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General Method for the Palladium-Catalyzed Allylation of Aliphatic Alcohols

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A palladium catalysis-mediated approach to coupling aliphatic alcohols with allyl carbonates has been developed. The method allows for the allylation of primary, secondary, and tertiary alcohols efficiently under mild conditions. Limitations were explored as well as the asymmetric application of the chemistry. Regiochemical and olefin geometry was controlled in the coupling of unsymmetrical allylating agents. Transient allyl carbonates were observed in the coupling, which comprised the trans-carboxylation of the allyl-carbonate with the requisite alcohol.

Introduction

The transition metal-catalyzed allylation of nucleophiles is a versatile methodology in organic synthesis.[1] A variety of nucleophiles such as carbanions,[1,2] amines,[1,3] sulfides,[1,4] and sulfinates,[1,5] have been shown to couple efficiently with palladium π-allyl complexes. With advances in regioselective[6] and enantioselective[7] reactions, the utility of this chemistry continues to expand. The palladium-catalyzed allylation of alcohols has been utilized to a lesser extent due to the poor nucleophilicity of alcohols. Most examples of oxygen nucleophiles have been limited to phenols,[8] intramolecular allylations,[9] substrate-specific systems,[10] or zinc[11] or stannyl[12] alkoxides. We report here on a general[13] method for the efficient allylation of aliphatic primary, secondary, and tertiary hydroxyl groups under palladium catalysis that does not require the preparation of metal alkoxides[11,12] or the removal of inorganic salts from the reaction mixtures.

In the course of our work, we required a method for the preparation of a substituted allyl ether appendage on a sterically hindered alcohol under mild conditions.[14] Typically, allyl ethers are prepared under strongly basic conditions by alkylation of the metal alkoxide with allyl halides or pseudohalides in a polar solvent[15] or by

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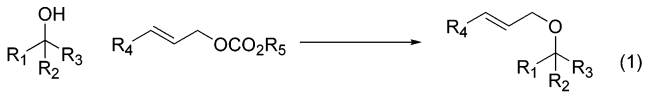
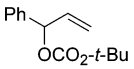
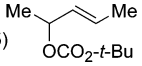
TABLE 1. Allylations of Alcohols[a]



Entry	Alcohol	R_1	R_2	R_3	Carbonate (equiv)	R_4	R_5	product	Yield(%)[b](isolated)
1	**1a**	$Ph(CH_2)_2$	H	H	**2b**(3.3)	H	Me	**3a**	>95
2	**1a**	$Ph(CH_2)_2$	H	H	**2c**(2.0)	H	*i*-Pr	**3a**	>99
3	**1a**	$Ph(CH_2)_2$	H	H	**2d**(1.2)	H	*t*-Bu	**3a**	>99 (89)
4	**1b**	$Ph(CH_2)_2$	Me	H	**2b**(>6.9)	H	Me	**3b**	78
5	**1b**	$Ph(CH_2)_2$	Me	H	**2c**(5.0)	H	*i*-Pr	**3b**	>95
6	**1b**	$Ph(CH_2)_2$	Me	H	**2d**(1.5)	H	*t*-Bu	**3b**	>95 (92)
7[c]	**4**	$Ph(CH_2)_2$	Me	Me	**2d**(5.0)	H	*t*-Bu	**5**	>99 (89)
8[d]	**6**	PhCH(OH)	H	H	**2d**(1.1)	H	*t*-Bu	**7a/b/c**[e]	21 (**7a**)[f] 48 (**7b**)[f] 16 (**7c**)[f]
9[c]	**8**	$PhCH_2$	CF_3	CF_3	**2d**(1.2)	H	*t*-Bu	**9**	>98 (68)
10	**1a**	$Ph(CH_2)_2$	H	H	**10**(1.2)	Ph	*t*-Bu	**11**	>95 (81)
11[d]	**EtOH**	Me	H	H	**10**(1.2)	Ph	*t*-Bu	**12**	>95 (74)
12[d]	**EtOH**	Me	H	H	**13**(1.2) 			**12**	>95 (65)
13[c]	**14**	Ph	H	H	**15** (1.0) 			**16**	nd
14[c]	**14**	Ph	H	H	**15** (0.05)			**16**	<50 (35)

[a] Reactions in THF at 60−65 °C for 1−3 h with 1−3 mol % $Pd(OAc)_2$/2−6 mol % Ph_3P. [b] HPLC yield. [c] Reaction run with 1−3 mol % $(Ph_3)_4Pd$. [d] Reaction run with 2−4 mol % $Pd_2(dba)_3$/4−8 mol % Ph_3P. [e] **7a**, primary ether; **7b**, secondary ether; **7c**, bis-ether. [f] GC yield.

