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Catalytic Asymmetric Phase-Transfer Michael Reaction and Mannich-Type Reaction of Glycine Schiff Bases with Tartrate-Derived Diammonium Salts

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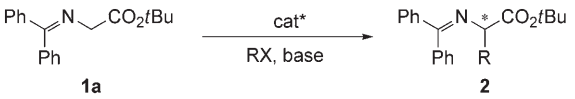
Abstract: Catalytic asymmetric Michael and Mannich-type reactions of glycine Schiff bases with chiral two-center organocatalysts, tartrate-derived diammonium salts (TaDiASs), are described. On the basis of conformational studies, optimized TaDiASs with a 2,6-disubstituted cyclohexane spiroacetal were newly designed. These TaDiASs catalyzed the asymmetric Michael and Mannich-type reactions of glycine Schiff bases with higher enantioselectivity than previous catalysts. In the Mannich-type reaction, aromatic *N*-Boc-protected imines (Boc = *tert*-butoxycarbonyl) as well as enolizable alkyl imines were applicable. As a synthetic application of the catalytic asymmetric Mannich-type reaction with the optimized TaDiASs, we developed a catalytic asymmetric total synthesis of (+)-nemonapride, which is an antipsychotic agent.

Keywords: amino acids · asymmetric catalysis · conformation analysis · phase-transfer catalysis · Schiff bases

Introduction

α-Amino acids are important chiral building blocks that are incorporated into natural compounds, medicinally relevant compounds, and chiral ligands. There are many methods for the preparation of optically active α-amino acids;[1] among them, asymmetric phase-transfer catalysis with the Schiff base of *tert*-butyl glycinate **1a** is a direct and atom-economical method (Scheme 1).[2] In 1989, O'Donnell et al. developed a catalytic asymmetric phase-transfer alkylation of **1a** by using *Cinchona* alkaloid-derived catalysts to afford monoalkylation product **2** in high yield with moderate enantioselectivity.[3] Later, Corey et al.[4] and Lygo and Wainwright[5] independently and dramatically improved the enantioselectivity with new catalysts that contain the *N*-9-anthracenylmethyl substituent. Several groups introduced new catalyst designs other than *Cinchona* alkaloid-derived catalysts,[6] such as the *N*-spiro binaphthyl derivatives developed by Maruoka and co-workers.[7,8] Although some of these catalysts effectively catalyze phase-transfer reactions of a glycine Schiff base with high enantioselectivity, there remains room for improvement in terms of stability under basic conditions and cost of catalyst preparation.



1a 2

Scheme 1. Catalytic asymmetric phase-transfer reaction of the Schiff base of *tert*-butyl glycinate.

We recently developed a novel two-center organocatalyst **3** (TaDiAS = tartrate-derived diammonium salt) that is easily prepared from inexpensive L-tartaric acid. A catalyst library containing more than 70 TaDiASs was constructed, and we found that these compounds efficiently catalyze asymmetric phase-transfer alkylations,[9a,b] Michael reactions,[9a,b] and Mannich-type reactions[9c] of the glycine Schiff base **1a**. We also accomplished an enantioselective total synthesis of the serine protease inhibitor aeruginosin 298A and its analogues by using asymmetric alkylation with TaDiASs.[10]

We previously performed conformational studies of (*S*,*S*)-TaDiAS **3a** (Scheme 2) to gain insight into the factors that influence enantioselectivity.[9c] We assumed that sterically congested acetal substituents would prevent an unfavorable

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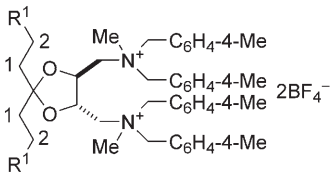


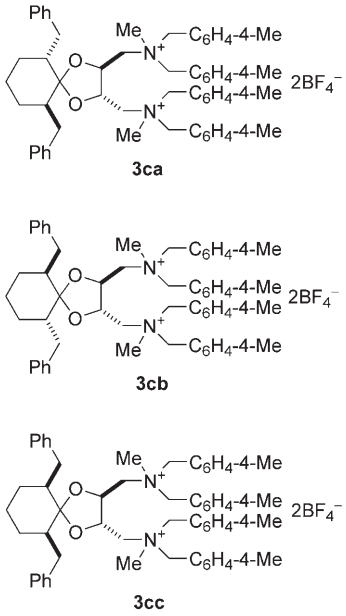
(*S*,*S*)-TaDiAS **3a**: R^1=CH_3
3b: R^1= 4-F-C_6H_4

Scheme 2. Structure of (*S*,*S*)-TaDiASs **3a** and **3b**.

