1,4-Asymmetric Induction using a Cobalt Alkyne Complex

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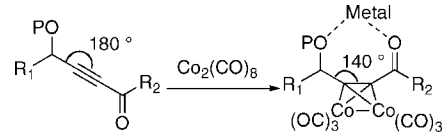
Received September 28, 2007

Summary: Remote stereocontrol is a difficult topic in current organic synthesis. We have developed a highly diastereoselective 1,4-asymmetric induction using a cobalt alkyne complex. This is the first example of using a cobalt alkyne complex for a stereoselective reaction via 1,4-chelation. Both anti and syn isomers were stereoselectively synthesized using two different methods.

Control of the 1,2-and 1,3-stereorelationship based on chelation is well established. However, it is a synthetic challenge to control a remote stereocenter, such as a 1,4-relationship, using a preexisting chiral center.[1] In particular, the stereoselective nucleophilic addition of a 4-alkoxy-2-butenal or 2-butynal system is difficult, because there are two sp^2 or sp carbon atoms between the stereogenic and prestereogenic centers, and control of the chelation is not expected.[1b] As far as we were aware, there is only a single precedent, that in which Nakamura and co-workers realized a good diastereoselectivity (up to 14:86) using R_2CuLi in combination with R_3SiCl.[2]

A metal template has been utilized for remote asymmetric induction, such as the elegant 1,5-asymmetric induction of Ley and co-workers using *p*-allyltricarbonyliron lactone complexes in the total synthesis of taurospongin.[3] On the other hand, cobalt alkyne complexes are widely used in organic synthesis,[4] such as in the Pauson−Khand reaction[5] and the Nicolas reaction, in which the propargyl cation is stabilized by dicobalt hexacarbonyl.[6] Intramolecular [4 + 2] cycloaddition has been initiated by cobalt alkyne complexation,[7] and a cobalt alkyne complex has been used in the elegant total synthesis of ingenol.[8] Though there are several reactions of cobalt-complexed acetylenic aldehydes with carbon nucleophiles,[9] there is no example of using a cobalt alkyne complex in a 1,4-diastereoselective reaction as far as we are aware. We thought that a cobalt alkyne complex could be utilized for a 1,4-asymmetric induction according to the following considerations: the angle of the triple bond of alkyne is 180°, while that of a cobalt alkyne complex is about 140°.[10] On formation of this complex, the stereogenic and prestereogenic centers would be forced to be close together, and thus metal chelation would be expected; this would generate a high stereoselectivity (eq 1), in which an appropriate choice of the protecting group and nucleophile would be essential. Successful realization of this scenario will be discussed in this communication.



(1)

Along with a protecting group, the nucleophile is a key to the success of this reaction, because of the possibility of side reactions. A Nicolas-type reaction would proceed with a nucleophile having a Lewis acidic character, and a nucleophile may attack the CO ligand on the cobalt. First, we selected the 4-hydroxy- or 4-alkoxy-4-phenyl-2-butynal cobalt complexes as our model compounds, in which the benzyl, methoxymethyl, and triisopropylsilyl groups were selected as the protecting groups of the hydroxy function.

As shown in Table 1, for the benzyl protecting group, a low selectivity and yield were obtained for nucleophiles such as MeLi, MeMgI, Me_2CuLi, $Ti(O\text{-}iPr)_2Me_2$, and Me_3ZnLi. Other nucleophiles, such as Me_3CuLi_2 and Me_4AlMgI, and a combination of $CeCl_3$ and MeLi were also ineffective. In spite of these unsuccessful results, a good selectivity was obtained when MOM was used as a protecting group. The diastereoselectivity was dependent on the nucleophile, and Me_3ZnLi, which was prepared from Me_2Zn and MeLi, was found to be a suitable reagent, affording the anti isomer in an excellent yield and diastereoselectivity.

It should be noted that cobalt complexation is essential for the excellent diastereoselectivity, because no selectivity was observed when uncomplexed alkynyl aldehyde was employed under the same reaction conditions as shown in eq 3.

