60.7, 53.1, 40.4, 38.9, 37.6.

MS (CI, NH₃): m/z = 341 [M + H]⁺

Dimethyl 3-(benzyl(methyl)amino)-5,7-dihydro-6H-cyclopenta[*c*]pyridine-6,6-dicarboxylate (213)



This compound was obtained following the general procedure **N**. Starting from diyne **109** (104 mg, 0.5 mmol), *N*-benzyl-*N*-methylcyanamide **158** (88 mg, 0.6 mmol, 1.2 equiv) and Cp**Ru*(CH₃CN)₃PF₆ (2.5 mg, 0.005 mmol). The reaction mixture was stirred at room temperature for 2 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 70/30) afforded **213** (168 mg, 95%) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0 x 10⁻³ mbar, 120 °C for 20 minutes). m.p. 136 – 138 °C.

R_f = **0.17** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

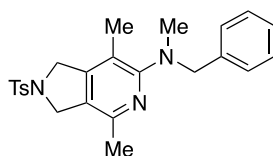
¹H NMR (300 MHz, CDCl₃) δ 8.00 (s, 1H), 7.36 – 7.15 (m, 5H), 6.38 (s, 1H), 4.78 (s, 2H), 3.75 (s, 6H), 3.49 (s, 2H), 3.47 (s, 2H), 3.03 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 172.0, 158.7, 151.5, 143.1, 139.1, 128.6, 127.2, 126.9, 124.1, 101.1, 60.7, 53.7, 53.1, 40.6, 37.6, 36.5.

HRMS (ESI⁺): calcd. for C₂₀H₂₃N₂O₄ [M+H]⁺: 355.1652, found 355.1654.

***N*-Benzyl-*N*,4,7-trimethyl-2-tosyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-amine (214)**

Experimental part



Chemical Formula: C₂₄H₂₇N₃O₂S
Exact Mass: 421.1824

This compound was obtained following the general procedure N. Starting from diyne **108** (137.5 mg, 0.5 mmol), *N*-benzyl-*N*-methylcyanamide **158** (88 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH₃CN)₃PF₆ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **214** (203 mg, 97%) as a pale brown solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 120 °C for 20 minutes). m.p. 132 – 134 °C.

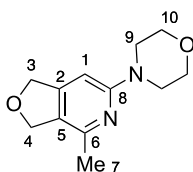
R_f = **0.3** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.81 – 7.70 (m, 2H), 7.39 – 7.27 (m, 6H), 7.26 – 7.19 (m, 1H), 4.53 – 4.90 (m, 4H), 4.26 (s, 2H), 2.68 (s, 3H), 2.42 (s, 3H), 2.28 (s, 3H), 2.13 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 161.7, 147.2, 146.7, 143.9, 139.6, 134.0, 130.0, 128.4, 128.1, 127.7, 127.0, 124.0, 116.0, 58.1, 53.4, 52.5, 39.8, 21.7, 14.8.

HRMS (ESI⁺): calcd. for C₂₄H₂₈N₃O₂S [M+H]⁺: 422.1897, found 422.1890.

4-Methyl-6-morpholino-1,3-dihydrofuro[3,4-*c*]pyridine (**217**)



Chemical Formula: C₁₂H₁₆N₂O₂
Exact Mass: 220.1212

This compound was obtained following the general procedure N. Starting from diyne **127** (54 mg, 0.5 mmol), 4-cyanomorpholine **155** (67 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH₃CN)₃PF₆ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 60/40) afforded **217** (95 mg, 86%, ratio > 99:1) as a pale yellow solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0x10⁻³ mbar, 90 °C for 10 minutes). m.p. 90 – 92 °C.

$R_f = 0.17$ (Petroleum ether/Ethyl acetate; 80/20, KMnO_4 , UV).

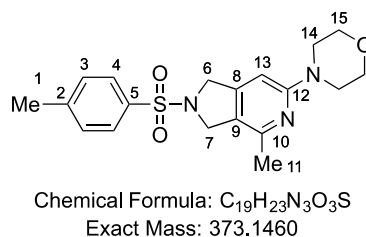
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.33 (s, 1H, H_1), 5.02 – 4.97 (m, 4H, $\text{H}_{3,4}$), 3.87 – 3.77 (m, 4H, H_{10}), 3.49 – 3.42 (m, 4H, H_9), 2.31 (s, 3H, H_7).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 159.6 (C_8), 151.0 (C_2), 149.4 (C_6), 123.8 (C_5), 96.5 (C_1), 73.5 (C_3), 71.8 (C_4), 66.9 (C_{10}), 46.4 (C_9), 22.4 (C_7).

NOESY (400 MHz, CDCl_3) H_1 (6.33 ppm) correlate to H_3 (5.02 – 4.97 ppm) and H_9 (3.49 – 3.42 ppm), H_4 (5.02 – 4.97 ppm) correlates to H_7 (2.31 ppm), H_7 (6.33 ppm) does not correlate to H_9 (3.49 – 3.42 ppm).

HRMS (ESI^+): calcd. for $\text{C}_{12}\text{H}_{17}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 221.1285, found 221.1285.

4-(4-Methyl-2-tosyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)morpholine (218)



This compound was obtained following the general procedure **N**. Starting from diyne **128** (130.5 mg, 0.5 mmol), 4-cyanomorpholine **155** (67 mg, 0.6 mmol, 1.2 equiv) and $\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 70/30) afforded **218** (168 mg, 90%, ratio > 99:1) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (conditions: 1.0×10^{-3} mbar, 90 °C for 10 minutes). m.p. 169 – 172 °C.

$R_f = 0.13$ (Petroleum ether/Ethyl acetate; 80/20, KMnO_4 , UV).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.78 – 7.72 (m, 2H, H_4), 7.34 – 7.28 (m, 2H, H_3), 6.24 (s, 1H, H_{13}), 4.51 (s, 2H, H_6), 4.45 (s, 2H, H_7), 3.81 – 3.75 (m, 4H, H_{15}), 3.45 – 3.39 (m, 4H, H_{14}), 2.41 (s, 3H, H_1), 2.26 (s, 3H, H_{11}).

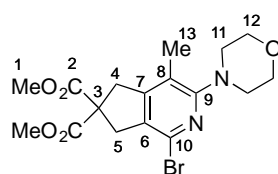
Experimental part

^{13}C NMR (101 MHz, CDCl_3) δ 159.5 (C_{12}), 150.9 (C_{10}), 147.5 (C_8), 143.9 (C_2), 133.8 (C_5), 130.0 (C_3), 127.6 (C_4), 120.6 (C_9), 97.7 (C_{13}), 66.8 (C_{15}), 53.8 (C_6), 51.8 (C_7), 46.1 (C_{14}), 22.1 (C_{11}), 21.7 (C_1).

NOESY (400 MHz, CDCl_3) H_{13} (6.24 ppm) correlate to H_6 (4.51 ppm) and H_{14} (3.45 – 3.39 ppm), H_7 (4.45 ppm) correlates to H_{11} (2.26 ppm), H_{11} (2.26 ppm) does not correlates to H_{14} (3.45 – 3.39 ppm).

HRMS (ESI^+): calcd. for $\text{C}_{19}\text{H}_{24}\text{N}_3\text{O}_3\text{S}$ [$\text{M}+\text{H}$] $^+$: 374.1533, found 374.1533.

Dimethyl 1-bromo-4-methyl-3-morpholino-5,7-dihydro-6H-cyclopenta[*c*]pyridine-6,6-dicarboxylate (**220**)



Chemical Formula: $\text{C}_{17}\text{H}_{21}\text{BrN}_2\text{O}_5$
Exact Mass: 412.0634

This compound was obtained following the general procedure **M**. Starting from diyne **129** (150 mg, 0.5 mmol), 4-cyanomorpholine **155** (112 mg, 1.0 mmol, 2.0 equiv) and $\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 60 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **220** (161 mg, 78%, ratio = 96:4) as a white solid. The excess of cyanamide was removed by bulb to bulb distillation (condition: 1.0×10^{-3} mbar, 90 °C for 10 minutes). m.p. 118 – 120 °C.

$R_f = 0.36$ (Petroleum ether/Ethyl acetate; 80/20, KMnO_4 , UV).

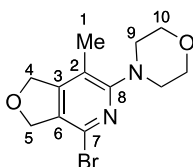
^1H NMR (400 MHz, CDCl_3) δ 3.85 – 3.79 (m, 4H, H_{12}), 3.77 (s, 6H, H_1), 3.55 (s, 2H, H_5), 3.54 (s, 2H, H_4), 3.11 – 3.06 (m, 4H, H_{11}), 2.12 (s, 3H, H_{13}).

^{13}C NMR (101 MHz, CDCl_3) δ 171.6 (C_2), 160.9 (C_9), 152.6 (C_7), 132.6 (C_{10}), 131.3 (C_6), 119.8 (C_8), 67.1 (C_{12}), 58.9 (C_3), 53.4 (C_1), 50.5 (C_{11}), 40.8 (C_4), 40.5 (C_5), 14.6 (C_{13}).

NOESY (400 MHz, CDCl_3) H_{13} (2.12 ppm) correlate to H_4 (3.54 ppm) and H_{11} (3.11 – 3.06 ppm).

HRMS (ESI⁺): calcd. for C₁₇H₂₁BrN₂O₅Na [M+Na]⁺: 435.0526, found 435.0526.

4-Bromo-7-methyl-6-morpholino-1,3-dihydrofuro[3,4-*c*]pyridine (221)



Chemical Formula: C₁₂H₁₅BrN₂O₂
Exact Mass: 298.0317

This compound was obtained following the general procedure **N**. Starting from diyne **130** (93 mg, 0.5 mmol), 4-cyanomorpholine **155** (67 mg, 0.6 mmol, 1.2 equiv) and Cp***Ru**(CH₃CN)₃PF₆ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at 50 °C for 2 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **221** (124 mg, 83%, ratio = 98:2) as a pale yellow solid. The excess of cyanamide was removed by bulb to bulb distillation (condition: 1.0x10⁻³ mbar, 90 °C for 10 minutes). m.p. 108 – 110°C.

R_f = **0.19** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

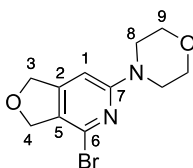
¹H NMR (400 MHz, CDCl₃) δ 5.07 (s, 2H, H₄), 5.03 – 4.95 (m, 2H, H₅), 3.88 – 3.77 (m, 4H, H₁₀), 3.18 – 3.08 (m, 4H, H₉), 2.10 (s, 3H, H₁).

¹³C NMR (101 MHz, CDCl₃) δ 161.2 (C₈), 152.4 (C₃), 130.5 (C₆), 129.0 (C₇), 117.1 (C₂), 73.9 (C₄), 73.6 (C₅), 67.0 (C₁₀), 50.5 (C₉), 14.8 (C₁).

NOESY (400 MHz, CDCl₃) H₁ (2.10 ppm) correlate to H₄ (5.07 ppm) and H₉ (3.18 – 3.08 ppm).

HRMS (ESI⁺): calcd. for C₁₂H₁₆BrN₂O₂ [M+H]⁺: 299.0390, found 299.0393.

4-Bromo-6-morpholino-1,3-dihydrofuro[3,4-*c*]pyridine (222)



Chemical Formula: C₁₁H₁₃BrN₂O₂
Exact Mass: 284.0160

Experimental part

This compound was obtained following the general procedure N. Starting from diyne **131** (89 mg, 0.5 mmol), 4-cyanomorpholine **155** (67 mg, 0.6 mmol, 1.2 equiv) and Cp**Ru*(CH₃CN)₃PF₆ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 2 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 60/40) afforded **222** (95 mg, 65%, ratio = 98:2) as a pale yellow solid. The excess of cyanamide was removed by bulb to bulb distillation (condition: 1.0x10⁻³ mbar, 90 °C for 10 minutes). m.p. 122 – 124 °C.

R_f = **0.1** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

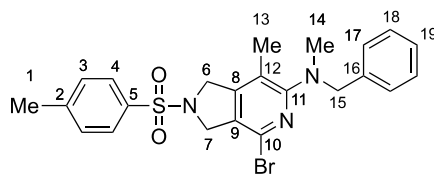
¹H NMR (400 MHz, CDCl₃) δ 6.40 (s, 1H, H₁), 5.06 (dd, *J* = 2.7, 1.8 Hz, 2H, H₃), 4.94 (t, *J* = 1.8 Hz, 2H, H₄), 3.83 – 3.75 (m, 4H, H₉), 3.53 – 3.41 (m, 4H, H₈).

¹³C NMR (101 MHz, CDCl₃) δ 159.6 (C₇), 153.1 (C₂), 132.7 (C₆), 126.0 (C₅), 97.7 (C₁), 74.1 (C₃), 72.8 (C₄), 66.7 (C₉), 45.9 (C₈).

NOESY (400 MHz, CDCl₃) H₁ (6.40 ppm) correlate to H₃ (5.06 ppm) and H₈ (3.53 – 3.41 ppm).

HRMS (ESI⁺): calcd. for C₁₁H₁₄BrN₂O₂ [M+H]⁺: 285.0233, found 285.0235.