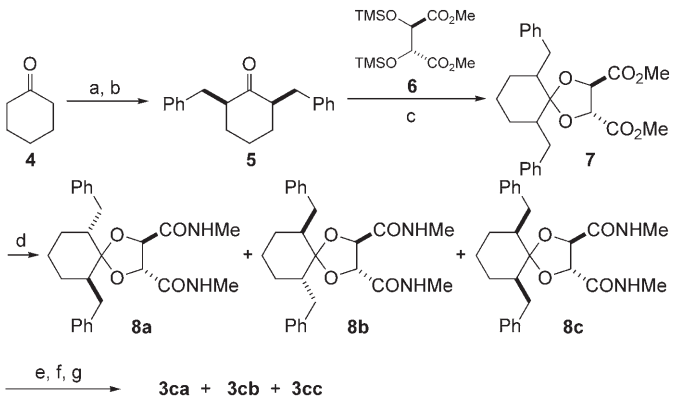
approach of electrophiles to the enolate of a glycine Schiff base. On the basis of this hypothesis, (*S*,*S*)-TaDiAS **3b**, which has an aromatic ring at the C3 position of the acetal side chains, was developed for an asymmetric Mannich-type reaction. Even with **3b**, however the enantiomeric excess was still moderate in the Mannich-type reaction (up to 82% *ee*) and was not further improved in the asymmetric Michael reaction. Recently, we introduced the catalysts **3ca–cc** (Scheme 3), all of which contain a 2,6-disubstituted cyclohexane spiroacetal, to affect the chiral environment more strongly around the quaternary ammonium salts. (*S*,*S*)-TaDiAS **3cb** efficiently catalyzed the asymmetric Michael reaction of a glycine Schiff base with an α,β-unsaturated ketone; we also accomplished a short synthesis of (+)-cylindricine C with this process followed by tandem cyclization.[11a,b] Herein, we describe further exploration with **3ca–cc** in an asymmetric Michael reaction[12] and a Mannich-type reaction[13] of a glycine Schiff base.

Results and Discussion

The synthesis of TaDiASs **3ca–cc** is summarized in Scheme 4. 2,6-Disubstituted cyclohexanone **5** was prepared from cyclohexanone (**4**) in two steps. To construct the acetal moiety, **5** and tartrate derivative **6** were treated with 1 equivalent of TMSOTf in the presence of 10 mol% TfOH without solvent. After conversion into methyl amide **8**, the three diastereomers **8a–c** were separated by silica-gel chromatography. Each diastereomer was reduced with $LiAlH_4$ and underwent arylmethylation to produce the quaternary ammonium salt. Finally, an exchange of the tetrafluoroborate counterions with silver salt furnished the (*S*,*S*)-TaDiAS products **3ca–cc**.



Scheme 3. Structure of (*S*,*S*)-TaDiASs **3ca–cc**.



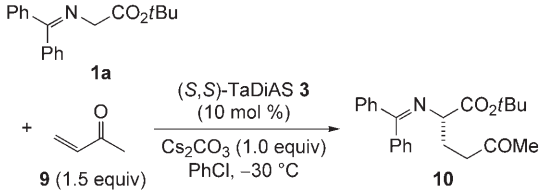
Scheme 4. Synthesis of (*S*,*S*)-TaDiASs **3ca–cc**. Reagents and conditions: a) benzaldehyde, aq. NaOH, CTACl (10 mol%), room temperature, 2 h, 90%; b) Pd/C (10 mol%), H_2, EtOAc, 4 h, 70%; c) **6**, TMSOTf, TfOH (10 mol%), 60°C, 48 h, quant.; d) $MeNH_2$, THF, room temperature, 5 h, 98% (**8a**/**8b**/**8c** = 3:1.5:1); e) $LiAlH_4$, THF, reflux, 2 h; f) *p*-methylbenzylbromide, K_2CO_3, CH_3CN, room temperature, 2 h, 81% (two steps); g) $AgBF_4$, CH_2Cl_2, room temperature, 30 min, 92%. CTACl = hexadecyltrimethylammonium chloride, TfOH = trifluoromethanesulfonyl, TMS = trimethylsilyl.

In contrast to the Michael reaction with α,β-unsaturated esters, the addition of glycine Schiff base **1a** to α,β-unsaturated ketones (enones) with TaDiAS **3a** proceeded with modest selectivity.[9a,b] As shown in Table 1, entry 1, 10 mol% of **3a** (the best catalyst for the Michael reaction in a previous report[9b]) gave Michael adducts with 60% *ee*. We

Abstract in Japanese:

分子内に二つの認識点を有する酒石酸由来の不斉有機分子触媒(*S*,*S*)-TaDiAS **3c** は以前報告した(*S*,*S*)-TaDiAS **3a** のX線結晶構造解析から新たにデザインした触媒である。その中でも、(*S*,*S*)-TaDiAS **3cb** はグリシンシッフ塩基のα,β-不飽和ケトン類に対する不斉マイケル反応において良好な不斉収率（最大80% *ee*）を与えることが分かった。また、(*S*,*S*)-TaDiAS **3ca** はアクリル酸エステル類に対する不斉マイケル反応および不斉マンニッヒ型反応において以前の触媒よりも不斉収率を改善させることが分かった（マイケル反応：最大88% *ee*, マンニッヒ型反応：最大 90% *ee*）。さらに本触媒を用いた不斉マンニッヒ型反応では芳香族イミン類のみならず異性化しやすい脂肪族イミンにおいても比較的良好な選択性（最大75% *ee*）および高いジアステレオ選択性（最大 >20:1, *syn*選択的）にて目的物を与えることが分かった。また本反応の有用性を示すべく抗精神病薬である(+)-ネモナプリドの触媒的不斉合成を行った。

Table 1. Effect of catalyst on the catalytic asymmetric Michael reaction of **1a** with methyl vinyl ketone.



