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Scope and Mechanism of Tandem Aza-Michael Reaction/Enantioselective Protonation Using a Pd–μ-Hydroxo Complex under Mild Conditions Buffered with Amine Salts

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Dedicated to Professor Eiichi Nakamura on the occasion of his 60th birthday

Abstract: The tandem aza-Michael reaction/enantioselective protonation of α-substituted α,β-unsaturated carbonyl compounds is described in detail. The key to success is the combined use of a Brønsted basic palladium–μ-hydroxo complex and amine salts, which allows for the controlled generation of active catalyst and nucleophilic free amines. This catalytic system was applicable to various acceptors and aromatic amines, and the desired β-amino acid derivatives with a chiral center at the α position were produced in good yield with excellent enantioselectivity (up to 98% *ee*). For electron-deficient amines, the introduction of free amine as an additive was effective in promoting the reaction. The results of mechanistic studies, including determination of the absolute configuration of the product, are discussed.

Keywords: amino acids · asymmetric catalysis · Michael addition · palladium · protonation

Introduction

Natural and unnatural optically active β-amino acids constitute an important class of chiral building blocks in organic synthesis,[1] and efficient methods for their preparation are important. For this purpose, much effort has been focused on the development of catalytic asymmetric Mannich-type reactions[2] and conjugate addition with hydroxylamine and azide as representative nitrogen nucleophiles.[3] As a part of our program on the synthesis of β-amino acid derivatives,[4] we previously reported a highly enantioselective aza-Michael reaction using chiral palladium–μ-hydroxo complexes **1**.[4a] Although there are many reports on the preparation of chiral β-substituted β-amino acids, the number of reactions that can afford α-substituted variants is quite limited. As such compounds are of value in medicinal chemistry, we became interested in the development of an efficient method to synthesize optically active α-substituted β-amino acid derivatives. For this purpose, we investigated the utility of a tandem aza-Michael reaction/enantioselective protonation of α-substituted α,β-unsaturated carbonyl compounds.

Enantioselective protonation of enolate equivalents has been intensively investigated because it is a powerful method to create a stereogenic carbon center at the α position of carbonyl compounds.[5] Among several approaches, enantioselective protonation of preformed metal enolate with a chiral proton source has been investigated primarily.[6] Alternatively, in situ generation of a chiral enolate followed by enantioselective protonation is also an attractive approach.[7] Most importantly, enantioselective protonation of enolates is directly relevant to the conjugate addition of (pro)nucleophiles to α,β-unsaturated carbonyl compounds. There are several reports of successful tandem conjugate addition–protonation sequences in the literature that involve the conjugate addition of sulfur,[8] phosphorus,[8c] aryl boronic acids,[9] substituted pyroles,[10] cyanide,[11] and malonates.[12] However, reactions initiated by the conjugate addition of nitrogen nucleophiles are rare, and there are only a few exam-

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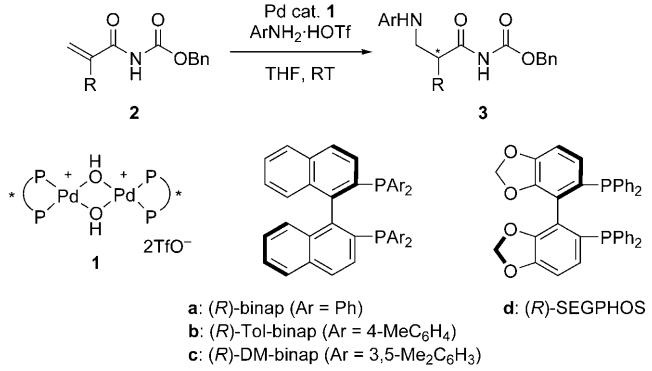
ples, including our original reports.[13,14] Hii et al. examined enantioselective protonation during their investigation on a catalytic asymmetric aza-Michael reaction using our cationic palladium–diaqua complex [Pd{(*R*)-binap}$(H_2O)_2$]$(TfO)_2$ (binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) or their cationic palladium–monoaqua-monoacetonitrile complex [Pd{(*R*)-binap}$(H_2O)(CH_3CN)$]$(TfO)_2$. They achieved reasonably high enantioselectivity when less basic aromatic amines, such as *para*-chloroaniline were employed as nucleophiles. But their catalytic system was difficult to apply to reactions with electron-rich anilines. For example, low asymmetric induction was observed in the case of *para*-methoxy aniline (anisidine) as a reaction partner. Therefore, there is scope to improve the reaction efficiency of the tandem aza-Michael reaction–protonation sequence.

We recently reported preliminary results on the title tandem sequence using α-substituted α,β-unsaturated carbonyl compounds **2**. The corresponding β-amino acid derivatives **3** were produced in a highly enantioselective manner (Scheme 1).[13] As this reaction shows excellent enantioselectivity of more than 90% with broad generality, we believe that it will be a useful method for the preparation of novel β-amino acids. In this paper, we present full details of our study. Firstly, the generality of the reaction was further investigated. Secondly, NMR spectroscopy and ESI-MS experiments were carried out to obtain insight into the reaction mechanism. The results were consistent with our original hypothesis (see below). Thirdly, the absolute configuration of the products was determined to shed light on the possible mechanism of the enolate protonation step.



Scheme 1. Tandem aza-Michael reaction/enantioselective protonation.

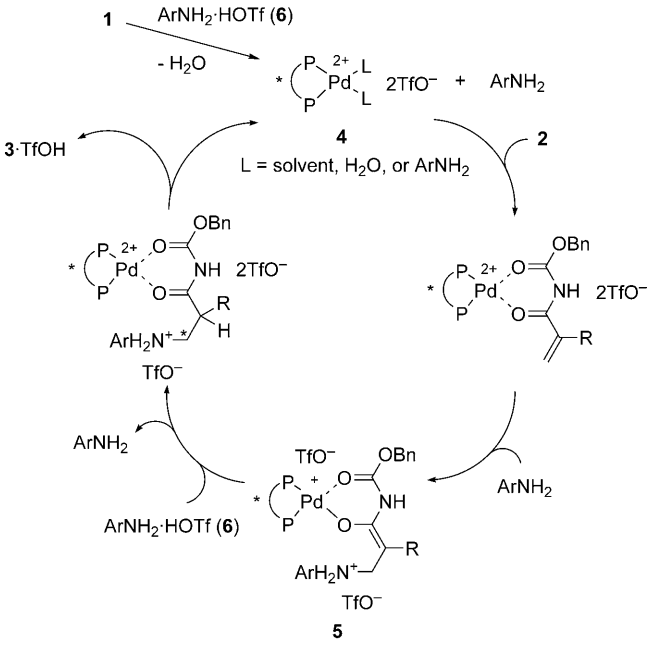
Abstract in Japanese:

本論文では、α-置換型α,β-不飽和カルボニル化合物に対する芳香族アミンの共役付加におけるエナンチオ選択的プロトン化反応の詳細について報告する。ブレンステッド塩基性を示すPd-μ-ヒドロキソ錯体とアミン塩を組み合わせて反応を行なったところ、様々な基質に対して反応は円滑に進行し、目的とするa位に不斉点を有するβ-アミノ酸誘導体を高選択的に合成することができた(~98% ee)。求核性の低いアミンを用いた場合における添加剤の効果および生成物の絶対配置を含めた反応機構に関する議論も併せて報告する。

Results and Discussion

Working Hypothesis

It is difficult to employ strongly basic amines in metal- or Brønsted acid catalyzed asymmetric reactions, because they coordinate to and deactivate the catalyst, and they also readily undergo uncatalyzed racemic reactions. However, highly reactive amine nucleophiles, such as anisidine and benzylamine could be successfully used in our previous asymmetric aza-Michael reaction.[4a] We expected that our reaction system would also be applicable to enantioselective protonation initiated by an aza-Michael reaction, as illustrated in Scheme 2. Indeed, the key to success was the combined use of chiral palladium–μ-hydroxo complex **1** and the trifluoromethanesulfonic acid salt of amines, which was essential to achieve excellent enantioselectivity. Under such conditions, the μ-hydroxo complex reacts with amine salts, and an acid–base reaction affords a catalytically active Lewis acidic palladium complex **4** with concomitant generation of free amine (Scheme 2). Then, the activation of **2** by **4** promotes the conjugate addition of the free amine. We expected that controlled generation of the nucleophilic amine under our reaction conditions would be effective to suppress the above-mentioned undesired reactions. Since the putative palladium enolate **5** is generated in a chiral environment, we anticipated that protonation of **5** would occur stereoselec-



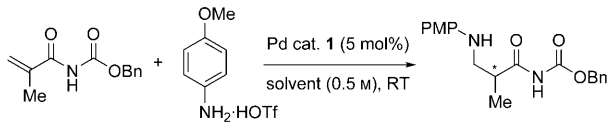
Scheme 2. Working hypothesis.

tively. In this step, the palladium enolate has two possible protonation pathways: intermolecular protonation from an excess amount of amine salt is likely to occur, but intramolecular proton transfer from the ammonium moiety at the β position cannot be ruled out. It is desirable that a single pathway is operative to achieve high asymmetric induction. Finally, to complete the catalytic cycle, the dissociation of the product as a salt would regenerate the active palladium catalyst **4**.

Optimization of the Reaction Conditions

At the outset, we selected a methacrylic acid derivative as a model substrate. The 2-oxazolidinone derivative did not show sufficient reactivity, probably because intramolecular steric interaction between the auxiliary and the α-substituent prevents the carbonyl group and the olefin from being coplanar. We next examined *N*-benzyloxycarbonyl (cbz)-protected methacrylimide **2a** and expected that such a steric interaction would be minimized.[15] As we had hoped, the reaction of **2a** with anisidine salt (**6a**) proceeded smoothly in tetrahydrofuran (THF) at room temperature in the presence of 5 mol% of the palladium complex **1a** (Table 1, entry 1),

Table 1. Optimization of aza-Michael reaction/enantioselective protonation.



