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Epimerization and kinetic resolution in copper-catalyzed enantioselective 1,4-additions of organozinc reagents to 6-substituted cyclohex-2-enones

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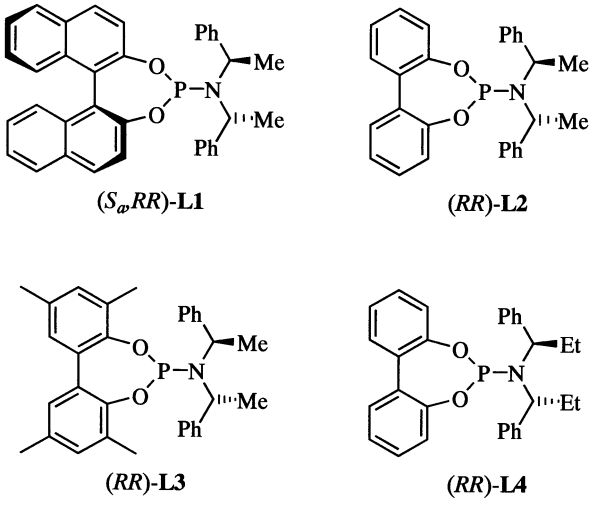
Abstract—Enantioselective 1,4-addition reactions of diethyl-, dimethyl-, and di-*n*-butylzinc to 6-methylcyclohex-2-enone (**1**) and 6-*t*-butylcyclohex-2-enone (**4**), catalyzed by $Cu(OTf)_2$ and phosphoramidites **L1**–**L4** were examined. The additions to enone **1** proceeded with high enantioselectivity; by acid- or base-catalyzed epimerization, adduct (*S*,*S*)-**2** can be obtained from racemic **1** in diastereo- and enantiomerically pure form. In contrast, Michael additions to substrate **4** were rather slow and could be used for the kinetic resolution of the enone.

Copper-mediated and -catalyzed transformations belong to the most important methods for the regio- and stereoselective formation of C–C bonds.[1] Among these, enantioselective 1,4-additions of organozinc reagents to simple enones, catalyzed by copper(II) triflate and a chiral phosphoramidite, have received particular attention.[2] Recently, these conditions have also been used for the kinetic resolution of certain 4- and 5-substituted enones.[3] Here, we present initial results of a study devoted to the corresponding reaction of 6-substituted cyclohex-2-enones using the BINOL- and biphenyl-derived phosphoramidites **L1**–**L4** (Fig. 1).[4–6] In contrast to the previous examples,[3] these transformations cannot only be performed as a classical kinetic resolution, but also with epimerization at C-6, which might give access to a single stereoisomeric product from the racemic enone.

We first examined addition reactions to 6-methylcyclohex-2-enone (**1**) which is readily available both in racemic[7] and enantiomerically pure[8] form (Table 1). The first reaction, performed under standard conditions for enantioselective 1,4-addition reactions to enones, catalyzed by $Cu(OTf)_2$ and phosphoramidite (S_a,*R*,*R*)-**L1**[4] (CH_2Cl_2, −30°C, 3 h, workup with dilute hydrochloric acid) gave mainly (*S*,*S*)-**2** (corresponding to 82% ee). Clearly, the enantioselective addition is followed by an acid-catalyzed epimerization of the *cis* to the thermodynamically more stable *trans* isomer.[9] This isomerization can be avoided by using the less acidic acetic acid for the protonation (entry 2), giving enantiomeric excesses of 85% for the *trans* and >99% for the *cis* product.[10] As observed also in the corresponding addition reactions to prochiral enones,[4] a slightly



(S_a,*RR*)-**L1** (*RR*)-**L2** (*RR*)-**L3** (*RR*)-**L4**

Figure 1. Chiral phosporamidite ligands used in this work.

Keywords: copper catalysis; enantioselectivity; epimerization; kinetic resolution; Michael addition; phosphoramidites.