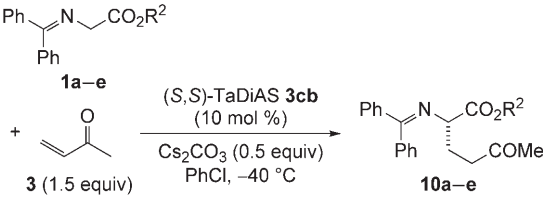
Entry	Catalyst	t [h]	Yield [%][a]	ee [%][b]
1	**3a**	48	86	60
2	**3ca**	24	91	66
3	**3cb**	24	92	71
4	**3cc**	48	46	28
5[c]	**3cb**	48	87	73

[a] Yield of isolated analytically pure compound. [b] Determined by chiral HPLC. [c] Reaction was performed at −40 °C.

then examined the reaction with optimized catalysts **3ca–cc** under reaction conditions that were based on the previous results (Table 1).[9b] When C_2-symmetric (*S*,*S*)-TaDiAS **3ca** or **3cb** was used as the catalyst, the enantioselectivity was improved to 66 and 71% *ee*, respectively (Table 1, entries 2 and 3). On the other hand, **3cc**, which is not C_2-symmetric, catalyzed the reaction with low enantioselectivity (Table 1, entry 4). The reaction with **3cb** at lower temperature (−40 °C) gave improved enantioselectivity of 73% *ee* (Table 1, entry 5).

In the alkylation of **1a** previously reported by Lygo et al,[8d] the protecting group of the carboxylic acid affected the enantioselectivity. We thus examined the effect of an ester moiety with 10 mol% **3cb** at −40 °C (Table 2). By changing the glycine Schiff base from *tert*-butyl ester **1a** to benzyl ester **1b**, the reaction was completed with 50 mol% of Cs_2CO_3, and enantioselectivity was improved to 75% *ee* (Table 2, entry 2). *p*-Chloro-substituted benzyl ester **1c** had a higher reactivity (Table 2, entry 3) than benzyl ester **1b**; the products were afforded in good yield with moderate enantioselectivity (65% *ee*). 2-Naphthylmethyl ester **1d** and

Table 2. Effect of the ester moiety on the glycine Schiff base in the catalytic asymmetric Michael reaction.



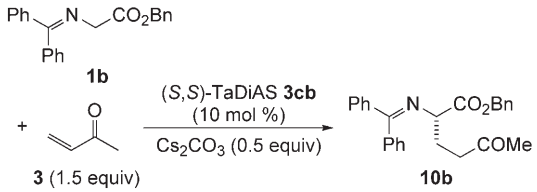
Entry	R^2	t [h]	Yield [%][a]	ee [%][b]
1[c]	*t*Bu (**1a**)	48	87	73
2	benzyl (**1b**)	36	91	75
3	*p*-chlorobenzyl (**1c**)	24	88	65
4	2-naphthyl (**1d**)	48	89	72
5	$CHPh_2$ (**1e**)	48	59	71

[a] Yield of isolated analytically pure compound. [b] Determined by chiral HPLC. [c] 1.0 equivalent of Cs_2CO_3 was used as the base.

diphenylmethyl ester **1e** were also reactive and gave the product with almost the same enantioselectivity (Table 2, entries 4 and 5). These results and the fact that **1b** can be readily prepared led us to choose benzyl ester **1b** as the substrate for further investigation.

With the best ester moiety in the glycine Schiff base, we investigated the effects of the solvent (Table 3). Because of the relatively high melting point of chlorobenzene (−45 °C), −40 °C was the lowest temperature used in this system

Table 3. Effect of solvent on the catalytic asymmetric Michael reaction.



Entry	Solvent	T [°C]	t [h]	Yield [%][a]	ee [%][b]
1	PhCl	−40	36	91	75
2	PhCl/*t*BuOMe (7:3)	−50	48	96	70
3	PhCl/toluene (7:3)	−50	48	80	74
4	PhCl/pentane (7:3)	−50	24	98	73
5	3-fluorotoluene	−40	48	97	77
6	3-fluorotoluene	−60	48	99	78
7	1,3-difluorobenzene	−40	48	91	72
8	1,3-difluorobenzene	−60	48	93	80

[a] Yield of isolated analytically pure compound. [b] Determined by chiral HPLC.

(Table 3, entry 1). To perform the Michael reaction at a lower temperature, a mixed-solvent system was examined at −50 °C. Table 3, entries 2–4 show that a number of mixed solvents with chlorobenzene gave similar enantioselectivity. Previous investigations revealed that halobenzenes were effective as solvents. The low polarity and dissolution ability of the catalyst appeared to result in good reactivity and enantioselectivity. Thus, 3-fluorotoluene and 1,3-difluorobenzene, which have lower melting points than chlorobenzene, were examined. When 3-fluorotoluene was used as the solvent, the enantioselectivity was improved to 77% *ee* at −40 °C (Table 3, entry 5) and 78% *ee* at −60 °C (Table 3, entry 6). 1,3-Difluorobenzene gave a lower selectivity at −40 °C (72% *ee*; Table 3, entry 7) than chlorobenzene, but when the reaction was performed at −60 °C, Michael adduct **10b** was afforded in good yield with further improved enantioselectivity (80% *ee*; Table 3, entry 8).

