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Deammoniative Condensation of Primary Allylic Amines with Nonallylic Amines†

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An unprecedented deammoniative condensation reaction of primary allylic amines with nonallylic amines has been developed through C—N bond cleavage. In the presence of 5 mol% palladium diacetate, 10 mol% 1,4-bis(diphenylphosphino)butane (dppb), and 5 mol% *p*-toluenesulfonic acid (TsOH), a range of α-unbranched primary allylic amines smoothly underwent deammoniative condensation with nonallylic amines in an α-selective fashion to give structurally diverse secondary and tertiary amines in good to excellent yields and *E* selectivity. Replacing dppb with racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) permitted the deammoniative condensation of enantioenriched α-chiral primary allylic amines with nonallylic amines to proceed with complete retention of configuration. Electrospray ionization (ESI) mass spectrometric analysis of the reaction mixture permitted the identification of some π-allylpalladium intermediates, and plausible mechanisms have been proposed to account for the regioselectivity and stereospecificity of the deammoniative condensation reaction.

Keywords amines, deammoniation, palladium, substitution, stereospecificity

Introduction

The nucleophilic substitution of allylic compounds is extremely useful for the introduction of the allyl moiety to target compounds, which permits a broad range of transformations such as oxidation, reduction, and addition.[1] While allylic halides and sulfonates frequently serve as reactive allylic electrophiles for the allylic substitution reaction in the absence of catalysts and additives, the employment of transition metals, particularly palladium (the Tsuji-Trost reaction),[2] as catalysts permits the allylic substitution reaction to proceed under relatively mild conditions, and more importantly, extends the scope of electrophiles to allylic alcohols and their derivatives such as carboxylates, carbonates, carbamates, phosphates, and epoxides. It is noteworthy that the allylic substitution reaction is significantly affected by the nature of the leaving groups of allylic electrophiles, and consequently, the exploration of new allylic electrophiles constitutes a promising strategy to address certain reactivity, selectivity, and productivity issues.

In sharp contrast to allylic halides and alcohol derivatives, allylic amines have rarely been employed directly as allylic electrophiles in the Tsuji-Trost reaction through allylic C—N bond cleavage despite its wide application in protective group chemistry.[3] Moreover, previous reports focus on the employment of secondary and tertiary allylic amines as allylic electrophiles,[4-6] and only very recently it has witnessed the disclosure of the allylic substitution reaction with primary allylic amines, which exhibits much higher atom-economy relative to that with commonly used allylic electrophiles.[7] Thus, it is challenging, but rewarding with regard to the exploration of new reactivity and selectivity, to develop new nucleophilic substitution reactions of allylic amines. Although in many cases the synthetic routes to allylic amines are not shorter than that to allylic halides and alcohol derivatives, chromatography can often be avoided during the purification of allylic amines. Owing to their basicity, allylic amines can be easily purified using simple extractive procedures.[7] Moreover, a number of racemic allylic amines can be readily resolved by inexpensive tartaric acid,[7,8] and consequently, optically active allylic amines can be easily prepared in large quantities.

Sporadic examples have shown that secondary and tertiary allylic amines can undergo metal-catalyzed substitution with nonallylic amines (amine exchange) [Scheme 1(a)]. As early as 1980, Trost and Keinan disclosed a $Pd(PPh_3)_4$-catalyzed exchange of 4,4'-dimethoxybenzhydrylsorbylamine with benzylamine in the presence of a stoichiometric amount of acetic acid.[5a] Seventeen years later, Mortreux and coworkers reported nickel- and palladium-catalyzed exchanges of *N*,*N*-

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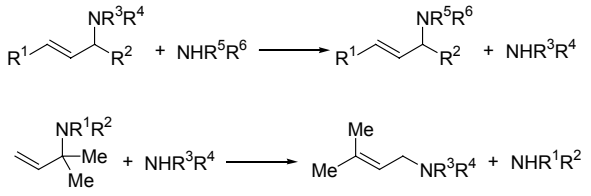
† Dedicated to Professor Chengye Yuan and Professor Li-Xin Dai on the occasion of their 90th birthdays.

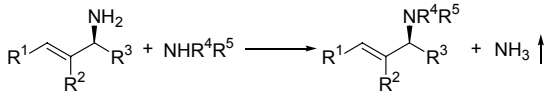
diethylallylamine with 10 equiv. of piperidine in the presence of 5—50 equiv. of acetic acid.[5b] In 2002, Hartwig and coworkers reported nickel- and palladium-catalyzed exchanges of *N*-substituted 2-cyclohexen-1-ylamines with primary and secondary nonallylic amines in the presence of 10 mol% trifluoroacetic acid.[5c] Moreover, they observed the racemization of (*S*)-*N*-(2-cyclohexen-1-yl)aniline under the exchange conditions. In 2005, Yudin and Waston[5d] reported palladium-catalyzed exchanges of *N*,*N*-disubstituted 2-amino-2-methyl-3-butenes with secondary nonallylic amines. In these reports, a large excess of nonallylic amines were required for the sake of attaining high conversion. Moreover, effective chirality transfer has not been addressed.

Scheme 1 Substitution of allylic amines with nonallylic amines

(a) Previous reports (amine exchange):[5]



(b) This work (deammoniative condensation):

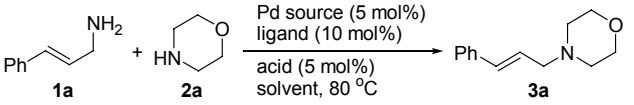


Reasoning that in the aforementioned reactions nonallylic amines were generated as byproducts and they could serve as nitrogen nucleophiles to compete with the starting amines, we envisioned that the reaction efficiency could be significantly improved by alternative use of primary allylic amines as the allylic electrophiles, yielding ammonia as a single byproduct, the extrusion of which would constitute a key driving force for the reaction to reach high conversion [Scheme 1(b)]. In the course of exploring the synthetic utilities of C(sp^3)-N bond cleavage,[7,9] we found that palladium/acid was able to catalyze the deammoniative condensation of primary allylic amines with nonallylic amines (1.2 equiv.) in a stereospecific manner. The reaction exhibits higher atom-economy than other relevant allylic substitution[2] and the *N*-alkylation of primary allylic amines (see below) for the synthesis of the same target amines, and moreover, it complements known asymmetric methods[10,11] in substrate scope via its unique ability to prepare acyclic α-chiral secondary and tertiary allylic amines with high optical purity starting from unsymmetrical allylic electrophiles whose α-substituents are different from γ-substituents.

Results and Discussion

At the outset we investigated the possibility to develop a deammoniative condensation reaction of α-unbranched primary allylic amines with nonallylic amines, wherein chirality transfer was not involved. A number of readily accessible palladium sources (5 mol%) and ligands were examined in the model reaction of α-unbranched primary allylic amine **1a** with nonallylic amine **2a** in dioxane under a nitrogen atmosphere at 80 ℃ (Table 1, Entries 1—12). While most of the palladium sources and ligands failed to promote the desired reaction, the use of $Pd(OAc)_2$/dppb (1∶2) resulted in the formation of tertiary amine **3a** in 15% yield (Table 1, Entry 10). Reasoning that the NH_2 group in allylic amine **1a** might be activated by an acid facilitating cleavage of the allylic C—N bond by the palladium catalyst,[7] we examined a few Brønsted and Lewis acids (5 mol%) and found that they dramatically affected

Table 1 Optimization of reaction conditions[a]



