ORGANIC LETTERS

2012
Vol. 14, No. 5
1266–1269

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

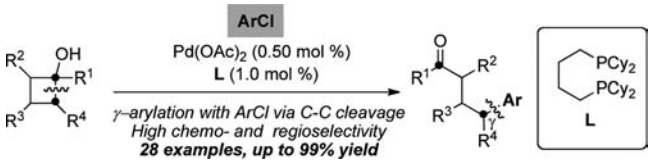
Asraa Ziadi and Ruben Martin*

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

rmartinromo@iciq.es

Received January 17, 2012

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

(1) Bew, S. P. In *Comprehensive Organic Functional Groups Transformation II*; Katritzky, A. R., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2005.

(2) For recent reviews, see: (a) Novák, P.; Martin, R. *Curr. Org. Chem.* **2011**, *15*, 3233–3262. (b) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082. (c) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676. (d) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234 and references therein.

(3) (a) Majetich, G.; Liu, S.; Fang, J.; Siesel, D.; Zhang, Y. *J. Org. Chem.* **1997**, *62*, 6928. (b) Huneck, S.; Akinniyi, J. A.; Cameron, A. F.; Connolly, J. D.; Mulholland, A. G. *Tetrahedron Lett.* **1981**, *22*, 351.

(4) For selected references: (a) Duez, S.; Bernhardt, S.; Heppekausen, J.; Fleming, F. F.; Knochel, P. *Org. Lett.* **2011**, *13*, 1690. (b) Huang, D. S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2010**, *49*, 5757. (c) Hyde, A. M.; Buchwald, S. L. *Org. Lett.* **2009**, *11*, 2663. (d) Hyde, A. M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 177.

(5) Murai, S. *Activation of unreactive bonds and organic synthesis*; Topics in Organometallic Chemistry; Springer-Verlag: Berlin, 1999; Vol. 3.

(6) For selected reviews: (a) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992. (b) McMurry, L.; ÓHara, F.; Gaunt, M. *Chem. Soc. Rev.* **2011**, *40*, 1885. (c) Lyons, T. W.; Sanford, M. *Chem. Rev.* **2010**, *110*, 1147. (d) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094 and references therein.

(7) For selected reviews: (a) Murakami, M.; Matsuda, T. *Chem. Commun.* **2011**, *47*, 1100. (b) Seiser, T.; Cramer, N. *Org. Biomol. Chem.* **2009**, *7*, 2835. (c) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (d) Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610. (e) Nishimura, T.; Uemura, S. *Synlett* **2004**, 201. (f) van der Boom, M. E.; Milstein, D. *Chem. Rev.* **2003**, *103*, 1759 and references therein.

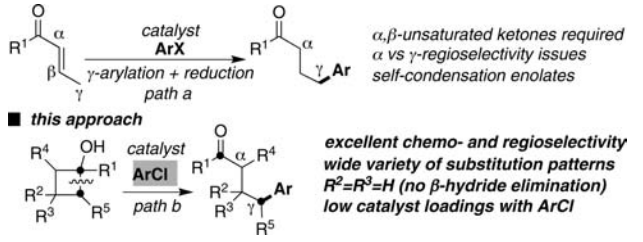
(8) For selected reviews, see: (a) Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 7740. (b) Aïssa, C. *Synthesis* **2011**, 3389. (c) Murakami, M.; Makino, M.; Ashida, S.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1315.

(9) For a selection of catalytic methods: (a) Schweinitz, A.; Chtchemelinine, A.; Orellana, A. *Org. Lett.* **2011**, *13*, 232. (b) Seiser, T.Cramer, N. *J. Am. Chem. Soc.* **2010**, *132*, 5340. (c) Seiser, T.; Roth, O. A.; Cramer, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6320. (e) Matsuda, T.; Shigeno, M.; Murakami, M. *J. Am. Chem. Soc.* **2007**, *129*, 12086. (f) Murakami, M.; Ashida, S.; Matsuda, T. *J. Am. Chem. Soc.* **2006**, *128*, 2166 and references therein.

