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Copper-catalyzed asymmetric conjugate addition with Grignard reagents and SimplePhos ligands

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ABSTRACT

Herein we report the copper-catalyzed asymmetric conjugate addition of Grignard reagents to cyclic and acyclic enones, with SimplePhos as chiral ligands. A variety of Grignard reagents can be added to a range of cyclic and acyclic enones, with moderate to good enantioselectivities (ee's up to 86%).

1. Introduction

The asymmetric conjugate addition (A.C.A.) of organometallic reagents to Michael acceptors is amongst the most important methodologies to create a chiral C–C bond.[1] In this field, much effort has been directed toward the development of copper-catalyzed reactions.[2] Organozinc reagents have been the most successful of the organometallic reagents in this respect. Dialkylzinc reagents offer some advantages because of their low reactivity and their high tolerance toward functional groups on the substrate, but also on the organozinc itself.[3] However, their diversity remains limited and this is why the use of Grignard reagents is a good option.

The first example of Cu-catalyzed conjugate addition with Grignard reagents as organometallics was reported by Karash in 1941, in a racemic version.[4] Since then, many groups have developed several methodologies to afford the chiral version of this reaction via diastereoselective or enantioselective ways. The first example of enantioselective Cu-catalyzed conjugate addition of Grignard reagents was reported by Lippard and co-workers in 1988, with a chiral bidentate *N*,*N*′-dialkyl-substituted aminotroponeimin ligand.[5] Since then, various bidentate ligands allowed high regio- and enantioselectivities of this reaction to a large scope of enones.[6] The only case where monodentate ligands were used in copper-catalyzed A.C.A. was described by Feringa with phosphoramidite-type ligands to acyclic enones in 2008 (ee's up to 80%).[7] In this respect, we herein report the use of SimplePhos ligands in the A.C.A. of Grignard reagents to cyclic and acyclic enones catalyzed by copper salts.

Monodentate SimplePhos ligands have already shown their efficiency in various asymmetric copper-catalyzed reactions, such as the conjugate addition of dialkylzinc or trialkylaluminium to di- and trisubstituted enones[8–10] or the allylic alkylation,[7] in kinetic resolution of vinyloxiranes[10] but also in desymmetrization of *meso* compounds.[11]

2. Results and discussion

We report herein a full account of our results in the copper-catalyzed A.C.A. of a large scope of Grignard reagents to various enones with SimplePhos ligands.

Cyclohexenone **1** is the archetypical enone in ACA. With this substrate, we have searched the optimal copper source, solvent, reaction temperature, ligand, and halide in the Grignard reagent for the addition of various Grignard reagents (alkyl or aryl). All the optimizations were carried out with SimplePhos ligand **L1** (Fig. 1).

We initially tested the addition of EtMgBr to cyclohexenone **1** in the presence of several copper salts (2 mol %) and ligand **L1** (4 mol %) in ether at −30 °C. All the results are summarized in Table 1. Various copper(I) and (II) salts were screened in this study. The first promising results were achieved with $CuBr_2$, which gave 54% ee in the addition of EtMgBr to the model substrate **1** (Table 1, entry 5). Some other copper salts such as CuI, $Cu(OAc)_2{\cdot}H_2O$, and $Cu(acac)_2$ showed almost the same results, 51% ee (entries 2, 8, 10). All other copper sources gave lower enantioselectivities. In contrast to diorganozinc or triorganoaluminium reagents, the 1,4-regioselectivity is not perfect. The direct carbonyl addition product (1,2-addition) is always observed, from negligible (entries 1, 3, 4, 6, 10, and 11) to 50% (entry 7, with CuCN). For the next experiments, we chose $CuBr_2$ as the best compromise.

Next, we examined the influence on the enantioselectivity of the copper/ligand ratio as well as the catalyst loading in the addition of EtMgBr to cyclohexenone **1** (Table 2). No improvement in enantioselectivity was observed with a ratio of $CuBr_2$/ligand ranging from 1/1.5 to 1/3 and 1/6 (Table 2, entries 1–3, 5–6). From these results, we concluded that the best results in terms of asymmetric induction were obtained with the copper to ligand ratio of 1/4 with 61% ee. Unfortunately, at the same time, a decrease of the 1,4-adduct production was observed (1,4:1,2 70:30) (Table 2, entry 4).

