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Use of Asymmetric Propargyl Dicobalt Hexacarbonyl Complexes in Organic Synthesis: Access to Enantiomerically Pure α-Hydroxy Acid Derivatives

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Abstract: The trapping under different conditions of the carbocation generated by acid treatment of chiral $Co_2(CO)_6$-complexed propargylic secondary alcohols permitted access to either diastereoisomer at the propargylic center. Further chemical manipulations provided either enantiomer of enantiomerically pure 1,2-difunctionalized molecules such as 1,2-diols, α-hydroxy-aldehydes or α-hydroxy-acids. © 1998 Elsevier Science Ltd. All rights reserved.

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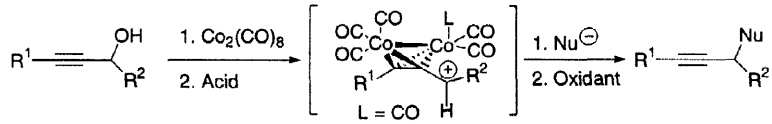
A great deal of attention has been paid to the Nicholas reaction (Scheme 1) as a very important tool in organic synthesis.[1] The reaction works well with many kind of nucleophiles to form new bonds between the propargylic carbon and atoms that include carbon, oxygen, hydrogen and nitrogen.[2] The procedure can be applied inter- or intra-molecularly.[1] The use of suitable unsaturated nucleophiles permit the sequential coupling by a Pauson-Khand reaction.[1,3]



Scheme 1

An important aspect of the reaction is its stereochemical course. In general, the intermolecular reaction of chiral $Co_2(CO)_6$-propargylic complexes with several nucleophiles leads to racemization,[4] although it has been reported that an intramolecular Friedel-Crafts reaction proceeded enantiospecifically.[5] The X-ray structure of a doubly stabilized $[Co_2(CO)_6]$-complexed propargyl cation shows a nearly ideal trigonal planar arrangement in the cationic center.[6]

In order to obtain enantiomerically enriched products using the Nicholas reaction, three approaches may be possible: a) the introduction of a chiral ligand into the cobalt complex, b) the use of chiral substrates with defined stereocenters at R^1 and R^2 that control the stereochemistry at the newly created sp^3 carbon, and c) the use of chiral nucleophiles. The first approach is strongly constrained since the use of the usual chiral ligands (e.g. L = chiral phosphine, Scheme 1) led to species unreactive to mild nucleophiles.[7] Only the use of the bulky, weakly α-donating, strongly π-accepting, $P[OCH(PF_3)_2]_3$, ligand permitted chirality transfer with virtually complete retention of stereochemistry.[8] The introduction of suitable chiral centers into R^2,[1,9] and the use of chiral nucleophiles[1,10] are the most common methods to perform diastereoselective variants of the Nicholas reaction.

Although at first sight the introduction of chirality in R^1 (Scheme 1) would appear likely to be ineffective for asymmetric induction because of the distance to the reacting carbocation center, such stereocontrol is known to increase with the increasing size of the remote acetylenic substituent, presumably as a consequence of the

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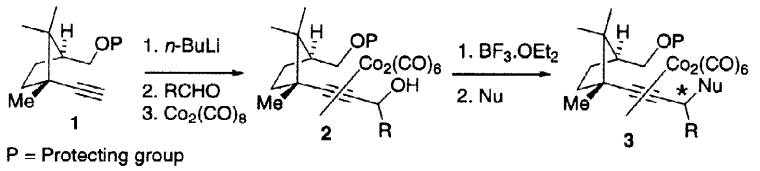
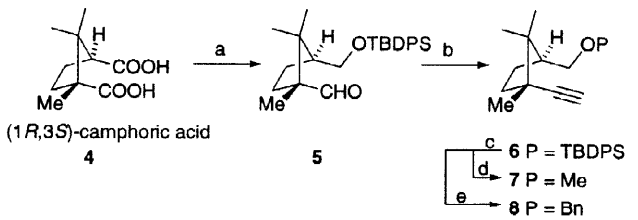
bent geometry of the coordinated acetylene unit.[11] In this communication we would like to report on our preliminary studies directed to the use of the Nicholas reaction in a stereoselective manner, based on the use of the chiral terminal acetylene **1** and oxygen- based nucleophiles (Scheme 2). Such auxiliaries with different protecting groups were easily prepared from camphoric acid (Scheme 3), which is commercially available in both enantiomeric forms.



