

Downsizing Copper in Modern Cuprate Couplings

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“This is very nice chemistry, but when it’s over, what do you do with all the copper?” This was the question posed to me by Seeman Pines, then the Executive Director of Process Research at Merck in Rahway, well over a decade ago, just after I had given a seminar there on our group’s “best unpublished stuff”. My answer was far less than satisfying: “I don’t know, Seeman. Can’t you guys tell me how to deal with it?” To which he replied, “No, and that’s why we cannot use your chemistry”.

This striking commentary, permanently imprinted on my mind, convinced me in this less than 30 s exchange that the cost of waste disposal for copper is one of, if not the, major factor insofar as its use in industry is concerned. Notwithstanding this “wake-up call”, it would be years before the message came back to haunt me. All along though, I knew that Seeman was right; that it was time to start thinking about novel ways of getting the copper out of organocuprate chemistry. Not entirely out, of course, but to an extent that would propel methodology based on copper(I) into the 1990s, in step with the times that for most other metals are now screaming “catalysis”.

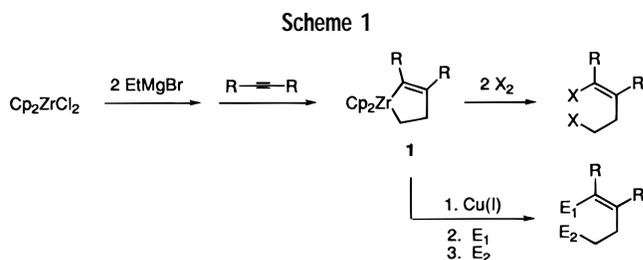
A shift away from processes relying on stoichiometric copper was far from a novel concept. Indeed, the very origins of the field trace back to Kharash, who in 1941 added catalytic amounts of CuCl to an excess of a Grignard reagent (MeMgBr) so as to effect conjugate addition of an alkyl moiety to an enone (isophorone).¹ But effecting similar chemistry within the context of more recent developments in this field, such as with functionalized cuprates or ligand exchanges between dissimilar organometallics... well, these are challenges for today. Fortunately, both my NSF and NIH grants were renewed and, hence, it seemed like we would actually be afforded the opportunity to make contributions that would hopefully be deemed palatable from both a chemical and environmental perspective.

Professor Bruce H. Lipshutz (born in New York City, December 1951) was introduced to organic chemistry by Howard Alper, with whom he worked as an undergraduate at SUNY at Binghamton (B.A. 1973). After taking a Ph.D. from Yale (1977) with Harry Wasserman, 2 years were spent as part of the maytansine contingent at Harvard working with E. J. Corey. He joined the faculty at UCSB in 1979. He has recently served as Chair on the international meeting OMCOS 8 (in Santa Barbara, 1995) and currently is co-editing (with T.-Y. Luh) a *Tetrahedron* Symposium-in-Print on organonickel chemistry. Much of his time, however, is now devoted to serving (for 4 years!) as a recent addition to the NIH Med Chem A study section. He directs a group of very active co-workers interested in developing new reagents and synthetic methods, many of which are in the organometallic area. Applications to targets being pursued in the group at this time include the polyene macrolide antibiotics, retinoids, michelamine B, BINOL and BINAP analogues, coenzyme Q, and polyacetylenes as NLO materials.

Cu(I) Salts vs Cuprates as Catalysts

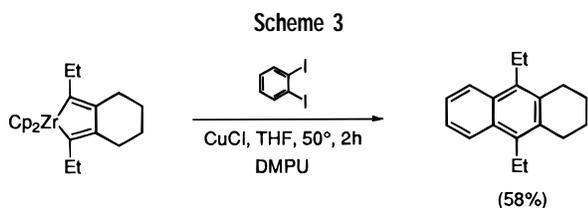
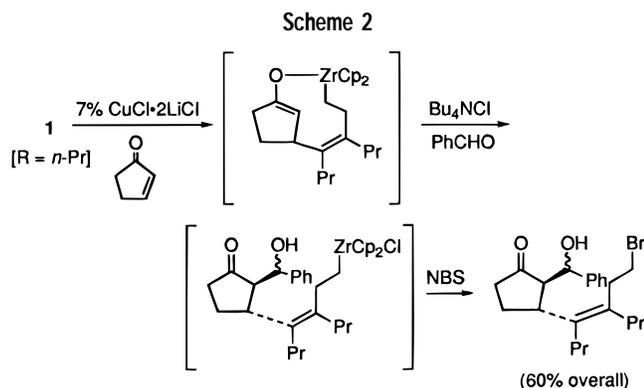
Zirconacyclopentenes. A few years ago, I had several opportunities to hear excellent lectures by some leading American authorities on zirconocene chemistry. As contributions mainly from the laboratories of Negishi² and Buchwald,³ among others from abroad,^{4,5} began to accrue, I could not help but wonder about the potential for transmetalations of intermediate zirconacyclopentenes. Their in situ generation and subsequent use in synthesis had reached the stage that the time seemed right to “jump in”. The immediate impetus behind this decision was a talk by Buchwald given at a meeting in Bristol in 1992, where zirconacyclopentenes were quenched with halogen to afford dihalo-containing products at both the sp²- and sp³-like carbons bearing the metal. After the seminar I asked Steve about the prospects for selective halogenation, or even better, site-specific transmetalation and further C–C bond constructions (Scheme 1). Such chemistry was not known at the time, and I suggested that copper should effect the desired transformation, given the facility with which vinyl zirconocenes exchange ligands with cyanocuprates (i.e., –78 °C in minutes).⁶ From the discussion it was clear that work on such a proposal, if pursued, was going to be done in Santa Barbara.

