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Pd^{II}-Catalyzed Asymmetric Addition Reactions of 1,3-Dicarbonyl Compounds: Mannich-Type Reactions with *N*-Boc Imines and Three-Component Aminomethylation

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Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday

Abstract: This paper describes catalytic asymmetric Mannich-type reactions of β-ketoesters and malonates using chiral palladium complexes. Although readily enolizable, carbonyl compounds are attractive substrates, the use of such compounds as nucleophiles in Mannich-type reactions has not been extensively investigated. In the presence of chiral Pd aqua complexes (2.5 mol%), β-ketoesters reacted with various *N*-Boc imines (Boc = *tert*-butoxycarbonyl) to afford the desired β-aminocarbonyl compounds in good yield with high to excellent stereoselectivity (up to 96:4 d.r., 95–99% *ee* in most cases). In these reactions, construction of highly crowded vicinal quaternary and tertiary carbon centers was achieved in one step. A chiral Pd enolate is considered to be the key intermediate. To elucidate the stereoselectivity observed in the reaction, possible transition-state models are discussed, taking into account steric and stereoelectronic effects. Furthermore, this catalytic system was applied to the Mannich-type reaction of malonates with *N*-Boc imine as well as one-pot classical aminomethylation of β-ketoesters using benzylamine salt and formalin. The reactions proceeded smoothly, and the corresponding Mannich products were obtained in high yield with moderate to good enantioselectivity.

Keywords: 1,3-dicarbonyl compounds · aminomethylation · Mannich reactions · palladium · quaternary centers

Introduction

Nucleophilic addition reactions of enolate equivalents to imines, the so-called Mannich-type reactions, represent a fundamental class of carbon–carbon bond-forming reactions.[1] Because this transformation can produce a stereogenic carbon center connected to a nitrogen atom, the Mannich adducts find many applications in the synthesis of natural and unnatural compounds. Therefore, the development of efficient methods for catalytic asymmetric Mannich-type reactions is of great interest.[2,3] In addition to reactions using preformed metal enolates,[4,5] the direct Mannich-type reaction has attracted much attention, and the use of simple aldehydes and ketones has become feasible as a result of the development of ingenious catalysts, including basic metal catalysts and organocatalysts.[6–8] In contrast, the reaction of readily enolizable 1,3-dicarbonyl compounds has not been intensively investigated. Before our preliminary report,[9] there had been only a few examples of the Mannich-type reaction using such pronucleophiles. Jørgensen and co-workers reported the reactions of β-ketoesters with highly activated *N*-Ts imino acetate (Ts = *p*-toluenesulfonyl).[10] Terada reported the organocatalytic reactions of acetylacetone with *N*-Boc imines (Boc = *tert*-butoxycarbonyl).[8d] Unfortunately, the scope of the available imines and dicarbonyl compounds was not fully investigated in their work. Recently, Shaus, Deng, and Dixon independently reported catalytic asymmetric Mannich-type reactions of 1,3-dicarbonyl compounds to acylimines using cinchona alkaloid derivatives.[11,12] They successfully demonstrated the conversion of the Mannich adducts to optically active, biologically important compounds such as dihydropyrimidones, highlighting the synthetic utility of these reactions. As a powerful tool for the

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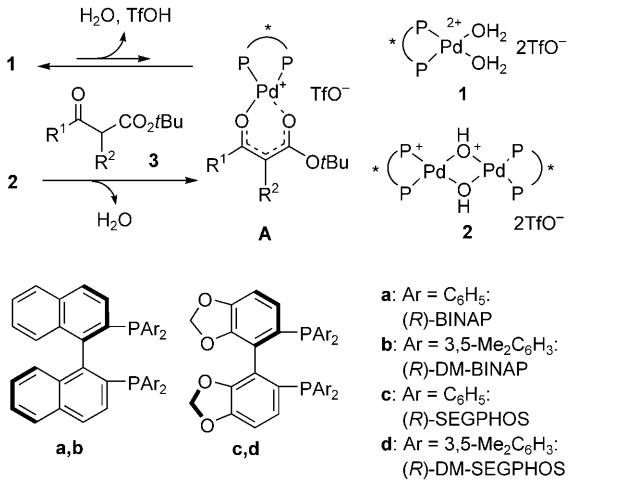
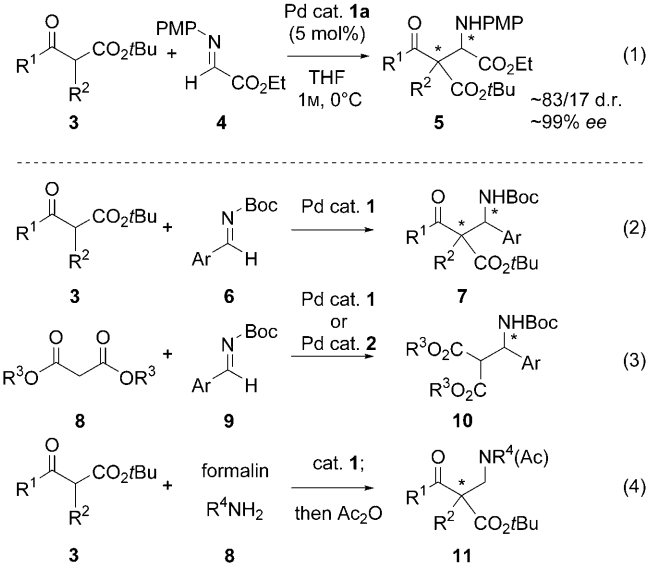
synthesis of highly functionalized β-aminocarbonyl compounds, the development of efficient asymmetric Mannich-type reactions of 1,3-dicarbonyl compounds with broad substrate generality is now attracting much attention.

We previously found that the chiral palladium complexes **1** and **2** acted as acid–base catalysts, and chiral palladium enolates **A** were formed by the reaction with 1,3-dicarbonyl compounds, such as β-ketoesters (Scheme 1).[13] Notably,



Scheme 1. Reaction of chiral Pd complexes **1** and **2** with 1,3-dicarbonyl compounds to give chiral Pd enolates.

these reactions occurred under non-basic conditions, and a strong protic acid was concomitantly generated in the case of **1**, and a water molecule in the case of **2**. Using these palladium enolates as key intermediates, we reported a highly enantioselective catalytic Mannich-type reaction of β-ketoesters.[9] Using the established catalytic conditions for the reactions with *N*-*p*-methoxyphenylimino esters [Scheme 2, Eq. (1)], we examined the reactions with other imines. In the first part of this paper, we present full details of our Mannich-type reaction of β-ketoesters with *N*-Boc imines, including the scope of the substrates and the reaction mechanism [Scheme 1, Eq. (2)]. Based on these results, the second part describes the applicability of this system to other substrate combinations. The reaction of malonates with *N*-Boc imine [Eq. (3)] and the classical Mannich reaction, namely aminomethylation of β-ketoesters using formalin and benzylamine [Eq. (4)], were examined.



Scheme 2. Mannich-type reaction catalyzed by the Pd complexes. PMP = *p*-methoxyphenyl; Boc = *tert*-butoxycarbonyl; Ac = acetyl.

Abstract in Japanese:

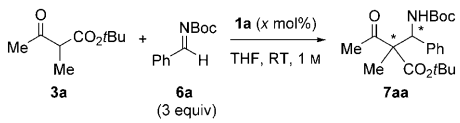
パラジウム二価錯体 ***1*** *または* ***2*** *が 1,3-ジカルボニル化合物と反応してキラルエノラートを与えることを利用し、触媒的不斉マンニッヒ型反応を開発した。β-ケトエステルと N-Boc イミンとの反応は、温和な条件下、円滑に進行し、様々な基質に対して 3 級および 4 級連続不斉中心を有するβ-アミノカルボニル化合物を高い立体選性で得ることに成功した。キラルエノラートが鍵中間体として生成することを基に、比較実験や NMR 実験と併せて、本反応の立体選択性について考察を行った。更に、この触媒系は、マロン酸エステルと N-Boc イミンとのマンニッヒ型反応や、β-ケトエステルを求核剤とするホルマリンおよびベンジルアミンとの三成分アミノメチル化反応にも適用可能であり、エナンチオ選択性は中程度ながらも収率よく反応が進行することを見出した。*

Results and Discussion

Part 1: Reactions of β-Ketoesters with *N*-Boc Imines

Anticipating high reactivity of the imine and practicability of a protecting group of the nitrogen atom, we chose *N*-Boc imines.[14] To our delight, the reaction of **3a** with the imine **6a** derived from benzaldehyde proceeded at room temperature (Table 1). When the reaction was carried out with **1a** at 10 mol%, the product **7aa** was isolated in 68% yield after 36 h, and promising stereoselectivity was observed (entry 1). We found that considerable decomposition of the unstable imine occurred during the reaction, including hydrolysis and polymerization, which might be associated with the acidic nature of the catalyst. After careful optimization, a decrease

Table 1. Initial reactions of **3a** with *N*-Boc imine **6a**.



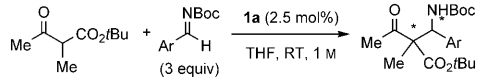
Entry	**1a** [mol%]	*c* [M]	*t* [h]	Yield [%]	d.r.[a]	*ee*[b] [%]
1	10	0.25	36	68	63:27	76/88
2	2.5	1	4	85	85:15	95/90
3	1	1	8	64[c]	87:13	ND[d]

[a] Determined based on ^{1}H NMR analysis of the crude products. [b] Major/minor; determined by chiral HPLC analysis. [c] NMR yield. [d] Not determined.

in the amount of catalyst was found to be effective to suppress such decomposition, and the desired product was obtained in 85% yield with excellent stereoselectivity, with 2.5 mol% **1a** [d.r. = 85:15, 95% *ee* (major), 90% *ee* (minor)] (entry 2). However, a further decrease in the amount of catalyst did not improve the yield (entry 3).

With the optimized reaction conditions established, we next investigated the generality regarding imines. As summarized in Table 2, *N*-Boc imines derived from various aromatic aldehydes were converted into the desired Mannich adducts in a highly enantioselective manner (up to 98% *ee*). Like **6a**, *para*- and *meta*-substituted imines **6b**–**6e** underwent the reaction smoothly (entries 3–6). Although the acyclic substrate **3a** is less reactive than cyclic β-ketoesters, the reaction reached completion within several hours in most cases, and good to high diastereoselectivity and excellent enantioselectivity were observed. In particular, in spite of steric repulsion, *ortho*-substituted imines were available in our reaction (entries 7–9). The reactions of **6f** and **6g** gave rise to the corresponding Mannich adducts in good yield with high diastereoselectivity (d.r. > 90:10). The *ee* values of these products were again 98% (major). Among the substrates tested, **6h** required a prolonged reaction time. This is probably due to bidentate coordination to the palladium complex, which may be competitive with that of **3a**. In entry 10, a furan-ring-substituted imine **6i**, which is basically unstable under acidic conditions, reacted with **3a** smoothly to afford **7ai** with high optical purity.

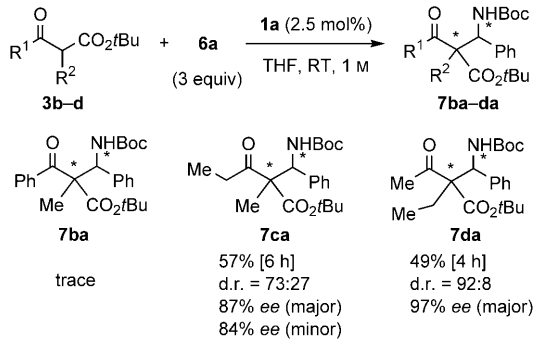
Table 2. Reactions of **3a** with various *N*-Boc imines **6**.



