

Cu(I) Tol-BINAP-Catalyzed Enantioselective Michael Reactions of Grignard Reagents and Unsaturated Esters

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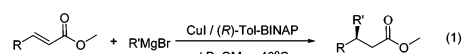
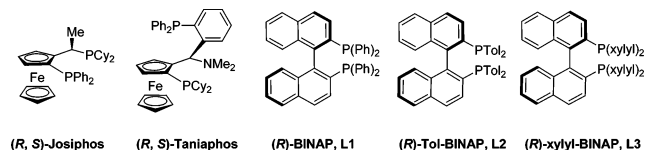
The copper-catalyzed conjugate addition (CA) of organometallic reagents to α,β -unsaturated compounds is one of the most versatile synthetic methods for the construction of C–C bonds.¹ The application of Grignard reagents, which are among the most widely used of organometallic compounds, in the asymmetric CA reactions has received much less attention.² Over the last 3 years, Feringa's group demonstrated that ferrocene-based diphosphine ligands such as (*R,S*)-Josiphos and (*R,S*)-Taniaphos were useful for the highly enantioselective conjugate addition of Grignard reagents onto several classes of Michael acceptors (Scheme 1).^{3,4} Recently, they had also proposed a mechanism to account for this high enantioselectivity. Copper N-heterocyclic carbene catalysts were also applied in the asymmetric CA of Grignard reagents to trisubstituted cyclic enones, which were reported in 2006 by Alexakis's group.⁵ Whereas extraordinary advances have been made in the copper-catalyzed conjugate addition with Grignard reagents, there are still drawbacks in existing systems.^{3c,6} Some of these limitations include the loss of enantioselectivity for sterically hindered alkyl, aryl Grignard reagents or Grignard reagents bearing double bond.²

In our effort to develop an enantioselective method for the synthesis of 8-deoxyanisatin,⁷ we are interested in the copper-catalyzed asymmetric 1,4-addition of Grignard reagents to α,β -unsaturated ester. In this Communication, we describe a new chiral CuI Tol-BINAP catalyst for the asymmetric 1,4-addition of Grignard reagents to α,β -unsaturated esters in high regio- and enantioselectivities.

Initial study was conducted using 1 mol % CuI and 1.2 mol % (*R*)-Tol-BINAP as the chiral catalyst for the reaction of EtMgBr with (*E*)-methyl 5-phenylpent-2-enoate **2** in *t*-BuOMe. The desired product was obtained with good enantioselectivity (82% ee).⁸ In our efforts to have a further understanding of this reaction, we had attempted to synthesize and isolate the chiral catalyst. The tetrahedral dinuclear Cu complex **1a** was synthesized by mixing equimolar amounts of CuI and (*R*)-Tol-BINAP in *t*-BuOMe or CH₂Cl₂ at room temperature (Scheme 2). The resulting complex was isolated as pure crystals, and the structure was elucidated through X-ray crystallography.⁹ However, when the pure complex was used in synthesis, lower enantioselectivity (57% ee) was observed (entry 2).

The above result encouraged us to evaluate the effect of the ratio of the copper complex to the chiral ligand ratio on the enantioselectivity of the reaction (Table 1). It is important to note that a 0.5 equiv excess of the chiral Tol-BINAP to CuI is essential to obtain the product with high enantioselectivities (entries 3 and 4). The addition of other phosphine ligands to complex **1a** also affects the enantioselectivity of the reaction especially when tricyclophosphine was used as the additive (entry 8). The best result was obtained using the catalytic system prepared from the CuI and (*R*)-Tol-BINAP (1:1.5) in *t*-BuOMe.⁹

Scheme 1. Selected Diphosphine Ligands



Scheme 2. Formation of Copper(I) (*R*)-Tol-BINAP Complex

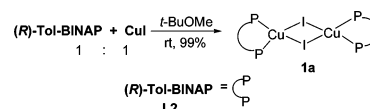


Table 1. Additions of EtMgBr to **1a**: Ligand Effect^a

entry	catalyst	yield (%) ^b	ee (%) ^c
1	1 mol % CuI + 1.2 mol % L2	85	82
2	0.5 mol % 1a	85	57
3	1 mol % CuI + 1.5 mol % L2	88	93
4	0.5 mol % 1a + 0.5 mol % L2	87	93
5	1 mol % CuI + 1.5 mol % L1	85	85
6	1 mol % CuI + 1.5 mol % L3	83	48
7	0.5 mol % 1a + 1 mol % Ph ₃ P	85	53
8	0.5 mol % 1a + 1 mol % C ₃ P	88	83
9	0.5 mol % 1a + 0.5 mol % dppe	86	65