***N*-Benzyl-4-bromo-*N*,7-dimethyl-2-tosyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-6-amine (223)**



Chemical Formula: C₂₃H₂₄BrN₃O₂S
Exact Mass: 485.0773

This compound was obtained following the general procedure N. Starting from diyne **132** (169.5 mg, 0.5 mmol), *N*-benzyl-*N*-methylcyanamide **158** (88 mg, 0.6 mmol, 1.2 equiv) and Cp**Ru*(CH₃CN)₃PF₆ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at 50 °C for 2 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 85/15) afforded **223** (182 mg, 75%, ratio = 98:2) as a white solid. m.p. 138-140 °C.

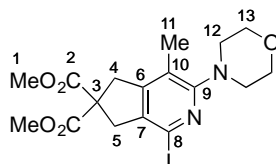
R_f = **0.46** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (400 MHz, CDCl₃) δ 7.80 – 7.72 (m, 2H, H₄), 7.40 – 7.35 (m, 2H, H₃), 7.35 – 7.29 (m, 4H, H_{17, 18}), 7.29 – 7.22 (m, 1H, H₁₉), 4.51 (s, 2H, H₆), 4.53 – 4.49 (m, 2H, H₇), 4.29 (s, 2H, H₁₅), 2.72 (s, 3H, H₁₄), 2.43 (s, 3H, H₁), 2.09 (s, 3H, H₁₃).

¹³C NMR (101 MHz, CDCl₃) δ 162.1 (C₁₁), 148.8 (C₈), 144.2 (C₂), 138.6 (C₁₆), 133.6 (C₁₅), 130.1 (C_{3, 10}), 128.5 (C₁₈), 128.0 (C₁₇), 127.7 (C₄), 127.2 (C₁₉), 126.5 (C₉), 117.4 (C₁₂), 57.8 (C₁₅), 54.1 (C₆), 53.7 (C₇), 39.6 (C₁₄), 21.7 (C₁), 15.0 (C₁₃).

NOESY (400 MHz, CDCl₃) H₁₃ (2.09 ppm) correlate to H₆ (4.51 ppm), H₁₅ (4.29 ppm) and H₁₄ (2.72 ppm).

Dimethyl 1-iodo-4-methyl-3-morpholino-5,7-dihydro-6H-cyclopenta[*c*]pyridine-6,6-dicarboxylate (224)



Chemical Formula: C₁₇H₂₁N₂O₅
Exact Mass: 460.0495

This compound was obtained following the general procedure **N**. Starting from diyne **133** (174 mg, 0.5 mmol), 4-cyanomorpholine **155** (67 mg, 0.6 mmol, 1.2 equiv) and Cp**Ru*(CH₃CN)₃PF₆ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at 50 °C for 30 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **224** (190 mg, 83%, ratio > 99:1) as a brown solid. The excess of cyanamide was removed by bulb to bulb distillation (condition: 1.0x10⁻³ mbar, 90 °C for 10 minutes). m.p. 126 – 128°C.

R_f = **0.14** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (400 MHz, CDCl₃) δ 3.84 – 3.79 (m, 4H, H₁₃), 3.77 (s, 6H, H₁), 3.57 (s, 2H, H₄), 3.49 (s, 2H, H₅), 3.10 – 3.03 (m, 4H, H₁₂), 2.11 (s, 3H, H₁₁).

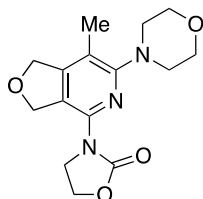
¹³C NMR (101 MHz, CDCl₃) δ 171.6 (C₂), 160.9 (C₉), 150.6 (C₆), 136.4 (C₇), 120.1 (C₁₀), 109.8 (C₈), 67.1 (C₁₃), 58.3 (C₃), 53.4 (C₁), 50.5 (C₁₂), 43.3 (C₅), 41.0 (C₄), 14.6 (C₁₁).

NOESY (400 MHz, CDCl₃) H₁₁ (2.11 ppm) correlate to H₄ (3.57 ppm) and H₁₂ (3.10 – 3.03 ppm).

Experimental part

HRMS (ESI⁺): calcd. for C₁₇H₂₁IN₂O₅Na [M+Na]⁺: 483.0387, found 483.0385.

3-(7-Methyl-6-morpholino-1,3-dihydrofuro[3,4-c]pyridin-4-yl)oxazolidin-2-one (225)



Chemical Formula: C₁₅H₁₉N₃O₄
Exact Mass: 305.1376

This compound was obtained following the general procedure **N**. Starting from diyne **134** (96.5 mg, 0.5 mmol), morpholine-4-carbonitrile **155** (67 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH₃CN)₃PF₆ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at 50 °C for 16 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 60/40 to 50/50) afforded **225** (120 mg, 79%, ratio > 99:1) as a white solid. m.p. 202 – 204 °C.

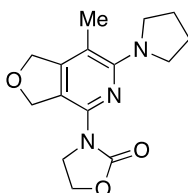
R_f = **0.21** (Petroleum ether/Ethyl acetate; 50/50, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 5.19 (s, 2H), 4.96 (s, 2H), 4.48 (t, *J* = 7.8 Hz, 2H), 4.22 (t, *J* = 7.9 Hz, 2H), 3.89 – 3.74 (m, 4H), 3.15 – 3.01 (m, 4H), 2.12 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 159.0, 155.1, 154.0, 140.1, 120.4, 114.5, 73.4, 72.5, 67.1, 62.9, 50.4, 44.9, 14.4.

MS (CI, NH₃): *m/z* = 306 [M + H]⁺.

3-(7-Methyl-6-(pyrrolidin-1-yl)-1,3-dihydrofuro[3,4-c]pyridin-4-yl)oxazolidin-2-one (226)



Chemical Formula: C₁₅H₁₉N₃O₃
Exact Mass: 289.1426

This compound was obtained following the general procedure **M**. Starting from diyne **134** (96.5 mg, 0.5 mmol), pyrrolidine-1-carbonitrile **156** (96.1 mg, 1.0 mmol, 2.0 equiv) and

Cp*Ru(CH₃CN)₃PF₆ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at 50 °C for 2 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 60/40 to 50/50) afforded **226** (135 mg, 93%, ratio > 99:1) as a white solid. m.p. 177 – 179 °C.

R_f = **0.6** (Petroleum ether/Ethyl acetate; 50/50, KMnO₄, UV).

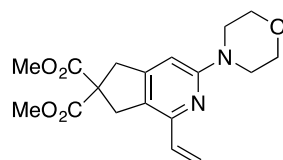
¹H NMR (400 MHz, CDCl₃) δ 5.16 (s, 2H), 4.95 (s, 2H), 4.45 (t, *J* = 7.9 Hz, 2H), 4.21 (t, *J* = 7.9 Hz, 2H), 3.52 – 3.40 (m, 4H), 2.14 (s, 3H), 1.93 – 1.84 (m, 4H).

¹³C NMR (101 MHz, CDCl₃) δ 157.4, 155.2, 153.6, 139.2, 115.8, 109.3, 73.4, 72.6, 62.8, 50.1, 44.9, 25.6, 15.8.

MS (CI, NH₃): *m/z* = 290 [M + H]⁺.

Elemental Analysis: Anal. Calcd for C₁₅H₁₉N₃O₃ (289.14): C, 62.27; H, 6.62; N, 14.52. Found: C, 62.20; H, 6.63; N, 14.26.

**Dimethyl 3-morpholino-1-vinyl-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate
(227)**



Chemical Formula: C₁₈H₂₂N₂O₅
Exact Mass: 346.1529

This compound was obtained following the general procedure **N**. Starting from diyne **135** (70 mg, 0.3 mmol), morpholine-4-carbonitrile **155** (40 mg, 0.36 mmol, 1.2 equiv) and Cp*Ru(CH₃CN)₃PF₆ (7.6 mg, 0.015 mmol). The reaction mixture was stirred at room temperature for 10 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **227** (94 mg, 90%, ratio > 99:1) as a white solid. m.p. 119 – 121 °C.

R_f = **0.18** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

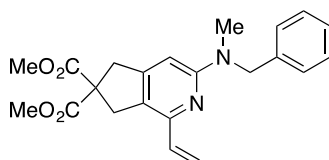
¹H NMR (300 MHz, CDCl₃) δ 6.70 (dd, *J* = 17.1, 10.6 Hz, 1H), 6.45 (s, 1H), 6.25 (dd, *J* = 17.1, 2.2 Hz, 1H), 5.42 (dd, *J* = 10.6, 2.2 Hz, 1H), 3.86 – 3.75 (m, 4H), 3.74 (s, 6H), 3.55 (s, 2H), 3.53 – 3.44 (m, 6H).

Experimental part

^{13}C NMR (75 MHz, CDCl_3) δ 171.8, 158.8, 152.3, 147.9, 134.0, 124.1, 118.6, 102.3, 67.0, 60.3, 53.2, 46.1, 40.5, 37.7.

HRMS (ESI⁺): calcd. for $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$: 347.1601, found 347.1603.

Dimethyl 3-(benzyl(methyl)amino)-1-vinyl-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (**228**)



Chemical Formula: $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_4$
Exact Mass: 380.1736

This compound was obtained following the general procedure **N**. Starting from diyne **135** (70 mg, 0.3 mmol), *N*-benzyl-*N*-methylcyanamide **158** (53 mg, 0.36 mmol, 1.2 equiv) and $\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ (7.6 mg, 0.015 mmol). The reaction mixture was stirred at room temperature for 30 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **228** (105 mg, 92%, ratio > 99:1) as a white solid. m.p. 146 – 148 °C.

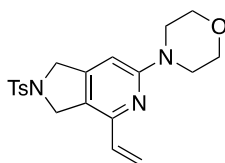
R_f = **0.33** (Petroleum ether/Ethyl acetate; 80/20, KMnO_4 , UV).

^1H NMR (300 MHz, CDCl_3) δ 7.35 – 7.18 (m, 5H), 6.72 (dd, J = 17.1, 10.6 Hz, 1H), 6.33 (s, 1H), 6.27 (dd, J = 17.1, 2.3 Hz, 1H), 5.39 (dd, J = 10.6, 2.3 Hz, 1H), 4.83 (s, 2H), 3.75 (s, 6H), 3.56 (s, 2H), 3.47 (d, J = 1.1 Hz, 2H), 3.05 (s, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ 172.0, 158.1, 152.1, 147.7, 139.4, 134.2, 128.6, 127.4, 126.9, 122.1, 118.2, 100.9, 60.3, 53.5, 53.2, 40.5, 37.6, 36.3.

MS (CI, NH_3): m/z = 381 $[\text{M} + \text{H}]^+$.

4-(2-Tosyl-4-vinyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)morpholine (**229**)



Chemical Formula: $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_3\text{S}$
Exact Mass: 385.1460

This compound was obtained following the general procedure **M**. Starting from diyne **136** (136.5 mg, 0.5 mmol), morpholine-4-carbonitrile **155** (112 mg, 1.0 mmol, 2.0 equiv) and Cp*Ru(CH₃CN)₃PF₆ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 3 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 60/40) afforded **229** (145 mg, 75%, ratio > 99:1) as a white solid. m.p. 168 – 170 °C.

R_f = **0.1** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

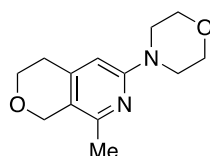
¹H NMR (300 MHz, CDCl₃) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 6.52 (dd, *J* = 17.2, 10.7 Hz, 1H), 6.35 (s, 1H), 6.18 (dd, *J* = 17.2, 1.9 Hz, 1H), 5.46 (dd, *J* = 10.6, 1.9 Hz, 1H), 4.56 (s, 2H), 4.51 (s, 2H), 3.85 – 3.70 (m, 4H), 3.53 – 3.40 (m, 4H), 2.40 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 159.0, 148.3, 147.3, 144.0, 133.8, 133.6, 130.0, 127.6, 120.1, 119.7, 99.9, 66.8, 53.4, 51.5, 45.9, 21.6.

MS (CI, NH₃): *m/z* = 386 [M + H]⁺.

Elemental Analysis: Anal. Calcd for C₂₀H₂₃N₃O₃S (385.15): C, 62.32; H, 6.01; N, 10.90. Found: C, 62.20; H, 6.04; N, 10.61.

8-Methyl-6-morpholino-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridine (**230**)



Chemical Formula: C₁₃H₁₈N₂O₂
Exact Mass: 234.1368

This compound was obtained following the general procedure **N**. Starting from diyne **138** (61 mg, 0.5 mmol), morpholine-4-carbonitrile **155** (112 mg, 1.0 mmol, 2.0 equiv) and Cp*Ru(CH₃CN)₃PF₆ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at 50 °C for 2 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 70/30) afforded **230** (95 mg, 81%, ratio > 99:1) as a white solid. m.p. 140 – 142 °C.

R_f = **0.2** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

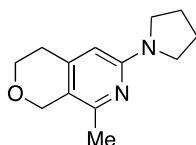
¹H NMR (300 MHz, CDCl₃) δ 6.23 (s, 1H), 4.63 (s, 2H), 3.89 (t, *J* = 5.6 Hz, 2H), 3.85 – 3.75 (m, 4H), 3.48 – 3.35 (m, 4H), 2.76 (dt, *J* = 5.8, 2.9 Hz, 2H), 2.22 (s, 3H).