Entry	Imine (Ar)	Product	*t* [h]	Yield [%]	d.r.[a]	*ee*[b] [%]
1	**6a** (C_6H_5)	**7aa**	4	85	85:15	95/90
2[c,d]	**6a** (C_6H_5)	**7aa**	4	84	86:14	98/95
3	**6b** (*p*-MeC_6H_4)	**7ab**	4	82	90:10	97/85
4	**6c** (*p*-$MeOC_6H_4$)	**7ac**	4	96	80:10	97/95
5	**6d** (*m*-MeC_6H_4)	**7ad**	6	57	89:11	95/90
6	**6e** (*m*-ClC_6H_4)	**7ae**	2	94	82:18	96/95
7	**6f** (*o*-MeC_6H_4)	**7af**	9	87	96:4	98/–[e]
8	**6g** (*o*-ClC_6H_4)	**7ag**	2	80	91:9	98/–[e]
9	**6h** (*o*-$MeOC_6H_4$)	**7ah**	47	54	79:21	96/–[e]
10[d]	**6i** (2-furyl)	**7ai**	3	71	82:18	96/99

[a] Determined based on ^{1}H NMR analysis of the crude products. [b] Major/minor; determined by chiral HPLC analysis. [c] **1c** was used. [d] The imine was added in three portions. [e] Not determined.

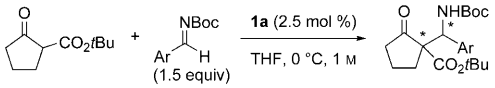
The scope regarding acyclic β-ketoesters was investigated (Scheme 3). This reaction seems to be sensitive to the steric bulk of the substrates, and a phenyl-substituted **3b** hardly reacted. However, ethyl-substituted β-ketoesters **3c** and **3d** underwent the desired reaction at room temperature. Because the reaction of such substrates was slow relative to those listed in Table 2, chemical yield was modest even after 6 h. But the Mannich adducts **7ca** and **7da** were obtained with high optical purity.



Scheme 3. Reactions of bulkier acyclic β-ketoesters with **6a**.

Next, the reaction was applied to cyclic β-ketoester **3e**. The results are summarized in Table 3. Because **3e** was more reactive than **3a**, the reaction could be carried out under cooling with an ice bath. In these reactions, the amount of the imines was decreased to 1.5 equiv, as decomposition of the imines was slow at 0 °C. Subjection of **3e** to reaction with **6a** gave the corresponding product **7ea** in 93% yield with high enantioselectivity. As in the case of **3a**, various imines with electron-donating and electron-withdrawing groups on the aromatic ring could be used. In some cases, we found that diastereoselectivity of the products changed substantially during purification, probably because one of the diastereomers was unstable. However, the diastereoselectivity remained high just after aqueous workup, as determined from the ^{1}H NMR spectra of the crude products. These observations led us to question if the diastereoselectivity of **7eb** might have been determined erroneously in our previous work.[9] After careful reinvestigation, we concluded that the reaction with **6b** also proceeded with high diastereoselectivity (d.r. = 90:10) on the basis of ^{1}H NMR data from the crude products obtained immediately after workup (entry 2). Other imines with a substituent at the *ortho* or *meta* position and the 2-furylimine were also good

Table 3. Reaction of cyclic **3b** with various *N*-Boc imines **6**.



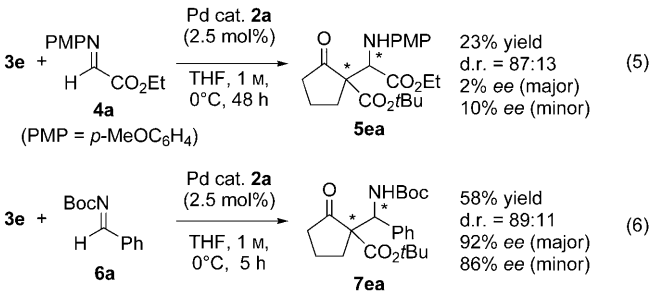
Entry	Imine (Ar)	Product	*t* [h]	Yield [%]	d.r.[a]	*ee*[b] [%]
1	**6a** (C_6H_5)	**7ea**	5	93	88:12	99/97
2	**6b** (*p*-MeC_6H_4)	**7eb**	2	93	90:10	95/99
3	**6d** (*m*-MeC_6H_4)	**7ed**	6	75	84:16	84/91
4	**6f** (*o*-MeC_6H_4)	**7ef**	5	74	93:7	94/–[c]
5	**6g** (*o*-ClC_6H_4)	**7eg**	1	52	95:5	93/–[c]
6[d]	**6h** (*o*-$MeOC_6H_4$)	**7eh**	2	75	80:20	93/–[c]
7[e]	**6i** (2-furyl)	**7ei**	2	75	> 95:5	86/–[c]
8[f,g]	**6a** (C_6H_5)	**7ea**	4	80	66:34	96/84

[a] Determined based on ^{1}H NMR analysis of the crude products. [b] Major/minor; determined by chiral HPLC analysis. [c] Not determined. [d] 3 equiv **6h** were used. [e] 5 mol% **1a**. [f] **1d** was used. [g] The diastereomer, which was minor in entry 1, was predominant.

substrates (entries 3–7). In entry 6, the reaction was complete after 2 h, which is in contrast to the reaction of **3a** with **6h** (Table 2, entry 9). We speculate that **3e** is more susceptible to reaction with **1a** to give the enolate **A**, and the coordination of **6h** to Pd did not significantly affect the reaction rate. Interestingly, when the bulkier Pd complex **1d** was used, the opposite diastereomer was obtained predominantly (entry 8).

Our reaction is therefore applicable to a variety of substrates, regardless of their electronic and steric properties. The reaction was completed within hours in most cases, and the desired adducts were obtained in good yield with excellent enantioselectivity. In these reactions, highly crowded vicinal tertiary and quaternary carbon centers were constructed in a single step, and optically active α,α-disubstituted β-aminocarbonyl compounds were produced.

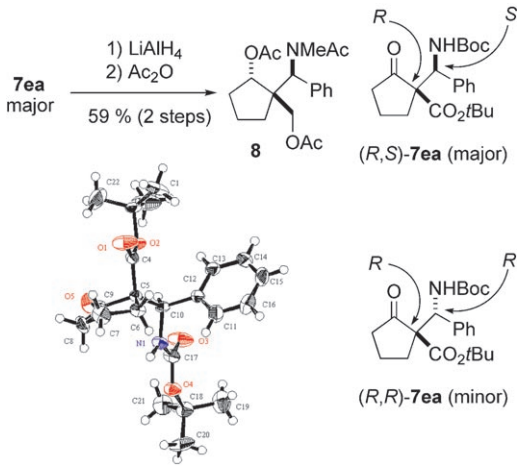
In our previous work,[9] we revealed that the Pd μ-hydroxo complex **2** was less reactive. Because **2** produces a water molecule and not a proton in the formation of the enolate, the imine was not activated effectively by protonation. Therefore, the reaction of **3e** with **4a** did not proceed well [Scheme 4, Eq. (5)], although the same reaction catalyzed by **1** was complete within 6 h [Scheme 2, Eq. (1)].



Scheme 4. Reactions using **2a** as a catalyst.

These results indicate that the Pd enolate acted with the proton to activate the imine, smoothly promoting the reaction. Unlike the case of **4a**, the reaction with **6a** proceeded even in the presence of **2a**, probably because of the high reactivity of the *N*-Boc imine [Eq. (6)]. However, the enantioselectivity was decreased, and the reaction was slower, even though twice the amount of Pd complex was used [**1a** (2.5 mol% to Pd): 93% after 5 h; **2a** (5 mol% to Pd): 58% after 5 h]. From these results, we were convinced that a proton plays a key role even in the reaction with the *N*-Boc imines.

The stereochemistry of **7ea** was determined as follows (Scheme 5). Stereoselective reduction of the major diastereomer of **7ea** with $LiAlH_4$, followed by acetylation, afforded compound **8**. The absolute stereochemistry was determined by comparing the optical rotation of **8** with the value reported by Karlsson and Högberg.[15] Consequently, the absolute configuration of the quaternary carbon center in the major diastereomer of **7ea** was revealed to be *R*, and that of the tertiary carbon center was *S*. This relative configuration



Scheme 5. Stereochemistry of **7ea**.

was further confirmed by a single-crystal X-ray analysis of the minor diastereomer of **7ea**.

On the basis of these results, coupled with our previous studies on the Michael reaction,[13] the excellent enantioselectivity may be associated with face selection of the chiral Pd enolate (Figure 1).[16,17] Thus, a bulky *t*Bu group was preferentially located at one of the faces of the Pd enolate to avoid steric repulsion with the equatorial phenyl group of BINAP. Therefore, the imines preferentially approached the enolate from the less crowded *re* face. Because the Pd complex **1** was superior to the Pd complex **2** as a catalyst (Scheme 4), we speculate that the protonated imines may be involved in the transition state. Face selection of the imines is most likely to be responsible for the relative stereochemistry, and the C–C bond formation occurs with the appropri-

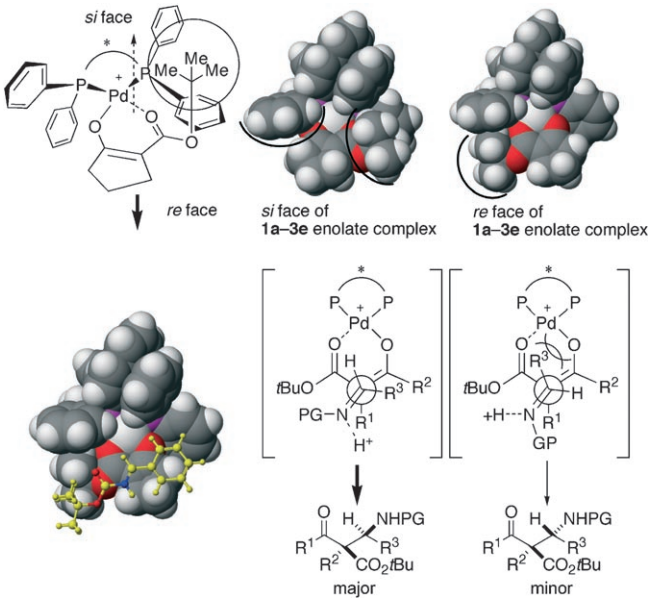
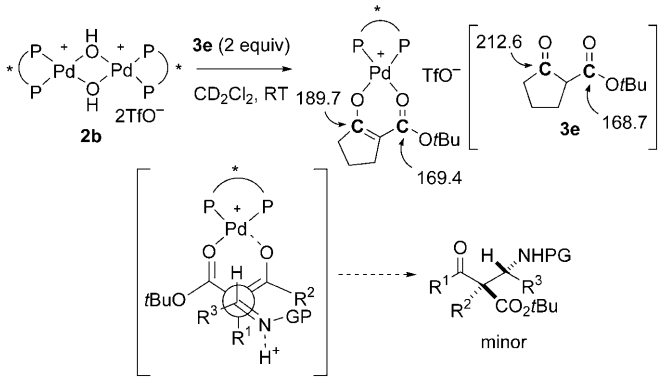


Figure 1. A working hypothesis for the transition state of the Mannich-type reaction.

ate geometry as shown in Figure 1 to minimize steric interactions.

In addition, the stereoelectronic effect also seems to be an important factor in controlling diastereoselectivity. ^{13}C NMR analysis of the Pd enolate derived from **2b** and **3e** revealed that the enolate is not completely delocalized, and the keto enolate form prevails over the ester enolate form.[18] Thus, the chemical shift of the ketone carbonyl group of **3e** alone moved upfield significantly (from $\delta =$ 212.6 to 189.7 ppm) upon formation of the Pd enolate, whereas only a small change was observed for the ester group (from $\delta = 168.7$ to 169.4 ppm) (Scheme 6).



Scheme 6. ^{13}C NMR spectroscopic data of **3e** and the corresponding Pd enolate derived from **2b**; chemical shifts are reported in ppm.

Provided that the overlap of the π orbital of the enolate with the π* orbital of the imine is most favorable, the imine should approach to the enolate as shown in Figure 1, and the alternative approach to the enolate (Scheme 6), which mainly gives the minor diastereomer in the present reaction, may be less involved.

