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Stereoselectivity of the Benzannulation Reaction: Efficient Central-to-Axial Chirality Transfer

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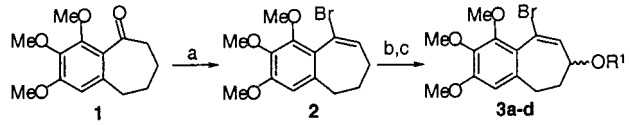
Axially chiral biaryls are not only common structural subunits in numerous pharmacologically important natural products,[1] but also the backbone of the growing number of highly effective chiral ligands[2] for the asymmetric synthesis. Despite the availability of various procedures for the resolution of racemic mixtures of chiral biaryls,[3] the development of atropisomer-selective methods is a topic of considerable current interest. This problem has been previously approached in a number of different ways,[4] including kinetic resolution of racemic substrates,[4c] desymmetrization of prochiral biaryls,[4d] chirality transfer from central,[4e−g] axial,[4h] and planar[4i,j] asymmetry present in the substrate, and, most recently, asymmetric catalytic coupling.[4k] Although the latter is certainly the most convenient approach, the coupling efficiency and stereochemical outcome of such processes is greatly influenced by the steric and electronic nature of substituents on the aromatic rings being coupled.[4k] Coupling reactions of planar chiral arene chromium tricarbonyl complexes developed by the groups of Nelson[4i] and Uemura[4j] can serve as examples of nearly complete atroposelectivity.

The benzannulation reaction of α,β-unsaturated chromium carbene complexes[5] allows for the construction of an arene ring in the coordination sphere of the metal from three different ligands: carbene, carbon monoxide, and alkyne. Since the arene ring is assembled at the metal center, asymmetric induction can be expected from existing chirality on one of the ligands, leading to a facial selectivity in chromium coordination,[6] which can have further stereochemical consequences. Up to this point, this has been reported for central-to-central,[6a,b] central-to-planar,[6c−g] and planar-to-axial[6h] chirality transfer. Here we report the first examples of central-to-axial chirality transfer in the benzannulation reaction of carbene complexes and these are set in the context of the design of a convergent synthesis[7] of configurationally stable ring C functionalized derivatives of allocolchicinoids.[8]

Synthesis of the carbene complexes **4** was performed starting from the known[9] benzosuberone **1**. Vinyl bromide **2** was prepared by the reaction of **1** with 2,2,2-tribromo-1,3,2-benzodioxaphosphole[10] (Scheme 1). Allylic bromination of **2** followed by solvolysis in the appropriate alcohol gave substrates **3a**−**d**.[11] Preparation of carbene complexes **4** was achieved from the bromides **3** by using a modified[7] Fischer procedure followed by alkylation of the intermediate lithium (R = Me, Et) or tetramethylammonium (R = *i*-Pr) salts of the corresponding metal acylates with ROTf.

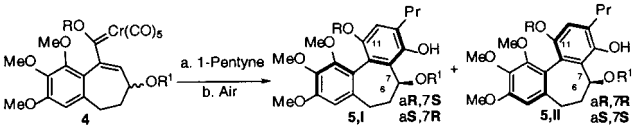
We have examined the reaction of carbene complexes **4**, substituted with R, R^1 groups of different size, with 1-pentyne followed by oxidative demetalation and were pleased to observe high to complete diastereoselectivity in every case (Table 1).

Scheme 1 [a]



[a] Key: (a) 2,2,2-tribromo-1,3,2-benzodioxaphosphole, CH_2Cl_2, 0 °C, 30 min., rt, 15 min, 74%; (b) NBS, $(PhCO)_2O_2$, CCl_4, reflux, 20 min; (c) R^1OH, $NaHCO_3$, rt, 12−36 h, **3a** (R^1 = Me) 54%, **3b** (R^1 = Et) 50%, **3c** (R^1 = *i*-Pr) 47%, **3d** (R^1 = *t*-Bu, not isolated[11]).

Table 1. Atropisomer-Selective Benzannulation of Carbene Complexes **4** with 1-Pentyne[a]



entry	4	R	R^1	yield 3 → 4 (%)	yield[b] 5 I + II (%)	dr[c] (I:II)
1	**4a**	Me	Me	67	40	**II** only[d]
2	**4b**	Me	Et	64	43	**II** only[d]
3	**4c**	Me	*i*-Pr	57	47	**II** only[d]
4	**4d**	Me	*t*-Bu	75	50	**II** only[d]
5	**4e**	Et	Me	69	73	1:13.2
6	**4f**	*i*-Pr	Me	36[e]	72	1:12.5

[a] All reactions were run in benzene at 55−58 °C for 36 h with 0.33 equiv of **4** in 1 M 1-pentyne. [b] Isolated yield. [c] Determined by ^{1}H NMR integration from the crude product mixture and then confirmed after chromatographic separation of diastereomers. [d] Diastereomer **I** could not be detected by NMR, HPLC, and TLC even in the mixture of side products. [e] Yield over two steps from **3**.

Variations in the steric size of the R^1 substituents had no effect on the stereoselectivity of the reaction (entries 1−4): the only phenolic products isolated from the reactions of **4a**−**d** were identified as the (aR,7R; aS,7S) diastereomers of **5a**−**d**. However, an increase in the size of the R group on **4** leads to a slight decrease in the stereoselectivity: from complete with **4a** (R = Me) to 12.5:1 with **4f** (R = *i*-Pr), all still favoring the (aR,7R; aS,7S) diastereomer (entries 1, 5, and 6).

