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Palladium-Catalyzed, One-Pot, Three-Component Synthesis of Homoallylic Amines from Aldehydes, Anisidine, and Allyl Trifluoroacetate

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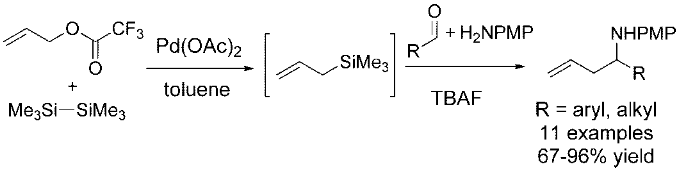
ABSTRACT



An allylation reaction that generates homoallylic amines using allyl trifluoroacetate as a nucleophilic allylmetal precursor is reported. A palladium complex catalyzes two transformations in one pot: formation of allylsilane from allyl trifluoroacetate using hexamethyldisilane and subsequent imine allylation. A three-component reaction was developed where preformed imines were replaced with aldehydes and anisidine. Under these reaction conditions a variety of substrates, including electron-rich aromatic and aliphatic aldehydes, react smoothly to afford homoallylic amines.

Allylation reactions of imines are important transformations that provide synthetic intermediates that are equipped with two orthogonal functional groups, an amine and an alkene. Such reactions are usually accomplished using a stoichiometric allylic metal species, often under the control of a transition metal catalyst.[1] Methods that replace the often toxic allylic metal species with allylic halides or allylic acetates minimize the number of functional group manipulations required prior to allylation. As part of our studies in the development of new catalytic allylation reactions,[2] we sought to develop an allylation reaction of imines in which a transition metal complex would catalyze the C−C bond-forming step to ensure control over chemoselectivity and eventually stereoselectivity, using allylic alcohol derivatives as starting materials.

In pioneering studies, Miyaura and co-workers have demonstrated palladium-catalyzed intramolecular coupling of allylic acetates and ketones using bis(pinacolato)diboron.[3] Intermolecular coupling of aldehydes and imines with allylic alcohols and acetates has been accomplished by Szabó and co-workers using diboronates.[4] In reactions of aldehydes a palladium complex catalyzes formation of the nucleophilic allylmetal species in situ; subsequent type I allylation of the

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(1) (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293. (b) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, Heathcock, C. H., Ed.; pp 1−53. (c) Fujita, M.; Nagano, T.; Schneider, U.; Hamada, T.; Ogawa, C.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 2914–2915. (d) Ferraris, D.; Dudding, T.; Young, B.; Drury, W. J., III; Letcka, T. *J. Org. Chem.* **1999**, *64*, 2168–2169. (e) Fang, X.; Johannsen, M.; Yoa, S.; Gathergood, N.; Hazell, R. G.; Jorgensen, K. A. *J. Org. Chem.* **1999**, *64*, 4844–4849. (f) Yamasaki, S.; Fujii, K.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 6536–6537.

(2) (a) Barczak, N. T.; Grote, R. E.; Jarvo, E. R. *Organometallics* **2007**, *26*, 4863–4865. (b) Shaghafi, M. B.; Kohn, B. L.; Jarvo, E. R. *Org. Lett.* **2008**, *10*, 4743–4746. (c) Waetzig, J. D.; Swift, E. C.; Jarvo, E. R. *Tetrahedron* **2008**, DOI: 10.1016/j.tet.2008.10.061.

(3) (a) Ahiko, T.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **1997**, 811–812. For palladium-catalyzed formation of allylic boronates, see: (b) Ishiyama, T.; Ahiko, T.; Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 6889–6892.

(4) (a) Selander, N.; Kipke, A.; Sebelius, S.; Szabó, K. J. *J. Am. Chem. Soc.* **2007**, *129*, 13723–13731. (b) Sebelius, S.; Szabó, K. J. *Eur. J. Org. Chem.* **2005**, 2539–2547.

