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Copper-catalysed selective hydroamination reactions of alkynes

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The development of selective reactions that utilize easily available and abundant precursors for the efficient synthesis of amines is a long-standing goal of chemical research. Despite the centrality of amines in a number of important research areas, including medicinal chemistry, total synthesis and materials science, a general, selective and step-efficient synthesis of amines is still needed. Here, we describe a set of mild catalytic conditions utilizing a single copper-based catalyst that enables the direct preparation of three distinct and important amine classes (enamines, α-chiral branched alkylamines and linear alkylamines) from readily available alkyne starting materials with high levels of chemo-, regio- and stereoselectivity. This methodology was applied to the asymmetric synthesis of rivastigmine and the formal synthesis of several other pharmaceutical agents, including duloxetine, atomoxetine, fluoxetine and tolterodine.

Complex organic molecules play a crucial role in the study and treatment of disease. The extent to which they can be utilized in these endeavours depends on the efficient and selective chemical methods for their construction[1]. Amines are widely represented in biologically active natural products and medicines[2] (a small selection of which are shown in Fig. 1a). Consequently, the selective assembly of amines from readily available precursors is a prominent objective in chemical research[3]. There are a number of powerful methods that address this challenge, including metal-catalysed cross-coupling[4,5], nucleophilic addition to imines[6], C–H nitrogen insertion[7] and enzymatic methods[8,9]. However, the direct production of amines from simple olefins or alkynes represents a highly attractive alternative, given the abundance and accessibility of these starting materials. For this reason, the addition of nitrogen and hydrogen across carbon–carbon multiple bonds (hydroamination) has long been pursued as a means to access amines[10–12]. Although much progress has been made, a generally effective strategy to achieve chemo-, regio- and enantioselective hydroamination of simple alkenes or alkynes remains elusive.

We became interested in developing hydroamination reactions of alkynes as a convenient and powerful means of accessing aminated products (Fig. 1b). Reactions that employ alkynes as starting materials are synthetically versatile, because alkynes can be prepared by a variety of strategies, including Sonogashira coupling[13], nucleophilic addition of metal acetylides[14] and homologation of carbonyl groups[15]. In addition, one or both π-bonds of alkynes may be utilized, further increasing their flexibility as starting materials. For these reasons, the hydrofunctionalization of alkynes has recently become an active area of research[16–22]. We recently detailed[23] (as have Hirano and Miura[24]) catalyst systems for the asymmetric hydroamination of styrenes that operate through the addition of a catalytic copper hydride species[25–32] to a carbon–carbon double bond followed by carbon–nitrogen bond formation using an electrophilic nitrogen source[33–36]. We surmised that we could apply this approach to the selective functionalization of alkynes wherein alkyne hydrocupration would give a stereodefined vinylcopper intermediate. We anticipated that, in analogy to our previous work, direct interception of this intermediate would potentially enable the stereoselective formation of enamines (Fig. 1b, A). Enamines are versatile intermediates in organic synthesis, and although catalytic methods have been developed for their synthesis by alkyne hydroamination, control of the regio- and stereochemistry of enamine formation is non-trivial[16].

In addition to enamine synthesis, we speculated on the possibility that conditions could be developed to convert alkynes to enantioenriched α-branched alkylamines and/or linear alkylamines in one synthetic operation (Fig. 1b, B). Such cascade processes are highly desirable in organic synthesis, because potentially difficult work-up and isolation steps can be avoided and the generation of chemical waste is minimized[37]. In particular, we envisioned a scenario in which the starting alkyne is initially reduced to a transiently formed alkene, which would then undergo hydroamination to afford the alkylamine product. If successful, this approach would be particularly attractive due to the ease and low cost of the Sonogashira process for the preparation of alkyne starting materials relative to the cross-coupling of stereodefined vinylmetal reagents or other routes used to access geometrically pure alkenes for hydroamination. We were aware that, mechanistically, the vinyl- and alkylcopper intermediates in the proposed process are required to react in a highly chemoselective manner (Fig. 1c). Specifically, the vinylcopper species formed upon hydrocupration of the alkyne would need to be selectively intercepted by the proton source in the presence of the aminating reagent to furnish the intermediate alkene, while the alkylcopper species formed upon hydrocupration of this alkene would need to selectively engage the electrophilic nitrogen source in the presence of a proton donor to ultimately furnish the desired alkylamine product. Although both steps (that is, alkyne semireduction[38–40] and alkene hydroamination[23]) are well precedented, the ability to achieve the desired selectivity in one pot via a cascade sequence has never been demonstrated[41,42]. Here, we report mild and scalable conditions for the highly chemo-, regio- and stereoselective synthesis of enamines ('direct hydroamination') and alkylamines ('reductive hydroamination') products from alkynes, using a single copper catalyst system.

