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Consecutive Intermolecular Reductive Hydroamination: Cooperative Transition-Metal and Chiral Brønsted Acid Catalysis

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Abstract: Enantiomerically pure chiral amines are of increasing importance and commercial value in the fine chemical, pharmaceutical, and agrochemical industries. Here, we describe the straightforward synthesis of chiral amines by combining the atom-economic and environmentally friendly hydroamination of alkynes with an enantioselective hydrogenation of in situ generated imines by using inexpensive hydrogen. By following this novel approach, a wide range of terminal alkynes can be reductively hydroaminated with primary amines including alkyl-, and arylalkynes as well as aryl and heteroaryl amines. Excellent yields and selectivities up to 94% *ee* and 96% isolated yield were obtained.

Keywords: amines · enantioselectivity · hydroamination · hydrogenation · iron

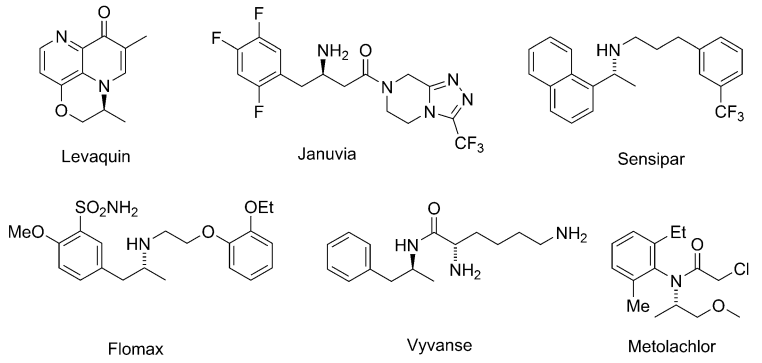
Introduction

The enantioselective synthesis of chiral amines continues to attract considerable academic and industrial interest due to the importance of the resulting enantiomers as resolving agents, chiral auxiliaries, agrochemicals, and pharmaceuticals. To illustrate their significance in chiral drugs, a selection of top 100 brand-name drugs with chiral amine building blocks is shown below. In addition, the herbicide S-Metolachlor[1] is produced on a multi-thousand ton-scale per year.

In the last two decades highly selective catalytic reductions of prochiral ketimines to α-chiral amines have been developed.[2] Unfortunately, in these procedures the corresponding imine has to be synthesized and isolated in an additional reaction step. A more efficient and direct synthesis constitutes the enantioselective reductive amination of ketones (Scheme 1). Although various methods have been developed[3] since the first report by Blaser et al. in 1999,[4] a highly selective and general method is still lacking.

Recently, significant progress has been achieved in the hydroamination of alkynes as this method constitutes an attractive alternative for the synthesis of imines.[5] A variety of catalysts based on early transition metals,[6] lanthanides,[7] actinides,[8] late transition metals,[9] strong bases,[10] even heterogeneous systems[11] have been developed for the hydroamination of C–C unsaturated bonds with primary amines.

Notably in 2009, Che[12] and Gong[13] developed independently from each other inter- and intramolecular reductive hydroaminations of alkynes. The enantioselective reduction was achieved by using stoichiometric amounts of a Hanztsch ester in the presence of a chiral organocatalyst, whereas stoichiometric amounts of pyridine were produced as co-products. Obviously, more convenient reducing agents would represent an important advancement in this methodology. However, to the best of our knowledge no catalytic reactions combining the atom economic hydroamination of C–C triple bonds with an enantioselective reduction using environmental friendly, inexpensive, and readily available hydrogen has been reported so far.



