UNIVERSITAT ROVIRA I VIRGILI

METAL-CATALYZED FUNCTIONALIZATION OF C-C BONDS IN FOUR-MEMBERED RINGS.

Asraa Ziadi

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DOCTORAL THESIS

Metal-catalyzed functionalization of C-C bonds in four-membered rings

Asraa Ziadi

Supervised by Dr. Rubén Martín Romo
Institut Català d'Investigació Quimica (ICIQ)

UNIVERSITAT ROVIRA I VIRGILI

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شكرا جزيلا الى امي وابي

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Abbreviations

BCB	Benzocyclobutenone
conv.	Conversion
eq.	Equivalents
et al.	*et. allí.* – latin, means “and others”
Ac$_2$O	Acetic Anhydride
DCM	Dichloromethane
THF	Tetrahydrofuran
PhMe	Toluene
MeCN	Acetonitrile
DMF	Dimethylformamide
DMA	Dimethylacetamide
^{t}BuOH	*tert*-butanol
NaHMDS	Sodium bis(trimethylsilyl)amide
DiBAL-H	Diisobutylaluminium hydride
r.t.	Room temperatura (approx. 22-25^{o}C)
TMS	Trimethyl silyl ether
δ	Chemical shift
J	Coupling Constant
CDCl$_3$	Deuterated Chloroform
d	Doublet
s	Singlet
t	Triplet
m	Multiplet
NMR	Nuclear Magnetic Resonance
ppm	Parts per million
Me	Methyl
OTf	Trifluoromethanesulfonate
OPiv	Pivalate

The rest of abbreviations and acronyms: “Guideline for authors” J. Org. Chem. **2008**, *73*, 23A-24A.

List of Publications

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

1. *"Ligand-Accelerated Pd-Catalyzed Ketone γ-Arylation via C-C Bond-Cleavage with Aryl Chlorides"* **Asraa Ziadi**, Rubén Martín. *Org. Lett.,* **2012**, *14*, 1266-1269.
2. *"Palladium-catalyzed alkynylation via β-carbon elimination: synthesis of γ- acetylene ketones"* **Asraa Ziadi**, Arkaitz Correa, Rubén Martín. *Chem. Comm.* **2013**, *44*, 4286-4288.

Besides the publications presented in this thesis, I have as well contributed as co-author in:

3. *"Mechanisms and kinetics for sorption of CO_2 on bicontinuous mesoporous silica modified with n-propylamine".* Zoltan Bacsik, Nanna Ahlsten, **Asraa Ziadi**, Guoying Zhao, Alfonso E. Garcia, Belén Martín-Matute, Niklas Hedin. *Langmui*r. **2011**, *27*, 11118-11128.
4. *"Manganese-Catalyzed Intermolecular C-H/C-H Coupling of Carbonyls and Heteroarenes".* Keika Hattori, **Asraa Ziadi**, Kenichiro Itami, Junichiro Yamaguchi. *Chem. Comm.* **2014**, *50*, 4105-4107.

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CHAPTER 1

INTRODUCTION TO C-C BOND CLEAVAGE

1.1 Introduction to C-C bond cleavage

In early 1970s, breakthrough discoveries using Fe[1], Ni[2] or Pd[3] catalysts set the standards for modern cross-coupling reactions of aryl, vinyl or pseudo halides (Figure 1.1) and so becoming a powerful and general strategy for C-C and C-heteroatom bond-forming reactions.[4] Despite the advances realized, there are still some issues to be addressed in this field of expertise; among them, particularly problematic, are the corresponding coupling partners, the general inherent instability of organometallic reagents (susceptible to undergo protodemetallation or β-hydride elimination), and the considerable amount of waste generated.

$$X-R^1 + [M]-R^2 \xrightarrow{\textit{transition metal catalyst}} R^2-R^1$$

Figure 1.1

In recent years, chemists have been challenged to find alternatives to such drawbacks via C-H, C-heteroatom and C-C bond functionalization. In this manner, no pre-functionalization is required and the reactions are, in principle, more atom-economical. Unlike remarkable progress in C-H bond functionalization, the means to promote C-C bond functionalization has received much less attention. This might be due to the fact that C-C bonds are robust and not polarized enough to facilitate the activation event. Industrially, such transformations are of interest, since the selective activation of carbon-carbon bonds is crucial for petroleum refining and transformation.[5]

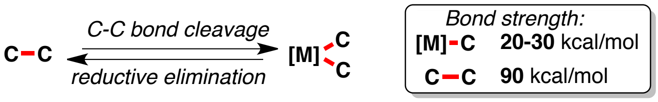

Figure 1.2

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[1] Tamura, M.; Kochi, J. *J. Am. Chem. Soc.* **1971**, *93*, 1487-1489.
[2] Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc., Chem. Comm.* **1972**, 144. (b) Tamao, T.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374-4376.
[3] Yamamura, M.; Moritani, I.; Murahashi, S.-I. *J. Organomet. Chem.* **1975**, *91*, C39-C42.
[4] Johansson, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062-5085.
[5] For reviews about carbon-carbon bond cleavage, see: (a) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245-269. (b) Rybtchinski, B.; Milstein, D. *Angew. Chem. Int. Ed.* **1999**, *38*, 870-883. (c) Masarwa, A.; Delaye, P.-O.; Leibeling, M.; Marek, I. *Angew. Chem., Int. Ed.* **2014**, *53*, 2-18. (d) Aïssa, C. *Synthesis* **2011**, 3389-3407.

The challenge of C-C bond functionalization is primarily associated to the fact that two relatively weak carbon-metal bonds (approx. 20-30 kcal/mol for each bond) are formed from a strong C-C bond (90 kcal/mol) (Figure 1.2), making this activation not favorable from a thermodynamic standpoint.[6] Yet another challenge deals with the directionality of the orbitals in C-C single bonds (Figure 1.3). A simple comparison of the orbitals in a C-C single bond with the orbitals in C-H and C-C double bond, indicates that the π-orbital of a C–C double bond is oriented sideways and therefore facilitates the interaction with a metal orbital. Although the σ-orbital of a C-H bond lies along the bond axis, the 1s orbital of the hydrogen atom is spherical, and since there are no other substituents except the bonded carbon, the interaction with a metal orbital is relatively facile.[7] In contrast, however, the σ-orbital of a C-C single bond is constrained straightway along the bond axis. Moreover, there are several substituents on both ends, making the C-C bond cleavage less accessible from a steric standpoint. Therefore, the interaction of such directionally and sterically constrained orbital with the corresponding metal orbitals is much more difficult than that of a C–C double bond or even C–H single bonds.

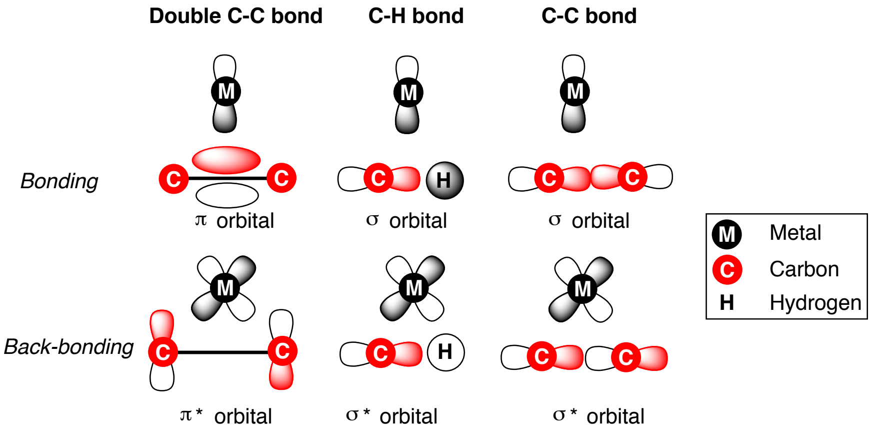

Figure 1.3

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[6] Ito, Y.; Murakami, M. Cleavage of carbon-carbon bonds by transition metals. In *Topics in Organometallic Chemistry*; Murai, S., Eds.; Springer-Verlag Berlin: Heidelberg, 1999; Vol. 3, pp. 97-127.

[7] Morehouse, S. M.; Lavin, M.; Holt, E. M.; Crabtree, R. H. *Inorg. Chem.* **1985**, *24*, 1986-1992.

Despite the considerable drawbacks associated to the cleavage of C-C single bonds, chemists have investigated several strategies to face such challenges. In early years, a myriad of stoichiometric methods using transition metals were reported but recently chemists have been mainly focused in the development of catalytic methods.[5,6] The available strategies for the activation of C-C single bonds involve the following: (1) strain-relief of strained molecules, (2) activation of more polarized C-C single bonds such as C-CO bonds, (3) chelation control, allowing the metal to be in close proximity of the targeted C-C bond and (4) using aromaticity as a driving force for promoting C-C bond cleavage.

1.1.1 Stoichiometric approaches for the activation of C-C single bonds

In 1955, Tipper observed the formation of a four-membered platinacycle (**II**, Figure 1.4) with cyclopropane.[8] The reaction proceeds most likely through the insertion of the $PtCl_2$ into the C-C bond of the cyclopropane, giving rise to **I** that in the presence of pyridine allows for the isolation of **II** in pure form.

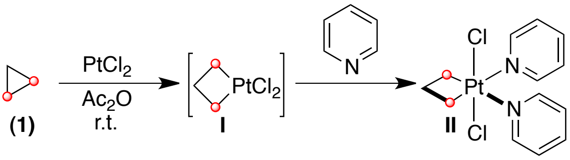

Figure 1.4

In analogy with Tipper's results,[8] it has been reported that $[Rh(CO)_2Cl]_2$ can be used for cyclopropane C-C bond cleavage, generating a four-membered rhodacycle **III** that ultimately generates **IV** via CO migratory insertion (Figure 1.5).[9]

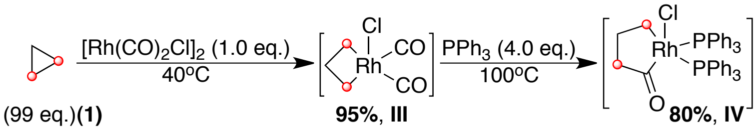

Figure 1.5

A few years later, Belluco and Graziani reported the insertion of $Pt(PPh_3)_4$ or $Pd(PPh_3)_4$ into a C-C single bond in 1,1,2,2-tetracyanocyclopropane (Figure 1.6).[10] Interestingly, the corresponding metal inserts into the most polarized bond, demonstrating that steric effects do not come into play.

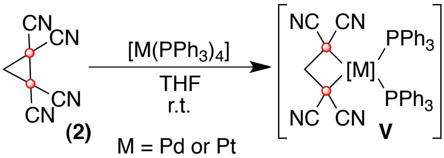

Figure 1.6

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[8] Tipper, C. H. F. *J. Chem. Soc.* **1955**, 2045-2048.

[9] (a) Roundhill, D. M.; Lawson, D. N.; Wilkinson, G. *J. Chem. Soc.* **1968**, 845-849. (b) Powell, K. G.; McQuillin, F. J. *Chem Commun.* **1971**, 931-932. (c) McQuilin, F. J.; Powell, K. G. *J. Chem. Soc. Dalton*. **1972**, 2123-2129.

[10] (a) Lenarda, M.; Ros, R.; Graziani, M.; Belluco, U. *J. Organomet. Chem.* **1974**, *65*, 407-416. (b) Yarrow, D. J.; Ibers, J. A.; Lenarda, M.; Graziani, M. *J. Organomet. Chem.* **1974**, *70*, 133-145.

In 1986, Bergman reported the mechanistic study of the oxidative addition of rhodium into single C-C bonds in cyclopropane (Figure 1.7).[11] The reaction is initiated by the insertion of the coordinatively unsaturated Rh(I)-complex into the C-H bond in cyclopropane at -60°C (**VI**). At such temperatures, the C-C bond cleavage was not observed, but upon heating to -20°C, the cleavage occurs and four-membered rhodacycle **VII** was obtained. Thus, the authors postulated that the formation of Rh-complex **VI** is kinetically favored, while the formation of Rh(III)-complex **VII** is controlled by thermodynamics. Interestingly, the kinetic preference of C-H insertion over C-C insertion clearly demonstrates the greater steric accessibility of the C-H bond compared with the C-C bond.

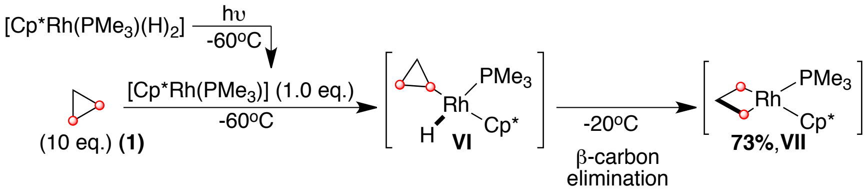

Figure 1.7

When dealing with the cleavage of four-membered rings, it is worth mentioning the work reported by Dickelman in 1964,[12] which involves the oxidative addition of $Cr(CO)_6$ into a C-C single bond of biphenylene (**3**) giving rise to 9-fluorenone (**4**, Figure 1.8). This report was of high interest, since just a few years earlier, Chatt et al. reported that no reaction was observed of biphenylene (**3**) with $Fe(CO)_5$, $Ni(CO)_4$, $Ni(PPh_3)_2(CO)_2$ or $PtCl_2(PPh_3)_2$.[13] The transformation is initiated by the oxidative addition of Cr(0) into the central C-C bond to obtain Cr(II)-complex **VIII.** A subsequent migratory insertion of the CO gave rise to Cr(II)-complex **IX** and a final reductive elimination step delivered **4** in 5% yield.

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[11] (a) Periana, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 7332-7346. (b) Periana, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 7346-7355.

[12] Atkinson, E. R.; Levins, P. L.; Dickelman, T. E. *Chem. Ind.* **1964**, 934

[13] Chatt, J.; Guy, R. G.; Watson, H. R. *J. Chem. Soc.* **1961**, 2332-2335.

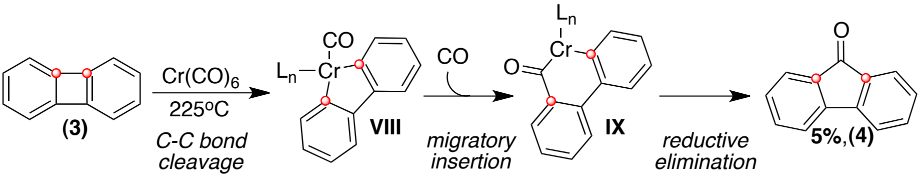


Figure 1.8

In 1985, Eisch et al. reported the Ni(0)-mediated cleavage of single C-C bonds in biphenylenes (**3**, Figure 1.9).[14] It was demonstrated that the insertion of Ni(0) into the single C-C bonds was influenced by the ligands attached to nickel. Thus, it was found that the more basic the ligand is, the easier the insertion of nickel into the single C-C bond (bipyridyl < PPh_3 << PEt_3). Subsequently, upon heating to 18-25ºC, the Ni(II)-complex **X** undergoes dimerization, giving rise to Ni(II)-complex **XI**.

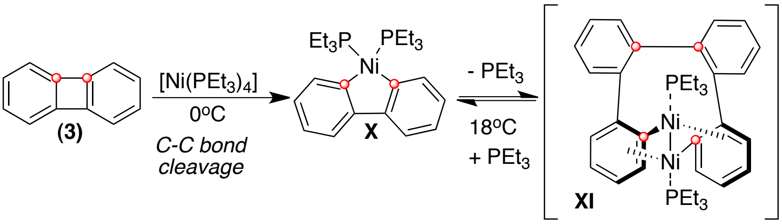
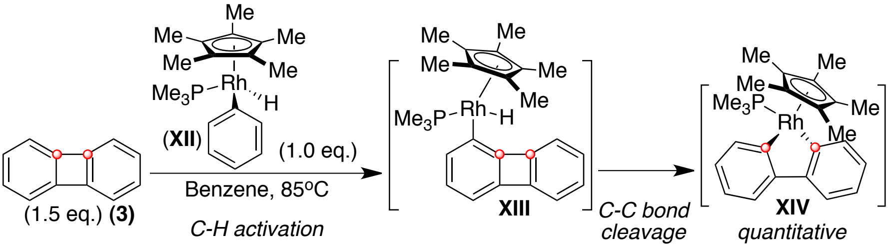


Figure 1.9

On the other hand, when biphenylene (**3**) was employed under the presence of coordinatively unsaturated Rh(III)-complex **XII**, C-H insertion occurred rapidly, giving rise to Rh(III)-complex **XIII**, that subsequently undergoes C-C bond cleavage upon heating to 85ºC (**XIV**, Figure 1.10).[11,15]



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[14] Eisch, J. J.; Piotrowski, A. M.; Han, K. I.; Krüger, C.; Tsay, Y. H. *Organometallics* **1985**, *4*, 224-231.
[15] Perthuisot, C.; Jones, W. D. *J. Am. Chem. Soc.* **1994**, *116*, 3647-3648.

Figure 1.10

Jones also reported the formation of Rh and Co complexes **XV** when employing biphenylene in the presence of [Cp*Rh(C_2H_4)$_2$] and [Cp*Co(C_2H_4)$_2$], respectively (Figure 1.11).[16] Upon treating metal-complex **XV** with carbon monoxide, five-membered metal-complex was formed that upon reductive elimination delivers fluorenone (**4**). Interestingly, Rh and Co complexes **XV** were particularly resistant to hydrogenation.

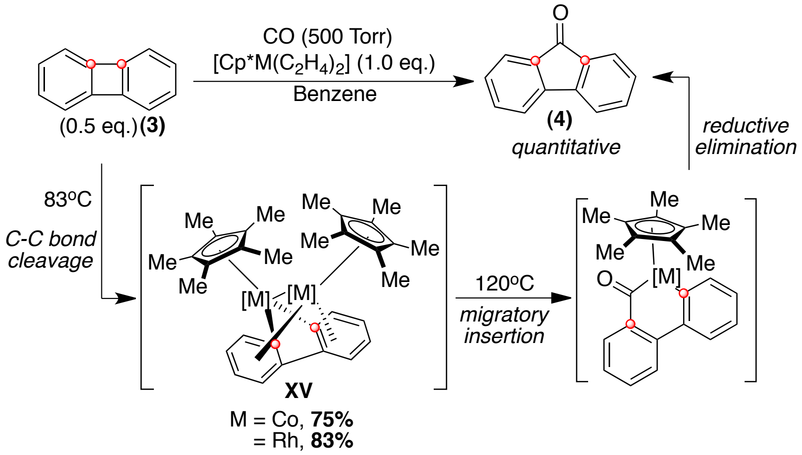
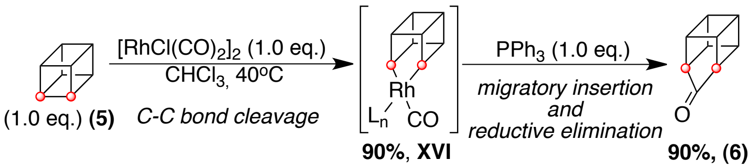


Figure 1.11

In 1970, Halpern reported the Rh(I)-mediated oxidative insertion into cubane (**5**, Figure 1.12).[17] The reaction is believed to proceed via oxidative addition of rhodium into the single C-C bond of cubane, (**XVI**), followed by treatment with PPh_3, that triggers carbonyl migratory insertion, affording a cyclic ketone after a reductive elimination step.



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[16] Perthuisot, C.; Edelbach, B. L.; Zubris, D. L.; Jones, W. D. *Organometallics* **1997**, *16*, 2016-2023.
[17] Cassar, L.; Eaton, P. E.; Halpern, J. *J. Am. Chem. Soc.* **1970**, *92*, 3515-3518.

Figure 1.12

In 1973, Russell demonstrated the formation of five-membered platinacycle **XVII** (Figure 1.13) from benzocyclobutane-1,2-dione (**7**) in the presence of Pt(PPh_3)$_4$.[18] Interestingly, the use of Rh(I), Co(I) or Fe(0)-complexes triggers a selectivity switch by forming **XVIII** that cleaves the distal C-C bond (**XVIII**, Figure 1.13).[19]

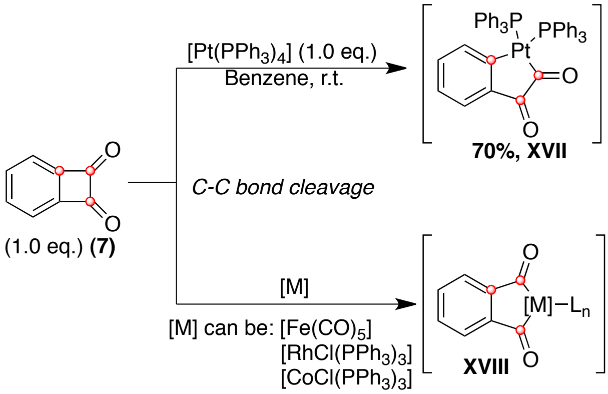

Figure 1.13

Analogously, cyclobutenedione (**8**) can undergo oxidative insertion in the presence of Pt(PPh_3)$_4$, giving rise to five-membered platinacycle **XIX** (Figure 1.14).[20] Similarly, **XX** could also be obtained with cyclobutanone **9** in the presence of [RhCl(PPh_3)$_3$] or [(η^5-C_9H_7)Co(PPh_3)$_2$] (Figure 1.14).[21]

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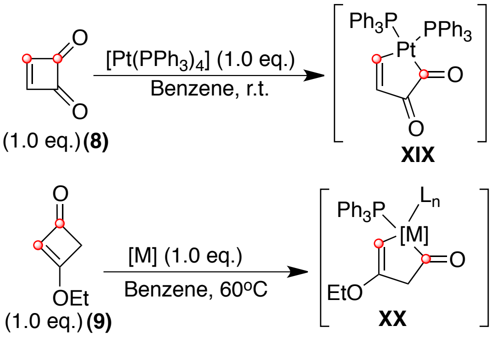
[18] Evans, J. A.; Everitt, G. F.; Kemmitt, R. D. W.; Russell, D. R. *J. Chem. Soc. Chem. Commun.* **1973**, 158-159.
[19] Baysdon, S. L.; South, M. S.; Blount, J. F.; Liebeskind, L. S. *J. Organomet. Chem.* **1980**, *202*, C73-C76.
[20] Hamner, E. R.; Kemmitt, R. D. W.; Smith, M. A. R. *J. Chem. Soc. Chem. Commun.* **1974**, 841-842.
[21] Huffman, M. A.; Pennington, W. T.; Liebeskind, L. S. *Organometallics* **1992**, *11*, 255-266.



[M] = $[RhCl(PPh_3)_3]$, **92%**
= $[(\eta^5\text{-}C_9H_7)Co(PPh_3)_2]$, **26%**

Figure 1.14

1.1.2 Catalytic strategies for the activation of C-C single bonds

1.1.2.1 Utilization of strained molecules

The use of cyclopropanes as substrates for C–C bond activation is advantageous kinetically as well as thermodynamically due to the energy gain from strain-relief and the fact that the orbitals connecting the carbon atoms are bent outward from the internuclear axis, therefore facilitating the interaction with the metal orbitals.[5,6] In 1990, Schwager et al. reported the first Ni-catalyzed cleavage of biphenylene (**3**, Figure 1.15) leading to the synthesis of tetraphenylene in quantitative yields (**10**).[22] Prompted by these precedents, Jones reported a related protocol that dealt with the utilization of $Pt(PEt_3)_2$ or $Pd(PEt_3)_3$.[23] The mechanism study reported a pathway consisting of an oxidative addition of [M(0)] into the targeted C-C bond accessing the five-membered metallacycle **XXI** (Figure 1.15). Subsequently, an additional oxidative addition of **3** onto **XXI** gave rise to the metallacycle **XXII**, that ultimately evolved to **10** via two consecutive reductive elimination steps.

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[22] Schwager, H.; Spyroudis, S.; Vollhardt, K. P. C. *J. Organomet. Chem.* **1990**, *382*, 191-200.
[23] Edelbach, B. L.; Lachicotte, R. J.; Jones, W.D. *J. Am. Chem. Soc.* **1998**, *120*, 2843-2853.

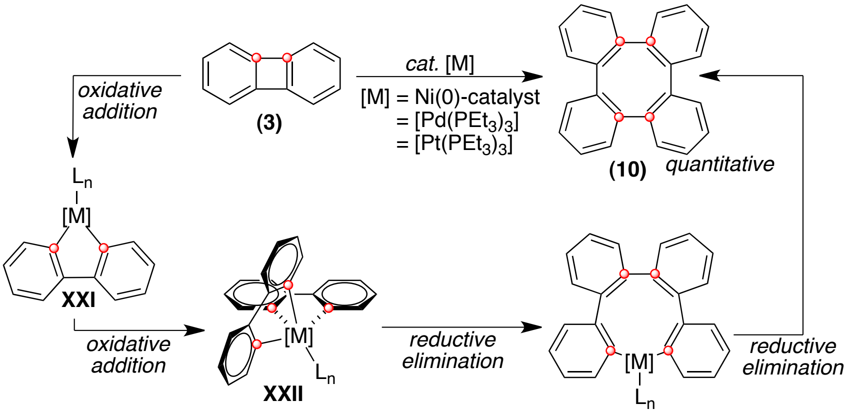

Figure 1.15

In 2006, Gallagher et al. extended the scope of this methodology to synthesize heterocyclic tetraphenylenes from biphenylene and 4-aryl-3-bromopyridine (Figure 1.16).[24] Although the corresponding tetraphenylenes were not obtained in excellent yields, the reaction allowed, for the first time, the access to unsymmetrical compounds, a matter of great interest in future synthetic applications. It is worth mentioning that the presence of an electron-withdrawing group (i.e. *para*-NO_2 group) increased the turnover numbers. Interestingly, it was determined that the C-H functionalization in the heterocyclic backbone via the in situ formation of a five-membered palladacycle was occurring prior to the C-C bond activation in biphenylene.

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[24] Masselot, D.; Charmant, J. P. H.; Gallagher, T. *J. Am. Chem. Soc.* **2006**, *128*, 694-695.

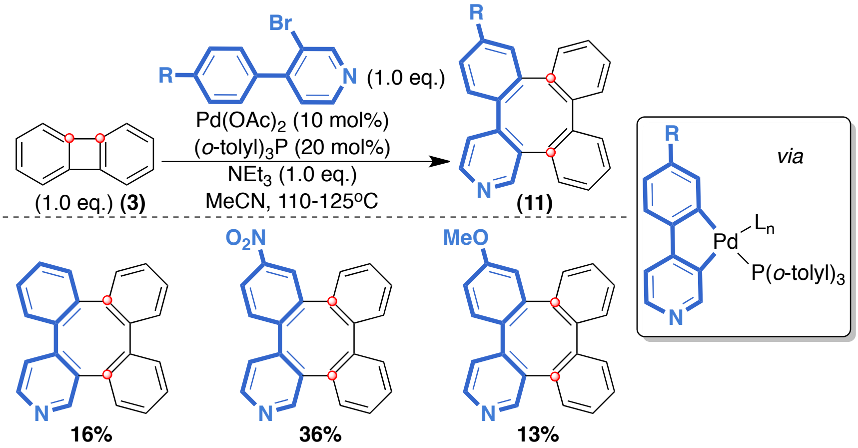

Figure 1.16

In 1997, Jones reported that fluorenone (**4**, Figure 1.17) could be obtained in the presence of carbon monoxide (CO) and catalytic amounts of [Cp*Rh(C_2H_4)$_2$] or [Cp*Co(C_2H_4)$_2$] at 120-160ºC.[25] The mechanism for this transformation was proposed to proceed via ligand exchange giving rise to [Cp*Rh(CO)$_2$] that undergoes oxidative addition into the C-C bond to deliver Rh(III)-complex (**XXIII**). Through a migratory insertion step, CO is inserted into the Rh(III)-carbon bond (**XXIV**) that triggers a reductive elimination en route to **4**. Interestingly, upon exposure of **3** to 500 Torr of H_2 in the presence of catalytic amounts of [Cp*Rh(H)$_2$], biphenyl was formed in quantitative yields,[15] thus reinforcing the notion that a rhodacycle was being formed. More recently, it has been shown that biphenylenes can participate in cross-coupling reactions when utilizing alkynes, alkenes, ketones and aryl boronic acids.[26]

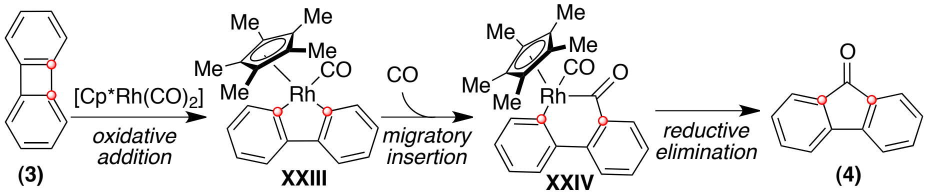

Figure 1.17

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[25] Perthuisot, C.; Edelbach, B. L.; Zubris, D. L.; Jones, W. D. *Organometallics.* **1997**, *16*, 2016-2023.
[26] Satoh, T.; Jones, W. D. *Organometallics.* **2001**, *20*, 2916-2919 and references therein.

In 2007, Murakami reported the Rh(I)-catalyzed C-C bond cleavage and insertion of CO into spiropentanes giving access to cyclopentenones (Figure 1.18).[27] The transformation is believed to proceed via oxidative addition of Rh(I) into the most accessible cyclopropane C-C bond, thus forming spirocyclic rhodacyclobutane **XXV**. Subsequently, migratory insertion of CO gives rise to five-membered rhodacycle **XXVI**, which is converted into the six-membered rhodacycle **XXVII** after a β-carbon elimination step, thus setting up the stage for a reductive elimination step. Notably, the methodology allows for the formation of a variety of cyclopentanones in good yields with retention of the stereochemistry.

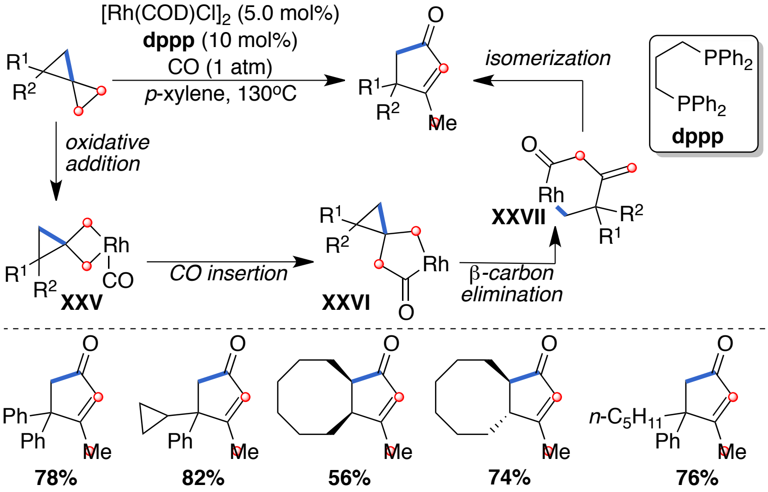

Figure 1.18

1.1.2.2 C-C bond cleavage α to a carbonyl motif

It is widely known that the C–C single bond between the carbonyl carbon and the α-carbon is slightly weaker than other C–C single bonds. Additionally, it might be anticipated that a carbonyl group kinetically facilitates insertion of a transition metal into the α C–C bond. In 1965, Rusina and Vlcek observed the extrusion of a carbonyl group from cyclohexanone in the presence of rhodium.[28] In 1972, Baddley and

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[27] Matsuda, T.; Tsuboi, T.; Murakami, M. *J. Am. Chem. Soc.* **2007**, *129*, 12596-12597.

[28] Rusina, A.; Vlcek, A. A. *Nature*. **1965**, *206*, 295-296.

Ramakers-Blom reported the Pt(0)-catalyzed activation of cyclopropenone **12** where Pt(0) coordinates to the olefin moiety **XXVIII** (path A, Figure 1.19) and subsequently undergoes a regioselective insertion to the less sterically hindered carbon giving rise to four-membered platinacycle **XXIX** (path A, Figure 1.19).[29] Intriguingly, if cyclopropenone **13** is allowed to react with [Rh(CO)$(PPh_3)_2$(OTf)] at 60-65°C, the cationic complex **XXX** (path B, Figure 1.19) in which the carbonyl function is coordinated to the metal center is formed.[30] Subsequently, the complex undergoes C-C bond activation and, subsequently, migratory insertion giving rise to the formation of the metal carbonyl insertion product **XXXI** (path B, Figure 1.19). It is worth noting that complex **XXXI** (path B, Figure 1.19) decomposes to diphenylacetylene upon heating.

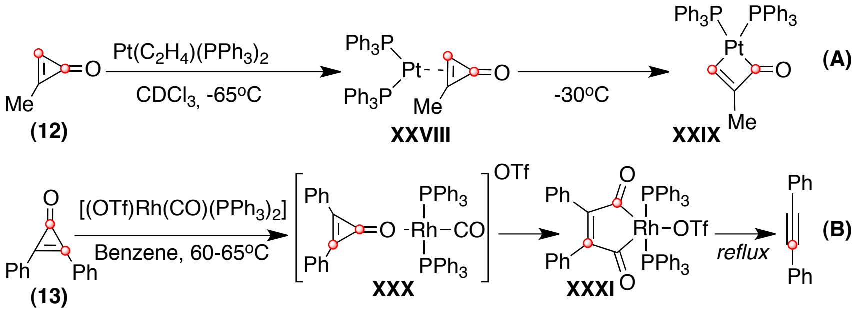

Figure 1.19

In 1996, Murakami reported the Rh(I)-catalyzed C-C bond cleavage of cyclobutanones, which resulted in a rather intriguing decarbonylation event leading to the selective formation of the corresponding cyclopropane in the presence of catalytic amounts of [Rh(COD)(dppb)]BF_4 (Figure 1.20).[31] In some cases, however, it was necessary to employ stoichiometric amounts of [RhCl$(PPh_3)_3$] in order to facilitate the key decarbonylation step (Figure 1.20). The transformation was initiated with the oxidative addition of the Rh(I)- complex into the C-CO bond giving

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[29] (a) Wong, W.; Singer, S. J.; Pitts, W. D.; Watkins, S. F.; Baddley, W. H. *J. Chem. Soc. Chem. Comm.* **1972**, 672-673. (b) Vissner, J. P.; Ramakers-Blom, J. E. *J. Organomet. Chem.* **1972**, *44*, C63-C65.

[30] Song, L.; Arif, A. M.; Stang, P. J. *Organometallics.* **1990**, *9*, 2792-2797.

[31] a) Amii, H.; Ito, Y.; Murakami, M. *Nature.* **1994**, *370*, 540-541. (b) Amii, H.; Shigeto, K.; Ito, Y.; Murakami, M. *J. Am. Chem. Soc.* **1996**, *118*, 8285-8290.

rise to the five-membered rhodacycle **XXXII** that subsequently undergoes decarbonylation and forms Rh(III)-complex **XXXIII** that sets the stage for a reductive elimination step en route to the targeted cyclopropane.

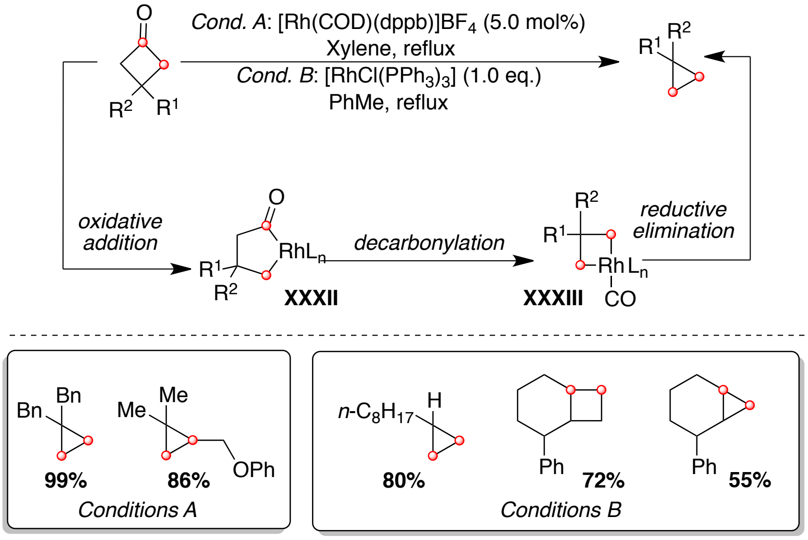

Figure 1.20

In 1997, Murakami reported the Rh(I)-catalyzed successive double cleavage of C-C bonds in spiro cyclobutanones giving rise to the corresponding cyclohexanone (Figure 1.21).[32] The transformation is initiated with the insertion of Rh(I)-complex into the more weak C-CO bond giving rise to rhodacycle **XXXIV** (Figure 1.21), that subsequently undergoes β-carbon elimination (**XXXV**). A final reductive elimination step delivers a methylenecyclohexanone, which upon isomerization forms the conjugated cyclohexanone.

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[32] Takahasi, K.; Amii, H.; Ito, Y.; Murakami, M. *J. Am. Chem. Soc.* **1997**, *119*, 9307-9308.

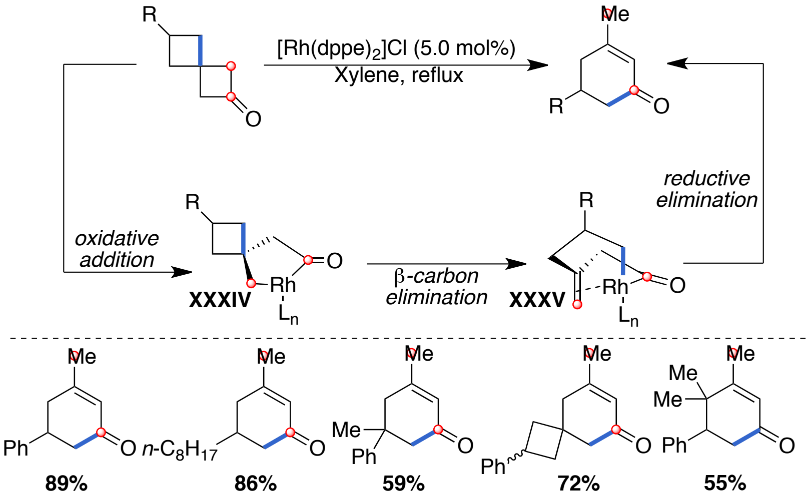

Figure 1.21

Intriguingly, when cyclobutanones with mono-substitution at the 3-position were employed in the presence of catalytic amounts of Rh(I), the authors did not observe high yields of cyclopropane (figure 1.20). In this case, alkenes resulting from a β-hydrogen elimination via the intermediacy of **XXXVII** were observed in the crude mixtures (Figure 1.22).

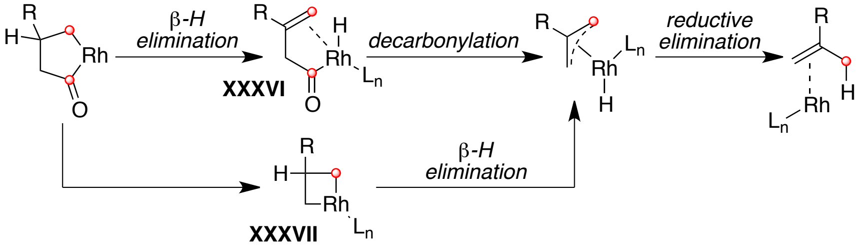

Figure 1.22

In 1993, Liebeskind reported the Rh(I)-catalyzed ring expansion reaction of cyclobutanones into cyclooctanones (Figure 1.23).[33] The transformation is initiated by oxidative addition of Rh(I) into the weak C-CO bond, giving access to five-membered rhodacycle **XXXVIII**. A β-carbon elimination then gives rise to an eight-

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[33] Huffman, M. A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 4895-4896.

membered rhodacycle **XXXIX**, which subsequently undergoes reductive elimination to give 2,4-cyclodienones or 3,5-cyclodienones via a thermal promoted [1,5]-hydrogen shift. Intriguingly, even cyclobutanes could be activated and the corresponding 2,4-cyclooctadienones were obtained.

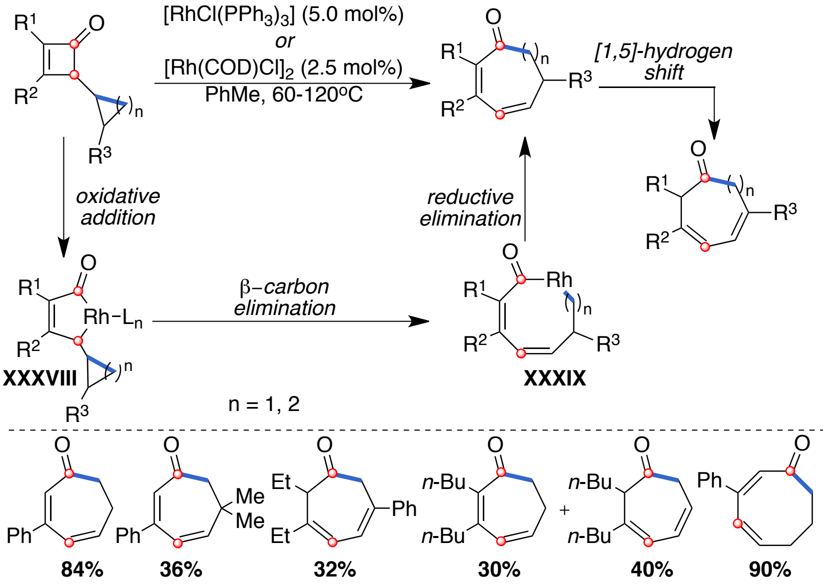

Figure 1.23

In 2012, Aïssa reported the Ni(0)-catalyzed cycloaddition reaction of 3-azetidinones and 3-oxetanones with alkynes via C-C bond cleavage.[34] When employed under the reaction conditions, 3-azetidinones and 3-oxetanones undergo C-C bond cleavage not on the C-N or C-O bond but on the C-CO bond (Figure 1.24) providing the ring-expanded product in good yields. The transformation is initiated with the coordination of Ni(0)-complex to 3-azetidinones or 3-oxetanones and the alkyne, giving rise to Ni(0)-complex **XL** (Figure 1.24) that subsequently undergoes a migratory insertion and later β-carbon elimination to give access to the nickelacycle **XLI** that gives rise to the ring-expanded product after a reductive elimination step. In 2005, Murakami reported the Ni-catalyzed intermolecular alkyne insertion into

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[34] Ho, K. Y. T.; Aïssa, C. *Chem. Eur. J.* **2012**, *18*, 3486-3489.

cyclobutanones instead.[35] Murakami also reported the synthesis of enantiopure dehydropiperidinones from α-amino acids and alkynes via azetidin-3-ones.[36] In 2012, Louie also reported the Ni-catalyzed synthesis of piperidines via β-carbon elimination.[37]

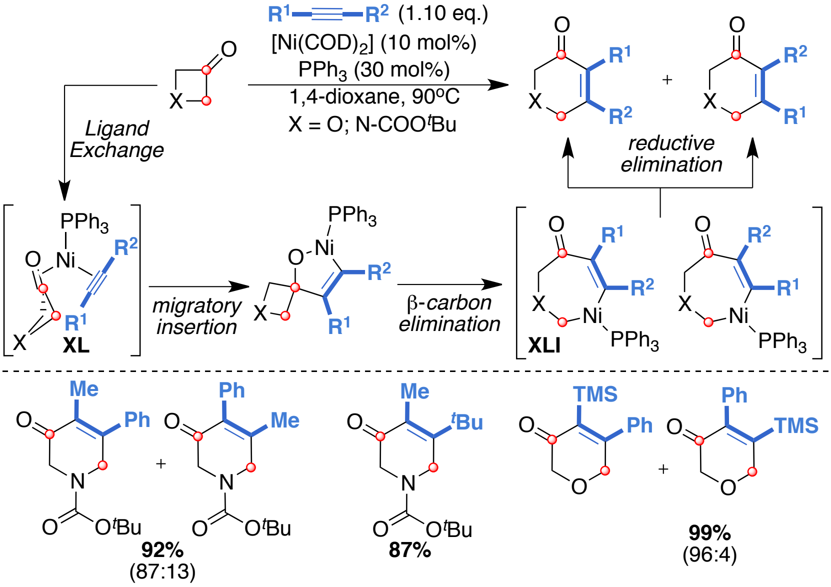

Figure 1.24

1.1.2.3 Utilization of chelating effects

An important strategy for the activation of C-C bonds is the presence of coordinating functionalities in the target molecule. In this manner, the metal center would be in close proximity to the targeted C-C bond. In 1993, Milstein designed a pincer-type bis-phosphine ligand (**14**, Figure 1.25) and observed that in the presence of rhodium,, a selective C-C bond cleavage of an unactivated methyl group occurred.[38] A few years later, Milstein developed the catalytic process with $[Rh(C_8H_{14})_2Cl]_2$ (1.0

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[35] (a) Ashida, S.; Matsuda, T.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127*, 6932-6933. (b) Ashida, S.; Matsuda, T.; Murakami, M. *Tetrahedron* **2006**, *62*, 7540-7546.

[36] Ishida, N.; Yuhki, T.; Murakami, M. *Org. Lett.* **2012**, *14*, 3898-3901.

[37] (a) Kumar, P.; Louie, J. *Org. Lett.* **2012**, *14*, 2026-2029. (b) Kumar, P.; Zhang, K.; Louie, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 8602-8606.

[38] Gozin, M.; Weisman, A.; Milstein, B.-D. Y. *Nature*. **1993**, *364*, 699-701.

mol%) in 1,4-dioxane at 180ºC under H_2 pressure (20-25 psi) or instead with an excess of $HSi(OEt)_3$ as hydrogen source (Figure 1.25).[39] The transformation is initiated by C-C bond cleavage forming Rh(III)-complex **XLII**, that, after a ligand exchange from the methane to the hydrogen, undergoes reductive elimination to yield **15** in 35% yield.

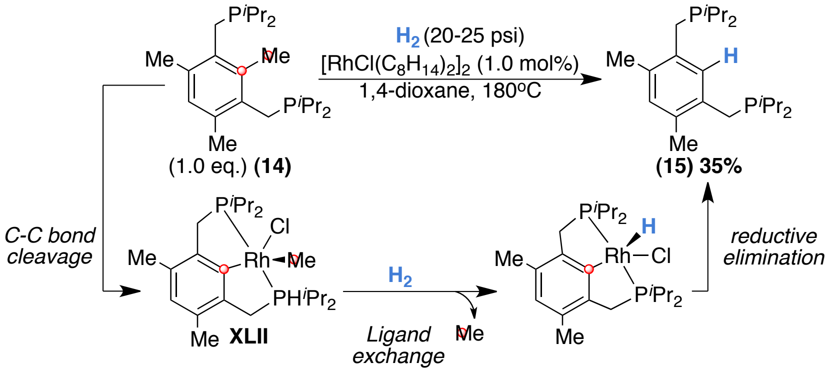

Figure 1.25

In 1985, Suggs reported the coordination of Rh(I)-catalyst to **16** and the subsequent C-C bond cleavage (Figure 1.26).[40] When **16** is exposed under $[(C_2H_4)_2RhCl]$ and ethylene, **17** is obtained along with styrene. The transformation is believed to proceed by the coordination and subsequently insertion of Rh(I)-complex into the Csp^2-CO bond, giving rise to Rh(III)-complex **XLIII**. Migratory insertion and a subsequent step of β-hydride elimination give styrene and Rh(III)-complex **XLV**, that incorporates ethylene into the Rh-CO bond giving access to **17** in quantitative yield.

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[39] Liou, S. Y.; van der Boom, M. E.; Milstein, D. *Chem. Commun.* **1998**, 687-688.
[40] Jun, C. H.; Suggs, J. W. *J. Chem. Soc. Chem. Commun.* **1985**, 92-93.

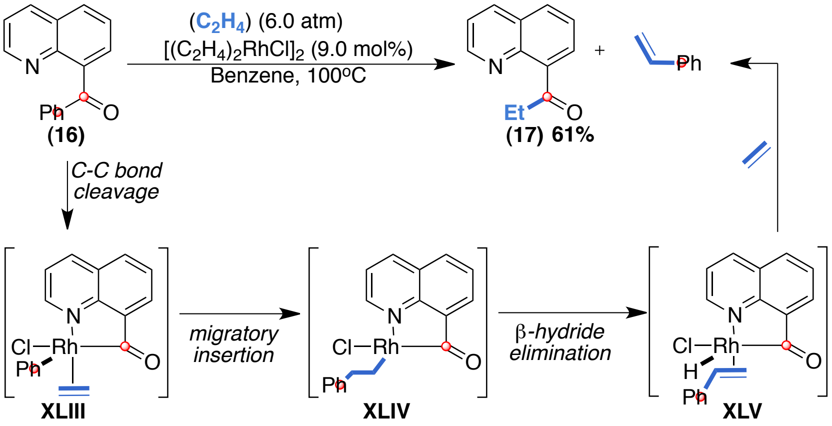

Figure 1.26

1.1.2.4 Aromaticity as a driving force

In 1969, Maitlis reported the synthesis of pentamethylcyclopentadienylrhodium and –iridium halides (Figure 1.27).[41] The transformation proceeds via the opening of the strained hexamethyldewar benzene (**18**, Figure 1.25) giving access to Rh(III)-complex **XLVI** that subsequently undergoes C-C bond cleavage to give Rh(III)-complex **XLVII**. A repetition of the steps mentioned gives the Rh(III)-complex dimer **XLVIII**.

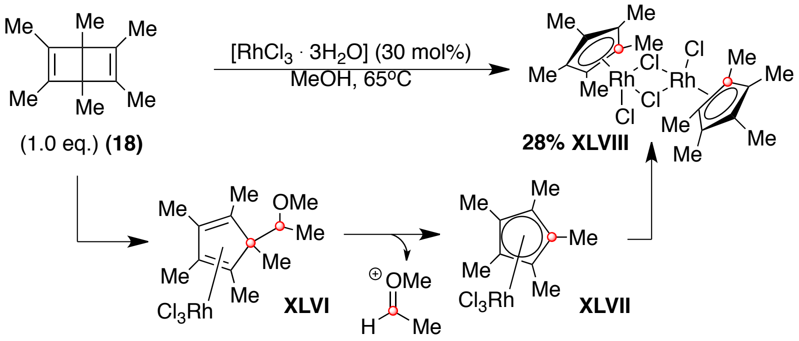

Figure 1.27

In 1991, Liebeskind reported the Ni(0)-catalyzed synthesis of substituted phenols from cyclobutanones via C-C bond cleavage and subsequent [4+2] cycloaddition with

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[41] Kang, J. W.; Moseley, K.; Maitlis, P. S. *J. Am. Chem. Soc.* **1969**, *91*, 5970-5977.

alkynes (Figure 1.28).[42] Initially, oxidative addition of Ni(0)-complex into the weak C-CO bond gives rise to nickelcyclopentenone **XLIX**. Subsequently, the alkyne inserts into the Ni-C bond giving rise to seven-membered metallacycle **L** *or* **LI** that deliver the corresponding phenols via reductive elimination.

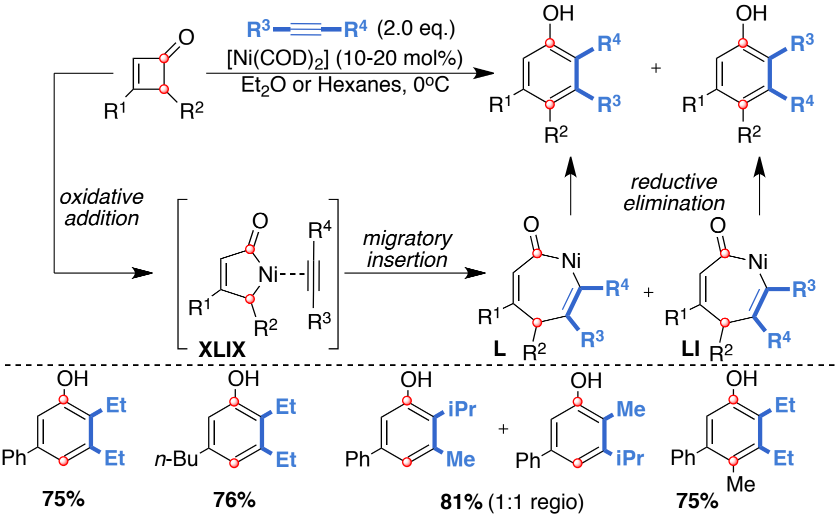

Figure 1.28

In 1974, Furukawa reported the Ni(II)-catalyzed C-C bond cleavage in norbornadiene **19** in the presence of *iso*-propyl amine, giving access to 5-tolyl-2-norbornene **20** (Figure 1.29).[43] The transformation is initiated by the dimerization of norbornadiene giving rise to Ni(II)-complex **LII** that undergoes β-carbon elimination (**LIII**). A final β-hydride elimination yields **20** in 70% isolated yield.

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[42] Huffman, M. A.; Liebesking, L. S. *J. Am. Chem. Soc.* **1991**, *113*, 2771-2772.

[43] Yoshikawa, S.; Aoki, K.; Kiji, J.; Furukawa, J. *Tetrahedron* **1974**, *30*, 405-407.

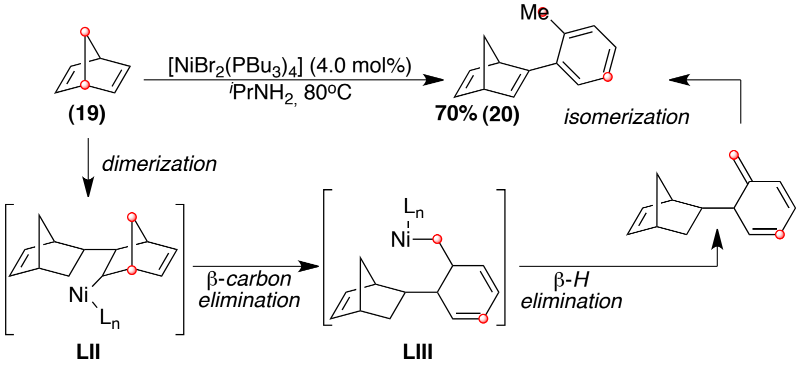

[NiBr$_2$(PBu$_3$)$_4$] (4.0 mol%)
^{i}PrNH$_2$, 80ºC
(19)
70% (20)
Me
isomerization
dimerization
Ni
L$_n$
β-carbon elimination
β-H elimination
LII
LIII

Figure 1.29

CHAPTER 2

A FORMAL KETONE γ-ARYLATION via Pd-CATALYZED C-C BOND-CLEAVAGE OF *tert*-CYCLOBUTANOLS

2.1 Objectives

The objectives of this chapter are the following:

- To develop a new methodology for the synthesis of γ-arylated ketones with aryl chlorides and aryl tosylates via catalytic C-C bond cleavage.
- To come up with a catalyst with high turnover numbers that operates with a wide substrate scope

2.2 *Tert*-cyclobutanols: useful platforms for molecular diversity

While a wide number of methodologies aimed at providing C-C bond-cleavage have been reported in the literature, the means to promote β-carbon elimination events have been particularly popular in recent years, thus providing a new handle for subsequent manipulation.[44,45] Although excellent results have been described with aliphatic tertiary alcohols, the low atom economy and the site-selectivity of these processes might constitute a drawback from a practical and synthetic standpoint (Figure 2.1, a vs. b vs. c).

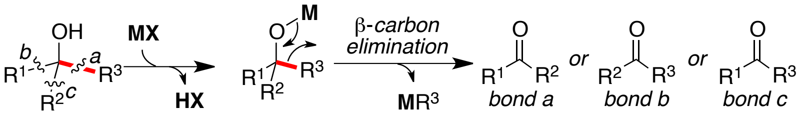
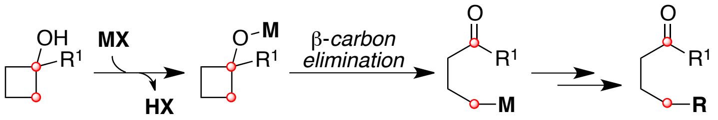


Figure 2.1

Beyond any doubt, the design of β-carbon elimination techniques that operates with an exquisite regioselectivity control would be highly appreciated. Among the different possibilities, the use of *tert*-cyclobutanols has attracted a great deal of attention at the Community as a manifold for effecting catalytic β-carbon elimination events (Figure 2.2). The strain relief associated to the C-C bond-cleavage of *tert*-cyclobutanols makes such a process irreversible, resulting in a straightforward technique that gives a new entry en route to heavily functionalized ketone derivatives.



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[44] For reviews on ring strain, see: (a) *Small Ring Compounds in Organic Synthesis I-IV*. In *Topics in Current Chemistry*; de Meijere, A., Ed.; Springer-Verlag: Berlin, 1986; Vol. 133; 1987; Vol. 135; 1988; Vol. 144; 1990; Vol. 155. (b) Durst, T.; Breau, L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U. K., 1991; Vol. 5, pp. 675-697. (c) Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 5, pp 899-970. (d) Piers, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 5, pp 971-998. (e) Bronson, J. J.; Danheizer, R. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 5, pp 999-1035.

[45] For reviews on transition metal catalyzed C-C bond cleavage in small rings, see: (a) Bishop, K. C. III. *Chem. Rev.* **1976**, *76*, 461-468. (b) Jennings, P. W.; Johnson, L. L. *Chem. Rev.* **1994**, *94*, 2241-2290.

Figure 2.2

The excellent reactivity of *tert*-cyclobutanols in C-C bond-cleavage reactions has prompted chemists to devise enantioselective activation techniques using unsymmetrically substituted backbones, providing a conceptually new handle for the synthesis of enantioenriched carbonyl motifs (Figure 2.3).

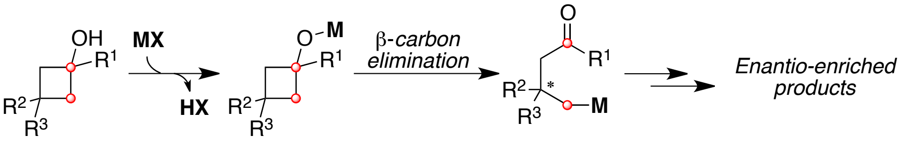

Figure 2.3

2.3 Catalytic transformations using *tert*-cyclobutanols as building blocks

2.3.1 Rh-catalyzed synthesis of indanols

In 2009, Cramer and Murakami independently reported the skeletal rearrangement of *tert*-cyclobutanols having an aryl group at the 3-position en route to densely substituted 1-indanols with excellent diastereoselectivities and asymmetric control (Figure 2.4).[46] The reaction is initiated by coordination of a Rh(I) species to the hydroxyl group, forming a Rh(I) alkoxide that undergoes a β-carbon elimination to give access to an alkylrhodium(I) species (**I**, Figure 2.4). Subsequently, a [1,4]-Rh migration generates an arylrhodium species (**II**, Figure 2.4) that inserts across the C=O bond, yielding a new Rh(I) alkoxide that promotes a ligand exchange with the starting *tert*-cyclobutanol to give rise to the desired product **21** (Figure 2.4).

