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Liang Chang

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Sorbonne Université

Chimie Moléculaire de Paris-Centre

Institut Parisien de Chimie Moléculaire / Chemical Biology

Sustainable Transformations of Methyl Coumalate: Efficient Preparations of Unsaturated Carboxylic Acids, 2*H*Pyrans, Trifluoromethyl Benzenes and Fluorescent Molecules

Par Liang CHANG

Thèse de doctorat de Chimie Organique

Dirigée par Pr. Serge THORIMBERT *et* Dr. Luc DECHOUX

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To learn without thinking is blindness, to think without learning is idleness.

<Analects>

子曰：学而不思则罔， 思而不学则殆。

《论语·为政》

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Abstract

The idea of producing new chemicals from renewable feedstocks has become of great interest in the field of synthetic chemistry and creates many potential opportunities for molecules based on renewable carbon sources. A main challenge lying ahead in the development synthesis from biorenewable feedstock is to generate such structural diversity in an efficient manner. Therefore, intensive synthetical studies on renewable chemicals by different method are required.

In this dissertation, our investigations are based on, but not only limited to sustainable synthesis from bio-based methyl coumalate, also involves other research fields, which includ electrocyclic reactions, conjugate addition of Grignard reagents, organocatalysis (Baylis-Hillman reaction) and dearomatization reactions.

Chapter 1 gives a review about the preparation and applications of methyl coumalate.

Chapter 2 discribes an efficient regio- and stereo-selective metal-catalyzed addition of two Grignard reagents. This synthetic approach opens an access to a wide variety of functionalized *β, γ*-unsaturated carboxylic acids in a modular way.

Chapter 3 explores reactions of methyl coumalate with a wide range of methylene active compounds such as keto-esters or keto-sulfones and cyclic or acyclic diketones afforded more than thirty 2,3,5,6-tetrasubstituted 2*H*-pyrans.

Chapter 4 reports a novel, efficient, and environmentally compatible method for CF_3-substituted benzene production which employs *t*BuOK as a catalyst, and is solvent-free.

Chapter 5 introduces an efficient C-C bond formation between the bio-based methyl coumalate and a variety of imines and aldehydes *via* Morita-Baylis-Hillman type process.

Chapter 6 is a novel, general Michael addition dearomatization reaction strategy

with an unprecedented pyrido[1, 2-*a*] fused heterocyclic scope, which can tolerate eleven types of aza-aromatics.

List of Abbreviations

Ac: acetyl

Ar: aryl

br: broad

Bu: butyl

d: doublet

DBU: 1,8-Diazabicycloundec-7-ene

DBN: 1,5-Diazabicyclo(4.3.0)non-5-ene

DCM: dichloromethane

DMAP: dimethylaminopyridine

DMF: dimethylformamide

DMSO: dimethylsulfoxide

EDG: electron-donating group

ee: enantiomeric excess

EWG: electron-withdrawing group

Et: ethyl

Hz: Hertz

i: iso

IR: infrared

J: coupling constant

m: *meta*

m: multiplet

M: molar

MBH: Morita-Baylis-Hillman

MC: methyl coumalate

Me: methyl

NMR: nuclear magnetic resonance

o: *ortho*

OTf: Trifluoromethanesulfonate

p: *para*

Ph: phenyl

Pr: propyl

PTC: phase-transfer catalyst

q: quartet

r.t. : room temperature

s: singlet

t: *tert*

t: triplet

T: temperature

TFA trifluoroacetic acid

THF tetrahydrofuran

TLC thin-layer chromatography

Ts toluenesulfonyl

UV ultraviolet

δ *:* chemical shift

Chapter 1 Introduction：Methyl Coumalate.

1.1 Introduction

Currently most of the organic compounds manufactured by the chemical industry are derived from fossil fuels.[1] Although numerous technological breakthroughs have been achieved in those fields,[2] this unsustainable pattern has provoked increasing worries over the oil supply diminish and the environmental impact of petrochemical processing.

Accordingly, the replacement of petroleum-based feedstocks by their renewable alternatives has attracted increasing attention.[3–5] Guided by this fundamental principle of green chemistry, many sustainable routes towards chemicals, fuels, and plastics from renewable starting materials have been investigated.[6]

Biorenewable chemicals are not only direct "drop-in" replacements for petrochemicals, more promisingly, they also enjoy a better potential to a broader access of novel chemical species, since petrochemicals which mainly focus on a highly constrained set of alkene and aromatic molecules are left with fewer possible transformations after decades of investigation.[7] In contrast, biorenewable chemicals usually show multi-functionalities rather than simple hydrocarbons, which gives the potential to generate a wide range of new and more diversified bio-products beyond petrochemicals reach. As such, innovative chemicals produce *via* sustainable route could complement new market needs, which further drives the development in next-generation plastics, insecticides, pharmaceuticals, and consumer goods.

In order to evaluate the potential of biorenewable compounds, many criteria have been developed. The most noteworthy one is their ability to be transformed into a large number of useful chemical derivatives with multiple downstream applications.

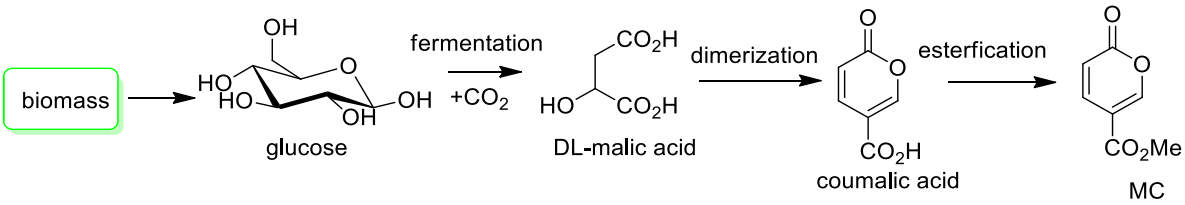
Some bio-based chemicals have received significant attention in the literature, in this context, we are going to focus on an important bio-based synthon methyl

coumalate (MC). MC is a 2-pyronic molecule substituted with methyl ester on 5-position. Due to its unique chemical structure, the efforts in utilizing MC for the synthesis mainly focus on its 2-pyrone molecular structure. The current review will summarize the preparations and applications of MC published previously.

1.2 Preparation of Methyl Coumalate

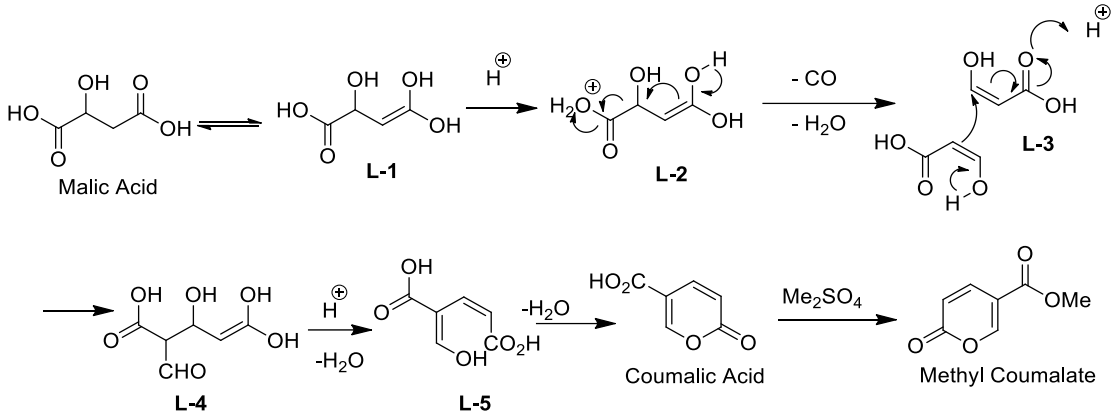
Bio-based methyl coumalate is usually produced from the fermentation of glucose to form malic acid (Scheme 1), which will further go through dimerization to form coumalic acid. The coumalic acid will then undergo esterification with methanol to generate MC eventually.

Scheme 1 The formation of bio-based MC



The synthesis of MC *via* this route has been well established (Scheme 2). In the first place, the malic acid fermentation is a highly atom efficient pathway, including the use of a CO_2 fixating process and rendering a theoretical yield of 2 moles of malate per mole of glucose.[8] Moreover, efficient fermentation technology has already been developed for this route. For example, Novozymes currently employs a metabolically engineered *aspergillus oryzae* capable of producing 1.38 mol malate per mole glucose with a theoretical yield of 69% and with high titers of 154 g L^{-1}, which is practical and could be applied on the industrial scale.[9]

Scheme 2 Synthesis of MC from malic acid



Levin et al.[10] reported a 100 gram-scale two-step synthesis, affording MC in 65% yield (Scheme 2). In the first step, dimerization of malic acid took place at 75°C in the strongly acidic dehydrating conditions in oleum. It is believed that this reaction proceeds *via* acid-catalyzed dehydration/decarbonylation of malic acid to give aldehyde acid enol **L-3** which is then condensed by Michael addition of enol to enone to give coumalic acid. The second step is the esterification by dimethyl sulphate, afford MC in 65% yield after recrystallization.

Later on, Kraus' group optimized the route towards malic acid, by applying trific acid in DCE giving coumalic acid in 86% yield in a gram scale.[11]

1.3 MC involved [4+2] Diels-Alder reaction

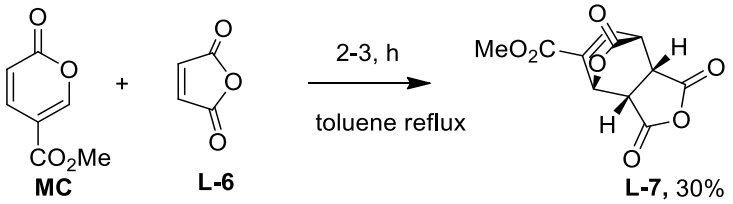
Diels-Alder (D-A) reaction is an atom economical [4+2] cycloaddition. Since first discovered in 1928, D-A reaction has become one of the most powerful reactions in organic synthesis.[12,13] This reaction could simultaneously build two carbon-carbon bonds with good regio- and stereo control. D-A reactions are particularly useful and have been regularly incorporated into numerous synthesis in order to construct six membered ring frameworks in both academia and industry.

1.3.1 MC as dienes in Diels-Alder reactions

With the constrained s-cis conjugated alkenes, MC often acts as an electro-deficient dienes for the inverse electron demand Diels-Alder (IEDDA).

The first D-A reaction with MC was reported by Diels and Alder themselves in 1931.[14] MC could react with maleic anhydride under reflux in toluene, and after 2-3 hours the tricyclic product was obtained in 30% yield after recrystallization (Scheme 3). In 1987, Effenberger et al.[15] reinvestigated this reaction and proved the endo stereo-selectivity of the product **L-7**.

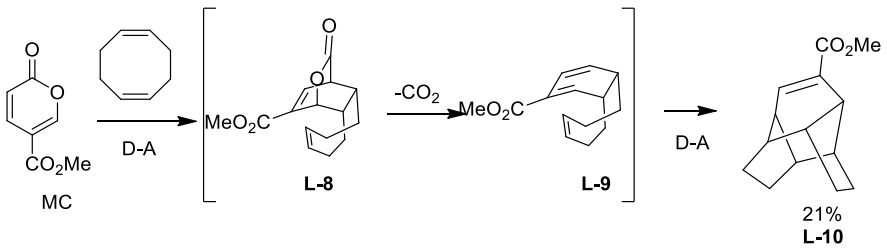
Scheme 3 The D-A reaction of the MC with maleic anhydride



In this context, in 1969, another pioneering work in this field was reported by Behringer et al.[16], in which MC reacted with electron-rich dienophile, giving bicyclic lactone in 84% yield.

Harano's group reported a double Diels-Alder (DDA) adduct derived from a three-step sequential [4+2] reaction of 2-pyrone with cycloocta-1,5-diene **L-10**.[17]

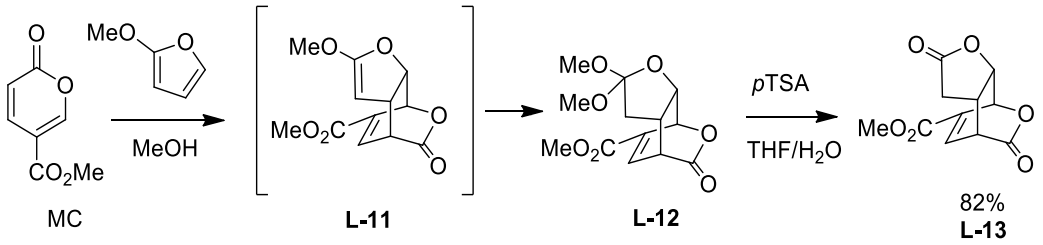
Scheme 4 Double Diels-Alder reaction from MC



Following a similar path Liao's group has described a one-pot synthesis of γ-butyrolactone moiety (Scheme 5),[18] which is a highly valuable core for a variety of natural products and biological active compounds. The reaction generated complex structures *via* highly chemo-, regio-, and stereo-selective D-A reactions

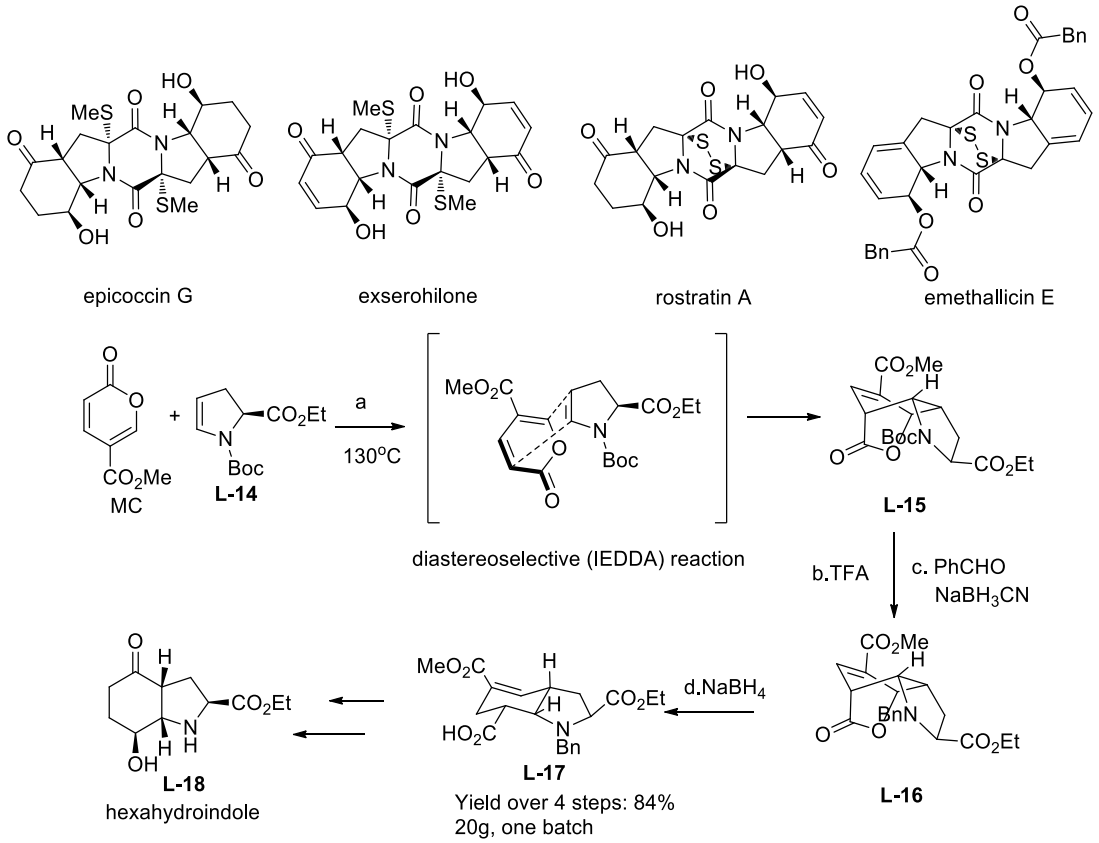
of MC with 2-methoxyfuran to butyrolactone in one pot. The electron-donating substituent on furan ring enhanced the rates of D-A cycloadditions, allowing the reaction to take place at room temperature.

Scheme 5 Tricyclic bislactones from MC



Another appealing application for MC in D-A reactions was reported by Jiang's group (Scheme 6).[19] In this case, an asymmetric synthetic strategy has been developed, in order to construct the divergent synthesis of bioactive epidithiodiketopiperazine (ETP) natural products. MC has been selected as diene synthon for building functionalized 2,3,3a,4,7,7a, hexahydroindole core by an IEDDA reaction in excellent yield with high diastereoselectivity (95%; *exo* : *endo* ≥ 10 : 1). In this context, a $NaBH_4$-promoted bridged-lactone ring opening reaction could convert lactone **L-16** to carboxylic acid **L-17**. In total, **L-17** was prepared over 4 steps in 84% yield, 20 grams in one batch. Then 2,3,3a,6,7,7a-hexahydroindole monomer could be prepared by a reliable approach.

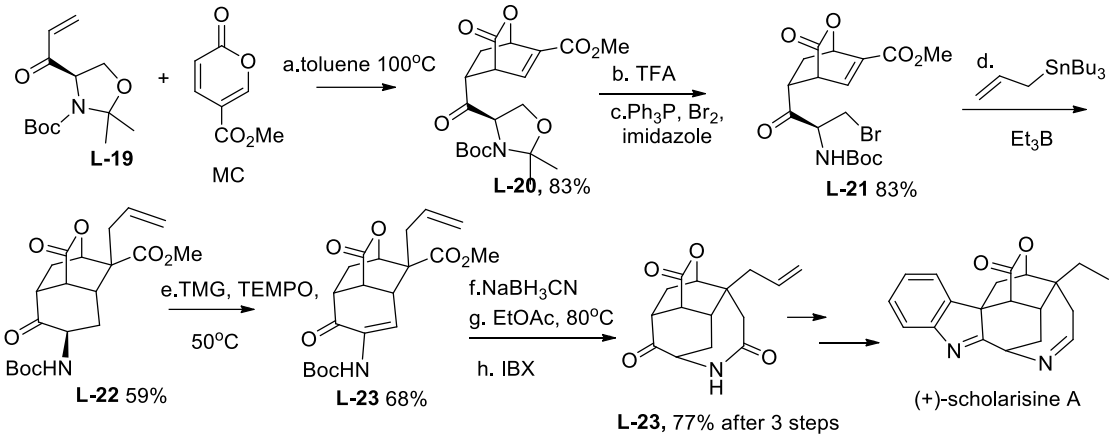
Scheme 6 Synthesis of hexahydroindole from MC



Conditions: (a) toluene, 130 °C, sealed operator; (b) TFA, DCM, rt; (c) PhCHO, $NaBH_3CN$, MeCN/AcOH, rt; (d) $NaBH_4$, EtOH, 0 °C, 84% over 4 steps.

Another innovative approach was disclosed by Snyder's group who used MC to a completed enantioselective synthesis of bio-active natural product (+)-scholarisine A in 14 steps (Scheme 7).[20] One of the key discoveries is an efficient and diastereoselective D-A reaction of MC and **L-19** rapidly forming appropriately functionalized [2.2.2]-bicyclic key intermediate **L-20** in 83% yield. An indolenine annulation at a non-enolizable tertiary center is processed *via* a novel late-stage radical C−H arylation, and the use of the hydroxyl group could facilitate the chemoselective reduction of an extremely inert lactam **L-22**.

Scheme 7 enantioselective synthesis of (+)-scholarisine A

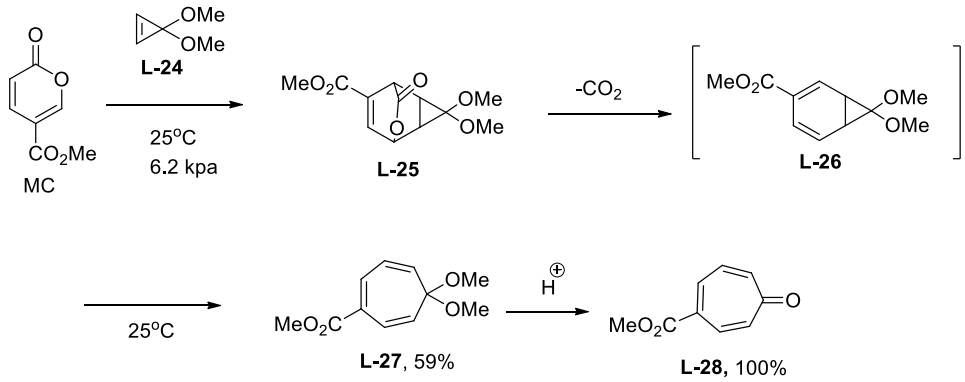


1.3.2. MC as Dienes to form Aromatics

Functionalized aromatic compounds are indispensable basic structure cores for industry and are often found in plenty of specific materials and common pharmaceutical products. Thus there is an incentive for the development of selective processes to produce aromatics from bio-based feedstocks.

Aiming at this goal, Boger's group reported an approach employing MC under pressure condition (Scheme 8), in a sequence initiated by the [4+2] D-A reaction of the cyclopropenone ketal **L-24**, followed by releasing carbon dioxide and a subsequent electrocyclic rearrangement to generate tropone **L-28**.[21,22]

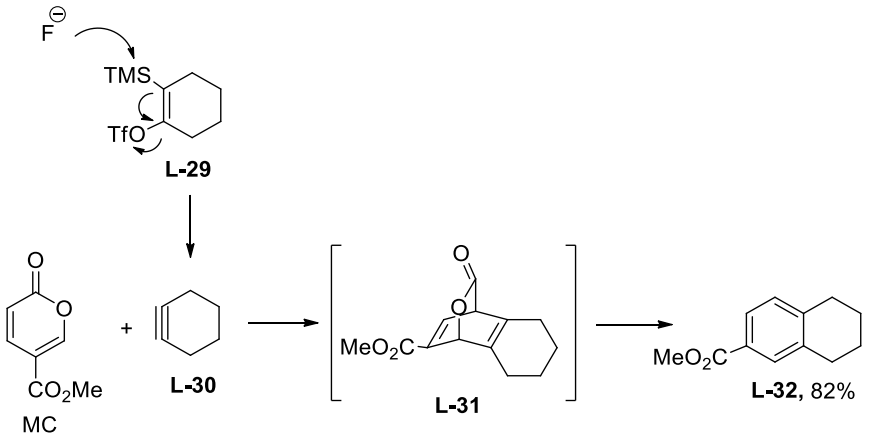
Scheme 8 Synthesis of tropone from MC



Another approach that can be used for the preparation of

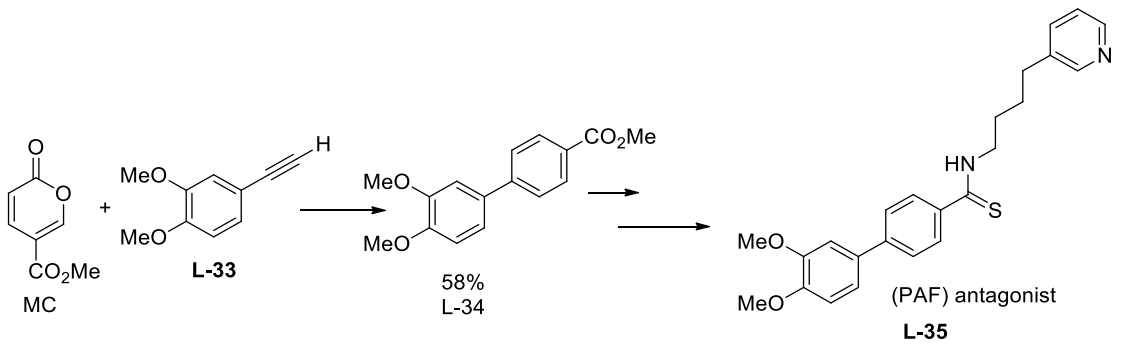
tetrahydronaphthalene was reported by Guitian and co-workers.[23] The dienophilic cyclohexyne **L-30** was generated by a milder variant involving 1,3-elimination of TMS and OTf , and then reacted with MC, affording tetrahydronaphthalene **L-32** in 82% yield (Scheme 9).

Scheme 9 The preparation of tetrahydronaphthalene from MC



Biphenyl aromatic rings core is one of the key pharmacophore among platelet-activating factor (PAF) antagonists (Scheme 10). Tilley and co-workers designed a new pathway,[24] empolying acetylenes and MC as starting material *via* D-A reaction, which could afford biphenyl core **L-34** regioselectivily.

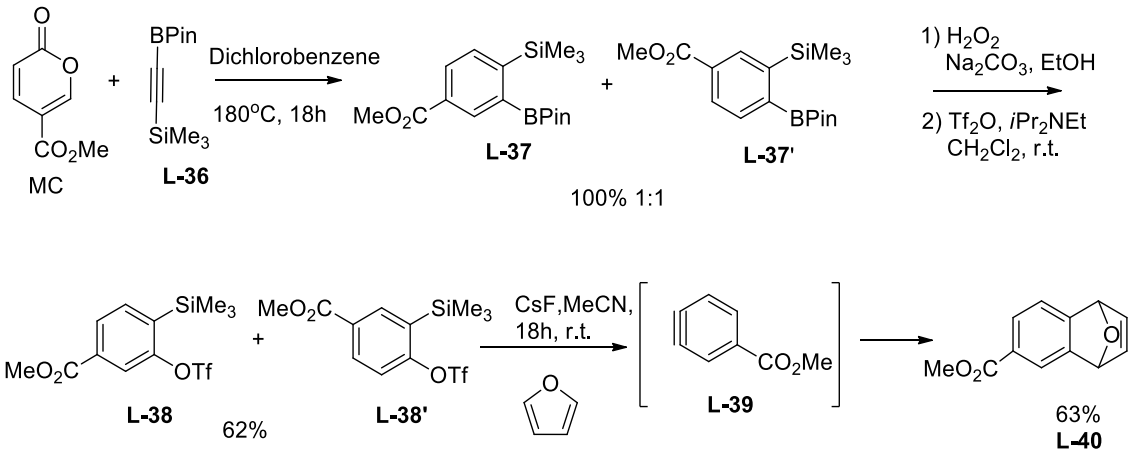
Scheme 10 The preparation of biphenyl core from MC



Another new approach which converted MC to benzyne and its precursors was reported by Harrity's group (Scheme 11).[25,26] This transformation started with a [4+2] cycloaddition of trimethylsilyl alkynylboronates with MC to form

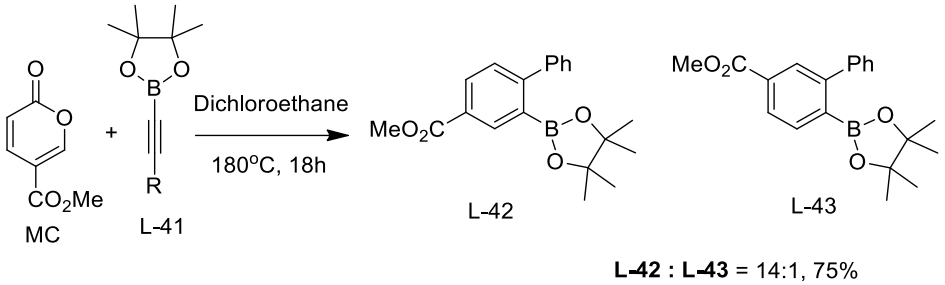
aromatic ring of the boronate in quantitive yield with no regioselectivities. Followed by C-B bond oxidation and trifluoromethylsulfonylation step of the regioisomeric mixtures **L-37** and **L-37'**, functionalised benzyne precursors **L-38** and **L38'** were generated in 62%. The [4+2] the cycloaddition took place by adding CsF to the mixture of **L38** and **L38'** in acetonitrile in the presence of furane to get **L40**. The desired product **L-40** was provided in 81% yield.

Scheme 11 Converted MC to benzyne precursors



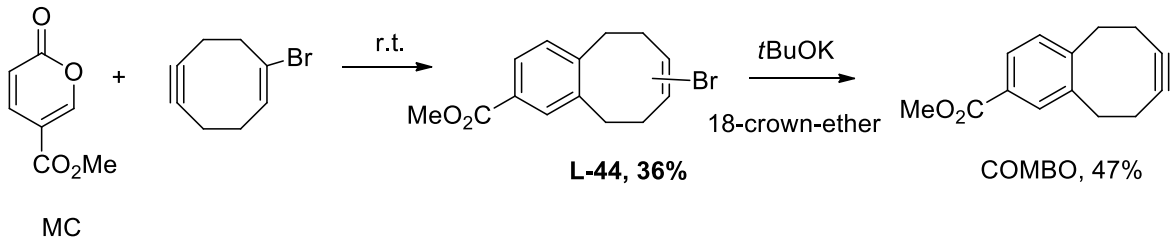
Later on, they investigated MC with a more electron-rich class of alkynylboronates (Scheme 12). The aromatic products could be further used for cross-coupling reactions to the additional functionalizations.[27] MC easily provided benzene boronate ester in 75% yield with a 14:1 regioselectivity upon reaction with alkynyl boronate. Although higher overall yields could be achieved with TMS- and *n*Bu-substituted alkynyl boronates, poor regioselective were achieved.

Scheme 12 MC react with alkynylboronates



Another very promising approach employing MC was reported by Kele's group (Scheme 13).[28] They designed and synthesized carboxymethyl-monobenzocyclooctyne through a copper-free pathway. The IEDDA reaction took place and chemoselectively afforded bromobenzocyclooctene **L-44**. Formation of the cyclooctyne (COMBO) by means of E2 elimination was brought about by treatment with *t*BuOK in the presence of 18-crown-ether. The carboxylic acid linker allows the synthesized COMBO to be used in bioorthogonal labelling plan, when employed to a fluorescent label for HeLa cells glycan imaging.

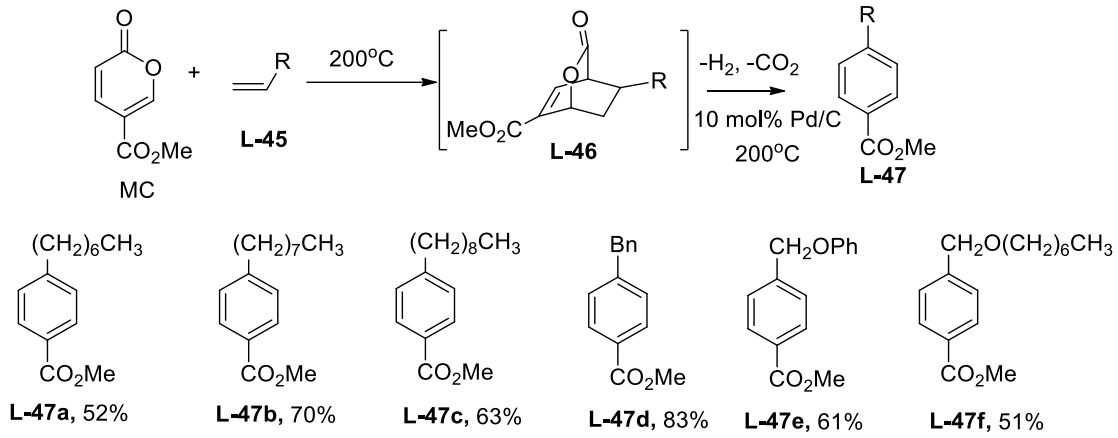
Scheme 13 The synthesis of COMBO from MC



Besides having wide potential applications in academic, MC can be further converted to important aromatic compounds for industrial use (Scheme 14). Kraus's group[29] reported an environmentally benign synthesis of alkyl benzoates *via* D-A reaction of methyl coumalate. The reaction with MC started with a cycloaddition, to produce bicyclo[2.2.2]octadiene intermediate **L-46**, followed by palladium promoted dehydrogenation which lost carbon dioxide to directly form the substituted benzene. These processes are regioselective and provides only

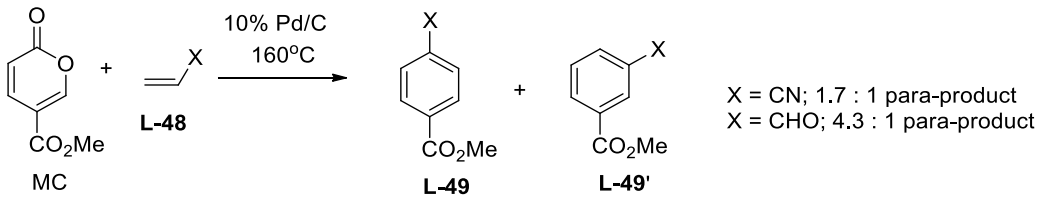
para-substituted benzene adducts **L-47** in good yield.

Scheme 14 Sustainable synthesis of aromatics from MC and alkene



Following the similar path, Kraus's group developed a D-A reaction of MC with electron-deficient alkenes (Scheme 15), providing terephthalates and isophthalates in good yields, with the para-selectivities which depends on the electron-withdrawing group. They proposed that during the key regioselective step electronic factors are the primary factors, which attributed to a secondary orbital interaction between the pyrone oxygen and the LUMO of the dienophile. This further switches the regio-chemistry expected from simple frontier molecular orbital theory arguments which results in a controllable regioselectivity in favor of the para-substituted product.[30]

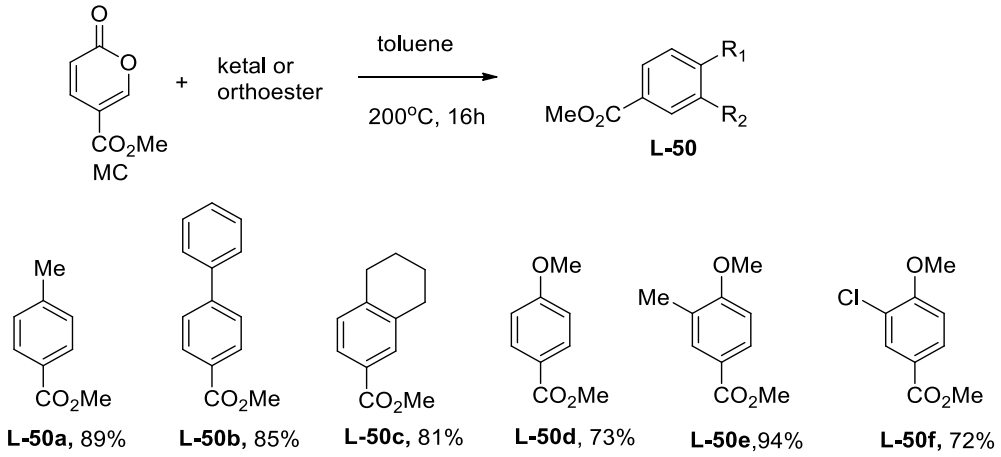
Scheme15 Regioselective synthesis of para-benzene



Later, they discovered another novel methodology based on a D-A sequence between MC and easily accessible ketals or orthoesters (Scheme 16). The merit of this methodology is that all dienophiles are either commercially available or can

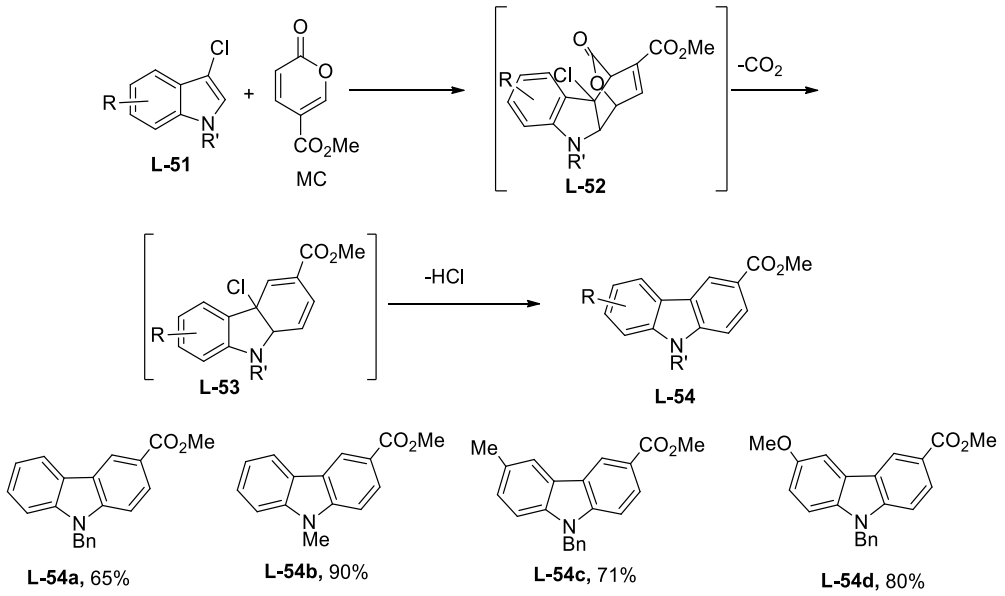
be prepared in one step and can be used without purification. The regioselective reactions generated in one pot diverse substituted aromatic systems in high yield without palladium catalysts.[31]

Scheme 16 MC react with ketals or orthoesters *via* D-A reaction



Another appealing application of MC in cycloaddition reactions is reported by the same group (Scheme 17).[32] In this case, they developed a D-A reaction using MC in conjunction with 1-alkyl-3-chloroindoles **L-51** which efficiently generated carbazoles **L-54** without the need for additional metal catalysts. Carbazoles are a class of aromatic compounds with wide applications in materials science and bio-active products. The chloride substituent acts as a good leaving group in this pathway, and also prevents ring-opening of the D-A adduct, rendering metal catalysts unnecessary by stimulating aromatization.

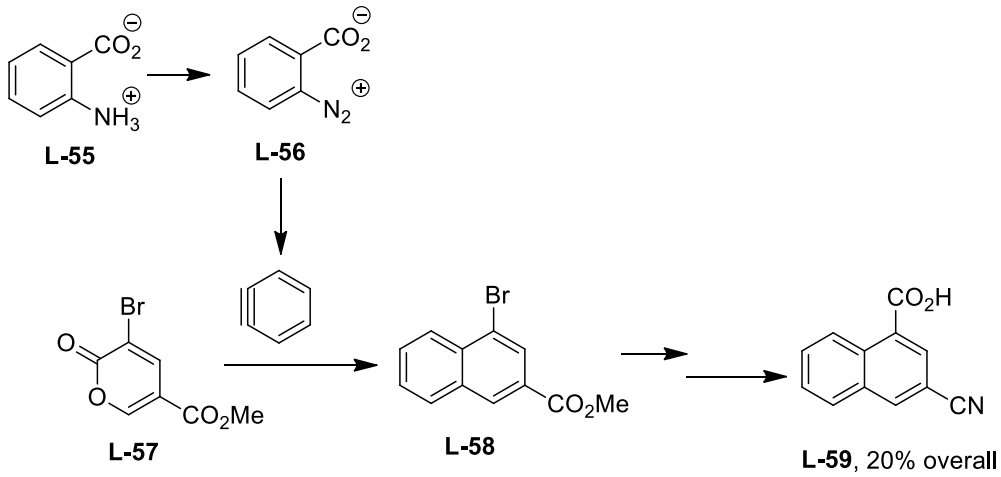
Scheme 17 The synthesis of carbazoles from MC by IEDDA reactions



Later on, Domingo's group reinvestigated the mechanism of the reaction between 3-chloroindole and MC yielding substituted carbazole by using DFT methods at the MPWB1K/6-311G (d,p) level. This polar-DA (P-DA) reaction proceeds in a completely regio-selective and slightly exo-selective manner. Thermodynamic calculations suggest that the DA reaction is the rate-determining step in this process. Kinetically and thermodynamically speaking this reaction should be unfavorable. Due to CO_2 extrusion, the P-DA reaction becomes irreversible, which makes this kinetically and thermodynamically unfavorable polar-DA reaction possible.

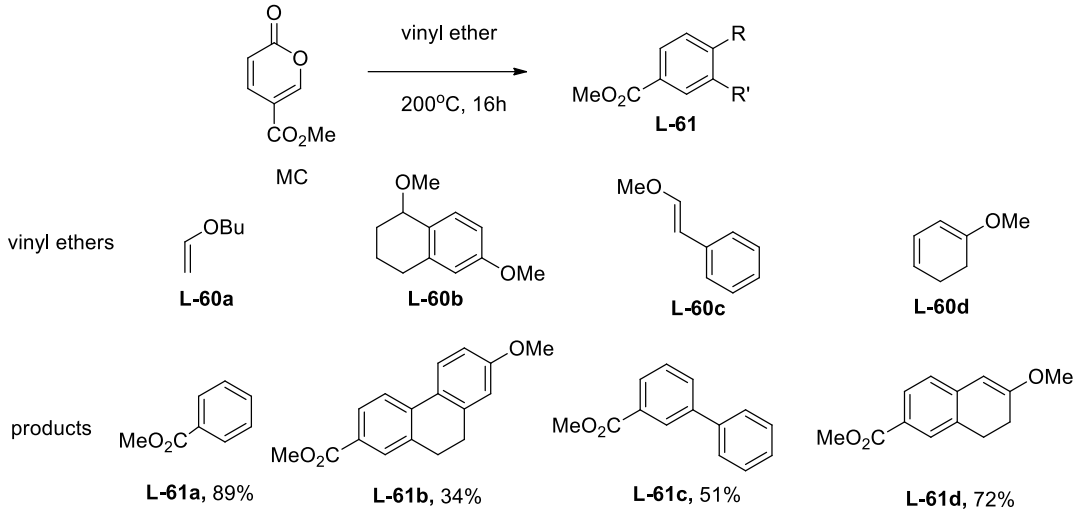
In pharmaceutical industry, 3-Cyano-1-naphthalenecarboxylic acid **L-59** is one of the key intermediate for manufacturing process of tachykinin receptor antagonists. Ashworth *et al*,[10] described an interesting new route by building the 1,3-substituted naphthalene 2-ring system, from 3-bromo-MC **L-57** with *in situ*-generated benzyne by D-A addition. This attractive route is able to scale-up and operate at around 100-L-scale at most of the step, improving yield of previous route from 5% to >20% (Scheme 18).

Scheme 18 The synthesis of 3-Cyano-1-naphthalenecarboxylic acid from MC



Kraus's group[11] reported a successful one-pot metal-free cascade regioselectively access aromatic systems (Scheme 19). The reaction provided tricyclic and biphenyl, frameworks **L-61** which supplemented the previous methodology of MC.

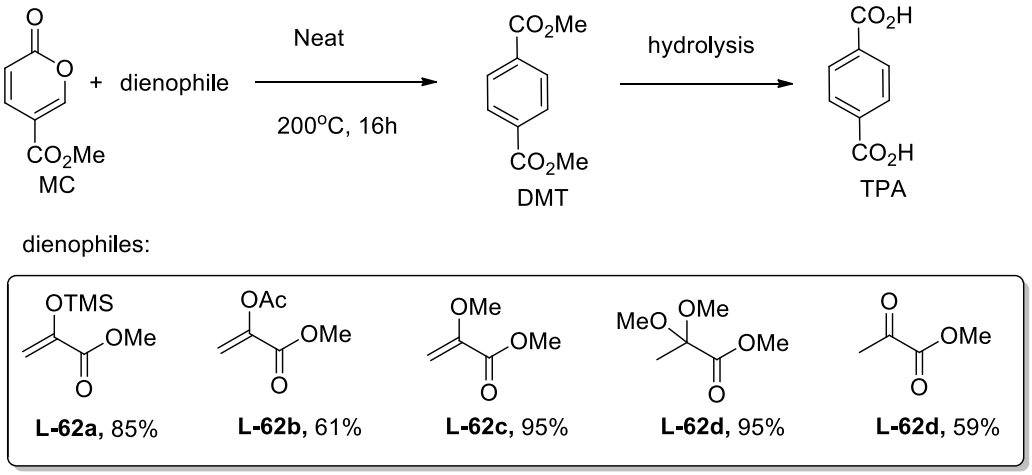
Scheme 19 Metal-free process towards tricyclic, biphenyl, frameworks



In 2014 the same group[33] reported a sustainable approach towards dimethyl terephthalate (DMT). The DMT obtained could be converted to terephthalic acid (TPA) by hydrolysis (Scheme 20), which is the key monomer for polyethylene

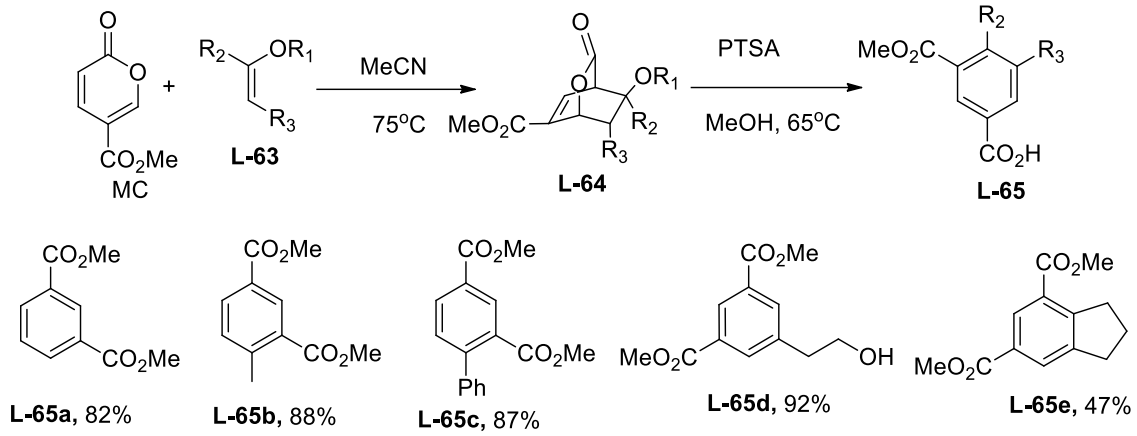
terephthalate production. This approach could provide a biorenewable drop-in replacement of the petrochemical-based polymer industry. This reaction applied MC and methyl pyruvate in one-pot, avoided harsh oxidation and do not required solvent application, affording the DMT with exclusive regioselectivity and in excellent yield. The further purification could be achieved through recrystallization.

Scheme 20 Sustainable approach towards dimethyl terephthalate from MC



In this context, Kraus's group described that MC reacted with enol ethers to form stable adducts. These compounds could be converted into isophthalates in good to excellent yields (Scheme 21). The two-step D-A/aromatization pathway was carried out under mild condition. The alkyl vinyl ethers could give better yields of isophthalates than those obtained with silyl enol ethers **L-63**.[34]

Scheme 21 Bio-based benzoates from MC

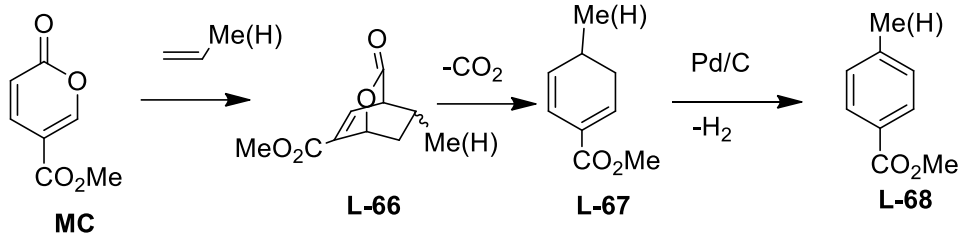


Shanks' group reported a D-A process for benzoate production,[35] in which the cycloaddition took place between MC and ethylene. It produces benzoic acid in high yield. The reaction employed bio-based MC and ethylene as feedstocks, which provided a renewable alternative to current benzoate production. Activation energies of each step provided by DFT calculations revealed that the releasing of CO_2 was the rate determing step. Multi-dimensional NMR studies demonstrated that water could accelerate the byproducts formation, so water-free condition is critical to improve the overall selectivity and yield. Additionally, the reaction ran in non-toxic bio-based solvent under heterogeneous catalytic system leading to yields up to 100%. The D-A reaction can be scaled up to a number of products based on the MC.

A similar approach was reported by the same group, in which MC precursor coumalic acid (CMA) was employed as starting material with propylene to produce toluic acid (TA) with high selectivity. TA could be converted to terephthalic acid which is a key monomer for plastic polyethylene terephthalate (PET) manufacture. The water-free solvent is very important for limiting CMA decomposition and maximizing product yield. The *para*-TA formation is a kinetically and thermodynamically favored process, rendering yield >85% in renewable solvent γ-valerolactone (GVL). This provides a bio-based alternative

monomer to PET.[36]

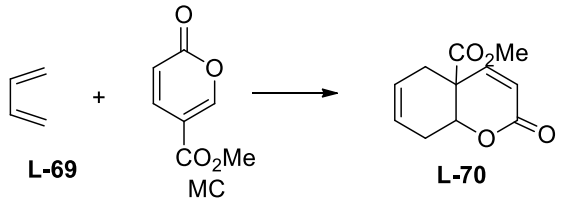
Scheme 22 Sustainable production of benzoate and toluic acid from MC



1.3.3 MC as dienophile in Diels-Alder reactions

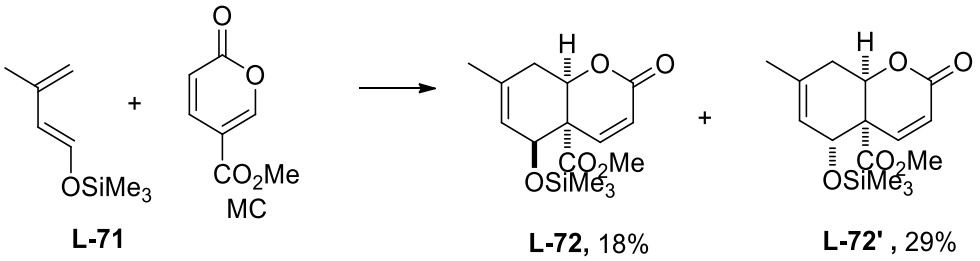
Kawanisi's group reported a D-A reaction of MC with 1, 3-dienes affording the tetrahydrocoumarin **L-70** and this reaction was the first example of utilizing a 2-pyrone (MC) as a dienophile (Scheme 23).[37,] Two years later, the same group published an update doing the reaction at room temperature [38]

Scheme 23 Synthesis of tetrahydrocoumarin from MC



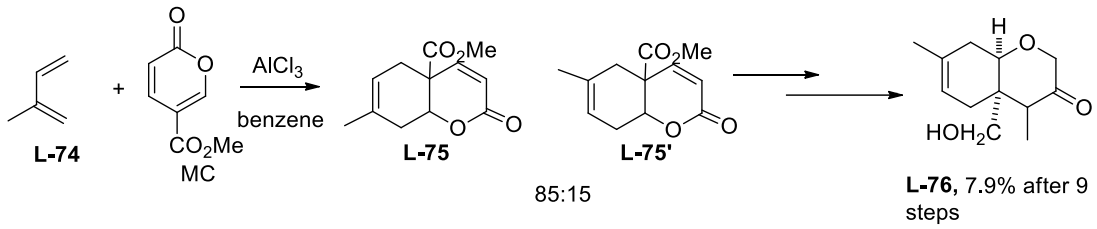
Colvin's group described a novel synthetic approach to the core of trichothecene deoxynivalenol, in which the hydroxycoumarin core was synthesized *via* a regioselective cycloaddition between a silyloxydiene and MC (Scheme 24).[39 40]

Scheme 24 D-A reaction MC with silyioxydiene



Kraus's described a synthetic route to the AB ring system of verrucaro **L-76** (Scheme 25). The key step was an aluminum chloride-catalyzed D-A reaction between MC and the 2-Me butadiene in benzene at 110°C. It produced a mixture of regioisomers in a 85:15 ratio.[41]

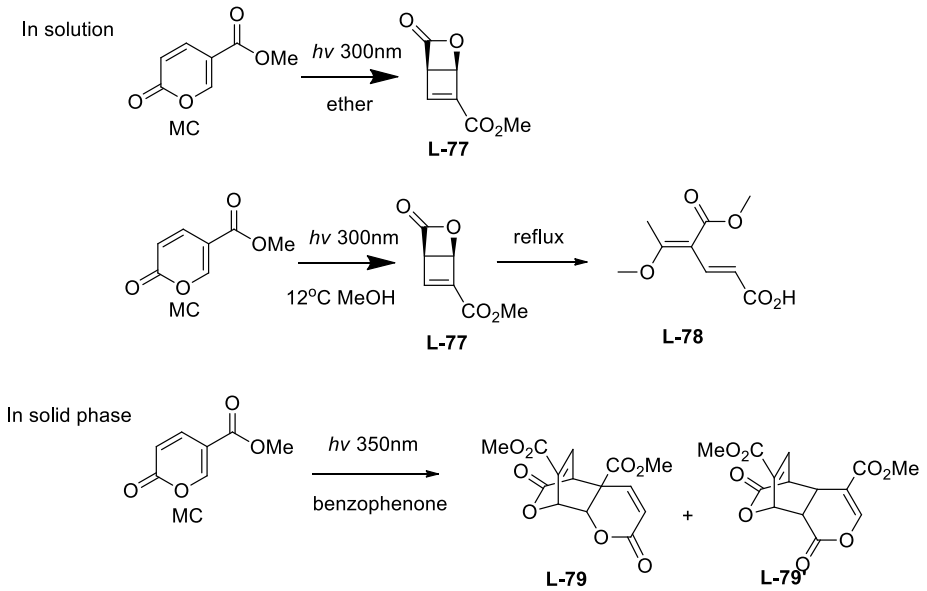
Scheme 25 Synthetic route towards AB ring system



1.4. MC participates in [2+2] cycloadditions

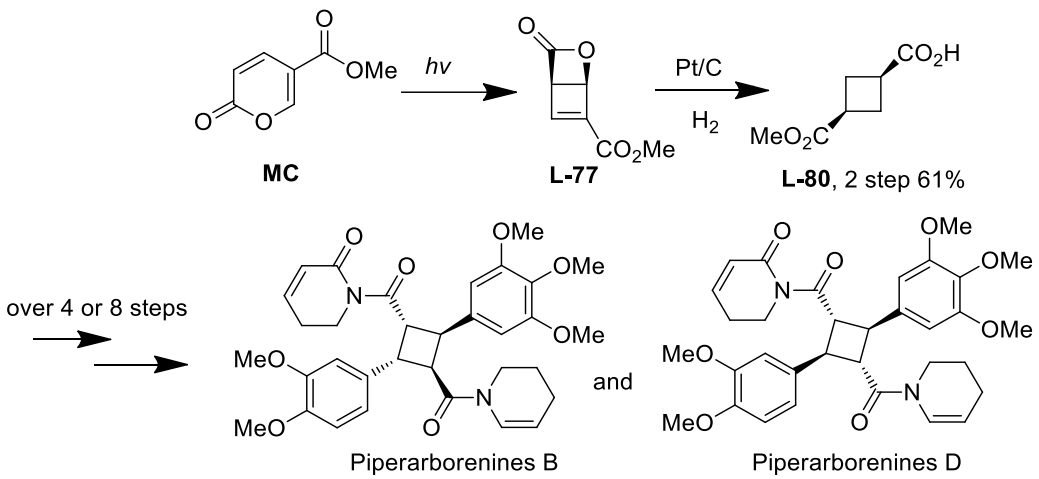
The pioneering experiment was reported by Corey et al. during his work on pyrone photochemistry.[42] Later on, Javaheripour *et al.*[43] investigated photochemical reactions of MC in both liquid and in solid phase. When MC was irradiated at 300 nm in ether solution, it forms a singlet excited states which further produced 3-oxabicyclo[2.2.0] hex-5-en-2-one **L-77** via [2+2] cycloaddition. In comparison, when irradiated at 350 nm in a KBr at solid phase, no cyclobutene product was found, and instead of [2+2], a [4+2] dimerization was observed. This D-A dimers **L-79**, **L-79'** are triplet state products. In the potassium bromide, the photochemical reaction took place and acted as a sandwich between quartz plates (Scheme 26).

