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Inter- and Intramolecular Biaryl Couplings *Via* Cyanocuprate Intermediates

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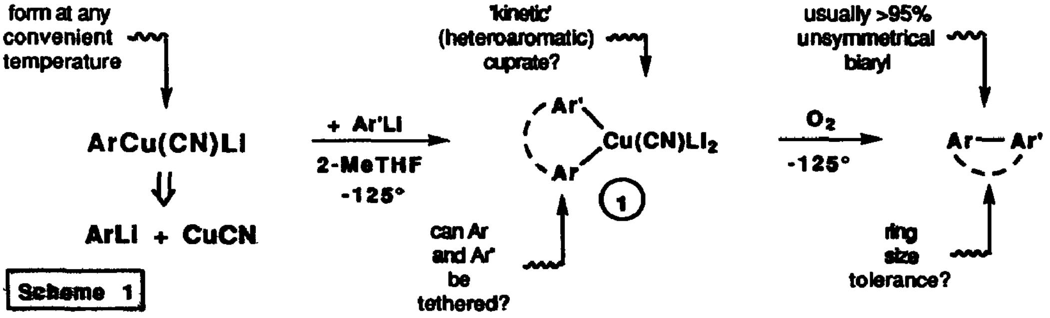
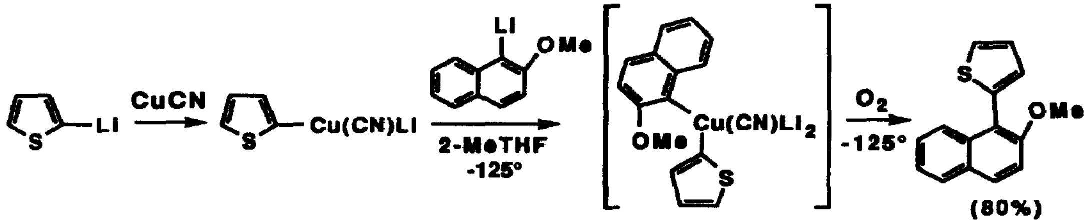
Summary. *Low temperature oxidations of selected higher order cyanocuprates composed of one or two heteroaromatic ligands can be oxidatively coupled in an inter- or intramolecular fashion to afford unsymmetrical biaryls. Non-heteroaromatic systems have also been studied in related intramolecular processes.*

In a series of recent reports,[1] we disclosed the concept of effecting unsymmetrical biaryl coupling reactions *via* kinetically prepared higher order (H.O.) mixed diarylcyanocuprates ($ArAr'Cu(CN)Li_2$, **1**, Scheme 1) which appear to proceed well only at very low temperatures. Products resulting from incorporation of various phenyl and naphthyl moieties include biphenyls, binaphthyls, and (substituted) phenylated naphthalenes. These can be arrived at by way of our standardized procedure,[1] which calls for the generation of **1** by addition of an aryllithium (Ar'Li) to a precooled solution of a lower order (L.O.) cyanocuprate, ArCu(CN)Li, followed by treatment of **1** with molecular oxygen. To further delineate the scope of these reactions, we have investigated the potential for one or both ligands (Ar, Ar') on copper in **1** to be of a heteroaromatic nature. In this *Letter*, we now describe our findings on these intermolecular cross-couplings, and demonstrate as well the first examples of the intramolecular variation on this theme.



Scheme 1

Attention was initially focussed on couplings between substituted thiophenes, since conjugated polythiophenes are of current interest as semiconductors, copolymers, etc.[2a] It was encouraging to find that a thienyl group could be attached to a naphthalene ring with the same levels of selectivity and yield normally observed in couplings between non-heteroaromatic ligands (Eq. 1).[1] In extending this scheme to dissimilarly substituted thiophenes[2b] (entries 1-3, Table 1), including a dithiophene case (entry 4), results were found to be mixed. Thus, when the 'cuprate in a bottle' (*i.e.*, commercially available ThCu(CN)Li; **2**, R = H)[3] was treated with 2-lithio-5-methylthiophene or the 5-benzyl analog, a good-to-excellent selectivity was realized (entries 1,3). Unfortunately, seemingly minor changes in going to the 5-ethyl case (entry 2), as well as using a 2-lithiated dithiophene (entry 4) did not afford synthetically useful levels of unsymmetrical biaryls **3**. Employing a 2-lithio-5-methylthiophene and the same 2-lithiated dithiophene, however, raised this otherwise statistical ratio to the 1:6:1 level (entry 5).



