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Highly Efficient Copper(I) Iodide-Tolyl-BINAP-Catalyzed Asymmetric Conjugate Addition of Methylmagnesium Bromide to α,β-Unsaturated Esters

Shun-Yi Wang,[a,b] Tze-Keong Lum,[a] Shun-Jun Ji,[b,*] and Teck-Peng Loh[a,*]

[a] Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 639798
Fax: (+65)-6791-1961; e-mail: teckpeng@ntu.edu.sg
[b] Key Lab. of Organic Synthesis of Jiangsu Province, College of Chemistry and Chemical Engineering, Suzhou (Soochow) University, Jiangsu 215123, People's Republic of China

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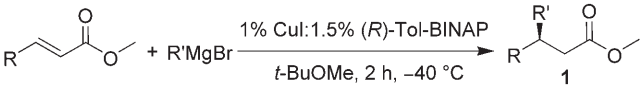
Abstract: A highly efficient asymmetric conjugate addition of methylmagnesium bromide (MeMgBr) to α,β-unsaturated esters catalyzed by copper(I) iodide-tolyl-BNIP (CuI-Tol-BINAP) is described.

Keywords: C–C bond formation; conjugate addition; copper(I) iodide; methylmagnesium bromide; tolyl-BINAP



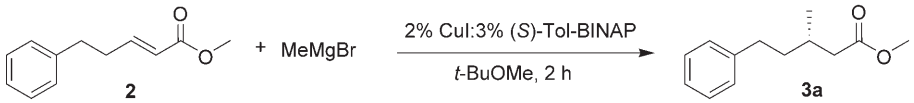
Scheme 1. Asymmetric CA of Grignard reagents to α,β-unsaturated esters.

The enantiopure β-methyl substituted unit is a common recurring motif in many deoxygenated polyketide-type natural products.[1] Therefore many methods have been developed for the synthesis of such compounds. Currently, most of the reported procedures are based on the use of chiral auxiliaries (enolate alkylations,[2] conjugate additions[3]), allylic substitutions[4] or substrate control methods.[5] Catalytic asymmetric methods include Negishi's Zr-catalyzed carboalumination,[6] Cu-catalyzed conjugate reduction,[7] Lipshutz's Cu-catalyzed hydrosilylation,[8] Ir-catalyzed hydrogenation[9] and Feringa's Josiphos-catalyzed conjugate addition.[10] Conjugate addition (CA) of MeMgBr to simple and commercially available α,β-unsaturated esters is one of the most direct entries into these structural elements. In addition, not only are α,β-unsaturated esters easier to handle, a larger scope of useful chemical transformations can also be applied. Unfortunately, unsatisfactory results were obtained in the asymmetric CA of the MeMgBr to various α,β-unsaturated esters under previous conditions (Scheme 1).[11] Despite these important advances, the development of enantioselective methods for the asymmetric CA of MeMgBr to simple and commercially available α,β-unsaturated esters continue to pose a challenge for organic chemists. In this paper, we report a highly efficient cooper(I) iodide-toyl-BINAP (CuI-Tol-BINAP)-catalyzed asymmetric CA of MeMgBr to α,β-unsaturated esters.

Preliminary studies have shown that CuI-Tol-BINAP catalyzed CA of MeMgBr to α,β-unsaturated ester at −40 °C afforded the desired β-methyl substituted methyl ester in low yield (20%), albeit excellent enanatioselectivity (99% *ee*).[11] The low yield was due to the formation of a substantial amount of the undesired β-methyl substituted methyl ketone. Therefore a systematic study was carried out by varying the reaction temperature to suppress the formation of the β-methyl substituted methyl ketone by-product and improve the yield of the β-methyl substituted methyl ester. In this investigation, the reaction was performed using 2 mol% CuI and 3 mol% (*S*)-Tol-BINAP as the chiral catalyst for the reaction of MeMgBr with (*E*)-methyl 5-phenylpent-2-enoate **2** in *t*-BuOMe at different temperatures (Table 1).

