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Copper-Catalyzed Enantioselective 1,4-Addition to α,β-Unsaturated Aldehydes

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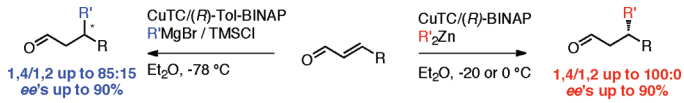
ABSTRACT



The first asymmetric Cu-catalyzed conjugate addition of dialkylzinc zinc reagents to a large scope of enals in presence of phosphoramidite, SimplePhos, or (*R*)-BINAP ligands with enantiomeric excesses up to 90% is reported. Moreover, ACA of Grignard reagents afforded moderate to good 1,4-regioselectivities with enantioselectivities up to 90%.

The asymmetric Cu-catalyzed conjugate addition (ACA) of organometallic reagents to Michael acceptors is among the most important methodologies to enantioselectively create C−C bonds.[1] In this field, a large variety of α,β-unsaturated compounds such as α,β-carbonyl derivatives, nitroalkenes, sulfones, etc. have been used with success. The only substrates that have not been reported are α,β-unsaturated aldehydes. This is not surprising, as these are much more challenging substrates due of their high reactivity, which allow the undesired direct carbonyl attack (1,2-addition). An interesting example has been reported by Marshall, in 2005, where the use of diorganozinc reagents allowed this reaction in racemic and diastereoselective versions.[2] In the same year, the enantioselective copper-free 1,4-addition of organozinc reagents to α,β-unsaturated aldehydes was described by Bräse using [2.2]-paracyclophaneketimine ligands.[3] Excellent enantioselectivities could be attained but with low regioselectivities, with the 1,2-adduct representing 1/3 to 1/2 of the converted product.

Other asymmetric 1,4-additions to enals using Rh[4] or Pd[5] catalysis were also reported by Miyaura, Hayashi, and Carreira. In all of these chiral systems, the 1,4-addition is limited to enals bearing an aromatic group. Moreover, for Cu and Cu-free catalysis, only diorganozinc reagents were used as nucleophiles. In Cu catalysis, alternative indirect ways have been described by Hoveyda with amides[6] and by Feringa with thioesters,[7] where the resulting adducts could be converted to aldehydes in a further step. Herein, we report the first successful enantioselective copper-catalyzed conjugate addition to several α,β-unsaturated aldehydes, with diorganozinc and Grignard reagents.

(1) For reviews, see: (a) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221–3223. (b) Alexakis, A.; Backvall, J. E.; Krause, N.; Pamies, O.; Dieguez, M. *Chem. Rev.* **2008**, *108*, 2796–2823. (c) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824–2852.

(2) Marshall, J. A.; Herold, M.; Eidam, H. S.; Eidam, P. *Org. Lett.* **2006**, *8*, 5505–5508.

(3) (a) Bräse, S.; Höfener, S. *Angew. Chem., Int. Ed* **2005**, *44*, 7879–7881. (b) Ay, S.; Nieger, M.; Bräse, S. *Chem.—Eur. J.* **2008**, *14*, 11539–11556. (c) See also in racemic version: Jones, P.; Reddy, C. K.; Knochel, P. *Tetrahedron* **1998**, *54*, 1471–1490.

(4) As a reference containing the results obtained for Rh-catalyzed ACA to enals, see: (a) Itooka, R.; Iguchi, Y.; Miyaura, N. *J. Org. Chem.* **2003**, *68*, 6000–6004. (b) Tokunaga, N.; Hayashi, T. *Tetrahedron: Asymmetry* **2006**, *17*, 607–613. (c) Paquin, J. F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850–10851.

(5) As a reference containing the results obtained for Pd-catalyzed ACA to enals, see: Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Chem. Commun.* **2004**, 1822–1823.

(6) Hird, A. W.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1276–1279.

(7) Des Mazery, R.; Pullez, M.; Lopez, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2005**, *127*, 9966–9967.

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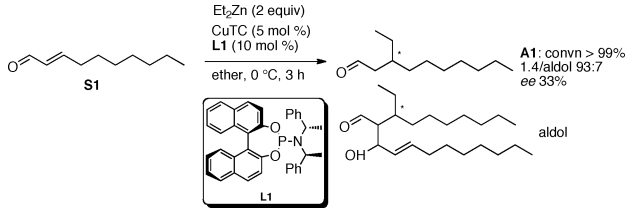
We initially investigated the ACA of dialkylzinc reagents because their low reactivity could probably prevent or slow the formation of the undesired 1,2-adduct. The first attempt was done with Et_2Zn and *trans*-2-decenal **S1**, in the presence of 5 mol % of CuTC (copper thiophene carboxylate) and 10 mol % of phosphoramidite-type ligand **L1** in Et_2O at 0 °C (Scheme 1). After only 3 h, the corresponding adduct **A1** was obtained with full conversion but with only 33% ee. No 1,2-adduct was observed, but aldol product was formed by reaction of the resulting zinc enolate with the highly reactive substrate **S1**. To prevent the formation of this byproduct, we optimized the sources of copper salt and the solvents in presence of **L1**.