Based on these results, the improved diastereoselectivity in the case of the *ortho*-substituted imines can be explained as follows: The stable conformation of the protonated form of **6f** was calculated by using the semiempirical PM5 method with CAChe 5.0. Among possible conformations, conformation **B** was found to be the most stable, with the methyl group pointed away from the nitrogen atom of the imine (Figure 2). On the assumption that the imine **6f** with this conformation is involved in the C–C bond-forming step, we compared two possible transition-state models by superimposing the imine over the enolate. When the imine approaches the enolate as depicted in Figure 1 (major pathway), the methyl group at the ortho position appears to be accommodated in the chiral cavity (**C**, Figure 2). However, when the other geometry was applied, the methyl group was required to approach the pseudo-equatorial phenyl group of the ligand, thus causing severe steric repulsion (**D**). We think that this destabilization effect is also a factor in enhancing the diastereoselectivity. Based on these considerations, together with the observations in Scheme 6, we think that the excellent diastereoselectivity was the result of steric

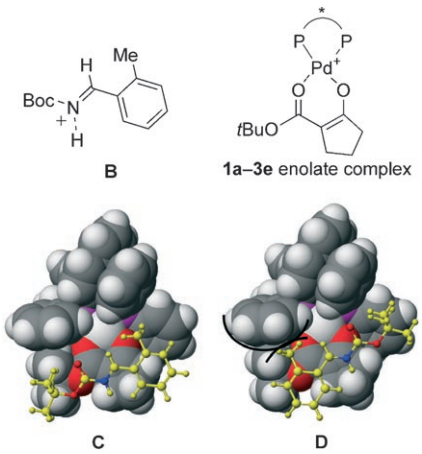


Figure 2. Transition-state (TS) models for **6f** (**B**): major TS (**C**) and minor TS (**D**).

and stereoelectronic factors operative in the cases of **6f** and **6g**.

In contrast, the diastereoselectivity was not improved in the case of **6h**. Computational studies predicted that the most stable conformation of the protonated **6h** would have the methoxy group close to the nitrogen atom of the imine, probably due to hydrogen bonding interactions (**E** in Figure 3). Molecular modeling studies suggested that the

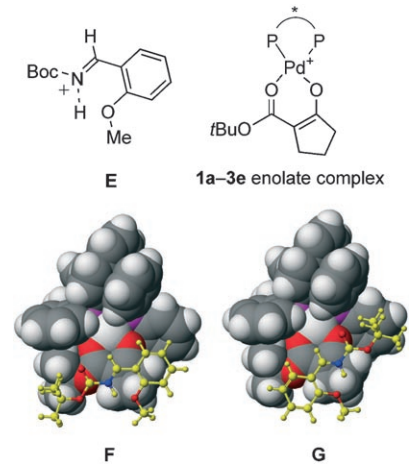


Figure 3. Transition-state (TS) models for **6h** (**E**): major TS (**F**) and minor TS (**G**).

imine would react with the enolate, with the methoxy group being remote from the chiral environment in both possible transition states (**F** and **G**). Thus, the energy difference between **F** and **G** that arises from the methoxy group was not marked. For this reason, the reaction of **6h** is likely to proceed along a similar energy profile to that in the case of **6a**, so that the diastereoselectivity was not improved.

Interestingly, our reaction is highly enantioselective, although protic acids are known to promote non-enantioselective Mannich reactions.[19] We think that the excellent enantioselectivity observed in our reaction can be explained by

assuming a cooperative action between the palladium enolate and the strong protic acid.

Part 2: Catalytic Asymmetric Mannich-Type Reactions Using Other Substrates

Encouraged by the above results, we next examined whether or not this catalytic system would be applicable to reactions with other substrates.

Mannich-type Reaction of Malonates with N*-Boc Imines*

We envisaged that malonates would also undergo Mannich-type reaction with the *N*-Boc imine [Scheme 2, Eq. (3)].[11] Because the catalyst is considered to activate the malonate and not the imine, face selection of the imine seems difficult. We thought, however, that reasonable enantioselectivity would be observed, because high diastereoselectivity was observed in the reactions of β-ketoesters with the imines. The results of optimization are summarized in Table 4.

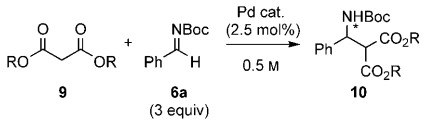
The reaction of dibenzyl malonate **9a** with **6a** proceeded smoothly at room temperature in the presence of **1a** (2.5 mol%), and the Mannich adduct **10a** was obtained with 22% *ee* (entry 1). Lowering the reaction temperature did not dramatically improve enantioselectivity (entries 2 and 3). The effect of the ester group of malonates was also examined, and it was found that the size of the ester group affected selectivity. Whereas the reaction of diethyl malonate **9b** gave a racemic compound, improved enantiomeric excess was observed in the case of diisopropyl malonate **9c** (entries 1 and 3–5). However, we selected **9a** for further investigation because of the synthetic utility of the benzyl ester. When CH_2Cl_2 was used as a solvent, the enantiomeric excess was improved (entry 6). Expecting that a more crowded chiral environment would be effective for improvement of the enantioselectivity, we examined the reaction by using the bulkier **1b**. However, probably due to the slow reaction of malonate with **1b**, decomposition of the unstable imine became predominant even at −20°C to afford a white suspension, and none of the desired product was obtained (entry 7). Such decomposition might be induced by the acidic nature of the Pd complex. Based on the results shown in Scheme 4, we examined the reaction using the less acidic Pd complex **2**. Although the reaction was slow, the desired product was formed in 94% yield, albeit with 26% *ee* (entry 8). As shown in entry 9, use of the Pd-μ-OH complex allowed the use of the bulkier ligand, and the reaction catalyzed by **2b** reached completion after 48 h to give **10a** in 93% yield with the improved enantioselectivity of 45% *ee*. Finally, the reaction in CH_2Cl_2 gave the best enantioselectivity of 59% *ee* (entry 10). Unfortunately, the reaction with **2b** did not proceed at temperatures below −20°C, probably because the imine was not activated with the less acidic **2**. Further investigation to improve enantioselectivity is underway in our research group.

Classical Three-Component Mannich Reaction of β*-Ketoesters*

In contrast to asymmetric Mannich-type reactions with isolated imines, the catalytic asymmetric version of the classical Mannich reaction, namely α-aminomethylation using aqueous formalin and amines has been less well studied. There are currently only a few examples of the synthesis of optically active aminomethylated compounds: 1) Enders et al. reported a highly diastereoselective α-aminomethylation of preformed Li enolates of chiral α-silylated ketones using a combination of dibenzylaminomethylmethylether and $BF_3{\cdot}OEt_2$.[20] 2) Shibasaki and co-workers reported the first example of a direct catalytic asymmetric α-aminomethylation of propiophenone with an *N,O*-acetal, for which a reasonable enantiomeric excess was achieved, although the chemical yield was unsatisfactory.[7a] 3) Organocatalytic asymmetric aminomethylations of carbonyl donors with the dibenzylaminomethylmethylether were also reported.[21] To our knowledge, there is only one example of a one-pot aminomethylation starting from ketones, formalin, and aromatic amines using L-proline as a catalyst to afford the corresponding products with excellent enantioselectivity.[22] In general, the classical Mannich reaction is usually performed in one pot using nucleophilic carbonyl donors, formalin and amine salts, and secondary amines are usually used so that the formation of undesired multi-alkylated products is suppressed.[1] Provided that the Pd complex is stable to water and β-ketoesters can be activated by the Pd complex under acidic conditions, we envisaged that three-component catalytic asymmetric α-aminomethylation of β-ketoesters using formalin and amine salts would be possible [Scheme 2, Eq. (4)].

Initially, we attempted the reaction of **3e** using formalin

Table 4. Reaction of malonates with **6a**.

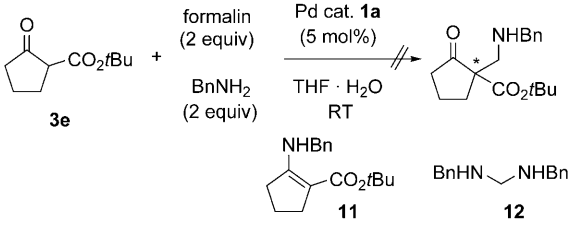


9 — 6a (3 equiv) — 10

Entry	Pd cat.	Malonate (R)	Product	Solvent	T [°C]	t [h]	Yield [%]	*ee* [%]
1	**1a**	**9a** (Bn)	**10a**	THF	RT[b]	3	89	22
2	**1a**	**9a** (Bn)	**10a**	THF	−20	6	90	31
3	**1a**	**9a** (Bn)	**10a**	THF	−40	24	88	33
4	**1a**	**9b** (Et)	**10b**	CH_2Cl_2	0	18	90	0
5	**1a**	**9c** (*i*Pr)	**10c**	THF	−40	24	99	48
6	**1a**	**9a** (Bn)	**10a**	CH_2Cl_2	−40	24	77	47
7[a]	**1b**	**9a** (Bn)	**10a**	THF	−20	6	–	–
8	**2a**	**9a** (Bn)	**10a**	THF	0	12	94	26
9	**2b**	**9a** (Bn)	**10a**	THF	0	48	93	45
10	**2b**	**9a** (Bn)	**10a**	CH_2Cl_2	0	24	75	59

[a] A white precipitate was formed. [b] RT = room temperature.

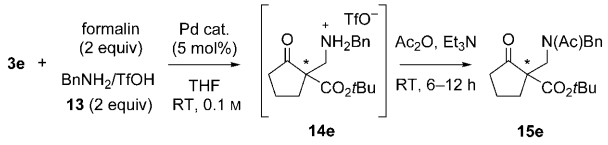
(37% aq) and benzylamine in the presence of **1a** (5 mol%) (Scheme 7). Probably because the catalyst was deactivated as a result of the coordination of the amine, the reaction did not proceed well, and the enamine **11** and the aminal **12** were formed.



Scheme 7. Aminomethylation using benzylamine.

To suppress such side reactions associated with the high nucleophilicity of benzylamine, we next examined the use of benzylamine trifluoromethanesulfonic acid salt (**13**).[23] In the absence of the Pd complex **1a**, spontaneous aminomethylation did not proceed, and instead hydroxymethylation was the dominant reaction. Interestingly, however, the desired aminomethylation occurred almost exclusively, only in the presence of a catalytic amount of **1** (Table 5). With **1a** as

Table 5. Aminomethylation of **3e**.

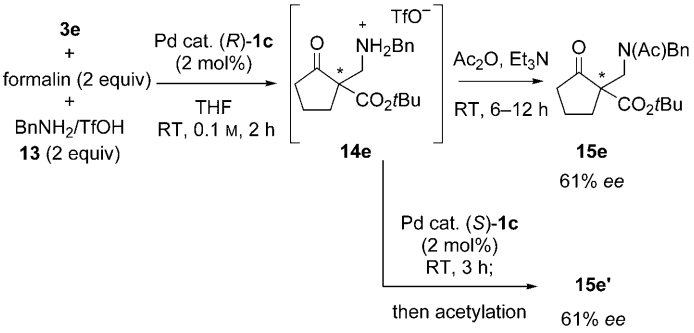


Entry	Pd cat.	t [h]	Yield[a] [%]	ee[b] [%]
1	**1a**	2	97	55
2	**1b**	1.5	90	50
3	**1c**	1.5	73	68
4	**1d**	1.5	88	61

[a] Isolated yields of **15e**. [b] Enantiomeric excess values of **15e**.

catalyst, the desired aminomethylated β-ketoester **14e** was obtained almost quantitatively with 55% *ee* (entry 1). Because the corresponding Mannich base tends to undergo the retro-Mannich reaction, the enantiomeric excess of the product was determined after acetylation. Among the ligands tested, (*R*)-SEGPHOS gave the best result, and 68% *ee* was observed with **1c** as a catalyst (entry 3). Unfortunately, distinct improvement of the enantiomeric excess was not achieved, although the effects of solvent,[24] reaction temperature,[25] and substituents on the nitrogen atom[26] were examined.

