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Authors
Hanna, Steven
Holder, Jeffrey C
Hartwig, John F

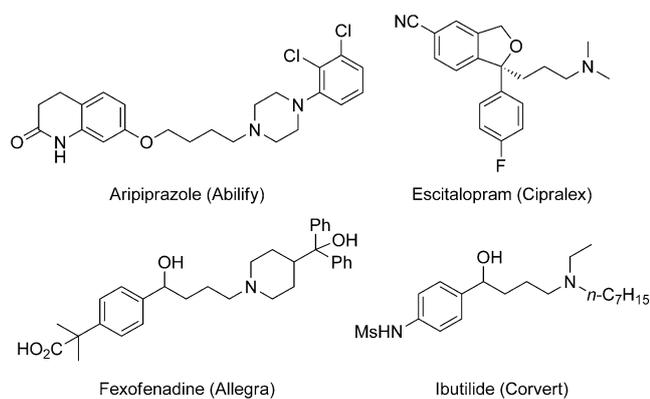**Publication Date**
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A Multicatalytic Approach to the Hydroaminomethylation of α-Olefins

Steven Hanna, Jeffrey C. Holder, and John F. Hartwig*

Abstract: *We report an approach to conducting the hydroaminomethylation of diverse α-olefins with a wide range of alkyl, aryl, and heteroarylamines at relatively low temperatures (70–80 °C) and pressures (1.0–3.4 bar) of synthesis gas. This approach is based on simultaneously using two distinct catalysts that are mutually compatible. The hydroformylation step is catalyzed by a rhodium diphosphine complex, and the reductive amination step, which is conducted as a transfer hydrogenation with aqueous, buffered sodium formate as the reducing agent, is catalyzed by a cyclometallated iridium complex. By adjusting the ratio of CO to H_2, we conducted the reaction at one atmosphere of gas with little change in yield. A diverse array of olefins and amines, including hetreroarylamines that do not react under more conventional conditions with a single catalyst, underwent hydroaminomethylation with this new system, and the pharmaceutical ibutilide was prepared in higher yield and under milder conditions than with a single catalyst.*

Amines are ubiquitous in industrial, biological, and synthetic chemistry. Many industrial products either contain linear amines or are synthesized from amines,[1] and some of the most commonly prescribed pharmaceuticals contain 1-aminoalkyl groups (Scheme 1). Such amines are most commonly synthesized by the amination of alcohols, the reductive amination of aldehydes, or the reduction of amides, nitriles, or nitro compounds.[1] However, the starting materials for


Scheme 1. APIs containing aminoalkyl groups.

[*] S. Hanna, Dr. J. C. Holder, Prof. J. F. Hartwig
      Department of Chemistry, University of California, Berkeley
      718 Latimer Hall, Berkeley, CA 94708 (USA)
      E-mail: jhartwig@berkeley.edu

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these processes are often synthesized from olefins. Therefore, a method for the synthesis of amines from olefins would be more direct, less expensive, and more environmentally benign than the multi-step alternatives.

The hydroaminomethylation of olefins is an atom-economical and operationally simple reaction involving hydroformylation of an olefin to form an aldehyde and reductive amination of this aldehyde to form an amine.[2] The reaction is commonly conducted with a rhodium-based catalyst ligated by a diphosphine (Scheme 2 A). Several limitations, such as the high pressure of synthesis gas (usually around 60 bar) required to achieve acceptable yields,[2a,b] have diminished the utility of this reaction. In addition, self-condensation of the aldehyde, hydrogenation of the aldehyde, and hydrogenation of the olefin have been reported to compete with hydroaminomethylation.[2a]
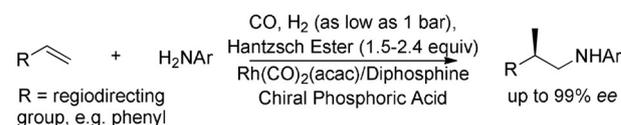
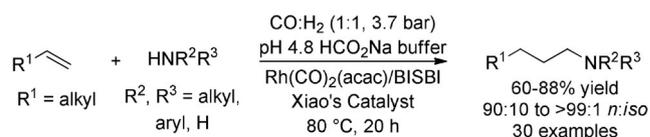**(A) Beller, 2003: hydroaminomethylation with a single metal and ligand**
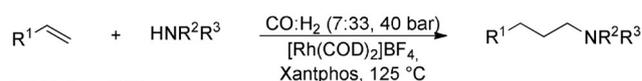
(B) Beller, 1999:
biphasic hydroaminomethylation with two metals and one ligand
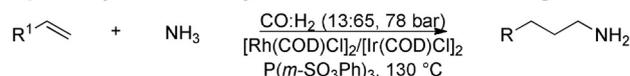
(C) Xiao 2015, Han, 2017:
Branched hydroaminomethylation with one metal and an organic acid

