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Highly Enantioselective Catalytic Conjugate Additions to Cyclohexadienones

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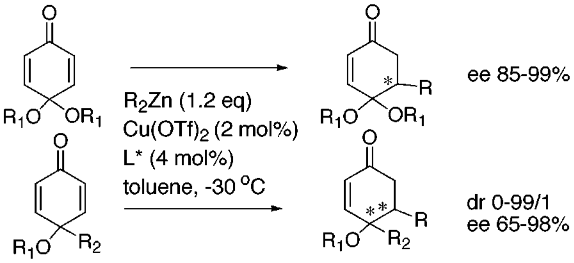
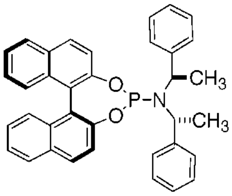
ABSTRACT



Enantioselective copper phosphoramidite-catalyzed conjugate addition of dialkylzinc reagents (R_2Zn) to several 4,4-disubstituted cyclohexadienones was achieved with dr's up to 99/1 and ee's up to 99%.

Organocopper compounds are among the most widely used reagents for C−C bond formation by virtue of their versatility in conjugate addition reactions.[1] Considerable progress has been made in the enantioselective copper-catalyzed 1,4-addition to prochiral enones, and this method offers an attractive way to form enantiomerically enriched β-substituted carbonyl compounds.[2] Recently, we reported a novel chiral $Cu(OTf)_2$−phosphoramidite catalyst based on ligand L*-**1** (for L*-**1** see Figure 1) which allowed for the first time highly enantioselective catalytic conjugate addition of several (functionalized) dialkylzinc reagents to cyclic α,β-unsaturated ketones.[3,4]



(*S*,*R*,*R*)-1

Figure 1. Phosphoramidite used as chiral ligand in the Cu-catalyzed 1,4-addition of R_2Zn.

Enantioselective annulations via a 1,4-addition−aldol cyclization protocol, employing functionalized organozinc reagents, were also achieved with this catalyst.[5]

Cyclohexadienones are attractive substrates for conjugate additions as the chiral products may be subject to further

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[1] For an excellent review on recent progress in organocopper chemistry, see: Krause, N., Gerold, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 186.

[2] (a) Krause, N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 283. (b) Knöbel, A. K. H.; Escher, I. H.; Pfaltz, A. *Synlett* **1997**, 1429. (c) Nakagawa, Y.; Kanai, M.; Nagaoka, Y.; Tomioka, K. *Tetrahedron* **1998**, *54*, 10295. (d) Yan, M.; Yang, L.-W., Wong, K.-Y.; Chan, A. S. C. *Chem. Commun.* **1999**, 11. (e) Alexakis, A.; Vastra, J.; Burton, J.; Benhaim, C.; Mangeney, P. *Tetrahedron Lett.* **1998**, *39*, 7869. (f) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771. (g) Feringa, B. L.; De Vries, A. H. M. In *Advances in Catalytic processes*, Vol. 1; Doyle, M. D., Ed.; JAI Press: Connecticut, 1995; p 151.

[3] Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; De Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620.

[4] Highly enantioselective rhodium-catalyzed asymmetric 1,4-addition of aryl- and alkenylboronic acids to enones has been reported by Hayashi et al.: Takaya, Y.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **1998**, *120*, 5579.

[5] Naasz, R.; Arnold, L. A.; Pineschi, M.; Keller, E.; Feringa, B. L. *J. Am. Chem. Soc.* **1999**, *121*, 1104.

