Angewandte
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Addition reactions

Palladium-Catalyzed Equilibrium Addition of Acidic OH Groups across Dienes**

Masaru Utsunomiya, Motoi Kawatsura, and
*John F. Hartwig**

Transition-metal-catalyzed additions of the O–H groups of water and alcohols across substrates with carbon–carbon multiple bonds could provide ethers and alcohols under mild conditions, with the potential for regio and enantiocontrol, and without the by-products of substitution chemistry.[1] However, such metal-catalyzed reactions have been difficult to develop, despite recent advances in the addition of C–H[2–5] and N–H[6–8] groups to olefins.

Palladium-catalyzed telomerization of dienes in the presence of alcohols[9–11] and the 1,4-oxidation of dienes[12] are well-known reactions. Yet, few examples of the formation of allylic ethers by the 1:1 addition of an alcohol across a diene without accompanying oxidation have been reported.[5] A catalyst for the addition of substrates with O–H bonds across dienes that is general enough to encompass additions of mildly acidic O–H groups and that selectively catalyzes 1:1 addition over telomerization is unknown.[13]

In parallel with our efforts to develop catalysis for olefin hydroamination,[7,8,14,15] we have sought transition-metal catalysts for the addition of the O–H groups of alcohols and carboxylic acids across substrates with carbon–carbon multiple bonds. Herein we report the transition-metal-catalyzed formation of allylic ethers and esters by the 1:1 addition of

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[*] Prof. J. F. Hartwig, M. Utsunomiya, Dr. M. Kawatsura
Department of Chemistry, Yale University
P.O. Box 208107
New Haven, CT 06520-8107 (USA)
Fax: (+1) 203-432-6144
E-mail: john.hartwig@yale.edu

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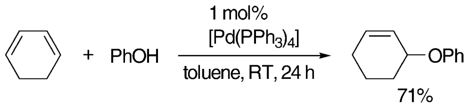
phenols and carboxylic acids across dienes [Eq. (1)]. These addition reactions are reversible, and the measurement of the equilibrium constant for this new type of OH-addition process shows that $\Delta G \approx 0$.



(1)

A series of metal complexes were tested for the addition of phenols across cyclohexadiene. $[Pd(PPh_3)_4]$ displayed good reactivity for the generation of cyclohexenyl phenyl ether under mild conditions (Table 1, entry 1). This simple complex catalyzes the addition of the O–H group of phenols and carboxylic acids across dienes without a co-catalyst. In contrast, this complex required an acid co-catalyst, such as trifluoroacetic or triflic acid, to catalyze the hydroamination of vinyl arenas and dienes.[8,14] The combination of $[\{Pd(allyl)Cl\}_2]$ and PPh_3 (4 equiv), which generates $[Pd(PPh_3)_4]$,[16] also catalyzes the addition of phenol to cyclohexadiene.

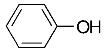
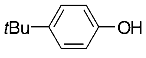
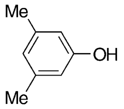
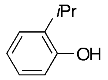
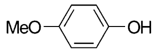
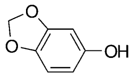
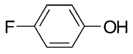
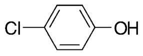
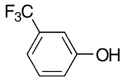
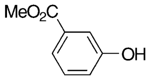
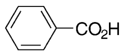
Table 1: Effect of phosphane ligand on the addition of phenol to cyclohexadiene.[a]

Entry	Pd precursor	Ligand[b]	Yield [%][c]
1	$[Pd(PPh_3)_4]$	none	73
2	$[\{Pd(allyl)Cl\}_2]$	PPh_3	62
3	$[\{Pd(allyl)Cl\}_2]$	PPh_2Cy	56
4	$[\{Pd(allyl)Cl\}_2]$	PCy_3	0
5	$[\{Pd(allyl)Cl\}_2]$	$P(p\text{-}MeOC_6H_4)_3$	25
6	$[\{Pd(allyl)Cl\}_2]$	$P(p\text{-}ClC_6H_4)_3$	25
7	$[\{Pd(allyl)Cl\}_2]$	$P(OPh)_3$	0
8	$[\{Pd(allyl)Cl\}_2]$	dppe	0
9	$[\{Pd(allyl)Cl\}_2]$	dppf	3
10	$[\{Pd(allyl)Cl\}_2]$	binap	0
11	$[\{Pd(allyl)Cl\}_2]$	xantphos	71

[a] Reactions were conducted on a 0.4-mmol scale in toluene (0.2 mL) at room temperature for 24 h (phenol/cyclohexadiene/$[Pd(PPh_3)_4]$ or $[\{Pd(allyl)Cl\}_2]$ 100:400:1). [b] P/Pd = 4. [c] Yields determined by GC.