2a **6a** (1.5 equiv) **3aa** PMP = *p*-MeOC$_6$H$_4$

Entry	Pd cat.	Solvent	*T*	*t* [h]	Yield[a] [%]	*ee* [%]
1	**1a**	THF	RT	8	80	94
2	**1a**	CH_2Cl_2	0 °C	24	79	77
3	**1a**	toluene	RT	3.5	82	88
4	**1a**	EtOH	RT	24	18	65
5	**1a**	DMF	RT	24	NR[b]	–
6	**1a**	THF	0 °C	12	31	93
7	**1d**	THF	RT	24	86	94
8	**1c**	THF	RT	71	7	53
9[c]	**1a**	THF	RT	24	79	94

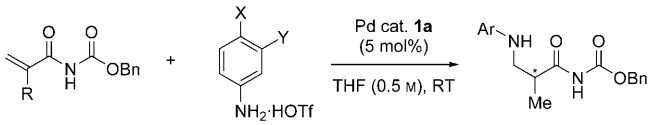
[a] Isolated yield. [b] NR = No reaction. [c] 1 mol% **1a**.

and the *ee* value of product **3aa** was determined to be 94% by chiral HPLC analysis. Among the solvents tested, THF was the best. Whereas less polar solvents, such as CH_2Cl_2 and toluene gave decreased enantioselectivity (entries 2 and 3), polar solvents, such as EtOH and *N*,*N*-dimethylformamide (DMF) were detrimental in terms of the catalytic activity (entries 4 and 5). Reaction temperature influenced the reaction rate. As shown in entry 6, reaction at 0 °C resulted in low conversion even after 12 h, and there was no improvement of the *ee* value. We also tested other chiral ligands. The 5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole (SEGPHOS) complex **1d** promoted the reaction, even though a longer reaction time was necessary for complete consumption of the substrate (entry 7). The more sterically demanding 2,2′-bis[bis(3,5-dimethylphenyl)phosphino]-1,1′-binaphthyl (DM-binap) complex **1c** did not serve as an efficient catalyst, and only a small amount of the product was formed (entry 8). It was possible to reduce the catalyst amount to as little as 1 mol%. Although the reaction did not go to completion after 12 h, results comparable to those in entry 1 were obtained after 24 h (entry 9). As our catalytic system could maintain a low concentration of the nucleophilic free amine during the reaction, slow addition of anisidine was not necessary, and we could achieve a high catalyst turnover number with high stereoselectivity.

Scope of the Reaction

To examine the generality of this reaction, reactions with various Michael acceptors and aromatic amines were carried out (Table 2). Under the optimized conditions, the reaction of ethyl-substituted compound **2b** afforded **3ba** in 54% yield with 88% *ee* (entry 1). Further optimization revealed that the chemical yield was improved to 78% without significant loss of enantioselectivity when a mixed solvent system of THF/CPME (1:1) was used (CPME = cyclopentyl methyl ether; entry 2). In addition to alkyl-substituted compounds, phenyl-substituted compound **2c** underwent the desired reaction without difficulty to give **3ca** in good yield with excellent enantioselectivity (79% yield, 93% *ee*; entry 3). Unfortunately, substrates with bulkier substituents, such as *i*Pr and Bn groups did not react well. Other electron-rich aromatic amines could be used as Michael donors. Both the dioxomethylene group and methyl thioether could tolerate the reaction conditions, and an excellent enantioselectivity of 96% was achieved in both cases (entries 4 and 5). Aniline salt **6d** also reacted with **2a** to give the corresponding product **3ad** with 97% *ee* (entry 6). However, aromatic amines

Table 2. Tandem aza-Michael reaction/enantioselective protonation using various substrates.



2a: R = Me
2b: R = Et
2c: R = Ph
2d: R = *i*Pr
2e: R = Bn

6a: X = MeO, Y = H
6b: X-Y = OCH_2O
6c: X = SMe, Y = H
6d: X = H, Y = H
6e: X = CF_3, Y = H

Entry	Acceptor	Salt	Product	*t* [h]	Yield [%]	*ee* [%]
1	**2b**	**6a**	**3ba**	24	54	88
2[a]	**2b**	**6a**	**3ba**	24	78	84
3	**2c**	**6a**	**3ca**	24	79	93
4	**2a**	**6b**	**3ab**	24	66	96
5	**2a**	**6c**	**3ac**	24	73	96
6	**2a**	**6d**	**3ad**	24	65	97
7[b]	**2a**	**6e**	**3ae**	50	11	ND[c]

[a] THF/CMPE = 1:1 (CPME = cyclopentyl methyl ether). [b] 40 °C. [c] ND = Not determined.

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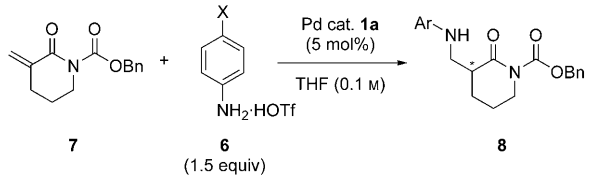
with electron-withdrawing groups, such as CF_3 and Br, failed to react smoothly. For example, the adduct **3ae** was obtained in only 11% yield at higher temperature (40°C; entry 7). This problem was overcome by modifying the reaction conditions, as will be discussed later.

The low reactivity of bulkier substrates, as described above, might be associated with the flexible conformation of the substituent, thereby resulting in steric repulsion with the incoming nucleophile. If this were the case, we envisaged that the reaction of a conformationally constrained cyclic compound might be more efficient. Under the standard conditions, the reaction of six-membered *exo*-methylene compound **7**[15] was carried out by using **6d** as a Michael donor. At room temperature, the starting material was completely consumed after 24 h, but the addition product **8d** was isolated in only 48% yield with 47% *ee* (Table 3, entry 1). The observation that compound **7** was prone to undergo polymerization during storage suggested that it is more reactive than the acyclic substrates, thus accounting for the lower chemical yield and enantioselectivity observed in entry 1. Better results were obtained when the concentration and temperature were decreased. But the reaction did not proceed at −40°C. The best results were obtained at −20°C, and the desired product **8d** was obtained in 77% yield with 98% *ee* (entry 4). Under the same reaction conditions, anisidine also reacted to afford the product **8a** without difficulty (entry 5). These results suggest that an s-*cis* conformer of acyclic substrates may be preferentially involved in the C–N bond-forming event. Unfortunately, however, we could not apply this reaction to the corresponding five-membered ring compound, as it was extremely unstable.

Table 3. Reactions of cyclic substrate **7**.



7 **6** (1.5 equiv) **8**

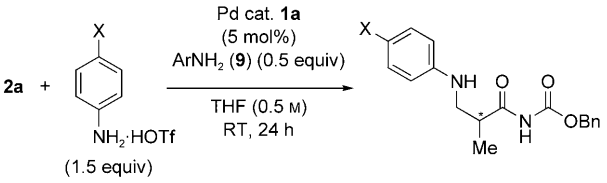
Entry	Salt	Product	T	t [h]	Yield [%]	*ee* [%]
1[a]	**6d**	**8d**	RT	24	48	47
2	**6d**	**8d**	0°C	24	67	91
3	**6d**	**8d**	−20°C	24	63	98
4	**6d**	**8d**	−20°C	48	77	98
5	**6a**	**8a**	−20°C	48	73	94

[a] 0.5 M.

Modification of the Reaction Conditions

As mentioned above, our reaction was not applicable to electron-deficient amines (Table 2, entry 7). Our original conditions were optimized for electron-rich amines by keeping the concentration low to avoid occurrence of the uncatalyzed reaction. In contrast, such a racemic pathway seems negligible in the case of less nucleophilic amines. Therefore, we next examined the addition of free *p*-$CF_3C_6H_4NH_2$ (**9e**) as an additive with the expectation that the initial aza-Michael reaction would be accelerated. Gratifyingly, the chemical yield was improved to 55% as the amount of **9e** was increased to 0.5 equiv (entries 1 and 2). But further addition of **9e** was not effective: when 1 equiv of **9e** was employed, the chemical yield was decreased to only 20% (entry 3). Interestingly, the *ee* value was in the range of 96–97% in these reactions. These results suggest that a higher concentration of the parent amine is necessary in the case of less nucleophilic amines, but the ratio of the salt to the added amine influences the reaction rate. Thus, by keeping their ratio the same as in entry 2, twice the amount of the reagents was used in entry 4. As a result, the chemical yield was improved, and the desired product **3ae** was obtained in 76% yield with 95% *ee*. When the concentration of the reaction mixture was increased to 1 M, comparable results were also obtained under the same conditions as shown in entry 3 (entry 5).

Additionally, we tested reactions with other less nucleophilic aromatic amines. As shown in Scheme 3, *para*-bromo- and *para*-iodoanilines were subjected to the modified reaction conditions. After 24 h, the desired products **3af** and **3ag** were produced in a highly enantioselective manner (96% *ee* in both cases). It is noteworthy that no detectable side reactions of the bromo and iodo groups with palladium were observed. Since bromo and iodo groups are useful functional handles for transition-metal-catalyzed cross-coupling reactions, the availability of these compounds should enhance the synthetic utility of this reaction. However, the sterically hindered *ortho*-bromoaniline failed to react efficiently (<10% after 24 hours).



Scheme 3. Reactions with halogen-substituted aromatic amines under the modified reaction conditions.