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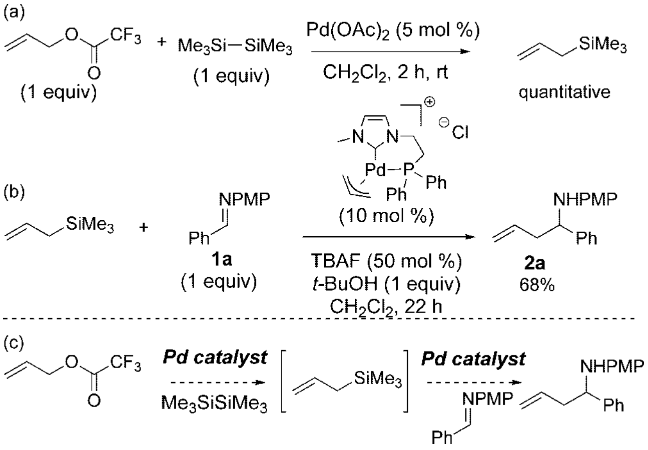
aldehyde occurs in the absence of a catalyst.[5] In reactions of imines, tandem catalysis occurs, with a palladium complex catalyzing both allylboronate formation and subsequent imine allylation. In addition, hexamethylditin has been used in allylations using allylic halides.[6]

We have recently identified several palladium complexes that catalyze the addition of allylic silanes to imines (Scheme 1b).[7,8] Palladium-catalyzed synthesis of allylic silanes from trifluoroacetates has been reported (Scheme 1a).[9] We reasoned that both transformations could be performed in the same reaction vessel using the same catalyst (Scheme 1c). To meet our objectives, the palladium complex would catalyze *both* allylsilane formation and allylation of the imine in a one-pot reaction.

Scheme 1. Development of a One-Pot Allylation Reaction Using Allyltrifluoroacetate



A set of reaction conditions that would be suitable for both transformations was determined by examining allylsilane formation and allylation of imine **1a** separately.[10,11] Under optimized reaction conditions, one-pot reaction of allyl trifluoroacetate with hexamethyldisilane and imine **1a** afforded 74% yield of homoallylic amine (eq 1). The palladium catalyst is required for both transformations: no homoallylic amine **2a** was formed in control experiments using preformed allylsilane, TBAF, and trimethylsilyl trifluoroacetate in the absence of palladium complexes.

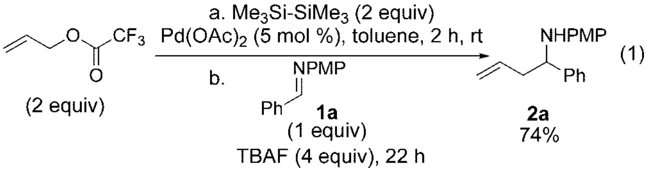
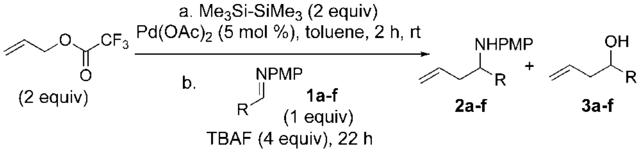
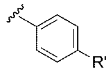
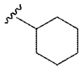


Table 1. Allylation of Imines with Allyl Trifluoroacetate and Hexamethyldisilane[a]



entry	R	substrate	homoallylic amine	yield of **2** (%)[b]	homoallylic alcohol	yield of **3** (%)[c]
1		**1a**, R' = H	**2a**	74	**3a**	23[b]
2		**1b**, R = NO_2	**2b**	94	**3b**	<5
3		**1c**, R' = Br	**2c**	86	**3c**	12
4		**1d**, R' = Cl	**2d**	83	**3d**	15
5		**1e**, R' = CO_2Me	**2e**	71	**3e**	15
6		**1f**	**2f**	0	**3f**	36[b]

[a] 2.0 equiv of hexamethyldisilane, 2.0 equiv of allyl trifluoroacetate, 5 mol % palladium acetate, toluene, room temperature, 2 h, then 1.0 equiv of imine, 4.0 equiv of TBAF (1.0 M in THF), room temperature, 22 h. See Supporting Information for full experimental details. [b] Isolated yield after silica gel column chromatography. [c] Yield determined by ^1H NMR spectroscopy of the unpurified reaction mixture.

