Asymmetric Carbolithiation of Cinnamyl Derivatives in the Presence of (−)-Sparteine

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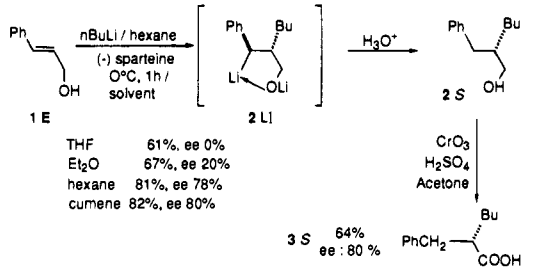
Received November 30, 1994
Revised Manuscript Received May 17, 1995

Carbometalation of a 1,2-disubstituted olefin leads to the formation of a new organometallic species bearing two contiguous stereogenic centers.[1] Although the carbolithiation reaction of isolated or unstrained double bonds[1a] is rather limited, the addition of alkyllithiums on allylic alcohols has received, recently, a great deal of interest,[2] and the beneficial effect of tetramethylethylene diamine (TMEDA) on the rate of carbolithiation of cinnamyl derivatives has been noted.[1e,2] However, in the presence of ligands such as TMEDA (or DABCO), which enhance the reactivity of organolithium derivatives by reducing their aggregation,[3] extensive polymerization is observed;[4] alkyllithium reagents are in fact excellent initiators for anionic polymerization, especially of styrene and conjugated dienes.[5] Consequently, the presence of a donor group proximal to the reacting alkene is essential to avoid polymerization and promote the carbolithiation reaction through precoordination of the lithium reagent with the heteroatom. If an efficient method were available to render such a process asymmetric, it would acquire utility as a method for the creation of asymmetric vicinal carbon atoms, particularly where acyclic substrates are employed. However, until now, such enantioselective carbometalations are scarce, due to the difficulty in enantiofacial differentiation of an unactivated alkene.[6] Herein, we report the results of our preliminary investigations in the area of asymmetric carbolithiation in the presence of the readily available chiral diamine (−)-sparteine.[7] Thus, addition of (*E*)-cinnamyl alcohol (**1E**) to a solution of nBuLi in various solvents in the presence of 1 equiv of (−)-sparteine leads to a red solution which is hydrolyzed to give the corresponding alcohol[2a] in the yields and enantiomeric excesses[11] shown in Scheme 1.

Scheme 1



Sparteine has the most pronounced effect in the absence of donor solvents, such as ether or THF. Indeed, in hexane or cumene,[8] higher enantiomeric excesses are obtained for the carbolithiation reaction. The purity of the chiral alcohol **2** was determined by the ^{31}P NMR analysis of derived diastereomeric phosphorus products.[9] The absolute configuration of the *chiral* center was determined to be *S*, through comparison with data reported for the corresponding acid[11] (Scheme 1). This simple method allows the enantioselective introduction of an alkyl group on the olefinic residue of a variety of cinnamyl derivatives, as described in Table 1. The presence of a free alcohol is not a necessity as a similar ee is obtained with a *tert*-butyl ether[12] (Table 1, entry 1 versus entry 2). Cinnamyldimethylamine[13] (Table 1, entry 3) also leads to the carbometalated product[2e] with a good ee, whereas a secondary amine affords a lower ee[14] (Table 1, entry 4). This drawback can be circumvented by the use of benzylmethylcinnamylamine (Table 1, entry 5), followed by hydrogenolysis of the benzyl moiety of the addition product. The secondary amine is now obtained in 84% ee; the absolute configuration was determined by correlation with the secondary amine **6**.[14b] Finally, carbolithiation of a homoallylic alcohol (Table 1, entry 6) shows only a slight decrease in the enantiomeric ratio.

The addition of nBuLi in Et_2O in the presence of LiBr and 1 equiv of sparteine slows down the reaction prohibitively (<5% conversion). This result implicates a mixed aggregate of lithium halide and sparteine which deactivates the carbolithiation reaction. Indeed, the reaction of cinnamyl alcohol with 3 equiv

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(8) Due to the low solubility of the starting material in hexane, cumene will be preferred for the following carbolithiation.

(9) Obtained by successive addition in an NMR tube of a C_2 symmetrical diamine,[10] $CDCl_3$, diethylaniline as neutralizing base, PCl_3, and the chiral alcohol. This instantaneous and quantitative reaction allows the preparation of the trivalent phosphorus derivative, and the enantiomeric composition is easily determined. (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.

