Synlett S. Tong, M.-X. Wang THIEME OPEN ACCESS Letter

Catalytic Enantioselective Synthesis of 4-Amino-1,2,3,4-tetrahydropyridine Derivatives from Intramolecular Nucleophilic Addition Reaction of Tertiary Enamides

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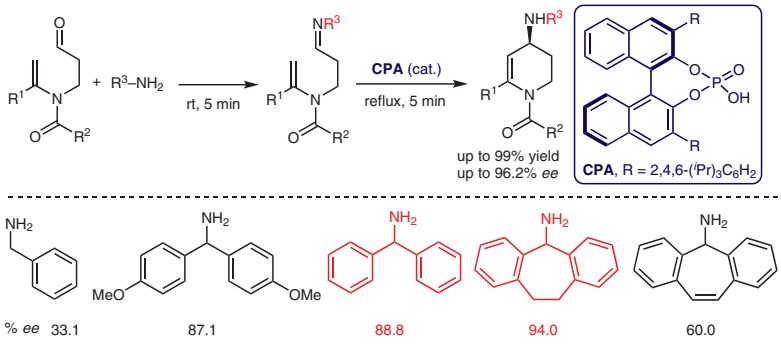
Published as part of the *30 Years SYNLETT – Pearl Anniversary Issue*



Received: 30.09.2018
Accepted after revision: 22.10.2018
Published online: 15.11.2018
DOI: 10.1055/s-0037-1610384; Art ID: st-2018-b0626-l

Abstract A general and efficient method for the synthesis of highly enantiopure 4-amino-1,2,3,4-tetradydropyridine derivatives based on chiral phosphoric acid catalyzed intramolecular nucleophilic addition of tertiary enamides to imines has been developed. We have also demonstrated a substrate engineering strategy to significantly improve the enantioselectivity of asymmetric catalysis

Key words tertiary enamides, 1,2,3,4-tetrahydropyridines, asymmetric catalysis, chiral phosphoric acid, substrate engineering

Chiral six-membered *N*-heterocyclic compounds such as functionalized 4-aminopiperidines are used extensively in the study of synthetic pharmaceutics and drug discovery.[1] (2S,4R)-1-(3,5-dimethylbenzoyl)-2-benzyl-4-((quinolin-3-ylmethyl)amino) piperidine CGP 49823, for instance, is an orally and centrally active nonpeptide NK1 antagonist[2] while carmegliptin is a potent and long-acting dipeptidyl peptidase IV inhibitor for the treatment of type II diabetes.[3] Synthesis of functionalized 4-aminopiperidine requires multistep reactions[4] or reductive amination of prefunctionalized piperidine-4-one derivatives.[5] The documented methods suffer, however, from drawbacks such as tedious stepwise chemical manipulations or low chemical yields. The development of general and asymmetric catalytic methods for the synthesis of highly enantiopure diverse 4-aminopiperidine derivatives is therefore highly desirable.

Tertiary enamides are variants of enamines in which one of the *N*-alkyl groups is replaced by an electron-attracting moiety such as carbonyl. Various synthetic methods have been established allowing facile accesses to tertiary enamides.[6] Unfortunately, due to the electronic effect of carbonyl group, tertiary enamides show much diminished enaminic activity and had been noted for a long time as inert and not useful chemical entities in organic synthesis.[7–10] However, we envisioned that tertiary enamides would be a type of shelf-stable nucleophiles with tunable reactivity based on the fluxional cross-conjugational system comprising carbon–carbon double bond, lone-pair electrons on nitrogen atom and carbonyl group (C=C–N–C=O). We have demonstrated in recent years that tertiary enamides behave indeed as unique and invaluable synthons in chemical synthesis. They are able to undergo stereoselective nucleophilic addition reactions to epoxides,[11] carbonyls,[12] iminiums,[13] nitriliums,[14] and activated alkynes,[15] furnishing diverse nitrogen-containing heterocyclic compounds which are not easily obtained by other means. To further explore the synthetic applications of tertiary enamides and to develop new methods for the construction of chiral 4-aminopiperidines,[16] we have undertaken the current study of catalytic asymmetric cyclization reactions of tertiary enamides. We disclose herein a chiral phosphoric acid catalyzed intramolecular nucleophilic addition of tertiary enamides to imines and a substrate engineering strategy to achieve high enantioselectivity in the synthesis of diverse 4-aminopiperidine derivatives.

