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Tetrahedron Letters 44 (2003) 7771–7774

TETRAHEDRON LETTERS

# Studies into diastereoselective Dötz benzannulations for the synthesis of axially chiral biaryls

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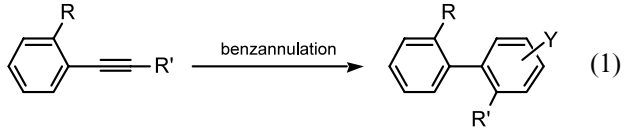
Received 14 July 2003; revised 15 August 2003; accepted 21 August 2003

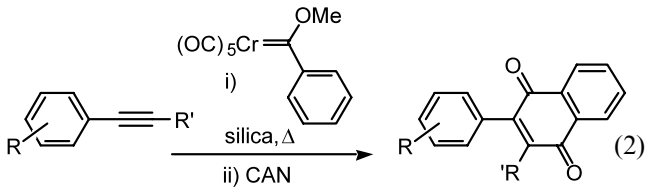
**Abstract**—A series of racemic chiral *ortho* substituents on 1-phenylhex-1-yne have been found to control the atroposelective formation of a biaryl from Dötz benzannulation with pentacarbonyl(methoxyphenylmethylene)chromium(0). The results show there is a subtle balance between the chiral *ortho* substituent controlling atroposelectivity with a *dr* 3–5:1 and allowing benzannulation to proceed in yields of 44–67%.


Axially chiral biaryls are important structural motifs in many biologically active molecules[1] and chiral ligands.[2] The two most effective strategies for preparing these systems are the atroposelective ring cleavage of configurationally unstable lactone-bridged biaryls developed by Bringmann[3] and the direct atroposelective coupling of two aromatic systems by stoichiometric[4] and catalytic methods.[5] The latter approach, although the more flexible of the two, still suffers from inherent difficulties associated with steric hindrance.[6] We have been pursuing a different strategy which relies upon the construction of the biaryl bond before the construction of the final aryl group (Eq. (1)).[7,8]



(1)

We have established the parameters for the racemic synthesis of axially chiral biaryl compounds from the Dötz benzannulation of a series of substituted aryl acetylenes (Eq. (2)).[7] In the *ortho* position it was found that methyl, methoxy, chloro and *N*-amide substituents gave moderate to good yields of product, whereas carbonyl derivatives and the nitro group were deleterious.



(2)

In order to render this process atroposelective we conceived of a number of stoichiometric strategies to control the stereochemistry of the benzannulation reaction. Disclosure by Wulff of the simultaneous and stereoselective construction of planar and axial centres of chirality by an identical reaction[8c] convinced us that the most promising strategy would be the incorporation of a chiral substituent *ortho* to the alkyne function. We had already determined that bulky *ortho* amide or anilide groups which exhibited evidence of atropisomerism in their $^1$H NMR spectra gave no benzannulation products with complex **2**, probably because these systems were too hindered.[7,8c] We had found that *ortho* achiral acetals gave moderate yields of benzannulated products.[7] Use of the chiral acetal[9] **1**; however, gave no evidence of diastereoselection in the crude $^1$H NMR spectrum and only a moderate 39% yield of the isolated quinone (Scheme 1).[10] Attempts to use chiral cyclic aminals, which are superior to chiral acetals due to stereochemical relay of the backbone chirality to the nitrogen,[11] were investigated, but benzannulation was thwarted again, presumably due to steric hindrance. It seemed that there was a subtle balance between the size of the chiral *ortho* substituent which would allow benzannulation to proceed, but which could also control atroposelectivity.

The inhibition of the Dötz benzannulation where axially chiral substituents and $C_2$ symmetric auxiliaries were used