In an attempt to gain selective access to the allocolchicinoids with an opposite biaryl twist, a series of complexes **8** with different substituents R, R^1 have been prepared from the corresponding precursors **7**, analogously to the above-described conversion of **3** to **4**. Bromides **7** can be readily synthesized by using a silver-assisted ring-opening reaction of dibromocyclopropane **6**[7] in the presence of the appropriate alcohol (Scheme 2).

The benzannulation reaction of carbene complexes **8** with 1-pentyne followed by oxidative demetalation afforded a mixture of atropisomers **9** with the (aR,7S; aS,7R) diastereomer as the major component (Table 2). In this case, the diastereoselectivity observed

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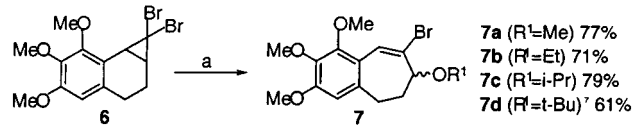
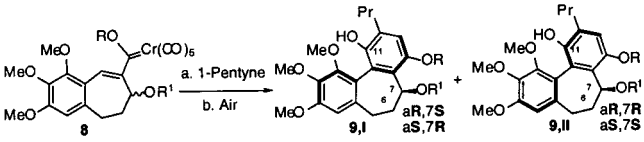
Scheme 2 [a]



[a] Key: (a) $AgBF_4$, $CaCO_3$, R^1OH, 65−80 °C, 24−36 h.

Table 2. Atropisomer-Selective Benzannulation of Carbene Complexes **8** with 1-Pentyne[a]



entry	**8**	R	R^1	yield[b] **7** → **8** (%)	yield[c] **9** **I** + **II** (%)	dr[d] (**I**:**II**)
1	**8a**	Me	Me	66	53	3.0:1
2	**8b**	Me	Et	55	45	2.4:1
3	**8c**	Me	*i*-Pr	42	51	2.4:1
4	**8d**[7]	Me	*t*-Bu	54	48	2.0:1
5	**8e**	Et	Me	52	45	2.1:1
6	**8f**	*i*-Pr	Me	47[e]	45	2.1:1
7	**8g**	*i*-Pr	*t*-Bu	29[e]	48	3.4:1

[a] All reactions were run in benzene at 55−58 °C for 24 h with 0.33 equiv of **8** in 1 M 1-pentyne. [b] Isolated as a mixture with 5−10% of OR^1-chelated tetracarbonyl complex. [c] Isolated yield. [d] Determined by ^1H NMR integration from the crude product mixture and then confirmed after chromatographic separation of diastereomers. [e] Yield over two steps from **7**.

Table 3. Thermal Epimerization of Phenols **9**, **I**, and **II**[a]

entry	**9**	R	R^1	*t*, h	**I**:**II**[b]	**I** + **II**,[c] %
1	**9a**	Me	Me	22	94:6	90
2	**9b**	Me	Et	28	95:5	96
3	**9c**	Me	*i*-Pr	48	96:4	95
4	**9e**	Et	Me	22	96:4	100
5	**9g**	*i*-Pr	*t*-Bu	22	97:3	82

[a] All epimerizations were run in toluene solution (10 mg/mL) at 120 °C in a sealed tube under Ar. [b] Determined by ^1H NMR integration. [c] Recovery after column chromatography.

was only moderate, decreasing gradually with an increase in the steric size of both R^1 (entries 1−4) and R (entries 1, 5 and 6) groups. It slightly recovers only when both R and R^1 represent sterically demanding substituents (entry 7).

To obtain information about the thermodynamics of the diastereomer distribution, selected allocolchicinoids **9** were subjected to thermal epimerization conditions. Equilibrium between the diastereomers was achieved starting from both pure **I** and **II** in each case in 22−48 h at 120 °C. We were glad to discover that in all cases the equilibrium mixture strongly favored the desired atropisomers **9**,**I** (Table 3). High levels of material recovery make these allocolchicinoids selectively available from the benzannulation reaction of **8** followed by a first-order asymmetric transformation.[4e]

Assignment of (aR,7S; aS,7R) configuration to **9a**,**I** has been secured by X-ray diffraction studies. Consequently, the (aR,7R; aS, 7S) configuration has been assigned to **9a**,**II**. The structure of other phenols **5** and **9** has been determined by analysis of their ^1H NMR spectra[12] relative to those of **9a**, based on the difference in chemical shifts of C7−H and coupling constants[8b] between C7−H and C6−HaHb for both atropisomers **I** and **II**.

In conclusion, we have developed a highly atropisomer-selective preparation of configurationally stable (aR,7R; aS,7S) allocolchicinoids **5** using a central-to-axial chirality transfer benzannulation strategy. We have demonstrated that (aR,7S; aS,7R) allocolchicinoids **9** can also be accessible in a stereoselective manner by using a benzannulation reaction−thermal epimerizaton protocol. Additional synthetic and mechanistic studies of these reactions are underway.

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Supporting Information Available: Full experimental details and characterization data for compounds **2**−**5** and **7**−**9** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For a more detailed description of the stereochemical assignment, see the Supporting Information.

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