C–C Coupling

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

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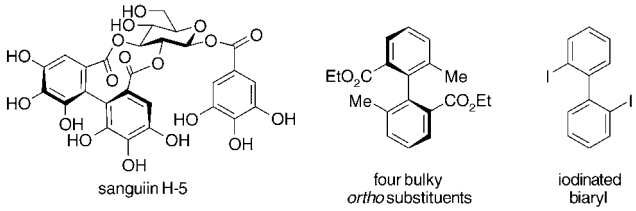
The importance of the biaryl motif is illustrated by its presence in an extensive range of natural products, pharmaceuticals, agrochemicals, dyes, and chiral catalysts. A variety of reactions are available to construct biaryls,[1] mostly through palladium-,[2,3] nickel-,[4] or copper-mediated processes.[5] 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



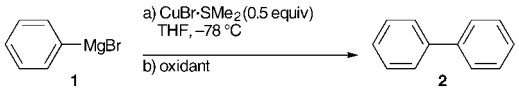
Scheme 1. Biaryl-containing medium-ring compounds, sterically hindered biaryls, and iodinated biaryls are all difficult synthetic targets using existing methodology.

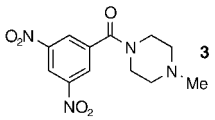
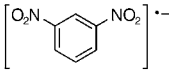
difficult to synthesize because of their associated torsional, transannular, and large angle strain; nevertheless, there are thousands of potent bioactive natural products that contain this motif, such as the ellagitannin class of natural products, of which sanguiin H-5 is one of over 500 members.[7] 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 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 sanguiin 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	 **3**	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 $CuCl_2$ (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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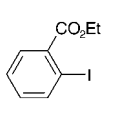
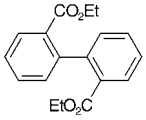
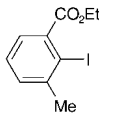
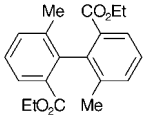
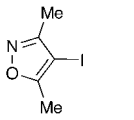
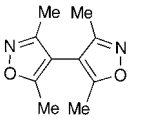
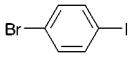
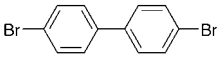
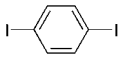
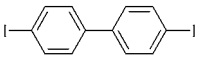
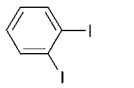
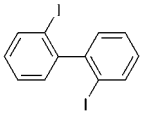
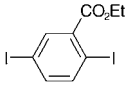
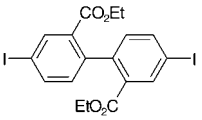
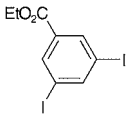
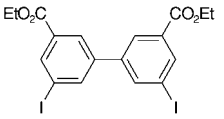
comes from the fact that the radical anion of *meta*-dinitrobenzene (available by reduction of *meta*-dinitrobenzene with one equivalent of potassium) may itself be used to perform the oxidation (entry 6).[18]

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

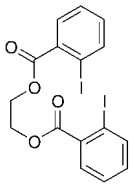
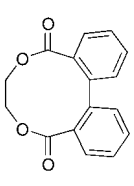
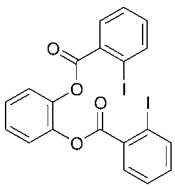
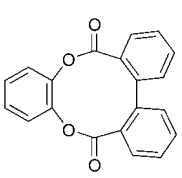
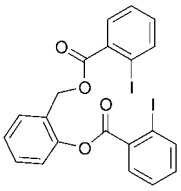
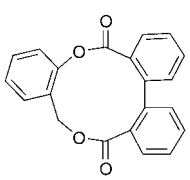
The reaction is equally successful when performed intramolecularly (Table 3) so that strained medium-ring compounds with 10- and 11-membered rings (**2i**,**j** and **2k**, respectively) can be constructed without the need for high-dilution conditions (approximately 0.3 M in THF).

Table 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

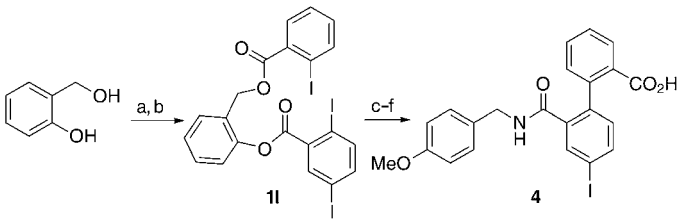
[a] Conditions: a) **1** (1 mmol), *i*PrMgCl (1 equiv), THF (3 mL), −20 °C, 10 min; b) CuBr·SMe_2 (0.5 equiv); c) **3** (1 equiv) in THF (3 mL).

