ORGANIC LETTERS

2009
Vol. 11, No. 11
2377−2379

Amination of Allylic Alcohols in Water at Room Temperature

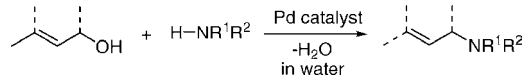
Takashi Nishikata and Bruce H. Lipshutz*

Department of Chemistry & Biochemistry, University of California, Santa Barbara, California 93106

lipshutz@chem.ucsb.edu

Received February 3, 2009

ABSTRACT

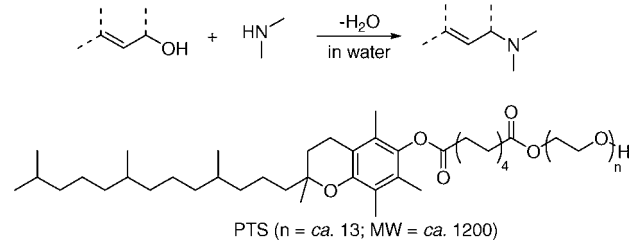


The "trick" to carrying out regiocontrolled aminations of allylic alcohols in water as the only medium is use of a nanomicelle's interior as the organic reaction solvent. When HCO_2Me is present, along with the proper base and source of catalytic Pd, allylic amines are cleanly formed at room temperature.

Among the many challenges facing organic synthesis today is the development of new technologies that allow less reactive functional groups to participate readily in bond-forming reactions. Representative cases include C−H activation,[1] reactions of unactivated C−F bonds,[2] and coupling between sp^3 carbons and other carbon or similarly hybridized atoms.[3] The opportunity to use allylic alcohols as substrates in Pd-catalyzed cross-couplings, without recourse to prior derivatization, is yet another advance included in this group.[4] Such reactions involving nitrogen nucleophiles translate into allylic aminations, leading to well-established, highly valuable intermediates.[5] However, direct aminations in the absence of hydroxyl activating groups, such as Lewis acids, are relatively rare.[4]

In fact, methods that are regioselective, can be run under environmenatlly attractive conditions in water as the only solvent at room temperature, and are applicable to water-insoluble educts are unknown.[6] In this paper, we describe the first technology for effecting allylic aminations of primary, secondary, and tertiary allylic alcohols that offers these desirable features (Scheme 1).

Scheme 1



There are currently two approaches to allylic substitution of the OH moiety in allylic alcohols by a nitrogen nucleo-

(1) Recent reviews: (a) Herrerías, C. I.; Yao, X.; Li, Z.; Li, C.-J. *Chem. Rev.* **2007**, *107*, 2546. (b) Bergman, R. G. *Nature* **2007**, *446*, 391. (c) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (d) Ishiyama, T.; Miyaura, N. *Pure Appl. Chem.* **2006**, *78*, 1369. See recent allylic C−H aminations: (e) Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 3316. (f) Liu, G.; Yin, G.; Wu, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4733.

(2) C−Cl bonds: (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. C−F bonds: (b) Terao, J.; Todo, H.; Watabe, H.; Ikumi, A.; Shinohara, Y.; Kambe, N. *Pure Appl. Chem.* **2008**, *80*, 941.

(3) Netherton, M. R.; Fu, G. C. In *Topics in Organometallic Chemistry: Palladium in Organic Synthesis*; Tsuji, J. Ed.; Springer-Verlag: Germany, 2005; pp 85−108.

(4) (a) Muzart, J. *Eur. J. Org. Chem.* **2007**, 3077, and references cited therein. (b) Tamaru, Y. *Eur. J. Org. Chem.* **2005**, 2647.

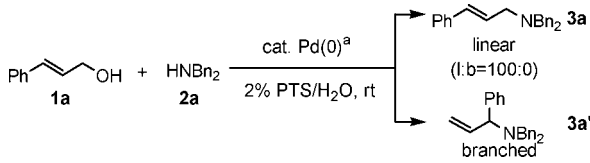
(5) (a) Liu, H.; Liang, X.; Søhel, H.; Bülow, A.; Bols, M. *J. Am. Chem. Soc.* **2001**, *123*, 5116. (b) Bower, J. F.; Jumnah, R.; Williams, A. C.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1411. (c) Burgess, K.; Liu, L. T.; Pal, B. *J. Org. Chem.* **1993**, *58*, 4758. (d) Cheikh, R. B.; Chaabouni, R.; Laurent, A.; Mison, P.; Nafti, A. *Synthesis* **1983**, 685.