10.1021/ol300119u
Published on Web 02/14/2012

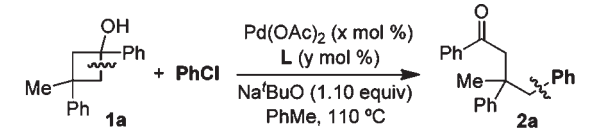
effective for rapidly constructing carbonyl compounds.[9] In 1999, Uemura described a ring expansion of *tert*-cyclobutanols[10] with *aryl bromides* via β-carbon elimination.[11] Unfortunately, however, no examples with functionalized or particularly hindered backbones were reported. Similarly, 3,3-unsubstituted *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

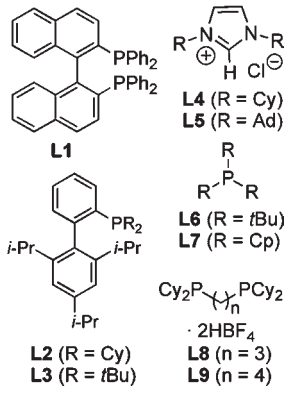


We began our study with chlorobenzene and **1a**[14] as the model substrate (Scheme 2). As expected, the previously reported procedure for aryl bromides resulted in very low conversion to **2a** (entry 1).[10,11] Therefore, a variety of experimental variables, such as the Pd precatalysts, ligands, bases, 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



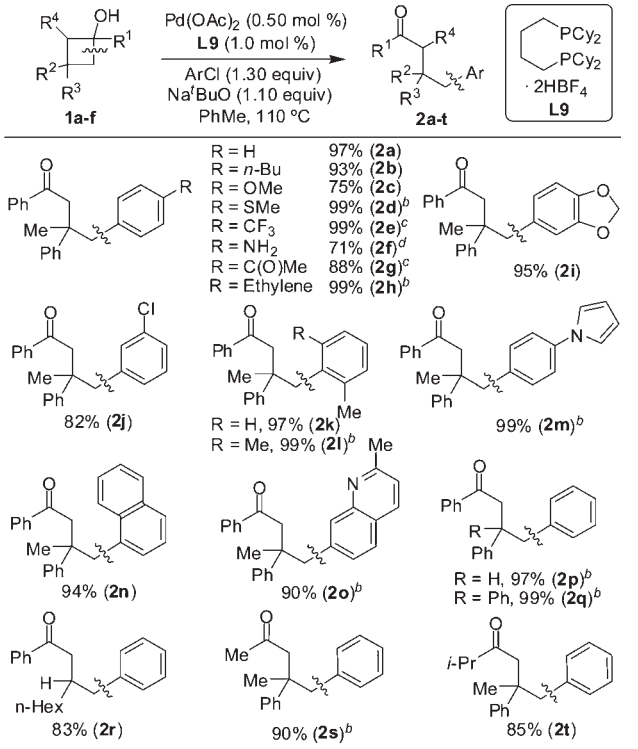
[a] Reaction conditions: **1a** (0.50 mmol), PhCl (1.30 equiv), $Pd(OAc)_2$ (*x* mol %), **L** (*y* mol %), Na*t*BuO (1.10 equiv), PhMe (2 mL) at 110 °C for 12 h. [b] GC yields using dodecane as internal standard. [c] **L1** was used following conditions reported in ref 10: Pd_2dba_3 (0.5 mol %), **L1** (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