Soon after I had “gone on the record” regarding the prospects for some form of copper(I) to enhance the already well-established virtues of zirconacyclopentenes,⁷ we were fortunate to welcome into the group a talented postdoctoral co-worker from Kanazawa University, Masahito (Masa) Segi. Masa and I immediately began our search for the Cu(I) species best suited to effect transmetalation. Naturally, we went right to the “higher order” (HO) cuprate Me₂Cu(CN)Li₂, given the success witnessed previously by Edmund Ellsworth in the group using this



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- (1) Kharasch, M. S.; Tawney, P. O. *J. Am. Chem. Soc.* **1941**, *63*, 2308.
- (2) Negishi, E.; Maye, J. P.; Chouei, D. *Tetrahedron* **1995**, *51*, 4447.
- (3) Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829. Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336.
- (4) de Rege, F. M. G.; Buchwald, S. L. *Tetrahedron* **1995**, *51*, 4291.
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- (6) Luker, T.; Whitby, R. J. *Tetrahedron Lett.* **1994**, *35*, 785.
- (7) Mori, M.; Uesaka, N.; Shibasaki, M. *J. Org. Chem.* **1992**, *57*, 3519.
- (8) Suzuki, N.; Kondakov, D. Y.; Kageyama, M.; Kotoru, M.; Hara, R.; Takahashi, T. *Tetrahedron* **1995**, *51*, 4519.
- (9) Lipshutz, B. H.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 7440.
- (10) Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124. Negishi, E. In *Comprehensive Organic Synthesis*; Paquette, L. A., Ed.; Pergamon Press: New York, 1991; Vol. 5, p 1163. Negishi, E. *Chim. Scripta* **1989**, *29*, 457. Negishi, E.; Takahashi, T. *Rev. Heteroatom Chem.* **1992**, *6*, 177. Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047.



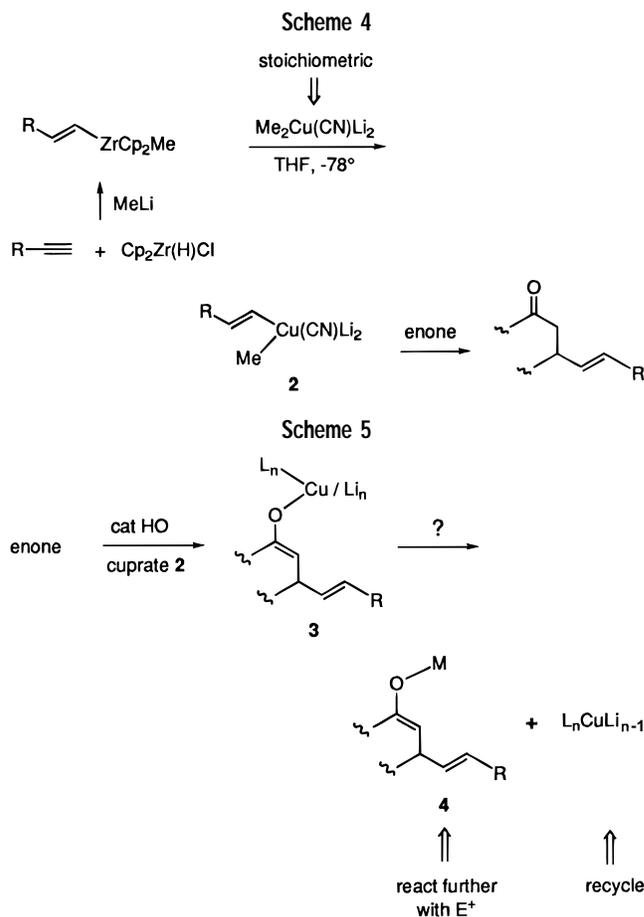
specific reagent with vinyl zirconocenes.⁶ It didn't take Masa long to conclude that what had worked for Ellsworth was *not* applicable to his cyclic analogues. But Masa persevered: mixed cuprates, Gilman cuprates, lower order cyanocuprates. . . no luck. Perhaps a copper salt would do something, but which one and how much of it? Logical candidates, including THF-solubilized halides of copper(I), CuCN, and CuOTf, were all screened, and sure enough, in the presence of an enone, 1,4-adducts could be realized. Optimum results were obtained with 7 mol % CuCl, and using this least expensive of the copper halides, a remarkable sequence of reactions was ultimately uncovered.⁸ As predicted, the vinyl–Zr bond reacts selectively, and the presumed halocuprate then transfers the vinyl moiety to a Michael acceptor. Both the resulting enolate and the sp^3 carbon which remains attached to ZrCp_2Cl are subject to further elaboration using different electrophiles. Thus, not only could the initial 1,4-adduct enolate in a three-component sense be coupled with an aldehyde or halide, but the pendant zirconocene could be quenched with halogen, all in one pot (Scheme 2).