1a **2a** **3a**

Entry	Pd source	Ligand	Acid	Solvent	Yield[b]/%
1	$Pd(PPh_3)_4$	none	none	dioxane	trace
2	$Pd_2(dba)_3$	none	none	dioxane	0
3	$Pd(PPh_3)_2Cl_2$	none	none	dioxane	0
4	$PdCl_2$	none	none	dioxane	0
5	$Pd(OAc)_2$	none	none	dioxane	0
6	$Pd(OAc)_2$	PPh_3[c]	none	dioxane	trace
7	$Pd(OAc)_2$	PCy_3[c]	none	dioxane	0
8	$Pd(OAc)_2$	(±)-BINAP	none	dioxane	10
9	$Pd(OAc)_2$	Xantphos	none	dioxane	trace
10	$Pd(OAc)_2$	dppb	none	dioxane	15
11	$Pd(OAc)_2$	TMEDA	none	dioxane	0
12	$Pd(OAc)_2$	(±)-BINOL	none	dioxane	0
13	$Pd(OAc)_2$	dppb	$PhCO_2H$	dioxane	17
14	$Pd(OAc)_2$	dppb	TsOH	dioxane	97[d]
15	$Pd(OAc)_2$	dppb	$B(OH)_3$	dioxane	24
16	$Pd(OAc)_2$	dppb	$ZnCl_2$	dioxane	trace
17	$Pd(OAc)_2$	dppb	$AlCl_3$	dioxane	21
18	$Pd(OAc)_2$	dppb	$Bi_2(SO_4)_3$	dioxane	0
19	$Pd(OAc)_2$	dppb	TsOH	DME	90
20	$Pd(OAc)_2$	dppb	TsOH	toluene	42
21	$Pd(OAc)_2$	dppb	TsOH	MeCN	88
22	$Pd(OAc)_2$	dppb	TsOH	DMF	trace
23	$Pd(OAc)_2$	dppb	TsOH	DMSO	trace
24	$Pd(OAc)_2$	dppb	TsOH	EtOH	21
25[e]	$Pd(OAc)_2$	dppb	TsOH	dioxane	60

[a] Reaction conditions: amine **1a** (0.50 mmol), amine **2a** (0.60 mmol), Pd source (5 mol%), ligand (if any, 10 mol%), acid (if any, 5 mol%), solvent (0.50 mL), 80 ℃, 10 min. [b] Isolated yield. [c] 20 mol% ligand was used. [d] 98∶2 *E*/*Z*. [e] The reaction was performed at 60 ℃.

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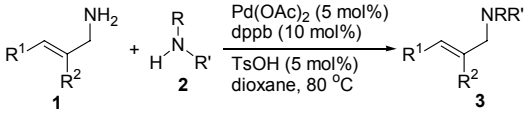
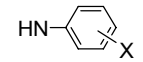
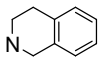
the deammoniative condensation reaction (Table 1, Entries 13—18). To our delight, in the presence of 5 mol% TsOH the reaction went to completion in only 10 min and gave tertiary amine **3a** in 97% yield with 98∶2 *E/Z* selectivity (Table 1, Entry 14). Replacing dioxane with other common solvents or lowering the temperature led to the formation of the desired product in much lower yields (Table 1, Entries 19—25).

In the presence of 5 mol% $Pd(OAc)_2$, 10 mol% dppb, and 5 mol% TsOH, a range of *α*-unbranched primary allylic amines smoothly underwent deammoniative condensation with nonallylic amines in an *α*-selective fashion to give the desired secondary and tertiary amines in good to excellent yields and *E* selectivity (Table 2). In some cases TsOH was replaced with $ZnCl_2$ and higher temperature was required in order to achieve better yields (Table 2, Entries 5, 7, 8, 16, and 17). Both alkyl- and arylamines served as suitable nitrogen nucleophiles, and the *β*- and *γ*-positions of the *α*-unbranched primary allylic amines could bear substituents such as aryl, heteroaryl, and alkyl groups. The reaction tolerated functional groups such as nitrile, chloro, and hydroxy groups. It is noteworthy that racemization was not observed in the deammoniative condensation reaction with optically active benzylic amines **2m** and **2n** (Table 2, Entries 13 and 14). When the *β*-position of the *α*-unbranched primary allylic amine was occupied by a substituent, significant geometric isomerization was observed for the olefinic C=C double bond (Table 2, Entry 24). Such geometric isomerization was attributed to the π-σ-π-isomerization of the π-allylpalladium intermediate generated from the palladium catalyst and the allylic amine (see below).

The standard reaction conditions were further applied to *α*-chiral primary allylic amine **4a**, whose optical purity was 97% *ee*. Whereas the deammoniative condensation of chiral amine **4a** with amine **2k** proceeded in an *α*-selective fashion with retention of configuration to give chiral amine **5a** in 85% yield with extremely high *E* selectivity, the optical purity of the product was determined to be only 35% *ee* (Table 3, Entry 1). The partial loss of enantiopurity could be attributed to the generation of the π-allylpalladium intermediate that would undergo racemization via Pd-Pd-exchange depending on the nature of the ligand (see below).[2] To achieve an effective chirality transfer, we surveyed a few phosphine ligands and found that the use of racemic BINAP as the ligand led to the formation of chiral amine **5a** in 84% yield with 97% *ee* (Table 3, Entry 3). Moreover, no change was observed with the enantiopurity of the product when prolonging the reaction time from 1 to 3 h. Both optically active (*R*)-BINAP and (*S*)-BINAP were examined for comparison. Although the use of (*R*)-BINAP gave a much higher yield than that of (*S*)-BINAP, in both cases the chirality was completely transferred with the same sense of chirality as substrate **4a** (Table 3, Entries 4 and 5). These results indicated that the stereochemistry of the reaction was determined by the substrate rather than the ligand. Finally, we decided to use racemic BINAP, which is less expensive than the optically active one, as the ligand since it resulted in complete retention of configuration as well as a good yield (Table 3, Entry 3).

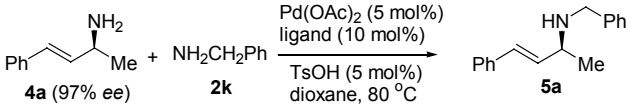
Table 2 Deammoniative condensation of *α*-unbranche dprimary allylic amines with nonallylic amines[a]



Entry	**1**, R^1, R^2	**2**, NRR'	**3**	Yield[b]/%	*E* ∶ *Z*[c]
1	**1a**, Ph, H	**2a**, $N(CH_2CH_2)_2O$	**3a**	97	98∶2
2	**1a**, Ph, H	**2b**, 1-Piperidinyl	**3b**	96	>99∶1
3	**1a**, Ph, H	**2c**, $N(CH_2Ph)_2$	**3c**	78	98∶2
4	**1a**, Ph, H	**2d**, $N(Me)CH_2Ph$	**3d**	88	98∶2
5[d]	**1a**, Ph, H	**2e**, N(Me)Ph	**3e**	84	>99∶1
6	**1a**, Ph, H	**2f**, NHPh	**3f**	85	99∶1
					
7[d]	**1a**, Ph, H	**2g**, X=2-OMe	**3g**	82	>99∶1
8[d]	**1a**, Ph, H	**2h**, X=2-CN	**3h**	67	>99∶1
9	**1a**, Ph, H	**2i**, X=4-OMe	**3i**	86	98∶2
10	**1a**, Ph, H	**2j**, X=4-Cl	**3j**	76	>99∶1
11	**1a**, Ph, H	**2k**, $NHCH_2Ph$	**3k**	60	>99∶1
12	**1a**, Ph, H	**2l**, $NHCHPh_2$	**3l**	70	>99∶1
					
13	**1a**, Ph, H	**2m**, X=H[e]	**3m**	62	>99∶1
14	**1a**, Ph, H	**2n**, X=OH[f]	**3n**	70	>99∶1
15	**1a**, Ph, H	**2o**, 	**3o**	89	99:1
16[d]	**1b**, 2-$MeOC_6H_4$, H	**2o**	**3p**	74	>99∶1
17[d]	**1c**, 4-$MeOC_6H_4$, H	**2o**	**3q**	98	>99∶1
18	**1d**, 4-$CF_3C_6H_4$, H	**2o**	**3r**	83	>99∶1
19	**1e**, 1-Naphthyl, H	**2o**	**3s**	84	94∶6
20	**1f**, 2-Thienyl, H	**2o**	**3t**	98	97∶3
21	**1g**, 3-Pyridinyl, H	**2o**	**3u**	83	97∶3
22	**1h**, $Me(CH_2)_6$, H	**2o**	**3v**	64	>99∶1
23[g]	**1i**, H, H	**2o**	**3w**	93	
24	**1j**, Ph, Me	**2o**	**3x**	97	84∶16

[a] Reaction conditions: amine **1** (0.50 mmol), amine **2** (0.60 mmol), $Pd(OAc)_2$ (5 mol%), dppb (10 mol%), TsOH (5 mol%), dioxane (0.50 mL), 80 ℃, 10 min. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopic analysis. [d] The reaction was performed with 5 mol% $ZnCl_2$ instead of TsOH at 110 ℃ for 4 h. [e] 95% *ee*. [f] >99% *ee*. [g] The reaction was performed in a sealed tube.

