Stereoselective Propargylation Mediated by a Chiral Metal Cluster: Reactions of [(Propargylium)$Co_2(CO)_5${$P(OR)_3$}][BF_4] with Carbon Nucleophiles

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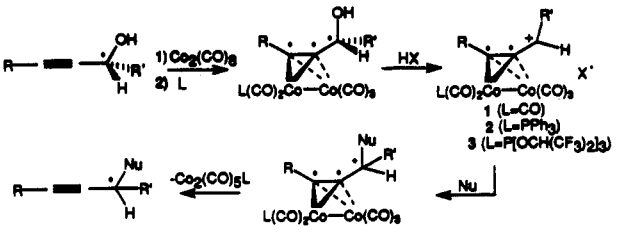
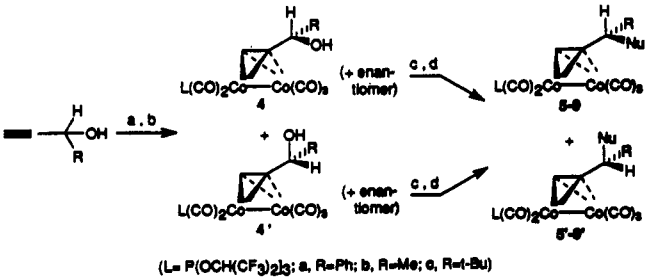
The reactions of (propargylium)$Co_2(CO)_6^+$ complexes **1** with nucleophiles provide a versatile method for regiocontrolled C–C bond construction,[1] free from the allenic byproducts which plague reactions of classical propargyl electrophiles. As the utilization of these complexes in organic synthesis has expanded,[2] so has interest in the prospects for controlling stereochemistry in their reactions. Although highly *diastereoselective* coupling reactions (generally from complexed aldehyde or acetal precursors) with enol and allyl nucleophiles have been reported,[3] facile racemization of these cations has previously thwarted attempts to develop general, *enantioselective* variants.[4]

In an effort to devise a general enantioselective propargylation scheme, we have investigated a novel approach (Scheme I) involving chirality transfer from readily available, enantioenriched propargyl alcohols[5] via conversion to diastereomeric dicobalt complexes (propargylium)$Co_2(CO)_5L$ (e.g., **2**, **3**) which, in turn, could control the stereoselectivity of nucleophilic attack. Following demetalation of the resulting alkylated complex, enantiomerically enriched propargylated products would be produced.[6] The success of this method depends on the configurational stability of the chiral -(C≡CR′)$Co_2(CO)_5L$ cluster fragment (no epimerization at C2, C3 of the cluster) and on the diastereoselectivity of its formation and subsequent reactions. An initial investigation of the PPh_3 derivatives **2** showed that while they were more configurationally rigid than **1** and were diastereoselectively quenched with oxygen-centered nucleophiles, they proved unreactive toward mild, synthetically important carbon nucleophiles.[8] In search of more electrophilic complexes with retained stereocontrolling capacity, a third generation system (**3**) possessing the bulky, weakly σ-donating, strongly π-accepting tris(1,1,1,3,3,3-hexafluoroisopropyl) phosphite[9] ligand was sought. We now report that complexes **3** couple diastereoselectively with mild carbon nucleophiles and, most importantly, that when derived from enantioenriched propargyl alcohols, these reactions occur with virtually complete enantioselectivity, resulting from the complete configurational stability of the cobalt cluster.

Scheme I



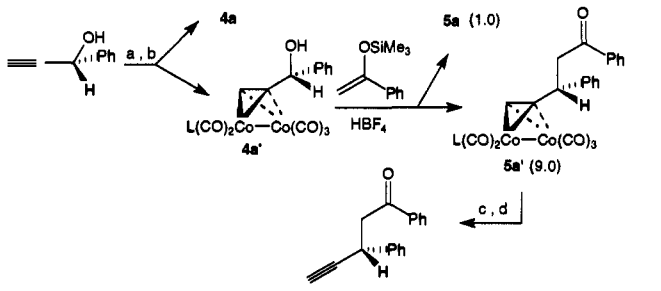
Scheme II[a]



(L= P(OCH(CF$_3$)$_2$]$_3$; a, R=Ph; b, R=Me; c, R=t-Bu)

[a] (a) $Co_2(CO)_8$, 20 °C (85–95%); (b) $P[OCH(CF_3)_2]_3$, 50 °C; (c) $HBF_4{\cdot}Et_2O$, –45 °C; (d) C-nucleophile, CH_2Cl_2, –40 to 0 °C.

