Asymmetric Catalysis

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Catalytic Asymmetric Michael Reactions with Enamides as Nucleophiles**

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The asymmetric Michael addition reaction is among the most powerful methods for the generation of enantiomerically enriched 1,5-dicarbonyl compounds. As these compounds are of great synthetic interest, many chiral metal complexes have been developed for their enantioselective synthesis. Evans et al. reported the Michael addition of silicon enolates to alkylidenemalonates under the catalysis of a copper(II)–bisoxazoline complex. Although they observed high yields and high selectivities when benzylidenemalonate or bulky alkylidenemalonates were used as electrophiles, the selectivities were lower when smaller alkylidenemalonates (such as ethylidene- or propylidenemalonate) were used, and the presence of an alcohol additive was essential for high catalytic turnover.[1] Several other methods, including the addition of nucleophiles to alkylidenemalonates[2] and the addition of malonates to enones,[3] mainly to chalcone,[3a–o] have been developed for the preparation of these valuable 1,5-dicarbonyl compounds. Whereas high enantioselectivities were observed when benzylidenemalonate or chalcone derivatives were used as electrophiles, low to moderate selectivities were observed with ethylidenemalonate and other enones.

Recently, we reported the first examples of the highly enantioselective addition of enamides and enecarbamates to various electrophiles by using complexes of copper with a chiral diamine or chiral diimine.[4] An advantage of the use of enamides and enecarbamates is that a proton is transferred very smoothly from these compounds during the addition step, and therefore no external proton source is necessary for high catalyst turnover. Moreover, the final products are imines, which can be hydrolyzed to carbonyl derivatives or reduced to provide a variety of valuable nitrogen-containing compounds. The usefulness of enamides and enecarbamates as nucleophiles prompted our interest in their use in Michael reactions. Herein, we describe catalytic asymmetric Michael reactions of enamides and enecarbamates with alkylidenemalonates.

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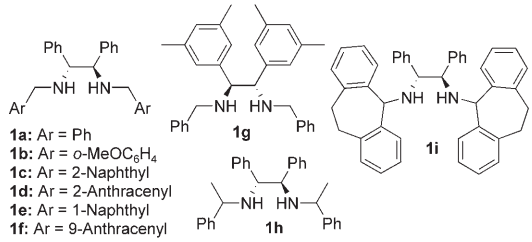
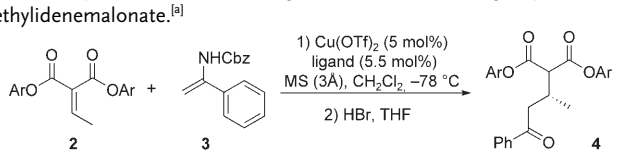
First, we investigated the reactivity of several Michael acceptors toward the acetophenone-derived enecarbamate **3** in the presence of copper(II) triflate ($Cu(OTf)_2$). The reactions did not proceed at all with chalcone, 2-cyclohexen-1-one, or ethyl crotonate in the presence of $Cu(OTf)_2$ (10 mol%) at room temperature during a reaction time of 3 h. Moreover, the enecarbamate decomposed completely under these reaction conditions. However, the use of diethyl ethylidenemalonate as an electrophile under the same reaction conditions, followed by hydrolysis, gave the desired ketone product in 66% yield, although decomposition of the enecarbamate was observed to some extent. This exceptionally high reactivity may be attributed to strong coordination of the copper ion to the diester functionality of the ethylidenemalonate through favorable bidentate chelation.

We then concentrated on this type of electrophile and examined several catalytic systems with dimethyl ethylidenemalonate as the electrophile and the acetophenone-derived enecarbamate **3** as the nucleophile. We screened a variety of Lewis acid catalysts and found copper(II)–diamine complexes to be the most promising. Furthermore, higher yields and selectivities were observed with diaryl ethylidenemalonates than with dialkyl ethylidenemalonates. We then optimized the reaction conditions. With ligand **1a**, the desired adduct was formed in high yield with 66% *ee* (Table 1, entry 1). The



presence of *ortho* substituents on the aromatic groups of the amino moieties (as in **1b**) led to the same level of enantioselectivity, although longer reaction times were required (Table 1, entry 2). An increase in the bulkiness of the diphenyl ethylene backbone (as in **1g**) did not improve the enantioselectivity (Table 1, entry 3), and the presence of alkyl substituents on the benzylic carbon atoms inhibited the reaction (entry 4). With the ligand **1i**, the reaction was sluggish, and no asymmetric induction was observed (Table 1, entry 5). The use of the 2-naphthyl-substituted ligand **1c** (Table 1, entry 6) and the 2-anthracenyl-substituted ligand **1d** (entry 7) led to improved enantioselectivity, and even higher enantioselectivity was observed with the bulkier 1-naphthyl-substituted ligand **1e** (entry 8). Finally, it was found that the