Mechanistic Studies

In our initial working hypothesis (Scheme 2), we speculated that the acid–base reaction of the Brønsted basic palladium–μ-hydroxo complex **1** and the amine salt **6** would give a monomeric Lewis acidic palladium complex **4**. To confirm this idea, we monitored the reaction by means of ^{1}H NMR spectroscopy and ESI-MS. In the ^{1}H NMR spectroscopic ex-

periments, we used 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl (Tol-binap) as a chiral ligand of the catalyst because it has characteristic methyl groups that are convenient for monitoring structural change of the complex. A selected region of the ^{1}H NMR spectrum of **1b** is shown in Figure 1 (top). Two methyl groups of **1b** were observed in this range. When this solution was treated with anisidine salt **6a** (Pd/

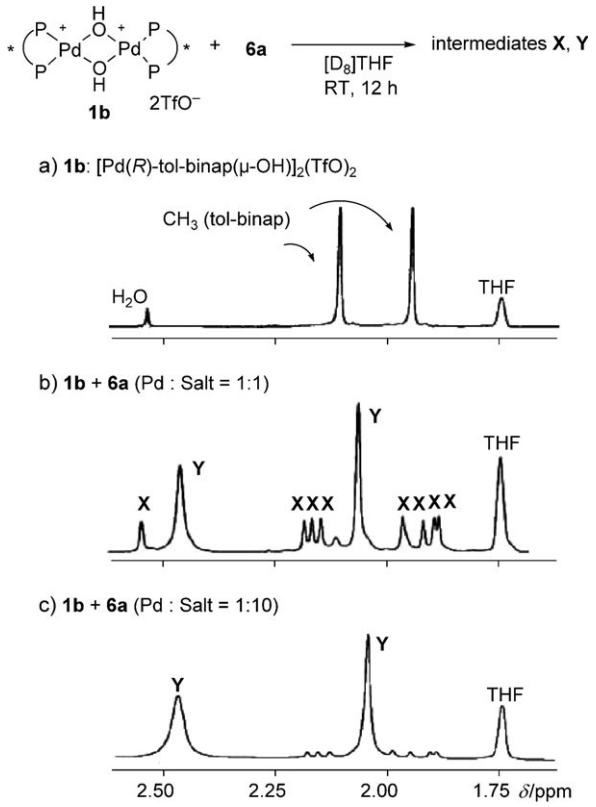


Figure 1. Selected region of the ^{1}H NMR spectrum of the reaction mixture of the Pd complex **1b** and salt **6a**.

6a = 1:1), a new complex **X** with one set of eight peaks (δ = 1.85, 1.87, 1.90, 1.94, 2.12, 2.15, 2.16, 2.53 ppm) appeared (middle). This was accompanied with the formation of another new complex **Y** with one set of two peaks (δ = 2.01, 2.48 ppm). When an excess amount of the salt **6a** was added to this solution (Pd/**6a** = 1:10), the complex **Y** became predominant, and the complex **X** almost disappeared (bottom).

To obtain further information on the nature of the complexes **X** and **Y**, ESI-MS measurements were carried out (Figure 2). From solution A (Figure 2, top left), a signal characteristic of a molecule containing two palladium atoms with six isotopes was observed, the molecular weight of which corresponded to a monocation of **1b** (**10**). A similar isotope distribution pattern was also observed in solution B (Figure 2, top right), and this signal corresponded to a monocation of a dimeric palladium–μ-hydroxo μ-amido

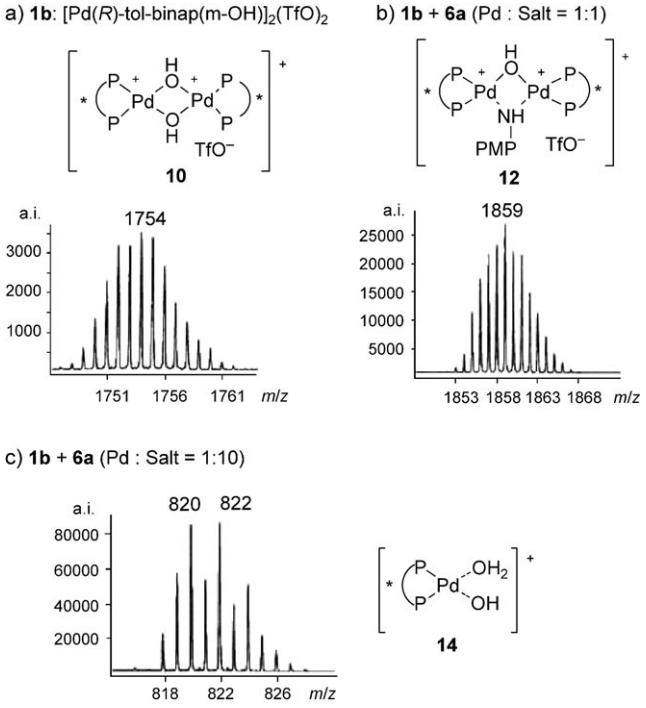


Figure 2. Observed ESI-MS spectra of Pd complexes. a.i. = arbitrary intensity.

complex **11** (**12**). As this complex is not C_2-symmetric, it is possible that the eight methyl groups of the tolyl groups are magnetically different. Therefore, it is likely that complex **X** is the palladium–μ-hydroxo μ-amido complex **11**.[16] Solution B also showed a signal with a different distribution pattern. Its molecular weight corresponded to a monocation of the palladium–diaqua complex **13** (**4**: **L** = H_2O) (**14**), thereby indicating that complex **Y** is a monomeric cationic palladium complex like **4**, although its neutral ligands are not identified. When an excess amount of the salt was added (solution C, bottom), monomeric **14** was mainly observed, whereas dimeric **11** became a minor peak.

Even though the dimeric palladium–μ-hydroxo μ-amido complex **11** is a minor species under the present catalytic reaction conditions, there is still a possibility that the palladium–amide complex acts as the actual nucleophile. To examine this scenario, the following experiment was carried out (Scheme 4). Treatment of the palladium complex **1b** with 1 equiv of anisidine (Pd/amine = 1:1) in [D_8]THF led to clean formation of the dimeric complex **11**. This result is consistent with findings from another laboratory.[16] Probably because the pH of the solution was not exactly the same and because the reaction did not go to completion, the ^{1}H NMR spectrum was slightly different from that of solution B (**1b**+**6a** (1:1)), but an identical isotopic distribution pattern was observed in ESI-MS measurements, which clearly indicated that the same dimeric palladium–μ-amido complex **12** was formed in each solution. 1 equiv of **2a** was added at room temperature to this mixture, but no formation of the product was observed. Although we cannot rule

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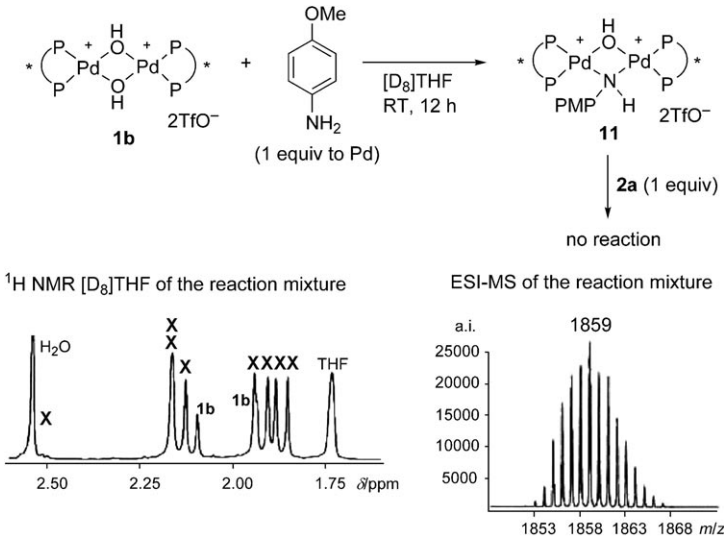


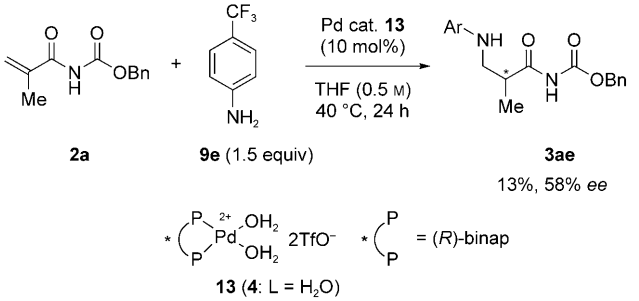
Scheme 4. Control experiment using the Pd–μ-hydroxo μ-amido complex **11**.

out other possibilities completely, it is most likely that the palladium–amide complex is not involved in the present reaction, and that the monomeric palladium complex acts as the active catalyst.

Consideration of the Mechanism

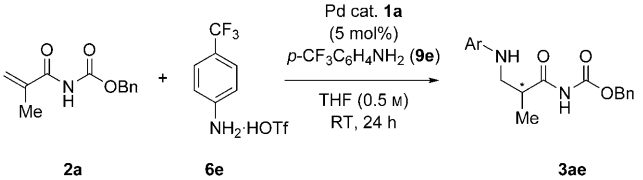
As discussed above, our reaction requires an appropriate free amine/salt ratio, depending on the nature of the amine nucleophile. In the case of anisidine, a low concentration of free anisidine is necessary to achieve high enantioselectivity. In contrast, less nucleophilic amines require a much higher concentration of the parent amine to promote the reaction. Nevertheless, too much free amine has a negative effect, perhaps due to deactivation of the catalyst through the formation of unreactive complexes, such as **11** and **15**–**17** (Scheme 6). Actually, we observed the formation of such complexes by means of ^{1}H NMR spectroscopic and ESI-MS measurements of mixtures of the palladium–diaqua complex **4** (**L** = H_2O) and amines. Hii et al. also reported stepwise formation of palladium–monoamine and palladium–diamine complexes upon mixing the palladium–aqua complex and aniline, as confirmed by ESI-MS and UV/Vis spectrometry.[14a] In addition, deprotonation of the imide proton of the substrate is likely to occur as a result of double activation of the Lewis acidic palladium complex and the free amine, so that the catalyst would be deactivated.[17] We considered the idea that these complexes were responsible for the decrease in the catalyst turnover observed in entry 3 of Table 4. This idea was supported by the results illustrated in Scheme 5. Without the amine salt, the reaction was slow even in the presence of the palladium–diaqua complex **13a** (10 mol% Pd), and the product **3ae** was formed in only 13% yield with 58% *ee*, which strongly indicates the importance of the coexisting amine salt.

