Enantioselective Carbolithiation of Cinnamyl Acetals. New Access to Chiral Disubstituted Cyclopropanes

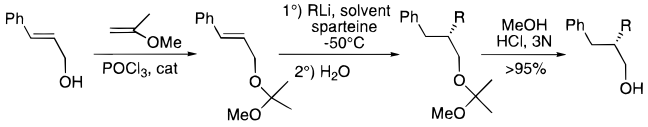
Stephanie Norsikian, Ilane Marek,*
Jean-François Poisson, and Jean F. Normant*

Laboratoire de Chimie des Organoéléments, Université P. et M. Curie, associé au CNRS URA 473, 4 Place Jussieu, 75252 Paris Cedex 05, France

Received March 21, 1997

The addition of an organometallic reagent to an unactivated olefin is generally difficult to control since such an addition may lead to polymerization of the olefin[1] unless the final organometallic adduct is stabilized[2] or differs markedly from the starting one.[3] Indeed, since the initial work of Wittig,[4] who showed that the presence of a donor group in the proximity of the double bond of the alkene promotes the carbolithiation reaction,[2] the stereochemical outcome of the addition of alkyllithiums (and the reactivity of the new carbon metal bond as stereogenic center) to substituted allylic alcohols were investigated.[2,5] However, enantioselective carbometalation reactions are still scarce, although actively studied by different groups,[6] due to the difficulty for enantiofacial differentiation of an unactivated alkene. In this context, we have recently described a new asymmetric carbolithiation of cinnamyl derivatives in the presence of (−)-sparteine, which leads to the corresponding carbometalated product in 66−80% enantiomeric excess.[7] In a search to increase these enantiomeric excesses, we decided to examine different chiral ligands[8] but none of them provided enantioselectivities as high as (−)-sparteine. So, we investigated this problem following a different approach. Indeed, recent theoretical studies by Houk[9] and Bailey[10] reveal that the initial step for the intermolecular as well as intramolecular carbometalation is an energetically favorable coordination of the lithium atom with the π-system,[11] which serves to establish the geometry of the system prior the addition to occur. Thus, in order to promote this initial π-chelation, we decided to increase the association between the organolithium and the functional group of the substrate to enforce the proximity effect (called complex induced proximity effects,[12] CIPE). So, we have prepared the dimethyl acetal[13] of the (*E*)-cinnamyl alcohol and studied the enantioselective carbolithiation, in the presence of (−)-sparteine, as described in Scheme 1.

Scheme 1



Addition of the substrate to a solution of various alkyl lithiums in hexane (or cumene) in the presence of 1 equiv of (−)-sparteine[14] leads, after hydrolysis, to the corresponding carbometalated products in good yield. After deprotection of the acetal moieties, the alcohols were obtained in very good enantiomeric excesses as determined according to Alexakis and Mangeney[15] (see Table 1). The use of the acetal allows the reaction to proceed at −50 °C instead of 0 °C for the carbolithiation of the corresponding alcohol.[7] Primary (in the absence (entries 1−3) or in the presence[7] (entry 5) of lithium salts)) and secondary organolithiums (entry 4) undergo enantioselective carbolithiations in the presence of 1 equiv of (−)-sparteine in hexane (or in cumene) *via* this simple method. The results summarized in Table 1 show also that addition to this cinnamyl acetal in the presence of a catalytic amount of (−)-sparteine (10%) also leads to good enantiomeric excess (entries 6, 8, and 9), even with 1% of chiral ligand (entry 7), whatever the nature of the alkyllithium used (primary or secondary). Moreover, the product itself is not an enantioselective catalyst[16] since the hydrolysis of the reaction mixture after only 30% conversion leads to the same enantiomeric excess.

With the chiral benzylic organolithium in hand (before hydrolysis), we then studied its reaction with an in-

(1) (a) Ziegler, K.; Gellert, H. G. *Liebigs Ann. Chem.* **1950**, *567*, 195. (b) Morton, M. *Anionic Polymerization: Principles and Practice*; Academic Press: New York, 1963.

