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Asymmetric Organocatalytic Intramolecular Aza-Michael Addition of Enone Carbamates: Catalytic Enantioselective Access to Functionalized 2-Substituted Piperidines

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Abstract: The synthetically useful functionalized 2-substituted piperidines containing a lateral ketone group have been strategically accessed *via* an organocatalytic enantioselective intramolecular aza-Michael addition of enone carbamates, in which a novel internal substrate combination of the enone moiety as Michael acceptor and the carbamate moiety as Michael donor was revealed in asymmetric bifunctional organocatalysis. This heteroatom conjugate addition, which was realized by using a catalytic chiral *Cinchona*-based primary-tertiary diamine and an achiral Brønsted acid, mostly proceeded in high yield and good to excellent stereocontrol (up to 99% *ee*). This reaction provides an alternative catalytic asymmetric method for installing the stereogenic nitrogen-containing carbon center in functionalized 2-substituted piperidines, leading to the development of a straightforward and expeditious synthesis of some naturally occurring bioactive 2-substituted piperidine alkaloids.

Keywords: alkaloids; aza-Michael addition; iminium catalysis; organocatalysis; piperidines

Introduction

The functionalized 2-substituted piperidine moiety with the crucial chiral stereogenic nitrogen-containing carbon center is ubiquitous in many biologically active natural products (Figure 1),[1,2] and its enantiocontrolled access is of great interest in modern organic synthesis of bioactive alkaloids and pharmaceuticals.[3] Strategically, as shown in Figure 1, the issue how to asymmetrically construct the chiral building blocks **A** definitely constitutes the key topic for the development of alternative synthetic routes to the various 2-substituted piperidine alkaloids mentioned in Figure 1. Encompassing the stereoselective construction of a nitrogen-containing stereogenic center in a functionalized 2-substituted piperidine ring system, many synthetically interesting one-step protocols have been designed and developed, for example, on the basis of polar additions, radical additions, polar substitutions, cycloadditions, electrocyclizations, rearrangements, carbene insertions as well as hydrogenations.[3] Among them, however, the asymmetric synthesis of these substituted piperidines was mostly developed by using stoichiometric chiral substrates[4] and chiral reagents[5] in a diastereoselective manner. Although advances were increasingly made in this area,[3–5] there is still a high demand for *direct catalytic asymmetric synthesis* of such chiral functionalized piperidines. To the best of our knowledge, only a few one-pot synthetic protocols *operating in catalytic enantioselective fashion* were revealed for the expeditious synthesis of these chiral piperidine derivatives with the key nitrogen-containing stereogenic center, which mainly included: (i) secondary amine-catalyzed aza-Michael addition[6a,b] and tandem Mannich-type/cyclization;[6c] (ii) titanocene-catalyzed hydrosilylation;[7] (iii) boron-, copper- and zirconium-catalyzed aza-Diels–Alder reaction;[8] (iv) rhodium-catalyzed

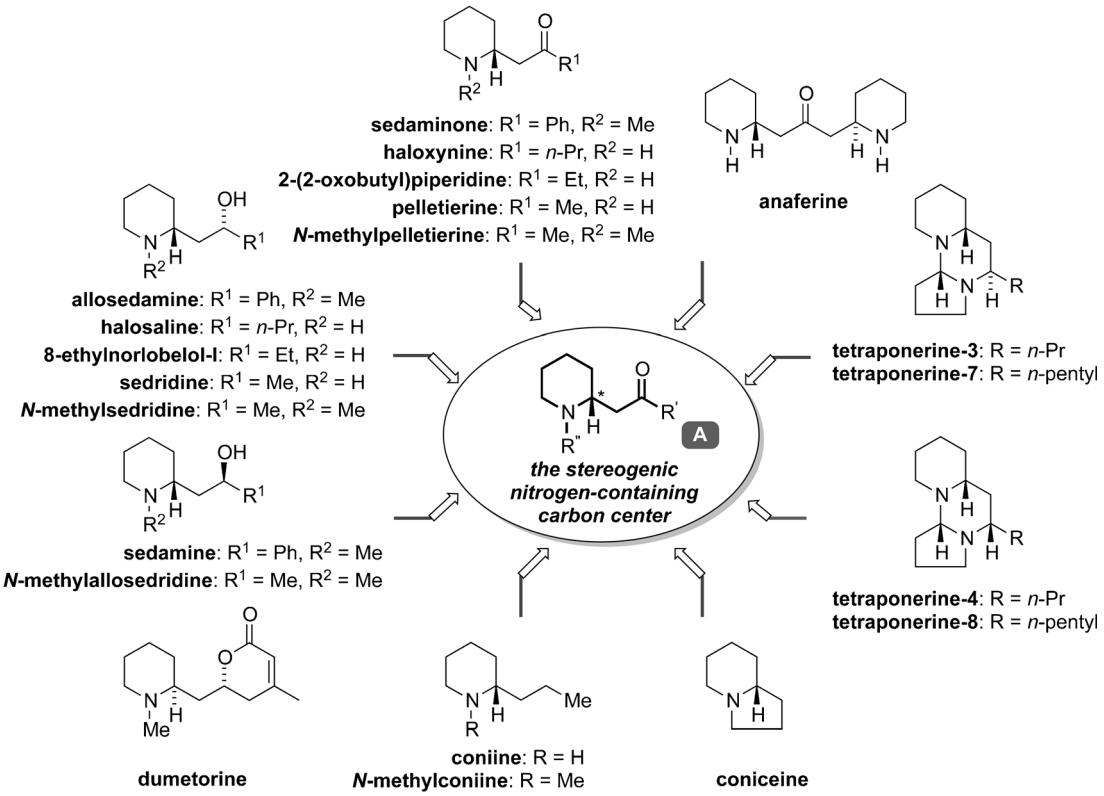
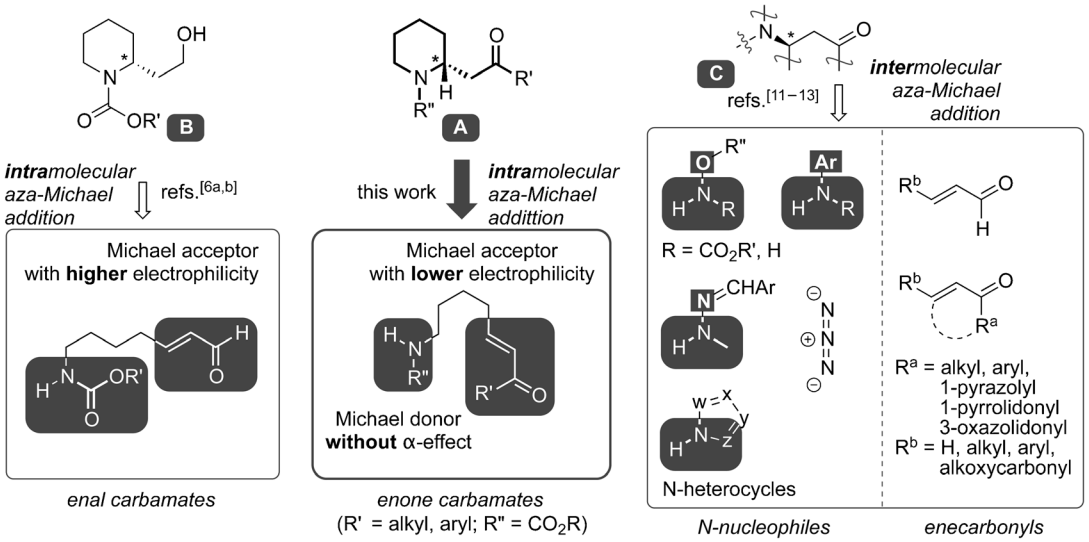