Scheme 26 [2+2] Cycloaddition in solid and liquid phase



Besides having wide potential applications, MC can be further apply to a novel strategy for the total synthesis of piperarborenine B and piperarborenine D.[44] Intramolecular [2+2] photocycloaddition of MC could efficiently build cyclobutene followed by hydrogenation catalyzed by Pt/C. This [2+2] new strategy toward cyclobutane natural products provided the cyclobutane **L-80** in one pot and with 61% isolated yield rather than the previous 20% overall yield after an 8-step pathway (Scheme 27).[45]

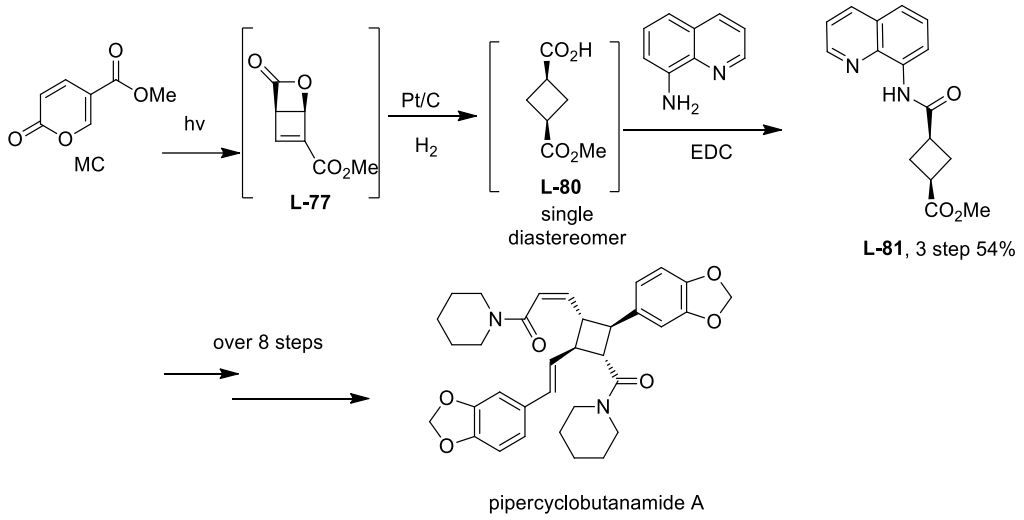
Scheme 27 Total synthesis of piperarborenine B and piperarborenine D



Baran's group reported on the asymmetric synthesis of Pipercyclobutanamide

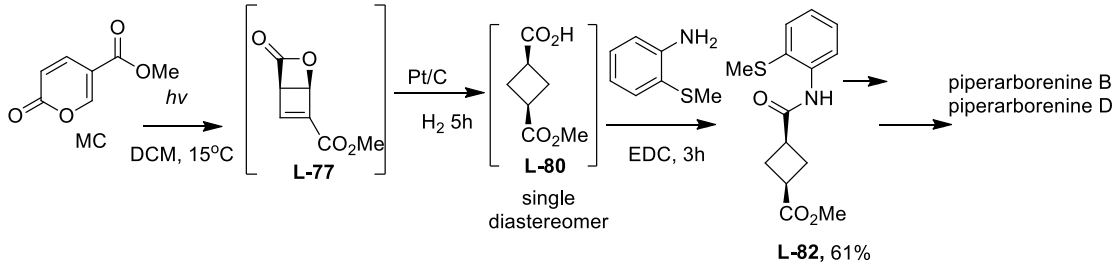
A,[46] which is a selective inhibitor of cytochrome P450 2D6. By applying the previously developed methodology, MC underwent a [2+2] 4π electrocyclization at reduced temperature to give the cyclobutene. This unstable intermediate was reducted by hydrogenation and condensation to 8-aminoquinoline in one pot, giving the desired cyclobutane **L-80** in 54% yield over 3 step (Scheme 28).

Scheme 28 Total synthesis of piperarborenine A



This strategy has been proven very useful for many natural products. Maulide's group developed an approach towards piperarborenine B and piperarborenine D (Scheme 29).[47]

Scheme 29 Total synthesis of piperarborenine B and piperarborenine D by Maulide's group

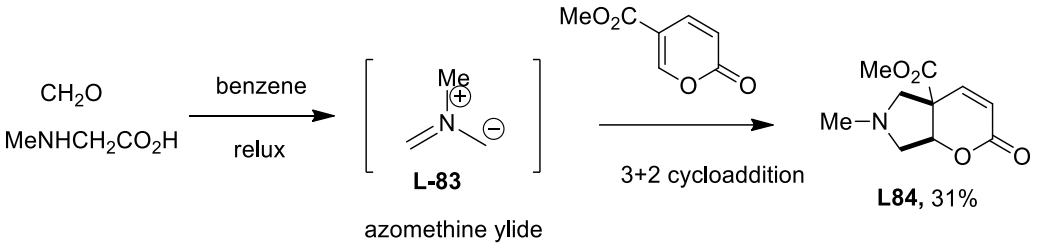


1.5. MC reacts with 1,3 dipoles

In addition to [4+2] D-A reactions, MC could also react with 1,3 dipole. The reaction could serve as an efficient complement for the sustainable five membered

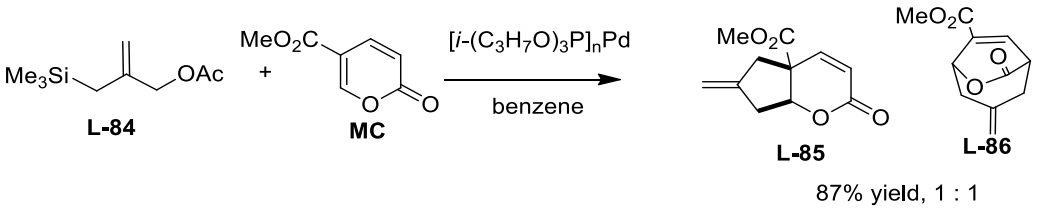
or seven membered ring construction. For example MC reacted with the nonstabilized azomethine ylide **L-83**, resulting in the regio-selective [3+2] cycloaddition (Scheme 30).

Scheme 30 [3+2] cycloaddition with MC



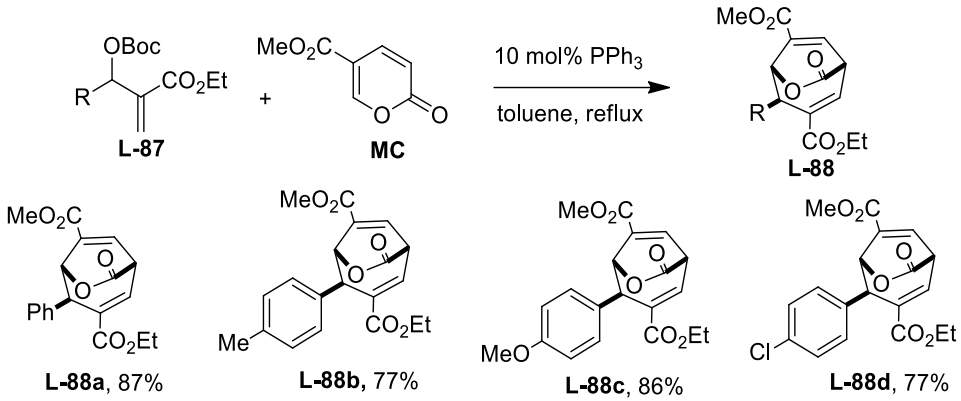
Trost's group propose an original [4+3] cycloaddition of MC with 2-[(trimethylsilyl) methyl] (TMM) allyl carboxylates catalyzed by Pd. In this work, the TMM complexes reacted with MC and give a 1 : 1 mixture of the [2 + 3] and [4 + 3] cycloadducts (Scheme 31).[48]

Scheme 31 Pd catalyzed [2 + 3] and [4 + 3] cycloadditions



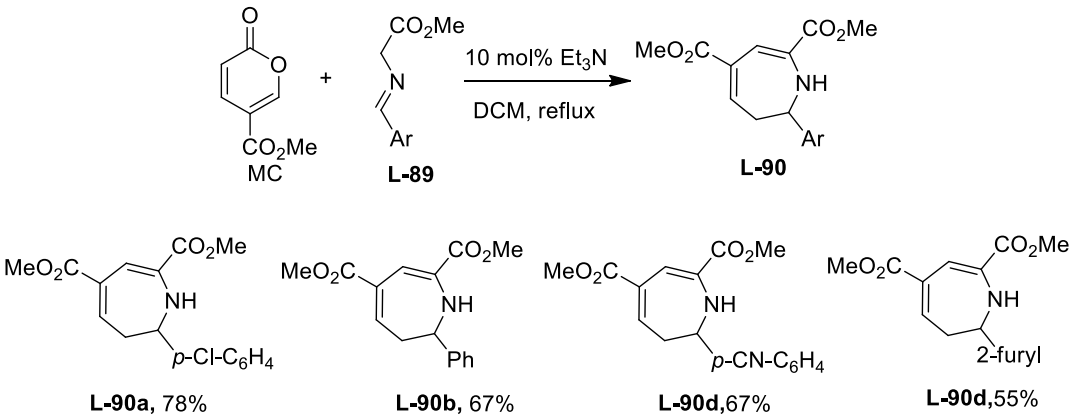
Another approach was reported by Lu's group (scheme 32).[49] In this [4+3] cycloaddition reaction, Baylis-Hillman carbonates **L-87** were chosen as 1,3 dipolar precursor. In the presence of triphenylphosphine, it generates the corresponding ylides which reacted first as a nucleophile then as electrophile to deliver the bicyclic compound. This phosphine-catalyzed reaction is stereoselective and offer a powerful method to build bicyclo[3.2.2]nonadiene skeleton

Scheme 32 phosphine catalyzed [4+3] cycloaddition with MC and Morita-Baylis-Hillman carbonates



Later on, Wang's group reported on a novel catalytic tandem reaction [4 + 3] of MC with imine esters **L-89**. This reaction regioselectively afforded a series of pharmaceutically interesting aza seven-membered azepine derivatives **L-90** in good yields. In this metal-free reaction the 1,3-dipoles were generated from deprotonation of imine esters, and further reaction with the dipolarophile MC (Scheme 33). [50]

Scheme 33 The synthesis of azepines from MC and imine esters

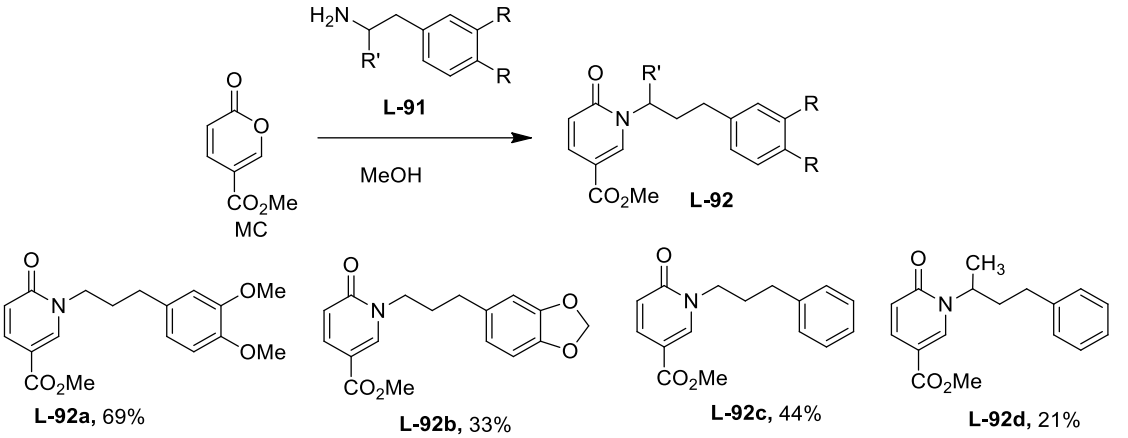


1.6. Preparation of pyridin-2(*1H*)-one from MC

Wiley's group reported in 1953, the preparation of 2-pyridones which have very interesting chemical and biological properties, by reaction of methyl

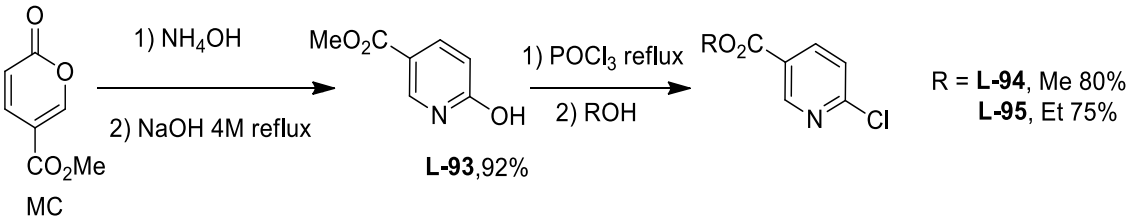
coumalate and 6-phenylethylamines **L-92** (Scheme 34).[51]

Scheme 34 The synthesis of phenylethylamines from MC



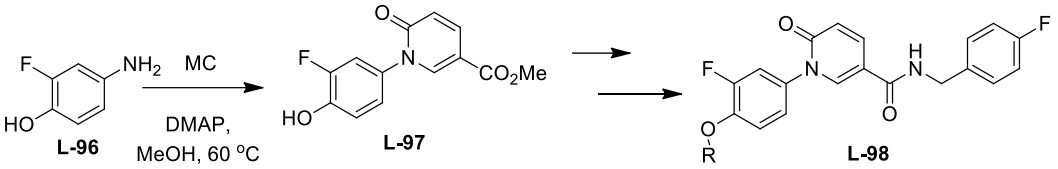
Kirsch's group described the synthesis of 6-chloronicotinate esters **L-94**, **L-95**. 6-Hydroxynicotinic acid **L-93** was prepared by reacting MC with ammonia, and was further transformed to 6-chloronicotinate esters using phosphorus oxychloride and either methanol or ethanol in good yield (Scheme 35).[52]

Scheme 35 The synthesis of 6-chloronicotinate esters from MC



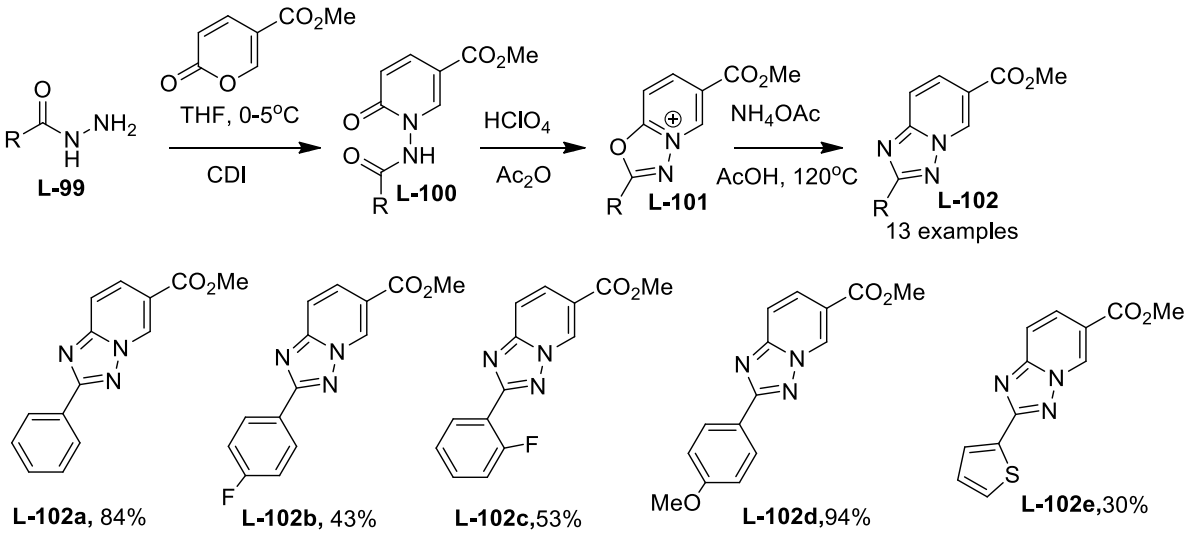
More recently Huang's group designed, synthesized and evaluated a series of highly selective pyridone-based class II MET inhibitors (Scheme 36). The key structure core of these MET inhibitors, pyridones are produced from MC by cycloaddition with phenylamines **L-97**. [53]

Scheme 36 The synthesis of MET inhibitors from MC



The s-[1,2,4]triazolo[1,5-a]pyridine system **L102** is the key structural core presented in a diverse range of biologically important small molecules.[54] Moloney and co-workers reported an efficient three-step pathway of a series of fused bicyclic s-[1,2,4]triazolo[1,5-a]pyridines **L102** synthesis, employing new intermediate starting from inexpensive, commercially available MC and hydrazides. Their approach started by formation of a dihydrazide intermediate **L100**, which give stable oxadiazolium salts after cyclization. The 1,2,4-triazole is built during the last step, avoiding the use of unsafe oxidative N−N bond formation step (Scheme 37).

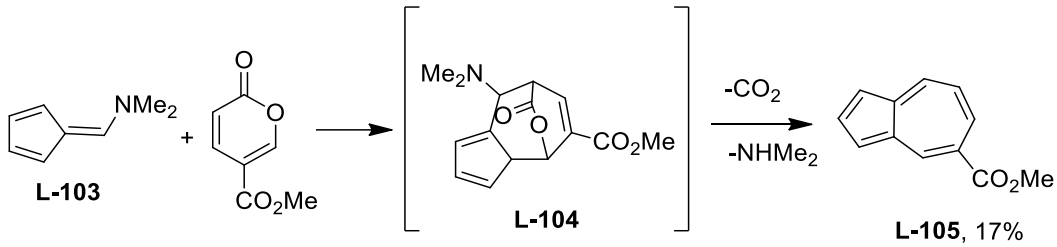
Scheme 37 The preparation of [1,2,4]triazolo[1,5-a]pyridine system from MC



1.7. MC participates in [6+4] cycloaddition

In this context, Ebine's group reported a one-step synthesis of Azulenes **L-105** from 6-aminofulvenes **L-103** with MC *via* [6+4] cycloaddition (Scheme 38). 6-dimethylaminofulvene and MC were dissolved in benzene and stirred for five days in dark at room temperature proceeding successfully to give azulenes by one-step in 17% yield.[55]

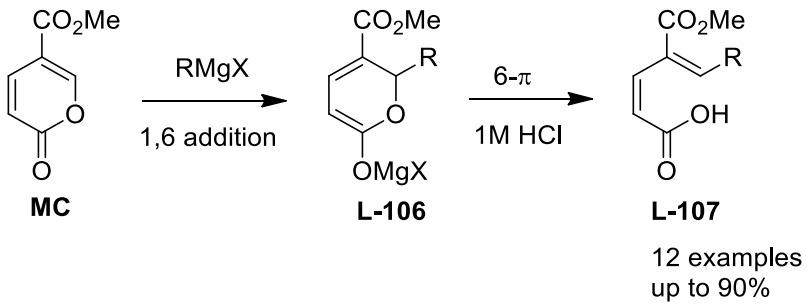
Scheme 38 MC involved [6+4] cycloaddition



1.8. MC *via* 1,6 Michael addition reactions

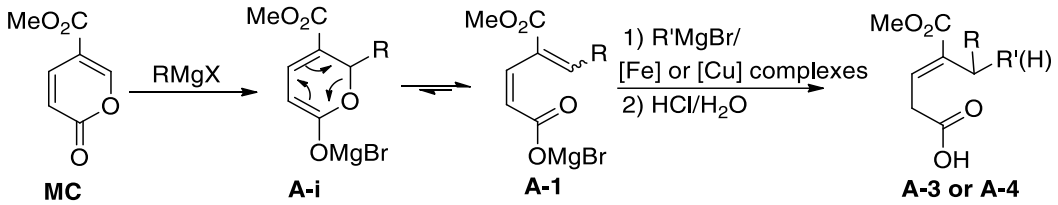
MC has also been employed as a starting material for the synthesis of conjugated α-Z/γ-Z or α-Z/γ-E dienoic acids with high regio- and stereoselectivity. The ester present in 5-position of MC assisted the regioselective 1, 6 addition leading to the 2*H*-pyran intermediate **L-106**, after a 6-p electrocyclic process give the dienoic carboxylate **L-107**. The stereochemical outcomes can be explained by a thermodynamic control sheltering the kinetic products.[56]

Scheme 39 preparation of dienoic acids from MC



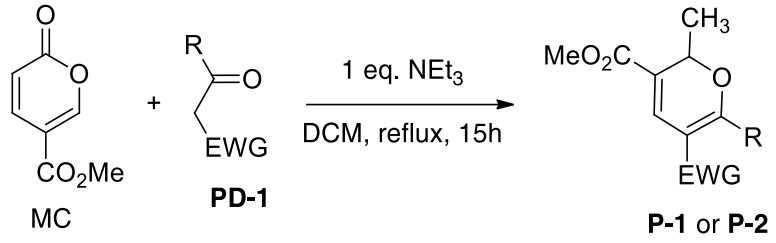
Our group has reported a one-pot sequential reaction with double alkyl-alkyl 1,6 addition on MC (Scheme 40). The methodology provides a facile access towards *β,γ*-unsaturated carboxylic acids in a highly regio-, and stereo-selectivity. We explained the key role of the Grignard reagent for the stereoselectivity outcome by proposing a constrained chair-like transition state stablized with bimetallic intermediate. This metal-catalyzed double 1, 6 addition of two Grignard reagents (homo-coupling, 2 RMgX or hetero-coupling, R1MgX+R2MgX) afforded *β,γ*-unsaturated carboxylic acids **A-3** or **A-4** in good yields and good to excellent stereoselectivities.[57] This part will be detail in the next chapter.

Scheme 40 Double 1,6 addition on MC towards *β,γ*-unsaturated carboxylic acids



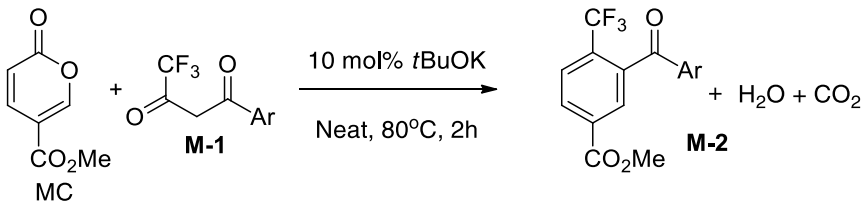
During this Phd thesis we also reported the reaction of MC with various methylene active keto-esters, cyclic or acyclic diketones and keto-sulfones, giving more than thirty 2,3,5,6-tetrasubstituted 2*H*-pyrans **P-1** or **P-2** in good to excellent yields. This reaction trigged by 1,6 Michael addition is followed by both 6π-electrocyclic ring opening and 6π electrocyclic ring-closing. In addition, this methodology could take advantage of the readily available starting materials, mild conditions and tolerate a variety of functional groups (Scheme 41).[58] This part will be the subject of the chapter 3.

Scheme 41 The synthesis of 2*H*-pyrans from MC and methylene active compounds



Recently, we discovered an efficient and environmentally friendly method towards trifluomethyl-substituted benzenes, and most of the obtained products bear the benzophenone core structure with great pharmaceutical interest. This solvent-free method employs bio-based MC as starting material, catalyzed by tBuOK, providing trifluoromethyl benzenes in good to excellent yields with regioselectivity. CF_3-substituted benzenes **M-2** were obtained from carba-6π-electrocyclic ring closure and oxidant-free aromatization sequence, with only water and CO_2 as byproducts.[59] This part will be the subject of the chapter 4.

Scheme 42 The synthesis of trifluomethyl-substituted benzenes *via* carba-6π-electrocyclic reaction



1.9. References

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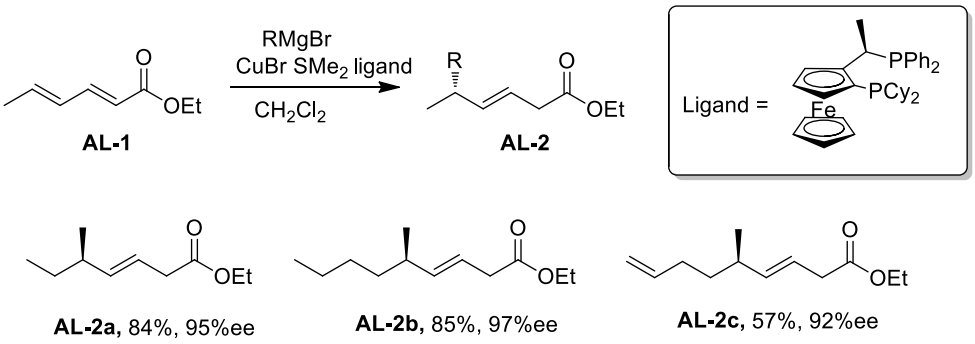
Chapter 2: *β,γ* -Unsaturated carboxylic acids by one-pot sequential double 1,6-addition of Grignard reagents onto methyl coumalate.

2.1. Introduction

The conjugated addition of organomagnesium halide to *α,β*-unsaturated carbonyl compounds were well reported.[1] In comparison, conjugated addition of Grignard reagents to the *α,β-γ,δ*- unsaturated systems are less documented.[2,3] There are several reasons of this lower investigation, which are most presumably due to the numerous difficulties to control the selectivity in general. First, the regioselectivity between 1,4- and 1,6-addition. Second, the region-slective reprotonation giving access to *α,β*- or *β,γ*-unsaturated carbonyl compounds is rather difficult. Third, the stereoselectivitiy of the new formed double bond is hard to control. Several copper-catalyzed 1,6-addition on dienoates[4] and dienones[5] have been described.

For example, Feringa's group developed a highly enantioselective 1,6- asymmetric conjugate addition from ethyl sorbate with Grignard reagents (up to 97 % ee), giving, *α,β-γ,δ*-unsaturated esters, which are valuable multifunctional building blocks. The 1,6 conjugate addition regioselectivity is dictated by catalyst.[4i]

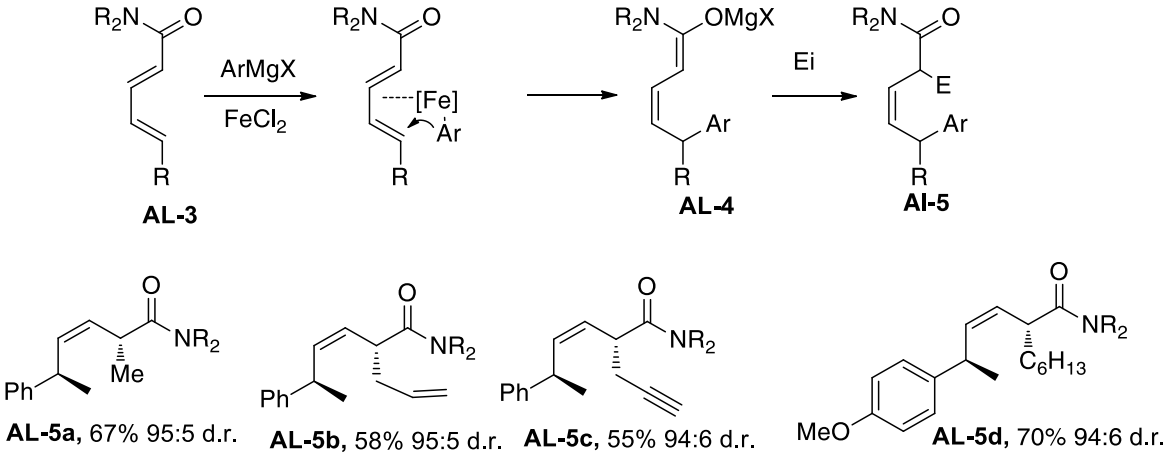
Scheme 1 Asymmetric 1,6-conjugate addition of Grignard reagents[6]



The group of Urabe reported rare examples of 1,6-conjugated addition by using iron catalyst ($FeCl_2$) on unsaturated amides. They observed the regio- and stereo-selective formation of *β*, *γ*-unsaturated carbonyl products. They proposed a mechanism in which the η-4 complexation of the iron complex could explain the total stereoselectivity observed during the reaction. Later on, iron-catalyzed 1,6 addition of aryl-Grignard reagents to *α,β-γ,δ*-unsaturated sulfones and its further cyclization was reported by the same group. In these reaction, the sulfonyl group plays important

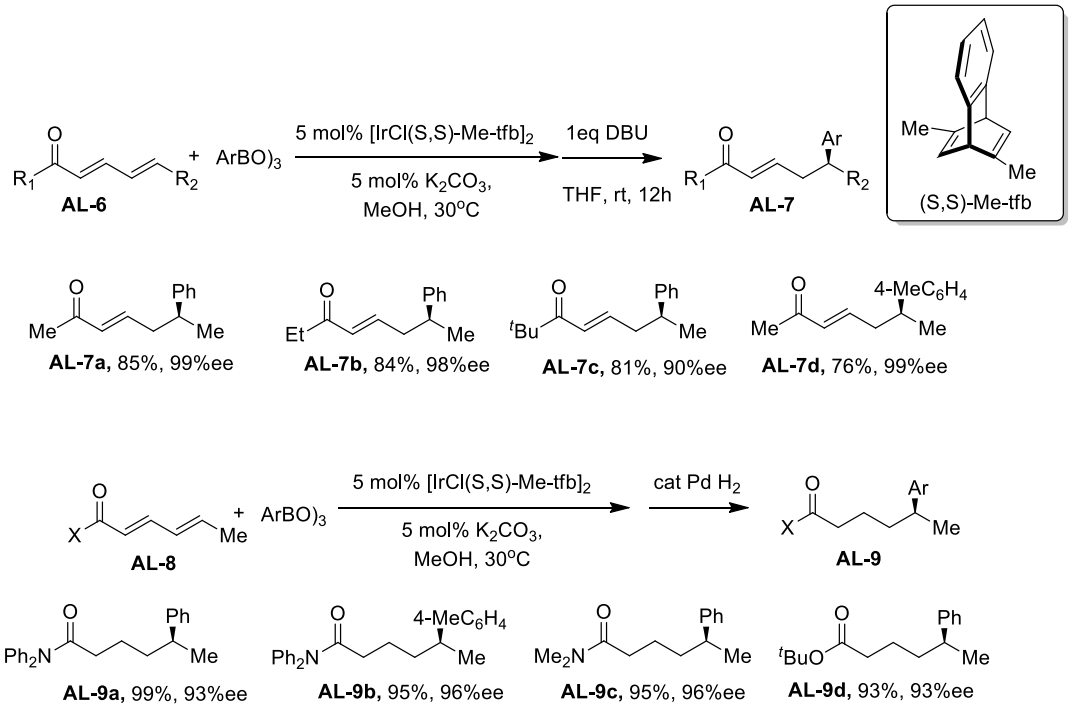
roles, first it activates the selective conjugate addition, moreover it works as a leaving group in the further Friedel–Crafts reaction.

Scheme 2 Products of Iron-catalyst 1,6 conjugate addition of Grignard reagents[6a]



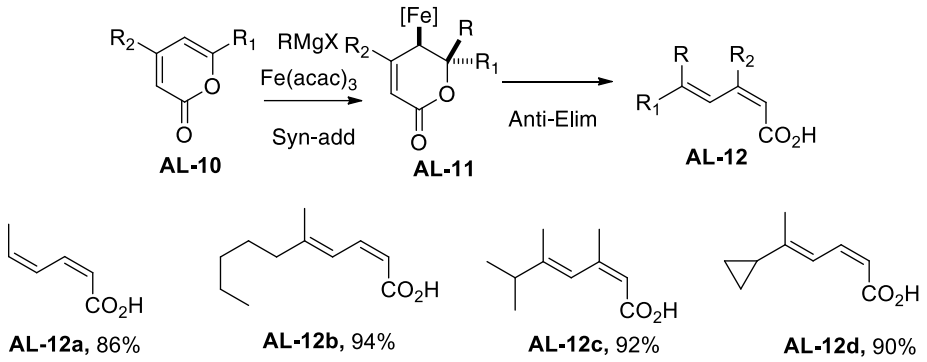
Nishimura and co-workers have developed an iridium-catalyzed asymmetric 1,6-addition of arylboroxines to *α,β-γ,δ*-unsaturated carbonyl compounds that is realized by the use of an iridium/chiral diene complex and gives δ-arylated carbonyl compounds in high yields with high enantioselectivity.[4]

Scheme 3 Iridium -Catalyzed Asymmetric 1,6-Addition



Fürstner's group[7b] published the regio- and stereoselective 1,6-addition of excess Grignard reagents to diverse substituted 2-pyrones in the presence of a catalytic amount of [Fe(acac)$_3$](Scheme 4). With this methodology, they developed an efficient diastereoselective synthesis of natural product granulatamide B.

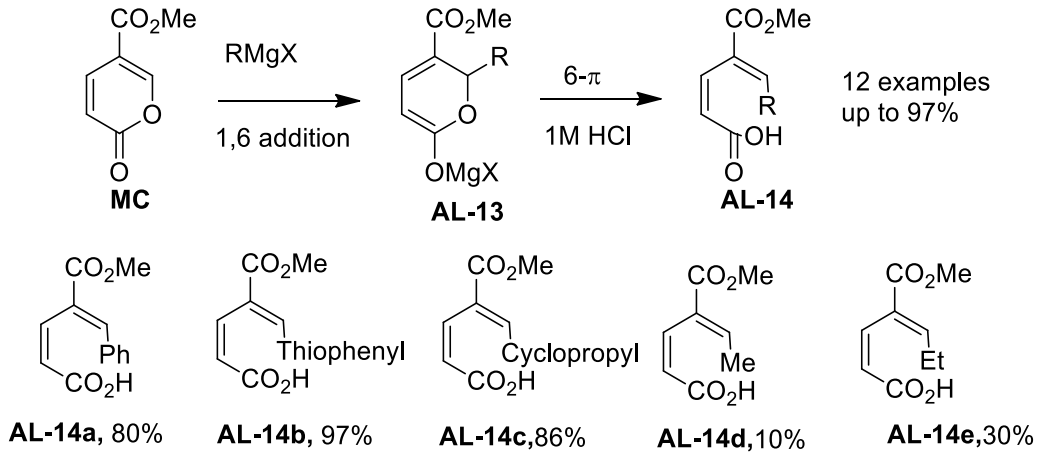
Scheme 4 Formal ring-opening/cross-coupling reactions of 2-pyrones



As proposed by Urabe,[6] after the 6π ring-opening stepwise formation of a η-4-dienic Iron complex followed by a *syn* 1,2- addition of the π-system into the Fe-Me bond and further *anti*-elimination was proposed.

In general, α-pyrones[7] derivatives such as methyl coumalate **1**, are considered as cyclic dienoates compounds.[8] Dechoux and Thorimbert recently demonstrated the efficient and stereoselective access to conjugated (*Z*,*Z*) or (*Z*,*E*)-dienoic acids **2** by regioselective 1,6- addition of Grignard reagents (1 equiv.) onto methyl coumalate **1** (Scheme 5).[9]

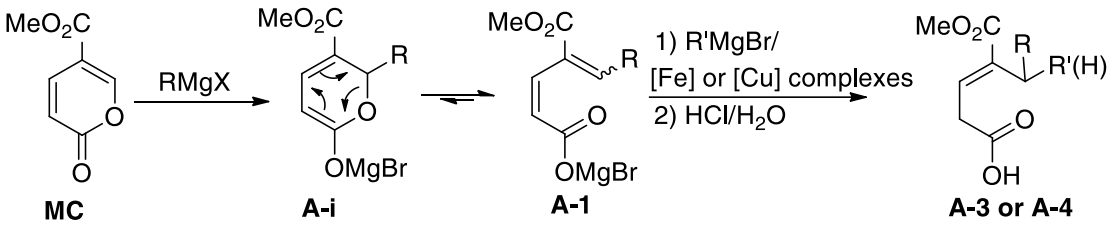
Scheme 5 Stereoselective synthesis of conjugated a-Z/-Eand a-Z/-Z dienoic acids



Continuing our interest in the conjugate addition of organometallic reagents. We begin our study on the possible 1,6 conjugate addition of Grignard reagents on ring-opening product.[11]

Scheme 6 Double 1,6 – addition on MC

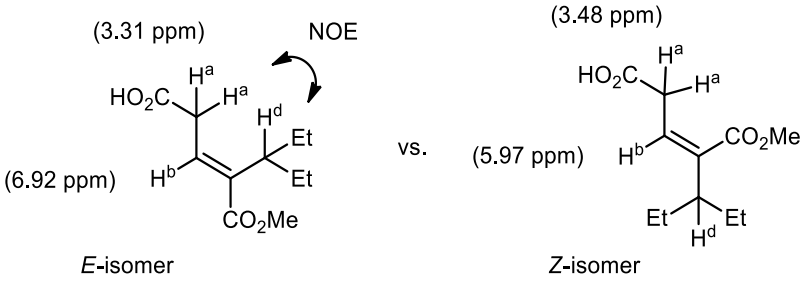
Present work



2.2. One-pot sequential double 1,6- addition of one same Grignard reagent

First, we investigated the conjugate addition of 4 equiv. Grignard reagents in the presence of TMSCl in THF at 0 ^{o}C (Table 1, entries 3, 6, and Table 3 entry 5). Interestingly, under these conditions, methyl Grignard reagent did not give the expected product **A-3** when sterically hindered nucleophiles such as *i*-PrMgBr or *t*-BuMgCl were used, the reaction stopped after the first addition.[9] These first results indicate that in the absence of a catalyst, bulky Grignard reagents do not add to the putative 2,4-dienic magnesium carboxylate. On the other hand, double addition of EtMgBr, n-BuMgBr and PhMgBr at the 6-position of methyl coumalate occurred, giving the expected β,γ unsaturated carboxylic acids **A-3b**, **A-3c**, and **A-3f** in 30, 92, and 90% yields, respectively, with *E/Z* ratios close to 80/20. Assignment of the configuration of the *β,γ*-double bond in (*Z*)- **A-3b** and (*E*)-**A-3b**, **A-3c** was achieved by NOESY experiments (strong correlation between Ha and Hd in the *E* isomers). It is noteworthy that in all ^{1}H NMR spectra, proton Hb of (*E*)-3 was deshielded at around 7 ppm versus 6 ppm for (*Z*)-3 (Figure 1).

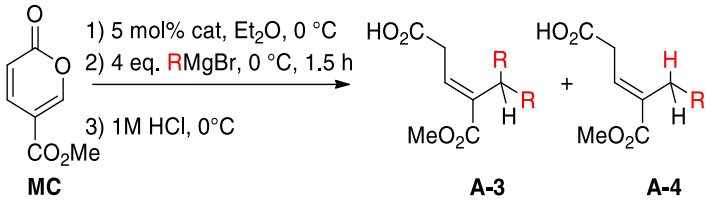
Figure 1. Example of assignment of configuration for compound **A-3b**



We presumed that the Lewis acidic salts could activate both the nucleophiles and the electrophiles. We thus turned our attention to the possible iron- or copper-catalyzed double addition.[12] In a typical experiment, methyl coumalate **1** was treated with 4 equiv. of MeMgBr in Et_2O at 0 ^oC in the presence of 5 mol% catalyst {$Cu(OTf)_2$ or $Fe(acac)_3$}. After 1.5 hours and an acidic quench, the β,γ-unsaturated acid (*E*)- **A-3a** was obtained in good yield and excellent regio- and stereoselectivity (Table 1, entries 1 and 2). The data gathered in Table 1 highlight the scope and limitations of this homo-double addition. Under these new conditions, using either copper or iron catalysis, the expected double 1,6-addition was more general and gave better stereoselectivity.

In the case of primary (Me, Et, and *n*-Bu) or phenyl Grignard reagents and using $Cu(OTf)_2$ as catalyst, the expected *β,γ*-unsaturated carboxylic acids **A-3(a–c)** and **A-3f** were now isolated in high yields and excellent stereoselectivity (Table 1, entries 2, 5, and 8). The iron catalyst was slightly less efficient than the copper one, since it resulted the formation of by-products or in one case formation of product **A-4c** arising from 1,6-addition of hydride (Table 1, entries 4, and 7).

Table 1. One-pot metal-catalyzed double 1,6-addition of primary Grignard reagents

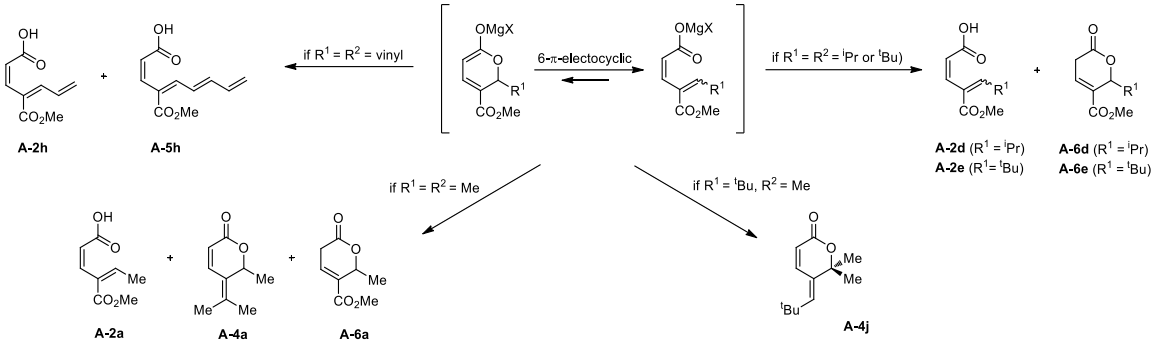


Entry	R	Catalyst	Products (yield %)	*E*/*Z* ratio[c]
1	Me	$Fe(acac)_3$	**A-3a** (76)	>95/5
2	Me	$Cu(OTf)_2$	**A-3a** (90)	>95/5
3	Et	/[a]	**A-3b** (30)	82/18
4	Et	$Fe(acac)_3$	**A-3b** (56)	>95/5
5	Et	$Cu(OTf)_2$	**A-3b** (92)	>95/5
6	*n*-Bu	/[a]	**A-3c** (92)	80/20
7	*n*-Bu	$Fe(acac)_3$	**A-3c**/**4c** (70) [b]	>95/5
8	*n*-Bu	$Cu(OTf)_2$	**A-3c** (98)	>95/5

[a] No catalyst but 1 equiv.of Me_3SiCl. [b] Total conversion, estimated yield based on ^1H NMR of the crude. [c] Determined by ^1H NMR of the crude.

Secondary and tertiary Grignard reagents afforded the *α*,*β*-unsaturated acids **A-4d, A-4e** using both catalysts (Table 3, entries 1– 4).[13] The presence of the ester moiety on the carbon-5 of methyl coumalate seems to be essential for the double addition on carbon-6 to occur. Indeed, the simplest pyrone reacted with PhMgBr in the presence of $Fe(acac)_3$ or $Cu(OTf)_2$ to give mixture of 1,4- and 1,6-addition products in low yields. Starting from methyl 2-pyrone-3-carboxylate, the reaction with PhMgBr provided the 1,4-addition product no matter what catalyst was used.

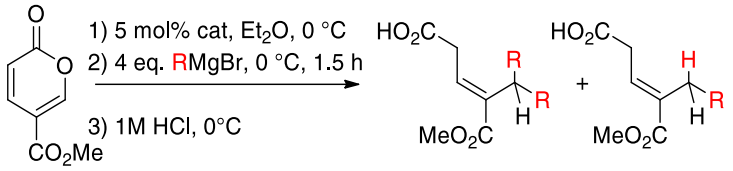
Table 2 Additions of excess of Grignard reagents to methyl coumalate



Entry	R^1	R^2	Catalyst	Product (yield)
1	Me	Me	TMSCl	A-2a/ A-4a/ A-6a
2	*i*-Pr	*i*-Pr	TMSCl	A-2d/ A-d
3	*t*-Bu	*t*-Bu	TMSCl	A-2e/ A-6e
4	vinyl	vinyl	$Fe(acac)_3$	A-2h/ A-5h
5	vinyl	vinyl	$Cu(OTf)_2$	A-2h/ A-5h
6	*t*-Bu	Me	$Cu(OTf)_2$	A-4j (76)

When sterically demanding nucleophiles were used, the reaction stopped after the first addition even if more than 4 equiv. of *i*-PrMgBr (Table 2, entry 2) or *t*-BuMgBr (Table 2, entry 3) were added. In these cases a mixture of (α-*Z*/γ-*E*)-dienoic acids **A-2(d-e)** and unsaturated lactones **A-6(d-e)** were obtained as previously reported. If vinyl magnesium bromide as a nucleophile was used, chemoselectivity was again modified. The formation of a mixture of two products **A-2h** and **A-5h** were observed

Table 3. One-pot metal-catalyzed double 1,6-addition of isopropyl, phenyl and *t*-butyl Grignard reagents



Entry	R	Catalyst	Products (yield %)	*E*/*Z* ratio[c]
1	*i*-Pr	$Fe(acac)_3$	/	/
2	*i*-Pr	$Cu(OTf)_2$	**A-(3/4d)** (60/40) [b]	/
3	*t*-Bu	$Fe(acac)_3$	**A-4e** (66)	>95/5
4	*t*-Bu	$Cu(OTf)_2$	**A-4e** (72)	>95/5
5	Ph	/[a]	**A-3f** (90)	79/21
6	Ph	$Fe(acac)_3$	**A-3f** (90)	>95/5
7	Ph	$Cu(OTf)_2$	**A-3f** (95)	>95/5

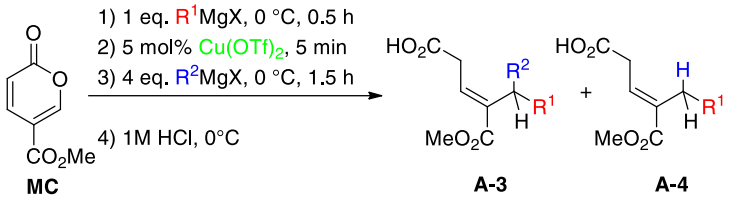
[a] No catalyst but 1 equiv.of Me_3SiCl. [b] Total conversion, estimated yield based on ^1H NMR of the crude. [c] Determined by ^1H NMR of the crude.

2.3. One-pot sequential double 1,6- addition of two different Grignard reagents

Next we examined the outcome of the copper-catalyzed one-pot reaction by using successively two different Grignard reagents (Table 3). We focused our attention on the use of $Cu(OTf)_2$, as we initially observed lower yields with $Fe(acac)_3$ (vide supra, Table 1). Due to obvious chemoselectivity issues, one equivalent of the first Grignard reagent was added before addition of catalyst (in order to ensure efficient formation of the mono-adduct and to avoid formation of the homo-coupling adduct. The new conditions were as follows: 1.1 equiv. of the first Grignard reagent was added without catalyst, then 5 mol% of $Cu(OTf)_2$, followed by addition of 4 equiv.

of the second Grignard reagent. The data in Table 4 illustrate the scope and limitations of the hetero-coupling method.

Table 4. One-pot copper-catalyzed hetero double 1,6- addition

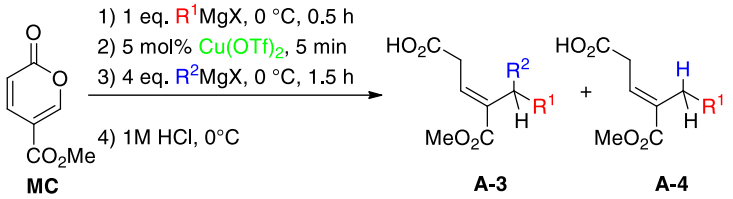


Entry	R^1	R^2	Products (yield %)	*E*/*Z* ratio[b]
1	Me	Ph	**A-3i** (71)	93/7
2	Me	*n*-Bu	**A-3k** (74)	94/6
3	Me	*i*-Pr	**A-3l** (90)	86/14
4	Me	vinyl	**A-3m** (61)	79/21
5	Ph	Me	degrad.	/
6	Ph	*n*-Bu	**A-3n** (68)	93/7
7	Ph	*i*-Pr	**A-3o** (59)	>95/5
8	Ph	*t*-Bu	**A-3p** (76)	>95/5
9	Ph	vinyl	**A-3q** (67)	80/20

[a] Total conversion, estimated yield based on ^{1}H NMR of the crude product. [b] Determined by ^{1}H NMR of the crude product.

In almost all cases, good yields and good to excellent stereoselectivities were attained. When MeMgBr or PhMgBr were added first, the expected *β,γ*-unsaturated acids **A-3(i–q)** were obtained as the *E*-isomers with good diastereoselectivity (Table 4). With other primary, secondary and tertiary Grignard reagents as first nucleophile, the outcome of the reaction depended on the structure of the second nucleophile (Table 5). When MeMgBr was used as second nucleophile, the reaction gave the expected product **A-3** in low yield (Table 4, entry 5, Table 5 entry 1). In contrast, the addition of phenyl and vinyl Grignards as second nucleophiles was successfully achieved affording compounds **A-3i**, **A-3m**, **A-3o**, **A-3p**, **A-3q**, **A-3s**, **A-3u**, and **w** in moderate to good yields (Table 4, entries 1, 4, 9, and Table 5 entries 4, 5, 9, 10, 13, and 14). Concerning the chemoselective C- versus H- addition during the second step, Me-, Ph- and vinyl Grignard reagents afforded the expected double alkylated products **A-3** (obviously, there is no possible *β*-hydride elimination).

Table 5. One-pot copper-catalyzed hetero double or mono1,6- addition



Entry	R^1	R^2	Products (yield %)	*E*/*Z* ratio[b]
1	*n*-Bu	Me	**A-3k** (30) [a]	/
2	*n*-Bu	*i*-Pr	**A-3r** (89)	91/9
3	*n*-Bu	*t*-Bu	/	/
4	*n*-Bu	Ph	**A-3n** (25) [a]	/
5	*n*-Bu	vinyl	**A-3s** (29)	89/11
6	*i*-Pr	Me	degrad.	/
7	*i*-Pr	*n*-Bu	**A-3r** (98)	>95/5
8	*i*-Pr	*t*-Bu	**A-3t**/ **A-4d** (52/48) [b]	/
9	*i*-Pr	Ph	**A-3o** (31)	>95/5
10	*i*-Pr	vinyl	**A-3u** (52)	>95/5
11	*t*-Bu	*n*-Bu	**A-4e** (19) [a]	>95/5
12	*t*-Bu	*i*-Pr	**A-4e** (82)	>95/5
13	*t*-Bu	Ph	**A-3p** (76)	>95/5
14	*t*-Bu	vinyl	**A-3w** (39)	>95/5

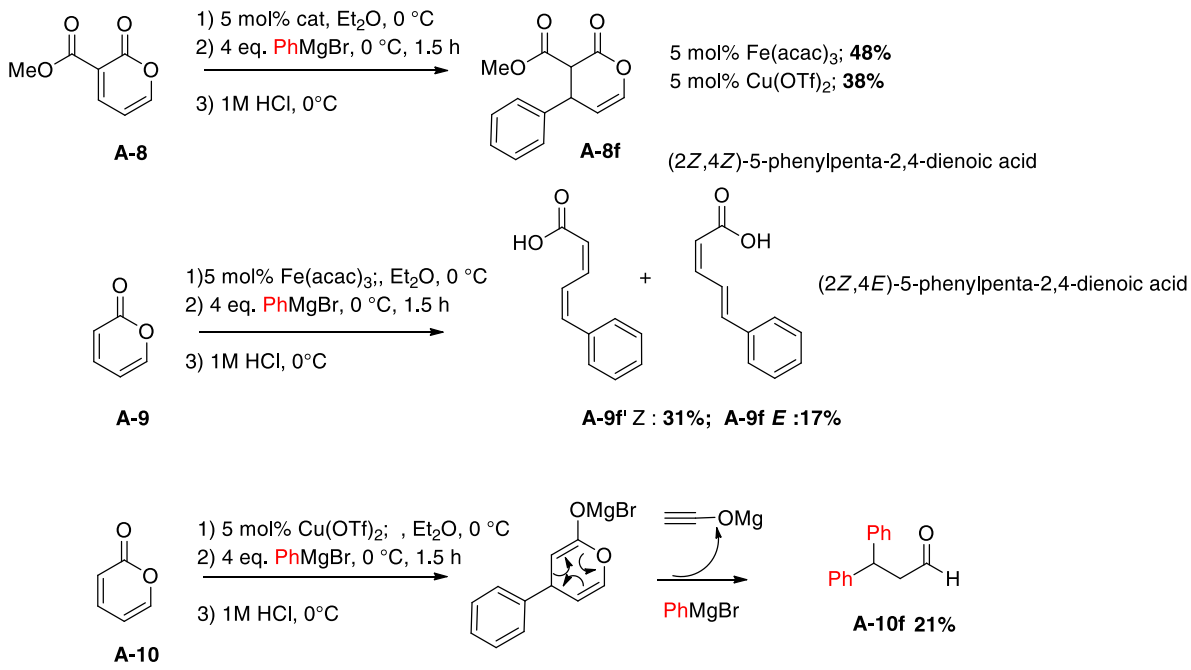
[a] Total conversion, estimated yield based on ^{1}H NMR of the crude product. [b] Determined by ^{1}H NMR of the crude product.

In the case of Grignard reagents bearing α,β -hydride, the course of the reaction changed and depended on the bulkiness of the first introduced alkyl group. Indeed,

inversion of the order of addition of *i*-PrMgBr and *t*-BuMgCl led to inversion of the chemoselectivity (Table 5, entries 8 and 12). More generally, introduction of a first bulky alkyl group favored the hydride addition except when *β*-hydride elimination of the second Grignard reagent was impossible (Table 5, entries 12 vs. 13).

2.4 The studies on other substituted α-pyrone substrates

Scheme 7 Other substituted α-pyrone as feedstocks

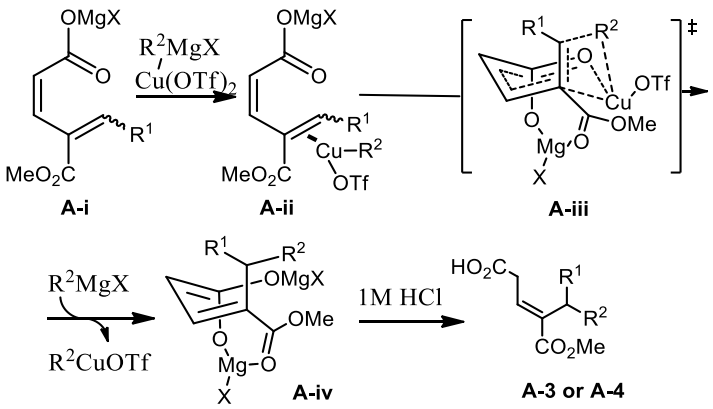


Some other substituted α-pyrones are tested (Scheme 7). However, when the Michael acceptor is extend to 3-ester α-pyrone **A-8** result in mono 1,4-addition of Grignard reagent afford product **A-8f** in 38% [with $Cu(OTf)_2$] or 48% [with $Fe(acac)_3$] respectively. Another $Fe(acac)_3$ catalyzed mono 1,6-addition approach is achieved when employing α-pyrone and phenyl Grignard reagent, giving (2*Z*,4*Z*)-5-phenylpenta-2,4-dienoic acid **A-9f'** and (2*Z*,4*E*)-5-phenylpenta-2,4-dienoic acid **A-9f** in 31% and 17% respectively. Double 1,4 addition product **A-10f** is isolated in 21% when employing $Cu(OTf)_2$ as catalyst.

2.5. Proposed mechanism for stereoselective 1,6-double addition

We proposed a mechanism for this transformation, the stereo-results of the process gave us some clues.[14] It is worth to notice, we should take into account the difference of stereo outcome observed between the reactions with or without metal catalysis (Table 1). Furthermore, the occurrence of a thermodynamic equilibrium between the stereoisomers during acid treatment of the reactions was ruled out. Indeed, even when the reaction mixture was hydrolyzed overnight (entry 6 in Table 3) with 1M HCl or when the reaction was quenched with higher concentrations of aqueous HCl, no change of the stereoisomeric ratio was observed (*E*/ *Z*=97/3). We propose the involvement of a highly chelated transition state **A-iii** in the second step of the reaction (Scheme 8). As previously demonstrated,[9] addition of the first Grignard reagent gives intermediate **A-ii** resulting in complex C by reaction with the organocopper complex (R_2CuOTf). Addition of the second Grignard reagent leads to a chair-like bicyclic transition state **A-iii** locking the overall stereoselectivity.

