Copper-catalyzed asymmetric conjugate addition of Grignard reagents to cyclic enones

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It is no longer necessary to use dialkylzinc reagents to obtain enantioselectivities >95% in the copper-catalyzed asymmetric conjugate addition of organometallic compounds to cyclic enones. We now report how this can be accomplished by using inexpensive and readily available Grignard reagents. Screening of bidentate ligands provided outstanding results with copper complexes of commercially available chiral ferrocenyl-based diphosphines, in particular TaniaPhos and JosiPhos derivatives. These catalysts tolerate a range of Grignard reagents and different cyclic enones as substrates, leading to high regioselectivities and unprecedented enantioselectivities. Moreover, the reactions are successful with moderate catalyst loading (5 mol %) under mild conditions and in the absence of additives.

The conjugate addition (1,4-addition) of carbon nucleophiles to α,β-unsaturated carbonyl compounds is one of the most widely used methods for the construction of C—C bonds (1). The development of highly enantioselective catalytic versions of this key transformation is of paramount importance (2–9). In recent years, the design of new chiral ligands and catalysts has led to the realization of asymmetric Michael additions (10, 11) and conjugate additions of dialkylzinc reagents (12, 13) as well as arylboronic acids (14) with excellent levels of stereocontrol. For the asymmetric conjugate addition of alkylmetals, the subject of the present study, particularly effective methods based on alkylzinc reagents are now available for various cyclic enones (12, 15) including the usually problematic cyclopentenones (16, 17), lactones (18), nitroalkenes (19, 20), and acyclic enones (21). Meanwhile, considerable difficulties have been experienced in attempts to reach high stereoselectivities in transition metal-catalyzed 1,4-addition of other organometallic reagents. Illustrative of this fact is that an effective copper-catalyzed enantioselective conjugate addition of Grignard reagents is lacking despite more than two decades of intensive research (2, 5–9).

In 1988, Lippard and coworkers (22, 23) reported the first enantioselective conjugate addition of a Grignard reagent to an enone using catalytic amounts of a copper amide complex. Shortly after this seminal work was published, various catalytic systems were developed based on copper thiolates (24–30) and monophosphine ligands (31–34), although in these systems, enantioselectivities rarely reached the 90% enantiomeric excess (ee) level. Notable exceptions are the two literature reports of 92% ee in the addition of BuMgCl to cyclic enones. Tomioka and coworkers (33) used 32 mol % of a chiral amidophosphine in the addition to cyclohexenone, and Stangeland and Sammakia (34) used 12 mol % of a chiral ferrocenyl monophosphine in the addition to cycloheptenone. Severe problems associated with the copper-catalyzed conjugate addition of Grignard reagents are the fast, uncatalyzed background reaction, the presence of competing chiral and achiral copper complexes in solution, the high sensitivity toward various reaction parameters, and the usually detrimental effect of the presence of halides on enantioselectivity (5, 35). Furthermore, the discovery of the efficiency of dialkylzinc reagents in the copper-catalyzed enantioselective conjugate addition clearly displaced the use of Grignard reagents in this asymmetric C—C bond formation (4–9). Dialkylzinc reagents have distinct advantages, compared with Grignard reagents, because they show low reactivity in uncatalyzed reaction and high tolerance for functional groups both in the substrate and the zinc reagent. Functionalized organozinc reagents are readily available from the corresponding alkenes through a hydroboration alkyl-transfer procedure (36). However, the use of alkylzinc halides instead of dialkylzinc reagents results in very low enantioselectivities. The Grignard version of this 1,4-addition remains challenging, because it is not only essential to obtain high ees but also to avoid the fast, uncatalyzed addition of the organomagnesium reagent to the carbonyl group (1,2-addition). Nevertheless, there are advantages in the use of common monoalkylmagnesium halide reagents as opposed to dialkylzinc compounds, most notably the ready availability of inexpensive Grignard reagents, the transfer of all the alkyl groups of the organometallic compound, and the higher reactivity of the magnesium enolate subsequently formed. The advantages of monoalkylmagnesium halides prompted us to search for a highly enantioselective family of ligands for this asymmetric transformation.