Scheme III[a]



[a] (a) $Co_2(CO)_8$; (b) $P[OCH(CF_3)_2]_3$; (c) CO; (d) $(NH_4)_2Ce(NO_3)_6$.

The requisite phosphite alcohol complexes **4a–c** were conveniently obtained (50–75%) by dropwise addition of $P[OCH(CF_3)_2]_3$ (0.9 equiv in 1:2 Et_2O/THF) to a warmed solution (50 °C, 3 h) of the corresponding hexacarbonyl complex (Scheme II). The diastereomeric products (1.3:1 for **4a**/**4a′**; 1.6:1 for **4b**/**4b′**; >20:1 for **4c**/**c′**) are readily separated chromatographically (Florisil)[10] and are configurationally stable for days at room temperature. Although the diastereoselectivity in forming the phosphite complexes **4** has not been optimized, the capability of isomer recycle via carbonylation/rephosphination (*vide infra*) moderates this limitation. The relative stereochemistry of the major isomer **4a** as shown in Scheme II was established by X-ray diffraction.[11] The electronic similarity of the $P[OCH(CF_3)_2]_3$ and CO ligands is reflected in the M–CO IR bands of **4**, which are ca. 40 cm^{-1} higher than the corresponding PPh_3 derivatives[8] and comparable to those of the parent -$Co_2(CO)_6$ complexes.[12]

Next, the cation salts **3** were generated, and their reactivity toward carbon nucleophiles was established. Protonation of racemic **4a–c** [$HBF_4{\cdot}Et_2O$, $(CH_3CH_2CO)_2O$, –45 °C, ether precipitation] provided **3a–c** as red, moisture-sensitive solids which

(1) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207.

(2) Representative recent reports: (a) Stuart, J. G.; Nicholas, K. M. *Heterocycles* **1991**, *32*, 949. (b) Montana, A. M.; Nicholas, K. M. *J. Org. Chem.* **1990**, *55*, 1569. (c) Marshall, J. A.; Gung, W. Y. *Tetrahedron Lett.* **1989**, *30*, 309. (d) Magnus, P.; Lewis, R. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 6921. (e) Tomoika, K.; Fujita, H.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 851. (f) Magnus, P.; Pitterna, T. *J. Chem. Soc., Chem. Commun.* **1991**, 541. (g) Magnus, P.; Carter, P.; Elliott, J.; Lewis, R.; Harling, J.; Pitterna, T.; Bauta, W. E.; Fortt, S. *J. Am. Chem. Soc.* **1992**, *114*, 2544.

(3) Schreiber, S. L.; Sammakia, T.; Crowe, W. E. *J. Am. Chem. Soc.* **1986**, *108*, 3128. Tester, R.; Varghese, V.; Montana, A. M.; Khan, M.; Nicholas, K. M. *J. Org. Chem.* **1990**, *55*, 186. Ju, J.; Reddy, B. R.; Khan, M. A.; Nicholas, K. M. *J. Org. Chem.* **1989**, *54*, 5426. Montana, A. M.; Nicholas, K. M.; Khan, M. A. *J. Org. Chem.* **1988**, *55*, 5193. Mukai, C.; Nagami, K.; Hanoaka, M. *Tetrahedron Lett.* **1989**, *30*, 5623; 5627. Roush, W. R.; Park, J. C. *J. Org. Chem.* **1990**, *55*, 1143. Rousch, W. R.; Park, J. C. *Tetrahedron Lett.* **1991**, *32*, 6285.

(4) Schreiber, S. L.; Klimas, M. T.; Sammakia, T. *J. Am. Chem. Soc.* **1987**, *109*, 5749.

(5) (a) Via enzymatic kinetic resolution: Burgess, K.; Jennings, L. D. *J. Am. Chem. Soc.* **1991**, *113*, 6129. (b) Via asymmetric reduction (review): Nogradi, M. *Stereoselective Synthesis*; VCH Publishers: Weinheim, Germany, 1987; Chapter 3.1, pp 105–130.

