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New advances in photoredox catalysis : applications in radical chemistry synthesis and dual catalysis

Ludwig Chenneberg

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THESE DE DOCTORAT DE L'UNIVERSITE PIERRE ET MARIE CURIE

Spécialité
CHIMIE ORGANIQUE

Ecole Doctorale de Chimie Moléculaire de Paris Centre – ED406
Institut Parisien de Chimie Moléculaire / Equipe MACO

Présentée par

M. Ludwig CHENNEBERG

Pour obtenir le grade de

Docteur de l'Université Pierre et Marie Curie

Sujet de la thèse:

**NOUVELLES AVANCEES EN CATALYSE PHOTOREDOX :
APPLICATIONS EN CHIMIE RADICALAIRE DE SYNTHESE ET EN
CATALYSE DUALE**

Soutenue le 19 Septembre 2016,

Devant un jury composé de :

Pr Laurence FERAY	Université d'Aix-Marseille, Marseille	Rapporteur
Dr Raphaël RODRIGUEZ	Institut Curie, Paris	Rapporteur
Dr Frédéric AVENIER	Université Paris-Sud, Orsay	Examineur
Pr Bernold HASENKNOPF	Université Pierre et Marie Curie, Paris	Examineur
Pr Jean-Philippe GODDARD	Université de Haute Alsace, Mulhouse	Examineur
Pr Louis FENSTERBANK	Université Pierre et Marie Curie, Paris	Examineur
Dr Cyril OLLIVIER	Université Pierre et Marie Curie, Paris	Invité

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Abbreviations

AIBN: 2,2'-azobis-iso-butyronitril

Ar: aryl

Bn: benzyl

Boc: tert-butoxycarbonyl

bpy: 2,2'-bipyridyl

Bz: benzoyl

Cat.: catalytic

CCl₄: carbon tetrachloride

CFL: Compact Fluorescent Lamp

COD: *cis,cis*-1,5-cyclooctadiene

Cy: cyclohexane

dap: dianisyl phenanthroline

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

DCM: dichloromethane

DIPEA: diisopropylethylamine, Hünig's base

DMAP: 4-dimethylaminopyridine

DMF: *N,N'*-dimethylformamide

DMPU: 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone

DMSO: dimethylsulfoxide

dpp: diphenyl phenanthroline

dtbbpy: 4,4'-di-*tert*-butyl-2,2'-dipyridyl

equiv.: equivalent

Et: ethyl

FLB: Fluorescent light bulb

h, min, s: hours, minutes, seconds

H.E: Hantzsch's ester

Im: Imidazole

IR: infrared

LEDs: Light-Emitting Diodes

MCRs: Multi-component reactions

Mes: Mesityl

Mp: Melting point

NMR: Nuclear Magnetic Resonance

Nu: nucleophile

o, p, m: orto, para, meta

OLEDs: Organic Light-Emitting Diodes

ppy: 2-phenylpyridine

quant.: quantitative

rt: room temperature

SCE: saturated calomel electrode

SET: single electron transfer

TEMPO: (2,2,6,6-tetramethylpiperidin-1-yl)oxy

THF: tetrahydrofuran

TMS: trimethylsilane

Tol: toluene

Ts: tosyl

UV: ultraviolet

V: volt

W: watts

Résumé détaillé en Français

Résumé

En raison de leurs atouts uniques, les processus mettant en jeu des espèces radicalaires se sont considérablement développés, durant ces cinquante dernières années, et font maintenant partie des outils indispensables pour la chimie de synthèse. En 2000, l'ensemble de la communauté de chimie radicalaire a célébré le 100^{ème} anniversaire de la découverte du premier radical organique – le radical triphénylméthyle – par Moses Gomberg. Malgré cette découverte précoce, l'évolution de ce domaine et notamment son application en synthèse a fait preuve d'une progression somme toute lente. Parmi les faits marquants qui ont jalonné son évolution, citons les réactions de Kharasch dans les années 30, la découverte de la RPE dans les années 40 et les déterminations structurales et cinétiques qui s'ensuivirent, impliquant aussi les réactions de polymérisation. Tout ceci a alors permis les premiers développements en synthèse organique.

Après les travaux pionniers de Julia et de Surzur sur les cyclisations radicalaires dans les années 60, les principales contributions de Giese, Curran, Barton, Stork entre autres, pour améliorer le contrôle de la réactivité de ces espèces grâce au développement de réactions en chaînes médiées principalement par des hydrures organiques ou organométalliques, ont considérablement élargi la portée des processus initiaux, et ont notamment ouvert la voie à des applications en synthèse totale, grâce par exemple au développement de cascades polycyclisantes très efficaces, ainsi que l'obtention de produits énantio-purs *via* des processus asymétriques hautement contrôlés. Les principaux avantages de ces réactions radicalaires sont inhérents au fait que les radicaux sont des espèces neutres hautement réactives. Dans les conditions utilisées, généralement sans sels, on s'affranchit également des problèmes d'agrégats et de solvation. Par ailleurs, la compatibilité des radicaux avec de nombreux groupements fonctionnels ainsi que la possibilité d'effectuer ces transformations dans des conditions douces, ont fait des réactions radicalaires un outil complémentaire aux réactions ioniques. Enfin, il convient de préciser que les réactions radicalaires ne se limitent pas aux seules cyclisations; les additions intermoléculaires, les substitutions homolytiques et les fonctionnalisations C-H par transfert d'hydrogène ont également donné naissance à de très belles applications, d'autant plus que des modèles de stéréosélectivité très fiables sont disponibles. Les réactions radicalaires permettent au chimiste d'accéder à un très large éventail de transformations, et notamment à la formation de liaisons carbone-carbone ou

carbone-hétéroatome. Ces réactions sont, généralement, réalisées dans des conditions douces, ce qui permet de ne pas utiliser de groupes protecteurs lors des synthèses et donc de réduire considérablement le nombre d'étapes réactionnelles. Cependant, les réactions radicalaires souffrent d'un certain nombre de problèmes qui entravent leur utilisation systématique en synthèse et en industrie. Tout d'abord, la montée en échelle est difficile vu que les réactions sont généralement conduites en milieu dilué. Mais le problème le plus aigu demeure l'utilisation de l'hydrure de tributylétain comme médiateur radicalaire le plus performant. Outre le fait qu'il soit toxique, les sous-produits stanniques issus des réactions radicalaires sont extrêmement difficiles à éliminer et restent généralement présents à l'état de traces.¹ D'un point de vue général, les médiateurs radicalaires sont souvent utilisés en quantité stœchiométrique voire sur-stœchiométrique.

Avec l'avènement et la structuration de la chimie verte, dans les années 90, un effort tout particulier a été dévoué, par un nombre régulièrement croissant de groupes de recherche, au développement d'une chimie radicalaire plus verte et plus soucieuse de l'environnement. En effet, comme l'a mentionné John Walton dans son article sur la « tyrannie de l'étain », le remplacement en synthèse de ce médiateur radicalaire toxique mais ultra-performant, a été à la base d'intenses travaux de recherche.² Plusieurs solutions ont déjà été proposées et divisées selon trois catégories. La première a consisté en l'utilisation de réactifs à base d'étain soit en quantités catalytiques, soit sur supports solides. La seconde a été le développement de nouveaux médiateurs comme par exemple des silanes, des dérivés du phosphore ou à base de métaux moins toxiques. Bien que certains de ces réactifs soient tout à fait intéressants, ils leur manquent le plus souvent un caractère général et souffrent parfois de coûts prohibitifs ou de difficultés d'accès. Le dernier domaine de recherche a un périmètre plus diffus et regroupe plusieurs familles de réactions. Les transferts de groupes d'atomes (sélénium, xanthates...) appartiennent à cette classe mais souffrent du fait qu'une réduction ultérieure est dans la plupart des cas nécessaires. Cependant des perspectives plus qu'intéressantes ont été ouvertes avec l'utilisation des organoboranes.

¹ Pour des ouvrages sur tous les aspects de la chimie radicalaire de synthèse, voir : a) *Encyclopedia of Radicals in Chemistry, Biology and Materials*, C. Chatgililoglu, A. Studer, Eds. John Wiley & Sons Ltd, Chichester, **2012**. b) P. Renaud, M. P. Sibi dans *Radicals in Organic Synthesis*, Vol. 1 & 2, Wiley-VCH, Weinheim, **2001**. c) D. P. Curran, N. A. Porter, B. Giese dans *Stereochemistry of Radical Reactions*, VCH, Weinheim, **1996**. d) C. R. J. Stephenson, A. Studer, D. P. Curran, *Beilstein J. Org. Chem.* **2013**, *9*, 2778 et références incluses.

² Pour des revues sur les processus radicalaires sans étain qui respectent les principes d'une chimie durable, voir : a) P. A. Baguley, J. C. Walton, *Angew. Chem. Int. Ed.* **1998**, *37*, 3072. b) A. Studer, S. Amrein, *Synthesis* **2002**, 835. c) B. C. Gilbert, A. F. Parsons, *J. Chem. Soc., Perkin Trans 2* **2002**, 367.

Les composés à l'origine de processus mettant en jeu des transferts monoélectroniques sont de plus en plus considérés comme des médiateurs radicalaires alternatifs aux hydrures d'étain, contribuant *de facto* au développement d'une chimie plus écoresponsable. Cependant, la plupart de ces réactifs, essentiellement des complexes métalliques à base de samarium, titane, cérium, cuivre, fer, nickel,... sont utilisés en quantités sur-stœchiométriques. D'autre part, ces réactions sont généralement spécifiques d'une fonction et impliquent parfois un ensemble de conditions rigoureuses. Des versions améliorées sont donc fortement souhaitables. Il convient alors d'en développer des versions catalytiques plus douces et plus soucieuses de l'environnement, s'affranchissant de l'utilisation de composés métalliques toxiques, de solvants toxiques et de rayonnements UV énergétiques, pour effectuer des transformations radicalaires et les appliquer en chimie fine.

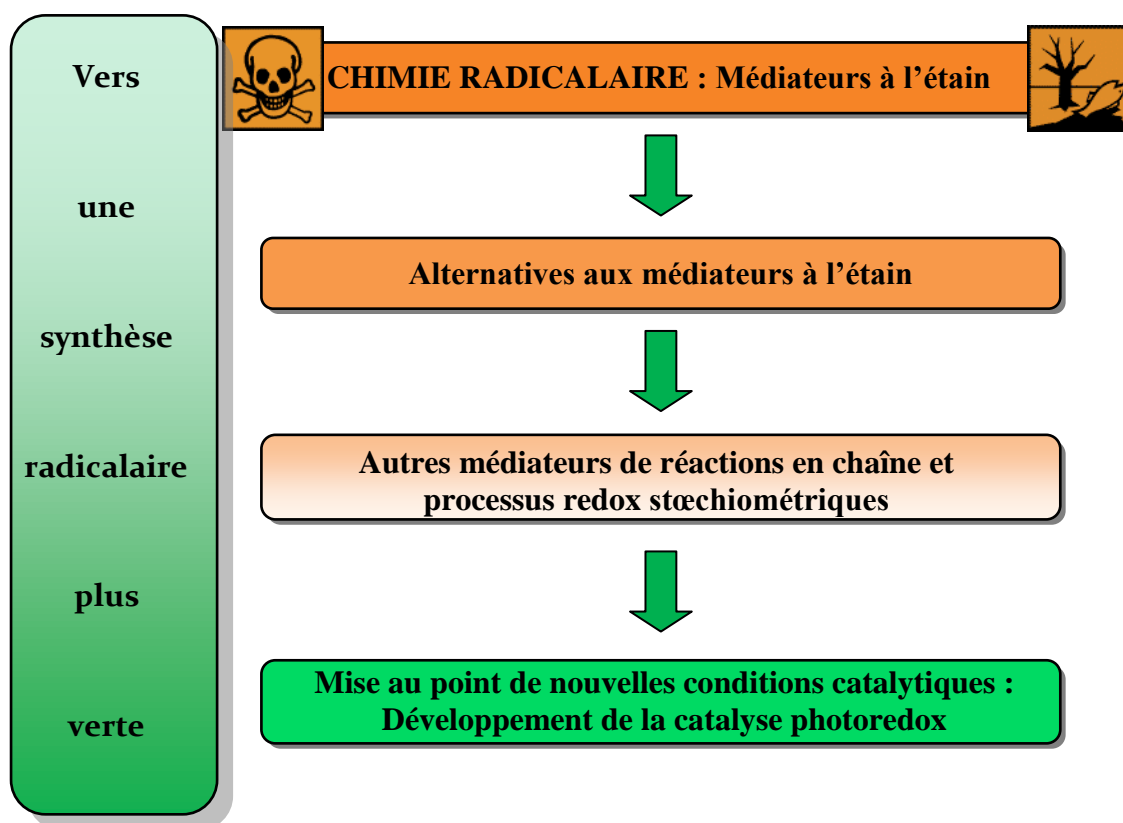


Figure 1. Evolution de la chimie radicalaire

Durant ma thèse, en gardant comme point de mire la réduction de l'impact écologique de la chimie radicalaire, nous avons développé de nouvelles stratégies de génération de radicaux pour des applications en synthèse. Un point crucial était de respecter le plus possible

les exigences que requièrent une chimie plus écoresponsable. Pour cela nous nous sommes affranchis de l'utilisation de médiateurs radicalaires de type hydrure de tributylétain et nous nous sommes donc tournés vers des processus mettant en jeu des transferts monoélectroniques amorcés par une source d'énergie inépuisable : la lumière visible. Ces processus de transfert monoélectronique nécessitent des photocatalyseurs absorbant dans le visible qui seront détaillés dans la suite.

Nous nous sommes focalisés, dans une première partie, sur l'une des plus célèbres réactions radicalaires contemporaines, la désoxygénation de Barton-McCombie³ qui est utilisée très fréquemment en synthèse. Comme illustré dans le Schéma 1, cette réaction consiste à réduire une fonction alcool d'une molécule en liaison carbone-hydrogène via un intermédiaire xanthate qui va réagir en présence d'hydrure de tributylétain et d'un amorceur sous activation thermique, afin d'obtenir le produit de réduction : l'alcane correspondant.

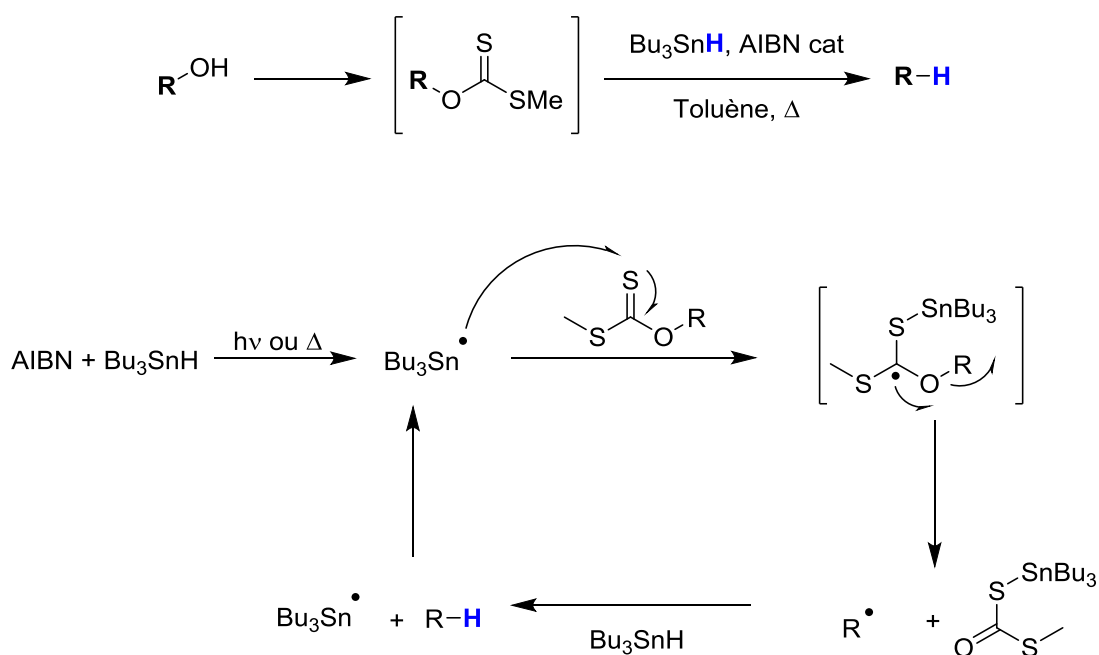


Schéma 1. Désoxygénation de Barton-McCombie

De nombreuses études ont été menées afin de rendre cette réaction beaucoup plus écoresponsable. Nous pouvons noter que deux catégories se distinguent.^{4,5} La première consiste au développement de versions centrées sur l'étain en rendant ce médiateur soit

³ D. H. R. Barton, S. W. McCombie, *J. Chem. Soc., Perkin Trans. I* **1975**, 1574.

⁴ a) S. W. McCombie, in "Comprehensive Organic Synthesis", Eds. B. Trost, I. Fleming, Pergamon Press, New York, **1991**, Vol. 8, p. 811; b) L. Chenneberg, J.-P. Goddard, L. Fensterbank, in "Comprehensive Organic Synthesis (2nd Edition)", Eds. G. Molander, P. Knochel, Elsevier, Oxford, **2014**, Vol. 8, p. 1011.

⁵ L. Chenneberg, C. Ollivier, *Chimia* **2016**, *70*, 67.

catalytique ou soit supporté en vue d'être recyclé plus facilement. La deuxième catégorie est, quant à elle, plus dédiée à des nouveaux médiateurs moins toxiques que les sels d'étain tels que des silanes, des dérivés du phosphore ou du bore ou d'autres métaux moins toxiques. Néanmoins, malgré toutes ces améliorations, de nombreuses problématiques demeurent par rapport à la version originale. En effet, ces nouvelles conditions se sont avérées soit moins efficaces ou peu sélectives.

Récemment nous avons développé une nouvelle méthode de désoxygénation radicalaire basée sur la photoréduction d'espèces thiocarbamates dérivés d'alcools, comme alternative photocatalytique à la traditionnelle réaction de désoxygénation de Barton-McCombie, évitant ainsi l'utilisation de stannanes comme médiateur radicalaire. En catalyse photoredox, des colorants organiques tels que l'éosine Y, la fluorescéine ou des complexes polypyridines à base de métaux de transition tels que le ruthénium (II), l'iridium (III) ou encore le cuivre (I) sont utilisés comme photocatalyseurs capables d'absorber la lumière dans le domaine du visible. Une fois irradiés à une longueur d'onde donnée, ces catalyseurs peuvent atteindre un état excité qui possède des propriétés physico-chimiques très intéressantes et utiles pour la synthèse.⁶ En fonction du photocatalyseur utilisé, ces états excités possèdent différentes durées de vie qui permettent de réaliser des transferts monoélectroniques et des potentiels redox assez variés en fonction du substrat à oxyder ou à réduire.

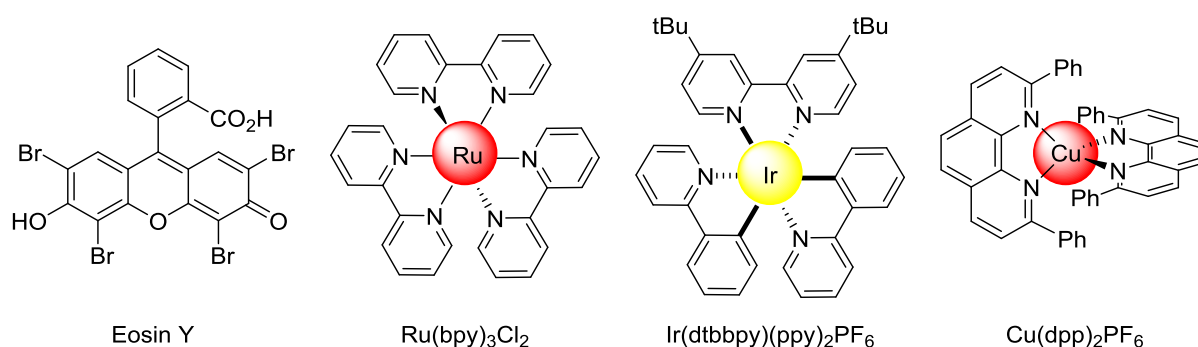


Schéma 2. Différents photocatalyseurs organiques et non-organiques

Ce type de catalyse ne nécessite, en effet, généralement que la lumière visible comme apport énergétique, une quantité catalytique de photocatalyseur, et peu d'additifs et de solvants toxiques. Un exemple de notre d'expertise dans ce domaine est la photoréduction

⁶ a) S. Campagna, F. Puntoriero, F. Nastasi, G. Bergamini, V. Balzani, *Top. Curr. Chem.* **2007**, 280, 117. b) K. Kalyanasundaram, *Coord. Chem. Rev.* **1982**, 46, 159. c) A. Juris, V. Balzani, F. Barigelletti, S. Campagna, P. Belser, A. von Zelewsky, *Coord. Chem. Rev.* **1988**, 84, 85.

d'époxydes et d'aziridines en utilisant le complexe ruthénium tris-bipyridine comme photocatalyseur.⁷

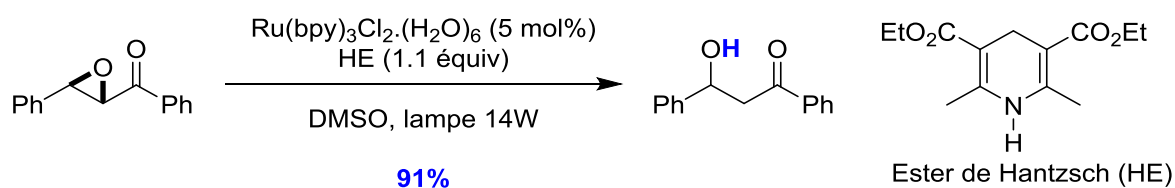


Schéma 3. Réduction de l'époxychalcone par catalyse photoredox

Un autre exemple de catalyse photoredox développé par notre groupe est la photoréduction de sels d'oniums (sulfoniums, iodoniums). Sous conditions photoréductrices, avec l'utilisation d'un complexe de ruthénium (II) ou de cuivre (I), les sels de sulfonium⁸ et d'iodonium⁹ sont réduits et génèrent un radical aryle qui est piégé par un accepteur radicalaire conduisant à de très bons rendements en produits d'allylation ou d'addition.

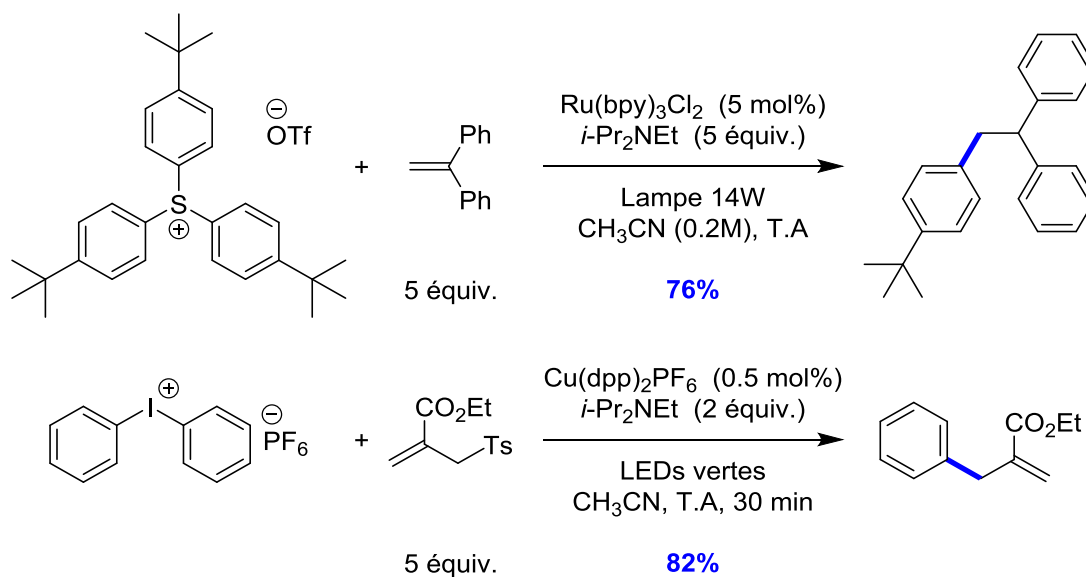


Schéma 4. Photoréduction de sels de sulfonium et d'iodonium

⁷ M.-H. Larraufie, P. Pellet, L. Fensterbank, J.-P. Goddard, E. Lacôte, M. Malacria, C. Ollivier, *Angew. Chem. Int. Ed.* **2011**, *50*, 4463.

⁸ S. Donck, A. Baroudi, L. Fensterbank, J.-P. Goddard, C. Ollivier, *Adv. Synth. Catal.* **2013**, *355*, 1477.

⁹ A. Baralle, L. Fensterbank, J.-P. Goddard, C. Ollivier, *Chem. Eur. J.* **2013**, *19*, 10809.

A partir de ces connaissances et de l'expertise acquise par notre laboratoire, nous avons commencé une étude sur la réduction de composés *O*-thiocarbamates par catalyse photoredox. Au début, il n'existait pas de précédents dans la littérature concernant la désoxygénation d'alcools catalysée par la lumière visible. Très rapidement, le groupe d'Overman, s'inspirant des travaux d'Okada, publia la désoxygénation d'alcools tertiaires, préalablement transformés en phthalimidoyl oxalates, par catalyse photoredox. La réduction du phthalimide, par un transfert monoélectronique, entraîne une série de fragmentations radicalaires afin d'obtenir un radical tertiaire qui est en suite piégé par la méthylvinylcétone.¹⁰

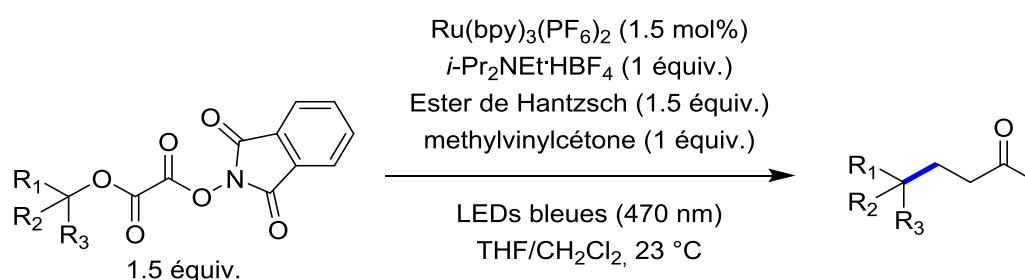


Schéma 5. Désoxygénation d'alcools tertiaires par catalyse photoredox de phthalimidoyl oxalates

Nous avons donc réalisé nos travaux en sélectionnant préférentiellement le groupement *O*-thiocarbamate (synthétisé à partir du thiocarbonyle diimidazole) par rapport aux traditionnels xanthates vu que ces derniers se sont révélés peu réactifs dans les nouvelles conditions réactionnelles. Le complexe d'iridium (III) ($\text{Ir}(\text{ppy})_3$) a été préféré au ruthénium car son caractère plus réducteur a permis d'obtenir les meilleurs résultats. De plus, l'utilisation de ce complexe nous a permis de diminuer la quantité catalytique à 1 mol% sans affecter les rendements.

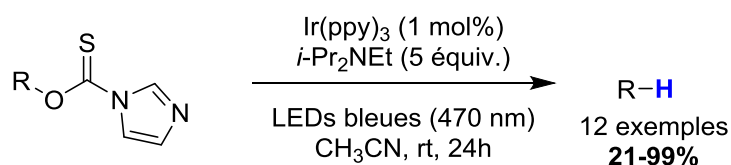


Schéma 6. Photoréduction d'*O*-thiocarbamates

Il est à noter que l'ajout d'une amine, telle que la base de Hünig ($i\text{-Pr}_2\text{NEt}$), est essentiel à la continuité du cycle catalytique. Comme illustré dans le schéma 7, notre méthode

¹⁰ G. L. Lackner, K. W. Quasdorf, L. E. Overman, *J. Am. Chem. Soc.* **2013**, *135*, 15342.

est applicable aux alcools secondaires cycliques mais aussi aux alcools acycliques non-activés. Cette réaction de réduction tolère très bien des groupements fonctionnels tels qu'un benzoyle ou un acétal, entre autres.

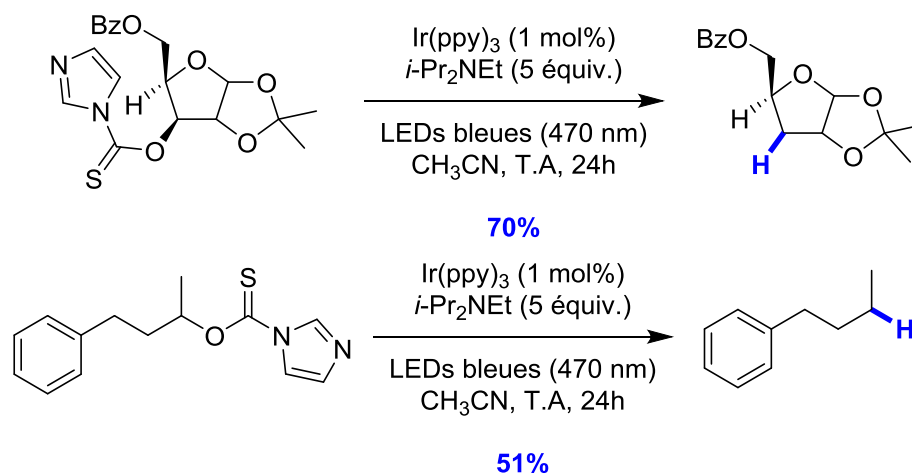


Schéma 7. Réduction d'alcools secondaires cyclique et acyclique

Les alcools tertiaires peuvent être aussi réduits dans ces conditions avec un bon rendement (Schéma 8). La tolérance à d'autres groupes fonctionnels de cette catalyse est une nouvelle fois mise en évidence avec la fonction lactone. L'accessibilité aux *O*-thiocarbamates formés à partir d'alcools tertiaires s'est révélée être un problème crucial et sera discutée dans la suite du manuscrit.

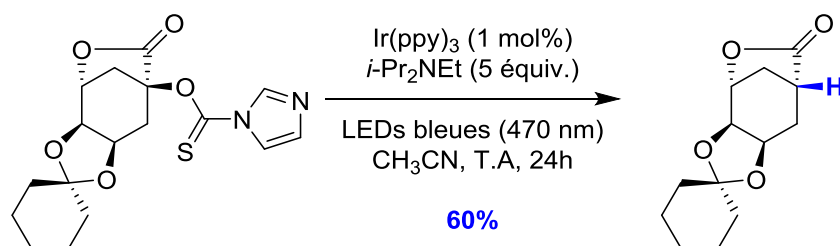


Schéma 8. Réduction d'un alcool tertiaire

Après avoir étendu ces conditions à différents types d'alcools, nous avons voulu ensuite connaître l'impact que nos conditions de désoxygénation pourraient avoir en synthèse. Pour évaluer cela, notre méthodologie a été comparée à une réaction réalisée dans les conditions optimisées de Barton-McCombie. Une addition lente sur 4 heures d'une solution de Bu_3SnH et AIBN (catalytique) dans le toluène, est effectuée au pousse seringue à une solution d'*O*-thiocarbamate portée au reflux du toluène. Après traitement et purification de la réaction, le rendement en produit réduit est inférieur à celui obtenu dans nos conditions. Notre procédé

photocatalytique s'est révélé donc être très compétitif. Nous avons par conséquent développé une méthode qui constitue un outil fondamental pour la synthèse organique.

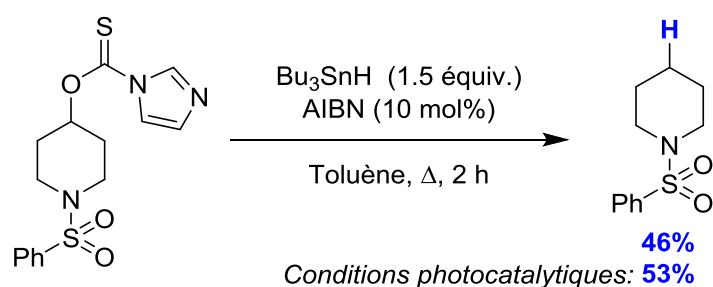


Schéma 9. Comparaison des conditions photoredox avec la classique Barton-McCombie

Pour illustrer l'intérêt et la compétitivité internationale que suscite la désoxygénation, un troisième groupe de recherche, le groupe de Reiser, a publié en même temps que nous une méthode de désoxygénation photocatalysée d'alcools secondaires activés (en position benzylique ou en α d'un carbonyle) (Schéma 10).¹¹ Cependant, cette méthode ne permet pas la photoréduction ni d'alcools secondaires non-activés, ni d'alcools primaires. De plus, le choix du bis-trifluorométhyle benzoate impose un léger chauffage du milieu réactionnel.

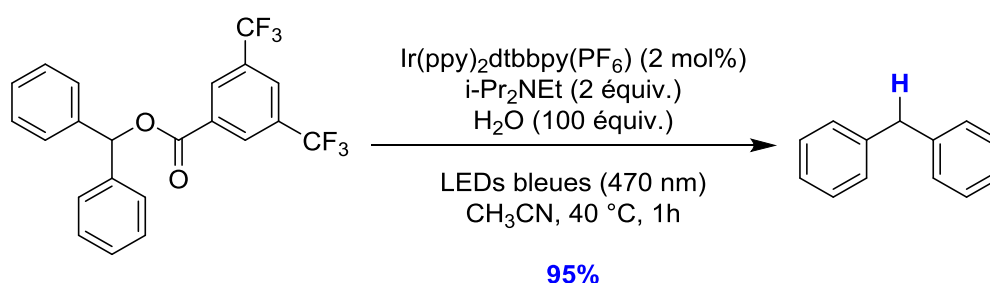


Schéma 10. Désoxygénation photocatalysée d'alcool benzylique

Par la suite, nous avons réalisé d'autres études, afin d'améliorer notre méthodologie. En effet, nous avons effectué des variations au niveau des groupements thiocarbamates dont la réactivité a pu être évaluée en conditions photocatalytiques. Les dérivés de type benzoyle, thionoformates n'ont conduit qu'à une faible conversion en produits de désoxygénation. En revanche, la dérivatisation d'alcools en groupements *O*-thiocarbamates portant des

¹¹ D. Rackl, V. Kais, P. Kreitmeier, O. Reiser, *Beilstein J. Org. Chem.* **2014**, *10*, 2157.

hétérocycles de types imidazoles, triazoles... a permis d'obtenir de bons rendements en produits réduits.

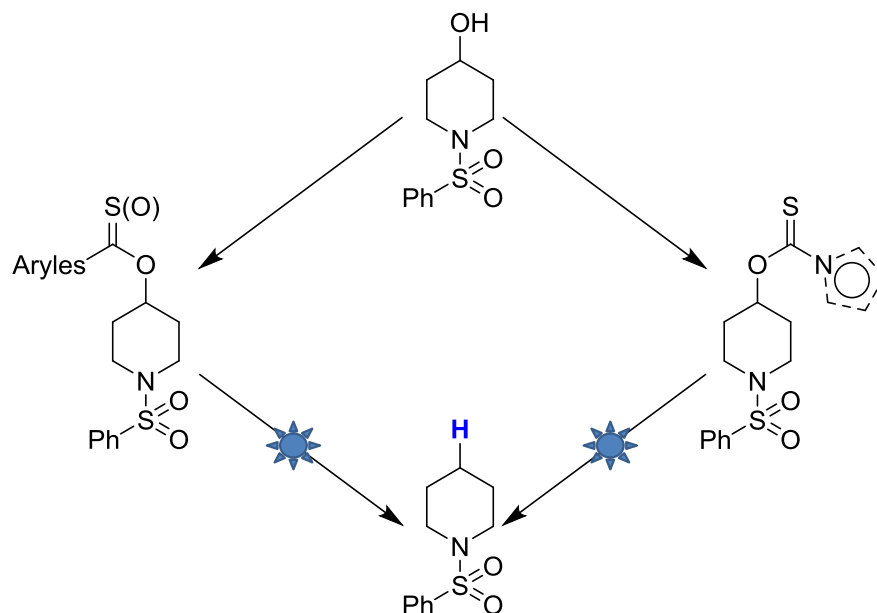


Schéma 11. Variation du groupement *O*-thiocarbamate

Nous avons ensuite étudié le mécanisme réactionnel impliqué dans cette transformation photocatalysée par la lumière visible. Après irradiation, le complexe d'iridium, placé dans un état excité permet la réduction du groupement *O*-thiocarbamate par transfert monoélectronique pour donner une espèce radical-anion. Cet intermédiaire subit des fragmentations successives qui permettent de générer un radical centré sur le carbone. La base d'Hünig (DIPEA) intervient en tant que donneur d'hydrogène pour la formation de l'alcane et donneur sacrificiel d'électron pour la régénération du photocatalyseur. Ce mécanisme a été démontré par des études de fluorescence et la comparaison des potentiels électrochimiques déterminés par voltammétrie cyclique

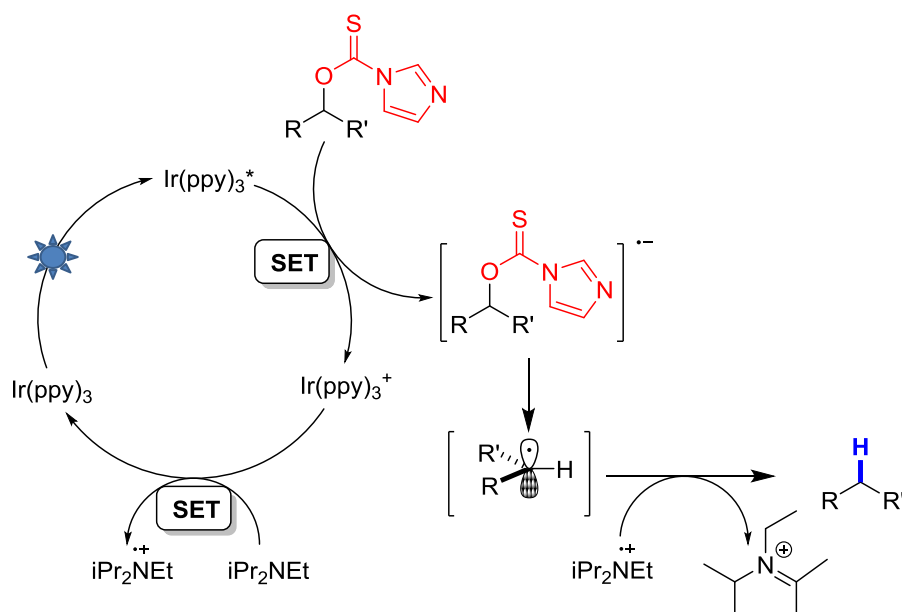


Schéma 12. Mécanisme proposé pour la réaction de désoxygénation

Ainsi, dans un contexte international compétitif, trois groupes de recherche, incluant le notre¹², ont développé des méthodes efficaces et attractives sans étain de désoxygénation dans le domaine de la catalyse photoredox. A ce jour, nous restons le seul groupe à vraiment proposer une alternative à la désoxygénation de Barton-McCombie la plus proche et la plus générale possible. Nous avons aussi essayé de développer une réaction qui s'inscrit au plus près d'une chimie radicalaire plus verte et plus moderne.

Malgré le développement d'un nombre important de précurseurs radicalaires divers et variés,¹³ la nécessité d'en trouver de nouveaux est toujours aussi forte, notamment lorsqu'il s'agit d'engendrer des radicaux alkyles primaires. La génération de ces entités hautement réactives est un enjeu majeur en synthèse. Nous nous sommes donc naturellement intéressés, dans un second temps, à l'étude d'une nouvelle façon d'engendrer ces radicaux alkyles primaires par catalyse photoredox. Au cours de ces dix dernières années, des entités anioniques stables, par exemple les organoborates et plus particulièrement les alkyles trifluoroborates, se sont révélés être de bons précurseurs de radicaux alkyles.¹⁴ En effet, ces derniers peuvent être engendrés par oxydation d'organoborates en utilisant des métaux de

¹² L. Chenneberg, A. Baralle, M. Daniel, L. Fensterbank, J.-P. Goddard, C. Ollivier, *Adv. Synth. Catal.* **2014**, 356, 2756.

¹³ a) M. Fagnoni, D. Dondi, D. Ravello, A. Albini, *Chem. Rev.* **2007**, 107, 2725. b) T. P. Yoon, M. A. Ischay, J. Du, *Nature Chem.* **2010**, 2, 527. c) J. M. R. Narayanaman, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, 40, 102. d) J. W. Tucker, C.R. J. Stephenson, *J. Org. Chem.* **2012**, 77, 1617. e) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, 113, 5322.

¹⁴ C. Carzola, E. Metay, B. Andrioletti, M. Lemaire, *Tetrahedron Lett.* **2009**, 50, 6855.

transition comme l'acétate de cuivre (II). Les radicaux peuvent être ensuite piégés par le TEMPO avec un très bon rendement (Schéma 13).¹⁵

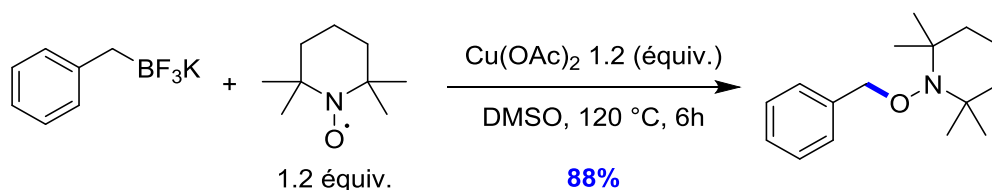


Schéma 13. Oxydation du benzyltrifluoroborate par l'acétate de cuivre (II)

L'inconvénient de cette méthode est l'utilisation sur-stœchiométrique d'oxydant. Une version photocatalytique d'oxydation des sels de trifluoroborates et trialkoxyborates a été développée par Akita en utilisant 2 mol% de charge catalytique d'un complexe d'iridium comme photocatalyseur.¹⁶ De très bons rendements en produits d'addition radicalaire ont été obtenus avec le TEMPO et l'acrylate de méthyle dans l'acétone.

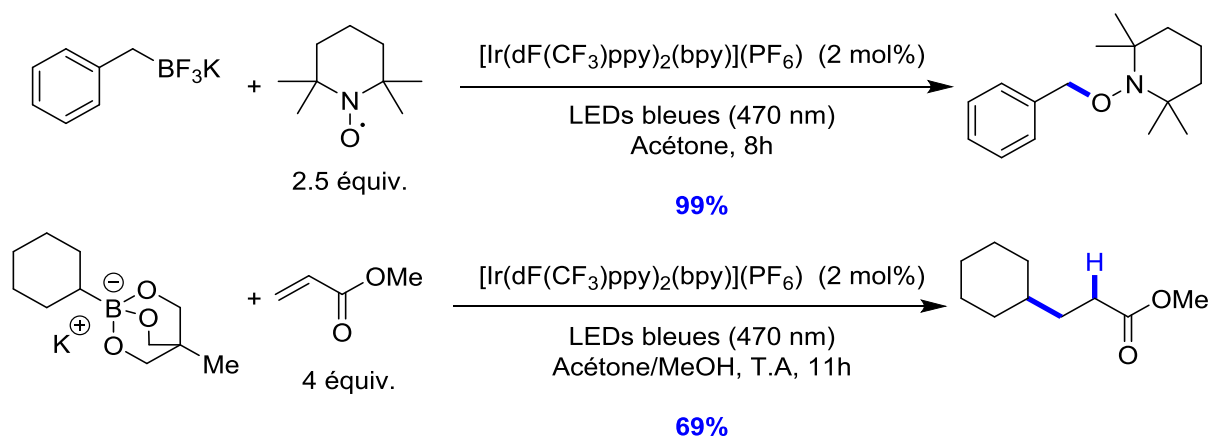


Schéma 14. Génération de radicaux par photooxydation des sels de trifluoroborates et trialkoxyborates

En partant sur cette base, nous avons démontré que les sels potassiques de trifluoroborates pouvaient être oxydés de façon très douce en utilisant des oxydants organiques. En effet, l'utilisation d'espèces cationiques (sel de tritylium) et d'espèces radical-cation (sel d'ammoniumyle), capables d'induire un transfert électronique provoque la génération de radicaux centrés sur le carbone qui sont piégés par la suite par le TEMPO. Le développement de conditions très douces était l'un de nos principaux objectifs.

¹⁵ G. Sorin, R. M. Mallorquin, Y. Contie, A. Baralle, M. Malacria, J-P. Goddard, L. Fensterbank, *Angew. Chem. Int. Ed.* **2010**, *49*, 8721.

¹⁶ Y. Yasu, T. Koike, M. Akita, *Adv. Synth. Catal.* **2012**, *354*, 3414.

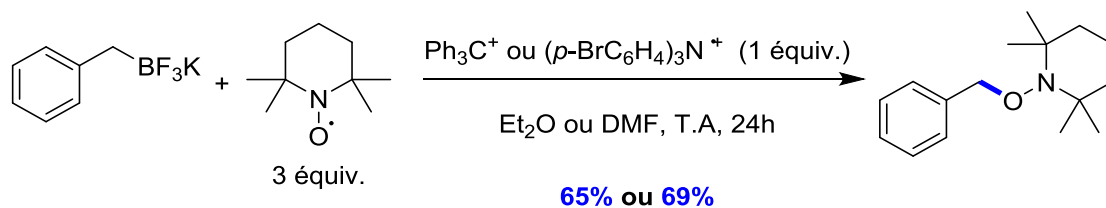


Schéma 15. Oxydation de trifluoroborates avec des oxydants organiques

Par la suite, nous avons montré que les trifluoroborates, dont l'inconvénient est la formation de sous-produits de fluorure de bore très polluants, pouvaient être remplacés par des espèces hypervalentes à base de silicium, lesquelles s'inscrivent plus dans le domaine d'une chimie radicalaire plus verte. Deux méthodes de synthèse ont été utilisées, la première consiste en la réaction entre un alkyle trichlorosilane avec du catéchol en présence de triéthylamine, dans le THF, suivie d'une métathèse de cation pour obtenir l'ammonium alkyl bis-catécholatosilicates (Schéma 16, conditions A). Une deuxième méthode permet quant à elle, d'obtenir à partir d'un alkyle tri(méthoxy ou éthoxy)silane, un sel potassique du silicate en utilisant du méthanolate de potassium comme base (Schéma 16, conditions B).¹⁷ Le potassium alkyl bis-catécholatosilicates ainsi formé cristallise avec une molécule de solvant ce qui réduit sa stabilité dans le temps. L'ajout de l'éther couronne [18-C-6], comme complexant du cation potassique, permet de résoudre ce problème de stabilité.

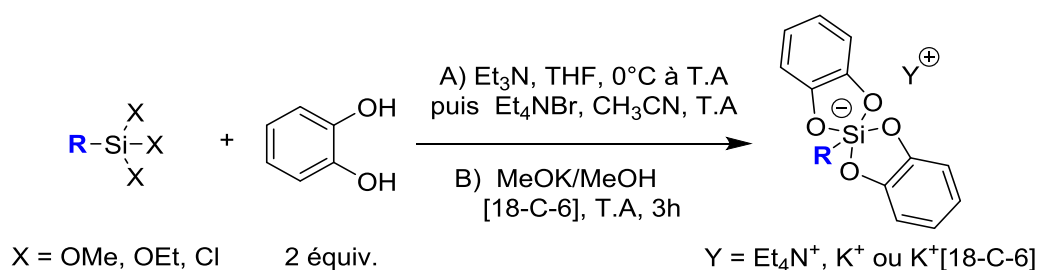


Schéma 16. Synthèse des bis-catécholatosilicates

Par la suite, un élégant procédé de génération de radicaux carbonés par oxydation d'espèces hypervalentes à base de silicium en présence d'un photocatalyseur d'iridium sous irradiation par la lumière visible (LEDs bleues) a été développé. Ces alkyles silicates permettent l'accès à des radicaux alkyles stabilisés et non stabilisés. L'oxydation de ces silicates en présence d'un accepteur radicalaire tel qu'une allyle sulfone activée (Schéma 16) ou le TEMPO donne de très bon rendements de produits de piégeage.

¹⁷ V. Corcé, L.-M. Chamoreau, E. Derat, J.-P. Goddard, C. Ollivier, L. Fensterbank, *Angew. Chem. Int. Ed.* **2015**, *54*, 11414.

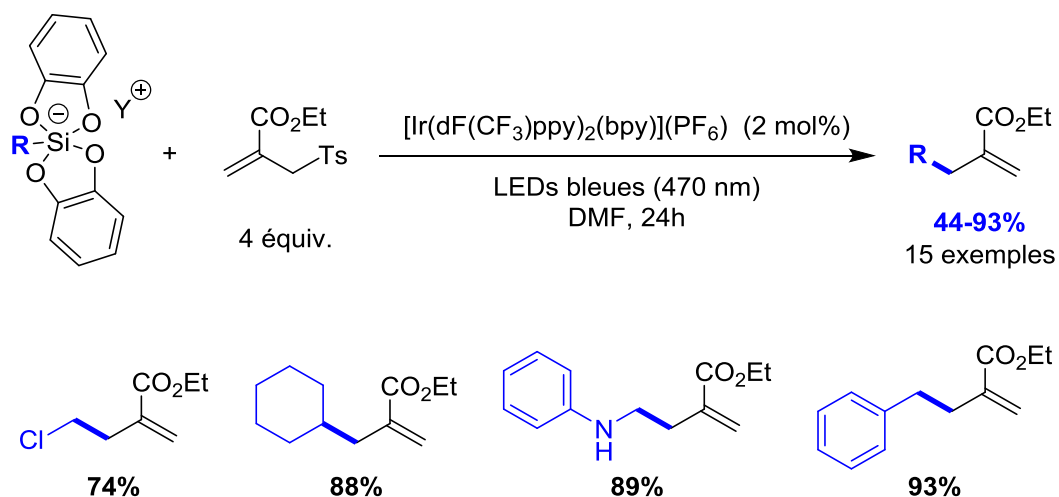


Schéma 17. Génération de radicaux par photooxydation et piégeage par allylation

L'alkyle bis-catécholatosilicate est oxydé par transfert monoélectronique avec le complexe d'iridium préalablement irradié. Après dissociation, le radical engendré est piégé par allylation. Le radical tosyloxy libéré est ensuite réduit permettant la régénération du photocatalyseur.

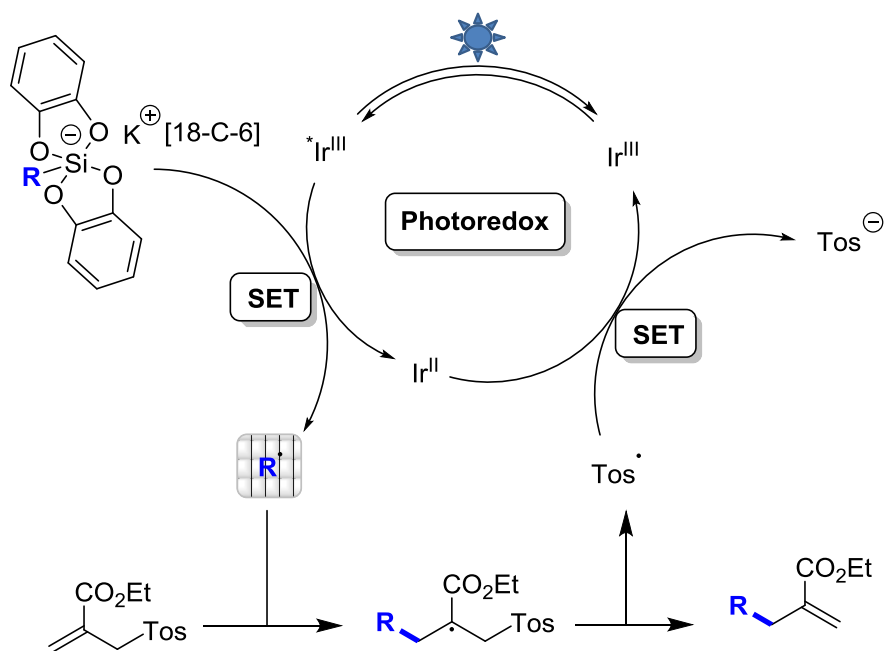
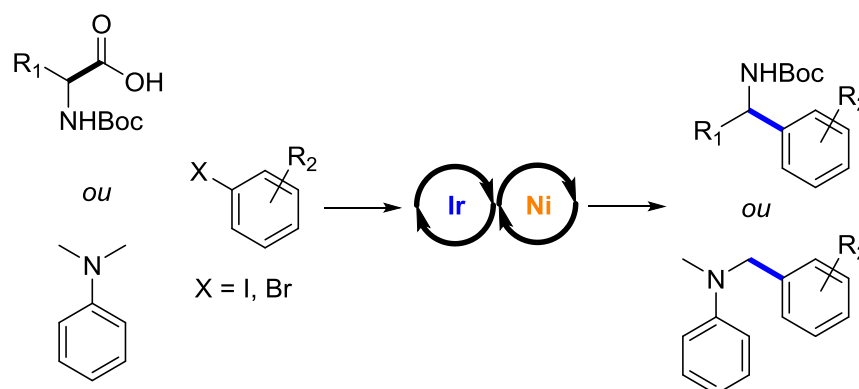


Schéma 18. Mécanisme de photooxydation des silicates

Nous avons ainsi proposé une méthode simple et facile d'accès pour engendrer des radicaux alkyles (primaires, secondaires et tertiaires) par catalyse photoredox. Ce procédé nous a permis de nous affranchir des sels d'organoborates assez polluants et de leur oxydation par des quantités stœchiométriques de métaux.

Depuis quelques années, une recherche intensive a été entreprise pour le développement de nouvelles réactions catalysées par des procédés photoredox. Grâce à celles-ci, il a été possible d'accomplir des transformations chimiques jusqu'alors difficiles. En 2014, Molander,¹⁸ MacMillan et Doyle¹⁹ ont publié simultanément, deux exemples spectaculaires de catalyse duale, photoredox / nickel, dans le but d'effectuer un couplage entre des halogénures d'aryle avec des radicaux alkyles. En combinant la génération de radicaux par catalyse photoredox avec un couplage au nickel, une impressionnante méthodologie a été élaborée dans des conditions extrêmement douces. En effet, cette catalyse duale ne requiert aucune activation thermique (par opposition à la catalyse au palladium par exemple), aucun additif toxique ou ligand onéreux de plus, les charges catalytiques en iridium et en nickel sont très faibles.

MacMillan & Doyle, 2014



Molander, 2014

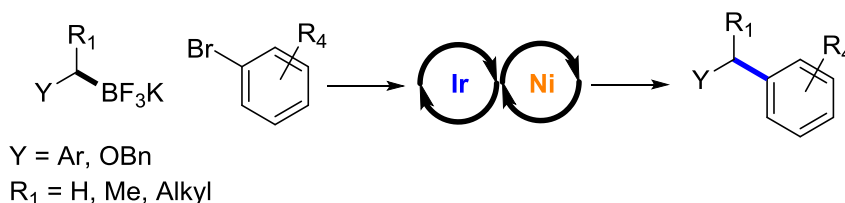


Schéma 19. Rencontre entre la catalyse au nickel et la catalyse photoredox

¹⁸ J. C. Tellis, D. N. Primer, G. A. Molander, *Science* **2014**, 345, 433.

¹⁹ Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terrett, A. G. Doyle, D. W. C. MacMillan, *Science* **2014**, 345, 437.

Nous avons donc naturellement engagé les alkyles biscatécholatosilicates que nous avons développés précédemment dans cette catalyse duale. Nous avons concentré nos efforts sur la génération et la réactivité de radicaux primaires non-stabilisés très réactifs, un domaine peu exploré jusqu'à présent. Nos résultats sont généralement très bons en termes de rendements et d'étendue de la réaction, puisque les fonctions notamment hétéroatomiques et les plates-formes hétérocycliques aromatiques sont compatibles avec ces transformations.

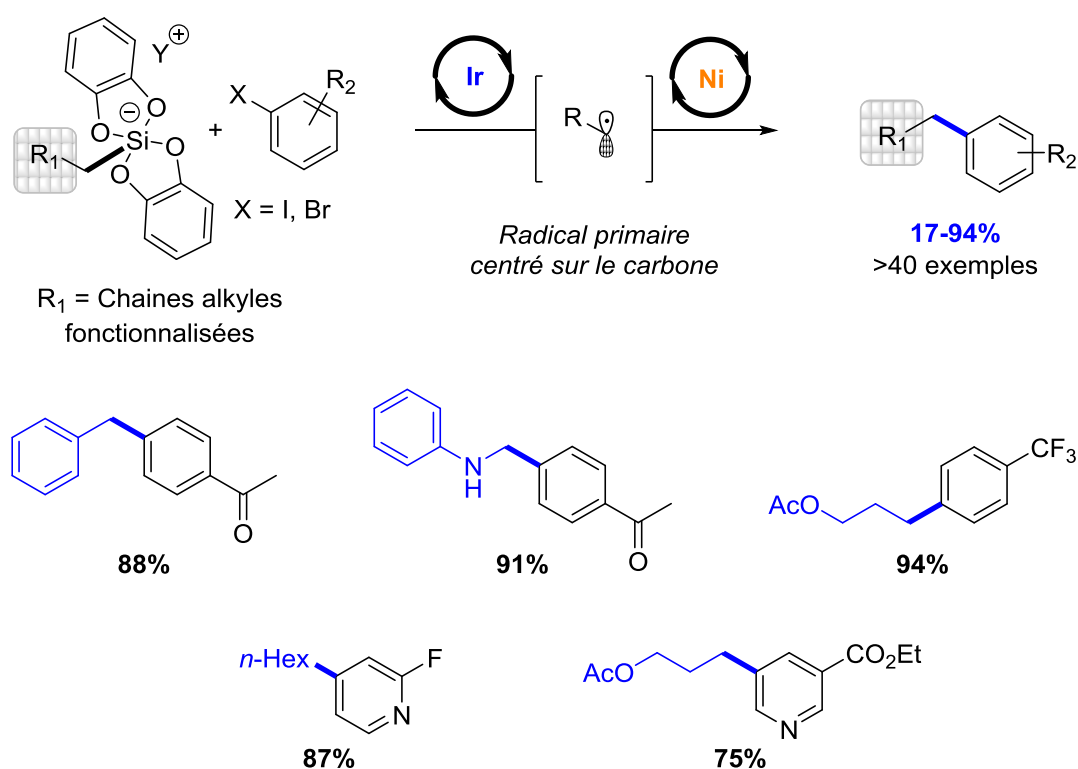


Schéma 20. Catalyse duale photoredox/nickel avec génération de radicaux primaires à partir de silicates

Toujours dans une dynamique d'amélioration de notre système catalytique, nous avons tenté de substituer l'utilisation de complexes d'iridium par des colorants organiques photo-activables. Les versions organo-photocatalysées sont généralement plus difficiles à mettre en œuvre car leurs propriétés physico-chimiques (potentiels redox ou temps de vie de l'état excité...) sont en général, moins favorables à celles rencontrées avec les complexes de métaux de transitions. Parmi tout le panel de photocatalyseurs organiques, nous avons essayé de trouver le plus adéquat. Nous avons finalement réalisé une étude montrant l'oxydation sans

précédent des trifluoroborates et de silicates pour la génération de radicaux alkyles avec l'acridinium de Fukuzumi comme organo-photocatalyseur. Ce dernier possède en effet un exceptionnel potentiel d'oxydation à l'état excité de l'ordre de +2.06V vs. SCE. Par ailleurs, nous avons observé que la réactivité des organotrifluoroborates était supérieure à celle des biscatécholatosilicates dans ces conditions.

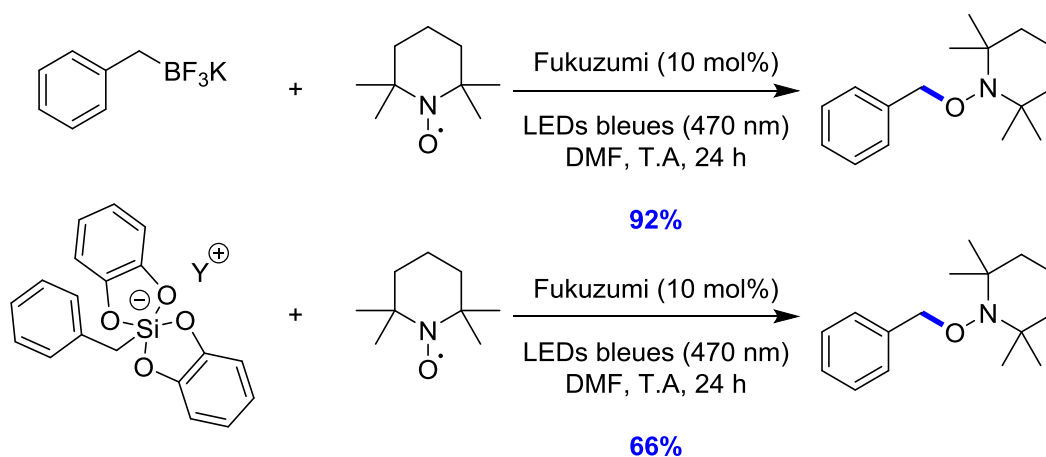


Schéma 21. Photooxydation des benzoyles trifluoroborate et silicate par le catalyseur de Fukuzumi

En 2012, le groupe d'Adachi a décrit, lors d'une étude sur le développement de diodes électroluminescentes organique (OLED, en anglais, pour Organic Light-Emitting Diode), une famille de molécules interagissant avec la lumière et ayant pour structure de base un squelette *n*-carbazolyl dicyanobenzène.²⁰ Ces molécules possèdent des propriétés photophysiques impressionnantes qui leur confèrent un intérêt synthétique. Inspirés par ces potentiels photocatalyseurs, Zhang et ses collaborateurs ont repris les travaux de Molander et de MacMillan en remplaçant le complexe d'iridium par le 1,2,3,5-tetrakis-(carbazol-yl)-4,6-dicyanobenzène (4CzIPN).²¹

²⁰ H. Uoyama, K. Goushi, K. Shizu, H. Nomura, C. Adachi, *Nature* **2012**, 492, 234.

²¹ J. Luo, J. Zhang, *ACS Catal.* **2016**, 6, 873.

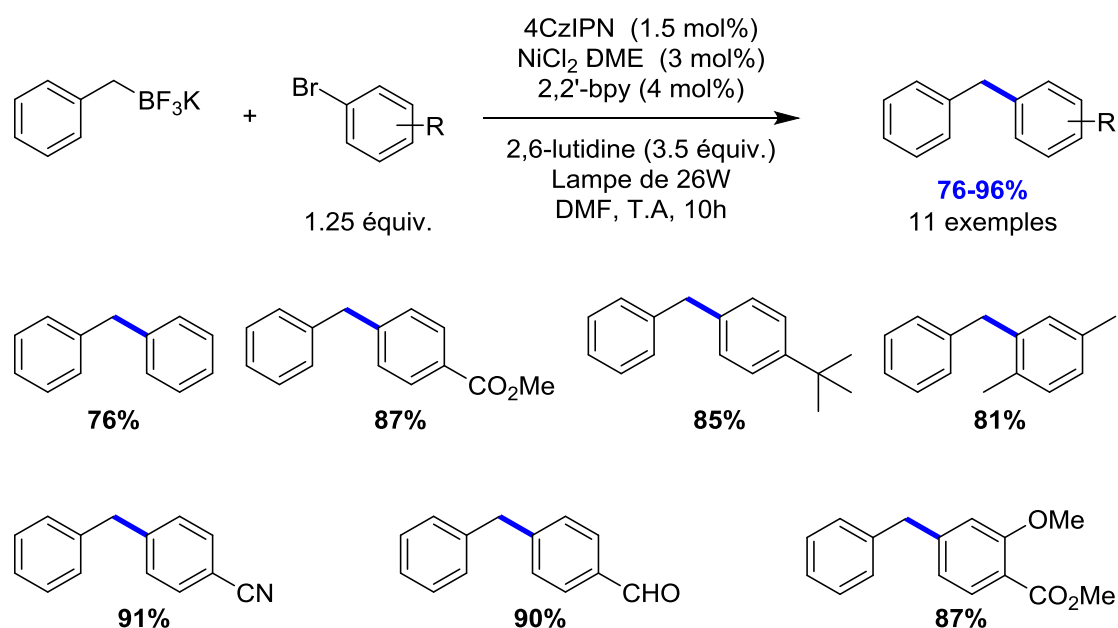


Schéma 22. Réaction de catalyse duale avec le benzyltrifluoroborate et l'organo-photocatalyseur 4CzIPN

Dans l'optique d'améliorer la photooxydation des silicates, nous avons mis en réaction ces espèces avec l'organo-photocatalyseur. Ce dernier nous a non seulement permis de réduire la charge catalytique jusqu'à 1 mol% mais surtout, d'assurer l'oxydation de tous nos silicates synthétisés. Les radicaux ainsi générés ont été piégés lors de réactions d'allylation, d'alcynation et de vinylation ou par simple piégeage avec le TEMPO, donnant des produits variés avec de hauts rendements.

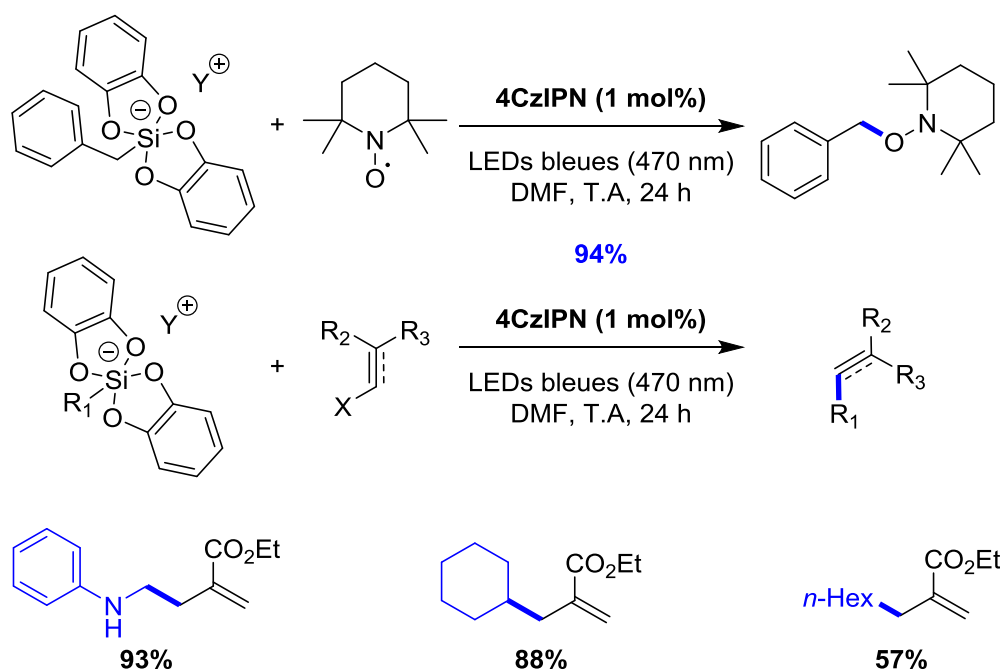


Schéma 23. Photooxydation des silicates par le catalyseur 4CzIPN

Les résultats de Zhang, obtenus en catalyse duale photoredox/nickel avec des acides aminés ou des trifluoroborates et en présence du catalyseur 4CzIPN, combinés à nos résultats sur la photooxydation des silicates, devraient nous permettre de réaliser des réactions de couplages croisés avec les silicates. En effet, une grande variété d'alkyles bis-catécholatosilicates peut être photooxydée par le 4CzIPN. D'autre part, les radicaux alkyles ainsi générés réagissent efficacement dans une catalyse au nickel avec des halogénures d'(hétéro)aryles et des halogénures d'alcènes. Ces derniers travaux, réalisés par Christophe Lévêque (en deuxième année de doctorat), montrent que la catalyse au nickel peut être combinée avec un organo photocatalyseur, utilisé avec une faible charge catalytique (de l'ordre de 1 mol%) ouvrant ainsi des perspectives très intéressantes sur le développement d'une catalyse photoredox plus verte.

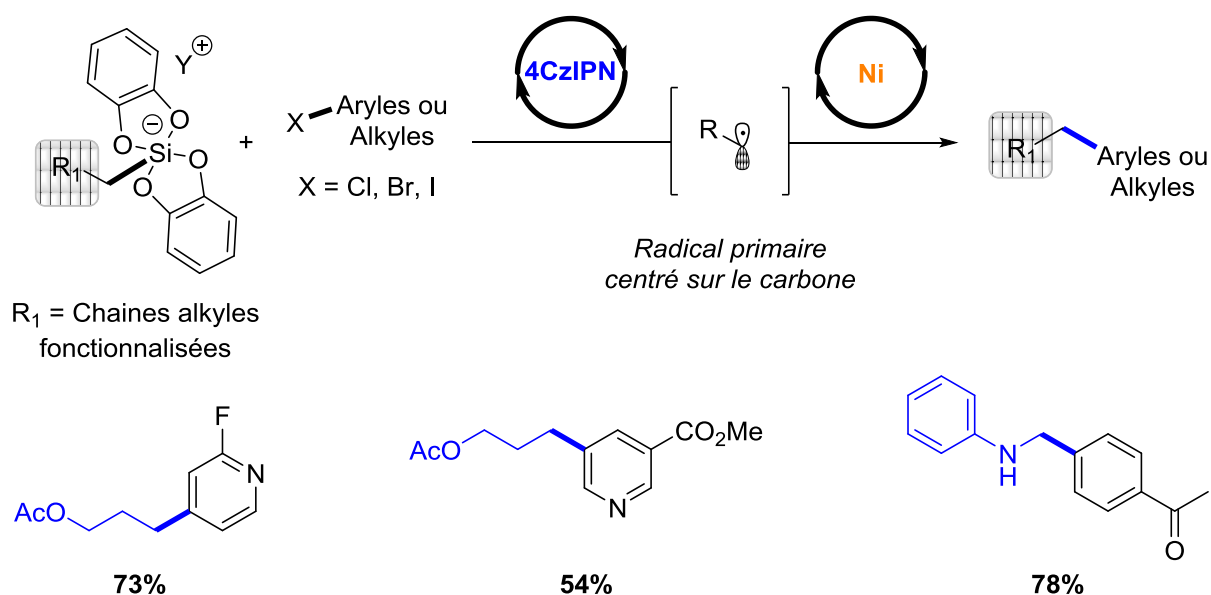


Schéma 24. Réaction catalyse duale avec l'organo-photocatalyseur 4CzIPN

En conclusion, les projets étudiés au cours de cette thèse s'appuient sur l'utilisation et la valorisation énergétique de la lumière visible, pour réaliser des transformations chimiques originales, sélectives et efficaces faisant intervenir principalement des processus d'oxydoréduction (redox) pour la génération d'espèces radicalaires. Nous souhaitons développer une chimie radicalaire faisant intervenir des processus de transfert

monoélectronique inédits permettant de transformer des dérivés organiques chargés ou non en espèces radicalaires.

Nous avons ainsi développé de nouvelles méthodes efficaces de génération de radicaux carbonés par catalyse photoredox à travers la photoréduction de thiocarbamates d'alcools secondaires ou tertiaires, ou la photooxydation de silicates. Nous avons essayé d'élaborer des méthodologies les plus éocompatibles possible en choisissant des catalyseurs moins toxiques, comme le colorant organique 4CzIPN, et en diminuant leur charge catalytique.

La photoréduction d'*O*-thiocarbamates pour la désoxygénation d'alcools représente un atout majeur pour la synthèse de molécules élaborées. Cette réaction douce et tolérante vis-à-vis de nombreux groupes fonctionnels peut devenir un outil très utile pour l'industrie. Une deuxième méthode innovante de génération de radicaux carbonés a été étudiée par photooxydation d'espèces hypervalentes de silicium. La formation de radicaux primaires non-stabilisés a été rendue possible par ces travaux. Ces derniers ont pu être engagés dans les réactions de piégeage direct ou de catalyse duale avec des complexes de nickel. Nous nous sommes tournés aussi vers l'utilisation d'organo-photocatalyseurs qui sont *de facto* moins onéreux et plus écologiques tout en gardant une excellente réactivité. Nous avons démontré par ces différentes méthodologies photocatalysées que la chimie radicalaire n'est plus une chimie polluante et qu'elle s'inscrit durablement dans le domaine d'une chimie verte.

Chapter I

Green Radical Chemistry and Photoredox Catalysis

I.A. Green Radical Chemistry

I.A.1. Introduction to Radical Synthesis

In 2000, the radical chemistry community celebrated the 100th anniversary of the discovery of the first organic radical - triphenylmethyl radical - by Moses Gomberg. Despite this early discovery, the development of this field and particularly its application in synthesis has shown a slow progression. The critical milestones in its evolution include Kharasch reactions in the 30s, the discovery of EPR in the 40s, the structural and kinetic determinations that followed, also the development in polymer sciences. All set the stage for the development of versatile organic reactions.¹

After the pioneering works of Julia and Surzur on radical cyclizations in the 60s, the main contributions of Giese, Curran, Barton, Stork and others, to improve the control of the reactivity of these species through the development of chain reactions mediated by organic or organometallic hydrides, have significantly expanded the scope of the initial processes and opened the way to total syntheses of natural products,¹ for instance through the development of highly effective polycyclisations, cascade reactions² and in obtaining enantiopure products *via* highly controlled asymmetric processes.^{1c}

The main advantages of these radical reactions are inherent in the fact that radicals are highly reactive neutral species. Because radical reactions generally take place in salt-free conditions, the influence of aggregation states and solvation is almost completely shut down. Furthermore, the compatibility of the radical with many functional groups as well as its ability to perform these transformations under mild conditions, have made the free radical reactions a complementary tool to ionic reactions. Finally, it should be mentioned that radical reactions are not limited only to cyclizations; intermolecular additions, substitutions and homolytic C-H functionalizations by hydrogen transfer also led to beautiful applications,

¹ For a comprehensive account on all aspects of radical chemistry in synthesis, see: a) *Encyclopedia of Radicals in Chemistry, Biology and Materials*, C. Chatgililoglu, A. Studer, Eds. John Wiley & Sons Ltd, Chichester, **2012**. b) P. Renaud, M. P. Sibi in *Radicals in Organic Synthesis*, Vol. 1& 2, Wiley-VCH, Weinheim, 2001. c) D. P. Curran, N. A. Porter, B. Giese in *Stereochemistry of Radical Reactions*, VCH, Weinheim, 1996. d) C. R. J. Stephenson, A. Studer, D. P. Curran, *Beilstein J. Org. Chem.* **2013**, *9*, 2778 and references included.

² For reviews: a) M. Albert, L. Fensterbank, E. Lacôte, M. Malacria, *Top. Curr. Chem.* **2006**, *264*, 1. b) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem., Int. Ed.* **2006**, *118*, 7134. For a book chapter, see: *Radical Cascade Reactions*. A. Baralle, A. Baroudi, M. Daniel, L. Fensterbank, J.-P. Goddard, E. Lacôte, M.-H. Larraufie, G. Maestri, M. Malacria, C. Ollivier, *Encyclopedia of Radicals in Chemistry, Biology and Materials*, C. Chatgililoglu, A. Studer, Eds. John Wiley & Sons Ltd, Chichester, **2012**, Chap 27, Vol 2, 729.

especially when very reliable stereoselectivity models are available. However, radical reactions have suffered from a number of problems which have hampered their routine use. First, the scale-up is difficult because reactions are generally run in dilute media. But the most troublesome cons remain the use of tributyltin hydride as the most effective radical mediator which is both easily available and extremely versatile. However this reagent is also extremely toxic and its byproducts – as well as those of all tin hydrides – tend to "stick" to the products during purification and are thus generally found in traces analyses, which consequently eliminate any possibility of radical reactions being used in industry.¹

I.A.2. To a Greener Radical Synthesis

Green chemistry is a new paradigm for chemistry emerged in the 90s which provides pollution prevention related to chemical activities. This benign chemistry to the environment aims to develop products and chemical processes that reduce or eliminate the use and synthesis of hazardous substances. It applies to both the preparation of new products or processes more environmentally friendly and the search for alternative solutions or to the improvement of existing approaches. This new concept was made popular in the scientific community by the American chemists Paul Anastas, director of the Green Chemistry Institute in Washington DC, and John Warner with the publication in 1998 of the 12 principles of Green Chemistry as cited Table 1.³

Table 1. The 12 principles of green chemistry

1	It is better to prevent waste than to treat or clean up waste after it is formed.
2	Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3	Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4	Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5	The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made

³ P.T. Anastas, J.C. Warner, *Green chemistry: theory and practice*, **1998**, Oxford University Press Inc., New York.

	unnecessary wherever possible and innocuous when used.
6	Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
7	A raw material or feedstock should be renewable rather than depleting wherever technically and economically practicable.
8	Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible.
9	Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10	Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.
11	Analytical methodologies need to be further developed to allow for real-time, in process monitoring and control prior to the formation of hazardous substances.
12	Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions, and fires.

About radical synthesis, as pointed out by J. Walton,⁴ it is time to escape from "the tyranny of the tin" and thus to invent new practical molecular devices to generate radicals. Several solutions have already been proposed and divided into three directions. The first consisted in the use of tin based reagents either in catalytic amounts or on solid supports.⁵ The second was the development of new mediators based for instance on silanes, phosphorus derivatives and less toxic metals. Although some of these reagents are quite interesting, they often lack generality and sometimes suffer from prohibitive costs or difficult accesses. The last avenue of research has a more diffuse perimeter and gathers several families of reactions. Group transfers (selenium, xanthates ...) belong to this class but suffer from the fact that a further reduction is in most cases required. Interesting perspectives have been opened with the use of organoboranes.⁶

⁴ For reviews on tin-free radical processes that respect the principles of safe, sustainable synthesis, see: a) P. A. Baguley, J. C. Walton, *Angew. Chem. Int. Ed.* **1998**, *37*, 3072. b) A. Studer, S. Amrein, *Synthesis* **2002**, 835. c) B. C. Gilbert, A. F. Parsons, *J. Chem. Soc., Perkin Trans 2* **2002**, 367.

⁵ A. Studer, S. Amrein, *Synthesis* **2002**, 835.

⁶ C. Ollivier, P. Renaud, *Chem. Rev.* **2001**, *101*, 3415.

Compounds responsible for processes involving one-electron transfers are increasingly regarded as alternative to tin hydrides as radical mediators, contributing *de facto* to the development of a more environmentally compatible chemistry.⁴ However, most of these reagents, essentially metal complexes based on samarium, titanium, cerium, copper, iron, nickel... are used in substoichiometric amounts.^{1,7} Furthermore, these reactions are generally specific of a function and sometimes involve a set of stringent conditions. Improved versions are therefore highly desirable. It should then develop milder catalytic versions⁸ and more environmentally conscious processes, avoiding the use of toxic metal compounds, toxic solvents and energetic UV radiations, to perform radical transformations and apply them in fine chemistry.

I.B. Visible-Light Photoredox Catalysis

Millions of years of evolution have allowed nature to implement chemical and biological processes in order to preserve life by maintaining a sustainable balance. For plants, the energy required for creation of organic matter comes from a virtually inexhaustible source: the sun. The light, absorbed by chlorophyll, promotes activation of ATP production which then allows carbon sequestration provided by the CO₂, thereby transforming solar energy into chemical energy.

Inspired by such a process the radical chemistry community participated over the last years to the use of visible light, to carry out original, selective and efficient chemical transformations involving redox processes for the generation of radical species. Visible light photoredox catalysis has recently established itself as one of the most versatile methods to conduct radical chemistry. It is also one of the most productive fields of activity in contemporary organic chemistry. As chlorophyll is fundamental in photoredox processes involved in photosynthesis, the envisaged chemical transformations require the intervention of an appropriate photocatalyst which absorbs light in the visible range. For that purpose, the photoactive complexe Ru(bpy)₃²⁺ was introduced in catalytic quantity. Well known in the inorganic chemistry community as a photoredox catalyst for diverse applications such as

⁷ For reviews on monoelectronic transfer reactions, see: a) P. I. Dalko, *Tetrahedron* **1995**, *51*, 7579. b) *Tetrahedron Symposium in Print on Electron Transfer Reagents in Organic Synthesis*, Eds: D. Procter, R. Flowers, *Tetrahedron* **2009**, *65*, 10725. See also: c) U. Jahn, *Top. Curr. Chem.* **2012**, *320*, 121; 191; 323.

⁸ A. Studer, D. P. Curran, *Angew. Chem. Int. Ed.* **2016**, *55*, 58.

hydrogen and oxygen production from water, methane evolution from carbon dioxide and reduction of carbon dioxide to formate,^{9,10} it has witnessed only sporadic uses in organic synthesis by the groups of Kellogg,¹¹ Pac¹² and Deronzier,¹³ until recently in 2008 when David MacMillan (Princeton University) used it to merge organocatalysis with photoredox catalysis and provide an asymmetric α -alkylation of aldehydes.¹⁴ Since this renaissance, two other teams, the groups of Corey Stephenson (Boston University) and Tehshik P. Yoon (University of Wisconsin, Madison) have published very interesting contributions on dehalogenative cyclization reactions¹⁵ and photocatalytic [2+2] cycloadditions of enones.¹⁶

I.B.1. Photophysical properties of Ru(bpy)₃ complexes and other photocatalysts

Known for many years for its photochemical properties and its activity in photoredox catalysis, the complex Ru(bpy)₃Cl₂,⁹ discovered by Burstall in 1936,¹⁷ has recently shown great potential in various organic redox processes used for synthetic purposes.¹⁸ If we consider the photochemical properties of such complex, the UV/Visible spectrum shows us

⁹ For reviews on the use of Ru(bpy)₃²⁺ complexes photoredox catalysts: a) S. Campagna, F. Puntoriero, F. Nastasi, G. Bergamini, V. Balzani, *Top. Curr. Chem.* **2007**, *280*, 117. b) K. Kalyanasundaram, *Coord. Chem. Rev.* **1982**, *46*, 159. c) A. Juris, V. Balzani, F. Barigelletti, S. Campagna, P. Belser, A. von Zelewsky, *Coord. Chem. Rev.* **1988**, *84*, 85.

¹⁰ J. Hawecker, J. Lehn, R. Ziessel, *J. Chem. Soc., Chem. Commun.* **1985**, 56.

¹¹ D. M. Hedstrand, W. H. Kruizinga, R. M. Kellogg, *Tetrahedron Lett.* **1978**, 1255.

¹² C. Pac, M. Ihama, M. Yasuda, Y. Miyauchi, H. Sakurai, *J. Am. Chem. Soc.* **1981**, *103*, 6495.

¹³ H. Cano-Yelo, A. Deronzier, *Tetrahedron Lett.* **1984**, *25*, 5517.

¹⁴ D. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77.

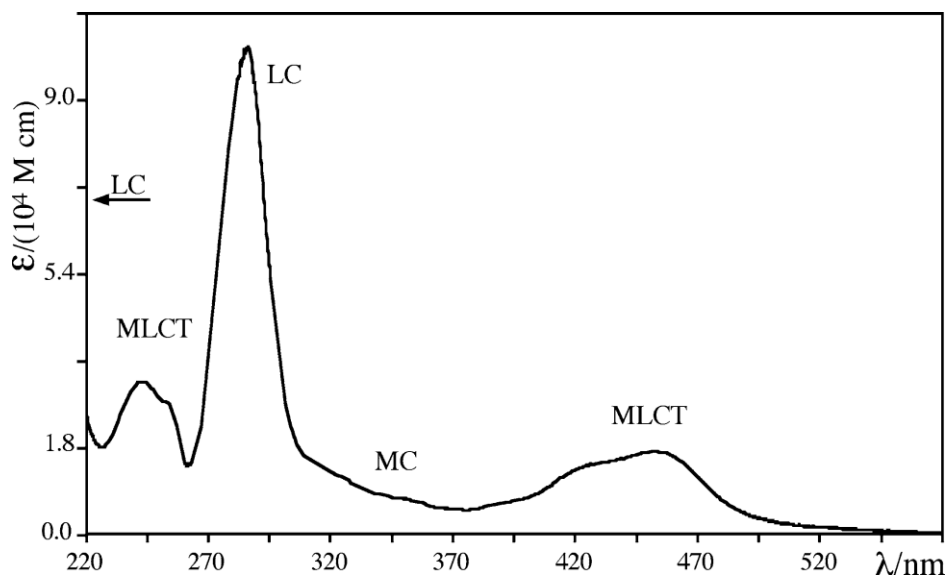
¹⁵ J. M. R. Narayanam, J. W. Tucker, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2009**, *131*, 8756.

¹⁶ M. A. Ischay, M. E. Anzovino, J. Du, T. Yoon, *J. Am. Chem. Soc.* **2008**, *130*, 12886.

¹⁷ F. H. Burstall, *J. Chem. Soc.* **1936**, 173.

¹⁸ a) M. Fagnoni, D. Dondi, D. Ravello, A. Albinì, *Chem. Rev.* **2007**, *107*, 2725. b) D. Ravelli, D. Dondi, M. Fagnoni, A. Albinì, *Chem. Soc. Rev.* **2009**, *38*, 1999. c) K. Zeidler, *Angew. Chem. Int. Ed.* **2009**, *48*, 9785. d) T. P. Yoon, M. A. Ischay, J. Du, *Nature Chem.* **2010**, *2*, 527. e) F. Teplý, *Collect. Czech. Chem. Commun.* **2011**, *76*, 859. f) J. M. R. Narayanam, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102. g) J. W. Tucker, C. R. J. Stephenson, *J. Org. Chem.* **2012**, *77*, 1617. h) J. Xuan, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2012**, *51*, 6828. i) M. A. Ischay, T. P. Yoon, *Eur. J. Org. Chem.* **2012**, 3359. j) C.-J. Wallentin, J. D. Nguyen, C. R. J. Stephenson, *Chimia* **2012**, *66*, 394. k) L. Shi, W. Xia, *Chem. Soc. Rev.* **2012**, *41*, 7687. l) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322. m) Y. Xi, H. Yi, A. Lei, *Org. Biomol. Chem.* **2013**, *11*, 2387. n) D. P. Hari, B. König, *Angew. Chem. Int. Ed.* **2013**, *52*, 4734. o) M. Reckenthäler, A. G. Griesbeck, *Adv. Synth. Catal.* **2013**, *355*, 2727. p) T. Koike, M. Akita, *Synlett* **2013**, *24*, 2492. q) J. Xuan, L.-Q. Lu, J.-R. Chen, W.-J. Xiao, *Eur. J. Org. Chem.* **2013**, 6755. r) J. Hu, J. Wang, T. H. Nguyen, N. Zheng, *Beilstein J. Org. Chem.* **2013**, *9*, 1977. s) M. N. Hopkinson, B. Sahoo, J.-L. Li, F. Glorius, *Chem. Eur. J.* **2014**, *20*, 3874. t) D. M. Schultz, T. P. Yoon, *Science* **2014**, *343*, 985. For recent books, see: u) *Chemical Photocatalysis* (Eds.: B. König), DeGruyter, Berlin, **2013**. v) *Photochemically generated intermediates in Synthesis* (Eds.: A. Albinì, M. Fagnoni) John Wiley & Sons, Hoboken, **2013**.

three different bands of absorption which correspond to three different types of electronic transitions: one is the LC (Ligand Centered) transfer, the second MC (Metal Centered) and the most interesting is the MLCT (Metal-to-Ligand Charge-Transfer) that absorbs in the visible region. The characteristic absorption band at 452 nm, as shown in scheme 1, is responsible for the visible-light excitation of the complex of $\text{Ru}(\text{bpy})_3\text{Cl}_2$.⁹ A tuning of ligands around the ruthenium metal center, can promote a red shift of the MLCT band which induces a modification of physical properties of the complex.

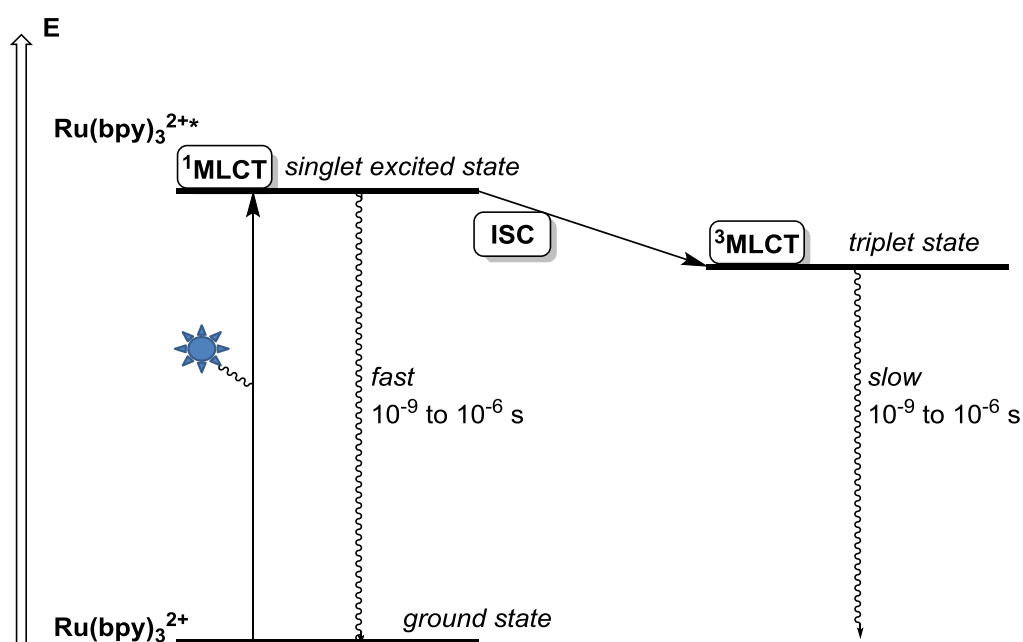


Scheme 1. Absorption spectrum of $\text{Ru}(\text{bpy})_3\text{Cl}_2$ (from ref. 9a)

Irradiation with the visible-light ($\lambda_{\text{max}} = 452 \text{ nm}$) activates the complex $[\text{Ru}(\text{bpy})_3]^{2+}$ to $[\text{Ru}(\text{bpy})_3]^{2+*}$. The absorption of a photon first converts the complex in an excited singlet state $^1\text{MLCT}$ which undergoes a rapid intersystem crossing (ISC) to an excited triplet state $^3\text{MLCT}$ lower in energy with a relatively long lifetime of 890 ns in acetonitrile and 650 ns in water, enough to trigger single electron transfer reactions.¹⁹ Thanks to this property, $\text{Ru}(\text{bpy})_3^{2+*}$ can interact through bimolecular reactions with other solute molecules.¹⁸ The triplet excited state can react as an electron donor (energy available = 2.12 eV) (oxidation potential: $\text{Ru}(\text{bpy})_3^{3+}/\text{Ru}(\text{bpy})_3^{2+*} = -0.86 \text{ V vs. SCE in MeCN}$) and electron acceptor (reduction potential: $\text{Ru}(\text{bpy})_3^{2+*}/\text{Ru}(\text{bpy})_3^+ = +0.84 \text{ V vs. SCE in MeCN}$). A number of other electronic processes can also occur that cause deactivation of the complex. To control this electron transfer, a cofactor called "quencher", acting as a donor or an acceptor of electron, should be chosen carefully. Electronic transfer kinetics are important parameters to control and are

¹⁹ M. Montalti, A. Cedi, L. Prodi, M. T. Gandolfi, *Handbook of Photochemistry 3rd edition* CRC press Taylor & Francis Group, **2006**, 379.

brought together under the kq constant that represents the ability of a compound to allow fast electron transfer. A rapid transfer ($kq > 10^9 \text{ M}^{-1} \cdot \text{s}^{-1}$) is fundamental to avoid the deactivation of the excited complex and to promote the redox process. The direct consequence is the increase of the transformation efficiency.⁹



Scheme 2. Schematic energy diagram for photoexcitation of Ru(bpy)₃²⁺

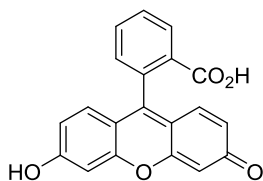
The photocatalyst can also consist of an organic dye such as Eosin Y, fluorescein, rose Bengal, methylene blue... or a homo- or heteroleptic transition metal complex of mainly ruthenium(II),⁹ iridium(III),²⁰ but also copper(I),²¹ gold(I)²² and iron(II)²³ on which the ligands (generally polypyridine ligands) influence the redox potentials.

²⁰ L. Flamigni, A. Barbieri, C. Sabatini, B. Ventura, F. Barigelletti, *Top. Curr. Chem.* **2007**, 281, 143.

²¹ S. Paria, O. Reiser, *Chem. Cat. Chem.* **2014**, 6, 2477.

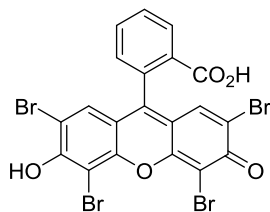
²² C. D. McTiernan, M. Morin, T. McCallum, J. C. Scaiano, L. Barriault, *Catal. Sci. Technol.* **2016**, 6, 201.