The addition of EtMgBr to **1** was next studied at different temperatures and in different solvents (Table 3). Performing the

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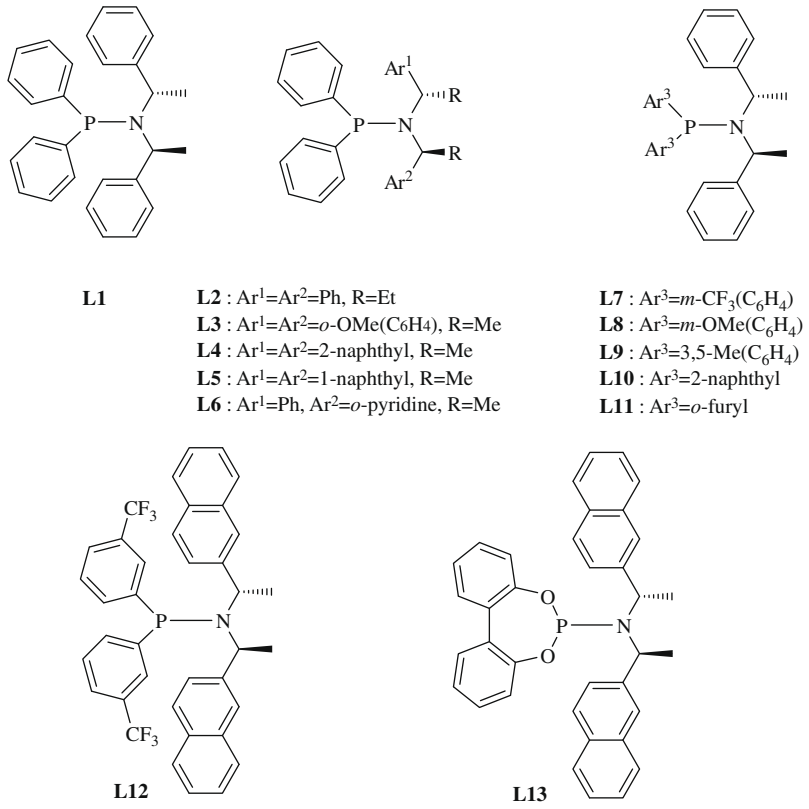
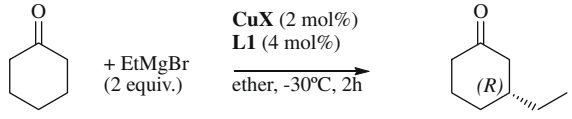


Figure 1. SimplePhos ligands used in this study.

Table 1
Optimizations of copper salts

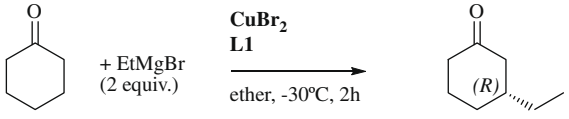


1 2

Entry	CuX	Conv.[a] (%)	1,4:1,2[a]	ee[b] (%)
1	CuTC	100	99:1	45
2	CuI	98	79:21	51
3	CuCl	99	97:3	47
4	CuBr	97	96:4	47
5	$CuBr_2$	98	84:16	**54**
6	$CuBr{\cdot}Me_2S$	99	97:3	46
7	CuCN	95	49:51	31
8	$Cu(OAc)_2{\cdot}H_2O$	98	92:8	51
9	$Cu(CH_3CN)_4BF_4$	98	76:24	49
10	$Cu(acac)_2$	98	93:7	51
11	$Cu(OTf)_2$	99	98:2	41

[a] Determined by GC–MS.
[b] Determined by chiral GC.

