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Access to the nicotine system by application of a guanidine-catalyzed asymmetric Michael addition of diphenyliminoacetate with 3-pyridyl vinyl ketone

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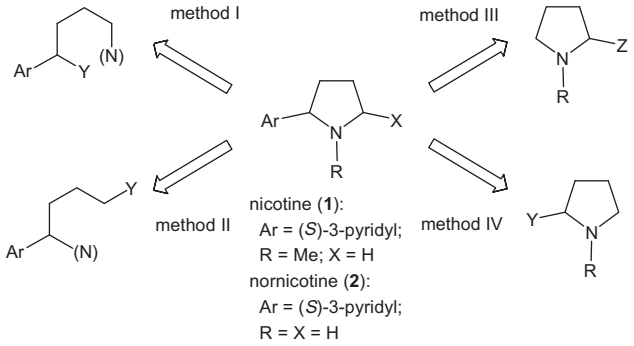
ABSTRACT

A guanidine-based chiral organocatalyst was successfully applied to the Michael addition of diphenyliminoacetate to pyridyl vinyl ketone as a key reaction for the construction of the nicotine system.

Nicotine (**1**) and nornicotine (**2**) are typical alkaloid components of tobacco (*Nicotina tabacum*), which play important roles as chemical mediators in the nervous system.[1] The first synthesis of **1** was disclosed by Pictet in 1904,[2] and, since then, much attention has been devoted to the construction of the 2-arylpyrrolidine ring system[3] because of the widespread occurrence of structurally related 5-arylprolines in nature.[4] A variety of these synthetic approaches to the 2-arylpyrrolidine ring system, including asymmetric versions, can be classified into four categories (Scheme 1): pyrrolidine ring construction from 1-functionalized 4-amino-1-arylbutanes (method I)[5], 4-functionalized 1-amino-1-arylbutanes (method II)[6], introduction of an aryl unit onto a pyrrolidine ring by direct insertion (method III)[7], and modification of proline derivatives (method IV).[8] However, there have been no reports of asymmetric synthesis of 2-arylpyrrolidines using organocatalysis.

Guanidine is a strong organic base and thus plays an important role as a base catalyst in organic synthesis.[9] Recently, we explored novel preparations of a variety of chiral guanidines[10] and observed that some of the guanidines prepared acted as effective base catalysts in asymmetric reactions such as the Michael reaction, TMS-cyanation, base-catalyzed epoxidation, alkylative esterification, and kinetic silylation.[11] Among them it was found that (+)-(*S*,*S*)-2-[(*R*)-1-(2-hydroxymethyl)phenyl ethylimino]-1,3-dimethyl-4,5-diphenylimidazolidine [(+)-ChibaG] (**3**) (and its enantiomer) affords satisfactory product formation with high enantioselectivity in both inter-[11b,e] and intramolecular Michael reactions.[11f] In the former reaction, using diphenyliminoacetate as a Michael donor, complex formation with ChibaG has been proposed in the transition state to rationalize the high asymmetric induction observed (see, Fig. 1). In order to provide further experimental support for this hypothesis, (+)-ChibaG was applied to the Michael addition of diphenyliminoacetate to 3-pyridyl vinyl ketone as a key reaction for the construction of optically active 5-pyridylprolines. We herein report the first example of organobase-catalyzed asymmetric synthesis of 5-(3-pyridyl)proline derivatives using our guanidine catalyst, ChibaG, in a formal synthesis of nicotine belonging to method I.

Our retrosynthetic analysis for the construction of the nicotine system is outlined in Scheme 2, in which (*R*)-5-*tert*-butoxycarbonyl-2-(3-pyridyl)-1,2-dehydropyrrolidine (**4**), a precursor to



Scheme 1.