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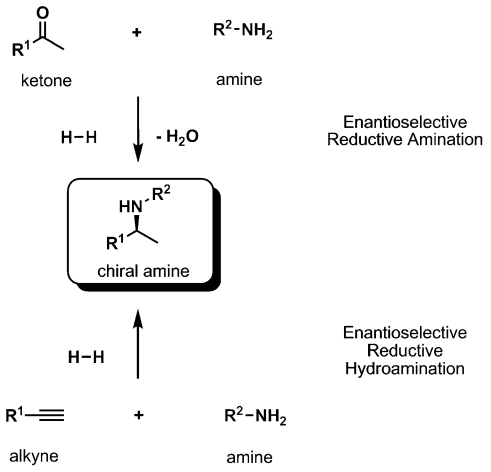
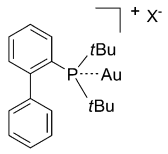


Scheme 1. Reductive hydroamination as alternative approach for the synthesis of amines compared to classical reductive amination.

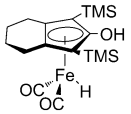
Results and Discussion

Based on our experience in both the catalytic hydroamination of alkynes[14] and the iron-catalyzed enantioselective reduction of imines,[15] we set up a project to combine these two methodologies for a more efficient synthesis of chiral amines.

Herein, we present for the first time a suitable catalyst system consisting of an active gold(I) complex **1**, Knölker's[16] iron complex **2**, and a chiral Brønsted acid **3** to yield chiral amines directly from alkynes.



1a: X = Cl
1b: X = BF_4



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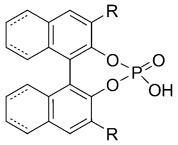


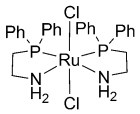
3

Owing to the industrial importance of 1-arylethyl amines, our initial catalytic investigations were carried out on the reaction of phenylacetylene **4a** with *p*-anisidine **5a** as the benchmark reaction (Table 1). According to our concept, we used well-known commercially available hydroamination catalysts in the presence of molecular hydrogen. The consecutive catalytic hydrogenation was catalyzed by a combination of (*R*)-TRIP **3e** (3,3′-bis(2,4,6-triisopropyl-phenyl)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate) with the iron complex **2**. Surprisingly, the hydroamination catalyst has a significant influence on both the yield and the enantiomeric excess (*ee*) of amine **6a**. First experiments revealed that the desired chiral amine **6a** was formed in the presence of various commercially available Zn^{II}, Cu^{II}, Au^{I}, Ru^{0}, Pt^{II}, and Pt^{IV} complexes (Table 1, entries 1–11). However, with $Zn(OTf)_2$ only the racemic amine was produced, whereas the use of $Cu(OTf)_2$ or AuCl yielded the amine **6a** with moderate enantioselectivities of 67 and 65% *ee*, respectively (Table 1, entries 3 and 4). Different Pt^{II} and Pt^{IV} salts showed only moderate activity giving **6a** in yields between 24–28% with 20–40% *ee* (Table 1, entries 9–11). It should be noted that the differences between conversion and product yield resulted from hydrolysis of the imine and from aldol condensation reactions, which are observed as side reactions.

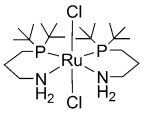
As Au^{I} precursors proved to be both active and selective in hydroamination reactions different Au^{I} complexes were applied to our reaction. Complex **1a** did not show any activity in the reductive hydroamination of **4a** with *p*-anisidine **5a**. Next, we exchanged the counteranion of **1a** to the less coordinating tetrafluoroborate anion to access complex **1b**. To our delight, 1 mol% of **1b** in combination with 2 mol% (*R*)-TRIP **3e** and 5 mol% iron complex **2** yielded **6a** in 80% yield and with an excellent enantiomeric excess of 94% *ee* (Table 1, entry 7). This phenomenon can be referred to the fact that the presence of a weakly coordinated anion like BF_4^- supports the formation of a cationic species.

For comparison we hydrogenated the isolated corresponding imine applying the same hydrogenation conditions by using 2 mol% (*R*)-TRIP and 5 mol% iron complex **2** and yielded **6a** in 90% yield and with 92% *ee*.[15b] These results clearly indicate that **1b** has no significant influence on the yield and enantioselectivity of this transformation.

