Stereoselective Synthesis of Hydroxylated Indolizidines via (–)-Sparteine-Mediated Kinetic Resolution Coupled with Intramolecular Carbolithiation

Michael J. Woltering, Roland Fröhlich[+], Birgit Wibbeling[+], Dieter Hoppe*

Organisch-Chemisches Institut der Universität Münster, Corrensstr. 40, D-48149 Münster, Germany

Fax +49(251) 833-9772

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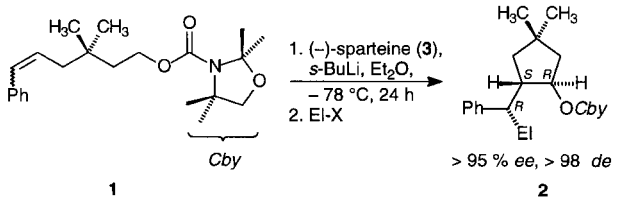
Abstract: Enantioenriched 1-oxy-2-benzyl-substituted indolizidines with functionalized side chains were easily prepared from racemic 2-(carbamoyloxy)methyl-*N*-cinnamylpiperidine by (–)-sparteine-mediated one-step kinetic resolution and intramolecular carbolithiation.

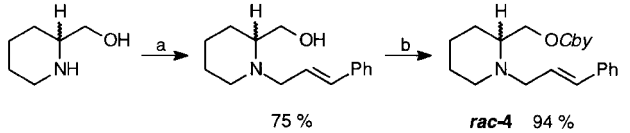
Hydroxylated indolizidine alkaloids such as lentiginosine, castanospermine, swainsonine, and related compounds[1] demonstrate a high pharmacological potential as specific inhibitors of glycosidase and glycoprotein processing[2] as well as anticancer, antiviral, antiretroviral, and immunoregulatory agents.[3] Thus, the development of methods for the synthesis of enantioenriched hydroxylated indolizidines has become important for the discovery of new pharmacologically interesting heterocyclic compounds and attracted great attention during the last decade.[4] Among a great diversity of synthetic methods, intramolecular cyclocarbometallation[5] reactions have been applied for the construction of five- and six-membered nitrogen heterocycles,[6] including one example utilizing an enantioenriched lithiated carbanion.[7]

We wish to report herein a short but efficient stereoselective approach to hydroxylated indolizidines via the (–)-sparteine-mediated enantioselective deprotonation.[8] As we previously reported, the enantioselective deprotonation and intramolecular 5-*exo*-*trig* cyclocarbolithiation of 6-phenyl-5-hexenyl carbamates **1** turned out to be a useful tool for generating enantiomerically pure 2-substituted cyclopentanol derivatives **2** (Scheme 1).[9]



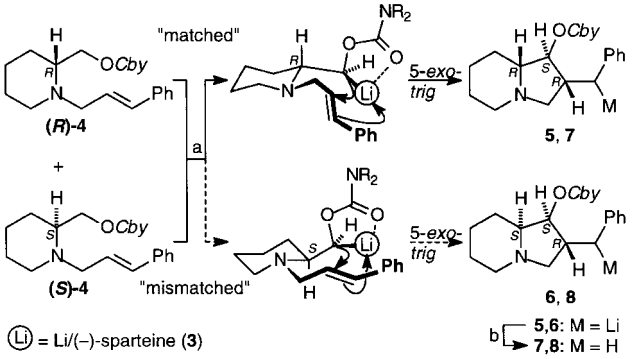
Scheme 1

In order to transfer this method to the synthesis of bicyclic heterocycles, we supposed that indolizidines can be synthesized by stereoselective intramolecular carbolithiation. The diastereoselectivity of the deprotonation and substitution of β-alkyl and β-amino-substituted alkyl carbamates as well as the (–)-sparteine-mediated kinetic resolution of these compounds have been investigated extensively in our group.[10] Therefore, the (–)-sparteine mediated deprotonation even of racemic 2-(carbamoyloxy)methyl-*N*-cinnamyl-piperidine ***rac*-4** seemed to be an elegant method to obtain enantioenriched indolizidines via kinetic resolution and subsequent diastereoselective anionic 5-*exo*-*trig* cyclization by a one-step procedure. The precursor ***rac*-4** was easily prepared by a two-step sequence (Scheme 2).



