Novel electron-transfer oxidation of Lipshutz cuprates with 1,4-benzoquinones: an efficient homo-coupling reaction of aryl halides and its application to the construction of macrocyclic systems

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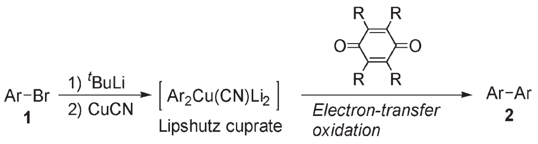
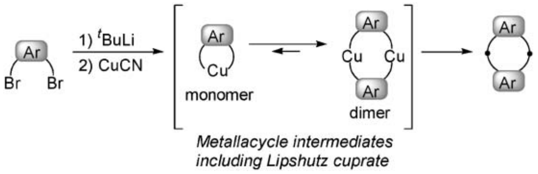
The electron transfer reaction from Lipshutz cuprates, which can be easily prepared from aryl bromides, to 1,4-benzoquinones was found to proceed smoothly, affording either the corresponding homo-coupling products, in modest to excellent yields, or macrocyclic products selectively.

Biaryl units, including the heteroaromatic analogues, are some of the most attractive substructures in natural products, bio-active compounds and organic materials, so aryl–aryl bond forming reactions have been studied extensively.[1] Oxidative "decomposition" of organic cuprates with oxidants is a promising method for homo-coupling of the ligands on the copper atom and is known to be useful for the construction of the biaryl skeleton.[2] In 1981, Lipshutz *et al.* reported a novel cuprate prepared by addition of two equiv. of a lithium reagent to one equiv. of CuCN, the so-called "Lipshutz cuprate" ($R_2Cu(CN)Li_2$)[3,4] and this cuprate has been reported to be an effective reagent for substitution reactions of alkyl halides and conjugate additions of α,β-unsaturated ketones.[3,5,6] Oxidation of Lipshutz cuprates with oxidants such as molecular oxygen[7] and nitrobenzenes[8] also occurs, to give the coupling products. In this paper, we report that a unique electron transfer reaction from Lipshutz cuprates to 1,4-benzoquinones proceeds efficiently, to afford biaryls as the homo-coupling product [eqn. (1)]. Aryl–aryl bond forming reactions can be useful for the synthesis of macrocycles. However, the yield of the macrocyclization step (intramolecular ring closure of the precursors or intermolecular cyclooligomerization of the monomer unit) is low in many cases, because of the strained structure of the macrocyclic compound and the preferable formation of linear oligomers. Here, we apply our novel electron transfer system to the construction of macrocyclic systems. We also summarize the new findings of the macrocyclization *via* a dimetallacycle intermediate including Lipshutz cuprate [eqn. (2)].[9]



(1)

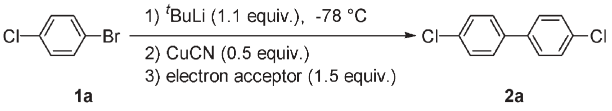


(2)

First, we investigated the reaction of the Lipshutz cuprate generated *in situ* from **1a** with an electron acceptor and typical results are shown in Table 1. We examined many electron acceptors, and several electron deficient compounds such as TCNQ and 1,4-benzoquinones worked as good acceptors (Table 1, entries 1–5). For example, the reaction of a Lipshutz cuprate from **1a** with tetramethyl-1,4-benzoquinone proceeded smoothly to afford the corresponding biaryl **2a** in 96% yield (Table 1, entry 5). Conjugate adducts of the aryl group to the electron acceptors were not detected in any of the cases and 1,4-benzoquinones were recovered in 80–90% yields (Table 1, entries 2–5). Under the same conditions, other copper salts such as CuI and CuSCN were not as efficient at this homo-coupling. When ⁿBuLi was used instead of ᵗBuLi as a lithiation reagent, the yield of **2a** decreased drastically.

Under the optimized conditions, the homo-coupling reaction of various aryl bromides **1** was next examined and the results are summarized in Table 2. Similarly to the case for **1a**, homo-coupling of **1b** (Ar = Ph) readily proceeded to afford biphenyl **2b** in 84% yield (Table 2, entry 1). A variety of aryl bromides bearing an electron-deficient group (**1c** and **1i**) or an electron-donating group (**1f** and **1g**) at the *para*-position also furnished high yields of the corresponding biaryl **2** (Table 2, entries 2, 5, 6 and 8). The reaction of *meta*-substituted aryl bromides **1e** and **1h** took place smoothly, providing the coupling products **2e** and **2h**, respectively (Table 2, entries 4 and 7). This reaction system can be applied to an aryl bromide having a substituent at the *ortho*-position (**1d**) and the biaryl **2d** was obtained in 87% yield (Table 2, entry 3). In the

Table 1 Homo-coupling of *p*-bromochlorobenzene **1a** *via* oxidation of Lipshutz cuprate with electron acceptors[a]



1a **2a**

Entry	Electron acceptor	Yield[b] (%)
1	Tetracyanoquinodimethane (TCNQ)	76
2	1,4-Benzoquinone	76
3	2,6-Dimethyl-1,4-benzoquinone	81
4	2,5-Dimethyl-1,4-benzoquinone	82
5	Tetramethyl-1,4-benzoquinone	96

[a] ᵗBuLi (1.1 equiv.) was added to a solution of **1a** (1.0 mmol) in Et_2O (60 mL) at −78 °C before CuCN (0.5 equiv.) was added. After electron acceptor (1.5 equiv.) was added, the mixture was stirred for 3 h at room temperature. [b] Isolated yield.