Scheme 1. First Attempt of ACA of Et_2Zn to **S1**



Performing the reaction in dichloromethane or in toluene, with CuTC, did not improve the ratio of 1,4/aldol product, even if the enantiomeric excess increased (55% in CH_2Cl_2 and 52% in toluene). However, when the reaction was done with copper(II) triflate, as copper salt, and **L1** in toluene, the corresponding 1,4-adduct was obtained with full conversion and 50% ee, without a trace of the aldol byproduct. With these conditions in hand, we screened various chiral ligands (Figure 1 and Table 1).

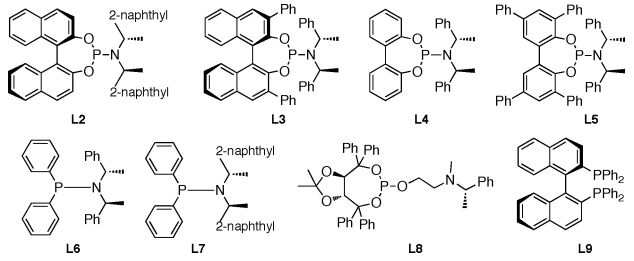
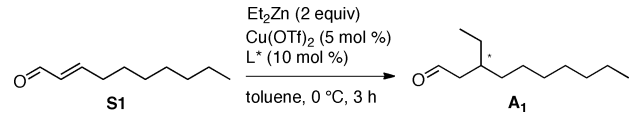


Figure 1. Chiral ligands tested with diorganozinc reagents.

Among the monodentate chiral ligands tested, two interesting results were obtained, one with phosphoramidite ligand **L3**, bearing *ortho*-phenyl groups on the chiral binaphthol part, and SimplePhos[8] **L7** with a 2-naphthyl group on the chiral amine (entries 3 and 7). Even if some traces of the aldol product were observed, the enantioselectivity was clearly better: 79% ee with **L3** and 73% ee with **L7**.

Table 1. Optimization of the Chiral Ligands



entry	ligand	convn (%)[a]	1,4/aldol[a]	ee (%)[b]
1	**L1**	>99	>99	50
2	**L2**	99	99:1	57
3	**L3**	88	95:5	79
4	**L4**	>99	94:6	34
5	**L5**	99	>99	64
6	**L6**	93	88:12	60
7	**L7**	99	93:7	73
8	**L8**	94	99:1	50
9	**L9**[c]	59	87:13	72

[a] Determined by ^{1}H NMR. [b] Determined by chiral GC. [c] Performed with 5.25 mol % of **L9**.

Moreover, bidentate ligand (*R*)-BINAP **L9** showed an interesting result[9] for the conjugate addition of Et_2Zn to **S1**, with 72% ee but only 87% of regioselectivity in favor of the 1,4-adduct (entry 9). Further refinements in the reaction conditions (Cu salt, solvent, temperature) allowed us to find two distinct sets, depending on the ligand used. For monodentate ligands **L3** or **L7**, $Cu(OTf)_2$ in toluene at 0 °C was best, whereas for (*R*)-BINAP, CuTC in ether at −20 °C was better. The enals used in this study were either commercially available or easily prepared according to the literature (Figure 2).

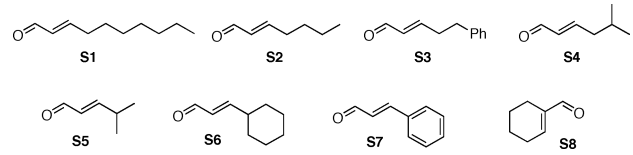


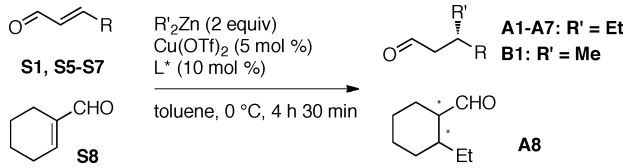
Figure 2. Cyclic and acyclic α,β-unsaturated aldehydes used.

