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Enhanced Diastereoselectivity in Asymmetric Crotylation Reactions Using Propargylic Dicobalt Hexacarbonyl Complexes

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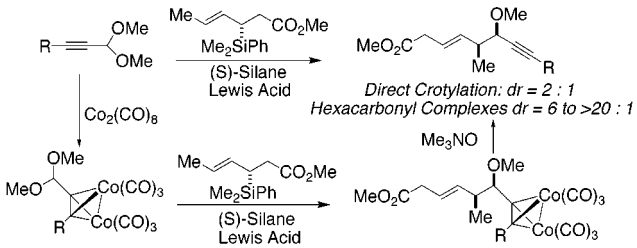
ABSTRACT



Hexacarbonyl dicobalt complexes of propargylic acetals undergo Lewis acid catalyzed crotylation reactions with enhanced levels of diastereoselectivity (dr 6 to >20:1, *synlanti*) while efficiently producing stereochemically well-defined homoallylic ethers. These results are in contrast to uncomplexed propargylic acetals, which undergo the crotylation reactions with low selectivity (dr < 2:1, *synlanti*). After removal of the cobalt complex, the reactions afford propargylic ethers in high yields.

The chemistry of functionalized acetylenes and their applications in synthesis have certainly been enhanced by the use of transition-metal complexes.[1] These complexes have been employed as temporary intermediates that have lead to the increased utility of functionalized propargylic systems.[2] For instance, it has been well documented that formation of mononuclear[3] and dinuclear[4] complexes results in significant changes in alkyne structure and reactivity.[2e] In that regard, dicobalt complexes of acetylenes are among the most useful members of the dinuclear class and have proven to be useful in synthesis. The purpose of this Letter is to report our findings concerning the increased levels of diastereoselectivity obtained in Lewis acid catalyzed crotylations of hexacarbonyl dicobalt complexes of propargylic acetals. In regards to our plans for the synthesis of cystothiazole A, we required a *syn*-crotylation reaction that would give access to a stereochemically well-defined propargylic ether. This α,β-branched alkyne **1** would serve as a precessor to a

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(3) For leading references, see: (a) Buchwald, S. L.; Lum, R. T.; Dervan, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 7441−7742. (b) Bennett, M. A.; Yoshida, T. *J. Am. Chem. Soc.* **1978**, *100*, 1750.

(4) Hoffman, D. M.; Hoffman, R.; Fisel, R. C. *J. Am. Chem. Soc.* **1982**, *104*, 3858−3875.

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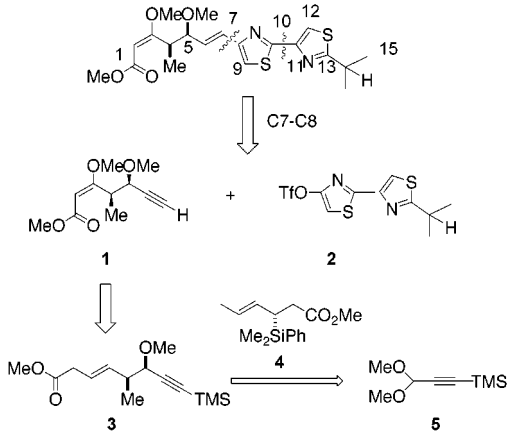
vinylmetal species, which would effectively participate in a cross-coupling reaction with bisthiazole **2**. The bisthiazole-containing antibiotics were recently isolated from a culture broth of the myxobacterium *Cystobacter fuscus*. Cystothiazole A exhibit enhanced antifungal and antitumor activities, and its cytotoxicity is lower than the related antibiotic myxothiazol.[5]

The retrosynthetic analysis of cystothiazole A leads to two fragments through the cleavage of the C_7-C_8 bonds (Scheme 1). Fragment **2** bearing the bisthiazole ring system can be

