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Communication

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Hemilabile Benzyl Ether Enables γ-C(sp^3)–H Carbonylation and Olefination of Alcohols

Keita Tanaka,[†] William R. Ewing,[‡] and Jin-Quan Yu*,[†]

[†]Department of Chemistry, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, California 92037, United States

‡ Discovery Chemistry, Bristol-Myers Squibb, PO Box 4000, Princeton, New Jersey 08543, United States

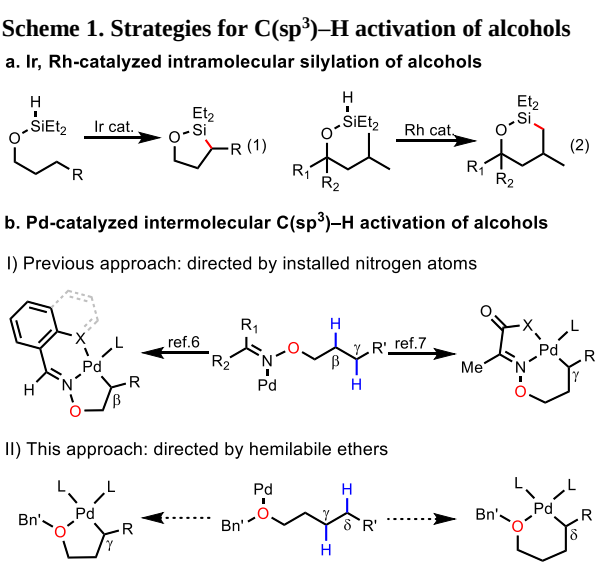
Supporting Information Placeholder

ABSTRACT: Pd-catalyzed C(sp^3)–H activation of alcohol typically shows β-selectivity due to the required distance between the chelating atom in the attached directing group and the targeted C–H bonds. Herein we report the design of hemilabile directing group, which exploit the chelation of a readily removable benzyl ether moiety to direct γ, δ-C–H carbonylation and olefination of alcohols. The utility of this approach is also demonstrated in the late-stage C–H functionalization of β-estradiol to rapidly prepare desired analogues that required multi-step syntheses with classical methods.

Alcohol is one of the most abundant structural motifs in the bioactive natural products and synthetic intermediates. Therefore, various strategies for the selective C–H functionalization of alcohols have been developed. Among them, selective C–H functionalizations of alcohol derived substrates through intramolecular nitrene insertion or radical abstraction have been most extensively investigated and applied to the synthesis of natural products.[1] Ir-catalyzed intramolecular γ-C(sp^3)–H silylation[2] (Scheme 1a, eq. 1) and Rh-catalyzed intramolecular δ-C(sp^3)–H silylation[3] have also been developed (Scheme 1a, eq. 2). However, development of hydroxyl-directed C–H metalation and subsequent reaction with diverse external reagents remains limited to C(sp^2)–H bonds.[4,5] The difficulty is largely due to the poor coordination of the hydroxyl or ether moiety with metal catalysts. To circumvent this problem, the installation of external chelating groups has been employed, which typically afforded β-C(sp^3)–H arylation of alcohols.[6] This regioselectivity is dictated by the distance between the native functional group (oxygen atom) and targeted C–H bonds (Scheme 1bI, left). Although the design of a chelating directing group using ring strain has led to a rare example of reversing β- to γ-selectivity in cyclopalladation[7] (Scheme 1bI, right), developing general strategies for directed γ-selective C(sp^3)–H activation remains a significant challenge. Furthermore, Pd-catalyzed δ-C(sp^3)–H activation of alcohol derived substrates via cyclometallation has not been developed thus far due to the long distance between the directing group and the δ-C–H bonds.

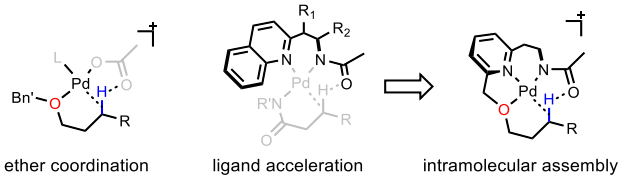
Prompted by recent success of using the combination of weakly coordinating carbonyl groups and a ligand to direct Pd-catalyzed C(sp^3)–H activation,[8] we embarked on exploring the hemilabile coordination of the oxygen atom in alcohols to direct γ- or δ-C(sp^3)–H metalation of alcohols (Scheme 1bII). Herein, we report the realization of this approach to achieve the first examples of γ- and δ-C(sp^3)–H carbonylation and olefination. Three key design elements are crucial for this development: 1) a readily removable benzyl ether as the directing moiety to control the regioselectivity, 2) a covalently attached ligand to accelerate the C–H activation, 3) the labile ether dissociation to create vacant coordination site to allow carbonylation and olefination to proceed.