Scheme 2. a) 1.5 eq. K_2CO_3, toluene, reflux, 2 h, then 1.05 eq. cinnamyl bromide, reflux, 20 h; b) 1.5 eq. NaH, THF, r.t., 1 h, then 1.5 eq. *Cby*Cl, reflux, 24 h

Compound ***rac*-4** was treated with *sec*-butyllithium in the presence of (–)-sparteine in diethyl ether at – 78 °C, the reaction mixture was stirred at this temperature for 8 to 32 h, and methanol was subsequently added. In order to improve the efficiency of the kinetic resolution, different reaction conditions were checked (Scheme 3, Table 1).



Scheme 3. a) (–)-sparteine (**3**), *s*-BuLi, Et_2O, – 78 °C, 8 – 32 h. b) MeOH, – 78 °C → r.t.

Table 1. Conditions for the kinetic resolution and resulting selectivities

Entry No.	Equiv. (–)-spart. (**3**)	Equiv. *s*-BuLi	Time [h]	*d.r.* (**7**:**8**)[a]	Yield **7** [%]	*Ee* **7**[b] [%]	Yield **4** [%]
1	-	1.00	20	96 : 4[c]	30	-	-
2	1.00	0.91	8	91 : 9	54	67	23
3	1.00	0.97	22	92 : 8	42	91	25
4	1.00	0.91	32	92 : 8	45	89	22
5	0.80	0.75	22	98 : 2[d]	34	95	46[e,f]

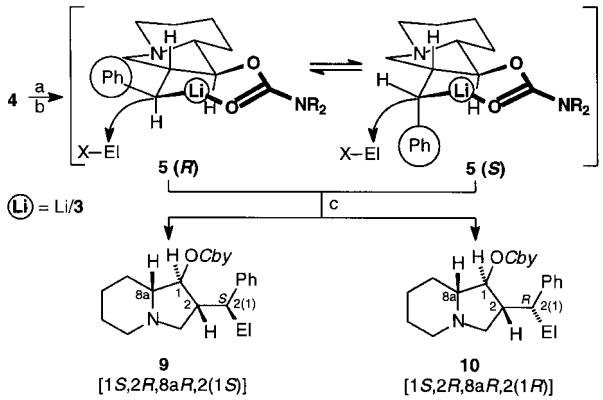
[a] Determined by gas chromatography. [b] Determined by ^{1}H NMR shift experiments with the acetates. [c] Racemates. [d] Optical rotation of **7**: $[\alpha]^{20}_D$ = + 3.9 (*c* = 1.09, CH_2Cl_2). [e] The *ee* of 63 % was determined by ^{1}H NMR after decarbamoylation and formation of the Mosher ester with (–)-(*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid. [f] Optical rotation of recovered **4**: $[\alpha]^{20}_D$ = – 23.2 (*c* = 1.13, CH_2Cl_2).

The 5-*exo*-*trig* cyclization reaction led to the *trans*-fused five-membered heterocycles **7** and **8** with excellent diastereoselectivity. The *cis*-fused heterocycles could not be detected in any case. The anion emerging from the matched pair as well as the anion derived from the mismatched pair underwent *trans*-selective 5-*exo*-*trig* cyclization.[11] Therefore, the two diastereomers resulted from incomplete differentiation within the deprotonation step and not within the cyclization step.

As Table 1 shows, the use of 0.80 eq. of (–)-sparteine (**3**), 0.75 eq. of *s*-BuLi and a reaction time of 22 h (Entry 5) resulted in a yield of 34 % of indolizidine **7** (based on ***rac*-4**) with high diastereoselectivity (**7**:**8** = 98:2) and an enantiomeric excess of 95 %.[12] Under these conditions, **(*S*)-(–)-4** was recovered with 46 % yield and 63 % *ee*.

