Cu-Catalyzed Asymmetric Michael Addition of Glycine Derivatives to α,β-Unsaturated Malonates†

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Michael addition of glycine imines with alkylidene and arylidene malonates has been developed using Cu/FcPhox as catalyst, providing corresponding Michael products in high yields with high diastereo- and enantioselectivities.

Keywords asymmetric catalysis, Michael addition, glycine derivatives, Cu-catalysis, alkylidene malonate

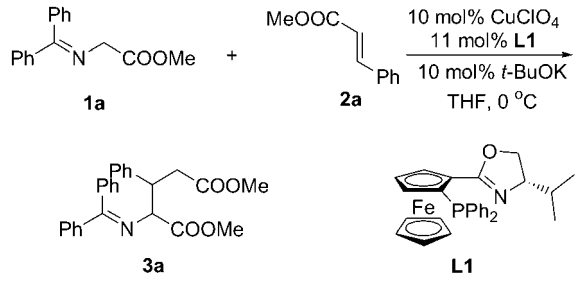
Introduction

Michael reaction as an versatile protocol to form carbon-carbon and carbon-heteroatom bond in organic synthesis attracted the attention of synthetic chemists for a long time.[1] Because the products are easily converted to the relevant α-amino acids when the glycine derivatives are used as donor, the Michael addition of them with α,β-unsaturated compound has widely been studied since Stork and co-workers reported the first example of Michael addition of glycine derivative with α,β-unsaturated ester in 1976.[2,3] Since then, many procedures have been developed and optically active products were afforded in some cases, however, catalytic asymmetric version of the reaction appeared only in recent years. Most of them employed chiral phase-transfer catalysts,[4] chiral organo bases,[5] and chiral crown-ethers[6] as catalyst, more excess of substrate and base as well as high catalytic loading sometime were needed. Transition-metal catalysts have successfully been used in the asymmetric cycloaddition reaction of glycine derivatives with many types of unsaturated compounds,[7,8a,9,10] to our surprise that there were a few reports on the use of transition-metal catalyst in the asymmetric Michael addition reaction of glycine derivatives.[9,11] As a program aimed at the synthesis and applications of chiral ligands in asymmetric catalysis,[12] we studied the use of glycine derivatives in asymmetric reaction.[8] Further studies revealed that Cu/*P*,*N*-ferrocene ligands are effective catalysts in the Michael addition reaction of glycine derivatives with α,β-unsaturated malonates, affording corresponding Michael addition products in high diastereo- and enantioselectivities. In this paper, we would like to disclose our preliminary results on this reaction.

Results and discussion

Initially the reaction of glycine derivative **1a** with methyl cinnamate **2a** using Cu-ligand **L1** as the catalyst was investigated (Scheme 1). After 3 d, 60% yield of Michael addition product **3a** was obtained, *dr* ratio being 1∶3 while *ee* value being 24%/42%. To increase the reaction efficiency, more electron-deficient alkene, benzylidene malonate **2b** was used as Michael acceptor. To our delight, quantitative product **3b** was provided by the reaction of **1a** with **2b** under the condition of Eq. 1 after 8 h, but the diastereoselectivities was still low (*dr* being 2∶1 with 84%/99% *ee*).

Scheme 1



Based upon the above results, the influence of copper salts on the reaction was studied (Table 1). It can be seen that all reactions using different copper salts pro-

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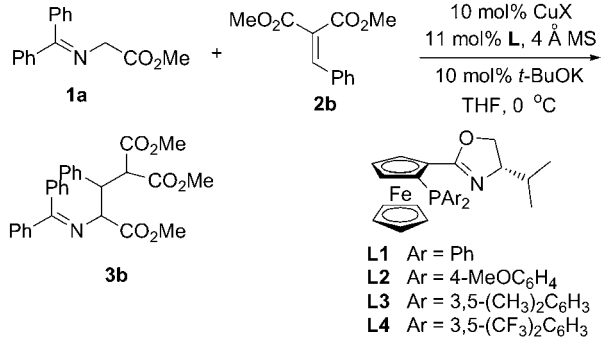
vided excellent yields of product (Table 1, Entries 1—4 and Entry 6) except that using CuI, which gave product in 34% yield only (Table1, Entry 5). However, there was almost no diastereoselectivity in all cases and enantioselectivity was also lower with exceptions when $CuClO_4$ and $Cu(OTf)_2$ were used (Entries 1, 3). We have found that electronic factor of ligands has great impact on the selectivity of the reaction.[8,13,14] We also found that regio- and diastereoselectivities of the reaction were switched by ligands with different electronic property.[8,14a] Thus, the ligands having the phenyl ring with different substituent on P atom were tested and the results are also compiled in Table 1. It can be seen that **L4** with two electron-withdrawing group, CF_3, at 3,5-position of phenyl ring gave the best diastereoselectivities (Entry 9) though the enantioselectivity is low, while ligands **L2** and **L3** with electron-donating group, Me and MeO, at phenyl ring provided the product with lower diastereoselectivity (Entries 7 and 8). THF proved to be the best among the common solvents, such as CH_2Cl_2, toluene, Et_2O and DME, while *t*-BuOK be the best among the bases screened (Et_3N, DABCO, DMAP, BuOLi, CsOH, LiOH) in terms of yields, diastereo- and enantioselectivities (not showed in Table). It was reported that *i*-PrOH has great effect in some reactions.[15] So under the condition of 10 mol% $Cu(OTf)_2$, 11 mol% **L4**, 4 Å MS, 10 mol% *t*-BuOK and THF as solvent, we added 100 mol% of *i*-PrOH as additive, finding that the enantioselectivity increased from 64% to 84% (Entry 11), however, the enantioselectivity was not improved when $CuClO_4$ was used as lewis acid under the same condition (Entry 12 vs. Entry 13).