Chiral diphosphine ligands have dominated the field of asymmetric catalysis in the last 30 years (37, 38); however, none of these ligands have been reported to be effective in the conjugate addition of Grignard reagents. In principle, diphosphines do not match with the metal-differentiating coordination concept (32). It should be emphasized that until now, most successful ligands in the field of copper-catalyzed 1,4-addition of Grignard reagents fulfill the criteria of combining P, S, or Se with N or O donor atoms in their structure to coordinate selectively with Cu and Mg of the organometallic species, respectively (24–34). Among the most important bidentate ligands in asymmetric catalysis are ferrocenyl diphosphine ligands, especially TaniaPhos (**1**; Fig. 1 and refs. 39 and 40) and JosiPhos (**6**; Fig. 1 and refs. 41 and 42). In recent years, these prominent ligands, developed originally for use in enantioselective hydrogenation reactions, have proven to be successful in other asymmetric transformations (43–45). In particular, JosiPhos ligands exhibit moderate enantioselectivities (up to 71% ee) in the copper-catalyzed conjugate addition of dialkylzinc reagents to enones (44).

Here, we report copper-catalyzed asymmetric conjugate additions of Grignard reagents to cyclic enones with enantioselectivities up to 96%. This level of stereocontrol is achieved by using CuCl or CuBr·SMe$_2$ as metal source, simple alkylmagnesium bromides as nucleophiles, and commercially available ferrocenyl diphosphines as chiral ligands.

Fig. 1. Chiral ferrocenyl-based diphosphines.
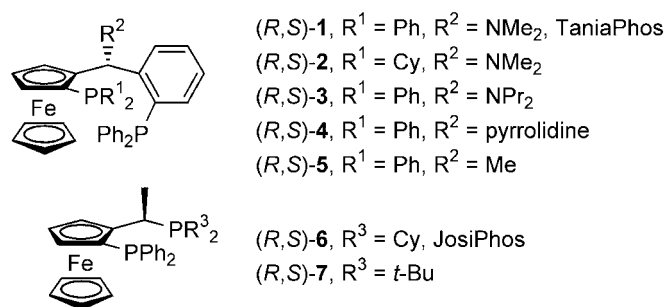

Fig. 2. Chiral diphosphine ligands.

Materials and Methods

General Procedures and Instrumental Techniques. All reactions were performed in a dry argon atmosphere using standard Schlenk techniques. Solvents were reagent-grade, dried, and distilled before use following standard procedures. We recorded ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra at room temperature in CDCl$_3$ on a Gemini 200 (200 MHz) or VXR300 (300 MHz) spectrometer (Varian). Chemical shifts were determined relative to the residual solvent peaks (CHCl$_3$, δ = 7.26 ppm for hydrogen atoms, δ = 77 ppm for carbon atoms; H$_3$PO$_4$, δ = 0 ppm for phosphorus atoms). Progress of the reactions was monitored by GC MS (GC, HP6890; MS, HP5973) with an HP1 column (Agilent Technologies, Palo Alto, CA). ees were determined by capillary GC analysis (HP5890 or HP6890) with a Chiraldex G-TA column for **9a**, **9e**, **9f**, and **12c**; a Chiraldex A-TA column for **9b–9d**, **9g–9i**, and **12b**; or a CP-Chiralsil-Dex-CB column for **12a**. Optical rotations were measured on a 241 MC polarimeter (Perkin–Elmer) at room temperature.

Materials. Cyclohexenone **8**, cycloheptenone **11a**, cyclopentenone **11b**, lactone **11c**, CuCl, and CuBr·SMe$_2$ were purchased from Aldrich and used without additional purification. Grignard reagents (RMgBr) were prepared from the corresponding alkyl bromides and magnesium turnings in Et$_2$O following standard procedures. Grignard reagents were titrated by using s-BuOH and catalytic amounts of 1,10-phenanthroline. Ligands **1**, **2**, **6**, and **7** were initially supplied as a gift in the Solvias ligand kit. Ligand **1** was also obtained from Strem Chemicals (Kehl, Germany) and used as received. Ligands **1** and **3–5** (39, 40) were prepared according to published procedures. Racemic 1,4-addition products **9a–9i** and **12a–12c** were obtained by reaction of the enones **8** or **11a–11c** with the corresponding Grignard reagent at 0°C in the presence of CuCl (100 mol %). Racemic 1,2-addition products **10a–10i** and **13a–13c** were prepared by reaction in the absence of copper source. All the products showed NMR and MS spectra in accordance with reported data: **9a**, **9d**, **9f**, **9h**, and **12b** (46); **9b** and **12a** (47); **9c** and **9e** (33); **9g** (48); **9i** (49); and **12c** (50).

