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Cu(I)-*Catalyzed* Substitution Reactions of Activated Vinyl Triflates with Functionalized Organozinc Reagents

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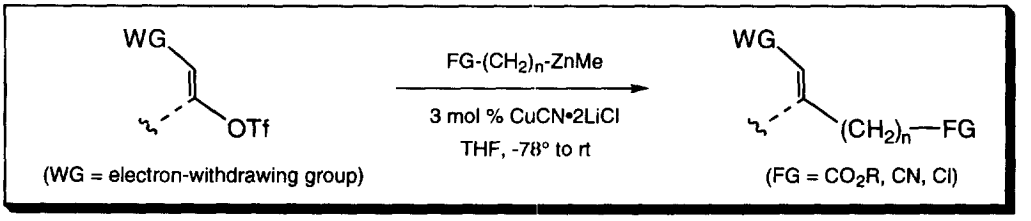
Summary: *Treatment of a mixed, functionalized dialkylzinc species with catalytic amounts of CuCN•2LiCl produces a reagent which readily displaces an activated vinyl triflate in high yields.*

While conjugate addition reactions of organocopper reagents comprise in large measure the cornerstone of modern cuprate chemistry,[2] substitution reactions by these mild yet potent organometallic species are highly valued processes.[3] Most require stoichiometric amounts of copper, which necessarily limits the extent to which such cross-couplings may be scaled-up. Recently, we described a process by which functionalized zinc reagents could be alkylated with allylic epoxides under the influence of 5 mol % of a trivial cyanocuprate ($Me_2Cu(CN)Li_2$).[4] In our continuing efforts to convert normally non-catalytic cuprate couplings to those which rely on only small percentages of Cu(I),[5] we now report that efficient and rapid displacement reactions of activated vinyl triflates, substrates which are readily available and useful in a variety of synthetic situations,[6] can be effected by mixed organozinc reagents in the presence of catalytic quantities of solubilized CuCN.[7]



Substitution reactions on vinyl triflates by Gilman cuprates were first described by McMurry years ago.[8] These substrates are unexpectedly challenging, even when subjected to an excess (*ca.* 3 equiv) of cuprate. Thus, it was not surprising to find that alkyl methylzinc **1**, with substoichiometric amounts of various sources of Cu(I), were completely ineffective toward this type of educt. On the other hand, vinyl triflates bearing a β-activating (*i.e.* electron-withdrawing) group proved to be responsive to copper catalysis in a synthetically meaningful way. Conversion of a functionalized zinc halide[9] to the mixed zinc **1** by addition of one equivalent of methylithium, followed by introduction of 3 mole percent CuCN•LiCl in THF leads to a reagent mix capable of replacing the triflate moiety *via* selective transfer of the functionalized alkyl ligand originally on zinc. Initial selection of the

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methyl moiety as the non-transferable ('dummy') group on zinc was made based on previous success with this ligand,[10] as well as its commercial availability in Et_2O. It was found that non-ethereal solvents in which some RLi are made (*e.g.*, *n*-BuLi in hexanes) can lead to significant mixed zinc reagent insolubility. A 2-thienyl group was also anticipated to serve in this capacity[11] (*i.e.*, in reagent **2**), and in fact replacement of methyl with 2-thienyl affords a coupling of roughly comparable efficiency and rate. The highly touted but as yet infrequently used trimethylsilylmethyl 'dummy' ligand[12] was also screened as its derived mixed zinc (**3**), however, solubility problems created by the pentane present in commercial TMSM-Li were encountered which precluded further evaluation.

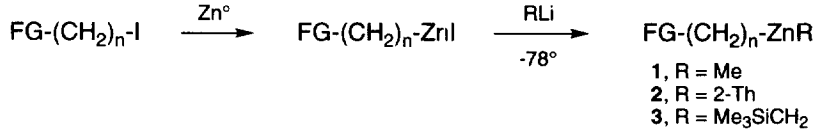
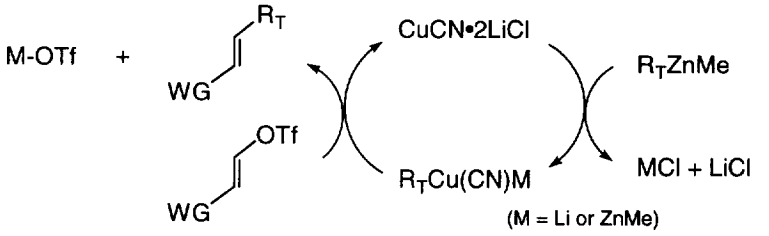


