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A direct approach to amines with remote stereocenters by enantioselective CuH-catalysed reductive relay hydroamination

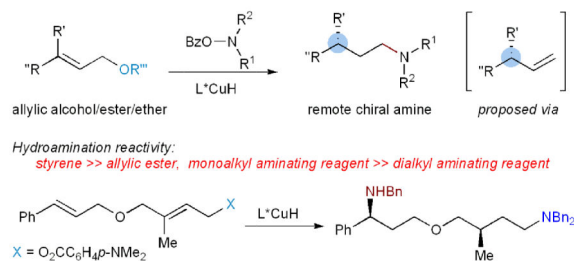
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Abstract

Amines with remote stereocenters (stereocenters that are three or more bonds away from the C–N bond) are important structural elements in many pharmaceutical agents and natural products. However, previously reported methods to prepare these compounds in an enantioselective manner are indirect and require multistep synthesis. Here we report a copper hydride-catalysed, enantioselective synthesis of γ - or δ -chiral amines from readily available allylic alcohols, esters, and ethers using a reductive relay hydroamination strategy (a net reductive process in which an amino group is installed at a site remote from the original C–C double bond). The protocol was suitable for substrates containing a wide range of functional groups and provided remote chiral amine products with high levels of regio- and enantioselectivity. Sequential amination of substrates containing several carbon-carbon double bonds could be achieved, demonstrating the high chemoselectivity of this process.

Graphical Abstract



Single operation transformations that enantioselectively install a stereogenic center while introducing a distal functional group are synthetically valuable but rare processes. Now, a copper-

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Author contributions

S.Z. and S.L.B. designed the project. S.Z., N.N., and S.L.B. co-wrote the manuscript, analyzed the data, discussed the results and commented on the manuscript. S.Z. and N.N. performed the experiments.

Supplementary information is available in the online version of the paper.

Competing financial interests

The authors declare no competing financial interests.

catalysed reductive relay hydroamination process that simultaneously creates a remote chiral center is described. The resulting γ - and δ -chiral amines are important structural elements in many pharmaceutical agents and natural products.

Aliphatic amines are featured prominently in therapeutic agents and clinically useful natural products and are often crucial for their biological activity¹. Consequently, synthetic organic chemists have long pursued general, efficient, and selective methods for the introduction of this functional group. Moreover, because the biological activities of stereoisomers may differ, methods for the synthesis of amines in high stereochemical purity are particularly valuable². Although approaches to chiral amines have been developed using a variety of strategies¹, these generally only allow control over the stereocenters α or β to the newly introduced amine. The concomitant construction of well-defined stereocenters at sites remote from a newly introduced functional group remains a long-standing challenge for synthetic organic chemists³⁻⁵. Despite the presence of amines containing remote stereocenters in a considerable number of biologically active molecules (see Fig. 1b), there are no reported direct asymmetric transformations that allow for the preparation of this structural motif. Known approaches to install this subunit require time-consuming multistep sequences, severely slowing, for example, high throughput production of analogues for screening in medicinal chemistry.

In this work, we describe a CuH-catalysed⁶⁻⁸ reductive relay⁹⁻¹² hydroamination¹³⁻¹⁵ strategy for the enantioselective synthesis of chiral amines bearing stereogenic centers γ - and δ - to the amino group (γ - and δ -chiral amines). Previously, we have reported¹⁶⁻¹⁹ (as have Hirano and Miura^{20,21}) the CuH-catalysed syntheses of α -chiral amines by the Markovnikov hydroamination of functionalized olefins (Fig. 1a, box I) and β -chiral amines by the anti-Markovnikov hydroamination of 1,1-disubstituted aliphatic alkenes (Fig. 1a, box II)²². The idea for our approach to the synthesis of remote-chiral amines stemmed from the observation that the reaction of allylic ethers, under our previously reported hydroamination conditions¹⁶⁻¹⁹, gave the corresponding terminal amine product instead of the anticipated 1,2-amino alcohol (Fig. 1c). We reasoned that this product was formed via initial insertion to produce **II** followed by β -alkoxide elimination and subsequent anti-Markovnikov hydroamination of the intermediate terminal olefin. Based on this, we hypothesized that a trisubstituted allylic ether might likewise deliver the terminal amine product while concurrently generating a chiral center distal from the amine.