The observation that neutralization of the reaction mixture with aqueous sodium bicarbonate induced the retro-Mannich reaction suggested that the reaction might be reversible. To clarify this point, we carried out the following experiments (Scheme 8): After the reaction catalyzed by



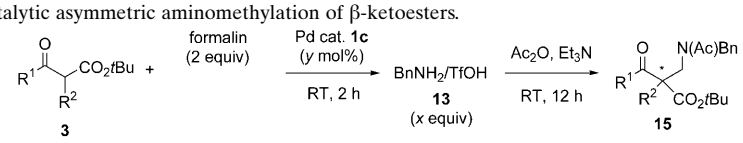
Scheme 8. Control experiments.

(*R*)-**1c** (2 mol%) was complete, the reaction mixture was divided into two fractions. The first fraction was subjected to the usual acetylation to give **15e**. The second fraction was further treated with (*S*)-**1c** (2 mol%) before acetylation to afford **15e′**. The *ee* values of both compounds were found to be the same. If the reaction is reversible, the enantiomeric excess of **15e′** should be lower than that of **15e**. Therefore, it is most likely that no retro-Mannich reaction takes place, and that the *ee* value does not change during the reaction. This is probably because the Mannich adduct is released as a TfOH salt, thereby significantly suppressing the backward reaction.

As shown in Table 6, this reaction was applicable to other β-ketoesters **3a** and **3f** (entries 1,2). Further optimization revealed that the reaction proceeded smoothly, even if the amounts of the amine salt **13** and the catalyst were decreased (entries 3–5). In the presence of **1c** at 1 mol%, all the substrates examined underwent the desired reaction to give the aminomethylated products in high yield with up to 68% *ee*. Notably, no organic solvent was used in these reactions.

To improve enantioselectivity, slow addition of either a solution of **3** in THF or a mixture of formalin and the salt

Table 6. Catalytic asymmetric aminomethylation of β-ketoesters.

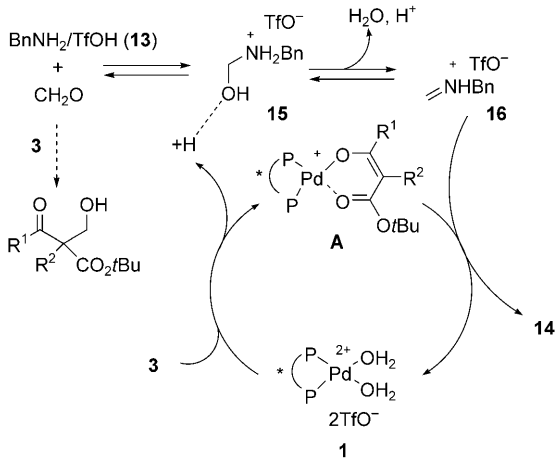


Entry	**3** {R^1/R^2}	Salt [equiv]	Pd cat. [mol%]	Solvent	Product	Yield[a] [%]	ee[b] [%]
1	**3a** {Me/Me}	2	5	THF	**15a**	42	61
2	**3f** {-$(CH_2)_4$-}	2	5	THF	**15f**	92	57
3	**3a** {Me/Me}	1	1	–	**15a**	75	57
4	**3e** {-$(CH_2)_3$-}	1	1	–	**15e**	99	68
5	**3f** {-$(CH_2)_4$-}	1	1	–	**15f**	80	61

[a] Isolated yields of **15**. [b] Enantiomeric excess values of **15**.

13 in THF was tested. However, the enantiomeric excess was not improved in any case. These results suggest that the noncatalyzed reaction between β-ketoesters and the in situ formed iminium ion was negligible. We speculate that the reaction might proceed even from the crowded face of the enolate (Figure 1), as the size of the reaction center of the putative iminium ion is small, and this may be the reason why the *ee* values were low relative to those observed in the first part. Although the enantioselectivity needs to be improved, the catalytic asymmetric aminomethylation of β-ketoesters to construct a chiral quaternary center has become feasible for the first time.

Finally, we propose the catalytic cycle illustrated in Scheme 9. Considering that the catalyst **1** was essential for



Scheme 9. Proposed catalytic cycle.

aminomethylation, we speculate that the catalyst facilitates formation of the iminium ion. The reaction of formalin and the salt **13** would give the hemiaminal **15**, and the proton, formed during enolate formation, would activate **15** to give the corresponding iminium ion **16**. We think that this cooperative action of the enolate with the proton is the key for smoothly promoting the reaction. In contrast, hydroxymethylation occurred in the absence of **1**.

Conclusions

We have succeeded in developing a highly enantioselective catalytic Mannich-type reaction of β-ketoesters. Our reaction is applicable to a wide range of aromatic *N*-Boc imines. This method allows easy access to stereochemically elaborated α-aminocarbonyl compounds in up to 99% *ee*. To explain the stereochemistry observed in the reaction, a transition-state model was proposed. In this reaction, the Pd enolate is an important intermediate, and its cooperative action with the protic acid is considered to be the key to high reactivity and high enantioselectivity. Furthermore, we applied the established conditions to the catalytic asymmetric Mannich-type reaction of malonates with the *N*-Boc imine and three-component aminomethylation of β-ketoesters. We believe that these results offer a basis for further design of novel reactions. Investigations to improve the stereoselectivity are underway in our research group.

Experimental Section

General: NMR spectra were recorded on a Jeol JNM-LA400 spectrometer operating at 400 MHz for ^{1}H NMR and at 100.4 MHz for ^{13}C NMR. Chemical shifts were reported downfield from TMS ($\delta=0$) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to $CDCl_3$ as an internal reference. FAB-LRMS was taken on a Jeol JMS GCmate II instrument using *m*-nitrobenzyl alcohol (*m*NBA) as the matrix. FAB-HRMS was also taken on a Jeol JMS GCmate II using *m*NBA as the matrix and with PEG 400 as an internal standard. MALDI-TOF MS was measured using a Bruker Reflex III instrument. Optical rotations were measured on a Jasco DIP-370 polarimeter. IR spectra were measured on a Thermo Nicolet Avatar 370 FTIR instrument equipped with DuraScope. Melting points were measured using a Yanaco MP-J3 instrument. Short-column chromatography was performed with silica gel 60 (40–100 μm) purchased from Kanto Chemical Co. Purification was carried out using medium-pressure liquid chromatography (MPLC) or gel permeation chromatography (GPC) with the following equipment: Shimadzu MPLC system [pump: LC-6AD, UV detector: SPD-10A, RI detector: RID-10A, column: Yamazen Ultra SI-40A, eluent: *n*-hexane/EtOAc]; Japan Analytical Industry recycling GPC system [pump: LC-918, UV detector: UV-50, RI detector: RI-50, column: Jaigel-1H,2H; eluent: $CHCl_3$]. Enantiomeric excesses were determined by chiral HPLC. HPLC analysis was performed on a Shimadzu HPLC system with the following equipment: pump: LC-10AD, detector: SPD-10A set at 220 nm or 254 nm. A Jasco HPLC system was also used: pump: PU-2080 Plus, detector: CD-2095 Plus set at 220 nm or 254 nm, column: Daicel Chiralpak AD-H, AS-H, or Daicel Chiralcel OD-H, OJ-H, OF; mobile phase: hexane/2-propanol (IPA). Dehydrated stabilizer-free tetrahydrofuran (THF) was purchased from Kanto Chemical Co., and was used directly. Other reagents were purified according to standard methods.

A Representative Procedure for the Catalytic Asymmetric Mannich-Type Reactions of β-Ketoesters to N*-Boc Imines* (Table 3, entry 1)

The β-ketoester **3e** (20 μL, 108.6 μmol) and the palladium complex **1a** (2.9 mg, 2.5 mol%) were added successively to a solution of the *N*-Boc imine **6a** (33.4 mg, 162.8 μmol) in THF (110 μL) at 0°C. This reaction mixture was stirred for 5 h at the same temperature. After completion of the reaction (TLC: *n*-hexane/EtOAc=3:1), EtOAc (5 mL) and brine (3 mL) were added for quenching. The aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were washed with water and brine, then dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. At this stage, the diastereomeric ratio was determined by ^{1}H NMR analysis of the crude products. Further purification was performed by MPLC to give **7ea** (SiO_2: *n*-hexane/EtOAc=4.1; major: 35.0 mg, 82%; minor: 4.6 mg, 11%). The *ee* values of the diastereomers were determined by chiral HPLC analysis.

Characterization of the Mannich Adducts

7aa (major diastereomer): white solid: mp: 78.0–78.5°C; IR (solid): $\tilde{\nu}=$ 3422, 2978, 2931, 1702, 1488, 1455, 1366, 1319, 1251, 1149, 1094, 1013, 844, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.26$ (s, 3H), 1.37 (s, 9H), 1.41 (s, 9H), 2.26 (s, 3H), 5.09 (d, $J=10.0$ Hz, 1H), 6.68 (br d, $J=$ 10.0 Hz, 1H), 7.23–7.31 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 20.1, 25.6, 27.7, 28.3, 58.8, 64.7, 79.5, 82.8, 127.8, 128.1, 128.4, 138.2, 155.0, 170.7, 206.2 ppm; FAB-LRMS (*m*NBA) *m*/*z* 400 $[M+Na]^+$, 378 $[M+1]^+$, 320 $[M-t\mathrm{Bu}]^+$; $[\alpha]_D^{28}=+13.2$ ($c=1.50$, acetone) (96% *ee*); HPLC (Daicel Chiralpak AD-H, *n*-hexane/IPA=90:10, 1.0 mL min^{-1}, 254 nm, τ_{major}

4.9 min, τ_{minor} 6.9 min); Anal. calcd for $C_{22}H_{31}NO_5$: C 66.82, H 8.28, N 3.71, found: C 66.68, H 8.27, N 3.69.

7aa (minor diastereomer): white solid: mp: 111.0–111.5 °C; IR (solid): $\tilde{\nu}$ = 3447, 2978, 2931, 1705, 1490, 1455, 1366, 1250, 1158, 1098, 1017, 844, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 3H), 1.37 (s, 9H), 1.46 (s, 9H), 2.07 (s, 3H), 5.15 (br d, J = 8.6 Hz, 1H), 6.29 (br s, 1H), 7.22–7.32 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6, 27.8, 28.3, 28.6, 59.2, 63.4, 79.4, 82.8, 127.6, 128.1, 128.8, 138.6, 154.8, 170.6, 207.3 ppm; $[\alpha]_D^{28}$ = −24.6 (c = 0.74, acetone) (92% *ee*); HPLC (Daicel Chiralpak AD-H, *n*-hexane/IPA = 90:10, 1.0 mL min^{-1}, 254 nm, τ_{major} 9.0 min, τ_{minor} 5.8 min).

7ab (major diastereomer): colorless oil; IR (neat): $\tilde{\nu}$ = 3432, 2975, 2927, 1715, 1490, 1367, 1252, 1164 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (s, 3H), 1.37 (s, 9H), 1.43 (s, 9H), 2.26 (s, 3H), 2.31 (s, 3H), 5.05 (d, J = 9.8 Hz, 1H), 6.65 (d, J = 9.8 Hz, 1H), 7.09 (d, J = 7.8 Hz, 2H), 7.20 ppm (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1, 21.0, 25.5, 27.8, 28.3, 58.5, 64.8, 79.4, 82.7, 128.3, 128.8, 135.2, 137.4, 154.9, 170.8, 206.4 ppm; MALDI-TOF MS (α-cyano-4-hydroxycinnamic acid) m/z 414 $[M+Na]^+$; $[\alpha]_D^{26}$ = +17.3 (c = 1.29, acetone) (95% *ee*); HPLC (Daicel Chiralpak AD-H, *n*-hexane/IPA = 90:10, 1.0 mL min^{-1}, 254 nm, τ_{major} 4.8 min, τ_{minor} 6.2 min); Anal. calcd for $C_{22}H_{33}NO_5$+0.25 H_2O: C 66.73, H 8.46, N 3.54, found: C 66.81, H 8.42, N 3.54.