²³ J. Zhang, D. Campolo, F. Dumur, X. Piao, J.-P. Fouassier, D. Gigmes, J. Lalevée, *J. Polym. Science, Polym. Chem.* **2016**, DOI: 10.1002/pola.28098



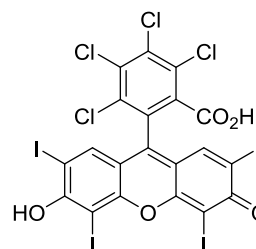
Fluorescein = PC

$E_{\text{red}}(\text{PC}/\text{PC}^-) = -1.23 \text{ V vs. SCE}$
 $E_{\text{ox}}(\text{PC}^+/\text{PC}) = 0.83 \text{ V vs. SCE}$
 $E^*_{\text{red}}(\text{PC}^*/\text{PC}^-) = 1.21 \text{ V vs. SCE}$
 $E^*_{\text{ox}}(\text{PC}^+/\text{PC}^*) = -1.61 \text{ V vs. SCE}$
 $\lambda_{\text{max}} = 528 \text{ nm}, \tau = 4.2 \text{ ns}$



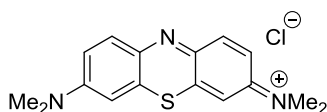
Eosin Y = PC

$E_{\text{red}}(\text{PC}/\text{PC}^-) = -1.14 \text{ V vs. SCE}$
 $E_{\text{ox}}(\text{PC}^+/\text{PC}) = 0.72 \text{ V vs. SCE}$
 $E^*_{\text{red}}(\text{PC}^*/\text{PC}^-) = 1.18 \text{ V vs. SCE}$
 $E^*_{\text{ox}}(\text{PC}^+/\text{PC}^*) = -1.60 \text{ V vs. SCE}$
 $\lambda_{\text{max}} = 539 \text{ nm}, \tau = 2.1 \text{ ns}$



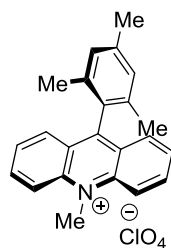
Rose Bengal = PC

$E_{\text{red}}(\text{PC}/\text{PC}^-) = -0.78 \text{ V vs. SCE}$
 $E_{\text{ox}}(\text{PC}^+/\text{PC}) = 1.09 \text{ V vs. SCE}$
 $E^*_{\text{red}}(\text{PC}^*/\text{PC}^-) = 0.99 \text{ V vs. SCE}$
 $E^*_{\text{ox}}(\text{PC}^+/\text{PC}^*) = -0.68 \text{ V vs. SCE}$
 $\lambda_{\text{max}} = \text{n.d}$



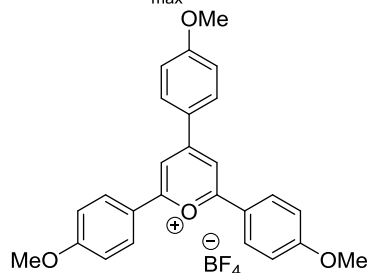
Methylene blue = PC

$E_{\text{red}}(\text{PC}/\text{PC}^-) = -0.15 \text{ V vs. SCE}$
 $E_{\text{ox}}(\text{PC}^+/\text{PC}) = \text{n.d V vs. SCE}$
 $E^*_{\text{red}}(\text{PC}^*/\text{PC}^-) = 1.72 \text{ V vs. SCE}$
 $E^*_{\text{ox}}(\text{PC}^+/\text{PC}^*) = \text{n.d V vs. SCE}$
 $\lambda_{\text{max}} = \text{n.d}$



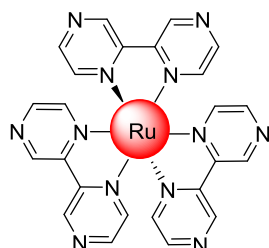
Fukuzumi Catalyst = PC

$E_{\text{red}}(\text{PC}/\text{PC}^-) = -0.57 \text{ V vs. SCE}$
 $E_{\text{ox}}(\text{PC}^+/\text{PC}) = \text{n.d V vs. SCE}$
 $E^*_{\text{red}}(\text{PC}^*/\text{PC}^-) = +2.06 \text{ V vs. SCE}$
 $E^*_{\text{ox}}(\text{PC}^+/\text{PC}^*) = \text{n.d V vs. SCE}$
 $\lambda_{\text{max}} = 430 \text{ nm}, \tau = 6 \text{ ns}$



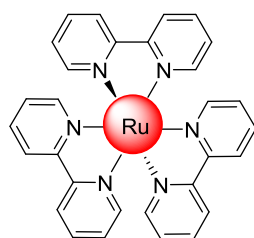
Pyrylium = PC

$E_{\text{red}}(\text{PC}/\text{PC}^-) = -0.35 \text{ V vs. SCE}$
 $E_{\text{ox}}(\text{PC}^+/\text{PC}) = \text{V vs. SCE}$
 $E^*_{\text{red}}(\text{PC}^*/\text{PC}^-) = 2.3 \text{ V vs. SCE}$
 $E^*_{\text{ox}}(\text{PC}^+/\text{PC}^*) = \text{V vs. SCE}$
 $\lambda_{\text{max}} = 417 \text{ nm}$



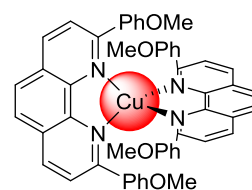
[Ru(bpz)₃]²⁺ = Ru(II)

$E_{1/2}(\text{Ru(III)}/\text{Ru(II)}^*) = -0.26 \text{ V vs. SCE}$
 $E_{1/2}(\text{Ru(II)}^*/\text{Ru(I)}) = +1.45 \text{ V vs. SCE}$
 $E_{1/2}(\text{Ru(III)}/\text{Ru(II)}) = +1.86 \text{ V vs. SCE}$
 $E_{1/2}(\text{Ru(II)}/\text{Ru(I)}) = -0.80 \text{ V vs. SCE}$
 $\lambda_{\text{max}} = 443 \text{ nm}, \tau = 740 \text{ ns}$



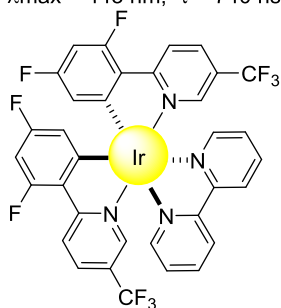
[Ru(bpy)₃]²⁺ = Ru(II)

$E_{1/2}(\text{Ru(III)}/\text{Ru(II)}^*) = -0.81 \text{ V vs. SCE}$
 $E_{1/2}(\text{Ru(II)}^*/\text{Ru(I)}) = +0.77 \text{ V vs. SCE}$
 $E_{1/2}(\text{Ru(III)}/\text{Ru(II)}) = +1.29 \text{ V vs. SCE}$
 $E_{1/2}(\text{Ru(II)}/\text{Ru(I)}) = -1.37 \text{ V vs. SCE}$
 $\lambda_{\text{max}} = 452 \text{ nm}, \tau = 1100 \text{ ns}$



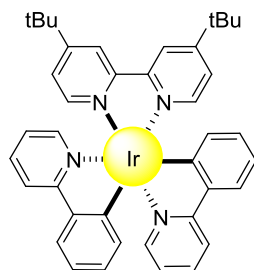
[Cu(dap)₂]⁺ = Cu(I)

$E_{1/2}(\text{Cu(II)}/\text{Cu(I)}^*) = -1.43 \text{ V vs. SCE}$
 $E_{1/2}(\text{Cu(I)}^*/\text{Cu(0)}) = \text{n.d V vs. SCE}$
 $E_{1/2}(\text{Cu(II)}/\text{Cu(I)}) = +0.62 \text{ V vs. SCE}$
 $E_{1/2}(\text{Cu(I)}/\text{Cu(0)}) = \text{n.d V vs. SCE}$
 $\lambda_{\text{max}} = \text{n.d}, \tau = 270 \text{ ns}$



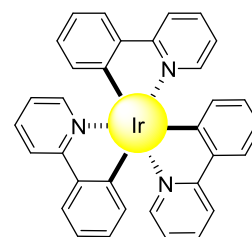
[Ir(dF(CF₃)ppy)₂bpy]⁺ = Ir(III)

$E_{1/2}(\text{Ir(IV)}/\text{Ir(III)}^*) = -0.89 \text{ V vs. SCE}$
 $E_{1/2}(\text{Ir(III)}^*/\text{Ir(II)}) = +1.21 \text{ V vs. SCE}$
 $E_{1/2}(\text{Ir(IV)}/\text{Ir(III)}) = +1.69 \text{ V vs. SCE}$
 $E_{1/2}(\text{Ir(III)}/\text{Ir(II)}) = -1.37 \text{ V vs. SCE}$
 $\lambda_{\text{max}} = 380 \text{ nm}, \tau = 2300 \text{ ns}$



[Ir(ppy)₂(dtbbpy)]⁺ = Ir(III)

$E_{1/2}(\text{Ir(IV)}/\text{Ir(III)}^*) = -0.96 \text{ V vs. SCE}$
 $E_{1/2}(\text{Ir(III)}^*/\text{Ir(II)}) = +0.66 \text{ V vs. SCE}$
 $E_{1/2}(\text{Ir(IV)}/\text{Ir(III)}) = +1.21 \text{ V vs. SCE}$
 $E_{1/2}(\text{Ir(III)}/\text{Ir(II)}) = -1.51 \text{ V vs. SCE}$
 $\lambda_{\text{max}} = \text{nm}, \tau = 557 \text{ ns}$



Ir(ppy)₃ = Ir(III)

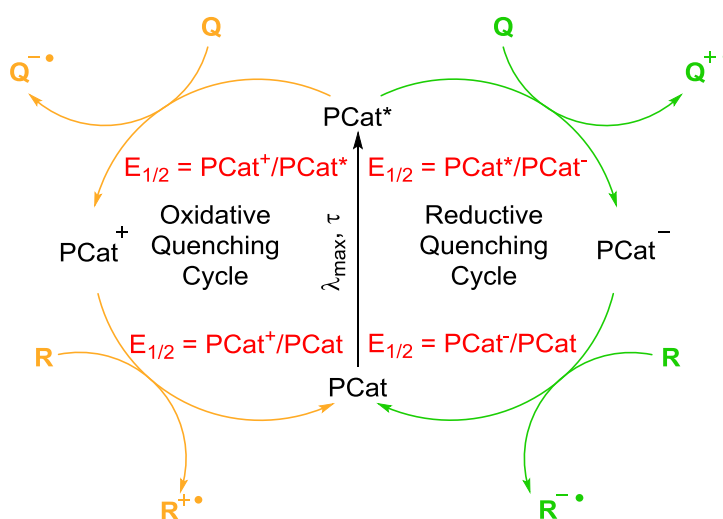
$E_{1/2}(\text{Ir(IV)}/\text{Ir(III)}^*) = -1.73 \text{ V vs. SCE}$
 $E_{1/2}(\text{Ir(III)}^*/\text{Ir(II)}) = +0.31 \text{ V vs. SCE}$
 $E_{1/2}(\text{Ir(IV)}/\text{Ir(III)}) = +0.77 \text{ V vs. SCE}$
 $E_{1/2}(\text{Ir(III)}/\text{Ir(II)}) = -2.19 \text{ V vs. SCE}$
 $\lambda_{\text{max}} = 375 \text{ nm}, \tau = 1900 \text{ ns}$

Scheme 3. Examples of photocatalysts

I.B.2. Basic of photoredox catalysis

Upon visible light irradiation at wavelength λ_{\max} , the photocatalyst **PCat** reaches its excited state **PCat***. Two scenarios can take place:

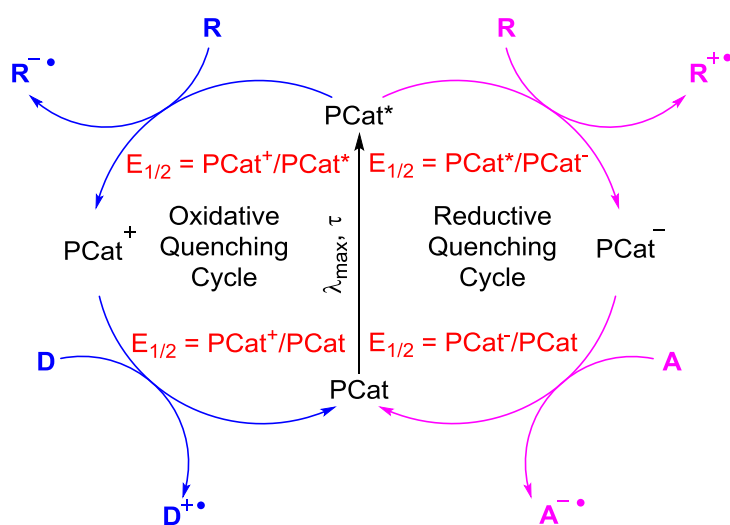
In the first one, a sacrificial electron donor is present in the reaction medium with adequate reduction potential (Scheme 2, green path) which can act as a reductive quencher (**Qred**) of **PCat*** and generate **PCat⁻**. The reduced complex then transfers an electron to the substrate **R** which regenerates **PCat** in a so-called “reductive quenching cycle”. The resulting radical anion **R^{-•}** then undergoes subsequent transformations. Similarly, if the photoexcited complex **PCat*** reacts with a sacrificial electron acceptor acting, as an oxidative quencher (**Qox**), it gets oxidized to **PCat⁺** and can be reduced by a substrate **R** to regenerate the starting catalytic species (oxidative quenching cycle) and liberate the radical cation **R^{+•}** (Scheme 2, orange path).



Scheme 4. Catalytic cycle in presence of a sacrificial quench Q

In the second scenario, the substrate **R** is also the quencher. If this one acts as reductive quencher (**Qred**), it transfers an electron to **PCat*** to form **PCat⁻**. The oxidized substrate **R^{+•}** will then participate in radical transformations. To regenerate the catalyst, a

sacrificial electron acceptor **A** must be introduced into the medium (reductive quenching cycle, Scheme 2, purple path). The alternative pathway can take place: if the complex transfers an electron to the substrate (or oxidative quencher (**Q_{ox}**)), this one is oxidized to **PCat⁺**. The reduced substrate **R^{-•}** undergoes radical transformations and the presence of a sacrificial electron donor **D** allows the regeneration of the photocatalyst **PCat** (oxidative quenching cycle) (Scheme 2, blue path). Many contributions in this area have been reported exhibiting photoreduction and photooxidation of various functions and illustrated in a series of important monographs and reviews.¹⁸



Scheme 5. Catalytic cycle when substrate and quencher are the same species

I.B.3. Photocatalytic Generation of C-Centered Radicals

I.B.3.a. Formation involving photoreductive processes

× *Reduction of onium salts*

In the context of photoredox catalysis under visible light activation, Deronzier was a pioneer in the reduction of diazonium salts with transition metal-based photocatalyst like $\text{Ru}(\text{bpy})_3\text{Cl}_2$. The arenediazonium salts to be the **Q_{ox}** of the ruthenium complex excited state

has been reported and applied to a photocatalytic version of Pschorr reaction (Scheme 6, eq 1).^{24,25}

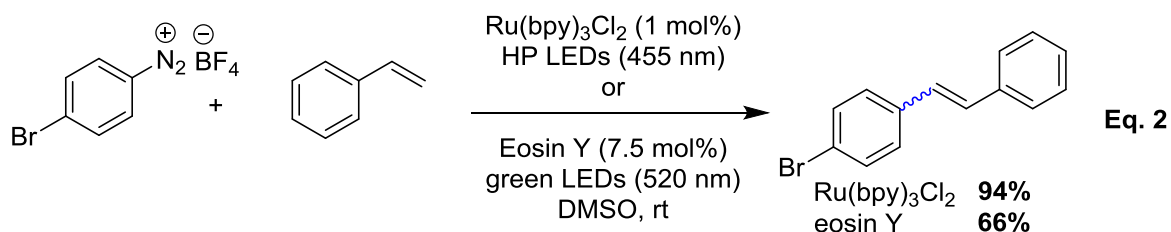
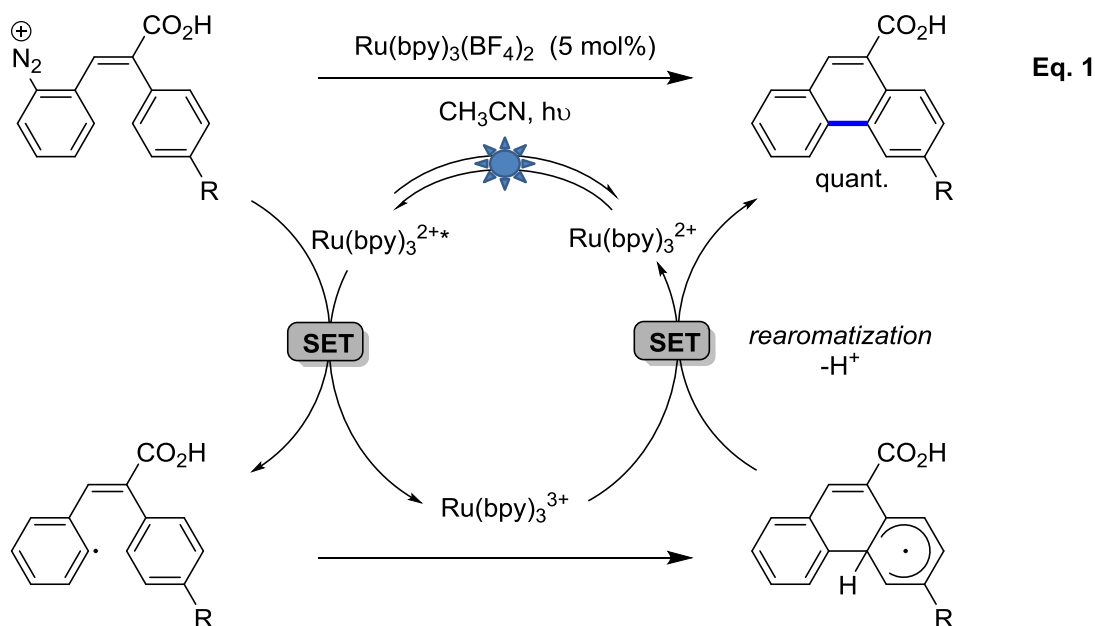
More recently, König extended this process to the Merwein arylation catalyzed by photoactive transition metal complexes or organic dyes.^{26,27} Arylation of unsaturated compounds has been reported with Ru(bpy)₃Cl₂ or eosin Y. A *p*-Bromodiazonium salt was reduced in the presence of 5 equivalents of styrene and the ruthenium complex to afford 94% of stilbene derivative whereas a lower yield of 66% was obtained with eosin Y (Scheme 6, eq 2). After oxidative quenching of the photocatalyst excited state, the reduced diazonyl radical decomposed to liberate the corresponding aryl radical. Addition to an olefin followed by oxidation of the resulting radical allowed the formation of stilbenyl derivatives and recovery of the catalyst. The same transformation was extended to biaryl synthesis in a metal-free manner with furan, thiophene and pyrrole acceptors in good yields (Scheme 9, eq 3).

²⁴ H. Cano-Yelo, A. Deronzier, *J. Chem. Soc., Perkin Trans. 2*, **1984**, 1093-1098.

²⁵ H. Cano-Yelo, A. Deronzier, *J. Photochem.*, **1987**, *37*, 315-321.

²⁶ P. Schroll, D.P. Hari, B. König, *ChemistryOpen*, **2012**, *1*, 130-133.

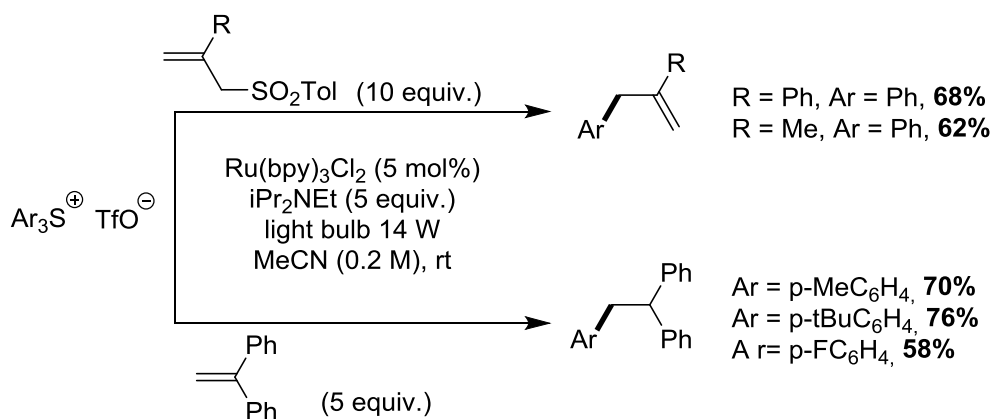
²⁷ D.P. Hari, P. Schroll, B. König, *J. Am. Chem. Soc.*, **2012**, *134*, 2958-2961.



Scheme 6. Formation of aryl radical by photoreduction of diazonium salts

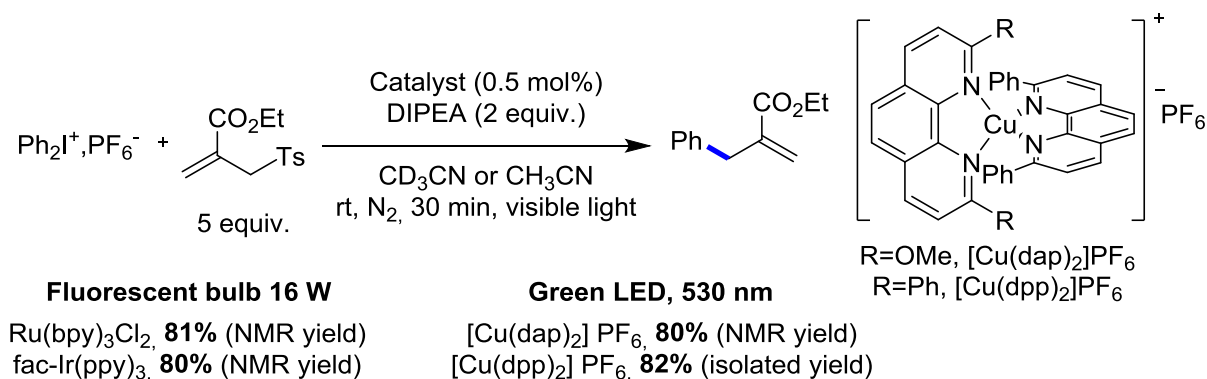
Our group reported the visible-light photocatalytic reduction of triarylsulfonium salts which proved to be a source of aryl radicals (Scheme 7).²⁸ The triarylsulfonium salts are difficult to reduce due to their high reduction potential (-1.2 V vs SCE for triphenylsulfonium). Nevertheless, they can produce aryl radical under mild conditions by using $\text{Ru}(\text{bpy})_3\text{Cl}_2$ catalyst and DIPEA as **Qred**. The so-generated radicals add onto olefin to afford alkylation or allylation products in good yields.

²⁸ S. Donck, A. Baroudi, L. Fensterbank, J.-P. Goddard, C. Ollivier, *Adv. Synth. Catal.* **2013**, 355, 1477.



Scheme 7. Formation of aryl radicals by photoreduction of sulfonium salts

It also worked with iodonium salts as source of aryl radical. This transformation gave the opportunity to evaluate cheaper and more sustainable alternatives to ruthenium and iridium catalysts. For that purpose, photoactive copper complexes appeared a valuable field of investigation. Copper(I)-biphenanthroline $\text{Cu}(\text{dap})_2^+$ (dap = 2,9-bis(*para*-anisyl)-1,10-phenanthroline) and $\text{Cu}(\text{dpp})_2^+$ (dpp = 2,9-diphenyl-1,10-phenanthroline) that have been reported by McMillin²⁹ raised as promising photoredox catalysts due to their excellent photophysical and redox properties (Scheme 8).³⁰ Indeed, reduction potentials of $\text{Cu}(\text{dap})_2^{+*}$ and $\text{Cu}(\text{dpp})_2^{+*}$ are lower than $\text{Ru}(\text{bpy})_3^{2+*}$ (-1.43 V and -1.11 V respectively vs -0.85 V vs SCE).



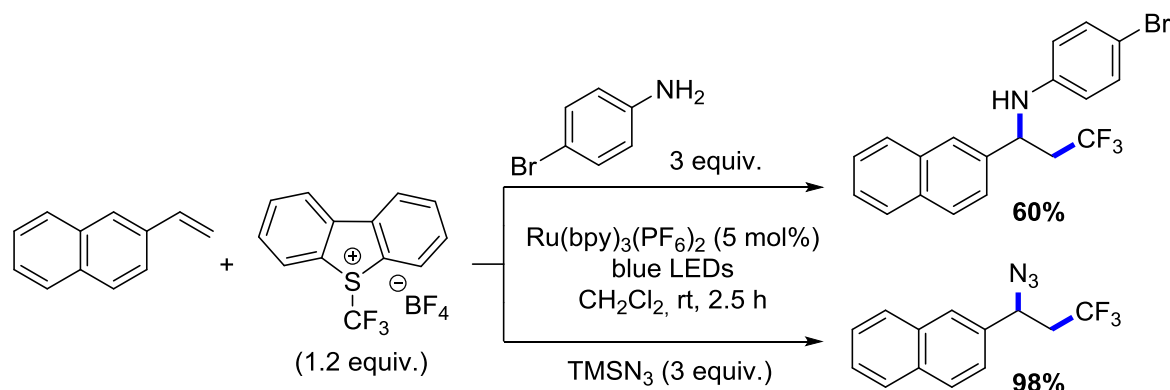
Scheme 8. Reduction of iodonium salts by a photoactive copper complex

Trifluoromethyl radical can be generated by photoreduction of Umemoto's reagent with photoactivated Ruthenium(II) or Iridium(III) photocatalyst and added onto alkenes. For

²⁹ D. R. McMillin, M. T. Buckner, B. T. Ahn, *Inorg. Chem.* **1977**, *16*, 943.

³⁰ N. Armaroli, G. Accorsi, F. Cardinali, A. Listorti, *Top. Curr. Chem.* **2007**, *280*, 69.

instance, radical-cationic MCRs have been reported by Masson for aminotrifluoromethylation of styrene type olefins³¹ and enecarbamates³². In these cases, the intermediate benzylic carbocation, generated after radical addition of the trifluoromethyl radical to the olefin/oxidation, can be trapped intermolecularly by an amine or an azide.



Scheme 9. Aminotrifluoromethylation of styrene

✕ *Reduction of halides*

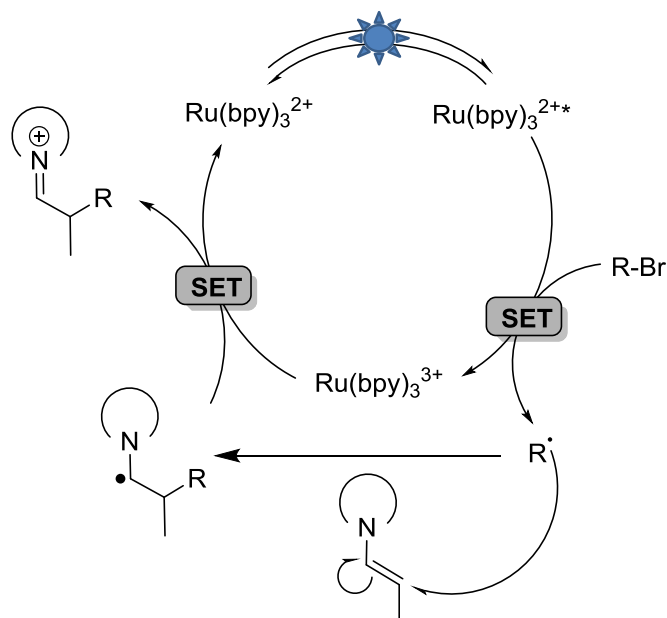
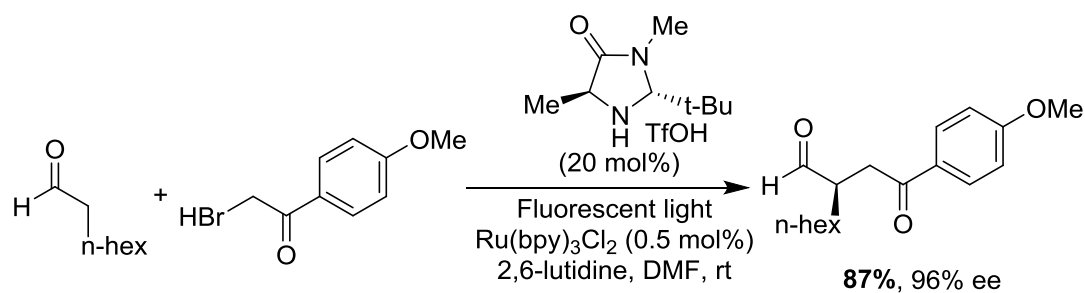
In 1990, Fukuzumi et al.³³ and more recently, MacMillan et al. showed that α -brominated carbonyl derivatives can generate carbon-centered radicals in the presence of catalytic amount of $\text{Ru}(\text{bpy})_3\text{Cl}_2$ during visible light irradiation. In this study, enantioselective α -alkylation of aldehydes was achieved by combining photoredox catalysis and organocatalysis.¹⁴ The catalytic system involves the reduction of the brominated compound by the complex $\text{Ru}(\text{bpy})_3^+$ generating a radical species which adds to an enamine double bond. Under irradiation, the activated $\text{Ru}(\text{II})^*$ complex formed oxidizes the radical adduct to an iminium which is subsequently hydrolyzed. Then, the regenerated $\text{Ru}(\text{bpy})_3^+$ can again participate in the catalytic cycle. An extension to enantioselective α -fluoroalkylation involving generation of fluoroalkyl radicals by photoreduction of the Ir-based catalyst ($[\text{Ir}(\text{dtbbpy})(\text{ppy})_2]^+$) was also reported.³⁴

³¹ G. Dagousset, A. Carboni, E. Magnier, G. Masson, *Org. Lett.* **2014**, *16*, 4340.

³² A. Carboni, G. Dagousset, E. Magnier, G. Masson, *Org. Lett.* **2014**, *16*, 1240.

³³ S. Fukuzumi, S. Mochizuki, T. Tanaka, *J. Phys. Chem.* **1990**, *94*, 722.

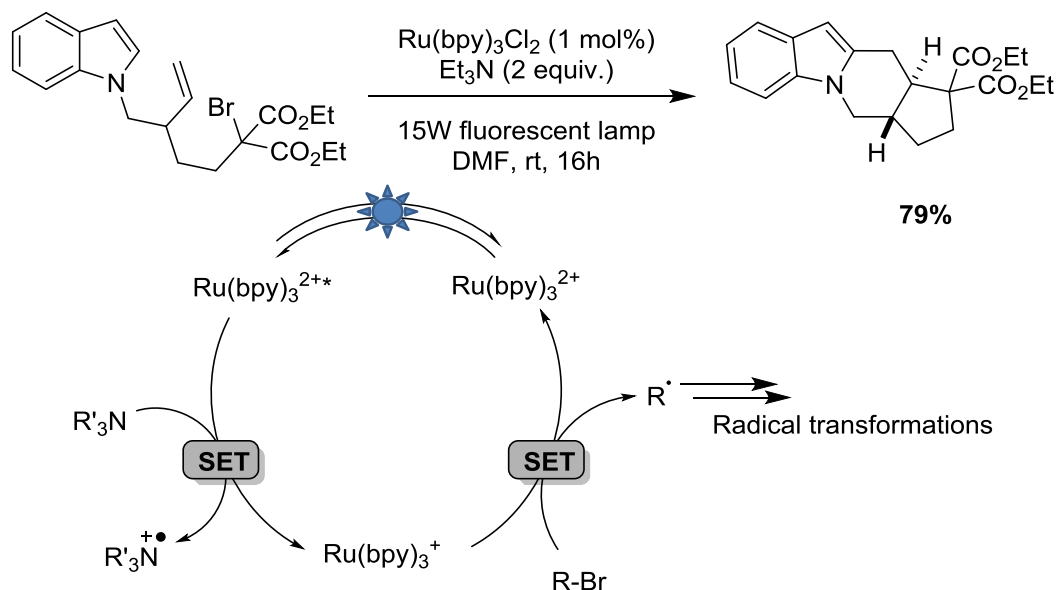
³⁴ D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875.



Scheme 10. Enantioselective α -alkylation of aldehydes

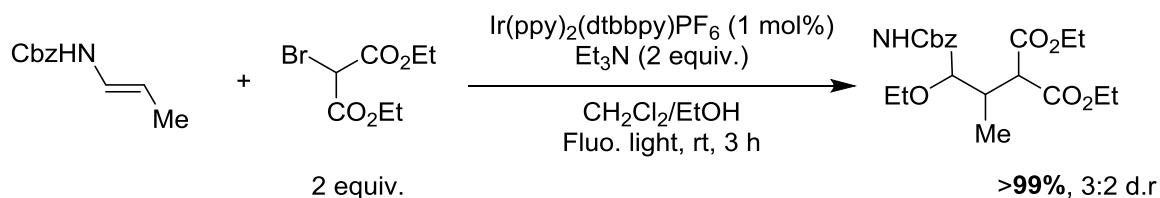
The reduction of the activated complex $[\text{Ru}(\text{bpy})_3^{2+}]^*$ may also be ensured by a tertiary amine such as diisopropylethylamine. Fukuzumi et al.³³ and later Stephenson et al. achieved the reduction of various activated halides. In this case, diisopropylethylamine has dual function as reductant of the activated complex $[\text{Ru}(\text{bpy})_3^{2+}]^*$ and hydrogen atom donor in the presence of formic acid.³⁵ The notion of cascade reactions becomes fully apparent with the construction of polycyclic molecules from polyunsaturated precursors upon a combination of intramolecular radical steps. In scheme 11, Stephenson reported the radical cyclization of a bromomalonate bearing indole and alkene moieties under $\text{Ru}(\text{bpy})_3\text{Cl}_2/\text{Et}_3\text{N}$ (Q_{red}) photoreductive conditions. The malonyl radical undergoes a 5-exo-trig cyclization to a terminal alkene followed by a 6-endo intramolecular homolytic aromatic substitution to an indole affording a tetracyclic alkaloid compound in 79% yield as a single product.³⁵

³⁵ J.W. Tucker, J.D. Nguyen, J.M.R. Narayanam, S.W. Krabbe, C.R.J. Stephenson, *Chem. Commun.* **2010**, 46, 4985.



Scheme 11. Polycyclization of unsaturated bromomalonates

Visible light photoredox catalysis proved to be efficient for promoting radical/cationic multicomponent reactions (MCR_S). Masson examined the reactivity of enecarbamates in combination with diethyl-2-bromomalonate and ethanol and observed the formation of the expected β -alkylated α -amino ethers (Scheme 12).



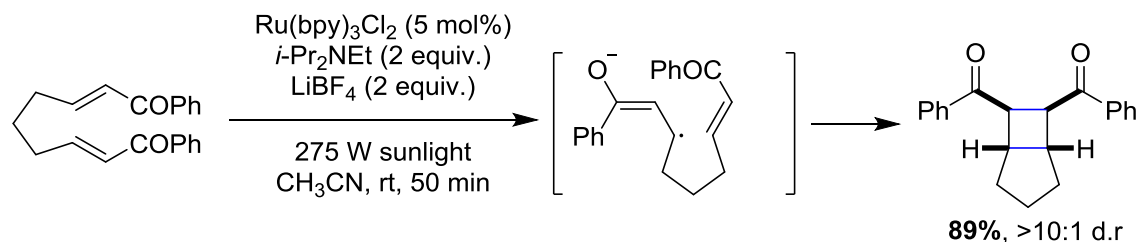
Scheme 12. Three-component radical/cationic oxyalkylation of alkenes

× Reduction of unsaturated ketones

Yoon's group has successfully tested this photoreductive process in intramolecular [2+2] cycloaddition of enones for the construction of bicyclic systems with cyclobutane units.^{16,36} Photoreduction of a lithium-activated enone with the

³⁶ J. Du, T. P. Yoon, *J. Am. Chem. Soc.* **2009**, *131*, 14604.

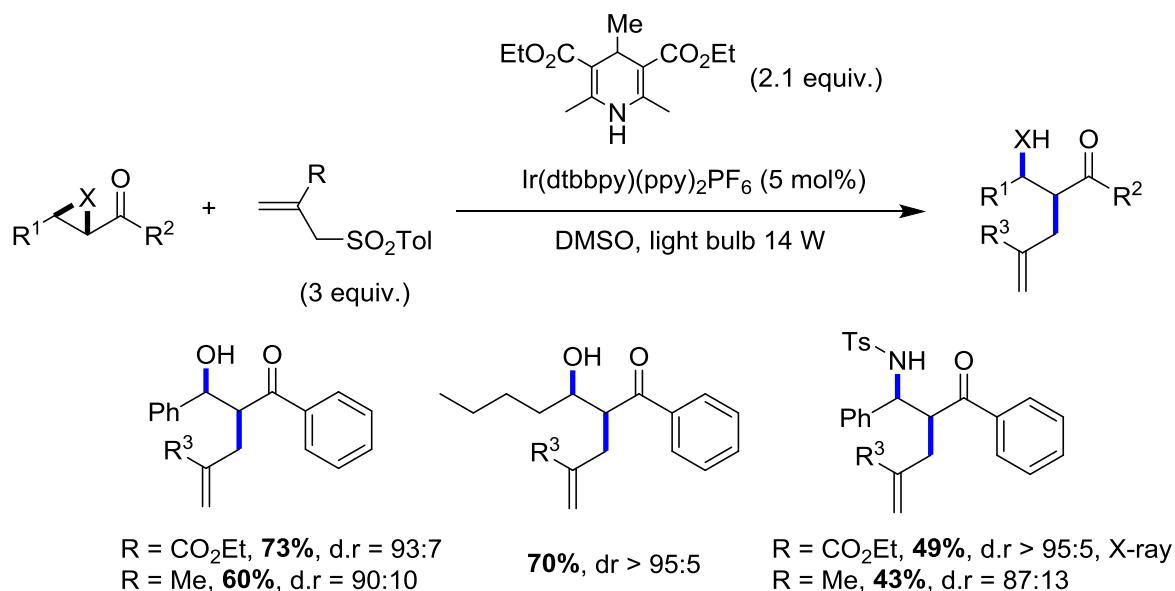
Ru(bpy)₃Cl₂/diisopropylethylamine (**Q_{red}**) system liberates a radical enolate intermediate which triggers a 5-*exo*-trig/4-*exo*-trig cyclization sequence in a diastereoselective manner.



Scheme 13. Intramolecular [2+2] cycloaddition of enones

× Reduction of ketoepoxides or ketoaziridines

Epoxides and aziridines are versatile targets, but a series of works have shown that their photoreduction required an alpha-activation by a carbonyl group.³⁷ Using Hantzsch ester as **Q_{red}** and presumably H donor, good yields of aldol type products or beta-amino keto derivatives could be obtained. Interestingly, the generated radical intermediate from ketoepoxides or -aziridines can be used for further diastereoselective allylation reactions.³⁸



Scheme 14. Reduction of ketoepoxides or ketoaziridines by photoreductive catalysis

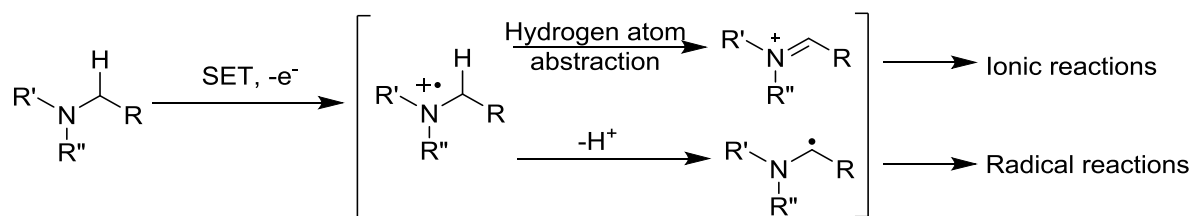
³⁷ E. Hasegawa, S. Takizawa, T. Seida, A. Yamaguchi, N. Yamaguchi, N. Chiba, T. Takahashi, H. Ikeda, K. Akiyama, *Tetrahedron* **2006**, *62*, 6581.

³⁸ M.-H. Larraufie, R. Pellet, L. Fensterbank, J.-P. Goddard, E. Lacôte, M. Malacria, C. Ollivier, *Angew. Chem. Int. Ed.* **2011**, *50*, 4463.

I.B.3.b. Formation involving photooxidative processes

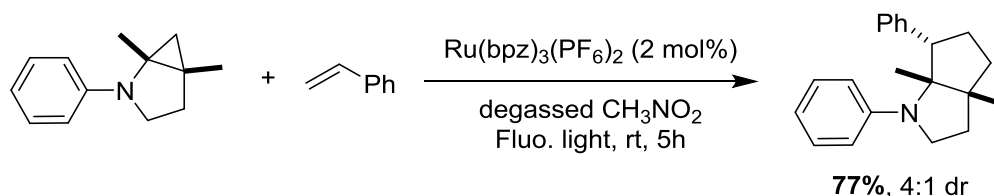
× Oxidation of amines

As already mentioned, tertiary amines are easily oxidized by single electron transfer into radical cations which can be transformed in the corresponding iminium salts by a loss of hydrogen atom or in the α -aminoalkyl radicals by a loss of a proton (Scheme 15). Number of groups have investigated this dual reactivity under photoredox catalysis mediated by visible light.³⁹



Scheme 15. Behavior of aliphatic tertiary amines under oxidative conditions

Zheng and co-workers have shown that cyclopropylamines can participate in radical cascade reactions with activated olefins under photooxidative conditions. The β -carbon radical iminium ion, obtained by oxidation of the bicyclic cyclopropylamine with the photoactivated ruthenium complex and ring opening, can add to the olefin and cyclize to form 5,5-fused bicyclic heterocycles.⁴⁰ Interestingly, the reaction was extended to alkynes, enynes and diynes with success.⁴¹



Scheme 16. Intermolecular [3+2] cycloaddition of a bicyclic cyclopropylamine with styrene

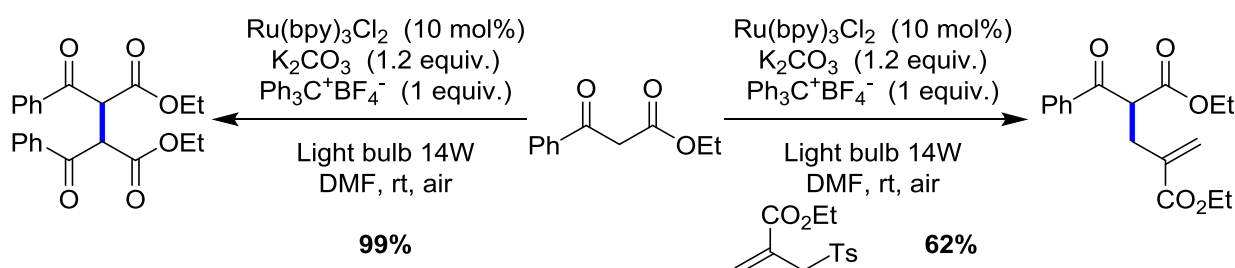
³⁹ J. Hu, J. Wang, T. H. Nguyen, N. Zheng, *Beilst. J. Org. Chem.* **2013**, *9*, 1977.

⁴⁰ S. Maity, M. Zhu, R. S. Shinabery, N. Zheng, *Angew. Chem. Int. Ed.* **2012**, *51*, 222.

⁴¹ T.H. Nguyen, S.A. Morris, N. Zheng, *adv. Synth. Catal.* **2014**, *356*, 2831.

× Oxidation of 1,3-dicarbonyl compounds

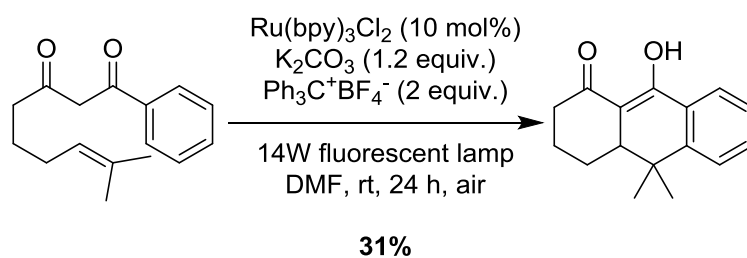
Enols SET oxidation has been extensively studied for the formation of carbon-centered radical, which were involved in intermolecular additions or cyclizations. These processes were generally based on cerium (IV) or manganese (III) and used with overstoichiometric amounts of metal salts. In 2014, our lab reported versatile conditions for intra or intermolecular carbon-carbon bond formations.⁴² Under photoredox catalysis, 1,3-dicarbonyl compounds such as ethyl benzoylacetate dimerized through the formation of intermediate radical species to give 1,3-dicarbonyl dimers in excellent yields. In the presence of a radical acceptor like allylsulfone, allylated products were observed in good yields. Formally resulting from a C-H activation, this transformation proceeded through the oxidation of an enolate to the corresponding stabilized radical.



Scheme 17. Photocatalyzed oxidation of 1,3-diketones

We developed also an intramolecular photocatalytic oxidation process. The carbon centered radical generated from 1,3-dicarbonyl compound can be involved in cascade reactions. Upon treatment with the Ru(bpy)₃Cl₂/O₂ (Q_{ox}) oxidative system in the presence of two equivalents of tritylium Ph₃CBF₄ as a sacrificial acceptor, two examples of cascade reactions have been realized starting from unsaturated phenyldiketones to obtain the tricyclic products with moderate yields.⁴²

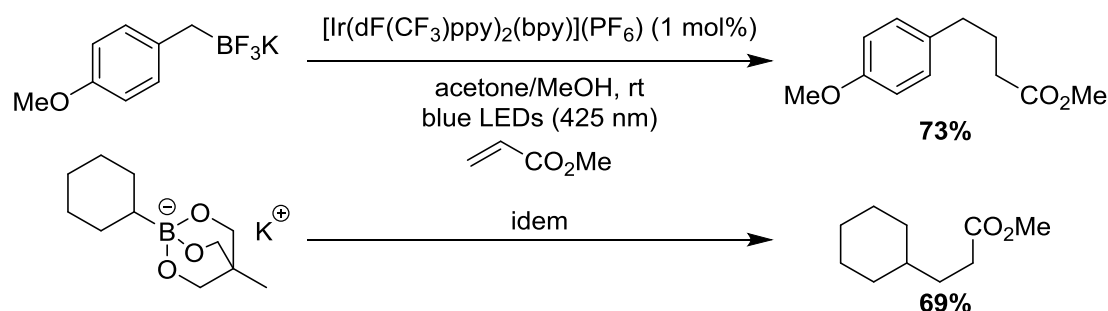
⁴² M. Daniel, L. Fensterbank, J.-P. Goddard, C. Ollivier, *Org. Chem. Front.* **2014**, *1*, 551.



Scheme 18. An intramolecular radical cascade reaction

✕ Oxidation of trifluoroborates

Boron ate-complexes proved to be also precursors of alkyl radicals by SET using stoichiometric amount of oxidant. In 2012, Akita and Koike extend this concept to the use of photoredox catalytic systems (Scheme 19).⁴³ Organotrifluoroborates and organo(triol)borates were investigated, first in the formation of C-O bond through radical trapping experiments with TEMPO and second in C-C bond formation processes with electron-poor olefins. The latest were more effective than trifluoroborate salts for the formation of secondary and primary alkyl and aryl radical. The most efficient catalyst among a set of ruthenium and iridium complexes was $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{bpy})](\text{PF}_6)$, which has the highest oxidation potential at the photoexcited state (+ 0.91 V vs Fc^+/Fc). This is consistent with the fact that no additional **Qox** is needed for this transformation and the organoborate itself is oxidized by the $[\text{Ir}(\text{III})]$ excited state to generate the corresponding alkyl radical and the reduced $[\text{Ir}(\text{II})]$ complex.



Scheme 19. Radical formation by photooxidation of tetraivalent boron compounds

⁴³ Y. Yasu, T. Koike, M. Akita, *Adv. Synth. Catal.* **2012**, 354, 3414.

I.C. Conclusion

The development of catalytic processes and more precisely photocatalytic redox processes using visible light appears quite appealing. For that purpose, a lot of work has relied on the use of $\text{Ru}(\text{bpy})_3^{2+}$ complex which is introduced in catalytic amount. Several photocatalytic developments in the field of a greener chemistry have been also investigated using organic dyes as green photocatalysts. An impressive number of research groups have embarked on this topic providing new ways to conduct ancestral radical organic chemistry. Photocatalysis can really improve reaction conditions and outcomes.

Chapter II
Barton-McCombie Deoxygenation of Alcohols to
Alkanes

II.A. Tin-Free Alternatives to the Barton-McCombie Deoxygenation of Alcohols to Alkanes Involving Reductive Electron Transfer

CHIMIA 2016, 70, 67

II.A.1. Abstract

Echoing the celebration of the fortieth anniversary of the Barton-McCombie reaction, this chapter focuses on another facet of the Barton-McCombie reaction dedicated to the deoxygenation of alcohols by considering SET reduction of carboxylic ester, thiocarbonate and thiocarbamate derivatives. Various methodologies have been developed relying on the use of organic and organometallic SET reagents, electrochemical conditions, photoinduced electron transfer processes and visible-light photoredox catalysis. Applications to the synthesis of molecules of interest provide a glimpse into the scope of these different approaches.

II.A.2. Introduction

Radical chemistry has witnessed an explosive growth over the last three decades. Owing to their mildness and high compatibility with functional groups, radical reactions have been firmly established as reliable and versatile tools for organic synthesis.¹ But the main drawback is associated with the overuse of tin mediators to propagate chain reactions. These reagents are known for being toxic and often associated to non-trivial reaction purifications. Thus, tin residues are often detected in traces eliminating any possibility of radical reactions being used in industry. As pointed out by J. Walton,² it is time to escape from "the tyranny of tin" and to devise valuable alternatives for the generation of radicals. One consists in using stannane derivatives in a catalytic fashion or as supported reagents.³ Another has dealt with the development of tin-free mediators based for instance on silanes, phosphorus derivatives

¹ For a comprehensive account on all aspects of radical chemistry, see: a) "Radicals in Organic Synthesis", Eds. P. Renaud, M. P. Sibi, Wiley-VCH, Weinheim, 2001; b) "Encyclopedia of Radicals in Chemistry, Biology and Materials", Eds. C. Chatgililoglu, A. Studer, John Wiley & Sons, Ltd, Chichester, UK, 2012.

² P. A. Baguley, J. C. Walton, *Angew. Chem. Int. Ed.* 1998, 37, 3072.

³ A. Studer, S. Amrein, *Synthesis* 2002, 835.

and less toxic metals.¹ Interesting perspectives have been opened with the use of organoboranes⁴ and compounds responsible for electron-transfer reactions have been increasingly seen as valuable alternatives to tin radical chemistry.⁵ However, mild and sustainable preparative redox processes limiting the utilization of substoichiometric amounts of metal complexes are still needed. Recently, visible-light photoredox catalysis has emerged as a valuable and efficient tool for the generation of radicals by single electron transfer reactions from an appropriate photocatalyst that absorbs light in the visible region. These conditions have demonstrated their high synthetic potential in various organic redox processes for fine chemical synthesis and contributed at the same time to the development of a greener radical chemistry.⁶

Among the mainstream transformations present in the synthetic toolbox of organic chemists, reduction of alcohols to alkanes has gained a place of choice. Hydroxyl functional groups can indeed participate in the construction of elaborated molecular structures and be removed in due course. However, the hydroxide anion is known as a poor leaving group, homolytic scission of non activated carbon-hydroxyl bonds is not thermodynamically feasible and direct electron transfer reduction of alcohols requires very low negative potentials. A proposed solution was to convert the hydroxyl group to a good leaving group or to a suitable radical precursor. Yet, limitations of deoxygenation by ionic processes were encountered with sterically hindered and/or non-activated secondary and tertiary alcohols.⁷ In 2015, the radical community has celebrated the 40th anniversary of the discovery of the Barton-McCombie deoxygenation reaction, unanimously considered as the most common and important process

⁴ a) C. Ollivier, P. Renaud, *Chem. Rev.* **2001**, *101*, 3415; b) P. Renaud, A. Beauseigneur, A. Brecht-Forster, B. Becattini, V. Darmency, S. Kandhasamy, F. Montermini, C. Ollivier, P. Panchaud, D. Pozzi, E. M. Scanlan, A.-P. Schaffner, V. Weber, *Pure Appl. Chem.* **2007**, *79*, 223.

⁵ a) P. I. Dalko, *Tetrahedron* **1995**, *51*, 7579; b) U. Jahn in "Top. Curr. Chem., Radicals in Organic Synthesis, Vol. 3", Eds. M. Heinrich, A. Gansäuer, Wiley-VCH, Weinheim **2012**, Vol. 320, p. 121, 191 and 323; c) A. Gansäuer, H. Bluhm, *Chem. Rev.* **2000**, *100*, 2771.

⁶ For selected reviews, see: a) J. M. R. Narayanaman, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102; b) F. Teplý, *Collect. Czech. Chem. Commun.* **2011**, *76*, 859; c) J. Xuan, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2012**, *51*, 6828; d) M. A. Ischay, T. P. Yoon, *Eur. J. Org. Chem.* **2012**, 3359; e) L. Shi, W. Xia, *Chem. Soc. Rev.* **2012**, *41*, 7687; f) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322; g) D. P. Hari, B. König, *Angew. Chem. Int. Ed.* **2013**, *52*, 4734; h) M. Reckenthäler, A. G. Griesbeck, *Adv. Synth. Catal.* **2013**, 355, 2727; i) T. Koike, M. Akita, *Synlett* **2013**, *24*, 2492; j) J. Xuan, L.-Q. Lu, J.-R. Chen, W.-J. Xiao, *Eur. J. Org. Chem.* **2013**, 6755; k) J. Hu, J. Wang, T. H. Nguyen, N. Zheng, *Beilstein J. Org. Chem.* **2013**, *9*, 1977; l) M. N. Hopkinson, B. Sahoo, J.-L. Li, F. Glorius, *Chem. Eur. J.* **2014**, *20*, 3874; m) D. M. Schultz, T. P. Yoon, *Science* **2014**, *343*, 985. For recent books, see: n) "Chemical Photocatalysis", Ed. B. König, DeGruyter, Berlin, **2013**; o) "Photochemically generated intermediates in Synthesis", Eds. A. Albini, M. Fagnoni, John Wiley & Sons, Hoboken, **2013**.

⁷ a) S. W. McCombie, in "Comprehensive Organic Synthesis", Eds. B. Trost, I. Fleming, Pergamon Press, New York, **1991**, Vol. 8, p. 811; b) L. Chenneberg, J.-P. Goddard, L. Fensterbank, in "Comprehensive Organic Synthesis (2nd Edition)", Eds. G. Molander, P. Knochel, Elsevier, Oxford, **2014**, Vol. 8, p. 1011.

to perform such type of transformation.⁸ Originally, this approach was based first on the activation of a secondary or tertiary alcohol as a thiocarbonate or thiocarbamate precursor including the well-known xanthate followed by its subsequent reduction to alkane through a $n\text{Bu}_3\text{SnH/AIBN}(\text{cat})$ -mediated radical chain process under thermal conditions (Scheme 1, eq. 1). Several improvements have been achieved by replacing the tin mediator with silicon hydrides,^{3,9} cyclohexadienyl compounds,¹⁰ phosphorous reagents,¹¹ organoboranes^{4,12} or DLP/isopropanol.¹³ In parallel, a great deal of effort has been devoted to the development of single electron transfer (SET) processes whose major advances will be highlighted in this brief review and will complement a former published by Hartwig in 1983.¹⁴ Specific focus will be laid on reduction of alcohols to alkanes with emphasis on Barton-McCombie type deoxygenations of alcohol derivatives involving SET reduction of carbonyl and thiocarbonyl-based functional groups. For that purpose, different methods using organic and organometallic SET reagents, electrochemical conditions and photoinduced electron transfer (PET) processes under UV light irradiation or by visible-light photoredox catalysis will be presented (Scheme 1, eq. 2). Applications to the synthesis of molecules of interest such as natural products will also be displayed.

⁸ a) D. H. R. Barton, S. W. McCombie, *J. Chem. Soc., Perkin Trans. I* **1975**, 1574. For reviews, see: b) D. Crich, L. Quintero, *Chem. Rev.* **1989**, *89*, 1413; c) S. W. McCombie, W. B. Motherwell, M. J. Tozer, *Org. React.* **2012**, *77*, 161.

⁹ a) D. H. R. Barton, D. O. Jang, J. C. Jaszberenyi, *Tetrahedron* **1993**, *49*, 2793; b) D. H. R. Barton, D. O. Jang, J. C. Jaszberenyi, *Tetrahedron* **1993**, *49*, 7193; c) M. Oba, K. Nishiyama, *Tetrahedron* **1994**, *50*, 10193; d) D. O. Jang, J. Kim, D. H. Cho, C.-M. Chung, *Tetrahedron Lett.* **2001**, *42*, 1073; e) J. Kim, D. H. Cho, D. O. Jang, *Tetrahedron Lett.* **2004**, *45*, 3031; f) M. Oba, K. Nishiyama, *Chem. Commun.* **1994**, 1703. For review on the use of silanes, see: g) "Organosilanes in Radical Chemistry", Ed. C. Chatgililoglu, John Wiley & Sons Ltd, Chichester, **2004**.

¹⁰ Silylated-cyclohexadienyl compounds: A. Studer, S. Amrein, *Angew. Chem. Int. Ed.* **2000**, *39*, 3080.

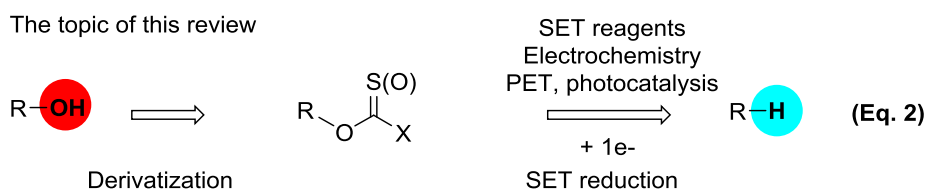
¹¹ a) D. O. Jang, D. H. Cho, D. H. R. Barton, *Synlett* **1998**, 39; b) A. E. Graham, A. V. Thomas, R. Yang, *J. Org. Chem.* **2000**, *65*, 2583; c) J. Boivin, R. Jrad, S. Juge, V. T. Nguyen, *Org. Lett.* **2003**, *5*, 1645.

¹² Phosphine-borane complexes: a) D. H. R. Barton, M. Jacob, *Tetrahedron Lett.* **1998**, *39*, 1331; b) D. A. Spiegel, K. B. Wiberg, L. N. Schacherer, M. R. Medeiros, J. L. Wood, *J. Am. Chem. Soc.* **2005**, *127*, 12513; c) G. A. Nishiguchi, R. D. Little, *J. Org. Chem.* **2005**, *70*, 5249; d) M. K. Kreilein, J. E. Hofferberth, A. C. Hart, L. A. Paquette, *J. Org. Chem.* **2006**, *71*, 7329. NHC-borane complexes: e) S.-H. Ueng, M. Makhlof-Brahmi, E. Derat, L. Fensterbank, E. Lacôte, M. Malacria, D. P. Curran, *J. Am. Chem. Soc.* **2008**, *130*, 10082; f) A. Solovyev, S.-H. Ueng, J. Monot, L. Fensterbank, M. Malacria, E. Lacôte, D. P. Curran, *Org. Lett.* **2010**, *12*, 2998; g) S.-H. Ueng, L. Fensterbank, E. Lacôte, M. Malacria, D. P. Curran, *Org. Lett.* **2010**, *12*, 3002. For a review on the use of NHC-boranes, see: h) D. P. Curran, A. Solovyev, M. Makhlof-Brahmi, L. Fensterbank, M. Malacria, *Angew. Chem. Int. Ed.* **2011**, *50*, 10294. For deoxygenation initiated by Et_3B , see: i) J. Boivin, V. T. Nguyen, *Beilstein J. Org. Chem.* **2007**, *3*, 1; j) J. Boivin, V. T. Nguyen, *Beilstein J. Org. Chem.* **2007**, *3*, doi:10.1186/1860-5397-3-47; k) F. Allais, J. Boivin, V. T. Nguyen, *Beilstein J. Org. Chem.* **2007**, *3*, doi:10.1186/1860-5397-3-46.

¹³ A. Liard, B. Quiclet-Sire, S. Z. Zard, *Tetrahedron Lett.* **1996**, *37*, 5877.

¹⁴ W. Hartwig, *Tetrahedron* **1983**, *39*, 2609.

Classical Barton-McCombie type-Radical Deoxygenation



Scheme 1. SET reduction of carbonyl and thiocarbonyl-based functional groups: Tin-free alternatives to the classical Barton-McCombie deoxygenation reaction of alcohols to alkanes

II.A.3. Metal-Promoted Deoxygenation

Low valent metals such as alkali metals behave as good electron donors towards organic compounds. Owing to their high negative potential, these have been widely exploited in Organic Synthesis for electron transfer reduction of a range of functional groups including carbonyl moieties. The earliest observations date back to the beginning of the nineteenth century with successively the so-called Bouveault-Blanc reduction of carboxylic esters to alcohols by excess of sodium in ethanol (or amyl alcohol)¹⁵ and their bimolecular reductive coupling in refluxing aprotic solvents, better known as acyloin condensation.¹⁶ Both involved formation of a common ketyl-like radical anion intermediate subsequent to electron transfer. Over the years, some other unexpected reactivities have been observed. In the sixties, two different groups reported independently the uncanny ability of allylic¹⁷ and β -keto acetates¹⁸ to be reduced to alkanes by dissolving metals (Li or Ca in liquid ammonia). Later, Stetter and Lehmann examined the behaviour of allyl and benzyl benzoates upon reductive treatment

¹⁵ a) L. Bouveault, G. Blanc, *C. R. Acad Sci Paris* **1903**, 136, 1676; b) L. Bouveault, G. Blanc, *C. R. Acad Sci Paris* **1903**, 137, 60 and 328; c) L. Bouveault, G. Blanc, *Bull. Soc. Chim. Fr.* **1903**, 29, 787. d) L. Bouveault, G. Blanc, *Bull. Soc. Chim. Fr.* **1904**, 31, 666, 1206 and 1213.

¹⁶ a) L. Bouveault, R. Locquin, *C. R. Acad. Sci. Paris* **1905**, 140, 1593. L. Bouveault, R. Locquin, *Bull. Soc. Chim. Fr.* **1906**, 35, 629; b) S. M. McElvain, *Org. React.* **1948**, 4, 256. K. T. Finley, *Chem. Rev.* **1964**, 64, 573; c) J. J. Bloomfield, D. C. Owsley, C. Ainworth, R. E. Robertson, *J. Org. Chem.* **1975**, 40, 393.

¹⁷ a) P. Bladon, H. B. Henbest, E. R. H. Jones, B. J. Lovell, G. F. Woods, *J. Chem. Soc.* **1954**, 125. b) A. S. Hallsworth, H. B. Henbest, T. I. Wrigley, *J. Chem. Soc.* **1957**, 1969.

¹⁸ J. H. Chapman, J. Elks, G. H. Phillipps, L. J. Wyman, *J. Chem. Soc.* **1956**, 4344.

with sodium. In this case, the transient radical anion of benzoates was supposed to undergo a β -fragmentation and expel an allyl or benzyl radical which should dimerize.¹⁹

In the same line, Boar, Barton *et al.* designed a selective method of deoxygenation of sterically hindered of secondary and tertiary alcohols to alkanes relying on the reduction of the corresponding acetates by alkali metals dissolved in amines. Two protocols involving either lithium in diethylamine or potassium solubilized by 18-crown-6 ether in *tert*-butylamine have been established and, applied for instance to the chemoselective cleavage of 6β and 12α acetates in $3\beta,6\beta$ -diacetoxy- 5α -cholestane and $3\beta,12\alpha$ -diacetoxy- 13α -oleanane respectively. Conversely, less hindered acetates such as these at the 3β position are more likely to regenerate the original hydroxyl groups. It means that the degree of selectivity is strongly related to the difference of steric environments (Scheme 2, eq. 1).²⁰ This methodology was applied to the synthesis of various natural products such as (-)-trichodiene²¹ using the Li/EtNH₂ system (Scheme 2, eq. 2), (-)-cladiella-6,11-dien-3-ol and its derivatives²² (Scheme 2, eq. 3) and (\pm)-Tormesol with K/18-C-6 in tBuNH₂/THF²³ (Scheme 2, eq. 4). A modified protocol with lithium/*t*-BuOH in liquid ammonia was used by Mander *et al.* in the synthesis of C20 gibberellins.²⁴

¹⁹ H. Stetter, K.-A. Lehmann, *Liebigs Ann. Chem.* **1973**, 499.

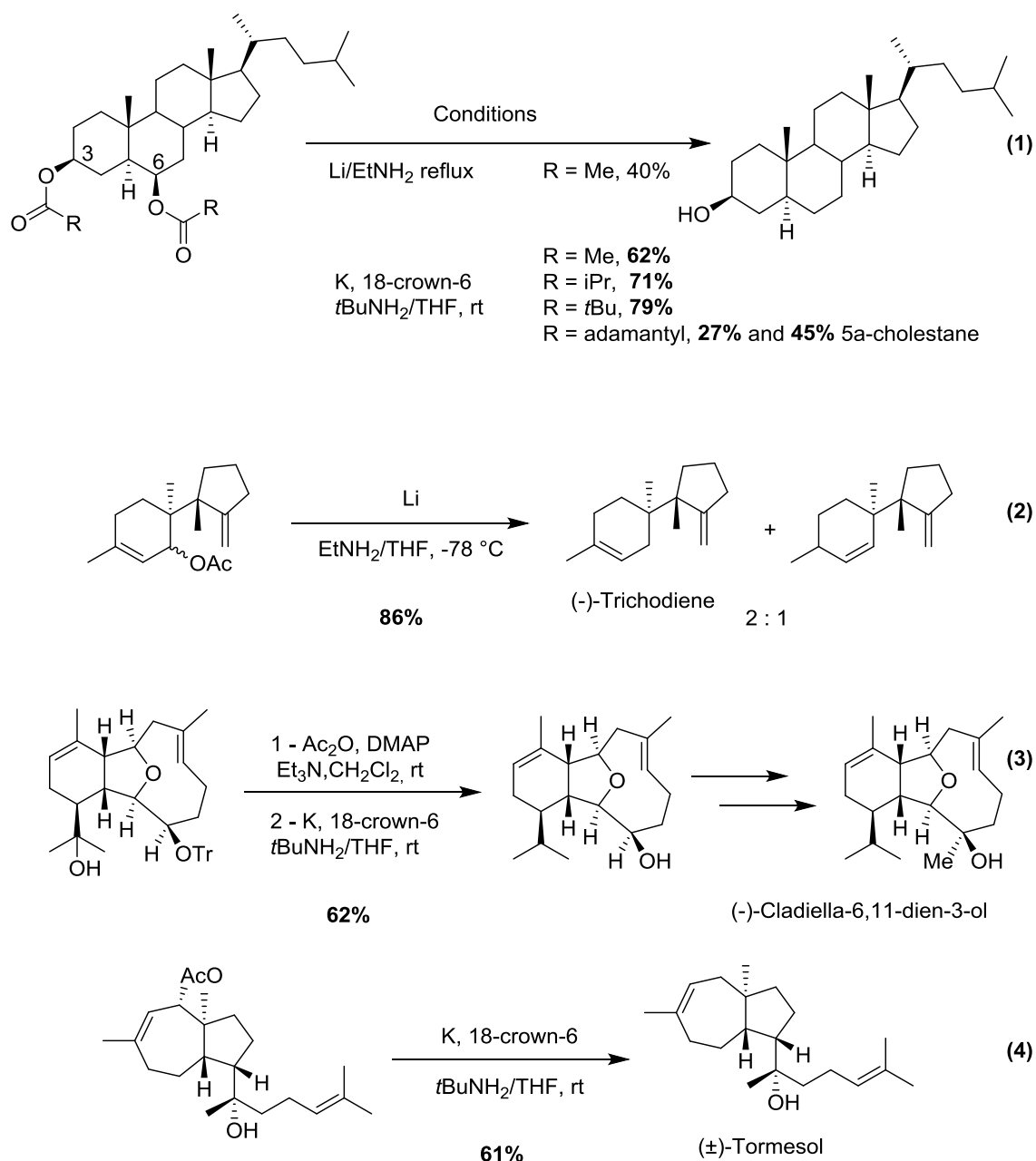
²⁰ R. B. Boar, L. Joukhadar, J. F. McGhie, S. C. Misra, A. G. M. Barrett, D. H. R. Barton, P. A. Prokopiou, *J. Chem. Soc., Chem. Commun.* **1978**, 68.

²¹ J. C. Gilbert, R. D. Selliah, *J. Org. Chem.* **1993**, 58, 6255.

²² a) H. Kim, H. Lee, J. Kim, S. Kim, D. Kim, *J. Am. Chem. Soc.* **2006**, 128, 15851; b) J. S. Clark, R. Berger, S. T. Hayes, L. H. Thomas, A. J. Morrison, L. Gobbi, *Angew. Chem. Int. Ed.* **2010**, 49, 9867.

²³ H. Kim, H. Bae, S. Kim, D. Kim, D. Lee, R. S. Paton, *Tetrahedron* **2011**, 67, 10017.

²⁴ R. D. Dawe, L. N. Mander, J. V. Turner, P. Xinfu, *Tetrahedron Lett.* **1985**, 26, 5725.

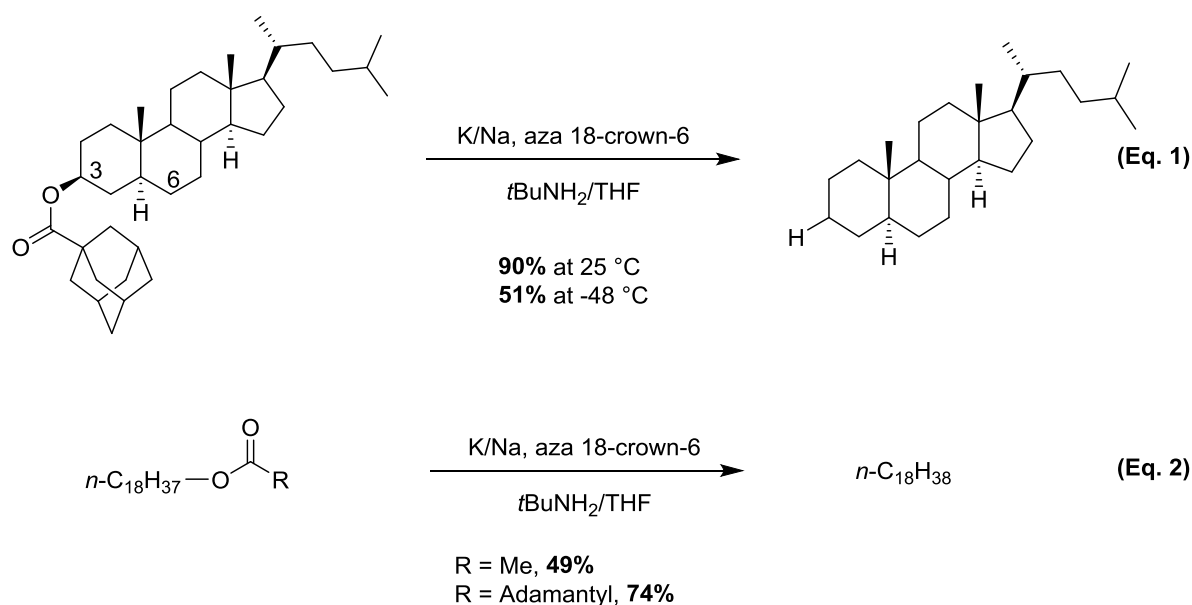


Scheme 2. Deoxygenation of sterically hindered secondary and tertiary alcohols by SET reduction of acetates with dissolving lithium and potassium

Further optimization of the reaction conditions and mechanistic studies were undertaken by Barrett, Barton *et al.*²⁵ They particularly showed that increasing the bulk of the acyl substituent from methyl to isopropyl, to *tert*-butyl and to adamantyl enhances the yield in deoxygenation products (Scheme 2, eq. 1). Running reactions in *tert*-butylamine or 1,2-

²⁵ a) A. G. M. Barrett, P. A. Prokopiou, D. H. R. Barton, R. B. Boar, J. F. McGhie, *J. Chem. Soc., Chem. Commun.* **1979**, 1173; b) A. G. M. Barrett, C. R. A. Godfrey, D. M. Hollinshead, P. A. Prokopiou, D. H. R. Barton, R. B. Boar, L. Joukhadar, J. F. McGhie, S. C. Misra, *J. Chem. Soc., Perkin Trans. 1* **1981**, 1501; c) D. H. R. Barton, W. B. Motherwell, *Pure and Appl. Chem.* **1981**, 53, 1081.

dimethoxyethane with THF as a co-solvent is more suitable than in nucleophilic solvent such as diethylamine for impeding competitive amidolysis of acetates and regeneration of the starting alcohol. Moreover, deacylation may also be caused by the presence of “adventitious” water and by crown ether-derived nucleophile generated by degradation along the process. Thus, a new reduction system based on the use of the eutectic potassium/sodium alloy solubilized by the aza 18-crown-6 1,4,7,10,13,16-hexamethyl-1,4,7,10,13,16-hexaazacyclooctadecane in *tert*-butylamine/THF was developed and allowed the reduction of both hindered and non-hindered esters including primary esters. As examples, reduction of 5 α -cholestan-3 β -yl and octadecyl adamantane-1-carboxylates gave the products of deoxygenation in 90% and 74% yields respectively, but in the former case a Bouveault-Blanc reduction predominates at lower temperature (Scheme 3).

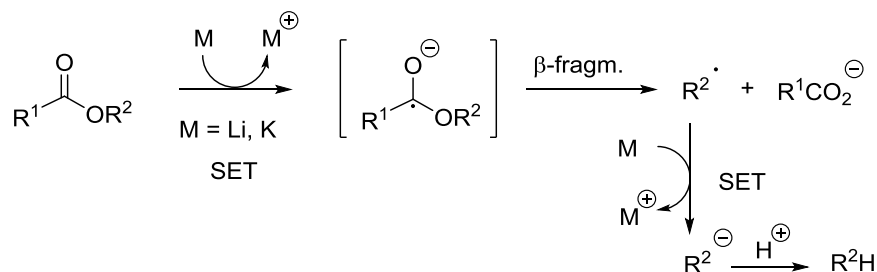


Scheme 3. Reduction of both hindered and non-hindered esters with eutectic potassium/sodium alloy solubilized by the aza 18-crown-6

These experiments are fully consistent with a mechanism that involves one electron transfer from dissolving metals to carboxylic ester, followed by formation of a ketyl-radical anion intermediate which fragments spontaneously leading to an alkyl radical and a carboxylate anion, an elementary step supported by *ab initio* calculations.²⁶ Then, the expelled radical is in turn reduced to a carbanion and protonated subsequently to afford the alkane

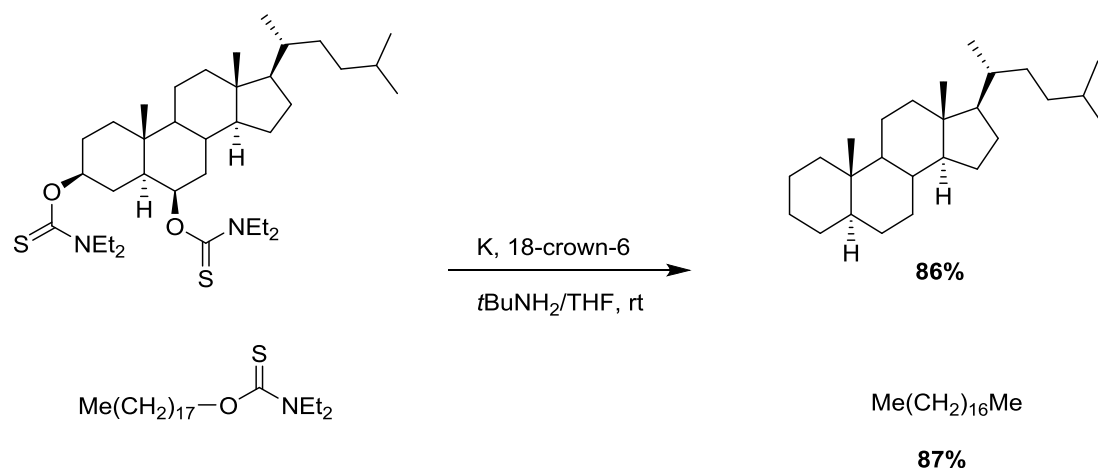
²⁶ P. Cremaschi, G. Morosi, M. Simonetta, *Angew. Chem. Int. Ed. Engl.* **1981**, 20, 673

(Scheme 4). These conclusions are in accordance with previous studies reported by Pete *et al.* on photoreduction of acetate and benzoate esters to alkanes in hexamethylphosphoramide (HMPA) and water (*vide infra*).



Scheme 4. A plausible mechanism for the reduction of carboxylic esters by dissolving metals

In parallel, Barrett, Prokopiou and Barton presented an interesting extension of their previous works to the deoxygenation of non-hindered primary and secondary alcohols. They found that more stable precursors such as N,N'-dialkylthiocarbamates, and precisely N,N'-diethylthiocarbamates, can be reduced to alkanes with potassium solubilized by 18-crown-6 ether in *tert*-butylamine/THF (Scheme 5) whereas S-methyl dithiocarbonate and N-monoalkylthiocarbamate compounds are precluded because the transformation becomes less effective. They also observed that low temperatures (-30 °C) have a detrimental effect on deoxygenation. Finally, a similar mechanism to that of carboxylic esters was considered.²⁷



Scheme 5. Deoxygenation of non-hindered primary and secondary alcohols by SET reduction of N,N'-diethylthiocarbamates with dissolving potassium

²⁷ A. G. M. Barrett, P. A. Prokopiou, D. H. R. Barton, *J. Chem. Soc., Chem. Commun.* **1979**, 1175.

At the same time, inspired by their successful results on photoreduction of carboxylic esters by photoactivated HMPA (*vide infra*), Deshayes and Pete have disclosed a more general but less selective protocol for the reduction of primary, secondary and tertiary carboxylic esters to alkanes which relies on the use of sodium in hexamethylphosphoramide (HMPA) as a reductive agent and *tert*-butanol as a proton source. As previously observed, the overall efficiency and selectivity of the deoxygenation process is highly dependent on the steric environment provided by the alcohol and the carboxylic acid residues. While homolytic scission of hindered tertiary esters to alkanes is almost quantitative in 5 min at room temperature, reductive cleavage of less hindered primary and secondary esters is partly achieved and the deoxygenated products are isolated in good to moderate yields along with the starting alcohols (Scheme 6, eq. 1).²⁸ Of particular importance is the presence of *tert*-butanol that ensures an optimal conversion in alkanes. Mechanistic investigations indicates the radical anion [HMPA]^{•-} generated from HMPA and sodium and described by Normant *et al.*,²⁹ is capable to reduce the ester carbonyl and form a classical ketyl-like radical-anion. Its fragmentation to a carbon-centered radical and a carboxylate anion turned out to be related to its stability, the steric hindrance of both alkyl residues and the solvation of the anion moiety by *tert*-butanol which accelerates the homolytic scission. As confirmed by deuterium labeling experiments, the process ends up with the formation of the alkane mainly obtained by reduction of the generated radical to a carbanion and its subsequent protonation by *tert*-butanol, and a small amount by abstraction of a hydrogen atom to HMPA. To explain the presence of alcohol, hydrolysis, amidolysis and transesterification reactions of carboxylic esters have been suggested.³⁰ Finally, extensive investigations have confirmed the high potential of thiocarbamates to participate in deoxygenation processes, as already observed in reduction studies with K/18-crown-6 ether (*vide supra*) and in photoreduction (*vide infra*).³¹ Starting from acetates or thiocarbamates, the method found applications in the synthesis of pentalene (Scheme 6, eq. 2)³² and (+)-taxadiene (Scheme 6, eq. 3).³³

²⁸ H. Deshayes, J.-P. Pete, *J. Chem. Soc., Chem. Commun.* **1978**, 567.

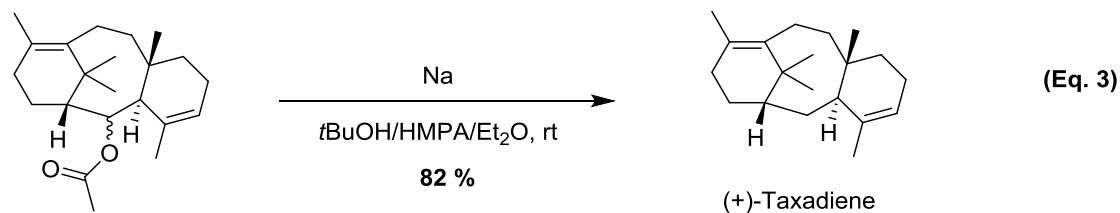
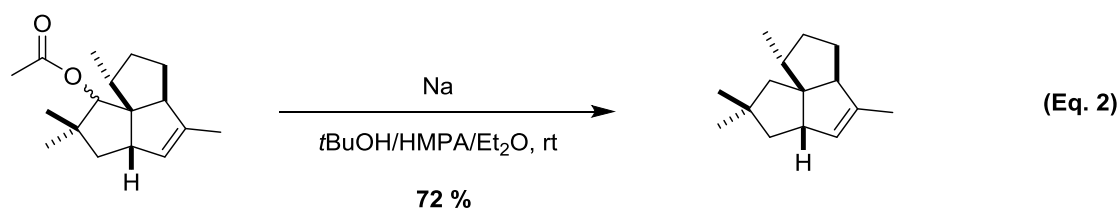
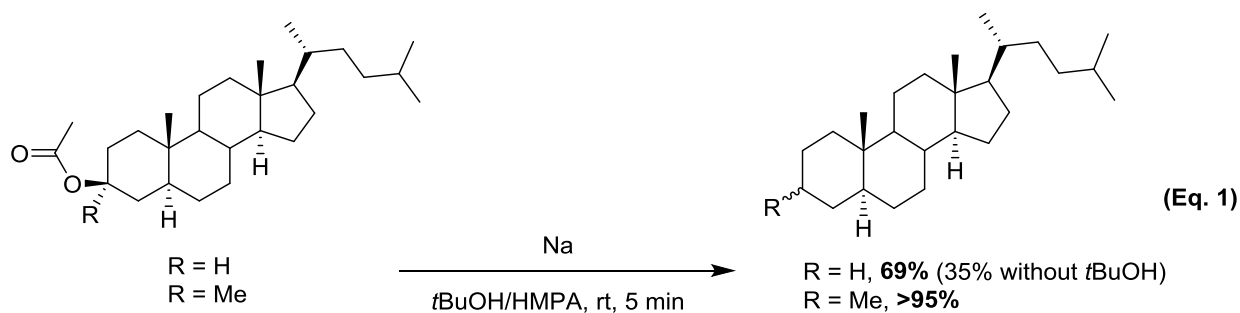
²⁹ a) H. Normant, *Bull. Soc. Chim. Soc.* **1968**, 791; b) H. Normant, *Angew. Chem. Int. Ed.* **1967**, *6*, 1046.

³⁰ H. Deshayes, J.-P. Pete, *Can. J. Chem.* **1984**, 2063.

³¹ a) Y. A. Dembélé, H. Deshayes, J.-P. Pete, *Tetrahedron Lett.* **1982**, *23*, 3489; b) A. Dembélé, H. Deshayes, J.-P. Pete, *Bull. Soc. Chim. Fr.* **1988**, 671.

³² L. A. Paquette, F. Geng, *Org. Lett.* **2002**, *4*, 4547.

³³ a) A. Mendoza, Y. Ishihara, P. S. Baran, *Nature Chem.* **2012**, *4*, 21; b) Y. Ishihara, A. Mendoza, P. S. Baran, *Tetrahedron* **2013**, *69*, 5685.



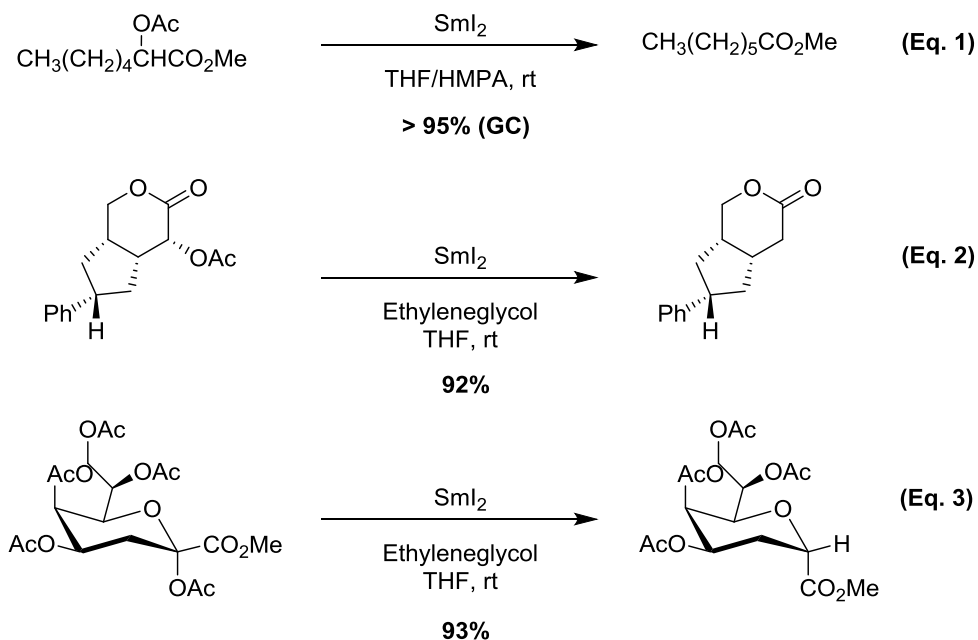
Scheme 6. Deoxygenation of primary, secondary and tertiary alcohols by reduction of acetates and N,N' -dimethylthiocarbamates with sodium/HMPA

Samarium(II) diiodide has been of paramount importance in the development of deoxygenation processes since in combination with HMPA it proved to be an efficient SET reagent for reduction of acetate and benzoate esters. In 1989, Inanaga *et al.* reported appropriate conditions for almost quantitative reduction of α -acetoxy esters to saturated esters with the system SmI_2/HMPA in THF in the presence of MeOH (or EtOH) as a proton source in less than 5 min (Scheme 7, eq. 1).³⁴ Somewhat related is the reductive cleavage of acetate groups at the α -position of γ - and δ -lactones (Scheme 7, eq. 2), which surprisingly does not require the use of HMPA,³⁵ and at the anomeric position of ulosonic acid derivatives (Scheme

³⁴ K. Kusuda, J. Inanaga, M. Yamaguchi, *Tetrahedron Lett.* **1989**, 30, 2945.

³⁵ a) J. Inanaga, J. Katsuki, M. Yamaguchi, *Chem. Lett.* **1991**, 20, 1025. b) S. Hanessian, C. Girard, J. L. Chiara, *Tetrahedron Lett.* **1992**, 33, 573.

7, eq. 3).³⁶ In the same vein, formation of carbon-carbon bond can be realized by homolytic scission of an activated acetate or benzoate ester followed by SET reduction of the transient radical and subsequent addition of the generated alkylsamarium to a carbonyl compound.³⁷



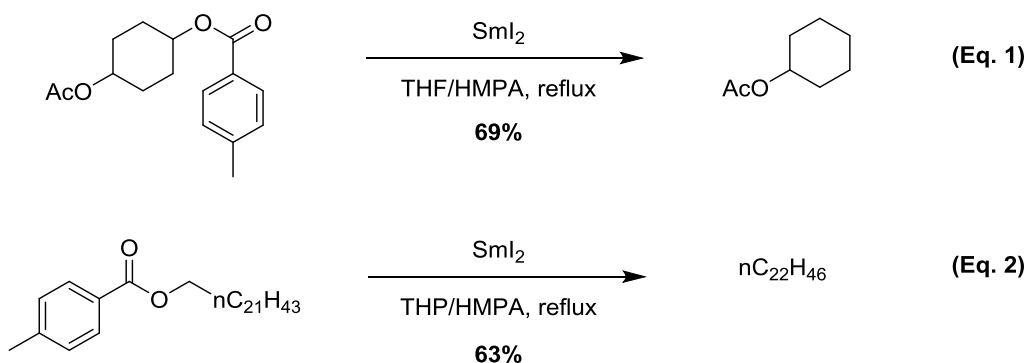
Scheme 7. Reduction of α -acetoxy esters with samarium diiodide

More recently, Markó *et al.* have extended the scope of this process to deoxygenation of non-activated primary, secondary and tertiary alkyl toluates by adding the substrate to a refluxing solution of SmI_2/HMPA in THF (or THP) and for a reaction time up to 5 minutes. Intramolecular cyclizations have also been performed under these modified reductive conditions which proved compatible with alcohol, TBDMS ether, acetal, acetate and amide functional groups (Scheme 8). Mechanism is assumed to involve formation of a toluate radical anion by SET reduction followed by its fragmentation to a carboxylate and an alkyl radical. Then, the alkane is formed by hydrogen abstraction. The rate of decomposition is related to the stability of the intermediate which depends on the nature of the residue (allyl>tertiary>secondary>primary) and the substitution of the aromatic (toluate>benzoate).³⁸

³⁶ S. Hanessian, C. Girard, *Synlett* **1994**, 863.

³⁷ a) E. J. Enholm, S. Jiang, *Tetrahedron Lett.* **1992**, 33, 6069; b) E. J. Enholm, S. Jiang, K. Abboud, *J. Org. Chem.* **1993**, 58, 4061; c) A. Malapelle, Z. Abdallah, G. Doisneau, J.-M. Beau, *Angew. Chem. Int. Ed.* **2006**, 45, 6016.

³⁸ a) K. Lam, I. E. Markó, *Org. Lett.* **2008**, 10, 2773; b) K. Lam, I. E. Markó, *Tetrahedron* **2009**, 65, 10930.



Scheme 8. Reduction of toluate esters with samarium diiodide

II.A.4. Electrochemical Deoxygenation

Electrochemical processes have proven to be some of the most economical and eco-friendly methods of achieving redox synthetic transformations since the unique source of electron is the current.³⁹ In particular, electroreduction of organic halides and carbonyl compounds has been widely studied compared to the reductive cleavage of alcohols which required high negative potential. To realize such deoxygenation processes, alcohols have been converted into acetates, oxalates or toluates prior being electrochemically reduced.

Early research studies on this subject began in 1960 with the polarographic reduction of 2-acetoxyacetophenone to acetophenone by Henning Lund.⁴⁰ Ten years after, Utley *et al.* have been interested in the reductive electrolysis of para-methoxycarbonyl benzylacetate at a lead cathode in a methanol solution of tetra-*n*-butylammonium acetate as the supporting electrolyte. When a potential of -1.8 V *vs.* SCE is applied, the corresponding methyl para-toluate was obtained in 95% yield and with a good current efficiency. It is worthy of note that under these conditions, the cathodic reduction of acetoxyacetophenone is not chemoselective and leads to a mixture of acetophenone (20%) and 1-phenylethanol (54%), which results from the cleavage of the benzylic carbon-oxygen bond and the subsequent reduction of the carbonyl group.⁴¹ Logically, the behavior of allylic acetates was then examined. A preparative electrolysis of vitamin A acetate at a mercury pool cathode was performed in an acetonitrile solution of tetra-*n*-butylammonium acetate and acetic acid as a proton source at a controlled potential (-1.35V *vs.* Ag/AgI) and delivered axerophthene in 71% yield after the passage of

³⁹ "Organic Electrochemistry, 4th ed.", Eds. H. Lund, O. Hammerich, Marcel Dekker: New York, **2001**.

⁴⁰ H. Lund, *Acta Chem. Scand.* **1960**, *14*, 1929.

⁴¹ a) J. P. Coleman, H. G. Gilde, J. H. P. Utley, B. C. L. Weedon, *J. Chem. Soc. D* **1970**, 738; b) J. P. Coleman, Naser-ud-din, H. G. Gilde, J. H. P. Utley, B. C. L. Weedon, L. Ebersson, *Chem. Commun.* **1973**, 1903.

2 F/mol of current.⁴² Also, as shown by Tsujimoto *et al.*, electrochemical reduction of 3-(2-naphthyl)-2-butenyl acetate at a platinum cathode gave (*E*)-2-(2-naphthyl)-2-butene in 73% yield.⁴³ In 2002, Frontana-Urbe *et al.* explored the ability of the electrogenerated tetrabutylammonium-mercury amalgam to reduce aliphatic acetates. For instance, electroreduction of diosgenin acetate under a constant current (5 mA, 2.1 F/mol) gave rise to a ca. 1:1 ratio of alkane and alcohol, and the deoxygenated product could be isolated in 53% yield. These results are comparable with those obtained using alkaline metals and a similar mechanism involving a ketyl-like radical-anion formation and fragmentation can be proposed (*vide supra*).⁴⁴

In that vein, oxalate esters exhibit a propensity to undergo reductive cleavage of carbon-oxygen bond from alcohols at lower negative potentials (ca -1.2 vs. Ag/AgI). Electron transfer from cathode to oxalates was first highlighted by Voss with the formation of a stable semidione radical anion intermediate, evidenced by EPR experiments. This reduction turned out to be reversible for diethyl oxalate and irreversible for diallyl and dibenzyl oxalates in aprotic solution.⁴⁵ Utley *et al.* suggested this irreversibility comes from a rapid fragmentation of the radical anion, as already observed with acetate (*vide supra*), which can be accelerated in protic conditions. Studies on benzyl oxalates supported a mechanism whereby transient radical anions collapse to benzyl radicals and oxalate anions and not the reverse. However, the process was hampered by competing hydrolysis of preformed oxalates, particularly of benzylic alcohols. The solution was found by generating *in situ* the reactive oxalate prior to be reduced *via* a co-electrolysis between benzylic (or allylic) alcohols and diethyl oxalate. For instance, reduction of diphenylmethanol under these conditions (mercury cathode, DMF-Bu₄NClO₄, -1.6 V vs. Ag/AgI, 1 F/mol) gave diphenylmethane in 70% yield. Of interest, controlled potential electrolysis of oxalate of vicinal diols gave rise to olefinic adducts.⁴⁶

As reported by Markó *et al.*, aromatic esters such as toluates can also be regarded as valuable substrates for electrochemical deoxygenation of alcohols. A series was electrolyzed at 130°C in a H-type cell equipped with a carbon graphic cathode and filled with tetrabutylammonium tetrafluoroborate and *N*-methylpyrrolidone (NMP) under a constant

⁴² G. Gourcy, M. Holder, B. Terem, J. H. P. Utley, *J. Chem. Soc., Chem. Commun.* **1976**, 779.

