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Intermolecular Hydroamination between Nonactivated Alkenes and Aniline Catalyzed by Lanthanide Salts in Ionic Solvents

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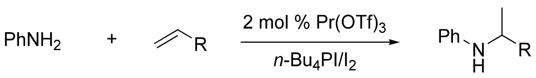
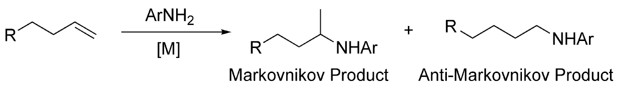
ABSTRACT



An efficient methodology for intermolecular hydroamination of unactivated alkenes and anilines catalyzed by lanthanide salts was developed. The Markovnikov products were obtained in moderate to good yields.

The catalytic hydroamination of alkenes has attracted tremendous attention because it provides efficient and direct entry to synthetically useful amines.[1] Accordingly, much effort has been focused on the development of new catalytic methods for the hydroamination of alkenes. Much progress in this area has been accomplished, especially in the intramolecular and intermolecular hydroamination of activated alkenes or/and activated amines.[2] However, the catalytic intermolecular hydroamination of nonactivated alkenes with unactivated amines is still a challenging task.[3] A few exceptions include the intermolecular hydroamination of 1-pentene with propylamine reported by Marks and co-workers[4] and hydroamination of unactivated olefins with aniline reported by Bergman[5a] and Doye.[5b] Brunet has reported a successful intermolecular hydroamination of unactivated alkenes with aniline catalyzed by $PtBr_2$ in n-Bu_4PBr in the presence of strong acid.[3e,f] Despite significant progress in the development of intermolecular hydroamination reactions, addition of more basic amines such as aniline to nonactivated alkenes using cheaper metal complexes under milder reaction conditions continues to pose significant challenges to synthetic chemists.[6] In this paper, we report an efficient method for the catalytic intermolecular hydroamination of nonactivated alkenes and aniline using $Pr(OTf)_3$ as catalyst (eq 1).



(1)

Initially, we screened the hydroamination of 4-phenyl-1-butene and aniline using a catalytic amount of $Pr(OTf)_3$ (2

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(1) For selected reviews, see: (a) Doye, S. *Sci. Synth.* **2009**, *40a*, 241–304. (b) Muller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795–3892. (c) Brunet, J.-J.; Chu, N.-C.; Rodriguez-Zubiri, M. *Eur. J. Inorg. Chem.* **2007**, 4711–4722. (d) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367–391. (e) Alonso, F.; Beletskaya Irina, P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079–3160. (f) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104–114. (g) Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 795–813. (h) Muller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675–703.

(2) For selected examples, see: (a) Hesp, K. D.; Stradiotto, M. *Org. Lett.* **2009**, *11*, 1449–1452. (b) Tsuhako, A.; Oikawa, D.; Sakai, K.; Okamoto, S. *Tetrahedron Lett.* **2008**, *49*, 6529–6532. (c) Liu, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 1570–1571. (d) Cho, J.; Hollis, T. K.; Helgert Theodore, R.; Valente Edward, J. *Chem. Commun.* **2008**, 5001–5003. (e) Carney, J. M.; Donoghue, P. J.; Wuest, W. M.; Wiest, O.; Helquist, P. *Org. Lett.* **2008**, *10*, 3903–3906. (f) Komeyama, K.; Morimoto, T.; Takaki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2938–2941. (g) Michuax, J.; Terrasson, V.; Marque, S.; Wehbe, J.; Prim, D.; Campagne, J.-M. *Eur. J. Org. Chem.* **2007**, 2601–2603. (h) Huang, J.-M.; Wong, C.-M.; Xu, F.-X.; Loh, T.-P. *Tetrahedron Lett.* **2007**, *48*, 3375–3377. (i) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Chem.-Asian J.* **2007**, *2*, 150–154. (j) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 1611–1614. (k) Taylor, J. G.; Whittall, N.; Hii, K. K. *Org. Lett.* **2006**, *8*, 3561–3564. (l) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798–1799. (m) Liu, X.-Y.; Li, C.-H.; Che, C.-M. *Org. Lett.* **2006**, *8*, 2707–2710. (n) Bender, C. F.; Widenhoefer, R. A. *Org. Lett.* **2006**, *8*, 5303–5305. (o) Brouwer, C.; He, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1744–1747. (p) Karshtedt, D.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2005**, *127*, 12640–12646.