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[46] a) Seiser, T.; Cramer, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 6320-6323. (b) Shigeno, M.; Yamamoto, T.; Murakami, M. *Chem.-Eur. J.* **2009**, *15*, 12929-12931.

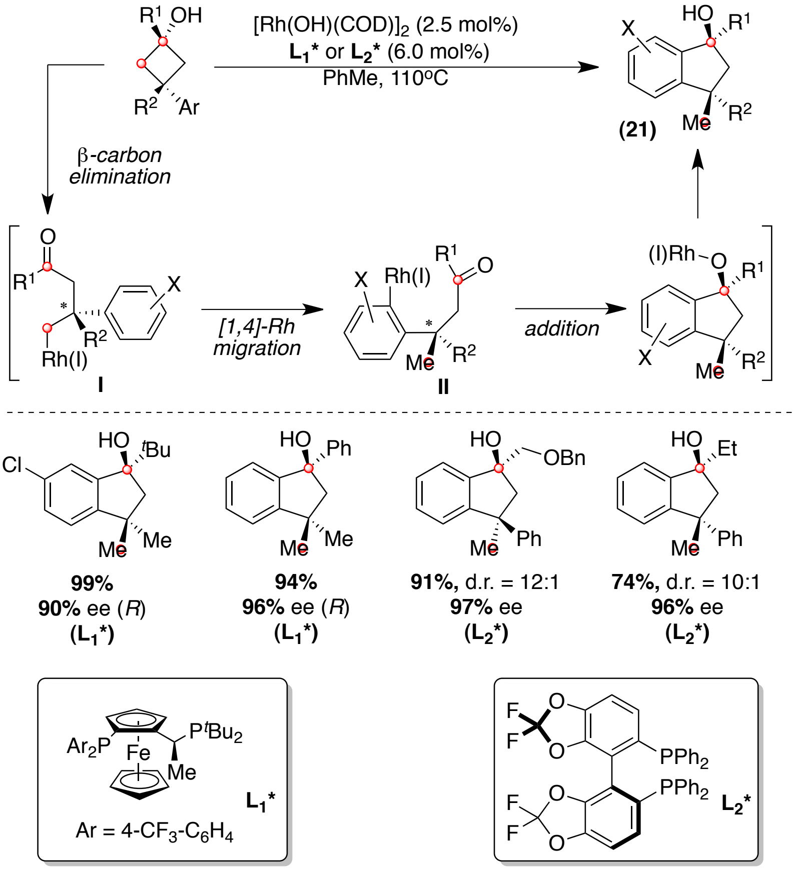

Figure 2.4

2.3.2 Rh-catalyzed synthesis of amides from *tert*-cyclobutanols

In 2013, Murakami reported the Rh(I)-catalyzed synthesis of alkyl amides from *tert*-cyclobutanols and isocyanates via C-C bond cleavage (**22**, Figure 2.5).[47] They observed that in the absence of the Rh(I)-catalyst, *O*-carbamoylation of the cyclobutanol occurred (**23**, Figure 2.5). It was suggested that the ring opening of the cyclobutane ring occurs more rapidly than O-addition of the hydroxyl moiety to the isocyanate.

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[47] Ishida, N.; Nakanishi, Y.; Murakami, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 11875-11878.

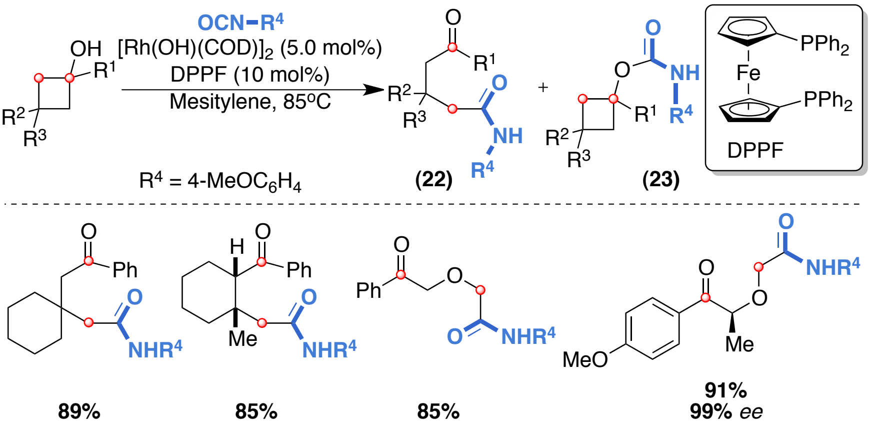

Figure 2.5

2.3.3 γ-halogenation of ketones via β-carbon elimination

In 1999, Kapustina et al. reported the γ-bromination and the γ-chlorination of ketones in the presence of $Pb(OAc)_4$ or $Mn(OAc)_3$ via mechanical activation with KBr and LiCl respectively (Figure 2.6).[48] The method required stoichiometric amounts of $Pb(OAc)_4$ or $Mn(OAc)_3$ and afforded the corresponding γ-bromo or γ-chloro ketones in good yields.

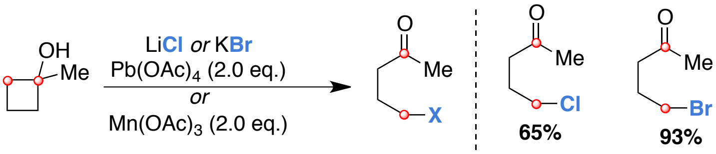

Figure 2.6

2.3.4 Rh-catalyzed ring-opening of *tert*-cyclobutanols

In 2010, Cramer et al. reported the Rh(I)-catalyzed synthesis of acyclic methyl substituted ketones (Figure 2.7).[49] The reaction involves the C-C bond cleavage by $[Rh(OH)(COD)]_2$ and a subsequent protonation to give rise to ketones in excellent yields and enantioselectivities. Interestingly, the authors demonstrated the utility of this methodology for preparing (*S*)-4-ethyl-4-methyl-octane, the simplest

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[48] Kapustina, N. I.; Sokova, L. L.; Makhaev, V. D.; Petrova, L. A.; Nikishin, G. I. *Russ. Chem. Bull.* **1999**, *48*, 2080-2082.
[49] Seiser, T.; Cramer, N. *J. Am. Chem. Soc.* **2010**, *132*, 5340-5341.

hydrocarbon with a quaternary stereogenic center, and with high asymmetric control.

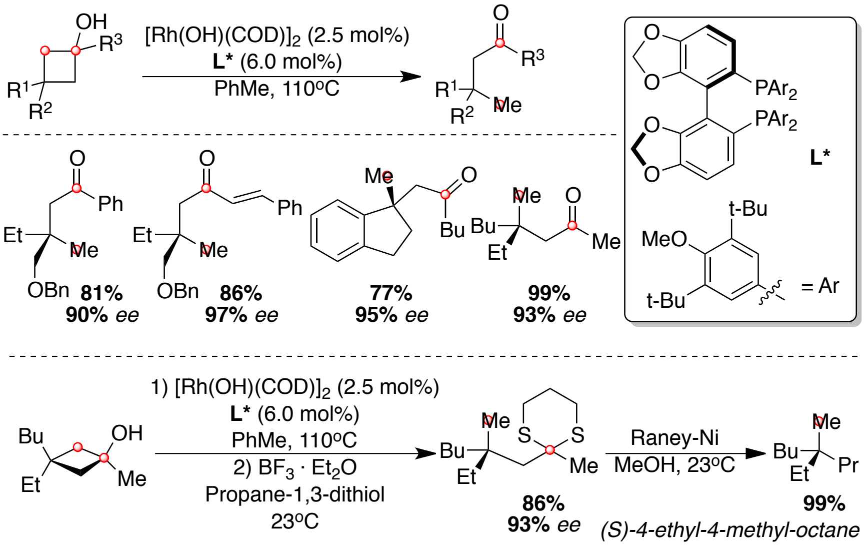
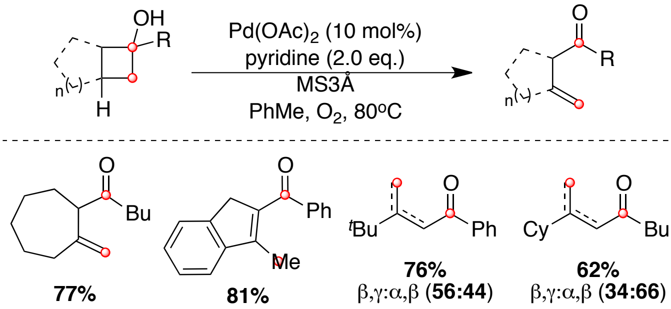


Figure 2.7

2.3.5 Pd-catalyzed intramolecular ring-expansion of *tert*-cyclobutanols

In 2001, Uemura reported the Pd(II)-catalyzed oxidative ring-opening of *tert*-cyclobutanols (Figure 2.8).[50] The authors found that bicyclic ring frameworks resulted in compounds bearing an *exo*-methylene motif (β,γ-unsaturated ketones); on the contrary, acyclic substituted backbones afforded a mixture of β,γ- and α,β-unsaturated ketones.



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[50] Nishimura, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2001**, *66*, 1455-1465.

Figure 2.8

Notably, the authors observed that *tert*-cyclobutanols bearing alkenyl- or alkynyl- moieties at C1-position led to an intramolecular ring-expansion, giving access to the corresponding cyclopentanones (Figure 2.9). The authors postulated a pathway consisting of an alkylpalladium intermediate that is generated upon β-carbon elimination (**III**, Figure 2.9) followed by 5-*exo*-trig-type cyclization (**IV**, Figure 2.9) and subsequent β-hydrogen elimination

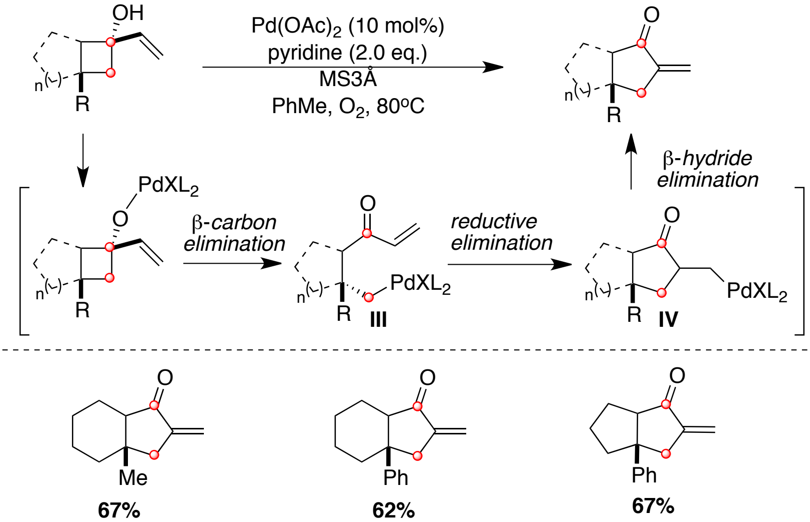

Figure 2.9

2.3.6 Pd-catalyzed oxidative transformations of *tert*-cyclobutanols

In 2011, Uemura described the oxidative skeletal rearrangement of *tert*-cyclobutanols in the presence of Pd-catalysts using atmospheric pressure of oxygen as a sole re-oxidant (Figure 2.10).[50] The transformation is initiated by the formation of a Pd(II) alkoxide followed by β-carbon elimination, giving rise to an alkylpalladium intermediate **V** (Figure 2.10). Subsequently, it was speculated that a migratory insertion takes place onto the aromatic ring followed by β-hydride elimination and a final re-oxidation to recover back the active Pd(II) species.

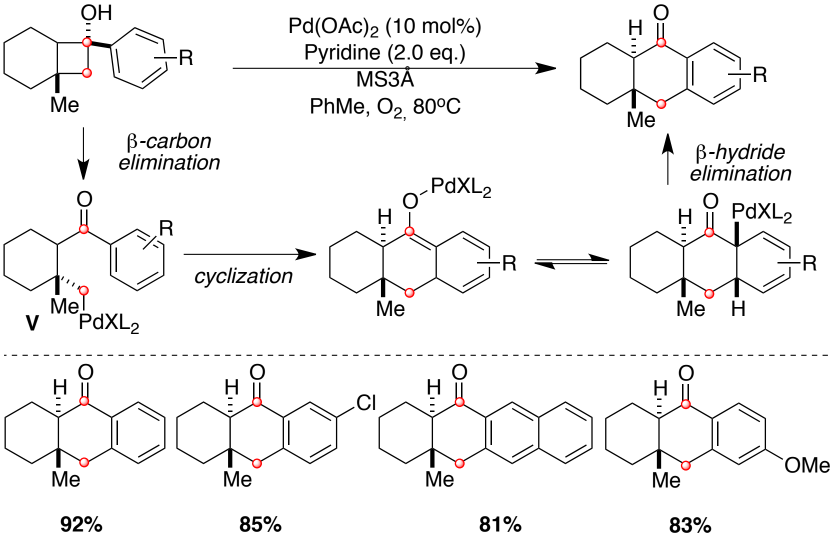

Figure 2.10

Intriguingly, the use of non-fused 1,3,3-substituted *tert*-cyclobutanols did not result in tetralone derivatives, but rather in ring-contracted products (Figure 2.11). The plausible mechanism for this transformation is depicted in Figure 2.11 and consists of a series of pathways that are in analogy to the ones shown in Figure 2.10. In this case, the initially-generated alkyl-Pd(II) undergoes C-H functionalization en route to a six-membered palladium enolate (**VI**, Figure 2.11) that is likely in equilibrium with a four-membered palladacycle (**VII**, Figure 2.11). Reductive elimination of the four-membered palladacycle **VII** (figure 2.11) affords the corresponding ring-contracted ketone (Figure 2.11).

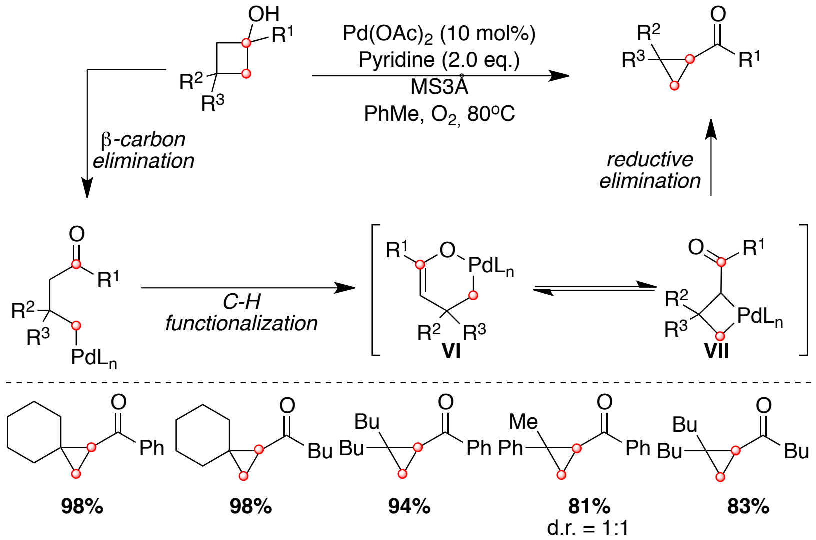

Figure 2.11

2.3.7 Pd-catalyzed γ-arylation, vinylation and allenylation of ketones

In 1999, Uemura reported, for the first time, the Pd-catalyzed arylation of *tert*-cyclobutanols with aryl bromides via β-carbon elimination.[51] The methodology involved the use of $Pd_2(dba)_3 \cdot CHCl_3$, (*R*)-BINAP and K_2CO_3 in 1,4-dioxane, yielding the corresponding γ-arylated ketones in excellent yields (Figure 2.12).

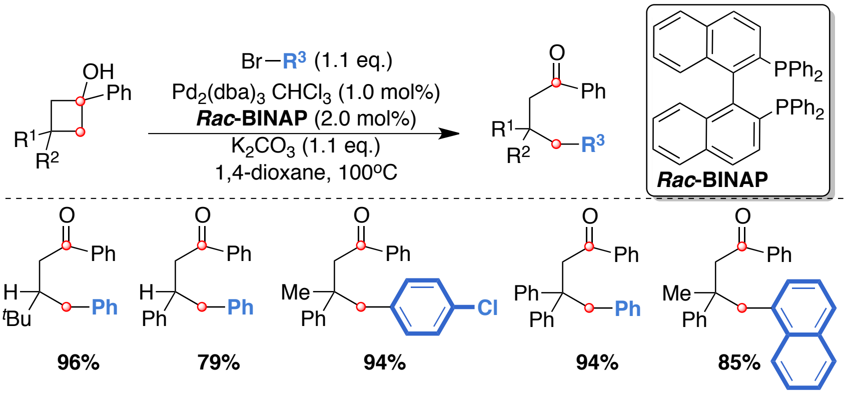

Figure 2.12

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[51] Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 11010-11011.

Unfortunately, however, no examples with functionalized or particularly hindered backbones were reported. Similarly, 3,3-unsubstituted *tert* -cyclobutanols were not described, likely due to the proclivity of the in situ formed σ-bound alkyl palladium intermediate towards β-hydride elimination. Yet an important limitation was the observation that the method was essentially restricted to the use of aryl bromides; thus, cheaper and more attractive aryl chlorides could not be utilized as coupling counterparts. A few years later, Uemura reported the Pd-catalyzed asymmetric γ-arylation (Figure 2.13), γ-vinylation (Figure 2.14) and γ-allenylation (Figure 2.15) of *tert*-cyclobutanols via C-C bond cleavage in the presence of chiral N,P-bidentate ligand (**L**, Figure 2.13).[52]

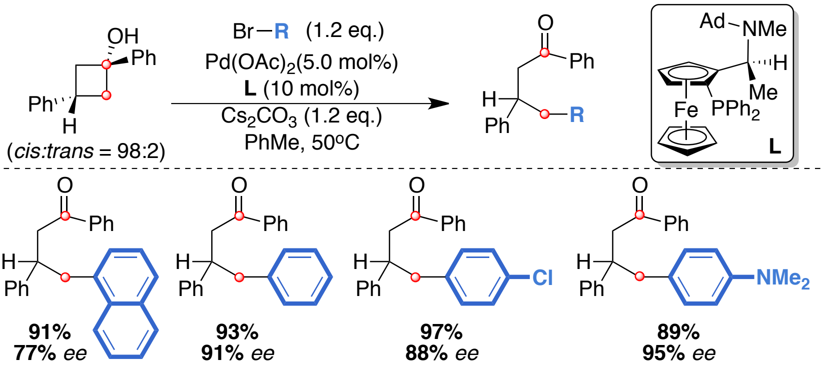

Figure 2.13

As shown in Figure 2.13, the γ-arylation protocol provided excellent yields and enantioselectivities; unfortunately, however, the method was once again restricted to the use of aryl bromides and the means to utilize 3,3-unsubstituted *tert*-cyclobutanols was not explored. Additionally, no examples in the presence of particularly sensitive functional groups were shown. Nevertheless, the authors showed that related reaction conditions could be applied for the asymmetric vinylation of *tert*-cyclobutanols using vinyl halides or vinyl triflates (Figure 2.14). When employing vinyl halides or vinyl triflates under the same conditions as for

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[52] (a) Nishimura, T.; Matsumura, S.; Maeda, Y.; Uemura, S. *Tetrahedron Lett.* **2002**, *43*, 3037-3039. (b) Matusumura, S.; Maeda, Y.; Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **2003**, *125*, 8862-8869.

Figure 2.13, the authors could obtain the desired γ-vinylated ketones in good to excellent yields and enantioselectivities.

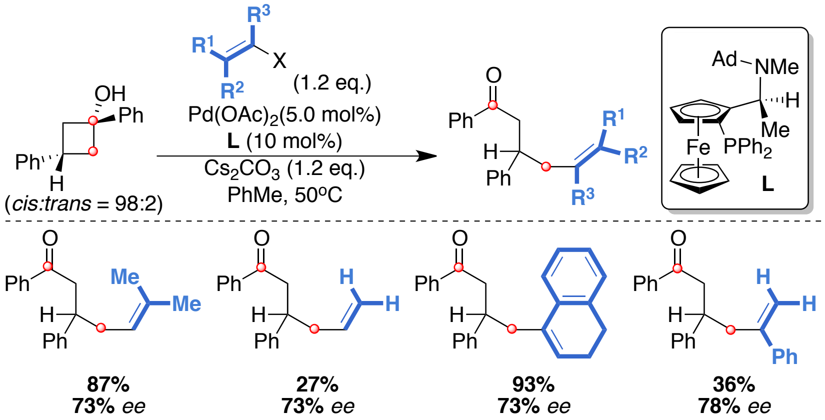

Figure 2.14

The authors showed that otherwise identical reaction conditions could be employed with propargyl acetates. These compounds undergo oxidative addition to Pd(0) to generate (σ-allenyl)palladium(II) complexes, setting up the stage for a γ-allenylation event. As shown in Figure 2.15, the method could be amenable for the preparation of tetrasubstituted allene derivatives; note, however, that otherwise related trisubstituted allenes could not be obtained under these reaction conditions.

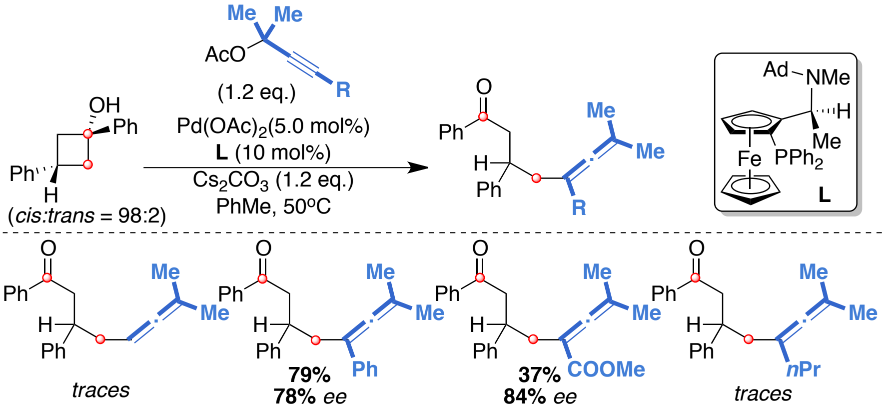

Figure 2.15

2.4 Results and discussions

As shown above, a variety of different transformations have effectively been described when using *tert*-cyclobutanols via catalytic β-carbon elimination pathways. Among them, the work developed by Uemura was highly attractive to promote the synthesis of γ-arylated ketone derivatives; unfortunately, however, Uemura's method was restricted to a rather specific type of substitution patterns and the method apparently did not tolerate the presence of sensitive functional groups. Additionally, aryl chlorides, which from the standpoint of cost and availability are more attractive coupling counterparts, remained unreactive. This was probably due to the reluctance of aryl chlorides to undergo oxidative addition, an observation that goes in line with the high activation energy required for effecting Csp^2-Cl cleavage (97 kcal/mol)[53] as compared to the activation energy for Csp^2-Br cleavage (82 kcal/mol). Encouraged by the excellent reactivity of *tert*-cyclobutanols, we set out to develop a methodology for the γ-arylation of *tert*-cyclobutanols via β-carbon elimination using cheaper and easily accessible aryl chlorides. We speculated that the discovery of a highly active and widely applicable catalyst, even with challenging substrate combinations, would allow for an excellent chemoselectivity, even at low catalyst loadings (Figure 2.16).

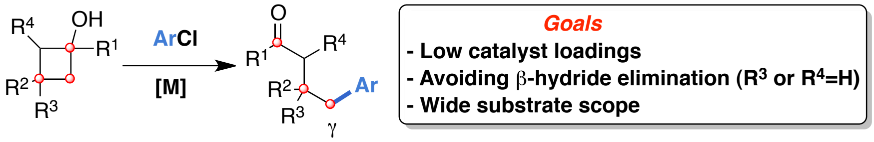

Figure 2.16

We hypothesized that the reaction would be initiated by an oxidative addition of a low-valent metal species to the aryl chloride (**VIII**, Figure 2.17) that would undergo a ligand exchange to afford a Pd(II)-alkoxide (**IX**, Figure 2.17), thus triggering a β-carbon elimination event en route to **X** (Figure 2.17). We anticipated that the ligand would be critical for all elementary steps within the catalytic cycle with the exception of the β-carbon elimination event, which probably will be driven by strain relief.

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[53] Sheppard, T. D. *Org. Biomol. Chem.* **2009**, *7*, 1043-1052.

Although tentative, we speculated that a bulky and electron-rich ligand would enhance the rather uphill oxidative addition; likewise, such a ligand would likely avoid β-hydride elimination by not having accessible binding sites at the metal center and would probably enhance the rate of reductive elimination to deliver the expected γ-arylated products.

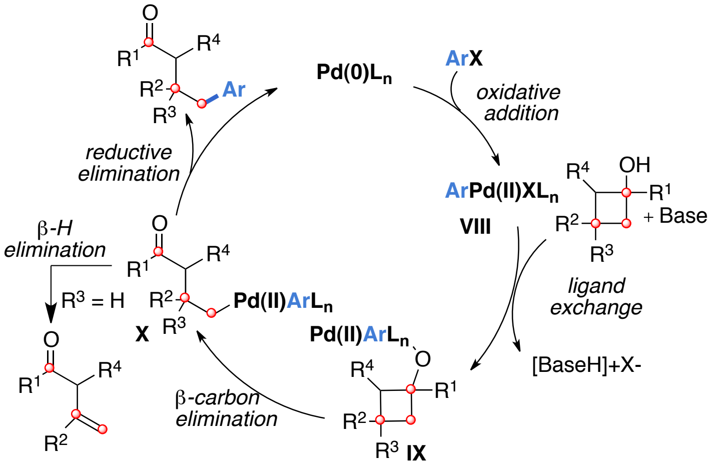

Figure 2.17

2.4.1 Optimization of the reaction conditions

2.4.1.1 Optimization of the reaction conditions for the synthesis of γ-arylated ketones via C-C cleavage of tert-cyclobutanols with aryl chlorides

Among all of the metals known to actively participate in catalytic C-C bond cleavage processes via β-carbon elimination, Pd and Rh precatalysts undoubtedly play a dominant role. Taking into consideration the high price of Rh, we focused our attention on the employment of Pd(II)-salts. We chose **24** (Figure 2.18) as our model substrate, since it could be prepared in multi-gram scale in essentially two steps from commercially available α-methyl styrene following up an approach previously described by Hassner[54] and Oehlschlager.[55] Thus, a [2+2] cycloaddition of α-methyl styrene with trichloroacetyl chloride in the presence of activated zinc ($[Zn(Cu)_n]$)

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[54] Krepski, L. R.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 2879-2882.
[55] Johnston, B. D.; Szyzewska, E.; Oehlschlager, A. C. *J. Org. Chem.* **1987**, *52*, 3693-3697.

gives access to **25** (Figure 2.18) that can subsequently be dehalogenated with Zn powder and NH_4Cl (aqueous solution) in MeOH and further transformed to **24** (Figure 2.18) by slow addition of PhMgCl.

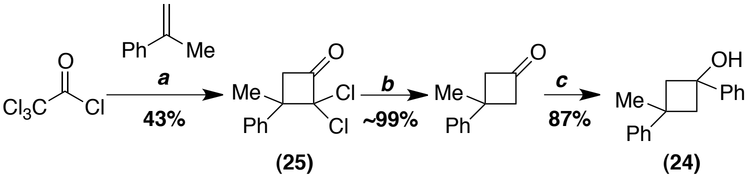
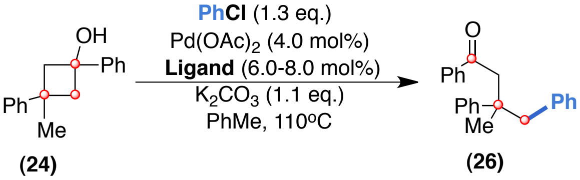


Figure 2.18

Reaction conditions: a) $[Zn(Cu)_n]$ (3.1 eq.) in Et_2O and 1,2-dimethoxyethane at r.t. b) Zn-powder (6.1 eq.), NH_4Cl (aq. solution) in MeOH at r.t. c) PhMgCl (1.5 eq.) in Et_2O, reflux.

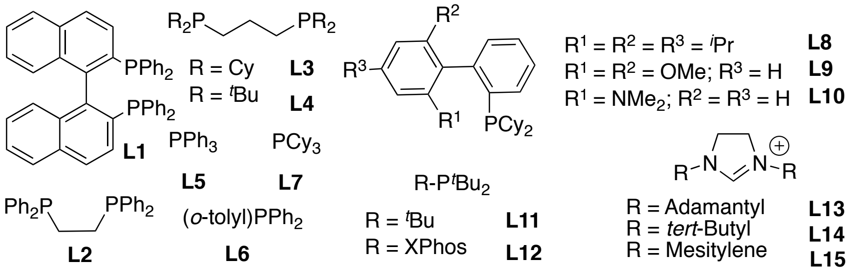
With substantial amounts of **24** in hand, we initially exposed **24** under the conditions reported by Uemura for the γ-arylation of *tert*-cyclobutanols with aryl bromides[51], but using chlorobenzene as coupling partner. As expected, we obtained a very low yield of the desired γ-arylated ketone (**26;** 4% yield). This finding reinforced the notion that the coupling of aryl chlorides is particularly problematic. Thus, we set out a systematic evaluation of the experimental variables such as metal, ligand, base, solvent and reaction temperatures. Specifically, we started our screening with $Pd(OAc)_2$ as catalyst, K_2CO_3 as the base in PhMe at 110ºC using chlorobenzene as coupling counterpart (Table 1).

Table 1. Screening of different ligands



Entry	Ligand	Conversion (%)	Yield (%) 26
		Bidentate phosphine ligands	
1	**L1**	40	38
2	**L2**	35	32

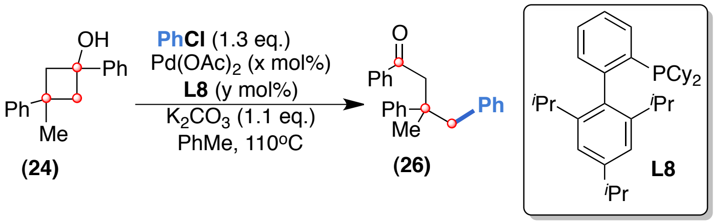
3	**L3**	40	35
4	**L4**	63	58
Aryl monodentate phosphine ligands			
5	**L5**	0	0
6	**L6**	0	0
Monodentate phosphine ligands bearing cyclohexyl groups			
7	**L7**	82	78
8	**L8**	100	100
9	**L9**	67	63
10	**L10**	56	52
Monodentate phosphine ligands bearing tertbutyl groups			
11	**L11**	50	45
12	**L12**	10	8
N-heterocyclic carbenes			
13	**L13**	75	73
14	**L14**	30	25
15	**L15**	0	0



Reaction conditions: [a] **24** (0.25 mmol), $Pd(OAc)_2$ (4.0 mol%), Ligand (6.0-8.0 mol%), K_2CO_3 (1.1 eq., 0.275 mmol), PhMe (0.13M) at 110°C for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

As shown in Table 1, we found that aryl phosphine ligands were not particularly efficient for promoting the targeted transformation (**L5-L6**). At present, we believe these results are in line with the low tendency of these electron-poor ligands to promote the oxidative addition of aryl chlorides. Among all ligands examined, it was found that monodentate alkyl phosphine ligands bearing a dicyclohexyl backbone provided the best results, particularly XPhos (**L8)**, indicating that a bulky electron-rich motif was probably critical for success (Entry 7 and 8, Table 1). Intriguingly, the use of bulkier phosphine ligands bearing *tert*-butyl groups or *N*-heterocyclic carbenes did not improve these results, thus showing the subtleties of our protocol. In light of these results, we next wondered whether our method based upon the utilization of XPhos (**L8)** was amenable to operate at lower catalyst loadings (Table 2).

Table 2. Screening of different amounts of Pd(OAc)$_2$

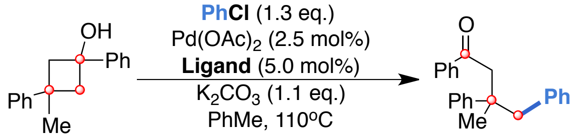


Entry	Amount [Pd] (x mol%)	Amount ligand (y mol%)	Conversion (%)	Yield (%) 26
1	1.0 mol%	2.0 mol%	10	6
2	1.5 mol%	3.0 mol%	15	11
3	2.0 mol%	4.0 mol%	20	18
4	2.5 mol%	5.0 mol%	53	51

Reaction conditions: [a] **24** (0.25 mmol), Pd(OAc)$_2$ (x mol%), **L8** (y mol%), K$_2$CO$_3$ (1.1 eq., 0.275 mmol), PhMe (0.13M) at 110°C for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

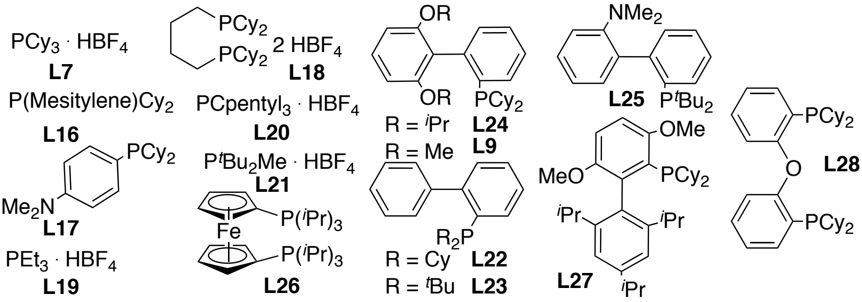
As shown in Table 2, we found a deleterious effect when lowering down the catalyst loading en route to **26**. However, we were delighted to see a promising 51% GC yield at 2.5 mol% Pd(OAc)$_2$ and 5.0 mol% of **L8**. Encouraged by these results, we next analyzed the performance of a family of phosphine ligands bearing alkyl groups at 2.5 mol% of Pd(OAc)$_2$ (Table 3). As shown, we found that **L7**, **L16**, **L18**, **L20** and **L22** performed better than **L8**, in all cases resulting in quantitative yields of **26**. Along the investigation of the performance of these ligands, we observed that the reaction required phosphine ligands possessing a balance of sterical hindrance and electron-donating ability. When employing phosphine ligands with bulky *tert*-butyl substituents, the reaction was either inhibited or slow (entries 5, 6, 12, 14, and 16), however, "Buchwald-type" ligands (entries 4, 13 and 15) or phosphine ligands with cyclic substituents (entries 2, 7, 9, 11, 13 and 19) easily promoted the reaction. We believe this is due to the fact that such ligands are both bulky and electron-rich, possessing a unique balance of electron-density and steric hindrance. As for entries 6 and 8, we believe that the lack of reactivity is associated to the steric bulk present in these ligands.

Table 3. Screening of different ligands



(24) **(26)**

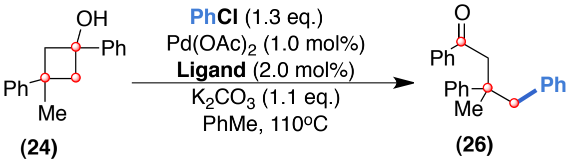
Entry	Ligand	Conversion (%)	Yield (%)
			26
1	**L7**	100	99
2	**L9**	55	52
3	**L16**	100	99
4	**L17**	35	31
5	**L18**	100	99
6	**L19**	0	0
7	**L20**	100	99
8	**L21**	0	0
9	**L22**	100	99
10	**L23**	56	52
11	**L24**	100	95
12	**L25**	63	58
13	**L26**	57	52
14	**L27**	0	0
15	**L28**	100	96



Reaction conditions: [a] **24** (0.25 mmol), $Pd(OAc)_2$ (2.5 mol%), Ligand (5.0 mol%), K_2CO_3 (1.1 eq., 0.275 mmol), PhMe (0.13M) at 110°C for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

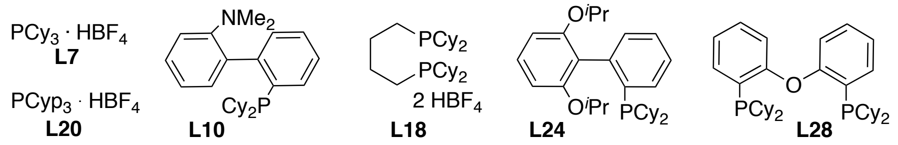
In view of the excellent reactivity of some ligands at 2.5 mol% of $Pd(OAc)_2$, we decided to screen the performance of the best ligands in Table 3, but at 1.0 mol% $Pd(OAc)_2$. With the exception of **L28** and **L24**, we found that **L7, L10, L18** and **L20** were particularly active at 1.0 mol% of $Pd(OAc)_2$, an important observation that highlights the better performance of bulky, electron-rich ligands in our arylative event. Among all of them, we found that **L18** and **L20** delivered the targeted γ-arylated product **26** with excellent yields and almost full conversion. While in lower yields, **L18** and **L20** were found to be still reactive at 0.5 mol% of $Pd(OAc)_2$, a rather promising result that indicated that the reaction could be even optimized further, particularly with **L18** that delivered the expected product in a non-negligible 35% yield (Table 5).

Table 4. Screening of different ligands with 1.0 mol% of $Pd(OAc)_2$



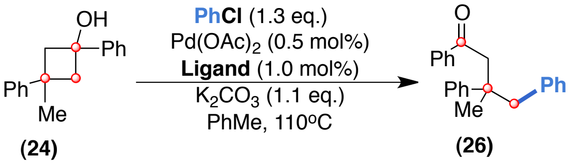
Entry	Ligand	Conversion (%)	Yield (%)
			26
1	**L7**	90	87
2	**L10**	82	75

3	**L18**	93	91
4	**L20**	100	99
5	**L24**	34	32
6	**L28**	10	8

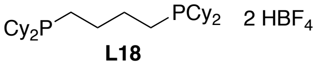


Reaction conditions: [a] **24** (0.25 mmol), $Pd(OAc)_2$ (1.0 mol%), Ligand (2.0 mol%), K_2CO_3 (1.1 eq., 0.275 mmol), PhMe (0.13M) at 110°C for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

Table 5. Screening of different ligands with 0.5 mol% of $Pd(OAc)_2$



Entry	Ligand	Conversion (%)	Yield (%)
			26
1	**L18**	38	35
2	**L20**	25	23

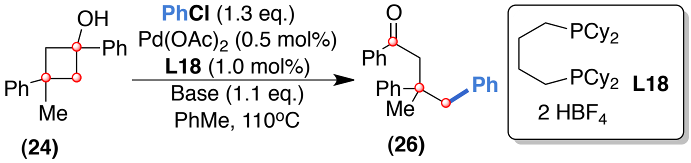


$P(Cyclopentyl)_3 \cdot HBF_4$
L20

Reaction conditions: [a] **24** (0.25 mmol), $Pd(OAc)_2$ (0.5 mol%), Ligand (1.0 mol%), K_2CO_3 (1.1 eq., 0.275 mmol), PhMe (0.13M) at 110°C for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

Next, we set out to screen different bases at 0.5 mol% of $Pd(OAc)_2$ (Table 6), since its presence might exert a notorious influence for deprotonating the *tert*-cyclobutanol backbone (pKa~14), setting up the stage for the key β-carbon elimination event. We set out to investigate a variety of inorganic bases in order to get an understanding of the reaction. Taking this into consideration, we tried bases such as NaOtBu, KOMe, KH_2PO_4, K_3PO_4, Na_2HPO_4, Cs_2CO_3, K_2CO_3 and $CaCO_3$, KOAc and LiOAc and KOH (Base strength: NaO^{t}Bu > KOMe > KOH > K_3PO_4 > Cs_2CO_3, K_2CO_3 and $CaCO_3$ > KH_2PO_4 > KOAc and LiOAc > Na_2HPO_4). We were also interested in employing inorganic bases with different cations, since it might exert a profound influence on reactivity. As shown, NaO^{t}Bu, KOMe and KOH (entries 1, 2 and 11) promoted the reaction considerably better than other bases, with NaO^{t}Bu providing the best results (entry 1). As a control experiment, we found no reaction in the absence of NaO^{t}Bu and in the absence of all other components as well. Similarly, lower conversions to products were observed when lowering down the catalyst loading to 0.1 mol% $Pd(OAc)_2$.

Table 6. Screening of different bases



Entry	Base	Conversion (%)	Yield (%)
			26
1	**NaO^{t}Bu**	100	99
2	**KOMe**	86	82
3	**KH_2PO_4**	0	0
4	**K_3PO_4**	35	32
5	**Na_2HPO_4**	0	0
6	**Cs_2CO_3**	63	61
7	**K_2CO_3**	37	33
8	**$CaCO_3$**	0	0
9	**KOAc**	0	0
10	**LiOAc**	0	0
11	**KOH**	98	93
12	**No base**	0	0

Reaction conditions: [a] **24** (0.25 mmol), $Pd(OAc)_2$ (0.5 mol%), **L18** (1.0 mol%), base (1.1 eq., 0.34), PhMe (0.13M) at 110ºC for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard. [d] The corresponding ester was formed.

2.4.2 Optimization of the reaction conditions for the utilization of 3,3-unsusbstituted *tert*-cyclobutanols

As highlighted in Figure 2.17, the alkyl-metal species generated from β-carbon elimination could trigger a subsequent β-hydride elimination step when using 3,3-unsubstituted *tert*-cyclobutanols (Figure 2.19). Not surprisingly, the ring-expansion methodologies described in the literature when employing *tert*-cyclobutanols have eluded the utilization of 3,3-unsubstituted derivatives. Taking into consideration the results obtained in Table 6, we wondered whether our catalytic protocol could be amenable for the coupling of the rather challenging 3,3-unsubstituted backbones en route to **26**. It was clear that a higher rate of reductive elimination was needed over the parasitic β-hydride elimination. Consequently, the ligand was expected to exert a profound influence on reactivity and we decided to systematically screen a wide number of ligands under similar conditions to these described in Table 6 (Table 7).

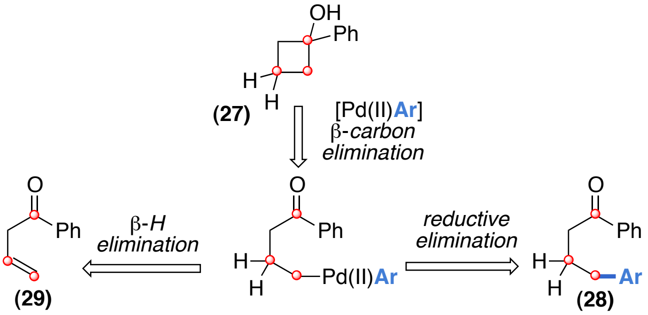
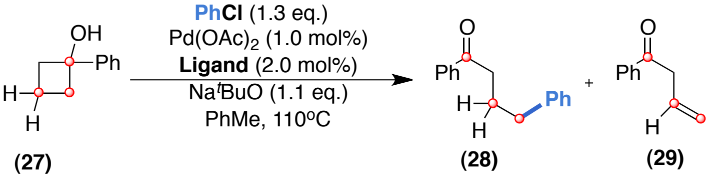


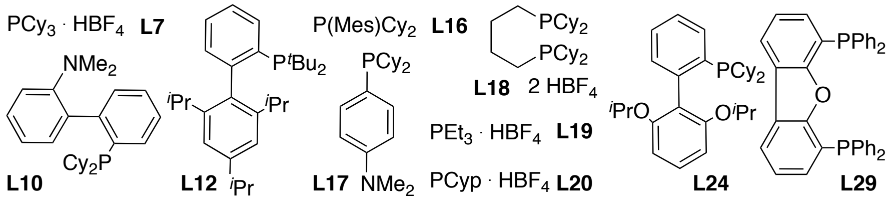
Figure 2.19

Table 7. Screening of different ligands



Entry	Ligand	Conversion (%)	Yield (%)	
			28	29
1	L7	100	79	17
2	L10	100	69	28

3	**L12**	58	25	31
4	**L16**	100	70	23
5	**L17**	100	86	12
6	**L18**	100	99	0
7	**L19**	99	21	76
8	**L20**	99	95	2
9	**L24**	100	58	40
10	**L29**	100	0	97



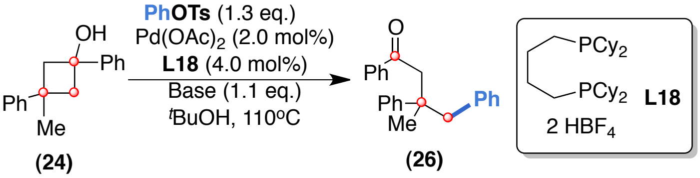
Reaction conditions: [a] **27** (0.25 mmol), $Pd(OAc)_2$ (1.0 mol%), Ligand (2.0 mol%), Na^{t}BuO (1.1 eq., 0.275 mmol), PhMe (0.13M) at 110°C for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

As shown in Table 7, we can conclude that the use of 1,4-bis(dicyclohexylphopshine)butane (**L18)** as ligand was particularly effective for delivering cleanly the γ-arylated ketone with little amounts, if any, of β,γ-unsaturated ketone via β-hydride elimination. We believe this observation is a clear indication that a bulky and bidentate ligand with a wide bite angle is critical for enhancing reductive elimination. Additionally, **L18** might avoid the agostic interaction of the β-hydrogens to the metal center that would set up the stage for a parasitic β-hydride elimination event. Entries 7 and 10 favored the formation of **29**; at present, we believe that these results can be interpreted in line with the lower electron-donation and lower steric bulk of these ligands, thus opening up coordination sites for β-hydride elimination.

2.4.3 Optimization of the reaction conditions for the synthesis of γ-arylated ketones via C-C bond cleavage and aryl tosylates

Prompted by the results of Tables 6 and 7, we wondered whether the γ-arylation protocol via C-C bond-cleavage could be affected using aryl tosylates as coupling counterparts. The use of C-O electrophiles has received a considerable momentum in recent years since these derivatives are prepared from phenol that is cheaper and more accessible than the corresponding aryl chlorides.[56] That being set, we decided to analyze the performance of PhOTs under the optimized reaction conditions of Tables 6 and 7. Unfortunately, we found no product at all, probably indicating that a more polar solvent would be required to include the more polar aryl tosylates. As shown in Table 8, entry 1, we found a rather promising result using NaO^{t}Bu in ^{t}BuOH as the solvent (18% yield) together with certain amounts of the corresponding phenol by deprotection of the aryl tosylate backbone in the presence of strong bases. Consequently, we next focused our attention on the employment of weaker bases that would not result in phenol formation. As shown in Table 8, entries 4, 6, 7 and 9, turned out to be correct, and we obtained the expected product in quantitative yield when utilizing K_2CO_3 as the base. These results confirmed the critical role of the base. Indeed, the deprotonation of the *tert*-cyclobutanol could potentially lead to the O-arylated product or phenol formation by nucleophile attack to the sulfonyl group. Not surprisingly, the best results were found with a weak base such as K_2CO_3, thus reducing the concentration of alkoxide and the formation of byproducts.

Table 8. Screening of different bases



Entry	Base	Conversion (%)	Yield (%)
			26
1	**NaO^{t}Bu**	20	18

---

[56] For a review about the usefulness of tosylates, see: Ritter, K. *Synthesis*. **1993**, *8*, 735-762. (b) Cornella, J.; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *Advance article* (DOI: 10.1039/c4cs00206g). For the use of aryl mesylates as counterpart in cross-coupling reactions, see: (a) Kobayashi, Y.; Mizojiri, R. *Tetrahedron Lett.* **1996**, *37*, 8531-8534. (b) Ueda, M.; Saitoh, A.; Oh-tani, S.; Miyara, N. *J. Org. Chem.* **1997**, *62*, 8024-8030.

2	**NaOMe**	3	2
3	**KH_2PO_4**	9	6
4	**K_3PO_4**	60	53
5	**Na_2HPO_4**	8	6
6	**Cs_2CO_3**	90	84
7	**K_2CO_3**	100	100
8	**$CaCO_3$**	10	7
9	**KOH**	41	40
10	**No base**	0	0

Reaction conditions: [a] **24** (0.25 mmol), $Pd(OAc)_2$ (2.0 mol%), **L18** (4.0 mol%), base (1.1 eq., 0.34), ^{t}BuOH (0.13M) at 110°C for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard. [d] The corresponding ester was formed.

2.4.3. Scope of the reaction

2.4.3.1 Synthesis of different *tert*-cyclobutanols

Having established the optimized reaction conditions for the coupling of different substrate combinations and arylating agents, we set out to explore the scope of this Pd(II)-catalyzed arylative ring-expansion reaction by preparing a wide variety of *tert*-cyclobutanols according to Figure 2.18. As shown in Figure 2.20, a wide variety of compounds bearing different substitution patterns including aliphatic or aromatic groups could be prepared in similar overall yields in essentially two-step operation (Figure 2.20).

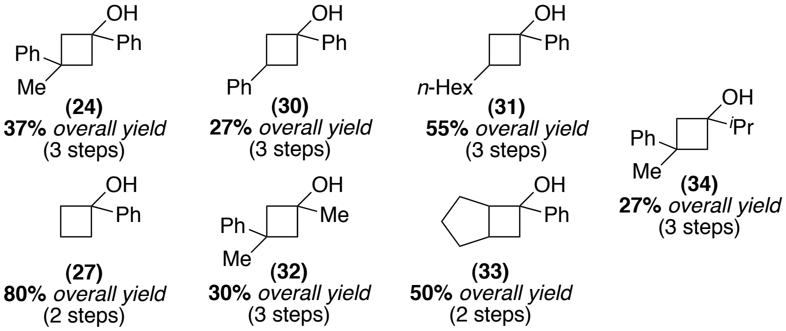


Figure 2.20

2.4.3.2 Pd-catalyzed arylative ring-expansion of *tert*-cyclobutanols with aryl

chlorides

With substantial amounts in hand of differently substituted *tert*-cyclobutanols, we focused our attention to explore the preparative scope of the Pd-catalyzed arylative ring-expansion of *tert*-cyclobutanols with aryl chlorides via C-C bond-cleavage. As shown in Figure 2.21, the methodology allowed for the coupling of *tert*-cyclobutanols with cyclic backbones (**36**), alkyl groups at C1-position (**35**, **38** and **41**) as well as di-substitution in C2-position (**37**). In all cases analyzed, the reaction resulted in similar yields operating at catalyst loadings as low as 0.5 mol% Pd(OAc)$_2$.

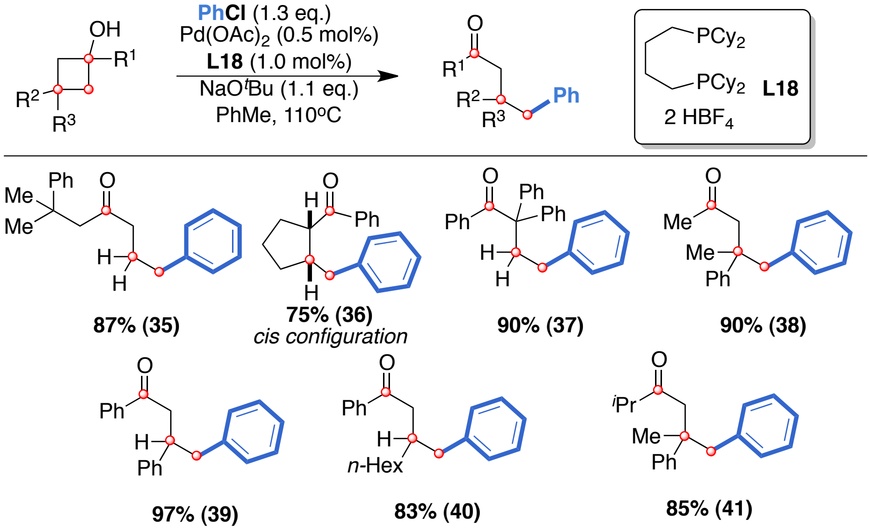
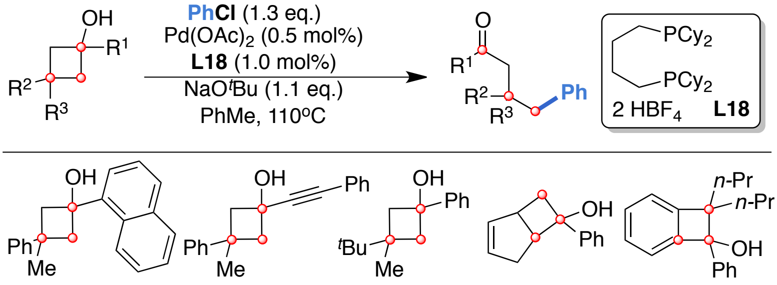


Figure 2.21

Unfortunately, the coupling of *tert*-cyclobutanols that are too sterically hindered (**44**), too rigid (**45**) or possessing alkyne moiety (**43**) did not deliver the expected γ-arylated ketone (Figure 2.22). In all of these cases, we recovered the *tert*-cyclobutanol unaltered. In the case of benzocyclobutenol (**46**) we observed the dehydration of the molecule.



(42) **(43)** **(44)** **(45)** **(46)**

Figure 2.22

Next, we turned our attention to study the influence of the aryl chloride motif when using **24** (Figure 2.23). We were pleased to find that a wide variety of aryl chlorides were tolerated regardless of the electronic effects present in their structure. In all cases, our methodology allowed the formation of differently substituted γ-aryl ketones in good to excellent yields. The method perfectly accommodated the presence of different functional groups (Figure 2.23) such as amines (**50**), ketone (**51**), alkene (**52**), thioethers (**55**), pyrrole (**60**), acetal (**61**) as well as substrates with groups in the *ortho* position (**56** and **57**). Interestingly, the use of 1,3-dichlorobenzene resulted in the formation of **53** in 82%; no exhaustive coupling via double C-Cl bond cleavage was found in the crude mixtures.

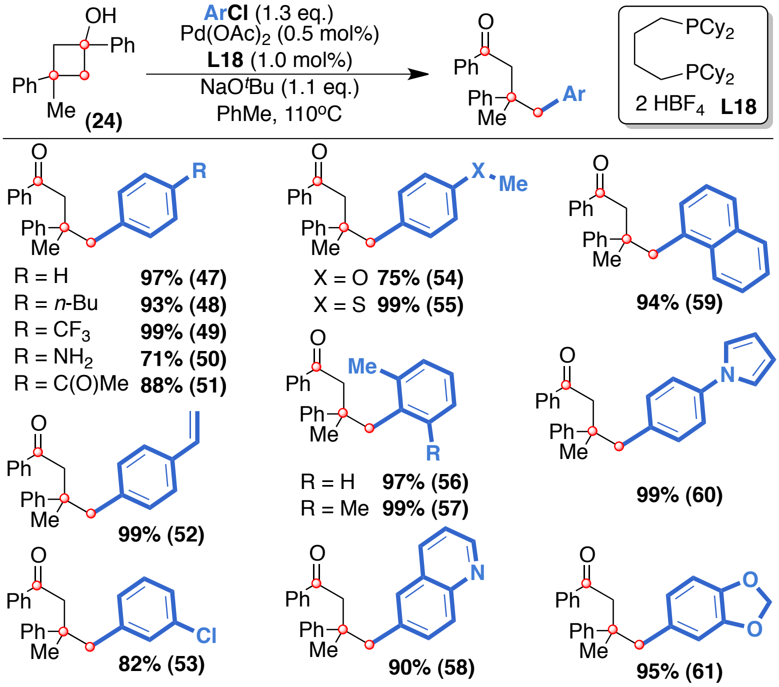


Figure 2.23

Unfortunately, our arylative method could not be applied to aryl chlorides bearing nitro groups in *para* position (**62**) and unprotected hydroxyl group in neither *ortho* or *meta* position (**67** and **69**), most likely due to the high coordination ability of these groups to the Pd-center. Aryl chlorides bearing ester groups (**65**) were not tolerated, an observation that is attributed to the unproductive attack of Na^{t}OBu to such motifs. Unfortunately, several heterocycles (**74**-**77**) could not be employed, probably due to the coordinating ability of such substrates to the Pd center at such low catalyst loadings. In the case of aryl chlorides with carboxylic acid moiety in *para* or *meta* position (**63** and **66**), we recovered the starting materials. We were disappointed to observe that aryl chlorides with aldehyde moieties in *ortho* or *meta* position (**68** and **70**) could not be obtained. Once again, the problems associated with the lack of reactivity of these substrates can be attributed to the high reactivity of Na^{t}BuO that is present in stoichiometric amounts. A similar lack of reactivity was found with substrates bearing nitrile or alkyne moieties.

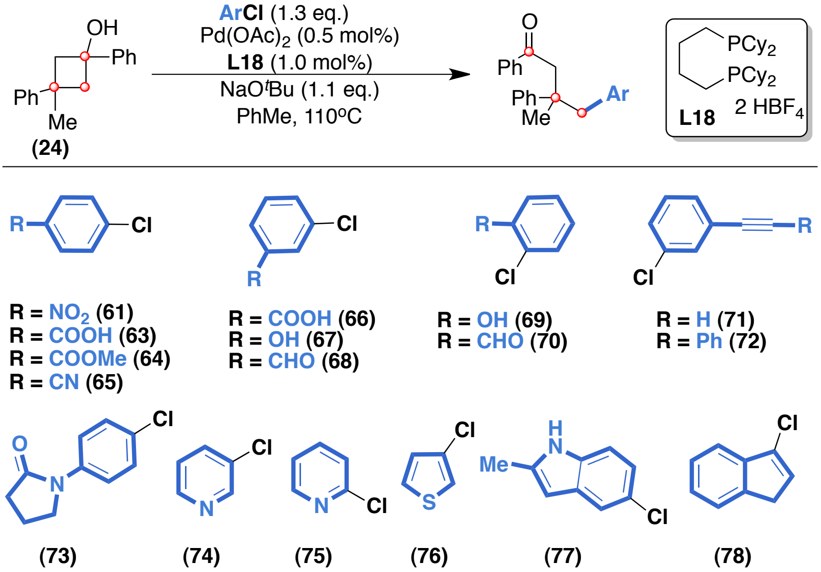


Figure 2.24

In order to test the generality of our protocol, we next examined our Pd-catalyzed arylative ring-opening reaction with 3,3-unsubstituted *tert*-cyclobutanols and different aryl chlorides. As shown in Figure 2.25, the scope encompassed different substitution patterns and groups such as alkenes or thioethers in the aryl chloride motif, invariably providing high yields of the desired γ-arylated ketones at 0.5 mol% Pd loadings without noticeable β-hydride elimination pathways.

