DOI: 10.1002/adsc.200505199

Catalytic Enantioselective Michael Reaction of 1,3-Dicarbonyl Compounds *via* Formation of Chiral Palladium Enolate

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Received: May 16, 2005; Accepted: August 18, 2005

Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: An efficient catalytic enantioselective Michael reaction has been developed using chiral palladium complexes. Various substrates including β-keto esters and 1,3-diketones reacted with α,β-unsaturated carbonyl compounds to give the corresponding Michael adducts in good yield with up to 99% ee, thereby affording chiral quaternary carbon centers. In these reactions, chiral palladium enolates were generated as key intermediates, which acted cooperatively with a strong protic acid to activate the Michael acceptors for promotion of the C–C bond-forming reaction.

Keywords: asymmetric catalysis; 1,3-dicarbonyl compounds; Michael reaction; palladium enolates; α,β-unsaturated compounds

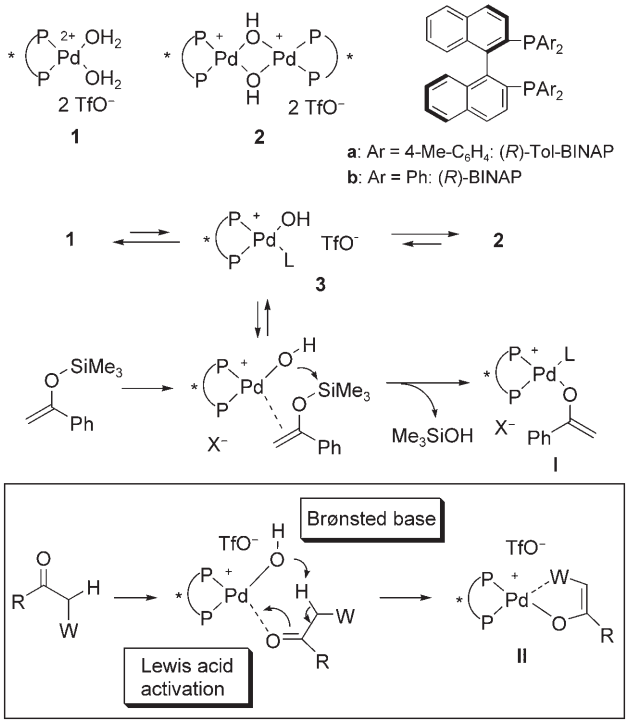
Introduction

The conjugate addition of acidic carbon nucleophiles to electron-deficient olefins, the so-called Michael reaction, is one of the most important carbon-carbon bond-forming reactions.[1] This reaction is atom-economical and environmentally benign, because complete assembly of a Michael donor and an acceptor is possible without stoichiometric pre-activation of the nucleophile. Due to the high synthetic utility of the Michael reactions, great efforts have been made for the development of efficient catalytic asymmetric Michael reactions.[2] The most frequently examined Michael donors are stabilized carbanions derived from readily enolizable compounds such as β-keto esters and malonates, although recent reports describe the use of less acidic compounds.[3] Among reactions using such nucleophiles, those involving the construction of chiral tertiary carbon centers have been well investigated. Over the past decade, great improvements have been made, and high substrate generality and excellent enantioselectivity have been achieved by developing ingenious catalysts; some of these reactions have reached the stage of practical use.[4–6] In contrast, as regards the synthesis of chiral quaternary carbon centers,[7] the number of general methods applicable to active methine compounds is quite limited.[8] After the early reports on the catalytic enantioselective Michael reaction,[9] which was demonstrated using the reaction of 1-oxo-2-indanecarboxylate with methyl vinyl ketone, this β-keto ester has been used as a model substrate. Even though Cram et al. achieved an outstanding enantioselectivity of 99% using a binaphthol-derived chiral crown ether,[10] most of the reported catalysts are effective only for this specific substrate, and expanding the scope of usable β-keto esters has been difficult until recently.[11,12] The most general catalyst for this transformation has been Shibasaki's LSB complex.[13] However, even this reaction sometimes requires high catalyst loading, low temperature, and a toxic solvent such as dichloromethane for high asymmetric induction. On the other hand, inspired by Saegusa's and Nelson's early reports on Cu- and Ni-catalyzed Michael reaction,[14] transition metal complexes have attracted attention as mild catalysts.[15] Among several chiral complexes of transition metals complexes including Co,[11a,b] Cu,[11e] Ni,[11b,f] Ru,[11g] Sc,[11h,i] only an Ag-BINAP complex was examined with several β-keto esters, affording the desired products with up to 83%

ee.[16] Thus, there is still much room to improve this type of Michael reaction, and development of a novel catalyst with high substrate generality and enantioselectivity remains highly desirable.

Previously, we reported a catalytic asymmetric aldol reaction and a Mannich-type reaction using chiral palladium complexes **1** and **2**.[17,18] In these reactions, the Pd complexes reacted with silyl enol ethers to give chiral palladium enolate **I** as a reactive intermediate.[19,20] For the generation of this palladium enolate, a hydroxo ligand on the palladium plays an important role as a nucleophile for promoting cleavage of the oxygen-silicon bond of silyl enolate (Scheme 1).