Table 2
Optimization of the copper/ligand ratio



1 2

Entry	Ratio $CuBr_2$/**L1** (mol %/mol %)	Conv.[a] (%)	1,4:1,2[a]	ee[b] (%)
1	1/1.5 (2/3)	98	84:16	51
2	1/2 (2/4)	99	84:16	54
3	1/3 (2/6)	99	81:09	55
4	1/4 (2/8)	91	70:30	**61**
5	1/5 (2/10)	98	75:25	42
6	1/6 (2/12)	96	69:31	54

[a] Determined by GC–MS.
[b] Determined by chiral GC.

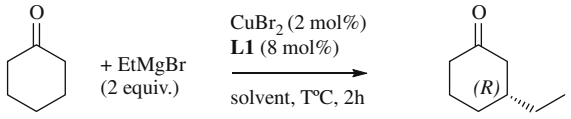
reaction in dichloromethane or in 1-methyl-THF at −30 °C allowed an increase in the regioselectivity (1,4-addition vs 1,2-addition) but a high decrease in the enantioselectivity from 27% and 22%, respectively (Table 3, entries 2 and 3). Different temperatures were evaluated in diethylether but both lower and higher temperatures produced a decrease in enantioselectivity (Table 3, entries 4–7).

To finish the optimizations of experimental conditions, several SimplePhos ligands were tested (Table 4)

The copper-catalyzed A.C.A. of EtMgBr to cyclohexenone **1** in the presence of ligand SimplePhos **L4** (with the 2-naphthyl group on the chiral amine) gave the corresponding adduct **2** in an improved regioselectivity (93:7) and enantioselectivity of 67% (Table 4, entry 4). Furthermore, the slow addition of the Grignard reagent over 1 h could increase the asymmetric induction to 72% ee (Table 4, entry 5). In other applications of SimplePhos ligands, we have often seen the importance of the steric bulkiness on the chiral amine part of the ligand in improving the enantioselectivity.[8–12] The ligand **L3**, with a chelating group ($Ar^1 = Ar^2 = o$-$OMe(C_6H_4)$), also showed good enantioselectivities up to 69% but with a decrease in the regioselectivity (83:17) (Table 4, entry 3). The enantioselectivities observed with the other ligands were consistently poorer.

With these optimized conditions in hand, we decided to use 2 mol % of $CuBr_2$ and 8 mol % of **L4** in ether to screen several Grignard reagents with a range of enones (cyclic or acyclic), to determine if the new system was viable (Table 5). Thus, various alkyl

Table 3
Optimizations of the temperature and the solvent of the reaction

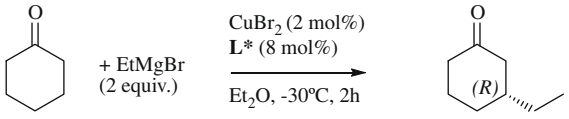


1 2

Entry	Temperature (°C)	Solvent	Conv.[a] (%)	1,4:1,2[a]	ee[b] (%)
1	−30	Et_2O	91	70:30	**61**
2	−30	CH_2Cl_2	100	99.5:0.5	27
3	−30	1-Me–THF	100	98:2	22
4	−78	Et_2O	100	89:11	32
5	−45	Et_2O	100	78:22	52
6	−10	Et_2O	100	90:10	52
7	0	Et_2O	100	99:1	52

[a] Determined by GC–MS.
[b] Determined by chiral GC.

Table 4
Optimization of SimplePhos ligands



1 2

Entry	Ligand	Conv.[b] (%)	1,4:1,2[b]	ee[c] (%)
1	**L1**	91	70:30	61
2	**L2**	97	93:7	39
3	**L3**	95	83:17	69
4	**L4**	95	93:7	67
5[a]	**L4**	100	93:7	**72**
6	**L5**	93	69:31	39
7	**L6**	98	58:42	20
8	**L7**	72	83:17	5
9	**L8**	95	85:15	46
10	**L9**	95	93:7	9
11	**L10**	98	86:14	20
12	**L11**	100	94:36	36
13	**L12**	95	94:6	29

[a] Addition of EtMgBr over 1 h.
[b] Determined by GC–MS.
[c] Determined by chiral GC.