To achieve high reaction efficiency, a precise balance between the salt (proton source) and the amine is important, and the optimum amine/salt ratio varies depending on the nature of the amine. It is considered that the salt plays an important role in maintaining the active catalyst. To summarize, a plausible catalytic cycle for the amine/salt combined system is outlined in Scheme 6. In accord with our initial hypothesis, the active catalyst is generated from the reaction of **1a** and the excess amount of salt. When the reaction requires additional free amine, the catalyst would be intercepted by the additional amine to form **11**, **15**, and **16**. Also, the substrate that coordinates to the palladium complex could be deprotonated to give the inactive imide complex **17**. But the salt may allow for the regeneration of the active catalyst by means of proton-exchange reactions. Even though the product potentially coordinates to the palladium complex, the proton exchange from the salt may facilitate dissociation of the product as the ammonium salt. As a result, the desired catalytic cycle operates smoothly.



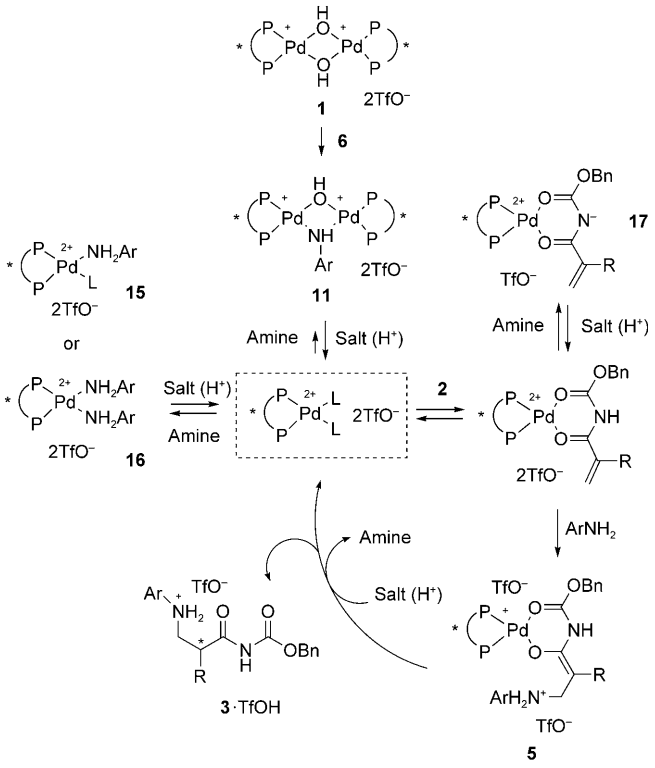
Scheme 5. Reaction with **13a** catalyzed by Pd–aqua complex without the amine salt.

Table 4. Modification of the reaction conditions in the reaction of **2a** with less reactive aromatic amines.



Entry	Salt [equiv]	Amine [equiv]	Yield [%]	*ee* [%]
1	1.5	0.25	35	97
2	1.5	0.5	55	96
3	1.5	1.0	20	97
4	3.0	1.0	76	95
5[a]	1.5	0.5	64	94

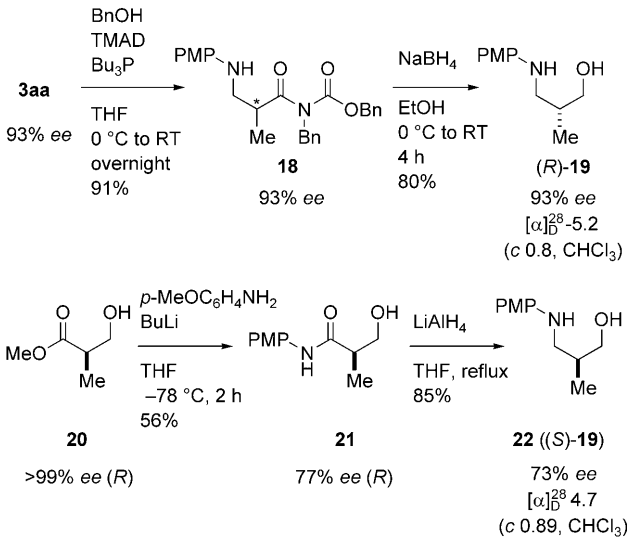
[a] 1 M.



Scheme 6. Plausible catalytic cycle.

Absolute Stereochemistry

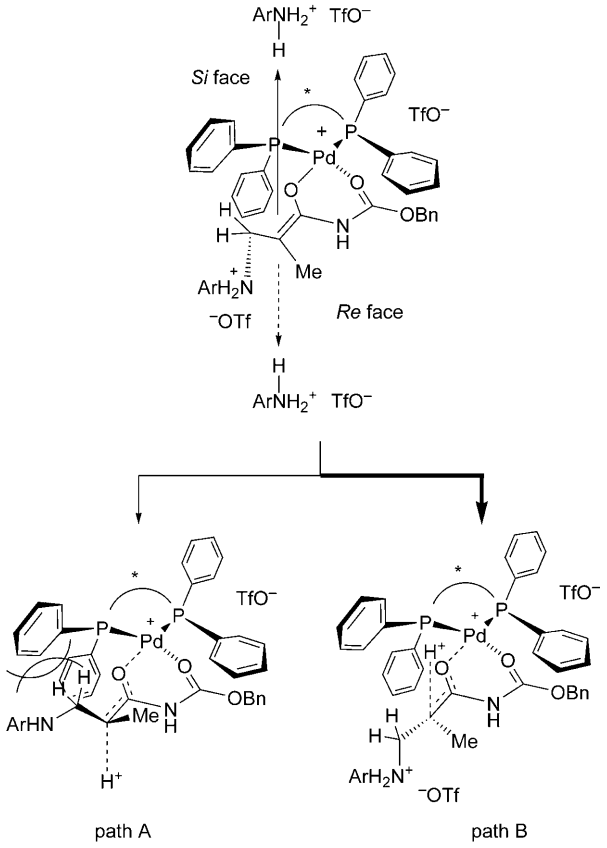
To determine the absolute stereochemistry of **3aa**, the following conversion into 1,3-amino alcohol **19** was carried out (Scheme 7). Thus, benzylation of the nitrogen atom of **3aa** was conducted by using a modified Mitsunobu reaction[18] to afford the corresponding product **18** in 91% yield. Reduction of **18** with $NaBH_4$ proceeded without racemization to give the 1,3-amino alcohol **19**, for which the sign of the optical rotation was negative. An authentic sample was prepared



Scheme 7. Comparison of optical rotation after the conversion.

from commercially available methyl (*R*)-3-hydroxy-2-methylpropanoate (**20**). It was converted into amide **21** under basic conditions, in which partial racemization occurred. The obtained amide was reacted with $LiAlH_4$, and the corresponding amino alcohol **22** ((*S*)-**19**) was obtained in good yield. The absolute configuration of **19** was determined to be *R* by comparison of optical rotation with that of **22**. This result clearly indicates that the product obtained by our method has *R* configuration. Similar conversion and HPLC analyses also showed that the absolute configuration of **3ad** and **3ae** is *R*.

The sense of enantioselection can be explained as depicted in Scheme 8. Based on our previous work,[4a] it is likely that the nucleophile approaches to the alkene from the open space opposite the phenyl group of the ligand.[19] On



Scheme 8. Proposed transition-state model.

the assumption that the putative palladium enolate intermediate is bidentate and that rotation of the σ bond between the α-carbon and β-carbon atoms is restricted, protonation should occur at the *Si* face of the enolate.[20] Even though proton transfer possibly occurs intramolecularly from the neighboring N–H group, the intermolecular protonation may be favored in the presence of a large excess amount of the salt. If protonation occurs at the *Re* face of the enolate (path A), the aminomethyl group at the developing sp^3-carbon center (α position) would be exposed to

the equatorial phenyl group. Such a negative interaction may disfavor the protonation step. In contrast, protonation from the *Si* face would minimize such steric interaction.

Additionally, it appears that sufficient open space is available for a proton source to access the α position, as judged from the X-ray structure of the complex of [Pd{(*R*)-binap}(*N*-benzoyl methacrylamide)](TfO)$_2$ (Figure 4 in Ref. [14a]). Furthermore, in path B, the aminomethyl group located at the *Re* face could be a good shielding group as well. Although other mechanisms, including O-protonation, cannot be ruled out at present, we believe that the palladium enolate is protonated from the *Si* face in a highly enantioselective manner.

Conclusion

In summary, we have succeeded in developing a tandem aza-Michael reaction/enantioselective protonation reaction. Our novel strategy using the palladium–μ-hydroxo complex and amine salts was the key to success. The obtained chiral β-amino acid derivatives with a chiral center at the α position are expected to be useful in the field of medicinal chemistry. Because catalytic enantioselective aminomethylation—namely, classical Mannich reaction—is still difficult to achieve,[21,22] the present work provides an important alternative method. Further studies to improve the catalytic activity and to establish the scope of the reaction are under way.

