Tetrahedron Vol. 48, No. 13, pp. 2579-2588, 1992
Printed in Great Britain

0040-4020/92 $3.00+.00

CONTROLLED 'DECOMPOSITION' OF "KINETIC" HIGHER ORDER CYANOCUPRATES: A NEW ROUTE TO UNSYMMETRICAL BIARYLS#

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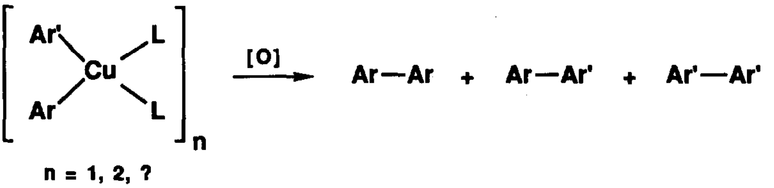
Abstract. By controlling two key reaction parameters (temperature and mode of formation), unprecedented "kinetic" higher order cyanocuprates can be generated. Under oxidative conditions, their chemistry is unique when compared with constitutionally identical reagents formulated in the usual manner. Employing mixed diaryl reagents ArAr'Cu(CN)Li_2, prepared from ArLi, Ar'Li, and CuCN, unsymmetrical biaryls (Ar-Ar') can be realized with remarkable selectivity, in high chemical yields, and in a predictable fashion.

The reviews were not encouraging.[1] In fact, even the thought of forming unsymmetrical biaryls *via* oxidative "decomposition" of an organocuprate is contrary to most other current methods of forming this valued functional group array.[1b] Usually, the mode of attachment calls for coupling of an electron-rich aryl component with an electron-deficient partner; thus, a substrate combined with a reagent affords a product. By invoking a cuprate such as **1**, however, the origin of which involves two different aryllithiums (ArLi, Ar'Li) together with a Cu(I) salt (*e.g.*, CuCN),[2] the substrate is the reagent...and *vice versa*. Here, two distinctly *anionic* species are coming together to result in one, two-electron carbon-carbon bond. It's a nice concept, but reducing it to practice is another matter. Sure, there are a few scattered

$$\mathrm{ArLi + Ar'Li + CuCN \longrightarrow \underset{\boxed{1}}{Ar(Ar')Cu(CN)Li_2} \xrightarrow[?]{[O]} Ar{-}Ar'}$$

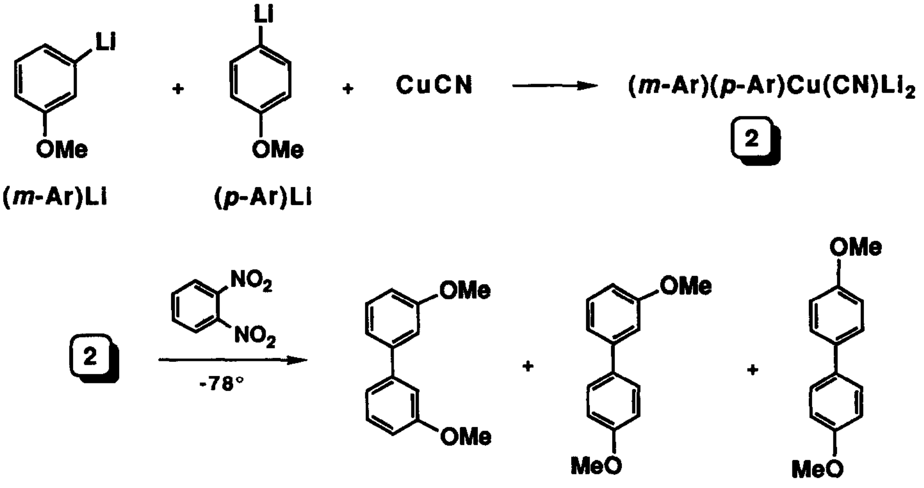
reports of successful reactions along these lines,[3] but one skilled in synthetic chemistry is not likely to advance such a scenario with enthusiasm in anticipation of any meaningful level of success. Why not? Because the expected outcome from oxidative treatment of dimeric, mixed diaryl cuprates[4] is a potpourri of products consisting of (in addition to by-products) usually three biaryls formed in highly variable yields with little to no selectivity and no obvious means of predicting this ratio (Eq. 1).[3]



(Eq. 1)

And so it was with little more than the recognition of this problem that we began this project. Our rationale for attack was not exactly scientifically based; we simply relied on our experience in organocopper chemistry to guide us, and an appreciation for the potential payoff should we realize our goals.