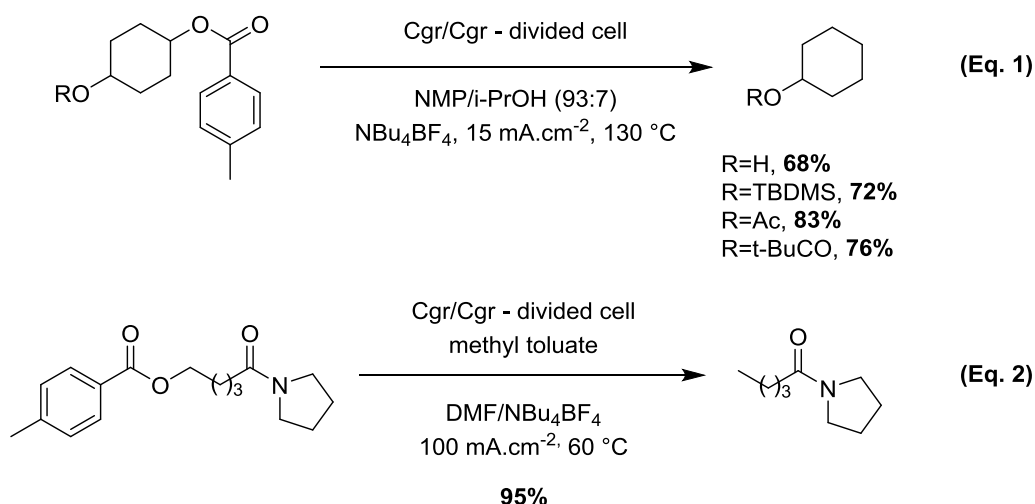
⁴³ K. Tsujimoto, Y. Kamiyama, Y. Furukawa, M. Ohashi, *Bull. Chem. Soc. Jpn.* **1983**, 56, 351.

⁴⁴ L. M. Fragoso-Luna, B. A. Frontana-Urbe, J. Cárdenas, *Tetrahedron Lett.* **2002**, 43, 1151.

⁴⁵ J. Voss, *Tetrahedron* **1971**, 27, 3753.

⁴⁶ a) D. W. Sopher, J. H. P. Utley, *J. Chem. Soc., Chem. Commun.* **1981**, 134; b) N. Islam, D. W. Sopher, J. H. P. Utley, *Tetrahedron* **1987**, 43, 959; c) N. Islam, D. W. Sopher, J. H. P. Utley, *Tetrahedron* **1987**, 43, 2741; d) K. G. Ellis, N. Islam, D. W. Sopher, J. H. P. Utley, H. L. Chum, M. Ratcliff, *J. Electrochem. Soc.* **1987**, 134, 3058; e) J. H. P. Utley, S. Ramesh, *ARKIVOC* **2003**, xii, 18.

current ($15 \text{ mA}\cdot\text{cm}^{-2}$). Secondary and tertiary toluate esters were efficiently reduced to the desired alkanes and addition of a protic co-solvent such as isopropanol improved the yields. These conditions were found to be tolerant to a number of functional groups, including alkyl esters, amides, silyl ethers, ketones and free-alcohols (Scheme 9, eq. 1).^{38b,47} In contrast, primary toluates gave only moderate yields but by analogy with oxalates, a co-electrolysis between primary alcohols and methyl toluate provided an effective solution to that issue (Scheme 9, eq. 2).⁴⁸



Scheme 9. Electrochemical reduction of toluate esters

II.A.5. Electron Transfer Deoxygenation from Carbon Dioxide Radical Anion

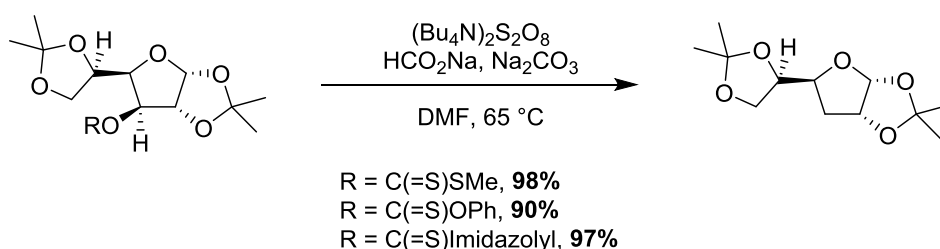
The chemical system $(\text{Bu}_4\text{N})_2\text{S}_2\text{O}_8/\text{HCO}_2\text{Na}$ has aroused keen interest for its ability to generate carbon dioxide radical anion $\text{CO}_2^{\cdot-}$ by oxidation with sulfate radical anion $\text{SO}_4^{\cdot-}$ and then promote one-electron reductive processes. In 1991, Hu and Qing took advantage of this reactivity to carry out per(poly)fluoroalkylation of olefins by reduction of per(poly)fluoroalkyl chlorides.⁴⁹ Based on this seminal work, Kim *et al.* developed a new method for the radical deoxygenation of alcohols from thiocarbonyl derivatives. Using a mixture of $(\text{Bu}_4\text{N})_2\text{S}_2\text{O}_8$ (3 equiv.)/ HCO_2Na (6 equiv.)/ Na_2CO_3 (8 equiv.) in DMF at 50°C , good to excellent yields in alkane (up to 98%) were reached whatever the nature of the radical precursor (xanthate,

⁴⁷ K. Lam, I. E. Markó, *Chem. Commun.* **2009**, 95.

⁴⁸ K. Lam, I. E. Markó, *Synlett* **2012**, 23, 1235.

⁴⁹ C.-M. Hu, F.-L. Qing, *J. Org. Chem.* **1991**, 56, 6348.

phenyl thionocarbonate or (thiocarbonyl)imidazolidine) and the functional groups present in the substrate. A SET mechanism was proposed involving electron transfer from carbon dioxide radical anion $\text{CO}_2^{\bullet-}$ to the thiocarbonyl function and β -scission of the tetrahedral radical anion intermediate. Deuterium labeling experiments then indicated that the expelled radical can abstract a hydrogen atom from the formate anion, the tetrabutylammonium cation and DMF to form the deoxygenated product.⁵⁰ This transformation has been applied to the synthesis of Platencin⁵¹ and a 3-des-hydroxyl analogue of (-)-clausenamide.⁵²



Scheme 10. Deoxygenation by reduction of thiocarbonyl derivatives with carbon dioxide radical anion

II.A.6. Photoinduced-Electron Transfer Deoxygenation

Single Electron Transfer (SET) processes involving donor and acceptor organic molecules upon Ultra-Violet (UV) light irradiation have received a great deal of attention over the past decades⁵³ while recent years have seen renewed interest for visible-light electron transfer photoredox catalysis.⁶ The potential of these photoinduced electron transfer phenomena have been widely exploited in organic synthesis. In particular, C-O homolytic cleavage of alcohols was successfully obtained by indirect reduction of carboxylic ester, thiocarbonate and thiocarbamate derivatives using photoactivated organic donors such as hexamethylphosphoramide (HMPA), carbazoles and polypyridyl organometallic complexes of ruthenium(II) and iridium(III) as photocatalysts under UV-visible light conditions.

⁵⁰ H. S. Park, H. Y. Lee, Y. H. Kim, *Org. Lett.* **2005**, 7, 3187.

⁵¹ G. N. Varseev, M. E. Maier, *Angew. Chem. Int. Ed.* **2009**, 48, 3685.

⁵² J. J. Xue, X. M. Yu, *Chinese Chemical Letters* **2011**, 22, 761.

⁵³ J. Cossy, in "Radical in Organic Synthesis", Eds. P. Renaud, M. P. Sibi, Wiley-VCH, Weinheim, Germany, **2001**, Vol. 1, p. 229 and references therein.

II.A.6.a. UV Light-Induced Photodeoxygenation Reactions

Pioneering works on photodeoxygenation of benzoate or acetate esters in dry HMPA with a high-pressure mercury lamp were reported in the late Sixties by Beugelmans *et al.*, who mentioned the presence of alkane side products (ca. 5% yield after 30h).⁵⁴ In 1975, Pete *et al.* optimized the reaction conditions by adding 5% of water to HMPA and irradiating with low-pressure mercury lamps (254 nm). Photoreduction of formate, acetate and benzoate esters gave the corresponding alkanes in moderate to good yields after 3 to 5 h of irradiation (Scheme 11, eq. 1). Primary, secondary, tertiary and neopentyl acetates could be smoothly converted into alkanes in short reaction times. While these conditions are compatible with a variety of functional groups including non-activated alkene, amide, acid, alcohol, ether and acetal (Scheme 11, eq. 2), limitations were encountered with activated alkenes, ketones and halides which are reduced at the same time and perfluorocarboxylic esters gave rise preferentially to α -elimination of a fluorine atom.⁵⁵ The presence of other chromophores in the starting material that absorbs UV radiation may also complicate the course of the reaction.⁵⁶

A detailed mechanistic study reported by Pete *et al.* suggests that the reaction proceeds through an electron transfer process from excited HMPA to the carboxylic ester as depicted in scheme 12. Irradiation of the reaction mixture at 254 nm preferentially activates HMPA rather than esters - except with benzoates - and subsequent ester/HMPA* - or ester*/HMPA-excimer formation promotes reduction of the ester leading to a radical-ion pair. In the presence of water, the radical anion $\text{RCO}_2\text{R}^{\bullet-}$ was supposed to be trapped by protonation of the alcoholate preventing a reversal electron transfer and a regeneration of the starting materials. The latter tetrahedral radical intermediate can undergo a β -fragmentation and release an alkyl radical which can abstract a hydrogen atom to the HMPA and furnish the deoxygenated product.⁵⁷ Further investigations based on laser flash photolysis of HMPA/H₂O solutions and quenching experiments support a mechanism involving photoionization of HMPA and reduction of carboxylic esters to transient radical anions by solvated electrons. To

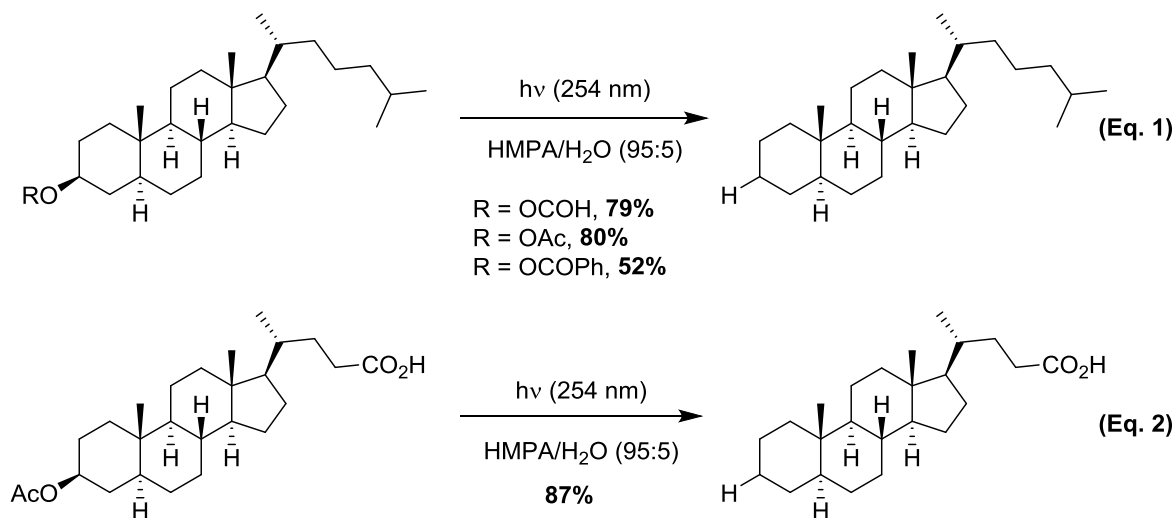
⁵⁴ R. Beugelmans, M. T. Le Goffand, H. Compaignon de Marcheville, *C. R. Acad Sci Paris* **1969**, 269, 1309.

⁵⁵ a) C. Portella, J. P. Pete, *Tetrahedron Lett.* **1985**, 26, 211; b) C. Portella, M. Iznaden, *Tetrahedron* **1989**, 45, 6467.

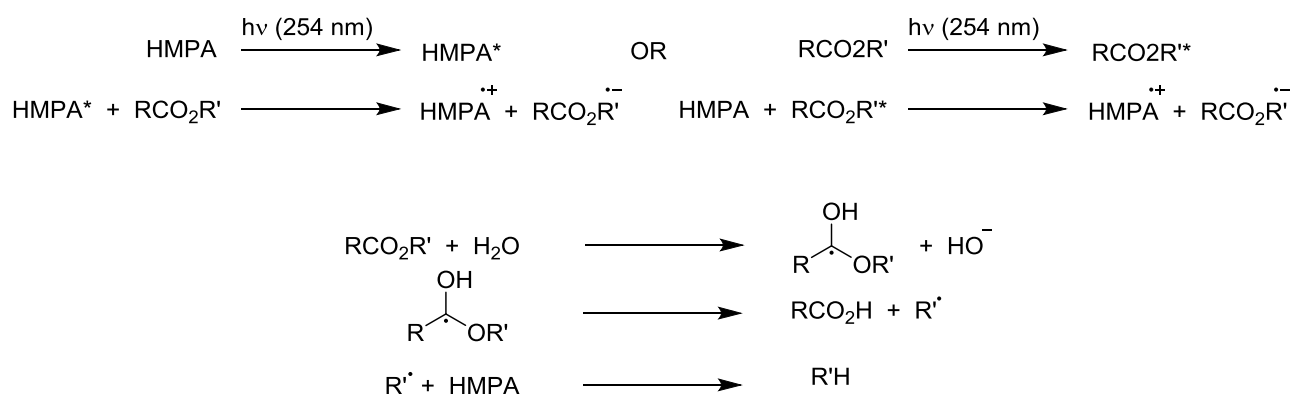
⁵⁶ a) H. Deshayes, J. P. Pete, C. Portella, D. Scholler, *J. Chem. Soc., Chem. Commun.* **1975**, 439; b) J. P. Pete, C. Portella, D. Scholler, *J. Photochemistry* **1984**, 27, 128.

⁵⁷ a) H. Deshayes, J. P. Pete, C. Portella, *Tetrahedron Lett.* **1976**, 24, 2019; b) C. Portella, H. Deshayes, J. P. Pete, D. Scholler *Tetrahedron* **1984**, 40, 3635.

complete, deuterium labeling experiments with HMPA-d₁₈ and D₂O reveal that hydrogen abstraction takes place preferentially at HMPA but also at the acid residue and the products.⁵⁸



Scheme 11. Photoinduced electron transfer reduction of steroid carboxylic esters by HMPA/H₂O under UV irradiation



Scheme 12. A plausible mechanism for the photoreduction of carboxylic Esters

The versatility of this methodology was illustrated by the synthesis of deoxysugars from carbohydrate⁵⁹ and amino-glucoside esters.⁶⁰ Primary, secondary and even sterically hindered tertiary acetates or pivalates (Scheme 13, eq. 1 and eq. 2) as well as 1,2 diacetates

⁵⁸ A. Klausener, G. Beyer, H. Leismann, H.-D. Scharf, E. Müller, J. Runsink, H. Görner, *Tetrahedron* **1989**, *45*, 4989.

⁵⁹ a) J. P. Pete, C. Portella, C. Monneret, J.-C. Florent, Q. Khuong-Huu, *Synthesis* **1977**, 774; b) M. Collins, V. R. Z. Munasinghe, *J. Chem. Soc., Chem. Commun.* **1977**, 927; c) R. Bonjouklian, B. Ganem, *Carbohydr. Res.* **1979**, *76*, 245; d) A. Klausener, E. Muller, J. Runsink, H.-D. Scharf, *Carbohydr. Res.* **1983**, *116*, 295.

⁶⁰ T. Kishi, T. Tsuchiya, S. Umezawa, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3015.

(Scheme 13, eq. 3), 2 or 3,6 dipivalates attached on pyranose and furanose rings could be easily reduced to the corresponding alkanes. It is worthy of note that thiocarbamates,^{31a,61} and dithiocarbonates,⁶² also revealed as excellent precursors (Scheme 13, eq. 4). This deoxygenation procedure has found applications in the synthesis of advanced intermediates for 2,1-dehydro-5-homoadamantanone,⁶³ (\pm)-trichodermol,⁶⁴ and (+)-thienamycin.⁶⁵

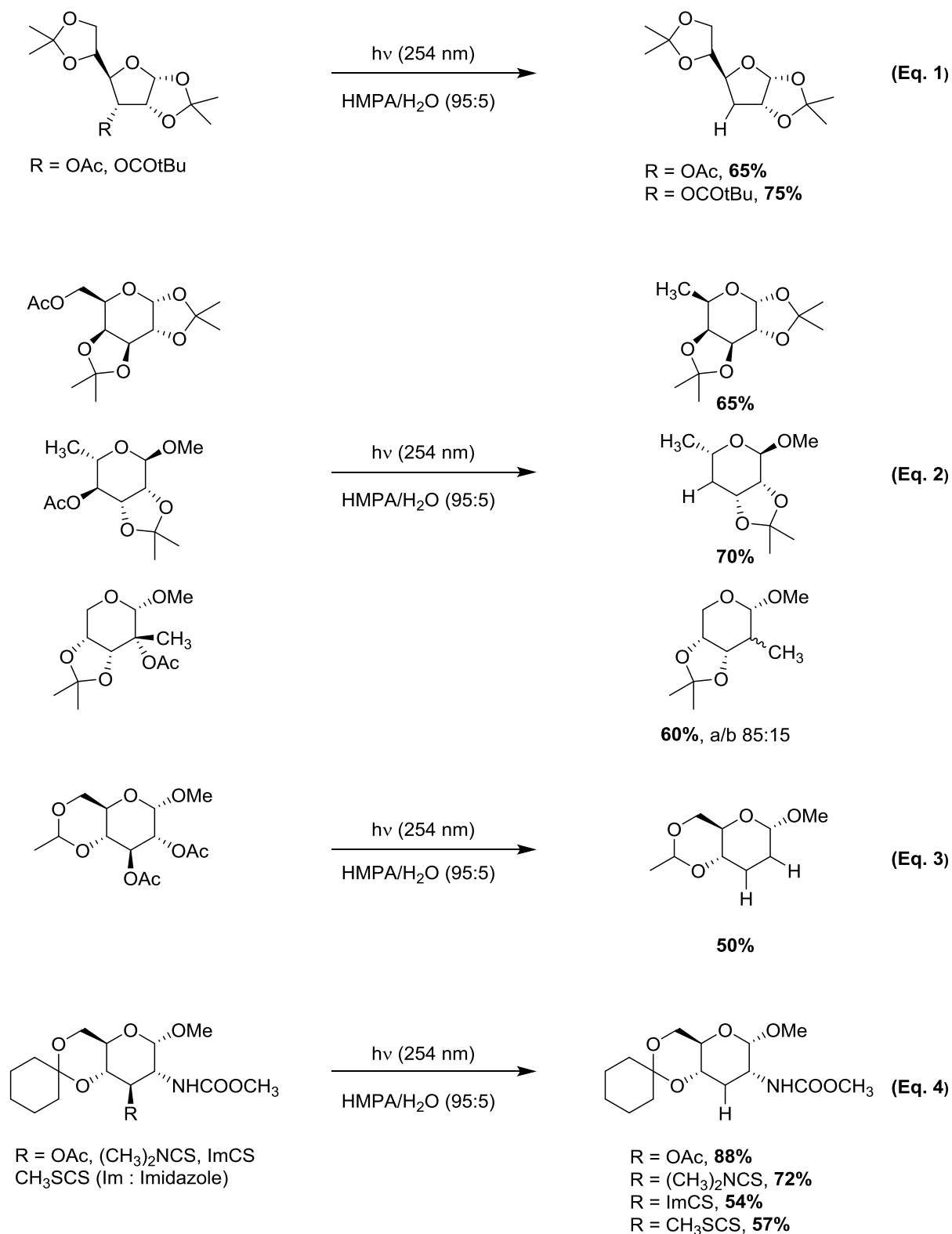
⁶¹ a) R. H. Ball, D. Horton, D. M. Williams, E. Winter-Mihaly, *Carbohydr. Res.* **1977**, *58*, 109; b) T. Kishi, T. Tsuchiya, S. Umezawa, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3015.

⁶² a) T. Kishi, T. Tsuchiya, S. Umezawa, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3015; b) J. P. Pete, C. Portella, *Bull. Soc. Chim. Fr.* **1985**, 195.

⁶³ R. K. Murray, Jr., T. M. Ford, *J. Org. Chem.* **1979**, *44*, 3504.

⁶⁴ W. C. Still, M.-Y. Tsai, *J. Am. Chem. Soc.* **1980**, *102*, 3654.

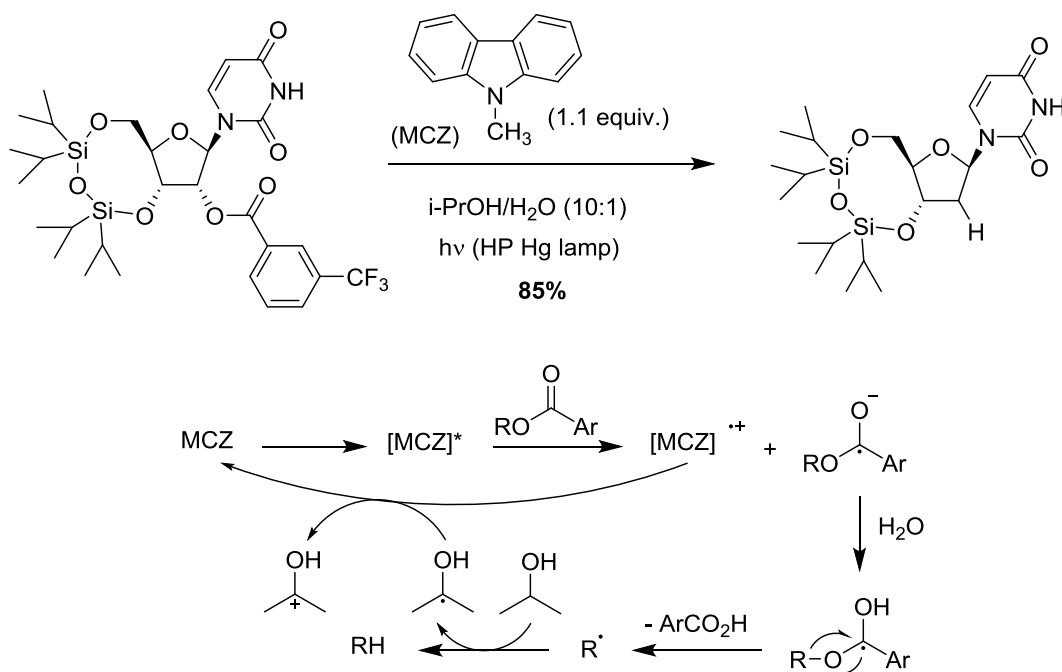
⁶⁵ M. Miyashita, N. Chida, A. Yoshikohsi, *J. Chem. Soc., Chem. Commun.* **1982**, 1354.



Scheme 13. Application to the synthesis of deoxysugars from carbohydrate and amino-glucoside esters

As valuable alternatives to the use of toxic HMPA, N-methylcarbazoles proved to be quite efficient and selective electron donor photosensitizers for the photoreduction of

benzoate esters, especially when other chromophores are present in the substrates. In 1986, Saito *et al.* found success with the development of a general procedure for deoxygenation of secondary alcohols taking advantage of this photochemical property. The transformation relies on a photoinduced electron transfer process from the excited state of 9-methylcarbazole (MCZ) obtained by irradiation with a 400 W high-pressure mercury lamp to a simple benzoate or a *m*-(trifluoromethyl)benzoate ester derived from the alcohol in a mixture THF/water or isopropyl alcohol/water (10:1) under nitrogen atmosphere at room temperature (Scheme 14). Of particular note, addition of magnesium perchlorate can speed up the photoreductive process. A similar mechanism to that obtained with HMPA was proposed. Reduction of the carboxylic ester by the photoactivated MCZ provides a transient radical anion which undergoes subsequent protonation with water and β -fragmentation. Then, H-abstraction from *i*-PrOH by the expelled radical was confirmed by deuterium labeling experiments. In theory, MCZ should be regenerated from the radical cation (MCZ)^{•+} by reduction with the solvent radical but in practice, at least one equivalent is required (Scheme 14). To explain, MCZ is irreversibly oxidized, as confirmed by cyclic voltammetry.⁶⁶



Scheme 14. The Saito photochemical reduction of a *m*-(trifluoromethyl)benzoate ester and the plausible mechanism

⁶⁶ I. Saito, H. Ikehira, R. Kasatani, M. Watanabe, T. Matsuura, *J. Am. Chem. Soc.* **1986**, *108*, 3115.

The Saito's process was then applied to various radical synthetic transformations.⁶⁷ This powerful methodology provides entries to α -deoxygenation of glucono, galactono and glucorono lactones derivatives, as illustrated by de Lederkremer and Marino. Surprisingly, in this case, the photoreduction was accomplished with only 10 mol% of MCZ (Scheme 15, eq. 1).⁶⁸ Cyclopropylmethyl radical rearrangement for the formation of γ,δ -unsaturated esters was achieved by Clive and Daigneault as depicted Scheme 15, eq. 2.⁶⁹ In the course of synthesis of Isocarbacyclin, Noyori *et al.* have demonstrated the utility of this methodology in the construction of the bicyclo[3.3.0]octane core structure obtained by generation of an α -silylated radical from the corresponding alcohol and its subsequent 5-*exo*-dig cyclization (Scheme 15, eq. 3).⁷⁰ In the same line, a radical cascade strategy implying transannular cyclizations in unsaturated macrocycles has been explored to elaborate 5-8-5 tricyclic ring systems. An elegant approach to the tobacco diterpenoid, 7,8-epoxy-4-basmen-6-one, based on a 5-*exo*-trig/11-*endo*-trig radical cascade from an 14-membered cycloalkene-allenol was proposed by Myers and Condroski. The radical sequence was triggered by a secondary radical generated from the alcohol by using a modified Saito photochemical reduction protocol in the presence of 1,4-cyclohexadiene as a better source of hydrogen atom than the solvent (Scheme 15, eq. 4).⁷¹

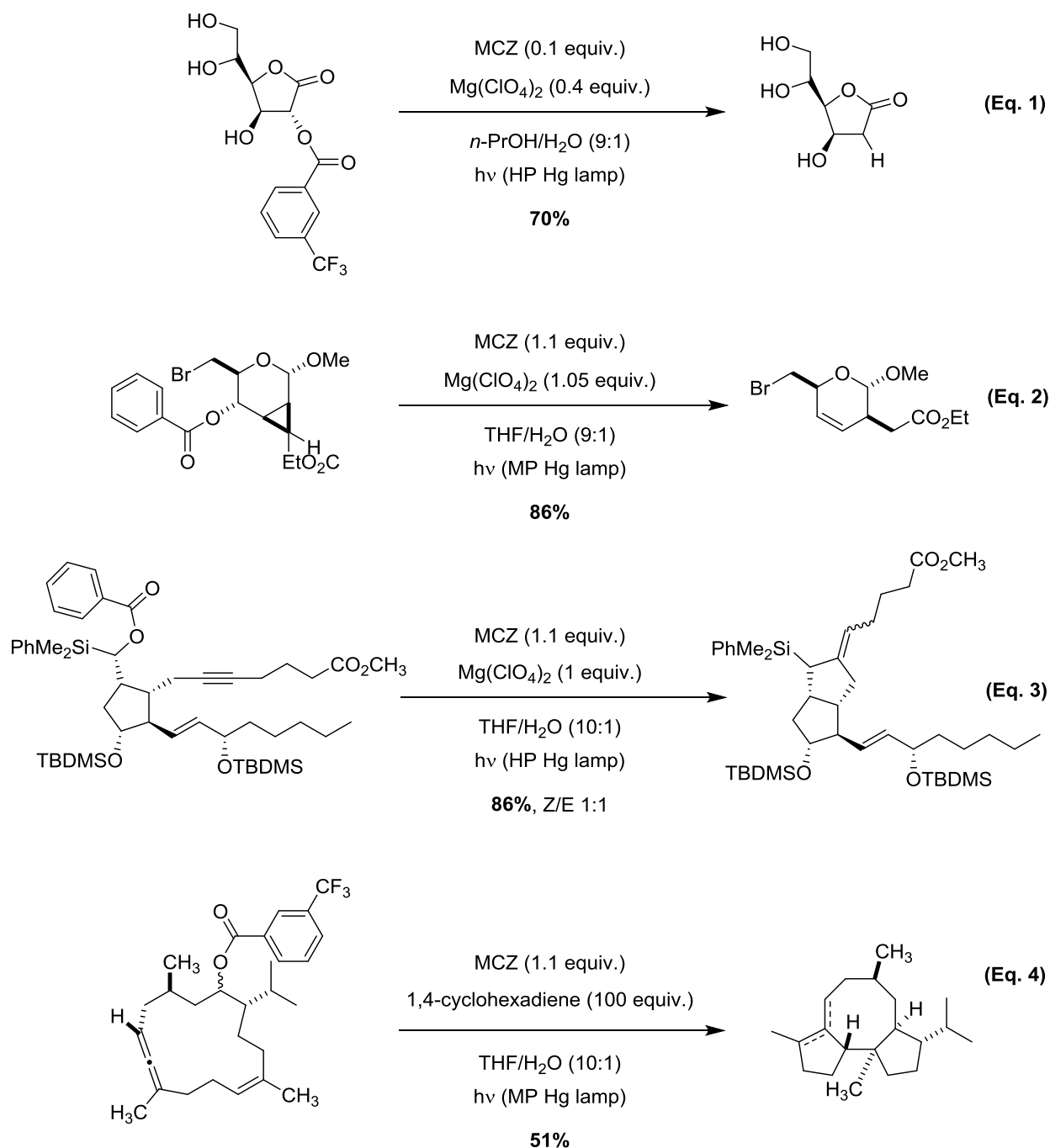
⁶⁷ a) R. E. Ireland, J. D. Armstrong, III, J. Lebreton, R. S. Meissner, M. A. Rizzacasa, *J. Am. Chem. Soc.* **1993**, *115*, 7152; b) S. Diethelm, C. S. Schindler, E. M. Carreira, *Org. Lett.* **2010**, *12*, 3950; c) S. Diethelm, C. S. Schindler, E. M. Carreira, *Chem. Eur. J.* **2014**, *20*, 6071.

⁶⁸ a) A. Chiocconi, C. Marino, E. Otal, R. M. de Lederkremer, *Carbohydr. Res.* **2002**, *337*, 2119; b) A. Bordoni, R. M. de Lederkremer, C. Marino, *Carbohydr. Res.* **2006**, *341*, 1788; c) A. Bordoni, R. M. de Lederkremer, C. Marino, *Tetrahedron* **2008**, *64*, 1703.

⁶⁹ a) D. J. L. Clive, S. Daigneault, *J. Chem. Soc., Chem. Commun.* **1989**, 332; b) D. J. L. Clive, S. Daigneault, *J. Org. Chem.* **1991**, *56*, 3801.

⁷⁰ M. Suzuki, H. Koyano, R. Noyori, *J. Org. Chem.* **1987**, *52*, 5583.

⁷¹ a) A. G. Myers, K. R. Condroski, *J. Am. Chem. Soc.* **1993**, *115*, 7926; b) A. G. Myers, K. R. Condroski, *J. Am. Chem. Soc.* **1995**, *117*, 3057.

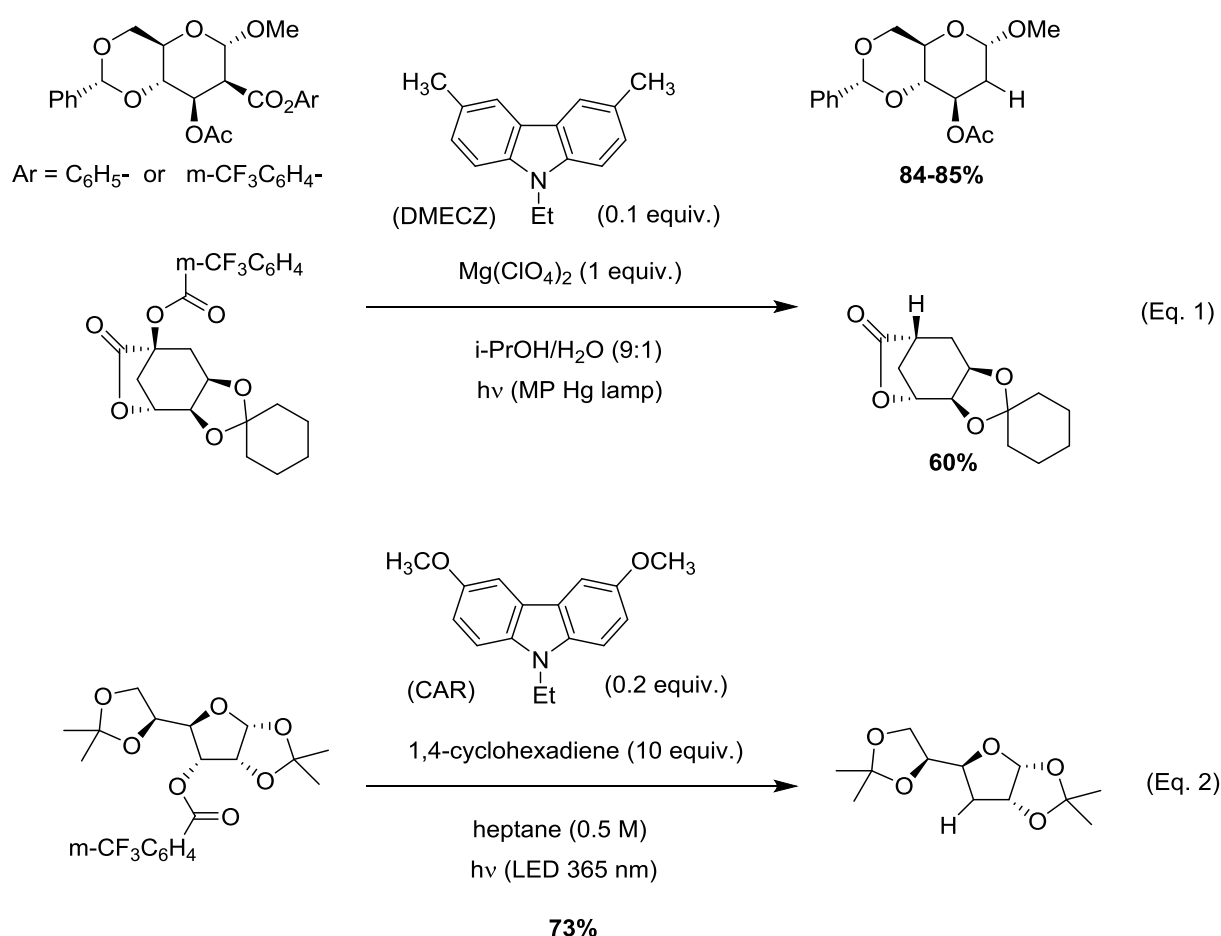


Scheme 15. Applications of the Saito's process to various radical synthetic transformations

Inspired by the electrochemical studies of Ambrose *et al.* on 3- and 6-substituted 9-alkylcarbazoles,⁷² a catalytic version was developed by Rizzo *et al.*, using 10-20 mol% of 3,6-dimethyl-9-ethylcarbazole (DMECZ) under the same conditions. These variations significantly improved the turnover and the reactivity of the photosensitizer. In contrast to

⁷² a) J. F. Ambrose, R. F. Nelson, *J. Electrochem. Soc.* **1968**, *115*, 1159; b) J. F. Ambrose, L. L. Carpenter, R. F. Nelson, *J. Electrochem. Soc.* **1975**, *122*, 876.

MCZ, DMECZ is reversibly oxidized during the process which ensures the regeneration of the photocatalyst. This modified protocol was tested to a series of substrates and proved to be compatible with alkene, ether, acetal, ester and lactone functions (Scheme 16, eq. 1).⁷³ Recently, the electron-rich 3,6-dimethoxy-9-ethylcarbazole (CAR) has emerged as a more efficient photocatalyst increasing significantly the reaction rate.⁷⁴ In addition, another study from Matsubara *et al.* showed that working at higher concentration (up to 0.5 M) avoids the formation of alkenes as side products. Finally, the best set of conditions relies on the use of 0.2 equiv. of CAR and 10 equiv. of 1,4-cyclohexadiene in heptane under LED (365 nm) irradiation (Scheme 16, eq. 2).⁷⁵



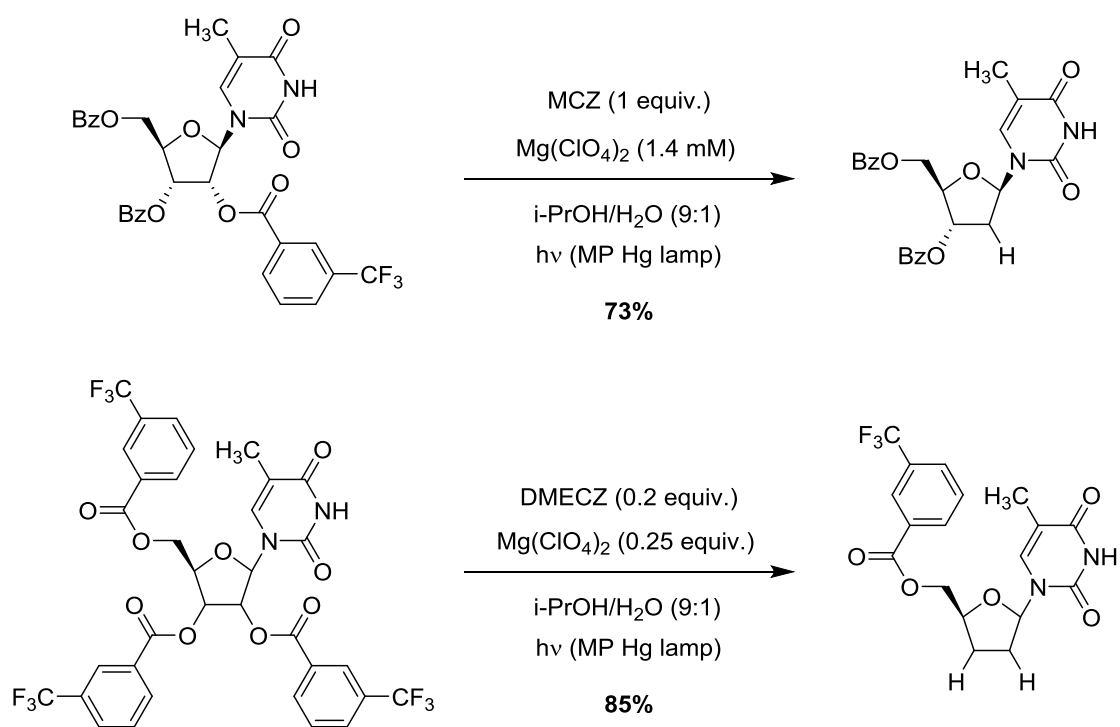
Scheme 16. The Saito photoreductive deoxygenation of benzoate esters under modified conditions with 3,6-disubstituted-9-ethylcarbazole as a new catalytic photosensitizer

⁷³ D. R. Prudhomme, Z. Wang, C. J. Rizzo, *J. Org. Chem.* **1997**, 62, 8257.

⁷⁴ B. Shen, M. W. Bedore, A. Jamison, *Chem. Commun.* **2012**, 48, 7444.

⁷⁵ R. Matsubara, Y.-S. Shin, T. Shimada, M. Hayashi, *Asian J. Org. Chem.* **2014**, 3, 1054.

The Saito photochemical reduction was then applied to the synthesis of relevant bioactive molecules including non-natural 2'-deoxy-, 3'-deoxy- and 2',3'-dideoxyribonucleosides as potent anti-cancer drugs and antiviral compounds against AIDS.⁷⁶ The strategy is based partly on the difference of reactivity between primary and secondary arylesters, benzoate and *m*-(trifluoromethyl)benzoate esters which can be reduced faster as illustrated Scheme 17.^{76b,c} In continuous flow the reaction time to produce 2'-deoxyribonucleosides can be reduced from 2 h to 10 min when the reaction is carried out at 45°C with 10 mol% of 3,6-dimethoxy-9-ethylcarbazole.⁷⁴ Finally, deoxygenation of aldonolactones was also accomplished through this methodology.⁶⁸



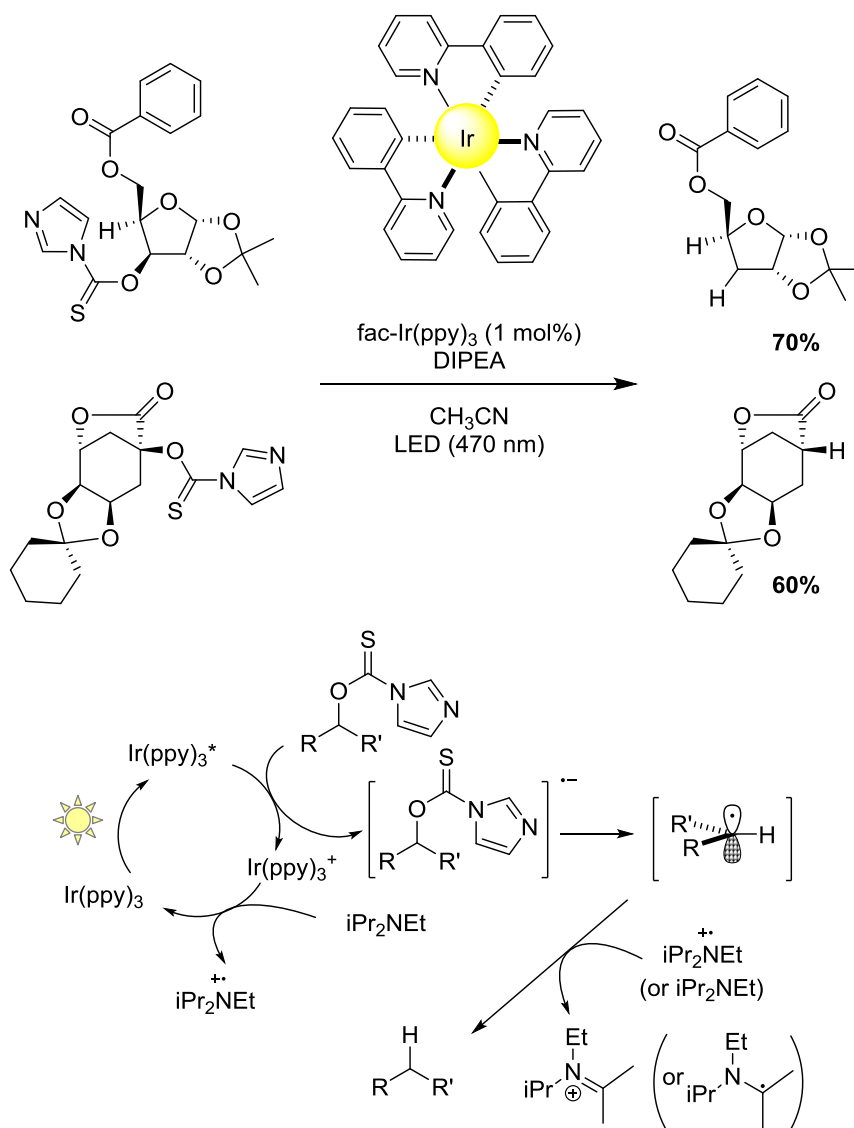
Scheme 17. Applications of the Saito's process to the synthesis of 2'-deoxy- and 2',3'-dideoxyribonucleosides

⁷⁶ a) M. R. Almond, J. L. Collins, B. E. Reitter, J. L. Rideout, G. A. Freeman, M. H. St Clair, *Tetrahedron Lett.* **1991**, 32, 5745; b) M. Park, C. J. Rizzo, *J. Org. Chem.* **1996**, 61, 6092; c) Z. Wang, D. R. Prudhomme, J. R. Buck, M. Park, C. J. Rizzo, *J. Org. Chem.* **2000**, 65, 5969.

II.A.6.b. Visible Light-induced Photodeoxygenation Reactions

More appealing routes to perform photoreductive deoxygenations under milder conditions were recently reported with the rebirth of photoredox catalysis using visible light irradiation.⁶ These photoinduced SET processes require the presence of photocatalysts (Pcat) that absorbs light in the visible range, which can be polypyridine transition metal complexes. We developed notably a photocatalytic alternative of the classical Barton-McCombie deoxygenation of aliphatic secondary and tertiary alcohols based on photoreduction of the corresponding imidazole *O*-thiocarbamates. Upon treatment with *fac*-Ir(ppy)₃ and diisopropylethylamine (DIPEA, Hünig's base) in acetonitrile under LED lights at room temperature, products of reduction were obtained in good to moderate yields (Scheme 18). Excellent functional group compatibility was observed with sulfonamide and *tert*-butoxycarbonyl protecting groups, aromatics, alkenes, acetals, alkyl esters, lactones. By comparison, this transformation performed under standard tin hydride conditions gave the same results. However, photoreduction of the benzhydrol derivative furnished a mixture of 1,1-diphenylmethane (21%) and dimer 1,1,2,2-tetraphenylethane (37%). To gain insights into the mechanism, fluorescence quenching experiments and comparison of reduction potentials of a set of thiocarbamates (-1.11 to -1.73 V) with the Ir(IV)/Ir(III)* redox system (-1.73 V) established that photoactivated *fac*-Ir(ppy)₃* reduce the *O*-thiocarbamates. These informations allowed to propose a reasonable mechanism where *fac*-Ir(ppy)₃* can transfer an electron to the thiocarbamate moiety and the photocatalyst is regenerate in the presence of DIPEA. Then, the generated thiocarbamate radical anion fragments and affords the intermediate carbon-centered radical which can abstract an hydrogen to the amine radical cation (Scheme 18).⁷⁷

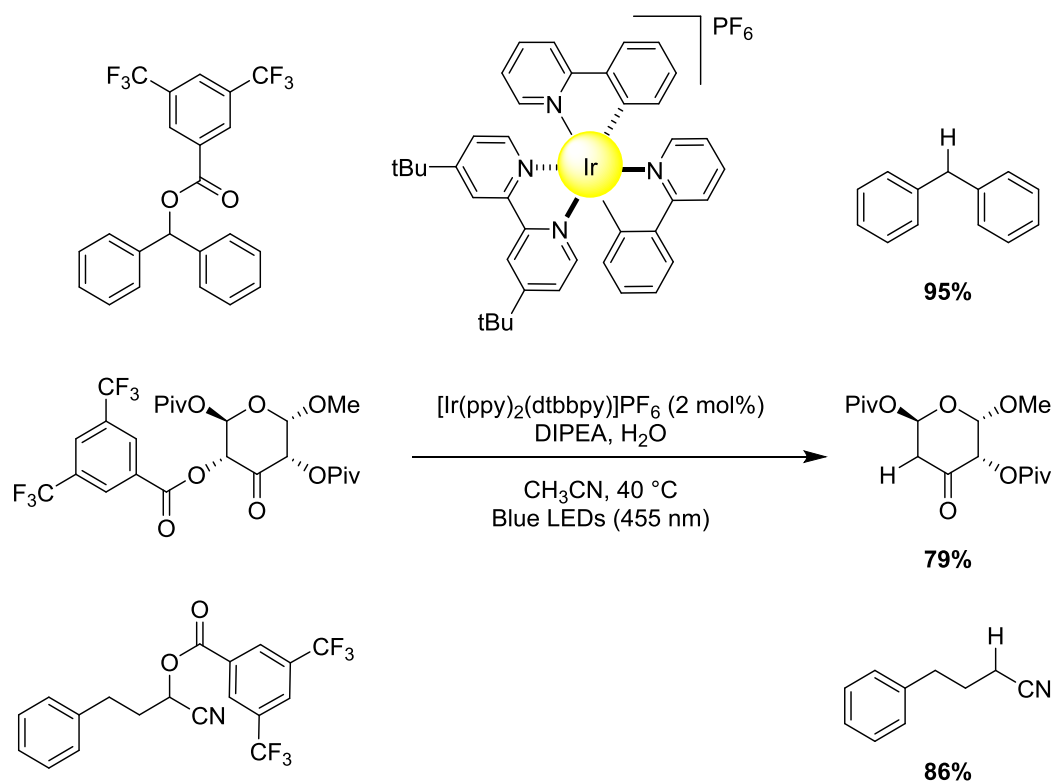
⁷⁷ L. Chenneberg, A. Baralle, M. Daniel, L. Fensterbank, J.-P. Goddard, C. Ollivier, *Adv. Synth. Catal.* **2014**, 356, 2756.



Scheme 18. Photocatalytic reduction of secondary and tertiary *O*-thiocarbamates and the plausible mechanism

In the same line, Reiser *et al.* have concentrated on deoxygenation of secondary benzylic, α -carbonyl and α -cyano alcohols. For that purpose, they revisited the Saito's procedure under visible-light illumination. Starting from 3,5-bis(trifluoromethyl)benzoate esters, the reaction proceeds smoothly upon exposure to $[\text{Ir(ppy)}_2(\text{dtb-bpy})]\text{PF}_6$ catalysis in the presence of DIPEA and water in acetonitrile under LED lights at 40 °C. This catalytic system proved tolerant to a large number of functional groups. In contrast with *O*-thiocarbamates, no dimer was formed in photoreduction of benzhydrol derivatives (Scheme 19). As seen before, it is assumed that the iridium complex acts as a visible-light

photocatalyst, DIPEA is required as both a sacrificial electron donor and a hydrogen atom donor, and water involves in the protonation of the transient radical anion $\text{RCO}_2\text{R}^{\bullet-}$.⁷⁸



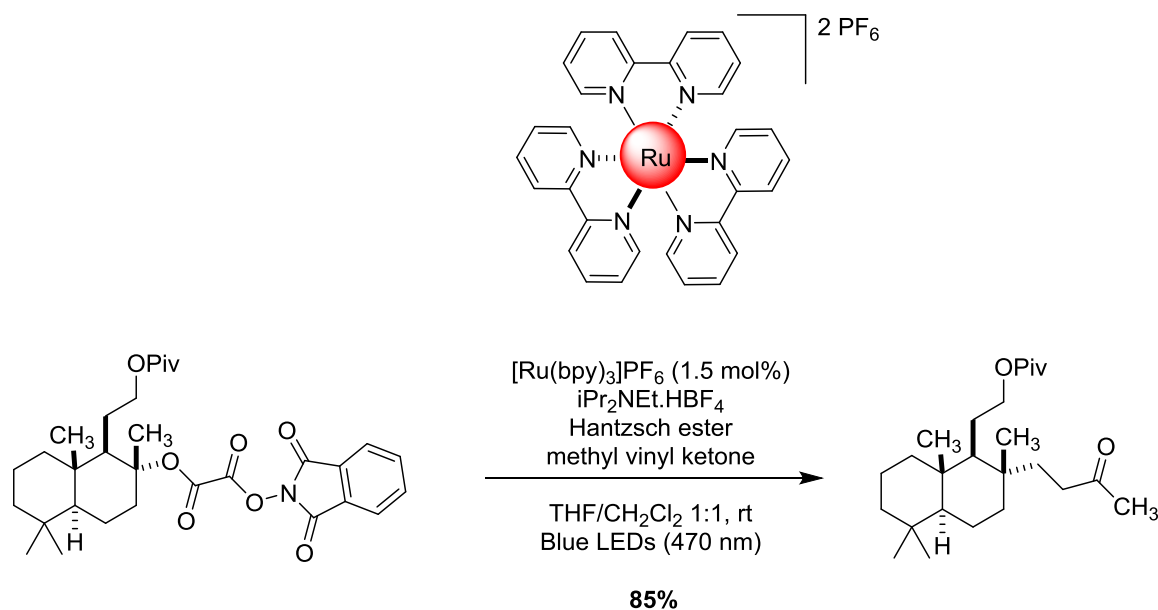
Scheme 19. Photocatalytic reduction of 3,5-bis(trifluoromethyl)benzoate esters

In 2012, Overman *et al.* made use of the Okada's decarboxylation⁷⁹ to provide an efficient method for the deoxygenation of aliphatic tertiary alcohols by photoreduction of the corresponding *tert*-alkyl *N*-(acyloxy)phthalimide oxalates. The reaction relies on a combination of $\text{Ru}(\text{bpy})_3(\text{PF}_6)$ photocatalyst (1.5 mol%) and visible-light (blue LEDs) with Hantzsch ester and $i\text{-Pr}_2\text{NEt}\cdot\text{HBF}_4$ which presumably serves as both a reductive quencher and H-atom donor. After two successive decarboxylations, the tertiary alkyl radicals can then be trapped by electron-deficient alkenes leading to the formation of quaternary centers (Scheme 20).⁸⁰

⁷⁸ D. Rackl, V. Kais, P. Kreitmeier, O. Reiser, *Beilstein J. Org. Chem.* **2014**, *10*, 2157.

⁷⁹ K. Okada, K. Okubo, N. Morita, M. Oda, *Tetrahedron Lett.* **1992**, *33*, 7377.

⁸⁰ G. L. Lackner, K. W. Quasdorf, L. E. Overman, *J. Am. Chem. Soc.* **2013**, *135*, 15342.



Scheme 20. Visible-light photoreductive coupling of a *tert*-alkyl N-(acyloxy)phthalimide oxalate and methyl vinyl ketone

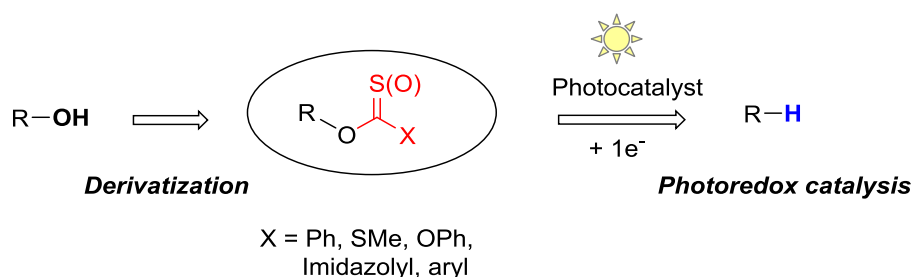
II.A.7. Conclusion

Since the pioneer work of D. H. R. Barton and S. W. McCombie on tin-mediated radical deoxygenation of alcohols from the corresponding xanthates, tremendous developments on tin-free alternative methods for synthesis have been widely reported. Among them, reductive single electron transfer (SET) approaches involving acetate, aromatic ester, dithiocarbonate and dithiocarbamate precursors prove to be extremely effective in the conversion of alcohols to alkanes, and particularly with sterically hindered substrates. This overview points out a variety of successful SET conditions including the use of low valent metal, such as dissolving alkali metals (Li, Na, K) and lanthanides (Sm(II)), and the chemical system $(Bu_4N)_2S_2O_8/HCO_2Na$ as a source of carbon dioxide radical anion, but also electrochemical and photoinduced electron transfer conditions which demonstrates their high synthetic potential. Finally, recent studies confirm the increasing importance of photoredox catalysis as a very attractive tin-free process and a valuable tool in modern organic synthesis for deoxygenation of alcohols, but far from being completely exploited.

II.B. Results: Visible-Light Photocatalytic Reduction of *O*-Thiocarbamates: Development of A Tin-Free Barton-McCombie Deoxygenation Reaction

II.B.1. Objectives of the Project

The Barton-McCombie deoxygenation is one of the most important transformations in the toolbox of organic chemists which has been the purpose of number of methodological developments. In this study, we reported an original deoxygenation of alcohols derivatives based on photoreductive catalysis under visible light activation (Scheme 1).



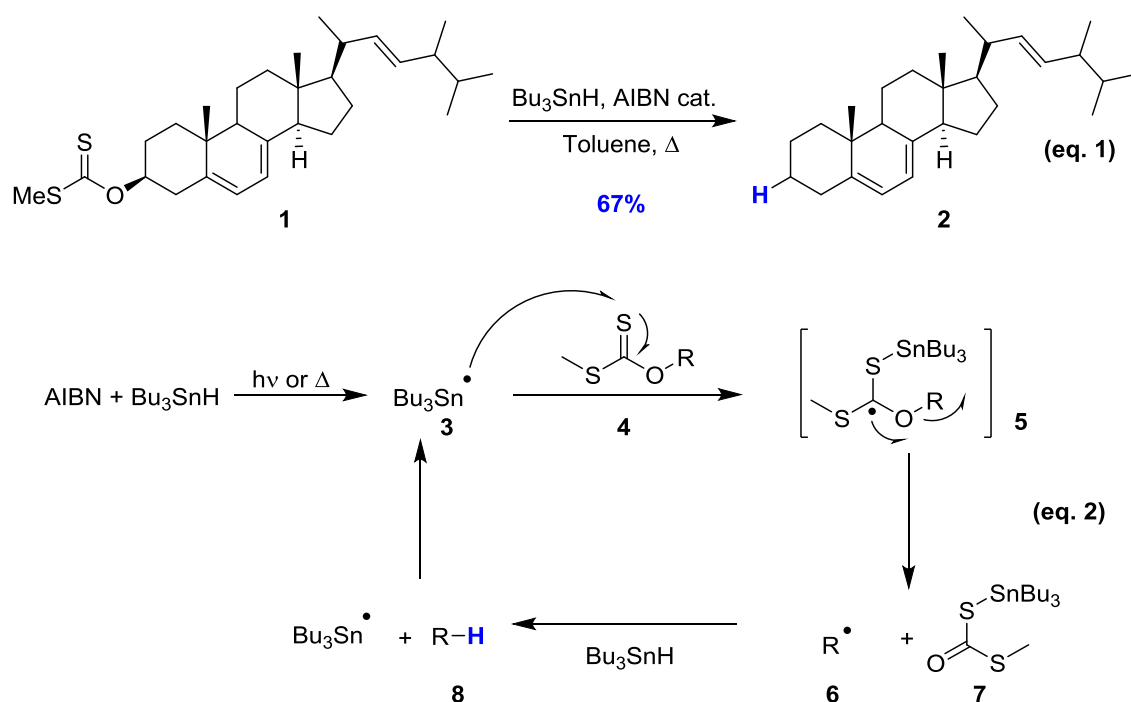
Scheme 1. Concept of the study: photoreduction catalysis alternative

II.B.2. Barton-McCombie Deoxygenation – State of the Art

Since the development of modern radical chemistry, number of related transformations have entered the mainstream chemistry and proved to be highly efficient tools to chemists for molecular and material sciences.¹ Indeed, applications in surface functionalization,⁸¹ polymer

⁸¹ a) K. Matyjaszewski, B. S. Sumerlin, N. V. Tsarevsky, *Progress in Controlled Radical Polymerization: Mechanisms and Techniques (ACS Symposium Series 1100)*, ACS, Washington DC, **2012**. b) K. Matyjaszewski, B. S. Sumerlin, N. V. Tsarevsky, *Progress in Controlled Radical Polymerization: Materials and Applications (ACS Symposium Series 1101)*, ACS, Washington, DC, **2012**.

preparation⁸² or organic synthesis^{1,83} have highlighted the strong impact of this field and demonstrated its ability to act at the interface of different scientific domains. Among the large number of known radical reactions, those dedicated to functional group transformations have been certainly the most intensively studied for methodological development and total synthesis. Notably, the Barton-McCombie deoxygenation is one of the most used radical reactions since it allows the reduction of an alcohol function to the corresponding alkane.^{7,8} The reaction usually proceeds in two steps through the preliminary formation of an intermediate thiocarbonyl precursor such as xanthate, thiocarbonate, thiocarbamate (Scheme 1 and 2). As an example, the *O*-ergosteryl *S*-methyl dithiocarbonate **1** was reduced in good yield to give ergosta-5,7,22-triene **2** (Scheme 2, eq. 1). In the original version, the radical chain reaction is initiated by AIBN under thermal conditions. Then, the generated tertiary carbon centered radical proceeds to a hydrogen abstraction from *n*Bu₃SnH used as chain mediator. The stannyl radical **3** attacks the thiocarbonyl bond of the xanthate **4** to give the intermediate **5**. This intermediate rapidly evolves through fragmentation and the subsequent formation of the carbon centered radical **6** and byproduct **7**. Hydrogen abstraction from *n*Bu₃SnH leads to the reduced product **8** and the regeneration of the chain mediator.⁷



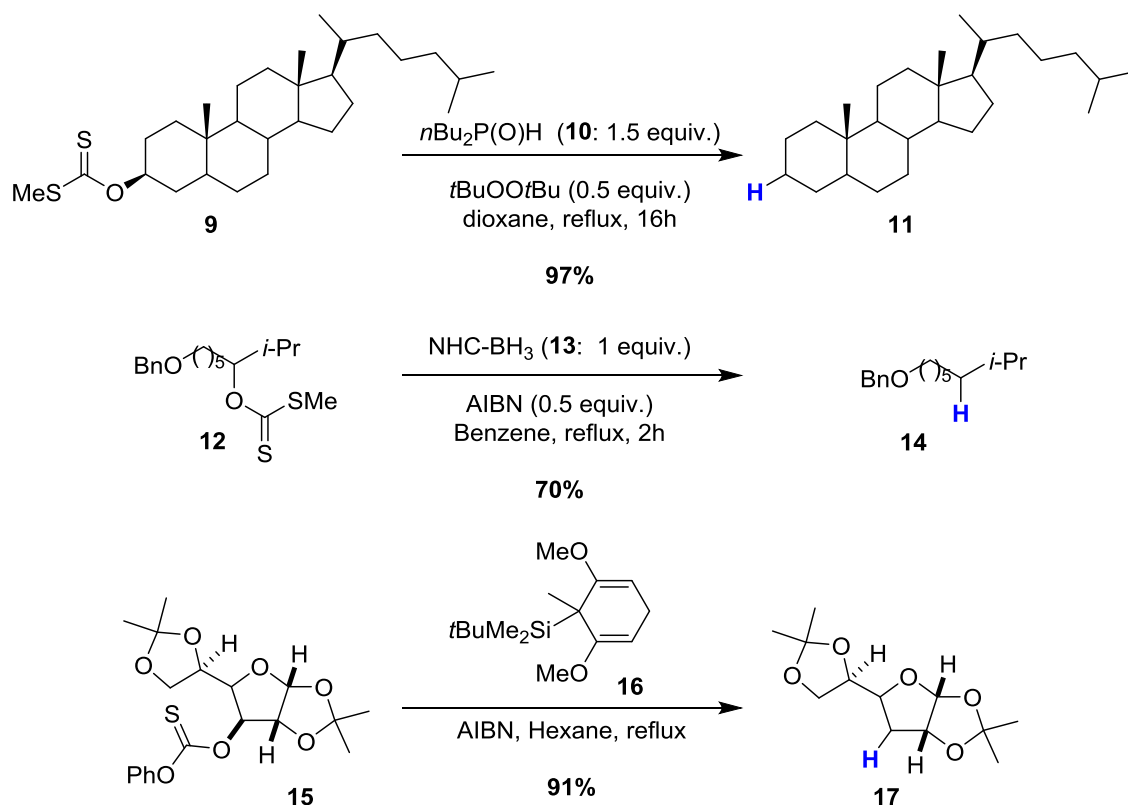
Scheme 2. Classical Barton-McCombie deoxygenation chain reaction

⁸² a) K. Matyjaszewski, T. Davis, *Handbook of Radical Polymerization*, John Wiley & Sons, New Jersey, **2002**.

b) N. V. Tsarevsky, B. S. Sumerlin, *Fundamentals of Controlled/"Living" Radical Polymerization (RSC Polymer Chemistry Series No. 4)*, RSC, Cambridge, UK, **2013**.

⁸³ A. Gansäuer *Radicals in Synthesis I & II, Vols. 263 & 264*, Springer, Berlin, Heidelberg, **2006**.

As illustrated in scheme 3, related protocols have been proposed with alternatives to the initiation process and the toxic tin hydride mediator such as silanes,⁹ phosphorous derivatives (**10**),¹¹ boranes (**13**)^{12,13} or cyclohexadienyl compounds (**16**).¹⁰ The secondary alcohols previously derivatized into xanthate (**9** and **12**) or thiocarbonate (**15**) can easily undergo a reduction reaction under thermal activation. AIBN, ACN (cyclohexanylidene analog of AIBN) or peroxide species are used as radical initiator mainly in catalytic amount.



Scheme 3. Tin alternatives for deoxygenation reaction

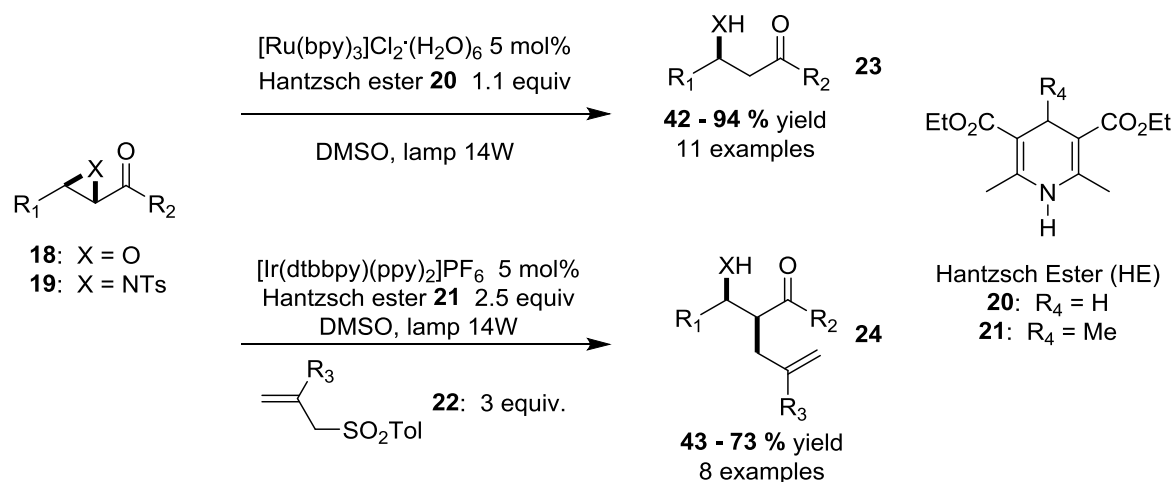
Deoxygenation reactions have also been investigated through the reduction of benzoyl derivatives by organometallic redox processes^{38, 84} as well as photoinduced electron transfer sensitized by N-alkylcarbazoles under Hg-lamp irradiation (See part II.A.).^{66, 73} As an efficient alternative to stoichiometric redox reactions or harsh UV conditions, visible-light photoredox catalysis has re-emerged over the last decade.⁸⁵ We and others have taken an active part in the development of new catalytic processes based on visible-light to activate

⁸⁴ G. Hilmersson, T. Ankner, *Tetrahedron* **2009**, 65, 10856.

⁸⁵ For seminal works, see: a) D. M. Hedstrand, W. H. Kruizinga, R. M. Kellogg, *Tetrahedron Lett.*, **1978**, 19, 1255. b) T. J. van Bergen, W. H. Kruizinga, R. M. Kellogg, *J. Org. Chem.*, **1979**, 44, 4953. c) H. Cano-Yelo, A. Deronzier, *Tetrahedron Lett.*, **1984**, 25, 5517. d) H. Cano-Yelo, A. Deronzier, *J. Chem. Soc. Faraday Trans. 1*, **1984**, 80, 3011. e) H. Cano-Yelo, A. Deronzier, *J. Chem. Soc. Perkin Trans. 2*, **1984**, 1093. f) H. Cano-Yelo, A. Deronzier, *J. Photochem.*, **1987**, 37, 315.

organic or organometallic photocatalysts and promote electron transfers and radical reactions.⁸⁶ Very few of them have been dedicated to the challenging reductive cleavage of C-O bonds because of its high bond strength.

Our group, developed an elegant photoreductive ring opening methodology of α,β -epoxyketones **18** extended also to α -keto-aziridines **19** (Scheme 4). Under photoredox conditions, the carbonyl group is reduced through a single electron transfer process to provide the corresponding ketyl radical which undergo a ring opening process. The so-formed carbone-centered radical can be directly reduced by Hantzsch ester **20** to give **23** or trapped by the allylsulfone **22** to give the allylation compound **24** with a good diastereoselectivity. High yields were obtained for both synthetic pathways.⁸⁷



Scheme 4. Photoreductive ring opening of epoxyketones and keto-aziridines

⁸⁶ For reviews on visible-light photoredox catalysis, see: a) K. Zeitler, *Angew. Chem. Int. Ed.* **2009**, *48*, 9785. b) T. P. Yoon, M. A. Ischay, J. Du, *Nature Chem.*, **2010**, *2*, 527. c) F. Teplý, *Collect. Czech. Chem. Commun.* **2011**, *76*, 859. d) J. M. R. Narayanaman, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102. e) J. W. Tucker, C. R. J. Stephenson, *J. Org. Chem.* **2012**, *77*, 1617. f) J. Xuan, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2012**, *51*, 6828. g) M. A. Ischay, T. P. Yoon, *Eur. J. Org. Chem.* **2012**, 3359. h) C.-J. Wallentin, J. D. Nguyen, C. R. J. Stephenson, *Chimia* **2012**, *66*, 394; i) S. Maity, N. Zheng, *Synlett* **2012**, *23*, 1851. j) L. Shi, W. Xia, *Chem. Soc. Rev.* **2012**, *41*, 7687. k) Y. Xi, H. Yi, A. Lei, *Org. Biomol. Chem.* **2013**, *11*, 2387. l) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322. m) D. P. Hari, B. König, *Angew. Chem. Int. Ed.* **2013**, *52*, 4734. n) M. Reckenthäler, A. G. Griesbeck, *Adv. Synth. Catal.* **2013**, *355*, 2727. o) T. Koike, M. Akita, *Synlett* **2013**, *24*, 2492. p) J. Xuan, L.-Q. Lu, J.-R. Chen, W.-J. Xiao, *Eur. J. Org. Chem.* **2013**, 6755. q) Y.-Q. Zou, J.-R. Chen, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2013**, *52*, 11701. r) J. Xie, H. Jin, P. Xu, C. Zhu, *Tetrahedron Lett.* **2014**, *55*, 36. For recent books, see: s) B. König *Chemical Photocatalysis*, DeGruyter, Berlin, **2013**. t) A. Albini, M. Fagnoni, *Photochemically generated intermediates in Synthesis*, John Wiley & Sons, Hoboken, **2013**. u) D. M. Schultz, T. P. Yoon *Science* **2014**, *343*, DOI: 10.1126/science.1239176.

⁸⁷ M.-H. Larraufie, P. Pellet, L. Fensterbank, J.-P. Goddard, E. Lacôte, M. Malacria, C. Ollivier, *Angew. Chem. Int. Ed.* **2011**, *50*, 4463.

Recently, Falvey reported a photorelease of carboxylic acids based on a formal deoxygenation reaction.⁸⁸ Stephenson combined the iodination of primary and secondary alcohols with the photoreduction of the so-formed aliphatic iodide to the corresponding alkane in a one-pot two steps sequence.⁸⁹ Finally, Overman developed a photoredox-catalyzed fragmentation of tertiary alkyl N-phthalimidoyl oxalates aiming at C-C bond formation.⁹⁰ Based on all these considerations, we surmised that the development of an efficient tin-free deoxygenation reaction of secondary and tertiary alcohols to alkanes that would use visible-light activation of a photoredox catalyst is of primary importance for the chemical community.

II.B.3. O-Thiocarbamates as New Class of Substrates for Visible-Light Triggered Generation of Radicals

II.B.3.a Optimization of the photocatalyzed deoxygenation of alcohols

We decided to investigate the photoreduction of thiocarbonyl compounds. We selected easy accessible thiocarbonyl derivatives and focused our attention on the imidazolyl-thiocarbonyl substrates (Scheme 1). This functional group has been introduced by Barton and McCombie for alcohol deoxygenation and gave comparable yields than methyldithiocarbonyl, and thiobenzoyl.^{8a} Imidazolyl thiocarbonyl substrates have been for instance used by Rasmussen for the deoxygenation of various protected carbohydrates.⁹¹ The authors demonstrated the strong potential of this functional group toward reductive tin conditions. As an example, in scheme 5, the 1,2,5,6-diisopropylidene-D-glucose derivate in imidazolyl thiocarbamate **25** was reduced in refluxing toluene with tri-*n*-butylstannane to give the deoxy

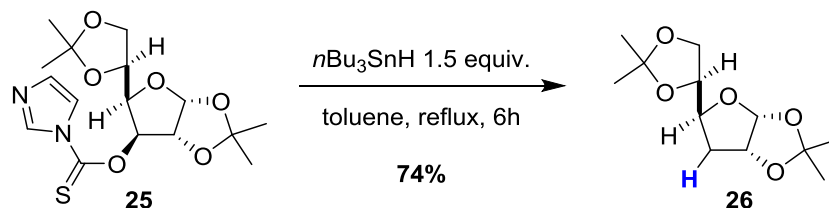
⁸⁸ J. B. Borak, D. E. Falvey *J. Org. Chem.* **2009**, *74*, 3894

⁸⁹ a) J. D. Nguyen, B. Reiß, C. Dai, C. R. J. Stephenson, *Chem. Commun.* **2013**, *49*, 4352. For photocatalytic transformation of alcohol into corresponding iodide, see: b) C. Dai, J. M. R. Narayanam, C. R. J. Stephenson, *Nature Chem.* **2011**, *3*, 140. For photoreduction of iodide, see: c) J. D. Nguyen, E. M. D'Amato, J. M. R. Narayanam, C. R. J. Stephenson, *Nature Chem.* **2012**, *4*, 854. d) M. Dobmeier, J. M. Herrmann, D. Lenoir, B. König *Beilstein J. Org. Chem.* **2012**, *8*, 330.

⁹⁰ G. L. Lackner, K. W. Quasdorf, L. E. Overman, *J. Am. Chem. Soc.* **2013**, *135*, 15342.

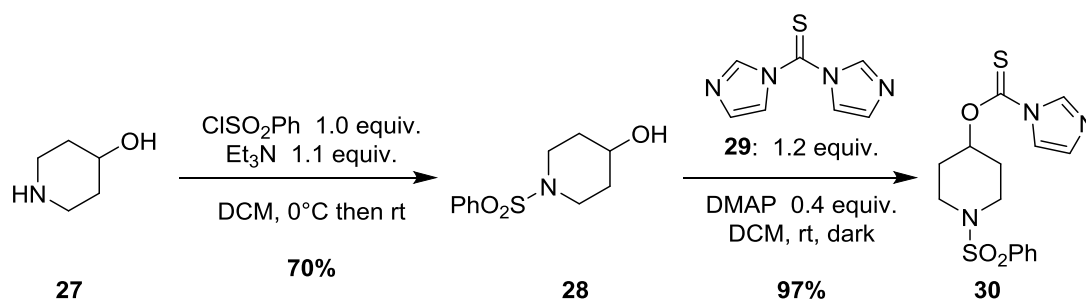
⁹¹ J. R. Rasmussen, C. J. Slinger, R. I. Kordish and D. D. Newman-Evans, *J. Org. Chem.* **1981**, *46*, 4843.

product **26** in 74% yield. Under these conditions, they were able to reduce a set of thiocarbamate derivatives in high yields.



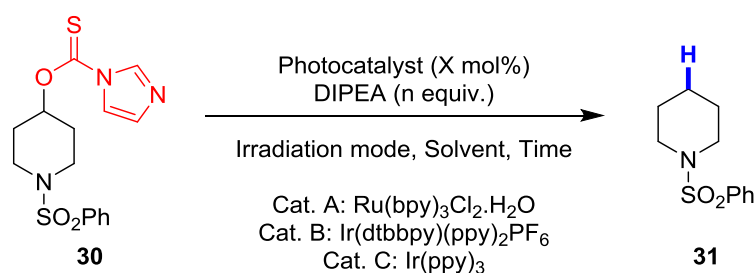
Scheme 5. Reduction of diisopropylidene protected furanose

Inspired by those results, we decided to start the conditions optimization with the *O*-thiocarbamate **30** (scheme 6). The substrate **30** was preferred to carbohydrate **25** because of the very sticky oily nature of sugars leading to a less practical handling. The synthesis of **30** starts with the nitrogen sulfonylation of **27** with benzenesulfonyl chloride to afford of the alcohol **28** in 70% yield. In the dark, **28** reacted with the 1,1'-thiocarbonyldiimidazole **29** in dichloromethane in the presence of 4-(dimethylamino)pyridine (DMAP) to provide the *O*-thiocarbamate **30** in high yield (97%).



Scheme 6. Synthesis of the *O*-thiocarbamate substrate candidate for optimization

Table 1. Optimization of the reaction conditions for photocatalytic reduction of *O*-thiocarbamate **30** into **31**

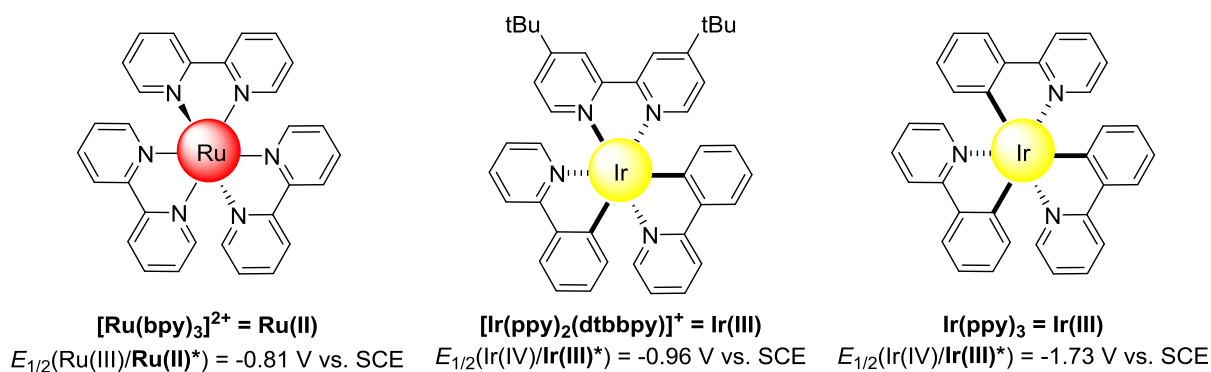


Entry	Cat. (X mol%)	DIPEA (n equiv.)	Light source ^{c)}	t (h)	Solvent, conc. ^{e)}	Yield% ^{a)}
1	Cat. A (5)	10	14W FLB	24	CH ₃ CN, C ₁	NR
2^{b)}	Cat. B (5)	10	14W FLB	24	CH ₃ CN, C ₁	20
3	Cat. C (5)	10	14W FLB	24	CH ₃ CN, C ₁	47
4	Cat. C (5)	10	14W FLB	18	DMPU, C ₁	51
5	Cat. C (5)	10	14W FLB	24	NMP, C ₁	27
6	Cat. C (5)	10	14W FLB	48	DMF, C ₁	42
7	Cat. C (5)	10	14W FLB	48	DMSO, C ₁	47
8^{d)}	Cat. C (5)	10	14W FLB	48	Acetone, C ₁	ND
9	Cat. C (5)	10	14W FLB	48	DCM, C ₁	29
10	Cat. C (5)	10	14W FLB	24	CH ₃ CN, C ₂	53
11	Cat. C (5)	10	blue LEDs (470 nm)	24	CH ₃ CN, C ₂	53
12	Cat. C (2)	10	blue LEDs (470 nm)	24	CH ₃ CN, C ₂	54
13	Cat. C (2)	5	blue LEDs (470 nm)	24	CH ₃ CN, C ₂	53
14	Cat. C (1)	5	blue LEDs (470 nm)	24	CH₃CN, C₂	53
15	Cat. C (5)	5	blue LEDs (470 nm)	24	DMPU, C₁	50

^{a)} Isolated yield. ^{b)} NMR Yield. ^{c)} FBL = Fluorescent Bulb Light. ^{d)} Not Determined, only traces of **31** were observed. ^{e)} C₁ = 0.1 M, C₂ = 0.067 M

× Selection of the photocatalyst

We investigated the ability of polypyridine ruthenium or iridium complexes to catalyze the photoreduction of **30** with Hunig's base (*N,N*-diisopropylethylamine = DIPEA) as sacrificial electron donor under visible light irradiation (Table 1).⁸⁶¹ We first tested the classical Ru(bpy)₃Cl₂ (5 mol%) with 10 equivalents of DIPEA in acetonitrile during 24 hours under 14W fluorescent light bulb (14W FLB) without success (Table 1, entry 1). This was attributed to the low reductive potential of its excited state ($E_{1/2}([\text{Ru}(\text{bpy})_3]^{3+}/[\text{Ru}(\text{bpy})_3]^{2+*}) = -0.87\text{V}$ (vs. SCE)). Under the same conditions, we change the catalyst to the more reductive Ir(dtbbpy)(ppy)₂PF₆ ($E_{1/2}([\text{Ir}]^{2+}/[\text{Ir}]^{+*}) = -0.96\text{V}$ (vs. SCE)). To our delight, the reduced compound **31** was isolated in 20%, which supported the viability of our photoreductive approach (Table 1, entry 2). With the strong reductive Ir(ppy)₃ ($E_{1/2}([\text{Ir}(\text{ppy})_3]^+/\text{Ir}(\text{ppy})_3^*) = -1.73\text{V}$ (vs. SCE)), we improved the reduction efficiency and obtained **31** in 47 % (Table 1, entry 3). We settled on this iridium catalyst for the rest of the study.



× Selection of the solvent

Using acetonitrile as solvent allowed us to obtain 47% of reduced product. Changing acetonitrile to DMPU (*N,N'*-dimethylpropyleneurea) gave a comparable yield (Table 1, entry 4) but any other solvent modification (NMP, DMF, DMSO and DCM; Table 1, entries 5-9) did not improve to the photoreduction process. It is worth noting that when the reactions were carried out with a concentration of 0.1 M, the iridium catalyst was not fully soluble in acetonitrile. At the concentration of 0.067 M, the photocatalyst was totally soluble in acetonitrile and we isolated 53% of product **31** (entry 10). So we selected acetonitrile as the best solvent for our reaction parameters.

× *Selection of the light source*

Fluorescent bulb lamp (14W) and blue LEDs (470 nm) gave similar results (Table 1, entries 10-11) which is consistent with a visible-light activation of the catalyst. Ir(ppy)₃ is activated at a wavelength of 375 nm, corresponding to a MLCT excitation. However blue LEDs provide a specific wavelength range without generating too much heat as the fluorescent lamps, and then limit the variation of the reaction temperature. We then selected blue LEDs as the light source for the photocatalyzed reactions.

× *Selection of the reagent stoichiometry*

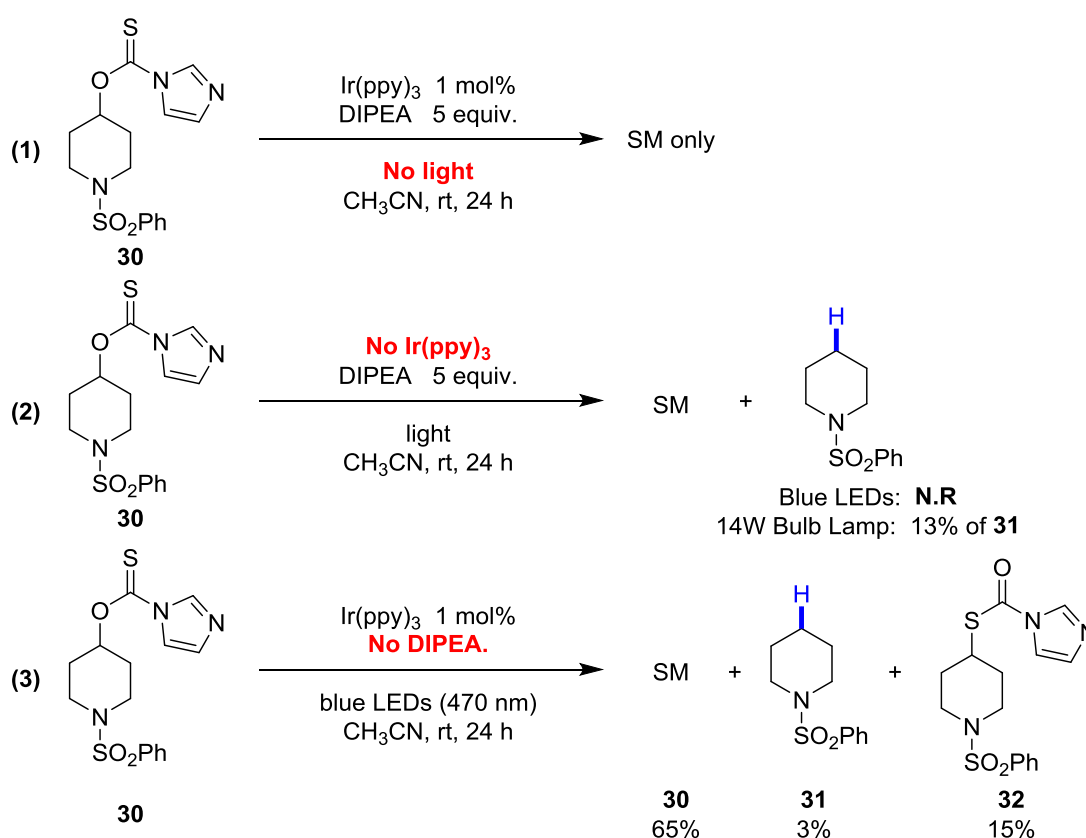
The next step was to decrease the catalyst concentration and the stoichiometry of the DIPEA. We observed that changing the catalytic loading of Ir(ppy)₃ from 5 mol% to 1 mol% did not affect the yield of the reaction (Table 1, entries 12-14). The same observation was made for diisopropylethylamine from 10 to 5 equivalents. Thus, Ir(ppy)₃ loading was fixed to 1 mol% in the presence of 5 equivalents of Hunig's base. The reaction was conducted in acetonitrile during 24 h under blue LED irradiation and reduced product **31** was obtained in 53% isolated yield (Table 1, entry 14). These last conditions were found as the best conditions for the photoreduction of **30**, and were kept as optimized conditions for the rest of the study. We decided to set alternative conditions involving DMPU that could be a helpful solvent for the deoxygenation of very lipophilic substrates and insoluble thiocarbamate in acetonitrile. Higher catalyst loading (5 mol%) was necessary to keep the same efficiency of the reduction (Table 1, entry 15). This modification was set as conditions B.

× *Control reactions*

Control reactions have been pursued in order to secure the role of each reagents and additives. The schlenk tube was shielded with an aluminum foil during 24 hours and no reaction occurred in the dark. All the starting material was recovered (Scheme 7, equation 1). In the absence of Ir(ppy)₃ photocatalyst, we ran the control experiment with both light sources (Scheme 7, equation 2). In the case of blue LEDs irradiation, no reaction occurred and only

starting material was recovered. When we used the 14W fluorescent light bulb, the reduced product **31** was isolated in 13% yield. The small amount of **31** formed could arise from a photoinduced electron-transfer (PET) between DIPEA and the thiocarbamate due to the presence of UV bands emitted by the fluorescent bulb lamp. This result definitively encouraged us to use the blue LEDs for deoxygenation reactions.

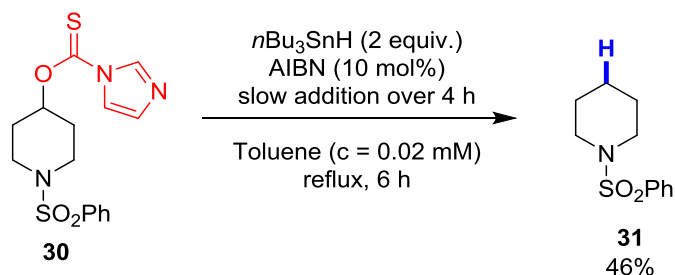
Then, only 3% of **31** were obtained when DIPEA was omitted (Scheme 7, equation 3) but interestingly, we isolated 15% of the thiocarbamate group transfer product (compound **32**). The formation of the *S*-thiocarbamate **32** will be explained and detailed in the mechanistic study of the photoreductive deoxygenation.



Scheme 7. Control reactions for reduction of *O*-thiocarbamates

Finally, we compared our photocatalytic conditions to the conventional Barton-McCombie deoxygenation reaction. The reduction of **30** was run in refluxing toluene ($c = 0.02$ mM) with a slow addition of AIBN (10 mol%) and $n\text{Bu}_3\text{SnH}$ (2 equiv) solution over 4 hours. Complete conversion was observed after two additional hours and **31** was obtained in 46% (NMR yield). The optimized tin conditions furnished a lower yield than our conditions. This finding was highly suggestive that a photocatalytic Barton-McCombie deoxygenation

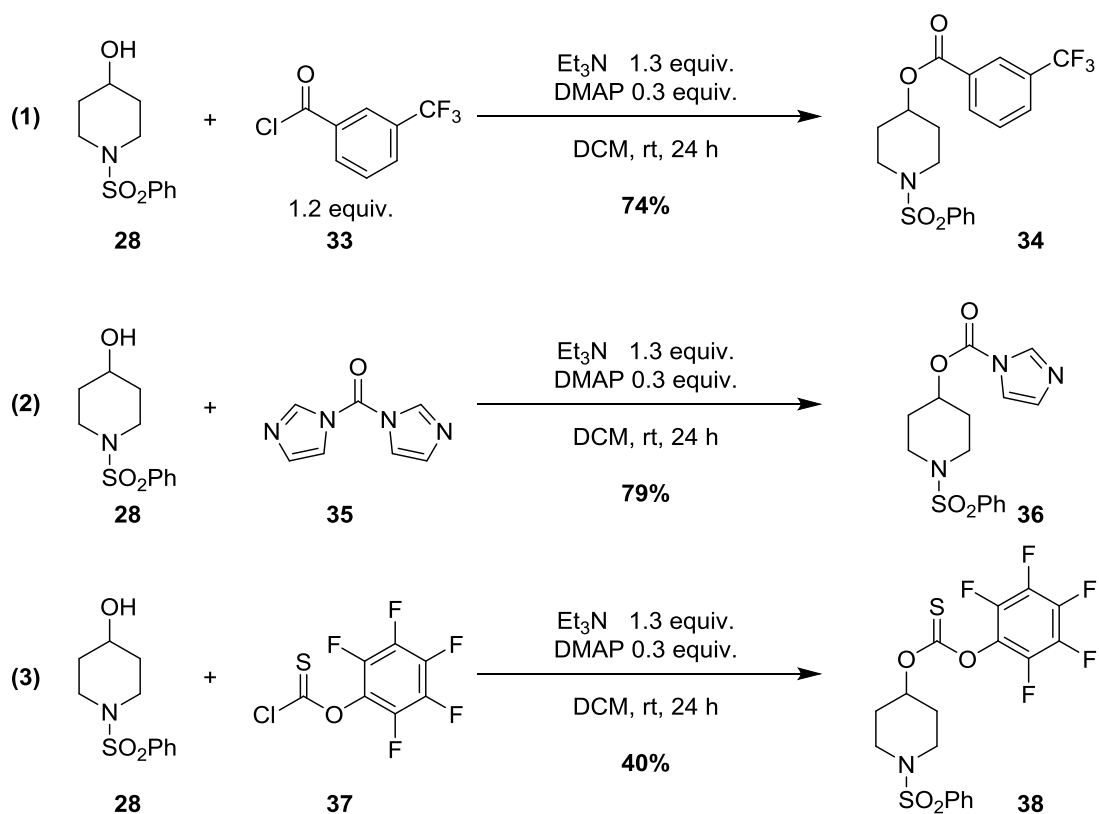
could be competitive with the original method and would constitute a versatile tool for applications in organic synthesis.



Scheme 8. Tin-mediated radical reduction of *O*-thiocarbamate **30** to **31**

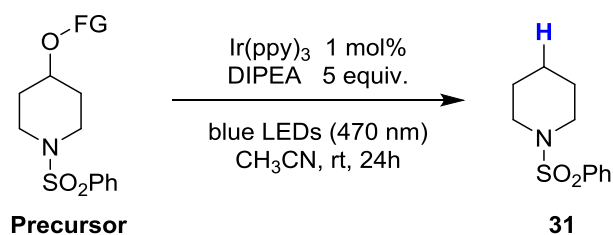
II.B.3.b. Influence of the leaving group

We investigated the influence of the leaving group on the deoxygenation reaction. Three different types of precursors were prepared from secondary alcohol **28** bearing a trifluoromethyl-substituted benzoate (**34**), an imidazolcarbamate (**36**) and a pentafluorophenyl *O*-thionoformate (**38**) group. These substrates are usually used in the conventional Barton-McCombie deoxygenation and are valuable alternatives to test in photoreductive conditions. To be mentioned, the synthesis of product **36** was almost quantitative, but the product was not stable on chromatography column.



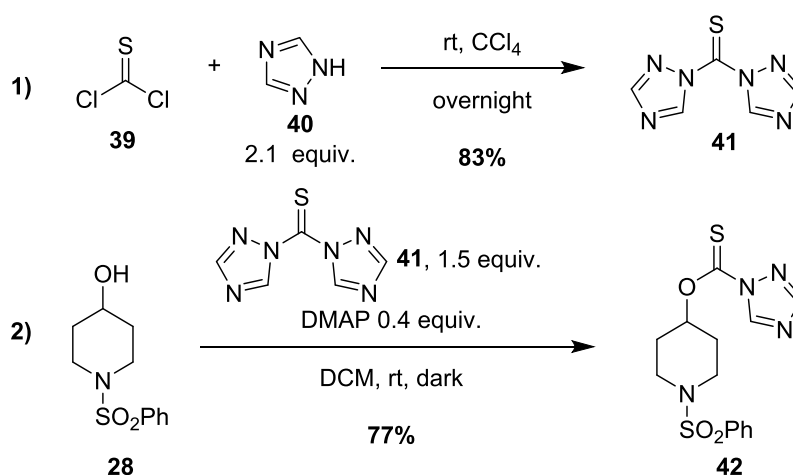
Scheme 9. Synthesis of other *O*-functional groups

Under the optimized photoreductive conditions, **36** and **34** did not afford the reduced product **31** and only the starting material was recovered. In the same conditions, **38** yielded less than 20% of reduced product **31** (Table 2). Based on this set of substrates, we are able to highlight the influence of the sulfur atom. Indeed, **30** was smoothly reduced while **36** was inert. Concerning the aromatic moiety, it is clear that it strongly influences the reductive ability of the substrate but we do not have enough examples to rationalize this effect.