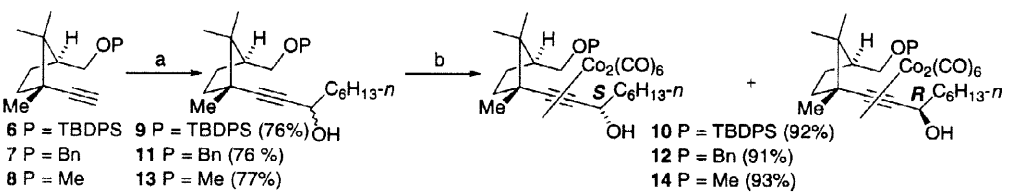
Scheme 2



a) (i) $BH_3.SMe_2$, 0 °C → rt, 90 %, (ii) TBDPSCl, imidazol, CH_2Cl_2, 0 °C, 90%, (iii) SO_3.Py, DMSO, Et_3N, CH_2Cl_2, rt, 75%. (b) (i) CBr_4, PPh_3, CH_2Cl_2, 0 °C → rt, 75%, (ii) *n*-BuLi, Et_2O, 0 °C, 86%. (c) *n*-Bu_4NF, THF, rt, 85%. (d) MeI, NaH, THF, 0 °C → rt, 92%. (e) BnBr, NaH, Bu_4NI, CH_2Cl_2, 0 °C → rt, 90%

Scheme 3

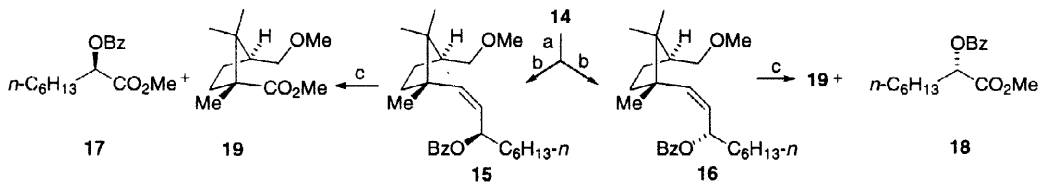
In order to explore our idea the free acetylenes were coupled with a non-branched aldehyde in a standard manner and the resulting propargylic alcohols treated with $Co_2(CO)_8$. In all cases the resulting complexes were obtained with satisfactory yields (Scheme 4). The choice of such substrates was done to achieve a highly demanding stereochemical situation with no additional influence from the R^2 substituent.



(a) *n*-BuLi, *n*-$C_6H_{13}CHO$, THF, -78 °C → -30 °. (b) $Co_2(CO)_8$, CH_2Cl_2, rt.

Scheme 4

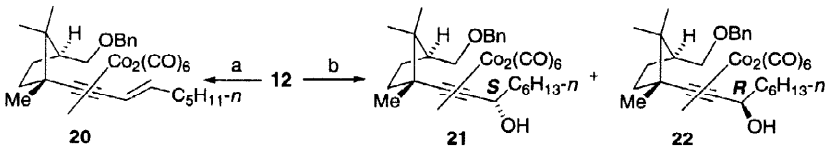
A very interesting feature of the $Co_2(CO)_6$-complexes (P = Me or Bn) is the outstanding resolution under silica gel chromatography. Thus, both diastereoisomers of **14** have R_f (*S* isomer) = 0.5 and R_f (*R* isomer) = 0.3, using a 10% ethyl acetate/hexane mixture as solvent, that permits a simple separation of both isomers. The treatment of both diastereoisomers with Ce(IV) provided the corresponding free acetylenes almost quantitatively and then, after selective hydrogenation and benzoyl protection of the secondary alcohol, yielded **15** and **16** in 35 and 32 (overall yield), respectively, relative to the 1:1 mixture of **14**. Ruthenium tetroxide oxidation[12] and further methylation of the free acid provided the enantiomerically pure α-hydroxy ester benzoates **17** and **18** along with **19** permitting the recovery of the chiral auxiliary.[13]