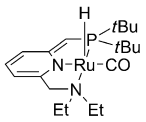
Next, well-known homogeneous hydrogenation catalysts (**7**–**11**) were tested instead of the iron complex **2** to promote the desired catalytic hydrogenation of the in situ formed imine. First experiments revealed that the desired *N*-(1-phenylethyl)aniline **6a** was formed in the presence of various Ru, Rh, and Ir catalysts. However, none of these established precious-metal hydrogenation catalysts in combination with chiral Brønsted acids, for example (*R*)-TRIP **3e**, induced any significant enantioselectivity.



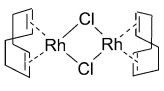
7
0% yield



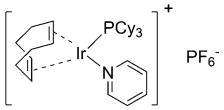
8
65% yield
2% *ee*



9 Milstein's complex
2% yield



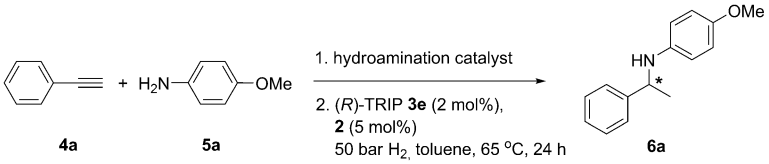
10
27% yield
<1% *ee*



11 Crabtree's complex
88% yield
<1% *ee*

As chiral 1,1′-binaphthalene-2,2′-diol (binol) phosphoric acids showed high selectivity in the enantioselective reduction of C=X bonds when using Hanztsch Ester as the reducing agent[17] we draw our attention towards the combination of **2** with different chiral phosphoric acids **3**. As expected, 1,1′-binaphthyl-2,2′-diyl hydrogen phosphate **3a** showed only

Table 1. Consecutive reductive hydroamination of phenylacetylene with *p*-anisidine: Variation of the hydroamination catalyst.[a]



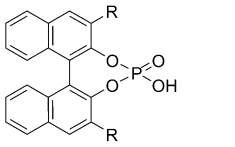
4a 5a 6a

Entry	Metal catalyst [mol%]	*T* [°C]	Conv. [%][d]	Yield [%][d]	*ee* [%][e]
1	$Zn(OTf)_2$ [5]	120	74	17	4
2	$Zn(OTf)_2$ [5] in situ	100	87	20	*rac*
3	$Cu(OTf)_2$ [4]	100	80	42	67
4	AuCl [4]	100	91	33	65
5	**1a** [2]	RT	<1	<1	–
6[b]	**1b** [1]	65	>99	78	92
7[c]	**1b** [1]	RT	>99	80	94
8	$Ru_3(CO)_{12}$ [1] NH_4PF_6 [3]	100	77	40	58
9	$PtCl_2$ [4]	100	76	29	40
10	$PtCl_4$ [4]	100	63	24	32
11	$PtBr_2$ [4]	100	70	28	20

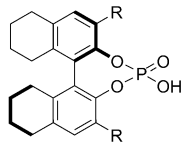
[a] Unless otherwise noted, the reaction was carried out with phenylacetylene **4a** (0.5 mmol), *p*-anisidine **5a** (0.5 mmol), hydroamination catalyst, toluene (0.5 mL) at various temperatures for 24 h, then (*R*)-TRIP **3e** (2 mol%), **2** (5 mol%), H_2 (50 bar) at 65°C for 24 h. [b] $t=5$ h. [c] $t=16$ h. [d] Determined by GC analysis using hexadecane as an internal standard. [e] Determined by chiral HPLC analysis.

a low enantioselectivity of 23% *ee* in the reductive hydroamination reaction (Table 2, entry 1). The selectivity was improved when sterically demanding 1,1′-binaphthyl-2,2′-diyl hydrogen phosphates were used (Table 2, entries 2 and 5), whereby **3e** achieved a high yield of 80% and excellent enantioselectivity of 94% *ee* (Table 2, entry 5).