Experimental part

^{13}C NMR (75 MHz, CDCl_3) δ 158.0, 152.0, 144.1, 119.1, 104.0, 67.0, 65.8, 64.6, 46.2, 28.9, 21.1.

HRMS (ESI⁺): calcd. for $\text{C}_{13}\text{H}_{19}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 235.1441, found 235.1440.

8-Methyl-6-(pyrrolidin-1-yl)-3,4-dihydro-1H-pyrano[3,4-c]pyridine (231)



Chemical Formula: $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}$
Exact Mass: 218.1419

This compound was obtained following the general procedure **N**. Starting from diyne **138** (61 mg, 0.5 mmol), pyrrolidine-1-carbonitrile **156** (96.1 mg, 1.0 mmol, 2.0 equiv) and $\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at 50 °C for 4 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **231** (50 mg, 46%, ratio > 99:1) as a white solid. m.p. 110 – 112 °C.

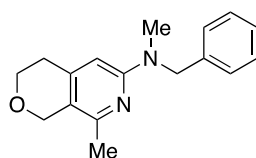
R_f = 0.28 (Petroleum ether/Ethyl acetate; 80/20, KMnO_4 , UV).

^1H NMR (400 MHz, CDCl_3) δ 5.96 (s, 1H), 4.64 (s, 2H), 3.89 (t, J = 5.7 Hz, 2H), 3.49 – 3.33 (m, 4H), 2.75 (t, J = 5.7 Hz, 2H), 2.22 (s, 3H), 2.03 – 1.91 (m, 4H).

^{13}C NMR (101 MHz, CDCl_3) δ 155.9, 151.9, 143.4, 115.9, 103.1, 66.0, 64.7, 46.8, 28.9, 25.7, 21.1.

MS (CI, NH_3): m/z = 219 $[\text{M} + \text{H}]^+$.

N-benzyl-N,8-dimethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridin-6-amine (232)



Chemical Formula: $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}$
Exact Mass: 268.1576

This compound was obtained following the general procedure **N**. Starting from diyne **138** (61 mg, 0.5 mmol), N-benzyl-N-methylcyanamide **158** (146 mg, 1.0 mmol, 2.0 equiv) and

Cp*Ru(CH₃CN)₃PF₆ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at 50 °C for 4 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **232** (45 mg, 34%, ratio > 99:1) as a white solid m.p. 78 – 79 °C.

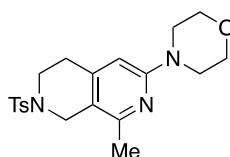
R_f = **0.47** (Petroleum ether/Ethyl acetate; 75/25, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.37 – 7.26 (m, 2H), 7.27 – 7.15 (m, 3H), 6.11 (s, 1H), 4.81 (s, 2H), 4.65 (s, 2H), 3.89 (t, *J* = 5.7 Hz, 2H), 3.00 (s, 3H), 2.85 – 2.62 (m, 2H), 2.23 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 157.2, 151.7, 143.8, 139.4, 128.5, 127.4, 126.9, 116.7, 102.3, 65.9, 64.7, 53.0, 36.0, 29.0, 21.2.

MS (CI, NH₃): *m/z* = 269 [M + H]⁺.

4-(1-Methyl-7-tosyl-5,6,7,8-tetrahydro-2,7-naphthyridin-3-yl)morpholine (233)



Chemical Formula: C₂₀H₂₅N₃O₃S
Exact Mass: 387.1617

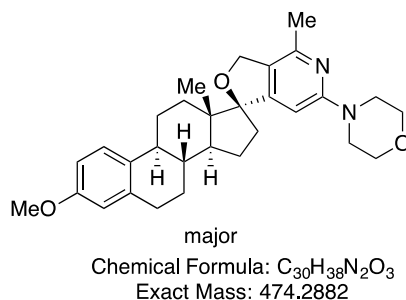
This compound was obtained following the general procedure N. Starting from diyne **139** (82.5 mg, 0.3 mmol), morpholine-4-carbonitrile **155** (67 mg, 0.6 mmol, 2.0 equiv) and Cp*Ru(CH₃CN)₃PF₆ (7.6 mg, 0.015 mmol). The reaction mixture was stirred at room temperature for 2 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 80/20 to 60/40) afforded **233** (100 mg, 86%, ratio > 99:1) as a white solid. m.p. 136 – 138 °C.

R_f = **0.2** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.17 (s, 1H), 4.06 (s, 2H), 3.86 – 3.72 (m, 4H), 3.48 – 3.35 (m, 4H), 3.30 (t, *J* = 5.8 Hz, 2H), 2.82 (t, *J* = 5.7 Hz, 2H), 2.42 (s, 3H), 2.27 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 157.9, 153.4, 143.9, 143.8, 133.6, 129.9, 127.8, 116.1, 103.7, 66.9, 46.0, 45.0, 43.0, 29.5, 21.7.

MS (CI, NH₃): *m/z* = 388 [M + H]⁺

(8*R*,9*S*,13*S*,14*S*,17*S*)-3-Methoxy-4',13-dimethyl-6'-morpholino-6,7,8,9,11,12,13,14,15,16-decahydro-3'*H*-spiro[cyclopenta[*a*]phenanthrene-17,1'-furo[3,4-*c*]pyridine (237)


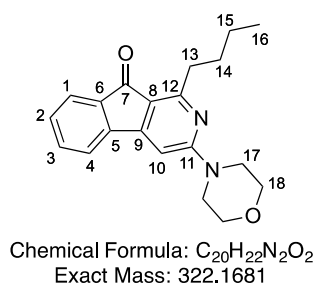
This compound was obtained following the general procedure **N**. Starting from diyne **143** (72.4 mg, 0.2 mmol), morpholine-4-carbonitrile **155** (27 mg, 0.24 mmol, 1.2 equiv) and Cp*Ru(CH₃CN)₃PF₆ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at 50 °C for 2 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **237** (48.5 mg, 51%, ratio = 10:1) as a white solid. m.p. 208 – 210 °C.

R_f = **0.14** (Petroleum ether/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.12 (d, *J* = 8.6 Hz, 1H), 6.68 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.62 (d, *J* = 2.8 Hz, 1H), 6.30 (s, 1H), 4.93 – 4.78 (m, 2H), 3.91 – 3.80 (m, 4H), 3.77 (s, 3H), 3.61 – 3.35 (m, 4H), 2.98 – 2.78 (m, 2H), 2.31 (s, 3H), 2.28 – 2.17 (m, 1H), 2.15 – 1.94 (m, 4H), 1.87 – 1.78 (m, 1H), 1.74 – 1.55 (m, 3H), 1.46 – 1.26 (m, 4H), 1.06 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 159.8, 157.6, 156.9, 149.0, 137.9, 132.4, 126.4, 124.8, 114.0, 111.6, 98.9, 98.3, 69.9, 67.0, 55.3, 49.9, 48.3, 46.6, 43.9, 39.3, 36.3, 33.6, 30.0, 27.7, 26.4, 23.7, 22.2, 15.5.

MS (CI, NH₃): *m/z* = 475 [M + H]⁺.

1-Butyl-3-morpholino-9*H*-indeno[2,1-*c*]pyridin-9-one (240)


This compound was obtained following the general procedure **M**. Starting from diyne **29** (105 mg, 0.5 mmol), 4-cyanomorpholine **155** (112 mg, 1.0 mmol, 2.0 equiv) and Cp*Ru(CH₃CN)₃PF₆ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 10 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **240** (142 mg, 92%, ratio > 99:1) as a light yellow solid. m.p. 106 – 108 °C.

R_f = **0.12** (Petroleum ether/Ethyl acetate; 90/10, KMnO₄, UV).

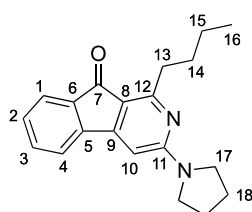
¹H NMR (400 MHz, CDCl₃) δ 7.69 – 7.64 (m, 1H, H₁), 7.54 (dd, *J* = 7.3, 0.9 Hz, 1H, H₄), 7.47 (td, *J* = 7.4, 1.2 Hz, 1H, H₃), 7.40 (td, *J* = 7.4, 1.1 Hz, 1H, H₂), 6.62 (s, 1H, H₁₀), 3.86 – 3.81 (m, 4H, H₁₈), 3.81 – 3.73 (m, 4H, H₁₇), 3.09 – 3.01 (m, 2H, H₁₃), 1.74 – 1.65 (m, 2H, H₁₄), 1.50 – 1.36 (m, 2H, H₁₅), 0.95 (t, *J* = 7.3 Hz, 3H, H₁₆).

¹³C NMR (101 MHz, CDCl₃) δ 191.3 (C₇), 163.0 (C₁₂), 161.0 (C₁₁), 154.1 (C₉), 140.8 (C₅), 136.9 (C₆), 133.3 (C₃), 130.8 (C₂), 123.6 (C₁), 120.7 (C₄), 116.1 (C₈), 95.5 (C₁₀), 66.8 (C₁₈), 45.3 (C₁₇), 34.1 (C₁₃), 30.9 (C₁₄), 22.8 (C₁₅), 14.2 (C₁₆).

NOESY (400 MHz, CDCl₃) H₁₀ (6.62 ppm) correlates to H₁₇ (3.81 – 3.73 ppm).

HRMS (ESI⁺): calcd. for C₂₀H₂₃N₂O₂ [M+H]⁺: 323.1754, found 323.1755.

1-Butyl-3-(pyrrolidin-1-yl)-9H-indeno[2,1-c]pyridin-9-one (**241**)



Chemical Formula: C₂₀H₂₂N₂O
Exact Mass: 306.1732

This compound was obtained following the general procedure **M**. Starting from diyne **29** (105 mg, 0.5 mmol), pyrrolidine-1-carbonitrile **156** (96.1 mg, 1.0 mmol, 2.0 equiv) and Cp*Ru(CH₃CN)₃PF₆ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 10 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **241** (133 mg, 87%, ratio > 99:1) as a light yellow solid. m.p. 90 – 91 °C.

Experimental part

R_f = **0.4** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

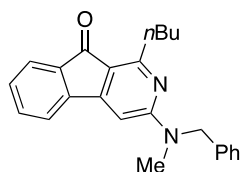
¹H NMR (400 MHz, CDCl₃) δ 7.70 – 7.61 (m, 1H, H₁), 7.58– 7.52 (m, 1H, H₄), 7.49 – 7.43 (m, 1H, H₃), 7.42– 7.35 (m, 1H, H₂), 6.37 (s, 1H, H₁₀), 3.62 (br, 4H, H₁₇), 3.07 (t, *J* = 7.6 Hz, 2H, H₁₃), 2.03 (br, 4H, H₁₈), 1.78 – 1.65 (m, 2H, H₁₄), 1.52 – 1.36 (m, 2H, H₁₅), 0.95 (t, *J* = 7.4 Hz, 3H, H₁₆).

¹³C NMR (101 MHz, CDCl₃) δ 191.3 (C₇), 163.8 (C₁₂), 159.2 (C₁₁), 153.1 (C₉), 140.8 (C₅), 137.4 (C₆), 132.9 (C₃), 130.5 (C₂), 123.3 (C₁), 120.7 (C₄), 114.8 (C₈), 96.2 (C₁₀), 47.4 (C₁₇), 34.2 (C₁₃), 31.0 (C₁₄), 25.5 (C₁₇), 22.9 (C₁₅), 14.2 (C₁₆).

NOESY (400 MHz, CDCl₃) H₁₀ (6.37 ppm) correlates to H₁₇ (3.62 ppm).

HRMS (ESI⁺): calcd. for C₂₀H₂₃N₂O₁ [M+H]⁺: 307.1805, found 307.1805.

3-(Benzyl(methyl)amino)-1-butyl-9*H*-indeno[2,1-*c*]pyridin-9-one (**242**)



Chemical Formula: C₂₄H₂₄N₂O
Exact Mass: 356.1889

This compound was obtained following the general procedure **N**. Starting from diyne **29** (105 mg, 0.5 mmol), *N*-benzyl-*N*-methylcyanamide **158** (88 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH₃CN)₃PF₆ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 30 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) afforded **242** (142 mg, 80%, ratio > 99:1) as a yellow solid. m.p. 106 – 108 °C.

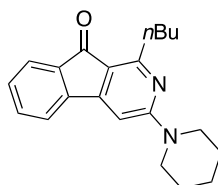
R_f = **0.34** (Petroleum ether/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.67 (dt, *J* = 7.1, 1.1 Hz, 1H), 7.58 – 7.50 (m, 1H), 7.50 – 7.38 (m, 2H), 7.38 – 7.24 (m, 5H), 6.57 (s, 1H), 4.99 (s, 2H), 3.20 (s, 3H), 3.15 – 3.04 (m, 2H), 1.80 – 1.67 (m, 2H), 1.52 – 1.40 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 191.2, 163.2, 161.1, 154.0, 140.9, 138.1, 137.2, 133.0, 130.6, 128.8, 127.5, 127.4, 123.5, 120.7, 115.6, 95.1, 53.5, 36.5, 34.1, 30.8, 22.8, 14.2.