While this project was underway, it was apparent that we were not alone in our quest for selective transmetalations/C–C bond-forming trappings of vinyl zirconocenes mediated by copper(I). In particular, Takahashi and co-workers described the coupling of vinylzirconocenes, derived from intermediates **1**, with allylic chlorides using 10 mol % $\text{CuCN}\cdot 2\text{LiCl}$.⁹ More recently, this group has used CuCl, albeit stoichiometrically, to induce a cycloaddition between electron-deficient dienophiles and unsymmetrically substituted zirconacyclopentadienes, leading to highly substituted benzene rings (Scheme 3).¹⁰

(8) Lipshutz, B. H.; Segi, M. *Tetrahedron* **1995**, *51*, 4407.

(9) Takahashi, T.; Aoyagi, K.; Hara, R.; Suzuki, N. *J. Chem. Soc., Chem. Commun.* **1993**, 1042; *Chem. Lett.* **1992**, 1693. Takahashi, T.; Aoyagi, K.; Kondakov, D. Y. *J. Chem. Soc., Chem. Commun.* **1994**, 747. Aoyagi, K.; Kasai, K.; Kondakov, D. Y.; Hara, R.; Suzuki, N.; Takahashi, T. *Inorg. Chem. Acta* **1994**, *220*, 319.

(10) Takahashi, T.; Hara, R.; Nishihara, Y.; Kotora, M. *J. Am. Chem. Soc.* **1996**, *118*, 5154.



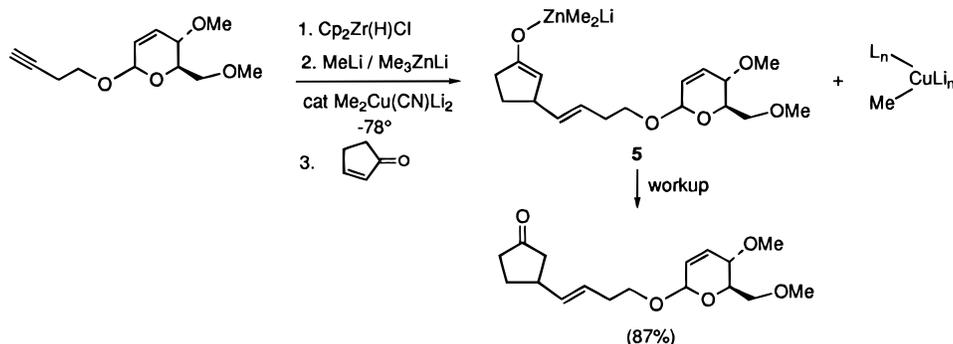
Vinyl- and Alkylzirconocenes

In the original contribution by Ellsworth, it was shown that products of terminal alkyne hydrozirconation (i.e., (*E*)-vinylzirconocenes) transmetalate to copper at -78°C , a process which requires a *stoichiometric* amount of $\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2$ (Scheme 4).^{6,11} Assigned to Mike Wood, another in a long line of outstanding graduate students trained, like Ellsworth, by Dave Ball at Cal State, Chico, was the task of “getting the copper out” of this transmetalation/1,4-addition sequence. The “trick” yet to be discovered was to somehow provide a species that would react with the initially formed copper/lithium enolate **3** so as to free the copper for re-entry into the catalytic cycle (Scheme 5). Clearly, the best species, in principle, is MeLi, needed in stoichiometric quantities, since this might regenerate $\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2$ and afford regioselectively a lithium enolate (**4**, $\text{M} = \text{Li}$) capable of even further elaboration. But MeLi was not an option, since the enone would never tolerate its presence. So the question became: what looks like MeLi to the enolate, but lacks interest in an enone? The answer came in the form of a “softened” MeLi; that is, have it occupied with Me_2Zn as zincate Me_3ZnLi . On thermodynamic grounds this equilibrium made sense, since a favorable O–Zn bond would result via transfer of “MeLi” from Me_3ZnLi to the copper/lithium enolate. Thus, the zincate would “shuttle” the MeLi to the required site, yet hopefully not compete for enone by adding either 1,2- or 1,4- to the educt.¹² What allows this process (e.g., Scheme 6) to occur with only