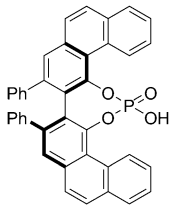
Table 2. Influence of different Brønsted acids on the enantioselective reductive hydroamination of phenylacetylene with *p*-anisidine.[a]



(*R*)-**3a** (R = H)
(*R*)-**3b** (R = 9-anthracenyl)
(*S*)-**3c** (R = 3,5-$(CF_3)_2$-C_6H_3)
(*S*)-**3d** (R = $SiPh_3$)
(*R*)-**3e** (R = [2,4,6-$(iPr)_3C_6H_2$])



(*R*)-**3f** (R = 2-naphthyl)
(*R*)-**3g** (R = 9-phenanthryl)



(*R*)-**3h**

Entry	Brønsted acid [mol%]	Conv. [%][b]	Yield [%][b]	*ee* [%][c]
1	**3a** [5]	99	16	23
2	**3b** [5]	99	9	41
3	**3c** [5]	98	65	11
4	**3d** [5]	97	40	7
5	**3e** [5]	>99	80	94
6	**3f** [5]	98	19	32
7	**3g** [5]	98	38	40
8	**3h** [5]	97	13	21

[a] Unless otherwise noted, the reaction was carried out with phenylacetylene **4a** (0.5 mmol), *p*-anisidine **5a** (0.5 mmol), **1b** (1 mol%), toluene (0.5 mL) at RT for 16 h, then **3** (2 mol%), **2** (5 mol%), H_2 (50 bar) at 65°C for 24 h. [b] Determined by GC analysis using hexadecane as an internal standard. [c] Determined by chiral HPLC analysis.

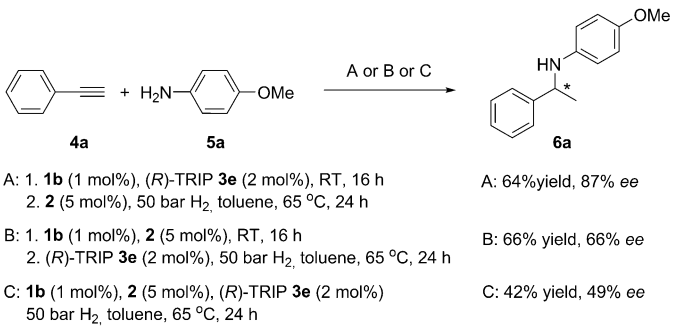
The H8-1,1′-binaphthyl-2,2′-diyl hydrogen phosphates **3f** and **3g** yielded **6a** in moderate yield and enantioselectivity whereas VAPOL **3h** showed only a low enantioselectivity of 21% *ee* in the enantioselective reductive hydroamination reaction.

Encouraged by these results, we wanted to expand the reaction protocol towards a direct enantioselective reductive hydroamination. Hence, we stirred **4a** and **5a** for 16 h at room temperature with the hydroamination catalyst **1b** and (*R*)-TRIP **3e** and added consecutively the hydrogenation catalyst **2**. Under these conditions, **6a** was obtained in good yield and with a high enantioselectivity of 87% *ee*. (Scheme 2; conditions A). A comparable yield and a lower *ee* of 66% are observed when (*R*)-TRIP **3e** was added consecutively after the hydroamination reaction by using the Knölker complex **2** in cooperation with the Au^I complex **1** (Scheme 2; conditions B). The direct reductive hydroamination with **1b** (1 mol%), **2** (5 mol%), and (*R*)-TRIP **3e** (2 mol%) gave **6a** after 24 h at 50 bar H_2 in a moderate yield of 42% and 49% *ee* (Scheme 2; conditions C). It is shown that the one step reaction is basically possible, whereas the two step one-pot synthesis is more reliable. Next, a series of control experiments were conducted to gain insight into the mechanism of the reaction sequence.