Figure 1. Representative 2-substituted piperidine alkaloids.

carbene insertion;[9] and (v) Brønsted acid-catalyzed tandem aza-ene/cyclization.[10]

Of these catalytic asymmetric synthetic methods reported in the literature, especially attractive from a synthetic point of view was the prospect of the synthesis of 2-substituted piperidines *via* enantioselective intramolecular aza-Michael addition, which is one of the most fundamental organic reactions for the formation of carbon-nitrogen bonds in modern organic chemistry. In this aspect, chiral 2-substituted nitrogen heterocycles bearing the side chain primary hydroxy group (**B**, Scheme 1) were accessed through the iminium catalysis of a chiral secondary amine,[6a,b] followed by the subsequent reduction, wherein α,β-unsaturated

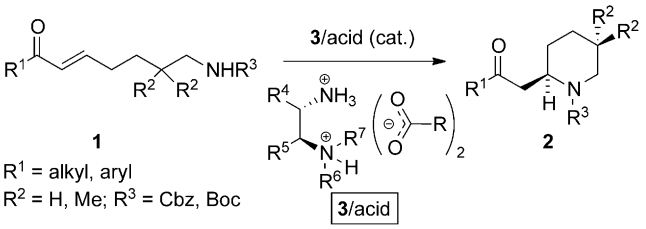


Scheme 1. Substrate combinations of donor and acceptor in organocatalytic asymmetric aza-Michael addition.

aldehydes containing carbamate as a nitrogen nucleophile, *enal carbamates*, have been considered as properly designed substrates for the intramolecular aza-Michael reaction catalyzed by the Jørgensen catalyst. Notably, in addition to the intramolecular heteroatom conjugate addition mentioned above, recently the organocatalytic asymmetric intermolecular aza-Michael addition was also developed for forging the nitrogen-containing asymmetric carbon center (**C**, Scheme 1).[11–13] Despite these elegant explorations of asymmetric installation of the stereogenic nitrogen-containing carbon center,[11–14] particularly in functionalized nitrogen heterocycles,[15] the straightforward catalytic enantioselective access to 2-substituted piperidines having a β-amino ketone moiety, the key synthons **A** in Figure 1, which will strategically provide an alternative effective route to many alkaloids containing 2-substituted piperidine nucleus, has not been presented to date by using organocatalytic conjugate addition strategy.

As was known, generally the carbonyl function of enones is less electrophilic than that of enals, thereof leading to the lesser efficiency of LUMO-lowering iminium activation for the enone carbonyl as Michael acceptor, particularly in chiral secondary amine catalysis.[16] Compared with the vast emergence of asymmetric protocols involving enals,[16] the enones remain to some extent challenging to asymmetric catalysis using chiral amine-catalyzed aza-Michael additions.[17,18] Of various nitrogen-centered nucleophiles, *N*-alkoxy carbamates (**R″O**−NH−CO_2R′), in which the N−O functionality could enhance nucleophilicity at the nitrogen center *via* the α-effect,[19] were appealing as a nucleophilically enhanced Michael donor and preferentially used in most cases of catalytic asymmetric intermolecular aza-Michael reaction, especially in organocatalysis.[11–14] Synthetically, however, the carbamates (**R″O**−NH−CO_2R′) without an α-effect would be one of the most desirable selections as Michael donors, due to the mild conditions for *N*-deprotection and the high potential for amine derivatization.

To address the synthesis of building blocks **A** in Figure 1 as well as explore the new substrate combination of donor and acceptor in conjugate addition, an asymmetric intramolecular aza-Michael reaction of *enone carbamates* can be rationally conceived as shown in Scheme 1, wherein an α,β-unsaturated ketone moiety and the carbamate motif would act as Michael acceptor and Michael donor, respectively. With the interest in the catalytic enantioselective access to functionalized 2-substuituted piperidines, recently we developed an asymmetric organocatalytic intramolecular aza-Michael reaction of enone carbamates **1** on the basis of bifunctional chiral primary-tertiary diamine/Brønsted acid catalysis (Scheme 2). Herein, we present our results on this topic.

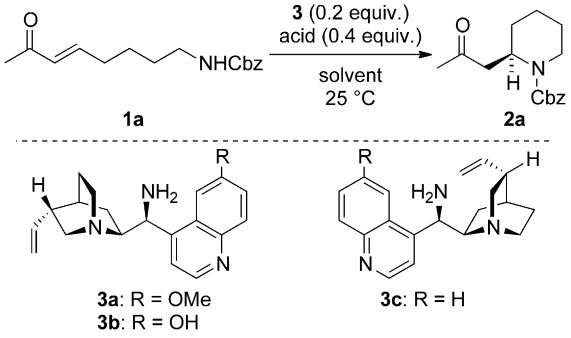


Scheme 2. Catalytic asymmetric aza-Michael addition catalyzed by primary-tertiary diamine/Brønsted acid.