Our investigation shows that the desired product was obtained in excellent enantioselectivity (98% *ee*) and good yield (74%) when the reaction was carried out at −20 °C in *t*BuOMe (Table 1, entry 4). Note that when the reaction temperature was increased beyond −20 °C, lower enantioselectivities were observed (entries 5 and 6). When toluene, diethyl ether, or CH_2Cl_2 were used as the solvent, yields were practically unchanged but the enantioselectivities were reduced to

Table 1. CuI-Tol-BINAP-catalyzed CA of MeMgBr to α,β-unsaturated esters **2**.[a]



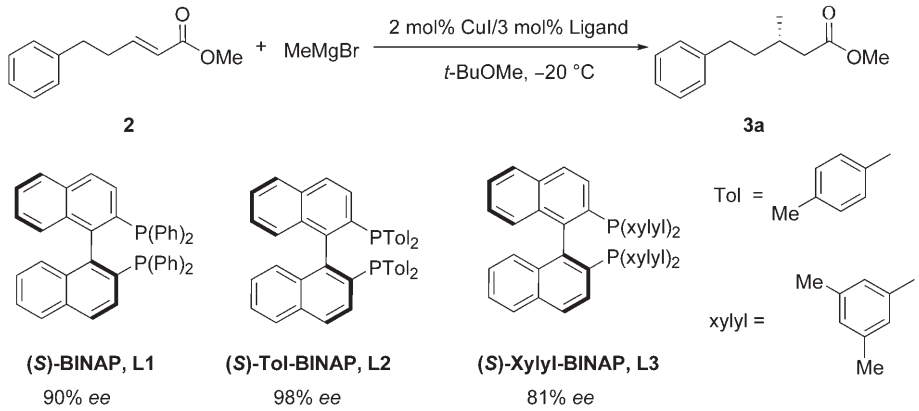
2 **3a**

Entry	Solvent	Temperature	Yield [%][b]	*ee* [%][c]
1	*t*-BuOMe	–78 °C	0	–
2	*t*-BuOMe	–40 °C	20	>98
3	*t*-BuOMe	–30 °C	32	98
4	***t*-BuOMe**	**–20 °C**	**85**	**98**
5	*t*-BuOMe	–10 °C	85	82
6	*t*-BuOMe	0 °C	83	50
7	Toluene	–20 °C	85	94
8	Et_2O	–20 °C	82	90
9	CH_2Cl_2	–20 °C	83	89
10	THF	–20 °C	0	–

[a] All reactions were performed with **2** (0.25 mmol) and MeMgBr (1.25 mmol, 3 M in ether) in *t*-BuOMe (1 mL).
[b] Isolated yield. From NMR of crude reaction mixtures $<5\%$ yields of 1,2-addition products were obtained determined.
[c] The *ee* value was determined by HPLC analysis employing a Daicel Chiracel OD-H column. Absolute configuration assigned by analogy (Table 2, entry 1).

94%, 90% and 89% respectively. There was no reaction when THF was used as the solvent.

We further investigated this asymmetric CA reaction under the same catalytic conditions in entry 4 by varying the chiral ligands. When either (*S*)-BINAP or (*S*)-Xylyl-BINAP was employed, **3a** was obtained in good yields (82% and 84%) but with slightly lower enantioselectivities (90% and 81% *ee*), respectively (Scheme 2).



Scheme 2. Cu with different chiral ligands catalyzed of **2** with MeMgBr.

With the optimized conditions, we analyzed the scope of this asymmetric CA reaction with various α,β-unsaturated esters. As shown in Table 2, these reactions proceeded smoothly either by using different enantiomers of the ligand or different geometrical isomers of the enoate. For example, when (*S*)-Tol-BINAP was used with the *trans*-enoate **2a** (Table 2, entry 6), enantiomer (−)-**3a** could be obtained in good yield and excellent *ee*. Alternatively, when (*R*)-Tol-BINAP was used with the *cis*-enoate **2b** (Table 2, entry 8), the same enantiomer (−)-**3a** could be obtained (Figure 1).