Table 1 lists several examples of these copper-catalyzed couplings and reflect the generality of the method. The mildness of the conditions involved allow for considerable functional group tolerance. Educts bearing ketone, ester, and amide (*e.g.*, β-lactam) moieties present no obstacles insofar as reagent compatibility is concerned. No competing 1,2-addition was observed, and most couplings were complete in an hour or less at reasonable substrate concentrations (*ca.* 0.25 M). Reactions aimed at further reductions in the mole percent catalyst employed demonstrated that as little as 0.5 mol % Cu(I) could in fact be used with comparable efficiency, although the rate was decreased accordingly.[13] Noteworthy examples include the derivatization of the cephalosporin skeleton in **7**,[14a] and farnesol derivative **8**, a potential inhibitor of protein-farnesyl transferase (PFTase).[14b] Acyclic example **8** also afforded a product which retained its original *E*-olefin geometry. Although triflates were mainly used in this study, the corresponding (albeit less expensive) nonaflate[15] of **4** afforded virtually identical results under similar reaction conditions.

The likely sequence of events that enables copper to function in a catalytic mode is shown in Scheme 1. Critical for such a cycle is regeneration of solubilized copper cyanide, presumably kept in solution by LiCl present or the triflate salt formed as a by-product.



Scheme 1. Possible catalytic role for Cu(I).

Reactions conducted in the absence of CuCN under otherwise identical conditions (*e.g.*, with triflate **4**) led to a far lower yield of **5**, along with side products (*e.g.*, from competing methyl and iodide addition) and recovered starting material (Eq. 1).

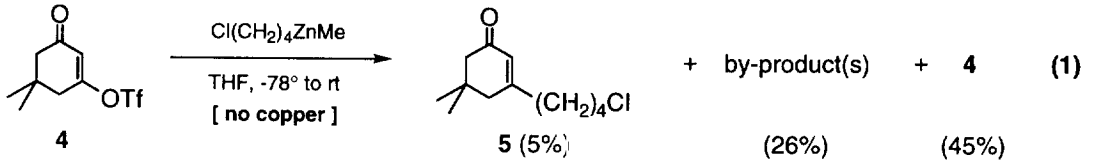
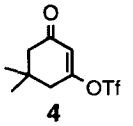
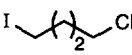
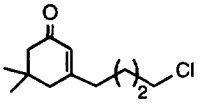
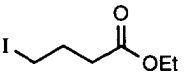
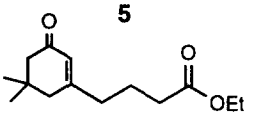
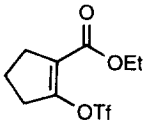
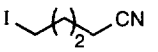
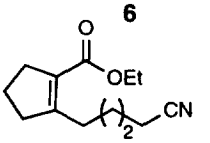
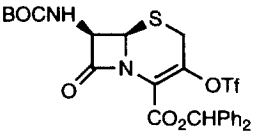
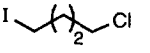
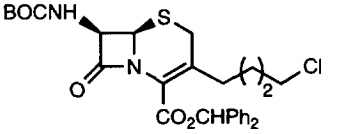
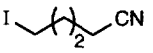
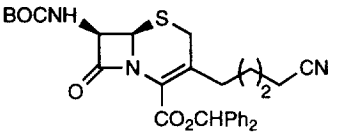
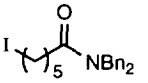
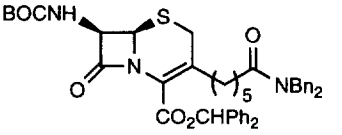
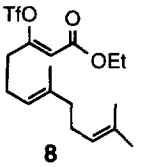
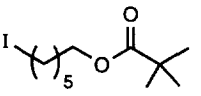
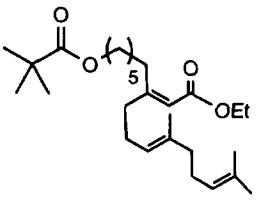
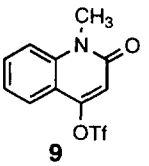
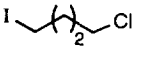
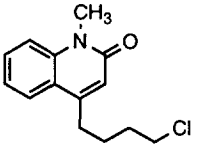


Table 1. Copper-catalyzed couplings of activated vinyl triflates with R_TZnMe[a]

Triflate	Halide Precursor	Time	Product[b]	Yield(%)[c]
 **4**		25 min	 **5**	88
		28 min	 **6**	84
		6 h		81
 **7**		25 min		86
		25 min		70
		20 min		59
 **8**		1.25 h		84
 **9**		7.5 h[d]		86

[a]See reference 16 for a typical procedure. [b]Fully characterized by IR, NMR, MS and/or HRMS or combustion data. [c]Isolated, chromatographically purified material. [d]Using 2.0 equivalents of starting iodide at 40° C.