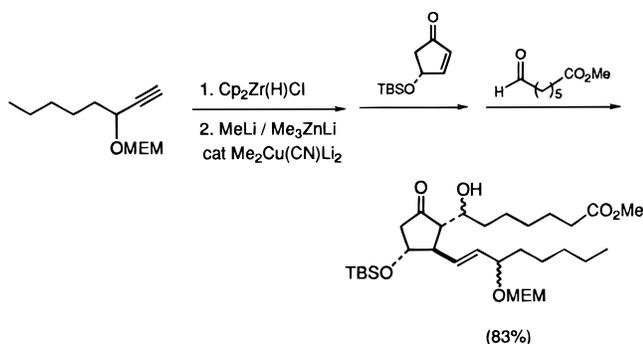
(11) Lipshutz, B. H.; Keil, R. *J. Am. Chem. Soc.* **1992**, *114*, 7919.

(12) Lipshutz, B. H.; Wood, M. R. *J. Am. Chem. Soc.* **1993**, *115*, 12625.

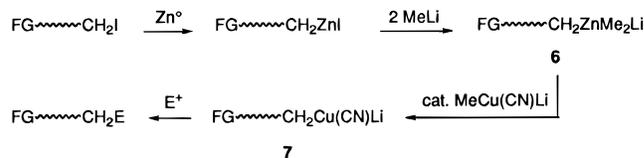
Scheme 6



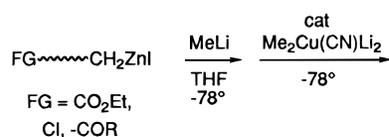
Scheme 7



Scheme 8



Scheme 9

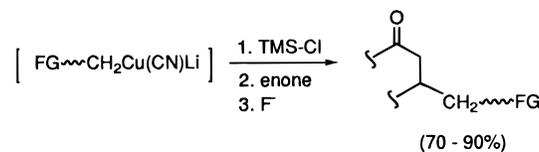


5–10 mol % $\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2$ is the ability to effect the sequence at -78°C . Had this not been so, the Me_3ZnLi might begin to compete as a Michael donor for the enone,¹³ thereby negating the otherwise desirable chemoselective properties of this *ate* complex.

Once the generality of this copper-catalyzed event had been established, the potential for the zinc enolate to complete what is commonly referred to as a “three-component coupling”¹⁴ was quickly recognized. Since this was normally viewed within the context of prostanoid synthesis,¹⁵ Mike focused on preparing the prostaglandin nucleus via this strategy. In time, he was able to fine-tune the stitching to produce several useful PG systems, although best results tended to require somewhat higher percentages (ca. 15–20%) of cuprate (Scheme 7). An extensive NMR study¹⁶ which identified the major species presumed to be involved at each step was also performed by Mike in short order. It indicated that the key intermediate responsible for the second coupling is likely to be a zinc enolate (e.g., 5).

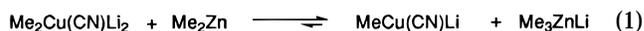
Transmetalations of Mixed Zincates

1,4-Additions of Functionalized Reagents. The ease with which zincates transmetalate enolates derived from cuprate 1,4-additions brought to light the intriguing possibility that the zincate could consist of different ligands. That is, rather than relying on zirconium reagents, a mixed

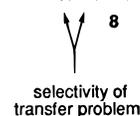


zincate formed from an alkyl iodide and 2MeLi, thus possessing two methyl groups and a third ligand R_T (in $\text{Me}_2\text{ZnR}_T\text{Li}$) should exchange R_T for Me on copper, which ultimately gets transferred to a substrate (Scheme 8). This notion combines our copper-catalyzed transmetalation sequence¹² with functionalized zinc reagents popularized by Knochel¹⁷ and Rieke.¹⁸

Although the idea had merit, we knew that it would not be a trivial exercise since Mike’s spectroscopic study¹⁶ had shown that a higher order cyanocuprate combined with a dialkylzinc completely favors a zincate and lower order cyanocuprate (eq 1). Thus, we were faced with the

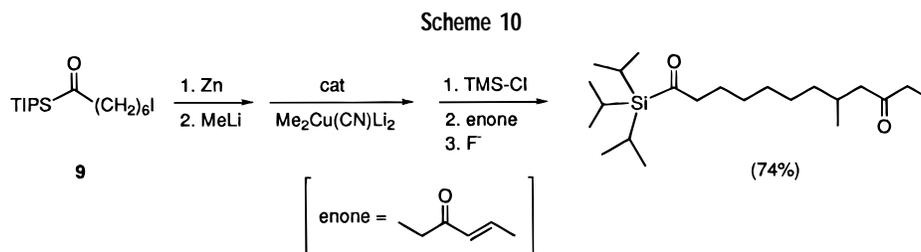


likelihood of generating a less reactive lower order cuprate 7 via ligand exchange between $\text{MeCu}(\text{CN})\text{Li}$ and zincate 6. By beefing-up the higher order content using zincate $\text{R}_T\text{ZnMe}_2\text{Li}$ and the dimethyl HO cuprate, the resulting mixed HO species 8 presumably now formed was likely to transfer (to some degree) the methyl ligand rather than just the desired R_T group (eq 2). This potential problem



of selectivity of ligand transfer was actually never tested at this stage. Rather, we enlisted the help of Raymond

