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Copper catalyzed oxidation of organozinc halides†

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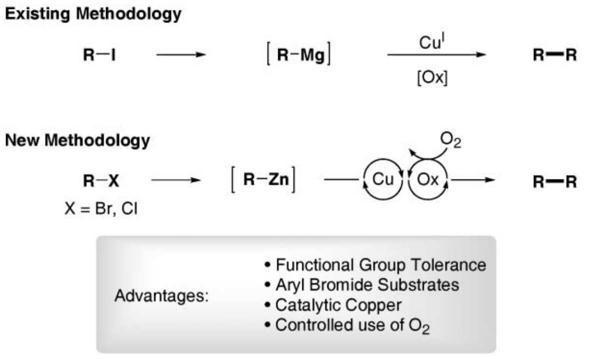
A wide range of organozinc substrates may be oxidized in the presence of catalytic copper to give carbon–carbon bonds in high yield.

There is a need for efficient and functional group tolerant methods for carbon–carbon bond formation, for example in biaryl synthesis.[1] Despite recent advances in palladium catalysis,[2] only copper-[3] and nickel-mediated Ullmann reactions have proved useful[4] for the closure of medium rings by the formation of a biaryl bond. A drawback of these methods is that they require the use of excess metal reagent and optimization of conditions for each substrate. Therefore, a general, efficient and functional group tolerant method is required for the synthesis of the biaryl-containing medium rings present in many ellagitannin, lignan and alkaloid natural products.[5]

Organocuprates, often used in conjugate addition, epoxide opening, halide displacement and carbocupration,[6] have a relatively high-lying HOMO, which means that carbon–carbon bond synthesis by organocuprate oxidation is a relatively easy process. The oxidation of lithium organocuprates[7,8] has been handicapped, however, by the poor functional group tolerance of the organolithium precursors. We have recently shown that the functional group tolerance can be improved somewhat by the use of magnesium organocuprates[9] made from organomagnesium halides by transmetallation at low temperature.[10] However, the method still suffers from the limitations of requiring electronically-activated aryl iodide precursors and a stoichiometric amount of copper(I) salt.

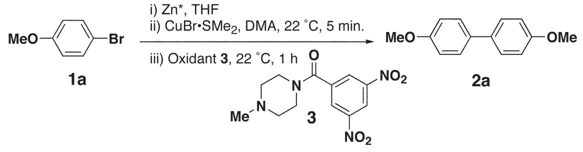
In the hope of overcoming these difficulties the use of organozinc halides in place of organomagnesium halides was investigated, a method not previously reported.[11] Organozinc reagents were appealing substrates for this chemistry because (a) they have improved functional group tolerance relative to aryl Grignard reagents,[12] (b) they undergo transmetallation readily with copper(I) salts,[13] and (c) there are a range of methods for their synthesis under very mild conditions (Scheme 1).[14] This last factor is highly significant, because it allows the use of aryl *bromides* as substrates, which are readily available and easier to synthesize than aryl iodides. For example, the application of highly active Rieke zinc (denoted Zn*),[14a] or cobalt-catalyzed insertion of zinc dust,[14b] allowed aryl zinc reagents to be generated from electronically activated and deactivated aryl bromides. Although there have been no previous investigations of the oxidation of zinc organocuprates, we discovered that on treating this aryl zinc reagent with copper(I) bromide in DMA[15] and subsequently oxidizing with dinitroarene **3** at room temperature (low temperatures were not required), an excellent yield of the biaryl could be obtained (Table 1, Entry 1).‡



Scheme 1 Conventional methodology and our new methodology.

The reaction can be catalyzed with copper, which has significant economic, purification and waste disposal advantages (Table 1). The diminution of the copper loading has not been possible starting from organolithium intermediates. However, in this case it proved feasible to reduce the amount of copper(I) salt used in these

Table 1 Initial optimization studies



Entry	Cu(I) [equiv.][a]	Oxidant **3** [equiv.]	Atmosphere	Isolated yield [%][b]
1	0.5	2.0	N_2	90
2	0.1	2.0	N_2	93
3[c]	0	2.0	N_2	20
4	0.1	1.0	N_2	85
5	0.1	0.2	N_2	68
6[c]	0.1	0	N_2	< 20
7	0.1	0.2	O_2	95
8[d]	0.1	0	O_2	81[d]
9[e]	0.1	0	Ar	trace
10[e]	0.1	0.2	Ar	< 20

[a] Equivalents are based on the starting material **1a** (0.5 mmol). [b] Yields obtained from chromatographic purification of the reaction mixtures (SiO_2; hexane : EtOAc, 8 : 1); average of two experiments. [c] Reaction left stirring for 12 h; major product was debrominated **1a**. [d] Phenolic products were also produced. [e] Residual gases removed from the DMA solution of ArZnBr by ten freeze–pump–thaw cycles backfilling with Ar. DMA = dimethylacetamide.