Results and Discussion

According to the acid-base activation mode for Michael acceptor (the enone unit) and Michael donor (the carbamate unit), a chiral catalyst salt *in situ* formed from quinine-derived primary-tertiary diamine **3a** and Brønsted acid TsOH·H_2O was firstly employed in the initial evaluation of the reaction conditions using **1a** as model substrate (Table 1). Among the solvents examined (entries 1–4), the aprotic THF as reaction medium showed the more promising enantioselectivity (57% *ee*) in the controlled experiments. Surprisingly, the reversed enantioselectivity in this model reaction was observed by means of chiral HPLC analysis of **2a** when using CH_3CN (entry 3) or *i*-PrOH (entry 4) as solvent, despite the unknown exact role of these solvents in the present asymmetric catalysis. To further improve the stereocontrol of this aza-Michael addition, several acid additives were investigated (entries 5–10). Structurally comparable with 4-methylbenzenesulfonic acid as acid additive in THF (entry 2), 2,4,6-trimethylbenzenesulfonic acid ($MesSO_3H$) was found ineffective in this reaction (entry 5), indicating that the steric bulkiness of the acid component had a negative impact on reactivity. In addition to arylsulfonic acids (entries 2 and 5), two alkylsulfonic acids (D-camphor-10-sulfonic acid and CF_3SO_3H) were also subjected to this model reaction. Interestingly, it was found that D-camphor-10-sulfonic acid (D-CSA, entry 6) could promote this conjugate addition to give the aza-Michael adduct in 91% yield with 85% *ee*, despite a longer reaction time of 72 h. When the more acidic CF_3SO_3H was used in this case (entry 7), the reaction proceeded readily, but without any asymmetric induction, demonstrating that the acidic property of Brønsted acid, to some extent, also had an obvious influence on the enantioselectivity in this aza-Michael addition. Based on this fact, three carboxylic acids were further examined (entries 8–10). Among them, gratifyingly, CF_3CO_2H as acid additive was found to be effective in this asymmetric aza-Michael reaction, readily affording **2a** in 95% yield with excellent enantioselectivity of 98% *ee* (entry 10), wherein its *R* absolute configuration was assigned by a comparison of the optical rotation of **2a** with the literature value.[21a] For examining the enantioselective

Table 1. Optimization of reaction conditions.[a]



Entry	3	Acid	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c,d]
1	**3a**	$TsOH·H_2O$	CH_2Cl_2	48	96	52 (*R*)
2	**3a**	$TsOH·H_2O$	THF	75	92	57 (*R*)
3	**3a**	$TsOH·H_2O$	CH_3CN	42	93	7 (*S*)
4	**3a**	$TsOH·H_2O$	*i*-PrOH	20	95	35 (*S*)
5	**3a**	$MesSO_3H$[f]	THF	168	trace[e]	ND[f]
6	**3a**	D-CSA[f]	THF	72	91	85 (*R*)
7	**3a**	CF_3SO_3H	THF	32	90	0
8	**3a**	*p*-NBA[f]	THF	168	trace[e]	ND[f]
9	**3a**	NBLP[f]	THF	168	trace[e]	ND[f]
10	**3a**	CF_3CO_2H	THF	8	95	98 (*R*)
11	**3b**	CF_3CO_2H	THF	8	95	78 (*R*)
12	**3c**	CF_3CO_2H	THF	7	95	80 (*S*)

[a] To a solution of the acid (0.04 mmol) in solvent (0.6 mL) was sequentially added the catalyst **3** (0.02 mmol) and the enone carbamate **1a** (0.1 mmol) at 25 °C. The reaction was monitored by TLC inspection (unless otherwise noted).

[b] Yield of isolated product.

[c] Determined by chiral HPLC.

[d] The absolute configuration of the major enantiomer is presented in parentheses, and was assigned by the chiral HPLC analysis and a comparison of the optical rotation of **2a** in entry 10 with the literature value (see ref.[21a]).

[e] The starting material was mainly recovered.

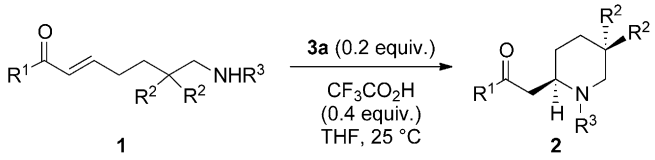
[f] Abbreviations: D-CSA = D-camphor-10-sulfonic acid; $MesSO_3H$ = 2,4,6-trimethylbenzenesulfonic acid; *p*-NBA = 4-nitrobenzoic acid; NBLP = *N*-Boc-L-phenylglycine; ND = not determined.

influence of the hydrogen-bonding interaction from the phenolic hydroxy group in the catalyst, the cupreine-derived primary-tertiary diamine **3b** was employed using THF as solvent in the presence of CF_3CO_2H as acid additive (entry 11). In this case, the aza-Michael addition proceeded smoothly in 95% yield, but the decreased enantioselectivity of 78% *ee* implied an absence of synergistic hydrogen bonding interactions, to some extent, demonstrating the incompatibility of the existence of a phenolic hydrogen-bonding site in the catalyst with the current stereocontrol. Notably to investigate the tunable stereochemistry in products, the primary-tertiary diamine **3c**, which was prepared from cinchonine (a pseudo-enantiomer of quinine), was subjected to this catalytic asymmetric aza-Michael addition (entry 12), expectedly affording **2a** with the reversed absolute configuration, albeit in a lower *ee* of 80%. From the above-mentioned investigation of reaction conditions, the optimal combination involving **3a** as catalyst, CF_3CO_2H as acid and THF as solvent (entry 10) was eventually identified for this enantioselective intramolecular aza-Michael addition of enone carbamates, whereby the opposite stereocontrol could be accessed by using **3c** instead of **3a**.

