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C−C Bond Formation via C−H Bond Activation: Catalytic Arylation and Alkenylation of Alkane Segments

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The ability to functionalize C−H bonds in a direct manner will have a major impact on the field of organic synthesis at both a conceptual and a practical level, owing to the ubiquitous nature of these bonds in organic compounds. The direct functionalization of arenes and alkenes (sp^2 C−H bonds), as well as that of activated sp^3 C−H bonds (FG−C−H), has been demonstrated through a variety of reaction modes, for instance, carbene insertion,[1] direct arylation,[2] alkene insertion,[3] and borylation.[4] However, unactivated alkane C−H bonds have largely been resistant to direct functionalization, particularly in the context of complex organic substrates.[5]

We herein present our investigations that led to the development of a catalytic system for arylation and alkenylation of alkane segments. According to our approach, a functional group present in the substrate would direct a metal complex to a desirable alkane region, facilitating metallacycle formation and subsequent functionalization (Figure 1).[6]

The *ortho-tert*-butylaniline substrate emerged in the context of the assembly of the teleocidin class of natural products.[7] On the basis of our preliminary results, we focused on the possibility of generating a phenylpalladium species (cf. **2**), followed by the C−H activation step (Figure 2). Phenylboronates,[8] phenylstannanes,[9] and phenylsilanols[9,10] have been suggested to undergo transmetalation with $Pd(OAc)_2$ in polar solvents. Consequently, through a systematic search of reaction conditions (Pd^{2+} salts, arene donors, solvents), we uncovered an exciting lead. While $PhB(OH)_2$ and $PhSnBu_3$ failed, Schiff base **1** was transformed to compound **4** in 53% isolated yield via *direct arylation of the tert-butyl group in the presence of PhSi(OH)Me$_2$ and Pd(OAc)$_2$* (Scheme 1). Note that the phenyl ring is attached at the *neo*-alkyl position[11] and that no bis-arylation products were identified (see discussion below). Thus, the first three steps of the cycle have been synchronized, and direct arylation of compound **1** in the presence of a stoichiometric amount of $Pd(OAc)_2$ was developed.[12]

The next critical question centered on the compatibility of this system with an oxidant. Following an extensive screen, we were delighted to find that *the reaction proceeded under conditions catalytic in palladium in the presence of Cu(OAc)$_2$*. A systematic mapping of the system included examining the Schiff base-directing element of the substrate, metal salts, oxidants, and solvents. 2-Thiomethoxybenzylidene Schiff base **5** afforded consistently higher yields than the dimethoxy substrate **1**, while $Pd(OAc)_2$ proved to be a catalyst of choice and DMF the best solvent. Out of the oxidants tested, $Cu(OAc)_2$ was the most efficient. Also, a number of phenyl donors were screened, and selected data are presented in Table 1 (for more data, see Supporting Information). We rapidly discovered that $Ph_2Si(OH)Me$ was a superior phenyl donor affording the highest yield of product **6**, with only traces of biphenyl and phenyl acetate side products.

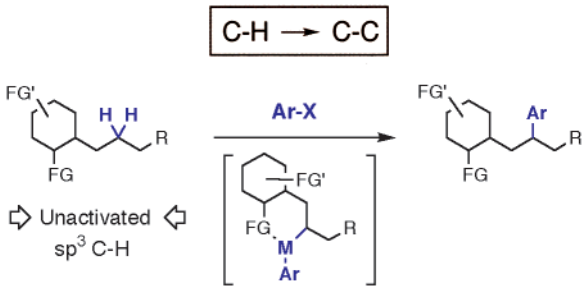


Figure 1. Catalytic arylation/alkenylation of alkane segments in complex substrates via metallacycle intermediates.

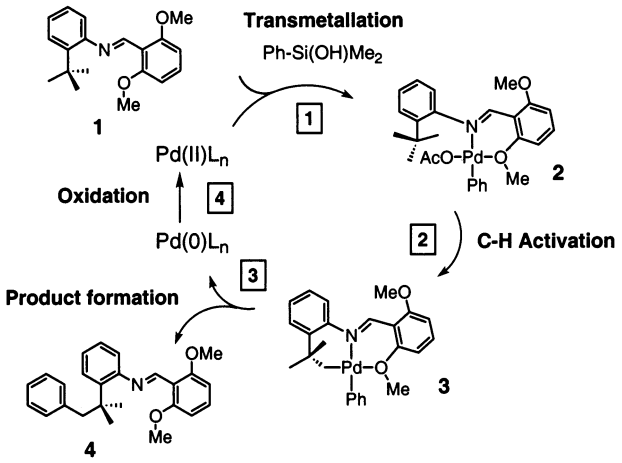
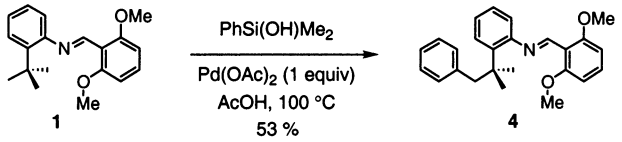


Figure 2. Design of a catalytic cycle. This outline represents a crude blueprint for the development of a new catalytic arylation transformation.