As shown in Table 2, the ACA proceeds with excellent conversions. With few exceptions, **L7** generally affords better 1,4-selectivities (92−100%), although the enantioselectivities are usually slightly lower. With **L3**, ee's up to 90% could be attained (entry 5). For the cyclic enal **S8**, the 1,2-product was observed with **L3** and **L7**, even if the 1,4-adduct was obtained with 82% ee with **L7** (entry 10). Finally, the addition of Me_2Zn was tested with acyclic enal **S1** and ligand **L3**. Both total conversion and 1,4-regioselectivity are observed, affording the corresponding adduct **B1** with 60% ee (entry 11).

(8) (a) Palais, L.; Mikhel, I. S.; Bournaud, C.; Micouin, L.; Falciola, C. A.; Vuagnoux-d'Augustin, M.; Rosset, S.; Bernardinelli, G.; Alexakis, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7462–7465. (b) Palais, L.; Alexakis, A. *Chem.—Eur. J.* **2009**, *15*, 10473–10485.

(9) BINAP has been shown to be a good ligand for ACA with Grignard reagents, not with dialkyl zinc reagents. See: (a) Wang, S. Y.; Ji, S. J.; Loh, T. P. *J. Am. Chem. Soc.* **2007**, *129*, 276–277. (b) Alexakis, A.; Burton, J.; Vastra, J.; Mangeney, P. *Tetrahedron: Asymmetry* **1997**, *8*, 3987–3990.

Table 2. ACA of R'_2Zn to Various Enals with **L3** and **L7**

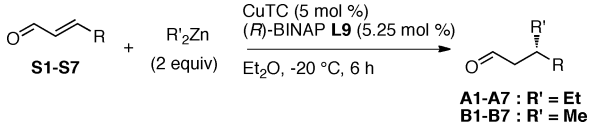


entry	L*	R	adduct	convn (%)[a]	1,4/1,2/aldol[a]	ee (%)[b]
1	**L3**	C_7H_{15}	**A1**	88	95:0:5	79, *R*
2	**L7**	C_7H_{15}	**A1**	99	93:0:7	73, *R*
3	**L3**	*i*-Pr	**A5**	100	77:11:12	51, *S*
4	**L7**	*i*-Pr	**A5**	100	100:0:0	60, *S*
5	**L3**	*c*-Hex	**A6**	100	100:0:0	90, *S*
6	**L7**	*c*-Hex	**A6**	100	100:0:0	81, *S*
7[c]	**L3**	Ph	**A7**	81	92:0:8	82, *S*
8[c]	**L7**	Ph	**A7**	71	92:0:8	71, *S*
9[c]	**L3**	**S8**	**A8**	100	53:47:0	60[d]
10[c]	**L7**	**S8**	**A8**	100	22:78:0	82[e]
11[c]	**L3**	C_7H_{15}	**B1**	100	100:0:0	60, *R*

[a] Determined by ^{1}H NMR. [b] Determined by chiral GC. [c] Reaction performed over 24 h. [d] Enantiomeric excess of the major diastereoisomer, dr 68:32. [e] Enantiomeric excess of the major diastereoisomer, dr 70:30.

In a second screening, the 1,4-addition of dialkylzinc reagents was performed using 5 mol % of CuTC and 5.25 mol % of (*R*)-BINAP **L9** (Table 3). Interestingly, in all cases, no traces

Table 3. ACA of R_2Zn to Various Enals with **L9**



entry	R	adduct	convn (%)[a]	ee (%)[b]
1	C_7H_{15}	**A1**	100 (75)[d]	75, *R*
2	*n*-Bu	**A2**	100 (60)[e]	64, *R*
3	*i*-Bu	**A4**	100	70, *R*
4	*i*-Pr	**A5**	100	27, *S*
5	*c*-Hex	**A6**	100 (50)[d]	52, *S*
6[c]	Ph	**A7**	100 (81)[d]	44, *S*
7[c]	C_7H_{15}	**B1**	85 (79)[d]	68, *R*
8[c]	*n*-Bu	**B2**	87	76, *R*
9[c]	*i*-Pr	**B5**	100	70, *S*
10[c]	*c*-Hex	**B6**	87 (61)[d]	60, *S*
11[c]	Ph	**B7**	50	64, *S*

[a] Determined by ^{1}H NMR. [b] Determined by chiral GC. [c] Reaction performed at 0 °C over 16 h. [d] Yield in parentheses. [e] Crude yield.

of 1,2-adduct or aldol formation were observed for the addition of Et_2Zn or Me_2Zn. However, the enantioselectivities are usually lower than with phosphoramidites **L3** and **L7**, except for the addition of Me_2Zn, where the ee's were better. With this reagent, the reaction was performed at higher temperature (0 °C) due to its lower reactivity. Tol-BINAP did not improve these results, and neither did the addition of trimethylchlorosilane (TMSCl).