Although a role of the hydroxo ligand in transmetallation has been suggested in several reactions,[21] the possibility of a ligand acting as a Brønsted base has rarely been examined in synthetic organic chemistry. It is anticipated that the Pd complexes **1** and **2** are in equilibrium with the Pd hydroxo complex **3**. Because the Pd complex **3** would show both Lewis acidity and Brønsted basicity, it should react with carbonyl compounds to give chiral enolates directly. Indeed, achiral palladium hydroxo complexes were reported to react with active methylene compounds to form Pd enolates.[22] But, the use of these enolates in organic synthesis has been limited.[22c,23] We expected that such enolates would undergo nucleophilic reactions with various electrophiles under mild and non-basic conditions and thus, reactions that are difficult under conventional basic conditions should become feasible. As a first step, we planned to examine the generation of chiral palladium enolates **II** from carbonyl compounds bearing an electron-withdrawing group, based on the following assumptions: 1) An acidic proton of such compounds would be abstracted even by weakly basic PdOH; 2) Bidentate nature of the substrate would be favorable for the formation of the enolate. This mild activation would be useful for development of an efficient Michael reaction which is applicable to various 1,3-dicarbonyl compounds. Herein we wish to report full details of the development of a novel catalytic asymmetric Michael reaction.[24] Under our reaction conditions, various compounds were converted to the Michael adducts with high to excellent enantioselectivity. In some diastereoselective reactions, highly crowded vicinal tertiary and quaternary carbon centers were created in a single step (up to 99% ee). In addition, several rarely exploited starting materials such as 1,3-diketones and α,β-unsaturated aldehydes, which are unstable under basic conditions, were successfully employed. Finally, mechanistic studies revealed that chiral palladium enolates were generated in accordance with our hypothesis, and we propose a unique cooperative action of the palladium enolate with a strong protic acid to activate the Michael acceptors.



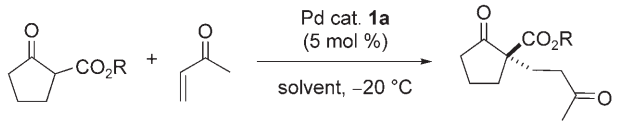
Scheme 1. Formation of chiral palladium enolate under mild conditions.

Results and Discussion

Catalytic Enantioselective Michael Reaction of β-Keto Esters

Initially, the reaction of the cyclic β-keto ester **4** with methyl vinyl ketone (**7a**) was carried out in CH_2Cl_2 under the influence of the palladium complex **1a** (5 mol %) (Table 1, entry 1). To our delight, the reaction proceeded smoothly at $-20\,^{\circ}C$, affording the corresponding Michael adduct in 83% yield, although the enantioselectivity of the product was only 25%. Interestingly, the ee of the product was increased with increasing the size of the ester moiety, and a high enantioselectivity of 89% was obtained when the *t*-Bu ester **6a** was used (entries 1–3). For this substrate, the reactivity of **1a** and **1b** seemed similar, but **1a** gave better enantioselectivity (entries 3 and 4). Further studies revealed that THF and acetone were good solvents (entries 5 and 6), and the best enantioselectivity (94% ee) was obtained in THF. Increasing the concentration of **6a** was effective for acceleration of the reaction, and **10a** was obtained after 24 h in 92% yield with 92% ee (entry 7). When the reaction was carried out without solvent, the ee was slightly decreased (entry 8). Notably, the Michael reaction proceeded even in alcoholic solvents and water due to the stability of the palladium complexes to protic solvents (entries 9–11). The fact that similarly high enantioselectivity was observed in most cases, regardless of the nature of the solvents, implies that the reac-

Table 1. Optimization of the reaction conditions.



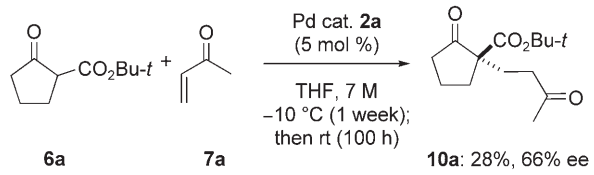
4 – 6a 7a 8 – 10a

Entry	Ester: R	Solvent	Conc. [M]	Time [h]	Product	Yield [%]	ee [%]
1	**4**: Me	CH_2Cl_2	1	24	**8**	83	25
2	**5**: Et	CH_2Cl_2	1	24	**9**	90	38
3	**6a**: *t*-Bu	CH_2Cl_2	1	36	**10a**	96	89
4[a]	**6a**	CH_2Cl_2	1	36	**10a**	97	82
5	**6a**	acetone	1	12	**10a**	92	90
6	**6a**	THF	1	84	**10a**	87	94
7	**6a**	THF	4	24	**10a**	92	92
8	**6a**	-	-	15	**10a**	quant.	88
9	**6a**	MeOH	1	72	**10a**	77	88
10	**6a**	EtOH	1	72	**10a**	72	91
11[a,b]	**6a**	H_2O	4	24	**10a**	92	86

[a] The Pd catalyst **1b** (5 mol%) was used.
[b] 4 °C.

tion might proceed through a configurationally stable common intermediate.

In striking contrast to **1**, the palladium μ-hydroxo complexes **2** were found to be less reactive (Scheme 2). Thus, the reaction of **6a** with **7a** in the presence of 5 mol % of **2a** (10 mol % Pd) resulted in only 28% yield even after 100 h at room temperature, and the ee was reduced to 66%.



6a 7a **10a**: 28%, 66% ee

Scheme 2. Michael reaction using **2a** as a catalyst.

To define the scope of this reaction, we next examined various β-keto esters (Table 2). Under the optimized reaction conditions, other cyclic and acyclic substrates reacted in a highly enantioselective manner (entries 2–4). In addition to the *t*-Bu ester, aryl esters also gave excellent enantioselectivities (~94% ee) (entries 5 and 6). Unfortunately, however, this reaction was sensitive to steric factors at other parts of the substrates. For example, when the bulkier ethyl-substituted compound **6g** was used, the desired product **10g** was obtained in only 41% yield, even after stirring for 1 week at room temperature (65% ee) (entry 7). Other substrates **6h–j** gave less satisfactory results [8%, 35% ee (3 weeks, rt); 88%, 30% ee (–20 °C, 54 h), 58%, 71% ee (66 h, 0 °C), respectively]. Notably, in the case of **6a**, the amount of catalyst could be reduced to as little as 2 mol % without any deterioration of the reaction efficiency (93%, 93% ee) (entry 8). In addition to **7a**, ethyl vinyl ketone (**7b**) was also used (entries 9, 10). There are a few reports in which more than 90% ee was achieved for one specific β-keto ester. In contrast, the catalyst reported here showed high asymmetric induction for various substrates, which would be useful for the synthesis of quaternary carbon centers. On the other hand, other acidic substrates, such as α-phenyl-α-cyano esters and β-ketophosphonates, gave unsatisfactory results.