Scheme 1. Strategies for C(sp^3)–H activation of alcohols



Since extensive search for ligands and reaction conditions to promote alcohol or ether-directed C(sp^3)–H palladation has not been successful, we decided to covalently attach a previously developed APAQ ligand[9] to alcohols so that the computed pre-transition state[10] can be assembled intramolecularly. Mindful of practicality of this approach, we employed a broadly used benzyl ether linkage so that the alcohol products can be furnished by a standard deprotection (Scheme 2). We also anticipate that the

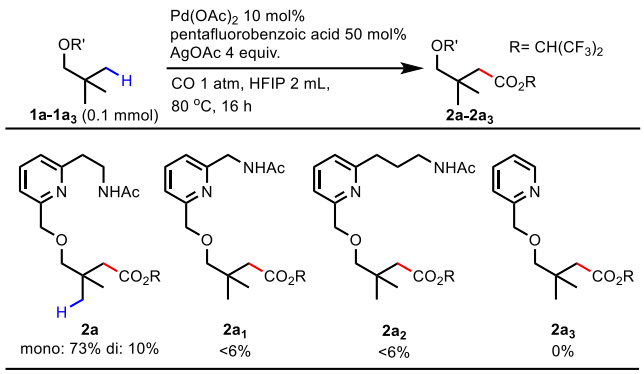
Scheme 2. Design of directing group



hemilabile ether must dissociate following the C–H palladation step to allow the binding of other reaction partners such as carbon monoxide and olefin (e.g. Scheme 3A, **int-I** to **int-II**).

Substrate **1a** was readily prepared by a standard benzylation of the alcohol substrate with the preformed benzyl chloride bearing the ligand scaffold (See Supporting Information). Through extensive screening of palladium catalysts, reaction partners and conditions, the carbonylation reaction with CO[11,12] was found to be the most efficient. A number of other directing groups are also evaluated with **1a** being optimal (Table 1). The complete loss of reactivity with **1a$_3$** suggest the acceleration from the internal ligand is crucial (See Supporting Information).

Table 1. Directing group evaluation for C(sp^3)–H carbonylation[a]

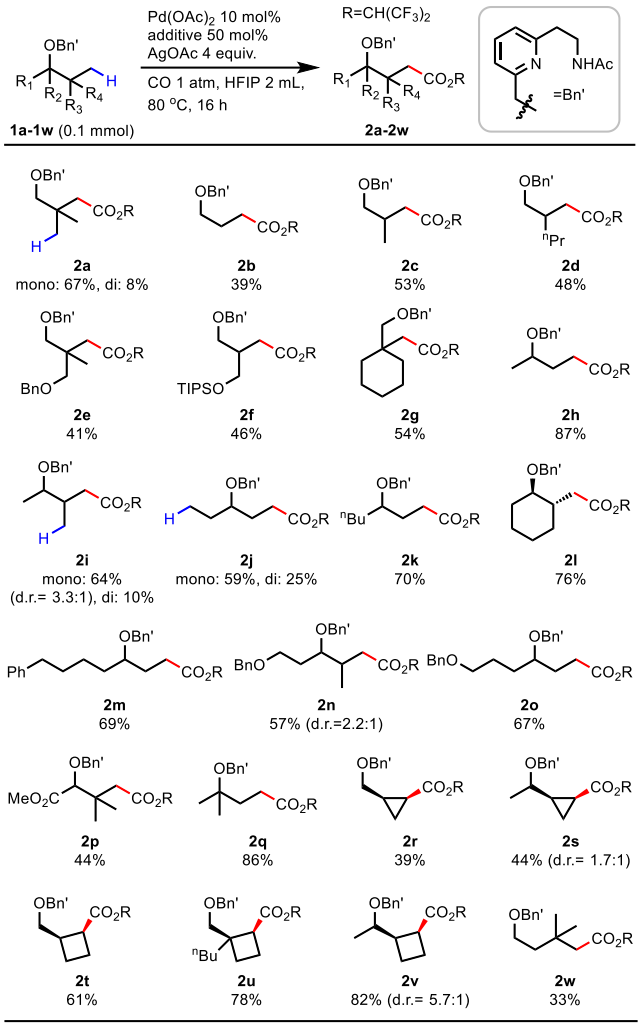


[a]The yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard.