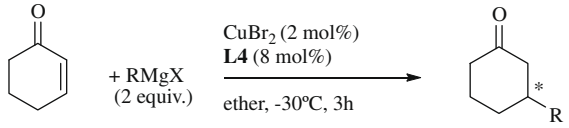
and aryl Grignard reagents were added to cyclohexenone **1**. When linear alkyl Grignard reagents (MeMgBr, EtMgBr, *n*-BuMgBr, *n*-Hex-5-enylMgBr, and *n*-octylMgBr) were used as nucleophiles, the corresponding adducts **2**–**6** were obtained with 51–86% ee (Table 5, entries 1–3, 6–7). We observed an improvement in the enantioselectivity with the length of the alkyl chain being added. The halide of the Grignard reagent was also important. A decrease in both the regio- and enantioselectivity was observed by using *n*-BuMgCl (1,4/1,2 66:34, 69% ee) instead of *n*-BuMgBr (80% ee) (Table 5, entry 5). For the sake of comparison, phosphoramidite ligand **L13** (Fig. 1) was also tested for the addition of *n*-BuMgBr to **1**. Unfortunately only 69% ee was obtained, with a slightly higher regioselectivity for the 1,4 adduct (Table 5, entry 4).

Other primary alkyl Grignard reagents were also screened without any increase in the asymmetric induction (ee's up to 72%) (Table 5, entries 8 and 9). For secondary alkyl Grignard reagents, *i*-PrMgBr and *c*-HexMgBr, enantioselectivities were found to be 64% and 76%, respectively (Table 5, entries 10 and 11). For the bulky Grignard reagents *t*-BuMgBr, only the racemate adduct was obtained (Table 5, entry 12). Finally, the addition of an aryl Grignard reagent, PhMgBr, proceeded in a moderate regioselectivity (77:23) and with a moderate enantioselectivity (60%) (Table 5, entry 13).

Next, the addition of EtMgBr was investigated with various cyclic enones with 5-, 7-, and 15-membered ring systems (Table 6). In comparison with cyclohexenone **1**, enones with a smaller ring, such as **13**, or a larger cycle, such as **14** or **15**, showed lower enantioselectivities: 44%, 55%, and 4%, respectively (Table 6, entries 1, 3 and 4).

Finally, we studied the addition of EtMgBr to alkyl linear and aryl acyclic α,β-unsaturated ketones (Table 7). However, regardless of which substrate was used, very low enantioselectivities were reported with at best 36% ee for the adduct **23** (Table 7, entry 1). Only racemate adducts were found with an aryl substrate (Table 7,

Table 5
Screening of Grignard reagents to **1**

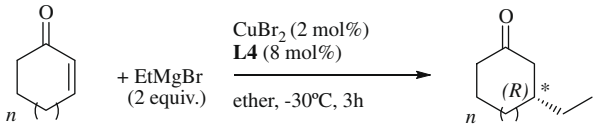


3 2-12

Entry	RMgX	Adduct	Conv.[b] (%)	1,4:1,2[b]	ee[c] (%) (Abs. Conf.)
1	EtMgBr	**2**	100	93:7	72 (*R*)
2	MeMgBr	**3**	100	93:7	51 (*R*)
3	*n*-BuMgBr	**4**	100	92:8	80 (*R*)
4[a]	*n*-BuMgBr	**4**	100	94:6	68 (*R*)
5	*n*-BuMgCl	**4**	80	66:34	69 (*R*)
6	*n*-Hex-5-enylMgBr	**5**	100	73:27	80
7	*n*-OctylMgBr	**6**	100	83:17	**86** (*R*)
8	*i*-BuMgBr	**7**	100	93:7	54 (*S*)
9	$Ph(CH_2)_2MgBr$	**8**	100	100:0	72 (*S*)
10	*i*-PrMgBr	**9**	100	100:0	64
11	*c*-HexMgBr	**10**	100	98:2	76
12	*t*-BuMgBr	**11**	100	100:0	0
13	PhMgBr	**12**	91	77:23	60

[a] With phosphoramidite ligand **L13**.
[b] Determined by GC–MS.
[c] Determined by chiral GC.

