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SUPPRESSION OF RACEMIZATION DURING THE DIASTEREOSELECTIVE C-3 FUNCTIONALIZATION OF 5-HYDROXYMETHYL-2-PHENYLTHIO-2-(*5H*)-FURANONES

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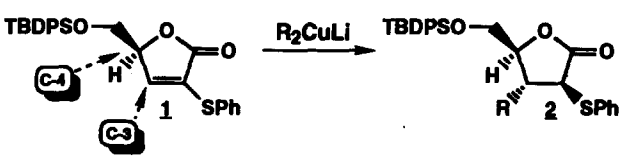
Summary: The methodology described herein examines the enantio- and stereoselective C-3 functionalization of 5-hydroxymethyl-2-(*5H*)-furanones via 1, 4-organocuprate addition as well as the involvement of temperature and TMSCl in the selectivity. The results imply that reactions carried out at -78°C and those carried out at 0°C to R.T. in the presence of TMSCl exhibit both high diastereoselection and enantioselection.

Chiral butyrolactones have shown considerable potential as synthetic intermediates in asymmetric synthesis. For example, Hanessian and co-workers have used chiral butyrolactones and butenolides in the stereocontrolled synthesis of acyclic molecules bearing multiple stereocenters.[1-4] In this methodology, the crucial stereoselective functionalization of the C-3 position in the butenolide systems was effected by the 1, 4-addition of a nucleophile.

In conjunction with several on-going projects, we sought to develop methodology for the C-3 functionalization of 1 via 1, 4-addition of an organocuprate reagent (**Scheme 1**). Our initial questions centered on the stereoselective

Scheme 1:

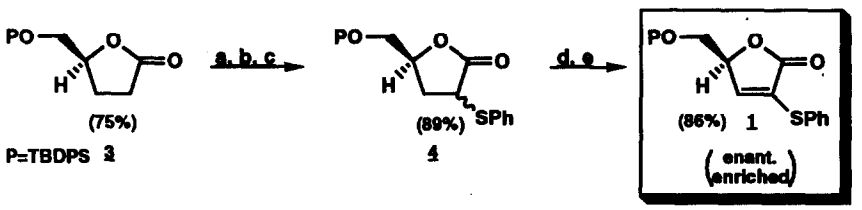


introduction of the nucleophile at C-3 and suppression of racemization at the acidic C-4 proton. The starting butenolide (1) was synthesized from protected hydroxymethyl butyrolactone 3 (available from L-glutamic acid[5]) by sulfenylation and subsequent elimination (**Scheme 2**). The unexpected degree of racemization at C-4 which was observed during the synthesis of 1 (82.46% enantiomeric excess (ee))[6], could be circumvented via crystallization of 1 to enantiomerically pure form (100% ee) from a chloroform/ petroleum ether mixture. The determination of the enantiomeric purity[6] of the starting material and that of subsequent reaction products, necessitated the use of racemic material as a standard comparison. The racemate of 3 (prepared via methods described by Hanessian)[7] was converted to racemic 1 using the same synthetic manipulations depicted in **Scheme 2**.

With butenolide (1) in hand, we turned to the main focus of our study, which was the 1,4-organocuprate additions to 1. Organocuprate additions can be problematic in cases in which the Gilman reagents decompose at approximately the same temperature at which they react.[8,9] Reported solutions to this problem include the use of $CuBr{\cdot}SMe_2$ to form the

cuprate, the use of higher order cuprates,[10-12] Lewis acid addition to increase reaction rate or any other variants which allow the desired reaction to proceed at low temperatures.[13,14] With butenolide (1), an additional problem could manifest itself. The considerable increase in the acidity of the proton at C-4 upon introduction of both the C-2/C-3 double bond and the 2-thiophenyl group could potentially lead to the racemization of the previously set C-4 stereocenter due to intermediate dienolate formation.