As the optimum reaction conditions have already been determined, the generality of the reaction was examined, with the results being summarized in Table 2. The phenyl and 2-naphthyl groups gave good results, and the reaction proceeded in a highly diastereoselective manner in both cases, in which the phenyl groups possessed an electron-withdrawing or electron-donating group. In the case of a heteroaromatic group, such as

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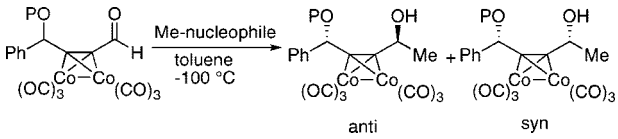
10.1021/om700961e CCC: $40.75
Publication on Web 12/29/2007

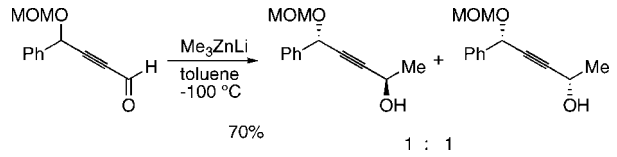
Table 1. 1,4-Asymmetric Induction of a Cobalt Alkyne Complex with Me-nucleophile[a]



(2)

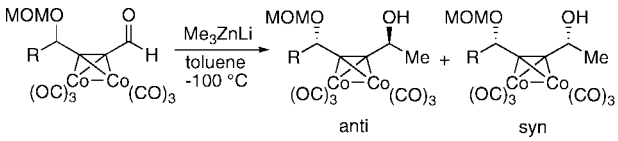
entry	P	reagent	yield (%)[b]	anti:syn[c]
1	Bn	MeLi	41	2.3:1
2	Bn	MeMgI	33	1:1
3	Bn	Me_2CuLi	0	
4	Bn	$Ti(O\text{-}i\text{-}Pr)_2Me_2$	44	2.1:1
5	Bn	Me_3ZnLi	0	
6	TIPS	MeMgI	92	4:1
7	TIPS	$Ti(O\text{-}i\text{-}Pr)_2Me_2$	88	4.8:1
8	TIPS	Me_3ZnLi	76	6.9:1
9	H	MeMgI	69	2:1
10	H	$Ti(O\text{-}i\text{-}Pr)_3Me$	61	14:1
11	H	Me_3ZnLi	76	1:1
12	MOM	MeLi	44	5.1:1
13	MOM	MeMgI	81	1.2:1
14	MOM	Me_2CuLi	0	
15	MOM	$Ti(O\text{-}i\text{-}Pr)_2Me_2$	73	3.3:1
16	MOM	Me_3ZnLi	90	16:1

[a] The reaction was performed using a cobalt complex (0.1 mmol) and nucleophile (0.5 mmol) at −100 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR.



(3)

Table 2. 1,4-Asymmetric Induction of Various Cobalt Alkyne Complexes with Me_3ZnLi[a]



(4)

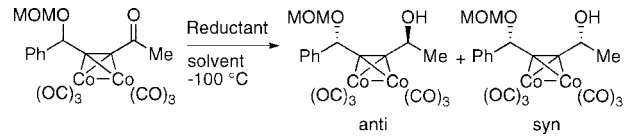
entry	R	yield (%)[b]	anti:syn[c]
1	Ph	90	16:1
2	2-Np	79	>20:1
3	*p*-MeOPh	98	16.5:1
4	*p*-BrPh	95	12.3:1
5	furyl	80	4.8:1
6	*n*-Pr	91	6:1
7	*c*-Hex	99	23:1

[a] The reaction was performed using a cobalt complex (0.06 mmol) and nucleophile (0.3 mmol) at −100 °C for 1 h. [b] Isolated yield. [c] Determined by ^{1}H NMR.

a furyl substituent, the diastereoselectivity was moderate, owing to the extra chelation observed with the furan moiety. Aromatic and alkyl groups, such as propyl and cyclohexyl groups, were suitable substituents, affording excellent diastereoselectivity.

Next, our methodology was applied to the 1,4-asymmetric reduction of γ-alkoxy ketones. For our model complex, we selected the cobalt complex of 5-methoxymethoxy-5-phenyl-3-pentyn-2-one, and the influence of reducing reagents was investigated, with the results being summarized in Table 3. When DIBAL-H or BH_3·THF was employed, the diastereoselectivity was low. A combination of Et_3SiH and a Lewis acid did not reduce the ketone, but a de-MOM reaction proceeded. When $LiAlH_4$ or $NaBH_4$ was used, an excellent syn selectivity was obtained with a good yield.

Table 3. 1,4-Asymmetric Reduction of a Cobalt Alkyne Complex[a]

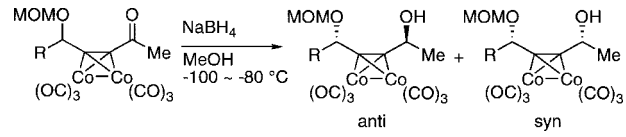


(5)

entry	reductant	solvent	temp (°C)	yield (%)[b]	anti:syn[c]
1	DIBAL-H	CH_2Cl_2	−100	99	1:1.5
2	BH_3·THF	THF	−100 to −10	91	1:1.5
3	$Et_3SiH + TiCl_4$	CH_2Cl_2	−100 to −30	0	
4	$LiAlH_4$	THF	−100	35	1:8.9
5	$NaBH_4$	MeOH	−100 to −80	99	1:11.1

[a] The reaction was performed using a cobalt complex (0.02 mmol) and reductant (0.12 mmol). [b] Isolated yield. [c] Determined by ^{1}H NMR.