(2) (a) Crandall, J. K.; Clark, A. C. *Tetrahedron Lett.* **1969**, 325. (b) Crandall, J. K.; Clark, A. C. *J. Org. Chem.* **1972**, *37*, 4236. (c) Felkin, H.; Swierczewski, G.; Tambute, A. *Tetrahedron Lett.* **1969**, 707. (d) Dimmel, D. R.; Huang, S. *J. Org. Chem.* **1973**, *38*, 2756.

(3) For the synthesis and reactivity of sp^3 organogembismetallic *via* a carbometalation reaction, see: Marek, I.; Normant, J. F. *Chem. Rev.* **1996**, *96*, 3241.

(4) (a) Wittig, G.; Otten, J. *Tetrahedron Lett.* **1963**, 601. (b) Klumpp, G. W.; Veefkind, A. H.; Graaf, W. L.; Bickelhaupt, F. *Liebigs Ann. Chem.* **1967**, *706*, 47. (c) Veefkind, A. H.; Bickelhaupt, F.; Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 1058. (d) Veefkind, A. H.; Schaaf, J. V. D.; Bickelhaupt, F.; Klumpp, G. W. *J. Chem. Soc., Chem. Commun.* **1971**, 722. (e) Kool, M.; Klumpp, G. W. *Tetrahedron Lett.* **1978**, 1873.

(5) (a) Kato, T.; Marumoto, S.; Sato, T.; Kuwajima, I. *Synlett* **1990**, 671. (b) Marumoto, S.; Kuwajima, I. *Chem. Lett.* **1992**, 1421. (c) Marumoto, S.; Kuwajima, I. *J. Am. Chem. Soc.* **1993**, *115*, 9021. (d) Klein, S.; Marek, I.; Normant, J. F. *J. Org. Chem.* **1994**, *59*, 2925.

(6) Asymmetric carbocupration of cyclopropene: (a) Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **1990**, *112*, 7428. Asymmetric allylzincation of cyclopropene: (b) Kubota, K.; Nakamura, M.; Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **1993**, *115*, 5879. (c) Nakamura, M.; Arai, M.; Nakamura, E. *J. Am. Chem. Soc.* **1995**, *117*, 1179. Zirconium-catalyzed asymmetric ethylmagnesiation: (d) Morken, J. P.; Didiuk, M. T.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6997. (e) Hoveyda, A. H.; Morken, J. P. *J. Org. Chem.* **1993**, *58*, 4237. (f) Morken, J. P.; Didiuk, M. T.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *116*, 3123. (g) Visser, M. S.; Heron, N. M.; Didiuk, M. T.; Sagal, J. F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 4291. (h) Bell, L.; Whitby, R. J.; Jones, R. V. H.; Standen, M. C. H. *Tetrahedron Lett.* **1996**, *37*, 7139. Zirconium-catalyzed asymmetric alkylalumination: (i) Kondakov, D. Y.; Neghishi, E. I. *J. Am. Chem. Soc.* **1995**, *117*, 10771. (j) Kondakov, D. Y.; Neghishi, E. I. *J. Am. Chem. Soc.* **1996**, *118*, 1577 Asymmetric ring opening of an oxabicyclic compound: (k) Lautens, M.; Gajda, C.; Chiu, P. *J. Chem. Soc., Chem. Commun.* **1993**, 1193. Intramolecular carbolithiation: (l) Coldham, I.; Hufton, R.; Snowden, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 5322. (m) Krief, A.; Bousbaa, J. *Synlett* **1996**, 1007. (n) Asymmetric carbometalation of zincated hydrazones to cyclopropene: Nakamura, E.; Kubota, K. *J. Org. Chem.* **1997**, *62*, 792.

(7) Klein, S.; Marek, I.; Poisson, J. F.; Normant, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 8853.

(8) The synthesis and the enantioselectivities of these different ligands will be reported in due course.

(9) Houk, K. N.; Rondan, N. G.; Schleyer, P.v.R.; Kaufmann, E.; Clark, T. *J. Am. Chem. Soc.* **1985**, *107*, 2821.

(10) Bailey, W. F.; Khanolkar, A. D.; Gavaskar, K.; Ovaska, T. V.; Rossi, K.; Thiel, Y.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 5720.

