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Catalytic Enantioselective Conjugate Addition of Dialkylzincs to α,β-Unsaturated Ketones Using Nickel Bromide - *N*, *N*-Dibutylnorephedrine

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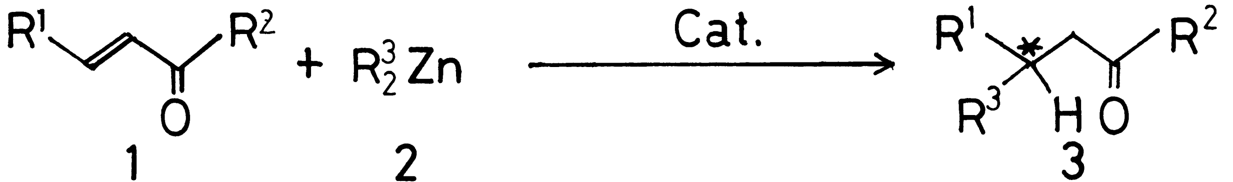
Combination of nickel bromide and *N*, *N*-dibutylnorephedrine catalyzed the enantioselective conjugate addition of dialkylzincs to α, β-unsaturated ketones to afford optically active β-substituted ketones in up to ca. 50% enantiomeric excess.

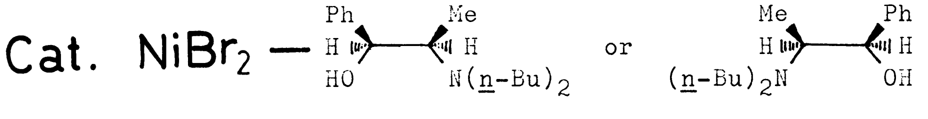
Enantioselective conjugate addition of organometallic reagents to prochiral α, β-unsaturated ketones has attracted increasing attention.1) However, nearly all of the reported methods require stoichiometric amounts of chiral auxiliaries. The only exception as far as we know is the very recently reported catalytic enantioselective conjugate addition of Grignard reagents to 2-cyclohexen-1-one using chiral organocopper(I) complex. However enantiomeric excesses(e.e.'s) of the products range from 4 - 14% e.e.2) Thus, it is a challenging problem to find a catalytic enantioselective conjugate addition reaction.

We found that chiral catalyst prepared from nickel bromide($NiBr_2$) and *N*, *N*-dibutylnorephedrine(DBNE)3) is efficient in enantioselective conjugate addition of dialkylzincs to α, β-unsaturated ketones to afford optically active β-substituted ketones of moderate e.e.'s. Reaction of diethylzinc with chalcone using $NiBr_2$ and (1*S*, 2*R*)-(-)-DBNE as catalyst afforded (*R*)-(-)-1,3-diphenylpentan-1-one(**3a**) in 32.2% isolated yield, $[\alpha]^{25}_{365}$ -41.1° (*c* 2.5, EtOH), 48.4% e.e. based on the HPLC analysis using chiral column (Table 1, entry 1).4, 5)



a; R^1=R^2=Ph
b; R^1=Ph, R^2=Me
c; R^1=Me, R^2=Ph

a; R^1=R^2=Ph, R^3=Et
b; R^1=R^2=Ph, R^3=*n*-Bu
c; R^1=Ph, R^2=Me, R^3=Et
d; R^1=Me, R^2=Ph, R^3=Et



(1*S*, 2*R*)-(-)-DBNE (1*R*, 2*S*)-(+)-DBNE

Table 1. Asymmetric Synthesis of Optically Active Ketones(3) by Catalytic Conjugate Addition of Dialkylzincs(2) to α, β-Unsaturated Ketones(1)[a]

	1		2		3				
Entry	R^1	R^2	R^3	Temp/°C		[α](temp/°C, c, solvent)	Yield/%	e.e./%[b]	Config.
1	Ph	Ph	Et	-30	a	$[\alpha]_{365}$ -41.1°(25, 2.5, EtOH)	32.2	48.4(54.8)	R
2	Ph	Ph	n-Bu	-30→0	b	$[\alpha]_D$ +3.47°(27, 1.9, EtOH)	16.0	43.1	-
3	Ph	Me	Et	0→r.t.	c	$[\alpha]_D$ +5.35°(27, 2.3, EtOH)	31.7	(17.8)	S
4	Me	Ph	Et	0→r.t.	d	$[\alpha]_D$ +2.77°(26, 6.9, Et_2O)	40.1	(14.1)	S

a) Molar ratio. 1 : 2 : $NiBr_2$: DBNE = 1 : 2.2 : 0.25 : 0.3.