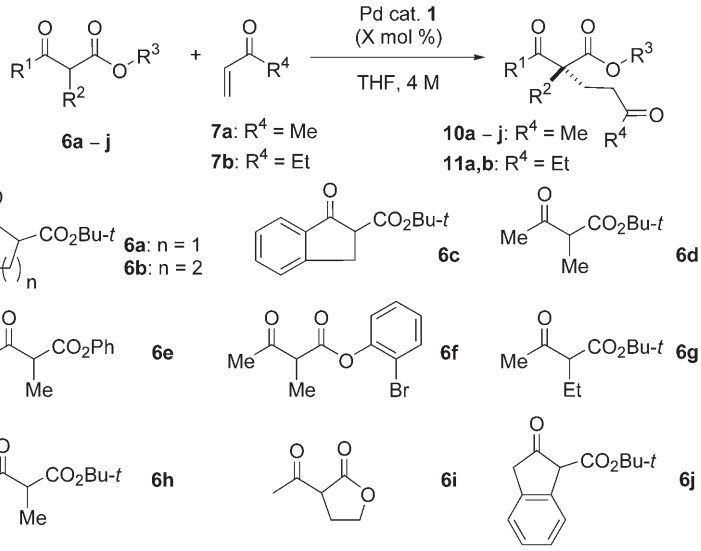
To determine the absolute configuration, **10b** was subjected to cyclization with pyrrolidine/AcOH, followed by usual transformations, and **12** was obtained without loss of enantioselectivity (Scheme 3). The same compound was also synthesized from the Michael adduct prepared by Belfield's method,[25] and the absolute configuration of **10b** was determined to be *R* by comparison of the retention times on chiral HPLC. Those of the other Michael adducts **10a**, **10c**, and **10e** were established directly or after transesterification by comparison with reported values of optical rotation.[26] In addition to these transformations, **10a** was subjected to Baeyer–Villiger reaction, and the lactone **13** having a unique quaternary chiral center was formed in 63% yield (Scheme 4); this result should enhance the usefulness of our Michael reaction.

Diastereo- and Enantioselective Michael Reaction

The success mentioned above led us to investigate the diastereoselective reaction with β-substituted enones. In spite of significant progress in asymmetric synthesis, it is still difficult to construct sterically hindered vicinal tertiary and quaternary carbon centers in an enantioselective manner. Even after we communicated our preliminary results, there have been, to our knowledge, only a few examples of diastereo- and enantioselective conjugate addition of acidic carbon nucleophiles.[4e,5c,6a,6f]

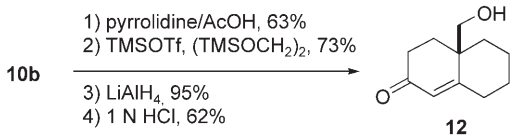
In the presence of 5 mol % of **1b**, the reaction of **6a** with less reactive β-substituted acceptors **14** proceeded smoothly (Table 3). The reaction with 3-penten-2-one (**14a**) afforded the desired product **15a** in 89% yield with 8/1 diastereoselectivity. Surprisingly, the ee of the major product was 99% (entry 1). The phenyl-substituted enone **14b** also underwent the Michael reaction with moderate diasreteoselectivity and excellent enantioselectivity (dr = 3.6/1, 97% ee) (entry 2). When *cis*-enones such as cyclopentenone (**14c**) and cyclohexenone (**14d**) were examined, the observed diastereoselectivity was poor. But, the enantioselectivity of both diastereomers was still excellent (86–97% ee) (entries 3 and 4). In addition, dimethyl ethylidenemalonate (**14e**) could be used, and the corresponding adduct **15e** was obtained with 96% ee (79%, dr = 2.9/1). In these reactions, high enantioselectivity was always attained regardless of

Table 2. Enantioselective Michael reaction of various β-keto esters catalyzed by **1**.

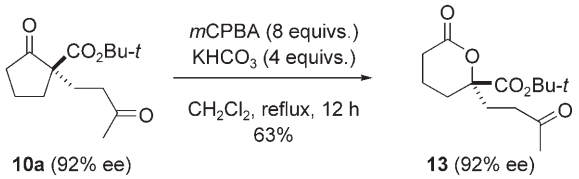


Entry	6	Enone	1 [mol %]	Temp. [°C]	Time [h]	Product	Yield [%]	ee [%]	Conf.
1	**6a**	**7a**	**1a** (5)	–20	24	**10a**	92	92	*R*[a]
2	**6b**	**7a**	**1b** (5)	0	72	**10b**	92	90	*R*[a]
3[b]	**6c**	**7a**	**1a** (10)	–20	48	**10c**	88	89	*S*[c]
4	**6d**	**7a**	**1b** (10)	0	72	**10d**	88	90	-
5	**6e**	**7a**	**1a** (10)	0	72	**10e**	69	93	*R*[a]
6	**6f**	**7a**	**1b** (10)	0	36	**10f**	82	94	-
7	**6g**	**7a**	**1b** (10)	rt	1 w	**10g**	41	65	-
8	**6a**	**7a**	**1b** (2)	–20	40	**10a**	93	93	*R*[a]
9	**6a**	**7b**	**1b** (5)	–20	20	**11a**	84	88	-
10	**6b**	**7b**	**1b** (5)	0	72	**11b**	89	86	-

[a] The absolute configuration was determined after conversion to known compounds.
[b] 1 M **6c**.
[c] See ref.[11i]



Scheme 3. Conversion of **10b**.



Scheme 4. Baeyer–Villiger oxidation of **10a**.

the structural difference of the electrophiles, and this might be attributed to excellent face selectivity of the putative Pd enolates. Unfortunately, however, the diastereoselective reaction was not effective with β-keto esters other than **6a**, probably due to the lower reactivity of the substrates.

