SYNTHESIS OF PHTHALIDES AND BENZOLACTONES VIA CATALYTIC C-H FUNCTIONALIZATION/C-O BOND-FORMING REACTIONS

Juan Gallardo Donaire

Dipòsit Legal: T 1365-2014

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DOCTORAL THESIS

Supervised by Dr. Rubén Martín Romo

Institut Català D'Investigació Química (ICIQ)

UNIVERSITAT ROVIRA I VIRGILI

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ICIQ
Institut Català d'Investigació Química

Av. Països Catalans, 16
43007 Tarragona
Tel. 977 920 200
Fax 977 920 225

UNIVERSITAT ROVIRA I VIRGILI

Departament de Química Física i Inorgànica
C/Marcel·lí Domingo s/n
Edifici N4
Campus Sescelades
43007 - Tarragona
secqfqi@urv.cat
Tel. +34 977 558 137 9696
Fax. 977 559 563

Dr. Rubén Martín Romo, Group Leader of Research Group,

CERTIFIES, that the present Doctoral Thesis entitled: "**Synthesis of phthalides and benzolactones via catalytic C-H functionalization/C-O bond forming reactions**", presented by Juan Gallardo Donaire to receive the degree of Doctor, has been carried out under his supervision at the Institute of Chemical Research of Catalonia (ICIQ).

Tarragona, 22nd April 2014.

PhD Supervisor

Rubén Martín Romo

Acknowledgements

This doctoral thesis has been carried out at ICIQ (Institut Català d´Investigació Química) under the supervision of Dr. Rubén Martín Romo, to whom I would like to express all my gratitude for giving me the opportunity to be part of his research group and for all the help, support and chemistry discussions during these 4 years.

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Fuera del ámbito profesional quería agradecer a mi padres, Simón y Montse y a mi hermano Jorge todo el amor incondicional mostrado a lo largo de mi vida. Sin ellos nada de esto hubiera sido posible.

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List of Publications

The results of this PhD thesis have delivered the following publications:

1. "*Synergistic Palladium-Catalyzed C(sp^3)-H Activation/C(sp^3)-O Bond Formation: A Direct, Step-Economical Route to Benzolactones*" Petr Novak, Arkaitz Correa, **Joan Gallardo-Donaire**, and Ruben Martin. *Angew. Chem. Int. Ed*. **2011**, 50, 12236.

2. "*Cu-Catalyzed Mild C(sp^2)–H Functionalization Assisted by Carboxylic Acids en Route to Hydroxylated Arenes*"Joan Gallardo-Donaire and Ruben Martin. *J. Am. Chem. Soc.*, **2013**, *135*, 9350.

Moreover, the following manuscript has been submitted:

3. "*A Mild C(sp2)– & C(sp3)-H Functionalization/C-O Bond Formation Catalyzed by in situ Generated Hypervalent Iodine (III) Reagents*" Xueqianq Wang, Joan Gallardo-Donaire and Ruben Martin. *Submitted*.

Besides the publications presented in this thesis I resulted as co-author in:

4. "***Total Synthesis of Entecavir***"Javier Velasco, Xavier Ariza, Laura Badía, Martí Bartra, Ramon Berenguer, Jaume Farràs, **Joan Gallardo**, Jordi Garcia, and Yolanda Gasanz. *J. Org. Chem.*, **2013**, *78*, 5482.

Abbreviations

δ	chemical shift
BQ	benzoquinone
$CDCl_3$	deuterated chloroform
Conv.	conversion
d	doublet
DCE	1,2-dichloroethane
dd	double doublet
DDQ	2,3-Dichloro-5,6-dicyano-p-benzoquinone
DIBAL-H	diisobutyl aluminum hydride
Dtbbpy	4,4'-di-*tert*-butyl-2,2'-bipyridine
DG	directing group
DMA	*N*,*N*-dimethylacetamide
DMEDA	*N*,*N*'-Dimethylethylenediamine
DMF	*N*,*N*-Dimethylformamide
Eq.	equivalents
h	hours
HAA	hydrogen atom abstraction
J	coupling constant
m	multiplete
m.p.	melting point
NBS	N-Bromosuccinimide
NFSI	N-Fluorobenzenesulfonimide
NMP	1-Methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
Oxone	monopersulfate compound ($2KHSO_5 \cdot KHSO_4 \cdot K2SO_4$)
o-xylene	1,2-Dimethylbenzene
PA	2-Pyridinecarboxamide
PCC	pyridinium chlorochromate
PIDA	(diacetoxyiodo)benzene
PIFA	[Bis(trifluoroacetoxy)iodo]benzene
s	singlet
Selectfluor	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
t	triplet
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
TIPS	triisopropylsilyl
TMS	trimethylsilyl

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Chapter 1. General Introduction

1.1 C-H functionalization reactions

Transition metal-catalyzed reactions have undoubtedly changed logics when assembling complex molecules. In the last three decades, catalytic cross-coupling techniqueshave provided new opportunities for C-C and C-heteroatom bond forming reactions, thus providing new *vistas*in total synthesis, medicinal chemistry, chemical biology and nanotechnology.[1] Moreover, these processeshave reached a level of sophistication that allow a wide range of coupling partners to be combined efficiently (Figure 1, paths a and b).Not surprisingly, the importance of these reactions was recognized by the the Nobel Prize in chemistry to Richard Heck, Ei-ichi Negishi and Akira Suziki in 2010 for "*palladium-catalyzed cross-couplings in organic synthesis*".

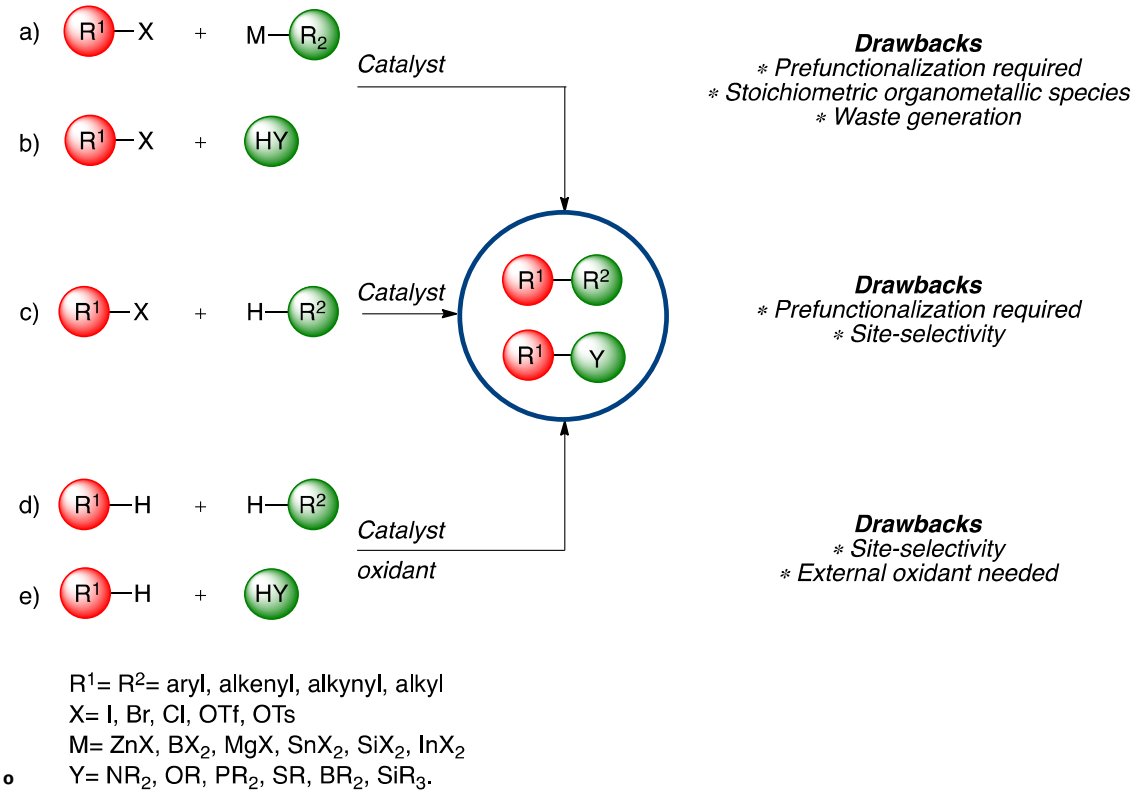


Figure 1.1

Despite the tremendous impact of these methodologies, there are still several issues to be addressed in classical cross-coupling reactions (Figure 1.1, paths a and b): 1) pre-functionalization in at least one of the counterparts is required, 2) general inherent

[1](a)Diederich, F., Stang, P. J., "Metal-catalyzed Cross-Coupling Reactions" Wiley-VCH, Weinheim, Germany, **1998**. (b) A. K. Yudin, "Catalyzed Carbon Heteroatom Bond Formation",Wiley-VCH, Weinheim, **2011**.

instability of organometallic reagents (susceptible to undergo proto-demetallation or β-hydride eliminationwhen alkyl organometallics are used), 3) the need for stoichiometric amounts of organometallic species and 4) a considerable amount of waste is generated.Accordingly, the development of more straigforward, atom- and step-economical reactions have received a great deal of attention.Pioneering work from Barton[2] and Breslow[3]regarding radical C-H oxidation of aliphatic C-H bonds set up the stage for the development of new technologies based upon C-H bond functionalization as a new platform for molecular diversity from simple available precursors.[4]Indeed, the possibility of converting inert and rather ubiquitous C-H bonds into advanced intermediates can hardly be underestimated. Innovative C-H bond functionalization reactions have been developed in the literature (Figure 1, path c), drastically reducing the amount of wastewhileavoiding the use of stoichiometric metal reagents.However, prefunctionalization of the electrophilic counterpart is required, hence becoming less attractive from anstep-economical point of view. Recently, chemistshave reported considerable advances by a two-fold C-H bond functionalization (Figure 1.1, d and e).[5] It is worth mentioning, however, that stoichiometric amounts of oxidant are required, and that site-selectivity in the presence of several C-H bonds still represents a considerable challenge that need to be addressed in this area.

One of the most widespread strategies for overcoming the site-selectivity problemamong different C-H bonds is the use of a directing group (DG),[6]by bringing the metal in close proximity to the targeted C-H bond, as depicted inFigure 1.2. To such end, directinggroups such as pyridine, imines, amides, etc. have been effectively employed for a plethora of C-H activation reactions via the formation of five- or six-membered metallacycles**II**. Although by no doubt powerful methods, theseprocedures

[2]Barton, D. H. R.; Doller, D. *Acc. Chem. Res.***1992**, *25*, 504
[3]Breslow, R. *Acc. Chem. Res.***1980**, *13*, 170.
[4]Selected reviews on C-H functionalization: (a) Sames, D.; Godula, K. *Science*, **2006**, *312*, 67. (b) Albericio, D.; Scott, M. E.; Lautens, M. *Chem. Rev.*, **2007**, *107*, 174. (c) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem. Int. Ed.***2009**, *48*, 5094. (d) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.*, **2009**, *48*, 9792 (e) Lyons, T. W.; Sanford, M. *Chem. Rev.***2010**, *110*, 1147. (f) Wencel-Delord, J.; Gröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.***2011**,*40*, 4740. Selected publications: (a) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem. Int. Ed.***2006**, *45*, 2619. (b) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.***2006**, *128*, 581. (c) Ferraccioli, R.; Carenzi, D.; Motti, E.; Catellani, M. *J. Am. Chem. Soc.***2006**, *128*, 722.
[5] Selected reviews: (a) Yeung, C. S.; Dong, V. M. *Chem. Rev*. **2011**, *111*, 1215. (b) Li, C. –J. *Acc. Chem. Res.***2009**, *42*, 335. (c) Scheuermann, C. J. *Chem. Asian J*. **2010**, *5*, 436. (d) Girard, S. A; Knauber, T.; Li, C.-J. *Angew. Chem. Int. Ed.***2014**, *53*, 74.
[6] For the use of directing groups in transition metal-catalyzed C-H functionalization reactions see: (a) Daugulis, O.; Do, H.; Shabashov, D. *Acc. Chem. Res*. **2009**, 42, 1074. (b) Daugulis, O. *Top. Curr. Chem.***2010**, *292*, 57. (c) Ackermann, L.; Vicente, R. *Top. Curr. Chem*. **2010**, *292*, 211. (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.***2010**, *110*, 624. (e) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.***2012**, *112*, 5879.

are not yet synthetically attractive, as the cleavage of such groups stillconstitutes a tremendous challenge. Moreover, the resulting metallacyclesare thermodynamically stable and kinetically inert. To overcome these limitations, Yu[7] recently introduced the use of ketones, carboxylic acids and ethers as weakly coordinating directing groups for effecting C-H bond functionalization reactions. These groups are capable of coordinating the metal while forming a less stable but rather reactive metallacycle.

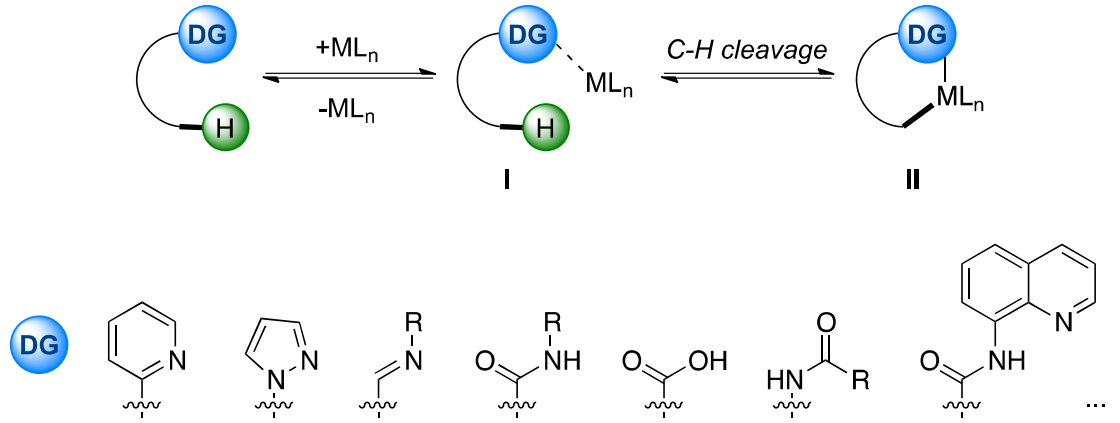
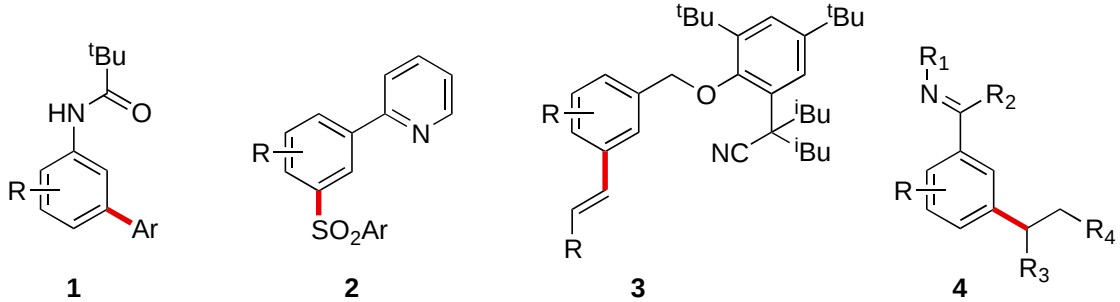


Figure 1.2

While the vast majority of C-H bond functionalization reactions are limited to the use of DG's in the *ortho* position, elegant approaches by Gaunt **1**, Frost **2**, Yu **3** and Ackermann **4**have demonstrated the *meta* C-H bonds[8]functionalization is also within reach (Figure 1.3).



1 *Gaunt*, **2009** **2** *Frost*, **2009** **3** *Yu*, **2012** **4** *Ackermann*, **2013**

Figure 1.3

[7]Engle, K. M.; Mei, T.; Wasa, M.; Yu, J.-Q.*Acc. Chem. Res*. **2012**, *45*, 788.
[8] (a) Phipps, R. J.; Gaunt, M. J. *Science***2009**, *323*, 1593. (b) Ciana, C.-L.; Phipps, R. J.; Brandt, J. R.; Meyer, F.-M.; Gaunt, M.*Angew. Chem. Int. Ed.***2011**, *50*, 458. (c) Saidi, O.; Marafie, J.; Ledger, A. E. W.; Liu, P. M.; Mahon, M. F.; Kociok-Köhn, G.; Whittlesey, M. K.; Frost, C. G. *J. Am. Chem. Soc.***2011**, *133*, 19298. (d) Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. *Nature***2012**, *486*, 518. (e) Truong, T.; Daugulis, O. *Angew. Chem. Int. Ed.***2012**, *51*, 11677. (f) Hofmann, N.; Ackermann, L. *J. Am. Chem. Soc.***2013**, *135*, 5877. (g) Yang, Y.-F.; Cheng, G.-J.; Liu, P.; Leow, D.; Sun, T.-Y.; Chen, P.; Zhang, X.; Yu, J.-Q.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.***2014**, *136*, 344.

In order to overcome the inertness of C-H bonds in catalytic functionalization eventsfour different mechanisms have been invoked;[9] 1) oxidative addition, 2) bond σ-bond metathesis, 3) electrophilic substitution and 4) base assisted metallation.

1) ***Oxidative Addition***.[9] The mechanism is characterized by the insertion of the metal center into the C-H bond, hence creating a M-C and M-H bond in the transition state (TS). Consequently, the formal oxidation state at the metal center increases by two, creating a change in the metal geometry of the complex to accommodate the two newly formed σ-bonds (Figure 1.4). This mechanism typically operates with electron richlate transition metals.

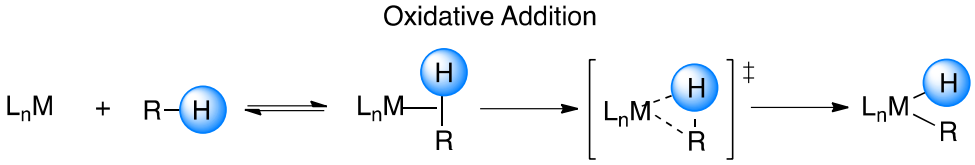


Figure 1.4

2) ***σ-Bond metathesis***.[9]In this case, low valent transition metals participate in a concerted process in whichtwo σ-bonds are broken at the same time that other two σ-bonds are formed without changing the oxidation state at the metal center, as shown in Figure 1.5.

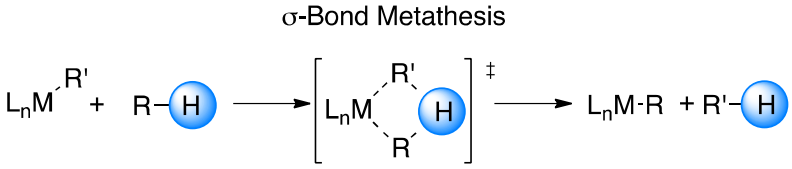


Figure 1.5

3) ***Electrophilic substitution***.[9]This mechanismis believed to proceed via the direct substitution of a metal for a proton without the observation of any organometallic intermediate (Figure 1.6). The proton acceptor can be an external base or solvent or a sufficiently basic group in the coordination sphere
of the metal. Reactions of that type operate in a highly polar medium or under acidic conditions.

[9] Selected reviews on mechanistic aspects of C-H bond functionalization: (a) Pfeffer, M. *Chem. Rev*. **2002**, *102*, 1731. (b) Bergman, R. G. *Nature***2007**, *417*, 507. (c) Balcells, D.; Clot, E.; Eisentein, O. *Chem. Rev*. **2010**, *110*, 749.

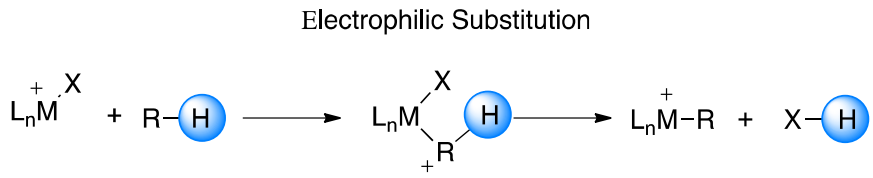


Figure 1.6

4) ***Base assisted metallation - Concerted-Metallation-Deprotonation (CMD)***.[10]These C-H bond transformations are proposed to proceed via the assistance of a bifunctional ligand (typically carboxylates) containing an additional Lewis-basic heteroatom, that subsequently participates in a concerted deprotonation event (Figure 1.7). Initial experimental and theoretical studies performed independently by the groups of MacGregor[11], Echavarren,[12] and Fagnou[13] conclude that the presence of a carboxylate unitsignificantly decreases the activation energy in the concerted process.

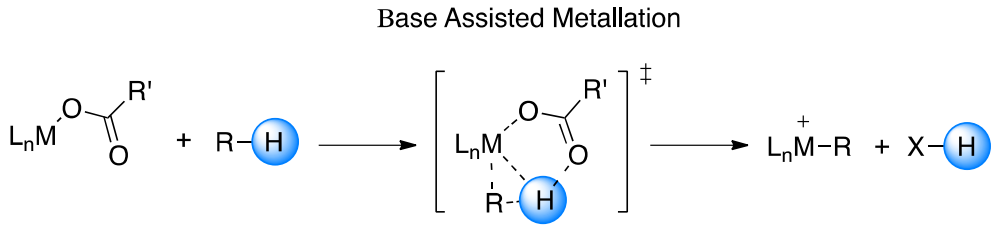


Figure 1.7

While ligand design has driven the development of many areas in homogenous catalysis, the field of C-H bond functionalizationstill lacks of suitable ligand scaffolds.[14]Indeed, strong σ-donors can compete with the substrate forbinding the metal centerthus making the metal unreactive (**III,** Figure 1.8). Additionally, such ligands might have a deleterious effect on catalytic activity, as in many cases C-H functionalization is better accomplished when using relatively electron-poor metal centers. Yet an important contributory factor is the control for assembling both the substrate and the ligand in the pre-transition state.As illustrated in Figure 1.8, a

[10](a) Lapointe, D.; Fagnou, K. *Chem. Lett.***2010**, *39*, 1118. (b) Ackermann, L. *Chem. Rev*. **2011**, *111*, 1315.
[11]Davies, D. L.; Donald, S. M.; Macgregor, S.*J. Am. Chem. Soc.***2005**, *127*, 13754.
[12](a) García-Cuadrado, D.; Braga, A.C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.***2006**, *128*, 1066. a) García-Cuadrado, D.; de Mendoza, P.; Braga, A.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.***2007**, *129*, 6880.
[13](a) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.***2006**, *128*, 581. (b) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.***2008**, *130*, 10848.
[14]Engle, K. M.; Yu, J.-Q. *J. Org. Chem.***2013**, *78*, 8927.

cooperative effect is necessary for influencing both reactivity and/or selectivity (**IV**).

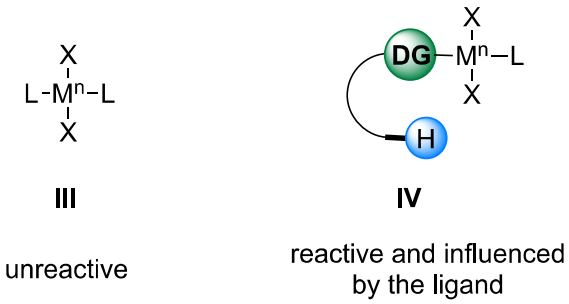
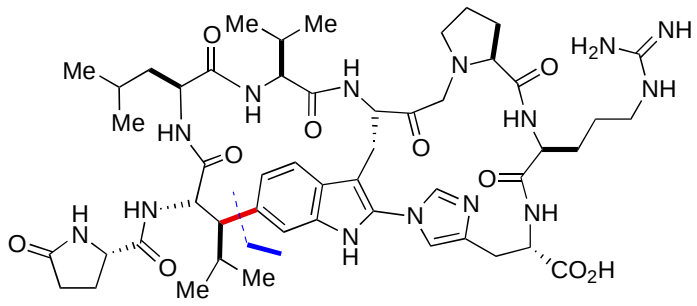


Figure 1.8

1.2 Applicability of C-H bond functionalization

Prompted by the excellent results in the area of C-H bond functionalization,[4,5] these methodologies have found widespread use in a great number of total synthesis[15] of complex molecules (Figure 1.9). Additionally, C-H bond functionalization methodologies can be applied in large scale, as illustrated in the synthesis of flubendiamide[16]**11** and the kilogram scale synthesis of the GABA agonist **10** developed by Merck.[17]

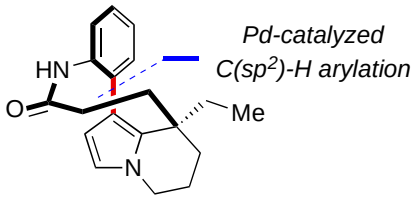
[15]For selected reviews on C-H functionalization in the context of total synthesis: (a) Wutekunst, W.; Baran, P. *Chem. Soc. Rev.***2011**, *40*, 1976. (b) McMurray, L.; O'Hara, F.; Gaunt, M. *Chem. Soc. Rev.* **2011**, *40*, 1885. (c) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.***2012**, *51*, 2. Examples from Figure 1.9: (a) Bowie, A. L.; Hughes, C. C.; Trauner, D. *Org. Lett.***2005**, *7*, 5207. (b) Fu, R.; Zhao, B.; Shi, Y. *J. Org. Chem.***2009**, *74*, 7577. (c) Feng, Y.; Chen, G. *Angew. Chem. Int. Ed.***2010**, *49*, 958. (d) Wang, D.; Yu, J.-Q. Am. Chem. Soc. **2011**, 133, 5767. (e) Gutekunst, W. R.; Baran, P. S. *J. Am. Chem. Soc.***2011**, *133*, 19076.
[16]Kodama, H.; Katsuhira, T.; Nishida, T.; Hino, T.; Tsubata, K. **2001***Patent* WO2001083421A1.
[17]Gauthier, D. R.; Limanto, J.; Devine, P. N.; Desmond, R. A.; Szumigala, R. H.; Foster, B. S.; Volante, R. P. *J. Org. Chem.***2005**, *70*, 5938.



Pd-catalyzed C(sp^3)-H arylation

5

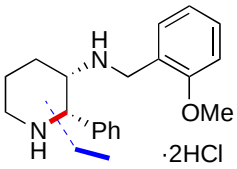
Celogentin (*Chen*, **2010**)



Pd-catalyzed C(sp^2)-H arylation

6

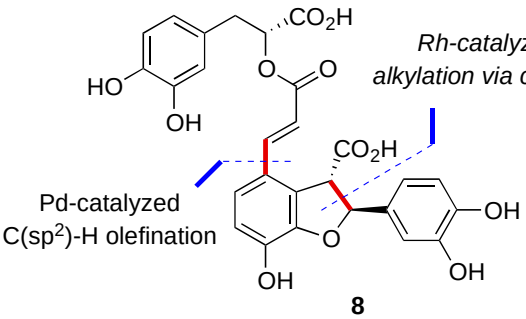
Rhazinilam (*Trauner,* **2005**)



Pd-catalyzed allylic C-H amination

7

(+)-CP-99,994 (*Shi*, **2009**)

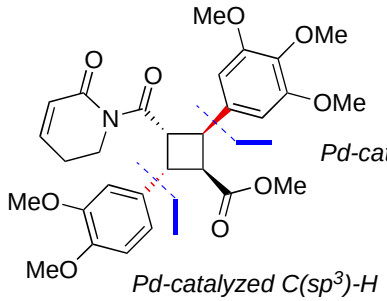


Rh-catalyzed C(sp^3)-H alkylation via carbene insertion

Pd-catalyzed C(sp^2)-H olefination

8

(+)-Lythospermic acid (*Yu*, **2011**)

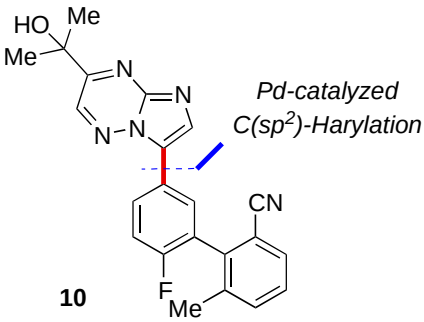


Pd-catalyzed C(sp^3)-H arylation

Pd-catalyzed C(sp^3)-H arylation

9

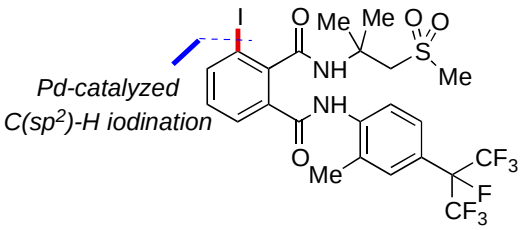
Piperarborenine B (*Baran*, **2011**)



Pd-catalyzed C(sp^2)-Harylation

10

GABA agonist (*Gauthier, Jr.*, **2005**)
kilogram scale



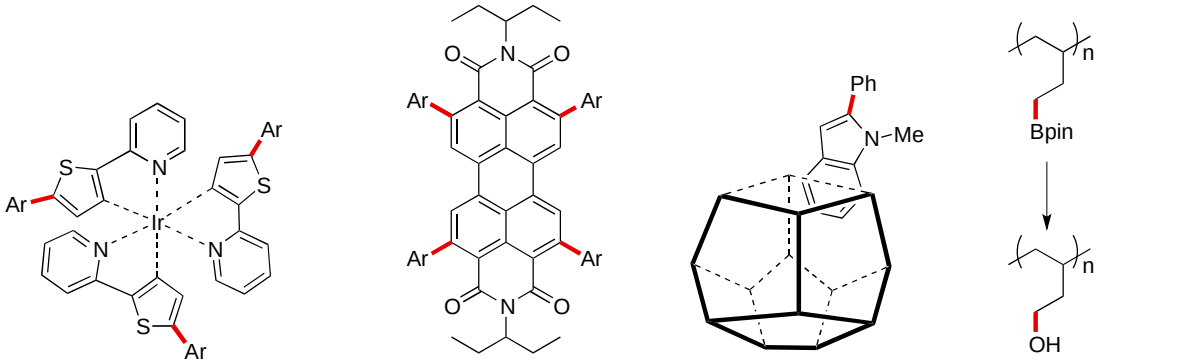
Pd-catalyzed C(sp^2)-H iodination

11

Flubendiamide (*Tsubata*, **2001**)
ton scale

Figure 1.9

Recently, the means to promote a *late stage diversification*[18]hasbeen applied within the C-H functionalization arena, providing a perfect opportunity toeasily access organic scaffolds in a straightforwardfashion. For instance, new luminescent compounds[19] for optical applications**12**-**15**, modification of complex polydispersed structures such as three-dimensional metal organic frameworks[20](MOF) **14**or polymers[21]**15**have been developed.



12 — OLED (*Doucet and Guerchais*, **2010**)

13 — OLED (*Kim, Shinokubu and Osuka*, **2012**)

14 — MOF (*Glorius*, **2011**)

15 — Polymer (*Hartwig and Hillmyer*, **2002**)

Figure 1.10

1.3 C-O bond forming reactions via C-H functionalization

While a myriad of C-C bond-forming reactions have been described in the literature, the means to promote related carbon-heteroatom bond formation processeswithin a C-H functionalization event has comparatively received much less attention. Beyond any doubt, the discovery of Buchwald-Hartwig amination[22]and Ullmannether synthesis,[23] has set up the standards in this area. Despite exceptional advances, the formationof C-O bonds still remains a considerable challenge in the cross-coupling arena. This is due to the large energy gap between the highest occupiedmolecular orbital (HOMO) of the M-O bond and the lowestunoccupied molecular orbital (LUMO)of the M-C bond,and the

[18]Wencel-Delord, J.; Glorius, F. *Nat. Chem.***2013**, *5*, 369.
[19] (a) Beydoun, K.; Zaarour, M.; Williams, J. A. G.; Doucet, H.; Guerchais, V.*Chem. Commun.***2012**,*48*,1260. (b) Nakazono, S.; Easwaramoorthi, S.; Kim, D.; Shinokubo, H; Osuka, A.*Org. Lett*. **2009**, *11*, 5426.
[20] Dröge, T.; Notzon, A.; Fröhlich, R.; Glorius, F. *Chem. Eur. J.***2011**, *17*, 11974.
[21] (a) Kondo, Y.; García-Cuadrado, D.; Hartwig, J. F.; Boaen, N. K.; Wagner, N. L.; Hillmyer, M. a. *J. Am. Chem. Soc.***2002**, *124*, 1164. (b) Jo, T. S.; Kim, S. H.; Shin, J.; Bae, C.*J. Am. Chem. Soc.***2009**,*131*, 1656.
[22] (a) Hartwig, J. F. *Angew. Chem. Int. Ed.***1998**, *37*, 2046. (b) Surry, D. S.; Buchwald, S. L.*Chem. Sci*.**2010**, *1*, 13. (c) Sci, C.; Surry, D. S.; Buchwald, S. L.*Chem. Sci*.**2011**,*2*, 27.
[23] (a) Ullmann, F. *Ber. Dtsch. Chem. Ges*. **1904**, *37*, 853.

substantial ionic character of the M-O bond.[24]However, early studies by Buchwalddemonstrated that C(sp^2)-O bond reductive elimination can easily take place in the presence of the right ligand(Figure, 1.11, eq. 1).[25]Recently, Hartwig described the C(sp^3)-O bond forming reductive elimination of ethers from bisphosphine-ligated benzylpalladium(II) aryloxide complexes(equation 2).[26]In bothcases, a judicious choice of the supporting ligand plays a critical role in the reaction outcome.

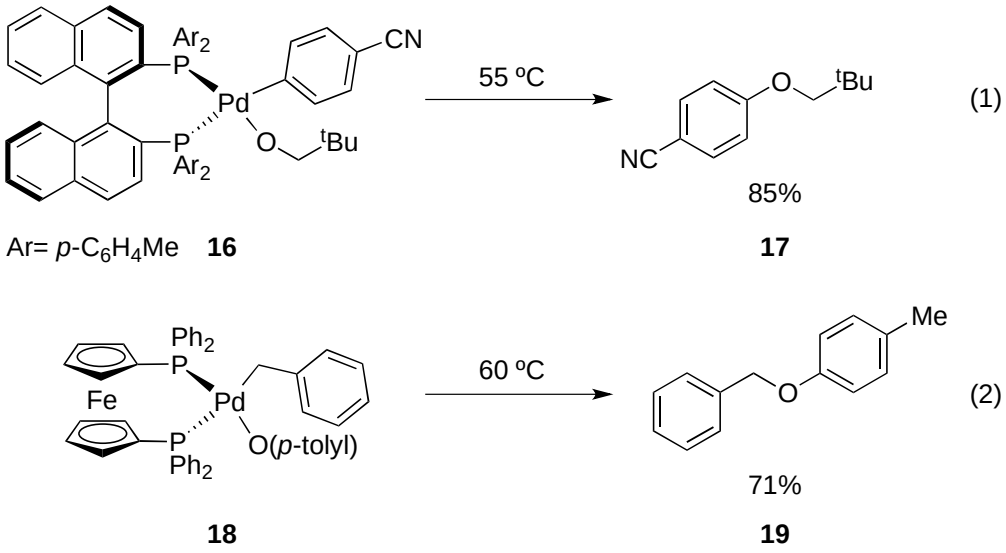


Figure 1.11

1.3.1 Palladium-catalyzed C(sp^2)-O bond formation via C-H functionalization

In the last decade, a considerable number of protocols for C-O bond formation via C(sp^2)-H bond functionalizationhave been reported in the literature. Among all transition-metals available, palladium, copper and ruthenium metal salts are the most widely utilized in these endeavors due to the following: 1) Pd, Ru and Cu complexes are easy to handle, 2) their knownpropensity to form cyclometallated products[27] and 3)

[24] (a) Bäckvall, J.; Bjorkman, E. E.; Pettersson, L.; Siegbahdb, *J. Am. Chem. Soc.***1984**, *106*, 4369. (b) Hartwig, J. F. *Inorg. Chem*. **2007**, *46*, 1936.
[25] (a) Widenhoefer, R. a.; Zhong, H. A.; Buchwald, S. L. *J. Am. Chem. Soc.***1997**, *119*, 6787. (b) Widenhoefer, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.***1998**, *120*, 6504.
[26] Marquard, S. L.; Hartwig, J. F. *Angew. Chem. Int. Ed.***2011**, *50*, 7119.
[27] C−H bond functionalization and cyclometalation: (a) Valeria, V. D.; Zalevskaya, O. A.; Potapov, V. M. *Russ.Chem. Rev.***1988**, *57*, 250. (b) Ryabov, A. D. *Chem. Rev.***1990**, *90*, 403. (c) Fernandez, S.; Pfeffer, M.; Ritleng, V.; Sirlin, C.*Organometallics***1999**, *18*, 2390. (d) Davies, D. L.; Al-Duaij, O.; Fawcett, J.; Giardiello, M.; Hilton, S. T.; Russell, D. R. *Dalton Trans*.**2003**, *4132*. (e) Dupont, J.; Consorti, C. S.;Spencer, J. *Chem. Rev.***2005**, *105*, 2527. (f) Boutadla, Y.; Al-Duaij, O.; Davies, D. L.; Griffith, G. A.; Singh, K. *Organometallics***2009**, *28*, 433. (g) Djukic, J. P.; Sortais, J. B.; Barloy, L.; Pfeffer, M. *Eur. J. Inorg. Chem.***2009**, 817.

compatibility with strong oxidants to reach higher oxidation states, thus facilitating the subsequent reductive elimination step.

1.3.2 Pd(II)/Pd(0) catalyzed C(sp^2)-H functionalization/C-O bond formation

Mechanistically, the Pd(II)/Pd(0) catalytic cycle is believed to proceed troughan initial C-H functionalization step (prior substrate coordination) to form **V**, followed by a ligand exchange with the corresponding alkoxyde to reach intermediate **VI**. Next, reductive elimination takes placeto form a new C-O bond with concomitant formation of Pd^0L_n, whichis re-oxidized to recoverthe active $Pd^{II}L_n$catalytic species (Figure 1.12).

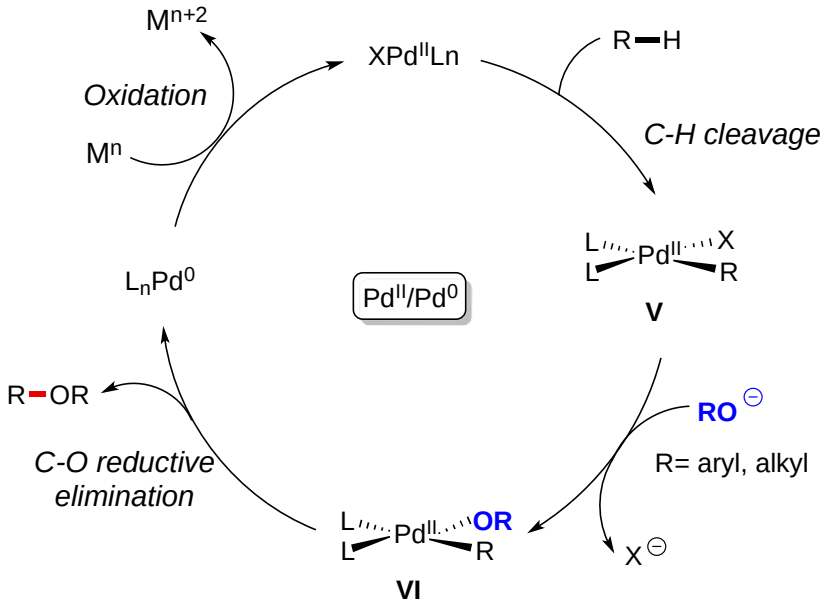


Figure 1.12

In 2011, Liu and co-workers[28] reported the intramolecular synthesis of dibenzofuranes via Pd(II)/Pd(0) using phenol as the directing group employing air as oxidant (Figure 1.13). Stoichiometric experiments showed that **23** was competetent as reaction intermedíate affording benzofurane **21** via C-O bond reductive elimination at high temperatures by using the bulky IPr as supporting ligand. Moreover, the inclusion of 4,5-diazafluoren-2-one **22**, firstly introduced by Stahl,[29] turned out to be important presumably by helping the aerobic oxidation of Pd(0) to regenerate the catalytically active Pd(II) catalyst.

[28]Xiao, B.; Gong, T.; Liu, Z.; Liu, J.; Luo, D.; Xu, J.; Liu, L.*J. Am. Chem. Soc.***2011**, *133*, 9250.
[29]Campbell, A. N.; White, P. B.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.***2010**, *132*, 15116.

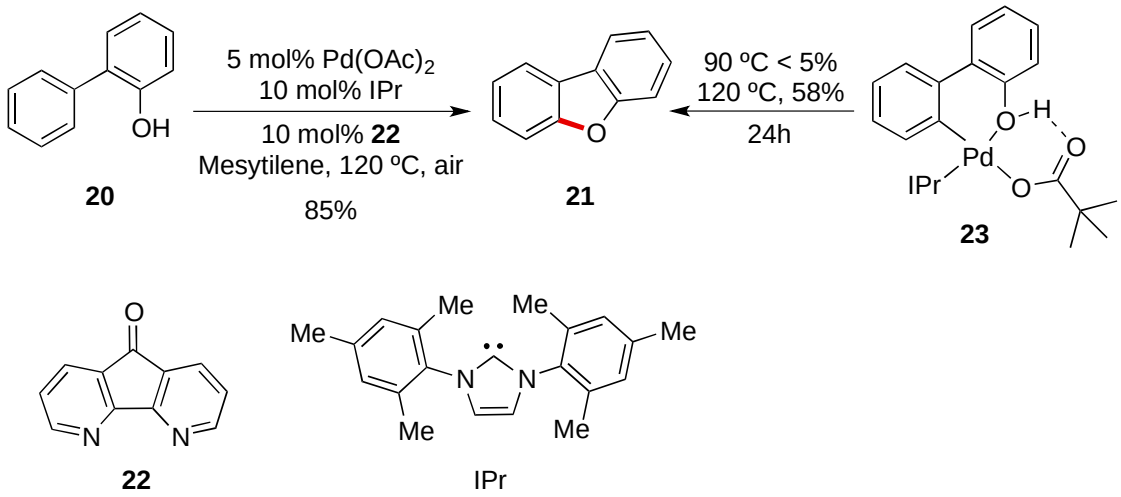


Figure 1.13

1.3.3 Pd(II)/Pd(IV) catalyzed C(sp^2)-H activation/C-O bond formation

Taking into consideration the difficulty for promoting C-O bond reductive elimination, a solution to such endeavor could be the utilization of metals in high oxidation states. In recent years, the development of new C-H bond functionalization reactions via the *in situ* generated Pd(IV) or Pd(III)-Pd(III) species have shown to be a viable and powerful alternative to classical protocols based on Pd(II)/Pd(0) redoxcouple.[30]Although consensus hasn't yet been reached, the most commonly proposed mechanism involves the generation of cyclometallated species **V**, arising from an initial C-H cleavage step (Figure 1.14). The resultant palladacycle **V** is then oxidized to a highly reactive Pd(IV) intermediate **VII**, which undergoes reductive elimination both releasing the product and the active Pd(II) catalyst.

[30] (a) Muñiz, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 9412. (b) Sehnal, P.; Taylor, R.; Fairlamb, I. *Chem. Rev.***2010**, *110*, 824. (c) Xu, L.; Li, B.; Yang, Z.; Shi. Z. J. *Chem. Soc. Rev.***2010**, *39*, 712. (d) Engle, K. M.; Mei, T.-S.; Wang, X.; Yu, J.-Q. *Angew. Chem. Int. Ed.***2011**, *50*, 1478.

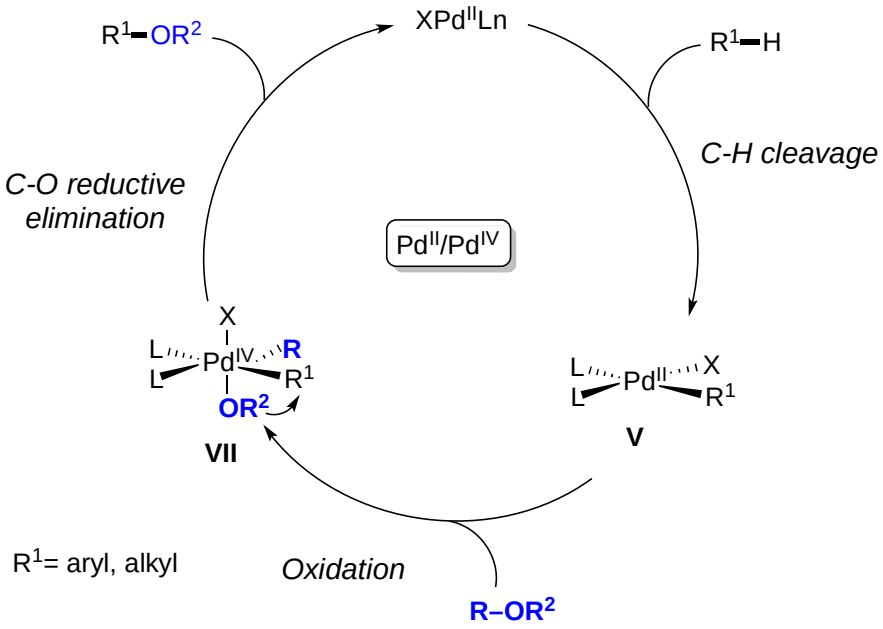


Figure 1.14

Prompted by an early precedent from Crabtree[31] (Figure 1.15), Sanford developed a new set of C-O bond forming reactions applying a Pd(II)/Pd(IV) redox strategy using $PhI(OAc)_2$or $K_2S_2O_8$as the terminal oxidant. The key aspect of Sanford's approach was the use of a suitable DG, allowing the formation of a cyclometallated Pd(II) intermediate that is easily oxidized to Pd(IV), setting the stage for the desired C-O bond reductive elimination.Accordingly, a highly chemo- and regioselectiveprocedure for the oxidative functionalization of C-H bonds was reported in 2004 (Figure 1.16, a).[32] Interestingly, while the use of acetonitrile as solvent resulted in the formation of acetoxylated products, the formation of alkyl aryl ethers was observed in the presence of alcoholic solvents.

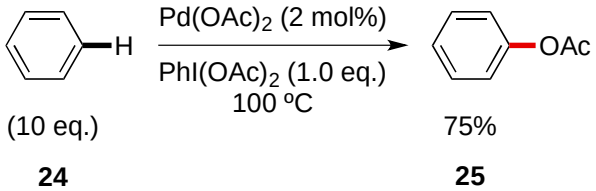


Figure 1.15

Besides, Sandord[32] demonstrated that this protocol could be extended to azobenzenes**29**or oximes derivatives**31**(Figure 1.16, b and c).[34,33] Later on, oxone or

[31]Yoneyama, T.; Crabtree, R. H. *J. Mol. Catal. A: Chem.***1996**, *108*, 35.
[32]Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.***2004**, *126*, 2300.
[33]Desai, L. V; Malik, H. A.; Sanford, M. S. *Org. Lett.***2006**, *8*, 1141.

potassium persulfate could be used as inexpensive, safe and environmentally friendly oxidants instead of $PhI(OAc)_2$.[33] In 2011, Sanford and co-workers[34] described that the addition of pyridine or diamine type ligands substantially enhance both reactivity and site-selectivity in the direct acetoxylation of benzene derivatives **34**. Moreover, the use of the more sterically hindered oxidant $MesI(OAc)_2$ in place of $PhI(OAc)_2$ was a contributory factor for success (Figure 1.16, d).

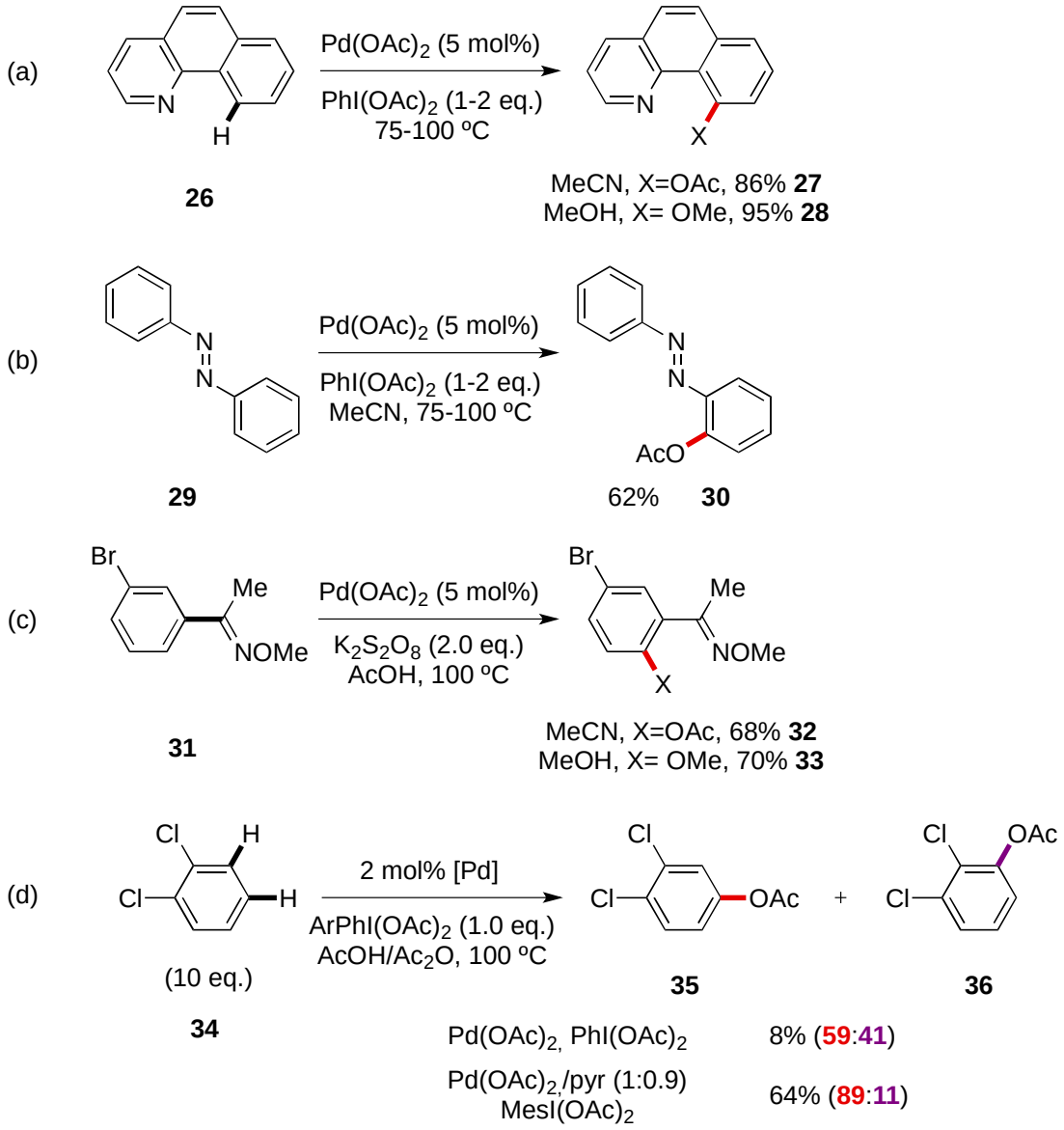


Figure 1.16

In recent years, the use of removable directing groups within the field of C-H functionalization has gained considerable momentum, thus avoiding the use of strongly

[34] Emmert, M. H.; Cook, A. K.; Xie, Y. J.; Sanford, M. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 9409.

chelating DG's.[35]Daugulis reportedthat the 8-aminoquinoline backbone allows for a regioselective palladium-catalyzed arylation of C(sp^2)-H.[36] This strategy was also applied by Liang[37] for the direct di-acetoxylation of C(sp^2)-H bonds, as in the previous case by using $PhI(OAc)_2$ as oxidant (Figure 1.17a and b). In both cases Pd(IV) species**VIII** were proposed as intermediates. In 2010, Gevorgyan introduced a silicon tethered traceless directing group for the mono-acetoxylation of C(sp^2)-H bonds (Figure 1.17 c).[38] The main advantage of this method as compared to others for similar means relies on the versatility of the silicon scaffold, as this motif can readily be transform into a wide range of products. A combination of two oxidants ($PhI(OAc)_2$ and AgOAc) was found to be crucial for reactivity and catalyst turnover, a rather surprising finding that it not clearly understood.

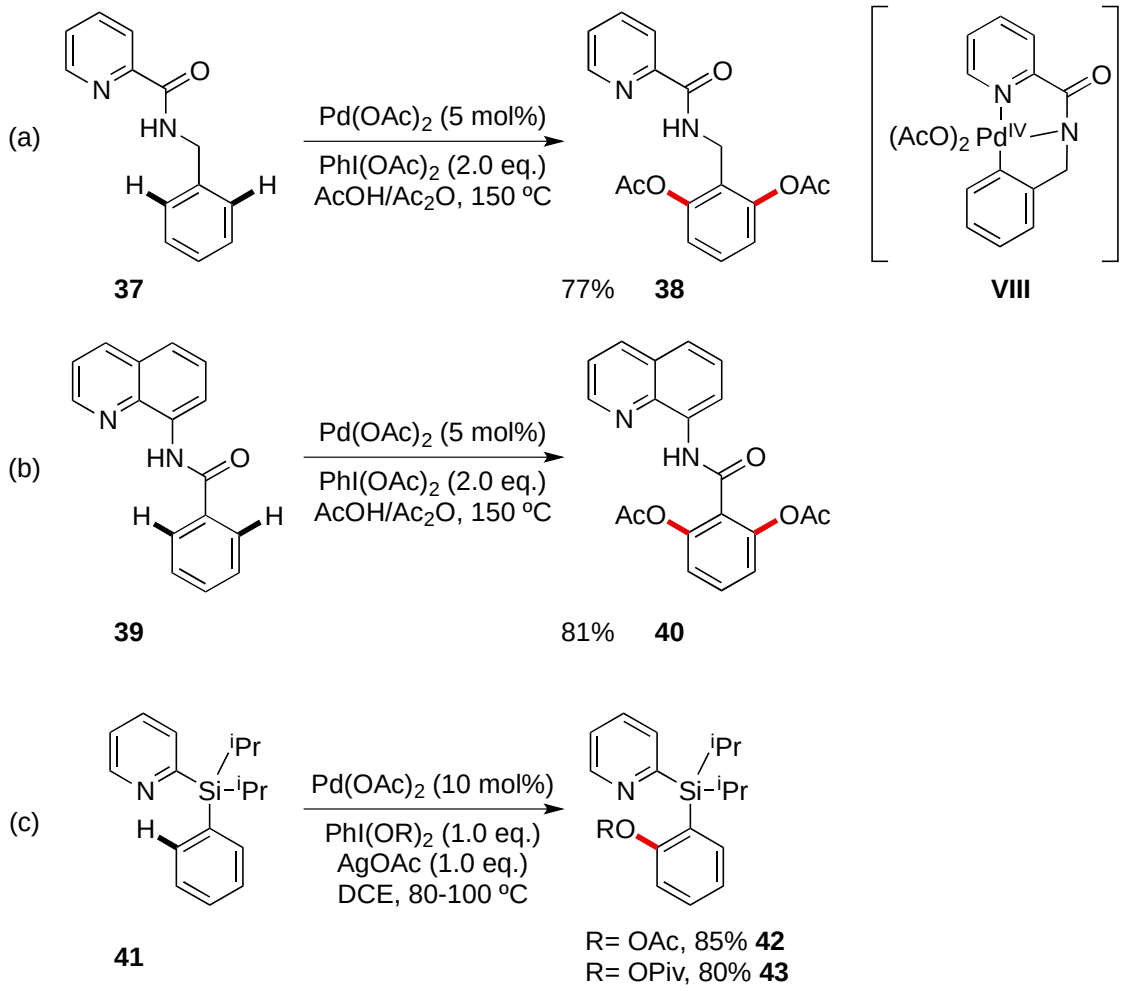


Figure 1.17

[35] For selected reviews see: (a) Rousseau, G.; Breit, B. *Angew. Chem. Int. Ed.***2011**, *50*, 2450. (b) Engle, K. M.; Mei, T.; Wasa, M.; Yu, J.-Q.*Acc. Chem. Res*. **2012**, *45*, 788. (c) Rouquet, G.; Chatani, N. *Angew. Chem. Int. Ed.***2013**,*50*, 11726.
[36]Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.***2005**, *127*, 13154.
[37]Gou, F.; Wang, X.; Huo, P.; Bi, H.; Guan, Z.; Liang, Y. *Org. Lett*. **2009**, *11*, 5726.
[38]Chernyak, N.; Dudnik, A. S.; Huang, C.; Gevorgyan, V. *J. Am. Chem. Soc.***2010**, *132*, 8270.

Another interesting Pd(II)-catalyzed *ortho* C(sp^2)-H acetoxylation reaction of phenylalanine and ephedrine derivatives **44**was reported by Yu (Figure 1.18, a).[39] In this particular case, a simple triflamide was used to activate selectively the desired C(sp^2)-H bond. A combination of $Pd(OAc)_2$/$MeO_3{}^tBu$/Ac_2O proved to be optimal for this reaction. While a dramatic acceleration was found with MeCN as solvent, DMF was used to control the selectivity profile. The Lei group[40] disclosed a C-H acetoxylation of indoles **46**in a highly regioselective fashion without the assistance of a directing group, in which a Pd(II)/Pd(IV) couple was proposed (Figure 1.18, b).

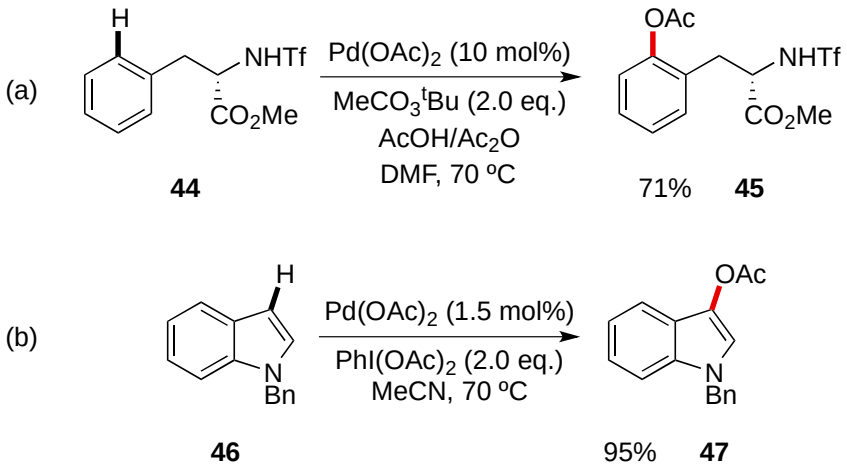


Figure 1.18

Alternatively, in 2010 Shi described the intermolecular Pd-catalyzed C(sp^2)-H functionalization/C-O benzoxylation of*O*-methy aryloxymes**48**(Figure 1.19).[41]A wide variety of aryl or alkyl carboxylic acids **49**could be coupled efficiently in good yields.

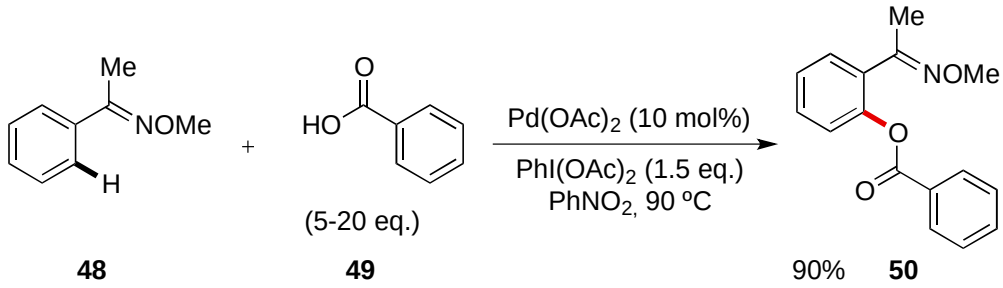


Figure 1.19

Phenols and its derivatives constitute important motifs in pharmaceutical, bulk and fine chemical industries, agrochemicals or even polymers.[42] Consequently, several efforts

[39]Vickers, C. J.; Mei, T.; Yu, J.-Q.*Org. Lett.***2010**, *12*, 2511.
[40]Liu, Q.; Li, G.; Yi, H.; Wu, P.; Liu, J.; Lei, A. *Chem. Eur. J*. **2011**, *17*, 2353.
[41]Sun, C.-L.; Liu, J.; Wang, Y.; Zhou, X.; Li, B.-J.; Shi, Z.-J. *Synlett***2011**, *2011*, 883.

for rapidly accessing these compounds have recently appeared exploiting the concept of C-H functionalization en route to hydroxylated arenes. In this regard, inspired by a previous work from Rybak-Akimova and Que using stoichiometric iron complexes,[43]Yu reported the direct ortho-hydroxylation of readily available benzoic acids**49**(Figure 1.20, a) under O_2 atmosphere.[44]Preliminary experiments with $^{18}O_2$and $H_2{}^{18}O$ showed fully ^{18}O incorporation into the final product**51**coming exclusively from$^{18}O_2$,suggesting a direct oxygenation of the arylpalladium(II) intermediates.

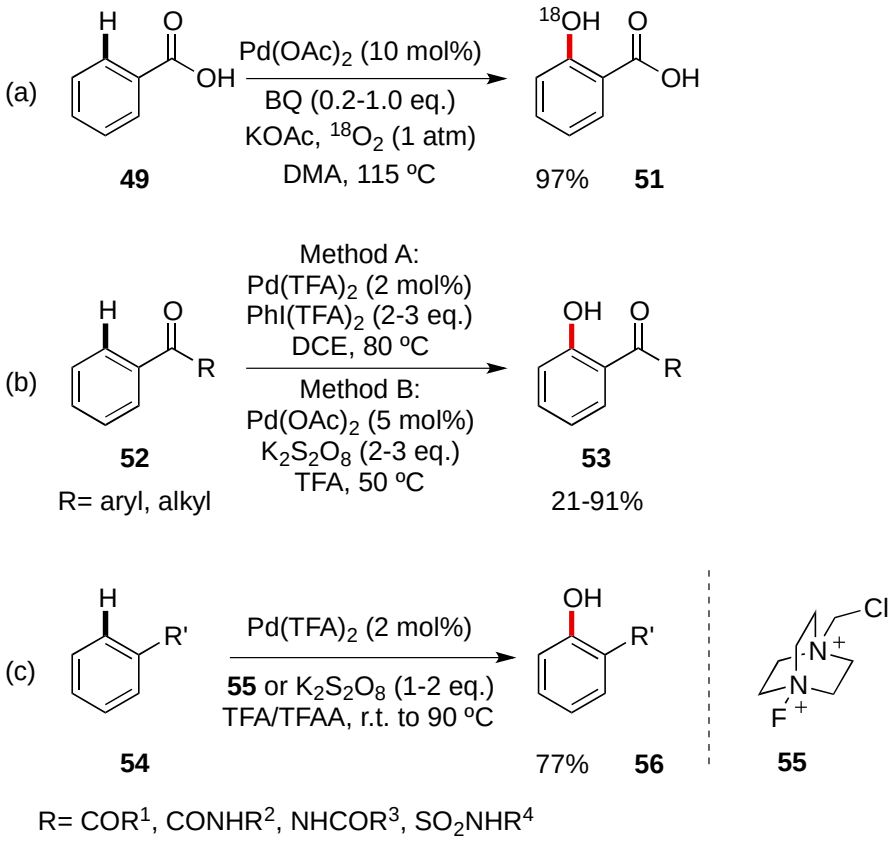


Figure 1.20

Another versatile and direct arene C(sp^2)-H hydroxylation protocol using ketones as directing groups was envisioned simultaneously by the Dong[45]and Rao group[46] (Figure 1.20, b and c). A wide variety of ketone derivatives**52**, for instance esters, amides or even sulfonamides could also be utilized en route to hydroxylated arenes in good

[42] (a) Enthaler, S.; Company, A. *Chem. Soc. Rev*. **2011**, *40*, 4912. (b) Alonso, D. A; Nájera, C.; Pastor, I. M.; Yus, M. *Chem. Eur. J*. **2010**, *16*, 5274.
[43]Taktak, S.; Flook, M.; Foxman, B. M.; Que, L.; Rybak-Akimova, E. V.; Akimova, R. *Chem. Commun.***2005**, 5301.
[44]Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.***2009**, *131*, 14654.
[45]Mo, F.; Trzepkowski, L. J.; Dong, G. *Angew. Chem. Int. Ed.***2012**, *51*, 13075.
[46]Shan, G.; Yang, X.; Ma, L.; Rao, Y. *Angew. Chem. Int. Ed.***2012**,*51*, 13070.

yields. The catalytic cycle is believed to proceed via an initial carbopalladation to reach bimetallic intermediate **IX**, an assumption corroborated by X-Ray crystallography (Figure 1.21). Subsequent oxidation to the presumably Pd(IV) species**X** and reductive elimination yielded the labile trifluoacetate **57**, which was readily converted into the corresponding phenol upon hydrolytic work-up. In both Dong and Rao's methods, a high inter- and intramolecular kinetic isotope effect (K_H/K_D>5) was observed,suggesting the C-H bond cleavage was rate-determining.

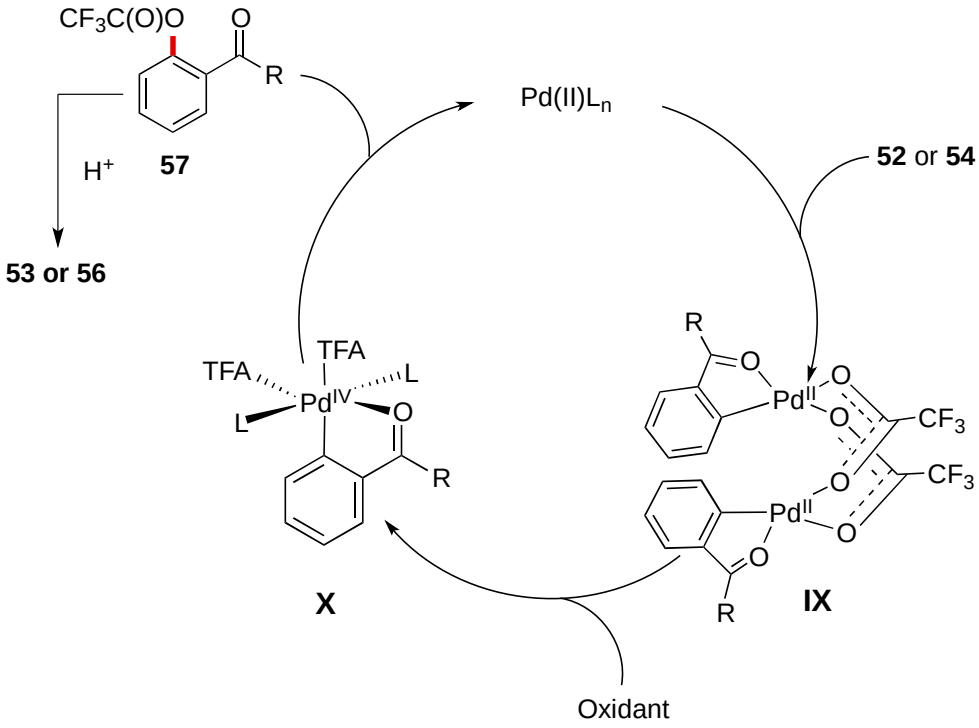


Figure 1.21

Yu and coworkers[47] elegantly showed a new Pd-catalyzed hydroxyl-directed C-H functionalization/C-O cyclization to form furan or pyran derivatives (Figure 1.22, a).Thereafter, this approach was used to construct enantioenriched benzofuranones employing quiral aminoacids as ligands, together with weekly coordinating carboxylic acids as directing groups via a Pd(II)/Pd(IV) redox catalysis (Figure 1.22, b).[48] Concurrently, the Shi group[49] published a related method also employing $PhI(OAc)_2$ as stoichiometric oxidant (Figure 1.22, c).

[47]Wang, X.; Lu, Y.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.***2010**, *132*, 12203.
[48]Cheng, X.-F.; Li, Y.; Su, Y.-M.; Yin, F.; Wang, J.-Y.; Sheng, J.; Vora, H. U.; Wang, X.-S.; Yu, J.-Q. *J. Am. Chem. Soc.***2013**, *135*, 1236.
[49]Yang, M.; Jiang, X.; Shi, W.-J.; Zhu, Q.-L.; Shi, Z.-J. *Org. Lett.***2013**, *15*, 690.

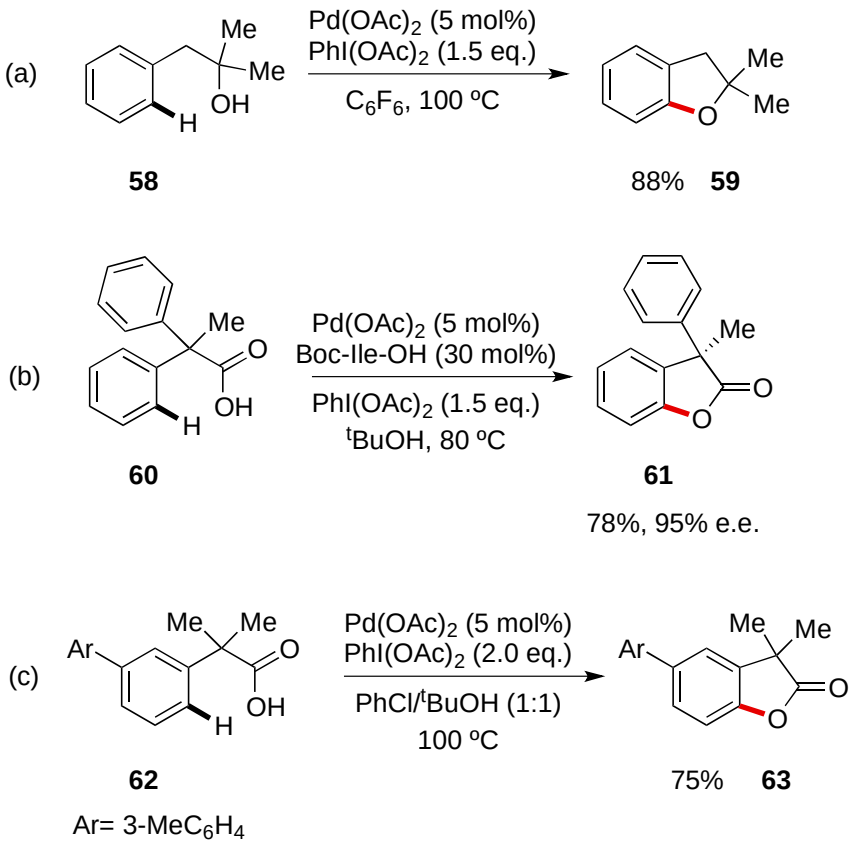


Figure 1.22

1.3.4 Palladium-catalyzed C(sp^3)-H functionalization/C-O bond formation

The directformation of C-O bonds via C(sp^3)-H functionalization constitutes afundamental challenge in thisfield of expertise. In 2004, Sanford reported the first Pd-catalyzed C-O bond formation of activated benzylic C(sp^3)-H bonds in high levels of chemo- and regioselectivityusing $PhI(OAc)_2$ as stoichiometric oxidant (Figure 1.23).[50]Depending on the solvent employed, the corresponding acetoxylated (**65**)or alkyl benzyl ether (**66**)products could be obtained in good yields, an observation that was already found by the same authors (Figure 1.16, c).

[50]Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.***2004**, *126*, 2300.

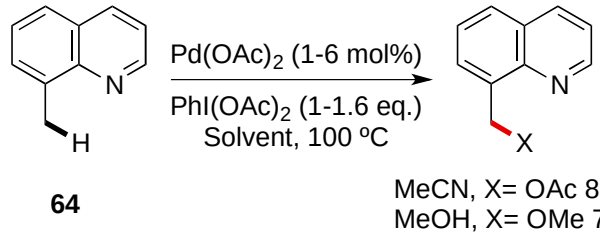
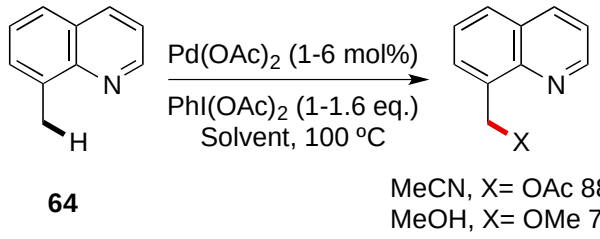
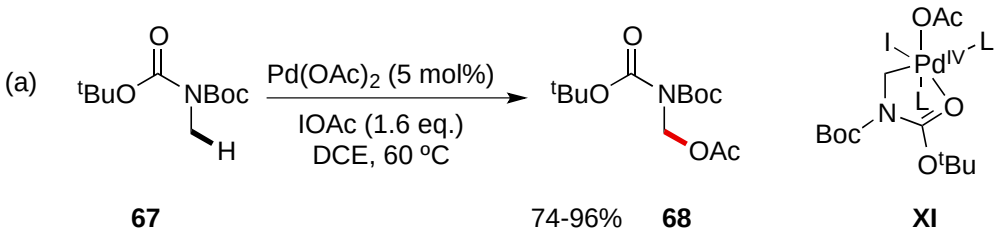


Figure 1.23

The Yugroup disclosed the acetoxylation of *Boc*-protected *N*-methylamines **67**with IOAc as the oxidant, generated *in situ* by mixing $PhI(OAc)_2$ and I_2(Figure 1.24, a).[51]The authors proposed the intermediacy of Pd(IV) species **XI**for this transformation. Additionally, a non-negligible intra- and intermolecular kinetic isotope effects (K_H/K_D 2.9-3.2) were observed. Subsequently, the same group developed a mild protocol for the oxidation of unactivated C(sp^3)-H bonds employing inexpensive peroxides as oxidantswith oxazolines as DG's (Figure 1.24, b).[52] Interestingly, the use of benzoyl *tert*-butyl peroxide as oxidant resulted in selective ether formation, thus showing the subtleties in these transformations.





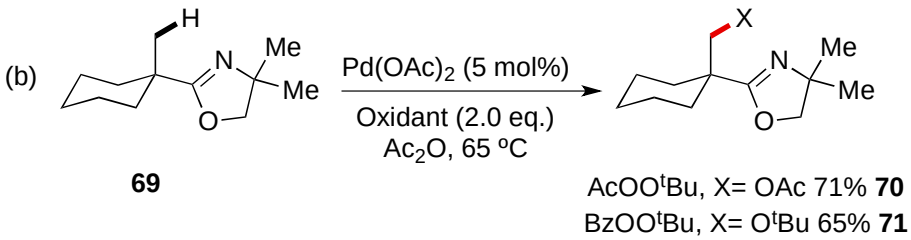


Figure 1.24

[51]Wang, D.-H.; Hao, X.-S.; Wu, D.-F.; Yu, J.-Q. *Org. Lett.***2006**, *8*, 3387.
[52]Giri, R.; Liang, J.; Lei, J.; Li, J.; Wang, D.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J.-Q.*Angew. Chem. Int. Ed*. **2005**, *44*, 7420.

An efficientC(sp^3)-H acyloxylation reaction under very mild conditions induced by a reusable bidentate *S*-methyl-*S*-2-pyridylsulfoximinedirecting group **72**was reported by Sahoo (Figure 1.25, a).[53] As forprevious examples, $PhI(OAc)_2$ performed better compared to other oxidants examined. A similar procedure for β-acyloxylation via C(sp^3)-H bond activation was reported by Lu in 2014 (Figure 1.25, b).[54] Alternatively, simple mono-*N*-substituted amides **74**were used as directing group. The combination $Pd(OAc)_2$/TFA/$K_2S_2O_8$ turned out to be crucial for achieving high reaction rates.

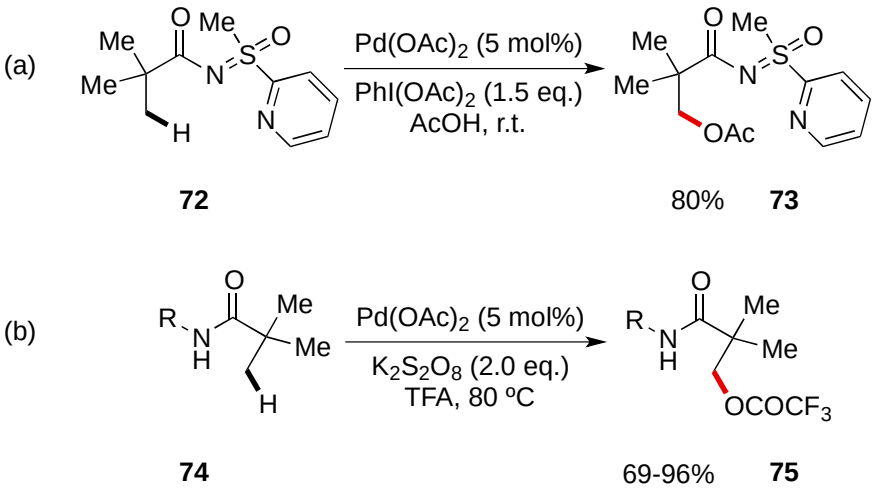


Figure 1.25

Sanford developed in 2004 a remarkable system for C(sp^3)-H bondacetoxylation using *N*-methyloxymes **76** as directing group (Figure 1.26, a). Interestingly, substrates bearing β-hydrogens are tolerated under the reaction conditions, presumably due to the rigidity of the palladacycle intermediate. Additionally, a high selectivityprofile was observed for primaryβ-C-H bonds *in lieu* of those at secondary C-H centers.[55]In order to improve the practicality of acetoxylationreactions via C-H functionalization, the same authors introduced *O*-acetyl oximes**77**as versatile directing groups to effect C(sp^3)-H bond functionalization. Importantly, *O*-acetyl oxymes are stable under the catalytic reaction conditions and can be readily manipulated to the corresponding ketones, alcohols, amines and heterocyles, if needed. Another acetoxylation protocol of densely functionalized aminoacids derivatives was reported by Corey (Figure 1.26, b) in 2006.[56] In this case,8-aminoquinolinewas the chelating group of choice, conferring a

[53]Rit, R. K.; Yadav, M. R.; Sahoo, A. K. *Org. Lett.***2012**, *14*, 3724.
[54]Zhou, L.; Lu, W. *Org. Lett.***2014**, *16*, 508.
[55]Desai, L. V; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.***2004**, *126*, 9542.
[56]Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.***2006**, *8*, 3391.

remarkable rigidity en route to palladacycle **XII**, which subsequently triggers a reductive elimination that delivers the corresponding alkylacetoxylated product**81**.

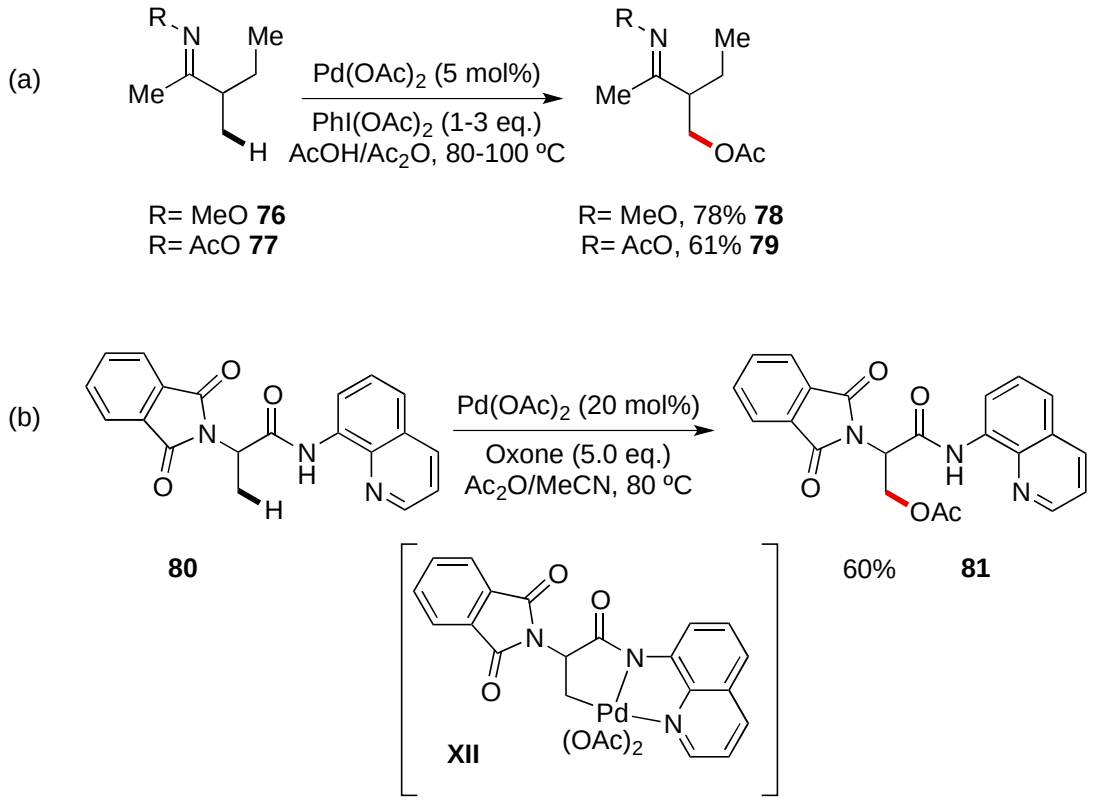


Figure 1.26

A general and highly efficient method for the synthesis of alkyl ethers via functionalization of non-activated γ-C(sp^3)-H bondswas disclosed by Chen in 2012utilizingpicolinamide (PA) as directinggroup (Figure 1.17, a).[57]A mixture of an apolar and alcoholic solvent, in combination with $PhI(OAc)_2$ as the stoichiometric oxidant, proved to be essential for the reaction outcome. A wide range of primary and secondaryaliphatic alcohols provided good to excellent yields. However, more hindered tertiary alcohols were less efficient for this transformation. Rao[58] described a complementary approach with hipervalent iodine(III) oxidants such as **85**or **86** of unactivated methyl groups (Figure 1.27 b) in β-position.Again, by modifying the alcoholic solvent, the corresponding ethers were obtained in moderate to good yields.Besides, this procedure served as an easytool for late-stage modification of ibuprofen-type anti-inflammatory drugs.