Scheme 1. Retrosynthesis of Cystothiazole A

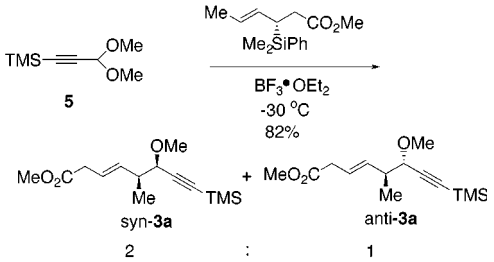


derived from commercially available 2,4-thiazolidinedione. Fragment **1** could be obtained from the cleavage of the double bond of β,γ-unsaturated ester **3**, followed by aldol reaction to install the β-methoxy enoate. The C_4-C_5 *syn* relationship of methoxy and methyl groups can be established by addition of chiral crotylsilane **4** to propargylic dimethyl acetal **5**.

Our approach required an efficient crotylation reaction between a chiral silane and a functionalized propargylic acetal. This crucial bond construction would introduce the necessary carbons for the C1−C7 acyclic fragment **1**. This functionalized subunit also possesses a *syn*-homoallylic ether bearing the C4−C5 stereocenters. However, the direct crotylation between silane **4** and uncomplexed propargylic acetals was unselective, which prompted us to seek other options (Scheme 2).[6] A reasonable and practical solution to this problem is the use of a dicobalt acetylene complex, which have been employed to enhance selectivity in Lewis acid promoted aldol reactions.[7]

Our initial experiments in this area were aimed at the direct crotylation between silane (*S*)-**4** and the propargylic acetal

Scheme 2

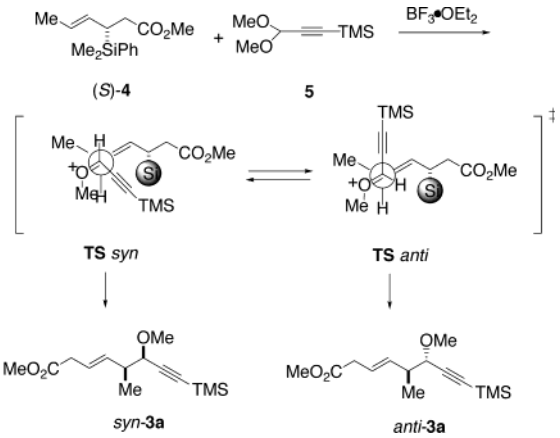


5. Two Lewis acids, TMSOTf and $BF_3{\cdot}OEt_2$, were compared as the catalysts for this reaction. For the cases that we examined, only a trace of product was observed using TMSOTf. $BF_3{\cdot}OEt_2$ produced considerably higher yields and therefore was chosen as the promoter for subsequent experiments.

Although the reaction produced the crotylation product in high yield (82%), it did so without useful levels of selectivity (∼2:1 *syn*/*anti*). The selectivity was not improved at lower temperature (−78 and −50 °C).

The stereochemical outcome of this reaction may be interpreted by two related anti-periplanar transition state models, where the participating π-bonds are oriented at 180° to each other (Scheme 3).[8] On the basis of steric destabilizing

Scheme 3. Transition State Analysis



interactions, TSsyn is only marginally favored over TSanti, suggesting that decreasing steric interactions between the TMS-acetylene and the vinyl methyl group of the silane is manifested in a loss of selectivity.

In the present case, the propargylic aldehyde lacks sufficient steric bulk, required to favor TSsyn versus TSanti. Therefore, the difference of $\Delta G^{\ddagger}$ of the competing transition states is not great enough to achieve useful levels of facial bias.

(5) Makoro, O.; Yoshihiro, S.; Akane, T.; Youji, S.; Ryosuke, F.; Toshihiko, Y.; Shigeru, Y. *Jpn. J. Antibiot.* **1998**, *51*, 275−281.

(6) (a) Panek, J. S.; Beresis, R. T. *J. Org. Chem.* **1993**, *58*, 809−811. (b) Jain, N. F.; Cirillo, P. F.; Pelletier, R.; Panek, J. S. *Tetrahedron Lett.* **1995**, *36*, 8727−8730.