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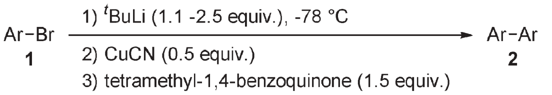
Table 2 Homo-coupling reaction of aryl bromides **1** *via* oxidation of Lipshutz cuprate with tetramethyl-1,4-benzoquinone[a]



$$\underset{\mathbf{1}}{\text{Ar−Br}} \xrightarrow[\substack{\text{2) CuCN (0.5 equiv.)} \\ \text{3) tetramethyl-1,4-benzoquinone (1.5 equiv.)}}]{\text{1) }^t\text{BuLi (1.1 -2.5 equiv.), -78 °C}} \underset{\mathbf{2}}{\text{Ar−Ar}}$$

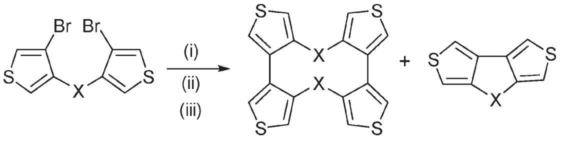
Entry	Ar	^{t}BuLi (equiv.)	Yield (%)[b]
1	C_6H_5 (**1b**)	1.1	84
2	4-FC_6H_4 (**1c**)	1.1	73
3	2-$MeOC_6H_4$ (**1d**)	1.1	87
4	3-$MeOC_6H_4$ (**1e**)	1.1	96
5	4-$MeOC_6H_4$ (**1f**)	1.1	91
6	4-MeC_6H_4 (**1g**)	1.1	90
7	3-BrC_6H_4 (**1h**)	1.1	95
8	4-BrC_6H_4 (**1i**)	1.1	88
9	2,4,6-$Me_3C_6H_2$ (**1j**)	2.5	64
10	1-Naphthyl (**1k**)	2.5	99
11	2-Naphthyl (**1l**)	2.5	99
12	2-Thienyl (**1m**)	1.1	62
13	3-Thienyl (**1n**)	1.1	82
14	4-Br-3-thienyl (**1o**)	1.1	87

[a] The reaction was carried out using a similar procedure to that noted in Table 1. [b] Isolated yield.

cases of sterically hindered aryl bromides such as **1j**, **1k** and **1l**, no homo-coupling reactions of cuprates proceeded under standard conditions and the corresponding reduction products at the bromo positions were obtained. When ^{t}BuLi (2.5 equiv.) was used, the reaction proceeded smoothly to afford the biaryls **2j**, **2k** and **2l** in moderate to good yields (Table 2, entries 9–11). This coupling reaction is useful for the synthesis of heteroaromatic dimers and bithiophenes such as **2m**, **2n** and **2o** were obtained in 62, 82 and 87% yields (Table 2, entries 12, 13 and 14). It is worth noting that the present reaction conditions allow employment of an aryl dihalide (**1h**, **1i** or **1o**), selectively affording the coupling products without loss of the bromo substituents (Table 2, entries 7, 8 and 14).

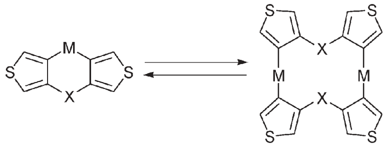
Although the reaction mechanism is not yet clear, we propose a plausible pathway as follows; (i) reaction of the aryl lithium species derived from **1** with CuCN affords the Lipshutz cuprate. (ii) Complexation of the Lipshutz cuprate to 1,4-benzoquinone results in the formation of the π-complex, with lithium–carbonyl and copper olefin coordinations.[10] (iii) Electron transfer from the cuprate to 1,4-benzoquinone occurs, followed by reductive elimination, to give the corresponding biaryl **2**.

This coupling reaction is applicable to the synthesis of 10-membered ring cyclophanes (Scheme 1). The homo-coupling reaction of **3a** *via* Lipshutz cuprate gave the intermolecular cyclization product **4a** as a major product in 50% yield, together with the intramolecular cyclization product **5a** (27%). Similar cyclization of **3b** took place smoothly, providing **4b** in 27% yield. When we investigated the palladium-catalyzed coupling reaction of **3a** with $Me_3SnSnMe_3$, the intramolecular cyclization proceeded to afford **5a** in good yield with no formation of **4a**.[11]



3a : X = $SiMe_2$
3b : X = SO_2
4a: 50%
4b: 27%
5a: 27%
5b: 0%

Scheme 1 *Reagents and conditions*: (i) ^{t}BuLi (2.0 equiv.), Et_2O, −78 °C; (ii) CuCN (1.0 equiv.), Et_3N, (iii) 1,4-bezoquinone.



6 **7**

Scheme 2

Key intermediates for the formation of **4** and **5** are metallacycles **6** and **7** containing a Lipshutz cuprate structure (M = Cu) (Scheme 2). The dithiophene **5a** is produced *via* six-membered monomeric metallacycle intermediate **6**, while **4a** is produced *via* 12-membered dimeric metallacycle **7**. In the palladium-catalyzed reaction, **6** should be thermodynamically stable and it is supposed that hardly any **7** is generated *in situ*. Because Lipshutz cuprates are known to have linear C–Cu–C linkages,[4] the intermediate **7**, which has linear C–Cu–C linkages, is expected to be more favorable than **6**, which has a bent structure.

In summary, we have demonstrated the efficient homo-coupling reaction of aryl bromides *via* Lipshutz cuprates under electron transfer conditions. A unique electron transfer step from the cuprates to the electron acceptors, without conjugate addition, is a key step for this reaction system and is a novel aspect of Lipshutz cuprates. We have also applied this system to the synthesis of 10-membered cyclophanes. Further studies on the reaction mechanism and applications of this electron transfer system to the construction of other functional macrocycles are now in progress.

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