With these optimized reaction conditions, catalytic asymmetric Michael reaction with highly functionalized dienone **11** was investigated (Scheme 5). Although the reactivity was lower than that of methyl vinyl ketone, we were pleased to observe clean formation of the monoaddition product. With 1.5 equivalents of Cs_2CO_3 and 3-fluorotoluene as the solvent at −40 °C, **12** was obtained in 84% yield and 82% *ee*. By using a combination of this catalytic asymmetric Michael reaction and tandem cyclization, we accomplished the short

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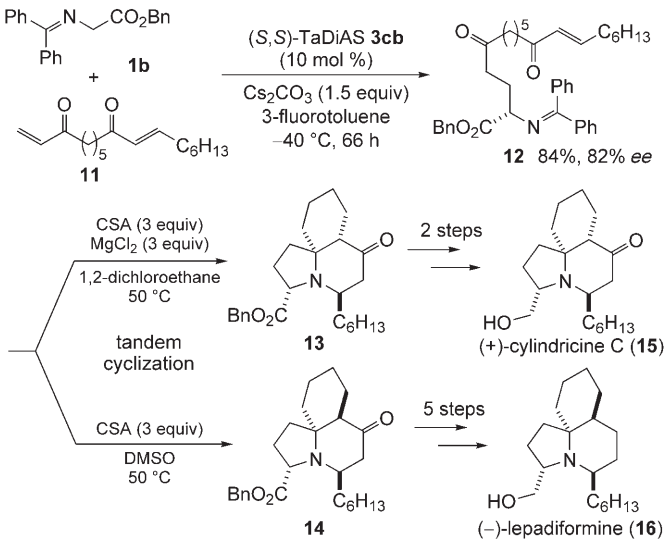
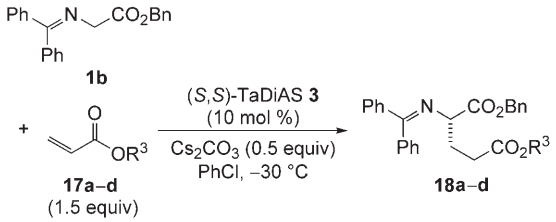


Scheme 5. Catalytic asymmetric Michael reaction with dienone **11** and its application to the synthesis of (+)-cylindricine C (**15**) and (−)-lepadiformine (**16**). CSA = camphor-10-sulfonic acid, DMSO = dimethyl sulfoxide.

synthesis of (+)-cylindricine C (**15**) and the formal synthesis of (−)-lepadiformine (**16**).[11]

Catalytic asymmetric Michael reaction of **1b** with methyl acrylate was also investigated with the optimized TaDiASs (Table 4). As expected, C_2-symmetric (*S*,*S*)-TaDiASs **3ca** and **3cb** were more efficient than the previous catalyst **3a** (Table 4, entries 1–3). In this reaction, **3ca** gave better enantioselectivity than **3cb**, which was the best catalyst in the Michael reaction with methyl vinyl ketone. The scope and limitations of the phase-transfer Michael reaction were examined with the best catalyst **3ca**. Reactions generally proceeded in good yield and better enantioselectivity than with **3cb** (Table 4, entries 4–6).

Table 4. Catalytic asymmetric Michael reaction of **1b** with acrylates.

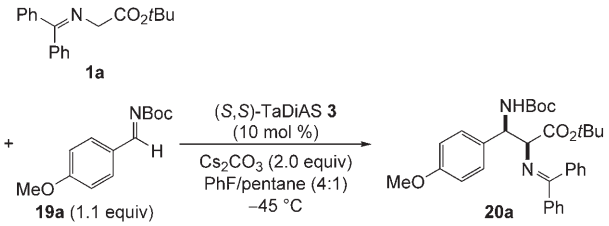


Entry	Catalyst	R^3	*t* [h]	Yield [%][a]	*ee* [%][b]
1	**3a**	Me	12	84	81
2	**3ca**	Me	12	96	88
3	**3cb**	Me	24	68	83
4	**3ca**	Et	13	92	88
5	**3ca**	Bn	11	96	87
6	**3ca**	*n*Bu	24	44	84

[a] Yield of isolated analytically pure compound. [b] Determined by chiral HPLC.

Next, we examined the catalytic asymmetric Mannich-type reaction of **1a** with *N*-Boc-protected imine **19a**, with **3ca** and **3cb** (Table 5). The reaction was performed under the optimized conditions previously reported[9c] (in that report, (*S*,*S*)-TaDiAS **3b** was the best catalyst for the Mannich-type reaction). We found that **3ca** was also effective in this reaction (Table 5, entry 2). When 10 mol% of **3ca** was used, the reaction proceeded smoothly, and the *syn* product was obtained in 12 h virtually as a single isomer (*syn*/*anti* = 99:1). The enantioselectivity was also improved to 90% *ee*. On the other hand, **3cb** gave a lower reactivity and enantioselectivity than **3b**.