Table 3 Survey of the ligands[a]

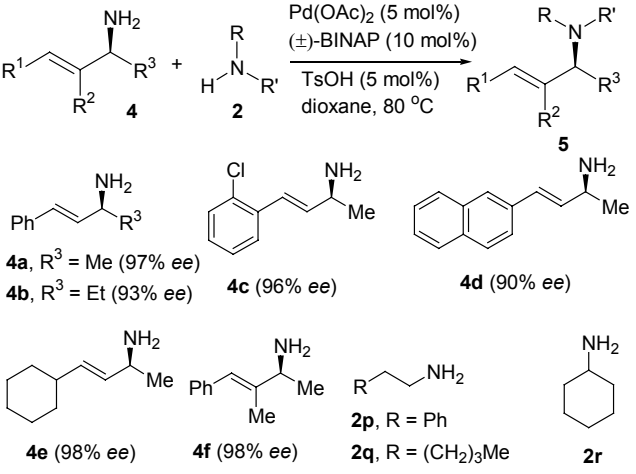


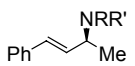
Entry	Ligand	Yield[b]/%	$E:Z$[c]	ee[d]/%
1	dppb	85	>99∶1	35
2	Xantphos	82	>99∶1	0
3	(±)-BINAP	84	>99∶1	97
4	(*R*)-BINAP	86	>99∶1	97
5	(*S*)-BINAP	54	>99∶1	97

[a] Reaction conditions: amine **4a** (0.50 mmol), amine **2k** (0.60 mmol), $Pd(OAc)_2$ (5 mol%), ligand (10 mol%), TsOH (5 mol%), dioxane (0.50 mL), 80 ℃, 1 h. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopic analysis. [d] Determined by HPLC analysis on a chiral stationary phase.

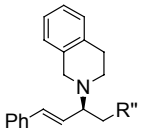
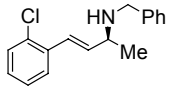
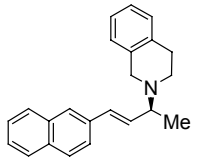
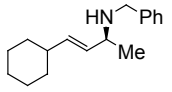
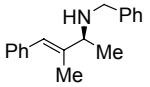
In the presence of 5 mol% $Pd(OAc)_2$, 10 mol% racemic BINAP, and 5 mol% TsOH, a range of unsymmetrical α-chiral primary allylic amines (α-substituent ≠ γ-substituent) smoothly underwent deammoniative condensation with various primary and secondary nonallylic amines in an α-selective fashion to give structurally diverse α-chiral amines in good to excellent yields with complete retention of configuration (Table 4). In some cases, the yields were enhanced significantly by replacing TsOH with $ZnCl_2$ and by prolonging the reaction time from 1 to 10 h (Table 4, Entries 5—7). The α-, β- and γ-positions of α-chiral primary allylic amines could bear aryl and alkyl groups, and alkyl- and arylamines served as suitable nitrogen nucleophiles.

Table 4 Deammoniative condensation of α-chiral primary allylic amines with nonallylic amines[a-c]



Entry	4	2	5		Yield[d]/%	ee[e]/%
						
1	**4a**	**2k**	**5a**	R=H, R'=CH_2Ph	84	97
2	**4a**	**2p**	**5b**	R=H, R'=$(CH_2)_2Ph$	95	97

Continued

Entry	4	2	5	Yield[d]/%	ee[e]/%	Entry
3	**4a**	**2q**	**5c**	R=H, R'=$(CH_2)_5Me$	96	97
4	**4a**	**2r**	**5d**	R=H, R'=Cy	87	97
5[f]	**4a**	**2f**	**5e**	R=H, R'=Ph	92	97
6[f]	**4a**	**2d**	**5f**	R=CH_2Ph, R'=Me	82	97
7[f]	**4a**	**2c**	**5g**	R=R'=CH_2Ph	69	97
8	**4a**	**2a**	**5h**	NRR'=$N(CH_2CH_2)_2O$	90	97
						
9	**4a**	**2o**	**5i**	R"=H	82	97
10[g]	**4b**	**2o**	**5j**	R"=Me	62	93
11[g]	**4c**	**2k**	**5k**		77	96
12	**4d**	**2o**	**5l**		80	90
13[g]	**4e**	**2k**	**5m**		85	98
14[g]	**4f**	**2k**	**5n**[h]		70	98

[a] Reaction conditions: amine **4** (0.50 mmol), amine **2** (0.60 mmol), $Pd(OAc)_2$ (5 mol%), racemic BINAP (10 mol%), TsOH (5 mol%), dioxane (0.50 mL), 80 ℃, 1 h. [b] Unless otherwise stated, the reaction gave >99∶1 *E/Z* selectivity. [c] See below for the assignment of the absolute configuration of products **5**. [d] Isolated yield. [e] Determined by HPLC analysis on a chiral stationary phase. [f] The reaction was performed in the presence of 5 mol% $ZnCl_2$ instead of TsOH for 10 h. [g] The reaction was performed for 4 h. [h] 91∶9 *E/Z*.

The regioselectivity depends largely on the structure of the unsymmetrical α-chiral primary allylic amine. Chiral amine **4g** is a regioisomer of chiral amine **4a**, and they were expected to go through the same π-allylpalladium intermediate to give the same product in the deammoniative condensation reaction with a nonallylic amine. Indeed, the deammoniative condensation of chiral amine **4g** with amine **2o** proceeded in a γ-selective fashion to give chiral amine **5i** in 90% yield with complete retention of configuration (Scheme 2). The γ-selectivity probably arises from both maximizing conjugation and minimizing steric hindrance prior to the attack of the nitrogen nucleophile on the π-allylpalladium intermediate (see below).

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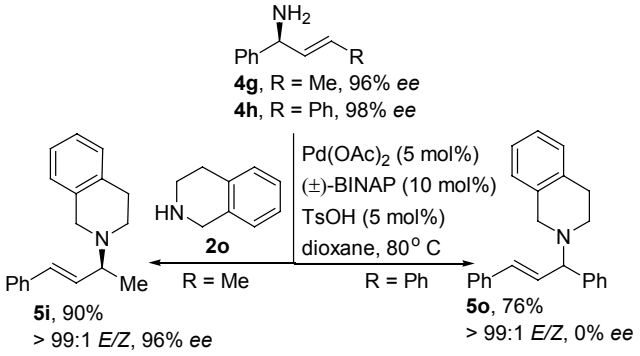
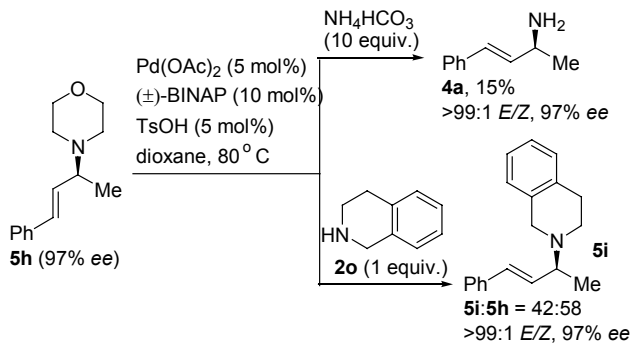
Scheme 2 Reactions of chiral amines **4g** and **4h**



We also examined the reaction of a symmetrical α-chiral primary allylic amine (α-substituent = γ-substituent). Treatment of chiral amine **4h** with amine **2o** under the standard reaction conditions led to the formation of racemic amine **5o** in 76% yield (Scheme 2). The complete loss of enantio purity was attributed to the symmetry of the resulting π-allylpalladium intermediate (see below).