[57]Zhang, S.-Y.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A; Chen, G. *J. Am. Chem. Soc.***2012**, *134*, 7313.
[58]Shan, G.; Yang, X.; Zong, Y.; Rao, Y. *Angew. Chem. Int. Ed.***2013**, *52*, 13606.

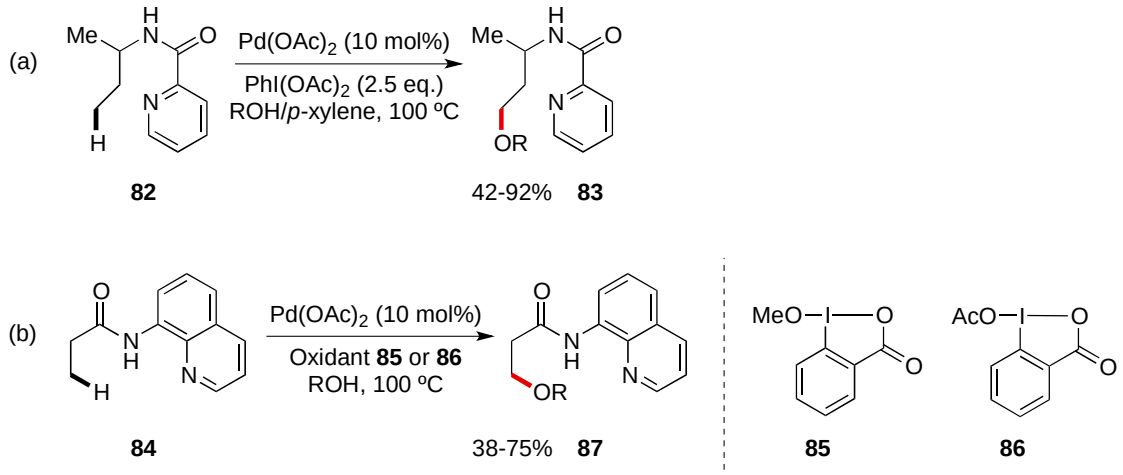


Figure 1.27

1.3.5 Copper-catalyzed C(sp^2)-O bond formation via C-H functionalization.

The utilization of Cu catalyst in cross-coupling reactions is particularly attractive since different different metal oxidation states (0, I, II, III) can be accessed, hence allowing one- or two-electron processes. As a consequence, both radical pathways[59]and two-electron bond-forming processes via organometallic intermediates,similar to those of palladium can occur.[60] Furthermore, compared to other transition-metal catalysts, copper salts are inexpensive, readily available, insensitive to air and easy to handle. Not surprisingly, C-H functionalization reactions for the construction of C-O bonds have gained substantial attention.

Considering the ability of pyridine motifsas directing groups in C-H functionalization, the Yu group developed a new Cu-catalyzed acetoxylation reaction of C(sp^2)-H bonds using O_2 as terminal oxidant (Figure 1.28).[61] Due to catalyst inhibition, acetic anhydride was required to achieve catalytic turnover by in situ derivatization of the corresponding phenol. Stoichiometric experiments with labeled $H_2{}^{18}O$in the absence of O_2 showed that the oxygen atom from$Cu(OAc)_2$ was incorporated into the product **88**. Based on mechanistic studies from an analogous chlorination process,[61] the authors suggested that this reaction could be initiated by a SET leading to **XIV**. Then, intramolecular acetate transfer was proposed to occur, followed by an additional SET step and loss of

[59]For selected reviews see: (a) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 11062. (b) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.***2012**, *41*, 3464.
[60]Hickman, A. J.; Sanford, M. S. *Nature***2012**, *484*, 177.
[61]Chen, X.; Hao, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc*.**2006**, *128*, 6790.

a proton to afford **88**. Unfortunately, a mixture of the mono **88**and di-functionalized oxygenated compounds **89**wasobtained.

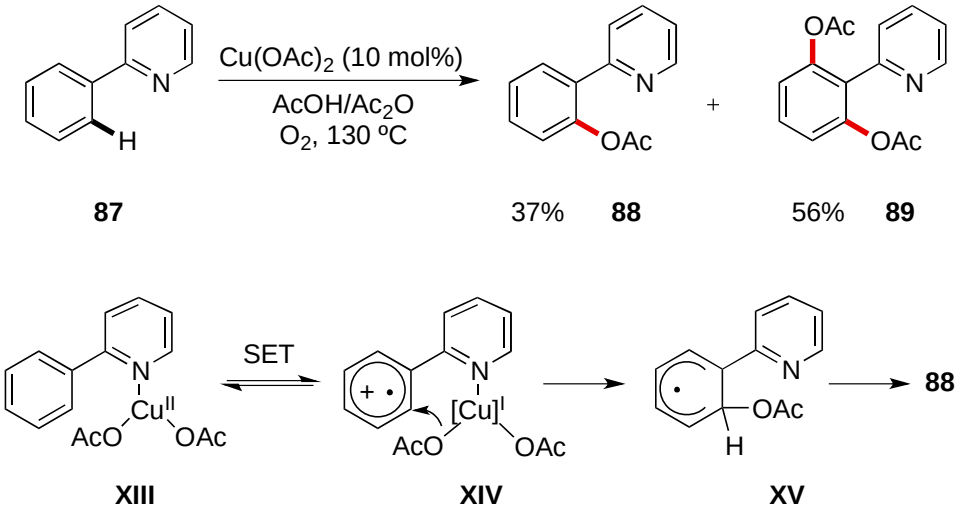


Figure 1.28

Cheng and co-workers subsequently expanded the results of Yu group (Figure 1.28) by developinga more selective approach utilizing anhydrides as oxygen source as depicted in Figure 1.29.[62] As for the previous case, O_2 was employed as oxidant and copper acetate showed the best catalytic activity. A wide range of mono and di-acetoxylated 2-arylpyridines were accessed in this manner.As outlined in Figure 1.29, the authors proposed an initial formation of copper benzoate **XVI**, followed by an electrophilic attack of Cu(II) on the phenyl ring to furnish the cyclometallated intermediate **XVII**.Next, **XVII**was believed to be oxidized to Cu(III) species**XVIII**mediated by CuX_2, which reductively eliminates to yield the product. The resultant Cu(I) salt is oxidized by O_2 to regenerate the active Cu(II) benzoate species.It is noteworthy that the authors did not conduct any mechanistic study to confirm whether the reaction goes via the proposed pathway highlighted in Figure 1.29.

[62]Wang, W.; Luo, F.; Zhang, S.; Cheng, J. *J. Org. Chem.***2010**, *75*, 2415.

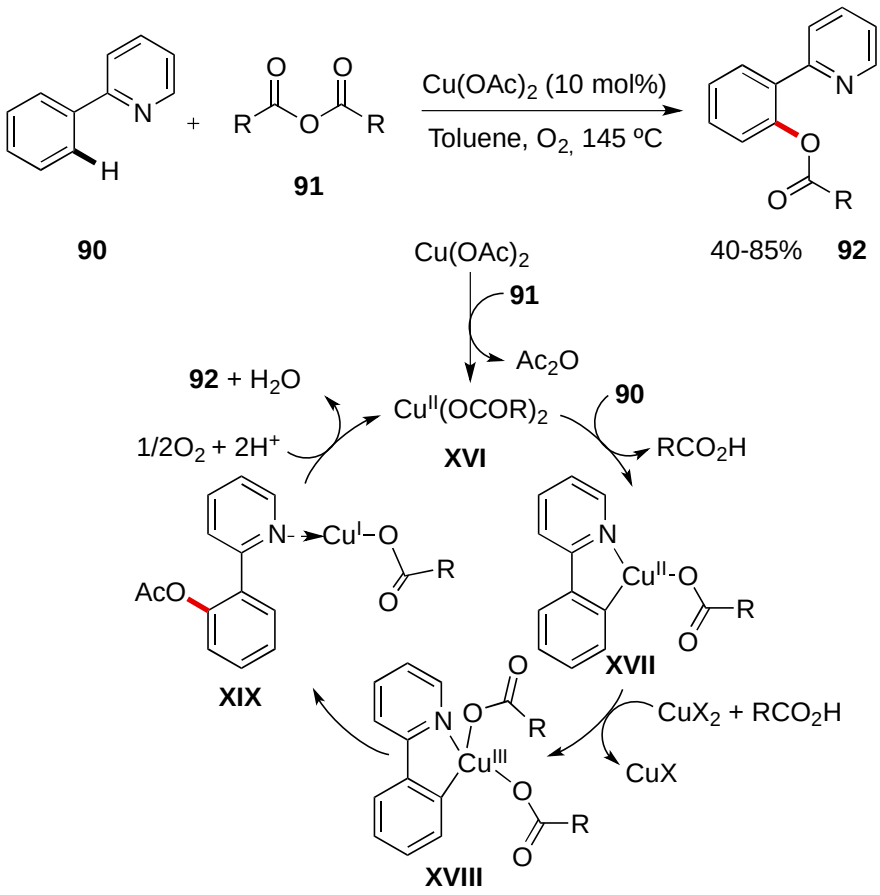


Figure 1.29

A relevant contribution to the field entailsthe direct synthesis of 2-arylbenzoxazoles via intramolecular Cu-catalyzed C(sp^2)-H functionalization (Figure 1.30, a).[63]In this case, a simple amide could be used as directing group in the presence of $Cu(OTf)_2$ as catalyst and O_2 as oxidant at 140 ºC. The regioselectivity of the cyclization strongly relies on the steric congestion around the C-H bond, taking place preferentially at the less hindered side. In this case, an electrophilic metallation process was suggested in the oxidative C-O coupling reaction via intermediate **XX**. Intramolecular competition experiments with deuterium labeling substrates suggested that hydrogen abstraction is not involvedin the rate-determining step. Recently, Daugulis disclosed an elegant ortho-etherification approach employing 8-aminoquinoline as directing group using simple phenols and aliphatic alcohols (Figure 1.30, b).[64] Remarkably, air was used as oxidant without a decrease in the reaction efficiency. Due to the poor nucleophilicity of

[63] (a) Ueda, S.; Nagasawa, H. *Angew. Chem. Int. Ed.***2008**, *47*, 6411. (b) Ueda, S.; Nagasawa, H. *J. Org. Chem.***2009**, *74*, 4272.
[64]Roane, J.; Daugulis, O. *Org. Lett.***2013**, *15*, 5842.

phenoxide and their incompatibilitywith strong oxidants such as $PhI(OAc)_2$, this protocol constitutes a useful approach to phenoxylated and alkoxylated arenes.

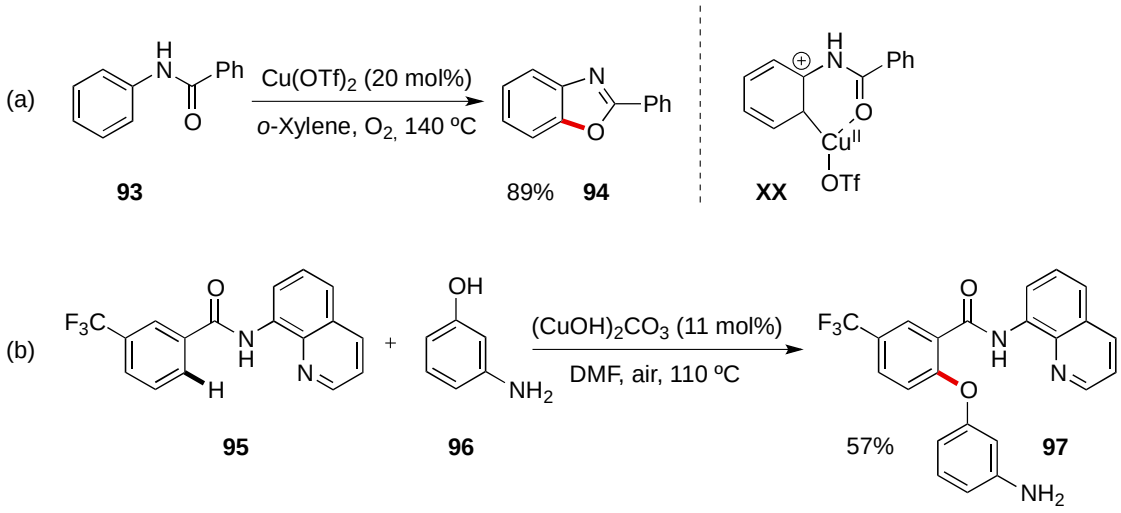


Figure 1.30

The means to provide a direct oxidation of simple benzene remains a considerable challenge, since current methodologies are neither efficient nor environmentally friendly. In 2011, Pérez reported a practicalphenol synthesis catalyzed by a Cu(I) complex in the absence of acidic conditions (Figure 1.31).[65]The scorpionate-type ligand $Tp^{*,Br}$ (hydrotris(2-bromo-3,5-dimethylpyrazolylborate) **100**showed the higher reactivity in combination with Cu(NCMe). Tetramethylene sulfone **98**was used as a co-solvent to avoid phenol over-oxidation via hydrogen-bonding interactions. Interestingly, selectivities up to 92% were obtained under relatively mild conditions, a considerable improvement in this area of expertise.

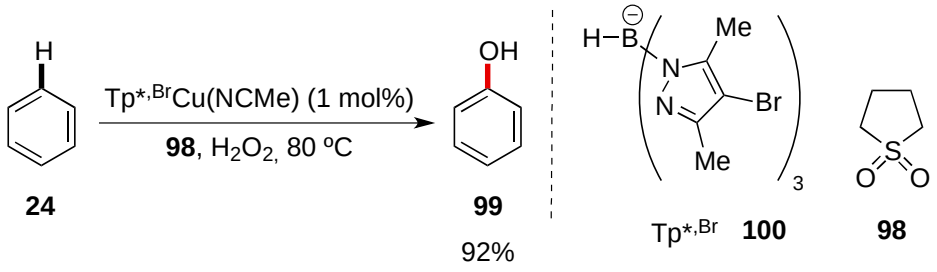


Figure 1.31

Despite tremendous progress in the area of Cu-catalyzed C-H functionalization, little knowledge has been gathered regarding the mechanism of these transformations.Ribas and Stahl provided compelling evidence for aryl Cu(III)

[65]Conde, A.; Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Commun.***2011**, *47*, 8154.

intermediates in the aerobic oxidative functionalization of aromatic C-H bonds (Figure 1.32).[66] Macrocyclic arene **101** was used to study the direct methoxylation under O_2 atmosphere. Kinetic and spectroscopic analysis suggested the in situ formation of an aryl-Cu(III)-Br intermediates.

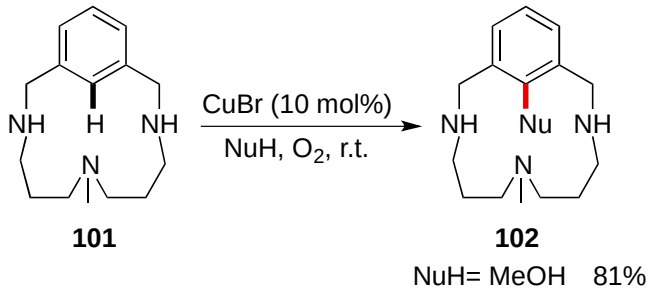


Figure 1.32

The proposed mechanism (Figure 1.33)consist of an initial complexation of the macrocycle to Cu(II), followed by C-H functionalization via a disproportionation event to give the aryl-Cu(III) intermediate **XXII**. Subsequent reaction with methanol results in the formation of methoxylated arene **XXIII**. A final oxidation of Cu(I) to Cu(II) by O_2 closes the catalytic cycle.

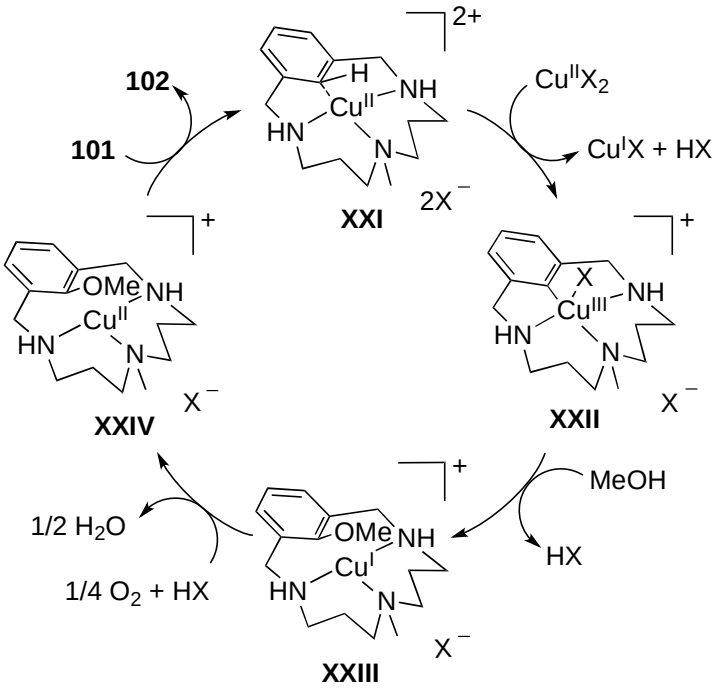


Figure 1.33

[66]King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.***2010**, *132*, 12068.

1.3.6 Copper-catalyzed C(sp^3)-O bond formation via C-H functionalization.

An early report by Kharasch and Sosnovskiin the late 1950's showed the potential of copper-catalyzed allylic oxidation of alkenes such as cyclohexene.[67]A common oxidant, *tert*-butyl perester with copper (II) ethylhexanoate at 80 ºC provided the allylic benzoate **104**in good yield (Figure 1.34). The mechanism presumably proceeds via radical intermediates in which copper species are believedto be involved in the C-O bond formation. Initial interaction between a Cu(I) source and *tert*-butylperoxybenzoate generates Cu(II) benzoate and*tert*-butoxy radical (^{t}BuO•)as shown in Figure 1.33, eq. 1. Such alkoxy radical engages a hydrogen-atom abstraction (HAA) with the allylic C-H bond, thus furnishing the corresponding allylic radical species (eq. 2). The latteroxidizes the Cu(II) benzoate to the corresponding allylcuprate(III) intermediate which reductively eliminatesto form **104**(eq. 3 and 4). Pfaltz[68] and Andrus[69](Figure 1.35, a) independently developed an asymmetric version by employing C2-symmetric (bis)oxazoline ligands**105** and **106**. Although the yields were rather moderate, a good level of enantioinduction was achieved (up to 80% e.e.).

A recent study by Warren[70] demonstrated the involvement of a radical mechanism when using copper catalyst **109** with dialkylperoxides as oxidants (Figure 1.35, b). In this case,inert alkylic C(sp^3)-H bonds were activated by employing copper(I) catalyst **109**. Several mechanistic investigations suggested the generation of free^{t}BuO• upon mixing **109**with tert-butylperoxide. Subsequent HHA could generate the cyclohexyl radical (Cy•) which, in analogy with the Kharasch-Sosnovski reaction, could immediately be trapped by [Cu(II)]-OtBu, thusforming a Cy-[Cu(III)]-O^{t}Bu that precedes the final C-O bond formation.

[67] (a) Kharasch, M. S.; G. Sosnovsky, G. *J. Am. Chem. Soc*. **1958**, *80*, 756. (b) M. S. Kharasch, M. S.; Sosnovsky, G.; Yang, N. C. *J. Am. Chem. Soc.***1959**, *81*, 5819. For a minireview on asymmentric Kharasch Sosnovski reaction see: K. S.; Eames, J.; Watkinson, M.*Angew. Chem. Int. Ed*. **2001**, *2*, 3567.
[68]Gokhale, A. S.; Minidis, A. B. E.; Pfaltz, A.*Tetrahedron Lett*. **1995**, *36*, 1831.
[69] Andrus, M. B.; Argade, A. B.; Chen, X.; Pamment, M. G.*Tetrahedron Lett*. **1995**, *36*, 2945.
[70]Gephart, R. T.; Mcmullin, C. L.; Sapiezynski, N. G.; Jang, E. S.; Aguila, M. J. B.; Cundari, T. R.; Warren, T. H. *J. Am. Chem. Soc*. **2012**, *134*, 17350.

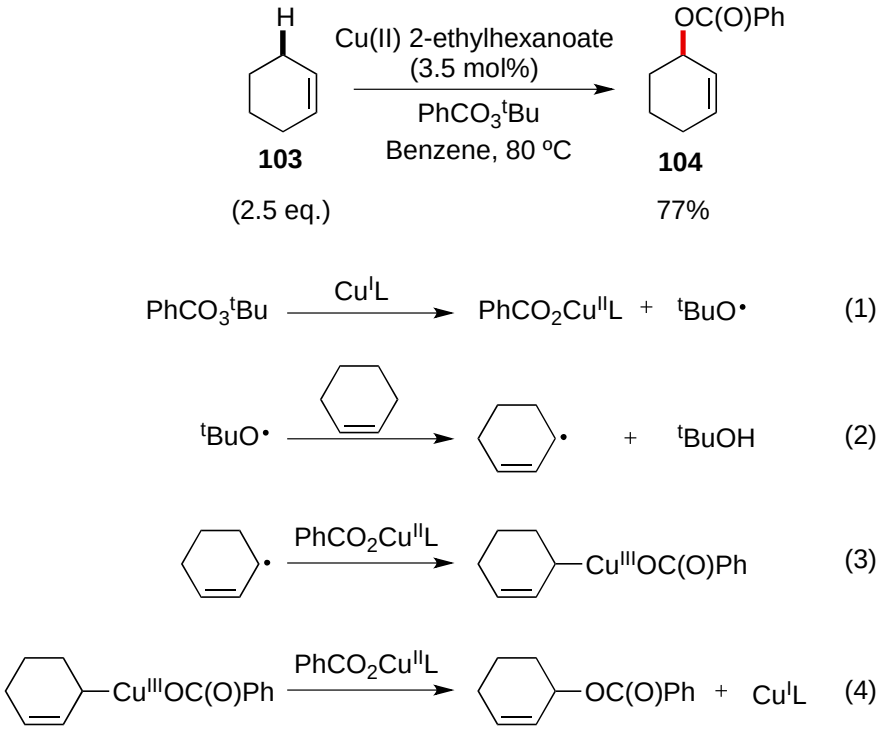


Figure 1.34

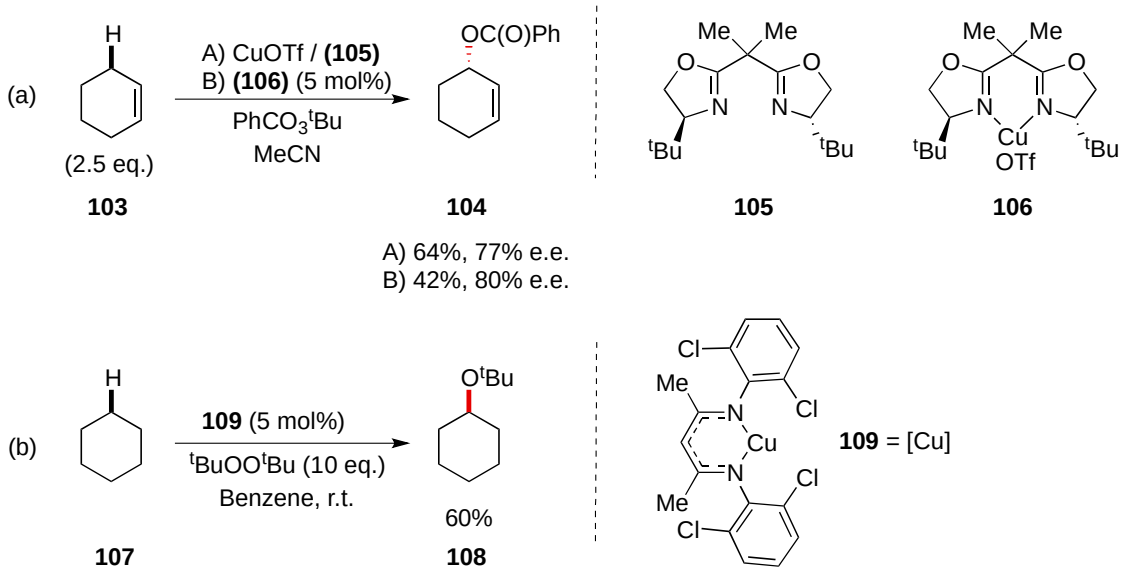


Figure 1.35

1.3.7 Ruthenium-catalyzed C(sp^2)-O bond formation via C-H functionalization.

In recent years, the use of Ru(II) catalyst have shown to be viable alternatives in the C-H functionalization arena.[71,7e] The advantages of Ru catalysts are the following: a) cyclometallated species are easy to obtain, b) high compatibility with commonly used oxidants and c) remarkable stability to both air and water. Not surprisingly, new Ru-catalyzed methodologies aimed at providing C-H functionalization/C-O bond formation have been described recently.

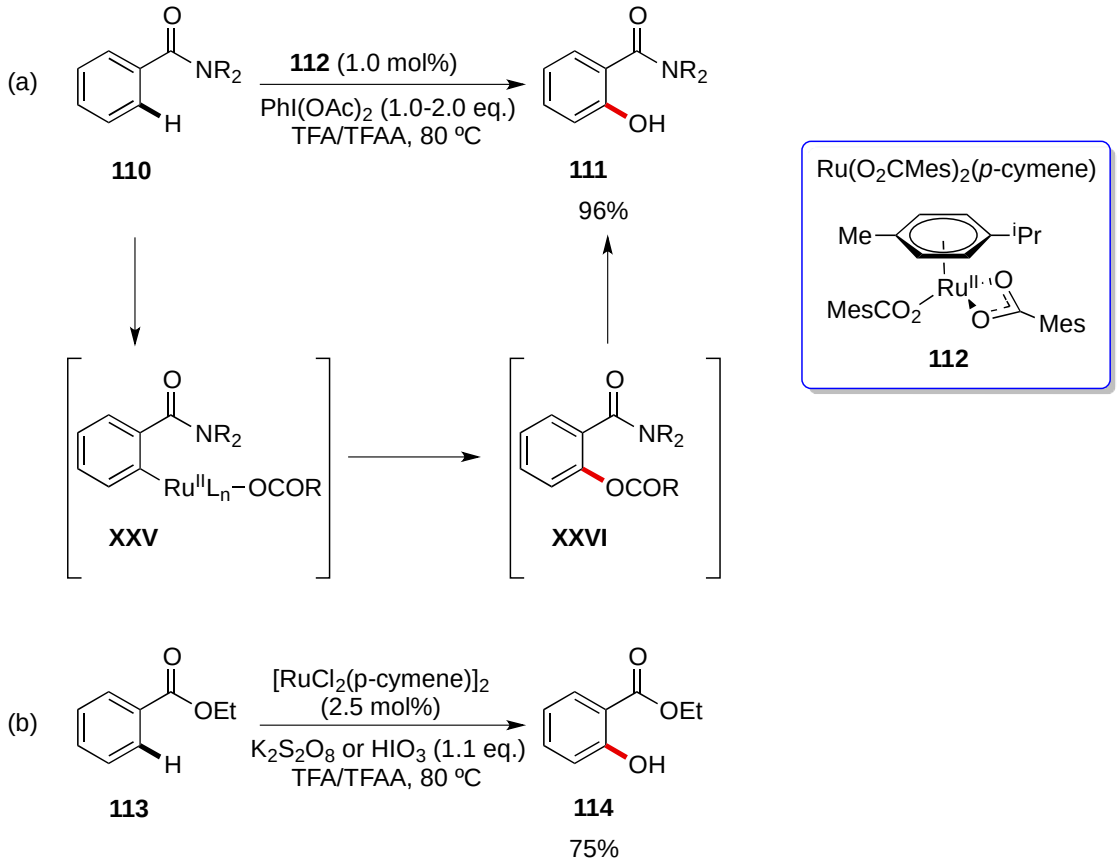


Figure 1.36

Ackermann highlighted the importance of the air stable ruthenium complex **112**for the direct formation of hydroxylated arenes**111** (Figure 1.36, a). Weakly coordinating benzamides were used astunable directing group.[72] The best oxidant for this

[71] (a) Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.***1998**, *98*, 2599 (b) Ackermann, L.; R. Vicente, R. "Ruthenium-Catalyzed Direct Arylations through C-H Bond Cleavages" *Top. Curr. Chem*. **2010**, *292*, 211. (c) Ackermann, L. *Acc. Chem. Res.***2014**, *47*, 281. (d) Thirunavukkarasu, V. S.; Kozhushkov, S. I.; Ackermann, L. *Chem. Commun.***2014**, *50*, 29.
[72]Thirunavukkarasu, V. S.; Hubrich, J.; Ackermann, L. *Org. Lett.***2012**, *14*, 4210.

transformation turned out to be $PhI(OAc)_2$, with a mixture of TFA/TFAA as solvent. Remarkably, only *mono*-hydroxylated compounds were obtained selectively in good to high yields. A high chemoselectivity profile was shown, as illustrated by the fact that nitro groups, esters or aryl halides were tolerated under the reactions conditions using low catalyst loadings (2 mol% of Ru).Simultaneously, Rao developed a similar protocol employing esters as effective directing group (Figure 1.36, b).[73] In this case, $K_2S_2O_8$ or HIO_3 gave better conversion to the corresponding hydroxylated arene product**114**.

Following a similar rationale, the hydroxylation protocol was extended to a wide variety of substrates possessing weakly coordinating directing groups such as ketones, Weinreb amides, carbamates or anilides (Figure 1.37).In all cases, good yields of the corresponding hydroxylated arenes were observed.

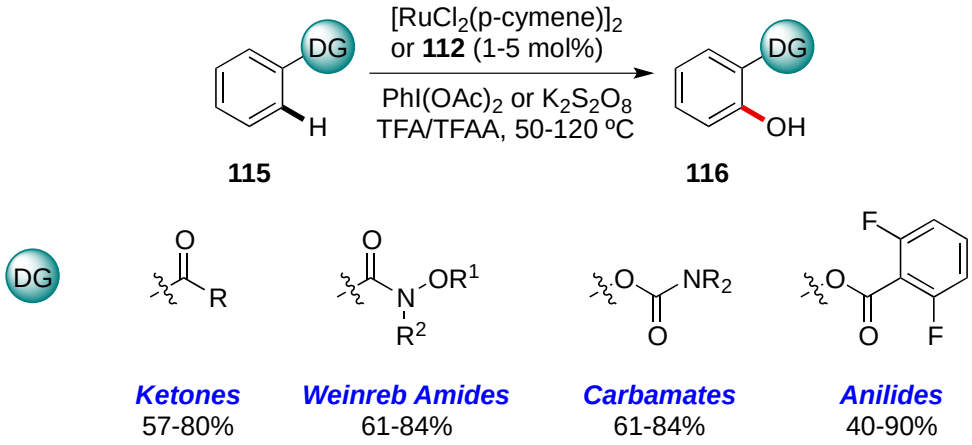


Figure 1. 37

In 2013 Jeganmohan group published the intermolecular Ru-catalyzed benzoxylation of acetanilides**117**with benzoic acids, as illustrated in Figure 1.38.[74]The combination $[RuCl_2(p\text{-cymene})]_2/AgSbF_6$ to forma cationic ruthenium complex was crucial for reactivity. Both electron-donating and electron-deficient acetanilide derivatives afforded the corresponding benzoxylated products in moderate to good yields.

[73]Yang, X.; Shan, G.; Rao, Y. *Org. Lett.***2013**, *15*, 2334.
[74]Chinnagolla, R. K.; Jeganmohan, M. *Chem. Commun.***2012**, *48*, 2030.

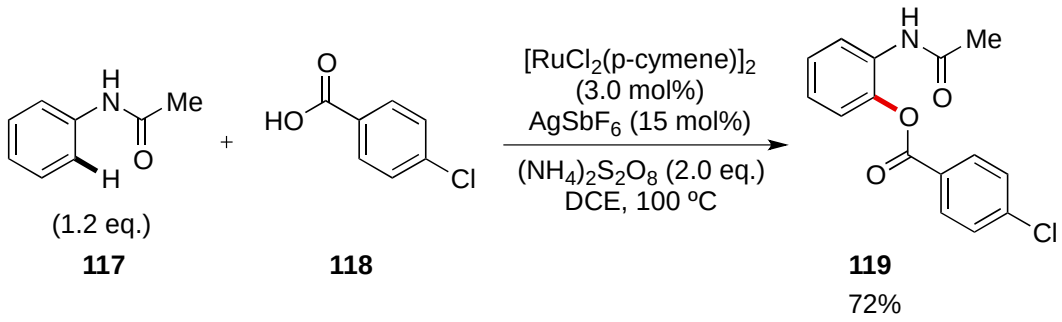


Figure 1.38

Oxidative annulation reactions with alkynes via C(sp^2)-H/C-O bond formation have also been described when using ruthenium (II) complexes thus,isocoumarins and α-pyrones were within reach by utilizing simple benzoic acids as directing groups (Figure 1.39).[75] A cationic ruthenium center and $Cu(OAc)_2$ were critical for success. This system was applicable to disubstituted aryl and alkyl substituted alkynes in good to high yields. Importantly, unsymmetrical alkynes showed high regioselectivity profile with only one regioisomer formed under the reaction conditions.The proposed mechanism consists of an initial C-H functionalization from in situ generated Ru(II) species **XXVII**. Isotope-labelling experiments revealed that C-H bond cleavage was irreversible with a $K_H/K_D \approx 7.3$. A subsequent migratory insertion into the alkyne motif resulted in **XXIX**, which upon reductive elimination would deliver the desired product **122**. Finally, an oxidation of Ru(O) to Ru(II) mediated by Cu(II) would recover the propagating catalytic Ru(II) species.

[75]Ackermann, L.; Pospech, J.; Graczyk, K.; Rauch, K. *Org. Lett.***2012**, *14*, 930.

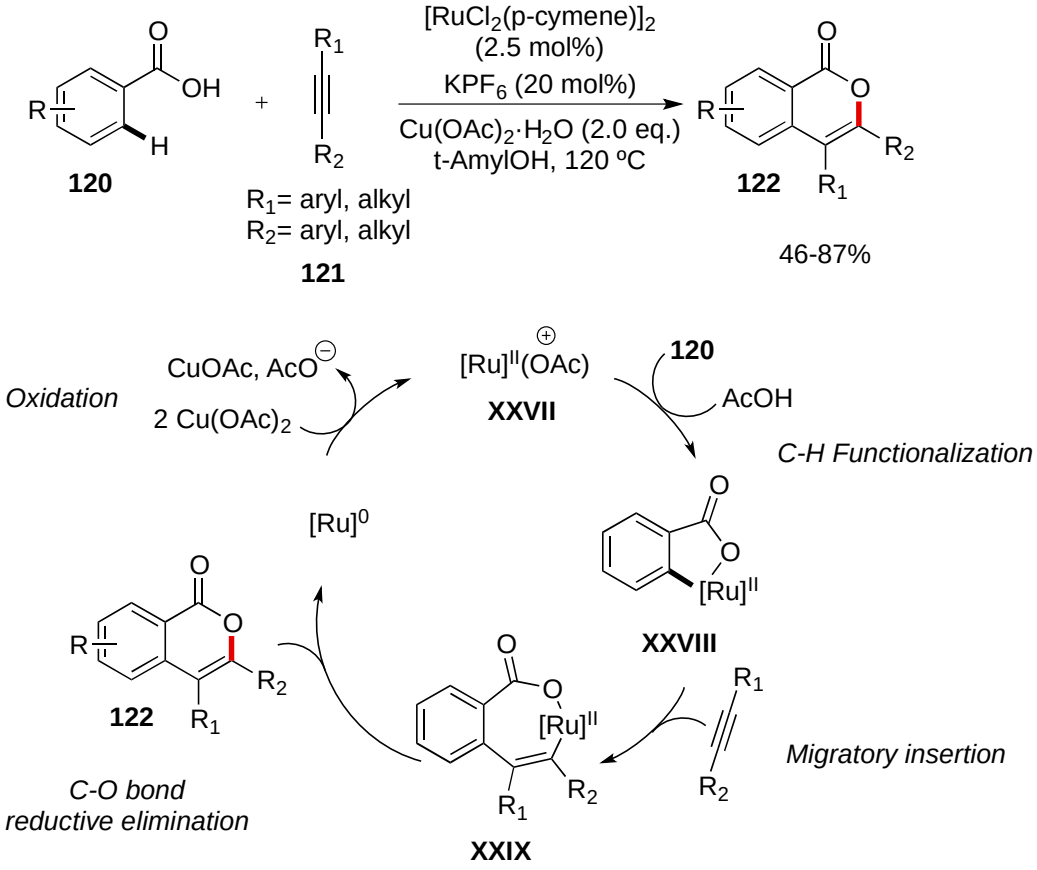


Figure 1.39

A remarkable hydroxyl-directed ruthenium catalyzed synthesis of fluoresecent pyrans via C-H fuctionalization have recently been disclosed by Ackermann (Figure 1.40).[76]As for the former case, excellent regioselectivity was observed when unsymmetrical alkynes were employed. In this particular reaction, kinetic isotope labeling pointed towards a reversible C-H bond metallation step.

[76]Thirunavukkarasu, V. S.; Donati, M.; Ackermann, L.*Org. Lett*. **2012**,*14*, 3416.

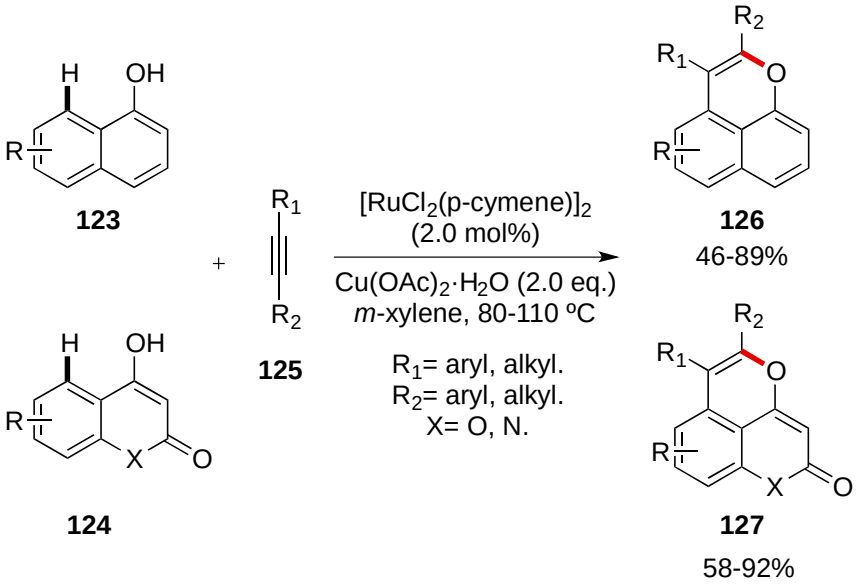


Figure 1.40

1.4 General Objectives

The main objectives of the present thesis are the following:

- To develop new catalytic transformations via C(sp^2)-H functionalization/C-O bond formation.

- To develop new catalytic transformations via C(sp^3)-H functionalization/C-O bond formation.

- To shed light into the mechanism of the proposed C-H functionalization/C-O bond formation.

Chapter 2. Pd-catalyzed C(sp^3)-H bond functionalization/C-O bond formation for the synthesis of phthalides

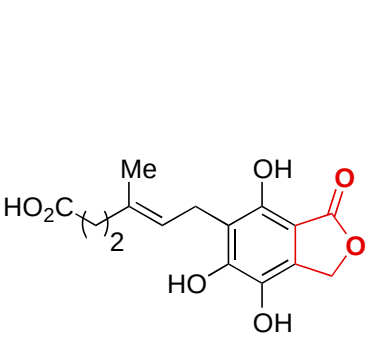
2.1 Objectives

The objectives of this chapter are the following:

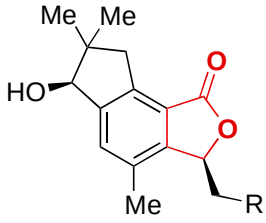
- To study the functionalization of C(sp^3)-H bonds via palladium catalysis en route to phthalides using carboxylic acids as directing groups, and to demonstrate the versatility and chemoselectivity of the process.
- To elucidate the mechanism of the reaction via the study of kinetic isotope effects and the isolation of putative intermediates within the catalytic cycle.

2.2 Importance of phthalides

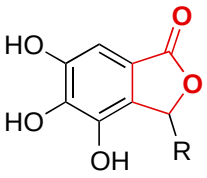
Phthalides are common motifs in nature with more than 180 naturally-occurring compounds produced from a wide number of organisms including marine and terrestrial fungi, plants or even liverworts.[77] As illustrated in Figure 2.1, phthalides exhibit a broad spectrum of bioactivity including remarkable DNA binding properties **128-129**,[78] antibiotic activity **130**,[79] antioxidant and antifungal activity **131**,[80] or inhibition of HIV-1 proliferation **132**,[81] among others. One of the most relevant members of this family of natural products is mycophenolyc acid **133**, used as an immunosuppressant drug. Although diverse in function, all these natural products share a common benzene ring fused to a γ-lactone.



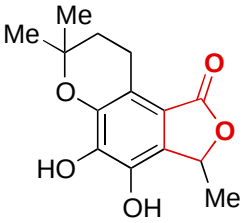
Mycophenolyc acid **133**
Immunosupressor



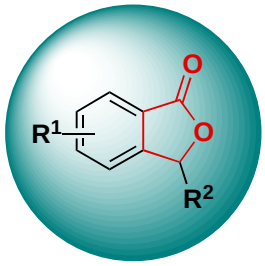
R = -Cl, Alcyopterosin L **128**
R = -ONO_2, *Alcyopterosin M* **129**
Remarkable DNA binding properties

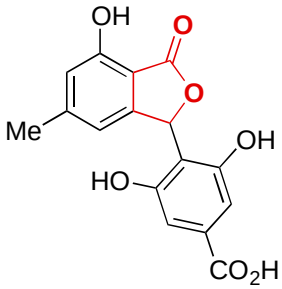


Cytosporone **130**
R = -$(CH_2)_6CH_3$
Antibiotic activity



Fuscinarin **132**
Prevent HIV-1 entry into cells, binding to human CCR5.





Cryphonectric acid **131**
Antifungal and antioxidant activity.

Figure 2.1

[77] Lin, G.; Chan, S.-K.; Chung, H.-S.; Li, S.-L. In *Studies in Natural Products Chemistry*; Rahman, A., Ed.; Elsevier: Amsterdam, Netherlands, 2005. Vol. 32, pp 611-671.
[78] Palermo, J. A.; Brasco, M. V. R.;Spagnuolo, C.; Seldes, A. M. *J. Org. Chem*. **2000**, *65*, 4482.
[79] Brady,S. F.; Wagenaar, M. M.; Singh,M. P.; Janso, J. E.; Clardy, J. *Org. Lett*. **2000**, *2*, 4043.
[80] Arnone, A.; Assante, G.; Nasini, G.; Strada, S.; Vercesi, A. *J. Nat. Prod*. **2002**, *65*, 48.
[81] Yoganathan, K.; Rossant, C.; Huang, Y.; Butler,M. S.; Buss, A. D. *J. Nat. Prod.***2003**, *66*, 1116.

2.3 Classical methods for the synthesis of phthalides

Taking into consideration the importance of this class of compounds, it is not surprising that the synthetic community became interested in the construction of phthalides. Traditional approaches towards the synthesis of this class of compounds rely on halolactonization processes and the cyclization of hydroxy acids or 2-formylbenzoic acidderivatives, as illustrated in Figure 2.2.[82]As a common trend, these approaches require a multistep procedure and functional group maneuvering to install the desired functionality prior to cyclization.

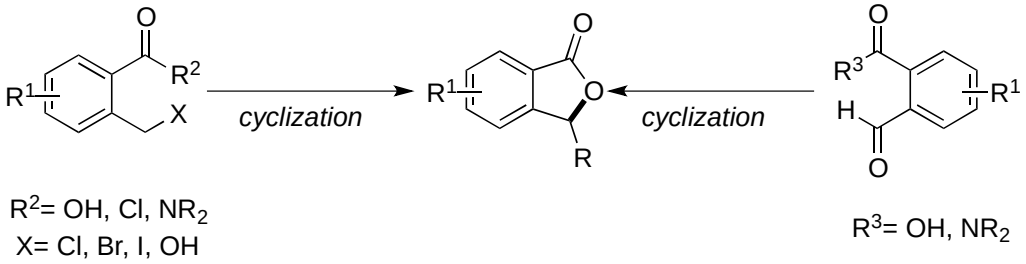


Figure 2.2

An example of these *classical* methods is shown in Figure 2.3. First, *N,N*-diethylamide **134**was converted into aldehyde **135**via *ortho*-lithiationupon treatment withsec-BuLi and DMF. A subsequent acid mediated cyclization provided **136** in 30% overall yield.[83] Unfortunately, stoichiometric amounts of Grignard reagents are needed to install the aldehyde functionality, thus limiting the chemoselectivity of the process.

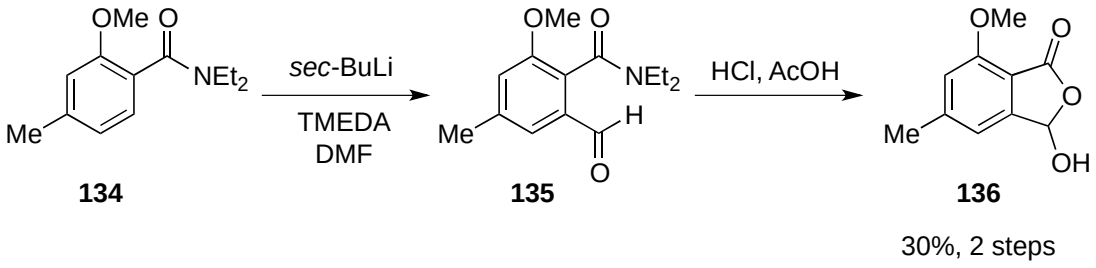


Figure 2.3

Several efforts have been made for the synthesis of enantioenriched phthalides. An early report by Mukaiyama showed the possibility of utilizing chiral auxiliaries for such

[82] For selected references see: (a) Boden, E. P.; Keck, G. E.*J. Org. Chem*.**1985**, *50*, 2394. (b) Semmelhack, M. F.; Epa, W. R.; Cheung, A. W.; Gu, Y.; Kim, C.; Zhang, N.; Lew, W. *J. Am. Chem. Soc.***1994**, *116*, 7455 (c) Pedrosa, R.; Sayalero, S.; Vicente, M. *Tetrahedron***2006**, *62*, 10400. (d) Karnik, A.; Kamath, S. *Synthesis* **2008**, 1832.
[83]Pahari, P.; Senapati, B.; Mal, D. *Tetrahedron Lett.***2004**, *45*, 5109.

purposes, as illustrated in Figure 2.4.[84] A multistep sequence was required for obtaining **141**, an essential oil of celery. First, an initial condensation of pyrrolidine **138** with aldehyde **137**, delivered aminal **139** quantitatively. Then chiral lithiated species generated in situ from **139** with *n*-BuLi, yielded lactol **140** in the presence of butyraldehyde. A final oxidation with Ag_2O delivered (S)-3-butylphathalide **141** in 88% e.e. The stereochemistry rationale behind these results implies a rigid tricyclic five membered ring structure **XXX**, with the aldehyde alkyl chain pointing away from the pyrrolidine ring due to steric effects. Similar methods were reported based on structurally related chiral auxiliary controlled reactions.[85]

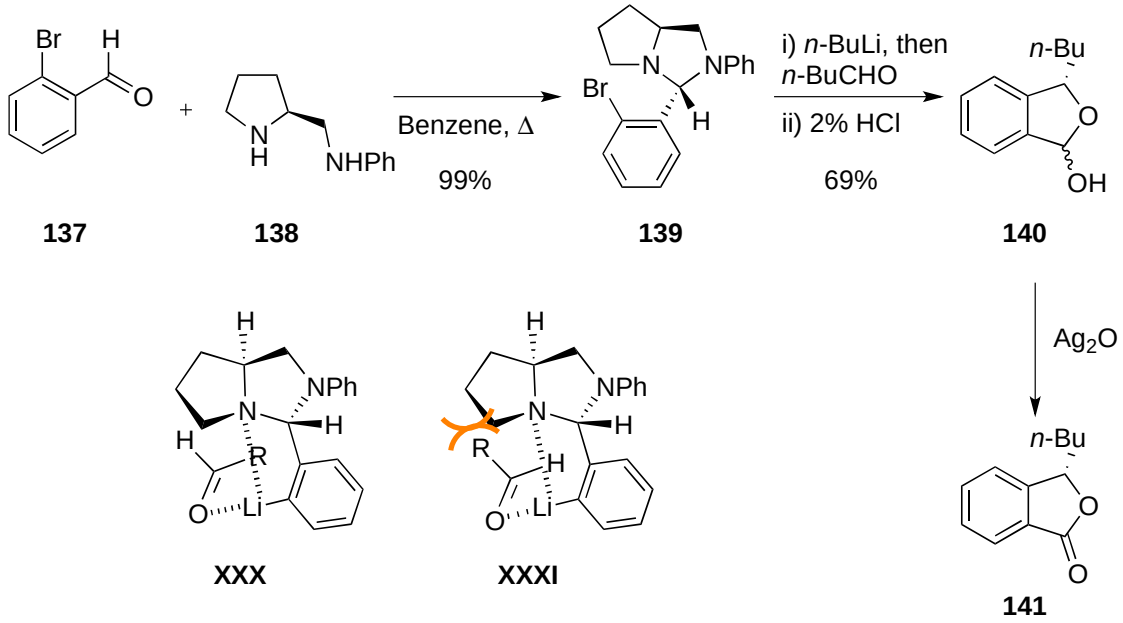


Figure 2.4

Although good asymmetric induction can be achieved with these protocols, the use of stoichiometric amounts of chiral auxiliaries is still a serious drawback to be overcome, hence lowering down the application profile of these methodologies.

[84] Asami, M.; Mukaiyama; T. *Chem. Lett.*, **1980**, 17.
[85] For other quiral auxiliary approaches see: (a) Ogawa, Y.; Hosaka, K.; Chin, M.; Mitsuhashi, H. *Heterocycles***1989**, *29*, 865. (b) Alexakis, A.; Sedrani, R.; Normant, J. F.; Mangeney, P. *Tetrahedron: Asymmetry***1990**, *1*,283. (c) Commercon, M.; Mangeney, P.; Tejero, T.; Alexakis, A. *Tetrahedron: Asymmetry***1990**, *1*,287. (d) Takahashi, H.; Tsubuki, T.; Higashiyama, K. *Chem. Pharm. Bull*. **1991**, *39*, 3136

2.4 Metal-catalyzed methods for the synthesis of phthalides

In recent years, metal-catalyzed procedures for the synthesis of phthalides have gained considerable attention. These methodologies allowed new retrosynthetic disconnections in an atom-economical fashion compared to the *classical methods* shown in the previous section. The most common catalytic approaches include carbonylation protocols, hydrocarboxylation of alkenes and alkynes, ring-closing strategies with *di*-haloalkanes, [2+2+2] cycloadditions and aldehyde or ketone hydroacylation, among others.

2.4.1 Catalytic-carbonylation reactions

Carbon monoxide can be used as an inexpensive and readily available C1 source for the construction of carbonyl-containing compounds. Inspired by early independent reports from Mori[86] and Stille,[87] Larock disclosed in 1982 a palladium-catalyzed cyclocarbonylation with stoichiometric thallium(III) salts providing a new route to phthalides (Figure 2.5).[88] The addition of LiCl and MgO turned out to be beneficial to suppress homocoupling product formation. The proposed mechanism is depicted in Figure 2.5. The sequence could be initiated by an initial transmetallation between the thallium salt and palladium(II) catalyst to yield intermediate **XXXII**. A subsequent CO insertion could form acylpalladium species **XXXIII**, which upon ligand exchange and reductive elimination would release the desired phthalide**143**. A final oxidation of Pd(0) by Tl(III) salts would recover the active catalyst.

[86] Mori, M.; Chiba, K.; Inotsume, N.; Ban, Y. *Heterocycles***1979**, *12*, 912.
[87] Coweil, A.; Stille, J. K. *J. Am. Chem. Soc*. **1980**, *102*, 4193.
[88] Larock, R.C.; Fellows, C.A. *J. Am. Chem. Soc.***1982**, *104*, 1900.

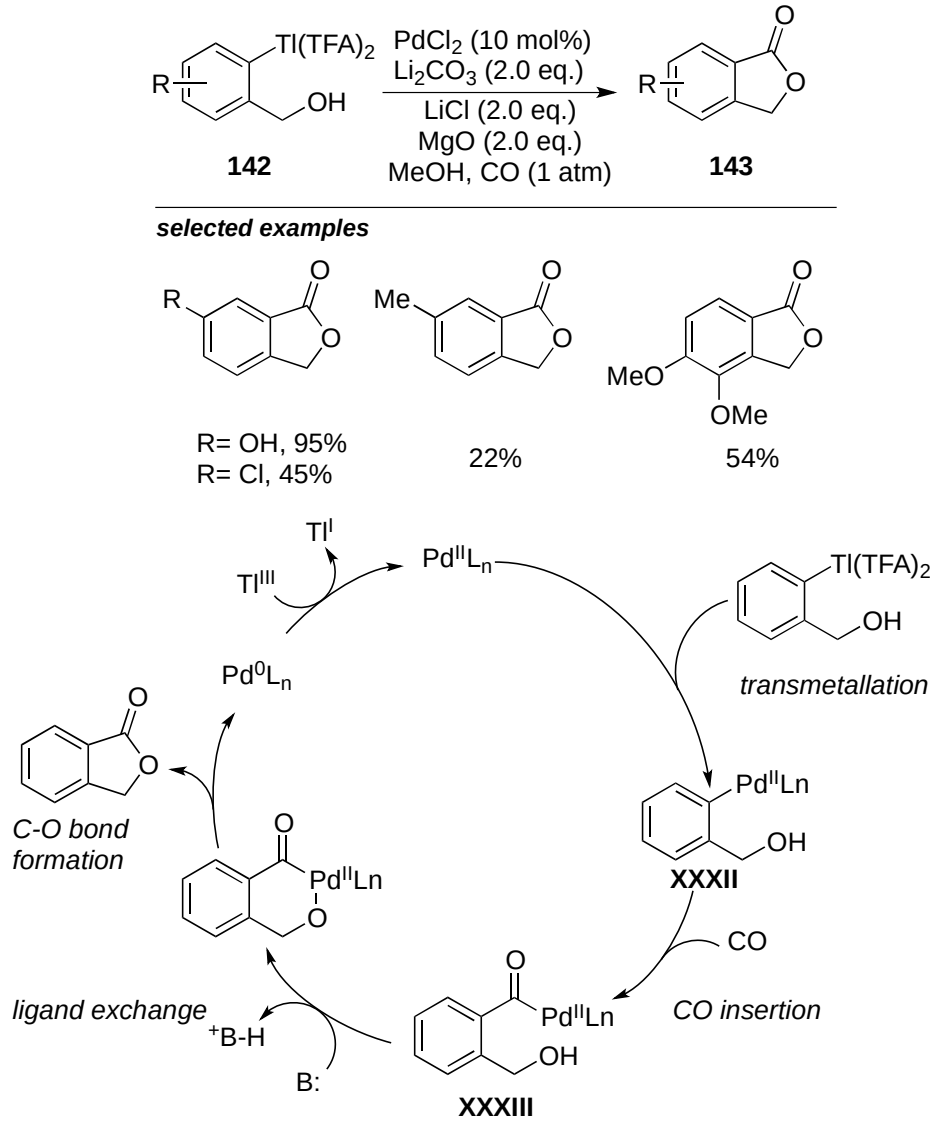


Figure 2.5

2.4.2 Catalytic-hydrocarboxylation of alkenes and alkynes

An alternative strategy for the construction of phthalides relies on the addition of the carboxylic acid -OH bond across a double or triple bond. Both inter and intramolecular reactions have been developed involving Pd and Rh catalysis. Pal envisioned in 1993 a tandem Sonogashira/hydrocarboxylation of alkynes to access 3-alkylidene phthalides in moderate to good yields, as shown in Figure 2.6.[89] Remarkably, only Z-isomers were obtained, hence showing the stereoselectivity of the process. After the Sonogashira type coupling, the mechanism is believed to proceed via an initial activation of the alkyne **XXXIV** by Lewis acidic Pd(II) species, followed by an intramolecular

[89]Kundu, N. G.; Pal, M. *J. Chem. Soc. Chem. Commun.***1993**, 86.

carboxymetallation event. Finally, β-hydride-elimination would deliver **145** while recovering the catalytically active Pd(0) species.

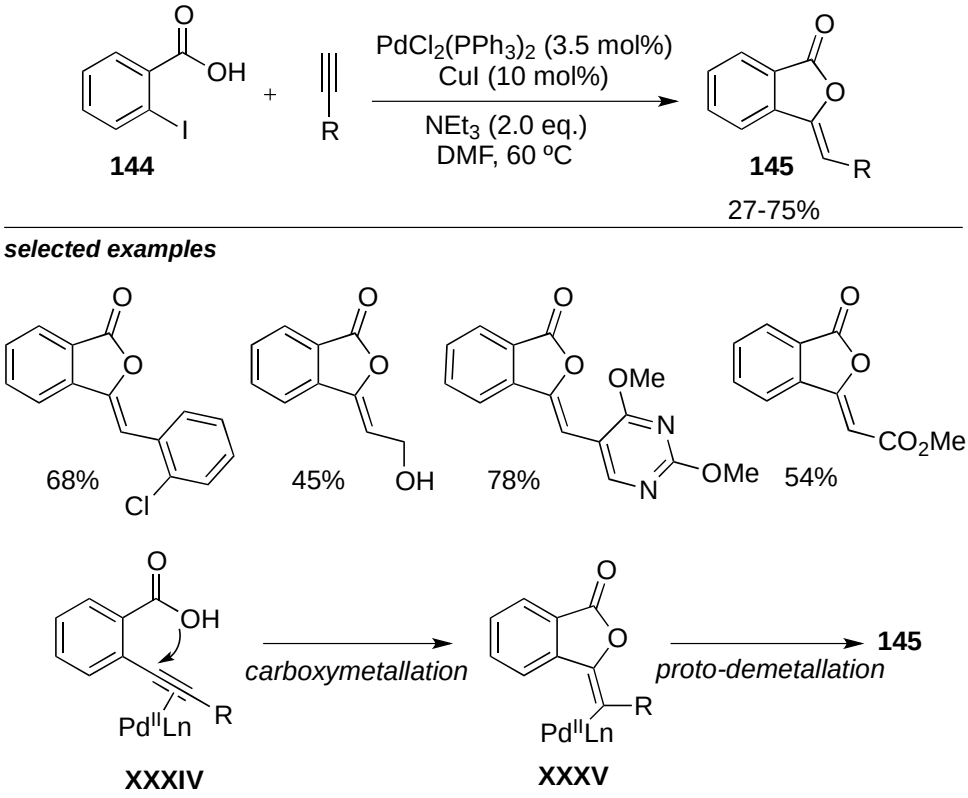


Figure 2.6

Alternatively, an intramolecular Pd-catalyzed oxidative Wacker-type cyclization was reported by Stoltz.[90] As depicted in Figure 2.7, the proposed mechanism involves the coordination of a cationic Pd(II) species **XXXVI** to the alkene motif, followed by oxymetallation, thus affording intermediate **XXXVII**. Then, β-hydride elimination would release phthalide **143** and HPd(II)X species which upon reductive elimination and subsequent oxidation by O_2 would regenerate the active Pd(II) salt.

[90]Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.***2003**, *42*, 2892.

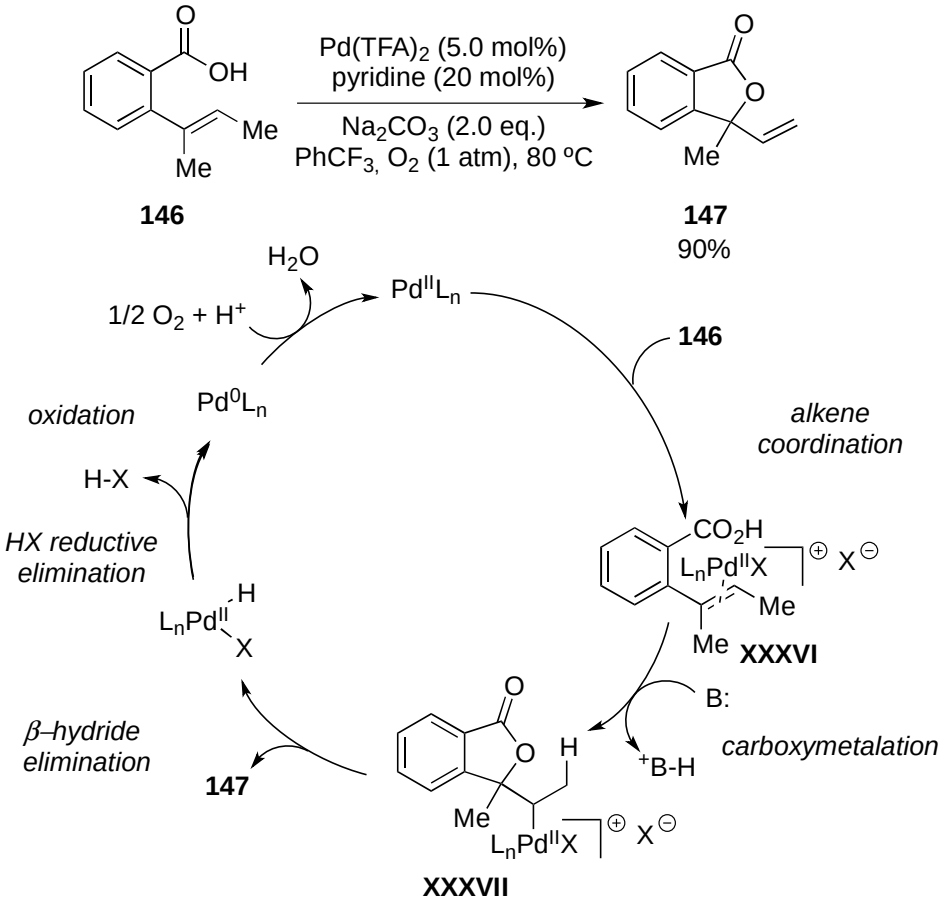


Figure 2.7

On the other hand, a Rh-catalyzed oxidative C(sp^2)-H functionalization strategy was reported by Miura for the synthesis of phthalides, involving the coupling between simple benzoic acids and acrylates under air atmosphere (Figure 2.8).[91] In this particular reaction, *di*-functionalization at both *ortho* positions could not be avoided.

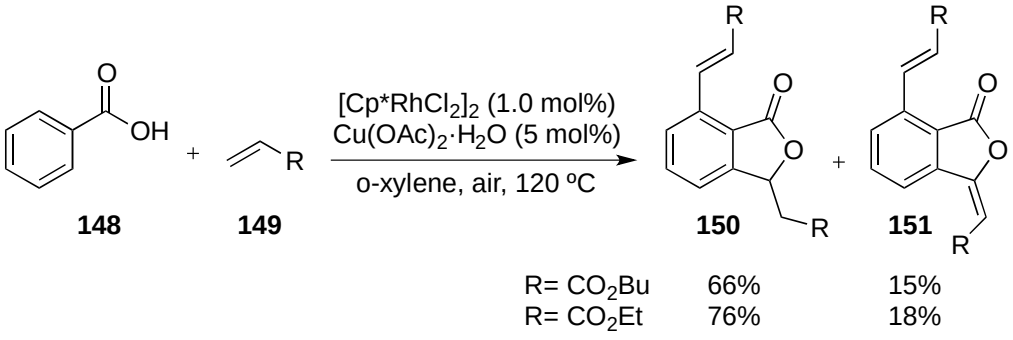


Figure 2.8

[91]Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.***2007**, *9*, 1407.

2.4.3 Catalytic ring-closing strategies with *di*-haloalkanes

Yu anticipated a C(sp^2)-H bond functionalization/ring closure strategy for the synthesis of phthalides utilizing simple benzoic acids**152** and *di*-bromomethane, as depicted in Figure 2.9.[92] This protocol tolerates a wide range of functional groups in good to high yields. In the case of unsymmetrical substrates, the less hindered C-H bond is activated preferentially.

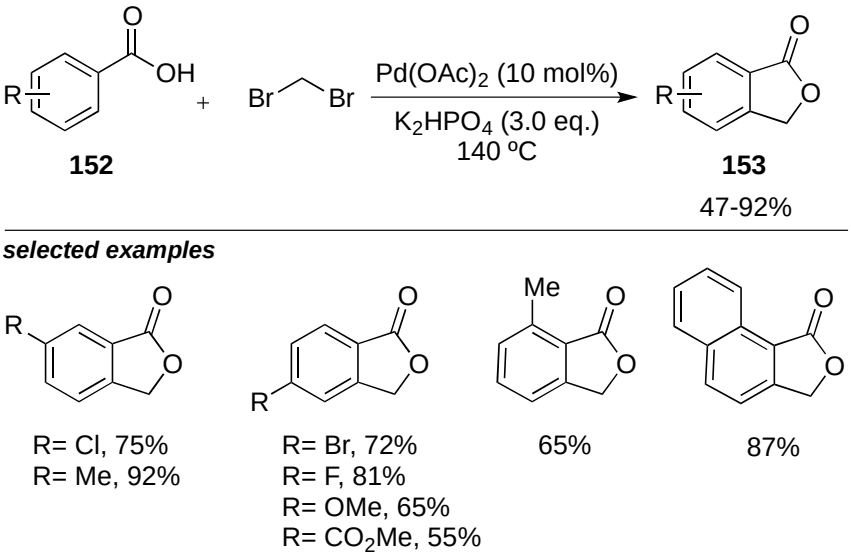


Figure 2.9

2.4.4 Catalytic [2+2+2] cycloaddition approaches

In 2005, Cheng[93] demonstrated the potential of [2+2+2] cobalt-catalyzed cyclotrimerization as a complementary synthetic tool en route to the phthalide core employing alkynyl alcohols **154** and propiolates **155**as coupling partners (Figure 2.10). Precatalyst CoI_2(dppe) in combination with Zn as reducing agent in MeCN/THF turned out to be optimal. Mechanistically, the authors proposed an initial Zn-mediated reduction of Co(II) to Co(I). After coordination of two molecules of acrylate, an oxidative cyclometallation would yield**XXXVIII** followed by an alkyne insertion en route to **XXXIX**. A final reductive elimination from intermediate **XLI**, would release the corresponding hydroxyester that cyclizes spontaneously to lactone **156**.

[92]Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *Angew. Chem. Int. Ed.***2009**, *48*, 6097.
[93]Chang, H.-T.; Jeganmohan, M.; Cheng, C.-H. *Chem. Commun.* **2005**, 4955

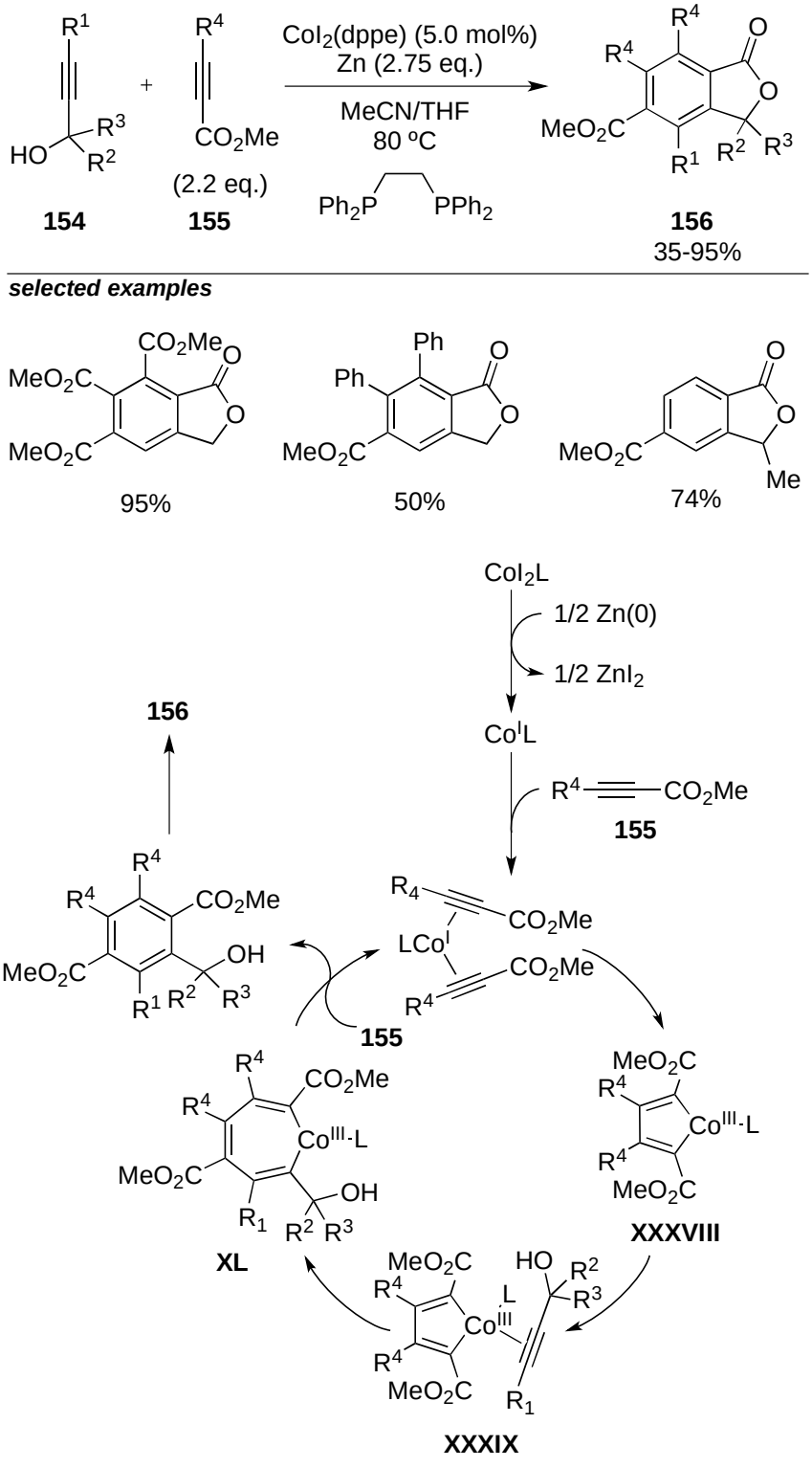

CoI2(dppe) (5.0 mol%)
Zn (2.75 eq.)
MeCN/THF
80 ºC
(2.2 eq.)
154
155
156
35-95%
selected examples
95%
50%
74%
CoI2L
1/2 Zn(0)
1/2 ZnI2
CoIL
155
156
155
XL
XXXVIII
XXXIX

Figure 2.10

2.4.5 Catalytic hydroacylation of aldehydes and ketones

Hydroacylation of carbonyl groups formally involves the insertion of an acyl unit and a hydrogen atom across a C=C or C=O bond.[94] Bosnich described in 1990 the first example of Rh-catalyzed hydroacylation for the construction of phthalides, as shown in Figure 2.11.[95] The mechanism presumably proceeds through an oxidative addition to the aldehydic C-H bond, forming acyl Rh(III)-hydride species **XLI**. Then hydride insertion could occur, thus accessing rhodacycle **XLII**, which upon C-O reductive elimination could release **154** while recovering the active Rh(I) catalyst.

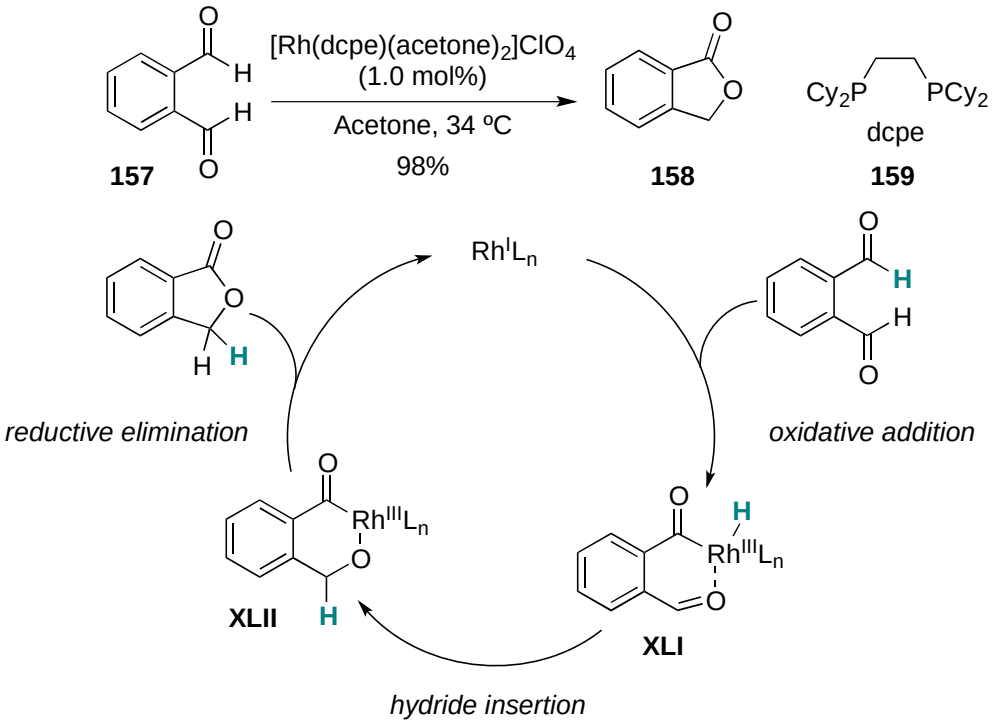


Figure 2.11

Recently, the Dong group developed an intramolecular asymmetric ketone hydroacylation reaction for the synthesis of enantioenriched lactones.[96]After evaluating a variety of ligands, solvents, and counterions, the combination of [{RhCl(cod)}$_2$], phosphine ligand (S,S,R,R)-Duanphos**162**, toluene, and a nitrate counterion were found to be optimal. Surprisingly, the nature of the counterion turned out to be crucial for both reactivity and enantioselectivity. The authors propose complex **XLIII**, which features a vacant coordination site, as a feasible intermediate en route to **161**.

[94] For recent reviews in hydroacylation chemistry see: (a) Leung, J. C.; Krische, M. J. *Chem. Sci.***2012**, *3*, 2202. (b) Willis, M. C. *Chem. Rev.***2010**, *110*, 725.
[95]Bergens, S. H.; Fairlie, D. P.; Bosnich, B.*Organometallics***1990**, 566.
[96]Phan, D. H. T.; Kim, B.; Dong, V. M. *J. Am. Chem. Soc.***2009**, *131*, 15608.

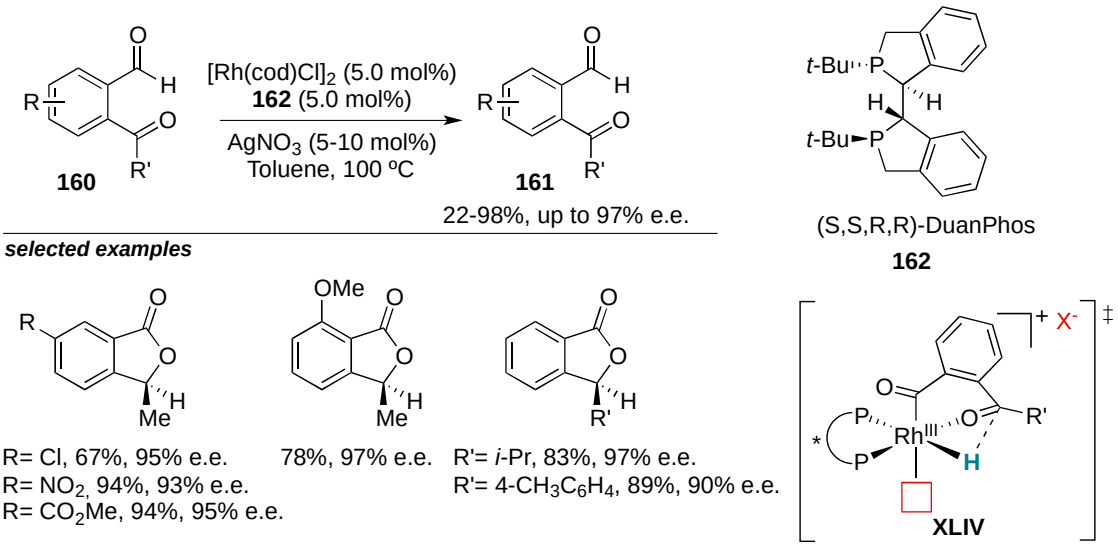


Figure 2.12

2.5 Results and discussion

As mentioned in section 2.3, the most widespread route towards the preparation of phthalides via classical methods consists of the intramolecular cyclization of either 1,2-dicarbonylic compounds or hydroxyacids (Figure 2.13, path a). However, these approaches inherently present the following drawbacks: a) prefunctionalization prior to cyclization is required, b) low functional group tolerance and c) stoichiometric chiral auxiliaries are needed to induce enantioselectivity. Consequently, new metal-catalyzed reactions were developed to tackle these limitations, therefore improving the chemoselectivity and atom-economy (Figure 2.13, path b).

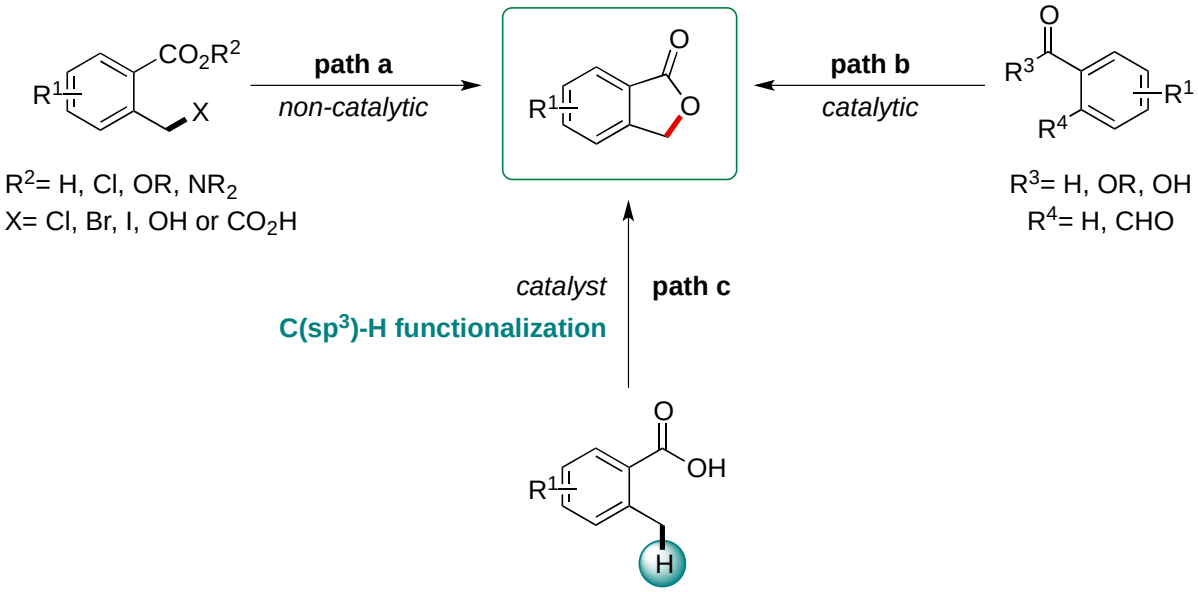


Figure 2.13

On the other hand, we wondered whether we could effect the synthesis of phtalides derivatives by a rather unexplored and challenging intramolecular C(sp^3)-H bond functionalization/C-O bond formation process (Figure 2.13, path c).[97] This transformation represents a great synthetic challenge for the following reasons:

a) The problematic C-O bond-forming event to yield the final phthalide via a C(sp^3)-O bond formation.

b) Site-selectivity between different C-H bonds when simple *ortho*-substituted benzoic acids are employed. As shown in Figure 2.14, *ortho* C(sp^2)-H functionalization will render a more stable 5-membered metallacycle **XLIV**, thus avoiding the formation of **XLV**, crucial intermediate en route to the targeted lactone.