- (13) Tuckmantel, W.; Oshima, K.; Nozaki, H. *Chem. Ber.* **1986**, *119*, 104. Kjonaas, R. A.; Vawter, E. J. *J. Org. Chem.* **1986**, *51*, 3993. Morita, Y.; Suzuki, M.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 1785.
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 (15) Sih, C. J.; Price, P.; Sood, R.; Salamon, R. G.; Periozzotti, G.; Caseg, M. *J. Am. Chem. Soc.* **1972**, *94*, 3643. Stork, G.; Isobe, M. *Ibid.* **1975**, *97*, 4745, 6260.
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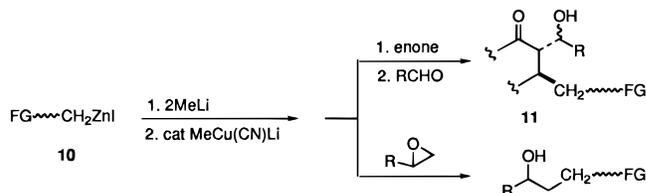


Tirado, a postdoc in our group from the University of Puerto Rico, anticipating that his excellent lab skills and critical thinking would greatly aid our task of finding the magic ligand other than methyl for the required selective transfer of R_T from copper. Of course, at this point, we were far from a solution; in fact, we had nothing but “paper chemistry”.

Raymond looked extensively for that ligand. Perhaps we even spent too much time searching. He tested thienyl, two thienyls, acetylenic dummy ligands, Lewis acids, temperatures, and solvent mixes. On many occasions, with progress virtually nonexistent, I heard him talking passionately in Spanish to his reactions, encouraging them to “gimme a break”. I am not sure whether Raymond’s expletives aided in our quest, but the solution did finally come to us. In retrospect, it seems disappointing, perhaps even somewhat embarrassing, that we did not early on test the simple expedient of having TMS–Cl in the pot, the “boost” commonly needed by lower order cuprates to do their job.¹⁹ Nonetheless, with this additive present, there was born the methodology for transferring a functionalized zinc reagent in a 1,4-fashion to an enone which requires only 5 mol % copper in the form of $\text{Me}_2\text{-Cu(CN)Li}_2$ (Scheme 9).²⁰ Mike and Raymond showed that several types of electrophilic-center-containing zinc species could be utilized in this chemistry, including the unprecedented transfer of an acyl silane **9**,²¹ which is synthetically equivalent, e.g., to an aldehyde (Scheme 10).²²

Three-Component Couplings and Alkylations of Functionalized Zincates. For Mike Wood, who had played a seminal role in the development of these copper-catalyzed couplings, it was time to move on to other chemistry prior to departure for Dave Evans’ group at Harvard and the demands of vancomycin total synthesis. However, Raymond was still “available” since there were a few months left before he was to return to the University of Puerto Rico (Humacao Campus) as an Assistant Professor. Moreover, Tim Gross, another terrific senior graduate student in the group (and yes, from Chico), who had been working