Experimental Section

General

NMR spectra were recorded with a JEOL JNM-LA 300 or 400 spectrometer operating at 300 or 400 MHz for ^{1}H NMR spectroscopy and 75 or 100.4 MHz for ^{13}C NMR spectroscopy. Chemical shifts were reported downfield from TMS ($\delta=0$ ppm) for ^{1}H NMR spectroscopy. For ^{13}C NMR spectroscopy, chemical shifts were reported in the scale relative to $CDCl_3$ as an internal reference. ^{19}F NMR spectra were measured at 376 MHz, and CF_3COOH (TFA) was used as an external standard. Fast atom bombardment (FAB) low-resolution mass spectrometry (LRMS) was taken with a JEOL JMS GCmate II by using *meta*-nitrobenzyl alcohol (*m*-NBA) as the matrix. FAB high-resolution (HR) MS was also taken with a JEOL JMS GCmate II using *m*-NBA as the matrix and with PEG 400 as an internal standard. ESI-MS experiments were carried out with a Bruker Bio-TOF II. Optical rotations were measured with a JASCO DIP-370 polarimeter. IR was measured with a Thermo Nicolet AVATAR 370 FTIR equipped with a DuraScope accessory. Melting points were measured with a Yanaco MP-J3. Short column chromatography was performed using silica gel 60 (40–100 μm) purchased from Kanto Chemical Co. Purification was carried out by using medium-pressure liquid chromatography (MPLC). The enantiomeric excesses (*ee* values) were determined by chiral HPLC. HPLC analysis was performed with a Shimadzu HPLC system with the following equipment: pump, LC-10AD; detector, SPD-10A set at 220 or 254 nm. A JASCO HPLC system was also used: pump, PU-2080 Plus; detector, CD-2095 Plus set at 220 or 254 nm; column, DAICEL CHIRALPAK AD-H, AS-H, or DAICEL CHIRALCEL OD-H, OJ-H, OF; mobile phase, hexane/2-propanol. Dehydrated stabilizer-free tetrahydrofuran (THF) was purchased from Kanto Chemical Co. and was used directly. Other reagents were purified according to usual methods.

General Procedure for Catalytic Tandem Aza-Michael Reaction/Enantioselective Protonation

The starting material **2** (0.1 mmol), amine salts **6** (0.15 mmol), and the Pd complex **1a** (5 mol%) were dissolved in THF (0.2 mL). In the case of less nucleophilic amines, the parent amine **9** (0.05 mmol) was included as an additive. The resulting solution was stirred at ambient temperature for the time given in the tables. For quenching, cold saturated aqueous $NaHCO_3$ (2 mL) was added under ice-bath cooling. The usual workup followed by flash column chromatography (silica gel, hexane/ethyl acetate system) gave the pure products.

Benzyl (R)-3-(4-methoxyphenylamino)-2-methylpropionylcarbamate (**3aa**)

Pale yellow oil; $[\alpha]_D^{25}=-26.0$ ($c=1.4$, $CHCl_3$) (94% *ee*); HPLC (Chiralpak AD-H, hexane/2-propanol = 1:1, 1.0 mL min^{-1}, 254 nm): t_r (minor) = 6.1 min, t_r (major) = 7.1 min; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.23$ (d, $J=6.8$ Hz, 3H), 3.18 (dd, $J=4.4$, 12.5 Hz, 1H), 3.22–3.42 (m, 2H), 3.74 (s, 3H), 5.16 (s, 2H), 6.70 (dt, $J=3.4$, 9.0 Hz, 2H), 6.77 (dt, $J=3.4$, 9.0 Hz, 2H), 7.23–7.41 (m, 5H), 8.06 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]acetone): $\delta=15.5$, 40.8, 48.6, 55.8, 67.4, 115.1, 115.4, 128.9, 129.0, 129.3, 137.0, 143.0, 152.1, 153.1, 175.7 ppm; IR (neat): $\tilde{\nu}=3275$, 2936, 1761, 1702, 1509, 1377, 1232, 1177, 1016 cm^{-1}; FAB-LRMS (*m*-NBA): *m*/*z*: 342 $[M]^+$; FAB-HRMS (PEG 400/*m*-NBA): *m*/*z*: calcd for $C_{19}H_{22}N_2O_4$: 342.1580 $[M]^+$, 343.1658 $[M+1]^+$; found: 342.1588 $[M^+]$, 343.1659 $[M+1]^+$.

Benzyl (R)-3-(benzo[*d*][1,3]dioxol-5-ylamino)-2-methylpropionylcarbamate (**3ab**)

Orange solid; m.p. 106.0–107.0 °C; $[\alpha]_D^{26}=-42.5$ ($c=0.89$, $CHCl_3$) (96% *ee*); HPLC (Chiralcel OD-H, hexane/2-propanol = 4:1, 1.0 mL min^{-1}, 280 nm): t_r (major) = 27.6 min, t_r (minor) = 40.4 min; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=1.23$ (d, $J=6.6$ Hz, 3H), 3.14–3.18 (m, 1H), 3.34–3.39 (m, 2H), 5.16 (s, 2H), 5.85 (s, 2H), 6.04 (dd, $J=2.2$, 8.3 Hz, 1H), 6.24 (d, $J=2.2$ Hz, 1H), 6.63 (d, $J=8.3$ Hz, 1H), 7.32–7.40 (m, 5H), 7.82 ppm (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=15.1$, 39.6, 48.1, 67.8, 96.4, 100.5, 104.9, 108.5, 128.2, 128.5, 134.7, 139.8, 143,0, 148.1, 150.9, 175.6 ppm; IR (solid): $\tilde{\nu}=3279$, 2974, 2879, 1759, 1700, 1635, 1502, 1489, 1380, 1290, 1196, 1038, 1014, 928, 812, 751, 698 cm^{-1}; FAB-LRMS (*m*-NBA): *m*/*z*: 356 $[M]^+$; FAB-HRMS (*m*-NBA): *m*/*z*: calcd for $C_{19}H_{21}O_5N_2$: 357.1450 $[M+H]^+$; found 457.1448.

Benzyl (R)-3-[4-(methythio)phenylamino]-2-methylpropionylcarbamate (**3ac**)

Pale yellow solid; m.p. 96.0–97.2 °C; $[\alpha]_D^{26}=-61.1$ ($c=0.87$, $CHCl_3$) (97% *ee*); HPLC (Chiralcel OD-H, hexane/2-propanol = 4:1, 1.0 mL min^{-1}, 280 nm): t_r (major) = 18.1 min, t_r (minor) = 21.4 min; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=1.24$ (d, $J=6.6$ Hz, 3H), 2.40 (s, 3H), 3.19–3.23 (m, 1H), 3.42–3.47 (m, 2H), 4.12 (br s, 1H), 5.15 (s, 2H), 6.54 (d, $J=8.5$ Hz, 2H), 7.19 (d, $J=8.5$ Hz, 2H), 7.32–7.39 (m, 5H), 7.67 ppm (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=15.2$, 19.1, 39.5, 46.8, 67.9, 113.5, 124.6, 128.3, 128.5, 128.6, 131.2, 134,6, 146.2, 150.9, 175.7 ppm; IR (solid): $\tilde{\nu}=3380$, 3276, 3292, 3062, 3030, 2975, 2918, 2877, 1759, 1701, 1598, 1499, 1455, 1377, 1313, 1289, 1219, 1175, 1063, 1013, 816, 752, 697 cm^{-1}; FAB-LRMS (*m*-NBA): *m*/*z*: 358 $[M]^+$; FAB-HRMS (*m*-NBA): *m*/*z*: calcd for $C_{19}H_{22}O_3N_2S$: 358.1351 $[M]^+$; found: 358.135.

Benzyl (R)-3-(phenylamino)-2-methylpropionylcarbamate (**3ad**)

Pale yellow oil; $[\alpha]_D^{25}=-43.9$ ($c=1.1$, $CHCl_3$) (97% *ee*); HPLC (Chiralpak AD-H, hexane/2-propanol = 1:1, 0.5 mL min^{-1}, 254 nm): t_r (major) = 12.2 min, t_r (minor) = 14.2 min; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.23$ (d, $J=6.6$ Hz, 3H), 3.21–3.24 (m, 1H), 3.43–3.48 (m, 2H), 4.01 (s, 1H), 5.15 (s, 2H), 6.58–6.60 (m, 2H), 6.69–6.73 (m, 1H), 7.14–7.19 (m, 2H), 7.32–7.41 (m, 5H), 7.82 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=15.2$, 39.7, 46.9, 67.9, 112.9, 117.7, 128.3, 128.5, 128.6, 129.2, 134.7, 147.4, 150.8, 175.6 ppm; IR (neat): $\tilde{\nu}=3272$, 2971, 1762, 1704, 1603, 1506, 1377, 1223, 1178, 1014 cm^{-1}; FAB-LRMS (*m*-NBA): *m*/*z*: 313 $[M+H]^+$; FAB-HRMS (*m*-NBA): *m*/*z*: calcd for $C_{18}H_{20}O_3N_2$: 312.1474 $[M]^+$; found: 312.1477.

Benzyl (R)-3-(4-trifluoromethylphenylamino)-2-methylpropionylcarbamate (**3ae**)

White solid; m.p. 82.2–83.2 °C; $[\alpha]_D^{24} = -41.5$ ($c = 0.95$, $CHCl_3$) (97 % *ee*); HPLC (Chiralpak AS-H, hexane/EtOH = 95:5, 1.0 mL min^{-1}, 280 nm): t_r (major) = 20.7 min, t_r (minor) = 26.0 min; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.25$ (d, $J = 6.8$ Hz, 3H), 3.26 (dd, $J = 4.4$, 12.9 Hz, 1H), 3.52 (dd, $J = 8.5$, 12.9 Hz, 1H), 3.60 (brs, 1H), 4.40 (brs, 1H), 5.16 (s, 2H), 6.57 (d, $J = 8.5$ Hz, 2H), 7.32–7.39 (m, 7H), 7.59 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 15.3$, 39.3, 46.1, 68.1, 111.8, 118.8 (q, $J_{C,F} = 32.5$ Hz), 124.8 (q, $J_{C,F} = 269.4$ Hz), 126.5 (q, $J_{C,F} = 3.3$ Hz), 128.3, 128.6, 128.6, 134.5, 150.0, 151.0, 176.0 ppm; ^{19}F NMR ($CDCl_3$, 372.4 MHz, std: TFA): $\delta = 14.9$ ppm; IR (solid): $\tilde{\nu} = 3380$, 3275, 3185, 3036, 2977, 2933, 2875, 2846, 1760, 1700, 1616, 1498, 1456, 1418, 1377, 1324, 1263, 1224, 1186, 1104, 1064, 1013, 940, 825, 779 cm^{-1}; FAB-LRMS (*m*-NBA): *m/z*: 403 $[M+Na]^+$; FAB-HRMS (*m*-NBA): *m/z*: calcd for $C_{18}H_{19}O_3N_2F_3Na$: 403.1245 $[M+Na]^+$; found: 403.1241.