(11) (a) Oliver, J. P.; Smart, J. B.; Emerson, M. T. *J. Am. Chem. Soc.* **1966**, *88*, 4101. (b) St. Denis, J.; Oliver, J. P. *J. Am. Chem. Soc.* **1972**, *94*, 8260. (c) Dolzine, T. W.; Oliver, J. P. *J. Organomet. Chem.* **1974**, *78*, 165. (d) St. Denis, J.; Oliver, J. P.; Smart, J. B.; Dolzine, T. W. *J. Organomet. Chem.* **1974**, *78*, 165.

(12) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.

(13) Klug, A. F.; Untch, K. G.; Fried, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 7827.

(14) For a recent review on the use of (−)-sparteine in asymetric syntheses, see: Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552 and references cited therein.

(15) (a) Alexakis, A.; Frutos, J. C.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1994**, *59*, 3326. (b) Alexakis, A.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1992**, *57*, 1224.

(16) For a highlight see: Bolm, C.; Bienewald, F.; Seger, A. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1657 and references cited therein.

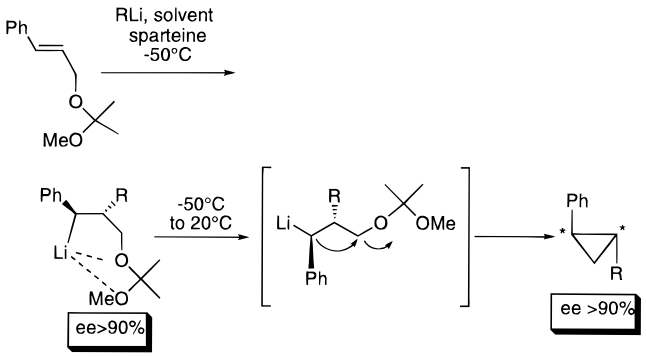
S0022-3263(97)00517-3 CCC: $14.00

Table 1

entry[a]	RLi	alcohol	(−)-sparteine (equiv)[b]	solvent	yield[c] (%)	ee[d] (%)
1	*n*-BuLi	**2**	1	cumene	72	95
2	*n*-BuLi	**2**	1	hexane	77	94
3	HexLi	**3**	1	cumene	70	94
4	*s*-BuLi[e]	**4**	1	cumene	80	90
5	HeptLi, LiBr[f]	**5**	1	cumene	50	90
6	*n*-BuLi	**2**	0.1	hexane	67	92
7	*n*-BuLi	**2**	0.01	hexane	50	85
8	HexLi	**3**	0.1	hexane	65	92
9	*s*-BuLi[e]	**4**	0.1	hexane	77	92

[a] The reactions were carried out by addition of the substrate to the RLi−sparteine mixture at −50 °C. [b] Based on the cinnamyl substrate. [c] Based on pure isolated product, after deprotection of the acetal (yield of the deprotection >95%). [d] ee was determined by ^{31}P NMR.[15] [e] As a mixture of two diastereomers from the use of *s*-BuLi. [f] The organolithium reagents were prepared in Et_2O, and the addition was carried out in cumene, see ref 7.

Scheme 2



tramolecular electrophile, namely the acetal moiety. Indeed, when the chelating moiety is a *dimethyl*-methoxymethyl ether, the formed benzylic organolithium species is not stabilized but becomes thermally labile,[17] when the reaction mixture is simply warmed to room temperature and leads to a pure chiral *trans* disubstituted cyclopropane,[18] *via* an internal nucleophilic substitution, as described in Scheme 2 and Table 2.