Scheme 11



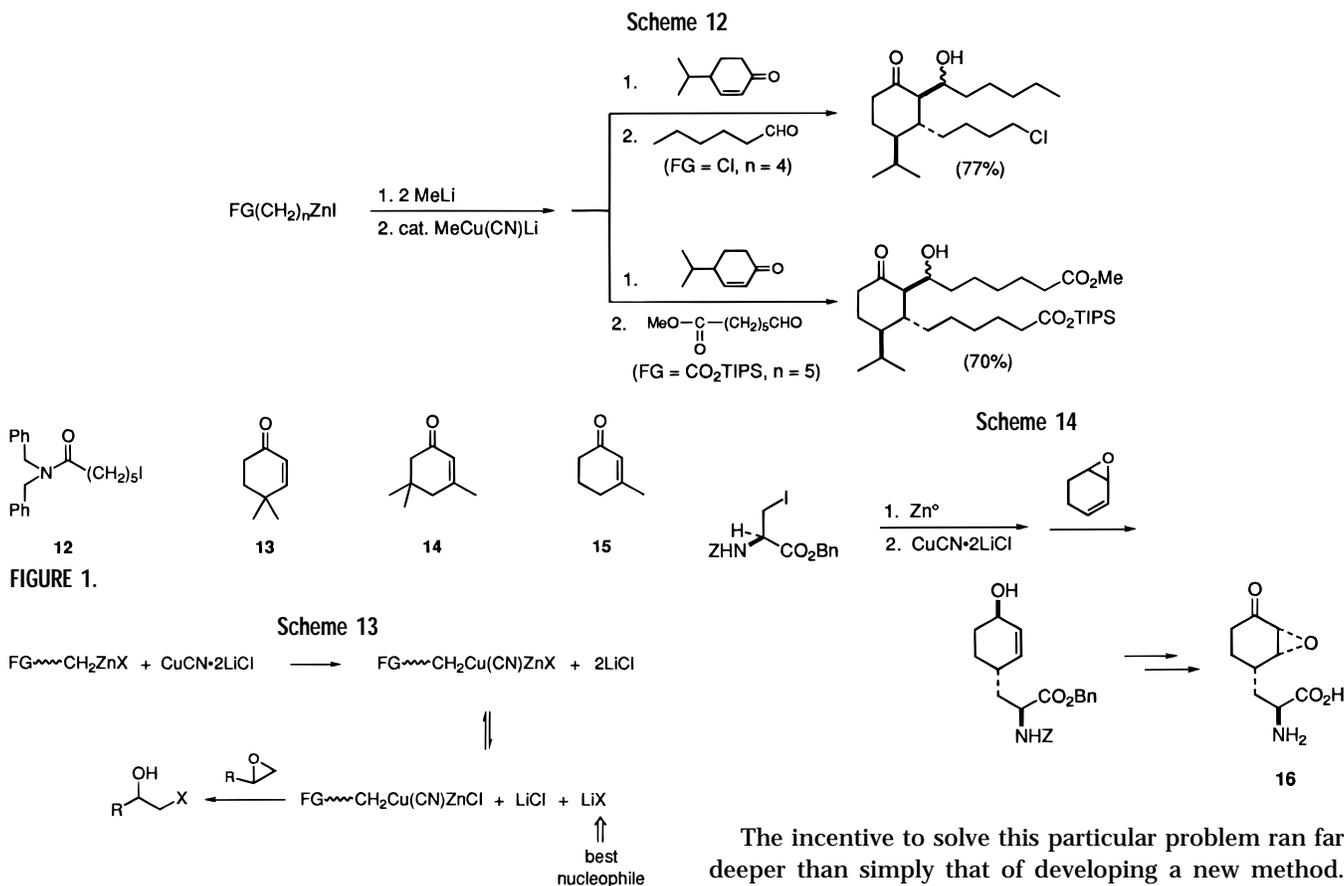
on THF-forming 5-endo-trig cyclizations,²³ was also interested in getting experience in cuprate chemistry. Two logical extensions of our new methodology were (1) to develop the three-component coupling (3-CC) of functionalized alkyl zincs and (2) to start looking at the nontrivial process of cuprate-catalyzed *alkylations*, in particular with an epoxide (Scheme 11). Raymond’s experience at using the MeLi shuttle, Me_3ZnLi , allowed him to establish quickly that this 3-CC sequence could, in fact, be realized. Tim, together with yet another promising fresh recruit from Chico, D.J. Buzard, pushed through the initial Tirado result, although not without complications. The protocol calls for generation of the usual functionalized zinc iodide **10**, followed by conversion to the corresponding zincate with addition of 2 equiv of MeLi. Transfer of 5 mol % MeCu(CN)Li to the zincate followed by an enone leads to 1,4-adduct. Last, introduction of an aldehyde affords the aldol products **11**.

Although it was possible to employ esters and chlorides, exemplified in Scheme 12, nitriles were unacceptable. An explanation for their reluctance to participate has yet to surface, especially in light of Tim’s success with an *N,N*-dibenzylamide **12**. D.J. made a considerable effort looking at hindered enones, e.g., **13–15** (Figure 1), finding them to be unwilling partners in this scheme. He was successful, however, in applying a TIPS acylsilane to this 3-CC.³¹

Epoxides, on the other hand, make up quite another story. Curiously, of all the electrophiles shown to react with $\text{FG(CH}_2\text{)}_n\text{Cu(CN)ZnX}$,²⁴ there seems to be one functionality that is conspicuously absent. Epoxides. Why? Obviously, lower order (LO) cyanocuprates had been shown long ago to react with oxiranes,²⁵ so why not here with zinc cuprates? Raymond was the first in our group to find out. But he did so rather reluctantly as he was sharp enough to see that, if there are problems with this chemistry using stoichiometric zinc halocuprates, there are likely to be bigger problems under catalytic conditions. Although nature was not about to disappoint us in this

- (17) For typical procedures, see: Knochel, P.; Rozema, M. J.; Tucker, C. E. Preparation of highly functionalized reagents. In *Organocopper Reagents, A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, U.K., 1994; pp 85–104.
- (18) Zhu, L.; Rieke, R. D. *Tetrahedron Lett.* **1991**, *32*, 2865. Rieke, R. D. *Science* **1989**, *246*, 1260.
- (19) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015. Corey, E. J.; Boaz, N. W. *Ibid.* **1985**, *26*, 6019. Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047. Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029. Linderman, R. J.; Godfrey, A. *Tetrahedron Lett.* **1986**, *27*, 4553.
- (20) Lipshutz, B. H.; Wood, M. R.; Tirado, R. *J. Am. Chem. Soc.* **1995**, *117*, 6126.
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- (22) Schinzer, D.; Heathcock, C. H. *Tetrahedron Lett.* **1981**, *22*, 1881.