(a) (i) Silica gel column chromatography. (b) (i) $Ce(NO_3)_6(NH_4)_2$, acetone, rt. (ii) H_2, Lindlar's catalyst, rt. (iii) BzCl, Et_3N, DMAP, CH_2Cl_2, 0 °C → rt. (c) (i) $RuCl_3$, $NaIO_4$, $CH_3CN/CCl_4/H_2O$, rt, (ii) CH_2N_2, ether, 0 °C.

Scheme 5

In view of the influence of the remote substituent over the complexed propargylic alcohol, we submitted the diastereomeric mixture to acid treatment ($BF_3.OEt_2$). The first experiments were carried out without any external nucleophiles and, as expected, at rt, the *E*-eliminated product **20** was produced in 86% yield.[14] However, at -20 °C, after 24 h, a 3 : 1 diastereomeric mixture (**22** : **21**) was obtained. The use of other acids such as CF_3COOH, CF_3SO_3H, camphorsulfonic acid or $HBF_4.OMe_2$, produced a significant amount of the elimination product, with no significant enrichment in any diastereoisomer. At temperatures lower than –20 °C neither elimination nor change of the diastereomeric ratio was observed.

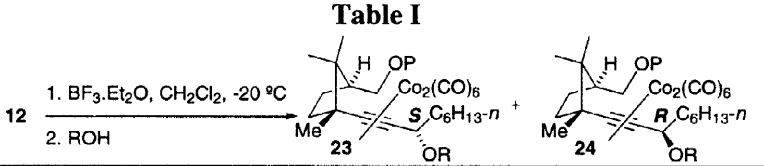


(a) $BF_3.OEt_2$, CH_2Cl_2, rt. (b) $BF_3.OEt_2$, CH_2Cl_2, -20 °C.

Scheme 6

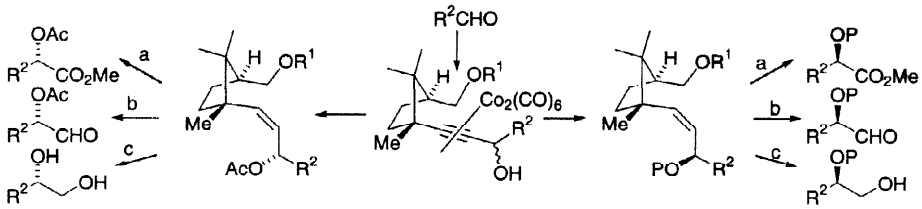
Although a usual way to generate cobalt complexed propargylic cations is by the acid treatment of compounds with C-O bonds such as ethers, alcohols or acetates, the fact that cyclic ethers are obtained when an additional hydroxyl group is present in the substrate[9] prompted us to use external oxygenated nucleophiles in our experiments. Thus, when the diastereomeric mixture **12** was treated with $BF_3.OEt_2$ and anhydrous methanol was added to the reaction mixture, after 15 min (Entry 1, Table 1), the corresponding ethers were obtained in 60% yield with a ≈1 : 9 diastereomeric ratio (**23** : **24**, P = Bn, R = Me) and the remaining alcohol (32%) was recovered with the complementary stereochemistry (9 : 1, **23** : **24**, P = Bn, R = H). When experiments were carried out at different reaction times the diastereomeric ratio remained almost unchanged. The use of acetic acid as the external nucleophile provided a very interesting and new situation. When the reaction was quenched after 15 min (Entry 4, Table I) roughly half of the starting alcohol was converted to a 4 : 1 enriched mixture (**23** : **24**, P = Bn, R = Ac). It is interesting to mention that the stereochemistry of both stereoisomers is coincident with that obtained when MeOH was used. However, when the reaction was allowed to stand for a longer period (ca. 13 h) a complete reversal of the stereochemistry was obtained (Entry 6, Table I). It is also noteworthy that the stereochemistry of the remaining alcohols is complementary to that obtained in the absence of external nucleophiles. The results suggest that, under the reaction conditions, when MeOH or no external nucleophile is used the kinetic product is the major one in the trapping of the carbocation (diastereoselective trapping of the carbocation). However, if AcOH is used the ability of the acetate group to act as nucleophile and leaving group allows equilibration to the most stable compound on standing.

