C_2-Symmetric Chiral Malonamides for Asymmetric Michael Reaction

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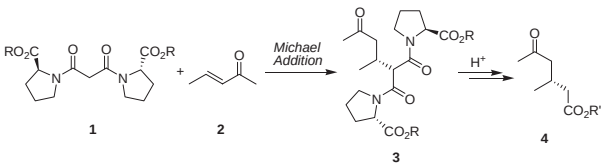
Described is the design and preparation of chiral C_2-symmetric malonamides and their application to asymmetric conjugate addition to enone. The mechanism of partial racemization observed in the course of hydrolysis–decarboxylation step is also elucidated.

The Michael reaction is one of the most efficient C–C bond-forming reactions by virtue of its simple, efficient, and atom-economical property.[1] Malonyl functionality is an efficient and readily available source of carbon nucleophile since it can form its enolate under mild reaction conditions, which is due to effective stabilization of the enolate by two neighboring carbonyl moieties. Many efforts have been made on the asymmetric Michael reaction of malonyl carbanion to various α,β-unsaturated systems.[2] Optically pure proline has shown its highly versatile talents in a variety of asymmetric organic reactions and is now thought to be one of the most essential elements to design new asymmetric organic transformations.[3] To date, proline by itself or proline-derived catalysts or additives have been used for the asymmetric Michael addition of malonates to electron-deficient olefins.[4]

The feature of our strategy to this goal lies in an employment of chiral malonyl anion as a Michael donor which is expected to stereoselectively attack β-carbon of α,β-unsaturated carbonyls. For this purpose, we adopted the advantages of proline to design chiral malonyl nucleophile (Scheme 1). Two identical optically pure proline moieties were fused into malonyl skeleton through amide-bond affording chiral C_2-symmetric malonamide **1**. We envisaged that stereoselectivity would be achieved in conjugate addition of **1** to enone **2** through the proposed transition state shown in Figure 1.

Chiral C_2-symmetric malonamide Michael donors **7**–**9** were prepared from malonic acid (**5**) and L-proline benzyl ester hydrochloride (**6**) as shown in Scheme 2. We first employed the ethyl



Scheme 1. Michael addition of chiral malonamide **1** to enone **2**.

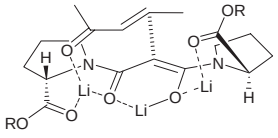
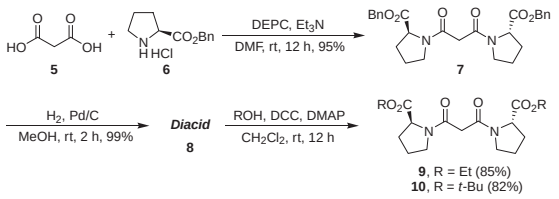
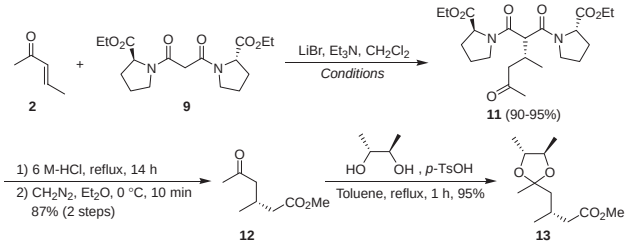


Figure 1. Proposed transition state of Michael addition of C_2-symmetric chiral malonamide to (*E*)-3-penten-2-one.



Scheme 2. Preparation of C_2-symmetric chiral malonamides.



Scheme 3. Asymmetric Michael addition of chiral malonyl nucleophile to enone.

ester variant **9** to the asymmetric conjugate addition to (*E*)-3-penten-2-one (**2**) (Scheme 3). The reaction was performed with chiral nucleophile **9** (1.0 equiv) and enone **2** (2.0 equiv) in the presence of triethylamine (1.0 equiv) and lithium bromide (5.0 equiv) in dichloromethane affording **11** in 90–95% yields. Detachment of the proline moieties from the Michael adduct **11** and subsequent decarboxylation of the resulting 1,3-dicarboxylic acid were performed by treatment with 6 M HCl, followed by esterification with diazomethane to give optically enriched δ-keto ester **12**. The absolute configuration of **12** was assigned to be R by comparison of the value of specific rotation with the literature data,[4b,5] which indicates that the reaction might proceed by the proposed transition state shown in Figure 1. The level of asymmetric induction of this conjugate addition was determined using ^{1}H NMR experiment by measuring diastereomeric ratio of one of the two methylene protons located on α-position to ester carbonyl in **13** which was obtained by ketalization with optically pure (2*R*,3*R*)-2,3-butanediol.