(6) Reactions in aqueous solution at reflux: (a) Komiya, S.; Hirano, M.; Komine, N.; Hirahara, S. Jpn. Kokai Tokkyo Koho, JP 2005075728; *Chem. Abstr.* **2005**, 253606. (b) Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2004**, *6*, 4085. Reactions in only water at reflux: (c) Yang, S.-C.; Hsu, Y.-C.; Gan, K.-H. *Tetrahedron* **2006**, *62*, 3949. (d) Yokoyama, Y.; Hikawa, H.; Mitsuhashi, M.; Uyama, A.; Hiroki, Y.; Murakami, Y. *Eur. J. Org. Chem.* **2004**, 1244. Yokoyama, Y.; Takagi, N.; Hikawa, H.; Kaneko, S.; Tsubaki, N.; Okuno, H. *Adv. Synth. Catal.* **2007**, *349*, 662.

10.1021/ol900235s CCC: $40.75
Published on Web 04/29/2009

phile: (1) activation by protic or Lewis acid,[4] such as CO_2, Et_3B, $SnCl_2$, Ti(O-*i*-Pr)$_4$, a carboxylic acid, Nb(OEt)$_5$,[7] or BPh_3[7] and (2) catalysis under strictly *anhydrous* conditions.[7−11] These are conducted in dry organic solvents, typically with heating. To avoid interference by in situ formed water (Scheme 1), molecular sieves or other drying agents (e.g., $MgSO_4$) are oftentimes present in the reaction mixture.[4] Limitations associated with OH substitution include regioselectivity issues (with *sec*- or *tert*-allylic alcohols), limited reactivity (of sterically hindered amines), and overall harsh conditions when conducted in pure water.[4,6c,d] Only allyl alcohol itself is prone to reaction under mild conditions or with bulky amines.[4,6b]

Table 1. Development of Conditions for Aminations[a]



entry	base (equiv)	additive (equiv)	yield[b] (%)
1	none	none	0
2	none	HCO_2Me (4.0)	15
3	^{t}BuONa (1.5)	K_2CO_3 (3.0)	0
4	^{t}BuONa (1.5)	none	0
5	^{t}BuONa (1.5)	ester (4.0)[c]	0−40
6	^{t}BuONa (1.5)	HCO_2Me (4.0)	58
7	**K_2CO_3 (3.0)**	**HCO_2Me (4.0)**	**84**

[a] [Pd(allyl)Cl]$_2$ (2.5 mol %) and dppf (5 mol %) were used. [b] Isolated yields. [c] AcOEt, AcOMe, AcOvinyl, dimethyl maleate, AcOBn, BzOMe, *i*-PrCO_2Me, HCO_2Et, and HCO_2-*i*-Bu were examined.

The first successful palladium-catalyzed allylic aminations of allylic alcohols could be achieved in pure water when run in the presence of commercially available[12] nanomicelle-forming amphiphile PTS (polyoxyethanyl α-tocopheryl sebacate).[13] Optimization studies used dibenzylamine (0.5 mmol) along with cinnamyl alcohol (**1a**; 1.5 mmol; Table 1), leading to a very efficient coupling procedure. Only 2 wt % of PTS−H_2O (0.5 M) was needed at room temperature. Both catalytic [Pd(allyl)Cl]$_2$ (0.0125 mmol, 2.5 mol %) and dppf (0.025 mmol, 5 mol %) are required.

In the absence of an ester additive or base, reactions are sluggish (entries 1−4). Screening several simple esters as additives led to low-to-modest levels of allylation product **3a**, with high linear selectively (entry 5). Four equivalents of HCO_2Me was eventually found to be ideal (entry 6), needed in part due to its volatility (bp 31−33 °C). K_2CO_3, rather than *tert*-butoxide, as base gave the best overall couplings when used in excess to ensure complete conversion (entry 7).

A survey examining the scope and limitations of PTS-enabled allylic aminations in water using base (K_2CO_3), ligand (dppf), additive (HCO_2Me), and [Pd(allyl)Cl]$_2$ is illustrated in Table 2. Cinnamyl alcohol (**1a**), allyl alcohol (**1b**), and methallyl alcohol (**1c**) smoothly reacted with with **2a** or *N*-methylaniline, **2b**, to produce the corresponding allylic amines in excellent yields. The corresponding reactions "on water"[14] were highly substrate-dependent and gave variable results, as seen previously[13] (entries 1−3).

