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ASYMMETRIC CONJUGATE ADDITION OF ZINCATES OR CUPRATES CONTAINING AN OPTICALLY ACTIVE AZAENOLATE OF erythro-ISOPROPYLIDENE-2-METHOXY-1,2-DIPHENYLAMINE TO 2-CYCLOALKENONES†

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Summary: Asymmetric conjugate addition to prochiral cycloalkenones was examined by utilizing a zinc azaenolate as well as a copper one derived from an acetone imine of optically active erythro-2-methoxy-1,2-diphenylethylamine, the best enantioselectivity of the resulting 3-acetonylcycloalkanones being as high as 92% ee.

Disclosed herein is an efficient asymmetric conjugate addition of an azaenolate of acetone imine to 2-cycloalkenones by way of a chiral zinc azaenolate, which constitutes, to our best knowledge, the first example of the conjugate transfer of a chirally functionalized ligand from the mixed zincate.

A variety of organocuprates containing alkyl or vinylic groups occupies a prominent place in the carbon nucleophiles which undergo definite conjugate addition to α,β-unsaturated carbonyl compounds. The importance of this reaction has incited numerous researches to effect highly diastereoselective conjugate addition to chiral substrates.1) Enantioselective conjugate additions employing cuprates with chiral nontransferable ligands have recently been reported with considerable success.2)

Less attention has been paid for the use of functionalized ligands to transfer. Among the more useful types of carbanion ligands are those of enolates of esters and ketones, if reactive complexes could be prepared.

Direct formation of either homocuprates or mixed-ligand cuprates may not be feasible in the case of these enolates, since the latter would function as nontransferable ligands.3) Thus, another line of research has been undertaken on asymmetric conjugate additions of chirally functionalized organocuprates: Among several candidates of functionalized systems of cuprates we have tried to utilize a lithium azaenolate derived from an optically active acetone imine for the preparation of chiral cuprate reagents.4,5)

Meanwhile, a recent report on the selective conjugate butylation of 2-cyclohexenone with lithium butyldimethylzincate6) has prompted us to examine

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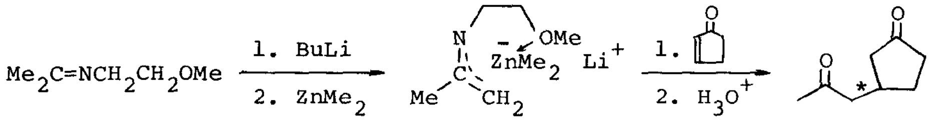
the conjugate addition of a mixed zincate which contains an azaenolate ligand. Preliminary experiments revealed that an azaenolate obtained from acetone imine of 2-methoxyethylamine was cleanly transferred in a conjugate manner to 2-cyclopentenone by way of functionalized mixed zincates,[7)] whereas 2-cyclohexenone was found to undergo both conjugate addition and competitive but minor 1,2-addition (Eq. 1).

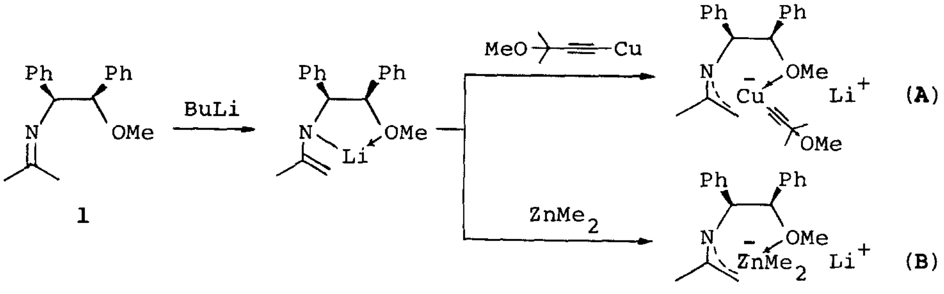


(1)

Encouraged with the findings that the zincates also work well in the conjugate addition of azaenolates as synthetic equivalent of enolates to cyclic enones, we have carried out the asymmetric conjugate addition of a chiral azaenolate and even better results than those with the corresponding cuprates are presented herein.