HRMS (ESI⁺): calcd. for C₂₄H₂₅N₂O₁ [M+H]⁺: 357.1961, found 357.1961.

1-Butyl-3-(piperidin-1-yl)-9H-indeno[2,1-c]pyridin-9-one (243)



Chemical Formula: C₂₁H₂₄N₂O
Exact Mass: 320.1889

This compound was obtained following the general procedure **N**. Starting from diyne **29** (105 mg, 0.5 mmol), piperidine-1-carbonitrile **157** (66 mg, 0.6 mmol, 1.2 equiv) and Cp^{*}Ru(CH₃CN)₃PF₆ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 99/1 to 98/2) afforded **243** (125 mg, 78%, ratio > 99:1) as a yellow solid. m.p. 100 – 102 °C.

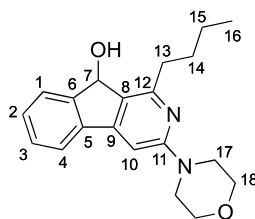
R_f = 0.4 (Petroleum ether/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.65 (dt, *J* = 7.1, 1.0 Hz, 1H), 7.55 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.46 (td, *J* = 7.4, 1.3 Hz, 1H), 7.38 (td, *J* = 7.3, 1.2 Hz, 1H), 6.64 (s, 1H), 3.86 – 3.68 (m, 4H), 3.06 (t, *J* = 7.5 Hz, 2H), 1.78 – 1.60 (m, 8H), 1.52 – 1.31 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 191.0, 163.3, 160.7, 153.7, 141.0, 137.3, 132.9, 130.5, 123.4, 120.6, 115.0, 95.4, 46.3, 34.2, 30.8, 25.9, 24.9, 22.8, 14.2.

HRMS (ESI⁺): calcd. for C₂₁H₂₅N₂O₁ [M+H]⁺: 321.1961, found 321.1962.

1-butyl-3-morpholino-9H-indeno[2,1-c]pyridin-9-ol (244)



Chemical Formula: C₂₀H₂₄N₂O₂
Exact Mass: 324.1838

This compound was obtained following the general procedure **M**. Starting from diyne **28** (106 mg, 0.5 mmol), 4-cyanomorpholine **155** (112 mg, 1.0 mmol, 2.0 equiv) and

Experimental part

Cp*Ru(CH₃CN)₃PF₆ (5.0 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **244** (110 mg, 68%, ratio > 99:1) as a light yellow solid. m.p. 156 – 158 °C.

R_f = **0.18** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

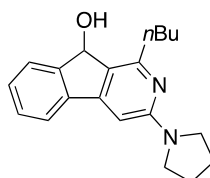
¹H NMR (400 MHz, CDCl₃) δ 7.67 – 7.52 (m, 2H, H_{1,4}), 7.46 – 7.32 (m, 2H, H_{2,3}), 6.58 (d, *J* = 1.5 Hz, 1H, H₁₀), 5.58 (s, 1H, H₇), 3.82 – 3.70 (m, 4H, H₁₈), 3.52 – 3.35 (m, 4H, H₁₇), 2.98 – 2.75 (m, 2H, H₁₃), 2.37 (br, 1H, OH), 1.80 – 1.65 (m, 2H, H₁₄), 1.50 – 1.35 (m, 2H, H₁₅), 0.96 (t, *J* = 7.3 Hz, 3H, H₁₆).

¹³C NMR (101 MHz, CDCl₃) δ 160.2 (C₁₁), 158.2 (C₁₂), 150.1 (C₉), 147.6 (C₆), 138.4 (C₅), 129.8 (C₃), 129.0 (C₂), 127.7 (C₈), 125.6 (C₁), 120.9 (C₄), 95.2 (C₁₀), 73.8 (C₇), 66.8 (C₁₈), 46.0 (C₁₇), 34.5 (C₁₃), 31.1 (C₁₄), 22.9 (C₁₅), 14.3 (C₁₆).

NOESY (400 MHz, CDCl₃) H₁₀ (6.58 ppm) correlates to H₁₇ (3.52 – 3.35 ppm).

HRMS (ESI⁺): calcd. for C₂₀H₂₅N₂O₂ [M+H]⁺: 325.1911, found 325.1912.

1-Butyl-3-(pyrrolidin-1-yl)-9H-indeno[2,1-c]pyridin-9-ol (**245**)



Chemical Formula: C₂₀H₂₄N₂O
Exact Mass: 308.1889

This compound was obtained following the general procedure **N**. Starting from diyne **28** (106 mg, 0.5 mmol), pyrrolidine-1-carbonitrile **156** (58 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH₃CN)₃PF₆ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 1 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **245** (124 mg, 81%, ratio > 99:1) as a yellow solid. m.p. 170 – 171 °C.

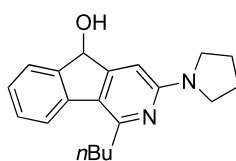
R_f = **0.23** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.68 – 7.52 (m, 2H), 7.46 – 7.29 (m, 2H), 6.26 (s, 1H), 5.58 (s, 1H), 3.45 – 3.24 (m, 4H), 3.11 – 2.63 (m, 2H), 2.42 (br, 1H), 1.95 – 1.81 (m, 4H), 1.80 – 1.67 (m, 2H), 1.49 – 1.34 (m, 2H), 0.95 (t, $J = 7.3$ Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 158.6, 158.0, 149.4, 147.9, 138.8, 129.4, 128.7, 125.5, 124.7, 120.8, 94.7, 73.9, 46.9, 34.6, 31.4, 25.5, 23.0, 14.3.

HRMS (ESI⁺): calcd. for C₂₀H₂₅N₂O₁ [M+H]⁺: 309.1961, found 309.1962.

1-Butyl-3-(pyrrolidin-1-yl)-5H-indeno[1,2-c]pyridin-5-ol (246)



Chemical Formula: C₂₀H₂₄N₂O
Exact Mass: 308.1889

This compound was obtained following the general procedure N. Starting from diyne **149** (106 mg, 0.5 mmol), pyrrolidine-1-carbonitrile **156** (58 mg, 0.6 mmol, 1.2 equiv) and Cp*Ru(CH₃CN)₃PF₆ (12.5 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 5 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 90/10 to 80/20) afforded **246** (110 mg, 71%, ratio = 99:1) as a slight pink solid. m.p. 140 – 142 °C.

R_f = **0.2** (Petroleum ether/Ethyl acetate; 90/10, KMnO₄, UV).

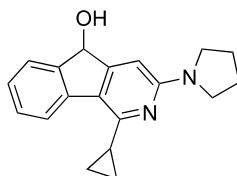
¹H NMR (300 MHz, CDCl₃) δ 7.66 – 7.55 (m, 1H), 7.44 (d, $J = 7.7$ Hz, 1H), 7.34 (td, $J = 7.5$, 1.2 Hz, 1H), 7.19 (td, $J = 7.4$, 1.0 Hz, 1H), 6.20 (s, 1H), 5.33 (s, 1H), 3.78 – 3.50 (br, 1H), 3.37 – 3.10 (m, 4H), 2.91 – 2.61 (m, 2H), 1.86 – 1.59 (m, 6H), 1.53 – 1.37 (m, 2H), 0.96 (t, $J = 7.3$ Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 156.3, 155.3, 144.7, 139.7, 129.0, 125.3, 125.2, 121.1, 100.4, 74.50, 46.7, 36.0, 30.4, 25.2, 22.9, 14.2.

MS (CI, NH₃): $m/z = 309$ [M + H]⁺.

1-Cyclopropyl-3-(pyrrolidin-1-yl)-5H-indeno[1,2-c]pyridin-5-ol (247)

Experimental part



Chemical Formula: C₁₉H₂₀N₂O
Exact Mass: 292.1576

This compound was obtained following the general procedure **N**. Starting from diyne **152** (56 mg, 0.3 mmol), pyrrolidine-1-carbonitrile **156** (35 mg, 0.36 mmol, 1.2 equiv) and Cp*Ru(CH₃CN)₃PF₆ (7.5 mg, 0.015 mmol). The reaction mixture was stirred at room temperature for 3 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 60/40 to 50/50) afforded **247** (68 mg, 78%, ratio > 99:1) as a white solid. m.p. 210 – 212 °C.

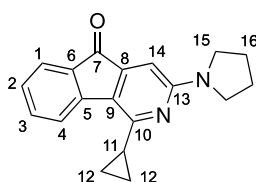
R_f = **0.23** (Petroleum ether/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.82 (d, *J* = 7.7 Hz, 1H), 7.52 (d, *J* = 7.3 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.18 (t, *J* = 7.4 Hz, 1H), 6.46 (s, 1H), 5.85 (d, *J* = 7.4 Hz, 1H), 5.37 (d, *J* = 7.4 Hz, 1H), 3.40 (s, 4H), 2.50 – 2.41 (m, 1H), 2.01 – 1.82 (m, 4H), 1.19 – 1.01 (m, 2H), 1.01 – 0.87 (m, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ 157.6, 155.6, 153.7, 145.3, 139.2, 128.4, 125.0, 124.9, 121.0, 120.7, 99.8, 73.0, 46.3, 25.0, 14.6, 8.4, 7.9.

HRMS (ESI⁺): calcd. for C₁₉H₂₁N₂O₁ [M+H]⁺: 293.1648, found 293.1649.

1-Cyclopropyl-3-(pyrrolidin-1-yl)-5H-indeno[1,2-*c*]pyridin-5-one (248)



Chemical Formula: C₁₉H₁₈N₂O
Exact Mass: 290.1419

This compound was obtained following the general procedure **N**. Starting from diyne **153** (58.2 mg, 0.3 mmol), pyrrolidine-1-carbonitrile **156** (58 mg, 0.6 mmol, 2.0 equiv) and Cp*Ru(CH₃CN)₃PF₆ (7.6 mg, 0.015 mmol). The reaction mixture was stirred at room temperature for 10 min. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from

98/2 to 90/10) afforded **248** (77 mg, 89%, ratio = 94:6) as a dark purple solid. m.p. 162 – 163 °C.

$R_f = 0.6$ (Petroleum ether/Ethyl acetate; 90/10, $KMnO_4$, UV).

1H NMR (300 MHz, $CDCl_3$) δ 7.73 – 7.58 (m, 2H, $H_{4,1}$), 7.49 – 7.37 (m, 1H, H_3), 7.17 – 7.02 (m, 1H, H_2), 6.50 (s, 1H, H_{14}), 3.56 – 3.36 (m, 4H, H_{15}), 2.35 – 2.19 (m, 1H, H_{11}), 2.04 – 1.88 (m, 4H, H_{16}), 1.24 – 1.15 (m, 2H, H_{12}), 1.02 – 0.91 (m, 2H, H_{12}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.8, 157.2, 155.5, 147.0, 143.3, 135.5, 133.8, 126.0, 124.9, 121.82, 121.6, 99.2, 47.0, 25.5, 15.0, 8.4.

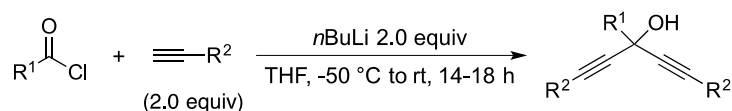
NOESY (400 MHz, $CDCl_3$) H_4 (7.73 – 7.58 ppm) correlates to H_{11} (2.35 – 2.19 ppm), H_{14} (6.50 ppm) correlates to H_{15} (3.56 – 3.36 ppm).

HRMS (ESI⁺): calcd. for $C_{19}H_{29}N_2O_1$ $[M+H]^+$: 291.1492 found 291.1493.

4. Formation of enantioenriched 1,3-dihydroisobenzofuran derivatives

4.1. Synthesis of prochiral triynes

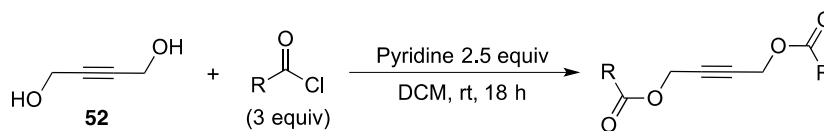
General procedure O:



In an oven-dried Argon-filled round bottom flask, *n*-butyl lithium (2 equiv) was added slowly to a solution of alkyne (2 equiv) in THF (5 M) at -50 °C, and the resulting mixture was stirred at -50 °C for 1 h. Acetyl chloride (1 equiv) was added at the same temperature, and the resulting mixture was allowed to warm to room temperature for 14-18 h. The reaction was quenched with water and extracted with ethyl acetate ($\times 3$). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the desired compound.

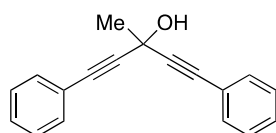
General procedure P:

Experimental part



To a stirred mixture of 2-butyn-1,4-diol **52** (1 equiv) and pyridine (2.5 equiv) in DCM (0.5 M) was cooled at 0 °C in an ice bath. Acyl chloride (3 equiv) was then added in DCM (0.5 M). The reaction mixture was stirred at room temperature for 18 h until completion (TLC monitoring). The organic layer was washed with water (×3) and brine (×3), dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the desired compound.