Scheme 8. Proposed mechanism for stereoselective addition leading to acids **A-3** and **A-4**



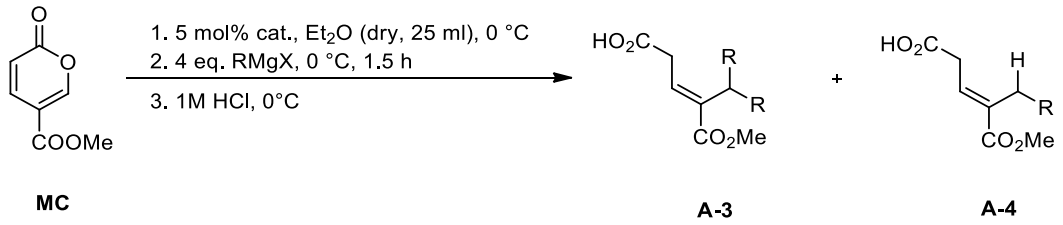
Axial positioning of the alkyl chain and equatorial positioning of the methyl ester group could be rationalized by the presence of a stabilizing electronic interaction through the formation of an 8-membered pseudo-cycle. Further transmetallation may give access to a stabilized bimetallic cyclic intermediate **A-iv**. In this stabilized intermediate, the non-planarity of the two C=C double bonds explains both the kinetic control (no change in the stereoselectivity with time) and the total regiocontrol of the reprotonation (a versus g) giving the β,γ unsaturated acids **A-3** or **A-4** as unique regioisomers.

2.6. Conclusions

In summary, we have developed a one-pot sequential double alkyl-alkyl or alkyl-hydride 1,6-addition starting from methyl coumalate. This is a valuable method for the preparation of β,γ-unsaturated carboxylic acids in a highly regio-, chemo- and stereoselective manner.[11] We also elucidated the pivotal role of the Grignard reagent as regards the stereoselectivity outcome of the reaction. The later could be rationalized by invoking a constrained chair-like transition state with the formation of a stable bimetallic intermediate.

2.7. Experimental Section

General method for homocoupling



To a solution of methyl coumalate (308 mg, 2 mmol) in dry Et_2O (25 mL) at 0 °C, under argon atmosphere, catalyst $Cu(OTf)_2$ (36 mg, 0.1 mmol) or $Fe(acac)_3$ (35

mg, 0.1 mmol) was added, followed by R^1MgX (8 mmol) dropwise addition (5 – 10 min). The mixture was stirred for 1.5 h, then quenched at 0 °C with saturated aq. NH_4Cl solution and washed with dichloromethane (2 × 20 mL). The aqueous layer, was then acidified with 1M HCl (until pH = 1 – 2) and extracted with CH_2Cl_2 (3 × 20 mL). Collected organic layers were dried over anhydrous $MgSO_4$, filtrated and evaporated under reduced pressure to afford target product.

(*E*/*Z*)-4-(methoxycarbonyl)-5-methylhex-3-enoic acid (**A-3a**)

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 6.70 (t, *J* = 7.2 Hz, 1H); 3.71 (s, 3H); 3.31 (d, *J* = 7.2 Hz, 2H); 2.86 – 2.79 (m, 1H,); 1.20 (s, 3H); 1.18 (s, 3H,). ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 176.1; 167.5; 141.1; 130.3; 51.6; 33.1; 28.1; 20.7. IR (film, cm^{-1}): ~3500-2400 (br); 2970; 2877; 1712; 1643; 1436; 1257; 1199; 1045; 985; 877; 767. HRMS (ESI-MS) calcd for $C_9H_{14}O_4Na$ [M+Na^+] = 209.0790, Found 209.0796.

(*E*/*Z*)-5-ethyl-4-(methoxycarbonyl)hept-3-enoic acid (**A-3b**)

Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): *E*-isomer: δ 6.92 (t, *J* = 7.2 Hz, 1H); 3.72 (s, 3H); 3.31 (d, *J* = 7.2 Hz, 2H); 2.37 – 2.26 (m, 1H); 1.73 – 1.56 (m, 4H); 0.81 (t, *J* = 7.5 Hz, 6H,). ^{13}C NMR (75 MHz, $CDCl_3$): *E*-isomer: δ 175.8; 167.4; 137.7; 133.1; 51.6; 43.3; 33.5; 26.4; 12.6. IR (film, cm^{-1}): ~3400-2400 (br); 1712; 1633; 1606; 1435; 1270; 1180; 1105; 864; 767; 705. HRMS (ESI-MS) calcd for $C_{11}H_{18}O_4Na$ [M+Na^+] = 237.1103, Found 237.1154.

(*E*/*Z*)-5-butyl-4-(methoxycarbonyl)non-3-enoic acid (**A-3c**)

Dark-orange oil; ^{1}H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 6.87 (t, *J* = 7.2 Hz, 1H); 3.72 (s, 3H); 3.30 (d, *J* = 7.2 Hz, 2H); 2.49 – 2.42 (m, 1H); 1.70 – 1.47 (m, 4H); 1.30 – 1.10 (m, 8H); 0.85 (t, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 176.2; 167.4; 138.4; 132.5; 51.6; 39.6; 33.5; 30.4; 22.9; 14.1. IR (film, cm-

^{1}):2954; 2858; 1710; 1635; 1435; 1257; 1209; 1145; 956; 756. HRMS (ESI-MS) calcd for $C_{15}H_{26}O_4Na$ [M+Na$^+$] = 293.1723, Found 293.1724.

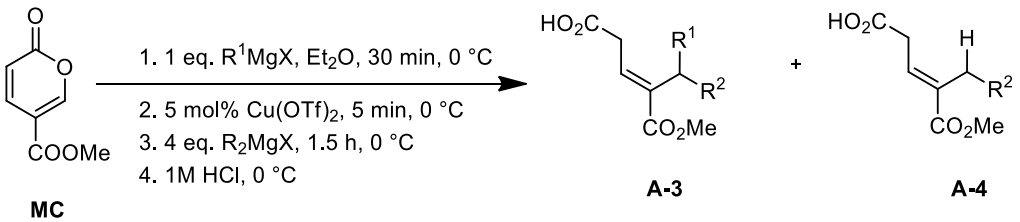
(*E*/*Z*)-4-(methoxycarbonyl)-6,6-dimethylhept-3-enoic acid (**A-4e**)

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 6.89 (t, *J* = 7.3 Hz, 1H); 3.73 (s, 3H); 3.27 (d, *J* = 7.3 Hz, 2H); 2.31 (s, 2H); 0.87 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 176.2; 169.1; 134.2; 133.3; 52.0; 39.4; 34.4; 33.2; 29.6. IR (film, cm^{-1}): ~3600-2600 (br); 2954; 2870; 1714; 1600; 1427; 1379; 1240; 1120; 843; 731. HRMS (ESI-MS) calcd for $C_{11}H_{18}O_4Li$ [M+Li$^+$] = 221.1360, Found 221.1362.

(*E*/*Z*)-4-benzhydryl-5-methoxy-5-oxopent-3-enoic acid (**A-3f**)

White-yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 7.24 – 7.06 (m, 11H); 5.56 (s, 1H); 3.60 (s, 3H); 2.84 (d, *J* = 7.1 Hz, 2H); *Z*-isomer (significant signals): δ 5.33 (s, 1H); 3.55 (s, 3H); 3.49 (d, *J* = 7.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 176.3; 167.7; 141.0; 137.0; 134.9; 128.9; 128.6; 126.7; 52.2; 49.6; 33.7; *Z*-isomer (significant signals): δ 141.4; 129.2; 53.8; 51.9. IR (film, cm^{-1}): ~3400-2700 (br); 2971; 1708; 1643; 1494; 1435; 1244; 1109; 958; 740. HRMS (ESI-MS) calcd for $C_{19}H_{18}O_4Na$ [M+Na$^+$] = 333.1097, Found 333.1097.

General method for heterocoupling



To a solution of methyl coumalate (308 mg, 2 mmol) in dry Et_2O (25 mL) at 0 °C, under argon atmosphere, R^1MgX (2.2 mmol) was dropwise added (5 – 10 min) and the mixture stirred for 0.5 h. Then $Cu(OTf)_2$ (36 mg, 0.1 mmol) was added and mixture was further stirred for 5 min. R^2MgX (8 mmol) was added dropwise

(5 min) and the solution stirred for 1.5 h at 0 °C. The reaction mixture was quenched at 0 °C with 1M HCl (until pH = 1 – 2) diluted with ethyl acetate (20 mL) and separated. The organic layer was washed once with 1M HCl (6 mL) and filtrated through celite. Collected organic layers were evaporated under reduced pressure to afford target acid.

(*E*/*Z*)-4-(methoxycarbonyl)-5-phenylhex-3-enoic acid (**A-3i**)

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 7.25 (s, 5H); 6.92 (t, *J* = 7.2 Hz, 1H); 4.17 (q, *J* = 7.2 Hz, 1H); 3.67 (s, 3H); 3.26 (dd, *J* = 18.5 Hz, *J* = 7.2 Hz, 1H); 3.16 (dd, *J* = 18.4 Hz, *J* = 7.1 Hz, 1H); 1.57 (d, *J* = 7.2 Hz, 3H); *Z*-isomer (significant signals): δ 6.14 (t, *J* = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 175.7; 167.3; 143.1; 139.7; 132.5; 128.4; 127.3; 126.2; 51.9; 37.0, 33.4; 31.0; 17.8. IR (film, cm^{-1}): ~3600-2500 (br); 2970; 1708; 1645; 1435; 1390; 1247; 1130; 1026; 991; 796; 748. HRMS (ESI-MS) calcd for $C_{14}H_{16}O_4Li$ [M+Li^+] = 255.1203, Found 255.1213.

(*E*/*Z*)-4-(methoxycarbonyl)-5-methylnon-3-enoic acid (**A-3k**)

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 6.77 (t, *J* = 7.2 Hz, 1H); 3.73 (s, 3H); 3.30 (dd, *J* = 7.2 Hz, *J* = 1.5 Hz, 2H); 2.66 – 2.57 (m, 1H); 1.70 – 1.46 (m, 2H); 1.31 – 1.23 (m, 4H); 1.16 (d, *J* = 7.0 Hz, 3H); 0.86 (t, *J* = 7.2 Hz); *Z*-isomer (significant signals): δ 6.01 (t, *J* = 6.9 Hz, 1H); 3.48 (d, *J* = 7.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 176.5; 167.9; 140.0; 131.3; 51.6; 34.6; 33.6; 33.3; 30.4; 22.8; 19.2; 14.1. IR (film, cm^{-1}): ~3500-2500 (br); 2954; 1710; 1643; 1435; 1257; 1205; 1091; 918; 808; 763. HRMS (ESI-MS) calcd for $C_{14}H_{24}O_4Li$ [M+Li^+] = 235.1522, Found 235.1521.

(*E*/*Z*)-4-(methoxycarbonyl)-5,6-dimethylhept-3-enoic acid (**A-3l**)

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 6.88 (t, *J* = 7.1 Hz, 1H); 3.73 (s, 3H); 3.29 (d, *J* = 5.8 Hz, 2H); 2.24 – 2.16 (m, 1H); 2.01 – 1.96 (m, 1H); 1.16

(d, J = 6.8 Hz, 3H); 0.96 (d, J = 6.4 Hz, 3H); 0.75 (d, J = 6.5 Hz, 3H); *Z*-isomer (significant signals): δ 5.97 (t, J = 6.7 Hz, 1H); 3.76 (s, 3H); 3.29 (d, J = 7.9 Hz, 2H); 1.05 (d, J = 6.8 Hz, 3H); 0.96 (d, J = 6.4 Hz, 3H); 0.83 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 176.4; 167.9; 140.0; 131.5; 51.6; 41.2; 33.5; 31.2; 21.9; 21.3; 17.5. IR (film, cm^{-1}): ~3600-2500 (br); 2960; 2872, 1710; 1643; 1435; 1246; 1199; 1141; 1083; 1020; 862; 759. HRMS (ESI-MS) calcd for $C_{11}H_{18}O_4Na$ [M+Na$^+$] = 237.1097, Found 237.1092.

(*E*/*Z*)-4-(methoxycarbonyl)-5-methylhepta-3,6-dienoic acid (**A-3m**)

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 6.84 (t, J = 7.3 Hz, 1H); 6.00 (ddd, J = 17.2 Hz, J = 10.3 Hz, J = 5.9 Hz, 1H); 5.05 – 5.00 (m, 2H); 3.73 (s, 3H); 3.48 – 3.44 (m, 1H); 3.37 (dd, J = 18.4 Hz, J = 7.4 Hz, 1H); 3.30 (dd, J = 18.4 Hz, J = 7.2 Hz, 1H); 1.27 (d, J = 7.1 Hz, 3H); *Z*-isomer (significant signals): δ 6.08 (td, J = 7.3 Hz, J = 7.1 Hz, J = 1.1 Hz, 1H); 3.76 (s, 3H); 3.52 (dd, J = 6.2 Hz, J = 5.4 Hz, 2H); 1.18 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 176.4; 167.3; 140.7; 138.4; 132.3; 114.1; 51.9; 36.6; 33.4; 18.3. IR (film, cm^{-1}): ~3600-2400 (br); 2972; 2883; 1708; 1641; 1435; 1246; 1195; 1163; 1082; 995; 916; 852; 763. HRMS (ESI-MS) calcd for $C_{10}H_{14}O_4Na$ [M+Na$^+$] = 221.0784, Found 221.0793.

(*E*/*Z*)-4-(methoxycarbonyl)-5-phenylnon-3-enoic acid (**A-3n**)

Orange-yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 7.27 – 7.21 (m, 5H); 6.92 (t, J = 7.2 Hz, 1H); 3.89 (t, J = 8.2 Hz, 1H); 3.65 (s, 3H); 3.36 – 3.26 (m, 2H,); 2.09 – 2.01 (m, 2H); 1.36 – 1.20 (m, 4H); 0.87 (t, J = 7.2 Hz); *Z*-isomer (significant signals): δ 7.27 – 7.21 (m, 5H); 6.16 (td, J = 7.1 Hz, J = 1.2 Hz 1H); 3.71 (s, 3H); 0.83 (t, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 176.1; 167.3; 142.5; 138.3; 132.9; 128.3; 127.9; 126.3; 51.9; 43.6; 33.6; 31.8; 30.4; 22.9; 14.1. IR (film, cm^{-1}): ~3600-2700 (br); 2954; 1710; 1645; 1494; 1435; 1251; 1099; 956;

833; 748. HRMS (ESI-MS) calcd for $C_{17}H_{22}O_4Na$ [M+Na$^+$] = 313.1410, Found 313.1407.

(*E*/*Z*)-4-(methoxycarbonyl)-6-methyl-5-phenylhept-3-enoic acid (**A-3o**)

Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 7.35 – 7.24 (m, 5H); 6.86 (t, *J* = 7.1 Hz, 1H); 3.70 (s, 3H); 3.44 (t, *J* = 7.2 Hz, 2H); 3.33 (d, *J* = 4.6 Hz, 1H); 2.88 – 2.78 (m, 1H); 0.92 (d, *J* = 6.6 Hz, 3H); 0.84 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 176.2; 167.3; 141.8; 138.1; 132.6; 129.0; 128.4; 126.5; 53.5; 51.8; 32.7; 29.1; 22.2; 21.6. IR (film, cm^{-1}): ~3600-2500 (br); 2972; 2873; 1712; 1651; 1436; 1249; 1085; 877; 800; 748. HRMS (ESI-MS) calcd for $C_{16}H_{20}O_4Na$ [M+Na$^+$] = 299.1254, Found 299.1252.

(*E*/*Z*)-4-(methoxycarbonyl)-6,6-dimethyl-5-phenylhept-3-enoic acid (**A-3p**)

Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 7.48 (d, *J* = 7.2 Hz, 2H); 7.29 – 7.19 (m, 3H); 6.70 (t, *J* = 7.0 Hz, 1H); 3.76 (s, 3H); 3.74 (s, 1H); 3.28 (dd, *J* = 16.9 Hz, *J* = 5.2 Hz, 1H); 3.19 (dd, *J* = 16.7 Hz, *J* = 5.0 Hz, 1H); 1.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 176.2; 169.3; 140.8; 138.5; 133.0; 130.5; 128.0; 126.4; 56.0; 52.1; 35.2; 33.5; 29.5. IR (film, cm^{-1}): 2974; 2868; 1712; 1634; 1435; 1249;1209; 1170; 1112; 746; 700. HRMS (ESI-MS) calcd for $C_{17}H_{22}O_4Li$ [M+Li$^+$] = 297.1673, Found 297.1675.

(*E*/*Z*)-4-(methoxycarbonyl)-5-phenylhepta-3,6-dienoic acid (**A-3q**)

Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 7.29 – 7.20 (m, 5H); 7.06 (t, *J* = 7.2 Hz, 1H); 6.31 (ddd, *J* = 17.4 Hz, *J* = 10.1 Hz, *J* = 7.5 Hz, 1H); 5.25 (dt, *J* = 10.1 Hz, *J* = 1.2 Hz, 1H); 5.16 (dt, *J* = 17.1 Hz, *J* = 1.3 Hz, 1H); 4.80 (d, *J* = 7.5 Hz, 1H); 3.69 (s, 3H); 3.29 (dd, *J* = 18.7, *J* = 7.4 Hz, 1H); 3.18 (dd, *J* = 18.7, *J* = 7.0 Hz, 1H); *Z*-isomer (significant signals): δ 7.29 – 7.20 (m, 5H); 6.13 (td, *J* = 7.3 Hz, *J* = 1.3 Hz, 1H); 5.20 (dt, *J* = 10.2 Hz, *J* = 1.3 Hz, 1H); 4.96 (dt, *J* = 17.2 Hz,

J = 1.4 Hz, 1H); 4.63 (d, *J* = 6.9 Hz, 1H); 3.65 (s, 3H); 3.60 (d, *J* = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 175.6; 167.1; 141.1; 137.3; 136.6; 134.2; 128.5; 127.4; 126.6; 117.5; 52.1; 47.5; 33.7. IR (film, cm^{-1}): ~3600-2500 (br); 2951; 1708; 1643; 1435; 1435; 1242; 1116; 1045; 921; 873; 746.HRMS (ESI-MS) calcd for $C_{15}H_{16}O_4Na$ [M+Na^+] = 283.0941, Found 283.0951.

(*E*/*Z*)-5-isopropyl-4-(methoxycarbonyl)non-3-enoic acid (**A-3r**)

Orange-yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 6.92 (t, *J* = 6.9 Hz, 1H); 3.72 (s, 3H); 3.29 (d, *J* = 6.9 Hz, 2H); 2.10 – 1.92 (m, 2H); 1.65 – 1.59 (m, 2H); 1.28 – 1.21 (m, 4H); 0.97 (d, *J* = 6.2 Hz, 3H); 0.84 (t, *J* = 7.3 Hz, 3H); 0.73 (d, *J* = 6.4 Hz, 3H); *Z*-isomer (significant signals): δ 5.95 (t, *J* = 7.1 Hz, 1H); 3.75 (s, 3H); 3.50 (d, *J* = 4.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 176.5; 167.9; 137.7; 133.2; 130.4; 51.7; 47.1; 30.8; 30.7; 30.6; 23.0; 21.9; 21.7; 14.1. IR (film, cm^{-1}): ~3600-2400 (br); 2956; 2870; 1712; 1640; 1436; 1253; 1141; 1097; 1013; 761. HRMS (ESI-MS) calcd for $C_{14}H_{24}O_4Na$ [M+Na^+] = 279.1567, Found 279.1558.

(*E*/*Z*)-4-(methoxycarbonyl)-5-vinylnon-3-enoic acid (**A-3s**)

Orange-yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 9.69 (bs, 1H); 6.86 (t, *J* = 7.2 Hz, 1H); 5.99 (ddd, *J* = 13.7 Hz, *J* = 7.2 Hz, *J* = 4.1 Hz, 1H); 4.99 (dt, *J* = 6.4 Hz, *J* = 1.4 Hz, 1H); 4.96 (d, *J* = 1.6 Hz, 1H); 3.71 (s, 3H); 3.31 (dd, *J* = 7.2 Hz, *J* = 0.8 Hz, 2H); 3.24 – 3.17 (m, 1H; 1.69 – 1.61 (m, 2H); 1.30 – 1.20 (m, 4H); 0.84 (t, *J* = 7.1 Hz, 3H) ; *Z*-isomer (significant signals): δ 6.06 (td, *J* = 7.0 Hz, *J* = 0.8 Hz, 1H); 3.74 (s, 3H); 3.51 (d, *J* = 7.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 176.4; 167.2; 139.8; 137.4; 132.6; 114.9; 51.8; 43.3; 32.6; 30.0; 22.6; 14.0. IR (film, cm^{-1}): ~3600-2700 (br); 2954; 2860; 1710; 1637; 1435; 1253; 1168; 1047; 916; 825; 763. HRMS (ESI-MS) calcd for $C_{13}H_{20}O_4Na$ [M+Na^+] = 263.1254, Found 263.1251.

(*E*/*Z*)-5-isopropyl-4-(methoxycarbonyl)hepta-3,6-dienoic acid (**A-3u**)

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 6.89 (t, *J* = 7.2 Hz, 1H); 6.05 (ddd, *J* = 16.9 Hz, *J* = 10.4 Hz, *J* = 8.6 Hz, 1H); 5.01 – 4.96 (m, 2H); 3.74 (s, 3H); 3.33 (d, *J* = 7.2 Hz, 2H); 2.76 – 2.71 (m, 1H); 2.19 – 2.11 (m, 1H); 0.92 (d, *J* = 6.6 Hz, 3H); 0.77 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 176.0; 167.1; 139.4; 137.4; 132.5; 116.0; 52.3; 51.8; 33.5; 29.6; 21.7; 21.1. IR (film, cm^{-1}): ~3600-2700 (br); 2962; 1712; 1639 1465; 1384; 1236; 1103; 916 792; 765. HRMS (ESI-MS) calcd for $C_{12}H_{18}O_4Na$ [M+Na^+] = 249.1094, Found 249.1097.

(*E*/*Z*)-5-(2,2-dimethylpropylidene)-6,6-dimethyl-5,6-dihydro-2H-pyran-2-one (**A-4j**)

Yellow-brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 10.1 Hz, *J* = 1.1 Hz, 1H); 5.91 (dd, *J* = 10.0 Hz, *J* = 1.8 Hz, 1H); 5.82 (dd, *J* = 1.7 Hz, *J* = 1.2 Hz, 1H); 1.55 (s, 6H); 1.21 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.15; 144.3; 138.3; 133.7; 117.6; 84.0; 33.8; 31.7; 29.0; 25.6. IR (film, cm^{-1}):2966; 1712; 1633; 1463; 1365; 1350; 1296; 1166; 1118; 1051; 991; 827; 790. HRMS (ESI-MS) calcd for $C_{12}H_{18}O_2Na$ [M+Na^+] = 217.1199, Found 217.1198.

(*E*/*Z*)-5-(tert-butyl)-4-(methoxycarbonyl)hepta-3,6-dienoic acid (**A-3w**)

Dark-orange oil; ^{1}H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 6.82 (t, *J* = 7.2 Hz, 1H); 6.33 (ddd, *J* = 17.0 Hz, *J* = 10.0 Hz, *J* = 9.2 Hz, 1H); 5.06 – 5.03 (m, 2H); 3.73 (s, 3H); 3.34 (dd, *J* = 7.2 Hz, *J* = 2.4 Hz, 2H); 3.13 (d, *J* = 8.7 Hz, 1H); 0.89 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 175.8; 168.4; 137.7; 137.3; 132.6; 116.6; 54.2; 52.0; 34.8; 34.2; 28.5. IR (film, cm^{-1}): ~3600-2800 (br); 2956; 1714; 1641; 1435; 1367; 1246; 1114; 916; 794. HRMS (ESI-MS) calcd for $C_{13}H_{20}O_4Na$ [M+Na^+] = 263.1254, Found 263.1256.

Methyl 2-oxo-4-phenyl-3,4-dihydro-2H-pyran-3-carboxylate (**A-8f**)

Yellow oil; 48%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 –7.12 (m, 5H), 6.59 (dd, J = 6.0, 1.9 Hz, 1H), 5.34 (dd, J = 6.0, 3.9 Hz, 1H), 4.15 (ddd, J = 8.3, 3.9, 1.9 Hz, 1H), 3.64 (s, 1H), 3.63 (s, 3H), 3.62 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 163.8, 141.3, 139.0, 129.2(2C), 128.0, 127.3(2C), 108.8, 54.1, 53.0, 40.3. IR (film, cm^{-1}):2922; 1768; 1737; 1654; 1454; 1435; 1340; 1219; 1130; 995; 910; 748. HRMS (ESI-MS) calcd for $C_{13}H_{12}O_4Na$ [M+Na^+] = 255.0628, Found 255.0621.

(2*Z*,4*E*)-5-phenylpenta-2,4-dienoic acid (**A-9f**)

White solid; 31%, m.p. 131-135ºC, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 – 7.82 (m, 1H), 7.52 – 7.40 (m, 2H), 7.37 – 7.19 (m, 4H), 6.91 – 6.68 (m, 2H), 5.68 (d, J = 10.9 Hz, 1H). ^{13}C NMR (100 MHz, CDCl3) δ 172.2, 147.2, 142.5, 136.2, 129.3, 128.8(2C), 127.7(2C), 124.9, 116.6.

(2*Z*,4*Z*)-5-phenylpenta-2,4-dienoic acid (**A-9f'**)

White solid; 17%, m.p. 146-149ºC ^{1}H NMR (400 MHz, MeOD) δ 7.42 (dd, J = 5.2, 3.4 Hz, 2H), 7.39 – 7.29 (m, 1H), 7.29 – 7.16 (m, 3H), 6.94 – 6.82 (m, 2H), 5.90 (d, J = 15.2 Hz, 1H). ^{13}C NMR (100 MHz, MeOD) δ 170.6, 146.7, 141.8, 137.6, 130.1, 129.9(2C), 128.4(2C), 127.4, 122.4.

3,3-diphenylpropanal (**A-10f**)

Yellow oil; 21% ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 7.36 – 7.03 (m, 10H), 4.55 (t, J = 7.8 Hz, 1H), 3.09 (dd, J = 7.8, 1.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.0, 143.2(2C), 128.8(4C), 127.8(4C), 126.7(2C), 49.4, 4

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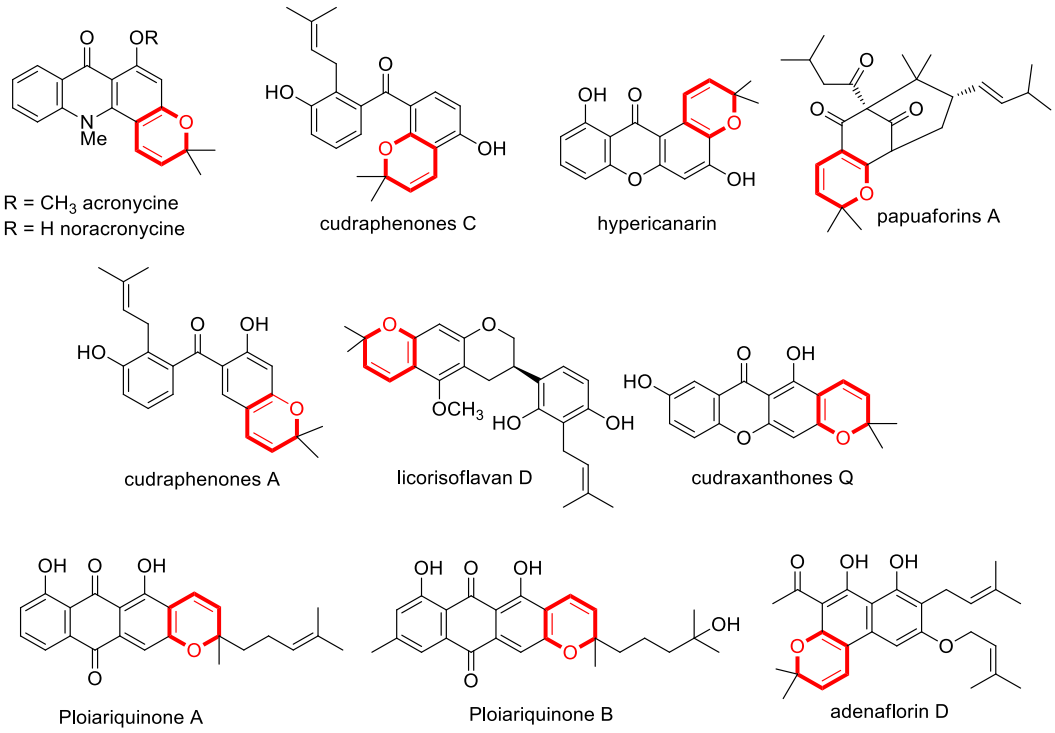
Chapter 3. Preparation of Substituted 2*H*-Pyrans *via* a Cascade Reaction from Methyl Coumalate and Activated Methylene Nucleophiles.

3.1. Introduction of the project

The 2*H*-pyran core is widely encountered in natural products[1] and is often used as a key structure core for synthesizing natural products.[2]

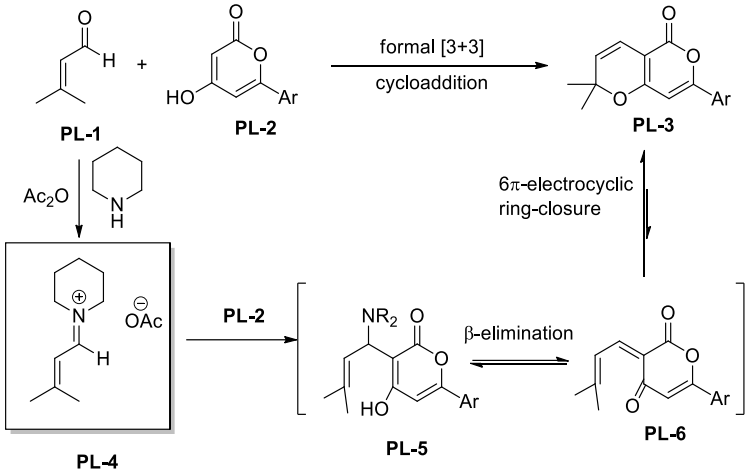
Figure 1 Natural products that contain 2*H*-pyran



Since 2*H*-pyrans are in equilibrium with 1-oxatrienes by a 6π electrocyclic process, 1-oxatrienes generally afford an entry into the 2*H*-pyran skeleton. The 6π disrotatory process has been already discussed at different levels of theory.[3] The equilibrium between 2*H*-pyrans and 1-oxatrienes depends on many factors such as the presence of electron-withdrawing substituents or increased steric interactions. The most common entry into the 1-oxatriene core is the Knoevenagel reaction (more specifically for oxatriene, condensation between an enal and a cyclic 1,3-dicarbonyl compound). From a synthetic point of view, the tandem Knoevenagel / 6π-electrocyclization (Figure 1) can be considered as a formal [3+3] cycloaddition.[4,5] Conjugated 1-oxatrienes can also be obtained through a Claisen rearrangement of propargyl vinyl ethers[6] or cycloisomerization of diynols.[7] Other

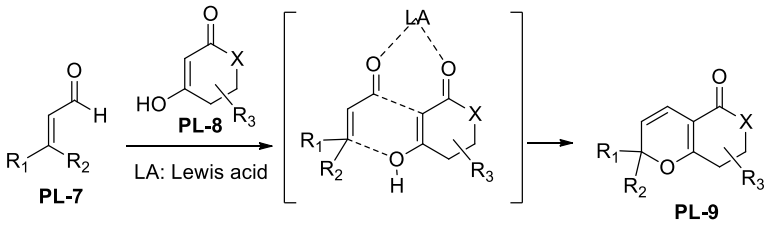
strategies towards 2*H*-pyrans that do not involve the "1-oxatriene pathway" but rather rely on formal [4+2]- or [3+3]-cycloaddition have been reported.[8,9]

Scheme 1 Knoevenagel condensation and 6π electrocyclic ring closure (ERC) toward 2*H*-pyran



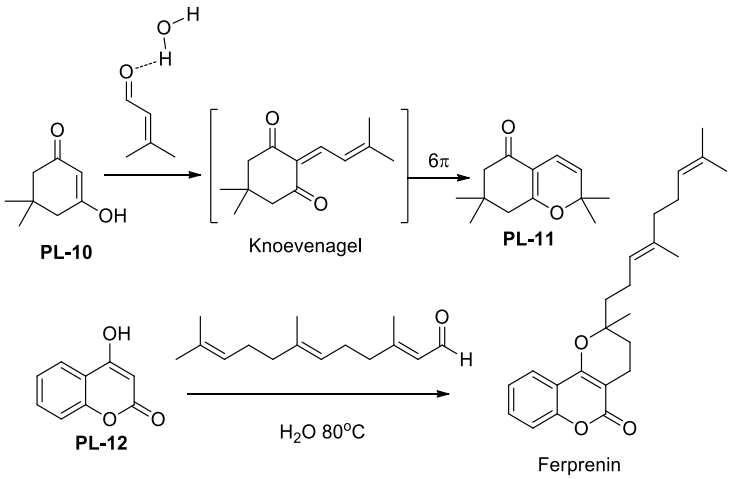
Shen et al described a formal [3 + 3] cycloaddition strategy that is synthetically useful for the 2*H*-pyranyl heterocycles construction (Scheme 1). [4] They showed unsaturated iminium salts are useful in controlling competing reaction pathways to give exclusively 2*H*-pyrans from 1,3-diketones. The mechanism of this reaction involves a sequential Knoevenagel condensation and 6π electrocyclic ring-closure.

Scheme 2 Lewis acid catalyzed oxa-[3 + 3] cycloaddition



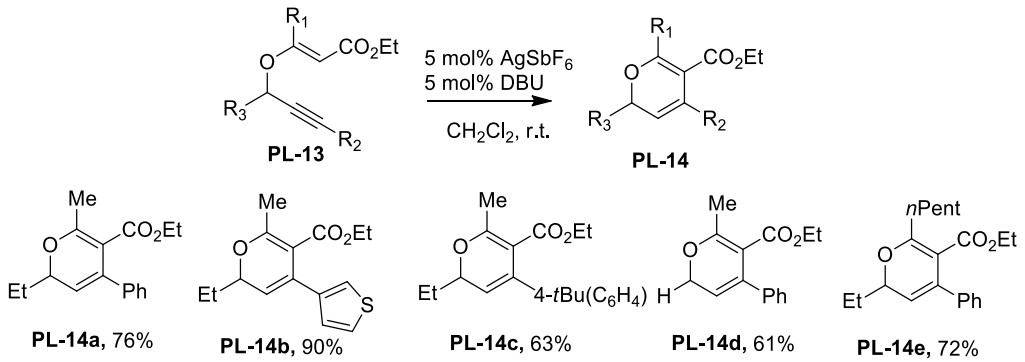
Later on, Hsung's group described a similar process which is catalyzed by Lewis acid *via* formal oxa-[3 + 3] cycloaddition of unsaturated aldehydes with 6-methyl-4-hydroxy-2-pyrone, 1,3-diketones, and vinylogous silyl esters (Scheme 2).[4]

Scheme 3 Sustainable synthesis of pyrans and application to natural product



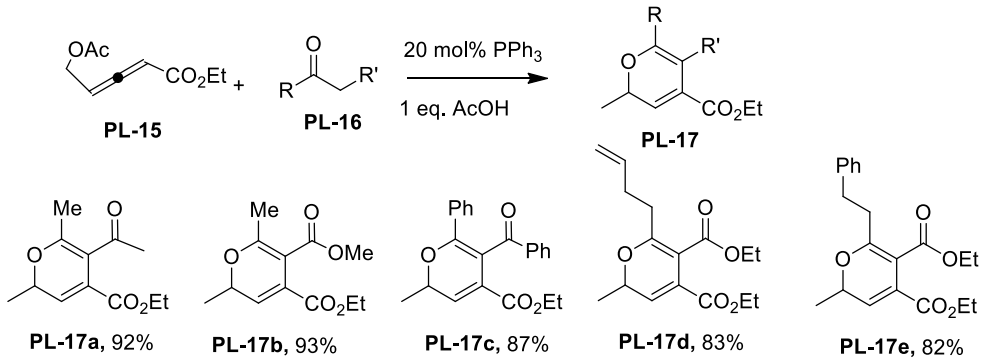
Lee's group have developed an efficient and sustainable method for the synthesis of a variety of pyrans starting from cyclic 1,3-dicarbonyls and *α,β*-unsaturated aldehydes in water. They successfully applied this methodology to the synthesis of biologically interesting natural product (Scheme 3).[4]

Scheme 4 Ag (I)-catalyzed Claisen rearrangement reactions towards 2*H*-pyrans



Kirsch's group reported the synthesis of highly substituted 2*H*-pyrans from easily accessible propargyl vinyl ethers. The reaction runs in one-pot sequence which triggered *via* a Ag(I)-catalyzed propargyl- Claisen rearrangement, followed by a base-promoted isomerization form oxatriene, and 6π-electrocyclization, giving the formation of stable 2*H*-pyrans in moderate to excellent yields (Scheme 4).

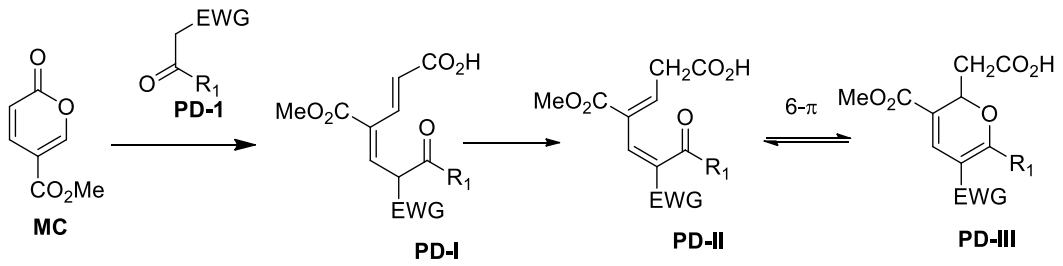
Scheme 5 Phosphine catalyzed formal (3 + 3) cycloaddition towards 2*H*-pyrans[4]



Hu *et al*. reported a phosphine catalyzed (3 + 3) cycloaddition between allenoate and ketones as bisnucleophiles; these annulations are achieved under acidic reaction conditions. The methodology provides easy access to 2H-pyrans (Scheme 5).

We have recently demonstrated that Grignard reagents add regioselectively on the C6 of **MC** (see chapter 1).[10] Our hypothesis was that **MC** should react with the same regiochemistry with stabilized nucleophiles **PD-1** like keto-esters or di-ketones. After the 1.6-Michael addition and 6π-electrocyclic ring opening, the intermediate **PD-I** could evolve in different manner. Be hydrolyzed or give a 1,5 H shift reaction offering an entry to 1-oxatrienes **PD-II** (Scheme 6). This highly strained 1-oxatriene bearing two electron-withdrawing groups should through a final 6π-electrocyclization, deliver the 2*H*-pyran systems **PD-III**.

Scheme 6 Our hypothesis of synthesizing 2*H*-pyran from MC



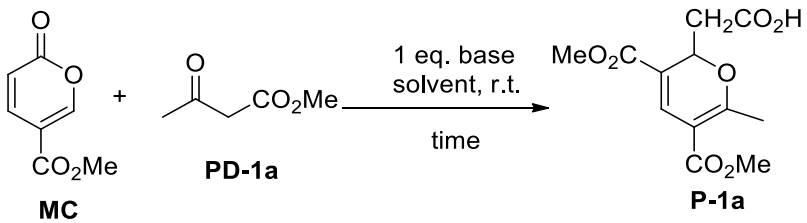
This hypothesis was also supported by a report of the literature[11] in which the aceto-phenylsulfone reacted with **MC** at high temperature to give the

corresponding decarboxylated 2*H*-pyran in a moderate 67% yield. In that publication, only one example was described and we decided to reinvestigate the reaction conditions and to study the scope and limitations.

3.2. Optimization of the reaction conditions for 2*H*pyran synthesis

We started our investigation with methyl acetoacetate (MAA) as a model nucleophile (Table 1). A stoichiometric amount of cesium carbonate in DCM gave compound **P-1a** with moderate yield (60%) (Table 1, entry 1).

Table 1 Optimization of the Reaction Conditions for compound **P-1a**[a]



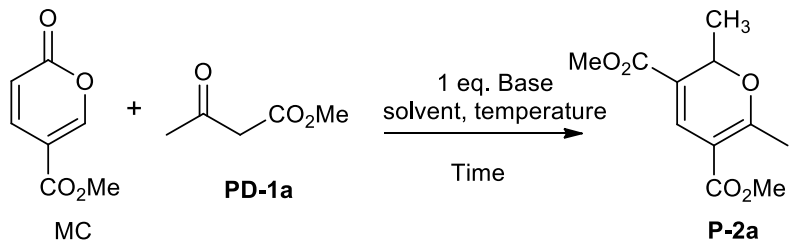
Entry	Base	Solvent	Time (h)	Products (yield %)
1	Cs_2CO_3	DCM	3	**1a** (60%)
2	Cs_2CO_3	EtOH	3	**1a** (80%)
3	Na_2CO_3	EtOH	1	**1a** (90%)
4	Et_3N	EtOH	3	**1a** (46%)[b]
5	Et_3N	DCM	3	**1a** (55%)

[a] Reaction conditions: All reactions were performed with MC (1 mmol) and MAA (1 mmol), in 5 mL of organic solvent. [b] 54% of MC was observed in the crude reaction mixture, determined by 1H NMR.

2*H*-Pyran **P-1a** was obtained with better yield when the reaction was performed in EtOH with either cesium or sodium carbonate (entries 2-3). At rt NEt_3 gave moderate conversions and yields using either EtOH or DCM as solvents (entries 4-5). Interestingly, after prolonged reaction time, some traces of the

decarboxylated 2*H*-pyran **P-2a** were observed. In order to favor the complete decarboxylation, the reaction mixture was heated to reflux for 15h in DCM. Product **P-2a** was thus isolated in good yield (87%, Table 2, entry 1). Changing DCM for toluene, EtOH or THF did not improve the yield of **P-2a** (Table 2, entries 2-4) and the use of DBU instead of NEt_3 in DCM gave only modest results (Table 2, entry 5). Interestingly, the reaction was successfully tested with a catalytic amount of Et_3N. Complete conversion of **MC** into the expected decarboxylated 2*H*-pyran **P-2a** was reached in 48 h with 86% yield (Table 2, entry 7). A solvent-free reaction led to the formation of the expected compound **P-2a**, however in a moderate 60% yield after 15 hours at 50°C (Table 2, entry 8).

Table 2 Optimization of the Reaction Conditions for compound **P-2a**[a]



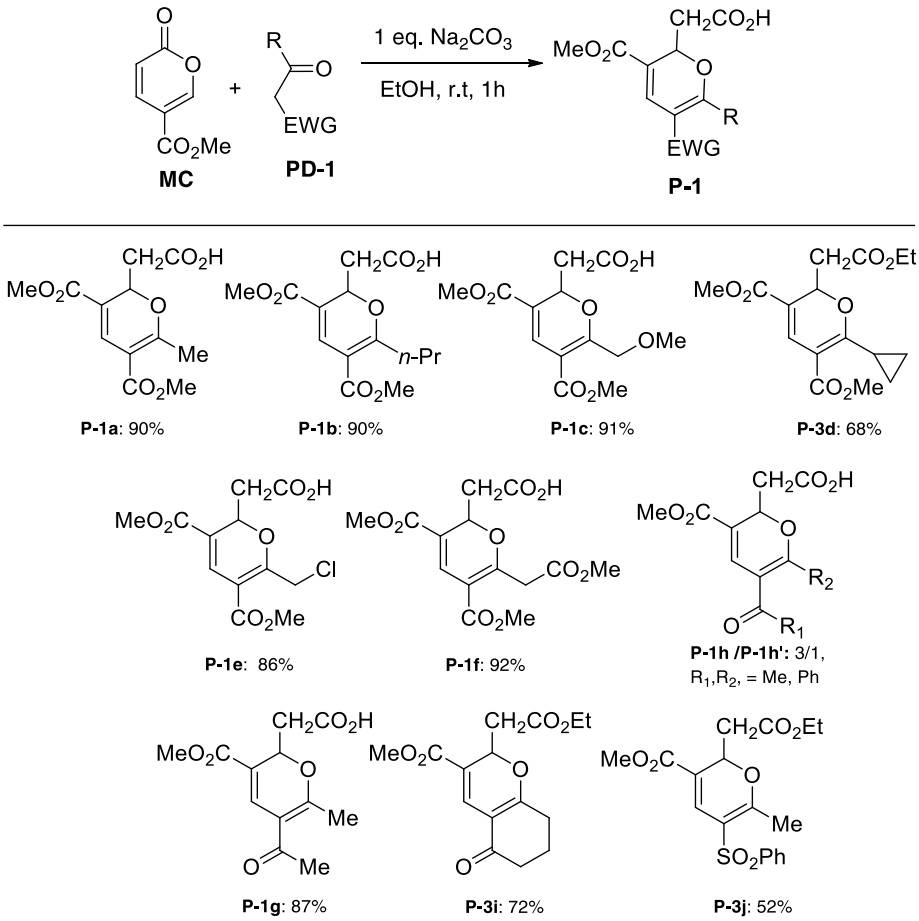
Entry	Base	Solvent	Temp	Time (h)	Products (yield)
1	Et_3N	DCM	reflux	15	**P-2a** (87%)
2	Et_3N	EtOH	reflux	15	**P-2a** (58%)
3	Et_3N	THF	reflux	6	**P-2a** (54%)[b]
4	Et_3N	Toluene	reflux	6	**P-2a** (80%)
5	DBU	DCM	reflux	1	**P-2a** (32%)[b]
6	Et_3N[c]	DCM	reflux	24	**P-2a** (77%)[d]
7	Et_3N[c]	DCM	reflux	48	**P-2a** (86%)
8	Et_3N	Neat	50°C	15	**P-2a** (60%)

[a] Reaction conditions: All reactions were performed with MC (1 mmol) and PD-1a (1 mmol), in 5 mL of organic solvent. [b] Degradation was observed. [c] 20 mol % of Et_3N. [d] 18% of MC was observed in the crude reaction mixture, determined by ^1H NMR

3.3. Substrate scope for preparation of 2*H*-pyran

Having in hand the best conditions to synthesize either 2*H*-pyran **P-1a** (Table 1, entry 3) or its corresponding decarboxylated analogue **P-2a** (Table 2, entry 1), we explored the scope and limitations of these reactions.

Table 3. Substrate scope for preparation of compound **P-1**.

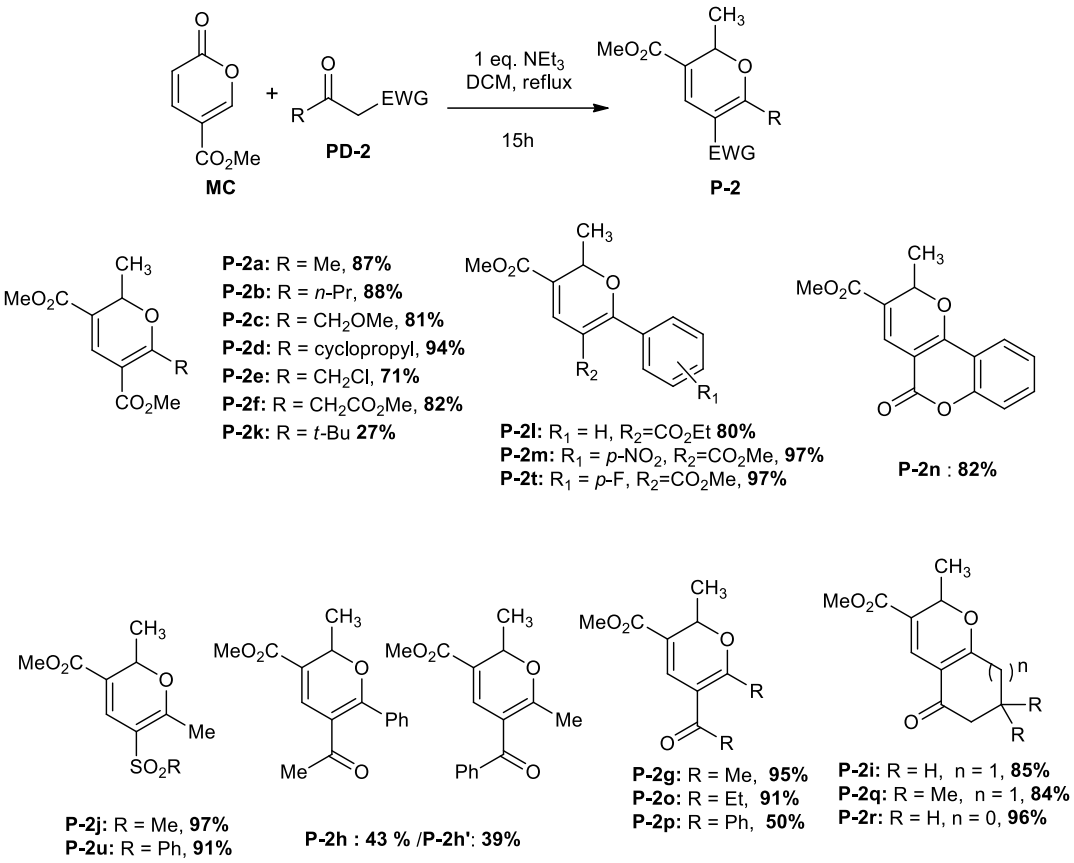


The data in Table 3 illustrate the reaction with Na_2CO_3 in EtOH for 1h at room temperature. 1,3-Ketoesters gave the expected 2*H*-pyrans **P-1a, P-1b, P-1c, P-1e, P-1f** in yields ranging from 86% to 92%. Diverse functions such as methylether (**P-1c**), cyclopropyl (**P-1d**), halogen (**P-1e**) or a second ester function (**P-1f**) gave the expected products whereas 1,3-Diketones gave moderate to good yields. For example, the symmetrical 1,3-pentanedione gave the 2*H*-pyran **P-1g** in 87% yield whereas the non-symmetrical acetoacetophenone gave the 2*H*-pyrans **P-1h** and **P-**

1h' in a 3/1 mixture, which can't be purified by flash chromatography, reflecting the two diastereoisomeric 1-oxatriene intermediates **P-5h** (EWG=COPh R=Me) and **P-5h'** (EWG=COMe and R=Ph). The cyclic 1,3-cyclohexadione delivered the corresponding 2*H*-pyran **P-1i** in a moderate yield (46%) whereas ketosulfone led to the 2*H*-pyrans **P-1j** in 52% yield. The purifications of some of 2*H*-pyrans **P-1** were not satisfying. We surmised that direct esterification of the carboxylic acid function following Steglich procedure[12] could solve the problem. Thus, compounds **P-3d, P-3i, P-3j** were efficiently prepared in a one-pot manner in 15h with yield from 68% to 78% (Table 3).

We next examined the outcome of the cascade reactions in the presence of NEt_3 in DCM under reflux. Under these conditions, more than 20 examples of 2*H*-pyrans **P-2** were synthesized. Results are reported in Table 4. The decarboxylated 2*H*-pyrans **P-2(a-f)** were prepared from the 1,3-ketoesters in excellent yields. Again, ether, halogen or ester moieties were tolerated in this cascade reaction. Satisfyingly and in contrast to the first conditions, the crowded 2*H*-pyran **P-2k** and the aromatic 2*H*-pyrans **P-2l, P-2m,** were synthesized with up to 97% yield. The 4-hydroxycoumarin gave the expected tricyclic product **P-2n** in 82% yield. In these conditions, β-oxosulfones led to 2*H*-pyrans **P-2j, P-2u** in almost quantitative yield.[11]

Table 4. Substrate scope toward compound **P-2**.



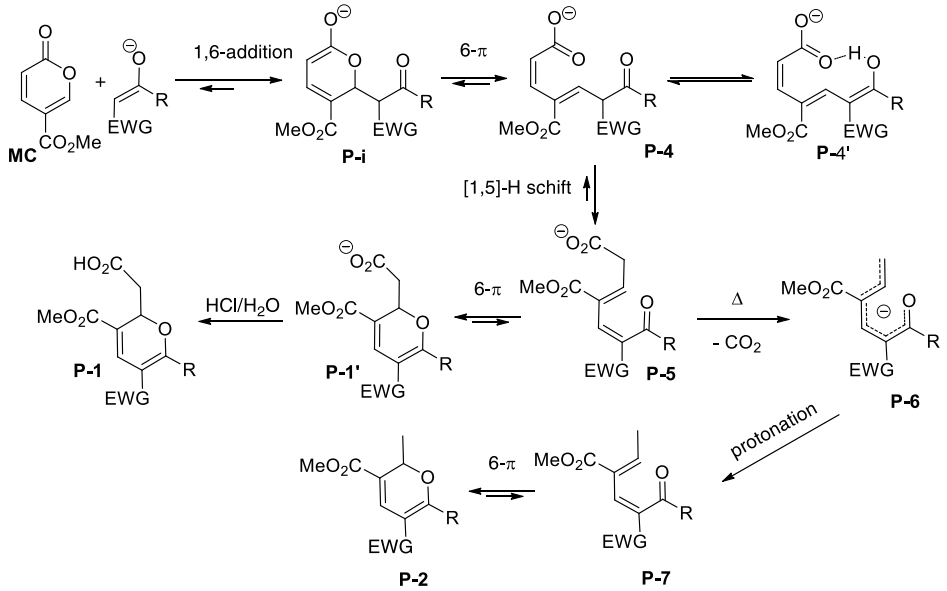
Various 1.3-diketones could also lead to the expected 2*H*-Pyrans in moderate to excellent yields. Even aromatic diketones, which were unproductive at rt produced the expected pyrans **P-2p** albeit in moderate yields. Again, aceto-acetophenone gave a 1.1/1 mixture of isomers **P-2h** and **P-2h'** in good yield (82%). This result seems to indicate that there is no stereoselectivity in the proton shift step. Finally 2*H*-pyrans **P-2i, P-2q, P-2r** resulting from the addition of 5- and 6-membered cyclic diketones were isolated in good yields (84-96 %).

3.4. Proposed unified mechanism

Our proposal for the mechanism of this cascade reaction might involve a 1,6-addition of the enolate on **MC** followed by a 6π-electrocyclic ring opening[13] leading to the dienoic carboxylates **P-4** (Scheme 7). The key [1,5]-H shift could occur through a deprotonation-reprotonation sequence. We ruled out a [1,5]-H

sigmatropic shift due to high steric constraint in the required planar transition state due to the *cis,cis* configuration of the dienoic system **P-4**.[14] A further rapid 6π electrocyclization would lead to the 2*H*-pyran **P-1'** from oxatriene **P-5**. This last electrocyclic reaction seemed to be a rapid process since oxatriene intermediate **P-5** was never detected. This observation suggests that even during the formation of 2*H*-pyran **P-2,** the mechanism involves intermediate **P-1'**. This proposition is confirmed by the fact that 2*H*-pyran **P-1a**, treated with NEt_3 in DCM delivered, after 15h at reflux, the corresponding decarboxylated 2*H*-pyran **P-2a** in 95 %. The mechanistic pathway to 2*H*-pyrans **P-2** implies that decarboxylation may operate on the transient 1-oxatriene **P-5** giving the stabilized enolate **P-6** which, after reprotonation from ammonium, gives the oxatriene **P-7** and regenerates NEt_3. The mechanistic pathway ends with the rapid 6π electrocyclization delivering the stable 2*H*-pyran **P-2**.

Scheme 7. Proposed unified mechanism for cascade reaction leading to *2H*-pyrans **P-1** and **P-2**.



A possible rationale for the modest yields obtained with aromatic di-ketones at rt could be explained by steric factors. The planarity of the substituents of the double

bonds (EWG=COAr and R=Ar) in the 6π transition state is required for the transformation of 1-oxatriene **P-5** to 2*H*-pyran **P-1'**. Since the 6π electrocyclization was inhibited and all the steps are reversible, starting materials were recovered accompanied by complex mixture of by-products. In contrast, by heating the reaction mixture, intermediate **P-5** was irreversibly converted to enolate **P-6** which after reprotonation and 6π electrocyclization gave the stable 2*H*-pyran **P-2**.