(D) This work: linear hydroaminomethylation with two metal catalysts

Scheme 2. Approaches to hydroaminomethylation.

Hydroaminomethylation is difficult to achieve, in part, because the properties of the most active catalysts for hydroformylation are different from those of the most active catalysts for reductive amination.[3] Moreover the reductive amination process must not be strongly inhibited by carbon monoxide. A single complex that meets these criteria and catalyzes hydroaminomethylations at low pressures and temperatures has not been identified. In 2003, Beller reported one of the most active and regioselective systems comprising the combination of $[Rh(COD)_2]BF_4$ with Xantphos, but these reactions were conducted with 40 bar of syngas at 125 °C (Scheme 2 A).[4] Hydroaminomethylations

reported by Eilbracht, Alper, Whiteker, Zhang, and others occur under similar conditions.[5] A set of hydroaminomethylations reported by Beller occurred at the lower temperature of 60°C. However, these reactions were limited to those of vinylarenes, and high pressures (30 bar, 1:5 CO:H_2) were still required.[6]

We envisioned an alternative approach in which two catalysts, one for each step, would react by mechanisms that are distinct and independent from each other, enabling hydroaminomethylation to occur under conditions that are milder than those with a single catalyst.[7] Beller and Luo published hydroaminomethylations conducted with a single phosphine and two metals, but these reactions still required high pressures of synthesis gas and high temperatures (Scheme 2B).[8] Following a different design, Xiao and Han published hydroaminomethylations catalyzed by the combination of a rhodium-based catalyst for the hydroformylation step and a chiral phosphoric acid for the reductive amination step that form enantioenriched, branched amines from α- and β-functionalized olefins (Scheme 2C). However, these systems have not been shown to catalyze linear-selective hydroaminomethylations of unfunctionalized alkenes, and the organic catalyst requires an expensive Hantzsch ester to reduce the imine intermediate.[7a,b,9]

Herein, we report a linear-selective hydroaminomethylation of α-olefins catalyzed by two distinct metal complexes and an approach to the reductive amination step not applied previously to hydroaminomethylation (Scheme 2D). A rhodium-diphosphine complex catalyzes the hydroformylation step, and a phosphine-free, cyclometallated iridium complex catalyzes the reductive amination step by transfer hydrogenation. Key features of this work include the identification of a catalyst for reductive amination that is not poisoned by CO and the use of buffered formic acid for the reduction step. With this system, aromatic, heteroaromatic, and aliphatic amines are formed in high yields and in high regioselectivities with pressures of synthesis gas and temperatures that are significantly lower than those used previously for hydroaminomethylation.

Our strategy for a low-pressure, multicatalytic hydroaminomethylation was based on the hypotheses that the high pressures of hydrogen in existing systems for hydroaminomethylation are required to ensure that reductive amination is faster than self-condensation of the aldehyde and that the reductive amination step of hydroaminomethylation is slow because catalysts for this step tend to be inhibited by carbon monoxide. In this case, a reductive amination catalyst that is unaffected by carbon monoxide could be combined with a suitable hydroformylation catalyst to conduct hydroaminomethylations at low pressures of synthesis gas. A complex that catalyzes reductive amination by transfer hydrogenation might meet this criterion.