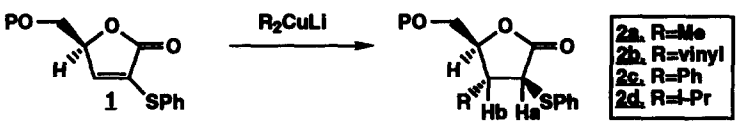
Scheme 2:



a. LDA (2.5 eq), THF, -78°C ; b. $(PhS)_2$, HMPA, THF,-78°C; c. $NH_4Cl_{(aq)}$, 25°C d. SO_2Cl_2, CCl_4, 0°C; e. $ZnCl_2$, $NaCO_3$, THF, 25°C.

The initial results of this study of the 1, 4-organocuprate addition (**Table I**) were in accord with this expectation. Our introductory studies used lithium dimethyl cuprate, according to the method of House *et al.*[12] (except that 1.04

Table I:



Cuprate /Type*‡	1 [% ee]	TMSCl (√)	Temp.	Time	R	2 [% ee] (% yield)
1. Me_2CuLi/ L.O.	94%		-78°C	24h	Me	...No Reaction
2. Me_2CuLi/ L.O.	94%		0°C	4h	Me	28% (73%)
3. Me_2CuLi/ L.O.	94%	√	0 - 25°C	14h	Me	84% (77%)
4. $R^1R^2CuCNLi_2$ / H.O.	82.46%		-78 - 0°C	0.5h	vinyl	35% (57%)
5. $R^1R^2CuCNLi_2$ / H.O.	100%	√	-78 - 0°C	0.5h	vinyl	100% (86%)
6. $(vinyl)_2CuLi$/ L.O.	99.64%		-78°C	1h	vinyl	100% (93.7%)
7. $(vinyl)_2CuLi$/ L.O.	99.64%	√	-78°C	1h	vinyl	99.85% (77%)
8. $(Ph)_2CuLi$/ L.O.	100%		-78°C	1h	Ph	100% (94%)
9. $(Ph)_2CuLi$/ L.O.	100%	√	-78 - 0°C	4h	Ph	100% (77%)
10. "(i-Pr)Cu"/ Cat.	100%	√	-78°C	3.5h	i-Pr	100% (50%)

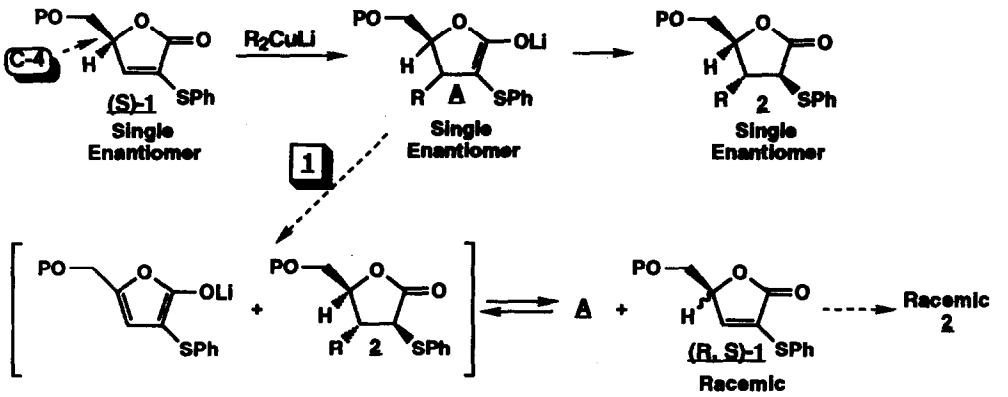
* R^1 = 2-thienyl; R^2 = vinyl; L.O. = Lower order; H.O. = Higher order; "(i-Pr)Cu" = cuprate formed from i-PrMgCl and catalytic copper bromide dimethyl sulfide complex[16]

‡ all products were fully characterized by both proton and carbon 13 NMR, combustion analysis, IR., and low resolution mass spectroscopy

equivalents of copper bromide dimethyl sulfide complex is used). In its reaction with 1, lithium dimethyl cuprate required an elevation in temperature from -78°C to 0°C for inducing reaction (**Table I, entries 1 and 2**). We observed also, that although reaction at 0°C proceeded in good chemical yield, we had effected almost total racemization of the previously set C-4 stereocenter (product ee of 28%).