Scheme 1. One-Pot Stoichiometric Arylation Reaction



Further optimization showed that the highest isolated yield of **6** (73%) was achieved in the presence of 4 mol % of $Pd(OAc)_2$ and benzoquinone (1:1), and 2 equiv of $Cu(OAc)_2$ (Table 2).[13] The new arylation methodology was also extended to alkenylation, as documented by the transfer of styrenyl group to substrate **5** furnishing compound **7** in 64% yield (Table 2). In addition to the *tert*-butylaniline substrate, 2-pivaloylpyridine also proved to be a good substrate for both arylation and alkenylation reactions. As in the previous case, substrate **8** underwent single arylation/alkenyl-

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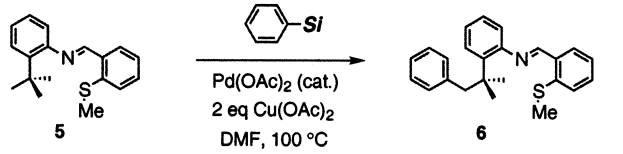
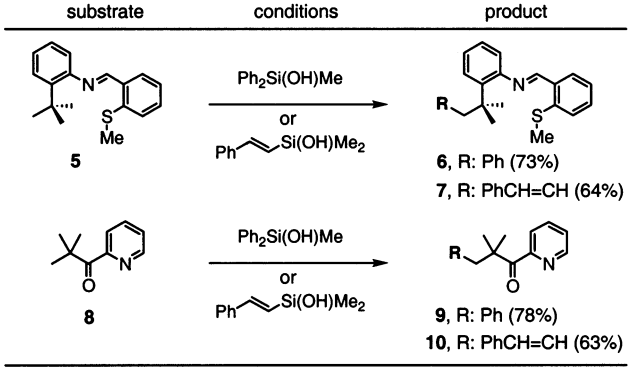
Table 1. Catalytic Arylation of Substrate **5** (Selected Data)



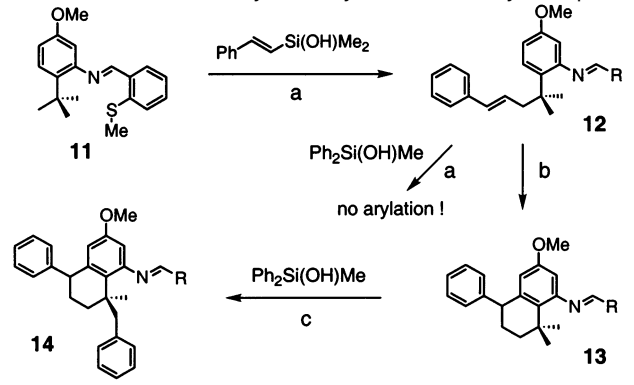
silanol	$Pd(OAc)_2$ mol %	yield %	TON	Ph-Ph (%)	PhOAc (%)
$PhSi(OH)Me_2$	2.5	33	13	5	5
$Ph_2Si(OH)Me$	**2.5**	**51**	**20**	**<1**	**<1**
$PhSi(OH)_2Me$	2.5	20	8	8	4
$PhSi(OMe)_3$	2.5	31	12	4	<1

Table 2. Catalytic Arylation and Alkenylation of Selected Substrates[a]



[a] Conditions: substrate ($c = 0.02$ M) in DMF, silanol (2 equiv), $Pd(OAc)_2$ (4 mol %), benzoquinone (4 mol %), $Cu(OAc)_2$ (2 equiv), 100 °C. The alkenylation reactions also yielded a side product $(PhCH{=}CH)_2$ in 10% yield.

Scheme 2. Tandem Alkenylation-Arylation of *tert*-Butyl Group[a]



[a] Conditions: (a) $Pd(OAc)_2$ (4 mol %), benzoquinone (4 mol %), $Cu(OAc)_2$ (2 equiv), DMF, 100 °C, 66%. (b) $MeSO_3H$, CH_2Cl_2, 52%. (c) $Pd(OAc)_2$ (8 mol %), benzoquinone (8 mol %), $Cu(OAc)_2$ (2 equiv), DMF, 100 °C, 45% of **14** (4:1 ratio of diastereomers). Configuration of the major isomer has not been determined. R = *o*-$MeSC_6H_4$.

ation at the *t*-butyl group. However, the Schiff base derived from *ortho*-*i*-propylaniline yielded no desired material, biphenyl (22%) being the major detected product (Supporting Information).