Table 4. 1,4-Asymmetric Reduction of Various Cobalt Alkyne Complexes[a]



(6)

entry	R	yield (%)[b]	anti:syn[c]
1	Ph	99	1:11.1
2	2-Np	83	1:16.5
3	*p*-MeOPh	98	1:11.5
4	*p*-BrPh	85	1:9.6
5	furyl	85	1:3.9

[a] The reaction was performed using a cobalt complex (0.06 mmol) and $NaBH_4$ (0.40 mmol) in MeOH. The reaction temperature is kept at −100 to −80 °C for 12 h. [b] Isolated yield. [c] Determined by ^{1}H NMR.

The generality of the reaction was investigated using $NaBH_4$ as a reductant, with the results being summarized in Table 4. The electronic nature of the aryl group did not affect the diastereoselectivity and afforded excellent syn selectivity in the cases of *p*-bromophenyl and *p*-methoxyphenyl groups.

It is noteworthy that the syn isomer was stereoselectively synthesized, which is in marked contrast to the diastereoselective formation of the anti isomer in eq 2; that is, the anti isomer was synthesized by nucleophilic addition to an aldehyde moiety of the cobalt alkyne complex, while the syn isomer was obtained by the $NaBH_4$-mediated reduction of a ketone moiety of the cobalt alkyne complex. Using these methods, the anti and syn isomers were stereoselectively synthesized.

The reactions were investigated using racemic starting materials. Chiral starting materials were easily synthesized, as there are several synthetically useful methods for the preparation of chiral propargyl alcohol derivatives with high optical purity, such as Corey's CBS reduction of alkynyl ketone,[11] the enantioselective addition of alkynes to aldehyde[12] developed by Carreira,[13] and a recent elegant contribution by Shibasaki.[14] Thus, we applied our method in the synthesis of chiral 1,4-diol units, as shown in Scheme 1. A CBS reduction of the alkynyl ketone **1** gave an (*S*)-alcohol with excellent enantioselectivity (97% ee). Three-step procedures, such as protection, deprotec-

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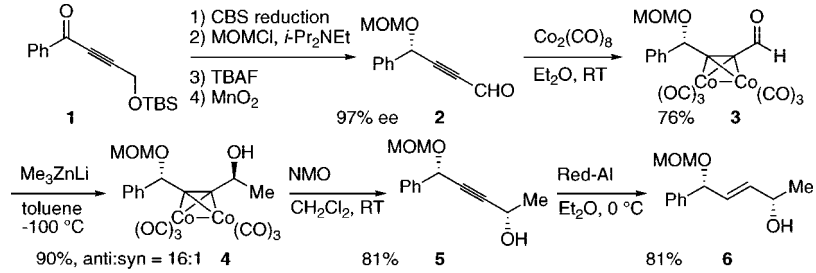
Scheme 1. Synthesis of Chiral 1,4-Diols



tion, and oxidation, afforded the aldehyde **2**, which was treated with $Co_2(CO)_8$ to give the chiral cobalt alkyne complex **3**. The reaction with Me_3ZnLi proceeded smoothly, with excellent diastereoselectivity, generating **4**. Demetalation with NMO gave the 1,4-diol **5** in good yield, which was also transformed into the trans 1,4-diol **6** stereoselectively on reduction with Red-Al. The absolute configuration of the newly generated chiral center was determined to be *S* by the advanced Mosher's MTPA method,[15] which also determined the relative configuration unambiguously. The 1,4-diols **5** and **6** with high optical purity were prepared in a diastereoselective manner using a substrate-based methodology.

In summary, a highly diastereoselective 1,4-asymmetric induction has been developed using a cobalt alkyne complex. This is the first example of using a cobalt alkyne complex for a stereoselective reaction via 1,4-chelation. Both the anti and syn isomers could be stereoselectively synthesized using two different methods: nucleophilic addition toward an aldehyde moiety of the cobalt alkyne complex to give the anti isomer, and reduction with $NaBH_4$ of a ketone moiety of the cobalt alkyne complex to afford the syn isomer. We are now applying this methodology to the total synthesis of a natural product, which will be reported in due course.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research on Priority Areas 16073219 from the MEXT.

Supporting Information Available: Text and figures giving detailed experimental procedures, full characterization data, and ^1H and ^{13}C NMR and IR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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