JOC Article

Mechanistic Studies on the Catalytic Asymmetric Mannich-Type Reaction with Dihydroisoquinolines and Development of Oxidative Mannich-Type Reactions Starting from Tetrahydroisoquinolines

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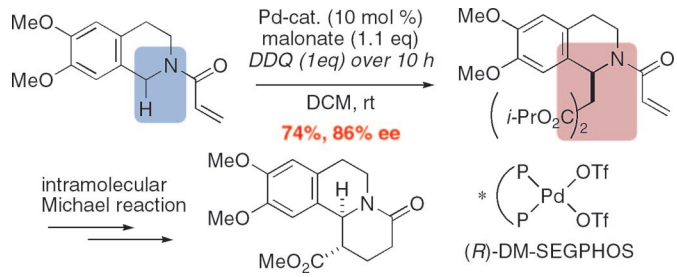
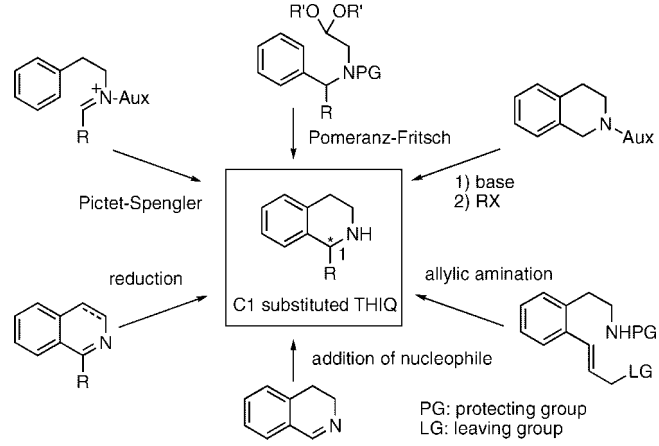


Detailed mechanistic studies on our recently reported asymmetric addition reactions of malonates to dihydroisoquinolines (DHIQs) catalyzed by chiral Pd(II) complexes were carried out. It was found that an *N*,*O*-acetal was generated in situ by the reaction of DHIQ with $(Boc)_2O$, and cooperative action of the Pd(II) complex as an acid−base catalyst allowed the formation of a chiral Pd enolate and a reactive iminium ion via α-fragmentation. The iminium ion was also accessible via oxidation with DDQ as an oxidant, and a catalytic asymmetric oxidative Mannich-type reaction was achieved with tetrahydroisoquinolines (THIQs) as starting materials. This oxidation protocol was applicable to *N*-acryloyl-protected THIQs, allowing the efficient synthesis of optically active tetrahydrobenzo[*a*]quinolizidine derivatives via intramolecular Michael reaction.

Introduction

C1-substituted tetrahydroisoquinolines (THIQs) represent an important family of biologically active alkaloids, and have been a target for synthetic organic chemists for decades.[1] Various approaches to construct this ring system have been developed (Scheme 1), including the Pictet−Spengler reaction, the Bischler−Napieralski reduction approach, the Pomeranz−Fritsch cyclization, the deprotonation−alkylation reaction, and addition reactions of nucleophiles to the C=N bonds of dihydroisoquinolines (DHIQs).[2] So far, most asymmetric syntheses of these molecules have relied on the use of optically active starting materials or chiral auxilaries. Such reactions require a stoichiometric amount of chiral sources, and therefore the development of efficient methods for asymmetric catalysis has also been of great interest. However, the number of practical catalytic reactions is still limited. High turnover numbers and excellent enantioselectivity were achieved in the catalytic asymmetric

SCHEME 1. Representative Methods for the Synthesis of Optically Active C1-Substituted THIQs



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(1) (a) Bentley, K. W. *Nat. Prod. Rep.* **2001**, *18*, 148–170. (b) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669–1730.

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transfer hydrogenation of C1-substituted DHIQs.[3] Recently, intramolecular allylic amination reactions with chiral Pd(0) complexes were also reported as a powerful method to obtain C1-vinyl-substituted THIQs in a highly enantioselective manner.[4]

In addition to these elegant methodologies, *catalytic asymmetric addition reactions to the C=N bonds of isoquinoline scaffolds* are also important alternative approaches. Several successful examples of such addition reactions with various nucleophiles, including dialkyl zinc,[5] trimethylsilylcyanide,[6] allylsilanes,[7] terminal alkynes,[8] and carbonyl compounds,[9] have been reported. Recently, addition reactions with other heterocyclic systems, such as pyridine, to furnish chiral nitrogen-containing cyclic compounds have also been gaining much attention, and unique methods have been devised for diastereoselective reactions[10] and (catalytic) enantioselective reactions.[11] Even catalytic asymmetric acyl Pictet−Spengler reactions became feasible with chiral thiourea-based organocatalysts, although available nucleophilic aromatic rings are limited to only indoles.[12]

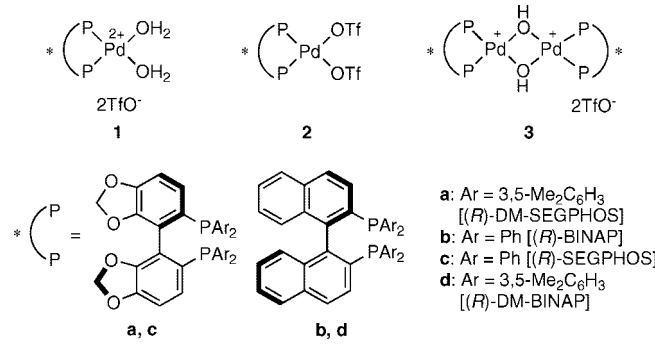

FIGURE 1. Chiral Pd complexes used in this work.

As regards addition reactions of carbonyl compounds to C=N bonds, great efforts have been made to develop Mannich-type reactions with *acyclic imines*, using ingenious chiral basic metal complexes and organic catalysts.[13] In striking contrast, reactions with cyclic imines have been less well studied, and only a few successful examples are known,[9] although many examples of diastereoselective reactions with chiral metal enolates were reported.[14] This might be due to difficulties associated with the lower reactivity of cyclic imines and less efficient face discrimination. Because the nitrogen atom of the cyclic imines is normally substituted by a simple alkyl group, the electrophilicity is insufficient compared with that of acyclic imines having electron-withdrawing groups such as acyl groups, sulfonyl groups, and diarylphosphonoyl groups. In addition, the difference in the steric size of two substituents on the nitrogen is not large, which makes it difficult to distinguish the two faces of the cyclic imines. Therefore, a novel system that can provide not only an appropriate chiral environment but also effective activation of the imine is highly desirable for the development of efficient Mannich-type reactions with cyclic imines.

Previously, we described catalytic asymmetric Mannich-type reactions of β-keto esters with acyclic imines using chiral Pd(II) complexes **1** (Figure 1).[15] Reaction of 1,3-dicarbonyl compounds with the Pd complex **1** affords a chiral Pd enolate, accompanied by the formation of a strong protic acid, and protonation of the imines is important to promote the reaction efficiently (Scheme 2). On the assumption that less reactive cyclic imines would be activated by protonation to form an iminium intermediate, we attempted the reaction of DHIQs with malonates. We finally found that the reaction of diisopropyl malonate with various DHIQs proceeded smoothly in the presence of a catalytic amount

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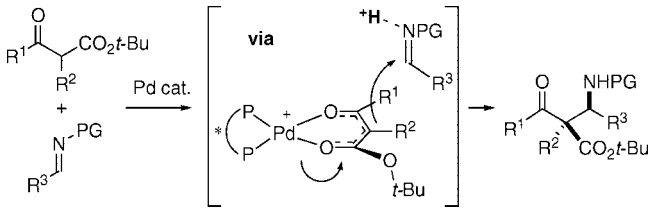
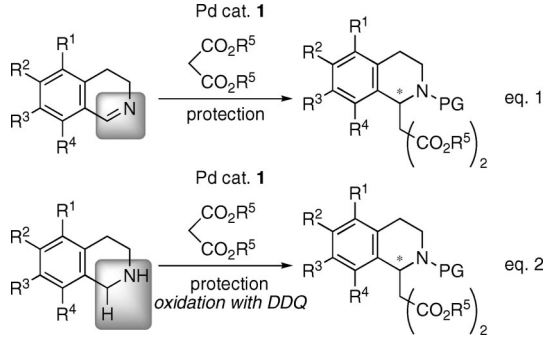
(15) (a) Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1525–1529. (b) Sodeoka, M.; Hamashima, Y. *Pure Appl. Chem.* **2006**, *78*, 477–494.

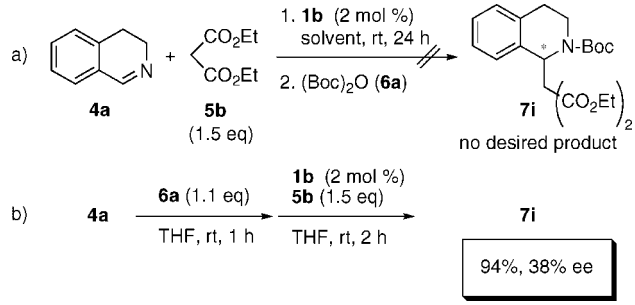
SCHEME 2. Reaction of β-Keto Esters with Acyclic Imines



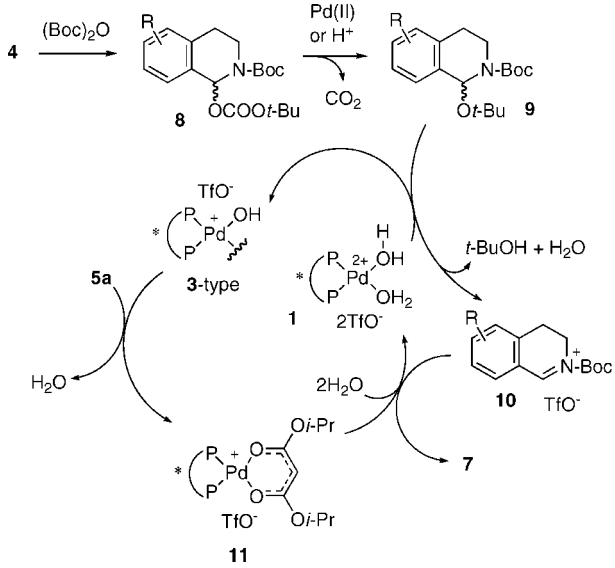
SCHEME 3. Mannich-Type Reaction To Give Optically Active THIQs



SCHEME 4. The Influence of the Reaction Procedure on the Reaction Efficiency



SCHEME 5. Proposed Catalytic Cycle



of [{(*R*)-dm-segphos}Pd$(H_2O)_2$]$(OTf)_2$ to furnish C1-substituted optically active THIQs with up to 97% ee (Scheme 3, eq 1).