Reactions of phenol with cyclohexadiene catalyzed by $[\{Pd(allyl)Cl\}_2]$ and a variety of phosphanes (Table 1) showed that monodentate ligands, such as PPh_3 (Table 1, entry 2) and cyclohexyldiphenylphosphane (Table 1, entry 3), generated catalysts for the addition of phenol across cyclohexadiene. Of the bisphosphanes[17] that we evaluated, only xantphos generated an active catalyst for the addition of the O–H bonds across dienes. Reactions conducted in the absence of catalyst did not form the O–H addition product in amounts detectable by GC. $[Pd(PPh_3)_4]$ was chosen to study the scope of the reaction because it led to faster reaction rates than $[\{Pd(allyl)Cl\}_2]$ and xantphos.

Table 2: Pd-catalyzed addition of acidic OH bonds to cyclohexadiene.[a]

Entry	ROH	Yield [%][b]	Conversion [%][c]
1		71	73
2		73	75
3		72	73
4		61	61
5		67	67
6[d]		53	90
7[d,e]		62	63
8[d,e]		57	60
9[d–f]		44	50
10[f–h]		47	85
11		50	51[k]
12[i]	CH_3CO_2H	52	52[k]

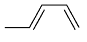
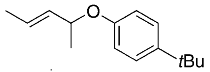
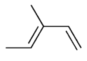
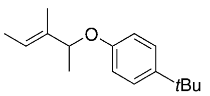
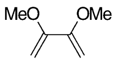
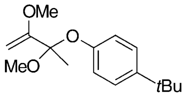
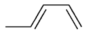
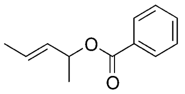
[a] Reaction conditions: ROH (1.0 mmol), cyclohexadiene (4.0 mmol), $[Pd(PPh_3)_4]$ (0.01 mmol), toluene (0.5 mL), room temperature, 24 h, unless otherwise noted. [b] Yields of isolated products. [c] Calculated by GC. [d] 50 °C. [e] $[Pd(PPh_3)_4]$: 0.02 mmol. [f] 18 h. [g] Toluene: 1.0 mL [h] $[Pd(PPh_3)_4]$: 0.05 mmol. [i] 2.0-mmol scale, 48 h. [j] Yields determined by GC. [k] Calculated by ^1H NMR spectroscopy.

Table 2 summarizes the yields from the addition of various phenols and carboxylic acids across cyclohexadiene. The reactions were typically run at room temperature and at a high concentration (2 M) to favor the addition process. Aryl alcohols with electron-withdrawing groups, such as 4-halophenols (Table 2, entries 7 and 8) and 3-trifluoromethylphenol (Table 2, entry 9), reacted with cyclohexadiene to form the addition product in moderate to good yields. Aryl alcohols with electron-donating groups (Table 2, entries 5 and 6) also formed the addition product in good yields. Phenols with a single *ortho* substituent, including an isopropyl group, reacted in good yields under the same conditions (Table 2, entry 4), but 2,6-disubstituted phenols gave only trace amounts of the addition product at room temperature or 100 °C. The addition reaction also occurred with methyl 3-hydroxybenzoate (Table 2, entry 10), which would react at the ester under classic acid-catalyzed conditions. All reactions in Table 2 gave 2-cyclohexenyl aryl ethers as the sole regioisomer. No 3- or 1-cyclohexenyl aryl ether was detected by GC/MS or NMR spectroscopy. In all cases, the addition processes were clean, and only excess aryl alcohol or ether product were found. Thus, the reaction yields largely paralleled the conversions.