A more complete depiction of the presumptive mechanism for this reductive relay hydroamination is shown in Fig. 1d. Copper(I) hydride **I** reacts with allylic ether (or ester) **1** to generate alkylcopper intermediate **II**, which readily undergoes β -alkoxide elimination to afford transient enantioenriched terminal alkene **IV** and ligated copper(I) alkoxide **III** in a net allylic substitution process. Alkene **IV** then undergoes anti-Markovnikov hydrocupration to form terminal alkylcopper species **V**. Subsequent interception of **V** by the hydroxylamine *O*-carboxylate aminating reagent **2** furnishes the desired γ -chiral amine **3** and ligated copper(I) benzoate **VI**. Copper(I) alkoxide **III** and copper(I) benzoate **VI** could both undergo transmetalation with a stoichiometric hydrosilane reagent to regenerate copper(I) hydride **I**. Although the Cu(I)-catalysed enantioselective allylic substitution reaction is a

well-precedented and versatile tool for the enantioselective introduction of carbon^{10,23,24}, boron²⁵⁻²⁸, and silicon²⁹ nucleophiles, the proposed enantioselective delivery of a hydride is an unprecedented process. Under our previously developed hydroamination conditions^{16,19}, unactivated (e.g. nonstyrenyl) trisubstituted olefins were generally unreactive. We ascribe this to the disfavored nature of the insertion reaction of the highly substituted alkene. We believe that the combination of the β -alkoxide elimination step followed by formation of a Si-O bond renders the overall process thermodynamically favorable and allows the desired process to take place.

Herein we report the development, substrate scope, and applications of the reductive relay hydroamination reaction. The protocol developed was found to be a flexible and general process for the preparation of a variety of γ -chiral amines. Notably, this approach was applicable to easily obtainable achiral allylic esters with both aliphatic and aromatic substituents. Moreover, chiral amines containing minimally differentiated alkyl substituents at the γ -position could be prepared with excellent enantioselectivity. In addition, the delivery of hydride and elimination of alkoxide could proceed iteratively in the case of allylic epoxides and acetonides to afford the corresponding δ -chiral amines. Several applications of the reductive relay hydroamination reaction are also described.

Results and discussion

Reaction development and optimization

We initiated our study by investigating the reactivity of substrates derived from geraniol under our previously reported hydroamination conditions (Table 1). A variety of leaving groups, including alkoxy, silyloxy, carbonate, phosphate, and carboxylates, provided the desired product with high levels of enantioselectivity (entries 1–6). The stable and readily-prepared allylic benzoate was found to provide the desired product in high yield. Hence, we subsequently investigated substituted benzoates as leaving groups. Incorporation of an electron-withdrawing group on the benzoate to increase the nucleofugality of the leaving group was found instead to significantly reduce the yield (entry 7). In contrast, the use of electron-donating substituents on the benzoate, such as a 4-dimethylamino group (entry 8), produced near quantitative yield of the γ -chiral amine (*S*)-**3a**. An evaluation of ligands revealed DTBM-SEGPHOS to give superior results compared to all others tested (entry 8 vs. entries 9–12).

Substrate scope

Under the optimized conditions, the scope of allylic benzoates that could be transformed was investigated (Table 2). A variety of substrates were converted into the corresponding chiral amines with high enantioselectivity and in moderate to excellent yields. A variety of 3,3-dialkyl substituted allylic 4-(dimethylamino)benzoates were first investigated (Table 2a). When the isomeric nerol-derived 4-(dimethylamino)benzoate containing a (*Z*)-configured allylic double bond was exposed to the optimized conditions, the opposite enantiomer (*R*)-**3a'** was obtained with slightly lower yield and enantioselectivity (**3a** vs. **3a'**). Bulky groups at the 3-position of the allylic system were tolerated and provided chiral amine products in moderate to good yields and exceptionally high enantioselectivity (**3b–d**). A