3.5. Conclusion

In summary, we described here a rapid and an efficient synthesis of more than thirty stable tetrasubstituted 2*H*-pyrans **P-1**, **P-2** and **P-3**. The reactions to **P-1** or **P-2** proceed through a cascade 1,6-Michael / 6π electrocyclic ring opening / [1,5]-H transfer / (decarboxylation) / 6π electrocyclization reaction. In addition to the broad substrate scope, this methodology has the advantage of using readily available starting materials and mild conditions.

3.6. Experimental section

General. All reactions were carried out under argon atmosphere with magnetic stirring in dry and distillated solvents. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz for ^{1}H nuclei, 100 MHz for ^{13}C nuclei. Chemical shifts are reported in δ units, parts per million (ppm) using, for ^{1}H and ^{13}C, solvent residual peak as internal standard references: chloroform (7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR). Coupling constants (*J*) are given in Hz, multiplicity are abbreviated as: s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublets of doublets), t (triplet), m (multiplet). High resolution mass spectra (HR-MS) were recorded on a LTQ-Orbitrap Mass Spectrometer [Thermo Scientific]. IR: Shimadzu IRAffinity-1CE spectrometer, wavenumbers in cm^{-1}.

Reactions were monitored by thin-layer chromatography carried out on silica plates (silica gel 60 F254, Merck) using UV-light for visualization. Column chromatography was performed on silica gel 60 (0.040−0.063 mm, Merck) using the indicated eluent given in volume ratio. All starting materials were purchased at the highest commercial quality and used without further purification unless otherwise stated.

Procedure A: General procedure for the synthesis of compounds P-1(a-c), P-1(e-j).

The corresponding methylene active compound (1 mmol, 1 equiv) was added at r.t. to a solution of methyl coumalate (154 mg, 1 mmol, 1 equiv) in EtOH (5 mL). After Na_2CO_3 (105 mg, 1 mmol, 1 equiv) was added to this colorless solution, it turned to orange. Thus prepared solution was stirred for 1 h at r.t. under Argon. Then the reaction mixture was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). Then the aqueous layer, containing the product as sodium salt, was acidified with 1M HCl (5 mL, until pH = 2) and extracted with DCM (3 × 20 mL). Collected organic layers were dried over anhydrous $MgSO_4$, filtrated and evaporated under reduced pressure to afford the target products.

Procedure B: General procedure for the synthesis of compounds P-2(a-u). T o a solution of methyl coumalate (154 mg, 1 mmol, 1 equiv) in CH_2Cl_2 (5 mL) at r.t. was added the corresponding methylene active compound (1 mmol, 1 equiv) followed by triethylamine (101 mg, 1 mmol, 1 equiv). The solution was stirred for 15 h under reflux, cool to r.t. then quenched with 1M HCl (10 mL). The mixture was extracted with DCM (3 × 20 mL). The organic layers were washed with brine and dried over anhydrous $MgSO_4$, filtrated and evaporated and the residue was subjected to column chromatography on silica yielding the respective title compounds.

Procedure C: General procedure for the synthesis of compounds P-3d, P-3i, P-3j. The corresponding methylene active compound (1 mmol, 1 equiv) was added at r.t. to a solution of methyl coumalate (154 mg, 1 mmol, 1 equiv) in EtOH (5 mL). After Na_2CO_3 (105 mg, 1 mmol, 1 equiv) was added to this colorless solution, it turned to orange. Thus prepared solution was stirred for 1h at r.t. under Argon. Then N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (192 mg, 1 mmol, 1 equiv) and DMAP (24 mg, 0.2 mmol, 0.2 equiv) was added in CH_2Cl_2 (5mL) solution, Once reaction was completed, the reaction mixture was quenched with 1M HCl (10 mL) and mixture was extracted into CH_2Cl_2 (3 × 20 mL) Collected organic layers were washed with brine and dried over anhydrous $MgSO_4$, filtrated and evaporated and the residue was subjected to column chromatography on silica yielding the respective title compounds.

2-(3,5-bis(methoxycarbonyl)-6-methyl-2*H*-pyran-2-yl) acetic acid (P-1a) : The title compound was prepared according to procedure A, 243 mg; 90% yield; yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 5.73 (dd, J = 10.1, 3.1 Hz, 1H), 3.77 (s, 6H), 2.84 (dd, J = 15.2, 10.1 Hz, 1H), 2.56 (dd, J = 15.2, 3.1 Hz, 1H), 2.37 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.9, 170.6, 165.4, 164.6, 132.3, 114.8, 104.4, 72.2, 51.9, 51.6, 37.9, 20.2; **IR** (film, cm^{-1}): ~3600-2600 (br), 2976, 2868, 1716, 1436, 1362, 1244, 1182, 1112, 933, 790; **HRMS** (ESI) Found *m/z* 293.0632 calcd for $[M+Na^+]$ $C_{12}H_{14}NaO_7$ 293.0632.

2-(6-butyl-3,5-bis(methoxycarbonyl)-2*H*-pyran-2-yl)acetic acid (P-1b): The title compound was prepared according to procedure A, 268 mg; 90% yield; yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 5.75 (dd, J = 10.1, 3.0 Hz, 1H), 3.77 (s, 3H), 3.77 (s, 3H), 2.98 – 2.76 (m, 2H), 2.55-2.57 (m, 2H), 1.66 – 1.52 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.2, 174.0,

165.3, 164.7, 132.6, 114.6, 104.1, 72.0, 51.9, 51.6, 37.7, 34.6, 20.7, 14.0; **IR** (film, cm^{-1}): ~3600-2600 (br), 2960, 2873, 1714, 1558, 1436, 1232, 1112, 1060, 977, 756; **HRMS** (ESI) Found *m/z* 321.0957 calcd for [M+Na^+] $C_{14}H_{18}NaO_7$ 321.0945

2-(3,5-bis (methoxycarbonyl) -6- (methoxymethyl)-2H-pyran-2-yl) acetic acid (P-1c): The title compound was prepared according to procedure A, 273 mg; 91% yield: colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 5.83 (dd, J = 9.9, 3.2 Hz, 1H), 4.65 (d, *J* = 14.0 Hz, 1H), 4.44 (d, *J* = 14.0 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.40 (s, 3H), 2.90 (dd, *J* = 15.6, 9.9 Hz, 1H), 2.57 (dd, *J* = 15.6, 3.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.9, 167.4, 164.8, 164.3, 131.5, 116.6, 105.9, 72.3, 69.3, 59.3, 52.1, 51.9, 37.6; **IR** (film, cm^{-1}): ~3700-2500 (br), 2953, 1710, 1641, 1570, 1242, 1112, 1064, 977, 756; **HRMS** (ESI) Found *m/z* 323.0748 calcd for [M+Na^+] $C_{13}H_{16}NaO_8$ 323.0737.

2-(6-(chloromethyl)-3,5-bis(methoxycarbonyl)-2*H*-pyran-2-yl) acetic acid (P-1e): The title compound was prepared according to procedure A , 303 mg; 86% yield; colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 5.81 (dd, *J* = 9.9, 3.1 Hz, 1H), 4.90 (d, *J* = 11.3 Hz, 1H), 4.29 (d, *J* = 11.3 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 2.93 (dd, *J* = 16.2, 9.9 Hz, 1H), 2.56 (dd, *J* = 16.2, 3.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.7, 164.2, 164.2, 164.1, 131.1, 117.9, 106.1, 72.0, 52.2 (2C), 39.8, 37.4; **IR** (film, cm^{-1}): ~3700-2400 (br), 2978, 1716, 1436, 1384, 1251, 1238, 1193, 1180, 1097, 1070, 1002, 933, 833, 756; **HRMS** (ESI) Found m/z 303.0266, calcd for [M-H^+] $C_{12}H_{12}ClO_7$ 303.0277.

2-(6-(2-methoxy-2-oxoethyl)-3,5-bis(methoxycarbonyl)-2*H*-pyran-2-yl) acetic acid (P-1f): The title compound was prepared according to procedure A, 302 mg; 92% yield; colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.55 (s, 1H); 5.80 (dd, *J* = 10.1, 2.7 Hz, 1H); 4.14 (d, *J* = 16.2 Hz, 1H); 3.79 (s, 3H); 3.77 (s, 3H); 3.71

(s, 3H); 3.48 (d, *J* = 16.2 Hz, 1H´); 3.07 (dd, *J* = 16.4, 10.1 Hz, 1H); 2.53 (dd, *J* = 16.4, 2.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.8; 168.7; 164.9; 164.6; 164.4; 131.4; 116.5; 106.4; 72.4; 52.6; 52.1; 52.0; 39.0; 37.4; **IR** (film, cm^{-1}): ~3500-2400 (br), 2960, 1714, 1697, 11435, 1357, 1247, 1093, 997, 877, 775; **HRMS** (ESI) Found *m/z* 351.0687, calcd for $[M+Na^+]$ $C_{14}H_{16}NaO_9$ 351.0691.

2-(5-acetyl-3-(methoxycarbonyl)-6-methyl-2*H*-pyran-2-yl)acetic acid (P-1g): The title compound was prepared according to procedure A, 220 mg; 87% yield; colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 5.74 – 5.54 (m, 1H), 3.73 (s, 3H), 2.77 (m, 1H), 2.50 (m, 1H), 2.28 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.6, 174.4, 171.1, 164.5, 132.3, 114.8, 112.9, 72.3, 52.0, 37.9, 28.9, 21.0; **IR** (film, cm^{-1}): ~3500-2400 (br), 2976, 2870, 1712, 1624, 1436, 1382, 1238, 1105, 1070, 1018, 935, 840; **HRMS** (ESI) Found *m/z* 277.0683, calcd for $[M+Na^+]$ $C_{12}H_{14}NaO_6$ 277.0688.

Dimethyl-2,6-dimethyl-2*H*-pyran -3,5-dicarboxylate (P-2a): The title compound was prepared according to procedure B, 196 mg; 87% yield; colorless oil; R_f = 0.2 [1:5 (v/v) EA/cyclohexane]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 5.34 (q, J = 6.5 Hz, 1H), 3.74 (s, 3H), 3.74 (s, 3H), 2.34 (s, 3H), 1.30 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.8, 165.8, 165.0, 130.8, 117.2, 103.5, 72.5, 51.6, 51.4, 20.5, 19.2; **IR** (film, cm^{-1}): 2951, 2918, 1716, 1689, 1637, 1433, 1379, 1309, 1226, 1128, 1045, 910, 752; **HRMS** (ESI) Found *m/z* 233.0996, calcd for $[M+Li^+]$ $C_{11}H_{14}LiO_5$ 233.0996.

Dimethyl-2-methyl-6-propyl-2*H*-pyran-3,5-dicarboxylate (P-2b): The title compound was prepared according to procedure B, 224 mg; 88% yield; white solid, m.p.123-126°C; R_f = 0.2 [1:5 (v/v) EA/cyclohexane]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 5.34 (q, *J* = 6.5 Hz, 1H), 3.73 (s, 3H), 3.73 (s, 3H), 3.04 – 2.84 (m,

1H), 2.51 – 242 (m, 1H), 1.67 – 1.50 (m, 2H), 1.27 (d, *J* = 6.5 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H) ; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.1, 165.6, 165.0, 131.0, 117.2, 103.4, 72.2, 51.6, 51.3, 34.7, 20.6, 19.0, 13.9; **IR** (film, cm^{-1}): 2974, 2872, 1701, 1639, 1556, 1435, 1307, 1224, 1122, 1068, 914, 756; **HRMS** (ESI) Found *m/z* 277.1051, calcd for $[M+Na^+]$ $C_{13}H_{18}NaO_5$ 277.1046.

Dimethyl-6-(methoxymethyl)-2-methyl-2*H*-pyran-3,5-dicarboxylate (P-2c): The title compound was prepared according to procedure B, 208 mg, 81% yield, white solid, m.p.140-141°C, R_f = 0.3 [1:5 (v/v) EA/cyclohexane]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 5.46 (q, *J* = 6.5 Hz, 1H), 4.67 (d, *J* = 14.3 Hz, 1H), 4.40 (d, *J* = 14.3 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.39 (s, 3H), 1.35 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.0, 165.1, 164.7, 130.1, 118.8, 104.9, 72.8, 69.6, 59.1, 51.8, 51.6, 19.0; **IR** (film, cm^{-1}): 2951, 2931, 1699, 1639, 1566, 1435, 1309, 1226, 1124, 1076, 991, 912, 752; **HRMS** (ESI) Found *m/z* 279.0835 calcd for $[M+Na^+]$ $C_{12}H_{16}NaO_6$ 279.0839.

Dimethyl-6-cyclopropyl-2-methyl-2*H*-pyran-3,5-dicarboxylate (P-2d): The title compound was prepared according to procedure B, 237 mg; 94% yield; white solid, m.p.101-103°C; R_f = 0.2 [1:5 (v/v) EA/cyclohexane]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 5.27 (q, *J* = 6.5 Hz, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.17 – 3.10 (m, 1H), 1.35 – 1.24 (m, 1H), 1.21 (d, *J* = 6.5 Hz, 3H), 1.09 – 0.97 (m, 1H), 0.97 – 0.88 (m, 1H), 0.88 – 0.74 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.8, 166.2, 165.1, 131.4, 116.3, 103.5, 72.0, 51.5, 51.4, 18.6, 13.1, 10.1, 7.1; **IR** (film, cm^{-1}): 2951, 2929, 1687, 1635, 1539, 1301, 1222, 1062, 1043, 931, 875, 815; **HRMS** (ESI) Found *m/z* 275.0885, calcd for $[M+Na^+]$ $C_{13}H_{16}NaO_5$ 275.0890.

Dimethyl-6-(chloromethyl)-2-methyl-2*H*-pyran-3,5-dicarboxylate (P-2e): The title compound was prepared according to procedure B, 179 mg; 71% yield;

colorless oil; R_f = 0.2 [1:5 (v/v) EA/cyclohexane]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 0.4 Hz, 1H), 5.43 (q, *J* = 6.5 Hz, 1H), 4.97 (d, *J* = 11.2 Hz, 1H), 4.24 (d, *J* = 11.2 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 1.36 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.6, 164.1, 129.6, 120.4, 105.5, 72.6, 52.0, 51.9, 40.1, 18.9; **IR** (film, cm^{-1}): 2953, 2926, 1703; 1643, 1573, 1435, 1307, 1228, 1124, 1076, 939, 796, 754; **HRMS** (ESI) Found *m/z* 267.0610, calcd for [M+Li^+] $C_{11}H_{13}ClLiO_5$ 267.0606.

Dimethyl-6-(2-methoxy-2-oxoethyl)-2-methyl-2*H*-pyran-3,5-dicarboxylate (P-2f): The title compound was prepared according to procedure B, 233 mg, 82% yield, colorless oil, R_f = 0.2 [1:5 (v/v) EA/cyclohexane]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 5.35 (q, *J* = 6.5 Hz, 1H), 4.05 (d, *J* = 16.2 Hz, 1H), 3.71 (s, 3H), 3.71 (s, 3H), 3.67 (s, 3H), 3.44 (d, *J* = 16.2 Hz, 1H), 1.32 (d, *J* = 6.5 Hz, 3H) ; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.7, 165.2, 164.8, 164.7, 129.8, 118.8, 105.4, 73.0, 52.2, 51.7, 51.6, 39.0, 19.1; **IR** (film, cm^{-1}): 3001, 2954, 1739, 1712, 1689, 1641, 1573, 1463, 1332, 1122, 1047, 948, 871; **HRMS** (ESI) Found *m/z* 307.0784, calcd for [M+Na^+] $C_{13}H_{16}NaO_7$ 307.0788.

Methyl-5-acetyl-2,6-dimethyl-2*H*-pyran-3-carboxylate (P-2g): The title compound was prepared according to procedure B, 199 mg; 95% yield, colorless oil, R_f = 0.2 [1:5 (v/v) EA/cyclohexane]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 5.32 (q, *J* = 6.5 Hz, 1H), 3.73 (s, 3H), 2.29 (s, 3H), 2.28 (s, 3H), 1.27 (d, *J* = 6.5 Hz, 3H) ; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.2, 171.1, 164.9, 131.0, 117.1, 112.3, 72.5, 51.6, 28.9, 21.3, 19.2; **IR** (film, cm^{-1}): 2976, 1703, 1633, 1558, 1436, 1274, 1228, 1147, 1122, 954, 756; **HRMS** (ESI) Found *m/z* 233.0783 calcd for [M+Na^+] $C_{11}H_{14}NaO_4$ 233.0784.

Methyl-5-acetyl-2-methyl-6-phenyl-2*H*-pyran-3-carboxylate (P-2h): The title

compound was prepared according to procedure B, 117 mg, 43% yield, yellow oil, R_f = 0.2 [1:5 (v/v) EA/cyclohexane]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.60 – 7.30 (m, 5H), 5.53 (q, *J* = 6.5 Hz, 1H), 3.78 (s, 3H), 1.88 (s, 3H), 1.48 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 196.8, 165.6, 165.0, 133.7, 131.7, 131.1, 129.9, 128.5, 119.0, 115.8, 72.6, 51.8, 29.8, 18.3; **IR** (film, cm^{-1}): 2976, 1705, 1625, 1435, 1363, 1283, 1119, 875, 771, 793; **HRMS** (ESI) Found *m/z* 295.0942, calcd for [M+Na^+] $C_{16}H_{16}NaO_4$ 295.0941.

Methyl-5-benzoyl-2,6-dimethyl-2*H*-pyran-3-carboxylate (P-2h'): The title compound was prepared according to procedure B, 106 mg, 39% yield, colorless oil, R_f = 0.3 [1:5 (v/v) EA/cyclohexane]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 – 7.38 (m, 5H), 7.32 (s, 1H), 5.43 (q, *J* = 6.5 Hz, 1H), 3.72 (s, 3H), 2.09 (s, 3H), 1.44 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.7, 169.2, 165.1, 139.1, 132.3, 131.6, 128.9, 128.6, 116.8, 112.2, 72.4, 51.6, 26.9, 20.7, 19.3; **IR** (film, cm^{-1}): 2976, 1703, 1624, 1435, 1381, 1238, 1147, 1043, 939, 877, 725; **HRMS** (ESI) Found *m/z* 311.0675, calcd for [M+K^+] $C_{16}H_{16}KO_4$ 311.0680.

Methyl-2-methyl-5-oxo-5,6,7,8-tetrahydro-2H-chromene-3-carboxylate (P-2i): The title compound was prepared according to procedure B, 188 mg, 85% yield, colorless oil, R_f = 0.3 [1:5 (v/v) EA/cyclohexane]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 5.39 (q, *J* = 6.5 Hz, 1H), 3.72 (s, 3H), 2.49 – 2.43 (m, 2H), 2.43 – 2.36 (m, 2H), 2.05 – 1.88 (m, 2H), 1.33 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 194.1, 175.0, 165.1, 126.7, 119.4, 110.9, 73.5, 51.6, 36.4, 28.8, 20.3, 20.2; **IR** (film, cm^{-1}): 2954, 2927, 1703, 1633, 1556, 1435, 1381, 1274, 1145, 1122, 1076, 954, 754; **HRMS** (ESI) Found *m/z* 245.0789, calcd for [M+Na^+] $C_{12}H_{14}NaO_4$ 245.0784.

Methyl-2,6-dimethyl-5-(methylsulfonyl)-2*H*-pyran-3-carboxylate (P-2j): The

title compound was prepared according to procedure B, 223 mg, 91% yield, colorless oil, R_f = 0.2 [1:5 (v/v) EA/cyclohexane]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 (s, 1H), 5.36 (q, *J* = 6.5 Hz, 1H), 3.73 (s, 3H), 2.95 (s, 3H), 2.33 (s, 3H), 1.34 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.0, 164.3, 128.0 (2C), 118.4, 113.8, 73.1, 51.9, 44.2, 19.3; **IR** (film, cm^{-1}): 2980, 2954, 1703, 1633, 1556, 1435, 1381, 1274, 1228, 1145, 1122, 1043, 954, 754; **HRMS** (ESI) Found *m/z* 269.0458, calcd for [M+Na^+] $C_{10}H_{14}NaO_5S$ 269.0454.

Dimethyl-6-(tert-butyl)-2-methyl-2*H*-pyran-3,5-dicarboxylate (P-2k): The title compound was prepared according to Procedure B, 71 mg, 27% yield, colorless oil, R_f = 0.2 [1:5 (v/v) EA/cyclohexane]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 5.36 (q, *J* = 6.5 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 1.27 (d, *J* = 6.5 Hz, 3H), 1.25 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.8, 167.4, 164.9, 132.7, 116.6, 105.2, 71.3, 51.7, 51.6, 38.2, 27.6, 17.5; **IR** (film, cm^{-1}): 2951, 1701,1637, 1529, 1435, 1384, 1301, 1230, 1215, 1107, 933, 914, 756; **HRMS** (ESI) Found *m/z* 291.1203, calcd for [M+Na^+] $C_{14}H_{20}NaO_5$ 291.1214.

5-ethyl-3-methyl-2-methyl-6-phenyl-2*H*-pyran-3,5-dicarboxylate (P-2l): The title compound was prepared according to procedure B, 262 mg, 80% yield, yellow oil, R_f = 0.2 [1:5 (v/v) EA/cyclohexane]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.53 – 7.30 (m, 5H), 5.53 (q, *J* = 6.5 Hz, 1H), 4.07 (q, *J* = 7.1, 2H), 3.78 (s, 3H), 1.49 (d, *J* = 6.5 Hz, 3H), 1.05 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.8, 165.7, 164.9, 133.9, 131.6, 130.8(2C), 129.5(2C), 127.7, 118.5, 105.3, 72.7, 60.4, 51.7, 18.5, 13.8; **IR** (film, cm^{-1}): 2978, 1697, 1637, 1548, 1487, 1436, 1375, 1300, 1230, 1124, 1080, 989, 920, 754; **HRMS** (ESI) Found *m/z* 325.1071, calcd for [M+Na^+] $C_{17}H_{18}NaO_5$ 325.1052.

5-ethyl-3-methyl-2-methyl-6-(4-nitrophenyl)-2*H*-pyran-3,5-dicarboxylate (P-2m): The title compound was prepared according to procedure B, 336 mg, 97% yield, yellow oil, R_f = 0.2 [1:5 (v/v) EA/cyclohexane]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.9 Hz, 2H), 7.62 (s, 1H), 7.61 (d, *J* = 8.9 Hz, 2H), 5.56 (q, *J* = 6.5 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 1.52 (d, *J* = 6.5 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.7, 164.6, 163.0, 148.8, 140.1, 130.6, 130.5, 123.0, 120.0, 106.7, 73.1, 60.9, 52.0, 18.9, 13.9; **IR** (film, cm^{-1}): 2989, 1693, 1633, 1546, 1435, 1371, 1298, 1236, 1134, 1018, 1991, 856, 752; **HRMS** (ESI) Found *m/z* 370.0910, calcd for $[M+Na^+]$ $C_{17}H_{17}NNaO_7$ 370.0897.

Methyl-2-methyl-5-oxo-2,5-dihydropyrano-[3,2-c]-chromene-3-carboxylate (P-2n) : The title compound was prepared according to procedure B, 222 mg, 82% yield, yellow oil; R_f = 0.2 [1:5 (v/v) EA/cyclohexane]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 – 7.81 (m, 1H), 7.66 (s, 1H), 7.64 – 7.55 (m, 1H), 7.36 – 7.28 (m, 2H), 5.71 (q, *J* = 6.5 Hz, 1H), 3.82 (s, 3H), 1.50 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.5, 161.4, 160.1, 153.9, 133.7, 127.4, 124.4, 123.6, 122.3, 117.1, 114.8, 100.4, 74.0, 52.0, 20.5; **IR** (film, cm-1): 2926, 2854, 1722, 1699, 1637, 1606, 1556, 1490, 1296, 1242, 1205, 1029, 975, 935, 752; **HRMS** (ESI) Found *m/z* 295.0584, calcd for $[M+Na^+]$ $C_{15}H_{12}NaO_5$ 295.0577.

Methyl-6-ethyl-2-methyl-5-propionyl-2*H*-pyran-3-carboxylate (P-2o): The title compound was prepared according to procedure B, 216 mg, 91% yield, colorless oil; R_f = 0.2 [1:5 (v/v) EA/cyclohexane]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 5.32 (q, *J* = 6.5 Hz, 1H), 3.72 (s, 3H), 2.98 – 2.77 (m, 1H), 2.73 – 2.50 (m, 2H), 2.48 – 2.29 (m, 1H), 1.25 (d, *J* = 6.5 Hz, 3H), 1.10 (t, *J* = 7.5 Hz, 3H), 1.06 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.8, 174.7, 164.9, 130.7, 117.1, 111.4, 71.9, 51.6, 33.5, 26.9, 18.7, 11.1, 8.1. **IR** (film, cm-1): 2980, 2941, 1707, 1678, 1624, 1531, 1436, 1377, 1290, 1220, 1195, 1068, 898, 761;

HRMS (ESI) Found *m/z* 277.0840, calcd for [M+K$^+$] $C_{13}H_{18}KO_4$ 277.0837.

Methyl-5-benzoyl-2-methyl-6-phenyl-2*H*-pyran-3-carboxylate (P-2p): The title compound was prepared according to procedure B, 166 mg, 50% yield, yellow oil, R_f = 0.3 [1:5 (v/v) EA/cyclohexane]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.53 – 7.46 (m, 2H), 7.26 – 7.14 (m, 3H), 7.15 – 6.97 (m, 5H), 5.57 (q, *J* = 6.5 Hz, 1H), 3.73 (s, 3H), 1.57 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.9, 165.0, 164.0, 138.1, 133.0, 132.2, 132.1, 131.1, 130.1(2C), 129.3(2C), 128.0(2C), 127.9(2C), 119.0, 113.4, 72.4, 51.8, 18.6; **IR** (film, cm-1): 2974, 2852, 1695, 1672, 1543, 1446, 1435, 1240, 1176, 1053, 1020 941, 904, 771; **HRMS** (ESI) Found *m/z* 357.1107, calcd for [M+Na$^+$] $C_{21}H_{18}NaO_4$ 357.1097.

Methyl-2,7,7-trimethyl-5-oxo-5,6,7,8-tetrahydro-2*H*-chromene-3-carboxylate (P-2q): The title compound was prepared according to procedure B, 210 mg, 84% yield, colorless oil, R_f = 0.2 [1:5 (v/v) EA/cyclohexane]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 5.41 (q, *J* = 6.5 Hz, 1H), 3.72 (s, 3H), 2.43 – 2.31 (m, 2H), 2.30 – 2.11 (m, 2H), 1.33 (d, *J* = 6.5 Hz, 3H), 1.08 (s, 3H), 1.00 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.8, 173.7, 165.1, 126.6, 119.1, 109.9, 73.6, 51.6, 50.3, 42.5, 32.3, 29.4, 27.2, 20.2; **IR** (film, cm-1): 2965, 2872, 1703, 1660, 1571, 1398, 1307, 1217, 1145, 1068, 939, 761; **HRMS** (ESI) Found *m/z* 273.1099, calcd for [M+Na$^+$] $C_{14}H_{18}NaO_4$ 273.1097.

Methyl-2-methyl-5-oxo-2,5,6,7-tetrahydrocyclopenta-[b]-pyran-3-carboxylate (P-2r): The title compound was prepared according to procedure B, 201 mg, 96% yield, colorless oil, R_f = 0.2 [1:5 (v/v) EA/cyclohexane]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 (s, 1H), 5.65 (q, *J* = 6.5 Hz, 1H), 3.76 (s, 3H), 2.81 – 2.57 (m, 2H), 2.54 (ddd, *J* = 12.1, 9.2, 6.4 Hz, 2H), 1.46 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.1, 187.9, 165.0, 125.2(2C), 120.3, 113.7, 51.9,

34.1, 26.7, 21.0; **IR** (film, cm-1): 2989, 2953, 1693, 1633, 1546, 1344, 991, 856, 752; **HRMS** (ESI) Found *m/z* 231.0637, calcd for [M+Na$^+$] $C_{11}H_{12}NaO_4$ 231.0628.

Dimethyl-6-(4-fluorophenyl)-2-methyl-2*H*-pyran-3,5-dicarboxylate (P-2s): The title compound was prepared according to procedure B, 251 mg, 82% yield, yellow oil, R_f = 0.2 [1:5 (v/v) EA/cyclohexane]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.52 – 7.42 (m, 2H), 7.12 – 7.03 (m, 2H), 5.54 (q, *J* = 6.5 Hz, 1H), 3.80 (s, 3H), 3.64 (s, 3H), 1.47 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.9, 165.6, 164.8, 131.9, 131.8, 131.4(2C), 118.7, 115.1(2C), 114.9, 104.7, 72.8, 51.8, 51.5, 18.5; **IR** (film, cm-1): 2976, 1699, 1637, 1602, 1595, 1367, 1083, 1049, 1024, 952, 914, 840, 754; **HRMS** (ESI) Found *m/z* 329.0796, calcd for [M+Na$^+$] $C_{16}H_{15}FNaO_5$ 329.0807.

Methyl-2,6-dimethyl-5-(phenylsulfonyl)-2*H*-pyran-3-carboxylate (P-2t): The title compound was prepared according to procedure B, 300 mg, 97% yield, colorless oil, R_f = 0.2 [1:5 (v/v) EA/cyclohexane]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 – 7.79 (m, 2H), 7.63 – 7.48 (m, 3H), 7.41 (s, 1H), 5.34 (q, *J* = 6.5 Hz, 1H), 3.75 (s, 3H), 2.29 (s, 3H), 1.28 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.1, 164.4, 142.5, 133.0 (2C), 129.3, 128.3(2C), 126.5, 118.4, 114.4, 73.1, 51.9, 19.5, 19.5; **IR** (film, cm^{-1}): 2980, 1703, 1633, 1556, 1435, 1274, 999, 927, 756; **HRMS** (ESI) Found *m/z* 331.0600, calcd for [M+Na$^+$] $C_{15}H_{16}NaO_5S$ 331.0611.

Dimethyl 6-cyclopropyl-2-(2-ethoxy-2-oxoethyl)-2*H*-pyran-3,5-dicarboxylate (P-3d): The title compound was prepared according to procedure C, 220 mg; 68% yield; colorless oil; R_f = 0.2 [1:5 (v/v) EA/cyclohexane]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 5.67 (dd, *J* = 10.2, 3.0 Hz, 1H), 4.27 – 4.09 (m, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.12 (tt, *J* = 8.2, 4.9 Hz, 1H), 2.74 (dd, *J* = 15.4, 10.2 Hz,

1H), 2.43 (dd, *J* = 15.4, 3.0 Hz, 1H), 1.34 – 1.31 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.05 – 1.00 (m, 1H), 0.95 – 0.80 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.9, 169.4, 165.8, 164.7, 132.8, 113.7, 103.8, 72.2, 60.9, 51.7, 51.47, 37.6, 14.1, 13.2, 10.8, 7.7. **IR** (film, cm^{-1}): 2968, 2954, 1732, 1707, 1693, 1547, 1449, 1393, 1175, 1114, 985, 908, 877, 752; **HRMS** (ESI) Found *m/z* 347.1107 calcd for [M+Na^+] $C_{16}H_{20}NaO_7$ 347.1101.

Methyl-2-(2-ethoxy-2-oxoethyl)-5-oxo-5,6,7,8-tetrahydro-2H-chromene-3-carboxylate (P-3i): The title compound was prepared according to procedure C, 211 mg; 72% yield; colorless oil; R_f = 0.2 [1:4 (v/v) EA/cyclohexane]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 5.79 (dd, *J* = 9.8, 3.2 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 2.78 (dd, *J* = 15.0, 9.8 Hz, 1H), 2.61 (dd, *J* = 15.0, 3.2 Hz, 1H), 2.55 – 2.37 (m, 4H), 2.10 – 1.95 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 194.0, 174.8, 169.2, 164.7, 128.1, 117.1, 111.4, 73.4, 61.0, 51.9, 39.3, 36.4, 28.4, 20.2, 14.2; **IR** (film, cm^{-1}): 2983, 2871, 1726, 1709, 1633, 1592, 1445, 1383, 1271, 1229, 759, 726; **HRMS** (ESI) Found *m/z* 317.1005, calcd for [M+Na^+] $C_{15}H_{18}NaO_6$: 317.0996.

Methyl-2-(2-ethoxy-2-oxoethyl)--6-methyl-5-(phenylsulfonyl)-2*H*-pyran-3-carboxylate (P-3j): The title compound was prepared according to procedure C, 193 mg; 52 % yield; yellow oil; R_f = 0.2 [1:5 (v/v) EA/cyclohexane]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 – 7.81 (m, 2H), 7.68 – 7.52 (m, 3H), 7.50 (d, *J* = 0.5 Hz, 1H), 5.72 (dd, *J* = 9.9, 3.3 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 2.73 (dd, *J* = 15.0, 9.9 Hz 1H), 2.50 (dd, *J* = 15.0, 3.3 Hz, 1H), 2.33 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.9, 168.0, 164.0, 142.2, 133.2, 129.6 (2C), 129.4 (2C), 126.7, 116.3, 115.2, 73.1, 61.0, 52.1, 38.5, 19.2, 14.2.; **IR** (film, cm^{-1}): 3061, 2847, 2360, 2341, 1663, 1645, 1620, 1459, 1386, 1276, 1150, 883, 759; **HRMS** (ESI) Found *m/z* 403.0823, calcd for [M+Na^+] $C_{18}H_{20}NaO_7S$

403.0822.

3.7. References

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(13) This hypothesis is supported by two results: a first experiment using stoichiometric amount of NaH as base in DCM with pentanedione gave **4g** in the enol form after acidic quench. When the reaction was followed by ^{1}H NMR, this compound was detected as an intermediate.

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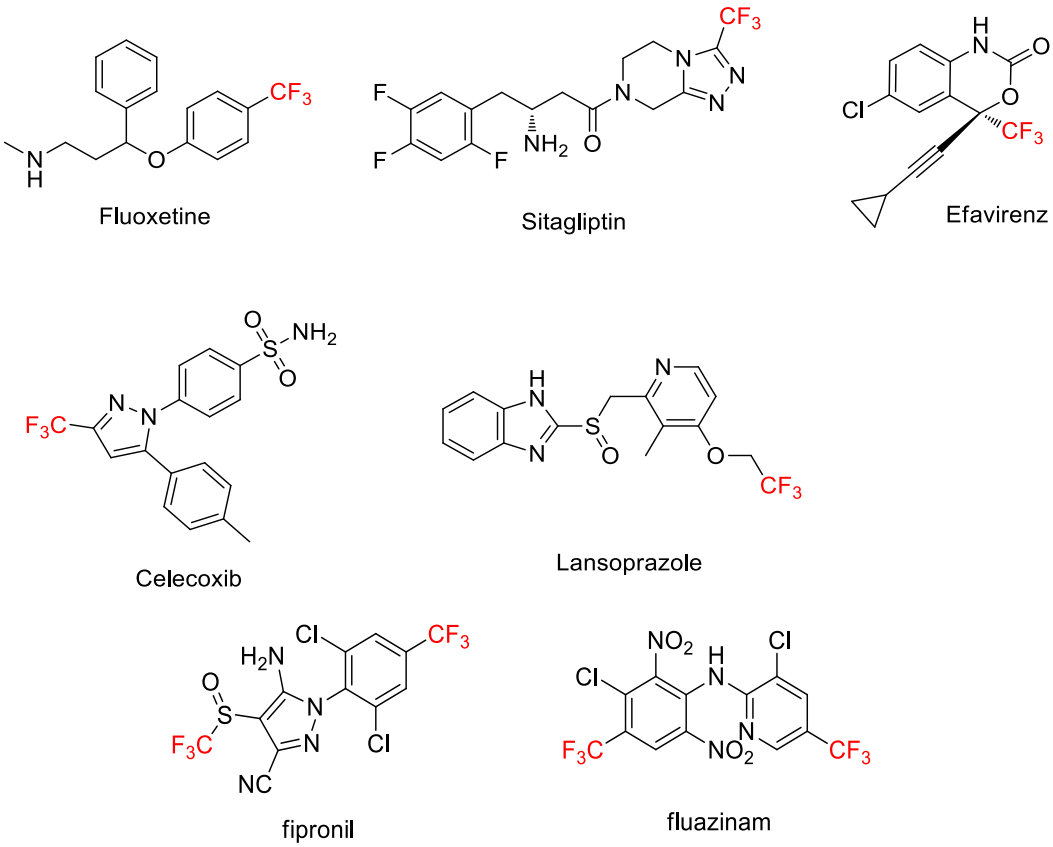
Chapter 4. A solvent-free, base-catalyzed domino reaction towards trifluoro methylated benzenes from bio-based methyl coumalate.

4.1. Introduction

Trifluoromethyl-functionalized aromatic and heterocyclic compounds are popular in medicinal chemistry and agro-chemistry field. The reason for this prevalent owing to their unique pharmacokinetic properties.[1]

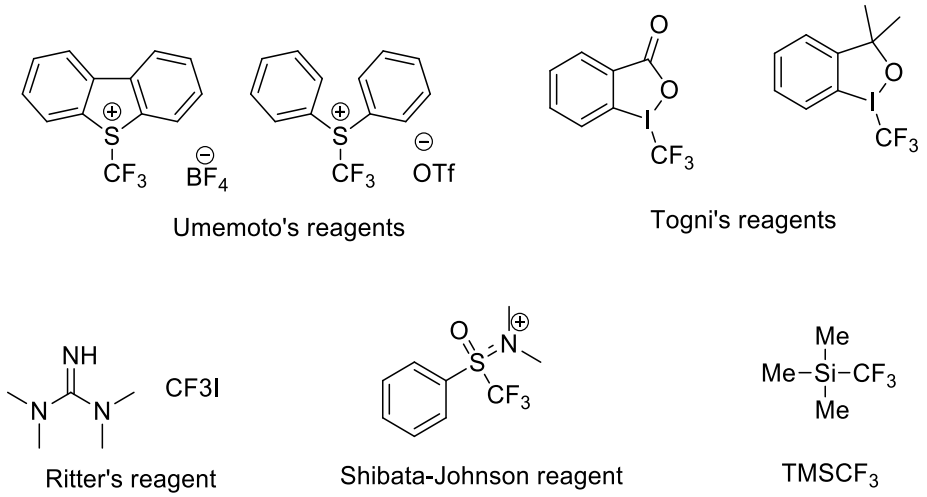
Scheme 1. Pharmaceutical products and common largely used pesticides fipronil and fluazinam



The CF_3 group could increase lipophilicity of the compounds, and further improve bioavailability of the therapeutic compounds. the CF_3 group may allow a better binding to target proteins, in order to improve the bio-activities of the compound.[2] Thus, a wide range of methods have been described to introduce CF_3 groups in general and more specifically to aromatics. For instance, the metal-mediated coupling of Ar-H,[3] ArX or $ArBX_2$,[4] with Trimethyl(trifluoromethyl)silane or the TMG.ICF_3 (Ritter's reagent) complex,[5,6] hypervalent iodine (Togni's reagents),[7] and by photoredox catalysis (scheme 2).[8] The major drawbacks to these

approaches are use of metals, large quantities of byproducts, or the production of waste.

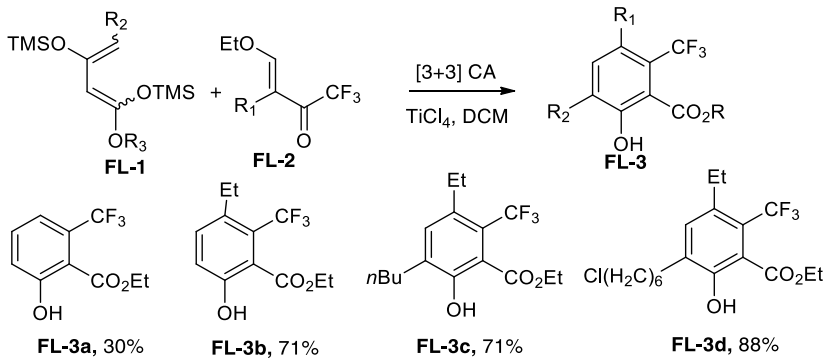
Scheme 2 Trifluoromethylating reagents



There are atom-economical alternatives for synthesis of trifluoromethyl-benzenes. Namely, cycloaddition (CA) reactions and formal-CA reactions, which employ a "trifluoromethylated building block approach". For example, Co- and Rh-mediated [2+2+2] cycloaddition reactions of fluoroalkylated alkynes[9], leading to trifluoromethyl arenes.[10]

4.1.1. Cycloaddition towards trifluoromethylated benzenes

Scheme 3 [3+3] Cycloaddition towards trifluoromethylated benzenes

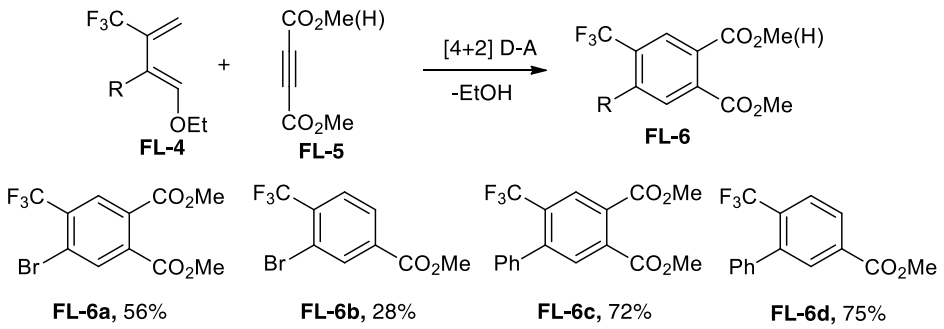


The formal [3+3]-CA between bis-silyl enol ethers and β-dimethyl thiounsaturated

trifluoromethyl-ketones is reported by Langer's group (Scheme 3). In this text, they discribed a new and versatile approach to CF_3 functionalized tri-tetra and penta substituted arenes based on cyclizations of 1,3-bis(silyl enol ethers) with open chain and cyclic *α,β*-unsaturated trifluoromethyl ketones.[10d]

In 2002, Schlosser's group reported Diels-Alder (DA) cycloadditions between 1-ethoxy-3-trifluoromethyl-1,3-butadiene, and electron-poor dienophiles to yield trifluoromethyl-substituted benzenes (Scheme 4).[10a]

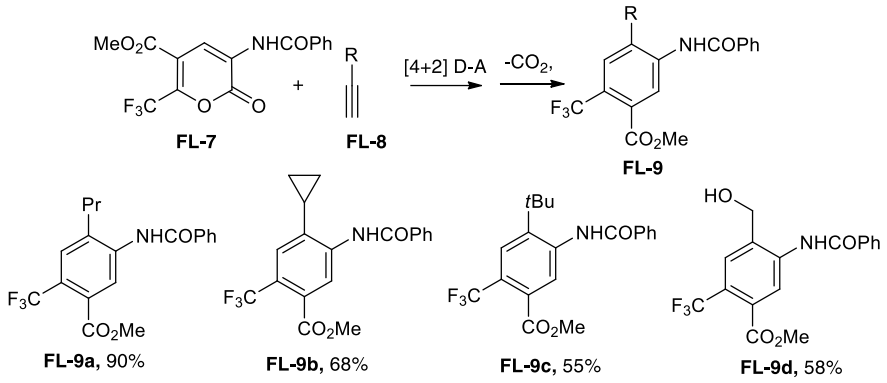
Scheme 4 Diels-Alder towards trifluoromethylated benzenes



However, the number of studies reporting cycloadditions based on CF_3 substrates is rather limited.

On the other hand, *α*-pyrones[11] (e.g. methyl coumalate, MC) with dienophiles like alkynes,[12] enolethers,[13] or even simple alkenes[14], give substituted aromatics (methylbenzoates from MC). This happens through a Diels-Alder process, after decarboxylation[15] and eventually releases of an alcohol molecule. As shown by Haufe and co-workers, CF_3-substituted α-pyrones react with electron-rich alkynes in an inverse electron-demand Diels-Alder (IEDDA) reaction. This occurs under microwave irradiation, providing CF_3-benzene in good yield (Scheme 5).[12c]

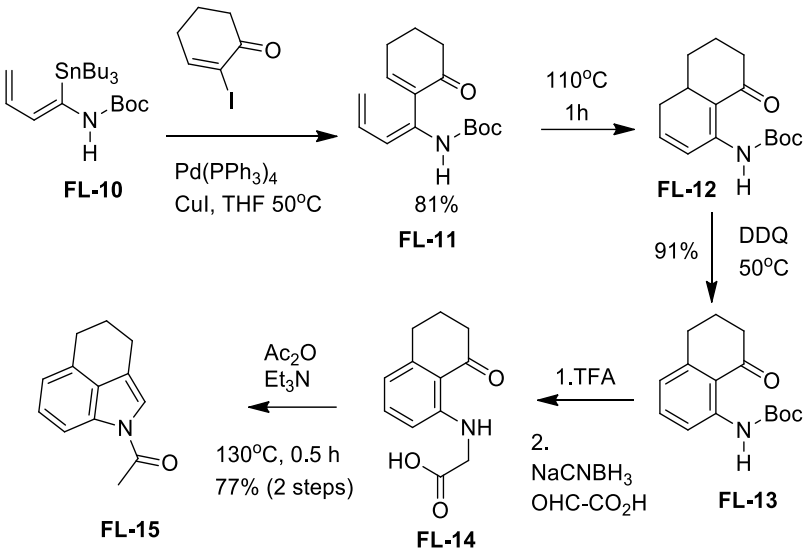
Scheme 5 CF_3 α-pyrones towards trifluoromethylated benzenes



Although the Diels–Alder reaction remains exceptional in its scope and versatility for building of aromatic six-membered rings, the development of thermal carba-6π-electrocyclization-aromatization process has come to complement [4+2] cycloadditions, when synthesizing poly-substituted benzene analogues. Funk and co-workers reported a streamlined electrocyclization-aromatization reaction of 2-acyl-3-amino-hexatrienes (Scheme 6).[16] The key intermediate amidotriene **FL-11** was achieved after a Stille coupling. Followed by electrocyclic ring closure at 110 ^{o}C, it affords cyclohexadiene **FL-12**. They proposed that this carba 6π electrocyclic ring-closing step is facilitated by a push/pull-type mechanism through an intramolecular hydrogen bond. This aromatization is accomplished in one-pot by DDQ oxidization. After the removal of the BOC group and reductive amination, it forms **FL-14**. The last cyclization proceeds through a Perkin-type reaction affording the desired N-acetylindole **FL-15**.

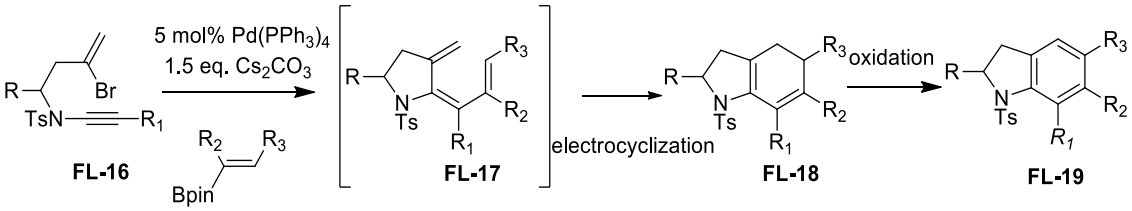
4.1.2. The synthesis of aromatics *via* a 6π-electrocyclic ring closure process

Scheme 6 Synthesis of indoles *via* a 6π-electrocyclic ring closure aromatization process



Anderson and co-workers developed a cascade cyclization of ynamides to azabicycles (Scheme 7).[17] The process begin with ynamide carbopalladation / Stille or vinylic Suzuki cross-coupling reactions to form the trienic intermediate **FL-17**. The 6-π electrocyclization produces the corresponding cyclohexadiene **FL-18**. The final nitrogen-containing bicyclic derivatives **FL-19**, which are important scaffolds for many natural products and drugs, could be obtained after a selective oxidation of aminodienes **FL-18**.

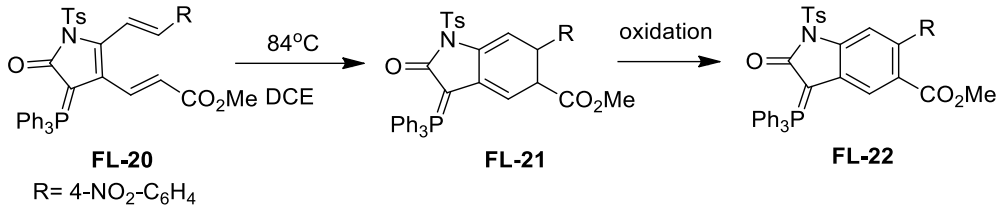
Scheme 7 Palladium-catalyzed cascade cyclization



Chuang's group reported approaches to isatin derivatives (Scheme 8).[18] The key intermediate 1,3,4,5-tetrasubstituted hexatrienes **FL-20** are obtained *via* three-component reactions of phosphines, cinnamaldimines and enynedioates. The key

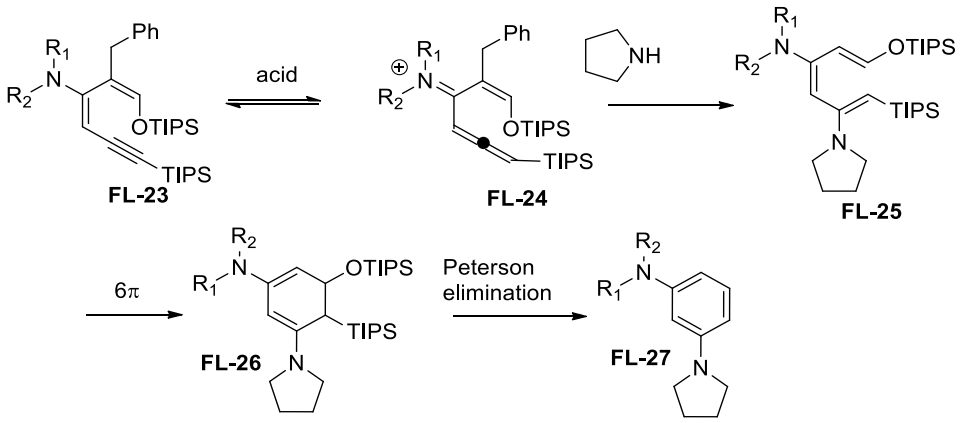
step, 6π electrocyclic ring-closing of hexatrienes **FL-20**, is facilitate by an unusually low activation barrier according to their computational and kinetic studies. 3-phosphorus ylide oxindoles **FL-22** could be obtained after oxidation of the cyclohexadiene **FL-21**.

Scheme 8 6π electrocyclization towards oxindoles



Recently, Huang and co-workers developed a new path to diaminobenzenes *via* a 6π -electrocyclization–aromatization reaction (Scheme 9).[19] The 6π electrocyclic ring-closing proceeds *via* highly electron-rich triene intermediate C with three electron-donating groups at the 1-, 3-, 5-positions. The aromatization is achieved by Peterson elimination, rendering the overall process redox neutral without applying extra oxidizer.

Scheme 9 Amine -triggered 6π electrocyclization aromatization

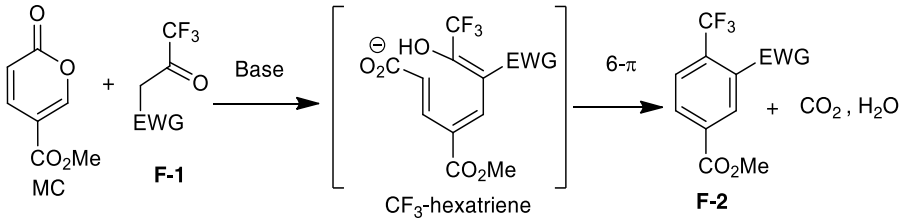


4.1.3. Our hypothesis from MC to CF_3 benzene

However, among these processes, the aromatization step often required extra oxidizers. Furthermore, 6π-electrocyclization aromatization reactions for polyfunctionalized benzenes remain challenging.[19] To the best of our knowledge, the synthesis of trifluoromethylated benzene *via* 6π-electrocyclization reaction has not been reported in previous literature. Thus, considering the pharmacokinetic

and pharmaceutical values of CF_3-functionalized compounds we launched a program in devising an environmentally friendly synthetic method for the preparation of trifluoromethylated benzenes. In order to reach the key intermediate CF_3-hexatriene (Scheme 10), **MC** was selected as an electrophilic pro-diene synthon. This choice was initially based on our recent finding that **MC** can be readily converted to diene in the presence of certain nucleophiles.[20]

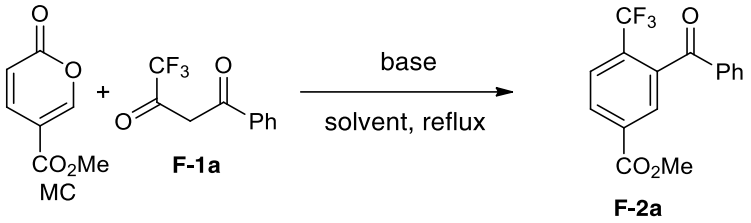
Scheme 10 Our hypothesis from MC to CF_3 benzene



4.2. Optimization of the Reaction Conditions

We began our study, by treating **MC** and trifluoroaceto-acetophenone **F-1a** with 1 equiv. of Et_3N in DCM at reflux for 30 h. It provided the expected arene **F-2a** in 54% yield (Table 1, entry 1).

Table 1. Optimization of the Reaction Conditions[a]



Entry	Base (eq.)	Solvent	Time (h)	Yield (%)[b]
1	Et_3N (1)	DCM	30	54
2	Et_3N (1)	THF	30	29
3	Et_3N (1)	EtOH	30	28
4	Et_3N (1)	H_2O	30	ND
5	Et_3N (1)	toluene	30	81
6	DBU (1)	toluene	1	70
7	DBU (0.1)	toluene	8	85
8	DBU (0.1)	toluene	15	89
9	*t*BuOK (0.1)	toluene	15	80

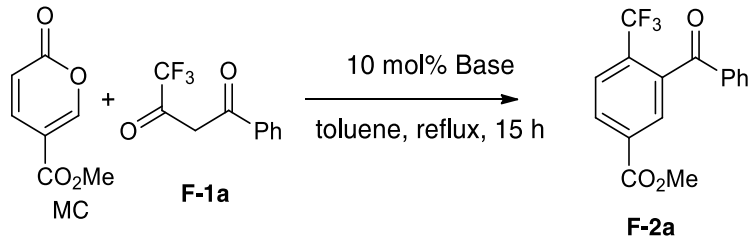
[a]Reaction conditions: All reactions were performed with **MC** (1 mmol) and trifluoroaceto-acetophenone **F-1a** (1 mmol). [b] isolated yields

Optimization of the reaction conditions to obtain trifluoromethyl-arene **F-2a** is presented in Table 1. The solvent plays an important role in this type of transformation. Low conversions were observed in THF, EtOH, and water. This is due to trimerization of the starting diketone **F-1a,** giving 1,3,5-trifluoromethyl-2,4,6-triphenylbenzene (entries 2-4). Comparatively, toluene is the solvent of choice. It yields benzene **F-2a** at 81% after 30 h at reflux, in the presence of stoichiometric amounts of Et_3N (entry 5). We found that simpler amines, such as the cyclic amidine 1,8 - diazabicyclo[5.4.0] - undec - 7 - ene (DBU), are highly efficient and output **F-2a** in 70% yields within an hour (entry 6).

To improve sustainability of the reaction conditions, we tested catalytic amounts of base. The quantity of DBU was successfully decreased to 10 mol%, providing product in 85% yield after 8 h (entry 7). However, separation of the expected product F-**2a** and the starting diketone **F-1a** was difficult. The reaction was extended to reach complete conversion and facilitate purification. After 15 h refluxing with 0.1 equiv. of DBU, trifluoromethyl benzophenone type **F-2a** was isolated in 89% yield (entry 8). No improvement in this transformation was observed when 10 mol% *t*BuOK was employed (entry 9).

Other bases such as Quinuclidine, DMAP, Imidazole, Et_3N, or even DBN were not as efficient as DBU (see Table 2).

