Asymmetric Propargylation/Allylation/ Pauson−Khand Cyclization of a Planar Chiral Anisole Tricarbonylchromium Complex

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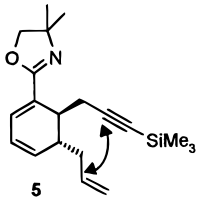
Reactions that transform benzene and substituted benzenes into functionalized hydrobenzenes with concomitant regio- and stereoselective C−C bond formation are scarce.[1] Two complementary transition metal mediated approaches for activating arenes for this reaction have been developed. The Harman group has shown that regioselective η^2-coordination of phenols and anilines to $Os(NH_3)_5^{2+}$ results in partial localization of the π-electron density and enhances the nucleophilic reactivity of the arenes.[2] Conversely, activation of arenes to C nucleophile addition results from η^6-coordination to electrophilic transition metal groups. The $Cr(CO)_3$ fragment has proven particularly efficient with both benzene and condensed aromatic ring systems.[3] Regioselective addition of carbanions followed by reaction with C electrophiles affords *trans*-disubstituted cyclohexadienes. Incorporation of CO in this sequence depends on the nature of the arene and the migratory aptitude of R″ (Scheme 1).[4]

Asymmetric versions of this methodology include the use of chiral *o*-directing auxiliaries (e.g., R = chiral oxazoline,[5a] SAMP-hydrazone[5b]), chiral nucleophiles (R′Li/L*),[5c] and chiral ligands on chromium,[5d] with the first two procedures being the most successful.

We here report a new approach that involves the generation of two stereogenic centers from an arene complex of planar chirality.[6] Other new features reported here are the use of propargyllithium as nucleophile in an arene addition reaction, the regioselectivity of the allylation, and the combination of the above methodology with a highly diastereoselective Pauson−Khand reaction.[7]



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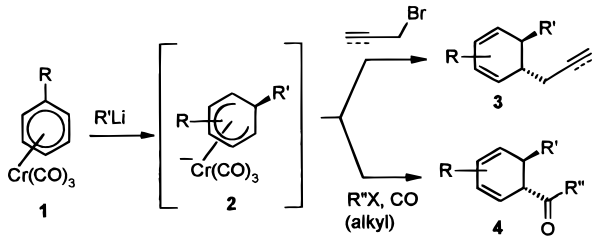
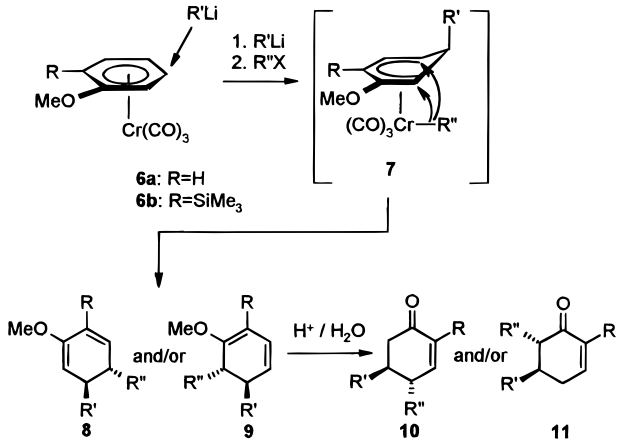
We reasoned that products **3** with an appropriate group R′ could be used for the preparation of *trans*-fused ring systems. First attempts at intramolecular cyclization of the oxazoline

Scheme 1



Scheme 2



cyclohexadiene **5** via Co- or Zr-mediated reactions did not meet with success, though, presumably because of the rigid *trans*-diaxial disposition of the two side chains in cyclohexadiene **5**.