3-Methyl-1,5-diphenylpenta-1,4-diyne-3-ol (**249**)



Chemical Formula: C₁₈H₁₄O
Exact Mass: 246.1045

This compound was obtained following the general procedure **O**. Starting from acetyl chloride (0.89 mL, 12.5 mmol), phenylacetylene (2.75 mL, 25 mmol, 2 equiv) and *n*BuLi (25 mmol, 2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate; 90/10) afforded **249** (2.2 g, 70%) as a white solid. m.p. 110 – 112 °C.

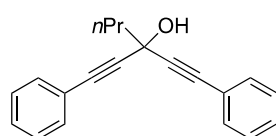
R_f = **0.4** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.54 – 7.44 (m, 4H), 7.37 – 7.28 (m, 6H), 2.80 – 2.73 (m, 1H), 1.97 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 132.0, 128.8, 128.4, 122.2, 90.2, 82.8, 61.0, 32.1.

MS (CI, NH₃): m/z = 229 [M - H₂O + H]⁺.

1-Phenyl-3-(phenylethynyl)hex-1-yn-3-ol (**250**)



Chemical Formula: C₂₀H₁₈O
Exact Mass: 274.1358

This compound was obtained following the general procedure **O**. Starting from butyl chloride (0.52 mL, 5 mmol), phenylacetylene (1.09 mL, 10 mmol, 2 equiv) and *n*BuLi (10 mmol, 2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **250** (1.17 g, 85%) as a white solid. m.p. 73 – 75 °C.

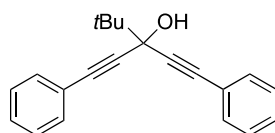
R_f = 0.4 (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.51 – 7.44 (m, 4H), 7.36 – 7.28 (m, 6H), 2.66 (s, 1H), 2.12 – 2.03 (m, 2H), 1.82 – 1.69 (m, 2H), 1.05 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 132.0, 128.8, 128.4, 122.3, 89.5, 83.7, 64.7, 46.3, 18.3, 14.1.

MS (CI, NH₃): *m/z* = 257 [M - H₂O + H]⁺.

3-(*tert*-Butyl)-1,5-diphenylpenta-1,4-diyn-3-ol (**251**)



Chemical Formula: C₂₁H₂₀O
Exact Mass: 288.1514

This compound was obtained following the general procedure **O**. Starting from pivaloyl chloride (1.23 mL, 10 mmol), phenylacetylene (2.2 mL, 20 mmol, 2 equiv) and *n*BuLi (20 mmol, 2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate; 95/5) afforded **251** (2.6 g, 90%) as a white solid. m.p. 83 – 85 °C.

R_f = 0.5 (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

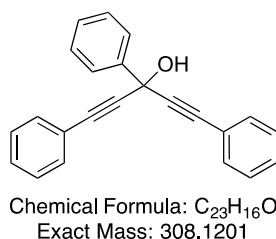
¹H NMR (300 MHz, CDCl₃) δ 7.54 – 7.46 (m, 4H), 7.36 – 7.30 (m, 6H), 2.64 – 2.60 (m, 1H), 1.29 (s, 9H).

¹³C NMR (75 MHz, CDCl₃) δ 132.0, 128.7, 128.4, 122.6, 88.9, 84.4, 71.8, 40.8, 25.1.

MS (CI, NH₃): *m/z* = 271 [M - H₂O + H]⁺.

1,3,5-Triphenylpenta-1,4-diyn-3-ol (**252**)

Experimental part



This compound was obtained following the general procedure **O**. Starting from benzoyl chloride (1.16 mL, 10 mmol), phenylacetylene (2.2 mL, 20 mmol, 2 equiv) and *n*BuLi (20 mmol, 2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate; 90/10) afforded **252** (3.06 g, 99%) as a yellow oil. The analytical data were identical to the literature.²⁰⁶

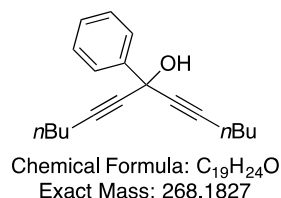
R_f = **0.33** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.01 – 7.88 (m, 2H), 7.60 – 7.27 (m, 13H), 3.09 (br, 1H).

¹³C NMR (75 MHz, CDCl₃) δ 143.5, 131.8, 129.4, 129.1, 128.7, 128.6, 126.0, 121.9, 91.3, 83.8, 64.7.

MS (CI, NH₃): *m/z* = 291 [M – H₂O + H]⁺.

7-Phenyltrideca-5,8-diyne-7-ol (**253**)



This compound was obtained following the general procedure **O**. Starting from benzoyl chloride (1.16 mL, 10 mmol), 1-hexyne (2.3 mL, 20 mmol, 2 equiv) and *n*BuLi (20 mmol, 2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **253** (2.45 g, 91%) as a colorless oil.

R_f = **0.3** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

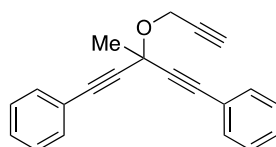
²⁰⁶ Ram, B.; Lee, H.; Kang, S.; Jung, K.; Hyeon, G.; Kim, J.; Lee, S.; Yoon, Y. *Tetrahedron* **2013**, *69*, 10331.

^1H NMR (300 MHz, CDCl_3) δ 7.86 – 7.72 (m, 2H), 7.46 – 7.27 (m, 3H), 2.73 (s, 1H), 2.29 (t, $J = 7.0$ Hz, 4H), 1.59 – 1.33 (m, 8H), 0.92 (t, $J = 7.2$ Hz, 6H).

^{13}C NMR (75 MHz, CDCl_3) δ 143.2, 128.4, 125.9, 85.9, 81.3, 65.4, 30.6, 22.1, 18.7, 13.7.

MS (CI, NH_3): $m/z = 251$ [$\text{M} - \text{H}_2\text{O} + \text{H}$] $^+$.

(3-Methyl-3-(prop-2-yn-1-yloxy)penta-1,4-diyne-1,5-diyl)dibenzene (254)



Chemical Formula: $\text{C}_{21}\text{H}_{16}\text{O}$
Exact Mass: 284.1201

This compound was obtained following the general procedure **F**. Starting from 3-methyl-1,5-diphenylpenta-1,4-diyne-3-ol **249** (1 g, 4.1 mmol), propargyl bromide (0.58 mL, 5.3 mmol, 1.3 equiv) and sodium hydride (0.22 g, 5.3 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **254** (1 g, 87%) as a white solid. m.p. 50 – 52 °C.

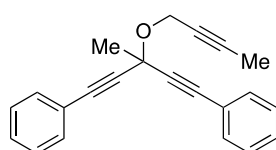
R_f = **0.6** (Cyclohexane/Ethyl acetate; 90/10, KMnO_4 , UV).

^1H NMR (300 MHz, CDCl_3) δ 7.55 – 7.44 (m, 4H), 7.39 – 7.28 (m, 6H), 4.59 – 4.53 (m, 2H), 2.52 – 2.46 (m, 1H), 1.99 (s, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ 132.0, 128.9, 128.4, 122.1, 87.3, 85.0, 80.3, 74.3, 67.3, 54.3, 31.1.

MS (CI, NH_3): $m/z = 229$ [$\text{M} - \text{C}_3\text{H}_4\text{O} + \text{H}$] $^+$.

(3-(But-2-yn-1-yloxy)-3-methylpenta-1,4-diyne-1,5-diyl)dibenzene (255)



Chemical Formula: $\text{C}_{22}\text{H}_{18}\text{O}$
Exact Mass: 298.1358

Experimental part

This compound was obtained following the general procedure **F**. Starting from 3-methyl-1,5-diphenylpenta-1,4-diyne-3-ol **249** (3.2 g, 13.1 mmol), 1-bromo-2-butyne (1.4 mL, 16 mmol, 1.2 equiv) and sodium hydride (0.64 g, 16 mmol, 1.2 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **255** (3 g, 76%) as a white solid. m.p. 110 – 112 °C.

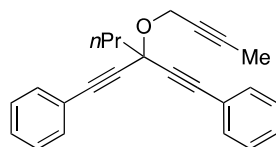
R_f = **0.6** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.52 – 7.45 (m, 4H), 7.37 – 7.30 (m, 6H), 4.52 (q, *J* = 2.4 Hz, 2H), 1.98 (s, 3H), 1.88 (t, *J* = 2.4 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 132.0, 128.9, 128.4, 122.2, 87.5, 84.8, 82.6, 75.4, 66.9, 54.9, 31.2, 4.0.

MS (CI, NH₃): *m/z* = 229 [M - C₄H₆O + H]⁺.

(3-(But-2-yn-1-yloxy)-3-propylpenta-1,4-diyne-1,5-diyl)dibenzene (**256**)



Chemical Formula: C₂₄H₂₂O
Exact Mass: 326.1671

This compound was obtained following the general procedure **F**. Starting from 1-phenyl-3-(phenylethynyl)hex-1-yn-3-ol **250** (0.27 g, 1 mmol), 1-bromo-2-butyne (0.1 mL, 1.2 mmol, 1.2 equiv) and sodium hydride (0.052 g, 1.3 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) afforded **256** (0.24 g, 74%) as a pale yellow sticky oil. The melting point was difficult to determine.

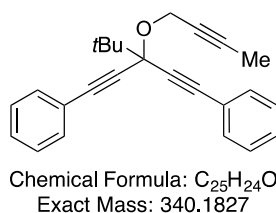
R_f = **0.65** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.57 – 7.41 (m, 4H), 7.38 – 7.28 (m, 6H), 4.53 (q, *J* = 2.4 Hz, 2H), 2.18 – 2.06 (m, 2H), 1.87 (t, *J* = 2.4 Hz, 3H), 1.83 – 1.71 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 132.0, 128.8, 128.4, 122.4, 87.0, 85.6, 82.4, 75.6, 70.8, 54.7, 45.4, 18.2, 14.1, 4.0.

MS (CI, NH₃): m/z = 257 [M - C₄H₆O + H]⁺.

(3-(But-2-yn-1-yloxy)-3-(tert-butyl)penta-1,4-diyne-1,5-diyl)dibenzene (257)



This compound was obtained following the general procedure **F**. Starting from 3-(*tert*-butyl)-1,5-diphenylpenta-1,4-diyne-3-ol **251** (2.6 g, 9 mmol), 1-bromo-2-butyne (0.95 mL, 11 mmol, 1.2 equiv) and sodium hydride (0.44 g, 11 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) afforded **257** (2.15 g, 70%) as a white solid. m.p. 82 – 84 °C.

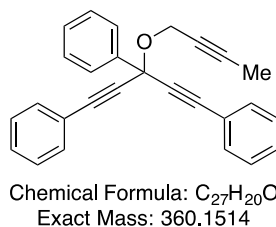
R_f = **0.5** (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.45 – 7.35 (m, 4H), 7.29 – 7.12 (m, 6H), 4.45 (q, *J* = 2.4 Hz, 2H), 1.78 (t, *J* = 2.4 Hz, 3H), 1.18 (s, 9H).

¹³C NMR (75 MHz, CDCl₃) δ 132.0, 128.7, 128.4, 122.6, 86.5, 86.2, 81.8, 78.0, 76.1, 55.1, 41.0, 25.5, 4.0.

MS (CI, NH₃): m/z = 271 [M - C₄H₆O + H]⁺.

(3-(But-2-yn-1-yloxy)penta-1,4-diyne-1,3,5-triyl)tribenzene (258)



This compound was obtained following the general procedure **F**. Starting from 1,3,5-triphenylpenta-1,4-diyne-3-ol **252** (3.06 g, 10 mmol), 1-bromo-2-butyne (1.05 mL, 12 mmol, 1.2 equiv) and sodium hydride (0.52 g, 13 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate; 95/5) afforded **258** (3.23 g, 90%) as a pale yellow solid.

Experimental part

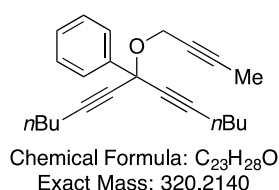
R_f = 0.5 (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.98 – 7.87 (m, 2H), 7.58 – 7.47 (m, 4H), 7.47 – 7.28 (m, 9H), 4.53 (q, *J* = 2.4 Hz, 2H), 1.85 (t, *J* = 2.4 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 140.4, 132.1, 129.0, 128.5, 128.4, 127.0, 122.2, 87.4, 86.5, 82.7, 75.4, 72.2, 54.7, 4.0.

MS (CI, NH₃): *m/z* = 291 [M - C₄H₆O + H]⁺.

(7-(But-2-yn-1-yloxy)trideca-5,8-diyn-7-yl)benzene (259)



This compound was obtained following the general procedure **F**. Starting from 7-phenyltrideca-5,8-diyn-7-ol **253** (1.34 g, 5 mmol), 1-bromo-2-butyne (0.57 mL, 6.5 mmol, 1.3 equiv) and sodium hydride (0.26 g, 6.5 mmol, 1.3 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) afforded **259** (1.4 g, 88%) as a colorless oil.