- (23) Lipshutz, B. H.; Gross, T. *J. Org. Chem.* **1995**, *60*, 3572.
- (24) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. Knochel, P. *Organozinc and Organo-cadmium Compounds in Organic Synthesis*. In *Comprehensive Organometallic Chemistry II*; McKillop, A., Ed.; Pergamon Press: New York, 1995; Vol. 11, pp 159–190.
- (25) Lipshutz, B. H.; Sengupta, S. *Org. React. (NY)* **1992**, *41*, 135.



regard, there was a month or so left to Raymond's tenure at UCSB; hence, I diplomatically "encouraged" him to test the waters.

Almost immediately Raymond came into my office: "I have bad news", he said. The problem we faced is that of competing halohydrin formation, even at $-78\text{ }^{\circ}\text{C}$. Recall that $\text{FG}(\text{CH}_2)_n\text{Cu}(\text{CN})\text{ZnX}$ comes from $\text{R}(\text{CH}_2)_n\text{I} + \text{Zn}^0$, which then undergoes transmetalation with $\text{CuCN}\cdot 2\text{LiCl}$.²⁴ Thus, even though our route generates an even more reactive lithiocuprate $\text{FG}(\text{CH}_2)_n\text{Cu}(\text{CN})\text{Li}$, there is still plenty of halide present, the iodide (or even bromide, if using $\text{R}(\text{CH}_2)_n\text{Br}$) being just too good a nucleophile toward an epoxide relative to a less reactive LO cyanocuprate (Scheme 13). "Now what?", he said, to which I asked, "can we get the iodide out?" We tried everything we could think of: Rieke Zn,²⁶ increasing cuprate reactivity using the HO analogue $\text{FG}(\text{CH}_2)_n(\text{Me})\text{Cu}(\text{CN})\text{Li}(\text{ZnX})$, and an unprecedented attempt with an alkyl *triflate* as precursor to " $\text{FG}(\text{CH}_2)_n\text{ZnOTf}$ ", rather than a halide. This latter notion, which Rueben Rieke and I discussed by phone and thought might work, gave the same results as the other trials: nichts! I even called a friend at Merck, praying that those process guys might have a solution in house. No dice.

Although even simple, monosubstituted epoxides had seemingly won this battle, we realized that a better match of LO cyanocuprate reactivity is with *allylic* epoxides.²⁷ Perhaps iodide ion would not be so prone toward addition to this softer electrophile.

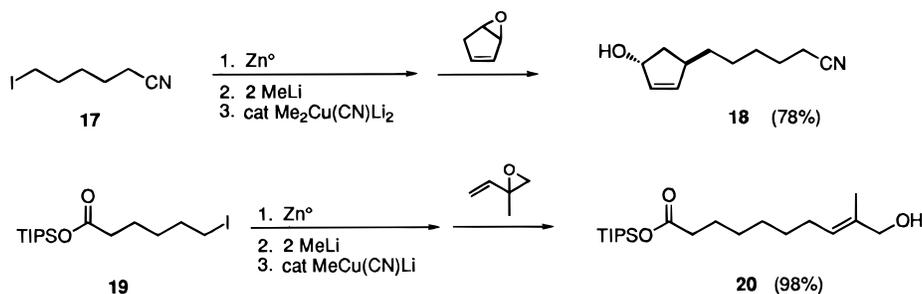
The incentive to solve this particular problem ran far deeper than simply that of developing a new method. While in the middle of our study on epoxide openings, an article appeared in *Chemical & Engineering News*²⁸ describing the reaction of a Knochel cuprate^{24,29} with cyclohexadiene monoepoxide. The cuprate was derived from alanine, and the product allylic alcohol was highlighted as a precursor to the potent antifungal agent anticapsin, **16** (Scheme 14). Needless to say I was caught by surprise by this report, from Jack Baldwin's laboratory in Oxford. Details of the coupling, however, were completely lacking, and so I immediately sent a letter to the student who had been cited as co-worker on this project, asking for information with respect to two critical issues: (1) How well does this work? and (2) Was it done with a stoichiometric amount of cuprate? Not too long after my inquiry a response was forthcoming which we interpreted as "encouraging". Their procedure used excess cuprate, and the best yield obtained at that time was 55%. We concluded that we were still in business.