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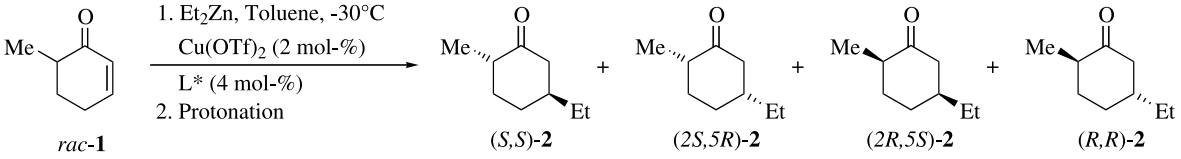
Table 1. Copper-catalyzed enantioselective 1,4-addition of diethylzinc to enone *rac*-**1**[a]



Entry	Ligand	Solvent	Protonation	*S*,*S* (%)	2*S*,5*R* (%)	2*R*,5*S* (%)	*RR* (%)
1	(S_a,*R*,*R*)-**L1**	CH_2Cl_2	HCl	89	0	2	9
2	(S_a,*R*,*R*)-**L1**	CH_2Cl_2	AcOH	51	0	45	4
3	(S_a,*R*,*R*)-**L1**	Toluene	AcOH	52	0	48	0
4	(S_a,*S*,*S*)-**L1**	Toluene	AcOH	51	0	41	8
5	(*R*,*R*)-**L2**	Toluene	AcOH	52	1	41	6
6	(*R*,*R*)-**L3**	Toluene	AcOH	48	0	49	3
7	(*R*,*R*)-**L4**	Toluene	AcOH	53.5	0	45	1.5

[a] Product ratio determined by gas chromatography on LIPODEX E.

improved enantioselectivity resulted with toluene as solvent (entry 3), whereas the diastereomeric ligand (S_a,*S*,*S*)-**L1** was inferior (entry 4). The biphenyl-derived ligands **L2**–**L4** provided slightly lower enantiomeric excesses, compared to (S_a,*R*,*R*)-**L1**; here, the best values (95%/>99% ee) were observed with (*R*,*R*)-**L4**. Interestingly, in all cases examined here, the (*S*)-enantiomer of enone **1** is reacting with higher enantioselectivity than the (*R*)-enantiomer; the absolute configuration of the new stereogenic center is the same as in the corresponding additions to cyclohex-2-enone.[4,5] Still, both enantiomers of the enone reacted with virtually the same rate, so that a kinetic resolution was not possible. This was also true for the corresponding addition reactions of dimethylzinc to *rac*-**1** which, however, gave a 1:1-mixture of the *cis* and *trans* adduct in enantiomerically pure form when (S_a,*R*,*R*)-**L1** or (*R*,*R*)-**L4** were used as chiral ligand (Fig. 2).

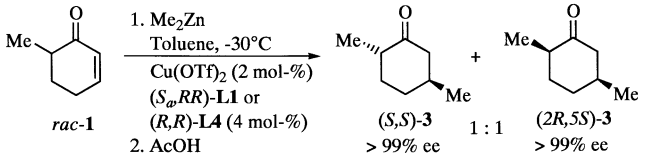


Figure 2. Copper-catalyzed enantioselective 1,4-addition of diethylzinc to enone *rac*-**1**.

The possibility to conduct the catalytic enantioselective Michael addition to enone **1** under reagent control and with or without subsequent epimerization enables the deliberate preparation of any stereoisomer of **2**. Thus, (*S*,*S*)-**2** was obtained with >99% ds and ee by treating *rac*-**1** with diethylzinc, as well as catalytic amounts of $Cu(OTf)_2$ and (S_a,*R*,*R*)-**L1** under epimerization conditions (treatment with sodium methanolate proved to be more efficient on larger scale than with dilute HCl), whereas (2*R*,5*S*)-**2** was formed with 96% ds and >99% ee in the corresponding reaction of enantiomerically pure enone (*R*)-(+)-**1**[8] under non-epimerization conditions (workup with acetic acid; Fig. 3). Consequently, the enantiomeric ketones (*R*,*R*)-**2** and (2*S*,5*R*)-**2** are accessible by using the enantiomeric ligand with *rac*-**1** or (*S*)-**1**.