Herein we describe full details of catalytic asymmetric Mannich-type reactions of malonates with in situ-formed iminium ions of DHIQs using chiral Pd(II) complexes as catalysts.[16,17] In the first part, the mechanism of the reaction with DHIQs in the presence of $(Boc)_2O$ is discussed. These studies indicate that the reaction proceeds via the formation of *N*,*O*-acetals, and consecutive α-fragmentation gives the reactive iminium ion intermediate. On the basis of these results, we attempted the direct generation of the iminium ion intermediate starting from *N*-Boc-protected THIQs or free THIQs. In the second part, a novel *catalytic asymmetric oxidative Mannich-type reaction*, in which the iminium ion intermediate is formed via oxidation with DDQ as an oxidant, is described (Scheme 3, eq 2).

Results and Discussion

1. Catalytic Asymmetric Addition Reactions of Malonates to DHIQs. Motivated by our previous results,[15] we attempted the reaction with DHIQs (**4**) using malonates (**5**) as nucleophiles in the presence of a catalytic amount of the Pd complex **1**. After examining various reaction conditions, we developed a highly enantioselective catalytic reaction to afford the corresponding C1-substituted tetrahydroisoquinoline derivatives.[16] According to an optimized procedure, DHIQs in CH_2Cl_2 were first treated with $(Boc)_2O$ (**6a**) at room temperature, and the catalyst (2 mol %) and the malonate were added to the resulting mixture at 0 °C. The best enantioselectivity was observed when **1a** and diisopropyl malonate **5a** were used. This reaction was found to be applicable to substrates having various substitutents on the aromatic ring.[18] The results are summarized in Table 1. In addition to a simple DHIQ **4a** (entry 1), substrates with electron-donating substituents (entries 2−7) and electron-withdrawing substituents (entry 8) were available, and the reaction was completed within several hours in most cases, affording **7**[19] in high yield with good to excellent enantioselectivity (∼98% yield, ∼97% ee). Interestingly, the substrates with neighboring methoxy groups (**4e** and **4f**) underwent the reaction without difficulty despite the possible bidentate coordination of the dimethoxy moiety to the catalyst (entries 5 and 6). Although the substrate **4g** with a methoxy group at the C8 position was expected to suffer severe steric repulsion, the reaction proceeded smoothly, affording **7g** in 94% yield with 82% ee (entry 7). For **4e** and **4f**, the catalyst loading could be reduced to 0.5 mol % without significant loss of reaction efficiency (entries 5 and 6). In the case of **7e**, a single recrystallization from ethyl acetate gave **7e** with 99% ee.

At the beginning of this project, we observed that the addition order of the reagents was extremely important for promoting the reaction. Thus, when DHIQ **4a** was mixed with diethyl malonate (**5b**) in the presence of **1b**, the desired product was not obtained at all, even if $(Boc)_2O$ was added to trap the free amine of the addition product (Scheme 4a). But, a slight modification of the procedure gave the desired coupling product

(16) Part of this work was reported as a communication: Sasamoto, N.; Dubs, C.; Hamashima, Y.; Sodeoka, M., *J. Am. Chem. Soc.* **2006**, *128*, 14010−14011.

(17) For preparation of the Pd complexes **1**−**3** see: Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450−5458.

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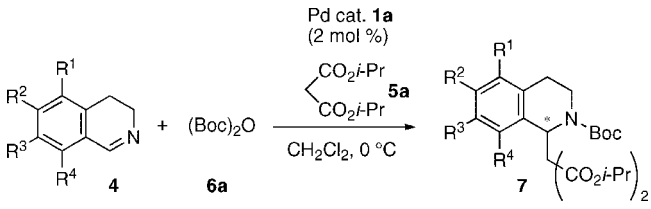
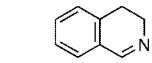
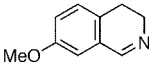
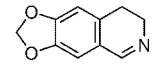
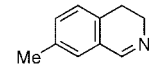
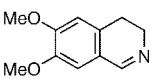
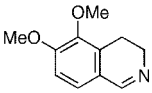
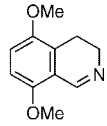
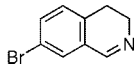
(19) All compounds **7a**−***l*** exist as a mixture of rotamers. See ref 16.

TABLE 1. Catalytic Asymmetric Addition Reactions to Various DHIQs[a–f]



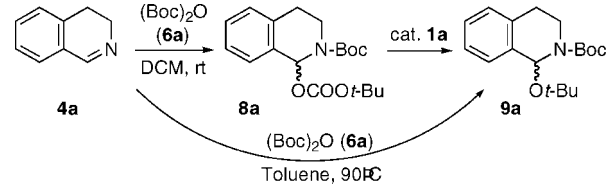
entry	DHIQ		products	time	yield[b] [%]	ee[c] [%]
1		**4a**	**7a**	1.5 h	89	85
2		**4b**	**7b**	1.5 h	98	81
3		**4c**	**7c**	5 h	57	91
4		**4d**	**7d**	1.5 h	93	96
5		**4e**	**7e**	1 h 3 h[d] 5 h[e]	98 93[d] 89[e]	92 94[d] 89[e] [99][f]
6		**4f**	**7f**	1 h 7 h[e]	92 71[e]	97 95[e]
7[g]		**4g**	**7g**	6 h	94	82
8		**4h**	**7h**	3 h	97	90

[a] Reaction conditions: 0.15 mmol of **4**, 0.225 mmol of **5a**, 0.225 mmol of **6a**, 2 mol % of **1a** in 0.15 mL of DCM at 0 °C. [b] Isolated yield after flash column chromatography. [c] Determined by HPLC (see ref 16). [d] 1 mol % **1a**. [e] 0.5 mol % **1a**. [f] After recrystallization from ethyl acetate. [g] 5 mol % **1a**.

in high yield. Premixing **4a** with **6a** for 1 h at room temperature, followed by the addition of **5b** and **1b**, gave the product **7i** with moderate enantioselectivity (Scheme 4b). Initially, we anticipated that the reaction with DHIQs would proceed in a similar fashion to that which we had reported for the reaction of β-keto esters with acyclic imines (Scheme 2).[15] We proposed that the imine would be activated by a proton generated during the formation of the chiral Pd enolate, which was considered to be crucial for the reaction. In the present reaction, however, the initial results (Scheme 4) suggested a different mechanism.

On the basis of the experimental data described below, we propose a unique reaction mechanism, as outlined in Scheme 5. The initial reaction of $(Boc)_2O$ with DHIQ **4** gives the carbonate **8**, and decarboxylation induced by the catalyst **1** itself or an acidic proton derived from **1** leads to the formation of the *N*,*O*-acetal **9**. Similar formation of *N*,*O*-acetals by the reaction of $(Boc)_2O$ with isoquinolines was reported in the literature.[20] α-Fragmentation is induced by the acidic proton released from **1a**, and *t*-BuOH and the iminium ion **10** are formed. The PdOH

SCHEME 6. Reaction of 4a with 6a



complex (**3**-type) is generated after deprotonation then reacts with the malonate to form the palladium enolate **11**, and subsequent nucleophilic attack of the enolate on the iminium ion gives the desired product **7**.[21] In spite of the formation of the highly reactive iminium species, high asymmetric induction was observed under mild reaction conditions (0 °C to room temperature), which may be attributed to simultaneous dual activation by the Pd complex as an acid−base catalyst.

This reaction mechanism is supported by the following experimental data:

(1) Formation of *N*,*O*-acetal 9: The reaction of **4a** with **6a** in DCM led to the complete formation of the carbonate **8a** in 15 min (Scheme 6). The resulting **8a** then slowly decarboxylated to give the *N*,*O*-acetal **9a**, but the reaction did not reach completion even after a prolonged time. However, mixing **4a** and **6a** in toluene at 100 °C gave **9a** exclusively. Like all the coupling products **7**, **9a** exists as a mixture of two rotamers at room temperature in $CDCl_3$. The conversion of **8a** to **9a** was also promoted by the addition of **1a**. A control experiment showed that the addition of a catalytic amount of TfOH is also effective for this purpose. Upon addition of a catalytic amount of **1a** to a DCM solution of **8a**, violent bubbling (decarboxylation) was observed and the formation of **9a** was complete in less than 15 min.

In Figure 2, the aromatic regions of the ^{1}H NMR spectra of

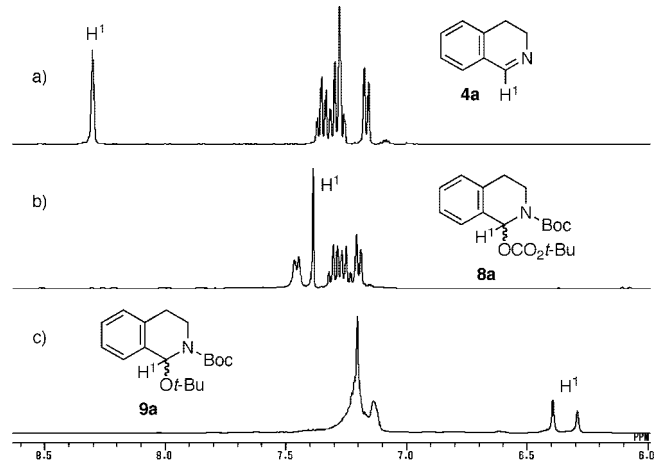


FIGURE 2. ^{1}H NMR in CD_2Cl_2 (aromatic region): (a) **4a**, (b) **6a** + **4a**, and (c) **6a** + **4a** + **1a**.

4a, **8a**, and **9a** are shown. The shift of the C1 proton signal is striking [for **4a**: 8.32 ppm; for **8a**: 7.38 ppm; for **9a**: 6.29 and 6.39 ppm (mixture of two rotamers)], indicating the stepwise formation of **9a**. Additionally, decarboxylation of **8a** promoted

(20) For the formation of *N*,*O*-acetal by the reaction of $(Boc)_2O$ with isoquinoline: see: Ouchi, H.; Saito, H.; Yamamoto, Y.; Takahata, H. *Org. Lett.* **2002**, *4*, 585–587.

(21) The asymmetric addition reaction of malonates to cyclic *N*,*O*-acetals has been reported: Onomura, O.; Kanada, Y.; Nakamura, T.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **2002**, *43*, 3229–3231.