Table 5. Effect of catalyst on the catalytic asymmetric Mannich-type reaction of **1a** with *N*-Boc imine **19a**.

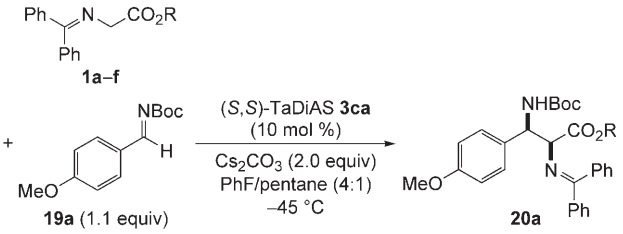


Entry	Catalyst	*t* [h]	Yield [%][a]	d.r. (*syn*/*anti*)[b]	*ee* of *syn* [%][c]
1	**3b**	48	95	95:5	82
2	**3ca**	12	96	99:1	90
3	**3cb**	24	76	98:2	72

[a] Yield of isolated analytically pure compound. [b] Determined by HPLC analysis. [c] Determined by chiral HPLC. Boc = *tert*-butoxycarbonyl.

In the Michael reaction, the structure of the ester moiety of the glycine Schiff base strongly influences reactivity and selectivity. Thus, we examined the effect of the ester moiety in the Mannich-type reaction with **3ca** (Table 6). The reaction was accelerated when benzyl ester **1b** was used as substrate, although enantioselectivity was substantially lowered

Table 6. Ester effects of a glycine Schiff base in catalytic asymmetric Mannich-type reaction.



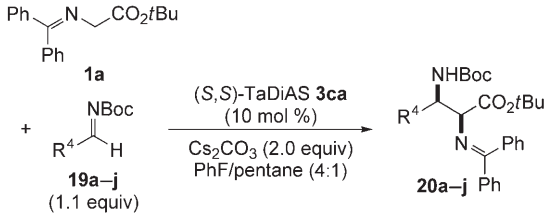
Entry	R^2	*t* [h]	Yield [%][a]	d.r. (*syn*/*anti*)[b]	*ee* of *syn* [%][c]
1	*t*Bu (**1a**)	12	96	99:1	90
2	benzyl (**1b**)	6	89	99:1	56
3[d]	**1b**	6	92	99:1	56
4[e]	**1b**	30	72	99:1	48
5	*p*-chlorobenzyl (**1c**)	4	97	95:5	28
6	*p*-methoxybenzyl (**1f**)	26	66	99:1	49
7	$CHPh_2$ (**1e**)	12	94	99:1	64

[a] Yield of isolated analytically pure compound. [b] Determined by HPLC analysis. [c] Determined by chiral HPLC. [d] 1.0 equivalent of Cs_2CO_3 was used as the base. [e] 0.5 equivalent of Cs_2CO_3 was used as the base.

(Table 6, entry 2). To gain insight into this unsatisfactory result, we examined the Mannich-type reaction of **1b** with **19a** in detail and found that the reaction of **1b** proceeded even without catalyst **3ca.** To prevent such background reactions, the amount of Cs_2CO_3 was decreased. As expected, the reaction slowed due to the smaller amount of base present, but the enantioselectivity was not improved (Table 6, entries 3 and 4). Benzyl esters with electron-withdrawing and electron-donating substituents (**1c** and **1f**, respectively) also reacted with **19a** to afford Mannich adducts, albeit with low enantioselectivity (Table 6, entries 5 and 6). Diphenylmethyl ester **1e** was also reactive and gave products with moderate enantioselectivity (Table 6, entry 7). Thus, we chose **1a** as a substrate for further investigation.

With **1a** as the best substrate, we examined the scope and limitations of *N*-Boc imines (Table 7). All the aromatic

Table 7. Scope and limitations of the catalytic asymmetric Mannich-type reaction.



Entry	R^4	*T* [°C]	*t* [h]	Yield [%][a]	d.r. (*syn*/*anti*)[b]	*ee* of *syn* [%][c]
1[c]	4-MeO-C_6H_4 (**19a**)	−45	12	96	99:1	90
2	C_6H_5 (**19b**)	−45	36	66	99:1	79
3	4-Me-C_6H_4 (**19c**)	−45	12	92	99:1	88
4	3-Me-C_6H_4 (**19d**)	−45	36	94	99:1	73
5[d]	4-F-C_6H_4 (**19e**)	−30	21	94	97:3	81
6[d]	4-Cl-C_6H_4 (**19f**)	−20	24	88	98:2	70
7	2-naphthyl (**19g**)	−45	3	96	97:3	69
8[d]	2-thiophenyl (**19h**)	−30	24	89	98:2	83
9[d]	*n*Pr (**19i**)	−30	12	95	>20:1	71
10[d]	$PhCH_2CH_2$ (**19j**)	−30	43	89	>20:1	75

[a] Yield of isolated analytically pure compound. [b] Determined by HPLC analysis. [c] Determined by chiral HPLC. [d] Solvent = PhF.