The first order of business was to insure, from the synthetic perspective, that the baseline for our departure was accurately portrayed by the reviews.[1] Accordingly, we prepared pure, crystalline *meta*- and *para*-anisyllithium,[5] and together with CuCN in a 1:1:1 relationship, formed the corresponding mixed diaryl higher order (H.O.) cyanocuprate, **2**, in THF. Exposure of **2** to *ortho*-dinitrobenzene[6] as oxidant at -78° indeed led to an uninteresting gemisch of biaryls (Scheme 1).



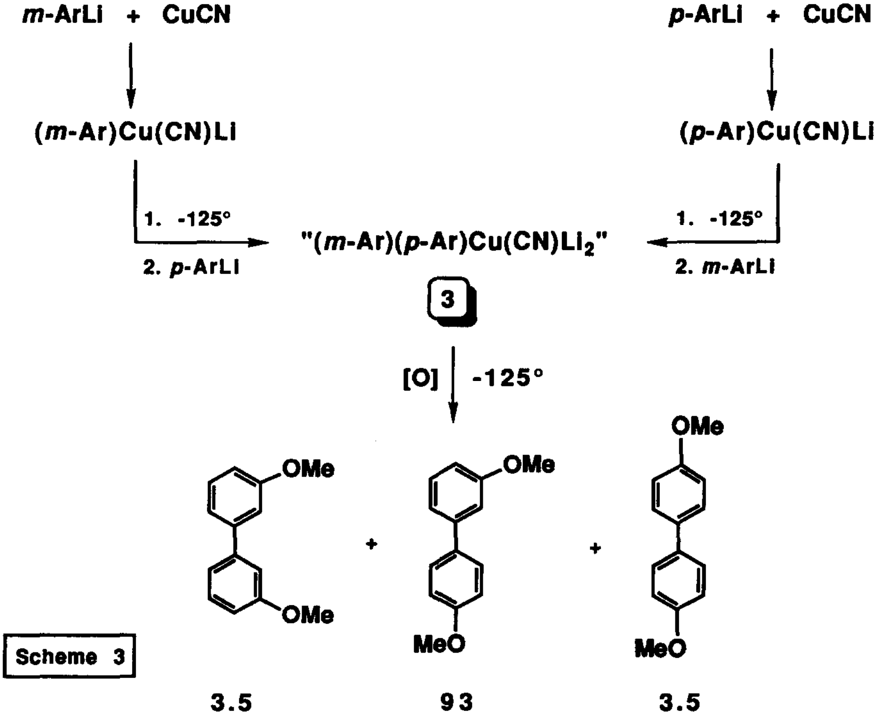
Scheme 1 Ratio: 1 2 1

In considering alternatives for enhancement of the percent Ar-Ar' obtained, we reasoned that two (among several) reaction parameters might play a pivotal role, either individually or collectively. Thus, attention was focussed on (1) temperature, perhaps an obvious choice, and (2) the mode of cuprate formation, a far more subtle variable. The former was easily checked. Preparation of **2** in the usual manner (*cf.* Scheme 1) substituting 2-methyltetrahydrofuran (2-methyl THF)[7] for THF, followed by cooling from -78 to -125° and then oxidation provided a quick answer to the question of temperature alone: it had no effect (Scheme 2).

$\boxed{2} \xrightarrow[-125^\circ]{[O]}$ *m*-Ar—Ar-*p*   *m*-Ar—Ar-*p*   *p*-Ar—Ar-*p*

Scheme 2   Ratio: 1   2   1

But the experiment which addressed the second variable; *i.e.*, the manner in which cuprate **2** is formed, was most enlightening. By preforming a *lower* order cyanocuprate[8] (*m*-Ar)Cu(CN)Li in 2-methyl THF as solvent, pre-cooling this solution to -125° and then introducing *p*-ArLi followed by oxidation at this lower temperature, 93% of the biaryl mix produced was the unsymmetrically coupled product (Scheme 3)! Moreover, reversal of the



Scheme 3

order of operations regarding the aryllithium precursors [*i.e.*, adding *m*-ArLi to (*p*-Ar)Cu(CN)Li], gave identical results.