Table 2. Photocatalyzed reduction of various functional groups

Entry	Precursor	Yield of 31
1	34	SM Only
2	36	SM Only
3	38	20%

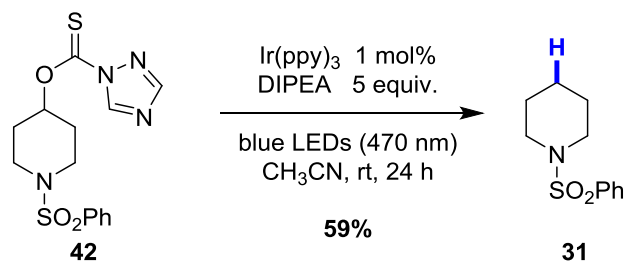
In the same line, we increased the electrodeficiency of the heterocyclic moiety in order to favor the SET reduction. We changed the imidazolyl residue to the corresponding triazolyl. As a donor of triazolyl thiocarbonyl group, we synthesized the 1,1'-thiocarbonyldi-1,2,4-triazole **41** according a previously described method.⁹² In carbon tetrachloride, a mixture of thiophosgene **39** and triazole **40** were stirred overnight to afford 83% of the desired thiocarbonyl precursor **41** (Scheme 10, equation 1). The *N*-protected 4-hydroxypiperidine **28** was successfully transformed into the corresponding thiocarbamate **42** in the presence of a catalytic amount of DMAP and **41** in a good yield of 77%.

**Scheme 10.** Synthesis of triazole *O*-thiocarbamate

⁹² C. Larsen, K. Steliou, D.N. Harpp *J. Org. Chem.* **1978**, *43*, 337.

We subjected compound **42** to our photoreduction conditions. We obtained a slight improvement in the reaction efficiency since the reduction product **31** was isolated in 59% yield (Scheme 11). In order to evaluate the influence of the redox parameters, we determined the reduction potential of this *O*-thiocarbamate **42** and compared it with **30**. We measured a potential of -1.59 V vs. SCE which is higher than the potential of the imidazolyl *O*-thiocarbamate equivalent **30** ($E_{\text{red}} = -1.68$ V vs. SCE). This observation suggested that the reduction of **42** is more thermodynamically favored than the reduction of **30** in our photoreductive conditions.

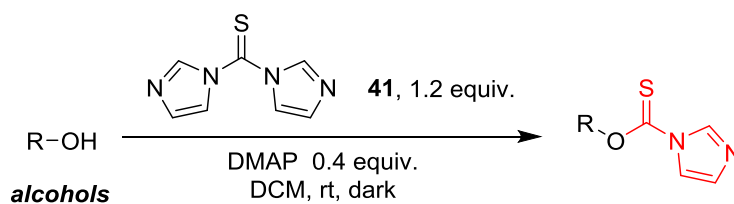
We considered this slight improvement not enough significant to justify other studies with this new precursor. So, we developed our methodology with the thiocarbamate imidazole moiety as leaving group.



Scheme 11. Photoreduction of triazole *O*-thiocarbamate

II.B.3.c. Synthesis of other *O*-thiocarbamates from the corresponding alcohols

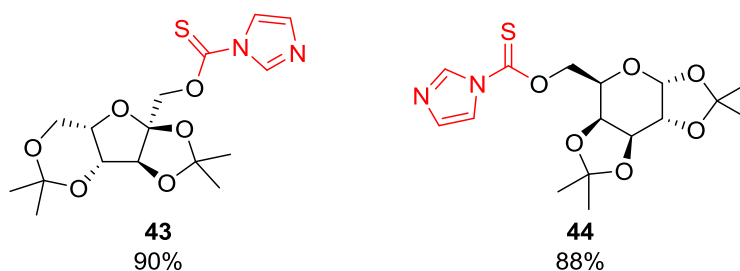
O-Thiocarbamates (all structures are reported below) were prepared following the procedure described in scheme 12 in high yields from the corresponding alcohols and *N,N'*-thiocarbonyldiimidazole (1.2 equiv) with a catalytic amount of DMAP (0.4 equiv). The reaction was done in the dark and the isolated *O*-thiocarbamates are stable and can be stored in freezer for a long period without any other precaution.



Scheme 12. One step synthesis of *O*-thiocarbamates from alcohols and commercially available reagents

✕ *Synthesis of O-thiocarbamates from primary alcohols*

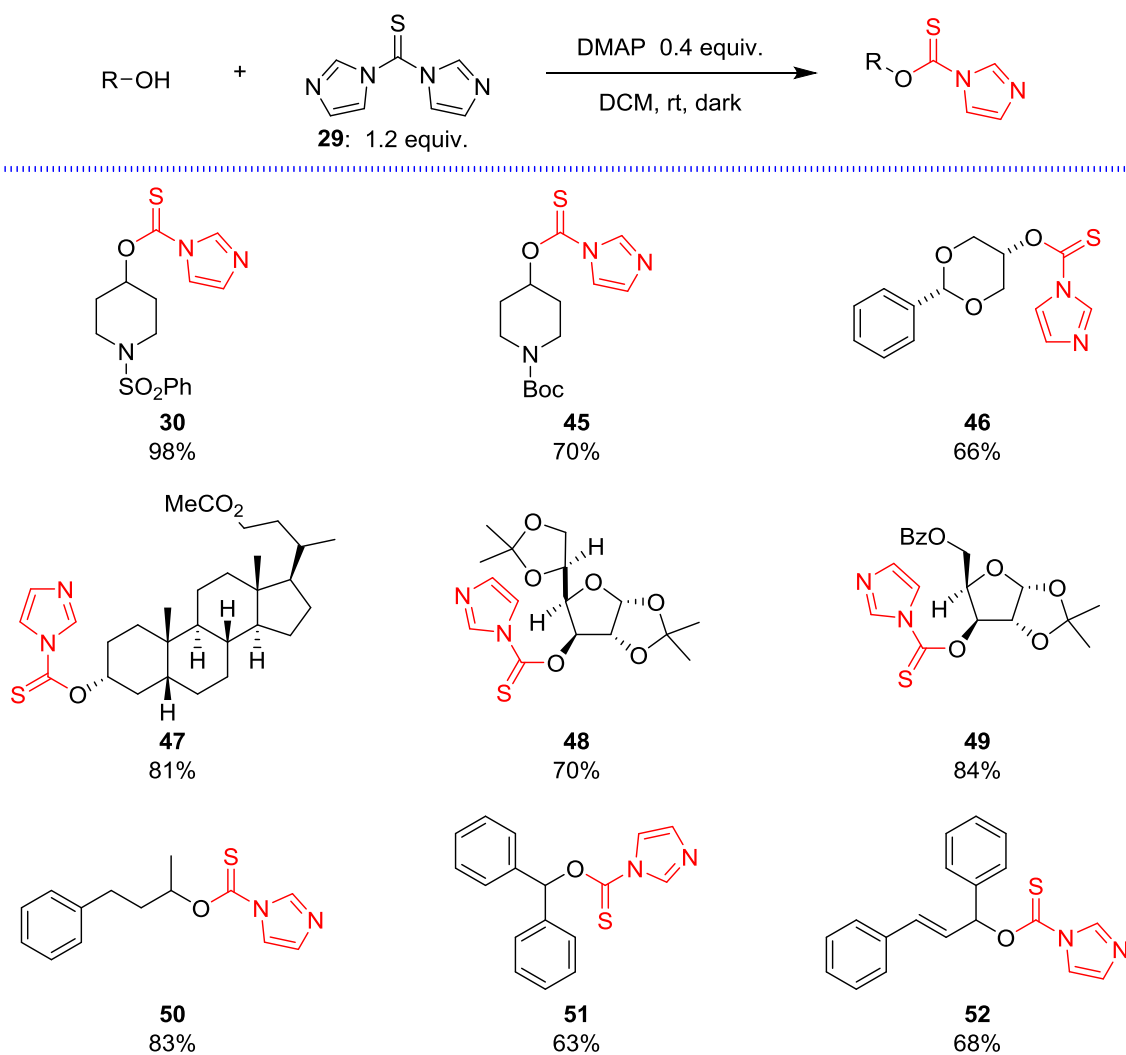
The commercially available free alcohols were successfully derivatized with *N,N'*-thiocarbonyldiimidazole following the classical procedure, and thiocarbamates **43** and **44** were isolated in high yields, 90% and 88% respectively (Scheme 13).



Scheme 13. Synthesis of *O*-thiocarbamates from primary alcohols

✕ *Synthesis of O-thiocarbamates from secondary alcohols*

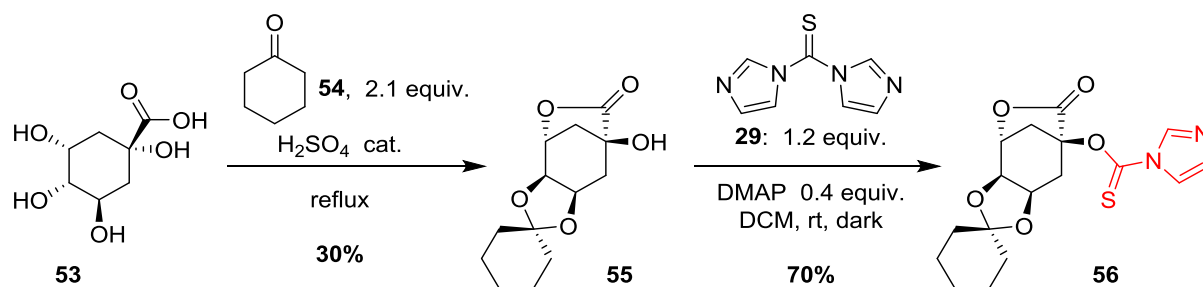
A set of thiocarbamates from secondary alcohols was designed with a large structural and functional diversity in order to investigate the functional group tolerance of our photoreduction reaction. Acyclic *O*-thiocarbamate **50** (83%), **51** (63%) and **52** (68%) were obtained in good yields from the corresponding alcohols. **51** and **52** would be also valuable precursors of benzylic radicals. In the cyclic series, compounds **30**, **45-49** were generated from the 6- and 5-membered cyclic alcohols in high yields (66-98%). All of these substrates contain functional groups such as carbamate, sulfonamide, acetal, ester and benzoyl groups.



Scheme 14. Synthesis of a set of *O*-thiocarbamates from secondary alcohols

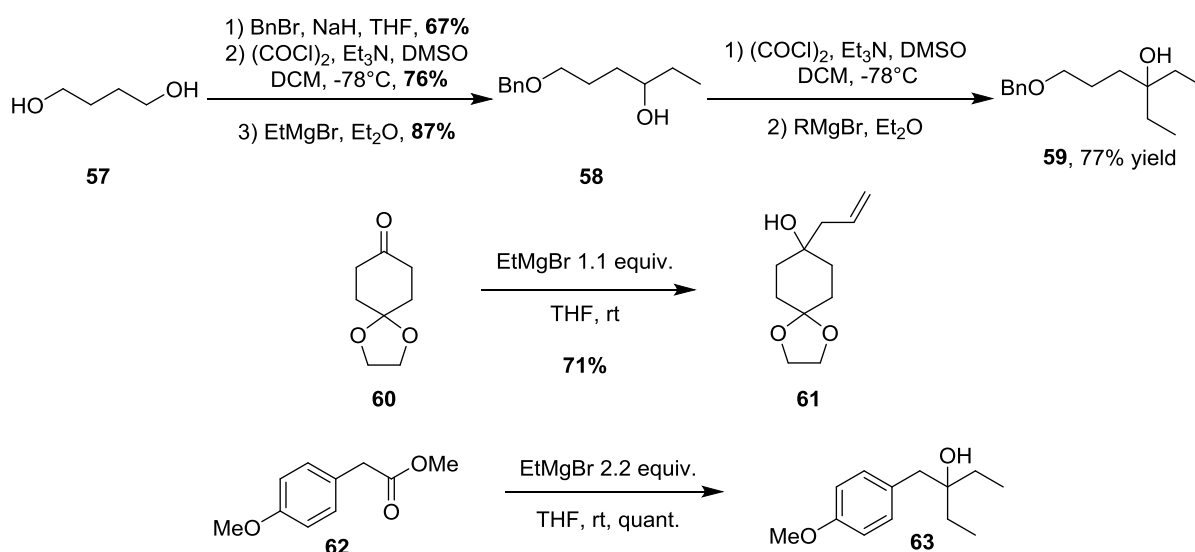
✕ *Synthesis of O-thiocarbamates from tertiary alcohols*

The synthesis of tertiary *O*-thiocarbamate **56** was envisioned as followed. The protection of the D-(-)-quinic acid **53** by the cyclohexanone **54** in presence of catalytic amount of sulfuric acid allowed to isolate **55** in 30% yield. Then, **55** reacted with the 1,1'-thiocarbonyldiimidazole **29** gives the desired thiocarbamate **56** in 70% yield.



Scheme 15. Synthesis of thiocarbamate **56** from quinic acid

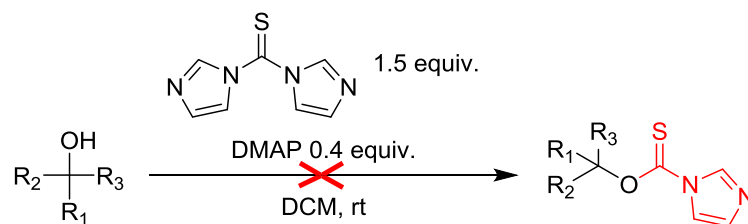
It was planned to prepare other different tertiary alcohols in order to bring more structural diversity (Scheme 16). The alcohol **59** was synthesized from the intermediate **58**, which was obtained according to the sequence monoprotection of **57**, alcohol oxidation and addition of ethyl Grignard reagent to the ketone. A second Swern oxidation followed by the addition of a second equivalent of ethyl Grignard reagent to the ketone afforded the desired tertiary alcohol **59**. The monoprotected 1,4-cyclohexanedione **60** and 4-methoxyphenylacetate **62** were treated with an excess of allyl and ethyl Grignard reagent to give **61** and **63** in 71% and quantitative yields respectively.



Scheme 16. Synthesis of tertiary alcohols

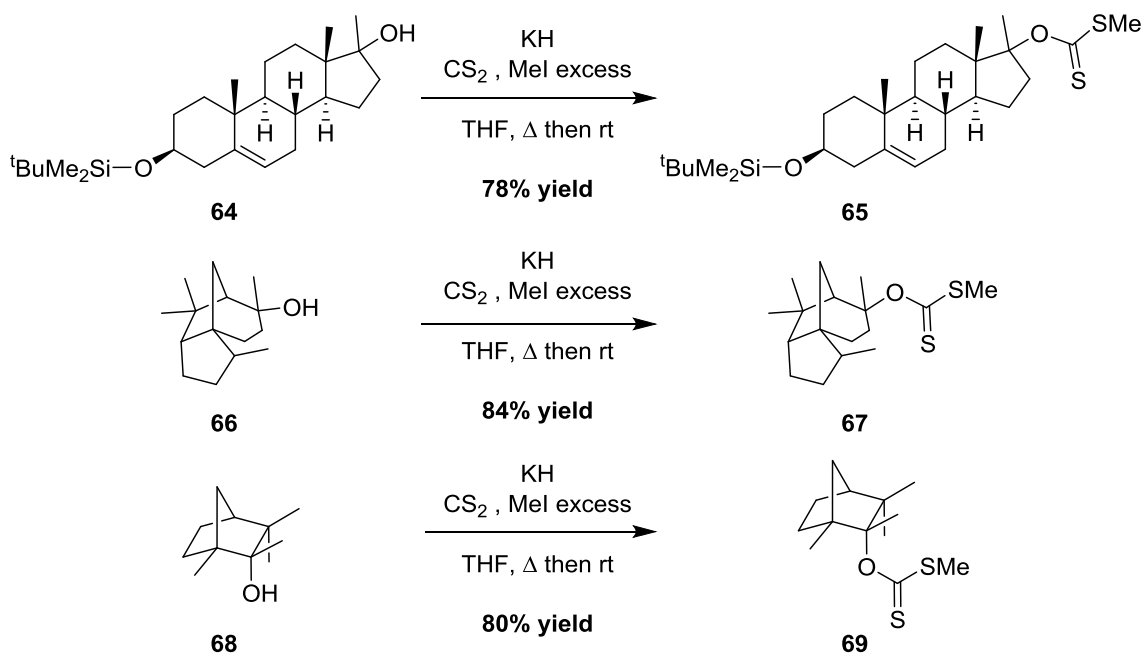
With these three tertiary alcohols in hand, we tried to transform them into the corresponding tertiary *O*-thiocarbamates using our classical conditions. Unfortunately, no formation of thiocarbamate was observed. Heating and/or changing the amount of reagents did not furnish any products and only the starting material was recovered (Scheme 17). It is

important to note that to the best of our knowledge, no *O*-thiocarbamates imidazolyl derivating from tertiary alcohols are reported in the literature.



Scheme 17. Synthesis of *O*-thiocarbamates from tertiary alcohols

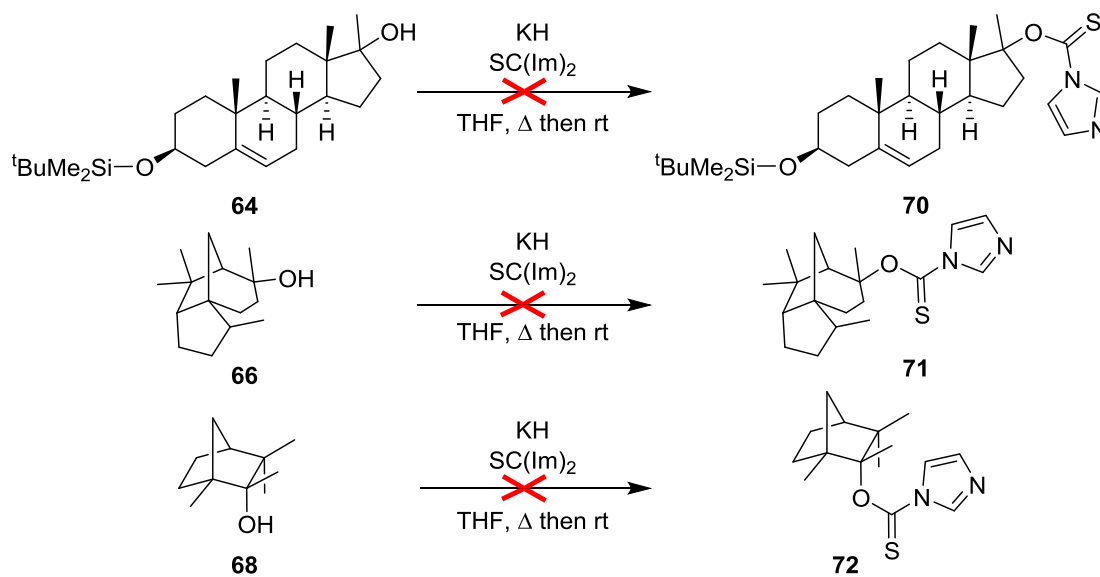
In 1993, Barton and co-workers reported the unique effective way to synthesize tertiary xanthates from three different tertiary alcohols.⁹³ The first alcohol **64** was prepared from the commercial *trans*-dehydroandrosterone (DHEA) after protection of the secondary alcohol with a silyl group followed by methyl Grignard addition to the ketone group. The cedrol **66** is commercially available and the alcohol **68** was prepared by 1,2 methylation of the L-fenchone. After refluxing tertiary alcohols **64**, **66** and **68** with potassium hydride, CS₂ was added at room temperature followed by addition of an excess of iodomethane to give the desired tertiary xanthates in high yields. They showed also that the use of sodium hydride or other alkyl lithium reagents was not effective for this transformation.



Scheme 18. Synthesis of tertiary xanthates

⁹³ D.H.R. Barton, S.I. Parekh, C.-L. Tse, *Tetrahedron Lett.* **1993**, 34, 2733.

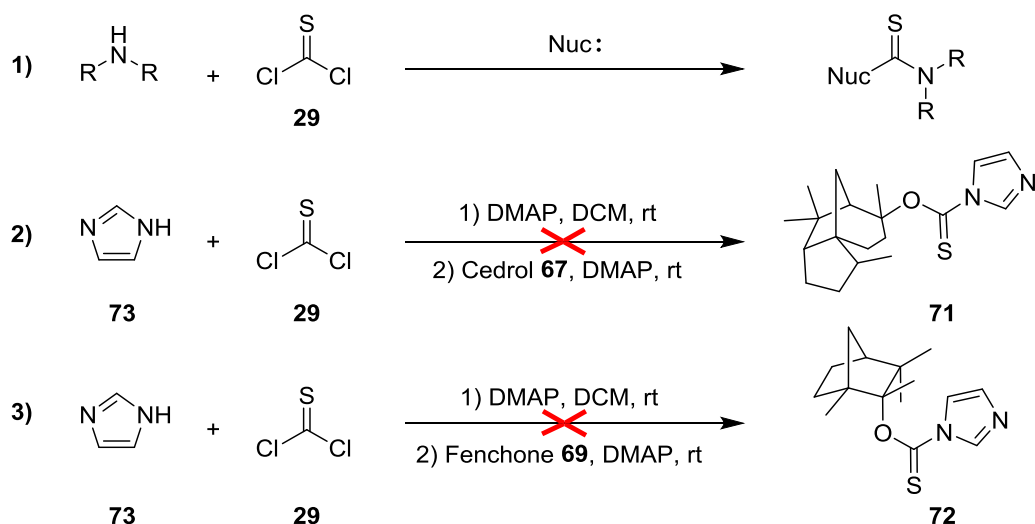
We decided to use this methodology for the synthesis of tertiary thiocarbamates. We synthesized the same alcohols **64** and **68** in good yields. Unfortunately, treatment with potassium hydride and 1,1'-thiocarbonyldiimidazole did not allow us to isolate the thiocarbamates compounds (Scheme 19). Modifications of the conditions, such as the temperature or the reagents stoichiometry, did not give the expected products.



Scheme 19. *O*-thiocarbamates formation from tertiary alcohols

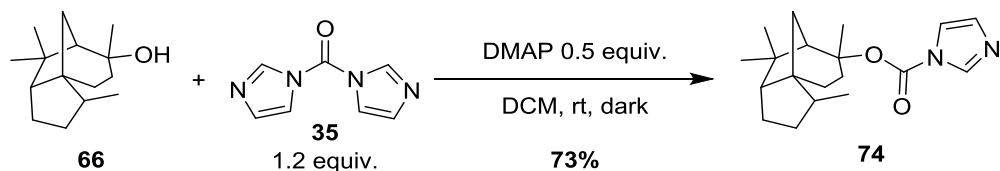
The group of Hirai published a study on nucleophilic reaction of alcohols or amines with *in-situ*-prepared thiocarbamoyl chloride precursor which allowed them to obtain the corresponding thiocarbamates or thioureas derivatives (Scheme 20, equation 1).⁹⁴ After premixing imidazole and thiophosgene in dichloromethane, a solution of tertiary alcohol is added but no reaction occurs and only the starting alcohol was isolated. The use of triethylamine instead of DMAP with a higher temperature and a longer reaction time did not give any improvement (Scheme 20, equations 2 and 3).

⁹⁴ H. Sugimoto, I. Makino, K. Hirai, *J. Org. Chem.* **1988**, *53*, 2263.



Scheme 20. Alternative synthesis of tertiary *O*-thiocarbamates

To date, tertiary *O*-thiocarbamates reported in the literature are limited to quinic γ -lactone derivatives⁹⁵ or tertiary alcohol with specific conformation.⁹⁶ Interestingly the synthesis of carbamate **74** from cedrol **66** worked smoothly in good yield (Scheme 21).

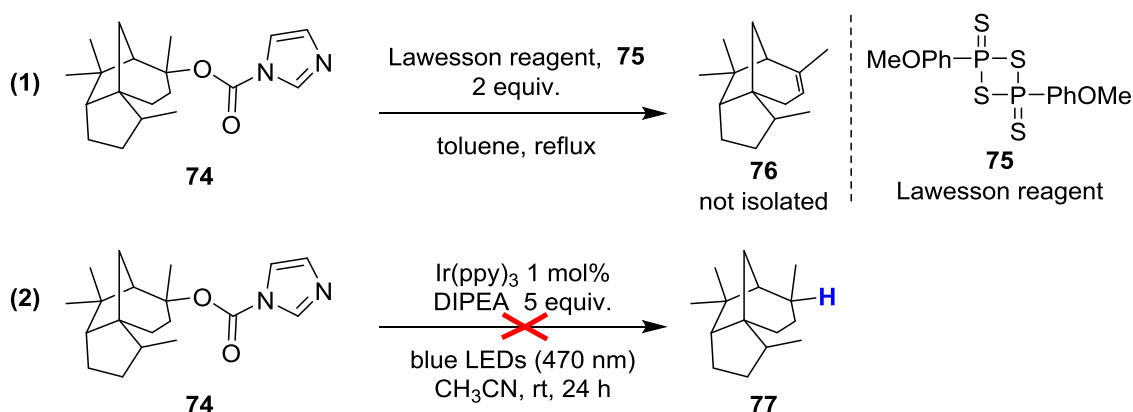


Scheme 21. Carbamate synthesis from tertiary alcohol

With this carbamate in hand, our first attempt was to transform the carbonyl into a thiocarbonyl group using the Lawesson reagent **75** in refluxing toluene. Only the product of elimination **76** was observed by ¹H NMR as major product of the reaction (Scheme 22, equation 1). We tried to reduce the carbamate **74** in cedrane **77** under our optimized photoreductive conditions. After reaction and work up, only the starting material was recovered without traces of the deoxygenated product **77** (Scheme 22, equation 2).

⁹⁵ a) S. Mills, R. Desmond, R.A. Reamer, R.P. Volante, I. Shinkai, *Tetrahedron Lett.* **1988**, 29, 281. b) Z.S. Su, L.A. Paquette, *J. Org. Chem.* **1995**, 60, 764. c) J.D. White, J. Deerberg, S.G. Toske, T. Yakura, *Tetrahedron* **2009**, 65, 6635.

⁹⁶ a) K.C. Nicolaou, P. Maligres, T. Suzuki, S.V. Wendeborn, W.M. Dai, R.K. Chadha, *J. Am. Chem. Soc.* **1992**, 114, 8890. b) F.A. Bermejo, A.F. Mateos, A.M. Escribano, R.M. Lago, L.M. Buron, M.R. Lopez, R.R. Gonzalez, *Tetrahedron* **2006**, 62, 8933.

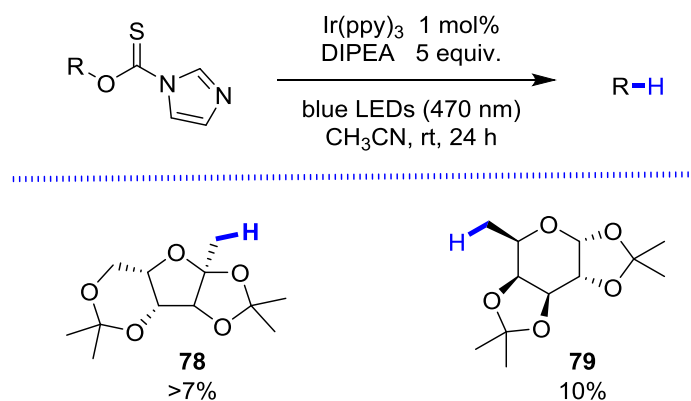


Scheme 22. Transformations of the carbamate **74**

II.B.3.d. Scope and limitations of the photoreductive deoxygenation of alcohols

✕ *Photoreductive deoxygenation of primary alcohols*

The *O*-thiocarbamates **43** and **44** were submitted to our optimized photoredox conditions. Photoreduction of **43** gave less than 7% of reduced product **78** (NMR yield). For the *O*-thiocarbamate **44** only 10% of product **79** were observed. In all cases, a large amount of degradation products was obtained with the presence of traces of the free alcohol. This can be explained by a slow fragmentation of the radical intermediate. Indeed, this process is not favored for a primary radical release and can explain the formation of a number of side products.

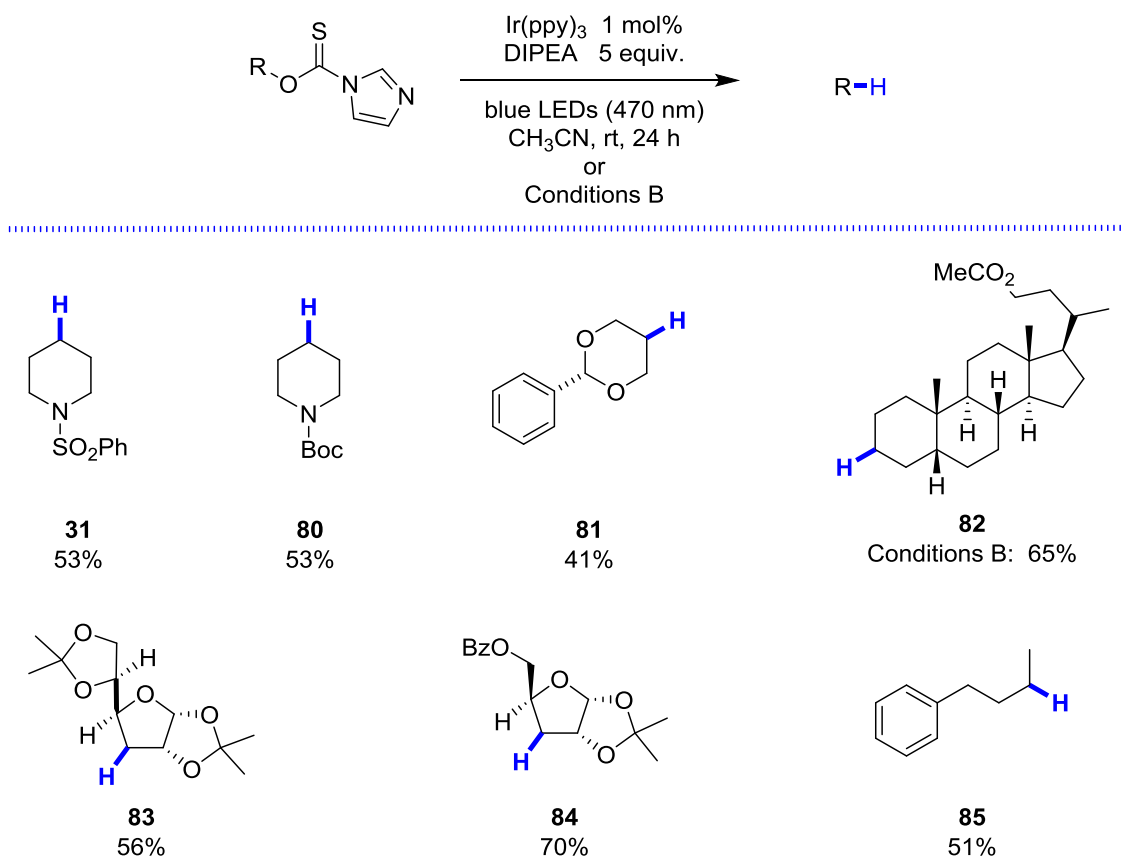


Scheme 24. Photoreduction of primary *O*-thiocarbamate

✕ *Photoreductive deoxygenation of secondary alcohols*

The model substrate **30** was modified by changing the *N*-sulfonyl group to a Boc carbamate **45** that was also compatible with the reaction conditions and **80** was obtained in a comparable yield of 53% (Scheme 25). The isolation of **81** in 41% yield from **46** was a bit tedious due to its volatility but the benzylidene acetal was tolerated under such mild reduction conditions. To extend the scope, lithocholic acid derivative **47** was reduced under conditions B due to its poor solubility in acetonitrile. Indeed, DMPU was more suitable for this reaction and the corresponding deoxygenated steroid **82** was obtained in good yield of 65%.

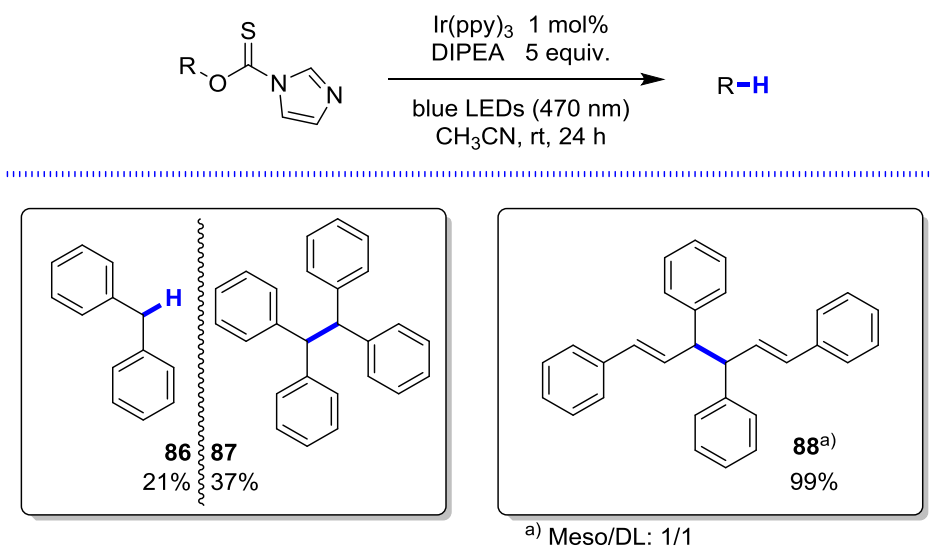
Other very interesting chemoselectivities were highlighted in the reduction of **48** and **49**. Indeed, the diacetone-D-glucopyranose derivative **48** was deoxygenated at the 3-position to afford the corresponding 3-deoxy compound **83** in 56% yield. Even more interestingly, the benzoyl group at the 5-position of xylofuranose derivative **49** stayed untouched and the reduction proceeded well in 70% yield (**84**).^{38, 84} The secondary aliphatic *O*-thiocarbamate **50** was smoothly deoxygenated giving **85** in 51% yield.



Scheme 25. Photodeoxygenated products scope

Secondary benzylic (**51**) and allylic (**52**) alcohol derivatives were engaged in this photocatalyzed deoxygenation sequence (Scheme 26). Benzhydrol derivative **51** was reduced under our optimized conditions to afford 1,1-diphenylmethane **86** (21%) and dimer 1,1,2,2-tetraphenylethane **87** (37%), characteristic of benzylic radical reactivity. Interestingly, **52** was efficiently reduced to afford the corresponding dimerization compound **88** in quantitative yield as a 1:1 mixture of DL and *meso* diastereoisomers.⁹⁷ No reduction product was observed, due to the specific reactivity of such stabilized radicals.

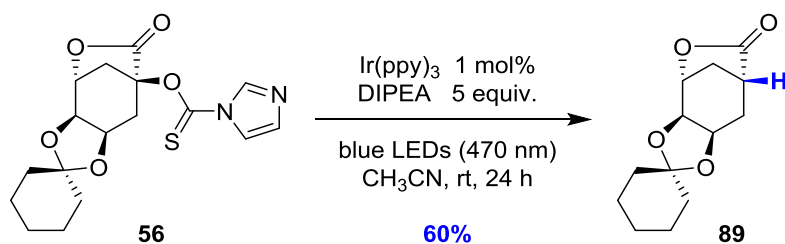
⁹⁷ W. v. E. Doering, L. Birladeanu, K. Sarma, G. Blaschke, U. Scheidemantel, R. Boese, J. Benet-Bucholz, F.-G. Klärner, J.-S. Gehrke, B. U. Zimny, R. Sustmann, H.-G. Korth, *J. Am. Chem. Soc.* **2000**, *122*, 193.



Scheme 26. Benzylic radical generation and dimerization

✕ *Photoreductive deoxygenation of tertiary alcohols*

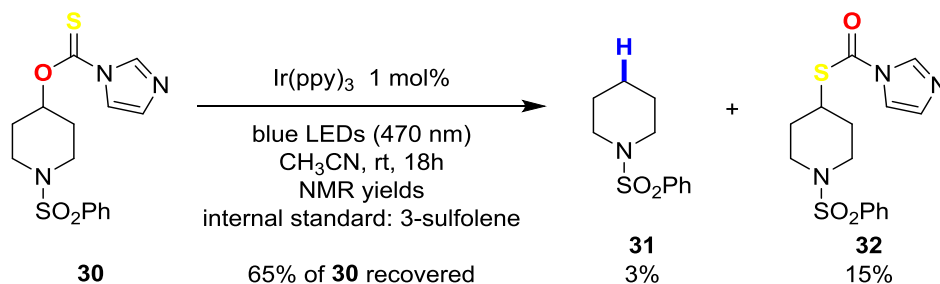
The reduction of the tertiary *O*-thiocarbamate **56** coming from the quinic acid allowed to isolate the corresponding product **89** in 60% yield as a single diastereoisomer. This reaction clearly showed the potentiality of the method to deoxygenate functionalized tertiary substrates in good yield.



Scheme 27. Photoreduction reaction of tertiary thiocarbamate

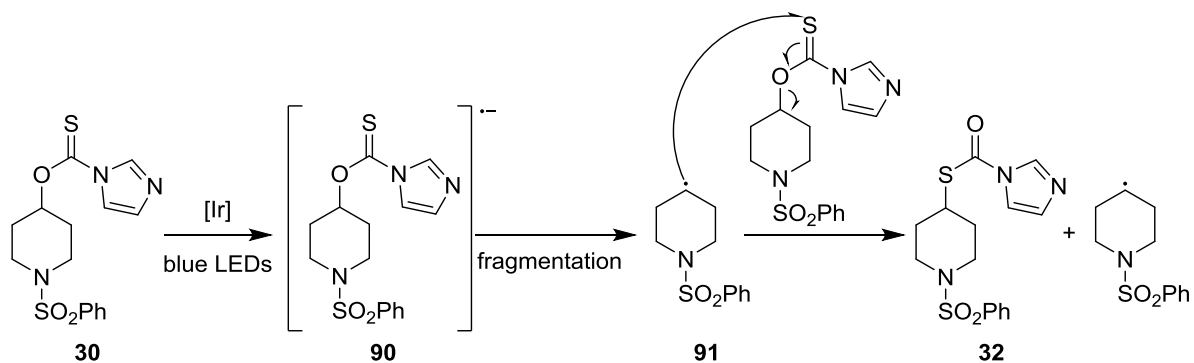
II.B.4. Mechanistic Studies of the Photoredox Catalyzed

To gain insight into the mechanism of this reaction and understand the role of each constituent, we engaged *O*-thiocarbamate **30** without DIPEA (Scheme 28).



Scheme 28. Reaction in absence of DIPEA: *O*-Thiocarbamate transfer to *S*-thiocarbamate

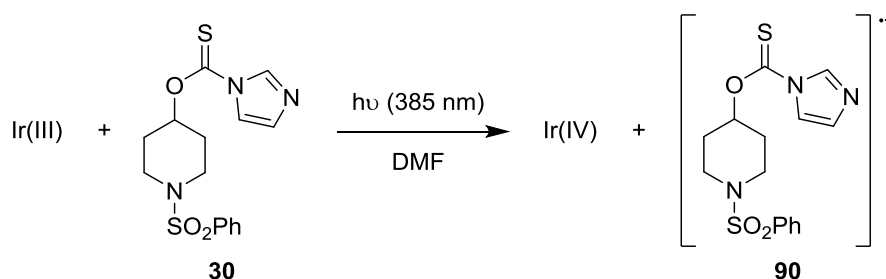
In the absence of a sacrificial donor of electron (DIPEA), the deoxygenated product **31** and the *S*-thiocarbamate **32** were isolated in 3% and 15% yield, respectively while 65% of **30** was recovered (determined by ¹H NMR with 3-sulfolene as internal standard). The formation of **32** presumably originates from a thiocarbamate group radical transfer (scheme 29). Thus, valuable information can be deduced: without DIPEA, the carbon-centered radical is formed and the DIPEA plays an important role in the terminal hydrogen transfer to afford the resulting reduced product.^{6k} Indeed, in the absence of the Hunig's base, the carbon-centered radical would add on the sulfur atom of **30** to propagate the radical chain reaction. This chain reaction seems to be moderately efficient because 1 mol% of photocatalyst resulted in 15% of the group transfer compound **32** but is quite interesting in terms of mechanistic implications and perspectives.



Scheme 29 Thiocarbamate group transfer reaction

At that stage, questions arose: How **30** can be reduced by Ir(ppy)₃? And how does DIPEA act in the catalytic process? We decided to answer these questions by studying the fluorescence quenching studies of Ir(ppy)₃* (Scheme 30 and figure 1).

✕ *Fluorescence quenching studies*



Scheme 30. The fluorescence quenching test considered

Our first attempt was to determine if a reduction reaction can occur between the iridium(III) complex and particularly its excited state, and the thiocarbamate substrate **30** as described in scheme 30. Fluorescence quenching experiment are perfectly adapted for this purpose. The principle of this study is the irradiation of a molecule, such as a transition metal complex, at its maximum of absorbance, and then the emission spectrum is recorded. Addition of a specific concentration of suspected interacting substrate should modify the emission by quenching the excited state of the molecule (such as the metal complex). Increasing amount of potential quencher is added until no effect is observed. It is called Stern-Volmer experiment.⁹⁸

⁹⁸ J. W. Verhoeven, *Pure Appl. Chem.* **1996**, 68, 2223

Fluorescence quenching has been done by addition of *O*-thiocarbamate **30** to a solution of Ir(ppy)₃ in DMF. This solvent was used because of its higher boiling point than acetonitrile that thus allowed an efficient degassing without concentration changes. The fluorescence signal of Ir(ppy)₃ was recorded under excitation at 385 nm for a maximum of fluorescence emission at 528 nm (Figure 1).⁹⁹ To a 1 mM solution of Ir(ppy)₃ maintained in the dark, **30** was added to obtain 0.6, 0.7 and 0.99 mM as final concentrations. The corresponding fluorescence spectra showed a significant decrease of the intensity while the concentration of **30** increased. The fluorescence intensity ratio (I_0/I_c , I_0 = fluorescence intensity without quench, I_c = fluorescence intensity with a quench concentration of c) at 528 nm was plotted against **30** concentration ($I_0/I_c = 1 + k_q \tau [c]$). A linear variation was observed and followed a Stern-Volmer law with a quenching rate constant $k_q = 6.5 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ that supports an energy transfer or an electron transfer process between the excited Ir(ppy)₃* and thiocarbamate **30**.¹⁰⁰

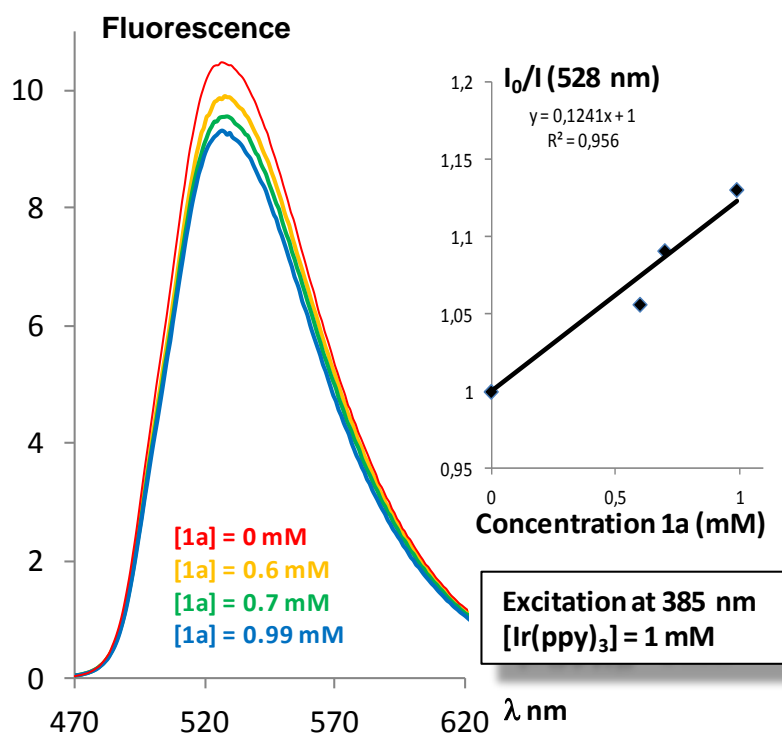


Figure 1. Fluorescence quenching studies of Ir(ppy)₃* with *O*-thiocarbamate **30**

⁹⁹ K. A. King, P. J. Spellane, R. J. Watts, *J. Am. Chem. Soc.* **1985**, *107*, 1431

¹⁰⁰ J. R. Lakowicz, *Principles of Fluorescence Spectroscopy*, third edition, Springer, **2006**.

× Cyclic voltammetry studies

To balance these two processes, we did cyclic voltammetry that allowed us to determine the reduction potentials of a representative set of thiocarbamates (Table 3). The redox potentials have been measured by cyclic voltammetry using a glassy-carbon electrode in a 0.1M solution of $[n\text{-Bu}_4\text{N}]\text{PF}_6$, as supporting electrolyte, in degassed HPLC grade acetonitrile; Fc^+/Fc as internal standard, under argon atmosphere. Scan rate: 0.1 V/s, Saturated Calomel Electrode used as reference electrode and platinum as counter electrode.

We found that modification of N-sulfonyl group of substrat **30** to the Boc group of **45** has an influence on the potential value. With an $E_{\text{red}}(\mathbf{45}) = -1.73$ V vs. SCE, the potential of **45** is lower than the one of **30** ($E_{\text{red}}(\mathbf{30}) = -1.63$ V vs. SCE). For substrate **49** and the tertiary *O*-thiocarbamate **56**, their potentials are much higher than the potential of **30**. Indeed, compounds **49** and **56** were reduced at -1.67 V and -1.56 V vs. SCE respectively. The benzylic substrate **52** appeared to be more easily reduced than the others thiocarbamates (-1.11 V vs. SCE). These measurements support that $\text{Ir}(\text{ppy})_3^* \{E_{1/2}([\text{Ir}(\text{ppy})_3]^+/\text{Ir}(\text{ppy})_3^*) = -1.73$ V (vs. SCE)} is able to reduce the *O*-thiocarbamates to the corresponding radical anions.

Table 3. Peaks reduction potentials of thiocarbamates ^{a)}

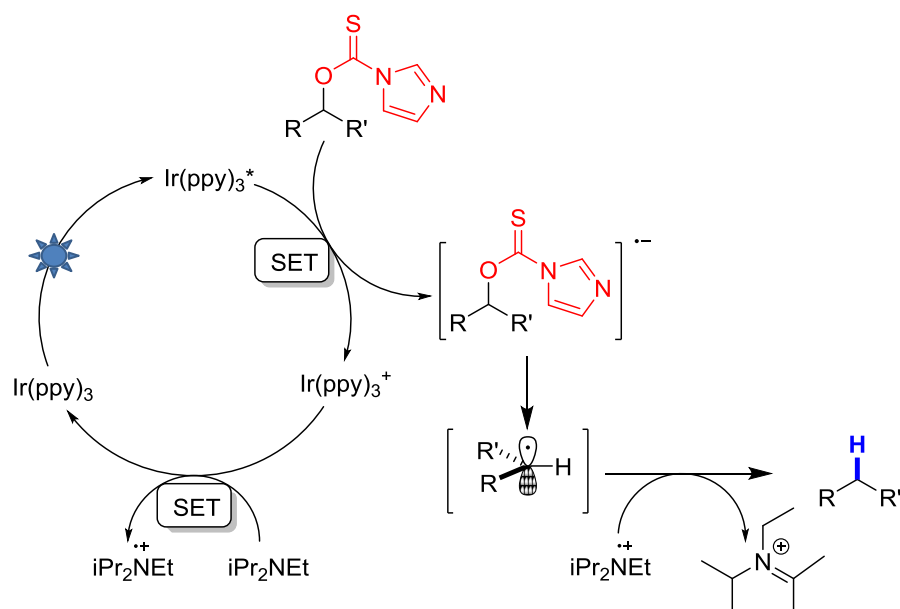
Substrate (Sub)	30	45	49
$E_{\text{red}}(\text{V})^{\text{b)}} [\text{Sub}]/[\text{Sub}]^-$	-1.68	-1.73	-1.67
Substrate (Sub)	52	56	32
$E_{\text{red}}(\text{V})^{\text{b)}} [\text{Sub}]/[\text{Sub}]^-$	-1.11	-1.56	<-2

^{a)} For cyclic voltamograms, see supporting information.

^{b)} The redox potentials are given in Volt versus SCE.

Moreover, no reduction wave is observed for the *S*-thiocarbamate **32** up to -2 V. This is consistent with the observed radical thiocarbamate group transfer (Scheme 28 and 29) when the reaction is conducted without Hünig's base and confirms that $\text{Ir}(\text{ppy})_3^*$ is not able to reduces *S*-thiocarbamates.

Based on all these findings, we were able to propose a mechanistic pathway for the photocatalyzed deoxygenation of imidazolyl *O*-thiocarbamate (Scheme 5). Under visible light activation, Ir(ppy)₃ is able to reach an excited state that could transfer one electron to the thiocarbamate moiety.¹⁰¹ This reduction process leads to the oxidation of Ir(III) to Ir(IV) species that would be reduced in turn to Ir(ppy)₃ by (*i*-Pr)₂NEt and starts a new catalytic cycle. Then, the thiocarbamate radical anion decomposes by fragmentation to afford the intermediate carbon-centered radical. The hydrogen transfer occurs either from the amine radical cation coming from the reduction of iridium catalyst or directly by (*i*-Pr)₂NEt.^{6k} This mechanism is supported by the fluorescence quenching experiments and the fact that in the absence of “H-donor”, the thiocarbamate transfer is observed.



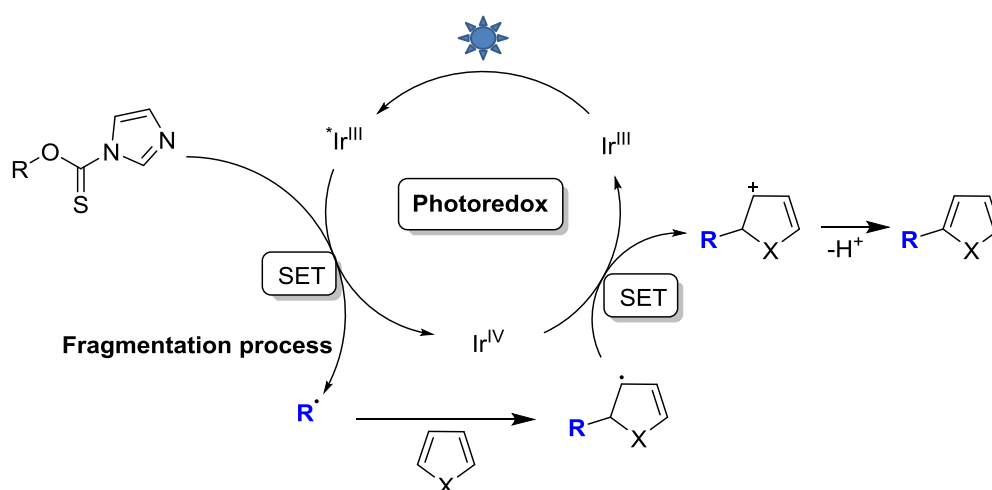
Scheme 30. A proposed mechanism for the photoreductive deoxygenation

× *Radical trapping experiments*

In order to increase the valuable impact of our photoreductive deoxygenation process, we tried to trap the secondary alkyl radical with heterocyclic compounds leading to more elaborated structures. Due to the previous mechanistic studies, we know a single electron

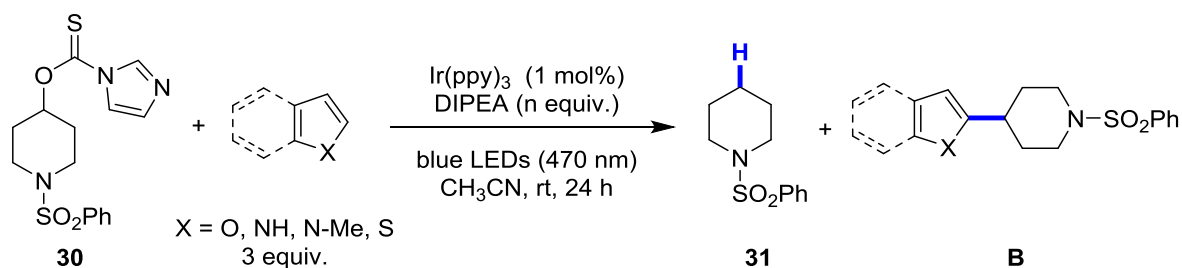
¹⁰¹ Q. Liu, H. Yi, J. Liu, Y. Yang, X. Zhang, Z. Zeng, A. Lei, *Chem. Eur. J.* **2013**, *19*, 5120.

transfer process occurs between the excited iridium and the thiocarbamate **30** to afford the C-centered radical. In absence of H-donor in the reaction medium, it could be possible to trap this radical by other acceptor and create C-C bond. The first attempt was to realize the transformation without the Hünig's base using the radical adduct as a donor of electron to regenerate the Ir(III) catalyst as shown in scheme 31. We selected furan and several heterocyclic derivatives as coupling partner for this reaction.



Scheme 31. Sequential deoxygenation/arylation in one-pot

With 1 mol% of Ir(ppy)₃ under irradiation, we tried to trap the secondary alkyl radical from the reduction of **30** with 3 equivalents of thiophene. Only starting material was observed (Table 4, entry 1). To confirm that the heterocyclic additive is not detrimental for the photoredox process, we performed the reaction in presence of DIPEA. We obtained a significant amount of reduced product **31** without formation of the arylation compound (Table 4, entries 2, 4, 6, 7, 9). With benzothiophene, methylindole, and furan, only traces of trapped adducts have been observed as well as the presence of the group transfer product, the *S*-thiocarbamate **32**, around 20% yield. The most encouraging result was obtained when 50 equivalents of furan were engaged leading to the formation of 15% of addition product **B** and 23% of **32** (Table 4, entry 10). Reactions performed with electron deficient olefins such as methyl vinyl ketone or activated allyl sulfones did not give any results. Intramolecular C-C bond formation reactions, such as 5-*exo*-trig cyclizations, have also been done without success.

Table 4. Conditions screening for C-C bond formation

Entry	Heterocycles	DIPEA	Yield ^a	Observations ^a
1	Thiophene	0	S.M.	
2	Thiophene	2 equiv.	54% (31)	
3	Benzothiophene	0	50% (S.M.)	Traces of B (9%) and 32 (20%)
4	Benzothiophene	2 equiv.	50% (31)	
5	1-Methylindole	0	50% (S.M.)	Traces of 31 (> 5%) and 32 (20%)
6	1-Methylindole	2 equiv.	57% (31)	
7	Pyrrole	2 equiv.	41% (31)	
8	Furan	0	40% (S.M.)	Traces of 31 (>3%)
9	Furan (3 to 10 equiv.)	2 equiv.	30% (31)	Traces of 32
10	Furan (50 equiv.)	0	15% (B)	S.M. (19%); 32 (23%). Traces of 31 (>7%)

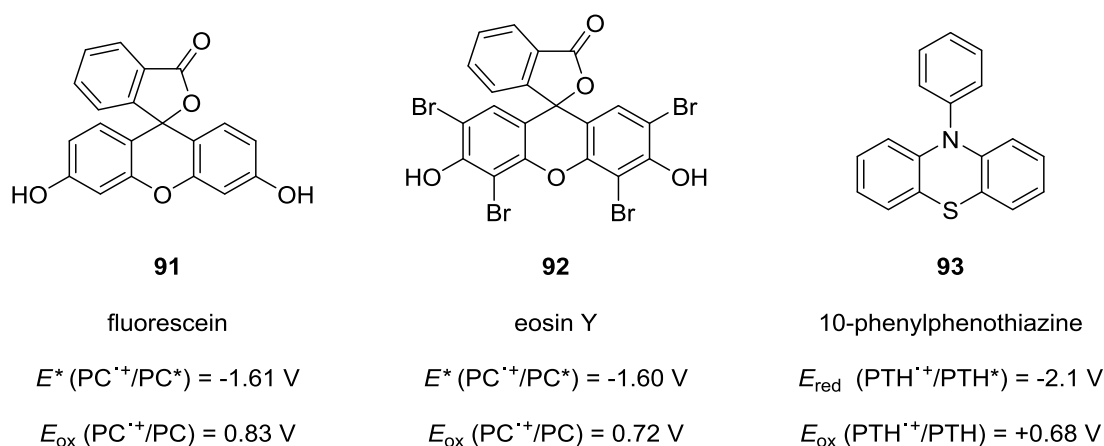
^a NMR yield.

The thiocarbamate transfer reaction would open new perspectives to highly versatile transformations in the fields of organic synthesis and polymer sciences. We have to investigate the radical trapping experiment under these experimental conditions. The field of carbon-heteroatom (nitrogen, sulfur...) bond-forming reaction would be also a promising research direction.

II.B.5. Miscellaneous Studies

The photocatalyzed deoxygenation of alcohols is still a challenging reaction for primary, secondary and a large variety of tertiary alcohols. We developed one of the few photocatalyzed reactions allowing the deoxygenation of the larger variety of alcohols. We tried to extend the impact of this methodology in modifying the photoredox conditions and we decided to focus on the efficiency of the reduction of secondary alcohols.

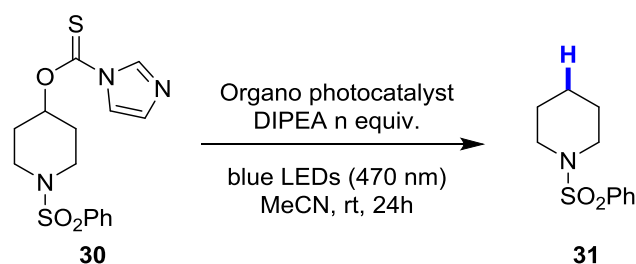
This specific reactivity of *O*-thiocarbamate groups forced us to consider another aspect of the photoredox reaction. We investigated other photocatalysts with a lower reductive potential at the excited state than Ir(ppy)₃ in order to target low reduction potential of thiocarbamates. As Ir(ppy)₃ is already the most reductive known metal-based photocatalyst (at the excited state), we naturally investigated organic photoredox compounds. The redox potentials at the excited state of the well-known fluorescein and eosin Y are substantially higher than for Ir(ppy)₃* and thus explains the absence of reactivity (Scheme 32, Table 5 entries 1-4).¹⁰² In contrast, the 10-phenylphenothiazine (Ph-PTH) excited state displays an interesting reductive potential estimated at -2.1 V. Hawker and co-workers highlighted the photoredox ability of the Ph-PTH during a photoredox atom transfer radical polymerization (ATRP) of methyl methacrylate using ethyl α -bromophenylacetate as a radical initiator.¹⁰³



Scheme 32. Redox potentials of organic photocatalysts

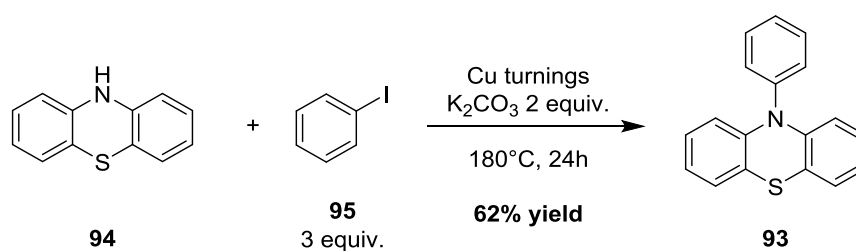
¹⁰² a) D.A Nicewicz, T.M. Nguyen *ACS Catal.* **2014**, *4*, 355. b) D. Ravelli, M. Fagnoni, *ChemCatChem* **2012**, *4*, 169.

¹⁰³ N.J. Treat, H. Sprafke, J.W. Kramer, P.G. Clark, B.E. Barton, J.R. Alaniz, B.P. Fors, C.J. Hawker, *J. Am. Chem. Soc.* **2014**, *136*, 16096.

Table 5. Screening of conditions for reduction with organic photocatalysts

Entry	Photocatalyst	mol%	DIPEA	Yields	LEDs
1	Fluorescein	1	5 equiv.	S.M.	Blue
2	Fluorescein	5	--	S.M.	Blue
3	Fluorescein	5	5 equiv.	S.M.	Blue
4	Fluorescein	5	5 equiv.	S.M.	Green
5	10-phenylphenothiazine	1 to 10	5 equiv.	S.M.	Blue

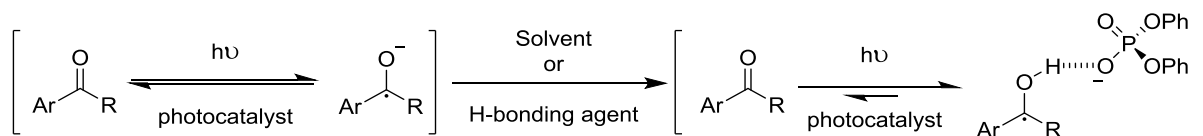
To this end, we synthesized the 10-Ph-PTH in good yield following a reported procedure from phenothiazonine **94** and iodobenzene **95** as depicted Scheme 33. Then, we engaged the photocatalyst **93** for the reduction of **30** in various loadings (from 1 to 10 mol%) under blue LEDs irradiation (Table 5, entry 5). Unfortunately, no reaction occurred with this catalyst.

**Scheme 33.** Synthesis of 10-phenylphenothiazine

Recently, Yayla and Knowles published a detailed study on a Proton-Coupled Electron Transfer (PCET) process involving in a photoreductive ketyl-olefin cyclization.¹⁰⁴ They showed, by kinetic and spectroscopic studies that adding a weak acidic proton donor in the reaction medium could drive the equilibrium of the ketone photoreduction reaction toward the formation of an H-bonded complex between the reduced ketone and the H-bonding agent

¹⁰⁴ H.G. Yayla, R.R. Knowles, *Synlett* **2014**, 25, 2819.

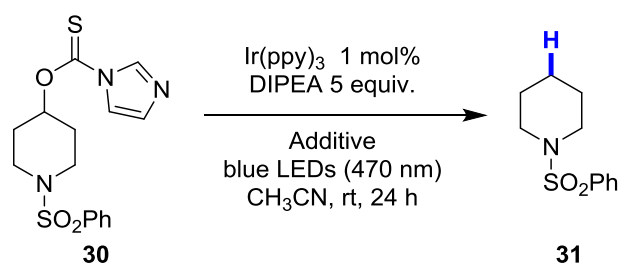
(Scheme 34). In fact, this proton assistance, promoted by diphenyl phosphoric acid, could stabilize the radical-anion intermediate species leading to easier accessible radical steps.



Scheme 34. Effect of H-bonding agent

Then we decided to evaluate the possible effect of the addition of diphenyl phosphoric acid in our photocatalytic conditions (Table 6). The presence of diphenyl phosphoric acid (5 mol%) has allowed to improve the formation of **31** in 60% yield. However, an equimolar amount or an excess of phosphoric acid had a dramatic effect on the yield (Table 6, entries 2-4). Encouraged by this result, we wanted to evaluate the effect of the solvent. When we used a protic solvent such as *tert*-butanol in a ratio of 95/5 or 90/10 with acetonitrile, the evolution of the yield was not enough significant. With hexafluoroisopropanol, a strong hydrogen bond donor solvent, the yield of reduced product was slightly increased to 58%. The best yield was obtained with 5% of water which allowed to isolate **31** in a very good 65% yield.

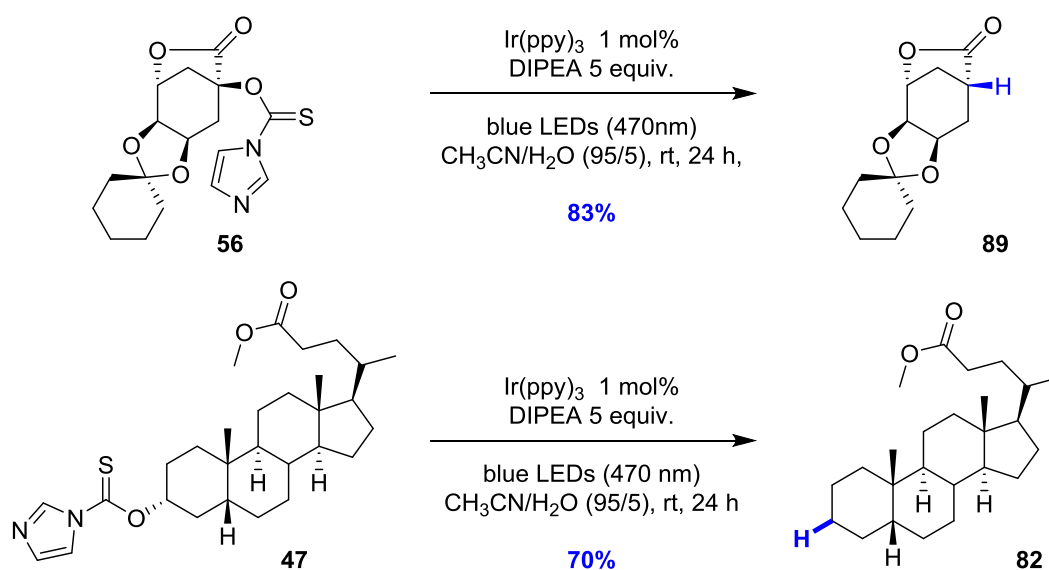
Table 6. H-donor phosphate or solvent assistance effects on the deoxygenation reaction



Entry	Additive	Equivalent	Ratio (Solvent/Add)	Yield
1	(PhO) ₂ PO ₂ H	5 mol%	--	60%
2	(PhO) ₂ PO ₂ H	1 equiv.	--	49%
3	(PhO) ₂ PO ₂ H	2 equiv.	--	S.M.
4	(PhO) ₂ PO ₂ H	5 equiv.	--	S.M.
5	^t BuOH	--	95/5	54%
6	^t BuOH	--	90/10	50%

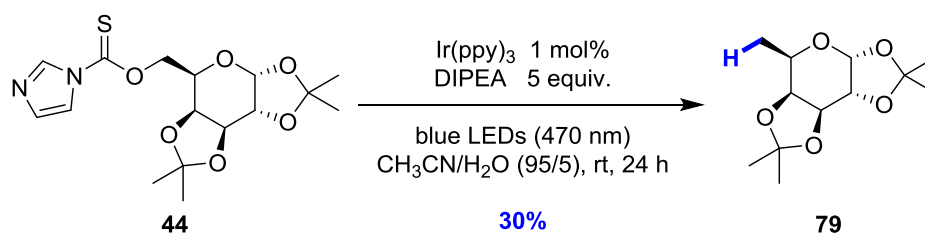
7	hexafluoroisopropanol	--	95/5	58%
8	H₂O	--	95/5	65%

To confirm this benefit with water as an additive, we submitted the *O*-thiocarbamates **47** and **56** to the new conditions of photoreduction and we were glad to obtain reduced products **82** and **89** in high yields (Scheme 35). With these examples, we can thus conclude that the presence of water in the middle has a significant effect on the reaction process, which needs to be studied more deeply.



Scheme 35. Photoreduction in the presence of water

These conditions allowed us to increase also the yield of the photoreduction of primary *O*-thiocarbamate **44**. Indeed product **44** was reduced in an encouraging 30% yield compare to 10% with the previous experimental conditions.



Scheme 36. Photoreduction of primary thiocarbamate **44** in the presence of water

II.B.6. Conclusion

We report a novel photocatalyzed deoxygenation method based on the activation of Ir(ppy)₃ by visible-light under very mild reductive conditions. This transformation allowed us to convert primary, secondary and tertiary aliphatic and benzylic alcohols to the corresponding alkanes in moderate to good yields. We also managed to improve the yield of few examples by adding 5% of water. A large range of *O*-thiocarbamates, from primary and secondary alcohols, needs to be tested in order to generalize these new conditions. Interesting functional group tolerances (ester, benzoyl, acetate, sulfonyl...) were observed. A preliminary mechanistic study based on fluorescence and cyclic voltammetry suggested the role of the *O*-thiocarbamate substrates as oxidative quenches of the [Ir(ppy)₃] excited state. The unsuccessful synthesis of *O*-thiocarbamates from tertiary alcohols still remains the main drawback of this photoredox reaction. However, the radical trapping experiments and the thiocarbamate transfer product created a new window of possibility to realize C-C or C-heteroatom bond formation reactions. Indeed, the thiocarbamate transfer reaction would open new perspectives to highly versatile transformations in the fields of organic synthesis and polymer sciences.

Experimental Section – Chapter II

II.B.7. Experimental Section

II.B.7.a. General remarks

Unless special mention, all reactions were carried out in oven-dried glassware and in anhydrous solvents under argon atmosphere. Photoredox reactions were run in Schlenk flask and with magnetic stirring. Solvents and liquid reagents were distilled under an argon atmosphere prior to use, particularly: Acetone, CH₃CN, CH₂Cl₂, DMF, DMSO, DMPU, NMP, toluene and *i*Pr₂NEt from calcium hydride. Thin Layer Chromatography (TLC) was performed on Merck 60 F254 silica gel and revealed with either a ultra-violet lamp ($\lambda = 254$ nm) or a specific color reagent (*p*-anisaldehyde, potassium permanganate). A Davisil LC 60 A silica gel (40-63 μ m) was used for flash column chromatography (FC) using Still's method.¹⁰⁵ PE refers to petroleum ether and EtOAc to ethyl acetate. The melting points reported were measured with a Bibby Stuart melting point apparatus and were uncorrected. NMR ¹H, ¹³C spectra were recorded at 400, 101 and 376 MHz, respectively, using a Bruker AVANCE 400 MHz spectrometer equipped with a BBFO probe. Some NMR ¹H, ¹³C were recorded at 300 and 75 MHz respectively, using a Bruker AVANCE 300 MHz spectrometer. Chemical shifts (δ) are reported in ppm, using, for ¹H and ¹³C, solvent residual peak as internal standard references (CDCl₃: $\delta_C = 77.16$ ppm; Residual CHCl₃ in CDCl₃: $\delta_H = 7.26$ ppm). Otherwise noted, NMR spectra were recorded in CDCl₃ at 300 K. The terms m, s, d, t, q and dd represent multiplet, singlet, doublet, triplet, quadruplet, quintuplet, and doublet of doublets respectively. Coupling constants (*J*) are given in Hertz (Hz). IR spectra were recorded on a Bruker Tensor 27 ATR diamond PIKE spectrophotometer. Wavenumbers (ν) are given in cm⁻¹. High resolution mass spectrometry (HRMS) analyses were performed at the IPCM on a Bruker micrOTOF mass spectrometer (electrospray source), using Agilent ESI-L Low Concentration Tuning Mix as reference.

¹⁰⁵ W. C. Still, M. Khan, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923-2925.

II.B.7.b. General procedures

General Procedure 1 (GP1). *O*-Thiocarbamate synthesis.¹⁰⁶ To a solution of alcohol (10 mmol) in CH₂Cl₂ (50 mL) was introduced 1-1' thiocarbonyldiimidazole (2.14 g, 12 mmol) and DMAP (244 mg, 2 mmol). The mixture was stirred at room temperature under argon in the dark until completion of the reaction (monitored by TLC). The mixture was concentrated under reduced pressure to give the crude thiocarbamate. The residue was purified by flash column chromatography on silica gel (Pentane/EtOAc or Et₂O) to afford the corresponding product.

General Procedure 2, Conditions A. (GP2.A). *Photoreduction of thiocarbamates.* In a Schlenk tube was introduced the *O*-thiocarbamate (0.5 mmol), Ir(ppy)₃ (3.3 mg, 0.005 mmol), then CH₃CN (7.5 mL) and DIPEA (435 μL, 2.5 mmol). The mixture was degassed using the freeze-pump-thaw method (3 cycles) and irradiated by blue LEDs (470 nm) (~ 0.5 cm away from the glassware) until completion of the reaction (monitored by TLC). The mixture was concentrated under reduced pressure and the crude was purified by flash column chromatography on silica gel (Pentane/EtOAc or Et₂O).

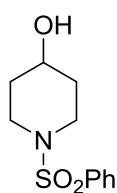
General Procedure 2, Conditions B. (GP2.B). *Photoreduction of thiocarbamates.* In a Schlenk tube was introduced the *O*-thiocarbamate (0.5 mmol), Ir(ppy)₃ (16.4 mg, 0.025 mmol) then DMPU (5 mL) and DIPEA (435 μL, 2.5 mmol). The mixture was degassed using the freeze-pump-thaw method (3 cycles) and irradiated by blue LEDs (470 nm) (~ 0.5 cm away from the glassware) until completion of the reaction (monitored by TLC). Water was added and the mixture was extracted with Et₂O (3 × 25 mL). The organic phases were gathered, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel (Pentane/EtOAc or Et₂O).

General Procedure 3 (GP3). *Reduction of thiocarbamates under Bu₃SnH/AIBN conditions.* A degassed solution of Bu₃SnH (269 μL, 1 mmol) and AIBN (8.2 mg, 0.05 mmol) in toluene (10 mL) was added over 4 h (0.25 mmol.h⁻¹ relative to Bu₃SnH) to a degassed solution of *O*-thiocarbamate (0.5 mmol) in toluene (13 mL) at reflux. The resulting solution was heated at reflux for an additional hour, cooled to RT and concentrated in vacuo. The crude was purified by was purified by flash column chromatography on silica gel (Pentane/EtOAc).

¹⁰⁶ M. Ruthkovsky, F. N. Castellano, G. J. Meyer, *Inorg. Chem.* **1996**, *35*, 6406-6412.

II.B.7.c. Compound characterizations

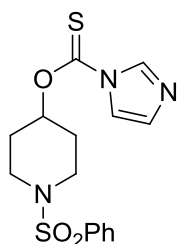
1-(Phenylsulfonyl)-4-piperidinol (**28**)



Prepared from the commercially available 4-piperidinol (2.00 g, 19.8 mmol), ClSO₂Ph (3.5 g, 19.8 mmol) and Et₃N (2.4 g, 23.7 mmol) in CH₂Cl₂ (25 mL) according to the literature procedure reported by S. Oberboersch *et al.*,¹⁰⁷ compound **28** was purified by FC (Pentane/EtOAc, 60:40) and isolated (2.09 g, 44%) as a white solid.

Spectral data are in accordance with those reported in the literature.⁸³ **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 7.78-7.45 (m, 2H), 7.62-7.57 (m, 1H), 7.55-7.51 (m, 2H), 3.79-3.73 (m, 1H), 3.35-3.30 (m, 2H), 2.90-2.84 (m, 2H), 1.96-1.86 (m, 2H), 1.69-1.61 (m, 2H). **¹³C NMR (101 MHz, CDCl₃)** δ (ppm) 136.5, 132.9, 129.2 (2C), 127.7 (2C), 66.0, 43.3 (2C), 33.4 (2C).

O-[1-(Phenylsulfonyl)piperidin-4-yl] 1H-imidazole-1-carbothioate (**30**)

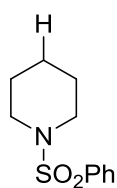


Following **GP1** with 1-(phenylsulfonyl)-4-piperidinol **28** (1.00 g, 4.14 mmol), 1-1' thiocarbonyldiimidazole (960 mg, 5.39 mmol) and DMAP (203 mg, 1.66 mmol) in CH₂Cl₂ (20 mL), compound **30** was purified by FC (Pentane/EtOAc, 60:40) and isolated (1.42 g, 98%) as a white solid.

Mp = 150-152 °C. **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.15 (s, 1H), 7.78-7.74 (m, 2H), 7.65-7.52 (m, 3H), 7.46 (s, 1H), 6.97 (s, 1H), 5.55-5.46 (m, 1H), 3.30-3.21 (m, 2H), 3.12-3.03 (m, 2H), 2.21-2.11 (m, 2H), 2.08-1.96 (m, 2H). **¹³C NMR (101 MHz, CDCl₃)** δ (ppm) 182.8, 136.6, 136.0, 133.2, 131.0, 129.3 (2C), 127.7 (2C), 117.9, 77.7, 43.4 (2C), 29.4 (2C). **IR** (neat): 3064, 2855, 2227, 1465, 1446, 1384, 1322, 1282, 1227, 1166, 1092, 1017, 982, 969, 934, 909, 731, 690, 655, 608. **HRMS (ESI)** calcd for C₁₅H₁₇N₃O₃S₂Na ([M+Na]⁺): 374.0609; found 374.060

¹⁰⁷ S. Oberboersch, M. Reich, S. Schunk, S. Hees, R. Jostock, M. Engels, A. Kless, T. Christoph, K. Schiene, T. Germann, E. Bijsterveld, PCT Int. Appl. 2008046573, 24 Apr 2008.

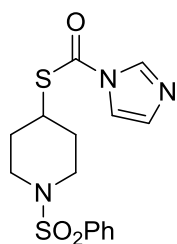
1-(Phenylsulfonyl)piperidine (31)



Following **GP2.A** with *O*-[1-(phenylsulfonyl)piperidin-4-yl] 1*H*-imidazole-1-carbothioate **30** (175.5 mg, 0.5 mmol), Ir(ppy)₃ (1.3 mg, 0.002 mmol) and DIPEA (174 μL, 1 mmol) in CH₃CN (3 mL), following GP4 with *O*-[1-(phenylsulfonyl)piperidin-4-yl] 1*H*-imidazole-1-carbothioate **30** (175.7 mg, 0.5 mmol), compound **31** was purified by FC (Pentane/Et₂O, 80/20) and isolated (24 mg, 53% and 52.4 mg, 46% respectively) as a white solid.

Spectral data are in accordance with those reported in the literature.¹⁰⁸ **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 7.77-7.73 (m, 2H), 7.59-7.48 (m, 3H), 2.98 (t, *J* = 5.4 Hz, 4H), 1.67-1.59 (m, 4H), 1.45-1.36 (m, 2H). **CAS Number:** 5033-23-8.

S-[1-(Phenylsulfonyl)piperidin-4-yl] 1*H*-imidazole-1-carbothioate (32)

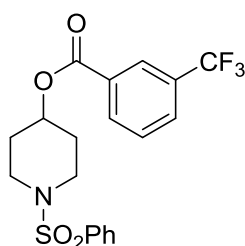


Following **GP2.A** with *O*-[1-(phenylsulfonyl)piperidin-4-yl] 1*H*-imidazole-1-carbothioate **30** (70.3 mg, 0.2 mmol), in absence of DIPEA. An analytical sample of compound **32** was isolated by preparative TLC (Pentane/EtOAc, 60/40) as a white solid.

Mp = 143-145 °C. **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.13 (s, 1H), 7.79-7.76 (m, 2H), 7.65-7.53 (m, 3H), 7.39 (s, 1H), 7.07 (s, 1H), 3.68-3.60 (m, 3H), 2.74-2.68 (m, 2H), 2.20-2.14 (m, 2H), 1.94-1.84 (m, 2H). **¹³C NMR (101 MHz, CDCl₃)** δ (ppm) 165.0, 136.2, 135.5, 133.2, 131.2, 129.3 (2C), 127.7 (2C), 115.9, 45.8 (2C), 41.5, 31.4 (2C). **IR** (neat): 2923, 2848, 1683, 1469, 1444, 1366, 1354, 1295, 1209, 1163, 1073, 939, 889, 857, 836, 731, 689, 667, 586, 572. **HRMS (ESI)** calcd for C₁₅H₁₇N₃O₃S₂Na ([M+Na]⁺): 374.0604; found 374.0616.

¹⁰⁸ H. Woolven, C. Gonzalez-Rodriguez, I. Marco, A. L. Thompson, M. C. Willis, *Org. Lett.*, **2011**, *13*, 4876-4878.

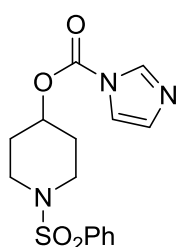
3-(Trifluoromethyl) benzoyl (1-(phenylsulfonyl)piperidin-4-yl) ester (34)



Following **GP1** with 1-(phenylsulfonyl)-4-piperidinol **28** (500 mg, 2.1 mmol), 3-(trifluoromethyl)benzoyl chloride (519 mg, 2.5 mmol), Et₃N (273 mg, 2.7 mmol) and DMAP (76 mg, 0.6 mmol) in CH₂Cl₂ (15 mL), compound **34** was purified by FC (Pentane/EtOAc, 80/20) and isolated (632 mg, 74%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.12-8.09 (m, 2H), 7.81-7.78 (m, 3H), 7.65-7.60 (m, 1H), 7.56-7.52 (m, 3H), 5.09-5.03 (m, 1H), 3.37-3.31 (m, 2H), 3.06-3.01 (m, 2H), 2.12-2.05 (m, 2H), 1.98-1.89 (m, 2H). **¹³C NMR (101 MHz, CDCl₃)** δ (ppm) 164.3, 136.2, 133.1, 132.8, 131.2 (q, *J* = 33.1 Hz), 131.1, 129.7 (q, *J* = 3.5 Hz), 129.2, 129.1 (2C), 127.7 (2C), 126.4 (q, *J* = 3.9 Hz), 123.7 (q, *J* = 272.2 Hz), 69.6, 43.5 (2C), 30.2 (2C). **¹⁹F NMR (376 MHz, CDCl₃)** δ (ppm) -62.9.

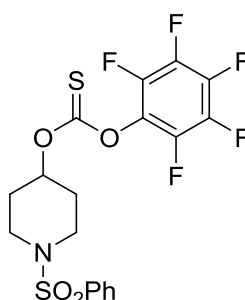
O-[1-(Phenylsulfonyl)piperidin-4-yl] 1*H*-imidazole-1-carbamate (36)



Following **GP1** with 1-(phenylsulfonyl)-4-piperidinol **28** (874mg, 3.6 mmol), 1,1'-Carbonyldiimidazole (881 mg, 5.4 mmol) and DMAP (133 mg, 1.1 mmol) in CH₂Cl₂ (20 mL), compound **36** was purified by FC (Pentane/EtOAc, 60/40) and isolated (507 mg, 42%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.96 (s, 1H), 7.78-7.70 (m, 2H), 7.65-7.56 (m, 1H), 7.58-7.48 (m, 2H), 7.29-7.26 (m, 1H), 7.02-6.96 (m, 1H), 5.03-4.94 (m, 1H), 3.34-3.23 (m, 2H), 3.06-2.94 (m, 2H), 2.14-2.02 (m, 2H), 2.00-1.86 (m, 2H). **¹³C NMR (101 MHz, CDCl₃)** δ (ppm) 147.7, 136.9, 136.0, 133.1, 130.8, 129.3 (2C), 127.6 (2C), 117.0, 73.1, 43.2 (2C), 29.9 (2C).

O-[1-(Phenylsulfonyl)piperidin-4-yl] pentafluorophenyl thionoformate (38)

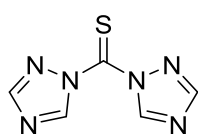


Following **GP1** with 1-(phenylsulfonyl)-4-piperidinol **28** (700 mg, 2.9 mmol), Pentafluorophenyl chlorothionoformate (914 mg, 3.5 mmol) and DMAP (500 mg, 4.1 mmol) in CH₂Cl₂ (20 mL), compound **38** was

purified by FC (Pentane/EtOAc, 60/40) and isolated (300 mg, 22%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.83-7.72 (m, 2H), 7.68-7.48 (m, 3H), 5.33-5.19 (m, 1H), 3.31-3.07 (m, 4H), 2.22-1.98 (m, 4H). **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 190.6, 136.3, 133.1, 129.3 (2C), 127.6 (2C), 80.8, 43.0 (2C), 29.3 (2C). **¹⁹F NMR (282 MHz, CDCl₃)** δ -152.1 – -152.4 (m, 2F), -156.6 (t, *J* = 21.7 Hz, 1F), -161.8 – -162.1 (m, 2F). **HRMS (ESI)** calcd for C₁₈H₁₄F₅NO₄S₂Na ([M+Na]⁺): 490.0177; found 490.0178.

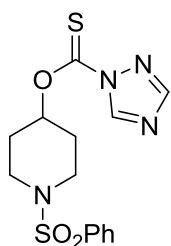
1,1'-Thiocarbonyldi-1,2,4-triazole (41)



Prepared from the commercially available thiophosgene (5.00 g, 43.5 mmol), 1,2,4-triazole (6.3 g, 91.3 mmol) in CCl₄ (125 mL) according to the literature procedure reported by D.N. Harpp *et al.*,¹⁰⁹ compound **28** was purified by precipitation at 0°C and isolated (6.5 g, 83%) as a yellow solid.

Spectral data are in accordance with those reported in the literature.⁸⁵ **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 9.20 (s, 1H), 8.17 (s, 1H). **¹³C NMR (101 MHz, CDCl₃)** δ (ppm) 167.7, 154.3 (2C), 147.6 (2C).

O-[1-(Phenylsulfonyl)piperidin-4-yl] 1H-1,2,4-triazole-1-carbothioate (42)

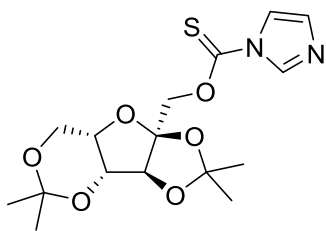


Following **GP1** with 1-(phenylsulfonyl)-4-piperidinol **28** (560 mg, 3.1 mmol), 1,1'-thiocarbonyldi-1,2,4-triazole **41** (500 mg, 2.1 mmol) and DMAP (101 mg, 0.8 mmol) in CH₂Cl₂ (10 mL), compound **42** was purified by FC (Pentane/EtOAc, 60/40) and isolated (567.5 mg, 77%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.93 (s, 1H), 7.98 (s, 1H), 7.80-7.77 (m, 2H), 7.66-7.61 (m, 1H), 7.58-7.52 (m, 2H), 5.59-5.53 (m, 1H), 3.39-3.33 (m, 2H), 3.13-3.07 (m, 2H), 2.24-2.16 (m, 2H), 2.14-2.06 (m, 2H).

¹⁰⁹ C. Larsen, K. Steliou, D.N. Harpp *J. Org. Chem.*, **1978**, *43*, 337-339

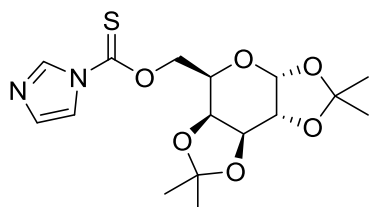
***O*-(2,3:4,6-di-*O*-isopropylidene- α -L-sorbofuranose) 1*H*-imidazole-1-carbothioate (**43**)**



Following **GP1** with 2,3:4,6-di-*O*-isopropylidene- α -L-sorbofuranose (1 g, 3.8 mmol), 1-1' thiocarbonyldiimidazole (820 mg, 4.6 mmol) and DMAP (94 mg, 0.77 mmol) in CH₂Cl₂ (20 mL), compound **43** was purified by FC (Pentane/EtOAc, 50/50) and isolated (1.3 g, 90 %) as a colorless syrup.

¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.23 (s, 1H), 7.55 (s, 1H), 6.90 (s, 1H), 4.90-4.70 (m, 2H), 4.40 (s, 1H), 4.26 (d, $J = 2.4$ Hz, 1H), 4.07-4.02 (m, 1H), 4.01-3.86 (m, 2H), 1.40 (s, 3H), 1.31 (s, 3H), 1.27 (s, 3H), 1.23 (s, 3H). **¹³C NMR (101 MHz, CDCl₃)** δ (ppm) 183.3, 136.7, 130.7, 117.9, 112.6, 111.8, 97.4, 84.6, 73.1, 72.6, 71.3, 60.0, 28.6, 27.3, 26.7, 18.6. **IR** (neat): 3127, 2990, 2932, 1466, 1384, 1326, 1285, 1189, 1125, 1082, 999, 917, 871, 835, 729. **HRMS (ESI)** calcd for C₁₆H₂₂N₂O₆SNa ([M+Na]⁺): 393.1091; found 393.1099.

***O*-(1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranose)-1*H*-imidazole-1-carbothioate (**44**)**

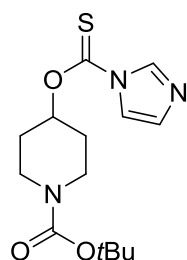


Following **GP1** with 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranose (1.0 g, 3.8 mmol), 1-1' thiocarbonyldiimidazole (820 mg, 4.6 mmol) and DMAP (94 mg, 0.77 mmol) in CH₂Cl₂ (20 mL), compound **44** was purified by FC (Pentane/EtOAc, 60/40) and isolated (1.3g, 88%) as a colorless syrup.

Spectral data are in accordance with those reported in the literature.¹¹⁰ **¹H NMR (400 MHz, CDCl₃)** δ (ppm) δ 8.39-8.32 (m, 1H), 7.65-7.61 (m, 1H), 7.07-6.99 (m, 1H), 5.55 (d, $J = 5.0$ Hz, 1H), 4.85 (dd, $J = 11.5, 3.9$ Hz, 1H), 4.77-4.63 (m, 2H), 4.36 (dd, $J = 5.0, 2.5$ Hz, 1H), 4.33-4.22 (m, 2H), 1.51 (s, 3H), 1.48 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H). **¹³C NMR (101 MHz, CDCl₃)** δ (ppm) 184.2, 137.0, 130.9, 118.1, 110.2, 109.1, 96.4, 72.2, 71.1, 70.9, 70.5, 65.7, 26.2, 26.1, 25.1, 24.6.

¹¹⁰ J. Boivin, V.T. Nguyen Beilstein *J. Org. Chem.*, **2007**, 3, No. 45.

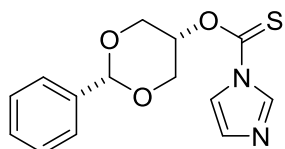
O-[1-(*tert*-Butyloxycarbonyl)piperidin-4-yl] 1*H*-imidazole-1-carbothioate (**45**)



Following **GP1** with 1-(*tert*-butyloxycarbonyl)piperidin-4-ol (2.01 g, 10 mmol), prepared from the commercially available 4-piperidinol according to the literature procedure reported by J. T. Palmer et al.,¹¹¹ 1-1' thiocarbonyldiimidazole (2.67 g, 15 mmol) and DMAP (489 mg, 4 mmol) in CH₂Cl₂ (30 mL), compound **45** was purified by FC (Pentane/EtOAc, 60/40) and isolated (2.34 g, 70%) as a white solid.

Mp = 70-72 °C. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.33 (s, 1H), 7.61 (s, 1H), 7.03(s, 1H), 5.70-5.63 (m, 1H), 3.76-3.70 (m, 2H), 3.40-3.33 (m, 2H), 2.08-2.02 (m, 2H), 1.90-1.82 (m, 2H), 1.47 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ (ppm) 183.1, 154.7, 136.9, 131.0, 117.9, 80.2, 79.5, 30.0 (2C), 28.5 (2C + 3C). **IR** (neat): 3119, 2975, 2929, 2864, 1693, 1530, 1478, 1465, 1423, 1385, 1365, 1316, 1283, 1218, 1162, 1006, 964, 861, 830, 770, 741, 656. **HRMS** (**ESI**) calcd for C₁₄H₂₁N₃O₃SNa ([M+Na]⁺): 334.1196; found 334.1188.

O-[2-Phenyl-1,3-dioxan-5-yl] 1*H*-imidazole-1-carbothioate (**46**)



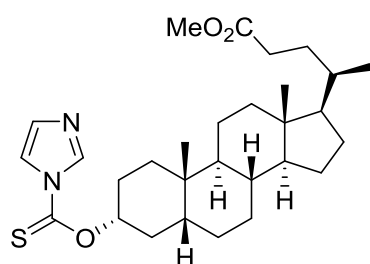
Following **GP1** with the commercially available *cis*-2-phenyl-1,3-dioxan-5-ol (2.00 g, 11.1 mmol), 1-1' thiocarbonyldiimidazole (2.37 g, 13.32 mmol) and DMAP (271 mg, 2.22 mmol) in CH₂Cl₂ (50 mL), compound **46** was purified by FC (Pentane/EtOAc, 80/20) and isolated (3.22 g, 66%) as a white solid.

Mp = 80-82 °C. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.48 (s, 1H), 7.75 (s, 1H), 7.52-7.49 (m, 2H), 7.43-7.38 (m, 3H), 7.07 (s, 1H), 5.64 (s, 1H), 5.46 (s, 1H), 4.55 (d, *J* = 12.2 Hz, 2H, A of AB system), 4.29 (d, *J* = 12.2 Hz, 2H, B of AB system). ¹³C NMR (101 MHz, CDCl₃) δ (ppm) 183.5, 137.5, 137.2, 131.1, 129.4, 128.5 (2C), 126.1 (2C), 118.2, 101.5, 74.4, 68.2 (2C). **IR** (neat): 3123, 3035, 2980, 2856, 1531, 1463, 1383, 1313, 1281, 1226, 1137, 1112,

¹¹¹ J.T. Palmer, C. Bryant, D.-X. Wang, D. E. Davis, E. L. Setti, R. M. Rydzewski, S. Venkatraman, Z.-Q. Tian, L. C. Burrill, R. V. Mendonca, E. Springman, J. McCarter, T. Chung, H. Cheung, J. W. Janc, M. McGrath, J. R. Somoza, P. Enriquez, Z. W. Yu, R. M. Strickley, L. Liu, M. C. Venuti, D. M. Percival, J.-P. Falguyret, P. Prasit, R. Oballa, D. Riendeau, R. N. Young, G. Wesolowski, S. B. Rodan, C. Johnson, D. B. Kimmel, G. Rodan, *J. Med. Chem.* **2005**, *48*, 7520-7534.