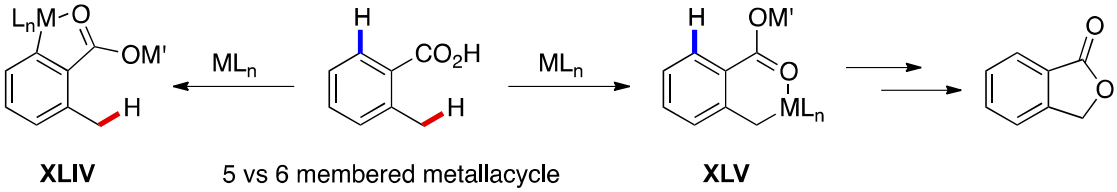


Figure 2.14

At the time we initiated our investigation there were two precedents related to the transformation depicted in Figure 2.13, path c. In 2001, Sames[98] described the synthesis of γ-lactones utilizing aminoacids as substrates via a Pt-catalyzed C(sp^3)-H activation followed by an intramolecular C-O bond-forming reaction. Despite the tremendous potential of this transformation, the corresponding γ-lactones were unfortunately prepared in low yields and moderate diastereoselectiviy. In 2006, Chang and co-workers[99]reported that 2-methylbenzoic acid derivatives could undergo a similar transformation employing exactly the same reaction conditions as Sames. Interestingly, palladium catalysts could also be employed, albeit in lower yields and higher catalyst loadings.Once again, however, the scope was rather limited despite the preparative potential of this transformation, an observation that was highlighted in a recent review,[97a]"*Chang et al. demonstrated that either Pt(II) or Pd(II) catalysts could activate the carbon Csp^3-H bond of o-alkyl-substituted aromatic carboxylic acids to generate the*

[97] For selected reviews on C(sp^3)-H bond functionalization see: (a) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem. Eur. J.***2010**, *16*, 2654. (b) Baudoin, O. *Chem. Soc. Rev.***2011**, *40*, 4902. (c) Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol.***2011**, *1*, 191 (d) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev.***2012**, *41*, 5588.
[98]Dangel, B.; Johnson, J.; Sames, D. *J. Am. Chem. Soc.* **2001,** *123,* 8149.
[99]Min, L; Chang, S.; *Tetrahedron Lett.***2006**, *47*, 1375.

corresponding lactones, but with a rather limited substrate scope and in moderate yield".

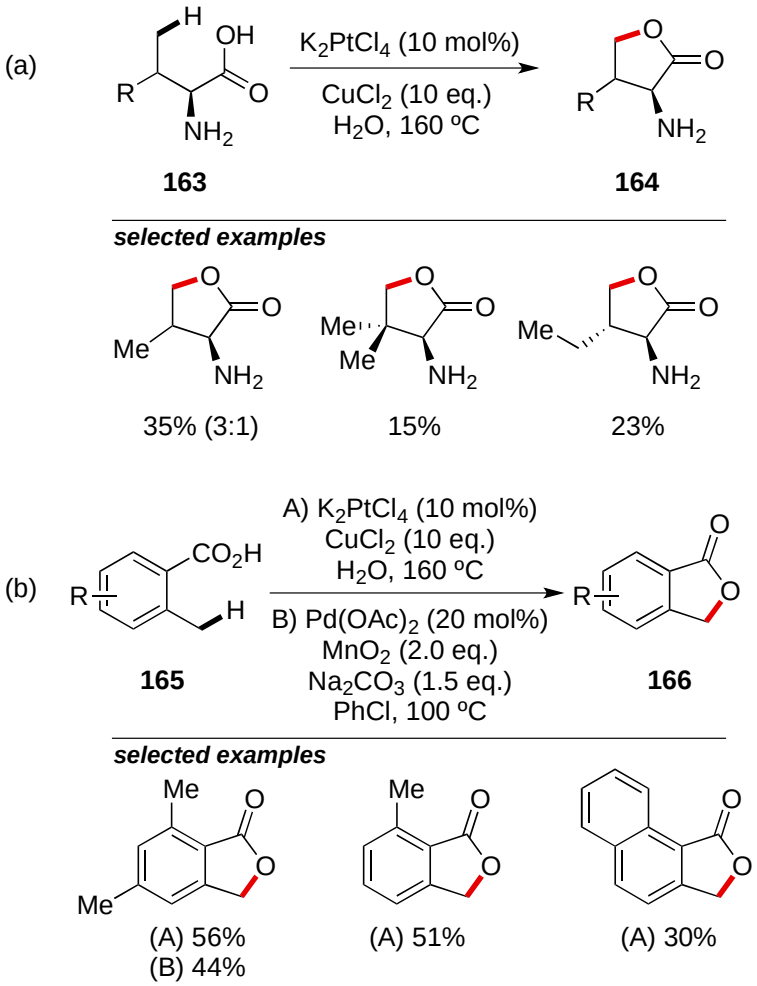


Figure 2.15

Convinced by the potential of this and related transformations, we decided to venture into this area of expertise by providing a better catalytic protocol for the synthesis of phthalides that would operate with a broad scope and that would avoid the use of expensive Pt-catalysts.Under a mechanistic point of view, we hypothesized that the inclusion of an inorganic base would generate the corresponding carboxylate and enhance the coordination to the metal catalyst. As depicted in Figure 2.16, we anticipated that **XLVII** would undergo C-H functionalization to form the 6-membered metallacycle **XLVIII**, which after C-O bond reductive elimination would afford the desired phthalide. A final oxidation step is needed to recover the active metal species. We also speculated a different mechanistic scenario in which metallacycle **XLVIII**could be oxidized to a high valent species **XLIX**, which upon reductive elimination could render **166** while recovering the active catalyst.

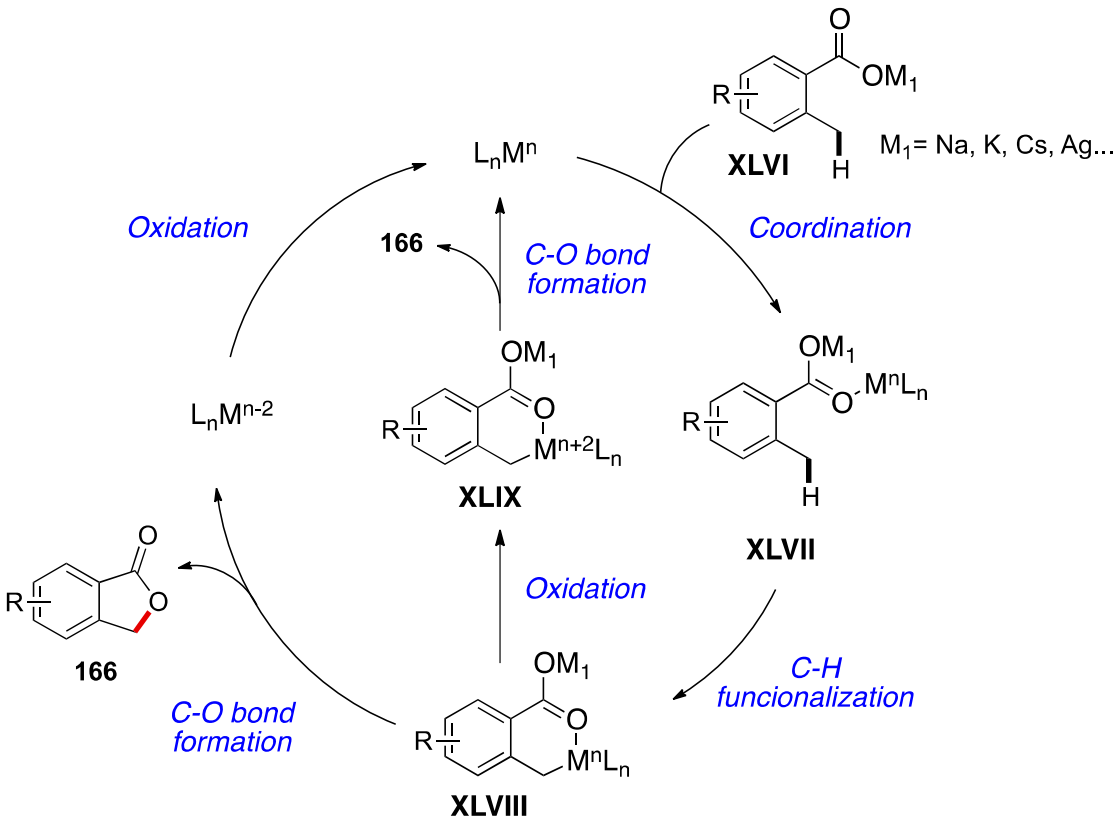


Figure 2.16

We expected C(sp^3)-H cleavage to be problematic due to the formation of a relatively unstable 6-membered metallacycle. However, several literature precedents have demonstrated that 6-membrered metallacycle intermediates can be functionalized with arylboron reagents, olefins, alkylboron species or even deuterium atoms.[100] Moreover, we also anticipated a crucial the role of additives to promote the C-H cleavage step, presumably via a concerted-metallation deprotonation (CMD) pathway.[10] Still, as for many other coupling reactions, we also anticipated that the nature of the ligand, base and solvent would also play an important role for promoting C-H cleavage step.[101]

[100] (a) Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.***2008**, *130*, 17676. (b) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.***2010**, *132*, 14137. (c) Engle, K. M.; Thuy-Boun, P. S.; Dang, M.; Yu, J.-Q. *J. Am. Chem. Soc.***2011**, *133*, 18183. (d) Thuy-Boun, P. S.; Villa, G.; Dang, D.; Richardson, P.; Su, S.; Yu, J.-Q. *J. Am. Chem. Soc.***2013**, *135*, 17508. (e) Ma, S.; Villa, G.; Thuy-Boun, P. S.; Homs, A.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2014**, *53*, 734.
[101] (a) Meyers, C.; Maes, B. U. W.; Loones, K. T. J.; Bal, G.; Lemière, G. L. F.; Dommisse, R. a. *J. Org. Chem.***2004**, *69*, 6010. (b) Proutiere, F.; Schoenebeck, F. *Angew. Chem. Int. Ed.***2011**, *50*, 8192. (c) Maiti, D.; Fors, B. P.; Henderson, J. L.; Nakamura, Y.; Buchwald, S. L. Chem. Sci.**2011**,*2* 57.

2.5.1 Screening of the reaction conditions for the synthesis of phthalides

Among all the metals that are known to actively participate in C-H bond functionalization processes, palladium pre-catalysts undoubtedly play a dominant role due to the functional group tolerance associated to these reactions, compatibility with a wide variety of oxidants and the ease for fine-tuning the properties of the active catalytic species by using proper supporting ligands.

We chose commercially available 2,4,6-trimethyl benzoic acid **167** as our model substrate, since it might avoid site-selectivity issues between ortho C(sp^2)-H and benzylic C(sp^3)-H bond functionalization. Prompted by seminal work from Fagnou and Yu, we hypothesized that the inclusion of carboxylates as additives may exert an important influence in the reaction outcome.[102] Thus, a series of reactions were carried out in the presence of $Pd(OAc)_2$ (10 mol%), pivalic acid as additive (1.0 eq.), oxidant (2.0 eq.), K_2HPO_4 (2.5 eq.), 1,4-dioxane (0.2M) at 130 ºC.[103] The reactions were analyzed by GC after 12h reaction time. As judged by the analysis of the crude reaction mixtures, **167** was converted into two main products in all cases: the expected phthalide **168** and the corresponding decarboxylated product **169**.

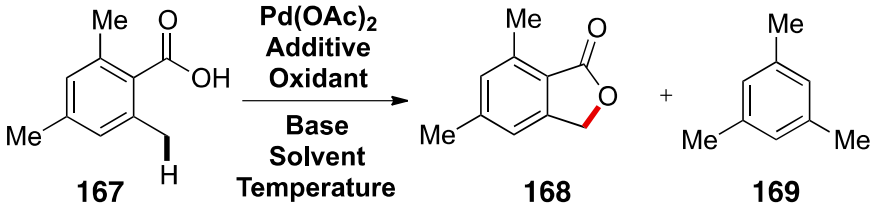


Figure 2.17

Formation of mesytilene derivative **169** can be explained via direct decarboxylation of mesitylbenzoic acid in the presence of a palladium catalyst. Indeed, Myers developed in 2002 an efficient palladium-catalyzed decarboxylative coupling of benzoic acids with olefinic substrates.[104] They stated that the combination of palladium precatalyst with silver salts was crucial for achieving high reaction efficiency and chemo-selectivity. Later, Kozloswki described a similar protocol for the

[102] (a) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.***2006**, *128*, 16496. (b) Giri, R.; Yu, J. Am. Chem. Soc. **2008**, 14082. (c) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science***2010**, *327*, 315.
[103] In collaboration with Dr. Petr Novák and Dr. Arkaitz Correa.
[104] Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.***2002**, *124*, 11250.

protodecarboxylation of electron-rich benzoic acids. Based on previous mechanistic studies, a four-membered transition state**LI** with loss of carbon dioxide delivers and aryl palladium species **LII**.

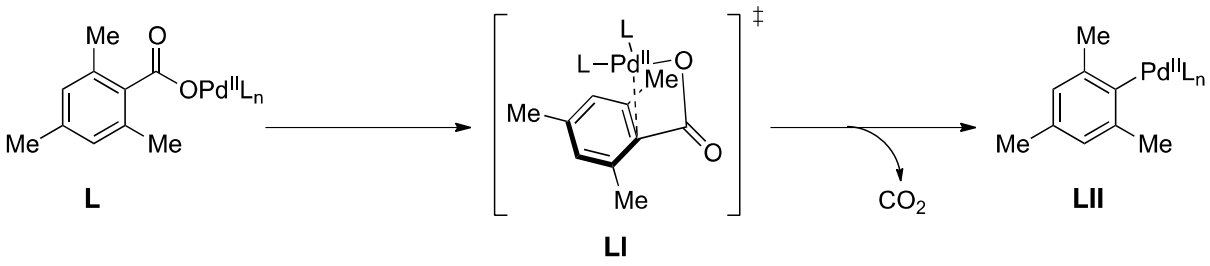
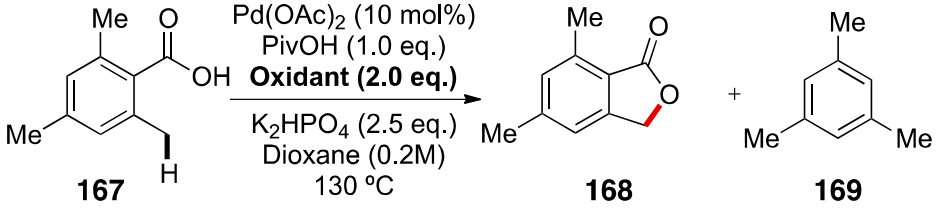


Figure 2.18

Table 2.1. Oxidant screening. [a]



Entry	Oxidant	Conv. (%)[b]	168 (%)[b]	169 (%)[b]
1	$Cu(OAc)_2$	84	6	7
2	$CuCl_2$	81	9	1
3	BQ	37	2	2
4	MnO_2	89	18	10
5	$K_2S_2O_8$	38	2	3
6	Oxone	11	0	3
7	Ag_2O	72	22	5
8	AgO	49	26	11
9	AgOAc	55	21	9
10	$AgNO_3$	98	23	55
11	AgI	57	4	2
12	AgOTf	99	15	51
13	$AgSbF_6$	90	6	63
14	Ag(OCOPh)	70	14	17
15	Ag_2CO_3 (1.0	85	8	6
16	Ag_2CO_3	84	40	6

[a] Benzoic acid (0.25 mmol), $Pd(OAc)_2$ (10 mol%), PivOH (1.0 eq.), Oxidant (2.0 eq.), K_2HPO_4 (2.5 eq.), dioxane (0.2M), 130 ºC, 12h, argon atmosphere. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

As judged by our initial screening shown in Table 2.1, low conversions to **168** as well as significant amounts of decarboxylated product **169** were observed with most of the oxidants analyzed. The use of copper salts was ineffective for promoting this reaction (entries 1 and 2). Other oxidants widely used on palladium oxidative couplings such as BQ, MnO_2, $K_2S_2O_8$ or Oxone (entries 3-6) gave poor conversions to **168**. However, when Ag_2CO_3 (2.0 eq.) was employed, a promising 40% of **168** was obtained (entry 16). Interestingly, the counteranion on Ag(I) was critical for both selectivity and reactivity as illustrated by the results shown in entries 7-14 versus entry 16.

Next, we examined the effect of different bases in the reaction outcome (Table 2.2). As shown in entry 1, CsOPiv turned out to be detrimental for our catalytic system. On the other hand, KH_2PO_4 favored the formation of decarboxylated product **169** (entry 2). Although Na_2HPO_4 and K_2HPO_4 provided comparable yields (entries 4 and 5), we continued our optimization process with the latter, as less amounts of decarboxylated product **169**were detected. Despite the exact role of the base still remains unclear, several reports from Yu's laboratory illustrated the importance of countercations for carboxyl-directed C-H functionalization.[27b] They observed that the coordination mode between the substrate and palladium catalyst plays an important role on reactivity. In the case of palladium, the energetic preference is to remain in an unreactive κ^2acetate-bound configuration (Figure 2.19, **LIII**). In contrast, the addition of a hard Lewis acidic metal can predominantly bind to the carboxylate and reorient Pd(II) into a κ^1-type coordination **LV**, therefore placing the metal in close proximity to the C-H bond. The authors proposed dimeric cyclometallated species **LVI** as competent intermediates within the catalytic cycle.

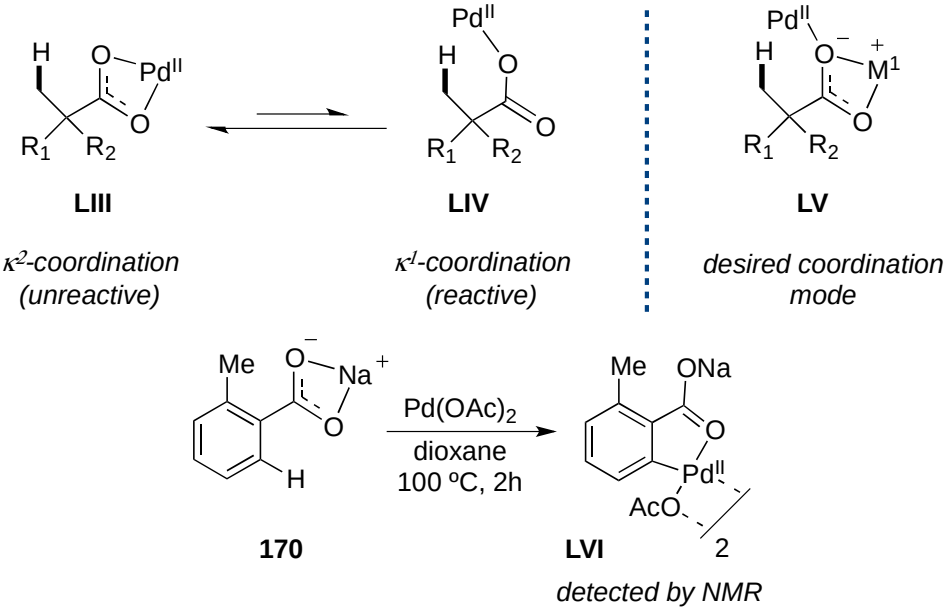
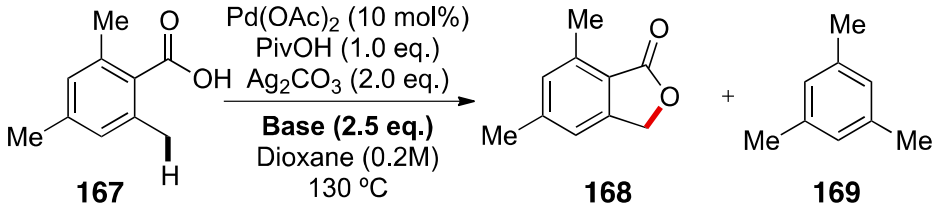


Figure 2.19

Table 2.2. Base effect.[a]



167 **168** **169**

Entry	Base	Conv. (%)[b]	168 (%)[b]	169 (%)[b]
1	CsOPiv	95	5	0
2	KH_2PO_4	82	22	38
3	NaOAc	84	25	13
4	Na_2HPO_4	79	43	18
5	K_2HPO_4	92	40	7

[a] Benzoic acid (0.25 mmol), $Pd(OAc)_2$ (10 mol%), PivOH (1.0 eq.), Ag_2CO_3 (2.0 eq.),Base (2.5 eq.), dioxane (0.2M), 130 ºC, 12h, argon atmosphere. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

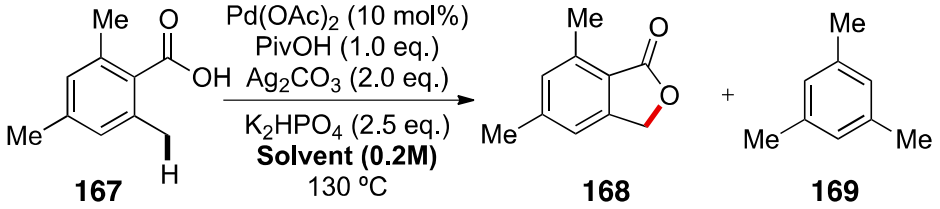
Afterwards, a variety of solvents were systematically examined. The results are summarized in Table 2.3. Among all the ethereal solvents tested (entries 2-4), dioxane showed superior activity providing 46% yield with 6% of decarboxylated product (entry 3).When employing alcoholic solvents such as ^{t}BuOH, the yield was decreased to 25% (entry 5). Moreover, in that particular case substantial amounts of **169** were detected. The use of DMF resulted in no product formation (entry 6). To our delight, chlorobenzeneprovided**168** in 51% yield(entry 8). Additionally, by increasing the reaction temperature from 130 ºC to 140 ºC (entry 9), 63% yield of our desired phthalide was obtained.Importantly, no decarboxylation was observed under these conditions.

We then turned our attention to the role of carboxylate-type ligands in our lactonization protocol. Carboxylates have been proposed to assist in the C-H cleavage step *via* intramolecular coordination with the palladium catalyst.[9] Several mechanistic models for the C-H cleavage step with Pd(II) are depicted in Figure 2.20. Ryabov originally proposed in 1985 an electrophilic palladation mechanism.[105] In this model, palladium coordinates to the π–system of the arene and the resulting Wheland intermediate **LVII** transfers a proton to the palladium-bound carboxylate to generate the cyclopalladated intermediate. On the other hand, a proton abstraction mechanism was put forward by Martinez, in which the C-H cleavage proceeds *via* 4-membered transition state **LVIII**,

[105] Ryabov, A. D.; Sakodinskaya, I. K.; Yatsimirsky, A. K. *J. Chem. Soc., Dalton Trans.***1985**, 2629.

with concerted transfer of the hydrogen to an intramolecular base.[106] Subsequent computational work by Davies and Macgregor pointed towards a 6-membered transition state **LIX**.[11]It is worth mentioning that proton abstraction with Pd(II) is conceptually related to the C-H functionalizationmechanism proposed independently by Echavarren and Fagnou.[12,13]

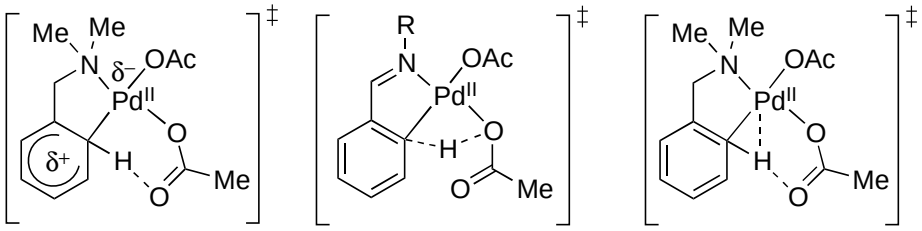
Table 2.3. Solvent screening.[a]



167 **168** **169**

Entry	Solvent	Conv. (%)[b]	168 (%)[b]	169 (%)[b]
1	Toluene	87	12	1
2	*n*-Bu_2O	84	23	1
3	Dioxane	92	46	6
4	Diglyme	96	22	14
5	^{t}BuOH	73	25	16
6	DMF	62	0	0
7	$PhCF_3$	100	37	2
8	PhCl	100	51	4
9	PhCl (140 ºC)	100	63	0

[a] Benzoic acid (0.25 mmol), $Pd(OAc)_2$ (10 mol%), PivOH (1.0 eq.), Ag_2CO_3 (2.0 eq.), K_2HPO_4 (2.5 eq.), solvent (0.2M), 130 ºC, 12h, argon atmosphere. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.



LVII **LVIII** **LIX**

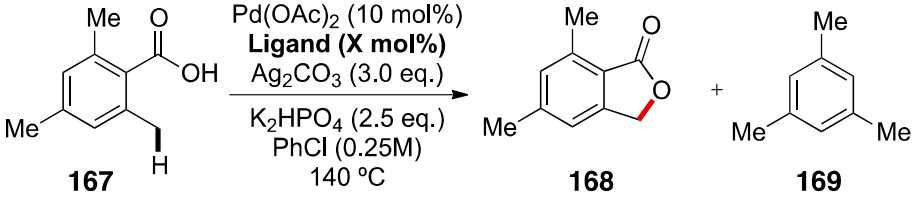
Ryabov (1985) Martinez (1997) Davies and Macgregor (2005)

electrophilic palladation *proton abstraction* *proton abstraction*

Figure 2.20

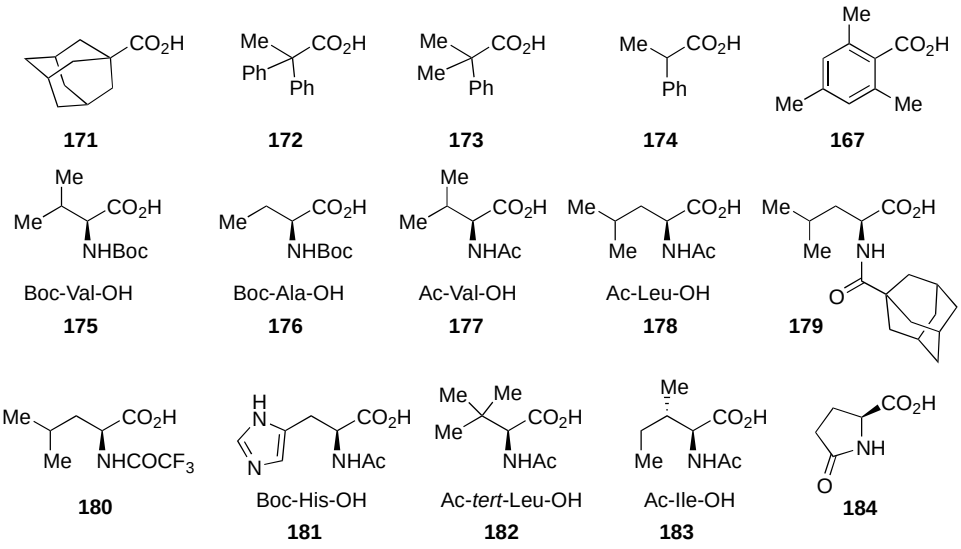
[106] (a) Gómez, M.; Granell, J.; Martinez, M. *Organometallics***1997**, *16*, 2539. (b) Gómez, M.; Granell, J.; Martinez, M. *J. Chem. Soc., Dalton Trans*. **1998**, 37.

Table 2.4. Additive screening. [a]



Entry	L	Conv. (%)[b]	168 (%)[b]	169 (%)[b]
1	**171** (100 mol%)	100	57	7
2	**171** (50 mol%)	100	58	1
3	**171** (30 mol%)	100	71	2
4	**171** (10 mol%)	100	52	3
5	**172**(100 mol%)	100	17	19
6	**173** (100 mol%)	100	36	15
7	**174** (100 mol%)	100	23	17
8	**167** (30 mol%)	88	49	18
9	**175** (30 mol%)	87	45	15
10	**176** (30 mol%)	82	38	10
11	**177** (30 mol%)	100	78	15
12	**178**(30 mol%)	100	95	2
13	**179** (30 mol%)	100	42	37
14	**180** (30 mol%)	100	36	32
15	**181** (30 mol%)	100	76	13
16	**182** (30 mol%)	100	72	8
17	**183** (30 mol%)	80	57	14
18	**184** (30 mol%)	50	7	4

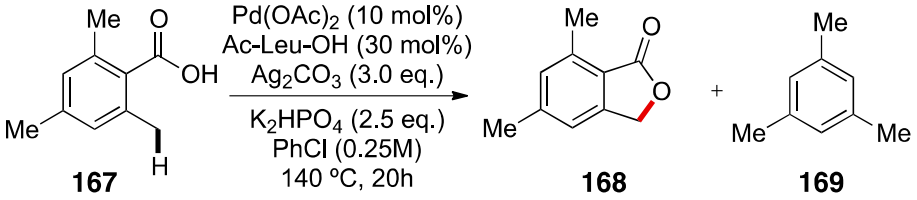
[a] Benzoic acid (0.25 mmol), $Pd(OAc)_2$ (10 mol%), L (30-100 mol%), K_2HPO_4 (2.5 eq.), PhCl (0.2M), 140 ºC, 24h, argon atmosphere. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.



In order to improve the catalytic efficiency of our system, different carboxylate-type ligands were employed. When changing the carboxylate nature, the yield increased up to 71% by using1-adamanthyl carboxylic acid **171**(Table 2.4, entry 3)in a 1:3 metal to ligand ratio. Indeed, a different metal to ligand ratio caused a deleterious effect as illustrated by entries 1,2 and 4.Other alkyl carboxylic acids such as**172**-**174**provided lower yields together with considerableamounts of decarboxylation (entries 5-7).Subsequently, we found that a collection of commercially available aminoacids could be successfully employed as ligands. The beneficial effect of using *N*-protected amino acids for the activation of various C(sp^2)-H bonds has already been demonstrated by the pioneering work of Yu and co-workers.[107]While the inclusion of Boc-protected aminoacids in our system provided moderate yields of **168**(entries 9 and 10), a markedly improve was observed by varying the N-protecting group from*tert*-butoxycarbonyl to acetyl (entries 11, 12, 15, 16). To our delight, ligand **178** was particularlyactivedrastically reducing the yield of **169** while increasing the yield of **168** up to 95% (entry 12). Intriguingly, the favorable profile when using Ac-Leu-OH **178** can not be explained simply by electronic or steric effects, as **179** or **180** (entries 13 and 14, respectively) are not particularly effective, thus showing the subtleties of our protocol.Finally, a modification on the amino acid side chain placing a chelating imidazole group (ligand **181,** entry 15) or introducing more steric hindrance (entries 16 and 17) proved to be detrimental thus decreasing the yield of **168**.

Table 2.5. Blank experiments.[a]

[107] (a) Lu, Y.; Wang, D.-H.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc*. **2010**, *132*, 5916.(b) Engle, K. M.; Wang, D.-H.; Yu, J.-Q*J. Am. Chem. Soc*. **2010**,*132*, 14137. (c) Lu, Y.; Leow, D.; Wang, X.; Engle, K. M.; J.-Q. Yu, *Chem. Sci.***2011**, *2*, 967. (d) Dai, H. -X.; Stepan, A. F.; Plummer, M. S.; Zhang, Y.-H; Yu, J.-Q.*J. Am. Chem. Soc*. **2011**, *133*, 7222.



Entry	$Pd(OAc)_2$	Ac-Leu-OH	Ag_2CO_3	K_2HPO_4	Conv. (%)[b]	168 (%)[b]	169 (%)[b]
1	✗	✔	✔	✔	85	0	2
2	✔	✔	✗	✔	46	0	24
3	✔	✔	✔	✗	93	15	76
4	✔	✗	✔	✔	88	48	18

[a] Benzoic acid (0.25 mmol), $Pd(OAc)_2$ (10 mol%), Ac-Leu-OH (30 mol%), Ag_2CO_3 (30 mol%), K_2HPO_4 (2.5 eq.), PhCl (0.2M), 140 ºC, 24h, argon atmosphere. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

As expected, background experiments shown in table 5 demonstrated that without metal catalyst (entry 1) or Ag_2CO_3(entry 2), no reaction took place. In the absence of base or ligand (entries 3-4) the yield decreases significantly.

2.5.2 Synthesis of the starting benzoic acids

Having established the optimized reaction conditions, we turned our attention to explore the scope of the reaction. A wide range of *ortho*-dimethylbenzoic acids were prepared containing different functional groups as well as several substitution patterns.[108] One of the most common strategies for the synthesis of benzoic acids relies on the direct carboxylation of aryl bromides. Compounds **187**-**191** were synthesized in that manner from the corresponding bromoarenes **185** with *n*-BuLi and CO_2 (Figure 2.21).

[108] In collaboration with Dr. Petr Novák.

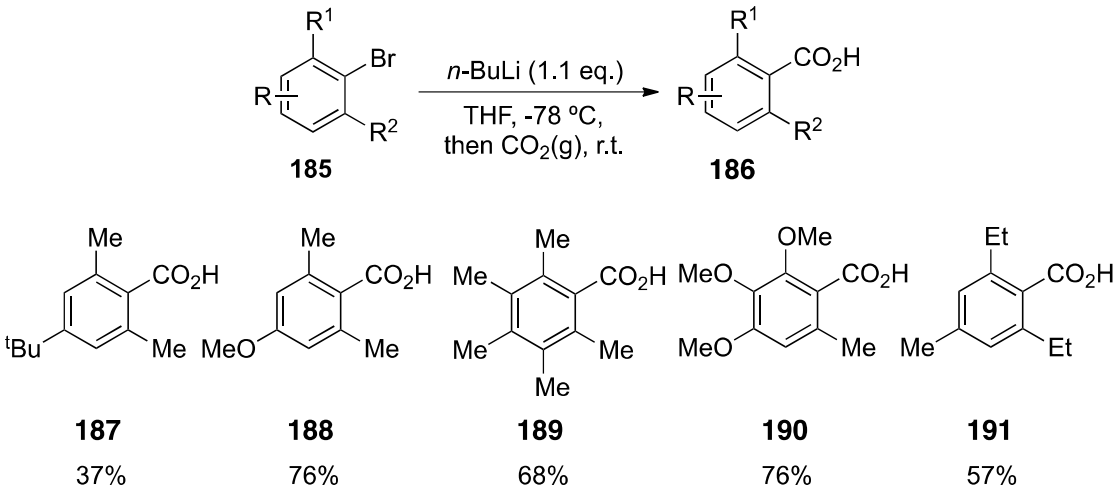


Figure 2.21

Alternatively, we were interested on preparing *bis*-orthosubstituted carboxylic acids bearing different functional groups on the 4-position of the aromatic ring. Compound **193** was obtained in 2 steps from **192** with 40% overall yield. An easy alcohol protection with triisopropylsililether followed by carboxylation yielded the corresponding acid**193**.

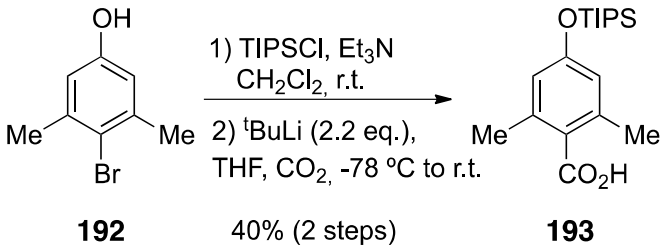


Figure 2.22

Similarly, compound **195** was synthetized in a 2-step sequence via diazotization of aniline **194** in the presence of $CuCl_2$(Figure 2.23). A subsequent carboxylation with ^{t}BuLi provided **195** in multigram scale. Subsequently, methylation of the previously prepared carboxylic acid followed by silylation of the aryl chloride under Buchwald´s

conditions[109] using CyJohnPhos **196**as the ligand, followedby a final hydrolysis of the methyl ester in basic media, **197** was obtained in a modest 15% overall yield.

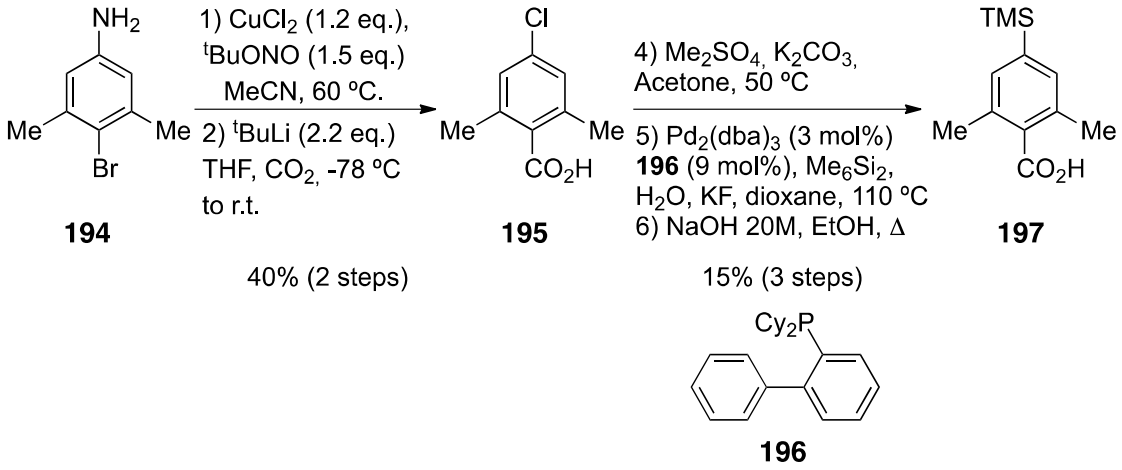
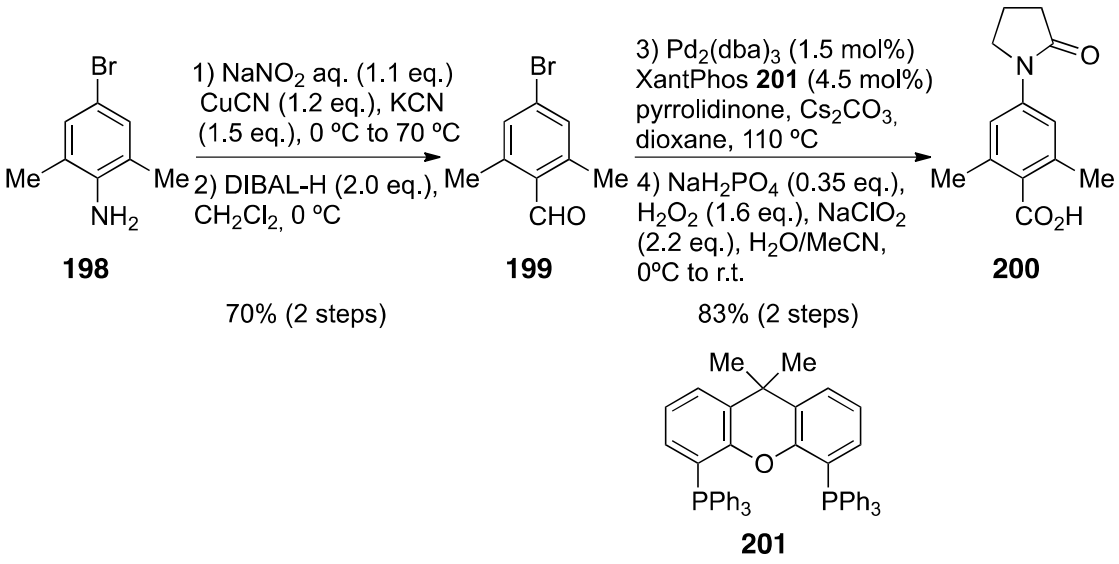


Figure 2.23

The installation of a pyrrolidinone in *para* position to the carboxylic acid was accomplished in 4 steps from **198** (Figure 2.24). An initial diazotization followed by treatment with CuCN afforded the corresponding benzonitrile, which upon reduction by DIBAL-H yielded aldehyde **199**in 70% overall yield. Next, following the procedure described by Buchwald[110] in 2002, the coupling of pyrrolidinone was performed in quantitative yield. A final Lindgren oxidation afforded benzoic acid **200** in 83% yield over the last 2 steps.



[109]McNeill, E.; Barder, T. E.; Buchwald, S. L. *Org. Lett.***2007**, *9*, 3785.
[110]Yin, J. and Buchwald, S. L. *J. Am. Chem. Soc.***2002**, *124*, 6043.

Figure 2.24

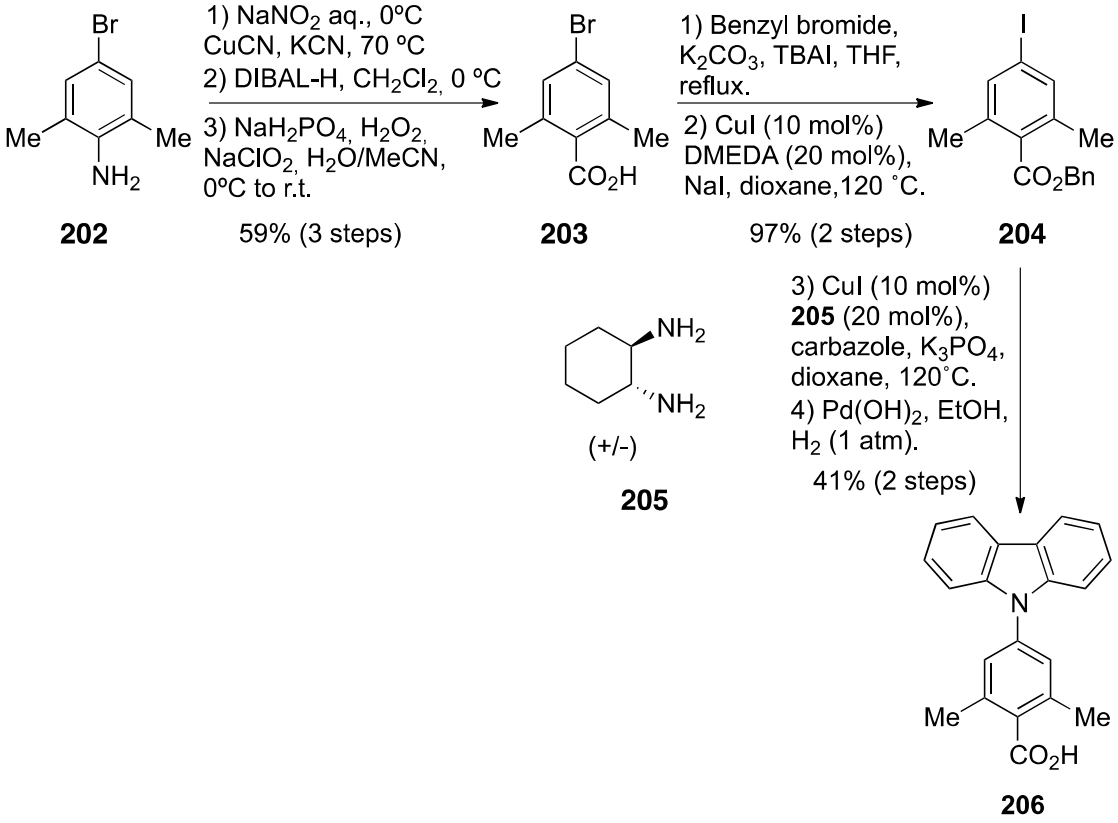


Figure 2.25

A longer synthetic sequence was required for obtaining benzoic acid **206** possessing a pendant carbazole group on the arene ring. First, the synthesis of acid **203**was accomplished via a 3 step sequence (cyanation/reduction/oxidation) from 4-bromo-2,6-dimethylaniline**202** as starting material (Figure 2.25).Protection of benzoic acid **203** as benzyl group and subsequent Br/I exchange following the methodology described by Buchwald[111] afforded intermediate **204** in a 97% overall yield. Next, *N*-arylation of carbazole following literature procedures[112] provided an intermediate carbazole-derivative that was hydrogenated to yield**206**. It is worth mentioning that among all the hydrogenation protocols used, Pearlman´s catalyst provided the best results, albeit in a low overall yield.

A 3-step synthesis allowed the preparation of compounds **210**-**213**, placing aromatic rings with different electronic properties as well as an aliphatic ketone containing α-enolizable protons. Starting from the simple precursor **207**, an iridium-catalyzed C-H

[111]Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.*, **2002**, *124*, 14844.
[112] Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S.L. *J. Am. Chem. Soc.,* **2001***, 123,* 7727.

borylation[113] followed by Suzuki couplingyielded the corresponding arylated products. A final hydrolisys event, as shown in Figure 2.26 furnished the corresponding benzoic acids in moderate yields.

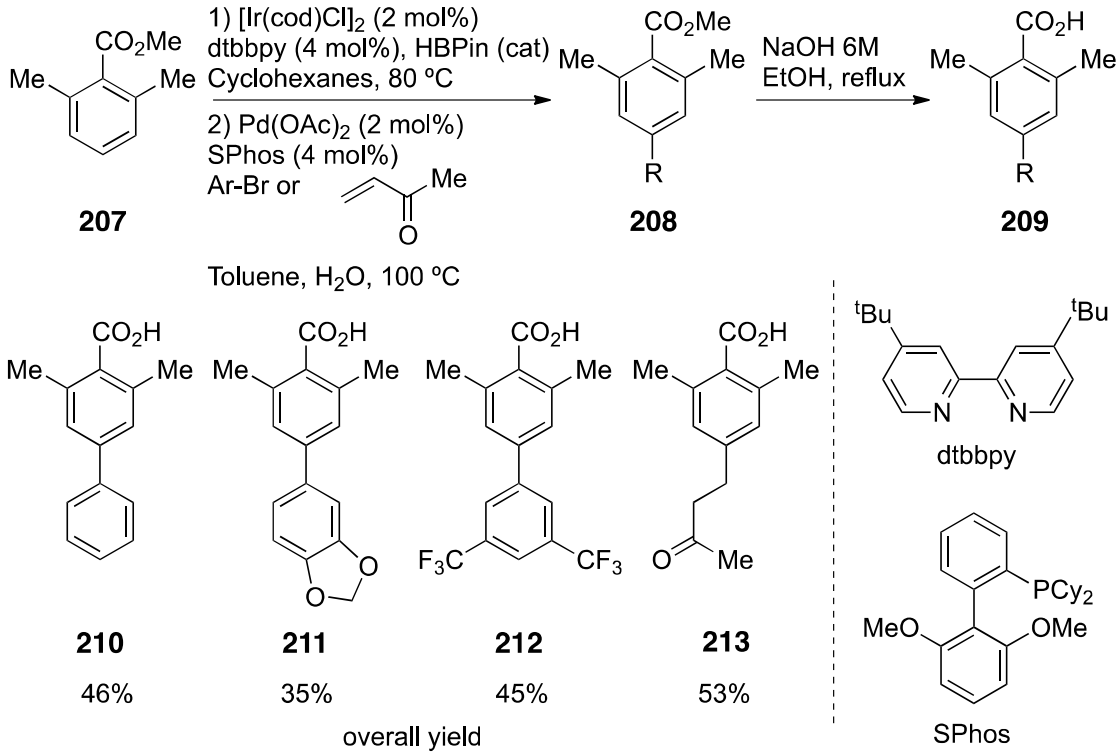
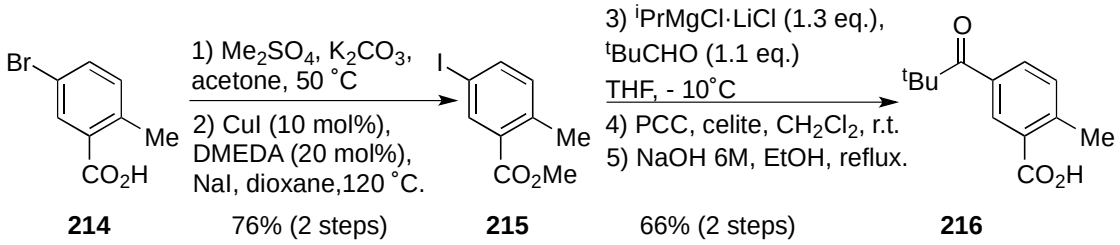


Figure 2.26

We also studied the influence of the substitution patterns located on the aryl ring of the benzoic acid as well as the functional group compatibility. The former is particularly important due to the competition among different C-H bonds, when utilizing non ortho,ortho-substitutedbenzoic acids.The preparation of compound **216** was accomplished by a 5-step sequence (Figure 2.27). The first step involved a methylation of the free carboxylic acid followed by a Br/I exchange using the Cu-catalyzed protocol reported by Buchwald.[111]Grignard formation at low temperatures following the methodology described by Knochel[114]and subsequent treatment with trimethylacetaldehyde afforded an alcohol that was easily oxidized employing PCC in the presence of celite. A final hydrolysis under basic conditions yielded the desired carboxylic acid **216**in a 50% yield over 4 steps.

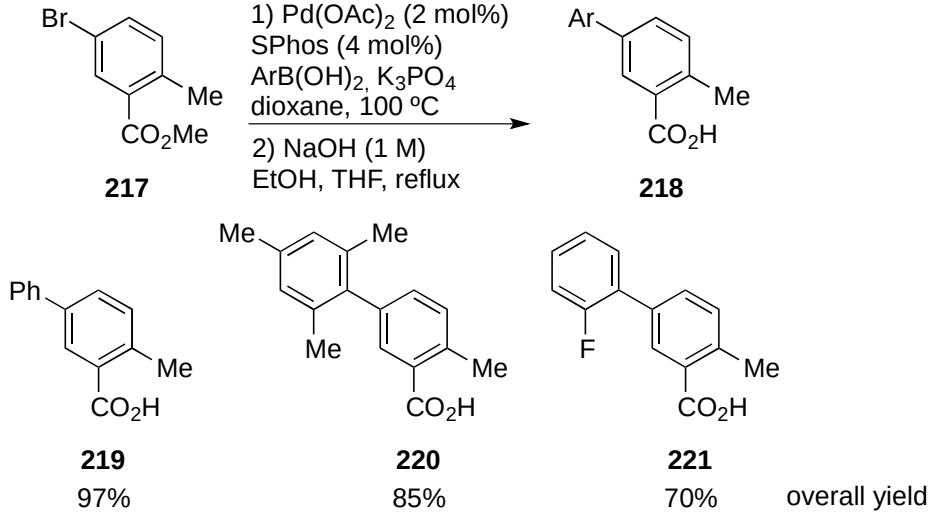
[113]Boebel, T. A.; Hartwig, J. F. *Tetrahedron***2008**, *64*, 6824.
[114]Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.***2004**, *43*, 3333.



214 76% (2 steps) **215** 66% (2 steps) **216**

Figure 2.27

Another set of *meta*-substituted benzoic acids were obtained in 2 steps from aryl bromide**217** (Figure 2.28). A palladium-catalyzed Suzuki coupling followed by hydrolysis furnished acids **219**, **220** and **221** in 97%, 85%, and 70% yield over 2 steps, respectively.



217 **218**

219 97% **220** 85% **221** 70% overall yield

Figure 2.28

2.5.3 Scope of the reaction for the synthesis of phthalides

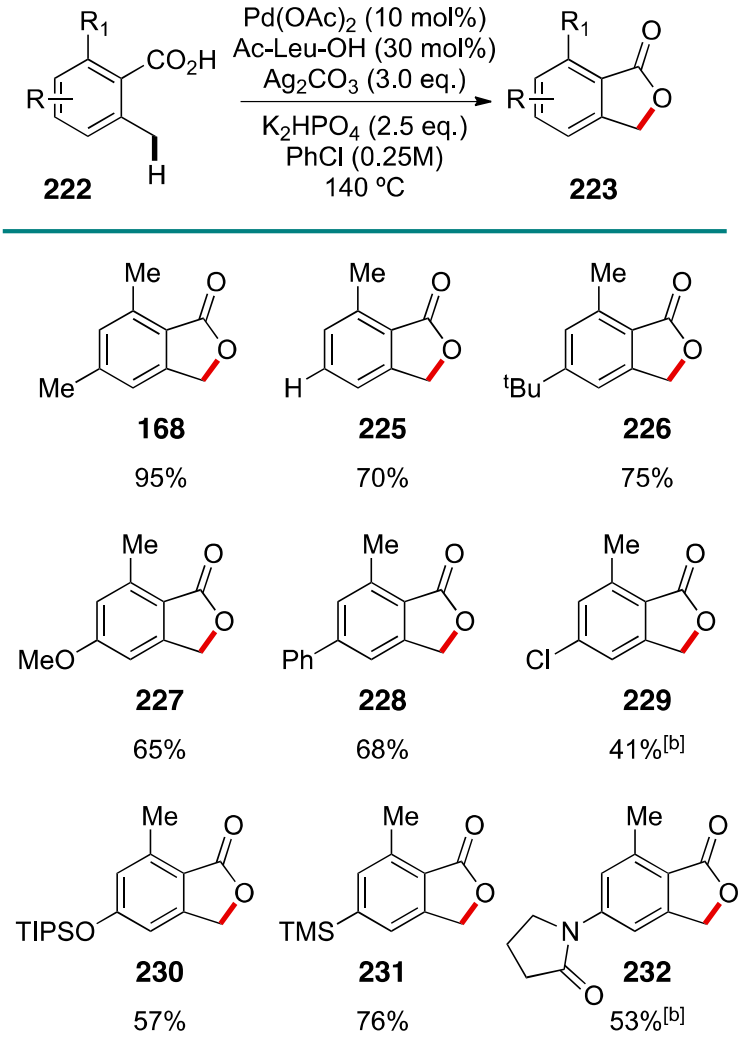
With a wide variety of 2-methylbenzoic acids in hand, we decided to explore the scope of the Pd-catalyzed synthesis of phthalides via C(sp^3)-H bond functionalization. As shown in Table 2.6, *ortho*-dimethyl substituted benzoic acids gave the corresponding lactones in moderate to good yields (**168**, **225** and **226**). Products containing an OMe and Ph group were also well accommodated as demonstrated by **227** and **228**. Moreover, the reaction could be conducted in the presence of aryl chlorides, thus allowing for further manipulation by conventional cross-coupling techniques, albeit in lower yields (**229**) due to degradation of the starting material.

Additionally, silyl groups and amides were also tolerated in our protocol as illustrated by the successful preparation of **230**, **231** and **232**. As it can be deduced from **227** and **232**, electronic effects do not play a dominant role in the formation of products. It is worth mentioning that our catalytic system is quite heterogenous. Some substrates containing polar substituents such as**229**and**232** were not efficiently cyclized under our reaction protocol. For these particular cases,we found that operating with a PhCl/NMP (4:1) solvent mixture provided better yields.Moreover, for substrate **232**, 32% of the corresponding decarboxylated product was isolated from the reaction mixture.

As depicted in Table 2.7, aryl motifs in *para* position containing acetals (**233**) or trifluoromethyl groups (**234**) are tolerated under our catalytic protocol. Interestingly, compounds bearing nitrogen-containing heterocycles (**235**) or carbonyl group possessing relatively acidic protons (**236**) remained unaffected. The successful preparation of **241**, albeit in lower yields, is equally instructive indicating that our reaction is not limited to *ortho*-methyl benzoic acids as substrates.[115] Additionally, the means to access **241** might suggest that asymmetric reactions could be within reach.

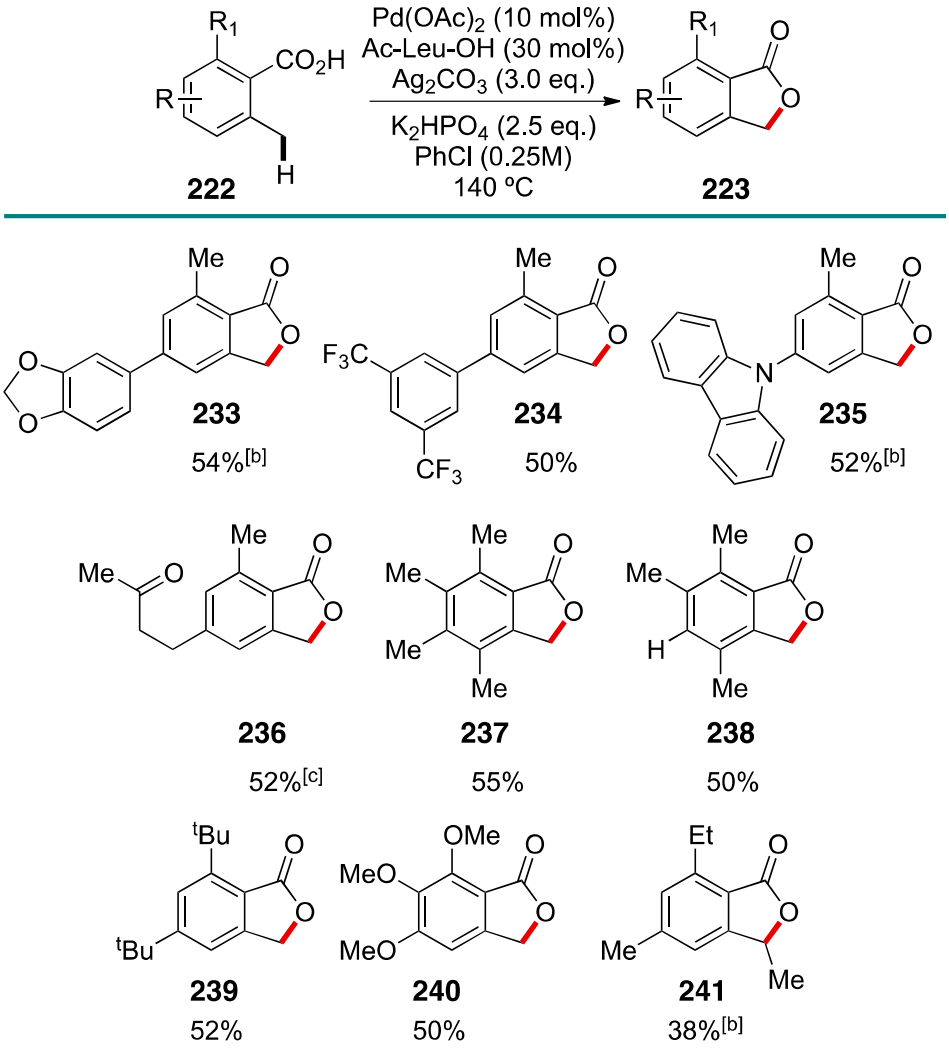
Table 2.5. Synthesis of phathalides.[a]

[115] Unfortunately, the cyclized product **241** provided a racemic mixture.



[a] Benzoic acid (0.25 mmol), $Pd(OAc)_2$ (10 mol%), Ac-Leu-OH (30 mol%), Ag_2CO_3 (30 mol%), K_2HPO_4 (2.5 eq.), PhCl (0.25M), 140 ºC, 24h, argon atmosphere. [b] A mixture of PhCl/NMP= 4:1 was used as solvent. NMP= *N*-Methylpyrrolidinone, TIPS= triisopropylsilyl, TMS= trimethylsylil.

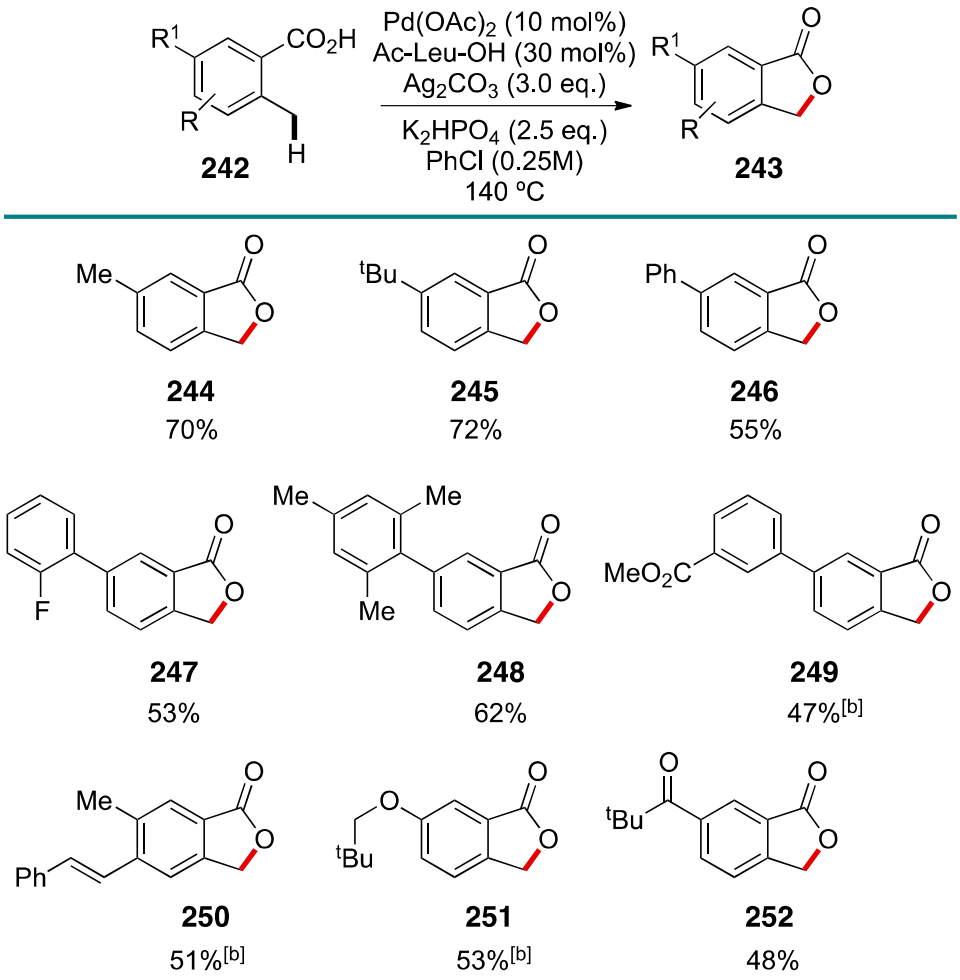
Table 2.6. Synthesis of phathalides.[a]



[a] Benzoic acid (0.25 mmol), $Pd(OAc)_2$ (10 mol%), Ac-Leu-OH (30 mol%), Ag_2CO_3 (30 mol%), K_2HPO_4 (2.5 eq.), PhCl (0.25M), 140 ºC, 24h, argon atmosphere. [b] A mixture of PhCl/NMP= 4:1 was used as solvent. NMP= *N*-Methylpyrrolidinone. [c] NMP was used as solvent.

Remarkably, our methodology allowed for the discrimination between different C-H bonds when substrates with substituents at the *meta* position of the benzoic acid were employed, as represented in Table 2.8. In these particular cases, selective C(sp^3)-H bond functionalization was observed. For instance, when a methyl (**244**) or a *tert*-butyl (**245**) group were placed in *meta*position, the yields were 70% and 72%, respectively. On the other hand, when performing the reaction with a phenyl ring(**246**), the yield dropped to 55%. The chemoselectivity was nicely illustrated by the fact that aryl fluorides (**247**), esters (**249**), alkenes (**250**), ethers (**251**) or ketones (**252**) can be easily accommodated, thus giving access to phthalides that are inaccessible by classical routes.

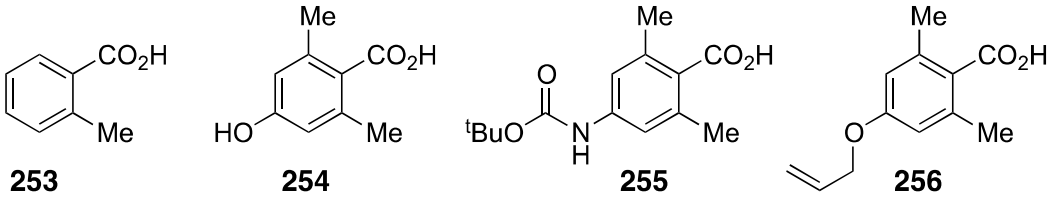
Table 2.7. Synthesis of phthalides.[a]



[a] Benzoic acid (0.25 mmol), $Pd(OAc)_2$ (10 mol%), Ac-Leu-OH (30 mol%), Ag_2CO_3 (30 mol%), K_2HPO_4 (2.5 eq.), PhCl (0.25M), 140 ºC, 24h, argon atmosphere. [b] A mixture of PhCl/NMP= 4:1 was used as solvent. NMP= *N*-Methylpyrrolidinone.

Although the scope of the reaction showed a good selectivity profile, we must confess that, in general, the yields were moderate. Unfortunately, all the efforts to improve the efficiency of this transformation were unsuccessful. The rest of the mass balance accounted for unreacted starting material or degradation to unidentified byproducts. In some particular cases, little amounts of the corresponding decarboxylated products were obtained. As shown in Figure 2.29, no product was detected when simple 2-methylbenzoic acid (**253**) were subjected to our optimized conditions, reinforcing the notion that a substituent in the meta position might prevent metallation at the C(sp^2)-H bond. Additionally, relatively acidic groups like phenols (**254**) can be deprotonated, thus making the product insoluble. In this case, full recovery of starting material was observed. Somewhat expected, relatively labile

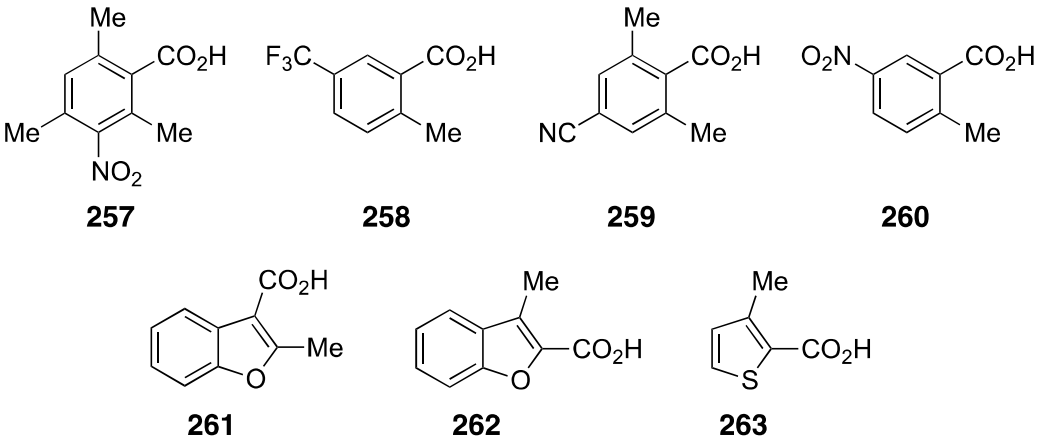
functional groups such as carbamates (**255**) or O-allyl (**256**)were not tolerated under our reaction conditions. For both cases, a complex reaction crude was observed with full consumption of the starting materials.



253 **254** **255** **256**

Figure 2.29

On the other hand, it is worth noting that the presence of electron withdrawing groups either in meta- (**257**, **258**, and **260**) or para-position (**259**)could also not be utilized with our lactonization protocol (Figure 2.30). Finally, a set of heterocycles (**261-263**)could also not be employed under our reaction conditions. It is worth mentioning that GC analysis of the crude reaction mixtures revealed decomposition with these substrate combinations.



257 **258** **259** **260**

261 **262** **263**

Figure 2.30

2.5.4 Mechanistic considerations

Next, we turned our attention to unravel several mechanistic aspects of our Pd-catalyzed C(sp^3)-H bond functionalization/C-O bond formation reaction. In this regard,

the measurement of kinetic isotope effects (KIE) as well as the study of several potential intermediates would provide valuable information about the mechanism. Considering the high KIE values reported for several C(sp^3)-H bond functionalization,[116] one might anticipate that C-H cleavage would be involved in the rate limiting step. Taking into consideration the reduction potential of Ag(I) (E^0_{red}= 0.799 V) compared to other strong oxidants like $S_2O_8^{2-}$ (E^0_{red}= 2.1 V), a mechanism involving Pd(IV) species seems rather unlikely.

2.5.4.1 Kinetic isotope effects

The measurement of the kinetic isotope effect provides indirect evidence about the rate determining step (rds) of many reactions.[117] Thus, a ratio K_H/K_D~ 1, indicates that the substitution of a H atom by a D atom does not effect the initial rate of the reaction; as a result, one might consider that the cleavage of the H atom is not involved in the rds. On the contrary K_H/K_D values >> 1 indicates that the C-H bond-cleavage participates, at least at some extent, in the rds. As a result, we decided to study both the intermolecular as well as the intramolecular kinetic isotope effect by synthesizing **265** and **268**,respectively. The former was prepared from **264**via an initial bromination with NBS followed by carboxylation. On the other hand, compound **268** required a 4-step sequence consisting of a reduction of ester **266** promoted by deuterated lithium-aluminium hydride (LAD) affording the corresponding benzyl alcohol. A subsequent bromination yielded **267** in 87% overall yield for the 2 steps. Then, reduction of benzyl bromide with LAD and carboxylation of the aryl bromide with *n*-BuLi furnished **268**.

[116](a) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.***2007**, *129*, 14570. (b) Rousseaux, S.; Gorelsky, S. I.; Chung, B. K. W.; Fagnou, K. *J. Am. Chem. Soc.***2010**, *132*, 10692.
[117] (a) Gómez-Gallego, M.; Sierra, M. A. *Chem. Rev.***2011**, *111*, 4857. (b) Simmons, E. M.; Hartwig, J. F. *Angew. Chem. Int. Ed.***2012**, *51*, 3066.

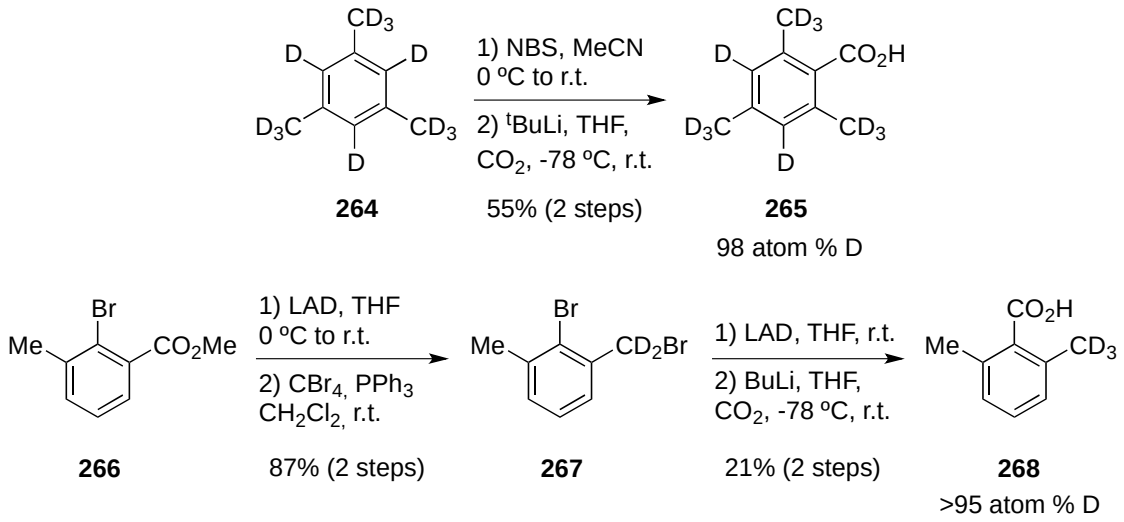


Figure 2.31

With both deuterated substrates in hand, we found a K_H/K_D= 1.17 when performing the intermolecular kinetic isotope effect (Figure 2.32). A similar value was observed in the intramolecular kinetic isotope effect(K_H/K_D= 1.56) as illustrated in Figure 2.33, suggesting that C(sp^3)-H bond-cleavage was not involved in the rate-determining step. These results are rather surprising taking into consideration that the vast majority of C-H bond functionalization reactions described in the literature C-H bond cleavage in rate-determining.[117]

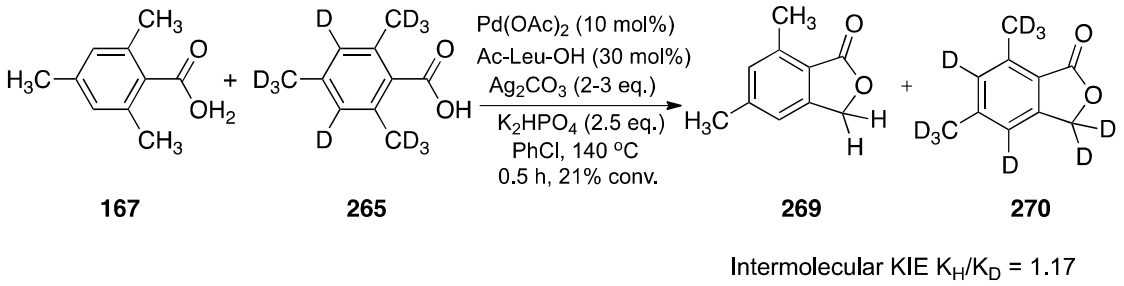


Figure 2.32

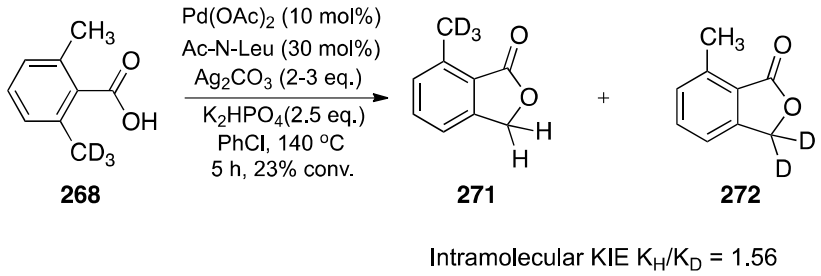


Figure 2.33

2.5.4.2 Other mechanistic experiments

As highlighted in the previous section, the performed kinetic isotopic effect experiments indicated that C(sp^3)-H functionalization was not rate limiting; therefore, we decided to turn our attention to the other steps within the catalytic cycle. According to Figure 2.16, our mechanistic hypothesis starts with the coordination of a M_1carboxylate to the Pd(II) catalyst, followed by C-H bond-functionalization and a final C-O bond formation event. As a result, we decided to prepare the corresponding silver carboxylate **273**and palladium carboxylate **274** according to the procedures reported by Englert[118]and Alessio,[119] respectively (Figure 2.34).

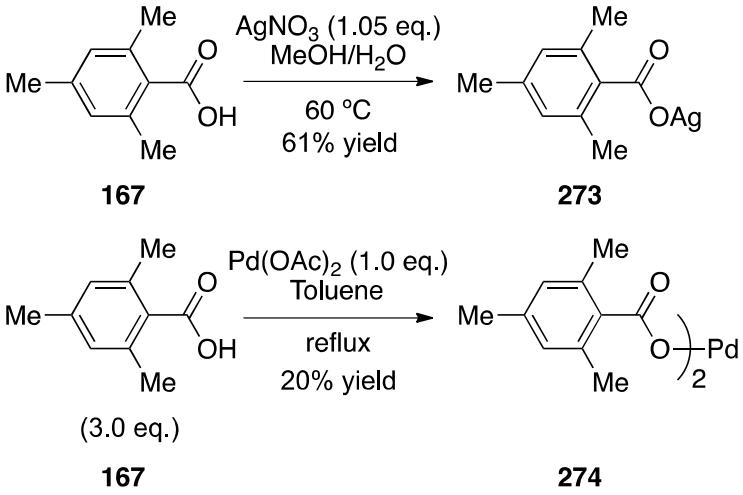


Figure 2.34

As shown in Figure 2.35, silver salt **273** was subjected under our optimized conditions, both in a stoichiometric (left) and catalytic fashion (right) yielding phthalide **168** in 61% and 85%, respectively. These experiments are in accordance with a ligand exchange between an *in situ* generated silver carboxylate and our palladium pre-catalyst. However,the blank experiments carried out in Table 2.5 showed that the absence of K_2HPO_4 had a deleterious effect and led exclusively to decarboxylated product **169**. Therefore, we tentatively suggestthe intermediacy of potassium carboxylates as competent species for this transformation.

[118]Wang, Y.; Englert, U. *Inorganica Chimica Acta, **2010**, 363, 2539.*
[119]Cenini, S.; Ragaini, F.; Pizzotti, M.; Porta, F.; Mestroni, G.; Alessio, E. *J. Mol. Catal*. **1991**, *64*, 179.

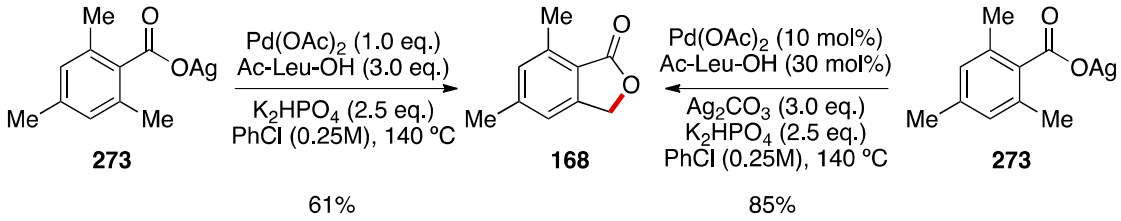


Figure 2.35

In order to determine whether **274** could be a potential intermediate in our catalytic cycle, we performed an analogous set of experiments as for **273**(Figure 2.36). Interestingly, stoichiometric reaction employing **274** gave **168** in 84% yield *in the absence of* Ag_2CO_3. Even though this experiment can not be used as an ultimate proof, they provided evidence that a Pd(II)/Pd(IV) catalytic cycle is highly unlikely. Similarly, **274**turned out to be a competent precatalyst for this reaction (Figure 2.36, right), obtaining the desired phthalide in comparable yields.

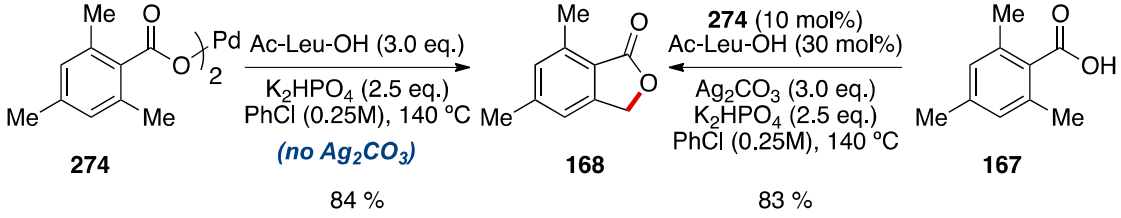


Figure 2.36

Finally, a tentative mechanism for the synthesis of phthalides is depicted in Figure 2.37. We propose a pathway consisting of a ligand exchange from an initially generated metal carboxylate **LX** to palladium(II) followed by C(sp^3)-H bond functionalization (**LXII**). C(sp^3)-O bond-formation then delivers **168** and Pd(0), which upon oxidation by Ag(I) regenerates the catalytically active Pd(0) species. At present, we cannot rule out a mechanistic pathway consisting of the dissociation of the carboxylate ligand in **LXII** to generate a π-benzylic Pd intermediate, followed by an intramolecular Pd-O bond-forming reaction.Similarly, we could not exclude that PhCl act as a co-oxidant in the reaction media.

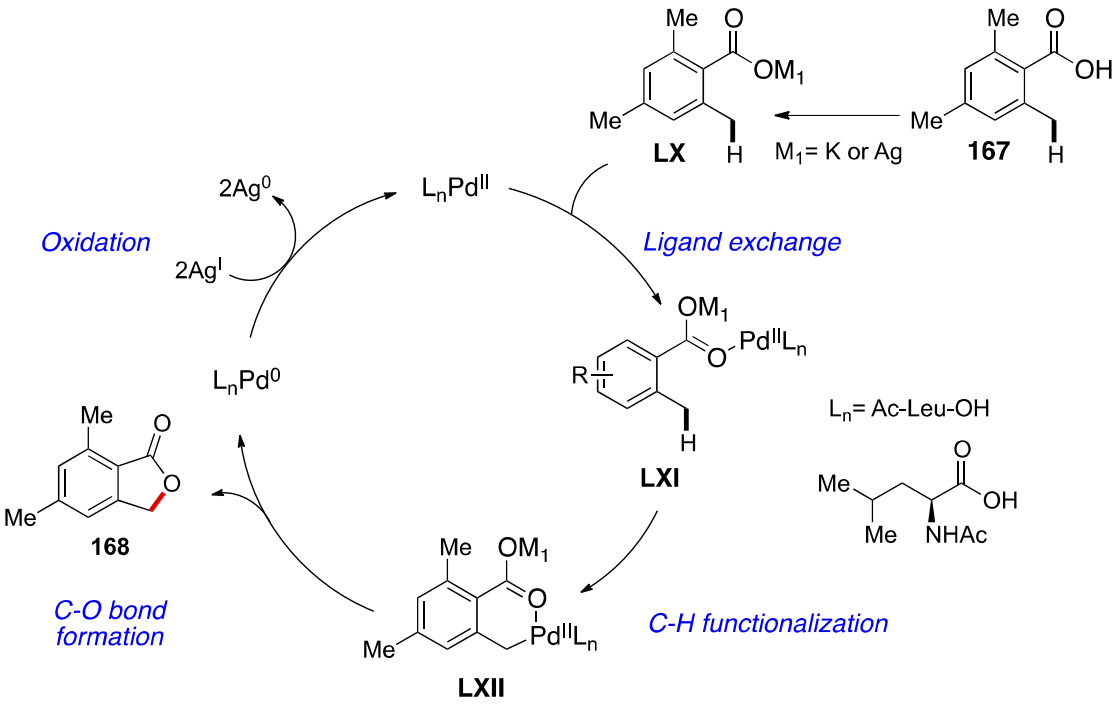

Me
O
OM1
Me
LX
M1= K or Ag
OH
167
2Ag0
LnPdII
Oxidation
2AgI
Ligand exchange
OM1
PdIILn
R
H
LXI
LnPd0
Ln= Ac-Leu-OH
Me
O
O
Me
168
OH
Me
NHAc
Me
OM1
O
PdIILn
Me
C-O bond formation
C-H functionalization
LXII

Figure 2.37

2.6 Conclusions

- In summary we have developed a Pd(II)-catalyzed lactonization reaction via C(sp^3)-H functionalization/C-O bond-formation event. This protocol allows us to rapidly generate phthalides, which are important motifs in nature and versatile intermediates in organic synthesis.