variety of functional groups were readily accommodated, including a ketal (**3d**), an aryl group (**3e**), a sulfonamide (**3f**), an alkyl chloride (**3g**), ethers (**3h**, **3j**), an ester (**3k**), a free alcohol (**3i**) and an unprotected secondary amine (**3l**). When an aldehyde-containing substrate was employed, not surprisingly, reduction to the alcohol was observed to produce the amino alcohol product (**3m**)^{30,31}. Protected amino acid-containing substrate **1n** could be transformed to γ -chiral amine (**3n**, **3n'**) without carbonyl reduction or epimerization, reflecting the mildness of the reaction conditions.

Additionally, 3-aryl-substituted allylic benzoates could also undergo reductive relay hydroamination (Table 2b). Substrates bearing electron-rich (**3p**, **3u**) and electron-poor (**3q**–**s**) aryl substituents were tolerated. A 3-thienyl substituted substrate (**3t**), as well as a chromane-derived bicyclic substrate (**3u**), were also compatible with these conditions. Likewise, a silyl-substituted allylic benzoate (Table 3a, **1v**) was converted into the γ -chiral silylamine (**3v**). In addition to 3,3-disubstituted allylic benzoates, this protocol was also applicable to racemic 1-aryl-3-alkyl-substituted allylic benzoate (Table 3a, **1w**), which reacted in an enantioconvergent manner to provide the α -branched chiral amine product (**3w**).

We reasoned that substrates containing an appropriate duo of vicinal allylic and homoallylic substituents would undergo sequential insertion/elimination sequences before undergoing hydroamination. Such a cascade process would lead to the formation of δ -chiral amines. To test this idea, allylic epoxide (Table 3a, **1x**) and allylic acetonide (Table 3a, **1y**) substrates were subjected to our previously developed reaction conditions. As predicted, racemic epoxide **1x** reacted in an enantioconvergent manner to provide the δ -chiral amine **3x** with high enantioselectivity. Likewise, enantioenriched acetonide **1y** also underwent the cascade hydroamination process to afford either enantiomer (**3y**, **3y'**) of the δ -chiral amine product under catalyst control. The successful extension of the reductive relay hydroamination protocol to this complex cascade serves to illustrate the flexibility and generality of this strategy.

In some cases, the free allylic alcohols could be used directly in the current catalytic system (Table 3b). By adding an extra equivalent of silane, the alcohol is first converted into silyl ether. Subsequently, in situ insertion, β -siloxy elimination and hydroamination provides the desired product. The use of the free alcohol did not affect the enantioselectivity of the process, although the yields obtained in this extended cascade were somewhat diminished relative to the use of the corresponding (4-dimethylamino)benzoate esters (Table 2a, 3a, 3e, 3g).

To demonstrate the scalability of this process, we conducted the reaction on a 10-mmol scale. Under slightly modified reaction conditions, a catalyst loading of 0.5 mol% proved sufficient for a reaction on this scale (Table 3c). As first observed by Lipshutz³², the inclusion of triphenylphosphine as an additive led to improved stability of the active catalyst, allowing higher catalyst turnover numbers to be attained without any significant effect on the enantioselectivity.

The utility of this catalytic system was further demonstrated through the use of a number of hydroxylamine esters as aminating reagents (Table 4). Despite the presence of a stereocenter adjacent to the nitrogen atom of the electrophilic aminating reagent, the hydroamination reaction proceeded in a completely catalyst-controlled manner (**4a**, **4a'**) to form a minimally differentiated stereocenter (methyl vs ethyl) with excellent selectivity. In addition, acyclic (**4b**), cyclic (**4d**), and sterically hindered (**4c**) hydroxylamine esters could be utilized, as could one containing a carbamate protecting group (**4d**). Furthermore, substrates containing heterocycles, such as pyridine (**4e**), pyrimidine (**4f**), benzothiadiazole (**4g**), and piperazine (**4f**, **4g**) were handled without event. Finally, duloxetine, a drug used to treat depression and generalized anxiety disorder, could be functionalized with complete control of diastereoselectivity (**4h**, **4h'**), demonstrating the potential utility of this protocol in the late-stage functionalization of complex molecules.