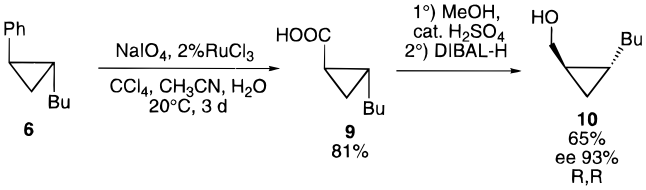
The alkyl and phenyl groups in these cyclopropanes are *anti* to each other and may result from a W-shaped transition state.[19] Indeed, in this transformation, the initially formed stereogenic center C−R is invariant, when established during the carbolithiation reaction step,

Table 2

entry[a]	RLi	cyclopropane	(−)-sparteine (equiv)[b]	solvent	yield[c] (%)
1	*n*-BuLi	**6**	1	cumene	60
2	*n*-BuLi	**6**	0.1	hexane	61
3	*s*-BuLi[d]	**7**	0.1	hexane	66
4	HexLi	**8**	0.1	hexane	59

[a] After the carbometalation reaction, the mixture is rapidly warmed to room temperature. [b] Based on the cinnamyl substrate. [c] Based on pure isolated product and calculated from the cinnamyl substrate. [d] As a mixture of two diastereomers from the use of *s*-BuLi.

Scheme 3



whereas the benzylic carbon is free to epimerize[19] and to promote the formation of the thermodynamically more stable *trans* cyclopropane.[5] According to this, the optical purities of the *trans* cyclopropanes thus obtained[20] are considered to be the same as those of the linear acetals described in Table 1.

In order to prove this enantioselection and the absolute configuration, the cyclopropane **6** was derivatized into a known product according to Scheme 3.

The 1(*R*)-phenyl-2(*R*)-butylcyclopropane (**6**) was first oxidized[21] into the corresponding acid **9** in 81% yield. The esterification followed by the reduction of the resulting ester leads to the 2(*R*)-butyl-1(*R*)-cyclopropylmethanol (**10**), known in the literature,[22] and the purity of the chiral disubstituted cyclopropanol (93% ee) was determined by NMR by the use of chiral derivating agents.[15] The same sequence was performed on the cyclopropane **6**, generated in the presence of a catalytic amount of (−)-sparteine, and the same enantiomeric excess was obtained for **10**.

In conclusion, the use of the dimethyl acetal of the (*E*)-cinnamyl alcohol allows a high enantioselective carbolithiation in the presence of a catalytic amount of (−)-sparteine to give, after hydrolysis at low temperature, the corresponding alkylated product in 90−95% ee. By warming the reaction mixture to room temperature, this benzylic organolithium intermediate undergoes a 1,3-elimination to give the chiral disubstituted cyclopropane in 90−93% ee.

Supporting Information Available: Typical experimental procedures and spectral data of products (10 pages).

JO9705172

(17) The formation of cyclopropane by 1,3-elimination between an organogembismetallic and a methoxymethyl ether was already described: (a) Marek, I.; Beruben, D.; Normant, J. F. *Tetrahedron Lett.* **1995**, *36*, 3695. (b) Beruben, D.; Marek, I.; Normant, J. F.; Platzer, N. *J. Org. Chem.* **1995**, *60*, 2488. (c) Beruben, D.; Marek, I.; Normant, J. F.; Platzer, N. *Tetrahedron Lett.* **1993**, *34*, 7575.

(18) For some representative formations of chiral cyclopropanes, see: (a) Charette, A. B.; Marcoux, J. F. *Synlett* **1995**, 1197 and references cited therein. (b) Salaün, J. *Chem. Rev.* **1989**, *89*, 1247. (c) Romo, D.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 6265. (d) Davies, H. M. L.; Huby, N. J. S.; Cantrell, W. R., Jr.; Olive, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 9468. (e) Doyle, M. P. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993; Chapter 3. (f) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339. (g) Evans, D. A.; Woerpel, K. A.; Scott, M. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 430. (h) Denmark, S. E.; O'Connor, S. P. *J. Org. Chem.* **1997**, *62*, 584.

(19) Krief, A.; Hobe, M. *Tetrahedron Lett.* **1992**, *33*, 6529.

(20) For a previous report on the synthesis of chiral cyclopropane mediated by a stoichiometric amount of (−)-sparteine see: Paetow, M.; Kotthaus, M.; Grehl, M.; Frölich, R.; Hoppe, D. *Synlett* **1994**, 1034.

(21) Carlsen, H. J.; Katsuki, T.; Martin, V. S. Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(22) Imai, T.; Mineta, H.; Nishida, S. *J. Org. Chem.* **1991**, *55*, 4986.