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The Enantiospecific Nicholas Reaction[1]

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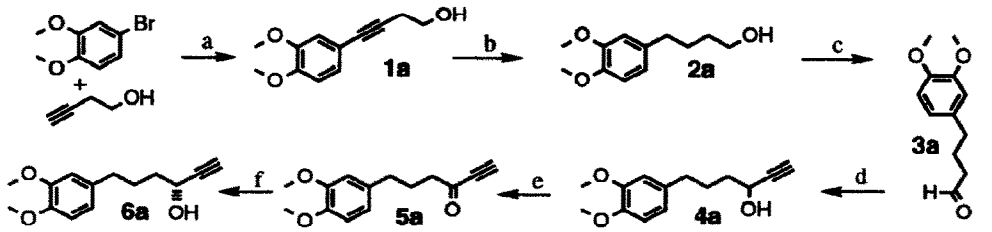
Key Words: Nicholas reaction; enantiospecific; cobalt-stabilized carbocations; 1-ethynyltetralin
Abstract: The enantiospecific Nicholas reaction, i.e. cobalt-promoted Friedel-Crafts reaction leading from chiral reactant to chiral product, was demonstrated for the first time.

The Nicholas reaction[2-5] is the reaction of a cobalt-stabilized propargyl cation with a nucleophile, including, but not limited to, an electron-rich aromatic ring. While this type of reaction is well-described, it is noteworthy that examples of capturing stereochemical information carried by the propargyl cation have remained elusive. Schreiber *et al.*[6] explored the intermolecular reaction of chiral Nicholas reagents, using enol ethers as nucleophiles; the products were racemic. Grove *et al.*[7,8] exploited the rapid racemization of cobalt-propargylium species in intramolecular Nicholas reactions, gaining highly stereoselective entry to fused ring systems. Our interest in this chemistry became focused on the question: Can the Nicholas reaction be engineered to yield chiral product from chiral precursors in an enantiospecific manner?

We constructed a series of compounds designed to address the question stated above, incorporating the following features: an aromatic nucleus substituted to improve reactivity, an oligomethylene tether to facilitate intramolecular closure, and a chiral secondary propargyl alcohol function at the end of the tether. When the carbinol carbon is the sole stereogenic center, extraneous influence on stereochemical outcome is eliminated. This is the salient feature contrasting this chemistry from Grove's stereoselective strategy. A modular, high-yielding synthesis was devised to allow independent variation of the aromatic substitution pattern as well as tether length. The synthetic path to a representative substrate for the stereospecific Nicholas reaction is illustrated in Scheme 1. The preparation of the other substrates is analogous, only using different bromobenzene and alkynol feedstocks.[9]

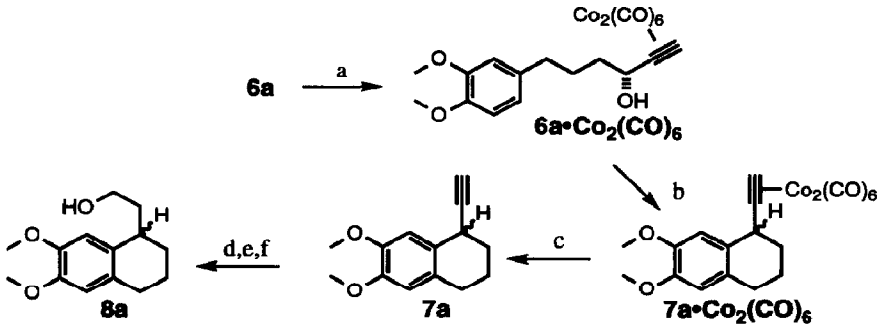
Scheme 1: Preparation of Enantiospecific Nicholas Substrates



Reagents and Conditions: a) i-Pr_2NH; 3 mol % $(PPh_3)_2PdCl_2$; 0.2 mol % CuI; 45 min reflux, 89%. b) 40 psi H_2, 10% Pd/C, 4 h, 99%. c) Swern, 98%. d) Ethynylmagnesium chloride, THF, 0°C, 1 h, 80%. e) Dess-Martin periodinane,[10] CH_2Cl_2, 30 min, 96%. f) 1.5 equiv neat Alpine-Borane®[11] freshly made from (+)-α-pinene, rt, 3 days, 97%.

Three parameters affecting enantiospecificity were examined in depth. These are ring size, substitution pattern on the aromatic nucleophile, and the effect of various Lewis acids on cyclization. Also examined was solvent choice for the cyclization reaction. The most suitable solvent proved to be dichloromethane; hydrocarbons did not dissolve all species present, and ethers competed for the Lewis acid.

Scheme 2: The Enantiospecific Nicholas Reaction



Reagents and Conditions: a) 1.1 equiv dicobalt octacarbonyl, CH_2Cl_2, rt, N_2, 1 hour. b) 2 equiv $BF_3{\cdot}Et_2O$, -65°C, 16h. c) 20 equiv $Fe(NO_3)_3$, MeOH, rt. d) 2 equiv thexylborane/THF, rt, 1 h. e) aq KOH, H_2O_2. f) $NaBH_4$ in THF/H_2O.