Table I



Entry	P	ROH (4 equiv)	Time	Yield	**23** : **24**	% Remaining alcohol (**23** : **24**, R = H)
1.	Bn	MeOH	15 min	66	12 : 88	32 (90 : 10)
2.	"	"	1 h	56	10 : 90	36 (91 : 9)
3.	"	"	13 h	51	12 : 88	
4.	"	AcOH	15 min	50	19 : 81	44 (80 : 20)
5.	"	"	1 h	79	35 : 65	15 (83 : 17)
6.	"	"	13 h	80	88 : 12	
7.	TBDPS	MeOH	13 h	62	9 : 91	
8.	"	AcOH	"	92	90 : 10	
9.	Me	MeOH	"	67	11 : 89	
10.	"	AcOH	7 h	84	77 : 23	
11.		"	22 h	85	58 : 42	

Although a synthetic application of our methodology has been outlined in Scheme 5 giving α-hydroxy ester benzoates, we have explored different synthetic alternatives that can be summarized in Scheme 7. Basically, the possibility of controlling the desired diastereoisomer and the different cleavage alternatives of the unsaturated bond provide different 1,2-difunctionalized compounds as pure enantiomers together, in each case, with a precursor of the chiral auxiliary that permits its recovery.



(a) (i) $RuCl_3$, $NaIO_4$, $CH_3CN/CCl_4/H_2O$, rt (ii) CH_2N_2, Et_2O, 0 °C. (b) (i) O_3, CH_2Cl_2/MeOH, -78 °C, (ii) Me_2S, -78 °C→rt. (c) (i) O_3, CH_2Cl_2, -78→0 °C, (ii) $LiAlH_4$, -78→0 °C

Scheme 7

In summary, we have described a conceptually new methodology based on the asymmetric Nicholas reaction. The use of a newly developed and easily recoverable chiral auxiliary obtained from commercially available camphoric acid permit access to a wide range of 1,2-difunctionalized molecules. Mechanistic insights of the reaction, the influence of additional substituents in R^2 (Scheme I) and the use of non-oxygenated nucleophiles are under study and will be published in due course.

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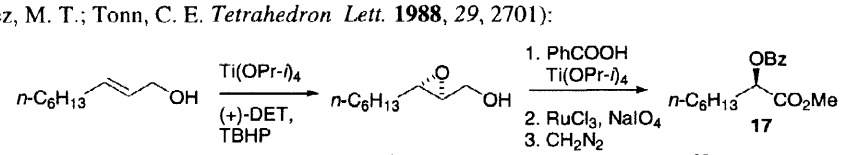
13. In order to determine the absolute configuration, **17** was obtained by the following alternative synthetic sequence (see Martín, V. S.; Núñez, M. T.; Tonn, C. E. *Tetrahedron Lett.* **1988**, *29*, 2701):



$[\alpha]_D^{25}$ = +5.34 (*c* 1.46, $CHCl_3$)

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