A variety of aromatic aldimines react under the optimized reaction conditions (Table 1). Electron-poor aromatic imines afforded the highest yields of products (entries 2−5). Electron-rich aromatic aldimines and aliphatic aldimines reacted more sluggishly (e.g., entry 6). Homoallylic alcohol products predominated for these substrates; these are presumably generated by hydrolysis of the imine to the aldehyde with subsequent allylation.

To expand the scope of this reaction to include less reactive substrates, we considered the product distribution of the palladium-catalyzed allylation reaction. Formation of homoallylic alcohol under the reaction conditions in Table 1 indicated the presence of at least trace quantities of water,[12] as water is needed to establish an equilibrium between the aldimine and aldehyde (Scheme 2). Electron-deficient aldimines reacted quickly with the palladium catalyst (e.g., **1b**),

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(5) In related studies, enantioselective catalysis of reactions of allenes affords a chiral allylic boronate that undergoes a stereospecific type I allylation reaction with aldehydes and imines: (a) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 74–75. (b) Woodward, A. R.; Burks, H. E.; Chan, L. M.; Morken, J. P. *Org. Lett.* **2005**, *7*, 5505–5507.

(6) A palladium complex is used to catalyze the formation of allylic stannanes, which are reacted in one-pot with electrophiles and a second palladium catalyst to provide the allylated products. (a) Wallner, O. A.; Szabó, K. J. *Org. Lett.* **2004**, *6*, 1829–1831. (b) Gagliardo, M.; Selander, N.; Mehendale, N. C.; van Koten, G.; Klein Gebbink, R. J. M.; Szabó, K. J. *Chem.−Eur. J.* **2008**, *14*, 4800–4809.

(7) Manuscript in preparation.

(8) Palladium-catalyzed allylation of imines with allylic silanes: (a) Nakamura, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 2614–2615. (b) Fernandez, R. A.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 735–738.

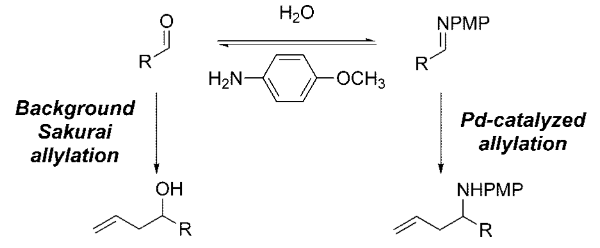
(9) (a) Matsumoto, H.; Yako, T.; Nagashima, S.; Motegi, T.; Nagai, Y. *J. Organomet. Chem.* **1978**, *148*, 97–106. (b) Urata, H.; Suzuki, H.; Moro-oka, Y.; Ikawa, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 607–608. (c) Tsuji, Y.; Funato, M.; Ozawa, M.; Ogiyama, H.; Kajita, S.; Kawamura, T. *J. Org. Chem.* **1996**, *61*, 5779–5787.

(10) See Supporting Information for details.

(11) NHC-ligated palladium complexes such as the one shown in Scheme 1b did not catalyze allylsilane formation under these reaction conditions. In related studies ligation of two monodentate ligands was shown to inhibit allylsilane formation. See: Macsára, I.; Hupe, E.; Szabó, K. *J. Org. Chem.* **1999**, *64*, 9547–9556.

(12) The source of the water was inferred to be the commercially available TBAF. The use of drying agents did not decrease the formation of homoallylic alcohol. See Supporting Information for details.

Scheme 2. Competitive Palladium-Catalyzed and Sakurai-Type Allylation May Consume Imine and Aldehyde



and this equilibrium did not pose a problem because the catalyst chemoselectively allylated the imine in the presence of the aldehyde.[13,14] Reactions of such substrates afforded high yield of homoallylic amine and little or no homoallylic alcohol. In reactions of sluggish substrates, however, the background Sakurai reaction predominated and consumed aldehyde, eventually funneling all of the starting material to homoallylic alcohol.

