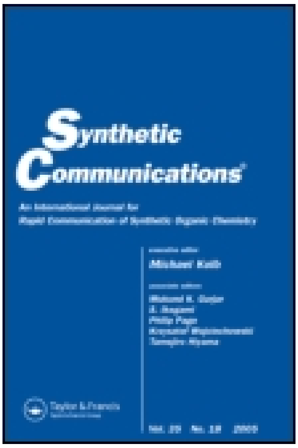

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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To cite this article: Gao Qi & Zaher M. A. Judeh (2012): Catalytic Enantioselective Conjugate Addition of Grignard Reagents to Cyclic Enones Using C_1-1,1′-Bisisoquinoline-Based Chiral Ligands, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:11, 1585-1592

To link to this article: http://dx.doi.org/10.1080/00397911.2010.541969

Synthetic Communications®, 42: 1585–1592, 2012
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ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.541969

CATALYTIC ENANTIOSELECTIVE CONJUGATE ADDITION OF GRIGNARD REAGENTS TO CYCLIC ENONES USING C_1-1,1′-BISISOQUINOLINE-BASED CHIRAL LIGANDS

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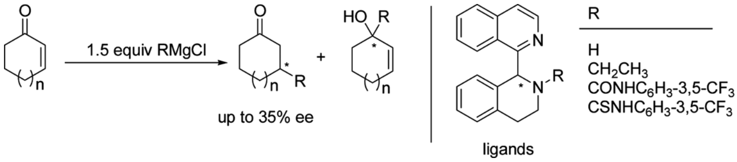
GRAPHICAL ABSTRACT



Abstract *New highly constrained chiral* C_1*-1,1′-bisisoquinoline ligands were examined in the enantioselective conjugate addition of Grignard reagents to cyclohexenone and cyclopentenone. The desired 1,4-adducts were obtained in excellent yield and moderate enantiomeric excess (up to 35%).*

Keywords Asymmetric catalysis; C_1-1,1′-bisisoquinoline; cyclic enones; enantioselective conjugate addition

INTRODUCTION

The conjugate addition (1,4-addition) of carbon nucleophiles to α,β-unsaturated carbonyl compounds is a key C-C bond-forming reaction. Tremendous efforts have been devoted over the past three decades to perfect and develop robust, widely applicable, and highly efficient chiral catalysts for the construction of numerous chiral compounds using this reaction. Various nucleophiles sources including Grignard reagents have been explored.[1] Because of the very high reactivity of Grignard reagents, their conjugate addition to α,β-unsaturated carbonyl systems normally leads to uncatalyzed 1,2- and/or 1,4-additions. However, because of their obvious advantages, such as ready availability and cheap price, considerable effort has been made to utilize Grignard reagents in copper-catalyzed asymmetric conjugated additions with variable success.[2]

Received August 31, 2010.

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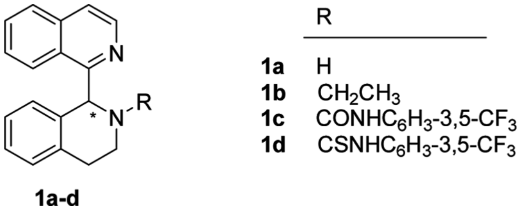


Figure 1. C_1-1,1′-Bisisoquinoline ligands **1a–d**.

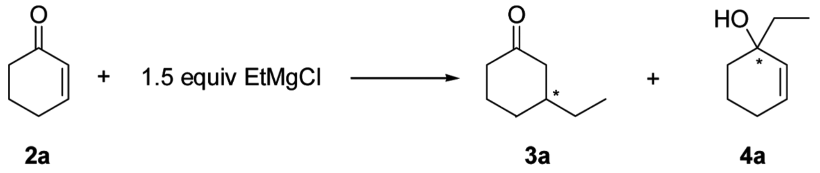
Villacorta and coworkers reported the first successful case of conjugate addition of Grignard reagents to enones using a catalytic amount of Cu-amide complexes.[3] Subsequently, a variety of catalytic systems, mainly based on Cu-thiolates[4] and phosphine-oxazolines,[5] were introduced. At this stage, the scope of the ligands remained limited and the enantiomeric excesses (ees) infrequently reached the 90% level. In 2004, Feringa and coworkers introduced chiral diphosphines, Taniaphos and Josiphos, that provided excellent *ees* using cyclic (up to 96% *ee*)[6] and acyclic (up to 98% *ee*)[7] enones. Recently, martin and coworkers reported extremely successful Cu-diaminocarbene ligands for asymmetric conjugate addition of Grignard reagents to β,β′-disubstituted enones (*ees* up to 96%).[8] Such catalytic results inspired many researchers to use Grignard reagents for selective conjugate addition to a wide range of substrates.

