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Direct Generation of Nucleophilic Chiral Palladium Enolate from 1,3-Dicarbonyl Compounds: Catalytic Enantioselective Michael Reaction with Enones

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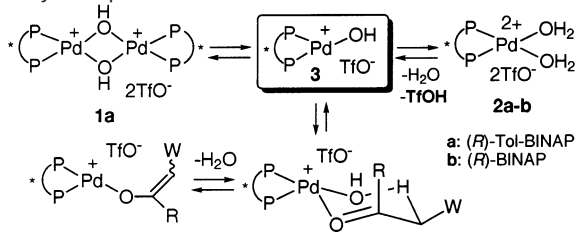
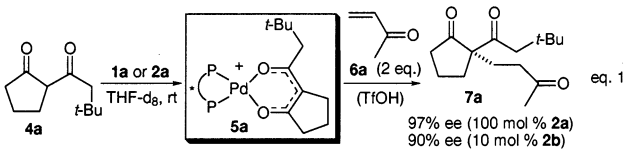
We recently reported catalytic generation of chiral palladium enolate from silyl enol ether using Pd complexes, **1** and **2**.[1] In this reaction, water or hydroxo ligand plays an important role as a nucleophile for promoting cleavage of the oxygen−silicon bond of silyl enolate. Although a role of hydroxo ligand in transmetalation has been suggested in several reactions,[2] the nature of the ligand as a Brønsted base has not been thoroughly evaluated in synthetic organic chemistry. On the basis of our palladium enolate chemistry, we anticipated that the Pd complexes **1** and **2** are in equilibrium with the monomeric Pd hydroxo complex **3**, which would show two distinct functions, Lewis acidity and Brønsted basicity. Pd complex **3** would react with carbonyl compounds to give chiral enolates, through a favorable six-membered transition state (Scheme 1). The resulting palladium enolate is expected to make possible the direct enantioselective functionalization of carbonyl compounds with a wide variety of electrophiles under mild and nonbasic conditions. As a first step, we herein describe the generation of chiral palladium enolates of 1,3-dicarbonyl compounds and its application to the efficient catalytic enantioselective Michael reaction with α,β-unsaturated ketones.

Scheme 1. Generation of PdOH and Direct Enolate Formation of Carbonyl Compounds

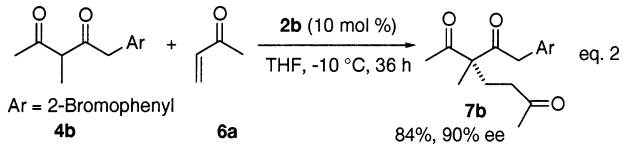


Catalytic asymmetric Michael reaction of active methylene compounds is now a powerful and reliable method for the synthesis of chiral tertiary carbon centers.[3] As for the construction of quaternary carbon centers,[4] after the first report on the reaction of 1-oxo-2-indanecarboxylate with methyl vinyl ketone using chiral bases,[5] several catalysts effective only for this specific substrate have been reported.[6] Therefore, development of an efficient catalyst which is applicable to various types of 1,3-dicarbonyl compounds would be extremely useful in synthetic organic chemistry.[7] In particular, there is no report of the use of a *1,3-diketone* as a nucleophile. Therefore, we chose the 1,3-diketone **4a** as a model compound to examine our hypothesis (eq 1).



Clean formation of the palladium enolate[8] **5a** was observed by ^{1}H NMR[9] when **4a** was treated with 0.5 equiv of **1a** (Pd: **4a** = 1:1) in THF-d_8 for 2 h. Observation of M^+ by ESI mass spectroscopy also showed formation of the Pd-enolate **5a**.[9] To this mixture was added 2 equiv of methyl vinyl ketone **6a** to examine the nucleophilicity of **5a**. Unfortunately, the reaction did not proceed, probably because palladium diketonato complex is very stable. Interestingly, however, the addition of 1 equiv of TfOH[10] was found to be effective to promote the reaction. The Michael product **7a** was obtained in 96% isolated yield (5 h, 0 °C), and *the enantioselectivity was determined to be 97% ee* by HPLC. After the completion of the reaction, formation of **2a** was observed by ^{1}H NMR.[9] Then, we carried out similar NMR experiments using the palladium aqua complex **2a**. Upon mixing **2a** and **4a** in THF-d_8 at room temperature, the reaction reached an equilibrium point between **4a** and **5a**.[9] After the addition of **6a** (2 equiv) to the mixture, **4a** was converted smoothly to **7a** in 5 h. The isolated yield was 99%, and the same enantioselectivity (97% ee) was observed. These results support our hypothesis that the coordinating hydroxo ligand of **3** can abstract an acidic α-proton of the substrate to form a square-planar palladium enolate complex **5a**. Although the electrophilicity of **6a** was not enough for reaction with **5a**, TfOH selectively activated the enone **6a** instead of the protonation of **5a**. It is interesting that the strong protic acid and inherently basic palladium enolate seem to act cooperatively to promote a carbon−carbon bond-forming reaction.

Next, we attempted the same reaction using a catalytic amount of Pd aqua complex. Using 10 mol % of **2b**, the reaction of **4a** proceeded smoothly (89%), and the enantioselectivity was 90% ee (THF, −10 °C, 30 h, 4 M) (eq 1). Also, the aryl-substituted substrate **4b** was converted to the desired product **7b** in 84% yield and with 90% ee (eq 2). In contrast to the ordinary basic conditions in which the chemical yield was low due to the instability of the product,[11] this reaction system gave the desired triketone in high yield.



