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Pd(II)-Catalyzed Asymmetric Addition of Malonates to Dihydroisoquinolines

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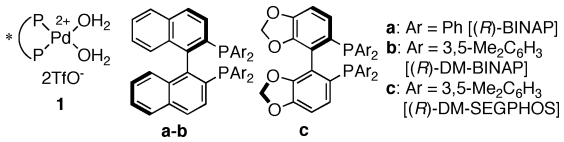
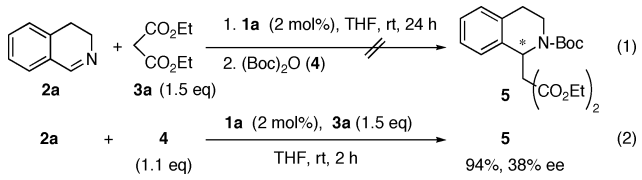
Tetrahydroisoquinolines (THIQs) bearing a stereogenic carbon center at the C1 position represent a fundamental structural motif found in many biologically active compounds.[1] Therefore, asymmetric synthesis of such molecules is of particular interest.[2] Although various reliable methods have been developed using a stoichiometric amount of chiral sources,[2,3] the number of practical catalytic asymmetric reactions is still limited. Among them, the asymmetric transfer hydrogenation of dihydroisoquinolines (DHIQs) and Pictet−Spengler reactions are noteworthy,[4,5] but an important alternative approach is the catalytic asymmetric addition of carbon-centered nucleophiles to C=N bonds of isoquinoline scaffolds.[6−9]

In contrast to reactions with acyclic imines,[10] only a few successful examples of catalytic asymmetric addition reactions of enolate equivalents to cyclic imines (and their iminium ions) are known.[11] This might be due to difficulties associated with the lower reactivity of cyclic imines and/or to less efficient face discrimination. Based on our recent work on the asymmetric Mannich-type reaction of β-ketoesters with acyclic imines,[12] we describe herein an efficient catalytic asymmetric addition reaction of malonates to DHIQs using chiral Pd complexes **1**.[13]

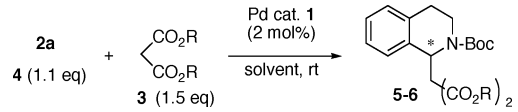


Initial reaction of DHIQ **2a** with diethyl malonate **3a** in the presence of the Pd complex **1a** (2 mol %) failed to give the desired product when $(Boc)_2O$ (**4**) was added after 24 h (eq 1). However, a slight modification of the reaction procedure was found effective (eq 2). Thus, premixing **2a** with **4**, followed by addition of **3a** and **1a**, afforded the desired product **5** in 94% yield with 38% ee after only 2 h.



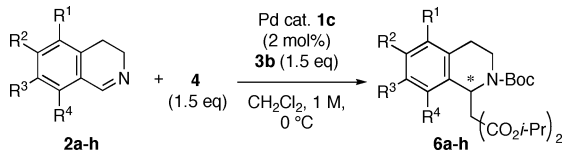
We next examined various reaction conditions. Despite the marked difference in solvent, reactions in CH_2Cl_2 and EtOH gave essentially equal enantioselectivity (Table 1, entries 1 and 2). The ee was greatly improved when bulkier ligands (**b**,**c**) were employed (entries 3 and 4). Further study revealed that the ester moiety of the nucleophile was also important for high asymmetric induction, and isopropyl malonate **3b** was the best among those examined (entry 5).[14] Combined use of **1c** and **3b** in EtOH afforded the highest enantioselectivity, although **2a** was not fully consumed even after 24 h (entry 6). Finally, reaction in CH_2Cl_2 was complete within 30 min at ambient temperature, affording the desired product **6a** in 90% yield with 80% ee (entry 7).

Table 1. Optimization of Reaction Conditions



entry	Pd cat.	R	product	solvent	time (h)	yield (%)	ee (%)
1	**1a**	Et (**3a**)	**5**	CH_2Cl_2	2	96	35
2	**1a**	Et	**5**	EtOH	2	quant.	41
3	**1b**	Et	**5**	EtOH	7	quant.	65
4	**1c**	Et	**5**	EtOH	3	quant.	73
5	**1a**	*i*-Pr (**3b**)	**6a**	THF	1	quant.	71
6	**1c**	*i*-Pr	**6a**	EtOH	12	67	80
7	**1c**	*i*-Pr	**6a**	CH_2Cl_2	<0.5	90	80