To test this reaction design, we studied the hydroaminomethylation of 1-decene (**1a**) with aniline (**2a**) in the presence of formic acid, the highly active and selective hydroformylation catalyst generated from Rh(CO)$_2$(acac) and BISBI, and various complexes known to catalyze the transfer hydrogenation of imines and iminium ions (Table 1). The most well-known catalysts for reductive amination by transfer hydro-

Table 1: Evaluation of conditions for the hydroaminomethylation of 1-decene with aniline.

Entry	DRA cat.[a]	H$_2$ source	Hydroformylation Ligand	Yield[b]	n:iso
1	**C1**	5:2 HCO$_2$H:TEA	BISBI	33	97:3
2	**C1**	HCO$_2$Na buffer[c]	BISBI	10	72:28
3	**C2**	5:2 HCO$_2$H:TEA	BISBI	29	98:2
4	**C2**	HCO$_2$Na buffer[c]	BISBI	10	70:30
5	**C3**	5:2 HCO$_2$H:TEA	BISBI	29	59:41
6	**C4**	5:2 HCO$_2$H:TEA	BISBI	34	88:12
7	**C5**	5:2 HCO$_2$H:TEA	BISBI	34	72:28
8	**C6**	5:2 HCO$_2$H:TEA	BISBI	48	85:15
9	**C7**	5:2 HCO$_2$H:TEA	BISBI	30	96:4
10	**C7**	HCO$_2$Na buffer[c]	BISBI	91	98:2
11	**C7**	HCO$_2$Na buffer[c]	Xantphos	82	98:2
12	**C7**	HCO$_2$Na buffer[c]	DPEPhos	75	90:10
13	**C7**	none	BISBI	0	N/A
14[d]	**C7**	HCO$_2$Na buffer[c]	BISBI	83	99:1
15[e]	**C7**	HCO$_2$Na buffer[c]	BISBI	76	99:1
16[f]	**C7**	HCO$_2$Na buffer[c]	BISBI	8	68:32
17	none	HCO$_2$Na buffer[c]	BISBI	0	N/A
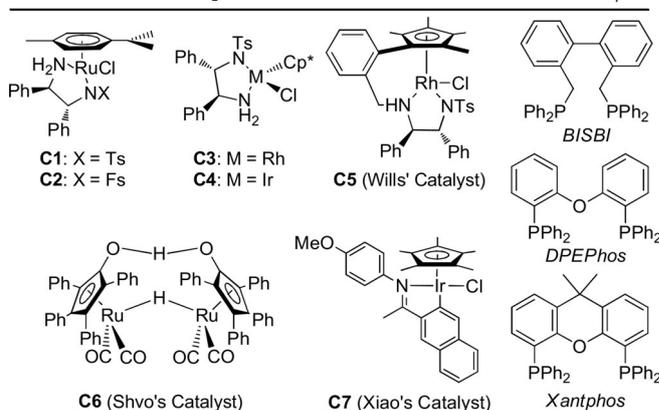
genation consist of a metal capable of transferring a hydride and a ligand capable of transferring a proton to a polarized multiple bond.[10] However, amine **3aa** formed in poor yield from olefin **1a** in the presence of ruthenium diamine complexes **C1** and **C2** (entries 1–4), even though these complexes are known to be active for transfer hydrogenation of imines. The group 9 congeners (catalysts **C3–C5**) of catalysts **C1** and **C2** are active for the reductive amination of aldehydes by transfer hydrogenation.[11] However, amine **3aa** formed with low regioselectivity and in poor yield in the presence of catalysts **C3**, **C4**, and **C5** and in the presence of Rh(CO)$_2$(acac) and BISBI (entries 5–7). Control experiments indicated that complexes **C3–C5** either degrade into unselective catalysts for hydroformylation or are themselves unselective catalysts for hydroformylation under the conditions in Table 1. This reactivity of the reductive amination catalyst toward hydroformylation leads to low n:iso ratios of the amine product. Amine **3aa** also formed in low yields in the presence of catalyst **C6** (entry 8). All of the hydroaminomethylations conducted with catalysts **C1–C6** (entries 1–8) proceeded to high conversions; the major side products of

the reactions were formed from self-condensation of unde-canal.

