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Formal anti-Markovnikov hydroamination of terminal olefins†

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Sarah M. Bronner and Robert H. Grubbs*

A new strategy to access linear amines from terminal olefin precursors is reported. This two-step, one-pot hydroamination methodology employs sequential oxidation and reduction catalytic cycles. The formal hydroamination transformation proceeds with excellent regioselectivity, and only the anti-Markovnikov product is observed. Up to 70% yield can be obtained from styrenes or aliphatic olefins and either primary or secondary aromatic amines. Additionally, the scope is broad with respect to the olefin and accommodates a variety of functionalities; we demonstrate that amines with removable aryl protecting groups may be utilized to allow access to a more diverse array of hydroamination adducts.

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Introduction

Due to the prevalence of amines in therapeutics, as well as in the production of dyes, solvents, agrochemicals, and commodity and fine chemicals, the formation of carbon–nitrogen bonds is of tremendous importance.[1] Hydroamination complements existing methods for the fabrication of carbon–nitrogen bonds and may also provide advantages – for example, catalytic hydroamination methodologies hold promise for being atom efficient and environmentally friendly,[2] not requiring harsh conditions, and utilizing readily available and inexpensive amine and olefin (**1** and **2** respectively, Fig. 1) starting materials. The construction of linear amines from terminal olefins represents a particularly significant and formidable transformation; selectivity is a consideration, as the amine may add at either of the two carbons of the alkene substrate (Fig. 1). Additions to give linear amines are generally more challenging, as Markovnikov addition is typically preferred. It should be noted that almost 20 years ago, the addition of amines to olefins in an anti-Markovnikov fashion was identified as one of the top ten challenges to be addressed by catalysis.[3]

Although substantial progress has been made, a general catalytic method of anti-Markovnikov hydroamination of olefins remains to be developed.[4,5] Previous approaches towards anti-Markovnikov hydroamination have traditionally involved activated olefins or intramolecular transformations.[6–11] However, in 1999 the Beller group disclosed the first example of transition metal-catalyzed anti-Markovnikov hydroamination of olefins; this seminal study accomplished a low-yielding hydroamination of styrenes with secondary aliphatic amines using rhodium catalysis.[12] More recently, some success in the metal-catalyzed intermolecular anti-Markovnikov hydroamination of unactivated olefins has been reported. For example, the Hultzsch and Beller groups have both performed the base-catalyzed anti-Markovnikov hydroamination of styrenes using $LiN(SiMe_3)_2$ and TMEDA[13] or *n*-BuLi[14] catalytic systems. Similarly, the Hartwig group has reported the rhodium-catalyzed anti-Markovnikov hydroamination of styrenes with secondary amines,[15] while the Marks group has demonstrated that organolanthanide-catalysis is conducive to the anti-Markovnikov hydroamination of styrenes and two additional substrates bearing directing groups.[16] Recently, Hill and coworkers disclosed the hydroamination of styrenes, dienes, and alkynes utilizing $[Ca\{N(SiMe_3)_2\}_2]_2$ or $[Sr\{N(SiMe_3)_2\}_2]_2$ precatalysts,[17] and the Lalic group has developed a one-pot, two-step hydroboration/amination approach for the synthesis of tertiary alkyl amines from aliphatic olefins.[18] However, these metal-catalyzed hydroamination methodologies have various limitations such as harsh basic conditions, the requirement of a directing group, and limited substrate scopes. Two additional approaches from the Studer[19] and Beauchemin[20] groups accomplish this transformation through free radical and pericyclic additions, respectively, although selectivity is substrate-dependent in the latter case.[21] Despite considerable advances in the area of metal-catalyzed anti-Markovnikov hydroaminations of olefins, a general method remains an elusive goal.[4c]

Considering the importance of carbon–nitrogen bond forming processes, we sought to develop a new, mild

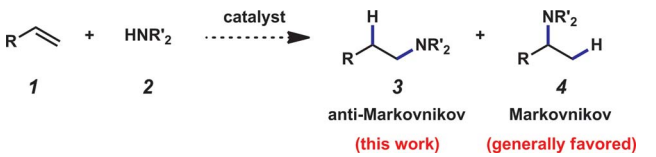

Fig. 1 Olefin hydroamination.