Table 2. Optimization of the base [a]



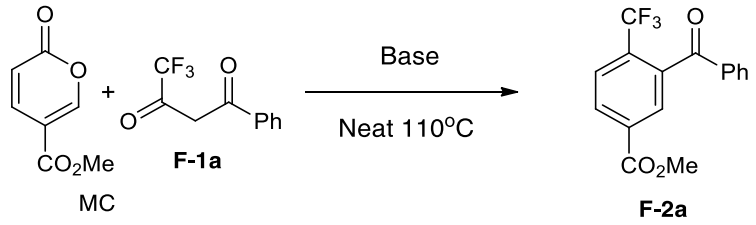
Entry	Base	Conversion (%)	Yield(%)[a]
1	Et_3N	25	26
2	DBN	100	70
3	quinuclidine	80	67
4	imidazol	55	34
5	DMAP	90	60

[a] isolated yields.

Solvent-free conditions led to the formation of expected compound **F-2a** in 1.5 h, but in a moderate 67% yield (Table 3 entry 1). Interestingly, the replacement of DBU by *t*BuOK (10 mol%) gave **F-2a** in excellent yield (Table 3 entry 2). Lowering the catalytic loading down to 5 mol% resulted in a longer reaction time to reach similar yield (entry 3). Finally, a slight decrease in reaction temperature

to 80 °C enhance the isolated yield up to 95% (entry 4). No amelioration was observed with the inorganic bases K_2CO_3 or KOH (entry 5-6).

Table 3. Optimization of the base in neat condition[a]



Entry	Base (equiv.)	Time (h)	Yield(%)[b]
1	DBU (0.1)	1.5	67
2	*t*BuOK (0.1)	1.5	90
3	*t*BuOK (0.05)	4	93
4[c]	*t*BuOK (0.1)	2	95
5[c]	K_2CO_3 (0.1)	1.5	74
6[c]	KOH (0.1)	1.5	70

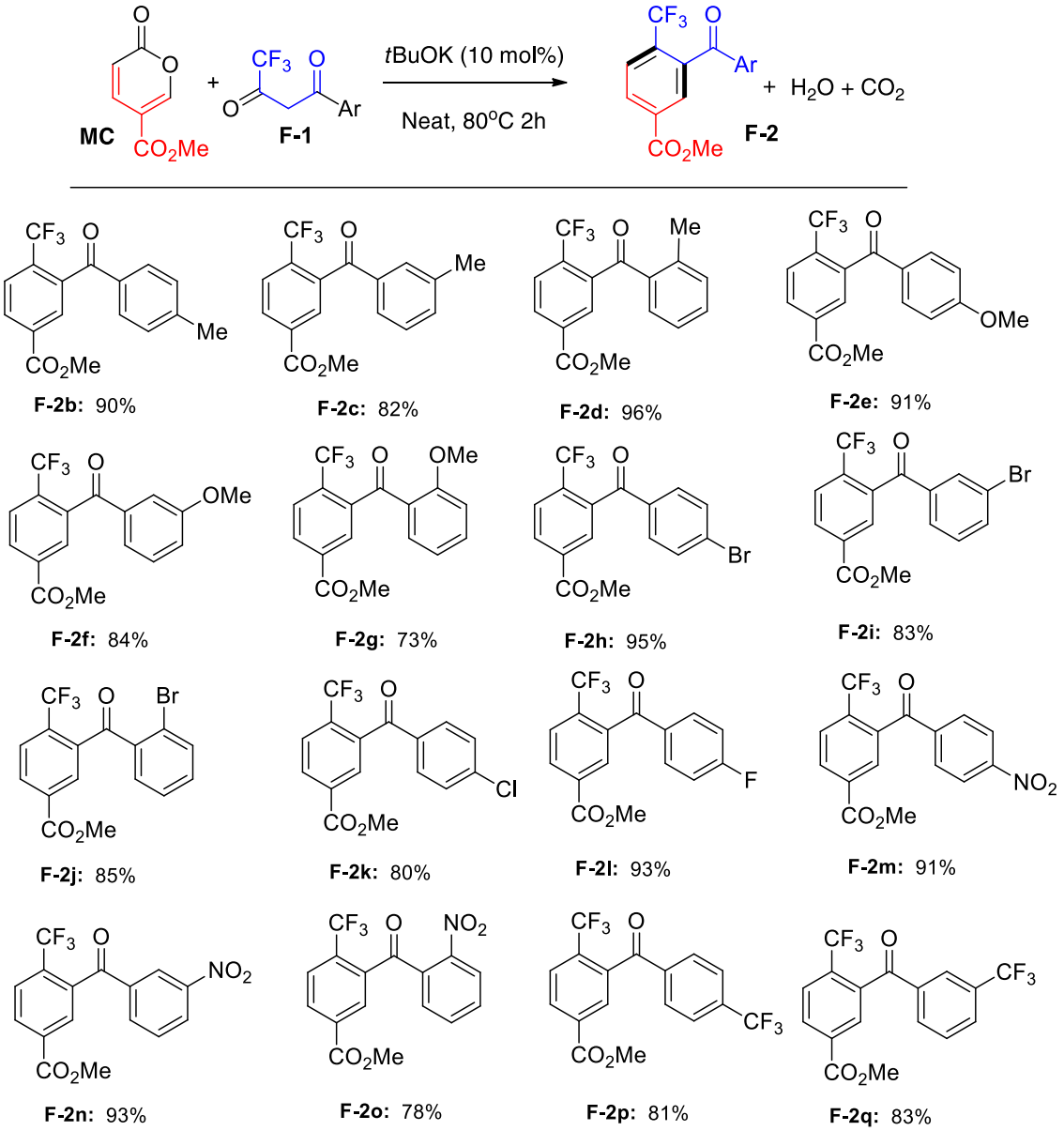
[a]Reaction conditions: All reactions were performed with **MC** (1 mmol) and trifluoroaceto-acetophenone **F-1a** (1 mmol). [b] isolated yields. .[c]At 80°C.

4.3. Application to a variety of trifluoromethyl benzenes

With the optimal conditions established, we prepared various trifluoromethyl-β-diketones **F-1a - F-1t**, according to known procedures.[21] We then subjected each to the reaction conditions (**MC**, *t*BuOK 10 mol%, neat, 80°C) (Table 4). Excellent regioselectivity is observed in the crude. ^{19}F NMR spectroscopy shows 100% selectivity in favor of the benzophenone type product **F-2** *vs* its trifluoro-acetophenone regioisomer ($ArCOCF_3$). Careful examination of the different spectra (See SI) shows the CF_3 group signal at around –60 ppm. This is consistent with an aromatic CF_3 moiety.[22] The putative trifluoro-acetophenone regioisomer

derivative would have its $COCF_3$ signal shifted up-field at around –70, –80 ppm.

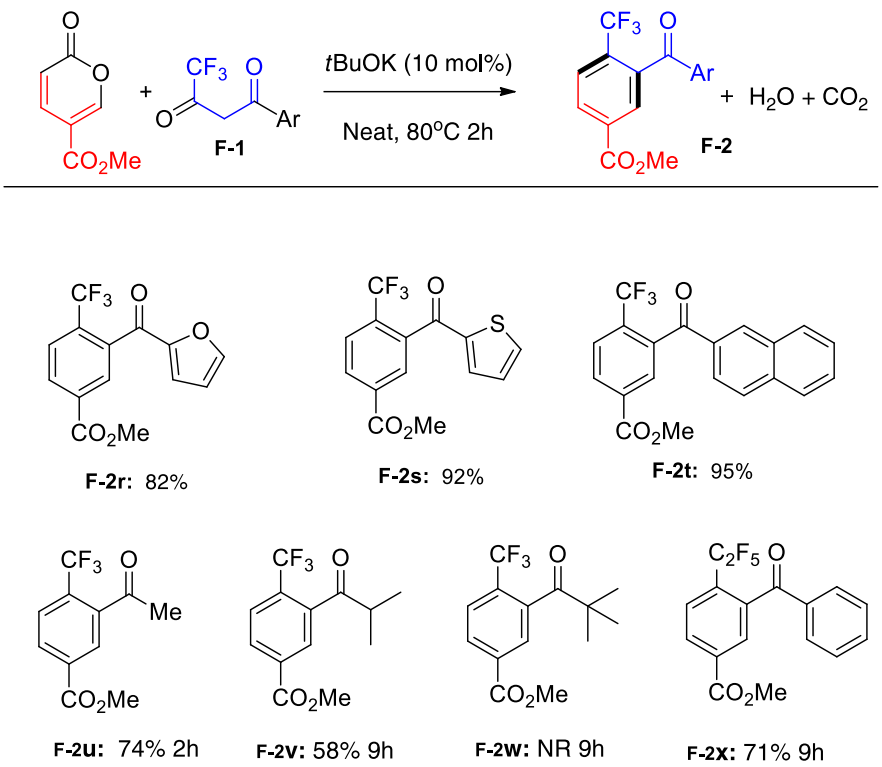
Table 4. Application to a variety of trifluoromethyl benzophenone



The effect of the substituent on the aromatic ring was investigated. Electron-neutral, electron-poor and electron-rich-groups were tolerated at the ortho-, meta- and para-positions. With the Methyl electron-donating groups, the corresponding benzenes **F-2b - F-2d** were formed in yields ranging from 90 to 96%. Similarly, the methoxy π-electron-donating group provided expected trifluoromethyl arenes (**F-2e - F-2g**) in yields up to 91%. Halogen-substituted benzenes were

obtained in 80-95% yields, no matter the halogen and its position on the aromatic ring (**F-2h - F-2l**). The ortho substituted nitro compound **F-2o** was formed in 78% yield, whereas meta- and para- isomers (**F-2m - F-2n**) were successfully isolated in 91-93% yield. The strongly electron-withdrawing trifluoromethyl group did not alter the efficiency of this domino reaction. It rendered the corresponding bis-trifluoromethyl derivatives **F-2p - F-2q**, in yields up to 83%. The reaction tolerates other aromatic rings like furan (**F-2r**, 82%), thiophene (**F-2s**, 92%), and naphthalene (**F-2t**, 95%).

Table 2. Application to a variety of trifluoromethyl benzenes



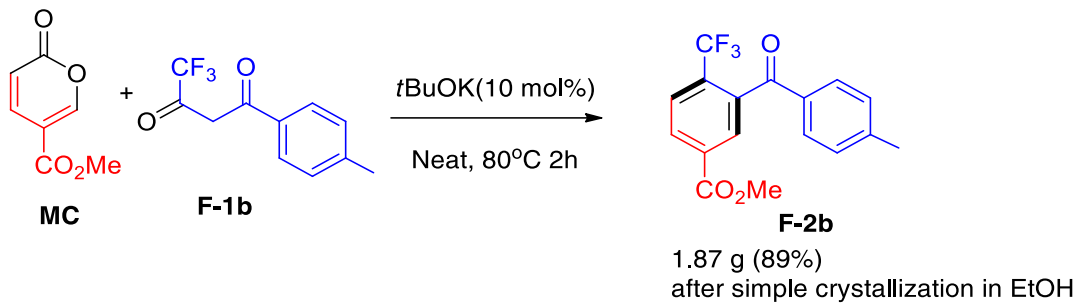
In contrast to the previous results, reaction outcome is more erratic with trifluoro-alkyl diketones. Trifluoroaceto-acetone **F-1u** gave the expected arene **F-2u** in 74% yield, while the hindered diketone (F-**1v**; R=*i*-Pr) reacts slowly, and gives the product **F-2v** in 58% yield after 9 h. It is noteworthy that the more hindered diketone (**F-1w**; R=*t*-Bu) did not react in these conditions. The reaction could be

extended to the pentafluoroethyl-acetophenone **F-1x**, which gave arene **F-2x** in 71% yield.

4.3.1 Gram scale synthesis of F-2b

With the developed protocol in hand, trifluoromethyl acetophenone synthesis could be readily scaled up to gram quantities without difficulty, providing 1.87 g (89%) of compound **F-2b** after simple crystallization in EtOH (Scheme 11).

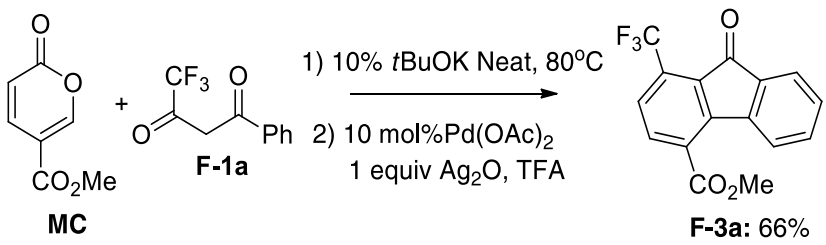
Scheme 11 Gram scale synthesis of **F-2b**



4.3.2. One-pot synthesis of CF_3-functionalized fluorenone

We also demonstrate that this reaction could incorporate with Pd-catalyzed dehydrogenative cyclization,[24] leading to CF_3-functionalized fluorenone (**F-3a,** 66%) in an efficient one-pot sequence (Scheme 12).

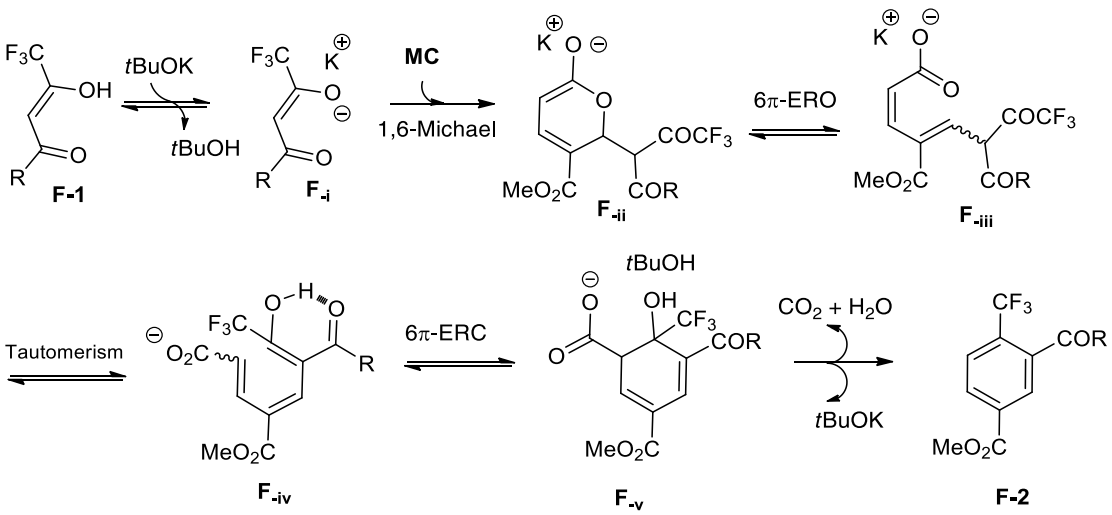
Scheme 12 One-pot synthesis of CF_3-functionalized fluorenone



4.4. Plausible mechanism for the cascade reaction leading to trifluoromethyl benzenes

To account for the generality of this method, a possible mechanism is presented in Scheme 13. The base promoted the deprotonation of trifluoromethyl keto-enol **1** to release enolate **F-i**. This enolate **F-i** adds to **MC** following a 1,6-Michael addition process, to generate the cyclic enolate **F-ii**. We propose that rapid 6π-electrocyclic ring opening (6π-ERO) of **F-ii** leads to dienoate **F-iii.**[20]

Scheme 13. Plausible mechanism for the cascade reaction leading to trifluoromethyl benzenes



The presence of the strong electron withdrawing CF_3 group should favor the tautoisomerization to carba-hexatriene **F-iv**. Carba-6π-ERC of hexatrienes is considered relatively disfavored; however, it is documented.[23,26] The presence of an electron withdrawing group on the C2 position, as in intermediate **F-iv**, decreases the activation barrier energy by about 25 kcal mol^{-1}. Moreover, the present case of 6π-ERC might be facilitated by a push/pull type mechanism, between the hydrogen bonded enol and the

proximal carbonyl (RCO).[27] ChemDraw® calculation of CF_3-triene intermediate **F-iv**, applying the extended Hückel method, suggested both large partial positive and negative charges at C-1 and C-6. Carba-6π-electrocyclic ring closure would therefore be favored.[23] Finally, the last step of the catalytic cycle involves a Doebner type[28] decarboxylation-dehydration of intermediate **F-v** to give trifluoromethyl benzenes **F-2**.

4.5. Conclusion

We have reported an efficient, solvent-free, and environmentally friendly reaction of methyl coumalate with trifluoromethyl-β-diketones, in a *t*BuOK-catalyzed domino Michael – 6*π*-ERO – tautomerization – 6*π*-ERC – aromatization sequence. This procedure is a practical and sustainable approach, sourced from bio-renewable molecules (**MC**), for easy synthesis of myriad trifluoromethyl-benzene derivatives. Most bear the benzophenone core structure,[29] which act on the biological targets of many diseases (e.g. cancer, Alzheimers, anti-viral and anti-bacterial drugs, prostatic hyperplasia, cardiovascular disease).[30] In addition to broad substrate scope, this unprecedented synthetic approach has the advantages of readily available starting materials, lack of oxidizers, proceeds without a metallic catalyst, and releases only water and CO_2. These soft experimental conditions do not need additive or special care (anhydrous or oxygen free conditions), and are applicable on the multi-gram scale.

4.6. Experimental section

Materials and general methods

All reactions were carried out under air with magnetic stirring. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz for ^{1}H nuclei, 100 MHz for ^{13}C nuclei. Chemical shifts are reported in δ units, parts per million (ppm) using, for ^{1}H and ^{13}C, solvent residual peak as internal standard references:

chloroform (7.26 ppm for ^{1}H NMR and 77.16 ppm). Coupling constants (*J*) are given in Hz, multiplicities are abbreviated as: s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublets of doublets), t (triplet), m (multiplet). High resolution mass spectra (HR-MS) were recorded on a LTQ-Orbitrap Mass Spectrometer [Thermo Scientific]. IR: Shimadzu IRAffinity-1CE spectrometer, wavenumbers in cm^{-1} .

Typical experimental procedure for the synthesis of compound F-1

Sodium (1.2 equiv) was added to methanol (10.0 equiv) at 0 °C and the mixture was stirred for 30 min. Ethyl trifluoroacetate (1.0 equiv) was added and the solution was stirred for further 30 min. To the solution was added corresponding acetophenone (1.0 equiv). The temperature of the reaction mixture was allowed to rise to 20 °C in the period of 3 h and the solution was stirred for 16 h at 20 °C. To the solution was added 1M HCl and the mixture was extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/ cyclohexane =1:10).[21]

Typical experimental procedure for the synthesis of compound F-2 (a-w).

Methyl coumalate (154 mg, 1 mmol, 1 equiv), trifluoromethyl-β-diketone **F-1** (1 mmol, 1 equiv) and *t*BuOK (11 mg, 0.1 mmol, 0.1 equiv) were mixed in a scklenk tube and stirred at 80 °C for 2 hours. The reaction mixture was cooled to room temperature, directly loaded to a plug of silica gel and eluted with cyclohexane/EtOAc (5/1 V/V). Evaporation of the solvent under vacuum delivered the expected products **F-2**.

4,4,4-trifluoro-1-(m-tolyl)butane-1,3-dione (**F-1c**):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.3 Hz, 1H), 7.41 (dt, *J* = 15.7, 8.0 Hz, 1H), 6.56 (s, 1H), 2.44 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 186.9, 177.5 (q, *J* = 36.1 Hz), 139.4, 135.4, 133.2, 129.8, 128.5, 117.7 (q, *J* = 283.3 Hz), 92.7, 21.6. **^{19}F NMR** (376 MHz, $CDCl_3$): δ / ppm = -76.53, -87.16. **IR:** 1595, 1488, 1264, 1198, 1150, 1112, 1077, 1000, 876, 815, 784, 744, 704, 675, 635.

4,4,4-trifluoro-1-(o-tolyl)butane-1,3-dione (**F-1d**):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.44 (td, *J* = 7.5, 1.4 Hz, 1H), 7.30 (dt, *J* = 7.2, 3.7 Hz, 2H), 6.33 (s, 1H), 2.55 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 191.6, 176.0 (q, *J* = 36.2 Hz), 138.8, 134.1, 132.6, 132.5, 129.4, 126.5, 117.8 (q, *J* = 282.6 Hz), 96.7, 21.4. **^{19}F NMR** (376 MHz, $CDCl_3$): -76.44, -87.15. **IR**: 1605, 1458, 1383, 1273, 1198, 1152, 1109, 1067, 1046, 916, 814, 771, 728, 703, 635.

4,4,4-trifluoro-1-(4-methoxyphenyl)butane-1,3 dione (**F-1e**):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.7 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 1H), 6.51 (s, 2H), 3.90 (s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 186.0, 175.5 (q, *J* = 35.9 Hz), 164.5, 129.2, 125.1, 117.2 (q, *J* = 281 Hz), 114.2, 113.5, 91.3, 55.3. **^{19}F NMR** (376 MHz, $CDCl_3$): -76.33. **IR**: 1585, 1509, 1446, 1310, 1252, 1192, 1167, 1141, 1129, 1112, 1069, 1023.28, 917, 841, 817, 801, 698.

4,4,4-trifluoro-1-(3-methoxyphenyl)butane-1,3-dione (**F-1f**):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (dd, *J* = 7.0, 0.8 Hz, 1H), 7.45 (s, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.16 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 6.56 (s, 1H), 3.88 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 186.8, 177.2 (q, *J* = 36.3 Hz), 160.5, 134.7, 130.4, 120.6, 120.5, 117.7 (q, *J* = 143 Hz), 112.8, 92.9, 55.8. **^{19}F NMR** (376 MHz, $CDCl_3$): δ -76.48. **IR**: 1649, 1570, 1491, 1471, 1454, 1440, 1397, 1337, 1293,

1254, 1201, 1177, 1141, 1113, 1061, 1039, 992, 918, 902, 874, 831, 785, 741, 706, 675, 619.

4,4,4-trifluoro-1-(2-methoxyphenyl)butane-1,3-dione (**F-1g**):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.54 (t, *J* = 7.9 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 7.02 (s, 1H), 7.00 (s, 1H), 3.94 (s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 184.9, 177.6 (q, *J* = 35.7 Hz), 159.9, 135.5, 131.0, 122.3, 121.3, 117.8 (q, *J* = 283.4 Hz), 112.2, 97.8, 56.1, 52.4. **^{19}F NMR** (376 MHz, $CDCl_3$): δ -76.45. **IR**: 1601, 1490, 1468, 128, 1252, 1227, 1195, 1155, 1110, 1066, 1044, 1019, 894, 855, 815, 765, 748, 707, 680, 622.

1-(4-bromophenyl)-4,4,4-trifluorobutane-1,3-dione (**F-1h**):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.8 Hz, 2H), 7.66 (d, *J* = 8.8 Hz, 2H), 6.54 (s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 185.4, 177.9 (q, *J* = 36.5 Hz), 132.9, 132.2, 129.8, 129.4, 117.5 (q, *J* = 283.3 Hz), 92.8. **^{19}NMR** (376 MHz, $CDCl_3$): δ = -76.49. **IR :** 1587, 148, 1269, 1246, 120, 1178, 1147, 112, 1107, 1077, 1064, 1011, 890, 83, 795, 750, 72, 655.

1-(3-bromophenyl)-4,4,4-trifluorobutane-1,3-dione (**F-1i**):

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (t, *J* = 1.8 Hz, 1H), 7.87 (ddd, *J* = 7.9, 1.7, 1.0 Hz, 1H), 7.75 (ddd, *J* = 8.0, 1.9, 1.0 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 184.8, 177.8 (q, *J* = 36.5 Hz), 137.2, 135.2, 130.9, 126.5, 123.7, 117.5 (q, *J* = 283.3 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -76.53.

IR: 1600, 1562, 1474, 127, 1238, 1202, 1154, 1117, 1103, 1066, 998, 919, 880, 822, 785, 738, 71, 666, 626.

1-(2-bromophenyl)-4,4,4-trifluorobutane-1,3-dione (**F-1j**):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (dd, *J* = 7.9, 1.2 Hz, 2H), 7.46 – 7.35 (m, 2H), 6.49 (s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 189.1, 175.4 (q, *J* = 36.7 Hz), 136.1, 134.7, 133.4, 130.7, 128.1, 120.9, 117.6 (q, *J* = 282.4 Hz), 98.3. **^{19}F NMR** (376 MHz, $CDCl_3$): δ -76.40. **IR**: 1598, 1472, 1441, 1279, 1232, 1201, 1152, 1111, 1080, 1027, 916, 868, 810, 765, 725, 659, 622.

4,4,4-trifluoro-1-(4-nitrophenyl)butane-1,3-dione (**F-1m**):

^{1}H NMR (400 MHz, CDCl3): δ 8.36 (d, *J* = 9.1 Hz, 2H), 8.12 (d, *J* = 9.1 Hz, 2H), 6.62 (s, 1H). **^{13}C NMR** (100 MHz, CDCl3): δ 182.2, 197.0 (q, *J* = 37.0 Hz), 150.7, 138.1, 128.6, 124.1, 116.8 (q, *J* = 284 Hz), 93.5. **^{19}F NMR** (376 MHz, CDCl3): δ -76.70. **IR :** $\tilde{\nu}$ / cF-1 1604, 1583, 1525, 1491, 1343, 1323, 1272, 1207, 1152, 1126, 1107, 1062, 1012, 869, 855, 806, 761, 728, 702, 655.

4,4,4-trifluoro-1-(3-nitrophenyl)butane-1,3dione (**F-1n**):

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (s, 1H), 8.48 (d, *J* = 9.3 Hz, 1H), 8.27 (d, *J* = 7.9 Hz, 1H), 7.75 (t, *J* = 8.0 Hz, 1H), 6.64 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ183.4, 178.5 (q, *J* = 36.9 Hz), 149.1, 135.0, 133.4, 130.8, 128.1, 122.9, 117.3 (q, *J* = 283.5 Hz), 93.5. **^{19}F NMR** (376 MHz, $CDCl_3$): δ -76.56. **IR**: 1594, 1537, 1482, 1348, 128, 1244, 1207, 1151, 1123, 1095, 1068, 1001, 920, 885, 811, 752, 70, 672, 655, 622.

4,4,4-trifluoro-1-(2nitrophenyl)butane-1,3-dione (**F-1o**):

^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 8.01 (d, *J* = 7.5 Hz, 1H), 7.71 (dd, *J* = 14.5, 7.4 Hz, 2H), 7.59 (d, *J* = 7.1 Hz, 1H), 6.22 (s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 189.5, 172.2 (q, *J* = 36.6 Hz), 147.4,133.6, 132.3, 132.3, 129.2, 124. 3, 96.9, 30.0. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -75.89. **IR:** 1704, 1646, 157, 153, 1368, 1349, 1309, 1265, 1242, 119, 1164, 1118, 110, 1036, 967, 85, 822, 784, 163, 729, 716, 657,629.

4,4,4-trifluoro-1-(4-(trifluoromethyl)phenyl)butane-1,3-dione (**F-1p**):

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 2H), 6.59 (s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 184.8, 178.5 (d, *J* = 42.5 Hz),136.9, 135.6 (q, *J* = 33.0 Hz), 128.4, 126.4 (d, *J* = 3.3 Hz), 123.9 (q, *J* = 272.7 Hz), 117.6 (q, *J* = 283.6 Hz), 93.3. **^{19}F NMR** (376 MHz, $CDCl_3$): δ -63.59, -76.84. **IR:** 1600, 1577, 1449, 1324, 1282, 1132, 1107, 1059, 1016, 857, 802, 715, 647.

4,4,4-trifluoro-1-(3-(trifluoromethyl)phenyl)butane-1,3-dione (**F-1q**):

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.13 (d, *J* = 7.9 Hz, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 6.60 (s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.7, 178.4 (q, *J* = 36.7 Hz), 134.2, 132.3 (q, *J* = 33.2 Hz), 131.1, 130.8 (q, *J* = 3.6 Hz), 130.2, 124.9 (q, *J* = 3.8 Hz), 120.8 (q, *J* = 271 Hz), 120.8 (q, *J* = 542 Hz), 93.2 (d, *J* = 1.7 Hz).**^{19}F NMR** (376 MHz, $CDCl_3$): δ -63.03, 76.59. **IR**: 1588, 1460, 1419, 1323, 1272, 1231, 120, 1190, 1169, 1152, 1117, 1066, 1001, 923, 878, 798, 764, 746, 720, 691, 657, 624.

New compound characterization data

Methyl 3-benzoyl-4-(trifluoromethyl) benzoate (F-2a): colorless oil (293 mg, 95%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.2 Hz, 1H), 8.05 (s, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 7.4 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 3.94 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 194.4, 165.1, 138.8 (q, *J* = 2.0 Hz), 136.0, 134.2, 133.1, 131.9 (q, *J* = 24.7 Hz), 130.7, 130.2 (2C), 129.1, 128.7 (2C), 127.1 (q, *J* = 4.6 Hz), 123.1 (q, *J* = 275.7 Hz), 52.7; **^{19}F NMR** (376 MHz, $CDCl_3$) δ —58.5; **IR** (film, cF-1): 2957, 1730, 1678, 1495, 1450, 1244, 988, 947, 754; **HRMS** (ESI) *m/z* calcd for [M+Na^{+}] $C_{16}H_{11}F_3NaO_3$ 331.0552, found 331.0543.

Methyl 3-(4-methylbenzoyl)-4-(trifluoromethyl) benzoate (F-2b): yellow solid (291 mg, 90 %); mp: 106-107 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.31 – 8.22 (m, 1H), 8.06 (d, *J* = 0.6 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 3.95 (s, 3H), 2.44 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 194.0, 165.1, 145.3, 139.0 (q, *J* = 2.0 Hz), 133.5, 133.0, 131.8 (q, *J* = 32.7 Hz), 130.6, 130.3, 129.4, 129.1, 127.03 (q, *J* = 4.6 Hz), 123.14 (q, *J* = 274.6 Hz). 52.7, 21.7; **^{19}F NMR** (376 MHz, $CDCl_3$) δ —58.5; **IR** (film, cF-1): 2957, 1300, 1170, 1140, 1108; **HRMS** (ESI) *m/z* calcd for [M+Li$^+$] $C_{17}H_{13}F_3LiO_3$ 329.0972, found 329.0976.

Methyl 3-(3-methylbenzoyl)-4-(trifluoromethyl) benzoate (F-2c): yellow solid (263 mg, 82 %); mp: 78-79 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.43 – 8.21 (m, 1H), 8.08 (d, *J* = 0.6 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.65 (s, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 3.97 (s, 3H), 2.42 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)) δ 194.6, 165.1, 139.0 (q, *J* = 2.0 Hz), 138.7, 137.7, 136.0, 135.0, 133.1, 131.8 (q, *J* = 32.7 Hz), 130.7, 130.4, 129.1, 128.5, 127.7, 127.1 (q, *J* = 4.6 Hz), 123.2 (q, *J* = 274.5 Hz), 52.7, 21.2; **^{19}F NMR** (376 MHz, $CDCl_3$) δ —58.5; **IR** (film, cm-1): 1696, 1638, 1580, 1305, 1064,; **HRMS** (ESI) *m/z* calcd for [M+Na$^+$] $C_{17}H_{13}F_3NaO_3$ 345.0709, 345.0721.

Methyl 3-(2-methylbenzoyl)-4-(trifluoromethyl) benzoate (F-2d): yellow solid (309 mg, 96 %); mp: 99-100 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.2 Hz, 1H), 8.01 (s, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 6.8 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 3.88 (s, 3H), 2.61 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)) δ 195.8, 164.7, 140.3, 140.1 (q, *J* = 1.8 Hz), 135.1, 132.8, 132.5, 132.4, 131.9, 131.4

(q, J = 32.0 Hz), 130.5, 129.3, 126.8 (q, J = 4.7 Hz), 125.2, 122.9 (q, J = 274.5 Hz), 52.3, 21.2; **^{19}F NMR** (376 MHz, $CDCl_3$) δ —58.5; **IR** (film, cm^{-1}): 1702, 1623, 1371, 1263, 1193, 1124, 1026; **HRMS** (ESI) *m/z* calcd for [M+Na^+] $C_{11}H_{19}F_3NaO_3$ 345.0709, found 345.0708.

Methyl 3-(4-methoxybenzoyl)-4-(trifluoromethyl) benzoate (F-2e): yellow solid (308 mg, 91 %); mp: 108-109 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.20 (d, J = 8.2 Hz, 1H), 8.02 (s, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.70 (d, J = 8.9 Hz, 1H), 6.90 (d, J = 8.9 Hz, 2H), 3.89 (s, 3H), 3.82 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 192.9, 165.1, 164.4, 133.0, 132.6 (2C), 139.1 (q, J = 2.0 Hz), 131.6 (q, J = 32.6 Hz), 130.5, 129.0, 129.0, 127.0 (q, J = 4.5 Hz), 123.2 (q, J = 274.6 Hz), 113.9 (2C), 55.5, 52.6; **^{19}F NMR** (376 MHz, $CDCl_3$): δ—58.6; **IR** (film, cm^{-1}): 1690, 1637, 1587, 1525, 1287, 1212, 1183, 1146; **HRMS** (ESI) *m/z* calcd for [M+Na^+] $C_{17}H_{13}F_3NaO_4$ 361.0658, found 361.0664.

Methyl 3-(3-methoxybenzoyl)-4-(trifluoromethyl) benzoate (F-2f): yellow solid (284 mg, 84 %); mp: 100-101 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.24 (d, J = 8.2 Hz, 1H), 8.06 (s, 1H), 7.85 (d, J = 8.2 Hz, 1H), 7.44 – 7.39 (m, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.19 (d, J = 7.7 Hz, 1H), 7.14 (dd, J = 8.2, 2.6 Hz, 1H), 3.91 (s, 3H), 3.81 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 194.5, 165.3, 160.2, 139.1 (q, J = 1.9 Hz), 137.6, 133.4, 132.1 (q, J = 32.7 Hz), 131.1, 129.9, 129.4, 127.4 (q, J = 4.5 Hz), 123.8, 123.5 (q, J = 274.6 Hz), 121.0, 114.1, 55.7, 53.0; **^{19}F NMR** (376 MHz, $CDCl_3$): δ —58.6; **IR** (film, cm^{-1}): 1693, 1638, 1589, 1542, 1378, 1312, 1289, 1258, 1214, 1183; **HRMS** (ESI): *m/z* calcd for [M+K^+] $C_{17}H_{13}F_3KO_4$ 377.0398, found 377.0388.

Methyl 3-(2-methoxybenzoyl)-4-(trifluoromethyl) benzoate (F-2g): yellow solid (247 mg, 73 %); mp: 100-101 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.2 Hz, 1H), 7.95 (s, 1H), 7.85 – 7.74 (m, 2H), 7.54 (ddd, *J* = 8.5, 7.4, 1.8 Hz, 1H), 7.05 (td, J = 7.4, 0.8 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 3.91 (s, 3H), 3.51 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.5, 165.2, 159.4, 142.0 (q, *J* = 2.0 Hz), 135.2, 132.7, 131.6, 130.5 (q, *J* = 32.6 Hz), 129.8, 127.9, 126.4 (q, *J* = 4.7 Hz), 125.8, 123.1 (CF_3, q, *J* = 274.4 Hz), 120.5, 111.9, 55.2, 52.4; **^{19}F NMR** (376 MHz, $CDCl_3$): δ —58.6; **IR** (film, cm^{-1}): 1693, 1626, 1543, 1318, 1295, 1271, 1208, 1162, 1143, 1067, 1028; **HRMS** (ESI) *m/z* calcd for [M+Na^+] $C_{17}H_{13}F_3NaO_4$ 361.0658, found 361.0665.

Methyl 3-(4-bromobenzoyl)-4-(trifluoromethyl) benzoate (F-2h): yellow solid (366 mg, 95 %); mp: 76-77 °C; **^{1}H NMR** (400 MHz, CDCl3): δ 8.27 (d, J = 8.2 Hz, 1H), 8.02 (s, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.62 (m, 4H), 3.90 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.0, 164.6, 137.8 (q, *J* = 2.0 Hz), 133.7, 134.5, 132.9, 131.8, 131.5 (q, *J* = 32.7 Hz), 131.2, 130.7, 129.4, 128.7, 126.9 (q, *J* = 4.6 Hz), 122.8 (q, *J* = 273.0 Hz), 52.5; **^{19}F NMR** (376 MHz, $CDCl_3$): δ —58.4; **IR** (film, cm^{-1}): 1707, 1628, 1522, 1260, 1211, 1185, 1159, 1127, 1083 ; **HRMS** (ESI): *m/z* calcd for [M+Na^+] $C_{16}H_{10}BrF_3NaO_3$ 408.9658, found 408.9641.

Methyl 3-(3-bromobenzoyl)-4-(trifluoromethyl) benzoate (F-2i): yellow solid (320 mg, 83 %); mp: 76-77 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.2 Hz, 1H), 8.03 (s, 1H), 7.92 (t, *J* = 1.8 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.75 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.64 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 3.95 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.3, 165.2, 138.2 (q, *J* = 1.9 Hz), 138.1, 137.3, 133.6, 132.9, 132.1 (q, *J* = 32.7

Hz), 131.4, 130.6, 129.3, 129.2, 127.6 (q, *J* = 4.5 Hz), 123.4, 123.4 (q, *J* = 274.6 Hz), 53.1; **^{19}F NMR** (376 MHz, $CDCl_3$): δ —58.4; **IR** (film, cm^{-1}): 1701, 1607, 1275, 1209, 1162, 1145, 1120, 1075; **HRMS** (ESI): *m/z* calcd for [M+Na^+] $C_{16}H_{10}BrF_3NaO_3$ 408.9658, found 408.9622.

Methyl 3-(2-bromobenzoyl)-4-(trifluoromethyl) benzoate (F-2j): yellow solid (330 mg, 85 %); mp: 97-98 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.2 Hz, 1H), 8.03 (s, 1H), 7.92 (t, *J* = 1.8 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.75 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.64 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 3.95 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.3, 165.2, 138.2 (q, *J* = 1.9 Hz), 138.1, 137.3, 133.6, 132.9, 132.1 (q, *J* = 32.7 Hz), 131.4, 130.6, 129.3, 129.2, 127.6 (q, *J* = 4.5 Hz), 123.4, 123.4 (q, *J* = 274.6 Hz), 53.1; **^{19}F NMR** (376 MHz, $CDCl_3$): δ —58.4; **IR** (film, cm^{-1}): 1705, 1602, 1380, 1311, 1291, 1268, 1247, 1210, 1189, 1168, 1151, 1133, 1121; **HRMS** (ESI): *m/z* calcd for [M+Na^+] $C_{16}H_{10}BrF_3NaO_3$ 408.9658, found 408.9650.

Methyl 3-(4-chlorobenzoyl)-4-(trifluoromethyl) benzoate (F-2k): yellow solid **(**273mg, 80%**)**; mp: 110-111 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.29 (ddd, *J* = 8.2, 1.6, 0.8 Hz, 1H), 8.08 – 8.02 (m, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.76 – 7.67 (m, 2H), 7.50 – 7.42 (m, 2H), 3.96 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.1, 164.9, 140.8, 138.2 (q, *J* = 2.0 Hz), 134.3, 133.2, 131.9 (q, *J* = 32.8 Hz), 131.5, 131.0 (2C), 127.2 (q, *J* = 4.6 Hz), 129.1 (2C), 129.0, 123.0 (CF_3, q, *J* = 274.6 Hz), 52.8; **^{19}F NMR** (376 MHz, $CDCl_3$) δ —58.4; **IR** (film, cm^{-1}): 2955, 1734, 1673, 1587, 1439, 1168, 1043, 1011, 943, 916, 855, 780, 707; **HRMS** (ESI) *m/z* calcd for [M+Na^+] $C_{16}H_{10}ClF_3NaO_3$ 365.0163, found 365.0167.

Methyl 3-(4-fluorobenzoyl)-4-(trifluoromethyl) benzoate (F-2l): yellow solid **(**304mg, 93%**)**; mp: 95-96 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 (ddd, *J* = 8.2, 1.6, 0.8 Hz, 1H), 8.10 – 8.02 (m, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.86 – 7.76 (m, 2H), 7.20 – 7.10 (m, 2H), 3.96 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 192.8, 166.3 (d, *J* = 257.1 Hz), 165.0, 138.4 (q, *J* = 2.0 Hz) 133.2, 132.9 (d, *J* = 9.7 Hz), 131.8 (q, *J* = 32.7 Hz) 130.9, 129.0, 127.16 (q, *J* = 4.6 Hz)，123.1 (q, *J* = 274.6 Hz), 115.96 (d, *J* = 22.1 Hz) 52.8; **^{19}F NMR** (376 MHz, $CDCl_3$) δ —58.50, —102.93 (m); **IR** (film, cm^{-1}) : 2955, 1733, 1672, 1598, 1306, 1173, 1158, 1114, 1045, 983, 926, 850, 782, 715; **HRMS** (ESI) *m/z* calcd for [M+Na^+] $C_{16}H_{10}F_4NaO_3$ 349.0458, found 349.0465.

Methyl 3-(4-nitrobenzoyl)-4-(trifluoromethyl) benzoate (F-2m): yellow solid (322 mg, 91%); mp: 108-109 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.32 – 8.30 (m, 3H), 8.05 (s, 1H), 7.96 – 7.89 (m, 3H), 3.91(s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.1, 165.1, 151.2, 140.7, 137.7, 133.9, 132.2 (q, *J* = 32.9 Hz), 131.7 (q, *J* = 1.7 Hz), 131.4, 129.3, 127.8 (q, *J* = 4.5 Hz), 124.2 (2C), 123.3 (q, *J* = 274.5 Hz), 53.2; **^{19}F NMR** (376 MHz, CDCl3): δ —58.3; **IR** (film, cm^{-1}): 1732, 1681, 1530, 1306, 1270, 1252, 1171, 1148, 1115, 1044; **HRMS** (ESI): m/z calcd for [M+Na^+] $C_{16}H_{10}F_3NNaO_5$ 376.0403, found 376.0393.

Methyl 3-(3-nitrobenzoyl)-4-(trifluoromethyl) benzoate (F-2n): yellow solid (327 mg, 93%); mp: 130-131 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.54 (t, *J* = 1.8 Hz, 1H), 8.48 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.33 (dd, *J* = 8.3 Hz, 1H), 8.09 (d, *J* = 7.7 Hz, 1H), 8.06 (s, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.71 (t, *J* = 7.7 Hz, 1H), 3.93 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 191.9, 164.5, 148.1, 137.1, 136.9 (q, *J* = 1.9 Hz), 135.1, 133.3, 131.6 (q, *J* = 32.8 Hz), 131.2, 129.9, 128.6, 128.0, 127.2 (q, *J* = 4.5 Hz), 124.3, 122.7 (q, *J* = 274.5

Hz), 52.5; **^{19}F NMR** (376 MHz, $CDCl_3$): δ —58.33; **IR** (film, cm^{-1}): 1732, 1608, 1581, 1438, 1350, 1304, 1269, 1197, 1158; **HRMS** (ESI): *m/z*, calcd for [M+Na^+] $C_{16}H_{10}F_3NNaO_5$ 376.0409, found 376.0403.

Methyl 3-(2-nitrobenzoyl)-4-(trifluoromethyl) benzoate (F-2o): yellow solid (275 mg, 78 %); mp: 97-98 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.2 Hz, 1H), 8.09 – 8.03 (m, 1H), 8.01 (s, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.79 – 7.67 (m, 2H), 7.57 – 7.50 (m, 1H), 3.90 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ190.8, 164.4, 147.7, 136.3 (q, *J* = 1.4 Hz), 134.0, 133.4, 133.1, 132.6, 132.5 (q, *J* = 33.3 Hz), 132.1, 130.7, 130.2, 127.9 (q, *J* = 5.6 Hz), 124.4, 122.6 (q, *J* = 274.5 Hz), 52.6; **^{19}F NMR** (376 MHz, $CDCl_3$): δ —59.0; **IR** (film, cm^{-1}): 1715, 1630, 1561, 1488, 1333, 1305, 1285, 1211, 1121, 1070; **HRMS** (ESI): *m/z* calcd for [M+Na^+] $C_{16}H_{10}F_3NNaO_5$ 376.0403, found 376.0415.

Methyl 3-(4-(trifluoromethyl)benzoyl)-4-(trifluoromethyl) benzoate (F-2p): yellow solid (304 mg, 81 %); mp: 78-79 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.2 Hz, 1H), 8.09 – 8.03 (m, 1H), 8.01 (s, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.79 – 7.67 (m, 2H), 7.57 – 7.50 (m, 1H), 3.90 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.7, 165.3, 139.1, 138.3 (q, *J* = 2.0 Hz), 135.8, 135.7 (q, *J* = 32.8 Hz), 135.5, 133.8, 132.3 (q, *J* = 32.8 Hz), 131.7, 130.8, 129.4, 127.7 (q, *J* = 4.5 Hz), 126.2 (q, *J* = 3.7 Hz), 123.9 (CF_3, q, *J* = 272.9 Hz), 123.5 (q, *J* = 274.5 Hz), 53.2; **^{19}F NMR** (376 MHz, $CDCl_3$): δ —58.48, —63.40; **IR** (film, cm^{-1}): 1732, 1706, 1602, 1390, 1284, 1262, 1214, 1129, 1085, 1054, 1027; **HRMS (ESI)**: *m/z* calcd for [M+Na^+] $C_{17}H_{10}F_6NaO_3$ 399.0426, found 399.0427.

Methyl 3-(3-(trifluoromethyl)benzoyl)-4-(trifluoromethyl) benzoate (F-2q): yellow solid (312 mg, 83 %); mp: 71-72 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ8.29 (d, *J* = 8.9 Hz, 1H), 8.06 (d, *J* = 6.4 Hz, 2H), 7.97 – 7.82 (m, 3H), 7.60 (t, *J* = 7.8 Hz, 1H), 3.93 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ193.5, 165.3, 138.2 (q, *J* = 1.9 Hz), 137.0, 133.9, 133.8,132.7 (q, *J* = 32.8 Hz), 132.3 (q, *J* = 23.2 Hz), 131.7, 130.9 (q, *J* = 3.5 Hz), 129.9, 129.4, 127.8 (q, *J* = 4.5 Hz), 126.9 (q, *J* = 3.8 Hz), 123.5 (CF_3, q, *J* = 274.5 Hz),123.9 (q, *J* = 272.6 Hz), 53.2; **^{19}F NMR** (376 MHz, $CDCl_3$): δ—58.44, —63.01; **IR** (film, cm^{-1}): 1732, 1706, 1602, 1390, 1284, 1262, 1214, 1129, 1085, 1054, 1027; **HRMS (ESI)**: *m/z* calcd for [M+Na^+] $C_{17}H_{10}F_6NaO_3$ 399.0426, found 399.0436.

Methyl 3-(furan-2-carbonyl)-4-(trifluoromethyl) benzoate (F-2r) : yellow solid (245 mg, 82 %); mp: 101-102 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 – 8.25 (m, 1H), 8.18 (d, *J* = 0.6 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.07 (d, *J* = 3.3 Hz, 1H), 6.60 (dd, *J* = 3.3, 1.7 Hz, 1H), 3.97 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 181.2, 165.0, 151.7, 148.4, 137.4 (q, *J* = 2.0 Hz), 133.1, 132.0 (q, *J* = 32.8 Hz), 131.2, 129.4, 127.2 (q, *J* = 4.7 Hz), 123.0 (q, *J* = 275.1 Hz), 121.7, 112.8, 52.8; **^{19}F NMR** (376 MHz, $CDCl_3$) δ —58.6; **IR** (film, cm^{-1}): 2961, 1733, 1659, 1565, 1498, 1305, 1261, 1151, 1132, 1115, 1014, 989, 958, 882, 784, 703; **HRMS** (ESI) *m/z* calcd for [M+Na^+] $C_{14}H_9F_3NaO_4$ 321.0345, found 321.0352.

Methyl 3-(thiophene-2-carbonyl)-4-(trifluoromethyl) benzoate: (F-2s) yellow solid **(**289mg, 92%**)**; mp: 103-104 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 (ddd, *J* = 8.2, 1.6, 0.8 Hz, 1H), 8.23 – 8.15 (m, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.81 (dd, *J* = 4.9, 1.2 Hz, 1H), 7.34 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.14 (dd, *J* = 4.9, 3.8 Hz, 1H), 3.97 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 186.3,

165.0, 143.3, 138.2 (q, *J* = 2.0 Hz), 136.2, 136.1, 133.1, 131.7 (q, *J* = 32.8 Hz), 131.0, 129.2, 128.4, 127.2 (q, *J* = 4.6 Hz), 123.0 (q, *J* = 274.6 Hz), 52.8; **^{19}F NMR** (376 MHz, $CDCl_3$) δ —58.5; **IR** (film, cm^{-1}): 2957, 1734, 1643, 1513, 1441, 1411, 1304. 1277, 1192, 1139, 1116, 972, 771, 729, 681; **HRMS** (ESI) *m/z* calcd for [M+Li^+] $C_{14}H_9F_3LiO_3S$ 321.0379, found 321.0389.

Methyl 3-(2-naphthoyl)-4-(trifluoromethyl) benzoate (F-2t): yellow solid **(**340mg, 95%**)**; mp: 133-134 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20 (ddd, *J* = 8.2, 1.6, 0.8 Hz, 1H), 8.03 (d, *J* = 0.6 Hz, 1H), 7.98 (s, 1H), 7.91 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.87 – 7.69 (m, 4H), 7.52 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.42 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 3.83 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 194.4, 165.1, 138.9 (q, *J* = 1.9 Hz), 136.1, 133.5, 133.4, 133.2, 132.2, 132.0 (q, *J* = 32.7 Hz), 130.8, 129.8, 129.2, 129.2, 128.8, 127.9, 127.2 (q, *J* = 4.6 Hz), 127.1, 124.5, 123.2 (q, *J* = 274.6 Hz). 52.7; **^{19}F NMR** (376 MHz, $CDCl_3$) δ —58.4. **IR** (film, cm^{-1}): 2977, 1735, 1669, 1436, 1280, 985; **HRMS** (ESI) *m/z* calcd for [M+Li^+] $C_{20}H_{13}F_3LiO_3$ 365.0972, found 365.0976.

Methyl 3-acetyl-4-(trifluoromethyl) benzoate (F-2u) : colorless oil (184mg 74%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (ddd, *J* = 8.2, 1.6, 0.8 Hz, 1H), 8.13 – 8.06 (m, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 3.95 (s, 3H), 2.60 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.6, 165.0, 140.7 (q, *J* = 1.9 Hz), 133.5, 131.0, 130.5 (q, *J* = 32.8 Hz), 128.1, 123.1 (q, *J* = 274.1 Hz), 52.8, 30.4 (q, *J* = 1.7 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$) δ —58.7. **IR** (film, cm^{-1}): 2958, 1730, 1711, 1497, 1439, 1302, 1263, 1172, 1129, 1038, 916, 859, 773, 748; **HRMS** (ESI) *m/z* calcd for [M+Li^+] $C_{11}H_9F_3LiO_3$ 253.0659, found 253.0667.

Methyl 3-isobutyryl-4-(trifluoromethyl) benzoate (F-2v): colorless oil (159mg, 58%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 – 8.14 (m, 1H), 8.08 (s, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 3.98 (s, 3H), 3.33 – 3.11 (m, 1H), 1.22 (s, 3H), 1.20 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 207.0, 165.1, 140.1 (q, *J* = 2.0 Hz), 131.1 (q, *J* = 32.6 Hz), 133.3, 130.8, 127.3 (q, *J* = 4.9 Hz), 128.1, 123.1 (q, *J* = 274.2 Hz), 52.7, 40.4, 18.0; **^{19}F NMR** (376 MHz, $CDCl_3$) δ —58.5. **IR** (film, cm^{-1}): 2977, 2877, 1732, 1709, 1438, 1302, 1258, 1164, 1114, 964, 918, 858, 770; **HRMS** (ESI) *m/z* calcd for [M+Na^+] $C_{13}H_{13}F_3NaO_3$ 297.0709, found 297.0720.

Methyl 3-benzoyl-4-(perfluoroethyl) benzoate (F-2w): yellow oil (255mg, 71%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22 – 8.15 (m, 1H), 7.93 (d, *J* = 1.1 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.66 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.57 – 7.45 (m, 1H), 7.45 – 7.31 (m, 2H), 3.84 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 194.1, 165.0, 136.1, 134.0, 133.2, 130.2, 130.1 (2C), 128.9, 128.6 (2C), 52.72; **^{19}F NMR** (376 MHz, $CDCl_3$) δ —83.48, —108.18. **IR** (film, cm^{-1}): 2957, 1731, 1682, 1450, 1438, 1206, 1163, 1148, 1114, 1080; **HRMS** (ESI) *m/z* calcd for [M+Na^+] $C_{17}H_{11}F_5NaO_3$ 381.0521, found 381.0531.

Procedure for the gram scale synthesis of compound F-2b

In a 25 mL round-bottom flask equipped with magnetic stir bar, Methyl coumalate (1g, 6.5 mmol, 1 equiv), 4,4,4-trifluoro-1-(p-tolyl)butane-1,3-dione **F-1b** (1.49g, 6.5 mmol, 1 equiv) and *t*BuOK (73 mg, 6.5 mmol, 0.1 equiv) were added, and the mixture was stirred at 80 °C for 2 hours. When the reaction was completed 10ml absolute EtOH was added and heated to reflex to 5 min, the mixture was cool down to room temperature and gave 1.87 g (89%) of recrystallized **F-2b**.

Procedure for the one-pot synthesis of compound F-3a

To an oven-dried sealed tube equipped with magnetic stir bar was added methyl coumalate (31 mg, 0.2 mmol, 1 equiv), **F-1a** (43 mg, 0.2 mmol, 1 equiv) and *t*BuOK (2 mg, 0.2 mmol, 0.1 equiv). The reaction was stirred at 80 °C for 2 hours, cool to rt then $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 equiv) followed by Ag_2O (69 mg, 0.3 mmol, 1.5 equiv) were added and the flask purged three times with argon. Trifluoroacetic acid (2 mL) was added to the system and the reaction mixture was stirred at 130 °C for 36 h. After completion of the reaction, the reaction mixture was cooled, filtered through a short pad of Celite® and washed several times with dichloromethane. The combined filtrate was concentrated under vacuum and the residue purified by flash chromatography on silica gel column using cyclohexane/EtOAc as eluent to give the desired product **F-3a**.

Methyl 9-oxo-1- (trifluoromethyl) -9H- fluorene-4-carboxylate (F-3a): yellow solid **(**43.4 mg, 66%**); ^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (dt, *J* = 7.8, 0.8 Hz, 1H), 7.95 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.75 (ddd, *J* = 7.4, 1.3, 0.7 Hz, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.54 (td, *J* = 7.7, 1.3 Hz, 1H), 7.41 (td, *J* = 7.4, 0.8 Hz, 1H), 4.05 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.0, 166.6, 145.4, 141.4, 135.3, 135.3, 133.7, 132.5, 130.6, 130.2 (q, *J* = 35.4 Hz), 130.1, 125.7 (q, *J* = 5.9 Hz), 125.4, 124.6, 122.1 (q, *J* = 274.6 Hz), 53.0; **^{19}F NMR** (376 MHz, $CDCl_3$) δ —61.7; **HRMS** (ESI) *m/z* calcd for $[M+Na^+]$ $C_{16}H_9F_3NaO_3$ 329.0396 found 329.0397.

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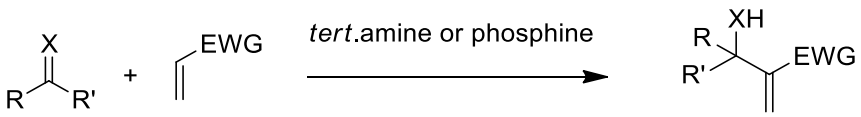
Chapter 5. Bio-based methyl coumalate involved Morita-Baylis-Hillman reaction.