imines **19a–h** reacted with glycine Schiff base **1a** catalyzed by 10 mol% **3ca** to afford Mannich adducts **20a–h** in high yield with higher diastereo- and enantioselectivity than the previous catalyst **1b**. Catalytic asymmetric Mannich-type reactions with enolizable aliphatic *N*-Boc protected imines **19i** and **19j** were also performed.[14] Although 5 equivalents of Cs_2CO_3 were required for good conversion, it is noteworthy that the Mannich adducts were obtained with excellent diastereoselectivity (*syn*/*anti* > 20:1) and relatively good enantioselectivity (Table 7, entries 9 and 10). Although the enantioselectivity of the reaction was still unsatisfactory, this is a promising catalytic asymmetric reaction for producing a wide range of chiral α,β-diamino esters.

The enantioselectivity of these reactions is attributed to the fixation of the substrate around the two-cationic moiety of (*S*,*S*)-TaDiAS. Preliminary molecular mechanics simulations by using the Monte Carlo method on Cerius^2 (Accelrys Inc.)[15] suggested that the *Z* enolate of glycine Schiff base **1a** is fixed between the two ammonium cations of (*S*,*S*)-TaDiAS **3d** (Figure 1).[9a,b] In a previous report, the obtained

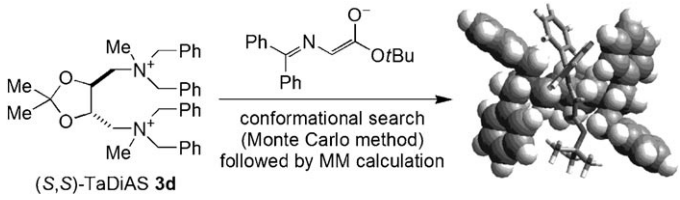
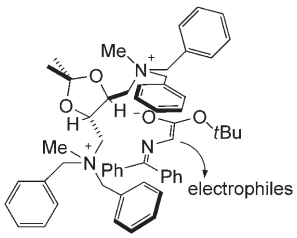


Figure 1. Results of the molecular mechanics (MM) simulations.

structure was further optimized by ab initio calculations, and it was suggested that the *Z* enolate of **1a** is fixed with (*S*,*S*)-TaDiAS through several hydrogen bonds between the α-methylene or methyne unit of the ammonium cation units and the enolate oxygen atom and imine nitrogen atom of **1a**.[9b] Given the absolute configuration of both Michael and Mannich adducts (*S* configuration), both reactions may proceed via our postulated transition states (Scheme 6). The

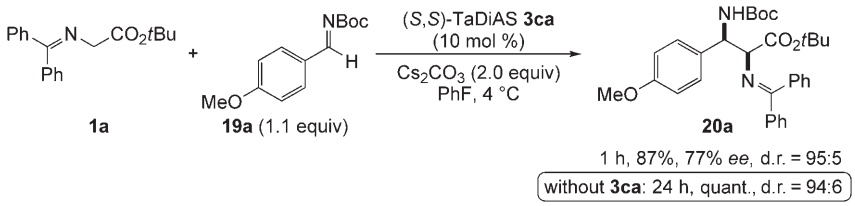


Scheme 6. Proposed transition-state model.

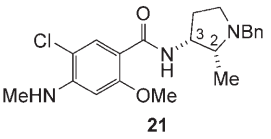
benzyl moieties around one ammonium cation of TaDiAS effectively covers the *si* face of the *Z* enolate of **1a**, and the electrophiles approach from the less-hindered face (*re* face) to afford the products with *S* configuration.

On the other hand, the excellent diastereoselectivities observed in the present Mannich-type reaction were obtained without any effect from the catalyst. As shown in Scheme 7, when the Mannich-type reaction was performed without catalyst at 4 °C, the diastereomer ratio was 94:6; reaction in the presence of (*S*,*S*)-TaDiAS **3ca** gave almost same result.

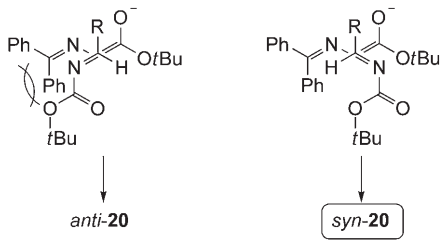
These results show that the reaction may proceed via the nonchelate, acyclic transition-state model. To avoid steric repulsion between the *N*-Boc and *N*-diphenylmethylene groups of enolate **1a**, the *syn* products would be afforded preferentially (Scheme 8). Although we proposed that the *Z* enolate of **1a** is the active nucleophile in the presence of (*S*,*S*)-TaDiAS, the *syn* products would also be obtained selectively from the *E* enolate in the same manner.