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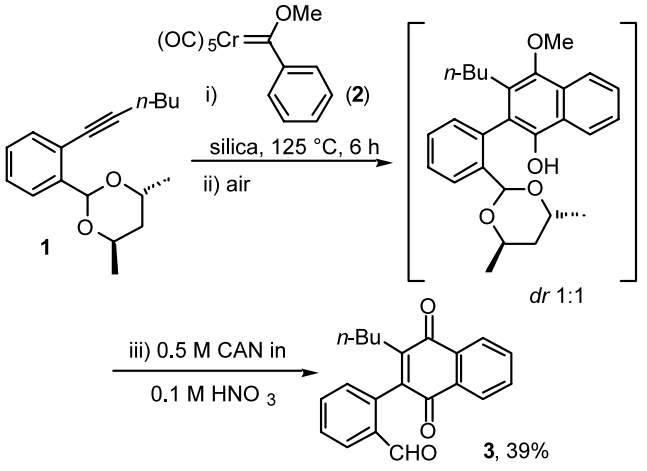
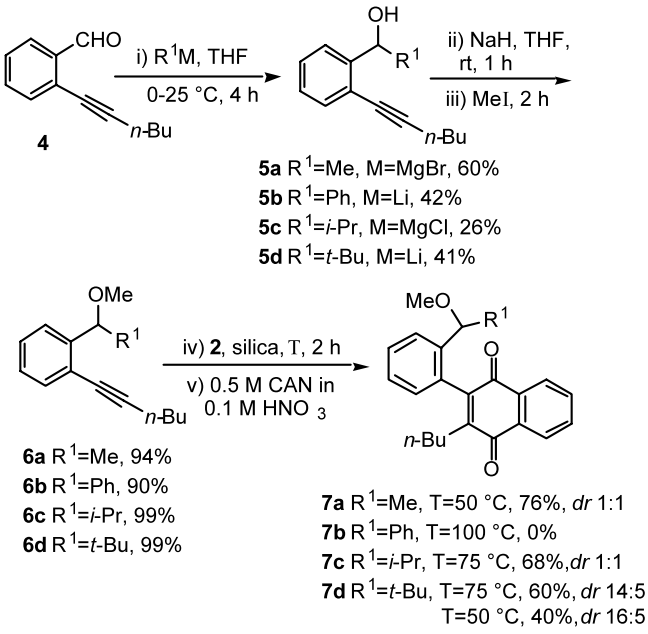
doi:10.1016/j.tetlet.2003.08.096




**Scheme 1.**



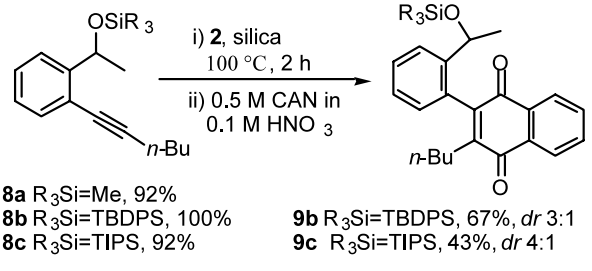

**Scheme 2.**

prompted an examination of more basic systems. The simplest class of compatible chiral sub-stituent it was thought possible to introduce was a chiral ether ($R = CR^1R^2OR^3$, Eq. (1)). Although such substituents would be able to rotate, it was thought there should be some conformational preference and plenty of opportunity for tuning through replacement of groups $R^1$, $R^2$ and $R^3$ ($R = CR^1R^2OR^3$, Eq. (1)). A short series of chiral benzylic ethers **6a–d** were synthesised from aldehyde **4** (Scheme 2).[12] Addition of an alkyl group to give benzylic alcohols **5a–d** proceeded in moderate yields due to complications from reduction by the Grignard or alkyl lithium reagent. Investigation of other organometallic alkylating reagents would no doubt circumvent this problem, but was not the immediate concern of this research. Standard methylation was high yielding and the ethers **6a–d** were subjected to solid state Dötz reaction conditions of which a selection are reported in Scheme 2.[13]

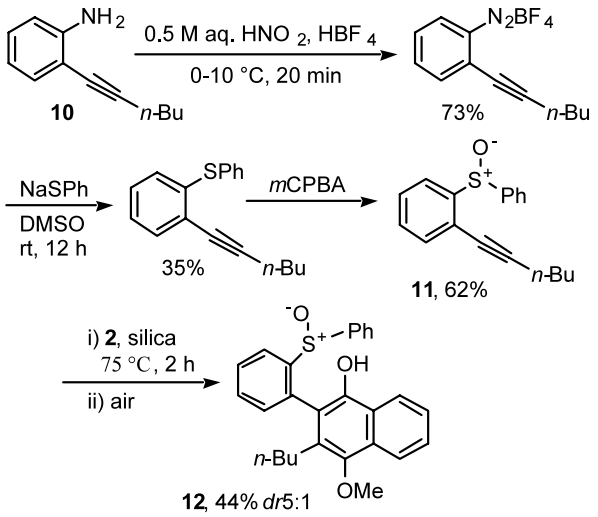
The aryl acetylenes **6a**, **c**, **d** gave reasonable yields of benzannulation products, but **6b** $R^1 = Ph$ gave a complex mixture of products. As expected as the *ortho* substituent became progressively larger the yield of the benzannulation product decreased slightly. The sterically most hindered ether **6d** $R' = t$-Bu gave a diastereomeric ratio of 14:5 by $^1H$ NMR at an optimum temperature of 75°C which ensured a reasonable yield of 60%. Heating product **7d** (*dr* 16:5) which had been adsorbed on silica, to mimic the reaction conditions, to 100°C led to an erosion in diastereomeric ratio to 2:1 over 2 h. This suggested that the diastereomeric ratio observed in this reaction was due to the formation of a kinetic final product.