With the optimized reaction conditions in hand[13], we examined the substrate scope (Table 2). Primary-(**1a**–**1g**), secondary-(**1h**–**1p**), tertiary-alcohols (**1q**) all gave moderate to high yields of products. Substrates containing coordinating oxygen (**1e**, **1f**, and **1n-1p**) are also compatible to the reaction conditions. Notably, these products contain three highly versatile functional groups with different protecting groups that are amenable for building complexity. The methylene C–H bonds in the cyclopropane (**1r** and **1s**) and cyclobutane (**1t-1v**) substrates are also successfully converted to ester under the same reaction conditions, affording highly valuable cyclopropyl and cyclobutyl carboxylic esters. δ-C(sp^3)–H bond activation through remote palladation was also feasible (**2w**). Although current conditions gave only moderate yield (33%), all previous directing groups displayed no reactivity with δ-C(sp^3)–H bond.[6,7]

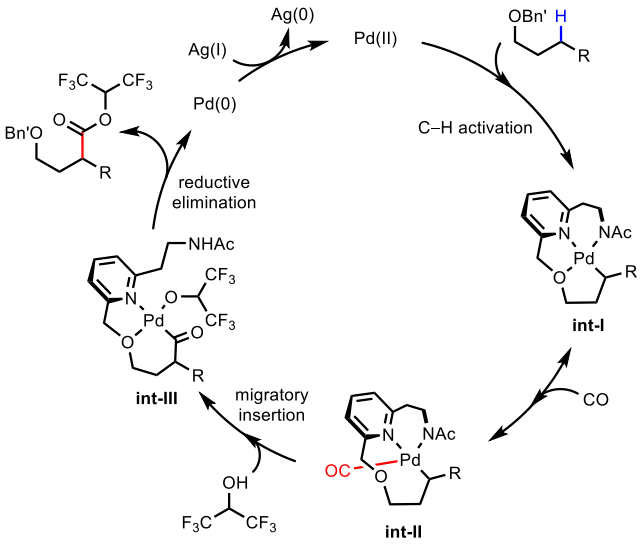
Based on our preliminary mechanistic studies (see supporting information) and literatures[11,12], we propose a catalytic cycle for the carbonylation reaction (Scheme 3A). First, the directing group coordinates to the Pd(II) and triggers the cyclopalladation of C–H bond accelerated by the NHAc motif participation (Scheme 2), affording **int-I**. Then, weak coordinating ether is displaced by incoming CO to give **int-II**. Subsequent migratory insertion and ligand exchange with solvent generate **int-III**. Finally, reductive elimination and reoxidation of Pd(0) by Ag(I) close the catalytic cycle. The essential role of ether coordination was further demonstrated by the lack of reactivity of substrate **1b$_1$** containing no ether linkage (Scheme 3B).

Table 2. C(sp^3)–H carbonylation of alcohols[a,b,c]

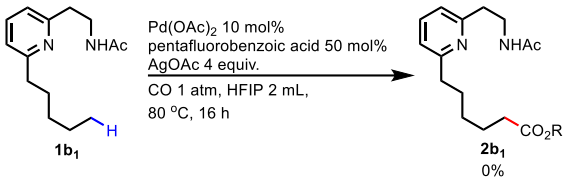


[a]Isolated yield. [b]The diastereomeric ratio was determined by ^{1}H NMR spectroscopy. [c]Additive = pentafluorobenzoic acid

Scheme 3A. Proposed catalytic cycle for C(sp^3)–H carbonylation

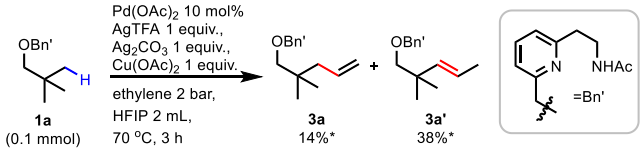


Scheme 3B. Control experiment



Considering the lack of success of C(sp^3)–H olefination with the unactivated olefin,[14,15] we applied the same catalytic system to ethylene insertion reaction, which proceeds through similar mechanism to carbonylation reaction (Scheme 4). Since ethylene is the most abundant two-carbon building block[16], this transformation is potentially useful upon further development.[17]