Results and discussion

Direct hydroamination: development and scope. To assess the feasibility of the outlined alkyne hydroamination (Fig. 1b, A), we treated 1,2-diphenylacetylene (**1a**) with *N*,*N*-dibenzyl-*O*-benzoylhydroxylamine (**2a**, 1.2 equiv.) and an excess of diethoxymethylsilane (**3**) in the presence of 2 mol% copper

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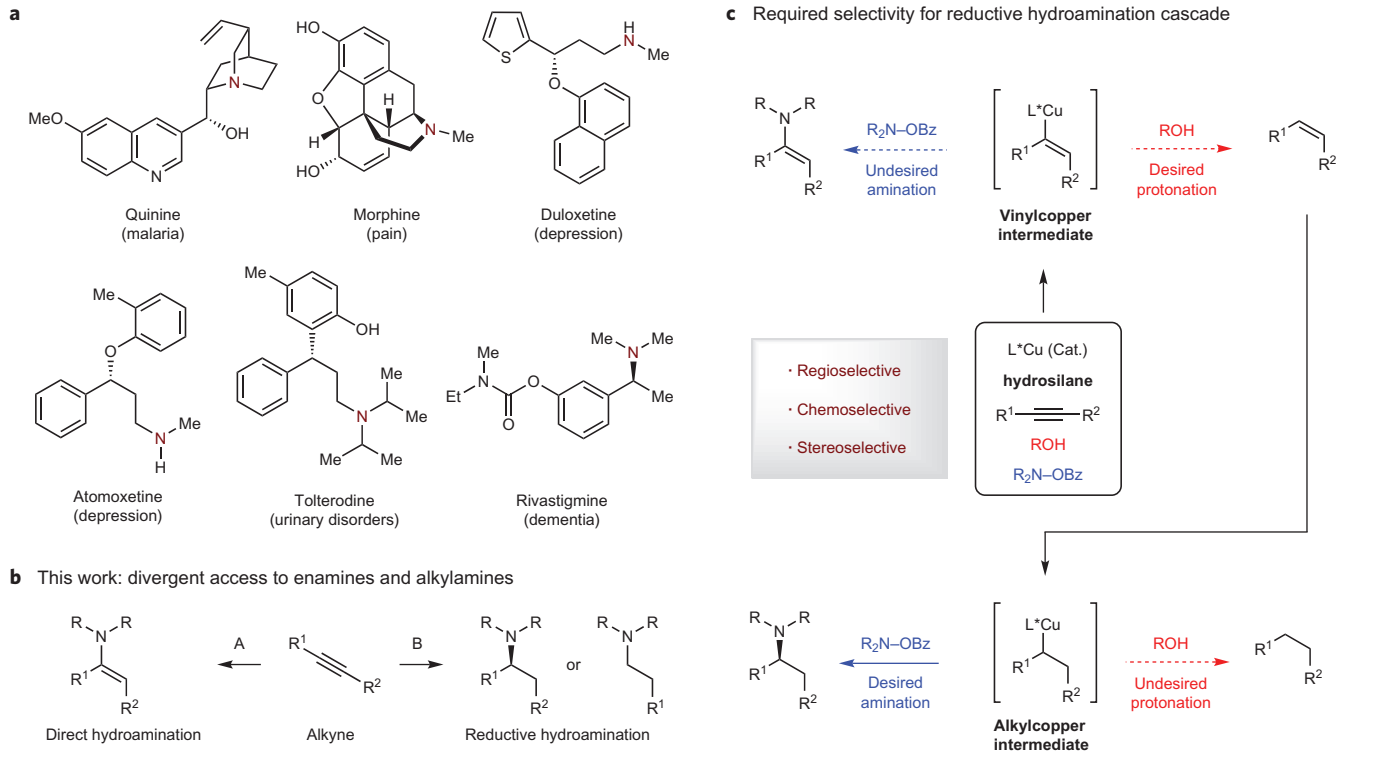


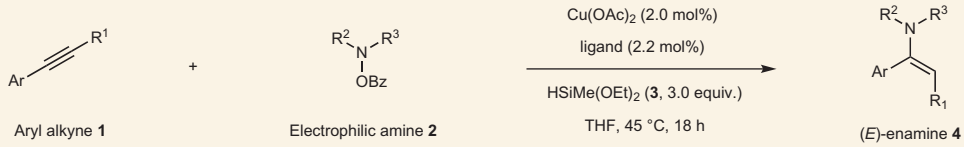
Figure 1 | Bioactive amines, the synthesis of amines from alkynes, and the reductive hydroamination cascade strategy. a, Representative alkaloids and drugs demonstrating the ubiquitous nature of amines in bioactive organic molecules. **b**, Catalytic hydroamination of alkynes to generate three product classes. **c**, Contrasting reactivities of vinyl- and alkylcopper intermediates required to achieve a reductive hydroamination cascade.