- The screening carried out for the preparation of benzolactones highlight the crucial role of *N*-protected aminoacids or carboxylics acids as additives for promoting C(sp^3)-H bond-cleavage. Our methodology is compatible with a wide range of functional groups –such as -TMS, -OTIPS, -OMe, -Cl, amides or carbonyl groups as well as a diverse set of substitution patterns. Importantly, site-selectivity can be achieved in the presence of*ortho*C(sp^2)-H bonds with substituents located in *meta* position.

- We have performed mechanistic studies via kinetic isotope effects that indicate that C-H bond-cleavage is likely not rate-limiting. Additionally, we have conducted stochiometric experiments with preformed silver carboxylates and Pd(II) intermediate species that have demonstrated that a Pd(II)/Pd(IV) seems highly unlikely.

- Our methodology, however, is far from being ideal as the method of choice for the synthesis of phthalides. Our method requires stochiometric amounts of external oxidant, relatively harsh reaction conditions and several substitution patterns are not yet within reach. However, we believe our method represents a proof of concept that a C(sp^3)-H bond functionalization/C-O bond formation is indeed feasible. Besides, we believe such a method will serve as an inspiration for developing new and practical methods in the near future, including asymmetric variants of this reaction.

2.7 Experimental section

2.7.1 General considerations

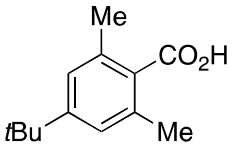
Reagents. Unless otherwise stated, all reactions were carried out under an argon atmosphere in resealable screw-cap test tubes using standard Schlenk techniques for the manipulation of solvents and reagents. $Pd(OAc)_2$ was a gift from Jonson Matthey. K_2HPO_4, anhydrous PhCl and NMP were purchased from Aldrich and used as received. All other reagents were purchased from commercial sources and used as received. Flash chromatography was performed with EM Science silica gel 60 (230-400 mesh). Ligands**179** and **180**were prepared according to literature procedures.[120]

Analytical methods. ^{1}H-NMR and ^{13}C-NMR spectra and melting points (where applicable) are included for all compounds. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker 400 MHz at 20 ºC. All ^{1}H-NMR spectra are reported in parts per million (ppm) and were measured relative to the signals for $CDCl_3$ (7.27 ppm), $(CD_3)_2CO$ (2.05 ppm), CD_3OD (3.34 ppm) or $(CD_3)_2SO$ (2.54 ppm). All ^{13}C-NMR spectra were reported in ppm relative to residual $CDCl_3$ (77.0 ppm), $(CD_3)_2CO$ (30.60 ppm), CD_3OD (49.86 ppm) $(CD_3)_2SO$ (40.45 ppm) and were obtained with ^{1}H decoupling. Coupling constants, *J*, are reported in hertz. Melting points were measured using open glass capillaries in a Mettler Toledo MP70 apparatus. Infrared spectra were recorded on a Bruker Tensor 27. Mass spectra were recorded on a Waters LCT Premier spectrometer. Gas chromatographic analyses were performed on Hewlett-Packard 6890 gas chromatography instrument with a FID detector using 25m x 0.20 mm capillary column with cross-linked methyl siloxane as the stationary phase.

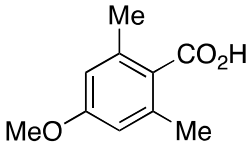
[120] (a) Jass, P.A.; Rosso, V. W.; Racha, S.; Soundararajan, N.; Venit, J.; Rusowicz, A.; Swaminathan, S.; Livshitza, J.; Delaney, E. *Tetrahedron***2003**, *59*, 9019. (b) Wagner, Carl E.; Mohler, Michael L.; Kang, Gyong Suk; Miller, Duane D.; Geisert, Eldon E.; Chang, Yu-An; Fleischer, Everly B.; Shea, Kenneth J. *J. Med. Chem.***2003**, *46*, 14, 2825

2.7.2 Synthesis of the starting materials.

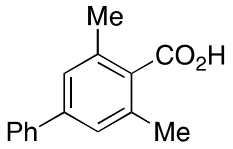
Ortho-substituted benzoic acids were prepared by carboxylation of aryl halides or arylmetal species with CO_2,[121] hydrolysis of methyl esters in basic media,[122] Pd-catalyzed hydrogenation benzyl esters,[123] Lindgren-Pinnick oxidation[124] of the corresponding benzaldehydes and Suzuki coupling of free or protected aryl carboxylic acids to install aromatic motifs.[125]



4-(*tert*-Butyl)-2,6-dimethylbenzoic acid 187.[126] White solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.11 (s, 2H), 2.49 (s, 6H), 1.34 (s, 9H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ175.7, 153.2, 135.8, 129.3, 125.1, 34.6, 31.2, 20.7 ppm.



4-Methoxy-2,6-dimethylbenzoic acid 188.[127] White solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.62 (s, 2H), 3.83 (s, 3H), 2.48 (s, 6H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ175.2, 160.6, 139.3, 124.3, 113.6, 55.2, 21.2 ppm.



3,5-Dimethyl-[1,1'-biphenyl]-4-carboxylic acid 210. White solid. M.p. = 163-164 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ7.65 (d, *J* = 8.3 Hz, 2H), 7.53-7.47 (m, 2H), 7.46-7.42 (m, 1H), 7.36 (s, 2H), 2.58 (s, 6H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ175.8, 142.9, 140.3, 136.6, 128.8, 128.4, 127.8, 127.2, 126.9, 20.6 ppm. IR (neat, cm^{-1}): 2861, 1680, 1432, 1289, 1222, 761, 699.HRMS *calcd* for ($C_{15}H_{14}O_2$-H^+): 225.0916, *found* 225.0910.

[121] (a) Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2009**, *131*, 15974. (b) Correa, A.; Martin, R. *Angew. Chem. Int., Ed.* **2009**, *48*, 6201. (c) Beak, P.; Carter, L. G. *J. Org. Chem.***1981**, *46*, 2363
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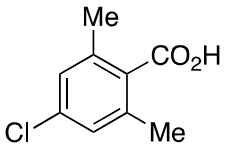
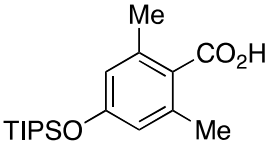
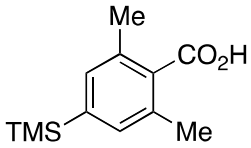
[127]Heckmann, D.; Meyer, A.; Laufer, B.; Zahn, G.; Stragies, R.; Kessler, H. *ChemBioChem***2008**, *9*, 1397



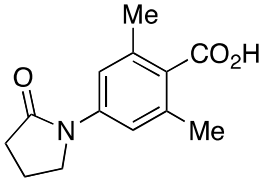
4-Chloro-2,6-dimethylbenzoic acid 195.[128] White solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ7.11 (s, 2H), 2.45 (s, 6H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ174.0, 137.9, 135.7, 130.6, 127.9, 20.2 ppm.



2,6-Dimethyl-4-((triisopropylsilyl)oxy)benzoic acid 193. White solid. M.p. = 214-215 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.60 (s, 2H), 2.45 (s, 6H), 1.29 (m, 3H), 1.13 (d, *J* = 8 Hz, 18H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ175.1, 157.4, 139.1, 119.5, 117.6, 21.0, 17.9, 12.7 ppm. IR (neat, cm^{-1}): 2956, 2925, 2650, 2545, 1675, 1687, 1331. HRMS *calcd* for ($C_{18}H_{30}O_3Si$-H^+): 321.1886, *found* 321.1896.

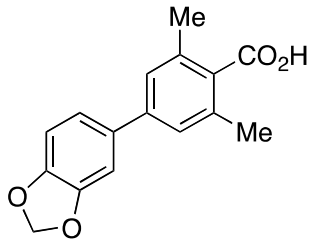


2,6-Dimethyl-4-(trimethylsilyl)benzoic acid 197. White solid. M.p. = 158-159 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ7.25 (s, 2H), 2.50 (s, 6H), 0.31 (s, 9H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 175.9, 143.1, 134.6, 132.9, 132.7, 20.2, -1.3 ppm. IR (neat, cm^{-1}) 2956, 2925, 2650, 2545, 1687, 1291, 1244, 1085, 827. HRMS *calcd* for ($C_{18}H_{30}O_3Si$-H^+): 221.0998, *found* 221.1000.

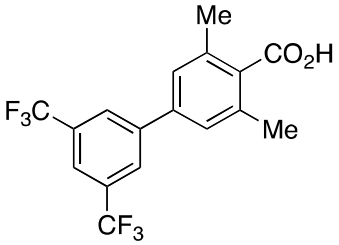


2,6-Dimethyl-4-(2-oxopyrrolidin-1-yl)benzoic acid 200. Yellowish solid. M.p. = 212-213 ºC. ^{1}H-NMR (400 MHz, CD_3OD): δ 7.42 (s, 2H), 3.97 (t, *J* = 8 Hz, 2H), 2.66 (t, *J* = 6 Hz, 2H), 2.43 (s, 6H), 2.22 (m, 2H) ppm. ^{13}C-NMR (126 MHz, CD_3OD): δ 175.7, 172.0, 139.7, 135.2, 131.5, 119.1, 49.0, 32.3, 18.8, 17.5 ppm. IR (neat, cm^{-1}): 2961, 2921, 1702, 1643, 1399, 1316, 1245, 1198. HRMS *calcd* for ($C_{13}H_{14}NO_3$-H^+): 232.0974, *found* 232.0983.

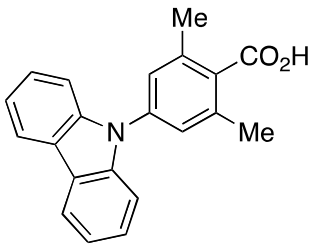
[128]Effenberg, F.; Epple, G.; Eberhard, J. K.; Buehler, U.; Sohn, E. *Chem. Ber.***1983**, *116*, 1183



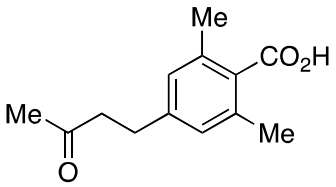
4-(Benzo[*d*][1,3]dioxol-5-yl)-2,6-dimethylbenzoic acid 211. White solid. M.p. = 219-220 ºC. ^{1}H-NMR (400 MHz, $(CD_3)_2CO$): δ 7.33 (s, 2H), 7.18 (m, 2H), 6.94 (d, *J* = 7.1 Hz, 1H), 6.06 (s, 2H), 2.42 (s, 6H) ppm. ^{13}C-NMR (100 MHz, $(CD_3)_2CO$): δ 169.9, 148.4, 147.5, 141.3, 135.1, 134.5, 133.3, 125.8, 120.5, 108.4, 107.2, 101.3, 19.2 ppm. IR (neat, cm^{-1}): 2903, 1678, 1502, 1299, 1238, 1032, 928, 852. HRMS *calcd* for ($C_{16}H_{14}O_4$-H$^+$): 269.0814, *found* 269.0810.



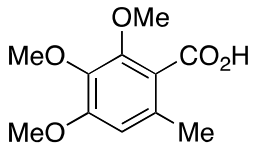
3,5-Dimethyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-4-carboxylic acid 212. White solid. M.p. = 160-161 ºC. ^{1}H-NMR (400 MHz, CD_3OD): δ8.22 (s, 2H), 8.01 (s, 1H), 7.48 (s, 2H), 2.50 (s, 6H) ppm. ^{13}C-NMR (100 MHz, CD_3OD): δ171.9, 143.0, 138.4, 135.6, 135.4, 131.9 (q, J_{CF2} = 33.3 Hz), 127.1 (q, J_{CF3} = 5.5 Hz), 126.1, 123.5 (q, J_{CF1} = 271.7 Hz), 120.6 (q, J_{CF3} = 4.2 Hz), 18.5 ppm. IR (neat, cm^{-1}): 2923, 1685, 1275, 1173, 1119, 683, 586. HRMS *calcd* for ($C_{17}H_{12}F_6O_2$-H$^+$): 361.0663, *found*361.0667.



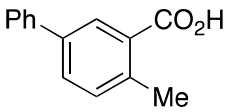
4-(9*H*-Carbazol-9-yl)-2,6-dimethylbenzoic acid 206. White solid. M.p. = decomp. ^{1}H-NMR (400 MHz, DMSO): δ8.26 (s, 1H), 8.24 (s, 1H), 7.45-7.42 (m, 4H), 7.36 (s, 2H), 7.32-7.28 (m, 2H), 2.41 (s, 6H) ppm. ^{13}C-NMR (100 MHz, DMSO): δ 170.7, 140.4, 137.4, 136.5, 135.1, 126.7, 125.7, 123.2, 121.0, 120.6, 110.3, 19.8. IR (neat, cm^{-1}) 2959, 2922, 2853, 2651, 2554, 2349, 1687, 1599, 1448, 1431, 1296. HRMS *calcd* for ($C_{21}H_{17}NO_2$-H$^+$): 314.1181, *found* 314.1192.



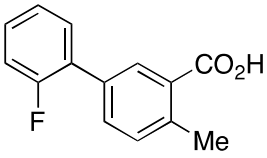
2,6-Dimethyl-4-(3-oxobutyl)benzoic acid 213. White solid. M.p. = 103-104 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ6.89 (s, 2H), 2.84 (dd, *J* = 11.4, 4.6 Hz, 2H), 2.77 (dd, *J* = 11.4, 4.6 Hz, 2H), 2.40 (s, 6H), 2.16 (s, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 208.6, 175.2, 142.9, 136.1, 130.4, 127.9, 44.8, 30.0, 29.3, 20.2 ppm. IR (neat, cm^{-1}): 2930, 1679, 1609, 1435, 1293, 1169, 944. HRMS *calcd* for ($C_{13}H_{16}O_3$+Na^+): 243.0997, *found* 243.1005.



2,3,4-Trimethoxy-6-methylbenzoic acid 190. White solid. M.p. = 140.2-141.8 ºC. ^{1}H-NMR (400 MHz, $(CD_3)_2CO$): δ6.69 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.80 (s, 3H), 2.31 (s, 3H) ppm. ^{13}C-NMR (100 MHz, $(CD_3)_2CO$): δ167.8, 154.3, 150.9, 140.1, 131.0, 122.0, 109.6, 61.0, 60.0, 55.5, 18.8 ppm.IR (neat, cm^{-1}): 2943, 1681, 1595, 1449, 1291, 1204, 1112, 1016. HRMS *calcd* for ($C_{11}H_{14}O_5$-H^+): 225.0763, *found* 225.0767.



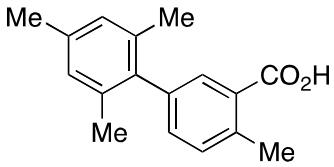
4-Methyl-[1,1'-biphenyl]-3-carboxylic acid 219.[129] White solid. ^{1}H-NMR (400 MHz, $(CD_3)_2CO$): δ8.24 (d, *J* = 2.1 Hz, 1H), 7.76 (dd, *J* = 7.9, 2.1 Hz, 1H), 7.72-7.67 (m, 2H), 7.53-7.46 (m, 2H), 7.45-7.38 (m, 2H), 2.64 (s, 3H) ppm. ^{13}C-NMR (100 MHz, $(CD_3)_2CO$): δ167.8, 139.9, 139.0, 138.6, 132.3, 130.4, 130.1, 128.9, 127.5, 126.7, 20.6 ppm. (one signal overlapped)



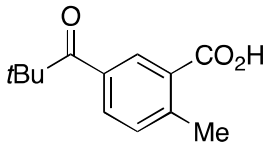
2'-Fluoro-4-methyl-[1,1'-biphenyl]-3-carboxylic acid 221. White solid. M.p. = 148-149 ºC. ^{1}H-NMR (400 MHz, $(CD_3)_2CO$): δ 8.18 (s, 1H), 7.68 (dt, *J* = 7.9, 1.8 Hz, 1H), 7.56 (td, *J* = 7.9, 1.8 Hz, 1H), 7.45-7.43 (m, 2H), 7.31 (td, *J* = 7.5, 1.2 Hz, 1H), 7.27 (ddd, *J* = 10.7, 8.2, 1.1 Hz, 1H), 2.66 (s, 3H) ppm. ^{13}C-NMR (100 MHz, $(CD_3)_2CO$): δ168.0, 159.7 (d, J_{CF1} = 246 Hz), 139.7, 132.3, 132.0, 131.6, 131.1 (d, J_{CF3} = 3 Hz),

[129]Halton, B.; Milsom, P. J.; Woolhouse, A. D. *J. Chem. Soc., Perkin 1, Chem.***1977**, 731.

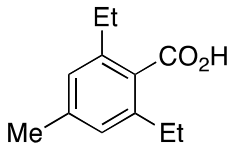
130.6 (d, J_{CF3} = 3 Hz), 130.1 (d, J_{CF2} = 13 Hz), 129.6, 129.5, 124.8, 116.0 (d, J_{CF2} = 23 Hz), 20.8 ppm. IR (neat, cm^{-1}): 2921, 1681, 1384, 1273, 1108, 926, 659. HRMS *calcd* for ($C_{14}H_{11}FO_2$-H^+): 229.0665, *found* 229.0668.



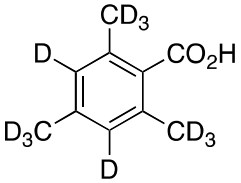
2',4',6'-Tetramethyl-[1,1'-biphenyl]-3-carboxylic acid 220. White solid. M.p. = 171-172 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ7.92 (d, *J* = 1.6 Hz, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.29 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.98 (s, 2H), 2.74 (s, 3H), 2.37 (s, 3H), 2.05 (s, 6H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ173.3, 139.6, 138.8, 137.7, 136.9, 136.0, 134.0, 132.5, 132.1, 128.4, 128.2, 21.9, 21.0, 20.8 ppm. IR (neat, cm^{-1}): 2957, 2914, 1686, 1463, 1158, 1047, 989.HRMS *calcd* for ($C_{17}H_{18}O_2$-H^+): 253.1229, *found* 253.1225.



2-Methyl-5-pivaloylbenzoic acid 216. White solid. M.p. 99-100 ºC. ^{1}H-NMR (500 MHz, $CDCl_3$): δ8.53 (s, *J* = 5 Hz, 1H), 7.85 (dd, *J* = 10 Hz, *J* = 5 Hz, 1H), 7.36 (d, *J* = 10 Hz, 1H), 2.73 (s, 3H), 1.40 (s, 9H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ207.4, 172.6, 144.6, 135.8, 132.6, 132.0, 131.4, 127.9, 44.2, 28.0, 22.1 ppm. IR (neat, cm^{-1}) 2969, 2929, 2874, 1683, 1667, 1598, 1260, 1181, 1162. HRMS *calcd* for ($C_{13}H_{16}O_3$-H^+): 219.1021, *found* 219.1015.



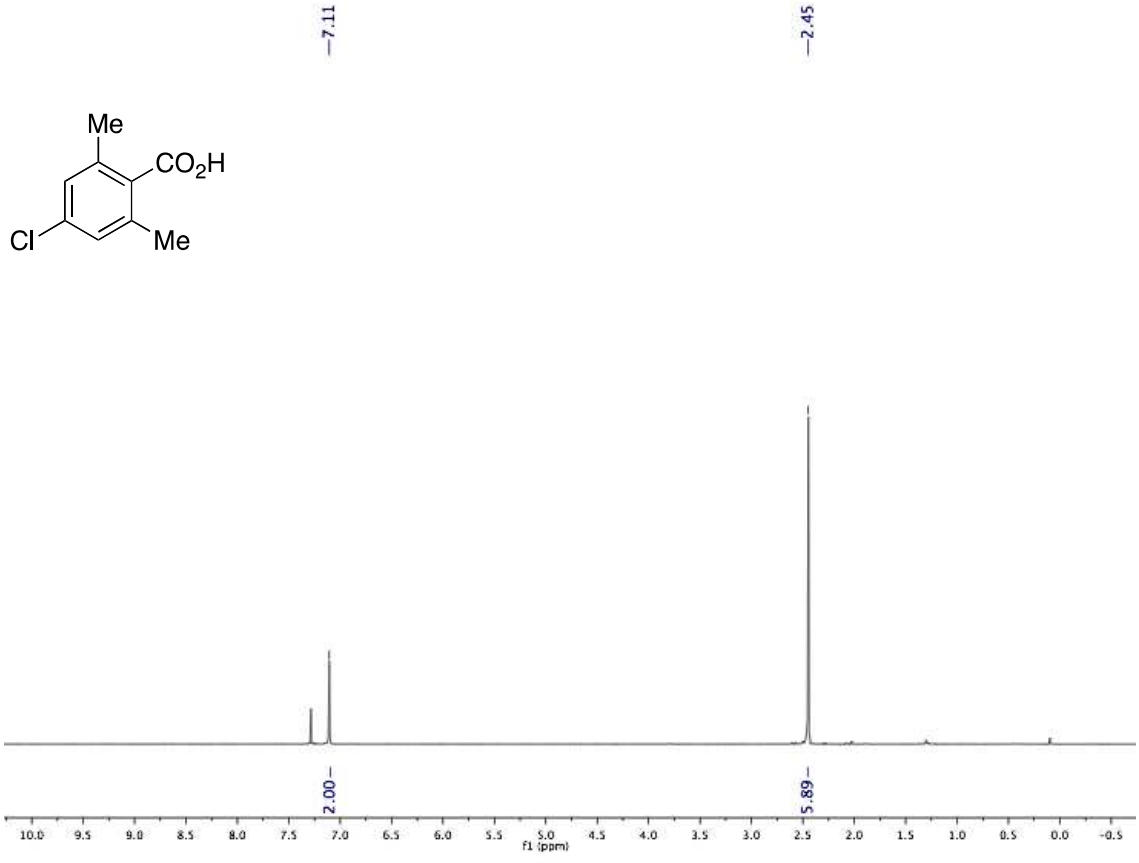
2,6-Diethyl-4-methylbenzoic acid 191. White solid. M.p. = 139-140 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ6.96 (s, 2H), 2.75 (q, *J* = 7.5 Hz, 4H), 2.36 (s, 3H), 1.29 (t, *J* = 7.5, 6H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ175.8, 141.4, 140.0, 128.9, 127.1, 27.0, 21.4, 15.8 ppm.IR (neat, cm^{-1}): 2967, 2873, 1687, 1607, 1290, 860, 601. HRMS *calcd* for ($C_{12}H_{16}O_2$-H^+): 191.1072, *found* 191.1082.

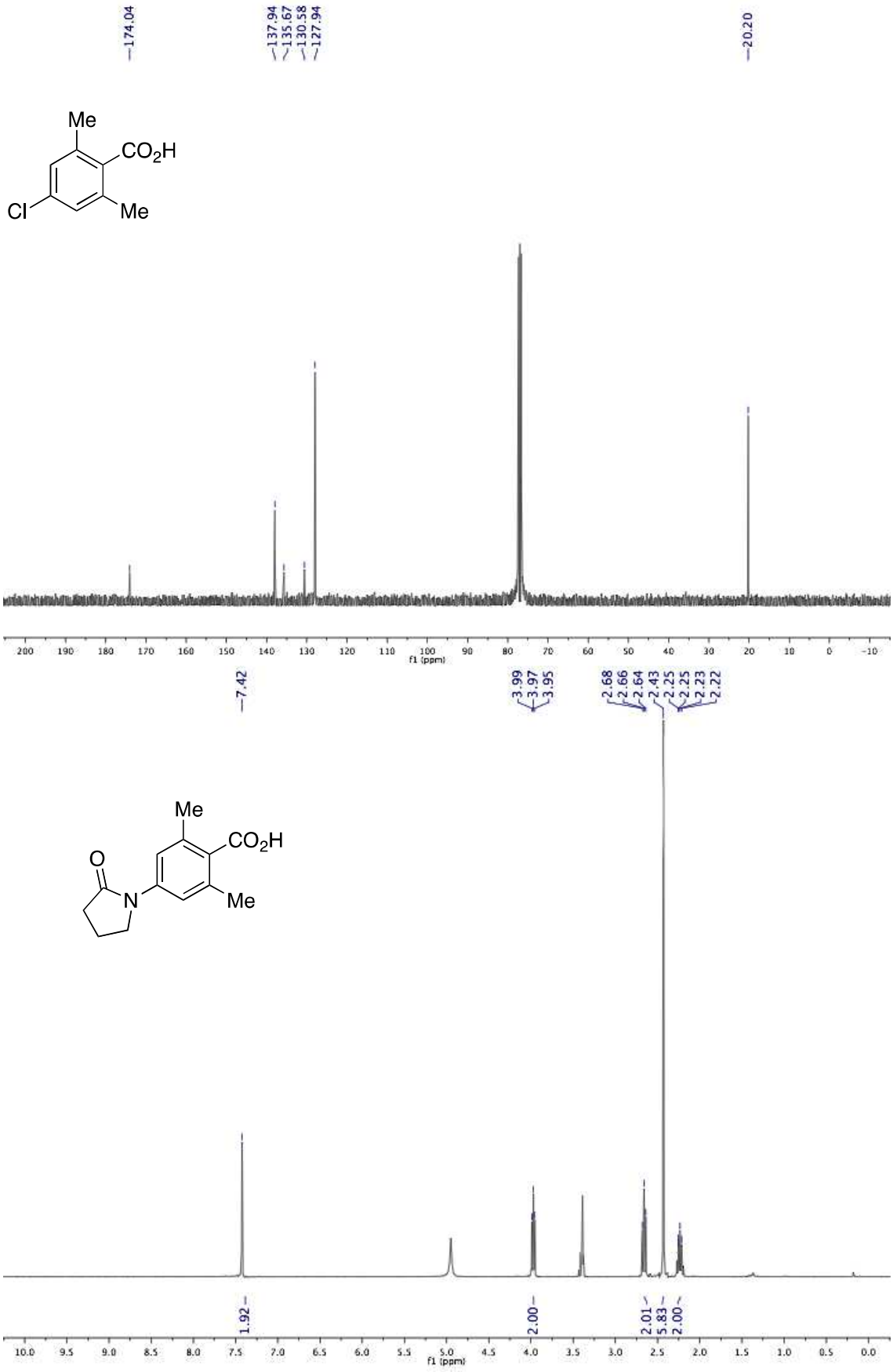


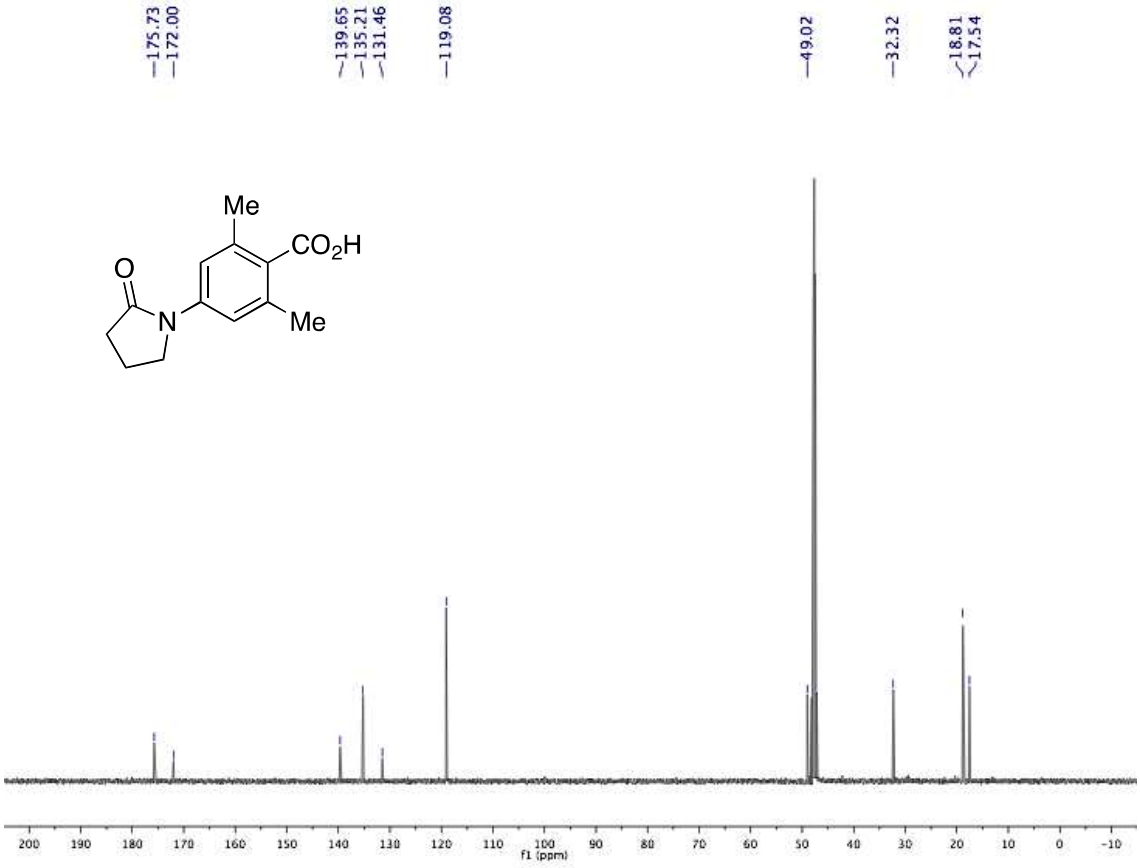
D_{11}-2,4,6-Triimethylbenzoic acid 265. White solid. ^{13}C-NMR (100 MHz, $CDCl_3$): δ176.0, 139.9, 136.1, 129.2, 128.5 (t, *J* = 16.1 Hz), 20.0 (t, *J* = 19.0 Hz), 19.6 (t, *J* =

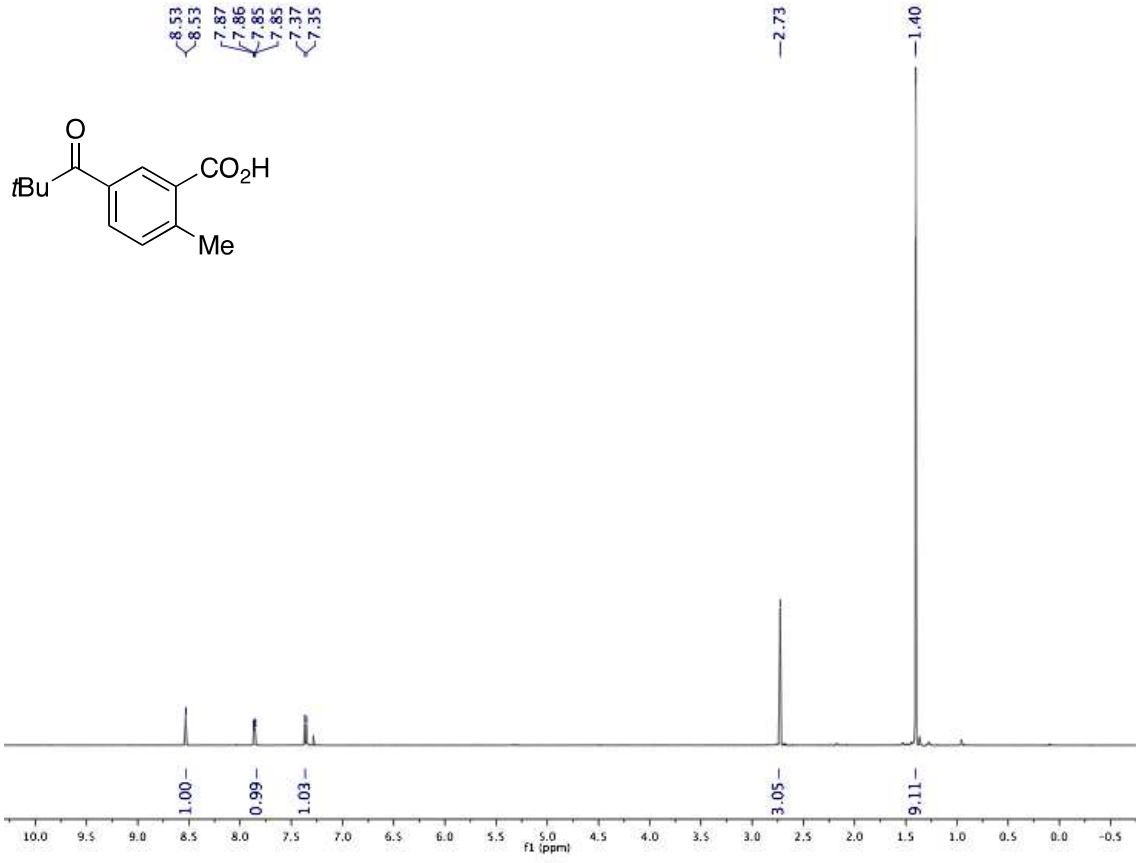
19.4 Hz) ppm. IR (neat, cm^{-1}): 2851, 1678, 1583, 1435, 1283, 938, 753.HRMS *calcd* for ($C_{10}D_{11}O^+$): 158.1500, *found* 158.1496.

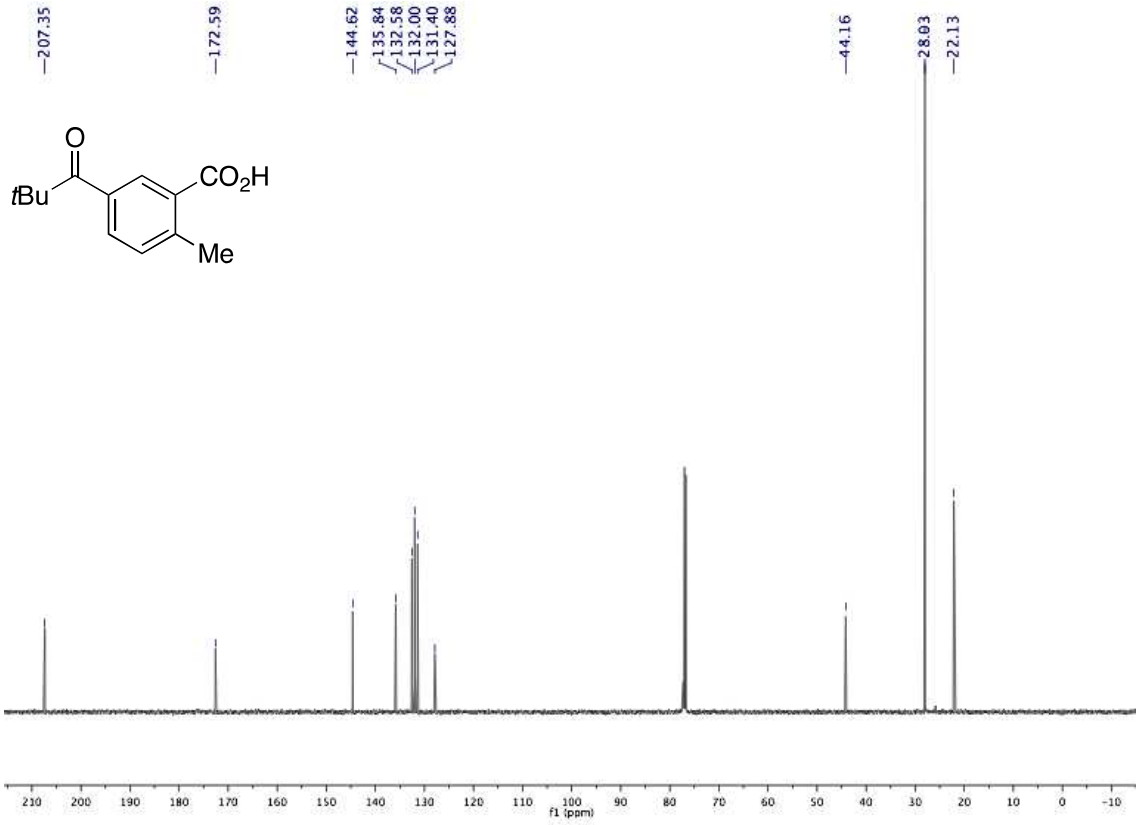
2.7.3 Selected examples of NMR spectra.




174.04
137.94
135.67
130.58
127.94
20.20
Me
CO2H
Cl
Me
f1 (ppm)
7.42
3.99
3.97
3.95
2.68
2.66
2.64
2.43
2.25
2.25
2.23
2.22
Me
CO2H
O
N
Me
1.92
2.00
2.01
5.83
2.00
f1 (ppm)





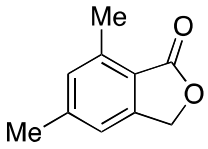


2.7.4 Synthesis of phthalides

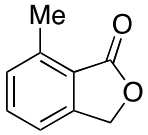
General procedure A for the Pd-catalyzed lactonization of aryl acids. An oven-dried screw-cap test tube containing a stirring bar was charged with the benzoic acid (0.50 mmol), $Pd(OAc)_2$ (11.2 mg, 10 mol%), Ac-Leu-OH (26.0 mg, 30 mol%), Ag_2CO_3 (414.0 mg, 1.5 mmol) and K_2HPO_4 (217.0 mg, 1.25 mmol) and evacuated three times. Then, PhCl (2 mL) was added by syringe under a positive argon atmosphere. The mixture was stirred in a pre-heated oil bath (140 ºC) for 14 h. The mixture was then allowed to warm to room temperature, diluted with ethyl acetate (5 mL) and filtered through a Celite® plug, eluting with additional ethyl acetate (10 mL). The filtrate was concentrated and purified by column chromatography on silica gel (eluting with hexanes/ethyl acetate mixtures).

General procedure B for the Pd-catalyzed lactonization of aryl acids. Same as for Procedure A, but using PhCl/NMP 4:1 mixture (4 mL/1mmol).

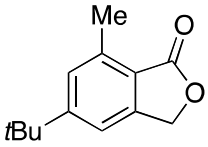
General procedure C for the Pd-catalyzed lactonization of aryl acids. Same as for Procedure A, but using NMP (4 mL/1mmol).



5,7-Dimethylisobenzofuran-1(3*H*)-one 168.[130]Following general procedure A, 2,4,6-trimethylbenzoic acid (0.5 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 4/1. White solid; yield: 77.0 mg (95% yield). M.p. = 89-90 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.08 (s, 2H), 5.20 (s, 2H), 2.64 (s, 3H), 2.44 (s, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ171.3, 147.6, 144.9, 139.3, 131.7, 120.8, 119.7, 68.7, 21.8, 17.2 ppm.

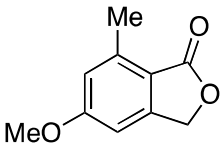


7-Methylisobenzofuran-1(3*H*)-one 225.[131]Following general procedure A, 2,6-dimethylbenzoic acid (0.5 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 4/1. White solid; yield: 52.0 mg (70% yield). M.p. = 80-81 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.54 (t, *J* = 7.6 Hz, 1H), 7.28 (m, 2H), 5.26 (s, 2H), 2.70 (s, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.3, 147.0, 139.7, 133.7, 130.6, 123.2, 119.3, 68.9, 17.3 ppm.

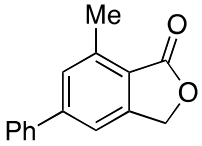


5-(*tert*-Butyl)-7-methylisobenzofuran-1(3*H*)-one 226.[132]Following general procedure A, 4-(*tert*-butyl)-2,6-dimethylbenzoic acid (0.5 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 5/1. White solid; yield: 77.0 mg (75% yield). M.p. = 81-83 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ7.30 (s, 1H), 7.29 (s, 1H), 5.23 (s, 2H), 2.68 (s, 3H), 1.37 (s, 9H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ171.3, 158.1, 147.4, 139.0, 128.2, 120.8, 116.1, 68.9, 35.4, 31.2, 17.6 ppm.

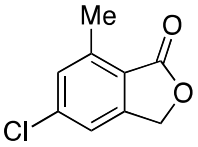
[130]Rudenko, A. P.; Korovina, N. S. *Zh. Org. Khimii***1995**, *31*, 1191
[131]Makhlouf, M. A.; Rickborn, B. *J. Org. Chem.***1981**, *46*, 4810
[132]Sargent, M.V. *J. Chem. Soc. PT1, Org. Bio-Org. Chem.***1987**,*1*, 231.



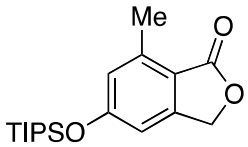
5-Methoxy-7-methylisobenzofuran-1(3*H*)-one 227.[15]Following general procedure A, 4-methoxy-2,6-dimethylbenzoic acid (0.5 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 5/1. White solid; yield: 56.0 mg (63% yield). M.p. = 171-172 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ6.79 (s, 1H), 6.74 (s, 1H), 5.19 (s, 2H), 3.89 (s, 3H), 2.65 (s, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ171.0, 164.3, 149.9, 141.4, 117.4, 115.9, 103.6, 68.5, 55.7, 17.5 ppm.



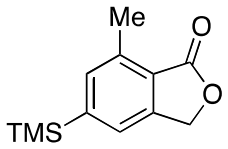
7-Methyl-5-phenylisobenzofuran-1(3*H*)-one 228. Following general procedure A, 3,5-dimethyl-[1,1'-biphenyl]-4-carboxylic acid (0.5 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 5/1. White solid; yield: 76.0 mg (68% yield). M.p. = 152-153 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ7.62 (d, *J* = 7.8 Hz, 2H), 7.48 (m, 5H), 5.30 (s, 2H), 2.76 (s, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ171.1, 147.9, 147.1, 140.0, 139.8, 129.9, 129.0, 128.5, 127.5, 122.1, 117.9, 68.9, 17.5 ppm. IR (neat, cm^{-1}): 2921, 1740, 1608, 1355, 1077, 1047, 788, 690. HRMS *calcd* for ($C_{15}H_{12}O_2$+Na^+): 247.0735, *found* 247.0733.



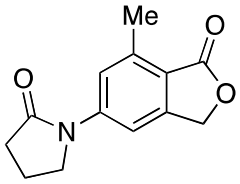
5-Chloro-7-methylisobenzofuran-1(3*H*)-one 229.Following general procedure B, 4-chloro-2,6-dimethylbenzoic acid (0.25 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 6/1. White solid; yield: 19.0 mg (41% yield). M.p. = 102-103 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ7.29 (s, 2H), 5.24 (s, 2H), 2.69 (s, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ170.1, 148.6, 141.4, 140.2, 131.0, 129.7, 119.8, 68.3, 17.2 ppm. IR (neat, cm^{-1}) 3081, 2961, 2926, 2855, 1779, 1749, 1586, 1462. HRMS *calcd* for ($C_9H_7ClO_2$+Na^+): 205.0032, *found* 205.0036.



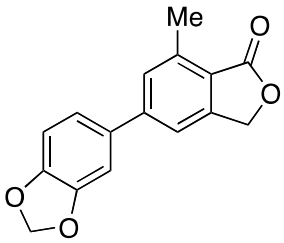
7-Methyl-5-((triisopropylsilyl)oxy)isobenzofuran-1(3*H*)-one 230.Following general procedure A, 2,6-dimethyl-4-((triisopropylsilyl)oxy)benzoic acid (0.25 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 6/1. White solid; yield: 46.0 mg (57% yield). M.p. = 71-72 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ6.77 (s, 1H), 6.72 (s, 1H), 5.18 (s, 2H), 2.64 (s, 3H), 1.29 (m, 3H), 1.14 (d, *J* = 7.4 Hz, 18H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ171.0, 161.3, 149.7, 141.4, 122.6, 117.6, 109.9, 68.4, 17.9, 17.8, 12.7 ppm. IR (neat, cm^{-1}): 2942, 2892, 2866, 2650, 1741, 1560, 1351, 1687, 1331, 1157. HRMS *calcd* for ($C_{18}H_{28}O_3Si+Na^+$): 343.1705, *found* 343.1709.



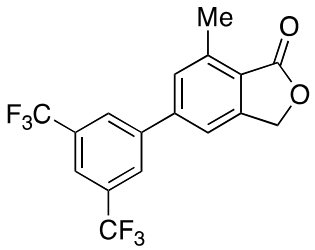
7-Methyl-5-(trimethylsilyl)isobenzofuran-1(3*H*)-one 231.Following general procedure A, 2,6-dimethyl-4-(trimethylsilyl)benzoic acid (0.25 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 6/1. White solid; yield: 42.0 mg (76% yield). M.p. = 83-84 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.45 (s, 1H), 7.42 (s, 1H), 5.31 (s, 2H), 2.71 (s, 3H), 0.33 (s, 9H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ172.1, 148.9, 146.3, 138.4, 135.4, 124.0, 123.5, 69.2, 17.3, -1.3 ppm.IR (neat, cm^{-1}): 2953, 1750, 1343, 1245, 1202, 1010, 831, 757. HRMS *calcd* for ($C_{12}H_{16}O_2Si+Na^+$): 243.0810, *found* 243.0815.



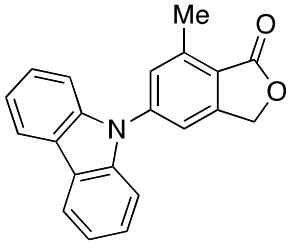
1-(7-Methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl)pyrrolidin-2-one 232. Following general procedure B (160 ºC, 40 h), 2,6-dimethyl-4-(2-oxopyrrolidin-1-yl)benzoic acid (0.25 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 3/1. White solid; yield: 31.0 mg (53% yield). M.p. = 212-213 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ7.86 (s, 1H), 7.36 (s, 1H), 5.24 (s, 2H), 3.93 (t, *J* = 7.0 Hz, 2H), 2.69 (s, 3H), 2.68 (t, *J* = 7.3 Hz, 2H), 2.24 (dd, *J* = 7.3, 7.0 Hz, 2H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ174.9, 170.8, 148.3, 144.2, 140.4, 120.7, 118.7, 110.0, 68.8, 48.8, 32.9, 17.9, 17.6. ppm. IR (neat, cm^{-1}): 2947, 2921, 1679, 1391, 1331, 1243, 1201, 1118. HRMS *calcd* for ($C_{13}H_{13}NO_3+Na^+$): 254.0793, *found* 254.0798.



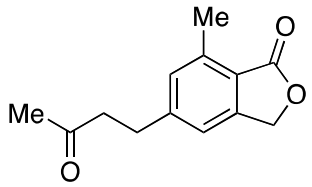
5-(Benzo[*d*][1,3]dioxol-5-yl)-7-methylisobenzofuran-1(3*H*)-one **233.**Following general procedure B (160 ºC, 40 h), 4-(benzo[*d*][1,3]dioxol-5-yl)-2,6-dimethylbenzoic acid (0.25 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 4/1. White solid; yield: 36.0 mg (54% yield). M.p.= 184-185 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ7.41 (s, 1H), 7.38 (s, 1H), 7.12-7.06 (m, 2H), 6.92 (d, *J*= 8.0 Hz, 1H), 6.04 (s, 2H), 5.29 (s, 2H), 2.73 (s, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ171.1, 148.4, 148.1, 147.9, 146.7, 139.9, 133.9, 129.5, 121.8, 121.3, 117.5, 108.8, 107.8, 101.5, 68.8, 17.5 ppm. IR (neat, cm^{-1}): 2913, 1739, 1603, 1504, 1360, 1243, 1065, 801. HRMS *calcd* for ($C_{16}H_{12}O_4$+Na^+): 291.0633, *found* 291.0638.



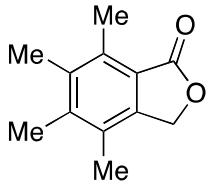
5-(3,5-bis(Trifluoromethyl)phenyl)-7-methylisobenzofuran-1(3*H*)-one 234.Following general procedure A, 3,5-dimethyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-4-carboxylic acid (0.50 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 5/1. White solid; yield: 88.0 mg (49% yield). M.p. = 221-222 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ8.06 (s, 2H), 7.96 (s, 1H), 7.53 (s, 2H), 5.36 (s, 2H), 2.81 (s, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ170.5, 148.2, 143.8, 142.0, 140.9, 132.5 (q, J_{CF2}= 34 Hz), 130.0, 127.6, 123.7, 123.0 (q, J_{CF1} = 278 Hz), 122.0 (q, J_{CF3} = 4 Hz), 118.3, 68.8, 17.4 ppm. IR (neat, cm^{-1}): 1748, 1382, 1272, 1124, 1050, 999, 900, 716.HRMS *calcd* for ($C_{17}H_{10}F_6O_2$+Na^+): 383.0494, *found* 383.0494.



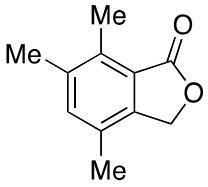
5-(9*H*-Carbazol-9-yl)-7-methylisobenzofuran-1(3*H*)-one 235.Following general procedure B (140 ºC, 40 h), 4-(9*H*-carbazol-9-yl)-2,6-dimethylbenzoic acid (0.25 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 5/1. White solid; yield: 41.0 mg (52% yield). M.p. = 259-260 ºC.^{1}H-NMR (400 MHz, $CDCl_3$): δ8.17 (d, *J* = 7.6 Hz, 2H), 7.54 (d, *J* = 7.6 Hz, 2H), 7.50-7.45 (m, 4H), 7.41-7.31 (m, 2H), 5.39 (s, 2H), 2.83 (s, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ170.4, 149.0, 143.0, 141.9, 140.2, 128.8, 126.3, 123.9, 121.9, 120.8, 120.6, 117.3, 109.7, 68.7, 17.6 ppm. IR (neat, cm^{-1}): 2925, 1754, 1604, 1477, 1446, 1029, 750, 422.HRMS *calcd* for ($C_{21}H_{15}NO_2$+Na^+): 336.1000, *found* 336.1008.



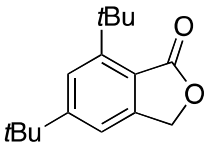
7-Methyl-5-(3-oxobutyl)isobenzofuran-1(3*H*)-one 236.Following general procedure C, 2,6-dimethyl-4-(3-oxobutyl)benzoic acid (0.25 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 2/1. White solid; yield: 28.0 mg (51% yield). M.p. = 100-101 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ7.11 (s, 1H), 7.10 (s, 1H), 5.21 (s, 2H), 2.98 (t, *J* = 7.3 Hz, 2H), 2.82 (t, *J* = 7.3 Hz, 2H), 2.66 (s, 3H), 2.18 (s, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ207.1, 171.1, 148.0, 147.7, 139.6, 130.9, 127.8, 119.2, 68.7, 44.4, 30.0, 29.6, 17.2 ppm. IR (neat, cm^{-1}): 2924, 1748, 1696, 1612, 1356, 1030, 1006, 684. HRMS *calcd* for ($C_{13}H_{14}O_3$+Na^+): 241.0841, *found* 241.0847.



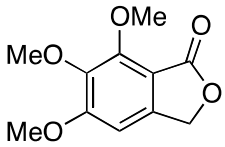
4,5,6,7-Tetramethylisobenzofuran-1(3*H*)-one 237.[15]Following general procedure A, 2,3,4,5,6-pentamethylbenzoic acid (0.50 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 5/1. White solid; yield: 52.0 mg (55% yield). M.p. = 211-212 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ5.12 (s, 2H), 2.64 (s, 3H), 2.30 (s, 3H), 2.27 (s, 3H), 2.21 (s, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ172.3, 143.5, 141.8, 136.9, 135.0, 127.1, 120.1, 67.9, 16.5, 15.6, 15.3, 13.5 ppm. HRMS *calcd* for ($C_{12}H_{14}O_2$+Na^+): 213.0891, *found* 213.0895.



4,6,7-Trimethylisobenzofuran-1(3*H*)-one 238.[133]Following general procedure A, 2,3,5,6-tetramethylbenzoic acid (0.50 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 4/1. White solid; yield: 45.0 mg (51% yield). M.p. = 98-99 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ7.23 (s, 1H), 5.14 (s, 2H), 2.61 (s, 3H), 2.34 (s, 3H), 2.27 (s, 3H) ppm.^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.0, 143.5, 138.2, 136.2, 135.3, 128.5, 122.8, 67.7, 19.0, 16.9, 12.7 ppm.



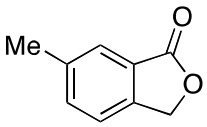
5,7-di-*tert*-Butylisobenzofuran-1(3*H*)-one 239. Following general procedure A, 2,4-di-*tert*-butyl-6-methylbenzoic acid (0.50 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 5/1. White solid; yield: 64.0 mg (52% yield). M.p. = 156-157 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ7.54 (s, 1H), 7.29 (s, 1H), 5.23 (s, 2H), 1.55 (s, 9H), 1.39 (s, 9H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ170.7, 157.9, 152.4, 149.8, 123.7, 120.5, 116.3, 68.6, 35.9, 35.6, 31.2, 29.9 ppm. IR (neat, cm^{-1}): 2958, 1744, 1607, 1362, 1201, 1047, 1022, 706. HRMS *calcd* for ($C_{16}H_{22}O_2$+Na^+):269.1517, *found* 269.1514.



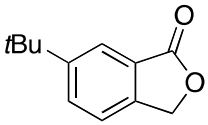
5,6,7-Trimethoxyisobenzofuran-1(3*H*)-one 240.[134]Following general procedure A, 2,3,4-trimethoxy-6-methylbenzoic acid (0.50 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 5/1. White solid; yield: 54.0 mg (48% yield). M.p. = 130-131 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ6.68 (s, 1H), 5.17 (s, 2H), 4.14 (s, 3H), 3.96 (s, 3H), 3.88 (s, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ168.7, 159.7, 152.5, 144.4, 141.8, 110.3, 99.5, 68.6, 62.4, 61.5, 56.5 ppm.

[133]Suzuki, H. *J. Chem. Soc., Chem. Comm.***1977**, *10*, 341.

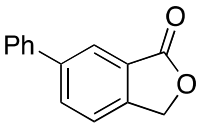
[134]Mali, R. S.; Jagtap, P. G.; Tilve, S. G. *Synth. Comm.***1990**, *20*, 2641.



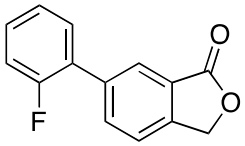
6-Methylisobenzofuran-1(3*H*)-one 244.[135]Following general procedure A, 2,5-dimethylbenzoic acid (0.50 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 4/1. White solid; yield: 52.0 mg (70% yield). M.p. = 81-82 ºC.^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.72 (s, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 5.29 (s, 2H), 2.48 (s, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.3, 143.9, 139.3, 135.2, 125.9, 125.7, 121.8, 69.6, 21.3 ppm.



6-(*tert*-Butyl)isobenzofuran-1(3*H*)-one245.[136]Following general procedure A, 5-(*tert*-butyl)-2-methylbenzoic acid (0.50 mmold) was used. Column chromatography: silica gel, hexanes/EtOAc 5/1. White solid; yield: 68.0 mg (72% yield). M.p. = 65-66 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ7.95 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 5.30 (s, 2H), 1.38 (s, 9H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ171.6, 152.9, 143.9, 131.8, 125.6, 122.2, 121.7, 69.6, 35.1, 31.3 ppm.

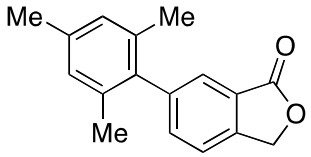


6-Phenylisobenzofuran-1(3*H*)-one 246.[137]Following general procedure A (160 ºC, 40 h), 4-methyl-[1,1'-biphenyl]-3-carboxylic acid (0.25 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 3/1. White solid; yield: 29.0 mg (55% yield). M.p. = 79-80 ºC.^{1}H-NMR (400 MHz, $CDCl_3$): δ8.16 (d, *J* = 1.0 Hz, 1H), 7.94 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.64 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.58 (dd, *J* = 8.0, 0.7 Hz, 1H), 7.51 (m, 2H), 7.44 (d, *J* = 7.3 Hz, 1H), 5.39 (s, 2H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ171.1, 145.3, 142.7, 139.4, 133.2, 129.1, 128.2, 127.2, 126.5, 123.9, 122.5, 69.7 ppm.

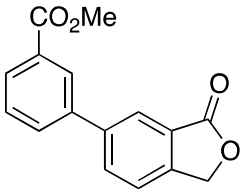


[135]Davies, H. M. L.; Matasi, J. J.; Ahmed, G. *J. Org. Chem.***1996**, *61*, 2305.
[136]Nelsen, S. F. *J. Org. Chem.***1973**, *38*, 2693.
[137]Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Nishiyama, H.; Itoh, K. *Org. Biomol. Chem.***2004**, *2*, 1287-1294.

6-(2-Fluorophenyl)isobenzofuran-1(3*H*)-one 247.Following general procedure A (160 ºC, 60 h), 2'-fluoro-4-methyl-[1,1'-biphenyl]-3-carboxylic acid (0.25 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 2/1. White solid; yield: 30.0 mg (53% yield). M.p. = 113-114 ºC.^{1}H-NMR (400 MHz, $CDCl_3$): δ8.11 (s, 1H), 7.91 (dt, *J* = 8.0, 1.8 Hz, 1H), 7.59 (dd, *J* = 8.0, 0.7 Hz, 1H), 7.48 (td, *J* = 7.7, 1.8 Hz, 1H), 7.40 (dddd, *J* = 8.2, 7.0, 5.0, 1.8 Hz, 1H), 7.31-7.27 (m, 1H), 7.26-7.20 (m, 1H), 5.40 (s, 2H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ170.9, 159.7 (J_{CF1} = 248 Hz), 145.7, 137.17, 135.0, 130.7 (J_{CF3} = 3 Hz), 130.0 (J_{CF3} = 8 Hz), 127.3 (J_{CF2} = 13 Hz), 126.3, 126.0, 124.7 (J_{CF3} = 4 Hz), 122.2, 116.3 (J_{CF2} = 23 Hz), 69.6 ppm. IR (neat, cm^{-1}): 2924, 1748, 1479, 1453, 1212, 1049, 998, 747. HRMS *calcd* for ($C_{14}H_9FO_2$+Na^+): 251.0484, *found* 251.0484.

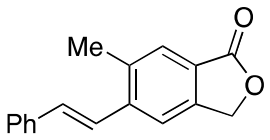


6-Mesitylisobenzofuran-1(3*H*)-one 248. Following general procedure A, 2',4,4',6'-tetramethyl-[1,1'-biphenyl]-3-carboxylic acid (0.50 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 5/1. White solid; yield: 78.0 mg (62% yield). M.p. = 187-188 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ7.75 (s, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 6.99 (s, 2H), 5.41 (s, 2H), 2.37 (s, 3H), 2.00 (s, 6H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ171.2, 145.0, 142.5, 137.4, 137.1, 135.7, 135.6, 128.4, 126.5, 126.2, 122.2, 69.7, 21.1, 20.8 ppm. IR (neat, cm^{-1}): 2917, 1757, 1611, 1457, 1186, 1050, 998, 839, 771. HRMS *calcd* for ($C_{17}H_{16}O_2$+Na^+): 275.1048, *found* 275.1046.

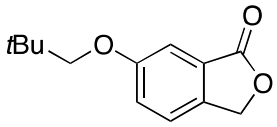


Methyl 3-(3-oxo-1,3-dihydroisobenzofuran-5-yl)benzoote 249. Following general procedure B (160 ºC, 40 h), 3'-(methoxycarbonyl)-4-methyl-[1,1'-biphenyl]-3-carboxylic acid (0.25 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 2/1. White solid; yield: 31.0 mg (46% yield). M.p. = 138-139 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ8.32 (dd, *J* = 14.2, 12.3 Hz, 1H), 8.19 (d, *J* = 1.1 Hz, 1H), 8.10 (ddd, *J* = 14.2, 7.9, 6.6 Hz, 1H), 7.97 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.85-7.82 (m, 1H), 7.63-7.56 (m, 2H), 5.41 (s, 2H), 3.98 (s, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$):δ170.9, 166.7, 145.7, 141.6, 139.6, 133.1, 132.5, 131.5, 131.1, 129.3, 128.4, 126.7, 124.1, 122.7, 69.6, 52.3 ppm. IR (neat,

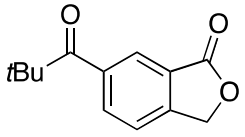
cm^{-1}): 2923, 1769, 1722, 1357, 1303, 1242, 995, 768.HRMS *calcd* for ($C_{16}H_{12}O_4$+Na^+): 291.0633, *found* 291.0640.



(*E*)-6-Methyl-5-styrylisobenzofuran-1(3*H*)-one 250.Following general procedure B (160 ºC, 40 h), (*E*)-2,5-dimethyl-4-styrylbenzoic acid (0.25 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 3/1. White solid; yield: 29.0 mg (47% yield). M.p. = 186-187 ºC.^{1}H-NMR (400 MHz, $CDCl_3$): δ7.74 (s, 1H), 7.69 (s, 1H), 7.60- 7.56 (m, 2H), 7.46-7.40 (m, 2H), 7.36 (m, 1H), 7.16-7.12 (m, 2H), 5.33 (s, 2H), 2.54 (s, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ171.2, 144.7, 142.9, 137.2, 136.7, 133.4, 128.9, 128.5, 127.0, 126.9, 125.3, 124.4, 118.4, 69.4, 20.2 ppm. IR (neat, cm^{-1}): 2923, 1747, 1613, 1448, 1104, 959, 774, 687, 496.HRMS *calcd* for ($C_{17}H_{14}O_2$+Na^+): 273.0891, *found* 273.0896.

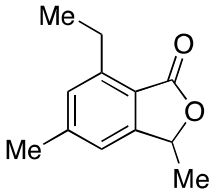


6-(Neopentyloxy)isobenzofuran-1(3*H*)-one 251.Following general procedure B (140 ºC, 40 h), 2-methyl-5-(neopentyloxy)benzoic acid (0.25 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 3/1. White solid; yield: 29.0 mg (53% yield). M.p. = 98-99 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ7.38 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 2.2 Hz, 1H), 7.29 (m, 1H), 5.28 (s, 2H), 3.67 (s, 2H), 1.07 (s, 9H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$):δ171.3, 160.5, 138.5, 126.9, 123.5, 122.7, 108.2, 78.5, 69.5, 31.9, 26.5 ppm. IR (neat, cm^{-1}): 2955, 1753, 1494, 1363, 1246, 1050, 1008. HRMS *calcd* for ($C_{13}H_{16}O_3$+Na^+): 243.0997, *found* 243.0998.



6-Pivaloylisobenzofuran-1(3*H*)-one 252. Following general procedure A (140 ºC, 40 h), 2-methyl-5-pivaloylbenzoic acid (0.25 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 3/1. White solid; yield: 24.0 mg (44% yield). M.p. = 76-77 ºC.^{1}H-NMR (400 MHz, $CDCl_3$): δ8.24 (s, 1H), 8.00 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.58 (dd, *J* = 8.0, 0.7 Hz, 1H), 5.38 (s, 2H), 1.38 (s, 9H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ207.7,

170.3, 148.5, 139.7, 133.9, 125.6, 124.8, 122.4, 69.6, 44.4, 27.9 ppm. IR (neat, cm^{-1}): 2923, 1758, 1689, 1365, 1155, 1055, 771. HRMS *calcd* for ($C_{13}H_{14}O_3$+Na^+): 241.0841, *found* 241.0847.



7-Ethyl-3,5-dimethylisobenzofuran-1(3*H*)-one 241. Following general procedure A, 2,6-diethyl-4-methylbenzoic acid (0.25 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 6/1. Yellowish solid; yield: 18 mg (38 % yield). M.p. = 110-111 ºC.^{1}H-NMR (400 MHz, $CDCl_3$): δ7.12 (s, 1H), 7.04 (s, 1H), 5.44 (q, *J* = 6.7 Hz, 1H), 3.10 (t, *J* = 7.6 Hz, 2H), 2.47 (s, 3H), 1.61 (d, *J* = 6.7 Hz, 3H), 1.29 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ170.4, 152.6, 145.7, 145.1, 130.0, 120.1, 119.3, 76.4, 24.1, 22.0, 20.5, 15.0 ppm. IR (neat, cm^{-1}): 2929, 1749, 1603, 1451, 1202, 1033, 696.HRMS *calcd* for ($C_{12}H_{14}O_2$+Na^+): 213.0891, *found* 213.0892.

2.7.5 Mechanistic considerations

1.1 Reaction of 273 with stochiometric amounts of Pd

An oven-dried screw-cap test tube containing a stirring bar was charged with the **273** (67.8 mg, 0.25 mmol), $Pd(OAc)_2$ (56.3 mg, 1 equiv), Ac-Leu-OH (129.8 mg, 3 equiv) and K_2HPO_4 (108.5 mg, 2.5 equiv) and evacuated three times. Then, PhCl (1 mL) was added by syringe under a positive argon atmosphere. The mixture was stirred in a pre-heated oil bath (140 ºC) for 15 h. The mixture was then allowed to warm to room temperature, diluted with ethyl acetate (5 mL) and filtered through a Celite® plug, eluting with additional ethyl acetate (10 mL). The filtrate was concentrated and purified by column chromatography on silica gel (eluting with hexanes/ethyl acetate mixtures 5/1). White solid; yield: 25 mg (61%).

1.2 Reaction of 273 with catalytic amounts of Pd

An oven-dried screw-cap test tube containing a stirring bar was charged with **273** (22.2 mg, 0.13 mmol), $Pd(OAc)_2$ (2.9 mg, 10 mol%), Ac-Leu-OH (6.7 mg, 30 mol%), Ag_2CO_3 (107.6 mg, 3 equiv) and K_2HPO_4 (56.6 mg, 2.5 equiv) and evacuated three times. Then, PhCl (0.5 mL) was added by syringe under a positive argon atmosphere. The mixture was stirred in a pre-heated oil bath (140 ºC) for 20 h. The mixture was then allowed to warm to room temperature, diluted with ethyl acetate (5 mL) and filtered

through a Celite® plug, eluting with additional ethyl acetate (10 mL). The filtrate was concentrated and purified by column chromatography on silica gel (eluting with hexanes/ethyl acetate mixtures 5/1). White solid; yield: 18 mg (85%).

1.3 Reaction of 274 in stochiometric amounts

An oven-dried screw-cap test tube containing a stirring bar was charged with the **277**(108.2 mg, 0.25 mmol), Ac-Leu-OH (129.8 mg, 3 equiv), K_2HPO_4 (108.5 mg, 2.5 equiv) and evacuated three times. Then, PhCl (1 mL) was added by syringe under a positive argon atmosphere. The mixture was stirred in a pre-heated oil bath (140 ºC) for 20 h. The mixture was then allowed to warm to room temperature, diluted with ethyl acetate (5 mL) and filtered through a Celite® plug, eluting with additional ethyl acetate (10 mL). The filtrate was concentrated and purified by column chromatography on silica gel (eluting with hexanes/ethyl acetate mixtures 5/1). White solid; yield: 69 mg (84%).

1.4 **Reaction of 167 with 274as precatalyst**

An oven-dried screw-cap test tube containing a stirring bar was charged with the aryl acid **167** (41 mg, 0.25 mmol), **274**(10.8 mg, 10 mol%), Ac-Leu-OH (13.0 mg, 30 mol%), Ag_2CO_3 (207.0 mg, 3 equiv) and K_2HPO_4 (108.5 mg, 2.5 equiv) and evacuated three times. Then, PhCl (1 mL) was added by syringe under a positive argon atmosphere. The mixture was stirred in a pre-heated oil bath (140 ºC) for 20 h. The mixture was then allowed to warm to room temperature, diluted with ethyl acetate (5 mL) and filtered through a Celite® plug, eluting with additional ethyl acetate (10 mL). The filtrate was concentrated and purified by column chromatography on silica gel (eluting with hexanes/ethyl acetate mixtures 5/1). White solid; yield: 35 mg (83%).

(2) Kinetic Isotope effects

Intermolecular KIE

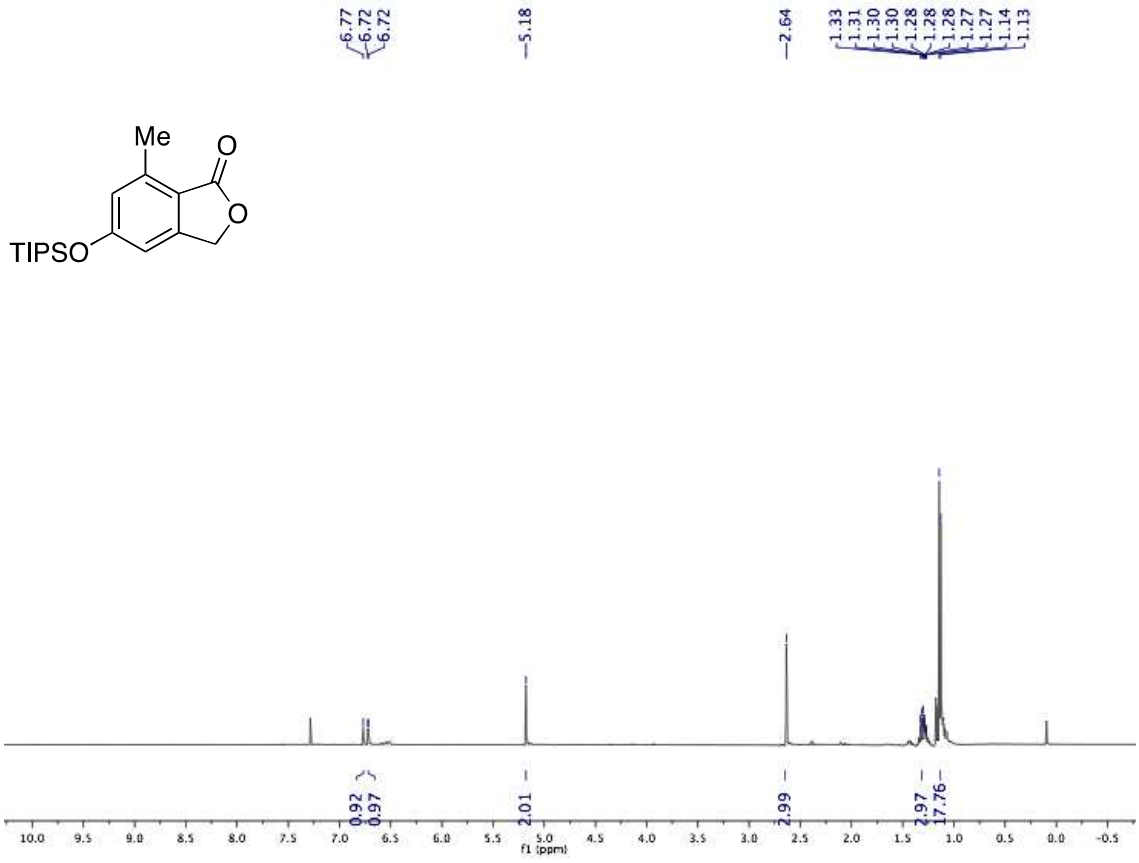
An oven-dried screw-cap test tube containing a stirring bar was charged with **167** (20.5 mg, 0.125 mmol) and **265** (21.9 mg, 0.125 mmol), $Pd(OAc)_2$ (5.6 mg, 10 mol%), Ac-Leu-OH (13.0 mg, 30 mol%), Ag_2CO_3 (207.0 mg, 3 equiv) and K_2HPO_4 (108.5 mg, 2.5 equiv) and evacuated three times. Then, PhCl (1 mL) was added by syringe under a positive argon atmosphere. The mixture was stirred in a pre-heated oil bath (140 ºC) for 0.5 h. The mixture was then allowed to warm to room temperature, diluted with EtOAc (5 mL) and filtered through a Celite® plug, eluting with additional EtOAc (10 mL). KIE k_H/k_D = 1.17 was established by ^{1}H-NMR with $MeNO_2$ as internal standard.[138]

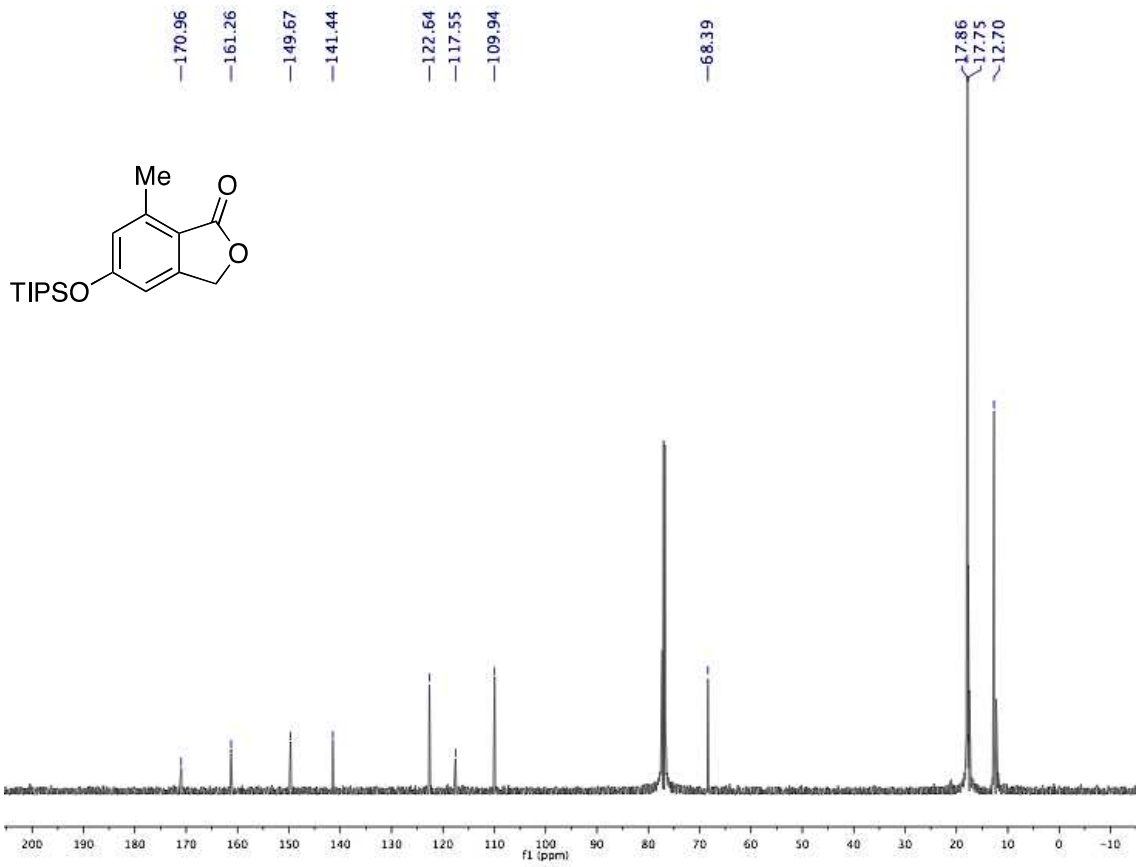
[138] Rong, Y.; Li, R.; Lu, W. *Organometallics*, **2007**, *26*, 4376.

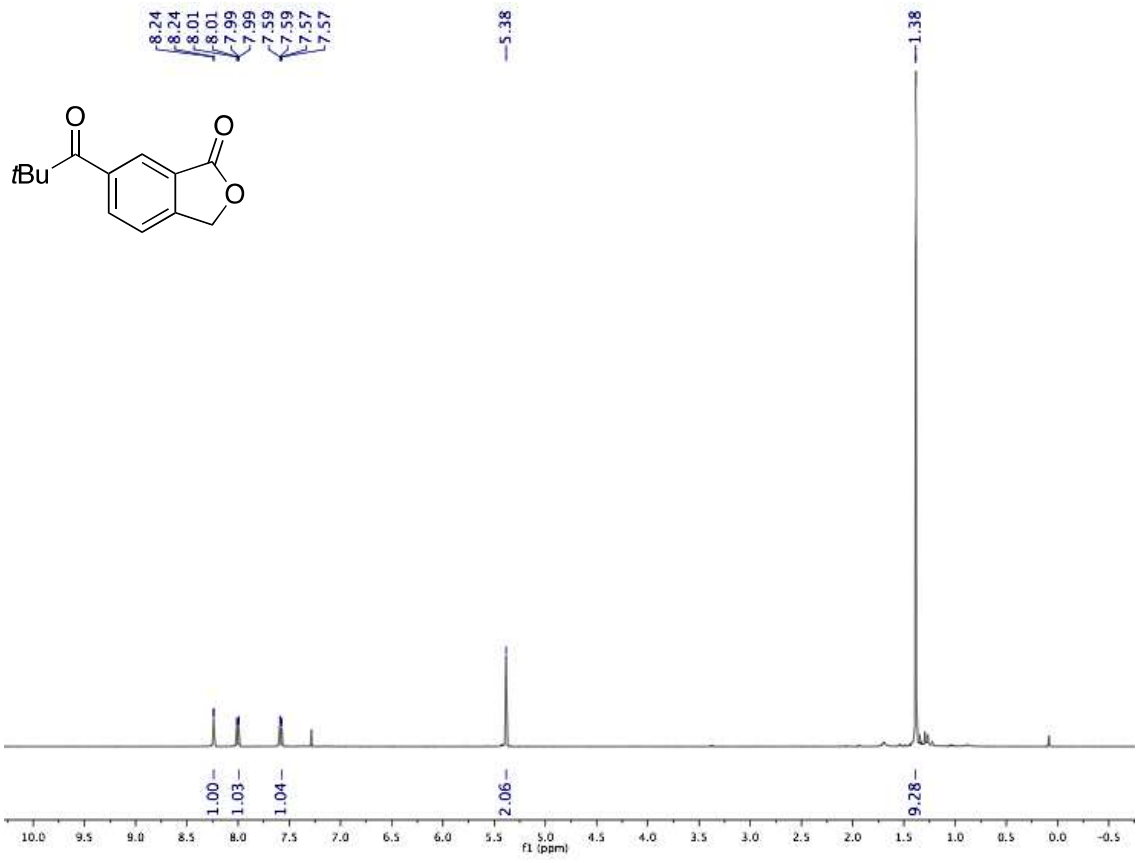
Intramolecular KIE

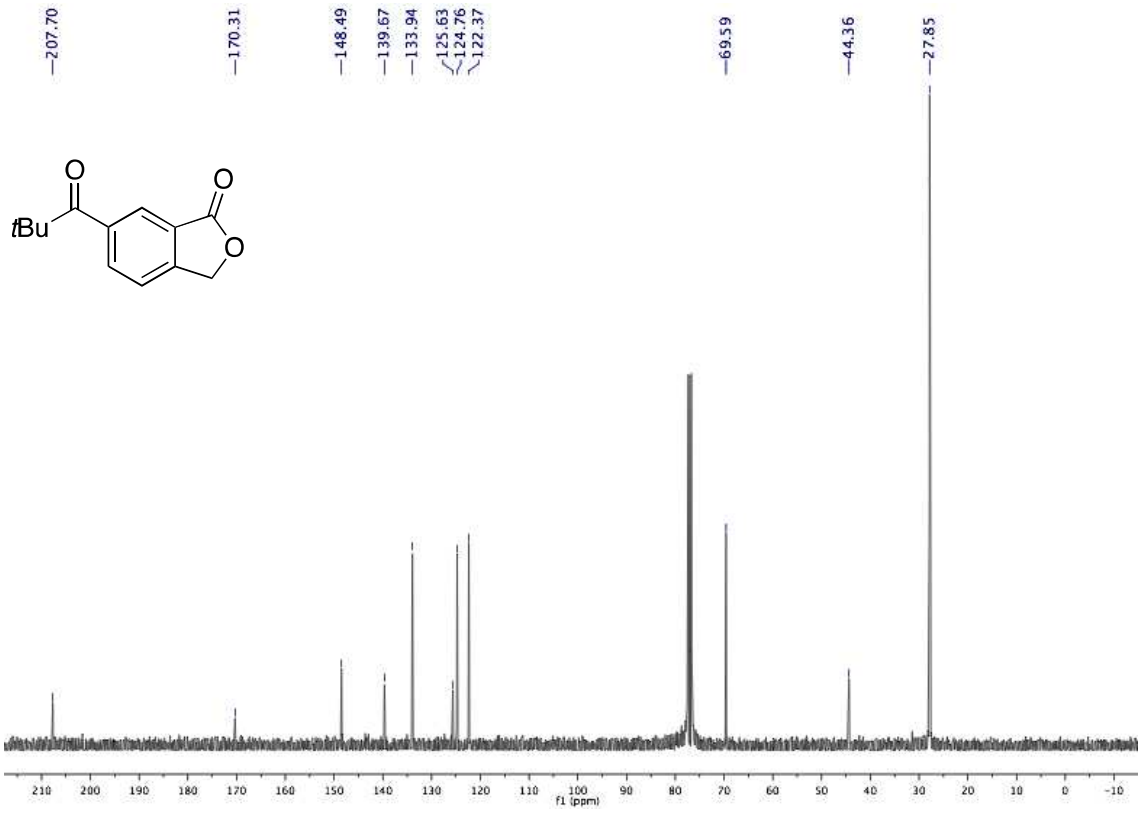
An oven-dried screw-cap test tube containing a stirring bar was charged with the aryl acid **268** (38.3 mg, 0.25 mmol), $Pd(OAc)_2$ (5.6 mg, 10 mol%), Ac-Leu-OH (13.0 mg, 30 mol%), Ag_2CO_3 (207.0 mg, 3 equiv) and K_2HPO_4 (108.5 mg, 2.5 equiv) and evacuated three times. Then, PhCl (1 mL) was added by syringe under a positive argon atmosphere. The mixture was stirred in a pre-heated oil bath (140 ºC) for 5 h. The mixture was then allowed to warm to room temperature, diluted with EtOAc (5 mL) and filtered through a Celite® plug, eluting with additional EtOAc (10 mL). KIE k_H/k_D = 1.56 was established by ^{1}H-NMR with $MeNO_2$ as an internal standard.