Water-insoluble allylic alcohol **1d** (entry 4) gave predominantly linear *E*-allylic amine **3e** with excellent regioselectivity using biphep as ligand. Although allylic aminations of either crotyl alcohol (**1e**) or isomeric secondary alcohol 3-buten-2-ol (**1f**) are known to suffer routinely from poor regioselectivity,[4,6b,c] both **1d** and **1e** gave good selectivities in the presence of biphep (2,2′-bis(diphenylphosphino)-1,1′-biphenyl) (entries 5 and 6). By contrast, related Ir-catalyzed reactions are selective toward branched materials.[7,11] Tertiary alcohol **1g** reacted in the presence of dppf with amine **2b**, strongly favoring the linear allylic amine **3g** (l/b = 63:1; 90%; entry 7). In general, reactions with *primary* amines[4] such as *o*-toluidine (**2c**) tend to give give rise to some double-allylated product; nonetheless, monoallylated **3h** was obtained selectively under our conditions (entry 8). A more functionalized amine, such as amino acid derivative **2d**, also resulted in an 80% yield of linear amine **3i** (entry 9).

This technology could readily be applied to a one-pot synthesis of the antifungal agent naftifine (**3j**) under exceedingly mild conditions (Scheme 2).[10,15] Previous routes to naftifine involved several steps and/or higher reaction temperatures to reach this target. Starting with *secondary* alcohol **1h**, drug **3j** was isolated in good yield (83%). Interestingly, the alternative *primary* coupling partner, cinnamyl alcohol **1a**, afforded naftifine only to the extent of 70% under otherwise identical conditions.

Mechanistically, an allylic formate might be generated as a key intermediate by transesterification of **1** and HCO_2Me. However, only trace amounts of cinnamyl formate are formed, with or without amine present, over the entire time frame of the reaction. Moreover, existing literature suggests that transesterification will not occur under the conditions being employed.[6b] Since these couplings take place with basic amines, it is unlikely that an allylic alcohol would

(7) Yamashita, Y.; Gopalarathnam, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7508.

(8) (a) Usui, I.; Schmidt, S.; Keller, M.; Breit, B. *Org. Lett.* **2008**, *10*, 1207. (b) Dubs, C.; Yamamoto, T.; Inagaki, A.; Akita, M. *Organometallics* **2006**, *25*, 1359. (c) Piechaczyk, O.; Doux, M.; Ricard, L.; Le Floch, P. *Organometallics* **2005**, *24*, 1204. (d) Liang, H.; Ito, S.; Yoshifuji, M. *Org. Lett.* **2004**, *6*, 425. (e) Ozawa, F.; Okamoto, H.; Kawagishi, S.; Yamamoto, S.; Minami, T.; Yoshifuji, M. *J. Am. Chem. Soc.* **2002**, *124*, 10968. See also ref 6b.

(9) Friedel−Crafts-type reaction: Jana, U.; Maiti, S.; Biswas, S. *Tetrahedron Lett.* **2008**, *49*, 858. See also: Shirakawa, S.; Shimizu, S. *Synlett* **2008**, 1539.

(10) Utsunomiya, M.; Miyamoto, Y.; Ipposhi, J.; Ohshima, T.; Mashima, K. *Org. Lett.* **2007**, *9*, 3371.

(11) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3139.

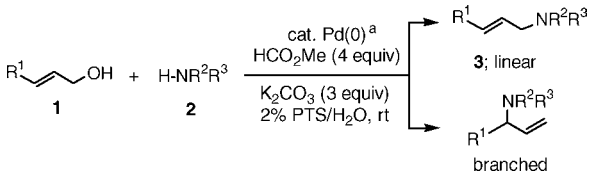
(12) PTS is available from Sigma-Aldrich, catalog no. 698717.

(13) (a) Lipshutz, B. H.; Taft, B. R. *Org. Lett.* **2008**, *10*, 1329. (b) Lipshutz, B. H.; Chung, D. W.; Rich, B. *Org. Lett.* **2008**, *10*, 3793. (c) Lipshutz, B. H.; Ghorai, S. *Aldrichim. Acta* **2008**, *41*, 58.

(14) Stuetz, A.; Georgopoulos, A.; Granitzer, W.; Petranyi, G.; Berney, D. *J. Med. Chem.* **1986**, *29*, 112.

(15) Also supported by observations en route to nafitifine (Scheme 2).

