Asymmetric Intramolecular Allylic Amination: Straightforward Approach to Chiral C1-Substituted Tetrahydroisoquinolines

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Abstract: Newly introduced Pd-catalyzed asymmetric intramolecular allylic amination provides an easy access to pharmaceutically important 1-substituted tetrahydroisoquinolines. With this amination as the key step, (*R*)-carnegine was synthesized in an enantioselective manner.

Key words: asymmetric allylic amination, tetrahydroisoquinoline, asymmetric catalysis, palladium, chiral P-N ligand

Alkaloids possessing 1-substituted tetrahydroisoquinoline skeleton include many pharmacologically active compounds such as (*S*)-laudanosine, (*S*)-sinactine, (*S*)-carnegine, and (*S*)-calycotomine (Figure 1).[1] Thus, construction of this class of compounds in optically active forms has drawn much attention of synthetic organic chemists and many efficient methodologies have been reported.[2] However, most of them use chiral building blocks or rely on diastereoselective reactions for introducing the chirality at C1[3–6] and, therefore, these syntheses are condemned to use stoichiometric amount of chiral sources.

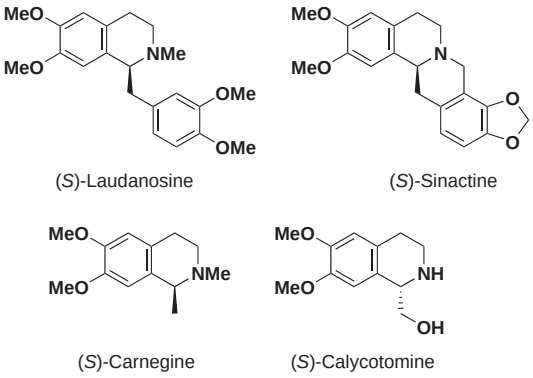
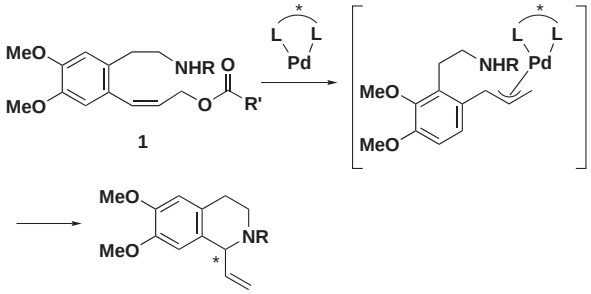


Figure 1

With the development of asymmetric reactions, much effort has been directed toward the synthesis using catalytic enantioselective reaction as the key step for chirality introduction at C1, but the asymmetric reactions successfully used for this purpose in terms of enantioselectivity are limited to the following three reactions: i) asymmetric reduction of 1-alkylidenetetrahydroisoquinolines[7] ii) alkylation of 3,4-dihydroisoquinolines prepared by the Bischler–Napieralski cyclization[8] and iii) Sharpless asymmetric dihydroxylation that was followed by Pomeranz–Fritsch cyclization.[9] In the syntheses using such asymmetric reactions, the chirality introduction and the hetero-cyclization have been carried out separately. We expected that the synthesis would become more efficient; if the chirality introduction and the hetero-cyclization are carried out in a single step and that asymmetric intramolecular allylic amination would be a good candidate for that purpose (Scheme 1). The resulting vinyl substituent at C1 is amenable to further functionalization to give various optically active 1-substituted tetrahydroisoquinolines.



Scheme 1

Although many asymmetric allylic amination reactions have been reported, most of them are intermolecular ones[10] and intramolecular version is limited to a few examples that provide pyrrolidine or piperidine derivatives with high enantioselectivity.[11] We have reported that chiral 2-(phosphinophenyl)pyridine ligands bearing 7-substituted dihydropyrindine unit are efficient chiral auxiliaries for palladium-catalyzed allylic alkylation of both acyclic and cyclic alkenyl substrates[12] We expected that palladium-mediated intramolecular allylic amination of allyl carboxylate **1** giving 1-vinyltetrahydroisoquinoline derivatives would be realized in a highly