2.7.6 Selected examples of NMR spectra.




170.96
161.26
149.67
141.44
122.64
117.55
109.94
68.39
17.86
17.75
12.70
Me
O
O
TIPSO
f1 (ppm)


8.24
8.24
8.01
8.01
7.99
7.99
7.59
7.59
7.57
7.57
5.38
1.38
O
O
tBu
O
1.00
1.03
1.04
2.06
9.28
f1 (ppm)


207.70
170.31
148.49
139.67
133.94
125.63
124.76
122.37
69.59
44.36
27.85
tBu
O
O
O
f1 (ppm)

UNIVERSITAT ROVIRA I VIRGILI
SYNTHESIS OF PHTHALIDES AND BENZOLACTONES VIA CATALYTIC
C-H FUNCTIONALIZATION/C-O BOND-FORMING REACTIONS
Juan Gallardo Donaire
Dipòsit Legal: T 1365-2014

Chapter 3. Pd- and Cu-catalyzed C(sp^2)-bond functionalization/C-O bond formation en route to benzolactones

3.1 Objectives

The objectives of this chapter are the following:

- To develop a mild metal-catalyzed C(sp^2)-H bond functionalization approach for the synthesis of benzo[c]chromen-6-ones and/or remote hydroxylated arene assisted by carboxylic acids.
- To gain mechanistic insights via the study of kinetic isotope effects and radical trapping experiments.

3.2 Biological relevance of benzo[c]chromen-6-ones

Benzo[c]chromen-6-ones are privilege scaffolds in many natural products[139] and compounds with important biological activities such as progesterone receptor agonists,[140]endothelial cell growth inhibitors,[141]antifungal and antitumor activities,[142]among others.Furthermore, **278** shows promising inhibition of cell proliferation and **277** have been employed as a potent *C*-glycoside antibiotic.[143]

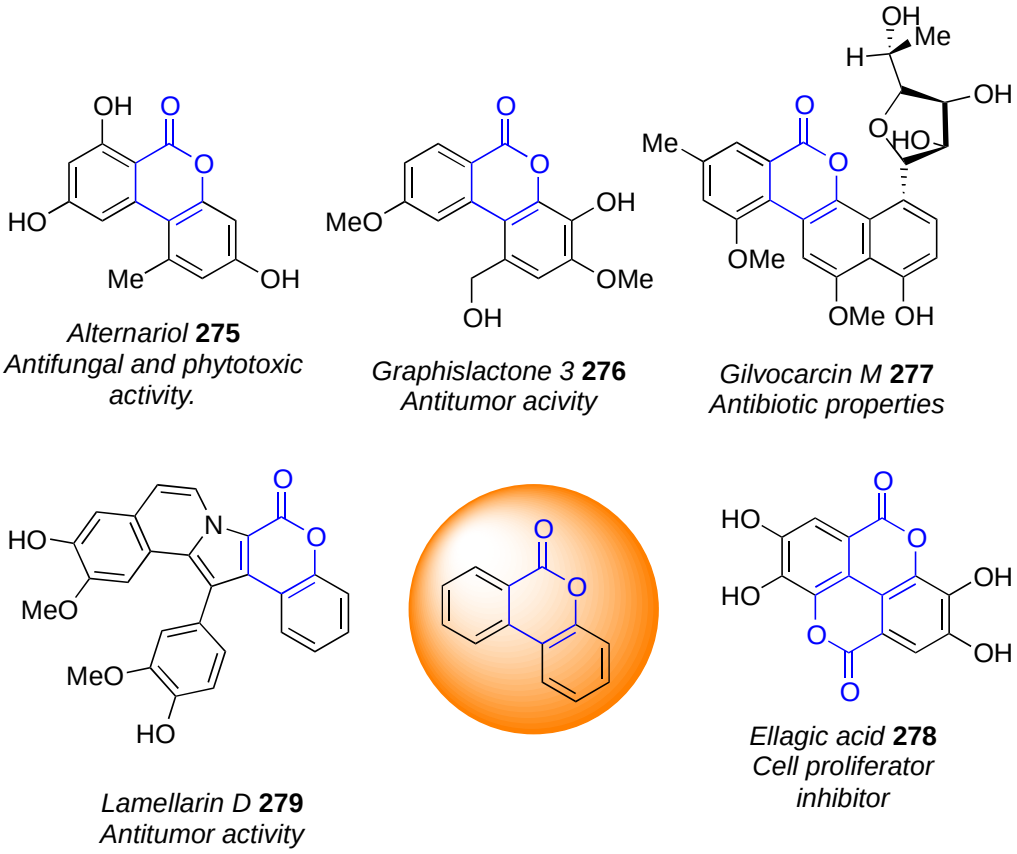


Figure 3.1

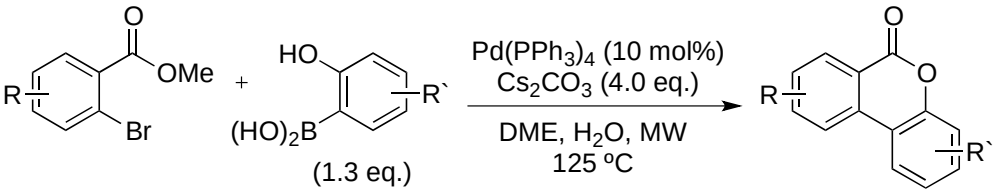
Although different in function, their structural relationship resides on the particular δ-lactone core. Driven by the intriguing properties of benzopyranone compounds, new

[139] Myrray, R.; Mendez, J.; Brown, S. The Natural Coumarins; Occurence, Chemistry and Biochemistry; JohnWiley&Sons: New York, 1982.
[140] (a) Zhi, L.; Tegley, C. M.; Marschke, K. B.; Mais, D. E.; Jones, T. K. *J. Med. Chem.***1999**, *42*, 1466. (b) Edwards, J. P.; West, S. J.; Marschke, K. B.; Mais, D. E.; Gottardis, M. M.; Jones, T. K. *J. Med. Chem*. **1998**, *41*, 303.
[141] Schmidt, J. M.; Tremblay, G. B.; Page, M.; Mercure, J.; Feher, M.; Dunn-Dufault, R.; Peter, M. G.; Redden, P. R. *J. Med. Chem.***2003**, *46*, 1289.
[142] (a) Koch, K.; Podlech, J.; Pfeiffer, E.; Metzler, M. *J. Org. Chem.***2005**, *70*, 3275. (b) Abe, H.; Nishioka, K.; Takeda, S.; Arai, M.; Takeuchi, Y.; Harayama, T. *Tetrahedron Lett.***2005**, *46*, 3197. (c) Thasana, N.; Worayuthakarn, R.; Kradanrat, P.; Hohn, E.; Young, L. *J. Org. Chem*. **2007**, *72*, 9379.
[143]Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.***1994**, *116*, 1004.

synthetic methods have been designed for constructing the key benzochromenone core.

3.3 *State of the art* of benzo[c]chromenones synthesis

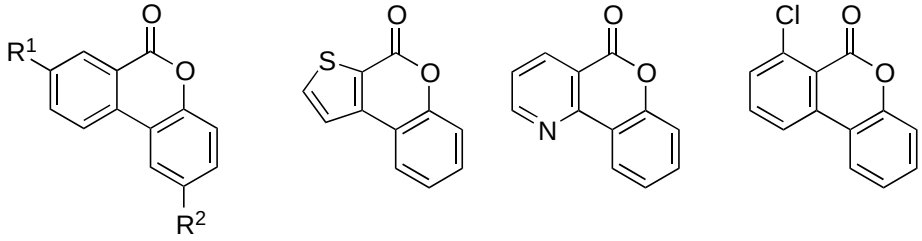
The traditional approach for the synthesis of lactones relies on the cyclization of carboxylic acids and alcohols.[144]Unfortunately, these methods suffer from multistep synthetic manipulations to install the desired functionality prior the lactonization event. Alternatively, Vishnumurthy and co-workers reported a one step synthesis of dibenzopyranones via Suzuki-Miyaura cross-coupling.[145] As shown in Figure 3.2, this protocol exhibits good chemoselectivity profile for a wide variety of aryl bromides and boronic acids. An intrinsic drawback of this transformation, however, relies on the use of highly functionalized coupling partners as well as the generation of stoichiometric amounts of halogen waste.



280 **281** **282**

68-98%

selected examples



R^1= NO_2, R^2= H, 95%
R^1= CO_2Me, R^2= H, 80%
R^1= OMe, R^2= Cl, 89%
R^1= CF_3, R^2= OH, 72%

85% 95% 68%

Figure 3.2

[144] L.G. Hamann, R. I. Higuchi, L. Zhi, J. P. Edwards, X. N. Wang, K. B. Marchke, J.W. Kong, L. J. Farmer, T. K. Jones, *J. Med. Chem.***1998**, *41*, 623. For a review of lactonization reactions applied in total synthesis see: A. Parenty, X. Moreau, J. M. Campagne, *Chem. Rev*. **2006**, *106*, 911.

[145]Vishnumurthy, K.; Makriyannis, A. *J. Comb. Chem.***2010**, *12*, 664. For similar multistep procedures involving Suzuki-Miyaura couplings see: (a) B. I. Alo, P. A. Patil, M. J. Sharp, M.A. Siddiqui, V. Snieckus, *J. Org. Chem*. **1991**, *56*, 3763. (b) Q. J. Zhou, K. Worm, R. E. Dolle, *J. Org. Chem*. **2004**, *69*, 5147. (c) G. J. Kemperman, B. Ter Horst, D. Van deGoor, T. Roeters, J. Bergwerff, R. Van der Eem, J. Basten, *Eur. J. Org. Chem*. **2006**, *14*, 3169. (d) I. Hussain, V. T. H. Nguyen, T. T. Yawer, C. Fiscer, H. Reinke, P. Langer, *J. Org. Chem*. **2007**, *72*, 6255.

Similarly, Deng group envisioned a decarboxylative cross-coupling/lactonization strategy en route to dibenzopyranones **268**(Figure 3.3)[146]using 2-nitrobenzoic acids**283**as coupling partners. As for other decarboxylative cross-coupling events,[147] the presence of an electron-withdrawing group in the ortho-position to carboxylic acid was found to be crucial for achieving good reaction efficiencies.

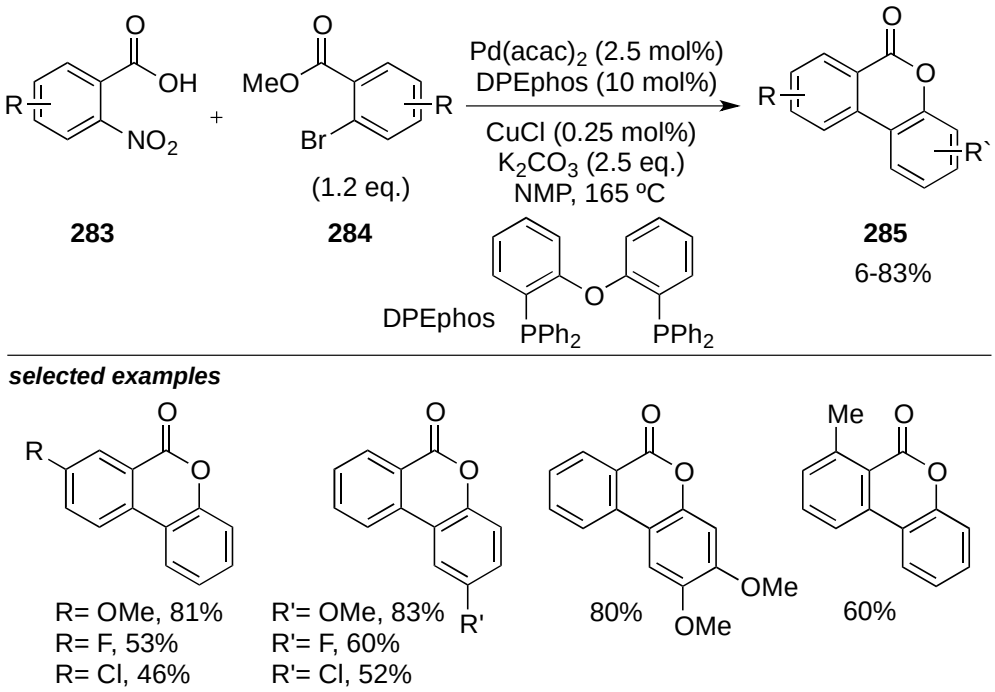


Figure 3.3

On the other hand, an intramolecular microwave assisted Ullman-type coupling was developed under ligand- and base-free conditions (Figure 3.4).[148]Aryl bromides and chlorides **286**can be used as electrophiles for the lactonization event, albeit stoichiometric amounts of copper are required in both cases. Interestingly, this procedure was applied by the authors for the synthesis of isomellarins, a new class of pyrroloisoquinoline alkaloids.

[146]Luo, J.; Lu, Y.; Liu, S.; Liu, J.; Deng, G.-J. *Adv. Synth. Catal.***2011**, *353*, 2604.
[147] For selected reviews on decarboxylative couplings see: (a) Rodríguez, N.; Goossen, L. J. *Chem. Soc. Rev.***2011**, *40*, 5030. (b) Cornella, J.; Larrosa, I. *Synthesis***2012**, *44*, 653.
[148]Thasana, N.; Worayuthakarn, R.; Kradanrat, P.; Hohn, E.; Young, L. *J. Org. Chem*. **2007**, *72*, 9379.

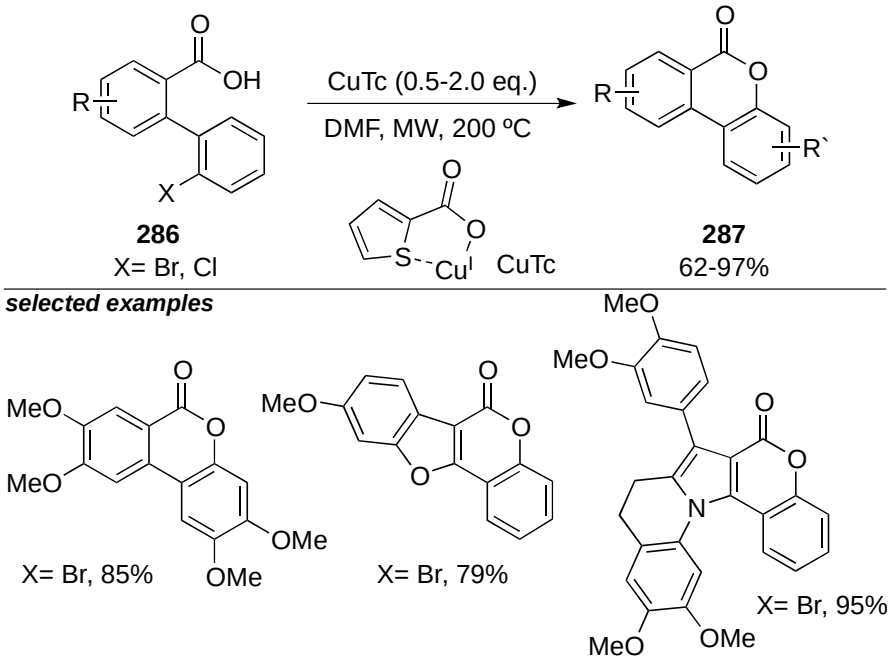


Figure 3.4

As it was explained in *section 2.4.4*, [2+2+2] cycloadditions are a feasible method for the construction of phthalides. This strategy can also be applied for the synthesis of benzo[c]chromenones, as demonstrated by Deiters in 2008 (Figure 3.5).[149] The Ru(II)-catalyzed cyclotrimerizationturned out to be regioselective when sterically hindered alkyneswere utilized.

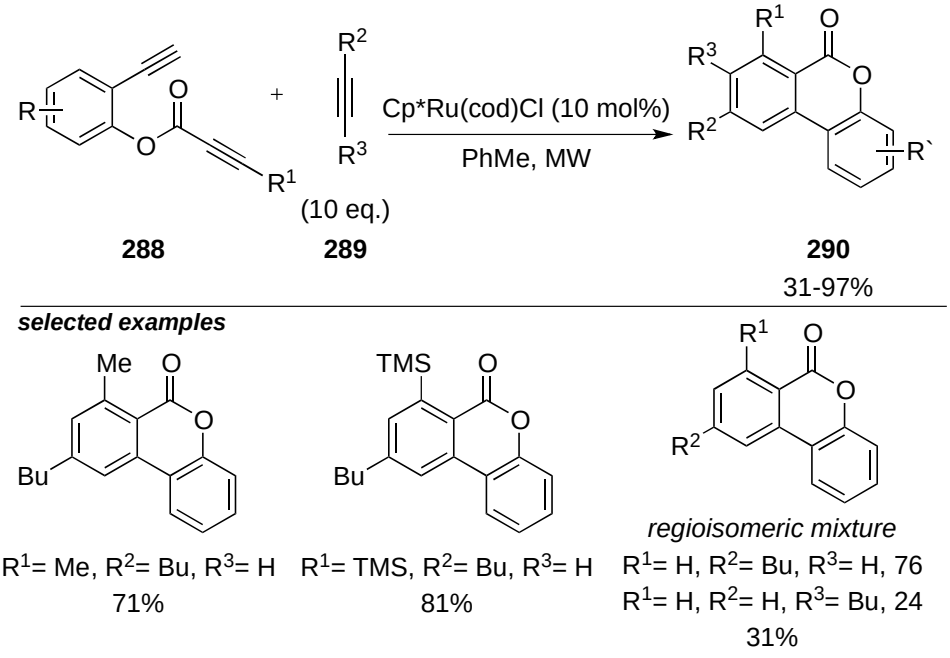


Figure 3.5

[149]Teske, J. A.; Deiters, A. Org. Lett. **2008**, *10*, 2195.

On the other hand, a Diels-Alder strategy has been employed for the construction of dibenzopyranones via a 2-step procedure (Figure 3.6).[150] First, Diels-Alder adduct **293** was isolated in good to high yields with moderate stereoselectivity. A subsequent basic treatment yielded intermediate **294**detected by ^{1}H-NMR spectroscopy, which upon exposure to SiO_2 aromatized to the desired 6-membered lactone **295**.

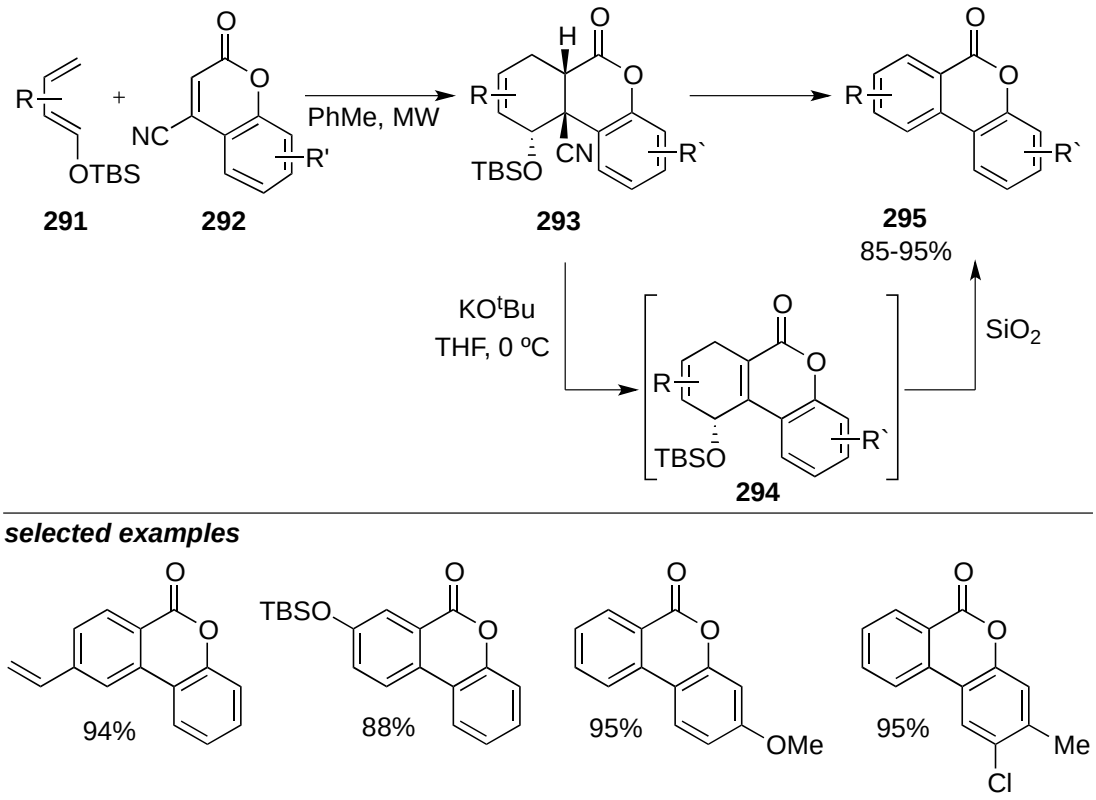


Figure 3.6

Alternatively, the Ison group developed a C-H functionalization protocol for the synthesis of 2-hydroxy-6H-benzo[c]chromen-6-ones from readily available benzoic acids using $[Cp^*IrCl_2]_2$ as catalyst and benzoquinone as coupling partner.[151] The mechanism proposed by the authors is depicted in Figure 3.7. A set of deuterium labeling experiments pointed towards**LXIII** as the active catalyst.Metallacycle **LXIV** could arise from an initial *ortho* C-H functionalization of **120**. Then, benzoquinone insertion followed by intramolecular proton transfer could result in aromatization of the benzoquinone ring, leading to species **LXVI**.A subsequent protonation of the benzoate could allow the intramolecular cyclization en route to **297**.

[150]Jung, M. E.; Allen, D. a. *Org. Lett.***2009**, *11*, 757.
[151]Engelman, K. L.; Feng, Y.; Ison, E. A. *Organometallics***2011**, *30*, 4572.

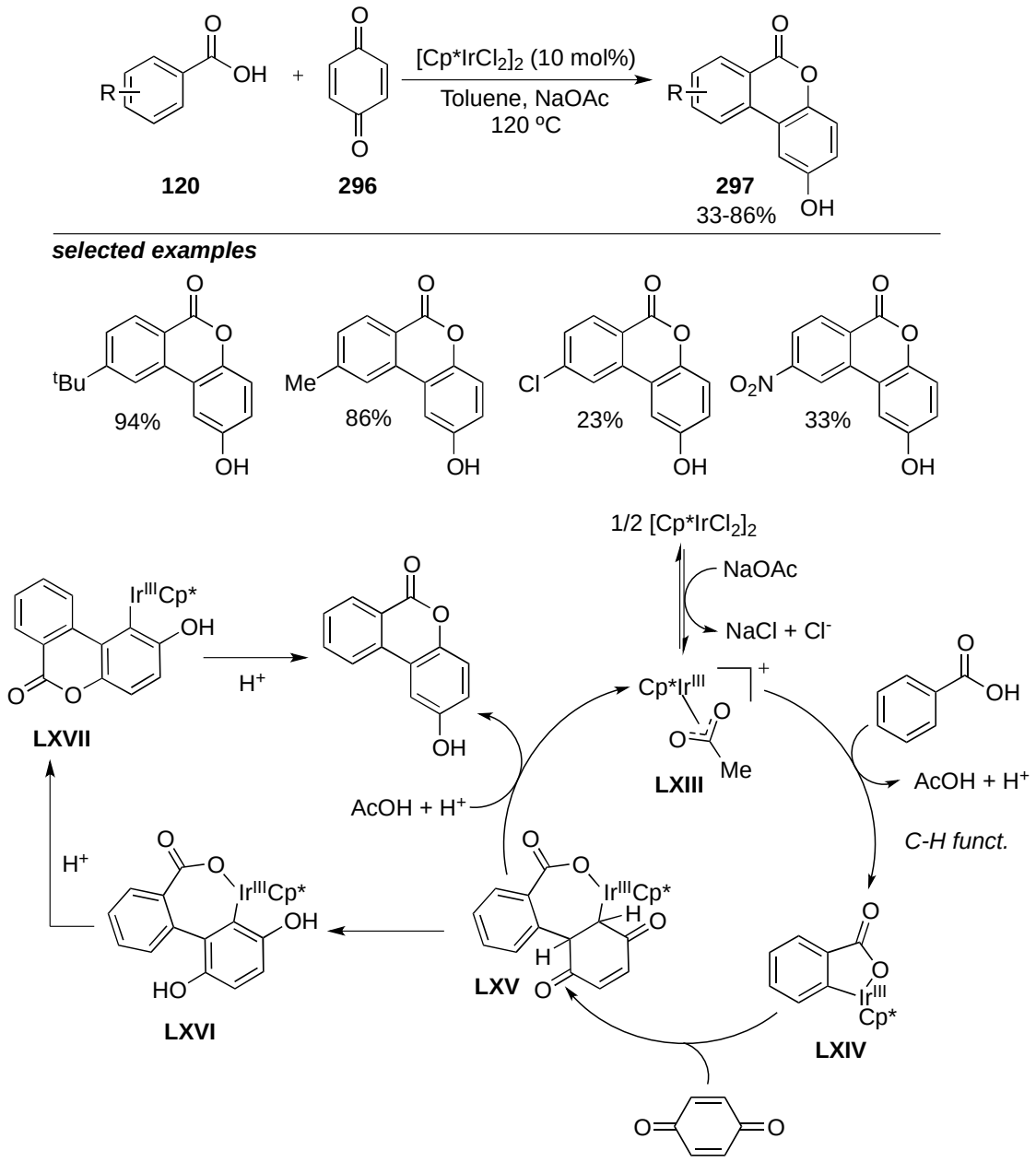

[Cp*IrCl2]2 (10 mol%)
Toluene, NaOAc
120 ºC
120
296
297
33-86%
selected examples
tBu
94%
Me
86%
Cl
23%
O2N
33%
1/2 [Cp*IrCl2]2
NaOAc
NaCl + Cl-
H+
LXVII
LXIII
AcOH + H+
C-H funct.
LXV
LXVI
LXIV

Figure 3.7

3.4 Results and discussion

Despite the utility of the protocols described in the previous section for the construction of dibenzopyranone core, the common synthetic maneuvering relies on the use of highly functionalized aryl halides as electrophiles with a suitable coupling partner. Besides, harsh reaction conditions are usually required for effectively promoting these transformations. That being set, it would be ideal to develop analternative new strategy that operates under milder reaction conditions and with high chemoselectivy profile. In *chapter 2* we described the formation of **298** via a challenging carboxyl-directed C(sp^3)-H bond functionalization event from **299**. In line with our research interest in the field of C-O bond formation *via* C-H functionalization processes, we wondered whether we could apply this concept for the direct synthesis of **300** from 2-arylbenzoic acids (Figure 3.8).

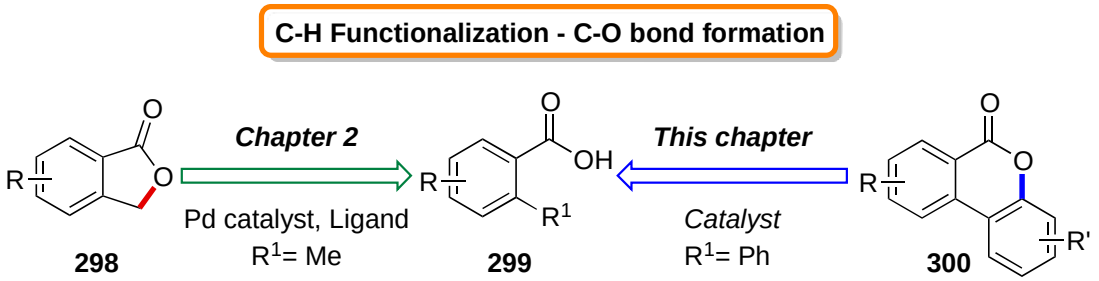


Figure 3.8

Moreover, we envisioned that remote hydroxylated arenes could be obtained after a subsequent hydrolysis event (Figure 3.9). These compounds rank among the most ubiquitous motifs in pharmaceuticals, agrochemicals and polymers, among others.[42]

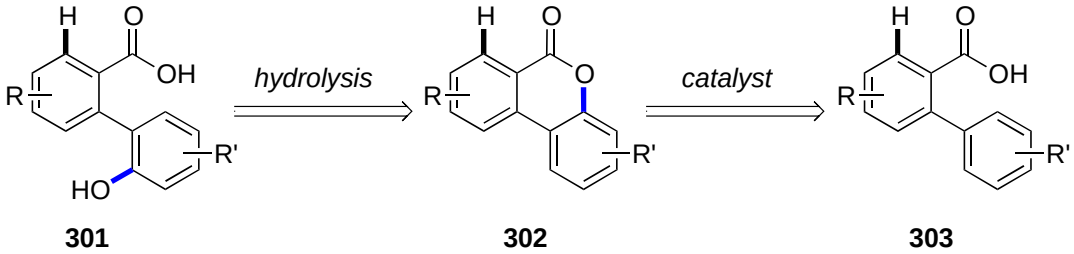


Figure 3.9

One of the main challenges associated with this transformation is the site-selectivity between H_a and H_b C-H bonds, as illustrated in Figure 3.10. At first, we hypothesized that a more stable and unproductive 5-membered metallacycle **LXIX** would be preferentially formed. In principle, however, we speculate that a 7-membered

metallacycle **LXVII** could be also formed, at least to some extend.We also wonder whether in the presence of a strong acid both **LXIX** and **LXX** would exist in equilibrium.

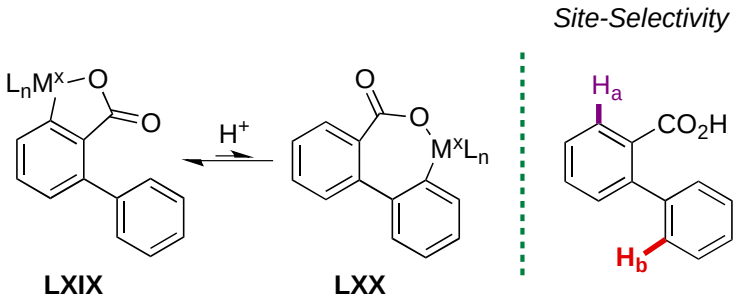


Figure 3.10

From a mechanistic point of view, we propose that two different catalytic cycles could come into play as depicted Figure 3.11. Both mechanisms would be initiated by coordination of benzoic acid **304** to the metal center to yield **LXXI**. We anticipated that such species would undergo C-H bond functionalization en route to **LXXII**. Then, C-O bond formation would afford product **305** under mechanistic hypothesis A and a final oxidation would recover the active catalyst. Alternatively, hypothesis B would consist of an oxidation of metallacycle **LXXII** to highly electrophilic metal species **LXXIII**, which upon C-O bond formation would deliver **305**and the active catalyst.

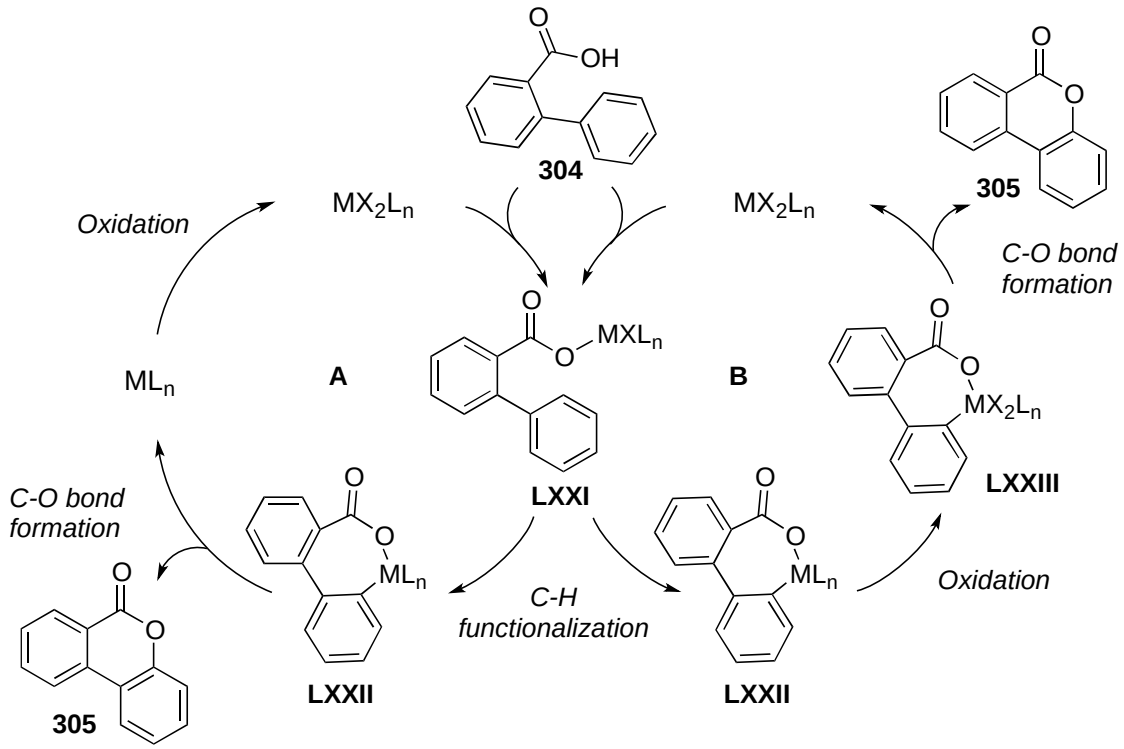


Figure 3.11

3.4.1 Pd-catalyzed synthesis of dibenzopyranones. Screenings of the reaction conditions

We expected that both C-H functionalization to yield a rather unstable 7 membered ring and the subsequent C-O bond formation would be rather problematic. We hypothesize that the inclusion of a strong acid might lower the activation barrier for C-H bond functionalization by forming an electrophilic metal center. We began our investigation with **304** as our model substrate and we studied the effect of several experimental variables such as palladium source, acid, solvent and temperature.

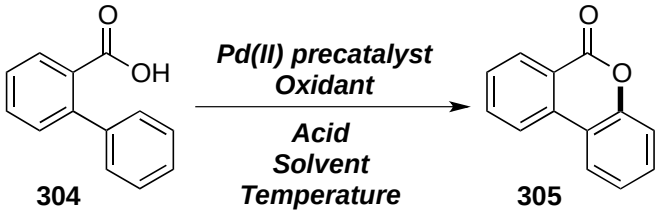
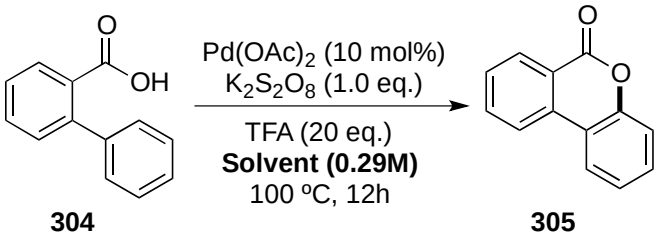


Figure 3.12

A series of reactions of **304** (0.25 mmol) were carried out in the presence of $Pd(OAc)_2$ (10 mol%), TFA as the acid (20 eq.), $K_2S_2O_8$ as the oxidant (1.0 eq.), solvent (0.5M) at 100 ºC. The reactions were analyzed by GC after 12h reaction time. As judged by the analysis of the crude reaction mixtures compiled in Table 3.1, apolar solvents gave no conversion to the final product (entries 1 and 2). The same trend was observed for ethereal or alcoholic solvents (entries 3-5). Moreover, polar coordinating solvents such as NMP or DMA (entries 6 and 7) resulted in no product formation. However, when chlorinated solvents like DCE or PhCl were employed, **305** was detected in 12% and 7% yield, respectively. In contrast, the use of TFA as solvent allowed for obtaining**305**in 35% yield (entry 11). This result is in line with the presumably ease for C-H functionalization in the presence of electrophilic palladium species.Interestingly, $PhCF_3$ was also competent for this transformationfurnishing **305** in 25% yield. This result issurprising taking into consideration that toluene as solvent gave no conversion to products.

Table 3.1. Solvent screening.[a]



304 **305**

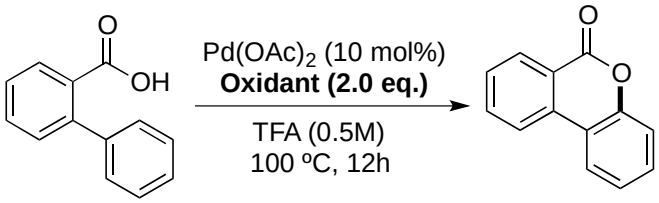
Entry	Solvent	305 (%)[b]
1	Mesitylene	0
2	Toluene	0
3	1,4-Dioxane	0
4	^{t}BuOH	0
5	^{t}Amyl-OH	0
6	NMP	0
7	DMA	0
8	AcOH	0
9	1,2-Dichloroethane (DCE)	12
10	PhCl	7
11	TFA	35
12	$PhCF_3$	25

[a] Benzoic acid (0.25 mmol), $Pd(OAc)_2$ (10 mol%), $K_2S_2O_8$ (1.0 eq.), TFA (20 eq.),solvent (0.5M), 100 ºC, 12h, argon atmosphere. [b] Yields were determined by GC analysis using dodecane as internal standard and after a basic treatment to remove TFA.

Next, we screened the impact of different oxidants in our Pd-catalyzed protocol when using TFA as the solvent of choice (Table 3.2). As shown in entries 1-5, both silver and copper salts were ineffective for this transformation, as well as benzoquinone (entry 6). When conducting the reaction under oxygen atmosphere (1 atm), no product was detected (entry 7). On the contrary, strong oxidants such as Oxone (26%), Selecfluor (43%) or NFSI (16%), were competent under the reactions conditions.[152] Interestingly, when $K_2S_2O_8$ was used at 25 ºC, the yield increased from 35% to 60% (entry 11 vs 12). When stirring at 100 ºC either **304** or isolated **305** in TFA no degradation was observed; these results suggest that the reaction might be inhibit by catalyst decomposition in such strong acidic and oxidizing conditions.

[152] It is worth mentioning that hypervalent I(III) oxidants were also tested on this reaction. Surprising results were obtained and will constitute the main topic of the next chapter of this thesis.

Table 3.2. Oxidant screening.[a]



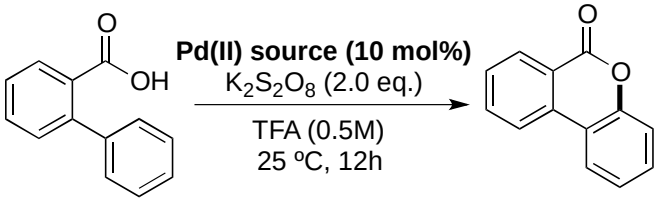
304 **305**

Entry	Oxidant	305 (%)[b]
1	Ag_2CO_3	0
2	AgOAc	0
3	Ag_2O	0
4	$CuCl_2$	0
5	$Cu(OAc)_2$	0
6	Benzoquinone (BQ)	0
7	O_2 (1 atm)	0
8	MnO_2	0
9	Oxone	26
10	Selectfluor	43
11	NFSI	16
12	$K_2S_2O_8$[c]	60

[a] Benzoic acid (0.25 mmol), $Pd(OAc)_2$ (10 mol%), Oxidant (2.0 eq.), TFA (0.5M), 100 ºC, 12h, argon atmosphere. [b] Yields were determined by GC analysis using dodecane as internal standard and after a basic treatment to remove TFA. [c] Reaction conducted at room temperature (25 ºC).

Later, we decided to explore whether the nature of the pre-catalyst can exert an influence in the reaction outcome or not. As summarized in Table 3.3, different Pd(II) precatalysts as $Pd(acac)_2$ (entry 2) or **306**-**309**(entries 3 to 5), were less efficient for this transformation. We could speculate that considering the chelating effect of olefins and acac to Pd(II), competing substrate binding might occur. On the other hand, when employing $PdCl_2X_2$ (X= MeCN, SMe, PhCN, cod) salts (entries 7 to 10), no **284** was detected by GC analysis. As expected, $Pd(TFA)_2$ or $Pd(OPiv)_2$ gave comparable yields to $Pd(OAc)_2$.

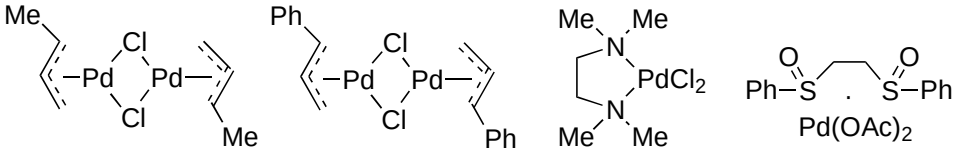
Table 3.3. Palladium precatalyst screening.[a]



304 **305**

Entry	Pd(II) source	305 (%)[b]
1	$PdCl_2$	7
2	$Pd(acac)_2$	33
3	**306**	17
4	**307**	20
5	**308**	12
6	**309**	24
7	$[PdCl_2(MeCN)_2]$	0
8	$[PdCl_2(SMe)_2]$	0
9	$[PdCl_2(PhCN)_2]$	0
10	$Pd(cod)Cl_2$	0
11	$Pd(TFA)_2$	62
12	$Pd(OPiv)_2$	61

[a] Benzoic acid (0.25 mmol), Pd(II) source (10 mol%), $K_2S_2O_8$ (2.0 eq.), TFA (20 eq.),solvent (0.5M), 25 ºC, 12h, argon atmosphere. [b] Yields were determined by GC analysis using dodecane as internal standard and after a basic treatment to remove TFA. [c] Reaction conducted at room temperature (25 ºC).

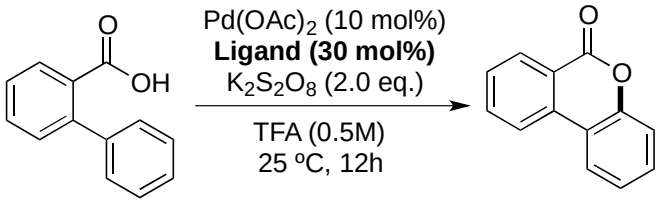


306 **307** **308** **309**

In line with the excellent results obtained in *chapter 2* by using carboxylic acids as ligands, we contemplate the possibility of adding carboxylic acids or aminoacids as additives in our reaction. We speculated that their inclusion might facilitate the rate of C-H functionalization, hence boosting the reactivity. The most relevant results are summarized in Table 3.4. Among all the aminoacids examined (entries 1-3), no significant improvement was observed. Subsequently, an array of carboxylics acids possessing different electronics and steric properties were tested. Alkyl carboxylic acids like PivOH, propionic acid or $AdCO_2H$ had no effect on the yield (entries 4,5 and 6). Analogously, hindered aryl carboxylic acids such as $MesCO_2H$, provided **305** in comparable yields (≈60%). Interestingly, the use of 2-fluorobenzoic acid (entry 8)

resulted in a slight increase in the yield,isolating 70% of dibenzopyranone**305**. While one might argue that such effect might be attributed to electronic effects, the lower yield when employing 2-nitrobenzoic acid as additive indicates otherwise (entry 9). At present we do not have any rationale behind these results. Not surprisingly, the use of significantly better σ-donors such as **310** and **311** resulted in lower conversions to **305** (entries 10 and 11).

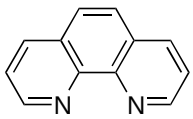
Table 3.4. Ligand effect.[a]



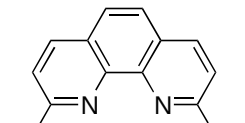
304 **305**

Entry	Ligand	305 (%)[b]
1	Ac-Ala-OH	50
2	Ac-Leu-OH	56
3	Ac-Ile-OH	62
4	PivOH	58
5	$CH_3CH_2CO_2H$	50
6	$AdCO_2H$	62
7	$MesCO_2H$	56
8	2-F-$C_6H_4CO_2H$	70
9	2-NO_2-$C_6H_4CO_2H$	45
10	**310**	44
11	**311**	10

[a] Benzoic acid (0.25 mmol), $Pd(OAc)_2$(10 mol%), ligand (30 mol%), $K_2S_2O_8$ (2.0 eq.), TFA (0.5M), 25 ºC, 12h, argon atmosphere. [b] Yields were determined by GC analysis using dodecane as internal standard and after a basic treatment to remove TFA. [c] Reaction conducted at room temperature (25 ºC).



310

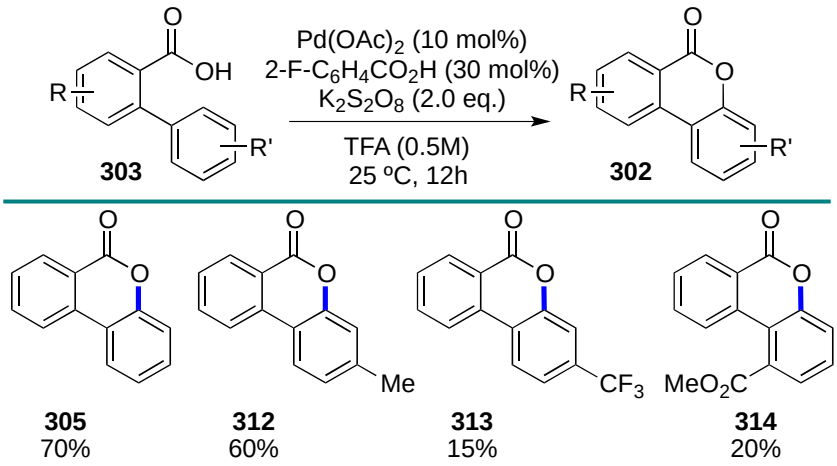


311

As a conclusion, the best conditions found consisted on $Pd(OAc)_2$ (10 mol%) as precatalyst, 2-F-$C_6H_4CO_2H$ (30 mol%) as additive, $K_2S_2O_8$ (2.0 eq.) as oxidant with TFA (0.5M) as solvent at 25 ºC. Full conversion of the corresponding starting material was detected by HPLC analysis, thus indicating unproductive reaction pathways. However, no byproduct for instance biphenyl was observed under these reactions conditions. All efforts made for improving the 70% yield obtained were

unfruitful.Furthermore, the use of TFA as solvent makes the process not yet synthetically attractive, particularly when employing highly functionalized substrates. A preliminary scope showed moderate yields for substrates **305** and **312**, whereas **313**and**314**, bearing electron-withdrawing groups in the bottom ring provided poor yields. In light of these results, we wondered whether we could effectively perform our C-H functionalization reaction using a different catalytic system.

Table 3.5. Pd-catalyzed C-H functionalization/C-O bond formation.[a],[b]



[a] Benzoic acid (0.25 mmol), 2-F-$C_6H_4CO_2H$ (30 mol%), $K_2S_2O_8$(2.0 eq.), TFA (0.5M), 25 ºC, 12h, argon atmosphere.[b] Isolated yields, average of two independent runs.

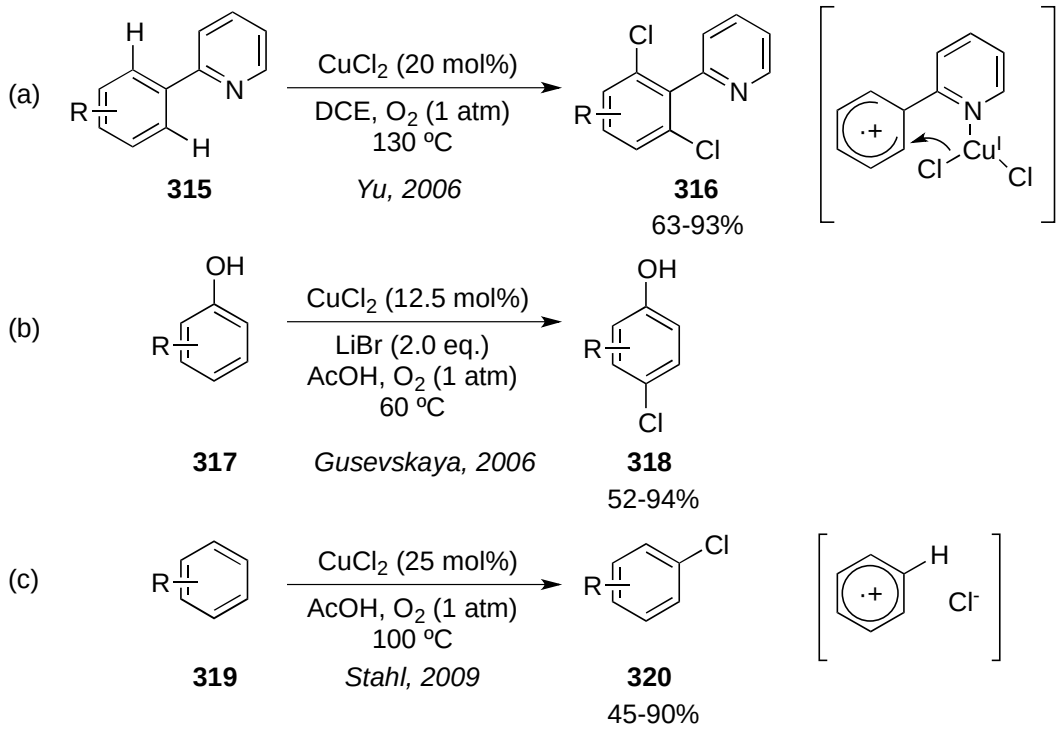
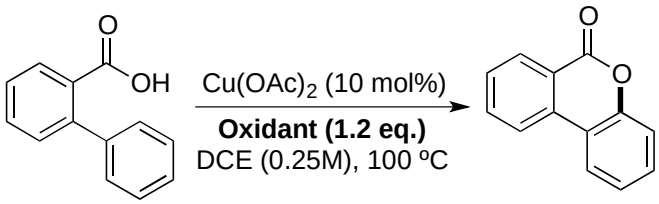


Figure 3.13

3.4.2 Cu-screenings for the synthesis of dibenzopyranones.

A non-negligible number of electron-rich arenes are particularly susceptible to one-electron oxidation. Many oxidants, including Cu(II) salts, are able to promote oxidative coupling reactionsinitiated by single-electron transfer (SET). Prompted by the work of Yu,[61] Gusevskaya[153] and Stahl[154] on copper-catalyzed chlorination of electron rich and neutral aromatic compounds (Figure 3.12), we considered the possibility of inducing the C-O bond formation by using copper complexes under oxidative conditions.

Table 3.6. Screening of oxidants.[a]



304 **305**

Entry	Oxidant	Conv.(%)[b]	305 (%)[b]
1	^{t}BuOOH (5M in decanes)	22	0
2	H_2O_2	10	0
3	BQ	31	0
4	DDQ	35	0
5	$CoBr_2$	25	0
6	O_2	16	0
7	MnO_2	14	0
8	$K_2S_2O_8$	18	0
9	Oxone	15	0
10	^{t}BuOOBz	25	11
11	$[PhCO_2]_2$	33	20

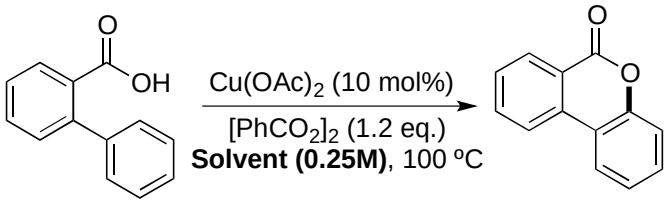
[a] Benzoic acid (0.25 mmol), $Cu(OAc)_2$ (10 mol%), Oxidant (1.2 eq.), DCE (0.25M, 100 ºC, 12h, argon atmosphere. [b] Conversions and yields were determined by GC analysis using decane as internal standard.

An initial set of reactions of (0.25 mmol) of **304**, in the presence of $Cu(OAc)_2$ (10 mol%), oxidant (1.2 eq.) in 1,2-dichloroethane (0.25M), at 100 ºC was analyzed by GC after 12h reaction time. As judged by our initial screening in Table 3.6, low conversions of **304** were systematically observed with all the oxidants analyzed. Hydroperoxides (entries 1 to 2) gave no product under these conditions. The same trend was detected for oxidants such as BQ, DDQ, $CoBr_2$, O_2, MnO_2, $K_2S_2O_8$ or Oxone (entries 3 to 9). To

[153] (a) Menini, L.; Gusevskaya, E. V. *Chem. Commun.***2006**, 209. (b) Menini, L.; da CruzSantos, J. C.; Gusevskaya, E. V. *Adv. Synth. Catal.***2008**, *350*, 2052.
[154] Yang, L.; Lu, Z.; Stahl, S. S. *Chem. Commun.***2009**, 6460.

our delight, when employing either ^{t}BuOOBz or $[PhCO_2]_2$, 11% and 20% of **305** was observed, respectively. Based on these results, we decided to continue our optimization with dibenzoyl peroxide as the oxidant.

Table 3.7. Solvent screening.[a]



304 **305**

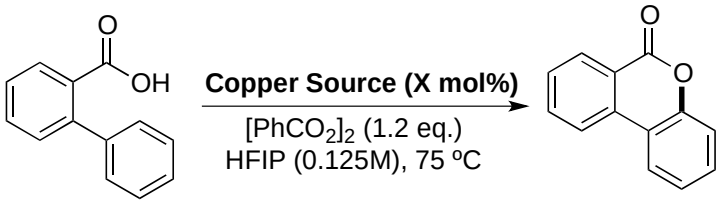
Entry	Solvent	Conv.(%)[b]	305 (%)[b]
1	Toluene	48	14
2	*o*-Xylene	59	16
3	Mesytilene	46	10
4	NMP	76	0
5	DMF	76	0
6	DMSO	75	0
7	^{t}Amyl-OH	33	4
8	MeOH	35	2
9	^{i}PrOH	100	0
10	MeCN	32	8
11	1,4-Dioxane	61	21
12	PhOMe	100	51
13	PhCl	55	47
14	$PhNO_2$	57	6
15	PhBr	100	16
16	PhF	100	18
17	$PhCF_3$	45	20
18	C_6H_6	100	67
19	CF_3CH_2OH	49	30
20	HFIP	100	80

[a] Benzoic acid (0.25 mmol), $Cu(OAc)_2$ (10 mol%), $[PhCO_2]_2$ (1.2 eq.), Solvent (0.25M, 100 ºC, 12h, argon atmosphere. [b] Conversions and yields were determined by GC analysis using decane as internal standard. HFIP: 1,1,1,3,3,3-Hexafluoro-2-propanol.

Afterwards, a quick temperature and concentration survey revealed 75 ºC as optimal, together with 0.125M of HFIP as the ideal concentration, hence providing **305** in 98% GC yield. A final copper source screening (Table 3.8) showed that catalyst loading could be decreased to 5 mol% (entry 1) without loss in efficiency. Other Cu(II)

catalyst such as $Cu(OTf)_2$ or $CuBr_2$ were less competent for this reaction. Interestingly, Cu(I) catalyst could also be employed without significant decrease in the yield (entry 5).

Table 3.8. Cu source screening.[a]



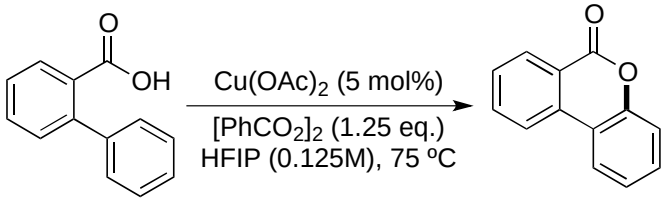
304 **305**

Entry	Cu source (X mol%)	Conv.(%)[b]	284 (%)[b]
1	$Cu(OAc)_2$ (5 mol%)	100	97
2	$Cu(OAc)_2$ (10 mol%)	100	98
3	$Cu(OTf)_2$(10 mol%)	100	21
4	$CuBr_2$(10 mol%)	100	79
5	CuOAc (10 mol%)	100	88

[a] Benzoic acid (0.25 mmol), Cu source (X mol%), $[PhCO_2]_2$ (1.25 eq.), HFIP (0.125M), 75 ºC, 12h, argon atmosphere. [b] Conversions and yields were determined by GC analysis using decane as internal standard.

Next, we decided to check whether a background reaction in the absence of any of the reagents used would also deliver **305**. As shown in Table 3.9 we found that only 15% yield was detected in the absence of metal source (entries 1 and 2).

Table 3.9. Control Experiments.[a]



304 **305**

Entry	$Cu(OAc)_2$	$[PhCO_2]_2$	Conv. (%)[b]	305 (%)[b]
1	✗	✔	20	15
2	✔	✗	0	0
3	✗	✗	0	0
4	✔	✔	100	97

[a] Benzoic acid (0.25 mmol), $Cu(OAc)_2$ (5 mol%), $[PhCO_2]_2$ (1.25 eq.), HFIP (0.125M, 75 ºC, 12h, argon atmosphere. [b] Conversions and yields were determined by GC analysis using decane as internal standard.

3.4.3 Synthesis of the starting benzoic acids

Having established the optimized reaction conditions, we set out to examine the scope of this transformation by preparing a wide variety of 2-phenylbenzoic acid derivatives. Several carboxylics acids containing different functional groups as well as substitution patterns were synthetized. As for the preparation of substrates possessing different groups on the bottom aryl ring, the same two-step procedure furnished compounds **324**-**332** (Figure 3.14). First, a Suzuki-Miyaura coupling under Buchwald conditions[155] between aryl bromide **321** and different boronic acids **322**, followed by a hydrolysis event yielded the desired acids in moderate to good yields over 2 steps.

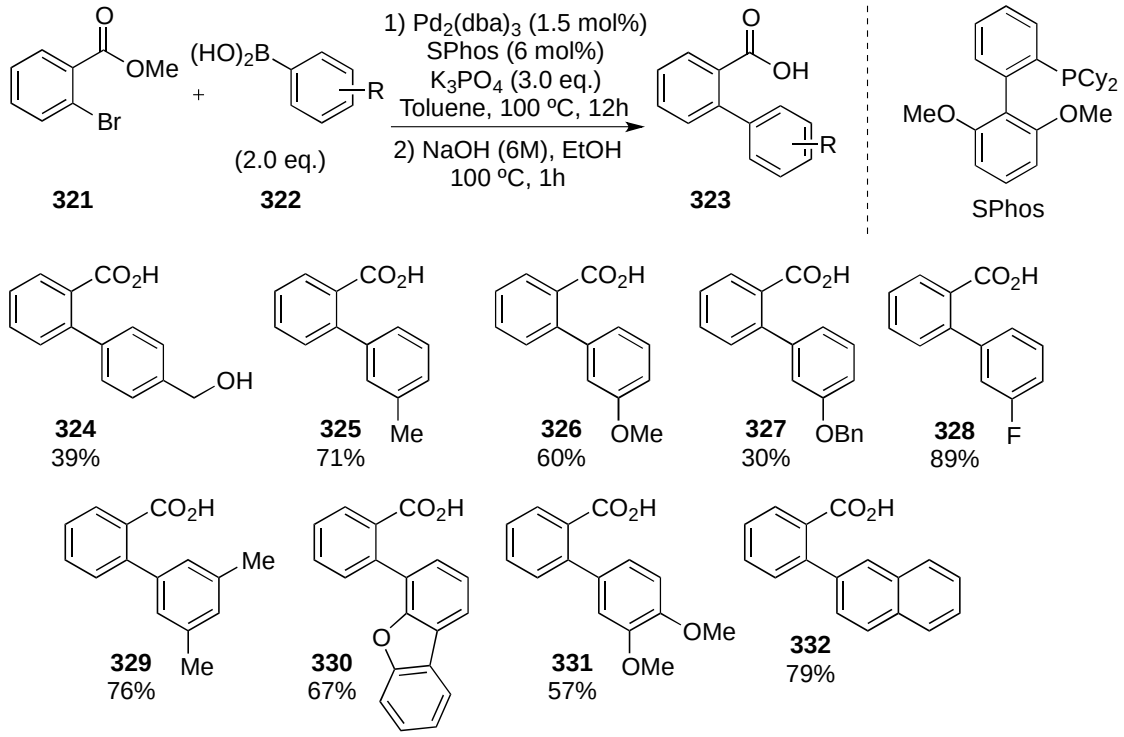
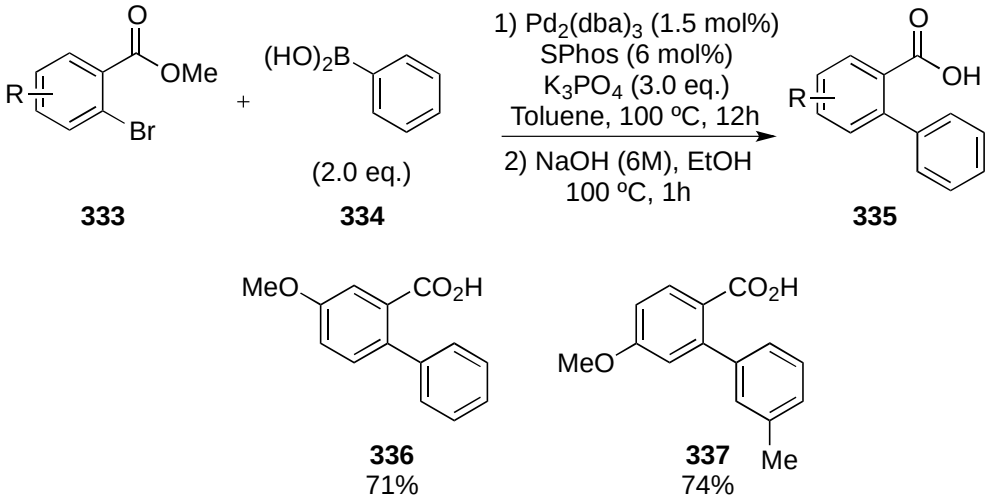


Figure 3.14

Afterwards, we focused our effort on modifying the upper aryl ring. Using a similar Suzuki-Miyaura approach as depicted in Figure 3.15, **336** and **337**were obtainedin71% and 74% overall yield.

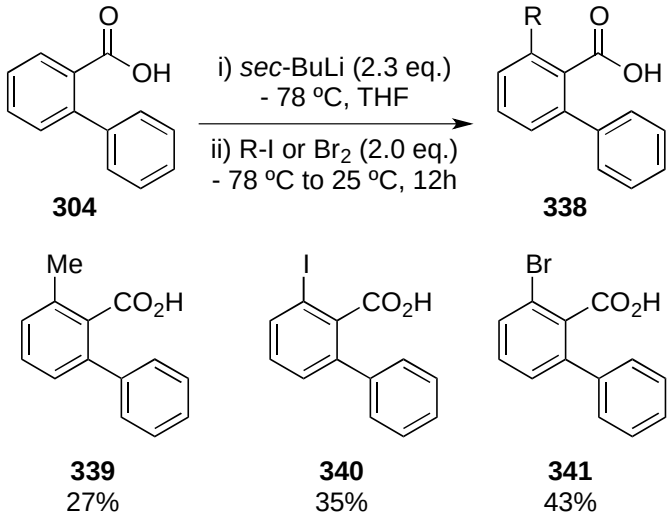
[155]Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.***2005**, *127*, 4685.

The installation of substituents in*ortho*-position to the carboxylic acid was easily accomplished in one step employing the procedure reported by Zuckerbraun.[156] Treatment of **304** with *sec*-BuLi followed by electrophilic quenching allowed the synthesis of **339**-**341**, albeit in low yields. However, this procedure was easily scalable and multigram quantities were obtained in all the cases analyzed (Figure 3.16).



333 **334** **335** **336** 71% **337** 74%

Figure 3.15

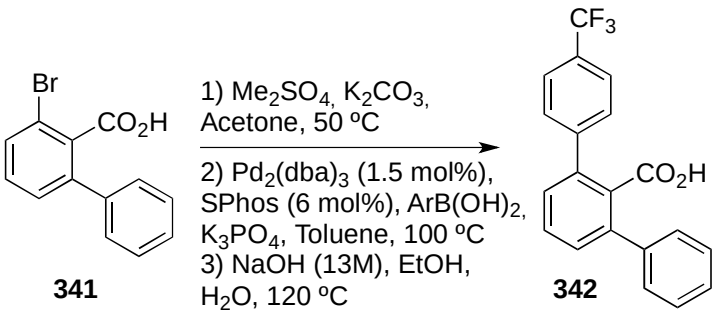


304 **338** **339** 27% **340** 35% **341** 43%

Figure 3.16

Compound**342**, was easily prepared from**341**in a two-step procedure. As shown in Figure 3.17, initial methyl ester protection of the carboxylic acid followed by Suzuki-Miyaura coupling under Buchwald conditions provided and intermediate that was hydrolyzed in aqueous NaOH, thus providing **341** in 45% yield over 3 steps.

[156]Parham, W.E.; Moulton, W.E.; Zuckerbraun, A. *J. Org. Chem.***1956**, *21*, 72.

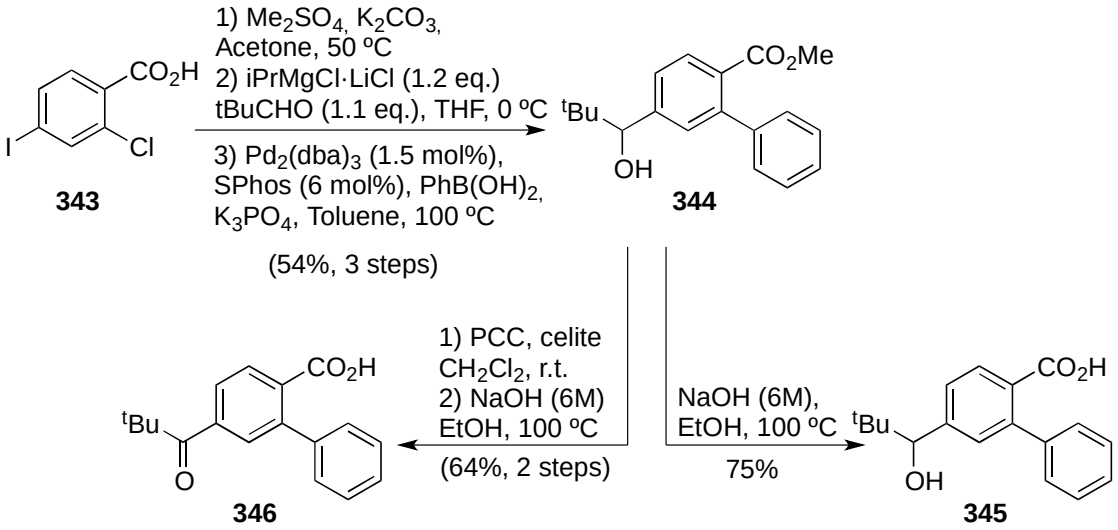


341 **342**

(45%, 3 steps)

Figure 3.17

Following up a similar synthetic sequence described in Figure 3.17, **344**was prepared in a 54% overall yield by using Knochel-type Grignards generated in situ. Then, saponification of **344** afforded **345** possessing a benzylic alcohol motif in *para* position to the carboxylic acid. A simple oxidation promoted by PCC followed by hydrolysis in basic media furnished a carboxylic acid with a ketone in the upper ring (**346**).



343 **344**

(54%, 3 steps)

(64%, 2 steps) 75%

346 **345**

Figure 3.18

Alternatively, aldehyde **347** served as a platform for introducing sensitive functional groups such as OAc or OTs, incompatible with a final hydrolysis event. As in the previous cases, the biphenyl motif was forged *via* a Pd-catalyzed Suzuki-Miyaura coupling between **347** and phenyl boronic acid as coupling partner. After standard alcohol protection with AcCl or TsCl, a Pinnick oxidation was conducted affording **349** and **350**in 25% and 79% overall yield, respectively (Figure 3.19).

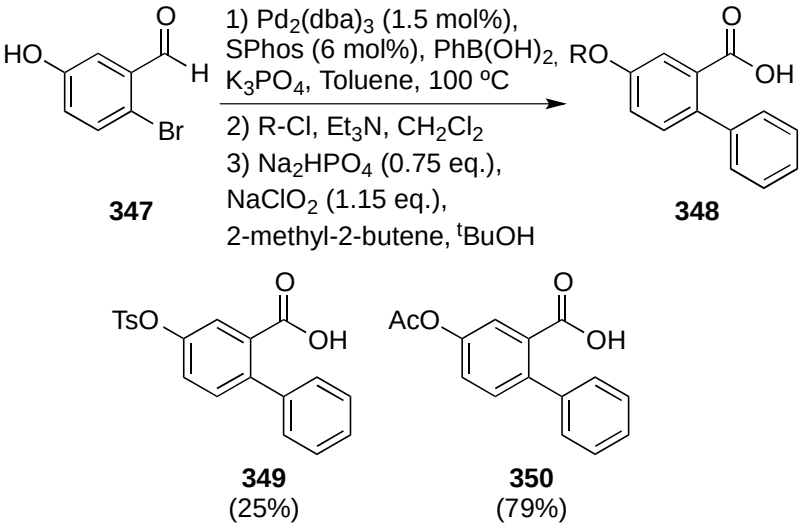


Figure 3.19

Finally, we wanted to check whether our methodology could be extended to non-aromatic carboxylic acids. For that purpose, compound **353** was prepared in 3 steps from cyclohexanone, as depicted in Figure 3.20. Treatment of **351** with PBr_3 and DMF in $CHCl_3$ furnished alkenyl bromide **352** in 65% isolated yield. After introduction of the phenyl motif via Pd-catalyzed Suzuki-Miyaura coupling, a final oxidation event yielded **315** in moderate yield over 2 steps.

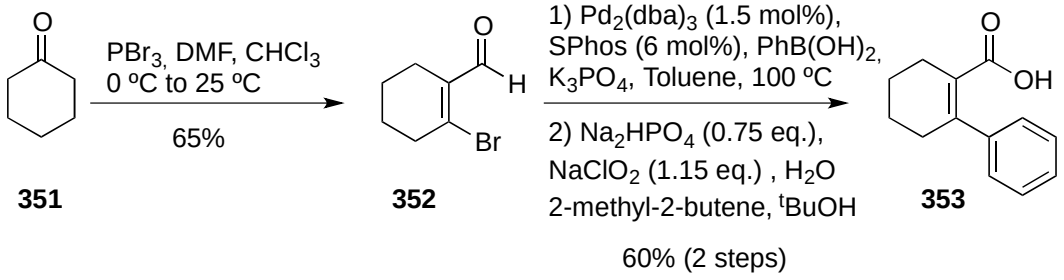


Figure 3.20

3.4.4 Scope of the reaction for the synthesis of dibenzopyranones

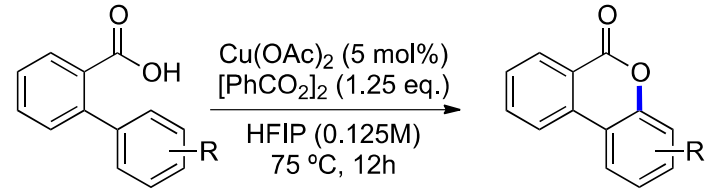
With a family of 2-phenylbenzoic acids in hand, we turned our attention to examine the scope of this transformation towards the synthesis of dibenzopyranones. As shown in Table 3.10, a host of benzoic acids could all be coupled with good to excellent

yields. While good results were found for electron-rich or neutral arenes, low yields were obtained with electron-deficient rings (**313**). Particularly noteworthy was the tolerance of our method for benzyl alcohols (**355**); under the limits of detection, no traces of the corresponding aldehyde or carboxylic acid were found in the crude reaction mixture. This is especially important, as primary alcohols are susceptible towards oxidation in the presence of copper catalyst and peroxides.[157] Similarly, benzyl ethers were tolerated as well (**358**). When using unsymmetrical substrates, moderate to good regioselectivities could be obtained. In all cases examined, the most accessible C-H bond was preferentially activated (**356-359** and **362**). As shown for **363**, a single isomer was obtained for naphthalene backbones. Moreover, introducing a substituent in *ortho* position to the targeted C-H bond did not hinder the reaction, as illustrated by the successful preparation of **360**. Heterocycles such as **361** could equally be accommodated under our optimized reaction protocol. Finally, we found that the presence of O_2 (1 atm) had a deleterious effect for reactivity, as illustrated by the significant lower yields of **305**, **312**, **358**and **363**.

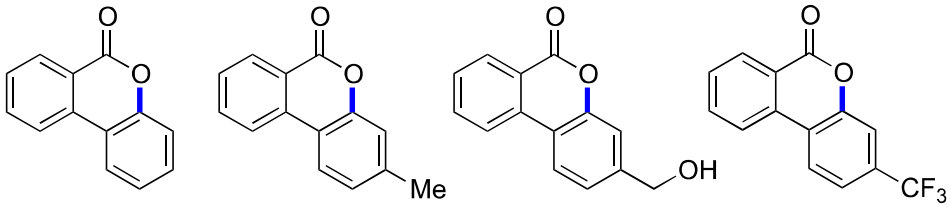
Next, we studied the electronic and steric effects on the upper aryl ring (Table 3.11). Both, electron-donating (**366** and **367**) and -deficient were well accommodated giving the corresponding products in moderate to high yields. The chemoselectivity profile of our method was nicely illustrated by the fact that sulfonates (**367**), esters (**368**), alcohols (**369**) or ketones (**372**) were well tolerated, giving access to the functionalized benzolactones in a straightforward fashion. As shown for **367** and **373**, the presence of aryl halides or pseudohalides did not hinder the reaction, thus leaving ample opportunities for further functionalization via standard cross-coupling methodologies. This protocol could also be applied to nonaromatic carboxylic acids (**370**), albeit in lower yields.

[157] For selected examples, see: (c) Kumpulainen, E. T. T.; Koskinen, A. M. P. *Chem.Eur. J*. **2009**, *15*, 10901. (b) Hoover, J. M.; Stahl, S. S. *J. Am. Chem. Soc*. **2011**, *133*, 16901. (c) Hoover, J. M.; Ryland, B. L.; Stahl, S. S. *J. Am. Chem. Soc*. **2013**, *135*, 2357.

Table 3.10. Substitution effects on the bottom ring.[a],[b]



323 **354**

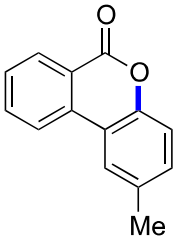


305 95%, 60%[c]

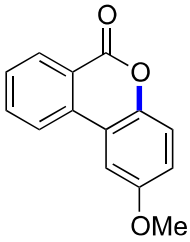
312 88%, 46%[c]

355 60%

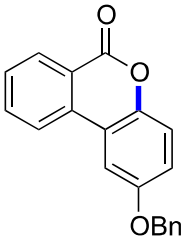
313 22%



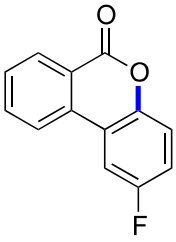
356 79%[d]



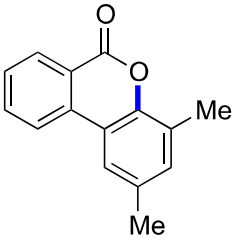
357 76%[e]



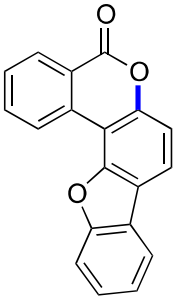
358 98%[f], 71%[c]



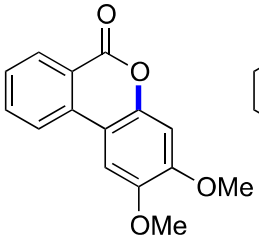
359 49%[g]



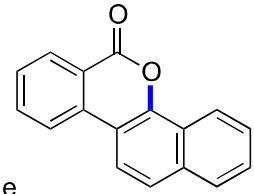
360 76%



361 70%



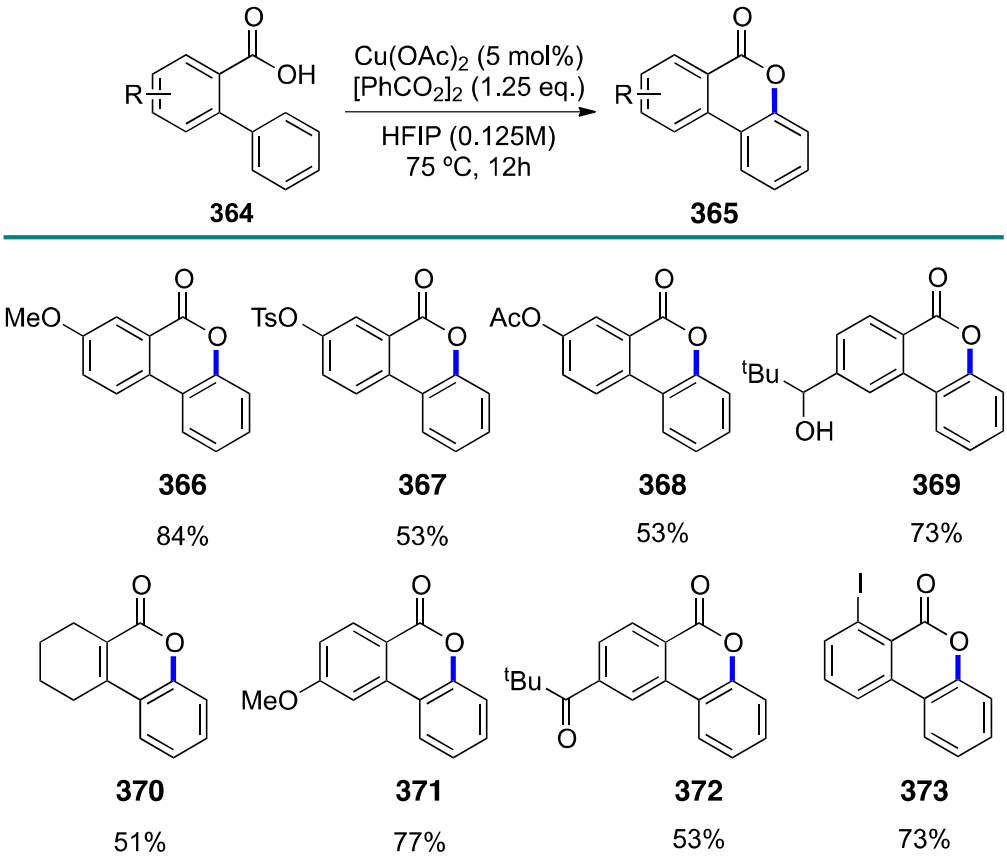
362 56%[h]



363 84%, 75%[c]

[a] Benzoic acid (0.25 mmol), $Cu(OAc)_2$ (5 mol%), $[PhCO_2]_2$ (1.25 eq.), HFIP (0.125M), 75 ºC, 12h, argon atmosphere. [b] Isolated yields, average of two runs. [c] O_2 atmosphere was used instead of Ar. [d] Isolated as a regioisomeric mixture (3:1). [e] Isolated as a regioisomeric mixture (5:1). [f] Isolated as a regioisomeric mixture (3:1). [g] Isolated as a regioisomeric mixture (4:1). [h] Isolated as a regioisomeric mixture (6:1).