These optimized conditions were used for trapping the intermediate benzylic anion with different electrophiles. Thus, further functionalization of the side chain and the generation of one more

stereogenic center via benzylic substitution was possible in the same reaction step (Scheme 4).[13]



Scheme 4. a) 0.80 eq. (–)-sparteine, 0.75 eq. *s*-BuLi, Et_2O, – 78 °C; b) 22 h, 5-*exo*-*trig*-cyclization; c) El-X, – 78 °C → r.t.

The reactions with all tin and silicon electrophiles yielded mixtures of **9** and **10** in different ratios which could be separated easily by flash chromatography (silica gel, petroleum ether/ethyl acetate/ triethylamine). With CO_2, after converting the crude acid to the methyl ester **9f** with diazomethane, one single diastereomer with the configuration [1*S*,2*R*,8a*R*,2(1*S*)] could be detected. Table 2 shows the results of benzylic substitution depending on the electrophile.

Table 2. Compounds **9** and **10** obtained by trapping the intermediate benzyllithium

El-X	Comp. No.[a]	*d.r.* **9** : **10**	Yield **9+10** [%]	Yield **4** [%]	$[\alpha]_D^{20}$ (**9**)[b]	$[\alpha]_D^{20}$ (**10**)[b]
D-OAc	**9a/10a**	25 : 75	40	31	-	-
Bu_3Sn-Cl	**9b/10b**	11 : 89	33	64	– 54.4	+ 56.1
Me_3Sn-Cl	**9c/10c**	25 : 75	31	67	– 42.4	+ 38.8
Me_3Si-Cl	**9d/10d**	45 : 55	29	61	– 24.7	+ 3.9
Me_2PhSi-Cl	**9e/10e**	75 : 25	32	63	– 30.6	+ 12.6
CO_2Me	**9f**	> 95 : 5	30	51	+ 34.6	-

[a] All compounds gave satisfactory elemental analyses (C ± 0.40; H ± 0.23; N ± 0.42) or correct high-resolution mass spectra. [b] Optical rotations measured in CH_2Cl_2 (c = 0.3 – 1.2)

The diastereomers **9** and **10** have the same relative configuration at C1, C2, and C8a, and must differ in the side chain. The absolute configuration of the minor diastereomer **9d**[14,15] (Figure 1) and the relative configuration of the racemic ester **9f**[15,16] (Figure 2) were determined by X-ray crystal structure analysis. The relative configuration of **9b**/**10b**, **9c**/**10c**, and **9e**/**10e** was determined by correlation of ^{1}H NMR data of the remaining proton at C1 with the data of **9d**/**10d** (Table 3).

The high diastereoselectivity found for the benzylic substitution of related carbocycles[9] is not operating in the indolizidine system. Obviously, the interconversion of the epimeric ion pairs **5 (*R*)** and **5 (*S*)** proceeds with a rate comparable to the rate of the substitution step, the latter differing significantly in both reaction pathways for each electrophile. We assume, with exception of the deuterolysis,[17] inversion of configuration in the substitution step. Inversion has been found for all silylations, stannylations, alkylations, and several carboxylations of α-hetero-substituted benzyllithium compounds.[18,19] Under these assumptions, the major products **10a** and **9f**, formed in very rapid deuterolysis or carboxylation, arise from the ion pair **5 (*R*)**, which is expected to be primarily formed in the intramolecular *syn*-addition. In contrast, the major products **10b-d** emerge from the ion pair **5(*S*)**, being