To extend the scope of this novel reaction, we turned our attention to the use of β-ketoester. Under the optimized conditions,[9]

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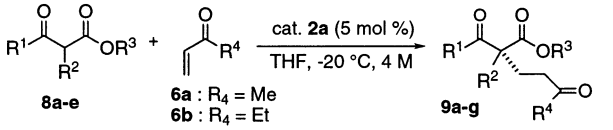
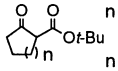
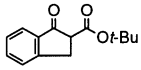
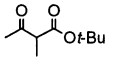
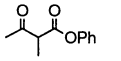
Table 1. Michael Reaction Using Various β-Ketoesters



entry	ketoester	enone	time (h)	product	yield (%)	ee (%)	conf.
1	 n = 1 : **8a**	**6a**	24	**9a**	92	92	*R*
2[a,b]	n = 2 : **8b**	**6a**	72	**9b**	92	90	*R*
3[c,d]	 **8c**	**6a**	48	**9c**	88	89	-
4[a,b,c]	 **8d**	**6a**	72	**9d**	88	90	-
5[b,c]	 **8e**	**6a**	72	**9e**	69	93	*R*
6[e]	**8a**	**6a**	40	**9a**	93	93	-
7[a]	**8a**	**6b**	20	**9f**	84	88	-
8[a,b]	**8b**	**6b**	72	**9g**	89	86	-

[a] Catalyst **2b** was used. [b] The reaction was conducted at 0 °C. [c] 10 mol % of Pd catalyst was used. [d] 1 M **8c**. [e] 2 mol % of catalyst **2b** was used.

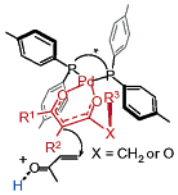
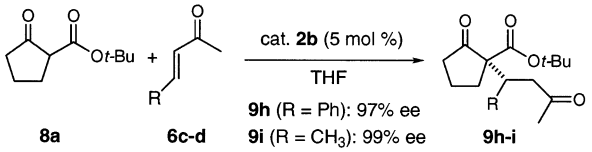


Figure 1. Proposed transition state.

Scheme 2. Catalytic Diastereo- and Enantioselective Michael Reaction



we examined various β-ketoesters (Table 1). All substrates examined, including a five- or six-membered ring substrate, an indanone derivative, and acyclic substrates, were converted with high enantioselectivities (entries 1−5). There are a few reports in which more than 90% ee was achieved for one specific substrate. In contrast, the catalyst reported here showed very high asymmetric induction for all these substrates, indicating the broad generality of this reaction. It was possible to reduce the catalyst loading to 2 mol % in the case of **8a** (entry 6). Instead of **6a**, ethyl vinyl ketone **6b** was also found to be a good acceptor (entries 7, 8). The absolute configuration of several products was determined to be *R* by comparison with reported data after conversion into known compounds.[9] The observed absolute configuration of products and the fact[9] that a bulky ester group is essential for high enantioselectivity strongly suggest that the reaction proceeded via the transition state model shown in Figure 1. The bulky substituent (R^3) would avoid severe steric interaction with the tolyl group located at one side of the enolate face. Thus, the *si* face of the palladium enolate is blocked prefentially, and the incoming enone would react with palladium enolate at the *re* face in a highly enantioselective manner.

Further examples were as follows (Scheme 2). The reaction with less reactive β-substituted enones (**6c,d**) proceeded smoothly. The reaction of **8a** with benzalacetone **6c** in THF at 0 °C afforded the Michael adduct **9h** in 83% yield (diastereomer ratio = 3.6/1), and *the ee of the major isomer was 97%* (36 h). Also, 3-penten-2-one **6d** was converted to **9i** in 89% isolated yield (−20 °C, 24 h). *The diastereomer ratio was 8/1, and the ee of the major product was 99%.* In these reactions, catalytic asymmetric construction of highly crowded vicinal tertiary and quaternary carbon centers was achieved in one step.

In conclusion, we have succeeded in developing a highly efficient catalytic asymmetric Michael reaction of 1,3-dicarbonyl compounds using a novel palladium aqua complex. The mechanism of this reaction is quite unique. The palladium aqua complex allows successive supply of a Brønsted base and a Brønsted acid. The former activates the carbonyl compound to give the chiral palladium enolate and the latter cooperatively activates the enone. This is quite distinct from conventional acid- or base-catalyzed reactions. Development of other addition and substitution reactions using this novel concept is now under intensive investigation in our laboratory.

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Supporting Information Available: General procedures, details of the NMR experiment, ESI-MS, and spectroscopic characterization of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) See Supporting Information.

(10) TfOH itself was reported to promote Michael reaction to give a racemic product: see, Kotsuki, H.; Arimura, K.; Ohishi, T.; Maruzasa, R. *J. Org. Chem.* **1999**, *64*, 3770−3773.

(11) Reaction of **4b** and **6a** promoted by common bases (triethylamine, DBU, *t*-BuOK, or tetrabutylammonium hydroxide) gave low or negligible yield of **7b** because of the formation of undesired products. The reasons for low yields under basic conditions have been discussed in the literature, see: Christoffers, J. *Synlett* **2001**, 723−732.

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