Synthesis of densely functionalised arenes using [2 + 2 + 2] cycloaddition reactions†

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Rh(I)–catalysed [2 + 2 + 2] cycloaddition allows the synthesis of aryl ethers and diaryl methanes containing a high degree of steric hindrance from relatively simple diyne and alkyne precursors. The diarylmethanes made in this way show no evidence in their NMR spectra, however, of rotational restriction.

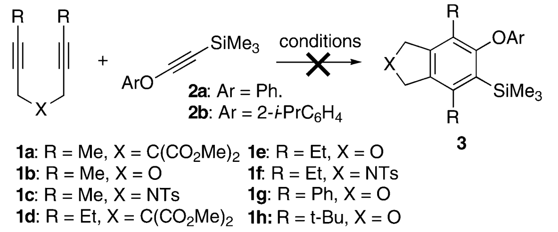
Introduction

Transition-metal catalysed cycloaddition reactions enable the rapid construction of complex molecular entities. In particular, the [2 + 2 + 2] cycloaddition reaction between 1,*n*-diynes and alkynes provides a valuable synthetic route to highly substituted benzene derivatives.[1] As part of a research programme aimed at uncovering new classes of atropisomeric molecules[2] and delineating structural requirements for atropisomerism in hindered systems, we were interested in developing a concise synthesis of diaryl ethers and diaryl methanes. Importantly, the method needed to be amenable to the asymmetric preparation of these types of compounds and also needed to be tolerant of substrates with a high level of steric encumbrance. Recent work by Tanaka and others on the asymmetric preparation of hindered, axially chiral biaryls and cyclophanes[3] or anilides[4] using Rh(I)-catalysed [2 + 2 + 2] cycloaddition reactions inspired us to investigate this method for the synthesis of other potentially atropisomeric systems, particularly as asymmetric variants of the Rh(I)-catalysed [2 + 2 + 2] cycloadditions are known.

Recently, we reported the syntheses of 2,6,2′-trisubstituted diaryl ethers and 2,6,2′,6′-tetrasubstituted diaryl ethers by *ortho*-lithiation of dibenzosiloxanes[5] and through the use of S_NAr reactions of aryl chlorides with phenols.[2a] The stereochemistry, stereodynamics, and stereoisomeric separation of these compounds were investigated and some empirical rules to describe the requirements for atropisomeric chirality in diaryl ethers were deduced.

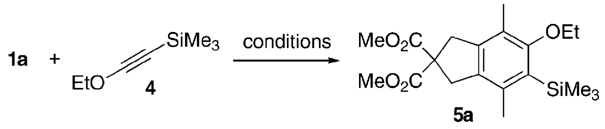
Results and discussion

The present study builds on these results and aims to provide an asymmetric route to these types of compounds. To this end, a series of diynes (**1a–1g**) were prepared and treated with alkynes **2a** and **2b** under various catalytic conditions.[6] Under none of the conditions tested (including all those listed in Table 1) was the expected cycloadduct **3** detected (Scheme 1).



Scheme 1 Attempted formation of diaryl ethers by [2 + 2 + 2] cycloaddition.

Attention was turned towards the reaction of alkyne **4** in the cycloaddition reaction (Scheme 2). No atropisomerism would be possible in the cycloadducts from this coupling partner, but we hoped nonetheless to gain an insight into the reactivity of alkynyl ethers towards cycloaddition. A variety of catalytic conditions was investigated, but only the combination of cationic Rh(I) with BINAP gave the product **5** (Table 1). The solvent used, the temperature, and the concentration all affected the yield. The best results were obtained with 10 mol% $Rh(cod)_2BF_4$ and 10 mol% *rac*-BINAP in methylene chloride (0.021 M) at ambient temperature (entry 7). In this case, cycloaddition occurred with diyne **1a** furnishing the cycloadduct in a moderate 50% yield. Heating the reaction in chloroform lead to a complex mixture of products, including **5**, but purification proved difficult (entry 4). A more concentrated methylene chloride solution proved less successful (entry 2), as did utilisation of toluene as solvent (entry 3).



Scheme 2 Formation of a hindered aryl ether.

Table 1 Aryl ether synthesis by [2 + 2 + 2] cycloaddition

Entry	Metal source	Ligand	Solvent	T/°C	Yield **5a** (%)[a]
1	$CpCo(CO)_2$	—	Heptane	80	0
2	$Rh(cod)_2BF_4$	(±)-BINAP	CH_2Cl_2[b]	r.t.	39
3	$Rh(cod)_2BF_4$	(±)-BINAP	Toluene	r.t.	37
4	$Rh(cod)_2BF_4$	(±)-BINAP	$CDCl_3$	50	n/d
5	$Rh(cod)_2BF_4$	—	CH_2Cl_2	r.t.	0
6	$Rh(cod)_2BF_4$	dppf	CH_2Cl_2	r.t.	0
7	$Rh(cod)_2BF_4$	(±)-BINAP	CH_2Cl_2[c]	r.t.	50
8	$Pd(PPh_3)_4$	—	Toluene	r.t.	0
9	Pd/C	—	THF	50	0

[a] Isolated product. [b] 0.21 M. [c] 0.021 M.

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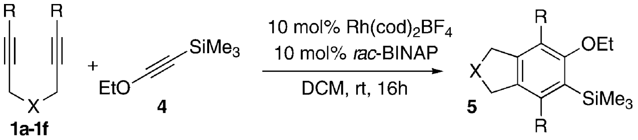
Table 2 Extending the aryl ether synthesis

Entry	Substrate	Conversion	Yield **5** (%)[a]
1	**1a**	>99	50
2	**1b**	>99	0
3	**1c**	>99	29[b]
4	**1d**	>99	0
5	**1e**	>99	0
6	**1f**	>99	0

[a] Isolated product. [b] Inseparable from side products.