General Procedure for the Asymmetric Conjugate Addition. In a Schlenk tube equipped with septum and stirring bar, a mixture of CuCl (12.5 μmol) and the ligand (**1-7**) (15 μmol) was dissolved in Et$_2$O (2.5 ml). After stirring under argon at room temperature for 30 min, the enone (**8** or **11a–11c**, 0.25 mmol) was added. After additional stirring for 10 min, the corresponding Grignard reagent (solution in Et$_2$O, 0.29 mmol) was added dropwise to the resulting mixture during 5 min at 0°C. After stirring under argon for 15 min, aqueous NH$_4$Cl solution (1 M, 1 ml) was added to the reaction mixture. The organic phase was separated, filtered over a short silica column, and subjected to conversion and ee determination (capillary GC). CuBr·SMe$_2$ was used instead of CuCl in 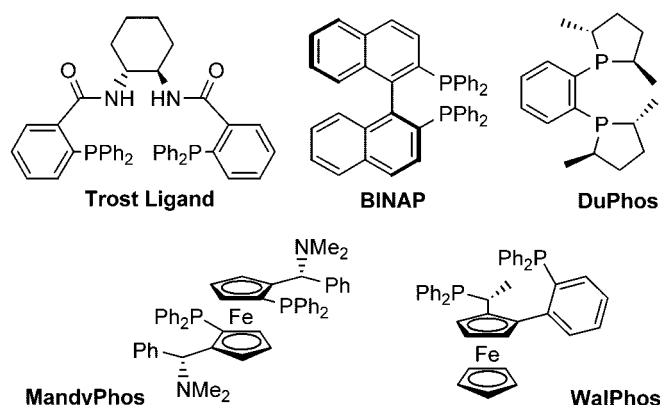reactions performed at low temperature. To avoid undesirable tandem aldol reactions, MeOH was used instead of aqueous NH$_4$Cl solution in the work-up of reactions using cyclopentenone **11b** as substrate. The configuration of the products was determined by comparing the sign of optical rotations with those reported: **9a** (51), **9h** (33), **12a** (47), **12b** (52), and **12c** (50).

Results and Discussion

Preliminary screening involved the addition of different ethyl-magnesium halides to cyclohexenone, the use of various Cu salts, and a systematic search for the optimal diphosphine ligand. Among those ligands initially tested that led to poor enantios-electivities (5–28% ee) were monodentate and bidentate phos-phoramidites (13) and bidentate phosphines (Fig. 2) such as Trost ligand (53), BINAP (54), and DuPhos (55). Remarkably, promising enantioselectivities (45–70% ee) were obtained by using ferrocenyl-based diphosphine ligands including Mandy-Phos (45), JosiPhos (42), and WalPhos (56), and in particular by using TaniaPhos (**1**; Fig. 1) and related ligands (39, 40).

Careful optimization of the reaction led to conditions using 5 mol % of CuCl, 6 mol % of TaniaPhos (**1**), and 1.15 eq of EtMgBr in Et$_2$O at 0°C, which afforded full conversion in 15 min with a regioselectivity of 95% (1,4-addition versus 1,2-addition product) and an excellent 96% ee (Scheme 1). The use of a higher copper-to-ligand ratio results in low enantioselectivity. An important factor for efficiency of the chiral catalyst based on the ferrocenyl diphosphine ligands seems to be that the presence of free copper salt has to be avoided as long as Grignard reagent is present in the system.

The combination of CuCl and ethylmagnesium bromide turned out to be particularly effective (Table 1). The use of different halides, either in the Grignard reagent or the copper salt, has a major influence on the regioselectivity, whereas the enantioselectivity is barely affected. The use of CuBr·SMe$_2$ at -60°C did not improve the enantioselectivity (Table 1, entry 5).
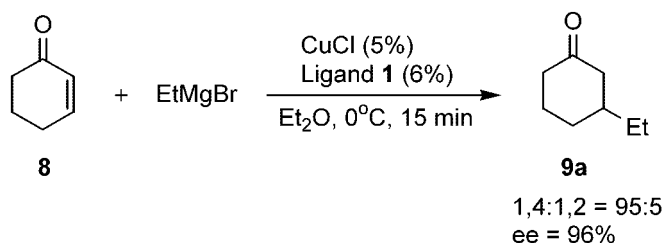
Scheme 1. Enantioselective copper-catalyzed conjugate addition of EtMgBr to cyclohexenone (8).