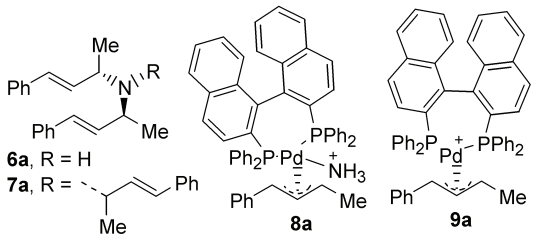
Racemization was not observed with chiral amine **5h** when treating it with 5 mol% $Pd(OAc)_2$, 10 mol% racemic BINAP, and 5 mol% TsOH, and moreover, the addition of a nonallylic amine did not change the optical purity of the remaining chiral amine. The extrusion of ammonia, a gaseous byproduct, from the reaction mixture was speculated to constitute a key driving force for the deammoniative condensation reaction to go to completion. For comparison, we carried out the following two experiments. Treatment of chiral amine **5h** with 10 equiv. of ammonium bicarbonate, which decomposed to generate ammonia at an elevated temperature, under the standard reaction conditions resulted in the formation of chiral amine **4a** in only 15% yield with complete retention of configuration (Scheme 3). On the other hand, the exchange reaction of chiral amine **5h** with amine **2o** (1 equiv.) proceeded in an α-selective fashion to give chiral amine **5i** in 42% conversion with complete retention of configuration. The conversion was unsatisfactory because of the generation of amine **2a** as a byproduct, which served as a nitrogen nucleophile to compete either with ammonia or with amine **2o** during the reaction.

Scheme 3 Reaction of chiral amine **5h** with ammonium bicarbonate or amine **2o**



To gain more insights into the reaction mechanism, we carried out electrospray ionization (ESI) mass spectrometric analysis of the reaction mixture of amine **4a** and amine **2a** in the presence of 5 mol% $Pd(OAc)_2$, 10 mol% racemic BINAP, and 5 mol% TsOH, and tentatively identified diallylic amine **6a**, triallylic amine **7a**, and π-allylpalladiums **8a** and **9a** according to the high resolution mass data (Table 5). These results indicate that the allylic C—N bond of the allylic amine is cleaved by a Pd(0) species, which is generated *in situ* from $Pd(OAc)_2$ through reduction with the amine substrate and/or the phosphine ligand.[12]

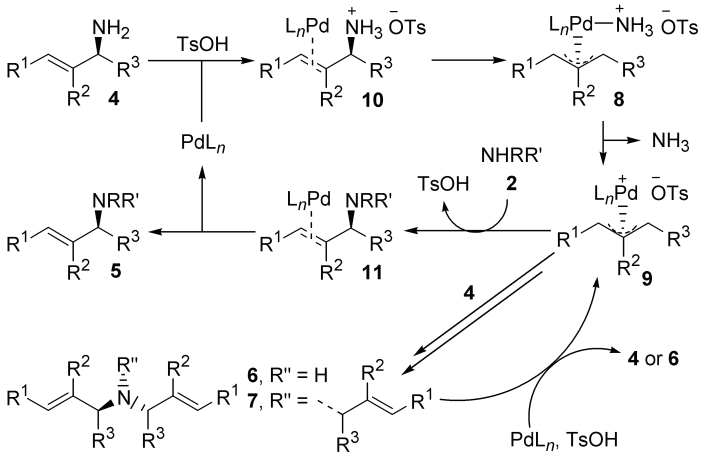
Table 5 High resolution mass data



Entry	Species	Formula	Mass (calcd)	Mass (found)
1	$[\mathbf{6a}+H]^+$	$C_{20}H_{24}N^+$	278.19033	278.18991
2	$[\mathbf{7a}+H]^+$	$C_{30}H_{34}N^+$	408.26858	408.26718
3	**8a**	$C_{54}H_{46}NP_2Pd^+$	876.21348	876.21350
4	**9a**	$C_{54}H_{43}P_2Pd^+$	859.18693	859.18909

On the basis of our experimental results and the general mechanism of the Tsuji-Trost reaction,[2] we propose the following catalytic cycles for the stereospecific deammoniative condensation of α-chiral primary allylic amines with nonallylic amines (Scheme 4). The NH_2 group in chiral amine **4** is activated by TsOH and the allylic C—N bond is cleaved by a Pd(0) species, PdL_n, with inversion of configuration to give π-allylpalladium **8**, which releases ammonia to yield a more electrophilic species, π-allylpalladium **9**. The allylic carbon of π-allylpalladium **9** is attacked by amine **2** with inversion of configuration to give chiral amine **5** and concurrently regenerate Pd(0) to continue the catalytic cycle. The double inversion of configuration leads to net stereoretention. Moreover, the regioselectivity is determined by the steric and electronic properties of the R^1 and R^3 groups, and the attack of amine **2** on π-allylpalladium **9** prefers to take place at the allylic position having less steric hindrance and/or leading to a higher degree of conjugation. If $R^1 = R^3$, the reaction would lose optical purity completely because of the symmetry of the π-allylpalladium intermediate. Although chiral amine **4** can serve as a nitrogen nucleophile to attack π-allylpalladium **9** to give diallylic amine **6**, which undergoes a similar reaction to give triallylic amine **7**, both amines are transformed into chiral amine **5** with retention of configuration through the intermediacy of π-allylpalladium **9**.

Scheme 4 Proposed catalytic cycles



Conclusions

We have developed, for the first time, an efficient deammoniative condensation reaction of primary allylic amines with nonallylic amines in a highly regioselective and stereospecific manner by taking advantage of yielding ammonia as a single byproduct, the extrusion of which constitutes a key driving force for the reaction to reach high conversion. In the presence of 5 mol% $Pd(OAc)_2$, 10 mol% dppb, and 5 mol% TsOH, a range of α-unbranched primary allylic amines smoothly underwent deammoniative condensation with nonallylic amines in an α-selective fashion to give structurally diverse secondary and tertiary amines in good to excellent yields and *E* selectivity. Replacing dppb with racemic BINAP permitted the deammoniative condensation of α-chiral primary allylic amines with nonallylic amines to proceed with complete retention of configuration. In addition, ESI mass spectrometric analysis of the reaction mixture allowed the identification of some π-allylpalladium intermediates, and plausible mechanisms have been proposed to account for the regioselectivity and stereospecificity of the deammoniative condensation reaction. The current study not only significantly extends the synthetic utilities of readily accessible primary allylic amines through $C(sp^3)$—N bond cleavage, but also provides a promising approach for the development of atom-economic and selective allylic substitution reactions.

Experimental

General information

^{1}H NMR and ^{13}C NMR spectra were recorded using tetramethylsilane as an internal reference. NMR multiplicities are abbreviated as follows: s＝singlet, d＝doublet, t＝triplet, m＝multiplet. High pressure liquid chromatography (HPLC) analyses were performed on an instrument equipped with an isostatic pump using a chiral stationary phase column (250 mm×4.6 mm) with *n*-hexane/isopropanol as the mobile phase, and the UV detection was monitored at 254 nm. The chiral HPLC methods were calibrated with the corresponding racemic mixtures. Optical rotations were measured on a polarimeter with a sodium lamp at λ＝589 nm and reported as $[\alpha]_D^T$ (c＝g/100 mL, solvent). Melting points are uncorrected.

All the starting amines are known compounds. Amines **1a**—**1h** and **1j** and chiral amines **4a**—**4h** were prepared according to literature procedures.[7a-7c] The rest of chemicals were purchased and used as received.