alkylation of stoichiometric alkoxyorganostannane derivatives.[16] Notably absent from this methodology have been efforts to allylate sterically hindered aliphatic alcohols.[17]

Rhodium-[18] and palladium-catalyzed[19] allylations have recently been explored in an effort to allylate hydroxyl functionalities. In Sinou's report on the palladium-catalyzed allylation of carbohydrate substrates using allyl ethyl carbonate, **2a**,[19] an excess of **2a** was required presumably due to the spectator ethoxide competing for the π-allyl palladium species.[19c] We reasoned that the sterics of the spectator alkoxide could be modulated to competitively favor allylation of the desired alcohol.

To test this hypothesis, we studied the allylation of 3-phenylpropan-1-ol, **1a**, with three allyl carbonates: allyl methyl carbonate, **2b**, allyl isopropyl carbonate, **2c**, and allyl *tert*-butyl carbonate, **2d**.[20] The carbonates were added to a refluxing THF mixture of alcohol **1a** and catalytic tetrakis(triphenylphosphine)palladium(0)[21] to obtain ether **3a** (eq 1; Table 1, entries 1−3). A sufficient amount of the allyl carbonates was added to convert >98% of the substrate alcohol, **1a**, to the allyl ether, **3a**. This called for 3.3, 2.0, and 1.2 equiv of **2b**, **2c**, and **2d**, respectively, for the allylation of **1a** (Table 1, entries 1−3). In the allylation of the secondary alcohol, **1b**, >5 equiv of either **2b** or **2c** was necessary to push the allylation to >95% conversion, compared to 1.5 equiv of **2d** (Table 1, entries 4−6).

High yields and minimal amounts of *tert*-butyl allyl ether were observed in the allylation of primary and secondary alcohols when carbonate **2d** was employed (Table 1, entries 3, 6). Unfortunately, no significant regioselectivity was seen in the allylation of diol **6**, which yielded ethers **7a**, **7b**, and **7c** in a 1:2:1 ratio using 1.1 equiv of **2d** (Table 1, entry 8).[22] Coupling to tertiary alcohols is possible with **2d**; however, 5 equiv of **2d** is necessary to obtain high conversion due to competitive allylation (Table 1, entry 7).

We found that the acidity of the substrate alcohol influences the selectivity of the reaction.[23] In the coupling of the highly acidic tertiary alcohol **8**, only 1.2 equiv of the carbonate **2d** was required to obtain >98% conversion to the allyl ether, **9**, as compared with 5.0 equiv in the allylation of **4** (Table 1, entries 7 vs 9).[24] In a competition

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(18) Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2000**, *122*, 5012.

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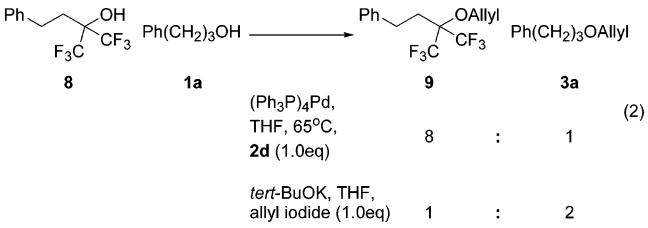
(20) **2b** was purchased from Aldrich Chemical Co. **2c** was prepared from allyl alcohol and isopropyl chloroformate. **2d** was prepared from $(BOC)_2O$. See: Houlihan, F.; Bouchard, F.; Frèchet, J. M. J.; Willson, C. G. *Can. J. Chem.* **1985**, *63*, 153.

(21) Preparing the presumed active catalytic species either from $(Ph_3P)_4Pd$ or in situ from $Pd(OAc)_2/Ph_3P$ or $Pd_2(dba)_3/Ph_3P$ showed no difference in reactivity or selectivity.

(22) Masaki, Y.; Miura, T.; Ochiai, M. *Synlett* **1993**, 847.

(23) Regioselectivity has been correlated to hydroxyl acidity. See ref 19a: and Massacret, M.; Lhoste, P.; Lakhmiri, R.; Parella, T.; Sinou, D. Eur. *J. Org. Chem.* **1999**, 2665.

experiment comparing the acidity effect to the sterics of the nucleophile, allylation of an equimolar mixture of primary alcohol **1a** and tertiary alcohol **8** with 1.0 equiv of **2d** gave 8:1 (**9**:**3a**) selectivity favoring tertiary ether **9**. This is in stark contrast to allylation under anionic conditions with KOtBu and allyl iodide, which favors **3a** in a 2:1 ratio (eq 2).