Under the optimized condition, the substrate scope was investigated (Table 2). All arylidene malonates **2**, in which R was phenyl ring with either electron-withdrawing or donating substituent at *para*- or *meta*-position and naphthyl, delivered the products in high yields (Entries 1—6). The diastereoselectivity was between 7—10∶1 (Entries 1—3, 5 and 6), but malonate **2e** with methoxy group at *meta*-position of phenyl ring gave **3e** in a *dr* ratio of 5∶1 (Entry 4). High *ee* was realized when substituent was phenyl (Entry 1), *para*-substituted phenyl (Entries 2, 3) and naphthyl (Entry 6), while *meta*-substituted benzylidene malonates **2e** and **2f** provided the products in 64% and 68% *ee* respectively (Entries 4 and 5). The reaction is also suitable for alkylidene malonates, providing corresponding products in high yields and high *ee* (Entries 7—10). When malonate **2l** with cyclohexyl as substituent was used the *dr* ratio was 10∶1 and the *ee* was 95% but the yield was

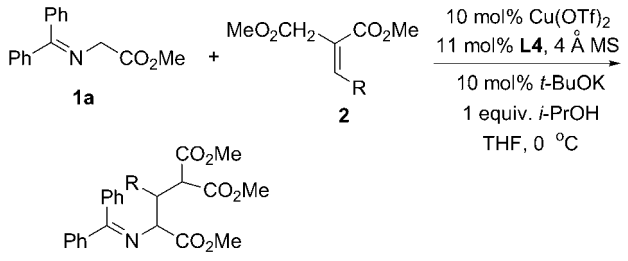
Table 1 Influence of copper salts and electronic factor of ligands on the selectivities of the reaction[a,16]



Entry	CuX	Ligand	Yield[b]/%	*dr*[c]	*ee*[d]/%
1	$CuClO_4$	L1	97	2∶1	84/99
2	CuOTf	L1	93	1∶1	7/35
3	$Cu(OTf)_2$	L1	98	1∶1	80/84
4	$CuPF_6$	L1	96	1∶1	63/41
5	CuI	L1	34	1∶1	13/43
6	$Cu(OAc)_2$	L1	97	1∶1	53/44
7	$Cu(OTf)_2$	L2	96	1∶1.5	99/—
8	$Cu(OTf)_2$	L3	94	4∶1	84/—
9	$Cu(OTf)_2$	L4	94	11∶1	64/—
10	$Cu(OTf)_2$	PPh_3	95	1∶3	—
11	$Cu(OTf)_2$[e]	L4	98	8∶1	84/—
12	$CuClO_4$	L4	98	12∶1	66/99
13	$CuClO_4$[e]	L4	98	12∶1	66/99

[a] Run at 0 ℃ under Ar, using 11 mol% of ligand, 10 mol% of copper salt and 4 Å MS. [b] Separated yield. [c] Determined by ^{1}H NMR. [d] Determined by HPLC using chiral column. [e] 100 mol% of *i*-PrOH as additive.

Table 2 Cu-catalyzed Michael addition of glycine imine with *α*,*β*-Unsaturated Malonates[a]



Entry	**2**, R	Product	Yield[b]/%	*dr*[c]	*ee*[d]/%
1	**2b**, Ph	**3b**	91	8∶1	84
2	**2c**, *p*-BrC_6H_4	**3c**	93	7∶1	80
3	**2d**, *p*-$NO_2C_6H_4$	**3d**	89	7∶1	81
4	**2e**, *m*-$MeOC_6H_4$	**3e**	100	5∶1	64
5	**2f**, *m*-ClC_6H_4	**3f**	100	10∶1	68
6	**2g**, 1-Naphtyl	**3g**	100	9∶1	79
7	**2h**, *i*-Bu	**3h**	100	2∶1	86
8	**2i**, *i*-Pr	**3i**	88	9∶1	82
9	**2j**, *n*-Pr	**3j**	100	4∶1	83
10	**2k**, Et	**3k**	100	2∶1	86
11	**2l**, *c*-Hexyl	**3l**	42	＞10∶1	95

[a] Run at 0 ℃ under Ar in 8 h, using 11 mol% of ligand and 10 mol% of $Cu(OTf)_2$, 4 Å MS, 100 mol% of *i*-PrOH as additive. [b] Separated yield. [c] Determined by ^{1}H NMR. [d] *ee* of the major diasteroisomer, determined by HPLC using chiral column.