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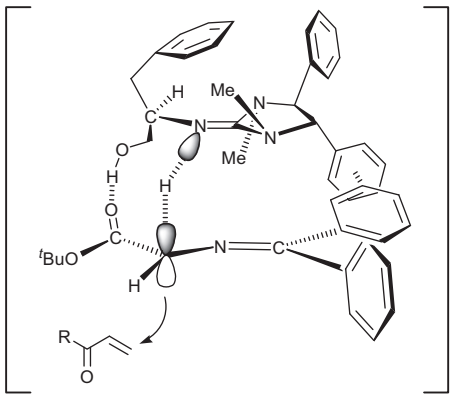


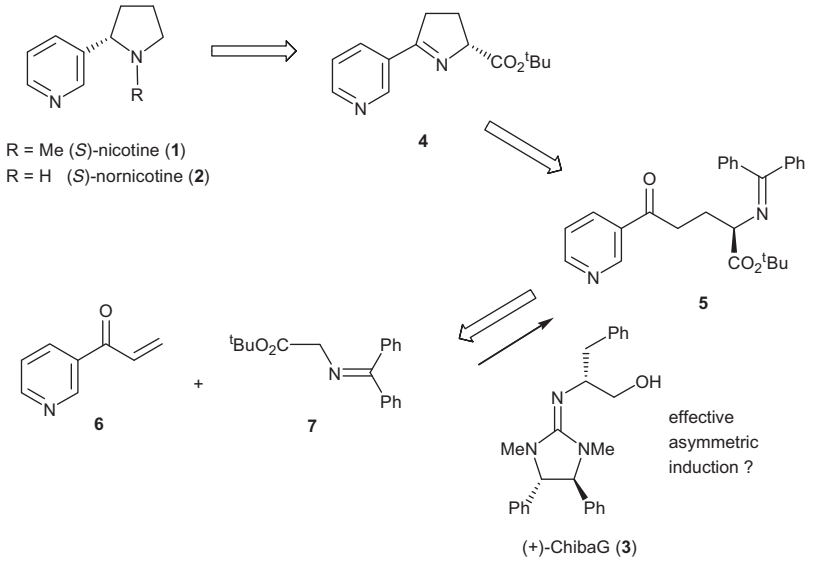
Figure 1.

(*S*)-nicotine (**1**) and (*S*)-nornicotine (**2**), would be afforded by cyclization of the (*R*)-Michael adduct **5**, itself obtained by the reaction of 3-pyridyl vinyl ketone (**6**) and *tert*-butyl diphenyliminoacetate (**7**) in the presence of (+)-ChibaG (**3**).

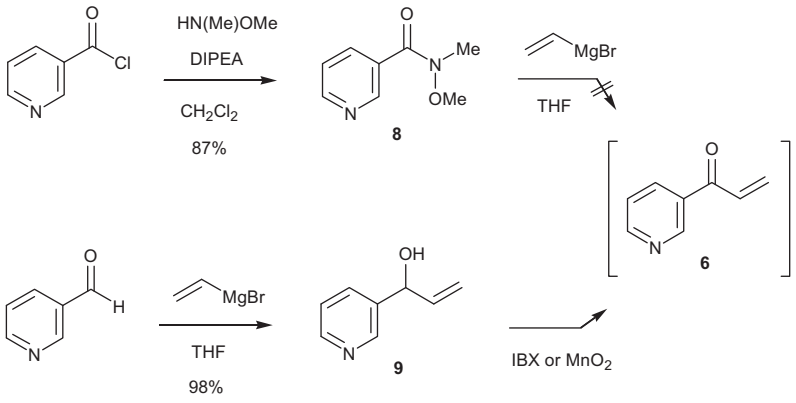
In the preparation of 3-pyridyl vinyl ketone (**6**) as a Michael acceptor, Grignard reaction of Weinreb amide **8** (derived from nicotinoyl chloride and *N,O*-dimethylhydroxylamine hydrochloride in 87% yield) with vinylmagnesium bromide failed. However, oxidation of allyl alcohol **9** (obtained by Grignard reaction of pyridine-3-carbaldehyde with vinylmagnesium bromide in 98% yield) with either activated manganese dioxide or 2-iodoxybenzoic acid (IBX)[12] successfully gave vinyl ketone **6**, which was found to be not only sensitive to air but also to polymerize readily during attempted purification by chromatography (Scheme 3). Thus, the pyridyl vinyl ketone **6** was used as a Michael acceptor in the reaction with diphenyliminoacetate **7** without further purification.