Treatment of (1S,2R)-2-methoxy-1,2-diphenylethylamine (3.19 g, 14 mmol), $[\alpha]_D=-84.7^\circ$ (MeOH) (lit.[8] $[\alpha]_D=+84^\circ$ (MeOH) for (1R,2S)-isomer), prepared from opotically pure 2-amino-1,2-diphenylethanol[9)], with dry acetone (45 mL) in the presence of 4A molecular sieves (4 g) gave N-isopropylidene-1-amino-2-methoxy-1,2-diphenylethane (**1**) as white solids (3.60 g, 96% yield).[10)]

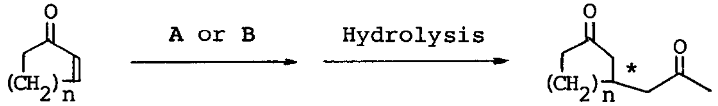
Deprotonation of the chiral acetone imine was carried out in a usual manner: To a stirred solution of **1** (2.3 mmol) in dry THF (10 mL) was added BuLi (1.6 M in hexane, 2.4 mmol) at -40 °C under argon atmosphere. The orange colored solution was stirred for 30 min at - 40 °C and then cooled to -78 °C for further complexation with either copper acetylide (prepared from $CuBr{\cdot}SMe_2$ and $LiC{\equiv}CCMe_2OMe$) or dimethylzinc (prepared from $ZnCl_2$·tetramethylethylenediamine complex and 2 equiv. of MeLi) as depicted in Scheme 1.



Scheme 1. (1S,2R)-Isomer shown.

To the mixed cuprate (**A**) or zincate (**B**) thus obtained was added 2-cycloalkenone in an equimolar amount or a one-half of the azaenolate reagent. Usual workup and purification of the product by column chromatography and distillation (Kugelrohr) afforded 3-acetonylcycloalkanones. In all these experiments the chiral auxiliary could be recovered by extractive isolation. The optical purity of each of 3-acetonylcyclopentanone (**2**) and 3-acetonylcyclohexanone (**3**)

Table 1. Asymmetric Conjugate Acetonylation of 2-Cycloalkenones



Entry	Enone n	Metalate	Auxiliary	Solvent	Temp. °C	Time h	Yield %	$[\alpha]_D$[a] deg.	Opt. Yield/%	(Confign)
1	1	**A**[a]	(1S,2R)-(-)	THF	-78	2	78	-59.8[b]	78	(R)
2	1	**A**	(1R,2S)-(+)	Et_2O	-50	4	41	+61.2	80	(S)
3	1	**A**	(1R,2S)-(+)	Et_2O	-78	3	56	+62.9	82[c]	(S)
4	1	**B**[a]	(1S,2R)-(-)	THF	-78	4.5	26	-67.7	88	(R)
5	1	**B**	(1S,2R)-(-)	THF	-78	5	73[d]	-70.6	92	(R)
6	2	**A**	(1R,2S)-(+)	THF	-50	2	78	+10.3[e]	71	(S)
7	2	**B**	(1R,2S)-(+)	THF	-78	4.5	55	+12.0	82	(S)
8	2	**B**	(1R,2S)-(+)	THF	-78	4	48[d]	+12.9	88	(S)

[a] Cuprate (**A**) and Zincate (**B**) in Scheme 1. [b] $[\alpha]_{Dmax}$ +76.7° (PhH) for (S)-2. [c] Me_3SiCl (1 equiv.) was added with 2-cyclopentenone. [d] Zincate (**B**) 2 equiv. [e] $[\alpha]_{Dmax}$ +14.6° for (S)-3 (Ref. 4a).

was determined on the basis of the maximum rotation of respective compounds which have previously been given by us.[4] Selected data for asymmetric conjugate acetonylation of 2-cycloalkenones are given in Table 1.

In the reaction of 2-cyclopentenone with cuprate **A**, the optical yields (% ee) were slightly solvent dependent ($Et_2O > THF$) at the expense of lowering chemical yield.

Generally, zincate **B** appears to be a little less reactive towards 2-cycloalkenones than the cuprate, attaining higher optical yields up to 92% ee for 3-acetonylcyclopentanone (**2**) as well as satisfactory chemical yield, when 2 equiv of the chiral reagent were used (Entry 5, in Table 1).

It is worthy of note that the enantioselectivities for 2-cyclopentenone were somewhat above those found with 2-cyclohexenone. This is not the case for conjugate butylation reported by Corey et al.[2a]

It is still hard to propose a model for the high level of enantioselectivities attained by the present conjugate addition of these chiral mixed cuprate or zincate to 2-cycloalkenones. Although the mechanistic features in conjugate addition of zincates to cyclic enones must differ considerably from those of cuprates,[11] the major isomer (R in Entries 1, 4, and 5 in Table 1) indicates the same enantiofacial preference for the conjugate addition of both reagents, specifically attack at the si face of C(3) of 2-cyclopentenone.

These results may stem, at least, from the least overlapping between the

2-cycloalkenone molecule with the si face of C(3) and the rear-side of the chelate ring structure presumed for both cuprate **A** and zincate **B** starting with (1S,2R)-**1** in the diastereomeric transition states.

It should be noted that zincates examined here react little with common acyclic α,β-enones such as benzalacetone in a conjugate manner.

References and Notes

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