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AMINE-DIRECTED ADDITION OF CUPRATE REAGENTS TO CYCLOPENTENYL SULFONES[1]

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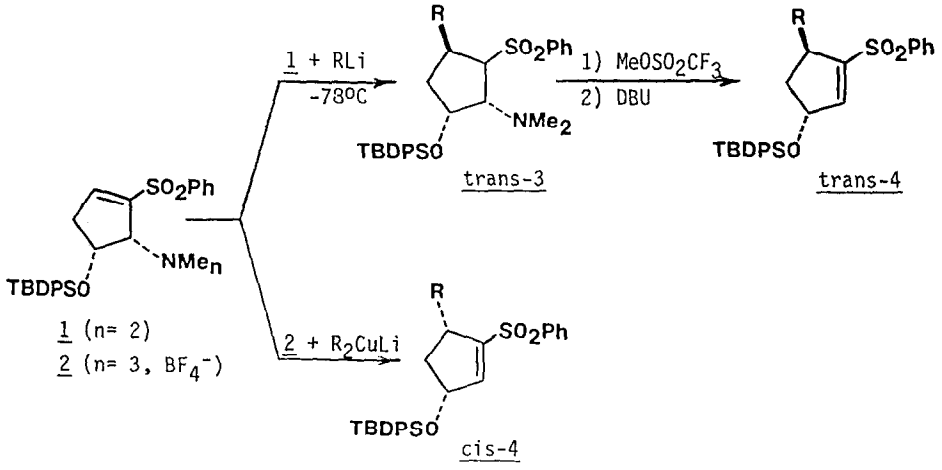
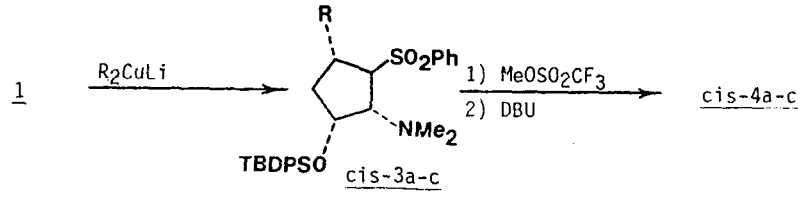
Abstract: Reaction of cuprate reagents with ß'-amino cyclopentenyl sulfones affords bond formation through amine-directed conjugate-addition. Comparison studies with cyclopentenyl sulfone implicate a halocuprate intermediate.

In connection with our synthetic program we have recently investigated the conjugate-addition of organometallic reagents to ß'-substituted cyclopentyl sulfones 1 and 2.[1] It was found that organolithium reagents added to amine 1 to produce adduct trans-3 in high yield with excellent trans specificity, while cuprate reagents added to allyl ammonium salt 2 to afford vinyl sulfone cis-4 in uniformly high yield with essentially complete cis stereospecificity.



It is interesting to note that the organolithium reagents avoided the opportunity to produce cis-adducts via an amine-directed addition mechanism. It was in the context of this question that we elected to probe the reactivity of amino vinyl sulfone 1 with cuprate reagents.

Treatment of 1 in THF with methyl, phenyl, or vinyl cuprate affords cis-adducts cis-3a-c in excellent yield.[2,3] Quaternization and elimination of the amino moiety produces the known cis vinyl sulfones cis-4a-c[1] in the yields and specificities recorded in Table 1. The reaction is tolerant of solvent, ether and toluene also affording the cis-3a from the reaction of lithium dimethyl cuprate with substrate 1.