To determine the relative configuration, the minor product of **15a** was converted to the bicyclic compound **16** (Scheme 5).[27] The structure of **16** was unequivocally determined by a single-crystal X-ray structural analysis (Figure 1). Consequently, coupled with the determined absolute configuration of **10**, the stereochemistry of the major product of **15a** was deduced to be *R* both at the quaternary and tertiary carbon centers. This relative stereochemistry was confirmed by NOE measurements, which were carried out for the bicyclic compounds **17** and **18**.

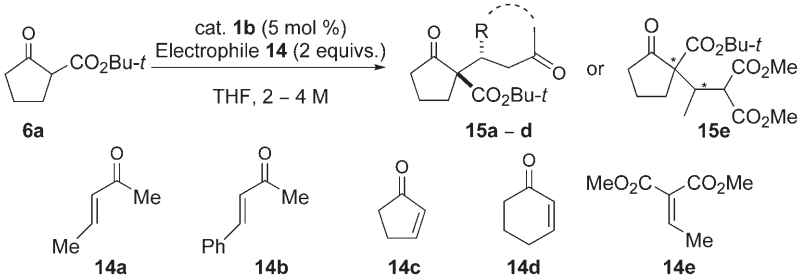
Michael Reactions using Rarely Investigated Starting Materials

α,β-Unsaturated Aldehydes

The reaction of β-ketoesters with enones provides a good method for the synthesis of chiral 1,5-dicarbonyl compounds. The product, however, has two keto groups, which potentially circumvents further selective functionalization. If α,β-unsaturated aldehydes can be used, the three carbonyl groups of the Michael adducts can in principle be discriminated easily.[28] Therefore, we next planned to examine the use of acrolein **19** (Table 4). Because of its high reactivity, the reaction of **6a** in THF gave a complex mixture, and the corresponding dimethyl acetal **20a** was isolated in only 10% yield, but with 90% ee, after treatment with MeOH (entry 1). We speculated that formation of undesired by-products would be induced by the reaction of the aldehyde in the product. Considering that the Michael reaction proceeded well even in alcoholic solvents (see, Table 1), we envisaged that the reaction in MeOH might prevent undesired reactions by protecting the aldehyde moiety as an acetal. As we hoped, the chemical yield was greatly improved (entries 2,3) when MeOH was used as a solvent. The reaction at 0 °C afforded the desired dimethyl acetal in 73% yield with 87% ee. In addition, **6b** was converted to the corresponding acetal **20b** with 80% ee, although the reaction was slow (entry 4).

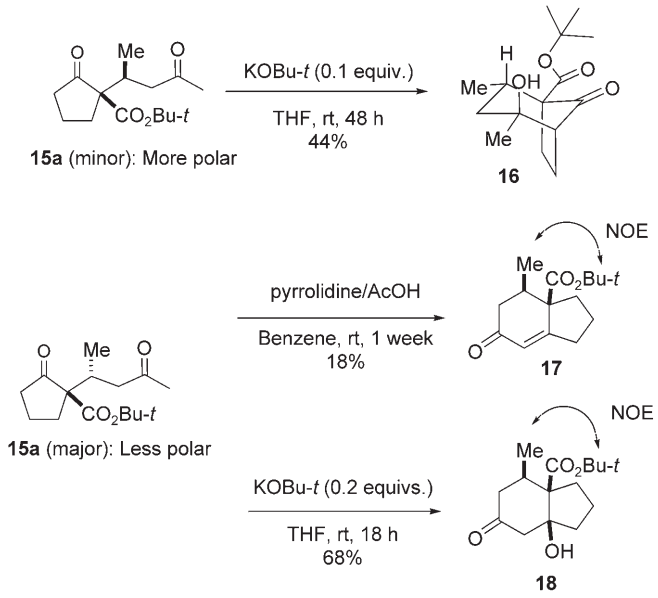
When crotonaldehyde (**21**) was used, formation of the by-products was suppressed even in THF, and subsequent addition of MeOH afforded the dimethyl acetal **22** in 90% yield (Scheme 6). Although diastereoselectivity was moderate, which was revealed by ^{1}H-NMR analysis of the crude products, the ee of the major product was as high as 99%. It should be noted that the dimethyl

Table 3. Catalytic diastereo- and enantioselective Michael reaction of **6a**.



Entry	Electrophile	Temp. [°C]	Time [h]	Product	Yield [%]	dr[a]	ee [%][a]
1	**14a**	–20	24	**15a**	89	8/1	99/-[b]
2	**14b**	0	36	**15b**	83	3.6/1	97/-[b]
3	**14c**	rt	12	**15c**	85	1.2/1	93/86
4	**14d**	rt	12	**15d**	98	1.6/1	96/97
5	**14e**	0 – rt	72	**15e**	79	2.9/1	96/-[b]

[a] Major/minor. The dr was determined on the basis of ^{1}H-NMR analysis of the crude products. For details, see Supporting Information.
[b] Not determined.



Scheme 5. Conversion of **15a**.

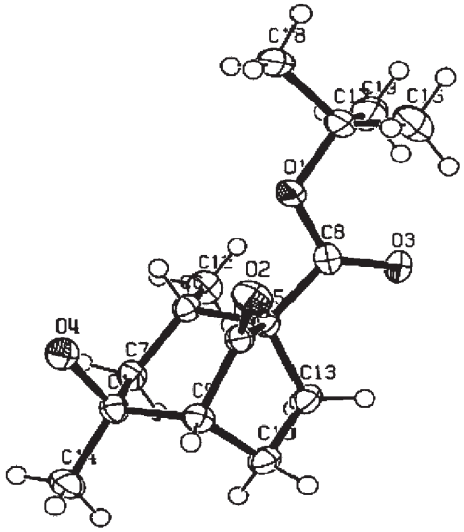


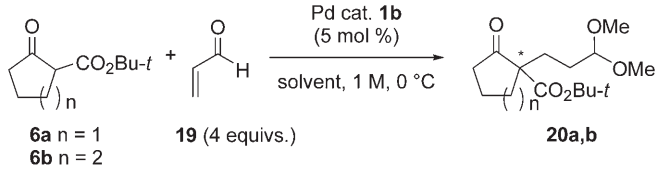
Figure 1. X-ray structure of **16**.

acetal was obtained directly, which would be of use for further chemoselective transformation.