Preliminary examination of (+)-ChibaG (**3**)-catalyzed Michael reaction of diphenyliminoacetate **7** using a crude pyridyl vinyl ketone **6** showed that a Michael adduct **5** was partially hydrolyzed to give a dehydropyrrolidine derivative **4** during purification dependent upon chromatographic conditions. Hopefully, estimation of enantioselectivity in a crude adduct **5** using chiral HPLC, as expected, allowed us to deduce high asymmetric induction (93–98% ee) in the (+)-ChibaG (**3**)-catalyzed Michael reaction. Therefore, we decided to directly prepare a dehydropyrrolidine derivative **4** from allyl alcohol **9** in overall three steps (Table 1).

Thus, crude 3-pyridyl vinyl ketone **6**, obtained by IBX oxidation of **9** (step 1), was treated with an equimolar amount of diphenyliminoacetate **7** in tetrahydrofuran (THF) at −15 °C for 3 days in the presence of 20 mol % of (+)-ChibaG (**3**) to give Michael

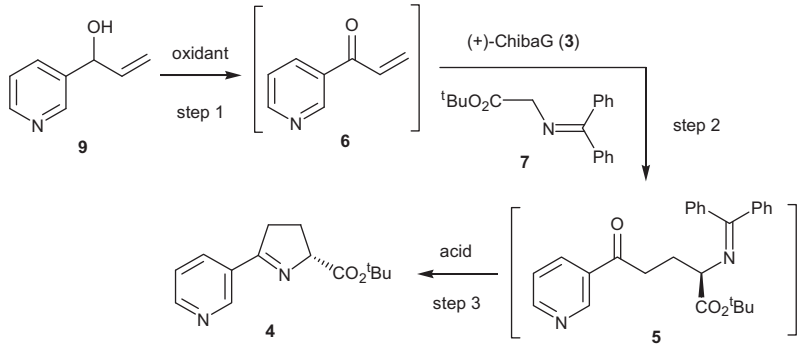


Scheme 2.



Scheme 3.

Table 1
Preparation of dehydropyrrolidine **4** from allyl alcohol **9** through (+)-ChibaG (**3**)-catalyzed Michael reaction



Entry	Step 1[a]	Step 2				Step 3	4	
	Oxidant	**3** (mol %)	Temp (°C)	Solvent	Time	Acid	Yield[b] (%)	ee[c] (%)
1	IBX	20	−15	THF	3 d	AcOH/THF/H_2O[d]	33	81
2	IBX	20	−15	THF	2 d	AcOH/THF/H_2O[e]	44	68
3	IBX	20	−15	THF	2 d	15% citric acid/THF[f]	43	89
4	MnO_2	20	−15	THF	3 d	15% citric acid/THF[f]	53	91
5	MnO_2	10	rt	THF	16 h	15% citric acid/THF[f]	28	82
6	MnO_2	10	−15	CH_2Cl_2	2 d	15% citric acid/THF[f]	34	82
7	MnO_2	5	−15	THF	5 d	15% citric acid/THF[f]	35	87
8	MnO_2	20[g]	−15	THF	3 d	15% citric acid/THF[f]	71	90
9	MnO_2	10[g]	−15	THF	7 d	15% citric acid/THF[f]	73	94

