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Palladium-Catalyzed/Lewis Acid-Promoted Alkene Dimerization and Cross-Coupling with Alcohols *via* C–H Bond Activation

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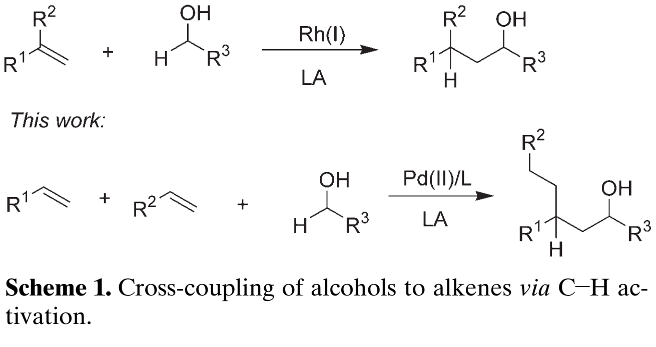
Abstract: The cross-couplings of alcohols to alkenes with the palladium/Lewis acid system are reported. This reaction occurs in a successive alkene dimerization, direct C–H activation of alcohol and sp^3–sp^3 bond forming sequence *via* an interesting domino process.

Keywords: C–C bond formation; C–H activation; domino reactions; Lewis acids; palladium

C–C bond formation reactions based on the transition metal-catalyzed sp^3 C–H bond activation have been one of the most challenging and active areas of research in modern organic chemistry due to their significant impact on both industrial and academic research.[1] Although remarkable progress has been achieved in the chemical functionalization of sp^3 C–H bonds adjacent to a nitrogen atom,[2] the activation of sp^3 C–H bonds adjacent to oxygen accompanied with subsequent C–C bond formation is still under development.[3]

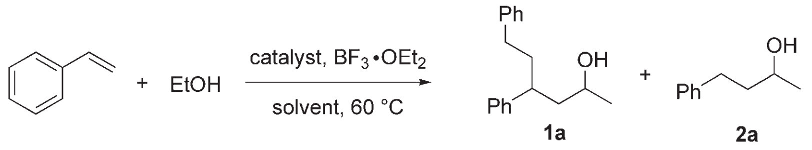
In connection with our recent investigation of C–C bond forming reactions *via* C–H bond activation of alcohols(Scheme 1),[3c] an interesting Pd-catalyzed[4]/Lewis acid-promoted domino[5] C–C bond coupling of alkenes and alcohols was recently discovered which involved the selective dimerization of alkenes[6] and the sp^3 C–H activation of alcohols. To the best of our knowledge, this kind of intermolecular domino coupling reactions containing two different C–C formation processes, the alkene dimerization and the sp^3 C–H bond activation, have not been reported previously. This combined palladium/Lewis acid catalyst system[7] is unique and plays pivotal dual roles for the two chemical transformations above, in which two new non-contiguous C–C bonds can be created in one operation. Herein, we present our preliminary results of this investigation.



Scheme 1. Cross-coupling of alcohols to alkenes *via* C–H activation.

We initially conducted the coupling reaction of styrene and ethanol in toluene by using of catalytic amount of Pd(OAc)$_2$ in the presence of the Lewis acid BF$_3$·OEt$_2$. A small amount of known cross-coupling product **2a** was observed (Table 1, entry 1).[3c] Interestingly, when PPh$_3$ was used as a ligand in this reaction (Table 1, entry 2), a different product **1a**, which was resulted from the head-to-tail dimerization of styrenes and subsequent cross-coupling with ethanol, was obtained albeit in low yield (8%). This domino sequence involving selective dimerization and C–H bond activation was unprecedent under the three-component catalyst system,[6] and it promoted us to further optimize the current reaction conditions. A survey of reaction conditions with variation of solvent, palladium source and ligand is summarized in Table 1. The reaction medium was found to have a dramatic influence on this domino reaction (entries 2–4), and the desired product **1a** could be obtained in 35% yield when CH$_3$NO$_2$ was used as a solvent (entry 4). It should be noted that the ratio of Pd(OAc)$_2$ to PPh$_3$ also had some influence on this protocol. For example, the yield of **1a** could further be improved from 35% to 50% by changing the ratio of Pd(OAc)$_2$/PPh$_3$ from 1:2 to 1:1.5 (entries 4 and 5). Among the palladium catalysts investigated (en-

Table 1. Optimization of reaction condition.[a]