(7) For several papers in which $Co_2(CO)_8$ complexes of propargylic aldehydes have been shown to give enhanced diastereoselectivity in aldol reactions, see: (a) Ju, J.; Reddy, B. R.; Khan, M.; Nicholas, K. M. *J. Org. Chem.* **1989**, *54*, 5426−5428. (b) Mukai, C.; Nagami, K.; Hanaoka, M. *Tetrahedron Lett.* **1989**, *30*, 5623−5426. (c) Mukai, C.; Nagami, K.; Hanaoka, M. *Tetrahedron Lett.* **1989**, *30*, 5627−5630.

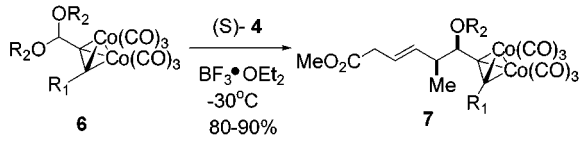
(8) (a) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293−1316. (b) Fleming, I. *Org. React.* **1989**, *37*, 57. (c) Birkover, L.; Stuhl, O. In *The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1989; Chapter 10.

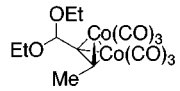
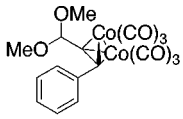
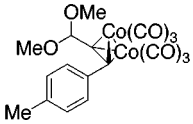
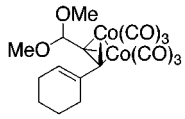
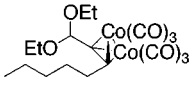
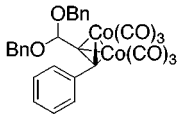
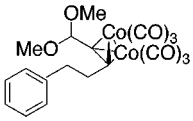
To get around this problem, a propargylic dicobalt complex was used to add steric bulk to the alkyne. As shown in Scheme 4, propargylic acetal **5** was converted to its dicobalt complex by treatment with dicobalt octacarbonyl. Crotylation reaction between **6a** and (*S*)-**4** provided the dicobalt complex of *syn*-homoallylic ether **7a**,[9] which was converted to propargylic ether **3a** by treatment with Me_3NO in MeOH. We were pleased to learn that the diastereoselectivity was significantly improved to 10:1 with good yield.

Encouraged by these results, we examined an array of propargylic acetals. The important results are summarized in Table 1.

Table 1 illustrates the effectiveness of dicobalt complexes **6** in crotylations. The reaction exhibits a useful level of selectivity for both branched alkyl and aromatic propargylic acetals. For example, the dibenzyl acetal cobalt complexes

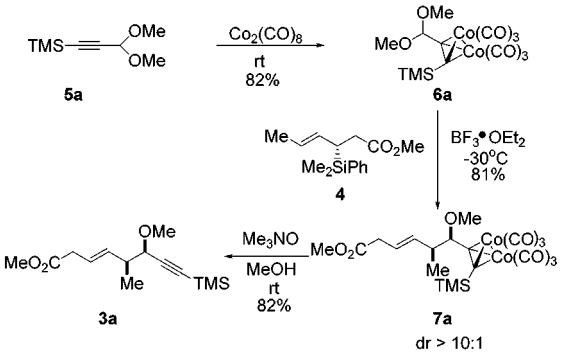
Table 1. Crotylation of Dicobalt Complexes of Propargylic Acetals



entry	propargylic acetal **6**		7 product ratio dr (*syn*/*anti*)[a,b,c] complexed	uncomplexed
1		**6b**	8:1	1:1
2		**6c**	20:1	<2:1
3		**6d**	18:1	<2:1
4		**6e**	10:1	1:1
5		**6f**	14:1	1:1
6		**6g**	>30:1[d]	1:1
7		**6h**	6:1	1:1

[a] Ratio of products was determined by ^{1}H NMR (400 MHz). [b] Isolated yields for free alkyne averaged 83%. [c] Isolated yields for the crotylation reactions ranged between 82% and 93%. [d] Only one isomer is observed by ^{1}H NMR.