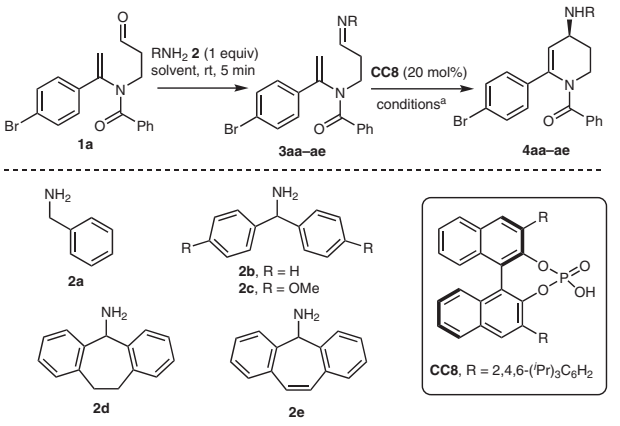
We started our study with the examination of the cyclization of tertiary enamide **3aa**, which was obtained quantitatively from the reaction of aldehyde **1a** with benzylamine **2a** (see Supporting Information for details), under asymmetric catalysis. Chiral Lewis acids catalysts such as BINOL-Ti/spiro-Ti complex, Salen-AlCl, Pybox/Sn(OTf)$_2$, Brønsted acids such as camphorsulphonic acid and a chiral thiourea were found to be able to effect the transformation of **3aa** to afford 4-aminopiperide product **4aa** in good to excellent yields. Disappointedly, the enantiomeric excess values obtained were very low in all cases (Supporting Information).[17] We then focused on chiral phosphoric acids (CPA) as they were renowned catalysts to activate imine

functionality enantioselectively.[18–20] A series of 17 chiral BINOL-derived phosphoric acids **CC1**–**CC17** (Supporting Information), which have fine-tuned electronic and steric effects, were tested as catalysts in the transformation of **3aa** into **4ab**. All chiral phosphoric acids showed appallingly low activity and enantioselectivity (Supporting Information) except 2,2′-bis(2,4,6-triisopropylpohenyl)-substituted chiral phosphoric acid **CC8** which produced **4aa** in 91% yield with 48.3% *ee* after 18 h in dichloromethane (DCM, Table 1). Unfortunately, further optimization of reaction conditions by screening reaction media, temperature, and reaction time did not lead to the improvement of enantiocontrol, with *ee* values never exceeding 48.3% (Supporting Information).

Although extensive examination of catalysts fabricated from different chiral scaffolds and of various reaction parameters may probably result in a better enantioselective reaction, we adopted completely a different approach to achieve efficient synthesis of highly enantiopure 4-aminopiperidine structures. In biocatalysis and biotransformation, substrate engineering, namely, structural modification of the reactants in order to best-fit the active site of enzymes, is a powerful strategy to realize high enzymatic activity and selectivity. In comparison to protein engineering, substrate engineering is generally easy-to-handle, time-saving, and cost-effective.[21] For example, we have demonstrated previously the dramatic improvement of enantioselectivity in enzyme-catalyzed hydrolysis of β-hydroxy and β-amino nitriles and carboxamides simply by protecting hydroxyl or amino with a benzyl group.[22]

Based on the assumption of effective recognition of a larger chiral pocket of **CC8** toward imine moiety through both steric and electronic (π/π and C–H/π) interactions, imine substrates bearing *N*-diphenylmethyl (DPM, **3ab**), *N*-di(4-methoxyphenyl)methyl (DMPM, **3ac**), 10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-yl (DHDBA, **3ad**) and 5*H*-dibenzo[*a*,*d*][7]annulen-5-yl (DBA, **3ae**) were designed and synthesized from the condensation reaction between aldehyde and the corresponding amines (Supporting Information). Their intramolecular cyclization reactions were investigated under the catalysis of **CC8**. To our delight, substrate engineering led to significant improvement of both efficiency and enantioselectivity of the catalytic transformation. As indicated in Table 1, under the identical conditions such as using CCl_4 as solvent, the *ee* values obtained from the reaction of **3ab** and of **3aa** were 77.8% and 35.2%, respectively, although comparable enantioselectivity was observed when reactions were performed in DCM (Table 1, entries 1, 2, 4, and 5). After further examining catalyst loading, reaction temperature and substrate concentration (Table 1, entries 6–10), an *ee* value of 88.8% was achieved for product **4ab** (Table 1, entry 11). On contrary, under such optimized conditions, namely, refluxing reactant (2.5 mM) with chiral catalyst (20 mol%) in CCl_4, reaction of **3aa** afforded product **4aa** with only 33.1% *ee* (Table 1, entry 3). Increasing the bulkiness of *N*-substituent by replacing DPM (**3ab**) with DMPM (**3ac**) caused slight decrease of enantioselectivity (Table 1, entry 12). After locking the conformation of two phenyl substituents by forming a fused carbocyclic structure, the resulting DHDBA-bearing substrate **3ad** underwent a remarkably high enantioselective cyclization reaction to afford **4ad** in an almost quantitative yield with 94.0% ee (Table 1, entry 13). Further rigidification of the carbocyclic ring substituent, however, had a detrimental effect on enantioselectivity of chiral catalysis. This has been exemplified by the drastic erosion of *ee* from 94.0% for the