Abbreviations: Ac＝acetyl, BINAP＝2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, BINOL ＝ 1,1'-binaphthol, Cy ＝ cyclohexyl, dba ＝ dibenzylideneacetone, DME ＝ 1,2-dimethoxyethane, DMF ＝ *N*,*N*-dimethylformamide, DMSO＝dimethylsulfoxide, dppb＝1,4-bis(diphenylphosphino)butane, TMEDA＝*N*,*N*,*N*′,*N*′-tetramethylethylenediamine, Ts＝*p*-toluenesulfonyl, Xantphos ＝ 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

General procedure for the deammoniative condensation of α-unbranched primary allylic amines with nonallylic amines

A mixture of α-unbranched primary allylic amine **1** (0.50 mmol), nonallylic amine **2** (0.60 mmol), TsOH•H_2O (4.76 mg, 5 mol%), dppb (21.3 mg, 10 mol%), and $Pd(OAc)_2$ (5.61 mg, 5 mol%) in dioxane (0.50 mL) was heated under nitrogen at 80 ℃ for 10 min. The mixture was cooled to room temperature and purified by silica gel chromatography, eluting with ethyl acetate/petroleum ether (1∶20—1∶2), to give amine **3**. The *E*/*Z* ratios of the products were determined by integrating the vinyl proton signals in the ^{1}H NMR spectra.

Analytical data for the new compounds are shown in Table 2.

Amine **3p**, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47 (dd, J＝7.6, 1.6 Hz, 1H), 7.23—7.15 (m, 1H), 7.12—7.05 (m, 3H), 7.03—6.87 (m, 3H), 6.86—6.83 (m, 1H), 6.37 (dt, J＝16.0, 6.8 Hz, 1H), 3.81 (s, 3H), 3.66 (s, 2H), 3.33 (dd, J＝6.8, 1.2 Hz, 2H), 2.91 (t, J＝6.0 Hz, 2H), 2.78 (t, J＝6.0 Hz, 2H); ^{13}C NMR (100

MHz, $CDCl_3$) δ: 156.6, 134.8, 134.2, 128.6, 128.5, 127.6, 127.4, 126.8, 126.6, 126.1, 125.9, 125.5, 120.7, 110.8, 61.3, 56.1, 55.4, 50.7, 29.1; HRMS (ESI) calcd for $C_{19}H_{22}ON^+$ $(M+H)^+$ 280.1696, found 280.1693.

Amine **3q**, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35−7.29 (m, 2H), 7.14−7.04 (m, 3H), 7.02−6.96 (m, 1H), 6.87−6.80 (m, 2H), 6.52 (d, J=15.6 Hz, 1H), 6.21 (dt, J=15.6, 6.8 Hz, 1H), 3.76 (s, 3H), 3.65 (s, 2H), 3.29 (dd, J=6.8, 1.2 Hz, 2H), 2.90 (t, J=6.0 Hz, 2H), 2.77 (t, J=6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.1, 133.6, 133.1, 131.4, 128.7, 127.6, 126.5, 125.5, 125.1, 124.5, 123.4, 113.0, 59.8, 54.9, 54.2, 49.6, 28.0; HRMS (ESI) calcd for $C_{19}H_{22}ON^+$ $(M+H)^+$ 280.1696, found 280.1691.

Amine **3r**, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (d, J=8.4 Hz, 2H), 7.47 (d, J=8.4 Hz, 2H), 7.16−7.06 (m, 3H), 7.04−6.97 (m, 1H), 6.62 (d, J=16.0 Hz, 1H), 6.45 (dt, J=16.0, 6.4 Hz, 1H), 3.68 (s, 2H), 3.34 (dd, J=6.4, 0.8 Hz, 2H), 2.93 (t, J=6.0 Hz, 2H), 2.79 (t, J=6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.6, 134.6, 134.2, 131.5, 130.0, 129.6, 129.2, 128.8, 126.7, 126.6, 126.4, 125.8, 125.7 (q, J_{C-F}=3.8 Hz), 60.6, 56.2, 51.0, 29.2; HRMS (EI) calcd for $C_{19}H_{18}NF_3$ (M) 317.1391, found 317.1393.

Amine **3s**, obtained as a 94∶6 mixture of *E/Z* isomers. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.13 (d, J=8.4 Hz, 1H), 7.82−7.78 (m, 1H), 7.75 (d, J=8.4 Hz, 1H), 7.62 (d, J=7.2 Hz, 1H), 7.55−7.39 (m, 3H), 7.34 (d, J=15.6 Hz, 1H), 7.16−6.97 (m, 4H), 6.38 (dt, J=15.6, 6.8 Hz, 1H), 3.73 (s, 2H), 3.43 (dd, J=6.8, 1.6 Hz, 2H), 2.93 (t, J=5.6 Hz, 2H), 2.84 (t, J=5.6 Hz, 2H); Partial ^{1}H NMR for the minor *Z*-isomer δ: 6.15 (dt, J=11.6, 6.4 Hz, 1H), 3.68 (s, 2H), 3.28 (dd, J=6.4, 1.6 Hz, 2H); HRMS (EI) calcd for $C_{22}H_{21}N$ (M) 299.1682, found 299.1674.

Amine **3t**, obtained as a 97∶3 mixture of *E/Z* isomers. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23−7.18 (m, 2H), 7.13−7.03 (m, 4H), 7.01−6.95 (m, 1H), 6.57 (d, J=16.0 Hz, 1H), 6.18 (dt, J=16.0, 6.8 Hz, 1H), 3.64 (s, 2H), 3.26 (dd, J=6.8, 1.2 Hz, 2H), 2.89 (t, J=6.0 Hz, 2H), 2.75 (t, J=6.0 Hz, 2H); partial ^{1}H NMR for the minor *Z*-isomer δ: 5.81 (dt, J=11.6, 6.4 Hz, 1H), 3.43 (dd, J=6.4, 2.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.6, 134.6, 134.1, 128.6, 127.1, 126.7, 126.6, 126.1, 126.0, 125.6, 125.0, 121.8, 60.6, 56.0, 50.7, 29.0; HRMS (EI) calcd for $C_{16}H_{17}NS$ (M) 255.1082, found 255.1075.

Amine **3u**, obtained as a 97∶3 mixture of *E/Z* isomers. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.63−8.59 (m, 1H), 8.49−8.45 (m, 1H), 7.74−7.70 (m, 1H), 7.27−7.22 (m, 1H), 7.16−7.08 (m, 3H), 7.04−6.99 (m, 1H), 6.60 (d, J=16.0 Hz, 1H), 6.44 (dt, J=16.0, 6.4 Hz, 1H), 3.69 (s, 2H), 3.36 (dd, J=6.4, 1.2 Hz, 2H), 2.94 (t, J=6.0 Hz, 2H), 2.81 (t, J=6.0 Hz, 2H); Partial ^{1}H NMR for the minor *Z*-isomer δ: 6.04 (dt, J=11.6, 6.8 Hz, 1H), 3.64 (s, 2H), 3.42 (dd, J=6.8, 1.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.6, 148.4, 134.5, 134.1, 132.7, 132.5, 129.4, 129.2, 128.7, 126.6, 126.3, 125.7, 123.5, 60.6, 56.1, 50.9, 29.0; HRMS (EI) calcd for $C_{17}H_{18}N_2$ (M) 250.1470, found 250.1468.

Amine **3v**, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.15−7.05 (m, 3H), 7.05−6.98 (m, 1H), 5.70−5.61 (m, 1H), 5.56 (dt, J=14.4,6.4 Hz, 1H), 3.62 (s, 2H), 3.16−3.06 (m, 2H), 2.91 (t, J=6.0 Hz, 2H), 2.73 (t, J=6.0 Hz, 2H), 2.11−2.02 (m, 2H), 1.45−1.28 (m, 10H), 0.89 (t, J=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.0, 134.5, 128.8, 126.8, 126.5, 126.2, 125.7, 60.8, 56.0, 50.6, 32.5, 32.0, 29.9, 29.4, 29.3, 29.2, 22.8, 14.3; HRMS (EI) calcd for $C_{19}H_{29}N$ (M) 271.2300, found 271.2285.

