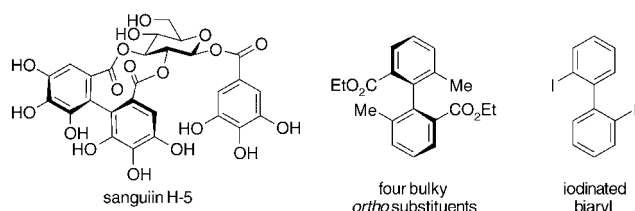


C–C Coupling

Medium-Ring and Iodinated Biaryl Synthesis by Organocuprate Oxidation**

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The importance of the biaryl motif is illustrated by its presence in an extensive range of natural products, pharmaceuticals, agrochemicals, dyes, and chiral catalysts. A variety of reactions are available to construct biaryls,^[1] mostly through palladium-,^[2,3] nickel-,^[4] or copper-mediated processes.^[5] Unfortunately, only a limited number of these methods is suitable for the synthesis of medium-ring compounds,^[6] sterically hindered systems, and iodinated biaryls (Scheme 1). Biaryl-containing medium-ring compounds are



Scheme 1. Biaryl-containing medium-ring compounds, sterically hindered biaryls, and iodinated biaryls are all difficult synthetic targets using existing methodology.

difficult to synthesize because of their associated torsional, transannular, and large angle strain; nevertheless, there are thousands of potent bioactive natural products that contain this motif, such as the ellagitannin class of natural products, of which sanguini H-5 is one of over 500 members.^[7] In addition, the synthesis of biaryls that contain four *ortho* substituents is often challenging, and palladium-catalyzed reactions that accomplish this goal have only recently been developed.^[8] Moreover, iodinated biaryls are powerful synthetic intermediates, yet they are only formed by a relatively small

number of reactions.^[9] New methodology that can overcome these caveats will allow efficient access to largely unexploited classes of biaryls.

Oxidation of organocuprates allows the formation of both intermolecular^[10] and intramolecular^[11] biaryl bonds; however, extreme reaction conditions and poor functional-group tolerance means that this reaction is not seen as being widely useful. We have endeavored to change this opinion. Herein, we report the optimization of organocuprate oxidation, which involves the design and utilization of a new oxidant, the exploitation of the iodine–magnesium exchange procedure developed by Knochel and co-workers,^[12] and the cross-coupling of different aryl units by an intramolecular process. The utility of the new methodology is illustrated by the efficient synthesis of the biaryl-containing medium-ring core of sanguini H-5.

Initial optimization studies revealed that a range of copper(I) salts could be used in the organocuprate oxidation reaction (Table 1), with the copper(I) bromide/dimethyl

Table 1: Substoichiometric amounts of dinitroarenes, such as **3**, could be used as effective oxidants.

Entry	Oxidant	Oxidant [equiv]	Yield [%]
1		1	68
2	3	0.2	62
3	3	0.1	31
4	CuCl ₂	0.2	12
5	CuCl ₂	1	60
6		1.5	57

sulfide complex proving the most convenient.^[13] In contrast, the choice of oxidant was crucial to the success of the reaction. Initially, *meta*-dinitrobenzene^[14] was the most successful oxidant examined,^[15] but it was difficult to obtain the pure product free of oxidant-derived by-products. Therefore, the new oxidant **3** was synthesized, which could be completely removed by an aqueous acid wash during the work up or by passage through silica gel.^[16] Under the reaction conditions employed, molecular oxygen as the oxidant caused significant formation of phenols, whilst none were detected when **3** was employed. Interestingly, as few as 0.2 equivalents of **3** (with respect to the aryl magnesium species formed) may be used without significant depreciation of yield (Table 1, entries 1 and 2). Further lowering of the quantity of dinitroarene to 0.1 equivalents, drastically decreased the yield of isolated product (entry 3). This “substoichiometric” effect was not observed for the inorganic, single-electron oxidant CuCl₂ (entries 4 and 5). A likely explanation of these findings is that the dinitroarene **3** can accept more than one electron during the oxidation process.^[17] Support for this hypothesis

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[**] We gratefully acknowledge financial support from the EPSRC and GSK (D.S.S.), Cambridge Trusts (X.S.), Pfizer UK (V.F.), and the BBSRC. We would also like to acknowledge the EPSRC National Mass Spectrometry Service Centre, Swansea, UK, for providing mass-spectrometric analysis.

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comes from the fact that the radical anion of *meta*-dinitrobenzene (available by reduction of *meta*-dinitrobenzene with one equivalent of potassium) may itself be used to perform the oxidation (entry 6).^[18]

The optimized methodology can be used for the preparation of a wide range of functionalized biaryls (Table 2). The

Table 2: Intermolecular-biaryl formation by using the optimized organocuprate oxidation methodology.^[a]

Entry	Substrate (1)	Product (2)	Yield [%]
a			88
b			75
c			82
d			67
e			72
f			66
g			75
h			53

[a] Conditions: a) **1** (1 mmol), *i*PrMgCl (1 equiv), THF (3 mL), -20°C , 10 min; b) CuBr·SMe₂ (0.5 equiv); c) **3** (1 equiv) in THF (3 mL).

reaction does not seem to be significantly influenced by steric interactions, thus allowing the synthesis of a biaryl bond with multiple *ortho* substituents (**2a** and **2b**). Iodinated aromatic heterocycles are also suitable substrates, which makes the synthesis of the corresponding dimer **2c** possible.^[19] The iodine–magnesium exchange can be performed in the presence of an aryl bromide,^[20] which allows the formation of brominated biaryls (**2d**). Furthermore, the ability to regioselectively perform a single iodine–magnesium exchange on multiply iodinated substrates permits the synthesis of iodinated biaryls **2e–h**, which are often extremely difficult to form directly by other methods because of oligomerization.