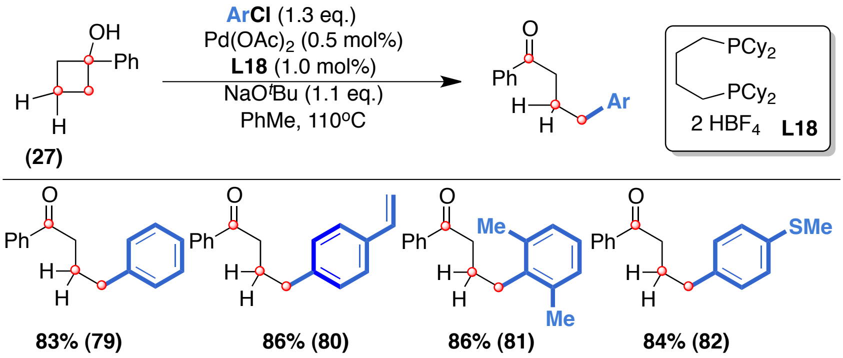


Figure 2.25

2.4.3.3 Pd-catalyzed arylative ring-expansion of *tert*-cyclobutanols with aryl tosylates as coupling partners

Although not explored in depth, we found that the optimized conditions in Table 8 could be employed for a host of different aryl tosylates using **24** as coupling partner. As shown, the final products were obtained in high yields, thus demonstrating that aryl tosylates can effectively be used, for the first time in the field, as surrogates of aryl chlorides in catalytic arylative ring-expansion reactions by C-C bond cleavage.

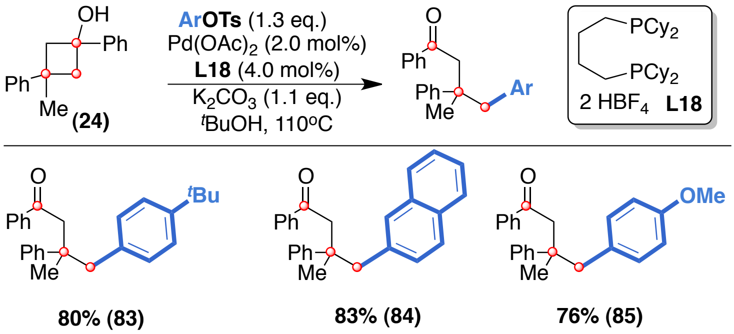


Figure 2.26

Unfortunately, we noticed that α-methyl ketones (**86**), nitrile groups (**89**), ester groups (**87**), aldehydes (**88**), amides (**90**) and nitro groups (**91**) could not be coupled; at present we don't have any rationale for such lack of reactivity. Aryl tosylates possessing 2,5-dimethyl substitution (**92**), resulted in recovered starting material, probably due to the steric hindrance exerted by the *ortho*-methoxy motif. Although in this PhD thesis we did not optimize this reaction further, we are confident that by varying the reaction conditions the catalytic arylative ring-expansion reaction of *tert*-cyclobutanols and aryl tosylates could tolerate a wide variety of sensitive functional groups.

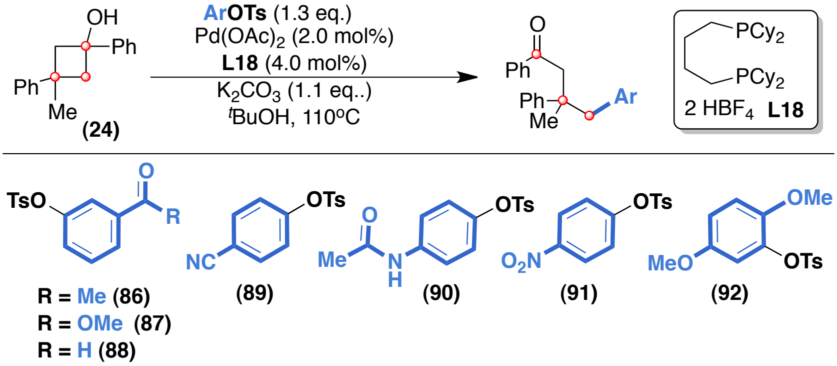


Figure 2.27

2.5 Conclusions

- A highly efficient Pd-catalyzed arylative ring expansion of *tert*-cyclobutanols via C-C bond cleavage has been found[57]. The method allows for the coupling of aryl chlorides at low catalyst loadings (0.5 mol% Pd) with a wide range of functional groups and substitution patterns, thus constituting a straightforward alternative for preparing rather elusive γ-arylated ketones.
- The methodology could also allow for the coupling of aryl tosylates as surrogates of aryl chlorides.
- The methodology could be employed for rather challenging substrate combinations that are susceptible for destructive β-hydride elimination by fine-tuning of the ligand backbone.

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[57] Ziadi, A.; Martin, R. *Org. Lett.* **2012**, *14*, 1266-1269.

2.6 Experimental section

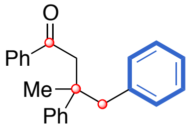
2.6.1 General Considerations

Reagents. All reactions were set up in air (with no use of a glovebox) and carried out under an argon atmosphere in resalable screw-cap test tubes. $Pd(OAc)_2$ was a gift from Johnson Matthey. 1,4-dicyclohexylphosphinebutane▪$2HBF_4$ was a gift from Nippon Chemical Industrial. Powdered Na*t*BuO was purchased from Acros Organics. The bulk of Na*t*BuO was stored under nitrogen in a nitrogen atmosphere glovebox. Small portions (~5 g) were removed from the glovebox in glass vials, stored in air in a desiccator filled with anhydrous calcium sulfate, and weighed in air. Dry PhMe was taken from the SPS (innovative technology, Newburyport, MA). 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).

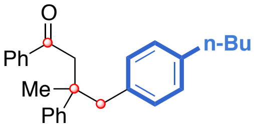
Analytical methods. ^1H NMR and ^{13}C NMR spectra and melting points (where applicable) are included for all compounds. ^1H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz, a Bruker 400 MHz and a Bruker 500 MHz at 20°C. All ^1H NMR spectra are reported in parts per million (ppm) downfield of 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 $CHCl_3$ (77.0 ppm) and were obtained with ^1H 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.

2.6.2 General procedure for the synthesis of γ-aryl ketones

An oven-dried screw-cap test tube containing a stirring bar was charged with the corresponding cyclobutanol (0.35 mmol, 1.0 eq.), 1,4-dicyclohexylphosphinebutane·2HBF$_4$ (2.20 mg, 1.0 mol%), Na^{t}BuO (37.0 mg, 0.39 mmol, 1.1 eq.) and the aryl chloride (0.45 mmol), if a solid. The test tube was evacuated and back-filled with dry argon (this sequence was repeated three times). The aryl chloride (if liquid), PhMe (2 mL) and Pd(OAc)$_2$ (70 μl of 0.025M solution in PhMe, 0.5 mol%,) were then added by syringe. The mixture was then stirred in a pre-heated oil bath (110ºC) for 14 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). The filtrate was concentrated and purified by column chromatography on silica gel (eluting with hexanes/EtOAc mixtures).

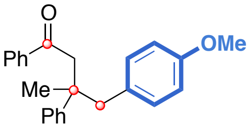


3-methyl-1,3,4-triphenylbutan-1-one. Following general procedure, chlorobenzene (46.0 μl, 0.45 mmol) was used. Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R$_f$=0.50). Yellowish oil; yield: 106 mg (97% yield). ^{1}H-NMR: (300 MHz, CDCl$_3$) δ 7.91 (d, *J* = 8.52 Hz, 2H), 7.54 (ddd, *J* = 1.27 Hz; 2.49 Hz; 6.95 Hz, 1H), 7.45 (t, *J* = 7.62 Hz, 2H), 7.41-7.32 (m, 4H), 7.22-7.18 (m, 4H), 6.91 (m, 2H), 3.61 (d, *J* = 16.7 Hz, 1H), 3.32 (d, *J* = 16.7 Hz, 1H), 3.23 (m, 2H), 1.57 (s, 3H). ^{13}C-NMR: (75 MHz, CDCl$_3$) δ 198.5, 146.8, 138.1, 137.9, 132.6, 130.6, 128.4, 128.0, 127.8, 127.5, 126.1, 125.8, 49.0, 47.7, 41.3, 25.0. HRMS *calcd* for [$C_{23}H_{22}O$+Na] 337.1568, *found* 337.1580.

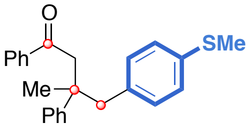


4-(4-butylphenyl)-3-methyl-1,3-diphenylbutan-1-one. Following general procedure, 1-Chloro-4-butylbenzene (76.0 μl, 0.45 mmol) was used. Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R$_f$=0.60). Yellowish solid; yield:

130 mg (93% yield). Mp: 49-50ºC. ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.46 Hz, 2H), 7.55 (t, *J* = 7.30 Hz, 1H), 7.44 (t, *J* = 7.60 Hz, 2H), 7.37-7.28 (m, 4H), 7.26-7.21 (m, 1H), 7.03 (d, *J* = 7.75 Hz, 2H), 6.85 (d, *J* = 7.77 Hz, 2H), 3.62 (d, *J* = 16.7 Hz, 1H), 3.32 (d, *J* = 16.73 Hz, 1H), 3.22 (q, *J* = 13.12Hz, 2H), 2.66-2.58 (m, 2H), 1.68-1.60 (m, 5H), 1.45-1.35 (m, 2H), 1.01-0.96 (m, 3H). ^{13}C-NMR: (100 MHz, $CDCl_3$) δ 198.6, 147.0, 140.6, 138.2, 135.0, 132.6, 130.5, 128.3, 127.9, 127.8, 127.6, 126.1, 125.7, 48.7, 47.7, 41.3, 34.9, 33.4, 25.1, 22.3, 13.9. IR (neat, cm^{-1}): 2928, 1691, 1446, 1214, 1003, 737, 690, 553. HRMS *calcd* for [$C_{27}H_{30}O$+Na] 393.2233, *found* 393.2194.

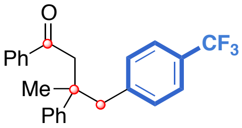


4-(4-methoxyphenyl)-3-methyl-1,3-diphenylbutan-1-one. Following general procedure, 1-Chloro-4-methoxybenzene (46.0 μl, 0.45 mmol) was used. Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.40). Colorless oil; yield: 90 mg (75% yield). ^{1}H-NMR: (500 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 1.20Hz; 8.33 Hz, 2H), 7.55 (t, *J* = 7.39 Hz, 1H), 7.44 (t, *J* = 7.72 Hz, 2H), 7.31-7.30 (m, 4H), 7.24-7.18 (m, 1H), 6.78 (d, *J* = 8.71 Hz, 2H), 6.73 (d, *J* = 8.74 Hz, 2H), 3.76 (s, 3H), 3.56 (d, *J* = 16.7 Hz, 1H), 3.28 (d, *J* = 16.7 Hz, 1H), 3.13 (m, 2H), 1.52 (s, 3H). ^{13}C-NMR: (125 MHz, $CDCl_3$) δ 198.7, 158.0, 146.9, 138.2, 132.7, 131.5, 130.0, 128.4, 128.0, 127.8, 126.2, 125.8, 113.0, 55.1, 48.2, 47.7, 41.4, 25.0. IR (neat, cm^{-1}): 2930, 1688, 1610, 1510, 1446, 1353, 1246, 1178, 1032, 826, 752, 690, 538. HRMS *calcd* for [$C_{24}H_{24}O_2$+Na] 367.1674, *found* 367.1658.

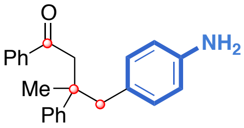


3-methyl-4-(4-(methylthio)phenyl)-1,3-diphenylbutan-1-one. Following general procedure, but using $Pd(OAc)_2$ (1.0 mol%) and 4-chlorothioanisole (72.0 mg, 0.45 mmol). Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.40). Colorless oil; yield: 125 mg (99% yield). ^{1}H-NMR: (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.29 (d, *J* = 4.56 Hz, 4H), 7.23-7.17 (m, 1H), 7.05 (d, *J* = 8.1 Hz, 2H), 6.77 (d, *J* = 8.1 Hz, 2H), 3.55 (d, *J* = 16.7 Hz, 1H), 3.27 (d, *J*

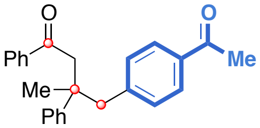
= 16.7 Hz, 1H), 3.18-3.10 (m, 2H), 2.43 (s, 3H), 1.50 (s, 3H). ^{13}C-NMR: (125 MHz, $CDCl_3$) δ 198.6, 146.7, 138.1, 134.9, 132.7, 131.1, 128.4, 128.0, 127.8, 126.1, 125.9, 125.8, 48.4, 47.7, 41.4, 25.0, 15.8. IR (neat, cm^{-1}): 3057, 2920, 1689, 1596, 1493, 1446, 1213, 1094, 1003, 819, 734, 689, 570. HRMS *calcd* for [$C_{24}H_{24}OS$+Na] 383.1437, *found* 383.1446.



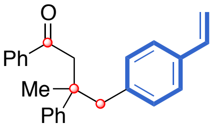
3-methyl-1,3-diphenyl-4-(4-(trifluoromethyl)phenyl)butan-1-one. Following general procedure, 4-chlorobenzotrifluoride (61.0 μl, 0.45 mmol) was used with K_2CO_3 (1.1 eq.) as base and P(cyclopentyl)·HBF_4 (1.0 mol%) as ligand. Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.50). Colorless oil; yield: 134 mg (99% yield). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 1.00 Hz; 8.21 Hz, 2H), 7.54 (t, *J* = 7.38 Hz, 1H), 7.45-7.37 (m, 4H), 7.32-7.26 (m, 4H), 7.24-7.18 (m, 1H), 6.92 (d, *J* = 8.06 Hz, 2H), 3.54 (d, *J* = 16.7 Hz, 1H), 3.28 (m, 3H), 1.51 (s, 3H). ^{13}C-NMR: (100 MHz, $CDCl_3$) δ 198.5, 146.2, 142.1, 138.1, 132.9, 130.8, 128.5, 128.2, 127.9, 126.1, 126.1, 124.4 ($J_{\text{c-F}}$ = 3.8 Hz), 124.4, 48.4, 47.7, 41.5, 24.9. IR (neat, cm^{-1}): 2925, 1689, 1416, 1322, 1160, 1110, 1066, 751, 689. HRMS *calcd* for [$C_{25}H_{24}O$+Na] 363.1737, *found* 363.1723.



4-(4-aminophenyl)-3-methyl-1,3-diphenylbutan-1-one. Following general procedure, but using $Pd(OAc)_2$ (2.5 mol%) and 4-chloroaniline (58.0 mg, 0.45 mmol). Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.40). Colorless oil; yield: 82 mg (71% yield). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 1.24 Hz; 8.32 Hz, 2H), 7.52 (t, *J* = 7.38 Hz, 1H), 7.46-7.15 (m, 6H), 7.11 (d, *J* = 8.77 Hz, 1H), 6.65 (d, *J* = 8.38 Hz, 2H), 6.49 (d, *J* = 8.40 Hz, 2H), 3.55 (d, *J* = 16.7 Hz, 1H), 3.25 (d, *J* = 16.7 Hz, 1H), 3.08-3.00 (m, 2H), 1.49 (s, 2H), 1.28 (s, 3H). ^{13}C-NMR: (75 MHz, $CDCl_3$) δ 198.8, 147.1, 144.5, 138.2, 132.6, 131.4, 128.4, 127.9, 127.8, 126.2, 125.7, 114.5, 48.4, 47.7, 41.4, 25.0. IR (neat, cm^{-1}): 2926, 1687, 1620, 1515, 1494, 1446, 1216, 1010, 824, 759, 549. HRMS: *calcd* for [$C_{23}H_{23}NO$+Na] 352.1684, *found* 352.1677.

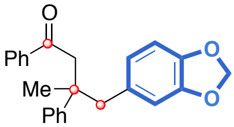


4-(3-acetylphenyl)-3-methyl-1,3-diphenylbutan-1-one. Following general procedure, but using $Pd(OAc)_2$ (2.5 mol%), K_2CO_3 as base, P(cyclopentane)·HBF_4 (5.0 mol%) as ligand and 1-(4-chlorophenyl)ethanone (59.0 μl, 0.455 mmol). Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.40). Colorless oil; yield: 110 mg (88% yield). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 1.20 Hz; 8.34 Hz, 2H), 7.72 (d, *J* = 8.34 Hz, 2H), 7.53 (t, *J* = 7.39 Hz, 1H), 7.41 (t, *J* = 7.64 Hz, 2H), 7.30-7.24 (m, 4H), 7.22-7.17 (m, 1H), 6.90 (d, *J* = 8.32 Hz, 2H), 3.54 (d, *J* = 16.6 Hz, 1H), 3.28 (d, *J* = 16.6 Hz, 1H), 3.25 (s, 2H), 2.53 (s, 3H), 1.50 (s, 3H). ^{13}C-NMR: (75 MHz, $CDCl_3$) δ 198.5, 197.9, 146.3, 143.9, 138.0, 135.2, 132.8, 130.8, 128.5, 128.1, 127.9, 127.6, 126.1, 48.7, 47.7, 41.5, 26.5, 25.0. IR (neat, cm^{-1}): 2976, 1605, 1446, 1414, 1356, 1266, 1215, 1003, 735, 690, 606. HRMS: *calcd* for [$C_{25}H_{24}O_2$+Na] 379.1685, *found* 379.1674.

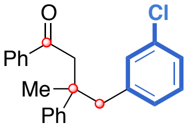


3-methyl-1,3-diphenyl-4-(4-vinylphenyl)butan-1-one. Following general procedure, but using $Pd(OAc)_2$ (1.0 mol%) and 4-chlorostyrene (55.0 μl, 0.45 mmol). Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.40). Colorless oil; yield: 118 mg (99% yield). ^{1}H-NMR: (500 MHz, $CDCl_3$) δ 7.86 (dt, *J* = 1.60 Hz; 8.50 Hz, 2H), 7.52 (t, *J* = 7.38 Hz, 1H), 7.41 (t, *J* = 7.61 Hz, 2H), 7.30-7.27 (m, 4H), 7.24-7.18 (m, 3H), 6.81 (d, *J* = 8.14 Hz, 2H), 6.66 (dd, *J* = 17.62 Hz; 10.90 Hz, 1H), 5.68 (dd, *J* = 17.61 Hz; 0.93 Hz, 1H), 5.19 (dd, *J* = 10.88 Hz; 0.90 Hz, 1H), 3.55 (d, *J* = 16.7 Hz, 1H), 3.27 (d, *J* = 16.7 Hz, 1H), 3.17 (m, 2H), 1.51 (s, 3H). ^{13}C-NMR: (125 MHz, $CDCl_3$) δ 198.6, 146.8, 138.2, 137.7, 136.6, 135.4, 132.7, 130.8, 128.4, 128.0, 127.9, 126.1, 125.9, 125.5, 113.1, 48.7, 47.7, 41.4, 25.1. IR (neat, cm^{-1}): 2925, 1689, 1596, 1510, 1446, 1353, 1213, 990, 905, 855, 751, 550. HRMS *calcd* for [$C_{25}H_{24}O$+Na] 363.1733, *found*

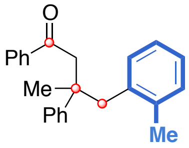
363.1725.



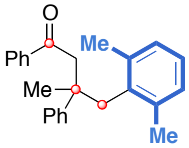
4-(benzo[*d*][1,3]dioxol-5-yl)-3-methyl-1,3-diphenylbutan-1-one. Following general procedure, 5-chloro-1,3-benzodioxole (53.0 μl, 0.45 mmol) was used. Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.50). Colorless oil; yield: 119 mg (95% yield). ^{1}H-NMR: (500 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 1.20 Hz; 8.34 Hz, 2H), 7.52 (t, *J* = 7.44 Hz, 1H), 7.41 (t, *J* = 7.71 Hz, 2H), 7.30-7.27 (m, 4H), 7.21-7.16 (m, 1H), 6.61 (d, *J* = 7.92 Hz, 1H), 6.35 (dd, *J* = 1.64 Hz; 7.94 Hz, 1H), 6.30 (d, *J* = 1.58 Hz, 1H), 5.87 (s, 2H), 3.55 (d, *J* = 16.6 Hz, 1H), 3.27 (d, *J* = 16.6 Hz, 1H), 3.12-3.06 (m, 2H), 1.50 (s, 3H). ^{13}C-NMR: (125 MHz, $CDCl_3$) δ 198.7, 146.8, 146.8, 145.8, 138.2, 132.7, 131.6, 128.4, 128.0, 127.8, 126.1, 125.9, 123.6, 110.9, 107.5, 100.6, 48.7, 47.7, 41.4, 25.0. IR (neat, cm^{-1}): 2923, 1492, 1444, 1236, 1171, 1091, 1038, 824, 760, 643, 545, 503. HRMS *calcd* for [$C_{24}H_{22}O_3$+Na] 381.1475, *found* 381.1467.



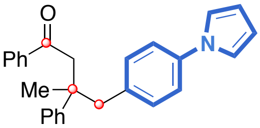
4-(3-chlorophenyl)-3-methyl-1,3-diphenylbutan-1-one. Following general procedure, 1,3-dichlorobenzene (56.0 μl, 0.45 mmol) was used. Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.40). Colorless oil; yield: 100 mg (82% yield). ^{1}H-NMR: (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 1.07 Hz; 8.23 Hz, 2H), 7.53 (t, *J* = 7.38 Hz, 1H), 7.42 (t, *J* = 7.63 Hz, 2H), 7.32-7.28 (m, 4H), 7.23-7.18 (m, 1H), 7.14 (ddd, *J* = 1.02 Hz; 1.89 Hz; 7.96 Hz, 1H), 7.05 (t, *J* = 7.79 Hz, 1H), 6.82 (t, *J* = 1.73 Hz; 1H), 6.70 (d, *J* = 7.60 Hz, 1H), 3.55 (d, *J* = 16.6 Hz, 1H), 3.27 (d, *J* = 16.6 Hz, 1H), 3.16 (s, 2H), 1.51 (s, 3H). ^{13}C-NMR: (75 MHz, $CDCl_3$) δ 198.5, 146.3, 140.0, 138.1, 133.3, 132.8, 130.6, 128.7, 128.7, 128.4, 128.1, 127.9, 126.3, 126.1, 48.5, 47.6, 41.4, 24.9. IR (neat, cm^{-1}): 2926, 1690, 1596, 1446, 1354, 1213, 1080, 1003, 783, 752, 545. HRMS *calcd* for [$C_{23}H_{21}ClO$+Na] 371.2318, *found* 371.2305.



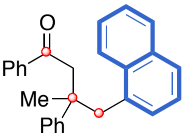
3-methyl-1,3-diphenyl-4-(*o*-tolyl)butan-1-one. Following general procedure, 2-chlorotoluene (61.0 μl, 0.45 mmol) was used. Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.50). Colorless oil; yield: 112 mg (87% yield). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.25 Hz, 2H), 7.53 (dd, *J* = 7.62 Hz; 15.02 Hz, 1H), 7.44 (t, *J* = 7.60 Hz, 2H), 7.32-7.20 (m, 5H), 7.12 (d, *J* = 3.98 Hz, 2H), 7.05-6.99 (m, 1H), 6.80 (d, *J* = 7.55 Hz, 1H), 3.77 (d, *J* = 16.7 Hz, 1H), 3.37 (d, *J* = 16.7 Hz, 1H), 3.26 (d, *J* = 13.6 Hz, 1H), 3.12 (d, *J* = 13.6 Hz, 1H), 2.06 (s, 3H), 1.61 (s, 3H). ^{13}C-NMR: (75 MHz, $CDCl_3$) δ 198.6, 146.9, 138.2, 137.7, 136.3, 132.7, 131.3, 130.3, 128.4, 128.0, 127.8, 126.2, 126.2, 125.8, 125.0, 48.2, 45.5, 42.1, 24.4, 20.0. IR (neat, cm^{-1}): 2926, 1688, 1596, 1447, 1212, 1002, 743, 569. HRMS *calcd* for [$C_{24}H_{24}O$+Na] 351.1738, *found* 351.1725.



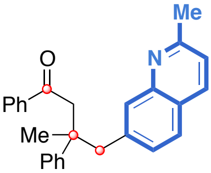
4-(2,6-dimethylphenyl)-3-methyl-1,3-diphenylbutan-1-one. Following general procedure, but using $Pd(OAc)_2$ (2.5 mol%) and 2-chloro-1,3-dimethylbenzene (60.0 μl, 0.45 mmol). Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.60). Colorless oil; yield: 119 mg (99% yield). ^{1}H-NMR: (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 1.24 Hz; 8.33 Hz, 2H), 7.54 (t, *J* = 7.37 Hz, 1H), 7.44 (t, *J* = 7.59 Hz, 2H), 7.24-7.13 (m, 5H), 7.06-7.02 (m, 1H), 6.97 (m, 2H), 3.91 (d, *J* = 16.8 Hz, 1H), 3.37 (d, *J* = 16.82 Hz, 1H), 3.27 (d, *J* = 14.0 Hz, 1H), 3.11 (d, *J* = 14.0 Hz, 1H), 1.97 (s, 6H), 1.64 (s, 3H). ^{13}C-NMR: (125 MHz, $CDCl_3$) δ 198.3, 147.1, 138.5, 138.2, 135.1, 132.7, 128.5, 128.2, 127.9, 127.8, 126.2, 1259.9, 125.8, 48.8, 43.0, 24.6, 21.0, 20.4. IR (neat, cm^{-1}): 2942, 1690, 1596, 1446, 1211, 1001, 751, 578. HRMS *calcd* for [$C_{25}H_{26}O$+Na] 365.1905, *found* 365.1893.



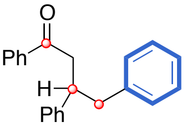
4-(4-(1*H*-pyrrol-1-yl)phenyl)-3-methyl-1,3-diphenylbutan-1-one. Following general procedure, but using $Pd(OAc)_2$ (1.0 mol%) and 1-(4-chlorophenyl)-1H-pyrrole (81.0 mg, 0.45 mmol). Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.40). Colorless oil; yield: 131 mg (99% yield). ^{1}H-NMR: (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 1.25 Hz; 8.38 Hz, 2H), 7.53 (t, *J* = 7.38 Hz, 1H), 7.42 (t, *J* = 7.62 Hz, 2H), 7.27 (d, *J* = 4.33 Hz, 4H), 7.23-7.17 (m, 1H), 7.16 (d, *J* = 8.54 Hz, 2H), 7.03 (t, *J* = 2.19 Hz, 2H), 6.86 (d, *J* = 8.53 Hz, 2H), 6.31 (t, *J* = 2.20 Hz, 2H), 3.56 (d, *J* = 16.6 Hz, 1H), 3.29 (d, *J* = 16.6 Hz, 1H), 3.19 (s, 2H), 1.52 (s, 3H). ^{13}C-NMR: (125 MHz, $CDCl_3$) δ 198.7, 146.6, 139.0, 138.2, 135.4, 132.8, 131.6, 128.5, 128.1, 127.9, 126.2, 126.0, 119.6, 119.1, 110.2, 48.2, 47.7, 41.5, 25.0. IR (neat, cm^{-1}): 3056, 2923, 1688, 1519, 1446, 1327, 1213, 1116, 1069, 1003, 724, 689, 569. HRMS: *calcd* for $[C_{27}H_{25}NO+H]$ 380.2030, *found* 380.2014.



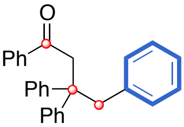
3-methyl-4-(naphthalen-1-yl)-1,3-diphenylbutan-1-one. Following general procedure, 1-chloronaphthalene (62.0 μl, 0.45 mmol) was used. Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.40). Colorless oil; yield: 120 mg (94% yield). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 8.02 (m, 1H), 7.84 (m, 3H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.51 (m, 1H), 7.43 (m, 4H), 7.28 (m, 5H), 7.21 (m, 1H), 6.93 (m, 1H), 3.83 (d, *J* = 13.7 Hz, 1H), 3.73 (d, *J* = 16.9 Hz, 1H), 3.51 (d, *J* = 13.7 Hz, 1H), 3.38 (d, *J* = 16.9 Hz, 1H), 1.56 (s, 3H). ^{13}C-NMR: (75 MHz, $CDCl_3$) δ 198.6, 147.2, 138.2, 134.4, 133.7, 133.4, 132.7, 128.9, 128.6, 128.4, 128.0, 127.8, 127.0, 126.2, 125.9, 125.4, 125.1, 124.8, 124.6, 48.4, 44.4, 42.3, 24.9. IR (neat, cm^{-1}): 2925, 1689, 1596, 1494, 1447, 121, 1080, 968, 780, 753, 546. HRMS *calcd* for $[C_{27}H_{24}O+Na]$ 387.1737, *found* 387.1725.



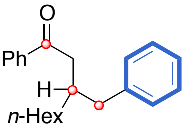
3-methyl-4-(2-methylquinolin-7-yl)-1,3-diphenylbutan-1-one. Following general procedure, but using Pd(OAc)$_2$ (2.5 mol%) and 7-chloro-2-methylquinoline (81.0 mg, 0.45 mmol). Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R$_f$=0.40). Colorless oil; yield: 119 mg (90% yield). ^{1}H-NMR: (400 MHz, CDCl$_3$) δ 7.98-7.72 (m, 5H), 7.51 (t, J = 7.39 Hz, 1H), 7.40 (t, J = 7.64 Hz, 2H), 7.31-7.22 (m, 3H), 7.21-7.17 (m, 3H), 7.11 (dd, J = 1.94 Hz; 8.64 Hz, 1H), 3.57 (d, J = 16.6 Hz, 1H), 3.33 (s, 2H), 3.30 (d, J = 16.6 Hz, 1H), 2.70 (s, 3H), 1.53 (s, 3H). ^{13}C-NMR: (100 MHz, CDCl$_3$) δ 198.7, 158.3, 146.6, 146.5, 138.1, 135.9, 135.6, 132.8, 132.7, 128.7, 128.4, 128.1, 127.9, 127.4, 126.1, 126.0, 125.9, 121.8, 48.7, 47.6, 41.7, 25.2, 25.1. IR (neat, cm^{-1}): 3056, 2923, 1689, 1599, 1496, 1446, 1265, 1218, 1003, 831, 733, 690, 574, 454. HRMS *calcd* for [C$_{27}$H$_{25}$NO+Na] 380.2008, *found* 380.1990.



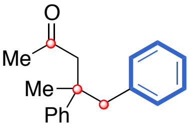
1,3,4-triphenylbutan-1-one. Following general procedure, but using Pd(OAc)$_2$ (2.5 mol%), chlorobenzene (46.0 μl, 0.45 mmol) and 1,3-diphenylcyclobutanol (78.0 mg, 0.35 mmol). Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R$_f$=0.40). Colorless oil; yield: 90 mg (86% yield). ^{1}H-NMR: (500 MHz, CDCl$_3$) δ 7.80 (dd, J = 1.26 Hz; 8.40 Hz, 2H), 7.53 (t, J = 7.40 Hz, 1H), 7.42 (t, J = 7.70 Hz, 2H), 7.27-7.14 (m, 8H), 7.09 (m, 2H), 3.68 (m, 1H), 3.32 (m , 2H), 2.99 (m, 2H). ^{13}C-NMR: (125 MHz, CDCl$_3$) δ 198.9, 144.1, 139.8, 137.2, 132.9, 129.3, 128.5, 128.3, 128.2, 128.0, 127.6, 126.4, 126.1, 44.1, 43.0, 42.9. HRMS *calcd* for [C$_{22}$H$_{20}$O+Na] 323.1412, *found* 323.1424.



1,3,3,4-tetraphenylbutan-1-one. Following general procedure, but using Pd(OAc)$_2$ (2.5 mol%), chlorobenzene (46.0 μl, 0.45 mmol) and 1,3,3-triphenylcyclobutanol (105.0 mg, 0.35 mmol). Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R$_f$=0.40). White solid; yield: 130 mg (99% yield). Mp=150-153 °C. ^{1}H-NMR: (500 MHz, CDCl$_3$) δ 7.75 (d, *J* = 1.12 Hz; 8.29 Hz, 2H), 7.46 (t, *J* = 7.39 Hz, 1H), 7.34 (t, *J* = 7.77 Hz, 2H), 7.23-7.13 (m, 10H), 7.10 (t, *J* = 7.35 Hz, 1H), 7.02 (t, *J* = 7.47 Hz, 2H), 6.60 (d, *J* = 7.09 Hz, 2H), 3.87 (s, 2H), 3.68 (s, 2H). ^{13}C-NMR: (125 MHz, CDCl$_3$) δ 198.9, 147.8, 138.4, 137.9, 132.5, 130.8, 128.2, 128.0, 127.8, 127.7, 127.4, 126.1, 125.9, 49.6, 43.7, 43.3. HRMS *calcd* for [C$_{28}$H$_{24}$O+Na] 399.1725, *found* 399.1710.

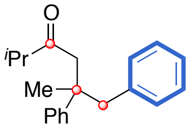


3-benzyl-1-phenylnonan-1-one. Following general procedure, chlorobenzene (46.0 μl, 0.45 mmol) and 3-hexyl-1-phenylcyclobutanol (81.0 mg, 0.35 mmol) were used. Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R$_f$=0.40). Colorless oil; yield: 90 mg (83% yield). ^{1}H-NMR: (300 MHz, CDCl$_3$) δ 7.85 (dd, *J* = 1.25 Hz; 8.23 Hz, 2H), 7.53 (t, *J* = 7.35 Hz, 1H), 7.42 (t, *J* = 7.69 Hz, 2H), 7.28 (m, 2H), 7.20 (m, 3H), 2.89 (m, 2H), 2.75 (dd, *J* = 6.56 Hz; 13.47 Hz, 1H), 2.59 (dd, *J* = 7.48 Hz; 13.45 Hz, 1H), 2.44 (m, 1H), 1.29 (m, 10H), 0.88 (t, *J* = 6.84 Hz, 3H). ^{13}C-NMR: (75 MHz, CDCl$_3$) δ 200.3, 140.6, 137.3, 132.8, 129.3, 128.4, 128.2, 128.0, 125.9, 42.5, 40.5, 36.4, 33.86, 31.8, 29.4, 26.7, 22.6, 14.0. HRMS *calcd* for [C$_{22}$H$_{28}$O+Na] 331.2038, *found* 331.2027.

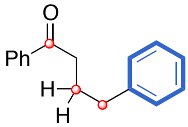


4-methyl-4,5-diphenylpentan-2-one. Following general procedure, but using Pd(OAc)$_2$ (2.5 mol%), chlorobenzene (46.0 μl, 0.45 mmol) and 1,3-dimethyl-3-phenylcyclobutanol (62.0 mg, 0.35 mmol). Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R$_f$=0.40). Colorless oil; yield: 79 mg (90% yield). ^{1}H-NMR: (400 MHz, CDCl$_3$) δ 7.35-7.27 (m, 4H), 7.24-7.19 (m, 2H), 7.16-7.13 (m, 2H), 6.84-6.79 (m, 2H), 3.07-2.99 (m, 3H), 2.65 (d, *J* = 15.3 Hz, 1H), 1.86 (s, 3H), 1.41 (s, 3H). ^{13}C-NMR:

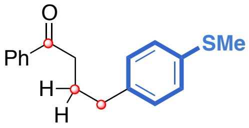
(100 MHz, $CDCl_3$) δ 207.8, 146.3, 137.7, 130.6, 128.1, 127.6, 126.3, 126.2, 126.1, 54.0, 49.3, 41.2, 32.0, 24.2. IR (neat, cm^{-1}): 2925, 1717, 1496, 1358, 765. HRMS *calcd* for [$C_{18}H_{20}O$+Na] 275.1412, *found* 275.1405.



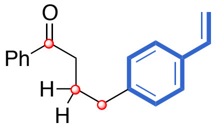
2,5-dimethyl-5,6-diphenylhexan-3-one. Following general procedure, chlorobenzene (46.0 μl, 0.45 mmol) and 1-isopropyl-2-methyl-2-phenylcyclobutanol (72.0 mg, 0.35 mmol) were used. Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.40). Colorless oil; yield: 83 mg (85% yield). ^1H-NMR: (500 MHz, $CDCl_3$) δ 7.32-7.26 (m, 4H), 7.20 (t, *J* = 6.87 Hz, 1H), 7.16-7.12 (m, 3H), 6.83 (dd, *J* = 3.02 Hz; 6.45 Hz, 2H), 3.12-3.06 (m, 2H), 3.03 (d, *J* = 16.1 Hz, 1H), 2.71 (d, *J* = 16.1 Hz, 1H), 2.39-2.31 (m, 1H), 1.42 (s, 3H), 0.96 (dd, *J* = 22.9 Hz, 6.9 Hz, 6H). ^{13}C-NMR: (125 MHz, $CDCl_3$) δ 213.4, 146.7, 138.0, 130.6, 128.0, 127.5, 126.2, 126.1, 125.9, 50.5, 48.7, 41.9, 41.1, 24.6, 18.2, 17.8. IR (neat, cm^{-1}): 2967, 1710, 1496, 1446, 1032, 764. HRMS *calcd* for [$C_{20}H_{24}O$+Na] 303.1733, *found* 303.1725.



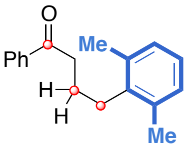
1,4-diphenylbutan-1-one. Following general procedure, but using $Pd(OAc)_2$ (1.0 mol%), chlorobenzene (46.0 μl, 0.455 mmol) and 1-phenylcyclobutanol (52.0 mg, 0.35 mmol). Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.40). Colorless oil; yield: 65 mg (83% yield). ^1H-NMR: (500MHz, $CDCl_3$) δ 7.93 (dd, *J* = 1.24 Hz; 8.34 Hz, 2H), 7.55 (t, *J* = 7.37 Hz, 1H), 7.45 (t, *J* = 7.56 Hz, 2H), 7.32-7.28 (m, 2H), 7.21 (d, *J* = 7.61 Hz, 3H), 2.99 (t, *J* = 7.29 Hz, 2H), 2.73 (t, *J* = 7.56 Hz, 2H), 2.09 (m, 2H). ^{13}C-NMR: (125 MHz, $CDCl_3$) δ 200.1, 141.7, 137.0, 132.9, 128.5, 128.4, 128.3, 128.0, 125.9, 37.7, 35.2, 25.7. HRMS *calcd* for [$C_{16}H_{16}O$+Na] 247.1099, *found* 247.1083.



4-(4-(methylthio)phenyl)-1-phenylbutan-1-one. Following general procedure, but using Pd(OAc)$_2$ (1.0 mol%), 4-chlorothioanisole (72 mg, 0.45 mmol) and 1-phenylcyclobutanol (52.0 mg, 0.35 mmol). Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R$_f$=0.40). Colorless oil; yield: 79 mg (84% yield). ^{1}H-NMR: (400 MHz, CDCl$_3$) δ 7.93 (d, *J* = 6.95 Hz, 2H), 7.55 (t, *J* = 7.32 Hz, 1H), 7.44 (t, *J* = 7.43 Hz, 2H), 7.21 (d, *J* = 8.35 Hz, 2H), 7.14 (d, *J* = 8.34 Hz, 2H), 2.97 (t, *J* = 7.22 Hz, 2H), 2.69 (t, *J* = 7.53 Hz, 2H), 2.47 (s, 3H), 2.07 (qu, *J* = 7.41 Hz, 2H). ^{13}C-NMR: (75 MHz, CDCl$_3$) δ 199.9, 138.7, 136.9, 135.4, 132.9, 129.0, 128.5, 127.9, 127.1, 37.5, 34.5, 25.5, 16.2. HRMS *calcd* for [$C_{17}H_{18}OS$+Na] 293.0976, *found* 293.0729.

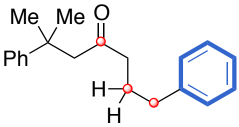


1-phenyl-4-(4-vinylphenyl)butan-1-one. Following general procedure, but using Pd(OAc)$_2$ (1.0 mol%), 4-chlorostyrene (55.0 μl, 0.45 mmol) and 1-phenylcyclobutanol (52.0 mg, 0.35 mmol). Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R$_f$=0.50). Colorless oil; yield: 75 mg (86% yield). ^{1}H-NMR: (400 MHz, CDCl$_3$) δ 7.92 (d, 2H, *J*= 6.98 Hz), 7.55 (t, 1H, *J*= 7.34 Hz), 7.44 (t, 2H, *J*= 7.46 Hz), 7.34 (d, 2H, *J*= 8.05 Hz), 7.17 (d, 2H, *J*= 8.18 Hz), 6.70 (dd, 1H, *J*= 10.87 Hz; 17.60 Hz), 5.71 (dd, 1H, *J*= 1.01 Hz; 17.67 Hz), 5.20 (dd, 1H, *J*= 1.01 Hz; 10.94 Hz), 2.98 (t, 2H, *J*= 7.27 Hz), 2.72 (t, 2H, *J*= 7.52 Hz), 2.08 (qu., 2H, *J*= 7.40 Hz). ^{13}C-NMR: (75 MHz, CDCl$_3$) δ 200.1, 141.4, 137.0, 136.7, 136.6, 132.9, 128.7, 128.6, 128.0, 126.3, 37.6, 34.9, 25.6. IR (neat, cm^{-1}): 2921, 2851, 1683, 1448, 1406, 1366, 1260, 1016, 798, 690. HRMS *calcd* for [$C_{18}H_{18}O$+Na] 273.1255, *found* 273.1220.

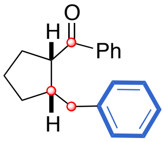


4-(2,6-dimethylphenyl)-1-phenylbutan-1-one. Following general procedure, but using Pd(OAc)$_2$ (1.0 mol%), 2-chloro-1,3-dimethylbenzene (60.0 μl, 0.45 mmol) and 1-phenylcyclobutanol (52.0 mg, 0.35 mmol). Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R$_f$=0.40). Colorless oil; yield: 72 mg (81% yield). ^{1}H-NMR: (400

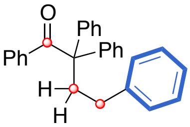
MHz, $CDCl_3$) δ 7.96 (d, 2H, *J*= 7.03 Hz), 7.57 (t, 1H, *J*= 7.32 Hz), 7.47 (t, 2H, *J*= 7.46 Hz), 7.00 (s, 3H), 2.74-2.68 (m, 2H), 2.35 (s, 6H), 1.98-1.90 (m, 2H). ^{13}C-NMR: (75 MHz, $CDCl_3$) δ 200.0, 138.7, 136.1, 133.0, 128.6, 128.1, 128.0, 125.7, 38.5, 29.3, 23.5, 19.8. IR (neat, cm^{-1}): 2918, 1682, 1494, 1449, 1023, 799, 755, 689. HRMS *calcd* for [$C_{18}H_{20}O$+Na] 275.1412, *found* 275.1403.



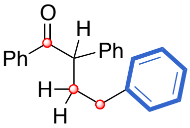
6-methyl-1,6-diphenylheptan-4-one. Following general procedure, but using $Pd(OAc)_2$ (1.0 mol%), chlorobenzene (46.0 μl, 0.45 mmol) and 1-(2-methyl-2-phenylpropyl)cyclobutanol (72 mg, 0.35 mmol). Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.40). Colorless oil; yield: 85 mg (87% yield). ^1H-NMR: (400 MHz, $CDCl_3$) δ 7.36-7.17 (m, 8H), 7.08 (d, 2H, *J*= 6.86 Hz), 2.69 (s, 2H), 2.44 (t, 2H, *J*= 7.55 Hz), 2.05 (t, 2H, *J*= 7.15 Hz), 1.71 (qu, 2H, *J*= 7.38), 1.44 (s, 6H). ^{13}C-NMR: (75 MHz, $CDCl_3$) δ 209.7, 148.2, 141.7, 128.4, 128.3, 128.2, 125.9, 125.8, 125.5, 56.1, 43.6, 37.4, 34.9, 28.9, 24.8. IR (neat, cm^{-1}): 2783, 2685, 1954, 1769, 1511, 1432, 1287, 1056, 823. HRMS *calcd* for [$C_{20}H_{24}O$+Na] 303.1725, *found* 303.1718.



(2-benzylcyclopentyl)(phenyl)methanone. Following general procedure, but using $Pd(OAc)_2$ (2.5 mol%), K_2CO_3 (1.1 eq.) as base, $P(cyclopentane)_3{\cdot}HBF_4$ (5.0 mol%) as ligand and chlorobenzene (46.0 μl, 0.45 mmol) and 6-phenylbicyclo[3.2.0]heptan-6-ol (65.9 mg, 0.35 mmol). Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.40). Colorless oil; yield: 70 mg (75% yield). ^1H-NMR: (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.9 Hz, 2H), 7.81 (d, *J* =7.1 Hz, 1H), 7.55-7.41 (m, 3H), 7.19-7.07 (m, 2H), 6.98 (d, *J* = 6.9 Hz, 2H), 3.88 (q, *J* = 7.4 Hz, 1H), 2.81-2.72 (m, 1H), 2.69-2.59 (m, 1H), 2.53 (dd, *J* = 5.5 Hz; 13.4 Hz), 2.38 (dd, *J* = 10.7; 13.5 Hz), 2.25-2.11 (m, 1H), 1.98-1.80 (m, 1H), 1.77-1.60 (m, 1H). ^{13}C-NMR: (75 MHz, $CDCl_3$) δ 202.7, 141.2, 132.7, 130.0, 128.8, 128.5, 128.3, 128.1, 125.7, 49.6, 45.7, 36.7, 31.3, 27.9, 23.4. IR (neat, cm^{-1}): 2949, 1493, 1446, 1068, 1003, 904, 725, 699, 648. HRMS *calcd* for [$C_{19}H_{20}O$+Na] 287.1423, *found* 287.1416.

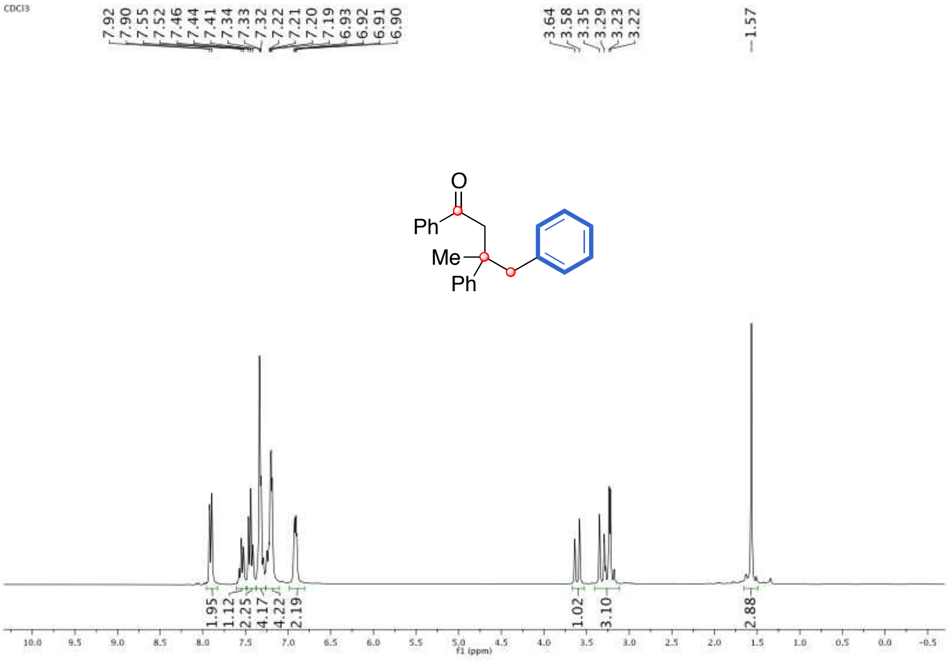


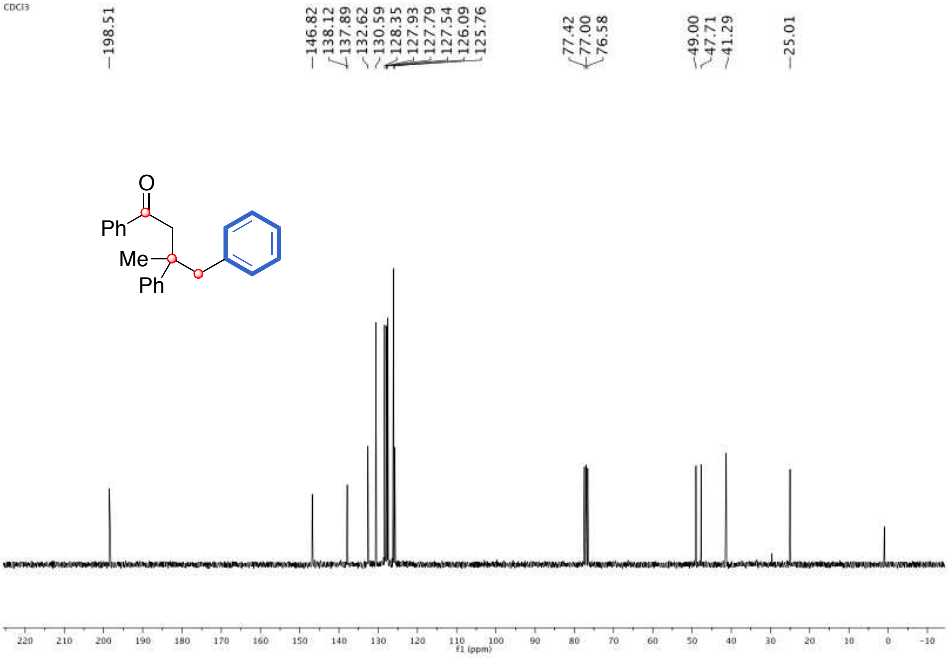
1,2,2,4-tetraphenylbutan-1-one. Following general procedure, but using Pd(OAc)$_2$ (1.0 mol%), chlorobenzene (46.0 μl, 0.45 mmol) and 1,2,2-triphenylcyclobutanol (105 mg, 0.35 mmol). Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f = 0.50). Colorless oil; yield: 119 mg (90% yield). ^{1}H-NMR: (400 MHz, CDCl$_3$) δ 7.93 (d, 2h, *J* = 6.84 Hz), 7.58-7.36 (m, 10h), 7.30-7.26 (m, 4H), 7.23-7.18 (m, 4H), 2.98 (t, 2H, *J* = 7.31 Hz), 2.73 (t, 2H, *J* = 7.35 Hz).^{13}C-NMR: (75 MHz, CDCl$_3$) δ 200.1, 141.7, 137.0, 132.9, 128.5, 128.5, 128.4, 128.0, 127.2, 125.9, 124.9, 42.1, 35.2, 25.7. IR (neat, cm^{-1}): 2954, 2782, 1760, 1467, 1409, 1389, 1232, 1019, 802. HRMS *calcd* for [$C_{28}H_{24}O$+Na] 399.1719, *found* 399.1711.

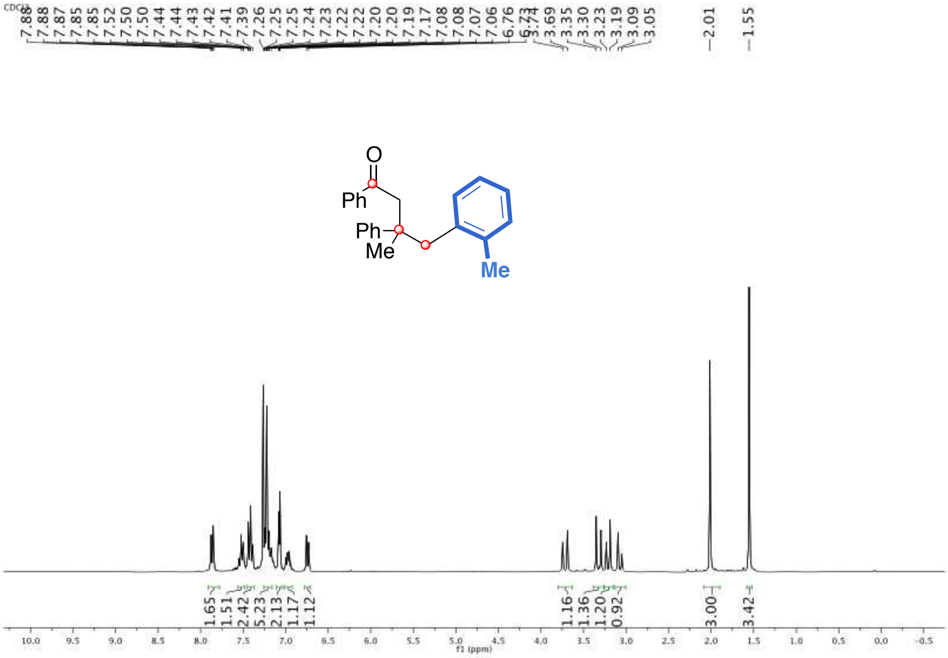


1,2,4-triphenylbutan-1-one. Following general procedure, but using Pd(OAc)$_2$ (1.0 mol%), chlorobenzene (46.0 μl, 0.45 mmol) and 1,2-diphenylcyclobutanol (79 mg, 0.35 mmol). Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.60). Colorless oil; yield: 82 mg (78% yield). ^{1}H-NMR: (400 MHz, CDCl$_3$) δ 7.38-7.08 (m, 15 H), 2.44 (t, 1 H, *J* = 7.24 Hz), 2.07 (t, 2 H, *J* = 7.19 Hz), 1.75-1.70 (m, 2H). ^{13}C-NMR: (75 MHz, CDCl$_3$) δ 208.9, 145.5, 141.7, 139.6, 130.2, 130.0, 129.3, 128.6, 128.2, 127.3, 126.7, 125.8, 125.5, 55.1, 48.4, 45.1. IR (neat, cm^{-1}): 3021, 2651, 1763, 1521, 1412, 1368, 1305, 1032, 912. HRMS *calcd* for [$C_{22}H_{20}O$+Na] 323.1412, *found* 323.1397.