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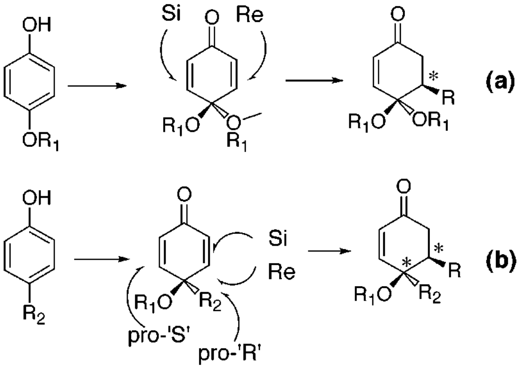
1,4-additions or may be employed in asymmetric cycloadditions. Furthermore, this class of compounds has hardly been explored in enantioselective catalysis and the highly symmetric nature offers a critical test for any chiral catalyst. Here we wish to report the use of the $Cu(OTf)_2$−phosphoramidite (L*-**1**) system in the catalytic conjugate addition of dialkylzinc reagents to several symmetric 4,4-disubstituted cyclohexadienones resulting in a short route to optically active cyclohexenones.

The 4,4-disubstituted cyclohexadienones are highly versatile benzoquinone equivalents[6] due to their multifunctional nature. Several elegant methods have been reported to obtain chiral synthons based on 4,4-disubstituted cyclohexadienones; most of these approaches involve the temporary conversion to tricyclic adducts which are obtained in optically active form, either by diastereoselective [4 + 2]-cycloaddition using a chiral cyclopentadiene,[7a] via desymmetrization of meso-tricycloadducts with the aid of lipase[7b] or by using Rh(I)(BINAP) catalysis.[7c]

Conjugate additions reactions of for example alkyllithium reagents,[8a] dimethylmalonate,[8b] and acyl−nickel complexes[8c] to 4,4-disubstituted cyclohexadienones have been reported, but none of these are catalytic or enantioselective. To our knowledge the only catalytic enantioselective conjugate addition to 4,4-disubstituted cyclohexa-2,5-dienones was reported by Iwata et al.[9] which involved Cu-catalyzed addition of trimethylaluminum to afford 3,4,4,5-tetramethylcyclohex-2-enone with ee's up to 68%.[10]

Conjugate addition to symmetric dienones results in desymmetrization of the prochiral dienone moiety (Scheme 1). Side selective addition affords a single stereocenter in case the 4,4-substituents are equal, i.e., Re versus Si face attack of the organometallic reagent (side selectivity; Scheme 1a). When the substituents at the 4-position are different, Si or Re face selective attack gives rise to the formation of two stereocenters in a single step (side and face selectivity; Scheme 1b). Will the chiral catalyst based on L*-**1** be able to distinguish Re/Si faces and pro-*R*/pro-*S* positions in these highly symmetric dienones? Since the 4,4-disubstituted cyclohexadienones can be easily prepared in one step from the corresponding phenols[10,11] Scheme 1 represents an attractive route for the preparation of chiral multifunctional synthons in just two steps from phenols.

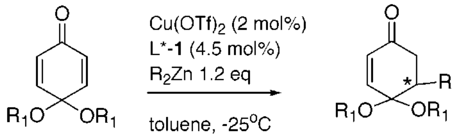
Scheme 1



To investigate the behavior of the novel catalytic system in the conjugate addition of R_2Zn to these cyclohexadienones and the influence of the substituents on product ratio and ee, cyclohexadienones **2**−**6** and **13**−**16** with different C-4 substituents were examined.

All reactions were performed under Ar on a 1 mmol scale at −30 °C. The catalyst was prepared in situ by stirring 2.0 mol % of $Cu(OTf)_2$ and 4 mol % of L*-**1** in 5 mL of dry toluene for 30 min and at −30 °C substrate (1.0 equiv) and 1.2 equiv of R_2Zn were added sequentially. After 24 h, the reaction mixture was quenched with water or diluted NH_4Cl solution and the product was immediately extracted with diethyl ether. Workup had to be performed fast to avoid aromatization of the 1,4-adduct to the corresponding 3-alkyl-4-alkoxy- or 3,4-dialkylphenols. After column chromatography (SiO_2, hexane/EtOAc, 5/1) the pure cyclohexenones (**7**−**12** and **17**−**20**) were obtained. The results are summarized in Tables 1 and 2.