acetate and a range of phosphine ligands. A number of ligands could be used to perform the direct hydroamination reaction, and the resulting enamine **4a** was efficiently produced as a single geometric isomer, as determined by ^{1}H NMR analysis (Table 1, entries 1–4). Although copper catalysts based on 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene (BINAP, **L1**), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos, **L2**) or 4,4′-bi-1,3-benzodioxole-5,5′-diylbis(diphenylphosphane) (SEGPHOS, **L3**) were effective in this context, the catalyst based on 5,5′-bis[di(3,5-di-tert-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole (DTBM-SEGPHOS, **L4**) was found to be the most efficient and generally applicable. We then evaluated the substrate scope of this reaction and, as shown in entries 5–9, a diverse range of aryl-substituted internal alkyne substrates could be converted to the corresponding (*E*)-enamines **4** with complete stereoselectivity (**4b**–**4e**; 80–99%). Notably, sterically hindered amines, which were problematic substrates for previously reported hydroamination reactions of alkynes[43], could be successfully transformed using the current conditions (**4b** and **4d**). More importantly, direct hydroamination of unsymmetrical internal alkynes occurred with excellent regioselectivity (**4c**–**4e**; >19:1). In addition, we found that a 1,2-dialkylacetylene was left intact under these conditions (**4e**) and pharmaceutically important heterocycles, including morpholine (**4c**), thiophene (**4d**), piperidine (**4e**) and pyrimidine (**4e**), were well-tolerated. Although the direct hydroamination of terminal alkynes to construct monosubstituted enamines was not successful, the current method represents a rare example of a highly regio- and stereoselective hydroamination of internal alkynes for the construction of dialkyl enamines[43].

Reductive hydroamination: development and scope. As previously described, we were hopeful that the addition of a protic additive could divert this reaction from direct alkyne hydroamination to the outlined reductive hydroamination by selective protonation of the formed vinylcopper intermediate (Fig. 1c). Indeed, inclusion of methanol as an additive under the reaction conditions in Table 1 resulted in the formation of the desired reductive hydroamination product **5a** in moderate yield, along with a significant amount of enamine **4a** (18%) and stilbene (17%) as side products (Table 2, entry 1). Fortunately, an evaluation of alcohol additives revealed that ethanol was a suitable proton source, which minimized the formation of these side products to afford benzylamine **5a** in excellent yield and high enantioselectivity (entry 2, 92% yield, 89% e.e.). Interestingly, in contrast to the direct alkyne hydroamination protocol for enamine formation, **L4** was uniquely able to perform the reductive hydroamination cascade reaction. Reaction utilizing copper catalysts based on **L1**, **L2** or **L3** provided only enamine **4a** in high yields, even in the presence of ethanol (entries 4–6). We attribute the success of the catalyst system based on **L4** to the ability of the CuH species to hydrocuprate alkynes and alkenes more rapidly. In contrast, the hydrocupration of alkynes occurred less efficiently when **L1**–**L3** were used, resulting in consumption of the alcohol additive by the CuH before alkyne hydrocupration could take place. Therefore, only the enamine product was obtained in these cases. In addition, we found that arylacetylenes could also undergo reductive hydroamination, although in the case of these substrates, isopropanol was a superior protic additive (entry 8).

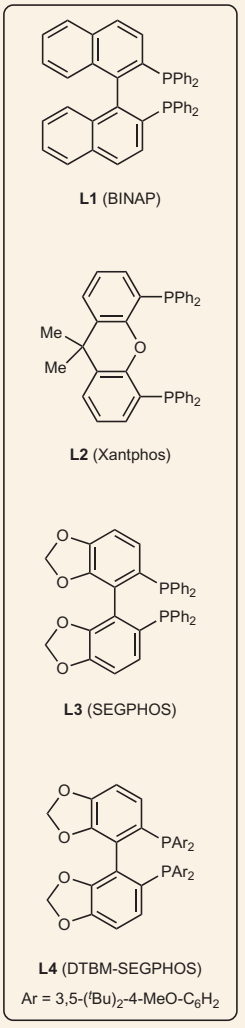
Under the optimized set of reaction conditions, a range of chiral benzylamine derivatives could be prepared in moderate to high yield (61–85%) with very high levels of enantioselectivity (≥97% e.e., Table 3). These mild catalytic conditions tolerated a range of common functional groups including ethers (**5c**, **5h**), alcohols (**5i**), aryl halides (**5e**, **5f**), pyridines (**5d**), indoles (**5g**), acetals (**5j**) and ketals (**5m**, **5n**). Moreover, a reaction conducted on a 10 mmol scale proceeded efficiently in the presence of 1 mol% catalyst, furnishing the product in undiminished yield and enantioselectivity (**5j**). The applicability of new synthetic methods to the late-stage

Table 1 | Optimization and scope of copper-catalysed direct hydroamination of aryl alkynes.



Aryl alkyne **1** + Electrophilic amine **2** → (*E*)-enamine **4**

Entry	1	2	Ligand	4	Yield
1			*rac*-**L1**		90%
2			**L2**		95%
3			*rac*-**L3**		87%
4	**1a**	**2a**	*rac*-**L4**	**4a**	99%
5*			*rac*-**L4**		99% (88%)
6*	**1a**	**2b**	*rac*-**L4**	**4b**	99% (93%)†
7*	**1b**	**2c**	*rac*-**L4**	**4c**	97%‡ (94%)
8*	**1c**	**2d**	*rac*-**L4**	**4d**	80%‡ (70%)
9*	**1d**	**2e**	*rac*-**L4**	**4e**	90%‡ (85%)