Arnold and Mabel Beckman Laboratories of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California, 91125, USA. E-mail: rhg@caltech.edu; Fax: +1 626-564-9297

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hydroamination methodology. In this manuscript, we present a two-step, one-pot hydroamination protocol that tolerates a variety of olefin substrates, including aliphatic olefins as well as electronically biased systems such as styrenes. Both the olefin and the amine substrate scope are explored, and this report demonstrates how the use of cleavable *N*-protecting groups can give access to a diverse library of hydroamination adducts.

Results and discussion

It was envisioned that anti-Markovnikov hydroamination could occur through a one-pot, two-step Wacker oxidation/transfer hydrogenative reductive amination approach (**1** → **3**, Fig. 2) that would proceed *via* an aldehyde intermediate (**5**). Key challenges associated with this methodology include: (a) regioselectivity of the initial oxidation (**1** → **5**), as Wacker chemistry typically favors formation of the Markovnikov product, (b) catalyst compatibility during the reductive amination step, and (c) chemoselectivity of the reduction step to favor formation of the hydroamination adduct (**3**) over the hydration product (**7**). We recently reported the aldehyde-selective Wacker oxidation of styrenes,[22] and it was expected that these optimized conditions, in which *t*-BuOH enhances anti-Markovnikov selectivity,[23] could be utilized in hydroamination to access the key aldehyde intermediate (Fig. 2). In order to execute the reductive amination, we expected that the addition of an amine (**2**) would provide an imine/iminium intermediate, which could subsequently be reduced in the presence of a transfer hydrogenation catalyst [M] and an appropriate hydride source (**6**). It should be noted that the proposed one-pot methodology is advantageous over a two-pot technique because in addition to allowing for direct formation of the linear amine, isolation of the unstable aldehyde is bypassed; in our previous report of the aldehyde-selective oxidation of styrenes, the high reactivity of the aldehyde product necessitated isolation as the hydrazone derivative.[22]

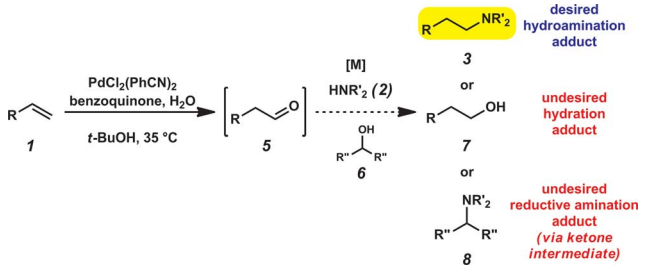
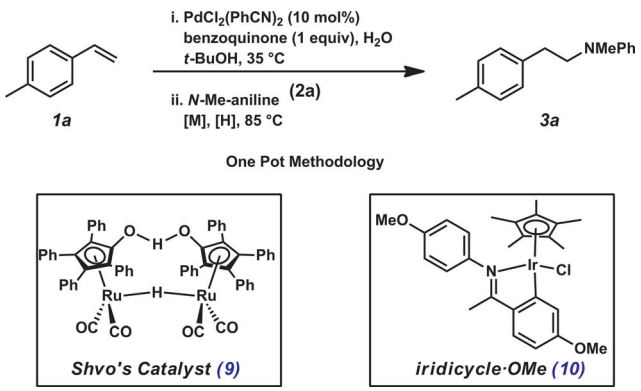


Fig. 2 Challenges of the formal anti-Markovnikov hydroamination methodology.

Previously, our group has demonstrated the compatibility of Shvo's catalyst (**9**, Table 1) with Wacker oxidation conditions;[24] thus Shvo's catalyst, which is also well known to be effective in the transfer hydrogenation of imines,[25] was chosen for our initial hydroamination studies. *p*-Methylstyrene (**1a**) and *N*-methylaniline (**2a**) were selected as the initial substrates for preliminary hydroamination studies. While *p*-methylstyrene was chosen for methodology development because this substrate yields exceptionally high anti-Markovnikov selectivities in Wacker oxidations when *t*-BuOH is used as a solvent,[22] *N*-methylaniline was selected because of the known compatibility of aryl amines with Pd(II)-catalyzed oxidations.[26]

Using our one-pot, two-step hydroamination approach,[27] a solution of *p*-methylstyrene (**1a**) in *t*-BuOH was treated with