Amine **3x**, obtained as a 84∶16 mixture of *E/Z* isomers. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36−7.27 (m, 4H), 7.21−7.16 (m, 1H), 7.11−7.06 (m, 3H), 7.01−6.93 (m, 1H), 6.49 (d, J=1.2 Hz, 1H), 3.61 (s, 2H), 3.16 (d, J=1.2 Hz, 2H), 2.88 (t, J=6.0 Hz, 2H), 2.70 (t, J=6.0 Hz, 2H), 1.95 (d, J=1.2 Hz, 3H); partial ^{1}H NMR for the minor *Z*-isomer δ: 6.52 (s, 1H), 3.51 (s, 2H), 3.26 (d, J=0.8 Hz, 2H), 2.82 (t, J=6.0 Hz, 2H), 2.58 (t, J=6.0 Hz, 2H), 1.98 (d, J=1.6 Hz, 3H); HRMS (EI) calcd for $C_{19}H_{21}N$ (M) 263.1674, found 263.1666.

General procedure for the deammoniative condensation of *α*-chiral primary allylic amines with nonallylic amines (Table 4 and Scheme 2)

A mixture of *α*-chiral primary allylic amine **4** (0.50 mmol), nonallylic amine **2** (0.60 mmol), $TsOH\cdot H_2O$ (4.76 mg, 5 mol%), racemic BINAP (31.1 mg, 10 mol%), and $Pd(OAc)_2$ (5.61 mg, 5 mol%) in dioxane (0.50 mL) was heated under nitrogen at 80 ℃ for 1.0 h. The mixture was cooled to room temperature and purified by silica gel chromatography, eluting with ethyl acetate/petroleum ether (1∶20−1∶2), to give chiral amine **5**.

Analytical data for the new compounds are shown in Table 4 and Scheme 2.

Chiral amine **5b**, colorless oil; $[\alpha]_D^{20}$ −70 (*c* 1.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39−7.15 (m, 10H), 6.43 (d, J=16.0 Hz, 1H), 6.05 (dd, J=16.0, 8.0 Hz, 1H), 3.43−3.33 (m, 1H), 3.06−2.64 (m, 4H), 1.23 (d, J=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.0, 137.1, 134.1, 130.0, 128.7, 128.5, 127.3, 126.3, 126.2, 56.2, 48.8, 36.5, 22.0; HRMS (EI) calcd for $C_{18}H_{21}N$ (M) 251.1674, found 251.1673. The *ee* was determined to be 97% by HPLC analysis (Chiralpak OJ, λ=254 nm, *n*-hexane/isopropanol=95∶5, flow rate=1.0 mL/min): t_R(minor)=14.1 min, t_R(major)=11.3 min.

Chiral amine **5c**, colorless oil; $[\alpha]_D^{20}$ −76 (*c* 1.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42−7.35 (m, 2H), 7.34−7.27 (m, 2H), 7.24−7.18 (m, 1H), 6.46 (d, J=16.0 Hz, 1H), 6.08 (dd, J=16.0, 8.0 Hz, 1H), 3.39−3.30 (m, 1H), 2.78−2.41 (m, 2H), 1.59−1.40 (m, 2H), 1.39−1.15 (m, 9H), 0.87 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.2, 134.4, 129.8, 128.5, 127.3, 126.3, 56.4, 47.7, 31.8, 30.3, 27.1, 22.6, 22.0, 14.1;

HRMS (EI) calcd for $C_{16}H_{25}N$ (M) 231.1987, found 231.1999. The *ee* was determined to be 97% by converting it to compound **5Bz-c** (see below).

Chiral amine **5d**, light yellow oil; $[\alpha]_D^{20}$ –94 (*c* 1.01, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.40－7.35 (m, 2H), 7.33－7.27 (m, 2H), 7.25－7.18 (m, 1H), 6.44 (d, *J*＝16.0 Hz, 1H), 6.07 (dd, *J*＝16.0, 8.0 Hz, 1H), 3.60－3.49 (m, 1H), 3.41 (s, br, 1H), 2.56－2.48 (m, 1H), 2.01－1.94 (m, 1H), 1.78－1.52 (m, 3H), 1.34－1.02 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.2, 134.9, 129.4, 128.5, 127.3, 126.3, 53.6, 52.6, 34.5, 33.3, 26.2, 25.3, 25.1, 22.5; HRMS (EI) calcd for $C_{16}H_{23}N$ (M) 229.1830, found 229.1833. The *ee* was determined to be 97% by converting it to compound **5Bz-d** (see below).

Chiral amine **5f**, colorless oil; $[\alpha]_D^{20}$ –81 (*c* 1.03, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.40－7.16 (m, 10H), 6.47 (d, *J*＝16.0 Hz, 1H), 6.31 (dd, *J*＝16.0, 7.2 Hz, 1H), 3.65 (d, *J*＝13.2 Hz, 1H), 3.52 (d, *J*＝13.2 Hz, 1H), 3.40－3.31 (m, 1H), 2.22 (s, 3H), 1.30 (d, *J*＝6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.8, 137.3, 132.0, 130.8, 128.9, 128.5, 128.2, 127.3, 126.8, 126.3, 60.4, 58.3, 37.9, 17.0; HRMS (ESI) calcd for $C_{18}H_{22}N^+$ $(M+H)^+$ 252.1747, found 252.1743. The *ee* was determined to be 97% by HPLC analysis (Chiralpak OJ, λ＝254 nm, *n*-hexane/isopropanol＝99∶1, flow rate＝1.0 mL/min): t_R(minor)＝8.7 min, t_R(major)＝9.7 min.

Chiral amine **5i**, light yellow oil; $[\alpha]_D^{20}$ –50 (*c* 1.07, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.41－7.36 (m, 2H), 7.34－7.28 (m, 2H), 7.26－7.19 (m, 1H), 7.12－7.05 (m, 3H), 7.04－6.99 (m, 1H), 6.52 (d, *J*＝16.0 Hz, 1H), 6.29 (dd, *J*＝16.0, 8.0 Hz, 1H), 3.86－3.67 (m, 2H), 3.37－3.22 (m, 1H), 2.99－2.71 (m, 4H), 1.36 (d, *J*＝6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.1, 135.1, 134.5, 132.3, 130.9, 128.7, 128.6, 127.4, 126.8, 126.3, 126.0, 125.6, 62.0, 53.0, 47.4, 29.4, 17.8; HRMS (EI) calcd for $C_{19}H_{21}N$ (M) 263.1674, found 263.1678. The *ee* was determined to be 97% by HPLC analysis (Chiralpak OD, λ＝254 nm, *n*-hexane/isopropanol＝95∶5, flow rate＝1.0 mL/min): t_R(minor)＝5.3 min, t_R(major)＝6.4 min.

Chiral amine **5j**, light yellow oil; $[\alpha]_D^{20}$ –16 (*c* 1.08, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.40－7.36 (m, 2H), 7.32－7.26 (m, 2H), 7.22－7.17 (m, 1H), 7.11－7.02 (m, 3H), 7.01－6.96 (m, 1H), 6.50 (d, *J*＝16.0 Hz, 1H), 6.18 (dd, *J*＝16.0, 8.8 Hz, 1H), 3.84－3.70 (m, 2H), 3.04－2.82 (m, 4H), 2.77－2.68 (m, 1H), 1.94－1.78 (m, 1H), 1.70－1.56 (m, 1H), 0.94 (t, *J*＝7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.0, 135.3, 134.6, 132.8, 129.7, 128.6, 128.5, 127.3, 126.7, 126.3, 125.9, 125.5, 68.9, 53.0, 47.1, 29.5, 25.2, 11.0; HRMS (EI) calcd for $C_{20}H_{23}N$ (M) 277.1830, found 277.1827. The *ee* was determined to be 93% by HPLC analysis (Chiralpak AD-H, λ＝254 nm, *n*-hexane/isopropanol＝99∶1, flow rate＝1.0 mL/min): t_R(minor)＝7.4 min, t_R(major)＝4.4 min.

Chiral amine **5k**, light yellow oil; $[\alpha]_D^{20}$ –61 (*c* 1.05, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.55－7.51 (m, 1H), 7.36－7.29 (m, 5H), 7.26－7.12 (m, 3H), 6.87 (d, *J*＝16.0 Hz, 1H), 6.08 (dd, *J*＝16.0, 8.0 Hz, 1H), 3.85 (d, *J*＝13.2 Hz, 1H), 3.74 (d, *J*＝13.2 Hz, 1H), 3.49－3.39 (m, 1H), 1.27 (d, *J*＝6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.5, 137.1, 135.3, 132.9, 129.7, 128.5, 128.3, 126.9, 126.8, 126.5, 55.5, 51.5, 22.1; HRMS (EI) calcd for $C_{17}H_{18}ClN$ (M) 271.1128, found 271.1122. The *ee* was determined to be 96% by converting it to compound **5Bz-k** (see below).