Table 6
Addition of EtMgBr to various cyclic enones



13 : n=0
1 : n=1
14 : n=2
15 : n=10

16 : n=0
2 : n=1
17 : n=2
18 : n=10

Entry	n	Conv.[a] (%)	1,4:1,2[a]	ee[b] (%)
1	0	100	94:6	44
2	1	100	93:7	**72**
3	2	100	75:25	55
4	10	100	81:19	4

[a] Determined by GC–MS.
[b] Determined by chiral GC.

entries 3 and 4). These results showed the limitations of the system with SimplePhos ligands.

3. Conclusion

In conclusion, we have demonstrated that monodentate SimplePhos ligands could efficiently perform the copper-catalyzed asymmetric conjugate addition of Grignard reagents to cyclohexenone **1**, with at best 86% ee. Lower results were observed with other cyclic and acyclic α,β-unsaturated ketones.

4. Experimental section

4.1. General procedure

4.1.1. Typical procedure for enantioselective copper-catalyzed conjugate addition with Grignard reagents

A flame-dried Schlenk tube was charged with $CuBr_2$ (0.01 mmol) and the chiral ligand (0.04 mmol). Ether (1 ml) was added and the mixture was stirred at room temperature for 30 min. Then the Michael acceptor (0.5 mmol) in ether (1 ml) was added at room temperature and the reaction mixture was stirred for a further 5 min before being cooled to −30 °C. Then, the Grignard reagent (2 equiv) dissolved in 2 mL of Et_2O was introduced dropwise over 1 h. Once the addition was completed, the reaction was left at −30 °C for 2 h. The reaction was hydrolyzed by the addition of a saturated NH_4Cl solution. All the conjugate adducts are described in the literature. Enantiomeric excesses were determined by chiral GC or SFC.

4.2. Determination of enantiomeric excesses

4.2.1. (*R*)-3-Ethyl-cyclohexanone 2

Enantiomeric excess was measured by chiral GC: LIPODEX E, isotherm T = 60 °C, Rt_1 = 16.8 (*R*), Rt_2 = 20.5 (*S*).

4.2.2. (*R*)-3-Methyl-cyclohexanone 3

Enantiomeric excess was measured by chiral GC: HYDRODEX TBDM, T: 60 °C—flow rate 1 °C/min, Rt_1 = 19.58 (*R*), Rt_2 = 20.35 (*S*).

4.2.3. (*R*)-3-Butyl-cyclohexanone 4

Enantiomeric excess was measured by chiral GC: HYDRODEX TBDM, T: 60 °C—flow rate 1 °C/min, Rt_1 = 52.77 (*S*), Rt_2 = 53.03 (*R*).

4.2.4. 3-(Hex-5-enyl)-cyclohexanone 5

Enantiomeric excess was measured by chiral GC: LIPODEX E, T = 60 °C, flow rate 1 °C/min, Rt_1 = 41.92, Rt_2 = 42.40.

4.2.5. (*R*)-3-Octyl-cyclohexanone 6

Enantiomeric excess was measured by chiral GC: HYDRODEX TBDM, T: 60 °C—flow rate 1 °C/min, Rt_1 = 98.16 (*R*), Rt_2 = 98.5 (*S*).

4.2.6. (*S*)-3-Isobutyl-cyclohexanone 7

Enantiomeric excess was measured by chiral GC: LIPODEX E, T: 60 °C—flow rate 1 °C/min, Rt_1 = 16.85 (*S*), Rt_2 = 17.93 (*R*).

4.2.7. (*S*)-3-Phenethyl-cyclohexanone 8

Enantiomeric excess was measured by chiral SFC: Chiralcel AD-H column (2% MeOH flow rate 2 mL/min), Rt_1 = 6.82 (*S*), Rt_2 = 7.87 (*R*).