1093, 1070, 974, 949, 829, 789, 744, 697, 654, 641. **HRMS (ESI)** calcd for $C_{14}H_{14}N_2O_3SNa$ ($[M+Na]^+$): 313.0617; found 313.0613.

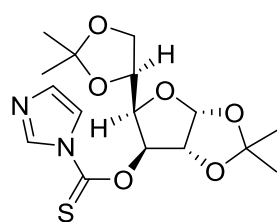
(4R)-Methyl 4-((3R,5R,10S,13R)-3-((1H-imidazole-1-carbonothioyl)oxy)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate (47)



Following **GP1** with methyl lithocholate (2.00 g, 5.12 mmol), prepared from the commercially available lithocholic acid according to the literature procedure reported by *J. T. Davis et al.*,¹¹² 1-1' thiocarbonyldiimidazole (1.09 g, 6.12 mmol) and DMAP (62 mg, 0.51 mmol) in CH_2Cl_2 (50 mL), compound **47** was purified by FC (Pentane/ Et_2O , 20/80) and isolated (2.07 g, 81%) as a white solid.

Spectral data are in accordance with those reported in the literature.¹¹³ **1H NMR (400 MHz, $CDCl_3$)** δ (ppm) 8.34 (s, 1H), 7.64 (t, $J = 1.4$ Hz, 1H), 7.18 (t, $J = 0.7$ Hz, 1H), 5.49-5.40 (m, 1H), 3.66 (s, 3H), 2.38-2.31 (m, 1H), 2.25-2.17 (m, 1H), 2.04-1.78 (m, 8H), 1.64-1.55 (m, 3H), 1.44-1.06 (m, 15H), 0.97 (s, 3H), 0.92 (d, $J = 6.4$ Hz, 3H), 0.66 (s, 3H).

***O*-[1,2:5,6-Di-*O*-isopropylidene- α -D-glucofuranosyl] 1H-imidazole-1-carbothioate (48)**



Following **GP1** with the commercially available 1,2:5,6-di-*O*-isopropylidene- α -D-glucofuranose (1.00 g, 3.84 mmol), 1-1' thiocarbonyldiimidazole (1.03 g, 5.76 mmol) and DMAP (188 mg, 1.54 mmol) in CH_2Cl_2 (20 mL), compound **48** was purified by FC (Pentane/ $EtOAc$, 50/50) and isolated (1.02 g, 70%) as a colorless syrup.

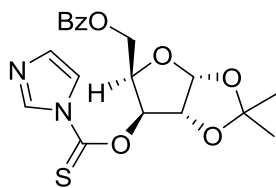
Spectral data are in accordance with those reported in the literature.¹¹⁴ **1H NMR (400 MHz, $CDCl_3$)** δ (ppm) 8.32 (s, 1H), 7.60 (s, 1H), 7.06 (s, 1H), 5.94 (d, $J = 3.8$ Hz, 1H), 5.83 (d, $J = 2.1$ Hz, 1H), 4.75 (d, $J = 3.8$ Hz, 1H), 4.32-4.23 (m, 2H), 4.18-4.13 (m, 1H), 4.09-4.05 (m, 1H), 1.57 (s, 3H), 1.41 (s, 3H), 1.34 (s, 3H), 1.29 (s, 3H). **CAS Number:** 79233-85-5.

¹¹² L. Ma, M. Melegari, M. Colombini, J. T. Davis, *J. Am. Chem. Soc.* **2008**, *130*, 2938-2939.

¹¹³ A. C. Burns, P. W. Sorensen, T.R. Hoye, *Steroids* **2011**, *76*, 291-300

¹¹⁴ H. S. Park, H. Y. Lee, Y. H. Kim, *Org. Lett.* **2005**, *7*, 3187-3190.

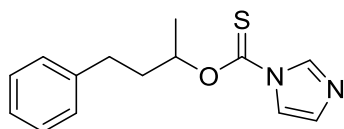
***O*-[1,2-Isopropylidene-5-benzoate- α -D-xylofuranosyl] 1*H*-imidazole-1-carbothioate (**49**)**



Following **GP1** with *O*-1,2-isopropylidene-5-benzoate- α -D-xylofuranose (1.57 g, 5.33 mmol), prepared from *O*-1,2-isopropylidene- α -D-xylofuranose according to the literature procedure reported by M. Gottschaldt et al.,¹¹⁵ 1-1' thiocarbonyldiimidazole (1.43 g, 8.02 mmol) and DMAP (261 mg, 2.13 mmol) in CH₂Cl₂ (20 mL), compound **49** was purified by FC (Pentane/EtOAc, 60/40) and isolated (1.81 g, 84%) as a colorless syrup.

Spectral data are in accordance with those reported in the literature.¹¹⁶ **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.33 (s, 1H), 8.00-7.97 (m, 2H), 7.57 (d, *J* = 1.3 Hz, 1H), 7.57-7.53 (m, 1H), 7.43-7.39 (m, 2H), 7.04 (dd, *J* = 0.7, 1.6 Hz, 1H), 6.04 (d, *J* = 3.8 Hz, 1H), 6.00 (d, *J* = 3.8 Hz, 1H), 4.79-4.76 (m, 2H), 4.60-4.58 (m, 2H), 1.57 (s, 3H), 1.35 (s, 3H). **CAS Number:** 160999-15-5.

***O*-[4-Phenylbutan-2-yl] 1*H*-imidazole-1-carbothioate (**50**)**



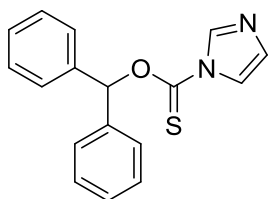
Following **GP1** with the commercially available 4-phenyl-2-butanol (970 mg, 6.46 mmol), 1-1' thiocarbonyldiimidazole (1.73 g, 9.70 mmol) and DMAP (158 mg, 1.30 mmol) in CH₂Cl₂ (30 mL), compound **50** was purified by FC (Pentane/EtOAc, 80/20) and isolated (1.40 g, 83%) as a yellow oil.

¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.27 (s, 1H), 7.59 (s, 1H), 7.29-7.27 (m, 2H), 7.20-7.17 (m, 3H), 7.03 (s, 1H), 5.71-5.62 (m, 1H), 2.81-2.68 (m, 2H), 2.29-2.19 (m, 1H), 2.12-2.03 (m, 1H), 1.47 (d, *J* = 6.2 Hz, 3H). **¹³C NMR (101 MHz, CDCl₃)** δ (ppm) 183.7, 140.8, 136.8, 130.8, 128.7 (2C), 128.4 (2C), 126.4, 118.0, 81.2, 37.2, 31.8, 19.2. **IR** (neat): 3127, 3026, 2978, 2932, 1463, 1383, 1321, 1282, 1231, 1128, 1095, 1034, 963, 892, 831, 744, 699, 656, 642. **HRMS (ESI)** calcd for C₁₄H₁₇N₂OS ([M+H]⁺): 261.1056; found 261.1050.

¹¹⁵ D. Koth, A. Fiedler, S. Scholz, M. Gottschaldt, *J. Carbohydr. Chem.* **2007**, 26, 267-278.

¹¹⁶ I. Zlatev, J.-J. Vasseur, F. Morvan, *Tetrahedron Lett.* **2008**, 49, 3288-3290.

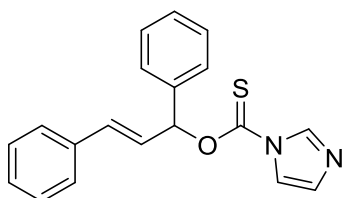
***O*-[Diphenylmethyl] 1*H*-imidazole-1-carbothioate (51)**



Following **GP1** with the commercially available diphenylmethanol (1.66 g, 9.01 mmol), 1-1' thiocarbonyldiimidazole (2.50 g, 14.03 mmol) and DMAP (400 mg, 3.27 mmol) in CH₂Cl₂ (50 mL), compound **51** was purified by FC (Pentane/EtOAc, 80/20) and isolated (1.67 g, 63%) as a white solid.

Mp = 51-53 °C. **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.18 (s, 1H), 7.45-7.42 (m, 5H), 7.38-7.34 (m, 4H), 7.32-7.28 (m, 2H), 7.08 (s, 1H), 6.14 (s, 1H). **¹³C NMR (101 MHz, CDCl₃)** δ (ppm) 164.9, 139.2 (2C), 135.6, 131.1, 128.9 (4C), 128.4 (4C), 128.1 (2C), 116.0, 54.2. **IR** (neat): 3121, 3061, 3028, 2928, 1765, 1689, 1599, 1491, 1469, 1450, 1364, 1289, 1270, 1214, 1097, 1075, 1065, 1021, 882, 830, 747, 716, 696, 664, 642. **HRMS (ESI)** calcd for C₁₇H₁₄N₂OSNa ([M+Na]⁺): 317.0719; found 317.0711.

***(E)*-*O*-[1,3-Diphenylallyl] 1*H*-imidazole-1-carbothioate (52)**

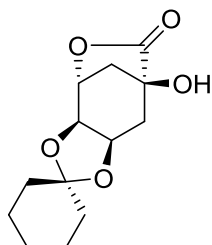


Following **GP1** with the commercially available *trans*-1,3-diphenyl-2-propyn-1-ol (2.0 g, 9.5 mmol), 1-1' thiocarbonyldiimidazole (2.03 g, 11.4 mmol) and DMAP (116 mg, 1 mmol) in CH₂Cl₂ (100 mL), compound **52** was purified by FC (Pentane/Et₂O, 30/70) and isolated (2.08 g, 68%) as a yellow oil.

¹H NMR (300 MHz, CDCl₃) δ (ppm). 8.49 (s, 1H), 7.79 (s, 1H), 7.51-7.27 (m, 10H), 7.12 (s, 1H), 6.72 (d, *J* = 15.8 Hz, 1H), 6.52 (dd, *J* = 15.7, 7.5 Hz, 1H), 5.97 (d, *J* = 7.5 Hz, 1H). **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 195.4, 137.6, 136.0, 135.7, 134.3, 131.6, 129.1 (2C), 128.7 (2C), 128.6 (2C), 128.5, 128.3, 126.8 (2C), 125.6, 117.8, 58.2. **IR** (neat): 3058, 3026, 2922, 2851, 2360, 2340, 1598, 1577, 1527, 1493, 1465, 1449, 1366, 1291, 1266, 1238, 1218, 1087, 1052, 1041, 1001, 959, 825, 744, 691, 640, 609. **HRMS (ESI)** calcd for C₁₉H₁₆N₂OSK ([M+K]⁺): 359.0615; found 359.0691.

Spiro[cyclohexane-1,2'-[4,7]methanol[1,3]dioxolo
tetrahydro-7'-hydroxy, (3'aR,4'R,7'S,8'aR) (55)

[4,5-c]oxepin]-6'(4'H)-one,

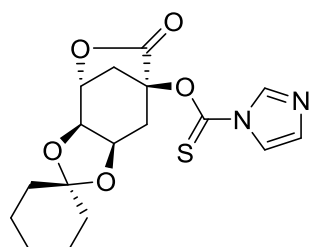


Prepared from the commercially available D-(-)-Quinic acid (3.84 g, 20 mmol) and cyclohexanone (4.20 g, 42 mmol) according to the literature procedure reported by J.D. Elliott *et al.*,¹¹⁷ compound **55** was purified by recrystallization from pentane and isolated (2.09 g, 44%) as a white solid.

The spectral data are in agreement with the data reported in the literature.

¹H NMR (300 MHz, CDCl₃) δ (ppm) 4.74 (dd, *J* = 6.1, 2.6 Hz, 1H), 4.48 (ddd, *J* = 7.6, 6.6, 3.0 Hz, 1H), 4.30 (ddd, *J* = 6.4, 2.7, 1.4 Hz, 1H), 2.80 (s, 1H), 2.67 (d, *J* = 11.8 Hz, 1H), 2.42-2.24 (m, 2H), 2.18 (dd, *J* = 14.6, 3.1 Hz, 1H), 1.76-1.60 (m, 4H), 1.60-1.49 (m, 4H), 1.47-1.33 (m, 2H). **¹³C NMR (101 MHz, CDCl₃)** δ (ppm) 179.0, 110.8, 76.1, 71.9, 71.7, 71.2, 38.6, 37.1, 34.5, 33.8, 25.2, 24.1, 23.7.

Spiro[cyclohexane-1,2'-[4,7]methano[1,3]dioxolo[4,5-c]oxepin]-6'(4'H)-one,
7'-(1*H*-imidazole-1-carbonothioyl) oxy) tetrahydro-, (3'aR,4'R,7'S,8'aR) (56)



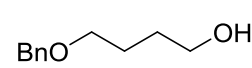
Following **GPI** with Spiro[cyclohexane-1,2'-[4,7]methanol[1,3]dioxolo [4,5-c]oxepin]-6'(4'*H*)-one, tetrahydro-7'-hydroxy, (3'aR,4'R,7'S,8'aR) **55** (1.32 g, 5.20 mmol), 1-1' thiocarbonyldiimidazole (1.4 g, 7.85 mmol) and DMAP (130 mg, 1.05 mmol) in CH₂Cl₂ (25 mL) then addition of 1-1' thiocarbonyldiimidazole (1.0 g, 5.61 mmol) and DMAP (130 mg, 1.05 mmol) after 17h and 1-1' thiocarbonyldiimidazole (1.0 g, 5.61 mmol) after 21h, compound **56** was purified by FC (Pentane/EtOAc, 55/45) and isolated (560 mg, 70%) as a white solid.

Mp = 130-132 °C. **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.32 (s, 1H), 7.61 (s, 1H), 7.04(s, 1H), 4.91 (dd, *J* = 6.5, 2.5 Hz, 1H), 4.62-4.57 (m, 1H), 4.39-4.35 (m, 1H), 3.59-3.53 (m, 1H), 2.90 (d, *J* = 11.6 Hz, 1H), 2.75-2.70 (m, 1H), 2.66-2.59 (m, 1H), 1.77-1.73 (m, 2H), 1.70-1.63 (m, 2H), 1.59-1.52 (m, 4H), 1.44-1.41 (m, 2H). **¹³C NMR (101 MHz, CDCl₃)** δ (ppm) 179.3,

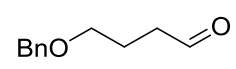
¹¹⁷ J. D. Elliott, A. B. Kelson, N. Purcell, R. J. Stoodley M. N. Palfreyman, *J. Chem. Soc. Perkin Trans 1*, **1983**, 2441-2449.

171.4, 136.8, 131.1, 118.1, 111.3, 82.5, 76.0, 72.2, 70.8, 37.0, 36.1, 33.8, 30.1, 25.1, 24.1, 23.6. **IR** (neat): 3127, 2935, 2861, 1797, 1533, 1464, 1448, 1390, 1328, 1285, 1228, 1164, 1101, 1086, 1063, 1032, 1008, 984, 964, 941, 926, 890, 731, 651. **HRMS (ESI)** calcd for $C_{17}H_{20}N_2O_5SNa$ ($[M+Na]^+$): 387.0985; found 387.0989.

6-(Benzyloxy)hexan-3-ol (58)

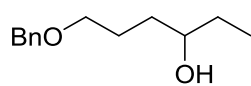
 To a solution of NaH (60 % dispersion in oil, 0.98 g, 24.4 mmol) in dry THF (110 mL) at 0 °C was added dropwise butane-1,4-diol (2 g, 22.2 mmol). The solution was then stirred at room temperature for 15 min and afterwards cooled to 0 °C. Benzylbromide (2.72 mL, 22.2 mmol) was added dropwise at 0 °C and the solution was stirred at room temperature. After 17 h, the solution was heated to reflux for 1 h. After cooling down to room temperature, water (15 mL) was added and the mixture was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined, dried over MgSO₄ and the solvents were evaporated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ EtOAc 70/30) to give product (3.09 g, 77 %) as a colorless oil.

The spectral data are in agreement with the data reported in the literature.¹¹⁸ **¹H NMR (300 MHz, CDCl₃)** δ (ppm) 7.44-7.20 (m, 5H), 4.53 (s, 2H), 3.62 (t, *J* = 5.9 Hz, 2H), 3.52 (t, *J* = 5.9 Hz, 2H), 2.73 (s, 1H), 1.80-1.58 (m, 4H). **¹³C NMR (101 MHz, CDCl₃)** δ (ppm) 138.1, 128.1 (2C), 127.4 (2C), 127.3, 72.6, 70.1, 61.9, 29.5, 26.2. **IR** (neat): 3361, 3063, 2937, 2860, 1453, 1361, 1229, 1156, 1093, 1059, 998, 957, 937, 734, 696.

 Prepared under Swern oxidation conditions with the 4-benzyloxybutane-1-ol (3 g, 16.6 mmol), oxalyl chloride (2.5 g, 19.9 mmol), DMSO (4.7 g, 59.8 mmol) and triethylamine (8.8 g, 86.6 mmol) in CH₂Cl₂ (120 ml). 4-Benzyloxybutanal was obtained in quantitative yield as a colorless oil and was engaged in the next step without further purification.

¹¹⁸ P. Prabhakar, S. Rajaram, D.K. Reddy, V. Shekar; Y. Venkateswarlu *Tetrahedron: Asymmetry*, **2010**, *21*, 216-221.

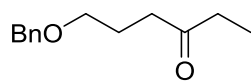
The spectral data are in agreement with the data reported in the literature.⁹⁴ **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 9.77 (t, J = 1.6 Hz, 1H), 7.39-7.24 (m, 5H), 4.49 (s, 2H), 3.50 (t, J = 6.1 Hz, 2H), 2.54 (td, J = 7.1, 1.6 Hz, 2H), 2.00-1.89 (m, 2H). **¹³C NMR (101 MHz, CDCl₃)** δ (ppm) 202.3, 138.3, 128.4 (2C), 127.7 (3C), 73.0, 69.2, 41.0, 22.6.



A 1.0 M solution of EtMgBr in THF (4.2 mL, 4.2 mmol) was added to dry THF (5 mL) and cooled to 0 °C. A solution of 4-benzyloxybutanal (500 mg, 2.8 mmol) in dry THF (5 mL) was then added dropwise and the solution was stirred at 0 °C for 10 min and then warmed to room temperature. After 1 h, the solution was cooled to 0 °C and EtMgBr (2.8 mL, 2.8 mmol) was added, and the solution was warmed to room temperature. After completion of the reaction, 10 % HCl (2 mL) were added, followed by saturated aqueous NaHCO₃ solution (15 mL). The mixture was extracted with diethyl ether (3 \times 15 mL), the organic layers were combined, dried over MgSO₄ and the solvents were evaporated under reduced pressure. Column chromatography of the residue (petroleum ether/EtOAc 70/30) gave alcohol **50** (418 mg, 72 %) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.78-7.45 (m, 2H), 7.62-7.57 (m, 1H), 7.55-7.51 (m, 2H), 3.79-3.73 (m, 1H), 3.35-3.30 (m, 2H), 2.90-2.84 (m, 2H), 1.96-1.86 (m, 2H), 1.69-1.61 (m, 2H). **¹³C NMR (101 MHz, CDCl₃)** δ (ppm) 138.3, 128.4, 127.7 (2C), 127.4 (2C), 73.0, 72.9, 70.6, 34.0, 30.2, 26.1, 10.0.

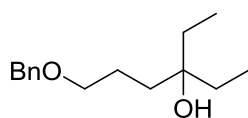
6-Benzyloxy-3-ethylhexan-3-ol (**59**)



Prepared under Swern oxidation conditions with the 6-(benzyloxy)hexan-3-ol (1.02 g, 4.9 mmol), oxalyl chloride (745.9 mg, 5.9 mmol), DMSO (1.4 g, 17.6 mmol) and triethylamine (2.6 g, 25.5 mmol) in CH₂Cl₂ (50 ml). After completion of the reaction, the 6-benzyloxy-3-hexanone was obtained in quantitative yield as a colorless oil and was engaged in the next step without further purification.

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.37-7.22 (m, 5H), 4.47 (s, 2H), 3.47 (t, J = 6.1 Hz, 2H), 2.51 (t, J = 7.2 Hz, 2H), 2.40 (q, J = 7.3 Hz, 2H), 1.96-1.83 (m, 2H), 1.03 (t, J = 7.4 Hz,

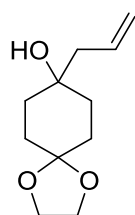
3H). ^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 211.2, 138.5, 128.4 (2C), 127.6 (2C), 127.6, 72.8, 69.4, 38.9, 35.9, 224.0, 7.8.



A 1.0 M solution of EtMgBr in diethyl ether (808 mg, 6.1 mmol) was added to dry diethyl ether (5 mL) and cooled to 0 °C. A solution of 6-benzyloxy-3-hexanone (506.8 mg, 2.5 mmol) in dry diethyl ether (5 mL) was then added dropwise and the solution was stirred at 0 °C for 10 min and then warmed to room temperature. After completion of the reaction, 10 % HCl (2 mL) were added, followed by saturated aqueous NaHCO_3 solution (15 mL). The mixture was extracted with diethyl ether (3 \times 15 mL), the organic layers were combined, dried over MgSO_4 and the solvents were evaporated under reduced pressure. Column chromatography of the residue (petroleum ether/ EtOAc 70/30) gave alcohol **59** (441.2 mg, 77 %) as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.38-7.29 (m, 5H), 4.52 (s, 2H), 3.49 (t, J = 6.3 Hz, 2H), 1.70-1.61 (m, 2H), 1.56-1.41 (m, 6H), 0.86 (t, J = 7.5 Hz, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 138.5, 128.5 (2C), 127.7 (2C), 127.6, 74.2, 73.0, 71.1, 35.2, 31.1, 23.9, 8.0 (2C).

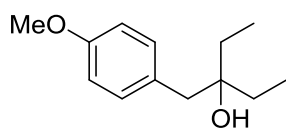
8-Allyl-1,4-dioxaspiro[4.5]decan-8-ol (**61**)



A 1.7 M solution of allyl magnesium chloride in THF (514 mg, 5.1 mmol) was added to dry THF (25 mL) and cooled to 0 °C. A solution of 1,4-Dioxaspiro[4.5]decan-8-one (780.9 mg, 5 mmol) in dry THF (5 mL) was then added dropwise and the solution was stirred at 0 °C for 10 min and then warmed to room temperature. After completion of the reaction, 10 % HCl (2 mL) were added, followed by saturated aqueous NaHCO_3 solution (15 mL). The mixture was extracted with diethyl ether (3 \times 15 mL), the organic layers were combined, dried over MgSO_4 and the solvents were evaporated under reduced pressure. Column chromatography of the residue (petroleum ether/ EtOAc 85/15) gave alcohol **62** (665 mg, 71 %) as a colorless oil.

Spectral data are in accordance with those reported in the literature.¹¹⁹ **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 5.95-5.78 (m, 1H), 5.19-5.05 (m, 2H), 3.98-3.87 (m, 4H), 2.22 (d, $J = 7.5$ Hz, 2H), 1.94-1.80 (m, 3H), 1.71-1.52 (m, 6H). **CAS Number:** 429691-42-9.

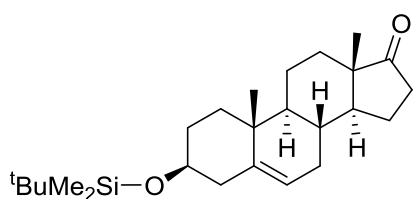
α,α -Diethyl-4-methoxy-benzene ethanol (63)



A 3.0 M solution of EtMgBr in diethyl ether (1.37g, 10 mmol) was added to dry diethyl ether (25 mL) and cooled to 0 °C. A solution of methyl 4-methoxyphenylacetate (901 mg, 5 mmol) in dry diethyl ether (5 mL) was then added dropwise and the solution was stirred at 0 °C for 10 min and then warmed to room temperature. After completion of the reaction, 10 % HCl (2 mL) were added, followed by saturated aqueous NaHCO₃ solution (15 mL). The mixture was extracted with diethyl ether (3 \times 15 mL), the organic layers were combined, dried over MgSO₄ and the solvents were evaporated under reduced pressure. Column chromatography of the residue (petroleum ether/ EtOAc 80/20) gave alcohol **63** (989 mg, 95 %) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.18-7.10 (m, 2H), 6.89-6.81 (m, 2H), 3.80 (s, 3H), 2.68 (s, 2H), 1.45 (q, $J = 7.6$ Hz, 4H), 0.92 (t, $J = 7.5$ Hz, 6H). **¹³C NMR (101 MHz, CDCl₃)** δ (ppm) 158.4, 131.6, 129.6, 113.8, 74.7, 55.4, 44.0, 30.5, 8.2.

3-[[1,1-Dimethylethyl]dimethylsilyloxy]-17-methyl-(3 β ,17 β)-androst-5-en-17-ol (64)

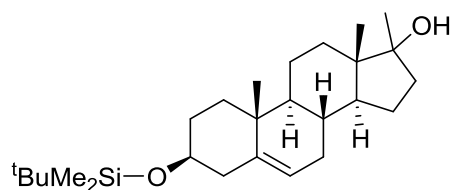


Prepared from the commercially available androst-5-ene-17-one-3 β -ol (2.00 g, 6.9 mmol), *tert*-butyldimethylsilyl chloride (1.25 g, 8.3 mmol), Et₃N (842 mg, 8.3 mmol) and DMAP (847 mg, 6.9 mmol) in CH₂Cl₂ (30 mL) and the solution was stirred overnight at room temperature. After completion of the reaction, saturated aqueous NaHCO₃ solution (15 mL) was added, followed by saturated aqueous NH₄Cl solution (15 mL) and then water (15 mL). The mixture was extracted with ethyl acetate (3 \times 15 mL), the organic layers were combined, dried over MgSO₄ and the solvents were evaporated under

¹¹⁹ S. Vanlaer, W.M. De Borggraeve, A. Voet, C. Gielens, M. De Maeyer, F. Compennolle *Eur. J. Org. Chem.*, **2008**, 2571–2581.

reduced pressure. Column chromatography of the residue (petroleum ether/ EtOAc 80/20) gave silylated product (2.61 g, 93%) as a white solid.

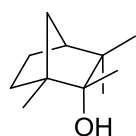
Spectral data are in accordance with those reported in the literature.¹²⁰ **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 5.38-5.31 (m, 1H), 3.54-3.43 (m, 1H), 2.52-2.40 (m, 1H), 2.33-2.15 (m, 2H), 2.15-2.02 (m, 2H), 2.00-1.90 (m, 1H), 1.89-1.78 (m, 2H), 1.78-1.41 (m, 8H), 1.34-1.22 (m, 2H), 1.12-0.94 (m, 4H), 0.91 (s, 3H), 0.88 (s, 9H), 0.06 (s, 6H).



A solution of methyl iodide (1.06 g, 7.5 mmol) in anhydrous ether (5 mL) was added dropwise to a stirred suspension of dry magnesium turnings (187.1 mg, 7.7 mmol) in anhydrous ether (2 mL). The resulting mixture was stirred under reflux for 1 h and a solution of silylated-DHEA (1.0 g, 2.5 mmol) in anhydrous ether (16 mL) was added dropwise. The reaction mixture was stirred under reflux for additional 4 h and then allowed to cool. A saturated aqueous solution of NH₄Cl (25 mL) was added dropwise, the resulting layers were separated, and the aqueous one was extracted with ether (3 \times 50 mL). The combined extracts were washed with brine (50 mL) and dried (MgSO₄). Evaporation of the solvent gave alcohol **64** (600 mg, 58%), which was used without purification.

Spectral data are in accordance with those reported in the literature.¹²¹ **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 5.38-5.27 (m, 1H), 3.53-3.42 (m, 1H), 2.33-1.89 (m, 4H), 1.89-1.39 (m, 12H), 1.36-1.23 (m, 4H), 1.21 (s, 3H), 1.02 (s, 3H), 0.88 (s, 9H), 0.86 (s, 3H), 0.06 (s, 6H).
CAS Number: 141779-17-1.

Homofenchol (68)



A solution of methyl iodide (4.7 g, 33 mmol) in anhydrous ether (25 mL) was added dropwise to a stirred suspension of dry magnesium turnings (850 mg, 66 mmol) in anhydrous ether (5 mL). The resulting mixture was stirred under reflux for 1 h and a solution of L-fenchone (1.68 g, 11 mmol) in anhydrous ether (70 mL) was added

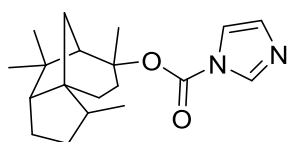
¹²⁰ M.A. Ponce, R. Erra-Balsells, A.C. Bruttomesso, E.G. Gros *Helvetica Chimica Acta*, **2004**, 87, 2987-3003.

¹²¹ D.H.R. Barton, S.I. Parekh, C.-L. Tse *Tetrahedron Lett.*, **1993**, 34, 2733-2736.

dropwise. The reaction mixture was stirred under reflux for additional 4 h and then allowed to cool. A saturated aqueous solution of NH_4Cl (25 mL) was added dropwise, the resulting layers were separated, and the aqueous one was extracted with ether (3×50 mL). The combined extracts were washed with brine (100 mL) and dried (MgSO_4). Evaporation of the solvent gave alcohol **68** (868 mg, 52%), which was used without purification.

Spectral data are in accordance with those reported in the literature.⁹⁷ ^1H NMR (400 MHz, CDCl_3) δ (ppm) 1.88 (dddd, $J = 12.6, 9.1, 5.3, 2.5$ Hz, 1H), 1.71 (ddt, $J = 12.5, 9.0, 3.3$ Hz, 1H), 1.64 (dt, $J = 3.8, 1.6$ Hz, 1H), 1.55 (dq, $J = 10.2, 2.2$ Hz, 1H), 1.47-1.36 (m, 1H), 1.14-1.07 (m, 5H), 1.07-1.02 (m, 1H), 0.99 (s, 3H), 0.94 (s, 3H), 0.92 (s, 3H).

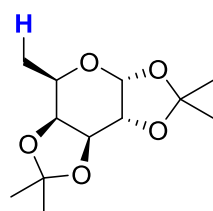
Compound (74)



Following **GP1** with commercially available Cedrol (1 g, 4.5 mmol), 1,1'-Carbonyldiimidazole (875 mg, 5.4 mmol) and DMAP (275 mg, 2.3 mmol) in CH_2Cl_2 (20 mL), compound **74** was purified by FC (Pentane/EtOAc, 50/50) and isolated (484 mg, 34%) as a white solid.

^1H NMR (400 MHz, CDCl_3) δ (ppm) 8.11-8.05 (m, 1H), 7.41-7.34 (m, 1H), 7.06-7.01 (m, 1H), 2.54 (d, $J = 5.2$ Hz, 1H), 2.21-2.10 (m, 2H), 1.96-1.81 (m, 2H), 1.80-1.67 (m, 5H), 1.65-1.36 (m, 4H), 1.36-1.22 (m, 2H), 1.14 (s, 3H), 1.01 (s, 3H), 0.86 (d, $J = 7.2$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 146.9, 137.1, 130.2, 117.2, 92.0, 57.0, 56.7, 54.07, 43.5, 41.2 (2C), 36.9, 33.1, 31.3, 28.4, 27.1, 25.9, 25.3, 15.5.

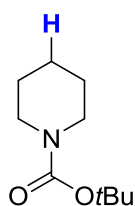
6-Deoxy-1,2:3,4-di-O-isopropylidene- α -D-galactopyranose (79)



Following **GP2.A** with 6-O-(1,2:3,4-di-O-isopropylidene- α -D-galactopyranose)-1H-imidazole-1-carbothioate **44** (185.2 mg, 0.5 mmol) and $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (95/5) as solvent, compound **80** was purified by FC (Pentane/EtOAc, 80/20) and isolated (39.2 mg, 35%) as a colorless syrup.

Spectral data are in accordance with those reported in the literature.¹²² **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 5.50 (d, *J* = 5.2 Hz, 1H), 4.57 (dd, *J* = 7.9, 2.3 Hz, 1H), 4.27 (dd, *J* = 5.1, 2.3 Hz, 1H), 4.07 (dd, *J* = 7.9, 2.0 Hz, 1H), 3.90 (qd, *J* = 6.6, 1.9 Hz, 1H), 1.51 (s, 3H), 1.45 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H), 1.24 (d, *J* = 6.6 Hz, 3H).

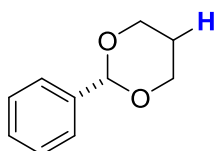
***tert*-Butyl piperidine-1-carboxylate (80)**



Following **GP2.A** with *O*-[1-(*tert*-butyloxycarbonyl)piperidin-4-yl] 1*H*-imidazole-1-carbothioate **45** (155.7 mg, 0.5 mmol), compound **80** was purified by FC (Pentane/EtOAc, 95/5) and isolated (49.2 mg, 53%) as a colorless oil.

Spectral data are in accordance with those reported in the literature.¹²³ **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 3.33 (t, *J* = 5.6 Hz, 4H), 1.65-1.43 (m, 6H), 1.43 (s, 9H). **CAS Number:** 75844-69-8.

2-Phenyl-1,3-dioxane (81)



Following **GP2.A** with *O*-[2-phenyl-1,3-dioxan-5-yl] 1*H*-imidazole-1-carbothioate **46** (145.2 mg, 0.5 mmol), compound **81** was purified by FC (Pentane/EtOAc, 95/5) and isolated (34.1 mg, 41%) as a white solid.

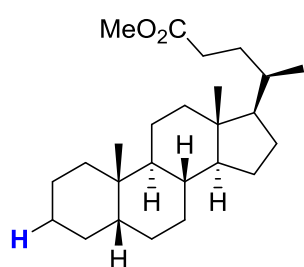
Spectral data are in accordance with those reported in the literature.¹²⁴ **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 7.50-7.46 (m, 2H), 7.40-7.32 (m, 3H), 5.51 (s, 1H), 4.31-4.24 (m, 2H), 4.04-3.95 (m, 2H), 2.32-2.15 (m, 1H), 1.48-1.42 (m, 1H). **CAS Number:** 772-01-0.

¹²² E. Vismara, A. Donna, R. Minisci, A. Naggi, N. Pastori, G. Torri, *J. Org. Chem.*, **1993**, *58*, 959-963. C.-C. Lin, M.-D. Jan, S.-S. Weng, C.-C. Lin, C.-T. Chen, *Carbohydrate Research*, **2006**, *341*, 1948-1953.

¹²³ G. Barker, P. O'Brien, K. R. Campos, *Org. Lett.*, **2010**, *12*, 4176-4179.

¹²⁴ F. Rajabi, A. M. Balu, F. Toreinia, R. Luque, *Catal. Sci. Technol.*, **2011**, *1*, 1051-1059.

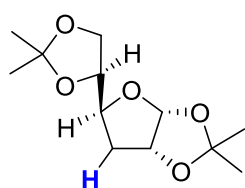
Methyl-5 β -cholanoate (**82**)



Following **GP2.B** with (4*R*)-Methyl 4-((3*R*,5*R*,10*S*,13*R*)-3-((1*H*-imidazole-1-carbothioyl)oxy)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)pentanoate **47** (250.4 mg, 0.5 mmol), compound **82** was purified by FC (Pentane/Et₂O, 70/30) and isolated (122.1 mg, 65%) as a white solid.

Spectral data are in accordance with those reported in the literature.¹²⁵ ¹H NMR (400 MHz, CDCl₃) δ (ppm) 3.66 (s, 3H), 2.38-2.30 (m, 1H), 2.25-2.16 (m, 1H), 1.97-1.95 (m, 1H), 1.86-1.71 (m, 6H), 1.59-1.55 (m, 1H), 1.42-1.04 (m, 19H), 0.91 (s, 3H), 0.90 (d, *J* = 6.4 Hz, 3H), 0.64 (s, 3H). **CAS Number:** 2204-14-0.

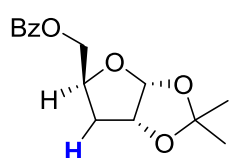
5-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3- δ][1,3]dioxole (**83**)



Following **GP2.A** with *O*-[1,2:5,6-di-*O*-isopropylidene- α -D-glucofuranosyl] 1*H*-imidazole-1-carbothioate **48** (185.2 mg, 0.5 mmol), compound **83** was purified by FC (Pentane/EtOAc, 70/30) and isolated (68 mg, 56%) as a colorless syrup.

Spectral data are in accordance with those reported in the literature.¹²⁶ ¹H NMR (400 MHz, CDCl₃) δ (ppm) 5.79 (d, *J* = 3.6, 1H), 4.73 (t, *J* = 4.3 Hz, 1H), 4.16-4.05 (m, 3H), 3.83-3.78 (m, 1H), 2.16 (dd, *J* = 13.3, 4.0 Hz, 1H), 1.78-1.70 (m, 1H), 1.49 (s, 3H), 1.40 (s, 3H), 1.33 (s, 3H), 1.30 (s, 3H). **CAS Number:** 4613-62-1.

[(3*aR*,5*S*,6*aR*)-2,2-Dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl]methyl Benzoate (**84**)



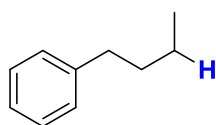
Following **GP2.A** with *O*-[1,2-isopropylidene-5-benzoate- α -D-xylofuranosyl] 1*H*-imidazole-1-carbothioate **49** (202.2 mg, 0.5 mmol), compound **84** was purified by FC (Pentane/EtOAc, 60/40) and isolated (97.6 mg, 70%) as a white solid.

¹²⁵ A.C. Burns, P.W. Sorensen, T.R. Hoye, *Steroids* **2011**, 76, 291-300

¹²⁶ J. D. Nguyen, E. M. D'Amato, J. M. R. Narayanam, C. R. J. Stephenson, *Nat. Chem.* **2012**, 4, 854-859.

Spectral data are in accordance with those reported in the literature.¹²⁷ **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 8.06-8.03 (m, 2H), 7.58-7.52 (m, 1H), 7.45-7.40 (m, 2H), 5.86 (d, *J* = 3.7 Hz, 1H), 4.77 (dd, *J* = 4.5, 4.0 Hz, 1H), 4.58-4.50 (2H, m), 4.35 (dd, *J* = 11.9, 5.7 Hz, 1H), 2.17 (dd, *J* = 13.2, 4.3 Hz, 1H), 1.75 (ddd, *J* = 13.4, 10.8, 4.8 Hz, 1H), 1.53 (s, 3H), 1.32 (s, 3H). **CAS Number:** 4105-29-7.

n-Butylbenzene (85)



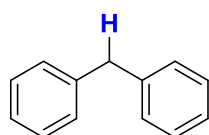
Following **GP2.A** with *O*-[4-phenylbutan-2-yl] 1*H*-imidazole-1-carbothioate **50** (130.2 mg, 0.5 mmol), compound **85** was purified by FC (Pentane) and isolated (34.2 mg, 51%) as a colorless oil.

Spectral data are in accordance with those reported in the literature.¹²⁸ **¹H NMR (300 MHz, CDCl₃)** δ (ppm) 7.33-7.25 (m, 2H), 7.22-7.16 (m, 3H), 2.64 (t, *J* = 7.6 Hz, 2H), 1.68-1.58 (m, 2H), 1.45-1.33 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H). **CAS Number** 104-51-8.

Diphenyl methane (86) and 1,1,2,2-tetraphenylethane (87)

Following **GP2.A** with *O*-[diphenylmethyl] 1*H*-imidazole-1-carbothioate **51** (147.2 mg, 0.5 mmol), compound **86** and **87** were purified by FC (Pentane/Et₂O 99/1) and isolated (18 mg, 21% and 31 mg, 37%) as a colorless oil and a white solid respectively.

Diphenyl methane (86)



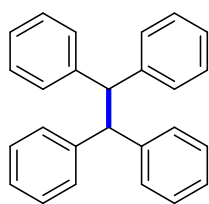
Spectral data are in accordance with those reported in the literature.¹²⁹ **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 7.33-7.28 (m, 4H), 7.24-7.20 (m, 6H), 4.01 (s, 2H). **CAS Number** 101-81-5.

¹²⁷ L. Zhang, M. Koreeda, *J. Am. Chem. Soc.* **2004**, *126*, 13190-13191.

¹²⁸ L. Ackermann, A. R. Kapdi, C. Schulzke, *Org. Lett.* **2010**, *12*, 2298-2301.

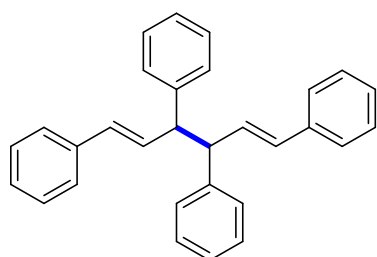
¹²⁹ M. Peña-López, M. Ayán-Varela, L. A. Sarandeses, J. P. Sestelo, *Chem. Eur. J.* **2010**, *16*, 9905-9909.

1,1,2,2-Tetraphenylethane (87)



Spectral data are in accordance with those reported in the literature.¹³⁰ ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.23-7.02 (m, 20H), 4.82 (s, 2H). CAS Number 632-50-8.

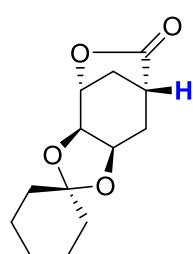
(1E, 5E)-1,3,4,6-Tetraphenyl-1,5-hexadiene (88)



Following GP2.A with (*E*)-*O*-[1,3-diphenylallyl] 1*H*-imidazole-1-carbothioate **52** (160.2 mg, 0.5 mmol), compound **88** was purified by FC (Pentane/Et₂O 99/1 then 98/2) and isolated as a 1:1 mixture of *meso*-(**E,E**)/*rac*-(**E,E**) (96 mg, 99%) as a white solid.

Spectral data are in accordance with those reported in the literature.¹³¹ *meso*-(**E,E**) **88**: ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.35-7.12 (m, 20H), 6.34 (ddd, *J* = 15.8, 5.5, 2.2 Hz, 2H), 6.22 (d, *J* = 15.8 Hz, 2H), 3.93-3.90 (m, 2H). *rac*-(**E,E**) **88**: ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.35-7.12 (m, 20H), 6.56 (ddd, *J* = 15.8, 5.5, 2.2 Hz, 2H), 6.45-6.42 (d, *J* = 15.8 Hz, 2H), 3.93-3.90 (m, 2H). CAS Number: 204578-86-9.

Spiro[cyclohexane-1,2'-[4,7]methano[1,3]dioxolo[4,5-*c*]oxepin]-6'(4'H)-one, tetrahydro-, (3'aR,4'R,7'S,8'aR) (89)



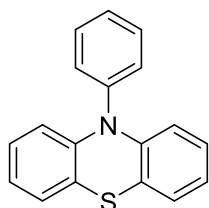
Following GP2.A with spiro[cyclohexane-1,2'-[4,7]methano[1,3]dioxolo[4,5-*c*]oxepin]-6'(4'H)-one, 7'-(1*H*-imidazole-1-carbothioyl) oxy) tetrahydro-, (3'aR,4'R,7'S,8'aR) **56** (182.2 mg, 0.5 mmol), compound **89** was purified by FC (Pentane/EtOAc 80/20) and isolated (71.5 mg, 60%) as colorless oil.

¹³⁰ H. Wakui, S. Kawasaki, T. Satoh, M. Miura, M. Nomura, *J. Am. Chem. Soc.* **2004**, *126*, 8658-8659.

¹³¹ W. V. E. Doering, L. Birladeanu, K. Sarma, G. Blaschke, U. Scheidemantel, R. Boese, J. Benet-Bulcholz, F.-G. Klarner, J.-S. Gehrke, B. U. Zimny, R. Sustmann, H.-G. Korth, *J. Am. Chem. Soc.* **2000**, *122*, 193-203.

Spectral data are in accordance with those reported in the literature.¹³² **¹H NMR (400 MHz, CDCl₃)** δ (ppm) 4.71 (dd, *J* = 5.7, 2.6 Hz, 1H), 4.47-4.42 (m, 1H), 4.33-4.29 (m, 1H), 2.60-2.56 (m, 1H), 2.41 (d, *J* = 12.2 Hz, 1H), 2.32-2.26 (m, 1H), 2.22-2.15 (m, 1H), 2.10-2.04 (m, 1H), 1.71-1.61 (m, 4H), 1.55-1.52 (m, 4H), 1.41-1.37 (m, 2H). **CAS Number:** 185900-33-8.

N-Phenylphenothiazine (93)



Prepared from the commercially available 10*H*-phenothiazine (2.00 g, 10.0 mmol), iodobenzene (6.14 g, 30.0 mmol), K₂CO₃ (2.77 g, 20.0 mmol) and some Cu turnings according to the literature procedure reported by D. Li et al.,¹³³ compound **93** was purified by recrystallization in absolute ethanol and isolated (1.70 g, 62%) as a white solid.

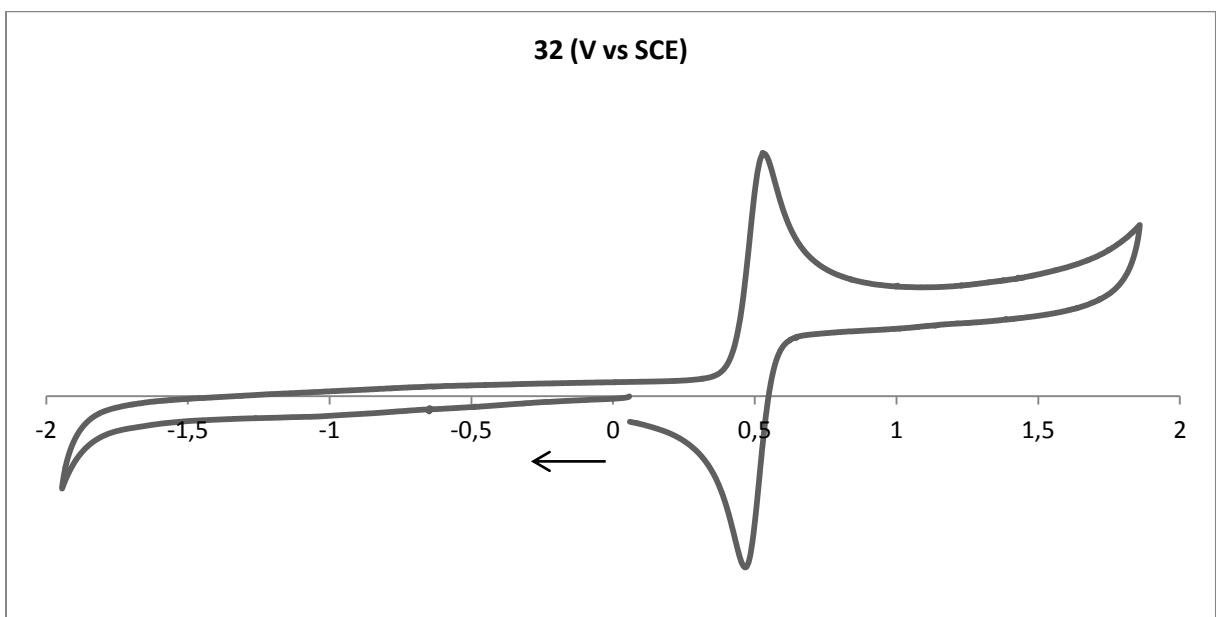
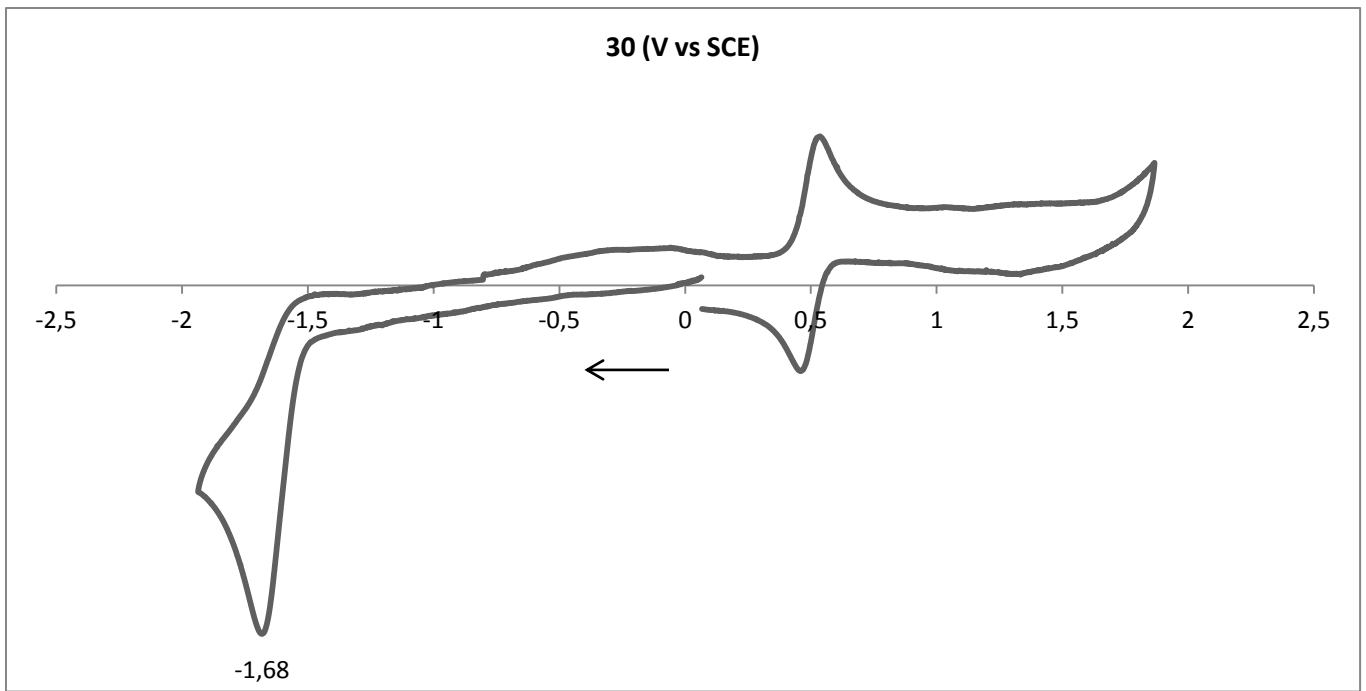
Spectral data are in accordance with those reported in the literature.¹⁰⁹ **¹H NMR (400 MHz, CDCl₃)** δ 7.61 (t, *J* = 7.7 Hz, 2H), 7.52-7.45 (m, 1H), 7.45-7.36 (m, 2H), 7.08-6.99 (m, 3H), 6.93-6.74 (m, 3H), 6.29-6.13 (m, 2H). **¹³C NMR (101 MHz, CDCl₃)** δ (ppm) 144.9, 141.2, 131.0, 130.7, 128.5, 127.0, 126.8, 122.6, 120.4, 116.1.

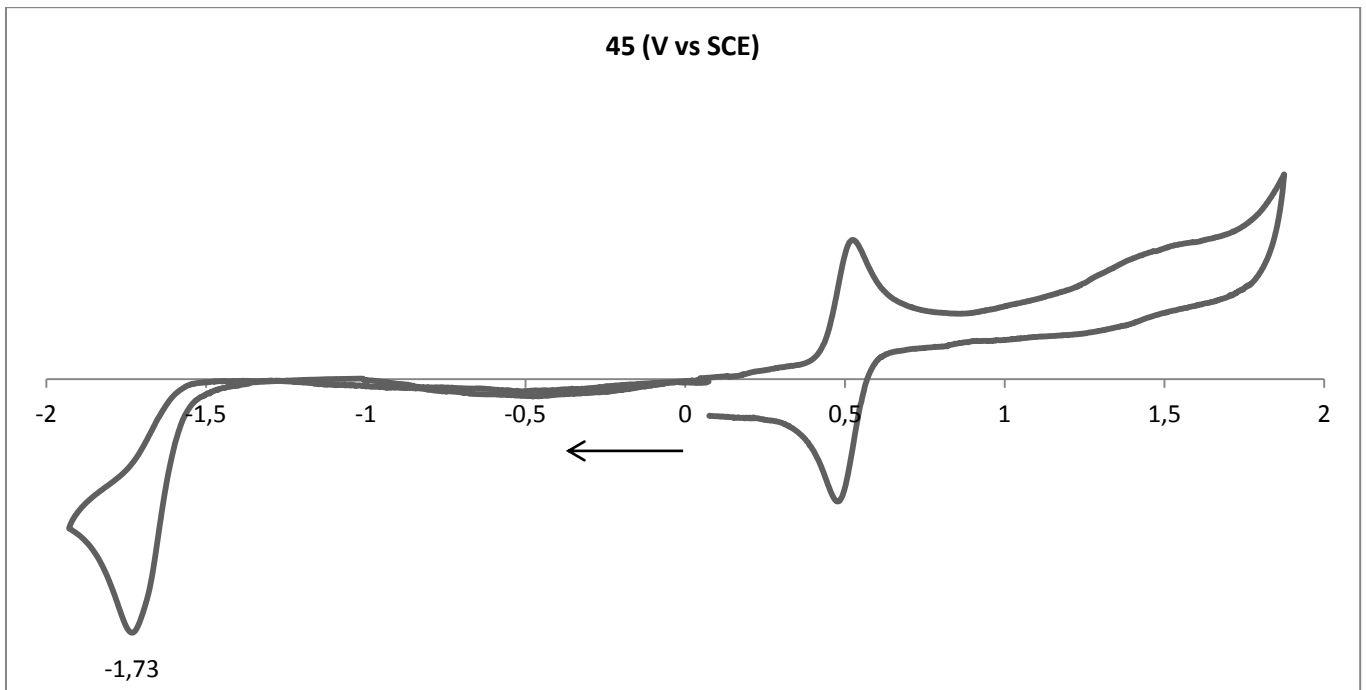
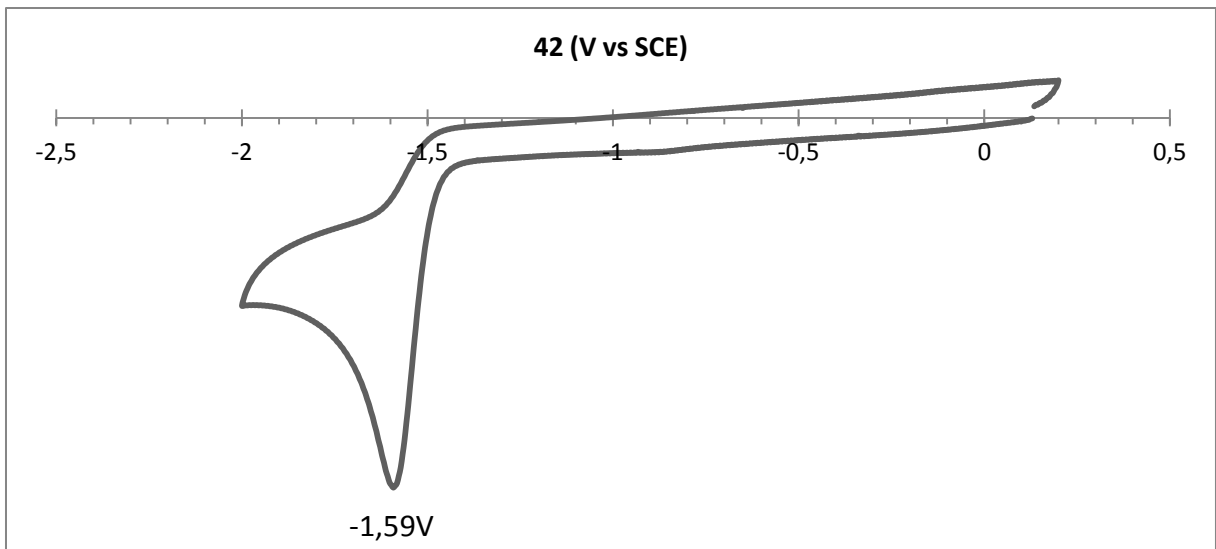
Cyclic Voltammograms

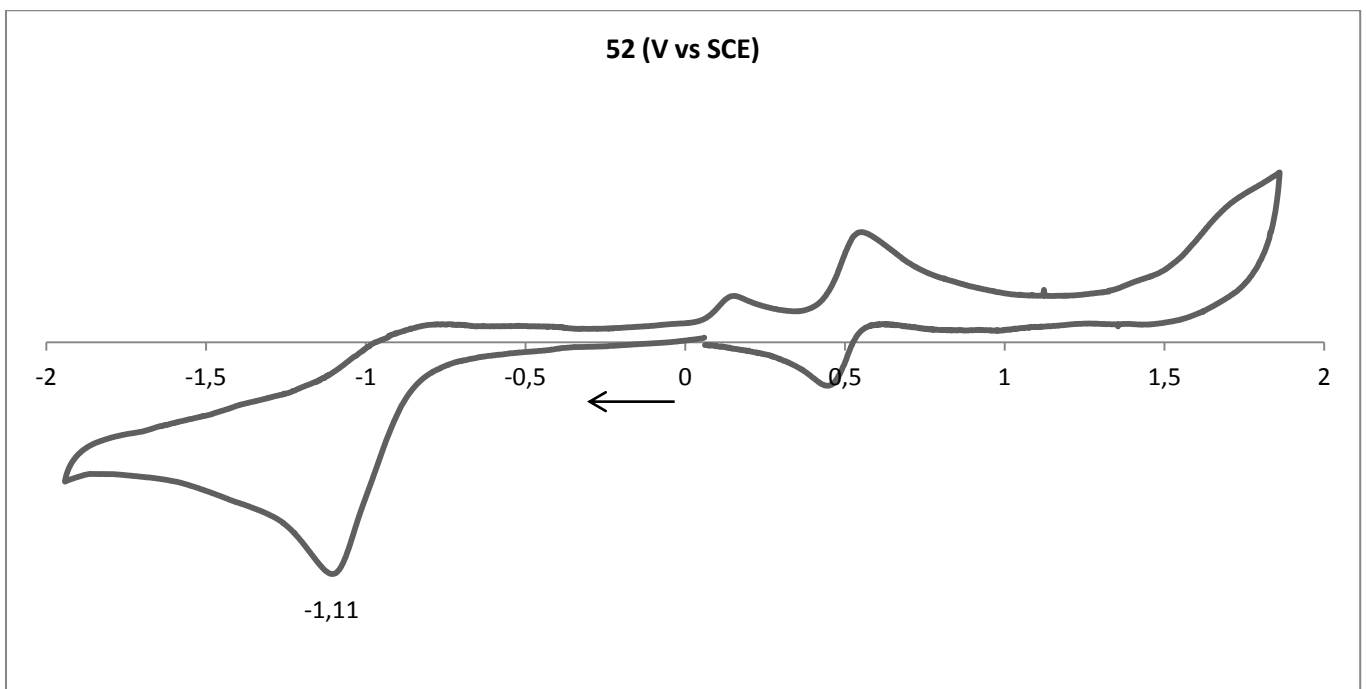
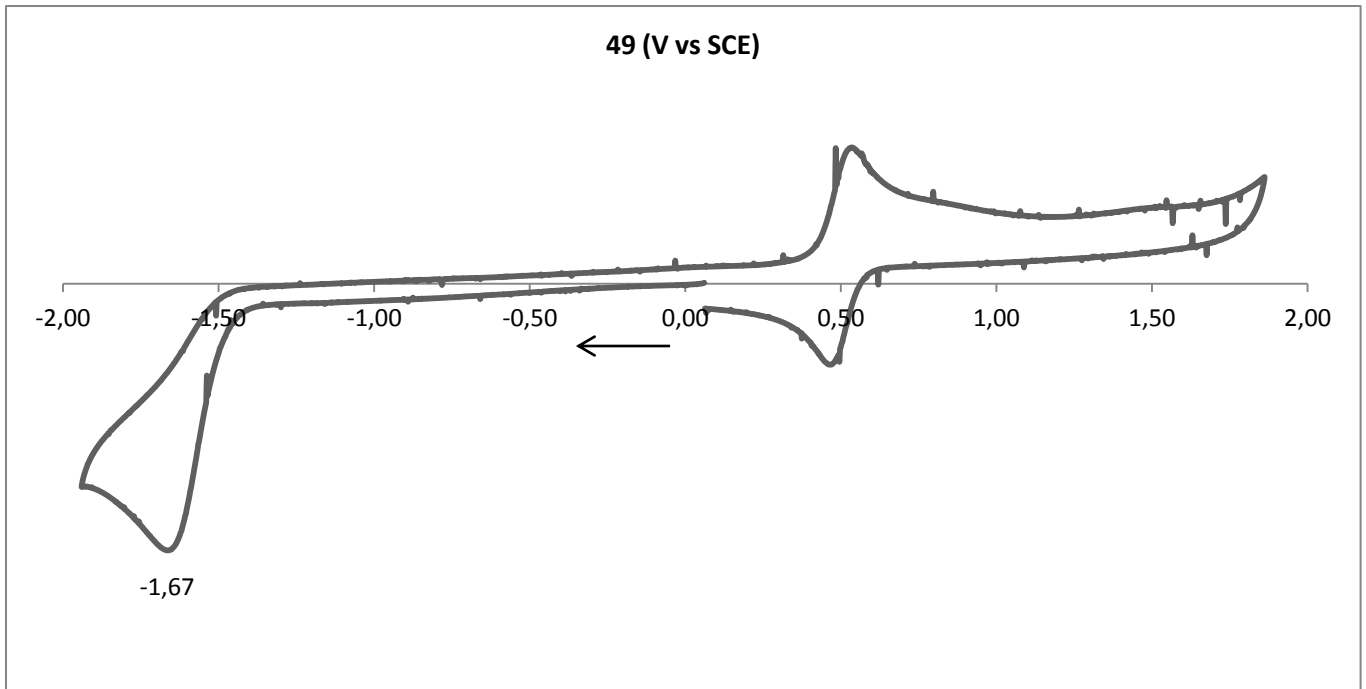
The redox potentials of *O*-thiocarbamates and the *S*-thiocarbamate have been measured by cyclic voltammetry using a glassy-carbon electrode in a 0.1M solution of [*n*-Bu₄N]PF₆, as supporting electrolyte, in degassed HPLC grade acetonitrile; Fc⁺/Fc as internal standard, under argon atmosphere. Scan rate: 0.1 V/s, Saturated Calomel Electrode used as reference electrode and platinum as counter electrode.

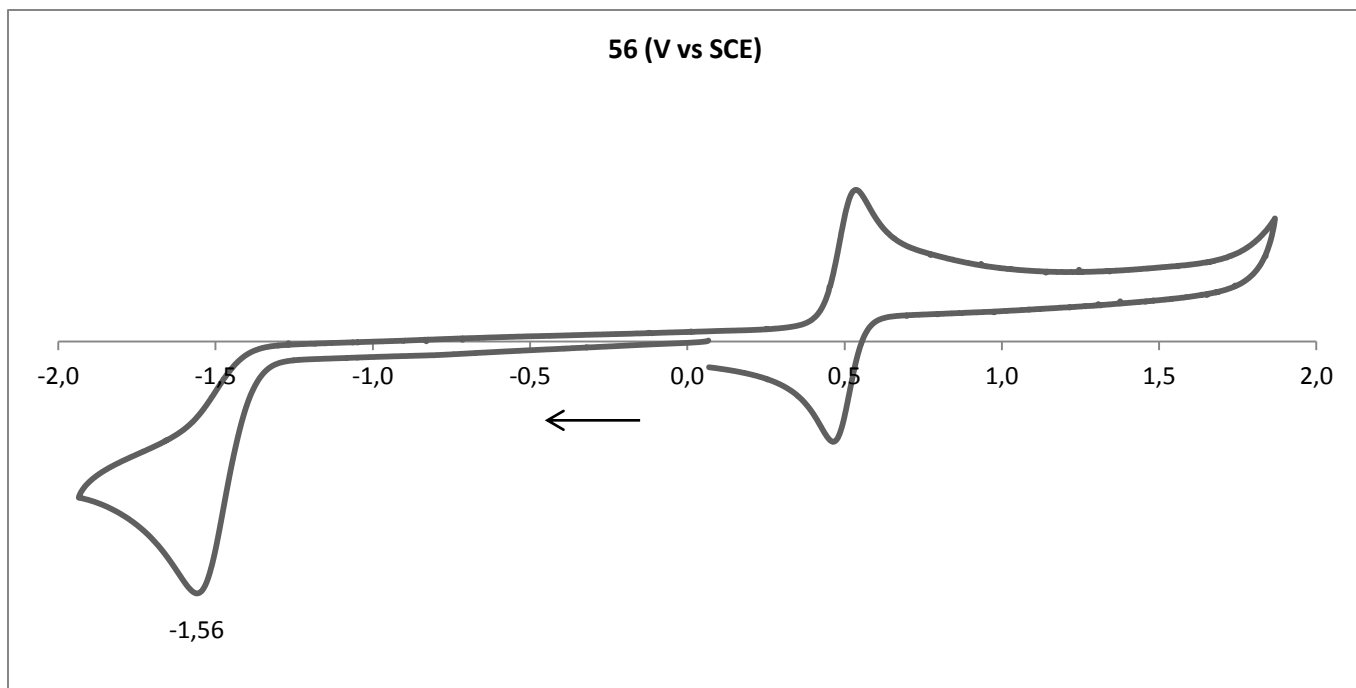
¹³² D. R. Prudhomme, Z. Wang, C. J. Rizzo, *J. Org. Chem.* **1997**, 62, 8257-8260.

¹³³ D. Li, J. Ren, J. Li, Z. Wang, G. Bo, *Dyes and pigments* **2001**, 49, 181-186









Chapter III

Visible Light-induced Photooxidative Generation of Radicals from Hypervalent Species and Development of a New Dual Photoredox/Nickel Catalysis Process

III.A. Bibliographical Background: When Photoredox Catalysis Merged with Organometallic Catalysis: Rising of Dual Catalysis Process

III.A.1. Introduction

Recently, photoredox catalysis has emerged as a powerful tool to realize challenging transformations under mild conditions. In 2011, this synthetic approach took a new twist with the emergence of a new catalytic process that combines the advantages of transition-metal catalysis and free radical processes involving the photoredox pathway. This new system opened the way to the development of very useful cross-coupling reactions catalyzed by various types of transition-metals.

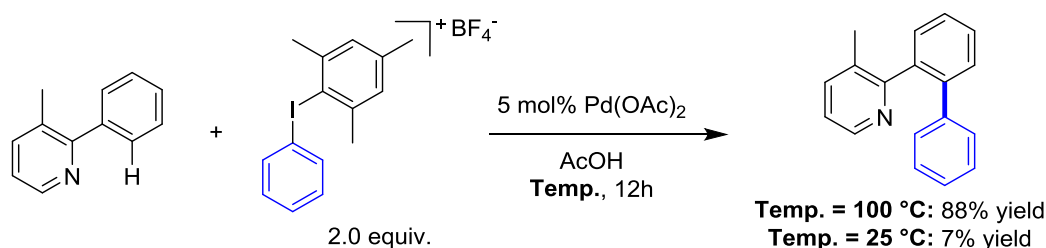
III.A.2. Merging of Visible-light Photoredox/Transition-Metal Catalysis

The recent development of this field starts with studies of Sanford and co-workers on room temperature C-H arylation of aromatics combining palladium catalyzed C-H activation and visible-light photoredox catalysis.¹ Most of C-H arylation methods require elevated temperatures. Typically, the palladium-catalyzed C-H arylation of arylpyridines with diaryliodonium salts was performed at 100 °C (Scheme 1) and the yield dropped dramatically when the reaction was done at room temperature (25 °C).^{2,3} This low reactivity is attributed to the difficulty of the arylating reagent to oxidize the dimeric Pd catalyst intermediate.

¹ D. Kalyani, K. B. McMurtrey, S. R. Neufeldt, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 18566.

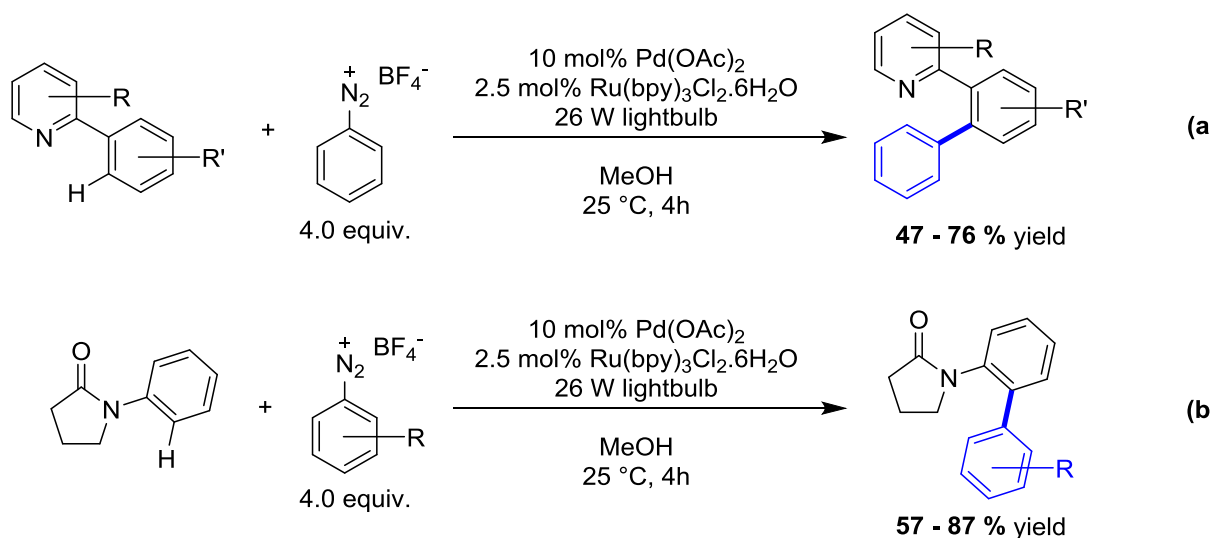
² D. Kalyani, N. R. Deprez, L. V. Desai, M. S. Sanford, *J. Am. Chem. Soc.* **2005**, *127*, 7330.

³ N. R. Deprez, M. S. Sanford, *J. Am. Chem. Soc.* **2009**, *131*, 11234.



Scheme 1. Pd-Catalyzed C-H arylation of arylpyridine with diaryliodonium salt

In 2009, Yu⁴ demonstrated that phenyl radicals generated from dibenzoylperoxide under thermal activation could be involved in a much faster Pd catalyzed C-H arylation of arylpyridines. Inspired by this work, Sanford investigated the same transformation by using a photoredox catalyst under visible-light irradiation and an aryldiazonium tetrafluoroborate salt as a source of aryl radical. Indeed, aryldiazonium salt can be easily reduced by Ru(bpy)₃Cl₂ under visible-light irradiation at room temperature.⁵ Combining this reactivity with the palladium catalysis, she performed the first Pd-catalyzed C-H arylation of phenyl rings containing different directing groups under visible-light photoredox catalysis, yielding 30% of arylated product. The visible-light process implies the use of mild conditions (room temperature reaction), non acidic solvent and easily removable byproducts. After optimization, the arylated product can be obtained in high yield with a good functional groups tolerance (Scheme 2).

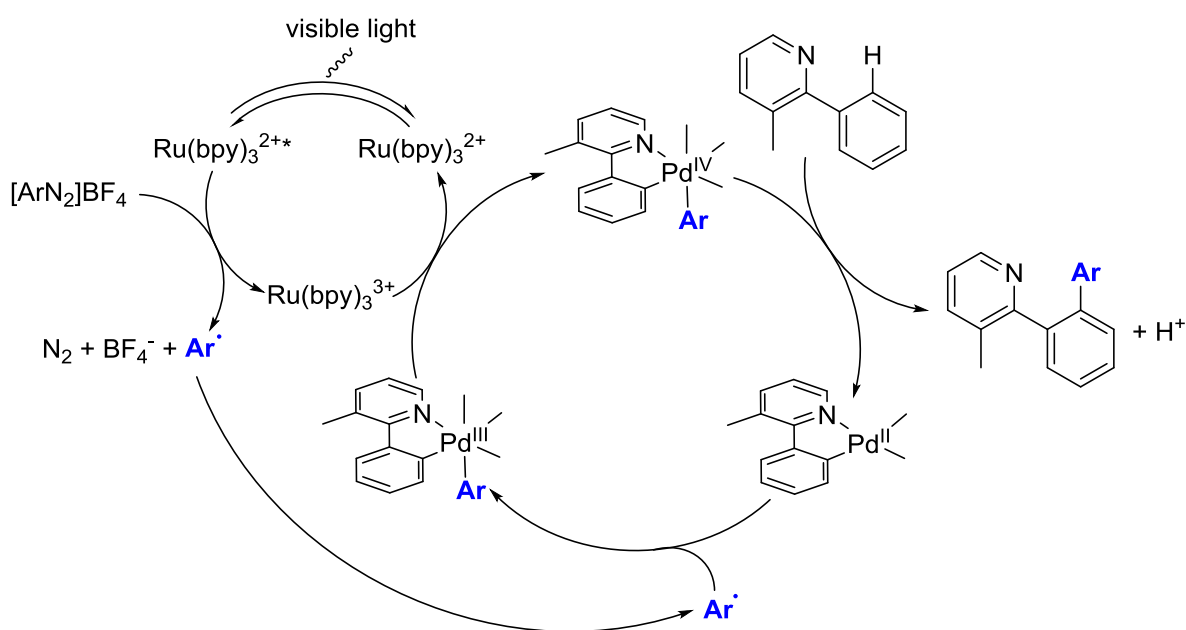


Scheme 2. Pd/Ru-catalyzed C-H arylation of phenyl rings with a directing group

⁴ W.-Y. Yu, W. N. Sit, Z. Zhou, A. S.-C. Chan, *Org. Lett.* **2009**, *11*, 3174.

⁵ H. Cano-Yelo, A. Deronzier, *J. Chem. Soc., Perkin Trans. 2*, **1984**, 1093.

For this transformation, Sanford proposed a mechanism based on a dual catalysis system (Scheme 3). After irradiation of the photocatalyst by visible light, the excited ruthenium reduces the aryldiazonium salt to generate the aryl radical and concomitant the oxidation of the complex to $\text{Ru}(\text{bpy})_3^{3+}$. At the same time, the substrate with a directing ligand is C-H activated by the Pd^{II} to generate the palladacycle, which reacts with the aryl radical to give the Pd^{III} intermediate. After a single-electron transfer (SET) from the $\text{Ru}(\text{bpy})_3^{3+}$ to the Pd^{III} , the oxidized Pd^{IV} undergoes a reductive elimination to give the arylated product. The Ru^{II} and the Pd^{II} catalysts are regenerated to afford new catalytic cycles.



Scheme 3. Proposed mechanism for the Pd/Ru-catalyzed C-H arylation

This first dual catalysis between [Pd]/[Ru] shown that the merger of these two reactivities leads to new synthetically useful cross-coupling reactions. The photoredox catalysis can generate under very mild conditions highly reactive species which can be engaged in organometallic catalysis.

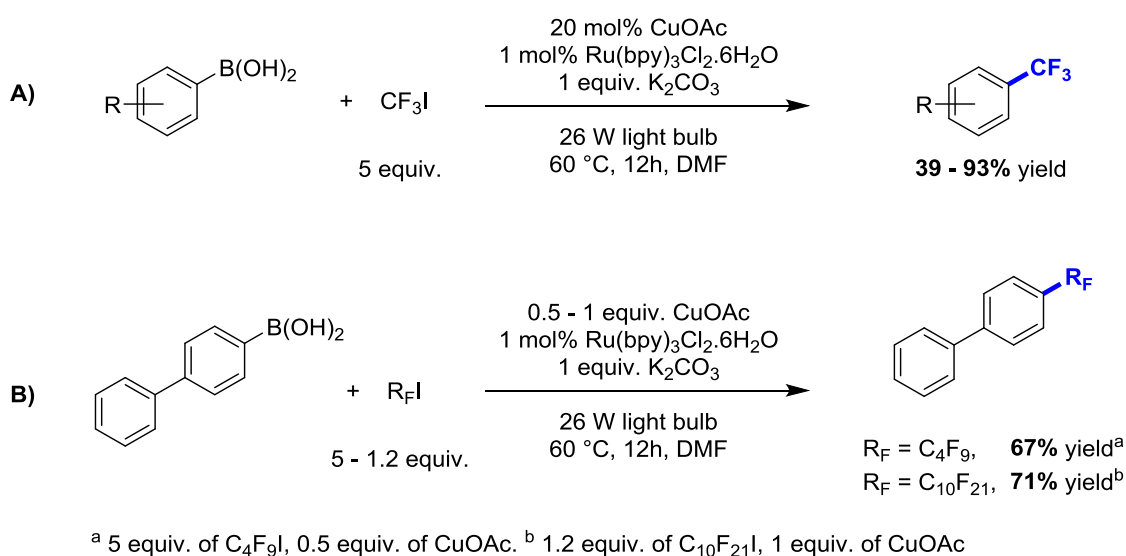
Few years later, Sanford took again advantages of the dual catalysis to perform a copper-catalyzed trifluoromethylation of boronic acids.⁶ Usually these transformations are catalyzed by [Pd]^{7,8} or [Cu] complexes and required harsh conditions (high temperature,

⁶ Y. Ye, M. S. Sanford, *J. Am. Chem. Soc.* **2012**, *134*, 9034.

⁷ V. V. Grushin, W. J. Marshall, *J. Am. Chem. Soc.* **2006**, *128*, 12644.

⁸ A. Zanardi, M. A. Novikov, E. Martin, J. Benet-Buchholz, V. V. Grushin, *J. Am. Chem. Soc.* **2011**, *133*, 20901.

strong acids or bases: trifluoroacetic acid or *ter*-BuOK for example). Moreover, the substrate scope of is limited. Through their studies on α -trifluoromethylation of aldehydes, MacMillan and co-workers, demonstrated that CF_3I can be reduced in the presence of $\text{Ir}(\text{ppy})_2(\text{dtbbpy})$ under visible light irradiation to generate CF_3^\cdot at room temperature.^{9,10} Inspired by these results, Sanford and co-workers investigated the alliance between photoreduction and copper catalysis.⁶ They showed they can performed a [Cu]/[Ru] dual catalysis to obtain the trifluoromethylated aryl in moderate yield. After optimization, they achieved this transformation with various aryl- and heteroarylboronic acids with good yields (scheme 4, equation A). The substitution of the arylboronic acid by either electron-donating (*ter*-butyl, methoxy...) or electron-withdrawing groups (trifluoromethyl, cyano...) gave moderate to high yields of coupling products; in addition, several groups (like ketones, aldehydes, amides, esters...) are well-tolerated. Perfluoroalkylation of 4-biphenylboronic acid was also possible but the loading of copper had to be increased to give a good yield of perfluoroalkylated product (scheme 4, equation B). Once again, this study highlights the powerful advantage of dual catalysis, here involving copper-catalyzed reactions and photoredox processes, to perform challenging organic transformations under mild conditions.



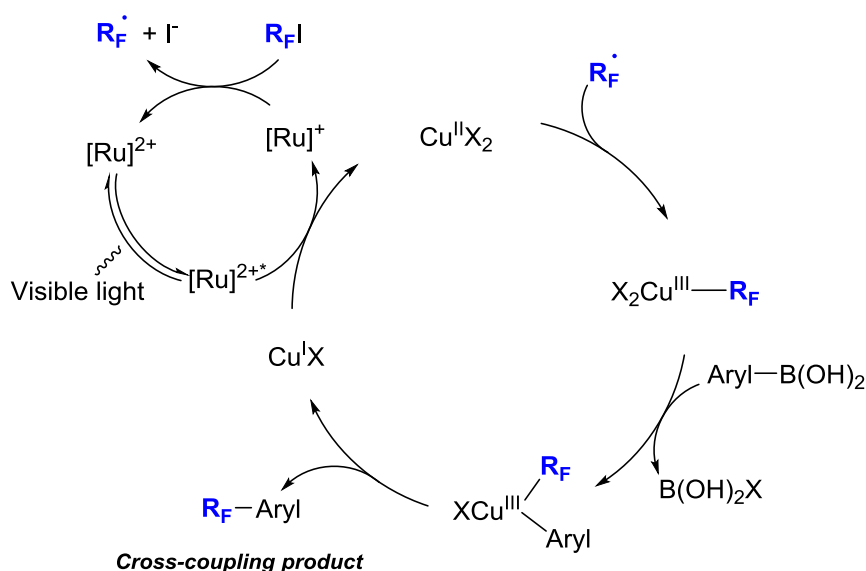
Scheme 4. Cu/Ru-catalyzed trifluoromethylation and perfluoroalkylation of boronic acid

To gain the mechanistic insight (scheme 5), the Cu^{I} complex is oxidized by the excited $\text{Ru}^{\text{II}*}$ in Cu^{II} complex. Then SET reduction of CF_3I by Ru^{I} complex affords the radical CF_3^\cdot and regenerates the photocatalyst. The radical can then react with Cu^{II} complex to generate a

⁹ D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875.

¹⁰ P. V. Pham, D. A. Nagib, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2011**, *50*, 6119.

$\text{Cu}^{\text{III}}(\text{CF}_3)$ intermediate. Base-promoted transmetalation between the arylboronic acid and Cu^{III} complex gives the $\text{Cu}^{\text{III}}(\text{aryl})(\text{CF}_3)$ species which can undergo a reductive elimination to generate the aryl- CF_3 coupling product and regenerate the Cu^{I} complex.

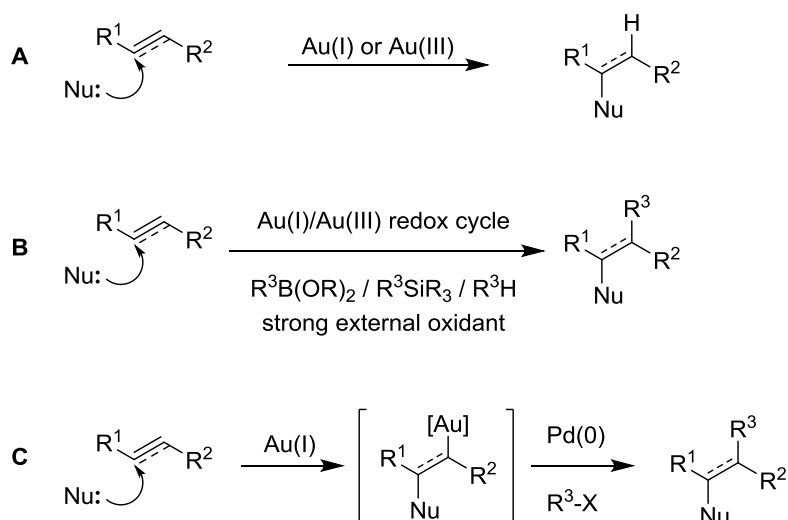


Scheme 5. Proposed mechanism for the Cu/Ru-catalyzed trifluoromethylation

Following the trend in dual catalysis development, other groups were interested in a smart combination between gold and photoredox catalysis for direct functionalization of alkenes. In 2013, gold chemistry has emerged as useful tool to functionalize alkenes, alkynes and allenes by nucleophilic addition processes. The conventional gold-catalysis with Au^{I} or Au^{III} was restricted to C-Nu formation followed by proto-deauration (Scheme 6, equation A). Recently, methodologies involving a catalytic $\text{Au}^{\text{I}}/\text{Au}^{\text{III}}$ cycle have been developed but they require strong oxidants such $\text{PhI}(\text{OAc})_2$ or Selectfluor in stoichiometric amounts (Scheme 6, equation 2).^{11,12} Then a bimetallic Au/Pd system was provided but the main drawback is the use of stoichiometric amounts of organogold intermediates as coupling partners in the palladium-catalyzed cross-coupling reactions (Scheme 6, equation C).

¹¹ M. N. Hopkinson, A. D. Gee, V. Gouverneur, *Chem. – Eur. J.* **2011**, *17*, 8248.

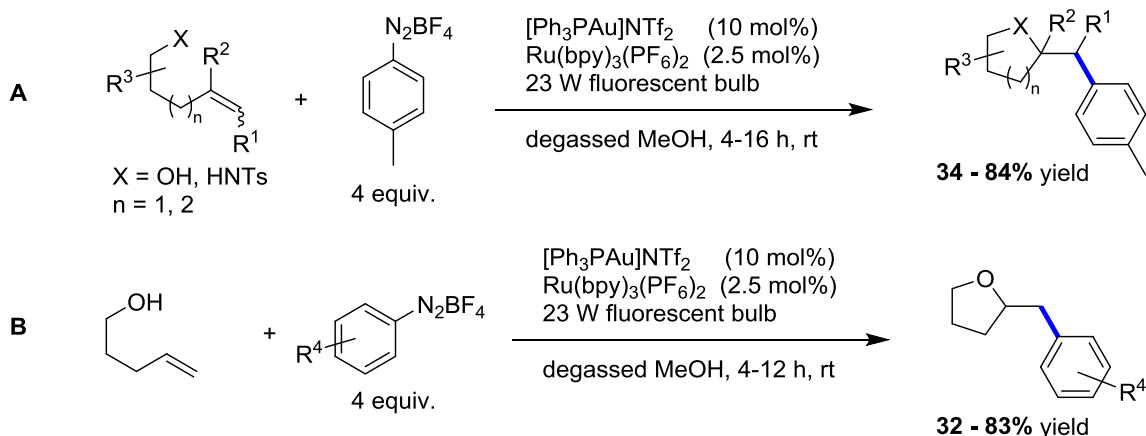
¹² H. A. Wegner, M. Auzias, *Angew. Chem. Int. Ed.* **2011**, *50*, 8236.



Scheme 6. Conventional gold catalysis

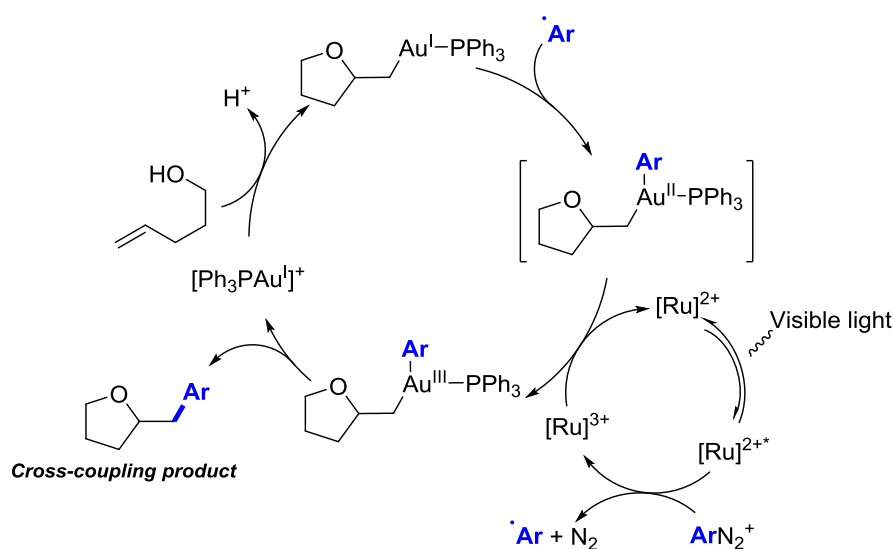
In 2013, Glorius and co-workers investigated the dual gold and photoredox catalytic system to functionalize C-C multiple bonds.¹³ They selected the aryldiazonium tetrafluoroborate salts as a source of aryl radical and the well known $\text{Ru}(\text{bpy})_3(\text{PF}_6)_2$ as photocatalyst complex. With these photoredox conditions, they used the Au^{I} catalyst Ph_3AuCl on 4-penten-1-ol in degassed methanol under 23W fluorescent bulb lamp irradiation which provided to the 5-*exo*-trig cyclization-arylation product. They next tested different gold complexes and they obtained the best yield with the cationic gold complex $\text{Ph}_3\text{PAuNTf}_2$. With the optimized conditions, the authors evaluated the scope of the process with various alkenes (Scheme 7, equation A) and aryldiazonium salts (Scheme 7, equation B). The presence of electron-withdrawing substituents and notably aryldiazoniums bearing halogen (chloro or bromo) gave better yields. The nucleophilic addition-arylation sequence worked successfully either with alcohols or tosylamides. Substitution of the alkene moiety gave good yields in 5-*exo* cyclic arylated products.

¹³ B. Sahoo, M. N. Hopkinson, F. Glorius, *J. Am. Chem. Soc.* **2013**, *135*, 5505.



Scheme 7. Au/Ru catalyzed oxy- aminoarylation of alkenes

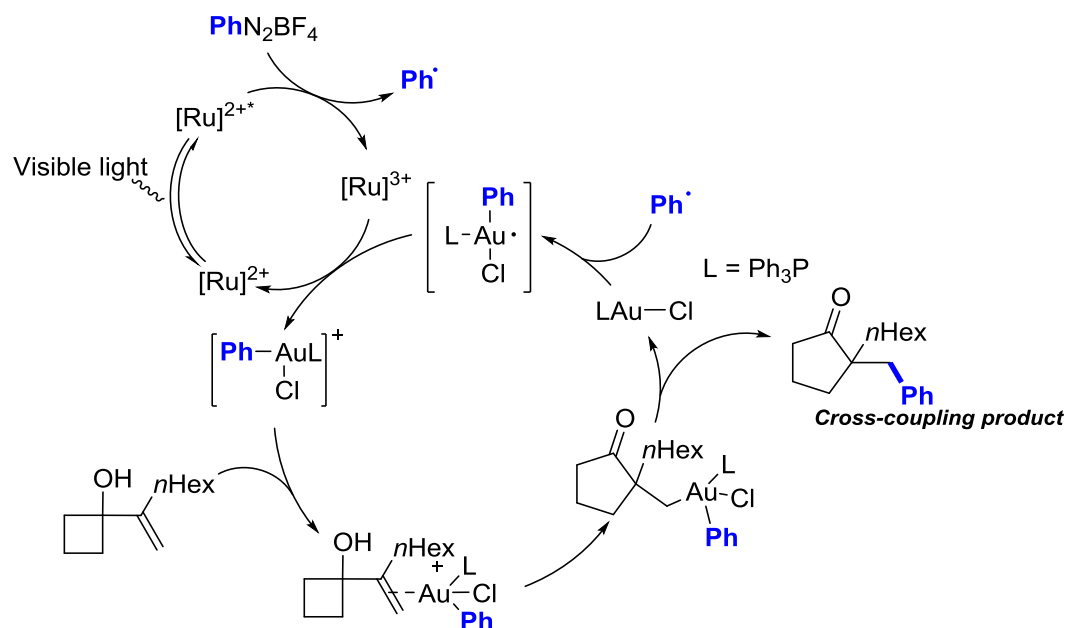
The authors proposed a mechanistic pathway starting from the cationic Au^{I} complex which reacts with the alkene to afford the cyclic alkylgold(I) intermediate. Then addition of aryl radical, generated by reduction of the aryldiazonium with the excited Ru^{II} catalyst, on the alkylgold(I) species gives the Au^{II} intermediate. This unstable species is supposed to be oxidized by the Ru^{III} leading to the Au^{III} intermediate and regenerating the photocatalyst. The arylated product is obtained after a reductive elimination step and regeneration of the cationic Au^{I} catalyst at the same time.



Scheme 8. A possible mechanism of Au/Ru dual catalysis

During this study, Glorius developed a novel gold and visible light-mediated photoredox dual catalytic system. The merging of these two catalytic processes allowed transformations avoiding the use of strong stoichiometric oxidants and stoichiometric

organogold compounds. This compatibility of gold and photoredox catalysis led to the development of a wide range of novel transformations. In fact, one year later, inspired by this work, Toste proposed an arylative ring expansion obtained from the coupling reaction of alkenyl and allenyl cycloalkanols with aryl diazonium salts by a similar gold/photoredox dual catalytic cross-coupling process.¹⁴ However there is a divergence in the mechanism. The authors suggested for the first step the addition on the Au^I of the phenyl radical, generated by reduction of the diazonium salt by the excited Ru^{II*}, to give the Au^{II} intermediate. Then this intermediate underwent a single electron transfer giving the oxidized Au^{III} complex and the Ru^{II} regenerated. This step was justified by the formation of 80% yield of the arylated phosphine ligand obtained by reductive elimination of the oxidized Au^{III} complex generated in the presence of 4-methylphenyldiazonium salt and without alkene. The gold (III) intermediate is now enough π -acidic to produce the coordinated alkene-gold species. After the ring expansion and the reductive elimination steps, the cross coupling product is obtained and the gold catalyst is regenerated.

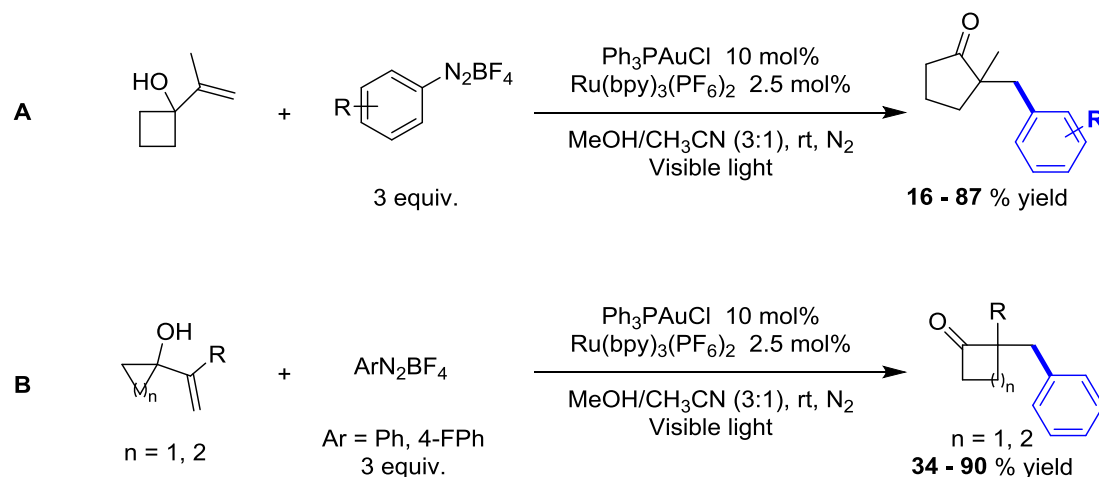


Scheme 9. Mechanism for the photoredox/gold-catalyzed ring expansion-arylation reaction

¹⁴ X. Shu, M. Zhang, Y. He, H. Frei, F. D. Toste, *J. Am. Chem. Soc.* **2014**, *136*, 5844.