We have studied the structures and properties of bisisoquinolines for a long time[9] and recently reported the synthesis of novel chiral C_1-1,1′-bisisoquinoline ligands and their successful application in the enantioselective addition of diethylzinc to various aldehydes.[10] Herein, application of chiral C_1-1,1′-bisisoquinolines **1a–d** (Fig. 1) is examined in the copper-prompted asymmetric conjugate addition of Grignard reagents to cyclic enones with the aim of expanding the utility of these ligands and finding the factors that affect the enantioinduction using these ligands.

RESULTS AND DISCUSSION

At first, the reaction conditions were optimized using EtMgCl as Grignard reagent, 2-cyclohexenone **2a** as the enone, and (−)-**1a** as a model ligand. During the experimental process, we found that almost all the reactions gave quantitative yield of products. Therefore, only the ratio between 1,4-/1,2-adduct and *ee* of 1,4-adduct were studied. The optimization was examined using metal ions $ZnCl_2$ and $Cu(OTf)_2$. The reaction with either $ZnCl_2$/(−)-**1a** or $Cu(OTf)_2$/(−)-**1a** was completed within 15 min at −90 °C to give a mixture of 1,4-adduct **3a** and 1,2-adduct **4a** (Table 1, entries 1 and 2). Reaction with $Cu(OTf)_2$/(−)-**1a** provided better regioselectivity (**3a**/**4a**: 87/13) and enantioselectivity (22% *ee*) of the desired product **3a** compared to the regioselectivity (**3a**/**4a**: 84/16) and enantioselectivity (2% *ee*) obtained with $ZnCl_2$/(−)-**1a**. Having confirmed that the copper ion was superior for this reaction, the effects of various copper sources [CuI, $CuCl_2$, and $Cu(AcAc)_2$] were investigated (Table 1, entries 3–5). The reactions using CuI and $Cu(AcAc)_2$ gave products with similar and moderate regioselectivity (**3a**/**4a** as 81/19 and 82/18, respectively) and poor enantioselectivity (4% and 7% *ee* of **3a**, respectively) (Table 1, entries 3 and 5). In comparison, the reaction performed with $CuCl_2$ (Table 1, entry 4)

Table 1. EtMgCl conjugate addition to enone **2a** in the presence of salt/ligand



Entry	Ligand (mol%)	Metal salt	Solvent	Temp. (°C)	**3a**/**4a**[a]	*ee* of **3a**[b] % (configuration)[c]
1	(−)-**1a** (10)	$ZnCl_2$	THF	−90	84/16	2 (*S*)
2	(−)-**1a** (10)	$Cu(OTf)_2$	THF	−90	87/13	22 (*S*)
3	(−)-**1a** (10)	CuI	THF	−90	81/19	4 (*S*)
4	(−)-**1a** (10)	$CuCl_2$	THF	−90	89/11	35 (*S*)
5	(−)-**1a** (10)	$Cu(AcAc)_2$	THF	−90	82/18	7 (*S*)
6	(−)-**1a** (10)	$CuCl_2$	Et_2O	−90	95/5	0
7	(−)-**1a** (10)	$CuCl_2$	toluene	−90	91/9	0
8	(−)-**1a** (10)	$CuCl_2$	CH_2Cl_2	−90	68/32	28 (*S*)
9	(−)-**1a** (10)	$CuCl_2$	THF	−30	100/0	3 (*S*)
10	(−)-**1a** (5)	$CuCl_2$	THF	−90	89/11	24 (*S*)
11	(−)-**1a** (20)	$CuCl_2$	THF	−90	97/3	13 (*S*)
12	(−)-**1a** (100)	$CuCl_2$	THF	−90	100/0	13 (*S*)
13	(+)-**1b** (10)	$CuCl_2$	THF	−90	94/6	8 (*S*)
14	(+)-**1c** (10)	$CuCl_2$	THF	−90	68/32	0
15	(+)-**1d** (10)	$CuCl_2$	THF	−90	85/15	0

[a] The ratio of **3a**/**4a** was determined by GC-mass using an HP-5 column.