However, anisole complexes **6** offer a convenient solution to this problem. Cyclohexadienes **8** or **9** should be readily hydrolyzed to the more flexible enones (**10** or **11**) (Scheme 2). Predominant *meta*-regioselectivity in nucleophilic additions to anisole complexes **6a** and **6b** is well documented[8] but the practicality of the formation of the cyclohexadienyl intermediate **7** and the regioselectivity of the ensuing reductive elimination to give **8** and/or **9** had not been investigated previously. The planar chirality of an *ortho*-substituted anisole complex also offered the possibility for the diastereoselective generation of two new stereogenic centers in the products.

Highly enantioenriched 1(*S*),2(*R*)-**6b**, obtained by enantioselective lithiation/electrophile addition of the anisole complex **6a** following Simpkins *et al.* procedure,[9] was treated sequentially with (3-(trimethylsilyl)propargyl)lithium (−78 → 0 °C, THF, 3 h) and allyl bromide (10 equiv, −78 → 20 °C) to afford cyclohexadiene **8b** (Scheme 3). *In situ* hydrolysis yielded the *trans*-disubstituted cyclohexe none **10** as a single regioisomer.[10] Desilylated product **12** was a side product. Modification of

(1) (a) For a review of the Birch reduction/alkylation of benzoic acid derivatives, see: Rabideau, P. W.; Marcinow, Z. *Org. React.* **1992**, *42*, 1. (b) For asymmetric examples, see: Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828 and references cited therein.

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(3) For a review, see: Semmelhack, M. F. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol 12, p 979.

(4) Kündig, E. P.; Ripa, A.; Liu, R.; Bernardinelli, G. *J. Org. Chem.* **1994**, *59*, 4773 and references cited therein.

(5) (a) Kündig, E. P.; Ripa, A.; Bernardinelli, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1071. (b) Kündig, E. P.; Amurrio, D.; Anderson, G.; Beruben, D.; Ripa, A.; Liu, R. *Pure Appl. Chem.* In press. (c) Amurrio, D.; Khan, K.; Kündig, E. P. *J. Org. Chem.* **1996**, *61*, 2258. (d) Kündig, E. P.; Quattropani, A.; Inage, M.; Ripa, A.; Dupré, C.; Cunningham, A. F., Jr.; Bourdin, B. *Pure Appl. Chem.* **1996**, *68*, 97.

(6) For precedent of a diastereoselective nucleophile addition/protonation sequence to a planar chiral complex derived from 1(*R*),2(*S*)-(-)-**6**, see: Schmalz, H.-G.; Schellhaas, K. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2146.

(7) For reviews, see: (a) Schore, N. E. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol 12, pp 703−739. (b) Schore, N. E. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 5, p 1037. (c) Schore, N. E. *Org. React.* **1991**, *40*, 1. (d) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081.

(8) (a) Semmelhack, M. F.; Clark, G. R. *J. Am. Chem. Soc.* **1977**, *99*, 1675. (b) Pearson, A. J.; Gontcharov, A. V.; Woodgate, P. D. *Tetrahedron Lett.* **1996**, *37*, 3087. (c) Semmelhack, M. F.; Schmalz, H.-G. *Tetrahedron Lett.* **1996**, *37*, 3089.

(9) (a) Simpkins, N. S.; Price, D. A.; MacLoed, A. M.; Watt, A. P. *J. Org. Chem.* **1994**, *59*, 1961. (b) Simpkins, N. S.; Price, D. A.; MacLoed, A. M.; Watt, A. P. *Tetrahedron Lett.* **1994**, *35*, 6159. (c) For similar results, see: Schmalz, H.-G.; Schellhaas, K. *Tetrahedron Lett.* **1995**, *36*, 5515. See also: (d) Kündig, E. P.; Quattropani, A. *Tetrahedron Lett.* **1994**, *35*, 3497. (e) Uemura, M.; Hayashi, Y.; Hayashi, Y. *Tetrahedron: Asymmetry* **1994**, *5*, 1427.