Table 2. Catalytic Asymmetric Addition of Malonate to DHIQs **2**



entry	$R^1/R^2/R^3/R^4$	product	time (h)	yield (%)	ee (%)
1	H/H/H/H (**2a**)	**6a**	1.5	89	85
2	H/H/MeO/H (**2b**)	**6b**	1.5	98	81
3	H/R^2-R^3 = OCH_2O/H (**2c**)	**6c**	5	57	91
4[a]	H/MeO/MeO/H (**2d**)	**6d**	3	93	94 (*S*)[b]
5	MeO/MeO/H/H (**2e**)	**6e**	1	92	97
6[c]	MeO/H/H/MeO (**2f**)	**6f**	6	94	82
7[d]	H/H/Me/H (**2g**)	**6g**	1.5	93	96
8	H/H/Br/H (**2h**)	**6h**	3	97	90
9[e]	**2d**	**6d**	5	89	89 (99)[f]
10[e]	**2e**	**6e**	7	71	95

[a] 1 mol % of **1c**. [b] For absolute stereochemistry, see Scheme 1. [c] 5 mol % of **1c**. [d] 2 M. [e] 0.5 mol % of **1c**. [f] The ee value after a single recrystallization from AcOEt.

With these results in hand, we examined the generality of the reaction as regards DHIQs. As shown in Table 2, various C1-substituted THIQs were accessible with high enantioselectivity (up to 97% ee). The reactions were complete within several hours, even under ice-bath cooling, and improved enantioselectivity was observed (85% ee, entry 1). It is noteworthy that substrates with various substitution patterns were available, and our reaction system was compatible with the oxygen functionality (entries 2−6). In particular, the imines **2d** and **2e** underwent the reaction without difficulty, regardless of the possible bidentate coordination of the dimethoxy moiety (>90% yield, 94 and 97% ee, respectively) (entries 4 and 5). Interestingly, in spite of the steric hindrance, the substrate with the MeO group at the ortho position to the imine reacted in good yield with reasonable enantioselectivity (entry 6). The reaction of the Me-substituted imine **2g** gave the desired adduct **6g** in 93% yield with 96% ee (entry 7). In addition, the reaction of

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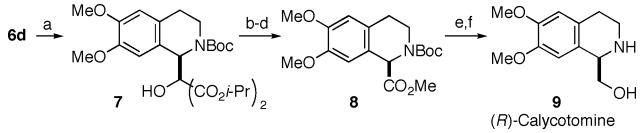
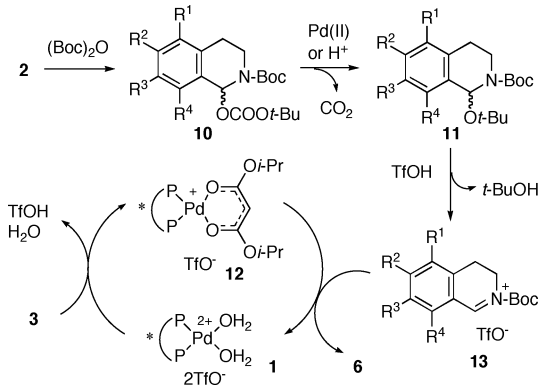
Scheme 1. Conversion of **6d**[a]



[a] Reagents and conditions: (a) NaHMDS, DMDO, 96%. (b) $LiAlH_4$. (c) $NaIO_4$, $KMnO_4$ (cat.). (d) $TMSCHN_2$, 50% for three steps. (e) $LiAlH_4$. (f) AcCl, MeOH, 90% for two steps.

Scheme 2. Plausible Catalytic Cycle



the electron-deficient substrate **2h** proceeded without problem (97%, 90% ee), and it is noteworthy that the Br group was completely intact (entry 8). In entries 9 and 10, the amount of catalyst could be reduced to as little as 0.5 mol % without significant deterioration of the reaction efficiency.

To determine the sense of enantioselection, conversion of **6d** was carried out (Scheme 1). Hydroxylation of **6d** with dimethyldioxirane (DMDO) and subsequent transformation afforded the amino ester **8** without racemization. Reduction with LAH, followed by removal of the Boc group, furnished the antipode of naturally occurring (*S*)-calycotomine (**9**).[15]

On the basis of preliminary mechanistic studies, we propose the catalytic cycle depicted in Scheme 2. First, the cyclic imines **2** react with $(Boc)_2O$ to give the carbonates **10**. Although uncatalyzed decarboxylation of **10** to the *N*,*O*-acetal **11** is not fast, addition of the Pd complex apparently accelerates the reaction, as indicated by vigorous gas evolution.[16,17] We speculate that the Pd enolate **12** would be a key intermediate on the basis of our previous results,[12] though this remains to be confirmed. A strong protic acid, generated during the formation of **12**, would facilitate formation of the acyl iminium intermediate **13**, which would react with the Pd enolate to complete the catalytic cycle. In spite of the formation of the highly reactive species, high asymmetric induction was observed under mild conditions (0 °C to room temperature),[18] which might be due to cooperative action of the enolate and the proton.