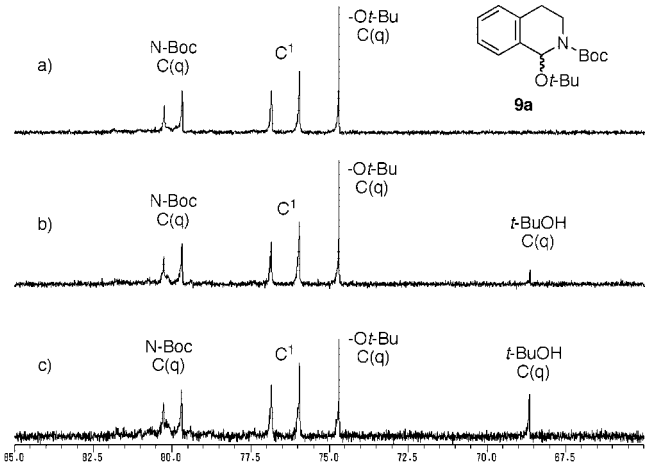


FIGURE 4. ^{13}C NMR in CD_2Cl_2 in the range 65−85 ppm: (a) **9a**, (b) **9a** + **1a** (0.1 equiv), and (c) **9a** + **1a** (0.2 equiv).

by **1a** was followed by IR, and the disappearance of one (CO) was observed (Figure 3). Upon addition of **1a** (2 mol %) to **8a**

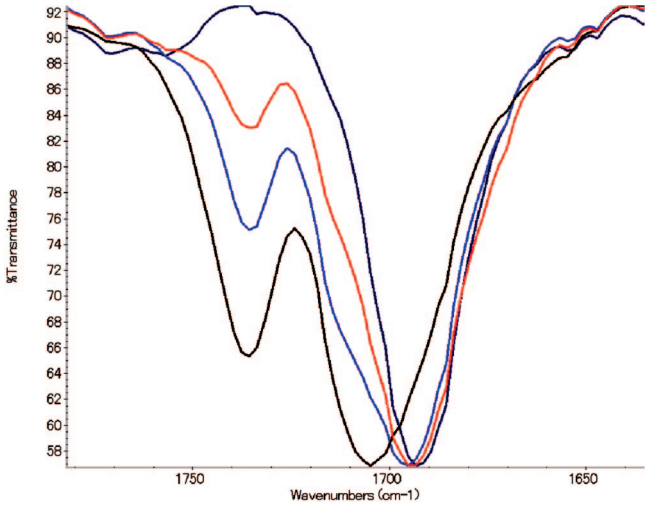
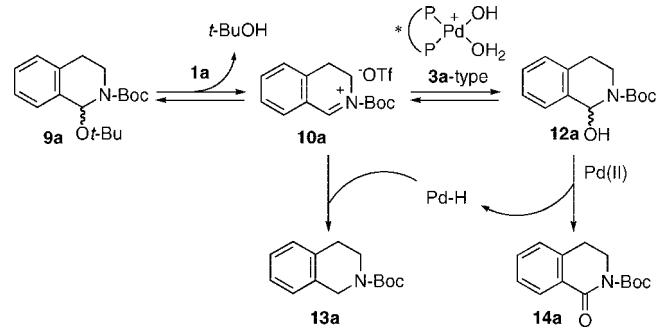


FIGURE 3. IR monitoring of the reaction of **4a** and **6a**: black line, **8a**; blue line, **8a** + **1a** (10 min); red line, **8a** + **1a** (20 min); and violet line, **8a** + **1a** (30 min, **9a**).

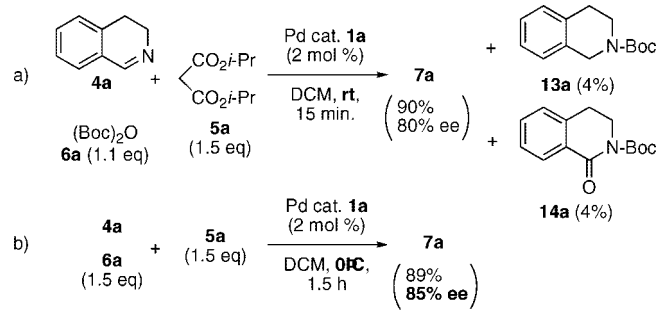
[(CO) = 1705, 1736 cm^{-1} (black line)], the band at 1736 cm^{-1} disappeared gradually and the band at 1705 cm^{-1} shifted to a smaller wavenumber (1692 cm^{-1}). After 30 min, a band at 1692 cm^{-1} alone remained, which corresponds to **9a** (violet line).

(2) α-Fragmentation of 9: To examine the further steps of the reaction, **9a** was treated with **1a**, and the formation of *t*-BuOH was observed by NMR. In Figure 4a, ^{13}C NMR spectra of **9a** in the range of 65−85 ppm are shown. The carbon signals attributed to C1 and the quaternary *tert*-butyl carbons were observed in this region. Upon the addition of **1a**, a new signal corresponding to *t*-BuOH appeared, which grew bigger when additional **1a** was added. The other signals, however, did not change significantly. These observations suggest the formation of the hemiacetal **12a**, which might be in equilibrium with **9a**. This can be understood in terms of α-fragmentation of **9a** to give the iminium ion **10a**, followed by a nucleophilic attack by the hydroxide ion or water molecule coordinated to Pd (Scheme 7). The iminium ion is a powerful intermediate in organic synthesis,[22] and α-fragmentation induced by Lewis or protic acids is a frequently used method.[23] The equilibrium between

SCHEME 7. Formation of 12a and Side Products 13a and 14a



SCHEME 8. Side Product Formation at Room Temperature



the precursor and the fragmented species is strongly dependent on the substituent on the nitrogen, the nature of the leaving group, and the Lewis acid used for activation.[24]

Generation of **12a** is also supported by the following results (Scheme 8). At room temperature, the reaction was complete after only 15 min. But, the Boc-amine **13a** (4% yield) and the amide **14a** (4% yield) were isolated as side products, which were not formed in the reaction performed at 0 °C. These compounds are considered to be generated via an oxidation−reduction pathway from the hemiacetal **12a** (Scheme 7). It is likely that **12a** reacted with Pd(II) to give **14a** together with a Pd−H species, which then reduced **10a** to give **13a**. We recently reported an efficient asymmetric conjugate reduction of enones using **3b** as a catalyst and ethanol as a reductant, in which Pd−H is considered to be a key intermediate.[25]

(3) Formation of the Pd−enolate complex 11:[26] Under the conditions described in Scheme 8, ESI-MS of the reaction mixture was measured after 5 min. A signal at *m*/*z* 1015.2 corresponding to the Pd−enolate complex **11** [{(*R*)-dm-

(22) (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407–1438. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron*, **2000**, *56*, 3817−1856. A general review on iminium ion cyclizations: (c) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311–2352.

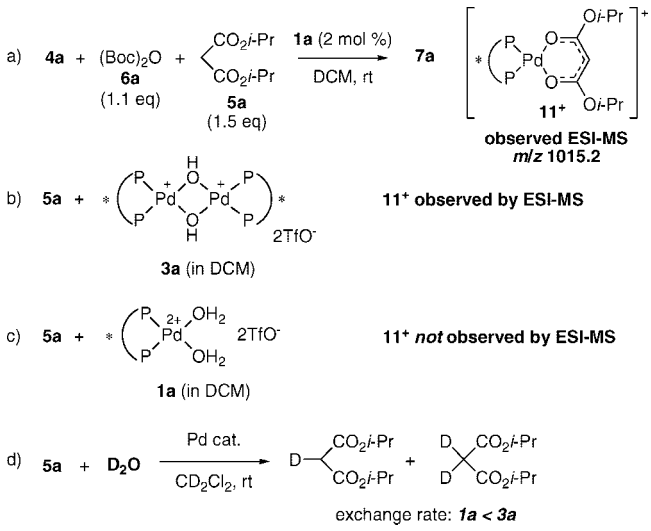
(23) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044–1070.

(24) Yamamoto, Y.; Nakada, T.; Nemoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 121–125.

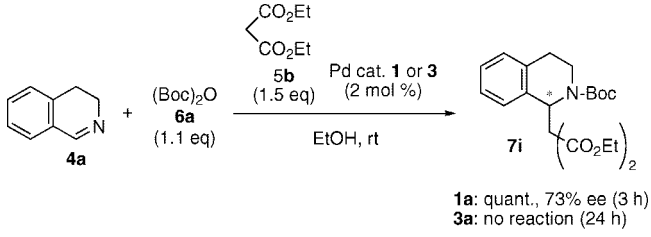
(25) (a) Tsuchiya, Y.; Hamashima, Y.; Sodeoka, M. *Org. Lett.* **2006**, *8*, 4851–4854. (b) Monguchi, D.; Beemelmanns, T.; Hashizume, D.; Hamashima, Y.; Sodeoka, M. *J. Organomet. Chem.* **2008**, *693*, 867–873.

(26) For the formation of Pd-enolate complexes of β-keto esters and β-diketones, see: (a) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240–11241. (b) Hamashima, Y.; Hotta, D.; Umebayashi, N.; Tsuchiya, Y.; Suzuki, T.; Sodeoka, M. *Adv. Synth. Catal.* **2005**, *347*, 1576–1586. (c) Sodeoka, M.; Hamashima, Y. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 941–956. (d) Kujime, M.; Hikichi, S.; Akita, M. *Organometallics* **2001**, *20*, 4049–4060. (e) Nama, D.; Pregosin, P. S.; Albinati, A.; Rizzato, S. *Organometallics* **2007**, *26*, 21112121. For the formation of Ru enolate complexes of β-ketoesters see: (f) Althaus, M.; Bonaccorsi, C.; Mezzetti, A.; Santoro, F. *Organometallics* **2006**, *25*, 3108–3110.

SCHEME 9. Formation of the Pd Enolate 11



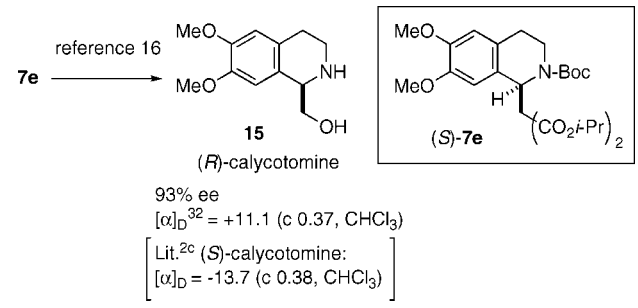
SCHEME 10. Comparison between 1b and 3b



segphos}Pd(**5a**-H)]$^+$ was observed, although a major peak ion was [{(*R*)-dm-segphos}Pd(OTf)]$^+$ (*m*/*z* 977.1) (Scheme 9a). Although the same enolate complex **11** was also detected in a solution containing **3a** and **5a** (Scheme 9b), no corresponding signal appeared from the mixture of **1a** and **5a** (Scheme 9c). Additionally, H/D exchange reaction was observed after the addition of D_2O to a CD_2Cl_2 solution of **1a** and **5a** (1:1), and it took 2 h to achieve 50% disappearance of the acidic methylene protons of **5a**. In contrast, in the case of **3a** and **5a**, the H/D exchange was much faster (30 min until completion) (Scheme 9d). These results suggest that the acidic complex **1a** induces α-fragmentation and the deprotonated complex PdOH corresponding to the monomer form of **3a** acts as a base to abstract the α-proton of **5a** to give the Pd−enolate complex **11**. Interestingly, in our optimization studies, we found that **3a** did not catalyze the reaction, although **1a** actually did, even in ethanol (Scheme 10). This result suggests that the formation of the Pd enolate alone is not sufficient for promoting the reaction and activation of both reactants is essential, highlighting the importance of the cooperative action of **1a** as an acid−base catalyst.