7ab (minor diastereomer): colorless oil; IR (neat): $\tilde{\nu}$ = 3445, 2978, 2922, 1709, 1485, 1366, 1251, 1159, 1018, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 3H), 1.37 (s, 9H), 1.46 (s, 9H), 2.07 (s, 3H), 2.30 (s, 3H), 5.11 (br d, J = 9.5 Hz, 1H), 6.27 (br d, J = 9.5 Hz, 1H), 7.08 (d, J = 7.8 Hz, 2H), 7.19 ppm (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6, 21.0, 27.8, 28.4, 28.6, 59.0, 63.4, 79.3, 82.8, 128.7, 128.7, 135.6, 137.2, 154.8, 170.7, 207.4 ppm; $[\alpha]_D^{27}$ = −23.3 (c = 0.37, acetone) (94% *ee*); HPLC (Daicel Chiralpak AD-H, *n*-hexane/IPA = 90:10, 1.0 mL min^{-1}, 254 nm, τ_{major} 5.5 min, τ_{minor} 9.4 min).

7ac (major diastereomer): colorless oil; IR (neat): $\tilde{\nu}$ = 3420, 3403, 2977, 2932, 1708, 1612, 1488, 1366, 1319, 1247, 1161, 1036, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (s, 3H), 1.37 (s, 9H), 1.42 (s, 9H), 2.25 (s, 3H), 3.79 (s, 3H), 5.03 (d, J = 9.8 Hz, 1H), 6.64 (br d, J = 9.5 Hz, 1H), 6.82 (m, 2H), 7.24 ppm (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1, 25.6, 27.8, 28.3, 55.2, 58.3, 64.9, 79.5, 82.7, 113.4, 129.5, 130.5, 154.9, 159.0, 170.9, 206.4 ppm; FAB-LRMS (*m*NBA) m/z 430 $[M+Na]^+$, 408 $[M+H]^+$; $[\alpha]_D^{28}$ = +18.7 (c = 0.99, acetone) (97% *ee*); HPLC (Daicel Chiralpak AD-H, *n*-hexane/IPA = 90:10, 1.0 mL min^{-1}, 254 nm, τ_{major} 6.2 min, τ_{minor} 8.3 min); Anal. calcd for $C_{22}H_{33}NO_6$: C 64.84, H 8.16, N 3.44, found: C 64.79, H 8.15, N 3.30.

7ac (minor diastereomer): white solid: mp: 102.5–103.0 °C (dec); IR (neat): $\tilde{\nu}$ = 3451, 2979, 2933, 1708, 1612, 1512, 1490, 1366, 1246, 1159, 1035, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 3H), 1.37 (s, 9H), 1.46 (s, 9H), 2.07 (s, 3H), 3.78 (s, 3H), 5.08 (br d, J = 7.8 Hz, 1H), 6.26 (br d, J = 7.3 Hz, 1H), 6.80 (m, 2H), 7.23 ppm (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6, 27.8, 28.4, 28.6, 55.2, 58.8, 63.5, 79.4, 82.8, 113.4, 129.9, 130.8, 154.8, 158.9, 170.8, 207.5 ppm; $[\alpha]_D^{29}$ = −25.6 (c = 0.30, acetone) (95% *ee*); HPLC (Daicel Chiralpak AD-H, *n*-hexane/IPA = 90:10, 1.0 mL min^{-1}, 254 nm, τ_{minor} 7.4 min, τ_{major} 14.0 min).

7ad (major diastereomer): colorless oil; IR (neat): $\tilde{\nu}$ = 3433, 2976, 2929, 2364, 1712, 1490, 1367, 1319, 1251, 1164, 1114 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.24 (s, 3H), 1.38 (s, 9H), 1.42 (s, 9H), 2.26 (s, 3H), 2.32 (s, 3H), 5.05 (br d, J = 9.8 Hz, 1H), 6.69 (br d, J = 9.5 Hz, 1H), 7.06–7.20 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.2, 21.4, 25.5, 27.8, 28.3, 58.8, 64.7, 79.5, 82.8, 125.5, 128.0, 128.5, 129.1, 137.6, 138.1, 155.0, 170.8, 206.4 ppm; FAB-LRMS (*m*NBA) m/z 414 $[M+Na]^+$, 392 $[M+H]^+$, 391 $[M]^+$; $[\alpha]_D^{28}$ = +8.7 (c = 0.89, acetone) (95% *ee*); HPLC (Daicel Chiralpak AD-H, *n*-hexane/IPA = 95:5, 1.0 mL min^{-1}, 254 nm, τ_{major} 5.8 min, τ_{minor} 10.7 min); Anal. calcd for $C_{22}H_{33}NO_5$+0.5 H_2O: C 65.97, H 8.56, N 3.50, found: C 65.97, H 8.34, N 3.40.

7ad (minor diastereomer): colorless oil; IR (neat): $\tilde{\nu}$ = 3453, 2980, 2932, 1715, 1491, 1367, 1253, 1163 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$): δ = 1.34 (s, 3H), 1.37 (s, 9H), 1.46 (s, 9H), 2.08 (s, 3H), 2.32 (s, 3H), 5.31 (br d, J = 8.0 Hz, 1H), 6.25 (br d, J = 7.8 Hz, 1H), 7.04–7.18 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.4, 21.5, 27.8, 28.4, 28.6, 59.1, 63.5, 79.4, 82.8, 125.7, 128.0, 128.3, 129.6, 137.5, 138.5, 154.8, 170.6, 207.4 ppm; $[\alpha]_D^{28}$ = −41.0 (c = 0.1, acetone) (90% *ee*); HPLC (Daicel Chiralpak AD-H, *n*-hexane/IPA = 95:5, 1.0 mL min^{-1}, 254 nm, τ_{minor} 7.4 min, τ_{major} 12.3 min).

7ae (major diastereomer): colorless oil; IR (neat): $\tilde{\nu}$ = 3417, 3362, 2978, 1709, 1488, 1368, 1250, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 3H), 1.39 (s, 9H), 1.43 (s, 9H), 2.25 (s, 3H), 5.05 (d, J = 9.5 Hz, 1H), 6.64 (br d, J = 9.8 Hz, 1H), 7.21–7.31 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1, 25.7, 27.7, 28.3, 58.4, 64.4, 79.8, 83.3, 126.9, 128.0, 128.4, 129.3, 134.1, 140.4, 154.9, 170.6, 205.7 ppm; FAB-LRMS (*m*NBA) m/z 434 $[M+Na]^+$, 412 $[M+H]^+$, 413, 414; $[\alpha]_D^{29}$ = +17.0 (c = 1.12, acetone) (96% *ee*); HPLC (Daicel Chiralpak AD-H, *n*-hexane/IPA = 90:10, 1.0 mL min^{-1}, 254 nm, τ_{major} 4.7 min, τ_{minor} 7.3 min); FAB-HRMS (*m*NBA) calcd for $C_{21}H_{31}NO_5Cl$ $[M+H]^+$ 412.1891, found: 412.1905.

7ae (minor diastereomer): colorless oil; IR (neat): $\tilde{\nu}$ = 2976, 1716, 1492, 1368, 1253, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 3H), 1.38 (s, 9H), 1.46 (s, 9H), 2.11 (s, 3H), 5.13 (br d, J = 8.1 Hz, 1H), 6.23 (br s, 1H), 7.20–7.37 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.4, 27.8, 28.1, 28.4, 60.5, 63.3, 79.7, 83.2, 124.3, 127.1, 127.8, 129.0, 129.3, 134.0, 154.8, 170.3, 211.9 ppm; $[\alpha]_D^{29}$ = −16.6 (c = 0.29, acetone) (95% *ee*); HPLC (Daicel Chiralpak AD-H, *n*-hexane/IPA = 90:10, 1.0 mL min^{-1}, 254 nm, τ_{minor} 5.3 min, τ_{major} 7.7 min).

7af (major diastereomer): colorless oil; IR (neat): $\tilde{\nu}$ = 3439, 2978, 2936, 1714, 1489, 1367, 1320, 1254, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.22 (s, 3H), 1.37 (s, 9H), 1.43 (s, 9H), 2.29 (s, 3H), 2.52 (s, 3H), 5.48 (br d, J = 9.5 Hz, 1H), 6.75 (br d, J = 9.3 Hz, 1H), 7.10–7.17 (m, 3H), 7.34–7.36 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1, 20.3, 25.9, 27.7, 28.3, 53.4, 65.3, 79.3, 82.9, 126.2, 127.4, 127.5, 130.5, 136.7, 137.8, 155.1, 171.3, 206.4 ppm; FAB-LRMS (*m*NBA) m/z 414 $[M+Na]^+$; $[\alpha]_D^{27}$ = +16.2 (c = 1.29, acetone) (98% *ee*); HPLC (Daicel Chiralcel OF, *n*-hexane/IPA = 90:10, 1.0 mL min^{-1}, 254 nm, τ_{minor} 5.8 min, τ_{major} 7.6 min); FAB-HRMS (*m*NBA) calcd for $C_{18}H_{24}NO_5$ $[M-tBu]^+$ 334.1654, found: 334.1652.

7ag (major diastereomer): colorless oil; IR (neat): $\tilde{\nu}$ = 3436, 2979, 1718, 1488, 1368, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 3H), 1.37 (s, 9H), 1.45 (s, 9H), 2.32 (s, 3H), 5.86 (d, J = 9.5 Hz, 1H), 6.93 (br d, J = 9.3 Hz, 1H), 7.19–7.27 (m, 2H), 7.35–7.38 (m, 1H), 7.44–7.46 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.6, 25.2, 27.8, 28.2, 53.5, 65.4, 79.6, 83.1, 127.0, 128.9, 129.1, 129.6, 134.5, 136.9, 154.8, 171.0, 206.1 ppm; FAB-LRMS (*m*NBA) m/z 434 $[M+Na]^+$, 412 $[M+H]^+$, 413, 414; $[\alpha]_D^{26}$ = −14.9 (c = 1.33, acetone) (98% *ee*); HPLC (Daicel Chiralpak AD-H, *n*-hexane/IPA = 97:3, 1.0 mL min^{-1}, 280 nm, τ_{minor} 6.5 min, τ_{major} 7.5 min); Anal. calcd for $C_{21}H_{30}ClNO_5$+0.2 H_2O: C 60.70, H 7.37, N 3.37, found: C 60.70, H 7.27, N 3.28.

7ah (major diastereomer): colorless oil; IR (neat): $\tilde{\nu}$ = 3445, 2977, 2934, 1716, 1491, 1367, 1244, 1158, 1095, 1029, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.22 (s, 3H), 1.37 (s, 9H), 1.44 (s, 9H), 2.29 (s, 3H), 3.85 (s, 3H), 5.83 (d, J = 10.0 Hz, 1H), 6.79 (d, J = 10.0 Hz, 1H), 6.85–6.92 (m, 2H), 7.21–7.33 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.5, 25.3, 27.8, 28.3, 50.3, 55.5, 65.7, 79.3, 82.5, 110.3, 120.5, 127.3, 128.6, 128.7, 154.9, 156.9, 171.1, 206.8 ppm; FAB-LRMS (*m*NBA) m/z 430 $[M+Na]^+$, 408 $[M+H]^+$, 407 $[M]^+$; $[\alpha]_D^{26}$ = −11.2 (c = 0.84, acetone) (96% *ee*); HPLC (Daicel Chiralcel OF, *n*-hexane/IPA = 95:5, 1.0 mL min^{-1}, 280 nm, τ_{minor} 18.0 min, τ_{major} 22.6 min); Anal. calcd for $C_{12}H_{33}NO_6$: C 64.84, H 8.16, N 3.44, found: C 65.14, H 8.44, N 3.25.