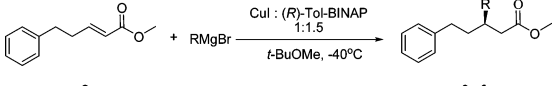
^a All reactions were performed with **2** (0.5 mmol), EtMgBr (2.0 mmol, 3 M in ether) in *t*-BuOMe (1 mL) at -40°C unless otherwise stated.
^b Isolated yield. ^c Determined by HPLC analysis employing a Daicel Chiralcel ODH column.


With the reaction conditions optimized, we analyzed the scope of this asymmetric conjugate addition to unsaturated ester **2** using various Grignard reagents, and high enantioselectivities (86–98% ee) were obtained (Table 2). Secondary Grignard reagent also works well to afford the product in excellent enantioselectivity (entry 3).¹⁰ In contrast to the system reported by Feringa,^{3c} the presence of a double bond in the Grignard reagent did not lead to a decrease in enantioselectivity (entries 4 and 7). However, the addition of MeMgBr to **2** gave the desired product **3g** in high ee but with poor conversion (entry 9).

The reaction was extended to different α,β -unsaturated esters, which were prepared through a Horner–Emmons reaction or a Wittig–Horner reaction. More reactive EtMgBr was used as the nucleophile. The results, summarized in Table 3, indicated that most of them gave the products in high to excellent enantioselectivities and high chemical yields. A maximum of 95% ee was obtained in the case of **4c** as the acceptor (entry 3).

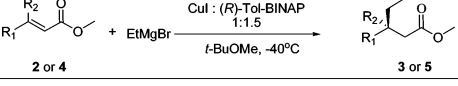
[†] Nanyang Technological University.

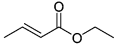
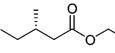
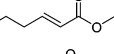
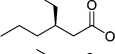
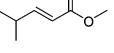
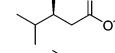
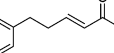
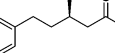
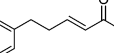
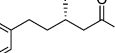
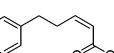
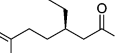
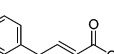
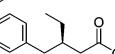
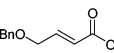
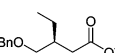
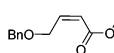
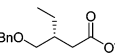
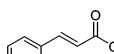
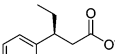
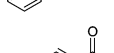
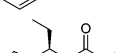
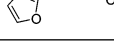
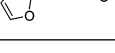
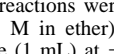
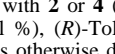
[‡] Suzhou (Soochow) University.

Table 2. Additions of Grignards to **2**^a


entry	RMgBr	product	yield (%) ^b	ee (%) ^c
1	EtMgBr	3a	88	93
2	<i>n</i> -PrMgBr	3b	90	92
3	<i>i</i> -PrMgBr	3c	89	91
4	<i>n</i> -BuMgBr	3d	90	92
5	<i>n</i> -PentMgBr	3e	86	90
6	<i>n</i> -HeptMgBr	3f	89	92
7	 MgBr	3g	90	94
8	<i>i</i> -BuMgBr	3h	91	86
9	MeMgBr	3i	20	>98

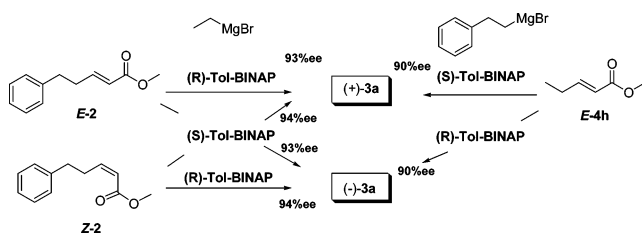
^a All reactions were performed with **2** (0.5 mmol), RMgBr (2.5 mmol, 3 M in ether), CuI (1 mol %), (*R*)-Tol-BINAP (1.5 mol %) in *t*-BuOMe (1 mL) at -40°C . ^b Isolated yield. ^c Determined by HPLC analysis employing a Daicel Chiralcel ODH or OJ column.