Table 3.11. Substituent effects on the upper ring.[a],[b]

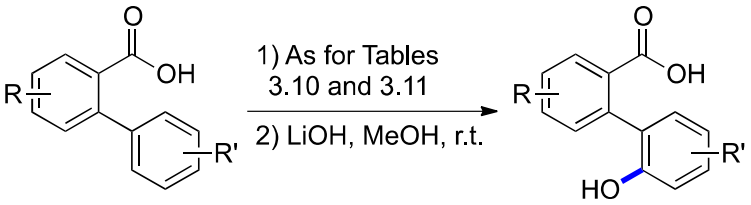


[a] Benzoic acid (0.25 mmol), $Cu(OAc)_2$ (5 mol%), $[PhCO_2]_2$ (1.25 eq.), HFIP (0.125M), 75 ºC, 12h, argon atmosphere. [b] Isolated yields, average of two runs.

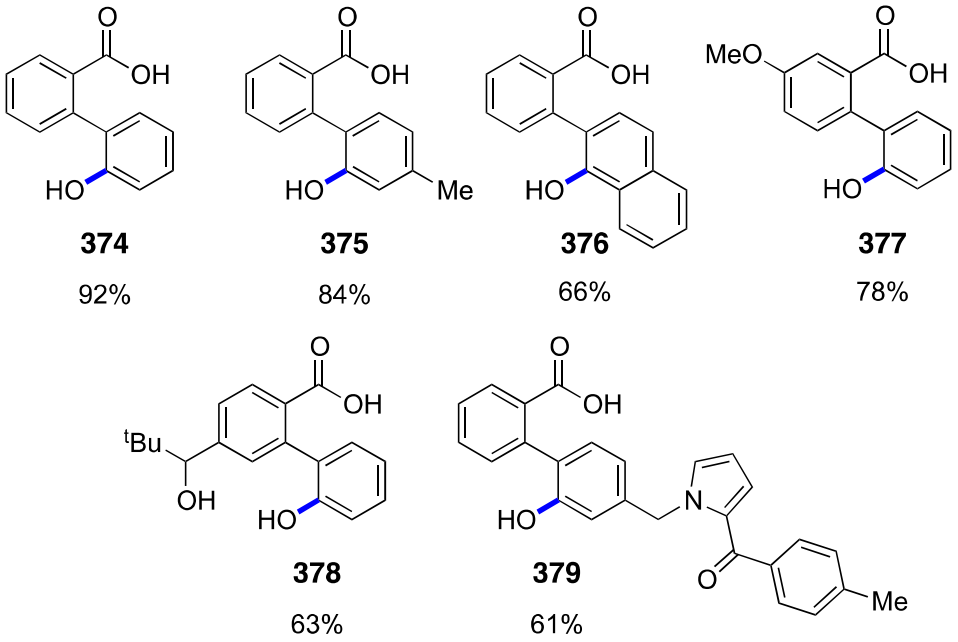
In view of the results compiled in Tables 3.10 and 3.11, we envisioned that remote hydroxylated arenes could be obtained upon a simple hydrolysis event. Consequently, Table 3.12 demonstrated the possibility of accessing different hydroxyacids from the corresponding lactone precursors in a sequential manner. The addition of LiOH at room temperature was found to be crucial for obtaining quantitative conversion to products. Of particular importance is the successful preparation of **379**, since the product lacking the hydroxyl group turned out to be a promising candidate to prevent arteriosclerosis.[158]

[158]Tomokazyu, N. Therapeutic agent for hyperlipemia, arteriosclerosisand/or metabolic syndrome. JP2006182668(A), July 13,2006.

Table 3.12. Remote C-H hydroxylation.[a],[b]



303 **301**



374 92%

375 84%

376 66%

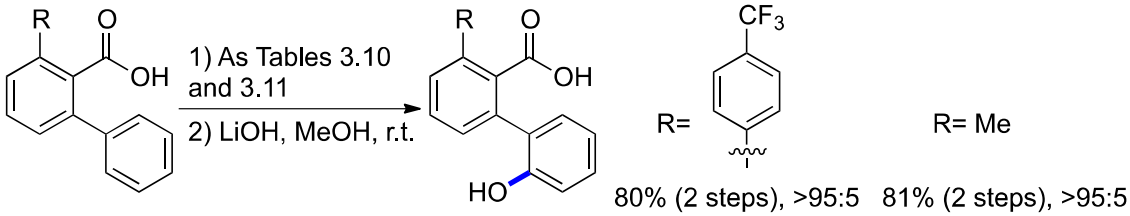
377 78%

378 63%

379 61%

[a] As for Tables 3.9 and 3.10 [b] Overall yield (2 steps).

On the basis of the results of Tables 3.10-3.12, we speculate that high selectivity levels among different C-H bonds could be achieved based on subtle electronic effects. For instance, as shown in Figure 3.21, **381** was obtained as the only isolated product in which the most electron-rich aromatic ring reacted at faster rate. Similarly, we obtained high selectivity profile between benzylic C(sp^3)- and C(sp^2)-H bond, as **382** was formed quantitatively.



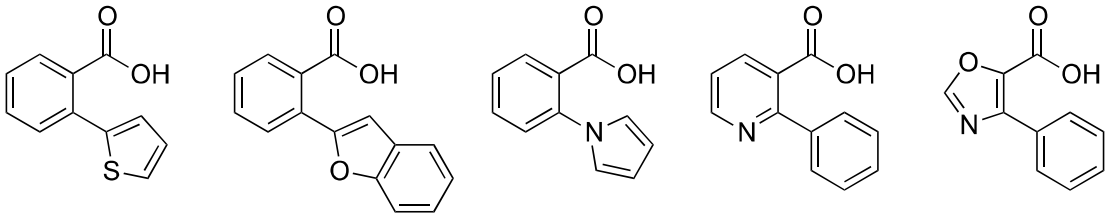
380

381 80% (2 steps), >95:5

382 81% (2 steps), >95:5

Figure 3.21

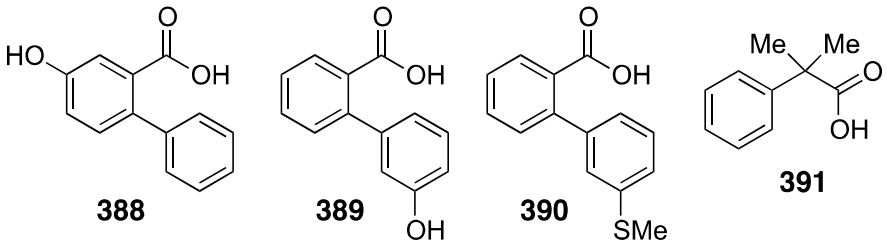
Despite the high chemoselectivity profile of our Cu-catalyzed C(sp^2)-H functionalization/C-O bond formation, we found that some substrates could not be cyclized under our reaction conditions. Figure 3.22 manifests a clear incompatibility with heterocycles (**383**-**387**). In all cases, no product was observed and degradation of the corresponding starting material was detected by analysis of the crude reaction mixtures. We believe that nitrogencontaining heterocycles such as **386** or **387**can bind strongly to copper, thus deactivating the catalyst. Furthermore, partial oxidation of S or N atoms or the corresponding electron-rich aromatic ring in **383**-**385**could lead to decomposition pathways.



383 **384** **385** **386** **387**

Figure 3.22

As shown in Figure 3.23, phenols could not be coupled under our oxidative conditions. However, we never detected benzoquinone type products when submitting **388** or **389**under our reaction conditions. In both cases, degradation of the starting carboxylic acid was observed. In the same line, benzothioethers **390** are also not competent for this reaction as well as alkyl carboxylic acids **391**. The latter, was recovered quantitatively from the crude reaction mixture.



388 **389** **390** **391**

Figure 3.23

3.4.5 Mechanistic considerations

In order to gain more insights into the mechanism, we decided to measure both intra- and intermolecular kinetic isotope effects. Deuterated substrates **394** and **395**

were synthetized in a straightforward fashion by an initial Suzuki-Miyaura coupling followed by basic hydrolysis (Figure 3.24).

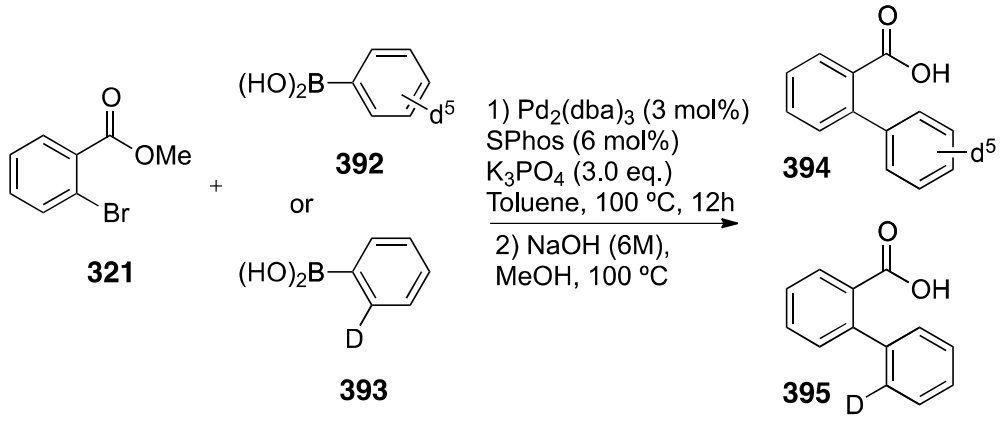
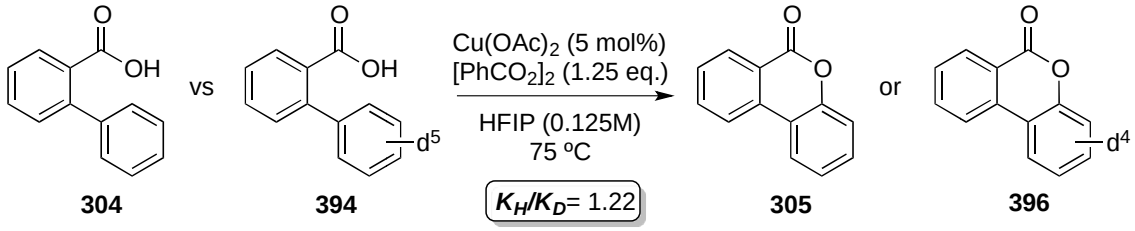


Figure 3.24

We studied the intramolecular isotope effect by comparing the initial rates of **304** and **394**. As shown in Figure 3.25, **304** reacted at a very similar rate than its deuterated analog. Indeed, such results can be translated into a K_H/K_D= 1.22, suggesting that C-H bond cleavage might not be involved in the rate-determining step.



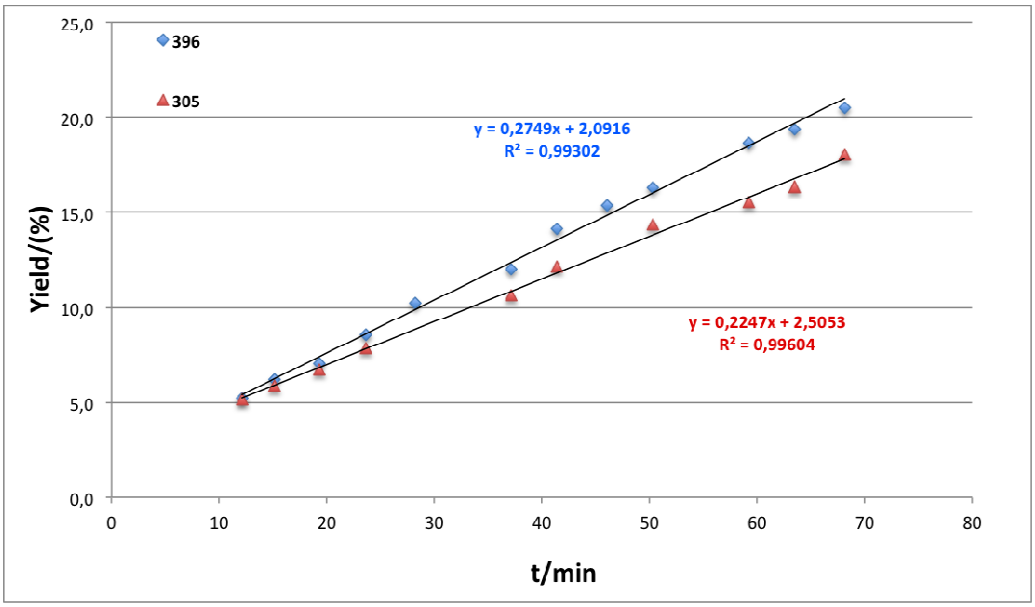


Figure 3.25

Additionally, intramolecular competition experiments (Figure 3.26) are in agreement with C-H bond functionalization not been rate-limiting step in the catalytic cycle, as a K_H/K_D= 1.50 was found.

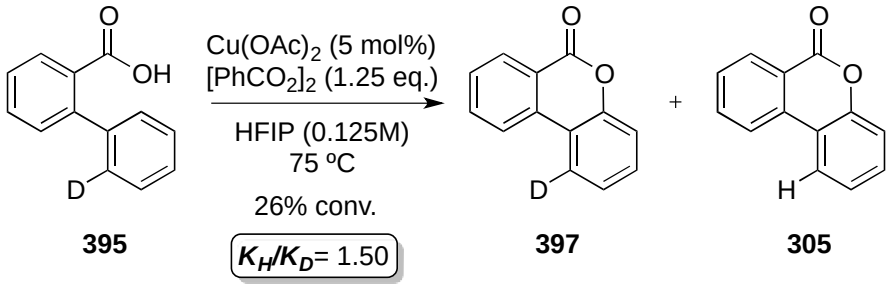
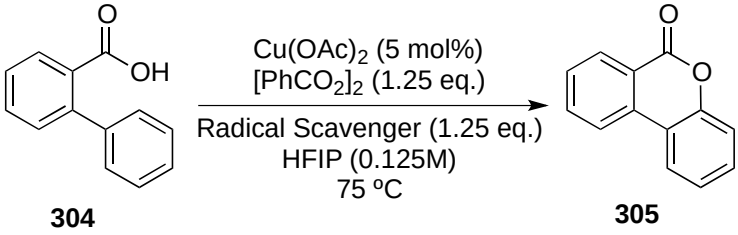
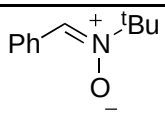


Figure 3.26

On the other hand, we found that the reaction of **304** was significantly inhibited by the addition of radical scavengers such as TEMPO, BHT, 1,1-diphenylethilene and N-*tert*-butyl-*α*-phenylnitrone, as illustrated in Table 3.13. Although these results are not conclusive, these experiments might suggest that single-electron transfer processes come into play.

Table 3.13. Radical scavenger tests.[a]



Entry	Radical Scavenger	305 (%)[b]
1	TEMPO	0
2	1,1-Diphenylethylene	3
3	BHT	17
4		20

[a] Benzoic acid (0.25 mmol), $Cu(OAc)_2$ (5 mol%), $[PhCO_2]_2$ (1.25 eq.), Radical scavenger (1.25 mmol), HFIP (0.125M), 75 ºC, 12h, argon atmosphere. [b] Yields were determined by GC analysis using decane as internal standard.

Even though and in depth-discussion should await further investigations, at present we contemplate two different mechanistic scenarios, as depicted in Figure 3.27. First, the reaction of Cu(II) with $[PhCO_2]_2$and **304**would give rise to a Cu(III) benzoate **LXXIV** and

a benzyloxy radical that could undergo CO_2 extrusion. Subsequently, a H-atom abstraction (HAA) event could afford **LXXV**or **LXXVI**that ultimately engages a C-O bond forming reaction (path a). Alternatively, a single-electron transfer (SET) process would give radical-cation species **LXXVII**, which would be transformed into **305** by C-O bond forming reaction.

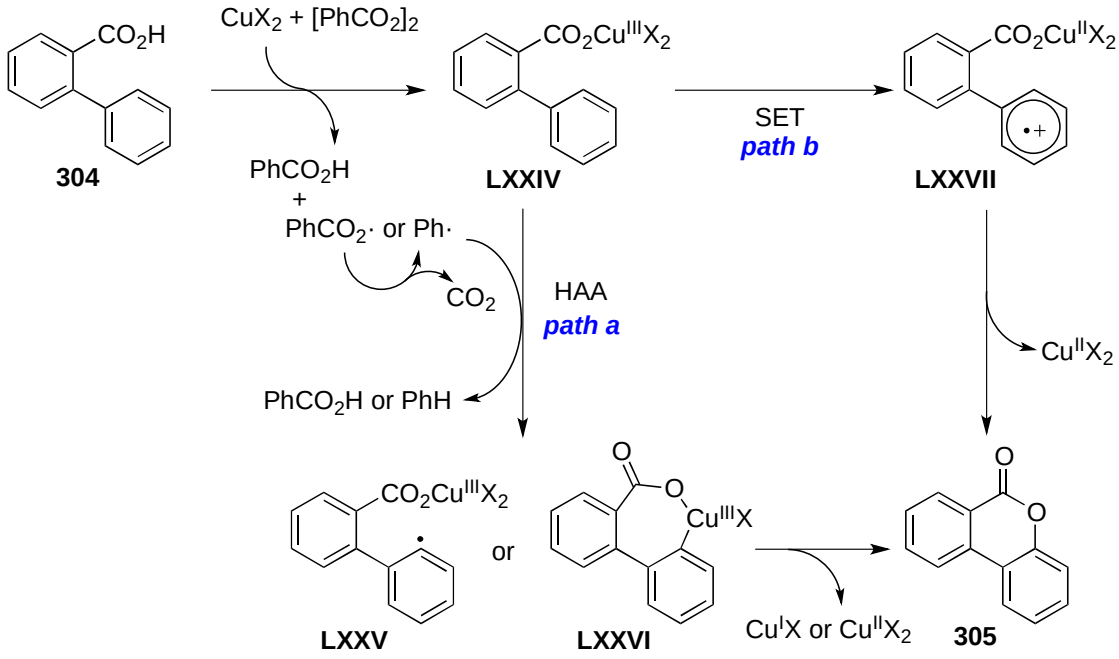


Figure 3.27

3.5 The sooner the better…

C-H bond functionalization has become one of the hottest areas in the cross-coupling arena and accordingly, competition has increased exponentially over the last five years. When our manuscript was under revision,[159] an alternative protocol employing palladium catalysts appeared in the literature (Figure 3.28, a).[160] Shortly after, the Gevorgyan group reported a similar Cu-catalyzed oxidative protocol, together with a metal free approach based upon $K_2S_2O_8$to yield benzopyranones (Figure 3.28, b).[161]

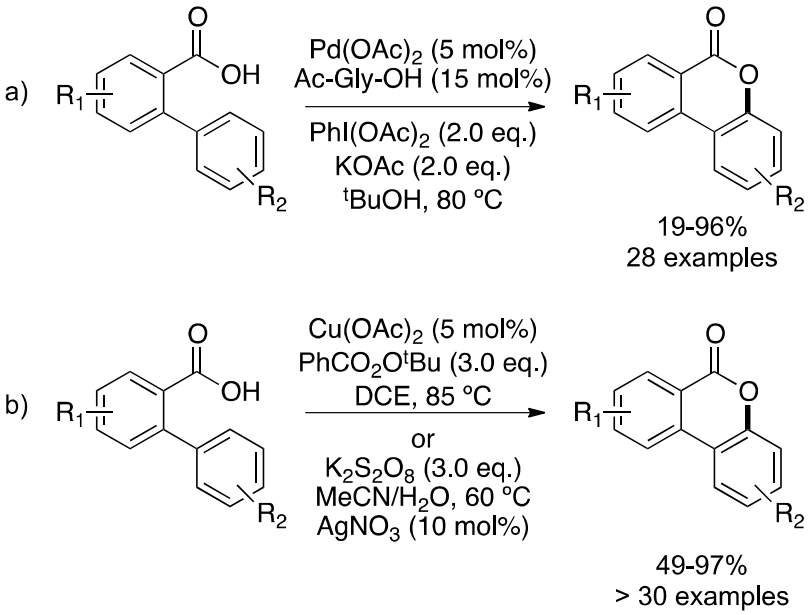


Figure 3.28

[159]Gallardo-Donaire, J.; Martin, R. *J. Am. Chem. Soc.***2013**, *135*, 9350.
[160]Li, Y.; Ding, Y.-J.; Wang, J.-Y.; Su, Y.-M.; Wang, X.-S. *Org. Lett.***2013**, *15*, 2574.
[161]Wang, Y.; Gulevich, A. V; Gevorgyan, V. *Chem. Eur. J.***2013**, *19*, 15836.

3.6 Conclusions

- In summary, we have developed a new, direct and efficient synthesis of benzopyranones via Cu-catalyzed C(sp^2)-H bond functionalization with weakly directing groups. Moreover, a sequential hydrolysis event afforded valuable remote hydroxylated arenes. This protocol constitutes a user-friendly, operationally simple reaction with excellent chemoseletivity that rival others for similar means.

- The measurement of both inter- and intra- kinetic isotope effect suggests that C-H bond cleavage is not involved in the rate-limiting step. Additionally, the use of radical scavengers suggested that SET might intervene in this reaction.

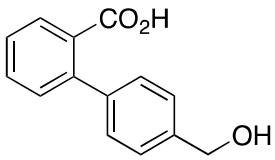
3.7 Experimental section

3.7.1 General considerations

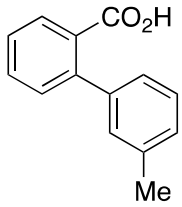
Reagents. Unless otherwise stated, all reactions were carried out under an argon atmosphere in resealable screw-cap test tubes using standard Schlenk techniques for the manipulation of solvents and reagents. $Cu(OAc)_2$ was purchased from Aldrich, $[PhCO_2]_2$ from Alfa Aesar and HFIP from Fluorochem. All chemicals were used as received. All other reagents were purchased from commercial sources and used also as received.

Analytical methods. ^1H NMR and ^{13}C NMR spectra and melting points (where applicable) are included for all compounds. ^1H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz and a Bruker 500 MHz at 20 ºC. All ^1H NMR spectra are reported in parts per million (ppm) downfield of TMS and were measured relative to the signals for $CHCl_3$ (7.27 ppm). All ^{13}C NMR spectra were reported in ppm relative to residual $CHCl_3$ (77 ppm) and were obtained with ^1H decoupling. Coupling constants, J, are reported in hertz. Melting points were measured using open glass capillaries in a Büchi B540 apparatus. Infrared spectra were recorded on a Bruker Tensor 27. Mass spectra were recorded on a Waters LCT Premier spectrometer. Gas chromatographic analyses were performed on Hewlett-Packard 6890 gas chromatography instrument with a FID detector using 25m x 0.20 mm capillary column with cross-linked methyl siloxane as the stationary phase. High Pressure Liquid Chromatographic (HPLC) analyses were performed on Agilent Technologies Model 1260 Infinity HPLC chromatography instrument equipped with Agilent Eclipse Plus C18 (3.5 um, 4.6 x 100 mm) column and UV/Vis detector. Flash chromatography was performed with EM Science silica gel 60 (230-400 mesh).

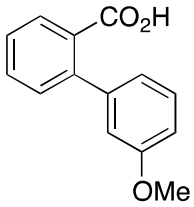
3.7.2 Synthesis of the starting materials.



4'-(hydroxymethyl)-[1,1'-biphenyl]-2-carboxylic acid 324. White Solid. M.p. = 144-146 ºC.^{1}H NMR (400 MHz, CD_3OD) δ 7.81 (ddd, *J* = 7.7, 1.5 Hz, 1H), 7.58 (td, *J* = 7.7, 1.4 Hz, 1H), 7.45 (td, *J* = 7.6, 1.3 Hz, 1H), 7.44-7.38 (m, 3H), 7.38-7.29 (m, 2H), 4.67 (s, 2H) ppm. ^{13}C NMR (101 MHz, CD_3OD) δ 173.3, 144.1, 142.6, 142.6, 134.1, 133.0, 132.7, 131.4, 130.4, 129.0, 128.6, 65.9. IR (neat, cm^{-1}): 3355, 3009, 1687, 1682, 1670, 1406, 1135, 759. HRMS *calcd* for ($C_{14}H_{11}O_3$-H^+): 227.0708, found 287.0714.

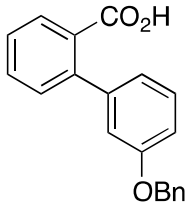


3'-methyl-[1,1'-biphenyl]-2-carboxylic acid 325. White solid. The spectroscopic data correspond to those previously reported in the literature.[162] M.p. = 97-98 ºC.^{1}H NMR (400 MHz, CD_3OD) δ 7.79 (d, *J* = 7.8 Hz, 1H), 7.55 (m, 1H), 7.43 (m, *J* = 7.8, 6.2 Hz, 1H), 7.37 (dd, *J* = 7.7, 2.6 Hz, 1H), 7.27 (m, *J* = 8.5, 6.7 Hz, 1H), 7.18 (m, 1H), 7.15 (m, 1H), 7.13 (m, 1H), 2.39 (s, 3H) ppm. ^{13}C NMR (101 MHz, CD_3OD) δ 173.4, 144.4, 143.5, 139.6, 134.0, 132.9, 132.6, 131.0, 129.8, 129.7, 128.9, 127.5, 22.4 ppm.

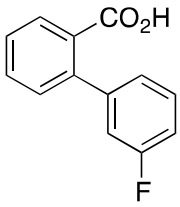


3'-methoxy-[1,1'-biphenyl]-2-carboxylic acid 326. White solid.The spectroscopic data correspond to those previously reported in the literature.[163]M.p. = 91-93 ºC.^{1}H NMR (400 MHz, CD_3OD)δ7.80 (m, *J* = 8 Hz, 1H), 7.56 (m, *J* = 8 Hz, 1H), 7.42 (m, *J* = 12 Hz, 1H), 7.40 (m, *J* = 12 Hz, 1H), 7.3 (m, 1H), 3.82 (s, 3H) ppm. ^{13}C NMR (101 MHz, Methanol-d4) δ 173.3, 161.7, 144.8, 144.1, 134.2, 132.9, 132.5, 131.2, 131.0, 129.1, 122.8, 116.1, 114.7, 56.5 ppm.

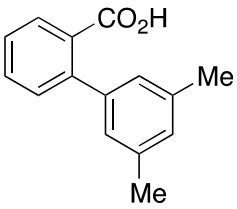
[162] Wang, C.; Rakshit, S.; Glorius, F. *J.Am. Chem. Soc.***2010**, *132*, 14006.
[163]Hoovera, J. R. E.; Chow, A.W.; Stedman, R., J.; Hall, N. M.; Greenberg, H. M.; Dolan, M. M.; Ferlauto, R. J. *J. Med. Chem.* **1964**, *7*, 245.



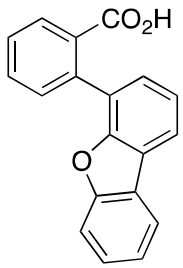
3'-(benzyloxy)-[1,1'-biphenyl]-2-carboxylic acid 327. White Solid. M.p. = 105-106 ºC.^{1}H NMR (500 MHz, CD_3OD) δ 7.79 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.54 (td, *J* = 7.7, 1.4 Hz, 1H), 7.48-7.40 (m, 3H), 7.41-7.34 (m, 3H), 7.35-7.25 (m, 2H), 7.05-6.96 (m, 2H), 6.96-6.92 (m, 1H), 5.08 (s, 2H) ppm. ^{13}C NMR (126 MHz, CD_3OD) δ 173.3, 160.9, 144.9, 144.0, 139.5, 134.1, 132.9, 132.5, 131.2, 131.0, 130.3, 129.7, 129.5, 129.1, 123.2, 117.1, 115.6, 71.9 ppm. IR (neat, cm^{-1}): 2922, 2858, 2224, 2063, 1689, 1675, 1580, 1566, 1344, 1276. HRMS *calcd* for ($C_{20}H_{15}O_3$-H^+): 303,1021 found 303.1027.



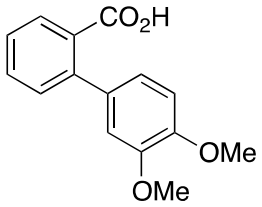
3'-fluoro-[1,1'-biphenyl]-2-carboxylic acid 328. White Solid. The spectroscopic data correspond to those previously reported in the literature.[2] M.p. = 128-130 ºC.^{1}H NMR (500 MHz, CD_3OD) δ 7.86 (ddd, J = 7.7, 1.4 Hz, 1H), 7.59 (d, J = 1.4 Hz, 1H), 7.48 (d, J = 1.3 Hz, 1H), 7.45-7.35 (m, 2H), 7.22-7.14 (m, 1H), 7.09 (dd, J = 9.4, 1.2 Hz, 2H) ppm. ^{13}C NMR (126 MHz, CD_3OD) δ 172.6, 165.7-163.8 (d, *J* = 246 Hz), 146.1, 146.0, 143.2, 143.2, 133.8, 133.2, 132.5, 131.6, 131.6, 129.6, 126.4, 126.4, 117.3, 117.2, 115.8, 115.6 ppm.



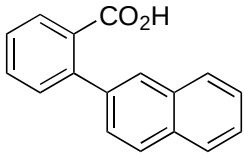
3',5'-dimethyl-[1,1'-biphenyl]-2-carboxylic acid 329. White solid. M.p. = 109-111 ºC. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.77 (m, *J* = 7.7 Hz, 1H), 7.54 (m, *J* = 1.5 Hz, 1H), 7.42 (m, *J* = 7.6 Hz, 1H), 7.36 (m, *J* = 7.7 Hz, 1H), 7.00 (s, 1H), 6.97 (s, 1H), 2.35 (s, 3H) ppm. ^{13}C NMR (101 MHz, CD_3OD) δ 173.5, 144.5, 143.4, 139.5, 134.1, 132.8, 132.5, 131.1, 130.6, 128.8, 128.2, 22.2 ppm. IR (neat, cm^{-1}): 3009, 2919, 2856, 2651, 1682, 1406, 1291, 1267. HRMS *calcd* for ($C_{15}H_{13}O_2$-H^+): 225,0916, found 225.0921.



2-(dibenzo[b,d]furan-4-yl)benzoic acid 330. Light yellow solid. M.p. = 179-180 ºC.[1]H NMR (500 MHz, CD_3OD) δ 8.04 (m, 2H), 8.02 (dd, J = 7.0, 2.0 Hz, 1H), 7.69 (m, J = 7.5, 1.2 Hz, 2H), 7.57 (m, 1H), 7.53 (m, 1H), 7.46 (d, J = 2.1 Hz, 3H), 7.37 (td, J = 7.5, 1.2 Hz, 1H). [13]C NMR (126 MHz, CD_3OD) δ 174.5, 146.8, 145.5, 130.1, 129.8, 128.9, 128.8, 34.5, 28.8, 24.5, 24.0 ppm. IR (neat, cm^{-1}): 3063, 3038, 2922, 2854, 1737, 1606, 1308, 1282. HRMS *calcd* for ($C_{19}H_{11}O_3$-H^+): 287.0708, found 287.0711.

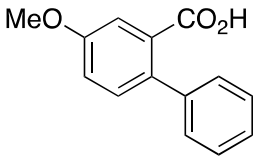


3',4'-dimethoxy-[1,1'-biphenyl]-2-carboxylic acid 331. White solid. The spectroscopic data correspond to those previously reported in the literature.[164]M.p. = 165-166 ºC.[1]H NMR δ(500 MHz, DMSO-d_6) δ 7.70 (dd, *J* = 7, 2 Hz, 1H), 7.57 (td, *J* = 7, 2 Hz, 1H), 7.47 (m, 2H), 7.03 (d, *J* = 2 Hz, 1H), 6.97 (d, *J* = 2.5 Hz, 1H), 6.91 (dd, *º* = 10, 2.5 Hz, 1H), 4.62 (s, 3H), 4.61 (s, 3H) ppm. [13]C NMR (126 MHz, DMSO-d_6)δ171.1, 149.2, 149.2, 141.3, 134..2, 133.6, 131.5, 131.2, 129.6, 127.7, 121.5, 113.2, 112.5, 56.5, 56.4 ppm.

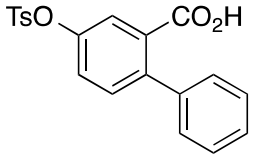


2-(naphthalen-2-yl)benzoic acid 332. White Solid. The spectroscopic data correspond to those previously reported in the literature.[1]M.p. = 190-192 ºC.[1]H NMR (500 MHz, CD_3OD)δ 7.95-7.86 (m, 4H), 7.85-7.80 (m, 1H), 7.68-7.56 (m, 1H), 7.55-7.45 (m, 5H).[13]C NMR (101 MHz, CD_3OD) δ 173.1, 144.5, 141.2, 135.6, 134.9, 134.1, 133.2, 133.0, 131.6, 129.9, 129.5, 129.3, 129.2, 129.0, 128.9, 128.1, 127.9.

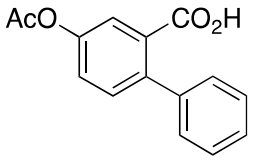
[164]Ciske, F.; Winton, J. *Synthesis*, **1995**, *8*, 1195.



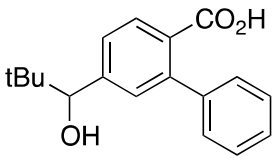
4-methoxy-[1,1'-biphenyl]-2-carboxylic acid 336. White Solid. The spectroscopic data correspond to those previously reported in the literature.[165] M.p. = 117-119 ºC.^{1}H NMR (400 MHz, CD_3OD) δ 7.46-7.25 (m, 7H), 7.13 (dd, J = 8.5, 2.8 Hz, 1H) ppm. ^{13}C NMR (101 MHz, CD_3OD) δ 173.0, 160.9, 143.3, 136.7, 134.9, 133.9, 130.5, 129.8, 128.7, 118.6, 116.5, 56.8 ppm.



4-(tosyloxy)-[1,1'-biphenyl]-2-carboxylic acid 349. White Solid. M.p. = 140-142 ºC. ^{1}H NMR (300 MHz, CD_3OD) δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.43-7.27 (m, 7H), 7.20 (dd, *J* = 8.4, 2.6 Hz, 1H), 2.49 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 171.2, 150.6, 148.3, 143.4, 142.2, 135.3, 134.2, 134.2, 132.0, 130.5, 130.4, 123.0, 129.4, 126.8, 125.2, 22.5 ppm. IR (neat, cm^{-1}): 3036, 1703, 1681, 1597, 1371, 785. HRMS *calcd* for ($C_{20}H_{15}O_5S$-H^+): 367,0640 found 367.0643.



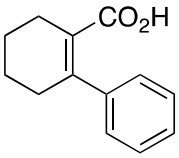
4-acetoxy-[1,1'-biphenyl]-2-carboxylic acid 350. White Solid. M.p. = 155-157 ºC.^{1}H NMR (400 MHz, CD_3OD) δ 7.57 (dd, J = 2.5, 0.4 Hz, 1H), 7.45-7.34 (m, 7H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ171.9, 171.8, 151.9, 142.7, 142.0, 134.9, 133.8, 130.5, 130.4, 129.9, 129.2, 126.3, 124.7, 21.7 ppm. IR (neat, cm^{-1}): 3068, 2924, 1757, 1689, 1482, 1194. HRMS *calcd* for ($C_{20}H_{15}O_5S$-H^+): 255.0657 found 255.060.



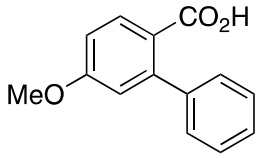
5-(1-hydroxy-2,2-dimethylpropyl)-[1,1'-biphenyl]-2-carboxylic acid 344. White Solid. M.p. = 163-165 ºC. ^{1}H NMR (500 MHz, CD_3OD) δ 7.79 (d, J = 8.0 Hz, 1H), 7.44-7.37 (m, 3H), 7.38-7.34 (m, 4H), 46.45 (s, 1H), 0.97 (s, 9H). ^{13}C NMR (101 MHz,

[165]Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.***2008**, *130*, 17676.

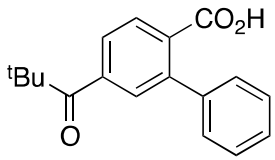
CD_3OD) δ 173.1, 148.4, 143.8, 143.6, 132.3, 132.2, 130.7, 130.4, 129.9, 128.9, 128.5, 83.3, 37.4, 27.4. IR (neat, cm^{-1}): 3410, 2954, 2908, 2867, 1688, 1297, 1266, 1232, 1053. HRMS *calcd* for ($C_{18}H_{19}O_3$-H^+): 283.1334 found 283.1337.



3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylic acid 353. White Solid. The spectroscopic data correspond to those previously reported in the literature.[166] M.p. = 129-131 ºC.^{1}H NMR (400 MHz, CD_3OD) δ 7.36-7.28 (m, 2H), 7.28-7.22 (m, 1H), 7.23-7.14 (m, 2H), 2.74-2.29 (m, 4H), 1.87-1.59 (m, 4H) ppm. ^{13}C NMR (126 MHz, CD_3OD) δ 174.5, 146.8, 145.5, 130.1, 129.8, 128.9, 128.8, 34.5, 28.8, 24.5, 24.0.

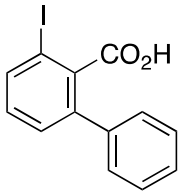


5-methoxy-[1,1'-biphenyl]-2-carboxylic acid 337. White Solid. The spectroscopic data correspond to those previously reported in the literature.[2] M.p. = 171-173 ºC. ^{1}H NMR (500 MHz, CD_3OD) δ 7.89 (d, *J* = 8.7 Hz, 1H), 7.48-7.23 (m, 5H), 6.99 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.85 (d, *J* = 2.6 Hz, 1H), 3.87 (s, 3H) ppm. ^{13}C NMR (126 MHz, CD_3OD) δ 172.3, 164.1, 147.5, 143.9, 134.3, 130.3, 129.7, 129.0, 125.3, 118.4, 114.1, 56.8 ppm.

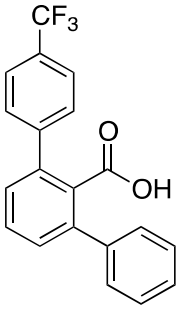


5-pivaloyl-[1,1'-biphenyl]-2-carboxylic acid 346. White Solid. M.p. = 160-161 ºC.^{1}H NMR (400 MHz, CD_3OD) δ 7.87 (dd, *J* = 8.0, 0.5 Hz, 1H), 7.72 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.59 (dd, *J* = 1.8, 0.5 Hz, 1H), 7.47-7.33 (m, 5H), 1.36 (s, 1H) ppm. ^{13}C NMR (126 MHz, CD_3OD) δ 211.7, 172.3, 144.1, 143.3, 142.7, 136.0, 131.5, 131.2, 130.3, 130.1, 129.5, 127.9, 46.2, 29.0 ppm. IR (neat, cm^{-1}): 2958, 2923, 2853, 2659, 1687, 1672, 1295, 1279. HRMS *calcd* for ($C_{18}H_{17}O_3$-H^+): 281.1178 found 281.1183.

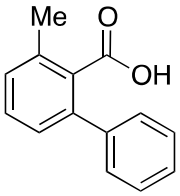
[166]Parham, W.E.; Moulton, W.E.; Zuckerbraun, A. *J. Org. Chem.***1956**, *21*, 72.



3-iodo-[1,1'-biphenyl]-2-carboxylic acid 340. White Solid. The spectroscopic data correspond to those previously reported in the literature.[167] M.p. = 172-173 ºC.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.38 (d, *J* = 1.5 Hz, 5H), 7.35 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.17 (t, *J* = 7.8 Hz, 1H) ppm. ^{13}C NMR (126 MHz, CD_3OD) δ 173.3, 142.9, 142.7, 141.9, 140.0, 132.3, 131.5, 130.4, 130.3, 130.2, 129.8, 93.4 ppm.



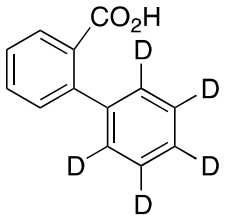
4-(trifluoromethyl)-[1,1':3',1''-terphenyl]-2'-carboxylic acid 342. White solid. M.p. = 183-186 ºC.^{1}H NMR (500 MHz, CD_3OD) δ 7.74 (d, *J* = 8.2 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 7.7 Hz, 7H), 7.52-7.36 (m, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 173.7, 146.9, 142.6, 142.2, 140.5, 136.0, 131.7 (d, J = 32.7 Hz), 131.6, 131.4 (d, J = 32.7 Hz), 131.3, 131.3, 130.6, 130.5, 130.2, 129.6, 127.7 (d, *J* = 272 Hz), 127.0 (d, *J* = 3.8 Hz), 127.0 (d, *J* = 3.8 Hz), 125.5 (d, *J* = 272 Hz). IR (neat, cm^{-1}): 2920, 2851, 2643, 1698, 1322, 1275, 1164, 1119, 1066, 775. HRMS *calcd* for ($C_{18}H_{17}O_3$-H^+): 341.0795 found 341.0797.



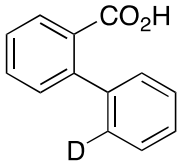
3-methyl-[1,1'-biphenyl]-2-carboxylic acid 339. White Solid. The spectroscopic data correspond to those previously reported in the literature.[6] M.p. = 138-139 ºC.^{1}H NMR (500 MHz, CD_3OD) δ 7.47-7.42 (m, 2H), 7.42-7.33 (m, 4H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.21 (d, *J* = 7.7 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 171.2, 150.6,

[167]Tilly, D.; Samanta, S. S.; Castanet, A.-S.; De, A.; Mortier, J. *Eur. J. Org. Chem.***2006**, *2006*, 174.

148.3, 143.4, 142.2, 135.3, 134.2, 134.2, 132.0, 130.5, 130.4, 123.0, 129.4, 126.8, 125.2, 22.5 ppm.



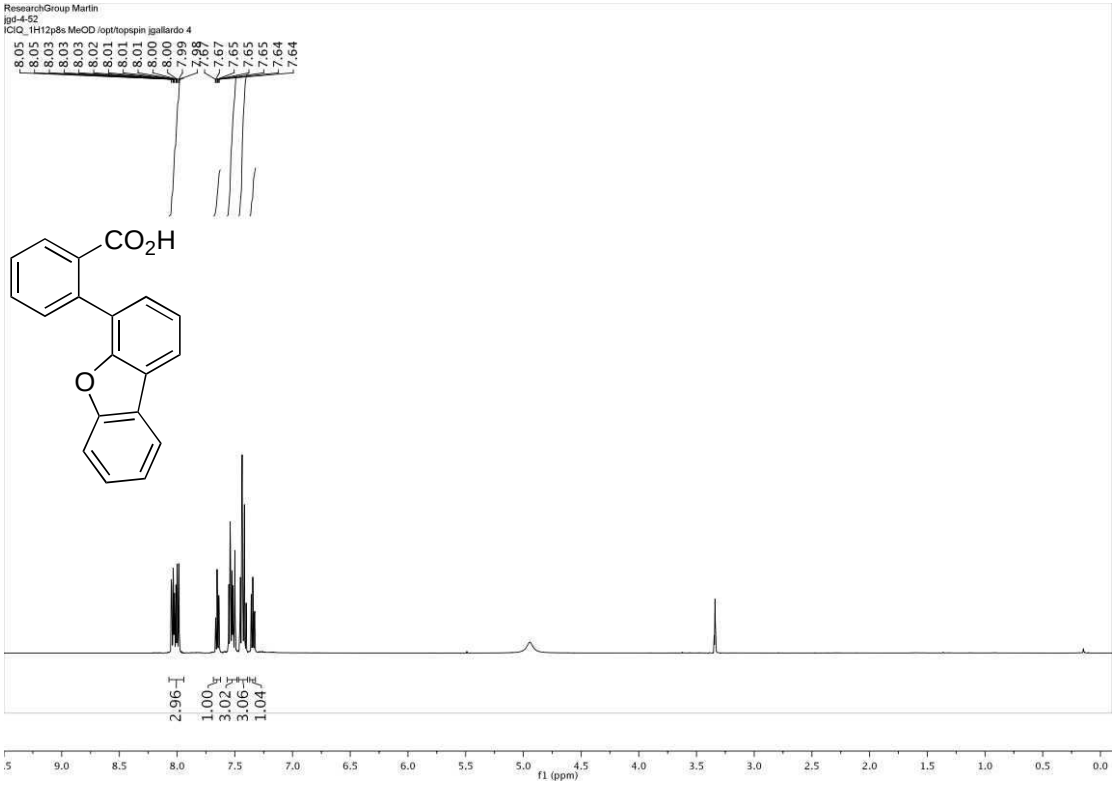
2-(D_5-phenyl)benzoic acid394. White Solid. The spectroscopic data correspond to those previously reported in the literature.[1] M.p. = 108-109 ºC.^{1}H NMR (400 MHz, CD_3OD) δ 7.82 (ddd, *J* = 7.7, 1.5, 0.5 Hz, 1H), 7.56 (td, *J* = 7.6, 1.4 Hz, 1H), 7.44 (td, *J* = 7.6, 1.3 Hz, 1H), 7.38 (ddd, *J* = 7.6, 1.3, 0.5 Hz, 1H) ppm. ^{13}C NMR (126 MHz, CD_3OD) δ 173.2, 144.3, 143.3, 134.0, 133.0, 132.6, 131.4, 130.2-129.2, 129.0, 128.8-128.3 ppm.

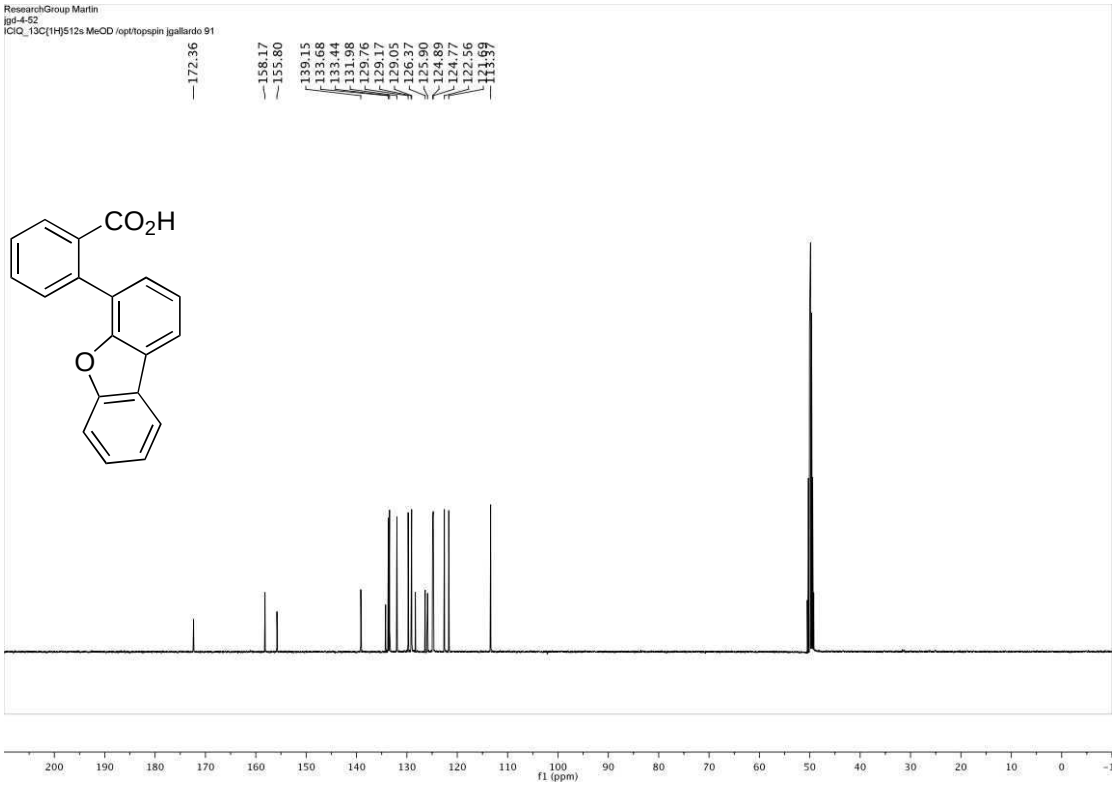


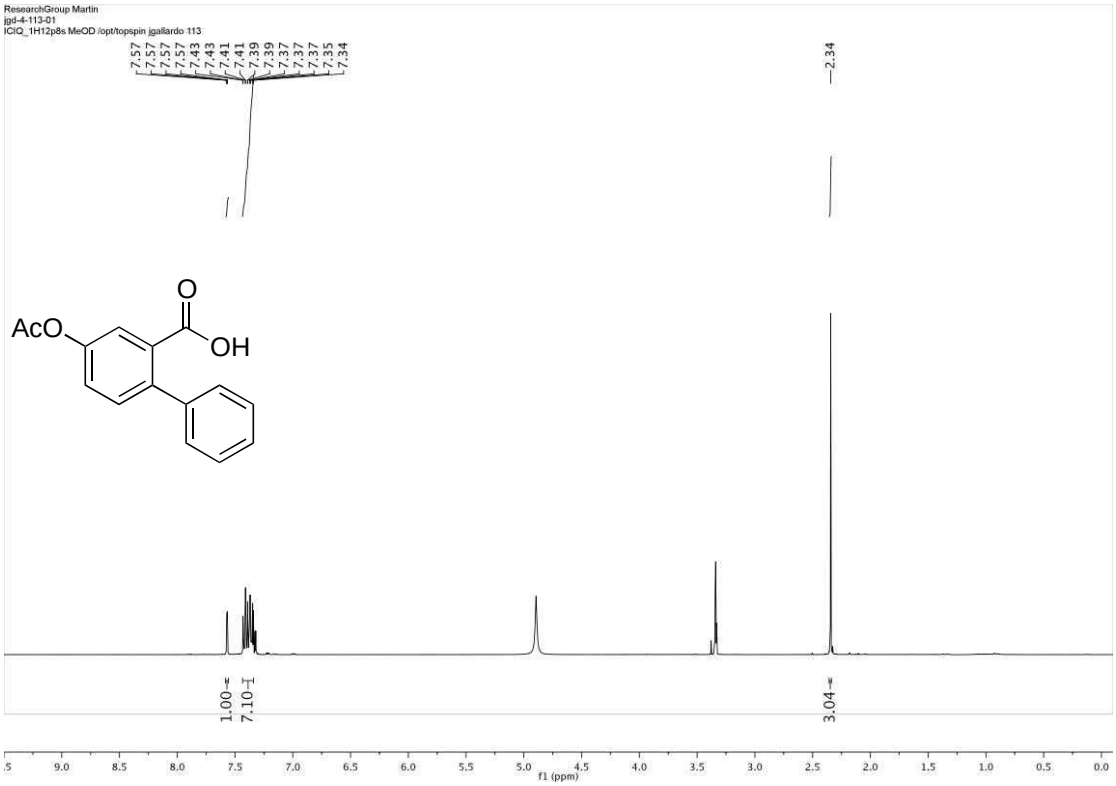
2-(D-phenyl)benzoic acid 395. White Solid. The spectroscopic data correspond to those previously reported in the literature.[168] M.p. = 110-111 ºC. ^{1}H NMR (500 MHz, CD_3OD) δ 7.82 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.56 (td, *J* = 7.6, 1.5 Hz, 1H), 7.44 (td, *J* = 7.6, 1.3 Hz, 1H), 7.41-7.31 (m, 5H) ppm. ^{13}C NMR (126 MHz, CD_3OD) δ 173.2, 144.3, 143.4, 133.9, 133.0, 132.6, 131.4, 130.4, 130.3-130.1, 129.9, 129.8, 129.0, 129.0 ppm.

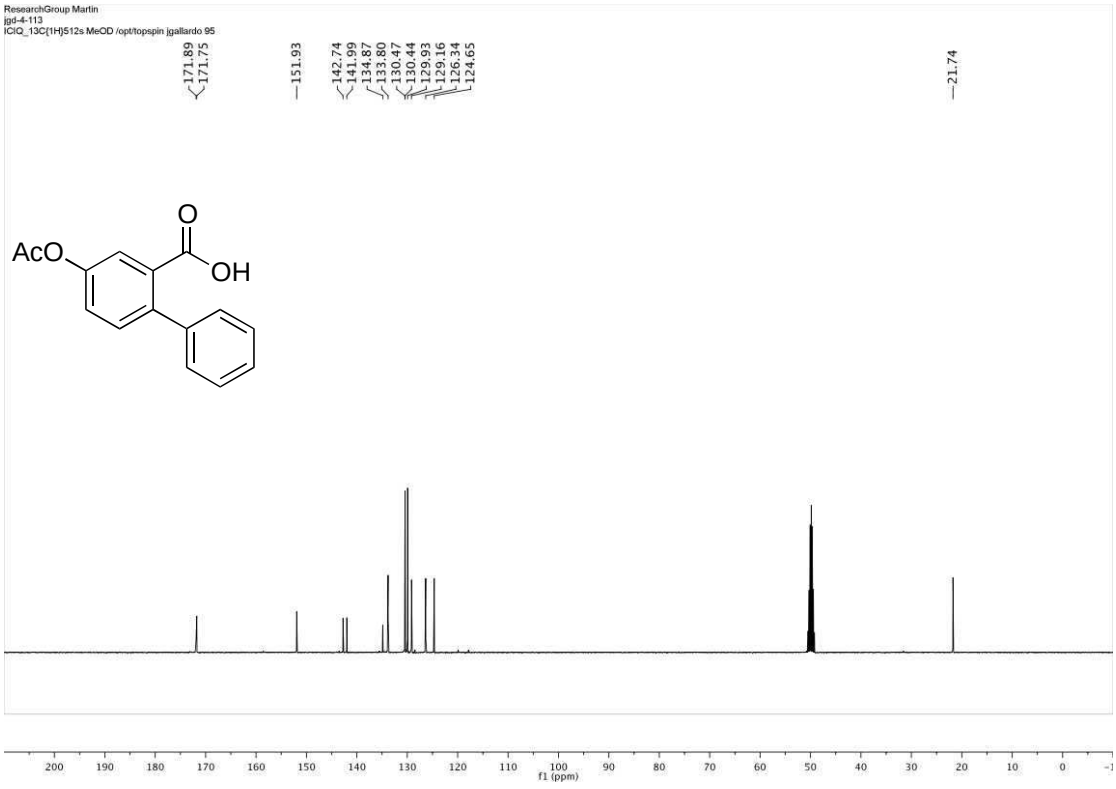
[168]Denney, D. B.; Klemchuk, P. *J. Am. Chem. Soc.*, **1958**, *80*, 3285.

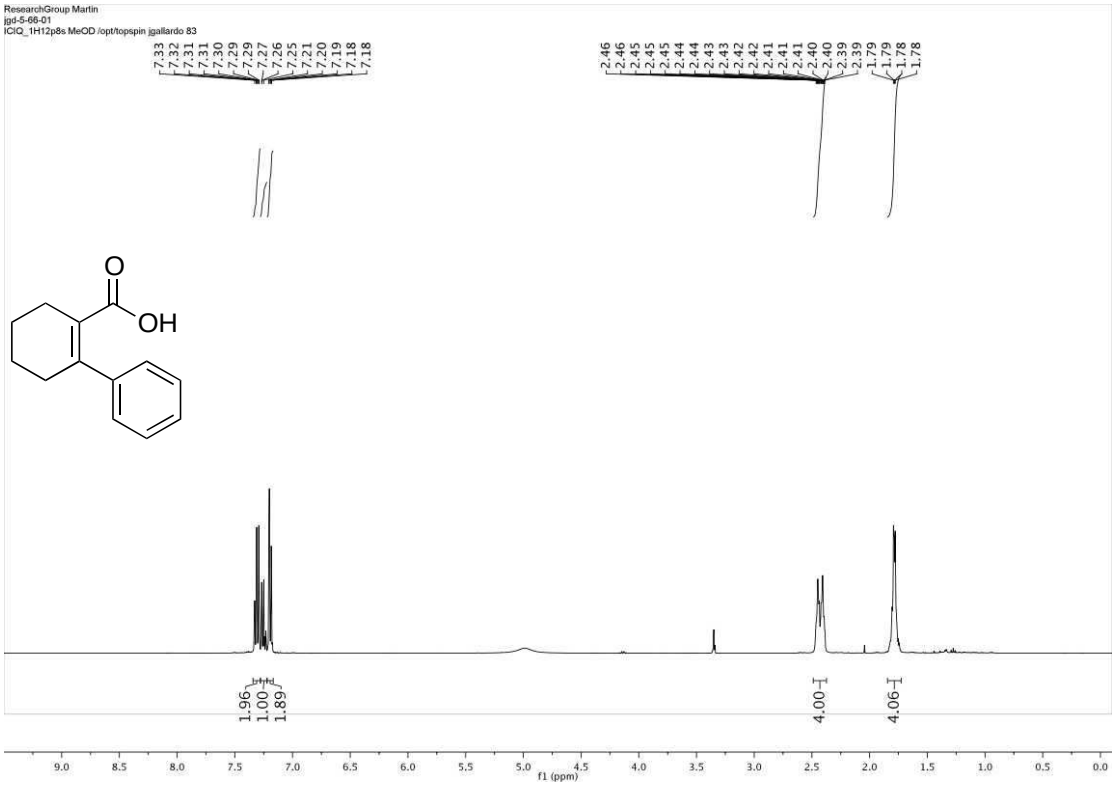
3.7.3 Selected examples of NMR spectra.

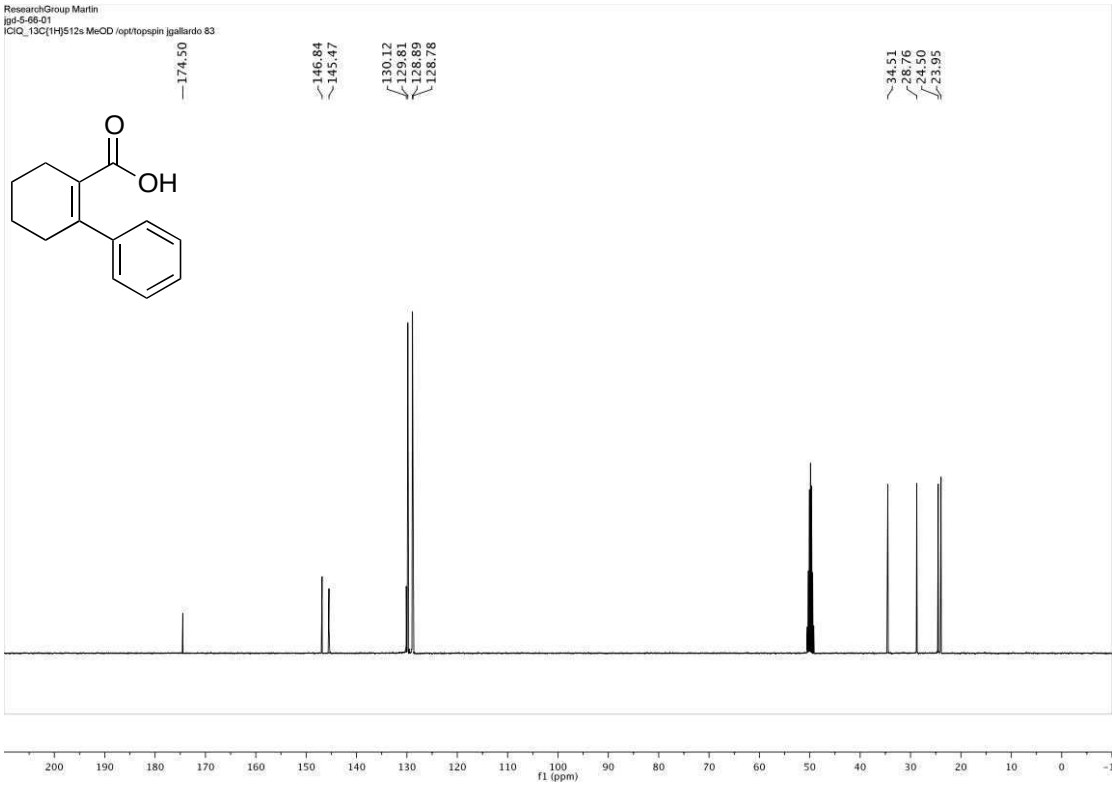





ResearchGroup Martin
jgd-4-113-01
ICIQ_1H12p8s MeOD /opt/topspin jgallardo 113
7.57
7.57
7.57
7.57
7.57
7.43
7.43
7.41
7.41
7.39
7.39
7.37
7.37
7.37
7.37
7.35
7.34
2.34
AcO
O
OH
1.00
7.10
3.04
f1 (ppm)


ResearchGroup Martin
jgd-4-113
ICIQ_13C{1H}512s MeOD /opt/topspin jgallardo 95
171.89
171.75
151.93
142.74
141.99
134.87
133.80
130.47
130.44
129.93
129.16
126.34
124.65
21.74
AcO
O
OH
f1 (ppm)

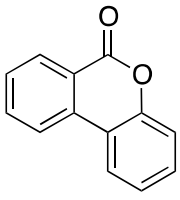

ResearchGroup Martin
jgd-5-66-01
ICIQ_1H12p8s MeOD /opt/topspin jgallardo 83
7.33 7.32 7.31 7.31 7.30 7.29 7.29 7.27 7.26 7.25 7.21 7.20 7.19 7.18 7.18
2.46 2.46 2.45 2.45 2.44 2.44 2.43 2.43 2.42 2.42 2.41 2.41 2.41 2.40 2.40 2.39 2.39 1.79 1.79 1.78 1.78
O
OH
1.96
1.00
1.89
4.00
4.06
f1 (ppm)


ResearchGroup Martin
jgd-5-66-01
ICIQ_13C{1H}512s MeOD /opt/topspin jgallardo 83
174.50
146.84
145.47
130.12
129.81
128.89
128.78
34.51
28.76
24.50
23.95
O
OH
f1 (ppm)

3.7.4 Synthesis of benzopyranones

General procedure A for the synthesis of benzo[c]chromenones: for the Cu-catalyzed lactonization of [1,1'-biphenyl]-2-carboxylic acids. An oven-dried screw-cap test tube containing a stirring bar was charged with the benzoic acid (0.50 mmol), $Cu(OAc)_2$ (4.5 mg, 5 mol%), benzoyl peroxide (202 mg, 0.625 mmol) and evacuated three times. Then, HFIP (4 mL) was added by syringe under a positive argon atmosphere. The mixture was stirred in a pre-heated oil bath (75 ºC) for 12 h. The mixture was then allowed to warm to room temperature and concentrated under vacuum. The resulting solid was washed with a saturated solution of $NaHCO_3$ and extracted with AcOEt (3 x 15 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to yield the final lactone, which was purified by column chromatography on silica gel (eluting with hexanes/ethyl acetate mixtures).

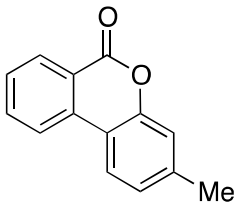
General procedure B for the synthesis 2'-hydroxy-[1,1'-biphenyl]-2-carboxylic acid: following a modified procedure in the literature[169], lactone (0.25 mmol) and LiOH monohydrate (252 mg, 6 mmol, 24 equiv.) was charged to a 25 mL flask. To this mixture was then added MeOH (4 mL), THF (2 mL), and H_2O (1 mL). The reaction was then stirred for 24 h when TLC indicated the completion of hydrolysis. The MeOH and THF was then removed in vacuo, and the resulting residue was diluted with H_2O (15mL), ice and EtOAc (20 mL). After acidification with 2 M HCl (pH 4-5), the solution was extracted with EtOAc for three times. The combined organic extract was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was washed with AcOEt furnishing the final hydroxyacids without further purification.



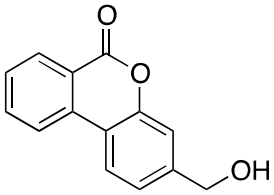
6H-benzo[c]chromen-6-one 305. Following general procedure A, [1,1'-biphenyl]-2 carboxylic acid (0.5 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 95:5. White solid; yield: 94 mg (95% yield). The spectroscopic data correspond to those previously reported in the literature.[170] M.p. = 88-89 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (ddd, J = 8.0, 1.4, 0.6 Hz, 1H), 8.14 (ddt, J = 8.1, 1.1, 0.5 Hz,

[169]Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. *Nature***2012**, *486*, 518.
[170] Vishnumurthy, K.; Makriyannis, A. *J. Comb. Chem.***2010**, *12*, 664.

1H), 8.08 (dd, J = 8.0, 1.5 Hz, 1H), 7.84 (ddd, J = 8.0, 7.3, 1.4 Hz, 1H), 7.60 (ddd, J = 8.2, 7.3, 1.1 Hz, 1H), 7.49 (ddd, J = 8.5, 7.2, 1.5 Hz, 1H), 7.41-7.37 (m, 1H), 7.35 (ddd, J = 8.0, 7.2, 1.3 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.2, 151.3, 134.9, 134.8, 130.6, 130.5, 128.9, 124.6, 122.8, 121.7, 121.3, 118.1, 117.8 ppm.

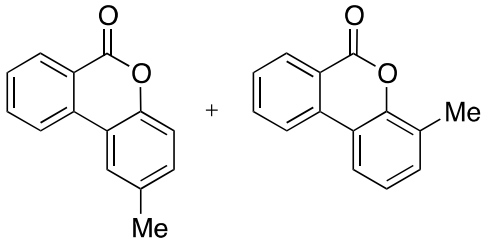


3-methyl-6H-benzo[c]chromen-6-one 312. Following general procedure A, [1,1'-biphenyl]-2 carboxylic acid (0.5 mmol) was used. Columnchromatography: silica gel, hexanes/EtOAc 95:5. White solid; yield: 92 mg (88% yield). The spectroscopic data correspond to those previously reported in the literature.[171]M.p. = 153-154 ºC.^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45-8.32 (m, 1H), 8.15-8.02 (m, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.81 (ddd, *J* = 8.1, 7.3, 1.4 Hz, 1H), 7.56 (ddd, *J*= 8.2, 7.3, 1.1 Hz, 1H), 7.21-7.12 (m, 2H), 2.46 (s, 3H) ppm.^{13}C NMR (126 MHz, $CDCl_3$) δ161.7, 151.6, 141.6, 135.3, 135.1, 130.8, 128.6, 126.0, 122.8, 121.7, 121.2, 118.2, 115.7, 21.8 ppm.



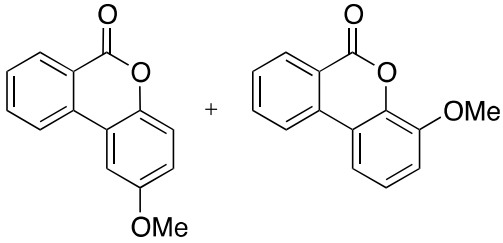
3-(hydroxymethyl)-6H-benzo[c]chromen-6-one 355. Following general procedure A, 4'-(hydroxymethyl)-[1,1'-biphenyl]-2-carboxylic acid (0.5 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 95:5. White solid; yield: 82 mg (78 % yield). M.p. = 176-177 ºC. ^{1}H NMR (500 MHz, CD_3OD) δ 8.47-8.28 (m, 1H), 8.23 (d, *J* = 8.1 Hz, 1H), 7.93 (ddd, *J* = 8.1, 7.3, 1.4 Hz, 1H), 7.73-7.56 (m, 1H), 7.48-7.30 (m, 1H), 4.74 (s, 2H) ppm. ^{13}C NMR (126 MHz, CD_3OD) δ 163.9, 153.5, 147.5, 137.3, 137.1, 132.0, 130.8, 125.2, 125.0, 124.1, 122.9, 119.0, 117.1, 65.1 ppm. IR (neat, cm^{-1}): 3294, 2920, 2850, 1732, 1608, 1307, 1267, 1049, 1030. HRMS *calcd* for ($C_{14}H_{10}O_3$+H^+): 227.0708, found 287.0732.

[171]Brown, B. P. M.; Russell, J.; Wylie, A. G. *J. Chem. Soc (C)***1968**, 842.



Both isomers are reported together (ratio 2.5:1 as determined by NMR).

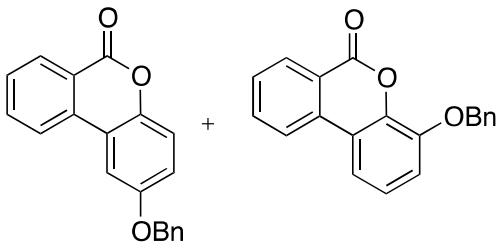
2-methyl-6H-benzo[c]chromen-6-one 356. Following general procedure A, [1,1'-biphenyl]-2 carboxylic acid (0.5 mmol) was used. Columnchromatography: silica gel, hexanes/EtOAc 95:5. White solid; yield: 82 mg (78 % yield). The spectroscopic data correspond to those previously reported in the literature.[1721]H NMR (300 MHz, $CDCl_3$) δ8.43 (dd, *J* = 7.9, 1.4 Hz, major + minor isomer), 8.15 (d, *J* = 8.1 Hz, major + minor), 8.01-7.90 (m, 1H), 7.90-7.72 (m, major + minor isomer), 7.59 (d, *J* = 1.1 Hz, major + minor isomer), 7.41-7.32 (m, 1H), 7.31-7.18 (m, major + minor isomer), 2.52 (s, major isomer, 3H), 2.48 (s, minor isomer, 1.18H) ppm.[13]C NMR (126 MHz, $CDCl_3$) δ 161.6, 161.5, 149.9, 149.6, 135.4, 135.1, 135.0, 135.0, 134.4, 132.0, 131.6, 130.8, 130.7, 128.9, 128.9, 127.3, 124.3, 123.0, 122.1, 121.9, 121.5, 121.3, 120.6, 117.9, 117.9, 117.7, 21.4, 16.3 ppm.



Both isomers are reported together (ratio 3:1 as determined by NMR).

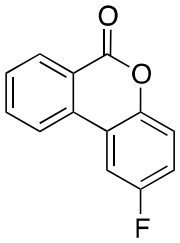
2-methoxy-6H-benzo[c]chromen-6-one 357. Following general procedure A, 3',5'-dimethyl-[1,1'-biphenyl]-2-carboxylic acid (0.5 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 95:5. White solid; yield: 82 mg (78 % yield). The spectroscopic data correspond to those previously reported in the literature.[1731]H NMR (300 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 7.9, 1.6 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.85 (td, *J* = 7.6, 1.5 Hz, 1H), 7.61 (td, *J* = 7.7, 1.3 Hz, 1H), 7.51 (d, *J* = 2.9 Hz, 1H), 7.45-7.22 (m, 1H), 7.07 (dd, *J* = 9.0, 3.0 Hz, 1H), 4.01 (s, 1H), 3.93 (s, 3H) ppm. [13]C NMR (126 MHz, $CDCl_3$) δ 161.5, 160.8, 156.6, 148.3, 145.8, 141.3, 135.2, 135.0, 135.0, 134.9, 130.9, 130.8, 129.2, 129.2, 124.5, 122.4, 122.0, 121.6, 121.5, 119.0, 118.9, 118.8, 117.4, 114.4, 112.5, 106.6, 56.5, 56.1 ppm.

[172]Zhou, Q.; Worm, K.; Dolle, R. E., *J. Org. Chem.***2004**, *69*, 5147.
[173]Bowman, W. R.; Mann, E.; Parr, J. *J. Chem. Soc., Perkin Trans. 1*, **2000**, *17*, 2991.



Both isomers are reported together (ratio 4:1 as determined by NMR).

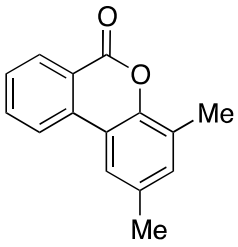
2-(benzyloxy)-6H-benzo[c]chromen-6-one 358. Following general procedure A, 3'-(benzyloxy)-[1,1'-biphenyl]-2-carboxylic acid (0.5 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 95:5. White solid; yield: 148 mg (98 % yield). ^{1}H NMR (500 MHz, CD_3OD) δ8.40-8.30 (m, major + minor isomer), 8.11 (dd, major + minor isomer, *J* = 8.3, 1.4 Hz), 8.01-7.92 (m, 1H), 7.83-7.70 (m, major + minor isomer), 7.50-7.44 (m, 3H), 7.43-7.38 (m, 2H), 7.37-7.33 (m, 1H), 7.25 (d, *J* = 9.0 Hz, 1H), 7.08 (dd, *J* = 9.0, 2.9 Hz, 1H), 5.13 (s, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 161.6, 161.0, 155.7, 147.2, 146.0, 141.9, 136.8, 136.8, 135.2, 135.0, 134.8, 134.0, 130.9, 130.8, 130.5, 129.6, 129.2, 129.2, 129.0, 129.0, 128.9, 128.8, 128.5, 128.3, 127.8, 127.6, 124.4, 122.4, 122.0, 121.6, 121.5, 119.3, 118.9, 118.9, 118.2, 114.9, 114.9, 108.0, 71.5, 71.0. IR (neat, cm^{-1}): 3063, 3028, 2928, 2874, 1728, 1684, 1450, 1417, 1318, 1292, 1069. HRMS *calcd* for ($C_{20}H_{14}O_3$+H^+): 303.1021, found 303.1022.



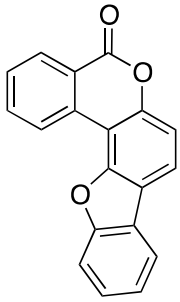
Separable isomers were isolated by column chromatography.

2-fluoro-6H-benzo[c]chromen-6-one 359. Following general procedure A, 3',5'-dimethyl-[1,1'-biphenyl]-2-carboxylic acid (0.5 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 98:2. White solid; yield: 52 mg, 36 mg major isomer (49 % yield). The spectroscopic data correspond to those previously reported in the literature.[101]^{1}H NMR (500 MHz, CD_3OD) δ 8.49-8.22 (m, 1H), 8.08-7.92 (m, 1H), 7.84 (ddd, *J* = 7.9, 7.3, 1.4 Hz, 1H), 7.69 (dd, *J* = 9.1, 2.9 Hz, 1H), 7.66-7.57 (m, 1H), 7.33 (dd, *J* = 9.0, 4.7 Hz, 1H), 7.18 (ddd, *J* = 9.0, 7.7, 2.9 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.1, 159.6 (d, *J* = 244.4 Hz), 147.69 (d, *J* = 2.1 Hz), 135.3,

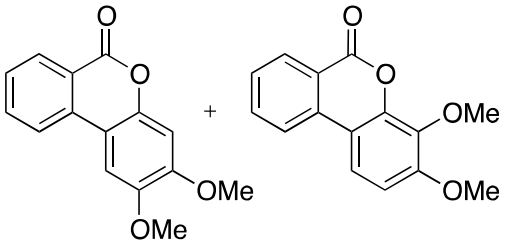
134.8 (d, *J* = 2.8 Hz), 131.0, 129.9, 122.2, 121.6, 119.60 (d, *J* = 8.6 Hz), 119.5 (d, *J* = 8.8 Hz) 118.00 (d, *J* = 24.2 Hz), 109.11 (d, *J* = 24.9 Hz) ppm.



2,4-dimethyl-6H-benzo[c]chromen-6-one 360. Following general procedure A, 3',5'-dimethyl-[1,1'-biphenyl]-2-carboxylic acid (0.5 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 95:5. White solid; yield: 82 mg (78 % yield). M.p. = 171-173 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.13 (d, *J* = 8.1 Hz, 1H), 7.81 (ddd, *J* = 8.2, 7.3, 1.5 Hz, 1H), 7.76-7.68 (m, 1H), 7.65-7.46 (m, 1H), 7.21-7.04 (m, 1H), 2.47 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161,7, 148.1, 135.5, 134.9, 133.7, 133.1, 130.8, 128.8, 127.0, 122.1, 121.4, 120.7, 117.6, 21.4, 16.2 ppm. IR (neat, cm^{-1}): 2919, 1714, 1600, 1279, 772. HRMS *calcd* for ($C_{15}H_{12}O_2$+H^+): 225.0916, found 225.0917.

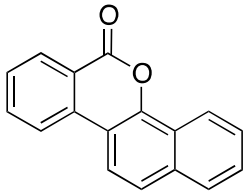


5H-benzo[c]benzofuro[2,3-f]chromen-5-one 361. Following general procedure A, 2-(dibenzo[b,d]furan-4-yl)benzoic acid (0.5 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 9:1. Yellowish solid; yield: 50 mg (70 % yield). M.p. = 189-191 ºC.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (dd, *J* = 7.9, 0.8 Hz, 1H), 8.18 (ddd, *J* = 7.9, 1.5, 0.6 Hz, 1H), 7.75-7.60 (m, 2H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.46-7.36 (m, 2H), 7.31 (ddd, *J* = 8.3, 7.2, 1.4 Hz, 1H), 7.21 (td, *J* = 7.4, 1.0 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.8, 156.5, 152.2, 150.7, 135.1, 132.8, 130.3, 128.9, 127.1, 126.5, 123.7, 123.2, 121.3, 121.0, 120.9, 120.4, 112.9, 111.9, 105.5 ppm. IR (neat, cm^{-1}): 2922, 2852, 1730, 1606, 1460, 1042. HRMS *calcd* for ($C_{19}H_{10}O_3$+H^+): 287.0708, found 287.07012.



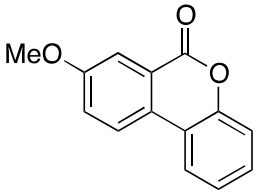
Both isomers are reported together (ratio 10:1 as determined by NMR).

2,3-dimethoxy-6H-benzo[c]chromen-6-one 366. Following general procedure A, 3',5'-dimethyl-[1,1'-biphenyl]-2-carboxylic acid (0.5 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 95:5. White solid; yield: 82 mg (78 % yield). The spectroscopic data correspond to those previously reported in the literature.[1741]^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (ddd, *J* = 7.9, 1.5 Hz, 1H), 7.92-7.81 (m, 1H), 7.69 (ddd, *J* = 8.1, 7.2, 1.4 Hz, 1H), 7.41 (ddd, *J* = 8.2, 7.3, 1.1 Hz, 1H), 7.28 (s, 1H), 6.75 (s, 1H), 3.91 (s, 3H), 3.86 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.9, 151.7, 146.8, 146.6, 135.4, 135.0, 130.9, 128.0, 121.3, 120.5, 110.2, 104.2, 101.1, 56.7, 56.5 ppm.

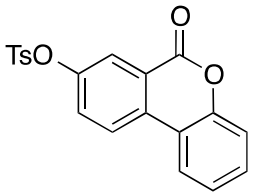


6H-dibenzo[c,h]chromen-6-one 363. Following general procedure A, 2-(naphthalen-2-yl)benzoic acid (0.5 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 95:5. White solid; yield: 82 mg (78 % yield). The spectroscopic data correspond to those previously reported in the literature.[1] M.p. = 181-182 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60-8.46 (m, 1H), 8.46-8.34 (m, 1H), 8.11 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.87-7.77 (m, 2H), 7.69 (dd, *J* = 8.9, 0.8 Hz, 1H), 7.64-7.52 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.5, 147.4, 135.6, 135.2, 134.5, 130.9, 128.9, 128.1, 127.9, 127.3, 124.7, 124.1, 122.6, 122.3, 121.4, 119.4, 113.2.

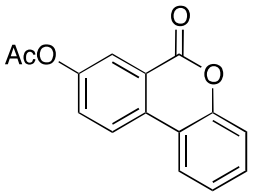
[174]Beugelmans, R.; Bois-Chonssy,M.; Chastanet, J.; Gleuher, M.; Zhu, J. P. *Heterocycles***1993**, *36*, 2737.



8-methoxy-6H-benzo[c]chromen-6-one 366. Following general procedure A, 4-methoxy-[1,1'-biphenyl]-2-carboxylic acid (0.5 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 9:1. White solid; yield: 95 mg (84 % yield). The spectroscopic data correspond to those previously reported in the literature.[8] M.p. = 149-151 ºC.^{1}H NMR (500 MHz, CD_3OD) δ 8.05 (d, *J* = 8.8 Hz, 1H), 7.99 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.82 (d, *J* = 2.8 Hz, 1H), 7.49-7.38 (m, 2H), 7.39-7.30 (m, 2H), 3.95 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.7, 160.4, 150.8, 129.7, 128.5, 124.9, 124.6, 123.8, 122.8, 122.5, 118.5, 118.0, 111.6, 56.2 ppm.

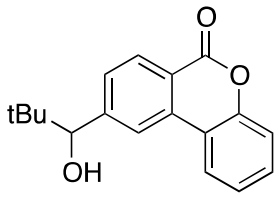


6-oxo-6H-benzo[c]chromen-8-yl 4-methylbenzenesulfonate 367. Following general procedure A, 4-(tosyloxy)-[1,1'-biphenyl]-2-carboxylic acid (0.5 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 9:1. White solid; yield: 98 mg (54 % yield).^{1}H NMR (300 MHz, CD_3OD) δ 8.12 (d, *J* = 8.8 Hz, 1H), 8.07-7.95 (m, 1H), 7.85 (d, *J* = 2.6 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.64 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.51 (s, 1H), 7.36 (t, *J* = 8.0 Hz, 4H), 2.46 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.2, 151.4, 149.8, 146.4, 133.9, 132.1, 131.3, 130.4, 129.9, 128.8, 125.2, 124.1, 123.8, 123.2, 122.7, 118.1, 117.4, 22.1 ppm. HRMS *calcd* for ($C_{20}H_{14}O_5S$+Na): 389.0460, found 389.0465.