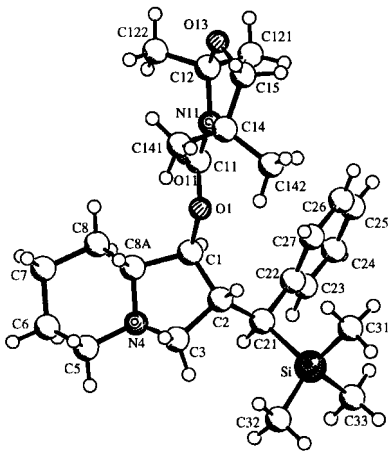


Figure 1. X- ray crystal structure of **9d**

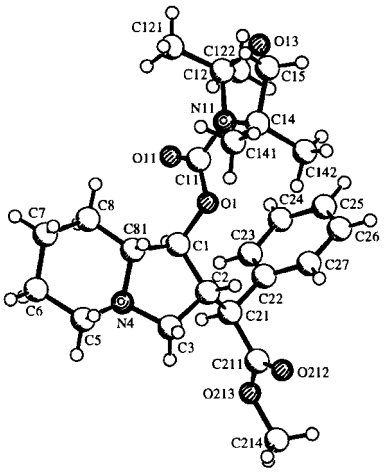


Figure 2. X-ray crystal structure of **9f**

Table 3. ^{1}H NMR data of the remaining proton at C1 of products **9** and **10**

Compd. No.	**9** δ(H1)[ppm]	**9** $^3J_{1,2}$ [Hz]	**9** $^3J_{1,8a}$ [Hz]	**10** δ(H1) [ppm]	**10** $^3J_{1,2}$ [Hz]	**10** $^3J_{1,8a}$ [Hz]
9a/10a	4.71	4.79	7.88	4.71	4.79	7.88
9b/10b	4.68	4.29	7.65	4.71	3.33	6.18
9c/10c	4.70	4.29	7.62	4.78	3.59	6.68
9d/10d	4.74	4.53	7.62	4.90	4.29	6.66
9e/10e	4.65	4.29	7.62	4.81	4.05	6.42
9f	4.73	5.24	7.88	-	-	-

in equilibrium with **5(*R*)**. Presumably, a dynamic kinetic resolution[8b,18d,20] is operating in the substitution reaction with slower electrophiles, such as silicon and tin chlorides.

The method described here allows a short but efficient approach to enantioenriched 1,2-disubstituted indolizidines establishing up to four stereogenic centers under the action of the recoverable auxiliary (–)-sparteine. The key steps are a kinetic resolution and a stereospecific and, as well, diastereoselective anionic cyclization starting from readily available racemic material. Moreover, further functionalization of the side chain can be established by trapping with electrophiles. The enantiomers ***ent*-5**, ***ent*-9** and ***ent*-10** are accessible from the recovered **(*S*)-(–)-4**.

Acknowledgement:

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+ X-ray crystal structure determination.

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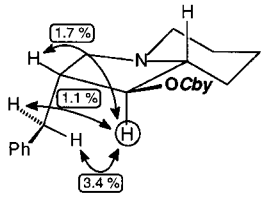
11. The determination of the relative configuration of **7** and **8** was established by ^{1}H NMR NOE experiments. We gratefully thank Dr. Klaus Bergander for the measurements at the 600 MHz NMR spectrometer.



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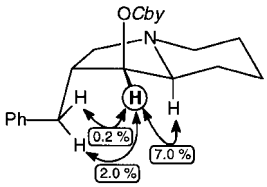

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12. The enantiomeric eccess of the acetate was determined by 300 MHz ^{1}H NMR shift experiment using 11 mol% (+)-Eu(hfc)$_3$ in $CDCl_3$.

