Organic LETTERS

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Palladium-Catalyzed Cross-Coupling of Benzyl Chlorides with Cyclopropanol-Derived Ketone Homoenolates

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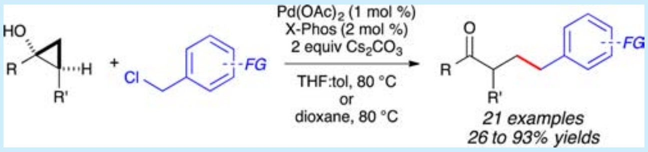
S *Supporting Information*

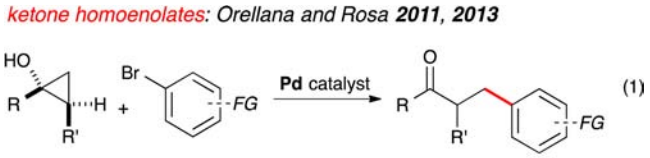
ABSTRACT: The palladium-catalyzed cross-coupling reaction of cyclopropanol-derived ketone homoenolates with benzyl chlorides is reported. This reaction proceeds in high yields with electron-neutral and electron-rich benzyl chlorides; however, yields are low with electron-poor benzyl chlorides. In addition, a range of cyclopropanols can be coupled in good yields. The reaction can be conducted with a low catalyst loading (1% Pd) and on a gram scale without reduction in yield.

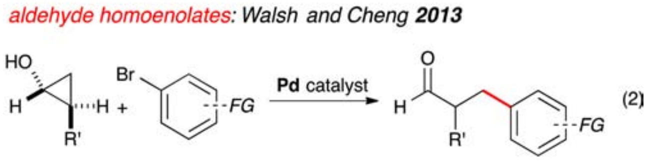


Modern synthetic organic chemistry benefits tremendously from advances in transition-metal-catalyzed reactions. Palladium catalysis in particular has revolutionized the way we construct small molecules. Well-established palladium-catalyzed reactions (named reactions) require the use of an oxidative addition partner and an organometallic reagent (Kumada, Suzuki–Miyaura, Stille, Negishi, Hiyama), a double bond (Heck), a terminal alkyne (Sonogashira), or a heteroatom (Buchwald–Hartwig). More recently, there have been significant advances that exploit the ubiquitous C–H bond as a functional group. Considerably less attention has been paid to the use of unusual functional groups in the development of new palladium-catalyzed reactions.

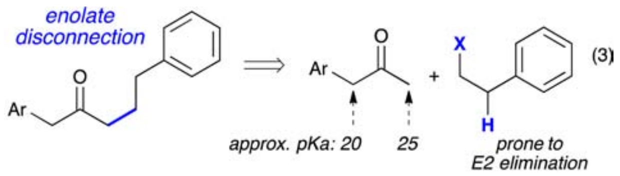
The use of umpolung[1] reagents in organic synthesis can yield access to unusual retrosynthetic disconnections and lead to more efficient synthesis. Homoenolates[2] are an important class of umpolung synthons that bear a charge affinity pattern opposite to that of ketones, esters, amides, etc. Although some homoenolates have been prepared by direct deprotonation of a ketone at the β-position,[3] these methods are exceedingly rare and require harsh reaction conditions. Furthermore, a useful homoenolate synthon must balance the nucleophilicity of the homoenolate carbon with the electrophilicity of the carbonyl group. This problem can be circumvented by the use of protecting group strategies.[4] However, the protection and deprotection steps required lead to longer synthesis[5] and may result in unexpected complications. As a result, there has been a sustained effort to develop practical homoenolate equivalents that avoid protecting group chemistry. The advent of N-heterocyclic carbenes has enabled the catalytic generation of aldehyde homoenolates form α,β-unsaturated aldehydes.[6] In contrast, the catalytic generation of ketone homoenolates remains a challenge.