1 → cis-3a-c → cis-4a-c

a R= Me; b R= Ph; c R= $CH=CH_2$

TABLE I: REACTION OF ORGANOCOPPER REAGENTS WITH AMINOVINYL SULFONE 1

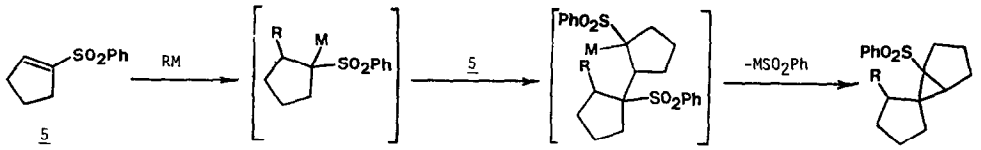
Reagent	Solvent	Conditions	% Yield cis-3	% Yield cis-4	Stereospecifity cis-4/trans-4
$(CH_3)_2CuLi$ (2 eq)	THF	0.125M, 0°C, 1h	84	89	>99:1[b]
$(C_6H_5)_2CuLi$ (2 eq)	THF	0.125M, 0°C, 1h	89	90	>95:5[c]
$(CH_2=CH)_2CuLi$ (10 eq)	THF	0.035M, 0°C, 1h	86	99	>99:1[b]
$(CH_3)_2CuLi$ (2 eq)	$(C_2H_5)_2O$	0.125M, 0°C, 1h	98	--	---
$(CH_3)_2CuLi$ (2eq)	$C_6H_5CH_3$[a]	0.125M, 0°C, 1h	95	--	---
CH_3Cu (2 eq)	THF/$(C_2H_5)_2O$	0.125M, 0°C, 1h	0	--	---
C_6H_5Cu (2 eq)	THF	0.125M, 0°C, 1h	0	--	---
$CH_3Cu(LiI)$[d] (5 eq)	$Et_2O/C_6H_5CH_3$	0.125M, 0°C, 2h	0	--	---
$CH_3Cu(LiI)$[d] (5 eq) +$2LiBr_2$	$Et_2O/C_6H_5CH_3$	0.125M, 0°C, 1h	75	99	---

(a) $(CH_3)_2CuLi$ prepared as a 0.5 M solution (CuI + CH_3Li) in ether at -10°C, then warming to 0°C for 30 min. Using a vacuum pump at 4mm Hg, the ether was removed in vacuo carefully at 0°C. Upon concentration to a yellow oil, the cold residue was diluted with 0°C $C_6H_5CH_3$;(b) Analysis by HPLC as described in reference 1;(c) Analysis by 470 MHz ^1H NMR as described in reference 1; d) Prepared from CuI.

It has been well known since the initial studies of Posner[4,5] that vinyl sulfones are quite poor substrates for reaction with cuprate reagents. Therefore we deemed it important to assess the magnitude of the effect elicited by the amino moiety in 1. In order to address this question we examined the reaction of organocopper reagents with the parent cyclopentenyl phenyl sulfone 5.[6] Treatment of vinyl sulfone 5 with lithium dimethyl cuprate under the same conditions as used with 1 does not proceed smoothly to afford the simple ß-methyl sulfone 8a. Although this material is produced in a variety of solvents (see Table II) it is always accompanied by two additional 2:1 adducts; bis-sulfone 10a and cyclopropyl sulfone 11a.[3] This problem is not encountered with diphenyl cuprate, where mono adduct 8b is isolated in 90% yield. Both 2:1 adducts would appear to arise from reaction of the initial 1:1 intermediate [6][7] with vinyl sulfone 5 at a rate competitive with that of cuprate addition, thus yielding intermediate [9] which either undergoes intramolecular displacement of the sulfone moiety to afford 11a or is ultimately protonated upon workup to generate adduct 10a.[8-10]

Organocopper reagents also show some interesting differential reactivity with vinyl sulfones 1 and 5. Reaction of 5 with methyl copper (containing one equivalent of associated lithium iodide from the CuI) produces 1:1 adduct 8a uncontaminated with either of the 2:1 adducts formed in the dimethyl cuprate reaction. Apparently this is a consequence of producing α-sulfonyl anion intermediate [7] as its copper counterion, thus eliminating the subsequent addition to vinyl sulfone 5. However, addition of 12-crown-4 (4 eq.) to the above reaction media renders the methyl copper unreactive with respect to vinyl sulfone 5.

The complementary effect is seen with vinyl sulfone 1. Treatment of 1 with organocopper reagents, in the absence of additional lithium halide produces no reaction; while addition of excess lithium bromide affords the normal adduct cis-3a in 75% yield. Apparently the unreactivity of vinyl sulfone 1 with even large excesses of polymeric organocopper reagents is a consequence of chelation of the lithium halide, thus removing lithium halide from the reactive "halocuprate" species. Finally, we have observed that vinyl sulfone 1 completely inhibits the reaction of CH_3Cu-LiI with vinyl sulfone 5. These observations are consistent with the findings of House and others that alkyl copper reagents which are prepared free of lithium or magnesium halides are unreactive in conjugate-addition reactions[11]



5

6 (M= Li)
7 (M= Cu)
8 (M= H)

9 (M= Li)
10 (M= H)

11

a R= Me; b R= C_6H_5

TABLE II. REACTION OF ORGANOCOPPER REAGENTS WITH VINYL SULFONE 5.