Ostensibly, cuprate **3** is no different from reagent **2**, at least insofar as stoichiometry is concerned. But the combination of temperature *and* sequence of ligand addition to copper appears to allow for maintenance of the initial positioning of the aryl groups in the organometallic complex. **In essence, we had discovered "kinetic" cuprates.**

Further evidence of this phenomenon was sought, and experiments aimed at testing the structural integrity of such species were carried out. Most significantly, simply warming the kinetically prepared cuprate **3** to -78° for a few minutes prior to recooling to -125° and oxidation now afforded the previously noted 1:2:1 ratio (*cf.* Scheme 1). The ratios realized from reactions run at intermediate temperatures between -78° and -125°, namely at -88°, -105° and -113° gave less impressive percentages of the desired unsymmetrical biaryl (Figure 1). Most unexpectedly, however, a plot of the data from these five experiments revealed an astonishing linear correlation between the % biaryl and the temperature of cuprate formation / oxidation! Such predictive power in cuprate chemistry is virtually nonexistent, yet there was no refuting the data obtained under this standardized set of conditions using the straightforward experimental setup shown schematically in Figure 2.

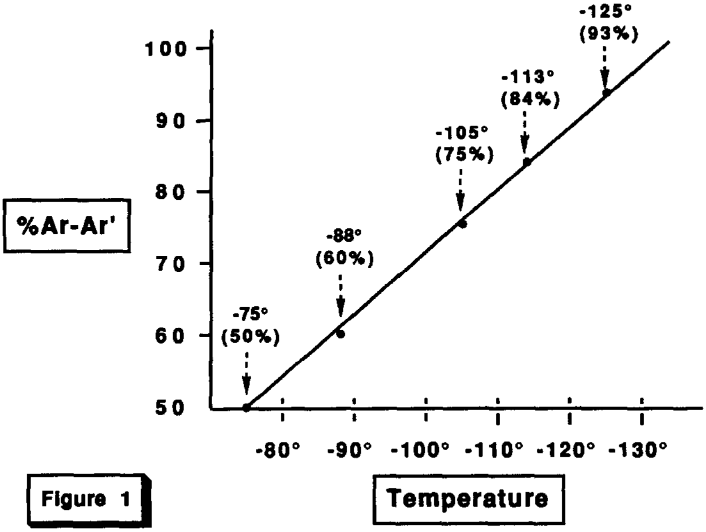


Figure 1

Although tempted to declare the problem 'solved', we proceeded with cautious optimism since one example does not make for generality. Might an alkoxy-substituted system be a special case which we just happened to choose initially? Questions regarding the roles of both stereoelectronic as well as steric factors sobered us further, and it would be some time before another major issue would be resolved: the yield.

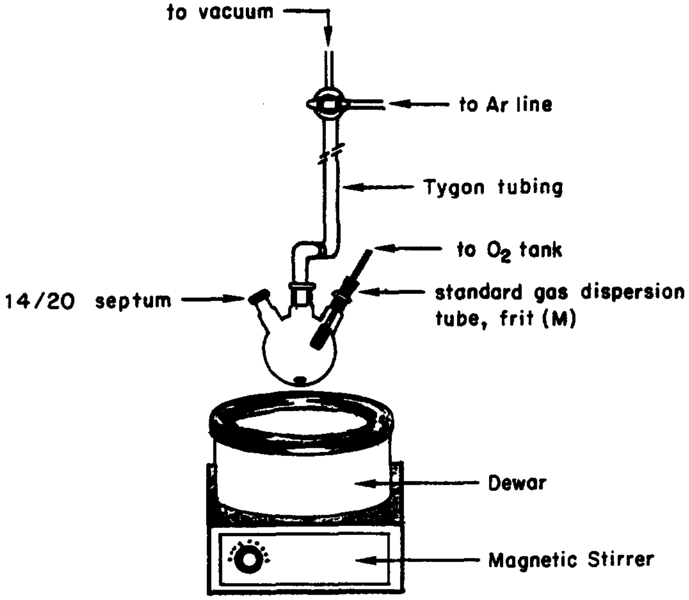


Figure 2. Experimental setup for low temperature oxidations of mixed diaryl cyanocuprates.

Fortunately, the problem of efficiency was more one of conversion than of by-product occurrence. By switching to ground state molecular oxygen ($^3O_2$) gas as oxidant and employing N,N,N',N'-tetramethylethylenediamine (TMEDA) in the pot, our 50-60% consumption of starting material rose to levels approaching 100%, with isolated yields of product routinely in the 80-90% category (*vide infra*). Just why or how this additive performs this feat remains an intriguing open question.