Table 1 Optimization of hydroamination methodology



Entry	[M]	Mol% [M]	[H]	Additives (step)	Equiv. amine	Equiv. H_2O	Yield[a]
1	9	10%	Isopropyl alcohol	$CuCl_2$ (ii)	2.5	1	15%
2	9	10%	2,4-Dimethyl-3-pentanol	Mol. sieves (i); CuCl (ii)	2.5	0	25%
3	10	10%	5 : 2 HCO_2H/TEA	—	2.5	1	63%
4	10	10%	5 : 2 HCO_2H/TEA	—	2.5	2	59%
5	10	1%	5 : 2 HCO_2H/TEA	—	2.5	1	65%
6	10	10%	5 : 2 HCO_2H/TEA	—	1.3	1	66%
7	10	1%	5 : 2 HCO_2H/TEA	—	1.3	1	59%

[a] Yield determined from analysis of the ^1H NMR spectrum using 1,4-dioxane as an external standard.

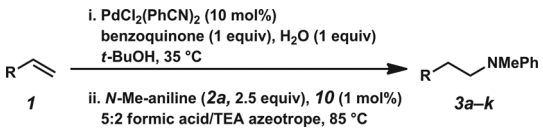
$PdCl_2(PhCN)_2$, the terminal oxidant benzoquinone, and H_2O (Table 1, entry 1). After allowing the oxidation to progress for 4 hours at 35 °C, a solution of *N*-methylaniline (**2a**), Shvo's catalyst (**9**), and hydride source isopropanol was added to the reaction vessel, which was subsequently heated at 85 °C. In addition to providing desired hydroamination adduct **3a** in 15% yield by ^{1}H NMR spectroscopy, the hydration product (*e.g.*, **7**) was also observed, suggesting unselective reduction. Additionally, significant quantities of **8** were observed, resulting from reductive amination between the oxidized hydride donor and amine **2a**. In order to minimize these undesired byproducts, a bulkier hydride source was used, and water was eliminated from the reaction conditions and replaced with molecular sieves (entry 2). Under these reaction conditions, hydroamination adduct **3a** was obtained in 25% yield.

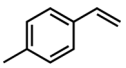
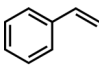
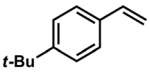
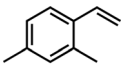
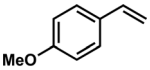
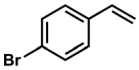
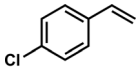
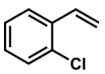
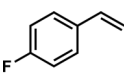
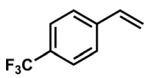
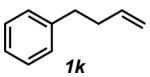
To address chemoselectivity issues in the reduction step, we found it necessary to replace Shvo's catalyst (**9**) with commercially available Ir-complex **10**,[28] which was developed by the Xiao group and has been demonstrated to be selective for transfer hydrogenative reduction of imines in the presence of carbonyls.[29] Also necessary for this reduction, a 5 : 2 formic acid : triethylamine azeotropic mixture[29,30] was utilized as the hydride source. Operationally, a solution of the hydride source, the Ir catalyst, and the amine was added to the reaction mixture after Pd-catalyzed oxidation had completed. Under these new conditions, in which formation of undesired hydration product **7** is significantly disfavored because of the inherent chemoselectivity of Ir-catalyst **10** for imine reduction, linear amine **3a** was obtained in 63% yield by ^{1}H NMR spectroscopy (entry 3).[31] Importantly, no Markovnikov hydroamination product was detected.[32] Brief attempts to further optimize the reaction conditions found no significant improvement in yield (*e.g.*, entry 4), although it was found that either Ir catalyst loading or amine equivalents could be reduced without negatively impacting yields (entries 5 and 6, respectively). However, reduction of both Ir-catalyst loading and amine equivalents resulted in a slight decline in yield (entry 7).