In summary, we have developed a highly efficient and enantioselective CuI-Tol-BINAP-catalyzed asymmetric CA of MeMgBr to α,β-unsaturated esters using simple reaction procedures. Further investigations will be directed toward understanding the mechanism, broadening the reaction scope and applying the catalytic system in the total synthesis of natural products. When we were preparing this manuscript, Prof. Feringa's group reported the asymmetric conjugate addition of Grignard reagents to α,β-unsaturated thioesters catalyzed by Tol-BINAP/CuI.[13]

Experimental Section

General Methods

Experiments involving moisture- and/or air-sensitive components were performed in oven-dried glassware under a positive pressure of nitrogen using freshly distilled solvents. Commercial grade solvents and reagents were used without further purification with the following exceptions: *t*-BuOMe was distilled from calcium hydride, dichloromethane was distilled from calcium hydride, diethyl ether was distilled from sodium, hexane and ethyl acetate were fractionally distilled.

Copper(I) iodide, enoates **4a** and **4b** were purchased from Aldrich or Acros. (*R* or *S*)-BINAP (**L1**), (*R* or *S*)-Tol-BINAP (**L2**) and (*R*)-xylyl-BINAP (**L3**) were purchased from Strem. Unsaturated esters (***E***)-**2**, (***Z***)-**2**, and **4c–f** were prepared from the corresponding aldehydes, using the Horner–Emmons or Wittig–Horner reaction.[1] The grignard reagent (MeMgBr, 3 M in diethyl ether) was purchased from Aldrich.

Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plates (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on a Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with a basic solution of potassium permanganate or an acidic solution of ceric molybdate.

Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as a slurry and equilibrated with the appropriate solvent system prior to use.

General Procedure for the Enantioselective Conjugate Addition

In a round-bottom flask equipped with septum and stirring bar, (*S*)-Tol-BINAP (5.1 mg, 0.0075 mmol) and CuI (0.95 mg, 0.005 mmol) were dissolved in *t*-BuOMe (1.0 mL) and stirred under nitrogen at room temperature until a bright yellow suspension was observed. Alternatively, (*S*)-Tol-BINAP and CuI were stirred in CH_2Cl_2 (1.0 mL) for 15 min, concentrated under vacuum and then stirred in *t*-BuOMe (1.0 mL) until the same bright yellow suspension was observed. The mixture was then cooled to −20 °C and MeMgBr (Aldrich, 3.0 M solution in Et_2O, 1.25 mmol) was added carefully into the reaction mixture. After stirring for 15 min, a solution of unsaturated ester (0.25 mmol) in *t*-BuOMe (0.30 mL) was added dropwise over 1 hour *via* a syringe pump. After vigorous stirring at −20 °C for another 1.5 h, MeOH (0.5 mL) and saturated NH_4Cl solution (2 mL) were sequentially added at −20 °C, and the mixture was warmed to room temperature. The aqueous layer was extracted with diethyl ether (5 mL × 3) and the combined organic extracts were dried over anhydrous magnesium sulfate, filtered and carefully concentrated under vacuum. The residual crude product was purified by flash chromatography (1:99 Et_2O/pentane) to afford the desired product as colorless oil.

Racemic 1,4-addition products were obtained by reaction of the enoates with MeMgBr (5.0 equiv., 3 M in diethyl ether) and CuI (0.05 mol%) at −20 °C in diethyl ether.

Supporting Information

Additional experimental procedures and spectral data for reaction products (PDF) are available as Supporting Information free of charge *via* the Internet.