b) Determined by HPLC analysis using chiral column(Daicel Chiralcel OD, 250 mm). Flow rate 0.5 ml/min, eluent 0.25% 2-propanol in hexane, UV detector(254 nm). Retention time for 3a, (S)-isomer (minor), 26.2 min, (R)-isomer (major), 29.3 min. For 3b, (S)-isomer (minor), 29.1 min, (R)-isomer (major), 34.0 min. Values in parentheses are those based on the reported values of optical rotations. For (S)-3a, $[\alpha]^{23}_{364}$ +75° (c 2.5, EtOH)(Ref. 6). For (S)-3c, $[\alpha]^{22}_D$ +30° (c 2.3, EtOH)(Ref. 6). For (S)-3d, $[\alpha]_D$ +19.6° (c 5, Et_2O)(Ref. 7).

It is surprising that the substituent R^2 attached to the carbonyl of the enone(1) determined the sense of the asymmetric induction. Chalcone(1a, R^2 = Ph) afforded (R)-3a, whereas benzalacetone(1b, R^2 = Me) afforded (S)-3c (entries 1 and 3). On the other hand, the substituent R^1 attached to the olefin of 1 did not affect the sense of the asymmetric induction (entries 1 and 4). This shows that the environment of the carbonyl group of 1 is more important to determine the sense of the asymmetric induction than that of the olefin part of 1.

DBNE is available in either enantiomeric form. Thus (S)-3a was synthesized in 44.2% e.e. (HPLC analysis) by using (1R, 2S)-(+)-DBNE.

Typical experimental procedure is as follows (Table 1, entry 1): a mixture of $NiBr_2$(0.055 g, 0.25 mmol)[8] and (1S, 2R)-(-)-DBNE(0.079 g, 0.3 mmol) in toluene (1 ml) was stirred at 80 °C for 1 h, and then cooled to room temperature. 1a(0.208 g, 1 mmol) in toluene (2 ml) was added, and the mixture was stirred for 20 min, then cooled to -30 °C. Et_2Zn(1 M solution in hexane, 2.2 mmol) was added dropwise, then the mixture was stirred at -30 °C for 13 h. The reaction was quenched with 1 M hydrochloric acid (7 ml), the organic layer was separated, and the aqueous layer was extracted with dichloromethane (4 x 8 ml). The combined organic layer was dried (Na_2SO_4) and then evaporated under reduced pressure. The residue was purified by preparative TLC over silica gel (eluent, hexane / chloroform = 1 : 1, v/v) to afford (R)-(-)-3a (0.077 g).

References

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2) G. M. Villacorta, C. P. Rao, and S. J. Lippard, J. Am. Chem. Soc., 110, 3175 (1988).
3) For the use of DBNE in catalytic enantioselective 1, 2-addition to aldehydes and formylesters, see K. Soai, S. Yokoyama, K. Ebihara, and T. Hayasaka, J. Chem. Soc., Chem. Commun., 1987, 1690; Chem. Lett., 1988, 843.
4) Reactions using $NiCl_2$ or NiI_2 instead of $NiBr_2$ gave (R)-3a in 29.9 and 2.6% e.e.'s respectively (HPLC analysis).
5) When N, N-diethylnorephedrine or N, N-dihexylnorephedrine were used instead of DBNE, e.e.'s of 3a were 28.6 and 3.8% respectively.
6) M. J. Brienne, C. Ouannes, and J. Jacques, Bull. Soc. Chim. Fr., 1967, 613.
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8) Reactions using 0.03 and 0.40 mmol of $NiBr_2$ ($NiBr_2$ / DBNE = 1 / 1.2) gave (R)-3a in 35.9% and 32.3% e.e.'s respectively.

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