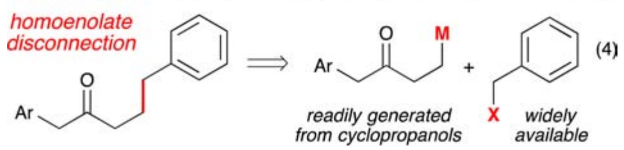
We have been interested in developing palladium-catalyzed reactions involving strained tertiary alcohols,[7] especially cyclopropanols. In particular, we aim to exploit the catalytic conversion of cyclopropanols to palladium homoenolates[8] in new carbon–carbon bond-forming reactions.[9] In 2011, we disclosed[10] the first palladium-catalyzed cross-coupling reaction of cyclopropanol derived ketones homoenolates with aryl bromides and iodides, and in 2013,[11] we expanded scope to homoenolates bearing β-hydrogens relative to palladium (eq 1). Walsh[12] has disclosed the related cross-coupling reaction of aldehyde homoenolates (eq 2).





We reason that in certain contexts the use of homoenolate disconnections avoids some problems associated with more traditional approaches. For instance, the synthesis of the γ-arylated ketone[13] shown below via a traditional enolate alkylation approach (eq 3) would be difficult due to the





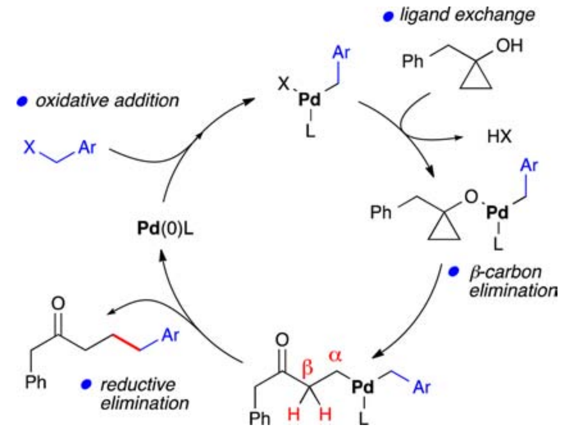
Received: September 15, 2014
Published: October 30, 2014

dx.doi.org/10.1021/ol5027188 | *Org. Lett.* 2014, 16, 5854–5857

unfavorable pK_a profile of the substrate.[14] In contrast, the use of a homoenolate disconnection (eq 4) circumvents the problem of regioselective enolization. Furthermore, cyclopropanols are readily prepared[15] and benzyl halides are widely available, making this disconnection attractive. In this paper, we report the first cross-coupling reaction of cyclopropanol-derived homoenolates with benzylic electrophiles.[16,17]

Our mechanistic model for the proposed cross-coupling reaction involves (i) oxidative addition of a Pd(0) catalyst to the benzyl halide, (ii) exchange of halogen for cyclopropanol (ligand exchange), (iii) palladium-catalyzed β-carbon elimination to give a palladium homoenolate, and (iv) reductive elimination (Scheme 1).

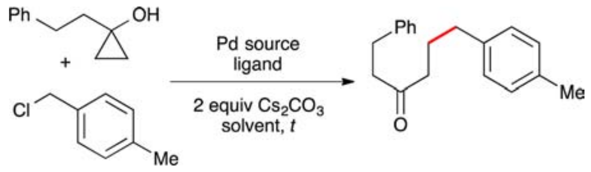
Scheme 1. Mechanistic Model for the Cross-Coupling of Cyclopropanols with Benzyl Halides



It is important to note that base is required to consume the acid generated during the ligand exchange step, although it is unclear if deprotonation of the cyclopropanol occurs prior to or after complexation to palladium. We speculate that formation of the homoenolate occurs via β-carbon elimination[18] given the difficulty in ring-opening O-protected cyclopropanols with palladium(II) intermediates.[19] Finally, the ligand on palladium must favor reductive elimination rather than β-hydride elimination to yield the desired product.

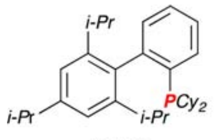
Our approach to reaction optimization benefited from our previous experience with cyclopropanol cross-coupling reactions (Table 1). We decided to use X-Phos, a bulky, electron-rich monodentate phosphine[20] as the ligand for palladium. In addition, Cs_2CO_3 was chosen as the base since it does not promote base-catalyzed ring-opening of the cyclopropanol to the corresponding ketone, even at elevated temperatures.[21] Treatment of a mixture of readily prepared phenethyl cyclopropanol and *p*-methylbenzyl chloride (1:1 ratio) with a catalytic system consisting of a Pd(0) source and X-Phos in toluene at 80 °C provided the coupled product in excellent yield (entry 1). However, with different benzyl chlorides this system provided variable results. We speculated that the solubility of the base plays an important role in the success of this reaction, and switched to THF as the solvent, which provided good yields of product (entry 2). The use of $Pd(OAc)_2$ instead of Pd_2dba_3 also provided the coupled product in excellent yield and obviated the need to separate dba from the reaction product (entry 3). This catalyst system was effective at low loadings (entry 4). A mixture of THF and toluene allowed us to conduct the reaction at 80 °C, which resulted in a further improvement in yield (entry 5). Using the same solvent system, we also tested the use of

