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A SURPRISING EFFECT OF A 3-PHENYL GROUP ON THE STEREOCHEMISTRY OF CYCLOPENTANONE ENOLATE ALKYLATION. HIGHLY STEREOSELECTIVE ORGANOCOPPER 2,3-DIALKYLATION OF 2-CYCLOPENTENONES. SYNTHESIS OF SESQUITERPENE HYDROCARBON (±)-LAURENE

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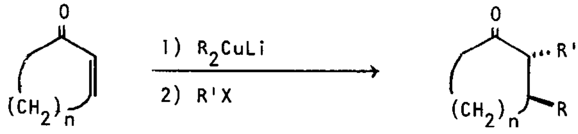
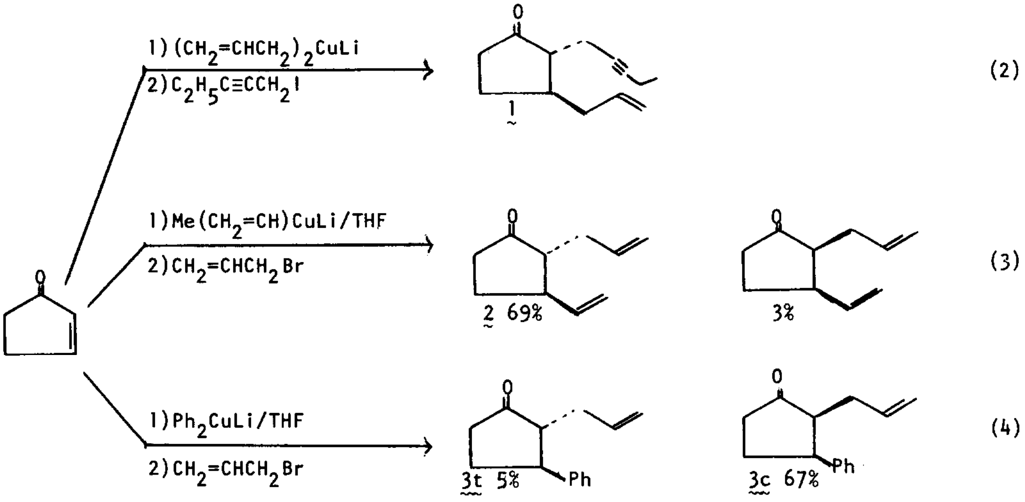
The intermediates generated via diorganocopperlithium addition to α,β-ethylenic ketones can react with certain electrophiles to form α,β-dialkylated ketones[1,2]. This vicinal dialkylation has been used as an effective key step in synthesis of different complex organic structures including alkaloids[3], sesquiterpenes[2f,4] and especially prostaglandins[5]. Most of the organocuprate β-addition - α-alkylations of 2-cyclopentenones and 2-cyclohexenones have involved introduction of the nucleophilic β-substituent and the electrophilic α-substituent preferentially in a trans stereochemical relationship (eq. 1)[2]. In contrast, we now report the surprising observation that lithium diphenylcuprate addition to 2-cyclopentenones followed by α-alkylation involves attachment of the two new substituents stereoselectively in a cis-relationship even through such cis-2-alkyl-3-phenylcyclopentanones are less stable than their trans-epimers.

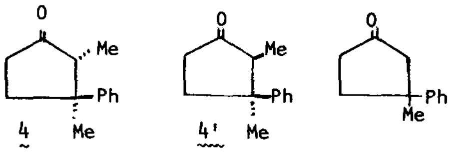


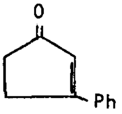
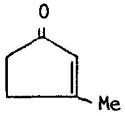
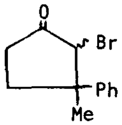
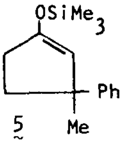
(1)

This influence of a β-phenyl substituent on the stereochemistry of cyclopentanone enolate α-alkylation is unique; even such π-electron substituents as β-allyl and β-vinyl groups do not direct α-alkylation cis to themselves. Thus β-allylation - α-propargylation of 2-cyclopentenone gave only trans-2,3-disubstituted cyclopentanone 1[6], and likewise β-vinylation - α-allylation gave trans-isomer 2 stereoselectively[2f]. In striking contrast, diphenylcuprate β-addition followed by α-allylation of 2-cyclopentenone gave cis-2-allyl-3-phenyl isomer 3c with very high stereoselectivity. This is the first example of an organocopper cis-2,3-dialkylation leading to the less stable of two epimers. In the presence of sodium acetate in ethanol, cis-isomer 3c equilibrated to a 95:5 trans:cis mixture of epimers 3t and 3c.