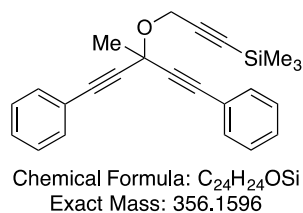
R_f = 0.5 (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.85 – 7.70 (m, 2H), 7.42 – 7.27 (m, 3H), 4.32 (q, *J* = 2.4 Hz, 2H), 2.30 (t, *J* = 7.0 Hz, 4H), 1.83 (t, *J* = 2.4 Hz, 3H), 1.61 – 1.48 (m, 4H), 1.48 – 1.35 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 6H).

¹³C NMR (75 MHz, CDCl₃) δ 141.2, 128.5, 128.2, 126.9, 87.9, 82.1, 78.4, 75.7, 71.5, 54.0, 30.6, 22.1, 18.7, 13.7, 3.9.

MS (CI, NH₃): *m/z* = 251 [M - C₄H₆O + H]⁺.

Trimethyl(3-((3-methyl-1,5-diphenylpenta-1,4-diyn-3-yl)oxy)prop-1-yn-1-yl)silane (260)



To a solution of (3-methyl-3-(prop-2-yn-1-yloxy)penta-1,4-diyne-1,5-diyl)dibenzene **254** (0.43 g, 1.5 mmol) in anhydrous THF (4 mL) was slowly added *n*BuLi (2.3 M in hexane, 0.72 mL, 1.65 mmol, 1.1 equiv) at $-70\text{ }^{\circ}\text{C}$. The solution was stirred at the same temperature for 30 min. To the resulting mixture was added chlorotrimethylsilane (0.14 mL, 1.65 mmol, 1.1 equiv) at $-70\text{ }^{\circ}\text{C}$, and the reaction mixture was allowed to warm to room temperature and stirred for additional 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl (1.0 mL). The aqueous layer was extracted with diethyl ether ($3 \times 20\text{ mL}$), and the combined organic layers were washed with brine, dried with MgSO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Cyclohexane/Ethyl acetate gradient from 98/2 to 95/5) to afford **260** (0.5 g, 93%) as a pale yellow solid. m.p. $70 - 72\text{ }^{\circ}\text{C}$.

$R_f = 0.3$ (Cyclohexane/Ethyl acetate; 95/5, KMnO_4 , UV).

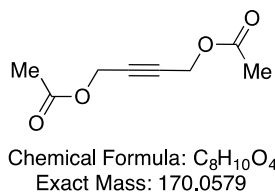
$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.55 – 7.41 (m, 4H), 7.39 – 7.27 (m, 6H), 4.59 (d, $J = 0.8\text{ Hz}$, 2H), 1.99 (d, $J = 0.8\text{ Hz}$, 3H), 0.18 (d, $J = 0.7\text{ Hz}$, 9H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 132.1, 128.9, 128.4, 122.2, 101.9, 91.1, 87.4, 85.0, 67.2, 55.0, 31.1, 0.0.

MS (CI, NH_3): $m/z = 229$ [$\text{M} - \text{C}_6\text{H}_{11}\text{OSi} + \text{H}$] $^+$.

4.2. Synthesis of internal alkynes

But-2-yne-1,4-diyl diacetate (262)



Experimental part

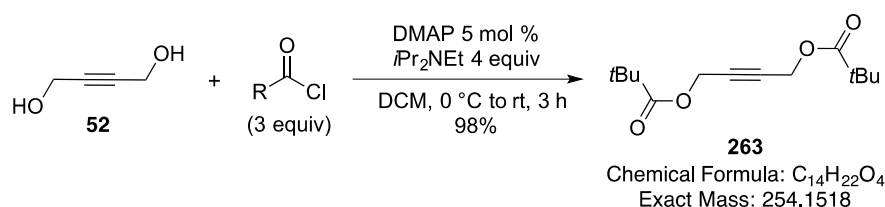
This compound was obtained following the general procedure **P**. Starting from 2-butyne-1,4-diol **52** (1.72 g, 20 mmol), acetyl chloride (4.3 mL, 60 mmol, 3 equiv) and pyridine (4 mL, 50 mmol, 2.5 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate; 80/20) afforded **262** (3.25 g, 96%) as a colorless oil. The analytical data were identical to the literature.²⁰⁷

$R_f = 0.4$ (Cyclohexane/Ethyl acetate; 70/30, $KMnO_4$, UV).

1H NMR (300 MHz, $CDCl_3$) δ 4.69 (s, 4H), 2.07 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 80.8, 52.1, 20.7.

But-2-yne-1,4-diyl bis(2,2-dimethylpropanoate) (**263**)



To a stirred mixture of 2-butyne-1,4-diol **52** (0.86 g, 10 mmol, 1 equiv) and iPr_2NEt (6.7 mL, 40 mmol, 4 equiv) in DCM (20 mL) was cooled at 0 °C in an ice bath. DMAP (0.1 g, 0.5 mmol, 5 mol %) and pivaloyl chloride (3.69 mL, 30 mmol, 3 equiv) in DCM (20 mL) were then introduced. The reaction mixture was stirred at room temperature for 3 h until completion (TLC monitoring). The organic layer was washed with water (3×30 mL) and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (Cyclohexane/Ethyl acetate; 80/20) to afford **263** (2.5 g, 98%) as a colorless oil.

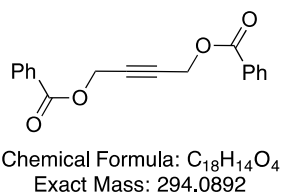
$R_f = 0.3$ (Cyclohexane/Ethyl acetate; 90/10, $KMnO_4$, UV).

1H NMR (300 MHz, $CDCl_3$) δ 4.69 (s, 4H), 1.21 (s, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8, 80.8, 52.3, 38.9, 27.2.

But-2-yne-1,4-diyl dibenzoate (**264**)

²⁰⁷ Muchow, G.; Brunel, J. M.; Maffei, M.; Buono, G. *J. Org. Chem.* **1995**, *60*, 852.



This compound was obtained following the general procedure **P**. Starting from 2-butyne-1,4-diol **52** (1.72 g, 20 mmol), benzoyl chloride (5.8 mL, 50 mmol, 2.5 equiv) and pyridine (4 mL, 50 mmol, 2.5 equiv). Purification on silica gel (Cyclohexane/Ethyl acetate; 90/10) afforded **264** (5.6 g, 95%) as a white solid. m.p. 80 – 82 °C.

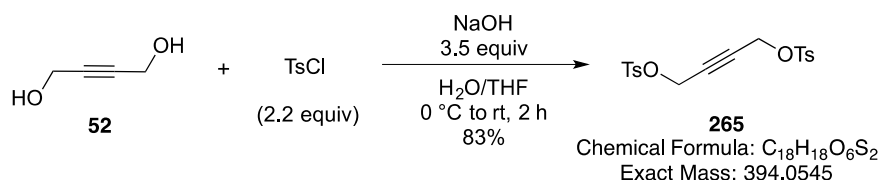
R_f = **0.3** (Cyclohexane/Ethyl acetate; 90/10, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 8.13 – 8.02 (m, 4H), 7.63 – 7.51 (m, 2H), 7.51 – 7.39 (m, 4H), 5.00 (s, 4H).

¹³C NMR (75 MHz, CDCl₃) δ 165.9, 133.5, 130.0, 129.6, 128.6, 81.1, 52.8.

MS (CI, NH₃): m/z = 312 [M + NH₄]⁺.

But-2-yne-1,4-diyl bis(4-methylbenzenesulfonate) (**265**)



In a round bottom flask, 2-butyne-1,4-diol **52** (2.15 g, 25.0 mmol) was dissolved in THF (50 mL) and combined with NaOH (3.5 g, 87 mmol, 3.5 equiv) in water (50 mL). The flask was cooled to 0 °C (ice bath), and a solution of *p*-toluenesulfonyl chloride (10.5 g, 55.0 mmol, 2.2 equiv) in THF (50 mL) was added dropwise. The resulting mixture was stirred at 0 °C for 2 h until complete reaction. The product was then extracted with ethyl acetate (2×50 mL) and washed with saturated NaHCO₃ (3×30 mL), water (2×50 mL), and brine (50 mL). The organic layer was dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure to

Experimental part

give the product **265** as a grey solid (8.2 g, 83%). m.p. 98-100 °C. The analytical data were identical to the literature.²⁰⁸

R_f = **0.21** (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.81 – 7.71 (m, 4H), 7.39 – 7.30 (m, 4H), 4.58 (s, 4H), 2.45 (s, 6H).

¹³C NMR (75 MHz, CDCl₃) δ 145.5, 133.0, 130.0, 128.2, 81.1, 57.2, 21.8.

4.3. Rhodium-catalyzed [2+2+2] cycloaddition of triynes and alkynes

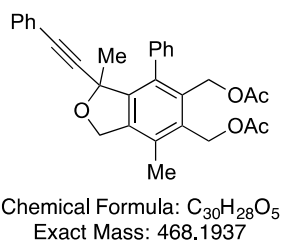
General procedure Q:



In a vacuum line, an oven-dried Schlenk tube was degassed and purged with argon three times. Rh(cod)₂BF₄ (5 mol %) and (R)-BINAP (5 mol%) were introduced under argon. The Schlenk flask was then degassed and purged with argon three additional times. Under argon, freshly distilled and degassed DCM (1.0 mL) was added and the mixture was allowed to stir at room temperature for 30 min. A solution of the corresponding alkyne (2 equiv) in distilled DCM (1.0 mL) was then introduced under argon. The Schlenk flask was tightly sealed and allowed to stir at room temperature for additional 10 minutes. A solution of the corresponding triyne (1 equiv) in distilled DCM (1.0 mL) was finally added dropwise at room temperature. The reaction mixture allowed to stir at 40 °C for 20-24 h, concentrated under reduced pressure, and the residue was purified by flash chromatography to afford the desired product.

(1,4-Dimethyl-7-phenyl-1-(phenylethynyl)-1,3-dihydroisobenzofuran-5,6-diyl)bis(methylene) diacetate (**266**)

²⁰⁸ Maisonia, A.; Billaud, E. M. F.; Besse, S.; Rbah-Vidal, L.; Papon, J.; Audin, L.; Bayle, M.; Galmier, M. J.; Tarrit, S.; Borel, M.; Askienazy, S.; Madelmont, J. C.; Moins, N.; Auzeloux, P.; Miot-Noirault, E.; Chezal, J. M. *Eur. J. Med. Chem.* **2013**, *63*, 840.



This compound was obtained following the general procedure **Q**. Starting from (3-(but-2-yn-1-yloxy)-3-methylpenta-1,4-diyne-1,5-diyl)dibenzene **255** (119 mg, 0.4 mmol), but-2-yne-1,4-diyl diacetate **262** (136 mg, 0.8 mmol, 2 equiv), $Rh(cod)_2BF_4$ (8 mg, 0.02 mmol, 5 mol %), and (*R*)-BINAP (12.4 mg, 0.02 mmol, 5 mol %). The reaction mixture was stirred at 40 °C for 20 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 80/20) afforded **266** (95 mg, 50%) as a white solid. m.p. 112 – 114 °C.

$R_f = 0.4$ (Cyclohexane/Ethyl acetate; 80/20, $KMnO_4$, UV).

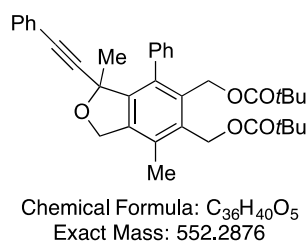
1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.20 (m, 10H), 5.28 (d, $J = 1.8$ Hz, 2H), 5.17 (AB_{sys}, $J = 9.3$ Hz, 2H), 4.93 (AB_{sys}, $J = 9.1$ Hz, 2H), 2.34 (s, 3H), 2.09 (s, 3H), 1.96 (s, 3H), 1.38 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 170.2, 141.7, 139.9, 136.7, 136.0, 134.0, 133.9, 131.9, 131.4, 130.7, 130.1, 128.3, 128.2, 127.9, 127.7, 127.6, 122.7, 90.8, 85.2, 82.1, 70.5, 61.0, 60.3, 28.2, 20.9, 20.8, 15.8.

SFC: $ee = 50\%$, Chiralpak OD-H, $scCO_2/MeOH$ 90/10, P = 150 bar, flow = 4.0 mL/min, 215nm, $t_{major} = 2.82$ min, $t_{minor} = 3.57$ min.

MS (CI, NH_3): $m/z = 486$ [$M + NH_4$]⁺.

