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syn-anti Diastereoselectivity in the Nicholas reaction via a chiral 1-alkoxy-propargylium cation

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Abstract—The Nicholas reaction between enantiopure propargyl acetal dicobalt–hexacarbonyl complexes, as precursors of chiral propargyl cobalt–hexacarbonyl cations, and several linear and cyclic silyl enol ethers is presented. A high yield up to 95% and high *syn-anti* diastereoselectivity (from 85:15 up to >99:1) is observed in the generation of the two new stereocenters. Moderate, but promising, *syn*(*R*,*R*)-*syn*(*S*,*S*), up to 70:30, is also observed in this preliminary work.

The reaction between a propargyl cation stabilized as a dicobalt hexacarbonyl complex and a wide variety of nucleophiles is known as the Nicholas reaction.[1] This reaction is very versatile and enables the introduction of different functional groups, especially by modification of the C–C triple bond, after demetallation. Thus, there have been many applications for this reaction,[2] leading recently to the synthesis of complex biologically active compounds.[3]

There are precedents in the literature[2–4] on the Nicholas reaction, regarding the *syn-anti* diastereoselectivity in the generation of two new stereocenters when the propargyl cation reacts with silyl enol ethers as nucleophiles. However, there are very few studies about the induction of enantioselectivity in this reaction. In some of them,[5] a dissymmetric cluster $C_2Co_2(CO)_5L$ is generated by exchanging one CO ligand for another suitable ligand, L, normally a conveniently substituted phosphine or phosphite molecule. These seminal and meritorious models require, in some cases, preliminary resolutions of racemic starting propargyl alcohols and also separation of the mixture (normally 1:1) of diastereomers resulting from the ligand exchange. There are other approaches based on the use of chiral nucleophiles[6] (to be reacted with an achiral propargyl cation), and also some authors induce dissymmetry in the Nicholas C–C coupling by using chiral propargyl precursors,[7] with the chiral moiety either as a substituent of the triple bond or as a chiral acetal function on the propargylic position.[8]

With these precedents in mind, our target was the design of a general model for the improvement of *syn-anti* diastereoselectivity and for the approach to the induction of enantioselectivity in the Nicholas reaction by introduction of a chiral auxiliary at the carbocation reactive center, instead of at the cobalt cluster.

We prepared enantiopure propargyl acetals, as precursors of chiral propargyl dicobalt–hexacarbonyl cation complexes, starting from cheap and commercially available enantiopure alcohols: (–)-*trans*-myrtanol, (which as a chiral auxiliary places a stereogenic center three bonds away from the reactive center of the cobalt cation), and (–)-menthol (which has the first stereo-differentiating asymmetric carbon, two bonds away from the cationic center).

For each model, we have evaluated the C–C coupling reaction with the prochiral enol silanes **1** to **6**[3a,9–12] and thoroughly studied the corresponding alkylation products, both metallated and demetallated. The chiral propargyl acetals, **8a** and **8b** were prepared by transacetalation of the commercially available diethyl acetal of phenylpropargylaldehyde, in the presence of catalytic amounts of anhydrous *p*-TsOH, with 2 equiv. of the corresponding enantiopure alcohol.[13] Dicobalt–hexacarbonyl complexes of these acetals were obtained, in quantitative yield, by reaction of the appropriate acetylenic acetal with $Co_2(CO)_8$ in an inert solvent, at room temperature.[4b] The yields for both steps of the synthetic pathway are quoted in Table 1.

Keywords: Nicholas reaction; *syn-anti* diastereoselectivity; enantioselectivity; cobalt complexes; enantiopure propargyl acetals.

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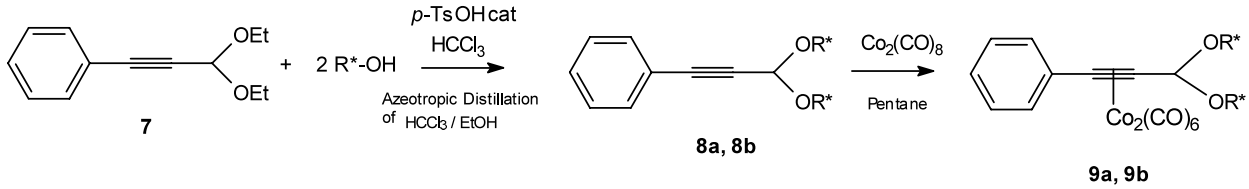
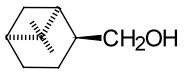
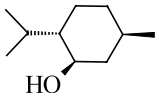
Table 1.