Applications of chemoselectivity

We investigated the reactivity of substrates containing multiple C–C double bonds and found that the hydroamination protocols described here and previously^{16,22} exhibited excellent chemoselectivity when different types of double bonds were present. In general, styrenyl and terminal double bonds both react in preference to trisubstituted allylic esters, and this difference in reactivity was exploited for sequential chemoselective hydroamination. For example, sequential hydroamination of diolefin **5** containing a trisubstituted allylic ester and terminal olefin with two different aminating reagents resulted in the formation of diamine **7** with excellent chemo- and enantioselectivity (Fig. 2a). Furthermore, by simultaneously taking advantage of the difference in reactivity between mono- and dialkyl aminating reagents¹⁹, as well as between styrenyl double bonds and trisubstituted allylic esters, a three component coupling of two aminating reagents with diolefin **8** could be achieved with good chemo-, diastereo-, and enantioselectivity (Fig. 2b). Importantly, this strategy can also be employed to form all four stereoisomers of a diamine product in uniformly high stereoselectivity depending on the enantiomer of chiral ligand used in each step (17:1 to 28:1 dr, >99% ee) (Fig. 2c, 11a-d).

Conclusions

In summary, we have developed a CuH-catalysed reductive relay process to access γ - and δ -chiral amines. This method allows for the installation of a stereocenter and a distal amino group in a single operation under mild conditions. Excellent enantio-, regio-, and chemoselectivity were observed for a broad range of substrates with high functional group tolerance. Furthermore, this system was found to be applicable to the late-stage modification of a pharmaceutical agent and was suitable for large-scale synthesis. Lastly, we also demonstrated that the CuH-catalysed protocol could be applied to the chemoselective sequential amination of substrates containing more than one olefin. The expansion of this relay strategy to other areas including drug and natural product synthesis is currently underway and will be reported in due course.

Methods

General procedure for reductive relay hydroamination

To an oven-dried 4 mL screw-cap vial equipped with a magnetic stir bar was added $\text{Cu}(\text{OAc})_2$ (2.0–5.0 mol%) and (*R*)-DTBM-SEGPPOS (2.2–5.5 mol%). The tube was sealed with a teflon-lined screw cap, evacuated, and backfilled with argon (this process was repeated a total of three times) by piercing with a needle attached to a Schlenk line. Anhydrous THF (1.0 mL) was added by syringe, and the mixture was stirred for 10 min at room temperature. At this time diethoxymethylsilane (560–720 μL , 3.5–4.5 mmol, 3.5–4.5 equiv) was added by syringe and stirring was continued for another 5 min. Into a separate oven-dried medium-sized screw-cap test tube was added γ -disubstituted allylic benzoate (1.0 mmol, 1.0 equiv) and *O*-benzoyl-*N,N*-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv). The tube was sealed with a teflon-lined screw cap, evacuated, and backfilled with argon (this process was repeated a total of three times). The catalyst solution was then transferred via syringe to the reaction tube containing the substrates, and the reaction mixture was stirred at 40–50 °C for up to 36 h. After the reaction was complete, the reaction mixture was allowed to cool to room temperature and was directly filtered through a short pad of silica gel (using ethyl acetate in hexanes) to give the crude product. Dodecane (100 μL) was added as an internal standard for GC analysis. 1,1,2,2-Tetrachloroethane (84 mg, 0.50 mmol) was added as internal standard for ^1H NMR analysis of the crude material. The product was purified by chromatography on silica gel or by acid-base extraction as indicated for each substrate. The enantiomeric excesses (% ee) were determined by HPLC analysis using chiral stationary phases as described in the Supplementary Information.