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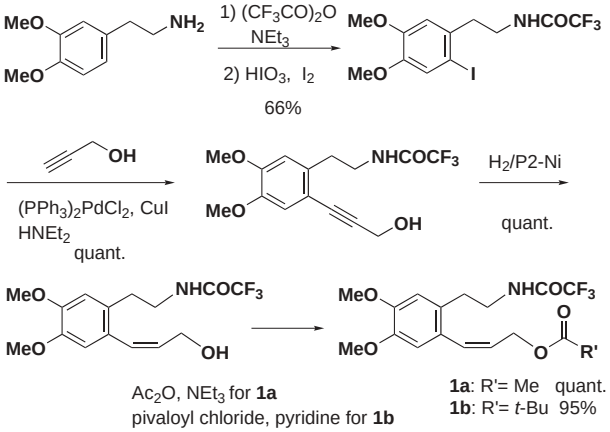
enantioselective manner by using chiral 2-(phosphinophenyl)pyridine as the chiral auxiliary. Here, we wish to report a new approach toward chiral 1-substituted tetrahydroisoquinolines using a palladium-mediated asymmetric allylic amination as the key step.

The requisite substrates **1a**,**b**[13] for the present study were prepared in a conventional manner, starting from commercial 3,4-dimethoxyphenethylamine as described in Scheme 2.



Scheme 2

We first examined the intramolecular allylic amination of **1a** using cesium carbonate as a base in dichloromethane in the presence of a catalytic amount of Pd(0) complex of 2-(phosphinophenyl)pyridine **2** (Table 1). The reaction proceeded smoothly at room temperature but enantioselectivity was low (entry 1). On the other hand, use of dimethylformamide (DMF) as the solvent inhibited the reaction: no reaction occurred at room temperature, but the reaction proceeded slowly at 60 °C in the absence of the base and showed moderate enantioselectivity of 67% ee (entries 2 and 3). The reaction was also examined with 2-(phosphinophenyl)oxazoline **3** that have been proved excellent chiral auxiliary for intermolecular and some intramolecular allylic substitutions,[14] but only modest enantioselectivity was observed (entries 4 and 5). In contrast, the reaction using BINAP (**4**) in dichloromethane showed moderate enantioselectivity of 53% ee, while the use of DMF as the solvent reduced enantioselectivity and reversed the sense of asymmetric induction (entries 6 and 7). We also examined the reaction using the bulkier tol-BINAP (**5**) but both the enantioselectivities of the reactions in dichloromethane and in DMF were modest (entries 8 and 9, Figure 2 and Scheme 3).

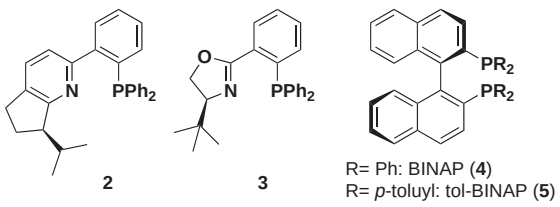
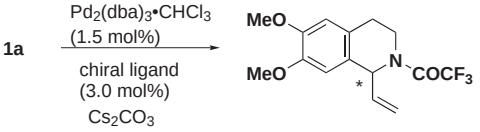


Figure 2



Scheme 3

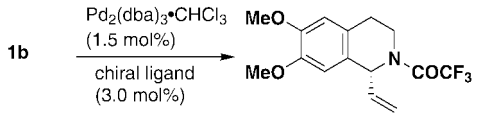
Table 1 Asymmetric Intramolecular Allylic Amination of **1a**

Entry	Ligand	Solvent	Temp	Time	Yield (%)	Ee[a]	Configuration[b]
1	**2**	CH_2Cl_2	r.t.	4 h	90	39	R
2	**2**	DMF	r.t.	–	–	–	–
3[c]	**2**	DMF	60 °C	18 d	52	67	*R*
4	**3**	CH_2Cl_2	r.t.	3 d	58	12	*R*
5[c]	**3**	DMF	60 °C	13 d	42	23	*R*
6	**4**	CH_2Cl_2	r.t.	4 d	83	53	*S*
7	**4**	DMF	60 °C	18 h	82	23	*R*
8	**5**	CH_2Cl_2	r.t.	4 d	76	24	*R*
9[c]	**5**	DMF	60 °C	24 d	51	32	*R*

[a] Enantiomeric excess was determined by HPLC analysis using chiral stationary phase column (Daicel Chiralcel OJ-H; hexane:*i*-PrOH = 90:10).
[b] Configuration was determined by comparison with the published value after converted to the 6,7-dimethoxy-1-ethyl-1,2,3,4-tetrahydroisoquinoline (ref.[7h]).
[c] Reaction was performed in the absence of cesium carbonate.