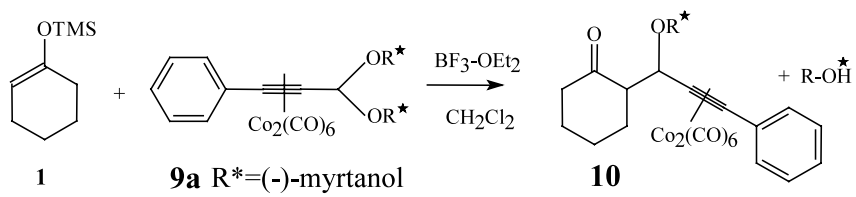


R*-OH	Transacetalation		Metallation	
	Product	Yield (%)	Product	Yield (%)
 (−)-*trans*-Myrtanol	**8a**	66	**9a**	99
 (−)-Menthol	**8b**	65	**9b**	80

A number of reaction parameters including temperature, stoichiometry and reaction time were explored to assess their effects on the yield and stereoselectivity of the Nicholas reaction. The parameters under evaluation and the results obtained from a selection of a large number of performed assays are presented in Table 2.

For a 1:1:1 stoichiometry, a decrease in the temperature was found to reduce the yield of C–C coupling, being zero at −78°C (entry 5). When the Nicholas C–C coupling was carried out at room temperature (entry 7), the yield of alkylation products decreased because of decomposition of the starting acetal and formation of phenylpropionaldehyde. This decomposition under strictly anhydrous conditions has also been previously observed by other authors.[14] Then, in order to enable a low working temperature (−78°C, favourable for stereocontrolled reactions) and to reach high conversions, in a reasonable period of time, it was necessary to use excess of either $BF_3{\cdot}OEt_2$ or silyl enol ether **1** (up to 2 equiv., entries 1–4). A relative excess of $BF_3{\cdot}OEt_2$ decreased the yield of C–C coupling due to the formation of phenylpropargylaldehyde (entries 1 and 4). Therefore, these results led us to conclude that the treatment of a 1:2 mixture of cobalt complex and silyl enol ether **1**, respectively, with 1.1 equiv. of Lewis acid gave the alkylation products in good yield (95%) and high diastereoselectivity (Table 2). None of the reaction parameters above evaluated considerably affected the stereochemical outcome of the reaction, which gave an average diastereomeric ratio (*syn*:*anti* ratio) of 85:15.

Table 2.



Entry	Reaction conditions[c]				Results	
	Cobalt complex (equiv.)	SEE[a] (equiv.)	$BF_3{\cdot}OEt_2$ (equiv.)	*T* (°C)	Yield[b] (%)	*syn*:*anti*[b] Diastereoselectivity
1	1	2	2	−78	50	85:15
2	1	2	1.5	−78	90	87:13
3	1	2	1.1	−78	95	85:15
4	1	1	2	−78	85	80:20
5	1	1	1	−78	0	–
6	1	1	1	0	41	85:15
7	1	1	1	rt	14[d]	78:22

[a] SEE: silyl enol ether **1**.

[b] Determined by 500 MHz ^{1}H NMR.

[c] Reaction time until disappearance of the starting acetal cobalt complex, as observed by TLC (1–5 h). Dichloromethane was used as a solvent with a dilution of 17–140 ml/g of cobalt complex. 4 Å molecular sieves powder was added to the reaction medium as a drying agent.

[d] A high % of complex decomposition products was observed at rt.

The Nicholas reaction of the chiral propargyl acetal cobalt–hexacarbonyl complex **9a** with silyl enol ethers of different nature (Fig. 1) was examined under the optimal conditions found in the previous experiments (see Table 2). The results obtained are presented in Table 3. In this case, as a result of generation of two new stereocenters, four diastereomers were observed by ^{1}H NMR (500 MHz): *syn*(*R*,*R*), *syn*(*S*,*S*), *anti*(*S*,*R*) and *anti*(*R*,*S*) (see Fig. 1).

