Pergamon

Tetrahedron Letters 43 (2002) 7329–7331

TETRAHEDRON LETTERS

Chiral diselenide ligands for the asymmetric copper-catalyzed conjugate addition of Grignard reagents to enones

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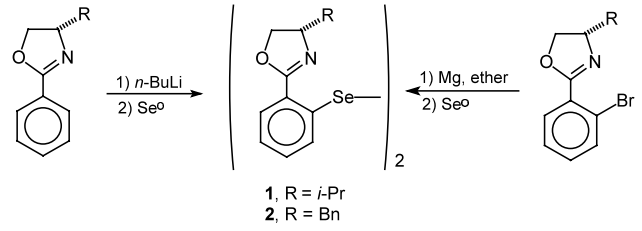
Received 8 August 2002; accepted 16 August 2002

Abstract—The copper-catalyzed conjugate addition of Grignard reagents to enones in the presence of chiral diselenide oxazoline ligands has been studied and found to provide good yields and useful levels of asymmetric induction.

Catalytic asymmetric synthesis using organometallic reagents is one of the most active areas of research in organic synthesis.[1] The enantioselective addition of organocuprates to enones is an attractive method to form a C–C bond and simultaneously introduce a new stereogenic center.[2] For this purpose, a variety of chiral catalysts have been developed. Among them, chiral sulfur ligands have been recognized to be efficient.[3] To the best of our knowledge, no chiral selenium ligand has been used so far. Moreover, certain features of selenium-containing compounds make these reagents particularly valuable for efficient stereoselective transformations in organic chemistry.[4] For example, chiral selenium reagents can be used for the stereoselective ring opening of epoxides,[5] *anti*-stereoselectivity and Markownikoff regioselectivity in the electrophilic selenenylation of alkenes,[6] for catalyzed stereoselective hydrosilylation of acetophenone[7] and for the addition of diethylzinc to aldehydes.[8] Selenium containing ligands should be especially suitable for 'soft' metals like those of the periodic table Groups 9 and 10.



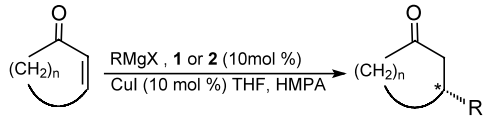
1, R = *i*-Pr
2, R = Bn

Scheme 1.

As part of a broader program to explore the preparation and use of chiral organochalcogen compounds in asymmetric catalysis,[9] we describe in this article, our studies on the use of chiral diselenide oxazolines (**1** and **2**, Scheme 1) as ligands in the enantioselective copper-catalyzed conjugate addition of Grignard reagents to enones (Eq. (1)).

The ligands required for this study were prepared as depicted in Scheme 1. Diselenide derived from valine (R = *i*-Pr, **1**) was prepared by direct *ortho*-lithiation[10] of the parent oxazoline, followed by addition of selenium powder and then oxidation with oxygen to give the desired diselenide.[11] The phenylalanine derivative (R = benzyl, **2**) was prepared in a similar way via organomagnesium derivatives[3a] obtained by reaction of the parent brominated oxazoline with activated magnesium.[12]

Our initial goal in this study was to assess the influence of our ligands on the rate and enantioselectivity of the reaction. We therefore examined conjugate addition in which we employed 5 and 10 mol% of the valine derived diselenide **1** with 10 mol% copper iodide.



(1)

Keywords: diselenide; catalyst; conjugate addition; chiral ligand.
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0040-4039/02/$ - see front matter
PII: S0040-4039(02)01713-6

As our substrates cyclohexenone and *i*-PrMgCl were used to determine the effects of solvent and additives on yield and enantioselectivity of the reaction. Carrying out the reaction using THF and ether as solvents without any additive, only a small amount of the product was observed. We then examined the influence of HMPA or TMSCl on the reaction and the best results were obtained when the Grignard reagent was slowly added at −78°C to a THF solution containing the catalyst (10 mol%), CuI (10 mol%), the enone, and 2 equiv. of hexamethylphosphoric triamide (HMPA) as additive.[13] Under these conditions, 3-isopropylcyclohexanone was formed in good yield (85%) and acceptable enantiomeric excess (60% *ee*) for first generation Se ligands. However, if the catalyst loading is decreased to 5 mol%, both the enantioselectivity and yield decreased (entry 5, Table 1).