Substrates with O–H groups that are more acidic than those in phenols also underwent additions across dienes. Benzoic acid reacted with 1,3-cyclohexadiene in the presence of the palladium catalyst to form 2-cyclohexenyl benzoate in moderate yield (Table 2, entry 11). Acetic acid added to cyclohexadiene in the presence of the palladium catalyst to form the O–H addition product in 52 % yield. Again, no addition product was observed at room temperature or at 70 °C in the absence of catalyst, and the reaction yields were similar to the conversions.

Table 3 summarizes reactions of acyclic dienes with aryl alcohols and carboxylic acids in the presence of [Pd(PPh$_3$)$_4$] catalyst. These reactions demonstrate that acyclic allylic ethers can also be prepared by the O–H addition process.

Table 3: Pd-catalyzed addition of acidic OH groups to acyclic dienes.[a]

Entry	Diene	Product	Yield [%] (*E*/*Z*)[b]	Conversion [%][c]
1			63 (88:12)	68
2			59 (89:11)	62
3[d]			62	64
4[e]			41 (85:15)	42[f]

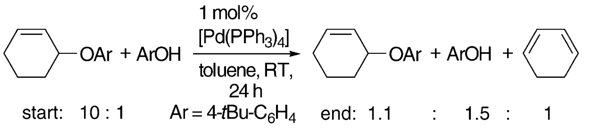
[a] Reaction conditions: 4-tert-butylphenol or benzoic acid (1.0 mmol), dienes (4.0 mmol), [Pd(PPh$_3$)$_4$] (0.01 mmol), toluene (0.5 mL), room temperature, 24 h, unless otherwise noted. [b] Yields of isolated products. [c] Calculated by GC. [d] Diene (2.0 mmol), [Pd(PPh$_3$)$_4$] (0.05 mmol). [e] Diene (8.0 mmol), [Pd(PPh$_3$)$_4$] (0.02 mmol), toluene (1.0 mL), 50 °C. [f] Calculated by ^{1}H NMR spectroscopy.

The reactions of 4-*tert*-butylphenol and benzoic acid with *trans*-1,3-pentadiene and (*E*)-3-methyl-1,3-pentadiene gave products with the aryloxy group at the more hindered, internal position by either 1,2- or 1,4-addition (Table 3, entries 1–2, 4). The reaction of 2,3-dimethoxybutadiene with 4-tert-butylphenol also formed the product with the more substituted carbon atom, this time by a clear 1,2-addition (Table 3, entry 3).

The reaction of [D$_1$]4-*tert*-butylphenol with 1,3-pentadiene formed products with the deuterium label at the two methyl groups in a 1:1 ratio, and the reaction of [D$_1$]4-*tert*-butylphenol with cyclohexadiene formed four products in equal amounts from both *syn* and *anti* additions with 1,2- and 1,4-regiochemistry. These labeling experiments suggest the intermediacy of a π-allyl intermediate and reversible C–O bond cleavage in the product. Indeed, catalytic exchange of the phenoxy group of the ether with another aryl alcohol was faster than the catalytic addition of phenol across cyclohexadiene.[18]

The similarities between the yields and conversions of the reactions between dienes and phenols or carboxylic acids suggest that the addition processes are reversible and that thermodynamic factors affect the conversion. This hypothesis was supported by two sets of results: First, reactions at lower temperatures provided higher yields than those conducted at higher temperatures. For example, the reaction of phenol and cyclohexadiene catalyzed by [Pd(PPh$_3$)$_4$] at room temperature consumed 73 % of the phenol and formed the addition product in 71 % yield (Table 2, entry 1), whereas the reaction at 60 °C consumed 51 % of the phenol and formed the addition product in 46 % yield. Second, the addition of a second portion of catalyst did not lead to further reaction.