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42% only (Entry 11). The substrates with substituent at α-position gave the products in high diastereoselectivity (Entries 8 and 11) while that with no substituent provided the products in lower diastereoselectivity (Entries 7, 9 and 10). X-Ray diffraction analysis of **3c** showed it has *syn*-stereochemistry.

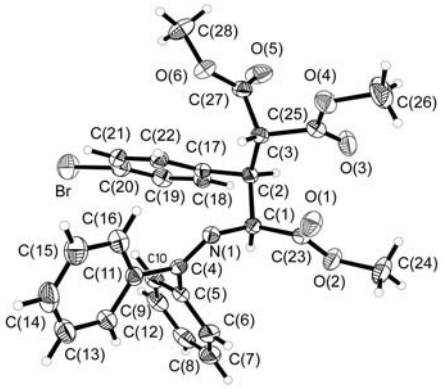
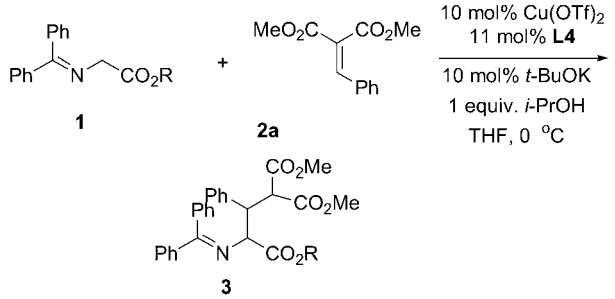


Figure 1 ORTEP drawing of **3c**.

The steric factor of glycine ester also influences the stereochemistry of the reaction. When *tert*-butyl esters **1c** were used, even better stereoselectivities were achieved while the reaction of ethyl ester **1b** provided the same stereoselectivities (Scheme 2).

Scheme 2



1b: R = Et, 91% yield, *dr* = 8:1, 85% *ee* (Major diastereomer)
1c: R = *t*-Bu, 88% yield, *dr* = 9:1, 94% *ee* (Major diastereomer)

Conclusion

In conclusion, Cu-catalyzed asymmetric Michael addition of glycine imine with α,β-unsaturated malonates has been developed, providing Michael adducts in high yields, high diastereo- and enantioselectivities. Both alkylidene and arylidene malonates are suitable substrates. Electronic factor of the ligand plays the role in the stereochemistry of the reaction. Investigations on the reaction using other Michael reaction acceptors as well as the applications of the products in organic synthesis and the determination of absolute configuration of adduct **3** are in progress.

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16 Typical procedure for the Michael addition of **1** and **2**. To a flame-dried Schlenk tube containing activated 4 Å MS were added $Cu(OTf)_2$ (3.6 mg, 0.01 mmol) and ligand **L4** (8.2 mg, 0.011 mmol) then freshly distilled anhydrous THF (1 mL) subsequently under argon atmosphere. Stirred for 30 min, the solution was cooled to 0 ℃ the glycine derivatives **1a** (0.1 mmol) was added, followed by *t*-BuOK (10 μL, 1 mol/L in THF, 0.01 mmol) and **2b** (0.11 mmol). The reaction mixture was stirred at 0 ℃ until the reaction completed (monitored by TLC), then filtered through a short plug of silica gel. After evaporation of the solvent, the crude product was analyzed by ^{1}H NMR spectroscopy to determine the diastereomeric ratio, and then purified by chromatography on silica gel (EtOAc/petroleum mixtures). Analytical data for **3b**: Major diastereomer: 84% *ee*; m.p. 119—121 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.39 (s, 3H), 3.57 (s, 3H), 3.64 (s, 3H), 4.32—4.43 (m, 3H), 6.84—7.70 (m, 15H); ^{13}C NMR ($CDCl_3$) δ: 48.50, 51.99, 52.25, 52.57, 54.01, 68.77, 127.20, 127.25, 128.03, 128.20, 128.35, 128.52, 128.99, 130.65, 135.75, 138.92, 139.21, 168.24, 168.50, 170.82, 171.89; MS (ESI) *m*/*z*: 474.2 ($M+H^+$), 496.2 ($M+Na^+$); HRMS (ESI) calcd for $C_{28}H_{27}NNaO_6$, 496.17127, found 496.17306; HPLC (Chiral AD, hexane/2-propanol=90/10, flow rate=1.0 mL/min), t_R=11.46 min, 17.77 min.

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