Scheme 3. Competition Experiments

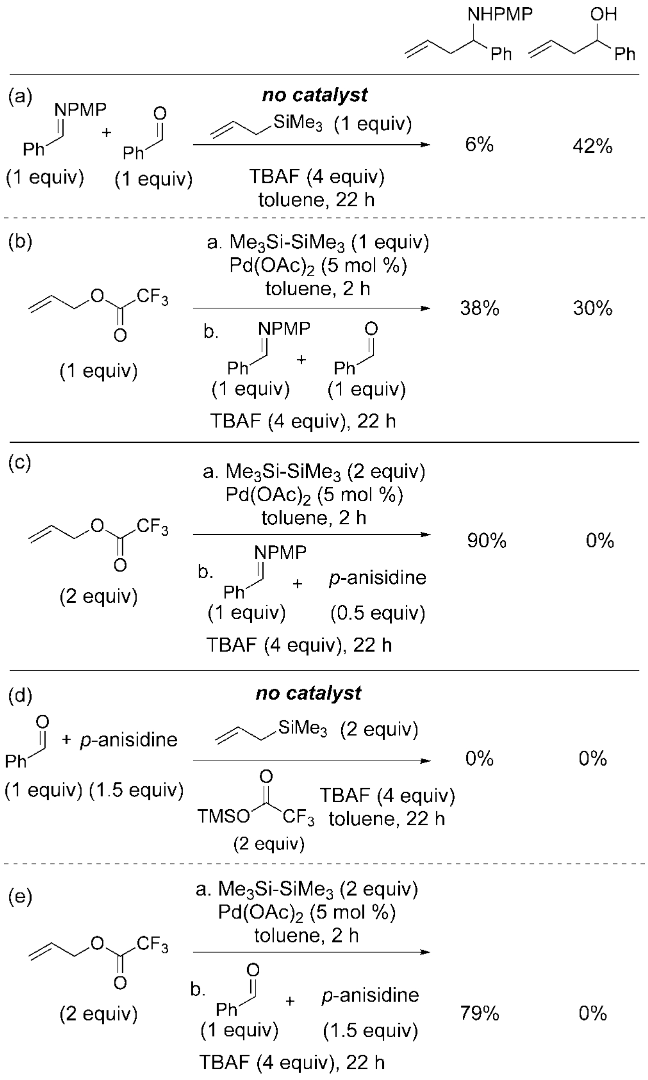
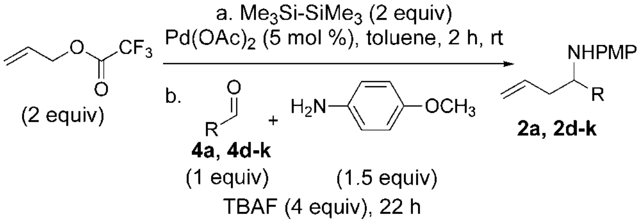
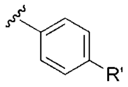
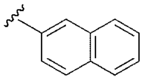
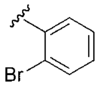
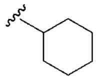
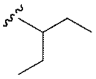
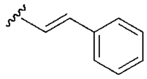
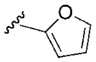


Table 2. One-Pot, Three-Component Reaction of Aldehydes, Anisidine, and Allyl Trifluoroacetate[a]



entry	R	substrate	product	yield (%)[b]
1		**4a**, R' = H	**2a**	79
2		**4b**, R' = NO_2	**2b**	90
3		**4c**, R' = Br	**2c**	76
		4d, R' = Cl	**2d**	78
		4e, R' = CO_2Me	**2e**	70
4		**4g**	**2g**	71
5		**4h**	**2h**	67
6		**4f**	**2f**	96[c]
7		**4i**	**2i**	77
8		**4j**	**2j**	92
9		**4k**	**2k**	95

[a] 2.0 equiv of hexamethyldisilane, 2.0 equiv of allyl trifluoroacetate, 5 mol % palladium acetate, toluene, room temperature, 2 h, then 1.0 equiv of aldehyde, 1.5 equiv of *p*-anisidine, 4.0 equiv of TBAF (1.0 M in THF), room temperature, 22 h. See Supporting Information for details. [b] Isolated yield after silica gel column chromatography. In all cases, <3% homoallylic alcohol was observed in the unpurified reaction mixture. [c] 2.0 equiv of *p*-anisidine used.