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(12) The enantiomeric excess was determined after deprotection of the *tert*-butyl ether into the alcohol according to Alexakis et al.: Alexakis, A.; Gardette, M.; Colin, S. *Tetrahedron Lett.* **1988**, *29*, 2954.

(13) The enantioselection of the carbolithiation of *N,N*-dimethyl-2(*S*)-benzyl-1-hexanamine was determined by chiral HPLC Chirasel O.D.

(14) (a) In this case the reaction does not occur in nonpolar solvents (hexane or cumene) and Et_2O is necessary to achieve this carbolithiation. The enantiomeric excess was determined by ^{31}P NMR analysis of the diastereomeric phosphorus product[9] derived from this amine. (b) The absolute configuration was determined by correlation with an authentic sample prepared by tosylation of the alcohol **2** and displacement with dimethylamine.

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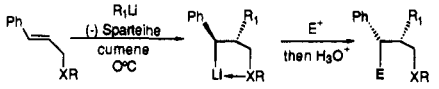
Table 1. Carbolithiation of Cinnamyl Derivatives



entry[a]	XR	R_1Li	prod.	E^+	yield[b] (%)	ee (%)
1	OH	nBuLi	2	H	82[j]	80[c]
2	OtBu	nBuLi	4	H	71	80[d]
3	NMe_2	nBuLi	5	H	70[k]	82[e]
4	NHMe	nBuLi	6	H	62	66[c]
5	NMeBn	nBuLi	7	H	64	84[f]
6	CH_2OH	nBuLi	8	H	72	70[c]
7	OH	nBuLi, LiBr[g]	2	H	60	66[c]
8	OH	EtLi, LiBr[g]	9	H	68[l]	85[c]
9	OH	*sec*-BuLi	10	H	65	72[c]
10	OH	*t*BuLi	11	H	40	0
11	OH	BenzylLi[h]	12	PhS	67	0
12	OH	nBuLi	13	PhS[i]	61[j]	83[c]
13	OH	nBuLi	14	CH_3[i]	63[j]	82[c]

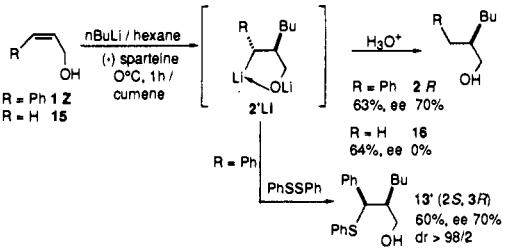
[a] The reactions were generally carried out by addition of the substrate to the RLi–sparteine mixture at −10 °C. [b] Based on pure isolated product. [c] The ee was determined by ^{31}P NMR.[9] [d] The ee was determined after deprotection of the *tert*-butyl ether into alcohol.[12] [e] The ee was determined by chiral HPLC.[13] [f] The ee was determined after transformation into a secondary amine.[9] [g] The organolithium reagents were prepared in Et_2O, and the addition was carried out in cumene; see text. [h] Obtained by metalation of toluene at 80 °C in the presence of sparteine. [i] Electrophiles are added at −50 °C, and the mixture is slowly warmed to room temperature before hydrolysis. In all cases the diastereomeric ratio was >98/2. [j] For proof of stereochemistry, see ref 2a. [k] See ref 2e. [l] See ref 2h.

of nBuLi and LiBr in the presence of 4 equiv of sparteine (1 equiv of diamine for each lithium bromide and 1 equiv for the alkyllithium) gives the carbometalated product with 60% chemical yield and 56% ee. However, in order to minimize the amount of chiral ligand with an alkyllithium prepared in ether from RBr and Li, we take advantage of the insolubility of the lithium salt in cumene; dry cumene is added, and Et_2O is stripped off. Under these conditions, the carbometalation reaction occurs with only 1 equiv of sparteine to lead, although with a modest yield, to the alkylated product with 66% ee (Table 1, entry 7). Accordingly, EtLi and LiBr were added to the olefin[2h] with good enantioselectivity (Table 1, entry 8). The addition of a secondary organolithium (*sec*-BuLi) followed by hydrolysis gave, as a mixture of two diastereoisomers, the corresponding alcohols in 72% ee for each diastereoisomer (Table 1, entry 9). The sparteine–RLi interaction should be strongest with the sterically less demanding organolithium derivatives but weak with sterically congested environments (Table 1, compare entries 1, 9, and 10).