To demonstrate the generality of this asymmetric intramolecular aza-Michael addition, as shown in Table 2, a series of enone carbamates **1** was examined under the above-optimized organocatalysis, yielding various functionalized piperidines with up to 99% *ee*. Structurally compared with the model substrate **1a** (entry 1 of Table 2), the enone carbamate **1b** containing the Michael donor moiety of the bulky *N*-Boc instead of *N*-Cbz was used in this case (entry 2), and a similar reactivity was observed, but following a decreased enantiocontrol of 90% *ee*. When the intramolecular aza-Michael addition of *gem*-dimethyl substituted enone carbamate **1c** was conducted, the positive *gem*-dimethyl effect[20] was observed and the product **2c** was readily obtained in 97% yield with 99% *ee* (entry 3). Notably, the reactivity of this intramolecular conjugate addition of carbamates to enones, to a large extent, depends upon the steric bulk and electrophilicity of enone carbonyl group as Michael acceptor center. For example, various substrates **1d**–**1j** with alkyl- and aryl-substituted enone moieties were further investigated (entries 4–10), and a prolonged reaction time was required to complete the corresponding addition transformation, especially for the cases using aryl-substituted enone carbamates **1g**, **1h** and **1j** (entries 7, 8 and 10). Despite the lower reactivity mentioned above, 2-substituted functionalized piperidine products **2d**–**2h** and **2j** were formed in good to excellent yield with high enantioselectivity in most of cases (entries 4–8 and 10). The employment of *para*-methoxyphenyl-substituted enone carbamate **1i** (entry 9) only resulted in the formation of trace amounts of product after 5 days, showing the ineffective LUMO-lowering iminium activation for the highly electron-enriched aryl enone motif under the current catalysis.

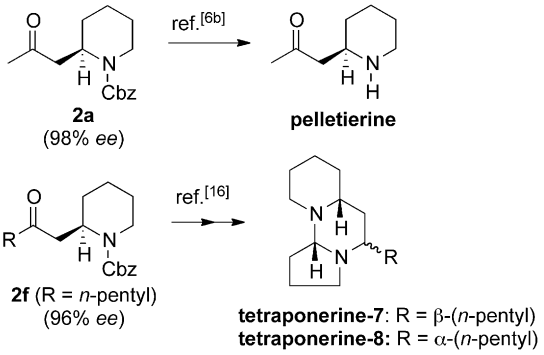
From a synthetic point of view, it is noteworthy that our catalytic enantioselective assembly of a stereogenic nitrogen-containing carbon center in the functionalized 2-substituted piperidines potentially provides a straightforward effective synthesis of many biologically interesting 2-substituted piperidine alkaloids described in Figure 1. For one example in Scheme 3, the one-step Cbz-deprotection of product **2a** (98% *ee*, entry 1 of Table 2) *via* the hydrogenation could deliver the anthelmintic alkaloid pelletierine,[6b] which was firstly isolated by Tanret in 1878 and later structurally

Table 2. Organocatalytic asymmetric synthesis of functionalized piperidines.[a]



Entry	Substrate	R^1	R^2	R^3	Product	*t* [h]	Yield [%][b]	Ee [%][c,d]
1	**1a**	Me	H	Cbz	**2a**	8	95	98 (*R*)
2	**1b**	Me	H	Boc	**2b**	8.5	94	90
3	**1c**	Me	Me	Cbz	**2c**	7	97	99
4	**1d**	Et	H	Cbz	**2d**	10	94	96 (*R*)
5	**1e**	*i*-Bu	H	Cbz	**2e**	14	96	99
6	**1f**	*n*-pentyl	H	Cbz	**2f**	12	93	96 (*R*)
7	**1g**	Ph	H	Cbz	**2g**	24	95	96
8	**1h**	4-Me-C_6H_4	H	Cbz	**2h**	120	75	96
9	**1i**	4-MeO-C_6H_4	H	Cbz	**2i**	120	trace[e]	ND[f]
10	**1j**	4-NO_2-C_6H_4	H	Cbz	**2j**	84	80	85

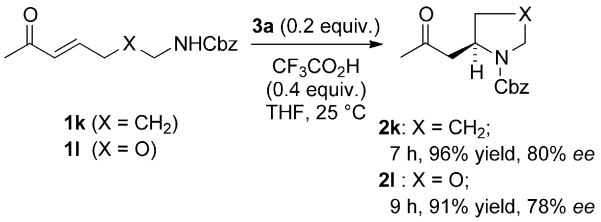
[a] To a solution of CF_3CO_2H (0.04 mmol) in THF (0.6 mL) was sequentially added the chiral diamine **3a** (0.02 mmol) and the enone carbamate **1** (0.1 mmol) at 25 °C (For details, see the Supporting Information).
[b] Yield of isolated product.
[c] Determined by chiral HPLC.
[d] The absolute configurations of **2a**, **2d** and **2f** were assigned as "*R*" by comparison of their optical rotations with the literature values (see ref.[21]), and accordingly the absolute stereochemistries of entries 2–3, 5, 7–8 and 10 were provisionally established as indicated.
[e] The starting material was mainly recovered.
[f] ND = not determined.



Scheme 3. Formal synthesis using functionalized 2-substituted piperidine products.

determined through NMR studies in 1961. Commencing with **2f**, another synthetic instance in Scheme 3 was exemplified by the formal synthesis of insecticidal alkaloids, tetraponerine-7 and tetraponerine-8,[21] which were initially isolated from the venom of New Guinean ant *Tetraponera* sp. in 1987 and structurally determined by X-ray diffraction analysis in the same year. Certainly, the present asymmetric organocatalytic methodology does constitute a direct route to synthetically useful 2-substituted piperidine building blocks **2** *via* intramolecular aza-Michael addition of enone carbamates.

In addition to the aforementioned synthesis of six-membered piperidine derivatives, two examples concerning an asymmetric access to five-membered heterocycles were also developed. As shown in Scheme 4, the 5-*exo*-trig addition of enone carbamates **1k** and **1l** took place under the catalysis of chiral salts consisting of **3a** and CF_3CO_2H, giving the related functionalized pyrrolidine **2k** (96% yield, 80% *ee* with *R* absolute configuration) and oxazolidine **2l** (91% yield, 78% *ee*).[22]



Scheme 4. Organocatalytic asymmetric synthesis of five-membered heterocycles.

