ORGANIC LETTERS

2011
Vol. 13, No. 1
110−113

Palladium-Catalyzed Cross-Coupling of Cyclopropanols with Aryl Halides Under Mild Conditions

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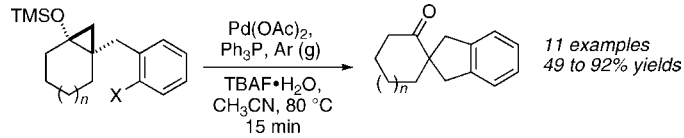
Received October 31, 2010

ABSTRACT



Intra- and intermolecular palladium-catalyzed cross-coupling of cyclopropanols with aryl halides can be achieved in good yields under mild conditions.

Reactivity umpolung is a powerful concept that often facilitates unusual or nonintuitive disconnections in synthetic planning. Homoenolates[1] represent an important class of umpolung synthons that display a charge affinity pattern opposite to that of an α,β-unsaturated ketone. While it is possible to deprotonate ketones directly to yield homoenolates in some cases, these reactions are not general or practical.[2] Consequently, significant effort has been spent seeking alternative means for the generation of homoenolates. The metal-catalyzed rearrangement of siloxycyclopropanes to nucleophilic homoenolates has received significant attention since Kuwajima's seminal report.[3] More recently, the palladium(II)-catalyzed formation of palladium homoenolates incapable of β-hydride elimination via directed C(sp^3)-H activation has been reported.[4] In addition, recent work with *N*-heterocyclic carbenes as organocatalysts has provided new avenues for the generation and use of homoenolate equivalents.[5]

The rearrangement of siloxycyclopropanes to homoenolates can be achieved by using a variety of metals, and in some cases the resulting homoenolates can be used in palladium-catalyzed cross-coupling reactions.[6] The palladium-catalyzed rearrangement of siloxycyclopropanes is of particular interest since it obviates the use of a second metal in the reaction mixture, and thus allows their direct use in cross-coupling reactions.[7] Although very useful, this method is not without limitations. The cross-coupling reaction of cyclopropane acetals with aryl *triflates* generally proceeds in good yield as a result of the enhanced nucleophilicity of the cyclopropane ring and a sufficiently electrophilic arylpalladium(II) intermediate. In contrast, the use of aryl halides results in no reaction (eq 1). Furthermore, when aryl triflates are utilized in the presence of LiCl the reaction

(1) For a good entry into the homoenolate literature see: Molander, G. A.; Jean-Gérard, L. *J. Org. Chem.* **2009**, *74*, 1297.

(2) (a) Nickon, A.; Lambert, J. L. *J. Am. Chem. Soc.* **1962**, *84*, 4004. (b) Shiner, C. S.; Berks, A. H.; Fisher, A. M. *J. Am. Chem. Soc.* **1988**, *110*, 957.

(3) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, *99*, 7360.

(4) (a) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazanno, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (b) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190. (c) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886.

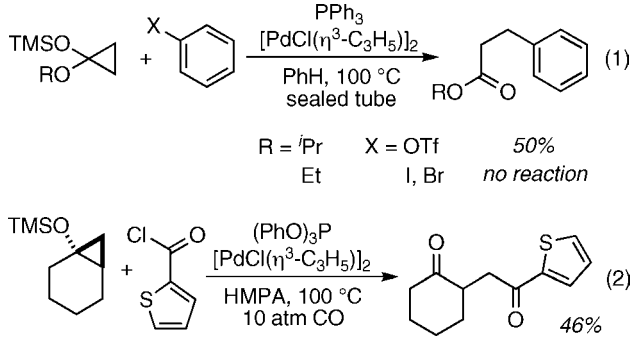
(5) Nair, V.; Vellalath, S.; Babu, N. P. *Chem. Soc. Rev.* **2008**, *37*, 2691.

(6) Reviews: (a) Kuwajima, I.; Nakamura, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 2, p 441. (b) Kuwajima, I.; Nakamura, E. In *Topics in Current Chemistry*; Springer-Verlag: Berlin, Germany, 1990; Vol. 155, p 1. (c) Kuwajima, I. *Pure Appl. Chem.* **1988**, *60*, 115.

(7) (a) Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1988**, *110*, 3296. (b) Aoki, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1988**, *29*, 1541. (c) Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 6541. (d) Aoki, S.; Nakamura, E. *Synlett* **1990**, 741. (e) Fujimura, T.; Aoki, S.; Nakamura, E. *J. Org. Chem.* **1991**, *56*, 2809. (f) Kang, F.-K.; Yamaguchi, T.; Ho, P.-S.; Kim, W.-Y.; Yoon, S.-K. *Tetrahedron Lett.* **1997**, *38*, 1947.