Determination of the Absolute Configuration and the Proposed Transition State Model. As reported previously,[16] the conversion of **7e** to calycotomine **15** was carried out, and (*R*)-calycotomine was obtained. The absolute configuration of **15** was determined by comparison of the optical rotation with the reported value.[2c,27] This result reveals that the sense of enantioselection of the present reaction is *S*-selective (Scheme 11).

SCHEME 11. Conversion of 7e and Determination of the Absolute Configuration



Although the exact mechanism of the asymmetric induction is not clear, the observed absolute configuration correlates to our proposed model of the Pd enolate complexes (Figure 5). The bulky *i*-Pr groups of the malonate would be located away from the aryl rings of the ligand, creating a new C_2 symmetric environment. The structurally rigid and bulky aromatic ring of the iminium intermediate **10** points away from the *i*-Pr group to avoid steric repulsion (model A vs model B), controlling the face selection of the C═N bond (model A). The experimental fact observed during the optimization that changing the size of malonate **5** had an influence on the enantioselection seems to be in accord with the proposed transition state model (R = Et: 73% ee; R = Bn: 66% ee) (Table 2, entries 1−3). Additionally, a significant effect of the substituent of the ligand was observed (entries 1 and 4−6). It is likely that the methyl substituents on the phenyl ring of the ligand might be important to disfavor the minor reaction pathway (model B) as a result of increased steric interaction with the Boc group, thus making the reaction pathway A more favorable.

2. Oxidative Mannich-Type Reaction of Malonates to THIQs. Because we found that the iminium ion is a key intermediate, we next became interested in its formation by oxidative methods starting from the corresponding THIQs (Scheme 12). In addition to α-fragmentation, various oxidative methods have been developed to generate iminium ions, including the use of chemical oxidizing reagents, photochemical methods, and electrochemical oxidations.[22,23] Such oxidative coupling reactions would have the great advantage that the imines **4**, preparation of which is often tedious, are no longer necessary, and instead the readily available and stable **13** can be used. Notably, since some of the starting imines **4** are prepared via oxidation of the corresponding amines with NBS as an oxidant, the direct use of the amines in the asymmetric Mannich-type reactions would reduce the overall number of steps necessary for the preparation of **7**. This type of oxidative Mannich reaction has been gaining much attention recently. Although the number of reports is increasing, no catalytic asymmetric version of the reaction has yet been reported, to our knowledge.[8a,28] Li et al. have reported various oxidative coupling reactions in which reactive iminium and oxonium species are formed either via oxidation with *tert*-butyl hydroperoxide (TBHP) in the presence of CuBr[28a,b] or via oxidation

(27) (a) Morimoto, T.; Suzuki, N.; Achiwa, K. *Tetrahedron: Asymmetry* **1998**, *9*, 183–187. For a review on calycotomine see: (b) Kaufmann, T. S. *Synthesis* **2005**, 339–360. See also ref 2c.

(28) Oxidative Mannich-type reactions: (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672–3673. (b) Li, Z.; Li, C.-J. *Eur. J. Org. Chem.* **2005**, 3173–3176. (c) Murahashi, S.-i.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312–15313. (d) Murahashi, S.-i.; Komiya, N.; Terai, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 6931–6933. (e) Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 5648–5649. (f) Zhang, Y.; Li, C.-J. *Angew. Chem., Int. Ed.* **2006**, *45*, 1949–1952. (g) Matsuo, J.; Tanaki, Y.; Ishibashi, H. *Org. Lett.* **2006**, *8*, 4371–4374. (h) Matsuo, J.; Tanaki, Y.; Ishibashi, H. *Tetrahedron Lett.* **2007**, *48*, 3233–3236.

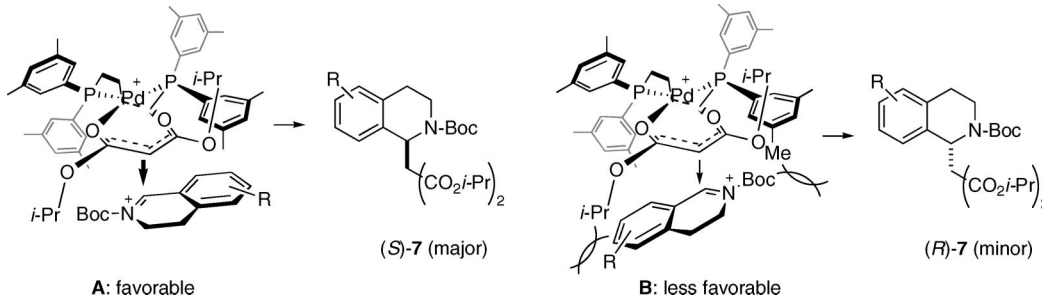
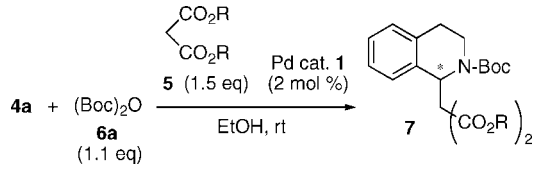


FIGURE 5. Proposed transition state model. The naphthyl moieties of the ligand were omitted for clarity.

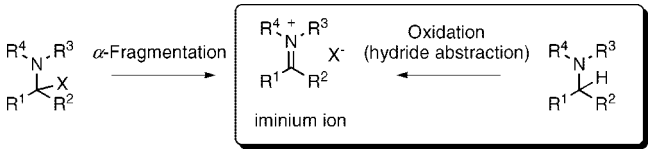
TABLE 2. The Effect of Malonates and Ligands[a]



entry	5(R)	1	7	time (h)	yield[b] (%)	ee[c] (%)
1	**5a** (*i*-Pr)	**1a**	**7a**	12	67	80
2	**5b** (Et)	**1a**	**7i**	3	quant.	73
3	**5c** (Bn)	**1a**	**7j**	12	62	66
4	**5b** (Et)	**1b**	**7i**	2	quant.	44
5	**5b** (Et)	**1c**	**7i**	1	quant.	48
6	**5b** (Et)	**1d**	**7i**	7	quant.	65

[a] Reaction conditions: 0.15 mmol of **4a**, 0.225 mmol of **5**, 0.165 mmol of **6a**, 2 mol % of **1** in 0.15 mL of anhydrous EtOH. [b] Isolated yield after flash column chromatography. [c] Determined by chiral HPLC (see ref 16).

SCHEME 12. Oxidative Routes to Iminium Ions



with DDQ.[28f] For example, they reported the oxidative coupling reaction of malonates with *N*-phenyl-protected THIQs using the TBHP/CuBr combination.[28b] Inspired by their pioneering work, we examined our reactions using DDQ as an oxidant, because we thought that DDQ would minimize the interference with our Pd-catalyst system compared to that with the THBP/CuBr system.[29]

From Isolated *N*-Boc-Amines. At first, we examined the reaction of the isolated *N*-Boc-THIQ **13e**. Because DDQ oxidation of **13e** did not occur at 0 °C, the reaction needed to be carried out at room temperature (Table 3). The addition of DDQ in one portion into a DCM solution of **13e** and **5a** containing 5 mol % of **1a** gave **7e** in low yield (9%), but with high enantioselectivity (80% ee) (entry 1). We considered the low yield to be due to the decomposition of the catalyst and undesired reactions induced by a high concentration of the reactive iminium ion. Consequently, we examined the slow addition of DDQ as a DCM solution. To our delight, the yield was dramatically increased when DDQ was added slowly over 5 h (83%, 86% ee) (entry 2). However, the chemical yield decreased when the amount of catalyst was reduced to 2 mol % (entry 3). Since 5 mol % of the catalyst was used and the reaction was carried out at room temperature, the substantial amount of water induced redox reactions to give the side products (see Scheme 7). Thus, we prepared anhydrous Pd complex **2a**. Structure determination by X-ray analysis confirmed that it contained no water molecule.[30] When **2a** was used instead of **1a**, the H_2O-induced side reactions were suppressed effectively, and **7e** was obtained in better chemical yield (entry 4). The molecular structure of **2a** displays a square-planar geometry of Pd(II) coordinated with two phosphorus atoms and two oxygen atoms of the trifluoromethanesulfonyl group (Figure 6). Two trifluoromethanesulfonyl groups are positioned in the open space to avoid unfavorable steric interaction with the dimethylphenyl group on the ligand. This supports the proposed structure of the Pd enolate as depicted in Figure 5. In the next section, we further examined the reaction using nonprotected THIQs, and full conversion and excellent chemical yield were achieved using **2a** as a catalyst.

From Amines. Further investigations revealed that the commercially available amine **14e** could be used directly (Table 4). Thus, premixing **14e** and **6a** forms **13e** quantitatively and the concomitantly formed *t*-BuOH did not have any negative effect on the reaction. Again, the slow addition of DDQ was important for high chemical yield and enantioselectivity (entries 1−3). Finally, the amount of DDQ and **5a** could be reduced, and the desired product **7e** was obtained in 97% yield with 86% ee (entries 5 and 6).

Substrate Scope. Under the optimized reaction conditions, THIQs with different substituents on the aromatic ring were subjected to the oxidative Mannich-type reaction. The results are summarized in Table 5. Good results were obtained when THIQs with electron-donating substituents were used (entries 2−4), although the reaction of **14g** was not so efficient, probably due to steric hindrance (entry 5). Unfortunately, however, only a low yield was observed for **14a** (entry 1), and no conversion occurred in the case of **14h**, which has a Br substituent on the aromatic ring. In contrast to the reaction with the *N*,*O*-acetals, this method is limited to THIQs with electron-donating substituents. However, for electron-rich substrates, this one-pot procedure is operationally convenient, and the coupling products were obtained at a synthetically useful level. It should be noted that an easily removable protecting group could be used in our reaction, whereas *N*-phenyl-substituted substrates have normally been used in the literature.[28]

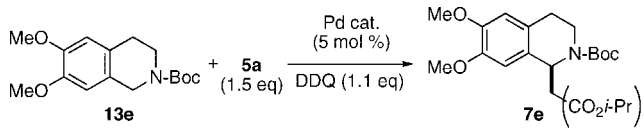
Proposed Catalytic Cycle. On the basis of the observations in the case of *N*,*O*-acetals, we propose a catalytic cycle of the oxidative Mannich-type reaction as shown in Scheme 13.[31] The reaction of **14** with **6a** gives the *N*-Boc-THIQs **13**, and oxidation

(29) Indeed, the reaction with CuBr−TBHP as an oxidant did not proceed at all. Benzoquinone was also ineffective.

(30) The crystallographic data for **2a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary no. CCDC 673878. These data can be obtained online free of charge.

(31) A similar reaction mechanism is proposed in ref 28b.