The styrene substrate scope was examined using the optimized conditions (Table 2). Hydroamination of aryl-substituted styrenes **1a–j** afforded desired linear amines **3a–j** in good to moderate yield and with excellent regioselectivity; in all cases, no Markovnikov hydroamination product was isolated or detected in ^{1}H NMR spectra of the unpurified reaction mixtures.[32] The hydroamination methodology was found to accommodate a variety of aryl-substitution patterns, including *ortho*-substitution (entries 4 and 8). In addition to alkyl substituents (entries 1, 3, and 4), several functional groups were tolerated including ether (entry 5), aryl halide (entries 6–9), and alkyl halide (entry 10) groups. Yields substantially declined when these hydroamination conditions were applied to aliphatic olefins, and in the case of 4-phenyl-1-butene (**1k**), amine adduct **3k** was isolated in 24% yield (entry 11).[33]

Next, the amine substrate scope was investigated, and efforts initially focused on aryl amines (*e.g.*, **2a–f**), which are prevalent in drug substances.[34] Hydroamination of **1a** with *N*-methylnaphthalene-2-amine (**2b**) gave a satisfactory 60% yield of desired product **3l** (Table 3, entry 2). Aniline (**2c**) was a more challenging substrate (entry 3), but interestingly, when *N*-benzylaniline (**2d**) was used as the nucleophile, *N*-(4-methylphenethyl)aniline (**3m**), resulting from tandem hydroamination and hydrogenolysis reactions, was isolated in 46% yield (entry 4) – an improvement from entry 3's yield of 32% of the same adduct. Although primary aryl amines often do not participate in high yielding hydroamination transformations, this result demonstrates that one possible tactic for maximizing yields is to use benzyl-protected derivatives. Furthermore, whereas a number of

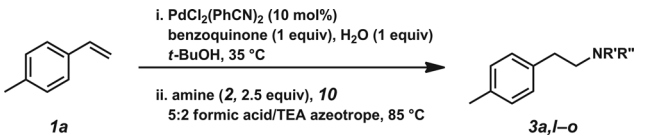
Table 2 Hydroamination of styrenes with *N*-methylaniline

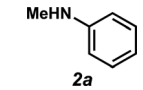
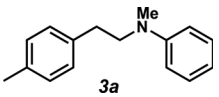
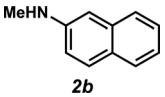
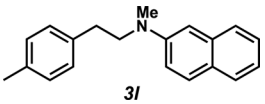
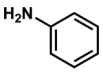
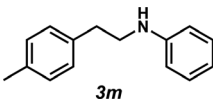
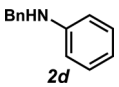
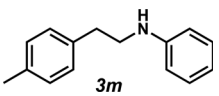
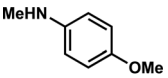
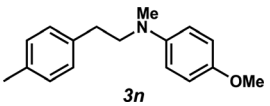
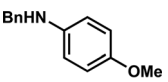
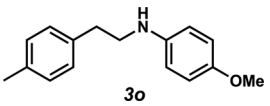


Entry	Substrate	Product	Yield[a]
1	 *1a*	**3a**	61% (66%[b])
2	 *1b*	**3b**	55%
3	 *1c*	**3c**	55%[c]
4	 *1d*	**3d**	62%
5	 *1e*	**3e**	65%
6	 *1f*	**3f**	52%
7	 *1g*	**3g**	57%[c]
8	 *1h*	**3h**	43%[c]
9	 *1i*	**3i**	70%
10	 *1j*	**3j**	50%[c]
11	 *1k*	**3k**	24%[c]

[a] Yields determined by isolation (0.6 mmol scale). [b] Yield determined from analysis of the ^{1}H NMR spectrum using 1,4-dioxane as an external standard. [c] Yield obtained with 10 mol% **10**.

Table 3 Hydroamination of *p*-methylstyrene with amines



Entry	Amine	Product	Yield[a]
1	 2a	 3a	66%[b]
2	 2b	 3l	60%[c]
3	 2c	 3m	32%[b]
4	 2d	 3m	46%[d]
5	 2e	 3n	60%[d]
6	 2f	 3o	61%[d]

[a] Yields determined by isolation (0.6 mmol scale). [b] Yield obtained with 1 mol% **10**. [c] Yield obtained with 5 mol% **10**. [d] Yield obtained with 10 mol% **10**.

previous anti-Markovnikov intermolecular hydroamination strategies do not accommodate aryl amines,[17] our approach is best suited for this class of compounds; thus, our methodology offers a complementary hydroamination approach.

Unfortunately, employing the optimized conditions gave only decomposition mixtures when applied to hydroamination using aliphatic amines. This shortcoming prompted us to examine hydroamination with amines possessing removable aryl protecting groups. Hydroamination of *p*-methylstyrene (**1a**) with *N*-methylanisidine (**2e**) proceeded in 60% yield (entry 5). Similarly, *N*-benzylanisidine (**2f**) proved to be a suitable substrate, providing the hydroamination adduct **3o** in 61% yield (entry 6). These two transformations furnished the linear amine product bearing a PMP (*p*-methoxyphenyl) protecting group, which can be readily cleaved by the action of dilute acid[35] (*e.g.* **3n** → **11**, Fig. 3); thus, the use of amines with removable aryl protecting groups allows access to a diverse array of hydroamination products.