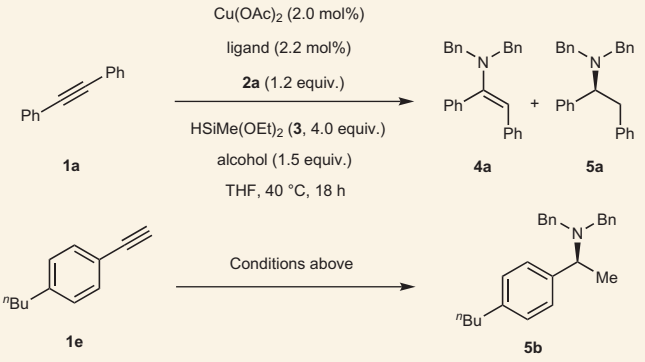


Conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), **3** (0.6 mmol), $Cu(OAc)_2$ (2.0 mol%), ligand (2.2 mol%), THF (1 M), 45 °C, 18 h. Yields and stereoselectivities were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. In all cases only (*E*)-enamine products were observed.
*Conditions: **1** (1.0 mmol), **2** (1.2 mmol), **3** (3.0 mmol), $Cu(OAc)_2$ (2.0 mol%), *rac*-**L4** (2.2 mol%), THF (1 M), 45 °C, 18 h. Isolated yields of products after reduction are given in parentheses (average of two runs). †Isolated yield of enamine after purification by flash column chromatography. ‡Major regioisomers are shown; in all cases, <5% of the minor regioisomer was observed as determined by ^{1}H NMR analysis of the crude enamine product.

modification of complex natural products is a highly desirable feature, as analogues of bioactive molecules can be prepared without the need for *de novo* synthesis. Accordingly, readily available alkynes derived from the natural products δ-tocopherol and oestrone were subjected to asymmetric reductive hydroamination conditions to afford aminated products with good yields and excellent catalyst-controlled diastereoselectivities (d.r.: 99:1, **5k–5n**). It is noteworthy that in all reductive hydroamination reactions employing aryl-substituted alkynes, the amination products were delivered with exclusive Markovnikov regioselectivity, with C–N bond formation occurring adjacent to the aryl group.

In addition to aryl-substituted alkynes, we found that terminal aliphatic alkynes readily participate in catalytic reductive hydroamination to deliver alkylamines (Table 4). In contrast to aryl-substituted alkynes, anti-Markovnikov regioselectivity was observed when simple alkylacetylene substrates were used, giving rise to linear tertiary amines in high yields (71–88% yield). We note that it was crucial to use a slight excess of isopropanol compared to the alkylacetylene substrate in the case of terminal alkyne substrates, probably due to deactivation of the catalyst through formation of a copper acetylide species when the amount of isopropanol was insufficient[40]. It is noteworthy that this methodology could be applied to a substrate bearing an unprotected secondary amine to provide 1,3-diamine **6a** in high yield. Furthermore, alkynol silyl ethers were suitable substrates for the current method. Upon reductive hydroamination and silyl deprotection, 1,3-amino alcohol products were prepared in good yields (**6f**, **6g**). An enantioenriched 1,3-amino alcohol could be generated from the optically active alkynol silyl ether (98% e.e.) without erosion of enantiomeric excess (**6g**, 98% e.e.). The use of

Table 2 | Optimization of reductive hydroamination.



Entry	Substrate	Ligand	Alcohol	Yield 4a	Yield 5a or 5b (e.e.)
1	**1a**	(*R*)-**L4**	MeOH	18%	60% (89% e.e.)
2	**1a**	(*R*)-**L4**	EtOH	2%	92% (89% e.e.)
3	**1a**	(*R*)-**L4**	^{i}PrOH	2%	83% (89% e.e.)
4	**1a**	(*R*)-**L1**	EtOH	83%	0
5	**1a**	**L2**	EtOH	95%	0
6	**1a**	(*R*)-**L3**	EtOH	80%	0
7	**1e**	(*R*)-**L4**	EtOH	–*	78% (99% e.e.)
8†	**1e**	(*R*)-**L4**	^{i}PrOH	–*	83% (99% e.e.)