Reagent	Solvent	Conditions	Yield:Products %8	%10	%11
$(CH_3)_2CuLi$ (2 eq)	THF	0.125M, 0°C, 1h	25	2.5	25
$(CH_3)_2CuLi$ (2 eq)	$(C_2H_5)_2O$	0.125M, 0°C, 1h	25	4.5	22
$(CH_3)_2CuLi$ (2 eq)	$C_6H_5CH_3$	0.125M, 0°C, 1h	35	5	23
$(CH_3)_2CuLi$ (2 eq)	$THF/(CH_3)_2S$	0.125M, 0°C, 1h	0	6	31
$(C_6H_5)_2CuLi$ (2 eq)	$THF/(CH_3)_2S$	0.125M, 0°C, 1h	90	--	--
$C_6H_5Cu(LiI)$ (5 eq)	$THF/(CH_3)_2S$	0.055M, 25°C, 18h	82	--	--
$CH_3Cu(LiI)$ (5 eq)	THF	0.054M, -78°C-RT, 18h	70	--	--
$CH_3Cu(LiI)$ (2 eq)	$(C_2H_5)_2O$	0.125M, 0°C, 1h	69	--	--
$CH_3Cu(LiI)$ (2 eq)	$C_6H_5CH_3$	0.125M, 0°C, 1h	90	--	--
$CH_3Cu(LiI)$ (5 eq) + 12-Crown-4 (4 eq)	Et_2O	0.125M, 0°C, 1h	0	--	--

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2. Lithium diallyl cuprate stereospecifically affords a trans allylated species. For a discussion of this result and its implications on the structure of the allyl cuprate reagent see: Hutchinson, D. K.; Fuchs, P. L., Tetrahedron Lett., following paper this issue.
3. Characterization of all new compounds was achieved by a combination of the standard spectral techniques. Yields refer to isolated material of >95% purity.
4. a) Posner, G. H.; Brunelle, D. J., Tetrahedron Lett. **1973**, 938; b) Posner, G. H.; Brunelle, D. J., J. Org. Chem. **1973**, 38, 2747.
5. Additional examples of conjugate-addition of cuprates to acyclic vinyl sulfones include: a) Eisch, J. J.; Galle, J. E., J. Org. Chem. **1979**, 44, 3278; b) Knochel, P.; Normant, J. F., Tetrahedron Lett. **1985**, 26, 425.
6. Hopkins, P. B.; Fuchs, P. L., J. Org. Chem. **1978**, 43, 1208.
7. The reluctance of intermediate 6b to undergo competitive addition to vinyl sulfone 5 is presumably a consequence of the size of the ß-phenyl substituent shielding the α-sulfonyl anion, thus slowing down the dimerization process relative to cuprate addition to 5.
8. Intramolecular carbon alkylation with sulfinate as a leaving group has been previously observed to afford cyclopropanes: a) Parker, W. L.; Woodward, R. B., J. Org. Chem. **1969**, 34, 3085; b) Julia, M.; Guy-Rouault, A., Bull. Soc. Chim. Fr. **1967**, 1411; c) Cambell, R. V. M.; Crombie, L.; Findley. D. A. R.; King, R. W.; Pattenden, G., J. Chem. Soc. Perkin Trans. I **1975**, 897; d) Agawa, T.; Yoshida, Y.; Komatsu, M.; Oshhiro, Y., J. Chem. Soc. Perkin Trans. I **1981**, 751.
9. It is probable that 10a and 11a have different relative stereochemistry at the points of attachment of the two five-membered rings since increasing the reaction time prior to workup does not increase the yield of 11a at the expense of 10a. Both compounds appear to be a single diastereomer by the criterion of carbon nmr. n-Butyl lithium treatment of the diastereomer of 10a which is isolated in the dimethylcuprate reaction produces intermediate 9 as demonstrated by deuterium incorporation, but this diastereomer does not cyclize to cyclopropyl sulfone 11a.
10. Slow addition of 0.5 equivalents of methyl lithium to vinyl sulfone 5 affords a mixture of 2:1 adducts 10a and 11a (30% each), demonstrating the viability of the proposed mechanism.
11. a) House, H. O.; Fisher, Jr., W, F., J. Org. Chem. **1968**, 33, 949; b) Luong-Thi, N.-T.; Riviere, H., Tetrahedron Lett. **1970**, 1579; c) Ibid., 1583.

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