10.1021/ol1026409
Published on Web 12/01/2010

fails. The related cross-coupling of the less nucleophilic ketone-derived cyclopropanols is also limited to the use of aryl triflates and acyl halides (eq 2).



Mechanistic studies by Nakamura point to C−C bond cleavage of the *siloxy*cyclopropane through a "corner attack" by an electrophilic palladium intermediate as a key step in the mechanism of these reactions. In 2000, Cha[8] developed palladium-catalyzed oxidative rearrangement of *unprotected* cyclopropanols to α,*β*-unsaturated ketones,[9,10] and invoked a mechanism involving coordination of the cyclopropanol oxygen to a Pd(II) species prior to C−C bond cleavage[11] (Figure 1).

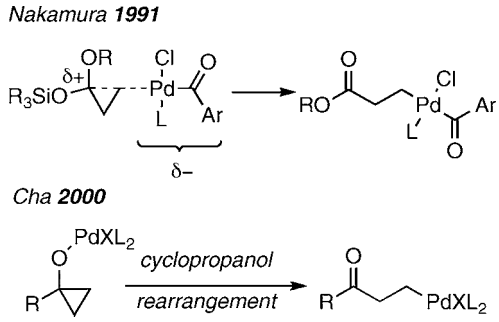
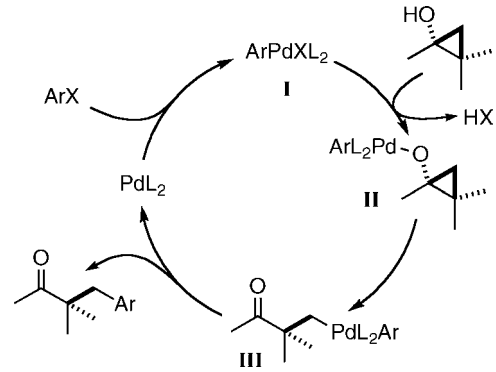


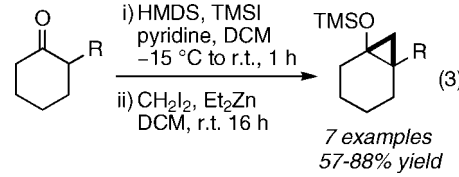
Figure 1. Mechanistic proposals for the palladium-catalyzed rearrangement of 1-alkoxy-1-siloxycyclopropanes (Nakamura) and cyclopropanols (Cha).

Given that the palladium-catalyzed rearrangement of *unprotected* cyclopropanols likely proceeds through a different mechanism than that established by Nakamura for the reaction of siloxycyclopropanes, it seemed plausible that this alternative route to palladium-homoenolates could facilitate their cross-coupling with aryl halides. We envisioned a mechanistic scenario wherein an arylpalladium(II) intermediate, resulting from oxidative addition of an aryl halide to PdL_2, would undergo a ligand exchange with the cyclopropanol (Scheme 1, **I** to **II**). Subsequent cyclopropanol rearrangement (**II** to **III**) and reductive elimination would result in the desired cross-coupled product (Scheme 1).

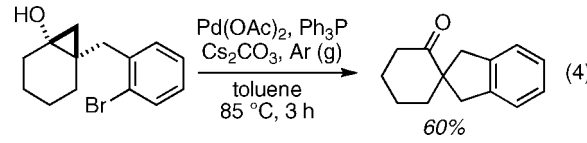
Scheme 1. Proposed Catalytic Cycle for the Cross-Coupling of Palladium Homoenolates with Aryl Halides



Substrates for this study were readily prepared from the corresponding ketones by formation of the thermodynamic silyl enol ether[12] followed by cyclopropanation using the Furukawa[13] modification of the Simmons−Smith reaction[14] (eq 3).



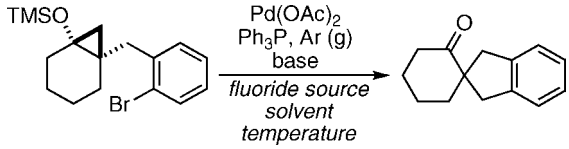
We began our reaction development studies by attempting the cross-coupling reaction of an *unprotected* cyclopropanol with a tethered aryl bromide. We were happy to observe that treatment of the free cyclopropanol with a simple catalyst system consisting of $Pd(OAc)_2$ and Ph_3P provided the desired spirocyclic ketone in 60% isolated yield (eq 4). We speculated that the moderate yield was perhaps due to decomposition of the cyclopropanol under the reaction conditions, and that in situ deprotection might have a salubrious effect on the reaction. Parenthetically, it is worth noting that this intramolecular process could serve as a valuable alternative to the double alkylation of ketone enolates to prepare spirocyclic ketones.