Chiral amine **5l**, light yellow oil; $[\alpha]_D^{20}$ –36 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.81－7.77 (m, 3H), 7.74－7.73 (m, 1H), 7.64－7.60 (m, 1H), 7.48－7.40 (m, 2H), 7.15－7.07 (m, 3H), 7.06－7.00 (m, 1H), 6.70 (d, *J*＝16.0 Hz, 1H), 6.43 (dd, *J*＝16.0, 7.6 Hz, 1H), 3.96－3.67 (m, 2H), 3.47－3.28 (m, 1H), 3.09－2.78 (m, 4H), 1.41 (d, *J*＝6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 134.5, 134.4, 133.6, 133.0, 132.4, 131.3, 128.7, 128.2, 127.9, 127.7, 126.8, 126.3, 126.1, 125.8, 125.6, 123.6, 62.1, 52.9, 47.4, 29.3, 17.8; HRMS (EI) calcd for $C_{23}H_{23}N$ (M) 313.1830, found 313.1812. The *ee* was determined to be 90% by HPLC analysis (Chiralpak AD, λ＝254 nm, *n*-hexane/isopropanol＝99∶1, flow rate＝1.0 mL/min): t_R(minor)＝12.4 min, t_R(major)＝10.2 min.

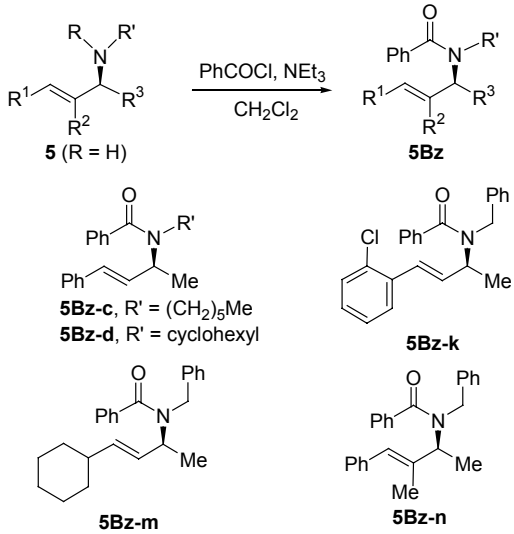
Chiral amine **5m**, light yellow oil; $[\alpha]_D^{20}$ –25 (*c* 1.03, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.34－7.28 (m, 4H), 7.26－7.21 (m, 1H), 5.47 (dd, *J*＝15.6, 6.4 Hz, 1H), 5.25 (ddd, *J*＝15.6, 8.0, 1.2 Hz, 1H), 3.78 (d, *J*＝13.2 Hz, 1H), 3.66 (d, *J*＝13.2 Hz, 1H), 3.19－3.10 (m, 1H), 2.00－1.87 (m, 1H), 1.78－1.60 (m, 4H), 1.34－1.00 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.8, 137.5, 131.4, 128.4, 128.2, 126.8, 55.3, 51.3, 40.4, 33.2, 33.1, 26.2, 26.1, 22.2; HRMS (EI) calcd for $C_{17}H_{25}N$ (M) 243.1987, found 243.1969. The *ee* was determined to be 98% by converting it to compound **5Bz-m** (see below).

Chiral amine **5n**, obtained as a 91∶9 mixture of *E*/*Z* isomers. Colorless oil; $[\alpha]_D^{20}$ －24 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.35－7.17 (m, 10H), 6.43 (s, 1H), 3.74 (d, *J*＝13.2 Hz, 1H), 3.63 (d, *J*＝13.2 Hz, 1H), 3.32－3.38 (m, 1H), 1.85 (d, *J*＝1.2 Hz, 3H), 1.23 (d, *J*＝6.8 Hz, 3H); Partial ^1H NMR for the minor *Z*-isomer δ: 6.47 (s, 1H); HRMS (EI) calcd for $C_{18}H_{21}N$ (M) 251.1674, found 251.1675. The *ee* was determined to be 98% by converting it to compound **5Bz-n** (see below).

Racemic amine **5o**, light yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.48－7.44 (m, 2H), 7.39－7.24 (m, 7H), 7.24－7.17 (m, 1H), 7.13－7.05 (m, 3H), 6.97－6.93 (m, 1H), 6.62 (d, *J*＝16.0 Hz, 1H), 6.40 (dd, *J*＝16.0, 8.8 Hz, 1H), 4.02 (d, *J*＝8.8 Hz, 1H), 3.80 (d, *J*＝15.2 Hz, 1H), 3.60 (d, *J*＝15.2 Hz, 1H), 2.96－2.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.1, 136.9, 135.0, 134.6, 131.7, 131.2, 128.7, 128.6, 128.5, 127.9, 127.5, 127.3, 126.8, 126.4, 126.1, 125.6, 73.7, 54.7, 48.5, 29.1; HRMS (EI) calcd for $C_{24}H_{23}N$ (M) 325.1830, found 325.1838. The *ee* was determined to be 0% by HPLC analysis (Chiralpak AD, λ＝254 nm, *n*-hexane/isopropanol＝99∶1, flow rate＝1.0 mL/min): $t_R(1)$＝6.8 min, $t_R(2)$＝8.0 min.

Benzoylation of chiral amines 5 for *ee* determination

To a solution of chiral amine **5** (0.20 mmol) and triethylamine (30.4 mg, 0.042 mL, 0.30 mmol) in dichloromethane (0.80 mL) at 0 ℃ was added dropwise a solution of benzoyl chloride (33.7 mg, 0.028 mL, 0.24 mmol) in dichloromethane (0.20 mL). The mixture was warmed to room temperature and stirred overnight. The mixture was quenched with water (1.0 mL) and extracted with dichloromethane (5.0 mL), and the aqueous layer was extracted with dichloromethane (3.0 mL). The organic layers were combined, dried over sodium sulfate, and concentrated. The residue was purified by silica gel chromatography, eluting with ethyl acetate/petroleum ether (1∶10—1∶5), to give amide **5Bz**.



Amide **5Bz-c**, prepared from chiral amine **5c** in 89% yield. Colorless oil; $[\alpha]_D^{20}$ −106 (*c* 1.07, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.48—7.22 (m, 9H), 7.27—7.22 (m, 1H), 6.50—6.30 (m, 1H), 6.25—6.05 (m, 1H), 4.68—4.44 (m, 1H), 3.55—3.37 (m, 1H), 3.23—3.11 (m, 1H), 1.85—1.05 (m, 11H), 0.91—0.75 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.8, 137.5, 136.5, 130.9, 129.9, 129.2, 128.7, 128.5, 127.8, 126.4, 126.3, 55.7, 42.6, 31.5, 29.4, 27.0, 22.5, 18.7, 14.0; HRMS (EI) calcd for $C_{23}H_{29}NO$ (M) 335.2249, found 335.2260. The *ee* was determined to be 97% by HPLC analysis (Chiralpak AD, λ=254 nm, *n*-hexane/isopropanol=95∶5, flow rate=1.0 mL/min): t_R(minor)=13.8 min, t_R(major)=16.5 min.

Amide **5Bz-d**, prepared from chiral amine **5d** in 84% yield. Colorless oil; $[\alpha]_D^{20}$ −88 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.46—7.31 (m, 9H), 7.30—7.21 (m, 1H), 6.55—6.35 (m, 2H), 4.45—4.05 (m, 1H), 3.45—3.10 (m, 1H), 1.85—1.45 (m, 10H), 1.20—0.98 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.2, 138.5, 137.0, 130.4, 128.8, 128.6, 128.5, 127.6, 126.5, 125.8, 31.4, 26.1, 25.3, 19.6; HRMS (EI) calcd for $C_{23}H_{27}NO$ (M) 333.2093, found 333.2096. The *ee* was determined to be 97% by HPLC analysis (Chiralpak OD, λ=254 nm, *n*-hexane/isopropanol=97∶3, flow rate=1.0 mL/min): t_R(minor)=13.3 min, t_R(major)=14.8 min.