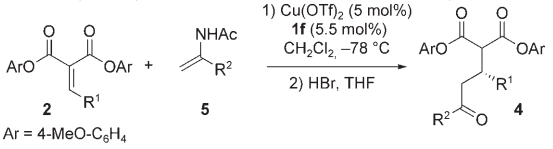
Table 1: Optimization of the ligand and the ester groups of the ethylidenemalonate.[a]



Entry	Ar	Product	Ligand	*t* [h]	Yield [%][b]	*ee* [%][c]
1	C_6H_5 (**2a**)	**4a**	**1a**	1	89	66
2	C_6H_5 (**2a**)	**4a**	**1b**	24	92	65
3	C_6H_5 (**2a**)	**4a**	**1g**	2	92	−63
4	C_6H_5 (**2a**)	**4a**	**1h**	48	0	–
5	C_6H_5 (**2a**)	**4a**	**1i**	24	50	0
6	C_6H_5 (**2a**)	**4a**	**1c**	1	96	76
7	C_6H_5 (**2a**)	**4a**	**1d**	2	83	73
8	C_6H_5 (**2a**)	**4a**	**1e**	1	80	78
9	C_6H_5 (**2a**)	**4a**	**1f**	18	85	82
10	2-MeC_6H_4 (**2b**)	**4b**	**1f**	48	80	28
11	3-MeC_6H_4 (**2c**)	**4c**	**1f**	10	79	82
12	4-MeC_6H_4 (**2d**)	**4d**	**1f**	7	88	80
13	4-$MeOC_6H_4$ (**2e**)	**4e**	**1f**	6	98	83

[a] The reaction was conducted with 1.1 equivalents of the diaryl ethylidenemalonate **2** and 1 equivalent of the enecarbamate **3**. [b] Yield of the isolated product. [c] Determined by HPLC analysis on a chiral phase (see the Supporting Information). Cbz = carbobenzyloxy, MS = molecular sieves.

Table 2: Catalytic asymmetric Michael reactions of acetyl enamines.[a]



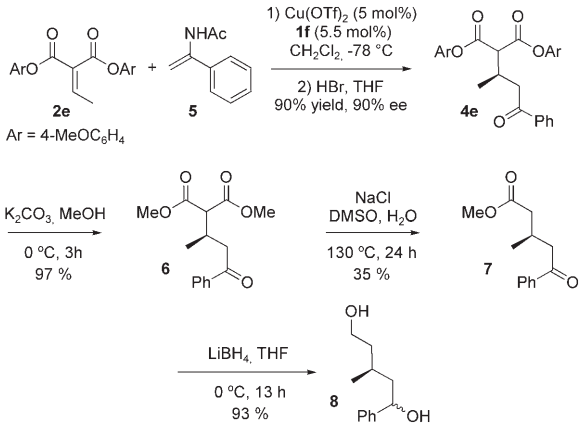
Entry	R^1	R^2	Product	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Me (**2e**)	C_6H_5 (**5a**)	**4e**	10	90	90
2	Me (**2e**)	4-MeC_6H_4 (**5b**)	**4f**	24	80	88
3	Me (**2e**)	4-ClC_6H_4 (**5c**)	**4g**	22	92	90
4	Me (**2e**)	2-naphthyl (**5d**)	**4h**	18	87	88
5	Me (**2e**)	Me[d] (**5e**)	**4i**	10	35	80
6	Me (**2e**)[e]	*i*Pr[d] (**5f**)	**4j**	10	88	83
7	Et (**2f**)	C_6H_5 (**5a**)	**4k**	24	85	94
8	Et (**2f**)	4-ClC_6H_4 (**5c**)	**4l**	46	64	93
9	Et (**2f**)	2-naphthyl (**5d**)	**4m**	48	57	85
10	Et (**2f**)	2-thienyl (**5g**)	**4n**	48	64	70
11[f]	*i*Pr (**2g**)	C_6H_5 (**5a**)	**4o**	24	63	80

[a] The reaction was conducted with 1.1 equivalents of the diaryl ethylidenemalonate **2** and 1 equivalent of the enamide **5**. [b] Yield of the isolated product. [c] Determined by HPLC analysis on a chiral phase (see the Supporting Information). [d] The ethyl enecarbamate was used instead of the acetyl enamine. [e] A mixture of the enecarbamate and isomerized enecarbamate (84:16) was used (see the Supporting Information). [f] The reaction was conducted at −40 °C.

product could be obtained with 82% *ee* when the 9-anthracenyl-substituted ligand **1f** was used (Table 1, entry 9). The substituents on the benzene rings of the diaryl ethylidenemalonates were found to influence significantly the reactivity of the substrates and the selectivity of the reaction (Table 1, entries 10–13). The presence of a substituent at the *ortho* position led to a dramatic decrease in both reactivity and enantioselectivity (Table 1, entry 10). The best result was obtained with bis(4-methoxyphenyl) ethylidenemalonate (**2e**): the adduct was formed in excellent yield in a relatively short reaction time with slightly improved enantioselectivity (Table 1, entry 13).