[b] The *ee* was determined by GC using a Chiraldex G-TA column.

[c] The configuration was determined by comparing the sign of optical rotation value with the literature value.[11a]

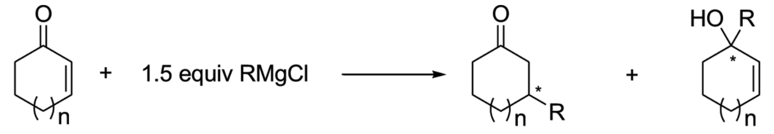
gave enhanced regioselectivity (**3a**/**4a** as 89/11) and enantioselectivity of **3a** (35% *ee*). Thus, $CuCl_2$ was chosen for further investigations.

The effect of typical coordinating [tetrahydrofuran (THF) and Et_2O] and noncoordinating solvents (toluene and CH_2Cl_2) were examined in the addition of EtMgCl to enone **2a**. Surprisingly, reactions using Et_2O or toluene gave *racemic* **3a** (Table 1, entries 6 and 7), while reactions in THF and CH_2Cl_2 gave **3a** in moderate *ees* (35% and 28% respectively, Table 1, entries 4 and 8). Furthermore, the reaction in THF showed much better regioselectivity than the reaction in CH_2Cl_2 (**3a**/**4a** as 89/11 *vs* 68/32). Thus, THF was inferred to be the best solvent. Temperature was found to greatly affect the reactions; increasing the temperature from −90 °C to −30 °C resulted in dramatic reduction of the enantioselectivity, where product **3a** showed only 3% *ee* (Table 1, entry 9). Catalyst loading was another factor examined. Reactions in the presence of 5, 10, 20, and 100 mol% loading of $CuCl_2$/(−)-**1a** (with respect to enone **2a**) were carried out in THF at −90 °C (Table 1, entries 4 and 10–12). An increase of $CuCl_2$/(−)-**1a** from 5 mol% to 100 mol% resulted in an increase in the ratio of **3a**/**4a** from 89/11 to 100/0. This observation indicated that ligand (−)-**1a** had positive influence on the regioselectivity of the reaction. However, the highest *ee* of **3a** was observed when 10 mol% of $CuCl_2$/(−)-**1a** was used; higher or lower catalyst loading afforded inferior ees. Thus, 10 mol% loading was chosen as the best loading amount of $CuCl_2$/(−)-**1a** for this reaction.

Other chiral ligands were examined in conjugate addition of EtMgCl to enone **2a** under the condition established in Table 1, entry 4. The reaction using ligand (+)-**1b** gave product **3a** in 8% *ee* with the major enantiomer having the (*S*) configuration (Table 1, entry 13). When using urea (+)-**1c** or thiourea (+)-**1d** as ligand, only *racemic* products were obtained (Table 1, entries 14 and 15). Those results might have arisen because of the crowdedness brought by the substituents on the amino nitrogen, which prevented inefficient coordination of $CuCl_2$ and Grignard reagent to the ligands.

Several Grignard reagents besides EtMgCl were added to enone **2a** under optimum conditions to study the scope and limitation of ligand (−)-**1a**. In general, good regioselectivities of the desired 1,4-adducts (compounds **3b**–**3e**) were obtained in all cases. Of the Grignard reagents examined, only BuMgCl gave the 1,4-adduct **3c** in significant *ee* (35%, Table 2, entry 2), while *i*-PrMgCl gave the 1,4-adduct **3b** in a low 8% *ee* (Table 2, entry 1), and the rest of the Grignard reagents such as PhMgCl

Table 2. Grignard reagent conjugate addition to enone **2a** or **2b** in the presence of copper salt/ligand



n	
1	**2a**
0	**2b**

n	R		
1	*i*-Pr	**3b**	**4b**
1	Bu	**3c**	**4c**
1	Ph	**3d**	**4d**
1	Bn	**3e**	**4e**
0	*i*-Pr	**3f**	**4f**
0	Cy	**3g**	**4g**