(2)

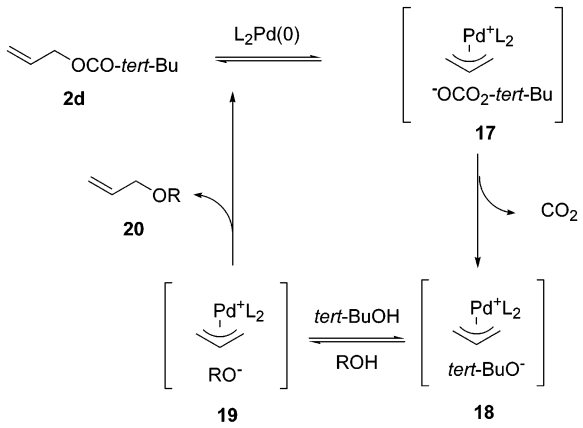
High regio- and chemoselectivity was observed in the coupling of 1.2 equiv of *tert*-butyl cinnamyl carbonate **10** with either **1a** or ethanol (Table 1, entries 10, 11). When ethanol was coupled with the secondary carbonate **13**, only the terminal (*E*)-alkene **12**[25] was observed, as expected from a π-allyl palladium intermediate (Table 1, entry 12). Alkyl substituents on the allyl portion of the carbonate fail to give acceptable yields in the coupling with benzyl alcohol even if a huge excess of the alcohol is employed (Table 1, entries 13, 14).[26]

Under comparable conditions and time, $Pd(PPh_3)_4$ gave higher conversions in the coupling of **2d** with **1a** relative to the catalyst prepared from $Pd(OAc)_2$ and Ph_3P (>95 vs 88%, respectively). Triphenylphosphine, dppf, dppb, and $(p\text{-}CF_3C_6H_4)_3P$ all were acceptable ligands for the coupling of **2d** with **1b**, while Cy_3P, $(o\text{-tol})_3P$, or Ph_3As gave either poor conversions or a significant amount of side-products. In terms of solvents, THF, DME, and toluene all gave comparable yields in the reaction, while acetonitrile and DMF generated significant side-products.

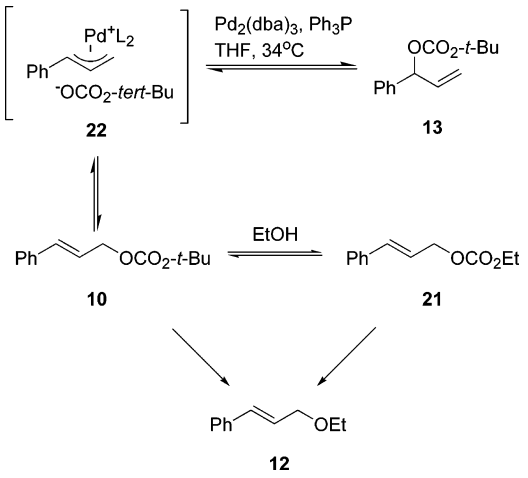
A typical procedure was to add $Pd(OAc)_2$ (0.005 equiv) and Ph_3P (0.04 equiv) to a 0.5 mM anhydrous degassed THF solution of **1b** with **2d** (1.5 equiv). The mixture was heated to reflux for 3 h, concentrated, and purified by column chromatography to yield **3b** in 92% yield.

In situ analysis shows the mechanism to be more complex than the literature would suggest for π-allyl palladium chemistry.[1,27] The generally accepted mechanism for allylations with allyl carbonates invokes the reversible[28] oxidative addition of **2d** to Pd(0) to give π-allyl palladium intermediate **17** (Scheme 1).[1,27] Decarboxylation yields the alkoxide intermediate **18**, which is in rapid protic equilibrium with the substrate alkoxide

SCHEME 1. Proposed Allylation Mechanism



SCHEME 2. Carbonate Isomerization



19. Addition of the alkoxide to the π-allyl palladium species then is proposed to yield the product, **20**, regenerating the Pd(0) catalyst.