TABLE 3. Oxidative Mannich-Type Reaction of 13e and 5a[a]



entry	Pd cat.	DDQ addition	time (h)	yield[b] (%)	ee[c] (%)
1	**1a**	one portion	12	9	80
2	**1a**	over 5 h	7	83	86
3[d]	**1a**	over 5 h	7	34	85
4	**2a**	over 5 h	7	89	81

[a] Reaction conditions: 0.15 mmol of **13e**, 0.225 mmol of **5a**, 5 mol % of Pd catalyst in 0.15 mL of anhydrous DCM; slow addition of DDQ in 1.5 mL of DCM. [b] Isolated yield after flash column chromatography. [c] Determined by chiral HPLC (see ref 16). [d] 2 mol % of **1a**.

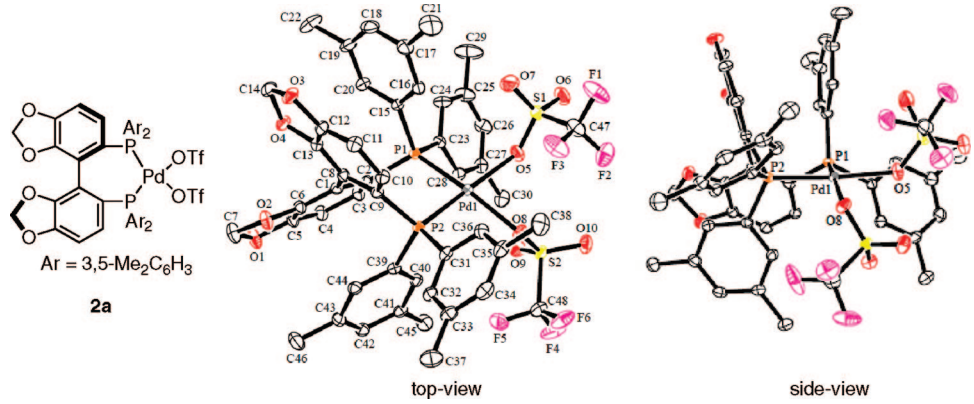
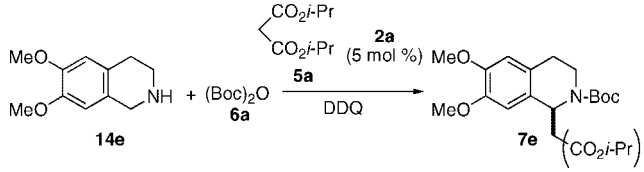


FIGURE 6. X-ray structure of **2a**. Hydrogen atoms are omitted for clarity. Selected distances (Å) and angles (deg) are as follows: Pd(1)−O(5) 2.1541(2), Pd(1)−O(8) 2.1595(2), Pd(1)−P(2) 2.2305(6), Pd(1)−P(1) 2.2382(6), O(5)−Pd(1)−O(8) 82.67(7), O(5)−Pd(1)−P(2) 172.21(5), O(8)−Pd(1)−P(2) 93.80(5), O(5)−Pd(1)−P(1) 94.90(5), O(8)−Pd(1)−P(1) 166.63(5), P(2)−Pd(1)−P(1) 90.10(2), C(15)−P(1)−Pd(1) 117.24(7), C(2)−P(1)−Pd(1) 117.63(7), C(23)−P(1)−Pd(1) 100.75(7), C(39)−P(2)−Pd(1) 111.87(7), C(9)−P(2)−Pd(1) 112.35(7), C(31)−P(2)−Pd(1) 108.62(8), S(1)−O(1)−Pd(1) 131.00(1), S(2)−O(8)−Pd(1) 117.09(1).

TABLE 4. Coupling Reaction of 14e and 5a[a]



entry	DDQ (equiv)	DDQ addition	**5a** (equiv)	time (h)	yield[b] (%)	ee[c] (%)
1	1.1	over 5 h	1.5	7	64	88
2	1.1	over 2 h	1.5	4	41	75
3	1.1	over 10 h	1.5	12	81	86
4	1.4	over 10 h	1.5	12	80	86
5	1.0	over 10 h	1.5	12	91	86
6	1.0	over 10 h	1.1	12	97	86

[a] Reaction conditions: 0.1 mmol of **14e**, **5a**, 0.11 mmol of **6a**, 5 mol % of **2a** in 0.15 mL of anhydrous DCM; slow addition of DDQ in 1.5 mL of DCM. [b] Isolated yield after flash column chromatography. [c] Determined by chiral HPLC (see ref 16).

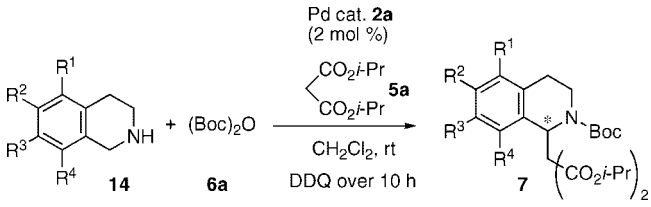
(hydride abstraction) by DDQ[32] gives the reactive iminium ion **10**. The concomitantly formed phenolate anion **15** may act as a weak base, which facilitates the formation of the Pd enolate **11**. Finally, these active species react to give the desired coupling product **7**. We suppose that the limited availability of the substrates is associated with the feasibility of the oxidation of **13**, which only proceeds in the case of the electron-rich substrates. We attribute the lower enantioselectivity compared to the reaction with *N*,*O*-acetals to the difference in the reaction temperature (0 °C vs rt) and concentration (0.5 M vs gradient from 0.75 to 0.1 M). In addition, the formed phenolic coproduct **16** may also interfere with the stereoselectivity of the reaction, although its exact action is not clear.

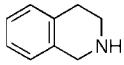
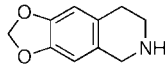
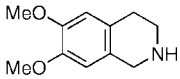
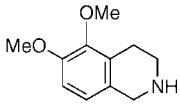
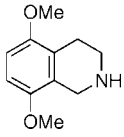
Asymmetric Synthesis of Tetrahydrobenzo[*a*]quinolizidine Derivatives. The tetrahydrobenzo[*a*]quinolizidine system can be found in various alkaloids, such as the ipecac alkaloids, which include emetine as a prominent member.[33,34] As described above, we normally used a Boc group as a protecting group of

(32) The initial reaction step in the oxidation with DDQ is believed to be hydrogen abstraction. See: Fu, P. P.; Harvey, R. G., *Chem. Rev.*, **1978**, *78*, 317−361.

(33) Fujii, T.; Ohba., M. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol *51*, pp 271−323.

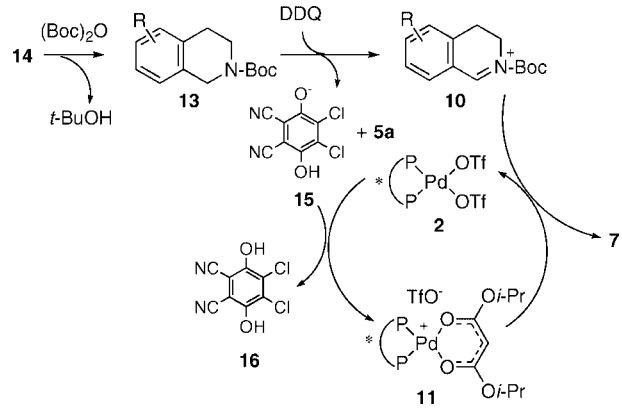
TABLE 5. Oxidative Mannich-Type Reaction of Various THIQs[ad]



entry	starting material	products	time	yield[b] (%)	ee[c] (%)
1	 **14a**	**7a**	12 h	15	82
2	 **14c**	**7c**	12 h	90	81
3	 **14e**	**7e**	12 h	97	86
4	 **14f**	**7f**	12 h	92	75
5[d]	 **14g**	**7g**	12 h	47	70

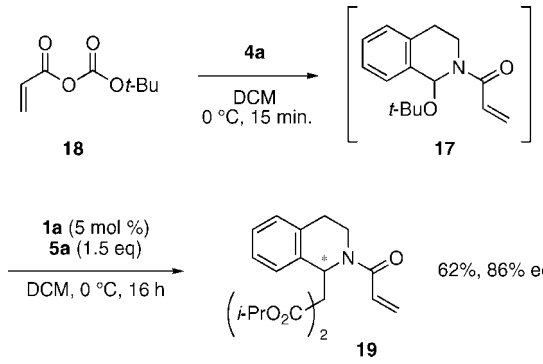
[a] Reaction conditions: 0.1 mmol of **14**, 0.11 mmol of **5a**, 0.11 mmol of **6a**, 5 mol % of **2a** in 0.15 mL of anhydrous DCM; slow addition of DDQ (1.0 equiv) in DCM (1.5 mL) over 10 h. [b] Isolated yield after flash column chromatography. [c] Determined by chiral HPLC (see ref 16). [d] 10 mol % of **2a**.

SCHEME 13. Proposed Reaction Mechanism for the Oxidative Mannich-Type Reaction



the starting materials. If this Boc group can be replaced by an acryloyl group, it is expected that the coupling product can be subjected to an intramolecular Michael reaction to construct the core structure of the tetrahydrobenzo[*a*]quinolizidine system. To test this hypothesis, we initially tried to synthesize *N*-acryloyl *N*,*O*-acetals such as **17** as substrates by the reaction of the imine

SCHEME 14. Formation of the Acryloyl-Protected Coupling Product



with acryloyl chloride, followed by treatment with suitable alcohols (Scheme 14). But these compounds were found to be unstable, being readily converted to the corresponding aldehyde by hydrolysis during column chromatography. Therefore, we looked at in situ preparation of the corresponding *N*,*O*-acetal using acryloyl carbonate **18** (Scheme 14). This carbonate was prepared according to the literature.[35] Treatment of **18** with **4a** in DCM at 0 °C gave **17**, and no *N*-Boc-protected compound was observed. To the resulting solution were added the Pd complex **1a** and the malonate **5a**. Probably because the formation of the corresponding iminium ion might be disfavored by the stronger electron-withdrawing nature of the acryloyl group, the reaction was slow compared to that of the Boc-protected substrate. After 16 h, the coupling product **19** was obtained in 62% yield with as high as 86% ee, indicating that the acryloyl group is also available in this Mannich-type reaction.

Encouraged by this result, we next examined the oxidative Mannich-type reaction with *N*-acryloyl THIQ **20** and its application to the asymmetric synthesis of the tetrahydrobenzo[*a*]quinolizidine system (Scheme 15). The amide **20** was prepared by the conventional method. The following coupling reaction using the DDQ procedure gave **21** in high yield with excellent enantioselectivity (74%, 86% ee). The formation of the six-membered ring by intramolecular Michael reaction gave the desired **22** without significant loss of optical purity (83% ee). Hydrolysis and decarboxylation under a basic condition, followed by methyl ester formation with $TMSCHN_2$, gave **24** as a single diastereomer.[36] The relative configuration of the acid **23** was unequivocally determined by X-ray analysis.[37] The absolute stereochemistry was assigned by analogy to the case of **7e**. The optical purity of **23** was enriched to 99% by recrystallization from methanol. It is noteworthy that catalytic asymmetric synthesis of **24** was achieved starting from *N*-acryloyl THIQ **20** and no preparation of the corresponding imine was necessary, highlighting the usefulness of the DDQ procedure.