Based on this mechanism manifold, extension of this process to alkynyl-¹⁵ and vinyl gold¹⁶ intermediates could also be reported.

Toste and co-workers investigated first the scope of this transformation with other aryldiazonium salts on the same vinylcyclobutanol (Scheme 10, equation A). However, diazonium salts bearing electron-rich substituents gave low yields whereas the use of electron-withdrawing group resulted in an efficient arylation. Cyclobutanol compounds have proven to be very good candidates for this reaction as well as cyclopropanol ones (Scheme 10, equation B). They showed also that the reaction proceeded in high yield with a wide range of alkyl substituted alkenes. A protected amine of the alkene can be tolerated during the transformation.



Scheme 10. Scope studies of the arylation ring expansion reaction

III.A.3. Photoredox/Nickel Dual Catalysis

III.A.3.a. Development of the nickel catalysis

In the periodic table, nickel is situated between cobalt and copper, and above palladium and platinum. As a group 10 metal and due to its relatively low price (8.56 \$/kg),

¹⁵ a) R. Cai, M. Lu, E. Y. Aguilera, Y. Xi, N. G. Akhmedov, J. L. Petersen, H. Chen, X. Shi, *Angew. Chem. Int. Ed.* **2015**, *54*, 8772. b) S. Kim, J. Rojas-Martinab, F. D. Toste, *Chem. Sci.* **2016**, *7*, 85. c), A. Tlahuext-Aca; M. N. Hopkinson, B. Sahooab, F. Glorius, *Chem. Sci.* **2016**, *7*, 89.

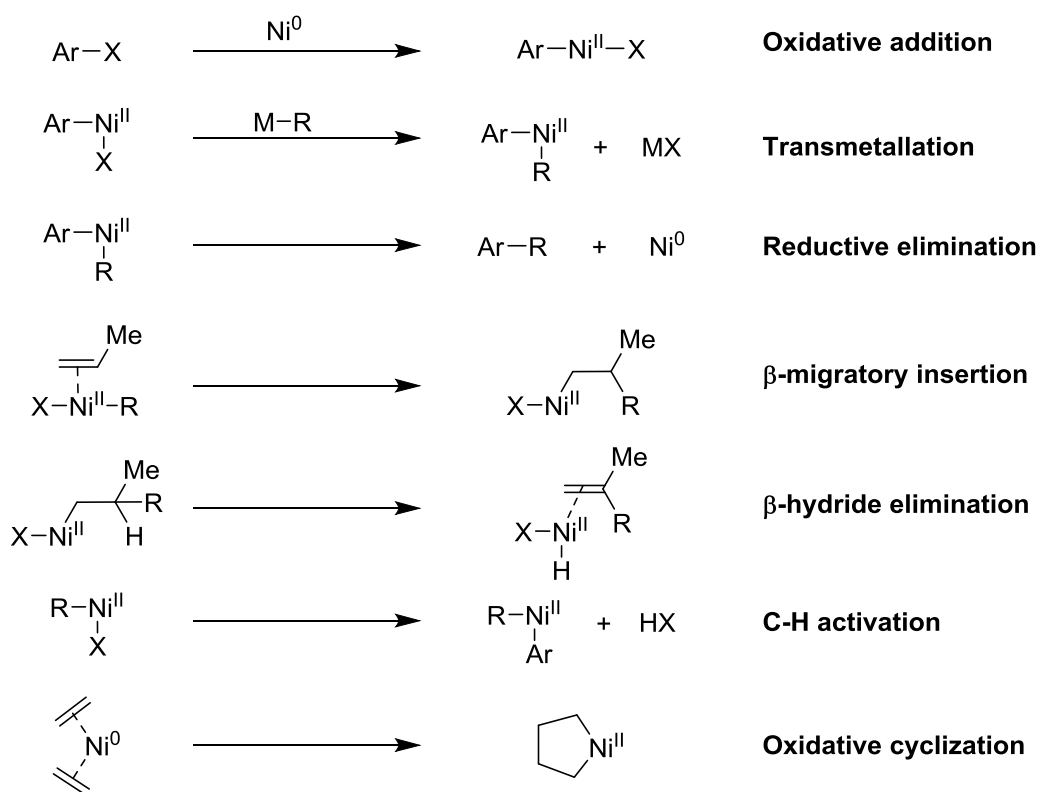
¹⁶ a) D. V. Patil, H. Yun, S. Shin, *Adv. Synth. Catal.* **2015**, *357*, 2622. b) J. Um, H. Yun, S. Shin, *Org. Lett.* **2016**, *18*, 484. c) L. Huang, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2016**, *55*, 4808. d) Tlahuext-Aca, A.; Hopkinson, M. N.; Garza-Sanchez, R. A.; Glorius, F. *Chem. Eur. J.* **2016**, DOI: 10.1002/chem.201600710.

nickel can easily replace palladium (18520 \$/kg) or platinum (31210 \$/kg). Recently, using the very interesting intrinsic properties of nickel, the organonickel catalysis underwent an intensive development to perform effective valuable and difficult transformations (Table 1 and scheme 11).¹⁷

Table 1. Comparison of intrinsic properties of nickel and palladium

Nickel	Palladium
-1 0 +1 +2 +3 +4	0 +1 +2 +3 +4
Smaller atomic radius	Larger atomic radius
Less electronegative	More electronegative
Harder	Softer
Facile oxidative addition	Facile reductive elimination
Facile β -migratory insertion	Facile β -hydride elimination
Radical pathways more accessible	

¹⁷ S. Z. Tasker, E. A. Standley, T. F. Jamison, *Nature* **2014**, 509, 299.



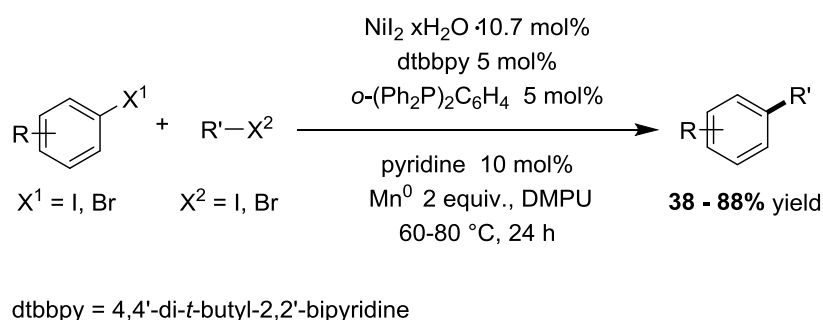
Scheme 11. Example of nickel catalyzed organometallic reaction steps

Nickel was isolated and classified as a chemical element in 1751 by Axel Fredrik Cronstedt. The most common oxidation state of nickel is +2, but this transition metal has also a number of other oxidation states easily accessible from -1 to +4 (Table 1). This property allows many transformations based on a wide range of catalytic cycles $\text{Ni}^0/\text{Ni}^{\text{II}}$ but also $\text{Ni}^{\text{I}}/\text{Ni}^{\text{III}}$, $\text{Ni}^{\text{II}}/\text{Ni}^{\text{I}}/\text{Ni}^{\text{III}}$ and $\text{Ni}^0/\text{Ni}^{\text{I}}/\text{Ni}^{\text{II}}/\text{Ni}^{\text{II}}$ and therefore radical synthetic pathways can be envisaged. Considering all of these significant advantages, researchers developed nickel-catalyzed reactions reproducing most of the processes involving palladium catalysis and also creating new transformations.

In 2010, the group of Weix showed that cross-coupling of aryl halides with alkyl halides could be catalyzed by a Ni^{II} complex in the presence of manganese (Scheme 12).¹⁸ In this reaction, only 1 equivalent of each halide is necessary and they used a combination of NiI_2 complex with two ligands: 4,4'-di-*tert*-butyl-2,2'-bipyridine and 1,2-bis(diphenylphosphino)benzene. The authors demonstrated that a wide range of functional groups on the aryl halide can be tolerated such as methyl ketone, nitrile, pinacol boronate ester and free hydroxyl group. The presence of an electron withdrawing or donating group on

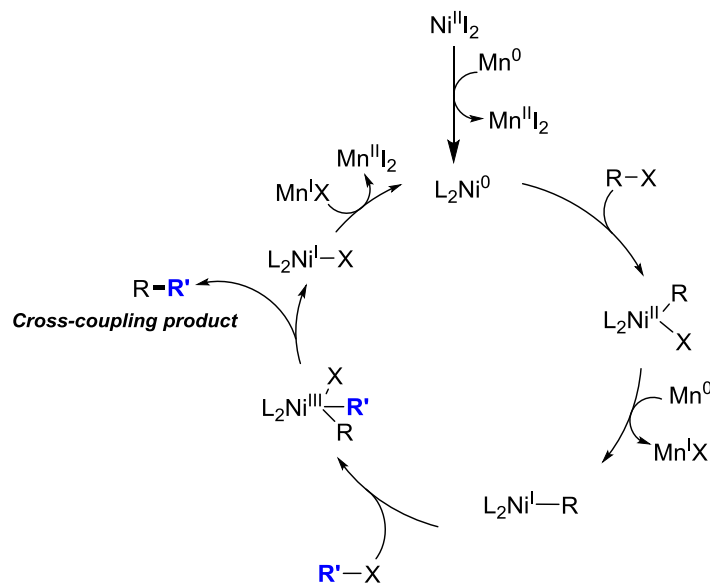
¹⁸ D. A. Everson, R. Shrestha, D. J. Weix, *J. Am. Chem. Soc.* **2010**, *132*, 920.

the aryl halide gave the same good yield. A variety of alkyl halide can be engaged in the coupling process with again a good functional group tolerance.



Scheme 12. Nickel catalyzed cross-coupling of aryl halides with alkyl halides

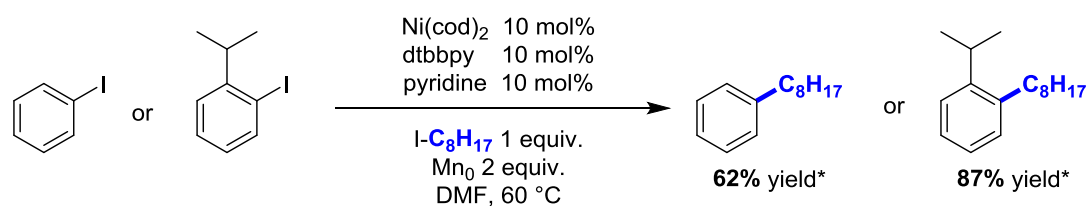
Weix and co-workers proposed in scheme 13, that the cross-coupling process starts by an early reduction of Ni^{II} into a Ni^0 catalyst. Then, the first oxidative addition of the organo-halide gives the $\text{RNi}^{\text{II}}\text{X}$ intermediate, which is reduced by manganese to form $\text{Ni}^{\text{I}}\text{R}$. A second oxidative addition of the other halide partner yields to $\text{XNi}^{\text{III}}\text{R}'\text{R}$ intermediate. The cross-coupled product is obtained by a reductive elimination and the Ni^0 is regenerated by reduction of the $\text{Ni}^{\text{I}}\text{X}$ residue with manganese.



Scheme 13. Proposed mechanism for the reductive cross-coupling

Three years later, Weix published a detailed study of this transformation, investigating the ligand effect and the mechanism. The authors started from a nickel(0) catalyst and 4,4'-di-*tert*-butyl-2,2'-bipyridine as ligand and performed the transformation in good to high yields

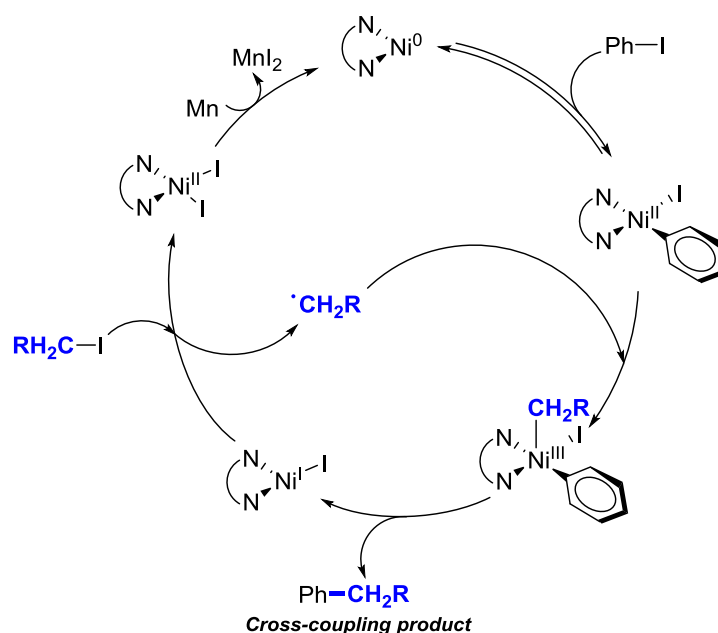
(Scheme 14). With a radical clock experiment using cyclopropylmethyl bromide as substrate, they highlighted a radical chain reaction involved in the cross-coupling mechanism.



* GC yields

Scheme 14. Nickel-catalyzed cross-coupling of iodo-aryl with iodo-octane

The mechanism proposed by the authors proceeds by an oxidative addition of the aryl halide to the nickel(0) complex. Then reaction of the alkyl radical with the arylnickel(II) forms the Ni^{III} intermediate which can undergo a reductive elimination to generate the cross-coupling product and the nickel(I) halide species. This reactive Ni^{I} reacts with the alkyl halide regenerating an alkyl radical and leading to the nickel(II) diiodide which is reduced by the manganese to regenerate the nickel(0) catalyst.



Scheme 14. Proposed mechanism for cross-coupling of aryl halide with alkyl halide

Weix demonstrated that homogeneous nickel catalysis is a powerful tool to carry out elegant aryl-alkyl cross-coupling reactions starting from alkyl and aryl halides. The ability of

radical species to react with nickel(II) complexes should be more exploited in organic synthesis.

III.A.3.b. The birth of visible-light photoredox/nickel dual catalysis

Since few years, an intensive research is conducted on the development of new photoredox processes in order to perform efficient and valuable organic transformations. In 2014, Molander¹⁹, MacMillan and Doyle²⁰ published simultaneously two challenging examples of photoredox/nickel catalyzed cross-coupling of aryl halides with alkyl nucleophile sources.

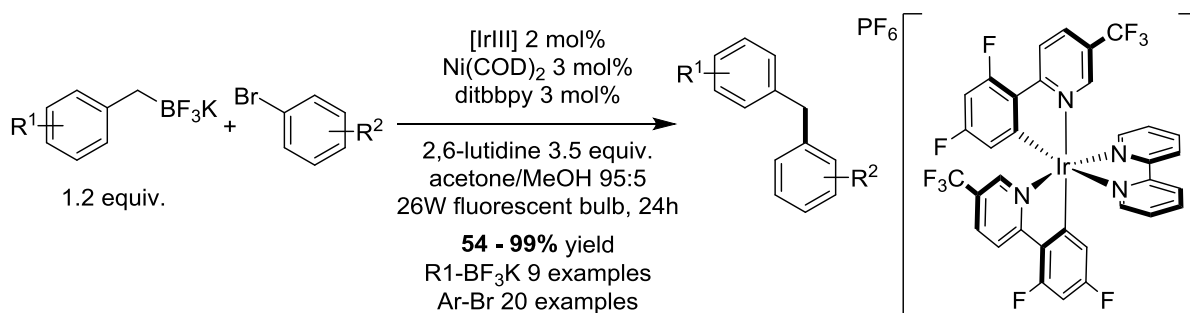
III.A.3.c. Molander's research

In 2012, Akita and co-workers reported the visible-light photocatalyzed generation of alkyl radicals from organotrifluoroborate salts in the presence of Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ as photocatalyst under blue LEDs irradiation.²¹ This effective study laid the foundations of photooxidation of organoborate salts. Inspired by these results, Molander combined this chemistry with nickel catalysis to establish a new dual catalysis method. The benzylic trifluoroborates are good sources of carbon centered radicals which can be involved in nickel catalysis. The transformation is carried out with 2 mol% of Ir^{III} catalyst and 3 mol% of Ni⁰ (Scheme 15). Under these conditions, the authors investigated the scope of the reaction with different benzyltrifluoroborate salts and bromoaryl partners. The presence of electron donating substituents on trifluoroborates provided more stabilized radicals and gave better yields in coupling products (94-97%) than trifluoroborates with electron withdrawing groups (70-75%). The reaction showed a good tolerance to a range of different functional groups on the aryl halide such as amide, phenol –NHBoc, pyrazole, etc.... A variety of heteroaryl bromides such as substituted pyridine, pyrimidine, indole, quinoline and thiophene proved to be good partner in this transformation giving moderate to good yields.

¹⁹ J. C. Tellis, D. N. Primer, G. A. Molander, *Science* **2014**, 345, 433.

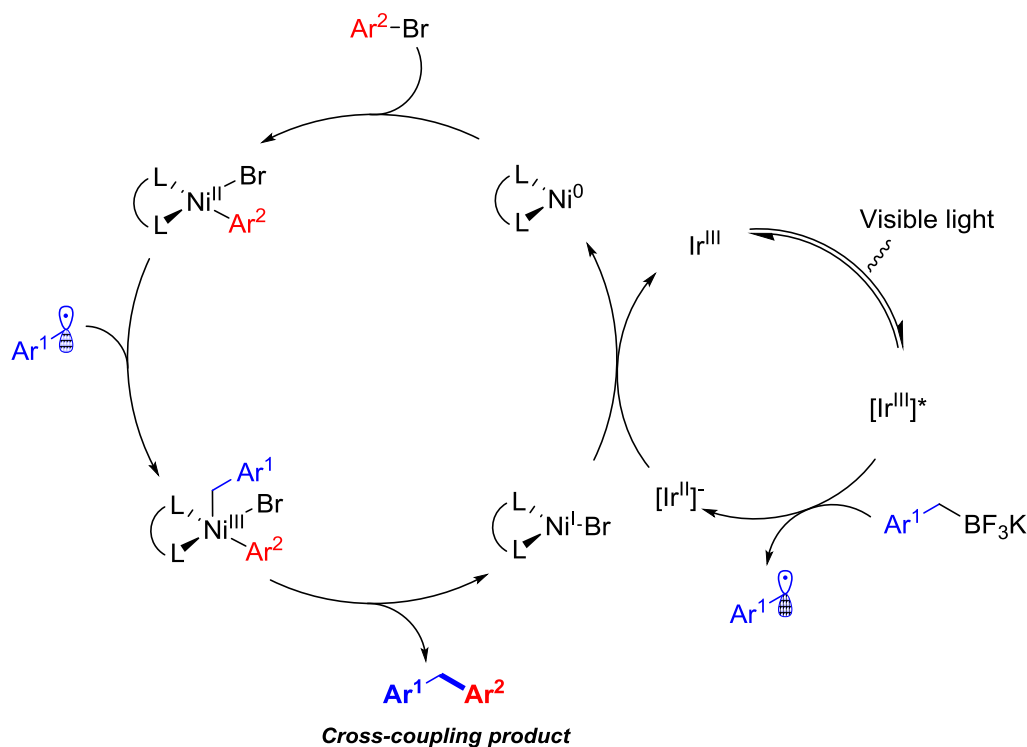
²⁰ Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terrett, A. G. Doyle, D. W. C. MacMillan, *Science* **2014**, 345, 437.

²¹ Y. Yasu, T. Koike,; M. Akita, *Adv. Synth. Catal.* **2012**, 354, 3414.



Scheme 15. Photoredox/nickel catalyzed cross-coupling of benzylic trifluoroborates and aryl bromides

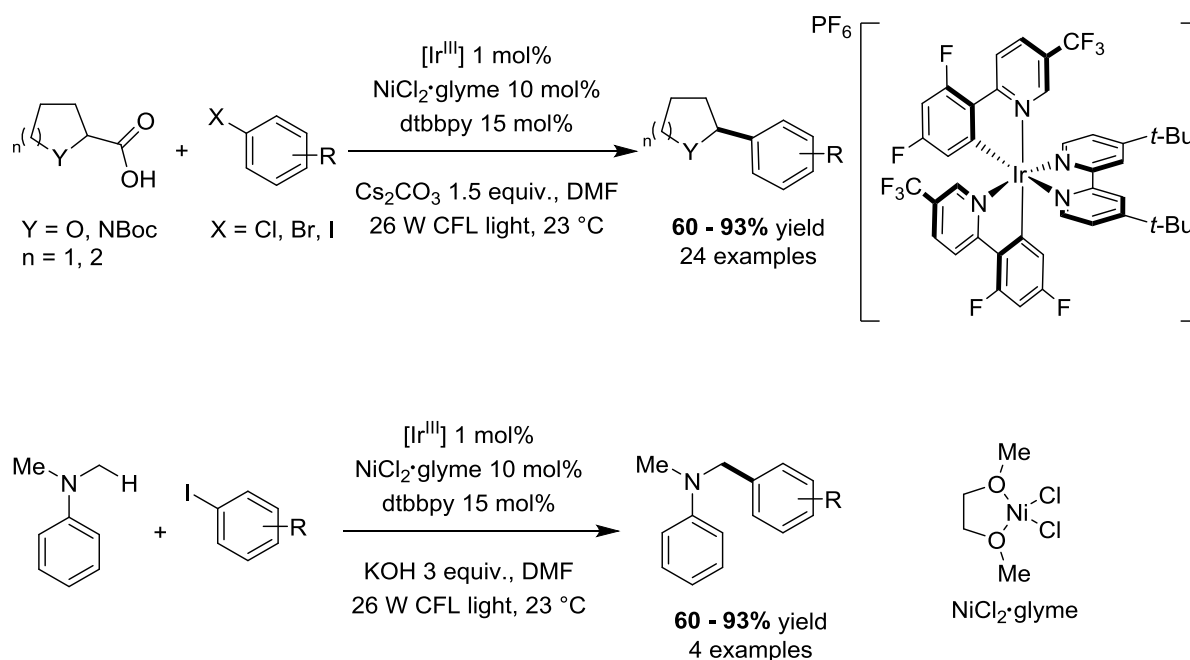
For this transformation, the authors proposed the generation of a Ni^{II} species by oxidative addition of the aryl bromide to Ni⁰ catalyst (Scheme 16). After visible-light irradiation, the excited Ir^{III} complex ($E_{1/2}^{\text{red}} [\text{Ir}^{\text{III}*}/\text{Ir}^{\text{II}}] = +1.21\text{V vs. SCE}$ in CH₃CN) oxidizes the benzyltrifluoroborate salt by a single-electron transfer yielding the reduced Ir^{II} and a carbon centered radical. Then the activated benzylic radical undergoes an addition to the Ni^{II} species to afford the reactive Ni^{III} intermediate. The cross-coupling product is obtained after a reductive elimination, leading to a Ni^I complex, which is reduced, into Ni⁰ by the Ir^{II} complex and consequently regenerating the catalytic system.



Scheme 16. Proposed mechanism of photoredox/nickel cross-coupling

III.A.3.d. MacMillan and Doyle's research

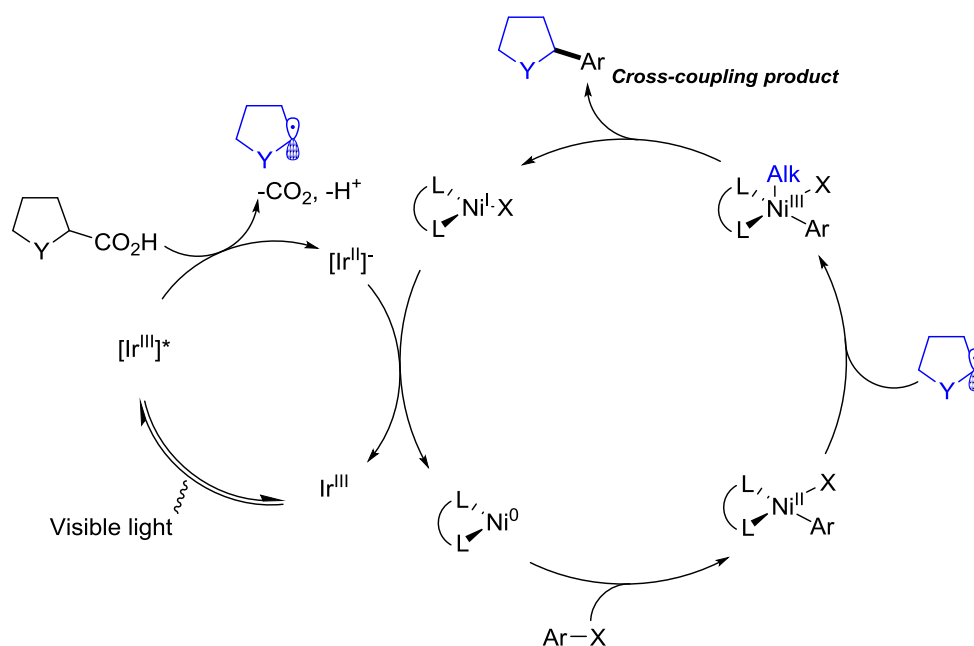
At the same time MacMillan, Doyle and co-workers proposed the cross-coupling of α -amino radicals with aryl halides. Those radicals can be generated by two different photoredox processes: photooxidative decarboxylation of an *in-situ* formed cesium carboxylate, particularly cyclic or linear N-Boc protected amino-acid compounds, and photooxidation of dimethylaniline. The authors selected the bench stable Ni^{II} source $\text{NiCl}_2\cdot\text{glyme}$ catalyst and $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbbpy})\text{PF}_6$ as photocatalyst as shown in scheme 17. Then, they investigated the scope of the reaction with different aryl halides partners and they obtained good to high yields with either arylchlorides, bromides or iodides. Either aromatics or heteroaromatics substituted with electron-donating or electron-withdrawing groups gave good results in cross-coupling reactions with both types of radical precursor.



Scheme 17. Dual catalysis of aryl halides with amino acids or dimethylaniline

The authors suggested that the starting Ni^{II} catalyst is preliminary reduced in Ni^0 via two single-electron transfer events with an excess of amino acid acting as a sacrificial reductant. Then the active Ni^0 catalyst undergoes an oxidative addition with the aryl halide to afford the $\text{XNi}^{\text{II}}\text{Ar}$. At the same time, under a 26 W compact fluorescent lamp irradiation, the

amino acid undergoes a radical decarboxylation *via* a photooxidation of the *in-situ* formed cesium carboxylate intermediate by the excited Ir^{III} complex ($E_{1/2}^{\text{red}} [\text{Ir}^{\text{III}*}/\text{Ir}^{\text{II}}] = +1.21\text{V}$ vs. SCE in CH₃CN), to liberate the α -amino radical species and the Ir^{II} reductant complex. This radical reacts with the aryl-nickel(II) leading to a reactive Ni^{III} species which undergoes readily a reductive elimination to generate the desired cross-coupled product and a Ni^I catalyst. The Ni⁰ is regenerated by single-electron transfer from Ir^{II} which returns to the starting photocatalyst Ir^{III}.



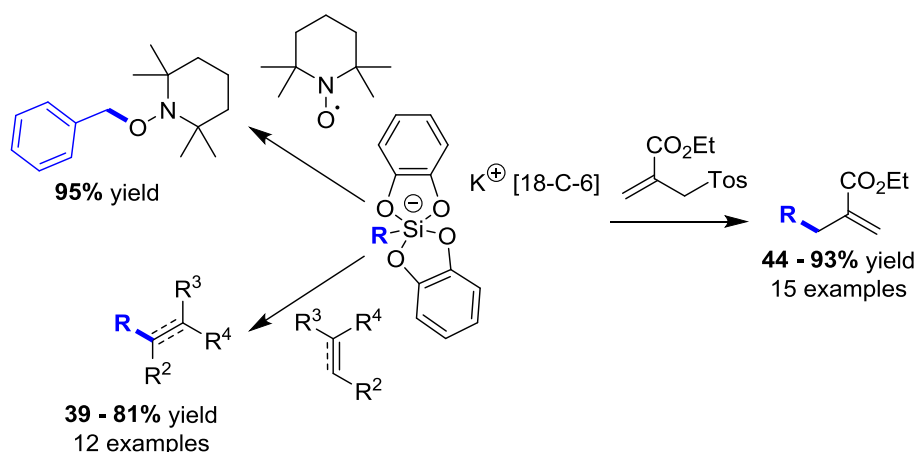
Scheme 18. Dual photoredox/nickel catalysis proposed mechanism

Molander, MacMillan and Doyle developed a very powerful process leading to a challenging cross-coupling reaction between aryl halides and photo-generated alkyl radical species. All of these reactions are realized under very mild conditions, with a very low loading of catalysts. This new dual catalysis opened up the field to new and valuable transformations.

III.A.3.e. Development of the photoredox/nickel dual catalysis

× Carbon-carbon bond formation

Recently, our group developed a groundbreaking versatile precursor of unstabilized primary alkyl radicals and its participation in dual catalytic transformations.^{22a} Inspired by the work of Kumada and co-workers on oxidation of organopentafluorosilicates²³, we then considered the more soluble pentavalent bis-catecholato silicon compounds easily obtained from the corresponding organosilane and first synthesized by Frye.^{22b} This kind of compound can be readily oxidized by [Ir(dF(CF₃)ppy)₂(bpy)]PF₆ complex ($E^{\text{red}}(\text{Ir}^{\text{III}*}/\text{Ir}^{\text{II}}) = +1.32\text{V vs. SCE}$ in CH₃CN) under blue LED irradiation. Indeed, these bench stable silicates exhibit oxidation potentials between +0.34V and +0.89V vs. SCE in DMF and suggest that these ones can be engaged in photocatalytic transformations. As a comparison the oxidation potential of MacMillan's cesium amino carboxylates are around +0.95V vs. SCE in CH₃CN and for Molander's primary alkyltrifluoroborate salts, close to +1.50V vs. SCE.²¹ As shown in scheme 19, we firstly proved by TEMPO radical trapping that silicates can generate benzylic radical easily. We next extended the scope of the reaction to the allylation of various primary silicates and intermolecular additions on various radical acceptors in moderate to high yields.

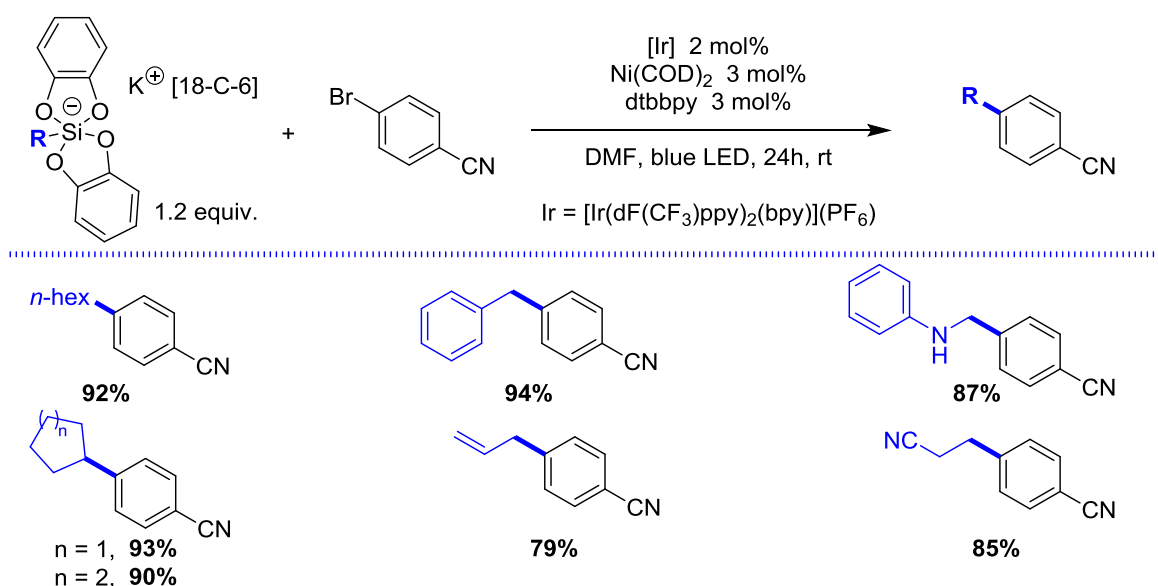


Scheme 19. Photooxidation of bis-catecholato silicate salt

²² a) V. Corcé, L.-M. Chamoreau, E. Derat, J.-P. Goddard, C. Ollivier, L. Fensterbank, *Angew. Chem. Int. Ed.* **2015**, *54*, 11414. b) C. L. Frye, *J. Am. Chem. Soc.* **1964**, *86*, 3170

²³ J. Yoshida, K. Tamao, T. Kakui, A. Kurita, M. Murata, K. Yamada, M. Kumada, *Organometallics* **1982**, *1*, 369.

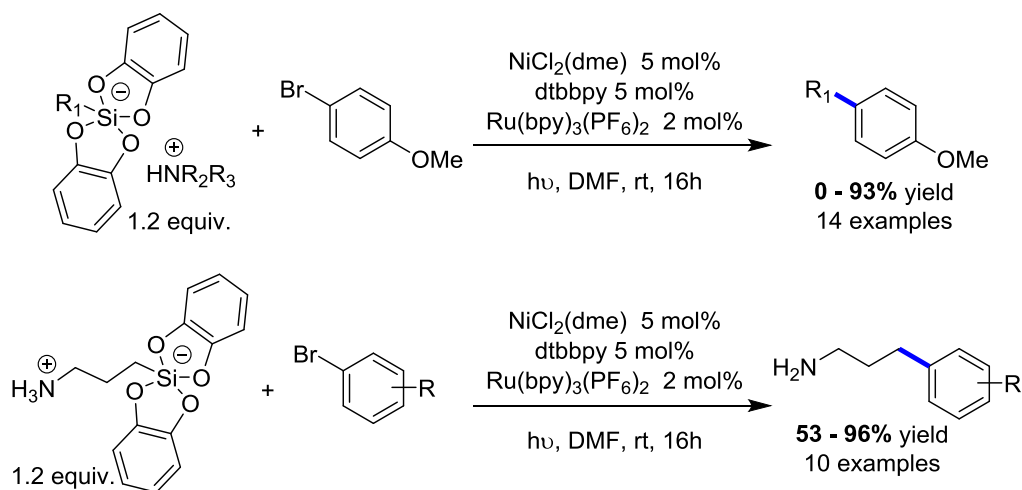
To illustrate the powerful synthetic potential of photooxidation of silicates, we focused on photoredox/nickel Csp^2 - Csp^3 cross-coupling reactions of bromobenzonitrile with bis-catecholato silicates (Scheme 20). Upon treatment with Nickel COD and diterbutyl bipyridine and the iridium photocatalyst, the reaction worked perfectly with stabilized radicals such as allyl, benzyl, α -amino primary radicals as well as less stabilized radicals such as secondary and especially primary radicals which gave high yields in coupling products.



Scheme 20. Dual photoredox/nickel catalysis with bromobenzonitrile and silicate salts

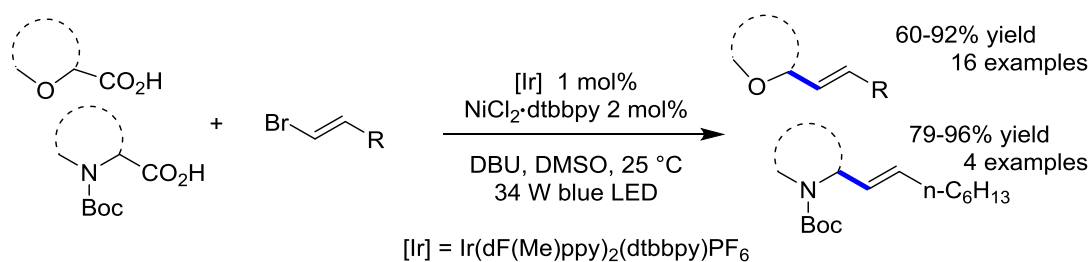
Six months later, Molander published very similar results²⁴ showing that ammonium silicates can be readily oxidized under visible-light irradiation with a ruthenium(II) complex. The radical was then engaged in a nickel catalysis starting a nickel(II) source allowing coupling reactions with 4-bromoanisole. Notably, unprotected amines can participate in this transformation.

²⁴ M. Jouffroy, D. N. Primer, G. A. Molander, *J. Am. Chem. Soc.* **2016**, *138*, 475.



Scheme 21. Cross-coupling of bis-catecholato silicates with bromoaryl

MacMillan also extended his methodology to the coupling of vinyl halides with α -amino or α -oxy carboxylic acids as shown in scheme 22.²⁵ A wide range of vinyl halides including various functional groups were successfully tested. Notably, the geometry of the olefin was not affected during the cross-coupling transformation by the reaction conditions. Cyclic or acyclic α -oxy carboxylic acids readily provided high yields of cross-coupling products.

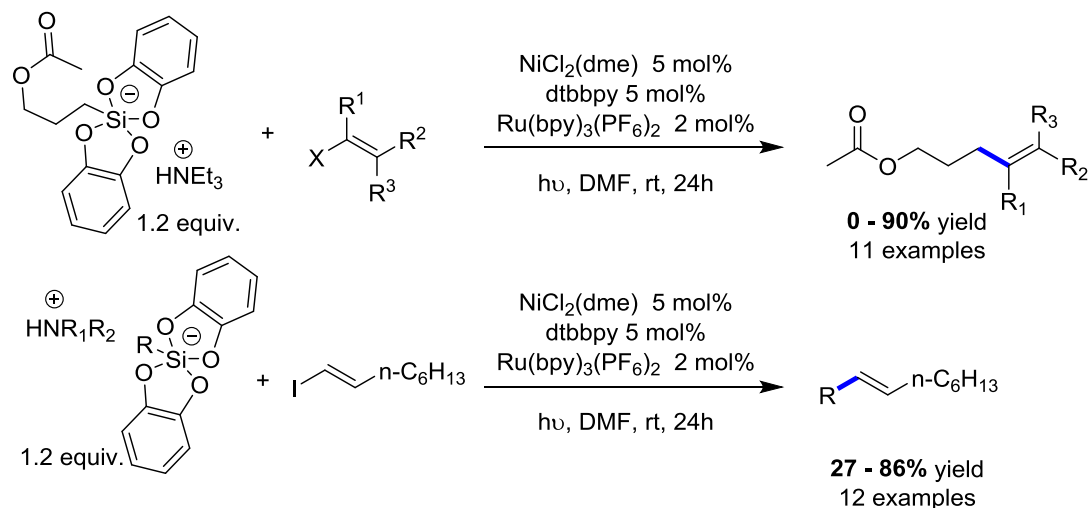


Scheme 22. Decarboxylative cross-coupling of carboxylic acids with vinyl halides

Two months later, the group of Molander inspired by these studies, performed the same transformation with biscatecholatoalkylsilicates and chloro-, bromo- and iodovinyl

²⁵ A. Noble, S. J. McCarver, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2015**, *137*, 624.

compounds²⁶. Whatever the electronic nature of the starting alkene, corresponding coupling products with silicates were isolated in moderate to good yields (Scheme 23).

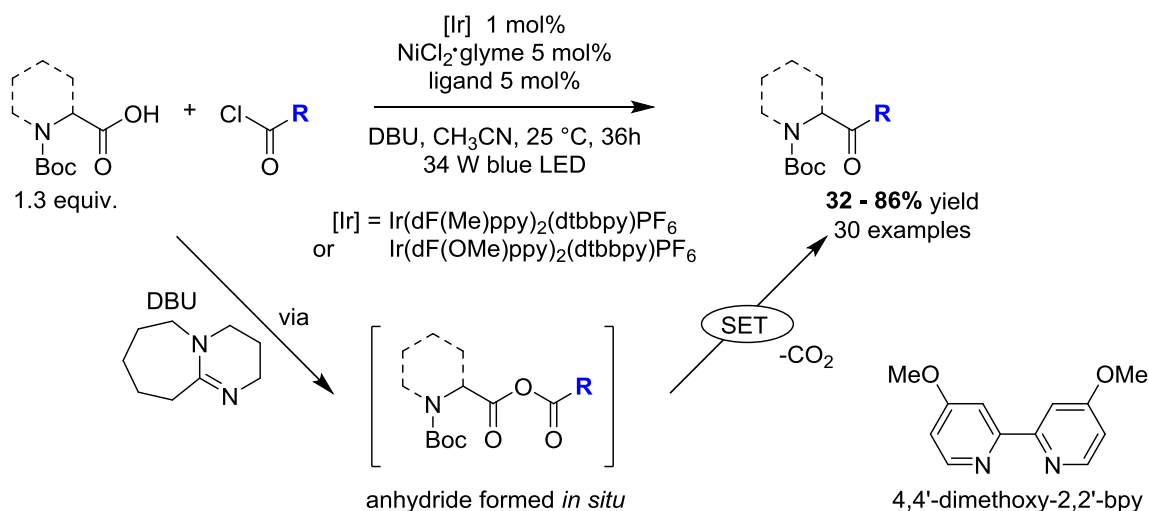


Scheme 23. Scope of alkenyl halides and biscatecholato silicates in dual cross-coupling

In another contribution, MacMillan reported an example of photoredox/nickel dual catalysis involving an elegant CO₂ extrusion-recombination sequence of intermediate mixed anhydrides formed *in situ* from carboxylic acid compounds and acyl chloride partners (Scheme 24).²⁷. They proposed an oxidative addition of the Ni⁰ to the C-O bond of the anhydride to afford the Ni^{II} intermediate, and then either an outer sphere oxidative decarboxylation or an inner sphere decarboxylation leading to a reactive Ni^{III} species. A reductive elimination gave the α -amino ketone and NiI which is reduced by a SET regenerating the iridium and nickel catalysts.

²⁶ N. R. Patel, C. B. Kelly, M. Jouffroy, G. A. Molander, *Org. Lett.* **2016**, *18*, 764.

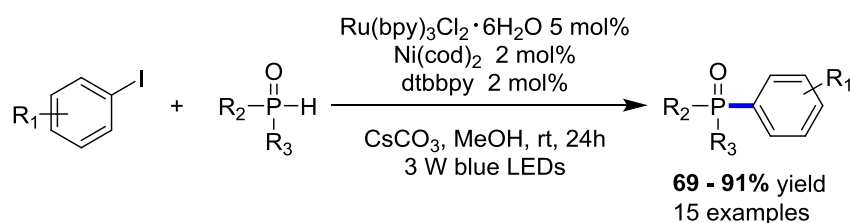
²⁷ C. “Chip” Le, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2015**, *137*, 11938.



Scheme 24. Ir/Ni Dual catalysis with acyl chlorides and α -amino carboxylic acids

× Carbon-heteroatom bond formation

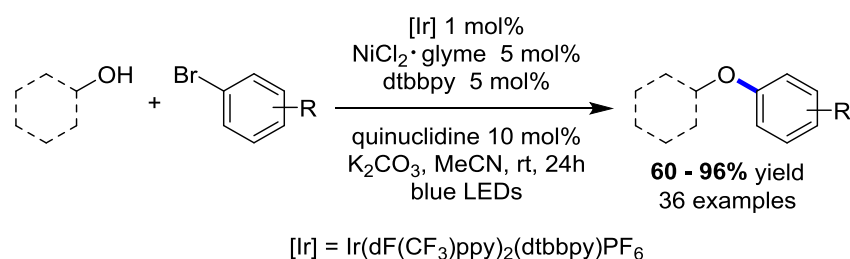
The photoredox/nickel catalysis revealed a powerful tool to generate carbon-carbon bond formation under mild conditions. Moreover, various groups have also devoted their studies to the formation of carbon-heteroatom bonds. The group of Xiao and Lu reported the first example of carbon-heteroatom formation merging photoredox and nickel catalysis. They developed a cross-coupling method between aryl iodides and diarylphosphine oxide using a ruthenium(II) photocatalyst and a nickel(0) complex.²⁸ The authors suggested the generation of a P-centered radical by single-electron transfer oxidation by the excited Ru^{II} photocatalyst. The radical is then intercepted by the arylnickel(II) iodide. A reductive elimination provides the cross-coupled product. Either electron-donating or electron-withdrawing group on the aryl iodide are well tolerated as well as phenol, amide, amine and ether.



Scheme 25. C-P Bond formation

²⁸ J. Xuan, T.-T. Zeng, J.-R. Chen, L.-Q. Lu, W.-J. Xiao, *Chem. – Eur. J.* **2015**, *21*, 4962.

In 2015, MacMillan and co-workers investigated the formation of carbon-oxygen bond via a dual catalysis process.²⁹ They developed an elegant process using the photoredox catalytic cycle to modulate the oxidation states of the nickel catalyst. After an oxidative addition of the aryl bromide to Ni⁰, the substitution of bromide on the organometallic arylnickel(II) by the alcohol provides an aryl-Ni^{II}-OR species which undergoes easily a SET by photooxidation with the ruthenium complex and then a reductive elimination to obtain the C(sp²)-O product. Because of the relatively inert character of Ni^{II} to reductive elimination, the photoredox catalysis plays a significant role in the nickel catalysis.

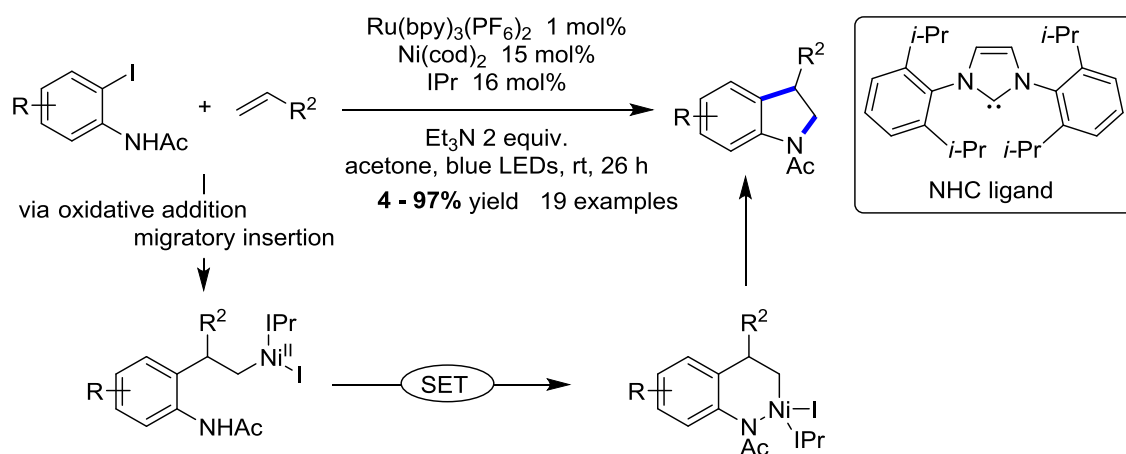


Scheme 26. C-O Bond formation

Taking advantage of the interesting properties of nickel and the dual catalysis process, the group of Jamison simultaneously developed a synthesis of indolines from iodoacetanilides and alkenes with a challenging carbon (sp³)-nitrogen bond formation.³⁰ In nickel catalysis, β -migratory insertion is easier than β -hydride elimination. This advantageous property allowed the authors to access an organometallic nickel(II) complex which undergoes a SET event leading to the reactive Ni(III) intermediate. After the reductive elimination step, indolines were obtained in good yields with a good tolerance to a variety of functional groups on both partners.

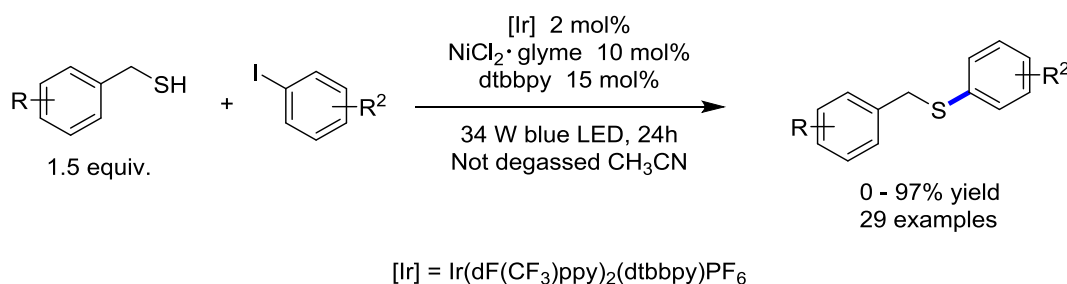
²⁹ J. A. Terrett, J. D. Cuthbertson, V. W. Shurtleff, D. W. C. MacMillan, *Nature* **2015**, 524, 330.

³⁰ S. Z. Tasker, T. F. Jamison, *J. Am. Chem. Soc.* **2015**, 137, 9531.



Scheme 27. C-N bond formation

More recently, Johannes and co-workers developed a dual photoredox/nickel catalyzed cross-coupling reaction of thiols with aryl halides.³¹ They showed with 4-methoxy- α -toluenethiol, it is possible to generate the thiyl radical and to trap it with an olefin under visible-light photoredox conditions in good yield. Starting with this result, the authors studied the scope of this dual catalysis process and showed that alkyl thiols are as effective as thiophenol compounds.

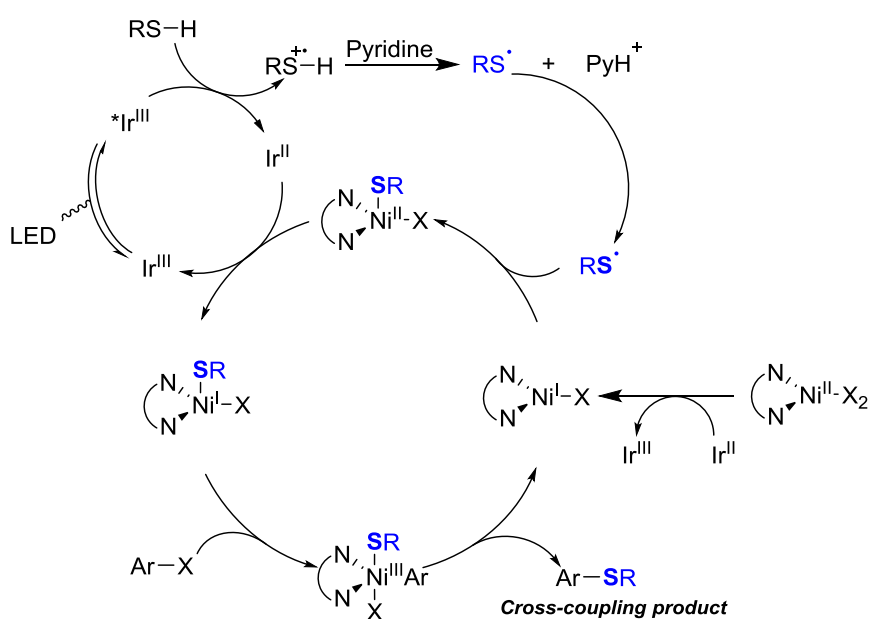


Scheme 28. C-S bond formation

Johannes and co-workers investigated deeply the mechanism of this transformation. Cyclic voltammetry experiments have been ran on the $\text{NiCl}_2 \cdot \text{glyme}$ catalyst showing an irreversible peak at -1.34V vs. SCE in MeCN assigned to the reduction of Ni^{II} to Ni^0 and a reversible peak at -1.88V , corresponding to $\text{Ni}^0/\text{Ni}^{0-}$. Compared to the reduction potential of the reductant $[\text{Ir}^{\text{II}}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})]$ ($E_{1/2}^{\text{red}}[\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = -1.37\text{V}$ vs. SCE in MeCN), the authors concluded that the reduction of Ni^{II} into Ni^0 by the Ir^{II} is not thermodynamically favored. However, studies on $\text{NiCl}_2 \cdot \text{dppe}$ ($E_{1/2}^{\text{red}}[\text{Ni}^{\text{II}}/\text{Ni}^{\text{I}}] = -0.88\text{V}$ and $[\text{Ni}^{\text{I}}/\text{Ni}^0] = -1.41\text{V}$

³¹ M. S. Oderinde, M. Frenette, D. W. Robbins, B. Aquila, J. W. Johannes, *J. Am. Chem. Soc.* **2016**, *138*, 1760.

vs. SCE in DMF/THF) demonstrate that the Ni^{II} can be easily reduced by the Ir^{II} complex and leads to Ni^{I} catalyst which may be the active species. This step of pre-reduction of nickel should be more thermodynamically favored. In the scheme 29, they proposed as mechanism, a SET oxidation of the thiol partner by the long lived excited $^*\text{Ir}^{\text{III}}$ followed by a deprotonation to afford the thiyl radical. After reduction of the pre-catalyst $\text{Ni}^{\text{II}}\text{Cl}_2$, the active Ni^{I} species intercepts the thiyl radical and gives the Ni^{II} intermediate which undergoes another SET reduction regenerating the Ir^{III} catalyst. Then oxidative addition of aryl halide gives the reactive Ni^{III} complex. Then the cross-coupled product is obtained by reductive elimination regenerating at the same way the catalytic system.



Scheme 29. Proposed mechanism for C-S cross-coupling

III.A.4. Conclusion

The dual catalysis and in particular the nickel/visible-light photoredox dual catalysis became during the last two years a powerful process for the formation of carbon-carbon or carbon-heteroatom bond under very mild conditions. This new kind of transformation allows access to challenging and valuable simple or more complex molecules.

III.B. Results: Alkyl Bis-Catecholato Silicates in Dual Photoredox/Nickel Catalysis: Aryl- and Heteroaryl-Alkyl Cross Coupling Reactions

III.B.1. Objectives

Photoredox/nickel dual catalysis^{32,33} has recently emerged as a novel opportunity to form C-C bonds and rapidly couple functionalized fragments for the elaboration of more complex molecules.³⁴ A key advantage of this strategy is to merge the mildness of visible light photoredox catalysis for the generation of hot radical entities³⁵ with the robustness of nickel catalyzed cross coupling reactions.³⁶ While the electrophilic partner involved in the oxidative addition to nickel has so far consisted of aryl halides and related substrates,³⁷ more functional variation has been brought on the radical source. To the best of our knowledge, all works have involved α -amino,^{30b,34,38} α -O,^{30b,6} α -phenyl,^{30b,39} α -oxo,⁴⁰ and secondary³⁴ carboxylic acids, mixed anhydrides,⁴¹ dimethylaniline,^{30b} benzyl,^{30a,42} secondary^{30a,37,43} and

³² For a recent review on dual catalysis, see: a) M. N. Hopkinson, B. Sahoo, J.-L. Li and F. Glorius, *Chem. Eur. J.* **2014**, *20*, 3874; for recent reviews on dual photoredox/nickel catalysis, see: b) C. Vila, *ChemCatChem* **2015**, *7*, 1790; c) J. J. Murphy and P. Melchiorre, *Nature* **2015**, *524*, 297.

³³ For seminal reports, see: a) J. C. Tellis, D. N. Primer and G. A. Molander, *Science* **2014**, *345*, 433; b) Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terret, A. G. Doyle and D. W. C. MacMillan, *Science* **2014**, *345*, 437.

³⁴ For C-O bond formation, see: a) J. A. Terrett, J. D. Cuthbertson, V. W. Shurtleff and D. W. C. MacMillan *Nature* **2015**, *524*, 330; for C-P bond formation, see: b) J. Xuan, T.-T. Zeng, J. R. Chen, L. Q. Lu and W. J. Xiao, *Chem. Eur. J.* **2015**, *21*, 4962.

³⁵ For reviews and books, see: a) J. M. R Narayanaman and C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102; b) F. Teplý, *Collect. Czech. Chem. Commun.* **2011**, *76*, 859; c) J. Xuan and W.-J. Xiao, *Angew. Chem. Int. Ed.* **2012**, *51*, 6828; d) M. A. Ischay and T. P. Yoon, *Eur. J. Org. Chem.* **2012**, 3359; e) L. Shi and W. Xia, *Chem. Soc. Rev.* **2012**, *41*, 7687; f) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322; g) D. P. Hari and B. König, *Angew. Chem. Int. Ed.* **2013**, *52*, 4734; h) M. Reckenthäler and A. G. Griesbeck, *Adv. Synth. Catal.* **2013**, *355*, 2727; i) T. Koike and M. Akita, *Synlett* **2013**, *24*, 2492; j) D. M. Schultz and T. P. Yoon, *Science* **2014**, *343*, 985; k) *Chemical Photocatalysis*, B. König, Ed., DeGruyter, Berlin, **2013**; l) *Photochemically generated intermediates in Synthesis*, A. Albini and M. Fagnoni, Eds., John Wiley & Sons, Hoboken, **2013**.

³⁶ For reviews on nickel-catalyzed coupling reactions, see: (a) S. Z. Tasker, E. A. Standley and T. F. Jamison, *Nature* **2014**, *509*, 299; b) D. J. Weix, *Acc. Chem. Res.* **2015**, *48*, 1767; c) V. P. Ananikov, *ACS Catal.* **2015**, *5*, 1964.

³⁷ For vinylation, see: A. Noble, S. J. McCarver and D. W. C. MacMillan, *J. Am. Chem. Soc.* **2015**, *137*, 624.

³⁸ M. El Khatib, R. A. M. Serafim and G. A. Molander, *Angew. Chem. Int. Ed.* **2016**, *55*, 254.

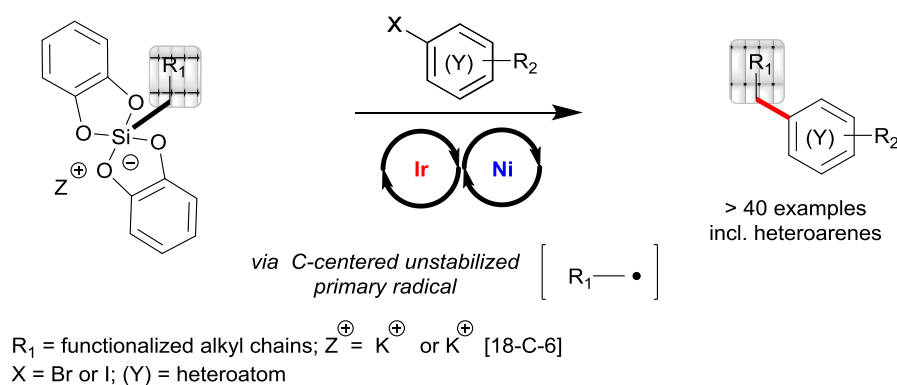
³⁹ D. Ryu, D. N. Primer, J. C. Tellis and G. A. Molander, *Chem. Eur. J.* **2016**, *22*, 120.

⁴⁰ L. Chu, J. M. Lipshultz and D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2015**, *54*, 7929.

⁴¹ C. C. Le and D. W. C. MacMillan, *J. Am. Chem. Soc.* **2015**, *137*, 11938.

⁴² Y. Yamashita, J. C. Tellis and G. A. Molander, *Proc. Natl. Acad. Sci. U. S. A.* **2015**, *112*, 12026.

activated (α -O) primary trifluoroborates.⁴⁴ More recently, potassium and ammonium bis-catecholato silicates have been reported by us as a valuable source of C-centered radicals upon visible light photooxidation using Ir[(dF(CF₃)ppy)₂(bpy)](PF₆) as catalyst.⁴⁵ The silicate substrates offer neat advantages over the related trifluoroborates in terms of solubility, of byproducts (no gas release, no fluoride, no boron) and of the scope of the possibly generated radicals (from stabilized alkyl ones to highly reactive primary ones). As a perspective, it was also found that they could be engaged in photoredox/nickel dual catalysis for C_{sp2}-C_{sp3} cross-coupling reactions, notably involving unstabilized primary radicals.^{45a,46} Subsequent to the first report of these cross coupling reactions by us,^{45a} the group of Molander described similar transformations of related ammonium bis-catecholato secondary and primary alkyl silicates with aryl- and heteroaryl- bromides.^{24,26} The limited sampling of these preliminary findings drove us to gain more insight into this transformation and define its scope by varying both partners silicates and arylbromides (Scheme 30). Herein, we focused on primary radical intermediates and bring a complementary picture to these highly powerful reactions and we decided to extend the scope of this reaction.



Scheme 30. Photoredox/nickel dual catalysis involving primary radicals from silicates

⁴³ D. N. Primer, I. Karakaya, J. C. Tellis and G. A. Molander, *J. Am. Chem. Soc.* **2015**, *137*, 2195.

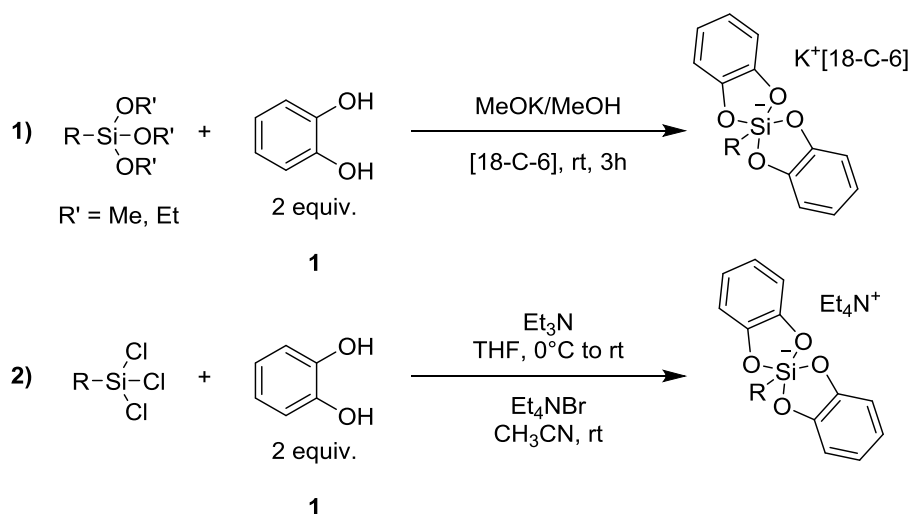
⁴⁴ I. Karakaya, D. N. Primer and G. A. Molander, *Org. Lett.* **2015**, *17*, 3294.

⁴⁵ a) V. Corcé, L. M. Chamoreau, E. Derat, J.-P. Goddard, C. Ollivier and L. Fensterbank, *Angew. Chem. Int. Ed.* **2015**, *54*, 11414; b) For the oxidation of silicates with organic reagents, see also: L. Chenneberg, C. Lévêque, V. Corcé, A. Baralle, J.-P. Goddard, C. Ollivier and L. Fensterbank, *Synlett* **2016**, DOI: 10.1055/s-0035-1561337.

⁴⁶ A primary carboxylic (5-phenylvaleric acid) has also been used as unstabilized radical precursor, providing the cross-coupling product but in 11% yield.

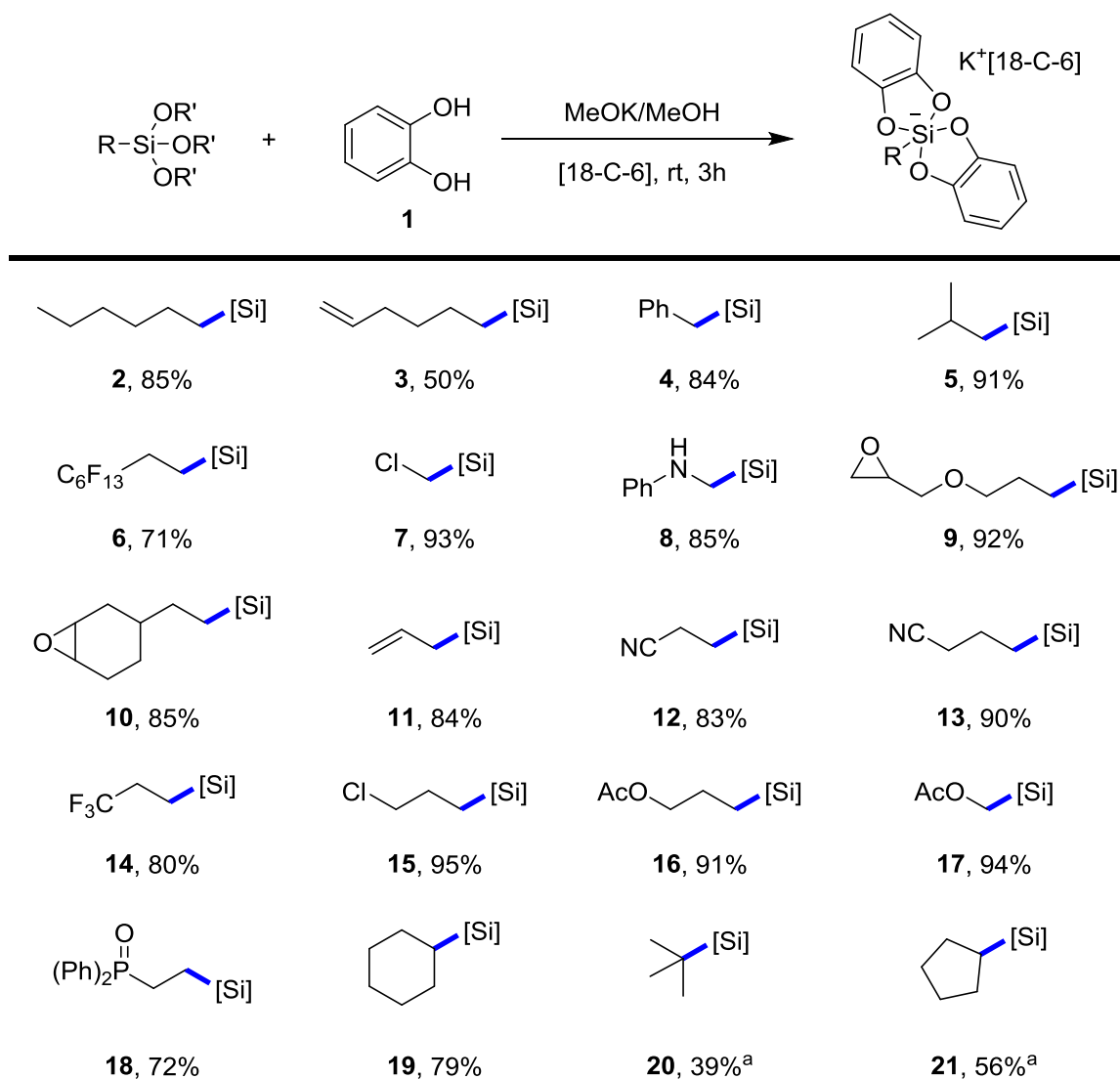
III.B.2. Synthesis of Alkyl Silicates Precursors

Bis-catecholato alkyl silicates can be easily prepared in high yield by trituration of the trialkoxysilane with 2 equivalents of catechol **1** in a mixture of potassium methoxide in methanol (Scheme 31, equation 1). The addition of crown ether allowed us to increase the stability of the silicate salt. Nevertheless, we will show later that this additive does not influence the reactivity and also is not necessary when the dual transformation is performed just after the silicate's synthesis. Another way to prepare these substrates consists of starting with the trichloroalkylsilane, 2 equivalents of catechol and triethylamine in THF. After this first step, a cation metathesis is carried out using tetraethyl ammonium bromide in acetonitrile (Scheme 31, equation B). The ammonium salts and the crown ether complexed potassium salts are bench stable and synthesized in high yields.



Scheme 31. Synthesis of bis-catecholato silicates

With these two procedures, we managed to synthesize a wide range of alkyl silicates such as *n*-hexyl **2** or 5-hexenyl **3** silicates and more activated alkyl such as benzyl **4**, α -amino methyl **8** and allyl **11** silicates (Scheme 32). We prepared alkyl silicates bearing a wide range of functional groups (cyano, ester, ether, epoxide, halogen) in yields between 39% and 95%. The *tert*-butyl silicate **20** and the cyclopentane silicate **21** were synthesized following the procedure described in scheme 31 equation 2.



^a **20** and **21** were synthesized with the procedure leading to the ammonium silicate salt.

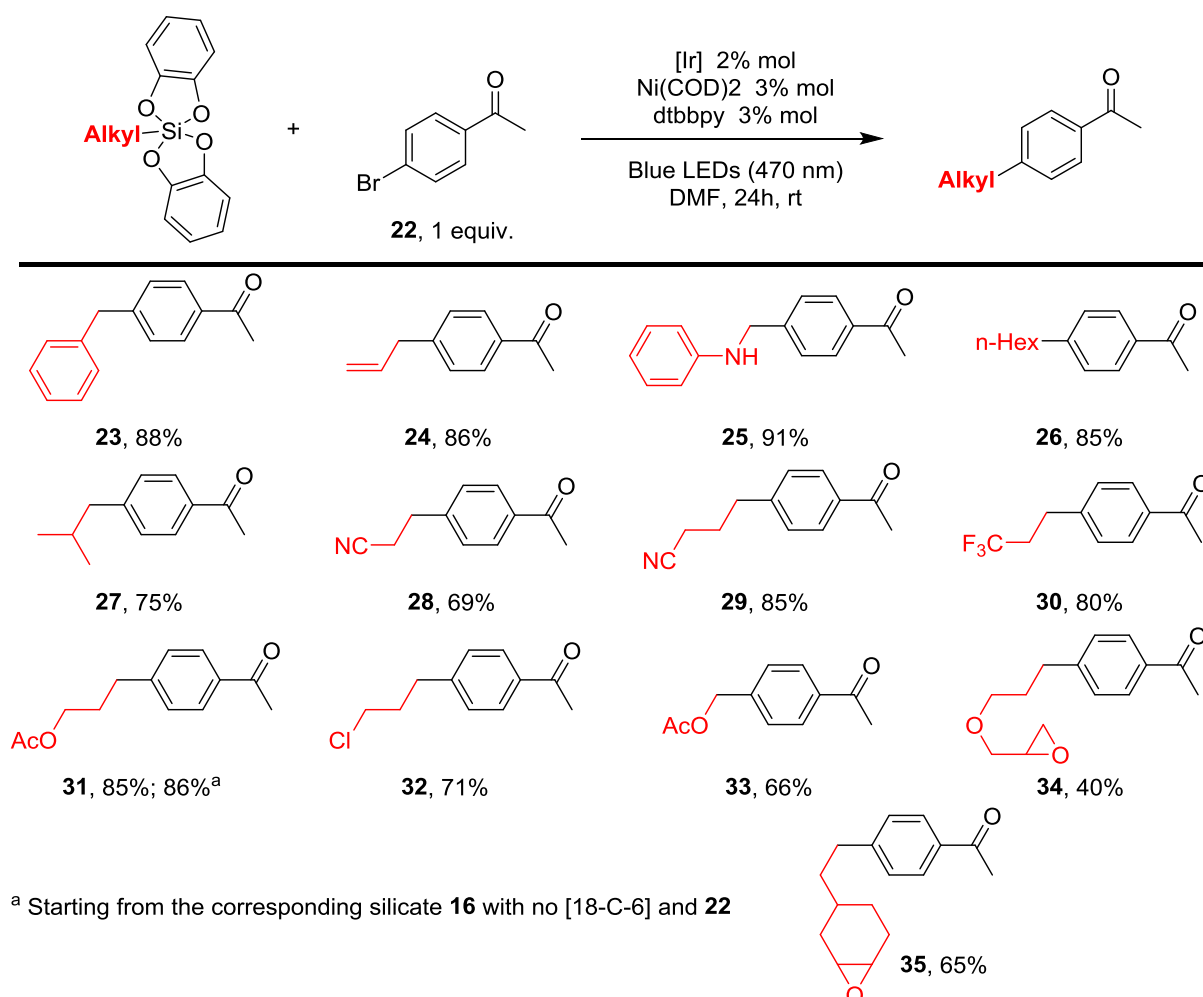
Scheme 32. Scope of alkyl bis-catecholato silicates synthesized

III.B.3. Photoredox/Nickel dual catalysis process

After the preparation of potassium silicates **2-21**, a preliminary screening of conditions with 4-bromoacetophenone **22**, as cross-coupling partner, led us to the following protocol. To a DMF solution of silicate (1.5 equiv, 0.1 M) in the presence of Ir[(dF(CF₃)ppy)₂(bpy)](PF₆) (2 mol%) as photocatalyst, Ni(COD)₂ (3 mol%) as dual catalyst partner and 4,4'-di-*tert*-butyl-2,2'-dipyridyl (dtbbpy, 3 mol%) as ligand was added 4-bromoacetophenone **22** (1 equiv). After stirring for 24 h at room temperature under blue LEDs irradiation, excellent yields of

cross-coupling products were obtained (Scheme 33). We firstly tested the activated alkyl silicates and products **23-25** were obtained from benzyl, allyl and α -amino silicates (**4**, **8** and **11**) in 88%, 86% and 91% yield respectively. The less stabilized hexyl radical from silicate **2** could also be involved furnishing the corresponding coupling product **26** in high yield (85%). With these encouraging results, we decided to extend the transformation to other silicates. We observed a very good tolerance for compounds bearing various functional groups such as an ester (**31**, **33**), a nitrile (**28**, **29**) an oxirane (**34**, **35**) or halogens (**30**, **32**).

To determine the influence of the crown ether additive, we performed the dual catalyst reaction using the potassium silicate salt **16** synthesized with no [18-C-6]. The reaction with 4-bromoacetophenone also provided a similar good yield (86%) of coupling product **31**. The crown ether additive does not have any impact on the dual catalysis process.



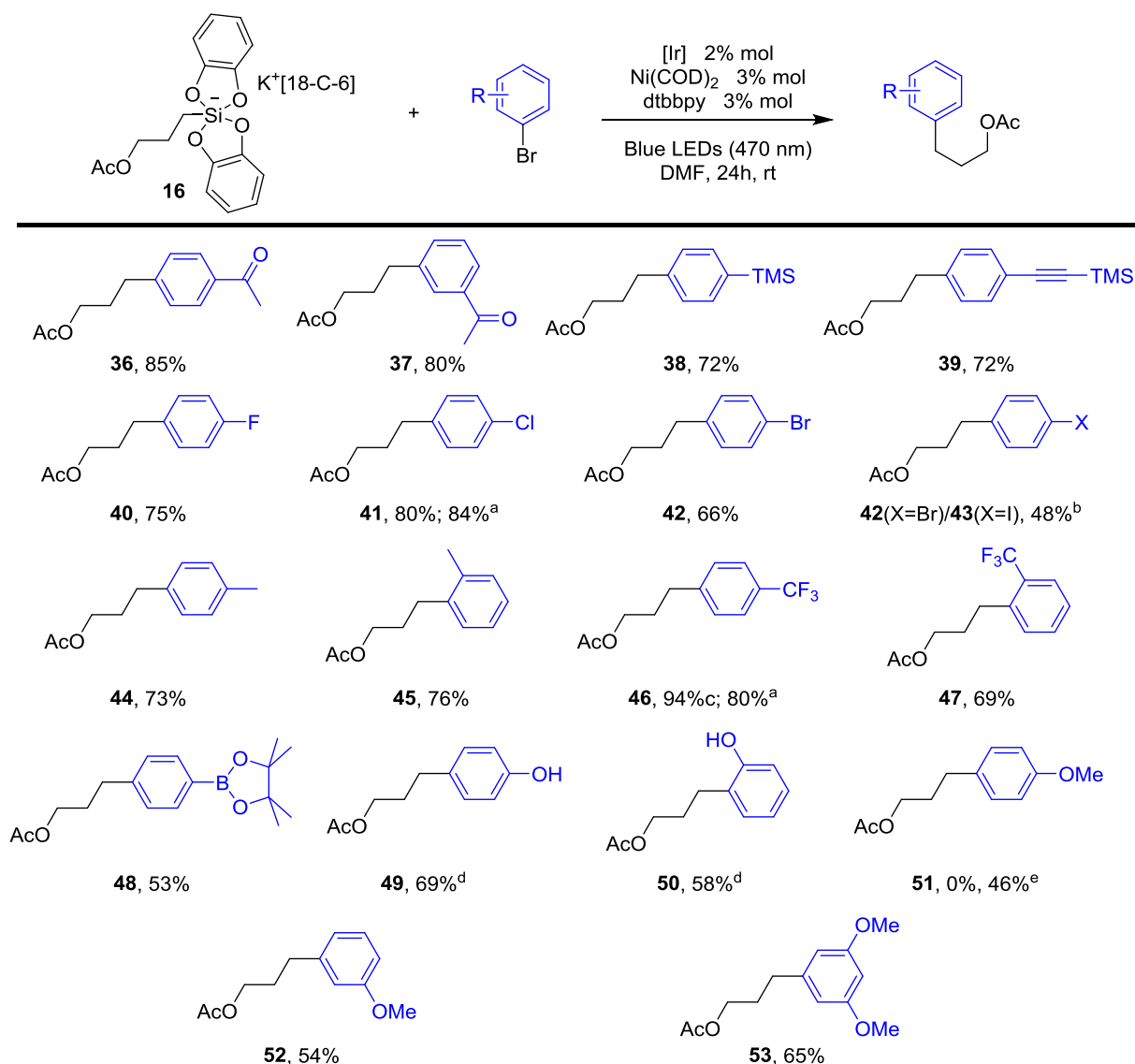
Scheme 33. Cross coupling reactions of silicates with 4-bromoacetophenone **22**

Using the same conditions, a series of arylbromides with varied substitution pattern could be used in conjunction with acetate silicate **16** (scheme 34). The reaction scope proved to be quite wide and a closer examination of these results revealed interesting features. Indeed, *para*- and *meta*-bromoacetophenone gave similar high yields (85% and 80%) of cross-coupled products **36** and **37**. Reaction with arylbromides bearing electron withdrawing group such as CF₃ group (**46**, **47**) and halogens (**40-42**) furnished good yields. Furthermore, the difference of reactivity between a C_{sp2}-Br and a C_{sp2}-I bond was also investigated with 1-bromo-4-iodobenzene for instance. Not surprisingly, a preferred oxidative addition took place at the carbon-iodide bond⁴⁷ giving a 10:1 ratio of products **42** (X = Br) and **48** (X = I). This appeared quite opportune for electron enriched aryl substrates.

In the case of bromobenzene with an electron-donating substituent such as *para*- or *ortho*-methyl (**44**, **45**), we observed good yields of cross-coupled products (73% and 76%). While *meta*-bromoanisoles could be effectively used (adducts **52** and **53**), only starting material was recovered with *ortho*-bromoanisole and *para*-bromoanisole. The reluctant behavior of *para*-bromoanisole could be partly fixed by using the corresponding iodo derivative since cross coupling product **51** was obtained albeit in modest yield (46%). These findings contrast with Molander's report^{44a} in which electron rich substrates proved to be competent. Their catalytic mixture (5 mol% NiCl₂(dme), 5 mol% dtbbpy, 2 mol% Ru(bpy)₃(PF₆)₂) differs from ours (3 mol% Ni(COD)₂, 3 mol% dtbbpy and 2 mol% Ir[(dF(CF₃)ppy)₂(bpy)](PF₆)) implying interesting metal and ligand differences.

Remarkably, a pinacol boronate function could also be tolerated in these conditions³⁹ as illustrated by the formation of **48** that could be utilized for further coupling reactions. Nevertheless, direct isolation of this product after column chromatography was detrimental to the yield. Instead, when the crude reaction mixture was oxidized (NaOH, H₂O₂), a higher yield (69% vs 53% for **48**) of phenol product **49** was recorded. Similar protocol was applied to give phenol product **50**.

⁴⁷ J. F. Hartwig, *Organotransition Metal Chemistry: From Bonding to Catalysis*, University Science Books, Sausalito, 2009.



^a Starting from the corresponding potassium silicate **16** with no [18-C-6].

^b Starting from 1-bromo 4-iodobenzene. A 10:1 mixture of **42** and **43** was isolated.

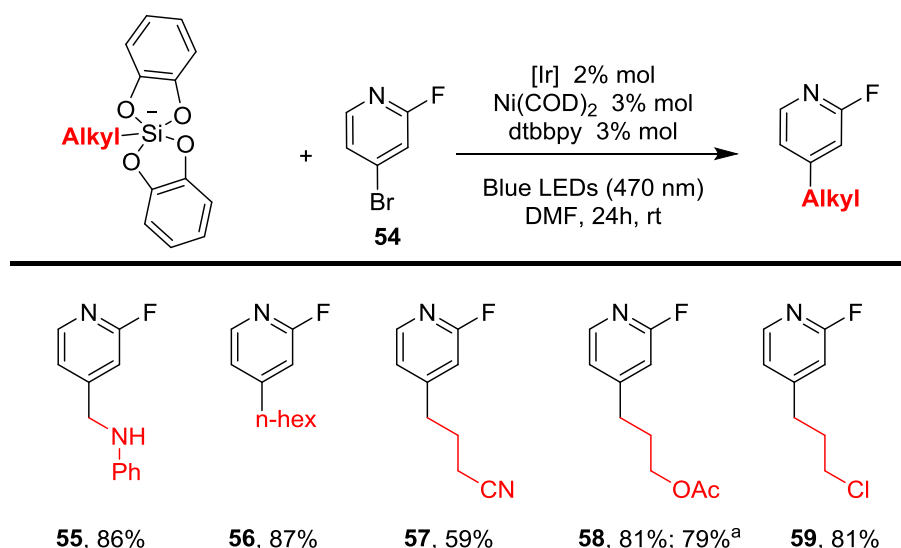
^c 2 mol% Ru(bpy)₃(PF₆)₂ was used instead of 2 mol% [Ir].

^d Pinacol borane directly oxidized before purification (H₂O₂, NaOH for 30 min at 0°C).

^e Starting from 4-iodoanisole.

Scheme 34. Cross coupling reactions of silicate **16** with various aryl bromides

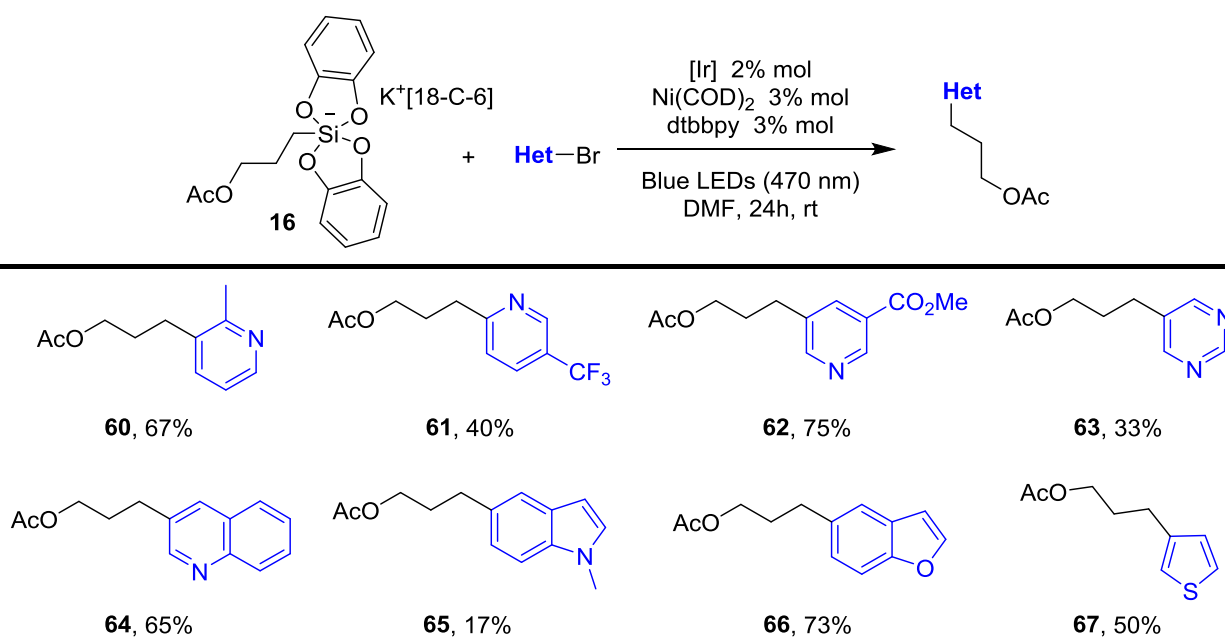
Heterocyclic bromides completed the reach of this transformation and established its high synthetic potential. 2-Fluoro-4-bromopyridine **54** was used as partner of the dual catalysis in the presence of silicates (**2**, **8**, **13**, **15** and **16**) and delivered a small library of new alkyl-fluoropyridines **55-59** in high yields 59-86% (Scheme 35). Once again, we realized the reaction using the alkyl silicate **16** without the crown ether additive. We obtained the cross-coupling product **58** a good yield of 79%.



^a Starting from the corresponding potassium silicate **16** with no [18-C-6]

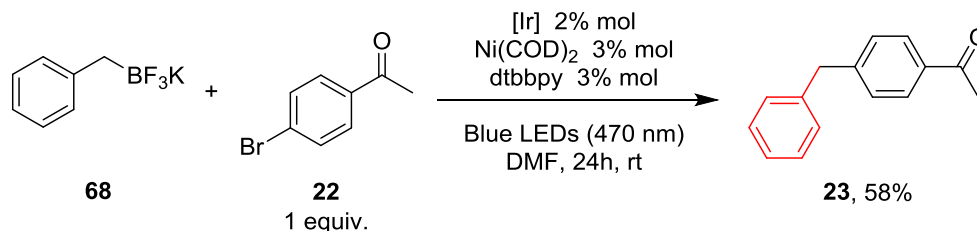
Scheme 35. Cross coupling reaction of 2-fluoro-4-bromopyridine with different silicates

We then looked at the heteroaryl partner. Other pyridyl systems such as methylpyridine, trifluoromethylpyridine and methyl nicotinate proved to be competent for this cross-coupling transformation. The corresponding products **60-62** were obtained in a 40-75% yield range. Finally, various heterocyclic systems such as pyrimidine, quinoline, indole, benzofuran and thiophene were engaged and yielded the corresponding cross coupling adducts **63-67** from mitigated to fair yields.



Scheme 36. Cross coupling reaction of silicate **16** with various heterocycles

Interestingly, a comparison was made with the corresponding benzyltrifluoroborate **68** precursor and showed in our conditions a more productive reaction (adduct **23**) from the silicate **16** (88% vs. 58% yield).



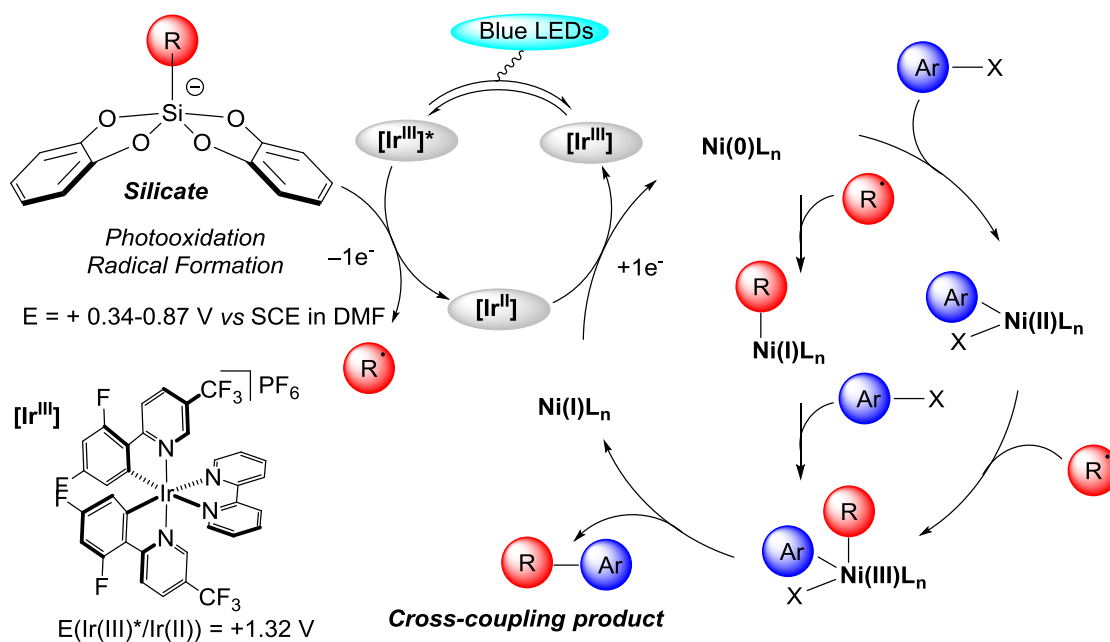
Scheme 37. Comparison between silicate **4** and trifluoroborate **68**

The proposed catalytic cycle is outlined in Scheme 38. It is well established that excitation of photoredox catalyst Ir[(dF(CF₃)ppy)₂(bpy)](PF₆) produces a long-lived photoexcited state *Ir[(dF(CF₃)ppy)₂(bpy)](PF₆).³² The latter acts as a strong oxidant (E [*Ir^{III}/Ir^{II}] = +1.32 V vs. SCE in MeCN)⁴⁸ and undergoes a single electron transfer (SET) with bis-catecholato silicates **2-21** (E_{ox} between +0.34 and +0.87 V vs. SCE in DMF)^{42a} generating a primary alkyl radical which interacts with a Ni species. However, the mechanism of this dual catalysis is still in debate.^{37,49} All proposals converge toward a Ni(III) intermediate which upon reductive elimination delivers the cross coupling product and a Ni(I) intermediate complex, the latter being further reduced (E [Ni^I/Ni⁰] = -1.2 V vs. SCE in DMF)⁵⁰ by SET from the iridium(II) (E [Ir^{III}/Ir^{II}] = -1.37 V vs. SCE in MeCN)⁴⁶ to generate a Ni(0) complex. From this zero-valent nickel entity, two possibilities have been advanced. Initial oxidative addition of the bromoaryl gives a Ni(II) species that would trap the nucleophilic radical intermediate. Alternatively, an alkyl Ni(I) species would result from the trapping of the radical intermediate by Ni(0) followed by oxidative addition of the bromoaryl to the Ni(III) intermediate (Scheme 38). Some of our results in Scheme 34 with the formation of **42** and **51** highlight the importance of the oxidative addition step but do not allow to conclude at this stage. Thus, this will necessitate more investigation to clarify these points.

⁴⁸ D. Hanss, J. C. Freys, G. Bernardinelli and O. S. Wenger, *Eur. J. Inorg. Chem.* **2009**, 4850.

⁴⁹ a) M. S. Oderinde, A. Varela-Alvarez, B. Aquila, D. W. Robbins and J. W. Johannes, *J. Org. Chem.* **2015**, *80*, 7642; b) O. Gutierrez, J. C. Tellis, D. N. Primer, G. A. Molander and M. C. Kozlowski, *J. Am. Chem. Soc.* **2015**, *137*, 4896.

⁵⁰ M. Durandetti, M. Devaud and J. Perichon, *New J. Chem.* **1996**, *20*, 659.



Scheme 38. Proposed mechanism of the photoredox/nickel dual catalysis using silicates

III.B.4. Conclusion

In conclusion of this first study, we demonstrated that bis-catecholato silicates are very reliable partners for photoredox/nickel dual catalysis. We have focused our efforts on the use of highly reactive primary radicals, which so far has remained an uncharted territory. Our generally successful results in terms of yields and structure scope, since notably heteroatomic functions and heterocyclic platforms do not appear as limiting factors in these transformations, augur well for the application of this methodology in different settings.

III.C. Results: Photooxidative Generation of Alkyl Radicals by a Metal Free Catalytic Process: Applications to Radical Synthesis and Dual Catalysis

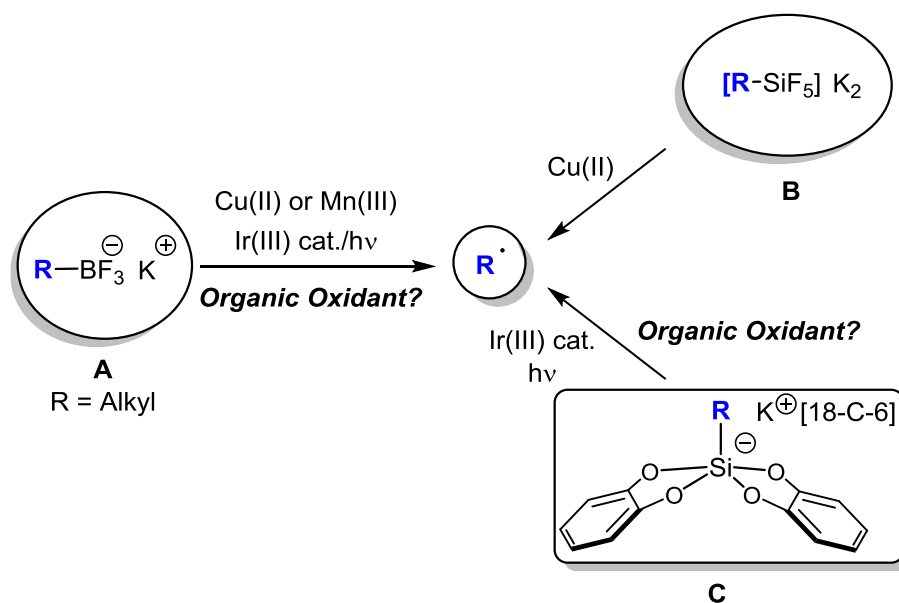
III.C.1. Introduction and objectives

The single-electron-transfer (SET) oxidation of soft carbanions is a very versatile method to access to C-centered radicals.⁵¹ Among possible candidates, ate complexes based for instance on boron, trifluoroborates being the most popular reagents, have already shown versatile reactivities for the generation of radicals.⁵² To a lesser extent, hypervalent biscatecholato silicon species have recently emerged as very promising alternatives to the boron derivatives, avoiding any release of noxious fluorinated byproducts.^{22,24} Their synthesis is known⁵³ yielding bench-stable compounds,⁵³ and their high electron density make them suitable candidates for oxidation. In this letter, we provide new elements on the SET oxidation of alkyl trifluoroborates **A** and silicates **C**, notably focusing on the use of organic oxidants (Scheme 39).