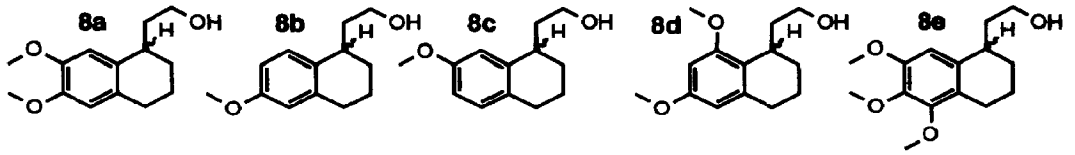
Cyclization was performed (Scheme 2) at the lowest effective reaction temperature in order to protect carbocation configuration. An aliquot was quenched at low temperature with ethanol and examined by TLC to monitor reaction progress. The cyclized complex was cleaved with methanolic ferric nitrate. The methoxylated 1-ethynyl-1,2,3,4-tetrahydronaphthalene products, **7**, proved thermolabile even at -20°C in solution. Suitable derivatives are the alcohols, **8**, accessible via hydroboration-oxidation;[12] these are stable indefinitely and do not change the enantiomeric purity initially present in the alkynes.[13]

Several acids were screened for effectiveness as cyclization catalysts. Titanium tetrachloride, stibic fluoride, boron triflate and methanesulfonic anhydride/butyllithium yielded slow reaction or decomposition. Boron trifluoride etherate was most effective. Ethylaluminum dichloride promoted cyclization at lower temperatures than boron trifluoride, but also catalyzed racemization of product complex.

The veratrole-derived compound **6a** was examined first. Reaction with boron trifluoride etherate occurred at -65°C, and **6a** of 91% enantiomeric excess led to **8a** of 88% e.e., as determined by chiral-stationary-phase HPLC (Table 1; corr. ee is e.e. of product divided by e.e. of substrate).[14] This establishes the capacity of using the Nicholas reaction to introduce preformed chiral centers enantiospecifically. Use of (-)-α-pinene in Scheme 1, step (f) yielded antipodal product. The effect of aromatic substitution was explored by changing the number and position of methoxy substituents. Removing one of the two methoxy groups in turn (**8b**) shows that a lone methoxy group *para* to the annulation site yields a reduced level of enantioselectivity, while *meta* substitution (**8c**) is insufficient to ensure enantiospecific cyclization. The product **8d** from 3,5-dimethoxyarene **6d** shows that the steric penalty exacted by an *ortho* substituent is almost balanced by the electronic incentive from two *o,p*-directing groups. The trimethoxy alcohol **8e** cyclized at -30°C; this suggests an unfavorable steric interaction between the 2-methoxy group and the

adjacent benzylic hydrogens in the transition state. This is mirrored in the decrease in degree of enantiospecificity relative to **8a**.

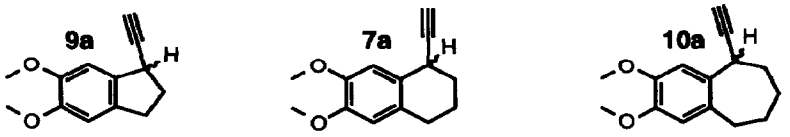
Table 1: Effect of Substitution on Stereochemical Outcome



Compound:	8a	8b	8c	8d	8e
rxn temp:	-65°C	-55°C	-25°C	-40°C	-30°C
corr. ee:	97%	71%	0%	88%	23%
yield, 6 to 8:	72%	68%	73%	72%	53%

Ring size was varied to yield 5- to 7-membered rings by using homologous terminal alkynols in the Scheme 1 preparation. Of the veratrylalkanols, only **6a** gave chiral product. (Table 2)

Table 2: Effect of Ring Size on Stereochemical Outcome



Compound:	9a	7a	10a
rxn temp:	-25°C	-65°C	0°C
corr. ee:	0%	97%	0%
Yield:	69%	72%	30%

The trend that emerges on inspecting the data shows that cyclization temperature broadly correlates with the degree of observed enantiospecificity. If the cyclization necessitates a reaction temperature much above –50°C, stereochemical information imported by the carbinol is lost. This suggests that at this temperature, the racemization of the cobalt-carbenium complex begins to compete with the rate-limiting step of the ring closure. Where steric effects become important (**8d,e**), a higher cyclization temperature is tolerated.

In summary, communicated herein are the first examples of an enantiospecific Nicholas reaction. We are currently addressing two areas of inquiry. Is the configuration at the carbinol carbon inverted or retained? Our goal is to determine the absolute stereochemistry of **8a** and gain insight into the cyclization mechanism. The longer-term effort is aimed at expanding the set of usable nucleophiles, including heterocycles. This should make this reaction a useful tool for building polycyclic systems whose chirality is determined by the configuration of the propargyl alcohol.

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9. NMR, MS and elemental analyses for compounds **6**, **8** and, where available, **7** were as expected. Elemental analyses were within 0.4% of theory. **6a** NMR: δ 2.45 (d, acetylenic H, J = 2Hz); 2.61 (t, 2H, J = 8Hz); 3.85 and 3.87 (2s, 6H, OMe); 4.39 (bm, carbinol, J = 8Hz); 6.71-6.81 m, 3H, aromatic H). **8a** NMR: δ 2.68 (bt, 2H, J = 7Hz); 2.88 (bm, 1H, benzylic H); 3.78 (t, 2H, J = 7Hz); 3.83 and 3.85 (2s, 6H, OMe); 6.56 and 6.68 (2s, 2H, aromatic H).
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13. A rapidly-handled sample of **7a** possessing 27.1% e.e. was converted to **8a** of 27.5% e.e. as determined by the HPLC method described below. Baseline separations were achieved.
14. HPLC analyses of **6** and **8** were run on a Chiralcel OD-H^R (Daicel Chemical Industries, Ltd.) analytical column with 8-12% isopropanol in hexane as eluent. **7a** resolved in 1% isopropanol-hexane.

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