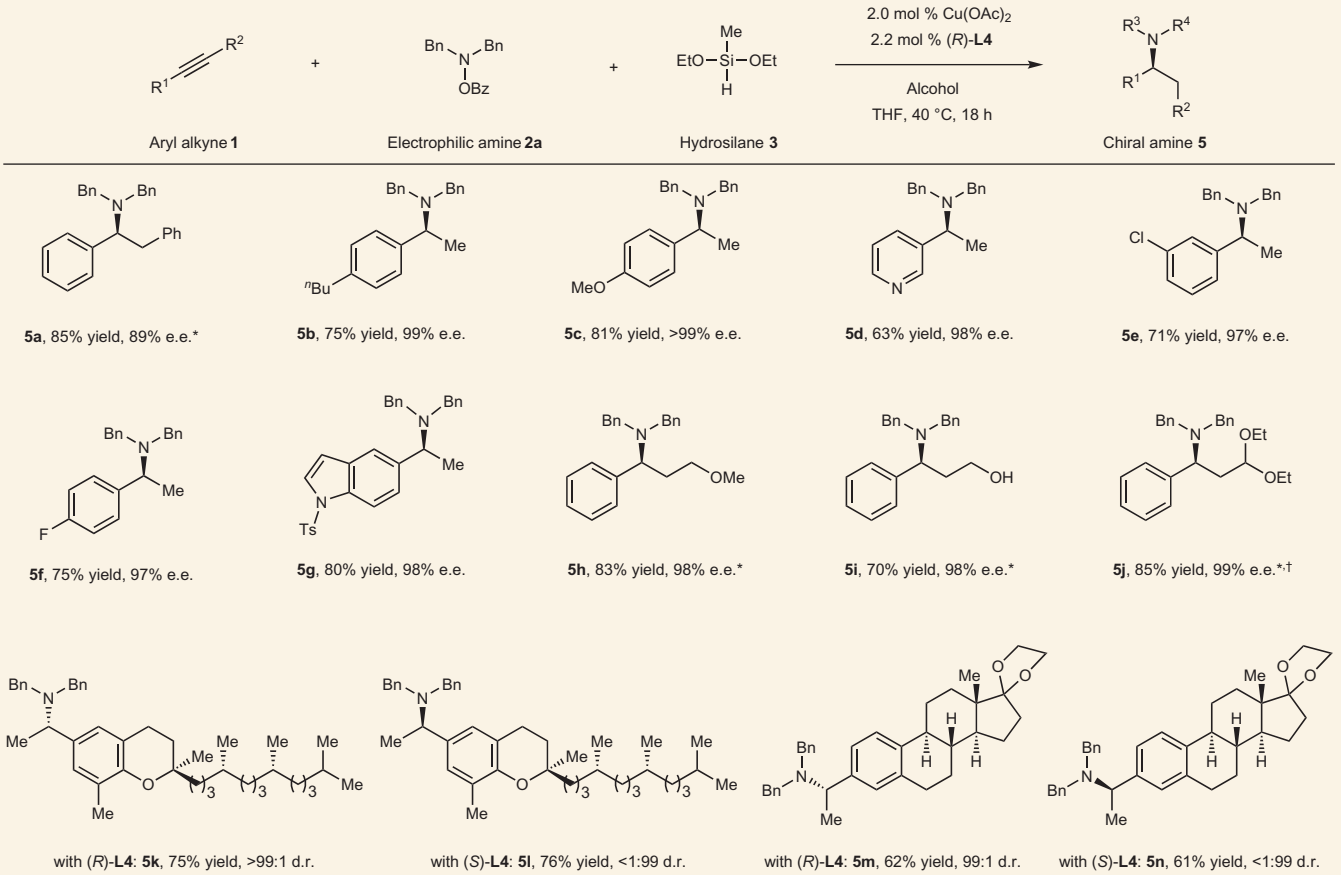
Conditions: **1a** or **1e** (0.2 mmol), **2a** (0.24 mmol), **3** (0.8 mmol), alcohol (0.3 mmol), $Cu(OAc)_2$ (2.0 mol%), ligand (2.2 mol%), THF (1 M), 40 °C, 18 h. Yields were determined by gas chromatography using dodecane as an internal standard. Enantiomeric excesses (e.e.) were determined by HPLC analysis using chiral stationary phases. *The corresponding enamines were not observed. †Conditions: **1e** (1.1 mmol), **2a** (1.0 mmol), **3** (4.0 mmol), *i*-PrOH (1.2 mmol), $Cu(OAc)_2$ (2.0 mol%), (*R*)-**L4** (2.2 mol%), THF (1 M), 40 °C, 18 h.

the current reductive hydroamination methodology, in conjunction with well-developed methods for the asymmetric synthesis of alkynols[14], represents an attractive approach for the synthesis of these biologically relevant compounds.

Application to drug synthesis. The functionalized amines obtained by the cascade hydroamination developed in this study have broad utility. To illustrate this point, 1,3-amino alcohol **6f** can be readily transformed to the antidepressant drug duloxetine following the literature procedure[44] (Fig. 2a). Moreover, 1,3-amino alcohol **6g** is a key intermediate for the synthesis of the attention deficit hyperactivity disorder (ADHD) drug atomoxetine[45], as well as the antidepressant drug fluoxetine[46] (Fig. 2b). Furthermore, diisopropylamine **8** could be prepared by reductive hydroamination of readily synthesized alkyne **7** (Fig. 2c). Tolterodine, a drug used for symptomatic treatment of urinary incontinence, could be prepared by demethylation of **8**[47]. Our method was also applied to a new two-step synthesis of rivastigmine, a drug used to treat dementia (Fig. 2d). Condensation of commercially available reagents gave carbamate **9**, which, upon asymmetric reductive hydroamination, furnished the target in an enantiopure form and good chemical yield. These syntheses exemplify the potential utility of the current hydroamination method for the rapid and efficient construction of medicinally relevant molecules.