⁵¹ a) P. I. Dalko, *Tetrahedron* **1995**, *51*, 7579. b) U. Jahn, *Radicals in Synthesis III*, In *Topics in Current Chemistry*; Vol. 320; Heinrich, M.; Gansäuer, A., Eds.; Wiley-VCH: Weinheim, **2012**, 121. c) U. Jahn, *Radicals in Synthesis III*, In *Topics in Current Chemistry*; Vol. 320; Heinrich, M.; Gansäuer, A., Eds.; Wiley-VCH: Weinheim, **2012**, 191. d) U. Jahn, *Radicals in Synthesis III*, In *Topics in Current Chemistry*; Vol. 320; Heinrich, M.; Gansäuer, A., Eds.; Wiley-VCH: Weinheim, **2012**, 323. e) A. Gansäuer, H. Bluhm, *Chem. Rev.* **2000**, *100*, 2771.

⁵² a) G. B. Schuster, *Pure Appl. Chem.* **1990**, *62*, 1565. b) L. A. Shundrin, V. V. Bardin, H.-J. Frohn, *Z. Anorg. Allg. Chem.* **2004**, *630*, 1253. c) G. A. Molander, V. Colombel, V. A. Braz, *Org. Lett.* **2011**, *13*, 1852. d) J. W. Lockner, D. D. Dixon, R. Risgaard, P. S. Baran, *Org. Lett.* **2011**, *13*, 5628. e) Y. Fujiwara, V. Domingo, I. B. Seiple, R. Gianatassio, M. D. Bel, P. S. Baran, *J. Am. Chem. Soc.* **2011**, *133*, 3292. f) T. W. Liwosz, S. R. Chemler, *Org. Lett.* **2013**, *15*, 3034. g) S. R. Neufeldt, C. K. Seigerman, M. S. Sanford, *Org. Lett.* **2013**, *15*, 2302. For the oxidation of boronic acids, see h) H. C. Brown, N. C. Hébert, C. H. Snyder, *J. Am. Chem. Soc.* **1961**, *83*, 1001. i) A. S. Demir, Ö. Reis, M. Emrullahoglu, *J. Org. Chem.* **2003**, *68*, 578. j) A. Dickschat, A. Studer, *Org. Lett.* **2010**, *12*, 3972. k) M. Tobisu, K. Koh, T. Furukawa, N. Chatani, *Angew. Chem. Int. Ed.* **2012**, *51*, 11363.

⁵³ a) R. R. Holmes, *Chem. Rev.* **1990**, *90*, 17. b) C. Chuit, R. J. P. Corriu, C. Reye, J. C. Young, *Chem. Rev.* **1993**, *93*, 1371.



Scheme 39. Generation of alkyl radicals by SET oxidation of trifluoroborates and silicates

III.C.2. Generation of radicals by organic oxidants

III.C.2.a. Stoichiometric oxidation

Our own endeavors in this domain started with the copper(II)-mediated oxidation of alkyl trifluoroborates **A** (Scheme 39),⁵⁴ a previously known reaction⁵⁵ but not exploited in radical chemistry. In conditions inspired from the related copper(II) oxidation of alkyl pentafluorosilicates **B** by Kumada and coworkers,⁵⁶ a series of alkyl (from primary to tertiary ones) trifluoroborates were engaged in oxidative processes. Postfunctionalization of the resulting radical intermediate was achieved by TEMPO spin trapping, allylation, and conjugate addition.⁵⁵

Following these preliminary reports, we wanted to investigate the use of nonmetallic oxidants. We initially showed that the Dess–Martin periodinane (DMP) could be efficiently used for the oxidation of trifluoroborates.⁵⁵ Tritylium tetrafluoroborate, an underexplored

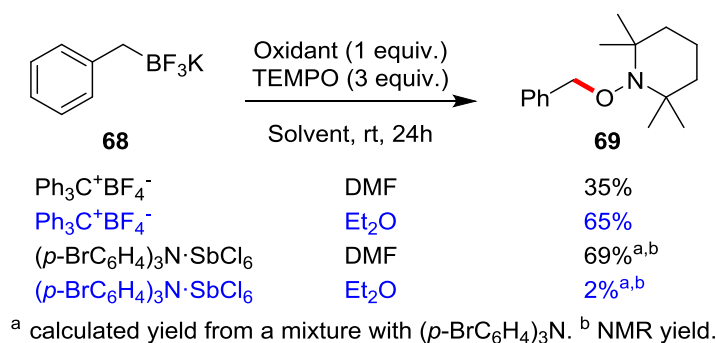
⁵⁴ G. Sorin, R. M. Mallorquin, Y. Contie, A. Baralle, M. Malacria, J-P. Goddard, L. Fensterbank, *Angew. Chem. Int. Ed.* **2010**, *49*, 8721.

⁵⁵ a) Y. Nishigaichi, T. Orimi, A. J. Takuwa, *Organomet. Chem.* **2009**, *694*, 3837. b) C. Carzola, E. Metay, B. Andrioletti, M. Lemaire, *Tetrahedron Lett.* **2009**, *50*, 6855.

⁵⁶ For seminal work, see: J.-I. Yoshida, K. Tamao, T. Kakui, A. Kurita, M. Murata, K. Yamada, M. Kumada, *Organometallics* **1982**, *1*, 369.

oxidant,⁵⁷ was also tested with a series of trifluoroborates (Scheme 2). For reasons which need to be elucidated, DMF did not appear as the best solvent for these oxidations. Gratifyingly, good yields of TEMPO adducts **69** were obtained in Et₂O as solvent with benzyl precursor **68**.

We also examined the possibility of using Ledwith–Weitz aminium salt (oxidation potential: 1.06 V vs. SCE)⁵⁸ as SET oxidative agent of soft carbanions which, to the best of our knowledge, has never been accomplished. A strong solvent effect (Et₂O vs. DMF) was observed in the oxidation of **68**, respectively 2% vs. 69% of **69**. This led us to pursue our study in DMF with this oxidant. However, even in this solvent, the results proved to be much less satisfying compared to the ones obtained with the tritylium oxidant.

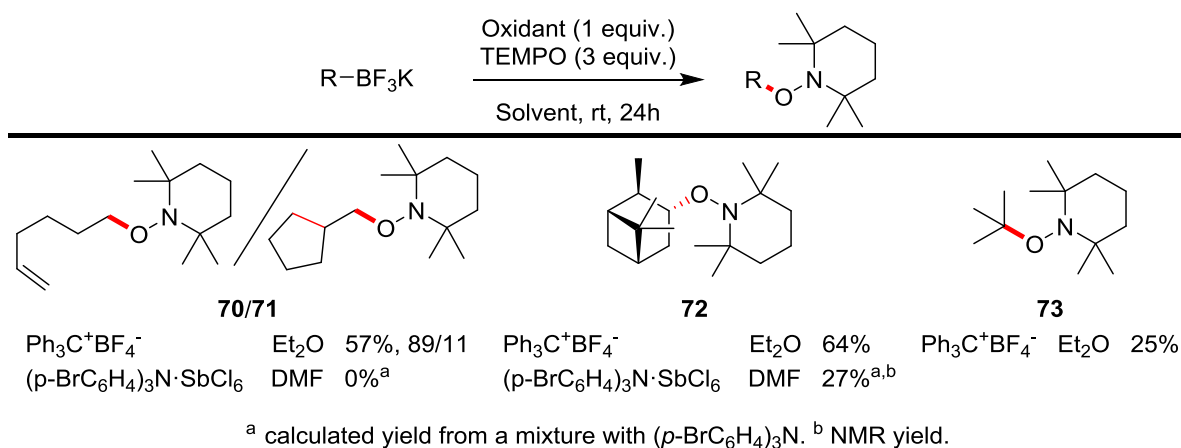


Scheme 40. Stoichiometric oxidation of trifluoroborates by organic reagents

Good yields were also obtained with the secondary (**72**) and primary series (**70** and **71**) using Et₂O and tritylium conditions. Only *tert*-butyl precursor gave a lower yield of product **73**, (25%), presumably for steric reasons. Only 27% yield of **72** with the secondary substrate and no TEMPO adduct in the primary alkyl series for the aminium salt oxidation version.

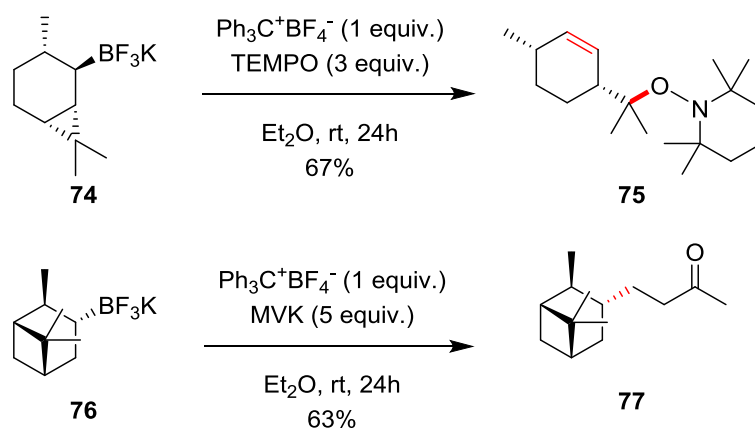
⁵⁷ Tritylium is known as a hydride abstractor, for a recent application, see: a) Z. Xie, L. Liu, W. Chen, H. Zheng, Q. H. Xu, H. Yuan, H. Lou, *Angew. Chem. Int. Ed.* **2014**, *53*, 3904; and references cited therein. It has been used as a sacrificial electron acceptor in photoredox catalysis, see: b) M. Daniel, L. Fensterbank, J.-P. Goddard, C. Ollivier, *Org. Chem. Front.* **2014**, *1*, 551.

⁵⁸ a) A. C. Herath, J. Y. Becker, *J. Electroanal. Chem.* **2008**, *619-620*, 98. b) K. H. G. Brinkhaus, E. Steckhan, W. Schmidt, *Acta Chem. Scand., Ser. B* **1983**, *37*, 499. c) R. Wend, E. Steckhan, *Electrochim. Acta* **1983**, *42*, 2027. For a recent use, see: d) S. L. Drew, A. L. Lawrence, M. S. Sherburn, *Angew. Chem. Int. Ed.* **2013**, *52*, 4221. e) For a review, see: X. Jia, *Synthesis* **2016**, *48*, 18.



Scheme 41. Oxidation of trifluoroborates by organic reagents

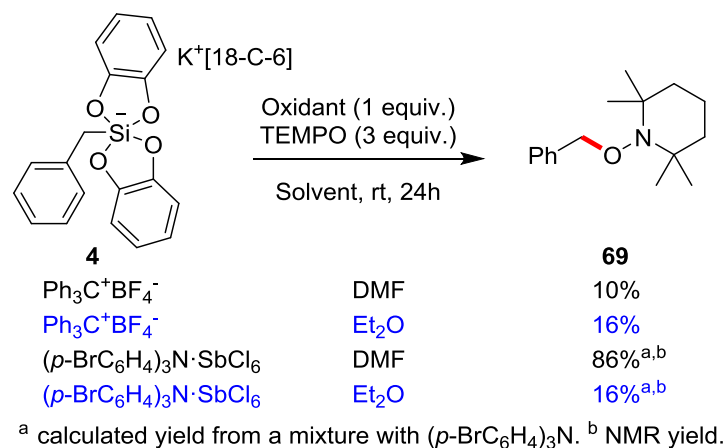
Then we were able to oxidize the trifluoroborate salt **74** leading to the generation of a secondary radical, **74** subsequently underwent a ring opening of the cyclopropane to give **75** (Scheme 42). This time the tertiary radical was trapped in good yield (67%). Interestingly, the tritylium in diethyl ether conditions proved to be also compatible with conjugate addition since methyl vinyl ketone (MVK) adduct **77** was isolated in satisfactory yield (63%).



Scheme 42. Generation of tertiary radical and conjugate addition

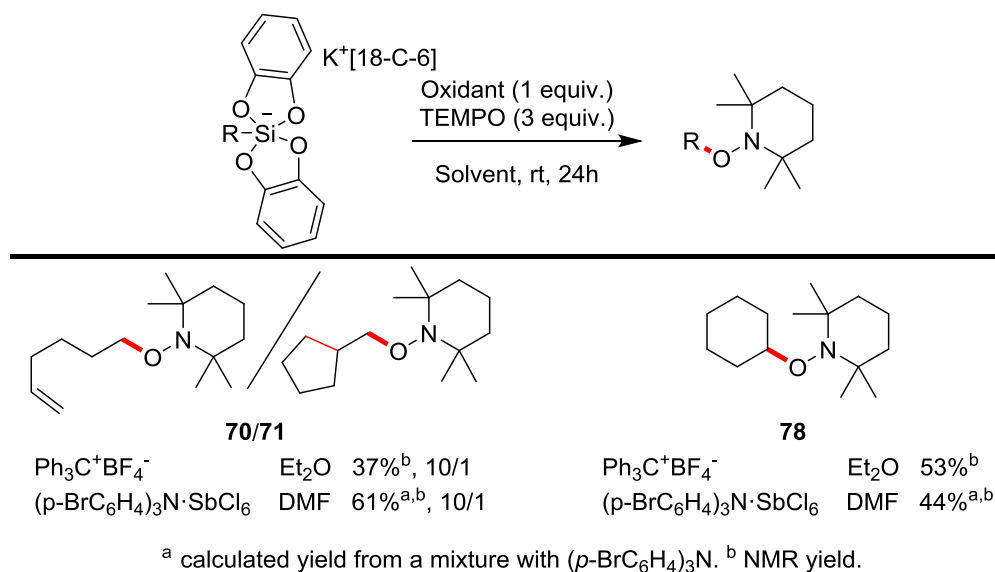
Next, we investigated the reactivity of biscatecholato pentavalent silicates. These substrates are amenable to large-scale synthesis and can be rendered rock stable by complexing the potassium counteranion by the [18-C-6] crown ether.^{53a} Benzyl silicate **4**

served as a preliminary probe (Scheme 43). It was submitted in Et₂O and DMF to one equivalent of tritylium and aminium salt. In both solvents, tritylium gave poor yields of **69** (< 20%). However, the use of the aminium salt was more rewarding (86% of **69** in DMF, 16% in Et₂O). In comparison, oxidation with 1 equiv. of Cu(OAc)₂ gave 45% yield of **69** and with 1 equiv of DMP, 26% of **69**.



Scheme 43. Stoichiometric oxidation of biscatecholato silicates by organic reagents

This oxidant proved to be competent in DMF for secondary and primary alkyl substrates giving, respectively, 44% of **78** and 61% of **70/71**. Tritylium can also be used as a reliable alternative oxidant for the silicates. In fact, tritylium conditions gave also moderate yield of 53% for **78**.

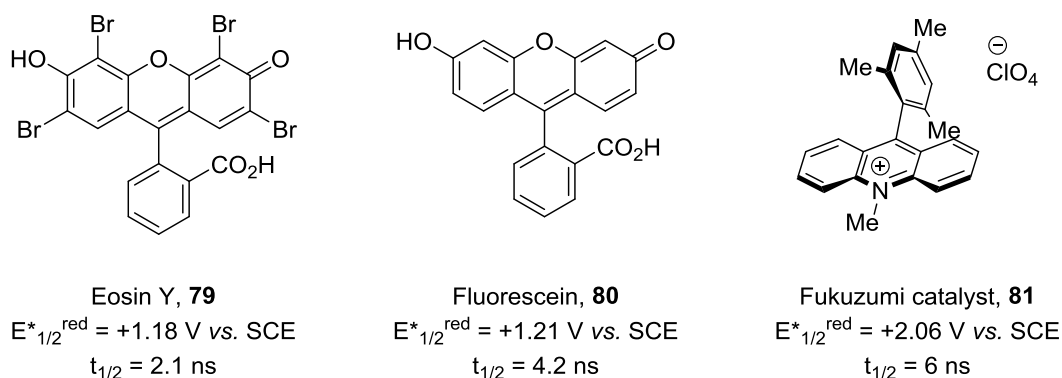


Scheme 44. Stoichiometric oxidation of biscatecholato silicates by organic reagents

III.C.2.b. Photocatalytic oxidation

Because of its mild conditions and high substrate tolerance, visible-light photocatalytic oxidation was the obvious next step. In the case of trifluoroborates, several groups have established the feasibility of this transformation using ruthenium(II)- or iridium(III)-based photocatalysts.⁵⁹ Of note, the resulting radicals can be engaged in photoredox/nickel dual catalysis.^{59g-k} While pentafluorosilicates **B** failed in our hands to undergo any oxidation, we recently showed that biscatecholato silicates constitute advantageous alternatives to the trifluoroborates since they allow the generation of very unstabilized primary radicals upon iridium(III) $\{Ir[(dF(CF_3)ppy)_2(bpy)](PF_6)\}$ photocatalysis, also successfully engaged in photoredox/nickel dual catalysis.^{53a}

Herein, we wanted to examine the possibility to use organic dyes⁶⁰ as possible catalysts for the oxidation of these soft carbanions. Based on their frequent use, the following dyes were considered: eosin Y, fluorescein,⁶¹ and Fukuzumi acridinium as catalysts.⁶²



Scheme 45. Commercially available Organic dyes

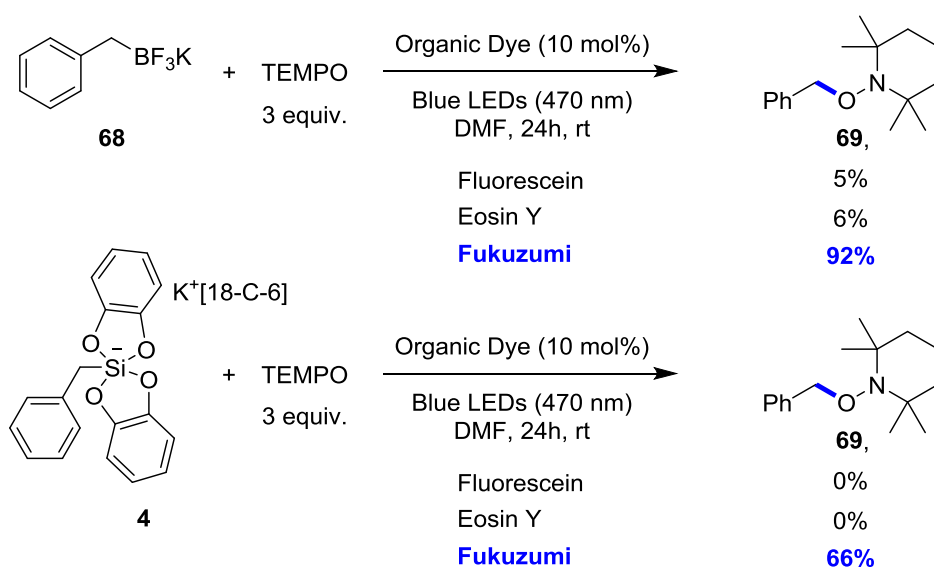
⁵⁹ a) Y. Yasu, T. Koike, M. Akita, *Adv. Synth. Catal.* **2012**, *354*, 3414. b) K. Miyazawa, Y. Yasu, T. Koike, M. Akita, *Chem. Commun.* **2013**, *49*, 7249. c) T. Koike, M. Akita, *Synlett* **2013**, *24*, 2492. d) K. Miyazawa, T. Koike, M. Akita, *Adv. Synth. Catal.* **2014**, *356*, 2749. e) Y. Li, K. Miyazawa, T. Koike, M. Akita, *Org. Chem. Front.* **2015**, *2*, 319. f) H. Huang, G. Zhang, L. Gong, S. Zhang, Y. Chen, *J. Am. Chem. Soc.* **2014**, *136*, 2280. g) J. C. Tellis, D. N. Primer, G. A. Molander, *Science* **2014**, *345*, 433. h) D. N. Primer, I. Karakaya, J. C. Tellis, G. A. Molander, *J. Am. Chem. Soc.* **2015**, *137*, 2195. i) O. Gutierrez, J. C. Tellis, D. N. Primer, G. A. Molander, M. C. Kozlowski, *J. Am. Chem. Soc.* **2015**, *137*, 4896. j) I. Karakaya, D. N. Primer, G. A. Molander, *Org. Lett.* **2015**, *17*, 3294. k) Y. Yamashita, J. C. Tellis, G. A. Molander, *Proc. Natl. Acad. Sci. U.S.A.* **2015**, *112*, 12026. l) H. Huang, K. Jia, Y. Chen, *Angew. Chem. Int. Ed.* **2015**, *54*, 1881.

⁶⁰ a) S. Fukuzumi, K. Ohkubo, *Org. Biomol. Chem.* **2014**, *12*, 6059. b) D. A. Nicewicz, T. M. Nguyen, *ACS Catal.* **2014**, *4*, 355. c) D. Ravelli, M. Fagnoni, *ChemCatChem* **2012**, *4*, 169. For a recent use, see: d) J. D. Griffin, M. A. Zeller, D. A. Nicewicz, *J. Am. Chem. Soc.* **2015**, *137*, 11340.

⁶¹ X.-F. Zhang, I. Zhang, L. Liu, *Photochem. Photobiol.* **2010**, *86*, 492.

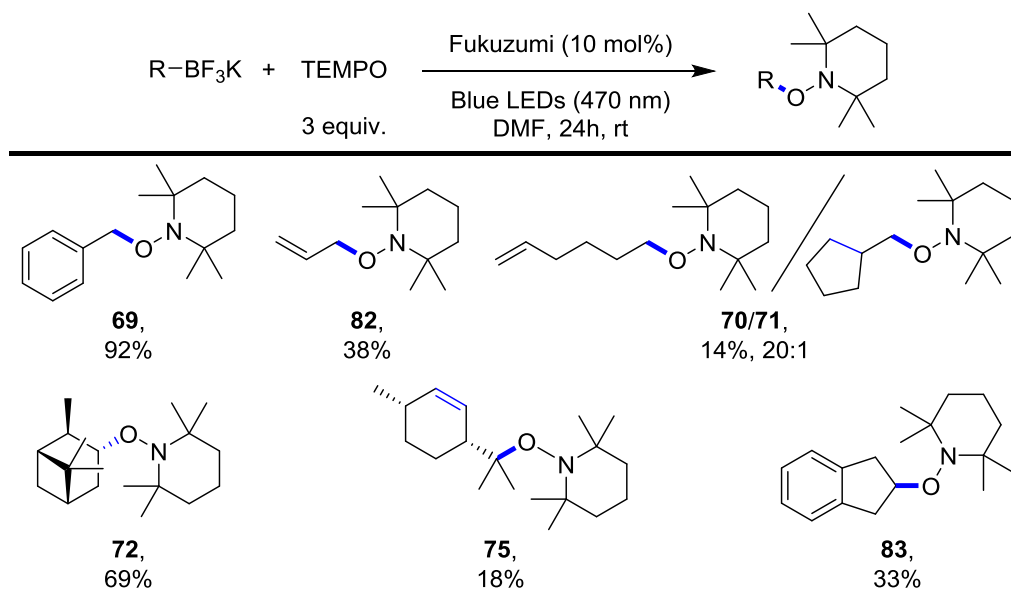
⁶² a) S. Fukuzumi, H. Kotani, K. Ohkubo, S. Ogo, N. V. Tkachenko, H. Lemmetyinen, *J. Am. Chem. Soc.* **2004**, *126*, 1600. b) A. C. Benniston, A. Harriman, P. Li, J. P. Rostron, H. J. van Ramesdonk, M. M. Groeneveld, H. Zhang, J. W. Verhoeven, *J. Am. Chem. Soc.* **2005**, *127*, 16054.

A preliminary screening with benzyltrifluoroborate **68** showed that the Fukuzumi catalyst was by far the best one (Scheme 46). Indeed, we obtained 92% of trapped adduct **69** using 10 mol% of catalyst. Similar behavior was observed for benzylsilicate **4** product yielding to 66% of **69** adduct. Therefore we kept this catalyst for further testing.



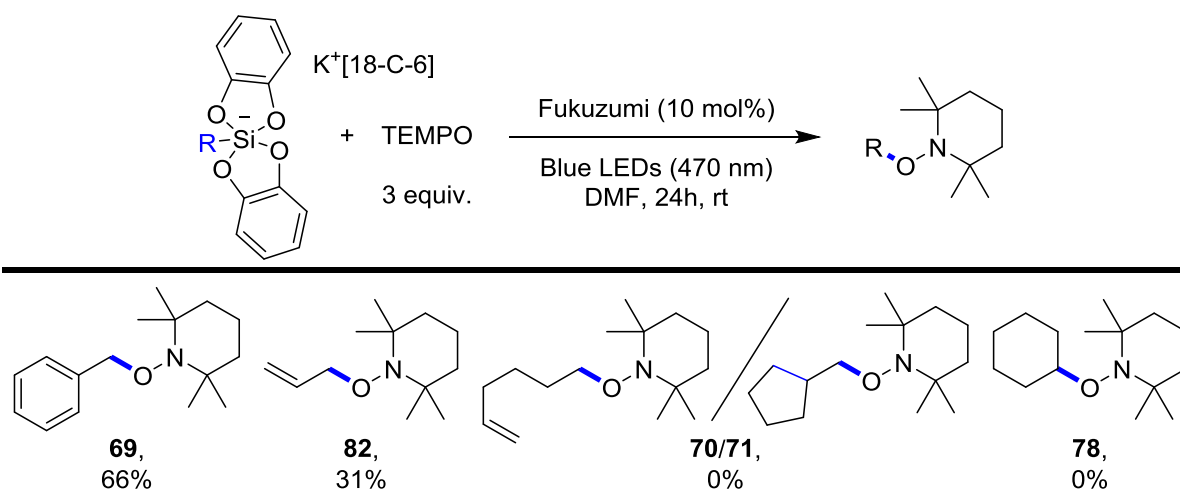
Scheme 46. Photocatalytic oxidation of borates and silicates by organic dyes

Both substrate families showed the same trend, that is, the less stabilized is the generated radical, the lower is the yield. Thus, for trifluoroborates (Scheme 47), a gradual decrease of yield was observed from benzyl product **69** (92% of yield) to least stabilized primary radical adducts **70/71** (14% of yield). One could argue that **74**, a secondary substrate, should have given a better yield. But in that case, the final radical is a tertiary one which may undergo competitive pathways and lead to only 18% of **75**.



Scheme 47. Photo-organocatalytic oxidation of borates

In the case of silicates (scheme 48), only stabilized benzyl and allyl radicals could be generated (66% for **69**, 31% for **82**). Interestingly, allyltrifluoroborate and allylsilicate salts provided **82** in close yields (38% vs. 31%). In sharp contrast however, secondary trifluoroborates could give TEMPO adducts **72** and **83** contrary to secondary silicate no traces of TEMPO adduct **78** was formed.



Scheme 48. Photo-organocatalytic oxidation of silicates

A direct correlation of these findings with redox potentials is not obvious. Oxidation potentials for trifluoroborates span from 1.1 V (benzyl et alkoxyethyl) to 1.83 V vs. SCE (primary and aryl)^{60a,b} while they have been determined to range from 0.61 V for benzylsilicate **4** to 0.75 V vs. SCE for **3**.⁵³ Some other key factors are at play in these

reactions that we will try to uncover. In all the successful oxidations, TEMPO would act as a sacrificial oxidant to regenerate the photocatalyst and sustain the photocatalytic cycle in agreement with the literature data.^{53a, 60a}

III.C.2.c. New generation of organic dyes

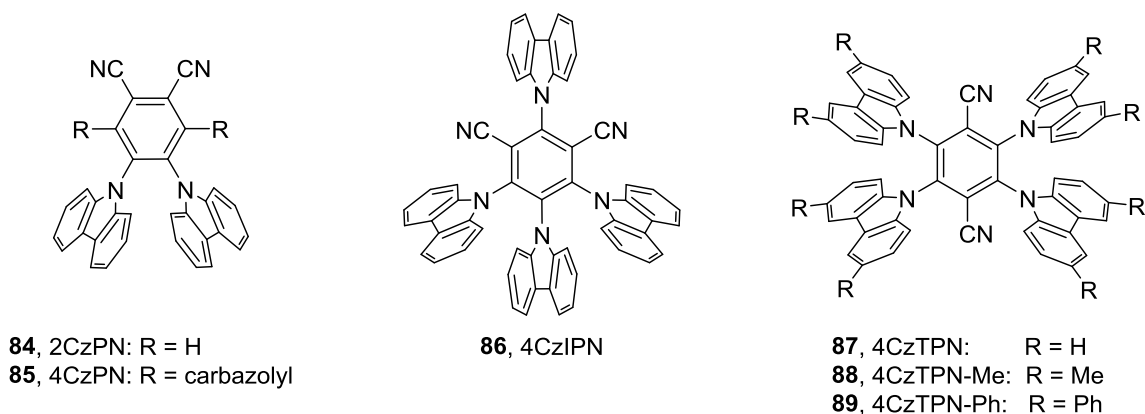
This study shows the unprecedented oxidation of trifluoroborates and silicates with a tritylium or an aminium salt as stoichiometric oxidant to generate C-centered radicals. Photocatalytic oxidation could also be achieved with the Fukuzumi acridinium showing a higher reactivity of trifluoroborates than silicates in these conditions. The improvement of biscatecholato silicates photooxidation with organic dyes became our principal goal.

We decided to investigate other organic dyes taking in consideration both the redox potential and the lifetime of the excited state of irradiated dye. In 2012, Adachi and coworkers described a family of carbazolyl dicyanobenzenes, with carbazole as a donor and dicyanobenzene as an acceptor of electron, as light-harvesters for organic light-emitting diodes (Scheme 49).⁶³ Among them, 1,2,3,5-tetrakis-(carbazol-yl)-4,6-dicyanobenzene (4CzIPN) displayed promising features for photoredox catalysis: a high photoluminescence quantum yield (94.6%), a long life-time at the excited state (5.1 μ s) and a strong green-emission (maximum at 507 nm). Recently, Zhang and coworkers reported the redox properties of this photosensitizer and the given value for the oxidative potential of the photoexcited 4CzIPN ($E_{1/2}^*(4CzIPN/[4CzIPN]^-)=+1.35$ V vs SCE) augured well for a possible photooxidation of alkyl bis(catecholato)silicates ($E_{1/2}(\text{Ox/red})=+0.3$ to $+0.9$ V vs SCE).⁶⁴ We thus decided to assess this reactivity with a series of alkylsilicates and the cheapest photocatalyst 4CzIPN (\$0.06/mmol for carbazole, \$2.2/mmol for tetrafluoroisophthalonitrile)⁶⁵ in both radical synthesis and dual catalysis.

⁶³ H. Uoyama, K. Goushi, K. Shizu, H. Nomura,; C. Adachi, *Nature* **2012**, 492, 234.

⁶⁴ J. Luo, J. Zhang, *ACS Catal.* **2016**, 6, 873.

⁶⁵ In comparison: \$1.3k/mmol for [Ir(dF(CF₃)ppy)₂(bpy)](PF₆), \$110/mmol for Ru(bpy)₃(PF₆)₂. Prices available at <http://www.Sigmaaldrich.com>.



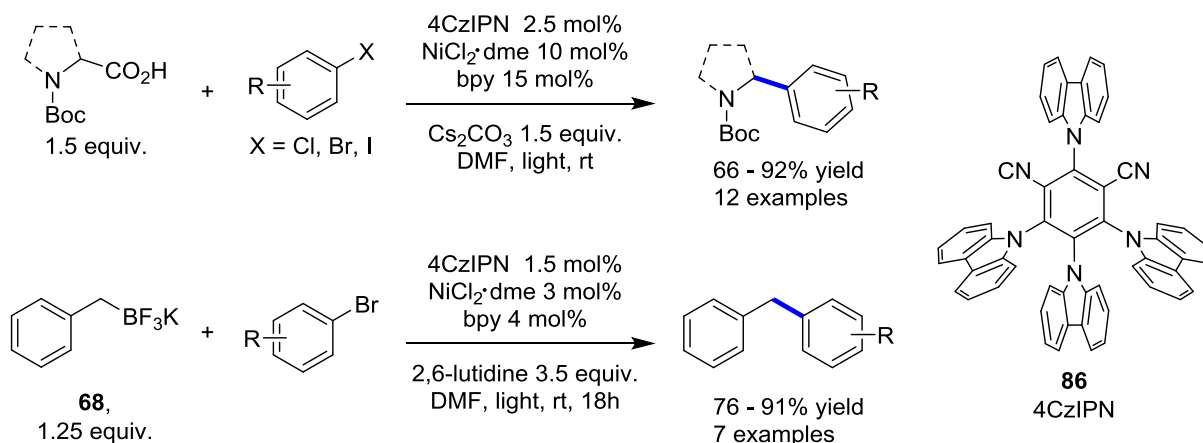
Scheme 49. Structures of carbazolyl dicyanobenzene organic dyes

As it showed in table 2, this organic dye shows photo-physical properties comparable even superior to polypyridine-based transition metal complexes and other organic dyes.

Table 2. Potentials and lifetime of excited state comparison of organic dyes with Ir complex

Entry	Photocatalysts	$E_{1/2}^{\text{red}} (\text{P}^*/\text{P}^-)$ V vs. SCE	Lifetime of excited state
1	Eosin Y	+1.18 V	2.1 ns
2	Fluorescein	+1.21 V	4.2 ns
3	[Ir(dF(CF ₃)ppy) ₂ (bpy)]	+1.32 V	2.28 μs
4	4CzIPN	+1.35 V	5.1 μs
5	Acr ⁺ -Mes (Fukuzumi)	+2.06 V	6 ns

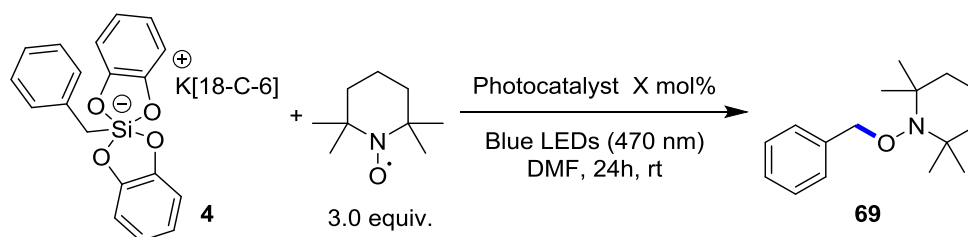
Taking advantage of these remarkable characteristics, Zhang and coworkers illustrated the efficiency of 4CzIPN to oxidize easily α -amino carboxylate and trifluoroborates in dual photoredox/nickel catalyzed transformations. They replaced the ruthenium or the iridium complex by this dye in the cross-coupling reactions of α -amino carboxylates and trifluoroborate salts with aryl halides developed by the group of MacMillan and Molander respectively. The results of this study are quite similar to those published before, and the cross-coupling products were obtained in high yield with nearly the same loading of photocatalyst under blue LEDs irradiation.



Scheme 50. Photoredox/nickel catalysis with organic photoredox catalyst

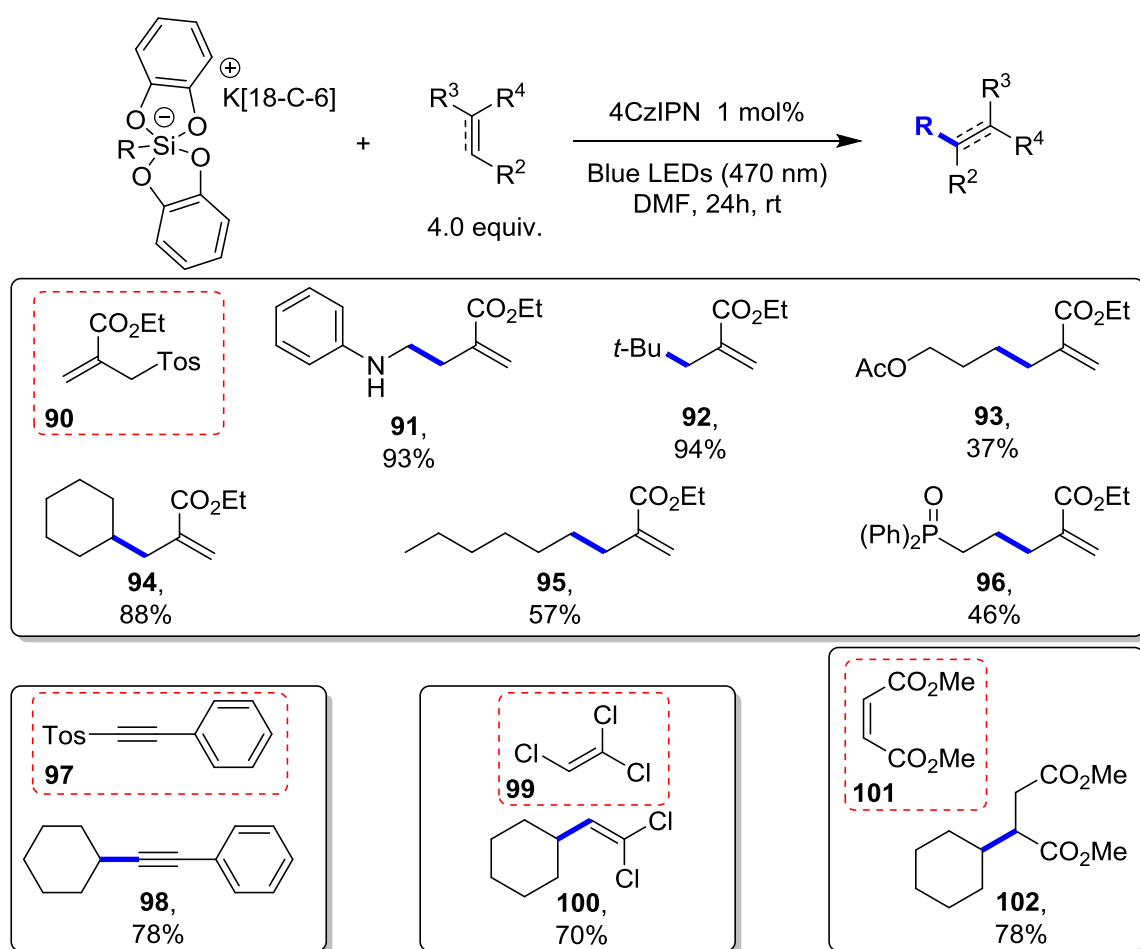
Since our previous work on oxidation of silicate species by organic reagents, our investigations with the Fukuzumi catalyst gave only moderate yields and we were limited only to the generation of stabilized radicals such as benzyl or allyl. We decided to test the photocatalytic activity of 4CzIPN on biscatecholato silicates. Gratifyingly, a very high yield of 92% of TEMPO adduct was obtained in spin trapping experiments (Table 3, entry 2). The reaction was performed in a 0.1 M DMF solution under blue LED irradiation (477 nm) with benzyl precursor **4** (0.3 mmol), TEMPO (0.9 mmol), acting both as radical trap and presumably also as sacrificial electron acceptor, and the organic dye **86** (10 mol%). As a reminder, we reached only a moderate yield of 66% with the Fukuzumi catalyst (Table 3, entry 1). Furthermore, the catalytic loading in 4CzIPN could be diminished down to 1 mol% without any erosion of the yield (Table 3, entry 3). These preliminary results excited our interest in further uses of 4CzIPN.

Table 3. Spin-trapping with TEMPO with benzyl silicate



Entry	Photocatalyst	X mol%	Yield
1	Fukuzumi	10 mol%	66%
2	4CzIPN	10 mol%	92%
3	4CzIPN	1 mol%	94%

We engaged various alkyl biscatecholatosilicates in photocatalytic reactions to explore the range of reactivity (Scheme 51). We first focused on the allylation reaction using the allylsulfone **90** as radical acceptor. The resulting adducts were obtained in excellent yields for stabilized radicals (**91**, **92**) and secondary radical (**94**), to moderate yields (37% for **93**, 57% for **95** and 48% for **96**) for primary radicals **2**, **16** and **18**. Interestingly, silicate **18** furnished the carbon allylation adduct, without fragmentation of the Ph₂PO radical.⁶⁶ Encouraged by these results, we engaged cyclohexylsilicate **19** in various radical reactions like alkynylation (**97**),⁶⁷ vinylation (**99**)⁶⁷ and Giese-type reaction (**101**) leading efficiently to products **98**, **100** and **102**.



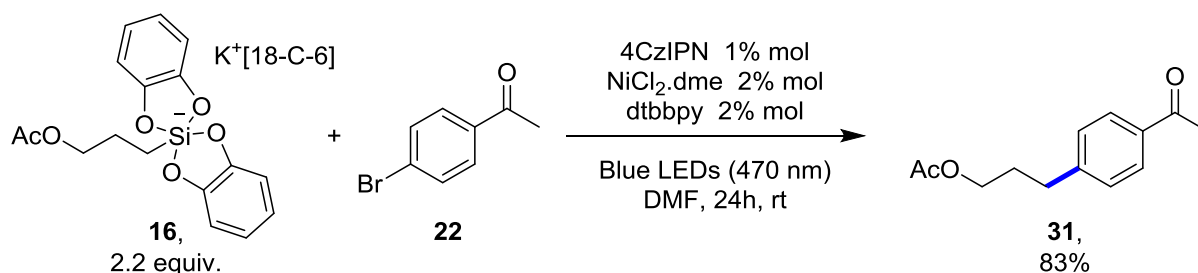
Scheme 51. Scope of intermolecular radical addition

Inspired by the work of Zhang and coworkers, we planned to extend this mixed photoorganic/metallic dual-catalysis to alkylsilicates. Thus, a mixture of 4'-bromoaceto-

⁶⁶ a) D. Leca, L. Fensterbank, E. Lacôte and M. Malacria, *Angew. Chem. Int. Ed.* **2004**, *43*, 4220; b) G. Ouvry, B. Quiclet-Sire and S. Z. Zard, *Angew. Chem. Int. Ed.* **2006**, *45*, 5002.

⁶⁷ A.-P. Schaffner, V. Darmency and P. Renaud, *Angew. Chem. Int. Ed.* **2006**, *45*, 5847.

phenone **22** with acetoxypropylsilicate **16** in the presence of 4CzIPN (1 mol%), NiCl₂.dme (5 mol %) and 4,4'-di-tert-butyl-LED) for 24 hours at rt. Under these conditions, an excellent 81% yield of coupling product **31** was observed. This result was extended and exploited by Christophe Lévêque in the context of his PhD research.⁶⁸



Scheme 52. Preliminary results on photoredox/nickel dual catalysis with 4CzIPN for arylation of silicates

III.C.3. Conclusion

In conclusion, all these results demonstrate that 4CzIPN is as efficient as metal based photocatalysts for the photooxidation of alkyl bis(catecholato)silicates generating stabilized or not primary, secondary and tertiary alkyl radicals. The generated radicals can be engaged efficiently with radical acceptors and also in organic photoredox/nickel dual-catalyzed processes with 4'-bromoacetophenone. Requiring only a low catalytic loading (1 mol%), 4CzIPN opens very exciting perspectives for more sustainable photoredox catalysis.

⁶⁸ C. Lévêque, L. Cheneberg, V. Corcé, C. Ollivier, L. Fensterbank, *Chem. Commun.* **2016**, DOI: 10.1039/C6CC04636C.

Experimental Section – Chapter III

III.C.4. Experimental Section

III.C.4.a. General informations

Unless otherwise noted, reactions were carried out under an argon atmosphere in oven-dried glassware. Methanol was distilled over CaH₂, THF and diethyl ether were distilled over sodium/benzophenone, triethylamine over potassium hydroxide. Catechol was purchased from commercial source and purified by crystallization from toluene followed by sublimation. Reagents and chemicals were purchased from commercial sources and used as received. Infrared (IR) spectra were recorded on a Bruker Tensor 27 (ATR diamond) spectrophotometer. Melting points were determined on a melting point apparatus SMP3 (Stuart scientific) and are uncorrected. ¹H, ¹⁹F, ¹³C NMR spectra were recorded at room temperature at 400, 377 and 100 MHz respectively, on a Bruker AVANCE 400 spectrometer. ²⁹Si NMR spectra were recorded at 119 MHz on a Bruker AVANCE III 600 spectrometer. Chemical shifts (δ) are reported in ppm and coupling constants (J) are given in Hertz (Hz). Abbreviations used for peak multiplicity are: s (singlet); bs (broad singlet); d (doublet); t (triplet); q (quartet); quint (quintet); sept (septet); m (multiplet). Thin layer chromatographies (TLC) were performed on Merck silica gel 60 F 254 and revealed with a UV lamp ($\lambda = 254$ nm) and KMnO₄ staining. Flash Column Chromatographies were conducted on silica Geduran[®] Si 60 Å (40 – 63 μ m). High resolution mass spectrometries were performed on a microTOF (ESI). Photocatalysts were synthesized as described.^{1,2} 1-phenyl-2-*p*-toluenesulfonylethylene,³ 1-phenyl-2-*p*-toluenesulfonylethyne,⁴ allylsulfone **90**, 2-phenylallyl *p*-tolyl sulfone and 2-cyanoallyl *p*-tolyl sulfone⁵ were synthesized as described.

¹ D. Hanss, J. C. Freys, G. Bernardinelli, O. S. Wenger, *Eur. J. Inorg. Chem.* **2009**, 4850.

² M. S. Lowry, J. I. Goldsmith, J. D. Slinker, R. Rohl, R. A. Pascal, G. G. Malliaras, S. Bernhard, *Chem. Mater.* **2005**, *17*, 5712.

³ S. Liang, R.-Y. Zhang, G. Wang, S.-Y. Chen, X.-Q. Yu, *Eur. J. Org. Chem.* **2013**, *2013*, 7050.

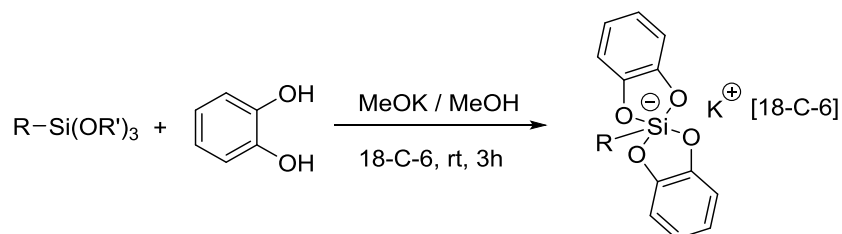
⁴ N. Riddell, W. Tam, *J. Org. Chem.* **2006**, *71*, 1934.

⁵ I. W. Harvey, E. D. Phillips, G. H. Whitham, *Tetrahedron* **1997**, *53*, 6493.

III.C.4.b. General procedures

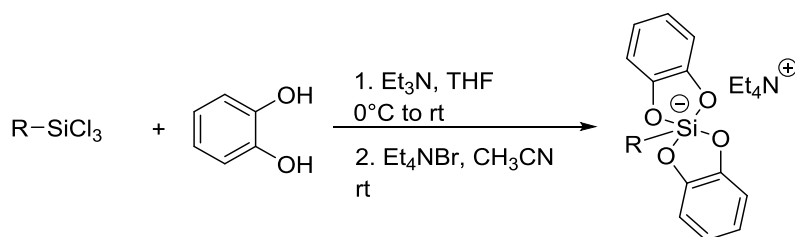
General procedure A for bis-catecholato silicate synthesis

Method A



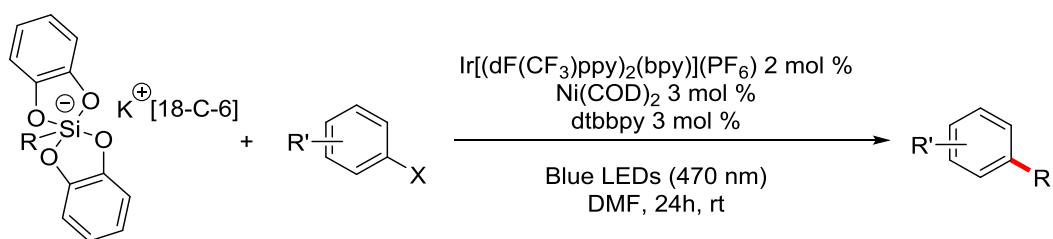
To a stirred solution of catechol (2 eq.) in dry methanol (0.25 M) was added 18-C-6 (1 eq.). After dissolution of the crown ether, the trialkoxy organosilane (1 eq.) was added, followed by a solution of potassium methoxide in methanol (1 eq.). The reaction mixture was stirred for 3 hours and the solvent was removed under reduced pressure. The residue was dissolved in the minimum volume of acetone and diethyl ether was added until a cloudy solution was obtained (scrapping on the edge of the flask could be done to induce crystallization). The flask was placed at $-20^{\circ}C$ overnight. The crystals were collected by filtration, washed with diethyl ether and dried under vacuum to afford [18-C-6] silicate.

Method B



To a stirred solution of catechol (2 eq.) in dry THF (0.1 M) was added triethylamine (4 eq.). The reaction mixture was cooled to $0^{\circ}C$ with an ice bath and organotrichlorosilane (1 eq.) was added dropwise. The mixture was stirred for an hour at $0^{\circ}C$ and an additional hour at room temperature. The triethylamine hydrochloride salt was filtered off and the filtrate was evaporated under reduced pressure. The residue was taken up in acetonitrile (0.3 M) and tetraethylammonium bromide (1 eq.) was added. The mixture was stirred for an hour and the solvent was evaporated under reduced pressure. The solid was taken up in water, filtered, washed with water and dried under high vacuum to afford tetraethylammonium silicate.

General procedure B for photoredox/nickel cross-coupling dual catalysis



To a schlenk flask was added aryl or heteroaryl halide (1 eq., 0.3 mmol), silicate (1.5 eq., 0.45 mmol), $Ir[(dF(CF_3)ppy)_2(bpy)](PF_6)$ (2 mol %, 6 μ mol, 6 mg), and 4,4'-di-*tert*-butyl-2,2'-bipyridine (3 mol %, 9 μ mol, 2.4 mg). The schlenk flask was taken into a glovebox and $Ni(COD)_2$ (3 mol %, 9 μ mol, 2.5 mg) was added. The schlenk flask was sealed with a rubber septum, removed from the glovebox, and evacuated / purged with vacuum / argon three times. Degassed DMF (3 mL) was introduced (followed by the aryl or heteroaryl halide if liquid) and the reaction mixture was irradiated with blue LEDs (477 nm) for 24 hours. The reaction mixture was diluted with diethyl ether (50 mL), washed with saturated $NaHCO_3$ (2 times), brine (2 times), dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the coupling adduct.

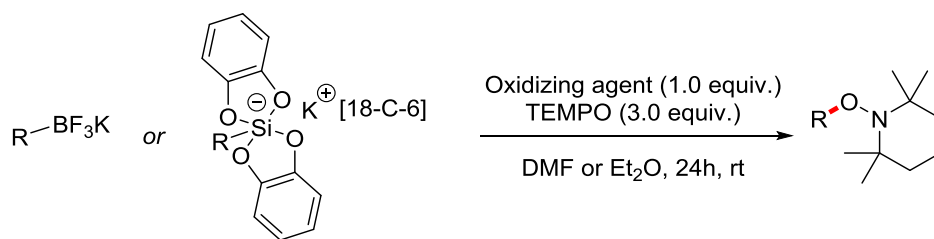
General procedure C for synthesis of organotrifluoroborate salt

All organotrifluoroborate salts were prepared following previously reported procedures.^{6,7}

General procedure D for stoichiometric oxidation of organo-trifluoroborate and organo-bis(catecholato)silicate

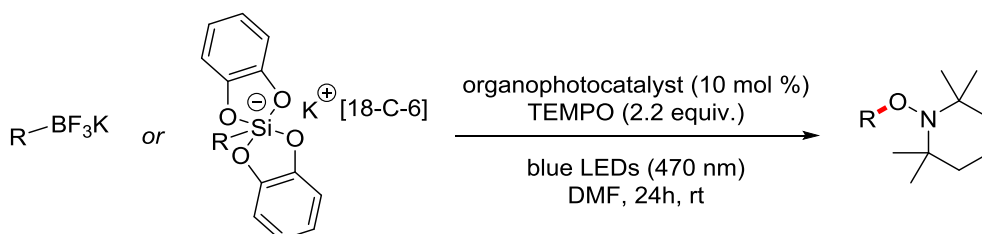
⁶ G. Sorin, R. Martinez-Mallorquin, Y. Contie, A. Baralle, M. Malacria, J.-P. Goddard, L. Fensterbank, *Angew. Chem. Int. Ed.*, **2010**, *49*, 8721.

⁷ Huang, H.; Jia, K.; Chen, Y. *Angew. Chem. Int. Ed.*, **2015**, *54*, 1881.



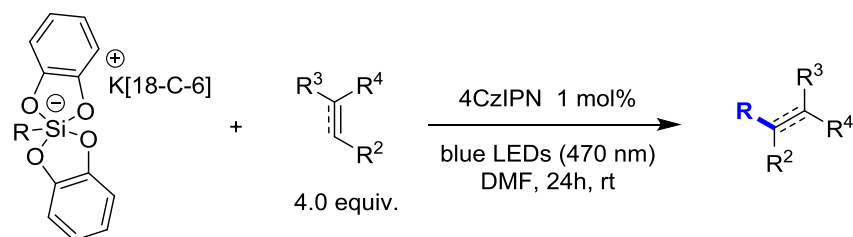
To a schlenk flask was added the appropriate trifluoroborate salt or silicate salt (0.3 mmol), the oxidizing agent (0.3 mmol) and TEMPO (0.9 mmol, 141 mg). The schlenk flask was sealed with a rubber septum, and evacuated / purged with vacuum / argon three times. Degassed DMF or diethyl ether (3 mL) was introduced followed by two freeze-pump-thaw cycles. The reaction mixture was stirred at room temperature for 24h under an argon atmosphere. The reaction mixture was diluted with diethyl ether (50 mL), washed with water (2 times), brine (2 times), dried over MgSO_4 and evaporated under reduced pressure. The reaction residue was purified by flash column chromatography on silica gel.

General procedure E for photooxidation of organo-trifluoroborate or organo-bis(catecholato)silicate



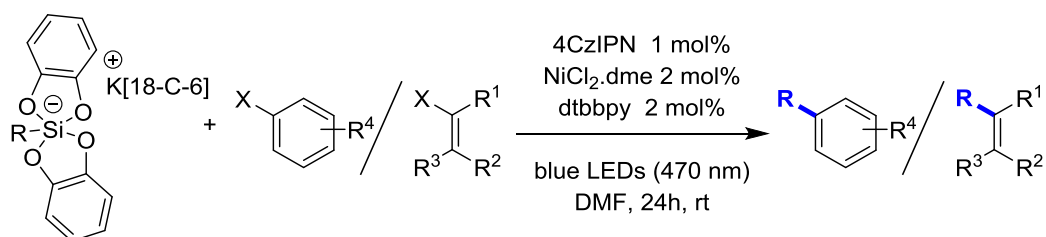
To a schlenk flask was added the appropriate trifluoroborate salt or silicate salt (0.3 mmol), the organophotocatalyst (0.03 mmol) and TEMPO (0.66 mmol, 103 mg). The schlenk flask was sealed with a rubber septum, and evacuated / purged with vacuum / argon three times. Degassed DMF (3 mL) was introduced followed by two freeze-pump-thaw cycles. The reaction mixture was stirred at room temperature under blue LEDs irradiation for 24h under an argon atmosphere. The reaction mixture was diluted with diethyl ether (50 mL), washed with saturated NaHCO_3 (2 times), brine (2 times), dried over MgSO_4 and evaporated under reduced pressure. The reaction residue was purified by flash column chromatography on silica gel.

General procedure F for photooxidation of bis(catecholato)silicate and addition on radical acceptors



To a schlenk flask was added potassium [18-C-6] bis(catecholato) silicate (1 eq., 0.3 mmol), 4CzIPN (1 mol %, 3 μ mol, 2.4 mg) and the desired acceptor (4 eq., 1.2 mmol) (liquid alkenes were added with the solvent). DMF was added (3 mL). The reaction mixture was degassed by argon bubbling for 20 minutes and irradiated with blue LED (477 nm) for 24 hours. The reaction mixture was diluted with diethyl ether (50 mL), washed with saturated aqueous NaHCO_3 (2 times), brine (2 times), dried over MgSO_4 and evaporated under reduced pressure. The crude product was purified by flash column chromatography.

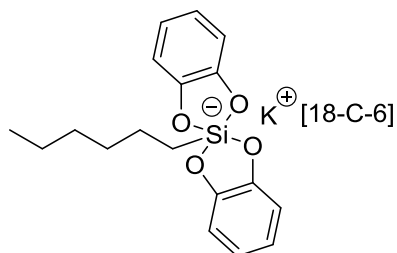
General procedure G for photooxidation of bis(catecholato)silicate and addition on radical acceptors



To a schlenk flask was added aryl, heteroaryl halide or alkenyl halide (1 eq., 0.3 mmol), appropriate silicate (1.5 eq., 0.45 mmol), 4CzIPN (1 mol%, 3 μ mol), and 4,4'-di-tert-butyl-2,2'-bipyridine (2 mol %, 6 μ mol). The schlenk flask was taken into a glovebox and $\text{NiCl}_2 \cdot \text{dme}$ (2 mol %, 6 μ mol) was added. The schlenk flask was sealed with a rubber septum, removed from the glovebox, and evacuated/purged with vacuum/argon three times. Degassed DMF (3 mL) was introduced (followed by the aryl or heteroaryl halide if liquid) and the reaction mixture was irradiated with blue LEDs (470 nm) for 24 hours. The reaction mixture was diluted with diethyl ether (50 mL), washed with saturated NaHCO_3 (2 times), brine (2 times), dried over MgSO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the coupling adduct.

III.C.4.c. Compound characterizations

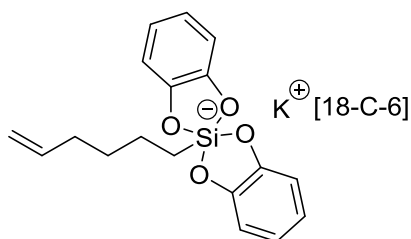
Potassium [18-Crown-6] bis(catecholato)-hexylsilicate (2)



Silicate **2** was synthesized as described following the general procedure A, method A. The spectroscopic data are in agreement with those reported in the literature.²²

¹H NMR (400 MHz, Methanol-*d*₄): δ 8.29 – 8.17 (m, 4H), 8.15 – 8.04 (m, 4H), 5.09 (s, 24H), 2.91 – 2.82 (m, 2H), 2.79 – 2.66 (m, 6H), 2.36 (t, *J* = 6.9 Hz, 3H), 2.27 – 2.16 (m, 2H). **¹³C NMR** (100 MHz, Methanol-*d*₄): δ 151.1 (4 C), 119.2 (4 C), 111.4 (4 C), 71.2 (12 C), 34.2, 32.9, 25.4, 23.6, 18.5, 14.5. **²⁹Si NMR** (119 MHz, Methanol-*d*₄): δ -75.6.

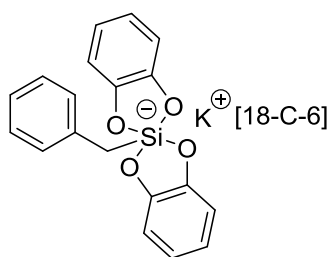
Potassium [18-Crown-6] bis(catecholato)-hexenylsilicate (3)



Silicate **3** was synthesized as described following the general procedure A, method A. The spectroscopic data are in agreement with those reported in the literature.²²

¹H NMR (400 MHz, Methanol-*d*₄): δ 6.71 – 6.62 (m, 4H), 6.58 – 6.52 (m, 4H), 5.69 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 4.89 – 4.82 (m, 1H), 4.80 – 4.75 (m, 1H), 3.54 (s, 24H), 1.96 – 1.85 (m, 2H), 1.39 – 1.20 (m, 4H), 0.71 – 0.62 (m, 2H). **¹³C NMR** (100 MHz, Methanol-*d*₄): δ 151.1 (4 C), 140.5, 119.2 (4 C), 114.1, 111.4 (4 C), 71.2 (12 C), 34.8, 33.9, 25.1, 18.3. **²⁹Si NMR** (119 MHz, Methanol-*d*₄): δ -75.7.

Potassium [18-Crown-6] bis(catecholato)-benzylsilicate (4)

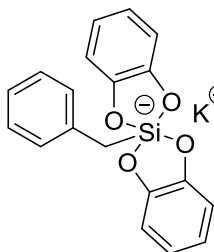


Silicate **4** was synthesized as described following the general procedure A, method A. The spectroscopic data are in agreement with those reported in the literature.²²

¹H NMR (400 MHz, Methanol-*d*₄): δ 7.09 – 6.75 (m, 5H), 6.66 – 6.60 (m, 4H), 6.56 – 6.49 (m, 4H), 3.55 (s, 24H), 2.14 (s, 2H). **¹³C**

NMR (100 MHz, Methanol-*d*₄): δ 150.9 (4 C), 142.8, 129.8 (2 C), 128.2 (2 C), 123.9, 119.3 (4 C), 111.5 (4 C), 71.3 (12 C), 27.9. **²⁹Si NMR** (119 MHz, Methanol-*d*₄): δ -80.90.

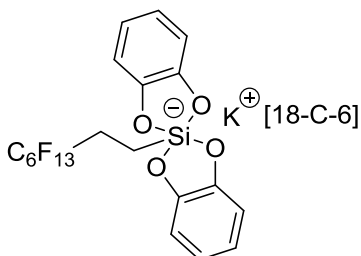
Potassium [18-Crown-6] bis(catecholato)-isobutylsilicate (5)



Silicate **5** was synthesized as described following the general procedure A, method A. The spectroscopic data are in agreement with those reported in the literature.²²

¹H NMR (400 MHz, Methanol-*d*₄): δ 6.73 – 6.65 (m, 4H), 6.60 – 6.52 (m, 4H), 3.57 (s, 24H), 1.80 (dp, *J* = 13.2, 6.6 Hz, 1H), 0.82 (d, *J* = 6.6 Hz, 6H), 0.67 (d, *J* = 6.8 Hz, 2H). **¹³C NMR** (100 MHz, Methanol-*d*₄): δ 151.1 (4 C), 119.2 (4 C), 111.5 (4 C), 71.3 (12 C), 29.4, 26.8 (2 C), 25.7. **²⁹Si NMR** (119 MHz, Methanol-*d*₄): δ -76.14.

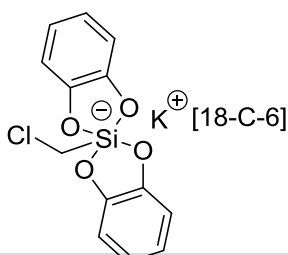
Potassium [18-Crown-6] bis(catecholato)-1H, 1H, 2H, 2H-perfluorooctylsilicate (6)



Silicate **6** was synthesized as described following the general procedure A, method A. The spectroscopic data are in agreement with those reported in the literature.²²

¹H NMR (400 MHz, Methanol-*d*₄): δ 6.75 – 6.68 (m, 4H), 6.62 – 6.56 (m, 4H), 3.56 (s, 24H), 2.26 – 1.90 (m, 2H), 0.90 – 0.73 (m, 2H). **¹³C NMR** (100 MHz, Methanol-*d*₄): δ 150.7 (4 C), 119.6 (4 C), 111.6 (4 C), 71.3 (12 C), 27.7 (t), 7.0. **¹⁹F NMR** (376 MHz, Methanol-*d*₄): δ -82.43 (tt, *J* = 10.3, 2.7 Hz, 3F), -117.03 – -117.59 (m, 2F), -122.81 – -123.09 (m, 2F), -123.67 – -124.06 (m, 2F), -124.32 – -124.87 (m, 2F), -126.78 – -127.54 (m, 2F). **²⁹Si NMR** (119 MHz, Methanol-*d*₄): δ -78.51.

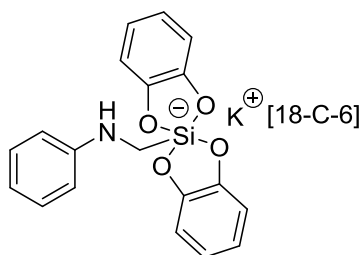
Potassium [18-Crown-6] bis(catecholato)-chloromethylsilicate (7)



Silicate **7** was synthesized as described following the general procedure A, method A. The spectroscopic data are in agreement with those reported in the literature.²²

^1H NMR (400 MHz, Methanol- d_4): δ 6.78 – 6.67 (m, 4H), 6.65 – 6.45 (m, 4H), 3.56 (s, 24H), 2.80 (s, 2H). **^{13}C NMR** (100 MHz, Methanol- d_4): δ 150.8 (4 C), 119.6 (4 C), 111.6 (4 C), 71.3 (12 C), 31.3. **^{29}Si NMR** (119 MHz, Methanol- d_4): δ -85.57.

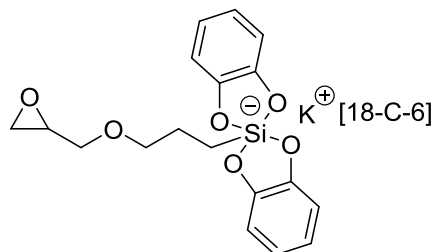
Potassium [18-Crown-6] bis(catecholato)-anilinomethylsilicate (**8**)



Silicate **8** was synthesized as described following the general procedure A, method A. The spectroscopic data are in agreement with those reported in the literature.²²

^1H NMR (400 MHz, Methanol- d_4): δ 7.27 – 6.90 (m, 2H), 6.87 – 6.71 (m, 4H), 6.70 – 6.54 (m, 4H), 6.55 – 6.39 (m, 3H), 3.56 (s, 24H), 2.52 (s, 2H), NH is missing. **^{13}C NMR** (100 MHz, Methanol- d_4): δ 152.2, 150.8 (4 C), 129.8 (2 C), 119.7 (4 C), 117.0, 113.4 (2 C), 111.9 (4 C), 71.3 (12 C), 34.1. **^{29}Si NMR** (119 MHz, Methanol- d_4): δ -50.08 and -81.36.

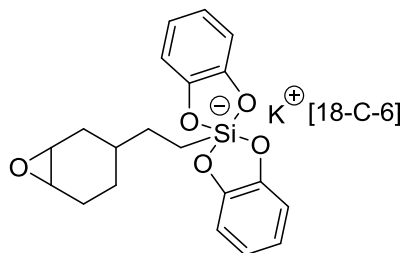
Potassium [18-Crown-6] bis(catecholato)-(3-glycidyoxypropyl)silicate (**9**)



Silicate **9** was synthesized as described following the general procedure A, method A. The spectroscopic data are in agreement with those reported in the literature.²²

^1H NMR (400 MHz, Methanol- d_4): δ 6.74 – 6.61 (m, 4H), 6.61 – 6.49 (m, 4H), 3.57 (s, 24H), 3.53 (dd, J = 11.6, 3.1 Hz, 1H), 3.40 – 3.32 (m, 2H), 3.20 (dd, J = 11.6, 6.0 Hz, 1H), 3.03 – 2.96 (m, 1H), 2.68 (dd, J = 5.1, 4.2 Hz, 1H), 2.49 (dd, J = 5.1, 2.7 Hz, 1H), 1.71 – 1.53 (m, 2H), 0.71 – 0.60 (m, 2H). **^{13}C NMR** (100 MHz, Methanol- d_4): δ 151.0 (4 C), 119.3 (4 C), 111.5 (4 C), 75.6, 72.4, 71.3 (12 C), 51.8, 44.9, 25.6, 13.9. **^{29}Si NMR** (119 MHz, Methanol- d_4): δ -76.13.

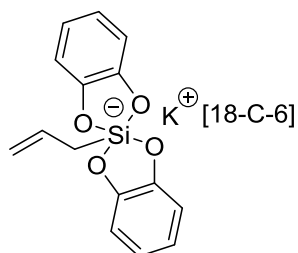
Potassium [18-Crown-6] bis(catecholato)-[2-(7-oxabicyclo[4.1.0]hept-3-yl)ethyl]silicate (10)



Silicate **10** was synthesized as described following the general procedure A, method A. The spectroscopic data are in agreement with those reported in the literature.²²

¹H NMR (400 MHz, Methanol-*d*₄): δ 6.81 – 6.63 (m, 4H), 6.61 – 6.50 (m, 4H), 3.58 (s, 24H), 3.13 – 2.99 (m, 2H), 2.08 – 1.84 (m, 2H), 1.75 – 1.53 (m, 1H), 1.47 – 1.34 (m, 1H), 1.34 – 1.11 (m, 4H), 1.12 – 0.97 (m, 1H), 0.95 – 0.70 (m, 1H), 0.71 – 0.60 (m, 2H). **¹³C NMR** (100 MHz, Methanol-*d*₄): δ 151.1 (4 C), 119.2 (4 C), 111.5 (4 C), 71.2 (12 C), 54.6, 54.1, 53.6, 53.4, 36.2, 33.5, 32.5, 32.5, 31.7, 31.7, 27.5, 26.4, 25.3, 24.4, 15.4, 15.1. **²⁹Si NMR** (119 MHz, Methanol-*d*₄): δ -75.75.

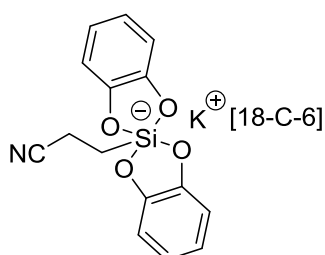
Potassium [18-Crown-6] bis(catecholato)-allylsilicate (11)



Silicate **11** was synthesized as described following the general procedure A, method A. The spectroscopic data are in agreement with those reported in the literature.²²

¹H NMR (400 MHz, Methanol-*d*₄): δ 6.69 – 6.65 (m, 4H), 6.59 – 6.53 (m, 4H), 5.77 (ddt, *J* = 16.9, 10.0, 8.0 Hz, 1H), 4.65 (ddt, *J* = 17.0, 2.8, 1.5 Hz, 1H), 4.50 (ddt, *J* = 10.0, 2.5, 1.2 Hz, 1H), 3.56 (s, 24H), 1.64 (dt, *J* = 8.0, 1.4 Hz, 2H). **¹³C NMR** (100 MHz, Methanol-*d*₄): δ 151.0 (4 C), 137.9, 119.3 (4 C), 111.8, 111.5 (4 C), 71.3 (12 C), 26.2. **²⁹Si NMR** (119 MHz, Methanol-*d*₄): δ -80.24.

Potassium [18-Crown-6] bis(catecholato)-2-cyanoethylsilicate (12)

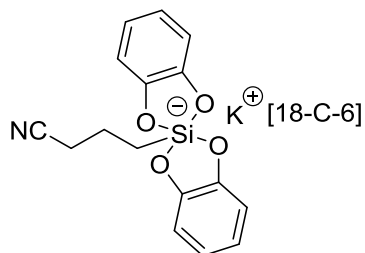


Silicate **12** was synthesized as described following the general procedure A, method A. The spectroscopic data are in agreement with those reported in the literature.²²

¹H NMR (400 MHz, Methanol-*d*₄): δ 6.80 – 6.66 (m, 4H), 6.63 – 6.55 (m, 4H), 3.54 (s, 24H), 2.32 – 2.24 (m, 2H), 1.04 – 0.95 (m,

2H). ^{13}C NMR (100 MHz, Methanol- d_4): δ 150.6 (4 C), 123.4, 119.7 (4 C), 111.7 (4 C), 71.2 (12 C), 14.5, 13.0. ^{29}Si NMR (119 MHz, Methanol- d_4): δ -80.17.

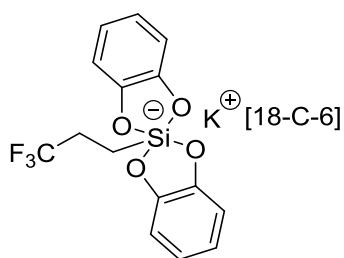
Potassium [18-Crown-6] bis(catecholato)-3-cyanopropylsilicate (**13**)



Following the general procedure A with 3-cyanopropyltriethoxysilane (5 mmol, 1.16 mL), catechol (10 mmol, 1.10 mg), 18-Crown-6 (5 mmol, 1.32 g) and potassium methoxide (5 mmol, 1.4 mL of a 3.56 M solution in methanol) in 20 mL of dry methanol. The crude product was purified according the general procedure to afford **13** (2.76 g, 90%) as a white solid.

M.p. 167.6°C. ^1H NMR (600 MHz, Methanol- d_4): δ 6.69 (dd, J = 5.6, 3.5 Hz, 4H), 6.57 (dd, J = 5.7, 3.4 Hz, 4H), 3.54 (s, 24H), 2.29 (t, J = 7.2 Hz, 2H), 1.69 – 1.60 (m, 2H), 0.82 – 0.75 (m, 2H). ^{13}C NMR (151 MHz, Methanol- d_4): δ 150.9 (4 C), 121.6, 119.5 (4 C), 111.6 (4 C), 71.2 (12 C), 22.5, 20.2, 17.6. ^{29}Si NMR (119 MHz, Methanol- d_4): δ -77.6. **IR** (neat): 3039, 2952, 2870, 2236, 1702, 1599, 1484, 1353, 1245, 1227, 1098, 1011, 953, 820, 737 cm^{-1} . **HRMS** (ESI-) calc. for $[\text{C}_{16}\text{H}_{14}\text{NO}_4\text{Si}]^-$ 312.0698; found 312.0699.

Potassium [18-Crown-6] bis(catecholato)-3,3,3-trifluoropropylsilicate (**14**)

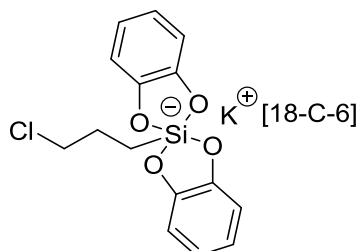


Following the general procedure A with 3,3,3-trifluoropropyltrimethoxysilane (5 mmol, 956 μL), catechol (10 mmol, 1.10 mg), 18-Crown-6 (5 mmol, 1.32 g) and potassium methoxide (5 mmol, 1.4 mL of a 3.56 M solution in methanol) in 20 mL of dry methanol. The crude product was purified according the general procedure to afford **14** (2.56 g, 80%) as a white solid.

M.p. 177.7°C. ^1H NMR (600 MHz, Methanol- d_4): δ 6.70 (dd, J = 5.6, 3.5 Hz, 4H), 6.59 (dd, J = 5.7, 3.4 Hz, 4H), 3.54 (s, 24H), 2.06 – 1.95 (m, 2H), 0.83 – 0.76 (m, 2H). ^{13}C NMR (151 MHz, Methanol- d_4): δ 150.8 (4 C), 130.6 (q, J = 275.6 Hz), 119.6 (4 C), 111.6 (4 C), 71.2 (12 C), 30.5 (q, J = 28.6 Hz), 9.6. ^{19}F NMR (376 MHz, Methanol- d_4): δ -70.5 (t, J = 11.1 Hz). ^{29}Si NMR (119 MHz, Methanol- d_4): δ -78.6. **IR** (neat): 3040, 2907, 2871, 1597, 1485, 1353,

1245, 1201, 1098, 1057, 820, 739 cm^{-1} . **HRMS** (ESI-) calc. for $[\text{C}_{15}\text{H}_{12}\text{F}_3\text{O}_4\text{Si}]^-$ 341.0462; found 341.0460.

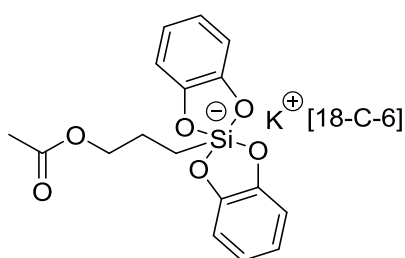
Potassium [18-Crown-6] bis(catecholato)-3-chloropropylsilicate (**15**)



Following the general procedure A with 3-chloropropyltrimethoxysilane (5 mmol, 910 μL), catechol (10 mmol, 1.10 mg), 18-Crown-6 (5 mmol, 1.32 g) and potassium methoxide (5 mmol, 1.4 mL of a 3.56 M solution in methanol) in 20 mL of dry methanol. The crude product was purified according the general procedure to afford **15** (2.96 g, 95%) as a white solid.

M.p. 147.7°C. **^1H NMR** (600 MHz, Methanol- d_4): δ 6.68 (dd, $J = 5.6, 3.4$ Hz, 4H), 6.56 (dd, $J = 5.6, 3.4$ Hz, 4H), 3.53 (s, 24H), 3.37 (t, $J = 7.2$ Hz, 2H), 1.80 – 1.69 (m, 2H), 0.79 – 0.69 (m, 2H). **^{13}C NMR** (151 MHz, Methanol- d_4): δ 150.9 (4 C), 119.4 (4 C), 111.5 (4 C), 71.2 (12 C), 48.8, 29.6, 15.8. **^{29}Si NMR** (119 MHz, Methanol- d_4): δ -76.9. **IR** (neat): 3044, 2894, 2872, 1598, 1485, 1351, 1243, 1104, 952, 817, 741 cm^{-1} . **HRMS** (ESI-) calc. for $[\text{C}_{15}\text{H}_{14}\text{ClO}_4\text{Si}]^-$ 321.0355; found 321.0367.

Potassium [18-Crown-6] bis(catecholato)-acetoxypopylsilicate (**16**)

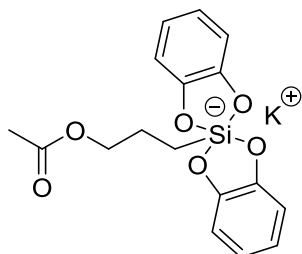


Following the general procedure A with acetoxypopyltrimethoxysilane (10 mmol, 1.76 mL), catechol (20 mmol, 2.20 mg), 18-Crown-6 (10 mmol, 2.64 g) and potassium methoxide (5 mmol, 2.8 mL of a 3.56 M solution in methanol) in 40 mL of dry methanol. The crude product was purified according the general procedure to afford **16** (5.88 g, 91%) as a white solid.

M.p. 160°C. **^1H NMR** (400 MHz, Methanol- d_4): δ 6.6 (dd, $J = 5.6, 3.5$ Hz, 4H), 6.6 (dd, $J = 5.6, 3.4$ Hz, 4H), 3.9 (t, $J = 7.1$ Hz, 2H), 3.5 (s, 24H), 1.9 (s, 3H), 1.7 – 1.5 (m, 2H), 0.7 – 0.6 (m, 2H). **^{13}C NMR** (101 MHz, Methanol- d_4): δ 173.1, 150.9 (4 C), 119.3 (4 C), 111.5 (4 C), 71.2 (12 C), 68.6, 24.9, 20.8, 13.9. **^{29}Si NMR** (119 MHz, Methanol- d_4): δ -76.6. **IR** (neat):

3016, 2950, 2882, 1735, 1597, 1486, 1351, 1242, 1105, 955, 819, 749, 725 cm^{-1} . **HRMS** (ESI-) calc. for $[\text{C}_{17}\text{H}_{17}\text{O}_6\text{Si}]^-$ 345.0800; found 345.0813.

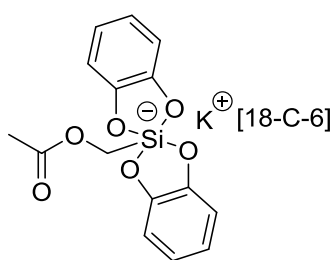
Potassium bis(catecholato)-acetoxypropylsilicate (**16'**)



Following the general procedure A with acetoxypropyltrimethoxysilane (5 mmol, 1.05 mL), catechol (10 mmol, 1.10 g) and potassium methoxide (5 mmol, 1.4 mL of a 3.56 M solution in methanol) in 20 mL of dry methanol. The crude product was purified according the general procedure to afford **16'** (1.55 g, 62%*) as a white solid. *Silicate without [18-Crown-6] crystallizes with a molecule of acetone.

M.p. 160°C. $^1\text{H NMR}$ (400 MHz, Methanol- d_4): δ 6.68 (dd, $J = 5.6, 3.5$ Hz, 4H), 6.56 (dd, $J = 5.6, 3.5$ Hz, 4H), 3.88 (t, $J = 7.0$ Hz, 2H), 1.92 (s, 3H), 1.66 – 1.56 (m, 2H), 0.7 – 0.65 (m, 2H). $^{13}\text{C NMR}$ (101 MHz, Methanol- d_4): δ 173.3, 150.8 (4 C), 119.4 (4 C), 111.5 (4 C), 68.6, 24.9, 20.8, 13.7. **IR** (neat): 3016, 2950, 2882, 1735, 1597, 1486, 1351, 1242, 1105, 955, 819, 749, 725 cm^{-1} . **HRMS** calc. for $[\text{C}_{17}\text{H}_{17}\text{O}_6\text{Si}]^-$ 345.0800; found 345.0813.

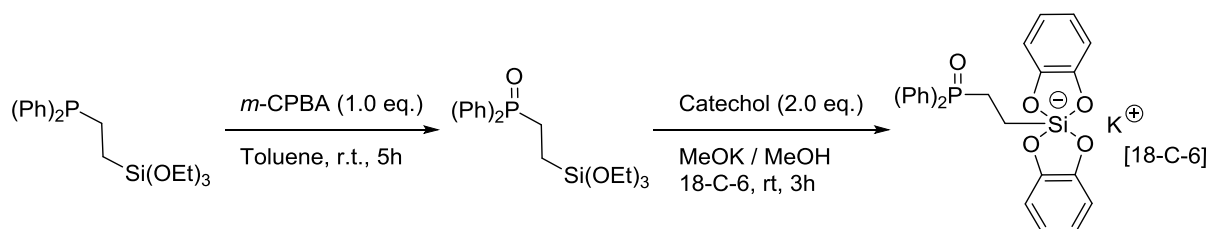
Potassium [18-Crown-6] bis(catecholato)-acetoxymethylsilicate (**17**)



Following the general procedure A with acetoxymethyltriethoxysilane (5 mmol, 1.13 mL), catechol (10 mmol, 1.10 mg), 18-Crown-6 (5 mmol, 1.32 g) and potassium methoxide (5 mmol, 1.4 mL of a 3.56 M solution in methanol) in 20 mL of dry methanol. The crude product was purified according the general procedure to afford **17** (2.92 g, 94%) as a white solid.

M.p. 110°C. $^1\text{H NMR}$ (600 MHz, Methanol- d_4): δ 6.68 (dd, $J = 5.6, 3.4$ Hz, 4H), 6.57 (dd, $J = 5.8, 3.5$ Hz, 4H), 3.82 (s, 2H), 3.53 (s, 24H), 1.83 (s, 3H). $^{13}\text{C NMR}$ (151 MHz, Methanol- d_4): δ 174.1, 150.9 (4 C), 119.5 (4 C), 111.7 (4C), 71.2 (12 C), 58.1, 20.7. $^{29}\text{Si NMR}$ (119 MHz, Methanol- d_4): δ -85.8 (t, $J = 5.7$ Hz). **IR** (neat): 3028, 2901, 2868, 1719, 1599, 1487, 1348, 1243, 1102, 963, 830, 737 cm^{-1} . **HRMS** (ESI-) calc. for $[\text{C}_{15}\text{H}_{13}\text{O}_6\text{Si}]^-$ 317.0487; found 317.0495.

Potassium [18-Crown-6] bis(catecholato)-2-(diphenylphosphine oxide)ethylsilicate (18)



a) Oxidation of diphenyl(2-(triethoxysilyl)ethyl)phosphine

The oxidation step has been realized according to a previous reported procedure.⁸ To a stirred solution of diphenyl(2-(triethoxysilyl)ethyl)phosphine (6 mmol, 2.15 mL) in 50 mL of distilled toluene was added, at 0°C under argon, a solution of *m*-chloroperbenzoic acid (6 mmol, 1.04 g) in 15 mL of distilled toluene. After complete addition the reaction mixture was warmed to room temperature and stirred for 5h. The reaction mixture was quenched with 50 mL of saturated Na₂CO₃ solution. The organic phase was then washed with 50 mL of saturated Na₂CO₃ solution (2 times), 50 mL of saturated NaCl solution and dried over MgSO₄. Toluene was then removed under reduced pressure to give a white waxy solid. The crude material was dissolved in the minimum volume of DCM and crystallized by slow addition of pentane. Finally, the diphenyl(2-(triethoxysilyl)ethyl)phosphine oxide was collected by filtration and washed with pentane (1.28 g, 54%).

M.p. 72°C. **IR** (neat): 3053, 2973, 2924, 1482, 1167, 1064, 758, 748, 729, 692 cm⁻¹. **¹H NMR** (400 MHz, Acetone-d₆): δ 7.86 – 7.81 (m, 4H), 7.58 – 7.49 (m, 6H), 3.80 (q, *J* = 6.9 Hz, 6H), 2.34 – 2.27 (m, 2H), 1.17 (t, *J* = 6.9 Hz, 9H), 0.78 – 0.71 (m, 2H). **¹³C NMR** (150 MHz, Acetone-d₆): δ 135.37 (d, *J* = 95.1 Hz, 2 C), 132.4 (d, *J* = 2.5 Hz, 2 C), 131.8 (d, *J* = 9.1 Hz, 4 C), 129.6 (d, *J* = 11.1 Hz, 4 C), 59.2, 23.7 (d, *J* = 71.0 Hz), 18.9 (3 C), 2.13 (d, *J* = 6.4 Hz). **³¹P NMR** (162 MHz, Acetone-d₆): δ 29.92. **²⁹Si NMR** (119 MHz, Acetone-d₆): δ -47.22 (d, *J* = 29.8 Hz). **HRMS** calc. for [C₂₀H₂₉NaO₄PSi]⁺ 415.1465; found 415.1461.

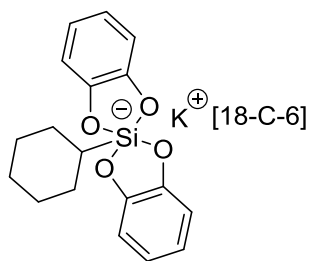
⁸ R. A. Komoroski, A. J. Magistro, P. P. Nicholas, *Inorg. Chem.*, **1986**, 25, 3917.

b) Silicate synthesis

Following the general procedure A, method A with 2-(diphenylphosphine oxide) ethylsilane (2.5 mmol, 981 mg), catechol (5 mmol, 550.6 mg), 18-Crown-6 (2.5 mmol, 660 mg) and potassium methoxide (2.5 mmol, 700 μ L of a 3.56 M solution in methanol) in 10 mL of dry methanol at room temperature. The crude product was purified according the general procedure to afford **18** (1.41 g, 72%) as a white solid.

M.p. 229°C. **IR** (neat): 2990, 2895, 1482, 1238, 1103, 826, 734, 723 cm^{-1} . **^1H NMR** (400 MHz, Methanol- d_4): δ 7.57 – 7.47 (m, 6H), 7.42 – 7.39 (m, 4H), 6.71 – 6.70 (m, 4H), 6.60 – 6.59 (m, 4H), 3.52 (s, 24H), 2.38 – 2.33 (m, 2H), 0.83 – 0.79 (m, 2H). **^{13}C NMR** (100 MHz, Methanol- d_4): δ 150.8 (4 C), 133.3 (d, $J = 97.5$ Hz, 2 C), 133.0 (d, $J = 2.6$ Hz, 2 C), 131.8 (d, $J = 9.3$ Hz, 4 C), 129.8 (d, $J = 11.6$ Hz, 4 C), 119.6 (4 C), 111.7 (4 C), 71.2 (12 C), 25.1 (d, $J = 70.4$ Hz), 8.2 (d, $J = 7.3$ Hz, 2 C). **^{31}P NMR** (162 MHz, Methanol- d_4): δ 40.12. **^{29}Si NMR** (119 MHz, Methanol- d_4): δ -78.10 (d, $J = 34.8$ Hz). **HRMS** calc. for $[\text{C}_{26}\text{H}_{22}\text{O}_5\text{PSi}]^-$ 473.0980; found 473.0964.

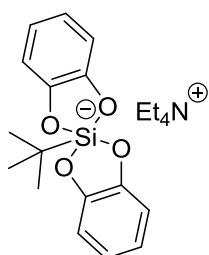
Potassium [18-Crown-6] bis(catecholato)-cyclohexylsilicate (19)



Silicate **19** was synthesized as described following the general procedure A, method A. The spectroscopic data are in agreement with those reported in the literature.²²

^1H NMR (400 MHz, Methanol- d_4): δ 6.72 – 6.60 (m, 4H), 6.57 – 6.49 (m, 4H), 3.53 (s, 24H), 1.69 – 1.48 (m, 5H), 1.34 – 1.02 (m, 5H), 0.84 (tt, $J = 12.2, 3.1$ Hz, 1H). **^{13}C NMR** (100 MHz, Methanol- d_4): δ 151.5 (4 C), 119.0 (4 C), 111.2 (4 C), 71.2 (12 C), 31.4, 29.6 (2 C), 29.4 (2 C), 28.3. **^{29}Si NMR** (119 MHz, Methanol- d_4): δ -77.93.

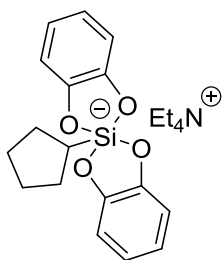
Tetraethylammonium bis(catecholato)-tertbutylsilicate (20)



Silicate **20** was synthesized as described following the general procedure A, method B. The spectroscopic data are in agreement with those reported in the literature.²²

¹H NMR (600 MHz, Acetonitrile-*d*₃): δ 6.61 – 6.54 (m, 4H), 6.51 – 6.45 (m, 4H), 3.09 (q, *J* = 7.3 Hz, 8H), 1.23 – 1.09 (m, 12H), 0.77 (s, 9H). **¹³C NMR** (150 MHz, Acetonitrile-*d*₃): δ 152.6 (4 C), 118.1 (4 C), 110.2 (4 C), 53.0 (t, *J* = 3 Hz, 4 C), 29.6 (3 C), 24.0, 7.6 (4 C). **²⁹Si NMR** (119 MHz, Acetonitrile-*d*₃): δ -76.21.

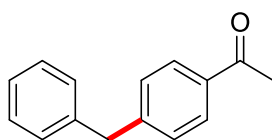
Tetraethylammonium bis(catecholato)-cyclopentylsilicate (**21**)



Silicate **21** was synthesized as described following the general procedure A, method B. The spectroscopic data are in agreement with those reported in the literature.²²

¹H NMR (600 MHz, DMSO-*d*₆): δ 6.55 – 6.48 (m, 4H), 6.46 – 6.40 (m, 4H), 3.17 (q, *J* = 7.3 Hz, 8H), 1.50 – 1.42 (m, 2H), 1.39 – 1.27 (m, 4H), 1.27 – 1.19 (m, 2H), 1.17 – 1.09 (m, 12H), 0.86 (tt, *J* = 10.1, 7.8 Hz, 1H). **¹³C NMR** (150 MHz, DMSO-*d*₆): δ 150.9 (4 C), 116.9 (4 C), 109.2 (4 C), 51.4 (t, *J* = 3 Hz, 4 C), 29.8, 28.6 (2 C), 25.9 (2 C), 7.0 (4 C). **²⁹Si NMR** (119 MHz, DMSO-*d*₆): δ -75.61.

4'-(Benzyl)acetophenone (**23**)

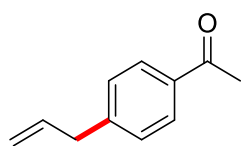


Following general procedure B with benzylsilicate **4** (0.45 mmol, 287 mg) and 4'-bromoacetophenone **22** (0.3 mmol, 60 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether, 95/5) to afford **23** as a colorless oil (56 mg, 88%). The spectroscopic data are in agreement with those reported in the literature.⁹

¹H NMR (400 MHz, CDCl₃): δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.32 – 7.17 (m, 7H), 4.04 (s, 2H), 2.58 (s, 3H). **¹³C NMR** (100 MHz, CDCl₃): δ 197.8, 146.8, 140.1, 135.3, 129.1 (2 C), 129.0 (2 C), 128.7 (4 C), 126.40, 41.9, 26.6. **IR** (neat): 2937, 1678, 1602, 1265 cm⁻¹.

⁹ N. Riddell, W. Tam, *J. Org. Chem.* **2006**, *71*, 1934.

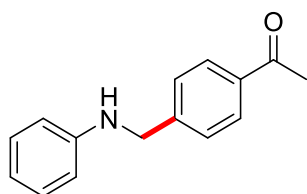
4'-(Allyl)acetophenone (**24**)



Following general procedure B with allylsilicate **11** (0.45 mmol, 265 mg) and 4'-bromoacetophenone **22** (0.3 mmol, 60 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether, 98/2) to afford **24** as a colorless oil (41 mg, 86%). The spectroscopic data are in agreement with those reported in the literature.¹⁰

¹H NMR (400 MHz, CDCl₃): δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 5.95 (ddt, *J* = 17.1 Hz, 10.5 Hz, 6.7 Hz, 1H), 5.13 – 5.08 (m, 2H), 3.45 (d, *J* = 6.7 Hz, 2H), 2.59 (s, 3H). **¹³C NMR** (100 MHz, CDCl₃): δ 197.8, 145.8, 136.3, 135.3, 128.8 (2 C), 128.6 (2 C), 116.7, 40.1, 26.6. **IR** (neat): 3050, 1680, 1604, 1356, 1266 cm⁻¹.

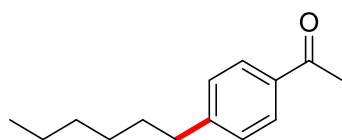
4'-(Anilinomethyl)acetophenone (**25**)



Following general procedure B with anilinomethylsilicate **8** (0.45 mmol, 294 mg) and 4'-bromoacetophenone **22** (0.3 mmol, 60 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether, 80/20) to afford **25** as a colorless oil (62 mg, 91%). The spectroscopic data are in agreement with those reported in the literature.¹¹

¹H NMR (400 MHz, CDCl₃): δ 7.93 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.17 – 7.15 (m, 2H), 6.75 – 6.71 (m, 1H), 6.66 – 6.60 (m, 2H), 4.42 (s, 2H), 4.16 (s, 1H), 2.59 (s, 3H). **¹³C NMR** (100 MHz, CDCl₃): δ 197.7, 147.7, 145.2, 136.2, 129.3 (2 C), 128.7 (2 C), 127.3 (2 C), 117.9, 112.9 (2 C), 47.9, 26.6. **IR** (neat): 3321, 1669, 1597, 1510 cm⁻¹.