Conclusion

We have developed a novel catalytic asymmetric Mannich-type reaction for the synthesis of optically active C1-substituted

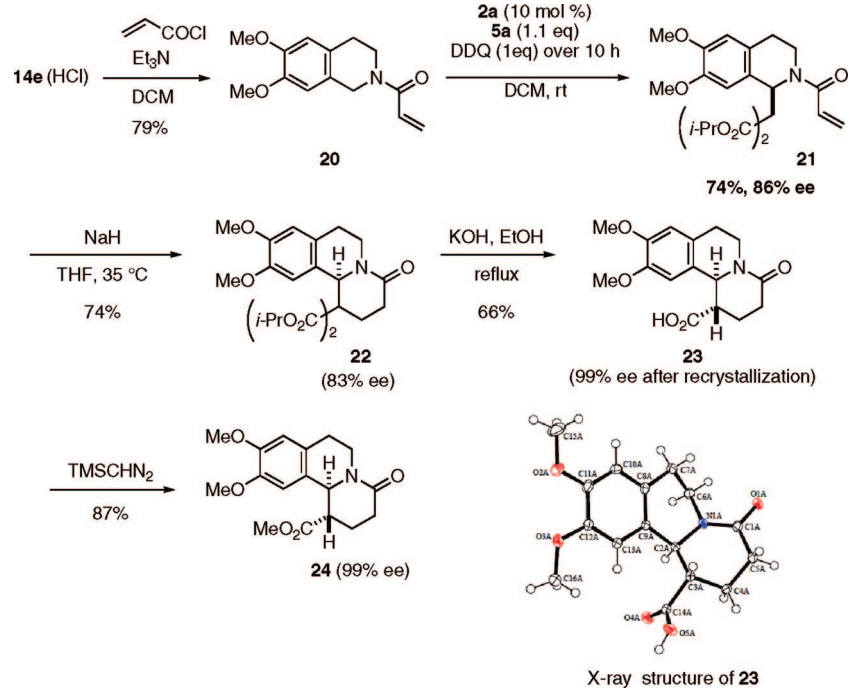
(34) For recent examples, see: (a) García, E.; Lete, E.; Sotomayor, N. *J. Org. Chem.* **2006**, *71*, 6776–6784. (b) Bassas, O.; Llor, N.; Santos, M.-M.; Griera, R.; Molins, E.; Amat, M.; Bosch, J. *Org. Lett.* **2005**, *7*, 2817–2820. (c) Tietze, L. F.; Rackelmann, N.; Müller, I. *Chem. Eur. J.* **2004**, *10*, 2722–2731. (d) Kirschbaum, S.; Waldmann, H. *J. Org. Chem.* **1998**, *63*, 4936–4946.

(35) (a) Yamamoto, Y.; Tarbell, D. S. *J. Org. Chem.* **1971**, *36*, 2954. (b) Vansteenkiste, S.; Matthijs, G.; Schacht, E.; Schrijver, F. D.; Damme, M. V.; Vermeersch, J. *Macromol. Rapid Commun.* **1999**, *20*, 333.

(36) For the synthesis of racemic **24** see: Ihara, M.; Yamada, M.; Ishida, Y.; Tokunaga, Y.; Fukumoto, K. *Heterocycle*, **1997**, *44*, 531−536.

(37) The crystallographic data for **23** have been deposited with the Cambridge Crystallographic Data Centre as supplementary no. CCDC 670312. These data can be obtained online free of charge.

SCHEME 15. Synthesis of Tetrahydrobenzo[*a*]quinolizidine Derivative 24



THIQs. The addition reaction of malonates to in situ-formed iminium ion intermediates of DHIQs proceeded smoothly to give the coupling product in high yield with good to excellent enantioselectivity. Mechanistic studies revealed that the reaction with DHIQs in the presence of $(Boc)_2O$ proceeds via the formation of *N*,*O*-acetals, and the chiral Pd complex as an acid−base catalyst allows the formation of the Pd enolate and the iminium ions via α-fragmentation of the *N*,*O*-acetals. On the basis of these observations, we succeeded in developing the oxidative asymmetric Mannich-type reaction of the THIQs using DDQ as a stoichiometric oxidant. The utility of the second method was further confirmed by an efficient asymmetric synthesis of the tetrahydrobenzo[*a*]quinolizidine system.

The use of *N*,*O*-acetals is unique in asymmetric catalysis, featuring the chiral enolates under acidic conditions. Additionally, the oxidative asymmetric Mannich-type reactions show great potential to improve the overall efficiency of Mannich-type reactions as a result of skipping of the separate preparation of the unstable imines. We believe that the present results provide a basis for the development of novel asymmetric reactions.

Experimental Section

Preparation of the Pd Complexes. The aqua complexes **1a** and **3a** were prepared according to the reported procedure.[17] Dropping a solution of the crude complex in CH_2Cl_2 into stirred hexane gave pure **1a** as a yellow powder.

{(*R*)-dm-segphos}$PdCl_2$: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 12H), 2.27 (s, 12H), 5.62 (s, 2H), 5.76 (s, 2H), 6.36 (d, J = 8.4 Hz, 2H), 6.52 (t, J = 8.4 Hz, 2H), 6.99 (s, 4H), 7.26 (d, J = 12.4 Hz, 4H), 7.48 (br s, 4H); ^{31}P NMR (160 MHz, $CDCl_3$, std. 85% H_3PO_4) δ 27.9; $[\alpha]^{25}_D$ +291.7 (*c* 0.53, CH_2Cl_2).

[{(*R*)-dm-segphos}$Pd(H_2O)_2$](OTf)$_2$, 1a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 12H), 2.35 (s, 12H), 3.16 (br s, 4H), 5.72 (s, 2H), 5.89 (s, 2H), 6.53 (d, J = 8.0 Hz, 2H), 6.83 (dd, J = 8.0, 12.9 Hz, 2H), 7.16 (s, 2H), 7.19 (s, 2H), 7.25 (br s, 4H), 7.49 (br s, 4H); ^{31}P NMR (100 MHz, $CDCl_3$, std. 85% H_3PO_4) δ 33.3; ^{19}F NMR (375 MHz, $CDCl_3$, std. TFA) δ −2.2; $[\alpha]^{26}_D$ +243.2 (*c* 0.67, CH_2Cl_2).

[{(*R*)-dm-segphos}$Pd(\mu\text{-}OH)]_2$(OTf)$_2$, 3a: ^{1}H NMR (400 MHz, $CDCl_3$) δ −2.14 (s, 2H), 2.05 (s, 24H), 2.42 (s, 24H), 5.81 (s, 4H), 5.91 (s, 4H), 6.19 (dd, J = 8.3, 12.9 Hz, 4H), 6.46 (d, J = 8.3 Hz, 4H), 6.80 (s, 12H), 7.25 (s, 4H) [the number of aromatic protons is insufficient due to broadening, but integration between 6.5 and 8.5 ppm gave 24.]; ^{31}P NMR (100 MHz, $CDCl_3$, std. 85% H_3PO_4) δ 28.6; ^{19}F NMR (375 MHz, $CDCl_3$, std. TFA) δ −2.10; $[\alpha]^{27}_D$ +408.7 (*c* 0.30, CH_2Cl_2).

The anhydrous complex **2a** was prepared as follows: AgOTf (128 mg, 0.51 mmol, 2.01 equiv) was added to [{(*R*)-dm-segphos}$PdCl_2$] (180.6 mg, 0.25 mmol) in a glovebox. Dry DCM (5 mL) was added under an N_2 atmosphere, and the resulting mixture was stirred for 12 h under shielding from light. After filtration through a membrane filter (PTFE), the solvent was removed under reduced pressure to give **2a** as a yellow powder (229 mg, 80%). This was stored in a glovebox and used directly as a catalyst. Recrystallization from $CDCl_3$ gave yellow needles suitable for X-ray analysis. The 3D structure of **2a** is shown in Figure 6.

2a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 12H), 2.36 (s, 12H), 5.62 (s, 2H), 5.86 (s, 2H), 6.50 (d, J = 8.0 Hz, 2H), 6.73 (dd, J = 8.0, 12.8 Hz, 2H), 7.13 (s, 2H), 7.18 (s, 2H), 7.40 (d, J = 12.8 Hz, 4H), 7.50 (br s, 4H); ^{31}P NMR (100 MHz, $CDCl_3$) δ 33.5; ^{19}F NMR (375 MHz, $CDCl_3$) δ −1.76; $[\alpha]^{26}_D$ +329.7 (*c* 0.33, CH_2Cl_2).

A Representative Procedure for the Addition Reaction with the *N*,*O*-Acetal Protocol. The imine **4e** (300 mg, 1.57 mmol) and $(Boc)_2O$ **6a** (513 mg, 2.35 mmol, 1.5 equiv) were dissolved in DCM (1.6 mL) under a nitrogen atmosphere. The resulting mixture was stirred for 30 min at ambient temperature. Under ice-bath cooling, diisopropyl malonate **5a** (446 μL, 2.35 mmol, 1.5 equiv) and the Pd complex **1a** (18.2 mg, 0.0156 mmol, 1 mol %) were added successively. After completion of the reaction, ethyl acetate (5 mL) and brine (5 mL) were added for quenching. The aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure, followed by flash column chromatography (SiO_2, hexane−ethyl acetate or hexane−ether system, ∼6/1) of the residue afforded the desired product **7e** as a white solid (718 mg, 95% yield). The ee was determined to be 94% by chiral HPLC analysis. Full characterization data of the new compound **7j** are listed below. Analytical data of other coupling products **7** were reported in ref 16.

Preparation of 7j. This compound exists as a mixture of rotamers in a ratio of 1.3/1 in $CDCl_3$ at 22 °C. Colorless oil; IR (neat) 2971, 1731, 1683, 1364, 1293, 1153, 1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.65−2.78 (m, 0.56H [major]), 2.82−2.94 (m, 1.44H), 3.27−3.39 (m, 0.56H [major]), 3.54−3.61 (m, 0.44H [minor]), 3.68−3.72 (m, 0.44H [minor]), 3.88−3.91 (m, 1H), 3.96−4.01 (m, 0.56H [major]), 4.90- 5.23 (m, 4H), 5.96 (d, J = 6.8 Hz, 0.56H [major]), 6.05 (d, J = 8.1 Hz, 0.44H [minor]) 7.04−7.34 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.9, 28.1, 28.3, 28.4, 38.4, 40.3, 53.5, 54.0, 58.8, 59.4, 67.2, 67.3, 67.6, 80.1, 80.6, 126.0, 126.1, 126.8, 126.9, 127.5, 127.6, 128.2, 128.2, 128.3, 128.5, 128.7, 128.8, 134.3, 134.5, 134.6, 134.7, 134.9, 134.9, 135.2, 154.1, 154.7, 166.6, 166.8, 166.9, 167.0; FAB-LRMS (*m*NBA) *m*/*z* 516 $[M + 1]^+$; FAB-HRMS (*m*NBA) calcd for $C_{31}H_{34}O_6N$ $[M + 1]^+$ 512.2386, found 512.2384; $[\alpha]^{26}_D$ +25.3 (*c* 0.34, CH_2Cl_2) (66% ee); HPLC (DAICEL CHIRALCEL OD-H, *n*-hexane/IPA = 95/5, 0.5 mL/min, 254 nm, τ_{major} 16.9 mi., τ_{minor} 18.3 min.)