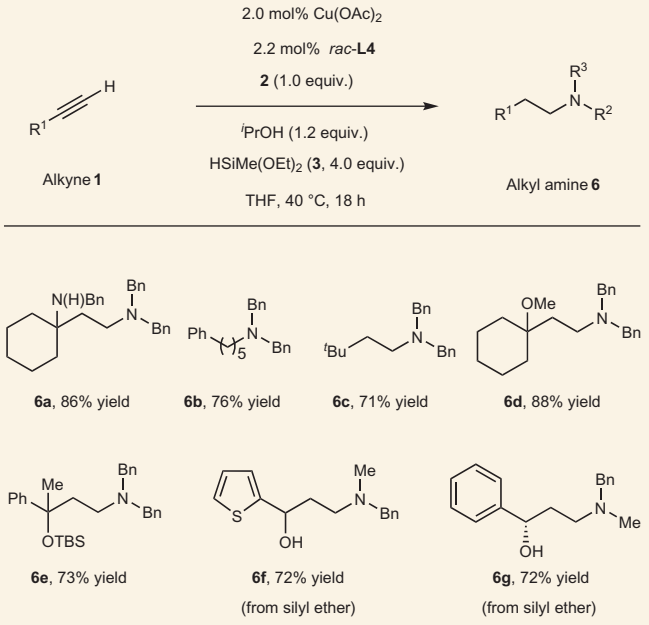
Mechanistic discussion. The proposed mechanisms for the formation of enamines and alkylamines (Fig. 3a) both commence with *syn*-selective Cu–H addition to the alkyne substrate to give vinylcopper species **11**. In the absence of a proton source

Table 3 | Scope of copper-catalysed reductive hydroamination of aryl alkynes.



Conditions: **1** (1.1 mmol), **2** (1.0 mmol), **3** (4.0 mmol), *i*-PrOH (1.2 mmol), $Cu(OAc)_2$ (2.0 mol%), (*R*)-**L4** (2.2 mol %), THF (1 M), 40 °C, 18 h. Isolated yields are reported (average of two runs). Enantiomeric excesses (e.e.) and diastereomeric ratios (d.r.) were determined by HPLC analysis.
*Using EtOH instead of *i*-PrOH. †Reaction performed on 10 mmol scale using 1 mol% of catalyst. See Supplementary Section 3 for details.

Table 4 | Reductive hydroamination of alkylacetylenes.



Conditions: **1** (1.1 mmol), **2** (1.0 mmol), **3** (4.0 mmol), *i*-PrOH (1.2 mmol), $Cu(OAc)_2$ (2.0 mol%), *rac*-**L4** (2.2 mol%), THF (1 M), 40 °C, 18 h. Isolated yields are reported (average of two runs). See Supplementary Section 3 for details.

(alcohol), direct interception by electrophilic amine **2** (likely via oxidative addition/reductive elimination) would produce the (*E*)-enamine product **4** and copper benzoate complex **13** that, upon transmetallation with hydrosilane, would regenerate the active CuH species **10**. On the other hand, in the presence of alcohol, direct protonation of the vinylcopper intermediate **11** could afford the *cis* disubstituted alkene **14**. A hydroamination similar to that we have previously reported via alkylcopper species **15** and **16** would deliver the alkylamine **5**. As previously detailed, these amination protocols both provide products in excellent regioselectivity; aryl-substituted internal alkynes (and alkenes) proceed through a Markovnikov selective hydrocupration event and terminal aliphatic alkynes (and alkenes) undergo anti-Markovinikov hydrometallation. This regioselectivity is in accord with results previously reported for copper-catalysed alkyne semireduction[39,40] and hydroamination[23]. We rationalize the Markovnikov regioselectivity observed for aryl alkynes as arising from the electronic stabilization of the vinyl- or alkylcopper species by an adjacent aryl group. In contrast, we attribute the anti-Markovnikov selectivity observed in the case of terminal aliphatic alkynes to steric effects (that is, formation of the less substituted vinyl- or alkylcopper species).

We conducted mechanistic experiments to gain a better understanding of the factors that result in the high selectivities observed in our system. Subjecting enamine **4a** to the conditions developed for either alkyne hydroamination or reductive hydroamination resulted in no observed reaction (Fig. 3b). The inertness of the enamine under these conditions accounts for the exclusive formation of monoamination product in the case of alkyne hydroamination. In addition, these experiments suggest that alkyne hydroamination followed by enamine reduction does not occur in the case of reductive hydroamination. Furthermore, we subjected *cis*-stilbene (**18**) to the hydroamination conditions in the presence of 1.5 equiv. ethanol (Fig. 3c). Although a small amount of 1,2-diphenylethane (**19**, 3% yield) was formed, presumably as a result of protonation of the alkylcopper intermediate[48], hydroamination adduct **5a** was generated as the predominant product (97% yield). This result suggests that amination of the alkylcopper species **15** occurs selectively in the presence of a proton source. Combined, the results of these experiments are in agreement with our original hypothesis that vinylcopper species **11** and alkylcopper species **15** undergo selective protonation and amination, respectively, thereby allowing the desired cascade reaction to proceed as designed.