Table 2. Representative Aminations in PTS/H_2O at rt

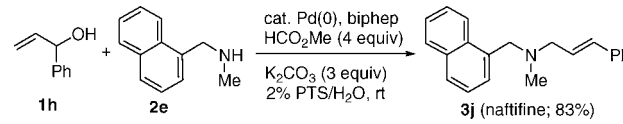


entry	1 (equiv)	2	product		yield (%)[b]	l:b (*E*:*Z*)[c]
1	**1a** (1.5)	**2b**[d]	Ph, N(Me)Ph	**3b**	94 (38)[e]	100:0 (100:0)
2	OH **1b** (5.0)	**2a**[d]	NBn_2	**3c**	93 (79)[e]	-
3	OH **1c** (1.5)	**2b**[d]	N(Me)Ph	**3d**	95 (31)[e]	-
4[f]	OH **1d** (1.5)	**2a**[d]	NBn_2	**3e**	84	>25:1 (16:1)
5[f]	OH **1e** (3.0) (*E*:*Z* = 8:1)	**2a**[d]	NBn_2	**3f**	81	46:1[g] (9.6:1)[g]
6[f]	OH **1f** (3.0)	**2a**[d]	NBn_2	**3f**	76	24:1[g] (11:1)[g]
7	OH **1g** (1.5)	**2b**[d]	N(Me)Ph	**3g**	90	63:1[g]
8	**1a** (1.5)	**2c**[d]	Ph, NH(*o*-tolyl)	**3h**	80	100:0 (100:0)
9[f]	OH Ph **1h** (1.0)	**2d**[h]	MeO_2C, Bn, Ph, N, Bn	**3i**	80	100:0 (100:0)

[a] $[Pd(allyl)Cl]_2$ (2.5 mol %), and dppf (5 mol %) were used. [b] Isolated yields. [c] The ratios of l/b were determined by ^1H NMR, and *E*:*Z* are shown in parentheses. [d] 1 equiv of amine was used. [e] Reaction was conducted "on water". [f] The biphep ligand was used instead of dppf. [g] Determined by GC. [h] 1.2 equiv of amine was used.

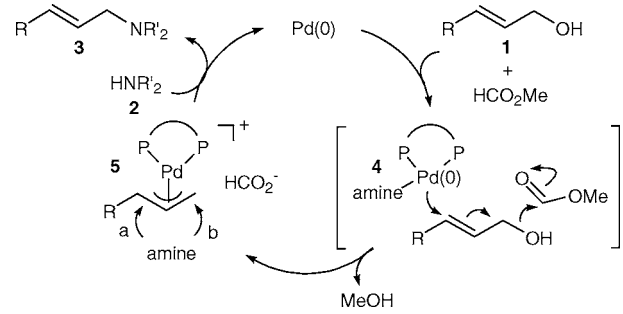
compete for formate; no formamide is observed. On the other hand, when phenyl formate (HCO_2Ph) was used in place of HCO_2Me, formamides were observed as competitive byproduct. Thus, transesterification is *not* likely to be involved. The difference in reactivity between **1a** and **1h** (i.e., with **1h** > **1a**) toward **2d** may be attributed to the oxidative addition step, where a bulky Pd(0) species having both phosphine ligand and amine (**4**, Scheme 3) reacts preferentially with a terminal alkene.[16] The reaction is initiated by the action of

Scheme 2. Synthesis of the Antifungal Agent Naftifine



Pd(0) on the allylic alcohol **1**. The leaving group ability of a hydroxyl moiety (shown, for simplicity, for a primary case) is enhanced by participation of methyl formate. A π-allylpalladium intermediate **5** is then formed, from which product allylic amine **3** is produced. Regiochemistry follows from site-selective nucleophilic attack by amine **2** on **5**, which shows a preference for the less hindered allylic carbon leading to linear products (path b).[10,17]

Scheme 3. Proposed Mechanism of Allylic Amination



Acknowledgment. We thank Zymes for support.

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

OL900235S

(16) DFT calculations for direct allylic substitution reactions with allylic alcohols: Piechaczyk, O.; Thoumazet, C.; Jean, Y.; Le Floch, P. *J. Am. Chem. Soc.* **2006**, *128*, 14306. See also ref 6b.

(17) **Typical Procedure.** Allylic alcohol **1** (0.75 mmol), amine **2** (0.5 mmol), dppf (0.025 mmol, 5 mol %), K_2CO_3 (1.5 mmol), and $[Pd(allyl)Cl]_2$ (0.0125 mmol, 2.5 mol %) were sequentially added under argon to a reaction tube equipped with a stir bar and a septum. PTS solution (1.0 mL, 2 wt %) and HCO_2Me (0.12 mL, 2.0 mmol) were added by syringe and vigorously stirred for 20 h at rt. Upon completion of the reaction, the contents of the flask were diluted with brine, and the mixture was extracted with EtOAc. The solution obtained was dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation. The residue was purified by flash chromatography eluting with hexane/EtOAc to afford the product.