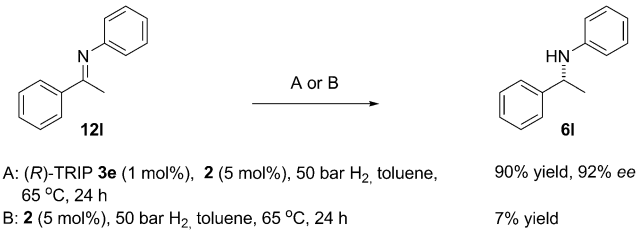
In the absence of iron complex **2**, phenylacetylene **4a** and *p*-anisidine **5a** afforded ketimine **12a** in 99% yield with the gold catalyst **1b**. However, by using Knölker complex **2** in the absence of **1b**, no product was obtained at all. Clearly, the Au^I-catalyzed hydroamination is the first step in this tandem sequence.

Treatment of ketimine **12l** with (*R*)-TRIP **3e** and **2** gave **6l** in 90% yield and with 92% *ee*, whereas in the absence of (*R*)-TRIP **3e** only minor amounts of the product were obtained.[15b] These results show that **2** in cooperation with (*R*)-TRIP **3e** is performing the enantioselective hydrogenation as a second step of this reaction (Scheme 3).

On the basis of these observations, a reaction mechanism for the formation of chiral amines from **4a** with **5a** in the presence of hydrogen gas is proposed in Scheme 4. Initially, alkyne **4** and the cationic gold(I) species **1b** form a cationic Au^I–alkyne complex. Next, *p*-anisidine is coordinated to the Au center prior to the C–N bond formation.[12,18]



Scheme 2. Direct reductive hydroamination of phenylacetylene with *p*-anisidine.



Scheme 3. Hydrogenation of the *N*-phenylimine **12l**.

After the gold(I)-catalyzed intermolecular hydroamination cooperative enantioselective phosphoric acid catalyzed hydrogenation of the ketimine intermediate **12** takes place through the formation of a chiral ion pair and hydrogen bonding.[19] Finally, the iminium ion is reduced by Knölker's iron complex **2** similar to that reported by Goodman[20] to form the chiral amine **6a**. To explore the scope and limitations of the presented catalytic system in more detail, reductive hydroamination reactions of different terminal alkynes **4** with *p*-anisidine **5a** were carried out. As shown in Table 3, various aromatic alkynes were reductively hydroaminated smoothly in high yields with excellent enantioselectivities. Both electron-donating and -withdrawing substituents on the aromatic ring at *meta*- or *para*-positions had little impact on the reductive hydroamination activity and high enantioselectivities were observed for unsubstituted as well as *meta*- and *para*-substituted 2-aryl alkynes with *p*-anisidine (91–94% *ee*; Table 3, entries 1, 2, 4, and 5).

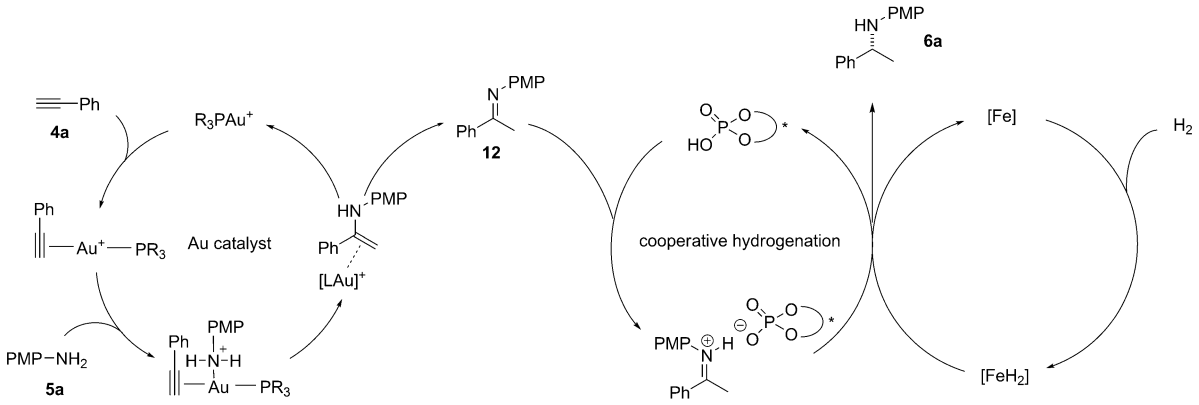
Gratifyingly, disubstituted alkynes and 4-ethynalbiphenyl were also transformed with high yield and enantioselectivity (81–93% *ee*; Table 3, entries 6 and 7). While acetophenoneimines are typical substrates for asymmetric hydrogenation reactions, we were also interested in using more challenging chiral dialkyl amines. Indeed, the reductive hydroamination of aliphatic alkynes occurred with high yields and good enantioselectivities (75–86% yield; 67–70% *ee*, Table 3, entries 9 and 10).