2.7 Selected examples of NMR spectra



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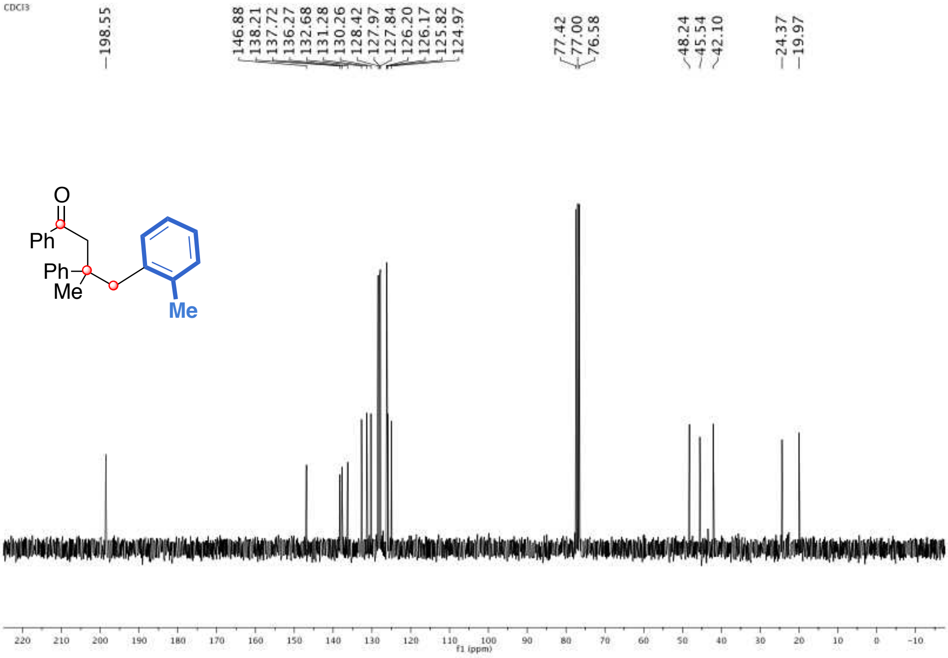
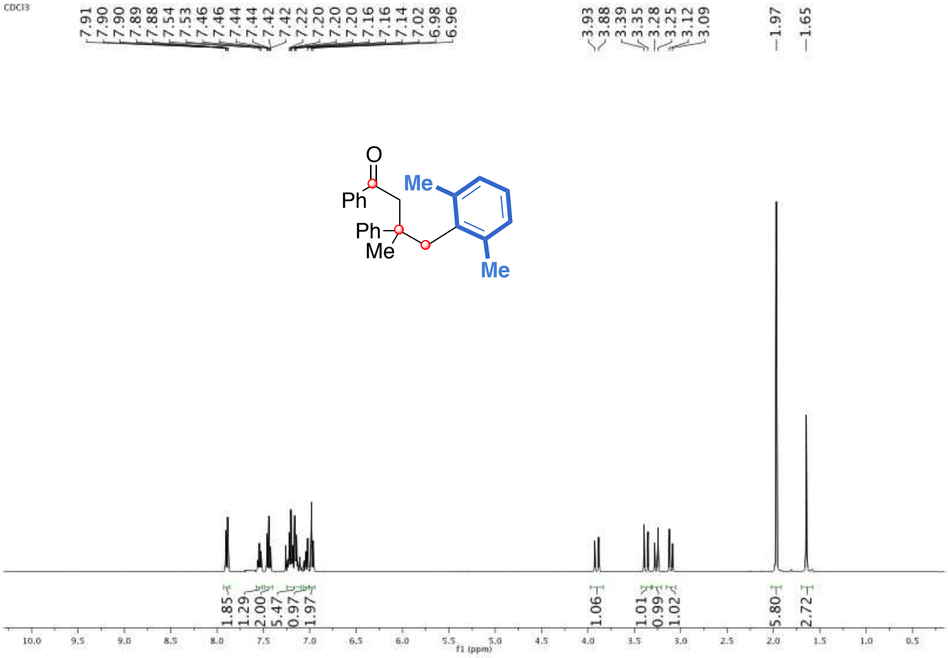
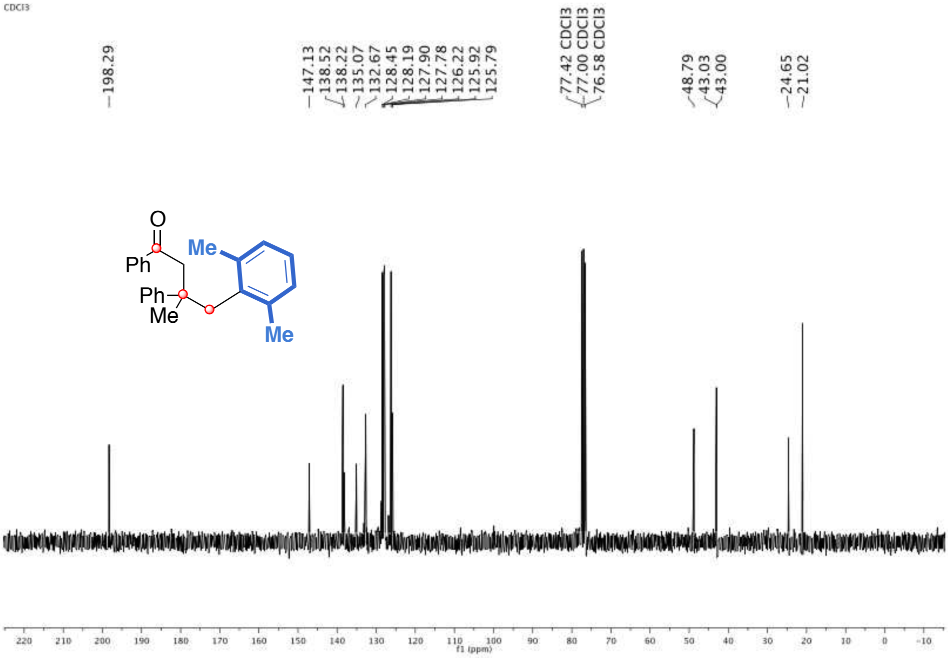
7.88
7.87
7.85
7.85
7.52
7.50
7.50
7.44
7.44
7.43
7.42
7.41
7.39
7.26
7.25
7.25
7.24
7.23
7.22
7.22
7.20
7.20
7.19
7.17
7.08
7.08
7.07
7.06
6.76
6.73
3.74
3.69
3.35
3.30
3.23
3.19
3.09
3.05
2.01
1.55
O
Ph
Ph
Me
Me
1.65
1.51
2.42
5.23
2.13
1.17
1.12
1.16
1.36
1.20
0.92
3.00
3.42
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


CDCl3
198.55
146.88
138.21
137.72
136.27
132.68
131.28
130.26
128.42
127.97
127.84
126.20
126.17
125.82
124.97
77.42
77.00
76.58
48.24
45.54
42.10
24.37
19.97
O
Ph
Ph
Me
Me
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


CDCl3
7.91 7.90 7.90 7.89 7.88 7.54 7.53 7.46 7.46 7.44 7.44 7.42 7.42 7.22 7.22 7.20 7.20 7.20 7.16 7.16 7.14 7.02 6.98 6.96
3.93 3.88 3.39 3.35 3.28 3.25 3.12 3.09
1.97
1.65
O
Ph
Me
Ph
Me
Me
1.85 1.29 2.00 5.47 0.97 1.97
1.06
1.01 0.99 1.02
5.80
2.72
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


CDCl3
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147.13 138.52 138.22 135.07 132.67 128.45 128.19 127.90 127.78 126.22 125.92 125.79
77.42 CDCl3 77.00 CDCl3 76.58 CDCl3
48.79 43.03 43.00
24.65 21.02
O
Ph
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Ph
Me
Me
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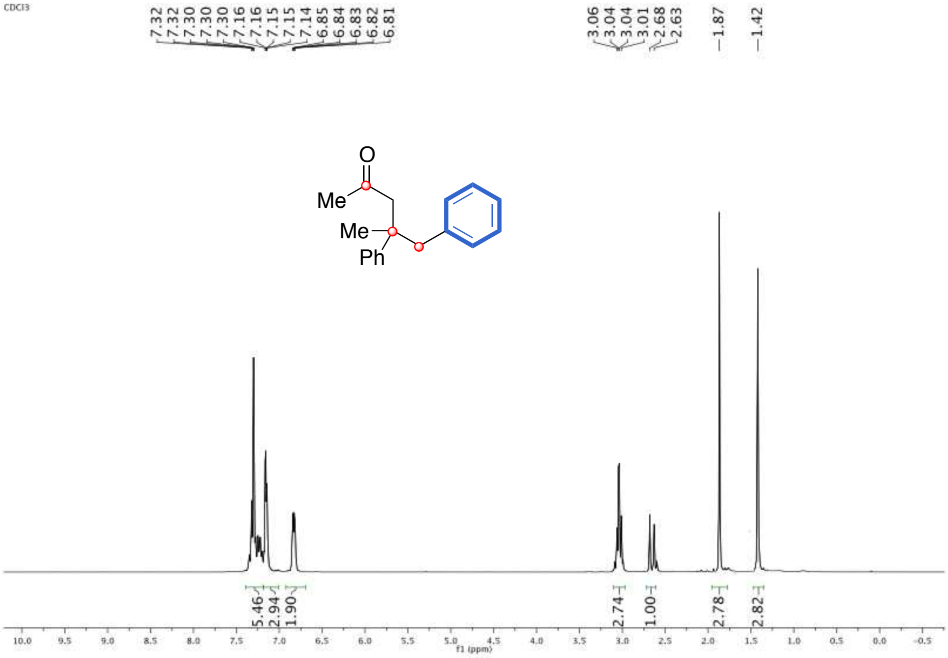
f1 (ppm)


CDCl3
7.32
7.32
7.30
7.30
7.30
7.16
7.16
7.15
7.15
7.14
6.85
6.84
6.83
6.82
6.81
3.06
3.04
3.04
3.01
2.68
2.63
1.87
1.42
O
Me
Me
Ph
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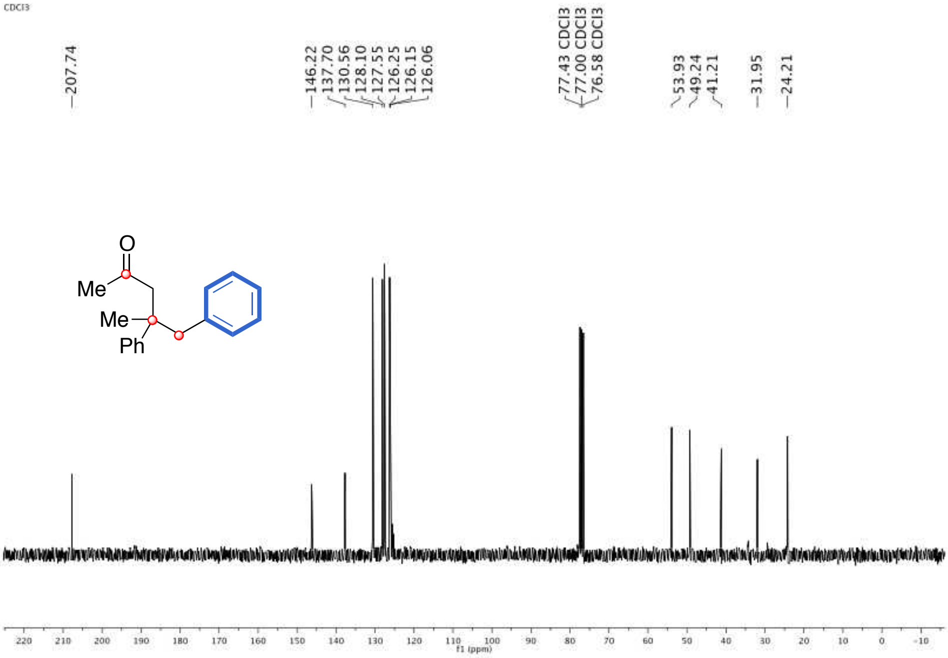
2.94
1.90
2.74
1.00
2.78
2.82
f1 (ppm)


CDCl3
207.74
146.22
137.70
130.56
128.10
127.55
126.25
126.15
126.06
77.43 CDCl3
77.00 CDCl3
76.58 CDCl3
53.93
49.24
41.21
31.95
24.21
O
Me
Me
Ph
f1 (ppm)

CHAPTER 3

A FORMAL KETONE γ-ALKYNYLATION via Pd-CATALAYZED C-C BOND-CLEAVAGE OF *tert*-CYCLOBUTANOLS

3.1 Objectives

The objectives of this chapter are the following:

- To develop a new methodology for the synthesis of γ-alkynylated ketones with bromoacetylenes via catalytic C-C bond cleavage.
- To come up with a catalyst with high turnover numbers that operates with a wide substrate scope.
- To test the applicability of our final γ-alkynylated ketones.

3.2 Acetylenes: promising building blocks

For decades, organic chemists have been fascinated with alkynes, which are chemically versatile and are widely used as key synthetic intermediates in chemical biology and material sciences. They possess an excellent coordinating ability for transition metal complexes; therefore, the metal-catalyzed activation of alkynes is considered to be a promising area for exploration. [58,59] Several methods for the α- and β-alkynylation of ketones have been developed (Figure 3.1) including the classical dehydrohalogenation of halogen derivatives, alkylation of terminal alkynes, Corey-Fuchs-type reactions or Seyferth-Gilbert homologation, among others.[58] Intriguingly, the means to provide γ-alkynylation of ketones has been virtually unexplored.

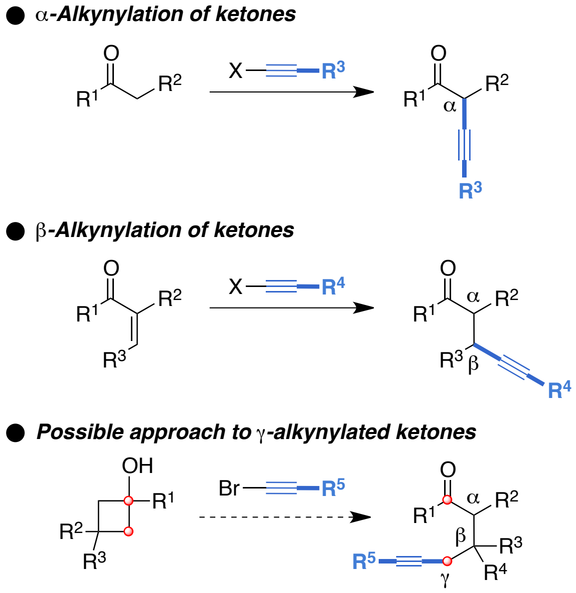


Figure 3.1

3.3 Synthesis of α-alkynylated and β-alkynylated ketones

3.3.1 Pd-catalyzed α-alkynylation via Suzuki-Miyamura cross-coupling reaction

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[58] (a) *Acetylene Chemistry*, ed. Diedrich, F.; Stang, P. J.; Tykwinski, R. R., Wiley-VCH, Weinheim, **2005**. (b) Fürstner, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 2794-2819.

[59] (a) Bunz, U. H. F. *Chem. Rev.* **2000**, *100*, 1605-1644. (b) Toyota, S. *Chem. Rev.* **2010**, *110*, 5398-5424. (c) Jenny, N. M.; Mayor, M.; Eaton, T. R. *Eur. J. Org. Chem.* **2011**, *25*, 4965-4983. (d) Lee, S. I.; Chatani, N. *Chem. Commun.* **2009**, 371-384.

In 2013, Molander reported the Pd-catalyzed α-alkynylation of 2-chloroacetates and 2-chloroacetamides with potassium alkynyltrifluoroborates via a Suzuki-Miyaura cross-coupling reaction (Figure 3.2).[60] The corresponding α-alkynylated ketones were obtained in good to excellent yields, using a Pd-precatalyst based upon the XPhos backbone (**Pd-cat**).

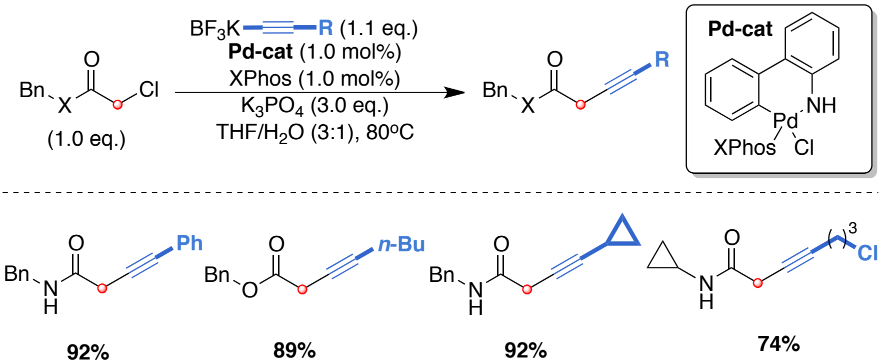

Figure 3.2

3.3.2 Organocatalytic asymmetric direct α-alkynylation of cyclic β-ketoesters

Jørgensen reported in 2006 the first organocatalytic enantioselective α-alkynylation of β-ketoesters and 3-acyl oxindoles (Figure 3.3).[61] The method provides the desired α-alkynylated ketones in excellent yields and chemoselectivities; unfortunately, the method required the presence of an electron-withdrawing group such as an ester or other carbonyl moiety. The α-alkynylation occurs at the most acidic position and employs bromo- and chloroacetylenes with ketone and ester groups as coupling counterparts.

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[60] Traister, K. M.; Molander, G. A. *Org. Lett.* **2013**, *15*, 5052-5055.

[61] Poulsen, T.B.; Bernardi, L.; Alemán, J.; Overgaard, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 441-449.

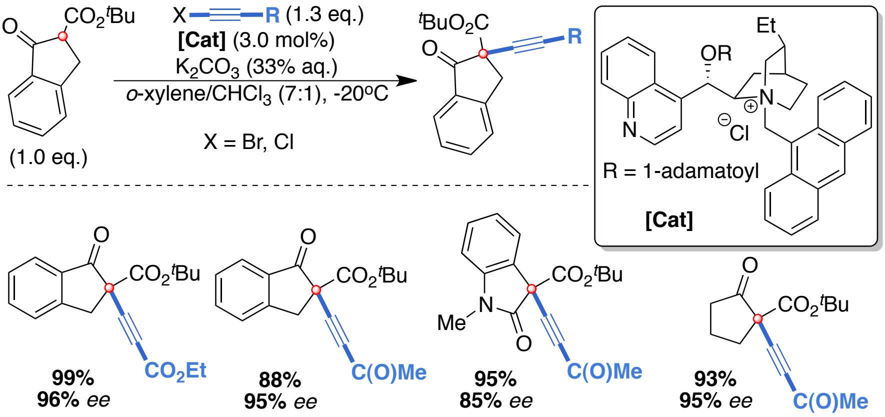

Figure 3.3

3.3.3 Electrophilic α-alkynylation with alkynyliodonium salts

Waser[62] and Ochiai,[63] among others, have developed several non-catalytic methods for the electrophilic α-alkynylation using alkynyliodonium salts as alkynylating agents. One method worth mentioning is the stoichiometric metal-free annulation developed by Ochiai in 1986 in the presence of quantitative amounts of *tert*-butoxide bases (Figure 3.4). The mechanism of this transformation involves the deprotonation of the most acidic proton, giving rise to **I**. Nucelophilic attack into the alkynyl iodonium salt likely forms **II**, that is in equilibrium with **III**, which ultimately generates carbenoid **IV** species that selectively undergoes an intramolecular [1,5]-hydride shift to yield **93**.

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[62] (a) Gonzalez, D. F.; Brand, J. P.; Mondiere, R.; Waser, J. *Adv. Synth. Catal.* **2013**, *355*, 1631–1639. (b) Gonzalez, D. F.; Brand, J. P.; Waser, J. *Chem.–Eur. J.* **2010**, *16*, 9457–9461.

[63] Kunishima, M.; Nagao, Y.; Fuji, K., Shiro, M.; Fujita, E.; Ochiai, M. *J. Am. Chem. Soc.* **1986**, *108*, 8281–8283.

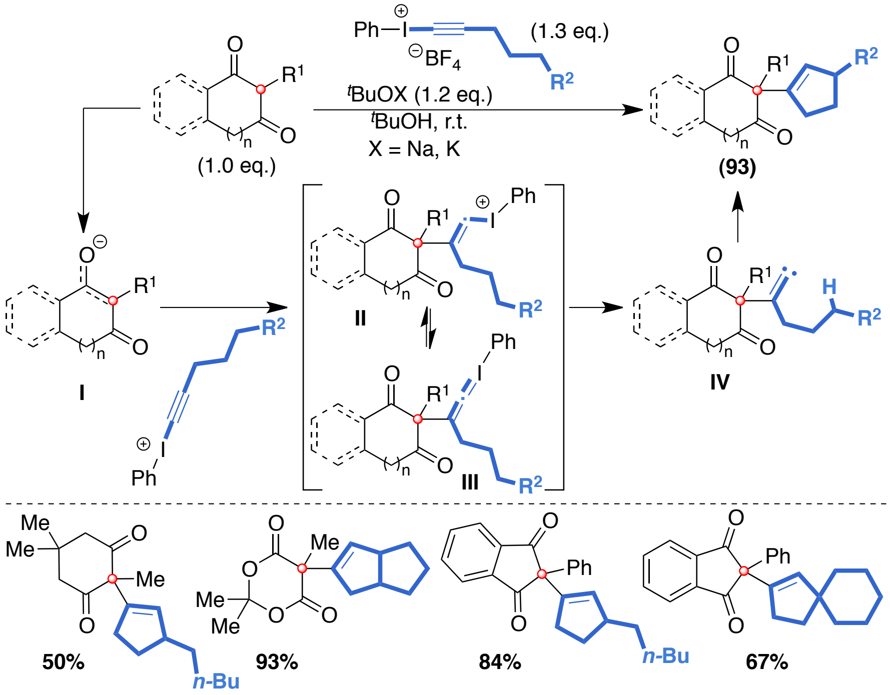

Figure 3.4

Intriguingly, in the absence of the long alkyl chain, the annulation does not occur since [1,5]-hydride shift cannot occur. In sharp contrast, the corresponding α-alkynylated di-ketones were obtained selectively (Figure 3.5).[64] Notably, the methodology also allowed for the α-alkynylation of *acyclic* diesters and 1-nitro-cyclohexane in good yields.

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[64] Ito, T.; Takaoka, Y.; Masaki, Y.; Kunishima, M.; Tani, S.; Nagao, Y.; Ochiai, M. *J. Chem. Soc. Chem. Commun.* **1990**, 118-119.

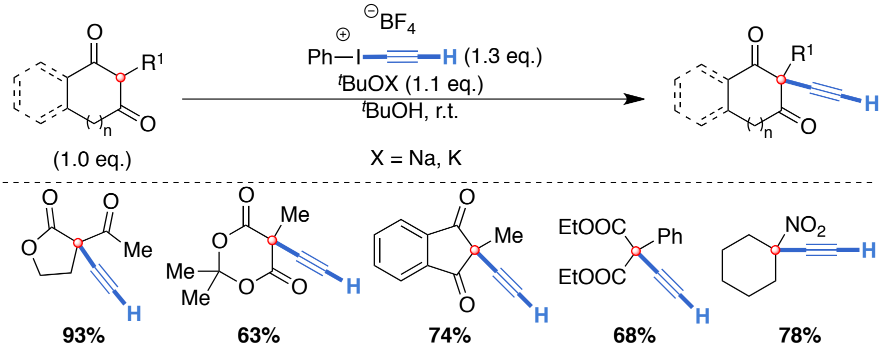

Figure 3.5

3.3.4 Ni-catalyzed β-alkynylation of α,β-unsaturated ketones

In 1979, Schwartz reported the Ni-catalyzed conjugate addition of alkynyl aluminum reagents to α,β-unsaturated ketones (Figure 3.6).[65] The method delivers β-alkynylated ketones in good to excellent yields and allows for the alkynylation of bicyclic compounds. However, the method is limited to α,β-unsaturated ketones. Interestingly, terminal alkynes can also be employed, yielding the corresponding β-alkynylated ketones, although in lower yields.

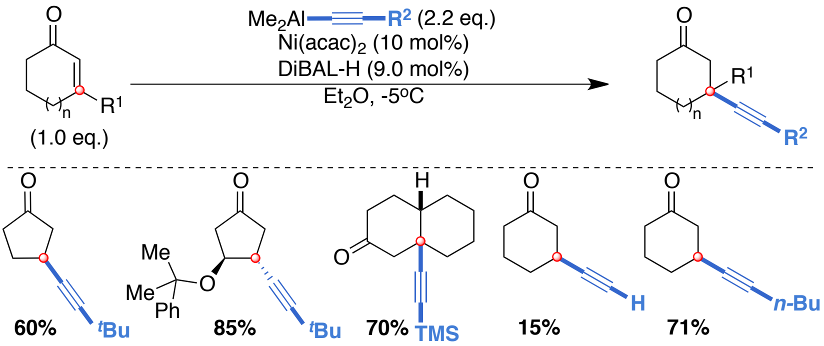

Figure 3.6

3.3.5 Ru-catalyzed β-alkynylation of α,β-unsaturated ketones via Michael addition

In 1999, Dixneuf reported the Ru-catalyzed β-alkynylation of α,β-unsaturated

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[65] Carr, D. B.; Hanses, R. T.; Dayrit, F. M.; Schwartz, J. *J. Org. Chem.* **1980**, *45*, 3053-3061.

ketones (Figure 3.7) having terminal alkynes as coupling counterparts.[66] The method allows the β-alkynylation of *acyclic* α,β-unsaturated ketones with terminal alkynes giving access to corresponding β-alkynylated ketone in good yields. The transformation is initiated by the coordination of the formate Ru-complex to the terminal alkyne en route to **I**, which subsequently forms **II** via hydromethalation. A final reductive elimination step gives access to the desired β-alkynylated ketone. Interestingly enough, the optimized conditions allowed for the β-alkynylation starting from terminal alkynes with alkene, nitro and linear alkyl chain moieties.

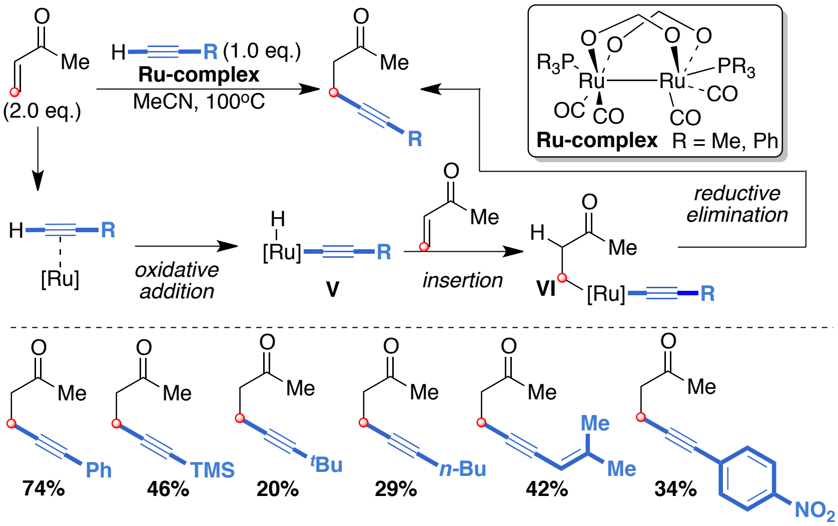

Figure 3.7

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[66] Picquet, M.; Burneau, C.; Dixneuf, P. H. *Tetrahedron*. **1999**, *55*, 3937-3948.

3.4 Results and discussions

As shown above, different methodologies have been developed for the synthesis of α- and β-alkynylated ketones, but the preparation of γ-alkynylated ketones remains elusive. Intrigued by the versatility of the alkyne moiety, we set out to develop a methodology for the γ-alkynylation of *tert*-cyclobutanols via β-carbon elimination using readily accessible bromoacetylenes as coupling counterparts (Figure 3.8).

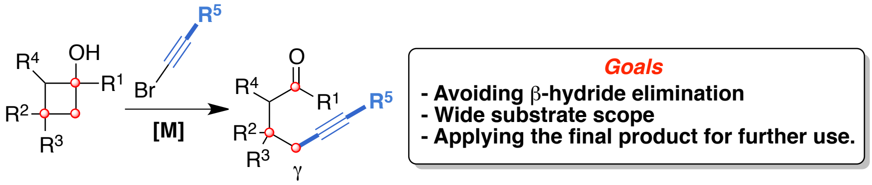


Figure 3.8

We hypothesized that the reaction would follow the same mechanism as the one presented in Chapter 2 (Figure 2.17). The mechanism would be initiated by a coordination followed by an oxidative addition of a low-valent metal species to the bromoacetylene (**I**, Figure 3.9) that would undergo a ligand exchange with *tert*-cyclobutanol to afford a Pd(II)-alkoxide **II**, thus triggering a β-carbon elimination event en route to **III**. We speculated that a bulky and electron-rich ligand would enhance the oxidative addition, avoid β-hydride elimination and enhance the rate of reductive elimination delivering the expected γ-alkynylated products.

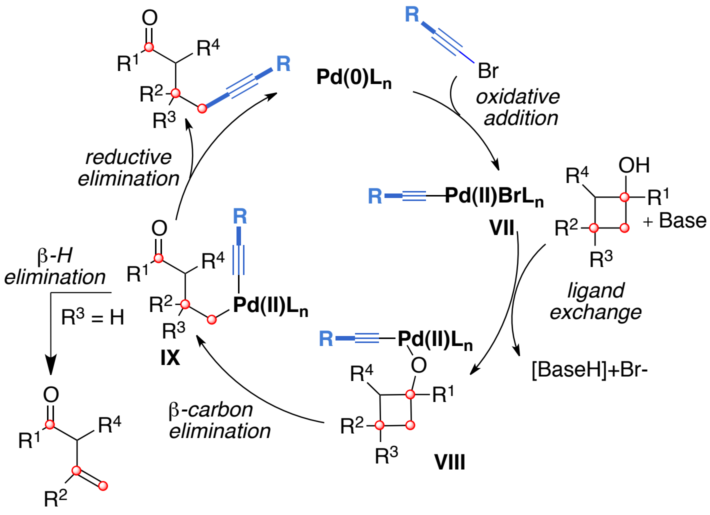


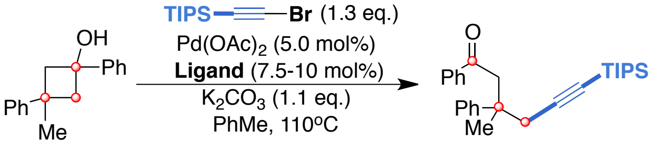
Figure 3.9

3.4.1 Optimization of the reaction conditions

3.4.1.1 Optimization of the reaction conditions for the synthesis of γ-alkynylated ketones from (bromoethynyl)triisopropylsilane

We chose **24** (Figure 2.18, Chapter 2) as our model substrate, since it could be prepared in multi-gram scale in essentially two steps from commercially available α-methyl styrene following up an approach previously described by Hassner[54] and Oehlschlager.[55] With substantial amounts of **24** in hand, we set out to investigate the optimized conditions by testing a variety of experimental variables such as metal, ligand, base, solvent and temperatures. Taking into consideration the previous results in Chapter 2, we started our screening for the optimized conditions with $Pd(OAc)_2$ as catalyst, K_2CO_3 as base in PhMe at 110°C using (bromoethynyl)triisopropylsilane as coupling counterpart and studied the influence of ligands on the reaction outcome (Table 1).

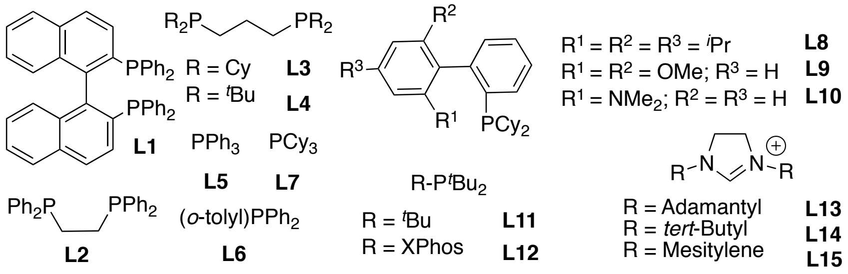
Table 1. Screening of different ligands



(24) **(94)**

Entry	**Ligand**	**Conversion (%)**	**Yield (%)**
			94
	Bidentate phosphine ligands		
1	**L1**	0	0
2	**L2**	0	0
3	**L3**	70	62
4	**L4**	54	52
	Aryl monodentate phosphine ligands		
5	**L5**	0	0
6	**L6**	0	0

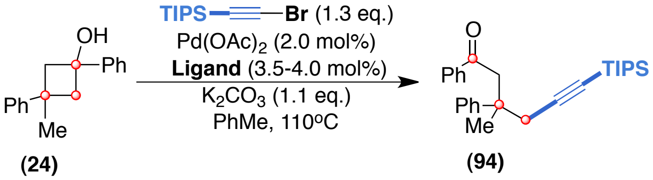
Monodentate phosphine ligands bearing cyclohexyl groups			
7	**L7**	100	98
8	**L8**	59	55
9	**L9**	43	41
10	**L10**	59	57
Monodentate phosphine ligands bearing tertbutyl groups			
11	**L11**	80	78
12	**L12**	0	0
N-heterocyclic carbenes			
13	**L13**	0	0
14	**L14**	0	0
15	**L15**	0	0



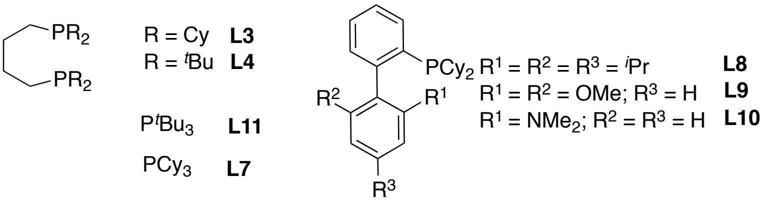
Reaction conditions: [a] **24** (0.25 mmol), Pd(OAc)$_2$ (5.0 mol%), Ligand (7.5-10 mol%), K$_2$CO$_3$ (1.1 eq., 0.275 mmol), PhMe (0.13M) at 110°C for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

As shown in Table 1, we could observe a similar trend as the one observed for the γ-arylation of ketones (Table 1, Chapter 2), in which aryl phosphine ligands did not promote the reaction at all (**L1**, **L2**, **L5** and **L6**). These results are in line with the low tendency of electron-poor ligands to promote the oxidative addition of bromoacetylenes. Among all ligands examined, it was found that monodentate alkyl phosphine ligands bearing a dicyclohexyl backbone provided the best results, particularly tricyclohexyl phosphine (**L7**), indicating that a bulky electron-rich motif was probably critical for success. In several cases where no conversion was observed, we noticed the formation of byproducts of complex nature that could be the results of homocoupling or [2+2] cycloaddition of the (bromoethynyl)triisopropylsilane. In light of these results, we next wondered whether we could lower the catalyst loading to 2.0 mol% in the presence of 4.0 mol% of **L7**. We were delighted to observe that under these conditions, **94** was obtained in a remarkable 68% GC yield (Table 2). Next, we set out to screen a selection of alkyl substituted phosphine ligands in order to increase the yield of **94** (Table 2).

Table 2. Screening of different ligands with 2.0 mol% of Pd(OAc)$_2$



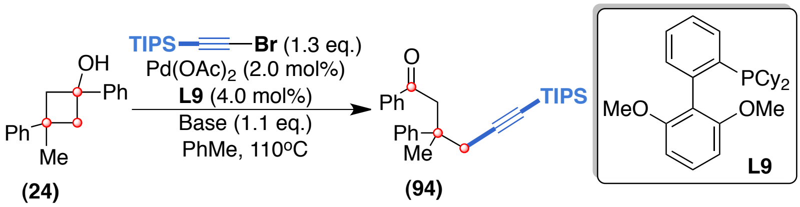
Entry	Ligand	Conversion (%)	Yield (%)
			94
1	**L3**	0	0
2	**L4**	4	2
3	**L7**	71	68
4	**L8**	33	31
5	**L9**	80	78
6	**L10**	0	0
7	**L11**	0	0



Reaction conditions: [a] **24** (0.25 mmol), Pd(OAc)$_2$ (2.0 mol%), Ligand (3.5-4.0 mol%), K$_2$CO$_3$ (1.1 eq., 0.275 mmol), PhMe (0.13M) at 110°C for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

As shown in Table 2, we found that **L9** performed better than **L7** for providing **94** in 78% GC yield (entry 5). Most likely, the presence of hemilabile ligands in the biaryl backbone plays a critical role. Surprisingly, no reactivity was found when using **L10**. We were expecting some reactivity since "Buchwald-type" ligands possess a balance of sterics and electron-density that usually promotes the reaction. Subsequently, we set out to screen different bases in the presence of 2.0 mol% of $Pd(OAc)_2$ and 4.0 mol% of **L9** (Table 3) in order to see whether the reaction can be optimized further. As mentioned in Chapter 2, we believe that the presence of base in the reaction media is crucial since it can have an impact on the initiation of the reaction by deprotonating the *tert*-cyclobutanol backbone. In order to perform the investigation, we employed bases with different properties. As shown, Cs_2CO_3 was found to be the most efficient base, providing the desired **94** in 92% GC yield (entry 3). Interestingly, the weaker base $CsHCO_3$ was found to have a detrimental impact on the reactivity. K_2CO_3 performs less efficiently than Cs_2CO_3 probably due to the bigger size of Cs^+ as compared to K^+, thus making Cs_2CO_3 a more efficient base. Stronger bases such as NaOMe or NaO^tBu resulted in the cleavage of the triisopropyl group, thus yielding little amounts of final product **94**.

Table 3. Screening of different bases



Entry	Base	Conversion (%)	Yield (%) 94
1	**NaO^tBu**	78	76
2	**NaOMe**	63	61
3	**Cs_2CO_3**	93	92
4	**K_2CO_3**	80	78
5	**$CsHCO_3$**	56	54

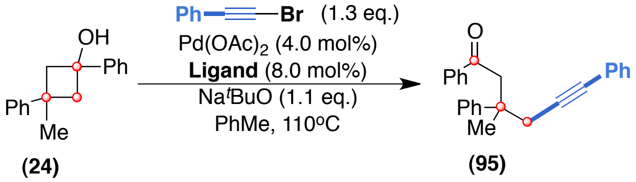
Reaction conditions: [a] **24** (0.25 mmol), $Pd(OAc)_2$ (1.0 mol%), **L9** (2.0 mol%), Base (1.1 eq., 0.275 mmol), PhMe (0.13M) at 110°C for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

In light of these results, we wondered whether it would be possible to conduct the reaction at 1.0 mol% $Pd(OAc)_2$ loading. Under otherwise reaction conditions, we obtained the desired final product in 50% GC yield. Although we tried to optimize the reaction further by modification of bases, ligands, solvents, Pd-salts, we were not able to obtain high yield of the desired final product. Interestingly, chloro- or iodo-acetylenes could not be employed as coupling partners, an observation that highlights the importance of using bromoacetylene moieties.

3.4.1.2 Screening of the reaction conditions for the synthesis of γ-alkynylated ketones from (bromoethynyl) benzene (In collaboration with Dr. Arkaitz Correa)

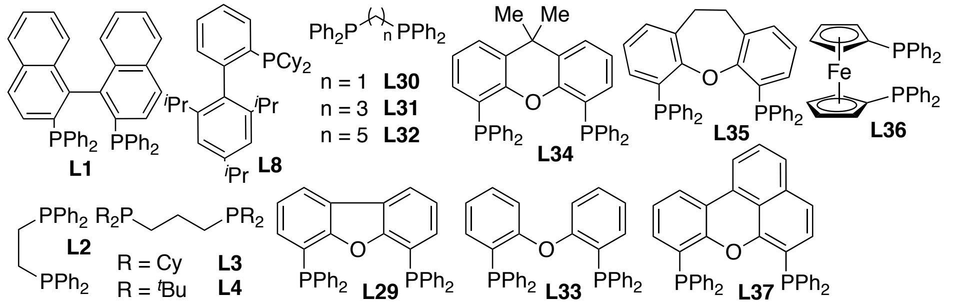
When trying to couple bromoacetylenes other than (bromoethynyl)triisopropylsilane under the optimized conditions with 2.0 mol% of $Pd(OAc)_2$ and 4.0 mol% of **L9**, we observed solely traces of the desired product. Thus, we started to screen for new more general reaction conditions that would allow the coupling of a variety of bromoacetylenes. We initiated our screening with 4.0 mol% of $Pd(OAc)_2$ as catalyst and Na^{t}BuO as base in PhMe at 110ºC using (bromoethynyl) benzene as coupling counterpart (Table 4).

Table 4. Screening of different ligands



Entry	Ligand	Conversion (%)	Yield (%)
			95
1	L1	0	0
2	L2	0	0
3	L3	0	0
4	L4	0	0

5	**L8**	0	0
6	**L30**	0	0
7	**L31**	0	0
8	**L32**	0	0
9	**L33**	0	0
10	**L34**	62	60
11	**L29**	0	0
12	**L35**	64	60
13	**L36**	0	0
14	**L37**	58	52

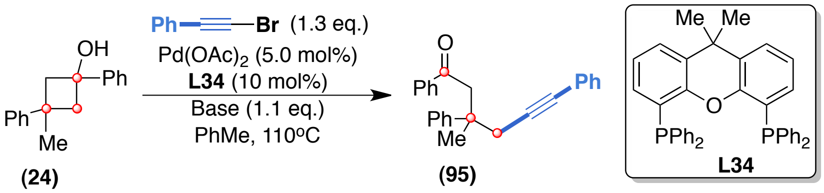


Reaction conditions: [a] **24** (0.25 mmol), Pd(OAc)$_2$ (4.0 mol%), Ligand (8.0 mol%), Na^{t}BuO (1.1 eq., 0.275 mmol), PhMe (0.13M) at 110^{o}C for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

After performing the screening of the different ligands, we observed that the reaction seemed to be very sensitive and only a small selection of ligands was found to promote the reaction (Table 4). Indeed, we found that the reaction could only be performed in the presence of **L34**, **L35** and **L37**; in the absence of these ligands, the *tert*-cyclobutanol **24** was fully recovered. In light of these results, we wondered whether the bite angle of these ligands could exert an influence or not. The bite angles of the ligands tested are as follows: **L30** (73^{0})< **L2** (86^{0})< **L31** (91^{0})< **L1** (93^{0})< **L36** (99^{0})< **L35** (102^{0})< **L33** (104^{0})< **L34** (108^{0})< **L37** (120.6^{0})< **L29**

(138^{0}).[67] Taking into account the success when employing **L34**, **L35** and **L37**, we can assume that the rigidity of the ligand might play a role since **L33**, structurally similar to **L34**, **L35** and **L37**, did not deliver **95**. It seems that **L34** and **L37** possess the best range of bite angle required for the reaction to proceed successfully. Encouraged by the 60% GC yield obtained with **L34** (Table 4), we set out a screening of different bases to investigate whether we are able to increase the yield (Table 5).

Table5. Screening of different bases



Entry	Base	Conversion (%)	Yield (%)
			95
1	**NaO^{t}Bu**	62	60
2	**KO^{t}Bu**	10	7
3	**Cs$_2$CO$_3$**	19	17
4	**CsOAc**	0	0
5	**KOH**	0	0

Reaction conditions: [a] **24** (0.25 mmol), Pd(OAc)$_2$ (5.0 mol%), **L34** (10 mol%), Base (1.1 eq., 0.275 mmol), PhMe (0.13M) at 110^{o}C for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

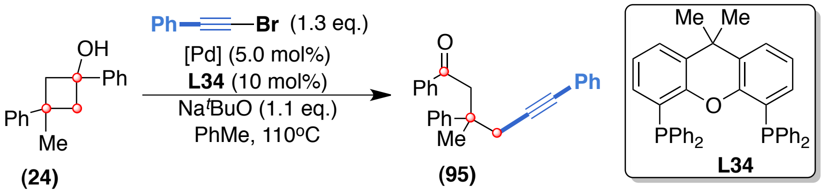
The screening of different bases did not result in an increase of the yield of the γ-alkynylated ketone **95** (Table 5), concluding that Na^{t}BuO was the most suited base for this transformation. When changing the solvent to 1,4-dioxane, we obtained solely 28% GC yield of the desired γ-alkynylated ketone. Next, we decided to look at the

---

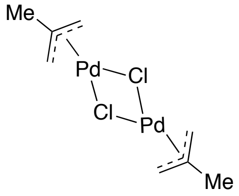
[67] For reviews about bite angles, see: (a) Dierkes, P.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Chem. Rev.* **2000**, *100*, 2741-2769. (b) Birkholz, M.-N.; Freixam Z.; van Leeuwen, P. W. N. M. *Chem. Soc. Rev.* **2009**, *38*, 1099-1118. (c) Reek, J. N.; van Leeuwen, P. W. N. M., Kamer, P. C. J. *Acc. Chem. Res.* **2001**, *34*, 895-904.

ability of different Pd-catalysts to promote the reaction (Table 6). As shown in Table 6, no significant improvement was found when operating with strongly related $PdCl_2$, $PdBr_2$, $PdCl_2(PhCN)_2$, $Pd(TFA)_2$ or π-allyl Pd-complexes.

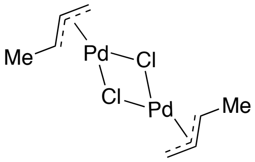
Table 6. Screening of different Pd-catalysts



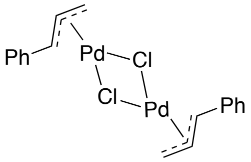
Entry	Pd-catalyst	Conversion (%)	Yield (%)
			95
1	**$Pd(OAc)_2$**	64	60
2	**$PdBr_2$**	40	37
3	**$PdCl_2$**	39	37
4	**$PdCl_2(PhCN)_2$**	45	42
5	**$Pd(TFA)_2$**	0	0
6	**Pd-1**	65	62
7	**Pd-2**	53	50
8	**Pd-3**	64	60



Pd-1



Pd-2



Pd-3

Reaction conditions: [a] **24** (0.25 mmol), [Pd] (5.0 mol%), **L34** (10 mol%), Na^{t}BuO (1.1 eq., 0.275 mmol), PhMe (0.13M) at 110°C for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

Interestingly, an increase of the amount of acetylene to 2.0 equivalents, allowed for obtaining the desired product in 72% GC yield. An additional increase in the yield was obtained when we decreased the temperature to 80°C, providing 78% GC yield

(75% isolated yield) of the desired γ-alkynylated ketone **95**. Unfortunately, all our attempts to improve these results were not satisfactory.

3.4.1.3 Optimization of the reaction conditions for the synthesis of γ-alkynylated ketones from ethynylbenzene

Encouraged by the results we obtained from the screening for the optimized reaction conditions for the γ-alkynylation of ketones from bromoacetylenes, we were interested in further exploring the methodology for the coupling of terminal alkynes under oxidative conditions (Figure 3.10). The reaction conditions were systematically investigated and we explored the conditions in the presence as well as absence ligands, screened different Pd-sources (e.g. $Pd(OAc)_2$, $Pd(COD)Cl_2$, $Pd(IPr)Cl_2$(2-chloropyridine) and **Pd-1**), different oxidants (e.g. $PhI(OAc)_2$, $K_2S_2O_8$, oxone and benzoquinone) and different temperatures. Despite all the experimentations, we never observed traces of the final product resulting in recovered *tert*-cyclobutanol and homocoupling of the starting alkyne.

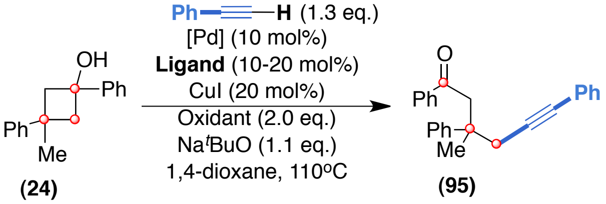
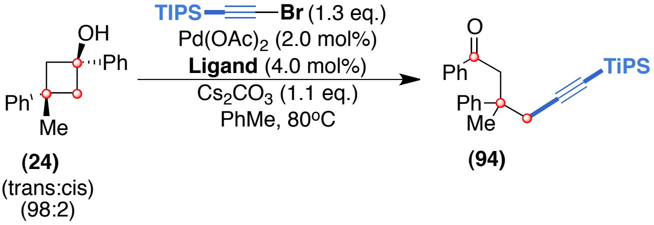


Figure 3.10

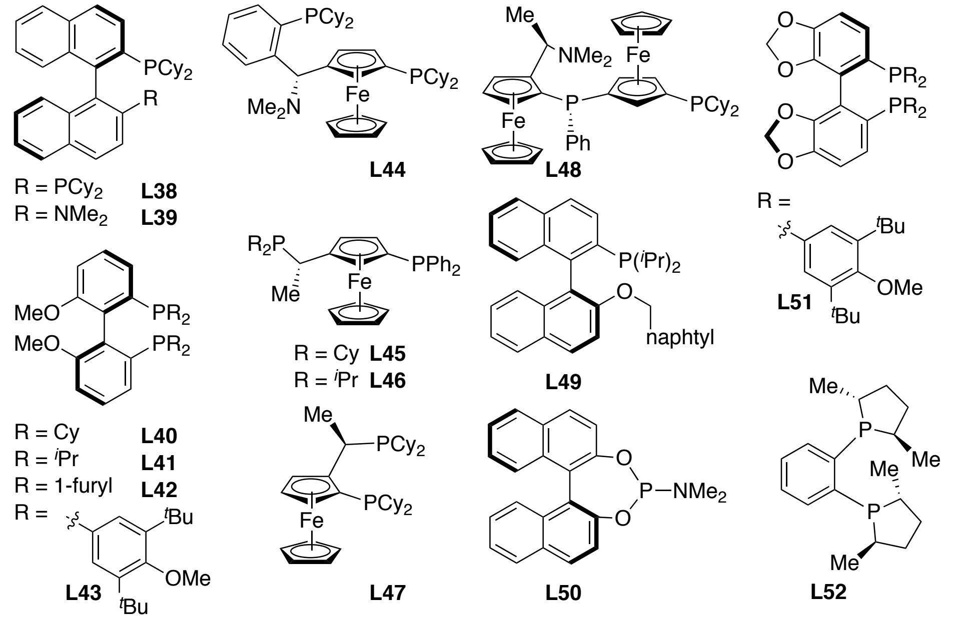
3.4.1.4 Optimization of the reaction conditions for the synthesis of enantio-pure γ-alkynylated ketones from (bromoethynyl)triisopropylsilane

Prompted by the results using (bromoethynyl)triisopropylsilane as counterpart, we wondered whether an asymmetric variant would be within reach by screening different chiral ligands under the optimized reaction conditions (Table 8).

Table 4. Screening of different ligands



Entry	**Ligand**	**Conversion (%)**	**Yield (%)**	**ee (%)**
			94	
1	**L38**	31	29	7
2	**L39**	25	23	0
3	**L40**	37	34	0
4	**L41**	11	9	-
5	**L42**	6	2	-
6	**L43**	32	30	0
7	**L44**	24	20	3
8	**L45**	4	2	-
9	**L46**	17	15	0
10	**L47**	43	40	0
11	**L48**	8	5	-
12	**L49**	9	6	-
13	**L50**	15	12	-
14	**L51**	21	18	22
15	**L52**	29	26	0



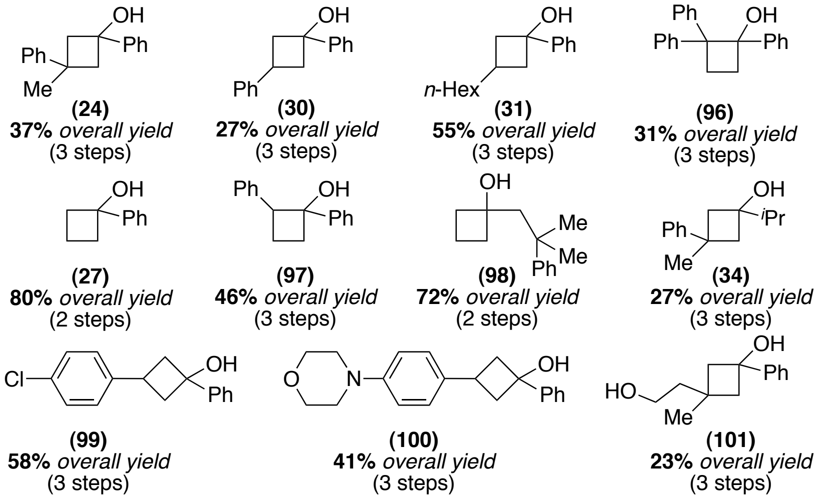
Reaction conditions: [a] **24** (0.25 mmol), $Pd(OAc)_2$ (2.0 mol%), Ligand (4.0 mol%), Cs_2CO_3 (1.1 eq., 0.275 mmol), PhMe (0.13M) at 80°C for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

Although in many cases we obtained a racemate, promising results were found with **L51**, obtaining **22% ee** of **94**. Unfortunately, we have so far not tried the *cis*-isomer but further investigations along these lines are currently on going in our laboratory.

3.4.2. Scope of the reaction

3.4.2.1 Synthesis of different *tert*-cyclobutanols

Having established the optimized reaction conditions, we set out to explore the scope of this reaction by preparing a wide variety of *tert*-cyclobutanols. As for the preparation of **24**, the general route to access this type of molecules involved an initial [2+2] cycloaddition, Zn-mediated dehalogenation and a final addition of a Grignard reagent. In this manner, a series of *tert*-cyclobutanols with different substituents were prepared in good overall yields and in essentially two-step process at large scale. By utilizing such route, a variety of substitution patterns including either aliphatic or aromatic groups could be equally prepared in similar overall yields (Figure 3.11).



(24) 37% *overall yield* (3 steps)
(30) 27% *overall yield* (3 steps)
(31) 55% *overall yield* (3 steps)
(96) 31% *overall yield* (3 steps)
(27) 80% *overall yield* (2 steps)
(97) 46% *overall yield* (3 steps)
(98) 72% *overall yield* (2 steps)
(34) 27% *overall yield* (3 steps)
(99) 58% *overall yield* (3 steps)
(100) 41% *overall yield* (3 steps)
(101) 23% *overall yield* (3 steps)

Figure 3.11

3.4.2.2 γ-Alkynylation of different *tert*-cyclobutanols with (bromoethynyl)triisopropylsilane

With substantial amounts in hand of differently substituted *tert*-cyclobutanols, we focused our attention on the preparative scope of the Pd-catalyzed intermolecular γ-alkynylation of ketones via C-C bond cleavage with (bromoethynyl)triisopropylsilane. As shown in Figure 3.12, the methodology allowed for the coupling of *tert*-cyclobutanols with alkyl groups in α-position to the ketone (**103** and **110**). Similarly, C2-substitution did not have any influence on the reaction outcome (**108** and **109**). Interestingly, unprotected hydroxyl group (**111**) or different substituents at C3 possessing different functionalities posed no problems (**104**, **105** and **106**).

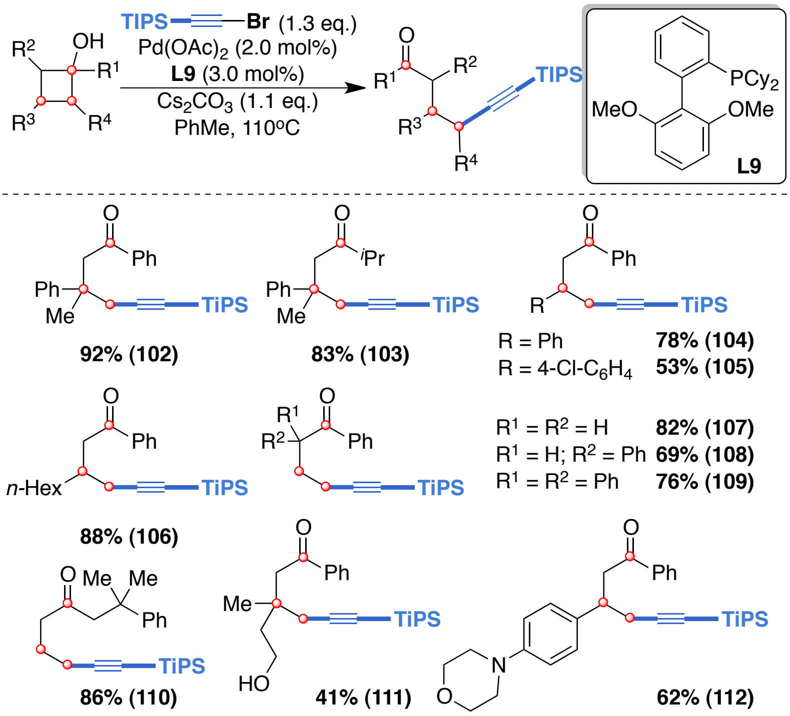


Figure 3.12

Unfortunately, the coupling of *tert*-cyclobutanols having an alkyne moiety (**47**), trifluoromethyl group at C1-position (**115**), bulky substituents at C3-position (**3.27**), bicyclic motifs (**116** and **49**) and heterocyclic backbones (**113**) did not deliver the expected γ-alkynylated ketone (Figure 3.13). In the case of **47**, the lack of reactivity could be due to the ability of the alkyne moiety to compete for substrate binding. In the case of **113**, the ability of the sulfoxide moiety to coordinate to the palladium complex might cause catalyst-poisoning. In all the other cases, the *tert*-cyclobutanol was recovered unaltered.

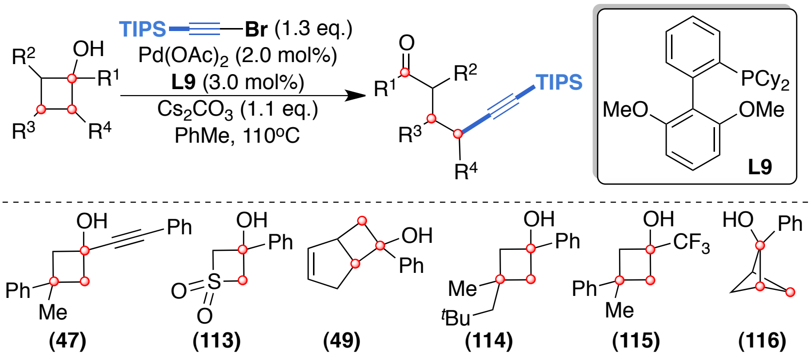


Figure 3.13

3.4.2.3 γ-Alkynylation of bromoacetylenes with different *tert*-cyclobutanols

Next, we turned our attention to the coupling of different bromoacetylenes. We were delighted to observe that several bromoacetylenes were tolerated under our newly optimized reaction conditions (Figure 3.14). The method allowed the coupling of bromophenyl acetylenes with halogens in different positions (**118**), electron-rich and electron-poor aromatics (**117**-**121**), *ortho*-substitution (**122**, **123** and **129**) as well as heteroaromatics (**127**). Notably, the reaction proceeded with non-aromatic frameworks (**124** and **125**).

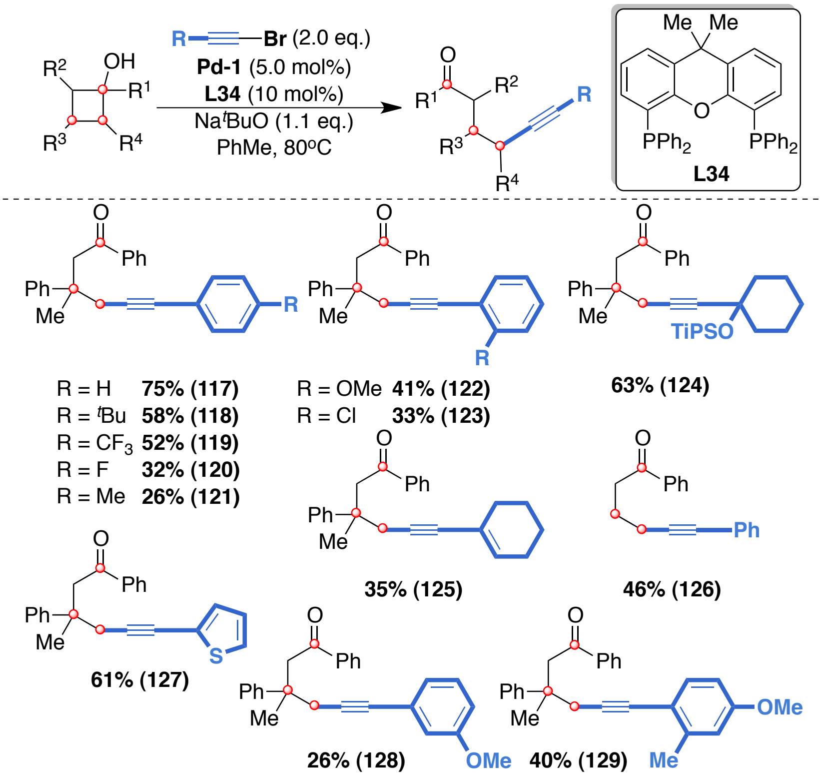


Figure 3.14

Unfortunately, the coupling of bromoacetylenes with an aliphatic (**131**), ester (**132**), pyridine (**130**), *o*,*m*-ditrifluoromethyl benzene (**133**) (Figure 3.15) was not successful. Bromo-acetylenes bearing an ester group were not tolerated, an observation that is attributed to the unproductive attack of Na^{t}BuO. A closer look into the reaction scope seems to indicate that the reaction is restricted to bulky groups on the bromoacetylene, an observation that could be attributed to homodimerization pathways.[68]

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[68] This was observed by others, for example: (a) Tobisu, M.; Ano, Y.; Chatani, N. *Org. Lett.* **2009**, *11*, 3250-3252. (b) Nicolai, S.; Waser, J. *Org. Lett.* **2011**, *13*, 6324-6327.

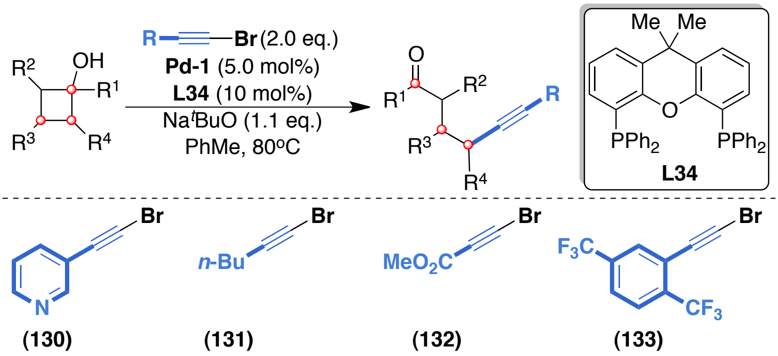

Figure 3.15

3.4.3 Synthetic applications of γ-alkynylated ketones

After exploring the scope of the reaction, we focused on the synthetic application of γ-alkynylated ketones (Figure 3.16). We were determined to explore whether the γ-alkynylated ketones were amenable for further manipulation to give access to more complex substrates.

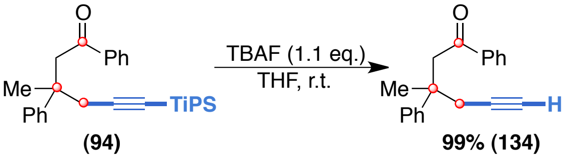

Figure 3.16

A simple deprotection of **94** in the presence of TBAF resulted in the formation of **134** in quantitative yield (Figure 3.16). As shown in Figure 3.17, **134** could successfully undergo a formal *anti*-Markovnikov hydration in the presence of Cy_2BH (1.0 eq.), $NaBO_3$ (3.0 eq.) in THF at r.t. via a hydroboration-oxidation sequence[69] to give synthetically-attractive aldehyde **135** in 58% overall yield (Figure 3.17).

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[69] Kabalka, G. W.; Yu, S.; Li, N.-S. *Can. J. Chem.* **1998**, *76*, 800-805.