From the results quoted in Table 3 it is possible to observe how the ring size in cyclic silyl enol ethers influences on the C–C coupling diastereoselectivity, probably due to steric conditioning in the approach of reactants in the transition state (see entries 1 and 3). Introduction of a methyl group at the reactive center in the nucleophilic silyl enol ether (entry 2), decreases the yield but increases the *syn*/*anti* diastereoselectivity (see entries 1 and 2); effects that could also have a stereoelectronic origin.

When a bulky and hindered silyl enol ether, having a low conformational freedom (entry 6), was used no reaction was observed, probably due to its difficulty to approach the electrophile. The use of linear silyl enol ethers (entries 4 and 5) considerably raised the *syn*/*anti* diastereoselectivity (affording stereo-specifically the *syn* diastereomer). These results could be interpreted on the basis of the smaller size of the linear carbon framework (maintaining the size and nature of the $OSiR_3$ group) of silyl enol ethers and their higher conformational freedom than the cyclic ones. This allows a better and less stereo-demanding approach of reactants and affords a better and less energetic matching in the transition state.

It is possible to distinguish the four diastereomeric products (the pair of *syn* diastereomers from the pair of *anti* diastereomers, Fig. 1) by 500 MHz ^{1}H NMR and 75 MHz ^{13}C NMR correlation studies, after a careful assignment of signals by 1D and 2D NMR experiments. ^{1}H NMR analysis of the reaction mixture allowed to conveniently determine the *syn*-*anti* ratio and, the *syn*1-*syn*2 and *anti*1-*anti*2 ratios, by integration of the separated CH(OR*) diagnostic resonance peaks for each diastereomer (prior to their separation).

The stereochemical assignment was carried out on the basis of a comparative analysis of high field ^{1}H and ^{13}C NMR data[15] (by correlation of both chemical shifts and values of coupling constants[16]) in conjunction with examination of molecular models and computational conformational analysis.[17] Once the minimum energy conformation was established for each configuration, the ^{1}H and ^{13}C NMR correlations of chemical shifts confirmed the stereochemical assignment. A coherence between the assignment of relative stereochemistry and the NMR data of diastereomers was observed by analyzing the stereo-electronic origin of the shielding and deshielding effects on the ^{1}H and ^{13}C nuclei, especially of the new stereocenters.

Due to the conformational freedom of (−)-*trans*-myrtanol, natural (−)-menthol was chosen as an alternative. In this new model, the C-1 stereogenic center of the chiral auxiliary is two bonds closer to the reactive cationic center than in the former model. The Nicholas reaction of the corresponding acetal (**9b**), with two silyl enol ethers (**1** cyclic and **4** acyclic), under the same stoichiometry and reaction conditions as in the primary model, proceeded with low yields of alkylation products. However, a promising 7:3 *syn*1-*syn*2 diastereoselectivity ratio for the major product was obtained when the nucleophile was the cyclic enol silane **1** (Table 3). Therefore, in this model a closer proximity of the first stereogenic center of the menthyloxy chiral auxiliary to the cationic center, together with the restriction of conformational rotation along the C1′-O and O-C1″ bonds, enable the nucleophile to differentiate between both faces of the carbocation, better than in the former model.[17]

On the other hand, there is a certain decrease on the yield in the reaction of menthyl chiral acetals versus myrtanyl acetals. This fact could be probably due to the higher difficulty of the approach of reactants in the transition state, because of their higher bulkiness (this