Entry	Catalyst	Solvent	Product (yield [%])[b]	
			1a	**2a**
1	Pd(OAc)$_2$	Toluene	0	10
2	Pd(OAc)$_2$/PPh$_3$ (1:2)	Toluene	8	0
3	Pd(OAc)$_2$/PPh$_3$ (1:2)	CH$_2$Cl$_2$	10	0
4	Pd(OAc)$_2$/PPh$_3$ (1:2)	CH$_3$NO$_2$	35	0
5	Pd(OAc)$_2$/PPh$_3$ (1:1.5)	CH$_3$NO$_2$	50	0
6[c]	Pd(OTFA)$_2$/PPh$_3$ (1:1.5)	CH$_3$NO$_2$	60	0
7[d]	Pd(acac)$_2$/PPh$_3$ (1:1.5)	CH$_3$NO$_2$	30	0
8[e]	Pd(dba)$_2$/PPh$_3$ (1:1.5)	CH$_3$NO$_2$	0	16
9[f]	Pd(OTFA)$_2$/P(Mesityl)$_3$ (1:1.5)	CH$_3$NO$_2$	20	0
10 g]	Pd(OTFA)$_2$/dppp (1:1.5)	CH$_3$NO$_2$	5	5

[a] *Reaction conditions:* styrene (3.0 mmol), ethanol (15.0 mmol), catalyst (0.3 mmol), acid (7.5 mmol) and solvent (12 mL) at 60 °C for 20 h.

[b] Isolated yields.

[c] TFA = trifluoroacetate.

[d] acac = acetylacetonate.

[e] dba = dibenzylidene-acetone.

[f] Mesityl = 2,4,6-trimethylphenyl.

[g] dppp = 1,3-bis(diphenylphosphanyl)-propane.

tries 5–8), Pd(OTFA)$_2$ gave the best result with a 60% yield of **1a** (entry 6), wherein Pd(dba)$_2$ was unable to produce the expected product **1a** and only resulted in a low yield of the undesired simple cross-coupling product **2a** (entry 8). Phosphanes [e.g., P-(Mesityl)$_3$ as a bulkyl ligand, and dppp as a bidentate ligand] were also examined in this screening investigation (entries 9 and 10), but a decrease in the reaction yield of **1a** was observed. Other acid promoters tested instead of BF$_3$·OEt$_2$ were proved to be not effective to this reaction (for more optimization studies see Supporting Information).

Based on the optimized conditions (entry 6, Table 1), the generality of this coupling reaction was then examined and these results are summarized in Table 2. Entries 1–4 indicated that primary aliphatic alcohols with different subsitituents, such as the bulkyl isopropyl group (entry 2) and the chain-type alkyl groups (entrie 3 and 4) were suitable for the domino process. In addition, substrates containing the cyclohexyl group (entry 5) as well as the phenyl group (entry 6) were also effective. Thus, various γ-branched secondary alcohols **1a–f** could be expeditiously generated in moderate to good yields. Moreover, *meta*- and *para*-methylstyrenes bearing an electron-donating group on the aromatic ring were also tested, and the corresponding secondary alcohol **1g** and **1h** were formed efficiently in moderate yield (entries 7 and 8).

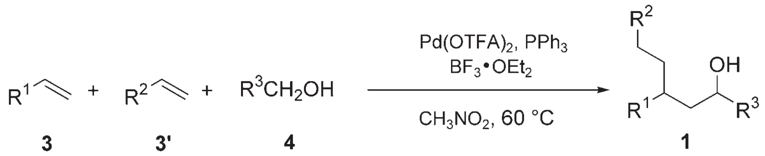
When *para*-chlorostyrene with an electron-withdrawing substituent was used in this reaction (entry 9), however, the expected **1i** was only obtained in a lower yield (30%) with longer reaction time (48 h), which might due to the unfavorable electronic effect of the *para*-chloro substituent.

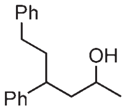
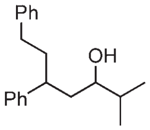
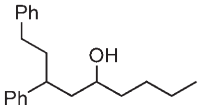
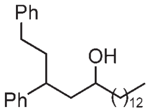
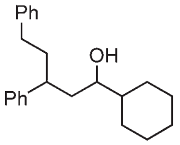
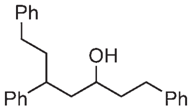
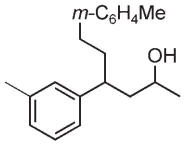
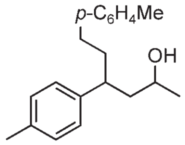
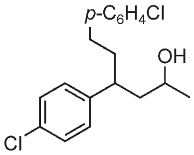
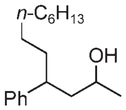
To further expand the substrate scope of the reaction, the terminal aliphatic alkene *n*-octene was chosen to react with styrene and ethanol under the standard conditions (entry 10), the heterodimerization/cross-coupling product **1j** was isolated gratifyingly with a reasonable yield.