(1,4-Dimethyl-7-phenyl-1-(phenylethynyl)-1,3-dihydroisobenzofuran-5,6-diyl)bis(methylene) bis(2,2-dimethylpropanoate) (267)



This compound was obtained following the general procedure **Q**. Starting from (3-(but-2-yn-1-yloxy)-3-methylpenta-1,4-diyne-1,5-diyl)dibenzene **255** (89 mg, 0.3 mmol), but-2-yne-1,4-diyl

Experimental part

bis(2,2-dimethylpropanoate) **263** (152 mg, 0.6 mmol, 2 equiv), Rh(cod)₂BF₄ (6.1 mg, 0.015 mmol, 5 mol %), and (*R*)-BINAP (9.3 mg, 0.015 mmol, 5 mol %). The reaction mixture was stirred at 40 °C for 20 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 99/1 to 95/5) afforded **267** (35 mg, 20%) as a colorless oil.

R_f = 0.4 (Cyclohexane/Ethyl acetate; 95/5, KMnO₄, UV).

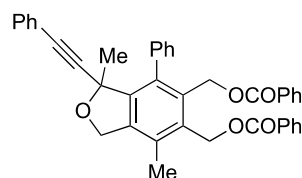
¹H NMR (300 MHz, CDCl₃) δ 7.50 – 7.40 (m, 1H), 7.40 – 7.23 (m, 8H), 7.23 – 7.13 (m, 1H), 5.21 (d, *J* = 1.2 Hz, 2H), 5.17 (AB_{sys}, *J* = 12.3 Hz, 2H), 4.85 (AB_{sys}, *J* = 12.0 Hz, 2H), 2.31 (s, 3H), 1.39 (s, 3H), 1.22 (s, 9H), 1.14 (s, 9H).

¹³C NMR (75 MHz, CDCl₃) δ 178.5, 177.9, 141.4, 139.8, 136.7, 136.3, 134.7, 134.2, 131.9, 131.6, 130.9, 130.4, 128.3, 128.0, 127.8, 127.6, 122.9, 91.2, 85.3, 82.3, 70.7, 61.2, 60.6, 39.1, 38.7, 28.5, 27.4, 27.3, 16.0.

SFC: *ee* = 36%, Chiralpak OD-H, scCO₂/MeOH 90/10, P = 150 bar, flow = 4.0 mL/min, 215nm, *t*_{major} = 2.03 min, *t*_{minor} = 2.54 min.

MS (ESI, NH₃): *m/z* = 570 [M + NH₄]⁺.

(1,4-Dimethyl-7-phenyl-1-(phenylethynyl)-1,3-dihydroisobenzofuran-5,6-diyl)bis(methylene) dibenzoate (**268**)



Chemical Formula: C₄₀H₃₂O₅
Exact Mass: 592.2250

This compound was obtained following the general procedure **Q**. Starting from (3-(but-2-yn-1-yloxy)-3-methylpenta-1,4-diyne-1,5-diyl)dibenzene **255** (89 mg, 0.3 mmol), but-2-yne-1,4-diyl dibenzoate **264** (176.4 mg, 0.6 mmol, 2 equiv), Rh(cod)₂BF₄ (6.1 mg, 0.015 mmol, 5 mol %), and (*R*)-BINAP (9.3 mg, 0.015 mmol, 5 mol %). The reaction mixture was stirred at 40 °C for 24 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **268** (50 mg, 28%) as a colorless oil.

R_f = 0.5 (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).

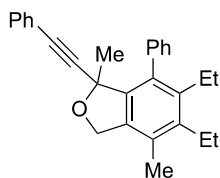
^1H NMR (300 MHz, CDCl_3) δ 8.00 – 7.93 (m, 2H), 7.93 – 7.84 (m, 2H), 7.57 – 7.41 (m, 3H), 7.39 – 7.22 (m, 13H), 5.60 (s, 2H), 5.39 – 5.12 (m, 4H), 2.44 (s, 3H), 1.42 (s, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ 166.4, 166.0, 141.8, 140.0, 136.9, 136.2, 134.5, 134.5, 133.1, 132.9, 132.2, 131.6, 130.9, 130.4, 130.0, 129.9, 129.8, 129.7, 128.4, 128.3, 128.1, 127.9, 127.8, 122.9, 91.1, 85.4, 82.3, 70.8, 61.8, 61.1, 28.4, 16.1.

SFC: *ee* = 46%, Chiralpak OD-H, $\text{scCO}_2/\text{MeOH}$ 90/10, P = 150 bar, flow = 4.0 mL/min, 215nm, t_{major} = 13.09 min, t_{minor} = 18.56 min.

MS (CI, NH_3): m/z = 610 $[\text{M} + \text{NH}_4]^+$.

5,6-Diethyl-1,4-dimethyl-7-phenyl-1-(phenylethynyl)-1,3-dihydroisobenzofuran (269)



Chemical Formula: $\text{C}_{28}\text{H}_{28}\text{O}$
Exact Mass: 380.2140

This compound was obtained following the general procedure **Q**. Starting from (3-(but-2-yn-1-yloxy)-3-methylpenta-1,4-diyne-1,5-diyl)dibenzene **255** (89 mg, 0.3 mmol), 3-hexyne **53** (50 mg, 0.6 mmol, 2 equiv), $\text{Rh}(\text{cod})_2\text{BF}_4$ (6.1 mg, 0.015 mmol, 5 mol %), and (*R*)-BINAP (9.3 mg, 0.015 mmol, 5 mol %). The reaction mixture was stirred at 40 °C for 20 h. Purification on silica gel (Cyclohexane/Ethyl acetate; 99/1) afforded **269** (92 mg, 79%) as a white solid. m.p. 114–118 °C.

R_f = **0.35** (Cyclohexane/Ethyl acetate; 95/5, KMnO_4 , UV).

^1H NMR (300 MHz, CDCl_3) δ 7.49 – 7.31 (m, 6H), 7.31 – 7.19 (m, 4H), 5.25 – 5.02 (m, 2H), 2.84 – 2.66 (m, 2H), 2.54 – 2.34 (m, 2H), 2.26 (s, 3H), 1.41 – 1.32 (m, 3H), 1.20 (td, J = 7.5, 2.1 Hz, 3H), 0.95 (td, J = 7.6, 2.5 Hz, 3H).

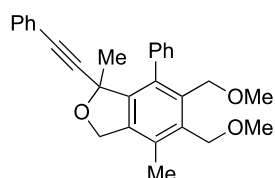
^{13}C NMR (75 MHz, CDCl_3) δ 140.9, 140.6, 138.4, 138.2, 136.2, 134.6, 131.6, 131.4, 130.6, 128.9, 128.2, 128.1, 127.6, 127.4, 127.2, 123.4, 92.0, 84.6, 82.3, 70.9, 28.8, 23.0, 22.5, 16.0, 14.8.

Experimental part

SFC: $ee = 21\%$, Chiralpak OD-H, $scCO_2/MeOH$ 95/5, $P = 150$ bar, flow = 4.0 mL/min, 215nm, $t_{major} = 4.15$ min, $t_{minor} = 5.51$ min.

MS (CI, NH_3): $m/z = 398$ $[M + NH_4]^+$.

5,6-Bis(methoxymethyl)-1,4-dimethyl-7-phenyl-1-(phenylethynyl)-1,3-dihydroisobenzofuran (270)



Chemical Formula: $C_{28}H_{28}O_3$
Exact Mass: 412.2038

This compound was obtained following the general procedure **Q**. Starting from (3-(but-2-yn-1-yloxy)-3-methylpenta-1,4-diyne-1,5-diyl)dibenzene **255** (89 mg, 0.3 mmol), 1,4-dimethoxybut-2-yne **51** (68.4 mg, 0.6 mmol, 2 equiv), $Rh(cod)_2BF_4$ (6.1 mg, 0.015 mmol, 5 mol %), and (*R*)-BINAP (9.3 mg, 0.015 mmol, 5 mol %). The reaction mixture was stirred at 40 °C for 20 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **270** (78 mg, 63%) as a colorless oil.

$R_f = 0.35$ (Cyclohexane/Ethyl acetate; 90/10, $KMnO_4$, UV).

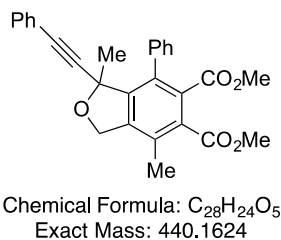
1H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.45 (m, 1H), 7.45 – 7.31 (m, 5H), 7.31 – 7.24 (m, 4H), 5.15 (AB_{sys}, $J = 12.3$ Hz, 2H), 4.62 (d, $J = 3.0$ Hz, 1H), 4.18 (AB_{sys}, $J = 10.2$ Hz, 2H), 3.50 (s, 3H), 3.17 (s, 3H), 2.35 (s, 3H), 1.36 (d, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 140.7, 139.1, 137.2, 136.1, 135.7, 131.5, 131.0, 130.5, 128.2, 128.1, 127.5, 127.3, 123.0, 91.4, 85.0, 82.1, 70.6, 68.7, 68.3, 58.9, 58.3, 28.3, 15.7.

SFC: $ee = 32\%$, Chiralpak OD-H, $scCO_2/MeOH$ 95/5, $P = 150$ bar, flow = 3.0 mL/min, 215nm, $t_{major} = 5.78$ min, $t_{minor} = 6.78$ min.

MS (CI, NH_3): $m/z = 430$ $[M + NH_4]^+$.

Dimethyl 1,4-dimethyl-7-phenyl-1-(phenylethynyl)-1,3-dihydroisobenzofuran-5,6-dicarboxylate (271)



This compound was obtained following the general procedure **Q**. Starting from (3-(but-2-yn-1-yloxy)-3-methylpenta-1,4-diyne-1,5-diyl)dibenzene **255** (89 mg, 0.3 mmol), dimethyl but-2-ynedioate **261** (85 mg, 0.6 mmol, 2 equiv), Rh(cod)₂BF₄ (6.1 mg, 0.015 mmol, 5 mol %), and (*R*)-BINAP (9.3 mg, 0.015 mmol, 5 mol %). The reaction mixture was stirred at 40 °C for 24 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **271** (67 mg, 51%) as a colorless oil.

R_f = **0.13** (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).

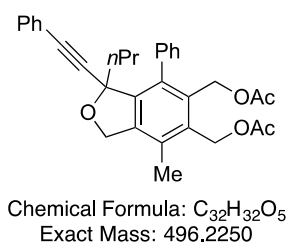
¹H NMR (300 MHz, CDCl₃) δ 7.71 – 7.45 (m, 1H), 7.45 – 7.23 (m, 8H), 7.22 – 7.14 (m, 1H), 5.16 (AB_{sys}, *J* = 12.9 Hz, 2H), 3.88 (s, 3H), 3.44 (s, 3H), 2.36 (s, 3H), 1.38 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 168.3, 168.1, 143.2, 141.3, 135.7, 134.6, 133.5, 131.7, 131.6, 130.6, 130.3, 129.7, 128.5, 128.3, 128.1, 127.6, 122.7, 90.5, 85.9, 82.1, 70.4, 52.6, 52.1, 28.0, 16.7.

SFC: *ee* = 47%, Chiralpak OD-H, scCO₂/MeOH 90/10, P = 150 bar, flow = 4.0 mL/min, 215nm, *t*_{major} = 2.74 min, *t*_{minor} = 3.48 min.

MS (CI, NH₃): *m/z* = 458 [M + NH₄]⁺.

(4-Methyl-7-phenyl-1-(phenylethynyl)-1-propyl-1,3-dihydroisobenzofuran-5,6-diyl)bis(methylene) diacetate (274)



This compound was obtained following the general procedure **Q**. Starting from (3-(but-2-yn-1-yloxy)-3-propylpenta-1,4-diyne-1,5-diyl)dibenzene **256** (98 mg, 0.3 mmol), but-2-yne-1,4-diyl

Experimental part

diacetate **262** (102 mg, 0.6 mmol, 2 equiv), Rh(cod)₂BF₄ (6.1 mg, 0.015 mmol, 5 mol %), and (*R*)-BINAP (9.3 mg, 0.015 mmol, 5 mol %). The reaction mixture was stirred at 40 °C for 20 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 80/20) afforded **274** (68 mg, 46%) as a colorless oil.

R_f = **0.2** (Cyclohexane/Ethyl acetate; 85/15, KMnO₄, UV).

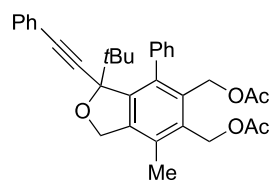
¹H NMR (300 MHz, CDCl₃) δ 7.51 – 7.22 (m, 9H), 7.22 – 7.10 (m, 1H), 5.26 (d, *J* = 3.6 Hz, 2H), 5.16 (AB_{sys}, *J* = 12.6 Hz, 2H), 4.91 (AB_{sys}, *J* = 12.3 Hz, 2H), 2.33 (s, 3H), 2.09 (s, 3H), 1.96 (s, 3H), 1.76 – 1.60 (m, 1H), 1.46 – 1.20 (m, 2H), 1.20 – 1.01 (m, 1H), 0.73 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 170.8, 170.3, 140.6, 140.2, 136.8, 136.2, 134.1, 131.9, 131.6, 131.0, 129.6, 128.3, 128.1, 127.8, 127.7, 123.0, 91.1, 85.6, 71.3, 61.2, 60.5, 42.1, 21.0, 21.0, 17.2, 16.0, 13.9.