It is known that the nature of the leaving group of the alkenyl substrate often affects enantioselectivity and/or reactivity in allylic substitution.[12] Thus, we examined the cyclization of **1b** bearing bulky pivaloyloxy group as the leaving group, by using Pd-**2** complex as the catalyst (Table 2, Scheme 4). Fortunately, the reaction in dichloromethane proceeded with good enantioselectivity of 75% ee as well as good chemical yield (entry 1). Lowering the reaction temperature diminished the enantioselectivity and the reaction rate (entry 2). On the other hand, the reaction in DMF at 60 °C showed a slightly better enantioselectivity of 82% ee, though the reaction was slow (entry 6). Further raising the reaction temperature accelerated the cyclization, but the enantioselectivity was somewhat reduced (entries 7 and 8). We next examined the effect of the base in the reaction in dichloromethane: the reaction rate became slow in the order of Cs_2CO_3>K_2CO_3>Na_2CO_3>Li_2CO_3, but the maximum enantioselectivity of 88% ee was observed when K_2CO_3 or Na_2CO_3 was used as the base (entries 3 and 4).[15] The reaction using BINAP (**4**) was also examined, but the reaction was slow and the enantioselectivity was low (entry 9).

The cyclization product **6**[16] was converted into alcohol **7a** by the sequence: i) deprotection of trifluoroacetyl group by LAH reduction, ii) ethoxycarbonylation of the



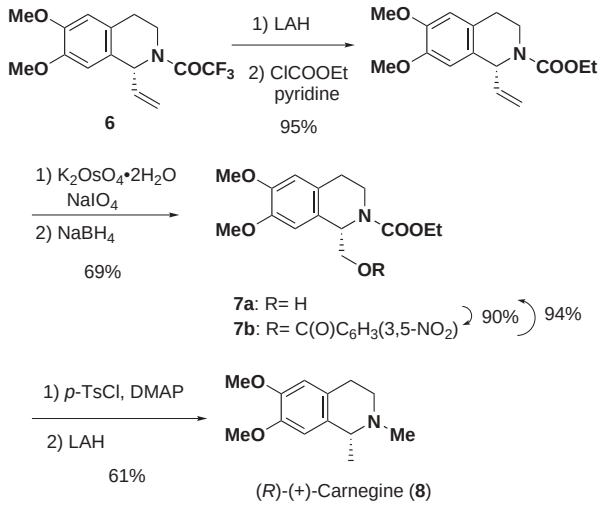
Scheme 4

Table 2 Asymmetric Intramolecular Allylic Amination of **1b**

Entry	Ligand	Solvent	Base	Temp	Time	Yield (%)	Ee[a]
1	**2**	CH_2Cl_2	Cs_2CO_3	r.t.	21 h	92	75
2	**2**	CH_2Cl_2	Cs_2CO_3	0 °C	5 d	89	40
3	**2**	CH_2Cl_2	K_2CO_3	r.t.	12 d	89	88
4	**2**	CH_2Cl_2	Na_2CO_3	r.t.	23 d	49	88
5	**2**	CH_2Cl_2	Li_2CO_3	r.t.	–	–	–
6[b]	**2**	DMF	–	60 °C	23 d	58	82
7[b]	**2**	DMF	–	80 °C	3 h	76	79
8[b]	**2**	DMF	–	100 °C	3 h	78	77
9[c]	**4**	CH_2Cl_2	Cs_2CO_3	r.t.	36 d	63	33

[a] Enantiomeric excess was determined by HPLC analysis using chiral stationary phase column (Daicel Chiralcel OJ-H; hexane:*i*-PrOH = 90:10).
[b] Reaction was performed in the absence of base.
[c] *S*-Isomer was obtained.

resulting secondary amine, and iii) oxidative cleavage of double bond under modified Lemieux–Johnson conditions and subsequent reduction with sodium borohydride (Scheme 5). The exchange of the N-protecting group was required, because the modified Lemieux–Johnson oxidation of **6** gave messy product. Enantiomeric excess of **7a** was enhanced to 98% ee by the following step: i) 3,5-dinitrobenzoylation of **7a** to **7b**, ii) recrystallization of **7b** from hexane–dichloromethane twice, iii) alcoholysis of **7b** (K_2CO_3–EtOH). Enantiomerically enriched **7a**[17] thus obtained was then converted to (*R*)-(+)-carnegine (**8**), the enantiomeric form of natural (*S*)-(–)-carnegine, according to the reported procedure with some modifications:[3d] i) tosylation using a combination of tosyl chloride and *N*,*N*-dimethylaminopyridine in dichloromethane and ii) LAH reduction in diethyl ether. The spectroscopic data were identical with those reported by Szarek et al.[3d] The specific rotation of **8** was +25.7° (*c* 0.042, EtOH) {Lit.[6a] [for (*R*)-carnegine] +23.4° (*c* 1.5, EtOH)}.