5.1. General introduction of Morita-Baylis-Hillman reaction

The C-C bond formation reactions are essential for constructing organic frameworks.[1–3] Morita– Baylis–Hillman (MBH) reaction represents a milestone for the C-C bond formation reactions not only for its atom economy and metal free catalytic system, but also attributed to its enormous synthetic utility, and potential application.[4–8]

The MBH reaction was first reported in 1968,[9] which can be described as the coupling between the α- position of an activated alkenes (esters, nitriles, aldehydes, ketones, amides, phosphonates, nitro, sulphonates, sulfones, and sulfoxides functionalized compounds have been applied) and an sp^2 electrophilic carbon (imines, aldehydes and activated ketones) in the presence of a catalyst (generally tertiary amine or phosphine) (Scheme 1), leading to the formation of a multifunctional molecule, which is generally referred to as the Baylis-Hillman adducts.

Scheme 1 Morita-Baylis-Hillman reactions

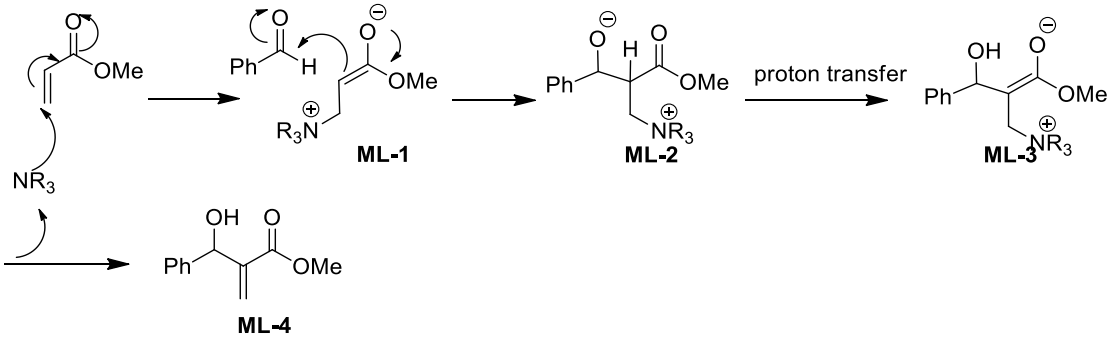


R = aryl, alkyl, heteroary; R' = H, COOR
X = O, NCOR, NTs, NSO_2Ph etc.

The most commonly adopted mechanism is presented in Scheme **2**.[10–12] The first step consists of a Michael-type nucleophilic 1,4-addition of the catalyst on the electron-deficient alkene, generating the zwitterion **ML-1**. The zwitterion **ML-1** is responsible for an nucleophilic attack on electrophile, forming intermediate **ML-2**. The following proton shift gives the enolate, which subsequently generates the final MBH adduct **ML-4** after release of the tertiary amine (or phosphine)

catalyst.

Scheme 2 Mechanism of Morita– Baylis−Hillman reaction



Intense academic study and industrial application of this reaction are evidenced by a large number of research papers and patents. Disappointingly, reactants are dominated by petroleum-based chemicals, though furfural and hydroxymethylfurfural have been reported as Baylis–Hillman acceptors.[13]

Progresses have been made to develop bio-derived Baylis–Hillman donors. Paine *et al*. and Corma *et al.* have described two bio-based pathways to acquire the Baylis–Hillman donors acrolein and methyl vinyl ketone (MVK).[14] Recently, Beckham *et al.* reported a sustainable synthesis of acrylonitrile from ethyl 3-hydroxypropanoate.[15] The problem remains, acrolein, acrylonitrile and methyl vinyl ketone are known hazardous chemicals. They are highly flammable, very toxic, corrosive and dangerous for the environment. In contrast, MC is a non-hazardous, bio-based chemical. Produced from dimerization of malic acid, MC is a biorenewable synthon with diverse synthetic applications. We recently discovered that MC can serve as Michael acceptor, which may readily be converted to pyran intermediates, after 1,6-conjugate addition in the presence of certain nucleophiles (see other chapters).[16–19] Inspired by these findings, we began studying the nucleophilicity of pyran zwitterionic intermediates in the MBH catalytic pathway (Figure 1). Challenges existed in trapping pyran intermediates with electrophiles, while competing with the side reactions (i.e.

ring opening and decarboxylation).[20] Moreover, dienolates generated from 1,6-addition are, theoretically, weaker nucleophiles than regular enolates. The delocalization of negative charge on an extra π bond confers greater thermodynamic stability. In addition, the C-C functionalization of 2-pyrones remains a challenge. To the best of our knowledge, neither the usage of methyl coumalate (or other 2-pyrone derivatives) as Baylis–Hillman donors, nor the 1,6-conjugate addition-triggered MBH reaction has been reported in previous literature.

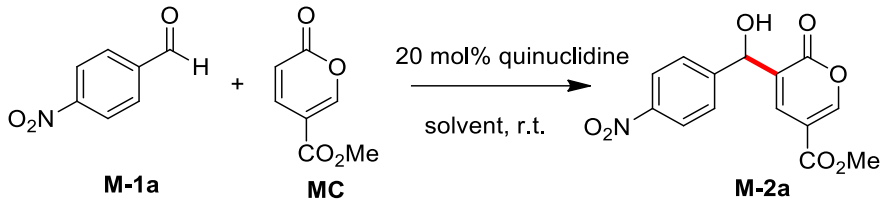
This research embodies four key principles of green chemistry: *less hazardous chemical syntheses, atom economy, catalysis,* and *use of renewable feedstocks*. Herein we report a novel MBH reaction, which employs bio-based feedstock, *via* a 1,6-conjugate addition triggered MBH mechanism.

5.2. Methyl coumalate involved MBH reaction

5.2.1.Optimization of reaction condition

We began our investigation by optimizing the solvent. We combined *p*-nitrobenzaldehyde **M-1a** and methyl coumalate (**MC**) in the presence of 20 mol% quinuclidine for the room-temperature model reaction (Table 1). No reaction occurred in toluene or DMSO (entries 1, 2). Low yields were obtained in DCM and THF after 2 to 4 days (entries 3, 4). Only trace amounts of **M-2a** were detected with acetonitrile (entry 5). We were pleased to find that the reaction ran smoothly in protic solvents: Yields of **M-2a** were substantial in ethanol (24h, 62%, entry 6) and isopropanol (36h, 51%, entry 7). Furthermore, the combination of water with THF (1:1) offered no improvement on the product yield (entry 8). Based on these data, ethanol was chosen as the ideal solvent.

Table 1 Optimization of solvents



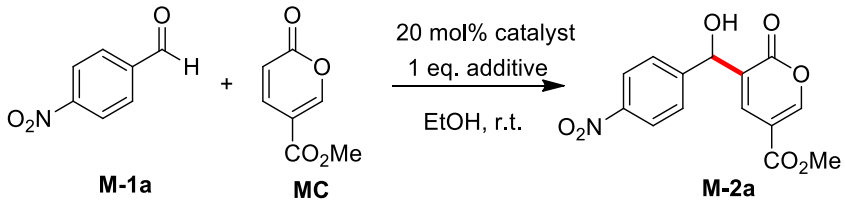
Entry	Solvent	Time (h)	Conversion	Yield % [b]
1	toluene	24	0	0
2	DMSO	48	0	0
3	THF	48	77	30
4	DCM	96	59	25
5	CH_3CN	48	100	trace
6	EtOH	24	100	62
7	*i*Pr-OH	38	100	51
8	THF/H_2O[c]	48	100	21

[a] Reaction conditions: All reactions were performed with MC (1 mmol) and p-nitrobenzaldehyde 1a (1 mmol). [b] isolated yields. [c] THF : H_2O (1 : 1) mixture.

The subsequent survey of different Lewis bases in ethanol is summarized in Table 2. It should be noted, that no reaction occurred in the absence of catalyst (entry 1). 20 mol% Ph_3P (entry 2) failed to initiate the reaction; however, the less hindered and more nucleophilic *n*Bu_3P generated **M-2a** in 14% yield (entry 3). There was not a dramatic difference in catalysis between quinuclidine (entry 4), DABCO (entry 5) and Et_3N (entry 6). The salt effect was investigated to improve MBH reaction efficiency. Intriguingly, we observed a dramatic acceleration of reaction rate. Addition of 1 equiv KCl to the quinuclidine catalyst facilitates reaction completion in 4 h, affording compound **M-2a** in 62% yield (entry 7). Similar results (4 h, 64%, entry 8) were obtained when employing 1 equiv LiCl. To our delight, K_2CO_3 spurred the reaction to completion in only 1.5 h (entries 9-11) whereas substoichiometric quantities were not as efficient (0.5 equiv., 6 h, 60%).

These results show an optimal combination Lewis base and salt: 20 mol% of Et_3N and 1 equiv. of K_2CO_3 in ethanol. It has to be pointed out that the synthesis could be readily scaled up to grams quantities without any difficulties, providing 2.14 g (70%) of compound **M-2a**.

Table 2 Optimization of catalysts and additives

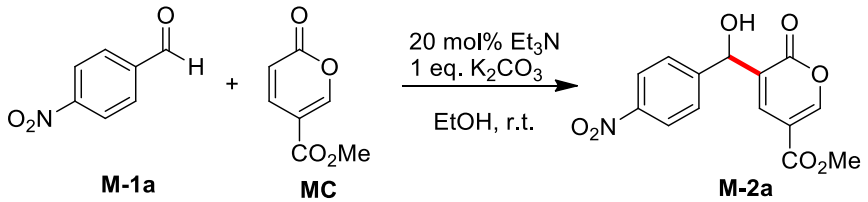


Entry	Catalyst	additive [b]	Time (h)	Yield % [c]
1	/	/	24	NR
2	Ph_3P	/	24	NR
3	*n*-Bu_3P	/	96	14
4	quinuclidine	/	24	62
5	DABCO	/	48	66
6	NEt_3	/	48	56
7	quinuclidine	KCl	4	62
8	quinuclidine	LiCl	4	64
9	quinuclidine	K_2CO_3	1,5	66
10	DABCO	K_2CO_3	1,5	63
11	**NEt_3**	**K_2CO_3**	**1,5**	**74**

[a] Reaction conditions: All reactions were performed with MC (1 mmol) and p-nitrobenzaldehyde **1a** (1 mmol) in EtOH 3 mL until **MC** completed . [b] 1 equiv of additive added. [c] isolated yields.

No significant yield enhancement was found when using 1.5 equiv of MC (Table 3, entry 1). Applying 2 equiv. of MC afford **M-2a** in 80% after 6 hours. However no improvement in yield was observed when adding more aldehyde. Considering these results therefor we believe the 1:1 reactant ratio to be the best choice.

Table 3 The study of the reactants ratio

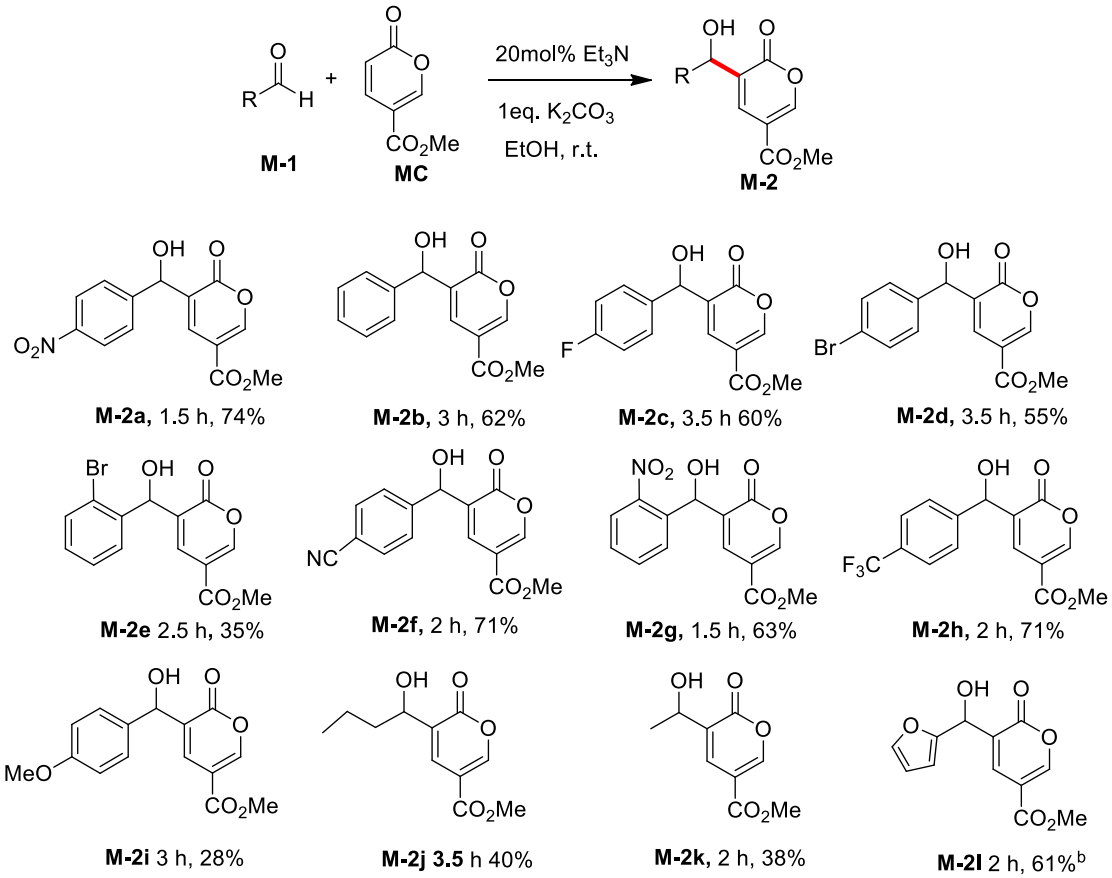


Entry	Ratio **1a : MC**	Time (h)	Yield %
1	1 : 1	1.5	74
2	1 : 1.5	3.5	75
3	1 : 2	6	80
4	2 : 1	1.5	72

5.2.2. Synthesis of bio-based MBH adducts

With the optimized conditions in hand, we explored the scope and limitations of these reactions (Table 4). A broad range of aldehydes was tolerated. Moderate yield was achieved with benzaldehyde as BHA (**M-2b**, 62%).

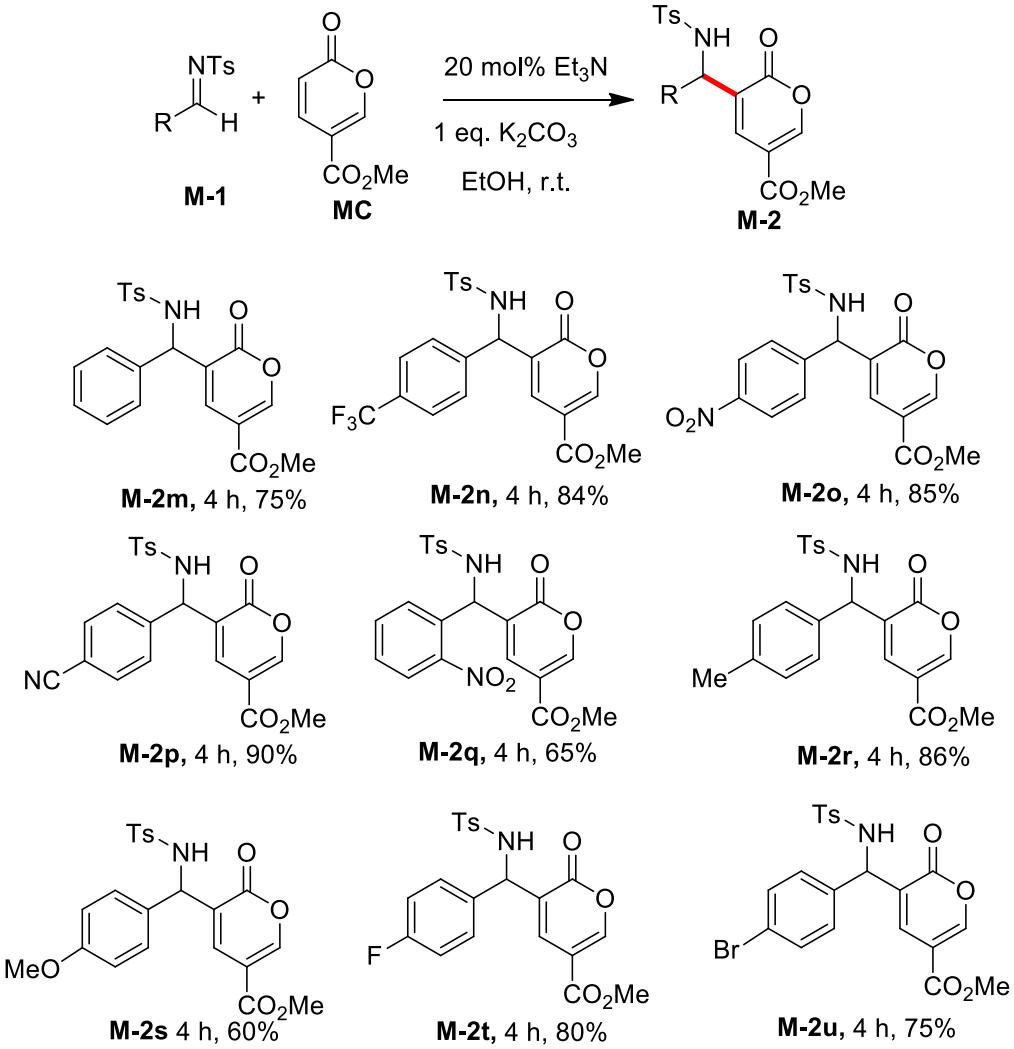
Table 4. Synthesis of bio-based MBH adducts **M-2**[a]



[a] isolated yields. [b] reactions was performed with 50% NEt_3 without additive

Halogen-substituted benzaldehydes were well tolerated, delivering the expected products in yields ranging from 35 to 60% (**M-2c - M-2e**). Higher yields are obtained when employing electron withdrawing groups on the aromatic ring, such as *p*-CN (**M-2f**, 71%), *o*-NO_2 (**M-2g**, 63%) and *p*-CF_3 (**M-2h**, 71%). The electron-rich *p*-MeO group gave lower yields (28% of adduct M-**2i**), since the aldehyde is less electrophilic. This catalytic system is applicable to aliphatic aldehydes. Ethanal and propanal gave the corresponding products **M-2j** and **M-2k** in 40% and 38% yields respectively. Biorenewable furfural was tested, giving **M-2l** in 61% yield.

Table 5. Synthesis of bio-based aza-MBH adducts **M-2**[a]



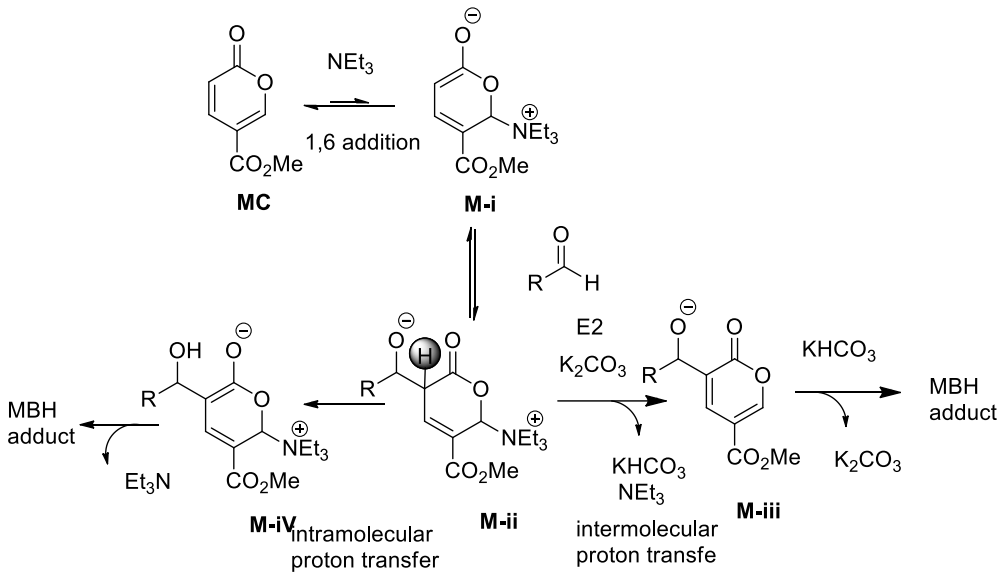
[a] isolated yields

5.2.3. Plausible mechanism for the novel MBH reaction

Notably, higher yields were observed with aryl N-tosyl imines as BHA (Table 5). The simplest phenyl tosyl imine produce the corresponding MBH adduct **M-2m** in 75%. Good to excellent yields were obtained when electron deficient imines were used, affording **M-2n** - **M-2q** in yields up to 90%. For comparison, electron enriched imines provided the corresponding amine in moderate to good yield lower (**M-2r**, 86%), (**M-2s**, 60%). Starting from the halogen substituted imines, the MBH adducts M-**2t**, M-**2u** were successfully isolated in 80% and 75% yields.

A tentative reaction mechanism was proposed, based on experimental reports and previous reporting. It is depicted in Scheme 3. The catalytic cycle is initiated by the conjugate 1,6 addition of trimethylamine to an electron-deficient MC, which generates zwitterionic 2*H* pyran **M-i**. Solvation effects could stabilize the dipole **M-i**, and ionic salts could stabilize the zwitterion. The electrophiles are trapped by zwitterion **M-i**, leading to formation of intermediate **M-ii** via an aldolic addition reaction. Currently, the rate-determining proton-transfer step has two proposed pathways. An intermolecular proton transfer could take place between K_2CO_3 and the acidic proton on **M-ii**. With the elimination of catalyst, the zwitterion becomes an anion of greater stability **M-iii**. The MBH adduct is finally achieved after protonation. In the other proposed pathway, we arrive at **M-iv** through solvent-assisted intramolecular proton transfer.[11] Elimination of the catalyst affords the MBH adduct.

Scheme 3 Plausible mechanism for the novel MBH reaction

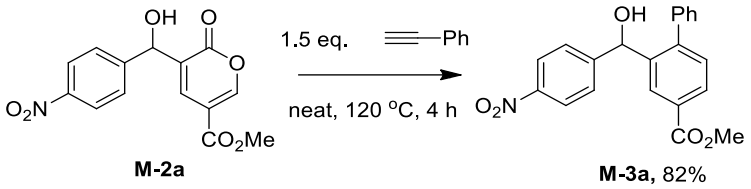


5.2.4. Synthesis of diphenylmethanol derivative from MBH adduct

The obtained MBH adduct **M-2a** could be applied for the synthesis of fine

chemicals such as diphenylmethanol derivatives. These are a key set of intermediates for antihistamines, antihypertensive agents, and agrochemical synthesis. The reaction was carried out in solvent-free conditions, and diphenylmethanol derivative **M-3a** obtained in 82% yield (Scheme 4).

Scheme 4 Synthesis of diphenylmethanol derivative from MBH adduct

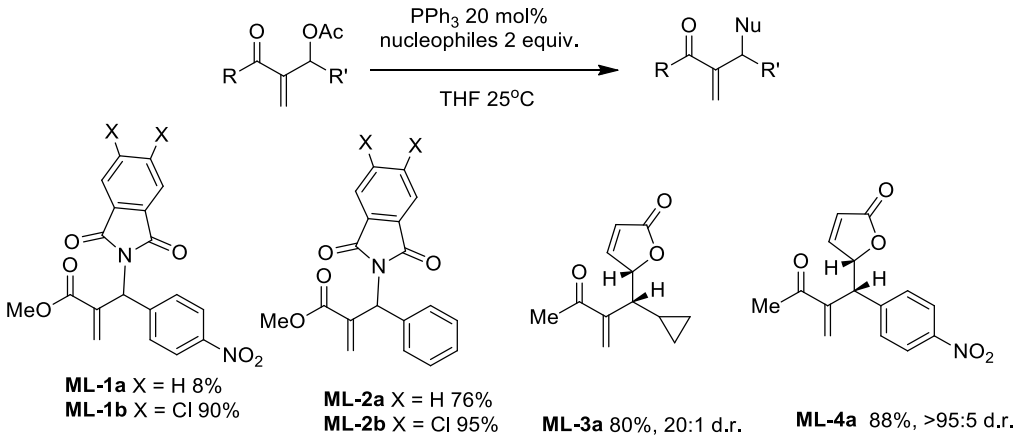


5.3. The regioselective transformation of MBH adducts

5.3.1 General introduction

The attractiveness and importance of the MBH reaction, to a large extent, can also be largely attributed to the vast applications of the MBH adducts for synthesis.[21–24] During the last decade, a remarkably diverse range of transformations from the Baylis-Hillman adducts acetates in a variety of organic transformation methodologies and also in the synthesis of several bioactive molecules and natural products.[25]

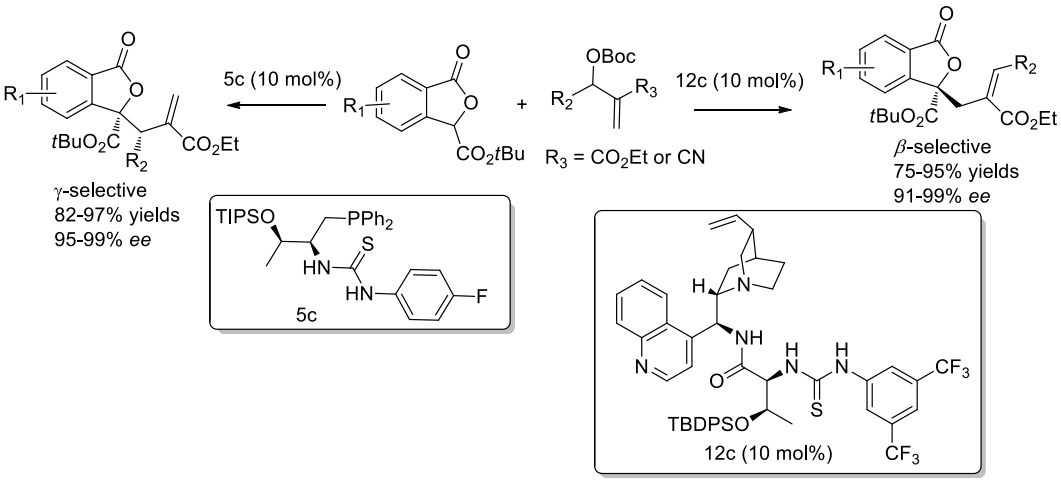
Scheme 5 Phosphine catalyzed allylic substitution of MBH acetates



Krische and co-workers have reported the phosphine catalyzed allylic substitution of MBH acetates with nitrogen nucleophiles[26] and carbon nucleophiles[27] (Scheme 5). The regioselective allylic substitution takes place through a tandem S_N2'-S_N2' substitution mechanism. By using chiral phosphine catalyst (*R*)-Cl-MeO-BIPHEP this transformation is able to provide the resulting allyllic amines in up to 56% ee. A key characteristic of these reactions relate to the generation of an electrophile-nucleophile ion pair, which would suppress direct addition of the nucleophile to the less substituted enone moiety of the starting MBH acetate.

In 2012, Lu's group has used phthalides in the asymmetric allylic alkylation reaction with MBH carbonates to access enantio enriched 3,3-disubstituted phthalides (Scheme 6). Bifunctional chiral phosphines or multifunctional tertiary amine−thioureas were employed as catalysts. They have developed a highly regiodivergent approach to enantioselective synthesis of γ-selective or β-selective allylic alkylation products, respectively.[28]

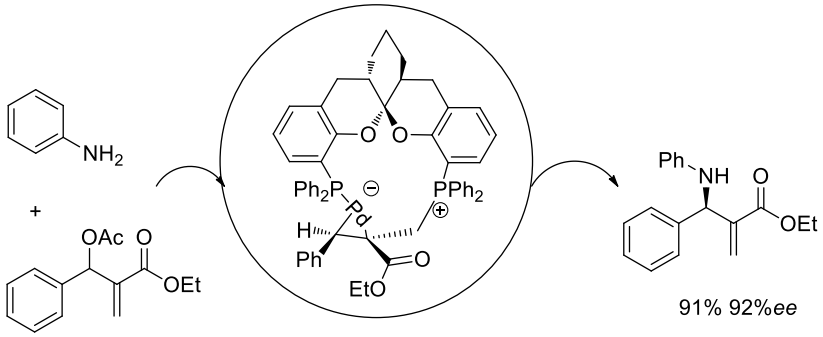
Scheme 6 Phosphine catalyzed asymmetric allylic alkylation reaction of MBH acetates



More recently, Ding and co-workers described an asymmetric allylic amination of racemic MBH adducts with aromatic amines (Scheme 7). In this reaction,

palladium complexes of spiroketal-based diphosphine ligand (SKP) has shown remarkably high activity (with a TON up to 4750). They proposed that SKP ligand plays both organo and organometallic catalysis bifunctional role in the catalysis cycle, giving high efficiency and excellent regioselectivities for the products.[29]

Scheme 7 Asymmetric allylic amination of MBH adducts



Lewis base-catalysed reactions with MBH adducts, have shown as a key platform for the construction of functionalized carbo- and heterocycles. These economical and readily available processes provide a metal free solution to the increasing growth of diverse-oriented synthesis (DOS).

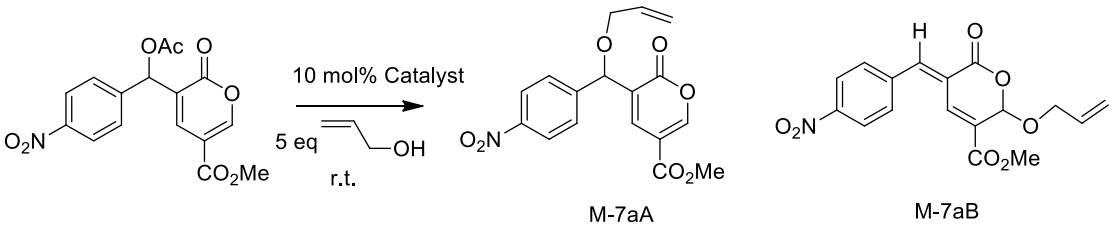
5.3.2. The study of regioselective substitution

To assess the feasibility of the regioselective substitution reactions, a series of solvents and chiral and achiral amines were tested with acetate-derived MBH adducts and 5 equiv of allylic alcohol at r.t (Table 6). During first survey, when employing quinuclidine (10%) in THF (Table 6, entry 1) two inseparable products α-substituted product **M-7aA** and C-6 substituted product **M-7aB** were formed in 1:1 ratio after 24 hours. Prolonged reaction time, favours the formation of the α-substituted product M-7aA, giving a 2:1 **M-7aA: M-7aB** ratio (entry 2). Several solvents were tested, in the presence of cinchonidine employed as catalysts. In THF, the reaction afforded **M-7aA: M-7aB** ratio of 1:1 after 3 days (entry 3). Toluene gives the highest ratio of A with 1.5:1 after 3 days. In DCM and DMF,

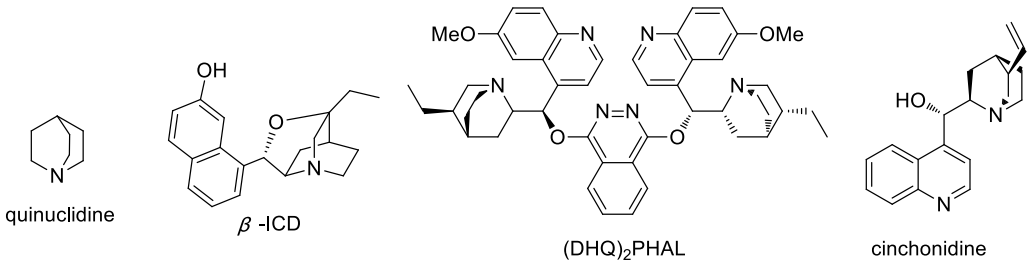
product **M-7aB** was found to be the only product. No reaction occured when employing MeCN as solvent.

Interestingly, quinine-derived catalysts such as *β*-ICD, $(DHQ)_2PHAL$ could not generate product **M-7aA** after long reaction time, only C-6 substituted product **M-7aB** was found .

Table 6 Regioselective substitution of MBH adducts

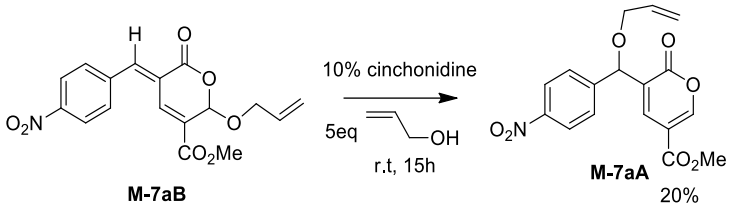


Entry	Catalyst	Solvent	Time (d)	Ratio **M-7aA**: **M-7aB**
1	quinuclidine	THF	1 d	1:1
2	quinuclidine	THF	2 d	2:1
3	cinchonidine	THF	3 d	1:1
4	cinchonidine	Toluene	3 d	1.5:1
5	cinchonidine	DCM	3 d	>5:95
6	cinchonidine	MeCN	/	No reaction
7	cinchonidine	DMF	3 d	>5:95
8	*β*-ICD	Toluene	3 d	>5:95
9	$(DHQ)_2PHAL$	Toluene	0.5 d	>5:95



It should be noted that the C-6 substituted product **M-7aB** could be transformed into A in the presence of allylic alcohol and 10% cinchonidine. After 15 hours at room temperature and by studying the ^{1}H NMR of the crude, we observe 20% of **M-7aA.** Inspired by this result, we realized that we could use higher temperature to directly obtain the final bicyclic product in one-pot.

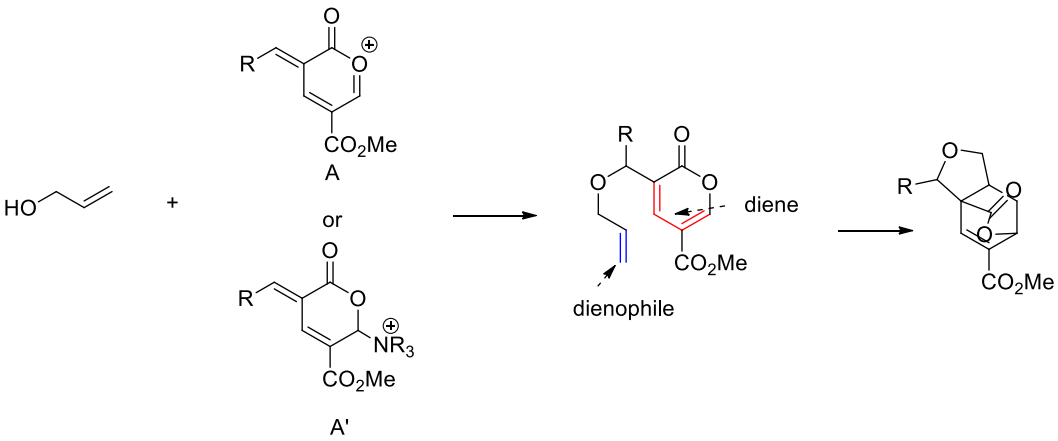
Scheme 8 Transformation of product **M-7aB** into product **M-7aA**



When we heat either **M-7aA** or **M-7aB** or the MBH acetate in the presence of allylic alcohol and catalyst, we observe the formation of a new tricyclic compound that corresponds to an intramolecular DA cycloaddition.

Indeed, because of the diene nature of the novel MBH adducts, an addition / Diels–Alder reaction sequence were performed when allylic alcohol was used as nucleophile (Scheme 9). These cascade reactions could provide a new synthetic approach to polyfunctionalyzed bicyclic compounds.

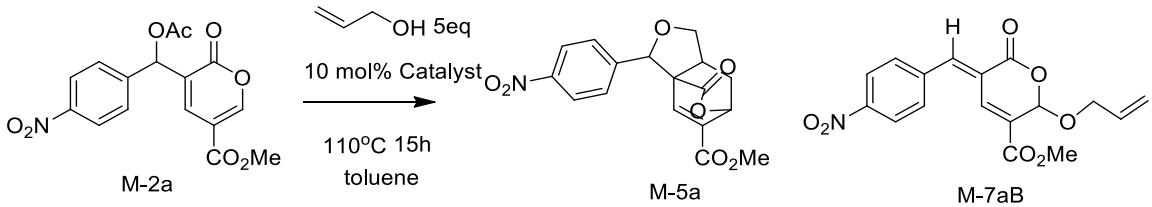
Scheme 9 The synthesis of bicyclic compound form MBH adducts



We thus decided to evaluate the possible direct transformation of the acetate derived from the MBH adduct in the presence of the various catalysts.

5.3.3. The study of enantioselective synthesis of bicyclic products

Table 7 The study of enantioselective synthesis of bicyclic product .



Entry	Catalyst	Yield of M-5a (%)	ee%
1	cinchonidine	87	14
2	cinchonine	49	0
3	*β*-ICD	93	6
4	quinine	46	3
5	quinidine	26	0
6	$(DHQ)_2PHAL$	20	3

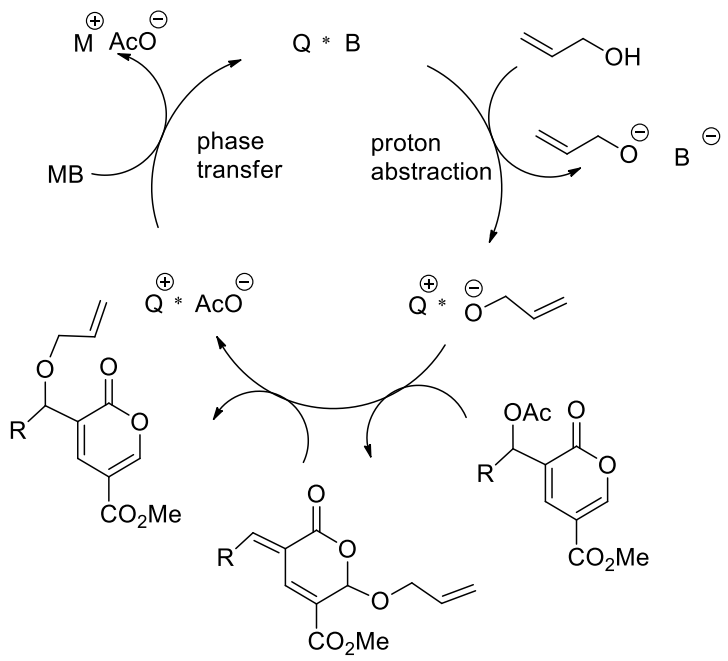
The tricyclic product **M-5a** was obtained in excellent yield 87- 93%(entry 1, 3), in the presence of cinchonidine or *β*-ICD. However moderate yields (46%, 49%) were achieved with cinchonine or quinine entry 2 and 4). When quinidine, $(DHQ)_2PHAL$ were employed, **M-5a** was generated in 26%, 20% respectively. Among those conditions in all cases very low enantiomeric excess was achieved. Cinchonidine being the best catalyst in term of enantioselectivity with only 14% ee (entry 1).

The enantioselective catalysts that operate by ion-pairing mechanisms have been well described. Since these discoveries, a number of methods identified that the catalyst-substrate or catalyst-intermediate interactions plays a key role in the

enantioselectivity. Such interaction between cation and anion, provided a chiral background to the ideal oxygen cation intermediate. In these conditions, chiral anion catalyst (PTC) could be ideal candidates for our reactions. Hopefully we could achieve high enantiomeric excess by some privileged chiral anion catalysts. Quaternary ammonium salts are the largest chiral phase-transfer catalysts (PTC). To introduce stereo-induction process in the Michael addition step, the alternative method could be the use of chiral PTC as the catalyst.

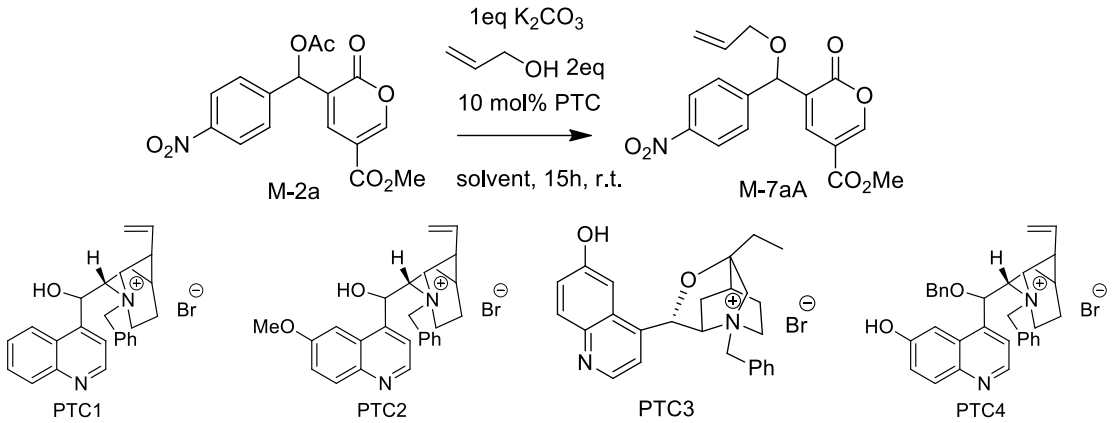
Theoretically the chiral PTC could proceed *via* a deprotonation step, generating the key chiral ion-pair. After the ion-pair has reacted with MBH adduct acetate, the chiral centre is formed though a double S_N2' addition (Scheme 10).

Scheme 10 Chiral PTC promoted region-selective substitution of MBH adducts.



Four chiral PTC were synthesised and evaluated. The reactions carried out at r.t. with 10 % of chiral PTC, 2 equiv of allylic alcohol, 1 equiv of potassium carbonate and MBH adduct acetate..

Table 8 Regio and enantioselective substitution catalyzed by PTC



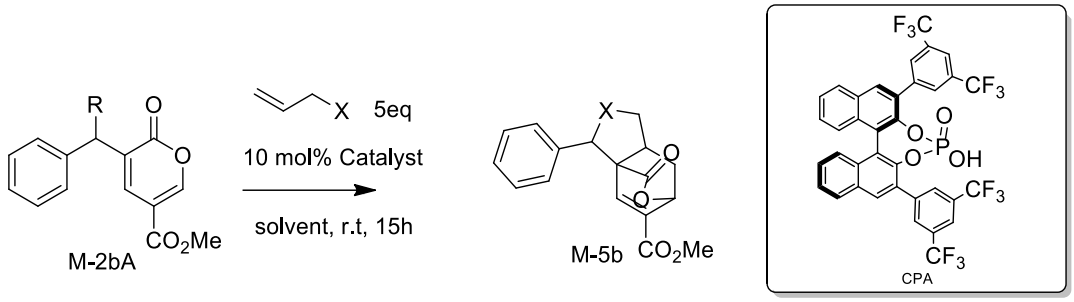
Entry	Catalyst	Solvent	Yield (%)	*ee* (%)
1	PTC1	toluene	96	1
2	PTC2	DCM	67	0
3	PTC3	toluene	96	0
4	PTC4	toluene	67	0

The four catalysts show excellent regioselectivitives, giving the α-substituted product in good to excellent yield, however almost no enantiomeric excess was found (Table 8).

The regioselective substitution process could also be achieved by using Brønsted acid catalyst. BINOL-derived phosphoric acids are also be used in our investigation.

Our initial attempts successfully obtained the bicyclic product in 2 hours with 64% yield Table 9, by empolying MBH adduct with Ts-allylamine catalysed by 10 mol% of *p*-toluenesulfonic acid (PTSA).

Table 9 Brønsted acid catalysed transformation of MBH adducts



Catalyst	Solvent	R	X	Temperature (°C)	Yield (%)
PTSA	THF	OH	TsNH	r.t.	64
CPA	THF	OH	TsNH	r.t.	0
CPA	THF	OH	TsNH	66	0
CPA	Toluene	OH	TsNH	r.t.	0
CPA	Toluene	OH	OH	r.t.	0
CPA	Toluene	OAc	TsNH	r.t.	0

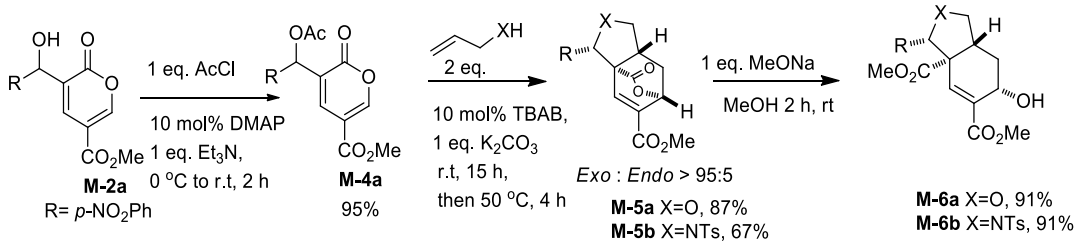
Disappointingly the use of chiral BINOL-derived monophosphoric acid (CPA) did not delivered the expected product. Moreover the same negative results were also found in those conditions including changing of the substrates, solvents or temperature. We proposed the unsuccessful reactions may result from the lower acidity (pH≈3) of chiral phosphoric acid than *p*-toluenesulfonic acid (pH≈-2).

5.3.4. The transformation to hydroisobenzofuran and hydroisoindole cores

Finally, to further demonstrate the synthetic potential of the obtained MBH adducts, we also developed an efficient access towards hexahydro-isobenzofuran and hexahydro-1H-isoindole (Scheme 11). Starting from MBH adduct acetate **M-4a**, A one pot domino reaction, triggered by a regioselective substitution of the

acetate of **M-4a** with allylic alcohol or allylic tosyl amine followed by an intramolecular Diels-Alder reaction provided **M-5a** and **M-5b** with excellent stereoselectivity (Exo:Endo > 95:5) in 87% and 67% yields respectively.

Scheme 11 The transformation to hydroisobenzofuran and hydroisoindole cores



A facile alcoholysis could transform **M-5a**, **M-5b** into the highly functionalized stereopure compounds **M-6a** and **M-6b. M-6a** contains the hydro-isobenzofuran core, which can be found in many bioactive nature products. Similarly, **M-6b** contains the hydro-1*H*-isoindole core, which interacts with biological targets involved in many diseases: cancer, Alzheimers, antiemetics, and benign prostatic hyperplasia.

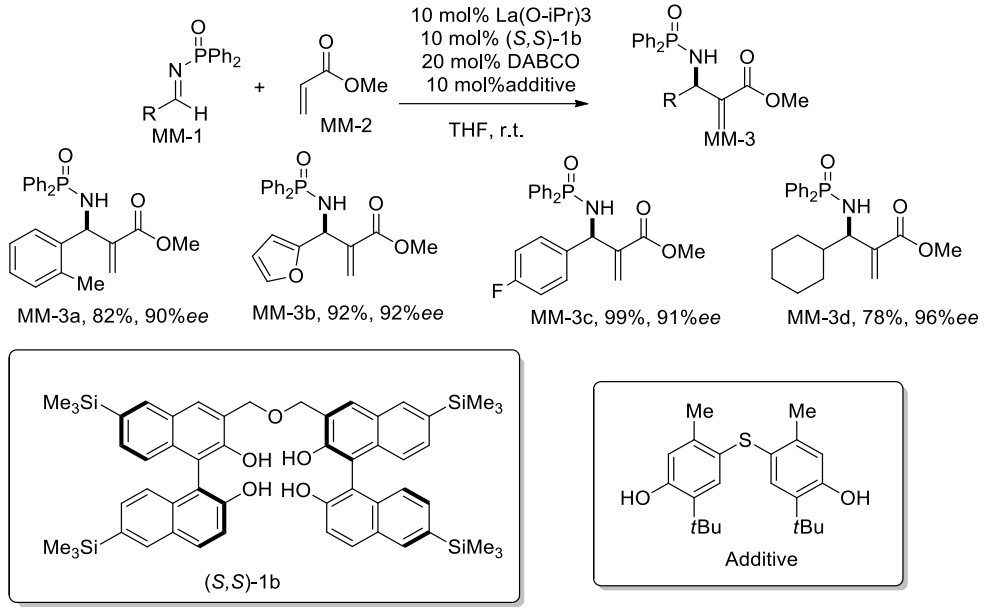
5.4 Asymmetric Morita-Baylis-Hillman reaction with MC

5.4.1 Bibliographic introduction

The Asymmetric MBH reaction has attracted considerable interest due to the fascinating tandem Michael-aldol sequence catalyzed by a chiral Lewis base and the promising utility of the multifunctional chiral products.

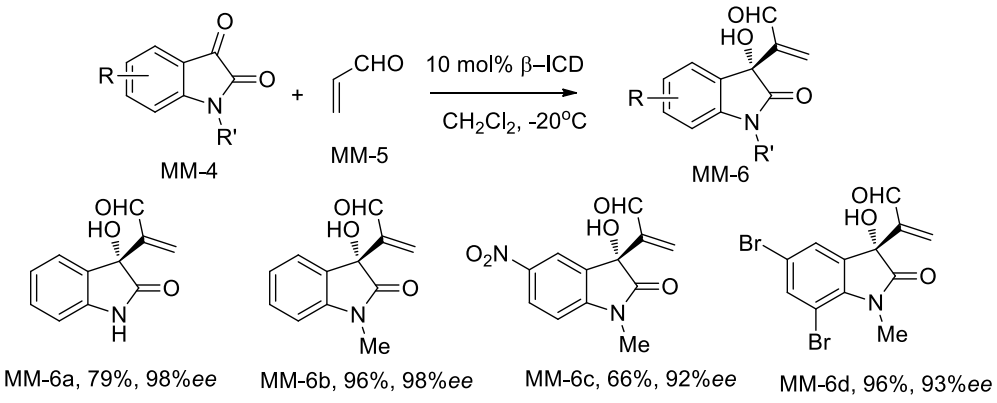
Shibasaki et al.[30] reported a catalytic asymmetric aza-Morita-Baylis-Hillman reaction using a chiral rare earth metal catalyst in combination with an achiral nucleophilic base catalyst. The La(O-iPr)$_3$ /(S,S)-TMS-linked-BINOL/DABCO system was applicable to a broad range of aryl, heteroaryl, alkenyl, and alkyl imines at ambient temperature, giving products in 66-99% yield and 81-98% *ee*.

Scheme 12 Chiral Lewis acid promoted asymmetric aza-Morita-Baylis-Hillman



In 2010, Zhou's group reported a highly enantioselective MBH reaction of isatins and acrolein to provide enantiomerically enriched 3-substituted 3-hydroxyoxindoles, which could serve as valuable synthetic building blocks. The *β*-Isocupreidine turned out to be a powerful catalyst for this transformation, and a variety of isatins worked well with acrolein to give the MBH adducts with excellent *ee*.[31]

Scheme 13 Enantioselective MBH reaction of isatins and acrolein



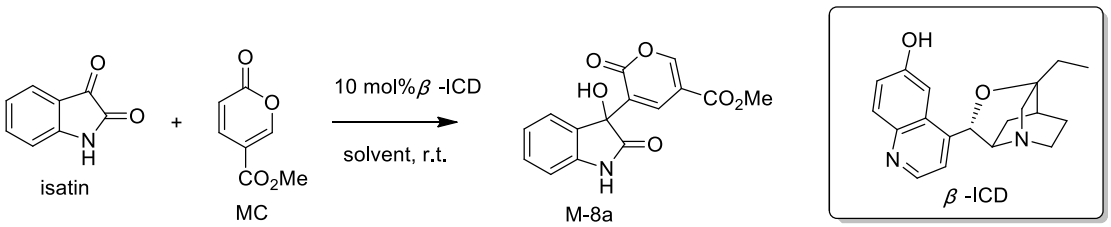
Previously in this chapter we reported a novel type of MBH reaction by 1,6

Michael-aldol type sequence instead of 1,4 addition process. Protic solvent is essential for the reaction of aldehydes and imines. However, protic solvent usually rendered a low enantiomeric excess of the product. So we became interested in using more efficient sp^2 electrophilic carbon feedstocks, for example isatin, for the sake of preceding the reactions in the aprotic solvents. Moreover, the use of isatin could allow an access to 3,3 -disubstituted-2-oxindoles cores which are widely present in natural products and bioactive molecules.

5.4.2. MC involved Asymmetric Morita-Baylis-Hillman reaction

We therefore applied our preliminary conditions presented in Table 10 using isatin as electrophile and commercially available cinchona type bifunctional amine *β*-Isocupreidine (*β*-ICD) as catalyst. In DCM the reaction run smoothly affording methyl 3-(3-hydroxy-2-oxoindolin-3-yl)-2-oxo-2H-pyran-5-carboxylate **M-8a** product in good yield but low *ee* (11% *ee* after 48h) (entry 1).

Table 10 Optimization of the solvent



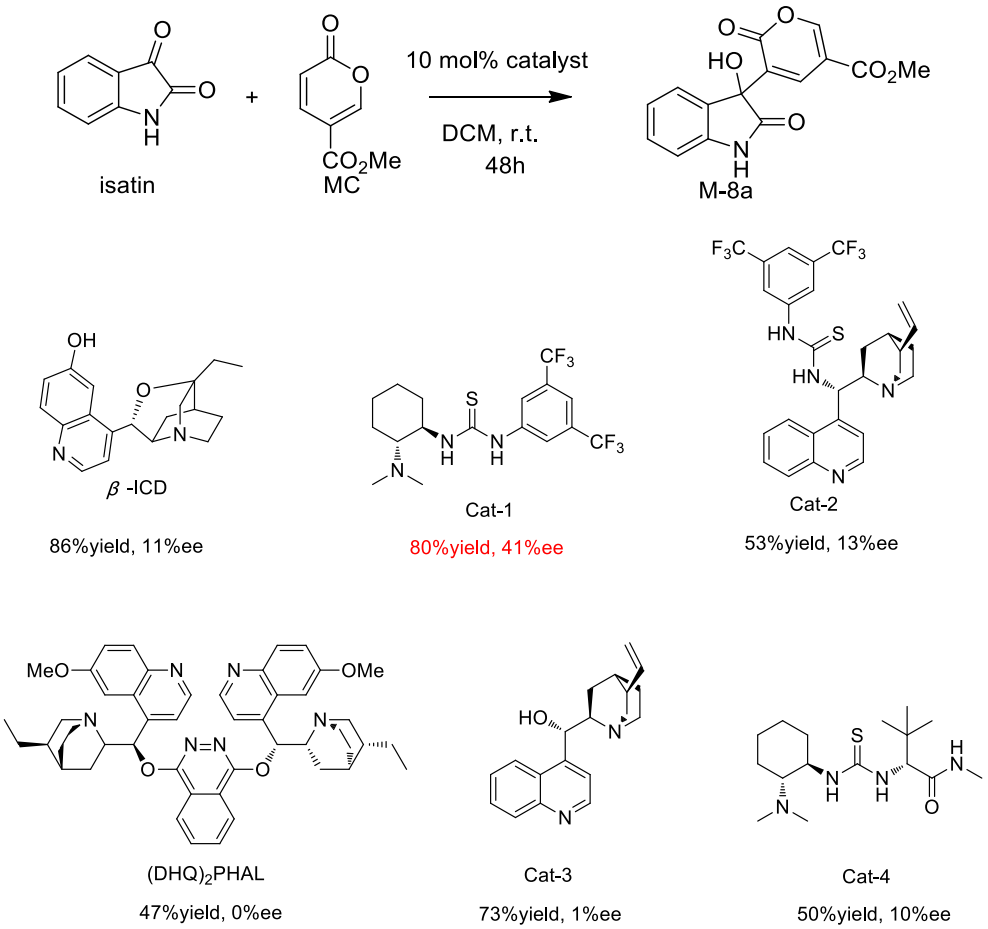
Entry	Solvent	Time (d)	Yield	ee(%)
1	DCM	2	86	11
2	MeCN	3	80	11
3	THF	7	66	13
4	toluene	3	NR	NR

In MeCN, MBH adduct was obtain in good yield in 3d and with the same low enantioselectivity. The reaction runs slowly in THF after 7 days giving the product

in 66% yield with low enantiomeric excess. No reaction occurs when employing toluene as solvent.

We thus decided to test various catalysts. Results are presented in Table 11.