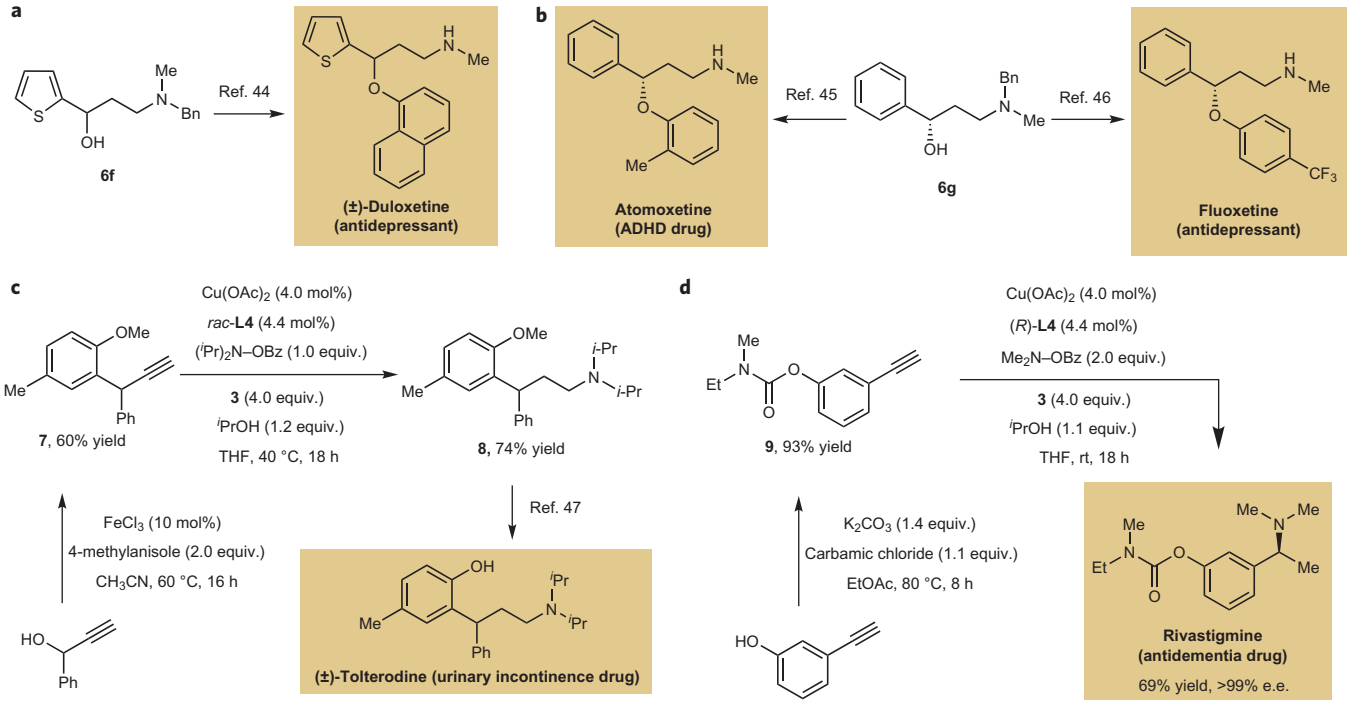


Figure 2 | Concise routes to drugs through cascade reductive hydroamination of alkynes. a, Hydroamination product **6f** as a key synthetic precursor for duloxetine synthesis. **b**, Hydroamination product **6g** as a known synthetic precursor to atomoxetine and fluoxetine. **c**, Rapid synthesis of **8**, a known precursor to tolterodine. **d**, Two-step synthesis of rivastigmine.