Table 3. Variation of α , β -unsaturated Esters^a


entry	esters	product	yield (%) ^b	ee (%) ^c		
1		4a		5a	83	74
2		4b		5b	85	87
3		4c		5c	90	95
4		2		3a	88	93
5 ^{d,e}		2		3a	88	93
6 ^d		2		3a	86	94
7		4d		5d	85	94
8		4e		5e	83	73
9		4e		5e	86	87
10 ^{f,g}		4f		5f	90	93
11 ^{f,h}		4f		5f	83	70
12 ^f		4g		5g	80	85
13 ^{f,h}		4g		5g	80	82

^a All reactions were performed with **2** or **4** (0.5 mmol), EtMgBr (2.5 mmol, 3 M in ether), CuI (1 mol %), (*R*)-Tol-BINAP (1.5 mol %) in *t*-BuOMe (1 mL) at -40°C unless otherwise described. ^b Isolated yield. ^c Determined by Chiral HPLC or GC analysis. ^d (*S*)-Tol-BINAP was used. ^e ($-$)-**3a** was obtained. ^f CuI (5 mol %), (*R*)-Tol-BINAP (7.5 mol %). ^g **4f** in 0.2 mL CH_2Cl_2 was added to the catalyst system in 1 mL of *t*-BuOMe. ^h The reaction was performed in CH_2Cl_2 .

In principle, the absolute stereochemistry of the product can be reversed by using the enantiomer of the ligand or by using the geometrical isomer of the starting material. This was demonstrated by the CA of EtMgBr to *trans*-enoates **2** carried out using (*S*)-Tol-BINAP under the general conditions, and the desired product ($-$)-**3a** with opposite configuration was obtained with similar enantioselectivity (Table 3, entry 5). Another strategy involves the use of the *cis*-enoate instead of the *trans*-enoate to obtain the opposite

**Figure 1.** The configuration relationship.

enantiomer using (*R*)-Tol-BINAP (Figure 1). To demonstrate, *cis*-enoate **2** was subjected to the same reaction conditions using CuI/(*R*)-Tol-BINAP. The (+)-**3a** was obtained in 94% ee (Table 3, entry 6). We had also obtained ($-$)-**3a** from the reaction of phenethylmagnesium bromide with *trans*-enoate **4h** catalyzed by CuI with (*R*)-Tol-BINAP (90% ee) (Figure 1). Interestingly, higher enantioselectivities was observed when the *cis*-enoates was used in the CA reactions (entries 6 and 9).

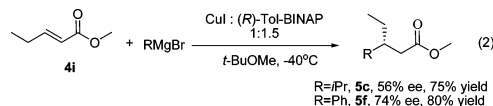
To summarize, we have developed a highly regio- and enantioselective addition of Grignard reagents to α,β -unsaturated esters using simple reaction procedures, employing commercially available chiral Tol-BINAP. Further work in our laboratory will be directed toward exploiting the reaction mechanism, the use of CuI-Tol-BINAP in the catalytic addition of MeMgBr to other Michael acceptors and other organic transformations.

Acknowledgment. We gratefully acknowledge the Nanyang Technological University for the funding of this research and we thank Dr. Y.-X. Li and Dr. K. F. Mok for X-ray support.

Supporting Information Available: Additional experimental procedures, all chromatograms, cif file of crystallographic data for **1a**, and spectral data for reactions products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- Reactions carried out in other solvents such as Et_2O , CH_2Cl_2 , and THF gave the product in lower ee (< 80% ee).
- See Supporting Information.
- The CA reaction of sterically hindered Grignard reagents, such as *i*-PrMgBr and PhMgBr also provided the desired products under the same reaction conditions (eq 2). In contrast to reported results of CuBr \cdot Me₂S/Josiphos catalyst system,^{3c} the desired products were obtained with improved yields and enantioselectivities.



JA0666046