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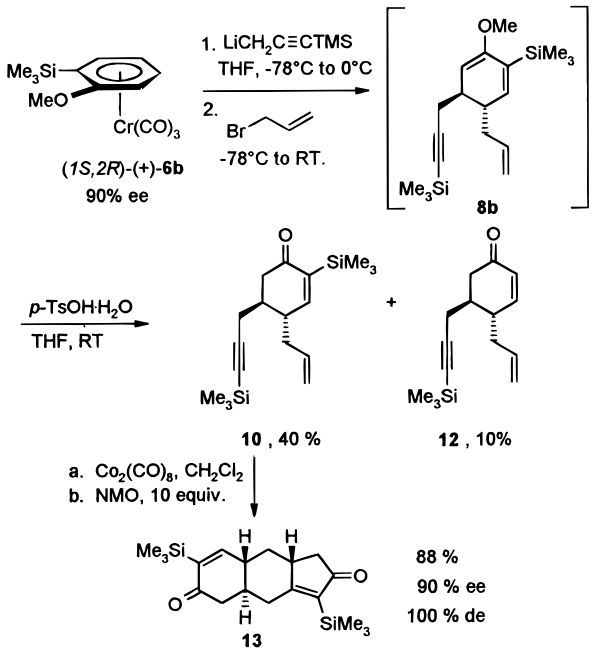
Scheme 3

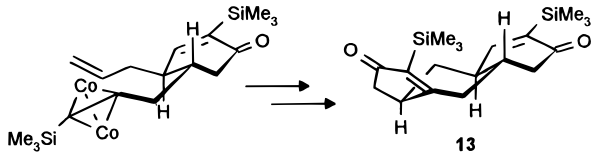


hydrolysis conditions aimed at the suppression of **12** has not yet met with success.

A sizable body of literature exists dealing with the synthesis of bicyclo[3.3.0]octan-3-ones by intramolecular Pauson−Khand cyclization of 1,6-enynes.[11] The analogous construction of bicyclo[4.3.0]octan-3-ones is not as well documented,[12] and we are not aware of the use of this reaction in the preparation of enantioenriched tricyclic molecules having a *trans* disposition of the substituents participating in the cyclization step.[13]

Coordination of the alkyne of **10** to the $Co_2(CO)_6$ fragment followed by *in situ* treatment with *N*-methylmorpholine *N*-oxide (NMO) gave the expected tricyclic diketone **13** in good yield. ^{1}H NMR and GC analyses of the crude product indicated **13** to be formed as a single diastereomer and chiral GC showed **13** to have an enantiomeric excess (ee) of 90%.[14] Both the nucleophile addition/allylation step and the Pauson−Khand reaction had thus occurred with complete diastereoselectivity. The sequence demonstrates the efficient transfer of the planar chirality in **6b** to the three new stereogenic centers in **13**.

Scheme 4



The relative stereochemistry of the single diastereomer formed was determined by X-ray analysis of *rac*-**13**.[15] This structural analysis also served to confirm the regioselectivity of the sequential nucleophilic/electrophilic addition.

A rational for the formation of **13** is presented in Scheme 4. The cyclohexenone side chains are in a diequatorial conformation. A chair-like arrangement for **10** then places the alkene in a pseudoequatorial position. Coordination to Co and insertion into the Co−C(alkyne) bond then leads to the diastereoisomer **13**.

Thus, we have shown that the highly regio- and stereoselective sequential addition of a propargyllithium reagent and of allyl bromide to the planar chiral anisole complex **66** followed by an efficient metal-mediated cyclocarbonylation provides a rapid access to the highly enantioenriched tricyclic **13**. This forcefully demonstrates the synthetic potential of planar chiral arene complexes in the synthesis of enantioenriched alicyclic systems.

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Supporting Information Available: Descriptions of syntheses, experimental details and characterization data for **10**, **12**, and (+)-**13** and details of the single-crystal X-ray analysis and perspective view of *rac*-**13** (9 pages). See any current masthead page for ordering and Internet access instructions.

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(10) Separation of **10** from **12** by chromatography (hexane/EtOAc 100:3). Yield of **10**: 40%.