7ai (major diastereomer): colorless oil; IR (neat): $\tilde{\nu}$ = 3450, 2976, 2920, 1713, 1488, 1367, 1318, 1254, 1161, 1009, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 3H), 1.41 (s, 9H), 1.47 (s, 9H), 2.23 (s, 3H), 5.30 (d, J = 10.0 Hz, 1H), 6.13 (br d, J = 10.0 Hz, 1H), 6.25 (d, J = 2.9 Hz, 1H), 6.29–6.31 (m, 1H), 7.30 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1, 25.8, 27.7, 28.3, 52.5, 64.0, 79.8, 82.7, 108.2, 110.3, 141.7, 152.1, 155.0, 170.3, 205.3 ppm; MALDI-TOF MS (α-cyano-4-hydroxycinnamic acid) m/z 390 $[M+Na]^+$; $[\alpha]_D^{27}$ = +33.1 (c = 0.9, $CHCl_3$) (96% *ee*); HPLC (Daicel Chiralcel OF, *n*-hexane/IPA = 97:3, 1.0 mL min^{-1}, 254 nm, τ_{major} 18.5 min, τ_{minor} 10.4 min; Anal. calcd for $C_{19}H_{29}NO_6$: C 62.11, H 7.96, N 3.81, found: C 62.20, H 8.02, N 3.79.

7ai (minor diastereomer): colorless oil; IR (neat): $\tilde{\nu}$ = 3457, 3422, 2975, 2931, 1716, 1490, 1368, 1255, 1162, 1013, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.37 (s, 3H), 1.41 (s, 9H), 1.45 (s, 9H), 2.21 (s, 3H), 5.41 (d,

J=9.3 Hz, 1H), 5.82 (br d, J=9.3 Hz, 1H), 6.22 (d, J=3.2 Hz, 1H), 6.29 (dd, J=1.9, 3.2 Hz, 1H), 7.29 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=18.3, 27.7, 28.3, 29.7, 52.8, 63.4, 79.8, 82.8, 108.2, 110.4, 141.6, 152.4, 154.9, 170.0, 205.8 ppm; $[\alpha]_D^{29}=-43.3$ (c=0.125, $CHCl_3$) (99% *ee*); HPLC (Daicel Chiralcel OF, *n*-hexane/IPA=97:3, 1.0 mL min^{-1}, 254 nm, τ_{major} 20.1 min, τ_{minor} 9.8 min).

7ca (major diastereomer): white solid: mp: 96.0–96.5 °C; IR (neat): $\tilde{\nu}$= 3430, 2979, 2943, 1714, 1491, 1458, 1368, 1319, 1251, 1163 cm^{-1}; H NMR (400 MHz, $CDCl_3$): δ=1.09 (t, J=7.2 Hz, 3H), 1.25 (s, 3H), 1.37 (s, 9H), 1.41 (s, 9H), 2.56–2.67 (m, 2H), 5.10 (d, J=9.8 Hz, 1H), 6.70 (d, J= 9.8 Hz, 1H), 7.24–7.31 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 8.0, 20.3, 27.8, 28.3, 30.6, 58.8, 64.6, 79.5, 82.7, 127.7, 128.1, 128.5, 138.4, 154.9, 171.0, 209.2 ppm; FAB-LRMS (*m*NBA) *m*/*z* 414 $[M+Na]^+$, 392 $[M+H]^+$, 391 $[M]^+$; $[\alpha]_D^{27}=+11.7$ (c=1.205, acetone) (89% *ee*); HPLC (Daicel Chiralpak AD-H, *n*-hexane/IPA=90:10, 1.0 mL min^{-1}, 280 nm, τ_{major} 4.9 min, τ_{minor} 5.7 min); Anal. calcd for $C_{23}H_{33}NO_5$: C 67.49, H 8.50, N 3.58, found: C 67.32, H 8.49, N 3.53.

7ca (minor diastereomer): colorless oil; IR (neat): $\tilde{\nu}$=2977, 2933, 1716, 1493, 1456, 1368, 1251, 1164 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.98 (t, J=7.2 Hz, 3H), 1.36 (s, 9H), 1.36 (s, 3H), 1.46 (s, 9H), 2.13–2.23 (m, 1H), 2.45–2.51 (m, 1H), 5.11 (br d, J=9.3 Hz, 1H), 6.44 (br d, J=7.1 Hz, 1H), 7.22–7.52 ppm (m, 5H); $[\alpha]_D^{26}=-27.7$ (c=0.29, acetone) (86% *ee*); HPLC (Daicel Chiralpak AD-H, *n*-hexane/IPA=90:10, 1.0 mL min^{-1}, 280 nm, τ_{minor} 5.2 min, τ_{major} 9.5 min).

7da (major diastereomer): colorless oil; IR (neat): $\tilde{\nu}$=2976, 1710, 1492, 1365, 1250, 1164 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.88 (t, J= 7.3 Hz, 3H), 1.37 (s, 9H), 1.43 (s, 9H), 1.64–1.78 (m, 2H), 2.22 (s, 3H), 5.12 (d, J=9.5 Hz, 1H), 6.71 (br d, J=9.5 Hz, 1H), 7.25–7.28 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=9.7, 27.1, 27.4, 27.9, 28.3, 58.5, 68.6, 79.5, 82.9, 127.8, 128.1, 138.4, 154.9, 170.5, 206.0 ppm; FAB-LRMS (*m*NBA) *m*/*z* 414 $[M+Na]^+$, 392 $[M+H]^+$, 391 $[M]^+$; $[\alpha]_D^{28}=-10.9$ (c= 0.80, $CHCl_3$) (97% *ee*); HPLC (Daicel Chiralpak AD-H, *n*-hexane/IPA= 90:10, 1.0 mL min^{-1}, 280 nm, τ_{major} 4.7 min, τ_{minor} 5.6 min); Anal. calcd for $C_{23}H_{33}NO_5$+0.2 H_2O: C 66.88, H 8.52, N 3.55, found: C 66.94, H 8.46, N 3.41.

7ea (major diastereomer): white solid: mp: 144.0–145 °C; IR (solid): $\tilde{\nu}$= 3440, 3342, 2977, 2930, 1710, 1693, 1493, 1454, 1366, 1243, 1148, 1118, 1048, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.34 (s, 9H), 1.39 (s, 9H), 1.87 (br s, 2H), 1.96–2.03 (m, 1H), 2.22 (br s, 1H), 2.31–2.37 (m, 1H), 2.44–2.51(m, 1H), 5.19 (d, J=9.5 Hz, 1H), 5.74 (br s, 1H), 7.22–7.31 (m, 3H), 7.37 ppm (br d, J=6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=18.9, 27.6, 28.3, 31.3, 37.7, 56.1, 65.7, 79.6, 82.6, 127.6, 128.2, 128.4, 139.0, 155.2, 168.4, 211.7 ppm; FAB-LRMS (*m*NBA) *m*/*z* 412 $[M+Na]^+$, 390 $[M+1]^+$; $[\alpha]_D^{28}=+7.9$ (c=1.28, $CHCl_3$) (98% *ee*); HPLC (Daicel Chiralpak AD-H, *n*-hexane/IPA=19:1, 1.0 mL min^{-1}, 254 nm, τ_{major} 11.7 min, τ_{minor} 24.0 min; Anal. calcd for $C_{22}H_{31}NO_5$: C 67.84, H 8.02, N 3.60, found: C 67.58, H 8.00, N 3.56.

7ea (minor diastereomer): white solid: mp: 151 °C; IR (solid): $\tilde{\nu}$=3426, 2976, 2931, 1716, 1494, 1367, 1248, 1156, 1027, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.37 (s, 9H), 1.48 (s, 9H), 1.68–1.88 (m, 3H), 2.24–2.39 (m, 3H), 5.15 (br d, J=9.5 Hz, 1H), 6.81 (br d, J=9.3 Hz, 1H), 7.22–7.30 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=19.4, 27.8, 28.4, 33.0, 39.5, 57.7, 63.9, 79.2, 82.8, 127.7, 128.3, 128.5, 138.8, 154.8, 170.3, 217.2 ppm; $[\alpha]_D^{28}=+18.3$ (c=0.58, $CHCl_3$) (98% *ee*); HPLC (Daicel Chiralpak AD-H, *n*-hexane/IPA=19:1, 1.0 mL min^{-1}, 254 nm, τ_{major} 18.4 min, τ_{minor} 8.1 min)

7eb (major diastereomer): colorless oil; IR (neat): $\tilde{\nu}$=3453, 3342, 2976, 2930, 1749, 1710, 1494, 1454, 1366, 1244, 1149, 1116, 1047, 842, 735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.36 (s, 9H), 1.38 (s, 9H), 1.77–2.02 (m, 3H), 2.12–2.38 (m, 2H), 2.30 (s, 3H), 2.43–2.49 (m, 1H), 5.15 (d, J= 9.5 Hz, 1H), 5.73 (br s, 1H), 7.09 (d, J=7.8 Hz, 1H), 7.24 ppm (d, J= 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=18.9, 21.0, 27.7, 28.3, 31.0, 37.7, 55.8, 65.7, 79.5, 82.6, 128.2, 128.9, 136.0, 137.2, 155.2, 168.4, 211.7 ppm; MALDI-TOF MS (α-cyano-4-hydroxycinnamic acid) *m*/*z* 426 $[M+Na]^+$; $[\alpha]_D^{28}=+4.4$ (c=0.79, $CHCl_3$) (89% *ee*), $[\alpha]_D^{28}=+1.6$ (c=0.79, acetone) (89% *ee*); HPLC (Daicel Chiralpak AD-H, *n*-hexane/IPA= 90:10, 1.0 mL min^{-1}, 254 nm, τ_{major} 6.6 min, τ_{minor} 15.5 min).; Anal. calcd for $C_{23}H_{33}NO_5$: C 68.46, H 8.24, N 3.47, found: C 68.24, H 8.31, N 3.42.

7eb (minor diastereomer): white solid: mp: 120.5–121.0 °C; IR (neat): $\tilde{\nu}$=3420, 2967, 2922, 1725, 1490, 1363, 1247, 1157 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.37 (s, 9H), 1.45–1.54 (m, 1H), 1.48 (s, 9H), 1.68–1.75 (m, 1H), 1.77–1.89 (m, 2H), 2.22–2.25 (m, 1H), 2.30 (s, 3H), 2.32–2.39 (m, 1H), 3.78 (s, 3H), 5.11 (d, J=9.3 Hz, 1H), 6.79 (br d, J= 9.3 Hz, 1H), 7.08 (d, J=7.8 Hz, 2H), 7.1 ppm1 (d, J=8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=19.4, 21.0, 27.8, 28.4, 33.0, 39.6, 57.4, 64.0, 79.1, 82.7, 128.3, 129.0, 135.7, 137.3, 154.7, 170.4, 217.3 ppm; $[\alpha]_D^{28}=+10.4$ (c=1.02, $CHCl_3$) (95% *ee*); HPLC (Daicel Chiralpak AD-H, *n*-hexane/IPA=90:10, 1.0 mL min^{-1}, 254 nm, τ_{major} 12.8 min, τ_{minor} 6.0 min

7ed (major diastereomer): colorless oil; IR (neat): $\tilde{\nu}$=2977, 2925, 1747, 1715, 1492, 1367, 1247, 1157 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.35 (s, 9H), 1.39 (s, 9H), 1.86–2.02 (m, 4H), 2.13–2.34 (m, 1H), 2.32 (s, 3H), 2.40–2.47 (m, 1H), 5.13 (d, J=9.5 Hz, 1H), 5.80 (br d, J=7.1 Hz, 1H), 7.05–7.18 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=18.9, 21.5, 27.7, 28.3, 31.2, 37.7, 56.0, 65.6, 79.6, 82.6, 125.4, 128.1, 128.3, 129.1, 137.8, 138.9, 155.2, 168.4, 211.6 ppm; FAB-LRMS (*m*NBA) *m*/*z* 426 $[M+Na]^+$, 404 $[M+H]^+$; $[\alpha]_D^{27}=+5.0$ (c=0.94, benzene) (84% *ee*); HPLC (Daicel Chiralpak AD-H, *n*-hexane/IPA=95:5, 1.0 mL min^{-1}, 254 nm, τ_{major} 9.8 min, τ_{minor} 23.5 min); FAB-HRMS (*m*NBA) calcd for $C_{23}H_{34}NO_5$ $[M+H]^+$ 404.2437, found: 404.2440.