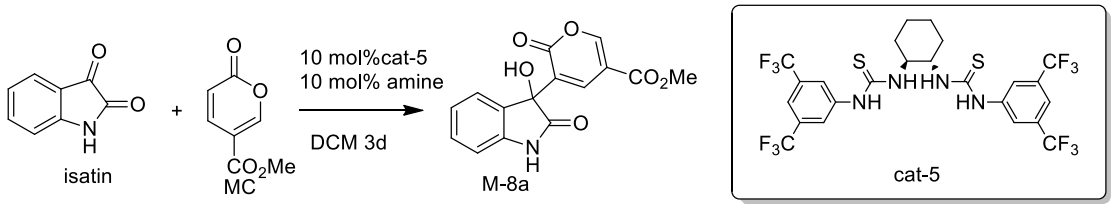
Table 11 Optimization of the catalysts



Under these conditions, the use of Cat-1 resulted in a slight improvement of the enantioselectivity up to 41% *ee*, with a good yield. In addition, several other chiral tertiary amine were applied to the model reaction, but all showed lower catalytic activity than Cat-1 in terms of both yield and enantioselectivity (Table 11).

The combination of chiral thiourea catalyst (Cat-5) with achiral amine catalyst has also been investigated.

Scheme 13 Chiral thiourea promoted enantioselective MBH reaction

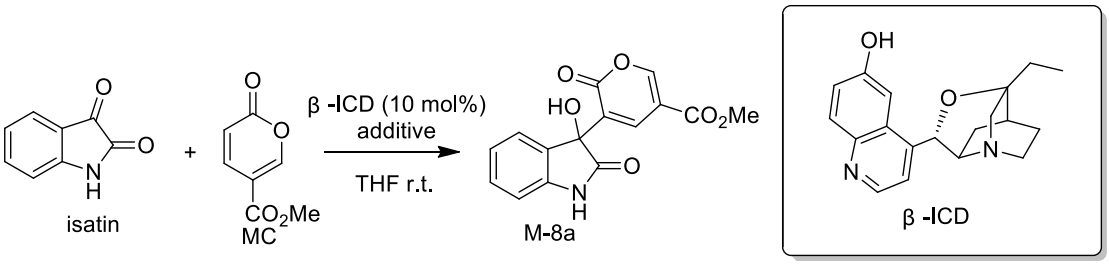


Entry	Amine	Temperature	Yield%	*ee*%
1	quinuclidine	r.t.	76	11
2	quinuclidine	-20ºC	70	12
3	DABCO	-20ºC	67	9

When catalysed by quinuclidine (10 mol %) the reaction works slowly and affords the product in 76% with 11% *ee* after 3 days. Reducing the temperature to -20ºC, could not improve the yield and *ee* whatever the added amine (quinuclidine or DABCO).

As we forementioned the presence of salts could enhance the reactivities of MBH reactions. Salt effects were also studied in these conditions and reported in table 12.

Table 12 The study of salts effect

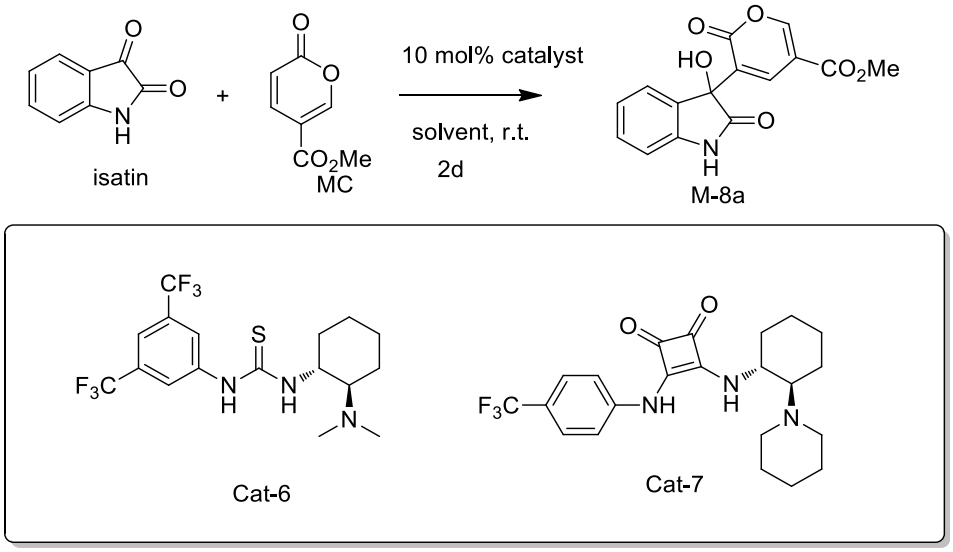


Entry	Additive (1eq.)	Solvent	Time (h)	Yield (%)	ee (%)
1	/	THF	168	70	13
2	LiCl	THF	15	80	32
3	NaCl	THF	15	74	69
4	NaCl	THF	15	71	75(0^oC)
5	KCl	THF	15	71	55
6	CsCl	THF	15	75	60
7	**$MgCl_2.6H_2O$**	**THF**	**15**	**80**	**75**
8	**$MgCl_2$**	**THF**	**2d**	**67**	**85**
9	0.1eq $MgCl_2$	THF	2d	70	21
10	1eq $Mg(OTf)_2$	THF	2d	55	30
11	1eq $Zn(OTf)_2$	THF	2d	15	13
12	1eq $La(OTf)_3$	THF	2d	60	33
13	1eq $Sc(OTf)_3$	THF	2d	0	0

When 1 equiv of LiCl was added, the reaction was very fast and finished in 15 hours affording **M-8a** in 80% yield and 32% *ee*. It is worth to mention that a remarkable improvement of *ee* was observed by adding 1 equiv of NaCl. It affords **M-8a** in 74% yield and 69% *ee* or even 71% yield and 75% *ee* at 0 °C. The use of KCl and CsCl affords moderate results. $MgCl_2.6H_2O$ 1 equiv could increase the

ee up to 75%. The highest enantiomeric excess was obtained with anhydrous $MgCl_2$ affording the expected product in longer reaction time but with a better *ee* 85%. Decreasing the loading of $MgCl_2$ also affected the *ee*, with only 21%. Other negative results were obtained with $Mg(OTf)_2$, $Zn(OTf)_2$, $La(OTf)_3$, $Sc(OTf)_3$.

Table 13 The effect of H_2O in the asymmetric MBH reaction

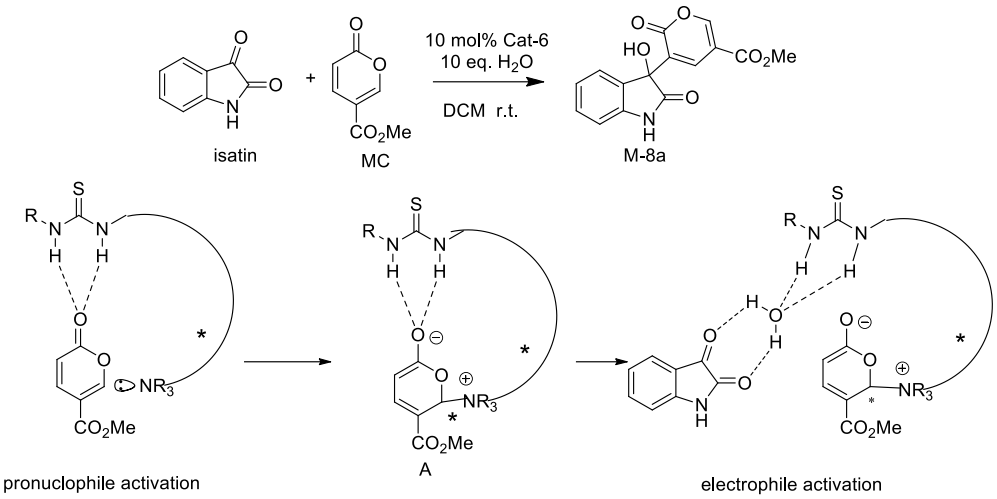


Entry	Catalyst	Additive (10eq.)	Solvent	Yield (%)	*ee* (%)
1	Cat-6	/	DCM	80	41
2	Cat-6	H_2O	DCM	80	79
3	Cat-7	/	DCM	40	32
4	Cat-7	H_2O	DCM	55	63
5	Cat-7	/	THF	33	-11
6	Cat-7	H_2O	THF	25	-9

During the repetition of our previous work, a slight variation of *ee* was observed. We presumed this variation may come from the moisture in the DCM. The later experiments proved our hypothesis. The extra 10 equiv of H_2O to cat-6 could improve the enantiomeric excess up to 79%. Similar results were found (entry 3-

4) with chiral squaric acid amides catalyst cat-7. However the same phenomena has not been found when employing THF as solvent.

Scheme 14 The proposed role of H_2O in the reaction



We propose that the chiral thiourea catalyst could activate the MC, which allows the amine to performe the1,6 addition in an enantioselective manner to form the stabilized zwitterion dienolate A. We assume a hydrogen bond exchange take place from oxygen anion -thiourea to water - thiourea. This H-bond exchange could restore the nucleophilicity of the zwitterion, also assembling of water and thiourea could extend the H-bond to further activate the electrophile isatin.

5.5. Conclusion

We have developed a novel reaction, for efficient C-C bond formation between the bio-based methyl coumalate and a variety of imines and aldehydes. Et_3N serves as catalyst in ethanol for this environmentally benign transformation, which occurs *via* an unprecedented 1,6-conjugated addition-triggered Morita-Baylis-Hillman pathway. Remarkable rate enhancement was achieved using K_2CO_3. This atom-economical approach has broad substrate scope, and the advantages of readily available starting materials, inexpensive catalysts, and accessible additives.

Both chiral amine and chiral PTC failed in enriching the enantioselectivity of our reaction. To our delight, a regioselective substitution of the MBH acetate has been

discovered with PTC catalyst. By using this transformation the original MBH adducts acetate could be applied into the synthesis of hydroisobenzofuran and hydro-isoindole derivatives.

A preliminary study of the asymmetric MBH has been done by employing several privileged chiral amine catalyst. To our surprise, the additional $MgCl_2$ or H_2O showed remarkable enantiomeric enhancement, and gave the MBH adducts in good *ee*.

5.6. Experimental section

Typical experimental procedure for the synthesis of compound M-2 (a-u).

In a round-bottom flask corresponding aldehyde or imine **M-1** (1 mmol) and methyl coumalate (154 mg, 1 equiv) were mixed in 5 mL of ethanol, then Et_3N (28 µL, 0.2 equiv) and K_2CO_3 (138 mg, 1 equiv) were added. The flask was purged with Ar and then stirred at room temperature until MC was consumed and the reaction quenched with 1M HCl 5 mL. The mixture was extracted with CH_2Cl_2 (20 mL), and the layers were separated. The organic layer was washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography gave the corresponding desired product **M-2a - M-2u**.

Methyl 3-(hydroxyl (4-nitrophenyl) methyl) -2-oxo-2H-pyran-5-carboxylate (M-2a): colorless oil (226 mg, 74%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 – 8.20 (m, 1H), 8.22 – 8.07 (m, 2H), 7.90 (dd, *J* = 2.5, 1.1 Hz, 1H), 7.68 – 7.55 (m, 2H), 5.84 (s, 1H), 3.87 (s, 3H), 3.40 (br, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.2, 160.0, 156.8, 147.8, 147.2, 137.0, 129.2, 127.5(2C), 123.9(2C), 112.4, 70.7, 52.7; **IR** (film, cm^{-1}): 3491, 2954, 1714, 1519, 1230, 989; **HRMS** (ESI) m/z calcd for $[M+Na^+]$ $C_{14}H_{11}NNaO_5$ 328.0428, found 328.0432.

Methyl 3-(hydroxy(phenyl)methyl)-2-oxo-2H-pyran-5-carboxylate (M-2b): colorless oil (155 mg, 62%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 2.5 Hz, 1H), 7.85 (dd, *J* = 2.5, 1.1 Hz, 1H), 7.46 – 7.28 (m, 5H), 5.75 (d, *J* = 4.0 Hz, 1H), 3.87 (s, 3H), 3.01 (d, *J* = 4.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.5, 160.2, 156.3, 140.1, 136.3, 130.2, 128.7(2C), 128.4(2C), 126.7, 112.3, 71.6, 52.5; **IR** (film, cm^{-1}): 3401, 2974, 1714, 1228, 950; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{14}H_{12}NaO_5$ 283.0577, found 283.0580.

Methyl 3-((4-fluorophenyl)(hydroxy) methyl)-2-oxo-2H-pyran-5-carboxylate (M-2c): colorless oil (167 mg, 60%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.29 – 8.20 (m, 1H), 7.83 (dd, *J* = 2.5, 1.1 Hz, 1H), 7.48 – 7.34 (m, 2H), 7.10 – 6.99 (m, 2H), 5.74 (d, *J* = 4.3 Hz, 1H), 3.87 (s, 3H), 2.98 (d, *J* = 4.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ163.4, 162.7 (d, *J* = 247.1 Hz), 160.1, 156.4, 136.2, 135.9 (d, *J* = 3.2 Hz), 130.0, 128.5 (d, *J* = 8.3 Hz, 2C), 115.6 (d, *J* = 21.7 Hz, 2C), 112.3, 71.0, 52.5.; **IR** (film, cm^{-1}): 2976, 1716, 1296, 1222, 989; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{14}H_{11}NaFO_5$ 301.0483, found 301.0488.

Methyl 3-((4-bromophenyl)(hydroxy)methyl)-2-oxo-2H-pyran-5-carboxylate (M-2d): colorless oil (185 mg, 55%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 2.2 Hz, 1H), 7.84 (d, *J* = 2.2 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 5.70 (s, 1H), 3.87 (s, 3H), 3.08 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.4, 160.1, 156.4, 139.2, 136.4, 131.8(2C), 129.8, 128.4(2C), 122.4, 112.3, 70.9, 52.6; **IR** (film, cm^{-1}): 2974, 2864, 1714, 1228, 1151, 989, 792; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{14}H_{11}BrNaO_5$ 360.9682, found 360.9676.

Methyl 3-((2-bromophenyl) (hydroxy)methyl)-2-oxo-2H-pyran-5-carboxylate (2e): colorless oil (118 mg, 35%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 2.5, 0.4 Hz, 1H),7.62 – 7.53 (m, 2H), 7.48 (dd, *J* = 2.5, 1.0 Hz, 1H), 7.39 (td, *J* = 7.5, 1.0 Hz, 1H), 7.25 – 7.17 (m, 1H), 6.08 (d, *J* = 4.5 Hz, 1H), 3.83 (s, 3H), 3.52 (d, *J* = 4.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ163.4, 160.7, 156.1, 138.4, 137.6, 133.0, 129.9, 128.6, 128.5, 127.9, 122.9, 112.3, 70.5, 52.5; **IR** (film, cm^{-1}): 2974, 1720, 1438, 1296, 1228, 1024, 945, 754; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{14}H_{11}BrNaO_5$ 360.9682, found 360.9697.

Methyl 3-((4-cyanophenyl)(hydroxy)methyl)-2-oxo-2H-pyran-5-carboxylate (M-2f): yellow oil (202 mg, 71%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 2.5 Hz, 1H), 7.89 (dd, *J* = 2.5, 1.1 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.57 (d, *J* = 8.2 Hz, 2H), 5.79 (s, 1H), 3.87 (s, 3H), 3.33 (br, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.3, 160.0, 156.7, 145.5, 136.8, 132.4(2C), 129.3, 127.4(2C), 118.5, 112.4, 112.0, 70.7, 52.6; **IR** (film, cm^{-1}): 2987, 1717, 1228, 111, 989; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{15}H_{11}NNaO_5$ 308.0529, found 308.0540.

Methyl 3-(hydroxyl (2-nitrophenyl) methyl)-2-oxo-2H-pyran-5-carboxylate (M-2g): colorless oil (192 mg, 63%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ8.27 (d, *J* = 2.3 Hz, 1H), 8.03 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.75 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.68 (td, *J* = 7.7, 1.2 Hz, 1H), 7.63 (dd, *J* = 2.5, 1.1 Hz, 1H), 7.57 – 7.42 (m, 1H), 6.33 (s, 1H), 3.85 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.3, 160.2, 156.7, 148.3, 137.0, 134.8, 133.9, 129.3, 129.1, 128.7, 125.0, 112.2, 67.0, 52.5; **IR** (film, cm^{-1}): 2976, 1720, 1350, 1072 931, 835; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{14}H_{11}NNaO_5$ 328.0428, found 328.0432.

Methyl 3-(hydroxy(4- (trifluoromethyl)phenyl) methyl)-2-oxo-2H-pyran-5-carboxylate (M-2h): colorless oil (233 mg, 71%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 2.5 Hz, 1H), 7.81 (d, *J* = 2.5, Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.49 (d, *J* = 8.3 Hz, 2H), 5.72 (s, 1H), 3.79 (s, 3H), 3.23 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ163.4, 160.1, 156.5, 144.2 (q, *J* = 1.0 Hz), 136.6, 130.50 (q, *J* = 32.5 Hz), 129.6, 127.0, 125.6 (q, *J* = 3.7 Hz), 123.96 (q, *J* = 272.2 Hz), 112.4, 70.9, 52.6; **IR** (film, cm^{-1}): 2976, 2856, 1716, 1571, 1440, 1323, 1230, 920; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{15}H_{11}F_3NaO_5$ 351.0451, found 351.0444.

Methyl 3-(hydroxy(4-methoxyphenyl)methyl)-2-oxo-2H-pyran-5-carboxylate (M-2i): colorless oil (82 mg, 28%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 2.2 Hz, 1H), 7.88 (d, *J* = 2.2 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 5.73 (s, 1H), 3.90 (s, 3H), 3.83 (s, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.5, 160.1, 159.7, 156.2, 135.9, 132.2, 130.3, 128.1(2C), 114.1(2C), 112.3, 71.2, 55.3, 52.5; **IR** (film, cm^{-1}): 2943, 1717, 1456, 1237, 998; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{15}H_{14}NaO_6$ 313.0683, found 313.0688.

Methyl 3-(1-hydroxybutyl) -2-oxo-2H-pyran -5-carboxylate (M-2j): colorless oil (90 mg, 40%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 11.9, 2.5 Hz, 1H), 7.80 (dd, *J* = 2.5, 1.0 Hz, 1H), 4.63 (s, 1H), 3.89 (s, 3H), 2.53 (br, 1H), 2.11-1.87 (m, 1H), 1.84 – 1.61 (m, 1H), 1.53 – 1.22 (m, 2H), 0.96 (td, *J* = 7.4, 2.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ156.2, 156.1, 138.4, 135.9, 130.6, 127.2, 70.0, 52.5, 37.6, 18.9, 13.8; **IR** (film, cm^{-1}): 2958, 1714, 1438, 1230, 111, 960; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{11}H_{14}NaO_5$ 249.0733, found 249.0738.

Methyl 3-(1-hydroxyethyl) -2-oxo-2H- pyran-5-carboxylate (M-2k): colorless oil (75 mg, 38%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 2.5, 1.1 Hz, 1H), 7.76 (dd, *J* = 2.5, 1.1 Hz, 1H),4.75 (q, *J* = 6.3 Hz, 1H), 3.82 (s, 3H), 2.61 (br, 1H), 1.44 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.6, 160.5, 156.1, 135.3, 131.4, 112.3, 65.9, 52.5, 21.6; **IR** (film, cm^{-1}): 3514, 2976, 1714, 1406, 1280., 1230, 943; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_9H_{10}NaO_5$ 221.0420, found 221.0413.

Methyl 3-(furan-2-yl (hydroxy)methyl)-2-oxo-2H-pyran-5-carboxylate(M-2l): yellow oil (151 mg, 61%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.35 – 8.22 (m, 1H), 7.92 (dd, *J* = 2.5, 1.2 Hz, 1H), 7.39 (t, *J* = 1.2 Hz, 1H), 6.36 (s, 1H), 6.36 (s, 1H), 5.77 (s, 1H), 3.89 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.4, 159.9, 156.7, 152.4, 142.8, 137.4, 127.2, 112.3, 110.6, 108.2, 65.9, 52.5; **IR** (film, cm^{-1}): 2975, 1717, 1300, 1278, 974; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{12}H_{10}NaO_6$ 273.0370, found 273.0376.

Methyl 3-((4-methylphenylsulfonamido)(phenyl)methyl)-2-oxo-2H-pyran-5-carboxylate (M-2m): white solid (310 mg, 75 %); mp: 191-192°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 2.5 Hz, 1H), 7.75 (d, *J* = 2.5, 1H), 7.71 – 7.59 (m, 2H), 7.26 – 7.18 (m, 5H), 7.17 – 7.10 (m, 2H), 5.73 (d, *J* = 8.4 Hz, 1H), 5.36 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 3H), 2.36 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.1, 159.4, 156.5, 143.7, 138.0, 137.2, 137.0, 129.7(2C), 128.9(2C), 128.4, 127.4(2C), 126.5(2C), 126.3, 112.1, 58.3, 52.6, 21.4; **IR** (film, cm^{-1}): 3215, 1708, 1446, 1330, 1288, 1072, 981; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{21}H_{19}NNaO_6S$ 436.0825, found 436.0824.

Methyl 3-((4-methylphenylsulfonamido) (4-(trifluoromethyl) phenyl)methyl)-2-oxo-2H-pyran-5-carboxylate (M-2n): white solid

(405 mg, 84 %); mp: 167-168°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 2.4 Hz, 1H), 7.80 – 7.69 (m, 1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.04 (d, *J* = 9.3 Hz, 1H), 5.44 (d, *J* = 9.2 Hz, 1H), 3.89 (s, 3H), 2.34 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ162.9, 159.3, 156.9, 144.0, 141.1 (q, *J* = 1.1 Hz), 138.6, 137.0, 130.7, 130.5 (q, *J* = 32.6 Hz), 129.7(2C), 125.7 (q, *J* = 3.7 Hz), 125.5, 127.2(2C), 127.0(2C), 123.8 (q, *J* = 272.3 Hz) 112.1, 58.1, 52.7, 21.4; **IR** (film, cm^{-1}): 3217, 1728, 1701, 1446, 1325, 999, 815; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{22}H_{18}F_3NNaO_6S$ 504.0699, found 504.0716.

Methyl 3-((4-methylphenylsulfonamido) (4-nitrophenyl) methyl) -2-oxo-2H-pyran-5-carboxylate (M-2o): white solid (390 mg, 85 %); mp: 188-189°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 2.4 Hz, 1H), 8.14 – 8.00 (m, 2H), 7.72 (d, *J* = 2.4 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 6.10 (d, *J* = 9.5 Hz, 1H), 5.46 (d, *J* = 9.5 Hz, 1H), 3.90 (s, 3H), 2.35 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.7, 159.3, 157.1, 147.7, 144.2, 144.1, 139.0, 136.9, 129.8(2C), 127.5(2C), 127.2(2C), 124.9, 123.9(2C), 112.1, 58.0, 52.8, 21.4; **IR** (film, cm^{-1}): 3219, 1697, 1521, 1340, 1238, 997, 817; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{21}H_{18}N_2NaO_8S$ 481.0676, found 481.0686.

Methyl 3-((4-cyanophenyl) (4-methylphenylsulfonamido) methyl) -2-oxo-2H-pyran-5-carboxylate (M-2p): white solid (395 mg, 90 %); mp: 219-220°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 2.4 Hz, 1H), 7.69 (d, *J* = 2.4 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.04 (d, *J* = 9.4 Hz, 1H), 5.41 (d, *J* = 9.4 Hz, 1H), 3.89 (s, 3H), 2.35 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.8, 159.3, 157.0, 144.1, 142.4, 139.0, 136.9, 132.5(2C), 129.8(2C),

127.3(2C), 127.2(2C), 125.02, 118.2, 112.2, 112.1, 58.15, 52.75, 21.42; **IR** (film, cm^{-1}): 3228, 2233, 1679, 1570, 1442, 1274, 918; **HRMS** (ESI) m/z calcd for $[M+Na^+]$ $C_{22}H_{18}N_2NaO_6S$ 461.0778, found 461.0792.

Methyl 3-((4-methylphenylsulfonamido) (2-nitrophenyl)methyl)-2-oxo-2H-pyran-5-carboxylate (M-2q): white solid; (298 mg, 65%)); mp: 155-156°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 2.4 Hz, 1H), 7.76 (dt, *J* = 9.4, 4.6 Hz, 1H), 7.70 – 7.63 (m, 2H), 7.59 (d, *J* = 8.3 Hz, 2H),7.52 – 7.44 (m, 1H), 7.39 – 7.31 (m, 1H), 7.12 (d, *J* = 8.3 Hz, 2H), 6.11 (d, *J* = 9.4 Hz, 1H), 6.05 (d, *J* = 9.4 Hz, 1H), 3.81 (s, 3H), 2.28 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ162.7, 159.7, 157.0, 147.8, 143.9, 139.7, 136.8, 133.5, 131.9, 130.6, 129.7, 129.3, 127.2, 126.5, 125.1, 112.23, 54.2, 52.7, 21.4; **IR** (film, cm^{-1}): 3213, 1724.32, 1444.98, 1147.23, 975.98; **HRMS** (ESI) m/z calcd for $[M+Na^+]$ $C_{21}H_{18}N_2NaO_8S$ 481.0676, found 481.0676.

Methyl 3-((4-methylphenylsulfonamido) (p-tolyl)methyl)-2-oxo-2H-pyran-5-carboxylate (M-2r): white solid (281 mg, 86 %); mp: 198-199°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 2.5 Hz, 1H), 7.76 (dd, *J* = 2.5, 0.7 Hz, 1H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 2H), 7.10-6.90 (m, 4H), 5.69 (d, *J* = 8.2 Hz, 1H), 5.50 (d, *J* = 8.2 Hz, 1H), 3.89 (s, 3H), 2.36 (s, 3H), 2.27 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.1, 159.4, 156.5, 143.7, 138.3, 137.8, 137.0, 134.3, 129.7(2C), 129.5(2C), 127.4(2C), 126.5, 126.4(2C), 112.1, 57.9, 52.6, 21.4, 21.0; **IR** (film, cm^{-1}): 3213, 1724, 1707, 1444, 1170, 975, 817; **HRMS** (ESI) m/z calcd for $[M+Na^+]$ $C_{22}H_{21}NNaO_6S$ 450.0982, found 450.0990.

Methyl 3-((4-methoxyphenyl) (4-methylphenylsulfonamido) methyl)-2-oxo-2H-pyran-5-carboxylate (M-2s): white solid (222 mg, 50 %); mp:

174-175°C; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.14 (d, *J* = 2.5 Hz, 1H), 7.75 (dd, *J* = 2.5, 0.7 Hz, 1H), 7.70 – 7.61 (m, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 2H), 5.63 (d, *J* = 8.0 Hz, 1H), 5.31 (d, *J* = 8.0 Hz, 1H), 3.89 (s, 3H), 3.74 (s, 3H), 2.37 (s, 3H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 163.1, 159.6, 159.4, 156.4, 143.7, 137.6, 137.0, 129.6(2C), 129.3, 127.9(2C), 127. 4(2C), 126.6, 114.2(2C), 112.1, 57.7, 55.3, 52.6, 21.4; **IR** (film, cm^{-1}): 3199, 1705, 1508, 1288, 1035, 821; **HRMS** (ESI) m/z calcd for [M+Na$^+$] $C_{22}H_{21}NNaO_7S$ 466.0931, found 466.0930.

Methyl 3-((4-fluorophenyl) (4-methylphenylsulfonamido) methyl)-2-oxo-2H-pyran-5-carboxylate (M-2t): white solid (345 mg, 80 %); mp: 150-151°C; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 8.15 (d, *J* = 2.5 Hz, 1H), 7.72 (dd, *J* = 2.5, 0.7 Hz, 1H), 7.67 – 7.61 (m, 2H), 7.20 (dd, *J* = 8.5, 0.6 Hz, 2H), 7.13 (dd, *J* = 8.5, 5.2 Hz, 2H), 6.92 (t, *J* = 8.6 Hz, 2H), 5.79 (d, *J* = 8.7 Hz, 1H), 5.35 (d, *J* = 8.6 Hz, 1H), 3.89 (s, 3H), 2.36 (s, 3H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 162.9, 162.5 (d, *J* = 248.0 Hz), 159.3, 156.6, 143.8, 138.1, 137.0, 133.1 (d, *J* = 3.2 Hz), 129.7(2C), 128.4 (d, *J* = 8.3 Hz, 2C), 127.3(2C), 126.1, 115.7 (d, *J* = 21.8 Hz, 2C) 112.1, 57.7, 52.6, 21.4; **IR** (film, cm^{-1}):3259, 3174, 1732, 1506, 1309, 1095, 975, 815; **HRMS** (ESI) m/z calcd for [M+Na$^+$] $C_{21}H_{18}FNNaO_6S$ 454.0731, found 454.0723.

Methyl 3-((4-bromophenyl) (4-methylphenylsulfonamido) methyl)-2-oxo-2H-pyran-5-carboxylate (M-2u): white solid (368 mg, 75 %); mp: 226-227°C; **^{1}H NMR** (400 MHz, DMSO) δ 8.76 (d, *J* = 9.6 Hz, 1H), 8.47 (d, *J* = 2.5 Hz, 1H), 7.81 (dd, *J* = 2.5, 0.9 Hz, 1H), 7.61 – 7.50 (m, 2H), 7.51 – 7.37 (m, 2H), 7.34 – 7.20 (m, 2H), 7.16 – 7.06 (m, 2H), 5.40 (d, *J* = 9.6 Hz, 1H), 3.83 (s, 3H), 2.30 (s, 3H); **^{13}C NMR** (100 MHz, DMSO) δ 163.0, 159.2, 157.5, 142.9, 137.77, 137.5, 137.3, 131.2(2C), 129.4(4C), 126.5(2C),

125.6, 120.9, 111.3, 55.1, 52.3, 20.8; **IR** (film, cm^{-1}):3197, 1707, 1586, 1433, 1168, 912; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{21}H_{18}NBrNaO_6S$ 513.9930, found 513.9924.

Methyl 2-(hydroxyl (4-nitrophenyl)methyl)-[1,1'-biphenyl]-4-carboxylate (M-3a): To an oven dried sealed tube **2a** (304 mg 1equiv) and ethynylbenzene (140 µL, 1.5 equiv) were added, The sealed tube was purged with Ar and then stirred at 120 ºC for 4 h. The crude product was direct purified by flash chromatography, afford **3a**, colorless oil (300 mg, 82%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 1.8 Hz, 1H), 8.12 – 8.05 (m, 2H), 8.01 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.48 – 7.40 (m, 3H), 7.39 – 7.32 (m, 1H), 7.31 – 7.28 (m, 1H), 7.28 – 7.24 (m, 3H), 6.08 (s, 1H), 3.92 (s, 3H), 2.53 (br, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.6, 150.5, 147.1, 145.8, 140.5, 139.5, 130.6, 130.0, 129.0, 128.9(2C), 128.6, 128.4(2C), 128.0, 127.3(2C), 123.5(2C), 71.6, 52.3; **IR** (film, cm^{-1}): 2929, 1712, 1453, 919; **HRMS** (ESI) m/z calcd for [M+H^+] $C_{21}H_{18}NO_5$ 364.1179, found 364.1177.

Methyl 3-(acetoxy(4-nitrophenyl)methyl) -2-oxo-2H-pyran-5-carboxylate (M-4a): yellow solid (330 mg, 95 %); mp: 96-97°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.31 – 8.24 (m, 1H), 8.22 – 8.07 (m, 2H), 7.92 (m, 1H), 7.78 – 7.51 (m, 2H), 6.79 (s, 1H), 3.89 (s, 3H), 2.19 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.0, 163.2, 158.6, 157.2, 148.0, 143.9, 136.8, 128.2(2C), 126.4, 123.9(2C), 112.0, 70.8, 52.7, 20.9; **IR** (film, cm^{-1}): 2958, 1714, 1230, 1101, 910; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{16}H_{13}NNaO_8$ 370.0533, found 370.0538.

Experimental procedure for the synthesis of compound M-5a, M-5b:

To a solution of **M-4a** (347 mg, 1.0 mmol), tetrabutylammonium bromide (32 mg, 0.1 mmol) and allyl alcohol or N-allyl-tosyl amine (2.0 mmol, 2 equiv) in THF (10 mL) at room temperature was added K_2CO_3 (138 mg, 1.0 mmol). The reaction was stirred at room temperature for 15 h, then heated to 50 ^oC for 4 h, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography.

Methyl 1-(4-nitrophenyl)-8-oxo-3,3a,4,5-tetrahydro-1H-5,7a-(epoxymethano)isobenzofuran-6-carboxylate (M-5a): yellow oil (300 mg, 87 %); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.30 – 8.10 (m, 2H), 7.76 (m, 2H), 6.55 – 6.34 (m, 1H), 5.81 – 5.67 (m, 1H), 5.62 (s, 1H), 4.26 (m, 1H), 3.68 (s, 3H), 3.34 (m, 1H), 3.05 – 2.89 (m, 1H), 2.51 (m, 1H), 1.53 – 1.40 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ170.6, 161.7, 147.8, 145.1, 138.3, 135.7, 127.2(2C), 123.9(2C), 77.2 74.971.0, 59.4, 52.4, 42.2, 28.0; **HRMS** (ESI) m/z calcd for [M+Na$^+$] $C_{17}H_{15}NNaO_7$ 368.0741, found 368.0729.

Methyl 1-(4-nitrophenyl)-8-oxo-2-tosyl-1,2,3,3a,4,5-hexahydro-5,7a-(epoxymethano) isoindole-6-carboxylate (M-5b): white solid (334 mg, 67 %); mp: 160-161°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.9 Hz, 2H), 7.89 (d, *J* = 8.9 Hz, 2H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 6.55 – 6.47 (m, 1H), 5.65 (dd, *J* = 3.9, 2.0 Hz, 1H), 5.46 (s, 1H), 3.94 (dd, *J* = 11.9, 7.0 Hz, 1H), 3.73 (s, 3H), 3.00 (t, *J* = 12.1 Hz, 1H), 2.47 (s, 3H), 2.32 (ddd, *J* = 14.3, 9.0, 4.7 Hz, 1H), 1.95 – 1.83 (m, 1H), 1.36 (dd, *J* = 14.3, 9.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.0, 161.4, 147.8, 145.0, 144.9, 138.0, 135.0, 133.2, 130.3(2C), 128.4(2C), 127.7(2C), 124.0(2C), 74.5, 62.6, 59.8, 53.1, 52.5, 39.4, 27.5, 21.7; **HRMS** (ESI) m/z calcd for [M+Na$^+$] $C_{24}H_{22}N_2NaO_8S$ 521.0989, found 512.0970.

Experimental procedure for the synthesis of compound M-6a, M-6b: To a solution of **M-5a** (300 mg, 1.0 equiv) or **M-5b** (334 mg, 1 equiv**)** in MeOH (1 mL) at room temperature was added MeONa 1.0 equiv. The reaction was stirred at room temperature for 2 h, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography. The reaction quenched with 1M HCl 5 mL, mixture was extracted with DCM (20 mL), and the layers were separated. The organic layer was washed with brine (10 mL), dried (MgSO4), and concentrated. The crude product was purified by flash chromatography gave the corresponding desired product **M-6a**, **M-6b**.

Dimethyl 6-hydroxy-3-(4-nitrophenyl)- 1,3,3a,6,7,7a-hexahydroisobenzofuran-3a,5-dicarboxylate (M-6a): colorless oil (298mg, 91%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.7 Hz, 2H), 6.19 (s, 1H), 5.33 (s, 1H), 4.70 – 4.52 (m, 1H), 4.28 – 4.13 (m, 1H), 3.90 (dd, *J* = 8.9, 5.0 Hz, 1H), 3.79 (s, 3H), 3.66 (s, 3H), 3.34 (br, 1H), 3.30 – 3.21 (m, 1H), 2.08 – 1.99 (m, 1H), 1.96 – 1.82 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ172.2, 166.4, 147.8, 144.4, 136.0, 135.2, 127.5(2C), 123.5(2C), 86.2, 71.4, 61.5, 58.1,53.3, 52.2, 39.7, 30.5; **HRMS** (ESI) m/z calcd for [M+H$^+$] $C_{18}H_{20}NO_8$ 378.1183, found 378.1182.

Dimethyl 6-hydroxy-3-(4-nitrophenyl)-2-tosyl-2,3,3a,6,7,7a-hexahydro-1H-isoindole-3a,5-dicarboxylate (M-6b): colorless oil (322mg, 91%) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 6.32 (s, 1H), 5.22 (s, 1H), 4.42 (t, *J* = 5.3 Hz, 1H), 3.75 – 3.67 (m, 1H), 3.66 (s, 3H), 3.56 (s, 3H), 3.54 – 3.46 (m, 1H), 2.45 (s, 3H), 1.98 – 1.79 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.6, 166.1, 147.6, 145.5, 144.5, 135.3, 134.3, 132.7, 129.9(2C),

128.5(2C), 128.0(2C), 123.5(2C), 69.6, 61.3, 58.4, 53.5, 52.5, 52.4, 36.4, 30.4, 21.6; **HRMS** (ESI) m/z calcd for [M+Na$^+$] $C_{25}H_{26}N_2NaO_9S$ 553.1251, found 553.1254.

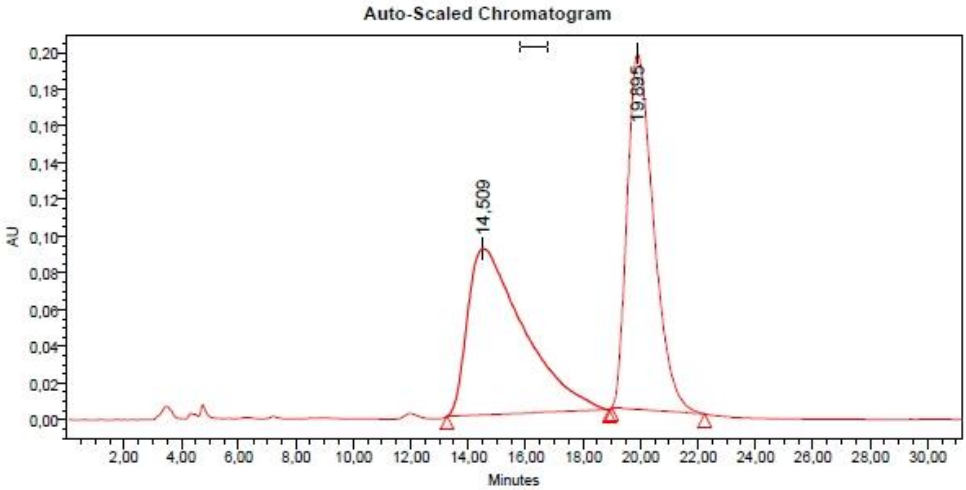
Methyl 3-(3-hydroxy-2-oxoindolin-3-yl)-2-oxo-2H-pyran-5-carboxylate (M-8a):

^{1}H NMR (400 MHz, MeOD) δ 8.59 – 8.36 (m, 2H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.08 (d, *J* = 7.3 Hz, 1H), 7.04 – 6.88 (m, 2H), 3.93 (s, 3H). **^{13}C NMR** (100 MHz, MeOD) δ 179.4, 165.1, 160.1, 158.7, 144.5, 139.2, 131.3, 131.2, 128.6, 124.9, 123.6, 113.6, 111.4, 76.3, 53.0.

The enantiomeric excess was determined by HPLC on chiral stationary phase with Daicel Chiralpack ADH column: eluent hexane/iPrOH = 65/35 flow rate 1 mL/min, λ=280 nm.

SAMPLE INFORMATION

Sample Name:	cl400-1 65:35 adh	Acquired By:	malacria
Sample Type:	Unknown	Date Acquired:	17/06/2016 12:19:09
Vial:	1	Acq. Method Set:	HPLC Malacria
Injection #:	22	Date Processed:	19/06/2018 12:24:32
Injection Volume:	10,00 ul	Processing Method:	avct599rac0
Run Time:	60,0 Minutes	Channel Name:	2487Channel 1
Sample Set Name:		Proc. Chnl. Descr.:	



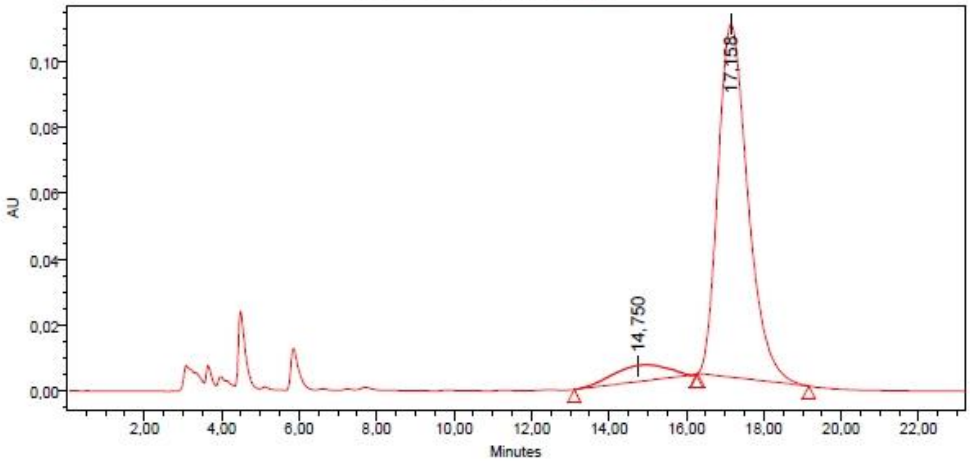
Peak Results

	Name	RT	Area	Height	% Area
1		14,509	12256292	90451	49,72
2		19,895	12396304	193587	50,28

SAMPLE INFORMATION

Sample Name:	cl571 ADH 65:35	Acquired By:	malacria
Sample Type:	Unknown	Date Acquired:	14/04/2017 18:28:20
Vial:	1	Acq. Method Set:	HPLC Malacria
Injection #:	8	Date Processed:	14/04/2017 18:52:44
Injection Volume:	20,00 ul	Processing Method:	avct599rac0
Run Time:	90,0 Minutes	Channel Name:	2487Channel 1
Sample Set Name:		Proc. Chnl. Descr.:	

Auto-Scaled Chromatogram



Peak Results

	Name	RT	Area	Height	% Area
1		14,750	474426	4848	7,63
2		17,158	5741394	107130	92,37

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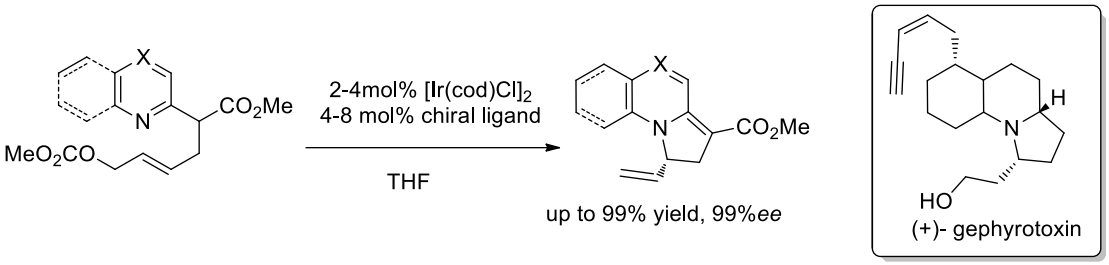
Chapter 6. A solvent-free, catalyst-free Michael addition dearomatization strategy: A sustainable protocol towards novel fluorescent dyes.

6.1. General introduction

Aromatic aza-heterocycles are a set of fundamental feedstocks in the chemical industry, pharmaceutical chemistry as well as agricultural and food chemistry.[1,2] Dearomatizaion reaction is an efficient method to convert those inert abundant chemicals to valuable-added or pharmaceutical interest scaffolds.[3–15] However, the structural diversity of aza-aromatic units renders general methods for dearomatization very challenging. Meanwhile, electrophile-triggered C-N bond forming dearomatization reactions of aza-heteroaromatic compounds, including pyridines,[16–18] pyrazines,[16] (iso)- quinolines,[19,20] benzoxazoles,[21,22] benzothiazoles,[21,22] benzimidazoles,[21,22] etc., have been reported respectively.

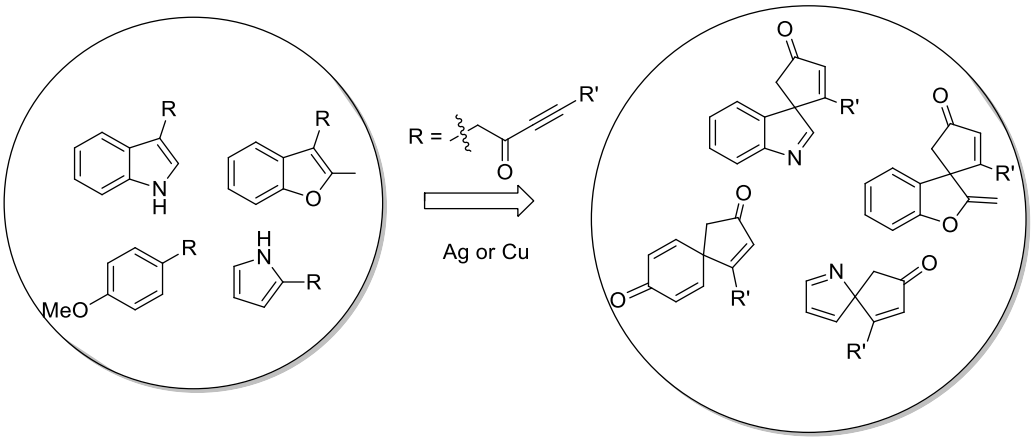
You and coworkers reported Ir-catalyzed intramolecular asymmetric allylic dearomatization reaction of pyridines, pyrazines, quinolines, and isoquinolines (Scheme 1). With chiral phosphoramidite (*S*,*S*,*Sa*)-L3 or (*R*,*Ra*)-L2 as the ligand, the desired asymmetric allylic dearomatization reactions took place in up to quantitative yield with excellent enantioselectivity. The robustness and practicality of this method were demonstrated by large-scale reactions. The utility of this method was further illustrated by formal synthesis of (+)-gephyrotoxin.

Scheme 1 Ir-Catalyzed Asymmetric Allylic Dearomatization of Electron-Deficient Arenes



Unsworth's group reported a high-yielding silver(I)- or copper(II)-catalyzed dearomatizing spirocyclization strategy, which allows the conversion of simple aromatic compounds that contain ynone substituents,including indole, anisole, pyrrole, and benzofuran derivatives into functionalized spirocyclic scaffolds.[17]

Scheme 2 Silver(I)- or copper(II)-catalyzed dearomatizing spirocyclization strategy

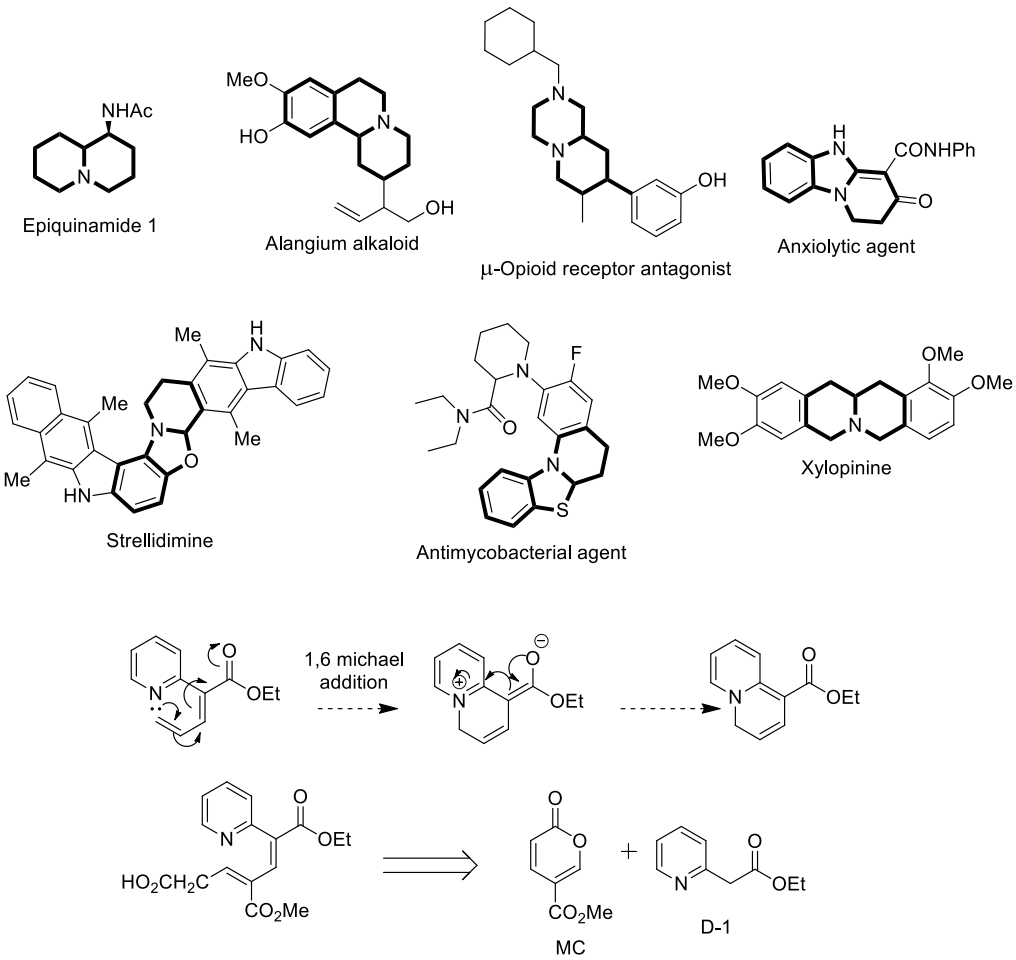


In this context, predominant methods mainly rely on N-nucleophilic aromatics with carbon electrophiles, *via* an allylic and propargylic substitution processes, which require presynthesis of electrophiles or their precursors, and also necessitate transition metals. Recently, in this field C-nucleophilic aromatics with a potent N-electrophiles have been proven useful, but restricted to electron rich aromatics.[23,24] Whereas numerous electrophiles exists for dearomatization reaction, the potential of common Michael acceptors for C-N bond forming dearomatization reactions

was still unexplored. We envisioned that the development of intramolecular 1,6 Michael addition dearomatization platform with broad heterocycles scope would provide a novel access to pyrido fused dearomatized cores which are found as core skeletons in natural products and bioactive compounds (Figure 1).[25–31]

Herein we describe a general, sustainable dearomative strategy for the conversion eleven types of basic aromatic rings to their pyrido[1, 2-*a*] fused derivatives in a solvent and catalysts-free condition. The usage of bio-based diene precursor methyl coumalate (MC)[32–34] provide a step-economy way to construct a 1,6 Michael acceptor on 2-position of aza-aromatics. Some of the resulting dearomatized heterocycles possess interesting fluorescence properties. The studies on site-selective labelling of two proteins (bovine serum albumin (BSA), immunoglobulin G (IgG)) with the obtained products are also reported.

Figure 1 Pyrido fused dearomatized cores and our strategy



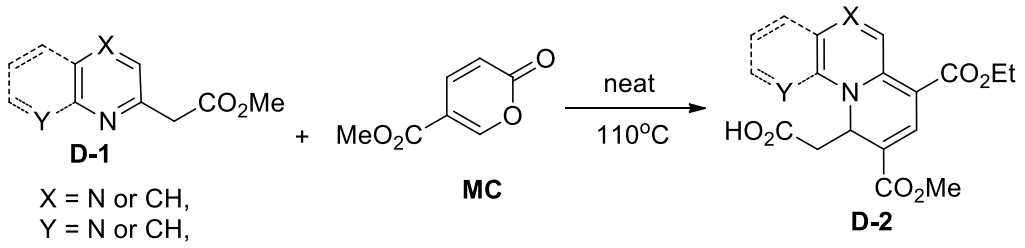
6.2. Self promoted Michael addition dearomatization protocol

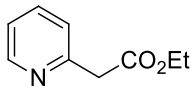
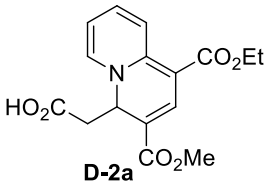
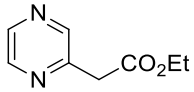
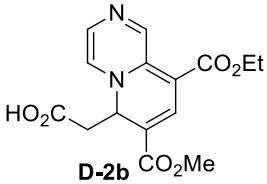
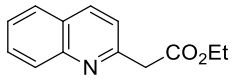
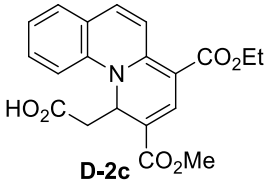
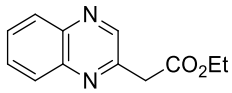
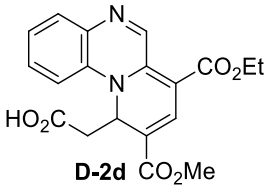
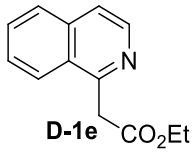
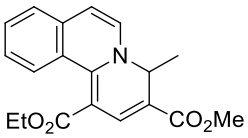
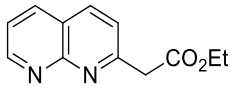
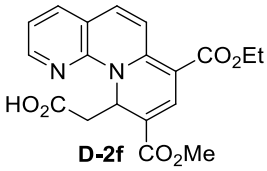
To begin our study, we discovered that the self-deprotonation by the basic aromatic ring could trigger the reaction in a solvent-free and catalysts-free condition (Table 1-3).

The dearomatization protocol succeeded with a wide range of different aza-aromatic, by employing same reaction condition. Six membered aza-aromatics, for example pyridine and pyridazine afforded the corresponding quinolizine and pydro-pyridazine products in high yield (89%- quant). Benzene and pyridine fused six membered aza-aromatics such as, quinoline, quinoxaline and naphthyridine were well tolerated (81-87% yield). Furthermore, this reaction also works well on isoquinoline affording the decarboxylated product in 75% yield. To our delight, mono five-membered aza-heterocycles, such as thiazole and N-methylimidazole were also viable substrates for this dearomatization reaction (**D-2g** 81%, and decarboxylated product **D-2h** 61%). Further, this protocol is compatible with benzoxazole, benzothiazole and unprotected benzoimidazole and the expected compounds **D-2i**, **D-2j**, **D-2k** were obtained in 82% to quantitive yield.

Wide ranges of substituted pyridines were found to be suitable feedstocks for dearomatization. Corresponding quinolizines were obtained with good to excellent yield. The dearomatization protocol was insensitive to the presence of electron-donor groups or electron-withdrawing groups at 5- position on the pyridine ring (**D-2l** – **D-2r**). Like 5-substituents, methyl and chloride group at 4- position afford **D-2s**, **D-2t** in good yields. Other electron-withdrawing group (–COMe, –COPh and –CN) linking on 2-methylpyridine were tolerated in this reaction, thus forming the products in good to excellent yield.