Amide **5Bz-k**, prepared from chiral amine **5k** in 86% yield. Colorless oil; $[\alpha]_D^{20}$ −54 (*c* 1.07, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.56—7.12 (m, 14H), 6.86—6.70 (m, 1H), 6.25—5.90 (m, 1H), 5.00—4.55 (m, 3H), 1.52—1.24 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.5, 139.2, 136.9, 134.8, 133.1, 132.8, 129.6, 129.5, 128.8, 128.6, 127.5, 127.3, 127.0, 126.9, 126.4, 56.1, 44.8, 18.5; HRMS (EI) calcd for $C_{24}H_{22}NOCl$ (M) 375.1390, found 375.1422. The *ee* was determined to be 96% by HPLC analysis (Chiralpak AD, λ=254 nm, *n*-hexane/isopropanol = 90 ∶ 10, flow rate = 1.0 mL/min): t_R(minor)=15.9 min, t_R(major)=21.4 min.

Amide **5Bz-m**, prepared from chiral amine **5m** in 81% yield. Colorless oil; $[\alpha]_D^{20}$ −47 (*c* 1.02, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.48—7.18 (m, 10H), 5.55—5.25 (m, 2H), 4.89—4.71 (m, 1H), 4.55—4.40 (m, 2H), 1.93—1.83 (m, 1H), 1.73—1.57 (m, 5H), 1.30—1.05 (m, 6H), 1.03—0.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.4, 139.3, 138.4, 137.2, 129.3, 128.5, 128.3, 127.3, 126.8, 126.4, 56.0, 44.6, 40.4, 32.7, 26.1, 26.0, 18.8; HRMS (EI) calcd for $C_{24}H_{29}NO$ (M) 347.2249, found 347.2273. The *ee* was determined to be 98% by HPLC analysis (Chiralpak AD, λ=254 nm, *n*-hexane/isopropanol=95∶5, flow rate=1.0 mL/min): t_R(minor)=21.3 min, t_R(major)=30.5 min.

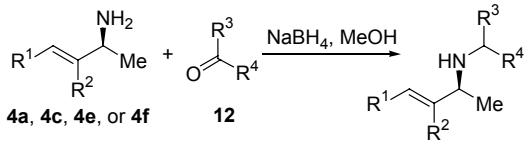
Amide **5Bz-n**, prepared from chiral amine **5n** in 90% yield. Colorless oil; $[\alpha]_D^{20}$ −45 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.55—7.15 (m, 15H), 6.41 (s, 1H), 5.15—4.85 (m, 1H), 4.60—4.35 (m, 1H), 4.32—4.16 (m, 1H), 1.85—1.54 (m, 3H), 1.33 (d, *J*=6.8 Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.1, 139.3, 137.3, 129.4, 129.0, 128.6, 128.4, 128.2, 127.6, 127.4, 126.9, 126.8, 126.4, 60.6, 44.7, 17.6, 17.0; HRMS (EI) calcd for $C_{25}H_{25}NO$ (M) 355.1936, found 355.1956. The *ee* was determined to be 98% by HPLC analysis (Chiralpak AD, λ=254 nm, *n*-hexane/isopropanol=90∶10, flow rate=1.0 mL/min): t_R(minor)=13.4 min, t_R(major)=17.5 min.

Assignment of the absolute configuration of chiral amines 5

Chiral amines **5e** and **5g** are known compounds. The absolute configuration of the rest of chiral amines **5** shown in Table 4 was determined by comparing their chiral HPLC traces or specific optical rotations with the authentic samples prepared by *N*-alkylation of chiral amines **4**. Shown below are the *N*-alkylation methods we used to convert chiral amines **4** to chiral amines **5**.

A mixture of chiral amine **4** (0.20 mmol) and carbonyl compound **12** (0.20 mmol) in methanol (2.4 mL) was stirred at room temperature for 1.0 h, cooled to 0 ℃, and added $NaBH_4$ (3.78 mg, 0.10 mmol). The mixture was stirred at room temperature for 1.0 h, added water (10 mL), and extracted with ethyl acetate (10 mL×2). The organic extracts were combined, dried over magnesium sulfate, and concentrated. The residue was purified by silica gel chromatography, eluting with ethyl acetate/petroleum ether (1∶20—1∶2), to give chiral amine **5**.

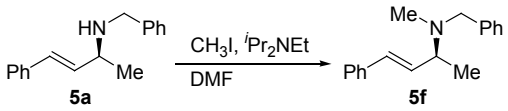
(a) Reductive amination



4a, **4c**, **4e**, or **4f** **12** **5a - 5d**, **5k**, **5m**, or **5n**

Entry	4	R^1	R^2	12	R^3	R^4	5	Yield/%
1	**4a**	Ph	H	**12a**	Ph	H	**5a**	75
2	**4a**	Ph	H	**12b**	CH_2Ph	H	**5b**	69
3	**4a**	Ph	H	**12c**	$(CH_2)_4Me$	H	**5c**	65
4	**4a**	Ph	H	**12d**	$R^3=R^4=(CH_2)_5$		**5d**	65
5	**4c**	2-ClC_6H_4	H	**12a**	Ph	H	**5k**	74
6	**4e**	Cy	H	**12a**	Ph	H	**5m**	63
7	**4f**	Ph	Me	**12a**	Ph	H	**5n**	76

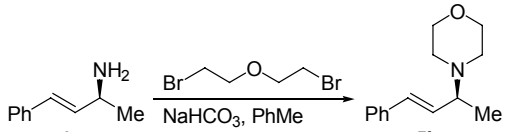
(b) Nucleophilic substitution



5a **5f**

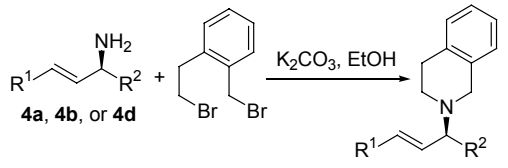
A mixture of chiral amine **5a** (47.5 mg, 0.20 mmol), iodomethane (28.4 mg, 0.012 mL, 0.20 mmol), and diisopropylethylamine (207 mg, 0.28 mL, 1.6 mmol) in DMF (0.60 mL) was stirred at room temperature for 3.0 h. The mixture was purified by silica gel chromatography, eluting with ethyl acetate/petroleum ether (1∶20), to give chiral amine **5f** (30.7 mg, 61%) as a colorless oil.

(c) Disubstitution



4a **5h**

A mixture of chiral amine **4a** (29.4 mg, 0.20 mmol), 1-bromo-2-(2-bromoethoxy)ethane (51.0 mg, 0.028 mL, 0.22 mmol), and sodium bicarbonate (37.0 mg, 0.44 mmol) in toluene (0.25 mL) was heated under nitrogen at 115 ℃ for 23 h. The mixture was cooled to room temperature and purified by silica gel chromatography, eluting with ethyl acetate/petroleum ether (1∶2), to give chiral amine **5h** (34.8 mg, 80%) as a colorless oil.



4a, **4b**, or **4d** **5i**, **5j**, or **5l**

Entry	4	R^1	R^2	5	Yield/%
1	**4a**	Ph	Me	**5i**	82
2	**4b**	Ph	Et	**5j**	76
3	**4d**	2-Naphthyl	Me	**5l**	84

A mixture of chiral amine **4** (0.20 mmol), 1-(2-bromoethyl)-2-(bromomethyl)benzene (55.6 mg, 0.33 mL, 0.20 mmol), and potassium carbonate (553 mg, 4.0 mmol) in ethanol (2.0 mL) was heated under nitrogen at 80 ℃ for 3.0 h. The mixture was cooled to room temperature and purified by silica gel chromatography, eluting with ethyl acetate∶petroleum ether (1∶10), to give chiral amine **5**.

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