Table 1. Conjugate Addition of R_2Zn to Symmetrical Cyclohexadienones, Catalyzed by $Cu(OTf)_2$−L*-**1**



entry	dienone	R_1	R_1	R	1,4-adduct	yield[a] (%)	ee[b] (%)
1	**2**	Me	Me	Et	**7**	65	97
2	**3**	Et	Et	Et	**8**	59	92
3	**4**	$-CH_2CH_2-$		Et	**9**	68	92
4	**5**	$-CH_2CH_2CH_2-$		Et	**10**	62	89
5	**6**	$-CH_2C(Me)_2CH_2-$		Et	**11**	75	85
6	**2**	Me	Me	Me	**12**	76	99

[a] Isolated yield. [b] Ee values of **7**−**12** were determined by GC (see Supporting Information); no 1,2-adducts were observed.

The conjugate addition of Et_2Zn to cyclohexadienone monoacetals with $R_1 = R_2$ (**2** and **3**) proceeded with high

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(6) Swenton, J. S. *The chemistry of quinoid compounds*; Rappoport, Z., Patai, S., Eds.; John Wiley: New York, 1988; Vol. 2, Part 2, p 899.

(7) (a) Jones, P. G.; Weinmann, H.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 448. (b) Takano, S.; Moriya, M.; Higashi, Y.; Ogasawara, K. *Chem. Commun.* **1993**, 177. (c) Kamikubo, T.; Hiroya, K.; Ogasawara, K. *Tetrahedron Lett.* **1996**, *37*, 499.

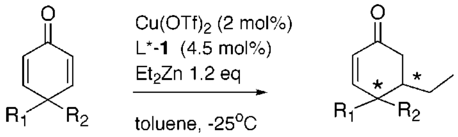
(8) (a) Stern, A. J.; Rhode, J. J.; Swenton, J. S. *J. Org. Chem.* **1989**, *54*, 4413. (b) Torii, S.; Hayashi, N.; Kuroboshi, M. *Synlett* **1998**, 599. (c) Semmelhack, M. F.; Keller, L.; Sato, T.; Spiess, E. J.; Wulff, W. *J. Org. Chem.* **1985**, 5567.

(9) Takemoto, Y.; Kuraoka, S.; Hamaue, N.; Iwata, C. *Tetrahedron: Asymmetry* **1996**, *7*, 993.

(10) Diastereoselective conjugate additions of trimethylaluminum to [(*p*-tolylsulfinyl)methyl]quinols have been reported: Pirrung M. C., Nunn D. S. *Tetrahedron Lett.* **1992**, *33*, 1992.

(11) (a) Pelter, A.; Elgendy, S. M. A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1891. (b) Tamura, Y.; Yakura, T.; Haruta, J.-I.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927.

Table 2. Conjugate Addition of Et_2Zn to 4,4-Disubstituted Cyclohexadienones with $R_1 \neq R_2$, Catalyzed by a $Cu(OTf)_2$−L*-**1** Complex



entry	dienone	R_1	R_2	1,4-adduct	yield (%)[a]	dr[b]	ee major (%)[b]	ee minor (%)[b]
1	**13**	OMe	Me	**17**	60	90/10	97	85
2	**14**	OMe	CH_2Ph	**18**	53	97/3	93	nd[c]
3	**15**	$CH_2CH_2CH_2O$		**19**	66	99/1	65	nd[c]
4	**16**	OMe	OCH_2Ph	**20**	58	1/1	98	98

[a] Isolated yield; no 1,2 adducts were detected. [b] Dr and ee determination for **17** and **18** could not be directly performed by either GC or HPLC. Hydrogenation of the double bonds afforded products which could be separated by HPLC, Daicel AS column. Dr and ee determination of **19** and **20** was performed by HPLC, Daicel AS column. (see Supporting Information for details). [c] Not determined.

enantioselectivity (Table 1, entries 1 and 2): for instance, 3-ethyl-4,4-dimethoxycyclohexenone (**7**) with an ee of 97% was isolated. When the methoxy substituents are replaced by the larger ethoxy groups, the ee of the enone **8** dropped to 92%; probably this is due to some steric interference.