The hydroamination approach described thus far is not best suited for aliphatic olefins (*e.g.*, Table 2, entry 11). Our group's olefin hydration research previously demonstrated that the initial oxidation proceeds in moderate to poor yield and with regioselectivity favoring the Markovnikov (ketone) product.[24] However, during the course of our studies, coworkers developed a new catalytic process for the aldehyde-selective Wacker oxidation of aliphatic olefins.[36] To our delight, it was found that the new Wacker oxidation conditions, which utilize $AgNO_2$, could be applied to our hydroamination methodology in order to offer an entry into the anti-Markovnikov hydroamination of aliphatic olefins. As shown in Table 4, hydroamination of 4-phenyl-1-butene (**1k**) with *N*-methylaniline (**2a**) furnished adduct **3k** in 64% yield (Table 4, entry 1), whereas our initial approach delivered **3k** in 24% yield (Table 2, entry 11). Anti-Markovnikov hydroamination of 1-dodecene (**1m**), a transformation that notably cannot be substrate-controlled, proceeded in 40% yield to provide **3p** (entry 3). The more sterically demanding allyl cyclohexane (**1n**) also proved to be a good

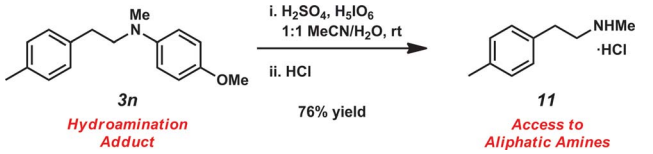
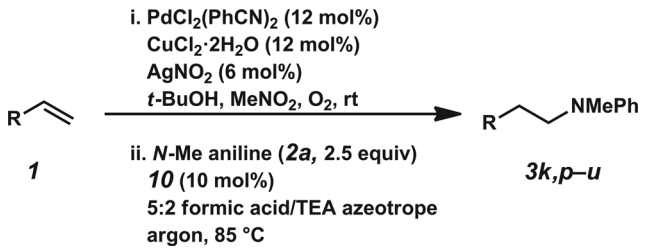
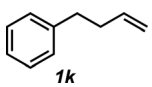
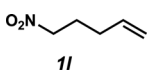
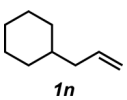
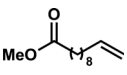
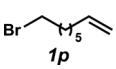
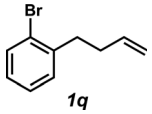


Fig. 3 Cleavage of removable aryl protecting group.

Table 4 Hydroamination of aliphatic olefins with *N*-methylaniline



Entry	Substrate	Product	Yield[a]
1	 1k	3k	64%
2	 1l	3p	65%
3	 1m	3q	40%
4	 1n	3r	56%
5	 1o	3s	60%
6	 1p	3t	39%
7	 1q	3u	46%

[a] Yield determined by isolation (0.6 mmol scale).

substrate (entry 4), delivering **3r** in 56% yield. Examination of the substrate scope revealed that this transformation could accommodate a variety of functional groups, including nitro (entry 2), ester (entry 5), alkyl halide (entry 6), and aryl halide (entry 7) groups. To the best of our knowledge, this methodology represents the first metal-catalyzed approach to the intermolecular anti-Markovnikov hydroamination of an unbiased olefin with an aryl amine. Furthermore, it should be noted that this catalytic system allows access to elusive linear amine adducts through a one-pot technique, thus avoiding isolation of less stable aldehyde intermediates.

Conclusions

In summary, a one-pot methodology for the intermolecular anti-Markovnikov hydroamination of olefins with aryl amines has been developed. The scope of the methodology is broad with respect to the olefin, and although the amine substrate scope is more limited, the use of amines with removable aryl protecting group expands the suite of accessible linear amines. This mild methodology complements existing literature and contributes to less developed areas of hydroamination research, namely the anti-Markovnikov intermolecular hydroamination of aliphatic olefins, as well as the use of aryl amines.

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