The X-ray crystallographic coordinate for **3g** is deposited at the Cambridge Crystallographic Data Centre (CCDC) under deposition number CCDC 1413400. These data can be obtained free of charge (http://www.ccdc.cam.ac.uk/data_request/cif).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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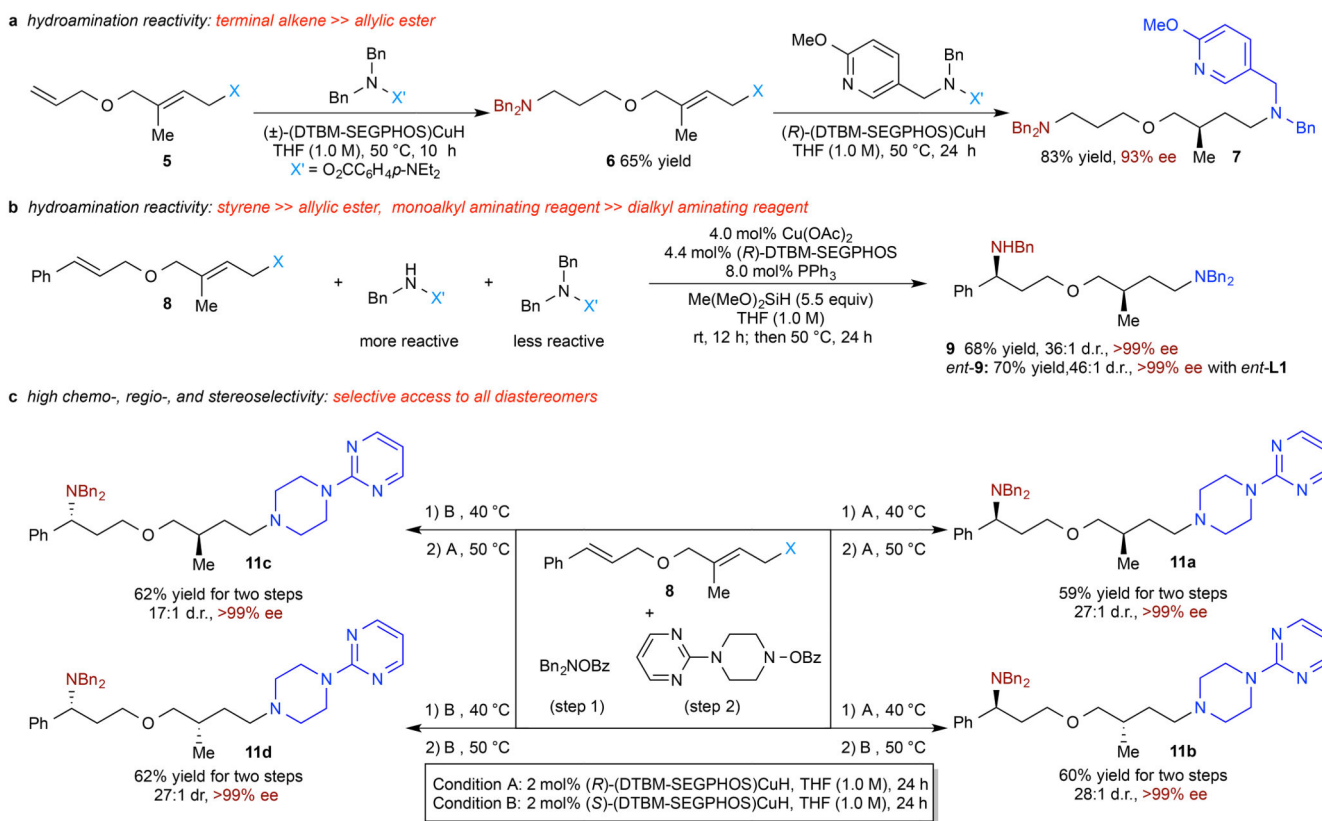


Figure 2. Synthetic applications of CuH-catalysed reductive relay hydroamination

a, Sequential hydroamination of an allylic ester substrate bearing a terminal olefin. **b**, Three-component hydroamination to install secondary and tertiary amines sequentially. **c**, High chemo-, regio-, and stereoselective hydroamination of an allylic ester substrate bearing a styrenyl olefin, stereodivergent access to all four diastereomers. Yield and e.e. are as defined in Table 2 legend. (See supplementary information for experimental details.)