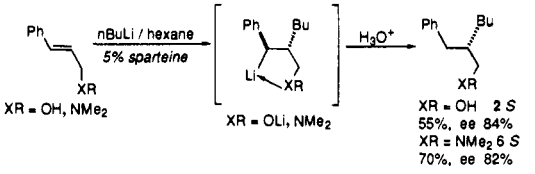
The chiral thermodynamically favored benzylic organolithium **2Li** (Scheme 1) may react with a number of electrophiles in a highly diastereoselective manner, according to previous work on the carbolithiation of cinnamyl alcohol.[2] All the compounds have the same ^1H and ^{13}C NMR spectra as the products prepared with TMEDA[2a] instead of (−)-sparteine, and then the reaction of the benzylic organolithiums thus formed with different electrophiles was determined to occur with inversion of configuration;[2a,15] the major isomers have thus been assigned to be the *syn* isomers.[16] In all cases examined, product is obtained in a diastereoisomeric ratio of >98/2 prior to purification, and in 83% ee (Table 1). Thus, two *chiral* centers on an acyclic system can be created in a single-pot operation.

The stereochemistry of the olefin is crucial for the enantioselectivity of the carbolithiation. Whereas the asymmetric carbolithiation of **1E** cinnamyl alcohol gives the *S* alkylated product (Scheme 1), the reaction of the **1Z** isomer, according to the same experimental conditions , leads to **2'Li**, the enantiomer of **2Li**. After acidic hydrolysis, **2Li** was converted to **2***R* in 70% ee, but to a racemic product when the allylic alcohol is not substituted, as is the case of 2-propen-1-ol

Scheme 2



Scheme 3



(Scheme 2). Addition of diphenyl disulfide to **2'Li** leads to the formation of two vicinal *chiral* centers with a diastereoselection of 98/2 and an enantioselection of 70% (Scheme 2). Thus, the two enantiomers of **2** and **13** can be synthesized from (−)sparteine by switching from the *E* to the *Z* stereochemistry of the double bond in **1**. Since the cinnamyl alcohol and cinnamyldimethylamine were shown to be unreactive toward the addition of nBuLi in cumene at 0 °C without external diamine, the potential for catalysis was obvious. The results summarized in Scheme 3 show that addition of these derivatives to nBuLi and catalytic amounts of (−)-sparteine (5%) also leads to good enantiomeric excess, even on a large scale, albeit with somewhat reduced yields in the case of cinnamyl alcohol.[17]

In summary, we have demonstrated that stoichiometric or catalytic amounts of (−)-sparteine can serve as promoters for the enantioselective carbolithiation of cinnamyl derivatives for primary and secondary organolithiums. The addition reaction is dependent on the stereochemistry of the initial double bond. The resulting benzylic organolithiums can be derivatized to the linear phenylated chain bearing two contiguous stereogenic centers with given configurations. Current investigation is focused on the generalization of this reaction and the use of organozinc reagents instead of organolithiums.

Acknowledgment. The authors thank Prof. Genêt J.-P. and Dr. Ratovelomanana-Vidal V. for the HPLC measurement.

Supporting Information Available: Typical experimental procedures and spectral data of products (59 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA943880O

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(16) **2***S*: $[\alpha]_D^{25} = -4.1°$ ($c = 0.175$, CH_2Cl_2). **3***S*: $[\alpha]_D^{25} = +18.2°$ ($c = 0.075$, benzene). **4***S*: $[\alpha]_D^{25} = -0.4°$ ($c = 0.103$, CH_2Cl_2). **5***S*: $[\alpha]_D^{25} = -11.96°$ ($c = 0.170$, CH_2Cl_2). **6***S*: $[\alpha]_D^{25} = -4.38°$ ($c = 0.091$, CH_2Cl_2). **7***S*: $[\alpha]_D^{25} = -6.2°$ ($c = 0.114$, CH_2Cl_2). **9***S*: $[\alpha]_D^{25} = +4°$ ($c = 0.078$, CH_2Cl_2). **13** (2*R*,3*S*): $[\alpha]_D^{25} = -156.4°$ ($c = 0.100$, CH_2Cl_2). **14** (2*R*,3*S*): $[\alpha]_D^{25} = +8.7°$ ($c = 0.012$, CH_2Cl_2). **2***R*: $[\alpha]_D^{25} = +3.5°$ ($c = 0.131$, CH_2Cl_2). **13'** (2*S*,3*R*): $[\alpha]_D^{25} = +131°$ ($c = 0.106$, CH_2Cl_2).

(17) The reaction was performed on 50 mmol scale of cinnamyl alcohol in the presence of 5% sparteine. The reduced yield in this case is due to telomerization of **2Li** on **1** leading to a dimer. This side reaction does not take place when a stoichiometric amount of sparteine is used.