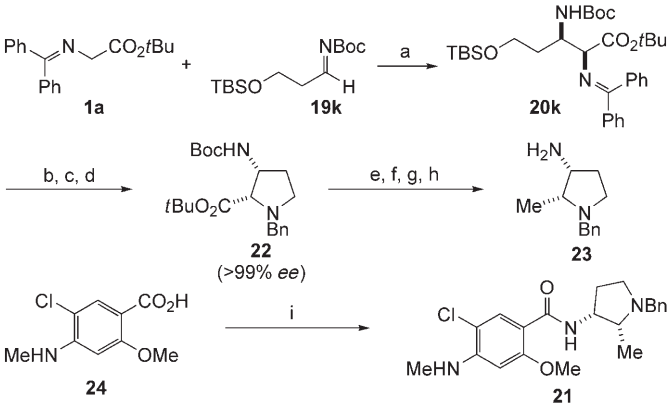
Scheme 7. Catalytic asymmetric Mannich-type reaction with and without (*S*,*S*)-TaDiAS **3ca**.



Scheme 9. Structure of nemonapride (**21**).



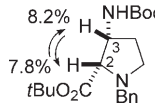
Scheme 8. Transition-state models of the Mannich-type reaction.



Scheme 10. Catalytic asymmetric synthesis of (+)-nemonapride (**21**). Reagents and conditions: a) (*S*,*S*)-TaDiAS **3ca** (10 mol %), $CsOH·H_2O$ (30 mol %), PhF/toluene (7:3), −45 °C, 36 h, 72 %, 65 % *ee*; b) aq. HCl (1 N), THF, room temperature, 1 h; c) CBr_4, PPh_3, iPr_2NEt, CH_2Cl_2, 4 °C, 30 min, then benzylbromide, 40 °C, 12 h, 78 % (two steps); d) recrystallization from hexane (three times), 36 %, >99 % *ee*; e) $LiAlH_4$, THF, 4 °C, 2 h, 98 %; f) CS_2, NaH, MeI, THF, room temperature, 16 h, 98 %; g) nBu_3SnH, AIBN (50 mol %), toluene, reflux, 3 h, 67 %; h) CF_3COOH, CH_2Cl_2, 4 °C to room temperature, 6 h, 99 %; i) $ClCO_2Et$, Et_3N, CH_2Cl_2, −20 °C, 1 h, then **23**, room temperature, 3 h, 67 %. AIBN = 2,2′-azobisisobutyronitrile, TBS = *tert*-butyldimethylsilyl.

Mannich adducts **20** with *N*-diphenylmethylene and *N*-Boc groups can be readily and chemoselectively converted into α,β-diamino acid products.[9c] As an application of this catalytic asymmetric Mannich-type reaction, and to demonstrate its usefulness, a catalytic asymmetric synthesis of nemonapride (**21**) (Scheme 9) was developed. Nemonapride is an antipsychotic agent developed by the Yamanouchi Pharmaceutical Company and sold as Emilace from Astellas Pharma Inc. in racemic form.[16] The racemic synthesis[16] and an asymmetric formal synthesis[17] of nemonapride have already been reported so far.

The asymmetric synthesis of nemonapride (**21**) began with a catalytic asymmetric Mannich-type reaction with alkyl imine **19k**, which was prepared from 1,3-propanediol in four steps (Scheme 10).[18] Initial attempts to promote the reaction of **1a** with **19k** under the optimized conditions (in Table 7) gave the Mannich adduct **20k** in low yield (26 %) with moderate enantioselectivity (65 % *ee*). Several investigations of the reaction conditions revealed that a catalytic amount of $CsOH·H_2O$ efficiently promoted the reaction at −45 °C and afforded **20k** in 72 % yield with 65 % *ee*. Conversion of **20k** into **21** required the formation of a pyrrolidine ring system and deoxidation of the ester moiety. First, the TBS and *N*-diphenylmethylene groups of **20k** were removed under aqueous acidic conditions. Formation of the pyrrolidine ring system was performed by using the Appel hydroxy activation protocol,[19] and subsequent benzylation of the secondary NH group afforded the pyrrolidine core **22** in 78 % yield (three steps). Recrystallization of **22** from hexane three times gave optically pure **22** (>99 % *ee*) in 36 % yield. The relative configuration of **22** was determined to be *cis* based on NOE experiments. Thus, upon selective irradiation of 2-H, an 8.2 % enhancement was observed for 3-H (Scheme 11). On the other hand, a 7.8 % enhancement of 2-H was observed by irradiation of 3-H. Next, as the first step for conversion of the ester group into a methyl group, **22** was reduced with $LiAlH_4$. To deoxygenate the hydroxy group, we initially examined the reduction of the corresponding mesylate without success. Because an aziridinium intermediate was formed in the course of mesylation, the corresponding mesylate could not be obtained. Several investigations showed that the deoxygenation of the hydroxy group under Barton–McCombie conditions proceeded well (67 % yield), and subsequent removal of the *N*-Boc group gave the pyrrolidine core **23** in 99 % yield. The spectroscopic data of **23**, including the optical data, were identical to those reported by Huang et al.[17] Finally, coupling of **24** with **23** gave (+)-nemonapride (**21**) in 67 % yield (two steps).



Scheme 11. One-dimensional NOE correlation of **22**.