4'-(Hexyl)acetophenone (**26**)



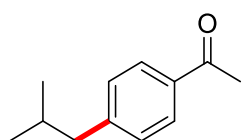
Following general procedure B with hexylsilicate **2** (0.45 mmol, 285 mg) and 4'-bromoacetophenone **22** (0.3 mmol, 60 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether, 99/1) to afford **26** as a colorless oil (53 mg, 85%). The spectroscopic data are in agreement with those reported in the literature.¹²

¹⁰ A. M. Echavarren, J. K. Stille, *J. Am. Chem. Soc.* **1987**, *109*, 5478.

¹¹ G.-N. Wang, T.-H. Zhu, S.-Y. Wang, T.-Q. Wei, S.-J. Ji, *Tetrahedron* **2014**, *70*, 8079.

¹H NMR (400 MHz, CDCl₃): δ 7.87 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 2.68 – 2.64 (m, 2H), 2.58 (s, 3H), 1.67 – 1.58 (m, 2H), 1.38 – 1.26 (m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃): δ 198.0, 149.0, 135.1, 128.7 (2 C), 128.6 (2 C), 36.1, 31.8, 31.2, 29.0, 26.7, 22.7, 14.2. **IR** (neat): 2900, 1681, 1605, 1265 cm⁻¹.

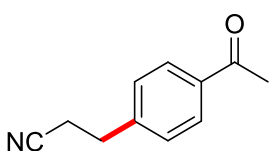
4'-(Isobutyl)acetophenone (**27**)



Following general procedure B with isopropylsilicate **5** (0.45 mmol, 272 mg) and 4'-bromoacetophenone **22** (0.3 mmol, 60 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether, 98/2) to afford **27** as a colorless oil (39 mg, 75%). The spectroscopic data are in agreement with those reported in the literature.¹³

¹H NMR (400 MHz, CDCl₃): δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.23 (d, *J* = 8.3 Hz, 2H), 2.58 (s, 3H), 2.53 (d, *J* = 7.2 Hz, 2H), 1.93 – 1.87 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 6H). **¹³C NMR** (100 MHz, CDCl₃): δ 198.0, 147.7, 135.1, 129.4 (2 C), 128.4 (2 C), 45.5, 30.2, 29.7, 22.5 (2 C). **IR** (neat): 2909, 1680, 1605, 1265 cm⁻¹.

4'-(2-Cyanoethyl)acetophenone (**28**)



Following general procedure B with 2-cyanoethylsilicate **12** (0.45 mmol, 271 mg) and 4'-bromoacetophenone **22** (0.3 mmol, 60 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether, 1/1) to afford **28** as a colorless oil (36 mg, 69%). The spectroscopic data are in agreement with those reported in the literature.¹⁴

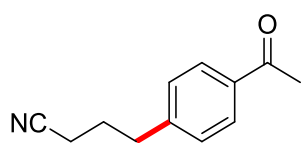
¹H NMR (400 MHz, CDCl₃): δ 7.93 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 3.01 (t, *J* = 7.3 Hz, 2H), 2.65 (t, *J* = 7.3 Hz, 2H), 2.58 (s, 3H). **¹³C NMR** (100 MHz, CDCl₃): δ 197.6, 143.3, 136.2, 129.0 (2 C), 128.6 (2 C), 118.7, 31.4, 26.6, 19.0. **IR** (neat): 2910, 2245, 1675, 1607, 1266 cm⁻¹.

¹² A. Fernandes, C. Romão, C. Rosa, V. Vieira, A. Lopes, P. Silva, A. Maçanita, *Eur. J. Org. Chem.* **2004**, 4877.

¹³ E. V. Bellale, D. S. Bhalerao, K. G. Akamanchi, *J. Org. Chem.* **2008**, *73*, 9473.

¹⁴ M. Amatore, C. Gosmini, J. Périchon, *J. Org. Chem.* **2006**, *71*, 6130.

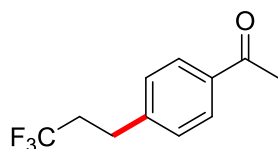
4'-(3-Cyanopropyl)acetophenone (**29**)



Following general procedure B with 2-cyanoethylsilicate **13** (0.45 mmol, 277 mg) and 4'-bromoacetophenone **22** (0.3 mmol, 60 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether, 1/1) to afford **29** as a colorless oil (48 mg, 85%). The spectroscopic data are in agreement with those reported in the literature.¹⁵

¹H NMR (400 MHz, CDCl₃): δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 2.86 – 2.82 (m, 2H), 2.58 (s, 3H), 2.33 (t, *J* = 7.0 Hz, 2H), 2.0 (dd, *J* = 7.5 Hz, 7.0 Hz, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 197.6, 145.3, 135.6, 128.8 (2 C), 128.6 (2 C), 119.1, 34.3, 26.5, 26.5, 16.4. **IR** (neat): 2905, 2258, 1675, 1605, 1266 cm⁻¹.

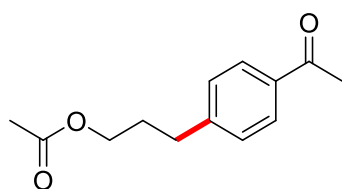
4'-(3,3,3-Trifluoropropyl)acetophenone (**30**)



Following general procedure B with 3,3,3-trifluoropropylsilicate **14** (0.45 mmol, 290 mg) and 4'-bromoacetophenone **22** (0.3 mmol, 60 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether, 99/1 then 95/5) to afford **30** as a colorless oil (52 mg, 80%).

¹H NMR (400 MHz, CDCl₃): δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 2.95 – 2.91 (m, 2H), 2.59 (s, 3H), 2.47 – 2.35 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 197.6, 144.4, 135.8, 128.8 (2 C), 128.5 (2 C), 126.5 (q, *J* = 275 Hz), 35.1 (q, *J* = 28 Hz), 28.2 (q, *J* = 3 Hz), 26.5. **¹⁹F NMR** (376 MHz, CDCl₃): δ -66.57. **IR** (neat): 2871, 1677, 1607, 1266 cm⁻¹.

4'-(Acetoxypropyl)acetophenone (**31**)

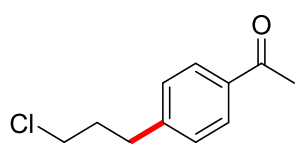


Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and 4'-bromoacetophenone **22** (0.3 mmol, 60 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether, 99/1 then 95/5) to afford **31** as a colorless oil (56 mg, 85%).

¹⁵ S. Sase, M. Jaric, A. Metzger, V. Malakhov, P. Knochel, *J. Org. Chem.* **2008**, *73*, 7380.

¹H NMR (400 MHz, CDCl₃): δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 4.08 (t, *J* = 6.5 Hz, 2H), 2.76 – 2.72 (m, 2H), 2.57 (s, 3H), 2.04 (s, 3H), 2.01 – 1.94 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 197.7, 171.0, 147.0, 135.3, 128.6 (2 C), 128.6 (2 C), 63.5, 32.2, 29.8, 26.5, 20.9. **IR** (neat): 2900, 1735, 1679, 1606, 1233 cm⁻¹. **HRMS** calc for [C₁₃H₁₆NaO₃]⁺ 243.0992; found 243.0999.

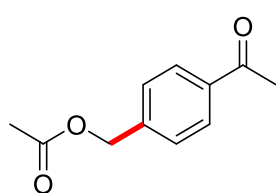
4'-(3-Chloropropyl)acetophenone (**32**)



Following general procedure B with chloropropylsilicate **15** (0.45 mmol, 282 mg) and 4'-bromoacetophenone **22** (0.3 mmol, 60 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether, 80/20) to afford **32** as a colorless oil (42 mg, 71%). The spectroscopic data are in agreement with those reported in the literature.¹⁶

¹H NMR (400 MHz, CDCl₃): δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 3.52 (t, *J* = 6.4 Hz, 2H), 2.86 – 2.82 (m, 2H), 2.58 (s, 3H), 2.13 – 2.07 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 197.8, 146.5, 135.5, 128.8 (2 C), 128.7 (2 C), 44.1, 33.6, 32.8, 26.6. **IR** (neat): 2935, 1678, 1605, 1358, 1265 cm⁻¹.

4'-(Acetoxymethyl)acetophenone (**33**)

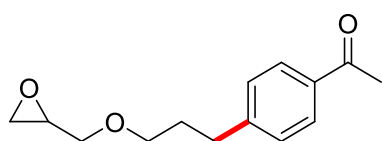


Following general procedure B with acetoxymethylsilicate **17** (0.45 mmol, 279 mg) and 4'-bromoacetophenone **22** (0.3 mmol, 60 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether, 99/1 then 95/5) to afford **33** as a colorless oil (38 mg, 66%).

¹H NMR (400 MHz, CDCl₃): δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 5.15 (s, 2H), 2.59 (s, 3H), 2.12 (s, 3H). **¹³C NMR** (100 MHz, CDCl₃): δ 197.6, 170.6, 141.2, 136.8, 128.6 (2 C), 127.9 (2 C), 65.4, 26.6, 20.9. **IR** (neat): 2905, 2855, 1736, 1681, 1264, 1224 cm⁻¹. **HRMS** calc for [C₁₁H₁₂NaO₃]⁺ 215.0673; found 215.0679.

¹⁶ X.-Q. Li, W.-K. Wang, C. Zhang, *Adv. Synth. Catal.* **2009**, 351, 2342.

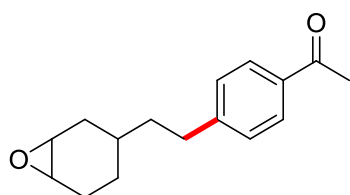
4'-(3-Glycidyoxypropyl)acetophenone (**34**)



Following general procedure B with 3-glycidyoxypropylsilicate **9** (0.45 mmol, 239 mg) and 4'-bromoacetophenone **22** (0.3 mmol, 60 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether, 95/5) to afford **34** as a colorless oil (29 mg, 40%).

¹H NMR (400 MHz, CDCl₃): δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 3.73 (dd, *J* = 11.5 Hz, 2.9 Hz, 1H), 3.57 – 3.42 (m, 2H), 3.36 (dd, *J* = 11.5 Hz, 5.9 Hz, 1H), 3.21 – 3.07 (m, 1H), 2.85 – 2.64 (m, 3H), 3.60 (dd, *J* = 5.0 Hz, 2.7 Hz, 1H), 2.58 (s, 3H), 1.92 (ddt, *J* = 12.7 Hz, 7.6 Hz, 6.3 Hz, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 197.8, 147.7, 135.1, 128.7 (2 C), 128.5 (2 C), 71.6, 70.3, 50.8, 44.2, 32.3, 30.9, 26.5. **IR** (neat): 2905, 1678, 1605, 1266, 1106 cm⁻¹. **HRMS** calc for [C₁₄H₁₈NaO₃]⁺ 257.1148; found 257.1155.

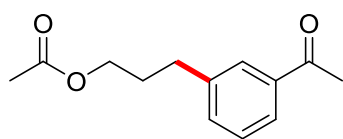
4'-(2-(7-Oxabicyclo-[4.1.0]hept-3-yl)ethyl)acetophenone (**35**)



Following general procedure B with 2-(7-oxabicyclo[4.1.0]hept-3-yl)ethylsilicate **10** (0.45 mmol, 303 mg) and 4'-bromoacetophenone **22** (0.3 mmol, 60 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether, 80/20) to afford a 45/55 mixture of diastereoisomers of **35** as a colorless oil (48 mg, 65%).

¹H NMR (400 MHz, CDCl₃): δ 7.88 – 7.85 (m, 4H), 7.26 – 7.21 (m, 4H), 3.20 – 3.14 (m, 4H), 2.69 – 2.66 (m, 4H), 2.60 (s, 6H), 2.25 – 1.99 (m, 4H), 1.89 – 1.51 (m, 10H), 1.44 – 1.37 (m, 2H), 1.25 – 0.95 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 197.8 (197.8), 148.4 (148.3), 135.0 (135.0), 128.5 (128.5), 128.5 (128.5), 53.0 (52.5), 51.8 (51.7), 38.1 (37.8), 33.3 (33.0), 32.1 (31.8), 30.6 (29.3), 27.0 (25.1), 26.5, 24.3 (23.5). **IR** (neat): 2935, 1671, 1604, 1568, 1298 cm⁻¹. **HRMS** calc for [C₁₆H₂₀NaO₂]⁺ 267.1365; found 267.1135.

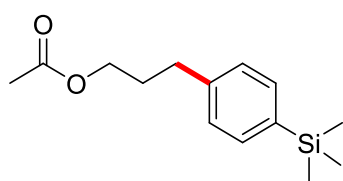
3-(3-Acetylphenyl)propyl acetate (37)



Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and 3'-bromoacetophenone (0.3 mmol, 35 μ l). The crude product was purified by flash column chromatography (pentane/diethyl ether, 90/10) to afford **37** as a colorless oil (53 mg, 80%).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.80 – 7.71 (m, 2H), 7.40 – 7.34 (m, 2H), 4.08 (t, $J = 6.5$ Hz, 2H), 2.76 – 2.72 (m, 2H), 2.59 (s, 3H), 2.04 (s, 3H), 2.01 – 1.94 (m, 2H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 198.2, 171.1, 141.7, 137.3, 133.2, 128.6, 128.0, 126.3, 63.6, 32.0, 30.0, 26.6, 20.9. **IR** (neat): 2941, 1734, 1684, 1601, 1232, 839 cm^{-1} . **HRMS** calc. for $[\text{C}_{13}\text{H}_{16}\text{NaO}_3]^+$ 243.0992; found 243.0992

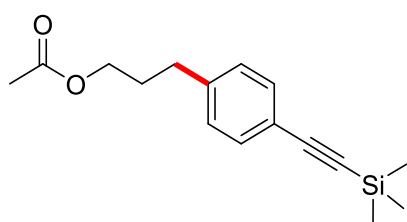
3-(4-(Trimethylsilyl)phenyl)propyl acetate (38)



Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and (4-bromophenyl)trimethylsilane (0.3 mmol, 59 μ l). The crude product was purified by flash column chromatography (pentane/diethyl ether, 90/10) to afford **38** as a colorless oil (54 mg, 72%).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.46 (d, $J = 8.0$ Hz, 2H), 7.19 (d, $J = 8.0$ Hz, 2H), 4.10 (t, $J = 6.6$ Hz, 2H), 2.71 – 2.67 (m, 2H), 2.06 (s, 3H), 1.99 – 1.91 (m, 2H), 0.27 (s, 9H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 171.1, 141.8, 137.7, 133.5 (2 C), 127.9 (2 C), 63.6, 32.1, 30.0, 20.9, -1.1 (3 C). **IR** (neat): 2936, 1739, 1601, 1233 cm^{-1} . **HRMS** calc. for $[\text{C}_{14}\text{H}_{22}\text{NaO}_2\text{Si}]^+$ 273.1281; found 273.1277.

3-(4-((Trimethylsilyl)ethynyl)phenyl)propyl acetate (39)

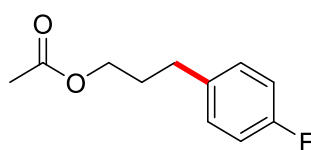


Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and ((4-bromophenyl)ethynyl)trimethylsilane (0.3 mmol, 76 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether, 95/5) to afford **39** as

a colorless oil (54 mg, 72%).

¹H NMR (400 MHz, CDCl₃): δ 7.38 (d, *J* = 8.3 Hz, 2H), 7.11 (d, *J* = 8.3 Hz, 2H), 4.06 (t, *J* = 6.5 Hz, 2H), 2.69 – 2.65 (m, 2H), 2.04 (s, 3H), 1.97 – 1.89 (m, 2H), 0.24 (s, 9H). **¹³C NMR** (100 MHz, CDCl₃): δ 171.0, 141.8, 132.0 (2 C), 128.3 (2 C), 120.8, 105.1, 93.6, 63.6, 32.21, 29.9, 20.9, 0.0 (3 C). **IR** (neat): 2944, 2156, 1738, 1608, 1233, 839 cm⁻¹. **HRMS** calc. for [C₁₆H₂₂NaO₂Si]⁺ 297.1281; found 297.1281.

3-(4-Fluorophenyl)propyl acetate (**40**)

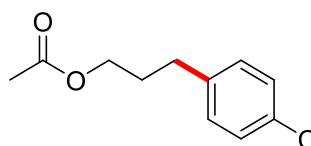


Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and 1-bromo-4-fluorobenzene (0.3 mmol, 33 μl).

The crude product was purified by flash column chromatography (pentane/diethyl ether, 80/20) to afford **40** as a colorless oil (45 mg, 75%).

¹H NMR (400 MHz, CDCl₃): δ 7.16 – 7.08 (m, 2H), 7.00 – 6.92 (m, 2H), 4.07 (t, *J* = 6.5 Hz, 2H), 2.68 – 2.64 (m, 2H), 2.05 (s, 3H), 1.95 – 1.89 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 171.1, 161.3 (d, *J* = 243.7 Hz), 136.7 (d, *J* = 3.2 Hz), 129.7 (d, *J* = 7.8 Hz, 2 C), 115.1 (d, *J* = 21.1 Hz, 2 C), 63.6, 31.3, 30.3, 20.9. **¹⁹F NMR** (376 MHz, CDCl₃): δ -117.48. **IR** (neat): 2930, 1733, 1600, 1509, 1218, 1036 cm⁻¹. **HRMS** calc. for [C₁₁H₁₃FN₂O₂]⁺ 219.0797; found 219.0792

3-(4-Chlorophenyl)propyl acetate (**41**)

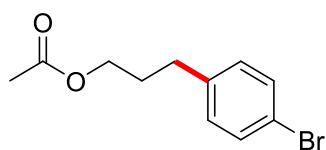


Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and 1-bromo-4-chlorobenzene (0.3 mmol, 58 mg).

The crude product was purified by flash column chromatography (pentane/diethyl ether, 90/10) to afford **41** as a colorless oil (51 mg, 80%).

¹H NMR (400 MHz, CDCl₃): δ 7.25 (d, *J* = 8.6 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 1H), 4.07 (t, *J* = 6.5 Hz, 2H), 2.68 – 2.64 (m, 2H), 2.05 (s, 3H), 1.97 – 1.89 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 171.0, 139.6, 131.7, 129.7 (2 C), 128.5 (2 C), 63.6, 31.5, 30.1, 21.9. **IR** (neat): 2936, 1736, 1597, 1231, 836 cm⁻¹. **HRMS** calc. for [C₁₁H₁₃ClNaO₂]⁺ 235.0496; found 235.0505.

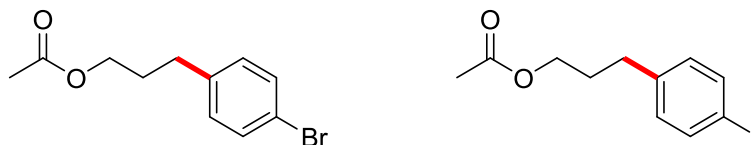
3-(4-Bromophenyl)propyl acetate (**42**)



Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and 1,4-dibromobenzene (0.3 mmol, 71 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether, 90/10) to afford **42** as a colorless oil (52 mg, 67%).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.40 (d, $J = 8.4$ Hz, 2H), 7.06 (d, $J = 8.4$ Hz, 2H), 4.07 (t, $J = 6.6$ Hz, 2H), 2.66 – 2.62 (m, 2H), 2.05 (s, 3H), 1.97 – 1.89 (m, 2H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 171.1, 140.1, 131.5 (2 C), 130.1 (2 C), 119.8, 63.6, 31.6, 30.0, 20.9. **IR** (neat): 2940, 1735, 1591, 1299, 1231 cm^{-1} . **HRMS** calc. for $[\text{C}_{11}\text{H}_{13}\text{BrNaO}_2]^+$ 278.9991; found 278.9991

3-(4-Bromophenyl)propyl acetate (**42**) and 3-(4-iodophenyl)propyl acetate (**43**)

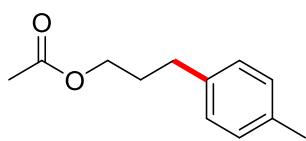


Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and 1-bromo-4-iodobenzene (0.3 mmol, 85 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether, 90/10) to afford a 10:1 mixture of **42** and **43** as a colorless oil (43 mg, 48%).

3-(4-Iodophenyl)propyl acetate (**43**)

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.60 (d, $J = 8.4$ Hz, 2H), 6.95 (d, $J = 8.4$ Hz, 2H), 4.07 (t, $J = 6.6$ Hz, 2H), 2.66 – 2.63 (m, 2H), 2.05 (s, 3H), 1.96 – 1.86 (m, 2H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 171.1, 140.8, 137.5 (2 C), 130.5 (2 C), 119.8, 63.6, 31.7, 30.0, 20.9. **IR** (neat): 2940, 1735, 1591, 1299, 1231 cm^{-1} . **HRMS** calc. for $[\text{C}_{11}\text{H}_{13}\text{INaO}_2]^+$ 326.9852; found 326.9847.

3-(*p*-Tolyl)propyl acetate (**44**)

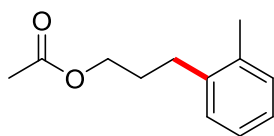


Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and 4-bromotoluene (0.3 mmol, 51 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether, 90/10) to afford **44** as a colorless oil (42 mg, 73%).

¹H NMR (400 MHz, CDCl₃): δ 7.12 – 7.07 (m, 4H), 4.09 (t, *J* = 6.6 Hz, 2H), 2.67 – 2.64 (m, 2H), 2.33 (s, 3H), 2.06 (s, 3H), 1.96 – 1.92 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 171.1, 138.1, 135.4, 129.1 (2 C), 128.2 (2 C), 63.8, 31.7, 30.3, 21.0 (2 C).* **IR** (neat): 2920, 1736, 1232, 1036 cm⁻¹. **HRMS** calc. for [C₁₂H₁₆NaO₂]⁺ 215.1043; found 215.1045.

*signal for both CH₃ (verified by HSQC)

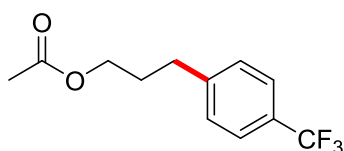
3-(*o*-Tolyl)propyl acetate (**45**)



Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and 2-bromotoluene (0.3 mmol, 36 μl). The crude product was purified by flash column chromatography (pentane/diethyl ether, 95/5) to afford **45** as a colorless oil (44 mg, 76%).

¹H NMR (400 MHz, CDCl₃): δ 7.17 – 7.11 (m, 4H), 4.13 (t, *J* = 6.5 Hz, 2H), 2.71 – 2.67 (m, 2H), 2.33 (s, 3H), 2.08 (s, 3H), 1.97 – 1.90 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 171.1, 139.4, 135.8, 130.2, 128.7, 126.1, 126.0, 64.0, 29.5, 29.0, 20.9, 19.2. **IR** (neat): 2942, 1736, 1601, 1231 cm⁻¹. **HRMS** calc. for [C₁₂H₁₆NaO₂]⁺ 215.1043; found 215.1035.

3-(4-(Trifluoromethyl)phenyl)propyl acetate (**46**)

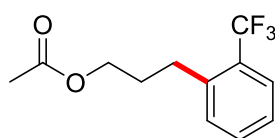


Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and 4-bromobenzotrifluoride (0.3 mmol, 41 μl). The crude product was purified by flash column chromatography (pentane/diethyl ether, 90/10) to afford **46** as a colorless oil (70 mg, 94%).

¹H NMR (400 MHz, CDCl₃): δ 7.54 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 4.09 (t, *J* = 6.5 Hz, 2H), 2.77 – 2.73 (m, 2H), 2.05 (s, 3H), 1.99 – 1.94 (m, 2H). **¹³C NMR** (100 MHz,

CDCl₃): δ 171.1, 145.3, 128.7, 128.5 (q, $J = 32.3$ Hz, 2 C), 125.4 (q, $J = 3.9$ Hz, 2 C), 124.3 (q, $J = 270$ Hz), 63.5, 32.1, 29.9, 21.9. ¹⁹F NMR (376 MHz, CDCl₃): δ -62.4. IR (neat): 2922, 1737, 1584, 1232, 845 cm⁻¹. HRMS calc. for [C₁₂H₁₃F₃NaO₂]⁺ 269.0760; found 269.0752.

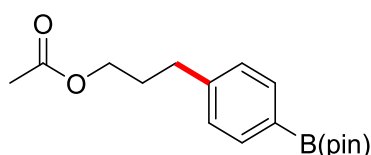
3-(2-(Trifluoromethyl)phenyl)propyl acetate (47)



Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and 2-bromobenzotrifluoride (0.3 mmol, 42 μ l). The crude product was purified by flash column chromatography (pentane/diethyl ether, 95/5) to afford **47** as a colorless oil (51 mg, 69%).

¹H NMR (400 MHz, Chloroform-*d*) δ 7.62 (dd, $J = 7.9, 1.3$ Hz, 1H), 7.47 (td, $J = 7.6, 1.3$ Hz, 1H), 7.36 – 7.27 (m, 2H), 4.13 (t, $J = 6.4$ Hz, 2H), 2.86 (ddd, $J = 9.7, 6.2, 1.3$ Hz, 2H), 2.06 (s, 3H), 2.01 – 1.91 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 171.1, 140.1, 131.8 (d, $J = 0.8$ Hz), 131.0, 128.6 (q, $J = 29.8$ Hz), 126.2, 126.0 (q, $J = 5.8$ Hz), 124.6 (q, $J = 5.8$ Hz), 63.8, 30.4, 29.1 (d, $J = 1.7$ Hz), 20.9. ¹⁹F NMR (376 MHz, CDCl₃): δ -59.7. IR (neat): 2940, 1737, 1608, 1311, 1111, 1030 cm⁻¹. HRMS calc. for [C₁₂H₁₃F₃LiO₂]⁺ 253.1022; found 253.1019

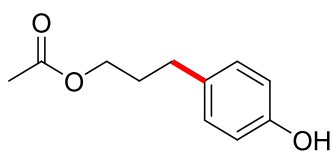
4-Acetoxypropylphenylboronic pinacol ester (48)



Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and 4-Bromophenylboronic acid pinacol ester (0.3 mmol, 85 mg). The crude product was purified by flash column chromatography (pentane/EtOAc, 90/10) to afford **48** as a brown oil (49 mg, 53%).

¹H NMR (400 MHz, CDCl₃): δ 7.74 (d, $J = 8.0$ Hz, 2H), 7.20 (d, $J = 8.0$ Hz, 2H), 4.08 (t, $J = 6.6$ Hz, 2H), 2.72 – 2.68 (m, 2H), 2.05 (s, 3H), 1.97 – 1.94 (m, 2H), 1.34 (s, 12H). ¹³C NMR (100 MHz, CDCl₃): δ 171.1, 144.6, 135.0 (2 C), 127.8 (2 C), 83.7 (2 C), 63.8, 32.4, 30.1, 24.9 (4 C), 21.0. ¹¹B NMR (128 MHz, CDCl₃): δ 30.6. IR (neat): 2960, 1737, 1611, 1357, 1235, 657 cm⁻¹. HRMS calc. for [C₁₇H₂₅BNaO₄]⁺ 327.1741; found 327.1754

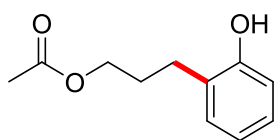
3-(4-Hydroxyphenyl)propyl acetate (**49**)



Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and 4-bromophenylboronic acid pinacol ester (0.3 mmol, 85 mg). After 24h of reaction, the crude reaction mixture was filtered through a plug of celite, washing with THF (15 mL). The filtrate was concentrated by rotary evaporation. The resulting solution of DMF was diluted with THF (10 mL) and cooled to 0°C in an ice water bath. To the cold stirring solution was added 1M NaOH (1.5 mL, 5 equiv.) and 30% aq. H₂O₂ (171 μL, 5 equiv.). After 30 min the mixture was diluted with water (10 mL) and diethyl ether (10 mL) and neutralized by addition of 1M HCl (2.5 mL). The organic layer was collected and washed with water (2 x 10 mL), brine (2 x 10 mL), dried over MgSO₄ and evaporated under reduced pressure. The crude product was purified by flash column chromatography (pentane/EtOAc, 90/10) to afford **49** as a brown oil (41 mg, 69%). The spectroscopic data are in agreement with those reported in the literature.¹⁷

¹H NMR (400 MHz, CDCl₃): δ 7.04 (d, *J* = 8.5 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 5.19 (s, 1H), 4.08 (t, *J* = 6.6 Hz, 2H), 2.63 – 2.59 (m, 2H), 2.06 (s, 3H), 1.95 – 1.89 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 171.5, 153.9, 133.2, 129.4 (2 C), 115.3 (2 C), 63.9, 31.2, 30.4, 21.0. IR (neat): 3356, 2978, 1707, 1595, 1514, 1227, 1035 cm⁻¹.

3-(2-Hydroxyphenyl)propyl acetate (**50**)



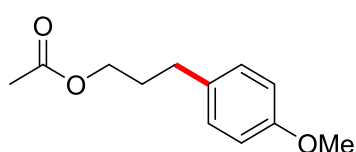
Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and 2-bromophenylboronic acid pinacol ester (0.3 mmol, 67 μL). After 24h of reaction, the crude reaction mixture was filtered through a plug of celite, washing with THF (15 mL). The filtrate was concentrated by rotary evaporation. The resulting solution of DMF was diluted with THF (10 mL) and cooled to 0°C in an ice water bath. To the cold stirring solution was added 1M NaOH (1.5 mL, 5 equiv.) and 30% aq. H₂O₂ (171 μL, 5 equiv.). After 30 min the mixture was diluted with water (10 mL) and diethyl ether (10 mL) and neutralized by addition of 1M HCl (2.5 mL). The organic layer was collected and washed with water (2 x 10 mL), brine (2 x 10 mL), dried over MgSO₄ and evaporated under reduced pressure. The crude product was purified by flash

¹⁷ Y. M. Chiang, H. K. Liu, J. M. Lo, S. C. Chien, Y. F. Chan, T. H. Lee, J. K. Su, Y. H. Kuo, *J. Chin. Chem. Soc.*, **2003**, 50, 161.

column chromatography (pentane/EtOAc, 90/10) to afford **50** as a colorless oil (34 mg, 58%). The spectroscopic data are in agreement with those reported in the literature.¹⁸

¹H NMR (400 MHz, CDCl₃): δ 7.12 – 7.06 (m, 2H), 6.88 – 6.84 (m, 1H), 6.77 – 6.75 (m, 1H) 5.43 (s, 1H) 4.12 (t, *J* = 6.5 Hz, 2H), 2.72 – 2.68 (m, 2H), 2.07 (s, 3H), 1.99 – 1.94 (m, 2H), **¹³C NMR** (100 MHz, CDCl₃): δ 171.6, 153.7, 130.3, 127.4, 127.3, 120.7, 115.4, 64.2, 28.6, 26.3, 21.0. **IR** (neat): 3355, 2999, 1707, 1491, 1236, 1032 cm⁻¹.

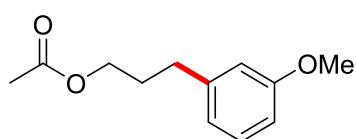
3-(4-Methoxyphenyl)propyl acetate (**51**)



Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and 4-iodoanisole (0.3 mmol, 70 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether, 90/10) to afford **51** as a colorless oil (29 mg, 46%).

¹H NMR (400 MHz, CDCl₃): δ 7.10 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 4.07 (t, *J* = 6.6 Hz, 2H), 3.79 (s, 3H), 2.65 – 2.61 (m, 2H), 2.05 (s, 3H), 1.96 – 1.89 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 171.2, 157.9, 133.2, 129.3 (2 C), 113.9 (2 C), 63.8, 55.3, 31.2, 30.4, 21.0. **IR** (neat): 2941, 1734, 1612, 1299, 1234 cm⁻¹. **HRMS** calc. for [C₁₂H₁₆NaO₃]⁺ 231.0992; found 231.0989.

3-(3-Methoxyphenyl)propyl acetate (**52**)

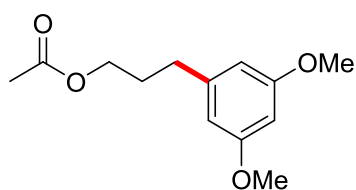


Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and 3-bromoanisole (0.3 mmol, 38 μl). The crude product was purified by flash column chromatography (pentane/diethyl ether, 90/10) to afford **52** as a colorless oil (34mg, 54%).

¹H NMR (400 MHz, CDCl₃): δ 7.22 – 7.18 (m, 1H), 6.79 – 6.74 (m, 3H), 4.09 (t, *J* = 6.6 Hz, 2H), 3.80 (s, 3H), 2.69 – 2.65 (m, 2H), 2.06 (s, 3H), 1.99 – 1.92 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 171.1, 159.7, 142.8, 129.4, 120.8, 114.2, 111.2, 63.8, 55.1, 32.2, 30.1, 21.0. **IR** (neat): 2941, 1734, 1600, 1594, 1234, 1035 cm⁻¹. **HRMS** calc. for [C₁₂H₁₆NaO₃]⁺ 231.0992; found 231.0992.

¹⁸ P. Allevi, P. Ciuffreda, A. Longo, M. Anastasia, *Tetrahedron: Asymmetry*, **1998**, 9, 2915.

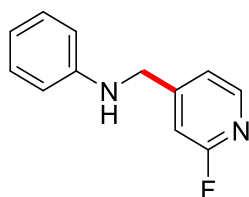
3-(3,5-Dimethoxyphenyl)propyl acetate (**53**)



Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and 1-bromo-3,5-dimethoxybenzene (0.3 mmol, 65 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether, 90/10) to afford **53** as a colorless oil (46 mg, 65%).

¹H NMR (400 MHz, CDCl₃): δ 6.37 – 6.29 (m, 3H), 4.09 (t, *J* = 6.6 Hz, 2H), 3.78 (s, 6H), 2.65 – 2.61 (m, 2H), 2.06 (s, 3H), 1.98 – 1.91 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 171.3, 161.0, 143.7, 106.6 (2 C), 98.1 (2 C), 63.9, 55.4 (2 C), 32.6, 30.1, 21.1. **IR** (neat): 1734, 1594, 1236, 1204, 1147, 1036 cm⁻¹. **HRMS** calc. for [C₁₃H₁₈NaO₄]⁺ 261.1097; found 261.1087.

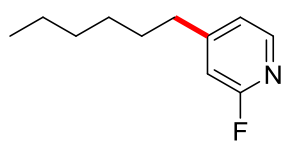
4-Anilinomethyl-2-fluoropyridine (**55**)



Following general procedure B with anilinomethylsilicate **4** (0.45 mmol, 294 mg) and 4-bromo-2-fluoropyridine (0.3 mmol, 31 μl). The crude product was purified by flash column chromatography (pentane/EtOAc, 80/20) to afford **55** as a colorless oil (53 mg, 86%).

¹H NMR (400 MHz, CDCl₃): δ 8.15 (d, *J* = 5.2 Hz, 1H), 7.20 – 7.16 (m, 3H), 6.94 (s, 1H), 6.78 – 6.74 (m, 1H), 6.58 – 6.56 (m, 2H), 4.41 (s, 2H), 4.41 (s, 1H (N-H)). **¹³C NMR** (100 MHz, CDCl₃): δ 164.3 (d, *J* = 238.8 Hz), 155.5 (d, *J* = 7.5 Hz), 147.7 (d, *J* = 15.1 Hz), 147.1, 129.34, 119.7 (d, *J* = 3.9 Hz), 118.3, 112.8, 107.7 (d, *J* = 37.8 Hz), 46.8 (d, *J* = 3.2 Hz). **¹⁹F NMR** (376 MHz, CDCl₃): δ -68.12. **IR** (neat): 3345, 3060, 1602, 1264, 732 cm⁻¹. **HRMS** calc. for [C₁₂H₁₂FN₂]⁺ 203.0979; found 203.0977.

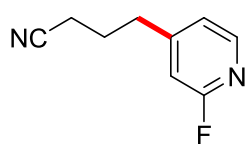
2-Fluoro-4-hexylpyridine (**56**)



Following general procedure B with hexylsilicate **2** (0.45 mmol, 285 mg) and 4-bromo-2-fluoropyridine (0.3 mmol, 31 μL). The crude product was purified by flash column chromatography (pentane/diethyl ether, 99/1 then 95/5) to afford **56** as a colorless oil (47 mg, 87%).

¹H NMR (400 MHz, CDCl₃): δ 8.07 (d, *J* = 5.1 Hz, 1H), 6.98 (dt, *J* = 5.1, 1.7 Hz, 1H), 6.72 (t, *J* = 1.8 Hz, 1H), 2.68 – 2.56 (m, 2H), 1.68 – 1.56 (m, 2H), 1.30 - 1.28 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃): δ 164.2 (d, *J* = 237.9 Hz), 158.0 (d, *J* = 7.8 Hz), 147.3 (d, *J* = 15.5 Hz), 121.7 (d, *J* = 4.2 Hz), 109.1 (d, *J* = 36.3 Hz), 35.2 (d, *J* = 2.7 Hz), 31.6, 30.1, 28.9, 22.6, 14.1. **¹⁹F NMR** (376 MHz, CDCl₃): δ -69.4. **IR** (neat): 2955, 2925, 2857, 1612, 1567, 1481, 1465, 1410, 1276, 1146, 1096, 1072 cm⁻¹. **HRMS** (ESI-) calc. for [C₁₁H₁₆FNNa]⁺ 204.1159; found 204.1166.

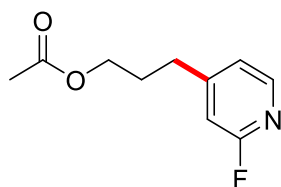
4-(2-Fluoropyridin-4-yl)butanenitrile (**57**)



Following general procedure B with cyanopropylsilicate **13** (0.45 mmol, 277 mg) and 4-bromo-2-fluoropyridine (0.3 mmol, 31 μl). The crude product was purified by flash column chromatography (pentane/EtOAc, 80/20) to afford **57** as a colorless oil (29 mg, 59%).

¹H NMR (400 MHz, CDCl₃): δ 8.15 (d, *J* = 5.1 Hz, 1H), 7.04 – 7.01 (m, 1H), 6.78 – 6.74 (m, 1H), 2.85 – 2.81 (m, 2H), 2.39 – 2.36 (m, 2H), 2.05 – 1.98 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 164.2 (d, *J* = 239.0 Hz), 154.6 (d, *J* = 7.7 Hz), 147.9 (d, *J* = 15.3 Hz), 121.5 (d, *J* = 4.0 Hz), 118.7, 107.7 (d, *J* = 37.0 Hz), 33.5 (d, *J* = 3.0 Hz), 25.6, 16.5. **¹⁹F NMR** (376 MHz, CDCl₃): δ -68.10. **IR** (neat): 3060, 1672, 1613, 1412, 1265, 731 cm⁻¹. **HRMS** calc. for [C₉H₁₀FN₂]⁺ 165.0823; found 165.0822

3-(2-Fluoropyridin-4-yl)propyl acetate (**58**)

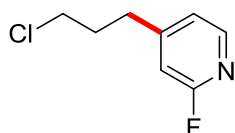


Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and 4-bromo-2-fluoropyridine (0.3 mmol, 31 μl). The crude product was purified by flash column chromatography (pentane/EtOAc, 80/20) to afford **58** as a colorless oil (48 mg, 81%).

¹H NMR (400 MHz, CDCl₃): δ 8.09 (d, *J* = 5.2 Hz, 1H), 7.02 – 6.98 (m, 1H), 6.74 (s, 1H), 4.08 (t, *J* = 6.4 Hz, 2H), 2.74 – 2.71 (m, 2H), 2.03 (s, 3H), 2.02 – 1.95 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 170.9, 164.1 (d, *J* = 238.5 Hz), 156.2 (d, *J* = 7.7 Hz), 147.5 (d, *J* = 15.4 Hz), 121.5 (d, *J* = 3.9 Hz), 109.1 (d, *J* = 36.9 Hz), 63.2, 31.5 (d, *J* = 3.0 Hz), 28.9, 20.8. **¹⁹F**

NMR (376 MHz, CDCl₃): δ -68.84. **IR** (neat): 2935, 1733, 1612, 1411, 1233 cm⁻¹. **HRMS** calc. for [C₁₀H₁₂FLiNO₂]⁺ 204.1007; found 204.1015.

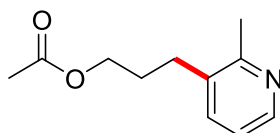
4-(3-Chloropropyl)-2-fluoropyridine (**59**)



Following general procedure B with 3-chloropropylsilicate **15** (0.45 mmol, 281 mg) and 4-bromo-2-fluoropyridine (0.3 mmol, 31 μ L). The crude product was purified by flash column chromatography (pentane/diethyl ether, 99/1 then 95/5) to afford **59** as a colorless oil (42 mg, 81%).

¹H NMR (400 MHz, CDCl₃): δ 8.12 (d, J = 5.1 Hz, 1H), 7.02 (dt, J = 5.0, 1.6 Hz, 1H), 6.85 – 6.68 (m, 1H), 3.53 (t, J = 6.3 Hz, 2H), 2.83 (dd, J = 8.4, 6.8 Hz, 2H), 2.19 – 2.02 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 164.1 (d, J = 239.5 Hz), 155.7 (d, J = 7.7 Hz), 147.6, 121.7, 109.3 (d, J = 38.0 Hz), 43.6, 32.5, 31.9 (d, J = 2.8 Hz). **¹⁹F NMR** (376 MHz, CDCl₃): δ -68.6. **IR** (neat): 2926, 1613, 1558, 1411, 1275, 1148, 908, 728 cm⁻¹. **HRMS** (ESI-) calc. for [C₈H₉ClFNNa]⁺ 196.0300; found 196.0306.7

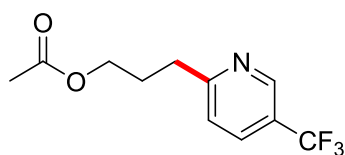
3-(2-Methylpyridin-3-yl)propyl acetate (**60**)



Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and 3-Bromo-2-methylpyridine (0.3 mmol, 35 μ L). The crude product was purified by flash column chromatography (pentane/diethyl ether, 50/50) to afford **60** as a colorless oil (39 mg, 67%).

¹H NMR (300 MHz, CDCl₃): δ 8.34 (d, J = 3.5 Hz, 1H), 7.40 (d, J = 7.5, 1H), 7.06 (dd, J = 7.6 Hz, J = 3.5 Hz, 1H), 4.10 (t, J = 6.4 Hz, 2H), 2.70 – 2.65 (m, 2H), 2.53 (s, 3H), 2.05 (s, 3H) 1.96 – 1.87 (m, 2H). **¹³C NMR** (75 MHz, CDCl₃): δ 171.0, 156.5, 147.7, 136.3, 134.4, 121.3, 63.6, 29.0, 28.5, 22.0, 20.9. **IR** (neat): 2942, 1736, 1574, 1441, 1232, 1035, 729 cm⁻¹. **HRMS** calc. for [C₁₁H₁₅NNaO₂]⁺ 216.0995; found 216.1003.

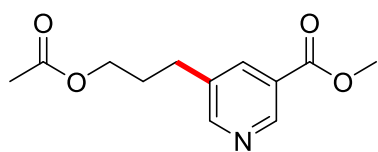
3-(5-(Trifluoromethyl)pyridin-2-yl)propyl acetate (61)



Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and 2-Bromo-5-(trifluoromethyl)pyridine (0.3 mmol, 67 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether, 80/20) to afford **61** as a colorless oil (30 mg, 40%).

¹H NMR (400 MHz, CDCl₃): δ 8.80 (d, *J* = 0.8 Hz, 1H), 7.84 (dd, *J* = 8.1 Hz, *J* = 1.9 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 4.10 (t, *J* = 6.4 Hz, 2H), 2.97 – 2.94 (m, 2H), 2.16 – 2.09 (m, 2H), 2.04 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃): δ 171.1, 165.0 (d, *J* = 1.3 Hz), 146.3 (q, *J* = 4.1 Hz), 133.5 (q, *J* = 3.5 Hz), 124.4 (q, *J* = 30 Hz), 123.7 (q, *J* = 270 Hz), 122.6, 63.6, 34.6, 28.2, 20.9. **¹⁹F NMR** (376 MHz, CDCl₃): δ -62.3. **IR** (neat): 2940, 1737, 1608, 1326, 1232, 1125, 732 cm⁻¹. **HRMS** calc. for [C₁₁H₁₂F₃NNaO₂]⁺ 270.0712; found 270.0707.

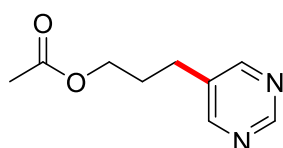
Methyl 5-(3-acetoxypropyl)nicotinate (62)



Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and Methyl 5-bromopyridine-3-carboxylate (0.3 mmol, 65 mg). The crude product was purified by flash column chromatography (pentane/ethyl acetate, 60/40) to afford **62** as a colorless oil (47mg, 75%).

¹H NMR (400 MHz, CDCl₃): δ 9.05 (d, *J* = 1.7 Hz, 1H), 8.61 (d, *J* = 1.9, 1H), 8.12 (dd, *J* = 1.9 Hz, *J* = 1.7 Hz, 1H), 4.09 (t, *J* = 6.4 Hz, 2H), 3.94 (s, 3H), 2.78 – 2.74 (m, 2H), 2.04 (s, 3H) 2.02 – 1.95 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 171.0, 165.8, 153.4, 148.6, 136.8, 136.5, 125.8, 63.3, 52.4, 29.7, 29.2, 20.9. **IR** (neat): 2942, 1722, 1426, 1231, 1027, 765 cm⁻¹. **HRMS** calc. for [C₁₂H₁₅NNaO₄]⁺ 260.0893; found 260.0897.

3-(Pyrimidin-5-yl)propyl acetate (63)

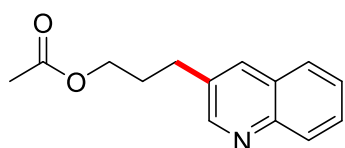


Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and 5-Bromopyrimidine (0.3 mmol, 48 mg). The crude product was purified by flash column chromatography

(pentane/ethyl acetate, 50/50) to afford **63** as a colorless oil (18 mg, 33%).

¹H NMR (300 MHz, CDCl₃): δ 9.09 (s, 1H), 8.60 (s, 2H), 4.12 (t, *J* = 6.3 Hz, 2H), 2.73 – 2.68 (m, 2H), 2.05 (s, 3H), 2.03 – 1.94 (m, 2H). **¹³C NMR** (75 MHz, CDCl₃): δ 170.9, 156.9 (2 C), 156.7, 134.2, 63.1, 29.4, 27.0, 20.9. **IR** (neat): 2942, 1734, 1232, 1040, 697 cm⁻¹. **HRMS** calc. for [C₉H₁₂N₂NaO₂]⁺ 203.0791; found 270.0797.

3-(Quinolin-3-yl)propyl acetate (**64**)

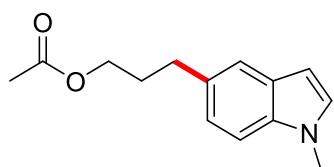


Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and 4-bromoquinoline (0.3 mmol, 41 μl).

The crude product was purified by flash column chromatography (pentane/diethyl ether, 90/10) to afford **64** as a colorless oil (45 mg, 65%).

¹H NMR (400 MHz, CDCl₃): δ 8.78 (d, *J* = 2.2 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 2.2 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.58 – 7.50 (m, 1H), 4.14 (t, *J* = 6.6 Hz, 2H), 2.90 – 2.85 (m, 2H), 2.10 – 2.06 (m, 2H), 2.05 (s, 3H). **¹³C NMR** (100 MHz, CDCl₃): δ 171.0, 151.9, 146.9, 134.2, 133.8, 129.2, 128.8, 128.0, 127.3, 126.7, 63.5, 29.8, 29.6, 20.9. **IR** (neat): 2938, 1732, 1605, 1494, 1365, 1232 cm⁻¹. **HRMS** calc. for [C₁₄H₁₆NO₂]⁺ 230.1176; found 230.1183.

3-(1-Methyl-1H-indol-5-yl)propyl acetate (**65**)



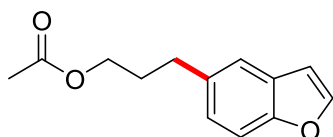
Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and 5-bromo-1-methyl-1H-indole (0.3 mmol, 63 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether, 90/10) to afford **65** as a

colorless oil (12 mg, 17%).

¹H NMR (400 MHz, CDCl₃): δ 7.47 – 7.42 (m, 1H), 7.28 (s, 1H), 7.09 – 7.04 (m, 2H), 6.44 (d, *J* = 3.1 Hz, *J* = 1.8 Hz, 1H), 4.13 (t, *J* = 6.6 Hz, 2H), 3.80 (s, 3H), 2.84 – 2.79 (m, 2H), 2.10 – 2.05 (m, 3H), 2.04 – 2.00 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 171.2, 135.5, 132.0, 129.0, 128.7, 122.4, 120.1, 109.1, 100.5, 64.0, 32.8, 32.2, 31.0, 21.0. **IR** (neat): 2912,

1732, 1615, 1239, 1101, 1036, 718 cm^{-1} . **HRMS** calc. for $[\text{C}_{14}\text{H}_{17}\text{NNaO}_2]^+$ 254.11151; found 254.1153.

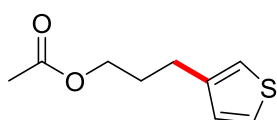
3-(Benzofuran-5-yl)propyl acetate (**66**)



Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and Methyl 5-bromopyridine-3-carboxylate (0.3 mmol, 38 μl). The crude product was purified by flash column chromatography (pentane/diethyl ether, 95/5) to afford **66** as a colorless oil (48mg, 73%).

^1H NMR (400 MHz, CDCl_3): δ 7.60 (d, $J = 2.2$ Hz, 1H), 7.41 (m, 2H), 7.12 (dd, $J = 8.4$ Hz, $J = 1.7$ Hz, 1H), 6.71 (dd, $J = 2.2$ Hz, $J = 0.9$ Hz, 1H), 4.10 (t, $J = 6.6$ Hz, 2H), 2.80 – 2.77 (m, 2H), 2.06 (s, 3H) 2.03 – 1.96 (m, 2H). **^{13}C NMR** (100 MHz, CDCl_3): δ 171.1, 153.6, 145.2, 135.6, 127.6, 124.8, 120.5, 111.1, 106.3, 63.8, 32.0, 30.8, 21.0. **IR** (neat): 2948, 1733, 1467, 1234, 1030, 734 cm^{-1} . **HRMS** calc. for $[\text{C}_{13}\text{H}_{14}\text{NaO}_3]^+$ 241,0835; found 241.0841.

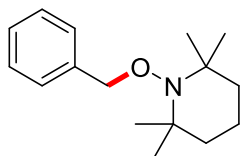
3-(Thiophen-3-yl)propyl acetate (**67**)



Following general procedure B with acetoxypropylsilicate **16** (0.45 mmol, 292 mg) and 3-bromothiophene (0.3 mmol, 29 μl). The crude product was purified by flash column chromatography (pentane/diethyl ether, 90/10) to afford **67** as a colorless oil (28 mg, 50%).

^1H NMR (400 MHz, CDCl_3): δ 7.13 (dd, $J = 5.2$ Hz, $J = 1.2$ Hz, 1H), 6.92 (dd, $J = 5.1$ Hz, $J = 3.4$ Hz, 1H), 6.80 (s, 1H), 4.12 (t, $J = 6.4$ Hz, 2H), 2.95 – 2.90 (m, 2H), 2.06 (s, 3H), 2.04 – 1.99 (m, 2H). **^{13}C NMR** (100 MHz, CDCl_3): δ 171.1, 143.9, 126.8, 124.5, 123.2, 63.5, 30.5, 26.3, 20.9. **IR** (neat): 2942, 1734, 1232, 1040, 697 cm^{-1} . **HRMS** calc. for $[\text{C}_9\text{H}_{12}\text{SLiO}_2]^+$ 191.0713; found 191.0710.

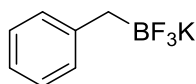
1-(Benzyloxy)-2,2,6,6-tetramethylpiperidine (69)



Following general procedure D with potassium benzyl trifluoroborate **68** (0.3 mmol, 59 mg) and triphenylcarbenium tetrafluoroborate (0.3 mmol, 99 mg) in diethyl ether. The crude product was purified by flash column chromatography (pentane/diethyl ether, 99/1) to afford **69** as a colorless oil (48 mg, 65%). The spectroscopic data are in agreement with those reported in the literature.¹⁹

¹H NMR (400 MHz, CDCl₃): δ 1.04 (s, 6H), 1.14 (s, 6H), 1.21-1.50 (m, 6H), 4.71 (s, 2H), 7.11-7.26 (m, 5H). ¹³C NMR (100 MHz, CDCl₃): δ 17.1, 20.3(2 C), 33.1(2 C), 39.7(2 C), 60.0(2 C), 78.7, 127.3, 127.4(2 C), 128.2(2 C), 138.3.

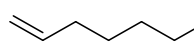
Potassium benzyltrifluoroborate (68)



Trifluoroborate **68** was synthesized as described following the general procedure C. The spectroscopic data are in agreement with those reported in the literature.¹⁹

¹H NMR (MeOD, 400 MHz): δ 1.70 (bs, 2H), 6.91-6.94 (m, 1H), 7.07-7.12 (m, 4H). ¹³C NMR (MeOD, 100 MHz): δ 122.2, 127.1 (2C), 128.7 (2C), 146.7. ¹¹B NMR (MeOD, 128 MHz): δ 4.4 (bs). ¹⁹F NMR (MeOD, 377 MHz): δ -142.7.

Potassium 5-hexenyl-1-trifluoroborate



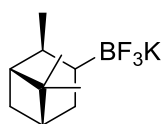
Trifluoroborate was synthesized as described. To a solution of trimethyl borate (9.1 g, 88 mmol, 1.46 equiv) in Et₂O was added dropwise a freshly prepared solution of 5-hexenyl-1-magnesium bromide (61 mL, 61 mmol, 1 equiv, 1.0 M Et₂O solution) over 10 min at -78 °C and then allowed to warm to rt for 1h. Then, the mixture was cooled to 0 °C and KHF₂ (27.4 g, 354 mmol, 5.9 equiv) was added followed by the addition of water (47 mL) over 50 min. After stirring at rt for 1h, the solution was evaporated and the resulting solid was

¹⁹ G. Sorin, R. Martinez-Mallorquin, Y. Contie, A. Baralle, M. Malacria, J.-P. Goddard, L. Fensterbank, *Angew. Chem. Int. Ed.*, **2010**, *49*, 8721.

dried under high vacuum for 4h. The solid was triturated in hot acetone, filtered and the solvent was removed under reduced pressure. Diethyl ether (80 mL) was added and the suspension was filtered to afford 5-hexenyl-1-trifluoroborate as a white solid (7.7 g, 70%). The spectroscopic data are in agreement with those reported in the literature.¹⁹

M.p. >320 °C. **¹H NMR** (400MHz, MeOD): δ 5.81 (ddt, *J* = 16.8, 10.1, 6.8 Hz, 1H), 4.93 (m, 1H), 4.85 (m, 1H), 2.01 (q, *J* = 7.3 Hz, 2H), 1.24-1.37 (m, 4H), 0.16-0.25 (m, 2H). **¹³C NMR** (100MHz, MeOD): δ 141.0, 113.0, 35.3, 34.0, 26.0. **¹¹B NMR** (128MHz, MeOD): δ 4.4 (bs). **¹⁹F NMR** (377MHz, MeOD): δ -142.7.

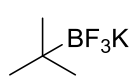
Potassium ((1*R*,2*S*,3*R*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)trifluoroborate



Following the reported procedure, the trifluoroborate salt was obtained as a white solid (9.41 g, 83%). The spectroscopic data are in agreement with those reported in the literature.¹⁹

¹H NMR (400MHz, DMSO *d*₆): δ 2.04 - 2.07 (m, 1H), 1.87 (m, 1H), 1.56 - 1.73 (m, 4H), 1.11 (s, 3H), 1.02 (s, 3H), 0.91 (d, *J* = 7.3 Hz, 3H), 0.87 (d, *J* = 8.3 Hz, 1H), 0.34 - 0.38 (m, 1H). **¹³C NMR** (100MHz, DMSO *d*₆): δ 48.9, 42.1, 38.9, 38.5, 33.0, 29.9, 28.9, 24.4, 23.2, 1.6. **¹¹B NMR** (128MHz, DMSO *d*₆): δ 4.4 (bs). **¹⁹F NMR** (377MHz, DMSO *d*₆): δ -145.1.

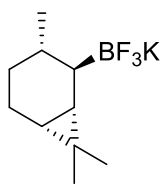
Potassium *tert*-butyltrifluoroborate



Following the reported procedure, the trifluoroborate salt was obtained as a white crystalline solid (2.15 g, 43%). The spectroscopic data are in agreement with those reported in the literature.¹⁹

¹H NMR (400MHz, Acetone *d*₆): δ 0.73 (s, 9H). **¹³C NMR** (100MHz, Acetone *d*₆): δ 27.9 (3C). **¹¹B NMR** (128MHz, Acetone *d*₆): δ 4.6 (bs). **¹⁹F NMR** (377MHz, Acetone *d*₆): δ -153.7. **HRMS** calc. for [C₄H₉BF₃]⁻ 125.0756; found 125.0757.

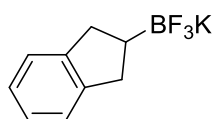
Potassium (1S,2R,3S,6R)-3,7,7-trimethylbicyclo[4.1.0] heptan-2-trifluoroborate



Following the reported procedure, the trifluoroborate salt was obtained as a white solid (1.7 g, 20%). The spectroscopic data are in agreement with those reported in the literature.¹⁹

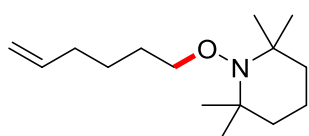
¹H NMR (400MHz, DMSO d₆): δ 1.46-1.66 (m, 2H), 1.10-1.16 (m, 1H), 0.89-0.94 (m, 1H), 0.85 (s, 3H), 0.80 (s, 3H), 0.71 (d, *J* = 6.4 Hz, 3H), 0.48-0.58 (m, 2H), 0.10-0.14 (m, 1H), -0.61 -0.52 (m, 1H). ¹³C NMR (100MHz, DMSO d₆): δ 34.0, 30.3, 30.1, 24.8, 22.7, 20.2, 18.8, 16.4, 16.1. ¹¹B NMR (128MHz, DMSO d₆): δ 5.1 (bs). ¹⁹F NMR (377MHz, DMSO d₆): δ -139.5.

Potassium indanyl-2-trifluoroborate

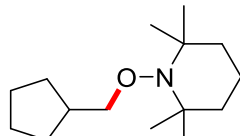


Trifluoroborate was synthesized as described. The spectroscopic data are in agreement with those reported in the literature.²⁰

2,2,6,6-Tetramethyl-N-(O-5-hexenyl)-piperidine (70) and 2,2,6,6-Tetramethyl-N-(O-cyclomethylpentyl)-piperidine (71)



70



71

Following general procedure E with potassium 5-hexenyl-1-trifluoroborate (0.3 mmol, 57 mg) and 9-mesityl-10-methylacridinium perchlorate (0.03 mmol, 12.4 mg). The crude product was purified by

flash column chromatography (pentane) to afford a mixture of **70** and **71** as a colorless oil (10 mg, 14%) with the ratio **70/71**: 20/1.

Following general procedure D with potassium 5-hexenyl-1-trifluoroborate (0.3 mmol, 57 mg) and triphenylcarbenium tetrafluoroborate (0.3 mmol, 99 mg) in diethyl ether. The crude product was purified by flash column chromatography (pentane) to afford a mixture of **70** and **71** as a colorless oil (41 mg, 57%) with a ratio **70/71**: 89/11.

²⁰ H. Huang, K. Jia, Y. Chen, *Angew. Chem. Int. Ed.* **2015**, *54*, 1881.

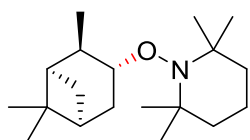
Following the same procedure with potassium [18-Crown-6] bis(catecholato)- 5-hexenyl-1-silicate **3** (0.3 mmol, 189 mg) in DMF gave **70** and **71** as a colorless oil (37%*) with the ratio **70/71**: 10/1. Replacing the oxidizing agent by tris(4-bromophenyl)ammoniumyl hexachloroantimonate (0.3 mmol, 245 mg), the products were obtained (61%*) with the same ratio.

*Yield determined by NMR with butadiene sulfone as internal standard.

The spectroscopic data are in agreement with those reported in the literature.¹⁹

¹H NMR for **70** (400MHz, CDCl₃): δ 1.09 (s, 6H), 1.14 (s, 6H), 1.20-1.55 (m, 10H), 2.07 (q, *J* = 7.2 Hz, 2H), 3.73 (t, *J* = 6.1 Hz, 2H), 4.94 (m, 1H), 5.01 (m, 1H), 5.82 (m, 1H). Characteristic signal for **71**: 3.64 (d, *J* = 6.8 Hz, 2H). ¹³C NMR for **71** (100MHz, CDCl₃): δ 17.3, 20.3 (2 C), 25.9, 28.4, 33.2 (2 C), 34.0, 39.7 (2 C), 59.8, 59.9, 80.8, 114.5, 139.1. Characteristic signal for **71**: 76.7.

2,2,6,6-Tetramethyl-1-((1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yloxy) piperidine (**72**)



Following general procedure E with potassium ((1R,2S,3R,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)trifluoroborate (0.3 mmol, 74 mg) and 9-mesityl-10-methylacridinium perchlorate (0.03 mmol, 12.4 mg).

The crude product was purified by flash column chromatography (pentane) to afford **72** as a colorless oil (61 mg, 69%).

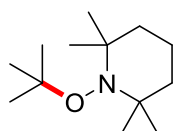
Following general procedure D with potassium ((1R,2S,3R,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)trifluoroborate (0.3 mmol, 74 mg) and triphenylcarbenium tetrafluoroborate (0.3 mmol, 99 mg) in diethyl ether. The crude product was purified by flash column chromatography (pentane) to afford **72** as a colorless oil (57 mg, 64%). Replacing the oxidizing agent by tris(4-bromophenyl)ammoniumyl hexachloroantimonate (0.3 mmol, 245 mg) in DMF, **72** was obtained with 27%* yield.

*Yield determined by NMR with butadiene sulfone as internal standard.

The spectroscopic data are in agreement with those reported in the literature.¹⁹

¹H NMR (400MHz, CDCl₃): δ 0.88 (s, 3H), 1.02 (d, *J* = 9.3 Hz, 1H), 1.06-1.25 (m, 18H), 1.40-1.45 (m, 6H), 1.73 (td, *J* = 5.9, 2.4 Hz), 1.85-1.91 (m, 1H), 2.05-2.14 (m, 1H), 2.20-2.37 (m, 3H), 4.21 (dt, *J* = 9.4, 4.5 Hz, 1H). **¹³C NMR** (100MHz, CDCl₃): δ 17.5, 20.5 (2 C), 22.0, 23.9, 27.6, 33.1, 34.7 (3 C), 38.5, 40.6, 40.8, 41.6, 44.5, 48.0, 59.9 (2 C), 82.4.

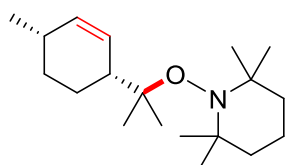
1-*tert*-Butoxy-2,2,6,6-tetramethylpiperidine (73)



Following general procedure D with potassium *tert*-butyltrifluoroborate **1f** (0.3 mmol, 49 mg) and triphenylcarbenium tetrafluoroborate (0.3 mmol, 99 mg) in diethyl ether. The crude product was purified by flash column chromatography (pentane/diethyl ether : 99/1) to afford **73** as a colorless oil (16 mg, 25%). The spectroscopic data are in agreement with those reported in the literature.¹⁹

¹H NMR (400MHz, CDCl₃): δ 1.07 (s, 6H), 1.12 (s, 6H), 1.18 (s, 9H), 1.44-1.48 (m, 6H). **¹³C NMR** (100MHz, CDCl₃): δ 17.5, 20.7 (2 C), 29.7 (3 C), 35.1 (2 C), 41.1 (2 C), 59.4 (2 C), 77.3.

2,2,6,6-Tetramethyl-1-(2-((1*R*,4*S*)-4-methylcyclohex-2-enyl)propan-2-yloxy)piperidine (75)



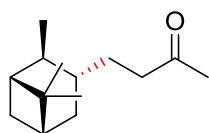
Following general procedure D with potassium (1*S*,2*R*,3*S*,6*R*)-3,7,7-trimethylbicyclo[4.1.0] heptan-2-trifluoroborate (0.3 mmol, 65 mg) and triphenylcarbenium tetrafluoroborate (0.3 mmol, 99 mg) in diethyl ether. The crude product was purified by flash column chromatography (pentane/diethyl ether : 99/1) to afford **75** as a colorless oil (48 mg, 67%).

Following general procedure E with potassium (1*S*,2*R*,3*S*,6*R*)-3,7,7-trimethylbicyclo[4.1.0] heptan-2-trifluoroborate (0.3 mmol, 65 mg) and 9-mesityl-10-methylacridinium perchlorate (0.03 mmol, 12.4 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether : 99/1) to afford **75** as a colorless oil (16 mg, 18%). The spectroscopic data are in agreement with those reported in the literature.¹⁹

¹H NMR (400MHz, CDCl₃): δ 0.98 (d, *J* = 7.2 Hz, 3H), 1.09 (s, 3H), 1.10 (s, 3H), 1.12 (s, 6H), 1.20 (s, 3H), 1.21 (s, 3H), 1.24-1.30 (m, 2H), 1.40-1.57 (m, 6H), 1.65-1.74 (m, 2H), 2.18

(m, 1H), 2.53 (m, 1H), 5.67 (m, 1H), 5.76 (m, 1H). ^{13}C NMR (100MHz, CDCl_3): δ 17.3, 20.7, 21.0 (2 C), 21.2, 23.8, 24.0, 29.0, 29.3, 35.1, 35.3, 41.2 (2 C), 47.2, 59.5 (2 C), 81.1, 128.8, 133.9.

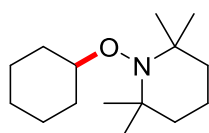
4-Isopinocampheyl-2-butanone (**77**)



Potassium ((1*R*,2*S*,3*R*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)trifluoroborate (1 mmol, 244 mg), methyl vinyl ketone (0.4 mL, 5 mmol), and triphenylcarbenium tetrafluoroborate (1 mmol, 330 mg) were added to a schlenk flask. The schlenk flask was sealed with a rubber septum, and evacuated / purged with vacuum / argon three times. Degassed diethyl ether (10 mL) was introduced followed by two freeze-pump-thaw cycles. The reaction mixture was stirred at room temperature for 24h under an argon atmosphere. The reaction was diluted with diethyl ether (50 mL), washed with water (2 times) and brine (2 times). The organic layer was dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford **77** as a colorless oil (131 mg, 63%). The spectroscopic data are in agreement with those reported in the literature.¹⁹

^1H NMR (400MHz, CDCl_3): δ 0.70 (d, $J = 9.7$ Hz, 1H), 0.96 (s, 3H), 0.99 (d, $J = 7.0$ Hz, 3H), 1.16 (s, 3H), 1.34-1.45 (m, 2H), 1.50-1.68 (m, 2H), 1.70-1.85 (m, 2H), 1.85-1.91 (m, 1H), 2.06-2.15 (m, 1H), 2.13 (s, 3H), 2.22-2.30 (m, 1H), 2.34 (ddd, $J = 16.5, 10.4, 5.1$ Hz, 1H), 2.46 (ddd, $J = 16.5, 10.1, 5.9$ Hz, 1H). ^{13}C NMR (100MHz, CDCl_3): δ 21.7, 23.0, 28.1, 30.0, 34.1, 34.5, 34.8, 36.1, 38.8, 42.0, 42.3, 43.7, 48.2, 209.5.

1-Cyclohexyloxy-2,2,6,6-tetramethylpiperidine (**78**)



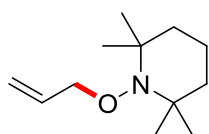
Following general procedure D with potassium [18-Crown-6] bis(catecholato)-cyclohexylsilicate **19** (0.3 mmol, 189 mg) and triphenylcarbenium tetrafluoroborate (0.3 mmol, 99 mg) in DMF. The crude product was purified by flash column chromatography (pentane/diethyl ether, 98/2) to afford **78** (53%*). Replacing the oxidizing agent by tris(4-bromophenyl)ammoniumyl hexachloroantimonate (0.3 mmol, 245 mg) in DMF, **78** was obtained with 44%* yield.

*Yield determined by NMR with butadiene sulfone as internal standard.

The spectroscopic data are in agreement with those reported in the literature.²¹

¹H NMR (400 MHz, CDCl₃): δ 3.61-3.55 (m, 1 H), 2.07-2.02 (m, 2 H), 1.77-1.75 (m, 2 H), 1.70-1.20 (m, 12 H), 1.12 (s, 12 H). **¹³C NMR** (100 MHz, CDCl₃): δ 81.5, 59.3, 40.1, 34.3, 32.6, 25.7, 24.8, 19.9, 17.1.

1-(Allyloxy)-2,2,6,6-tetramethylpiperidine (**82**)

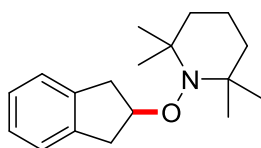


Following general procedure E with potassium allyl trifluoroborate (0.3 mmol, 44 mg) and 9-mesityl-10-methylacridinium perchlorate (0.03 mmol, 12.4 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether, 98/2) to afford **82** as a colorless oil (19 mg, 32%). Following the same procedure with potassium [18-Crown-6] bis(catecholato)-allylsilicate **11** (0.3 mmol, 177 mg) gave **82** (18 mg, 31%).

The spectroscopic data are in agreement with those reported in the literature.¹⁹

¹H NMR (400MHz, CDCl₃): δ 1.16 (s, 6H), 1.33 (s, 6H), 1.30-1.58 (m, 6H), 4.28 (dt, *J* = 5.5, 1.5 Hz, 2H), 5.09-5.30 (m, 1H), 5.26 (dq, *J* = 17.3, 3.6 Hz, 1H), 5.84-5.94 (m, 1H). **¹³C NMR** (100MHz, CDCl₃): δ 17.2, 20.1 (2 C), 32.9 (2 C), 39.7 (2 C), 59.7 (2 C), 78.3, 115.9, 134.2.

1-(Indan-2-yloxy)-2,2,6,6-tetramethylpiperidine (**83**)



Following general procedure E with potassium indanyl-2-trifluoroborate (0.3 mmol, 67 mg) and 9-mesityl-10-methylacridinium perchlorate (0.03 mmol, 12.4 mg). The crude product was purified by flash column chromatography (pentane) to afford **83** as a colorless oil (27 mg, 33%).

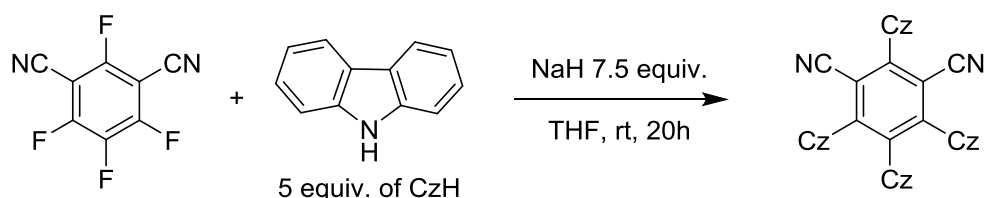
The spectroscopic data are in agreement with those reported in the literature.²⁰

¹H NMR (300MHz, CDCl₃): δ 1.11 (s, 6H), 1.21 (s, 6H), 1.30-1.54 (m, 6H), 3.04 (dd, *J* = 7.7, 15.8 Hz, 2H), 3.28 (dd, *J* = 7.7, 15.8 Hz, 2H), 4.77 (p, *J* = 7.7 Hz, 2H), 7.14 (m, 4H). **¹³C NMR** (75 MHz, CDCl₃): δ 17.3, 20.3(2 C), 34.1(2 C), 39.6(2 C), 40.2, 59.5(2 C), 87.4,

²¹ Yasu, Y.; Koike, T.; Akita, M. *Adv. Synth. Catal.*, **2012**, *354*, 3414–3420.

124.4(2 C), 126.3(2 C), 141.11(2 C). **HRMS** (m/z): [C₁₈H₂₈NO⁺], calc. 274.2165, found 274.2166.

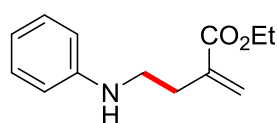
1,2,3,5-Tetrakis(carbazol-yl)-4,6-dicyanobenzene (4CzIPN, **86**)



Photocatalyst 4CzIPN was synthesized following a previous reported procedure.²² In a 100 mL round-bottom-flask was added NaH (60% in mineral oil) (7.5 eq., 15 mmol, 600 mg). Under argon was added 40 mL of distilled THF followed by the slow addition of carbazole (5.0 eq., 10 mmol, 1.67 g). After 30 min of stirring at room temperature the tetrafluoroisophthalonitrile (1.0 eq., 2 mmol, 400 mg) was added and the mixture stirred again at room temperature. A yellow precipitate progressively appeared. After 20 hours of reaction 1 mL of water was added to neutralize the excess of NaH. Then the mixture was evaporated to give a yellow solid. The solid was successively washed with water and ethanol. The crude product was dissolved in the minimum of DCM and crystallized by addition of pentane to give the pure **86** (1.13g, 71% yield). The spectroscopic data are in agreement with those reported in the literature.

¹H NMR (400 MHz, CDCl₃): δ 8.35 (dt, *J* = 7.7, 1.0 Hz, 1H), 8.19 (d, *J* = 8.3 Hz, 1H), 7.87 – 7.84 (m, 2H), 7.76 – 7.72 (m, 3H), 7.55 – 7.44 (m, 3H), 7.12 (dtd, *J* = 17.9, 7.3, 1.3 Hz, 4H), 6.83 – 6.79 (m, 1H), 6.72 – 6.68 (m, 1H). **¹³C NMR** (100 MHz, CDCl₃): δ 145.6, 144.8, 139.9, 138.5, 137.6, 136.4, 126.8, 125.4, 124.1, 123.6, 123.2, 122.8, 121.9, 121.3, 121.0, 120.5, 120.1, 119.4, 116.7, 112.2, 111.1, 110.9, 110.8.

Ethyl 2-methylene-4-(phenylamino)butanoate (**91**)



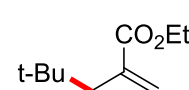
Following general procedure F with **8** (0.3 mmol, 196.2 mg) and allylsulfone **90** (4 eq., 1.2 mmol, 322 mg). The crude product was

²² Luo, J.; Zhang, J. *ACS catal.* **2016**, *6*, 873-877

purified by flash column chromatography (pentane/ethyl acetate, 95/5) to afford **91** as a colorless oil (62 mg, 93%). The spectroscopic data are in agreement with those reported in the literature.^{22a}

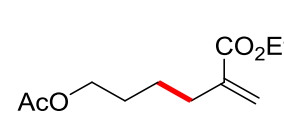
¹H NMR (300 MHz, CDCl₃): δ 7.22 – 7.16 (m, 2H), 7.74 – 7.69 (m, 2H), 6.65 – 6.62 (m, 2H), 6.27 (d, *J* = 1.4 Hz, 1H), 6.54 (d, *J* = 1.3 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.68 (bs, 1H), 3.31 (d, *J* = 6.8 Hz, 2H), 2.64 (td, *J* = 6.8, 1.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H). **¹³C NMR** (75 MHz, CDCl₃): δ 167.1, 148.0, 138.4, 129.3 (2 C), 126.7, 117.4, 112.9 (2 C), 61.0, 43.0, 32.1, 14.3.

Ethyl 4,4-dimethyl-2-methylenepentanoate (**92**)

 Following general procedure F with **20** (0.3 mmol, 129.5 mg) and allylsulfone **90** (4 eq., 1.2 mmol, 322 mg). The crude product was purified by flash column chromatography (pentane/ethyl acetate, 95/5) to afford **92** as a colorless oil (48 mg, 94%). The spectroscopic data are in agreement with those reported in the literature.^{22a}

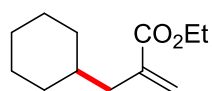
¹H NMR (400 MHz, CDCl₃): δ 6.17 (d, *J* = 1.4 Hz, 1H), 5.44 – 5.44 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.28 (d, *J* = 0.8 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.88 (s, 9H). **¹³C NMR** (100 MHz, CDCl₃): δ 168.2, 139.1, 126.8, 60.6, 53.4, 44.5, 31.5, 29.2 (3 C), 14.2.

Ethyl 5-(diphenylphosphoryl)-2-methylenepentanoate (**93**)

 Following general procedure F with **16** (0.3 mmol, 194.6 mg) and allylsulfone **90** (4 eq., 1.2 mmol, 322 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether, 90/10) to afford **93** as a colorless oil (24 mg, 37%).

¹H NMR (400 MHz, CDCl₃): δ 6.15 (d, *J* = 1.5 Hz, 1H), 5.52 (d, *J* = 1.4 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.07 (t, *J* = 6.5 Hz, 2H), 2.35 – 2.31 (m, 2H), 2.04 (s, 3H), 1.69 – 1.62 (m, 2H), 1.58 – 1.50 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃): δ 171.3, 167.3, 140.6, 124.8, 64.4, 60.8, 31.6, 28.3, 25.0, 21.1, 14.4. **IR** (neat): 2995, 2949, 1741, 1710, 1630, 1368, 1234, 1187, 1146, 1028, 944, 813 cm⁻¹. **HRMS** calc. for [C₁₁H₁₈NaO₄]⁺ 237.1097; found 237.1097.

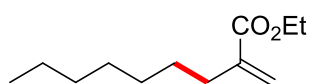
Ethyl 2-(cyclohexylmethyl)acrylate (**94**)



Following general procedure F with **19** (0.3 mmol, 189.3 mg) and allylsulfone **90** (4 eq., 1.2 mmol, 322 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether, 95/5) to afford **94** as a colorless oil (52 mg, 88%). The spectroscopic data are in agreement with those reported in the literature.^{22a}

¹H NMR (400 MHz, CDCl₃): δ 6.13 (d, *J* = 1.8 Hz, 1H), 5.45 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.18 (dd, *J* = 7.1, 1.1 Hz, 2H), 1.72 – 1.61 (m, 5H), 1.46 – 1.41 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.23 – 1.08 (m, 3H), 0.92 – 0.85 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 167.7, 139.8, 125.6, 125.5, 60.6, 40.1, 36.8, 33.4, 33.2, 26.7, 26.4, 14.3.

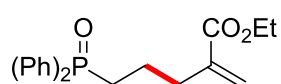
Ethyl 2-methylenonanoate (**95**)



Following general procedure F with **2** (0.3 mmol, 184.7 mg) and allylsulfone **90** (4 eq., 1.2 mmol, 322 mg). The crude product was purified by flash column chromatography (pentane/diethyl ether, 95/5) to afford **95** as a colorless oil (34 mg, 57%). The spectroscopic data are in agreement with those reported in the literature.^{22a}

¹H NMR (400 MHz, CDCl₃): δ 6.11 (d, *J* = 1.5 Hz, 1H), 5.50 (q, *J* = 1.5 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.31 – 2.27 (m, 2H), 1.47 – 1.42 (m, 2H), 1.32 – 1.25 (m, 12H), 0.87 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 167.7, 141.3, 124.2, 60.7, 32.0, 32.0, 29.3, 29.2, 28.6, 22.8, 14.4, 14.2.

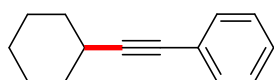
Ethyl 5-(diphenylphosphoryl)-2-methylenepentanoate (**96**)



Following general procedure F with **18** (0.3 mmol, 129.5 mg) and allylsulfone **90** (4 eq., 1.2 mmol, 322 mg). The crude product was purified by flash column chromatography (pentane/ethyl acetate, 95/5) to afford **96** as a colorless oil (48 mg, 46%).

¹H NMR (400 MHz, CDCl₃): δ 7.74 – 7.69 (m, 4H), 7.52 – 7.42 (m, 6H), 6.14 (d, *J* = 1.3 Hz, 1H), 5.49 (d, *J* = 1.3 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.42 – 2.38 (m, 2H), 2.29 – 2.22 (m, 2H), 1.84 – 1.80 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃): δ 167.0, 139.7, 133.1 (d, *J* = 98.2 Hz, 2 C), 131.8 (d, *J* = 2.7 Hz, 2 C), 130.9 (d, *J* = 9.2 Hz, 4 C), 128.7 (d, *J* = 11.6 Hz, 4 C), 125.6, 60.8, 32.9 (d, *J* = 15.3 Hz), 29.2 (d, *J* = 72.2 Hz), 20.5 (d, *J* = 3.4 Hz), 14.3. **³¹P NMR** (162 MHz, CDCl₃): δ 32.2. **IR** (neat): 3120, 2944, 1903, 1710, 1629, 1437, 1176, 1105, 717, 694 cm⁻¹. **HRMS** calc. for [C₂₀H₂₃NaO₃P]⁺ 365.1277; found 365.1268, for [(C₂₀H₂₃O₃P)₂Na]⁺ 707.2662; found 707.2366.

(Cyclohexylethynyl)benzene (**98**)

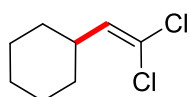


Following general procedure F with **19** (0.3 mmol, 189.3 mg) and 1-phenyl-2-p-toluenesulfonylethyne **97** (1.2 mmol, 307.6 mg).

The crude product was purified by flash column chromatography (pentane) to afford **98** as a colorless oil (44 mg, 78%). The spectroscopic data are in agreement with those reported in the literature.^{22a}

¹H NMR (300 MHz, CDCl₃): δ 7.42 – 7.39 (m, 2H), 7.31 – 7.24 (m, 3H), 2.64 – 2.55 (m, 1H), 1.92 – 1.85 (m, 2H), 1.79 – 1.74 (m, 2H), 1.58 – 1.52 (m, 3H), 1.40 – 1.33 (m, 3H). **¹³C NMR** (75 MHz, CDCl₃): δ 131.7 (2 C), 128.3 (2 C), 127.5, 124.3, 94.6, 80.7, 32.9, 29.8, 26.1 (2 C), 25.1 (2 C).

(2,2-Dichlorovinyl)cyclohexane (**100**)

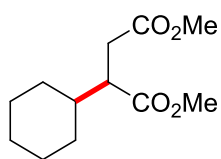


Following general procedure F with **19** (0.3 mmol, 189.3 mg) and trichloroethylene **99** (1.2 mmol, 108 μL). The crude product was purified by

flash column chromatography (pentane) to afford **100** as a colorless oil (39 mg, 70%). The spectroscopic data are in agreement with those reported in the literature.^{22a}

¹H NMR (300 MHz, CDCl₃): δ 5.70 (d, *J* = 9.2 Hz, 1H), 2.43 – 2.32 (m, 1H), 1.77 – 1.62 (m, 5H), 1.37 – 1.04 (m, 6H). **¹³C NMR** (75 MHz, CDCl₃): δ 135.2, 118.7, 39.3, 31.8 (2 C), 25.9, 25.7 (2 C).

Dimethyl 2-cyclohexylsuccinate (**102**)



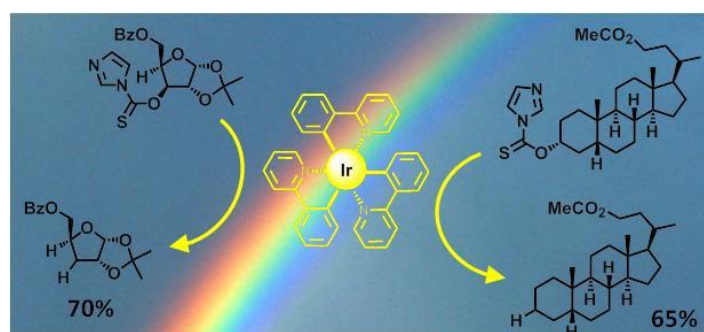
To a stirred schlenk flask was added potassium [18-C-6] bis(catecholato) cyclohexylsilicate **19** (1 eq., 0.3 mmol, 189.3 mg), KH_2PO_4 (1.2 eq., 0.36 mmol, 49 mg), 4CzIPN **86** (1 mol %, 3 μmol , 2.4 mg) and dimethyl maleate **101** (4 eq., 1.2 mmol, 150 μL). DMF was added (3 mL). The reaction mixture was degassed by argon bubbling for 20 minutes and irradiated with blue LED (477 nm) for 24 hours. The reaction mixture was diluted with diethyl ether (50 mL), washed with saturated aqueous NaHCO_3 (2 times), brine (2 times), dried over MgSO_4 and evaporated under reduced pressure. The crude product was purified by flash column chromatography to afford the 1,4 adduct **102** as a colorless oil (84 mg, 78%). The spectroscopic data are in agreement with those reported in the literature.^{22a}

^1H NMR (300 MHz, CDCl_3): δ 3.67 (s, 3 H), 3.64 (s, 3 H), 2.76 – 2.65 (m, 2 H), 2.48 – 2.38 (m, 1 H), 1.74 – 1.85 (m, 6 H), 1.29 – 0.97 (m, 5 H). **^{13}C NMR** (100 MHz, CDCl_3): δ 175.0, 173.0, 51.80, 51.6, 47.1, 40.03, 33.3, 30.7, 30.2, 29.8, 26.4, 26.2.

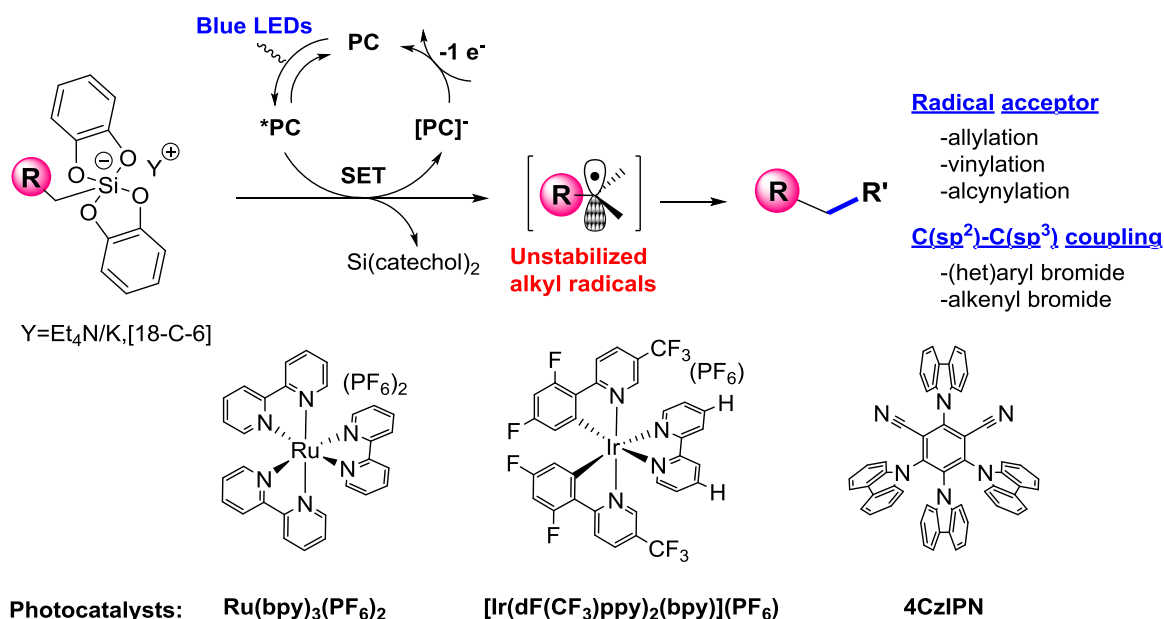
General Conclusion

The visible-light photoredox catalysis has emerged as a very powerful strategy to generate radical species replacing more and more tin-mediated or some stoichiometric redox methodologies. Many opportunities are now available to access to a large range of C-centered radicals, based either on photooxidative or reductive processes.

In this Ph. D. thesis, we reported a photocatalytic alternative of Barton-McCombie deoxygenation based on a visible-light photoreduction of *O*-thiocarbamates derived from secondary and tertiary alcohols. The iridium complex Ir(ppy)₃ proved to be the most efficient catalyst in the presence of Hünig's base as a sacrificial electron donor. A mechanistic determination based on fluorescence quenching and cyclic voltammetry experiments was successfully investigated to determine the photocatalytic process involved.



However, generation of unstabilized alkyl radicals is still a challenge. Indeed methodologies have been developed to generate stabilized alkyl radicals by photooxidation of organotrifluoroborates or α -aminocarboxylates. In the second part of my Ph. D., we reported the generation of unstabilized alkyl primary radicals by photooxidation of bis(catecholato)-alkylsilicates. These radicals can be trapped by radical acceptors or engaged with (hetero)aryl halides or alkenyl halides as electrophiles in dual photoredox/nickel catalysis for the formation of C(sp³)-C(sp²) bonds. Usually, metal complexes based on ruthenium or iridium are used as photocatalysts but increasing efforts have been realized to develop processes involving organic photocatalysts. We developed an iridium-free alkyl radicals generation by photooxidation of the bis(catecholato)-alkylsilicates using the organic dye 4CzIPN.



This Ph. D. thesis work led to four scientific publications, one review and one book chapter.

- **“Organic photoredox catalysis for the oxidation of silicates: applications in radical synthesis and dual catalysis.”** C. Lévêque, L. Chenneberg, V. Corcé, C. Ollivier, L. Fensterbank, *Chem. Commun.* **2016**, DOI: 10.1039/C6CC04636
- **“Tin-free Alternatives to the Barton-McCombie Deoxygenation of Alcohols to Alkanes Involving Reductive Electron Transfer.”** L. Chenneberg and C. Ollivier, *CHIMIA* **2016**, 70, 67.
- **“Primary alkyl bis-catecholato silicates in dual photoredox/nickel catalysis: aryl- and heteroarylalkyl cross coupling reactions.”** C. Lévêque, L. Chenneberg, V. Corcé, J.-P. Goddard, C. Ollivier and L. Fensterbank, *Org. Chem. Front.* **2016**, 3, 462.
- **“Single-Electron-Transfer Oxidation of Trifluoroborates and Silicates with Organic Reagents: A Comparative Study.”** L. Chenneberg, C. Lévêque, V. Corcé, A. Baralle, J.-P. Goddard, C. Ollivier and L. Fensterbank, *Synlett* **2016**, 27, 731.
- **“Visible Light Photocatalytic Reduction of O-Thiocarbamates: Development of a Tin-Free Barton-McCombie Deoxygenation Reaction.”** L. Chenneberg, A. Baralle, M. Daniel, L. Fensterbank, J.-P. Goddard, C. Ollivier, *Adv. Synth. Catal.* **2014**, 356, 2756.
- **“Reduction of Saturated Alcohols and Amines to Alkanes.”** L. Chenneberg, J.-P. Goddard, L. Fensterbank in *Comprehensive Organic Synthesis (2nd Edition)*; G. A. Molander, P. Knochel (Eds.), Elsevier, Oxford, Vol. 8, **2014**, 1011.

NOUVELLES AVANCEES EN CATALYSE PHOTOREDOX : APPLICATIONS EN CHIMIE RADICALAIRE DE SYNTHESE ET EN CATALYSE DUALE

L'objectif principal des travaux de recherche décrits dans ce manuscrit de thèse, est de concevoir de nouvelles méthodes de synthèse en chimie radicalaire et organométallique, de les associer dans une catalyse duale afin qu'elles puissent être appliquées à l'élaboration de briques moléculaires élaborées.

Nous avons développé dans une première étude une alternative photocatalytique à la réaction de désoxygénation classique de Barton-McCombie d'alcools secondaires et tertiaires par l'hydrure de tributylétain. Celle-ci repose sur l'utilisation d'un précurseur *O*-thiocarbamate dérivé d'alcools pouvant être réduit par catalyse photorédox. Une étude mécanistique, basée sur des expériences de fluorescence et de voltammétrie cyclique, est aussi présentée. Dans une seconde étude, une élégante méthode de génération de radicaux alkyles non stabilisés, par photooxydation de « ate-complexes » de bore ou d'espèces hypervalentes à base de silicium est présentée. Ces radicaux sont piégés en présence d'accepteurs radicalaires ou engagés dans une catalyse duale avec des complexes de Nickel.

Mots clés : *Catalyse photoredox, Catalyse duale, Oxydation, Réduction, Désoxygénation, Thiocarbamates, Silicates, Réactions radicalaires*

NEW ADVANCES IN PHOTOREDOX CATALYSIS: APPLICATIONS IN RADICAL CHEMISTRY SYNTHESIS AND DUAL CATALYSIS

Visible-light photoredox catalysis has emerged as a very powerful strategy to generate radical species replacing more and more tin-mediated or stoichiometric redox methodologies. The main objective of the research described in this Ph. D. thesis is to develop new synthetic methodologies in radical and organometallic chemistry, and merge them in a dual catalysis process for the preparation of elaborated molecular building blocks.

In a first study, we report a photocatalytic alternative of Barton-McCombie deoxygenation based on a visible-light photoreduction of *O*-thiocarbamates derived from secondary and tertiary alcohols. A mechanistic investigation is presented based on fluorescence quenching and cyclic voltammetry experiments. In a second study, a challenging method of generation of unstabilized alkyl radicals by photooxidation of borate salts or hypervalent silicon species is reported. These radicals are trapped by free radical scavengers or engaged in a photoredox/nickel dual catalysis.

Key words: *Photoredox catalysis, Dual catalysis, Oxidation, Reduction, Deoxygenation, Thiocarbamates, Silicates, Radical reactions*