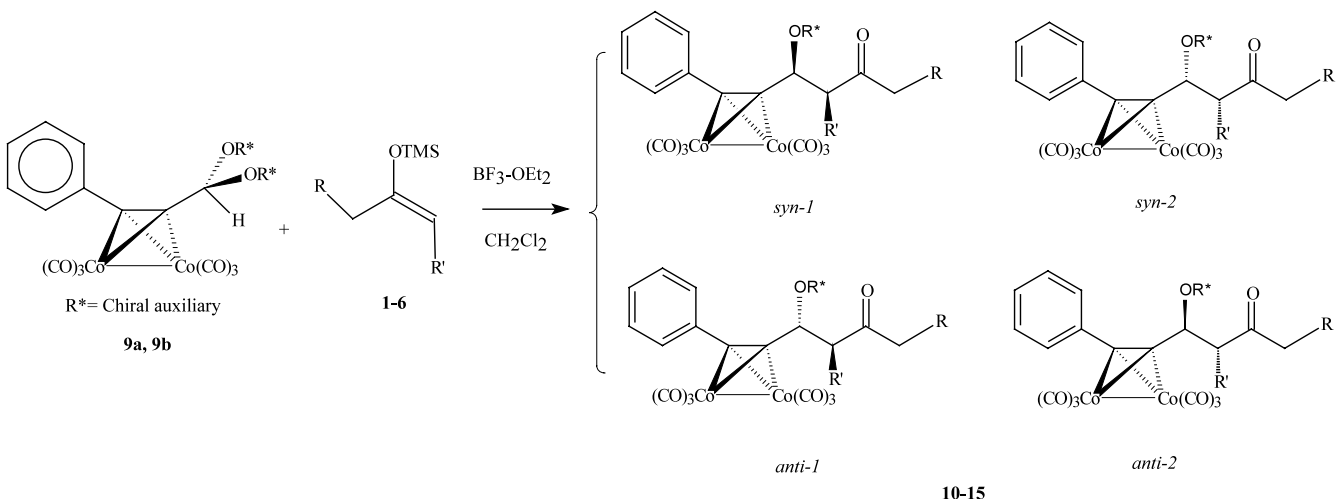
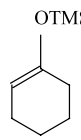
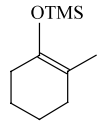
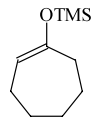
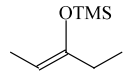
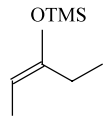
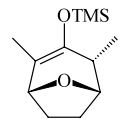
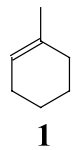
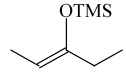


Figure 1.

Table 3.

Entry	SEE[d]	Reaction conditions				Stereoselectivity[b]	
		T (°C)	*t* (h)	Yield (%)	Product	Diastereoselectivity (*syn*:*anti*)	Diastereoselectivity (*syn*1:*syn*2; *anti*1:*anti*2)[a]
				Reactions of cobalt complex **9a**			
1	 **1**	−78	4	95	**10**	85:15	Overlapped; 50:50
2	 **2**	−78	3.5	69	**11**	94:6	55:45; 50:50
3	 **3**	−78	3	95	**12**	72:28	60:40; 50:50
4	 **4**	−78	3	70	**13**	>99:1[c]	50:50; Not detected
5	 **5**	−78	3	95	**13**	>99:1[c]	58:42; Not detected
6	 **6**	−78 −23	4 3	0 0			
				Reactions of cobalt complex **9b**			
7	 **1**	−78 (0)	5 (1)	40	**14**	75:25	70:30; 50:50
8	 **4**	−78	4.5	74	**15**	85:15	60:40; 50:50

[a] The *syn*1-*syn*2 or *anti*1-*anti*2 diastereoselectivities would correspond to the 'enantioselectivity' of the Nicholas reaction after the removal of the chiral auxiliary.
[b] Determined by 500 MHz ^{1}H NMR.
[c] Sensitivity limit of the 500 MHz NMR apparatus.
[d] Silyl enol ethers were prepared according to Refs. 3a, 9–12.

could be the explanation for the lower reactivity of cobalt complex **9b** versus **9a**).

We could conclude that the Nicholas reaction between silyl enol ethers and chiral propargyl acetals derived from enantiopure alcohols (myrtanol and menthol) proceeds with excellent *syn*/*anti* diastereoselectivity (from 7:3 up to >99:1). Furthermore, when a double conformational restriction was introduced at the level of both the cation and the silyl enol ether, a *syn*1-*syn*2 diastereoselectivity 7:3 for the major product was obtained. Studies with new chiral propargyl acetals are currently in progress, in order to improve the *syn*1-*syn*2 or *anti*1-*anti*2 diastereoselectivity.

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