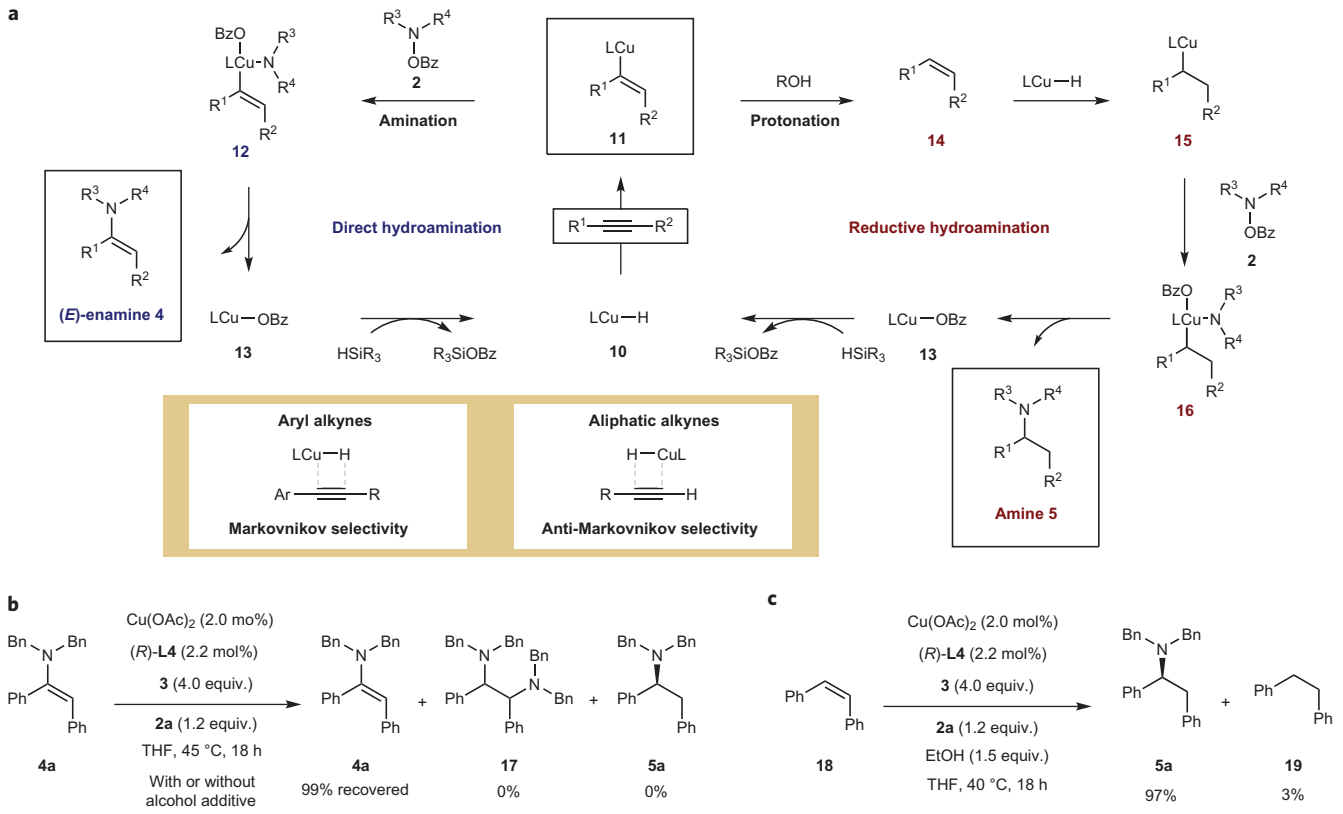


Figure 3 | Proposed catalytic cycles and mechanistic experiments. a, Both direct hydroamination and reductive hydroamination are proposed to proceed through vinylcopper intermediate **11**. In the absence of alcohol additive, electrophilic amination occurs directly to give the enamine product (left cycle). In the presence of alcohol additive, protonation of **11** affords alkene **14**, which undergoes further hydrocupration and electrophilic amination to furnish the alkylamine product (right cycle). Internal aryl alkynes and terminal aliphatic alkynes undergo hydrocupration with Markovnikov and anti-Markovnikov regioselectivity, respectively. **b**, Enamine **4a** is inert to direct hydroamination conditions (no alcohol additive), thus accounting for the lack of over-reduction or diamination products observed under these conditions. Enamine **4a** is also inert to reductive hydroamination conditions (alcohol additive present). Enamine **4a** is thus unlikely to be an intermediate in the reductive hydroamination reaction. **c**, In the presence of ethanol as a proton source and electrophilic amination reagent **2a**, *cis*-stilbene selectively undergoes hydroamination rather than reduction. Hence, the presence of alcohol does not interfere with the hydroamination of proposed alkene intermediate **14**, allowing the reductive hydroamination cascade to proceed efficiently to afford the alkylamine product.

Conclusion

We have developed catalytic conditions that allow for the controlled construction of enamines or alkylamines from alkynes and electrophilic amine sources. The products from these complementary systems were obtained with uniformly high levels of regio- and stereocontrol. Both catalytic processes operate through the formation of a vinylcopper intermediate, the product being determined by the presence or absence of an alcohol additive. The development of a protocol for the direct conversion of alkynes to alkylamines is especially notable, given the ease of access to requisite substrates and the demonstrable applicability of this method to the rapid synthesis of a number of pharmaceutical agents. Beyond the broad utility of this new protocol, we anticipate that this cascade strategy will motivate the design of other cascade processes for the more efficient synthesis of valuable targets.

Methods

A typical procedure for the copper-catalysed reductive hydroamination of alkynes **1** is as follows (all reactions were set up on the benchtop using a standard Schlenk technique). An oven-dried screw-top reaction tube equipped with a magnetic stir bar was charged with $Cu(OAc)_2$ (3.6 mg, 0.02 mmol, 2 mol%) and (*R*)-**L4** (26 mg, 0.022 mmol, 2.2 mol%). The reaction tube was sealed with a screw-cap septum, then evacuated and backfilled with argon (this process was repeated a total of three times). Anhydrous THF (0.5 ml) and hydrosilane **3** (0.64 ml, 4.0 mmol, 4.0 equiv.) were added sequentially via syringe. The resulting mixture was stirred at room temperature (RT) for 15 min and the colour of the mixture changed from blue to orange. A second oven-dried screw-top reaction tube equipped with a stir bar was charged with alkyne substrate **1a** (178 mg, 1.0 mmol, 1.0 equiv.) and hydroxylamine ester **2a** (381 mg, 1.2 mmol, 1.2 equiv.). The reaction tube was sealed with a screw-cap septum, and then evacuated and backfilled with argon (this process was repeated a total of three times). Anhydrous THF (0.5 ml) and EtOH (88 µl, 1.5 mmol, 1.5 equiv.) were added, followed by dropwise addition of the catalyst solution from the first vial to the stirred reaction mixture at RT. The reaction mixture was then heated at 40 °C for 18 h. After cooling to RT, the reaction was quenched by addition of EtOAc and a saturated aqueous solution of Na_2CO_3. The phases were separated, the organic phase was concentrated, and product **5a** was purified by flash column chromatography. The e.e. of each product was determined by HPLC analysis using chiral stationary phases. All new compounds were fully characterized (see Supplementary Information).

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Author contributions

S-L.S. and S.L.B. designed the project, analysed the data and wrote the manuscript. S-L.S. performed the experiments.

Additional information

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Competing financial interests

The authors declare no competing financial interests.