To increase the rate of reductive amination of undecanal, relative to that of its self-condensation, we sought catalysts for transfer hydrogenation that might be more stable to carbon monoxide than catalysts **C1**–**C6**. Reports that catalyst **C7** is more active for the reduction of *N-p*-anisylketimines than catalyst **C4** and the robustness of catalyst **C7** endowed by cyclometallation prompted us to attempt hydroaminomethy-lations with complex **C7** as catalyst for the reductive amination step of hydroaminomethylation.[12]

Initial studies with catalyst **C7** showed that amine **3aa** formed in only 30% yield from olefin **1a**, CO, H$_2$, and amine **2a** in the presence of catalyst **C7** and the combination of Rh(CO)$_2$(acac), and BISBI with a 5:2 HCO$_2$H:Et$_3$N azeo-trope as the reducing agent (entry 11). On the basis of prior reports showing that the reductive amination of acetophe-none with *p*-anisidine catalyzed by complex **C7** occurs significantly more rapidly with an aqueous sodium formate buffer at pH 4.8 as the reducing agent than with a 5:2 HCO$_2$H:Et$_3$N azeotrope as the reducing agent,[13,14] we conducted the hydroaminomethylation of olefin **1a** with amine **2a** with this reducing agent in the presence of **C7**. Amine **3aa** formed in 91% yield under these conditions (entry 10). Amine **3aa** formed in lower yields in the presence of XantPhos and DPEPhos than in the presence of BISBI (entries 11–12), and the product was not formed in the absence of formate (entry 13). The hydroaminomethylation occurred at lower loadings of the two catalysts with only a small sacrifice in yield (entries 14–15). Amine **3aa** formed in 8% yield and 68:32 *n:iso* in the presence of catalyst **C7** with no Rh(CO)$_2$(acac) (entry 16), indicating that catalyst **C7** is only slightly active towards hydroformylation under the developed conditions. Amine **3aa** was not formed in the absence of a reductive amination catalyst (entry 17).

We attribute the high yields and regioselectivities of the reaction in entry 10 to several factors. First, Xiao's cyclo-metallated catalyst is not significantly inhibited by low pressures of CO; control experiments indicated that the yield of the reductive amination of undecanal catalyzed by complex **C7** was the same in the absence of CO as in the presence of 1.7 bar of CO. In contrast, complexes **C1**, **C2** and **C6** were poisoned by CO, even at this low pressure (see the Supporting Information for details). Second, Xiao's catalyst is compatible with the aqueous HCO$_2$Na buffer, a mild, inex-pensive hydrogen surrogate. Finally, Xiao's catalyst does not hydrogenate imines by a metal–ligand bifunctional mecha-nism.[12] Instead, Xiao's catalyst transfers a hydride to an iminium ion that is formed by protonation of an imine or enamine in an acidic medium.[12]

The scope of olefins that undergo this hydroaminomethy-lation is illustrated by the examples in Table 2. Phenols (**3ca**), malonates (**3da**), nitriles (**3ea**), enolizable ketones (**3fa**), allylic acetates (**3ga**), allylic alcohols (**3ha**), and disubstituted olefins (**3ka**) were all tolerated. Olefins bearing electron-withdrawing groups in the allylic position reacted with excellent regioselectivities (**1b**, **1c**, **1d**, **1g**, **1h**); such β-functionalized olefins often undergo hydroformylations with low *n:iso* ratios, owing to their tendencies to isomerize to

Table 2: Hydroaminomethylations of various olefins with aniline.
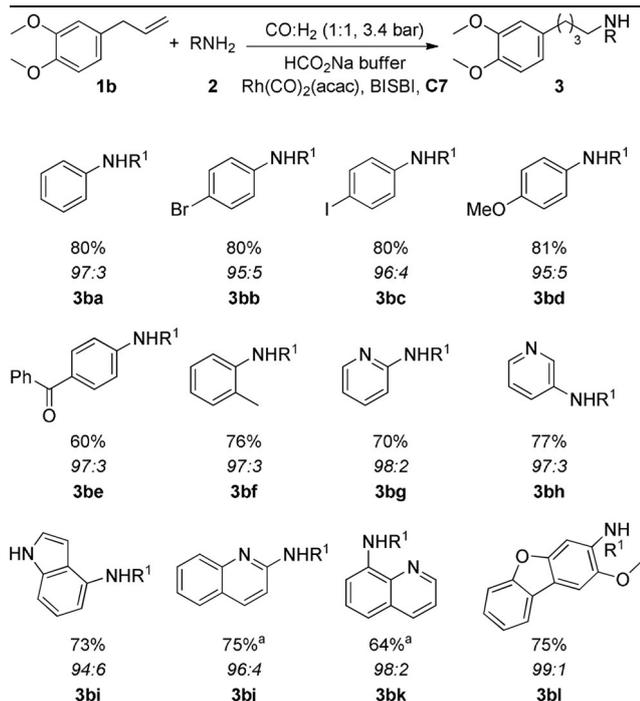