Table 1
Optimization of reductive relay hydroamination

entry	L	X	%yield [*]	%ee [†]
1	L1	OBn	77	97
2	L1	OTBS	68	98
3	L1	O ₂ COMe	70	98
4	L1	OPO(OEt) ₂	80	97
5	L1	OAc	70	96
6	L1	OBz	88	98
7	L1	<i>p</i> -CO ₂ MeC ₆ H ₄ CO ₂	27	97
8	L1	<i>p</i> -NMe ₂ C ₆ H ₄ CO ₂	92	99
9	L2	<i>p</i> -NMe ₂ C ₆ H ₄ CO ₂	74	-95
10 [‡]	L3	<i>p</i> -NMe ₂ C ₆ H ₄ CO ₂	52	98
11 [‡]	L4	<i>p</i> -NMe ₂ C ₆ H ₄ CO ₂	12	-70
12 [‡]	L5 or L6	<i>p</i> -NMe ₂ C ₆ H ₄ CO ₂	0	—

Ar = 3,5-*t*-Bu-4-MeO-C₆H₂
(R)-DTBM-SEGPHOS (L1)

Ar = 3,5-*t*-Bu-4-MeO-C₆H₂
(R)-DTBM-MeO-BIPHEP (L2)

Ar = 3,5-*t*-Bu-C₆H₃
(R)-DTB-BINAP (L3)

(*R,R*)-Ph-BPE (L4)

(*R*)-(*S*)-JOSIPHOS (L5)

Xantphos (L6)

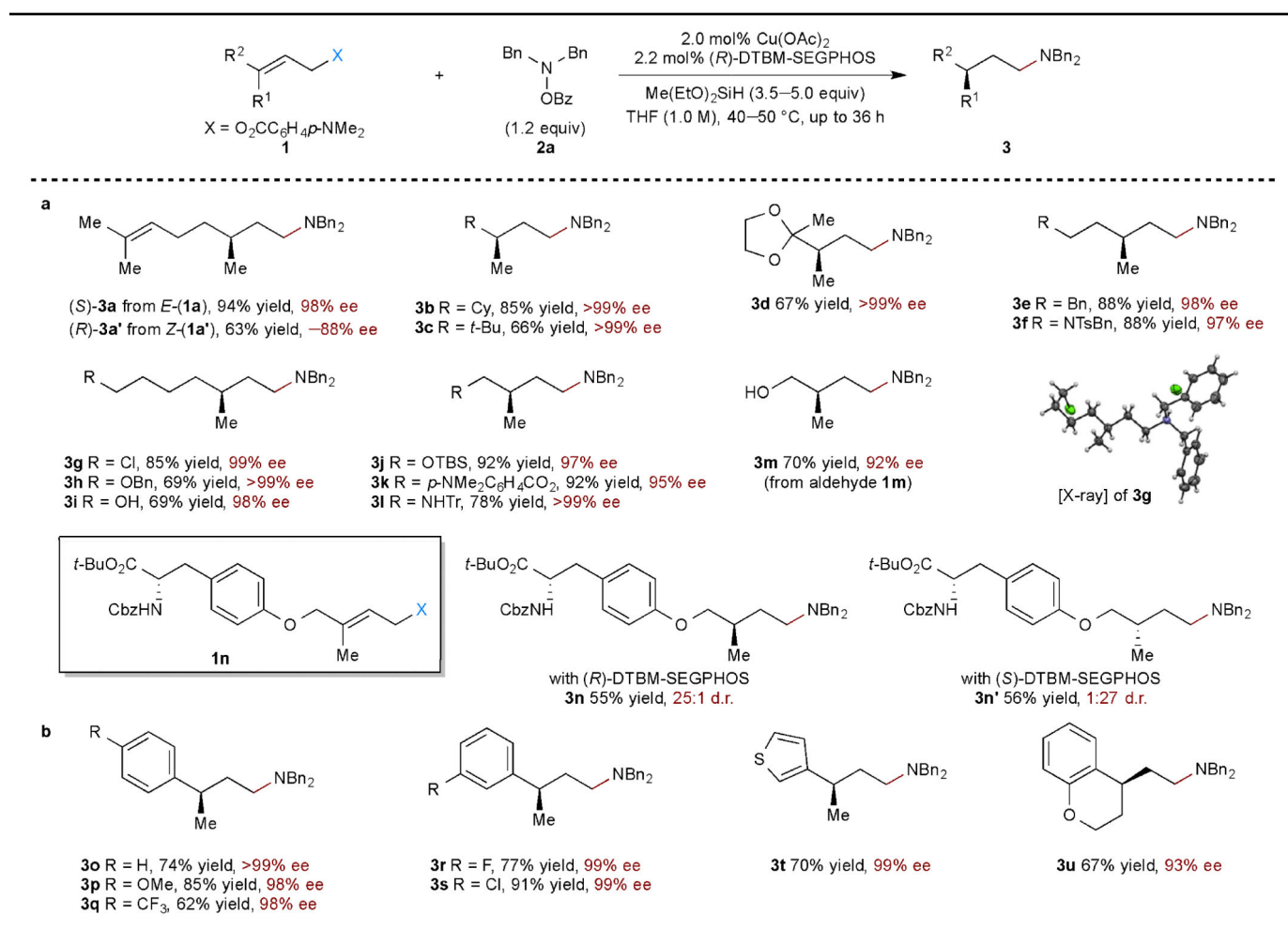
Conditions: **1a** (0.20 mmol), **2a** (0.24 mmol), HSiMe(ET)₂ (0.70 mmol), Cu(OAc)₂ (2.0 mol %), ligand (2.2 mol %), THF (1.0 M), 40 °C, 36 h.