SFC: *ee* = 51%, Chiralpak OD-H, scCO₂/MeOH 95/5, P = 150 bar, flow = 4.0 mL/min, 215nm, *t*_{major} = 4.91 min, *t*_{minor} = 5.78 min.

MS (CI, NH₃): *m/z* = 514 [M + NH₄]⁺.

(1-(*tert*-Butyl)-4-methyl-7-phenyl-1-(phenylethynyl)-1,3-dihydroisobenzofuran-5,6-diyl)bis(methylene) diacetate (**275**)



Chemical Formula: C₃₃H₃₄O₅
Exact Mass: 510.2406

This compound was obtained following the general procedure **Q**. Starting from (3-(but-2-yn-1-yloxy)-3-(*tert*-butyl)penta-1,4-diyne-1,5-diyl)dibenzene **257** (102 mg, 0.3 mmol), but-2-yne-1,4-diyl diacetate **262** (102 mg, 0.6 mmol, 2 equiv), Rh(cod)₂BF₄ (6.1 mg, 0.015 mmol, 5 mol %), and (*R*)-BINAP (9.3 mg, 0.015 mmol, 5 mol %). The reaction mixture was stirred at 40 °C for 24 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **275** (80 mg, 51%) as a pale yellow oil.

R_f = 0.16 (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).

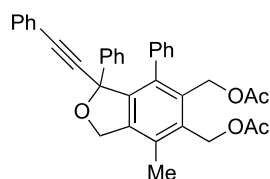
¹H NMR (300 MHz, CDCl₃) δ 7.51 (dt, *J* = 8.2, 1.3 Hz, 1H), 7.43 – 7.18 (m, 8H), 7.18 – 7.06 (m, 1H), 5.24 (AB_{sys}, *J* = 12.3 Hz, 2H), 5.19 (d, *J* = 3.9 Hz, 2H), 4.80 (AB_{sys}, *J* = 12.0 Hz, 2H), 2.30 (s, 3H), 2.08 (s, 3H), 1.96 (s, 3H), 0.79 (s, 9H).

¹³C NMR (75 MHz, CDCl₃) δ 170.9, 170.3, 142.0, 139.3, 138.5, 137.7, 134.7, 134.5, 132.0, 131.6, 128.3, 127.9, 127.3, 127.2, 123.2, 93.3, 91.2, 87.7, 72.4, 61.7, 60.5, 42.6, 26.6, 21.0, 15.8.

SFC: *ee* = 38%, Chiralpak OD-H, scCO₂/MeOH 90/10, P = 150 bar, flow = 4.0 mL/min, 215nm, *t*_{major} = 2.59 min, *t*_{minor} = 3.03 min.

MS (ESI, NH₃): *m/z* = 528 [M + NH₄]⁺.

(4-Methyl-1,7-diphenyl-1-(phenylethynyl)-1,3-dihydroisobenzofuran-5,6-diyl)bis(methylene) diacetate (276)



Chemical Formula: C₃₅H₃₀O₅
Exact Mass: 530.2093

This compound was obtained following the general procedure **Q**. Starting from (3-(but-2-yn-1-yloxy)penta-1,4-diyne-1,3,5-triyl)tribenzene **258** (108 mg, 0.3 mmol), but-2-yne-1,4-diyl diacetate **262** (102 mg, 0.6 mmol, 2 equiv), Rh(cod)₂BF₄ (6.1 mg, 0.015 mmol, 5 mol %), and (*R*)-BINAP (9.3 mg, 0.015 mmol, 5 mol %). The reaction mixture was stirred at 40 °C for 24 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 80/20) afforded **276** (75 mg, 48%) as a pale yellow oil.

R_f = 0.22 (Cyclohexane/Ethyl acetate; 80/20, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.51 – 7.40 (m, 2H), 7.38 – 7.20 (m, 5H), 7.19 – 7.02 (m, 6H), 6.81 – 6.71 (m, 1H), 6.09 – 6.00 (m, 1H), 5.40 (s, 2H), 5.34 – 5.22 (m, 2H), 4.82 (AB_{sys}, *J* = 12.0 Hz, 2H), 2.43 (s, 3H), 2.11 (s, 3H), 1.91 (s, 3H).

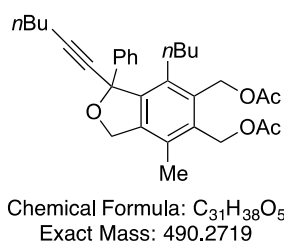
Experimental part

^{13}C NMR (75 MHz, CDCl_3) δ 170.8, 170.2, 142.8, 141.7, 139.8, 137.6, 135.5, 134.6, 134.3, 131.8, 131.6, 130.6, 129.5, 128.6, 128.4, 127.8, 127.7, 127.3, 127.1, 122.8, 89.3, 88.4, 87.0, 72.0, 61.1, 60.5, 21.0, 20.9, 16.1.

SFC: $ee = 41\%$, Chiralpak OD-H, $\text{scCO}_2/\text{MeOH}$ 90/10, $P = 150$ bar, flow = 4.0 mL/min, 215nm, $t_{\text{major}} = 7.36$ min, $t_{\text{minor}} = 13.03$ min.

MS (ESI, NH_3): $m/z = 548$ $[\text{M} + \text{NH}_4]^+$.

(7-Butyl-1-(hex-1-yn-1-yl)-4-methyl-1-phenyl-1,3-dihydroisobenzofuran-5,6-diyl)bis(methylene) diacetate (**277**)



This compound was obtained following the general procedure **Q**. Starting from (7-(but-2-yn-1-yloxy)trideca-5,8-diyn-7-yl)benzene **259** (96 mg, 0.3 mmol), but-2-yne-1,4-diyl diacetate **262** (102 mg, 0.6 mmol, 2 equiv), $\text{Rh}(\text{cod})_2\text{BF}_4$ (6.1 mg, 0.015 mmol, 5 mol %), and (*R*)-BINAP (9.3 mg, 0.015 mmol, 5 mol %). The reaction mixture was stirred at 40 °C for 20 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 90/10) afforded **277** (80 mg, 54%) as a pale yellow oil.

$R_f = 0.27$ (Cyclohexane/Ethyl acetate; 80/20, KMnO_4 , UV).

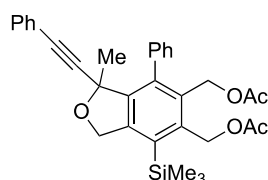
^1H NMR (300 MHz, CDCl_3) δ 7.63 – 7.46 (m, 2H), 7.36 – 7.26 (m, 3H), 5.26 – 5.20 (m, 4H), 5.18 (s, 2H), 2.53 (td, $J = 13.2, 12.8, 4.7$ Hz, 1H), 2.42 – 2.30 (m, 3H), 2.29 (s, 3H), 2.09 (s, 3H), 2.03 (s, 3H), 1.65 – 1.52 (m, 2H), 1.52 – 1.37 (m, 2H), 1.19 – 0.97 (m, 2H), 0.93 (t, $J = 7.2$ Hz, 3H), 0.88 – 0.78 (m, 1H), 0.66 (t, $J = 7.3$ Hz, 3H), 0.55 – 0.33 (m, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ 170.9, 170.8, 142.8, 140.1, 136.2, 134.9, 134.4, 130.0, 128.4, 128.3, 127.4, 90.5, 86.9, 79.1, 72.1, 60.6, 60.2, 32.8, 30.7, 29.2, 23.3, 22.2, 21.0, 19.0, 15.9, 13.7.

SFC: *ee* = 24%, Chiralpak OD-H, scCO₂/MeOH 90/10, P = 150 bar, flow = 4.0 mL/min, 215nm, *t*_{minor} = 3.21 min, *t*_{major} = 5.86 min.

MS (ESI, NH₃): *m/z* = 508 [M + NH₄]⁺.

(1-Methyl-7-phenyl-1-(phenylethynyl)-4-(trimethylsilyl)-1,3-dihydroisobenzofuran-5,6-diyl)bis(methylene) diacetate (278)



Chemical Formula: C₃₂H₃₄O₅Si
Exact Mass: 526.2176

This compound was obtained following the general procedure **Q**. Starting from trimethyl(3-((3-methyl-1,5-diphenylpenta-1,4-diyn-3-yl)oxy)prop-1-yn-1-yl)silane **260** (107 mg, 0.3 mmol), but-2-yne-1,4-diyl diacetate **262** (102 mg, 0.6 mmol, 2 equiv), Rh(cod)₂BF₄ (6.1 mg, 0.015 mmol, 5 mol %), and (*R*)-BINAP (9.3 mg, 0.015 mmol, 5 mol %). The reaction mixture was stirred at 40 °C for 24 h. Purification on silica gel (Cyclohexane/Ethyl acetate gradient from 95/5 to 80/20) afforded **278** (42 mg, 26%) as a pale yellow oil.

R_f = **0.21** (Cyclohexane/Ethyl acetate; 85/15, KMnO₄, UV).

¹H NMR (300 MHz, CDCl₃) δ 7.48 – 7.17 (m, 10H), 5.28 (s, 2H), 5.21 (AB_{sys}, *J* = 12.6 Hz, 2H), 4.87 (AB_{sys}, *J* = 12.0 Hz, 2H), 2.09 (s, 3H), 1.96 (s, 3H), 1.35 (s, 3H), 0.43 (s, 9H).

¹³C NMR (75 MHz, CDCl₃) δ 170.6, 170.3, 146.6, 141.7, 140.8, 140.4, 136.0, 135.1, 134.4, 131.6, 130.6, 130.0, 128.4, 128.3, 128.2, 127.9, 127.7, 122.9, 91.0, 85.3, 80.6, 72.1, 63.9, 60.8, 28.2, 21.1, 20.9, 2.3.

SFC: *ee* = 52%, Chiralpak OD-H, scCO₂/MeOH 90/10, P = 150 bar, flow = 4.0 mL/min, 215nm, *t*_{major} = 2.13 min, *t*_{minor} = 3.13 min.

MS (ESI, NH₃): *m/z* = 544 [M + NH₄]⁺.

Publications

Abstract

This manuscript focused on the development of eco-friendly and mild processes to access original carbocyclic and heterocyclic scaffolds of biological interest through transition-metal-catalyzed [2+2+2] cycloaddition reactions. Initially, an efficient and practical route for the preparation of highly substituted fluorenones and analogues via solventless $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ -mediated [2+2+2] cycloaddition of benzoyl bridged α,ω -diynes and alkynes was developed. Secondly, various functionalized 2-aminopyridine derivatives were synthesized using both neutral $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ and cationic $\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ complexes to catalyze the [2+2+2] cycloaddition of diynes and cyanamides under solvent-free conditions. With $\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ as catalyst, excellent regioselectivities were achieved to provide a wide range of 2-aminopyridines of high synthetic utility involving halopyridines, vinyl pyridines and amino-aza-fluorenones. Finally, the enantioselective rhodium-catalyzed [2+2+2] cycloaddition of prochiral triynes and monoalkynes was carried out in the presence of cationic $[\text{Rh}(\text{cod})_2]\text{BF}_4/(\text{R})\text{-BINAP}$ complex to provide enantioenriched 1,3-dihydroisobenzofuran derivatives containing a quaternary carbon stereogenic center.

Keywords: solvent-free reactions, ruthenium, rhodium, [2+2+2] cycloadditions, fluorenones, 2-aminopyridines, 1,3-dihydroisobenzofurans.

Résumé

Ce manuscrit traite de la mise au point d'une méthode d'accès éco-compatible à des squelettes carbocycliques et hétérocycliques, présents dans de nombreux composés d'intérêt biologique. Cette méthode met en œuvre une réaction de cycloaddition [2+2+2] catalysée par un métal de transition. Dans un premier temps, une voie d'accès à des fluorénones hautement substituées, ainsi qu'à des analogues a été développée. Cette voie utilise une réaction de cycloaddition [2+2+2] de diynes- α,ω pontés par un groupe benzoylé, avec des alcynes, en présence de $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$. Dans un deuxième temps, des dérivés 2-aminopyridines diversement fonctionnalisés ont été synthétisés via une catalyse au ruthénium neutre ($\text{RuCl}_3 \cdot n\text{H}_2\text{O}$) ou cationique ($\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$), et ce à partir de la cycloaddition [2+2+2] de diynes et de cyanamides. Dans le cas où $\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ a été utilisé comme catalyseur, une excellente régiosélectivité a été observée, ce qui a permis d'isoler une grande variété de 2-aminopyridines, dont des halopyridines, des vinylpyridines, ou des amino-aza-fluorénones. Dans une dernière partie, la cycloaddition [2+2+2] énantiosélective de triynes prochiraux avec des mono alcynes a été examinée. Elle a été conduite en utilisant un catalyseur cationique au rhodium, le complexe $[\text{Rh}(\text{cod})_2]\text{BF}_4/(\text{R})\text{-BINAP}$, et a permis la préparation de dérivés de 1,3-dihydroisobenzofuranes énantiomériquement enrichis, contenant un carbone quaternaire stéréogène.

Mots-clés : réactions sans solvant, ruthénium, rhodium, cycloadditions [2+2+2], fluorénones, 2-aminopyridines, 1,3-dihydroisobenzofuranes