Table 1 Development of Catalytic Enantioselective Nucleophilic Addition of Tertiary Enamides to Imines by Means of a Substrate Engineering Strategy

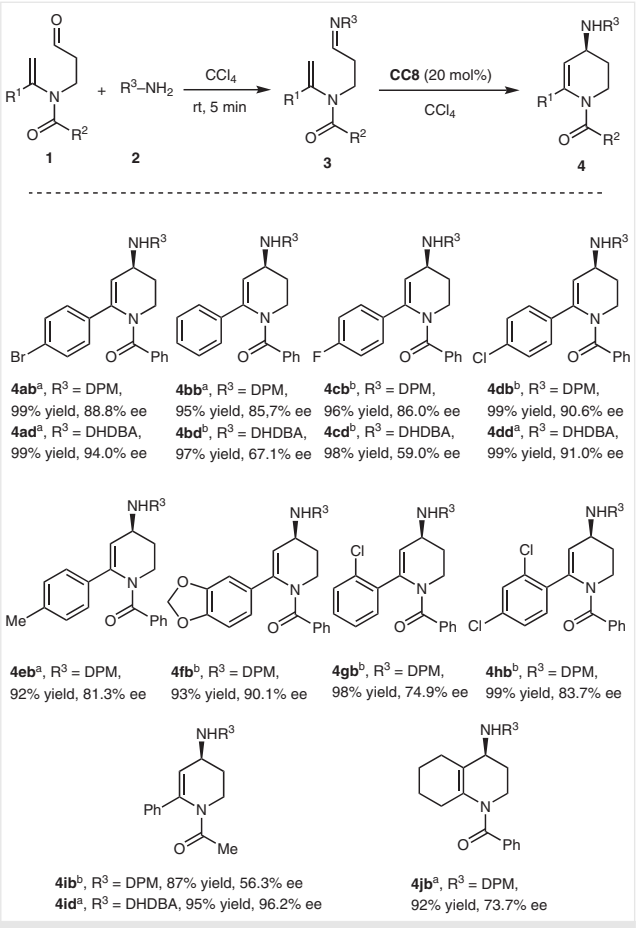


Entry	2	CC8 (mol%)	Solvent	Temp (°C)	Time	Yield (%)[b]	*ee* (%)[c]
1	**2a**	10	DCM	rt	18 h	91	48.3
2	**2a**	10	CCl_4	rt	48 h	88	35.2
3[d]	**2a**	20	CCl_4	reflux	7 h	92	33.1
4	**2b**	10	DCM	rt	2 h	97	41.1
5	**2b**	10	CCl_4	rt	8 h	99	77.8
6	**2b**	10	CCl_4	0	48 h	trace	n.d.
7	**2b**	10	CCl_4	40	1.5 h	95	80.5
8	**2b**	10	CCl_4	reflux	10 min	98	84.6
9	**2b**	5	CCl_4	reflux	30 min	96	72.9
10	**2b**	20	CCl_4	reflux	5 min	98	87.2
11[d]	**2b**	20	CCl_4	reflux	10 min	98	88.8
12[d]	**2c**	20	CCl_4	reflux	10 min	97	87.1
13[d]	**2d**	20	CCl_4	reflux	5 min	99	94.0
14[d]	**2e**	20	CCl_4	reflux	5 min	97	60.0

[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.5 mmol), solvent, rt, 5–10 min, then CPA **CC8**, *c* 10 mM.
[b] Isolated yield.
[c] Enantiomeric excess of **4** was determined by HPLC analysis on chiral stationary phase.
[d] The reaction was carried out in the concentration of *c* 2.5 mM.

reaction of DHDBA-substituted imine **3ad** to 60.0% for the reaction of DBA-substituted imine analogue **3ae** (Table 1, entries 13 and 14).

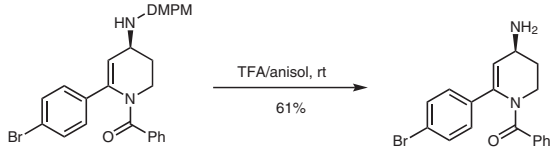
Since *N*-DPM- and *N*-DHDBA-substituted imines exhibited high level of enantiocontrol under catalysis of chiral phosphoric acid **CC8**, the scope of intramolecular nucleophilic addition of tertiary enamides to imines was then surveyed on substrates derived from amines **2b** and **2d**. The reactions were conveniently conducted using imines formed in situ. The results summarized in Scheme 1 show clearly that tertiary enamides undergo generally efficient cyclization reaction to produce 4-amino-1,2,3,4-tetrahydropyridine derivatives irrespective of the nature of the substituents. For example, reaction of all aryl-substituted tertiary enamides in which phenyl group contains either electron-withdrawing or electron-donating group(s) at different position(s) went completion within 0.5 h to generate heterocyclic products in high yields. Only in the case of *N*-acetyl-substituted enamide **3ib** and cyclohexanone-derived enamide **3jb**, a long reaction time (ca. 24–36 h) was required due to their lower enaminic reactivity. Good to excellent enantioselectivity was achieved using either DPM or DHDBA substituent on imine moiety. It is worth noting that, however, DPM outweighed DHDBA in a number of cases in the control of enantioselectivity of chiral phosphoric acid catalyzed transformation. It implied that the enantioselectivity of intramolecular nucleophilic addition of enamide moiety to chiral phosphoric acid activated imine moiety is governed by both the *N*-substituent on imine and the variation of steric and electronic effects of substituents bonded to enamide segment. The outcomes manifested again the potential of substrate engineering strategy in the synthesis of a targeted enantiopure 4-amino-1,2,3,4-tetrahydropyridine compound under the catalysis of chiral phosphoric acid.[23]