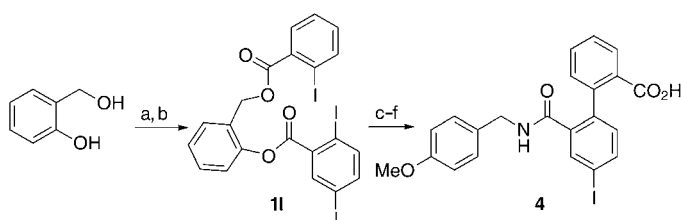
The reaction is equally successful when performed intramolecularly (Table 3) so that strained medium-ring compounds with 10- and 11-membered rings (**2i,j** and **2k**, respectively) can be constructed without the need for high-dilution conditions (approximately 0.3 M in THF).

Table 3: Intramolecular-biaryl formation using the optimized organocuprate oxidation methodology.^[a]

Entry	Substrate (1)	Product (2)	Yield [%]
i			82
j			70
k			85

[a] Conditions: a) **1** (1 mmol), *i*PrMgCl (2 equiv), THF (3 mL), -20°C , 10 min; b) CuBr·SMe₂ (1 equiv); c) **3** (1 equiv) in THF (3 mL).

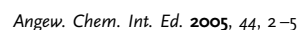
The success of this cyclization allows cross-coupling of different aryl units (Scheme 2). Two different aryl units can be tethered with 2-hydroxybenzyl alcohol to give **11**,^[21] which can



Scheme 2. Formal cross-coupling of aryl units by intramolecular biaryl formation followed by selective aminolysis: a) 2-iodobenzoyl chloride, Et₃N, DMAP, DMA, -20°C , 6 h; b) 2,5-diiodobenzoyl chloride, Et₃N, DMAP, DMA, -20°C , 6 h, 90%; c) *i*PrMgCl (2 equiv), THF, -20°C ; d) CuBr·SMe₂ (1 equiv); e) **3** (1 equiv), 79% from **11**; f) 4-methoxybenzylamine, 1,4-dioxane, 60°C , 6 h, 84%. DMAP = 4-(dimethylamino)pyridine, DMA = *N,N*-dimethylacetamide.

be readily cyclized in 79% yield by using our methodology. The 11-membered ring product readily undergoes aminolysis with concomitant loss of the tether to give **4** directly, thus, allowing an overall cross-coupling of two aryl iodides. This procedure could be readily exploited for the generation of a library of functionalized biaryls derivatives, which could then be further modified.

Most importantly, this methodology was used to form **2m**, a model for the highly strained medium-ring core of sanguin H-5 in 67% yield and with complete diastereoselectivity (Scheme 3).^[22] This significant result represents a high-yielding synthesis of bisester biaryl-containing medium rings that can be applied to the preparation of the ellagitannin



- dicyano-1,4-benzoquinone (DDQ), and potassium nitrosodisulfonate (Fremy's salt), gave unsatisfactory yields.
- [16] This compound is readily synthesized in high yield on a large scale from commercially available starting materials (see the Supporting Information) and can be stored indefinitely at room temperature.
- [17] The dianion of dinitrobenzene has been studied electrochemically; for an example see: H. Wang, V. D. Parker, *Acta Chem. Scand.* **1994**, *48*, 933.
- [18] An alternative possibility is that the biphenyl product can itself act as a single-electron oxidant; however, this possibility was ruled out as biphenyl did not act as an oxidant in control reactions.
- [19] It has recently been found that this dimerization proceeds in only moderate yield in a palladium-catalyzed system, see: C. F. Nising, U. K. Schmid, M. Nieger, S. Bräse, *J. Org. Chem.* **2004**, *69*, 6830.
- [20] The halogen–metal exchange has recently been extended to allow the formation of aryl magnesium compounds from the corresponding aryl bromides: A. Krasovskiy, P. Knochel, *Angew. Chem.* **2004**, *116*, 3396; *Angew. Chem. Int. Ed.* **2004**, *43*, 3333. Our preliminary investigations suggest that Grignard reagents formed in this way may also be used to form organocuprates, which may be successfully oxidized under our conditions.
- [21] a) M. Takahashi, T. Ogiku, K. Okamura, T. Da-te, H. Ohmizu, K. Kondo, T. Iwasaki, *J. Chem. Soc. Perkin Trans. 1* **1993**, 1473; b) M. Takahashi, T. Kuroda, T. Ogiku, H. Ohmizu, K. Kondo, T. Iwasaki, *Heterocycles* **1993**, *36*, 1867; c) M. Takahashi, T. Kuroda, T. Ogiku, H. Ohmizu, K. Kondo, T. Iwasaki, *Heterocycles* **1992**, *34*, 2061; d) M. Takahashi, T. Kuroda, T. Ogiku, H. Ohmizu, K. Kondo, T. Iwasaki, *Tetrahedron Lett.* **1991**, *32*, 6919.
- [22] The axial configuration of **2m** was assigned by comparison to literature data: G. Capozzi, C. Ciampi, G. Delogu, S. Menichetti, C. Nativi, *J. Org. Chem.* **2001**, *66*, 8787.
- [23] G. van Koten, S. L. James, J. T. B. H. Jastrzebski in *Comprehensive Organometallic Chemistry II* (Ed.: E. W. Abel, F. G. A. Stone, G. Wilkinson, J. L. Wardell), Pergamon, Oxford, **1995**, chap. 2.