1,3-Diketones

Presumably because 1,3-diketones and their Michael adducts are thought to be unstable under basic conditions, there has been no report of the use of 1,3-diketones in catalytic asymmetric Michael reactions.[29] In contrast, our reaction conditions were found to be effective for such compounds (Scheme 7). In the presence of 10 mol % of **1b**, the reactions of **23a** and **23b** proceeded well with high enantioselectivity (90% ee, respectively). As in the case of the reaction of β-keto esters, the steric demand of R^3 was important for high asymmetric induction, and the reaction of less bulky **23c** and **23d** gave ees of around 70% [**24c**: 50%, 72% ee (20 h); **24d**: 76%, 73% ee (48 h)]. In contrast with the common basic conditions (triethylamine, DBU, *t*-BuOK, or tetrabutylammonium hydroxide) under which none of the desired products was obtained due to instability,[30] this reaction system gave the desired triketone in high yield. These examples, including the reactions of α,β-unsaturated aldehydes, indicate that our reaction system is quite mild.

Table 4. Catalytic enantioselective Michael reaction with acrolein.



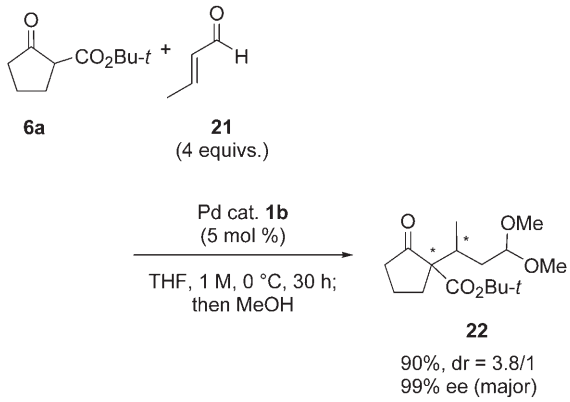
6a n = 1
6b n = 2

19 (4 equivs.)

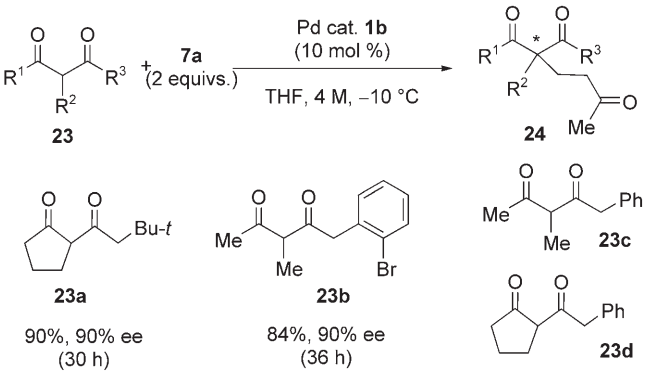
20a,b

Entry	6	Solvent	Temp. [°C]	Time [h]	Product	Yield [%]	ee [%]
1[a]	**6a**	THF	0	26	**20a**	10	90
2	**6a**	MeOH	rt	18	**20a**	71	84
3	**6a**	MeOH	0	48	**20a**	73	87
4	**6b**	MeOH	rt	120	**20b**	31	80

[a] After **6a** was consumed, MeOH was added.



Scheme 6. Diastereo- and enantioselective Michael reaction with crotonaldehyde.