(Eq. 1)

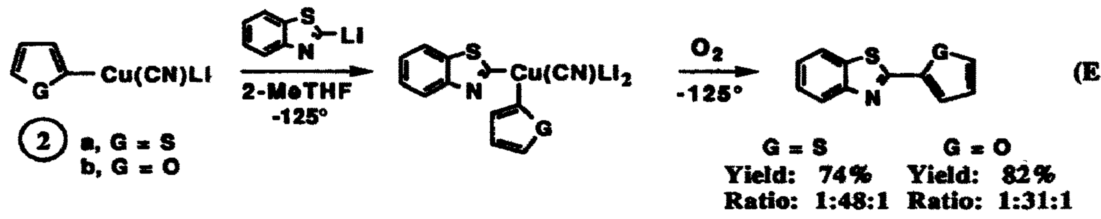
Table 1. Biaryl couplings of (substituted) thienyl H.O. cyanocuprates

Entry	R	R'	Ratio[a]	Yield (%)[b]
1	H	5-Me	3 : 16 : 1	97
2	H	5-Et	1 : 2 : 1	90
3	H	5-Bn	1 : 48 : 1	92
4	H	5-Th	1 : 2 : 1	90
5	5-Me	5-Th	1 : 6 : 1	87

[a]Ratio corresponds to Th(R)-Th(R) : Th(R)-Th(R') : Th(R')-Th(R'). [b]Isolated, overall yields.

Upon switching to a synthetically versatile benzthiazole ligand, together with the lower order cyanocuprate **2** (R = H), 96% of the product mix corresponded to the cross-coupled biaryl (Eq. 2). Replacing the thiophene residue with its oxygen analog (*i.e.*, a furan ligand) gave a similar ratio and a somewhat better isolated yield.

Couplings under these controlled conditions in the bipyridyl series were unexpectedly random. In no case using, *e.g.*, 2-lithiopyridine with a (substituted) 2-lithiopyridine, was the desired unsymmetrical bipyridyl even the major product. Surprisingly as well, lithiation at the 3-position, where opportunities for chelation *via*



② a, G = S
b, G = O

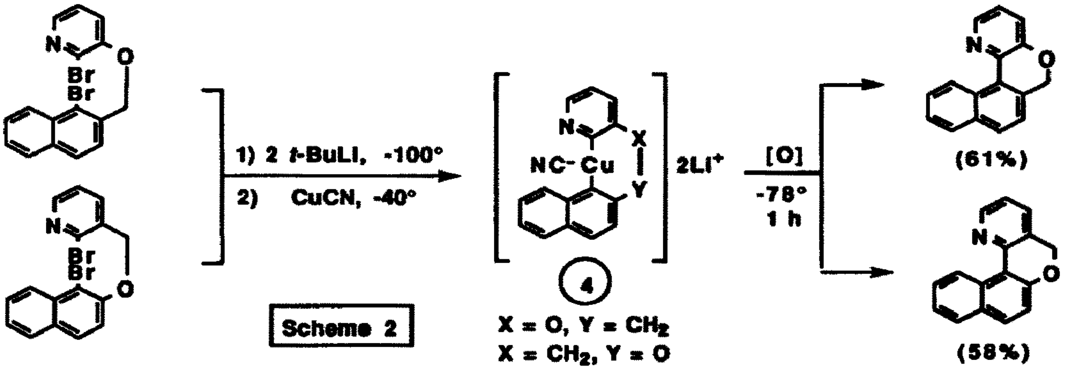
(Eq. 2)