Preparation of 13. *N*-Boc-protected THIQs were prepared by the reaction of the amines **14** with $(Boc)_2O$ in CH_2Cl_2 and their NMR spectra were found to be identical with the data reported in the literature (**13a**, **13e**).[38]

In Situ Preparation of Carbonate 8a. To an NMR sample tube containing CD_2Cl_2 (0.7 mL) were added **4a** (13 mg, 0.1 mmol) and **6a** (22 mg, 0.1 mmol). After 10 min, clean formation of **8a** was observed by NMR. Colorless oil; IR (in CH_2Cl_2) 1736, 1705 cm^{-1} (both CO); ^1H NMR (400 MHz, CD_2Cl_2) δ 1.49 (s, 9H), 1.51 (s, 9H), 2.7−2.9 (m, 2H), 3.38 (br s, 1H), 4.04 (br s, 1H), 7.15−7.5 (m, 3H), 7.38 (s, 1H), 7.45 (d, J = 6.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 28.3, 28.4, 38.4, 79.7, 80.0, 81.9, 126.6, 127.9, 128.1, 128.8, 132.5, 135.5, 152.9, 153.8; FAB-LRMS (*m*NBA) *m*/*z* 232 [**10a**−OTf]$^+$ (decarboxylation occurred readily during the FAB-LRMS measurement).

Preparation of the *N*,*O*-Acetal 9a. The imine **4a** (13 mg, 0.1 mmol) and **6a** (22 mg, 0.1 mmol) were dissolved in toluene, and the mixture was heated to 90 °C for 1 h. Evaporation of the solvent under reduced pressure gave **9a**. This compound was a mixture of the rotamers in a ratio of 1.3/1 in $CDCl_3$ at 24 °C. IR (in CH_2Cl_2) 1692 cm^{-1} (CO); ^1H NMR (400 MHz, CD_2Cl_2) δ 1.37 (s, 9H), 1.45−1.80 (m, 9H), 2.30−2.39 (m, 1H), 2.8−3.1 (m, 1H), 3.4−3.6 (m, 1H), 3.9−4.3 (m, 1H), 6.29 (s, 0.56H [major]), 6.39 (s, 0.44H [minor]), 7.1−7.25 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 27.9, 28.2, 28.3, 28.6, 28.7, 35.9, 37.3, 74.7, 75.9, 76.9, 79.7, 80.2, 125.9, 126.0, 127.5, 127.6, 128.2, 128.4, 128.7, 129.0, 135.1, 135.2, 136.5, 136.5, 152.8, 153.6; FAB-LRMS (*m*NBA) *m*/*z* 232 [**10a**−OTf]$^+$.

Conversion to (*R*)-Calycotomine. Conversion of **7e** to **15** was conducted as described in ref 16. The product was found identical with the reported material by comparison of NMR data.[2c,27] The absolute configuration of **15** was determined by comparison of the optical rotation with the reported value.

Preparation of the Amine 14. The amines **14a** and **14e** (hydrochloride salt) are commercially available. Other amines **14c**, **14f**, and **14g** were prepared by a modified Pictet−Spengler procedure[39] and the NMR spectra were found to be identical with the data reported in the literature.[40]

14c: Yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 1.75 (br s, 1H, NH), 2.69 (t, J = 5.6 Hz, 2H), 3.09 (t, J = 5.8 Hz, 2H), 3.90 (s, 2H), 5.88 (s, 2H), 6.47 (s, 2H), 6.55 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.3, 43.9, 48.4, 100.4, 106.0, 108.8, 108.8, 127.4, 128.6, 145.5, 145.6.

14f: White solid. ^1H NMR (400 MHz, $CDCl_3$) δ 1.83 (br s, 1H, NH), 2.77 (bt, 2H), 3.11 (bt, 2H), 3.80 (s, 3H), 3.84 (s, 3H), 3.94 (s, 2H), 6.72 (d, J = 8.8 Hz, 1H), 6.74 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 43.6, 47.8, 55.9, 60.0, 110.2, 121.4, 129.0, 146.6, 150.5.

14g: White solid. ^1H NMR (400 MHz, $CDCl_3$) δ 2.18 (s, 1H, NH), 2.65 (t, J = 5.6 Hz, 2H), 3.08 (t, J = 5.8 Hz, 2H), 3.76 (s, 3H), 3.77 (s, 3H), 3.93 (s, 2H), 6.60 (d, J = 9.0 Hz, 1H), 6.63 (d, J = 9.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 43.0, 43.4, 55.5, 55.6, 106.6, 107.0, 125.0, 125.7, 149.9, 151.2.

Oxidative Mannich-Type Reaction Starting from the *N*-Boc-amine 13e. The *N*-Boc amine **13e** (29.3 mg, 0.1 mmol), diisopropyl malonate **5a** (28.5 μL, 0.15 mmol), and the Pd complex **1a** or **2a** (5 mol %) were dissolved in DCM (0.2 mL) under a nitrogen atmosphere. DDQ (25 mg, 0.11 mmol) in CH_2Cl_2 (1.5 mL) was slowly added over 5 h to the reaction mixture with a syringe pump (addition speed: 0.3 mL/h). After the addition was complete, the reaction was stirred for an additional 2 h. The mixture was diluted with ether (4 mL) and filtered through a silica pad with ether as the eluent. The obtained yellow solution was evaporated under reduced pressure and the remaining yellow oil was purified by flash column chromatography (hexane/ether = 5/1 to 4/1) to give the desired product **7e** (39.8 mg, 83% yield, 86% ee).

A Representative Procedure for the Oxidative Mannich-Type Reaction Starting from the Amine 14. The amine **14e** (19.3 mg, 0.1 mmol) and **6a** (25.3 μL, 0.11 mmol) were dissolved in DCM (0.15 mL) under a nitrogen atmosphere. After 30 min, **5a** (20.8 μL, 0.11 mmol) and **2a** (5.6 mg 0.005 mmol, 5 mol %) were added, and DDQ (22.8 mg, 0.1 mmol) dissolved in DCM (1.5 mL) was added slowly with a syringe pump (addition speed: 0.15 mL/h). After the addition was complete, the mixture was stirred for an additional 2 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and the mixture was extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. Further purification on a silica gel column gave **7e** (46.6 mg, 0.97 mmol, 97% yield, 86% ee). Recrystallization from ethyl acetate gave **7e** with 99% ee (37 mg, 0.77 mmol, 77% yield).

Preparation of 18. *tert*-Butyl acryloyl carbonate **18** was obtained in quantitative yield according to a reported procedure.[35b] IR (neat) 2985, 2939, 1795, 1744, 1632, 1405, 1372, 1253, 1199, 1170, 1133 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.56 (s, 9H), 6.03 (dd, J = 1.5, 10.6 Hz, 1H), 6.12 (dd, J = 10.6, 16.9 Hz, 1H), 6.55 (dd, J = 1.5, 16.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.4, 85.6, 126.8, 134.4, 146.9, 160.8.

Procedure for the Addition Reaction with the Acryloyl Carbonate 18. The DHIQ **4a** (13.1 mg, 0.1 mmol) was dissolved in dry DCM (0.15 mL) under a nitrogen atmosphere. The resulting solution was cooled to 0 °C and *tert*-butyl acryloyl carbonate **18** (25.8 mg, 0.15 mmol) in DCM (0.15 mL) was added dropwise. This mixture was stirred for 15 min, then diisopropyl malonate **5a** (28.5 μL, 0.15 mmol) and **1a** (5.8 mg, 0.005 mmol, 5 mol %) were added, and the resulting mixture was stirred for 16 h at 0 °C. Saturated aqueous NaCl was added for quenching and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane−ethyl acetate 3/1) afforded **19** as a colorless oil (23.2 mg, 0.062 mmol, 62%, 86% ee). This compound was a mixture of the rotamers in a ratio of 1.9:1 in $CDCl_3$ at room temperature. IR (neat) 2981, 2936, 1723, 1650, 1615, 1428, 1375, 1262, 1181, 1160, 1100, 977, 935, 906, 822, 791, 757 cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) δ 1.07 (d, J = 6.4 Hz, 1H [minor]), 1.11 (d, J = 6.4 Hz, 1H [minor]), 1.13 (d, J = 6.0 Hz, 2H [major]), 1.20−1.25 (m, 8H), 2.80−3.10 (m, 2H), 3.34 (ddd, J = 5.4, 9.5, 13.4 Hz, 0.66H [major]), 3.73 (d, J = 7.2 Hz, 0.34H [minor]), 3.80−3.98 (m, 1.34H [major + minor]), 4.47−4.54 (m, 0.66H [major]), 4.91 (quint, J = 6.1 Hz, 0.34H [minor]), 4.99−5.07 (m, 1.66H), 5.70 (dd, J = 1.7, 10.5 Hz, 0.34H [minor]), 5.73 (dd, J =

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2.0, 10.5 Hz, 0.66H [major]), 5.84 (d, J = 9.2 Hz, 0.66H [major]), 6.29 (dd, J = 2.0, 16.6 Hz, 0.66H [major]), 6.30 (dd, J = 1.7, 16.6 Hz, 0.34H [minor]), 6.43 (d, J = 7.3 Hz, 0.34H [minor]), 6.59 (dd, J = 10.5, 16.6 Hz, 0.34H [minor]), 6.93 (dd, J = 10.5, 16.6 Hz, 0.66H [major]), 7.10−7.24 (m, 3.66H), 7.43 (d, J = 7.6 Hz, 0.34H [minor]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 21.5, 21.6, 21.6, 21.7, 27.2, 28.6, 37.6, 41.3, 51.4, 54.9, 59.3, 59.5, 69.2, 69.5, 69.8, 70.1, 126.2, 126.4, 126.7, 127.5, 127.7, 127.9, 128.0, 128.1, 128.3, 128.4, 129.2, 133.7, 134.3, 134.7, 134.8, 166.0, 166.3, 166.7; FAB-LRMS (*m*NBA) *m/z* 374 $[M + 1]^+$; FAB-HRMS (*m*NBA) calcd for $C_{21}H_{27}O_5NNa$ $[M + Na]^+$ 396.1787, found 396.1792; $[\alpha]^{20}_D$ +34.0 (*c* 0.78, CH_2Cl_2); HPLC (Daicel Chiralcel OD-H, *n*-hexane/IPA = 9/1, 1 mL/min, 280 nm, τ_{minor} 40.2 min, τ_{major} 46.3).