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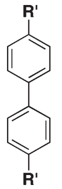
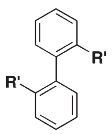
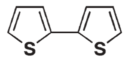
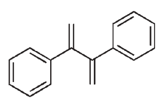
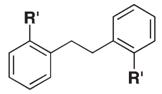
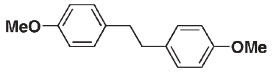
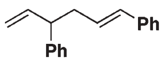
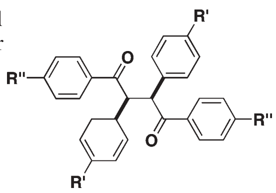
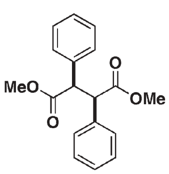
† Electronic supplementary information (ESI) available: Full experimental details, characterization and spectra of key compounds. See DOI: 10.1039/b610218b

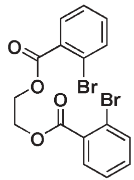
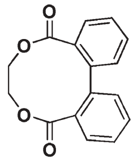
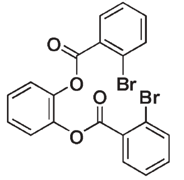
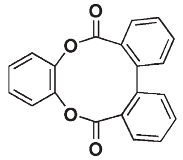
Table 2 Intermolecular catalytic zinc organocuprate oxidation[a]

$$\underset{\mathbf{1}}{\text{R–X}} \xrightarrow[\text{ii) CuBr•SMe}_2\text{, DMA, 22 °C, 5 min.; iii) Oxidant } \mathbf{3}\text{, 22 °C, 1 h}]{\text{i) Zn*, THF}} \underset{\mathbf{2}}{\text{R–R}}$$

Entry	X	Product (**2**)			Isolated yield [%]
a	Br		$R' = OMe$		95
b	Br		$R' = CO_2Et$		90
c	I		$R' = CO_2Et$		82
d	I		$R' = Br$		92
e	Br		$R' = CO_2Et$		86
f	Br		$R' = COMe$		87
g	Br		$R' = CH{=}CH_2$		84
h	Br		$R' = OCH_2CH{=}CH_2$		76
i	Br		$R' = CN$		90
j	Br				92
k	Br				86
l	Br		$R' = Br$		89
m	Br		$R' = CN$		95
n	Cl				85
o[b]	Br				67
p[c]	Cl		$R' = H$	$R'' = H$	90
q[d]	Br		$R' = Me$	$R'' = Cl$	95
r[e]	Br				92

[a] Conditions: Organozinc (1 equiv.), CuBr·SMe$_2$ (0.1 equiv.), **3** (0.25–0.5 equiv.). [b] Major isomer shown, isolated from cinnamyl bromide as a 16 : 5 : 1 mixture (92% combined yield). [c] Major diastereomer shown (10 : 1). [d] Major diastereomer shown, determined by crystallography (> 20 : 1). [e] Major diastereomer shown, determined by crystallography (5 : 1).

Table 3 Intramolecular catalytic zinc organocuprate oxidation[a]

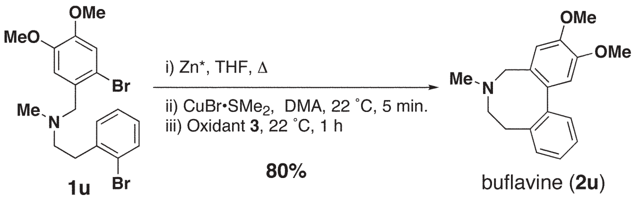
Entry	Substrate (**1**)	Product (**2**)	Isolated yield [%]
s			83
t			81

[a] Conditions: (i) Organozinc formation (1 equiv.); (ii) CuBr·SMe$_2$ (0.2 equiv.), DMA, 22 °C, 5 min; (iii) Oxidant **3** (0.5 equiv.), DMA, 22 °C, 1 h.