Table 1. Influence of halides on the regioselectivity and enantioselectivity

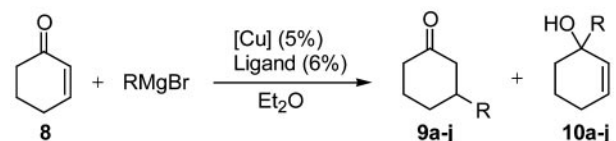| Entry*	EtMgX	[Cu]	Regioselectivity 1,4-:1,2-addition	9a ee, %
1	EtMgCl	CuI	43:57	93
2	EtMgCl	CuBr	61:39	95
3	EtMgCl	CuCl	71:29	95
4	EtMgBr	CuCl	**95:5**	**96**
5[†]	EtMgBr	CuBr·SMe$_2$	90:10	94

*See Scheme 1. Full conversion after 15 min.
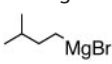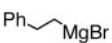[†]Full conversion after 2 h at −60°C.

With the aim of relating the key structural features of the ligand with the high selectivity observed, analogues of Tania-Phos (**1**) were tested in the reaction under the same experimental conditions. The use of ligand **2** (Table 2, entry 2), with cyclohexyl groups instead of phenyl groups at the phosphorus attached to the cyclopentadienyl ring, led to a drastic decrease in the ee (10%). Surprisingly, variation of the amine substituents in **1**, as present in ligands **3** and **4**, led to similarly high enantio- and regioselectivities, both exceeding 90% (Table 2, entries 3 and 4). The use of ligand **5**, with a methyl group instead of the dialkylamine moiety, resulted in a significant decrease in both ee and regioselectivity, although the regioselectivity was strongly improved at −60°C (Table 2, entries 5 and 6). To determine

whether the presence of the arylphosphine moiety plays a crucial role in the stereocontrol, JosiPhos (**6**) was also tested. This chiral ligand afforded only moderate enantioselectivity, and the use of low temperature and CuBr·SMe$_2$ as copper source was necessary (Table 2, entries 7 and 8). Interestingly, however, the sense of enantioselectivity was found to be opposite that obtained when using TaniaPhos. Both ligands share the same planar chirality in the ferrocenyl group, and although chelate rings of different sizes (6- or 8-membered chelate) are formed, these results suggest that it is the central chirality (in the side chain) that controls the configuration of the 1,4-addition product (Table 2, entries 1 and 7). In all cases, the 1,2-addition product **10a** was always obtained as a racemic mixture, suggesting its formation via an uncatalyzed 1,2-addition of the Grignard reagent to the carbonyl group.

We next examined the addition of a variety of Grignard reagents by using the optimal conditions that were found for TaniaPhos (**1**). It was satisfying that **9b–9d** were obtained with 90–96% ee by using RMgBr reagents with linear alkyl chains (R = Me, Pr, Bu; entries 9–11). When using Grignard reagents with branched alkyl chains, the substitution pattern was found to have a strong influence on the enantioselectivity obtained. In particular, isopropyl and isobutyl fragments both resulted in poor ees (entries 12 and 13), whereas isoamylmagnesium bromide afforded the 1,4-addition product **9g** with 95% ee (entry 14). Accordingly, Grignard reagents substituted at the β and δ positions also led to good ees (entries 15 and 16, respectively). Surprisingly, when we tested JosiPhos (**6**) with the α- and

Table 2. Enantioselective copper-catalyzed conjugate addition of Grignard reagents to cyclohexenone (8)

Entry*	RMgBr	Ligand	Regio, %[†]	ee 9, %	9	Conf, R/S[‡]
1[§]	EtMgBr	1	95 [69]	**96**	9a	(+)-R
2	EtMgBr	2	80	10	9a	(+)-R
3	EtMgBr	3	96	**94**	9a	(+)-R
4	EtMgBr	4	92	93	9a	(+)-R
5	EtMgBr	5	69	45	9a	(+)-R
6[¶]	EtMgBr	5	89	40	9a	(+)-R
7[‖]	EtMgBr	6	99	56	9a	(−)-S
8*	EtMgBr	6	93	30	9a	(−)-S
9	MeMgBr	1	83	**90**	9b	n.d.
10	PrMgBr	1	81	**94**	9c	n.d.
11	BuMgBr	1	88	**96**	9d	n.d.
12[§]	i-PrMgBr	1	78 [72]	1	9e	n.d.
13[§]	i-BuMgBr	1	62 [70]	33	9f	(+)
14[§]	(isoamyl)MgBr	1	76 [75]	**95**	9g	(+)
15	Ph(~)MgBr	1	80	77	9h	(+)-S
16	4-Cl-BuMgBr	1	79	85	9i	n.d.
17[‖]	i-PrMgBr	6	99	54	9e	n.d.
18[‖]	i-BuMgBr	6	99	**92**	9f	(−)
19[‖]	PhMgBr	6	50	40	9j	n.d.