Benzyl (R)-3-(4-bromophenylamino)-2-methylpropionylcarbamate (**3af**)

White solid; m.p. 110.0–111.0 °C; $[\alpha]_D^{26} = -45.0$ ($c = 1.03$, $CHCl_3$) (96 % *ee*); HPLC (Chiralpak AS-H, hexane/EtOH = 4:1, 1.0 mL min^{-1}, 280 nm): t_r (major) = 7.9 min, t_r (minor) = 17.0 min; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.23$ (d, $J = 6.8$ Hz, 3H), 3.18 (dd, $J = 4.4$, 12.9 Hz, 1H), 3.43 (dd, $J = 8.8$, 12.9 Hz, 1H), 3.51 (brs, 1H), 4.07 (brs, 1H), 5.15 (s, 2H), 6.43–6.45 (m, 2H), 7.20–7.23 (m, 2H), 7.32–7.40 (m, 5H), 7.70 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 15.2$, 39.4, 46.7, 68.0, 109.1, 114.4, 128.3, 128.5, 128.6, 131.8, 134,6, 146.4, 150.9, 175.9 ppm; IR (solid): $\tilde{\nu} = 3397$, 3265, 3177, 3089, 3063, 3030, 2877, 2935, 2879, 2848, 1757, 1700, 1595, 1496, 1455, 1396, 1376, 1324, 1226, 1177, 1071, 1036, 1014, 811, 776, 739, 695 cm^{-1}; FAB-LRMS (*m*-NBA): *m/z*: 393 $[C_{18}H_{19}O_3N_2{}^{81}Br+H]^+$, 392 $[C_{18}H_{19}O_3N_2{}^{81}Br]^+$, 391 $[C_{18}H_{19}O_3N_2{}^{79}Br+H]^+$, 390 $[C_{18}H_{19}O_3N_2{}^{79}Br]^+$; FAB-HRMS (*m*-NBA): *m/z*: calcd for $C_{18}H_{19}O_3N_2Br$: 390.0579 $[M]^+$; found: 390.0583.

Benzyl (R)-3-(4-iodophenylamino)-2-methylpropionylcarbamate (**3ag**)

White solid; m.p. 99.0–100.0 °C; $[\alpha]_D^{27} = -50.6$ ($c = 0.72$, $CHCl_3$) (96 % *ee*); HPLC (Chiralpak AS-H, hexane/EtOH = 4:1, 1.0 mL min^{-1}, 280 nm): t_r (major) = 8.0 min, t_r (minor) = 15.4 min; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.22$ (d, $J = 6.8$ Hz, 3H), 3.18 (dd, $J = 13.2$, 4.6 Hz, 1H), 3.43 (dd, $J = 13.2$, 8.5 Hz, 1H), 3.51 (brs, 1H), 4.09 (brs, 1H), 5.15 (s, 2H), 6.36 (d, $J = 8.1$ Hz, 2H), 7.33–7.40 (m, 7H), 7.64 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 15.2$, 39.4, 46.5, 68.0, 78.1, 115.0, 128.3, 128.5, 128.6, 134.6, 137.6, 147.0, 150.9, 175.9 ppm; IR (solid): $\tilde{\nu} = 3379$, 3269, 3189, 3059, 3030, 2970, 2931, 2874, 1757, 1699, 1590, 1494, 1455, 1376, 1318, 1293, 1249, 1220, 1174, 1080, 1059, 1012, 992, 917, 810, 750, 695 cm^{-1}; FAB-LRMS (*m*-NBA): *m/z*: 461 $[M+Na]^+$; FAB-HRMS (*m*-NBA): *m/z*: calcd for $C_{18}H_{19}O_3N_2NaI$: 461.0338 $[M+Na]^+$; found: 461.0325.

Benzyl (R)-2-[(4-methoxyphenylamino)methyl]butanoylcarbamate (**3ba**)

Yellow oil; $[\alpha]_D^{27} = -35.5$ ($c = 0.6$, $CHCl_3$) (84 % *ee*); HPLC (Chiralpak AD-H, hexane/2-propanol = 3:1, 1.0 mL min^{-1}, 254 nm): t_r (minor) = 11.0 min, t_r (major) = 14.2 min; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.98$ (t, $J = 7.6$ Hz, 3H), 1.56–1.66 (m, 1H), 1.74–1.84 (m, 1H), 3.23–3.27 (m, 2H), 3.40 (dd, $J = 9.3$, 13.0 Hz 1H), 3.74 (s, 3H), 5.16 (s, 2H), 6.58 (d, $J = 8.8$ Hz, 2H), 6.74–6.76 (d, $J = 8.8$ Hz, 2H), 7.32–7.40 (m, 5H), 7.92 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 11.7$, 23.2, 46.5, 46.9, 55.8, 67.8, 114.6, 114.8, 128.2, 128.4, 128.5, 134.7, 141.6, 150.9, 152.6, 175.2 ppm; IR (neat): $\tilde{\nu} = 3266$, 2962, 1759, 1695, 1508, 1459, 1382, 1232, 1173, 1027, 914 cm^{-1}; FAB-LRMS (*m*-NBA): *m/z*: 356 $[M]^+$; FAB-HRMS (PEG-400/*m*-NBA): *m/z*: calcd for $C_{20}H_{24}O_4N_2$: 356.1736 $[M]^+$; found: 356.1738.

Benzyl (R)-3-(4-methoxyphenylamino)-2-phenylpropionylcarbamate (**3ca**)

Pale yellow oil; $[\alpha]_D^{25} = +64.6$ ($c = 0.82$, $CHCl_3$) (93 % *ee*); HPLC (Chiralpak AD-H, hexane/2-propanol = 3:1, 1.0 mL min^{-1}, 254 nm): t_r (minor) = 17.2 min, t_r (major) = 20.9 min; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.38$ (dd, $J = 5.5$, 13.0 Hz, 1H), 3.74 (s, 3H), 3.84 (dd, $J = 8.7$, 13.0 Hz, 1H), 4.48 (brs, 1H), 5.08 (s, 2H), 6.58 (d, $J = 8.8$ Hz, 2H), 6.78 (d, $J = 8.8$ Hz, 2H), 7.26–7.39 (m, 10H), 7.55 ppm (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 48.0$, 51.2, 55.7, 67.9, 114.7, 115.0, 128.0, 128.4, 128.5, 128.6, 128.7, 129.1, 134.7, 136.0, 141.2, 150.6, 152.5, 172.4 ppm; IR (neat): $\tilde{\nu} = 3268$, 3030, 2950, 2932, 2831, 1760, 1699, 1510, 1454, 1375, 1291, 1233, 1191, 1177, 1035, 912, 820, 751, 698 cm^{-1}; FAB-LRMS (*m*-NBA): *m/z*: 404 $[M^+]$, 405 $[M+H]^+$; FAB-HRMS (PEG 400/*m*-NBA): *m/z*: calcd for $C_{24}H_{24}N_2O_4$: 404.1736 $[M]^+$; found: 404.1739.

Benzyl (R)-2-oxo-3-[(4-methoxyphenylamino)methyl]piperidine-1-carboxylate (**8a**)

Pale yellow oil; $[\alpha]_D^{26} = -29.0$ ($c = 0.61$, $CHCl_3$) (93 % *ee*); HPLC (Chiralpak AD-H, hexane/2-propanol = 1:1, 1.0 mL min^{-1}, 254 nm): t_r (minor) = 10.1 min, t_r (major) = 12.4 min; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.58$–1.68 (m, 1H), 1.81–1.94 (m, 2H), 2.00–2.07 (m, 1H), 2.68–2.80 (m, 1H), 3.29 (dd, $J = 4.6$, 13.4 Hz, 1H), 3.45 (dd, $J = 7.1$, 13.4 Hz, 1H), 3.63–3.69 (m, 1H), 3.74 (s, 3H), 3.81–3.92 (m, 1H), 5.28 (s, 2H), 6.65 (d, $J = 8.8$ Hz, 2H), 6.78 (d, $J = 8.8$ Hz, 2H), 7.29–7.44 ppm (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 21.6$, 24.5, 43.1, 45.7, 46.3, 55.8, 68.6, 114.7, 114.9, 128.2, 128.4, 128.6, 135.3, 141.9, 152.3, 153.7, 173.7 ppm; IR (neat): $\tilde{\nu} = 3272$, 2936, 2826, 1776, 1764, 1708, 1692, 1558, 1540, 1512, 1502, 1231, 1173, 1011, 819, 735, 696 cm^{-1}; FAB-LRMS (*m*-NBA): *m/z*: 368 $[M^+]$; FAB-HRMS (PEG 400/*m*-NBA): *m/z*: calcd for $C_{21}H_{24}O_4N_2$: 368.1736 $[M]^+$; found: 368.1741.