As an insight into the mechanism of this reaction, a deuterium-labeling experiment between styrene and α-deuterated ethanol was performed to provide the deuterated product **1k** exclusively (Scheme 2). This clearly demonstrated the cleavage of C−D bond of the deuterated ethanol and the regioselectivity of the subsequent cross-coupling during this domino process.

Based on the experimental facts given above, a plausible mechanism involving two catalytic cycles was proposed as shown in Scheme 3. In the catalytic cycle of the dimerization of alkene, the Pd(II) cation intermediate **C** was formed *via* the pathway described by Shirakawa and co-workers.[6a] The following intramolecular nucleophilic attack afforded palladacycle **D**, which would undergo *β*-H elimination to give intermediate **E** or **F** with a dynamic equilibrium. Subse-

Table 2. Domino synthesis of γ-branched secondary alcohols.[a]



Entry	Substrate		Product	Yield [%][b]
1	R^1, R^2 = Ph, R^3 = Me	**1a**		60[c] (1:0.6)
2	R^1, R^2 = Ph, R^3 = *i*-Pr	**1b**		40 (1:0.8)
3	R^1, R^2 = Ph, R^3 = *n*-Bu	**1c**		53 (1:0.7)
4	R^1, R^2 = Ph, R^3 = *n*-$C_{13}H_{27}$	**1d**		45 (1:0.5)
5	R^1, R^2 = Ph, R^3 = *c*-Hexyl	**1e**		68[d] (1:0.7)
6	R^1, R^2 = Ph, R^3 = CH_2CH_2Ph	**1f**		70 (1:0.8)
7	R^1, R^2 = *m*-C_6H_4Me, R^3 = Me	**1g**		51 (1:0.8)
8	R^1, R^2 = *p*-C_6H_4Me, R^3 = Me	**1h**		56 (1:0.6)
9	R^1, R^2 = *m*-C_6H_4Cl, R^3 = Me	**1i**		30[e] (1:0.6)
10	R^1 = Ph, R^2 = *n*-C_6H_{13}, R^3 = Me	**1j**		27[c] (1:0.8)

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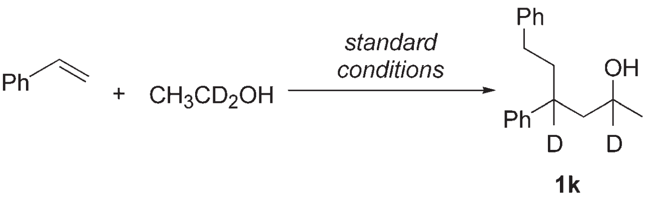
[a] *Standard reaction conditions:* **3** (1.5 mmol), **3’** (1.5 mmol), **4** (15.0 mmol), $Pd(OTFA)_2$ (0.3 mmol), PPh_3 (0.45 mmol), $BF_3{\cdot}OEt_2$ (7.5 mmol) and CH_3NO_2 (12 mL) at 60 °C for 20 h.

[b] Isolated yields calculated on the basis of olefine **3**; the ratio of two diastereoisomers determined by ^{1}HNMR is given in parenthesis.

[c] The ratio of two diastereoisomers is calculated by isolated yields.

[d] Reaction time: 8 h.

[e] Reaction time: 48 h.



Scheme 2. Deuterium labeling experiment.

quently, a reductive elimination gave the terminal alkene **G** and the disubstituted alkene **H**.[8] It should be noted that the alkene **H**, to some extent, could be transformed to **G** *via* Pd(0)-catalyzed double bond migration in the current system.[9] Intermediate **G** resulting from **E** or **H** was further consumed by C–H bond activation and cross-coupling in the second catalytic cycle, from which the driving force made the **E**⇄**D**⇄**F** equilibrium in Scheme 3 direct to the favorable formation of **G** in the first catalytic cycle again. The less hindered alkene **G** then readily coordinated to palladium catalyst to give the Pd(0)-alkene complex **I** in the C–H activation catalytic cycle. With simultaneous coordination of alcohol and Lewis acid, the C–H bond adjacent to oxygen in the alcohol was activated by the palladium catalyst through the key transition state **J** by Pd(0) oxidative addition.[10] The subsequent olefin insertion into the Pd–H bond by a less hindered way afforded the intermediate **K**, which underwent reductive elimination to provide the desired product **1** with the release of Pd(0) catalyst into the next cycle. These two catalytic cycles were realized by the combination of Pd(0) and Lewis acid, and therefore two different chemical transformations were accomplished in one operation.

In conclusion, we have developed a novel Pd-catalyzed/Lewis acid-promoted coupling reaction between primary alcohols and aromatic/aliphatic alkenes, through which a series of γ-branched secondary alcohols could be synthesized from simple and readily available starting materials. Further studies towards a deeper insight into the reaction mechanism, substrate scope and the synthetic application are currently ongoing in our group.