The scope of this reaction was surveyed under the optimized reaction conditions. As higher selectivity was observed with enamides with an acetyl protecting group than with enecarbamates, *N*-acetyl enamines were used as the nucleophile. In most cases high yields and high enantioselectivities were observed, in particular with enamides derived from aromatic ketones (Table 2). The reaction of the enecarbamate prepared from acetone gave the adduct in just 35% yield with 80% *ee* (Table 2, entry 5); however, the enecarbamate derived from isopropyl methyl ketone reacted well to afford the product in high yield with high enantioselectivity (entry 6). Although the reactions of the propylidenemalonate **2f** and the isobutylidenemalonate **2g** were slower, high yields and high enantioselectivities were observed in most cases (Table 2, entries 7–11).

The absolute configuration of the products was determined by converting an adduct into a known derivative by the synthetic pathway described in Scheme 1. Thus, transesterification of the Michael adduct **4e** yielded the methyl ester **6**, which underwent hydrolysis followed by decarboxylation to

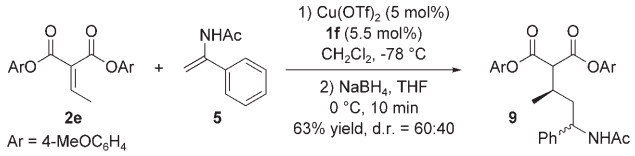


Scheme 1. Determination of the absolute configuration of the adduct **4e**. DMSO = dimethyl sulfoxide.

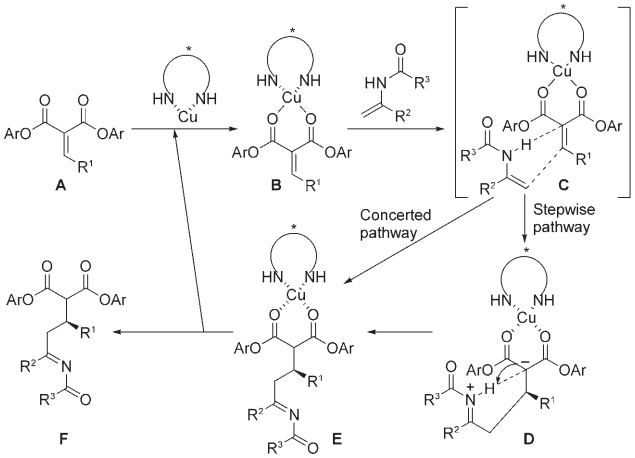
afford the ketoester **7**. The reduction of **7** with $LiBH_4$ gave the known diol **8** with the *S* absolute configuration.[5]

An advantage of our system is that the initial adduct generated in the Michael addition is an imine, which can be reduced to afford an amino ester. We found that this reduction occurred simply upon the treatment of the initial product with $NaBH_4$. In this way, the Michael addition of the enamide **5** to the ethylidenemalonate **2e** followed by reduction instead of hydrolysis gave the amino ester **9** (Scheme 2). Thus, the nitrogen atom of the enamide is retained in the product.

A plausible mechanism for the reaction is shown in Scheme 3. Initially, the copper–diamine complex coordinates to an electrophile **A**, and an enamide then approaches in two possible ways. The first involves a six-membered-ring tran-



Scheme 2. Conversion of the adduct into an aminomalonate.



Scheme 3. A plausible mechanism for the Michael addition of enamides to alkylidenemalonates. It is known whether the copper center carries a charge or has a counterion.

sition state and leads directly through a concerted pathway to the adduct **E**.[6] In the alternative stepwise pathway, the enamide first attacks the electrophile to generate **D**, and the abstraction of the proton from the imine by the negatively charged carbon atom then occurs in an intramolecular fashion. Finally, the copper–diamine complex is released from **E** to give **F**. The high enantioselectivity observed is probably induced by the bulkiness of the 9-anthracenyl moieties of the diamine ligand. Moreover, π stacking between the 9-anthracenyl moieties and the aromatic groups on the ester may be an important effect, as the enantioselectivity dropped when nonaromatic esters were used.

In summary, we have developed a copper-catalyzed asymmetric Michael reaction of enamides with alkylidenemalonates. Enamides derived from both aromatic and aliphatic ketones can be used, and the corresponding adducts are formed in high yields with high enantioselectivities. Furthermore, no external proton source is necessary for catalytic turnover, as proton transfer occurs rapidly in an intramolecular manner.

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