^{*}Yield refers to isolated yield of purified product and is an average of two runs (0.20 mmol scale).

[†]The e.e. was determined by HPLC analysis using chiral stationary phases.

[‡]10 mol% Cu(OAc)₂, 11 mol% ligand was used. Me, methyl; Bz, benzoyl; Ph, phenyl; Bn, benzyl; TBS, tert-butyldimethylsilyl; Ac, acetyl. (See supplementary information for experimental details.)

Table 2
Substrate scope of allylic esters



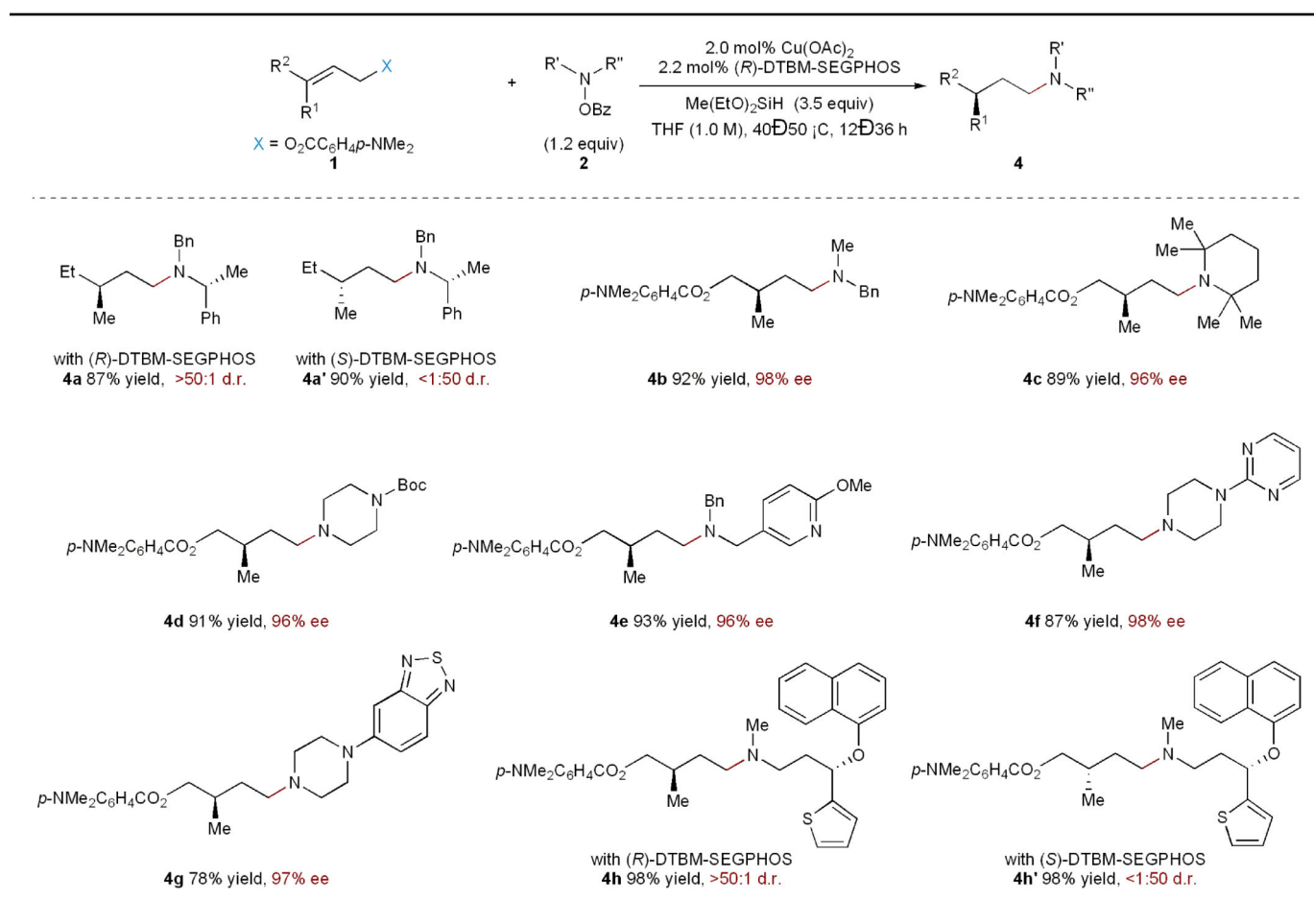
a, Substrates bearing 3,3-dialkyl substituted allylic ester. **b**, Substrates bearing 3,3-alkyl,aryl substituted allylic ester. Under each product are given yield in percent, and either enantiomeric excess (e.e.) or diastereomer ratio (d.r.). Yield refers to isolated yield of purified product (1 mmol scale, average of two runs). The e.e. was determined by HPLC analysis using chiral stationary phases. Me, methyl; Ph, phenyl; Bn, benzyl; Ts, tosyl; Tr, triphenylmethyl; Cbz, carboxybenzyl; TBS, tert-butyldimethylsilyl. (See supplementary information for experimental details.)

Table 3
Extension of scope to other substrate classes and reaction on large scale