According to the assignment of absolute configuration by literature comparisons,[21,22] a mechanistic rationale, which was exemplified by the conjugate reaction of **1a** catalyzed by **3a**/CF_3CO_2H, was proposed for the observed enantioselectivity in the current organocatalytic asymmetric heteroatom Michael addition. As demonstrated in Figure 2, the energetically favored (*E*)-*s*-*trans* conformer of α,β-unsaturated imi-

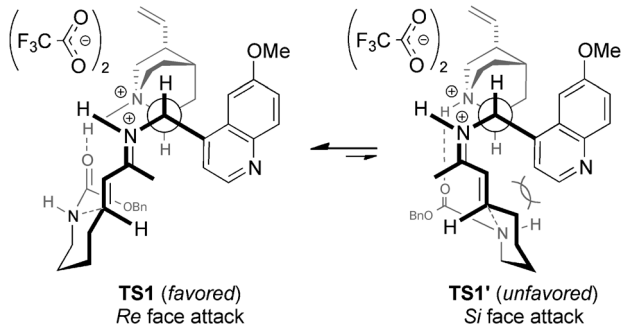


Figure 2. Proposed mechanistic model for the observed enantioselectivity under the catalysis of **3a**.

nium ion was preferentially formed *in situ*, simultaneously followed by the hydrogen-bonding interaction between the protonated tertiary amine and the carbamate carbonyl oxygen, giving the proposed acid-base bifunctional catalysis mode. Owing to the existence of unfavorable steric hindrance in transitional state **TS1′**, the carbamate nitrogen-centered nucleophilic attack onto the *Re* face of unsaturated iminium moiety proceeded predominantly *via* the favored **TS1**, delivering the aza-Michael adduct **2a** with *R* absolute configuration.

Conclusions

In conclusion, a novel intramolecular aza-Michael addition of enone carbamates was developed on the basis of acid-base bifunctional organocatalysis, in which the less electrophilic enone acceptor and the less nucleophilic carbamate donor constitute the novel substrate combination for the heteroatom Michael reaction. Importantly, a series of synthetically useful 2-substituted six- and five-membered heterocycles (up to 99% *ee*), which resulted from the current aza-Michael addition protocol using the catalytic combination of chiral primary-tertiary diamine and simple achiral Brønsted acid, were accessed in catalytic enantioselective fashion. This methodology does provide an alternative enantioselective pathway for establishing the stereogenic nitrogen-containing carbon center in the functionalized 2-substituted piperidines, which could facilitate the development of a straightforward expeditious synthesis of many naturally occurring bioactive 2-substituted piperidine alkaloids.

Experimental Section

NMR spectra were recorded with TMS as an internal standard in $CDCl_3$ or CD_3COCD_3 by means of a Mercury-plus 300BB spectrometer (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR spectra) and a Bruker AM-400 spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR spectra). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), brs (broad singlet). The mass spectra were recorded on an HP5988 A or a TRACE DSQ mass spectrometer by means of the EI technique, and the high-resolution mass spectra were recorded on a Bruker APEX II spectrometer by means of the ESI technique. Optical rotations were measured at 589 nm at 20 °C by Perkin–Elmer 341. TLC was performed on glass-backed silica plates. Enantiomeric excess was determined by HPLC analysis on Daicel Chiralcel AD, OD, OD-H columns by Agilent-1100 series. Silica gel (200–300 mesh) for flash column chromatography and GF_{254} for TLC were produced by Qingdao Marine Chemical Company (China). Solvents for reaction were distilled prior to use: THF and Et_2O from Na and benzophenone, MeOH from Mg and I_2, CH_2Cl_2, Et_3N, CH_3CN and DMF from CaH_2, and toluene from $LiAlH_4$. All air- or moisture-sensitive reactions were conducted under an argon atmosphere.

General Procedure for Organocatalytic Asymmetric Intramolecular Aza-Michael Addition of Enone Carbamates

To a solution of CF_3CO_2H (0.04 mmol) in THF (0.6 mL) was sequentially added the chiral diamine **3a** (0.02 mmol) and enone carbamates **1** (0.1 mmol) at 25 °C. The reaction was monitored by TLC inspection (unless otherwise noted) and proceeded for the indicated time. After removal of the solvent, the residue was purified by flash column chromatography on silica gel (petroleum ether:AcOEt = 4:1), affording the aza-Michael adducts **2**.

(*R*)-*N*-Benzyloxycarbonyl-2-(2-oxopropyl)piperidine (2a): Following the *General Procedure* mentioned above, the reaction gave the product **2a**; yield: 26.1 mg (0.095 mmol, 95%); R_f = 0.6 (petroleum ether/EtOAc = 2:1); $[\alpha]_D^{20}$: +9 (*c* 1.0 in $CHCl_3$). The enantiomeric excess of 98% was measured by HPLC (chiralcel OD-H, *n*-hexane/*i*-PrOH = 95/5; flow rate 0.5 mL min^{-1}; λ = 220 nm): t (minor) = 28.4 min, t (major) = 30.4 min. The absolute configuration of **2a** was assigned as "*R*" by a comparison of its optical rotation with the literature value {$[\alpha]_D^{25}$: +10.18 (*c* 2.5 in $CHCl_3$)}.[21a] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 5H), 5.14, 5.11 (ABq, *J* = 12.8 Hz, 2H), 4.81 (d, *J* = 4 Hz, 1H), 4.10–4.00 (m, 1H), 2.89–2.83 (m, 1H), 2.74–2.68 (m, 2H), 2.14 (s, 3H), 1.68–1.40 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.8, 155.2, 136.7, 128.4, 127.9, 127.8, 67.1, 47.5, 44.3, 39.8, 30.0, 28.2, 25.2, 18.8; MS (70 eV, EI): *m*/*z* (%) = 275 (< 1) $[M]^+$, 218 (1), 184 (12), 174 (19), 140 (61), 91 (100), 65 (8), 43 (8); HR-MS (ESI): *m*/*z* = 276.1596, calcd. for $C_{16}H_{22}NO_3$ $[M+H]^+$: 276.1594.