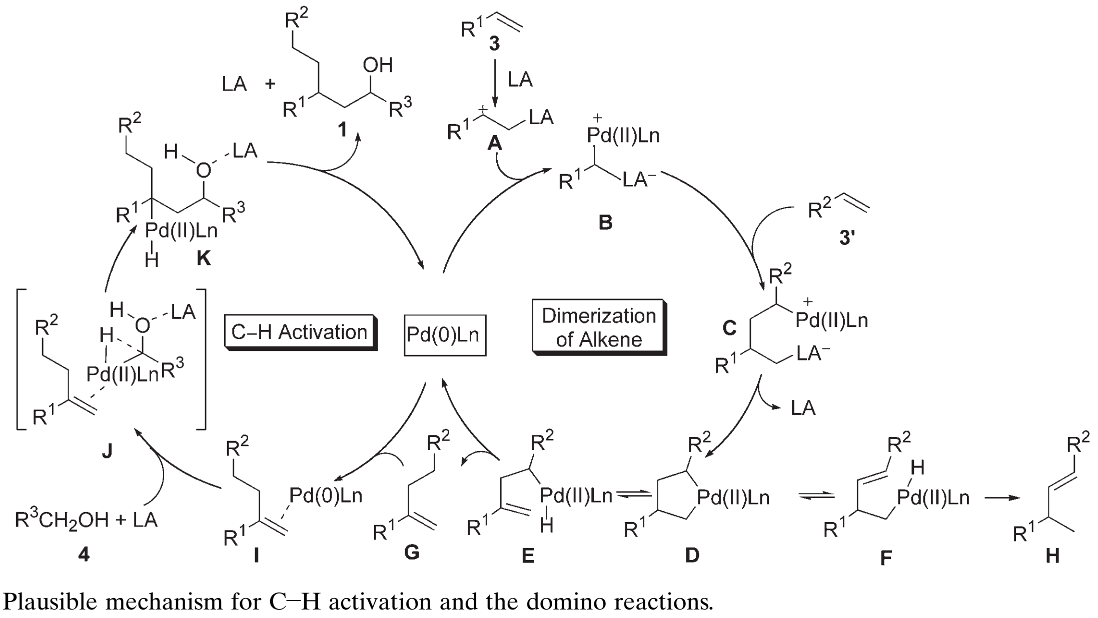
Experimental Section

General Remarks

The solvents were purified prior to use. Other commercially available materials were used as received. Flash column chromatography was performed using 200–300 mesh silica gel. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury-plus 300 or 400 instruments in $CDCl_3$ solution using TMS as internal standard. MS were measured on an HP-5988 spectrometer by direct inlet at 70 eV. High-resolution mass spectral analysis (HR-MS) data were obtained on a Bruker ApexII by means of the ESI technique.

Typical Procedure for the Cross-Coupling Reaction

To a flame-dried 25-mL flask were sequentially added CH_3NO_2 (12 mL), styrene (312 mg, 3.0 mmol), ethanol (690 mg, 15.0 mmol), PPh_3 (118 mg, 0.45 mmol) and Pd(OTFA)$_2$ (100 mg, 0.3 mmol) under argon atmosphere. The resulting mixture was stirred at 60 °C for 10 min, and then freshly distilled $BF_3·OEt_2$ (0.9 mL, 7.5 mmol) was added. After further stirring at 60 °C for 20 h, the mixture was cooled to room temperature and diluted with ethyl acetate (5 mL) followed by addition of saturated aqueous $NaHCO_3$ solution (10 mL). The organic layer was separated, and the aqueous phase was re-extracted with ethyl acetate (2×



Scheme 3. Plausible mechanism for C–H activation and the domino reactions.

20 mL). The combined organic phase was washed with brine (20 mL), dried over Na_2SO_4, concentrated under reduced pressure and purified by the flash chromatography to afford the product **1a**; yield: 60% (229 mg, 1.8 mmol; diastereomeric ratio 1:0.6).

Supporting Information

Characterization data for all products and details of optimization studies are given in the Supporting Information.

Acknowledgements

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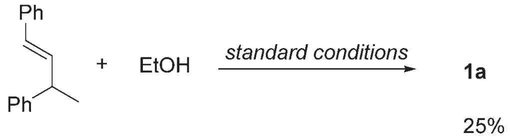
[8] Alkene **H** could be separated as the main by-product of the reaction.

[9] A supporting experiment was performed using the isolated alkene **5** under current standard conditions, and



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the desired product **1a** could be obtained in 25% yield.

[10] For a mechanism containing sp^3 C–H bond activation step catalyzed by Ir and subsequent alkenen insertion see: B. DeBoef, S. J. Pastine, D. Sames, *J. Am. Chem. Soc.* **2004**, *126*, 6556.