G = S Yield: 74% Ratio: 1:48:1

G = O Yield: 82% Ratio: 1:31:1

nitrogen in the cuprate are considerably reduced did not improve the outcome. Using only one pyridyl ligand in the cuprate, rather than two, along with a simple *ortho*-anisyl group, still led to a limited degree of selectivity. This latter observation points to the overriding influence exerted by the pyridyl moiety in perturbing the normally highly ordered mode of H.O. kinetic cuprate behavior toward oxidation.[1]

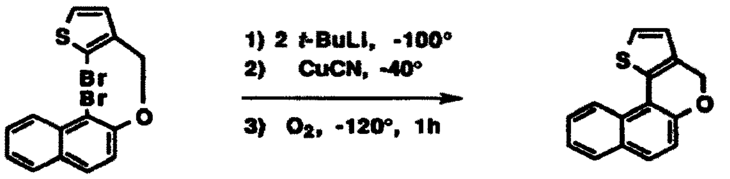
The corresponding *intra*molecular variant was far more consistent and rewarding. Treatment of either 2-bromopyridine below, each tethered to a 1-bromonaphthalene derivative, with two equivalents of *t*-BuLi at low temperature followed by introduction of CuCN leads to a homogeneous solution upon warming to -40°. Oxidation of presumed intermediate cuprates 4 at -78° (or up to 0°) afforded the desired biaryls, as shown in Scheme 2.



Scheme 2

④
X = O, Y = CH$_2$
X = CH$_2$, Y = O

Similar treatment of the thienyl analog 5 likewise led to a tetracyclic product bearing the biaryl unit in good isolated yield (Eq. 3).

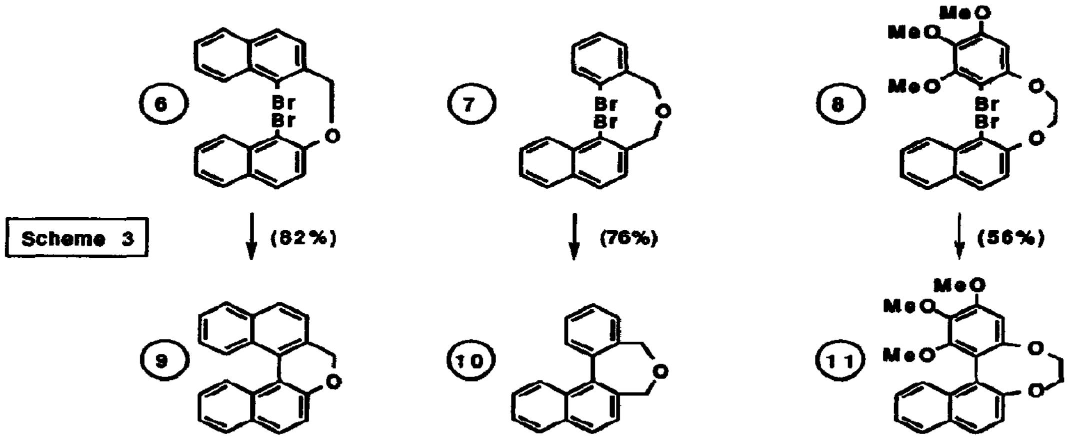


⑤

(72%)

(Eq. 3)

Finally, it should be noted that the facility with which these intramolecular couplings occur provides strong justification for applying these concepts to targets containing biaryl systems that involve issues of atropisomerism (*e.g.*, in natural products of current interest such as the ellagitannins[4a] and michellamines,[4b] and with regard to biaryl-based reagents which induce chirality such as binaphthyl derivatives BINAP, BINAL-H, etc.[4c]). As test cases, two, three, and four-atom-tethered educts **6**-**8** could be converted to tetracycles **9**-**11** under our standard cuprate formation/oxidation conditions in good yields (Scheme 3). These early data suggest that this cuprate-mediated sequence is clearly superior to a traditional Ullmann approach,[5,6] and may be quite competitive with Heck/Stille type couplings based on Pd(II) reagents.[6] Further extension of this methodology to related systems using appropriate *nonracemic* tethers will be reported in due course.



Scheme 3

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References and Notes

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