Competition experiments in the presence and absence of palladium catalysts were consistent with a background Sakurai reaction generating homoallylic alcohol in this system. Reactions were first performed with aldehyde and preformed imines (Scheme 3a and b). In the absence of catalyst, homoallylic alcohol was formed preferentially. The allylation of aldehyde is attributed to a competitive fluoride-mediated Sakurai reaction.[15] In the presence of catalyst a mixture of homoallylic alcohol and amine were formed, consistent with simultaneous background allylation that

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(13) This hypothesis was based primarily on our preliminary studies of palladium-catalyzed imine allylation using allylstannanes. Grote, R. E.; Jarvo, E. R. Unpublished results. See also ref 4a.

(14) This chemoselectivity may be due to increased ability of imine to coordinate to the palladium catalyst. For a discussion, see: Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1993**, *115*, 3133–3139.

provided homoallylic alcohol and a palladium-catalyzed allylation that provided homoallylic amine.

We hypothesized that Le Châtelier's principle could be used to maintain the imine concentration in solution and favor imine allylation for sluggish substrates. This strategy was successful in practice: addition of excess anisidine to an allylation reaction improved the yield of homoallylic amine and diminished formation of homoallylic alcohol (Scheme 3c). For example, the allylation reaction of imine **1a** afforded only the homoallylic amine upon addition of 0.5 equiv of *p*-anisidine to the reaction.

This understanding of the reaction was used to develop a three-component coupling reaction. We examined the background and palladium-catalyzed allylation reaction using aldehyde and anisidine (Scheme 3d and e). While studying the equilibrium between aldehyde and imine, we found that trimethylsilyl trifluoroacetate, a byproduct of allylsilane formation, accelerated imine formation. Trimethylsilyl trifluoroacetate was therefore included in the catalyst-free competition experiment. In the absence of palladium catalyst neither homoallylic amine nor homoallylic alcohol was formed. We attribute the supression of aldehyde allylation by the background Sakurai reaction to lack of aldehyde in solution.[16] In the palladium-catalyzed competition experiment, however, imine was allylated and no homoallylic alcohol was observed. These results underscore our finding that tandem palladium catalysis is required for imine allylation under these conditions.

We sought to determine the scope of this three-component coupling reaction. Across a range of substrates preformed imine was found not to be necessary for high yields of homoallylic amine products; instead, aldehyde (1 equiv) and anisidine (1.5 equiv) are added (Table 2). Substrates that performed well using preformed imine reacted smoothly under these conditions as well (e.g, **4a**, **4d**, and **4e**). A dramatic improvement was observed with challenging aliphatic substrates under the amended conditions. For example, the yield of homoallylic amine **2f** derived from cyclohexanecarboxyaldehyde was improved to 96% under the three-component coupling conditions using 2 equiv of anisidine. Aromatic, heteroaromatic, aliphatic, and α,β-unsaturated substrates provided homoallylic amines in good to excellent yields.

We present a palladium-catalyzed three-component coupling of aldehydes, anisidine, and allyl trifluoroacetate using hexamethyldisilane as a terminal reducing agent. A palladium complex catalyzes both allylsilane formation and imine allylation in this tandem, one-pot, two-step transformation. Future studies will include the development of enantioselective methods for imine allylation.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] (a) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, 1295–1298. (b) Hosomi, A.; Shirahata, A.; Sakurai, H. *Tetrahedron Lett.* **1978**, 3043–3046. (c) Wang, D.; Zhou, Y.; Tang, Y.; Hou, X.; Dai, L. *J. Org. Chem.* **1999**, *64*, 4233–4237.

[16] By ^{1}H NMR <5% of benzaldehyde was in solution after 22 h.