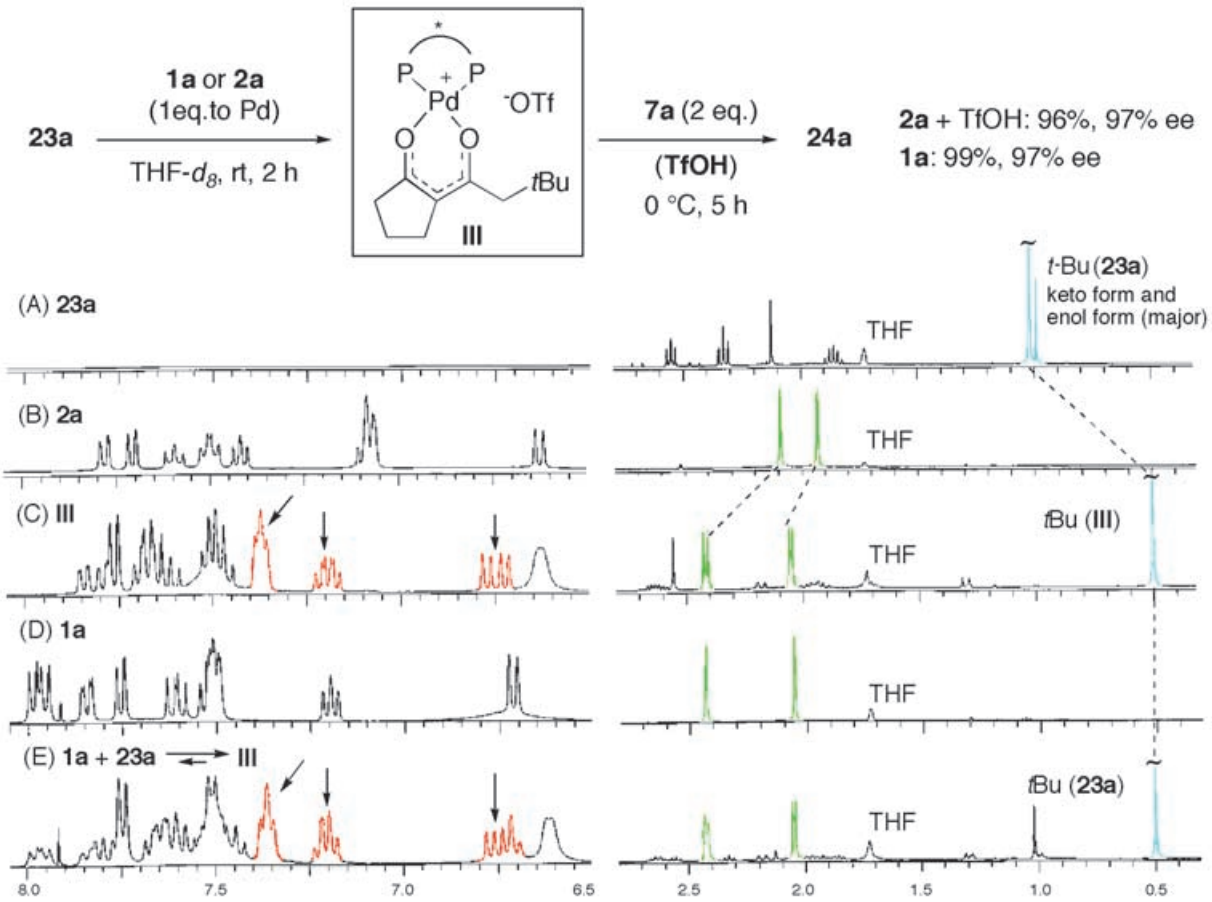


Scheme 7. Catalytic asymmetric Michael reaction of 1,3-diketones.

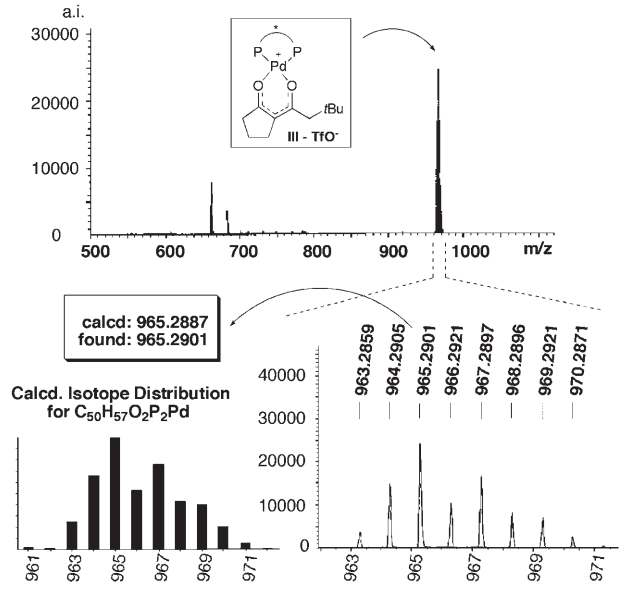
Mechanistic Studies

In order to gain insight into the reaction mechanism, we next carried out NMR experiments using **23a** as a model compound.[26] The results are summarized in Scheme 8. In accord with our hypothesis, clean formation of the palladium enolate **III** was observed by ^{1}H NMR when **23a** was treated with 0.5 equivalents of **2a** (Pd : **23a** = 1 : 1) in THF-d_8 for 2 h.[22] The singlets (1.0 ppm, blue) derived from *t*-Bu of **23a** were moved upfield by 0.5 ppm due to the anisotropic effect of the neighboring tolyl group (A, C). The two characteristic singlets (green) of the tolyl groups at 1.9 and 2.1 ppm changed to four singlets, 2.05, 2.06, 2.40, and 2.42 ppm, indicating that the four methyl groups on (*R*)-Tol-BINAP were located in different environments (B, C). In the aromatic field, the original peaks changed and distinct peaks appeared (red). As shown in Scheme 9, observation of M^+ by ESI mass spectroscopy strongly supported the formation of the Pd-enolate **III**.[31] To examine the nucleophilicity of **III**, **7a** (2 equivs.) was added to this mixture. Unfortunately, however, the reaction did not proceed, probably because the square-planar palladium diketonato complex is very stable, and the bidentate coordination of **23a** might prevent the Lewis acidic activation of the enone. Interestingly, the addition of 1 equivalent of TfOH was found to be effective to promote the reaction.[32] The Michael product **24a** was obtained in 96% isolated yield (5 h, 0 °C) and the enantioselectivity was determined to be 97%. Notably, after completion of the reaction, formation of the Pd aqua complex **1a** was observed by ^{1}H-NMR. We then performed similar experiments using **1a** (D, E). Upon mixing **1a** and **23a** in THF-d_8 at room temperature, characteristic peaks of the same Pd enolate were detected even though the reaction had reached an equilibrium point between **23a**, **1a**, and **III** (C, E). After the addition of **7a** (2 equivs.) to the mixture, **23a** was converted smoothly to **24a** with the same absolute stereochemistry in 5 h without the addition of TfOH, and results comparable to those above were obtained (99%, 97% ee). Interestingly, a similar phenomenon was observed when the β-keto ester **6a** was treated with **2a**, whereas the amount of the detectable enolate was significantly reduced when **6a** was mixed with **1a**.

These results indicate that the coordinating hydroxo ligand of **3** can abstract an acidic α-proton of the substrate to form the palladium enolate **III**. Because the same Pd enolate was observed in both cases [Scheme 8, (C) and (E)], the Pd enolate **III** would be an important intermediate. Moreover, it is likely that participation of TfOH was essential for this reaction. When TfOH was added to the solution of **III**, some of the enolates would be protonated, and then **1a**, **23a**, and **III** would exist as an equilibrium mixture, which raises the possibility that the remaining **1a** would activate the enone as a Lewis acid to promote the reaction. If this is the case, kinetic data would show a second-order dependency on the concentration of the catalyst, because two Pd complexes should be involved in the C–C bond-forming step, which is expected to be the rate-determining step.