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.[10] However, their commercial diversity remains limited, and this is why the use of Grignard reagents was envisaged for this reaction. First, we screened several chiral mono- and bidentate ligands for the ACA of EtMgBr to *trans*-2-decenal **S1** catalyzed by CuTC (Figure 3 and Table 4).

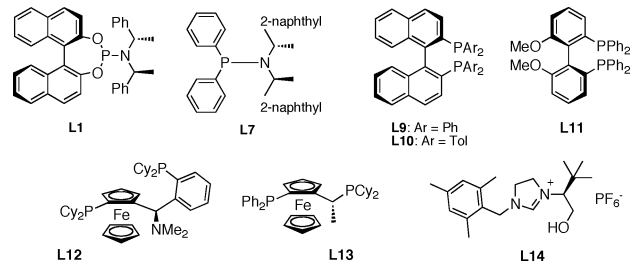
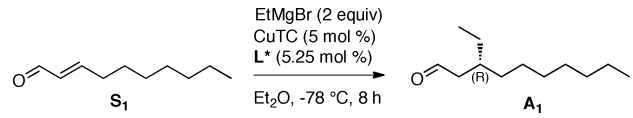


Figure 3. Chiral ligands tested with Grignard reagents.

The reaction was performed at low temperature (−78 °C) due to the high reactivity of both the Grignard reagent and the enal itself. Not unexpectedly, large amounts of 1,2-adducts were obtained, as well as some aldol products. However, (*R*)-BINAP **L9** and (*R*)-tol-BINAP **L10** gave the best regio- and enantioselectivities, up to 92% (entries 3 and 4). Other mono- and bidentate phosphorus ligands afforded the corresponding adduct with lower ee's and 1,4-regioselectivities. Finally, N-heterocyclic carbene precursor **L14**[11] underwent mainly 1,2-addition (entry 8).

Table 4. ACA of EtMgBr to Enal **S1** with Various Chiral Ligands



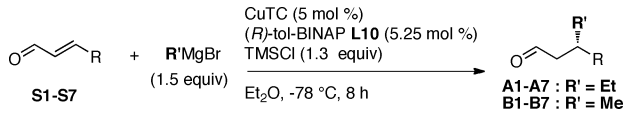
entry	L*	convn (%)[a]	1,4/1,2/aldol[a]	ee (%)[b]
1[c]	**L1**	100	24:76:0	50
2[c]	**L7**	100	21:79:0	44
3	**L9**	98	62:38:0	89
4	**L10**	99	32:42:26	92
5	**L11**	98	21:59:20	68
6	**L12**	96	2:97:1	nd[d]
7	**L13**	98	16:64:20	88
8	**L14**	97	8:89:3	nd[d]

[a] Determined by ^{1}H NMR. [b] Determined by chiral GC. [c] Reaction performed with 10 mol % of ligand at −30 °C. [d] Not determined.

(10) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117–2188.
(11) Wencel, J.; Mauduit, M.; Hénon, H.; Kehrli, S.; Alexakis, A. *Aldrichimica Acta* **2009**, *42*, 43–50.

After defining the best ligand, some optimizations were attempted (solvent, temperature, Cu salt)[12] with **L9** and **L10** to increase the 1,4-regioselectivity. The key point was the beneficial effect of added TMSCl. TMSCl is well-known to increase the rate of the conjugate addition of cuprates[13] and to favor the 1,4-addition on enals.[14] However, TMSCl had never been used in ACA with Grignard reagents, although its detrimental effect was noticed with Et_2Zn.[1a] As we had expected, the addition of TMSCl (1.3 equiv) gave a promising result for 1,4-regioselectivity, which increased from 32 to 85% with **L10**. Moreover, the ee of 90% was not altered. With these new experimental conditions in hand, we screened the addition of EtMgBr and MeMgBr to a large scope of acyclic α,β-unsaturated aldehydes (Table 5).