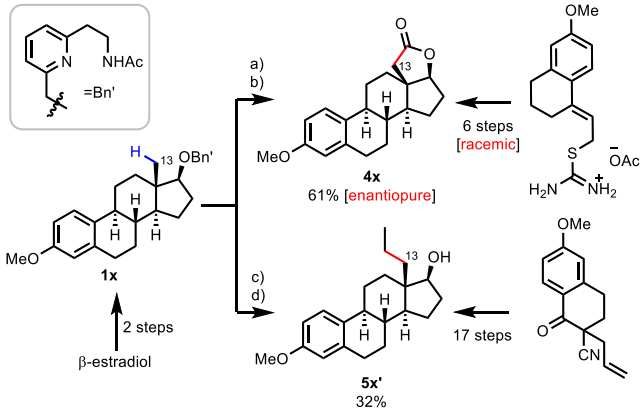
Scheme 4. C(sp^3)–H olefination with ethylene[a]



[a]The yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard.

Finally, we demonstrated the potential utility of both the carbonylation and olefination with late-stage modification of estrogen steroid hormone, β-estradiol (Scheme 5). The substitution at C13 position was believed to be important for the high bioactivity, and great number of derivatives at C13 position were prepared by both pharmaceutical company and academic laboratories.[18,19] We envisioned that these compounds can be synthesized more efficiently by using the new strategy. **1x** can be easily prepared from commercially available β-estradiol by methylation of phenol-moiety and subsequent auxiliary installation. **1x** was subjected to the carbonylation reaction conditions. Subsequent deprotection under the hydrogenation conditions gave the cyclized product **4x** in enantiomeric pure form. In contrast, the corresponding racemate required 6-step syntheses previously.[18] Like-wise, subjecting **1x** to the ethylene insertion conditions and subsequent debenzylation afforded **5x'** which required 17-step syntheses.[19]

Scheme 5. Late-stage derivatization of β-estradiol[a]



Conditions a); **1x** 1 equiv., $Pd(OAc)_2$ 10 mol%, pentafluorobenzoic acid 50 mol%, AgOAc 4 equiv., CO 1 atm, HFIP 2 mL, 80 °C, 16 h. Yield 54%. Conditions b); 10% Pd/C 30 mg, conc. HCl 50 μL, MeOH 3 mL, H_2 1 atm. Conditions c); **1x** 1 equiv. $Pd(OAc)_2$ 10 mol%, AgTFA 1 equiv., Ag_2CO_3 1 equiv., $Cu(OAc)_2$ 1 equiv., ethylene 2 bar, HFIP 2 mL, 70 °C, 12 h. Conditions d); 10% Pd/C 30 mg, conc. HCl 50 μL, MeOH 3 mL, H_2 1 atm, then 10% Pd/C 30 mg, MeOH 1 mL, H_2 1 atm. (See Supporting Information) [a]Isolated yield.

Guided by the ligand development for C(sp^3)–H activation and computational studies in our laboratory, we have developed hemilabile benzyl ether directing group to enable γ- and δ-C(sp^3)–H functionalization of alcohols. Both the acceleration from the internal ligand and the lability of the ether to dissociate during the catalytic cycle is essential. The practicality of the benzyl ether linkage is also an advantageous feature of this reaction. Notably, Pd-catalyzed C(sp^3)–H olefination with ethylene was achieved for the first time.[20] Considering the abundance of hydroxyl containing natural products and drug molecules, these reactions provide valuable means to access bioactive analogues through late-stage modifications.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Full experimental details and characterization of new compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: yu200@scripps.edu

ORCID

Jin-Quan Yu: 0000-0003-3560-5774

Notes

The authors declare no competing financial interests.

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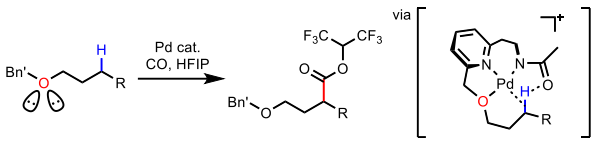
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