

Asymmetric Addition of Bis(homoallyl)zinc to the Propargyl Aldehyde Dicobalt Hexacarbonyl Complexes in the Presence of Chiral Disulfonamide Followed by Pauson-Khand Reaction[†]

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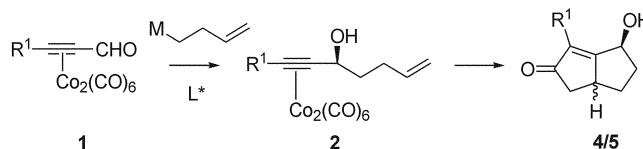
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The preparation of the optically active secondary propargyl alcohols has been a subject of intensive researches.¹ These include the addition of dialkynylzinc or mixed alkyl alkynylzinc to aldehydes by the aid of chiral ligands in moderate to excellent yields,^{2,3} and the reduction of alkynyl ketones in relatively high enantioselectivity.⁴ And an alternative approach by the addition of dialkylzinc to propargyl aldehyde in the presence of catalytic amount of the chiral ligands has not been satisfactory until recent years.^{5,6} This relatively poor efficiency was attributed to smaller steric differences. Exaggeration of the steric environment of alkyne by introducing temporary protecting group would be the choice of trials to increase the enantioselectivity. Dicobalt carbonyl moiety on triple bond had been often used to improve enantioselectivity in this line. Roush and Park demonstrated a significant improvement of enantioselectivity in the reactions of homopropargyl aldehyde with a stoichiometric amount of allylborane by introducing dicobalt hexacarbonyl on alkyne moiety.⁷ Nicholas also studied the reaction of the cobalt-complexed propargyl aldehydes with chiral (γ -alkoxyallyl)borane under the same condition and showed high enantioselectivities as well as diastereoselectivities.⁸ Recently, Pericas showed that asymmetric diethylzinc addition to the same complex by the aid of chiral aminoalcohol ligand provided virtually single enantiomers of secondary propargyl alcohol.⁹

At the same time, we also envisioned that this approach would give not only high enantioselectivities, but also an efficient way for the more elaborated systems. For example, the asymmetric addition to dicobalt carbonyl complexed propargyl aldehydes by analogs higher than ethyl, such as bis(homoallyl)zinc and higher analogs, would allow products which can be subjected to Pauson-Khand reaction (PKR here after) afterward.

The subsequent reaction can be run separately or in one-pot, and would furnish the optically active bicyclic [3,3,0] or [4,3,0] compounds. These bicyclic compounds can be served for the synthesis of various natural products in optically



Scheme 1

active form.¹⁰ (Scheme 1)

Herein, we would like to report the results of our preliminary study about the reactions of dicobalt complexed propargyl aldehydes and dialkylzinc in the presence of chiral catalysts.

We first examined the scope of the compatibility of these dicobalt hexacarbonyl complexes of propargyl aldehydes with currently available asymmetric 1,2-addition conditions. Either amino alcohol catalysts² or TADDOL catalysts⁶ together with diethylzinc proved to be inappropriate for this transformation in our hand.⁹ Low yield (6-10%) of the metal complexes of propargyl alcohol was obtained along with some of the unreacted starting materials (10-20%). Most of the complexes had been destroyed during the reaction. However, a catalyst prepared by mixing of chiral disulfonamide (0.2 eq) and titanium tetra-isopropoxide (1.2 eq) turned out to be the choice of the reaction.

We adapted the procedure developed by Ohno¹¹ and generalized by Knochel.¹² The catalytic species was prepared by mixing of (1*S*, 2*S*)-(+)-cyclohexyl disulfonamide (**6**) and freshly distilled titanium tetra-isopropoxide in *n*-hexane followed by heating at 60 °C for 2 h. After cooling the resultant catalytic species to -78 °C, dialkylzinc and the corresponding aldehyde were added. The resulting mixture was allowed to warm to -25 °C over 12 h. Metal complexed propargyl aldehydes smoothly reacted to give the corresponding propargyl alcohol complexes in high yields (72-98%) and excellent enantioselectivities (>93%) after usual work-up (Table 1).