The results of our optimization studies are summarized in Table 1. Before screening fluoride sources for in situ

(8) Park, S.-B.; Cha, J. K. *Org. Lett.* **2000**, *2*, 147.
(9) For a similar report see: Okumoto, H.; Jinnai, T.; Shimizu, H.; Harada, Y.; Mishima, H.; Suzuki, A. *Synlett* **2000**, 629.
(10) (a) Shan, M.; O'Doherty, G. A. *Org. Lett.* **2008**, *10*, 3381. (b) Shan, M.; O'Doherty, G. A. *Synthesis* **2008**, 3171. For a related iridium catalyzed transformation, see: (c) Ziegler, D. T.; Steffens, A. M.; Funk, T. W. *Tetrahedron Lett.* **2010**, *51*, 6726.
(11) Terao, Y.; Wakui, H.; Nomoto, M.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* **2003**, *68*, 5236.
(12) Miller, R. D.; McKean, D. R. *Synthesis* **1979**, 730.
(13) (a) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1966**, *7*, 3353. (b) Furukawa, J.; Kawabata; Nishimura, J. *Tetrahedron* **1968**, *24*, 53.
(14) See the Supporting Information for details.

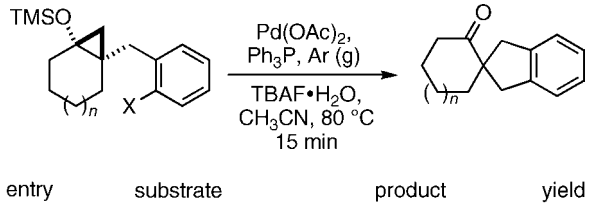
Table 1. Reaction Development[a]

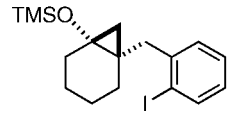
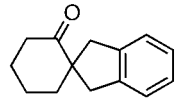
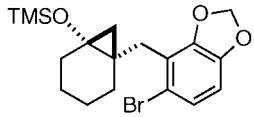
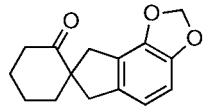
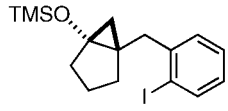
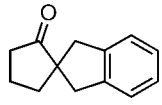
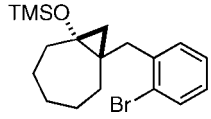
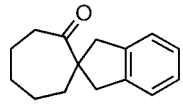


	solvent	base	fluoride source	time	temp (°C)	yield[b] (%)
1	toluene	Cs_2CO_3	none	16 h	110	60
2	toluene	Cs_2CO_3	CsF	10 h	90	68
3	toluene	Cs_2CO_3	TBAF 1 M (THF)	45 min	90	56
4	toluene	Cs_2CO_3	TBAF·H_2O + 4 Å ms	45 min	90	27
5	toluene	Cs_2CO_3	TBAT[c]	4 h	90	45
6	toluene	Cs_2CO_3	TBAF·H_2O	45 min	90	68
7	toluene	Ag_2CO_3	CsF	16 h	90	59
8	toluene	K_2CO_3	CsF	16 h	90	50
9	toluene	Et_3N	CsF	16 h	90	59
10	THF	Cs_2CO_3	TBAF·H_2O	16 h	65	56
11	DME	Cs_2CO_3	TBAF·H_2O	30 min	90	61
12	DMA	Cs_2CO_3	TBAF·H_2O	20 min	80	56
13	CH_3CN	Cs_2CO_3	TBAF·H_2O	15 min	80	78[d]
14	CH_3CN	none	TBAF·H_2O	15 min	80	92

[a] All reactions were conducted with 0.15 mmol of substrate at 0.08 M concentration, 10 mol % of $Pd(OAc)_2$, and 30 mol % of Ph_3P. [b] Isolated yields of pure product after column chromatography on SiO_2. [c] TBAT = tetrabutylammonium difluorotriphenylsilicate. [d] Using these conditions, the reaction was shown to be effective with reduced catalyst loading: 5 mol % (75% yield), 2 mol % (71% yield). No reaction was observed with 1 mol % catalyst. For convenience, a 10 mol % catalyst loading was used for all subsequent reactions.