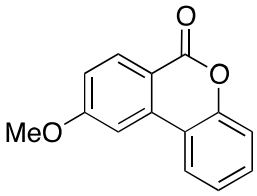


6-oxo-6H-benzo[c]chromen-8-yl acetate 368. Following general procedure A, 4-acetoxy-[1,1'-biphenyl]-2-carboxylic acid (0.5 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 9:1. White solid; yield: 68 mg (53 % yield). M.p. = 134-136 ºC.^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (d, *J* = 8.8 Hz, 1H), 8.12 (dd, *J* = 2.5, 0.5 Hz, 1H), 8.04 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.59 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.52-

7.45 (m, 1H), 7.42-7.31 (m, 2H), 2.37 (s, 3H) ppm. IR (neat, cm^{-1}): 3071, 2923, 2852, 1742, 1685, 1608, 1221, 947. ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 160.7, 151.4, 151.1, 132.8, 130.8, 129.3, 125.1, 123.6, 123.2, 123.0, 122.8, 118.1, 117.8, 21.4 ppm. HRMS *calcd* for ($C_{15}H_{10}O_4+H^+$): 254.0579, found 255.0652.

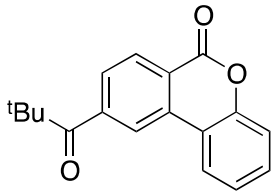


9-(1-hydroxy-2,2-dimethylpropyl)-6H-benzo[c]chromen-6-one **369.**Following general procedure A, 5-(1-hydroxy-2,2-dimethylpropyl)-[1,1'-biphenyl]-2-carboxylic acid(0.5 mmol) was used. Columnchromatography: silica gel, hexanes/EtOAc 4:1. White solid; yield: 104 mg (73 % yield). M.p. = 141-142 ºC.^1H NMR (500 MHz, CD_3OD) δ8.17 (d, *J* = 8.2 Hz, 1H), 8.03-7.97 (m, 1H), 7.98 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.44 (ddd, *J*= 8.0, 7.4, 1.5 Hz, 2H), 7.33-7.25 (m, 2H), 4.58 (s, 1H), 0.99 (s, 9H) ppm.^{13}C NMR (126 MHz, $CDCl_3$) δ161.7, 151.5, 150.3, 134.3, 130.6, 129.9, 128.9, 124.9, 123.0, 120.7, 120.1, 118.3, 117.9, 82.2, 36.1, 26.2 ppm.^{13}C NMR (126 MHz, $CDCl_3$) δ161.7, 151.5, 150.3, 134.3, 130.6, 129.9, 128.9, 124.9, 123.0, 120.7, 120.1, 118.3, 117.9, 82.2, 36.1, 26.2.IR (neat, cm^{-1}): 3478, 2952, 2869, 1705, 1613, 1282, 747. HRMS *calcd* for ($C_{18}H_{18}O_3$+Na): 305.1148, found 305.1155.

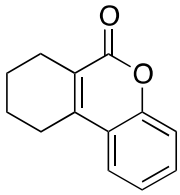


9-methoxy-6H-benzo[c]chromen-6-one **371.**Following general procedure A, 5-methoxy-[1,1'-biphenyl]-2-carboxylic acid (0.5 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 9:1. White solid; yield: 92 mg (78 % yield). The spectroscopic data correspond to those previously reported in the literature.[175] M.p. = 117-119 ºC.^1H NMR (500 MHz, CD_3OD) δ 8.36 (d, *J* = 8.8 Hz, 1H), 8.02 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.51 (dd, *J* = 2.7, 1.9 Hz, 2H), 7.44-7.32 (m, 2H), 7.14 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.02 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.1, 161.3, 151.9, 137.2, 133.2, 130.8, 124.6, 123.0, 118.3, 118.1, 116.5, 114.6, 105.4, 56.0 ppm.

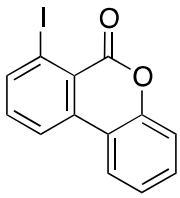
[175]Cook, J. W.; Dickson, G.T.; Jack, J.; Loudon, J. D.; McKeown, J.; MacMillan, J.; Williamson, W.F. *J. Chem. Soc.***1950**,*0*, 139.



9-pivaloyl-6H-benzo[c]chromen-6-one 372. Following general procedure A, 5-pivaloyl-[1,1'-biphenyl]-2-carboxylic acid(0.5 mmol) was used. Columnchromatography: silica gel, hexanes/EtOAc 95:5. White solid; yield: 75 mg (54 % yield). M.p. = 85-86 ºC.^{1}H NMR (500 MHz, CD_3OD) δ8.39 (dd, *J* = 8.2, 0.6 Hz, 1H), 8.29-8.14 (m, 1H), 8.10-7.97 (m, 1H), 7.74 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.48 (ddd, *J*= 8.5, 7.2, 1.5 Hz, 1H), 7.41-7.32 (m, 2H), 1.38 (s, 9H) ppm.^{13}C NMR (101 MHz, $CDCl_3$) δ209.6, 160.7, 151.7, 145.3, 135.1, 131.3, 130.7, 127.2, 125.0, 123.2, 122.5, 121.1, 118.1, 117.8, 44.8, 27.9 ppm. HRMS *calcd* for ($C_{18}H_{16}O_3$+H^+): 281.1172, found 281.1177.



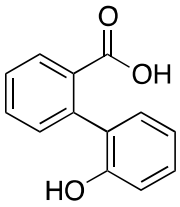
7,8,9,10-tetrahydro-6H-benzo[c]chromen-6-one 370. Following general procedure A, 3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylic acid(0.5 mmol) was used. Columnchromatography: silica gel, hexanes/EtOAc 95:5. White solid; yield: 65 mg (51 % yield). M.p. = 118-120 ºC.^{1}H NMR (500 MHz, CD_3OD) δ7.56 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.45 (ddd, *J* = 8.5, 7.2, 1.5 Hz, 1H), 7.34-7.23 (m, 2H), 2.92- 2.74 (m, 2H), 2.70-2.51 (m, 2H), 1.95-1.71 (m, 4H) ppm.^{13}C NMR (126 MHz, $CDCl_3$) δ162.0, 152.3, 147.3, 130.5, 124.3, 124.1, 123.4, 120.5, 117.0, 25.5, 24.4, 21.9, 21.7 ppm. HRMS *calcd* for ($C_{13}H_{12}O_2$+Na): 223.0730, found 223.0737.



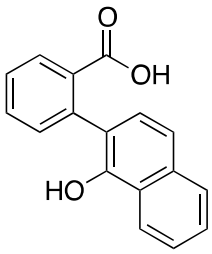
7-iodo-6H-benzo[c]chromen-6-one 373. Following general procedure A, 3-iodo-[1,1'-biphenyl]-2-carboxylic acid (0.5 mmol) was used. Column chromatography: silica gel, hexanes/EtOAc 95:5. White solid; yield: 120 mg (75 % yield). M.p. = 176-178 ºC.^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 7.7, 1.1 Hz, 1H), 8.15 (dd, *J* = 8.1, 1.1 Hz, 1H), 8.00 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.50 (ddd, *J* = 8.6, 7.3, 1.5 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.36-7.31 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 151.2, 143.9, 137.3,

134.8, 131.3, 124.8, 123.3, 122.5, 121.9, 117.95, 117.8, 97.7 ppm. IR (neat, cm^{-1}): 2955, 2922, 2853, 1727, 1253, 1220, 1048, 749. HRMS *calcd* for ($C_{13}H_7IO_2$+Na): 344.9383, found 344.9398.

Synthesis of 2'-hydroxy-[1,1'-biphenyl]-2-carboxylic acid

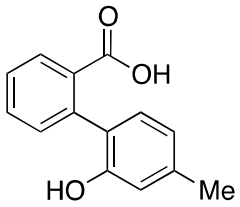


2'-hydroxy-[1,1'-biphenyl]-2-carboxylic acid 374. Following general procedure B, 1,1'-biphenyl]-2 carboxylic acid (0.25 mmol) was used. White solid; yield: 50 mg (72 % yield). The spectroscopic data correspond to those previously reported in the literature.[176] M.p. = 176-178 ºC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.39-8.25 (m, 1H), 8.21 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.90 (ddd, *J* = 8.1, 7.3, 1.4 Hz, 1H), 7.64 (ddd, *J* = 8.2, 7.3, 1.1 Hz, 1H), 7.53 (ddd, *J* = 8.2, 7.3, 1.5 Hz, 1H), 7.45-7.20 (m, 1H). ^{13}C NMR (126 MHz, CD_3OD) δ 163.5, 153.2, 137.2, 136.9, 132.5, 131.9, 130.9, 126.7, 125.1, 124.1, 122.9, 120.1, 119.2.

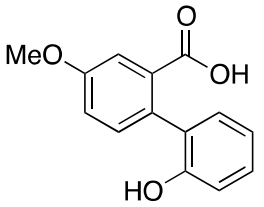


2-(3-hydroxynaphthalen-2-yl)benzoic acid 376. Following general procedure B, 6H-dibenzo[c,h]chromen-6-one(0.25 mmol) was used. White solid; yield: 51 mg (77 % yield). M.p. = 193-194 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (dd, *J* = 8.0, 1.1 Hz, 1H), 8.42-8.36 (m, 2H), 8.34 (dd, *J* = 7.9, 1.4 Hz, 1H), 8.10-7.97 (m, 2H), 7.92 (dd, *J* = 8.8, 0.8 Hz, 1H), 7.79-7.67 (m, 3H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.1, 147.3, 136.4, 135.7, 134.8, 130.7, 130.1, 128.8, 128.2, 125.3, 123.9, 123.8, 122.2, 121.5, 121.0, 113.9 ppm. IR (neat, cm^{-1}): 2951, 2904, 2880, 1736, 1719, 1609, 1101, 755. HRMS *calcd* for ($C_{17}H_{12}O_3$-OH): 247.0754, found 247.0762.

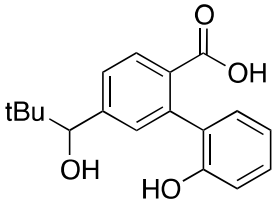
[176]Hey, D. H.; Saunders, F. C.; Williams, G. H.*J. Chem. Soc*.**1961**,554.



2'-hydroxy-4'-methyl-[1,1'-biphenyl]-2-carboxylic acid 375. Following general procedure B, 3-methyl-6H-benzo[c]chromen-6-one(0.25 mmol) was used. White solid; yield: 54 mg (95 % yield). M.p. = 131-132 ºC. ^{1}H NMR (400 MHz, CD_3OD) δ8.30 (dd, *J* = 20.2, 8.0 Hz, 2H), 8.11 (d, *J* = 8.1 Hz, 1H), 8.02-7.70 (m, 0H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.43-6.96 (m, 1H), 2.47 (s, 2H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.3, 151.6, 142.1, 136.2, 135.4, 130.6, 129.7, 126.7, 124.3, 123.3, 121.1, 118.2, 116.0, 21.8. IR (neat, cm^{-1}): 3063, 3038, 2922, 2854, 1737, 1606, 1459, 1308. HRMS *calcd* for ($C_{14}H_{12}O_3$-OH): 226.0624, found 226.0631.

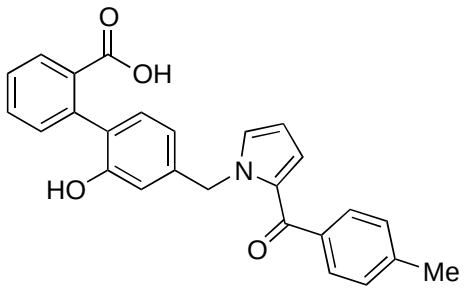


2'-hydroxy-4-methoxy-[1,1'-biphenyl]-2-carboxylic acid 377. Following general procedure B, 3-methyl-6H-benzo[c]chromen-6-one(0.25 mmol) was used. White solid; yield: 54 mg (95 % yield). M.p. = 131-132 ºC. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.38 (d, *J* = 8.9 Hz, 1H), 8.30 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.67 (d, *J* = 2.8 Hz, 1H), 7.62-7.49 (m, 2H), 7.47-7.37 (m, 2H), 3.94 (s, 1H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.0, 160.6, 150.8, 130.5, 128.5, 125.7, 125.5, 124.6, 124.0, 122.8, 118.7, 118.0, 112.1, 56.6. IR (neat, cm^{-1}): 3006, 2922, 2845, 1710, 1612, 1481, 1460, 1298, 1279, 1242. HRMS *calcd* for ($C_{14}H_{12}O_4$-OH): 227.0703, found 227.0714.

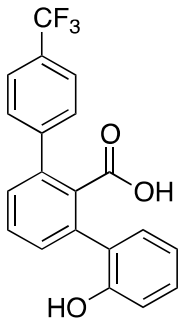


2'-hydroxy-5-(1-hydroxy-2,2-dimethylpropyl)-[1,1'-biphenyl]-2-carboxylic acid 378. Following general procedure B, 9-(1-hydroxy-2,2-dimethylpropyl)-6H-benzo[c]chromen-6-one(0.25 mmol) was used. White solid; yield: 51 mg (88 % yield). M.p. = 143-145 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.32 (d, *J* = 1.5 Hz, 1H), 8.24 (d, *J* = 8.2 Hz, 1H), 7.67 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.64-7.57 (m, 1H), 7.51-7.40 (m, 2H), 5.60 (d, *J* = 4.4 Hz, 1H), 4.53 (d, *J* = 4.3 Hz, 1H), 0.93 (s,

9H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.6, 162.1, 161.2, 143.6, 141.0, 139.3, 139.1, 135.2, 133.8, 131.7, 129.5, 128.3, 127.7, 90.0, 45.8, 36.3 ppm. IR (neat, cm^{-1}): 3481, 2953, 2868, 1705, 1613, 1420, 1283, 1235, 747. HRMS *calcd* for ($C_{18}H_{20}O_4$-OH): 283.1329, found 283.1337.

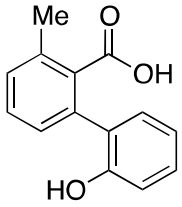


2'-hydroxy-4'-((2-(4-methylbenzoyl)-1H-pyrrol-1-yl)methyl)-[1,1'-biphenyl]-2 carboxylic acid 379. Following general procedure B, 3-((2-(4-methylbenzoyl)-1H-pyrrol-1-yl)methyl)-6H-benzo[c]chromen-6-one was used.White solid; yield: 40 mg (95 % yield). M.p. = 169.8-171.2 ºC. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.39 (d, J = 8.1 Hz, 1H), 8.32 (d, J = 8.3 Hz, 1H), 8.25 (dd,J = 7.9, 1.4 Hz, 1H), 8.02-7.91 (m, 1H), 7.78-7.67 (m, 1H), 7.64 (d, J = 8.1 Hz,2H), 7.59-7.50 (m, 1H), 7.33 (d, J = 7.8 Hz, 2H), 7.18 (dd, J = 8.2, 1.7 Hz,1H), 7.11 (d, J = 1.7 Hz, 1H), 6.81 (dd, J = 4.1, 1.7 Hz, 1H), 6.35 (dd, J = 4.0,2.5 Hz, 1H), 5.78 (s, 2H), 2.40 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ185.8, 161.2, 151.7, 143.3, 142.9, 137.5, 136.4, 135.1, 133.1, 130.7, 130.2,130.2, 130.0, 129.8, 124.9, 124.0, 123.9, 123.5, 121.4, 117.6, 116.0, 109.9, 51.9, 22.0 ppm. IR (neat, cm^{-1}): 3121, 1736, 1621, 1605, 1407, 1393, 1102,744. HRMS calcd for ($C_{26}H_{20}NO_3$-OH): 394.1438, found 394.1438.



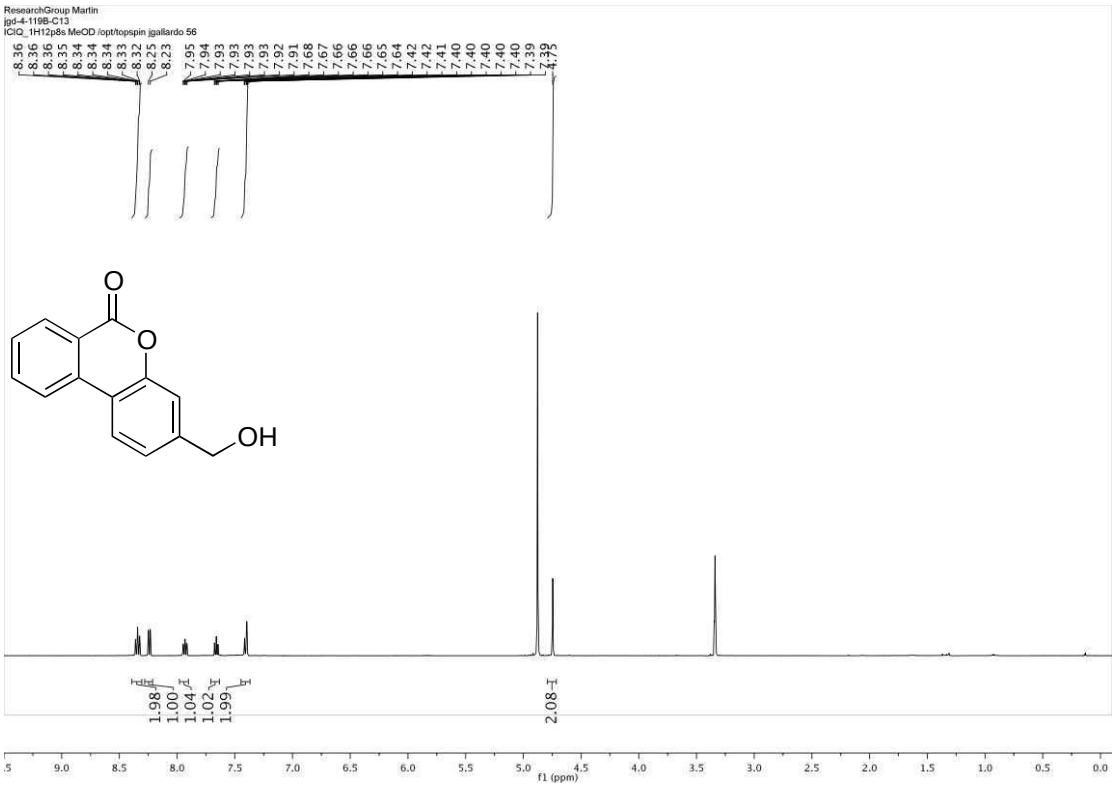
2-hydroxy-4''-(trifluoromethyl)-[1,1':3',1''-terphenyl]-2'-carboxylic acid 381. Following general procedure B, 7-(4-(trifluoromethyl)phenyl)-6H-benzo[c]chromen-6-one (0.25 mmol) was used. White solid; yield: 85 mg (95 % yield). M.p. = 95-97 ºC.^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (dd, *J* = 8.2, 1.2 Hz, 1H), 8.46 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.01 (t, *J* = 7.7 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.67-7.59 (m, 3H), 7.50 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.48-7.40 (m, 2H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.5,

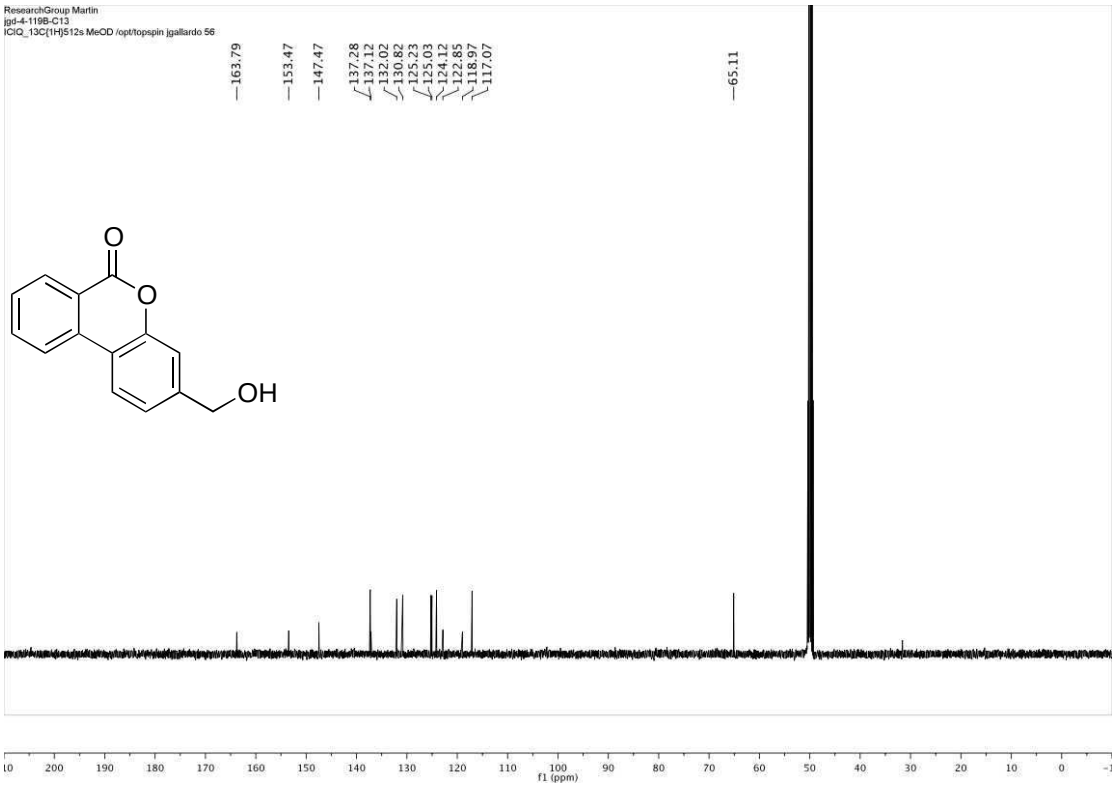
151.7, 147.1, 144.9, 136.7, 135.3, 133.0, 131.9, 130.1, 128.4 (d, *J* = 31.8 Hz), 126.5 (d, *J* = 272 Hz), 125.6 , 125.3 (q, *J* = 3.8 Hz), 125.0 , 124.3 (d, *J* = 272 Hz), 123.7 , 119.0, 118.6 , 117.8 ppm. IR (neat, cm^{-1}): 3065, 2959, 2923, 1682, 1293, 1272. HRMS *calcd* for ($C_{18}H_{20}O_4$-OH): 283.1329, found 283.1337.



2'-hydroxy-3-methyl-[1,1'-biphenyl]-2-carboxylic acid 382. Following general procedure B, 7-methyl-6H-benzo[c]chromen-6-one(0.25 mmol) was used. White solid; yield: 46 mg (81 % yield). M.p. = 100-101 ºC.^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (ddd, *J* = 16.2, 8.1, 1.3 Hz, 2H), 7.74 (t, *J* = 7.8 Hz, 1H), 7.52 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.47-7.41 (m, 1H), 7.40-7.27 (m, 2H), 2.73 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.4, 151.6, 135.3, 133.2, 131.5, 130.2, 129.5, 125.4, 124.7, 121.5, 119.8, 118.8, 117.7, 24.3 ppm. IR (neat, cm^{-1}): 3422, 3069, 3044, 2961, 2920, 2850, 1717, 1599, 1242, 1206. HRMS *calcd* for ($C_{14}H_{12}O_3$-OH): 211.0759, found 211.0763.

3.7.5 Selected examples of NMR spectra.


ResearchGroup Martin
jgd-4-119B-C13
ICIQ_1H12p8s MeOD /opt/topspin jgallardo 56
8.36 8.36 8.36 8.35 8.34 8.34 8.33 8.32 8.25 8.23
7.95 7.94 7.93 7.93 7.93 7.92 7.91 7.68 7.67 7.66 7.66 7.66 7.65 7.64 7.42 7.42 7.41 7.40 7.40 7.40 7.40 7.39 7.39 7.35
O
O
OH
1.98 1.00 1.04 1.02 1.99
2.08
f1 (ppm)


ResearchGroup Martin
jgd-4-119B-C13
ICIQ_13C{1H}512s MeOD /opt/topspin jgallardo 56
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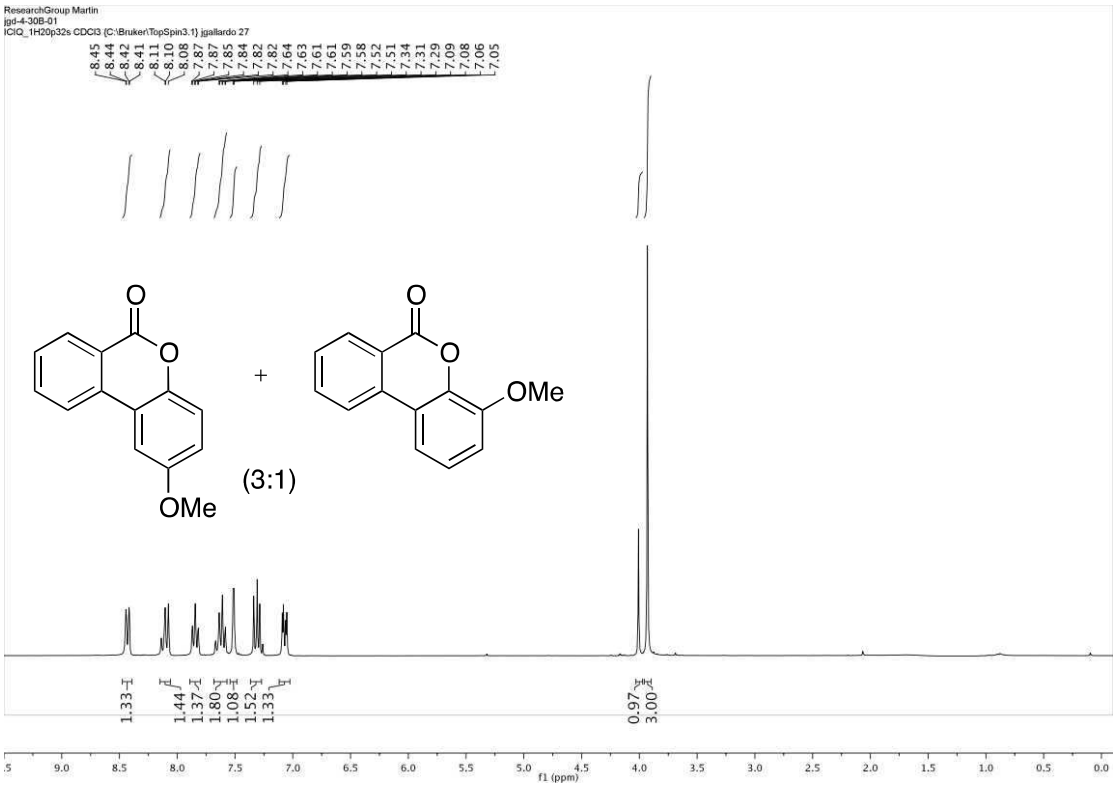
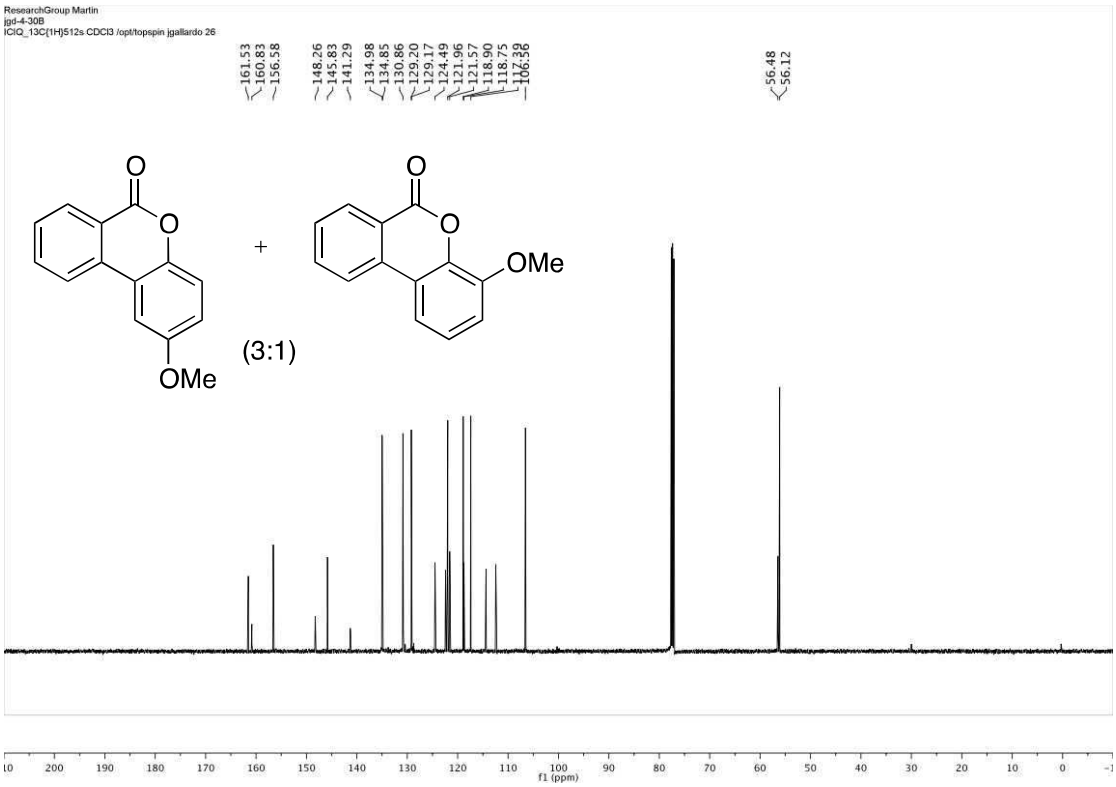
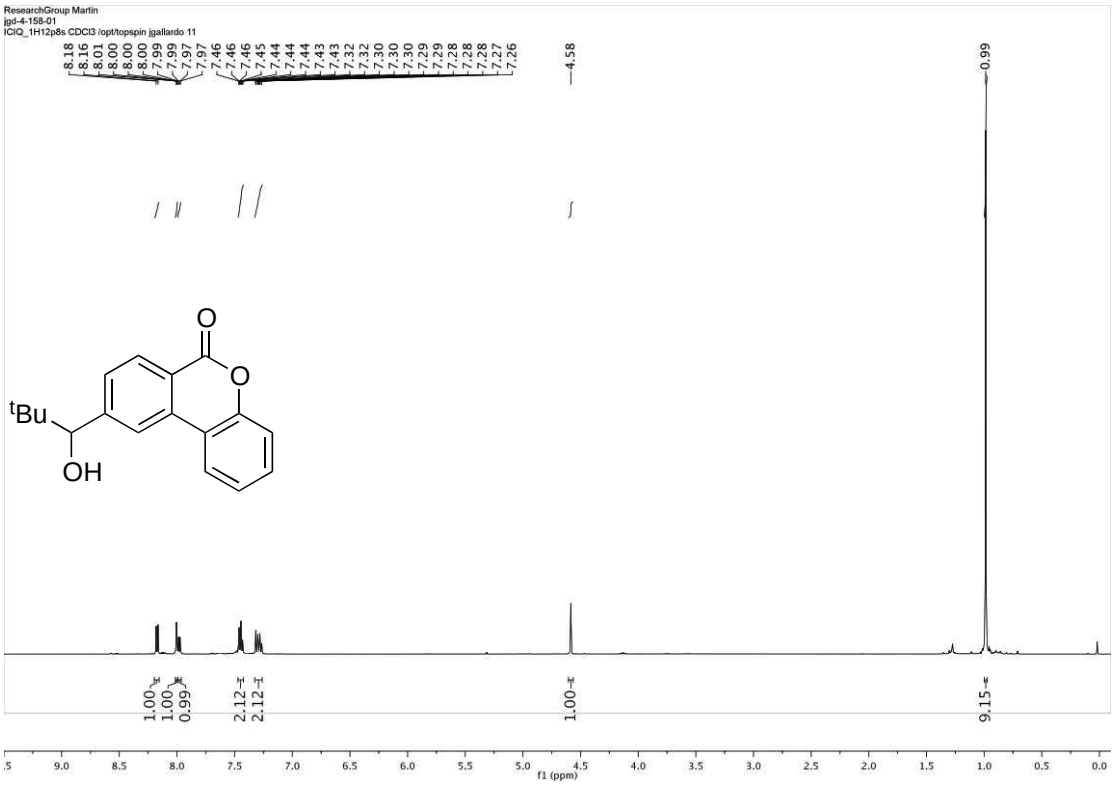
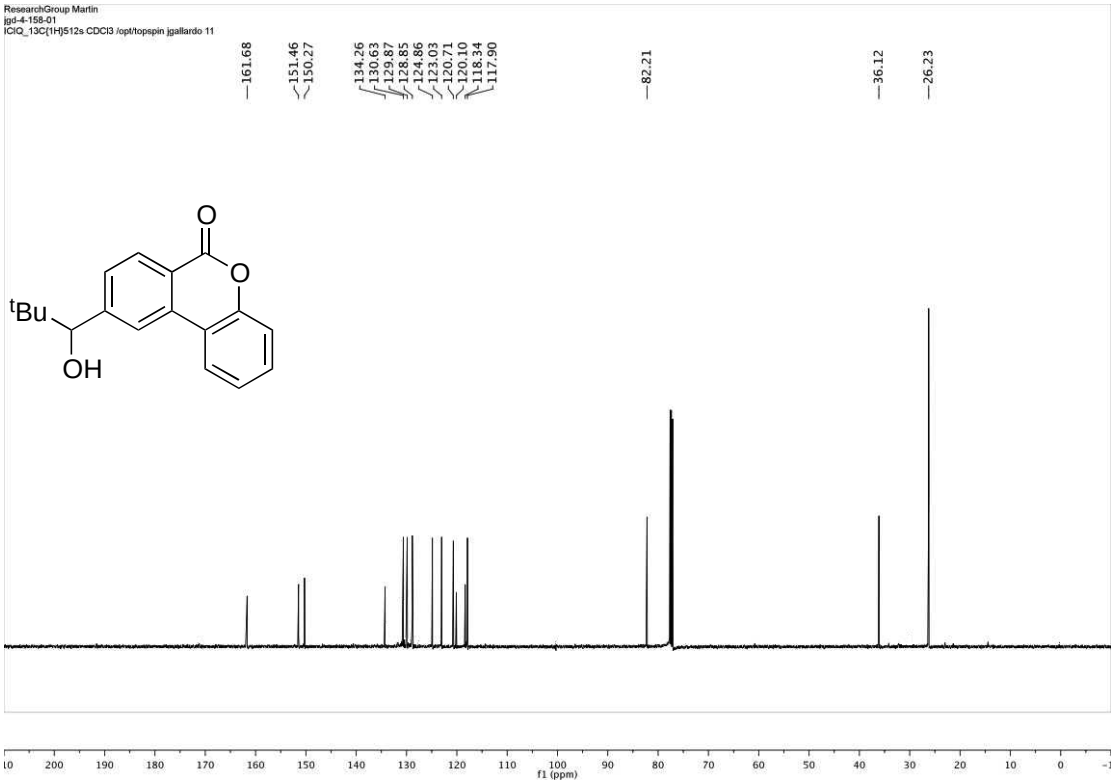
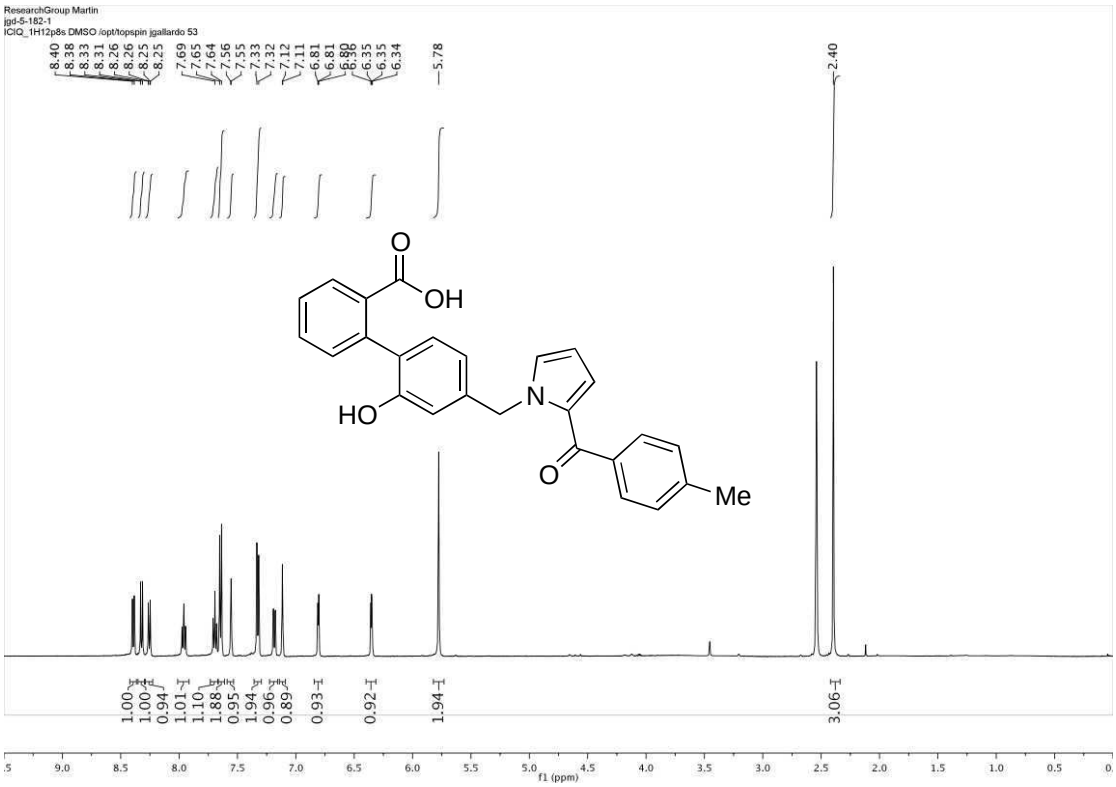
153.47
147.47
137.28
137.12
132.02
130.82
125.23
125.03
124.12
122.85
118.97
117.07
65.11
O
O
OH
f1 (ppm)

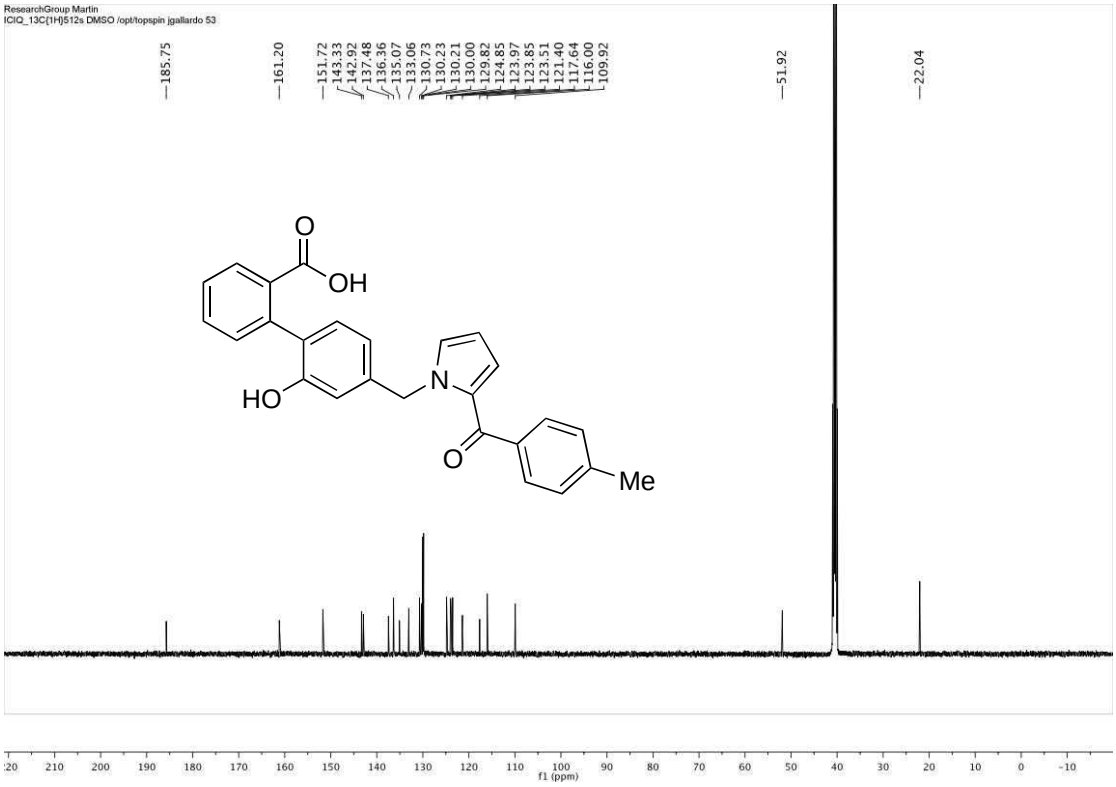

ResearchGroup Martin
jgd-4-30B-01
ICIQ_1H20p32s CDCl3 {C:\Bruker\TopSpin3.1} jgallardo 27
8.45
8.44
8.42
8.41
8.11
8.10
8.08
7.87
7.87
7.85
7.84
7.82
7.82
7.64
7.63
7.61
7.61
7.59
7.58
7.52
7.51
7.34
7.31
7.29
7.09
7.08
7.06
7.05
O
O
OMe
+
O
O
OMe
(3:1)
1.33
1.44
1.37
1.80
1.08
1.52
1.33
0.97
3.00
f1 (ppm)


ResearchGroup Martin
jgd-4-30B
ICIQ_13C{1H}512s CDCl3 /opt/topspin jgallardo 26
161.53
160.83
156.58
148.26
145.83
141.29
134.98
134.85
130.86
129.20
129.17
124.49
121.96
121.57
118.90
118.75
56.48
56.12
O
O
OMe
+
O
O
OMe
(3:1)
f1 (ppm)


ResearchGroup Martin
jgd-4-158-01
ICIQ_1H12p8s CDCl3 /opt/topspin jgallardo 11
8.18
8.16
8.01
8.00
8.00
8.00
7.99
7.99
7.97
7.97
7.97
7.46
7.46
7.46
7.45
7.44
7.44
7.44
7.43
7.43
7.32
7.32
7.30
7.30
7.30
7.29
7.29
7.28
7.28
7.28
7.27
7.26
4.58
0.99
O
O
tBu
OH
1.00
1.00
0.99
2.12
2.12
1.00
9.15
f1 (ppm)


ResearchGroup Martin
jgd-4-158-01
ICIQ_13C{1H}512s CDCl3 /opt/topspin jgallardo 11
161.68
151.46
150.27
134.26
130.63
129.87
128.85
124.86
123.03
120.71
120.10
118.34
117.90
82.21
36.12
26.23
O
O
tBu
OH
f1 (ppm)

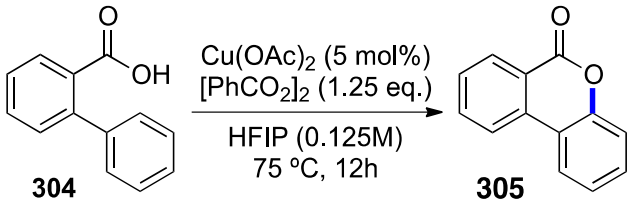




3.7.6 Mechanistic considerations

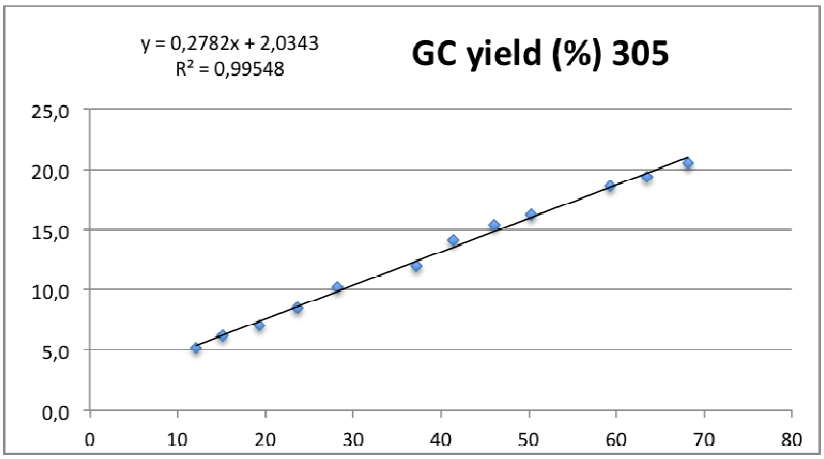
Kinetic isotope effect

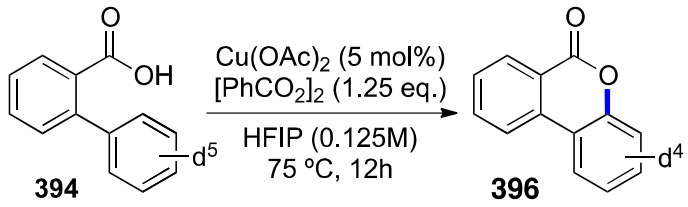
General Procedure. Kinetic experiments were run in a reactor tube filled with Ar. Reactions were run up to 50 % conversions. Only values up to 5-25% were considered for measuring the kinetic isotope effect and the data (% product versus time) was analyzed using the initial rates method.Product yield from the corresponding reaction was monitored by GC analysis using decane as internal standard in the indicated interval based on the amount of 6H-benzo[c]chromen-6-one. The calculated KIE = 1.22.



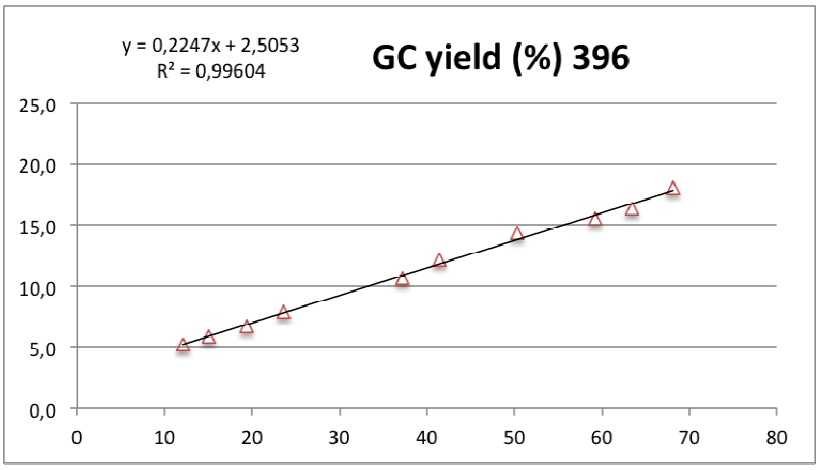
304 305

t (min)	A(decane)	A (lactone)	GC yield (%)
12,12	93,95	6,05	5,2
15,12	92,91	7,09	6,2
19,34	91,97	8,03	7,1
23,6	90,45	9,551	8,6
28,24	88,79	11,21	10,2
37,16	87,104	12,895	12,0
41,4	85,16	14,84	14,1
46,06	84,05	15,95	15,4
50,32	83,26	16,74	16,3
59,22	81,273	18,727	18,7
63,44	80,69	19,306	19,4
68,12	79,814	20,186	20,5





t (min)	A(decane)	A (lactone)	GC yield (%)
12,12	93,98	6,018	5,2
15,12	93,22	6,7765	5,9
19,34	92,32	7,679	6,7
23,6	91,149	8,85	7,9
37,16	88,407	11,593	10,6
41,4	86,97	13,032	12,1
50,32	84,741	15,009	14,3
59,22	83,917	16,083	15,5
63,44	83,222	16,777	16,3
68,12	81,794	18,21	18,0


y = 0,2247x + 2,5053
R² = 0,99604
GC yield (%) 396
25,0
20,0
15,0
10,0
5,0
0,0
0
10
20
30
40
50
60
70
80

UNIVERSITAT ROVIRA I VIRGILI
SYNTHESIS OF PHTHALIDES AND BENZOLACTONES VIA CATALYTIC
C-H FUNCTIONALIZATION/C-O BOND-FORMING REACTIONS
Juan Gallardo Donaire
Dipòsit Legal: T 1365-2014

Chapter 4. Mild C(sp^2)-H functionalization/C-O bond formation mediated by hypervalent iodine (III) reagents

4.1 Objectives

The objectives of this chapter are the following:

- To develop a mild and operationally simple metal-free C(sp^2)-H bond functionalization/C-O bond formation mediated by I(III) reagents towards the synthesis of dibenzopyranones.
- To explore both the chemo- and regioselectivity associated to this transformation.

4.2 Brief introduction to hypervalent iodine(III) chemistry

Hypervalent iodine chemistry has witnessed a *reinassance* in recent years owing to their high versatility, low toxicity and the mild conditions at which these reagents operate.[177]The term 'hypervalent' was defined in 1969 and covers molecules of the groups 15-18 bearing more than 8 electrons on the valence shell.[178]Aryl iodine(III) compounds, also defined as aryl λ^3-iodanes or $ArIL_2$ (L= heteroatom ligand), exhibits a pseudotrigonal bipyramidal geometry (Figure 4.1). The two ligands (L) are accommodated in the apical position, while the aryl group and the two lone pair of electrons are in an equatorial position. The aryl group is bound by a normal two-electron covalent bond with $5sp^2$ hybridization. On the other hand, the linear L−I−L bond uses two electrons from the occupied 5p orbital on iodine and one electron from each ligand. Overall, $ArIL_2$ can be visualized as reagents with 3-centers and 4-electrons (3c-4e). This is defined as a hypervalent 3-center 4-electron bond (3c-4e). As illustrated in Figure 4.1, the two lower energy molecular orbitals (bonding and nonbonding) of this 3c-4e bond are occupied. Due to nodal plane of the filled nonbonding orbital on the central iodine, partial negative charge relies on the apical heteroatom ligands, hence making the iodine particularly electrophilic.

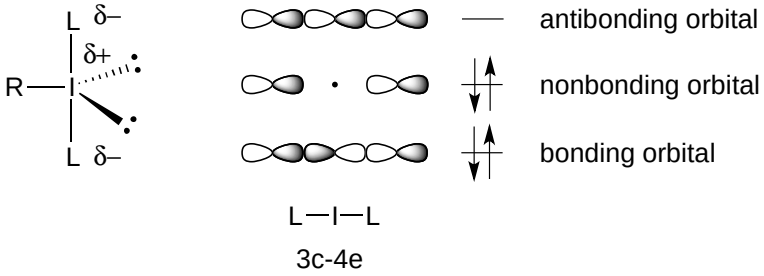


Figure 4.1

Although the mode of action of λ^3-iodanes is not yet well understood, associative or dissociative mechanistic scenarios have been considered (Figure 4.2). The former presumably starts with a nucleophilic attack on the positively charged iodine atom, thus resulting in the *trans*-tetracoordinated square-planar intermediate **LXXVIII** (Figure 4.2 a). Next, an isomerization would take place leading to the *cis* iodate species **LXXIX**,

[177] For a selection of reviews dealing with hypervalent I(III) see: (a) Wirth, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 3656. (b) In *Topics in Current Chemistry;* Wirth, T., Ed.; Springer: Berlin, 2003. (c) Ochiai, M. *Chem. Rec.* **2007**, *7*, 12. (d) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (e) Uyanik, M.; Ishihara, K. *Chem. Commun.* **2009**, 2086. (f) Yusubov, M. S.; Maskaev, A. V.; Zhdankin, V. V. *ARKIVOC* **2011**, *1,* 370.
[178] Musher, J. J. *Angew. Chem. Int. Ed.***1969**, *54*, 8.

affording a new aryl-λ^3-iodane **LXXX**. The overall process is called ligand exchange and involves the swap of a heteroatom ligand on the I(III) for an incoming nucleophile via addition-elimination sequence. On the other hand, despite no evidence have been provided for the dissociative pathway, it is believed to proceed *via* initial ligand dissociation, followed by nucleophilic attack (Figure 4.2 b).

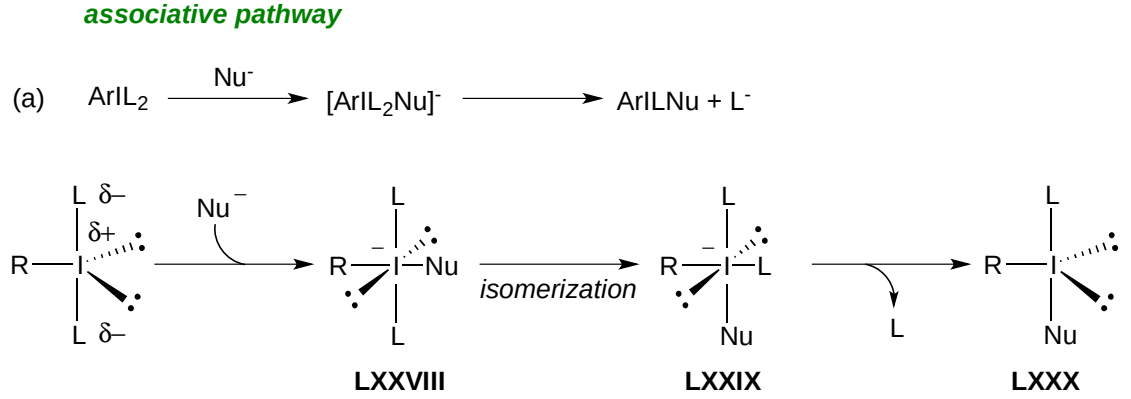
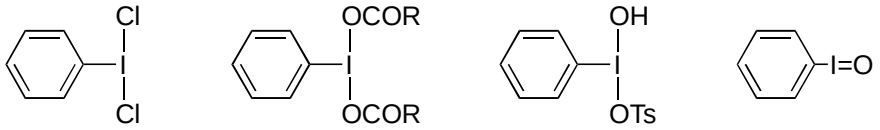


Figure 4.2

Representative examples of hypervalent iodine(III) reagents are shown in Figure 4.3. Whereas most of these compounds were originally developed as alternative oxidants replacing other heavy-metal oxidizers such as Pb(IV), Hg(II) or Tl(III), they have been employed in many other useful synthetic transformations including cyclizations,[179]α-functionalization of carbonyl compounds,[180] atom-transfer reactions[181] and oxidative rearrangements.[182]

[179] (a) Pardo, L. M.; Tellitu, I.; Domínguez, E. *Synthesis2010*, 971.(b) Singh, F. V.; Wirth, T.*Org. Lett*. **2011**, *13*, 6504.(c) Du, X.; Chen, H.; Chen, Y.; Chen, J.; Liu, Y. *Synlett***2011**, 1010. (d)Huang, P.; Fu, X.; Liang, Y.; Zhang, R.; Dong, D.*Aust. J. Chem.***2011**, *65*, 121. (e)Wardrop, D. J.; Yermolina, M. V.; Bowen, E. G.*Synthesis***2012**, *44*, 1199. (f) Paz, N. R.; Santana, A. G.; Suarez, C. G.; Francisco, E.; Gonzalez, C.C.*Org. Lett*. **2012**, *14*, 3388.(g) Singh, S. V.; Wirth, T. *Synthesis***2012**, *44*, 1171. (h) Kajiyama, D.; Saitoh, T.; Yamaguchi, S.; Nishiyama, S. *Synthesis***2012**, *44*, 1667.
[180]Merritt, E. A.; Olofsson, B.*Synthesis***2011**, 517.
[181] Brand, J. P.; Gonzalez, D. F.; Nicolai, S.; Waser, J. *Chem. Commun*. **2011**, *47*, 102.
[182](a) Richardson, R. D.; Wirth, T. *Angew. Chem. Int. Ed*. **2006**, *45*, 4402. (b) Ochiai, M., K. Miyamoto, K. Eur. J. Org. Chem. **2008**, 4229. (c)Dohi, T.; Kita, Y.*Chem. Commun.***2009**, 2073.



Willgerodt's reagent **398** | R= CH_3 (PIDA) **399**, R= CH_3 (PIFA) **400** | Koser's reagent **401** | Iodosobenzene **402**

Figure 4.3

4.3 I(III)-mediated intramolecular C-H bond functionalization/C-O bond forming reactions

Recently, the use aryl λ^3-iodanes in C-H functionalization processes have gained considerable momentum,[183] due to the avoidance of expensive metal salts and the formation of environmentally acceptable byproducts. Moreover, catalytic strategies for generating the active I(III) reagent *in situ* have emerged as viable alternatives with a suitable choice of the terminal oxidant. Not surprisingly, metal-free carbon-heteroatom bond formation has become an active field of research in the last years, hence providing alternative methods for the construction of C-N,[184] C-S[185] and C-O bonds. The latter will be discussed below in detail.

Several intramolecular oxidative C(sp^2)-O bond forming reactions have been reported for the construction of 5,6 and 7 membered rings. In this regard, Rodrigues disclosed in 1994 one of the first examples of I(III) C-O bond forming reactionsen route to the synthesis of cularine alkaloids (Figure 4.4).[186] The highly electrophilic reagent **405** was employed to active the sodium phenoxide **403**. The authors proposed **LXXXI**as a feasible intermediate, generated by an *in situ*ligand exchange. After

[183]Samanta, R.; Matcha, K.; Antonchick, A. P. *Eur. J. Org. Chem.* **2013**, 576.
[184] For selected examples see: (a) Röben, C.; Souto, J. A.; González, Y.; Lishchynskyi, A.;Muñiz, K. Angew. Chem. Int. Ed. 2011, 50, 9478. (b) Souto, J. A.; González, Y.; Iglesias, Á.; Zian, D.; Lishchynskyi, A.; Muñiz, K. Chem. Asian J. 2012, 7, 1103. (c) Kim, H. J.; Kim, J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc*. **2011**, *133*, 16382. (d) Kantak, A. A.; Potavathri, S.; Barham, R. A.; Romano, K. M.; de-Boef, B. *J. Am. Chem. Soc*. **2011**, *133*, 19960. (e) Ochiai, M.; Miyamoto, K.; Kaneaki, T.; Hayashi, S.; Nakanishi, W. Science**2011**, *332*, 448. (f)Yoshimura, A.; Nemykin, V. N.; Zhdankin, V. V. *Chem.—Eur. J*. **2011**, *17*, 10538. (g) Richardson, R.D.; Desaize, M.; Wirth, T. *Chem.—Eur. J*. **2007**, *13*, 6745. (h) Li, J.; Chan, P. W. H.; Che, C.-M. *Org. Lett*. **2005**, *7*, 5801. (i) Moriarty, R. M.; Tyagi, S. *Org. Lett.***2010**, *12*, 364. (j) Chung, R.; Yu, E.; Incarvito, C. D.; Austin, D. J. *Org. Lett*. **2004**, *6*, 3881.
[185] For seleted examples see:
[186] (a) Joana, D. F.; Rodrigues, J. A. *J. Am. Chem. Soc.***1994**, 116, 9745. (b) Rodrigues, J. A. R.; Abramovitch, R. a; de Sousa, J. D. F.; Leiva, G. C. *J. Org. Chem.***2004**, *69*, 2920.

cleavage of the weak I-O bond, an electrophilic aromatic substitution is believed to take place ultimately affording **404** via **LXXXII**.

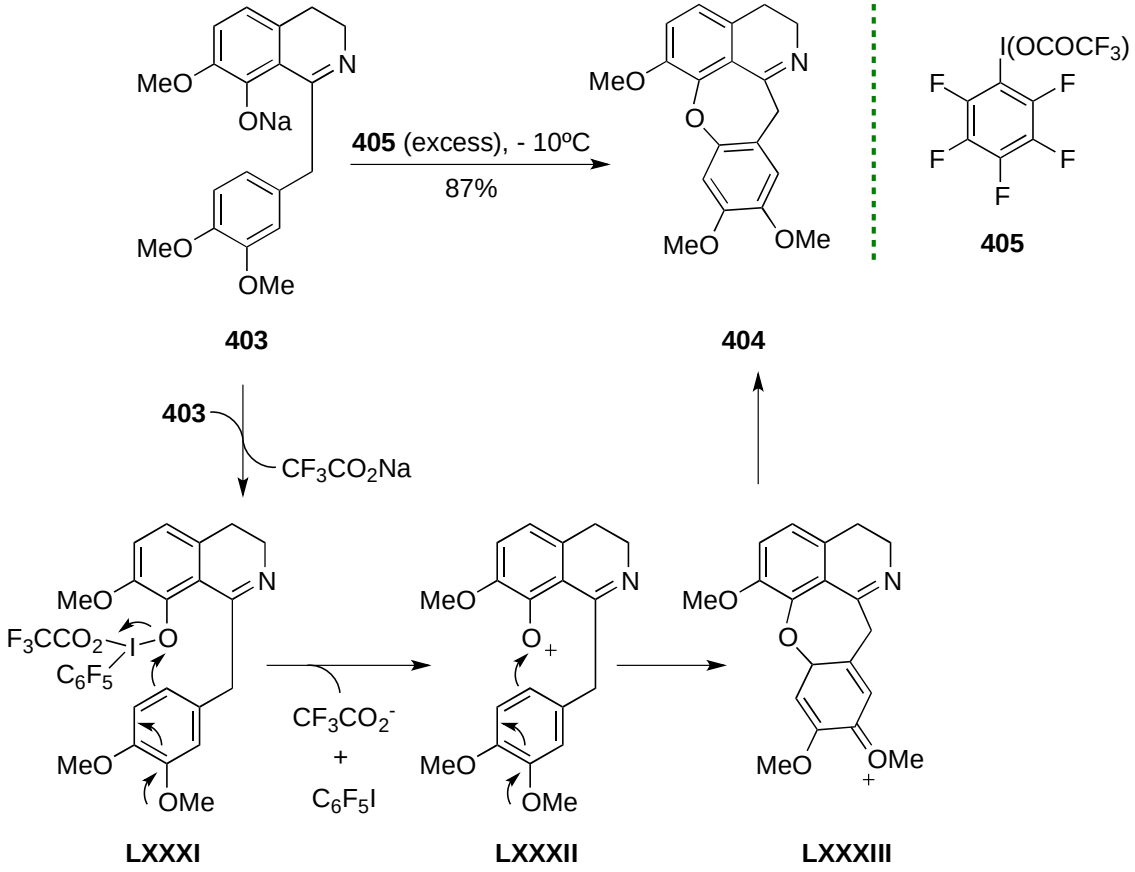


Figure 4.4

Kita reported a PIFA mediated approach towards chroman derivatives **407**(Figure 4.5).[187] This procedure is restricted to anisol-type compounds, and only moderate yields were obtained. The use of HFIP as polar non-nucleophilic solvent turned out to be highly beneficial for the reaction. In addition, the inclusion of solid acidic additives such as montmorillonite MK-10 also improved the yield. A radical mechanism was proposed probably initiated by formation of radical cation **LXXXIV**when treated with PIFA. Subsequent attack of the hydroxyl group into the aromatic ring would form either **LXXXV** (path a) or **LXXXVI** (path b). The successful isolation of**LXXXVII**pointed towards *path b* as the most plausible scenario for this transformation.

[187]Hamamoto, H.; Hata, K.; Nambu, H.; Shiozaki, Y.; Tohma, H.; Kita, Y. *Tetrahedron Lett.***2004**, *45*, 2293.

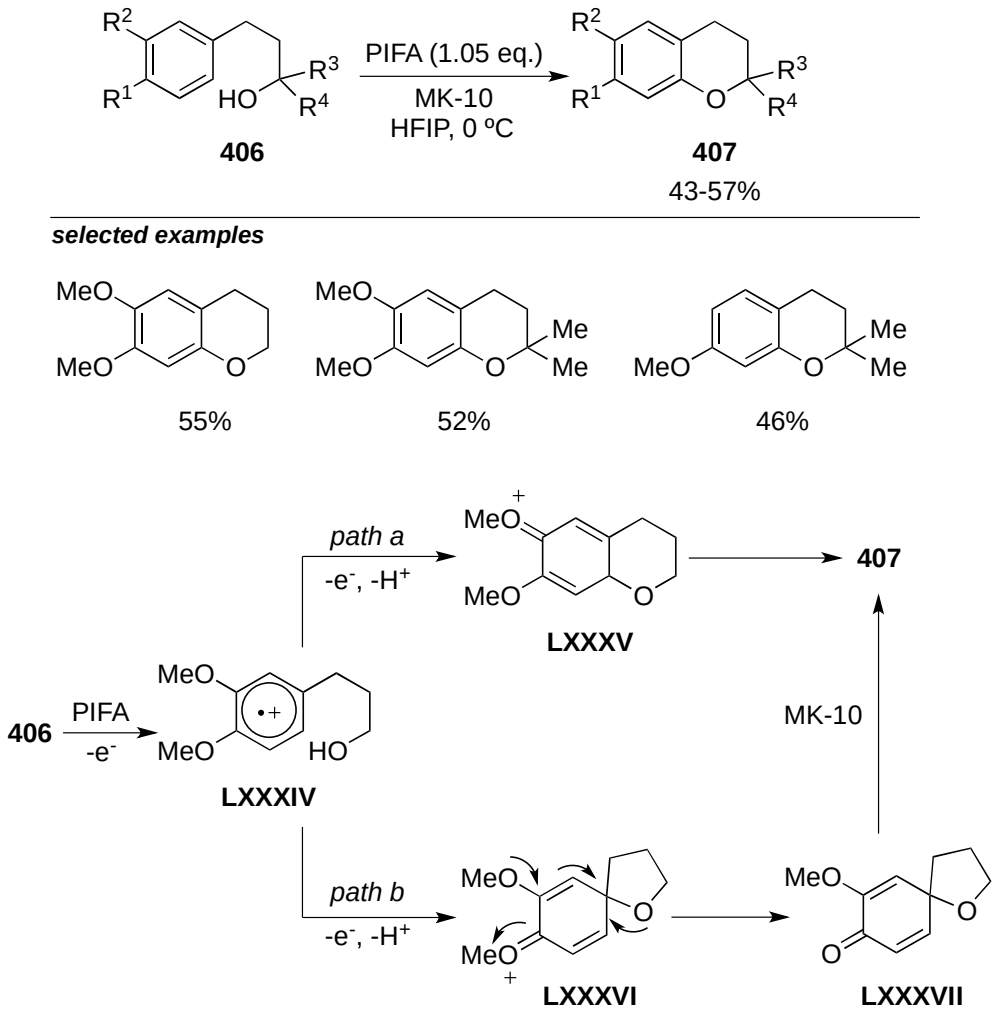


Figure 4.5

Alternatively, the synthesis of benzoxazoles and benzofurans was described by a PIFA-mediated oxidative cyclization of phenylbenzamides **408** (Figure 4.6).[188] In this case, TMSOTf was used as Lewis acid to activate the I(III) reagent. Two different mechanistic scenarios were proposed. First, a nitrenium ion might be formed by the cleavage of N-I bond from **LXXXVIII**. On the contrary, radical cation **LXXXIX** was also proposed as a result of SET between the electron-rich aromatic ring and PIFA.

Wirth reported the synthesis of naphto- and benzofurans from *ortho*-hydroxylstylbenes induced by PIDA under mild conditions.[189] As shown in Figure 4.7, high yields were obtained of the corresponding 2-arylbenzofurans with good chemoselectivity profile. The mechanism is believed to proceed *via* an initial activation of the double bond by the electrophilic hypervalent I(III) forming a 3-membered

[188]Yu, Z.; Ma, L.; Yu, W. *Synlett***2012**, *23*, 1534.
[189]Singh, F.; Wirth, T. *Synthesis***2012**, *44*, 1171.

iodonium species **XC**. Subsequent attack of the phenolic oxygen would lead to **XCI**, which upon deprotonation followed by PhI elimination would form **411**.

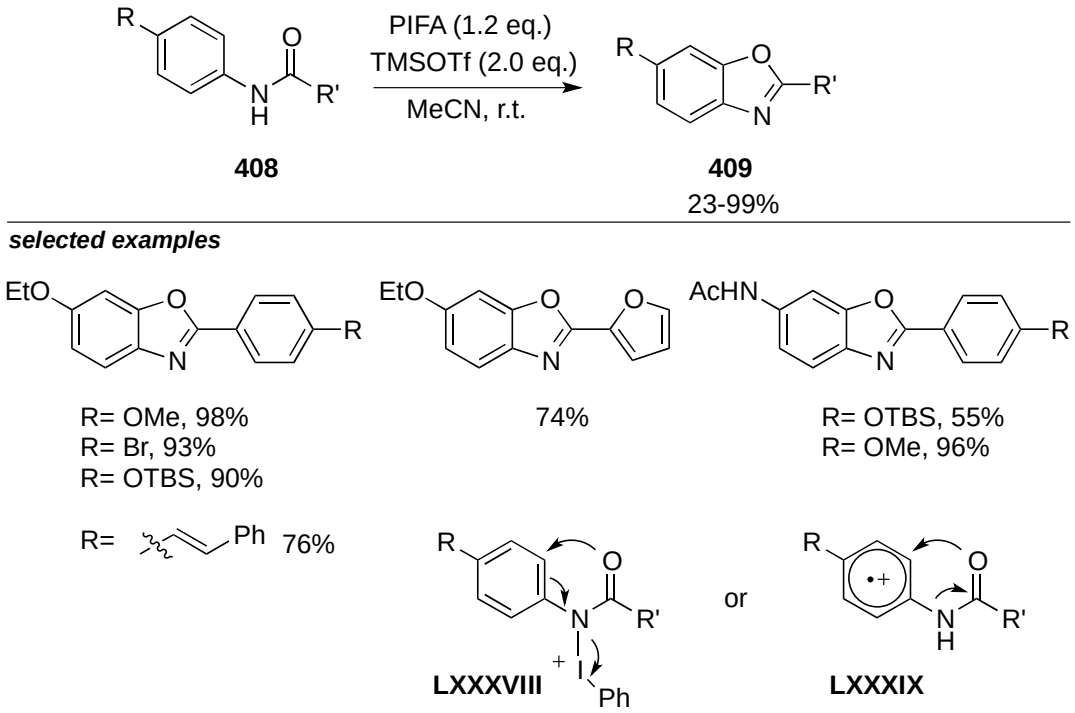


Figure 4.6

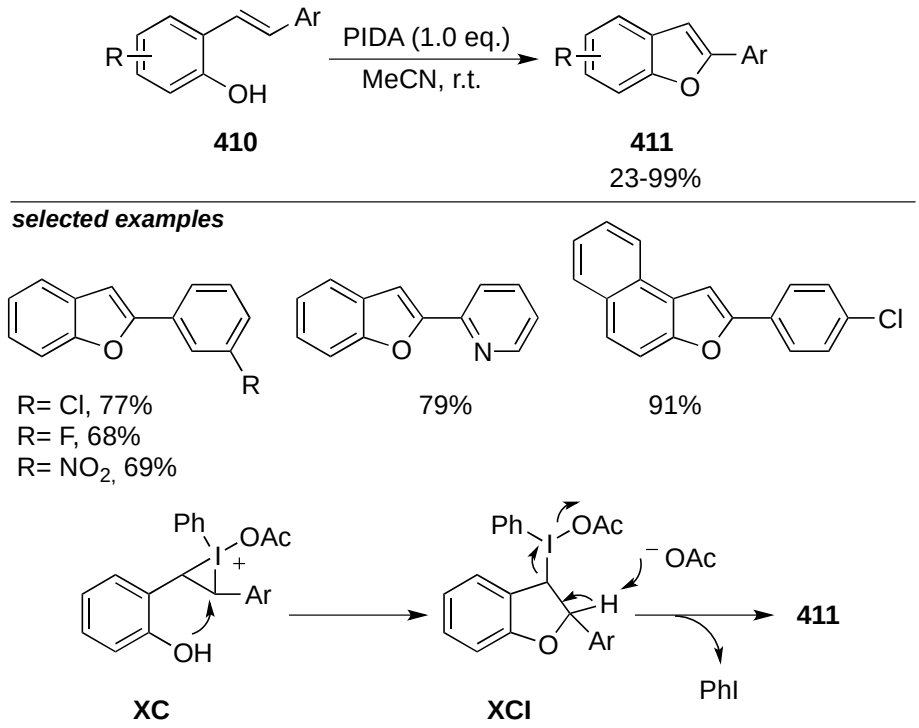


Figure 4.7

Similarly, Zhao described in 2012 the construction of densely functionalized oxazoles (Figure 4.8).[190] This protocol tolerated a wide variety of functional groups in good yields as well as substitutions patterns. Moreover, the synthesis of several oxaprozin analogs was accomplished employing PIDA oxidative ring closure to construct the main oxazole core. The authors proposed intermediate **XCII** after the reaction of PIDA and enamide **412**, which is in equilibrium with **XCIII**. Then, depending on the electronic nature of R^2, two different pathways were envisioned. If R^2 is an EWG, nucleophilic addition of the carbonyl oxygen atom to the sp^2 carbon would occur, providing species **XCIV** en route to **413** with concomitant formation of PhI. On the other hand, when $R^2 \neq$ EWG, direct formation of intermediate **XCVI** would deliver**412**.

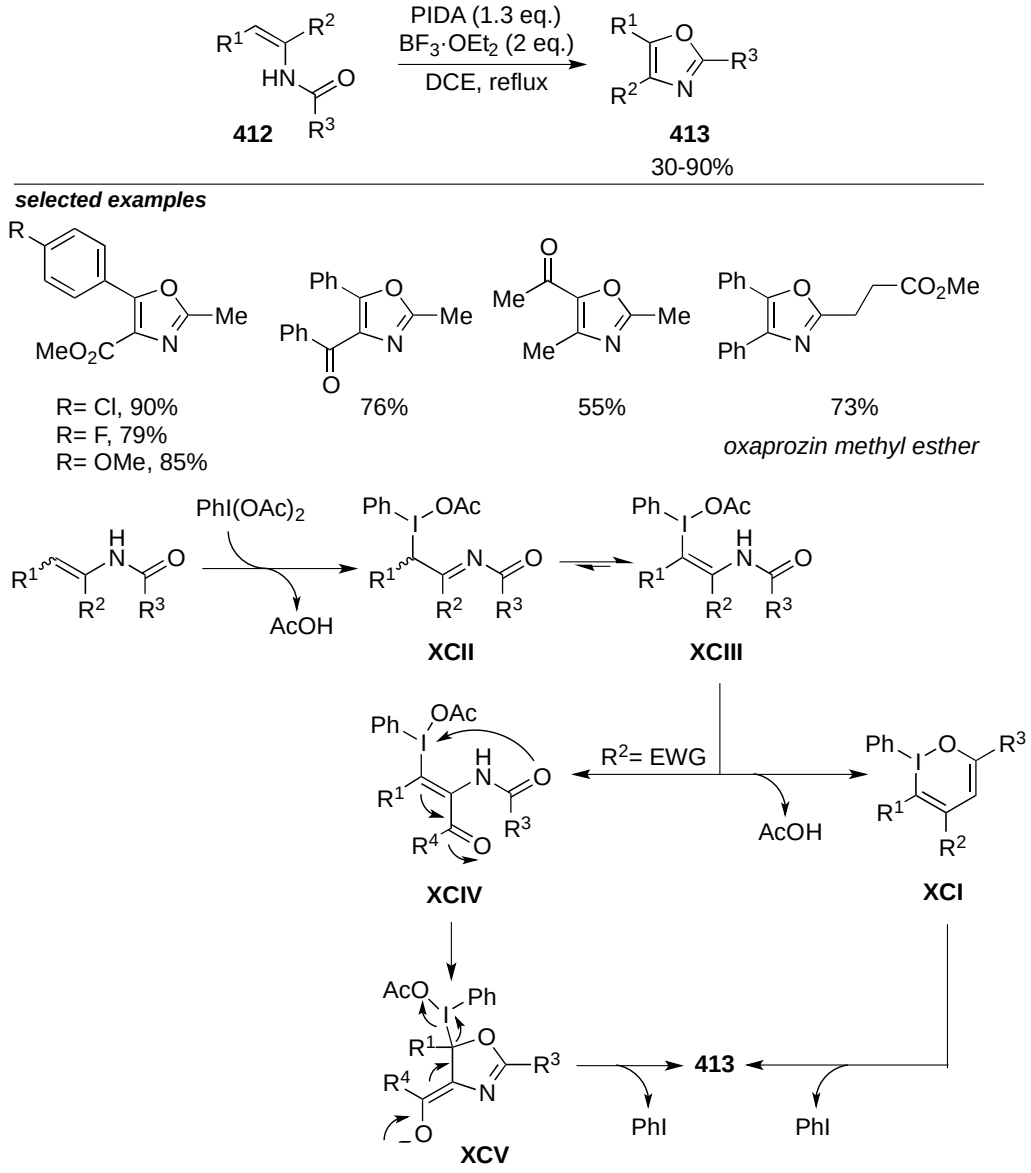


Figure 4.8

[190]Zheng, Y.; Li, X.; Ren, C.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *J. Org. Chem.***2012**, *77*, 10353.

A new alyllic oxycarbonylation reaction was disclosed for the synthesis of dihydropyrimidine fused lactone **415** (Figure 4.9).[191] The treatment of**414** in the presence of PIFA in CH_2Cl_2, allowed the formation of **415** in low to moderate yields. Mechanistically, the authors suggested an initial PIFA-mediated formation of nitrenium ion **XCVII**. Then, a [1,5] hydride shift with concomitant release of PhI delivered**XCVIII**.A final intramolecular C-O bond formation and subsequent work-up yielded **415**.

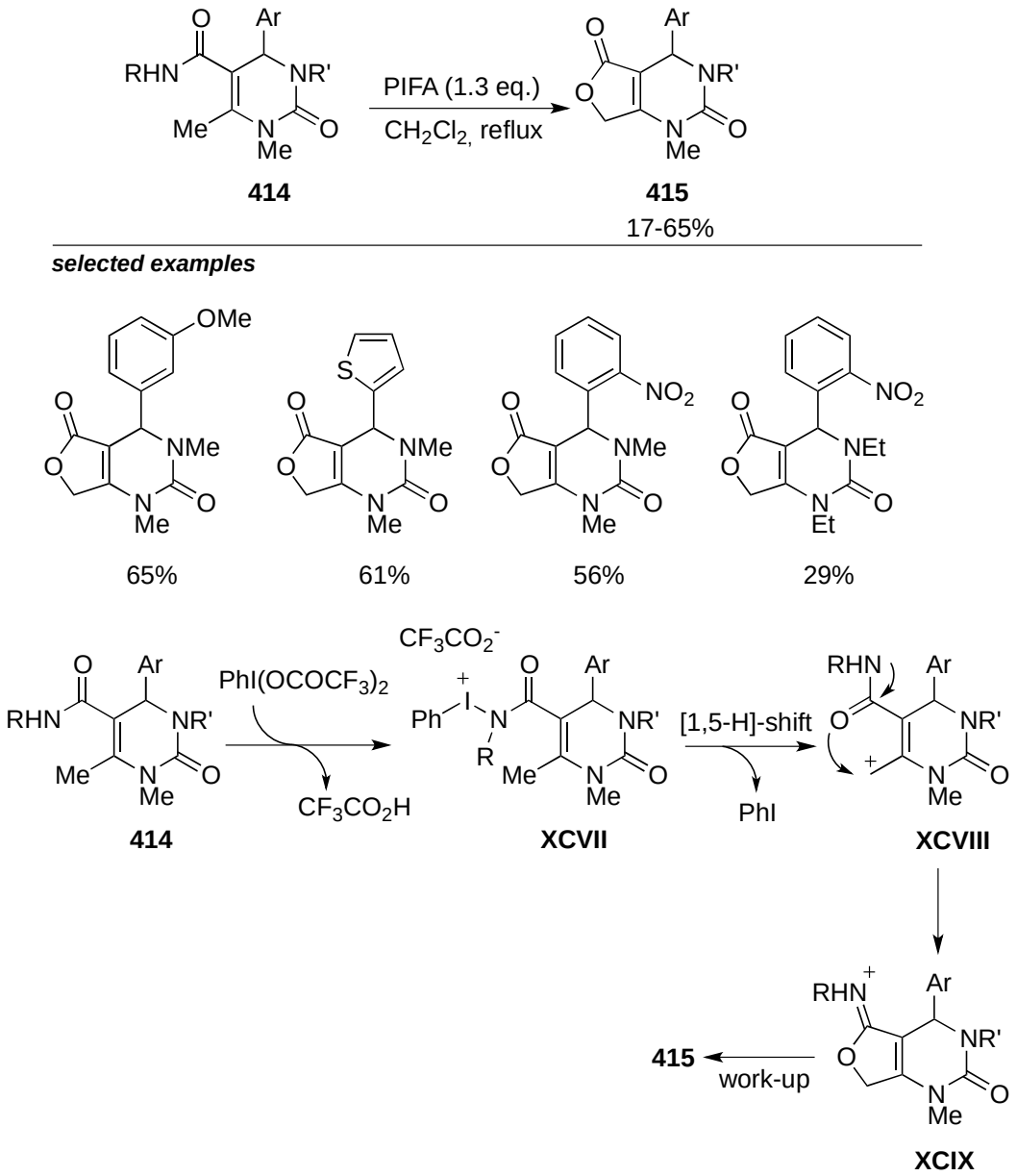


Figure 4.9

[191]Couto, I.; Tellitu, I.; Domínguez, E. *J. Org. Chem.***2010**, *75*, 7954.