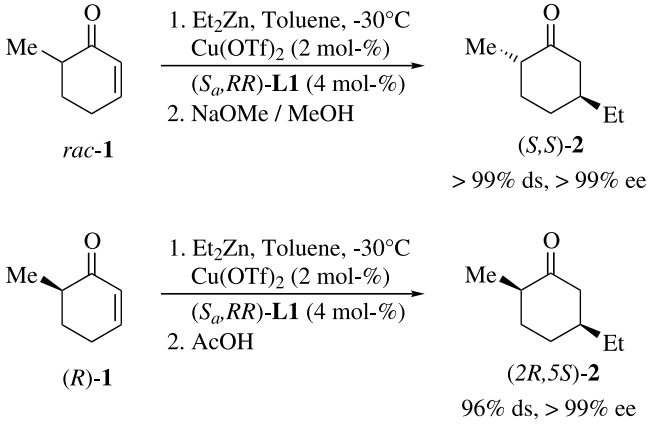
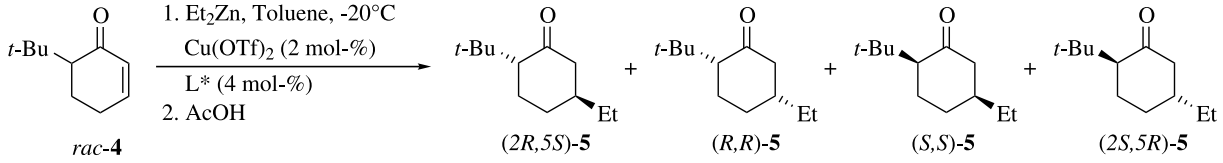


Figure 3. Selective formation of (*S*,*S*)-**2** and (2*R*,5*S*)-**2** by copper-catalyzed enantioselective Michael addition.

Not surprisingly, the corresponding copper-catalyzed enantioselective 1,4-additions to the *t*-butyl-substituted enone *rac*-**4**[11] gave distinctly different results (Table 2). In contrast to substrate **1**, the (*S*)-enantiomer of enone **4**[12] is reacting with higher rate and enantioselectivity with the catalysts used here than (*R*)-**4**. An exception is the ligand (*R*,*R*)-**L3** which gave a very slow and unselective reaction (Table 2, entry 4). In all other cases, (*S*,*S*)-**5** was the major addition product, although the reaction rates differ considerably; whereas with ligand (*R*,*R*)-**L2** the addition was virtually complete within 12 h at −20°C (entry 3), the corresponding reactions with (S_a,*R*,*R*)-**L1** and (*R*,*R*)-**L4** were sufficiently slow to allow a kinetic resolution of the enone. Thus, with (S_a,*R*,*R*)-**L1** and 0.8 equiv. of Et_2Zn, (*R*)-(−)-**4**[14] was recovered with 81% ee after 42% consumption (entry 2), whereas (*R*,*R*)-**L4** gave the enone with 67% ee/65% consumption (entry 5).

Table 2. Copper-catalyzed enantioselective 1,4-addition of diethylzinc to enone *rac*-**4**[a]



rac-**4** (2*R*,5*S*)-**5** (*R*,*R*)-**5** (*S*,*S*)-**5** (2*S*,5*R*)-**5**

Entry	Ligand	Time (h)	(2*R*,5*S*)-**5** (%)	(*R*,*R*)-**5** (%)	(*S*,*S*)-**5** (%)	(2*S*,5*R*)-**5** (%)	(*R*)-**4** (%)	(*S*)-**4** (%)
1	(S_a,*R*,*R*)-**L1**	36	27.7	16.9	51.3	0.4	3.7	0
2	(S_a,*R*,*R*)-**L1**[b]	36	3.2	2.6	35.5	0.4	52.7	5.6
3	(*R*,*R*)-**L2**	12	5.9	42.2	50.5	0.6	0.8	0
4	(*R*,*R*)-**L3**	72	5.2	5.4	6.5	3.0	42.3	37.6
5	(*R*,*R*)-**L4**	72	6.5	6.6	50.2	1.9	29.0	5.8

[a] Product ratio determined by gas chromatography on heptakis-(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin.[10,12,13]
[b] Reaction with 0.8 equiv. of Et_2Zn, 1 mol% of $Cu(OTf)_2$, and 2 mol% of (S_a,*R*,*R*)-**L1**.