Finally, the reductive hydroamination of phenylacetylene **4a** with different anilines was investigated. *Meta*- and *para*-substituted anilines with both electron-donating and -withdrawing groups reacted with phenylacetylene **4a** smoothly with excellent yields up to 96% and enantioselectivities up to 93% to the corresponding amines (Table 3, entries 11, 12, and 14–16). Also heterocyclic primary amines like benzothiophene-6-amine can be used in the reported reductive hydroamination procedure to give 94% *ee* (Table 3, entry 17).

Unfortunately, aliphatic amines and anilines with electron-withdrawing groups in the *ortho*-position did not react under the optimized conditions. The secondary amine *N*-methylaniline gave a lower yield of 25% but only the racemic amine was formed.

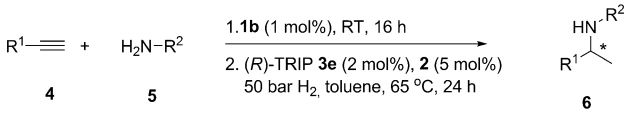
Conclusion

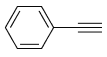
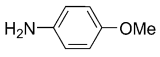
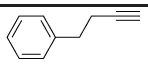
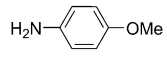
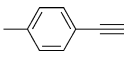
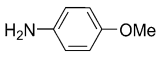
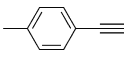
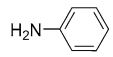
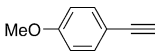
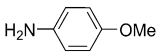
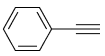
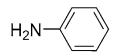
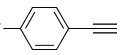
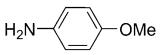
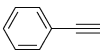
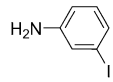
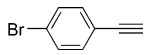
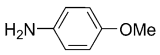
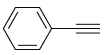
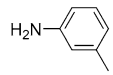
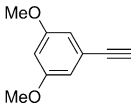
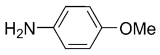
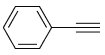
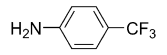
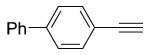
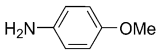
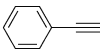
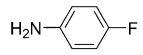
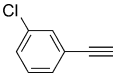
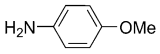
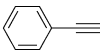
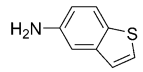
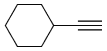
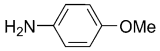
We have demonstrated the enantioselective reductive hydroamination of alkynes with primary amines in the presence of molecular hydrogen as the reducing agent. Key to success is the use of a three-component catalyst system consisting of a hydroamination, an imine activation, and a hydrogen activation catalyst. Notably, Au^I complexes do not interfere significantly with the iron-catalyzed stereoselective hydroamination. In general, this reaction sequence constitutes an interesting alternative to the classic reductive amination protocols. Excellent enantioselectivities and high yields were observed for a variety of alkynes and amines.



Scheme 4. Proposed mechanism for the sequential reductive hydroamination of alkynes with amines.