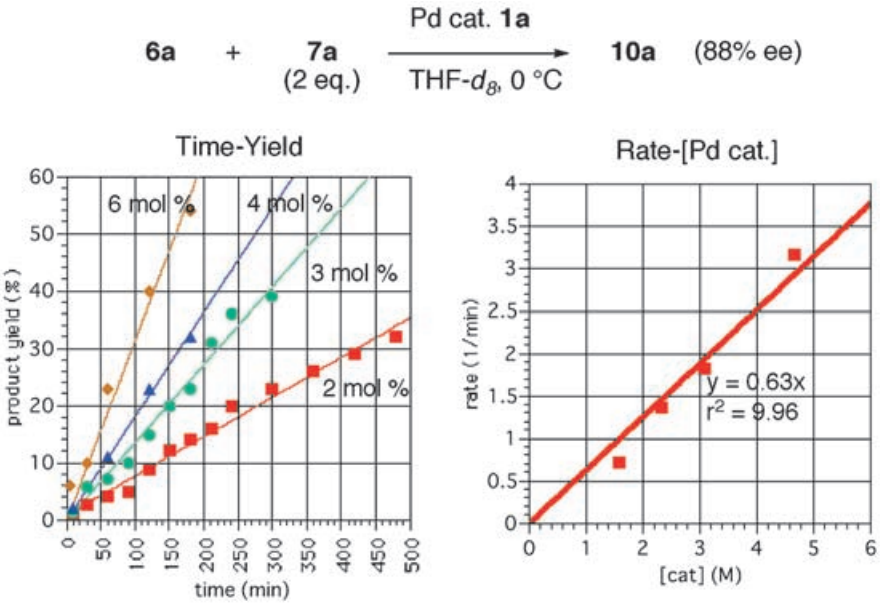
Scheme 8. Mechanistic studies using ^{1}H NMR measurements. ^{1}H NMR spectra in THF-d_8: (A) **23a**; (B) **2a**; (C) reaction mixture 2 h after the addition of **23a** (1 equiv.) to **2a** (0.5 equivs.); (D) **1a**; (E) reaction mixture 2 h after the addition of **23a** (1 equiv.) to **1a**.



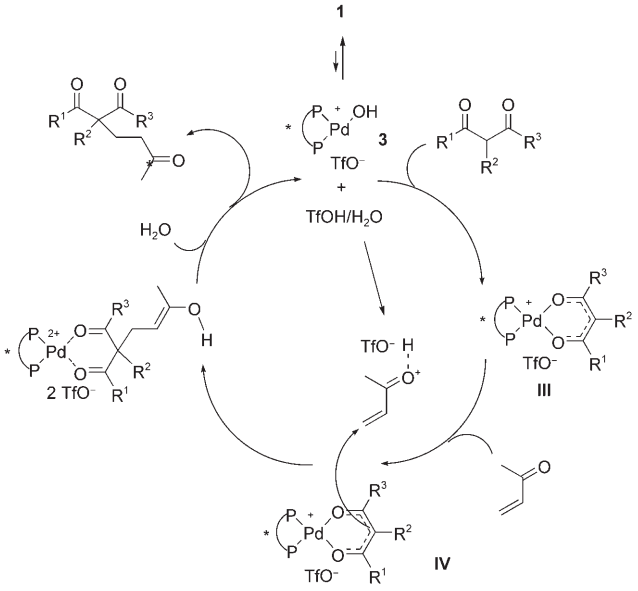
Scheme 9. ESI-MS measurement of the Pd enolate **III**.

When the reaction profiles were measured at several catalyst concentrations (Scheme 10, left), the reaction was revealed to be first-order-dependent on the catalyst concentration (Scheme 10, right). This implies that only one Pd complex existing as the enolate was operative in the C–C bond-forming step. Consequently, we speculate that **1a** did not act as a Lewis acid, and rather it is TfOH that favorably activates the enone.

A proposed catalytic cycle is presented in Scheme 11. From the palladium aqua complex, a Brønsted base (PdOH) and a Brønsted acid (TfOH) are generated as a result of an equilibrium reaction. The former activates the nucleophile to give the chiral palladium enolate **III** and the latter cooperatively activates the enone. Concerning to the enolization step, we cannot rule out the possibility that Lewis acidic activation of the nucleophiles by the cationic Pd(II) complex allows an acidic proton to be abstracted by a weak base, such as water molecules. The enolate **III** could undergo Michael reaction with the aid of TfOH to activate the enone (**IV**). Finally, tautomerization of the resulting enol to the ketone, followed by ligand exchange reaction, completes the catalytic cycle. It is interesting that the strong protic



Scheme 10. Kinetic profile of the Michael reaction catalyzed by **1a**.



Scheme 11. Proposed catalytic cycle.

acid and inherently basic palladium enolate seem to act cooperatively to promote the C–C bond-forming reaction.

The observed absolute configuration of the products can be explained by postulating involvement of the configurationally stable, square-planar palladium enolate shown in Figure 2.[33] The bulky ester (*t*-Bu) would avoid steric interaction with the aryl group located at one side of the enolate face. Thus, the *Si* face of the palladium enolate is blocked preferentially, and the incoming enone would react with palladium enolate at the *Re* face in a highly enantioselective manner. On the other hand, face selection of the enone would be responsible for the relative configuration. Since the proton is proposed to activate the enone, a linear transition state model is plausible. The enone might react with the Pd enolate from the *Re* face, with a substituent at the β-position directed to the less crowded space in the chiral environment. This model is in accord with the absolute and relative stereochemistry observed in this Michael reaction.

Conclusion

We have succeeded in developing a highly enantioselective Michael reaction of 1,3-dicarbonyl compounds using chiral palladium enolates as key intermediates. This reaction was applicable to various substrates, including β-keto esters, and unstable substrates such as 1,3-diketones and α,β-unsaturated aldehydes. In some cases, diastereoselective reactions with β-substituted enones were successfully demonstrated, enabling simultaneous construction of highly crowded vicinal tertiary and quaternary carbon centers (up to 99% ee). The mechanism of this reaction appears to be unique. The Pd complexes **1** function as an acid-base catalyst to activate both Michael donors and acceptors, and the C–C bond-formation is promoted by cooperative action of chiral Pd enolate with a concomitantly formed strong protic acid. We believe that the unique character of the Pd complexes **1** will be of use for the development of novel asymmetric reactions. Further studies are currently under way in our laboratory.