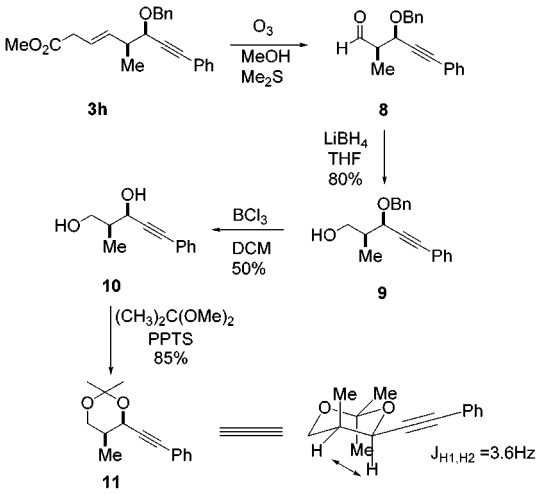
Scheme 4



derived from 4-phenyl-1-butyne gave a single isomer when reacted with (*S*)-crotylsilane (entry 6). The selectivity is indepentent of the type of acetals, as good diastereoselectivity was observed for ethyl, benzyl, and methyl acetal. The powerful effect of the cobalt carbonyl unit is underscored by comparison of the above results with the reactions of the free propargylic acetals **5** with chiral crotylsilane **4** in which case little or no stereoselctivity was observed.

The relative stereochemical assignment for the reaction products was assigned on the basis of anology with propargylic ether **3g**.[10] Specifically, measurement of the three-bond coupling constants ($^3J_{H1,H2}$ = 3.6 Hz) of the derived acetonide **11** permitted the stereochemical assignment as a

Scheme 5. Assignment of Relative Stereochemistry



syn bond construction. Accordingly the ester **3g** was converted to actonide **11** in four steps as shown in Scheme 5:

(9) **Typical Procedure.** A solution of propargyl acetal cobalt complex (52.6 mg, 0.11 mmol) and *S*-crotylsilane (37.6 mg, 0.14 mmol) in 1 mL of CH_2Cl_2 was cooled to −30 °C, and freshly distilled (CaH_2) BF_3·OEt_2 (25 μL, 0.197 mmol, 1.8 equiv) was added. The solution was stirred for 12 h at −30 °C, diluted with saturated $NaHCO_3$, and warmed to room temperature with stirring. The reaction mixture was extracted with CH_2Cl_2 (2 × 5 mL), dried ($MgSO_4$), and concentrated in vaccum. Purification by chromatography on silica gel (2% EtOAc/hexane eluent) afforded 80% of product.

(i) oxidation of the *trans* double bond of **3g** resulting in the formation of the intermediate aldehyde **8**, (ii) reduction of the aldehyde to alcohol **9** by $LiBH_4$ in THF,[11] (iii) deprotection of the benzyloxy group,[12] and (iv) conversion of the diol **10** into acetonide **11** in a solution of 2,2-methoxy propane containing a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS).

(10) Analysis to determine ee was carried out using chiral HPLC (with chiral OD column); see Supporting Information for details.

(11) (a) Schwab, J. M.; Lin, D. C. T. *J. Am. Chem. Soc*. **1985**, *107*, 6046−6052. (b) Williams, D. R.; White, F. H. *J. Org. Chem.* **1987**, *52*, 5067−5079.

(12) Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923−1925.

In summary, the diastereoselective crotylations of dicobalt complexes of propargylic acetals provides a convenient route to stereochemically well-defined homoallylic ethers. Applications in natural product synthesis will be reported in due course.

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Supporting Information Available: General experimental procedures and full characterization of compounds **3a**−**h** and procedures for ee analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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