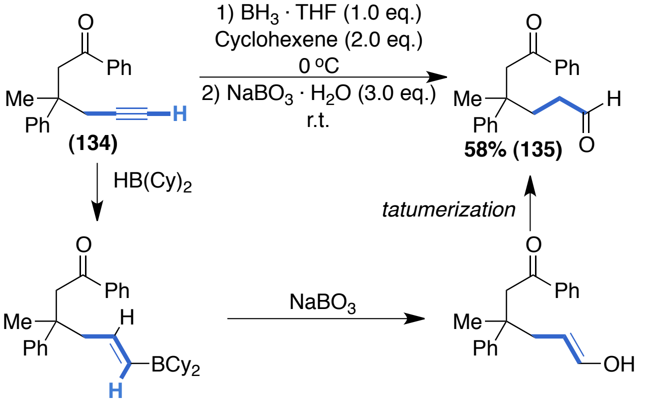

Figure 3.17

On the other hand, we found that **134** could be engaged in a Au(III)-catalyzed cycloisomerisation under conditions reported by Yamamoto[70] obtaining **136** in quantitative yields. The reaction is believed to proceed via exo-cyclization of the carbonyl unit to give intermediate **X** that ultimately results in **137** (Figure 3.18). Hydrolysis of the pyran **137** gives access to diketone **138** that gives access to the desired product **136** in 99% yield via α-deprotonation of the α-methyl ketone and S_N2 attack on the α-phenyl ketone.

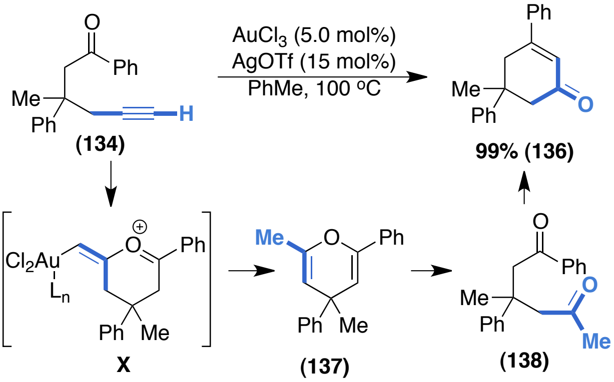

Figure 3.18

3-methyl-1,3-diphenylhex-5-yn-1-one (**134**) could get converted into the

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[70] Jin, T.; Yamamoto, Y. *Org. Lett.* **2007**, *9*, 5259-5262.

corresponding triazole **139** by Cu-cycloaddition with the corresponding azide moiety (Figure 3.19 and 3.20).[71] The mechanism for the Cu-catalyzed cycloaddition goes via the formation of the Cu(I)-acetylide **XI** that gives access to the triazole **139** by stepwise cyclization. Proceeding via an elusive six-membered copper containing intermediate **XII** (Figure 3.19).

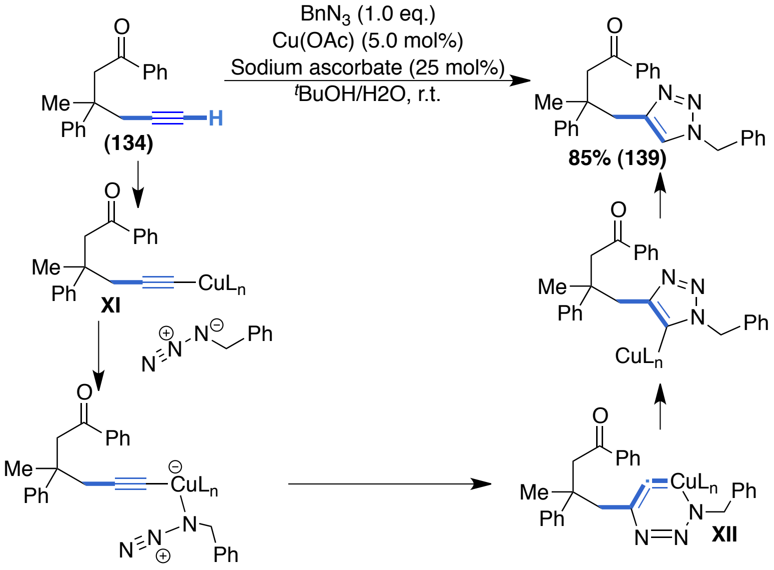

Figure 3.19

On the other hand, we found that the Ru-catalyzed conditions developed by Fokin resulted in a triazole with a different regioselectivity pattern. The mechanism of this reaction is believed to proceed via coordination of the alkyne and azide to form a ruthenacycle **XIII** (Figure 3.20). Fokin et al. believe this step to be the one that controls the regioselectivity of the overall process. Later, the metallacycle intermediate undergoes reductive elimination releasing the aromatic triazole product **140** and regenerating the catalyst.

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[71] Rostovtsev, V.; Green, L.; Fokin, V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596-2599.

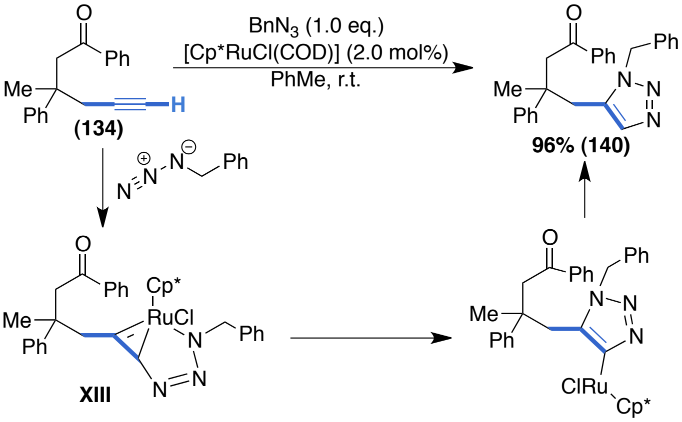

Figure 3.20

Although we tried to promote the hydrogenation of **134** under a wide variety of conditions, we found in most of the cases recovered starting material.

3.5 Conclusions

- The first route to γ-alkynylated ketones via Pd-catalyzed C-C bond cleavage has been developed.[72] The approach is highly convergent and involves a minimum number of manipulations due to the ready availability of the starting materials.
- The route provides a direct access to scaffolds that are beyond reach otherwise and allows the conversion of γ-alkynyl ketones into a diverse array of advances synthetic intermediates.

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[72] Ziadi, A.; Correa, A.; Martin, R. *Chem. Comm.* **2013**, *49*, 4286-4288.

3.6 Experimental section

3.6.1 General considerations

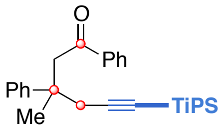
Reagents. All reactions were set up in the air (with no use of a glovebox) and carried out under an argon atmosphere in resalable screw-cap test tubes. $Pd(OAc)_2$ was a gift from Johnson Matthey. Dry PhMe was taken from the SPS (innovative technology, Newburyport, MA). All other reagents were purchased from commercial sources and used as received. Flash chromatography was performed with EM Science silica gel 60 (230-400 mesh).

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 300 MHz, 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 $CHCl_3$ (77.0 ppm) and were obtained with ^1H 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.

3.6.2 Synthesis of γ-alkynylated ketones via Pd-catalyzed C-C bond-cleavage

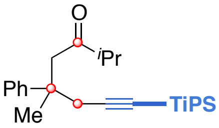
General procedure A. An oven-dried screw-cap test tube containing a stirring bar was charged with the corresponding *tert*-cyclobutanol (0.35 mmol, 1.0 eq.), SPhos (**L9**) (6.7 mg, 4.0 mol%), $Pd(OAc)_2$ (1.6 mg, 2.0 mol%) and Cs_2CO_3 (125.0 mg, 0.39 mmol, 1.1 eq.). The test tube was evacuated and back-filled with dry argon (this sequence was repeated three times). **2a** (0.42 mmol) and PhMe (2 mL) were added. The mixture was then stirred in a pre-heated oil bath (110^{o}C) for 12 h. The mixture was then allowed to reach room temperature, diluted with EtOAc (5 mL) and filtered through a Celite® plug, eluting with additional EtOAc (10 mL). The filtrate was concentrated and purified by column chromatography on silica gel (eluting with hexanes/EtOAc mixtures).

General procedure B. An oven-dried screw-cap test tube containing a stirring bar was charged with the corresponding *tert*-cyclobutanol (0.50 mmol, 1.0 eq.), $[PdCl(2\text{-methylallyl})]_2$ (0.0125 mmol, 2.5 mol%, 4.9 mg) and Xantphos (**L34**) (0.05 mmol, 10 mol%, 29 mg). Next the tube was introduced in the glovebox to weigh anhydrous NaOtBu (0.6 mmol, 1.1 equiv, 53 mg). The test tube was evacuated and back-filled with dry argon (this sequence was repeated three times). The corresponding 1-bromoalkyne (1.0 mmol, 2.0 eq.) and PhMe (1mL) were subsequently added by syringe. The mixture was then stirred in a pre-heated oil bath (80^{o}C) for 12 h. The mixture was then allowed to reach room temperature, diluted with EtOAc (5 mL) and filtered through a Celite® plug, eluting with additional EtOAc (10 mL). The filtrate was concentrated and purified by column chromatography on silica gel (eluting with hexanes/dichloromethane mixtures).

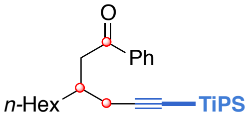


3-Methyl-1,3-diphenyl-6-(triisopropylsilyl)hex-5-yn-1-one. Following general procedure A, 3-methyl-1,3-diphenylcyclobutanol (**1a**, 83 mg, 0.35 mmol) and **2a** (119.0 mg, 0.45 mmol) were used. Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.60). Yellowish oil; yield: 134 mg (92% yield). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 1.34 Hz; 8.32 Hz, 2H), 7.53-7.49 (m, 1H), 7.39-7.37

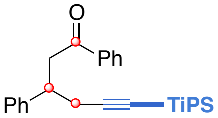
(m, 4H), 7.29-7.25 (m, 2H), 7.19-7.14 (m, 1H), 3.62 (d, *J* = 16.93 Hz, 1H), 3.52 (d, *J* = 16.89 Hz, 1H), 2.94 (d, *J* = 16.75 Hz, 1H), 2.81 (d, *J* = 16.74 Hz, 1H), 1.63 (s, 3H), 1.10 (s, 3H), 0.99 (s, 18H). ^{13}C-NMR: (101 MHz, $CDCl_3$) δ 198.1, 146.5, 137.9, 132.7, 128.1, 127.9, 126.1, 125.7, 106.1, 83.3, 47.7, 40.3, 33.3, 26.3, 18.6, 11.3, 11.3. IR (neat, cm^{-1}): 2981, 1786, 1761, 1698, 1446, 1220, 1010, 823, 690, 553. HRMS *calcd* for [$C_{28}H_{38}OSi$+Na] 441.2590, *found* 441.2591.



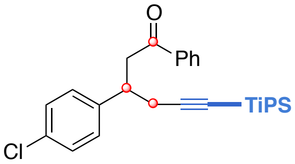
2,5-Dimethyl-5-phenyl-8-(triisopropylsilyl)oct-7-yn-3-one. Following general procedure A, 1-isopropyl-3-methyl-3-phenylcyclobutanol (**1b,** 72 mg, 0.35 mmol) and **2a** (119.0 mg, 0.45 mmol) were used. Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.60). Brownish oil; yield: 112 mg (83% yield). ^{1}H-NMR: (300 MHz, $CDCl_3$) δ 7.39-7.14 (m, 5H), 3.00 (dd, *J* = 16.59 Hz; 15.94 Hz, 2H), 2.75 (dd, *J* = 16.70 Hz; 21.90 Hz, 2H), 2.36 (p, *J* = 6.91 Hz, 1H), 1.55 (s, 3H), 1.26-0.93 (m, 27H). ^{13}C-NMR: (75 MHz, $CDCl_3$) δ 212.9, 146.3, 128.1, 126.0, 125.7, 106.2, 83.1, 50.0, 41.8, 40.1, 32.9, 25.9, 18.6, 17.9, 11.3. IR (neat, cm^{-1}): 2989, 1872, 1811, 1791, 1762, 1544, 1452, 1324, 1241, 1128, 1003, 935, 785, 682, 453. HRMS *calcd* for [$C_{25}H_{40}OSi$+Na] 407.2746, *found* 407.2748.



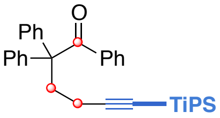
1-Phenyl-3-(3-(triisopropylsilyl)prop-2-yn-1-yl)nonan-1-one. Following general procedure A, 3-hexyl-1-phenylcyclobutanol (**1c,** 81 mg, 0.35 mmol) and **2a** (119.0 mg, 0.45 mmol) were used. Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.70). Brownish oil; yield: 127 mg (88% yield). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 7.86 (dd, *J*=1.38 Hz; 8.40 Hz, 1H), 7.55-7.19 (m, 4H), 2.90 (m, 2H), 2.76 (dd, *J* = 6.56 Hz; 13.45 Hz, 1H), 2.60 (dd, *J* = 7.47 Hz; 13.44 Hz, 1H), 2.49-2.38 (m, 1H), 1.39-1.25 (m, 13H), 0.91-0.87 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$) ? 200.40, 140.63, 132.81, 129.37, 128.26, 77.38, 77.06, 76.74, 42.60, 40.51, 36.46, 33.92, 31.82, 29.49, 26.79, 22.65, 18.77, 14.11, 11.26. IR (neat, cm^{-1}): 2982, 1782, 1752, 1680, 1562, 1476, 13442, 1118, 1063, 834, 742, 493. HRMS *calcd* for [$C_{27}H_{44}OSi+Na$] 435.3059, *found* 435.3057.



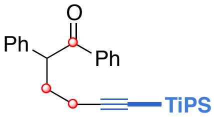
1,3-Diphenyl-6-(triisopropylsilyl)hex-5-yn-1-one. Following general procedure A, 1,3-diphenylcyclobutanol (**1d,** 79 mg, 0.35 mmol) and **2a** (119.0 mg, 0.45 mmol) were used. Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.80). Yellowish oil; yield: 110 mg (78% yield). ^{1}H-NMR: (300 MHz, $CDCl_3$) δ 8.01-7.92 (m, 2H), 7.57-7.25 (m, 8H), 3.70-3.62 (m, 2H), 3.48-3.21 (m, 1H), 2.73-2.60 (m, 2H), 1.09-1.00 (m, 21H). ^{13}C-NMR: (75 MHz, $CDCl_3$) δ 198.2, 148.3, 136.5, 133.0, 128.5, 128.4, 128.0, 127.5, 126.5, 106.8, 87.0, 47.2, 31.3, 26.9, 18.6, 11.3. IR (neat, cm^{-1}): 3414, 3295, 2961, 2941, 2920, 2889, 2863, 2164, 1687, 1597, 1462, 1215, 991, 572, 436. HRMS *calcd* for [$C_{27}H_{36}OSi+Na$] 427.2433, *found* 427.2422.



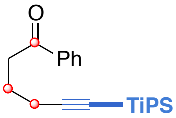
3-(4-Chlorophenyl)-1-phenyl-6-(triisopropylsilyl)hex-5-yn-1-one. Following general procedure A, 3-(4-chlorophenyl)-1-phenylcyclobutanol (**1e,** 91 mg, 0.35 mmol) and **2a** (119.0 mg, 0.45 mmol) were used. Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.70). Yellowish oil; yield: 120 mg (78% yield). ^{1}H-NMR: (300 MHz, $CDCl_3$) δ 7.95-7.93 (m, 2H), 7.56-7.23 (m, 7H), 3.68-3.59 (m, 2H), 3.37-3.30 (m, 1H), 2.71-2.57 (m, 2H), 1.03-1.01 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 142.0, 136.9, 133.1, 132.3, 128.9, 128.8, 128.6, 128.5, 128.2, 127.9, 127.8, 105.7, 83.4, 43.2, 38.9, 26.9, 18.5, 11.2. IR (neat, cm^{-1}): 3004, 1750, 1712, 1438, 1418, 1358, 1220, 1091, 901, 785, 529, 418. HRMS *calcd* for [$C_{27}H_{35}OClSi+Na$] 461.2043, *found* 461.2041.



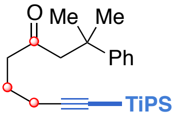
1,2,2-Triphenyl-6-(triisopropylsilyl)hex-5-yn-1-one. Following general procedure A, 1,3,3-triphenylcyclobutanol (**1f,** 105 mg, 0.35 mmol) and **2a** (119.0 mg, 0.45 mmol) were used. Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.60). Yellowish oil; yield: 128 mg (82% yield). ^{1}H-NMR: (300 MHz, $CDCl_3$) δ 7.38-7.20 (m, 15H), 2.27 (t, *J* = 6.29 Hz, 2H), 2.14 (t, *J* = 6.34 Hz, 2H), 1.07-1.05 (m, 21H). ^{13}C-NMR: (75 MHz, $CDCl_3$) δ 198.0, 142.1, 135.8, 134.0, 129.7, 127.6, 126.9, 126.6, 125.2, 99.7, 85.7, 59.2, 35.5, 21.0, 18.3, 12.9. IR (neat, cm^{-1}): 3065, 1897, 1762, 1684, 1542, 1436, 1345, 1214, 1120, 1006, 746, 691, 553. HRMS *calcd* for [$C_{33}H_{40}OSi$+Na] 503.2746, *found* 503.2744.



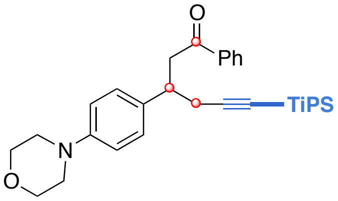
1,2-Diphenyl-6-(triisopropylsilyl)hex-5-yn-1-one. Following general procedure A, 1,2-diphenylcyclobutanol (**1g,** 79 mg, 0.35 mmol) and **2a** (119.0 mg, 0.45 mmol) were used. Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.60). Yellowish oil; yield: 97 mg (69% yield). ^{1}H-NMR: (300 MHz, $CDCl_3$) δ 7.99-7.96 (m, 2H), 7.50-4.93 (m, 8H), 4.96 (t, *J* = 7.09 Hz, 1H), 2.36-2.00 (m, 2H), 1.97 (p, *J* = 6.98 Hz, 4H), 1.09-0.86 (m, 21H). ^{13}C-NMR: (75 MHz, $CDCl_3$) δ 199.6, 153.2, 138.9, 132.9, 129.0, 128.7, 128.4, 128.3, 127.2, 108.0, 92.8, 51.7, 32.6, 18.7, 17.8, 11.3. IR (neat, cm^{-1}): 3450, 3050 2889, 2863, 1762, 1715, 1681, 1562, 1436, 1276, 1214, 1003, 798, 612, 540. HRMS *calcd* for [$C_{27}H_{36}OSi$+Na] 427.2433, *found* 427.2429.



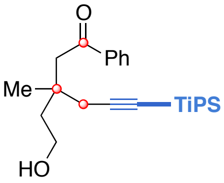
1-Phenyl-6-(triisopropylsilyl)hex-5-yn-1-one. Following general procedure A, 1-phenylcyclobutanol (**1h,** 52 mg, 0.35 mmol) and **2a** (119.0 mg, 0.45 mmol) were used. Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.70). Brownish oil; yield: 94 mg (82% yield). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 7.98 (m, 2H), 7.56 (m, 1H), 7.46 (m, 2H), 3.16 (t, *J* = 7.29 Hz, 2H), 2.40 (t, *J* = 6.73 Hz, 2H), 1.97 (p, *J* = 6.98 Hz, 2H), 1.11-0.99 (m, 21H). ^{13}C-NMR: (101 MHz, $CDCl_3$) δ 199.7, 137.0, 133.0, 128.5, 128.0, 108.0, 81.3, 37.1, 23.2, 19.4, 18.6, 11.3. IR (neat, cm^{-1}): 3002, 1789, 1659, 1465, 1240, 1093, 896, 690, 542. HRMS *calcd* for [$C_{21}H_{32}OSi$+Na] 351.2120, *found* 351.2118.



1,2,2-Triphenyl-6-(triisopropylsilyl)hex-5-yn-1-one. Following general procedure A, 1-(2-methyl-2-phenylpropyl)cyclobutanol (**1i,** 72 mg, 0.35 mmol) and **2a** (119.0 mg, 0.45 mmol) were used. Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.60). Orange oil; yield: 116 mg (86% yield). ^{1}H-NMR: (300 MHz, $CDCl_3$) δ 7.37-7.16 (m, 5H), 2.72 (s, 2H), 2.25 (t, *J* = 7.16 Hz, 2H), 2.12 (t, *J* = 6.88 Hz, 2H), 1.61-1.56 (m, 2H), 1.43 (s, 6H), 1.06-1.04 (m, 21H). ^{13}C-NMR: (75 MHz, $CDCl_3$) δ209.4, 148.3, 128.2, 125.9, 125.4, 108.1, 89.3, 56.0, 43.0, 37.4, 28.9, 22.5, 19.1, 18.6, 11.3. IR (neat, cm^{-1}): 3014, 1785, 1654, 1346, 1284, 1245, 1093, 897, 657, 540, 433. HRMS *calcd* for [$C_{25}H_{40}OSi$+Na] 407.2746, *found* 407.2748.

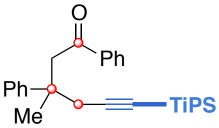


3-(4-Morpholinophenyl)-1-phenyl-6-(triisopropylsilyl)hex-5-yn-1-one. Following general procedure A, 3-(4-morpholinophenyl)-1-phenylcyclobutanol (**1j,** 108 mg, 0.35 mmol) and **2a** (119.0 mg, 0.45 mmol) were used. Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.60). Yellowish solid; yield: 125 mg (82% yield). ^{1}H-NMR: (300 MHz, $CDCl_3$) δ 7.94-7.92 (m, 2H), 7.55-7.40 (m, 3H), 7.29-7.23 (m, 4H), 4.15-3.85 (m, 4H), 3.68-3.58 (m, 2H), 3.36-3.30 (m, 1H), 2.99-2.94 (m, 4H), 2.70-2.56 (m, 2H), 1.02-1.01 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$) δ198.1, 144.7, 137.9, 136.9, 133.2, 128.8, 128.6, 127.2, 115.6, 105.8, 91.6, 65.9, 49.8, 45.9, 29.8, 29.6, 18.6, 11.3. IR (neat, cm^{-1}): 3009, 1752, 1720, 1437,1420, 1368, 1240, 1191, 930, 840, 532, 419. HRMS *calcd* for [$C_{31}H_{43}NO_2Si$+Na] 512.2961, *found* 512.2958.

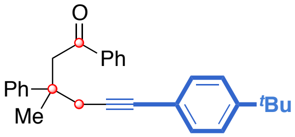


3-(2-Hydroxyethyl)-3-methyl-1-phenyl-6-(triisopropylsilyl)hex-5-yn-1-one.

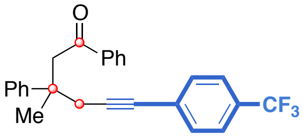
Following general procedure A, 3-(2-hydroxyethyl)-3-methyl-1-phenylcyclobutanol (**1k,** 72 mg, 0.35 mmol) and **2a** (119.0 mg, 0.45 mmol) were used. Column chromatography: silica gel, (hexanes/EtOAc, 15:1, R_f=0.30). Yellowish solid; yield: 55 mg (41% yield). ^{1}H-NMR: (300 MHz, $CDCl_3$) δ 7.96-7.93 (m, 2H), 7.57-7.26 (m, 3H), 4.17 (t, *J* = 6.87 Hz, 1H), 3.27-3.26 (bs, 1H), 3.11 (s, 1H), 2.81-2.46 (m, 3H), 1.95-1.91 (m, 2H), 1.09-0.97 (m, 24H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 135.8, 132.9, 128.5, 127.9, 99.8, 88.6, 56.6, 48.5, 44.5, 30.9, 23.6, 20.7, 18.6, 11.3. IR (neat, cm^{-1}): 3003, 1750, 1712, 1438, 1418, 1358, 1220, 1091, 901, 785, 529. HRMS *calcd* for [$C_{24}H_{38}O_2Si$+Na] 409.2539, *found* 409.2536.



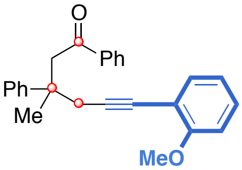
3-Methyl-1,3,6-triphenyl-5-hexyn-1-one. Following the general procedure B, using **1a** (0.50 mmol, 119 mg) and 1-bromophenylacetylene (1.0 mmol, 181 mg) provided 127 mg (75% yield) of the corresponding product as a brown oil. Column chromatography: silica gel, (hexanes/CH_2Cl_2, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99-7.96 (m, 2H), 7.60-7.56 (m, 1H), 7.53-7.44 (m, 4H), 7.42-7.38 (m, 4H), 7.33-7.26 (m, 4H), 3.69 (dd, *J* = 48, 20 Hz, 2H), 3.11 (dd, *J* = 58, 20 Hz, 2H), 1.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13C NMR (100 MHz, CDCl3) δ 198.4, 146.4, 137.8, 132.7, 131.4, 128.4, 128.1, 127.9, 127.6, 126.1, 125.6, 123.6, 112.8, 87.6, 83.3, 47.5, 40.6, 32.7, 26.3. IR (neat, cm^{-1}): 1681, 1578, 1496, 1444, 1352, 1180, 1029, 1008, 934, 887, 699, 602, 544. HRMS *calcd.* for ($C_{25}H_{22}O$+Na): 316.1568, *found* 316.1563.



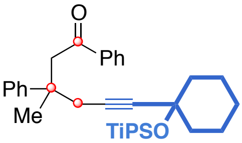
6-(4-(Tert-butyl)phenyl)-3-methyl-1,3-diphenyl-5-hexyn-1-one. Following the general procedure B, using **1a** (0.50 mmol, 119 mg) and 1-bromo-4-tert-butylphenylacetylene (1.0 mmol, 237 mg) provided 114 mg (58% yield) of the corresponding product as a brown oil. Column chromatography: silica gel, (hexanes/CH_2Cl_2, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94-7.92 (m, 2H), 7.55-7.53 (m, 1H), 7.48-7.42 (m, 4H), 7.37-7.23 (m, 7H), 3.64 (dd, *J* = 48, 20 Hz, 2H), 3.04 (dd, *J* = 56, 20 Hz, 2H), 1.72 (s, 3H), 1.32 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 198.3, 150.8, 146.6, 137.9, 132.7, 131.2, 128.4, 128.1, 127.9, 126.1, 125.7, 125.1, 120.7, 86.9, 83.3, 47.6, 40.6, 34.6, 32.9, 31.1, 26.3. IR (neat, cm^{-1}): 1692, 1671, 1596, 1497, 1406, 1361, 1352, 1267, 1179, 1108, 1002, 922, 798, 664. HRMS *calcd.* for ($C_{29}H_{30}O$+Na): 417.2189, *found* 417.2201.



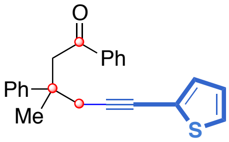
3-Methyl-1,3-diphenyl-6-(4-(trifluoromethyl)phenyl)-5-hexyn-1-one. Following the general procedure B, using **1a** (0.30 mmol, 71.4 mg) and 1-(bromoethynyl)-4-(trifluoromethyl)benzene (1.2 mmol, 298 mg) provided 63 mg (52% yield) of the corresponding product as a brown oil. Column chromatography: silica gel, (hexanes/CH$_2$Cl$_2$, 8:2). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.93-7.91 (m, 2H), 7.58-7.51 (m, 3H), 7.47-7.33 (m, 8H), 7.26-7.22 (m, 1H), 3.63 (dd, *J* = 40, 20 Hz, 2H), 3.10 (dd, *J* = 52, 20 Hz, 2H), 1.72 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 198.2, 146.3, 137.8, 132.9, 131.7, 129.3 (d, *J* = 40 Hz), 128.5, 128.3, 127.9, 127.3, 126.3, 125.7, 125.0 (m), 90.6, 82.2, 47.7, 40.6, 32.5, 26.4. IR (neat, cm^{-1}): 1691, 1597, 1165, 1065, 1002, 751, 688, 664, 596. HRMS *calcd.* for ($C_{26}H_{21}F_3O$+Na): 429.1437, *found* 429.1424.



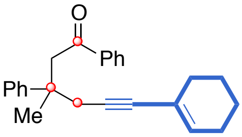
6-(2-Methoxyphenyl)-3-methyl-1,3-diphenyl-5-hexyn-1-one. Following the general procedure B, using **1a** (0.50 mmol, 119 mg) and 1-(bromoethynyl)-2-methoxybenzene (1.0 mmol, 211 mg) provided 73 mg (41% yield) of the corresponding product as a brown oil. Column chromatography: silica gel, (hexanes/CH$_2$Cl$_2$, 8:2). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.97-7.95 (m, 2H), 7.56-7.41 (m, 5H), 7.36-7.21 (m, 5H), 6.91-6.85 (m, 2H), 3.80 (s, 3H), 3.75 (dd, *J* = 52, 20 Hz, 2H), 3.08 (dd, *J* = 60, 20 Hz, 2H), 1.73 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 198.3, 160.0, 146.6, 137.9, 133.2, 132.6, 128.9, 128.3, 128.1, 127.9, 125.9, 125.7, 120.3, 112.9, 110.5, 91.9, 79.5, 55.59, 47.5, 40.5, 33.5, 26.2. IR (neat, cm^{-1}): 1688, 1595, 1491, 1376, 1291, 1179, 1072, 1002, 946, 880, 664, 604. HRMS *calcd.* for ($C_{26}H_{24}O_2$+Na): 391.1669, *found* 391.1676.



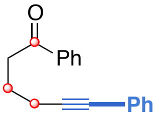
3-Methyl-1,3-diphenyl-6-(1-((triisopropylsilyl)oxy)cyclohexyl)-5-hexyn-1-one. Following the general procedure B, using **1a** (0.30 mmol, 71.4 mg) and 1-(bromoethynyl)cyclohexyl)oxy)triisopropylsilane (0.6 mmol, 187 mg) provided 99 mg (64% yield) of the corresponding product as a colorless oil. Column chromatography: silica gel, (hexanes/CH_2Cl_2, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91-7.89 (m, 2H), 7.56-7.52 (m, 1H), 7.45-7.40 (m, 4H), 7.33-7.28 (m, 2H), 7.22-7.18 (m, 1H), 3.55 (dd, *J* = 44, 20 Hz, 2H), 2.89 (dd, *J* = 56, 20 Hz, 2H), 1.87-1.76 (m, 2H), 1.66 (s, 3H), 1.62-1.55 (m, 4H), 1.41-1.06 (m, 26H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.0, 146.5, 137.8, 132.7, 128.4, 128.1, 127.8, 126.0, 125.7, 87.4, 82.2, 77.3, 76.7, 69.2, 47.9, 41.6, 40.3, 32.1, 26.2, 25.3, 23.1, 18.4, 13.1. IR (neat, cm^{-1}): 2940, 2289, 1694, 1461, 1446, 1105, 1054, 881, 750, 697, 687, 637. HRMS *calcd.* for ($C_{34}H_{48}O_2Si$+Na): 539.3316, *found* 539.3321.



3-Methyl-1,3-diphenyl-6-(3-thienyl)-5-hexyn-1-one. Following the general procedure B, using **1a** (0.50 mmol, 119 mg) and 3-(bromoethynyl)thiophene (2.0 mmol, 374 mg) provided 104 mg (61% yield) of the corresponding product as a yellow oil. Column chromatography: silica gel, (hexanes/CH_2Cl_2, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94-7.91 (m, 2H), 7.57-7.53 (m, 1H), 7.46-7.44 (m, 4H), 7.37-7.33 (m, 2H), 7.29-7.28 (m, 1H), 7.25-7.21 (m, 2H), 7.01 (dd, *J* = 5.0, 1.2 Hz, 1H), 3.63 (dd, *J* = 44, 20 Hz, 2H), 3.04 (dd, *J* = 56, 20 Hz, 2H), 1.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 146.5, 137.9, 132.7, 129.9, 128.4, 128.2, 127.9, 127.9, 127.7, 126.1, 125.7, 124.9, 122.6, 87.2, 78.3, 47.6, 40.6, 32.7, 26.4. IR (neat, cm^{-1}): 1688, 1596, 1520, 1495, 1375, 1215, 1179, 1119, 858, 751, 688, 641, 568. HRMS *calcd.* for ($C_{23}H_{20}OS$+Na): 367.1127, *found* 367.1132.



6-(1-Cyclohexenyl)-3-methyl-1,3-diphenyl-5-hexyn-1-one. Following the general procedure B, using **1a** (0.30 mmol, 71.4 mg) and 1-(bromoethynyl)cyclohex-1-ene (0.6 mmol, 110 mg) provided 36 mg (35% yield) of the corresponding product as a colorless oil. Column chromatography: silica gel, (hexanes/CH_2Cl_2, 7:3). ^1H NMR (400 MHz, $CDCl_3$): δ 7.92-7.89 (m, 2H), 7.56-7.52 (m, 1H), 7.45-7.39 (m, 3H), 7.22-7.18 (m, 1H), 5.98-5.96 (m, 1H), 3.57 (dd, *J* = 48, 20 Hz, 2H), 2.90 (dd, *J* = 64, 20 Hz, 2H), 2.07-2.03 (m, 5H), 1.65 (s, 3H), 1.64-1.55 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 146.6, 137.9, 133.4, 132.7, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 126.0, 125.8, 125.7, 120.8, 85.2, 84.6, 47.5, 40.5, 32.9, 29.4, 26.2, 25.5, 22.3, 21.5. IR (neat, cm^{-1}): 2285, 1691, 1596, 1446, 1354, 1179, 1029, 946, 799, 697, 689, 663. HRMS *calcd.* for ($C_{25}H_{26}O$+Na): 365.1876, *found* 365.1862.



1,6-Diphenyl-5-hexyn-1-one.[73] Following the general procedure B, using **1h** (0.50 mmol, 74.1 mg) and 1-bromophenylacetylene (1.0 mmol, 181 mg) provided 57 mg (46% yield) of the corresponding product as an orange oil. Column chromatography: silica gel, (hexanes/CH_2Cl_2, 1:1). ^1H NMR (400 MHz, $CDCl_3$): δ 8.04-8.02 (m, 2H), 7.59-7.57 (m, 1H), 7.51-7.47 (m, 1H), 7.43-7.40 (m, 1H), 7.30-7.28 (m, 2H), 3.21 (t, *J* = 7 Hz, 2H), 2.59 (t, *J* = 7 Hz, 2H), 2.13-2.06 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.7, 136.9, 133.0, 131.5, 128.6, 128.2, 128.1, 127.7, 123.8, 89.3, 81.5, 37.3, 23.2, 18.9.

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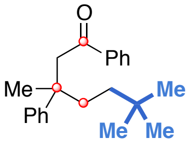
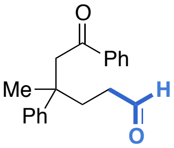
[73] Crandall, J. K.; Ayers, T. A. *Organometallics* **1992**, *11*, 473-477.



3,6,6-trimethyl-1,3-diphenylheptan-1-one. Following the general procedure A, using **1a** (0.35 mmol, 83 mg), Na^{t}BuO (1.10 equiv), Dicyclohexylphosphinobutane (4.0 mol%) and neopentyliodide (0.46 mmol, 61 μL) provided 268 mg (87% yield) of the corresponding product as colorless oil. Column chromatography: silica gel, (hexanes/EtOAc, 15:1). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.81 (dd, *J* = 8.5 Hz; 1.3 Hz, 1H), 7.47-7.14 (m, 8H), 3.32 (dd, *J* = 15.6 Hz; 53.2 Hz, 1H), 1.90 (td, *J* = 12.9, 4.3 Hz, 1H), 1.74 (td, *J* = 12.9, 4.7 Hz, 1H), 1.51 (s, 3H), 1.06 (td, *J* = 12.8, 4.6 Hz, 1H), 0.81 (s, 9H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 199.1, 147.2, 138.4, 132.5, 128.3, 128.0, 127.9, 126.1, 125.6, 77.4, 77.0, 76.6, 50.3, 40.5, 37.7, 37.5, 30.1, 29.3, 24.4. IR (neat, cm^{-1}): 2285, 1691, 1596, 1446, 1354, 1179, 1029, 946, 799, 697, 689, 663. HRMS *calcd.* for ($C_{22}H_{28}O$+Na): 331.2038, *found* 331.2022.

3.6.3 Synthetic application profile



4-methyl-6-oxo-4,6-diphenylhexanal. Following reported procedure[74], borane monohydrate (1.0 M in THF) was charged in a flask under Ar. Cyclohexene (61μL, 0.60 mmol) was added dropwise at 0 °C and the mixture was stirred for 1h. 3-methyl-1,3-diphenylhex-5-yn-1-one (**4a,** 80 mg, 0.30 mmol) in THF was added to the mixture (which turned to clear yellow almost immediately) and the mixture was stirred at room temperature for an additional hour. Thereafter, sodium perborate monohydrate (90 mg, 0.90 mmol) and water (0.3mL) were added and the mixture was stirred at room temperature overnight (the mixture turned colorless). The product was obtained as a colorless oil after column chromatography

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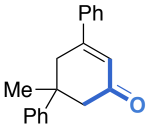
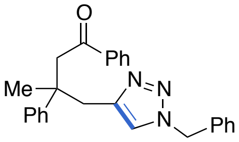
[74] Kabalka, G. W.; Yu, S.; Li, N.-S. *Can. J. Chem.* 1998, **76**, 800.

(Hexanes:EtOAc; 15:1, R_f=0.4) in 58% yield (50 mg). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.90-7.87 (m, 2H), 7.54-7.20 (m, 8H), 3.56 (dd, *J* = 16.92 Hz; 13.51 Hz, 2H), 2.87 (ddd, *J* = 2.66 Hz; 16.64 Hz; 30.09 Hz, 2H), 2.02 (s, 2H), 1.64 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6, 198.2, 146.2, 137.8, 132.8, 128.4, 128.2, 127.9, 126.2, 125.6, 47.5, 40.0, 34.2, 31.6, 26.2. IR (neat, cm^{-1}): 3005, 2928, 1781, 1658, 1547, 1475, 1312, 1103, 937, 781, 435. HRMS *calcd.* for ($C_{19}H_{20}O_2$+Na): 303.1361, *found* 303.1345.



1'-methyl-1',6'-dihydro-[1,1':3',1''-terphenyl]-5'(2'*H*)-one. Following reported procedure[75], $AuCl_3$ (4.5 mg, 5.0 mol%) and AgOTf (11.6 mg, 15 mol%) were charged in a schlenk inside of a glovebox. PhMe (1.5mL) and 3-methyl-1,3-diphenylhex-5-yn-1-one (**4a,** 80 mg, 0.30 mmol) were added under Ar and the mixture was stirred at room temperature outside of the glovebox overnight. The product was obtained as a yellowish oil after column chromatography (Hexanes:EtOAc; 15:1, R_f=0.4) in 99% yield (78mg). ^{1}H-NMR: (300 MHz, $CDCl_3$) δ 7.55-7.26 (m, 10H), 6.39 (s, 1H), 3.33-3.27 (m, 1H), 3.07-2.98 (m, 2H), 2.73-2.68 (m, 1H), 1.48 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.1, 152.7, 145.2, 137.4, 130.0, 128.8, 128.6, 127.2, 126.5, 126.2, 125.4, 61.3, 49.8, 29.6, 25.5. IR (neat, cm^{-1}): 2929, 1782, 1701, 1396, 1452, 1214, 1102, 1008, 835, 780, 653. HRMS *calcd.* for ($C_{19}H_{18}O$+Na): 285.1256, *found* 285.1248.



1,2,2-triphenyl-6-(triisopropylsilyl)hex-5-yn-1-one. 3-methyl-1,3-diphenylhex-5-yn-1-one (**4a,** 77 mg, 0.29 mmol) was mixed with sodium ascorbate (12 mg, 0.06 mmol), $CuSO_4$ (1.45 mg, 0.006 mmol) and benzyl azide (36 μL) in tBuOH/H_2O (1:1; 3 mL). The mixture was stirred at room temperature for 48h. The product was

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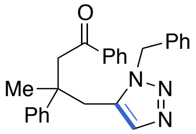
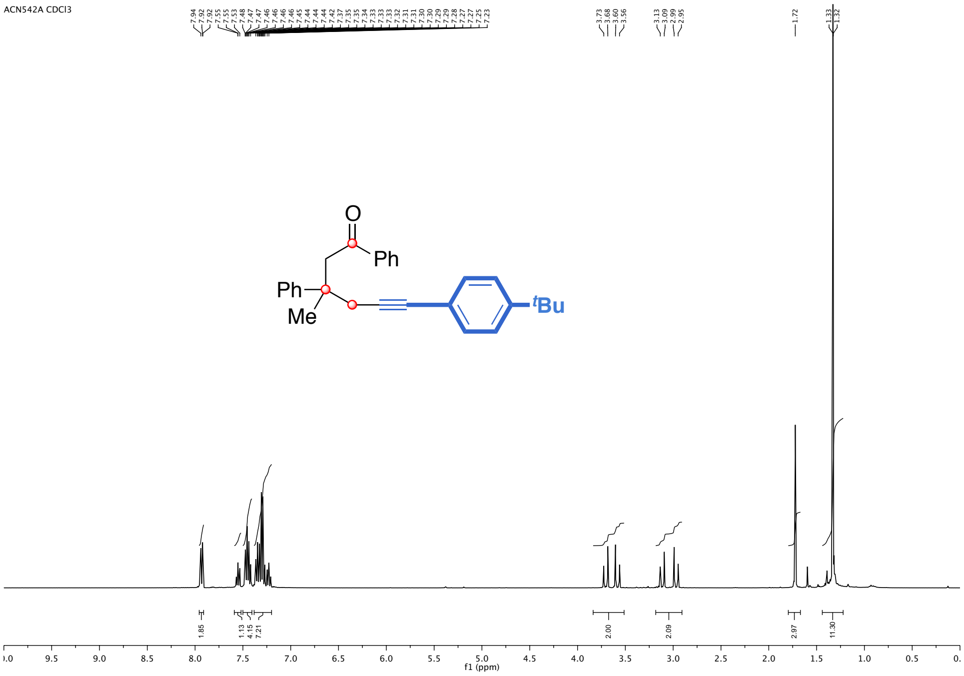
[75] Jin, T.; Yamamoto, Y. *Org. Lett.* 2007, **9**, 5259.

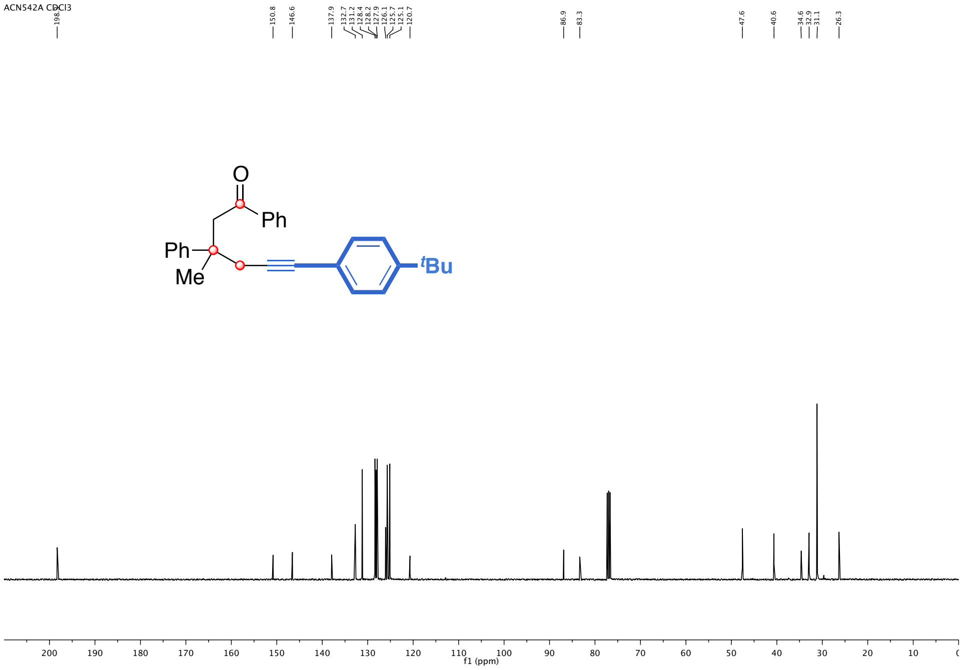
obtained as a thick yellowish oil after column chromatography (Hexanes:EtOAc; 1:1) in 96% yield (110 mg). ^{1}H-NMR: (300 MHz, $CDCl_3$) δ 7.87-7.84 (m, 2H), 7.50-7.05 (m, 13H), 6.49 (bs, 1H), 5.34 (s, 2H), 3.65-3.14 (m, 4H), 1.56 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 146.2, 137.8, 134.7, 132.6, 128.8, 128.3, 128.3, 127.9, 127.8, 127.6, 125.9, 125.8, 53.7, 48.1, 40.8, 39.7, 24.9. IR (neat, cm^{-1}): 3004, 1750,1712, 1438, 1419, 1357, 1220, 1091, 902, 784, 529, 426. HRMS *calcd.* for ($C_{26}H_{27}ON_3$+Na): 420.2052, *found* 420.2035.

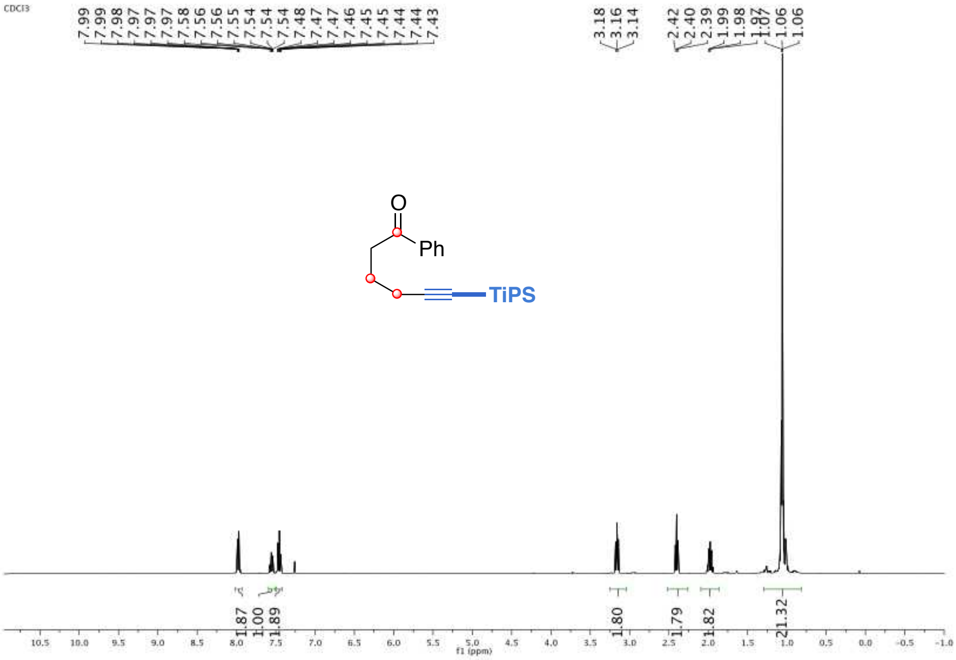


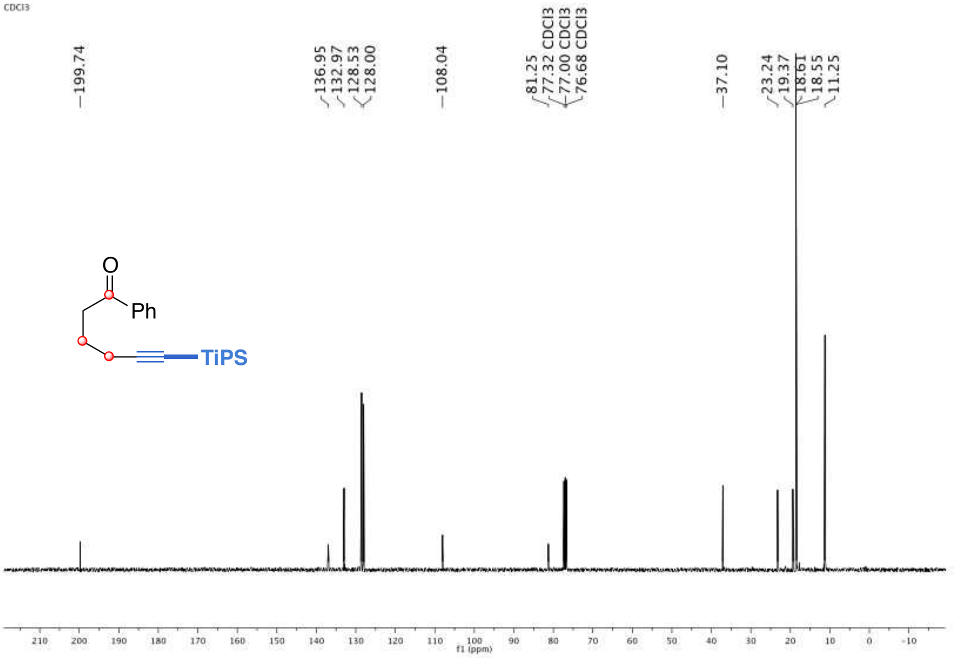
1,2,2-triphenyl-6-(triisopropylsilyl)hex-5-yn-1-one. To a schlenk charged with 3-methyl-1,3-diphenylhex-5-yn-1-one (**4a,** 100 mg, 0.38 mmol) was added Cp*RuCODCl (2.9 mg, 2.0 mol%) under Argon atmospheres. PhMe was then added (3 mL) as the solvent. After stirring at room temperature for 30 minutes, a solution of benzyl azide (47 µL) in PhMe (0.20 mL) was added to the flask. The mixture was stirred at room temperature for 14 h. The solvent was evaporated and the product was obtained after column chromatography (Hexanes:EtOAc; 1:1) as a colorless oil in 85% yield (127 mg). ^{1}H-NMR: (300 MHz, $CDCl_3$) δ 7.87-7.84 (m, 2H), 7.55-7.20 (m, 11H), 7.06-6.98 (m, 3H), 5.09 (dd, *J* = 15.69 Hz; 37.12 Hz 2H), 3.56-3.50 (dd, *J* = 16.48 Hz, 1H), 3.25-3.10 (m, 3H), 1.46 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.3, 145.5, 137.7, 135.2, 134.2, 133.6, 133.1, 128.8, 128.6, 128.5, 128.0, 127.8, 126.9, 126.8, 125.7, 51.0, 47.2, 40.9, 35.4, 24.5. IR (neat, cm^{-1}): 3003, 1750, 1712, 1438, 1418, 1358, 1220, 1091, 901, 785, 529, 438. HRMS *calcd.* for ($C_{26}H_{27}ON_3$+Na): 420.2052, *found* 420.2040.

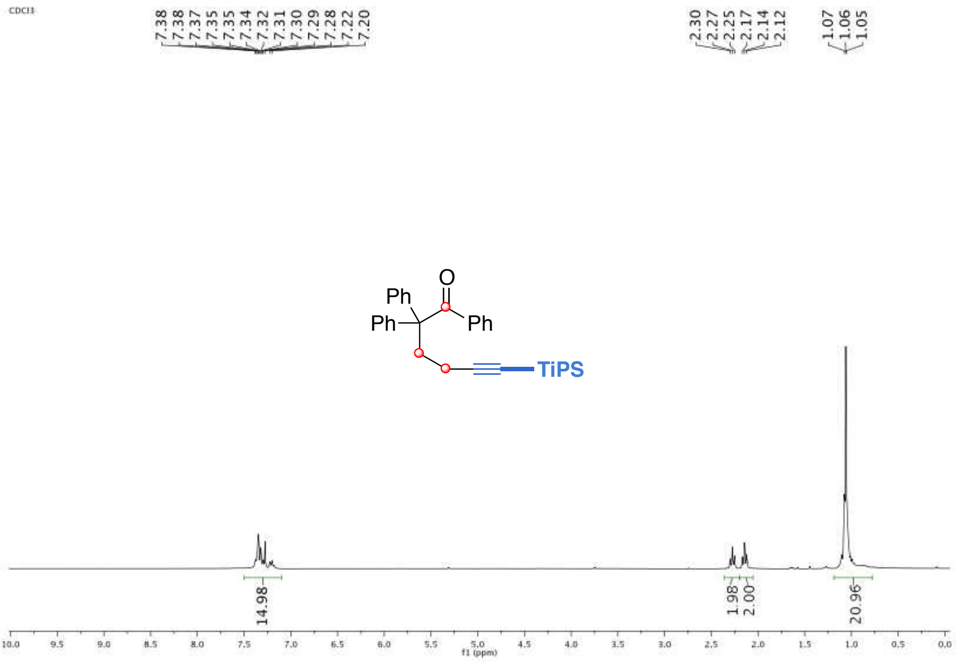
3.7 Selected examples of NMR spectra

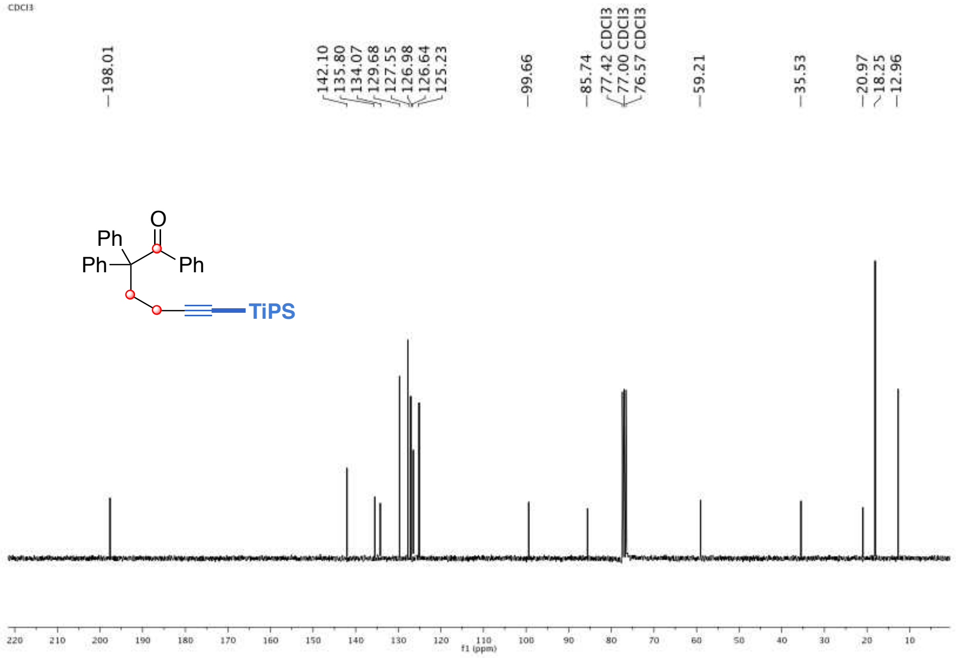


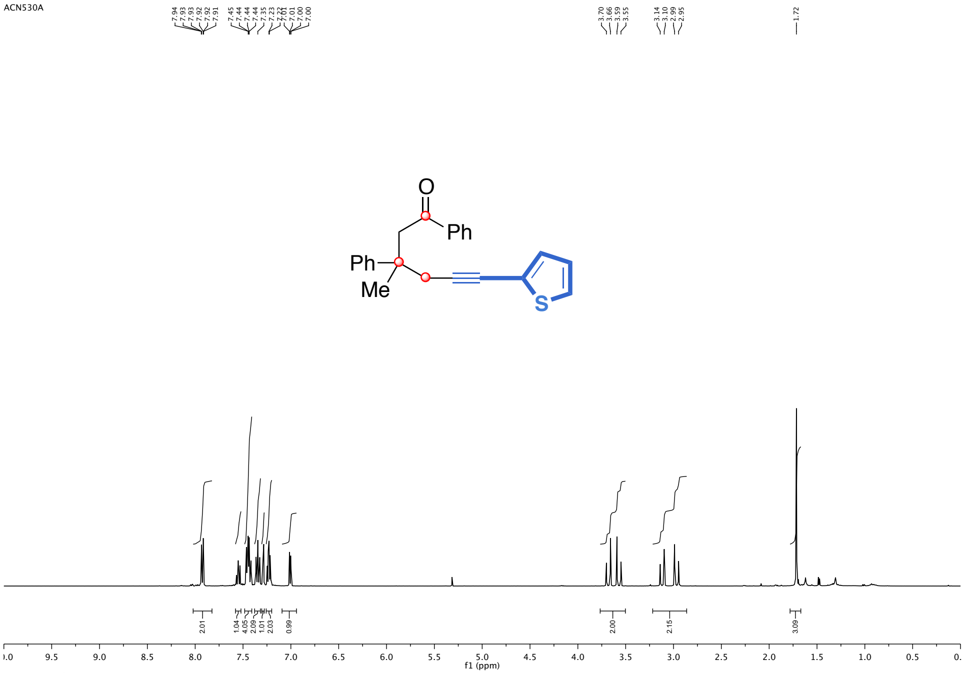


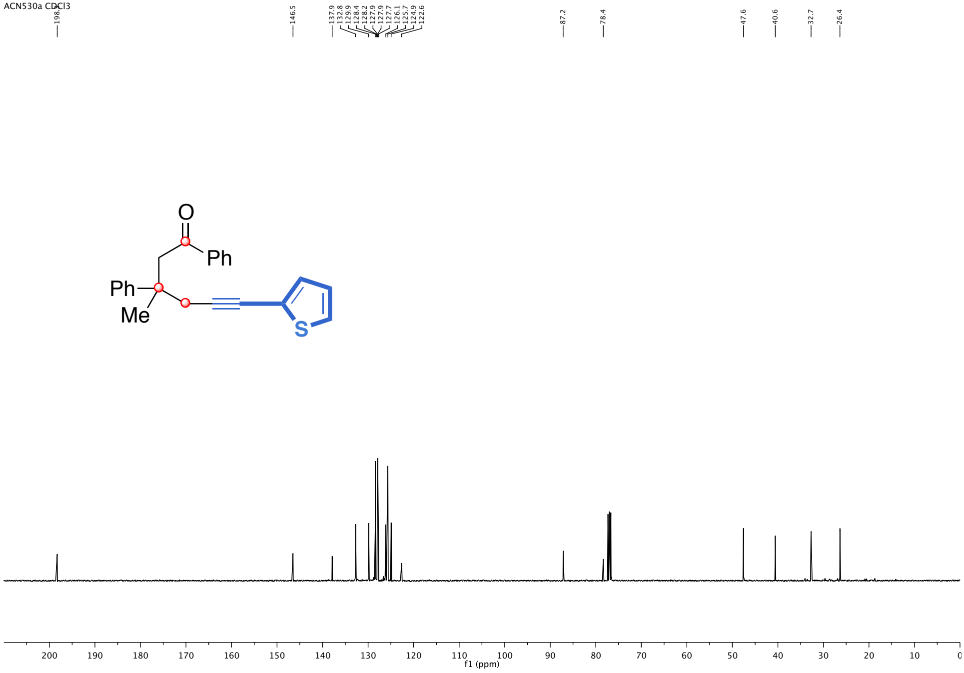

CDCl3
7.99
7.99
7.98
7.97
7.97
7.97
7.58
7.56
7.56
7.55
7.54
7.54
7.54
7.48
7.47
7.47
7.46
7.45
7.45
7.44
7.44
7.43
3.18
3.16
3.14
2.42
2.40
2.39
1.99
1.98
1.97
1.07
1.06
1.06
O
Ph
TiPS
1.87
1.00
1.89
1.80
1.79
1.82
21.32
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


CDCl3
199.74
136.95
132.97
128.53
128.00
108.04
81.25
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
37.10
23.24
19.37
18.61
18.55
11.25
O
Ph
TiPS
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


CDCl3
7.38
7.38
7.37
7.35
7.35
7.34
7.32
7.31
7.30
7.29
7.28
7.22
7.20
2.30
2.27
2.25
2.17
2.14
2.12
1.07
1.06
1.05
O
Ph
Ph
Ph
TiPS
14.98
1.98
2.00
20.96
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


CDCl3
198.01
142.10
135.80
134.07
129.68
127.55
126.98
126.64
125.23
99.66
85.74
77.42 CDCl3
77.00 CDCl3
76.57 CDCl3
59.21
35.53
20.97
18.25
12.96
O
Ph
Ph
Ph
TiPS
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


ACN530A
7.94
7.93
7.93
7.92
7.92
7.91
7.45
7.44
7.44
7.44
7.35
7.23
7.22
7.01
7.01
7.00
7.00
3.70
3.66
3.59
3.55
3.14
3.10
2.99
2.95
1.72
O
Ph
Ph
Me
S
2.01
1.04
4.05
2.09
1.01
2.03
0.99
2.00
2.15
3.09
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.
f1 (ppm)


ACN530a CDCl3
198.4
146.5
137.9
132.8
129.9
128.4
128.2
127.9
127.9
127.7
126.1
125.7
124.9
122.6
87.2
78.4
47.6
40.6
32.7
26.4
O
Ph
Ph
Me
S
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

CHAPTER 4

Ni-CATALYZED INTERMOLECULAR [4+4] AND [4+2] CYCLOADDITION OF BENZOCYCLOBUTENONES via SELECTIVE C-C BOND-CLEAVAGE

4.1 Objectives

The objectives of this chapter are the following:

- To develop a new methodology for the synthesis of unsaturated β-tetralones via a catalytic intermolecular [4+2] cycloaddition of benzocyclobutenones via C-C cleavage.
- To develop a new catalytic intermolecular [4+4] cycloaddition of benzocyclobutenones via C-C cleavage.
- To further extend these methodologies by initiating the reaction with 2-halo-α-arylaldehydes and thus making the benzocyclobutenones in situ.