Next, the scope of this cycloaddition reaction of alkyne **4** with alkynes **1b–1f** was investigated (Scheme 3). Surprisingly, the cycloaddition failed to generate the desired products for all of the other diynes, except **1c**, where a low yield of impure **5c** was obtained (Table 2). In all cases, complete conversion of the diynes was observed, and unidentified self-condensation products were formed. We conclude that alkynyl ethers are rather unreactive to the cycloaddition reaction. Removal of the terminal silyl group, to increase reactivity, was not investigated as these compounds undergo ready polymerisation at ambient temperature.

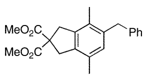
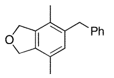
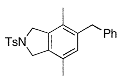
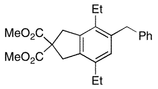
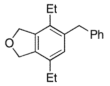
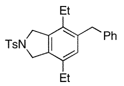
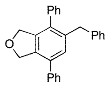
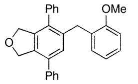
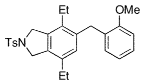
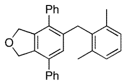
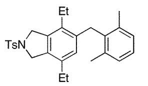


Scheme 3 Other aryl ethers.

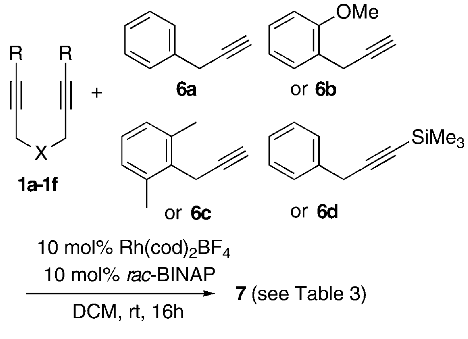
We expected hindered diaryl methanes to exhibit stereochemical features comparable with those of diaryl ethers, and the [2 + 2 + 2] cycloaddition route seemed a potentially valuable way of making hindered diaryl methanes. Diaryl methanes as a compound class have been the subject of considerable attention. Several biologically active compounds[7] and drugs[8] including trimethoprim, a synthetic antibiotic, papaverin, a muscle relaxing agent, and piritrexim, a dihydrofolate reductase inhibitor for the potential treatment of cancer, are based on this framework. Indeed, the synthesis of diaryl methanes and trimethoprim *via* a copper-catalysed cross-coupling of aryl magnesium reagents with benzylic phosphates was published late in 2006 by Knochel and Kofink.[9] This elegant chemistry is somewhat limited however as it uses highly reactive Grignard species which are incompatible with certain functional groups. More importantly, for our purposes, the incorporation of *ortho* aromatic substituents is essential, and such hindrance tends to shut down cross-coupling pathways. Molander and Elia have also published recently a Suzuki–Miyaura cross-coupling approach to diaryl methanes with benzyl halides and potassium aryl trifluoroborates as substrates.[10]

The use of the [2 + 2 + 2] cycloaddition has the potential to offer an alternative route to hindered diaryl methanes, and one for which an asymmetric modification would be readily available. Building on our experience of the reaction, we investigated the reaction between diynes **1a–1g** and alkynes 2-propynylbenzene **6a** and the more hindered **6b** and **6c** (Scheme 4). The cycloaddition reactions were successful in all instances (Table 3), regardless of the steric bulk inherent in the molecules.[11] However, NMR at ambient temperature or at -50 °C showed no evidence of rotational restriction in any of the diaryl methanes. Consequently, a more

Table 3 Synthesis of diaryl methanes

Entry	Diyne	Alkyne	Product	Yield (%)[a]
1	**1a**	**6a**	 **7a**	86
2	**1b**	**6a**	 **7b**	46
3	**1c**	**6a**	 **7c**	60
4	**1d**	**6a**	 **7d**	82
5	**1e**	**6a**	 **7e**	65
6	**1f**	**6a**	 **7f**	92
7	**1g**	**6a**	 **7g**	93
8	**1g**	**6b**	 **7h**	82
9	**1f**	**6b**	 **7i**	70
10	**1g**	**6c**	 **7j**	56
11	**1f**	**6c**	 **7k**	64
12	**1a**	**6d**	—	0
13	**1h**	**6a**	—	0

[a] Isolated product. [b] Inseparable from side products.



Scheme 4 Diarylmethanes by [2 + 2 + 2] cycloaddition.

hindered system was required, and diyne **1h**, bearing *t*-butyl groups at the alkyne termini, was synthesised. Unfortunately, this diyne did not undergo cycloaddition with any of the alkynes investigated and starting materials were recovered. Installation of a terminal trimethylsilyl group in alkyne **6d** would lead to the formation of even more hindered 2,6,2′,6′-tetrasubstituted diaryl methanes upon cycloaddition, however, in the event, no reaction occurred with any of the diynes investigated (Table 3, entry 11).

In summary, a straightforward synthesis of densely substituted benzenoids and diaryl methanes has been developed through use of a Rh(I)-catalysed [2 + 2 + 2] cycloaddition. This protocol complements cross-coupling strategies, but allows the synthesis of more hindered systems. Progress towards the preparation of compounds exhibiting atropisomerism continues in our laboratories.

Acknowledgements

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