4.4 I(III)-mediated intermolecular C-H bond functionalization/C-O bond forming reactions

Hypervalent I(III) reagents have also been employed for the oxidative intermolecular formation of C-O bonds via C-H functionalization. A pioneering work by Kita in 1994 describing the I(III)-induced acetoxylation of *para*-substituted phenyl-ethers served as inspiration for Kikugawa, which reported in 2002 the direct hydroxylation of anilides.[192] Likewise, Gu described the acetoxylation,[193] etherification[193] and tosyloxilaton[194] of anilides (Figure 4.10). An electrophilic aromatic substitution on**C** was proposed as the operating mechanism for this transformation. In most cases, good *para* selectivities were obtained, as expected from a cationic pathway.

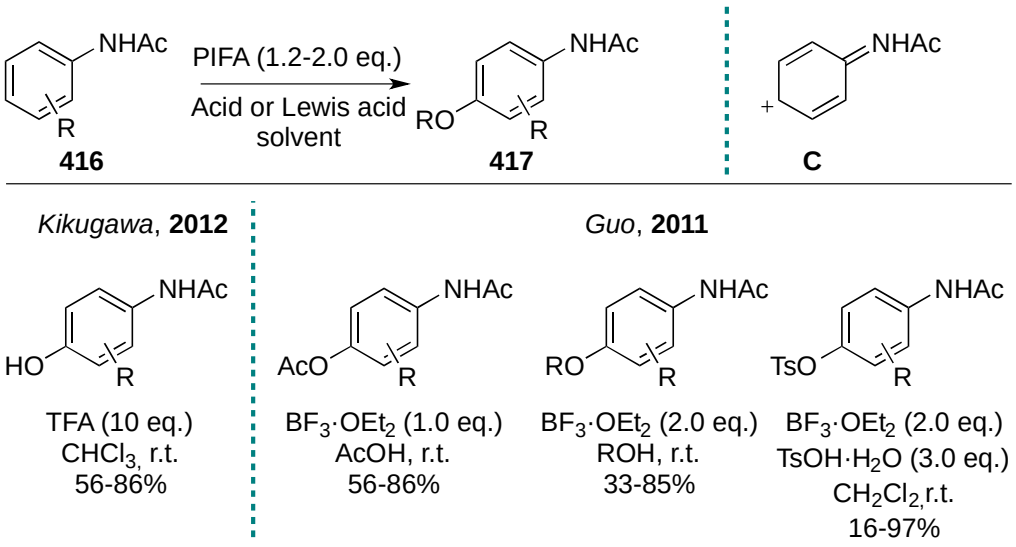


Figure 4.10

Similarly, Wang disclosed a PIFA-promoted one-pot oxidative heteroannulation of *N*-protected anilines **418**with styrenes for the construction of 5-aminocoumaran derivatives**420**.[195] As shown in Figure 4.11, the use of anilines with no substituent at the *para* position resulted in initially formed aminophenol **CII**that was further transformed into **CIV**. Subsequently, a Michael addition was believed to occur thus providing species **CV**, followed by intramolecular cyclization. On the contrary, a leaving group (LG) in the *para* position in **418**resulted in the formation of **CIII** was suggested. It is worth mentioning that the use of less activated styrenes required the addition of $Cu(OTf)_2$.

[192]Itoh, N.; Sakamoto, T.; Miyazawa, E.; Kikugawa, Y.*J. Org. Chem.***2002**, *2*, 7424.
[193]Liu, H.; Wang, X.; Gu, Y. *Org. Biomol. Chem.***2011**, *9*, 1614.
[194]Liu, H.; Xie, Y.; Gu, Y. *Tetrahedron Lett.***2011**, *52*, 4324.
[195]Fan, R.; Li, W.; Ye, Y.; Wang, L. *Adv. Synth. Catal.***2008**, *350*, 1531.

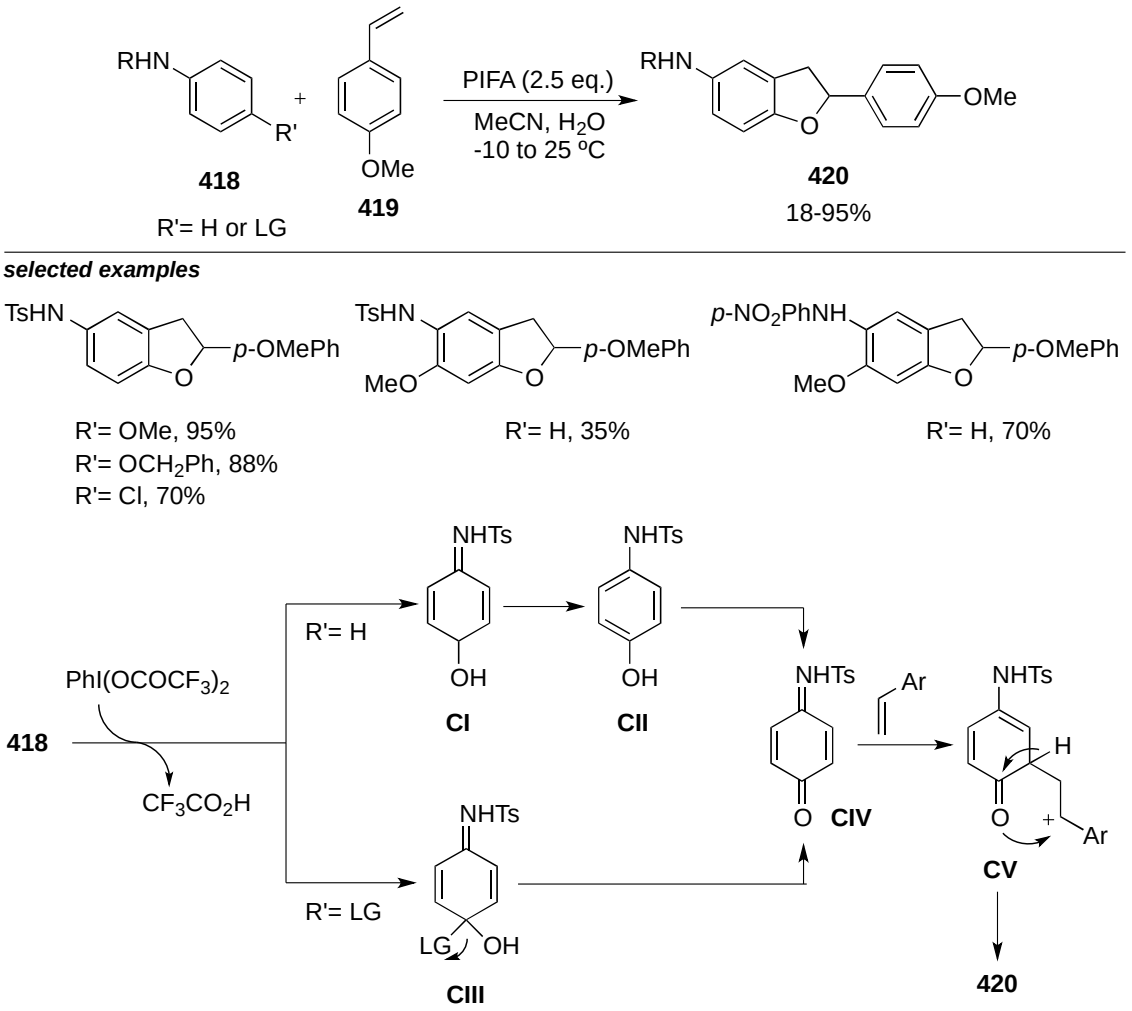
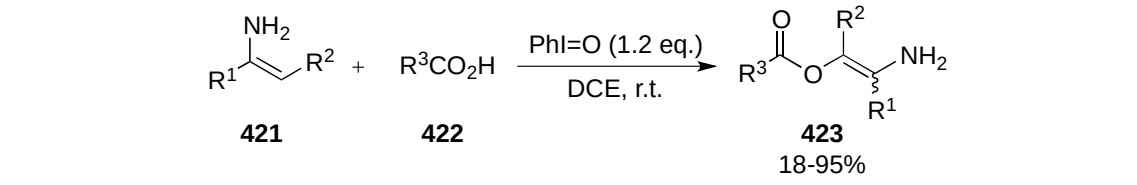


Figure 4.11

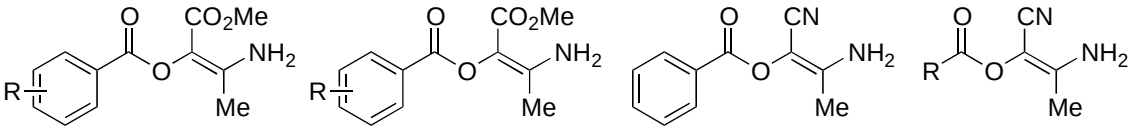
Recently, Zhao described the β-acyloxilation of enamides via PhIO-mediated intermolecular C-O bond-formation (Figure 4.12).[196] Interestingly, both aryl and alkyl carboxylic acids could be employed in moderate to good yields.

Liang disclosed a PIDA-mediated selective *cis*-di-acetoxylation of C(sp^3)-H bonds adjacent to the N-atom of *N*-phenylpiperidine system (Figure 4.13).[197] Unfortunately, low to moderate yields were reported and only neutral or electron-rich *N*-aryl rings were compatible under the reaction conditions. The authors proposed an initial PIDA-mediated oxidation of tertiary amine **424** en route to enamine **CVII**. Subsequent formationof iodonium species**CVIII** triggered the nucleophilic attack of 2 consecutive acetoxy units, thus forming **425**.

[196]Liu, X.; Cheng, R.; Zhao, F.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Org. Lett.***2012**, *14*, 5480.
[197]Shu, X.-Z.; Xia, X.-F.; Yang, Y.-F.; Ji, K.-G.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.***2009**, *74*, 7464.



selected examples



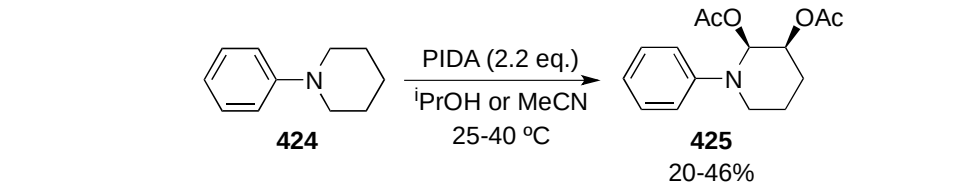
R= *p*-MeO-Ph, 63%
R= *p*-F-Ph, 80%
R= *m*-NO_2-Ph, 65%

R= cyclopropil, 67%
R= PhCH=CH-, 67%
R= EtO_2CCH=CH-, 76%
R= $BocNHCH_2$-, 61% (Z/E= 1/4)

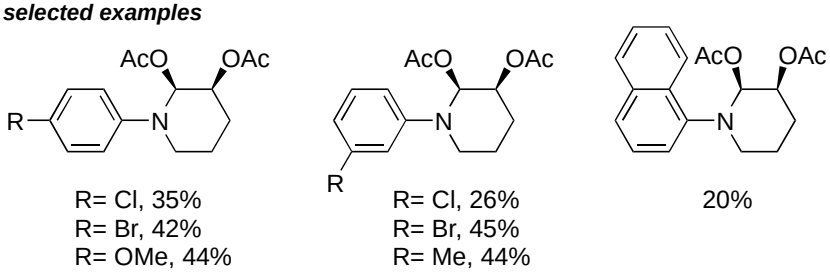
56%

56%

Figure 4.12



selected examples



R= Cl, 35%
R= Br, 42%
R= OMe, 44%

R= Cl, 26%
R= Br, 45%
R= Me, 44%

20%

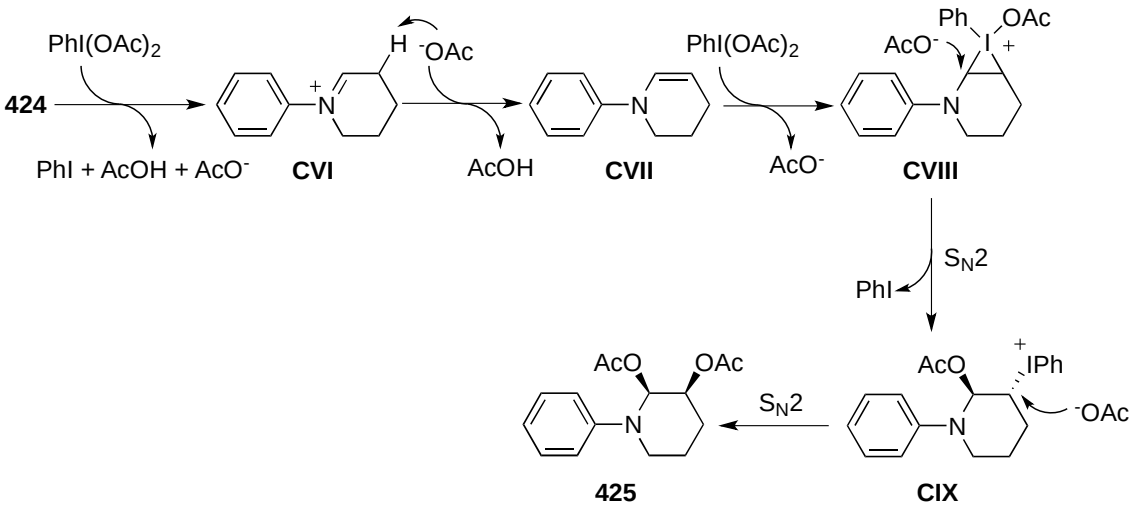


Figure 4.13

Ishibashi described the α-acetoxylaton of 2,3-disubstituted indoles by acetyl hipoiodite (IOAc), presumably generated *in situ* from PIDA and TBAI (Figure 4.14).[198] This method was applied for the α-acetoxylation of various indole derivatives in good yields. Interestingly, when *1*-methyl-tetrahydrocarbazole was subjected to the reaction conditions, the selectivity switched to the 3α-position of the indole. The mechanism is believed to proceed through the IOAc-mediated formation of iodonium intermediate **CX**, that would isomerize to **CXI**. In the case of non-substituted hydrocarbazole (R'= H), elimination of the 2α-proton would provide dearomatized indole **CXIII** followed by acetate attack to yield **427**. Alternatively, the 3α-acetoxylated product was explained by the formation of **CXII** avoiding undesirable 1,3-allylic strain interactions.

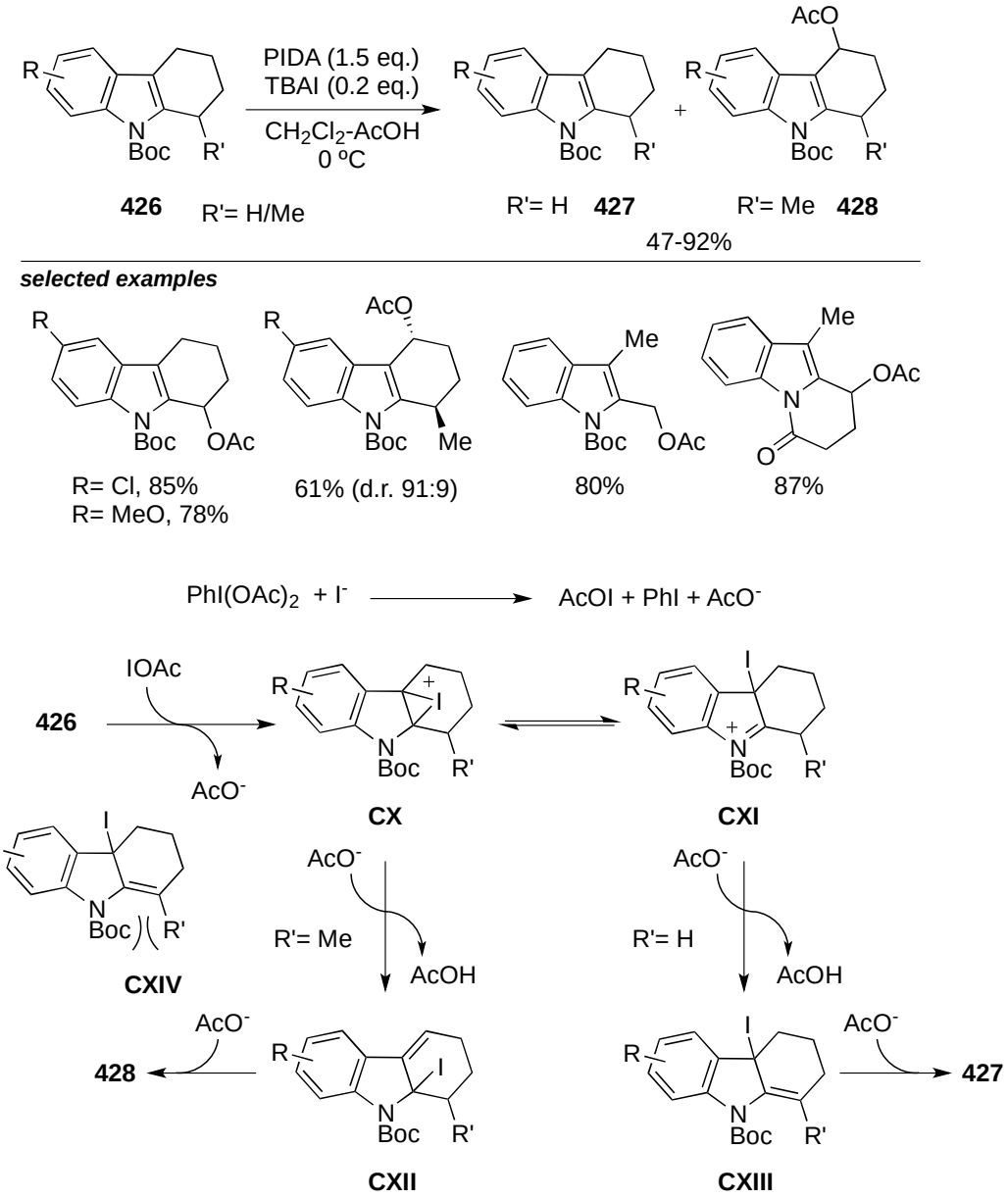


Figure 4.14

[198]Zaimoku, H.; Hatta, T.; Taniguchi, T.; Ishibashi, H.*Org. Lett*.**2012**, 6728.

4.5 Results and discussion

As illustrated in c*hapter 3* of this PhD thesis, a palladium-catalyzed C(sp^2)-H bond functionalization/C-O bond formation for the synthesis of benzo[c]chromenones was developed. Despite a promising 70% isolated yield of **305** (Figure 4.15), all attempts for improving the yield were unsuccessful.

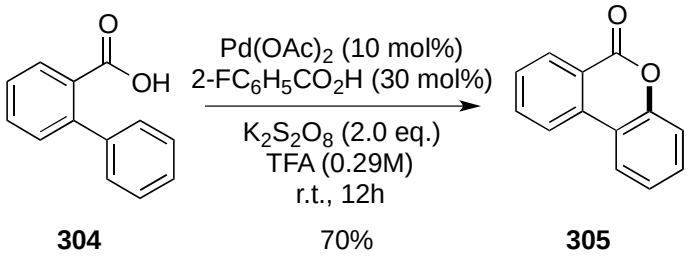
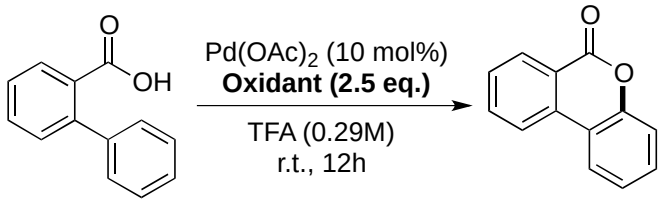


Figure 4.15

To our delight, as compiled in Table 4.1, it was found that a combination of $Pd(OAc)_2$ and hypervalent I(III) oxidants were highly beneficial for this transformation as compared to the use of $K_2S_2O_8$ (entry 1 vs entries 2 and 3). The inclusion of $PhI(OAc)_2$ or $PhI(OCOCF_3)_2$ increased the yield up to 76% and 79%, respectively. Interestingly, no *ortho*-hydroxylated product was detected by analysis of the crude reaction mixtures, an observation that is in contrast with the myriad of methods for effecting such transformation with carbonyl type compounds serving as directing groups.[44-46]

Table 4.1. Hypervalent I(III) oxidant screening.[a]



Entry	Oxidant	305 (%)[b]
1	$K_2S_2O_8$	60
2	PIDA	76
3	PIFA	79

[a] Benzoic acid (0.25 mmol), $Pd(OAc)_2$(10 mol%), $PhI(OCOCF_3)_2$ (2.5 eq.), TFA (0.29M), 25 ºC, 12h, argon atmosphere. [b] Isolated yields.

Considering the potential of I(III) reagents to promote the formation of oxygen-centred radical or SET processes, we immediately performed the blank experiments for

this reaction. As deduced by the results obtained in Table 4.2, PIFApromoted this transformation in the absence of palladium precatalyst, hence providing 40% yield of **305** (entry 1). On the other hand, no product was detected without the employment of oxidant (entry 2 and 3).

Table 4.2. Blank Experiments.[a]

304 **305**

Entry	$Pd(OAc)_2$	PIFA	305 (%)[b]
1	✗	✔	40
2	✔	✗	0
3	✗	✗	0
4	✔	✔	79

[a] Benzoic acid (0.25 mmol), $Pd(OAc)_2$(10 mol%), PIFA (2.5 eq.), TFA (0.29M), 25 ºC, 12h, argon atmosphere. [b] Isolated yields.

Encouraged by these results, we were determined to further explore this reactivity, hoping to develop a metal-free I(III)-promoted cyclization en route to **302**(Figure 4.16). Additionally, we wondered whether it will be possible to generate catalytically the active I(III) species from simple aryliodides with a suitable oxidant.

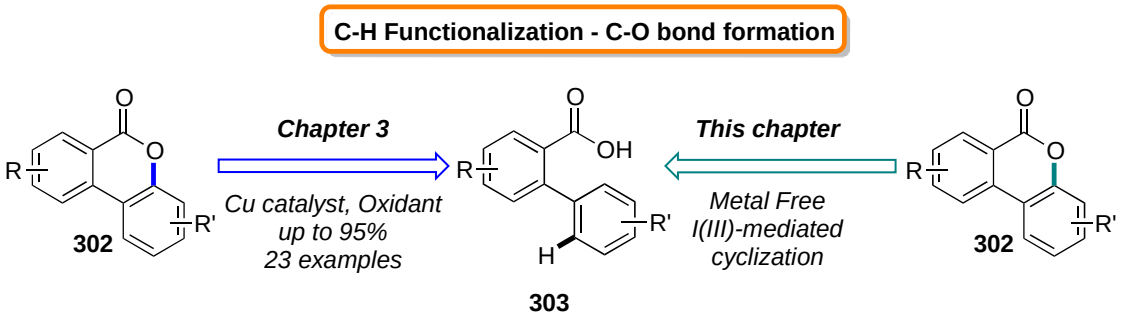


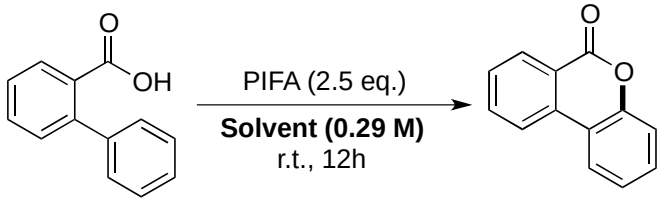
Figure 4.16

4.5.1 Stoichiometric I(III)-mediated synthesis of dibenzopyranones

Following our initial breakthrough shown in Table 4.2, a series of reactions were carried out in the presence of **304** (0.25 mmol), PIFA (2.5 eq.), solvent (0.29 M) at 25 ºC, under argon atmosphere. As shown, non-polar aromatic solvents such as toluene

gave 40% yield of **305**(entry 1). PhCl was also effective for this transformation providing similar results (entry 3). In contrast, alcoholic solvents completely shut down the reactivity (entries 4 and 5). While the use of AcOH resulted in no conversion of **304**, TFA provided moderate yields of the final lactone (entries 6 and 7). Additionally,CH_2Cl_2 turned out to be competent for this transformation (entry 8). On the other hand, THF provided the best yield (45%) as shown in entry 11. It is worth noting that polar, coordinating solvents such as DMA, NMP or DMF were completely ineffective for this transformation (entries 12-14).

Table 4.3. Solvent screening.[a]



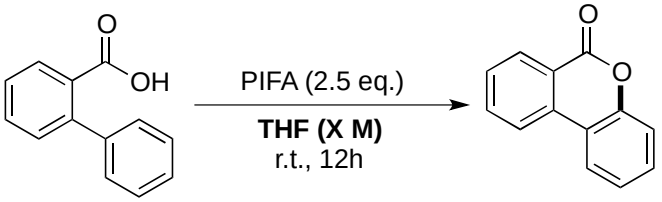
304 **305**

Entry	Solvent	305 (%)[b]
1	Toluene	41
2	$PhCF_3$	0
3	PhCl	35
4	^{t}BuOH	0
5	^{t}Amyl-OH	0
6	AcOH	0
7	TFA	40
8	CH_2Cl_2	29
9	DCE	0
10	1,4-Dioxane	18
11	THF	45
12	DMA	0
13	NMP	0
14	DMF	0

[a] Benzoic acid (0.25 mmol), PIFA (2.5 eq.),solvent (0.29M), 25 ºC, 12h, argon atmosphere. [b] Yields were determined by GC analysis using dodecane as internal standard.

Next, we analyzed the impact of dilution on the reaction outcome with THF as our solvent of choice. As judged by the results complied in Table 4.4, no significant improvement was observed at higher or lower concentrations (entries 1-6).

Table 4.4. Concentration effect.[a]



304 **305**

Entry	THF (X M)	305 (%)[b]
1	1	40
2	0.5	50
3	0.29	45
4	0.17	44
5	0.125	41
6	0.1	41

[a] Benzoic acid (0.25 mmol), PIFA (2.5 eq.),THF (X M), 25 ºC, 12h, argon atmosphere. [b] Yields were determined by GC analysis using dodecane as internal standard.

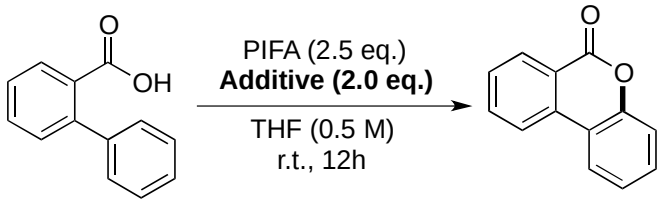
Afterwards, we decided to evaluate the influence of additives in order to promote this transformation by activating the λ^3-iodane reagent (Table 4.5). As shown in entries 1-4, the addition of commonly employed halide salts had a deleterious effect on reactivity, resulting in low yields of **305**. Following the same trend, quaternary ammonium salts hampered the reactivity and no product could be detected by GC analysis (entries 5-6). Alternatively, we wondered whetherthe inclusion of different Lewis acids would enhance the electrophilicity of the hypervalent I(III) oxidant and therefore its reactivity. Among all the acids examined, only $Al(OTf)_3$ provided 51% yield of **305**(entry 12), suggesting thatthose additives do not play a significant role, an assumption that was corroborated when comparing such result with no Lewis acid added (entry 14).

At that stage of our screening process, we decided to revisit all the solvents examined in Table 4.3. Based on Kita's success employing fluorinated alcoholic solvents for I(III)-promoted oxidative couplings[199] and intramolecular cyclization,[200] we wonder whether we could improve the reaction efficiency by employing these solvents on our C-H functionalization protocol. To our delight, as depicted in Figure 4.17, the use of HFIP as solvent turned out to be critical, thus obtaining **305** in 92% yield. In

[199]For selected references see: (a) Y. Kita; Tohma, H.; Inagaki, M.; Hatanaka, K.; Yakura, T. *Tetrahedron Lett*., **1991**, *32*, 4321. (b) Kita, Y.; Takada, T.; Gyoten, M.; Tohma, H; Zenk, H; Eichhorn, J.*J. Org. Chem.*, **1996**, *61*, 5857.
[200] Selected examples: (a)Kita, Y.; Arisawa, M.; M. Gyoten; M. Nakajima; Hamada, R.; Tohma, H.; Takada, T. *J. Org. Chem.*, **1998**, *63*, 6625. (b) Kita, Y.; Egi, M.; Okajima, A.; Ohtsubo, M.; Takada, T.; Tohma, H.*Chem. Commun.*, **1996**,1491. (c) Kita, Y.; Egi, M.; Ohtsubo, M.; Saiki, T.; Takada, T. AndTohma, H.*Chem. Commun.*, **1996**, 2225.

contrast, other commonly used fluorinated solvent like 2,2,2-trifluoroethanol provided very low yields.

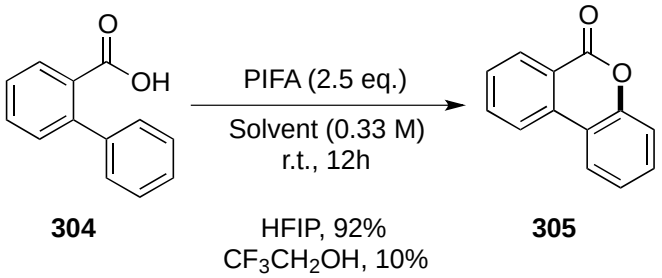
Table 4.5. Additive screening.[a]



304 **305**

Entry	Additive	305 (%)[b]
1	KBr	14
2	KI	16
3	NaBr	10
4	NaI	0
5	*n*-Bu_4NBr	0
6	*n*-Bu_4NI	0
7	$ZnCl_2$	4
8	$Sn(OTf)_2$	2
9	$Sc(OTf)_2$	0
10	$Yb(OTf)_3$	8
11	$In(OTf)_3$	21
12	$Al(OTf)_3$	51
13	$BF_3{\cdot}OEt_2$	26
14	none	49

[a] Benzoic acid (0.25 mmol), PIFA (2.5 eq.), additive (2.0 eq.)THF (0.5 M), 25 ºC, 12h, argon atmosphere. [b] Yields were determined by GC analysis using dodecane as internal standard.



304 HFIP, 92% CF_3CH_2OH, 10% **305**

Figure 4.17

To the best of our knowledge, at the time we started this project the main literature precedent related to this transformationwas reported by Togo in 1995 (Figure 4.18). A combination of PIFA,I_2 and hv (Tungsten lamp) could efficiently promote this

transformation in nearly quantitative yield (Figure 4.19, a).[201] Unfortunately, the employment of light-irradiation and the limitation to use specifically **304**, severely diminished the practicality of the process. In order to demonstrate the crucial role of high-energy light irradiation in Togo's procedure, a series of revealing experiments were conducted, as described in Figure 4.18, b. We found that employing the same conditions with rigorously exclusion of light at 25 ºC and 70 ºC, only 18% and 10% yield was obtained, respectively. This finding corroborates the importance of our optimized protocol, as high yield were obtained with PIFA (2.2 eq.) as oxidant in HFIP under very mild conditions. Nonetheless, from an environmental point of view this transformation is not yet desirable, due to the generation of stoichiometric amounts of iodobenzene (halogen waste) as the main byproduct.

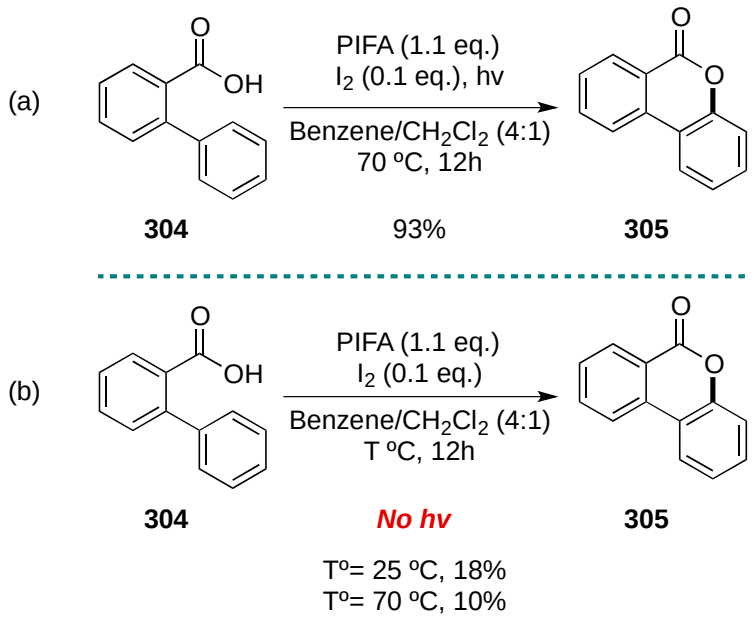


Figure 4.18

4.5.2. Catalytic I(III)-mediated synthesis of dibenzopyranones.

The electrochemical *in situ* generation of hypervalent I(III) compounds firstly disclosed by Fuchigami and Fujita[202] in 1994 served as a source of inspiration for Ochiai and Kita, which independently reported in 2005 a reliable I(III)-catalyzed α-oxidation of ketones and phenols, respectively.[203] On both cases, *m*-CPBA was

[201] Togo, H.; Muraki, T.; Yokoyama, M. *Tetrahedron Lett.* **1995**, *36*, 7089.
[202] Fuchigami, T.; Fujita, T.*J. Org. Chem*. **1994**, *59*, 7190.
[203] (a) Dohi, T.; Maruyama, A.; Yoshimura, M.; Morimoto, K.; Tohma, H.; Kita, Y. *Angew. Chemie Int. Ed.***2005**, *44*, 6193. (b) Ochiai, M.; Takeuchi, Y.; Katayama, T.; Sueda, T.; Miyamoto, K. *J. Am. Chem. Soc.***2005**, *127*, 12244.

employed as terminal oxidant. The basic catalytic cycle is depicted in Figure 4.19. As shown, the in situ generation of I(III) reagents would be achieved if the released iodoarene **429** are efficiently reoxidized to species **430**. Ideally, the oxidant should only react with the iodoarene and not interact with the starting materials and products or at least the generation of hypervalent iodine species should be faster than the rates of undesired side reactions. After these initial reports, the discovery of new and mild processes by *in situ* formation hypervalent iodine (III) reagents has become an active research area in the last years.[204]

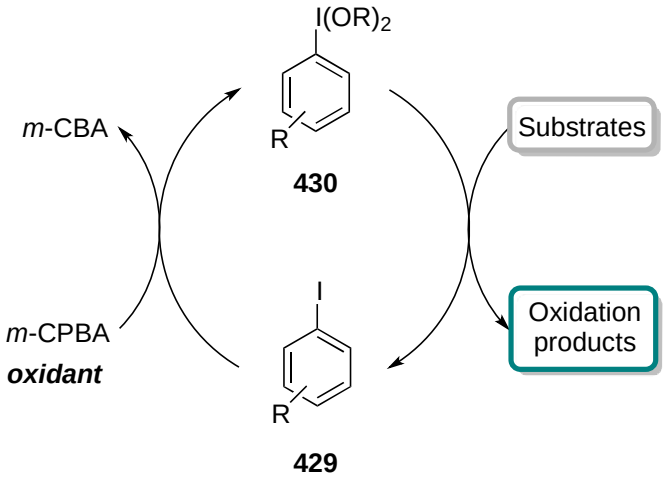


Figure 4.19

Several precedents were reported in the literature involving the catalytic formation of λ^3-iodane reagents for the construction of 5-membered lactones *via* C-O bond formation. As depicted in Figure 4.20 a, Kita demonstrated the potential of such processes by the oxidative spyrocyclization of phenol derivatives **431**in good to high yields.[203] Catalytic amounts of *4*-MeC_6H_5Iwere sufficient to induce the cyclization in the presence of *m*-CPBA as an external oxidant. Interestingly, Ishihara and Kita later on developed asymmetric variants of this transformation with the use of quiral hypervalent iodine reagents.[205] Alternatively, a PhI-catalyzed oxylactonization reaction was reported for the synthesis of ketolactones **434**, with m-CPBA as the preferred oxidant (Figure 4.21, b).[206]

[204] For selected reviews see: (a) Richardson, R. D.; Wirth, T. *Angew. Chem. Int. Ed.***2006**, *45*, 4402. (b) Ochiai, M.; Miyamoto, K. *Eur. J. Org. Chem*. **2008**, 4229. (c) Dohi, T.; Kita, Y. *Chem. Commun*. **2009**, 2073. (d) Dohi, T. *Chem. Pharm. Bull*. **2010**, *58*, 135. (e) Yusubova, M. S.; Zhdankin, V. V. Mendeleev Commun. **2010**, *20*, 185. (f) Romero, R. M.; Wöste, T. H.; Muñiz, K. *Chem. –Asian J.***2014**, 1. (g) Singh, F. V.; Wirth, T. *Chem. –An Asian J*. **2014**, *9*, 950.
[205] (a) Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem. Int. Ed.***2010**, *49*, 2175. (b) Dohi, T.; Takenaga, N.; Nakae, T.; Toyoda, Y.; Yamasaki, M.; Shiro, M.; Fujioka, H.; Maruyama, A.; Kita, Y. *J. Am. Chem. Soc*. **2013**, 135, 4558.
[206]Uyanik, M.; Yasui, T.; Ishihara, K. *Bioorg. Med. Chem. Lett.***2009**, *19*, 3848.

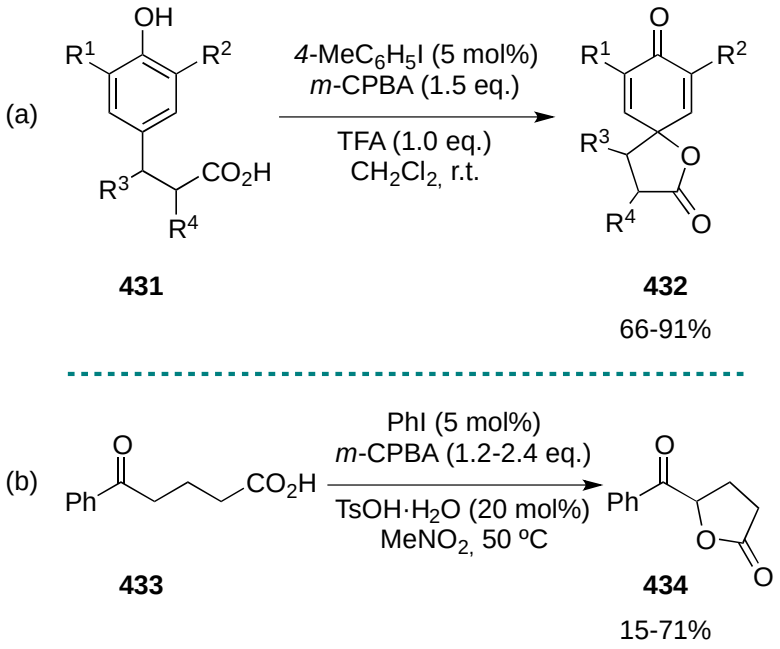


Figure 4.20

Encouraged by these literature data and based on our stoichiometric results, we decided to study whether our PIFA-mediated lactonization event could be conducted with catalytic amounts of in situ generated I(III) reagents. This work was carried out by Xueqianq Wang at Ruben's Martin laboratories and the conditions found resulted in the utilization of**437**(20 mol%) as catalyst,CH_3CO_3H (2.0 eq.) as oxidant in HFIP (0.2M). Remarkably this reaction operates under mild conditions and in open air.

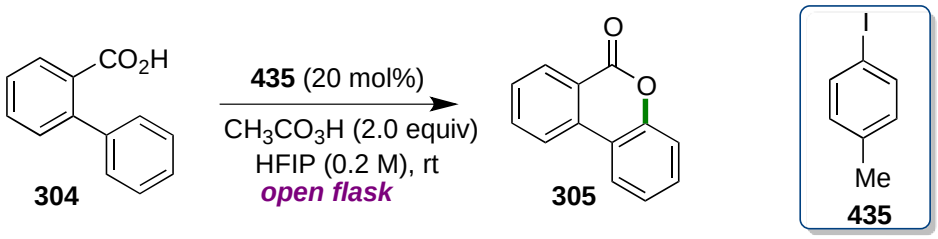


Figure 4.21

4.5.3. Synthesis of starting materials.

I order to evaluate whether the formation5 of benzolactones under catalytic I(III) conditions was general, we set out to explore the preparative scope of this reaction. Since the starting materials were the same as for our copper-catalyzed protocol, we took advantage of our synthetic route to prepare other 2-phenylbenzoic acid derivatives that could be coupled as well. Apart from the substrates shown in Figure 3.14, 3.16, 3.19 and 3.20, we also prepared benzoic acids **441**and **442** in a 2 step manner via Suzuki-Miyaura coupling of aldehydes **438**with **439**followed by oxidation (Figure 4.22).

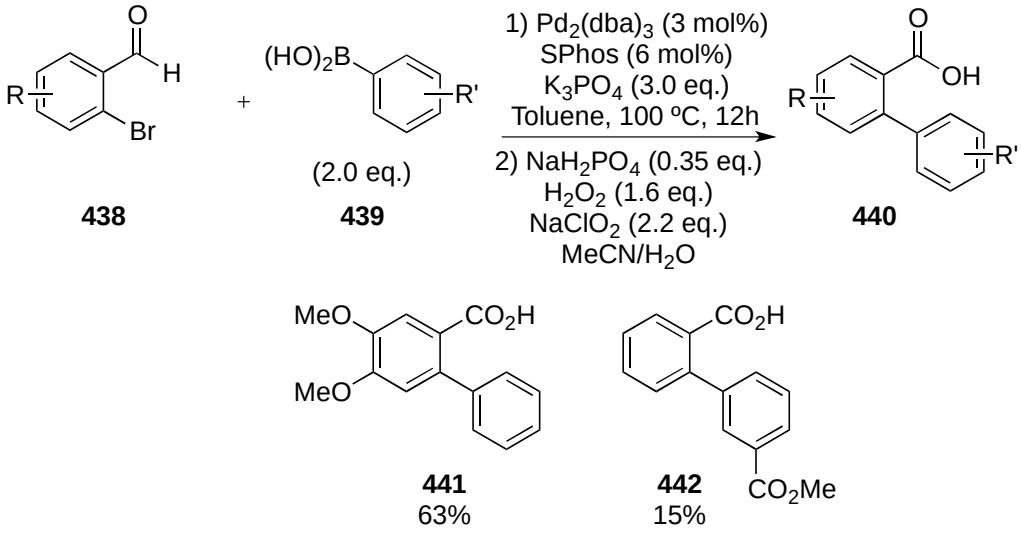


Figure 4.22

On the other hand, compound **445**bearing a nitro-group in *para*-position was synthetized in 2 steps from **444** following the same route as depicted in Figure 3.14.

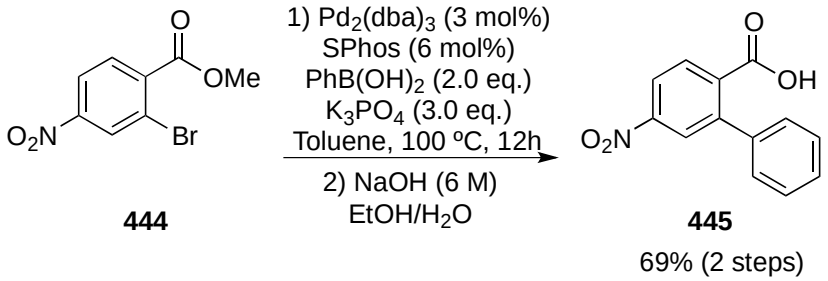


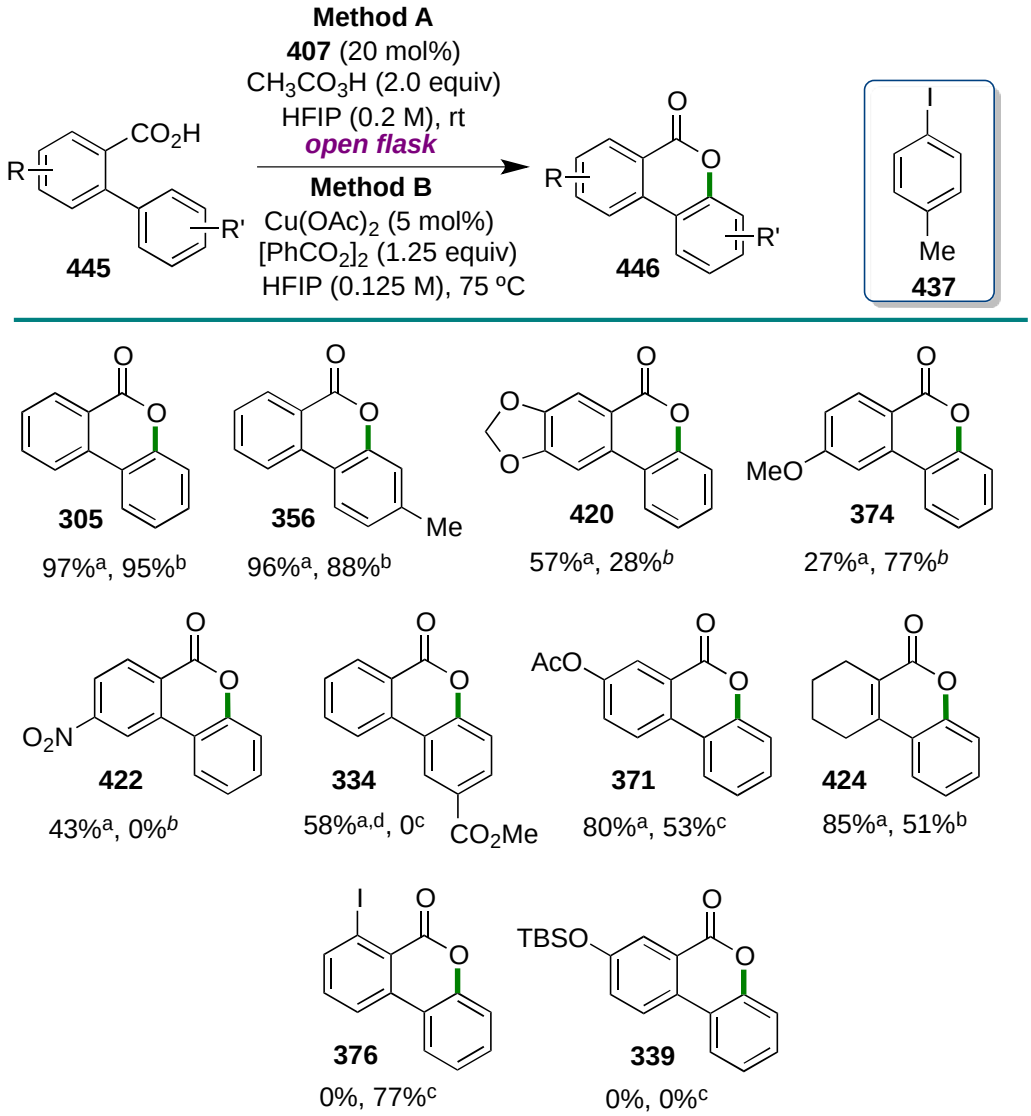
Figure 4.23

4.5.4. Scope for the ArI-catalyzed synthesis of dibenzopyranones

With the optimized reaction conditions in hand, we turned our attention to explore a preliminary scope of the aryl iodide-catalyzed C(sp^2)-H bond functionalization/C-O bond formation (Table 4.7).[207]Compounds **305** and **356** were obtained in high yields employing the protocol based upon **437** (Method A) and our Cu-catalyzed procedure (Method B). Remarkably, electron-deficient aromatic rings such as **422**and **334**gave 43% and 67% isolated yield respectively, whereas no product was observed under the previously developed Cu-catalyzed protocol (Method B).[208] Interestingly, a high selectivity profile was detected with unsymmetrical substrates like **334**, isolated as a single regioisomer. These results are rather valuable since previous techniques for similar means provided regioisomeric mixtures, thus showing the distinctive features of our I(III) lactonization method.[159,161]Besides, substrates that provided moderate to low yields employing Method B (**420**, **371** and **424**) showed enhanced reactivity with our catalytic I(III) protocol thus obtaining higher yields and under milder conditions. On the contrary, whereas very poorreactivity was observed under our **437**-catalytic protocol for **374** and **376**, our Cubased system allowed for obtaining77% isolated yield for both substrates, hence showing the complementary reactivity of both catalytic methods. Finally, O-silyl protected groups **(339)** did not work neither using Method A nor employing Method B. In both cases, fully degradation of the starting material was observed.

[207] In collaboration with Xueqianq Wang.
[208] See Chapter 3 for further details.

Table 4.6. Substituent effect on the bottom ring.[a],[b],[c]



[a] ***Method A***: benzoic acid (0.2 mmol), **407** (20 mol%), CH_3CO_3H (2.0 eq.), HFIP (0.2 M), 25 ºC, 12h, open air. [b] ***Method B***: benzoic acid (0.25 mmol), $Cu(OAc)_2$ (5 mol%), $[PhCO_2]_2$ (1.25 eq.), HFIP (0.125M), 75 ºC, 12h, argon atmosphere [c] Isolated yields, average of two runs. [d] A single regioisomer was observed.

Although a detailed mechanistic picture will require *in depth* studies, we tentatively propose that the hypervalent iodine (III) reagent generated *in situ* by AcO_2H might initiate the formation of a radical cation with an electron-rich aromatic motif that facilitates the addition of the incoming carboxylic acid motif. When electron-poor aromatic frameworks are employed, however, it is highly unlikely that a radical cation will be formed, and we speculate that in this particular case, the hypervalent iodine (III) reagent might trigger the formation of acyloxy radical **CXIV**that subsequently promotes the cyclization event (Figure 4.24). Next, an homolytic aromatic substitution could take

place en route to radical species **CXV**, as depicted in Figure 4.24, path a. Finally, a hydrogen atom abstraction would deliver product **426**. On the other hand, an alternative mechanism involving a hydrogen atom abstraction from the aromatic ring to form radical intermediate **CXVI** (path b) can not be ruled out at this stage.

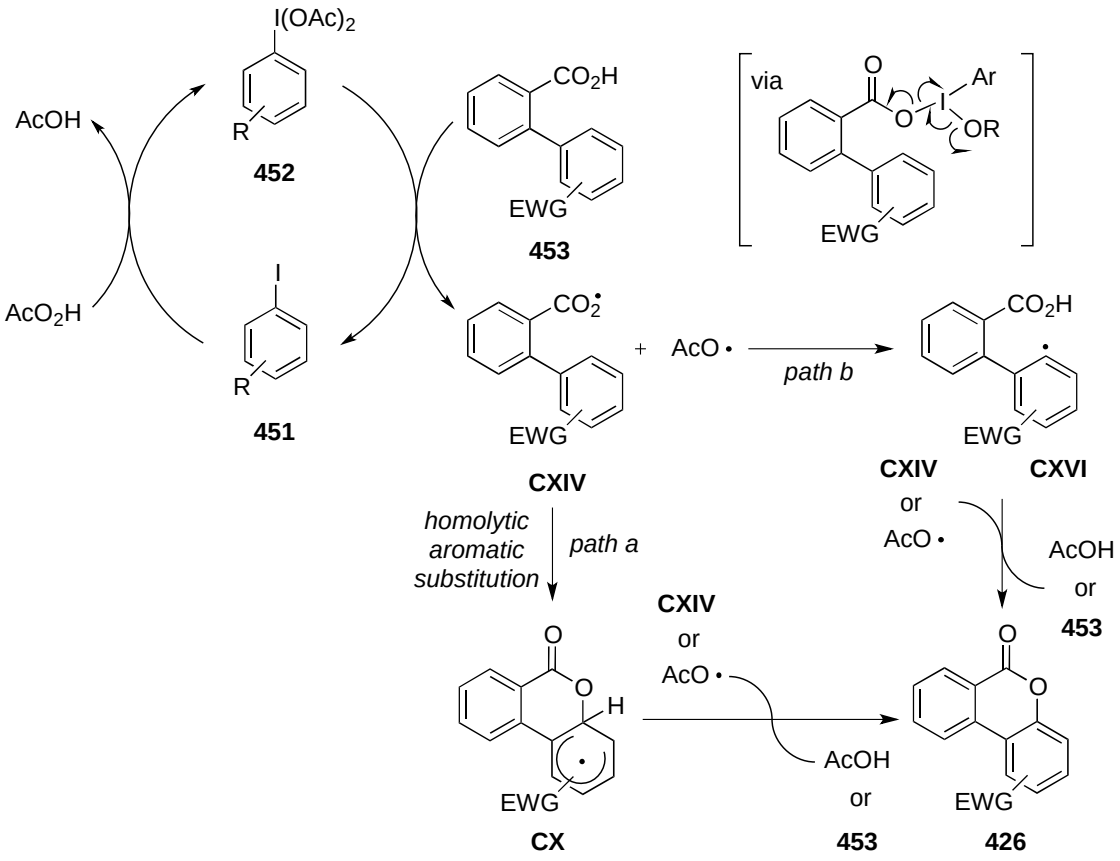


Figure 4.24

4.6 Conclusions

- We have developed a metal-free C(sp^2)-H bond functionalization/C-O bond formation mediated by hypervalent I(III) reagents that occurs under mild conditions.The ability to perform this reaction with I(III) reagents generated in situ is quite remarkable, holding great promise for future developments of this and related coupling events.

4.7 Experimental section

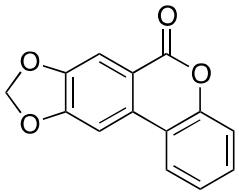
4.7.1 General considerations

Reagents. Unless otherwise stated, all reactions were carried out open to air in resealable screw-cap test tubes.Peracetic acid (AcO_2H), PIDA and PIFA were purchased from Acros. 4-Methyliodobenzene was purchased from Aldrich.1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was purchased from Fluorochem. All chemicals were used as received. All other reagents were purchased from commercial sources and used as received.

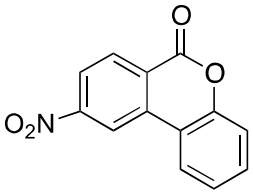
Analytical methods. ^{1}H NMR and ^{13}C NMR spectra and melting points (where applicable) are included for all compounds. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz and a Bruker 500 MHz at 20 ºC. All ^{1}H NMR spectra are reported in parts per million (ppm) downfield of TMS and were measured relative to the signals for $CHCl_3$ (7.27 ppm). All ^{13}C NMR spectra were reported in ppm relative to residual $CHCl_3$ (77 ppm) and were obtained with ^{1}H decoupling. Coupling constants, J, are reported in hertz. Melting points were measured using open glass capillaries in a Büchi B540 apparatus. Infrared spectra were recorded on a Bruker Tensor 27. Mass spectra were recorded on a Waters LCT Premier spectrometer. Gas chromatographic analyses were performed on Hewlett-Packard 6890 gas chromatography instrument with a FID detector using 25m x 0.20 mm capillary column with cross-linked methyl siloxane as the stationary phase. High Pressure Liquid Chromatographic (HPLC) analyses were performed on Agilent Technologies Model 1260 Infinity HPLC chromatography instrument equipped with Agilent Eclipse Plus C18 (3.5 um, 4.6 x 100 mm) column and UV/Vis detector. Flash chromatography was performed with EM Science silica gel 60 (230-400 mesh).

4.7.2 Synthesis of benzopyranones

General Procedure: ascrew-cap test tube containing a stirring bar was charged with the corresponding benzoic acid (0.20 mmol), 4-methyliodobezene (8.7 mg, 0.04 mmol, 20 mol%), HFIP (2 mL) and AcO_2H (83µL, 2.20 equiv, 35% in AcOH). The reaction mixture was then stirred at room temperature for 16 h. The solvents were concentrated under reduced pressure and the crude was purified by column chromatography on silica gel (eluting with hexanes/ethyl acetate mixtures).

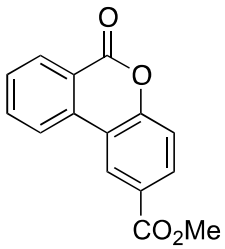


6*H*-[1,3]dioxolo[4',5':4,5]benzo[1,2-*c*]chromen-6-one447. White solid. 28.8 mg, Yield: 56%. The spectroscopic data correspond to those previously reported in the literature.[209] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 (d, *J* = 7.9 Hz, 1H), 7.70 (s, 1H), 7.43 (d, *J* = 15.4 Hz, 1H), 7.43 (s, 1H), 7.33 (d, *J* = 16.9 Hz, 1H), 7.29 (d, *J* = 17.6 Hz, 1H), 6.14 (s, 2H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 160.6, 154.0, 150.7, 148.8, 132.1, 129.8, 124.4, 122.3, 118.1, 117.6, 116.1, 108.4, 102.4, 100.7 ppm.



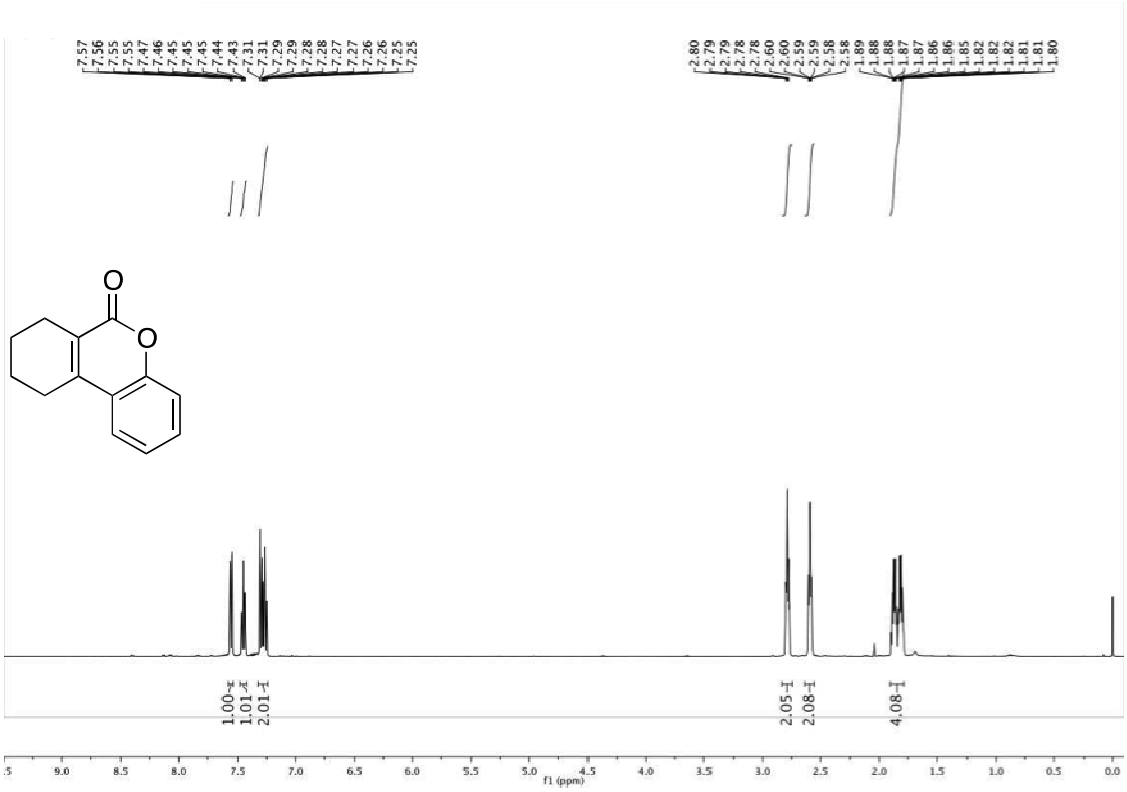
9-nitro-6*H*-benzo[*c*]chromen-6-one 448. White solid; yield: 19 mg, 41%. The spectroscopic data correspond to those previously reported in the literature.[210] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.97 (d, *J* = 2.2 Hz, 1H), 8.60 (d, *J* = 8.7 Hz, 1H), 8.36 (dd, *J* = 8.8, 2.3 Hz, 1H), 8.16 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.67 – 7.55 (m, 1H), 7.52 – 7.38 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 152.0, 151.8, 136.6, 132.8, 132.3, 125.6, 125.5, 123.5, 122.9, 118.32, 117.5, 116.9 ppm.

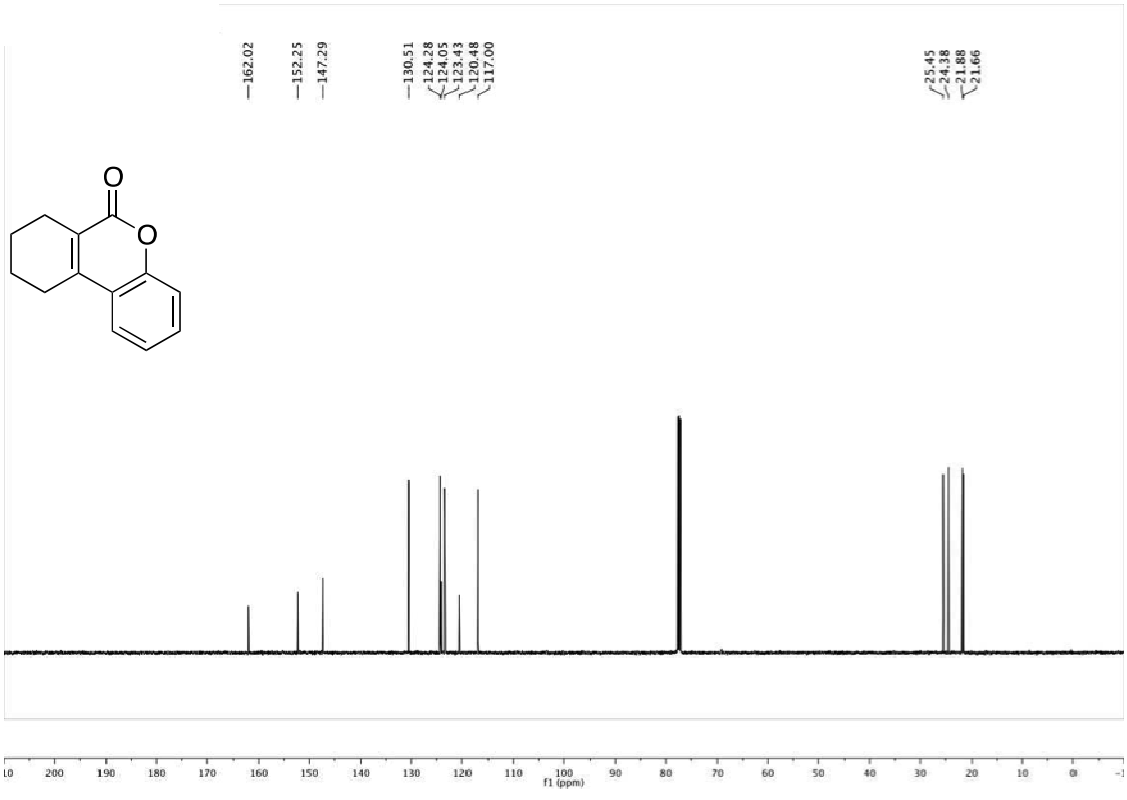
[209] Lee, T. H.; Jayakumar, J.; Cheng, C, H.; Chuang, S. C. *Chem. Commun.***2013**, *49*, 11797.
[210] Wang, Y.; Gulevich, A. V.; Gevorgyan, V.*Chem. Eur. J.***2013**, *19*, 15836.

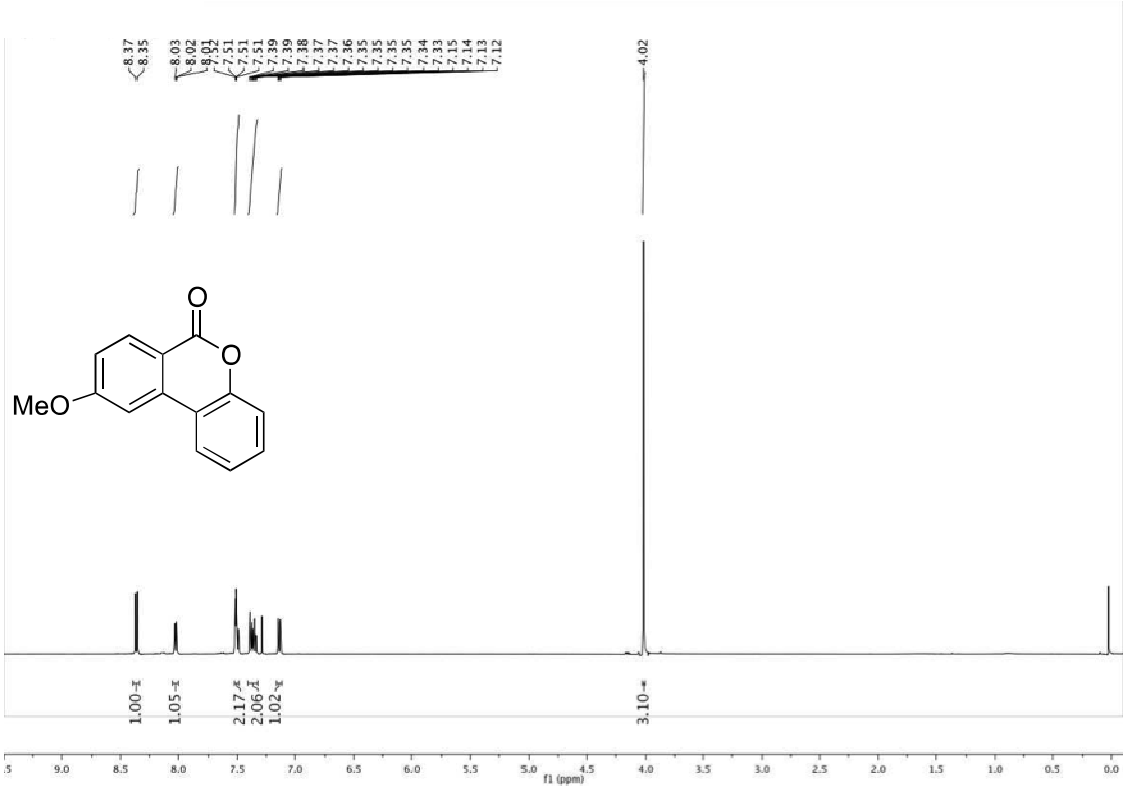


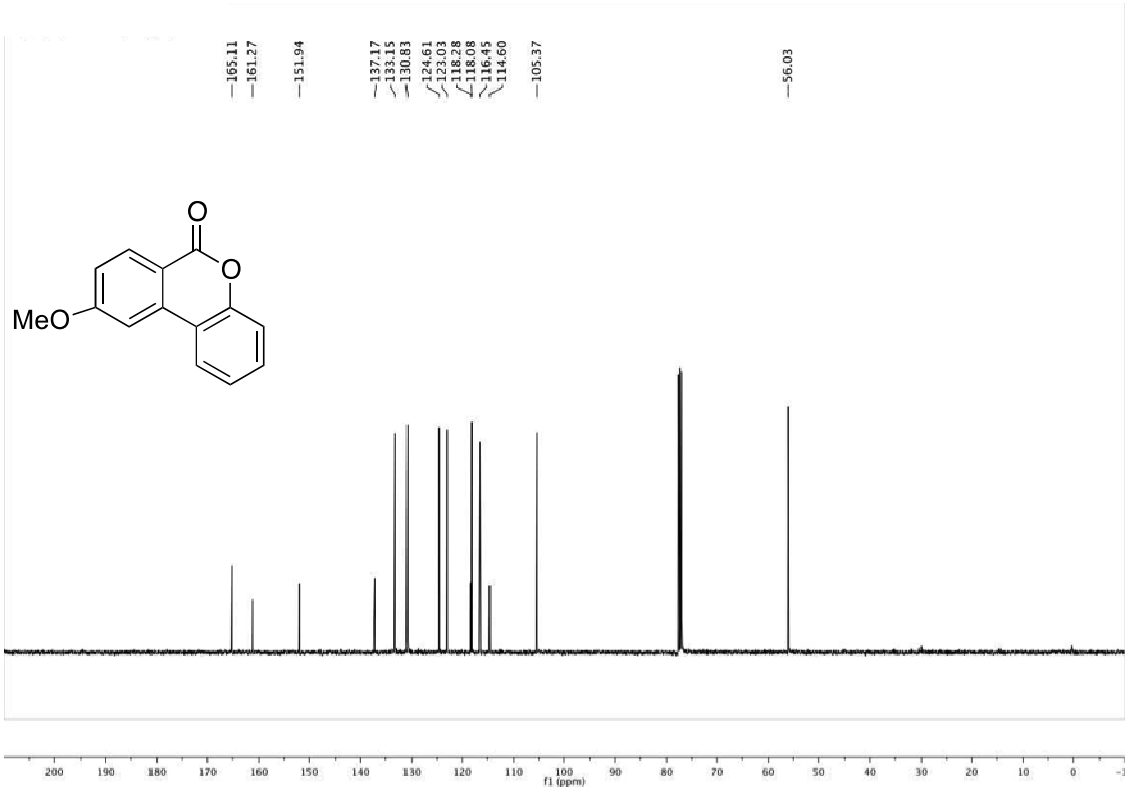
Methyl 6-oxo-6*H*-benzo[*c*]chromene-2-carboxylate 449. White solid; yield: 30 mg, 58%. The spectroscopic data correspond to those previously reported in the literature.[51] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.76 (d, *J* = 2.0 Hz, 1H), 8.39 (ddd, *J* = 8.0, 1.5, 0.6 Hz, 1H), 8.21 (ddt, *J* = 8.1, 1.1, 0.5 Hz, 1H), 8.12 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.86 (ddd, *J* = 8.1, 7.3, 1.4 Hz, 1H), 7.62 (ddd, *J* = 7.9, 7.3, 1.1 Hz, 1H), 7.39 (dd, *J* = 8.7, 0.4 Hz, 1H), 3.97 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 160.6, 154.3, 135.3, 134.2, 131.6, 130.8, 129.7, 126.7, 125.2, 122.2, 121.3, 118.2, 118.1, 52.6 ppm.

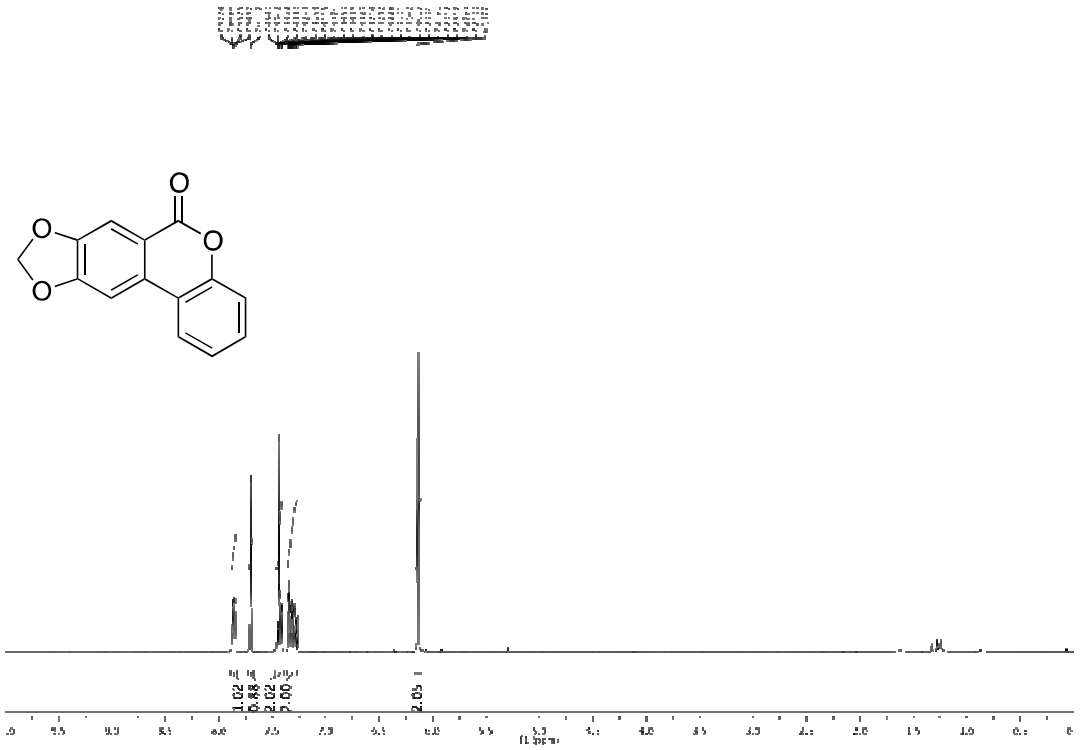
4.7.3 Selected examples of NMR spectra.

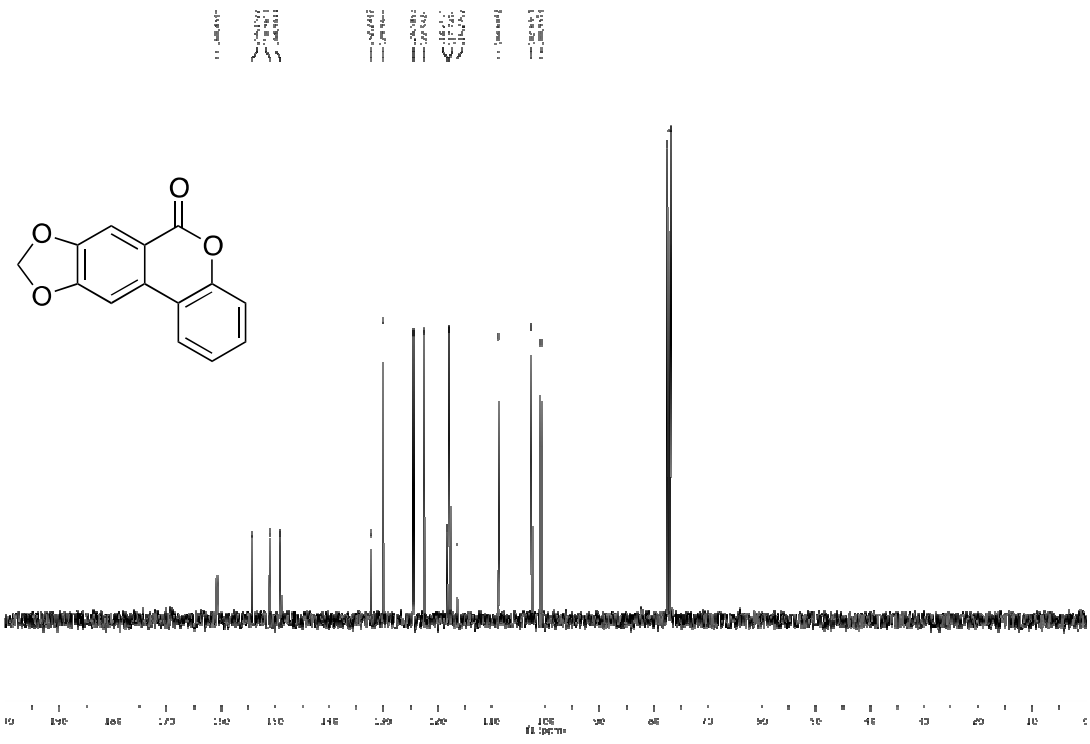





8.37
8.35
8.03
8.02
8.01
7.52
7.51
7.51
7.39
7.39
7.38
7.37
7.37
7.36
7.35
7.35
7.35
7.35
7.34
7.33
7.15
7.14
7.13
7.12
4.02
O
O
MeO
1.00
1.05
2.17
2.06
1.02
3.10
f1 (ppm)


165.11
161.27
151.94
137.17
133.15
130.83
124.61
123.03
118.28
118.08
116.45
114.60
105.37
56.03
O
O
MeO
f1 (ppm)





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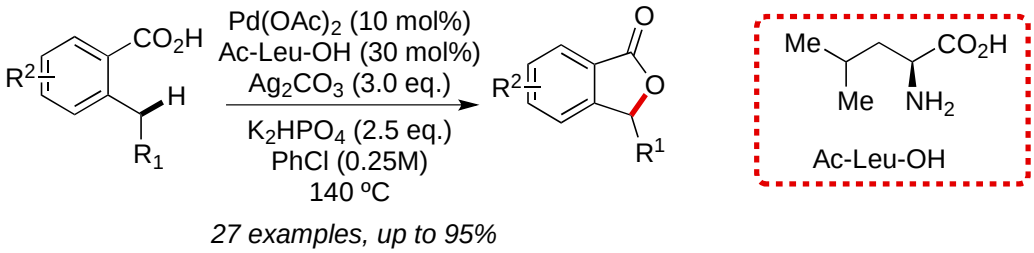
Dipòsit Legal: T 1365-2014

General conclusions and outlook

In this PhD thesis we have developed several catalytic protocols towards the synthesis of phthalides and benzolactones by exploiting C-H bond functionalization strategies for the formation of C-O bonds. In Chapter 2 we described a direct method to prepare phthalides via Pd-catalyzed C(sp^3)-H bond functionalization (Figure 5.1) employing simple carboxylic acids as weakly directing groups. This method is characterized by its wide substrate scope, including challenging substrate combinations with particularly sensitive functional groups and a diverse set of substitution patterns. The use of Ac-Leu-OH as ligand was crucial for reactivity, presumably accelerating the C-H cleavage step. Besides, deuterium labelling experiments revealed an unusual isotope effect ($K_H/H_D \approx 1$), suggesting that C-H bond cleavage might not be involved in the rate determining step of the process. This striking observation is in contrast with the vast majority of C-H bond functionalization protocols, which possess high K_H/H_D values.



27 examples, up to 95%

Figure 5.1

Following up with our interest in the synthesis of lactones, a mild and operationally simpleCu-catalyzed C(sp^2-H) bond functionalization/C-O bond formationreaction for accessing benzopyranones was disclosed in Chapter 3 (Figure 5.2). This method is compatible with a wide variety of functional groups both in the upper and bottom ring of the biaryl scaffold. Besides, weanticipated that remote hydroxylated arenes could be within reach by a sequential hydrolysis event.Initial mechanistic investigations suggest that C-H bond cleavage is not involved in the rate-determined step (Intramolecular K_H/K_D=1.22). In addition we found that the reaction was significantly inhibited by the addition of radical scavengers by TEMPO, BHT or 1,1-diphenylethylene. While not yet conclusive, these experiments may suggest that single electron transfer processes come into play.

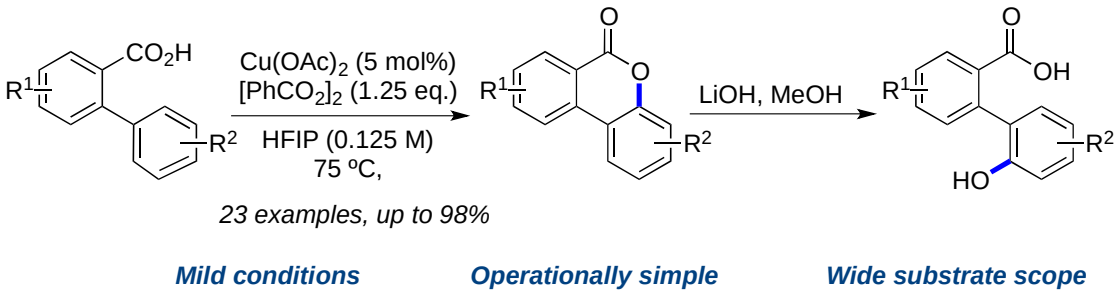


Figure 5.2

Interestingly, in Chapter 4 we were able to developa C(sp^2)-H bond functionalization/C-O bond-formation event mediated by I(III) reagents (Figure 5.3). This method represents a cheap, practical and powerful synthetic alternative to metal-catalyzed protocols. A preliminary reaction scope showed that in situ generated I(III) reagents could be used in this reaction, providing complementary resultsto our Cu-catalyzed method developed in Chapter 3.

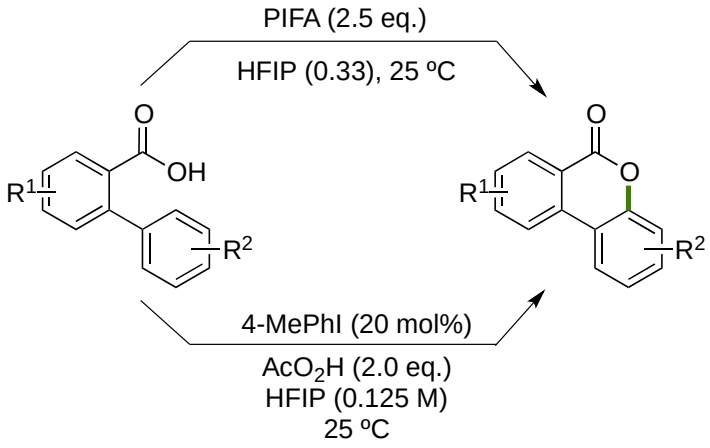


Figure 5.3