(11) (a) Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*, 4851. (b) Magnus, P.; Exon, C.; Albaugh-Robertson, P. *Tetrahedron* **1985**, *41*, 5861. (c) Hua, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 3835. (d) Hua, D. H.; Coulter, M. J.; Badejo, I. *Tetrahedron Lett.* **1987**, *28*, 5465. (e) Montana, A.-M.; Moyano, A.; Pericàs, M. A.; Serratosa, F. *An. Quim., Ser. C* **1988**, *84*, 82. (f) Gynin, A. S.; Smit, W. A.; Caple, R.; Veretenov, A. L.; Shaskov, A. S.; Vorontsova, L. G.; Kurella, M. G.; Chertkov, V. S.; Carapetyan, A. A.; Kosnikov, A. Y.; Alexanyan, M. S.; Lindeman, S. V.; Panov, V. N.; Maleev, A. V.; Struchkov, Y. T.; Sharpe, S. M. *J. Am. Chem. Soc.* **1992**, *114*, 5555. For an asymmetric version, see: (g) Castro, J.; Sörensen, H.; Riera, A.; Morin, C.; Moyano, A.; Pericàs, M. A.; Greene, A. E. *J. Am. Chem. Soc.* **1990**, *112*, 9388. (h) Mukai, C.; Uchiyama, M.; Sakamoto, S.; Hanaoka, M. *Tetrahedron Lett.* **1995**, *36*, 5761.

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(13) Krafft, M. E.; Chirico, X. *Tetrahedron Lett.* **1994**, *35*, 4511.

(14) The enantiomeric excess of **13** was determined by GC analysis on the chiral column MN FS-Lipodex-E: H_2, 200°C isotherm, t_1 = 26.6 min (95%), t_2 = 27.2 min (5%).

(15) *Rac*-**13** was obtained by the same sequence starting with *rac*-**6b**. Crystal structure determination of *rac*-**13**: $C_{19}H_{30}O_2Si_2$, M_r = 346.6; μ = 1.58 mm^{-1}, $F(000)$ = 752, d_x = 1.10 g cm^{-3}, triclinic, $P\bar{1}$, Z = 4, a = 6.8483(5), b = 14.531(2), and c = 22.560(2) Å, α = 106.602(6)°, β = 93.405(5)°, γ = 101.127(5)°, V = 2095.3(4) Å^3, from 22 reflections (43° < 2θ < 67°), colorless prism 0.15 × 0.30 × 0.37 mm. Cell dimensions and intensities were measured at room temperature on a Nonius CAD4 diffractometer with graphite-monochromated Cu Kα radiation (λ = 1.5418 Å), $\omega - 2\theta$ scans, scan width 1.5° + 0.14 tan θ, and scan speed 0.092°/s. Two reference reflections measured every 30 min showed variation of about 5.5%, all intensities were corrected for this drift: $-7 < h < 7$; $-14 < k < 15$; $0 < l < 23$; 5255 measured unique reflections of which 4375 were observables ($|F_o| > 4\sigma(F_o)$). Data were corrected for Lorentz and polarization effects and for absorption[16a] (A^* min, max = 1.268 , 1.725). The structure was solved by direct methods using MULTAN 87[16b] all other calculations used XTAL[16c] system and ORTEP[16d] programs. Full-matrix least-squares refinement based on F using weight of $1/\sigma 2(F_o)$ gave final values R = 0.076, R_w = 0.052 for 488 variables and 4375 contributing reflections. Hydrogen atoms (excepted these of the methyl groups, which are calculated) were observed and refined with a fixed value of isotropic displacement parameters (U = 0.05 Å^2). The final difference electron density map showed a maximum of +0.36 and a minimum of −0.46 eÅ^{-3}. The two molecules of the asymmetric unit are similar and only differ by the orientation of the trimethylsilyl substituent bound to the five-membered ring.

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