substrate (1)	product (3)	%yield	%ee
a synthesis of chiral γ-silylamine, enantioconvergent transformation, synthesis δ-chiral amines			
 X = O ₂ CC ₆ H ₄ p-NMe ₂ 1v	 3v	92	98
 X = O ₂ CC ₆ H ₄ p-NMe ₂ 1w (\pm)	 3w	71	98
 1x (\pm)	 3x	50	93
 1y	 3y with (R)-DTBM-SEGPBOS	75	90
	 3y' with (S)-DTBM-SEGPBOS	51	-81
b from corresponding free allylic alcohols (4.5 equiv Me(EtO)₂SiH was used)			
 (S)- 3a , from geraniol		84	>99
 3e		82	99
 3g		81	99
c large scale synthesis			
 X = O ₂ CC ₆ H ₄ p-NMe ₂ 10 mmol-scale (E)- 1a	 (1.2 equiv) 2a	 3a 95% yield, 96% ee	

a. Extension of reductive relay hydroamination to the synthesis of a chiral γ -silylamine, enantioconvergent transformation of an allylic ester, and synthesis of δ -chiral amines. **b.** Reductive relay hydroamination of allylic alcohols. **c.** A 10 mmol-scale reductive relay hydroamination with 0.5% catalyst loading. Yield, e.e., and d.r. are as defined in Table 2 legend. (See supplementary information for experimental details.)

Table 4
Scope of hydroxylamine electrophiles



Yield, e.e., and d.r. are as defined in Table 2 legend. (See supplementary information for experimental details.)