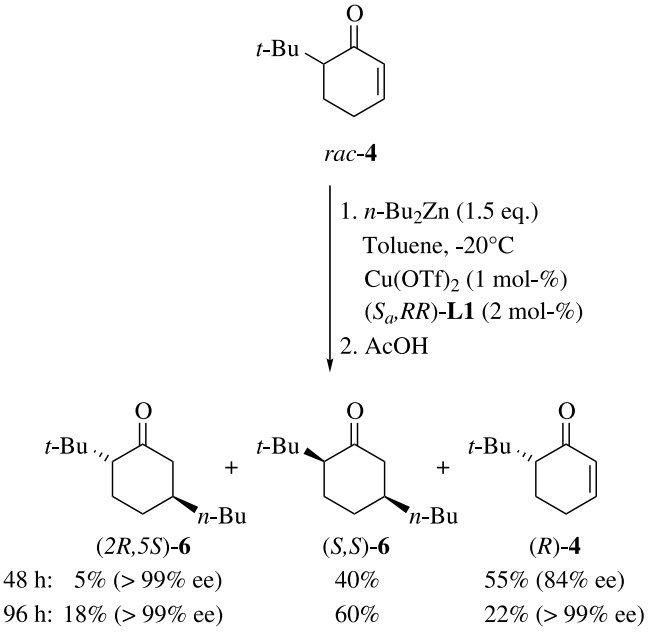


Figure 4. Kinetic resolution of enone **4** by copper-catalyzed 1,4-addition of di-*n*-butylzinc (product ratio determined by gas chromatography on heptakis-(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin; (*R*,*R*)- and (*S*,*S*)-**6** could not be separated).

A similar efficiency was observed in the corresponding Michael addition of di-*n*-butylzinc to *rac*-**4**, catalyzed by $Cu(OTf)_2$ and (S_a,*R*,*R*)-**L1** (Fig. 4) which was even slower than the addition of diethylzinc. After 48 h at −20°C, 55% of enone (*R*)-**4** was recovered with 84% ee, whereas enantiomerically pure enone resulted after 96 h (78% consumption).

To summarize the results of this work, we have found that copper-catalyzed enantioselective Michael additions of organozinc reagents to 6-substituted enones can be conducted 'substrate-oriented', i.e. as a kinetic resolution, or 'product-oriented' with or without subsequent enolization to the thermodynamically more stable *trans* isomer. The latter strategy allows the deliberate preparation of any stereoisomer of a 2,5-disubstituted ketone. Further work with differently substituted enones is continuing in our laboratories.

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9. Equilibrium ratio obtained by base-catalyzed epimerization with NaOMe/MeOH: *trans*-**2**:*cis*-**2** = 91:9.
10. Slight deviations from the expected 1:1 ratio of (*2R*)- and (*2S*)-enantiomers are probably due to a slow epimerization even under the less acidic workup conditions.

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12. Equilibrium ratio obtained by base-catalyzed epimerization with NaOMe/MeOH: *trans*-**5**:*cis*-**5** = 90:10.
13. The Cahn–Ingold–Prelog rules cause a priority change, so that (*R*)-**1** and (*S*)-**4** have the same absolute configuration.
14. Optical rotation for (*R*)-**4** (72% ee): $[\alpha]_D^{20}$ −22 (*c* 3.0, $CHCl_3$), corresponding to a value of $[\alpha]_D \approx -30$ for the enantiomerically pure enone (cf.: $[\alpha]_D^{21}$ +70 (*c* 3.0, $CHCl_3$) for (*R*)-(+)-**1**[8a]).