Conf, absolute configuration; n.d., not determined.
*More than 98% conversion after 15 min at 0°C using CuCl.
[†]Regioselectivity [**9**/(**9** + **10**)] × 100.
[‡]Absolute configuration and/or sign of optical rotation.
[§]Isolated yields are given in brackets.
[¶]More than 98% conversion after 2 h at −60°C using CuCl.
[‖]More than 98% conversion after 2 h at −60°C using CuBr·SMe$_2$.

Table 3. Enantioselective copper-catalyzed conjugate addition of EtMgBr to cyclic enones

11a, X = CH$_2$, n = 2
11b, X = CH$_2$, n = 0
11c, X = O, n = 1

Entry*	11	Ligand	Regio, %[†]	ee12, %	12	Conf(R/S)[‡]
1[§]	11a	1	80 [60]	87	12a	(+)-R
2	11a	6	96	78	12a	(−)-S
3	11b	1	69	6	12b	(−)-S
4	11b	6	99	82	12b	(+)-R
5	11b	7	99	92	12b	(+)-R
6	11c	1	99	47	12c	(+)-R
7[§]	11c	6	99 [75]	79	12c	(−)-S
8	11c	7	99	82	12c	(−)-S

Conf, absolute configuration.
*More than 98% conversion after 2 h at −60°C using CuBr·SMe$_2$.
[†]Regioselectivity = [12/(12 + 13)] × 100.
[‡]Absolute configuration and sign of the optical rotation.
[§]Isolated yields are given in brackets.

β-branched Grignard reagents i-PrMgBr and i-BuMgBr, excellent regiocontrol (99%) with moderate (9e, 54% ee) to high (9f, 92% ee) enantioselectivities (entries 17 and 18) were obtained, which is in sharp contrast with the results when using TaniaPhos. The present catalytic system shows only modest enantioselectivity with phenylmagnesium bromide (Table 2, entry 19).

This copper-catalyzed conjugate addition is not limited to cyclohexenone. Representative results with cyclic enones 11a–11c are shown in Table 3. TaniaPhos (1) is the ligand of choice for the 1,4-addition of simple alkylmagnesium bromides to cyclohexenone with excellent enantioselectivities. For other enones, the most appropriate ferrocenyl diphosphine ligand is highly dependant on the nature of the cyclic enone. Several ferrocenyl diphosphines led to ees exceeding 70% for the addition to cycloheptenone; in particular, TaniaPhos and JosiPhos afforded 12a with 87% and 78% ee, respectively (Table 3, entries 1 and 2), once again with opposite enantioselectivities.

Cyclopentenone (11b, entries 3–5) is well known to be a highly demanding substrate in conjugate-addition reactions, and therefore it provides a critical test for any new catalytic 1,4-addition. With this enone, JosiPhos-type ligands were found to be clearly superior to TaniaPhos, and the use of ligand 7 provided the 1,4-adduct 12b with a remarkable 99% regioselectivity and 92% ee (entry 5). In an analogous fashion to the observation by Stangeland and Sammakia (34), a puzzling inversion in the sense of the asymmetric induction was found when cycloheptenone 11a or cyclopentenone 11b were used (compare entries 2 and 4). With the lactone 11c as substrate, the use of JosiPhos (entry 7) and the related ligand 7 (entry 8) led to a higher level of enantioselectivity (79% and 82% ee, respectively) compared with TaniaPhos (47% ee, entry 6). As expected, an inversion of the absolute configuration of the product 12c was observed when using JosiPhos in place of TaniaPhos (compare entries 6 and 7). It is remarkable that both TaniaPhos- and JosiPhos-type ligands, which can bind copper in 8- and 6-membered chelated structures, respectively, are effective in the 1,4-addition of Grignard reagents. Additional detailed study of complexes in solution involving both the copper salt and the Grignard reagent will be necessary to present a useful model to rationalize the high π-face selectivity in this conjugate-addition reaction.

Conclusions

This study presents high enantioselectivities (up to 96% ee) in the copper-catalyzed conjugate addition of Grignard reagents to cyclic enones. Despite the high reactivity of these organometallic reagents and the presence of halide ions, excellent stereocontrol can be achieved by using commercially available chiral ferrocenyl diphosphine ligands. The system described here works with moderate catalyst loading (5 mol %) under mild conditions (0°C and 5 min of addition time) in the absence of additives, although in some cases low temperature (−60°C) is still required to reach high ee. The proper selection of TaniaPhos or JosiPhos derivatives, in a complementary way, allows the use of a broad range of inexpensive and readily available organomagnesium reagents and cyclic enones.

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