Also, the effect of a different substituent at the oxazoline ring were studied. We found that the isopropyl substituted oxazoline ligand provides better enantioselectivity and chemical yield (compare entries 4 and 8, Table 1). An effect of the halide in the Grignard reagent was also studied, and in one experiment was observed that Grignard reagent derived from *i*-PrCl gives slightly better results than that from *i*-PrBr (entries 4 and 9, Table 1). Furthermore, the behavior of other copper salts was examined. The reaction was carried out with CuBr, CuCl and CuCN under the same experimental conditions and none of them promoted the alkylation reaction more efficiently than CuI.

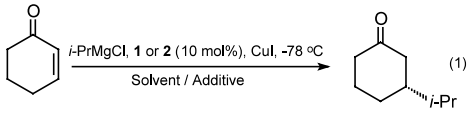
It should be mentioned that the ligand in the active catalyst likely does not retain C_2-symmetry. The diselenide bond of the C2-ligand is probably cleaved in situ by *i*-PrMgCl to result in two corresponding identical oxazolinylselenides, which form the real catalytically active ligand.[8b] However, for synthetic application purposes the diselenides are much easier to obtain and to handle.

We briefly explored the scope of this reaction and examined the Grignard addition of isopropyl and butyl groups to several enones, as shown in Table 2. For cyclic enones, the enantioselectivities increase as the ring size increases from cyclopentenone cycloheptenone. We also examined the addition of *i*-PrMgCl to the acyclic chalcone, and observed low levels of asymmetric induction (Table 2).

For the rationalization of the induction process, transition states similar to those discussed for lithium cuprates[3d,e] may be considered in analogy.

In summary, we described in this paper for the first time the use of oxazoline containing diselenides as chiral ligands in the enantioselective copper-catalyzed addition of Grignard reagents to enones. The resulting 1,4-addition products were obtained in good yields. The enantiomeric excesses were obtained using cyclic enones as substrates. The levels of asymmetric induction increased with ring size.

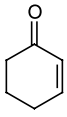
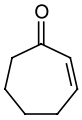
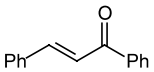
Table 1. 1,4-Addition of *i*-PrMgX to cyclohexenone: comparison of ligands and influence of solvent and additives



Entry	Solvent/additives[a]	Ligand	Yield (%)	*ee*[b] (%)
1	THF	**1**	11	27
2	Et_2O	**1**	0	0
3	Toluene/HMPA	**1**	70	51
4	THF/HMPA	**1**	85	60
5[c]	THF/HMPA	**1**[c]	25	17
6	THF/TMSCl	**1**	5	25
7	THF/HMPA/TMSCl	**1**	30	3
8	THF/HMPA	**2**	56	33
9[d]	THF/HMPA	**1**	80	56

[a] 2 equiv. of each additive with regard to the substrate were used.
[b] Enantiomeric excesses were determined by chiral GC using (2,6-Me-3-Pe)-β-cyclodextrin as stationery phase.
[c] 5 mol% of catalyst were used.
[d] *i*-PrMgBr was used instead of *i*-PrMgCl.

Table 2. 1,4-Addition of Grignard reagents to enones using diselenide **1** (10 mol%) as catalyst

Enone	Grignard Reagent	Temp. (°C)	Yield (%)	*ee* (%)
	*i*-PrMgCl	-78	89	22
	n-BuMgCl	-45	91	32
	*i*-PrMgCl	-78	85	60
	n-BuMgCl	-78	89	62
	*i*-PrMgCl	-78	53	85
	i-PrMgCl	-45	94	85
	n-BuMgCl	-78	92	61
	*i*-PrMgCl	-78	70	5

Acknowledgements

The authors wish to thank CAPES and the DAAD (German Academic Exchange Service) for travel grants as part of a PROBRAL Program, CNPq and FAPERGS for financial support. S.J.N.S. thanks CAPES for a Ph.D. fellowship.