Conclusions

We have performed the catalytic asymmetric Michael reaction and Mannich-type reaction of a glycine Schiff base with

optimized (*S*,*S*)-TaDiASs **3ca** and **3cb**, which were newly designed based on conformational studies. The design was successful, and **3cb** was suitable for catalytic asymmetric Michael reaction with α,β-unsaturated ketones (up to 80% *ee*). (*S*,*S*)-TaDiAS **3ca** was effective in the catalytic asymmetric Michael reaction with acrylates (up to 88% *ee*) and the Mannich-type reaction (up to 90% *ee*, *syn*/*anti* up to 99:1). In the Mannich-type reaction, not only aromatic *N*-Boc-protected imines but also enolizable alkyl imines were applicable. By using a catalytic asymmetric Mannich-type reaction with alkyl imine **19k**, we accomplished an asymmetric total synthesis of (+)-nemonapride.

Experimental Section

General

Spectral data of all new compounds as well as detailed procedures for the Michael reaction, Mannich-type reaction, and the synthesis of **3ca–cc** and **21** are available in the Supporting Information.

Syntheses

Representative procedure for the catalytic asymmetric Michael reaction: (*S*,*S*)-TaDiAS **3cb** (15.0 mg, 0.015 mmol) and methyl vinyl ketone (18.8 mL, 0.225 mmol) were added to a solution of **1b** (49.4 mg, 0.15 mmol) in 1,3-difluorobenzene (1 mL, 0.15 M) under Ar atmosphere. The mixture was cooled to −60 °C, and then Cs_2CO_3 (24.4 mg, 0.075 mmol) was added. The reaction mixture was stirred at this temperature until **1b** was consumed, the reaction was quenched by the addition of water (3 mL), and the mixture was extracted with Et_2O (2×5 mL), washed with brine (5 mL), and dried over Na_2SO_4. After the solvent was evaporated, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 5:1) to give **10b** (55.8 mg, 0.14 mmol, 93%, 80% *ee*) as a colorless oil. $[\alpha]_D^{22} = -63.6$ ($c = 1.10$ M, $CHCl_3$, 80% *ee*); FTIR (neat): $\tilde{\nu} = 1738$, 1160, 698 cm^{-1}; ^1H NMR (500 MHz, CDCl3): $\delta =$ 7.64–7.62 (m, 2H), 7.42–7.31 (m, 11H), 7.11–1.09 (m, 2H), 5.17 (d, $J =$ 12.5 Hz, 1H), 5.12 (d, $J = 12.5$ Hz, 1H), 4.13 (t, $J = 6.0$ Hz, 1H), 2.55–2.46 (m, 2H), 2.18 (dd, $J = 14.0$, 7.0 Hz, 2H), 2.08 ppm (s, 3H); ^{13}C NMR (126 MHz, CDCl3): $\delta = 207.8$, 171.5, 171.0, 139.2, 136.1, 135.8, 130.4, 128.7, 128.6, 128.5, 128.4, 128.13, 128.10, 128.0, 127.6, 66.4, 64.0, 39.5, 29.8, 27.5 ppm; LRMS (ESI+): $m/z = 422$ $[M+Na]^+$; HRMS (FAB+): m/z calcd for $C_{26}H_{26}NO_3^+$: 400.1907 $[M+H]^+$; found: 400.1902; HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 20:1, 1.0 mL min^{-1}): $t_R = 13.6$ (minor), 15.6 min (major).

Representative procedure for the catalytic asymmetric Mannich-type reaction: Cs_2CO_3 (65.2 mg, 0.2 mmol) was added to a solution of **19a** (25.9 mg, 0.11 mmol), **1a** (29.5 mg, 0.1 mmol), and **3ca** in fluorobenzene/pentane (4:1, 1.0 mL) at −45 °C. After 12 h, the reaction was quenched by the addition of water. The water layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/diethyl ether = 10:1) to give **20a** (51.1 mg, 96%) as a colorless amorphous solid. $[\alpha]_D^{22} = -74.4$ ($c = 1.04$ M, $CHCl_3$, 90% *ee*); FTIR (KBr): $\tilde{\nu} = 3436$, 2977, 2925, 1718, 1636, 1490, 1149, 781 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.57$ (d, $J = 7.4$ Hz, 2H), 7.40–7.27 (m, 6H), 7.08 (d, $J =$ 8.5 Hz, 2H), 6.76 (d, $J = 8.6$ Hz, 2H), 6.56 (br s, 2H), 6.31 (br d, $J =$ 8.9 Hz, 1H), 5.36 (br d, $J = 8.9$ Hz, 1H), 4.10 (br s, 1H), 3.76 (s, 3H), 1.46 (s, 9H), 1.44 ppm (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 172.0$, 169.1, 158.5, 155.1, 138.9, 136.1, 133.0, 130.4, 128.8, 128.4, 128.2, 128.0, 127.7, 127.2, 113.5, 81.8, 79.2, 70.2, 56.2, 55.2, 28.4, 27.9 ppm; elemental analysis: calcd (%) for $C_{32}H_{38}N_2O_5$: C 72.43, H 7.22, N 5.28; found: C 72.28, H 7.34, N 5.17; HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 95:5, 1.0 mL min^{-1}): $t_R = 9.1$ (minor), 11.5 (*trans*), 12.2 (*trans*), 26.0 min (major).

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