(6) A conceptually similar method for the stereoselective alkylation of easily racemized lactic acid and α-amino acids has been reported by Seebach and co-workers (ref 7).

(7) Seebach, D.; Naef, R. *Helv. Chim. Acta* **1981**, *64*, 2704. Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390.

(8) (a) Bradley, D. H.; Khan, M. A.; Nicholas, K. M. *Organometallics* **1989**, *8*, 554. (b) Bradley, D. H.; Khan, M. A.; Nicholas, K. M. *Organometallics* **1992**, *11*, 2598.

(9) (a) Collman, J. P.; Hegedus, L.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; p 67. (b) Van Leeuwven, P. W. N. M.; Roobeek, C. F. *J. Organomet. Chem.* **1983**, *258*, 343.

(10) All new compounds gave appropriate spectroscopic and, in most cases, elemental analyses. Characterizational data and representative procedures are included as supplementary materials.

(11) Khan, M. A., unpublished results, 1992. Full details of the X-ray structures of **4a** and **5′** including crystallographic tables will be provided in a forthcoming full account.

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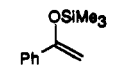
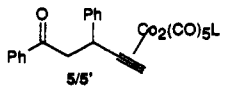
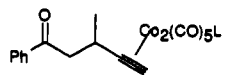
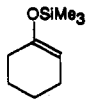
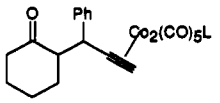
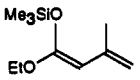
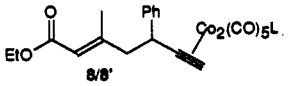
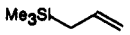
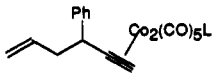
Table I. Alkylation Reactions of [(Propargylium)$Co_2(CO)_5${P(OR)$_3$}][BF_4] (3)

entry	nucleophile	alcohol complex	product	yield, %[a] (diasteromer ratio)
1		**4a′**	 **5/5′**	85 (1:9)
2		**4b′**	 **6/6′**	47 (1:1.2)
3		**4b**	**6/6′**	30 (1:1.2)
4		**4a**	 **7/7′**	90 (1:1.1)[b]
5		**4a′**	 **8/8′**	73 (1:7.1)
6		**4a′**	 **9/9′**	94 (1:10.5)

[a] Unoptimized; isolated after chromatography on Florisil. [b] Traces of two other isomers detected.

were used directly in subsequent reactions. In contrast to the nonreactivity of PPh_3 derivatives **2**, the phosphite derivatives **3** react readily (CH_2Cl_2, −40 °C to 0 °C) with mild carbon nucleophiles, including trimethylsilyl enol ethers and allyltrimethylsilane (Scheme II, Table I), to afford propargylated complexes **5**–**9** and **5′**–**9′** in moderate to excellent yield.[10] The diastereoselectivity of the reactions ranges from modest to excellent and clearly depends on both the nucleophilic partner (cf. entries 1,5,6) and the α-substituent of the complex, Ph vs Me (cf. entries 1,2), with the former giving better results. Interestingly, for the reactions of **2** and **3** studied to date, the diastereoselectivity is qualitatively *independent* of the relative stereochemistry of the alcohol precursor, suggesting formation of a common cationic intermediate; cf. entires 2,3 and aqueous quenching results of **3a**[13] of **2**.[8b] Moreover, the relative stereochemistry of the major product, **5′**, from the reaction of racemic **4a** with 1-OTMS styrene (entry 1 and Scheme II) was shown by X-ray diffraction to be *inverted* compared to the alcohol precursor.[11] Exclusive production of the (*E*)-isomer of **8**/**8′** and preferential formation of two of the four possible isomers of **7** is also noteworthy.