Table 2. Intramolecular Cross-Coupling Reactions[a,b]

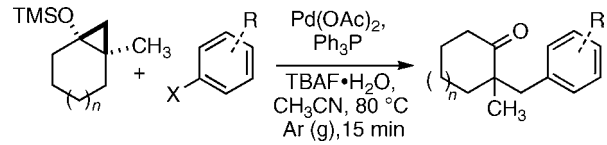


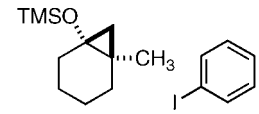
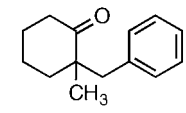
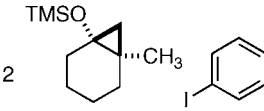
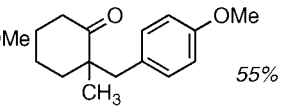
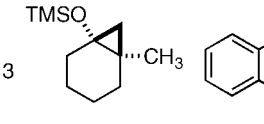
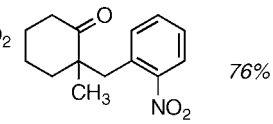
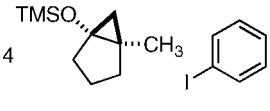
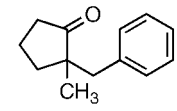
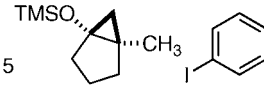
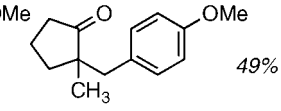
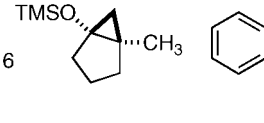
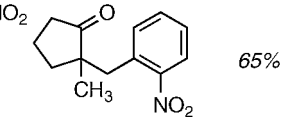
entry	substrate	product	yield
1			90%
2			91%
3			90%
4			90%

[a] All reactions were conducted at 0.08 M concentration with respect to the siloxycyclopropane with the optimized conditions in Table 1. [b] Isolated yields after purification on SiO_2.

deprotection we assessed the viability of the reaction using the TMS-protected cyclopropanol. While the desired cross-coupling product was observed, there was no improvement in the yield and the extended reaction time was impractical (entry 1).[15]

Table 3. Intermolecular Cross-Coupling Reactions[a,b]



entry	substrate	product	yield
1			57%
2			55%
3			76%
4			57%
5			49%
6			65%

[a] All reactions were conducted at 0.08 M concentration with respect to the siloxycyclopropane with use of the optimized conditions in Table 1 and with 2 equiv of aryl halide. [b] Isolated yields after purification on SiO_2.

The use of CsF resulted in an improved yield at lower temperature; however, no reduction in reaction time was observed, presumably due to the low solubility of the salt in toluene (entry 2). The use of more soluble fluoride sources under anhydrous conditions dramatically reduced the reaction time; however, this was accompanied by a reduction in yield (entries 3−5). Fortunately, the use of TBAF·H_2O generated the product in good yield after a short reaction time (entry 6). A concurrent screen of bases revealed Cs_2CO_3 to be optimal (entries 7−9). A screen of ligands and palladium salts did not improve the results. Finally, a screen of solvents

(15) Since arylpalladium(II) intermediates resulting from oxidative addition to aryl halides have been shown to be incapable of ring opening siloxycylopropanes, we suspect that the 60% yield observed in this reaction is likely due to base-catalyzed deprotection of the siloxycyclopropane.

revealed that the use of DMA, DME, and THF provided the product in comparable yield (entries 10−12). In contrast, the use of CH_3CN resulted in a nearly 20% increase in yield (entry 13). Finally, omission of the base furnished the desired ketone in 92% yield (entry 14).

With a satisfactory protocol at hand we began to examine the scope of this reaction (Table 2). Intramolecular cross-coupling reactions result in uniformly high yields with cyclopentanone-, cyclohexanone-, or cycloheptanone-derived cyclopropanols (entries 1−4). Notably, we observed no evidence of ring-expanded products resulting from cleavage of the ring-fusion bond. The use of aryl iodides instead of aryl bromides appears to have no effect on the reaction (entry 1).

Next we explored the intermolecular variant of the cross-coupling reaction using an excess of the aryl halide (Table 3). In general, a considerable drop in yield is observed for these reactions. Cross-coupling reactions with cyclohexanone-derived cyclopropanols proceed in slightly higher yield than those of cyclopentanone-derived cyclopropanols. In addition, it is apparent that electron-withdrawing substituents on the oxidative addition partner result in an increased yield (entries 1−3 and 4−6).

In conclusion, we have shown that cyclopropanol-derived palladium homoenolates can be cross-coupled with aryl halides under mild conditions by using a simple catalyst system. It is likely that this reaction proceeds through a different mechanism than that previously established for the cross-coupling of aryl triflates and acyl halides with siloxycyclopropanes and 1-alkoxy-1-siloxycyclopropanes. The reaction proceeds in excellent yield in intramolecular cases, and moderate to good yield in intermolecular cases.

Acknowledgment. This work was generously supported by the Natural Science and Engineering Research Council of Canada (NSERC), the York University Faculty of Science and Engineering, and the York University Faculty Association.

Supporting Information Available: Full experimental details and ^{1}H and ^{13}C NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1026409