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COPPER-CATALYZED ALLYLIC ALKYLATIONS OF ALKYLZIRCONIUM INTERMEDIATES

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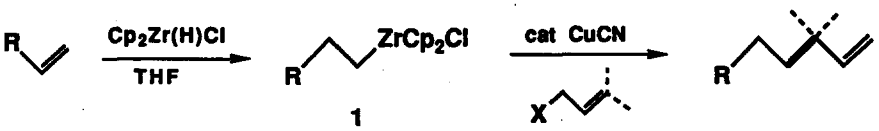
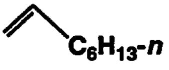
Summary: *Hydrozirconation of olefins followed by exposure of the resulting alkylzirconium species to catalytic CuCN in the presence of activated halides or phosphonates gives rise to products of alkylation in good yields under mild conditions.*

In general, alkylation reactions promoted by catalytic amounts of copper(I) salts are normally considered within the domain of Grignard chemistry.[1] While organometallics derived from metals other than magnesium (*e.g.*, organotitanium[2a], zinc[2b], manganese[3a] and aluminum[3b] reagents) are beginning to offer distinct advantages, their preparation is oftentimes tied to their organolithium precursors. Given the ease with which organozirconium intermediates undergo ligand exchange with Cu(I) dianions,[4] and bearing in mind the benefits of excellent regio- and stereoselectivity associated with the addition of $Cp_2Zr(H)Cl$ across monosubstituted alkenes,[5] it was anticipated that transmetalation from Zr to Cu would occur to arrive at cuprates capable of effecting alkylations. We now report that such a process does indeed allow for the generation of copper reagents which couple regioselectively with allylic substrates, and that only *catalytic* quantities of the Cu(I) source need be invested (Scheme 1).



Scheme 1

Hydrozirconation of terminal olefins **2**-**6** takes place smoothly in THF over 30 minutes between room temperature and 35-40° (water bath), giving rise in each case to the corresponding zirconates **1**. Addition of 10 mol% CuCN (or a THF solution of $CuCN{\cdot}2LiCl$)[6] and then the alkylating agent led to products of carbon-carbon bond formation in good yields. Allylic chlorides, bromides, and phosphates all reacted with roughly equal facility, as illustrated in Table 1. For unsymmetrically substituted allylic systems **7**-**10**, clearly the predominant, if not exclusive, mode of attack by the cuprate is S_N2' in nature. Perturbation of the allylic unit, as in γ-bromo methyl crotonate **11**, resulted in mixtures from both S_N2 and S_N2' attack. (entries 7,8). Particularly noteworthy are the observations that a primary bromide is tolerated throughout the sequence (entry 3), and allylic alkylation (*vs.* 1,4-addition) is not compromised to any extent notwithstanding the presence of a Michael acceptor in enoate **11**. This chemospecificity is expected on the basis of extensive studies by Ibuka and Yamamoto,[7] although the comparatively poor regioselectivity in these cases must reflect the change in reagent composition and/or conditions involved. Attempted couplings using a monosubstituted epoxide, allylic acetate, an aryl or vinylic iodide or bromide, and even a benzylic bromide were uniformly unsuccessful (essentially complete recovery of the alkylating reagent).



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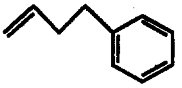

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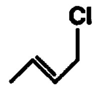
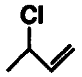
6

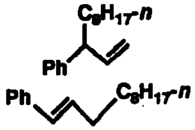
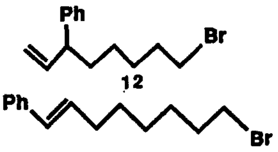
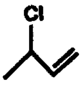
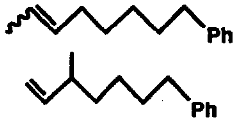
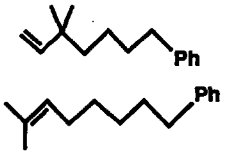
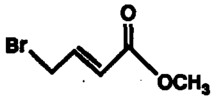
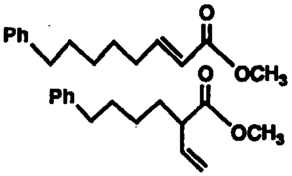
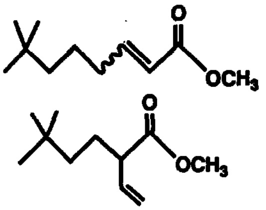
The regioselectivities of various reagents toward three allylic halides are summarized in Table 2. These attest to the highly γ-selective approach inherent to this method based on a Zr-to-Cu ligand exchange, even where γ,γ-disubstitution occurs (*e.g.*, as with prenyl bromide). The similarity between the data from the catalytic process and that derived from use of Yamamoto's reagent[8,9] is striking and points to the impact here on regiocontrol of a good Lewis acid (BF_3 and, perhaps, "$ZrCp_2Cl^+$") in an ethereal medium.