13. Typical procedure:
To a solution of racemic 2-(carbamoyloxy)methyl-*N*-cinnamylpiperidine (***rac*-4**, 193 mg, 0.50 mmol) and (–)-sparteine (**3**, 94 mg, 0.40 mmol) in diethyl ether (3 mL) a 1.3M *sec*-butyllithium solution in hexanes (0.375 mmol) was added at – 78 °C. The solution was stirred for 22 h at this temperature and subsequently chlorotrimethylsilane (0.13 ml, 1.0 mmol) was added. The reaction mixture was slowly warmed to rt (5 h), aq. K_2CO_3 solution (2mL) was added, the layers were separated and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo*. The purification of the remaining crude product by flash chromatography (silica gel, petroleum ether/EtOAc/Et$_3$N 10:0.5:0.15) yielded 36 mg of **10d** (R_f = 0.50) and 30 mg of **9d** (R_f = 0.36) [*d.r.* (**9d**:**10d**) = 45:55, 29 %) as well as 118 mg (61 %) of remaining **4**.
10d: R_f = 0.50 (PE/EtOAc/NEt$_3$ 10:0.5:0.15). $[\alpha]^{20}_D$ = + 3.9; $[\alpha]^{20}_{365}$ = + 51.4 (*c* = 0.28 in CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.00 (s, 9H, *Si*(C*H*$_3$)$_3$); 1.46, 1.48 (s, 6H), 1.62 (s, 6H, *Cby*-CH$_3$); 1.40 - 1.64 (m, 5H), 1.79 (m, 1H), 1.90 (m, 2H, H-5$_a$/6/7/8/8a); 2.39 (dd, 1H, $^3J_{2,3a}$ = 9.75 Hz, $^2J_{3a,3b}$ = 8.82 Hz, H-3$_a$); 2.43 (d, 1H, $^3J_{2,2(1)}$ = 10.98 Hz, H-2(1)); 2.69 (m, 2H, H-2/3$_b$); 2.85 (m, 1H, H-5$_b$); 3.78 (s, 2H, *Cby*-CH$_2$); 4.90 (dd, 1H, $^3J_{1,8a}$ = 6.66 Hz, $^3J_{1,2}$ = 4.29 Hz, H-1); 7.07 – 7.28 (m, 5H, H-aryl). ^{13}C NMR (75 MHz, $CDCl_3$): δ = – 1.4 q (*Si*(C*H*$_3$)$_3$); 24.1 t, 24.2 t (C-6/7); 25.5, 25.1 q, 25.7, 26.1 q (*Cby*-C*H*$_3$); 29.2 t (C-8); 41.3 d (C-2(1)); 43.5 d (C-2); 52.9 t (C-5); 58.9 t (C-3); 59.7, 61.1 s (*Cby*-C(*CH*$_3$)$_2$); 70.5 d (C-8a); 76.5, 76.2 t (*Cby*-C*H*$_2$); 82.4 d (C-1); 96.0, 95.1 s (*Cby*-C(*CH*$_3$)$_2$); 124.7 d, 128.0 d, 128.8 d, 143.9 s (C-aryl); 152.6, 151.6 s (*NC*=*O*). IR (Film): ν [cm^{-1}]: 3060 - 2780 (s, C-H); 1685 (s, NC=O); 1450, 1365. $C_{26}H_{42}N_2O_3Si$ (458.718): Calc.: C 68.08, H 9.23, N 6.11. Found: C 68.36, H 9.46, N 6.53. **9d:** R_f = 0.36 (PE/EtOAc/NEt$_3$ 10:0.5:0.15). Mp: 89 °C (*n*-hexane). $[\alpha]^{20}_D$ = – 24.7, $[\alpha]^{20}_{365}$ = – 109.4 (*c* = 0.32 in CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = – 0.05 (s, 9H, *Si*(C*H*$_3$)$_3$); 1.15 - 1.90 (m, 19H, *Cby*-C*H*$_3$/H-6/7/8/8a); 2.03 (m, 1H, H-5$_a$); 2.38 (d, 1H, $^3J_{2,9}$ = 11.19 Hz, H-2(1)); 2.65 (m, 2H, H-2/3$_a$); 3.01 (m, 2H, H-3$_b$/5$_b$); 3.72 (s, 2H, H-5'); 4.74 (dd, 1H, $^3J_{1,8a}$ = 7.62 Hz, $^3J_{1,2}$ = 4.53 Hz, H-1); 7.02 - 7.07 (m, 3H), 7.15 - 7.22 (m, 2H, H-aryl). ^{13}C NMR (75 MHz, $CDCl_3$): δ = – 1.1 q (*Si*(C*H*$_3$)$_3$); 24.0 t (C-7); 24.8 t (C-6); 25.4 q, 25.6, 25.9, 27.0 q (*Cby*-C*H*$_3$); 28.7 t (C-8); 42.1 d (C-2(1)); 43.0 d (C-2); 53.3 t (C-5); 58.8 t (C-3); 59.3, 60.3 s (*Cby*-C(*CH*$_3$)$_2$); 69.0 d (C-8a); 76.4, 76.1 t (*Cby*-C*H*$_2$); 82.9 d (C-1); 95.7 [94.4] s (*Cby*-

C(CH_3)$_2$); 124.7 d, 127.6 d, 128.9 d, 142.6 s (C-aryl); 151.6, 151.0 s (*N*C=*O*). IR (KBr): ν [cm^{-1}]: 3050 - 2780 (s, C-H); 1695 (s, NC=O); 1465, 1395, 1365, 1335. $C_{26}H_{42}N_2O_3Si$ (458.718): Calc.: C 68.08, H 9.23, N 6.11. Found: C 68.48, H 9.42, N 6.07.