To our surprise, when we monitored by HPLC the coupling of ethanol with carbonate **10** at 35 °C, we observed the transient appearance of the ethyl carbonate, **21** (Scheme 2).[29] As the reaction progressed, the ratio of **21** to **10** present in the mixture shifted from 90:10 (**21**:**10**) at 4% conversion to 45:55 (**21**:**10**) at 89% conversion. The equilibrium ratio of **21** to **10** is approximately 10:1 as established by monitoring a 35 °C THF solution of an equimolar mixture of **10** and ethanol in the presence of $Pd_2(dba)_3/(o\text{-furyl})_3P$ under which conditions little coupling is observed. As expected, control experiments demonstrated that both palladium and a phosphine ligand are necessary for the formation of carbonate **21**.

π-Allyl palladium(II) alkyl carbonate complexes are known to react rapidly with water to generate hydrogen carbonate complexes.[30] We are aware of only one example where such a transalkoxylation has been demonstrated with an alcohol.[31] The observation of the ethyl carbonate **21** during the coupling of **10** with ethanol would suggest that these transalkoxylation reactions are more general

(24) Low isolated yield of **9** appears to be due to the stability of the material during isolation.

(25) Barluenga, J.; Alonso-Cires, L.; Campos, P. J.; Asensio, G. *Tetrahedron* **1984**, *40*, 2563.

(26) Recently reported solution to this problem employs a zinc alkoxide as the nucleophile.[11]

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(29) Carbonate **21** was independently prepared from cinnamyl alcohol and ethylpyrocarbonate for comparison (Cravotto, G.; Giovenzana, G. B.; Sisti, M.; Palmisano, G. *Tetrahedron* **1998**, *54*, 1639).

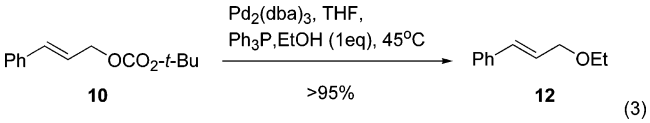
(30) Ozawa, F.; Son, T.; Ebina, S.; Osakanda, K.; Yamamoto, A. *Organometallics* **1992**, *11*, 171.

and might offer a method of preparing mixed carbonates.[33]

In the coupling of carbonate **13**, rapid formation of the (*E*)-cinnamyl carbonate **10** was initially observed, followed by carbonate **21** and ultimately allyl ether **12** (Scheme 2). The isomerization of the secondary carbonate **13** to the more stable **10** is the result of the reversibility of the oxidative addition/reductive elimination process.[34]

We investigated the effect of the nucleophile structure on the rate of the alcohol allylation reaction. Under the standard conditions of $Pd_2(dba)_3$ (5 mol % Pd) and Ph_3P (10 mol %) in THF (0.25 M) at 55 °C, coupling of carbonate **10** with *tert*-butyl alcohol, ethanol, and 2,2,2-trifluoroethanol gave relative rates of 1, 18, and 833, respectively. The rate differences between ethanol and *tert*-butyl alcohol can be attributed to a steric differentiation between the two. The surprisingly fast reaction with 2,2,2-trifluoroethanol, an alcohol of extremely low nucleophilicity, suggests to us that the reaction rate is highly sensitive to either formation or concentration of the alkoxide.

Organotin alkoxides have previously been shown to be efficient coupling partners with π-allyl palladium species,[12] presumably due to their enhanced nucleophilicity. Unfortunately, preparation of the stannyl ethers and removal of the stannyl byproducts is a hindrance to this approach. We found that when the coupling of ethanol with **10** was carried out under the standard conditions, addition of 10 mol % tributyltin ethoxide generated **12** much more rapidly, avoiding the need for preparation the stannyl ethers and reducing the concerns for removal of stoichiometric amounts of organotin byproducts (eq 3).



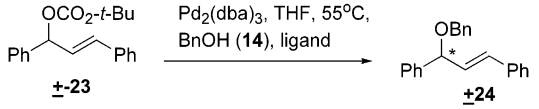
(3)

No Bu_3SnOEt 6 hours

10mol% Bu_3SnOEt 15 minutes

To further expand the utility of this chemistry, we explored the enantioselective alkylation of secondary carbonate **23** with various ligands (Table 2).[35] Only in the case of BINAP was good conversion (>99%) and moderate enantiomeric excess (73−88%) observed in the coupling (entries 5, 6). Careful monitoring of the coupling with BINAP revealed that the enantiopurity of the product, **24**, decreased as the reaction progressed. Since the product was shown to be stable under the reaction conditions, this suggests to us that a competitive catalyst may be involved.