(10) Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 11010.
(11) (a) Nishimura, T.; Matsumura, S.; Maeda, Y.; Uemura, S. *Chem. Commun.* **2002**, 50. (b) Maysumura, S.; Maeda, Y.; Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **2003**, *125*, 8862.
(12) According to Aldrich Chemical Co., PhCl is about three times cheaper than PhBr (approximately 0.027€/mL vs 0.078€/mL).
(13) (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (b) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047.
(14) Multigram quantities of *tert*-cyclobutanols can be easily prepared from readily available compounds: Johnston, B. D.; Czyzewska, E.; Oehlschlager, A. C. *J. Org. Chem.* **1987**, *52*, 3693.
(15) (a) Novák, P.; Correa, A.; Gallardo-Donaire, J.; Martin, R. *Angew. Chem.* **2011**, *123*, 12444. (b) Flores-Gaspar, A.; Martin, R. *Adv. Synth. Catal.* **2011**, *353*, 1223. (c) Álvarez-Bercedo, P.; Flores-Gaspar, A.; Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2010**, *132*, 466. (d) Álvarez-Bercedo, P.; Martin, R. *J. Am. Chem. Soc.* **2010**, *132*, 17352. (e) Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2009**, *131*, 15974.
(16) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366.
(17) It is worth mentioning that, while good yields were achieved for **2m** and **2o**, the use of other heteroaromatics such as 2-chloropyridine, 3-chloropyridine, or 3-chlorothiophene gave no conversion to products. See Supporting Information for details.

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]

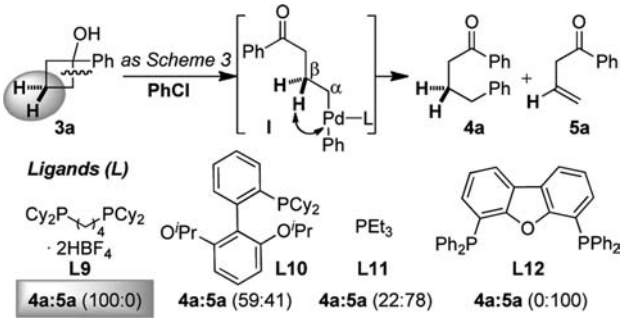


[a] Reaction conditions same as those for Scheme 2 (entry 13); isolated yields, average of at least two independent runs. [b]$Pd(OAc)_2$ (1.0 mol %). [c]K_2CO_3 (1.10 equiv) and **L7** were used. [d]$Pd(OAc)_2$ (2.5 mol %).

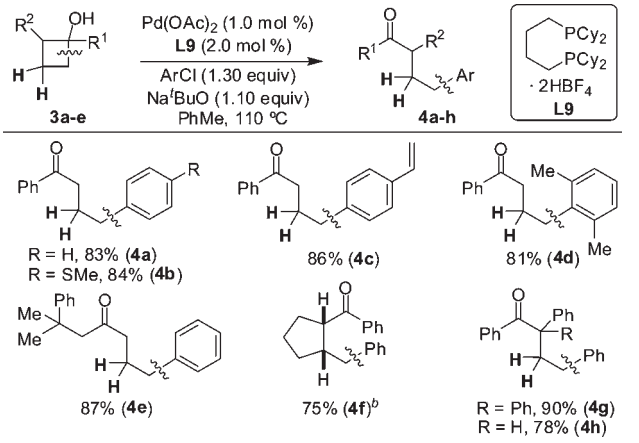
Next, we turned our attention to study the substitution pattern on the cyclobutanol backbone. As becomes apparent from the results in Scheme 3, a diverse set of substitution patterns including aliphatic or aromatic groups gave the corresponding γ-arylated ketones in good to excellent yields (**2p**–**2t**). 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_2CO_3 (1.10 equiv), and **L7** were used.

(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.

Acknowledgment. We thank the ICIQ Foundation, Consolider Ingenio 2010 (CSD2006-0003), European Research Council (ERC-277883) and MICINN (CTQ2009-13840) for financial support. Johnson Matthey, Umicore, and Nippon Chemical Industrial are acknowledged for a gift of metal and ligand sources. Dr. X. Cambeiro at ICIQ is acknowledged for insightful discussions. R.M. thanks MICINN for a RyC fellowship.

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.

(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.