7ed (minor diastereomer): white solid: mp: 113.0–113.5 °C (dec); IR (solid): $\tilde{\nu}$=2969, 1721, 1495, 1454, 1367, 1246, 1159 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.38 (s, 9H), 1.48 (s, 9H), 1.64–1.89 (m, 4H), 2.22–2.38 (m, 2H), 2.32 (s, 3H), 5.17 (d, J=9.3 Hz, 1H), 6.99 (br d, J= 9.5 Hz, 1H), 7.00–7.06 (m, 3H), 7.17 ppm (t, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=19.5, 21.4, 27.8, 28.4, 33.0, 39.6, 57.7, 63.9, 79.2, 82.7, 125.4, 128.3, 128.5, 129.4, 137.9, 138.7, 154.8, 170.4, 217.3 ppm; $[\alpha]_D^{27}=-5.9$ (c=0.29, CH_3CN) (91% *ee*); HPLC (Daicel Chiralpak AD-H, *n*-hexane/IPA=95:5, 1.0 mL min^{-1}, 254 nm, τ_{minor} 8.0 min, τ_{major} 15.0 min).

7ef (major diastereomer): colorless oil; IR(neat): $\tilde{\nu}$=2977, 1712, 1490, 1367, 1249, 1153 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.20 (s, 9H), 1.39 (s, 9H), 1.83–2.59 (m, 6H), 2.50 (s, 3H), 5.39 (d, J=10.0 Hz, 1H), 5.46 (br d, J=10.0 Hz, 1H), 7.12–7.18 (m, 3H), 7.73–7.75 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=19.0, 20.2, 27.4, 28.3, 34.0, 37.9, 51.3, 66.3, 79.5, 82.4, 126.2, 127.5, 128.4, 130.5, 137.0, 138.3, 155.4, 169.4, 213.0 ppm; FAB-LRMS (*m*NBA) *m*/*z* 426 $[M+Na]^+$, 404 $[M+H]^+$; $[\alpha]_D^{29}=+71.0$ (c=1.43, $CHCl_3$) (94% *ee*); HPLC (Daicel Chiralcel OF, *n*-hexane/IPA=97:3, 1.0 mL min^{-1}, 254 nm, τ_{major} 9.6 min, τ_{minor} 12.3 min); Anal. calcd for $C_{23}H_{33}NO_5$: C 68.46, H 8.24, N 3.47, found: C 68.01, H 8.31, N 3.35.

7eg (major diastereomer): colorless oil; IR (neat): $\tilde{\nu}$=3439, 2977, 2934, 1746, 1714, 1491, 1368, 1250, 1152 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.29 (s, 9H), 1.39 (s, 9H), 1.92–1.95 (m, 1H), 2.10–2.17 (m, 2H), 2.42–2.45 (m, 3H), 5.64 (br d, J=9.3 Hz, 1H), 5.91 (br s, 1H), 7.17–7.24 (m, 2H), 7.33–7.36 (m, 1H), 7.79 ppm (d, J=6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=19.0, 27.6, 28.3, 32.7, 37.7, 51.7, 65.5, 79.6, 82.8, 127.1, 128.8, 129.6, 130.2, 134.4, 137.4, 155.2, 168.8, 212.1 ppm; FAB-LRMS (*m*NBA) *m*/*z* 446 $[M+Na]^+$, 424 $[M+H]^+$, 425, 426; $[\alpha]_D^{25}=+57.8$ (c=0.85, acetone) (93% *ee*); HPLC (Daicel Chiralpak AD-H, *n*-hexane/IPA=95:5, 0.5 mL min^{-1}, 280 nm, τ_{major} 14.4 min, τ_{minor} 16.0 min); Anal. calcd for $C_{22}H_{30}ClNO_5$: C 62.33, H 7.13, N 3.30, found: C 62.44, H 7.23, N 3.24.

7eh (major diastereomer): colorless oil; IR (neat): $\tilde{\nu}$=2973, 1723, 1493, 1366, 1245, 1157, 1028, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.38 (s, 9H), 1.48 (s, 9H), 1.54–1.88 (m, 4H), 2.27–2.36 (m, 2H), 3.83 (s, 3H), 5.80 (d, J=9.5 Hz, 1H), 6.82–6.90 (m, 3H), 7.19–7.27 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=19.6, 27.8, 28.4, 32.6, 39.2, 50.1, 55.4, 64.2, 78.9, 82.4, 110.3, 120.7, 127.6, 128.6, 128.7, 154.8, 157.0, 170.6, 217.2 ppm; FAB-LRMS (*m*NBA) *m*/*z* 442 $[M+Na]^+$, 420 $[M+H]^+$, 419 $[M]^+$; $[\alpha]_D^{27}=+18.2$ (c=1.03, $CHCl_3$) (93% *ee*); HPLC (Daicel Chiralcel OD-H, *n*-hexane/IPA=99:1, 0.5 mL min^{-1}, 280 nm, τ_{major} 17.6 min, τ_{minor} 22.7 min); Anal. calcd for $C_{23}H_{32}NO_6$: C 65.85, H 7.93, N 3.34, found: C 65.77, H 7.89, N 3.29.

7ei (major diastereomer): colorless oil; IR (neat): $\tilde{\nu}$=3442, 3330, 2972, 2928, 1749, 1710, 1492, 1367, 1245, 1149, 1010, 735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.40 (s, 9H), 1.41 (s, 9H), 1.88–2.04 (m, 3H),

2.24–2.38 (m, 2H), 2.50–2.56 (m, 1H), 5.33 (d, $J=10.0$ Hz, 1H), 5.44 (br d, $J=10.0$ Hz, 1H), 6.22 (d, $J=3.2$ Hz, 1H), 6.28 (dd, $J=1.7$, 3.2 Hz, 1H), 7.29 ppm (dd, $J=0.7$, 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=18.9$, 27.7, 28.2, 30.8, 37.7, 50.7, 64.9, 79.8, 82.5, 107.9, 110.4, 141.6, 152.3, 155.2, 167.9, 211.1 ppm; MALDI-TOF MS (α-cyano-4-hydroxycinnamic acid) m/z $[M+Na]^+$ 402; The optical rotations were measured after purification by chiral HPLC. $[\alpha]_D^{27}=+5.7$ ($c=1.80$, acetone) (>99% *ee*); $[\alpha]_D^{25}=+2.4$ ($c=1.80$, $CHCl_3$) (>99% *ee*); HPLC (Daicel Chiralpak AD-H, *n*-hexane/IPA=90:10, 1.0 mL min^{-1}, 254 nm, τ_{major} 5.7 min, τ_{minor} 7.5 min); Anal. calcd for $C_{20}H_{29}NO_6$: C 63.31, H 7.70, N 3.69, found: C 62.99, H 7.61, N 3.66.

Transformation of 7ea to 8 and Determination of the Relative and Absolute Stereochemistry

$LiAlH_4$ (327.4 mg, 8.6 mmol, 30.0 equiv) was slowly added to a solution of the major diastereomer of Mannich product **7ea** (112.0 mg, 0.29 mmol, 85% *ee*) in dry THF (3.5 mL) at room temperature. The mixture was heated at reflux under N_2 for 24 h. The reaction mixture was diluted with CH_2Cl_2 (10.0 mL) at −78 °C. To this solution were added H_2O (0.33 mL), 1 N NaOH (0.33 mL, aq), then H_2O (1.0 mL) successively. The resulting mixture was gradually warmed to room temperature. The precipitate was filtered through a Celite pad, which was washed with CH_2Cl_2 (3×10 mL). The solvent was removed under reduced pressure to afford the crude product.

Pyridine (5.0 mL) and acetic anhydride (2.5 mL) were added to this residue, and the resulting mixture was stirred for 12 h. Excess pyridine and acetic anhydride were removed directly with a vacuum pump. Further purification was performed by MPLC (diol-SiO_2; *n*-hexane/EtOAc=1:1) to give the pure product **8** (61.6 mg, 59.3%). The *ee* value of this product was determined by chiral HPLC analysis.

All spectroscopic data obtained (^{1}H NMR at RT, ^{13}C NMR, LRMS) were found to be identical with those of the opposite enantiomer reported by Karlsson et al.[15] By comparing the sign of optical rotation, the absolute stereochemistry of **8** was determined to be as depicted in Scheme 5. It was concluded that the major diastereomer of **7ea** had the stereochemistry shown above.

8 from 7ea (major diastereomer): $[\alpha]_D^{25}=+59.5$ ($c=1.17$, $CHCl_3$, 73% *ee*) [Lit. $[\alpha]_D^{25}=-75.2$ ($c=0.39$, $CHCl_3$, 91% *ee*); ^{1}H NMR [$(CD_3)_2SO$, 60 °C]; $\delta=1.18$–2.17 (m, 6H), 1.76 (s, 3H), 1.93 (s, 3H), 1.97 (s, 3H), 2.93 (s, 3H), 3.89 (d, $J=12.0$ Hz, 1H), 4.09 (d, $J=12.0$ Hz, 1H), 5.13–5.16 (m, 1H), 5.25 (br s, 1H), 6.04 (s, 1H), 7.25–7.39 ppm (m, 5H); ^{13}C NMR ($CDCl_3$, 22 °C): $\delta=20.8$, 20.9, 21.1, 21.2, 22.0, 22.4, 30.9, 31.1, 31.8, 34.1, 52.7, 53.0, 57.5, 63.0, 65.8, 67.0, 79.2, 79.7, 127.2, 127.6, 128.3, 128.6, 128.6, 129.5, 138.9, 139.2, 169.9, 170.4, 170.4, 170.9, 171.2, 171.5 ppm; ^{13}C NMR ($CDCl_3$ at 50 °C): $\delta=20.8$, 21.2, 21.2, 22.4, 31.1, 32.0, 34.2, 53.2, 57.8, 66.1, 79.3, 127.2, 128.3, 128.6, 129.6, 139.5, 170.3, 170.8, 171.2 ppm; MS (EI) $m/z=361$ $[M]^+$; HPLC (Daicel Chiralcel OJ-H, *n*-hexane/IPA=90:10, 1.0 mL min^{-1}, 220 nm, τ_{major} 16.0 min, τ_{minor} 19.1 min).