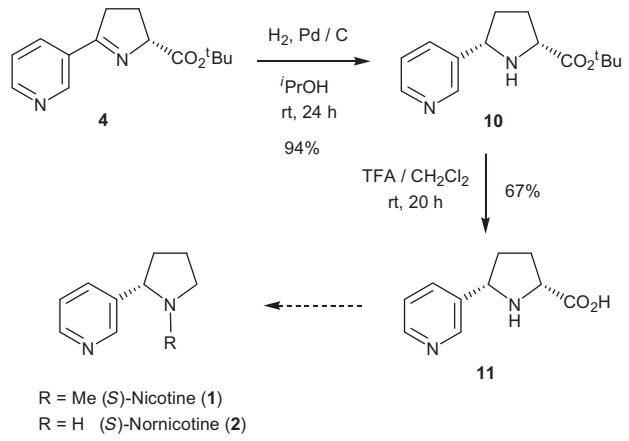
[a] IBX (1.5 M equiv) was used in DMSO at rt for 6 h, whereas MnO_2 (10 M equiv) in CH_2Cl_2 under relux for 1 d.
[b] Isolated yield.
[c] Determined by HPLC.
[d] AcOH/THF/H_2O = 1:1:1 at rt for 8 h.
[e] AcOH/THF/H_2O = 1:1:1 at rt for 12 h.
[f] 15% citric acid/THF = 2:1 at rt for 12 h.
[g] The reaction was carried out in a ratio of **7**:**9** = 1:2.

adduct **5** (step 2), which was hydrolyzed with aqueous acetic acid and THF (step 3) to afford dehydropyrrolidine **4** in 33% overall yield and with 81% ee (entry 1). Prolonging the reaction time in step 3 increased the yield, but decreased the ee (entry 2). These results showed that partial epimerization occurs during acid hydrolysis using aqueous acetic acid. The use of 15% citric acid in THF slightly improved the product formation (43%) and enantioselectivity (89% ee) (entry 3). Oxidation of **9** with MnO_2 in the place of IBX in step 1 afforded a better result (entry 4). Optimization of the molar ratios of (+)-ChibaG (**3**) and Michael donor **7** resulted in the use of 10 mol % of **3** and 200 mol % of diphenyliminoacetate **7** as the optimum situation, in which dehydropyrrolidine **4** was obtained in 73% yield with 94% ee (entry 9). From the atom economy viewpoint it should be noted that the benzophenone could be recovered and recycled as the starting material for diphenyliminoacetate **7** after the reaction.

Generation of the stereogenic center of the adduct obtained in the intermolecular Michael reaction using diphenyliminoacetate **7** is strictly controlled by matched chiral centers of the 2-imino substituent and imidazolidine ring of the ChibaG catalyst,[11b,11e] as shown in a proposed transition state for this reaction (Fig. 1). Thus, (*R*)-1,5-dehydroprolinate **4** would be predicted when (+)-ChibaG (**3**) is used as a catalyst. In addition, a negative sign in the optical rotation of **4** {$[\alpha]_D$ −91.0 (*c* 0.5, CH_2Cl_2)} strongly supported an *R* configuration of the stereogenic center by comparison with that of the closely related methyl (*S*)-5-(3-pyridyl)-3,4-dihydro-2*H*-pyrrole-2-carboxylate {$[\alpha]_D$ +82.7 (*c* 0.5, CH_2Cl_2)}.[5h]

Catalytic hydrogenation of 1,5-dehydroprolinate **4** smoothly afforded reduction product **10** as a sole isomer, the cis-configuration of which was assigned by comparison of the ^1H NMR spectrum with literature data. Hydrolysis of the *tert*-butyl ester of **10** with trifluoroacetic acid afforded 5-(3-pyridyl)proline (**11**) as a trifluroacetic acid salt (Scheme 4) and thus, the formal asymmetric synthesis of nicotine system was achieved as **11** has been previously converted into nicotine (**1**).[5a]

In summary, we have demonstrated the preparation of highly enantioenriched 5-(3-pyridyl)proline derivatives using guanidine-catalyzed asymmetric Michael reaction of diphenyliminoacetate and pyridyl vinyl ketone as the key reaction. This not only provides additional experimental evidence to support our proposed transition state for the ChibaG-catalyzed Michael reaction using diphenyliminoacetate as a Michael donor, but is also the first application of organocatalysis to the construction of the nicotine system.



Scheme 4.

Supplementary data

Supplementary data (Experimental procedures and spectroscopic data for all new compounds.) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.086.

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12. Production of complex mixtures was observed under the conditions of Swern, Dess–Martin, PCC and TPAP oxidation.