When cyclic acetals are used, it is interesting to notice that the ee drops from 92% to 85% with an increase of ring size and the bulk of substituents (Table 1, entries 3−5). Cyclohexadienone−ethylene glycol monoacetal (**4**) gave a slightly lower enantioselectivity in the 1,4-addition compared to dimethoxy dienone **2** (92 vs 97% ee). Probably this is due to the rigidity of the ethylene glycol acetal and not the result of a difference in size. Conjugate addition of Me_2Zn to dimethoxycyclohexadienone **2** affords the 1,4-adduct **12** with a rewarding 99% enantiomeric excess.

Since the acetal moiety might have a coordinating effect to the chiral Cu catalyst, it is interesting to know what the stereochemical result of the conjugate addition of Et_2Zn would be in the case of 4,4-disubstituted cyclohexadienones with only one alkoxy moiety attached to the cyclohexadienone. The introduction of two different substituents at C-4 will give rise to the formation of two stereogenic centers as depicted in Scheme 1. It is interesting to elucidate if this substitution pattern leads to a high diastereoselectivity and a considerable enantioselectivity for both diastereoisomers and if the stereoselectivity only depends on the size of the C-4 substituents.

The 1,4-additions to substrates **13**−**16** reveal that for cyclohexadienone **13** with one MeO and one Me substituent the formation of a mixture of two diastereoisomers of **17** occurs. The diastereomeric ratio was 9/1, and the ee's of the major and minor product are 97% and 85%, respectively (see Table 2).

In the case of cyclohexadienone **14,** with the methoxy substituent and a substantially larger benzyl group, nearly one diastereoisomer of adduct **18** is observed (dr 97/3) with an ee of 93% for the major diastereoisomer. When the alkoxy and alkyl substituent are linked as in spiro dienone **15**, a high diastereoselectivity (dr 99/1) in the formation of adduct **19** is observed. The ee of the major diastereoisomer was, however, only 65%. NOESY experiments indicated that in the cyclohexenones **17**−**19** the ethyl substituent was introduced cis to the alkoxy group in the major isomer.[12]

The origin of the observed diastereoselectivity could be a steric effect or coordination of the oxygen of the alkoxy moiety to the catalytic species. The conjugate addition of diethylzinc was therefore performed with cyclohexadienone **16**, which contains two alkoxy substituents of different sizes. Adduct **20** was obtained as a 1:1 mixture of the two possible diastereoisomers, but much to our delight both isomers were nearly enantiomerically pure (ee 98%). It is therefore likely that the oxygen of the acetal or alkoxy substituent interacts with the metal complex and therefore exerts a directing effect on the activated organometallic species in the copper-catalyzed enantioselective conjugate addition of dialkylzinc reagents to 4,4-disubstituted cyclohexadienones.

In conclusion the copper−phosphoramidite chiral catalyst shows remarkably high levels of stereoselectivity in the 1,4-addition to symmetric dienones. On the basis of this finding, a new catalytic method was developed to prepare several multifunctional cyclohexenones with high dr and high ee.

Acknowledgment. Financial support from The Netherlands Foundation of Scientific Research is gratefully acknowledged.

Supporting Information Available: Standard procedure for conjugate addition of R_2Zn reagents to cyclohexadienones, spectroscopic data for 1,4-adducts **7**−**12** and **17**−**20**, and NOESY interactions for **17**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) A cis-directing effect of the methoxy substituent in the organoaluminum mediated conjugate addition of RLi and RMgBr to quinol ethers has been observed, see ref 8a.