Entry	N	R	Ligand (mol%)	1,4-Adduct/ 1,2-adduct[c]	*ee* of 1,4-adduct[d] (%) (configuration)[e]
1[a]	1	*i*-Pr	(−)-**1a** (10)	90/10	8 (*S*)
2[a]	1	Bu	(−)-**1a** (10)	100/0	35 (*S*)
3[a]	1	Ph	(−)-**1a** (10)	91/9	0
4[a]	1	Bn	(−)-**1a** (10)	100/0	0
5[b]	0	*i*-Pr	(−)-**1a** (15)	89/11	27 (*S*)
6[b]	0	*i*-Pr	(+)-**1a** (15)	97/3	30 (*R*)
7[b]	0	*i*-Pr	(+)-**1b** (15)	96/4	25 (*S*)
8[b]	0	*i*-Pr	(+)-**1c** (15)	89/11	0
9[b]	0	*i*-Pr	(+)-**1d** (15)	83/17	0
10[b]	0	Cy	(−)-**1a** (15)	100/0	18 (*S*)

[a] Reaction conditions: 10 mol% (−)-**1a**, 10 mol% $CuCl_2$, THF, −90 °C, 15 min.

[b] Reaction conditions: 15 mol% ligand, 15 mol% $Cu(OTf)_2$, THF, −90 °C, 15 min.

[c] The ratio of 1,2-adduct/1,4-adduct was determined by GC-mass using HP-5 column.

[d] The *ee* was determined by GC using Chiraldex G-TA column or TBDAc column.

[e] The configuration was determined by comparing the sign of optical rotation value with literature.[4b,11]

and BnMgCl provided only *racemic* products (Table 2, entries 3 and 4). Those results indicated that the bulkiness of the alkyl substituents in the Grignard reagents affected the *ees* of products significantly. The Grignard reagents with small groups such as Et and Bu gave the products in greatest *ee*, while bulkier groups (*i*-Pr, Ph, and Bn) gave negligible *ee* or *racemic* products.

Next, the substrate scope was examined where 2-cyclopentenone **2b** was used. The optimization of the reaction conditions was performed using *i*-PrMgCl as the standard Grignard reagent and (−)-**1a** as the standard ligand. After careful screening of the factors such as copper salts, solvents, reaction temperature, and loading of catalyst, the optimum condition was established as shown in Table 2. Addition of *i*-PrMgCl to enone **2b** under this condition afforded 1,4-adduct **3f** in moderate *ee* (27%, Table 2, entry 5). The efficiencies of other chiral ligands on addition of *i*-PrMgCl to enone **2b** were also investigated under the optimum reaction conditions. The reaction catalyzed by $Cu(OTf)_2$/(+)-**1a** gave the complementary (*R*)-**3f** in a similar *ee* of 30% (Table 2, entry 6). It was interesting that ligand (+)-**1b** gave product **3f** in similar *ee* as that of (+)-**1a** but with inverse configuration [25% *ee* of (*S*)-**3f**, Table 2, entry 7]. Not surprisingly, ligands (+)-**1c** and (+)-**1d** gave product **3f** in *racemic* form (Table 2, entries 8 and 9). Only CyMgCl was attempted besides *i*-PrMgCl in the addition to enone **2b**, and the reaction proceeded to give exclusively the 1,4-adduct **3g** in 18% *ee* (Table 2, entry 10).

CONCLUSION

Chiral C_1-1,1′-bisisoquinoline ligand **1a** showed moderate efficiency in the enantioselective conjugate addition of EtMgCl and BuMgCl to cyclohexenone and *i*-PrMgCl to cyclopentenone. The desired 1,4-adducts were obtained in excellent yield and moderate *ee* (up to 35%). However, other chiral bisisoquinoline ligands **1c** and **1d** were found inefficient for this reaction because of the ineffective coordination of $CuCl_2$ and Grignard reagent to the ligands.

EXPERIMENTAL

All commercial materials were used as received. Anhydrous THF, diethyl ether, and toluene were obtained from the Pure Solv PS-400-5-MD system. Anhydrous CH_2Cl_2 was distilled from calcium hydride. Gas chromatography (GC) was performed on an Agilent 6890 using Agilent HP-5, Astec Chiraldex G-TA, or MN Hydrodex-β-TBDAc column. GC–mass spectra were recorded on an Agilent 6890 GC system with an Agilent 5973 mass selective detector. Optical rotations were measured using a Jasco P-1020 polarimeter.