Table 2. Comparison of reagents: regioselectivity of attack on allylic halides

Substrate		*n*-BuLi[a]	*n*-Bu_2CuLi[a]	*n*-$BuCu{\cdot}BF_3$[a]	$Ph(CH_2)_4ZrCp_2Cl$ + cat CuCN	
 Cl	α	54	96	6	0	90%[b]
	γ	46	4	94	100	
 Cl	α	8	22	4	<2	98%[b]
	γ	92	78	96	>98	
 Br	α	88[c]	100	10	11	89%[b]
	γ	12	0	90	89	

[a]Taken from data in reference 8. [b]Isolated yield; see Table 1 for structures. [c]Using MeLi.

Table 1. Copper-catalyzed allylations of zirconium alkyls

Entry	RZrCp$_2$Cl,[a] from:	Halide/Phosphate	Product(s)[b]	Ratio	Yield(%)[c]
1	2	 7		(93) (7)	85
2	3	7	 12	(93) (7)	94
3	4	 8		—	90
4	4	 9		(>98)[d] (<2)	98
5	4	 10		(89) (11)	89
6	4	 11		(27) (73)	91
7	5	11		(53)[e] (47)	82
8	6	[f]		—	85[g]

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[a] 1.5 eq *vs* electrophile. [b] Isolated & characterized by spectral means. [c] Isolated; based on electrophile. [d] E:Z ratio = 54:44. [e] E:Z Ratio =16.7:1. [f] 5 eq were used to insure consumption of educt. [g] By GC.

A typical procedure for the preparation of 12 (Table 1, entry 2) is as follows. A dry 10 mL round bottom flask is charged with 100 mg (0.39 mmol) $Cp_2Zr(H)Cl$. To this is added 3 mL of dry THF and 58 mg (0.39 mmol) of 5-bromopentene. The mixture is stirred at room temperature for 1 h to give a clear yellow solution. At this point, 70 mg (0.27 mmol) of diethyl cinnamylphosphate are added followed by 5 mg (0.06 mmol) of CuCN. The suspension is stirred overnight and then poured into 10 mL of pentane/15 mL of 10% aqueous NaOH. The organic layer is removed and washed with 10 mL of 1N HCl and then 10 mL of saturated aqueous NaCl. Further drying over magnesium sulfate, filtration through a silica pad, and removal of solvent *in vacuo* yields 68 mg (94%) of a 93:7 mix of S_N2' and S_N2 products; [8-bromo-3-phenyloctene] IR (neat, cm^{-1}) 2960, 1705, 1495, 1450, 1260, 1020, 905, 750, 695; NMR (500 MHz, $CDCl_3$) δ7.30-7.15 (m, 5H), 5.96-5.89 (m, 1H), 5.02-4.99 (dd, J=10,12, 2H), 4.11-4.08 (m, 1H), 3.39-3.34 (t, 2H, J=7Hz), 1.84-1.18 (m, 8H); EIMS (m/z, rel int) 268(4), 266(4), 118(100), 117(12); HREIMS calcd for $C_{14}H_{19}Br$, 266.0669; found, 266.0658.

In summary, a new experimentally straightforward, 1-pot procedure has been developed which allows for the copper-catalyzed regioselective γ-allylic alkylation of alkylzirconium intermediates, readily formed *in situ* from terminal alkenes. These results highlight a process which is complementary to that recently reported for effecting 1,4-additions to enones *via* similar chemistry.[10,11]

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References and Notes

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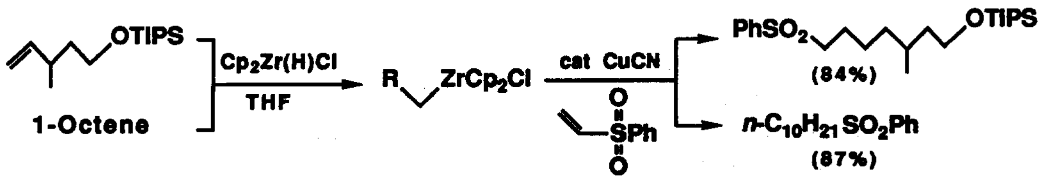
11. Conjugate additions to vinyl sulfones also occur under these conditions (*e.g.*, see below).



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