Conditions: olefin (0.5 mmol), aniline (0.75 mmol), pH 4.8 aqueous sodium formate buffer (500 µL), CO:H$_2$ (1:1, 3.4 bar), Rh(CO)$_2$(acac) (0.5 mol%), BISBI (2.5 mol%), Xiao's catalyst (1 mol%), 9:1 PhMe:MeOH (2.5 mL), 80 °C, 20 h. All yields reported are isolated yields. Regioselectivities were determined by GC analysis of the crude reaction mixture. [a] 0.25 mmol olefin.

internal olefins. Sterically hindered α-olefins (**1g**, **1i**, **1j**, **1k**) also underwent hydroaminomethylation. As expected, the regioselectivities of the reactions of these alkenes were higher than those of reactions of less hindered alkenes. In addition, the double hydroaminomethylation of olefin **1l** proceeded in high yield and with high regioselectivity.
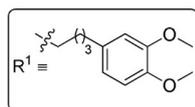
The scope of arylamines that undergo hydroaminomethy-lation was studied with the olefin methyl eugenol (**1b**) as the coupling partner. The results are given in Table 3. Both electron-poor (**2b**, **2c**, **2e**) and electron-rich (**2d**) anilines underwent hydroaminomethylation. Anilines bearing *ortho* substituents (**2f**) and those bearing ketones (**2e**) also under-went hydroaminomethylation.

The scope of heteroarylamines that undergo hydroami-nomethylation with olefin **1b** is also shown in Table 3. Heteroarylamines are widespread in pharmaceuticals and agrochemicals, but hydroaminomethylations with such regents are limited.[15] For reference, we conducted the reaction of olefin **1b** with 2-aminopyridine (**2g**) under standard conditions for hydroaminomethylation (125°C, 40 bar 1:5 CO:H$_2$) with the single catalyst formed from the combination of [RhCOD$_2$]BF$_4$ and Xantphos. Only trace amounts of amine **3bg** were formed; the major species present in the crude reaction mixture was the starting olefin **1b**.[16] In contrast, the reactions of methyl eugenol with heteroarylamines, including aminopyridines (**2g**, **2h**), amino-indoles (**2i**), aminoquinolines (**2j**, **2k**), and aminodibenzofur-ans (**2l**) occurred in good yield under the conditions we
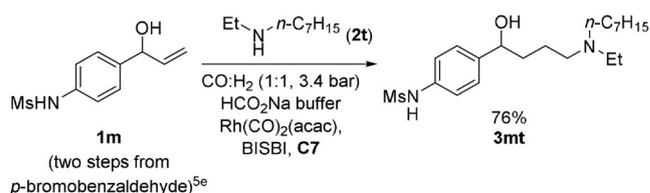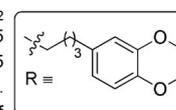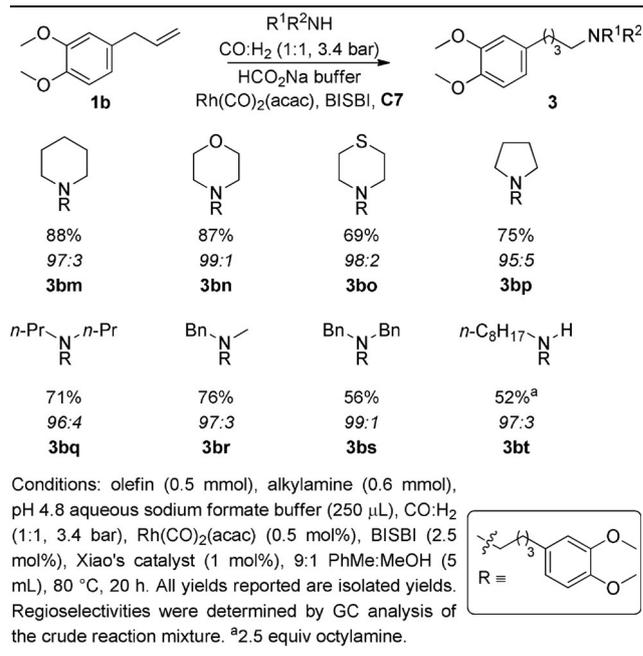
Table 3: Hydroaminomethylations of methyl eugenol with various arylamines.