In order to investigate a removable chiral directing group a series of benzylic silyl ethers were synthesised in which the bulky silyl substituent could be hydrolysed off after the benzannulation step. Treatment of **5a**[14] with a range of silyl protecting groups led to **8a–c** in good yield (Scheme 3). Subsequent benzannulation with **2** revealed that the TMS group was not stable to the reaction conditions, but the more bulky TBDPS and TIPS silyl ethers **8b** and **8c** led to benzannulated products. Due to their steric bulk a reaction temperature below 100°C gave very low yields. However at 100°C good yields and atroposelectivites were obtained. The results again demonstrate a balance between steric bulk in the *ortho* position which will allow benzannulation, but also control atropisomer selectivity. The TBDPS silyl ether **8b** gave a 67% yield of **9b** with an atropisomer selectivity of 3:1. Heating product **9b** to 140°C on silica for 2 h resulted in equilibration to a 2:1 mixture of diastereoisomers, while further heating led to degradation of material.

Chiral sulfoxides are well known to be powerful auxiliaries for asymmetric synthesis and they have recently been shown to be useful for the atropisomer selective synthesis of axially chiral amides.[15] Synthesis of a benzannulation precursor with an *ortho* sulfoxide **11** began with diazotisation[16] of aniline **10**,[17] treatment with sodium thiophenolate[18] and finally oxidation of the sulfide with *m*CPBA (Scheme 4). Benzannulation with **2** under identical reaction conditions as before gave a 44% yield of biaryl **12** with a diastereomeric ratio of 5:1.[19] A small portion was adsorbed on silica and heated to 140°C for 2 h. Epimerisation to a 3:2 mixture of diastereoisomers was observed.




**Scheme 3.**




**Scheme 4.**

In order to begin to unravel how stereoselection was being achieved we verified that the regiochemistry of the Dötz benzannulation, in the chiral benzylic ether series, was occurring with the aryl group of the acetylene being positioned adjacent to the phenolic hydroxyl group before CAN oxidation. The mixture of diastereoisomers **13** was too complicated by $^1$H NMR for NOE analysis, but the corresponding biaryl **14**, which did not possess a centre of chirality, showed key NOE enhancements which verified the course of the Dötz benzannulation had proceeded according to literature expectations (Fig. 1).[20]

Unfortunately in all the cases we investigated we could not separate diastereoisomers of **7d**, **9b**,**c**, **12** or **13** and could not determine the structures of the major diastereoisomers. However, if we accept that for the chiral substituents in **6d** $R_L = t$-Bu and $R_S$ = OMe, but in **8b**,**c** $R_L$ = OSiR$_3$ and $R_S$ = Me then we would expect the opposite diastereoisomers to be formed from these compounds with respect to the ether substituent. This was supported in the $^{13}$C NMR spectra where the major–minor pattern of peaks in the butyl and aromatic region of **7d** are reversed in **9b**,**c**. The sense of atroposelection in the final products **7d**, **9b**,**c**, **12** and **13**

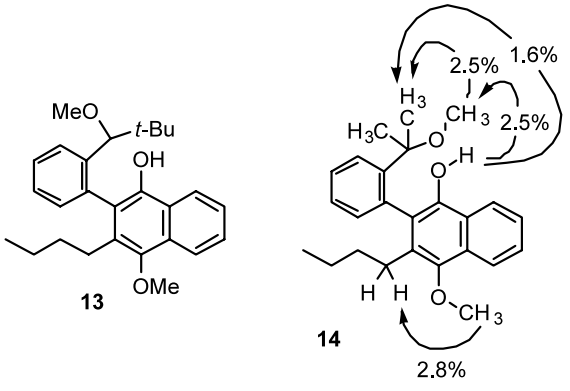



**Figure 1.**

is complex as it can arise through kinetic formation of an intermediate tricarbonyl-$\eta^6$-arene chromium(0) complex or thermodynamic epimerisation of this complex.[8c,21] Due to our epimerisation studies of the diastereomerically enriched final compounds we can conclude that either route leads to kinetic biaryl products after decomplexation of chromium(0).

These results show that a chiral *ortho* substituent on an aryl acetylene can dictate the formation of an axially chiral biaryl system possessing three *ortho* substituents that exhibits atropisomerism. This is an example of central-to-axial chirality transfer in the benzannulation of an aryl acetylene with a carbene complex.[22] This strategy requires a subtle steric balance between the chiral *ortho* substituent being able to dictate atroposelectivity, but not hinder biaryl formation.

## Acknowledgements

We would like to thank the EPSRC and GlaxoSmithKline for financial support, Mr. T. Hollingworth and Mr. D. Hooper for providing mass spectra and Mr. T. J. Spencer for micro analytical data.

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