Table 5. ACA of Et and MeMgBr to Various Enals with **L10**



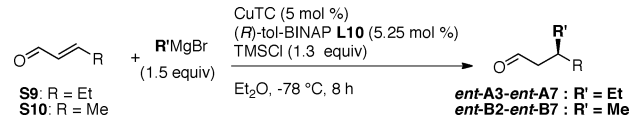
entry	R	adduct	convn (%)[a]	1,4/1,2[a]	*ee* (%)[b]
1	C_7H_{15}	**A1**	100 (75)[c]	85:15	90, *R*
2	*n*-Bu	**A2**	100 (46)[c]	60:40	90, *R*
3	$(CH_2)_2Ph$	**A3**	100 (59)[c]	77:23	83, *R*
4	*i*-Bu	**A4**	100 (44)[c]	71:29	90, *R*
5	*i*-Pr	**A5**	100	36:64	74, *S*
6	*c*-Hex	**A6**	100 (51)[c]	63:37	80, *S*
7	Ph	**A7**	100	20:80	53, *S*
8	C_7H_{15}	**B1**	100 (40)[c]	65:35	81, *R*
9	*n*-Bu	**B2**	100	40:60	86, *R*
10	$(CH_2)_2Ph$	**B3**	97	48:52	88, *R*
11	*i*-Pr	**B5**	86	43:57	84, *S*
12	*c*-Hex	**B6**	100 (49)[c]	63:37	80, *R*
13	Ph	**B7**	100	10:90	nd

[a] Determined by ^1H NMR. [b] Determined by chiral GC. [c] Isolated yield in parentheses.

The best ee's (up to 90%) were obtained with enals bearing a primary alkyl group in the β-position (**S1**, **S2**, **S3**, and **S4**). However, despite the improvement provided by TMSCl, the regioselectivity was moderate, ranging from 71 to 85% for primary alkyl chains (entries 1−4). With MeMgBr, both the regio- and enantioselectivities were lower, with the notable exception of enal **S3**, bearing a phenethyl group, which gave 88% ee (entry 10). It could be noticed that adduct **B3** is a floral fragrance called Citralis.

Finally, we screened the behavior of various Grignard reagents to *trans*-2-pentenal **S9** and crotonaldehyde **S10** in order to get the enantiomers of the adducts obtained from the addition of EtMgBr or MeMgBr to various enals (Table 6).

Table 6. ACA of Various R′MgBr to **S9** and **S10** with **L10**



entry	R′	adduct	convn (%)[a]	1,4/1,2[a]	ee (%)[b]
1	$(CH_2)_2Ph$	***ent*-A3**	100 (50)[c]	67:33	88, *S*
2	*i*-Bu	***ent*-A4**	100	36:64	80, *S*
3	*i*-Pr	***ent*-A5**	100	67:33	74, *R*
4	*c*-Hex	***ent*-A6**	100	53:47	86, *R*
5	Ph	***ent*-A7**	88	33:67	80, *R*
6	*n*-Bu	***ent*-B2**	100	36:74	88, *S*
7	$(CH_2)_2Ph$	***ent*-B3**	100	45:55	74, *S*
8	*i*-Pr	***ent*-B5**	100	63:37	65, *R*
9	*c*-Hex	***ent*-B6**	100 (60)[c]	71:29	89, *R*
10	Ph	***ent*-B7**	96	26:74	48, *R*

[a] Determined by ^1H NMR. [b] Determined by chiral GC or SFC. [c] Isolated yield in parentheses.

The small alkyl chains of **S9** and **S10** have a profound effect. Although the enantioselectivities remain moderate to good, the 1,4-regioselectivities are lower, particularly for the addition of primary and secondary alkyl Grignard reagents to substrate **S9** (with an ethyl group in the 4-position). The two exceptions were observed for the addition of phenethylMgBr, which gave 88% ee and a ratio 1,4/1,2 of 67:33 (entry 1), whereas the addition of EtMgBr to **S3** gave only 83% ee but 77% of 1,4-adduct (Table 5, entry 3). For the addition of a phenyl group, a large improvement was also obtained from 53 to 80% ee (Table 5 entry 7 vs Table 6 entry 5), even if the regioselectivity was not perfect. Concerning the addition of Grignard reagents to crotonaldehyde **S10**, the best result was observed for the addition of *c*-HexMgBr, which gave 89% ee and 71% of 1,4-adduct (entry 9). This result is better than the addition of MeMgBr to enal **S6** bearing a cyclohexyl group (Table 5, entry 12).

Finally, a brief test with R_3Al reagents showed that the increased Lewis acidity of these reagents was deleterious, as both 1,2 and aldol products were obtained in significant amounts.

To conclude, we have described the first copper-catalyzed conjugate addition of dialkylzinc and Grignard reagents to a large variety of α,β-unsaturated aldehydes with moderate to excellent 1,4-regioselectivities and ee's up to 90%. Key to the success with Grignard reagents was the addition of TMSCl. Further work is in progress to improve these results through screening of new ligands.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) See Supporting Information for more details.

(13) (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015−6018; 6019−6022. (b) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047–1050. (c) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029–4032.

(14) Chuit, C.; Foulon, J. P.; Normant, J. F. *Tetrahedron* **1980**, *36*, 2305–2310.