General Procedure for Conjugate Addition of Grignard Reagents to Enones

Ligand and copper salt were dissolved in THF to form a solution. The mixture was stirred at room temperature for 1 h, and the enone was injected via a syringe needle. The mixture was stirred for another 1 h at room temperature and then cooled to −90 °C (MeOH mixed with liquid nitrogen). The Grignard reagent was injected in a dropwise fashion over a period of 5 min, and the mixture was stirred for another 15 min. The reaction was then quenched with saturated NH_4Cl solution, and the resulting mixture was allowed to warm up to rt. The organic phase was separated, washed with HCl solution and saturated Na_2CO_3 solution, dried over $MgSO_4$, and filtered. The resulting organic solution was diluted with THF and subjected to GC-mass and GC directly for analysis. The ratio of 1,4-/1,2 adduct was determined by GC-mass using HP-5 column. The *ee* value was determined by GC using a Chiraldex G-TA column or Hydrodex-β-TBDAc column. The absolute configuration of the major enantiomer of product was assigned by comparing the sign of optical rotation value with literature data.

Selected Data

(*S*)-3-Ethylcyclohexanone (*S*)-3a (Table 1, Entry 4). The *ee* of 35% was determined by GC. GC (Chiraldex G-TA column): helium flowrate = 2.0 mL/min, oven = 110 °C, $t_1 = 5.48$ min for (*R*) and $t_2 = 5.64$ min for (*S*). $[\alpha]_D^{25} = -13.3$ ($c = 0.66$, $CHCl_3$) (lit.[11a] $[\alpha]_D = +119.7$ ($c = 1.0$, $CHCl_3$) for 76% *ee* (*R*)).

(*S*)-3-Isopropylcyclohexanone (*S*)-3b (Table 2, Entry 1). The *ee* of 8% was determined by GC. GC (Hydrodex-β-TBDAc column): helium flowrate = 2.0 mL/min, oven = 130 °C, $t_1 = 8.73$ min for (*R*) and $t_2 = 9.22$ min for (*S*). $[\alpha]_D^{25} = -5.3$ (c = 0.70, $CHCl_3$) (lit.[4b] $[\alpha]_D = +13.6$ (c = 1.92, $CHCl_3$) for 72% *ee* (*R*)).

(*S*)-3-Butylcyclohexanone (*S*)-3c (Table 2, Entry 2). The *ee* of 35% was determined by GC. GC (Hydrodex-β-TBDAc column): helium flowrate = 2.0 mL/min, oven = 130 °C, $t_1 = 14.78$ min for (*R*) and $t_2 = 15.31$ min for (*S*). $[\alpha]_D^{25} = -10.5$ (c = 1.24, $CHCl_3$) (lit.[11b] $[\alpha]_D^{22} = +12.2$ (c = 1.0, $CHCl_3$) for 90% *ee* (*R*)).

(*S*)-3-Isopropylcyclopentanone (*S*)-3f (Table 2, Entry 5). The *ee* of 27% was determined by GC. GC (Chiraldex G-TA column): helium flowrate = 0.8 mL/min, oven = 77 °C, $t_1 = 40.70$ min for (*S*) and $t_2 = 41.93$ min for (*R*). $[\alpha]_D^{25} = -13.8$ (c = 0.30, $CHCl_3$) (lit.[11c] $[\alpha]_D^{23} = -87.5$ (c = 0.28, $CHCl_3$) for (*S*)).

(*S*)-3-Cyclohexylcyclopentanone (*S*)-3g (Table 2, Entry 10). The *ee* of 18% was determined by GC. GC (Hydrodex-β-TBDAc column): helium flowrate = 2.0 mL/min, oven = 160 °C, $t_1 = 11.83$ min for (*S*) and $t_2 = 12.10$ min for (*R*). $[\alpha]_D^{25} = -6.3$ (c = 0.75, $CHCl_3$) (lit.[11b] $[\alpha]_D^{22} = +8.6$ (c = 1.0, $CHCl_3$) for 93% *ee* (*R*)).

ACKNOWLEDGMENT

We gratefully acknowledge Nanyang Technological University for financial support (Grant No. RG27/07).

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