4.2.8. 3-Isopropyl-cyclohexanone 9

Enantiomeric excess was measured by chiral GC: HYDRODEX TBDM, isotherm T: 90 °C, Rt_1 = 29.03, Rt_2 = 29.51.

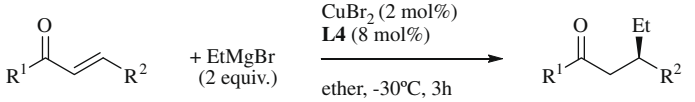
4.2.9. 3-Cyclohexyl-cyclohexanone 10

Enantiomeric excess was measured by chiral GC: HYDRODEX TBDM, T: 60 °C—flow rate 1 °C/min, Rt_1 = 72.86, Rt_2 = 73.01.

4.2.10. 3-*tert*-Butyl-cyclohexanone 11

Enantiomeric excess was measured by chiral GC: LIPODEX E, T: 60 °C—flow rate 1 °C/min, Rt_1 = 17.99, Rt_2 = 18.84.

Table 7
Addition of EtMgBr to various cyclic enones



19 : R^1=Me, R^2=*i*-Pr
20 : R^1=Me, R^2=C_5H_{11}
21 : R^1=Me, R^2=Ph
22 : R^1=Ph, R^2=Ph

23 : R^1=Me, R^2=*i*-Pr
24 : R^1=Me, R^2=C_5H_{11}
25 : R^1=Me, R^2=Ph
26 : R^1=Ph, R^2=Ph

Entry	Substrate	Conv.[a] (%)	1,4:1,2[a]	ee[b] (%) (Abs. Conf.)
1	**19**	100	97:3	36 (*R*)
5	**20**	94	66:34	15 (*S*)
6	**21**	100	100:0	0
7	**22**	100	100:0	3

[a] Determined by GC–MS.
[b] Determined by chiral GC.

4.2.11. 3-Phenyl-cyclohexanone 12

Enantiomeric excess was measured by chiral SFC: Chiralcel AD-H column (2% MeOH flow rate 2 mL/min), Rt_1 = 5.97, Rt_2 = 6.64.

4.2.12. (*R*)-3-Ethylcyclopentanone 16

Enantiomeric excess was measured by chiral GC: HYDRODEX B-3P isotherm T = 60 °C, Rt_1 = 27.79, Rt_2 = 28.57.

4.2.13. (*R*)-3-Ethyl-cycloheptanone 17

Enantiomeric excess was measured by chiral GC: LIPODEX E, isotherm 60 °C, Rt_1 = 35.78 (*S*), Rt_2 = 37.14 (*R*).

4.2.14. (*R*)-3-Ethylcyclopentadecanone 18

Enantiomeric excess was determined by chiral GC: HYDRODEX B-3P, isotherm T: 140 °C, Rt_1 = 62.8 (*R*), Rt_2 = 64.3 (*S*).

4.2.15. (*R*)-4-Ethyl-5-methylhexan-2-one 23

Enantiomeric excess was measured by chiral GC: LIPODEX E, T: 60 °C—flow rate 1 °C/min, Rt_1 = 5.88 (*R*), Rt_2 = 7.29 (*S*).

4.2.16. (*R*)-4-Ethylnonan-2-one 24

Enantiomeric excess was measured by chiral GC: LIPODEX E, isotherm 75 °C, Rt_1 = 38.21 (*S*), Rt_2 = 41.37 (*R*).

4.2.17. (*R*)-1,3-Diphenylpentan-1-one 25

Enantiomeric excess was measured by chiral SFC: Chiralcel OJ-H column (26% MeOH flow rate 2 mL/min), Rt_1 = 5.87 (*S*), Rt_2 = 6.63 (*R*).

4.2.18. (*R*)-1,3-Diphenylbutan-1-one 26

Enantiomeric excess was measured by chiral SFC: Chiralcel OD-H column (2% MeOH flow rate 2 mL/min), Rt_1 = 5.85 (*R*), Rt_2 = 6.25 (*S*).

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