Table 3. Reductive hydroamination of different alkynes and amines.[a]



Entry	Alkyne		Amine		Yield [%][b]	*ee* [%][c]	Entry	Alkyne		Amine		Yield [%][b]	*ee* [%][c]
1		**4a**		**5a**	**6a** 76	94	10		**4j**		**5a**	**6j** 86	67
2		**4b**		**5a**	**6b** 71	93	11		**4k**		**5k**	**6k** 84	87
3		**4c**		**5a**	**6c** 72	79	12		**4a**		**5k**	**6l** 91	87
4		**4d**		**5a**	**6d** 74	94	13		**4a**		**5m**	**6m** 76	90
5		**4e**		**5a**	**6e** 73	91	14		**4a**		**5n**	**6n** 96	93
6		**4f**		**5a**	**6f** 76	93	15		**4a**		**5o**	**6o** 82	86
7		**4g**		**5a**	**6g** 76	81	16		**4a**		**5p**	**6p** 83	90
8		**4h**		**5a**	**6h** 75	75	17		**4a**		**5q**	**6q** 93	94
9		**4i**		**5a**	**6i** 75	70							

[a] General reaction conditions: alkyne **4** (0.5 mmol), amine **5** (0.5 mmol), **1b** (1 mol%), toluene (0.5 mL), RT, 16 h, then (*R*)-TRIP **3e** (2 mol%), **2** (5 mol%), H_2 (50 bar) at 65 °C for 24 h. [b] Isolated yield of the pure product. [c] Determined by chiral HPLC analysis.

Experimental Section

All experiments have been performed in 4 mL glass vials. The hydrogen experiments were carried out in a Parr Instruments 4560 series autoclave (300 mL) containing an alloy plate with wells for seven 4 mL glass vials.

Representative experimental procedure: A vial was charged under an argon atmosphere inside a glove box with alkyne **4** (0.5 mmol), amine **5** (0.5 mmol), $(t\text{Bu})_2(o\text{-diphenyl})\text{PAuBF}_4$ (**1b**) (0.005 mmol), dry toluene (0.2 mL), and a magnetic stirring bar and capped with a septum. The mixture was stirred for 16 h at room temperature. (*R*)-TRIP **3e** (0.01 mmol in 0.2 mL toluene) and iron complex **2** (0.025 mmol) were added and the septum was equipped with a needle. The vial was placed in the alloy plate, which was then placed into the predried autoclave. Once sealed, the autoclave was purged 3 times with hydrogen, then pressurized to 50 bar and heated at 65 °C for 24 h. The autoclave was cooled to RT, depressurized, and the reaction mixture was transferred to a flask, evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: heptane/ethyl acetate = 10:1) to give the corresponding amine **6**, which was then analyzed by HPLC to determine the *ee* value.

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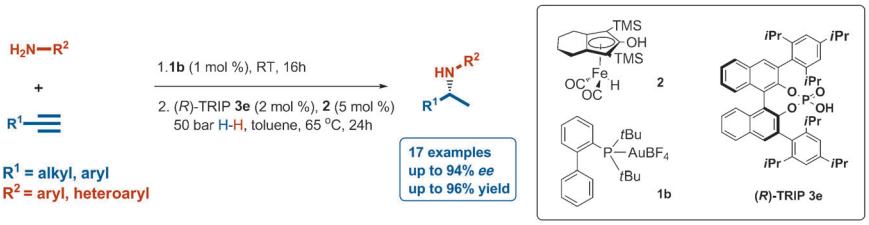

The three musketeers! The enantioselective reductive hydroamination of alkynes with primary amines in the presence of molecular hydrogen as the reducing agent is demonstrated (see scheme). Key to success is the use of a three-component catalyst system consisting of a hydroamination, an imine activation, and a hydrogen activation catalyst.

Enantioselectivity

*S. Fleischer, S. Werkmeister, S. Zhou, K. Junge, M. Beller** ..... ▮▮▮▮–▮▮▮▮

Consecutive Intermolecular Reductive Hydroamination: Cooperative Transition-Metal and Chiral Brønsted Acid Catalysis