Conditions: methyl eugenol (0.5 mmol), amine (0.75 mmol), pH 4.8 aqueous sodium formate buffer (500 µL), CO:H$_2$ (1:1, 3.4 bar), Rh(CO)$_2$(acac) (0.5 mol%), BISBI (2.5 mol%), Xiao's catalyst (1 mol%), 9:1 PhMe:MeOH (2.5 mL), 80 °C, 20 h. All yields reported are isolated yields. Regioselectivities were determined by GC analysis of the crude reaction mixture. [a]1.25 mmol amine
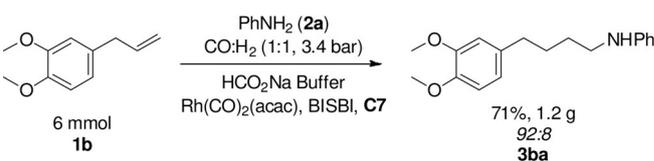
Table 4: Hydroaminomethylations of methyl eugenol with various aliphatic amines.

Conditions: olefin (0.5 mmol), alkylamine (0.6 mmol), pH 4.8 aqueous sodium formate buffer (250 µL), CO:H$_2$ (1:1, 3.4 bar), Rh(CO)$_2$(acac) (0.5 mol%), BISBI (2.5 mol%), Xiao's catalyst (1 mol%), 9:1 PhMe:MeOH (5 mL), 80 °C, 20 h. All yields reported are isolated yields. Regioselectivities were determined by GC analysis of the crude reaction mixture. [a]2.5 equiv octylamine.

Conditions for Hydroaminomethylation: olefin (0.5 mmol), alkylamine (0.6 mmol), pH 4.8 aqueous sodium formate buffer (250 µL), CO:H$_2$ (1:1, 3.4 bar), Rh(CO)$_2$(acac) (1 mol%), BISBI (5 mol%), Xiao's catalyst (2 mol%), 9:1 PhMe:MeOH (5 mL), 80 °C, 20 h.

Scheme 3. Synthesis of Ibutilide.

developed with two catalysts. Even heteroarylamines capable of chelating metal catalysts (**2k**) reacted. This contrast in reactivity demonstrates the unusual compatibility of the new system for hydroaminomethylation with biologically important heteroarenes.

Alkylamines might be expected to be quenched by the acidic buffer containing formic acid, but both primary and secondary alkylamines underwent hydroaminomethylation under the conditions we developed with two catalysts and a pH 4.8 formate buffer (Table 4). Both cyclic (**2m**, **2n**, **2o**, **2p**) and acyclic (**2q**, **2r**, **2s**) secondary amines underwent the hydroaminomethylation. Sterically hindered aliphatic amines were less reactive towards hydroaminomethylation than unhindered aliphatic amines, presumably due to slow reduction of sterically hindered iminium ions. Primary aliphatic amines (**2t**) also underwent hydroaminomethylation to form secondary amines without the formation of tertiary amines.