4.2 Benzocyclobutenones: versatile building blocks in organic synthesis

In the last few decades, the interest of organic chemists in benzocyclobutenones has increased rapidly. The use of such molecules has evolved from a mere curiosity to indispensable tools for building up a high degree of molecular complexity.[76] Benzocyclobutenones are a fascinating class of four-membered ring ketones possessing a particularly high ring strain that is responsible for their great reactivity. The presence of a fused ring makes benzocyclobutenones considerably more reactive than their corresponding cyclobutanones analogues (Figure 4.1).[77] Unlike cyclobutanones, benzocyclobutenones possess three distinctive and highly reactive C-C bonds that are amenable for functionalization, thus setting up the stage for the design of stereoselectivity approaches.

Figure 4.1.

Although benzocyclobutenones can potentially be used for catalytic C-C bond-cleavage, the ring strain of benzocyclobutenones remarkably influences the electrophilicity of the carbonyl group, thus, making it more prone to nucleophilic attack than regular aliphatic or other cyclic ketones (Figure 4.2). Furthermore, the high ring strain of benzocyclobutenoens can also allow for a thermal conrotatory *retro*-4-π cyclization leading to vinyl-ketene type intermediates (**141**, Figure 4.2) that can participate in a multiple number of synthetic transformations.[78]

---

[76] a) *Small Ring Compounds in Organic Synthesis*; de Meijere, A. Springer: Berlin, *Top. Curr. Chem.*, **2000**, 1-230. b) *Strained Organic Molecules* (Eds.: A. Greenberg, J. F. Liebman), Academic Press, New York, **1978**.

[77] For reviews dealing with other four-membered rings, see: (a) Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. *Angew. Chem. Int. Ed.* **2011**, *50*, 7740. (b) Sadana, A. K.; Saini, R. K.; Billups, W. E. *Chem. Rev.* **2003**, *103*, 1539.

[78] For a review on benzocyclobutenones, see: Flores-Gaspar, A.; Martin, R. *Synthesis*. **2013**, *45*, 563.

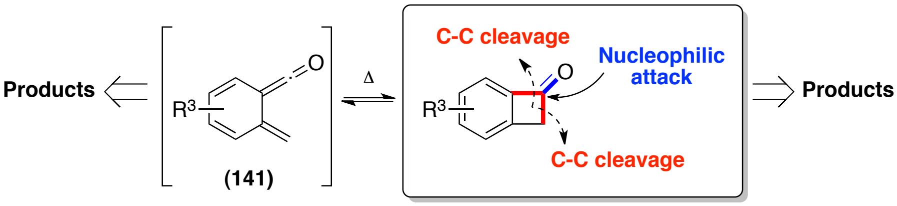

Products
R3
O
(141)
Δ
C-C cleavage
Nucleophilic attack
R3
O
C-C cleavage
Products

Figure 4.2.

4.3 Synthetic application of benzocyclobutenones

4.3.1 Synthesis of polycyclic compounds via o-quinone methides

As mentioned in the previous section, benzocyclobutenones can undergo thermal conrotatory *retro* 4π-cyclization giving access to vinyl-ketene-type intermediates that can react further in cycloaddition reactions (Figure 4.3). However, high temperatures are usually required for such transformations, lowering down the application profile of these methods (Figure 4.3, bottom pathway). In order to avoid the high temperatures, the *retro* 4π-cyclization can be performed at low temperatures via the intermediacy of oxy-anions (Figure 4.3, top pathway).

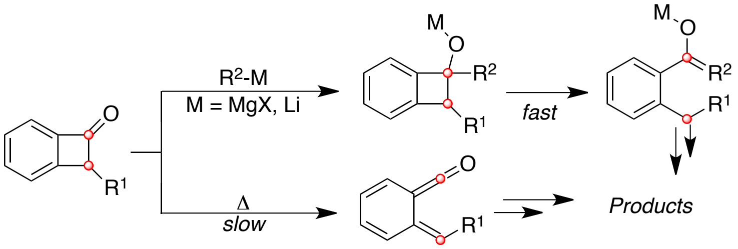
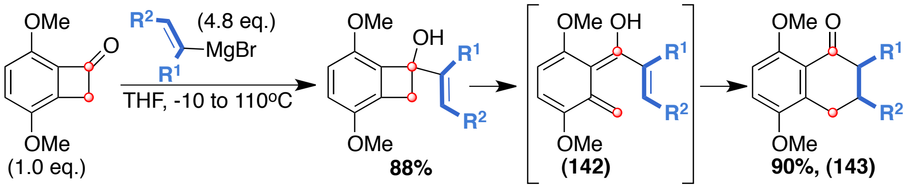


Figure 4.3

4.3.1.1 Synthesis of α-tetralones

In 1996, Wardleworth et al. described, for the first time, the thermal conversion of in situ generated alkenylbenzocyclobutanol into α-tetralone derivatives from benzocyclobutenones (Figure 4.4).[79] The formation of the key intermediate (*o*-quinone methide, **142**), is followed by a disrotatory 4π-electrocyclization, giving rise to the enol derivative that would furnish the corresponding substituted α-tetralone (**143**).



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[79] Hickman, D. N.; Hodgetts, K. J.; Mackman, P. S.; Wallace, T. W.; Wardleworth, J. M. *Tetrahedron*. **1996**, *52*, 2235-2260.

Figure 4.4

4.3.1.2 Synthesis of benzo[n]annulenes

Aguilar et al. recently reported a methodology that directly converts benzocyclobutenones into benzo[7]annulenes via an unprecedented [4+3]-cycloaddition in which the initially generated quinone methides (**144**) act as a four-carbon synthon (Figure 4.5).[80] It was also observed that the solvent and the nature of the substituents predicted the selectivity pattern for preparing either benzocycloheptene ketals (**145**) or benzocycloheptenones (**146**), respectively.

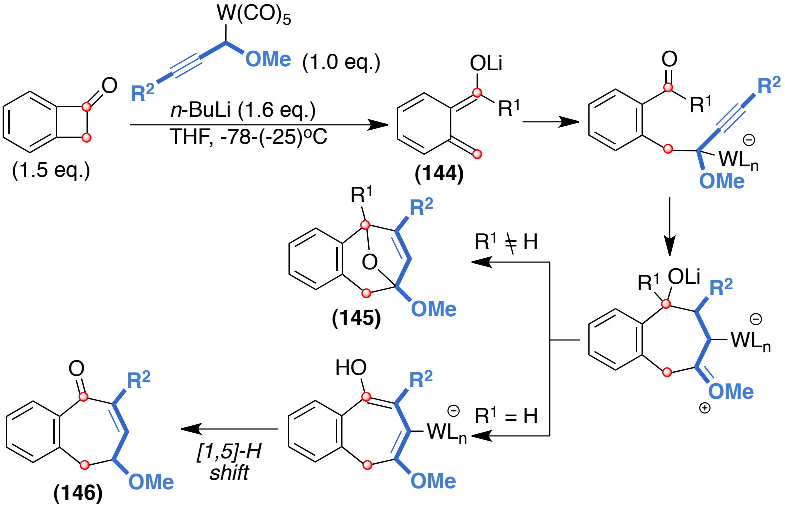


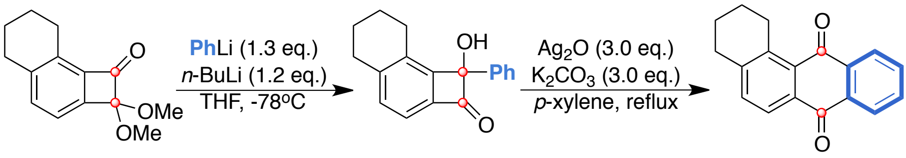
Figure 4.5

4.3.1.3 Synthesis of anthraquinones

Benzocyclobutenones can also be employed in the synthesis of anthraquinones (Figure 4.6).[81] The method is initiated by the addition of aryl lithium species to the benzocyclobutenone motif (**147**). Later, hydrolysis of the acetal, thermal *retro*-4π cyclization, 6π-electrocyclization and a final oxidation of the hydroquinone afford the expected anthraquinone (**148**).

---

[80] Garcia-Garcia, P.; Novillo, C.; Fernandez-Rodriguez, M. A.; Aguilar, E. *Chem. Eur. J.* **2011**, *17*, 564-571.
[81] Tiedemann, R.; Heilman, M. J.; Moore, H. W. *J. Org. Chem.* **1999**, *64*, 2170-2171.



(147)

(148)

Figure 4.6

4.3.1.4 Synthesis of naphthalene derivatives

Using the same principle as the one for the synthesis of α-tetralones, different naphthalene derivatives (Figure 4.7) can be formed via the addition of an organometallic reagent that facilitates the formation of an *o*-quinone methide that subsequently triggers a *disrotatory* 6π-electrocyclization giving rise to 1-naphthol derivatives. The method is, however, limited to 1,3-disubstituted naphtols, since allenyl or propargyl organometallic species are used.[82]

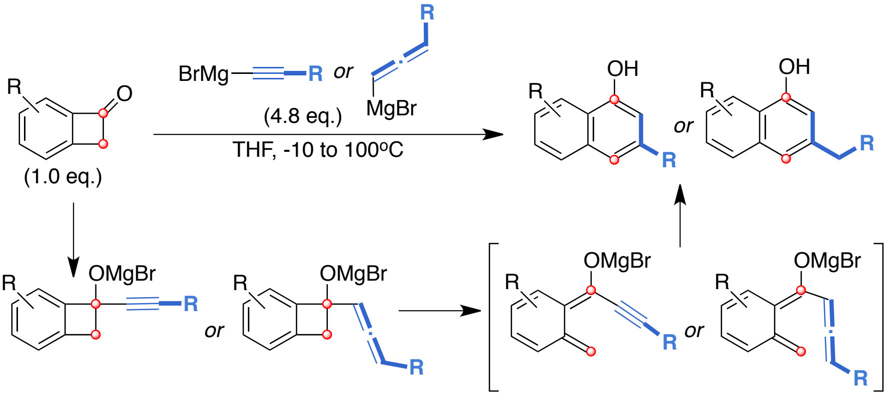


Figure 4.7

4.3.1.5 Synthesis of benzodiazepines

As previously stated, benzocyclobutenones can function as building blocks for the construction of carbocycles, but others have demonstrated that the versatility of benzocyclobutenones goes even further. In 2006, Nemoto et al. demonstrated that benzocyclobutenones could also participate in electrocyclization reactions for the

---

[82] (a) Bungard, C. J.; Morris, J. C. *Synthesis* **2001**, *5*, 741-744. (b) Bungard, C. J.; Morris, J. C. *Org. Chem.* **2002**, *67*, 2361-2364.

synthesis of benzodiazepines through the in situ generation of *o*-quinone methides (Figure 4.8).[83] The sequence is initiated by a nucleophilic attack of a diazomethylene anion that rapidly forms an *o*-quinone methide via *retro* 4π-cyclization, setting the stage for the formation of the benzodiazepine backbone (Figure 4.8).

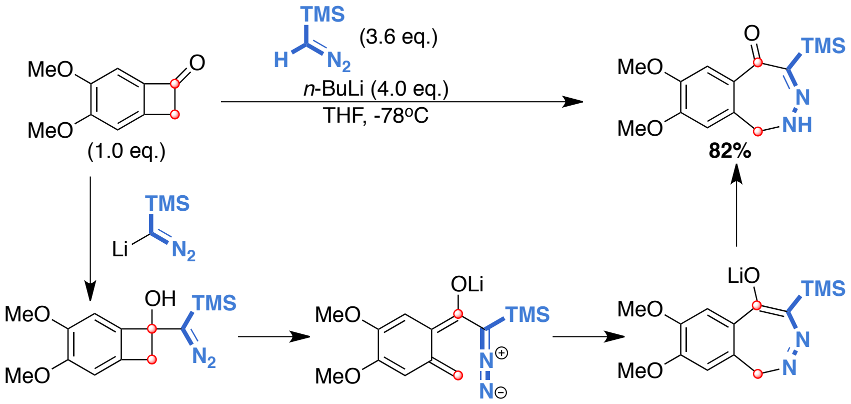


Figure 4.8

4.3.2 Synthesis of fused rings via non-electrocyclization techniques via [4+2] cycloaddition

Recently, Murakami reported an interesting Rh-catalyzed [4+2] cycloaddition event using benzocyclobutenols as substrates (Figure 4.9).[84] The reaction proceeded via the formation of alkoxyrhodium species that undergo regioselective β-carbon elimination, alkyne insertion and intramolecular 1,2-addition across the C=O bond to give dehydronaphtalene derivatives (Figure 4.9).

---

[83] Matsuya, Y.; Ohsawa, N.; Nemoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 13072-13073.

[84] (a) Ishida, N.; Sawano, S.; Masuda, Y.; Murakami, M. *J. Am. Chem. Soc.* **2012**, *134*, 17502-17504. (b) Aïsa, C. *Synthesis*. **2011**, 3389. (c) Murakami, M.; Makino, M.; Ashida, S.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1315.

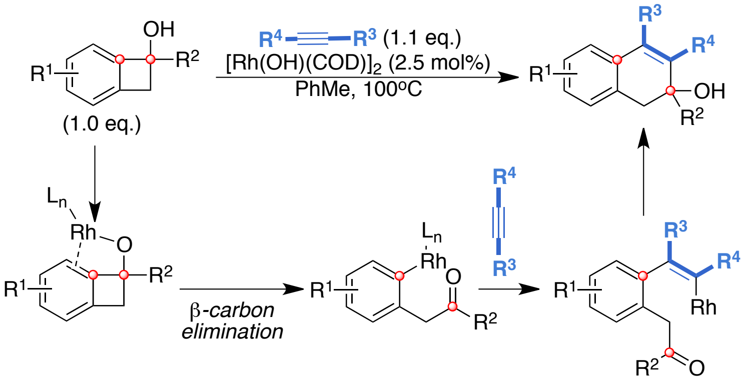


Figure 4.9

In 2012, Dong described an intramolecular Rh-catalyzed carboacylation of olefins in benzocyclobutenone giving access to polyfused ring systems (Figure 4.10).[85 a] Similarly to Murakami's approach, the method involved a regioselective β-carbon elimination that generates a stable C(sp^2)-Rh intermediate (Figure 4.10) that further coordinates with the pending alkene, triggering a migratory insertion step to the final product (**149**, Figure 4.10) via reductive elimination. Very recently, an enantioselective version of this reaction has been reported in the literature.[85b]

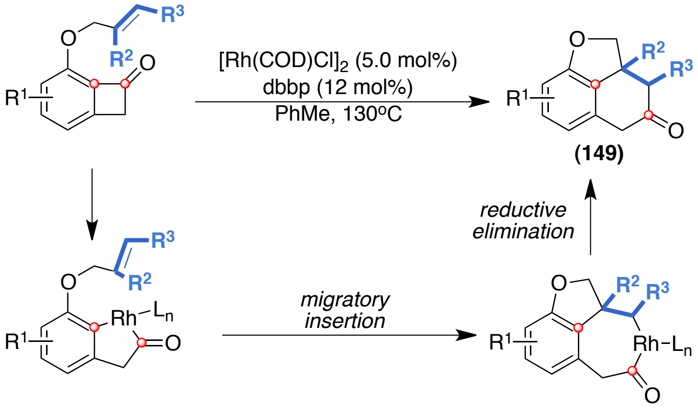


Figure 4.10

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[85] (a) Xu, T.; Dong, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 7567-7571. (b) Xu, T.; Min Ko, H.; Dong, G. *J. Am. Chem. Soc.* **2012**, *134*, 20005-20008.

4.4 Results and discussions

As mentioned in the introduction, the selective cleavage of C-C bonds in the benzocyclobutenone backbones can be particularly difficult. Prompted by these challenges, we wondered whether a catalytic [4+2] or [4+4] intermolecular cycloaddition would be within reach under appropriate reaction conditions in the presence of alkynes or dienes (Figure 4.11). Unlike related intramolecular approaches, our pathway would offer a highly divergent approach to β-tetralones and benzocyclooctanones without earlier manipulations of the benzocyclobutenone motif.[86]

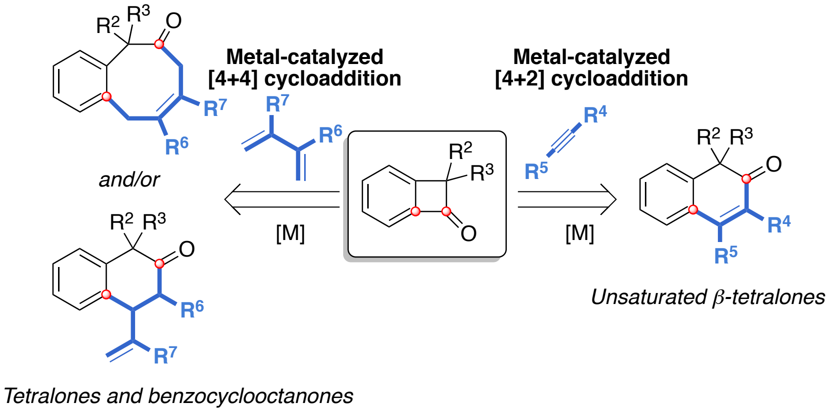


Figure 4.11

The interest for promoting a [4+n]-cycloaddition reactions of benzocyclobutenones arises from the expertise of our research group when preparing such compounds. In 2010, our group reported a Pd-catalyzed C-H bond functionalization en route to benzocyclobutenones; interestingly, the nature of the ligand decided the selectivity pattern, allowing for the synthesis of styrenes or benzocyclobutenones at will.[87] We

---

[86] (a) Khan, H. A.; Kou, K. G. M.; Dong, V. M. *Chem. Sci.* **2011**, *2*, 407-410. (b) Coulter, M. M.; Dornan, P. K.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 6932-6933. (c) Shen, Z.; Khan, H.; Dong, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 2916-2917. (d) Rickert, A.; Krombach, V.; Hamers, O.; Zorn, H.; Maison, W. *Green. Chem.* **2012**, *14*, 639-344.

[87] (a) Álvarez-Bercedo, P.; Flores-Gaspar, A.; Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2010**, *132*, 466-467. (b) Flores-Gaspar, A.; Gutiérrez-Bonet, Á.; Martin, R. *Org. Lett.* **2012**, *14*, 5234-5237. (c) Flores-Gaspar, A.; Martin, R. *Adv. Synth. Cat.* **2011**, *8*, 1223-1228. (d) Flores-Gaspar, A.; Martin, R. *Org. Synth.* **2013**, *45*, 563-580.

were also intrigued by the work of Murakami,[35.36] Aïssa[34] and Louie,[37] where they report the nickel-catalyzed cycloaddition reaction with alkynes via C-C bond cleavage (Figure 1.23).

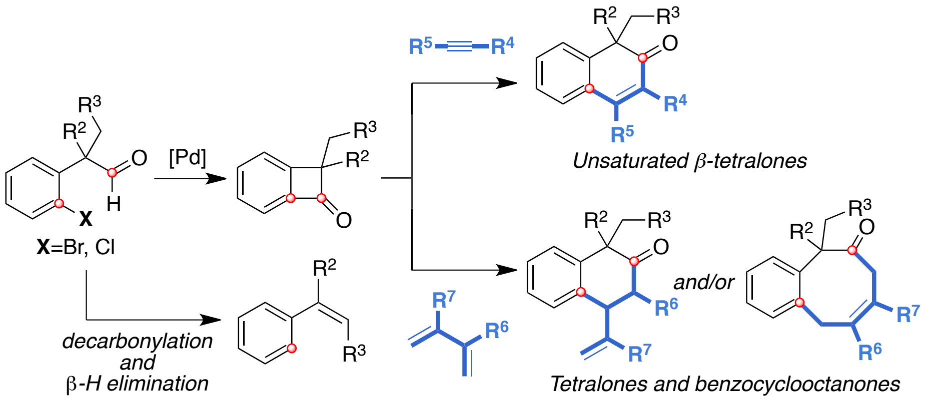


Figure 4.12

We hypothesized that the reaction would consist of an initial coordination of a low-valent metal species to the carbonyl group on the benzocyclobutenone and the alkyne motif (**I**, Figure 4.13). Taking into consideration the high electrophilicity of the carbonyl group on the high strain four-membered ring, we speculate that oxidative cyclization might give rise to **II** (Figure 4.13) that subsequently will evolve via β-carbon elimination to **III** (Figure 4.13) and a final reductive elimination, thus delivering the final product while recovering back the active propagating species.

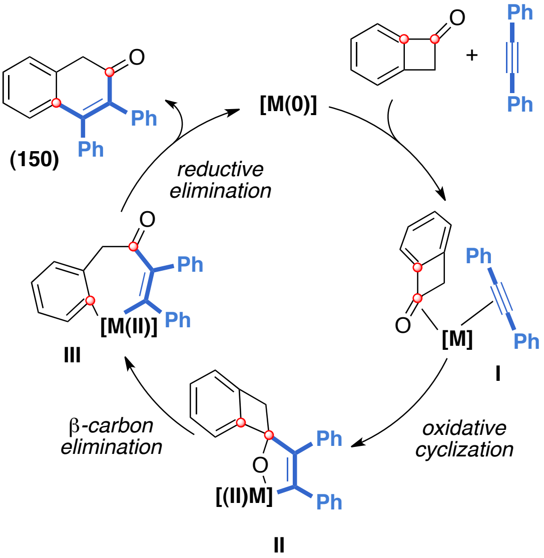


Figure 4.13.

In analogy, we propose that the [4+4] cycloaddition might follow a similar sequence of events. In this case, however, the reaction would be initiated by a coordination of a low-valent metal species to the carbonyl group on the benzocyclobutanone as well as a diene backbone (**IV**, Figure 4.14). Oxidative cyclization, β-carbon elimination and a final reductive elimination would result in the formation of eight-membered rings. Depending on the reductive elimination step, six-membered rings **152** could potentially also be obtained.[88]

---

[88] For mechanistic discussions, see: (a) Nishimura, A.; Ohashi, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2012**, *134*, 15692-15695. (b) Yamasaki, R.; Ohashi, M.; Maeda, K.; Kitamura, T.; Nakagawa, M.; Kato, K.; Fujita, T.; Kamura, R.; Kinoshita, K.; Masu, H.; Azumaya, I.; Ogoshi, S.; Saito, S. *Chem. Eur. J.* **2013**, *19*, 3415-3425. (c) Hoshimoto, Y.; Hayashi, Y.; Suzuki, H.; Ohashi, M.; Ogoshi, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 10812-10815.

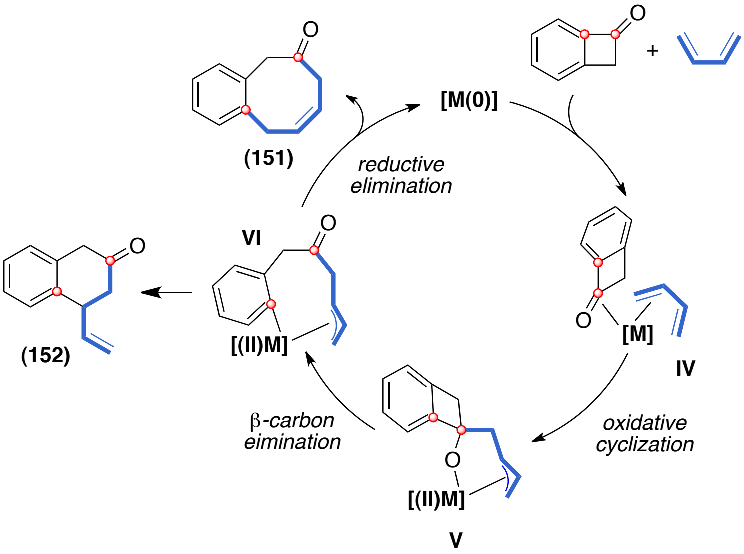


Figure 4.14

4.4.1 Optimization of the reaction conditions for the synthesis of unsaturated β-tetralones and benzocyclooctanones

Among all of the metals that are known to actively participate in catalytic C-C bond cleavage processes, Pd, Rh and Ni pre-catalysts undoubtedly play a dominant role. We chose **153** (Figure 4.15) as our model substrate, since it could be prepared in multi-gram scale in essentially three steps from commercially available 2-(2-bromophenyl)acetonitrile following up an approach previously described in our research group.[87] Thus, a simple deprotonation of 2-(2-bromophenyl)acetonitrile in the presence of NaHMDS in THF and further treatment with an excess of *n*-propyl iodide provided **154** (Figure 4.15) in essentially quantitative yield. With no need for purification, the crude reaction was treated with DIBAL-H in DCM at -78ºC to afford aldehyde **155** (Figure 4.15) in 75% overall yield in essentially two-step procedure from 2-bromophenylacetonitrile. The aldehyde was reacted intramolecularly in the presence of $Pd(OAc)_2$ to give access to the corresponding benzocyclobutenone in 70% yield.[87]

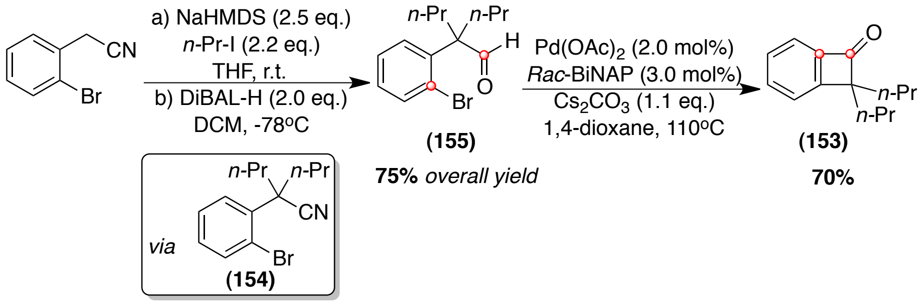
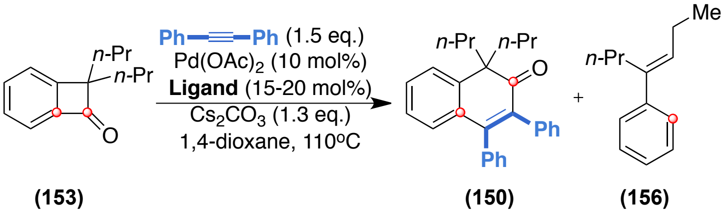


Figure 4.15

4.4.1.1 Optimization of the reaction conditions for the synthesis of unsaturated β-tetralones

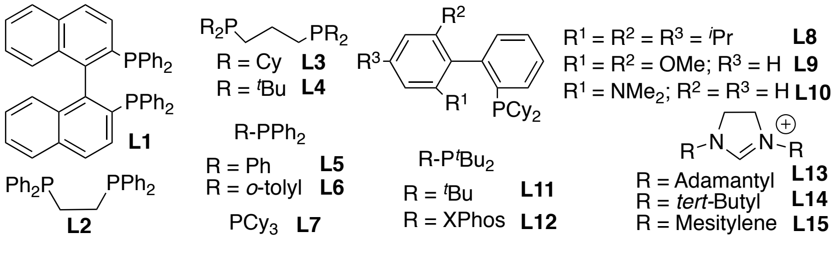
With substantial amounts of **153** (Figure 4.15) in hand, a variety of experimental variables such as metal, ligand, base, solvent, ligand to metal ratio and temperatures were systematically examined. Taking into account the excellent results of chapters 2 and 3, we started our screening with Pd catalysts and using diphenylacetylene as substrate.[34-37] Despite the extensive experimental screening of all reaction parameters, we did not detect even traces of **150**. In all cases analyzed, we found that styrene **156** was obtained as side product. It is worth mentioning that such side-products have previously been observed by Larock and our group when employing 2-halophenylaldehyde derivatives.[87] In this case, however, we observed such products deriving from **153** (Tables 1-5). At present we believe such reaction outcome might be explained by selective cleavage of the less-accessible C-C bond followed by β-hydride elimination and CO extrusion.

Table 1. Screening of $Pd(OAc)_2$ with different ligands



Entry	Ligand	Conversion (%)	Yield (%)	
			150	156

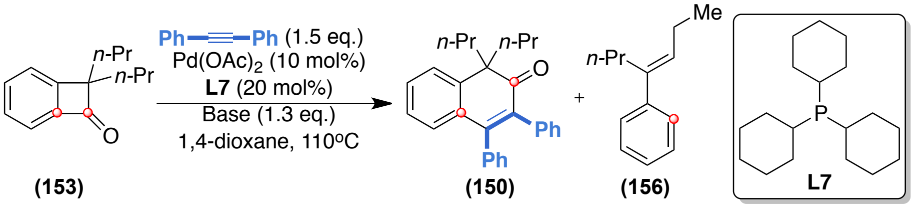
Bidentate phosphine ligands				
1	**L1**	23	0	23
2	**L2**	20	0	20
3	**L3**	58	0	58
4	**L4**	9	0	9
Aryl monodentate phosphine ligands				
5	**L5**	0	0	0
6	**L6**	6	0	6
Aliphatic monodentate phosphine ligands				
7	**L7**	45	0	45
8	**L8**	24	0	24
9	**L9**	24	0	24
10	**L10**	20	0	20
tBu monodentate phosphine ligands				
11	**L11**	3	0	3
12	**L12**	6	0	6
N-heterocyclic carbenes				
13	**L13**	0	0	0
14	**L14**	0	0	0
15	**L15**	54	0	54
16	**No ligand**	0	0	0



Reaction conditions: [a] **153** (0.29 mmol), $Pd(OAc)_2$ (10 mol%), Ligand (15-20 mol%), Cs_2CO_3 (1.3 eq., 0.34 mmol), 1,4-dioxane (0.15M) at 110°C for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

Subsequently, we set out to investigate the effect of the base on the formation of the styrene since we hypothesized that with weaker bases, the formation of the styrene was going to be less feasible (Table 2). We decided to carry on the screenings using tricyclohexyl phosphine as ligand, assuming that an electron-rich ligand might facilitate the cleavage of C-C bonds, the oxidative cyclization step and the final reductive elimination.

Table 2. Screening of different bases

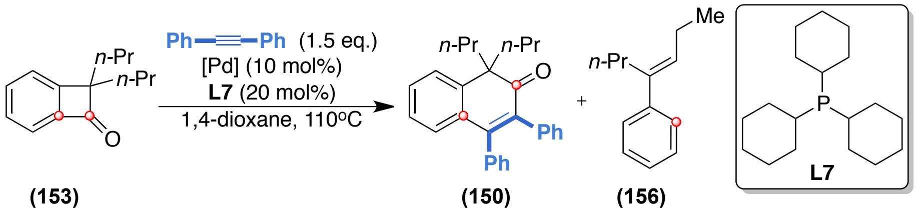


Entry	Base	Conversion (%)	Yield (%)	
			150	156
1	KO^tBu	99[d]	0	0
2	LiO^tBu	0	0	0
3	NaO^tBu	72	0	72
4	KH_2PO_4	0	0	0
5	K_3PO_4	44	0	44
6	Na_2HPO_4	6	0	6
7	Cs_2CO_3	45	0	45
8	Na_2CO_3	3	0	3
9	K_2CO_3	7	0	7
10	$CaCO_3$	7	0	7
11	$KHCO_3$	33	0	33
12	LiOAc	13	0	13
13	KOH	78	0	78
14	CsOPiv	34	0	34
15	No base	0	0	0

Reaction conditions: [a] **153** (0.29 mmol), $Pd(OAc)_2$ (10 mol%), **L7** (20 mol%), base (1.3 eq., 0.34 mmol), 1,4-dioxane (0.15M) at 110ºC for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

As shown in Table 2, however, we observed that in the presence of base decarbonylation and β-hydride elimination steps were kinetically more favored. Thus, we decided to exclude the presence of base in the reaction media and initiate the screening by trying a variety of Pd(II) pre-catalysts (Table 3).

Table 3. Screening of different palladium(II) pre-catalysts

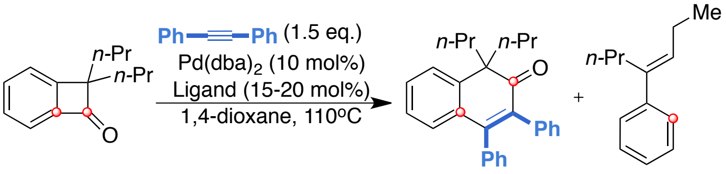


Entry	[Pd]	Conversion (%)	Yield (%)	
			150	156
1	PdI_2	0	0	0
2	$PdBr_2$	0	0	0
3	$PdCl_2$	0	0	0
4	$Pd(OTf)_2$	1	0	1
5	$Pd(OPiv)_2$	3	0	3
6	$Pd(acac)_2$	10	0	10
7	*Trans*-$[(PPh_3)_2PdCl_2]$	0	0	0
8	$Pd(COD)Cl_2$	0	0	0
9	$Pd(TMEDA)Cl_2$	0	0	0
10	$Pd(BnCN)Cl_2$	0	0	0
11	$Pd(MeCN)Cl_2$	0	0	0
12	$[Pd(cinnamyl)Cl]_2$	5	0	5
13	*Trans*-$[(SMe_2)PdCl_2]$	0	0	0
14	$[Pd(1\text{-metallyl})Cl_2]_2$	0	0	0
15	$[Pd(2\text{-metallyl})Cl_2]_2$	2	0	2

Reaction conditions: [a] **153** (0.29 mmol), [Pd] (10 mol%), **L7** (20 mol%), 1,4-dioxane (0.15M) at 110ºC for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

Although Pd(II) salts are more appropriate in catalytic cross-coupling reactions, the reduction of Pd(II) to Pd(0) might be, in some cases, troublesome. Therefore, we continued our screening with $Pd(dba)_2$ and the effect of the ligand backbone was systematically analyzed. Unfortunately, we observed little conversion, but in none of these cases we detected **150** in the crude mixtures. Interestingly, the use of simple PPh_3 allowed for obtaining **156** in 70% GC yield.

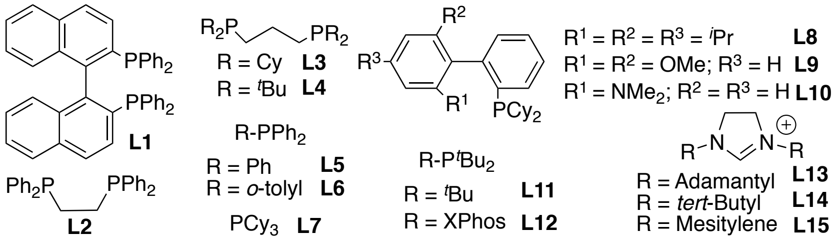
Table 4. Screening of $Pd(dba)_2$ with different ligands



(153) **(150)** **(156)**

Entry	Ligand	Conversion (%)	Yield (%)	
			150	156
		Bidentate phosphine ligands		
1	L1	5	0	5
2	L2	20	0	20
3	L3	0	0	0
4	L4	0	0	0
		Aryl monodentate phosphine ligands		
5	L5	70	0	70
6	L6	2	0	2
		Aliphatic monodentate phosphine ligands		
7	L7	3	0	3
8	L8	0	0	0
9	L9	1	0	1
10	L10	1	0	1
		tBu monodentate phosphine ligands		
11	L11	0	0	0
12	L12	0	0	0

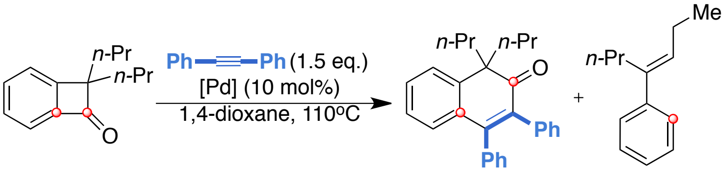
		N-heterocyclic carbenes		
13	**L13**	0	0	0
14	**L14**	0	0	0
15	**L15**	0	0	0
16	**No ligand**	3	0	3



Reaction conditions: [a] **153** (0.29 mmol), Pd(dba)$_2$ (10 mol%), Ligand (20 mol%), 1,4-dioxane (0.15M) at 110°C for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

As shown in Table 5, we also tested the ability of other Pd(0)-catalysts to see whether the targeted [4+2] cycloaddition would be within reach. Unfortunately, this was not the case and little conversion was observed in all cases.

Table 5. Screening of different palladium (0) pre-catalysts



(153) **(150)** **(156)**

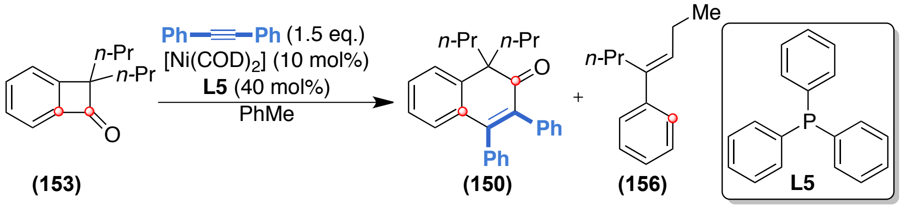
Entry	[Pd]	Conversion (%)	Yield (%)	
			150	**156**
1	**Pd(dba)$_2$**	0	0	0
2	**Pd$_2$(dba)$_3$**	5	0	5
3	**Pd(PCy$_3$)$_2$**	0	0	0
4	**[Pd(Ph$_2$P-(CH$_2$)-PPh$_2$)]**	0	0	0
5	**[Pd((*o*-tolyl)$_3$P)$_2$]**	12	0	12

6	**[Pd(styrene)$_2$IPr]**	0	0	0

Reaction conditions: [a] **153** (0.29 mmol), [Pd] (10 mol%), 1,4-dioxane (0.15M) at 110°C for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

Inspired by the work of Dong et al. on the intramolecular carboacylation of olefins and benzocyclobutenones with [Rh(COD)Cl]$_2$,[89] we initiated a screening of different Rh-catalysts, ligands, bases, solvents and temperatures. As for the use of Pd-catalysts, only traces or a small amount of the desired final product was observed. Next, we focused our attention on the employment of Ni(0) pre-catalysts since they have been reported on the C-C bond-cleavage of compounds with large ring-strain.[34-37,88,90] After some preliminary screenings, we were delighted to find that Ni(COD)$_2$ did not only result on the clean production of **150**, but also avoided the formation of **156** byproducts. Prompted by these results, we turned our attention to the fine-tuning of the key reaction parameters. As shown in Table 6, optimal reactivity was found at 110°C.

Table 6. Screening of Ni-catalysts at different temperatures



Entry	**[Pd]**	**Conversion (%)**	**Yield (%)**	
			150	**156**
1	**80°C**	59	56	0
2	**90°C**	61	60	0

---

[89] (a) Xu, T.; Ko, H. M.; Savage, N.; Dong, G. *J. Am. Chem. Soc.* **2012**, *134*, 20005-20008. (b) Chen, P.H.; Xu, T.; Dong, G. *Angew. Chem., Int. Ed.* **2014**, *53*, 1674-1678.

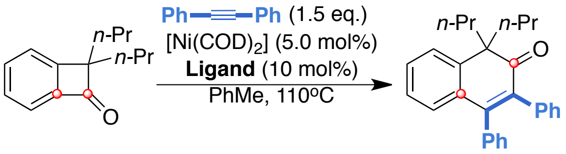
[90] (a) Liu, L.; Ishida, N.; Murakami, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 2485-2488. (b) Ashida, S.; Murakami, M. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 885-893. (c) Ashida, S.; Murakami, M. *Chem. Comm.* **2006**, 4599-4601. (d) Ashida, S.; Matsuda, T.; Murakami, M. *Tetrahedron*, **2006**, *62*, 7540-7546. (e) Ashida, S.; Matsuda, T.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127*, 6932-6933.

3	**110ºC**	87	85	0

Reaction conditions: [a] **153** (0.29 mmol), Ni(COD)$_2$ (10 mol%), **L5** (40 mol%), PhMe (0.15M) for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

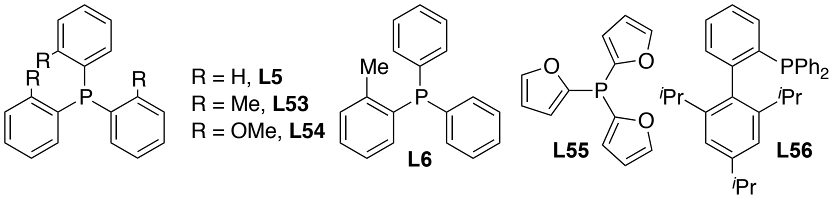
Next we turned our attention to lower down the catalyst loading from 10 mol% to 5.0 mol% of [Ni(COD)$_2$] and set out the investigation by screening a variety of phosphine ligands (Table 7).

Table 7. Screening of different phosphine ligands



(153) **(150)**

Entry	Ligand	Conversion (%)	Yield (%)
			150
1	**L5**	60	56
2	**L6**	9	7
3	**L53**	55	53
4	**L54**	23	20
5	**L55**	22	21
6	**L56**	16	13
7	**No ligand**	0	0

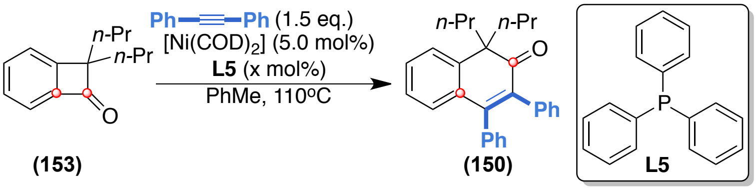


Reaction conditions: [a] **153** (0.29 mmol), Ni(COD)$_2$ (5.0 mol%), Ligand (10 mol%), PhMe (0.15M) at 110ºC for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

As shown in Table 7, **L5** proved to be the best providing **150** in 56% GC yield.

Interestingly, alkyl phosphines did not yield **150** in significant amounts. Subsequently, we chose to investigate the ligand to metal ratio (Table 8) and noticed that with 1:1 ratio of ligand to metal, we obtain a full conversion of the starting material to the corresponding desired final product (Table 8, entry 1). We hypothesize that such M/L ratio indicates that the alkyne competes with substrate binding.

Table 8. Screening of different ligand to metal ratio



Entry	Amount ligand (mol%)	Conversion (%)	Yield (%)
			4.32
1	5	100	<99%
2	10	60	56%
3	30	63	61%
4	40	43	43%

Reaction conditions: [a] **153** (0.29 mmol), $Ni(COD)_2$ (5.0 mol%), PhMe (0.15M) at 110°C for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

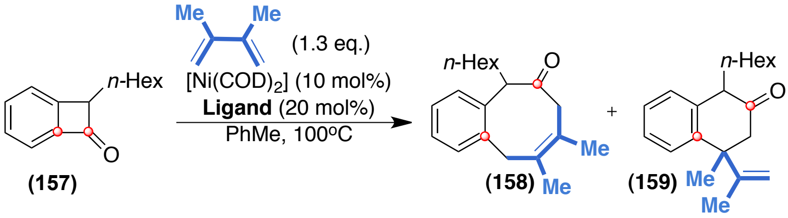
Encouraged by the results in Table 8, we wondered whether the reaction could be conducted at 2.5 mol% loading of $Ni(COD)_2$. Unfortunately, variable results were obtained and we decided to fix the final reaction conditions using 5.0 mol% loading of $Ni(COD)_2$, 5.0 mol% of PPh_3 in PhMe at 110°C. Since the optimal reaction conditions involved the presence of Ni/PPh_3, we decided to study if $[Ni(CO)_2(PPh_3)_2]$ or $[Ni(PPh_3)_2Cl_2]$/Zn could be used for similar purposes. Unfortunately, no reaction was observed in these cases.

4.4.1.2 Optimization of the reaction conditions for the synthesis of benzocyclooctanones (In collaboration with Akira Nishimura and Francisco

Julià)

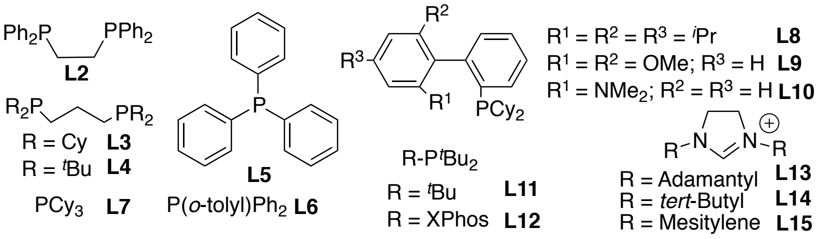
After optimizing the reaction conditions for the [4+2] cycloaddition of diphenyl acetylene with benzocyclobutenones, we turned our attention to the [4+4] cycloaddition of dienes with benzocyclobutenones (Table 9). Upon exposure of **157** and 2,3-dimethyl-1,3-butadiene to the optimized reaction conditions for the [4+2] cycloaddition approach, we found a respectful 10% GC yield.

Table 9. Screening of different ligands for [4+4] cycloaddition reaction



Entry	Ligand	Conversion (%)	Yield (%)	
			158	**159**
		Bidentate phosphine ligands		
1	**L2**	0	0	0
2	**L3**	0	0	0
3	**L4**	0	0	0
		Aryl monodentate phosphine ligands		
4	**L5**	100	88	12
5	**L6**	88	78	10
		Aliphatic monodentate phosphine ligands		
6	**L7**	0	0	0
7	**L8**	0	0	0
8	**L9**	0	0	0
9	**L10**	0	0	0
		tBu monodentate phosphine ligands		
10	**L11**	0	0	0
11	**L12**	0	0	0
		N-heterocyclic carbenes		

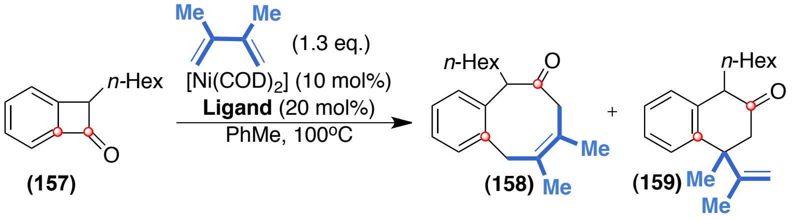
12	**L13**	0	0	0
13	**L14**	0	0	0
14	**L15**	0	0	0
15	**No ligand**	0	0	0



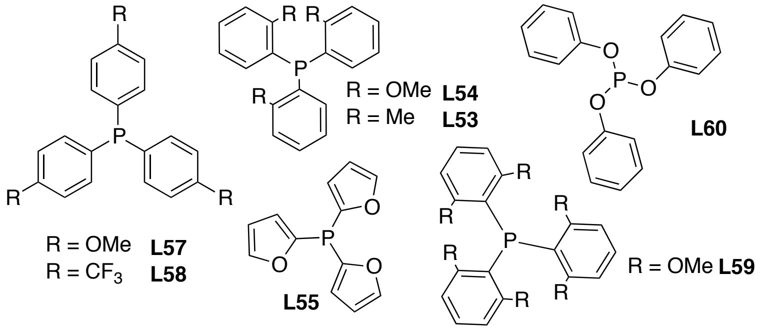
Reaction conditions: [a] **157** (0.29 mmol), Ni(COD)$_2$ (10 mol%), Ligand (20 mol%), PhMe (0.15M) at 100°C for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

Intriguingly, the reaction showed a markedly difference in reactivity, with triarylphosphines providing the best results. As shown in entries 4 and 5, the use of **L5** and **L6** in a M:L ratio of 1:2 allowed for obtaining **158** in 88% and 78% GC yield respectively, with small conversion to **159**.[37] Next, we decided to focus our attention on the screening of related triarylphosphines. As shown in Table 10, we noticed that sterics played a notable role in the reaction. We realized that the more electron-deficient the ligand is, the better the preference for the formation of **158**. This can be observed when comparing the results obtained with **L57**, **L58**, **L53** and **L55**, where the more electron deficient ligands (**L55** and **L58**) provide a better selectivity for the formation of **158**. The lack of reactivity in **L54** and **L59** might be related to the sterical hindrance in these ligands. **L60** can be considered electron deficient enough to favor the formation of **158**, but it still did not promote the reaction exceedingly well.

Table 10. Screening of different Arylphosphine ligands for the [4+4] cycloaddition reaction



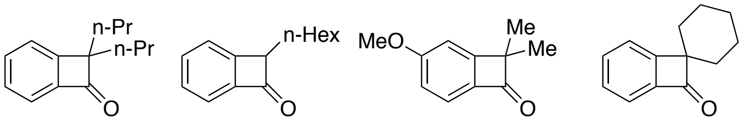
Entry	Ligand	Conversion (%)	Yield (%)	
			158	159
1	L57	100	75	25
2	L58	100	96	4
4	L53	88	78	10
6	L55	100	94	6
7	L54	40	40	0
8	L60	30	27	0
9	L61	39	34	5



Reaction conditions: [a] **157** (0.16 mmol), Ni(COD)₂ (10 mol%), Ligand (20 mol%), PhMe (0.08M) at 100ºC for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

4.4.1.2 Synthesis of different benzocyclobutanones

Having established the optimized reaction conditions, we set out to explore the scope of this reaction by preparing a wide variety of benzocyclobutenones. As for the preparation of **153**, the general route to access this type of molecules is illustrated in Figure 4.15 and involved an initial alkylation of 2-(2-bromophenyl)acetonitrile, followed by treatment with DiBALH to afford the corresponding aldehydes, which were converted into the benzocyclobutenone motif by reacting with $Pd(OAc)_2$/*Rac*-BiNAP. In this manner, a series of benzocyclobutenones with different substituents were prepared in good overall yields and in essentially three-step process at large scale. By utilizing such route, not only aliphatic but also cyclic motifs were introduced in α-position in order to evaluate the influence of such groups in the coupling event (Figure 4.17).



(153) **(157)** **(160)** **(161)**

Figure 4.17

Alternatively, other benzocyclobutenones can be obtained by a recent procedure reported by Dong et al.[91] The sequence was based on the generation of benzyne under basic conditions followed by a [2+2] cycloaddition with a lithium enolate (step b, Figure 4.18) prepared from THF, thus resulting in **162** in a 65% isolated yield. A final oxidation with Dess-Martin periodide (DMP) allowed the formation of **163** in 85% isolated yield.

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[91] Chen, P.-H.; Savage, N. A.; Dong, G. *Tetrahedron* **2014**, *70*, 4135-4146.

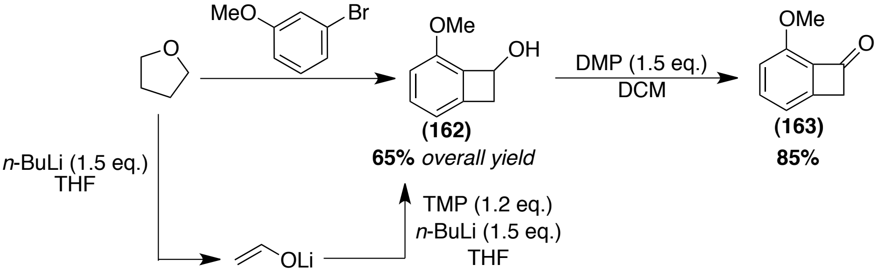


Figure 4.18

4.4.1.3 Scope of the [4+2] cycloaddition of benzocyclobutenones with alkynes

With substantial amounts in hand of differently substituted benzocyclobutenones, we set out to explore the scope for the Ni-catalyzed intermolecular [4+2] cycloaddition of benzocyclobutenones with alkynes (Figure 4.19). As shown, the presence of both linear and cyclic chains in α-position did not have a significant effect on the reaction outcome, invariably affording the corresponding unsaturated β-tetralones in high yields.

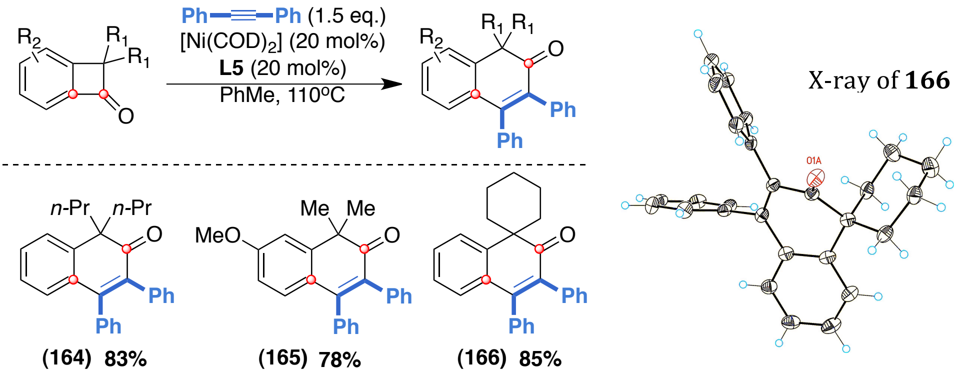


Figure 4.19

Unfortunately, the coupling of benzocyclobutenones possessing unprotected hydroxyl group (**167**), α-methyl ketone (**169**), trifluoromethyl ether (**168**) or nitro groups (**170**) did not deliver the expected tetralone backbone (Figure 4.20). In all of these cases, we obtained recovered benzocyclobutenone. At present, we believe that the free hydroxyl group in **167** and the nitro moiety in **170** might compete with substrate binding. As for the presence of a methyl ketone, the formation of a rather stable Ni(II)-enolate might account for the lower reactivity. On the other hand, the unsuccessful coupling of **168** could be associated to electronic effects.

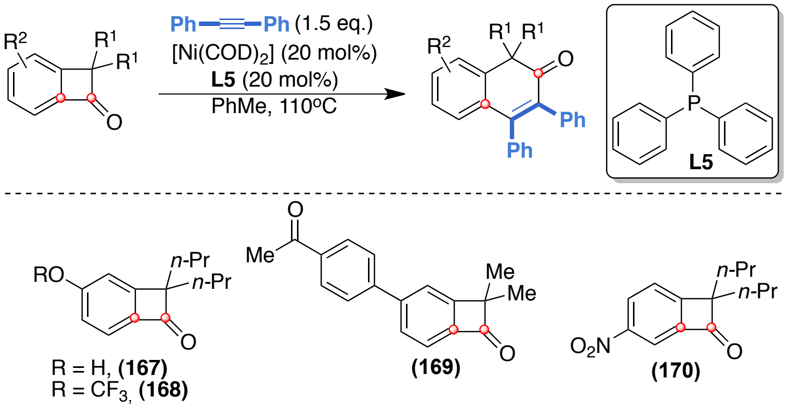


Figure 4.20

Next, we turned our attention on the alkyne motif. Unfortunately, the method seemed to be limited to diphenyl acetylene, (Figure 4.21) as acetylenes bearing dialkyl substitutions (**171**), unprotected hydroxyl groups (**172**) or di-ester (**173**) among others, resulted in no formation of products. In the case of **172**, we believe the acidity of the proton of the hydroxyl group is problematic due to the intermediacy of Ni(II)-H species and the coordination of this substrate to nickel. While **171** and **174** have successfully been employed in other Ni-catalyzed cross-coupling reactions,[35] we did not observe product formation. At present, we don't have any explanation for such results. As for **173** we believe that the lack of reactivity is the possibility of such substrate to act as a π-acceptor. In all cases, we recovered **161**.

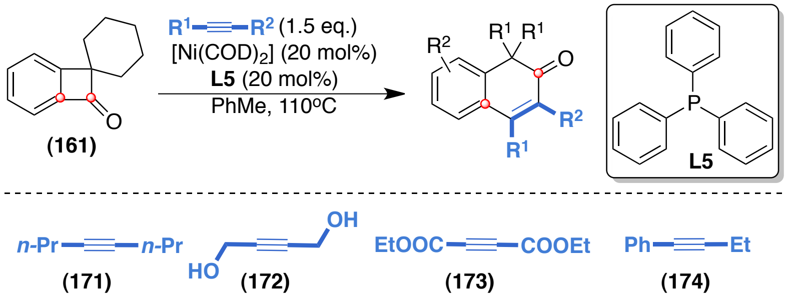


Figure 4.21

4.4.1.3 Scope of the [4+4] cycloaddition of benzocyclobutenones with dienes (In

collaboration with Dr. Francisco Julià)

Prompted by the results shown, we set out to explore the scope of our intermolecular [4+4]-cycloaddition of benzocyclobutenones with dienes (Figure 4.22). Although the scope is preliminary, we were delighted to find that the methodology allowed for the coupling of benzocyclobutenones with α,α-disubstitution (**176**) as well as α-mono-substitution (**158**). Unsymmetrically substituted dienes are also coupled in good yields and regioselectivity (**176**), in which the substituent is located close to the aromatic ring preferentially. Gratifyingly, we found that cyclohexadiene could also participate in the [4+4] cycloaddition event, giving rise to single diastereoisomer **177** as judged by ^{1}H-NMR and NOESY analysis.