In summary, conditions have been found which allow for clean C-C bond formation between activated vinyl triflates and functionalized mixed zinc reagents mediated by halocyanocuprates (*e.g.*, XCu(CN)Li).[16] The couplings require a modest 3 mol % Cu(I) in the form of a commercially inexpensive, stable, copper(I) salt. Vinyl triflates activated by carbonyl units (ketones, esters and amides) readily participate, and appendages bearing ω-electrophilic functionality (esters, nitriles, halides, amides) may be introduced *via* the corresponding mixed zinc reagents. Further studies aimed at developing other useful alkylation reactions based on copper catalysis are under study and will be reported in due course.

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References and Notes

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13. This reaction (Table 1, entry 1) required 1.25 h, instead of the 25 min needed in the presence of 3 mol % CuCN•2LiCl.
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15. (a) Knochel, P.; Rottlander, M. *J. Org. Chem.* **1998**, *63*, 203; (b) Subramanian, L.R.; Bentz, H.; Hanack, M. *Synthesis* **1973**, 293.
16. *General Procedure* (Table 1, entry 2). Ethyl 4-iodobutyrate (0.60 g, 1.8 mmol) is added to a THF (1 mL) slurry of activated Zn dust (<10 μm, 0.183 g, 2.0 mmol) as described by Knochel.[8] The mixture is allowed to stir overnight at *ca* 35°C. The resulting opaque solution is transferred *via* cannula to a round bottom flask double sealed with rubber septa, leaving any remaining Zn dust behind. The residual material is then rinsed twice with THF (0.5 mL) and the washings transferred to the reaction flask. The solution is cooled to -78°C and MeLi (1.80 mL, 1.2 M in Et_2O, 2.1 mmol) is added, followed by CuCN•2LiCl (0.21 mL, 0.2 M in THF, 0.042 mmol). The solution is allowed to stir at -78°C for 5 min. In a separate flask, 5,5-dimethyl-3-trifluoromethanesulfonyloxycyclohex-2-ene-1-one (**4**, 383 mg, 1.4 mmol) is azeotropically dried with toluene under high vacuum, dissolved in THF (1.5 mL), cooled to -78°C, and added to the reaction mixture dropwise by cannula. The Dry Ice/acetone bath is removed, and the reaction mixture allowed to warm to rt while monitored by TLC until complete. After 30 min, the reaction is cooled to 0°C in an ice-water bath and diluted with Et_2O (5 mL) before quenching with 5 mL of 10% sat NH_4OH / 90% sat NH_4Cl solution. The solution is allowed to warm to rt and is gently agitated until both layers become homogeneous. The layers are separated and the aqueous layer extracted with 2 x 5 mL Et_2O. The organics are adsorbed onto silica gel and the product (**6**) isolated by flash chromatography (5 / 1 petroleum ether / EtOAc, R_f = 0.31); 286 mg of a light yellow oil (84%); ^1H NMR ($CDCl_3$, 400 MHz): δ 5.88 (t, *J* = 1.6 Hz, 1H); 4.14 (q, *J* = 7.2 Hz, 2H); 2.33 (t, *J* = 7.2 Hz, 2 H); 2.23 (br t, *J* = 7.6 Hz, 2H); 2.22 (s, 2H); 2.18 (br s, 2H); 1.84 (q, *J* = 7.6 Hz, 2H); 1.26 (t, *J* = 7.2 Hz, 3H); 1.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.1, 173.2, 162.9, 125.2, 60.7, 51.2, 44.0, 37.4, 33.8, 33.7, 28.5 (2C), 22.2, 14.4; IR (neat) cm^{-1} 2958, 2871, 1733, 1668, 1628, 1451, 1414, 1370, 1300, 1246, 1187, 1158, 1028; HRMS (EI) m/z calcd for $C_{14}H_{22}O_3$ 238.1569, found 238.1565.