Table 1. Reaction Optimization[a,b]

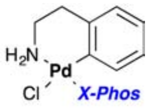


	catalyst system	solvent	temp (°C)	yield (%)
1[c]	5% Pd_2dba_3, 10% X-phos	tol	80	93
2[c]	5% Pd_2dba_3, 10% X-phos	THF	60	82
3[d]	5% $Pd(OAc)_2$,10% X-phos	THF	60	82
4[e]	1% $Pd(OAc)_2$, 2% X-phos	THF	60	80
5[e]	1% $Pd(OAc)_2$, 2% X-phos	THF:tol (1:1)	80	87
6[d]	1% Buchwald precatalyst	THF:tol (1:1)	60	NR
7[d]	1% Buchwald precatalyst	THF:tol (1:1)	80	75

[a] All reactions conducted at 0.1 M concentration of cyclopropanol. [b] Yield of isolated products. [c] Conducted using 50 mg of cyclopropanol. [d] Conducted using 100 mg of cyclopropanol. [e] Conducted using 300 mg of cyclopropanol.

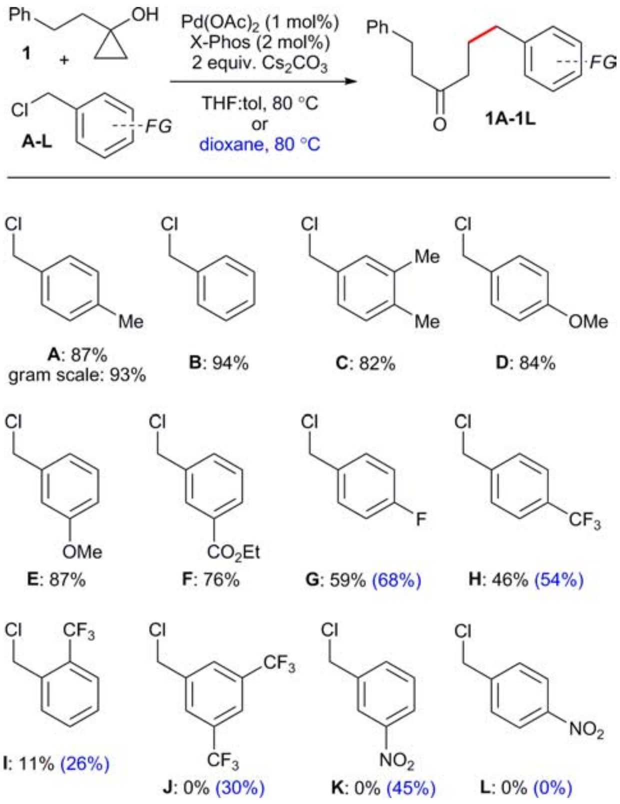


X-Phos



Buchwald precatalyst

Scheme 2. Benzyl Chloride Scope[a,b]



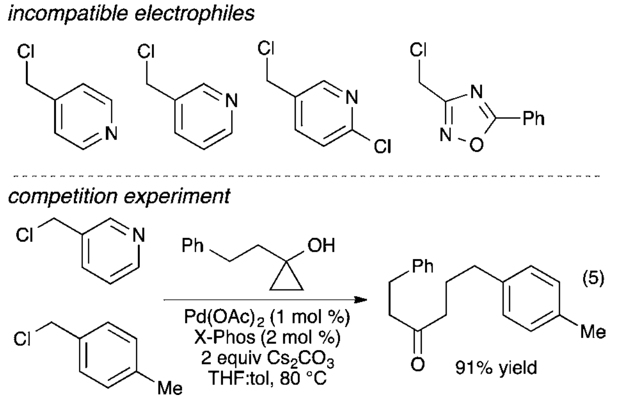
[a] All reactions conducted using 150 mg (0.93 mmol) of cyclopropanol at 0.1 M concentration. [b] Yield of isolated products.