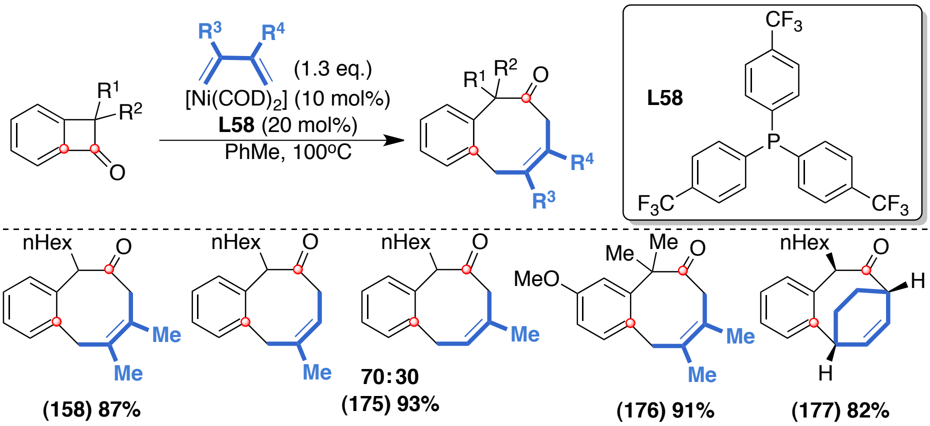


Figure 4.22

When exploring the scope of the [4+4] cycloaddition reaction of 1,3-dienes with benzocyclobutenones, we discovered several 1,3-dienes that were not tolerated under the reaction conditions and could not give us the desired benzocyclooctanones (Figure 4.23). We observed that sterically hindered dienes (**180**-**186**) were not tolerated under the reaction conditions and the reaction resulted in the recovery of the benzocyclobutenone. As far as **185** and **188**, the conjugation of the diene moiety might become an issue, making the diene less electron-rich and, therefore, less prone to binding. In the case of **187**, we believe that the hydroxyl group might coordinate to the Ni-catalyst. While we observed that cyclohexadiene could be employed as substrate, we found that otherwise related cyclic dienes **178** and **179** provided little conversion to products. At present, we believe that transannular interactions come into play for these compounds.

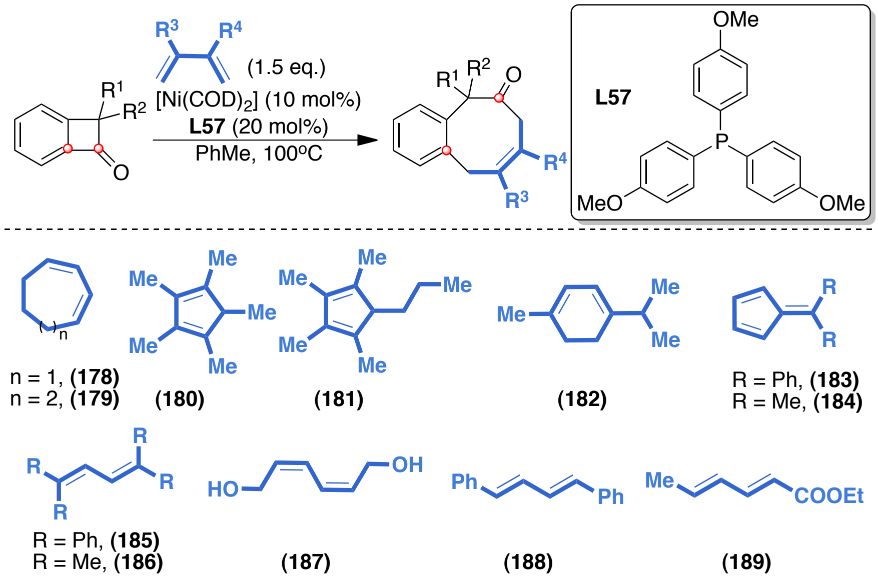


Figure 4.26

4.5 Conclusions

- We have developed a new protocol for the intermolecular [4+4] as well as [4+2] cycloaddition reaction of benzocyclobutanones with respectively dienes and alkynes. The methodology is not fully developed, but holds great potential.
- The methodology provides an access to a variety of tetralones and benzocyclooctanones in a straightforward fashion.

4.6 Experimental section

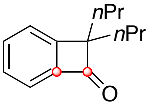
4.6.1 General considerations

Reagents. The reactions were set up as follows: First, the ligand and the benzocyclobutanone (oil or solid) were added into a resealable screw-cap test tubes in the air (with no use of the glovebox) and were then introduced in the glovebox to add the Ni(COD)$_2$ catalyst and the anhydrous PhMe. Later on, the tube was taken out from the glovebox and under Ag atmosphere, the alkyene (if liquid) or the diene (if liquid) was added via Hamilton syringes. To ensure that no air would enter, the cap of the tube was packed with para-film. Ni(COD)$_2$ was purchased from Strem and stored in the freezer of the glovebox at approx. -24^{o}C, triphenyl phosphine was purchased from Alfa (Cymit) where small portions of it was stored in a dessicator and tri-(4-OMe-phenyl) phosphine was purchased from Strem. Anhydrous PhMe was purchased from Acros and introduced in the glovebox. The benzocyclobutanones were all prepared according to standard literature procedures in multigram scale. 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).

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 300 MHz, a Bruker 400 MHz and a Bruker 500 MHz at 20^{o}C. All ^{1}H NMR spectra are reported in parts per million (ppm) downfield of TMS and were measured relative to the signals for CHCl3 (7.27 ppm). All ^{13}C NMR spectra were reported in ppm relative to residual CHCl3 (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.

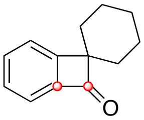
4.6.2 Synthesis of the starting materials

General procedure for the preparation of the benzocyclobutenones from 2-bromophenylacetonitril. A flask equipped with a magnetic stirring bar and a septum inlet was flushed with argon. The flask was charged under argon atmosphere with 2-bromophenyl acetonitrile (1.0 eq.) and dry THF (4 mL/1.0 mmol). Then, NaHMDS (2.2 eq., 1M in THF) was added dropwise, and the solution was stirred for 20 min at r.t. At this time, alkyl halide (2.2 eq.) was introduced gradually by syringe. After stirring for 2 h at room temperature, 2 mL of aqueous saturated NH_4Cl solution were added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over magnesium sulfate, and finally concentrated under vacuum. The crude nitrile thus obtained was used directly in the next step without further purification. To a well-stirred solution of the above mentioned crude nitrile in dichloromethane (4 mL/1.0 mmol) under argon atmosphere was added DIBAL-H (1.2 eq., 1M in hexanes) and stirred for 2 h at -78^{o}C. The reaction was then quenched after 2 h of further stirring by slow addition of 2M HCl and EtOAc. The organic phase was washed twice with brine, dried over magnesium sulfate and concentrated. the crude was then purified by column chromatography on silica gel (hexanes/EtOAc) to give the corresponding α-aryl aldehyde. A schlenk flask equipped with a magnetic stirring bar was charged with $Pd(OAc)_2$ (2.0 mol%), *Rac*-BiNAP (3.0 eq.) and the α-aryl aldehyde. The flask was introduced into the glovebox where Cs_2CO_3 (1.1 eq.) and 1,4-dioxane were charged. The Schlenk flask was taken outside from the glovebox and let to stir at 110^{o}C for 12 h. The mixture was then allowed to cool to room temperature, diluted with EtOAc and filtered through celite, eluting with additional EtOAc. The filtrate was concentrated and purified by column chromatography on silica gel to give the corresponding benzocyclobutenone.

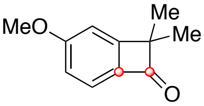


8,8-Dipropylbicyclo[4.2.0]octa-1,3,5-trien-7-one. Following the general procedure reported above, *iso*-propyl iodide was used. Column chromatography of the aldehyde: silica gel, 18:1 (hexanes:EtOAc). Colorless oil; 75% overall yield.

Column chromatography of the benzocyclobutenone: silica gel, 15:1 (hexanes:EtOAc). Colorless oil; 82% yield.



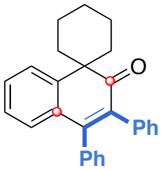
8,8-Cyclohexylbicyclo[4.2.0]octa-1,3,5-trien-7-one. Following the general procedure reported above, 1,6-dibromohexane was used. Column chromatography of the aldehyde: silica gel, 18:1 (hexanes:EtOAc). Colorless oil; 60% overall yield. Column chromatography of the benzocyclobutenone: silica gel, 15:1 (hexanes:EtOAc). Colorless oil; 68% yield.



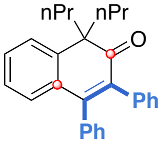
3-Methoxy-8,8-dimethylbicyclo[4.2.0]octa-1,3,5-trien-7-one. Following the general procedure reported above, (2-bromo-5-methoxyphenyl)acetonitrile and methyl iodide were used. Column chromatography of the aldehyde: silica gel, 10:1 (hexanes:EtOAc). White solid; 52% overall yield. Column chromatography of the benzocyclobutenone: silica gel, 8:1 (hexanes:EtOAc). Colorless oil; 42% yield.

4.6.3 Synthesis of 6- and eight-membered benzocycloketones

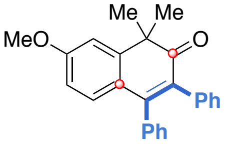
General procedure for the preparation of six-membered [4+2] cycloaddition products from benzocyclobutenones. An oven-dried screw-cap test tube containing a stirring bar was charged with PPh_3 (10 mol%, 0.025mmol), benzocyclobutenone (1.0 eq., 0.25mmol) and diphenylacetylene (1.2 eq., 0.275mmol). The tube was introduced into the glove-box and was charged there with $Ni(COD)_2$ (10 mol%, 0.25mmol) and anhydrous PhMe (2ml). The tube was taken out from the glovebox and heated to 110^{o}C for 12 h. The mixture was then allowed to cool to room temperature, diluted with EtOAc (5 mL) and filtered through a Celite® plug, eluting with additional EtOAc (10 mL). the filterate was then concentrated and purified by column chromatography on silica gel (eluting with hexanes/EtOAc mixtures).



3',4'-diphenyl-2'H-spiro[cyclohexane-1,1'-naphthalen]-2'-one. ^{1}HNMR (300 MHz, CDCl$_3$): δ 7.63 (dd, J = 7.9, 1.2 Hz, 1H), 7.37 (td, J = 7.6, 1.5 Hz, 1H), 7.30-7.22 (m, 3H), 7.21-7.06 (m, 9H), 7.01 (dd, J = 7.8, 1.4 Hz, 1H), 2.47-2.33 (m, 2H), 1.99 (ddd, J = 13.1, 11.6, 3.8 Hz, 2H), 1.92-1.63 (m, 5H), 1.48-1.28 (m, 1H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 206.3, 148.3, 146.4, 137.1, 135.5, 134.1, 132.3, 130.3, 129.7, 129.4, 129.0, 128.0, 127.4, 126.7, 126.3, 124.8, 77.5, 77.1, 76.6, 51.9, 35.1, 25.8, 23.0. EtOAc:Hex (1:9; Rf=0.8). White/yellowish solid. Mp = 141.0^{o}C. HRMS: [C27H25O] measured mass: 365.1897 m/z; calculated mass: 365.1900 m/z.

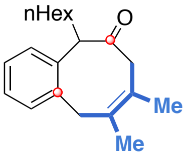


3,4-diphenyl-1,1-dipropylnaphthalen-2(1*H*)-one. ^{1}H NMR (300 MHz, Chloroform-d) δ 7.36-7.18 (m, 3H), 7.18- 7.07 (m, 6H), 7.04-6.95 (m, 3H), 6.71 (dd, J = 8.8, 2.6 Hz, 1H), 3.88 (s, 3H), 1.66 (s, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 202.8, 152.6, 145.1, 137.4, 136.3, 135.6, 132.8, 130.5, 129.5, 129.4, 129.2, 127.8, 127.4, 127.3, 126.6, 126.2, 126.0, 77.3, 77.0, 76.8, 56.1, 46.51, 29.7, 17.9, 14.5.



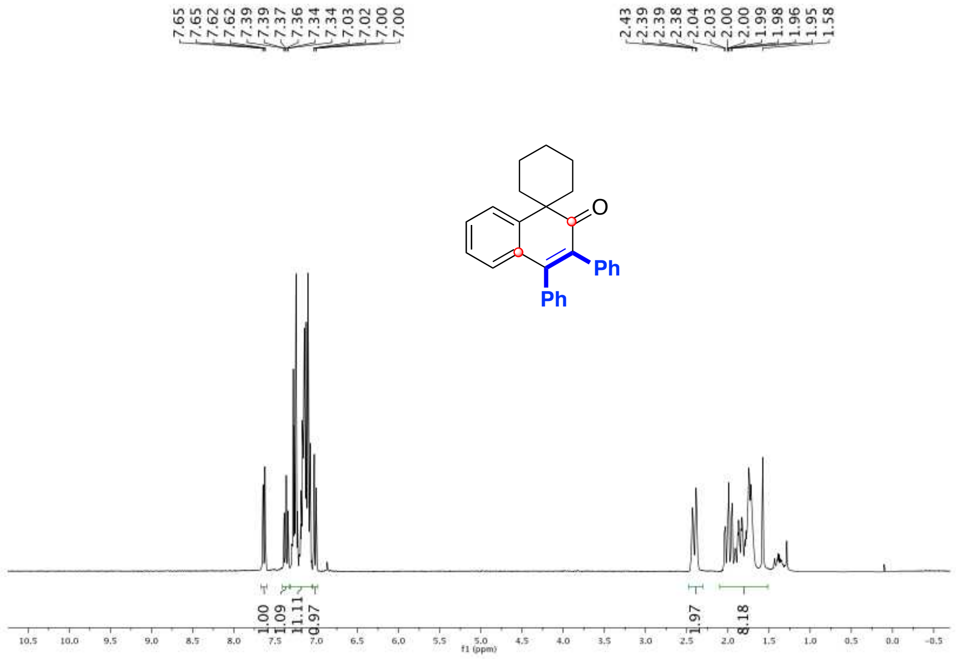
6-methoxy-1,1-dimethyl-3,4-diphenylnaphthalen-2(1H)-one. ^{1}H NMR (300 MHz, Chloroform-d) δ 7.36-7.18 (m, 3H), 7.18- 7.07 (m, 6H), 7.04-6.95 (m, 3H), 6.71 (dd, J = 8.8, 2.6 Hz, 1H), 3.88 (s, 3H), 1.66 (s, 6H). ^{13}C NMR (75 MHz, CDCl3) δ 202.89, 160.82, 151.51, 149.37, 137.52, 135.76, 131.97, 131.18, 130.67, 129.43, 127.88, 127.36, 127.25, 126.48, 123.85, 112.59, 110.88, 77.46, 77.04, 76.62, 55.40, 47.99, 28.15. Mp = 180.1^{oC}. HRMS: [C25H23O2] measured mass: 355.1699 m/z; calculated mass: 355.1693 m/z.

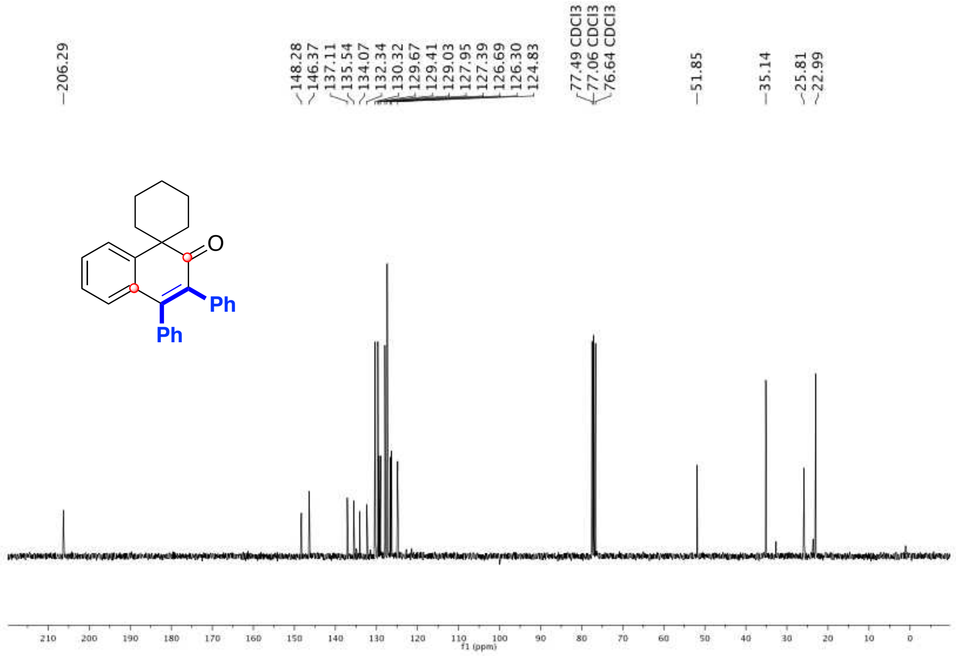
General procedure for the preparation of eight-membered [4+4] cycloaddition products from benzocyclobutenones. An oven-dried screw-cap test tube containing a stirring bar was charged with tri-(4-CF_3-phenyl) phosphine (10 mol%, 0.025mmol), benzocyclobutenone (1.0 eq., 0.25 mmol) and the diene (if solid). The tube was introduced into the glove-box and charged there with Ni$(COD)_2$ (10 mol%, 0.25mmol) and anhydroud PhMe (2mL). The tube was taken out from the glovebox and the diene (if liquid) was added under argon atmosphere. The tube was then heated to 100°C for 12 h. The mixture was then allowed to cool to room temperature, diluted with EtOAc (5 mL) and filtered through a Celite® plug, eluting with additional EtOAc (10 mL). the filterate was then concentrated and purified by column chromatography on silica gel (eluting with hexanes/EtOAc mixtures).

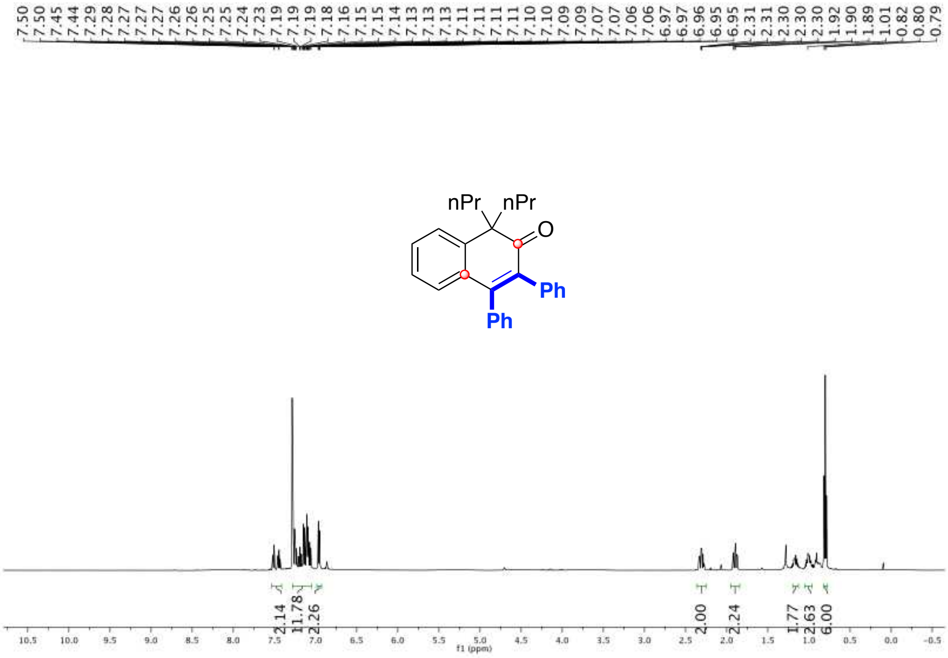


(Z)-5-hexyl-8,9-dimethyl-7,10-dihydrobenzo[8]annulen-6(5H)-one. ^{1}H NMR (300 MHz, Chloroform-d) δ 7.26-7.10 (m, 4H), 3.92 (dd, J = 7.8, 6.5 Hz, 1H), 3.58- 3.22 (m, 3H), 3.05 (d, J = 13.4 Hz, 1H), 2.39-2.17 (m, 1H), 2.19-1.66 (m, 7H), 1.38- 1.18 (m, 9H), 0.94-0.83 (m, 4H). ^{13}C NMR (75 MHz, CDCl3) δ 210.3, 137.7, 137.7, 130.3, 129.8, 128.5, 127.1, 126.6, 124.8, 77.4, 77.0, 76.6, 57.9, 50.5, 40.8, 31.7, 30.9, 29.5, 27.8, 22.6, 21.7, 20.4, 14.1. HRMS: [C20H28ONa] measured mass: 307.2039 m/z; calculated mass: 307.2032 m/z.

4.7 Selected examples of NMR spectra



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2.31
2.31
2.30
2.30
2.30
1.92
1.90
1.89
1.01
0.82
0.80
0.79
nPr
nPr
O
Ph
Ph
2.14
11.78
2.26
2.00
2.24
1.77
2.63
6.00
10.5
10.0
9.5
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8.0
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7.0
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6.0
5.5
5.0
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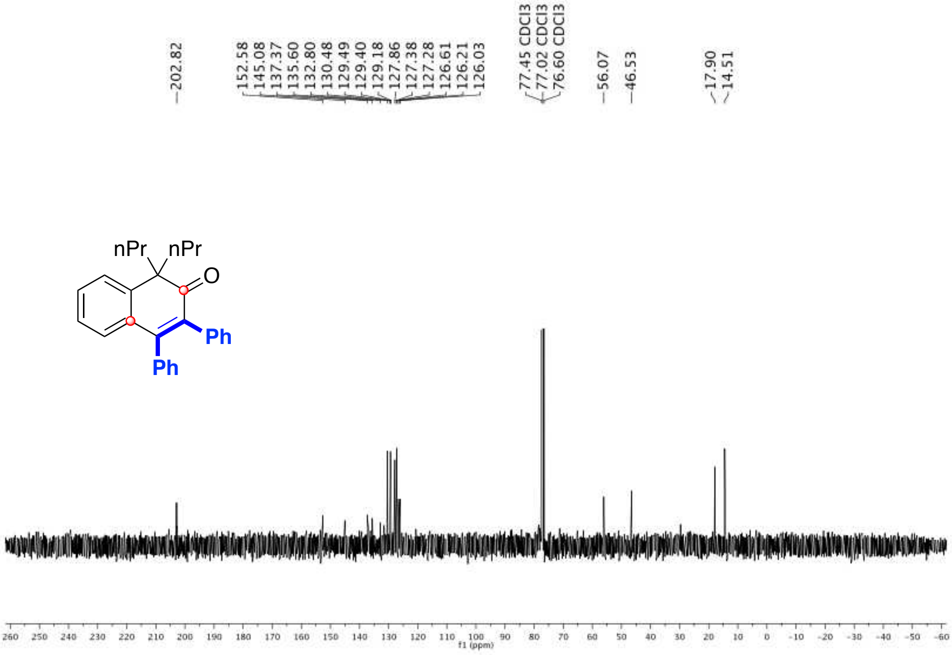
-0.5
f1 (ppm)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127.28
126.61
126.21
126.03
77.45 CDCl3
77.02 CDCl3
76.60 CDCl3
56.07
46.53
17.90
14.51
nPr
nPr
O
Ph
Ph
260
250
240
230
220
210
200
190
180
170
160
150
140
130
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110
100
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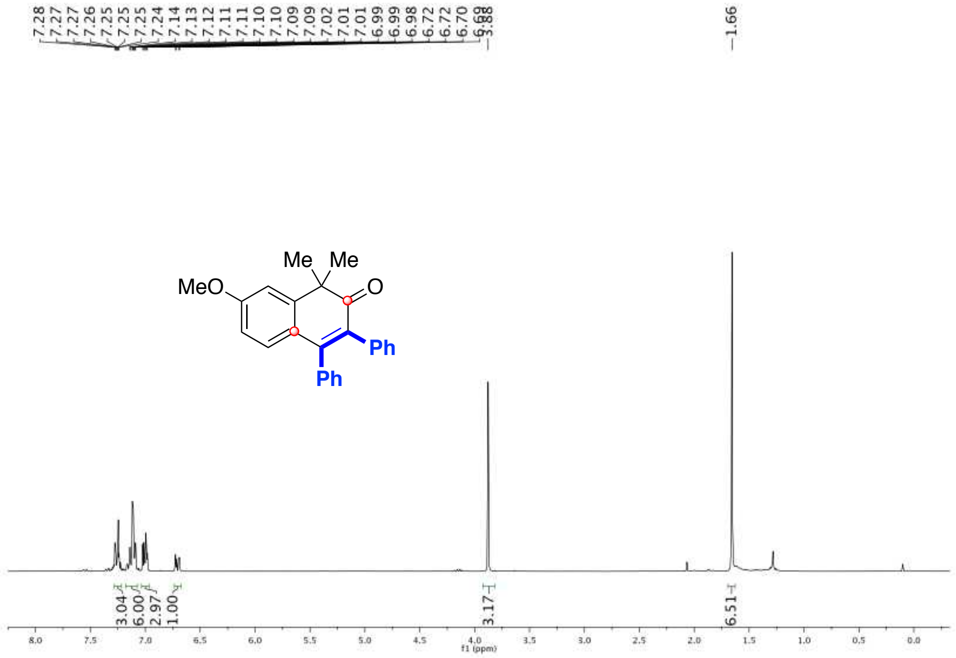
f1 (ppm)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6.70
6.69
3.88
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Me
Me
MeO
O
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Ph
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2.97
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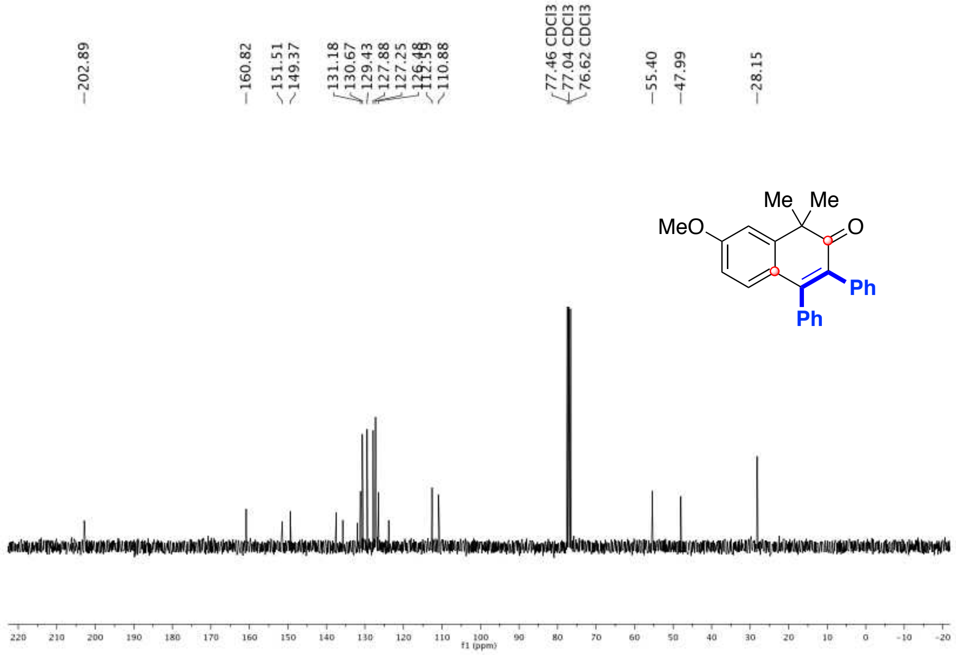
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77.04 CDCl3
76.62 CDCl3
55.40
47.99
28.15
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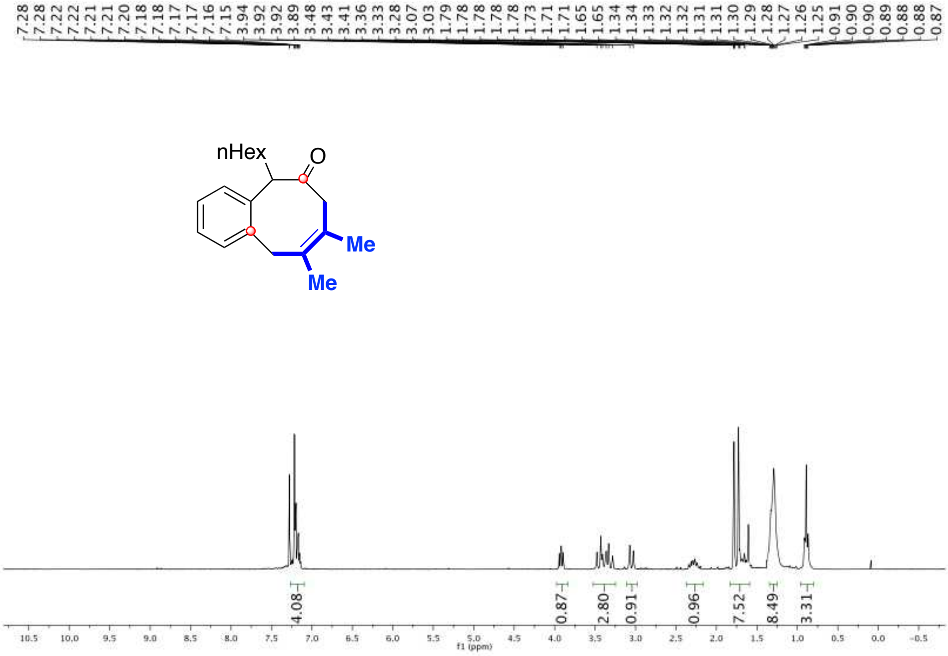
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5.0
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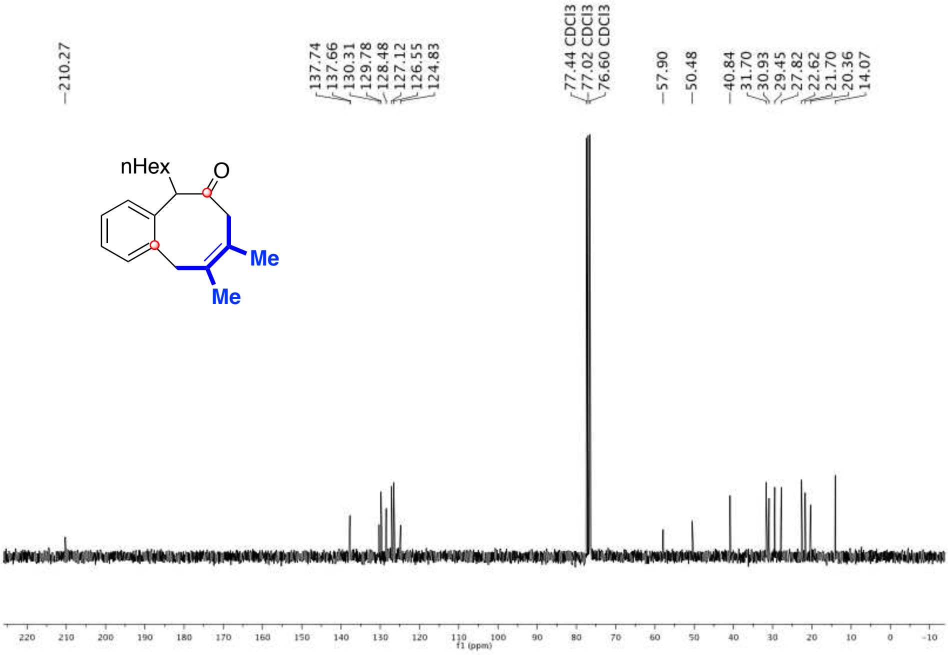
f1 (ppm)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50.48
40.84
31.70
30.93
29.45
27.82
22.62
21.70
20.36
14.07
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O
Me
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210
200
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180
170
160
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120
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100
90
80
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60
50
40
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-10
f1 (ppm)

CHAPTER 5

TOWARDS CO_2 FIXATION AND C-F BOND FORMATION via C-C BOND CLEAVAGE

“I have not failed. I have just found 10,000 ways that will not work.”

- Thomas A. Edison

5.1 Introduction and summary

In recent years, *tert*-cyclobutanols have been employed as key building blocks in metal-catalyzed C-C bond cleavage reactions via β-carbon elimination processes. Pinoeering work in this area has been reported, among others, by Uemura, Murakami[46-52] and Cramer.[46,49,77] In 2012, we reported the Pd-catalyzed γ-arylation of ketones via β-carbon elimination of *tert*-cyclobutanols (Chapter 2)[57] and subsequently, the Pd-catalyzed γ-alkynylation of ketones via β-carbon elimination of *tert*-cyclobutanols (Chapter 3).[72] Intrigued by the promising results we obtained in this field, we next turned our attention to find new reactivity of *tert*-cyclobutanols in cross-coupling reactions via C-C bond cleavage. During this PhD-thesis, we have focused a considerable attention on the development on new β-carbon elimination pathways using *tert*-cyclobutanols as substrates. Although many methods were envisioned, this chapter contains the information obtained when attempting a metal-catalyzed carboxylation or fluorination via C-C bond cleavage.

5.2 γ-functionalization of ketones via β-carbon elimination of tert-cyclobutanols

5.2.1 γ-carboxylation of tert-cyclobutanols via β-carbon elimination (In collaboration with Dr. Arkaitz Correa and Dr. Akira Nishimura)

In recent years, carbon dioxide (CO_2) has gained a considerable attention due to its abundance, low cost, non-toxicity and high potential as a renewable source.[92] In 2009, we reported the first Pd-catalyzed carboxylation of aryl bromides (Figure 5.1) in the presence of $Pd(OAc)_2$, ^{t}BuXPhos (Figure 5.1) and Et_2Zn under CO_2 (10 bars) in

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[92] For recent reviews: (a) Sakakura,T.; Kohno, K. *Chem. Commun.* **2009**, 1312-1330. (b) Yu, K. M. K.; Curcic, I.; Gabriel, J.; Tsang, S. C. E. *ChemSusChem* **2008**, *1*, 893-899. (c) Sakakura, T.; Choi, J.-C.; Yasuda, H. *Chem. Rev.* **2007**, *107*, 2365-2387. (d) Mori, M. *Eur. J. Org. Chem.* **2007**, 4981-4993. (e) Arakawa, H.; Aresta, M.; Armor, J. N.; Barteau, M. A.; Beckman, E. J.; Bell, A. T.; Bercaw, J. E.; Creutz, C.; Dinjus, E.; Dixon, D. A.; Domen, K.; DuBois, D. L.; Eckert, J.; Fujita, E.; Gibson, D. H.; Goddard, W. A.; Goodman, D. W.; Keller, J.; Kubas, G. J.; Kung, H. H.; Lyons, J. E.; Manzer, L. E.; Marks, T. J.; Morokuma, K.; Nichloas, K. M.; Periana, R.; Que, L.; Rostrup-Nielson, J.; Sachtler, W. M. H.; Schmidt, L. D.; Sen, A.; Somorjai, G. A.; Stair, P. C.; Stults, B. R.; Tumas, W. *Chem. Rev.* **2001**, *101*, 953-996. (f) Yin, X.; Moss, J. R. *Coord. Chem. Rev.* **1999**, *181*, 27-59. (f) Keilland, N.; Whiteoak, C. J.; Kleij, A. W. *Adv. Synth. Catal.* **2013**, *355*, 2115-2138. (g) Martin, R.; Kleij, A. W.*ChemSucChem* **2011**, *4*, 1259-1263. (h) Aresta, M., Eds. *Carbon Dioxide as Chemical Feedstock*; Wiley-VCH: Weinheim, 2010.

DMA at 40ºC.[93] The method allowed the carboxylation of a wide variety of aryl bromides with diverse substitution patterns in good yields. The mechanism of this transformation is believed to be initiated with an oxidative addition (**I**) that undergoes CO_2 insertion giving rise to Pd(II)-complex (**II**) (Figure 5.1). Subsequently, transmetallation with Et_2Zn delivers the zinc carboxylate **190-Zn**, which ultimately affords the benzoic acid **190** after an acidic work-up. The active species are then generated by reductive elimination or β-hydride elimination.

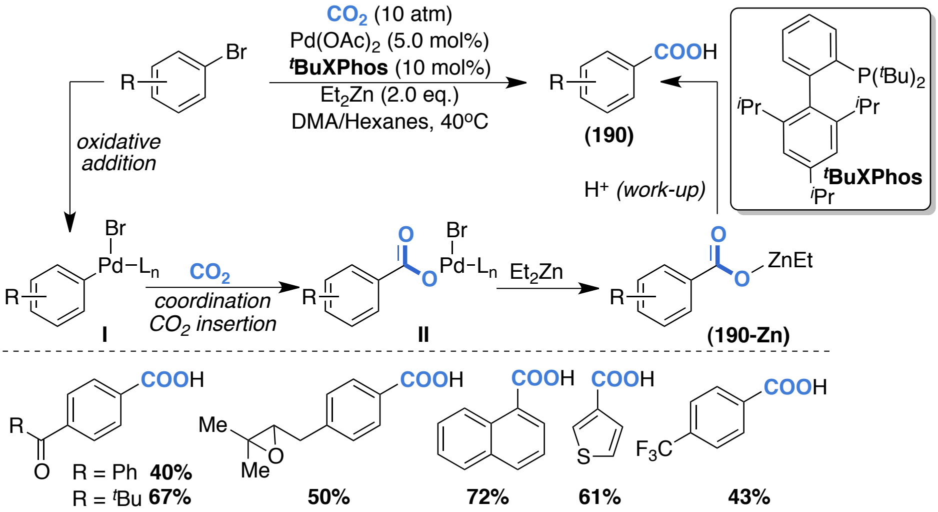

Figure 5.1

Later, Tsuji and Daugulius reported a follow-up of this reaction, describing a Ni and Cu-catalyzed carboxylation of aryl chlorides and iodides in presence of carbon dioxide.[94]

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[93] Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2009**, *131*, 15974-15975.

[94] (a) Fujihara, T.; Nogi, K.; Xu, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* **2012**, *134*, 9106-9109. (b) Tran-Vu, H.; Daugulis, O. *ACS Catal.* **2013**, *3*, 2417-2420.

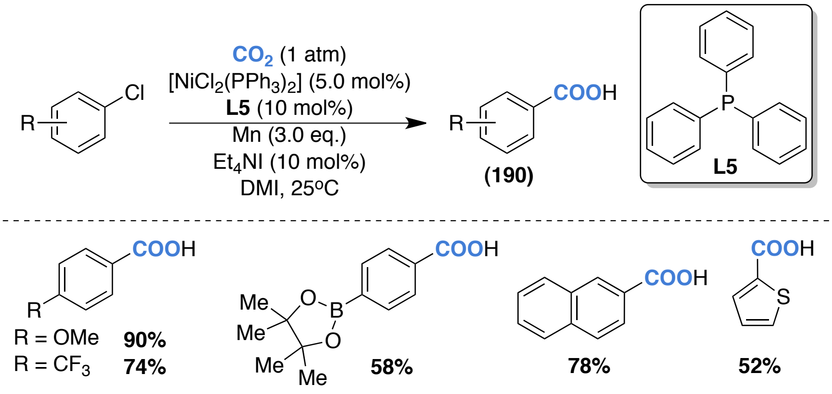

Figure 5.2

In 2013, our group reported the Ni-catalyzed direct carboxylation of benzyl halides with carbon dioxide[95a] as well as the Ni-catalyzed carboxylation of Csp^2- and Csp^3-O bonds with carbon dioxide using aryl and benzyl pivalates as coupling counterparts.[95b] More recently, our group reported the direct reductive carboxylation of unactivated alkyl halides and C-O electrophiles with carbon dioxide.[95c]

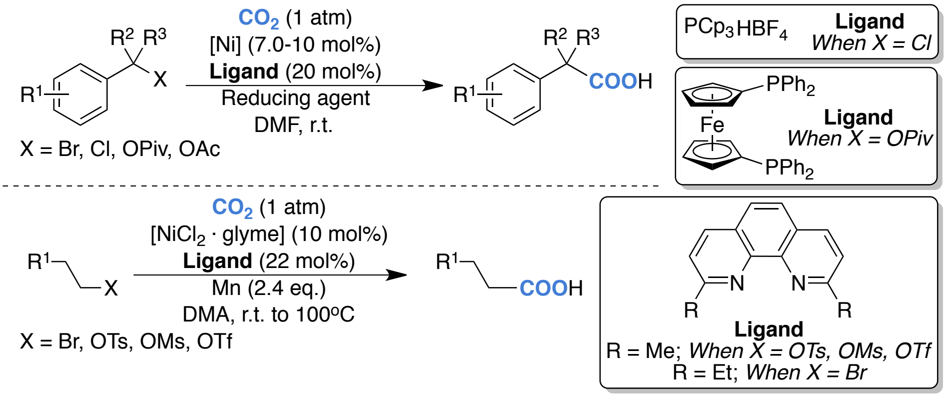

Figure 5.3

Inspired by these results, we envisioned whether a carboxylation event could be conducted via β-carbon elimination pathways using *tert*-cyclobutanols as substrates.

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[95] (a) León, T.; Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2013**, *135*, 1221-1224. (b)Correa, A.; León, T.; Martin, R. *J. Am. Chem. Soc.* **2014**, *136*, 1062-1069. (c) Liu, Y.; Cornella, J.; Martin, R. *J. Am. Chem. Soc.* **2014**, *136*, 11212-11215.

We hypothesized that the transformation would be initiated by coordination of the metal center to the *tert*-cyclobutanol forming metal complex (**III**) (Figure 5.2), followed up by a β-carbon elimination to deliver an alkyl C-metal species (**IV**). In principle, several pathways are conceived from (**IV**): (a) CO_2 insertion into the alkyl-M bond, ultimately generating **191**; (b) Intramolecular proton transfer en route to enolate (**V**) that would generate **192**; (c) Intramolecular 1,4-metal shift to give rise to a Csp^2-Metal bond followed by addition across the C=O bond to form **193** that might trigger a dehydration to yield **194**.

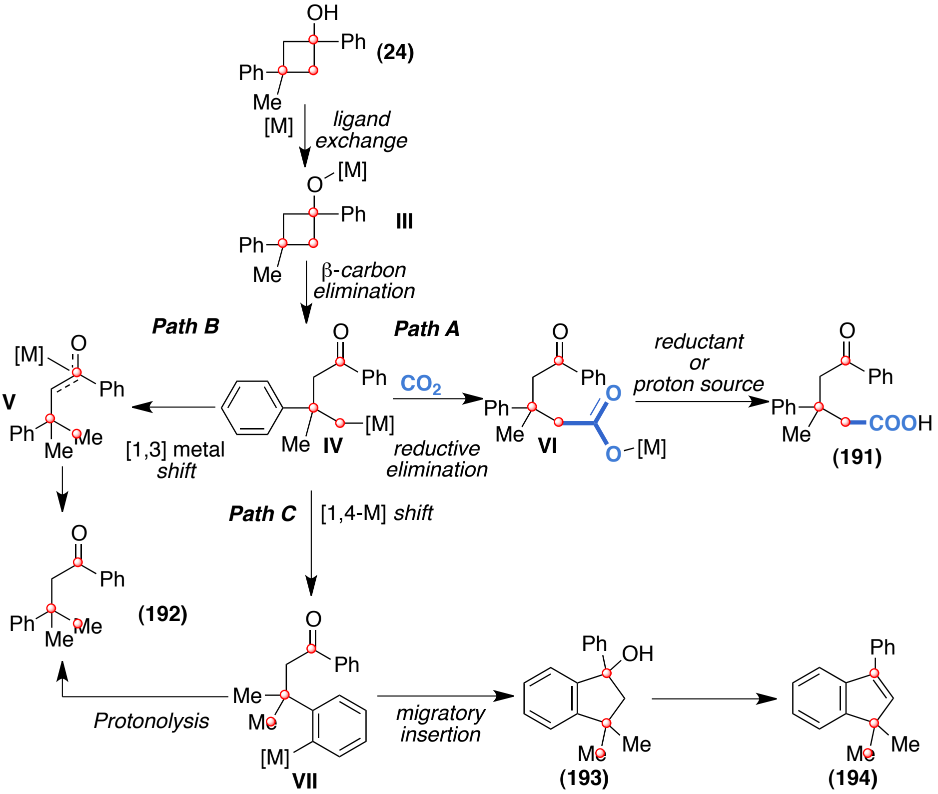
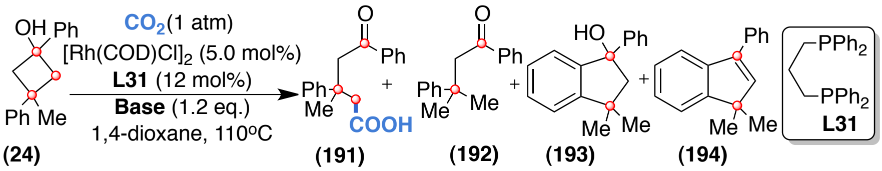


Figure 5.2

Taking into consideration the known ability of Rh-catalysts to promote β-carbon elimination[46-49] and also carboxylation events[96], we initiated our screening with **24** as model substrate in the presence of $[Rh(COD)Cl]_2$ with 1,3-bis(diphenylphosphino) propane as ligand under 1 atm pressure of CO_2 in 1,4-dioxane at 110ºC. We speculated that the presence of a base would be crucial, for deprotonating **24** and for recovering back the active Rh-species while releasing the expected carboxylate product. Therefore, we initiated the screening by trying different bases and studying their effect on the reaction outcome (Table 1).

Table 1. Screening of different bases



Entry	Base	Conversion (%)	Yield (%)			
			191	192	193	194
1	KO^tBu	100	0	0	88	12
2	NaO^tBu	100	0	0	82	18
3	Cs_2CO_3	100	0	0	81	19
4	K_2CO_3	100	0	0	85	15
5	KOH	100	0	0	81	19
6	CsOPiv	100	0	0	92	8
7	No base	0	0	0	0	0

Reaction conditions: [a] **24** (0.25 mmol), $[Rh(COD)Cl]_2$ (5.0 mol%), **L31** (12 mol%), Base (1.2 eq., 0.275 mmol), 1,4-dioxane (4mL/mmol) at 110ºC for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

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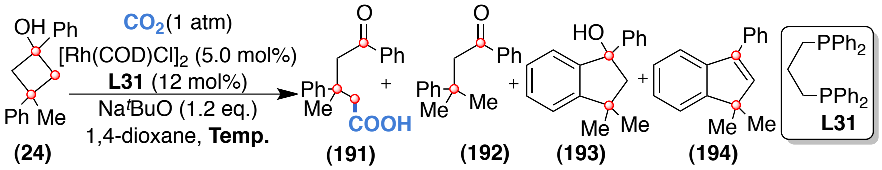
[96] For Rh-catalyzed carboxylation reactions, see: (a) Suga, T.; Mizuno, H.; Takaya, J.; Iwasawa, N. *Chem. Commun.* **2014**, Advance article (DOI:10.1039/C4CC06188H). (b) Ukai, K.; Aoki, M.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2006**, *128*, 8706-8707. (c) Mizuno, H.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2011**, *133*, 1251-1253.

As shown in Table 1, a base was necessary for achieving full conversion. In the presence of a base, however, **191** and **192** were exclusively observed regardless of the base utilized. In light of these results, we wondered whether the reaction was temperature sensitive. Therefore, we next turned our attention to screen different temperatures using NaO*t*Bu as base (Table 2).

Table 2. Screening of different temperatures

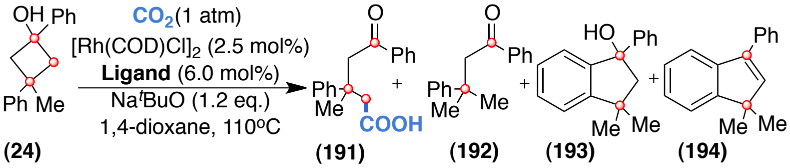


Entry	Temp. (ºC)	Conversion (%)	Yield (%)			
			191	192	193	194
1	**110**	100	0	0	82	18
2	**90**	100	0	0	73	16
3	**60**	0	0	0	0	0
4	**r.t.**	0	0	0	0	0

Reaction conditions: [a] **24** (0.25 mmol), [Rh(COD)Cl]$_2$ (5.0 mol%), **L31** (12 mol%), Na*t*BuO (1.2 eq., 0.275 mmol), 1,4-dioxane (4mL/mmol) for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

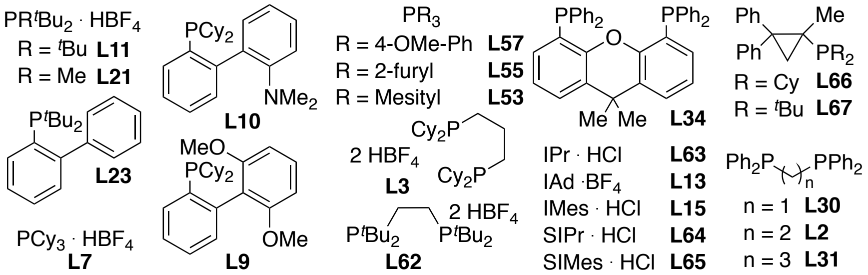
As shown in Table 2, we found that **191** and **192** were obtained selectively at 90ºC. Interestingly, no conversion was found at lower temperatures. Next, we turned our attention to screen ligands since our research group has ample experience that the nature of the ligand exert a critical influence on β-carbon elimination events[57,72] and, in particular, in carboxylation processes (Table 3).[93,95]

Table 3. Screening of different ligands



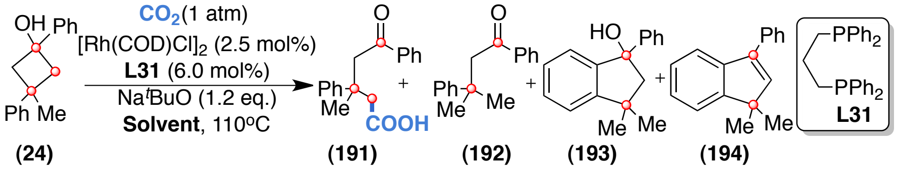
Entry	**Ligand**	**Conversion (%)**	**Yield (%)**			
			191	**192**	**193**	**194**
1	**L11**	100	0	0	91	9
2	**L21**	100	0	0	86	14
3	**L23**	100	0	0	99	1
4	**L7**	100	0	0	95	5
5	**L10**	100	0	0	96	4
6	**L9**	100	0	0	99	1
7	**L57**	100	0	0	92	8
8	**L55**	100	0	0	94	6
9	**L53**	100	0	0	99	1
10	**L3**	41	0	0	40	1
11	**L62**	54	0	0	52	2
12	**L34**	100	0	87	11	0
13	**L63**	100	0	0	74	9
15	**L13**	100	0	0	99	1
16	**L15**	61	0	0	58	3
17	**L64**	100	0	0	83	8
14	**L65**	100	0	0	64	7
18	**L66**	100	0	0	91	7
19	**L67**	100	0	0	98	2
20	**L30**	100	0	0	86	14
21	**L2**	100	0	0	82	15
22	**L31**	85	0	0	82	2

Reaction conditions: [a] **24** (0.25 mmol), $[Rh(COD)Cl]_2$ (2.5 mol%), ligand (6.0 mol%), Na^tBuO (1.2 eq., 0.275 mmol), 1,4-dioxane (4mL/mmol) at 110°C for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.



We were quite disappointed to find that none of the ligands utilized gave the desired carboxylated ketone **191**. Instead, **193** and **194** were formed preferentially except for **L34** where **192** was obtained in 87% GCyield. We assumed such reaction outcome is directly linked to the difference in the bite angle of **L34** compared to **L31** (108º vs. 91º respectively) as well as the higher flexibility of **L31** vs. **L34**. Next, we wondered whether the solvent would have an influence on the reaction outcome. That being set, a number of solvents were tested in the presence of **L34** as well as **L31** (Table 4 and Table 5 respectively). We chose to carry on the screenings with **L31** since it was the only ligand that showed a different trend in the transformation of *tert*-cyclobutanol. In the case of **L34**, however, we chose to continue the screening with this ligand since we believed it to be promoting the C-C bond cleavage of the *tert*-cyclobutanol.

Table 4. Screening of different solvents with L31 as ligand



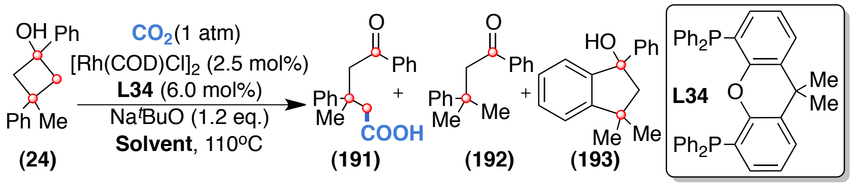
Entry	Solvent	Conversion (%)	Yield (%)			
			191	192	193	194
1	DMF	100	0	0	99	1
2	DMA	100	0	0	99	1
3	NMP	52	0	0	51	1
4	Bu_2O	100	0	0	99	1
5	Methylcyclohexane	100	0	0	99	1

6	**DME**	100	0	0	99	1

Reaction conditions: [a] **24** (0.25 mmol), $[Rh(COD)Cl]_2$ (2.5 mol%), **L31** (6.0 mol%), Na^{t}BuO (1.2 eq., 0.275 mmol), solvent (4mL/mmol) at 110°C for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

Prompted by our knowledge in CO_2 fixation processes[95,93], we hypothesized that the presence of a polar aprotic solvent would be crucial for success. Unfortunately, however, **193** was predominantly obtained with not even traces of **191** detected in the crude reaction mixture when employing **L34** as ligand.

Table 5. Screening of different solvents with L34 as ligand

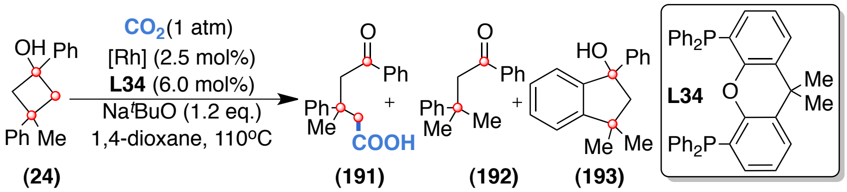


Entry	Solvent	Conversion (%)	Yield (%)		
			191	**192**	**193**
1	**DMF**	35	0	33	2
2	**DMA**	75	0	66	5
3	**NMP**	43	0	35	3
4	**Bu_2O**	0	0	0	0
5	**Methylcyclohexane**	100	0	86	14
6	**DME**	100	0	86	14

Reaction conditions: [a] **24** (0.25 mmol), $[Rh(COD)Cl]_2$ (2.5 mol%), **L34** (6.0 mol%), Na^{t}BuO (1.2 eq., 0.275 mmol), Solvent (4mL/mmol) at 110°C for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

Unlike the use of **L31**, the presence of **L34** resulted in the formation of **192** preferentially. Assuming that **192** was formed from the in-situ generated alkyl-Rh(I) species, we decided to try different Rh-sources in the presence of **L34**, hoping that CO_2 insertion would take place more rapidly (Table 6). Unfortunately, although different catalysts were utilized, no product was observed, obtaining exclusively **192**.

Table 6. Screening of different Rh catalysts

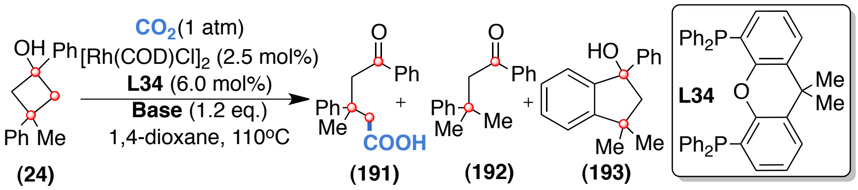


Entry	[Rh]	Conversion (%)	Yield (%)		
			191	192	193
1	$RhClCO(PPh_3)_2$	15	0	13	0
2	$RhCl(PPh_3)_3$	74	0	69	6
3	[Rh(norbornadiene)$_2$] BF_4	0	0	0	0
4	$[Rh(C_2H_4)Cl]_2$	100	0	98	2

Reaction conditions: [a] **24** (0.25 mmol), [Rh] (2.5 mol%), **L34** (6.0 mol%), Na^{t}BuO (1.2 eq., 0.275 mmol), 1,4-dioxane (4mL/mmol) at 110°C for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

Since **192** was formed preferentially with **L34**, we reasoned that the nature of the base might exert an influence for CO_2 insertion or for recovering back the active metal-species after CO_2 insertion. Although a number of bases were tested (Table 7), we found a similar reactivity pattern and **192** was formed almost exclusively.

Table 7. Screening of different bases



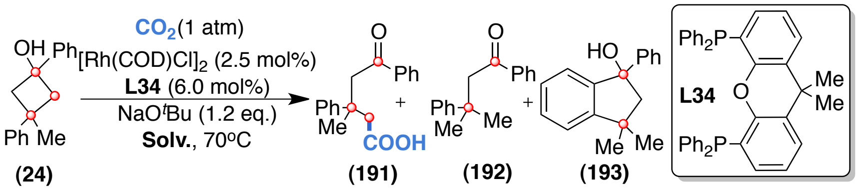
Entry	Base	Conversion (%)	Yield (%)		
			191	192	193
1	NaO^{t}Bu	100	0	91	8
3	Cs_2CO_3	100	0	87	13
4	K_2CO_3	100	0	91	8
5	KOH	72	0	65	7

6	**K_3PO_4**	88	0	82	4

Reaction conditions: [a] **24** (0.25 mmol), $[Rh(COD)Cl]_2$ (2.5 mol%), **L34** (6.0 mol%), Base (1.2 eq., 0.275 mmol), 1,4-Dioxane (4mL/mmol) at 110°C for 48 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

In light of these results, we hypothesized that decarboxylation might be occurring at high temperatures. Therefore, we looked at the reactivity of **24** with **L34** at lower temperatures (Table 8). Unfortunately, we did not see any traces of **191**, obtaining predominantly **192**.

Table 8. Screening of different solvents at 70°C

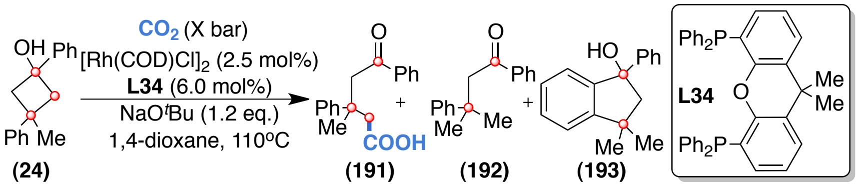


Entry	Solvent	Conversion (%)	Yield (%)		
			191	**192**	**193**
1	**DMF**	84	0	45	3
2	**DMA**	25	0	19	4
3	**THF**	70	0	55	15
4	**Methylcyclohexane**	100	0	77	23
5	**DME**	70	0	65	5

Reaction conditions: [a] **24** (0.25 mmol), $[Rh(COD)Cl]_2$ (2.5 mol%), **L34** (6.0 mol%), Na^tBuO (1.2 eq., 0.275 mmol), Solvent (4mL/mmol) at 70°C for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

Next we decided to look at the influence of CO_2 pressure, hoping that the alkyl-Rh(I) species that ultimately delivered **192** would preferentially result in **191** (Table 9).