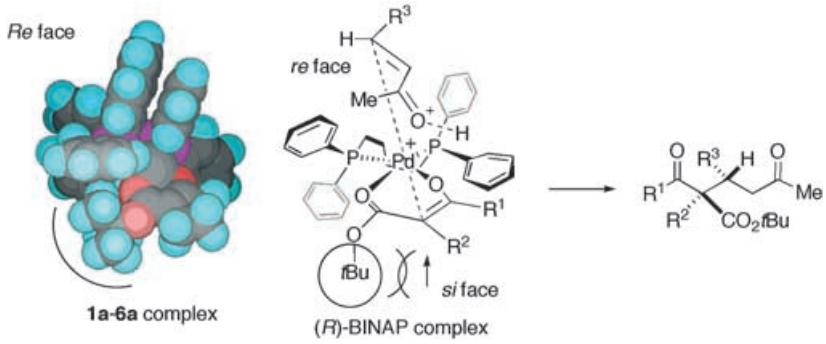


Figure 2. Working hypothesis for the transition state model of the Michael reaction.

Experimental Section

General Remarks

NMR spectra were recorded on a JEOL JNM-LA400 spectrometer, operating at 400 MHz for ^{1}H NMR, and 100.4 MHz for ^{13}C NMR. Chemical shifts were reported downfield from TMS ($\delta = 0$) for ^{1}H-NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to the solvent used as an internal reference. FAB-MS (low and high resolution) were taken on a JEOL JMS GCmate II using *m*-nitrobenzyl alcohol (*m*NBA) as the matrix. ESI-MS experiments were carried out using a Bruker Bio-TOF II. Optical rotations were measured on a JASCO DIP-370 polarimeter. Column chromatography was performed with silica gel 60 (40–100 μm) purchased from Kanto Chemical Co. The enantiomeric excesses (ees) were determined by HPLC analysis. HPLC analysis was performed on Shimadzu HPLC systems: pump, LC-10AD; detector, SPD-10A measured at 254 nm or 280 nm; column, DAICEL CHIRALPAK AS, AD, AD-H or DAICEL CHIRALCEL OJ, OD, OD-H, OB-H; mobile phase, hexane/2-propanol (IPA). Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Other reagents were purified by usual methods.

General Procedure for the Catalytic Enantioselective Michael Reaction

The palladium catalyst **1** (0.02 mmol, 5 mol%) was dissolved in a solvent (0.1 mL, 4 M). To this solution was added the 1,3-dicarbonyl compound (0.4 mmol) at ambient temperature. At the indicated temperature, the enone (0.8 mmol, 2 equivs.) was added. The resulting mixture was stirred at the same temperature. After completion of the reaction (TLC), saturated aqueous NH_4Cl (2 mL) was added for quenching. In the case of the reactions with acrolein, MeOH (0.5 mL) was added before addition of NH_4Cl, and the mixture was stirred for 30 min. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, and dried over Na_2SO_4. Removal of the solvent under reduced pressure, followed by flash column chromatography, (SiO_2, eluent: hexane-ethyl acetate system) afforded the desired product.

Spectral data of the new compounds and experimental procedures for the conversion of the products are given in Supporting Information.

X-Ray Crystallographic Study of *rac*-16

The molecular structure of *rac*-**16** was determined by a single-crystal X-ray analysis. All measurements were made on a Rigaku-RAXIS-RAPID imaging plate area detector with graphite-monochromated MoKα radiation.

Molecular formula: $C_{15}H_{24}O_4$, molecular weight: 268.35, unit-cell dimension: $a = 6.6478(2)$ Å, $\alpha = 90°$, $b = 20.9357(6)$ Å, $\beta = 98.092(1)°$, $c = 11.0490(3)$ Å, $\gamma = 90°$, $Z = 4$, $d = 1.17$ g/cm^3, crystal system: monoclinic, space group: $P2_1$, crystal size, $0.30 \times 0.40 \times 0.20$ mm, temperature: 133 K, theta range: 2.7 to 30.0°, reflections measured: 17640, independent reflections: 4562 ($R_{int} = 0.064$), linear absorption coefficient: 0.8 cm^{-1}, transmission factors: 0.30 to 1.43, structure solution: direct method, refinement method: full-matrix least-squares on F^2, reflection/parameter ratio: 14.52, goodness on fit indicator: 1.00, R1 = 0.076, wR2 = 0.234. programs used: CrystalStructure 2.00: Crystal Structure Analysis Package, Rigaku and MSC (2001).

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-271705. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk].

Procedure for Kinetic Measurements

A dry NMR tube was charged with **6a** (100 μL, 0.543 mmol), **7a** (90 μL, 1.09 mmol), and THF-d_8 (0.51 mL). CH_2Cl_2 (20 μL) was added as an internal standard. In each run, $[\mathbf{6a}]_0 = 0.78$ M, $[\mathbf{7a}]_0 = 1.56$ M. To this mixture was added **1a** (2, 3, 4, and 6 mol % to **6a**, respectively) under ice-bath cooling. The sample was quickly loaded into an NMR machine, of which the probe was cooled to 0 °C. Formation of the Michael adduct was measured by comparison of the integration ratio between added CH_2Cl_2 (5.52 ppm) and the generated product **10a** (2.57–2.64 ppm). In this way, the initial rate of reaction was calculated for each run [Scheme 10 (left)]. A linear relation-

ship between the velocity of the reaction and the concentration of the catalyst was obtained [Scheme 10 (right)].

Acknowledgements

This work was supported in part by PRESTO project of JST. Y. H. thanks JSPS for a Grant-in-Aid for Encouragement of Young Scientists (B). We also thank Mr. Higo of Nihon Bruker Daltonics K. K. for ESI-MS measurements.

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[32] TfOH itself was reported to promote the Michael reaction to give a racemic product, see: H. Kotsuki, K. Arimura, T. Ohishi, R. Maruzasa, *J. Org. Chem*. **1999**, *64*, 3770–3773; see also for hetero-Michael addition reactions: T. C. Wabnitz, J.-Q. Yu, J. B. Spencer, *Chem. Eur. J.* **2004**, *10*, 484–493.

[33] The space-filling model depicted in Figure 2 was generated by MM3 calculation using CAche 5.0.