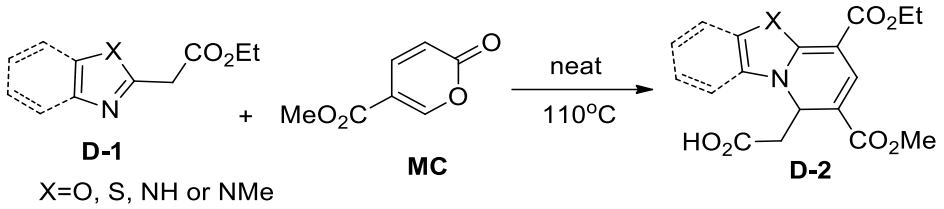
Table 1 Substrate scope for six membered aza-aromatics

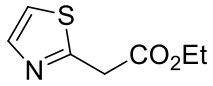
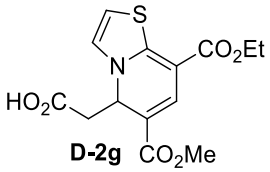
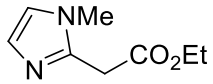
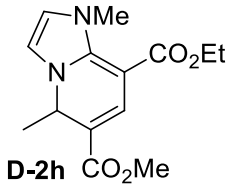
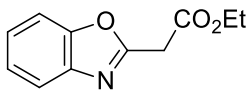
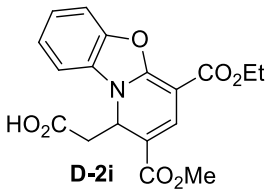
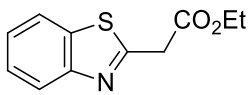
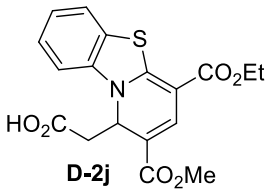
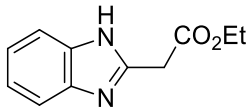
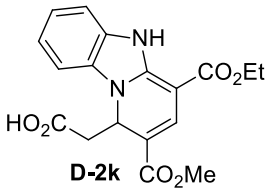


Entry	D-1	Time (h)	D-2	Yield (%)[a]
1	 **D-1a**	3	 **D-2a**	quant.
2	 **D-1b**	3	 **D-2b**	89
3	 **D-1c**	3	 **D-2c**	83
4	 **D-1d**	4	 **D-2d**	81
5	 **D-1e**	4	 **D-2e**	75
6	 **D-1f**	3	 **D-2f**	87

[a] isolated yield, **D-1** 1 mmol and MC 1 mmol

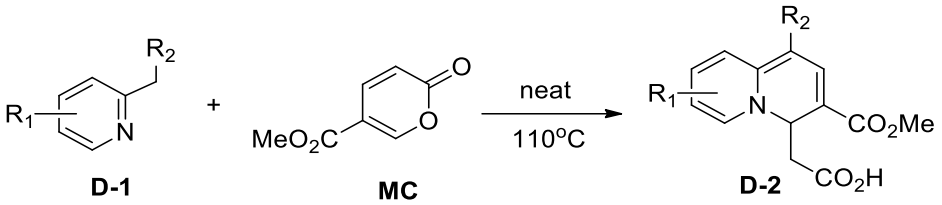
Table 2 Reaction substrate scope with five membered aza-aromatics



Entry	D-1	Time (h)	D-2	Yield (%)[a]
1	 **D-1g**	3	 **D-2g**	81
2	 **D-1h**	5	 **D-2h**	61
3	 **D-1i**	3	 **D-2i**	quant
4	 **D-1j**	3	 **D-2j**	91
5	 **D-1k**	5	 **D-2k**	82

[a] isolated yield, **D-1** 1 mmol and MC 1 mmol

Table 3 the reaction substrate scope of pyridine derivatives



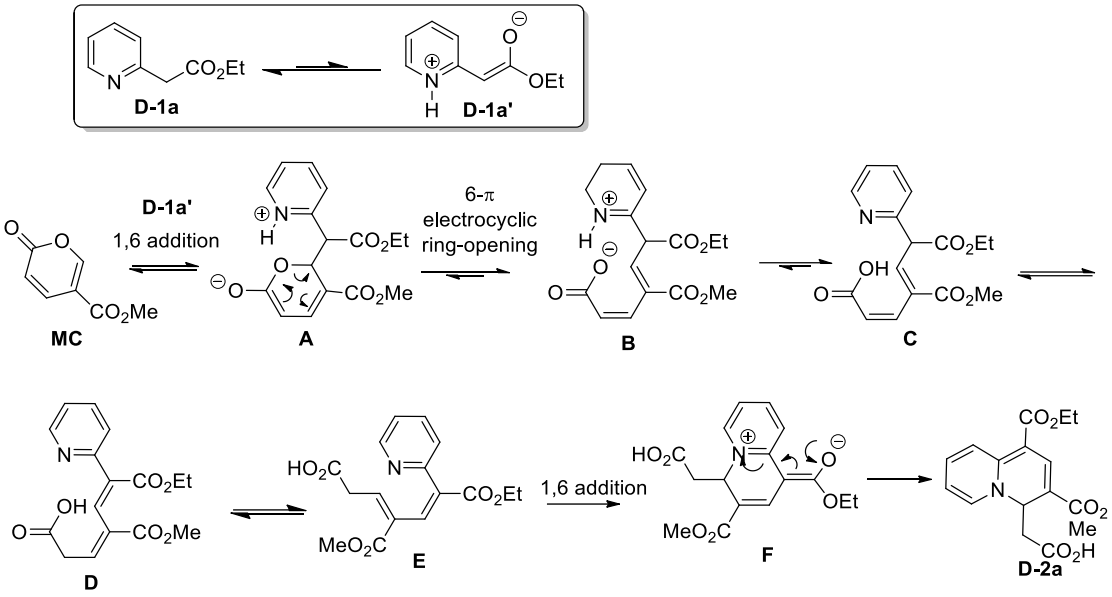
Entry	R_1	R_2	Time (h)	product	Yield (%)[a]
1	5-Me	CO_2Et	3	D-2l	90
2	5-Et	CO_2Et	3	D-2m	56[b]
3	5-Ph	CO_2Et	3	D-2n	87
4	5-Br	CO_2Et	4	D-2o	91
5	5-CF_3	CO_2Et	4	D-2p	90
6	5-NHAc	CO_2Et	3	D-2q	81
7	5-NO_2	CO_2Et	3	D-2r	80
8	4-Me	CO_2Et	3	D-2s	79
9	4-Cl	CO_2Et	3	D-2t	83
10	H	COMe	3	D-2u	85
11	H	COPh	3	D-2v	78
12	H	CN	2	D-2w	86

[a] isolated yield, **D-1** 1 mmol and MC 1 mmol. [b] decarboxylated product.

6.3. Plausible mechanism for the dearomatization

Figure 2 illustrates one plausible mechanism for the dearomatizaion reaction. The nucleophile undergoes a 1,6 addition on MC, after a self-deprotonative activation. The resulting intermediate A could run a 6π electrocyclic ring-opening, followed by proton transfer and isomerization furnish the diene intermediate E. It is presumed that the intramolecular Michael addition take place form the C-N bond and generate the pyridinium F. Subsequent the dearomatized product D-2 was formed by an enol-pyridinium tautomerization.

Figure 2 Plausible mechanism for the dearomatization



6.4. Photophysical properties of D-2j and its application for protein labelling

The photophysical properties exhibited by **D-2j** (Table 4) could be interesting for the labeling of biomolecules such as amino acids, peptides, proteins, DNA and immunoglobulins. Indeed, fluorescent probes are widely used to monitor *in vitro* or *in vivo* biological processes.[35–37]

Table 4 Photophysical data of the dearomative products **D-2j** in MeCN

Dyes	λ_{abs}[nm]	ε[$M^{-1}cm^{-1}$]	λ_{em}[nm]	Δλ[nm]	φ[%]
D-2j	417	16845	489	72	35

[a] The quantum yield was determined using quinine sulfate as reference, **φ**=0.55 in 1n H_2SO_4, **λex**=366 nm

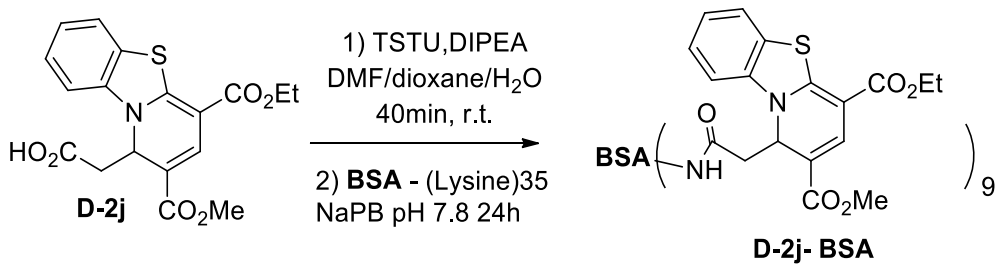
We were interested in the possible use of this derivative with fluorescent properties. Our team has a strong knowledge in targeting biomolecules for medicinal purpose.

In collaboration with Dr. Nathalie Fischer Durand, we thus started to explore the possible labelling of biomolecules with **D-2j**.

In particular, in the case of protein labelling, classical chemical modification relies on functional groups carried mainly by lysine and cysteine side chains, *i.e.* amine and thiol. **D-2j** has a reactive carboxylic acid function suitable for direct coupling with primary amines of lysine residues to form amide linkages.

As a model protein, we chose bovine serum albumin (BSA) that has 35 accessible lysines for potential conjugation. **D-2j** was first reacted with TSTU in DMF/dioxane/water at room temperature to afford the activated N-succinimidyl ester and added to a solution of BSA in sodium phosphate buffer pH 7.8 (scheme 1).

Scheme 1 BSA labelling with **D-2j**



After incubation for 24h at 25°C, the conjugate was purified by extensive dialysis and ultrafiltration. The average number of fluorescent probe **D-2j** conjugated per BSA was evaluated by UV-Vis spectroscopy by measuring the concentrations of **D-2j** and BSA using calibration curves established at 280 and 420 nm, which are the maximal absorbance wavelengths (λ_{max}) of BSA and **D-2j** respectively. The conjugation ratio was estimated to be 9 starting with 30 equiv of **D-2j** per BSA. The covalent nature of the linkage between the protein and **D-2j** was evidenced by performing an assay without activation of the acid with TSTU. After purification, we detected neither absorbance at 420 nm nor fluorescence emission at λ = 420 nm (figure 3, black line) showing that there are no nonspecific interactions.

Conjugate BSA-(**D-2j**)$_9$ showed strong fluorescence emission at 490 nm upon excitation at 420 nm in PBS pH 7.4 whereas excitation of BSA alone at 420 nm did not result in any fluorescence emission (figure 3).

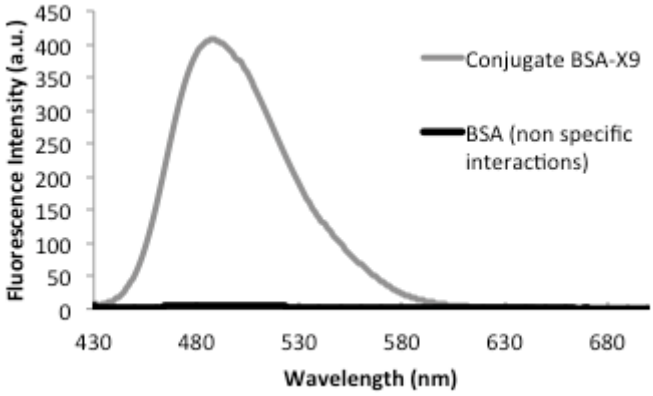
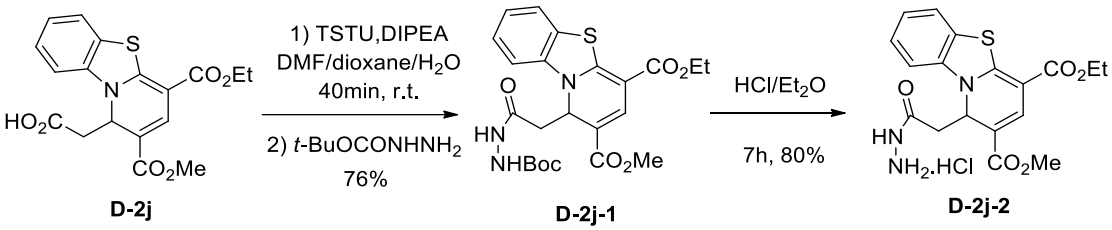


Figure 3. Fluorescent emission spectra (λ_{exc} = 420 nm) recorded in PBS pH 7.4 at 20.0 °C. BSA-x$_9$ conjugate (grey line) ([**x**]= 10 μM); non specific interactions assay (recovery of BSA alone, black line).

We then turned to a more selective protein labelling method. Indeed lysine residues are relatively abundant in proteins and are located uniformly on the surface. Developments in bioconjugation are directed towards alternative approaches exploiting chemoselective reactions between functional groups that are not naturally occurring in biomacromolecules and that only react with each other to ensure high selectivity and site-specificity. Among these reactions, the reaction between an acyl-hydrazine and an aldehyde to form an acyl-hydrazone bond has been frequently used. In particular, this approach is used for the site-selective labelling of glycoproteins after oxidation of polysaccharide residues. As a model glycoprotein, we chose an immunoglobulin G (or antibody). This choice was motivated by the relevance of fluorophore-antibody conjugates in the field of immunoassays. For this purpose the acid group of **D-2j** was activated into the N-succinimidyl ester and converted to the protected acyl-hydrazine **D-2j-1** upon reaction with *t*-Bu-carbazate. Cleavage of the Boc group by HCl in

ether/chloroform afforded the acyl hydrazine hydrochloride **D-2j-2** (scheme 2).

Scheme 2 modification of **D-2j** for IgG labelling



Site-selective labelling of immunoglobulin G (IgG) was then performed in two steps. First, the carbohydrate moieties located on the Fc region of IgG were oxidized with sodium periodate in acetate buffer pH 4.0 to generate aldehyde groups and subsequent reaction with a large excess of acyl hydrazine **D-2j-2** (20 equiv) in acetate buffer pH 5.5 for 18h at 25°C afforded acyl hydrazone bonds that were reduced with $NaBH_3CN$ into more stable acyl hydrazine bonds. The acidic pH conditions used for the oxidation step and the formation of acyl hydrazone bonds ensured that aldehyde groups reacted only with acyl hydrazine groups and not with amine groups, thus avoiding protein homo-coupling side-reaction. After extensive dialysis and ultrafiltration to remove unbound **D-2j-2**, the average number of fluorescent molecule conjugated per IgG was again evaluated by UV-Vis spectroscopy. We thus measured the concentrations of **D-2j-2** and IgG using calibration curves established at 280 and 420 nm. This conjugation rate was estimated to be 6 which is consistent with the average number of labelling sites expected to be generated given the chosen oxidation conditions (10 mM $NaIO_4$, pH 4.0, 1 h). Again, nonspecific interactions were not observed when incubating IgG and **D-2j-2** without the oxidation step (*i.e.* no absorbance at 420 nm and no fluorescence detected after dialysis, see figure 4, black line: IgG recovered). Fluorescence emission spectrum of conjugate IgG-(**D-2j-2**)$_6$ was recorded in PBS pH 7.4 upon excitation at 420 nm and showed strong fluorescence emission at 490 nm whereas excitation of IgG alone at 420 nm did not result in any fluorescence

emission (figure 4).

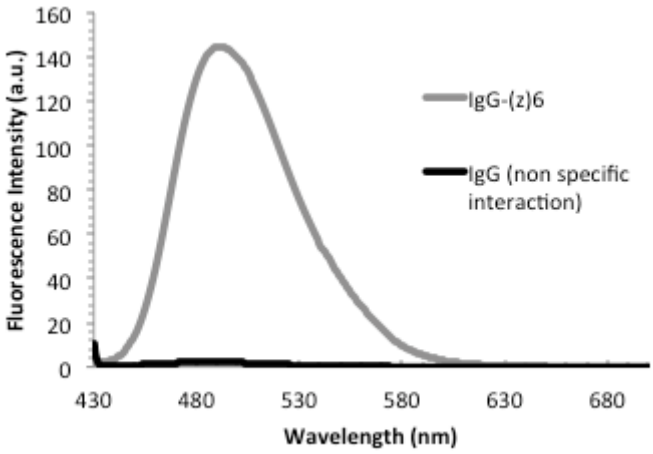


Figure 4. Fluorescent emission spectra (λ_{exc} = 420 nm) recorded in PBS pH 7.4 at 20.0 °C. IgG-z_6 conjugate (grey line) ([**z**]= 10 μM); non specific interactions assay (recovery of IgG alone, black line).

6.5. Conclusion

In summary, we outlined a novel, general Michael addition dearomatization reaction with an unprecedented pyrido[1, 2-*a*] fused heterocyclic scope, which can tolerate eleven types of aza-aromatics. This environmentally friendly protocol employs biorenewable diene precursor MC without requiring solvent and catalyst. This step-economical reaction allows to build C-C and C-N bond in one pot. The dearomative products possess novel prototypical structures, are novel fluorescent dyes, and finally the carboxyl group could serve as linker for proteins labelling.

6.6. Experimental part

Materials and general methods

All reactions were carried out under air with magnetic stirring. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz for ^{1}H nuclei, 100 MHz for ^{13}C

nuclei. Chemical shifts are reported in δ units, parts per million (ppm) using, for ^{1}H and ^{13}C, solvent residual peak as internal standard references: chloroform (7.26 ppm for ^{1}H NMR and 77.16 ppm). Coupling constants (*J*) are given in Hz, multiplicities are abbreviated as: s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublets of doublets), t (triplet), m (multiplet). High resolution mass spectra (HR-MS) were recorded on a LTQ-Orbitrap Mass Spectrometer [Thermo Scientific]. IR: Shimadzu IRAffinity-1CE spectrometer, wavenumbers in cm^{-1}. Starting materials **D-1a**, **D-1b**, **D-1g**, **D-1i**, **D-1j**, **D-1u**, **D-iv** and **D-1w** was purchased from Aldrich.

Typical experimental procedure for the synthesis of compound 2

The rest of Starting materials was synthesized according to the reported procedure (*Angew.Chem. Int. Ed*. **2015**, *54*, 10975; *Angew.Chem.Int. Ed*. **2015**, *54*, 15545; *J. Med. Chem.* **2016**, *59*, 6070;)

Typical experimental procedure for the synthesis of compound 2 (a-u).

In a finger reactor corresponding aza-aromatics D-**1** (1 mmol) and methyl coumalate (154 mg, 1 equiv) were mixed in neat condition. The reactor was purged with Ar and then stirred at 110°C until MC was consumed **D-2e**, **D-2h**, **D-2m** were purified by flash chromatography gave the corresponding desired product, the crude product **D-2a**, **D-2i** were pure enough without further purification, the crude **D-2b** – **D-2d** and **D-2f**, **D-2g, D-2j, D-2k** and **D-2n** – **D-2w** were grinded and the grinded compounds were washed with 1 ml mixture of toluene and cyclohexane v:v =1:1, after filtration afford corresponding desired products.

2-(1-(ethoxycarbonyl)-3-(methoxycarbonyl)-4H-quinolizin-4-yl) acetic acid (**D-2a**): 319mg, red solid, m.p. =194-195°C. **^{1}H NMR** (400 MHz, MeOD) δ 8.62 (d,

J = 9.2 Hz, 1H), 7.99 (d, *J* = 1.0 Hz, 1H), 7.97 (d, *J* = 6.5 Hz, 1H), 7.55 (ddd, *J* = 9.2, 6.8, 1.5 Hz, 1H), 6.83 (td, *J* = 6.8, 1.5 Hz, 1H), 5.81 (dd, *J* = 9.2, 3.1 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.77 (d, *J* = 4.3 Hz, 3H), 2.79 (dd, *J* = 15.7, 9.2 Hz, 1H), 2.36 (dd, *J* = 15.7, 3.1 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.6, 165.9, 165.6, 148.5, 139.1, 137.2, 136.2, 122.2, 114.6, 100.3, 92.9, 59.9, 59.4, 51.5, 37.1, 14.7. **IR** (film, cm^{-1}): 3413, 1706, 1654, 1626, 1186, 1039, 961, 708; **HRMS** (ESI) calcd for [M+Na^+] $C_{16}H_{17}NNaO_6$ 342.0948, Found *m/z* 342.0954.

2-(9-(ethoxycarbonyl)-7-(methoxycarbonyl)-6H-pyrido[1,2-a]pyrazin-6-yl)acetic acid (**D-2b**): 285mg, black solid, m.p. = 177-178ºC. **^{1}H NMR** (400 MHz, DMSO) δ 12.56 (s, 1H), 9.71 (s, 1H), 7.88 (d, *J* = 4.3 Hz, 1H), 7.82 (d, *J* = 4.3 Hz, 1H), 7.73 (s, 1H), 5.74 (dd, *J* = 9.3, 3.6 Hz, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.70 (s, 3H), 2.64 (dd, *J* = 15.6, 9.3 Hz, 1H), 2.31 (dd, *J* = 15.6, 3.6 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO) δ 171.4, 164.4, 164.2, 147.4, 140.7, 134.8, 132.2, 130.7, 104.5, 93.6, 59.8, 59.1, 51.8, 37.3, 14.9. **IR** (film, cm^{-1}): 2996, 1702, 1671, 1444, 1123, 1072, 944, 787. **HRMS** (ESI) calcd for [M+Na^+] $C_{15}H_{15}N_2NaO_6$ 343.0901, Found *m/z* 343.0887.

2-(4-(ethoxycarbonyl)-2-(methoxycarbonyl)-1H-pyrido[1,2-a]quinolin-1-yl)acetic acid (**D-2c**): 306mg, red solid, m.p. = 203-205ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 9.7 Hz, 1H), 8.03 (d, *J* = 0.5 Hz, 1H), 8.00 (d, *J* = 8.8 Hz, 1H), 7.58 (ddd, *J* = 8.8, 7.5, 1.5 Hz, 1H), 7.56 – 7.47 (m, 2H), 7.31 (t, *J* = 7.5 Hz, 1H), 6.64 (t, *J* = 6.5 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 2.60 (dd, *J* = 6.5, 3.3 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.2, 165.9, 165.6, 148.2, 137.6, 136.3, 134.3, 131.1, 128.5, 125.5, 124.3, 121.1, 114.5, 105.6, 97.7, 59.9, 51.6, 50.4, 36.4, 14.5. **IR** (film, cm^{-1}): 2984, 1742, 1681, 1560,

1465, 1330, 1196, 1148, 1072, 864, 827, 759. **HRMS** (ESI) calcd for [M+Na$^+$] $C_{20}H_{19}NNaO_6$ 392.1105, Found *m/z* 392.1103.

2-(7-(ethoxycarbonyl)-9-(methoxycarbonyl)-10H-pyrido[1,2-a]quinoxalin-10-yl)acetic acid. (**D-2d**). 300mg, black solid, m.p. = 181-182°C. **^{1}H NMR** (400 MHz, DMSO) δ 12.43 (s, 1H), 9.77 (s, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.81 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.74 (s, 1H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 6.42 (t, *J* = 6.2 Hz, 1H), 4.33 – 4.17 (m, 2H), 3.75 (s, 3H), 2.53 – 2.49 (m, 1H), 2.44 (dd, *J* = 14.0, 6.2 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO) δ 171.1, 164.6, 164.6, 148.5, 139.0, 138.2, 133.9, 131.8, 130.6, 130.0, 125.9, 114.3, 109.6, 99.7, 60.5, 52.1, 50.1, 36.7, 14.7. **IR** (film, cm^{-1}): 2954, 1717, 1680, 1487, 1213, 1141, 1076, 768;
HRMS (ESI) calcd for [M+Na$^+$] $C_{19}H_{18}N_2NaO_6$ 348.1206, Found *m/z* 348.1216.

1-ethyl 3-methyl 4-methyl-4H-pyrido[2,1-a]isoquinoline-1,3-dicarboxylate.(**D-2e**): 244mg, red oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.5 Hz, 1H), 7.99 (s, 1H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 1H), 7.19 (s, 1H), 6.89 (s, 1H), 5.36 (q, *J* = 5.7 Hz, 1H), 4.43 – 4.20 (m, 2H), 3.81 (d, *J* = 10.9 Hz, 3H), 1.37 (d, *J* = 6.5 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100MHz, $CDCl_3$) δ 167.9, 165.5, 148.3, 138.0, 135.3, 132.0, 131.1, 130.8, 126.8, 126.2(2C), 124.7, 114.2, 60.2, 59.8, 51.3, 19.1, 14.5. **IR** (film, cm^{-1}): 1681, 1602, 1364, 1147, 1029, 943, 815, 790. **HRMS** (ESI) calcd for [M+Na$^+$] $C_{19}H_{19}NNaO_4$ 348.1206, Found *m/z* 348.1216.

2-(7-(ethoxycarbonyl)-9-(methoxycarbonyl)-10H-pyrido[1,2-a][1,8] naphthyridin-10-yl)acetic acid. **(D-2f**): 322mg, red solid, m.p. = 165-166°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 9.7 Hz, 1H), 8.55 (dd, *J* = 4.6, 1.6 Hz, 1H), 7.99 (s, 1H), 7.79 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.50 (t, *J* = 6.3 Hz, 1H), 7.41 (d, *J* =

9.8 Hz, 1H), 7.23 (dd, *J* = 7.7, 4.7 Hz, 1H), 6.05 – 5.59 (br, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 2.63 – 2.49 (m, 2H), 1.37 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.2, 165.7, 165.5, 149.6, 148.3, 148. 3, 135.6, 132.3, 122.3, 120.0, 119.7, 109.3, 99.0, 77.2, 60.1, 51.7, 48.1, 37.3, 14.5. **IR** (film, cm^{-1}): 2987, 1752, 1652, 1452, 1352, 1299, 1197, 1178, 918, 846, 767, 702.

HRMS (ESI) calcd for [M+Na^+] $C_{19}H_{18}N_2NaO_6$ 393.1057, Found *m/z* 393.1045.

2-(8-(ethoxycarbonyl)-6-(methoxycarbonyl)-5H-thiazolo[3,2-a]pyridin-5-yl)acetic acid. (**D-2g**): 263mg, yellow solid. M.p.= 148-149ºC. **^{1}H NMR** (400 MHz, DMSO) δ 12.44 (br, 1H), 7.58 (s, 1H), 7.55 (d, *J* = 4.2 Hz, 1H), 7.19 (d, *J* = 4.2 Hz, 1H), 5.90 (dd, *J* = 7.1, 3.5 Hz, 1H), 2.60 (dd, *J* = 15.2, 7.1 Hz, 1H), 2.50-2.44 (m, 1H), 1.26 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (100MHz, DMSO) δ 171.7, 165.4, 164.7, 160.6, 133.3, 130.9, 112.3, 103.4, 90.4, 59.7, 55.8, 51.6, 40.7, 15.1. **IR** (film, cm^{-1}): 1707, 1680, 1649, 1437, 1239, 1206, 1052, 977, 884, 759; **HRMS** (ESI) calcd for [M+Na^+] $C_{14}H_{15}NNaO_6S$ 348.0512, Found *m/z* 348.0518.

8-ethyl 6-methyl 1,5-dimethyl-1,5-dihydroimidazo[1,2-a]pyridine-6,8-dicarboxylate.(**D-2h**), 169mg, yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 0.7 Hz, 1H), 6.64 (d, *J* = 2.2 Hz, 1H), 6.63 (d, *J* = 2.2 Hz, 1H), 5.30 (q, *J* = 6.1 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 3.71 (s, 3H), 1.33 (d, *J* = 6.1 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.7, 166.4, 164.3, 145.3, 138.7, 120.9, 115.2, 101.3, 78.8, 58.9, 53.7, 50.9, 38.1, 21.7, 14.8. **IR** (film, cm^{-1}): 16751602, 1466, 1405, 1351, 1184, 1109, 1002, 985, 913, 790. **HRMS** (ESI) calcd for [M+H^+] $C_{14}H_{19}N_2O_4$ 279.1339, Found *m/z* 279.1329.

2-(4-(ethoxycarbonyl)-2-(methoxycarbonyl)-1H-benzo[4,5]oxazolo[3,2-a]pyridin-1-yl)acetic acid. (**D-2i**): 359mg, yellow solid, m.p.= 207-208ºC. **^{1}H NMR** (400 MHz, DMSO) δ 12.37 (s, 1H), 7.73 (s, 1H), 7.69 (t, *J* = 8.6 Hz, 2H),

7.41 (t, *J* = 7.3 Hz, 1H), 7.33 (t, *J* = 7.3 Hz, 1H), 6.03 (t, *J* = 4.2 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.72 (s, 3H), 2.77 (dd, *J* = 15.0, 4.2 Hz, 1H), 2.66 (dd, *J* = 15.0, 4.2 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO) δ 171.7, 165.2, 162.9, 160.4, 147.3, 136.7, 129.2, 125.9, 124.7, 111.5, 111.1, 105.7, 79.6, 59.4, 53.0, 51.8, 38.1, 15.1. **IR** (film, cm^{-1}): 2962, 1715, 1659, 1480, 1312, 1244, 1206, 973, 775; **HRMS** (ESI) calcd for [M+Na$^+$] $C_{18}H_{17}NNaO_7$ 382.0897, Found *m/z* 382.0909.

2-(4-(ethoxycarbonyl)-2-(methoxycarbonyl)-1H-benzo[4,5]thiazolo[3,2-a]pyridin-1-yl)acetic acid. (**D-2j**): 341mg. yellow soild. m.p. = 203-204ºC. **^{1}H NMR** (400 MHz, MeOD) δ 7.79 (s, 1H), 7.76 (d, *J* = 7.3 Hz, 1H), 7.67 (d, *J* = 8.3 Hz, 1H), 7.57 – 7.46 (m, 1H), 7.40 – 7.28 (m, 1H), 6.21 (t, *J* = 5.1 Hz, 1H), 4.35 – 4.17 (m, 2H), 3.83 (s, 3H), 2.72 (dd, *J* = 13.9, 5.5 Hz, 1H), 2.62 (dd, *J* = 13.9, 4.7 Hz, 1H), 1.38 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO) δ 171.4, 165.4, 164.9, 160.3, 138.9, 133.0, 127.8, 127.5, 124.6, 123.3, 112.7, 107.3, 92.3, 60.1, 53.2, 51.8, 38.5, 15.0. **IR** (film, cm^{-1}): 1731, 1629, 1414, 1167, 1049, 1021, 853, 774. **HRMS** (ESI) calcd for [M+Na$^+$] $C_{18}H_{17}NNaO_6S$ 398.0669, Found *m/z* 398.0660.

2-(4-(ethoxycarbonyl)-2-(methoxycarbonyl)-1,5-dihydrobenzo[4,5]imidazo[1,2-a]pyridin-1-yl)acetic acid. (**D-2k**): 294mg. yellow solid. m.p. = 173-175ºC. **^{1}H NMR** (400 MHz, DMSO) δ 7.78 (s, 1H), 7.69 – 7.61 (m, 1H), 7.60 – 7.49 (m, 1H), 7.37 – 7.18 (m, 2H), 6.00 (t, *J* = 4.1 Hz, 1H), 4.19 (q, *J* = 7.1, 2H), 3.69 (s, 3H), 2.75 (dd, *J* = 14.5, 4.1 Hz, 1H), 2.66 – 2.57 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO) δ 171.8, 165.7, 164.8, 148.9, 136.6, 131.9, 130.4, 123.9, 123.2, 112.5, 110.6, 100.9, 78.4, 58.9, 51.8, 51.3, 38.5, 15.3. **IR** (film, cm^{-1}): 1741, 1675, 1550, 1435, 1333, 1246, 1202, 1167, 1010, 938, 750, 717. **HRMS** (ESI) calcd for [M+Na$^+$] $C_{18}H_{18}N_2NaO_6$ 381.1045, Found *m/z* 381.1057.

2-(1-(ethoxycarbonyl)-3-(methoxycarbonyl)-7-methyl-4H-quinolizin-4-yl)acetic acid. (**D-2l**)： 300mg, red solid, m.p. = 191-192°C. **^{1}H NMR** (400 MHz, DMSO) δ 12.46 (s, 1H), 8.52 (d, *J* = 9.2 Hz, 1H), 7.95 (s, 1H), 7.81 (s, 1H), 5.72 (dd, *J* = 9.2, 4.0 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.67 (s, 3H), 2.58 (dd, *J* = 15.0, 9.2 Hz, 1H), 2.30 (dd, *J* = 15.0, 4.0 Hz, 1H), 2.15 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO) δ 171.5, 165.0, 164.6, 146.9, 140.0, 138.2, 136.2, 125.0, 120.9, 100.1, 90.8, 60.3, 58.9, 51.3, 38.0, 17.3, 15.0. **IR** (film, cm^{-1}): 2950, 1707, 1342, 1257, 1117, 955, 760,;

HRMS (ESI) calcd for [M+H$^+$] $C_{17}H_{18}NO_6$ 332.1140, Found *m/z* 332.1151.

1-ethyl 3-methyl 7-ethyl-4-methyl-4H-quinolizine-1,3-dicarboxylate.(**D-2m**): 170mg, red oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 9.9 Hz, 1H), 7.88 (d, *J* = 0.8 Hz, 1H), 7.23 – 7.20 (m, 1H), 7.20 – 7.17 (m, 1H), 5.29 (q, *J* = 6.5 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.68 (s, 3H), 2.43 (q, *J* = 7.6 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.20 (d, *J* = 6.5 Hz, 3H), 1.14 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.0, 165.7, 147.8, 137.3, 136.0, 134.4, 130.9, 122.3, 102.2, 90.9, 60.4, 59.0, 51.1, 25.0, 20.3, 14.7, 14.3. **IR** (film, cm^{-1}): 2978, 1646, 1538, 1422, 1301, 1184, 1002, 985, 941, 908, 758. **HRMS** (ESI) calcd for [M+Na$^+$] $C_{15}H_{17}NNaO_4$ 298.1050, Found *m/z* 298.1055.

2-(1-(ethoxycarbonyl)-3-(methoxycarbonyl)-7-phenyl-4H-quinolizin-4-yl) acetic acid. (**D-2n**). 343mg, orange solid, m.p. =201-202°C. **^{1}H NMR** (400 MHz, DMSO) δ 12.49 (s, 1H), 8.64 (d, *J* = 9.5 Hz, 1H), 8.48 (s, 1H), 8.03 (dd, *J* = 9.5, 1.7 Hz, 1H), 7.84 (s, 1H), 7.72 (d, *J* = 7.5 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 1H), 5.95 (dd, *J* = 9.7, 3.5 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.70 (s, 3H), 2.68 (dd, *J* = 15.1, 9.7 Hz, 1H), 2.37 (dd, *J* = 15.1, 3.5 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO) δ 171.7, 165.0, 164.6, 146.9, 138.0, 136.1, 135.9,

135.2, 129.5(2C), 128.5, 127.1, 126.1(2C), 121.2, 101.6, 91.5, 60.4, 59.2, 51.5, 38.0, 15.1. **IR** (film, cm^{-1}): 2987, 1735, 1682, 1583, 1400, 1214, 1190, 1100, 1065, 933, 886, 798, 758. **HRMS** (ESI) calcd for [M+Na^+] $C_{22}H_{21}NNaO_6$ 418.1267, Found *m/z* 418.1290.

2-(7-bromo-1-(ethoxycarbonyl)-3-(methoxycarbonyl)-4H-quinolizin-4-yl)acetic acid. (**D-2o**): 345mg, red solid, m.p. = 172-174°C, **^{1}H NMR** (400 MHz, DMSO) δ 8.46 (d, *J* = 9.8 Hz, 1H), 8.34 (d, *J* = 1.9 Hz, 1H), 7.75 (s, 1H), 7.69 (dd, *J* = 9.8, 2.1 Hz, 1H), 5.78 (dd, *J* = 9.3, 3.7 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.67 (s, 3H), 2.62 (dd, *J* = 15.3, 9.4 Hz, 1H), 2.29 (dd, *J* = 15.3, 3.8 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO) δ 171.1, 164.4, 163.9, 146.4, 139.8, 139.2, 135.0, 121.7, 106.0, 102.1, 91.8, 59.4, 58.8, 51.1, 37.0, 14.5. **IR** (film, cm^{-1}): 3082, 1733, 1676, 1584, 1418, 1216, 1000, 932, 770, 713; **HRMS** (ESI) calcd for [M+Na^+] $C_{16}H_{16}BrNNaO_6$ 422.0034, Found *m/z* 422.0049.

2-(1-(ethoxycarbonyl)-3-(methoxycarbonyl)-7-(trifluoromethyl)-4H-quinolizin-4-yl)acetic acid. (**D-2p**): 348mg, orange solid, m.p. = 170-173°C. **^{1}H NMR** (400 MHz, DMSO) δ 12.59 (s, 1H), 8.56 (d, *J* = 9.7 Hz, 2H), 7.75 (s, 1H), 7.71 (dd, *J* = 9.7, 1.9 Hz, 1H), 5.88 (dd, *J* = 9.8, 3.5 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.71 (s, 3H), 2.68 (dd, *J* = 15.7, 9.8 Hz, 1H), 2.33 (dd, *J* = 15.7, 3.5 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO) δ 171.7, 164.8, 164.3, 148.3, 140.2 (q, *J* = 5.5 Hz), 134.8, 131.6 (q, *J* = 2.4 Hz), 123.58 (q, *J* = 270.3 Hz), 121.4, 114.96 (q, *J* = 34.6 Hz), 105.4, 94.2, 59.7, 59.6, 51.8, 37.0, 14.9. **IR** (film, cm^{-1}): 1738. 1688. 1515, 1413, 1322, 1292, 1100, 946, 857, 760. **HRMS** (ESI) calcd for [M+Na^+] $C_{17}H_{16}F_3NNaO_6$ 410.0822, Found *m/z* 410.0814.

2-(7-acetamido-1-(ethoxycarbonyl)-3-(methoxycarbonyl)-4H-quinolizin-4-yl)acetic acid. (**D-2q**): 305mg, red solid, m.p. = 196-198°C. **^{1}H NMR** (400 MHz,

DMSO) δ 12.51 (s, 1H), 10.22 (s, 1H), 8.62 (s, 1H), 8.59 (d, *J* = 9.7 Hz, 1H), 7.80 (s, 1H), 7.62 (d, *J* = 9.7 Hz, 1H), 5.65 (dd, *J* = 8.9, 3.0 Hz, 1H), 4.14 (q, *J* = 7.0 Hz, 2H), 3.67 (s, 3H), 2.61 (dd, *J* = 15.2, 8.9 Hz, 1H), 2.30 (dd, *J* = 15.2, 3.0 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO) δ 171.4, 169.1, 165.0, 164.6, 145.0, 136.0, 131.1, 129.6, 129.1, 121.8, 99.8, 91.1, 61.4, 59.1, 51.4, 38.2, 24.0, 15.1. **IR** (film, cm^{-1}): 1726, 1651, 1527, 1203, 1179, 1033, 937, 772. **HRMS** (ESI) calcd for [M+H$^+$] $C_{20}H_{21}N_2O_7$ 377.1343, Found *m/z* 377.1342.

2-(1-(ethoxycarbonyl)-3-(methoxycarbonyl)-7-nitro-4H-quinolizin-4-yl)acetic acid. (**D-2r**): 331mg, red solid, m.p. = 166-167°C. **^{1}H NMR** (400 MHz, MeOD) δ 9.02 (d, *J* = 2.3 Hz, 1H), 8.50 (d, *J* = 10.3 Hz, 1H), 7.93 (dd, *J* = 10.3, 2.4 Hz, 1H), 7.85 (s, 1H), 5.84 (dd, *J* = 10.1, 3.0 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 2.86 (dd, *J* = 16.4, 10.1 Hz, 1H), 2.45 (dd, *J* = 16.4, 3.1 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.2, 164.3, 146.4, 140.4, 135.5, 134.9, 134.8, 127.1, 120.9, 107.6, 98.5, 60.4, 59.9, 51.9, 35.5, 14.5. **IR** (film, cm^{-1}): 2954, 1702, 1679, 1507, 1429, 1250, 1217, 1040, 996, 715. **HRMS** (ESI) calcd for [M+Na$^+$] $C_{16}H_{16}N_2NaO_8$ 387.0799, Found *m/z* 387.0805.

2-(1-(ethoxycarbonyl)-3-(methoxycarbonyl)-8-methyl-4H-quinolizin-4-yl)acetic acid. (**D-2s**): 265mg, red solid, m.p. = 183-185°C. **^{1}H NMR** (400 MHz, DMSO) δ 12.45 (s, 1H), 8.41 (s, 1H), 7.97 (d, *J* = 6.9 Hz, 1H), 7.81 (d, *J* = 0.6 Hz, 1H), 6.77 (dd, *J* = 6.9, 1.9 Hz, 1H), 5.71 (dd, *J* = 9.4, 3.5 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.66 (s, 3H), 2.59 (dd, *J* = 15.3, 9.4 Hz, 1H), 2.29 (s, 3H), 2.28 – 2.24 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H).**^{13}C NMR** (100 MHz, DMSO) δ 171.6, 165.0, 164.7, 149.6, 148.1, 139.8, 136.4, 120.0, 117.3, 100.6, 90.3, 59.7, 58.9, 51.3, 37.9, 21.8, 15.1. **IR** (film, cm^{-1}): 1717, 1679, 1436, 1164, 1050, 760. **HRMS** (ESI) calcd for [M+Na$^+$] $C_{17}H_{19}NNaO_6$ 356.1105, Found *m/z* 356.1112.

2-(8-chloro-1-(ethoxycarbonyl)-3-(methoxycarbonyl)-4H-quinolizin-4-yl)acetic acid. (**D-2t**): 293mg, red solid, m.p. 177-179°C. **^{1}H NMR** (400 MHz, DMSO) δ 12.51 (s, 1H), 8.60 (d, *J* = 2.4 Hz, 1H), 8.09 (d, *J* = 7.2 Hz, 1H), 7.76 (s, 1H), 6.96 (dd, *J* = 7.2, 2.4 Hz, 1H), 5.76 (dd, *J* = 9.2, 3.7 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.69 (s, 3H), 2.64 (dd, *J* = 15.4, 9.2 Hz, 1H), 2.31 (dd, *J* = 15.4, 3.7 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO) δ 171.5, 164.9, 164.5, 148.2, 143.8, 142.1, 135.3, 119.3, 115.2, 103.0, 91.5, 59.5, 59.4, 51.6, 37.7, 15.0. **IR** (film, cm^{-1}): 2988, 1711, 1652, 1438, 1254, 1201, 1187, 959, 788, **HRMS** (ESI) calcd for [M+Na$^+$] $C_{16}H_{16}NClNaO_6$ 376.0558, Found *m/z* 376.0570.

2-(1-acetyl-3-(methoxycarbonyl)-4H-quinolizin-4-yl)acetic acid. (**D-2u**): 242mg, orange solid, m.p. 162-163°C. **^{1}H NMR** (400 MHz, DMSO) δ 12.52 (s, 1H), 8.90 (d, *J* = 9.0 Hz, 1H), 8.17 (d, *J* = 6.4 Hz, 1H), 7.01 (t, *J* = 6.4 Hz, 1H), 5.79 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.69 (s, 3H), 2.62 (dd, *J* = 15.3, 9.6 Hz, 1H), 2.33 (dd, *J* = 15.3, 3.6 Hz, 1H), 2.27 (s, 3H). **^{13}C NMR** (100 MHz, DMSO) δ 190.1, 171.6, 164.6, 148.0, 140.6, 138.9, 137.2, 122.2, 116.8, 102.6, 101.2, 60.3, 51.5, 37.9, 28.1. **IR** (film, cm^{-1}): 3048, 1716, 1633, 1523, 1447, 1355, 1244, 772. **HRMS** (ESI) calcd for [M-H$^+$] $C_{15}H_{14}NO_5$ 288.0877, Found *m/z* 288.0867.

2-(1-benzoyl-3-(methoxycarbonyl)-4H-quinolizin-4-yl) acetic acid. (**D-2v**): 274mg, red solid, m.p. = 186-187°C. **^{1}H NMR** (400 MHz, DMSO) δ 12.56 (s, 1H), 9.03 (d, *J* = 8.8 Hz, 1H), 8.30 (d, *J* = 6.4 Hz, 1H), 7.82 (t, *J* = 7.9 Hz, 1H), 7.47 (s, 5H), 7.40 (s, 1H), 7.11 (t, *J* = 6.7 Hz, 1H), 5.87 (dd, *J* = 9.3, 3.7 Hz, 1H), 3.60 (s, 3H), 2.79 (dd, *J* = 15.3, 9.3 Hz, 1H), 2.46 (dd, *J* = 15.3, 3.7 Hz, 1H). **^{13}C NMR** (100 MHz, DMSO) δ 189.5, 171.6, 164.5, 148.9, 142.8, 140.9, 139.4, 138.9, 130.1, 128.5(2C), 128.3(2C), 122.2, 117.4, 101.3, 101.2, 60.5, 51.5, 38.3. **IR** (film, cm^{-1}): 3084, 1709, 1652, 1505, 1436, 1301, 1191, 1164, 1099, 1000, 937, 739, 698. **HRMS** (ESI) calcd for [M+H$^+$] $C_{20}H_{18}NO_5$ 352.1179, Found *m/z* 352.1171.

2-(1-cyano-3-(methoxycarbonyl)-4H-quinolizin-4-yl)acetic acid. (**D-2w**): 261mg, orange solid, m.p. = 173-175°C. **^{1}H NMR** (400 MHz, DMSO) δ12.53 (s, 1H), 8.05 (d, *J* = 6.3 Hz, 1H), 7.63 (t, *J* = 8.4 Hz, 1H), 7.25 (s, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 6.87 (t, *J* = 6.3 Hz, 1H), 5.83 (dd, *J* = 9.0, 3.7 Hz, 1H), 3.67 (s, 3H), 2.68 (dd, *J* = 15.3, 9.0 Hz, 1H), 2.35 (dd, *J* = 15.3, 3.7 Hz, 1H). **^{13}C NMR** (100 MHz, DMSO) δ 171.5, 163.9, 148.9, 140.5, 138.7, 135.1, 120.3, 119.7, 115.5, 101.7, 71.4, 59.6, 51.6, 38.4. **IR** (film, cm^{-1}): 1727, 1665, 1492, 1303, 1151, 982, 761. **HRMS** (ESI) calcd for $[M+H^+]$ $C_{14}H_{13}NO_4$ 273.0870, Found *m/z* 273.0870.

Dialysis were performed with Spectra/Por 4 membranes with a molecular weight cutoff of 6,000-8,000 or 12,000-14,000 Da (from Spectrum Laboratories, Inc.). Ultracentrifugation was performed using Amicon® Ultra-15 centrifugal filter devices (10 or 30 KDa, Millipore) or Vivaspin-6 centrifugal filter devices (10 or 30 KDa, Sartorius). Size exclusion chromatographies were performed with HiTrap fast-desalting columns purchased from GE Healthcare. UV/Vis spectra were recorded on a Varian Cary 50 spectrophotometer. Fluorescence spectra were recorded on a Jasco FP-6200 spectrofluorometer equipped with a temperature controller Jasco ETC-272T. Reactions of protein labelling were carried out in a Mixing block MB-102 (BIOER Technology Co., ltd).

Labelling of BSA with compound **D-2j**

Acid **D-2j** (1.7 mg, 4.53 μmol) was dissolved in DMF (90 μL), dioxane (90 μL) and H_2O (20 μL). DIPEA (1.58 μL, 9.06 μmol) and TSTU (2.05 mg, 6.8 μmol) were added. The solution was stirred for 40 min at room temperature and added to a solution of BSA (10 mg, 0.15 μmol) in 40 mM NaPB pH 7.8. The reaction mixture was incubated for 24 h at 25°C in the mixing block and dialyzed in PBS pH 7.4 at 4°C for 3 days during which the buffer was changed every day. The

solution was transferred into an Amicon® Ultra-15 (30 KDa) centrifugal filter device and concentrated. The concentrate was reconstituted to 10 mL with PBS pH 7.4 and concentrated. This process was repeated twice, and the recovered solution was analyzed by measuring absorbance at 420 and 280 nm. Absorbance measurement at 420 nm (ε= 10 200 $M^{-1}.cm^{-1}$) afforded the concentration of **D-2j** and after subtraction of the contribution of **D-2j** at 280 nm (ε= 6 200 $M^{-1}.cm^{-1}$), the BSA concentration ((ε= 44 682 $M^{-1}.cm^{-1}$) was deduced. Fluorescence spectroscopy was performed in PBS pH 7.4, at 10 μM in **D-2j**, at 20.0°C upon excitation at 420 nm.

4-ethyl 2-methyl 1-(2-hydrazinyl-2-oxoethyl)-1H-benzo[4,5]thiazolo[3,2-a]pyridine-2,4-dicarboxylate hydrochloride salt *(***D-2j2***)*

0.75 mL of 2M HCl in ethyl ether were added to compound **D-2j1** (50 mg, 0.102 mmol) in $CHCl_3$ (0.75 mL) and stirred in the dark for 7 h. The precipitate was filtered off, rinsed with Et_2O, CH_2Cl_2, and EtOAc and dried to yield a yellow solid (35 mg, 80%). %). ^{1}H NMR (300 MHz, DMSO-d6) δ 11.03 (s, 1H), 7.95 (d, 1H, *J*= 7.8 Hz), 7.81 (d, 1H, *J*= 8.4 Hz), 7.64 (s, 1H), 7.52 (t, 1H, *J*= 7.35 Hz), 7.36 (t, 1H, *J*= 7.5 Hz), 7.36 (t, 1H, *J*= 7.5 Hz), 6.16 (t, 1H, *J*= 4.6Hz), 4.21 (q, 2H, *J*= 7.2 Hz), 3.74 (s, 3H), 2.69 (m, 2H), 1.30 (3H, *J*= 7.2 Hz); ^{13}C NMR (75 MHz, DMSO-d6) δ 168.1, 165.7, 165..1, 160.3, 138.5, 133.4, 127.8 , 127.6, 124.9, 123.1, 112.37, 106.6, 92.4, 60.1, 52.7, 52.0, 36.8, 14.8.

HRMS (ES+) *m/z* calculated for $C_{18}H_{20}N_3O_5S^+$ $(M+H)^+$ 390.1118, found 390.1118.

Labelling of IgG with compound **D-2j2**

Rabbit IgG (2 mg in 0.15 M NaCl) were first buffer exchanged into 20 mM NaOAc +150 mM NaCl pH 4.0 using Amicon® Ultra-30 K centrifugal filter device (final volume of 300 μL) and $NaIO_4$ (20 mM in 20 mM NaOAc, 150 mM NaCl pH 4.0, freshly prepared) was added (300 μL, final concentration of 10 mM).

This solution was incubated for 1 h at 25°C in the dark then purified on a 5 mL HiTrap fast-desalting column (50 mM AcONa, 150 mM NaCl pH 5.0). Oxidized IgG solution was collected, concentrated and transferred into 0.1 M AcONa pH 5.5 (350 μL) and allowed to react with hydrazide **D-2j2** (0.07 mg, 20 mol equiv, 1mg/mL solution prepared in DMF/0.1 M AcONa pH 5.5, 18:82, v/v) for 18 h at 25°C in the dark, in the mixing block. Ethanolamine.HCl (1 M in H_2O, pH 10.3, 60 μL) was added and the incubation was pursued for 2 h then 5 M $NaBH_3CN$ in 1 M NaOH (15 μL) was added and the incubation was continued for 2 h. The solution was dialyzed in PBS pH 7.4 at 4°C for 48 h during which the buffer was changed 3 times then transferred into an Amicon® Ultra-30 K centrifugal filter device and concentrated. The concentrate was reconstituted to 10 mL with PBS pH 7.4 and concentrated. This process was repeated twice, then the recovered solution was analyzed by measuring absorbance at 420 and 280 nm as described for the labelling of BSA using A_{280}(IgG)= 1.4 for 1 mg/mL solution. Fluorescence spectroscopy was performed in PBS pH 7.4, at 10 μM in **z**, at 20.0°C upon excitation at 420 nm.

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Conclusion

In this work, we have described the development of new transformations using bio-based renewable methyl coumalate as feedstock. An iron and copper catalyzed a one-pot sequential double alkyl-alkyl or alkyl-hydride 1,6-addition with methyl coumalate was discribed. This chemistry is valuable for the preparation of *β,γ*-unsaturated carboxylic acids in a highly regio-, chemo- and stereoselective manner. We also elucidated the pivotal role of the Grignard reagent as regards the stereoselectivity outcome of the reaction. The later could be rationalized by invoking a constrained chair-like transition state with the formation of a stable bimetallic intermediate.

We then described an efficient synthesis of tetrasubstituted 2*H*-pyrans under mild condition. We proposed the reactions proceed through a cascade 1,6-Michael / 6π electrocyclic ring opening / [1,5]-*H* transfer / (decarboxylation) / 6π electrocyclization process. In addition to the broad substrate scope, this methodology has the advantage of using readily available starting materials and mild conditions.

We later reported an efficient, solvent-free reaction of methyl coumalate with trifluoromethyl-*β*-diketones, in a *t*BuOK-catalyzed domino sequence. This procedure is a practical and sustainable approach, using bio-based feedstock for an easy synthesis of myriad trifluoromethyl-benzene derivatives, and releases only water and CO_2. Most of the products have the biological core benzophenone structure. moreover this method could corporate with Pd catalyzed dehydrogenation give CF_3-functionalized fluorenone in one pot.

A novel reaction, for efficient C-C bond formation between the bio-based methyl coumalate and a variety of imines and aldehydes was reported. Et_3N serves as catalyst in ethanol for this environmentally benign transformation, which occurs *via* an unprecedented 1,6-conjugated addition-triggered Morita-Baylis-Hillman pathway. Remarkable rate enhancement was achieved using K_2CO_3. Both chiral amine and chiral PTC failed in enriching the enantioselectivity of our reaction. To

our delight, a regioselective substitution of the MBH acetate has been discovered with PTC catalyst. By using this transformation the original MBH adducts acetate could be applied into the synthesis of hydroisobenzofuran and hydro-isoindole derivatives. A preliminary study of the asymmetric MBH has been done by employing several privileged chiral amine catalyst. To our surprise, the additional $MgCl_2$ or H_2O shown remarkable enantiomeric enhancement, and gives the MBH adducts in good *ee*.

Finally, we reported a novel, general Michael addition dearomatization reaction strategy with an unprecedented pyrido[1, 2-*a*] fused heterocyclic scope, which can tolerate eleven types of aza-aromatics. This environmentally friendly protocol employs biorenewable diene precursor MC without requiring solvent and catalyst. This step-economical reaction allows to build C-C and C-N bond in one pot. The dearomative products possess novel prototypical structures, are novel fluorescent dyes, and finally the carboxyl group could serve as linker for proteins labelling.

Publications

L. Chang, S. Thorimbert, L. Dechoux, Bio-based methyl coumalate-involved Morita-Baylis-Hillman reaction. *Green Chem.* Under review.

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Conferences & Communications

- ***Oral communication,*** 16th Rencontres de Chimie Organique, Sorbonne University, 2018, Paris
- ***Poster,*** Journées de Chimie Organique (JCO), 2016, Palaiseau
- ***Poster,*** 14th Rencontres de Chimie Organique, Université Paris 13, 2016, Bobigny
- ***Oral communication,*** Doctoral School JCM, UPMC, 2016, Paris
- ***Oral communication,*** Doctoral School JBED, UPMC, 2015, Paris

Résumé

Dans ce travail, nous décrivons le développement de nouvelles transformations utilisant le coumalate de méthyle, composé renouvelable biosourcé. Un couplage double séquentiel d'alkyl-alkyle ou d'alkyl-hydrure *one pot* conduit à des acides insaturés d'intérêt. Nous décrivons une synthèse efficace de 2*H*-pyranes tétrasubstitués dans des conditions douces, puis nous décrivons une réaction efficace et sans solvant avec des dicétones trifluorométhylées, pour conduire à des benzènes trifluorométhylés. Enfin, nous avons rapporté une nouvelle stratégie générale de réaction de désaromatisation de composés hétérocycliques de type pyrido [1, 2-a] bicycliques.

Mots clés: Matière première renouvelable, réaction de Morita-Baylis-Hillman, processus électrocycliques, 1,6 addition, dearomatisation, composés fluorescents.

Abstract

In this work, we have described the development of new transformations using bio-based renewable methyl coumalate as feedstock. An iron and copper catalyzed one-pot sequential double alkyl-alkyl or alkyl-hydride 1,6-addition with methyl coumalate was described. We then described an efficient synthesis of tetrasubstituted 2*H*-pyrans under mild condition. Later we reported a solvent-free reaction of methyl coumalate with trifluoromethyl-*β*-diketones, in a *t*BuOK-catalyzed domino sequence. A novel reaction, for efficient C-C bond formation between the bio-based methyl coumalate and a variety of imines and aldehydes *via* MBH pathway was reported. Finally, we reported a novel, general dearomatization strategy with an unprecedented pyrido[1, 2-*a*] fused heterocyclic scope.

Keywords: Renewable feedstock, Morita-Baylis-Hillman reaction, electrocyclic reactions, 1,6 addition, dearomatizaion, fluorescent probes.