X-ray Structural Analysis of 7ea (minor)

The structure of **7ea** (minor) was determined by a single-crystal X-ray analysis using a Rigaku R-AXIS-CS instrument. A single crystal suitable for X-ray analysis was obtained by recrystallization from hexane/EtOAc. CCDC 288294 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

A Representative Procedure for the Catalytic Asymmetric Mannich-Type Reactions of Malonates to N*-Boc Imines* (Table 4, entry 9)

Dibenzyl malonate **9a** (30 μL, 120 μmol, 1.0 equiv) and the Pd complex **2a** (3.0 mg, 1.5 μmol, 2.5 mol% Pd) were dissolved in CH_2Cl_2 (0.24 mL). *N*-Boc imine **6a** (74 mg, 360 μmol, 3.0 equiv) was added to this solution, and the reaction mixture was stirred at 0 °C for 24 h. Saturated aqueous NaCl was added for quenching, and the water layer was extracted by EtOAc (3×5 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Further purification was carried out by MPLC (SiO_2; hexane/EtOAc=6:1) to afford the desired product **10a** in up to 75% yield; chiral HPLC analysis indicated 59% *ee*. The product **10a** was reported previously.[11g]

10a:[11g] white solid: mp: 96.0–97.0 °C; IR (neat): $\tilde{\nu}=3426$, 3425, 3028, 2975, 1715, 1494, 1454, 1366, 1349, 1245, 1220, 1156 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.41$ (s, 9H), 4.01 (s, 1H), 5.04 (s, 2H), 5.13 (d, $J=12.2$ Hz, 1H), 5.16 (d, $J=12.2$ Hz, 1H), 5.55 (br s, 1H), 6.19 (br s, 1H), 7.08–7.10 (m, 2H), 7.22–7.32 ppm (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=28.3$, 53.5, 56.9, 67.3, 67.6, 79.7, 126.2, 127.6, 128.0, 128.2, 128.3, 128.4, 128.5, 128.6, 128.6, 134.8, 135.0, 139.3, 155.0, 166.8, 167.8 ppm; FAB-LRMS (*m*NBA) m/z 490 $[M+H]^+$, 434 $[M-t\text{Bu}+2H]^+$; ESI-LRMS(+): m/z 512 $[M+Na]^+$, 456 $[M-t\text{Bu}+H+Na]^+$; $[\alpha]_D^{24}=+8.5$ ($c=2.43$, $CHCl_3$) (45% *ee*); HPLC (Daicel Chiralpak AS-H, *n*-hexane/IPA=97:3, 1.0 mL min^{-1}, 220 nm, τ_{major} 22.5 min, τ_{minor} 28.2 min); Anal. calcd for $C_{29}H_{31}NO_6$ C: 71.15, H: 6.38, N: 2.86, found: C: 71.08, H: 6.46, N: 2.83.

10b: colorless oil; IR (neat): $\tilde{\nu}=3432$, 3380, 2980, 2936, 2907, 1714, 1497, 1454, 1391, 1368, 1347, 1289, 1249, 1165, 1040, 1032, 1018 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.13$ (t, $J=7.1$ Hz, 3H), 1.26 (t, $J=7.1$ Hz, 3H), 1.41 (s, 9H), 3.89 (br s, 1H), 4.02–4.27 (m, 4H), 5.50 (br s, 1H), 6.19 (br s, 1H), 7.24–7.31 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=13.9$, 14.0, 28.3, 53.4, 56.9, 61.6, 62.0, 79.6, 126.2, 127.5, 128.4, 139.5, 154.9, 167.0, 167.9 ppm; ESI-LRMS(+): m/z 388 $[M+Na]^+$, 332 $[M-t\text{Bu}+H+Na]^+$; HPLC (Daicel Chiralpak AS-H, *n*-hexane/IPA=90:10, 1.0 mL min^{-1}, 254 nm, τ_{faster} 5.8 min, τ_{slower} 6.9 min).

10c: white solid: mp: 58.8–59.2 °C; IR (neat): $\tilde{\nu}=3433$, 3375, 2980, 2936, 2879, 1720, 1496, 1467, 1455, 1369, 1332, 1287, 1246, 1167, 1102, 1049, 1025 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.04$ (d, $J=6.3$ Hz, 3H), 1.18 (d, $J=6.3$ Hz, 3H), 1.23 (d, $J=6.3$ Hz, 3H), 1.25 (d, $J=6.3$ Hz, 3H), 1.41 (s, 9H), 3.83 (br d, $J=3.9$ Hz, 1H), 4.95 (sept, $J=6.3$ Hz, 1H), 5.05 (sept, $J=6.3$ Hz, 1H), 5.47 (br s, 1H), 6.22 (br s, 1H), 7.20–7.33 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=21.4$, 21.5, 21.6, 28.3, 53.4, 57.1, 69.2, 69.7, 79.5, 126.2, 127.4, 128.4, 139.7, 154.8, 166.6, 167.5 ppm; $[\alpha]_D^{29}=-10.2$ ($c=1.43$, acetone) (48% *ee*); HPLC (Daicel Chiralpak AD-H, *n*-hexane/IPA=90:10, 1.0 mL min^{-1}, 254 nm, τ_{major} 15.9 min, τ_{minor} 12.7 min); FAB-HRMS (*m*NBA) calcd for $C_{21}H_{31}NO_6Na$ $[M+Na]^+$ 416.2049, found: 417.2083.

A Representative Procedure for the Catalytic Asymmetric α-Aminomethylation of β-Ketoesters (Table 6, entry 4)

Palladium complex **1c** (2.2 mg, 1 mol%) and the β-ketoester **3e** (80 μL, 434 μmol) were successively added to a mixture of benzylamine TfOH salt **13** (112 mg, 434 μmol) and formalin (37% aq, 72 μL, 868 μmol). This reaction mixture was stirred for 1 h at room temperature. After consumption of **3e** (TLC: *n*-hexane/EtOAc=3:1), anhydrous Na_2SO_4 and EtOAc were added. Filtration followed by evaporation under reduced pressure gave the crude product. Ac_2O (3 equiv) and Et_3N (2 equiv) were added to a stirred solution of this crude product in CH_2Cl_2 (3 mL) under cooling in an ice bath, and the resulting mixture was stirred overnight. After usual workup, purification was performed by MPLC (SiO_2; *n*-hexane/acetone=2:1) to give **15e** (149 mg, 99%). The *ee* value was determined by chiral HPLC analysis.

15a: This compound was a mixture of rotamers in a ratio of 4.1:1 at 22 °C in $CDCl_3$: colorless oil; IR (neat): $\tilde{\nu}=2975$, 2931, 1705, 1648, 1416, 1359, 1254, 1145, 1114, 978, 956, 838, 728, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) for major rotamer: $\delta=1.37$ (s, 3H), 1.45 (s, 9H), 2.06 (s, 3H), 2.23 (s, 3H), 3.66 (d, $J=14.4$ Hz, 1H), 4.18 (d, $J=14.4$ Hz, 1H), 4.49 (d, $J=17.5$ Hz, 1H), 4.63 (d, $J=17.5$ Hz, 1H), 7.25 (d, $J=7.3$ Hz, 2H), 7.38–7.25 ppm (m, 3H); for minor rotamer: $\delta=1.37$ (s, 3H), 1.47 (s, 9H), 2.17 (s, 3H), 2.18 (s, 3H), 3.71 (d, $J=15.6$ Hz, 1H), 3.98 (d, $J=15.6$ Hz, 1H), 4.32 (d, $J=14.9$ Hz, 1H), 4.67 (d, $J=14.9$ Hz, 1H), 7.38–7.12 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) for major rotamer: $\delta=17.9$, 21.7, 27.7, 49.1, 53.4, 61.0, 82.2, 125.9, 127.5, 128.9, 136.6, 171.2, 172.4, 204.5 ppm; for minor rotamer: $\delta=18.5$, 22.0, 26.3, 47.7, 49.2, 61.0, 83.2, 127.2, 128.0, 128.4, 137.0, 170.8, 171.6, 204.3 ppm; FAB-LRMS (*m*NBA) m/z 356 $[M+Na]^+$, 276 $[M-t\text{Bu}]^+$, 242 $[M-\text{Bn}]^+$; FAB-HRMS (*m*NBA) calcd for $C_{19}H_{28}NO_4$ 334.2018 $[M+H]^+$, found: 334.2019; $[\alpha]_D^{29}=+11.6$ ($c=1.30$, $CHCl_3$) (57% *ee*); HPLC (Daicel Chiralcel OD-H, *n*-hexane/IPA=90:10, 0.5 mL min^{-1}, 254 nm, τ_{major} 13.9 min, τ_{minor} 15.6 min).

15e: This compound was a mixture of rotamers in a ratio of 3.6:1 at 22 °C in $CDCl_3$: colorless oil; IR (neat): $\tilde{\nu}$ = 2975, 2936, 1744, 1719, 1650, 1434, 1413, 1368, 1251, 1140, 1005, 845, 733, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) for major rotamer: δ = 1.41 (s, 9H), 2.07 (s, 3H), 1.88–2.46 (m, 6H), 3.70 (d, J = 13.9 Hz, 1H), 3.98 (d, J = 13.9 Hz, 1H), 4.64 (s, 2H), 7.17 (d, J = 7.3 Hz, 2H), 7.37–7.23 ppm (m, 3H); for minor rotamer: δ = 1.42 (s, 9H), 2.20 (s, 3H), 1.88–2.46 (m, 6H), 3.72 (d, J = 14.6 Hz, 1H), 3.95 (d, J = 14.6 Hz, 1H), 3.99 (d, J = 14.6 Hz, 2H), 4.87 (d, J = 14.6 Hz, 1H), 7.17 (d, J = 7.3 Hz, 2H), 7.37–7.23 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for major rotamer: δ = 20.0, 21.8, 27.8, 33.8, 38.4, 48.1, 52.7, 61.3, 82.1, 126.2, 127.4, 128.8, 137.1, 170.9, 172.7, 214.0 ppm; FAB-LRMS (*m*NBA) *m*/*z* 346 $[M+H]^+$; FAB-HRMS (*m*NBA) calcd for $C_{20}H_{27}NO_4$ 345.1940 $[M]^+$, found: 345.1934; $[\alpha]_D^{30}$ = −15.6 (c = 3.5, $CHCl_3$) (60 % *ee*); HPLC (Daicel Chiralpak AD-H, *n*-hexane/IPA = 90:10, 0.5 mL min^{-1}, 254 nm, τ_{major} 20.4 min, τ_{minor} 17.5 min)

15f: This compound was a mixture of rotamers in a ratio of 1.8:1 at 22 °C in $CDCl_3$: colorless oil; IR (neat): $\tilde{\nu}$ = 2972, 2939, 2867, 1708, 1651, 1434, 1416, 1364, 1251, 1146, 1096, 991, 842, 728, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) for major rotamer: δ = 1.47(s, 9H), 2.03–1.31 (m, 5H), 2.06 (s, 3H), 2.60–2.36 (m, 3H), 3.72 (d, J = 14.2 Hz, 1H), 4.09 (d, J = 14.2 Hz, 1H), 4.52 (d, J = 17.5 Hz, 1H), 4.63 (d, J = 17.5 Hz, 1H), 7.37–7.12 ppm (m, 5H); for minor rotamer: δ = 1.48 (s, 9H), 2.03–1.31 (m, 5H), 2.18 (s, 1H), 2.60–2.36 (m, 3H), 3.41 (d, J = 15.4 Hz, 1H), 4.00 (d, J = 15.4 Hz, 1H), 4.35 (d, J = 14.6 Hz), 4.80 (d, J = 14.6 Hz, 1H), 7.37–7.12 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) for major rotamer δ = 21.9, 22.3, 27.2, 27.8, 34.4, 41.0, 48.3, 52.8, 62.5, 82.4, 125.9, 127.4, 128.9, 137.0, 169.8, 172.5, 207.4 ppm; for minor rotamer δ = 22.1, 22.8, 27.4, 27.8, 36.8, 41.2, 47.8, 48.9, 63.4, 83.5, 127.2, 128.4, 128.5, 137.6, 169.4, 171.7, 206.7 ppm; FAB-LRMS (*m*NBA) *m*/*z* 360 $[M+H]^+$, 302 $[M-t\text{Bu}]^+$; FAB-HRMS (*m*NBA) calcd for $C_{21}H_{30}NO_4$ 360.2175 $[M+H]^+$, found: 360.2162; $[\alpha]_D^{28}$ = +61.6 (c = 2.55, $CHCl_3$) (61 % *ee*); HPLC (Daicel Chiralpak AS-H, *n*-hexane/IPA = 95:5, 1.0 mL min^{-1}, 254 nm, τ_{major} 15.7 min, τ_{minor} 24.4 min)

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[25] Lowering the reaction temperature improved the enantiomeric excess by <10% at the cost of the reaction rate. Thus, the reaction catalyzed by **1a** at −20 °C gave the product **15e** in 66% yield with 64% *ee* after 15 h.

[26] The reaction using diphenylmethylamine salt gave similar results to those in the case of benzylamine salt. Tosyl amide and $BocNH_2$ were not available in this reaction, and the hydroxymethylated product alone was obtained.

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