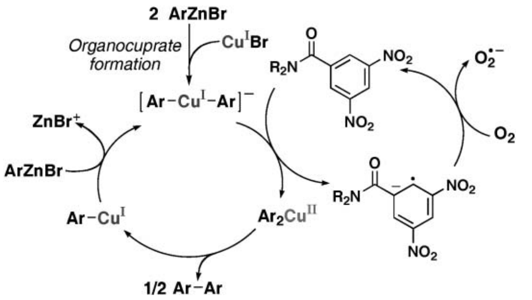
reactions to 0.1 equivalents (with respect to **1a**) with no decrease in isolated yield or apparent reaction rate.[16] We have previously found that substoichiometric oxidant can be successfully used to oxidise magnesium organocuprates.[9] Pleasingly, it was found that this was also possible in conjunction with aryl zinc halides in the catalytic copper system (0.2 equiv.), although the yield suffered slightly. The yield recovered if more oxidant was used,[17] or if an atmosphere of dry air or molecular oxygen was used above the reaction mixture. When an oxygen atmosphere was used without the arene oxidant present then significant quantities of phenolic products were produced. If the reaction mixture was rigorously degassed, then substoichiometric quantities of oxidant were ineffective. These results suggest that the radical anion of **3** is able to catalyze the reduction of molecular oxygen and avoid undesired products in such reactions (Table 1, Entry 7).

The scope of this reaction was investigated with other organozinc reagents. A generic reaction procedure with substoichiometric quantities of CuBr·SMe$_2$ and oxidant **3** was employed to generate a range of carbon–carbon bonds (Table 2). The methodology was found to be applicable to a wide range of aryl, heteroaryl, vinyl and benzyl bromides. Particularly noteworthy is the dimerization in the presence of ketones (Table 2, Entries f, p–q), a functional group that would not be compatible with arylmagnesium halides, even at low temperature. The range of substrates include mechanistic probes such as styrenes and *ortho*-hydroxyallyl substituents (Table 2, Entries g–h, k), which provide evidence against a simple radical termination mechanism. The diastereoselectivity for the racemic over *meso* products (Table 2, Entries p–r) was likely to be due to equilibration since the isolated ratios were similar to the thermodynamic ratios.§

The new methodology was used to forge biaryl bonds within a medium ring in high yields (Table 3). It should be noted that in these cases the acyclic substrates were aryl bromides rather than iodides. These are valuable results as attempted cyclization of aryl bromides in the presence of esters using the Ullmann reaction gave polymeric material.[18] The applicability of our methodology was illustrated by the total synthesis of buflavine, an *Amaryllidaceae* alkaloid with anti-serotonin properties (Scheme 2).[19] Buflavine



Scheme 2 Total synthesis of buflavine.



Scheme 3 Proposed catalytic cycle for oxidation of zinc diarylcuprates.

features a rare 5,6,7,8-tetrahydrobenzo[*c*,*e*]azocine skeleton consisting of a biaryl encompassed within an eight-membered *N*-heterocyclic ring and constitutes a challenging synthetic target. It has been synthesized previously by several groups,[20] but not by the most direct strategy of medium ring *and* biaryl formation in one step. Treatment of the acyclic aryl bromide with Rieke zinc under the standard conditions, followed by transmetallation to the intramolecular cuprate and oxidation provided an excellent yield of buflavine, the spectroscopic data of which matched that reported for the natural material.[19]

There have been several discussions on the mechanism of the stoichiometric organocuprate oxidation reaction.[7a,d] In order to account for the use of substoichiometric amounts of copper(I) and oxidant the catalytic cycle in Scheme 3 is proposed. Consistent with this mechanism is the finding that aryl zinc halides are not oxidised at an appreciable rate under the reaction conditions. Also, the inorganic residue that remained after catalytic organocuprate oxidation could be used successfully in subsequent reactions, suggesting that the copper salt is acting in a truly catalytic manner.

In summary, we have shown that zinc organocuprates may be oxidized to give a wide range of carbon–carbon bonds in high yield in the presence of electrophilic functional groups such as esters, nitriles and ketones. We have disclosed for the first time the use of copper and organic oxidant loadings well below the level of one equivalent for each carbon–carbon bond made and have presented a tentative catalytic cycle to explain these results. The new methodology was applied in the total synthesis of the *Amaryllidaceae* alkaloid buflavine, by concomitant biaryl bond (from aryl bromides) and medium ring formation. Taken together, these findings represent a significant advance and should herald greater use of organocuprate oxidation in synthesis. Ongoing studies in our laboratories are concerned with the expansion of the substrate scope beyond organic halides and with further application in the synthesis of natural products.

Notes and references

‡ *General procedure*: Aryl bromide (1.0 mmol) in THF (2 mL) was added to Rieke zinc (4 mL, 5 g/100 mL suspension in THF). After addition the reaction mixture was heated at reflux and then concentrated *in vacuo*. The aryl zinc was dissolved in DMA (4 mL) and transferred *via* cannula onto solid copper(I) bromide–dimethyl sulfide complex (20 mg, 0.1 mmol). Oxidant **3** (147 mg, 0.5 mmol) in DMA (2 mL) was then added and the solution was kept stirring for 1 h at room temperature. The reaction mixture was filtered through a plug of silica eluting with hexane and EtOAc. The filtrate was concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel.

§ CCDC 609161–609164. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b610218b

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