Scheme 5

In conclusion, we were able to develop new intramolecular allylic amination and to demonstrate its utility for enantioselective synthesis of C1-substituted isoquinoline alkaloids. Further study on the mechanism of asymmetric induction is in progress in our laboratory.

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(13) All the compounds in Scheme 2 gave satisfactory ^{1}H NMR (400 MHz) spectra. Compound **1a**: δ = 6.73 (dt, *J* = 1.2 and 11.2 Hz, 1 H), 6.65 (s, 1 H), 6.64 (s, 1 H), 5.81 (dt, *J* = 6.8 and 11.2 Hz, 1 H), 4.71 (dd, *J* = 1.2 and 6.8 Hz, 2 H), 3.87 (s, 6 H), 3.52 (dt, *J* = 6.8 and 6.8 Hz, 2 H), 2.87 (t, *J* = 6.8 Hz, 2 H), 2.03 (s, 3 H). Compound **1b**: δ = 6.95 (br s, 1 H), 6.74 (dt, *J* = 1.2 and 11.2 Hz, 1 H), 6.65 (s, 1 H), 6.62 (s, 1 H), 5.77 (dt, *J* = 6.8 and 11.2 Hz, 1 H), 4.73 (dd, *J* = 1.2 and 6.8 Hz, 2 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.53–3.43 (m, 2 H), 2.89 (t, *J* = 6.8 Hz, 2 H), 1.13 (s, 9 H).

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(15) **Typical Experimental Procedure for Allylic Amination:** Tris(dibenzylideacetone)dipalladium(0) chloroform adduct (1.9 mg, 1.8 μmol) and ligand **2** (1.5 mg, 3.6 μmol) was placed in a flask under nitrogen and CH_2Cl_2 (0.36 mL) was added. After being stirred for 30 min at r.t., compound **1b** (50 mg, 0.12 mmol) in CH_2Cl_2 (0.24 mL) and K_2CO_3 (49.8 mg, 0.36 mmol) was added successively and the mixture was stirred at the temperature for 12 d. The mixture was quenched with H_2O and extracted with CH_2Cl_2. The extract was dried over anhyd $MgSO_4$ and concentrated. Silica gel chromatography of the residue (hexane–EtOAc = 9:1) gave the desired product (33.7 mg, 89%) as an oil. $[\alpha]_D^{23}$ –157.7 (*c* 0.38, $CHCl_3$). ^{1}H NMR analysis of the product at 24 °C revealed that it existed as a 78:22 mixture of two rotamers based on the amide function. ^{1}H NMR (400 MHz): δ = 6.64 (s, 0.22 H), 6.61 (s, 0.78 H), 6.60 (s, 0.78 H), 6.56 (s, 0.22 H), 6.06–5.93 (m, 1.78 H), 5.48–5.45 (m, 0.22 H), 5.33–5.29 (m, 1 H), 5.17–5.11 (m, 0.78 H), 5.05 (d, *J* = 17.2 Hz, 0.22 H), 4.55–4.48 (m, 0.22 H), 4.09–3.98 (m, 0.78 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.56 (dt, *J* = 4.0 and 12.0 Hz, 0.78 H), 3.26 (dt, *J* = 4.8 and 12.4 Hz, 0.22 H), 3.02–2.92 (m, 1 H), 2.78–2.71 (m, 1 H). Anal. Calcd for $C_{15}H_{16}F_3NO_3$: C, 57.14; H, 5.12; N, 4.44. Found: C, 57.02; H, 5.16; N, 4.42. Enantiomeric excess of the product was determined to be 88% by HPLC using a chiral stationary phase column (Daicel Chiralcel OJ-H; hexane:*i*-PrOH= 9:1).

(16) A larger scale cyclization of **1b** (0.64 mmol scale) afforded **6** with slightly reduced enantioselectivity (85% ee). This compound **6** was used for the following reactions.

(17) The specific rotation of **7a** (98% ee) was $[\alpha]_D^{24}$ –91.0 (*c* 2.03, $CHCl_3$) {Lit. *R*-isomer[3d] $[\alpha]_D^{23}$ +88.8 (*c* 2.08, $CHCl_3$)}. Since the enantiomer of **7a** has been converted into the enantiomers of (*S*)-calycotomine and (*S*)-*N*-methyl-calycotomine respectively, the synthesis of **7a** means that formal total syntheses of those isoquinoline alkaloids have been achieved.[3d]