14. X-ray crystal structure analysis of **9d**: formula $C_{26}H_{42}N_2O_3Si$, *M* = 458.71, 0.30 x 0.10 x 0.10 mm, *a* = 8.146(1), *b* = 16.250(2), *c* = 10.581(1) Å, β = 104.28(1)°, *V* = 1357.4(3) $Å^3$, ρ_{calc} = 1.122 g cm^{-1}, μ= 9.71 cm^{-1}, empirical absorption correction via φ scan data ($0.973 \le C \le 0.999$), *Z* = 2, monoclinic, space group $P2_1$ (No. 4), λ= 1.54178 Å, *T* = 223 K, ω/2θ scans, 6169 reflections collected (+*h*, ±*k*, ±*l*), [(sinθ)/λ] = 0.62 $Å^{-1}$, 5562 independent and 4492 observed reflections [$I \ge 2\ \sigma(I)$], 296 refined parameters, *R* = 0.043, wR^2 = 0.105, max. residual electron density 0.41 (-0.22) e $Å^{-3}$, Flack parameter 0.00(3), hydrogens calculated and refined as riding atoms.

15. Data sets were collected with an Enraf Nonius CAD4 diffractometer. Programs used: data reduction MolEN, structure solution SHELXS-86, structure refinement SHELXL-93, graphics SCHAKAL-92.
Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the number: 101328 at the Cambridge Crystallographic Data Centre as supplementary publication. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: int. code +44(1223)336-033, e-mail: deposit@ccdc.cam.ac.uk].

16. From a 28 mg portion of the highly enantioenriched methyl ester **9f** could be crystallized less than 2 mg of racemic material.
X-ray crystal structure analysis of **9f**: formula $C_{25}H_{36}N_2O_5$, *M* = 444.56, 0.50 x 0.30 x 0.10 mm, *a* = 9.120(1), *b* = 12.047(1), *c* = 12.252(1) Å, α = 78.17(1), β = 80.14(1), γ = 70.96(1)°, *V* = 1237.5(2) $Å^3$, ρ_{calc} = 1.193 g cm^{-3}, μ = 6.69 cm^{-1}, empirical absorption correction via φ scan data ($0.953 \le C \le 0.999$), *Z* = 2, triclinic, space group *P*1bar (No. 2), λ = 1.54178 Å, *T* = 223 K, ω/2θ scans, 5387 reflections collected (+*h*, ±*k*, ±*l*), [(sinθ)/λ] = 0.62 $Å^{-1}$, 5053 independent and 4144 observed reflections [$I \ge 2\ \sigma(I)$], 295 refined parameters, *R* = 0.060, wR^2 = 0.171, max. residual electron density 0.59 (-0.36) e $Å^{-3}$, hydrogens calculated and refined as riding atoms.

17. For similar observations see: a) Faibish, N. C.; Park, Y. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 11561. b) Thayumanavan, S.; Basu, A., Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 8209.

18. a) Hoppe, D.; Carstens, A.; Krämer, T. *Angew. Chem.* **1990**, *102*, 1455; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1424. b) Derwing, C.; Hoppe, D.; *Synthesis* **1996**, 149. c) Hammerschmidt, F.; Hanninger, A. *Chem. Ber.* **1995**, *128*, 1069. d) Gallagher, D. J.; Du, H.; Long, S. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 11391.

19. Little is known about the stereochemistry of the substitution in carbon-substituted benzyllithium compounds; a different reaction pattern cannot be strictly excluded.

20. Review: Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, 447.