Benzyl (R)-2-oxo-3-[(phenylamino)methyl]piperidine-1-carboxylate (**8d**)

Pale yellow oil; $[\alpha]_D^{26} = -29.4$ ($c = 0.65$, $CHCl_3$) (98 % *ee*); HPLC (Chiralpak AD-H, hexane/2-propanol = 4:1, 1.0 mL min^{-1}, 254 nm): t_r (minor) = 12.4 min, t_r (major) = 14.1 min; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.59$–1.68 (m, 1H), 1.80–1.96 (m, 2H), 2.02–2.10 (m, 1H), 2.70–2.78 (m, 1H), 3.34 (dd, $J = 4.6$, 13.7 Hz, 1H), 3.51 (dd, $J = 7.1$, 13.7 Hz, 1H), 3.62–3.68 (m, 1H), 3.85–3.91 (m, 1H), 4.44 (brs, 1H), 5.28 (s, 2H), 6.62 (d, $J = 8.6$ Hz, 2H), 6.70 (dt, $J = 0.76$, 7.3 Hz, 1H), 7.16 (t, $J = 7.3$ Hz, 2H), 7.31–7.44 ppm (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 21.6$, 24.4, 43.2, 45.0, 45.7, 68.6, 113.1, 117.6, 128.2, 128.4, 128.6, 129.3, 135.3, 147.7, 153.7, 173.6 ppm; IR (neat): $\tilde{\nu} = 3385$, 2950, 1767, 1707, 1601, 1502, 1454, 1376, 1248, 1164, 1087, 985, 748, 692 cm^{-1}; FAB-LRMS (*m*-NBA): *m/z*: 338 $[M^+]$; FAB-HRMS (PEG 400/*m*-NBA): *m/z*: calcd for $C_{20}H_{22}O_3N_2$: 338.1631 $[M]^+$; found: 338.1632.

*Compound **18** (N*-Benzylated **3aa**)

A solution of 1,1′-azobis-*N*,*N*′-dimethylformamide (40 mg, 0.22 mmol) in THF (1 mL) was slowly added to a solution of **3aa** (50 mg, 0.146 mmol, 93 % *ee*), benzyl alcohol (23 μL, 0.22 mmol), and tributylphosphine (54 μL, 0.22 mmol) in THF (0.5 mL) at 0 °C. The resulting mixture was stirred for 30 min at the same temperature and then overnight at room temperature. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (hexane/ethyl acetate 20:1) to give the benzylated product **18** in 91 % yield (57.2 mg, 0.13 mmol, 93 % *ee*) as a colorless oil. HPLC (Chiralpak AS-H, hexane/2-propanol = 7:1, 0.5 mL min^{-1}, 254 nm): t_r (major) = 24.0 min, t_r (minor) = 27.8 min; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.23$ (d, $J = 6.6$ Hz, 3H), 3.18 (dd, $J = 5.0$, 12.5 Hz, 1H), 3.46 (dd, $J = 8.4$, 12.5 Hz, 1H), 3.74 (s, 3H), 3.98–4.12 (m, 1H), 4.92 (d, $J = 15.0$ Hz, 2H), 5.14 (s, 2H), 6.51 (d, $J = 8.8$ Hz, 2H), 6.77 (d, $J = 8.8$ Hz, 2H), 7.10–7.40 ppm (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 15.9$, 40.2, 47.5, 48.8, 55.8, 68.7, 114.2, 114.8, 127.2, 127.5, 128.3, 128.4, 128.56, 128.58, 134.7, 137.6, 142.1, 152.0, 154.3, 178.9 ppm; IR (neat): $\tilde{\nu} = 3387$, 2933, 1732, 1693, 1514, 1455, 1385, 1236, 1186, 999 cm^{-1}; FAB-LRMS (*m*-NBA): *m/z*: 432 $[M]^+$.

(R)-3-(4-Methoxyphenylamino)-2-methylpropan-1-ol (**(*R*)-19**)

$NaBH_4$ (45 mg, 10 equiv) was added in one portion to a solution of **18** (54 mg, 0.126 mmol, 93 % *ee*) in EtOH (2.0 mL) at 0 °C. The resulting mixture was stirred for 30 min at the same temperature and then for 4 h at room temperature. Saturated aqueous NH_4Cl was added for quenching and the mixture was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4.

After evaporation, the obtained residue was purified by flash column chromatography (hexane/acetone = 9:1) to give the desired amino alcohol in 80% yield (19.7 mg, 0.1 mmol, 93% *ee*) as a colorless oil. $[\alpha]_D^{28} = -5.2$ ($c = 0.80$, $CHCl_3$) (93% *ee*); HPLC (Chiralpak AS-H, hexane/2-propanol = 1:1, 0.5 mL min^{-1}, 254 nm): t_r (minor) = 16.6 min, t_r (major) = 26.6 min; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.96$ (d, $J = 6.9$ Hz, 3H), 1.95–2.10 (m, 1H), 2.69 (bs, 2H), 3.08–3.16 (m, 2H), 3.62 (dd, $J = 7.2$, 10.5 Hz, 1H), 3.68 (dd, $J = 4.8$, 10.5 Hz, 1H), 3.75 (s, 3H), 6.63 (d, $J = 8.8$ Hz, 2H), 6.79 ppm (d, $J = 8.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 15.5$, 35.4, 50.6, 55.8, 68.1, 114.8, 114.9, 142.3, 152.4 ppm; IR (neat): $\tilde{\nu} = 3367$, 2928, 1514, 1463, 1236, 1036, 821; FAB-LRMS (*m*-NBA): *m*/*z*: 195 $[M]^+$.

(R)-2-(Hydroxymethyl)-*N*-(4-methoxyphenyl)propanamide (**21**)

*n*BuLi (2.5 M solution in hexane, 450 μL) was added to a solution of *p*-anisidine (139 mg, 2.5 equiv) in THF (5.0 mL) at −78 °C. The resulting mixture was stirred for 1 h at the same temperature, and then methyl (*R*)-3-hydroxy-2-methylpropionate (50 μL, 0.45 mmol, 1 equiv) was slowly introduced at −78 °C. The mixture was stirred for an additional 2 h at the same temperature. After quenching with saturated aqueous NH_4Cl, the mixture was extracted with ethyl acetate (2 × 10 mL) and the combined organic phase was dried over Na_2SO_4. Further purification was carried out using flash column chromatography (hexane/acetone = 6:1) to give the desired amide **21** in 53% yield (53 mg, 0.25 mmol) as a white solid. The *ee* value of the product was determined to be 77% by chiral HPLC analysis. HPLC (Chiralpak AS-H, hexane/2-propanol = 7:1, 1.0 mL min^{-1}, 254 nm): t_r (minor) = 11.9 min, t_r (major) = 17.9 min; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.26$ (d, $J = 6.9$ Hz, 3H), 2.50–2.65 (m, 2H), 3.78–3.82 (m, 5H), 6.83 (d, $J = 8.8$ Hz, 2H), 7.41 (d, $J = 8.8$ Hz, 2H), 7.65 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 14.1$, 43.2, 55.5, 65.0, 114.1, 121.7, 130.7, 156.3, 173.4 ppm; IR (solid): $\tilde{\nu} = 3270$, 1648, 1534, 1512, 1242, 1018, 824 cm^{-1}; FAB-LRMS (*m*-NBA): *m*/*z*: 209 $[M]^+$, 210 $[M+1]^+$.

(S)-3-(4-Methoxyphenylamino)-2-methylpropan-1-ol (**22**)

A solution of **21** (50 mg, 0.238 mmol) in THF (2 mL) was slowly added under ice-bath cooling to a suspension of $LiAlH_4$ (40 mg, 5 equiv) in THF (2 mL). The resulting mixture was stirred for 30 min at room temperature and then heated to reflux for 2 h. After quenching with saturated aqueous NH_4Cl under ice-bath cooling, the precipitated white solid was filtered off. The obtained organic phase was concentrated under reduced pressure. Further purification was performed by flash column chromatography (hexane/acetone = 6:1), and colorless amino alcohol **22** was obtained in 85% yield (39 mg, 0.20 mmol). The *ee* value of the product was determined to be 73% by chiral HPLC analysis. Colorless oil; $[\alpha]_D^{26} = 4.7$ ($c = 0.89$, $CHCl_3$) (73% *ee*); HPLC (Chiralpak AS-H, hexane/2-propanol = 1:1, 0.5 mL min^{-1}, 254 nm): t_r (major) = 18.8 min, t_r (minor) = 31.4 min; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.96$ (d, $J = 6.9$ Hz, 3H), 1.95–2.10 (m, 1H), 2.69 (br s, 2H), 3.08–3.16 (m, 2H), 3.62 (dd, $J = 7.2$, 10.5 Hz, 1H), 3.68 (dd, $J = 4.8$, 10.5 Hz, 1H), 3.75 (s, 3H), 6.63 (d, $J = 8.8$ Hz, 2H), 6.79 ppm (d, $J = 8.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 15.5$, 35.4, 50.6, 55.8, 68.1, 114.8, 114.9, 142.3, 152.4 ppm; IR (neat): $\tilde{\nu} = 3367$, 2928, 1514, 1463, 1236, 1036, 821 cm^{-1}; FAB-LRMS (*m*-NBA): *m*/*z*: 195 $[M]^+$.

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[1] Reviews on the synthesis of β-amino acids: a) *Enantioselective Synthesis of β-Amino Acids* (Ed.: E. Juaristi), Wiley-VCH, New York, **1997**; b) M. Liu, M. P. Sibi, *Tetrahedron* **2002**, *58*, 7991; c) J.-A. Ma, *Angew. Chem.* **2003**, *115*, 4426; *Angew. Chem. Int. Ed.* **2003**, *42*, 4290.

[2] Reviews on catalytic asymmetric Mannich-type reactions: a) S. Kobayashi, M. Ueno in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Supplement 1, chapter 29.5, Springer, Berlin, **2004**; b) A. Córdova, *Acc. Chem. Res.* **2004**, *37*, 102; c) S. Matsunaga, M. Shibasaki, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 60.