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11. A stirred solution of 4-*S*-isopropyl-2-phenyloxazoline (1.3 g, 10 mmol) in dry ether (30 mL) under argon was treated dropwise with a 1.7 M solution of *n*-BuLi (6.5 mL, 11 mmol) at 0°C. After stirring for 6 h at this temperature a brown colored solution of the lithiated product was obtained. To this solution, selenium powder (0.87 g, 11 mmol) was added at 0°C and stirring was continued for an additional 2 h at this temperature. The reaction mixture was quenched with cold aqueous $NaHCO_3$ and O_2 was bubbled through it in a moderate rate for 15 min, followed by extraction with dichloromethane. The organic phase was dried with $MgSO_4$ and concentrated under vacuum to give a yellow oil which crystallizes upon slow evaporation of ethanol. Yield: 30%. Mp 148.2–149.6°C. Anal. calcd for $C_{24}H_{28}O_2N_2Se_2$: C, 76.56; H, 7.50; N, 7.44. Found: C, 76.20; H, 7.60; N, 7.25%; $[\alpha]_D^{20}$ −28° (*c* 1.6 $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.04 (d, 3H, $J=7.0$ Hz), 1.12 (d, 3H, $J=7.0$ Hz), 1.81–1.89 (m, 1H), 4.14–4.22 (m, 1H), 4.24–4.28 (m, 1H), 4.45–4.53 (m, 1H), 7.26–7.81 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.9, 19.0, 33.2, 70.6, 73.3, 125.5, 126.0, 129.4, 130.5, 131.3, 133.6, 162.9; IR (KBr, cm^{-1}): 1464, 1647, 2959, 3091.
12. A solution of 4-*S*-benzyl-2-(2′-bromophenyl)oxazoline (0.82 g, 2.60 mmol) in 5 mL of THF was added dropwise to a suspension of activated magnesium (0.062 g, 2.60 mmol) in THF (10 mL). The reaction mixture was stirred for 8 h under reflux and then selenium powder (0.21 g, 2.60 mmol) was added. The resulting mixture was stirred under reflux for an additional 6 h, and after this time cooled to room temperature and diluted with ethyl ether. The organic phase was washed with saturated NH_4Cl, 2 M NaOH and brine, dried with $MgSO_4$. Removal of the solvent under vacuum afforded a yellow oil which crystallizes upon slow evaporation of ethanol. Yield: 35%. Mp 155.6–157.0°C. Anal. calcd for $C_{32}H_{28}O_2N_2Se_2$: C, 81.33; H, 5.97; N, 5.93. Found: C, 81.30; H, 5.95; N, 5.90%; $[\alpha]_D^{20}$ −45° (*c* 2.1 $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.77 (dd, 1H, $J=8.0$ Hz, $J=14.0$ Hz), 3.18 (dd, 1H, $J=6.0$ Hz, $J=14.0$ Hz), 4.08 (dd, 1H, $J=8.0$ Hz, $J=16.0$ Hz), 4.32 (dd, 1H, $J=8.0$ Hz, $J=16.0$ Hz), 4.64–4.72 (m, 1H), 7.12–7.78 (m, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 41.9, 68.1, 71.7, 125.5, 125.9, 126.4, 128.2, 128.4, 129.3, 129.6, 131.4, 133.4, 137.9, 163.4; IR (KBr, cm^{-1}): 1361, 1464, 1653, 3026, 3061.
13. **Typical procedure for the copper-catalyzed 1,4-addition**: To a suspension of diselenide **1** (53 mg, 0.1 mmol) and CuI (19 mg, 0.1 mmol) in 10 mL THF under argon, 0.35 mL (2 mmol) of HMPA was added. The resulting yellow solution was cooled to −78°C. After addition of cyclohexenone (1 mmol), 2 mL (1 mmol, 0.5 M in THF) of *i*-PrMgCl was added at −78°C over a period of 2 h. The reaction mixture was then stirred for an additional 4 h at that temperature. After quenching with a saturated aqueous NH_4Cl solution, the mixture was warmed to room temperature and extracted with CH_2Cl_2. The organic phase was dried with $MgSO_4$ and removal of the solvent under vacuum followed by flash chromatography on silica with hexanes/AcOEt (98:2) afforded the pure product. Yield: 80% *ee*: 60%. $[\alpha]_D^{20}$ +45° (*c* 1.5 $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.81 (d, 6H), 1.21–2.17 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.0, 25.4, 28.2, 32.4, 41.2, 45.2, 212.3; IR (KBr, cm^{-1}): 1713.