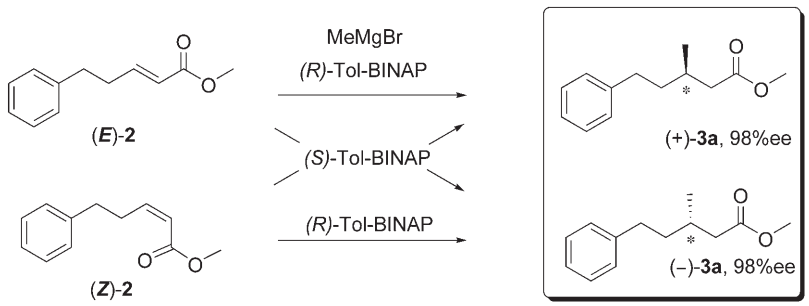
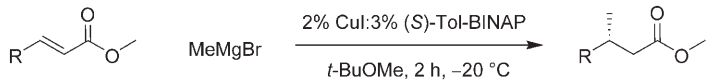
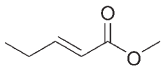
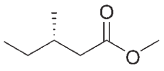
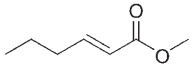
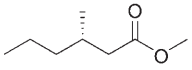
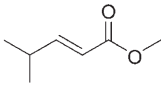
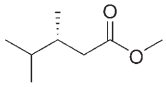
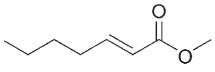
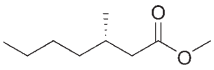
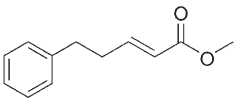
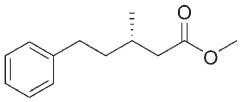
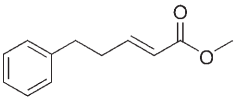
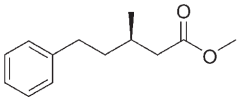
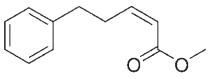
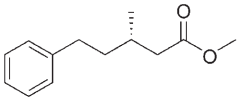
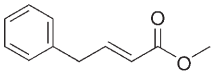
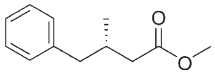
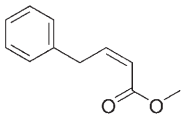
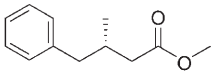


Figure 1. The configuration relationship.

Table 2. Variation of the α,β-unsaturated ester.[a]



2 or **4** **3** or **5**

Entry	Esters		Product		Yield [%][b]	*ee* [%][c]
1		**4a**		**5a**	85	96[d]
2		**4b**		**5b**	80	96
3		**4c**		**5c**	50	>99
4[e]					80	>99
5		**4d**		**5d**	81	97
6		**2a**		(−)-**3a**	85	98
7[f]		**2a**		(+)-**3a**	85	98
8[f]		**2b**		(−)-**3a**	86	98
9		**4e**		**5e**	83	95
10[f]		**4f**		**5e**	60	95

[a] Reactions were performed with **2** or **4** (0.25 mmol), MeMgBr (1.25 mmol, 3 M in diethyl ether), CuI (2.0 mol%), (*S*)-Tol-BINAP (3.0 mol%) in *t*-BuOMe (1 mL) at −20 °C unless otherwise described.

[b] Isolated yield and in all cases < 10% yields 1,2 and 1,4 addition products (β-methyl ketone products) were obtained determined by ^{1}H NMR of crude reaction mixtures.

[c] The *ee* value was determined by Chiral HPLC or chiral GC analysis. Absolute configurations were assigned by analogy (entry 1).

[d] Absolute configuration assigned by comparison with known compounds.[9c]

[e] CuI (5 mol%), (*S*)-Tol-BINAP (7.5 mol%).

[f] (*R*)-Tol-BINAP was used and < 10% yields 1,2- and 1,4-addition products were obtained as determined by ^{1}H NMR of the crude reaction mixture.

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[12] The CA reaction of MeMgBr with esters **4** (R = Ph, furyl, cyclohexyl) provided 1,4- and 1,2-addition products with very poor enantioselectivities.

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