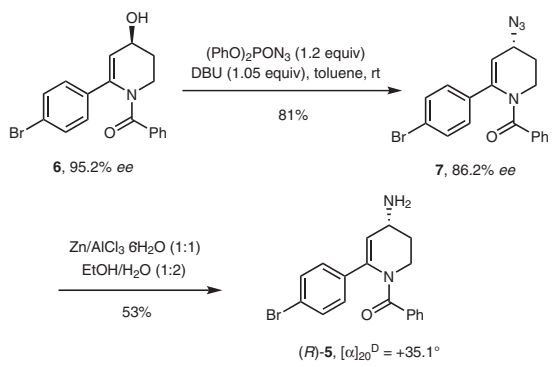
Scheme 1 Catalytic enantioselective synthesis of 4-amino-1,2,3,4-tetrahydropyridine derivatives from tertiary enamides. [a] Reflux in CCl_4. [b] Room temperature in CCl_4.

Advantage of substrate engineering protocol was further demonstrated by easy removable of the *N*-protection group. Treatment of **4ca** with trifluoroacetic acid at ambient temperature thus gave product **5** (Scheme 2). Derivatization of free amino group would therefore feasibly permit the generation of diverse compounds. To determine the absolute configuration of the product **4**, an authentic sample of (*S*)-4-hydroxy-1,2,3,4-tetrahydropyridine **6**[11b] was converted into (*R*)-4-amino-1,2,3,4-tetrahydropyridine (*R*)-**5** through azide intermediate **7** (Scheme 3). The absolute *S*-configuration was assigned to products **4ac** on the basis of the comparison of specific rotation values between (S)-**5** (Scheme 2) and (R)-**5** (Scheme 3).

In conclusion, we have shown a general and efficient method for the synthesis of highly enantiopure 4-amino-1,2,3,4-tetrahydropyridine derivatives based on intramolecular nucleophilic addition of tertiary enamides to



Scheme 2 Synthesis of (S)-**5** from **4ac** through deprotection of DMPM group



Scheme 3 Synthesis of (*R*)-**5** from authentic sample (*S*)-**6**

imines. We have also demonstrated a substrate engineering strategy enabling significant improvement of the enantioselectivity of chiral phosphoric acid catalyzed reaction.

Funding Information

We thank the National Natural Science Foundation of China (No. 21320102002, 91427301) for financial support.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610384.

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(23) **General Reaction Procedure**
A mixture of enamides **1a** (0.5 mmol) and amines **2b** (0.5 mmol) in dry CCl_4 (25 mL) was stirred at ambient temperature for 5 min. Chiral phosphoric acid catalyst **CC8** (75 mg, 0.1 mmol, 0.2 equiv) was added to the reaction system. Upon completion of the reaction, which was monitored by TLC, the reaction mixture was quenched with 10 mL sat. $NaHCO_3$ solution, then extracted with 3 × 10 mL CH_2Cl_2. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by

column chromatography on silica gel to yield pure product **4ab**. Oil (98% yield); *ee* 88.8% (chiral HPLC analysis). IR (KBr): 3422, 1723, 1656, 1601 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.44 (m, 17 H), 6.99 (br s, 2 H), 5.50 (br s, 1 H), 5.08 (s, 1 H), 4.05 (br s, 1 H), 3.74 (br s, 1 H), 3.41 (br s, 1 H), 2.00 (br s, 2 H), 1.62 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 144.0, 143.8, 140.6, 137.8, 136.2, 131.2, 130.7, 128.7, 128.6, 128.3, 128.1, 127.5, 127.34, 127.27, 127.2, 121.3, 118.6, 64.4, 48.8, 44.1, 31.2. HRMS (ESI): *m/z* calcd for $C_{31}H_{27}BrN_2O$ $[M + Na]^+$, $[M + 2 + Na]^+$: 521.1229, 523.1213; found: 521.1226, 523.1216.