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

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

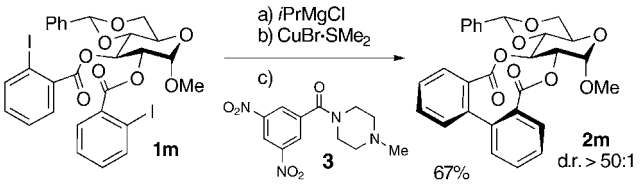
[a] Conditions: a) **1** (1 mmol), *i*PrMgCl (2 equiv), THF (3 mL), −20 °C, 10 min; b) CuBr·SMe_2 (1 equiv); c) **3** (1 equiv) in THF (3 mL).

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 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.



Scheme 2. Formal cross-coupling of aryl units by intramolecular biaryl formation followed by selective aminolysis: a) 2-iodobenzoyl chloride, Et_3N, DMAP, DMA, −20 °C, 6 h; b) 2,5-diiodobenzoyl chloride, Et_3N, DMAP, DMA, −20 °C, 6 h, 90%; c) *i*PrMgCl (2 equiv), THF, −20 °C; d) CuBr·SMe_2 (1 equiv); e) **3** (1 equiv), 79% from **1l**; f) 4-methoxybenzylamine, 1,4-dioxane, 60 °C, 6 h, 84%. DMAP = 4-(dimethylamino)pyridine, DMA = *N*,*N*-dimethylacetamide.

Most importantly, this methodology was used to form **2m**, a model for the highly strained medium-ring core of sanguiin 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



Scheme 3. Synthesis of **2m**, a model for the highly strained, medium-ring core of sanguiin H-5.

family of natural products. The success of this reaction in forming biaryl bonds in hindered systems and strained rings may be because the two aryl moieties that eventually bond in the intermediate organocuprate are a considerable distance apart. The C-Cu-C bond angle is approximately 180° and the C–Cu bond is somewhat long at 1.9 Å,[23] thereby reducing unfavorable interactions.

In summary, we report a new functional-group-tolerant methodology for the synthesis of sterically hindered biaryls, including highly strained medium-ring-containing biaryls, which are key structural units within the ellagitannin family of natural products. The methodology can also be used to cross-couple different aryl units by use of a tether. We are currently working towards exploiting this methodology in the synthesis of ellagitannin natural products.

Experimental Section

General procedure for the biaryl bond-forming reaction: Titrated *i*PrMgCl (1 mmol, 2.0 M solution in THF) was added to a solution of an aryl iodide (1 mmol) in THF (3 mL) at −20 °C. The reaction mixture was then stirred for 10 min at −20 °C and then transferred by cannula onto freshly recrystallized, solid $CuBr{\cdot}SMe_2$ (0.5 mmol). After stirring the reaction mixture for 30 s, a solution of **3** (1 mmol) in THF (3 mL) was added and the resulting solution was warmed to ambient temperature. The reaction mixture was then filtered through a plug of silica by using a mixture of hexane and EtOAc (1:1) as the eluant. The filtrate was concentrated under reduced pressure and the residue purified by flash column chromatography on silica gel.

3: 3,5-Dinitrobenzoic acid (21.2 g, 0.1 mol) was dissolved in thionyl chloride (100 mL), heated at reflux for 10 h, and then cooled to ambient temperature. Excess thionyl chloride was removed under reduced pressure and by azeotropic distillation with toluene. The residue was dissolved in $CHCl_3$ (200 mL) and added dropwise to a stirred slurry of 1-methylpiperazine (12.0 g, 0.12 mol) and K_2CO_3 (14 g, 0.1 mol) in $CHCl_3$ (200 mL) at 0 °C. The reaction mixture was warmed to ambient temperature over 1 h, washed with water (4 × 400 mL), dried over K_2CO_3, filtered, and the solvent removed under reduced pressure. The residue was recrystallized from hexane as yellow needles (20.4 g, 70 %); m.p. 138–141 °C; IR (film): $\tilde{\nu}$ = 1633, 1531, 1435, 1339, 1295, 1277, 1133, 995, 917, 908, 720, 681 cm^{-1}; ^1H NMR (500 MHz; $[D_6]$DMSO; 120 °C): δ = 8.87 (t, J = 2.0 Hz, 1H), 8.56 (d, J = 2.0 Hz, 2H), 3.54 (br, 4H), 2.42 (t, J = 5.0 Hz, 4H), 2.27 ppm (3H, s); ^{13}C NMR (125 MHz; $[D_6]$DMSO; 120 °C): δ = 165.5, 149.1, 139.8, 127.6, 119.4, 54.7, 45.7 ppm; HRMS (ESI) $[M]H^+$ m/z = 295.1042, $[C_{12}H_{15}N_4O_5]^+$ calcd m/z = 295.1043.

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Keywords: biaryls · C–C coupling · medium-ring compounds · organocuprates · oxidation

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