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ENANTIOCONTROLLED SYNTHESIS OF QUATERNARY CARBON CENTERS. 3,3-DISUBSTITUTED CYCLOPENTANONES. (+)-α-CUPARENONE.

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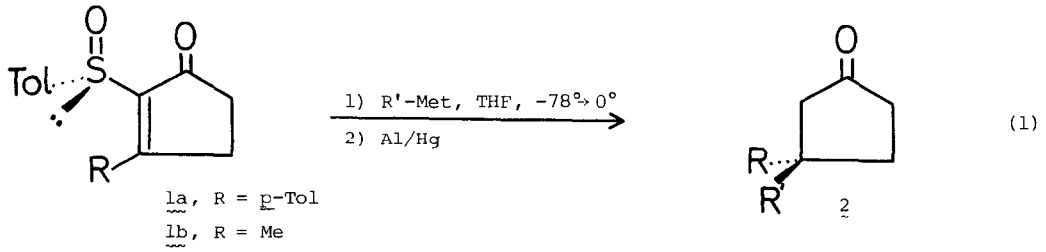
Summary: Asymmetric synthetic methodology is introduced for preparation of 3,3-disubstituted cyclopentanones, including (+)-α-cuparenone, of high enantiomeric purity.

We have recently introduced a highly effective, new synthetic method for enantiocontrolled preparation of tertiary carbon centers; various 3-substituted cycloalkanones of high enantiomeric purity were produced *via* asymmetric conjugate addition of organometallic reagents to easily-prepared enantiomerically pure 2-(arylsulfinyl)cycloalkenones.[1] Although quaternary carbon centers are pivotal and synthetically challenging structural components of many complex intermediates and natural products,[2] no general method has been available for stereocontrolled formation of molecules containing such quaternary centers in high enantiomeric purity.[3] We now report our success in preparing a series of 3,3-disubstituted cyclopentanones in 78-93% enantiomeric purity *via* asymmetric conjugate addition of different organocopper reagents to enantiomerically pure 3-methyl- and 3-p-tolyl-2-(p-tolylsulfinyl)cyclopentenones 1 (eq. 1 and Table I), as well as application of this enantiocontrolled carbon-carbon bond-forming process to a total synthesis of natural (+)-α-cuparenone, which contains two vicinal quaternary carbon centers.



1a, R = p-Tol
1b, R = Me

2

(1)

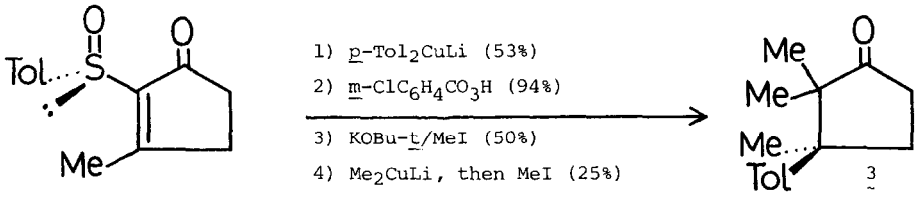
Table I. Asymmetric Synthesis of 3,3-Disubstituted Cyclopentanones 2 *via* eq. 1.

Entry	1, R =	R'-Met	% isolated yield	% e.e.
1	p-Tol	Me_2CuLi	58	78[a,b]
2	p-Tol	Me(PhS)CuMgBr	77	73[b]
3	p-Tol	$Me_5Cu_3Li_2$	44	65[a,b]
4	p-Tol	n-Bu_2CuLi	0	-
5	p-Tol	n-Bu(PhS)CuMgCl	69	81[b]
6	Me	p-Tol_2CuLi	53	90-93[a,b]
7	Me	n-Bu(PhS)CuMgCl	79	53[b]
8	Me	n-Bu(t-BuO)CuMgCl	61	88[a]

a. Determined by polarimetry. b. Determined by ^{13}C NMR spectroscopy of the corresponding diastereomeric (R,R)-(−)-2,3-butanediol ketals: Hiemstra, H. and Wynberg, H., Tetrahedron Lett. 1977, 2183.

Several features of the results summarized in Table I deserve comment. First and foremost, quaternary centers have been formed successfully and in a highly enantiocontrolled fashion *via* addition of methyl, n-butyl, and p-tolyl groups. Second, adding a methyl group to 3-tolylcyclopentenone sulfoxide 1a leads to (S)-3-methyl-3-tolylcyclopentanone, whereas reversing the sequence by adding a tolyl group to 3-methylcyclopentenone sulfoxide 1b leads to the opposite (R)-enantiomer; these are, therefore, complementary conjugate addition reactions the absolute stereochemistry of which is predictable using our proposed chelate model.[1] Third, adding zinc dibromide followed by Grignard reagents[1b,d] or dimethylmagnesium[1e] to 3-substituted cyclopentenones 1 produces only 1,2- and not 1,4-adducts. Fourth, despite the many advances in organocopper chemistry during the past 15 years,[4] there remains much subtlety and trial and error in selection of the best organocopper reagent for difficult carbon-carbon bond formations such as those in eq. 1. For example, although dimethylcopperlithium and ditolylcopperlithium work well (entries 1 and 6), di-n-butylcopperlithium does not (entry 4). Likewise, although $Me_5Cu_3Li_2$ works well (entry 3),[5] $Me_2Cu(CN)Li_2$[6] and $MeCu{\cdot}BF_3$[7] (and MeTi(OPr-i)$_3$[8]) do not. Furthermore, several alkyl(hetero)cuprate reagents,[9] especially n-Bu(t-BuO)CuMgCl (entry 8), work extremely well. It is clear, therefore, that no one type of organocopper reagent will be universally preferred over others for all different kinds of carbon-carbon bond-forming reactions.

We have now applied this asymmetric synthesis of quaternary carbon centers to preparation of natural (+)-α-cuparenone[3,10] (3) in 71% enantiomeric purity (eq. 2). The sulfinyl group serves as a temporary chiral auxiliary faithfully transferring chirality from sulfur to carbon during the asymmetric conjugate addition step;[1] the corresponding sulfonyl group promotes enolate ion C-methylation[11] and then serves as a precursor for regiospecific generation of the more hindered enolate of a 2,3,3-trisubstituted cyclopentanone under aprotic conditions,[1a] thus allowing C-methylation and formation of two adjacent quaternary centers[12] (eq. 2). This direct, short, and enantiocontrolled[13] preparation of (+)-α-cuparenone (3, $[\alpha]_D^{25}$ + 121°)[13] can also be applied to synthesis of the opposite enantiomer, natural (−)-α-cuparenone, simply by reversing the sequence of introducing the 3-tolyl and the 3-methyl groups (see the table, entries 1-3 vs. 6).



(2)

The results described here represent an important and effective new procedure for construction of quaternary carbon centers with excellent control of absolute stereochemistry. We are actively pursuing the scope and limitations of this asymmetric methodology as well as its application to preparation of other natural products of high enantiomeric purity.

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11. *cf.* Carroll, N. M. and O'Sullivan, W. I. J. Org. Chem. (1965), 30, 2830. We thank Chris Switzer of this department for this reference.

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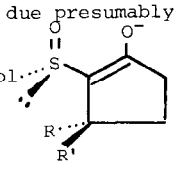
13. Apparently enolate i was transformed into cuparenone at a rate different from that of diastereomeric enolate ii; although the initial conjugate addition proceeded with 93% asymmetric induction, (+)-cuparenone of 71% enantiomeric purity was obtained due presumably to one or more diastereolective steps in eq. 2.



i, R = Tol, R' = Me
ii, R = Me, R' = Tol

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