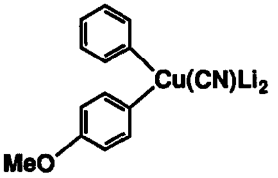
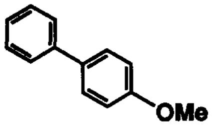
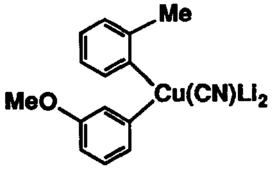
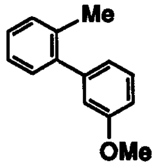
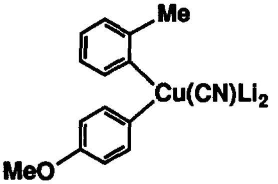
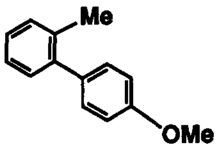
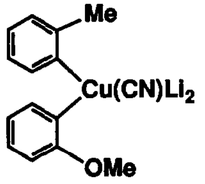
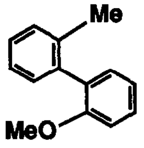
The impact of steric effects was examined next, most readily utilizing *ortho*-anisyllithium and *ortho*-toluyllithium, coupling either with other aryl ligands and, in what should be a far more demanding case, with each other. As illustrated in Table I, the bottom line appears to be that sterics are not major factors in these couplings (*e.g.*, see entry 4), although doubly *ortho*-substituted lithiated benzenes have not as yet been examined.

Turning our attention to stereoelectronic concerns, we immediately opted to test fluorine-containing systems, for although our experience in organofluorine chemistry was not extensive, it quickly taught us the vagaries of experimental work surrounding this element. As a trial example, fluoro iodide 4[9] was lithiated and added to preformed PhCu(CN)Li at -125° and the resulting solution oxidized. The result: no change in ratio, no change in yield (Scheme 4). To push this coupling still further, recalling that a cuprate derived from two electron-rich aryllithiums readily participates (*vide supra*), we wondered whether an example at the opposite end of the spectrum would do likewise. Metal-halogen exchange on both 4 and

5,[9] therefore, was effected and the resulting organolithiums put through the usual paces. The outcome: the same (Scheme 5).

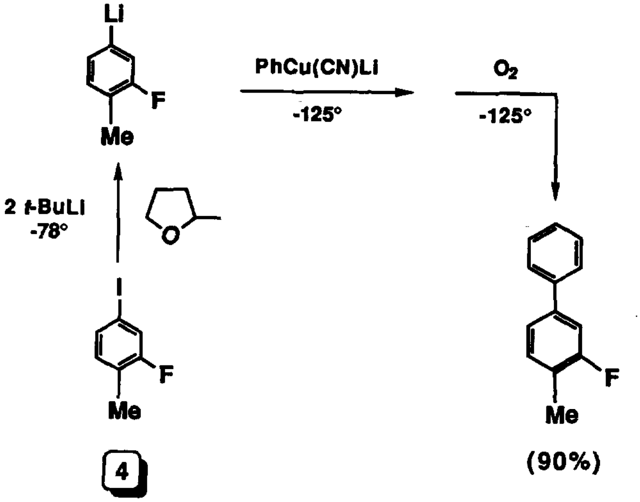
Things were looking up. Way up. It was time to expand; time to consider aromatics other than monocyclic benzenes. Should naphthalenes be next, or bipyridines? What about 5-membered heteroaromatic rings,[10] an obvious overlap with our program in cyclopeptide alkaloid total synthesis utilizing oxazoles,[11] imidazoles,[12] and isoxazoles.[13] To date, we have

Table I. Oxygen-mediated biaryl couplings of kinetically generated, mixed diaryl H.O. cyanocuprates at -125° in 2-methyltetrahydrofuran.

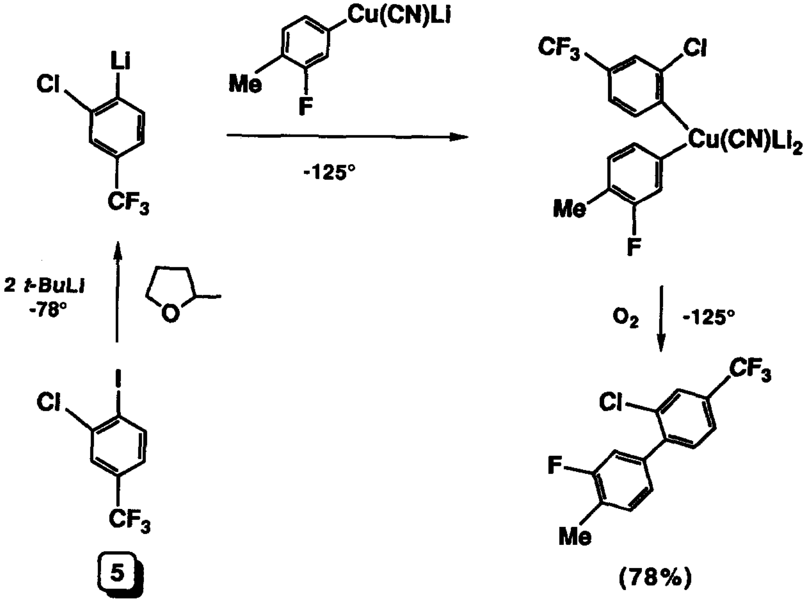
Entry	Cuprate	Coupling Product	Yield(%)
1			82
2			84
3			83
4			81