This racemization (**Scheme 3**) is presumably due to the deprotonation-reprotonation at C-4 of 1 by the resultant enolate (A) formed in the 1, 4-addition reaction. Trapping enolate (A) with an electrophile such as TMSCl should, and does suppress this racemization (**Table I**, entry 3). However, inclusion of TMSCl retards the reaction rate (**Table I**, entries 2 and 3). This is contrary to literature precedents[13,15-17] which claim that TMSCl accelerates organocuprate reactions. This acceleration is not presumed to be due to prior complexation of TMSCl with the carbonyl oxygen of the α, β-unsaturated system. Rather, it has been proposed the this acceleration is due to TMSCl trapping of an initial dπ* complex, thereby forcing the conversion to the β carbonyl adduct.[14,15]

Scheme 3:



Lithium dimethyl cuprate is often considered to be a special case due to its low reactivity. In the interest of obtaining more widely applicable results, we decided to examine cuprates of greater reactivity. Also, in keeping with our original hypothesis that higher order cuprates might facilitate the 1, 4-addition, lithium (cyano)(2-thienyl)(vinyl)-cuprate[18] was chosen (**Table I, entries 4 and 5**). The results of using the higher order cuprate for reaction with 1 indicated that the absence of TMSCl, once again allowed racemization (**Table I, entry 4**), and the inclusion of TMSCl again prompted a marked suppression of racemization (**Table I, entry 5**). However, because TMSCl has previously been shown to sequester the cyano ligand from the higher order cuprate leaving the lower order cuprate as the reactive species,[19] it proved to be more pragmatic to perform the cuprate reaction under conditions previously used, employing lower order cuprates for more consistent results.

The lower order cuprates chosen for this study were formed using the copper bromide dimethyl sulfide complex used previously in the formation of lithium dimethyl cuprate. **Table I** depicts the results of the reaction of 1 with a number of these cuprates. Our results were consistent with those obtained in the dimethyl cuprate reactions with 1. We observed that the inclusion of TMSCl not only suppressed racemization but also retarded the reaction rate and often required the use of higher temperatures (0°C - R.T.) to effect reaction (**Table I, entries 7 and 9**). We also observed a suppression of racemization in the absence of TMSCl if the reaction did not necessitate higher temperatures, but rather could be performed at -78°C to effect reaction (**Table I, entries 6 and 8**).

In an effort to determine the generality of this highly stereoselective methodology, other examples of this 1, 4-addition were performed, one of which involves the use of a catalytic source of copper and a Grignard reagent in cuprate formation[16] (**Table I, entry 10**). This catalytic system provides the same enantioselective trend as shown in the previous examples. Additional examples not depicted in **Table I** include di-n-butyl and bis-trimethylsilylmethyl cuprates. These examples were carried out as in entries **6-9**, **Table I** and their reaction with 1 followed the previously defined (see **Table I**) trends.

Noteworthy also is the diastereoselectivity of these organocuprate reactions with 1. We observe only one diastereomer in each instance which we assign to be the trans/trans isomer based on well established literature precedents.[4] Furthermore, NMR assignment of the protons Ha and Hb (**Table I, 2a-d**) produced coupling constants, in all cases measured , greater than 11 Hz (e.g., **2a.** J_{HaHb}=11.41Hz; **2b.** J_{HaHb}=11.63 Hz) indicating a trans relationship of those protons.

As the mechanism of organocuprate reactions has been surrounded by controversy, many ideas, such as the single electron transfer mechanism,[20] have been proposed. Though the constraints this article do not lend themselves to mechanistic discussion, we note that the observed rate retardation, in the presence of TMSCl, is consistent with the trapping of a cuprate/ substrate complex prior to the rate-determining step. The results of our continuing efforts to elucidate mechanistic aspects of this study will appear in later publications.

In conclusion, we have demonstrated the stereo and enantioselective C-3 functionalization of thiobutenolide 1 via 1, 4-addition of organocuprate reagents. Our results indicate that: (a) although racemization can occur at elevated temperatures (0°C and higher), the use of low temperatures suppresses any racemization in these systems, and (b) if higher temperatures are necessary (i.e., when using less reactive cuprates) the inclusion of TMSCl suppresses racemization.

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