The metal complexes (**1**) were demetalated by using ammonium cerium(IV) nitrate (CAN) in methanol and optical purities of the propargyl alcohols (**3**) were found to be better than 90% ee for all examined cases.

The overall efficiency of the reaction of metal complex in terms of chemical yields and enantioselectivities are apparently better than that with metal free propargyl aldehyde.^{6,9} Especially, this approach allowed to have a reliable process

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Table 1. Asymmetric addition of dialkylzinc in the presence of chiral bis(sulphonamide) ligand and titanium alkoxide

entry	Substrates	R ¹	R ²	Yield (%) ee (%)	
				2/3	3
1	a	H	Et	86/78	93 (R)
2	b	Me	Et	89/85	95 (S)
3	c	CH ₂ =CHCH ₂	Et	88/87	96 (S)
4	d	TBDMSOCH ₂	Et	72/54	99 (S)
5	e	H	CH ₂ =CH ₂ -CH ₂ CH ₂	95/82	90 (R)
6	f	Me	CH ₂ =CH ₂ -CH ₂ CH ₂	98/99	95 (R)
7	g	CH ₂ =CH ₂ -CH ₂	CH ₂ =CH ₂ -CH ₂ CH ₂	94/94	95 (R)
8	h	TBDMSOCH ₂	CH ₂ =CH ₂ -CH ₂ CH ₂	85/69	94 (S)

even for the volatile low molecular weight propargyl aldehydes, such as propynal (entry 1 in Table 1).

Subsequent Pauson-Khand reaction of the homoallylated propargyl alcohol complexes (**2e-2h**) were studied under the promoter assisted reaction conditions. All of the substrates derived from the 1,2-addition of bis(3-buten-1-yl)zinc underwent PKR smoothly. TMANO promoted PKR of the resultant propargyl alcohol complexes provided the corresponding bicyclic compounds in high yield as a mixture of diastereomers. The resultant mixture of diastereomers except entry 4 in Table 2 were transformed into the MOM protected derivatives for facile separation and analysis. The results are summarized in Table 2.

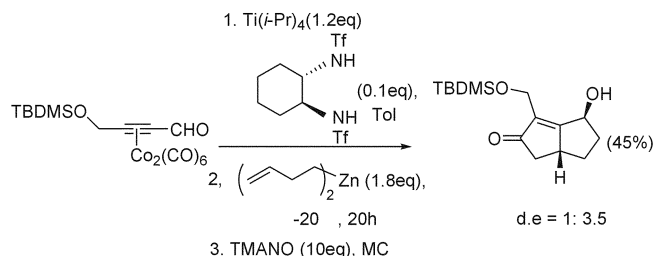
Diastereoselectivity is dependent on the substituent on terminal alkyne, which range from 1 : 1 for H to 7 : 1 for allyl under our condition, but has not been optimized. Optical purity of each diastereomer was measured by chiral GC analysis and reflected that of propargyl alcohol obtained

Table 2. Pauson-Khand reaction of the resulting propargyl alcohol-cobalt carbonyl complexes (2)

entry	R ¹	combined yield (%)	ds 4 : 5	ee (%)
				4/5
1	H (e)	56	1.1 : 1	89/89
2	Me (f)	72	7.5 : 1	95/95
3	CH ₂ =CHCH ₂ (g)	71	6.7 : 1	95/95
4	TBDMSOCH ₂ (h)	66	4 : 1	94/94

from nucleophilic addition directly.

In one case we carried out the reaction all the way in one pot operation, we were able to obtain the corresponding product in reasonable yield and diastereoselectivity.



In summary, we were able to find out the reaction condition of the 1,2-nucleophilic addition to the dicobalt hexacarbonyl-propargyl aldehydes, which allowed high enantioselectivity and chemical yield. And subsequent Pauson-Khand reaction of the resultant products (**2e-2h**) provided the bicyclic compounds (**4** and **5**) efficiently. The application of this process to the natural products synthesis is underway.

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