Table 9. Screening of different pressures of CO_2



Entry	X	Conversion (%)	Yield (%)		
			191	192	193
1	10(18)	12	0	10	2
2	20(36)	17	0	14	3
3	30(57)	22	0	20	2
4	40(76)	84	0	77	13

Reaction conditions: [a] **24** (0.25 mmol), [Rh(COD)Cl]$_2$ (2.5 mol%), **L34** (6.0 mol%), Na^{t}BuO (1.2 eq., 0.275 mmol), 1,4-dioxane (4mL/mmol) at 110°C for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard. In parenthesis is the real pressure when heating the reaction vessel. [1 bar = 0.987 atm]

As shown in Table 9, an increase of CO_2 pressure to 10 bar, dropped the conversion, but invariably provided **192** and **193**. A similar effect was found at 20 and 30 bars (entries 2 and 3). On the basis of these results, we though that the employment of a transmetalating agent would be important for generating a metal carboxylate, thus resulting in the thermodynamic driving force of the reaction. To such end, we looked at the inclusion of Et_2Zn, $AlMe_3$, Et_3SiH or the influence of Lewis acids such as $AlCl_3$, $ZnCl_2$, $Zn(OTf)_2$, $Cu(OTf)_2$, $Sc(OTf)_2$ and $FeCl_3$. Under these conditions, we found either no conversion or **197** deriving from the dehydration of **24** (Figure 5.3).

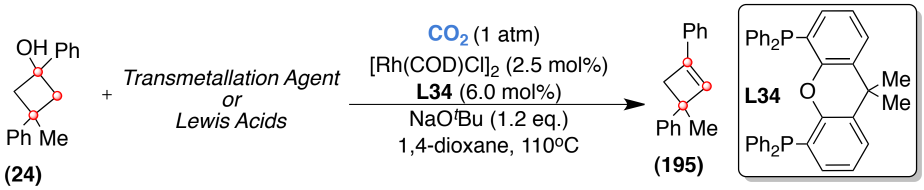


Figure 5.3

Later, we turned our attention to screen different parameters, such as other bases (e.g. KO^{t}Bu, NaO^{t}Bu, KOMe, Cs_2CO_3, K_2CO_3, KOH, CsOPiv, KOAc), ligands (as for Table 3), solvents (DMF, DMA, NMP, Bu_2O, Methylcyclohexane, DME), temperatures (110, 90, 60ºC or r.t.), transmetalating agents (Et_2Zn, $AlMe_3$ and Et_3SiH) and Lewis acids ($AlCl_3$, $ZnCl_2$, $Zn(OTf)_2$, $Cu(OTf)_2$, $Sc(OTf)_2$ and $FeCl_3$) in the presence of $Pd(OAc)_2$ as transition metal. Unfortunately, we solely observed the transformation of **24** to **192**.

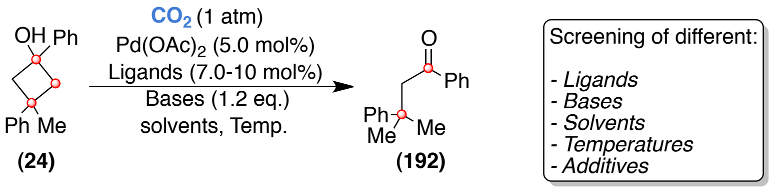


Figure 5.4

We also looked at the utilization of $[Ir(COD)Cl]_2$ and screened different parameters, such as base (e.g. KO^{t}Bu, NaO^{t}Bu, KOMe, Cs_2CO_3, K_2CO_3, KOH, CsOPiv, KOAc), ligand (as in Table 3), solvent (DMF, DMA, NMP, Bu_2O, Methylcyclohexane, DME), temperature (110, 90, 60ºC or r.t.), transmetalating agents (Et_2Zn, $AlMe_3$ and Et_3SiH) and Lewis acids ($AlCl_3$, $ZnCl_2$, $Zn(OTf)_2$, $Cu(OTf)_2$, $Sc(OTf)_2$ and $FeCl_3$), but it all resulted in the recovery of **24**.

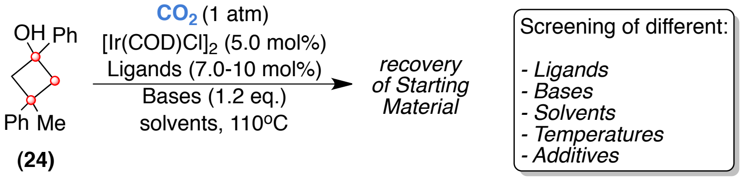


Figure 5.5

Prompted by known Cu-catalyzed carboxylation reactions[97], we employed different Cu-catalysts (e.g. CuCl, CuBr, CuBr · SMe_2, $CuCl_2$, CuF_2 and $Cu(OAc)_2$) and performed screening of different parameters such as base (e.g. KO^{t}Bu, NaO^{t}Bu, KOMe, Cs_2CO_3, K_2CO_3, KOH, CsOPiv, KOAc), ligand (as for Table 3), solvent (DMF, DMA, NMP, Bu_2O, Methylcyclohexane, DME), temperature (110, 90, 60ºC or r.t.), transmetalating agents (Et_2Zn, $AlMe_3$ and Et_3SiH) and Lewis acids ($AlCl_3$, $ZnCl_2$, $Zn(OTf)_2$, $Cu(OTf)_2$, $Sc(OTf)_2$ and $FeCl_3$), but sadly it all resulted in the recovery of **24**.

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[97] For examples, see: (a) Zhang, L.; Cheng, J.; Ohishi, T.; Hou, Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 8670-8673. (b) Tran-Vu, H.; Daugulis, O. *ACS Catal.* **2013**, *3*, 2417-2420.

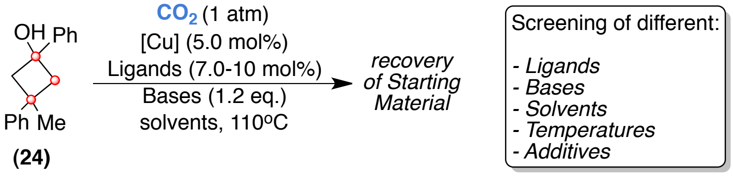


Figure 5.6

Next, we wondered whether other *tert*-cyclobutanol backbones could provide better results. Thus, we looked at the reactivity of **114**, since the absence of aromatic groups in C3 would avoid the problematic [1,4-Rh]-shift. With considerable amounts of **114** in hand, we set out to investigate its reactivity in the presence of $[Rh(COD)Cl]_2$, and we screened different parameters such as base (e.g. KO*ᵗ*Bu, NaO*ᵗ*Bu, KOMe, Cs_2CO_3, K_2CO_3, KOH, CsOPiv, KOAc), ligand (as in Table 3), solvent (DMF, DMA, NMP, Bu_2O, Methylcyclohexane, DME), temperature (110, 90, 60ºC or r.t transmetalating agents (Et_2Zn, $AlMe_3$ and Et_3SiH) and Lewis acids ($AlCl_3$, $ZnCl_2$, $Zn(OTf)_2$, $Cu(OTf)_2$, $Sc(OTf)_2$ and $FeCl_3$). Unfortunately, the only product observed was **197** and no formation of the desired γ-carboxylated ketone **196** was observed.

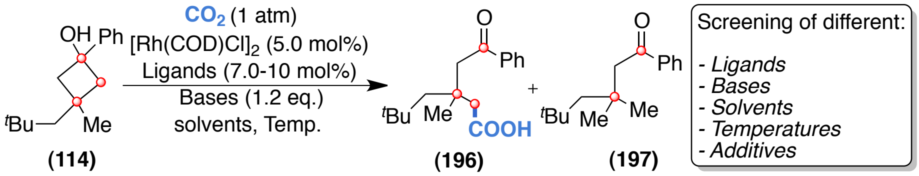


Figure 5.7

Promted by our knowledge in Ni-catalyzed carboxylation reactions, several Ni(I) and Ni(II)-sources ($[NiBr(PPh_3)_3]$, $[NiCl_2(PMe_3)_2]$, $[NiCl_2(PPh_3)_2]$, $[NiCl_2(dppe)]$, $[NiCl_2(dppp)]$, $[NiCl_2(dppf)]$), bases (NaO*ᵗ*Bu, KO*ᵗ*Bu, NaOMe, Cs_2CO_3, K_2CO_3, K_3PO_4, Na_2HPO_4), additives ($MgCl_2$, MgF_2, $MgBr_2$, MgI_2, ZnF_2, $ZnCl_2$, $ZnBr_2$, ZnI_2), ligands (diamine ligands in Figure 5.8) were screened in DMA at 70ºC but unfortunately we either observed no conversion of **114** or conversion to **197**.

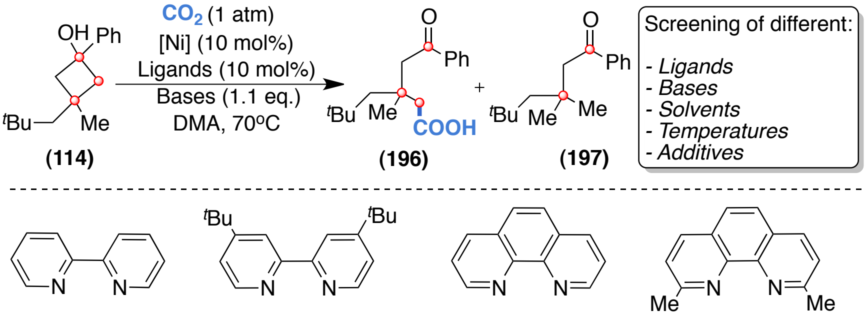
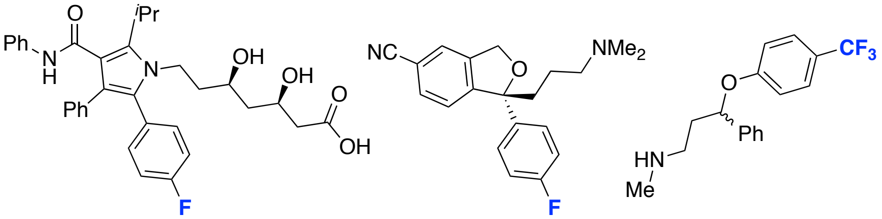


Figure 5.8

In light of these results, we decided to look at other projects, hoping that our research group will gather an in depth understanding about metal-catalyzed carboxylation processes.

5.2.2 Fluorination of *tert*-cyclobutanols via C-C bond cleavage

Fluorine uniquely affects the properties of organic molecules through strong polar interaction due to the atom's high electronegativity and small size (van der Waals radius: 1.35 Å compared to H that has approx. 1.20 Å radius).[98,99] Thus, the presence of fluorine in an organic substrate generally has a positive effect on the biological activity, metabolism, solubility, hydrophobicity and sterical properties. For these reasons, the means to promote C-F bond-forming reactions have become an intense area of research, particularly for preparing pharmaceuticals[100], agrochemicals[101] and materials.[102] Indeed, approximately 30% of all agrochemicals and 20% of all pharmaceuticals contain fluorine[100], including drugs such as Lipitor©, Lexapro© and Prozac© (Figure 5.9).



Lipitor **Lexapro** **Prozac**

Figure 5.9

There are three main pathways for introducing fluorine into an organic molecule; electrophilic fluorination, nucleophilic fluorination and radical fluorination (Figure 5.10). As fluorine is difficult to handle and can often react indiscriminately[103], several electrophilic as well as nucleophilic fluorinating reagents have been developed in

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[98] (a) Emsley. J. *The Elements*; Oxford University Press: Oxford, 1998. (b) Rossotti, H. *Diverse Atoms*; Oxford University Press: Oxford, 1998.

[99] For reviews about C-F bond forming reactions, see: (a) O'Hagan, D. *Chem. Soc. Rev.* **2008**,*37*, 308–319. (b) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470-477. (c) Adams, D. J.; Clark, J. H. *Chem. Soc. Rev.* **1999**, *28*, 225-231. (d) Ma, J. –A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1-PR43. (e) Sibi, M. P.; Landais, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 2-5. (f) Liu, H.; Gu, Z.; Jiang, X. *Adv. Synth. Catal.* **2013**, *355*, 617-626.

[100] (a) Müller, K.; Faeh, C.; Diedrich, F. *Science*. **2007**, *317*, 1881-1886. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouvemeur, V. *Chem. Soc. Rev.* **2008**, *37*, 320-330.

[101] Jeschke, P. *ChemBioChem.* **2004**, *5*, 570-589.

[102] Hung, M. H.; Farnham, W. B.; Feiring, A. E.; Rozen, S. *Fluoropolymers: Synthesis Vol. 1*; Hougham, G.; Cassidy, P. E.; Johns, K.; Davidson, T., Eds.; Plenum Press: New York, 1999; pp. 51–66.

[103] Rozen, S. *Acc. Chem. Res.* **1988**, *21*, 307-312.

order to provide selectivity and ease of handling.[104] Several *N*-fluorinated amines, quaternary salts, amides and sulfonamides have been utilized as reagents for selective electrophilic fluorination under mild conditions.[105] Taking into account the solubility of the fluorinating reagents, dipolar aprotic solvents (e.g. DMF, MeCN, Acetone or DMSO) are often required.

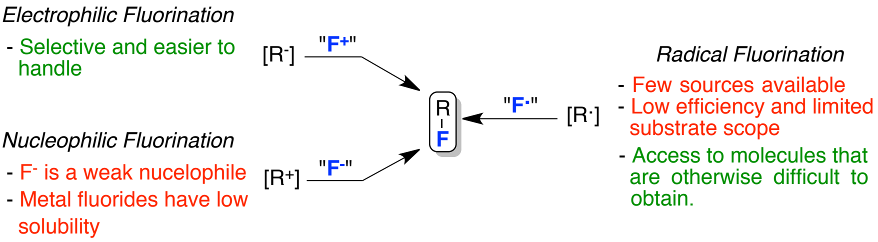

Figure 5.10

Considering the great benefits of the presence of fluorine in organic substrates, the recent years have witnessed a meteoric development in C-F bond forming reactions.[106] Among the several transition metals that are known for these transformations, Pd-catalysts have played a dominant role.[107,108] In 2006, Sanford reported the first Pd-catalyzed fluorination of C-H bonds using electrophilic fluorinating reagents (Figure 5.11).[109] The method allowed for the formation of several aromatic and benzylic C-F bonds in good yields and is believed to follow a Pd(II)/Pd(IV) pathway (Figure 5.11). Although the mechanism was proposed to go via a Pd(II)/Pd(IV) pathway, the reductive elimination from transition metal complexes to form C-F bonds was still unknown. It was not until 2008, when Ritter

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[104] Kirk, K. L. *Org. Process. Res. Dev.* **2008**, *12*, 305-351.

[105] Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737-1756.

[106] For metal-catalyzed α-fluorination of carbonyl compounds, see: (a) Ibrahim, H.; Togni, A. *Chem. Commun.* **2004**, 1147-1155. (b) Hamashima,Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2005**, *127*, 10164-10165 (and references therein).

[107] For several examples, see: (a) Handbook of Organopalladium Chemistry for Organic Synthesis; Negishi, E. I., Ed.; Wiley-Interscience: New York, 2002. (b) Chan, K. S. L.; Wasa, M.; Wang, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 9081-9084. (c) Hollingworth, C.; Hazari, A.; Hopkinson, M. N.; Tredwell, M.; Benedetto, E.; Huiban, M.; Gee, A. D.; Brown, J. M.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2011**, *50*, 2613-2617. (d) Katcher, M. H.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 17402-17404. (e) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science.* **2009**, *325*, 1661-1664.

[108] For reviews, see: (a) Grushin, V. V. *Chem.-Eur. J.* **2002**, *8*, 1006-1014. (b) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature.* **2011**, *473*, 470-477. (d) Liu, G. *Org. Biomol. Chem.* **2012**, *10*, 6243-6248.

[109] Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134-7135.

reported the first evidence to C-F reductive elimination from a Pd(IV) complex.[110]

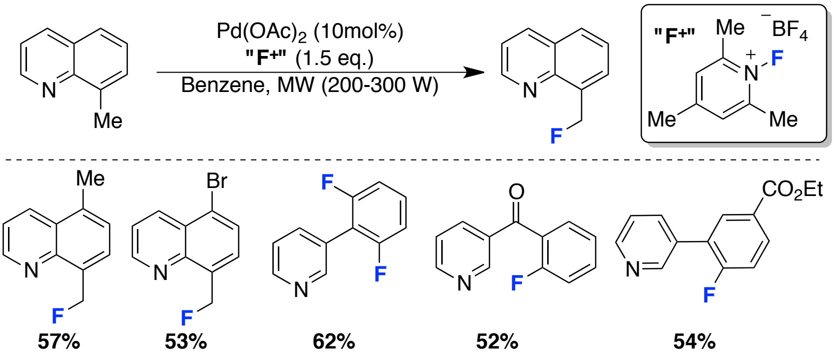

Figure 5.11

Buchwald reported the first Pd(0)-catalyzed Csp^2-F bond forming cross-coupling reaction in 2009 using aryltriflates and CsF as a nucleophile fluorine source (Figure 5.12). The use of bulky monodentate phosphine ligand, ^{t}BuBrettPhos (**L**, Figure 5.12) gave access to arylpalladium fluoride complex that could undergo C-F reductive elimination. The methodology allowed the formation of a variety of functional groups, e.g. nitro, amine, ester and ketones (Figure 5.12).[111]

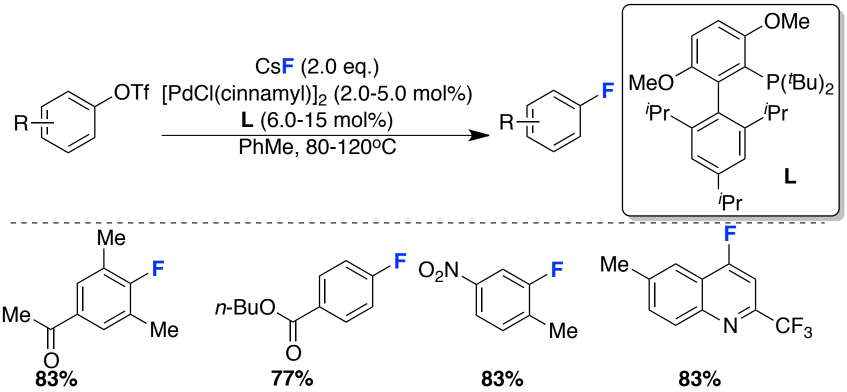

Figure 5.12

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[110] (a) Ritter, T.; Furuya, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060-10061. (b) Furuya, T.; Benitez, D.; Tkatchouk, E.; Strom, A. E.; Tang, P.; Goddard III, W. A.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 3793-3807.

[111] Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science.* **2009**, *325*, 1661-1664.

Inspired by these reports, we were interested in the γ-fluorination of *tert*-cyclobutanols via C-C bond cleavage. We hypothesized that the mechanism for the synthesis of γ-fluorinated ketones would go via ligand exchange giving rise to Pd(II)-complex **VIII** (Figure 5.13) and β-carbon elimination giving access to Pd(II)-complex **IX**. Such species could either undergo a direct fluorination of the alkyl-Pd bond (*Path A*) or an oxidation, giving access to Pd(IV)-complex **X** that subsequently undergoes reductive elimination to give the γ-fluorinated ketone **198** (*Path B*).

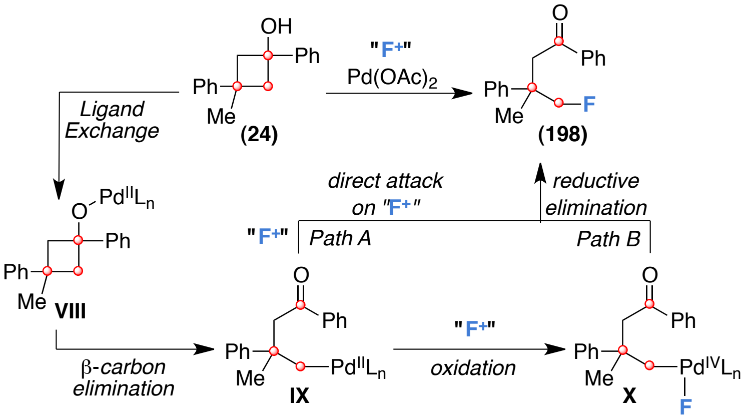
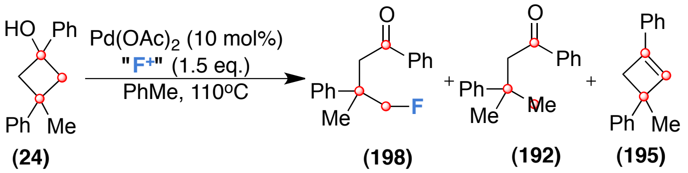


Figure 5.12

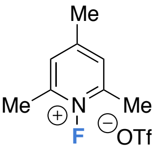
Thus, we started our screening with **24** as model substrate in the presence of Pd(OAc)$_2$ in PhMe at 110°C and screened different electrophilic fluorinating reagents (Table 10). As shown in Table 10, we did not detect in any case the desired γ-fluorinated ketone **198**. In all of the cases, we either obtained no conversion of **24** or we observed the formation of **192** or **195** as well as traces of some small peaks that were not possible to isolate and identify. We then tried to screen different solvents (DCE, DMF and 1,4-dioxane) as well as different temperatures (70, 80 and 90°C) in the presence of different electrophilic fluorinating reagents but, unfortunately, nothing resulted in the formation of the desired final product **198**.

Table 10. Screening of different electrophilic fluorinating reagents

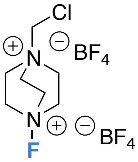


Entry	"F+"	Conversion (%)	Yield (%)
			198
1	F+-1	80	0
2	F+-2	0	0
3	F+-3	93	0
4	F+-4	68	0
5	F+-5	0	0

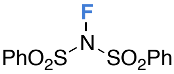
Reaction conditions: [a] **24** (0.25 mmol), $Pd(OAc)_2$ (10 mol%), **"F+"** (1.5 eq.), PhMe (4mL/mmol) at 110ºC for 12 h. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.



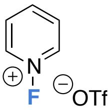
F+-1



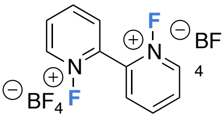
F+-2



F+-3



F+-4



F+-5

Although we did not obtain good results and we only looked at the targeted C-F bond-forming reactions specifically, members of our research group will look into such approach in the future.

CHAPTER 6

GENERAL CONCLUSIONS AND OUTLOOK

The means to promote catalytic C-C bond-functionalization has gained a considerable attention in recent years and probably can be considered one of the most challenging and vibrant subjects in organometallic chemistry. This PhD thesis deals with such challenge by designing new metal-catalyzed functionalization of C-C bonds in four-membered ring frameworks. Specifically, we have demonstrated the viability of preparing γ-arylated ketones via Pd-catalyzed cleavage of C-C bonds in *tert*-cyclobutanol backbones using aryl chloride or aryl tosylate counterparts (***Chapter 2***). The transformation is distinguished by its wide substrate scope, including particularly challenging substrate combinations, and at remarkable low catalyst loadings (0.5 mol% of Pd). The selectivity profile was easily controlled by the ligand backbone, with electron-rich and sterically-hindered phosphine ligands providing an unique reaction outcome that avoided the proclivity of alkyl metal species towards destructive β–hydride elimination (Figure 6.1).

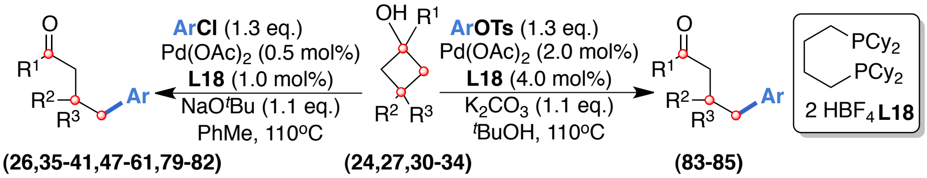


Figure 6.1

Prompted by the precedents in Chapter 2, we have successfully extended the scope of the metal-catalyzed C-C bond-cleavage of *tert*-cyclobutanols to the coupling of halo acetylene counterparts en route to rather elusive γ-alkynylated ketone derivatives (***Chapter 3***, Figure 6.2). Interestingly, the substituents on the alkyne motif showed a remarkable influence on reactivity that could be easily tuned by the inclusion of an appropriate ligand backbone. Of particular interest is the application profile of such methodology since we have demonstrated that γ-alkynylated ketone derivatives could be a functional handle by promoting a consecutive metal-catalyzed transformation into valuable synthetic intermediates.

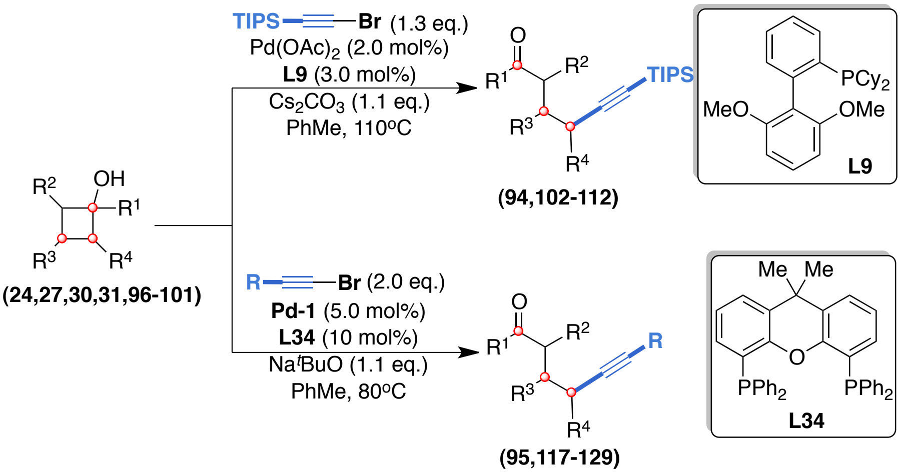


Figure 6.2

In ***Chapter 4***, we have extended the interest for C-C bond-cleavage in four-membered ring frameworks beyond the utilization of *tert*-cyclobutanols as coupling partners. Specifically, we have developed a conceptually new Ni-catalyzed C-C bond-cleavage event in benzocyclobutenones for preparing eight-membered rings via a formal [4+4]-cycloaddition with simple dienes (Figure 6.3). Intriguingly, such a method shows a specific preference for eight-membered rings over the *a priori* thermodynamically more stable six-membered rings, a matter of great synthetic and mechanistic significance.

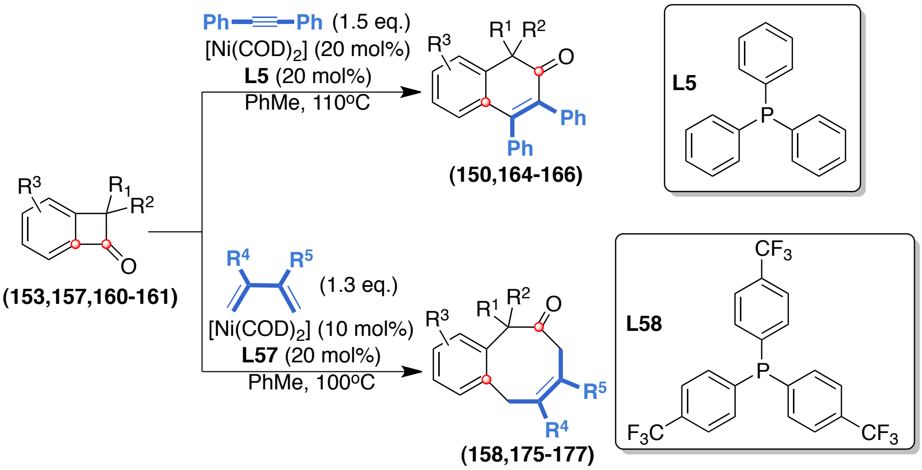


Figure 6.3

Although not explored in detail, this PhD thesis has also studied the viability of promoting a catalytic CO_2 fixation and C-F bond-formation via metal-catalyzed C-C bond-cleavage of *tert*-cyclobutanols (***Chapter 5)***. While we have not found reaction conditions to effect the desired transformations, our research group is actively involved in related catalytic endeavors and it is expected that such research will shed light into the targeted CO_2 fixation or C-F bond-forming reactions via C-C bond-cleavage.

CHAPTER 7
PUBLICATIONS

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Formal γ-alkynylation of ketones *via* Pd-catalyzed C–C cleavage†‡

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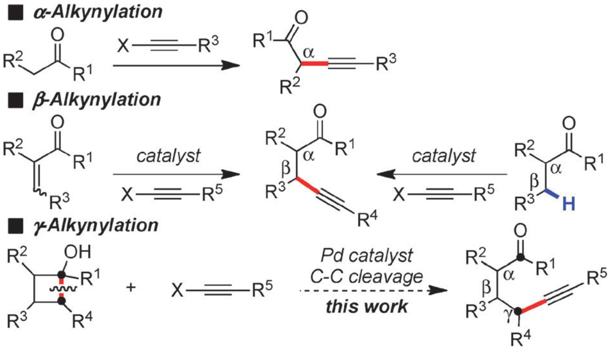
Asraa Ziadi, Arkaitz Correa and Ruben Martin*

A formal γ-alkynylation of ketones *via* Pd-catalyzed C–C bond-cleavage is presented. The method allows for the coupling of *tert*-cyclobutanols and bromoacetylenes, giving access to versatile alkynes that are beyond reach otherwise.

The high chemical versatility of alkynes and their pivotal role as key synthetic intermediates in chemical biology and material sciences have attracted the attention of organic chemists for decades.[1,2] Classical methods for preparing alkyne-containing compounds involve the classical dehydrohalogenation of halogen derivatives, alkylation of terminal alkynes, Corey–Fuchs-type reactions or Seyferth–Gilbert homologation, among others.[1] Recent catalytic strategies have shown their advantages over the classical methods in which harsh conditions are avoided with good chemoselectivities.[1] Unlike the preparation of aromatic alkyne derivatives,[3] the metal-catalyzed installation of alkynes into functionalized aliphatic backbones *via* C(sp^3)–C(sp) bond-forming processes is still a remarkable challenge.[4] Although formidable advances have been made in the α- and β-alkynylation of carbonyl compounds (Scheme 1),[5–7] the development of a general route for the catalytic γ-alkynylation of carbonyl compounds has not yet been described.[8] We wondered whether the propensity of *tert*-cyclobutanols to undergo β-carbon elimination[9,10] could step up the stage for a Pd-catalyzed C(sp)–C(sp^3) bond-formation as a means to access γ-alkynylated ketones (Scheme 1, bottom), thus constituting a complementary approach to the well-established γ-arylation processes.[11] As part of our ongoing investigations on inert bond-activation,[12] we disclose our results that demonstrate the feasibility of this hypothesis and exploit a previously unrecognized opportunity for the catalytic coupling of *tert*-cyclobutanols and haloacetylene derivatives.

We began our investigations with **1a**, readily prepared in a large scale from commercially available starting materials,[13] as the model substrate. The effects of palladium precatalyst, ligand, base, solvent and temperature were systematically examined. After considerable optimization, we pleasingly found that the combination of $Pd(OAc)_2$, SPhos and Cs_2CO_3 in toluene at 110 °C provided the best results for the desired coupling reaction, affording the γ-alkynylated ketone **3a** in 92% isolated yield. Subsequently, we found that the coupling of the chloro- and iodoethynyl derivatives also afforded **3a**, but in lower yields.[14] Similarly, solvents other than toluene and inorganic bases such as K_2CO_3, Na*t*BuO or K_3PO_4 had a deleterious effect on the reactivity, affording **3a** in much lower yields.[14]

Encouraged by these findings, we turned our attention to studying the generality of this reaction regarding the substitution pattern on the *tert*-cyclobutanol backbone. The results of this investigation are summarized in Table 1. As shown, the reaction manifests a broad substrate scope in which both aromatic and aliphatic groups at different positions on the *tert*-cyclobutanol backbone gave access to the corresponding γ-alkynylated ketones in good yields. The successful preparation of **3e** highlights the greater reactivity of **2a** as compared to aryl chlorides. Interestingly, the coupling reaction was not limited to 3,3-disubstituted *tert*-cyclobutanols; as shown for **3c**–**3e** and **3j**, 3-monosubstituted derivatives yielded the final products in comparable yields. Remarkably, 3,3-unsubstituted *tert*-cyclobutanols could be applicable as well (**3f**–**3i**); no competitive β-hydride elimination from the initially generated C(sp^3)–metal species was observed in the crude reaction mixtures.[15] As illustrated for **3f** and **3g** high levels of regioselectivity were found when using unsymmetrical *tert*-cyclobutanols in which the C–C bond cleavage



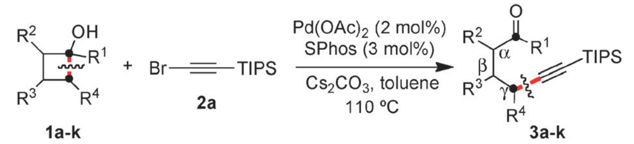
Scheme 1 Alkynylation methods of carbonyl compounds.

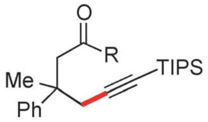
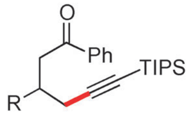
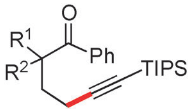
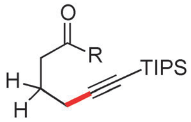
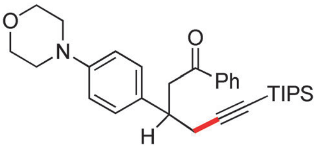
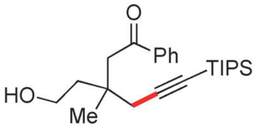
Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007, Tarragona, Spain. E-mail: rmartinromo@iciq.es; Tel: +34 977920248

† This article is part of the *ChemComm* 'Emerging Investigators 2013' themed issue.

‡ Electronic supplementary information (ESI) available. See DOI: 10.1039/c2cc37281a

Table 1 Reaction scope[a]



Entry	Product	Yield[b] (%)
1 2		R = Ph, 92 (**3a**) R = iPr, 83 (**3b**)[c]
3 4 5		R = *n*Hex, 88 (**3c**)[c] R = Ph, 78 (**3d**) R = 4-ClC$_6$H$_4$, 53 (**3e**)
6 7		R^1 = R^2 = Ph, 76 (**3f**) R^1 = Ph, R^2 = H, 69 (**3g**)
8 9		R = Ph, 82 (**3h**) R = CH$_2$C(Me)$_2$Ph, 86 (**3i**)
10		62 (**3j**)
11		41 (**3k**)[d]

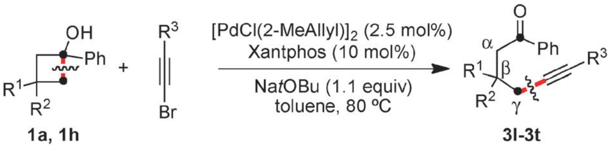
[a] Reaction conditions: **1** (0.35 mmol), **2a** (0.52 mmol), Pd(OAc)$_2$ (2 mol%), SPhos (4 mol%), Cs$_2$CO$_3$ (0.40 mmol), toluene (2 mL) at 110 °C. [b] Isolated yields, average of at least two independent runs. [c] Pd(OAc)$_2$ (4 mol%). [d] Cs$_2$CO$_3$ (2.50 equiv.).

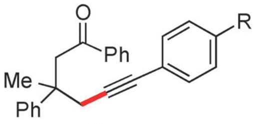
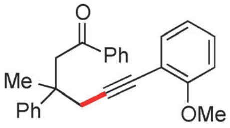
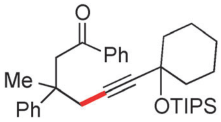
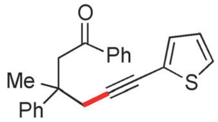
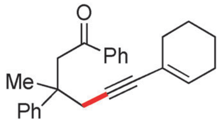
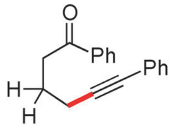
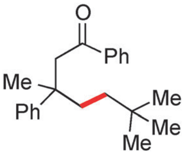
takes place at the less hindered position. The successful coupling of amine derivative **1j** demonstrates little Lewis acidity of our catalyst, if any. In line with the same notion, the method allowed for the coupling of *tert*-cyclobutanol derivatives possessing unprotected primary alcohols (**1k**); in this particular case, 2.5 equivalents of Cs$_2$CO$_3$ were required, thus yielding **3k**, albeit in lower yields.[16]

Prompted by the precedents shown in Table 1, we hypothesized whether the method could be extended to bromoacetylene derivatives other than (bromoethynyl)triisopropylsilane. Unfortunately, neither aromatic nor aliphatic bromoalkyne derivatives could be coupled with **1a** under the optimized reaction conditions in Table 1 based on SPhos. Indeed, not even traces of γ-alkynylated ketone could be detected by GC analysis of the crude reaction mixtures. These results manifest the remarkable and unique reactivity of **2a** as compared to other coupling partners.[6] However, after a careful re-optimization of the reaction conditions we found that the use of allylpalladium dimers in combination with Xantphos provided good yields for the coupling of (bromoethynyl)benzene (Table 2, **3l**).[17] As shown in entries 2 and 3, our method could be extended to other aromatic-substituted acetylenes possessing either electron-rich (**3m**) or electron-deficient groups (**3n**). Interestingly, the coupling of *ortho*-substituted and heteroaromatic alkynes could also be accomplished in moderate to good yields under otherwise similar reaction conditions (**3o**, **3q**). However, the coupling of bromoenynes resulted in partial decomposition, leading to **3r** in low yields. Furthermore, bromoacetylenes substituted with aliphatic backbones possessing bulky silyl-protected ethers could be tolerated under the reaction conditions based on Xantphos (**3q**). As for **3f–3i**, 3,3-unsubstituted *tert*-cyclobutanols could be utilized for the coupling with (bromoethynyl)benzene, affording **3s** in moderate yields.[16] Gratifyingly, our method was not restricted to bromoethynyl derivatives; as shown for **3t**, our protocol allowed for the coupling of alkyl halides in high yields, formally constituting a powerful catalytic manifold for preparing γ-alkylated ketones in a straightforward manner.

With substantial amounts of **3a** in hand, we focused our attention on demonstrating whether our method could be

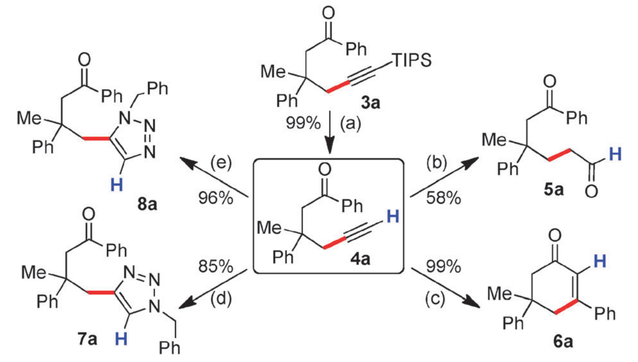
Table 2 Reaction scope[a]



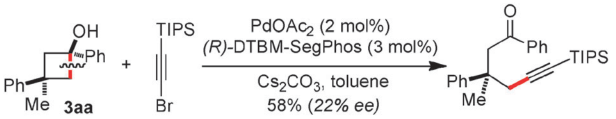
Entry	Product	Yield[b] (%)
1 2 3		R = H, 75 (**3l**) R = *t*Bu, 58 (**3m**) R = CF$_3$, 52 (**3n**)[b]
4		41 (**3o**)
5		64 (**3p**)
6		61 (**3q**)[b]
7		35 (**3r**)
8		46 (**3s**)
9		87 (**3t**)[c]

[a] Reaction conditions: **1** (0.50 mmol), **2** (1 mmol), [PdCl(2-Me-allyl)]$_2$ (2.50 mol%), Xantphos (10 mol%), Na*t*BuO (0.60 mmol), toluene (1 mL) at 80 °C; isolated yields, average of two independent runs. [b] 4 equivalents of bromoacetylene were used. [c] Using reaction conditions in Table 1.

Table 3 Synthetic applicability



Reaction conditions: (a) TBAF (1.1 equiv.), THF, rt, 99%; (b) $(Chex)_2BH$, $NaBO_3$, THF, 58%; (c) $AuCl_3$ (5 mol%), AgOTf (15 mol%), DCM, 99%; (d) BnN_3, $Cu(OAc)_2$ (5 mol%), sodium ascorbate (25 mol%), *t*BuOH-H_2O, rt, 96%; (e) BnN_3, Cp*RuClCOD (2 mol%), toluene, rt, 85%.



Scheme 2 Enantioselective γ-alkynylation of ketones.

employed as a platform for molecular diversity. As shown in Table 3, this was indeed the case; the significant increase in molecular complexity achieved by otherwise simple and reliable transformations is quite appealing, thus giving access to structures that are difficult to obtain by other means. Notably, a formal anti-Markovnikov hydration of alkyne **4a** *via* a hydroboration–oxidation sequence[18] gave synthetically-attractive aldehyde **5a** in 58% overall yield. Interestingly, cyclohexenone **6a** could quantitatively be obtained by a Au-catalyzed cycloisomerization event in which the aromatic group formally migrates to the C3 position of the cyclohexenone motif.[19] Furthermore, we also demonstrate that triazoles **8a** and **9a** could easily be prepared as single regioisomers *via* Cu-[20] or Ru-catalyzed[21] [3+2]-type cycloadditions with benzyl azide.

Despite remarkable advances in the field of C–C bond-cleavage in recent years, particularly *via* β-carbon elimination pathways,[9] the development of enantioselective C–C bond cleavage approaches still remains a formidable challenge.[22] Although a thorough investigation awaits further studies, we have preliminarily found that a certain level of asymmetric induction can be obtained when using DTBM-SegPhos for the coupling of **3aa** and **2a** (Scheme 2). While modest, this result represents the first asymmetric route for preparing γ-alkynylated ketones and holds great promise for future developments in this area.

In summary, we have developed the first route to γ-alkynylated ketones *via* Pd-catalyzed C–C bond-cleavage. The chosen approach is highly convergent and involves a minimum number of manipulations due to the ready availability of the starting materials. Such a route provides a direct access to scaffolds that are beyond reach otherwise and allows the conversion of γ-alkynyl ketones into a diverse array of advanced synthetic intermediates. Further investigations along these lines and the development of an enantioselective route to γ-alkynyl ketones are currently ongoing in our laboratories.

The authors thank the ICIQ Foundation, the European Research Council (ERC-277883) and MICINN (CTQ2009-13840 & CTQ2012-34054) for financial support. Johnson Matthey, Umicore and Nippon Chemical Industrial are acknowledged for a gift of metal and ligand sources. R.M and A.C thank MICINN for RyC and JdC fellowships.

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Ligand-Accelerated Pd-Catalyzed Ketone γ-Arylation via C–C Cleavage with Aryl Chlorides

Asraa Ziadi and Ruben Martin*

Institute of Chemical Research of Catalonia (ICIQ), Av Països Catalans 16, 43007, Tarragona, Spain

rmartinromo@iciq.es

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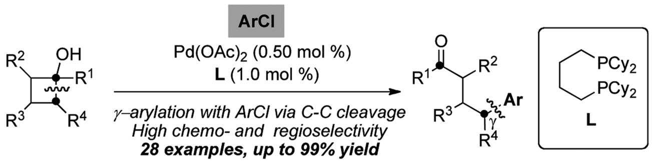
ABSTRACT



A highly efficient Pd-catalyzed arylative ring expansion of cyclobutanols via C–C bond cleavage is presented. The method allows the coupling of aryl chlorides at low catalyst loadings with a wide range of functional groups and substitution patterns, thus constituting a straightforward alternative for preparing rather elusive γ-arylated ketones.

While the functionalization of carbonyl compounds has evolved into routine tools in organic synthesis,[1] only recently have extensions of this chemistry to α-arylation processes become possible.[2] In striking contrast, catalytic methods in route to rather elusive but naturally occurring γ-arylated ketones[3] have been much less explored. Despite formidable advances in the field of γ-arylation (Scheme 1, path a),[4] these methods still have some limitations with respect to the α- vs γ-regioselectivity: the need for α,β-unsaturated ketones, which necessarily requires a subsequent reduction step, self-condensation under basic conditions, and low reactivity of the resulting enolates. Therefore, a more flexible and general approach to γ-arylated ketones is still of critical importance.

Over the past few years, the functionalization of inert bonds[5] has widely been recognized as a powerful tool in the arsenal of the synthetic organic chemist, particularly in the field of C–H functionalization.[6] However, the development of catalytic methods for C–C bond cleavage still constitutes a tremendous challenge.[7] Among the available strategies for promoting catalytic C–C bond cleavage, β-carbon elimination[8] has been shown to be particularly

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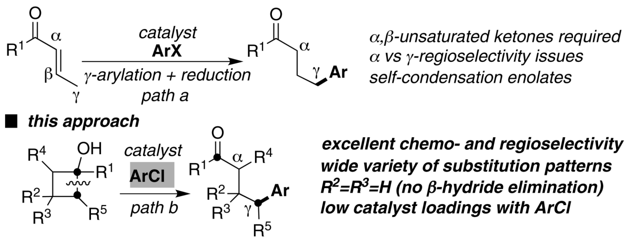
10.1021/ol300119u

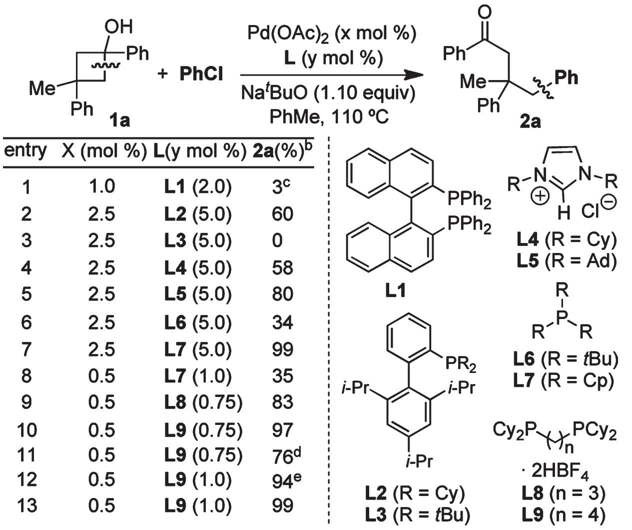
effective for rapidly constructing carbonyl compounds.[9] In 1999, Uemura described a ring expansion of *tert*-cyclobutanols[10] with *aryl bromides* via β-carbon elimination.[11] Unfortunately, however, no examples with functionalized or particularly hindered backbones were reported. Similarly, 3,3-unsubstituted *tert*-cyclobutanols (Scheme 1, $R^2 = R^3 =$ H) were not described, likely due to the proclivity of the σ-bound palladium intermediate to β-hydride elimination. Importantly, *the method was restricted to aryl bromides*; thus, aryl chlorides, which from the standpoint of cost and availability are more attractive coupling counterparts,[12] remained unreactive.[13] Consequently, a new catalytic system capable of operating at low catalyst loadings employing the more readily available aryl chlorides[13] as substrates would be an extremely valuable tool for the synthetic community. Herein, we present a general ketone γ-arylation via C–C bond cleavage that not only allows the coupling of aryl chlorides at low catalyst loadings but also tolerates a wide range of functional groups and substitution patterns (Scheme 1, bottom), including hindered substrate combinations and the use of elusive 3,3-unsubstituted *tert*-cyclobutanols (Scheme 1, $R^2 = R^3 =$ H) in which no β-hydride elimination was observed.

Scheme 1. Ketone γ-Arylation via C–C Cleavage



We began our study with chlorobenzene and **1a**[14] as the model substrate (Scheme 2). As expected, the previously reported procedure for aryl bromides resulted in very low conversion to **2a** (entry 1).[10,11] Therefore, a variety of experimental variables, such as the Pd precatalysts, ligands, bases, and solvents were systematically examined. On the basis of our own findings when activating inert molecular bonds,[15] we hypothesized that the use of bulky and electron-rich ligands would be critical for achieving success as many elementary steps within the catalytic cycle can dramatically be accelerated. Among the ligands examined, **L7** was found to be particularly effective when using 2.5 mol % $Pd(OAc)_2$, and Na*t*BuO in toluene at 110 °C (entry 7). Prompted by these results, we wondered whether the method could operate at lower catalyst loadings. As shown in entries 8–13, this was indeed the case. After some optimization, we found that the use of **L9** allowed the preparation of **2a** in a quantitative yield at 0.50 mol % Pd loadings in a Pd/L ratio of 1:2 (entry 13). At present, we believe that the bulky and electron-donating character of **L9** is crucial for stabilizing monoligated $L_1Pd(0)$ species, which are believed to be the key propagating species in many cross-coupling reactions,[16] thus allowing the oxidative addition to proceed at a faster rate.

Scheme 2. Optimization of Reaction Conditions[a]



entry	X (mol %)	L(y mol %)	2a(%)[b]
1	1.0	**L1** (2.0)	3[c]
2	2.5	**L2** (5.0)	60
3	2.5	**L3** (5.0)	0
4	2.5	**L4** (5.0)	58
5	2.5	**L5** (5.0)	80
6	2.5	**L6** (5.0)	34
7	2.5	**L7** (5.0)	99
8	0.5	**L7** (1.0)	35
9	0.5	**L8** (0.75)	83
10	0.5	**L9** (0.75)	97
11	0.5	**L9** (0.75)	76[d]
12	0.5	**L9** (1.0)	94[e]
13	0.5	**L9** (1.0)	99

[a] Reaction conditions: **1a** (0.50 mmol), PhCl (1.30 equiv), $Pd(OAc)_2$ (*x* mol %), L (*y* mol %), Na^{t}BuO (1.10 equiv), PhMe (2 mL) at 110 °C for 12 h. [b] GC yields using dodecane as internal standard. [c] **L1** was used following conditions reported in ref 10: Pd_2dba_3 (0.5 mol %), **L1** (2.0 mol %), K_2CO_3 (1.10 equiv) in dioxane (0.20 M). [d] Diglyme (2 mL) was used as the solvent. [e] KOH (1.10 equiv) was used as the base.

Having established the optimized reaction conditions, we set out to explore the scope of this reaction. As shown in Scheme 3, a host of aryl chlorides with electron-withdrawing (**2e**) or electron-donating substituents (**2c**, **2d**, and **2f**) reacted equally well with **1a** in good to excellent yields. Our protocol was found to be tolerant of a number of functional groups such as thioethers (**2d**), amines (**2f**), ketones (**2g**), alkenes (**2h**), acetals (**2i**), and heterocycles (**2m** and **2o**).[17] Interestingly, we could effect monofunctionalization when employing 1,3-dichlorobenzene, affording **2j** in 82% yield. Particularly noteworthy is the preparation of **2g** as it has been shown that classical α-arylation of carbonyl

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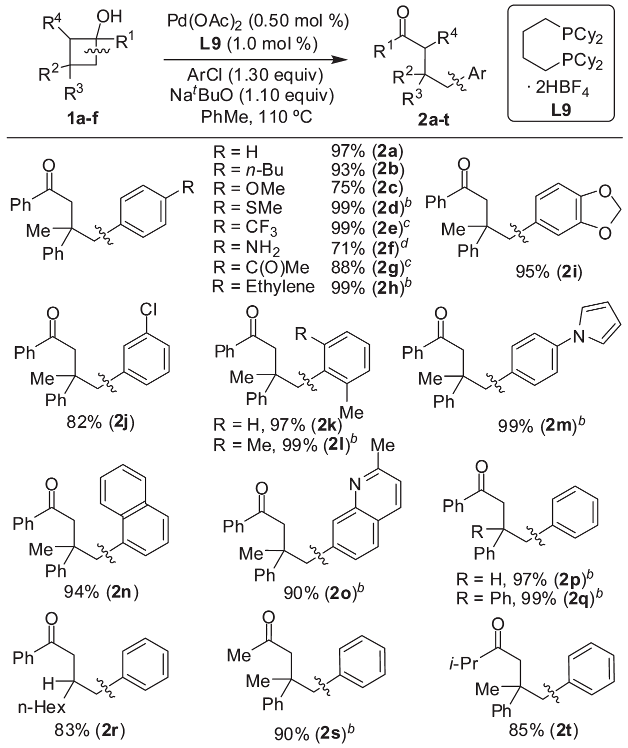
compounds usually requires strong bases;[2] in our hands, however, α-arylation was completely suppressed and exclusive formation of the γ-arylated ketone **2g** was observed. Similarly, the reaction of 4-chloroaniline also showed complete selectivity for the α-arylated ketone **2f**; no *N*-arylation at the free aniline was observed by NMR spectroscopy of the crude reaction mixture. Notably, unlike previous β-carbon elimination procedures utilizing aryl bromides,[10,11] our method allows, for the first time, the use of *bis-ortho* substituted electrophiles in essentially quantitative yields (**2l**). We believe that the excellent activity and functional group compatibility in Scheme 3 illustrates the robustness and the application profile of our method based upon **L9**.

Scheme 3. Reaction Scope with Different ArCl[a]

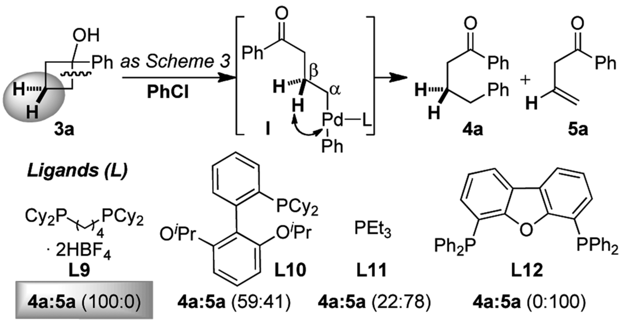


[a] Reaction conditions same as those for Scheme 2 (entry 13); isolated yields, average of at least two independent runs. [b] Pd(OAc)$_2$ (1.0 mol %). [c] K$_2$CO$_3$ (1.10 equiv) and **L7** were used. [d] Pd(OAc)$_2$ (2.5 mol %).

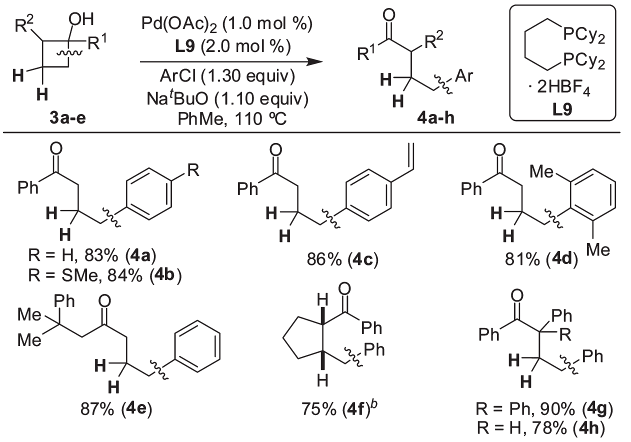
Next, we turned our attention to study the substitution pattern on the cyclobutanol backbone. As becomes apparent from the results in Scheme 3, a diverse set of substitution patterns including aliphatic or aromatic groups gave the corresponding γ-arylated ketones in good to excellent yields (**2p**–**2t**). Remarkably, no side products were obtained for **2s** and **2t**, thus indicating that the presence of acidic α-protons in alkyl-substituted ketones does not interfere with productive formation of the corresponding coupling products.

While some progress has been achieved when employing 3-monosubstituted *tert*-cyclobutanols (Scheme 3, **2p** and **2r**),[10,11] there are no catalytic methods dealing with the use of completely unsubstituted *tert*-cyclobutanols **3a** (Scheme 3, R$^{2-4}$ = H) in intermolecular reactions via β-carbon elimination pathways. This is likely due to the high reactivity of the initially generated alkylmetal species toward *syn*-β-hydride elimination, thus preventing the coupling process. An illustrative example is shown in Scheme 4. While **L9** exclusively afforded the desired γ-arylation product (**4a**) via reductive elimination from **I**, the use of structurally related bidentate ligands such as **L12**, among others, showed the exclusive formation of the β-hydrogen elimination product (**5a**). The use of **L10** or **L11** resulted in **4a**:**5a** mixtures in which competitive β-hydride elimination could not be avoided. We believe the experiments in Scheme 4 illustrate the unique reactivity of our new catalytic γ-arylation protocol based upon **L9**. We currently propose that **L9** retards β-hydride elimination[18] and enhances the subsequent reductive elimination step within the catalytic cycle.[19]

Scheme 4. Ligand Effect in Unsubstituted *tert*-Cyclobutanols



Scheme 5. Reaction Scope with 3,3-Unsubstituted Backbones[a]



[a] Reaction conditions same as those for Scheme 3; isolated yields, average of at least 2 independent runs. [b] Pd(OAc)$_2$ (2.0 mol %), K$_2$CO$_3$ (1.10 equiv), and **L7** were used.

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(18) (a) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215. (b) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217.

(19) Hartwig, J. F. *Inorg. Chem.* **2007**, *46*, 1936.

As shown in Scheme 5, our arylative ring-opening reaction employing unsubstituted *tert*-cyclobutanol **3a** cross-coupled, with high yields, a representative set of aryl chlorides possessing thioethers (**4b**), alkenes (**4c**), or even with di-*ortho*-substitution as well (**4d**). As for **2s** and **2t** (Scheme 3), the reaction of alkyl substituted *tert*-cyclobutanol **3b** possessing acidic α-protons afforded **4e**. On the basis of these results, we anticipated that high levels of regioselectivity could be obtained when using unsymmetrically substituted backbones. As expected, this was indeed the case and *cis*-fused **4f**, **4g**, and **4h** were obtained as single regioisomers in which the C–C bond cleavage occurs at the less sterically hindered position.

In summary, a highly active Pd-catalyzed ketone γ-arylation via C–C cleavage with aryl chlorides at low catalyst loadings has been developed. The broad scope and high chemoselectivity profile makes this method a straightforward alternative to the existing methods for the synthesis of γ-arylated ketones. In further studies, we aim to explore the enantioselective variant of this reaction, unravel the mechanism,[20] and fully explore the potential of this and related transformations.

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Supporting Information Available. Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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[20] Deuterium labeling on the *tert*-cyclobutanol backbone showed a constant $k_H/k_D = 0.60$. Whether this kinetic isotope effect might be attributed to a steric isotope effect is a matter of current mechanistic investigations in our laboratories, and it will be reported in due course.