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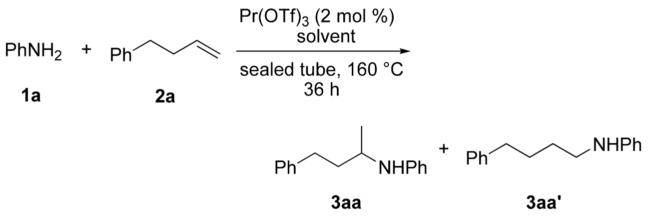
mol %) at 160 °C in a sealed tube under various conditions for 36 h. The results are summarized in Table 1. The reaction in n-Bu_4PBr without iodine afforded the product in low yield (22%, Table 1, entry 5). The addition of a catalytic amount of iodine increased the yield of the product (Table 1, entries 6 and 8). The best yield (75%) was obtained when the reaction was carried out in n-Bu_4PI in the presence of a catalytic amount of I_2 at 160 °C (Table 1, entry 8). No product was observed when the reaction was performed in toluene, DMF, [Omim]Cl, or [Omim]BF_4 (Table 1, entries 1−4). It is important to note that, contrary to the reaction conditions reported by Brunet,[3e,f] our method does not require the use of strong acids.

Table 1. Hydroamination between 4-Phenyl-1-butene and Aniline under Different Conditions[a]

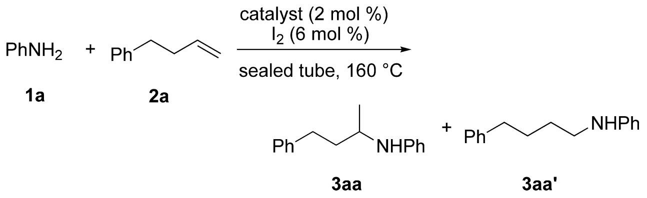


entry	solvent	iodine	yield (%)[b]	ratio (**3aa**:**3aa'**)[c]
1	DMF	6 mol %	0	
2	toluene	6 mol %	0	
3[d]	[Omim]Cl		0	
4[d]	[Omim]BF_4		0	
5[d]	n-Bu_4PBr		22	97:3
6	n-Bu_4PBr	6 mol %	69	91:9
7[d]	n-Bu_4PI		71	93:7
8	n-Bu_4PI	6 mol %	75	95:5
9	n-Bu_4PI	6 mol %	64	91:9[e]

[a] All reactions were performed with aniline (1 equiv), $Pr(OTf)_3$ (2 mol %), solvent (0.3 equiv), I_2 (indicated above), and 4-phenyl-1-butene (2 equiv) in sealed tube at 160 °C (oil temperature) for 36 h. [b] Combined yield. [c] Ratio of the two isomers as determined by ^{1}H NMR analysis. [d] No iodine was added. [e] No $Pr(OTf)_3$ was added.

Next, we investigated the catalytic activity of various rare earth metals using our optimized conditions. The results are summarized in Table 2. In all cases, the desired product was obtained in moderate to excellent yields. Dysprosium triflate exhibited better catalytic activity than dysprosium trichloride (Table 2, entries 5 and 6). Luterium triflate was the best catalyst, affording the desired product in 80% yield with the Markovnikov product as the major product (95:5, Table 2, entry 8). It is important to note that reaction carried out in the presence of TfOH resulted in only 10% yield of the product (Table 2, entry 9).

Table 2. Effects of Different Catalysts

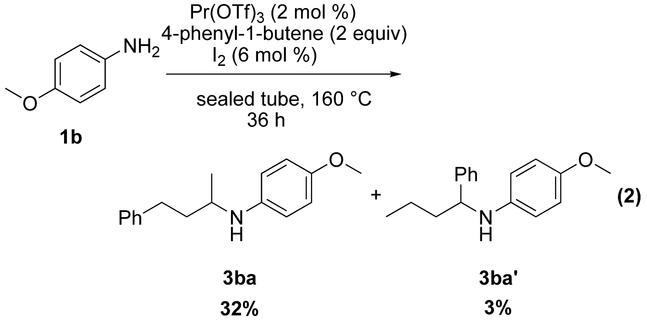


entry	catalyst	yield (%)[a]	ratio (**3aa**:**3aa'**)[b]
1	$La(OTf)_3{\cdot}H_2O$	60	98:2
2	$Ce(OTf)_3{\cdot}H_2O$	48	94:6
3	$Pr(OTf)_3$	75	95:5
4	$Gd(OTf)_3$	76	94:6
5	$Dy(OTf)_3$	77	96:4
6	$DyCl_3$	70	94:6
7	$Er(OTf)_3$	78	96:4
8	$Lu(OTf)_3$	80	95:5
9	TfOH	10	

[a] Combined yield. [b] Ratio of the two isomers as determined by ^{1}H NMR analysis.

Furthermore, since there are no notable differences for the catalytic abilities of these lanthanide triflates, reactions with various alkenes were investigated using cheap $Pr(OTf)_3$ as catalyst. The results are summarized in Table 3. Cyclopentene, cyclohexene, and cycloheptene gave the desired products in good yields (Table 3, entries 2−4). In the case of terminal olefins, Markovnikov addition products were obtained as the major products (Table 3, entries 6−8). For allylbenzene, the Markovnikov product was obtained as a single isomer (Table 3, entry 8).