(*R*)-*N*-*tert*-Butoxycarbonyl-2-(2-oxopropyl)piperidine (2b): Following the *General Procedure* mentioned above, the reaction gave the product **2b**; yield: 22.6 mg (0.094 mmol, 94%); R_f = 0.6 (petroleum ether/EtOAc = 2:1); $[\alpha]_D^{20}$: +12 (*c* 1.0 in $CHCl_3$). The enantiomeric excess of 90% was measured by HPLC (chiralcel AD, *n*-hexane/*i*-PrOH = 99/1; flow rate 1.0 mL min^{-1}; λ = 220 nm): t (major) = 13.8 min, t (minor) = 15.5 min. The *R* absolute configuration of **2b** was provisionally assigned according to the stereochemical determination of **2a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.73 (brs, 1H), 3.96 (brs, 1H), 2.78 (t, *J* = 12.8 Hz, 1H),

2.66–2.64 (m, 2H), 2.19 (s, 3H), 1.67–1.37 (m, 6H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.2, 153.7, 78.6, 46.3, 43.3, 38.4, 29.1, 27.4, 24.3, 17.9; MS (70 eV, EI): *m/z* (%) = 241 (4) $[M]^+$, 184 (12), 168 (18), 84 (57), 71 (53), 57 (100), 43 (71); HR-MS (ESI): *m/z* = 242.1757, calcd. for $C_{13}H_{24}NO_3$ $[M+H]^+$: 242.1751.

(*R*)-*N*-Benzyloxycarbonyl-5,5-dimethyl-2-(2-oxopropyl) piperidine (2c): Following the *General Procedure* mentioned above, the reaction gave the product **2c**; yield: 29.4 mg (0.097 mmol, 97% yield); R_f = 0.5 (petroleum ether/EtOAc = 2:1); $[\alpha]_D^{20}$: −9 (*c* 1.0 in $CHCl_3$). The enantiomeric excess of 99% was measured by HPLC (chiralcel OD-H, *n*-hexane/*i*-PrOH = 95/5; flow rate 0.5 mL min^{-1}; λ = 220 nm): t (minor) = 19.7 min, t (major) = 21.1 min. The *R* absolute configuration of **2c** was provisionally assigned according to the stereochemical determination of **2a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.31 (m, 5H), 5.17–5.08 (m, 2H), 4.83 (brs, 1H), 3.64 (brs, 1H), 2.65 (brs, 3H), 2.24–2.02 (brs, 3H), 1.96–1.86 (m, 1H), 1.44–1.39 (m, 2H), 1.32–1.26 (m, 1H), 0.92 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.8, 155.6, 136.8, 128.4, 127.9, 127.8, 67.1, 50.2, 46.9, 44.2, 32.5, 30.9, 30.5, 28.8, 24.4, 23.0; MS (70 eV, EI): *m/z* (%) = 304 (1) $[M+H]^+$, 246 (2), 212 (7) , 202 (12), 168 (42), 91 (100), 65 (20), 43 (87); HR-MS (ESI): *m/z* = 304.1914, calcd. for $C_{18}H_{26}NO_3$ $[M+H]^+$: 304.1907.

(*R*)-*N*-Benzyloxycarbonyl-2-(2-oxobutyl)piperidine (2d): Following the *General Procedure* mentioned above, the reaction gave the product **2d**; yield: 27.2 mg (0.094 mmol, 94%); R_f = 0.6 (petroleum ether/EtOAc = 2:1); $[\alpha]_D^{20}$: +8 (*c* 1.0 in $CHCl_3$). The enantiomeric excess of 96% was measured by HPLC analysis (chiralcel OD-H, *n*-hexane/*i*-PrOH = 95/5; flow rate 0.5 mL min^{-1}; λ = 220 nm): t (minor) = 20.8 min, t (major) = 22.8 min. The absolute configuration of **2d** was assigned as "*R*" by a comparison of its optical rotation with the literature value {$[\alpha]_D^{20}$: +9.5 (*c* 0.64 in $CHCl_3$)}.[21b] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 5H), 5.12 (s, 2H), 4.79 (d, *J* = 5.6 Hz, 2H), 4.04 (brs, 1H), 2.87–2.84 (m, 1H), 2.72–2.64 (m, 2H), 2.42 (brs, 2H), 1.64–1.39 (m, 6H), 1.00 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.3, 155.2, 136.7, 128.4, 127.8, 127.7, 67.0, 47.6, 42.8, 39.7, 36.0, 28.2, 25.2, 18.8, 7.6; MS (70 eV, EI): *m/z* (%) = 289 (<1) $[M]^+$, 218 (1), 198 (3), 174 (7), 154 (36), 98 (9), 91 (100), 65 (11); HR-MS (ESI): *m/z* = 290.1758, calcd. for $C_{17}H_{24}NO_3$ $[M+H]^+$: 290.1751.

(*R*)-*N*-Benzyloxycarbonyl-2-(4-methyl-2-oxopentyl)-piperidine (2e): Following the *General Procedure* mentioned above, the reaction gave the product **2e**; yield: 30.4 mg (0.096 mmol, 96%); R_f = 0.6 (petroleum ether/EtOAc = 2:1); $[\alpha]_D^{20}$: +4 (*c* 1.0 in $CHCl_3$). The enantiomeric excess of 99% was measured by HPLC (chiralcel OD-H, *n*-hexane/*i*-PrOH = 97/3; flow rate 0.5 mL min^{-1}; λ = 220 nm): t (minor) = 19.4 min, t (major) = 22.4 min. The *R* absolute configuration of **2e** was provisionally assigned according to the stereochemical determinations of **2a**, **2d** and **2f**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.22 (m, 5H), 5.06, 5.03 (ABq, *J* = 12.4 Hz, 2H), 4.75–4.68 (m, 1H), 3.98 (d, *J* = 12 Hz, 1H), 2.77 (t, *J* = 12.8 Hz, 1H), 2.65–2.59 (m, 1H), 2.53–2.48 (m, 1H), 2.20–2.18 (m, 2H), 2.05–1.98 (m, 1H), 1.62–1.11 (m, 6H), 0.80 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.7, 155.2, 136.8, 128.4, 127.9, 127.8, 67.0, 51.9, 47.5, 43.6, 39.8, 28.1, 25.2, 24.5, 22.49, 22.46, 18.8; MS (70 eV, EI): *m/z* = (%) = 260 (<1), 226 (1), 218 (1), 196 (15) , 182 (18), 174 (10), 98 (12), 91 (100), 65 (17), 57 (13); HR-MS (ESI): *m/z* = 318.2067, calcd. for $C_{19}H_{28}NO_3$ $[M+H]^+$: 318.2064.