To demonstrate further the applicability of this work to the preparation of medicinally relevant amines, we synthesized amine **3mt**, the active ingredient in a drug sold under the generic name ibutilide (Scheme 3). Under the conditions in Scheme 3, olefin **1m** underwent hydroaminomethylation in 76% yield. Previous examples of this hydroaminomethylation occurred in significantly lower yields and required pressures

of syngas that are much higher than those in the current work.[5e]

Finally, the hydroaminomethylations reported in this work can be conducted easily on large scales and at atmospheric pressure of syngas. The hydroaminomethylation of 6 mmol of methyl eugenol with aniline gave 1.24 g of amine **3ba** (71% yield, Scheme 4). By adjusting the ratio of CO to H$_2$ to 1:2 CO:H$_2$, the reaction of 1-decene (**1a**) with aniline (**2a**) formed N-undecyl aniline (**3aa**) in 65% yield at a total pressure of only 1 atm at 70 °C (Scheme 5).
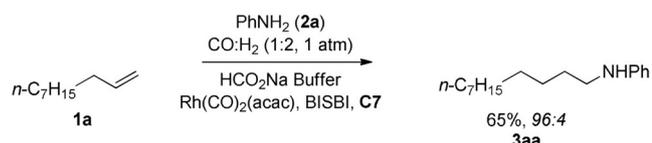

Conditions: methyl eugenol (6 mmol), aniline (9 mmol), pH 4.8 aqueous sodium formate buffer (6 mL), CO:H$_2$ (1:1, 3.4 bar), Rh(CO)$_2$(acac) (0.5 mol%), BISBI (2.5 mol%), Xiao's catalyst (1 mol%), 9:1 PhMe:MeOH (30 mL), 80 °C, 20 h.

Scheme 4. Hydroaminomethylation on a 6-mmol scale.

PhNH₂ (2a)

n-C₇H₁₅ with structure
1a

CO:H₂ (1:2, 1 atm)
HCO₂Na Buffer
Rh(CO)₂(acac), BISBI, **C7**

n-C₇H₁₅ ⟶ NHPh
65%, 96:4
3aa

Conditions: 1-decene (0.15 mmol), aniline (0.23 mmol), pH 4.8 aqueous sodium formate buffer (250 μL), CO:H₂ (1:2, 15 psi), Rh(CO)₂(acac) (2 mol%), BISBI (8 mol%), Xiao's catalyst (2 mol%), 9:1 PhMe:MeOH (750 μL), 70 °C, 64 h.

Scheme 5. Hydroaminomethylation at atmospheric pressure.

In summary, we have developed a scalable, linear-selective, dual-catalytic hydroaminomethylation of α-olefins occurring at low temperature and pressure by exploiting the combination of a catalyst for hydroformylation and a catalyst for reductive amination that is active under carbon monoxide and that reduces imines by transfer hydrogenation. The pressures and temperatures of the reaction are the lowest reported for linear-selective hydroaminomethylations, and the reactions can even be conducted at atmospheric pressure of synthesis gas. The reaction occurs with a broad range of olefins and amines and is uniquely suitable for the preparation of a wide range of medicinally relevant heteroarylamines. Efforts to further increase the activity of dual catalysts and the scope of reactants are ongoing.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

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[14] The precise pH of the buffer strongly influences the outcomes of reductive aminations with Xiao's catalyst. Under basic conditions, neither imines nor ketones are protonated, and the reduction does not occur. In contrast, under highly acidic conditions, amines, ketones, and imines are protonated and both the chemoselectivity for the reduction of C=N bonds and the rate of the reductive amination are low. See reference [13].

[15] Beller has shown that 1,1-diphenylethylene undergoes hydroaminomethylations with piperidines bearing remote pyridyl and pyrimidyl groups, but this olefin undergoes hydroaminomethylation with 4-aminopyridine in low yield. M. Ahmed, C. Buch, L. Routaboul, R. Jackstell, H. Klein, A. Spannenberg, M. Beller, *Chem. Eur. J.* **2007**, *13*, 1594–1601.

[16] Reaction Conditions: 0.5 mmol methyl eugenol, 0.5 mmol 2-aminopyridine, 40 bar CO:H₂ (1:5), [Rh(COD)₂]BF₄ (0.1 mol%), Xantphos (0.4 mol%), 1.5 mL PhMe:MeOH (1:1), 125 °C, 20 h.