Equations 5 and 6 represent a complementary pair of experiments. Whether the β-phenyl group is present in the reactant (eq. 5) or is attached via diphenylcuprate β-addition (eq. 6), the major product of α-methylation is the *cis*-2-methyl-3-phenyl isomer **4'**. Equation 7 shows that a β-phenylcyclopentanone enolate intermediate generated via organocuprate-halogen *exchange*[7] (and not organocuprate *addition*) also undergoes α-methylation leading stereoselectively to *cis*-isomer **4'**. Basic equilibration of *cis*-2-methyl-3-phenylcyclopentanone **4'** led to a 95:5 mixture of isomers 4:4'. That the 2-methyl and 3-phenyl groups of isomer **4'** are *cis* to each other is further shown by the nmr chemical shift of the 2-methyl doublet (δ 0.78) which is deshielded relative to the chemical shift of the methyl doublet (δ 0.95) of the more stable epimer **4**; this nmr methyl deshielding effect of a 3-aryl group in a *cis*-2-methyl-3-arylcyclopentanone has been noted previously[8]. For comparison, equation 8 is included to show that the cyclopentanone lithium enolate ion derived from enol silyl ether **5**[9] undergoes α-methylation to form mainly the more stable isomer **4**. We choose at this time not to compare the *nature* of the lithium enolate derived from enol silyl ether **5** with that of the intermediate generated *via* organocuprate addition as in eqs. 5 and 6 or via organocuprate exchange as in eq. 7; such a comparison is being examined and will be the subject of a future publication. Intramolecular metal-arene π-coordination could be involved in controlling the stereoselectivity of this enolate alkylation process (*cf* our accompanying publication)[10,11]. We emphasize now, however, the *operational* simplicity and reproducibility with which *cis*-2-alkyl-3-phenylcyclopentanones can be prepared stereoselectively using organocuprate reagents. That the organocuprate reagents and reaction conditions cause essentially no epimerization of the less to the more stable isomers (**3c** → **3t**, **4'** → **4**)[12] is a highly significant and useful feature of these nucleophilic and relatively non-basic organometallic reagents.



	1) Me_2CuLi, Et_2O, 0°, 2 hr 2) MeI, HMPA, 25°, 4 hr	4 : 96(40%)	49%	(5)
	1) Ph_2CuLi, Et_2O, 0°, 2 hr 2) MeI, HMPA, 25°, 4 hr	10 : 90(65%)	22%	(6)
	1) Me_2CuLi, Et_2O, 0°, 1 hr 2) MeI, HMPA, 25°, 2hr	4 : 96(74%)	5%	(7)
	1) MeLi, Et_2O, 25°, 1 hr 2) MeI, HMPA, 0°, 0.5 hr 25°, 4 hr	95 : 5(43%)	45%	(8)

Using these organocuprate non-epimerizing reactions and this *cis*-directing effect of a β-aryl group, we have prepared *cis*-2-methyl-3-tolylcyclopentane **6** stereoselectively *via* dimethylcuprate β-addition - α-methylation of 3-tolyl-2-cyclopentenone (eq. 9). *cis*-2-Methyl-3-tolylcyclopentanone **6** has been prepared previously by a long and tedious route and has been methylenated without epimerization to give sesquiterpene hydrocarbon (±)-laurene[8a]. Thus this organocuprate regiospecific and stereoselective β-addition - α-alkylation sequence represents a new and efficient synthetic approach for preparation of *cis*-2-alkyl-3-arylcyclopentanes such as (±)-laurene and possibly related α,β-disubstituted cyclopentane derivatives such as α-cuparenone[13], α-cuparenol and α-isocuparenol[14,15].

We are studying the effect of a β-phenyl group on cyclo*hex*anone enolate alkylation, and we are examining the nature of the organocopper generated enolate intermediates.

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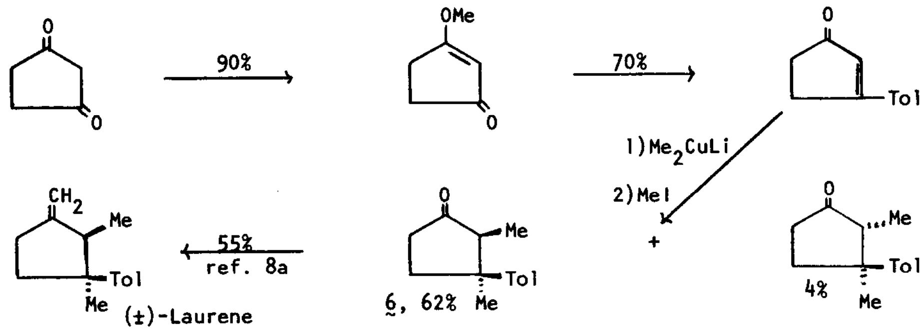