To determine if the intermediate cations **3** resist the stereochemically compromising racemization characteristic of the parent -$Co_2(CO)_6$ derivatives **1**[4] and thus to assess the viability of the approach of Scheme I for *enantioselective* synthesis, the reaction of 1-OTMS styrene with optically active **4a′** was examined. The latter was produced (along with its diastereomer **4a**, 1.0/1.6, 65% yield) from (*S*)-HC≡CCHPhOH (92% ee)[14] according to Scheme III. Protonation of **4a′** followed by addition of the silyl enol ether afforded ketone derivatives **5**/**5′** (1:9) in 77% yield. The major product **5′** was carbonylated (65 psi CO, THF, 20 °C) and then oxidatively decomplexed [$(NH_4)_2Ce(NO_3)_6$/acetone/−78 °C, 86% overall] to give HC≡CCHPhCH$_2$COPh, *whose enantiomeric purity was virtually identical to the original* HC≡CCHPhOH, 91 ± 2% by Eu(hfacam)$_3$ ^{1}H NMR analysis. Furthermore, the absolute stereochemistry of the acetylenic ketone was established as (*S*) by chemical correlation,[16,17] demonstrating a net *retention* of stereochemistry at the propargylic carbon in the conversion **4a′** → **5′**. This result clearly indicates the stability of the intermediate cations to cluster epimerization.

This study has demonstrated the capability of achieving absolute stereocontrol in propargyl coupling reactions using a properly designed chiral metal cluster. Although epimerization at the propargylic carbon occurs to a varying degree in alkylations by chiral **3**, the resulting diastereomers are not racemized by virtue of the configurational stability of the -(C≡CR)$Co_2(CO)_5$L cluster core. Furthermore, the enantiomerically enriched diastereomeric product complexes can be separated easily, affording optically active alkylation products after demetalation. These results are especially significant in light of the fluxionality and facile racemization of many metal carbonyl clusters[18] and suggest that chiral polymetallic clusters may offer new and unique opportunities in asymmetric synthesis.

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Supplementary Material Available: Experimental details and characterization data (6 pages). Ordering information is given on any current masthead page.

(12) IR data: e.g., IR(hexane) **4a**, 2089 s, 2045 s, 2033 s, 2003 sh cm^{-1}; (HC≡CCHPhOH)$Co_2(CO)_6$, 2095 s, 2057 s, 2033 s, 2017 sh cm^{-1}; (HC≡CCHPhOH)$Co_2(CO)_5(PPh_3)$ (ref 8a), 2045 s, 1995 s, 1990 s, 1985 sh cm^{-1}.

(13) Similar isomer ratios are obtained from aqueous quenching of **3a** derived from **4a** or **4a′**: Caffyn, A. J. M.; Nicholas, K. M., unpublished results, 1992.

(14) Prepared by lipase-catalyzed acetylation/kinetic resolution of racemic HC≡CCHPhOH according to the general method of Burgess (ref 5a). The (*S*) configuration was assigned on the basis of the sign of its [α] (ref 15).

(15) Issai, K.; Tomita, K. *J. Pharm. Soc. Jpn.* **1960**, *80*, 156.

(16) HC≡CCHPhCH$_2$COPh from **5a′** was hydrogenated [H_2(1 atm)/Pd on C/MeOH] to (−)-(*R*)-$CH_3CH_2CHPhCH_2COPh$ (ref 17).

(17) (a) Brienne, M.-J.; Ouannes, C.; Jacques, J. *Bull. Soc. Chim. Fr.* **1967**, 613. (b) The *apparent* inversion of configuration between HC≡C-CHPhCH$_2$COPh and $CH_3CH_2CHPhCH_2COPh$ is the result of converting the HC≡C- group (CIP sequence priority 2) to the CH_3CH_2- group (priority 3).

(18) Review: McGlinchey, M. J.; Mlekuz, M.; Bougeard, P.; Sayer, B. G.; Marinetti, A.; Saillard, J.-Y.; Jaouen, G. *Can. J. Chem.* **1983**, *61*, 1319. Sutin, K. A.; Kolis, J. W.; Mlekuz, M.; Bougeard, P.; Sayer, B. G.; Quilliam, M. A.; Faggiani, R.; Lock, C. J. L.; McGlinchey, M. J.; Jaouen, G. *Organometallics* **1987**, *6*, 439. Clark, D. T.; Sutin, K. A.; McGlinchey, M. J. *Organometallics* **1989**, *8*, 155. Helvenston, M. C.; Lynch, T. J. *Organometallics* **1987**, *6*, 208.