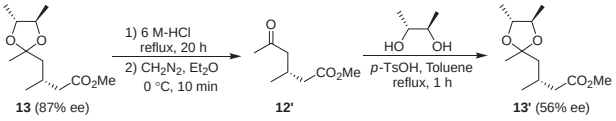
Table 1 summarizes the variation of diastereoselectivity of the asymmetric Michael addition step (**2** + **9** → **11**) with the change of reaction temperature. A steady increase of the stereoselectivity was observed as the reaction temperature lowered to −43 °C. No further increase in diastereoselectivity was achieved below −43 °C. The other chiral Michael donors **7** and **10** also gave the optically enriched Michael adducts under the same reaction conditions (Entries 6 and 7), however, a slightly decreased enantioselectivity was obtained in each case.

Interestingly, we found that optical purity of the initially formed Michael adduct **11** gradually decreased during acid catalyzed hydrolysis–decarboxylation process. In order to confirm

Table 1. Stereoselectivity in asymmetric Michael addition (**2** + **9** → **11**)[a]

Entry	Temp/°C	Time/h	Yield/%	de/%
1	rt	0.5	95	58
2	0	2	95	64
3	−10	4	94	75
4	−43	10	92	87
5	−78	18	90	87
6[b]	−78	18	90	82
7[b]	−78	20	90	85

[a]The reaction was carried out with 2.0 equiv of (*E*)-3-penten-2-one (**2**), 1.0 equiv of C_2-symmetric chiral malonamide **9**, 1.0 equiv of triethylamine, and 5.0 equiv of lithium bromide in dichloromethane under the given conditions. [b]Benzyl- (**7**, for Entry 6) and *tert*-butyl ester derivatives (**10**, for Entry 7) were used as chiral Michael donors instead of **9**, respectively.



Scheme 4. Partial racemization.

this racemization, we repeated the acidic hydrolysis of 87% ee **13**, methyl esterification and ketalization to give **13′** as shown in Scheme 4. The enantiomeric excess of **13′** has decreased to 56% ee which strongly supports the partial racemization occurred in acidic medium.

Based on our experiments, a plausible racemization mechanism in acidic condition is described in Figure 2. 1,3-Dicarboxylic acid **A** obtained from acid-catalyzed hydrolysis of Michael adduct is converted to monoacid **B** through decarboxylation. Then, **B** undergoes acid-catalyzed Dieckmann type condensation where chirality disappears as **B** is transformed to achiral 5-methylcyclohexane-1,3-dione (**F**). Finally, **F** goes back to **H**, a racemic form of **B**, through retro-Dieckmann process. Another possible way of racemization proceeds in sequence of Dieckmann condensation (**A** → **E**), decarboxylation (**E** → **F**), retro-Dieckmann process (**F** → **H**).

According to the racemization mechanism in Figure 2, 1,3-dicarboxylic acid **A** is not influenced by racemization, which indicates that diacid **A** can reflect the real stereoselectivity generated in the course of Michael addition. Based on this hypothesis, we prepared diester **15** from the Michael adduct **11**, obtained from the asymmetric Michael reaction between **2** and **9** at 0 °C, by a short-time acidic hydrolysis with AcOH–HCl (1:1) followed by sequential esterification and ketalization (Scheme 5). The enantioselectivity of the Michael addition performed at 0 °C was found to be 79% ee. Compared with the previous result (64% ee) shown in Entry 2 in Table 1, this revised process would be more suitable for exact evaluation of this type of Michael addition.

In summary, an asymmetric conjugate addition of chiral malonyl nucleophiles to enone was developed in which chiral C_2-symmetric malonamides were employed as chiral Michael donors. Optically enriched δ-keto ester was obtained with high level of enantioselectivity up to 87% ee. We found that the acid-catalyzed Dieckmann ring closure occurred during hydrolysis–decarboxylation step causes partial racemization. A revised

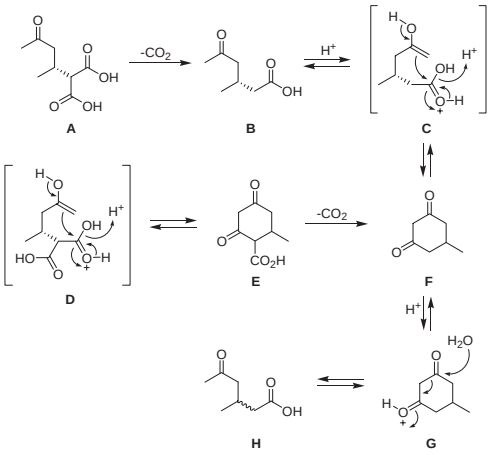
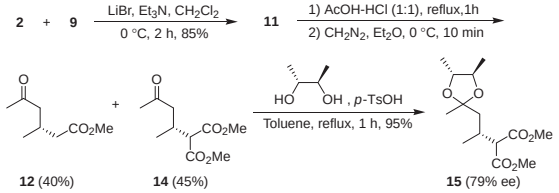


Figure 2. Plausible mechanism of racemization.



Scheme 5. New process for the exact evaluation of stereoselectivity.

process was developed for the exact measurement of stereoselectivity in the Michael addition step.

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