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References

1. For reviews, see: (a) G. H. Posner, Org. Reactions, 19, 1 (1972); (b) J. d'Angelo, Tetrahedron, 32, 2979 (1976); (c) H. O. House, Accts. Chem. Research, 9, 59 (1976); (d) J. F. Normant, J. Organometal Chem. Lib., 1, 219 (1976).
2. For specific examples see: (a) R. M. Coates and L. O. Sandefur, J. Org. Chem., 39, 275 (1974); (b) R. K. Boeckman, Jr., ibid., 38, 4450 (1973); (c) R. K. Boeckman, Jr., J. Amer. Chem. Soc., 95, 6867 (1973); (d) R. K. Boeckman, Jr., ibid., 96, 6179 (1974); (e) G. Stork and J. Singh, ibid., 96, 6181 (1974); (f) G. H. Posner, J. J. Sterling, C. E. Whitten, C. M. Lentz, and D. J. Brunelle, ibid., 97, 107 (1975), and references cited therein; (g) F. Naf, R. Decorzant, and W. Thommen, Helv. Chim. Acta, 58, 1808 (1975); (h) G. Stork and M. Isobe, J. Amer. Chem. Soc., 97, 6260 (1975); (i) K. K. Heng and A. J. Smith, Tetrahedron Lett., 589 (1975); (j) G. Büchi, D. Berthet, R. Decorzant, A. Grieder, and A. Hauser, J. Org. Chem., 41, 3208 (1976); (k) E. S. Binkley and C. H. Heathcock, ibid., 40, 2156 (1975).
3. G. Stork, Pure Appl. Chem., 17, 383 (1968).
4. (a) R. A. Kretchmer and W. M. Schafer, J. Org. Chem., 38, 95 (1973); (b) A. F. Thomas, M. Ozainne, R. Decorzant and F. Naf, Tetrahedron, 32, 2261 (1976).
5. (a) T. Toru, S. Kurozumi, T. Tanaka, and S. Miura, Tetrahedron Lett., 4087, 4091 (1976); (b) G. Stork and M. Isobe, J. Amer. Chem. Soc., 97, 4745 (1975); (c) T. Tanaka, S. Kurozumi, T. Toru, M. Kobayashi, S. Miura, and S. Ishimoto, Tetrahedron Lett., 1535 (1975); (d) J. W. Patterson, Jr. and J. H. Fried, J. Org. Chem., 39, 2506 (1974).
6. A. E. Greene and P. Crabbé, Tetrahedron Lett., 4867 (1976).
7. (a) G. H. Posner, Org. Reactions, 22, 253 (1975); (b) G. H. Posner and J. J. Sterling, J. Amer. Chem. Soc., 95, 3076 (1973).
8. (a) J. E. McMurry and L. A. von Beroldingen, Tetrahedron, 30, 2027 (1974), and references therein; (b) T. Irie, T. Suzuki, Y. Yasunari, E. Kurosawa, and T. Masamune, ibid., 25, 459 (1969).
9. G. Stork and P. Hudrlik, J. Amer. Chem. Soc., 90, 4462, 4464 (1968)
10. G. H. Posner and C. M. Lentz, Tetrahedron Lett., 000 (1977).
11. (a) Lithium-arene π-coordination has been noted (e.g. S. P. Patterman, I. L. Kark, and G. D. Studky, J. Amer. Chem. Soc., 92, 1150 (1970); (b) copper(I)-arene π-coordination has been observed (e.g. R. G. Solomon, J. K. Kochi, Chem. Commun., 559 (1972); (c) the effect of a 3-naphthyl group on the stereochemistry of cyclopentanone enolate alkylation in a steroid synthesis has been noted by A. J. Birch and G. S. R. S. Rao, Aust. J. Chem., 23, 547 (1970).
12. cis-4-Acetyl-t-butylcyclohexane is also not epimerized by organocopper reagents: N. T. Luong-Thi, H. Rivière, J.-P. Begue, C. Forrestier, Tetrahedron Lett., 3187 (1967).
13. T. Irie, T. Suzuki, S. Ito, and E. Kurosawa, Tetrahedron Lett., 3187 (1967).
14. For a recent unsuccessful attempt to use an organocuprate addition to a 2-cyclopentenone, see A. Casares and L. A. Maldonado, Synth. Commun., 6, 11 (1976).
15. T. Suzuki, M. Suzuki, and E. Kurosawa, Tetrahedron Lett., 1975, 3057.