TABLE 2. Asymmetric Allylation of ±-23 with Benzyl Alcohol[a]

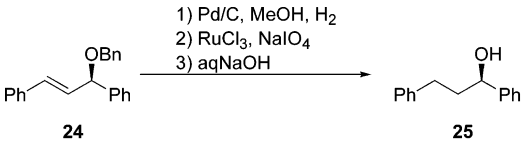


(4)

entry	ligand	**24**	time (h)	ee[b]	config-uration
1	(*R*,*R*)-BDPP	30%	3	30%	*R*
2	(*R*,*R*)-BDPP	>98%	8	28%	*R*
3[c]	(*R*,*R*)-BDPP	>98%	4	25%	*R*
4	(*R*,*R*)-DiACyh-PyCar[d]	2%	24	nd	nd
5	(*R*)-BINAP	>98%	8	65−88%	*R*
6	(*S*)-BINAP	>98%	8	73%	*S*
7	(*S*,*S*)-DIOP	>98%	<1	9%	*R*
8	(*R*,*R*)-DIOP	>98%	<1	9%	*S*
9	(*R*,*R*)-EtDuphos	50%	4	5%	*S*
10	(*R*,*R*)-Norphos	>98%	4	41%	*R*
11	(*R*)-Quinap	10%	24	6%	*R*
12	(*R*,*R*)-Me-BPE	>98%	1	41%	*R*
13	(*R*)-MOP	>98%	20	16%	*S*

[a] Reaction in 0.1 M THF at reflux with 14 (6 equiv), 1 mol % $Pd_2(dba)_3$, and 4 mol % ligand. [b] Chiral HPLC for yield and enantiomeric purity. [c] Performed with 10% Bu_3SnOEt. [d] *C*(−)-*N*,*N*′-(1*R*,2*R*)-1,2-Diaminocyclohexanediylbis-(2-pyridinecarboxamide).

The absolute stereochemistry of **24** was determined from a sample of synthesized using (*R*)-BINAP as the ligand. The alkene was first reduced followed by selective benzylic oxidation with $RuCl_3/NaIO_4$[36] to give, after hydrolysis, the known secondary alcohol **25** (eq 5).[37] The sense of stereochemical induction is consistent with that observed in the malonate alkylation of the comparable π-allyl palladium complex prepared from the acetate,[38] as well as the stereochemistry obtained in the coupling with phenol.[39]



(5)

$[\alpha]_D^{20}$ = +15.6 (c=0.226, $CHCl_3$)
lit[37], $[\alpha]_D^{20}$ = +13.4
(c=0.22, $CHCl_3$) 47% ee, *R*

In conclusion, this work demonstrates that employing the sterically hindered spectator *tert*-butyl alkoxide in

(31) Davis, A. P.; Dorgan, B. J.; Mageean, E. R. *J. Chem. Soc., Chem. Commun.* **1993**, 492. Alkyl allyl carbonates have been prepared via palladium catalysis.[32]

(32) McGhee, W. D.; Riley, D. P.; Christ, M. E.; Christ, K. M. *Organometallics* **1993**, *12*, 1429.

(33) Carbonate **21** decomposes to ether **12** in THF at 34 °C in the presence of $Pd_2(dba)_3/Ph_3P$. No transient intermediates could be detected by HPLC in this reaction. However, carbonate **10** was observed in situ to be present prior to and during the formation of ether **12** in the decomposition of carbonate **21** under the same conditions with 1 equiv of *tert*-butyl alcohol present. A trace of the *tert*-butyl ether was also observed by LC/MS in the crude reaction product, but it could not be isolated.

(34) Catalyzed sigmatropic rearrangement cannot be ruled out at this time.

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(36) Booker-Milburn, K. I. *Tetrahedron* **1997**, *53*, 12319.

(37) Node, M.; Nishide, K.; Shigeta, Y.; Shiraki, H.; Obata, K. *J. Am. Chem. Soc.* **2000**, *122*, 1927.

(38) Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143.

(39) BINAP with phenol: Iourtchenko, A.; Sinou, D. *J. Mol. Catal. A: Chem.* **1997**, *122*, 91.

the allyl carbonate moiety gives a general method for the allylation of aliphatic primary, secondary, and tertiary alcohols under conditions amenable to complex substrates.[13,14] The mechanism for the coupling is complex due, in part, to a number of equilibria that exist with regards to the allyl carbonate species as well as the nucleophile employed. Further studies of the catalyst system are being pursued to improve the understanding as well as the utility of the chemistry.

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Supporting Information Available: Experimental procedures and spectral data for starting materials **8**, **15**, **13**, and **23** and products **3a**, **3b**, **5**, **11**, **12**, **16**, and **24** and selected elemental analyses thereof. This material is available free of charge via the Internet at http://pubs.acs.org.

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