(*R*)-*N*-Benzyloxycarbonyl-2-(2-oxoheptyl)-piperidine (2f): Following the *General Procedure* mentioned above, the reaction gave the product **2f**; yield: 30.8 mg (0.093 mmol, 93%); R_f = 0.6 (petroleum ether/EtOAc = 2:1); $[\alpha]_D^{20}$: +5 (*c* 1.0 in $CHCl_3$). The enantiomeric excess of 96% was measured by HPLC (chiralcel OD-H, *n*-hexane/*i*-PrOH = 95/5; flow rate 0.5 mL min^{-1}; λ = 220 nm): t (minor) = 16.7 min, t (major) = 18.8 min. The absolute configuration of **2f** was assigned as "*R*" by a comparison of its optical rotation with the literature value {$[\alpha]_D^{20}$: +4.4 (*c* 1.54 in $CHCl_3$)}.[21b] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 5H), 5.12 (s, 2H), 4.82–4.76 (m, 1H), 4.06 (d, *J* = 12.8 Hz, 1H), 2.87 (t, *J* = 12.8 Hz, 1H), 2.73–2.59 (m, 2H), 2.40 (brs, 2H), 1.68–1.41 (m, 8H), 1.33–1.26 (m, 4H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.0, 155.3, 136.8, 128.4, 127.9, 127.8, 67.0, 47.6, 43.2, 39.8, 31.3, 28.2, 25.2, 23.4, 22.4, 18.8, 13.9; MS (70 eV, EI): *m/z* (%) = 332 (<1) $[M+H]^+$, 277 (<1), 240 (3), 196 (46), 174 (13), 98 (11), 91 (100), 43 (21); HR-MS (ESI): *m/z* = 332.2216, calcd. for $C_{20}H_{30}NO_3$ $[M+H]^+$: 332.2220.

(*R*)-*N*-Benzyloxycarbonyl-2-(2-oxo-2-phenylethyl)-piperidine (2g): Following the *General Procedure* mentioned above, the reaction gave the product **2g**; yield: 32.0 mg (0.095 mmol, 95%); R_f = 0.5 (petroleum ether/EtOAc = 2:1); $[\alpha]_D^{20}$: −13 (*c* 1.0 in $CHCl_3$). The enantiomeric excess of 98% was measured by HPLC (chiralcel OD-H, *n*-hexane/*i*-PrOH = 95/5; flow rate 0.5 mL min^{-1}; λ = 230 nm): t (minor) = 26.8 min, t (major) = 28.3 min. The *R* absolute configuration of **2g** was provisionally assigned according to the stereochemical determinations of **2a**, **2d** and **2f**, as well as by a comparison of its optical rotation with that of the Boc-protected analogue in the literature {$[\alpha]_D^{20}$: −9.7 (*c* 1.0 in $CHCl_3$)}.[23] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (brs, 2H), 7.48–7.44 (m, 1H), 7.32–7.23 (m, 7H), 5.01 (brs, 2H), 4.84 (brs, 1H), 4.03 (brs, 1H), 3.22–3.12 (m, 2H), 2.88 (t, *J* = 12.4 Hz, 1H), 1.57–1.36 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.2, 155.3, 136.63, 135.56, 133.1, 128.6, 128.4, 128.2, 127.86, 127.81, 67.0, 48.2, 39.9, 39.2, 27.8, 25.1, 18.7; MS (70 eV, EI): *m/z* (%) = 338 (<1) $[M+H]^+$, 246 (2), 218 (3), 202 (45), 174 (10), 105 (34), 91 (100), 77 (26); HR-MS (ESI): *m/z* = 338.1756, calcd. for $C_{21}H_{24}NO_3$ $[M+H]^+$: 338.1751.

(*R*)-*N*-Benzyloxycarbonyl-2-(2-oxo-2-*para*-tolylethyl)-piperidine (2h): Following the *General Procedure* mentioned above, the reaction gave the product **2h**; yield: 26.3 mg (0.075 mmol, 75%); R_f = 0.6 (petroleum ether/EtOAc = 2:1); $[\alpha]_D^{20}$: −46 (*c* 1.0 in $CHCl_3$). The enantiomeric excess of 96% was measured by HPLC (chiralcel OD-H, *n*-hexane/*i*-PrOH = 95/5; flow rate 0.5 mL min^{-1}; λ = 254 nm): t (minor) = 24.0 min, t (major) = 26.6 min). The *R* absolute configuration of **2h** was provisionally assigned according to the stereochemical determinations of **2a**, **2d** and **2f**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (brs, 2H), 7.28–7.21 (m, 5H), 7.12 (brs, 2H), 5.02 (brs, 2H), 4.86–4.78 (m, 1H), 4.06–4.02 (m, 1H), 3.19–3.04 (m, 2H), 2.88 (t, *J* = 12.4 Hz, 1H), 2.32 (s, 3H), 1.65–1.47 (m, 5H), 1.44–1.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.9, 155.3, 143.9, 136.7, 134.2, 129.3, 128.43, 128.37, 127.86, 127.85, 67.1, 48.4, 39.9, 39.1, 27.8, 25.2, 21.6, 18.7; MS (70 eV, EI): *m/z* (%) = 351 (<

1) $[M]^+$, 217 (<1), 173 (8), 149 (14), 108 (34), 91 (100), 57 (27), 43 (27); HR-MS (ESI): m/z = 352.1901, calcd. for $C_{22}H_{26}NO_3$ $[M+H]^+$: 352.1907.