Buchwald's X-Phos precatalyst system.[22] At 60 °C, no product formation was observed, and we attribute this to lack of catalyst formation (entry 6). At 80 °C, this system provides the desired product, albeit in lower yields than all the other systems assayed.

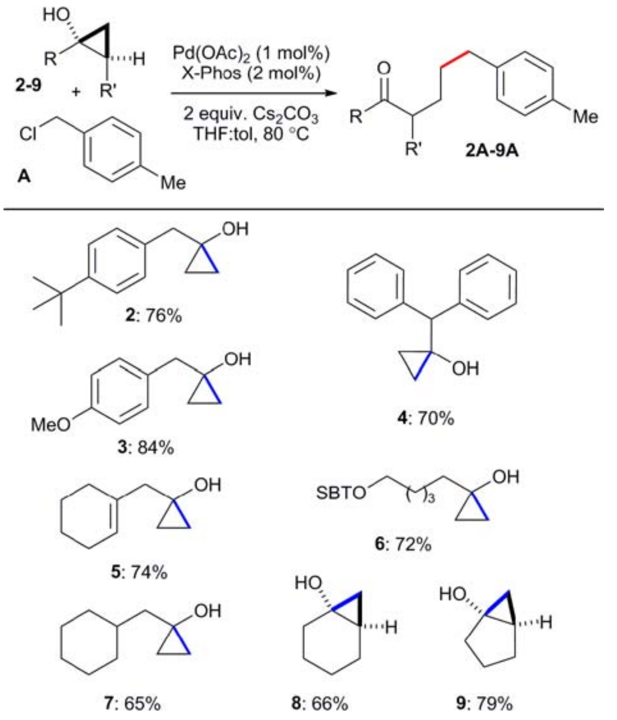
The conditions outlined in entry 5 were used for substrate scope studies.

Scheme 2 shows that a range of functionalized benzyl chlorides (**A**–**E**) yield the corresponding γ-arylated ketones in good-to-excellent yield (**1A**–**1E**). The reaction can be conducted on a gram scale with no reduction in yield (**1A**). The use of electron-poor benzyl halides results in decreased yields as the electron-withdrawing ability of the substituents (**1F** to **1I**, **1K** and **1L**) or the number of substituents (**1J**) increases. This problem can be ameliorated somewhat by using dioxane as the solvent (**1G** to **1K**), although the same trend is observed.

Unfortunately, the use of electron-poor heterocycles does not yield the cross-coupling product. This observation is consistent with the trend observed in Scheme 2. A competition experiment using our initial optimization substrate (*p*-methyl benzyl chloride) and 3-chloromethylpyridine provided the cross-coupled product with the benzyl chloride in good yield, suggesting that the inability to couple electron-poor heterocycles is not a result of catalyst poisoning (eq 5).



Scheme 3. Cyclopropanol Scope[a,b]



[a] Reactions conducted using 46–100 mg of cyclopropanol at 0.1 M concentration. [b] Yield of isolated products.

Finally, we have also shown that a number of cyclopropanols (**2**–**9**) participate in this reaction to give the cross-coupled products (**2A**–**9A**) in good yields (Scheme 3).

In summary, we have developed the first palladium-catalyzed cross-coupling reaction of cyclopropanols with benzylic halides. This reactions proceeds in good yields with a range of cyclopropanols and electron-rich and electron-neutral benzyl halides. The reaction can be conducted with low catalyst low loadings (1% Pd) and on a gram scale with no reduction in yield. The yields diminish when electron-poor benzyl halides are used, and the cross-coupling of heterobenzyl halides is not yet possible. The reason for this reduction in yield with electron-poor benzyl halides is unclear and will be the subject of future studies.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the support of this work from York University, the Natural Sciences and Engineering Research Council (NSERC) of Canada, and Boehringer–Ingelheim Canada, Ltd. We also thank Professor Michael Organ of York University for generous sharing of resources.

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■ NOTE ADDED AFTER ASAP PUBLICATION

Schemes 2 and 3 were corrected and the SI was replaced on November 21, 2014.