Asymmetric Synthesis of Tetrahydrobenzo[*a*]quinolizidine Derivative. 20: The starting material **14e**·HCl (1 g, 4.3 mmol) was suspended in DCM (50 mL). At 0 °C, triethylamine (1.8 mL, 13.0 mmol) was added, and the solution was stirred for 30 min at room temperature. Acryloyl chloride (384 μL, 4.73 mmol) was slowly added at 0 °C, and the reaction mixture was stirred for 1 h at 0 °C and for 2 h at room temperature. The solution was washed with saturated aqueous NH_4Cl and brine. The organic phase was dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure, followed by flash column chromatography (SiO_2, hexane−acetone 5:1) afforded **20** as a white solid (840 mg, 79% yield). This compound was a mixture of the rotamers in a ratio of 1.2/1 in $CDCl_3$ at room temperature. IR (neat) 2840, 1650, 1610, 1519, 1460, 1431, 1201, 1120, 1016 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78−2.85 (m, 2H), 3.74−3.88 (m, 8H), 4.65 (s, 0.9H [minor]), 4.72 (s, 1.1H [major]), 5.72 (d, J = 10.5 Hz, 1H), 6.30 (s, 0.45H [minor]), 6.34 (s, 0.55H [major]), 6.57−6.68 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 29.2, 40.1, 43.7, 44.3, 47.3, 56.0, 108.8, 109.3, 111.1, 111.5, 124.0, 125.1, 125.6, 126.8, 127.7, 127.9, 147.5, 147.7, 165.6, 165.7; FAB-LRMS (*m*NBA) *m/z* 270 $[M + Na]^+$; FAB-HRMS (*m*NBA) calcd for $C_{14}H_{17}O_3NNa$ $[M + Na]^+$ 270.1106, found 270.1107.

21: The obtained **20** (247 mg, 1 mmol), **5a** (208 μL, 1.1 mmol), and **2a** (112 mg, 10 mol %) were dissolved in DCM (1.5 mL). DDQ (250 mg, 1.1 mmol) in DCM (15 mL) was slowly added over 10 h to the reaction mixture with a syringe pump (addition speed: 1.5 mL/h). After the addition was complete, the mixture was stirred for an additional 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. The solution was filtered, reduced in vacuo, and purified by flash column chromatography (hexane/ethyl acetate = 4/1 to 3/1) to give **21** as a colorless oil (309 mg, 0.72 mmol, 74% yield, 86% ee). This compound was a mixture of the rotamers in a ratio of 2.0/1 in $CDCl_3$ at room temperature. IR (neat) 2981, 2936, 1722, 1650, 1611, 1515, 1431, 1255, 1098 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, J = 6.8 Hz, 1H [minor]), 1.09 (d, J = 7.6 Hz, 1H [minor]), 1.15 (d, J = 6.4 Hz, 2H [major]), 1.18−1.25 (m, 8H), 2.70−2.78 (m, 0.67H [major]), 2.87 (t, J = 6.4 Hz, 0.67H [major]), 2.91−3.01 (m, 0.67H), 3.22−3.30 (m, 0.67H), 3.72−3.87 (m, 7.67H), 4.53−4.60 (m, 0.67H), 4.90 (q, J = 6.4 Hz, 0.33H [minor]), 4.97−5.06 (m, 1.67H), 5.67−5.74 (m, 1.67H), 6.25−6.35 (m, 1.33H), 6.54−6.62 (m, 1.33H), 6.77 (s, 0.67H [major]), 6.90 (dd, J = 6.4, 16.9 Hz, 0.68H [major]), 7.03 (s, 0.32H [minor]); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 21.5, 21.6, 21.6, 21.6 (these peaks are too close to identify), 26.9, 28.3, 37.2, 41.0, 50.9, 54.5, 55.8, 59.5, 59.7, 69.1, 69.4, 69.8, 70.0, 109.6, 110.9, 111.0, 111.5, 125.5, 126.3, 126.5, 127.6, 128.0, 128.2, 147.0, 147.1, 148.1, 148.4, 165.6, 165.9, 166.0, 166.7, 166.8, 166.9; FAB-LRMS (*m*NBA) *m/z* 456 $[M + Na]^+$; FAB-HRMS (*m*NBA) calcd for $C_{23}H_{31}O_7NNa$ $[M + Na]^+$ 456.1998, found 456.1998; $[\alpha]^{20}_D$ +63.0 (*c* 1.98, $CHCl_3$) (86% ee); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA = 4/1, 1.0 mL/min, 280 nm, τ_{minor} 9.0 min, τ_{major} 12.3 min).

22: The obtained **21** (36.4 mg, 0.084 mmol) was dissolved in dry THF (0.3 mL). One grain of NaH (paraffin 60%) was added and the reaction mixture was stirred at 35 °C for 32 h. The solution was reduced in vacuo and the residue was directly purified by flash column chromatography (hexane/ethyl acetate = 3/1 to 2/1) to give **22** as a colorless oil (26.4 mg, 0.062 mmol, 74% yield, 83% ee). IR (neat) 2978, 2936, 1732, 1712, 1670, 1516, 1464, 1454, 1411, 1264, 1229, 1195, 1173, 1145, 1121, 1105 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75 (d, J = 6.3 Hz, 3H), 1.03 (d, J = 6.0 Hz, 3H), 1.25 (d, J = 6.3 Hz, 3H), 1.28 (d, J = 6.3 Hz, 3H), 2.3−2.7 (m, 5H), 2.7−2.9 (m, 2H), 3.77 (s, 3H), 3.81 (s, 3H), 4.55 (br d, J = 11.8 Hz, 1H), 4.67 (quint, J = 6.3 Hz, 1H), 5.15 (quint, J = 6.3 Hz, 1H), 5.41 (s, 1H), 6.53 (s, 1H), 6.96 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 21.4, 21.5, 21.6, 28.4, 29.5, 29.8, 40.0, 55. 9, 55.9, 58.3, 60.2, 69.3, 69.8, 69.3, 69.8, 111.0, 111.1, 124.5, 129.8, 147.0, 148.0, 168.4, 171.0, 171.8; FAB-LRMS (*m*NBA) *m/z* 456 $[M + Na]^+$; FAB-HRMS (*m*NBA) calcd for $C_{23}H_{31}O_7NNa$ $[M + Na]^+$ 456.1998, found 456.1996; $[\alpha]^{20}_D$ −15.1 (*c* 0.41, $CHCl_3$) (83% ee); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA = 4/1, 0.5 mL/min, 280 nm, τ_{minor} 14.4 min, τ_{major} 15.7 min).

23: The diester **22** (66.3 mg, 0.15 mmol, 83% ee) was dissolved in EtOH (6.0 mL), and H_2O (3 mL) and KOH (64 mg, 7.5 equiv) were added. The reaction was refluxed for 36 h and cooled to ambient temperature, then all volatiles were removed by evaporation. The residue was dissolved in 1 N NaOH (5 mL) and washed twice with Et_2O, and the organic layer was extracted with 1 N NaOH. The combined aqueous layers were acidified with 2 N HCl to pH 1−2 and extracted with AcOEt (7 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to yield the monocarboxylic acid **23** as a white solid (31.9 mg, 0.10 mmol, 66%). Mp 227−229 °C; IR (neat) 2930, 2851, 1972 (br), 1701, 1564, 1522, 1463, 1448, 1357, 1330, 1288, 1254, 1241, 1227, 1191, 1122, 1102, 1083, 1042, 1020, 980, 955, 889, 864, 850 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 2.02−2.15 (m, 2H), 2.39 (ddd, J = 6.0, 9.2, 17.4 Hz, 1H), 2.53 (dt, J = 6.0, 17.4 Hz, 1H), 2.75 (dt, J = 4.6, 16.0 Hz, 1H), 2.92 (ddd, J = 4.6, 10.1, 16.0 Hz, 1H), 3.00−3.07 (m, 1H), 3.13 (ddd, J = 4.6, 10.1, 12.4 Hz, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 4.37 (dt, J = 4.6, 12.4 Hz, 1H), 5.05 (d, J = 7.8 Hz, 1H), 6.78 (s, 1H), 6.87 (s, 1H); ^{13}C NMR (400 MHz, CD_3OD) δ 23.3, 28.2, 30.6, 41.7, 45.0, 56.0, 56.1, 57.1, 107.7, 111.7, 127.7, 128.4, 147.5, 148.2, 169.1, 176.3; ESI-MS (MeOH) *m/z* 306 $[M + 1]^+$, FAB-LRMS (Gly) *m/z* 306 $[M + 1]^+$; $[\alpha]^{20}_D$ −57.0 (*c* 0.24, MeOH) (83% ee).

24: The acid **23** (14.2 mg, 0.046 mmol) was dissolved in DCM/MeOH (5/3, 0.8 mL) under a N_2 atmosphere. $TMSCHN_2$ (1.5 equiv, 35 μL, 2 M in diethyl ether, 0.069 mmol) was added at 0 °C. The mixture was stirred for 3 h while it was allowed to warm to room temperature. The solvent was removed by evaporation and flash column chromatography (SiO_2, DCM/MeOH = 95/5) of the residue afforded the methyl ester **24** as a colorless oil (12.7 mg, 0.040 mmol, 87%, 83% ee). IR (neat) 2954, 2928, 2854, 1732, 1639, 1519, 1464, 1439, 1360, 1331, 1259, 1224, 1167, 1119, 1019 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02−2.18 (m, 2H), 2.39 (ddd, J = 5.6, 8.4, 17.2 Hz, 1H), 2.58 (dt, J = 6.0, 17.2 Hz, 1H), 2.65−2.73 (m, 2H), 2.88−3.07 (m, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 3.86 (s, 3H), 4.58 (dt, J = 4.0, 11.2 Hz, 1H), 5.04 (d, J = 8.4 Hz, 1H), 6.58 (s, 1H), 6.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 28.3, 30.8, 41.3, 46.1, 52.5, 55.9, 56.0, 57.1, 107.8, 111.7, 127.8, 128.4, 147.5, 148.1, 168.9, 174.3; FAB-LRMS (Gly) *m/z* 320 $[M + 1]^+$; FAB-HRMS (Gly) calcd for $C_{17}H_{22}O_5N$ $[M + 1]^+$ 320.1498, found 320.1501; $[\alpha]^{20}_D$ −47.0 (*c* 0.13, DCM) (83% ee); HPLC (Daicel Chiralcel OD-H, *n*-hexane/IPA = 4/1, 1 mL/min, 280 nm, τ_{minor} 18.3 min, τ_{major} 20.9 min).

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Supporting Information Available: NMR spectra of the Pd complexes **1a**, **2a**, and **3a**, the new compounds **7j**, **18**, **19**, and **21**−**24**, experimental details of X-ray analysis, and crystallographic information files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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