(*R*)-*N*-Benzyloxycarbonyl-2-(2-*para*-nitrophenyl-2-oxoethyl)-piperidine (2j): Following the *General Procedure* mentioned above, the reaction gave the product **2j**; yield: 30.6 mg (0.08 mmol, 80% yield); R_f = 0.4 (petroleum ether/EtOAc = 2:1); $[\alpha]_D^{20}$: −22 (*c* 0.5 in $CHCl_3$). The enantiomeric excess of 85% was measured by HPLC (chiralcel OD-H, *n*-hexane/*i*-PrOH = 95/5; flow rate 0.5 mL min^{-1}; λ = 254 nm): t (minor) = 42.0 min, t (major) = 56.9 min. The *R* absolute configuration of **2j** was provisionally assigned according to the stereochemical determinations of **2a**, **2d** and **2f**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35–7.90 (m, 4H), 7.37–7.27 (m, 5H), 5.06 (brs, 2H), 4.89–4.83 (m, 1H), 4.12 (brs, 1H), 3.25 (d, J = 7.6 Hz, 2H), 2.98 (t, J = 12.4 Hz, 1H), 1.76–1.41 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.8, 155.3, 150.2, 140.8, 136.4, 129.2, 128.5, 128.1, 127.9, 123.8, 67.3, 48.2, 39.9, 27.9, 25.0, 18.7; MS (70 eV, EI): m/z (%) = 382 (< 1) $[M]^+$, 291 (1), 247 (23) , 174 (8), 150 (7), 104 (7), 91 (100), 65 (13); HR-MS (ESI): m/z = 383.1607, calcd. for $C_{21}H_{23}N_2O_5$ $[M+H]^+$: 383.1601.

(*R*)-*N*-Benzyloxycarbonyl-2-(2-oxopropyl)-pyrrolidine (2k): Following the *General Procedure* mentioned above, the reaction gave the product **2k**; yield: 25.1 mg (0.096 mmol, 96%); R_f = 0.6 (petroleum ether/EtOAc = 2:1); $[\alpha]_D^{20}$: +37 (*c* 1.0 in $CHCl_3$), consisting of two rotamers **A** and **B** at room temperature (**A**/**B** ≈ 3:2). The enantiomeric excess of 80% was measured by HPLC (chiralcel OD-H, *n*-hexane/*i*-PrOH = 95/5; flow rate 0.5 mL min^{-1}; λ = 220 nm): t (minor) = 33.2 min, t (major) = 41.0 min. The absolute configuration of **2k** was assigned as "*R*" by a comparison of its optical rotation with the literature value of the *S*-enantiomer {$[\alpha]_D^{20}$: −37.5 (*c* 0.72 in $CHCl_3$)}.[22] ^{1}H NMR (400 MHz, $CDCl_3$, two rotamers **A** and **B**): δ = 7.38–7.29 (m, 5H; A+B), 5.12 (brs, 2H; A+B), 4.26–4.18 (m, 1H; A+B), 3.46–3.39 (m, 2H; A+B), 3.18 (d, J = 15.2 Hz, 0.6×1H; A), 2.89 (d, J = 16 Hz, 0.4×1H; B), 2.46–2.40 (m, 1H; A+B), 2.19–2.01 (m, 4H; A+B), 1.89–1.79 (m, 2H; A+B), 1.73–1.60 (m, 1H; A+B); ^{13}C NMR (100 MHz, $CDCl_3$, two rotamers **A** and **B**): δ = 207.2 (A), 206.9 (B), 154.6 (2×1C; A+B), 136.9 (A), 136.7 (B), 128.4 (2×2C; A+B), 128.0–127.8 (2×1C + 2×2C; A+B), 66.8 (B), 66.6 (A), 54.0 (A), 53.2 (B), 48.5 (B), 47.6 (A), 46.6 (B), 46.3 (A), 31.6 (B), 30.9 (A), 30.3 (A), 29.6 (B), 23.6 (A), 22.8 (B); MS (70 eV, EI): m/z (%) = 262 (<1) $[M+H]^+$, 204 (1), 170 (10), 126 (48), 91 (100), 84 (22), 65 (21), 43 (57); HR-MS (ESI): m/z = 262.1433, calcd. for $C_{15}H_{20}NO_3$ $[M+H]^+$: 262.1438.

(*S*)-*N*-Benzyloxycarbonyl-4-(2-oxopropyl)oxazolidine (2l): Following the *General Procedure* mentioned above, the reaction gave the product **2l**; yield: 23.9 mg (0.091 mmol, 91%); R_f = 0.5 (petroleum ether/EtOAc = 2:1); $[\alpha]_D^{20}$: +87 (*c* 1.0 in $CHCl_3$), consisting of two rotamers **A** and **B** at room temperature (**A**/**B** ≈ 5:3). The enantiomeric excess of 78% was measured by HPLC (chiralcel OD, *n*-hexane/*i*-PrOH = 90/10; flow rate 1.0 mL min^{-1}; λ = 220 nm): t (minor) = 11.7 min, t (major) = 14.6 min. The *S* absolute configuration of **2l** was provisionally assigned according to the stereochemical determination of **2k**. ^{1}H NMR (400 MHz, $CDCl_3$, two rotamers **A** and **B**): δ = 7.30–7.22 (m, 5H; A+B), 5.10–5.00 (m, 2H; A+B), 4.89–4.78 (m, 1H; A+B), 4.74–4.71 (m, 1H; A+B), 4.18–4.09 (m, 2H; A+B), 3.68–3.65 (m, 1H; A+B), 3.17 (d, J = 16 Hz, 0.62×1H; A), 2.88 (brs, 0.38×1H; B), 2.56–2.50 (m, 1H; A+B), 2.06 (s, 3H; A+B); ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer): δ = 206.7, 152.9, 136.1, 128.5, 128.2, 128.0, 78.4, 72.4, 67.0, 51.6, 45.6, 30.1; MS (70 eV, EI): m/z (%) = 263 (<1) $[M]^+$, 232 (1), 188 (1), 172 (6), 128 (36), 91 (100), 83 (19), 43 (11); HR-MS (ESI): m/z = 286.1056, calcd. for $C_{14}H_{17}NO_4Na$ $[M+Na]^+$: 286.1050.

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