looked, albeit to a very limited degree, into a few of these combinations, and as startling as were our initial observations on these well-behaved reagents (*cf.* Fig. 1), so has been the finding that *all* of the aromatic moieties tested thus far appear to subscribe to our protocol for unsymmetrical coupling *via* the intermediacy of kinetic H.O. cuprates. Thus, as shown in Table II, naphthalenes can be linked to a substituted benzene ring (entry 1) or to another

Scheme 4

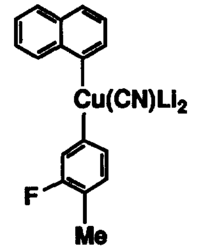
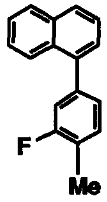
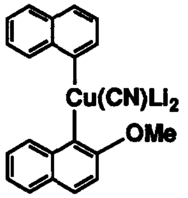
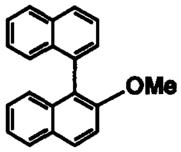
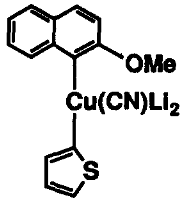
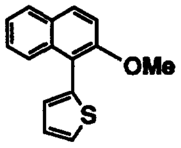


Scheme 5



naphthalene (entry 2), and a heteroaromatic thiophene nucleus has been affixed to a protected 2-naphthol at the more hindered 1-position (entry 3).[14]

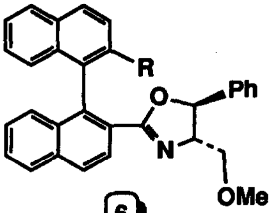
Table II. Biaryl couplings of kinetic cyanocuprates containing ligands other than of the monocyclic, benzene-type.

Entry	Cuprate	Coupling Product	Yield(%)
1			76
2			80
3			80

So what is it about "kinetic" H.O. cyanocuprates that allows us to construct such unsymmetrical biaryl skeleta, in many cases, on the order of *ca.* 400° below traditional Ullmann couplings?[15] Why is the corresponding chemistry with reagents derived from CuI quite different?[16] What mechanistic pathway(s) prevails during the oxidation of these Cu(I) dianions? Are there truly unique structural features associated with *aryl* H.O. cyanocuprates, or can other types of ligands (*e.g.*, vinylic, acetylenic, etc.) be utilized?

As is so often the case with organometallic intermediates, especially when there is an element of sensitivity to handling involved, we must await further experimentation, oftentimes such questions requiring a time frame on the order of decades before a grasp on these details can be claimed. At this point, the synthetic front will continue to advance, perhaps soon arriving at, *e.g.*, a route to chiral, non-racemic binaphthyls complimentary to that of Meyers'

oxazoline route (*via* 6)[17]. Potentially, a trivial entry to Noyori's 2,2'-disubstituted 1,1'-binaphthyl derivatives (7 and 8),[18] which have been developed and applied with stunning success,[19] is within reach. For now, at least, we're on a roll.[20]



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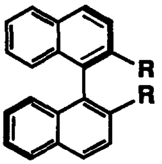
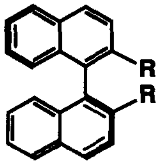


7 (R)



8 (S)

Acknowledgement. Financial support provided by the National Science Foundation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Swiss National Science Foundation (post-doctoral fellowship to K.S.) is gratefully acknowledged.

References and Notes

 # This contribution is dedicated to Professor Harry H. Wasserman on behalf of *all* Wasserman students, past and present, with warmest congratulations, respect, and admiration, on the occasion of his 70th birthday.

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16. Interestingly, quite different results are obtained when CuI is used in place of CuCN (thus forming lower order or Gilman-like cuprates, R_2CuLi) to effect these types of unsymmetrical biaryl couplings. The implications of such observations are the focus of an ongoing study, the results from which will be reported in due course.

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