Finally, inspired by the recent work of Li et al.,[8a] we examined the dehydrogenative addition reaction with malonate (eq 3). Slow addition of DDQ allowed *in situ* generation of the reactive intermediate, such as **13**, from the *N*-Boc-protected THIQ **14**, and interestingly, the coupling product **6d** was obtained at a synthetically useful level (82%, 86% ee). This one-pot procedure is operationally convenient. Also, it should be noted that an easily removable protecting group could be used in our reaction, whereas *N*-phenyl-substituted substrates were normally used in the literature.[8a]

In summary, we have developed a highly efficient catalytic asymmetric addition reaction of malonates to various DHIQs. This method can provide highly optically active C1-substituted THIQs, many of which would find a multitude of applications in medicinal studies. Because the use of *N*,*O*-acetals is unique in asymmetric catalysis, we believe that the present results provide a basis for the discovery of other novel reactions. Further examination of the scope of the reaction and mechanistic studies are under way.

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Supporting Information Available: Experimental details of the asymmetric reactions, and the spectroscopic characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(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.

(2) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev*. **2004**, *104*, 3341−3370.

(3) For a recent example of stoichiometric syntheses: Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc*. **2006**, *128*, 9646−9645.

(4) Reduction of DHIQs: Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc*. **1996**, *118*, 4916−4917 and references therein.

(5) Pictet−Spengler reaction: (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2004**, *126*, 10558−10559. (b) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc*. **2006**, *128*, 1086−1087.

(6) Pioneering work on catalytic asymmetric cyanation of isoquinolines: Funabashi, K.; Ratni, H.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2001**, *123*, 10784−10785.

(7) Catalytic asymmetric allylation: Itoh, T.; Miyazaki, M.; Fukuoka, H.; Nagata, K.; Ohsawa, A. *Org. Lett*. **2006**, *8*, 1295−1297.

(8) Catalytic asymmetric alkynylations: (a) Li, Z.; MacLeod, P. D.; Li, C.-J. *Tetrahedron: Asymmetry* **2006**, *17*, 590−597. (b) Taylor, A. M.; Schreiber, S. L. *Org. Lett*. **2006**, *8*, 143−146.

(9) Catalytic asymmetric addition of diethylzinc: Ukaji, Y.; Shimizu, Y.; Kenmoku, Y.; Ahmed, A.; Inomata, K. *Chem. Lett*. **1997**, 59−60.

(10) Kobayashi, S.; Ueno, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Supplement 1; Springer: Berlin, 2004; Chapter 29.5.

(11) For selected examples: (a) Murahashi, S.-I.; Imada, Y.; Kawakami, T.; Harada, K.; Yonemushi, Y.; Tomita, N. *J. Am. Chem. Soc*. **2002**, *124*, 2888−2889. (b) Itoh, T.; Yokoya, M.; Miyauchi, K.; Nagata, K.; Ohsawa, A. *Org. Lett*. **2003**, *5*, 4301−4304. (c) Taylor, M. S.; Tokunaga, N.; Jacobsen, E. N. *Angew. Chem., Int. Ed*. **2005**, *44*, 6700−6704. (d) Frisch, K.; Landa, A.; Saaby, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed*. **2005**, *44*, 6058−6063.

(12) (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.

(13) Recently, the use of active methylene compounds in the catalytic asymmetric Mannich-type reaction has attracted much attention. (a) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc*. **2006**, *128*, 6048−6049 and references therein. (b) Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Commun*. **2006**, 1191−1193. (c) Ting, A.; Lou, S.; Schaus, S. E. *Org. Lett*. **2006**, *8*, 2003−2006.

(14) Reactions of dimethyl and dibenzyl malonates with **2a** under the same reaction conditions gave the products with 29 and 37% ee, respectively.

(15) (a) Morimoto, T.; Suzuki, N.; Achiwa, K. *Tetrahedron: Asymmetry* **1998**, *9*, 183−187. (b) Pedrosa, R.; Andrés, C.; Iglesias, J. M. *J. Org. Chem*. **2001**, *66*, 243−250. For a review on calycotomine: (c) Kaufman, T. S. *Synthesis* **2005**, 339−360.

(16) The reaction with the isolated acetal **11** gave comparable results. Similar formation of *N*,*O*-acetal by the reaction of isoquinoline with $(Boc)_2O$ is known. Ouchi, H.; Saito, Y.; Yamamoto, Y.; Takahata, H. *Org. Lett*. **2002**, *4*, 585−587.

(17) The asymmetric addition reaction of malonates to cyclic *N*,*O*-acetals was reported. Onomura, O.; Kanda, Y.; Nakamura, Y.; Maki, T.; Matsumura, Y. *Tetrahedron Lett*. **2002**, *43*, 3229−3231.

(18) In contrast, most reported reactions require low reaction temperature (−78 to −40 °C). See refs 6, 8, and 11.

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