[3] A short review on catalytic asymmetric aza-Michael reactions: a) L.-W. Xu, C.-G. Xia, *Eur. J. Org. Chem.* **2005**, 633; for more recent examples, see: b) N. Yamagiwa, N. Qin, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 13419; c) Y. K. Chen, M. Yoshida, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 9328; d) M. P. Sibi, K. Itoh, *J. Am. Chem. Soc.* **2007**, *129*, 8064; e) X. Lu, L. Deng, *Angew. Chem.* **2008**, *120*, 7824; *Angew. Chem. Int. Ed.* **2008**, *47*, 7710; f) D. Uraguchi, D. Nakashima, T. Ooi, *J. Am. Chem. Soc.* **2009**, *131*, 7242.

[4] a) Y. Hamashima, H. Somei, Y. Shimura, T. Tamura, M. Sodeoka, *Org. Lett.* **2004**, *6*, 1861; b) Y. Hamashima, N. Sasamoto, D. Hotta, H. Somei, N. Umebayashi, M. Sodeoka, *Angew. Chem.* **2005**, *117*, 1549; *Angew. Chem. Int. Ed.* **2005**, *44*, 1525; c) N. Sasamoto, C. Dubs, Y. Hamashima, M. Sodeoka, *J. Am. Chem. Soc.* **2006**, *128*, 14010; d) C. Dubs, Y. Hamashima, N. Sasamoto, T. M. Seidel, S. Suzuki, D. Hashizume, M. Sodeoka, *J. Org. Chem.* **2008**, *73*, 5859; e) Y. Hamashima, N. Sasamoto, N. Umebayashi, M. Sodoeka, *Chem. Asian J.* **2008**, *3*, 1443; for our review articles: f) M. Sodeoka, Y. Hamashima, *Bull. Chem. Soc. Jpn.* **2005**, *78*, 941; g) M. Sodeoka, Y. Hamashima, *Pure Appl. Chem.* **2006**, *78*, 477; h) M. Sodeoka, Y. Hamashima, *Chem. Commun.* **2009**, 5787.

[5] Reviews on enantioselective protonation: a) L. Duhamel, P. Duhamel, J.-C. Plaquevent, *Tetrahedron: Asymmetry* **2004**, *15*, 3653; b) A. Yanagisawa, H. Yamamoto in *Comprehensive Asymmetric Catalysis*, *Vol. 3* (Eds.: E. N. Jacobsen; A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**; c) A. Yanagisawa in *Comprehensive Asymmetric Catalysis*, Supplement 2 (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **2004**; d) J. T. Morh, A. Y. Hong, B. M. Stoltz, *Nat. Chem.* **2009**, *1*, 359.

[6] For recent examples of protonation of preformed enolates, see: a) S. Nakamura, M. Kaneeda, K. Ishihara, H. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 8120; b) E. Vedejs, A. W. Kruger, N. Lee, S. T. Sakata, M. Stec, E. Suna, *J. Am. Chem. Soc.* **2000**, *122*, 4602; c) A. Yanagisawa, T. Touge, T. Arai, *Angew. Chem.* **2005**, *117*, 1570; *Angew. Chem. Int. Ed.* **2005**, *44*, 1546; d) C. H. Cheon, H. Yamamoto, *J. Am. Chem. Soc.* **2008**, *130*, 9246; e) T. Poisson, V. Dalla, F. Marsais, G. Dupas, S. Oudeyer, V. Levacher, *Angew. Chem.* **2007**, *119*, 7220; *Angew. Chem. Int. Ed.* **2007**, *46*, 7090; f) C. Fehr, *Angew. Chem.* **2007**, *119*, 7249; *Angew. Chem. Int. Ed.* **2007**, *46*, 7119; g) J. Martin, J.-C. Plaquevent, J. Maddaluno, J. Rouden, M.-C. Lasne, *Eur. J. Org. Chem.* **2009**, 5414; h) D. Uraguchi, N. Kinoshita, T. Ooi, *J. Am. Chem. Soc.* **2010**, *132*, 12240.

[7] Reactions starting from ketenes: a) B. L. Hodous, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 10006; b) S. L. Wiskur, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 6176; c) C. Schaefer, G. C. Fu, *Angew. Chem.* **2005**, *117*, 4682; *Angew. Chem. Int. Ed.* **2005**, *44*, 4606; decarboxylative protonation starting from β-ketoesters: d) M. A. Baur, A. Riahi, F. Hénin, J. Muzart, *Tetrahedron: Asymmetry* **2003**, *14*, 2755; e) P. Kukula, V. Matousek, T. Mallat, A. Baiker, *Chem. Eur. J.* **2008**, *14*, 2699; f) S. C. Marinescu, T. Nishitama, J. T. Mohr, B. M. Stoltz, *Org. Lett.* **2008**, *10*, 1039; reactions using a chiral carbene catalyst: g) N. T. Reynolds, T. Rovis, *J. Am. Chem. Soc.* **2005**, *127*, 16406; Proton transfer reaction: h) Y. Saga, R. Motoki, Y. Shimizu, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 7905.

[8] a) E. Emori, T. Arai, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1998**, *120*, 4043; b) K. Nishimura, M. Ono, Y. Nagaoka, K. Tomioka, *Angew. Chem.* **2001**, *113*, 454; *Angew. Chem. Int. Ed.* **2001**, *40*, 440; c) D. Leow, S. Lin, S. K. Chittimalla, X. Fu, C.-H. Tan, *Angew. Chem.* **2008**, *120*, 5723; *Angew. Chem. Int. Ed.* **2008**, *47*, 5641.

[9] a) L. Navarre, S. Darses, J.-P. Genet, *Angew. Chem.* **2004**, *116*, 737; *Angew. Chem. Int. Ed.* **2004**, *43*, 719; b) R. J. Moss, K. J. Wadsworth,

C. J. Chapman, C. G. Frost, *Chem. Commun.* **2004**, 1984; c) M. P. Sibi, H. Tatamidani, K. Patil, *Org. Lett.* **2005**, *7*, 2571; d) T. Nishimura, S. Hirabayashi, Y. Yasuhara, T. Hayashi, *J. Am. Chem. Soc.* **2006**, *128*, 2556; e) C. G. Frost, S. D. Penrose, K. Lambshead, P. R. Raithby, J. E. Warren, R. Gleave, *Org. Lett.* **2007**, *9*, 2119; f) L. Navarre, R. Martinez, J.-P. Genet, S. Darses, *J. Am. Chem. Soc.* **2008**, *130*, 6159.

[10] M. P. Sibi, J. Coulomb, L. M. Stanley, *Angew. Chem.* **2008**, *120*, 10061; *Angew. Chem. Int. Ed.* **2008**, *47*, 9913.

[11] M. Morita, L. Drouin, R. Motoki, Y. Kimura, I. Fujimori, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 3858.

[12] T. Poisson, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2010**, *132*, 7890.

[13] We communicated our preliminary results in reference [4a] and the following paper: Y. Hamashima, T. Tamura, S. Suzuki, M. Sodeoka, *Synlett* **2009**, 1631.

[14] a) P. H. Phua, S. P. Mathew, A. J. P. White, J. G. de Vries, D. G. Blackmond, K. K. (Mimi) Hii, *Chem. Eur. J.* **2007**, *13*, 4602; b) M. P. Sibi, N. Prabagaran, S. G. Ghorpade, C. P. Jasperse, *J. Am. Chem. Soc.* **2003**, *125*, 11796.

[15] The synthesis of the starting material was carried out based on the reported procedure; a) X. Liu, X. E. Hu, X. Tian, A. Mazur, F. H. Ebetino, *J. Organomet. Chem.* **2002**, *646*, 212; b) T. Tsujimoto, J. Ishihara, M. Horie, A. Murai, *Synlett* **2002**, 0399.

[16] A similar Pd complex was previously reported. D. Nama, D. Schott, P. S. Pregosin, L. F. Veiros, M. J. Calhorda, *Organometallics* **2006**, *25*, 4596.

[17] D. Nama, P. S. Pregosin, A. Albinati, S. Rizzato, *Organometallics* **2007**, *26*, 2111.

[18] T. Tsunoda, J. Otsuka, Y. Yamamiya, S. Ito, *Chem. Lett.* **1994**, 539.

[19] We believe that the substrate is activated in s-*cis* conformation. Since the sign of the optical rotation of **3ba** suggests that it also has *R* configuration, the reaction is considered to proceed with the same conformation of the alkene part. When s-*trans* conformation of **2b** is taken in coordinating to the Pd complex, severe steric repulsion would occur compared with the reaction of **2a**. This idea is also supported by the results obtained in the case of the cyclic substrate **7**.

[20] Hii and her co-workers reported similar reactions in reference [14a]. In analogy to the reaction of *N*-benzoyl methacrylamide with anisidine, they assigned the absolute configuration of the *N*-methoxycarbamate derivative to be *S*, which suggests that the sense of enantioselection is different from ours. Although the substrate structure, preparation method of the catalysts, and the reaction solvent are different factors to be considered, it is somewhat surprising that opposite enantiomers were produced even though (*R*)-binap was used in both cases. We think that this may be attributed to the use of the amine salt, and thus we need a distinct model to explain our result.

[21] Several practical aminomethylation reactions of aldehydes using organocatalysts have been reported: a) Y. Chi, S. H. Gellman, *J. Am. Chem. Soc.* **2006**, *128*, 6804; b) I. Ibrahem, P. Dziedzic, A. Córdova, *Synthesis* **2006**, 4060.

[22] Asymmetric three-component classical Mannich reactions: a) I. Ibrahem, J. Casa, A. Córdova, *Angew. Chem.* **2004**, *116*, 6690; *Angew. Chem. Int. Ed.* **2004**, *43*, 652. See also Ref. [4e].

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