It occurred to us, having learned from the past,²⁰ that the recycling of copper might be facilitated by the presence of $\text{TMS}\text{---}\text{Cl}$ to trap the $\text{S}_{\text{N}}2'$ product alkoxide. Raymond was somewhat skeptical, notwithstanding the Oxford contribution,^{28,30} but once again, his mentor's influence prevailed. On this occasion, however, as the early returns came in, we knew we had a winner. With what seemed like a reasonable protocol, good yields, and the need for only 5 mol % cuprate, Raymond could now

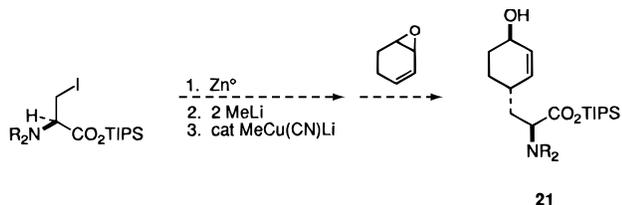
(26) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445.
 (27) Marino, J. P.; Jaen, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 3165. Wender, P. A.; Erhardt, J. M.; Letendre, L. J. *Ibid.* **1981**, *103*, 2114.

(28) *Chem. Eng. News* **1995** (April 24), 37.
 (29) For typical procedures, see: Lipshutz, B. H. In *Synthetic Procedures Involving Organocopper Reagents. Organometallics in Synthesis: A Manual*; Schlosser, M., Ed.; Wiley: New York, 1994; pp 283–382.
 (30) See also: Baldwin, J. E.; Adlington, R. M.; Mitchell, M. B. *Tetrahedron* **1995**, *51*, 5193.

Scheme 15



Scheme 16



leave Santa Barbara on a highly positive note. As he exited my office for the last time, I may have even caught him smiling. . .

Tim and D.J. were happy to examine further this highly useful and unprecedented copper-catalyzed cross-coupling of functionalized zinc reagents. As insurance, we welcomed to our team another talented postdoc, Dr. Kyoungja Woo, who, while trained at Brown in inorganic chemistry, was excited about learning organic synthesis. This trio has only recently completed the obligatory tabular survey of functionalized cuprates and allylic epoxides, which together with our catalytic cuprate-mediated 3-CC (vide supra) are soon to be published.^{31,32} Examples include zinc reagents derived from iodides **17** and **19**, giving allylic alcohol products **18** and **20**, respectively (Scheme 15). Moreover, in time we found that TMS-Cl was not an essential ingredient for our recipe. What's left undone for us (well, more specifically, for D.J.) is the challenge of applying this zincate-to-cuprate transmetalation methodology to a suitably derivatized alanine, which is one of two coupling partners along with cyclohexadiene monoepoxide (Scheme 16). In my view, this is by no means a sure bet. I may be guilty, however, of having forgotten to mention this to D.J.

Most chemistry professors, myself-included, must live vicariously; it is virtually impossible to have the time to do careful labwork. And while there are *many* days when I long for that relatively uncomplicated lifestyle as a student in the lab, accomplishments as discussed herein *by my co-workers* continue to make it all worthwhile. With

(31) Lipshutz, B. H.; Gross, T.; Buzard, D. J.; Tirado, R. *J. Chin. Chem. Soc.* **1997**, *44*, 1.

(32) Lipshutz, B. H.; Woo, K.; Gross, T.; Buzard, D. J.; Tirado, R. *Synlett* **1997**, in press.

these studies, interestingly enough, comes the odd realization that for now there are no other ongoing synthetic projects in the group featuring Cu(I) as the key metal. Perhaps we took too much of the copper out of our chemistry. . .

Concluding Remarks

At a time when the term “downsizing” among chemists engenders rather negative connotations, it can only be a blessing when used with respect to the amount of a transition metal required for a given transformation. Usually, it is the up-front costs, as with, for example, palladium, that drive the requirement that procedures be catalytic in a given metal. With copper, however, this has never been true. Rather, it is the “back end” of its use, the disposal issue driven by valid environmental concerns that necessitate alternatives which rely on lower percentages of copper. For small-scale usage, it is far from guaranteed that the new procedures developed in our labs or in others worldwide will find immediate acceptance. As Lou Hegedus (at Colorado State University) put it during one conversation, “Saving the world from 20 mg of copper is not what it's all about”. And, obviously, the acceptance of stoichiometric uses of higher order cuprates, and cuprate chemistry in general, has not waned according to the literature. The trend, however, is clear and indisputable. Had I acted sooner on the comments of Seeman Pines, by now we might have already known if these catalytic methods of recent vintage are to find utility. Funny thing is, this was the second time I did not (at least immediately) heed the advice of Seeman: the first was back in 1979, when he offered me a job at Merck.

It is always a pleasure to acknowledge the efforts of the co-workers who brought the “paper chemistry” to fruition, their names having been cited herein. We are also very appreciative of the support of our programs extended by the Organic Synthesis Division at the NSF (CHE 93-03883), overseen by George Rubottom, and the Institute of General Medical Sciences at the NIH (GM 40287).

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