A concise synthesis of compound **14**, depicted in Scheme 2, demonstrated the synthetic power of the new methodology, and simultaneously revealed both the remarkable selectivity as well as the limitations of this system. Substrate **11** was converted to complex product **14** in three steps via catalytic alkenylation of **11**, Friedel−Crafts cyclization, and finally catalytic arylation. Thus, tandem alkenylation-arylation of the *tert*-butyl group provided a product of considerable complexity via a novel bond construction strategy. It is of note that no products originating from the activation of generally more reactive C−H bonds (OCH_3, SCH_3, arene C−H bonds) were detected. Also, it seems that the alkyl group must be of sufficient steric bulk (^{t}Bu versus ^{i}Pr) for the reaction to proceed. At the same time, the arylation/alkenylation products (cf. **6**, **12**) apparently already exceeded the optimal steric requirement and did not undergo subsequent functionalization.[14] Remarkably, the cyclized isomer **13** did in fact undergo the second arylation, albeit at a slower rate as compared to that of **11**.

In summary, a new system for the catalytic arylation and alkenylation of alkane segments has been developed. The *ortho*-*tert*-butylaniline substrates and 2-pivaloylpyridine may be arylated and alkenylated on the *tert*-butyl group, while no functionalization occurred at more reactive C−H and other bonds. We hypothesize that the high selectivity of this system stems from the confluence of the directing effect of the Schiff base or pyridine moiety and the unique reactivity properties of a phenyl-palladium acetate species (Ph-Pd-OAc·L_n).

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Supporting Information Available: Experimental procedures, preparation, and spectral data for compounds **1**, **4**−**14** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc*. **2000**, *122*, 3063−3070.
(2) (a) Miura, M.; Nomura, M. *Top. Curr. Chem*. **2002**, *219*, 211−241. (b) Yonehara, F.; Kido, Y.; Morita, S.; Yamaguchi, M. *J. Am. Chem. Soc*. **2001**, *123*, 11310−11311.
(3) (a) Kakiuchi, F.; Murai, S. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, 1999; pp 47−79. (b) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res*. **2001**, *34*, 633−639.
(4) (a) Cho, J.-Y.; Tse, M. N.; Holmes, D.; Maleczka, R. E.; Smith, M. R., III. *Science* **2002**, *295*, 305−308. (b) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc*. **2002**, *124*, 390−391. For catalytic borylation of alkanes, see: Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995−1997.
(5) (a) Corey, E. J.; Hertler, W. R. *J. Am. Chem. Soc*. **1958**, *80*, 2903−2904. (b) Buchschacher, P.; Kalvoda, J.; Arigoni, D.; Jeger, O. *J. Am. Chem. Soc*. **1958**, *80*, 2905−2906. (c) Barton, D. H. R.; Beaton, J. M. *J. Am. Chem. Soc*. **1961**, *83*, 4083−4089. (d) Breslow, R.; Baldwin, S.; Flechtner, T.; Kalicky, P.; Liu, S.; Washburn, W. *J. Am. Chem. Soc*. **1973**, *95*, 3251−3262. (e) Corey, E. J.; Felix, A. M. *J. Am. Chem. Soc*. **1965**, *87*, 2518−2519. (f) Taber, D. F.; Stribia, S.-E. *Chem.-Eur. J*. **1998**, *4*, 990−992.
(6) Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc*. **2002**, *124*, 6900−6903.
(7) Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc*. **2002**, *124*, 11856−11857.
(8) (a) Dieck, H. A.; Heck, R. F. *J. Org. Chem*. **1975**, *40*, 1083−1090. (b) Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem*. **1996**, *61*, 2346−2351.
(9) Hirabayashi, K.; Ando, J.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn*. **2000**, *73*, 1409−1417.
(10) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc*. **2001**, *123*, 6439−6440.
(11) For intramolecular functionalization of a *tert*-butyl group, see: (a) Dyker, G. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 103−105. (b) Laaziri, H.; Bromm, L. O.; Lhermitte, F.; Gschwind, R. M.; Knochel, P. *J. Am. Chem. Soc*. **1999**, *121*, 6940−6941.
(12) Formation of putative intermediate **3** (and ultimately product **4**) may occur via an alternative route wherein the cyclopalladation takes place first, followed by transmetalation (the order of steps 1 and 2 is reversed, Figure 2). This was ruled out as the corresponding palladacycle acetate (not shown) did not afford the product under reaction conditions.
(13) In addition to the desired products and biphenyl, there were no other products formed. The starting material was recovered to yield a satisfactory mass balance (∼90%).
(14) It is also conceivable that the double bond or phenyl ring of the product coordinates to the metal, thus preventing subsequent functionalization.

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