Noticeably, the reaction of 4-phenyl-1-butene with p-anisidine afforded the desired Markovnikov product (**3ba**) in moderate yield (32%) and 3% yield of the compound **3ba′** using praseodymium triflate as catalyst (eq 2). Other nitrogen-containing compounds, such as o-anisidine, morpholine, benzylamine, and diethylamine, did not afford any of the desired products.



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(3) (a) Beller, M.; Breindl, C.; Eichberger, M.; Hartung, C. G.; Seayad, J.; Thiel, O. R.; Tillack, A.; Trauthwein, H. *Synlett* **2002**, 1579–1594. (b) Zhao, J.; Marks, T. J. *Organometallics* **2006**, *25*, 4763–4772. (c) Khedkar, V.; Tillack, A.; Benisch, C.; Melder, J.-P.; Beller, M. *J. Mol. Catal. A: Chem.* **2005**, *241*, 175–183. (d) Rodriguez-Zubiri, M.; Anguille, S.; Brunet, J.-J. *J. Mol. Catal. A: Chem.* **2007**, *271*, 145–150. (e) Brunet, J.-J.; Cadena, M.; Chu, N. C.; Diallo, O.; Jacob, K.; Mothes, E. *Organometallics* **2004**, *23*, 1264–1268. (f) Brunet, J.-J.; Chu, N. C.; Diallo, O. *Organometallics* **2005**, *24*, 3104–3110.

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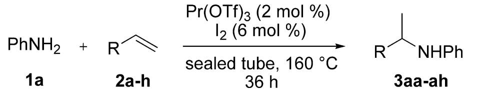
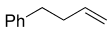
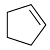
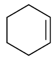
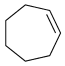
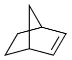
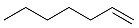
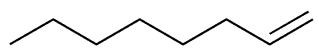
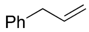
(6) McBee, J. L.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2008**, *130*, 16562–16571.

Table 3. Intermolecular Hydroamination of Aniline with Various Alkenes[a]

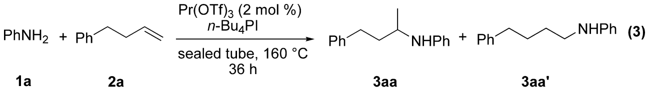


1a **2a-h** **3aa-ah**

entry	alkene	product	yield(%)[b]
1[c]		**3aa**	75
2		**3ab**	71[d]
3		**3ac**	75
4		**3ad**	70
5		**3ae**	61
6[c]		**3af**	79
7[c]		**3ag**	79
8[e]		**3ah**	56

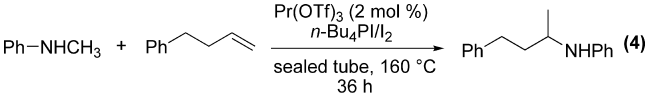
[a] All reactions were performed with aniline (1 equiv), Pr(OTf)$_3$ (2 mol %), I$_2$ (6 mol %), *n*-Bu$_4$PI (0.3 equiv), and alkenes (2 equiv) in sealed tube at 160 °C (oil temperature) for 36 h. [b] Isolated yield. [c] Up to 5% yield of other isomers were also observed. [d] Reation time was 48 h. [e] A single isomer was obtained.

To know more about the mechanism of the reaction, the following reaction (eq 3) was carried out in the presence of trapping reagents. The addition of three catalytic equivalents of NEt$_3$ or three catalytic equivalents of 2,6-di-*tert*-butylpyridine could not completely inhibit hydroamination, giving both the two products in the yield of 40% and 60%, respectively. Surprisingly, the reaction of 4-phenyl-1-butene with *N*-methylaniline gave the same product as with aniline with the yield of 27% (eq 4). Therefore, the reaction does not proceed simply via an acid-catalyzed mechanism.[5]



1a **2a** **3aa** **3aa'**

base	overall yield (%)	ratio (**3aa** : **3aa'**)
–	71	93 : 7
2,6-di-*tert*-butylpyridine	40	96 : 4
triethylamine	60	95 : 5



1c **2a** **3aa**
27%

In summary, the catalytic system of Pr(OTf)$_3$/*n*-Bu$_4$PI/I$_2$ has been shown to have excellent catalytic activity for the hydroamination of nonactivated alkenes with aniline. This protocol offers several advantages including using simple and cheap catalyst, being atom-economical, and giving products in high yields. Therefore, this new technology offers an attractive strategy for the synthesis of synthetically and pharmaceutically useful amines. The detailed study of the mechanism and further work to explore new catalysts that tolerate a variety of functional groups under very mild reaction conditions are in progress. Further extensions of this methodology are also in progress.

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Supporting Information Available: Additional experiment procedures and spectrum data for reactions products. This material is available free of charge via the Internet at http://pubs.acs.org.

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