To determine definitively if the reaction was reversible, we subjected 4-*tert*-butylphenyl cyclohexenyl ether to catalytic quantities of [Pd(PPh$_3$)$_4$] at room temperature, along with 4-*tert*-butylphenol (0.1 equiv) to activate the catalyst. Consistent with the proposed equilibrium, 55 % of the ether was consumed to give a 1.1:1.5:1 ratio of ether/4-*tert*-butylphenol, and cyclohexadiene after 24 h [Eq. (2)]. The final concentrations from both the forward and reverse reactions at room temperature indicated that the K_{eq} was 1.7 ± 0.7; with estimated activity coefficients, the equilibrium constant was 0.62 ± 0.25. These values are smaller than those for the addition of methanol to isobutylene.[19]



(2)

This thermodynamic analysis of the addition process underscores that the value of Δ*G* for O–H addition across olefins is close enough to 0 that small changes in the structures and concentrations of the reactants can influence the conversion. Catalysts active enough to allow the reactions to be conducted under low temperatures conditions with high reactant concentrations are important to obtain high yields of products. Under these conditions, we have shown that the transition-metal-catalyzed addition of phenolic and carboxylic acids across dienes occurs in good yields and with broad scope.

Experimental Section

General procedure (Table 2, entry 1): In a glovebox, 1,3-cyclohexadiene (381 μL, 4.00 mmol) and phenol (94 mg, 1.00 mmol) were added to a suspension of [Pd(PPh$_3$)$_4$] (12 mg, 0.01 mmol) in toluene (0.5 mL) in a screw-capped vial. The vial was sealed with a teflon-lined septum, capped, and removed from the glovebox. The reaction mixture was then stirred at room temperature for 24 h. The mixture was absorbed onto silica gel and purified by flash column chromatography to give a colorless oil (124 mg, 71 %).

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[1] S. A. Godleski, B. M. Trost, I. Fleming in *Comprehensive Organic Synthesis*, *Vol. 4* (Eds.: S. A. Godleski, B. M. Trost, I. Fleming), Pergamon, New York, **1991**, p. 585.
[2] L. J. Gooßen, *Angew. Chem.* **2002**, *114*, 3929; *Angew. Chem. Int. Ed.* **2002**, *41*, 3775.
[3] T. Pei, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2001**, *123*, 11290.

[4] B. M. Trost, C. Jäkel, B. Plietker, *J. Am. Chem. Soc.* **2003**, *125*, 4438.
[5] P. W. Jolly, N. Kokel, *Synthesis* **1990**, 771.
[6] T. E. Müller, M. Beller, *Chem. Rev.* **1998**, *98*, 675.
[7] M. Utsunomiya, R. Kuwano, M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 5608.
[8] M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **2000**, *122*, 9546.
[9] W. Keim, A. Behr, M. Roper in *Comprehensive Organometallic Chemistry*, *Vol. 8* (Eds.: G. Wilkinson, F. G. A. Stone), Pergamon, Oxford, **1982**, p. 371.
[10] J. Tsuji, *Acc. Chem. Res.* **1973**, *6*, 8.
[11] R. Jackstell, A. Frisch, M. Beller, D. Rottger, M. Malaun, B. Bildstein, *J. Mol. Catal. A* **2002**, *185*, 105.
[12] J. E. Backvall, *Adv. Met.-Org. Chem.* **1989**, *1*, 135.
[13] For an example of a nickel-catalyzed addition of phenol to for a mixture of telomerization and 1:1 addition products, see: V. J. Beger, C. H. Duschek, G. W. Füllbier, *J. Prakt. Chem.* **1974**, *316*, 26.
[14] O. Löber, M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, *123*, 4366.
[15] J. Pawalas, Y. Nakano, M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 3669.
[16] C. F. J. Barnard, M. J. H. Russell in *Comprehensive Organometallic Chemistry*, *Vol. 5* (Eds.: G. Wilkinson, R. D. Gillard, J. A. McCleverty), Pergamon, Oxford, **1987**, p. 1101.
[17] DPPE = 1,2-Bis(diphenylphosphino)ethane, DPPF = 1,1′-Bis(-diphenylphosphino)ferrocene, BINAP = 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl, Xantphos = 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene
[18] See supporting information for data.
[19] J. F. Izquierdo, F. Cunill, M. Vila, M. Iborra, J. Tejero, *Ind. Eng. Chem. Res.* **1994**, *33*, 2830.