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Organolithium additions to styrene derivatives — III.[1,2] Enantioselective routes to 2-arylalkanoic acids

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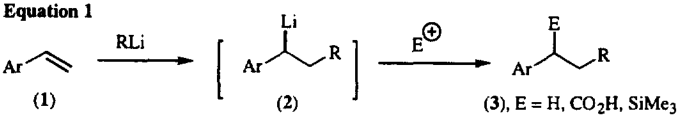
Abstract: Organolithium addition to styrene and its derivatives, followed by electrophilic trapping, has been investigated in the presence of (−)-sparteine. With styrene, enantiomeric excesses up to 30% were observed, the ee depending on the solvent, temperature and electrophile. With 2-substituted styrenes, butyllithium addition followed by carboxylation gave a range of 2-arylheptanoic acids with ee's up to 72% (with 2-methoxystyrene in cumene at −95°C). © 1997 Elsevier Science Ltd. All rights reserved.

We recently reported that styrene and its substituted derivatives **1** undergo efficient addition and addition–trapping reactions with a range of organolithium reagents to give adducts **3** (Equation 1).[1,2]

Equation 1



In pioneering work, the groups of Noyori,[3] Beak,[4] Normant,[5] Schlosser,[6] and others,[7] have developed benzyllithium trapping reactions mediated by (−)-sparteine **4** as versatile, enantioselective synthetic procedures. Given that the transformation in Equation 1 proceeds by way of benzyllithium intermediates **2**, and that some of the addition reactions have been shown to be promoted by the presence of TMEDA, we decided to investigate the effect of (−)-sparteine on these processes. The initial studies, carried out using styrene itself, are summarised in Table 1. It should be noted that the styrene addition route in the presence of sparteine cleanly produces benzyllithium reagent **2**, (Ar=Ph, R=Bu) whereas the deprotonation of ethylbenzene using BuLi/sparteine leads to a predominance of products resulting from ring metallation.[3]

Carboxylation of the intermediate benzyllithium reagent **2**, (Ar=Ph, R=Bu) was investigated first (entry i).[8] The enantiomeric excess (ee) of the product was readily determined using NMR spectroscopy with *S*-1-naphthylethylamine or *R*-trifluoroanthranylethanol,[9] capillary electrophoresis[10] or by comparison of the optical rotation with the published value.[11] With diethyl ether as solvent, the use of two equivalents of sparteine and a reaction temperature of −65°C gave an ee of 24% (26% when 5 equivalents of sparteine were employed). Similar ee's were obtained when one equivalent of sparteine or a higher temperature (−30°C) were used, but surprisingly, on cooling the reaction to −100°C the ee was reproducibly only 3%. The use of hexane as solvent over a range of temperatures gave a 13% ee but cumene[5] at −78 or −94°C gave the best enantioselectivity (30% ee). This result is extremely encouraging given that there are no auxiliary binding sites to stabilise the intermediate organolithium reagent. Other electrophilic trapping agents were also explored (Table 1, entries ii–iv): all yields were satisfactory but only the sulfide was obtained with a reasonable ee (entry ii). The use of CS_2 gave a racemic product – a surprising result in view of the success with CO_2.

We next turned our attention to 2-substituted styrenes[12] using the BuLi–CO_2 procedure (Table 2). 2-Methoxystyrene was investigated first (entry i) and gave the best results in terms of enantiomeric

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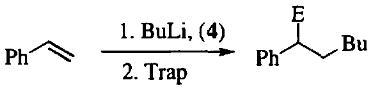
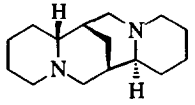
Table 1.





(4)

	Trap	Conditions[a]	Equiv. 4	E	%Yield	% ee[b]
i	CO_2	Et_2O, -30°C	2	CO_2H	64	20
		Et_2O, -65°C	1	CO_2H	73	18[c]
		Et_2O, -65°C	2	CO_2H	76	24[c]
		Et_2O, -65°C	5	CO_2H	75	26[c]
		Et_2O, -78°C	2	CO_2H	74	14[c,d]
		Et_2O, -100°C	2	CO_2H	45	3
		Hexane, -90° to -65°C	2	CO_2H	70	13
		Cumene, -78°C	2	CO_2H	76	30[e]
ii	MeSSMe	Et_2O, -65°C	2	SMe	73	24
iii	$ClCONMe_2$	Et_2O, -78°C	2	$CONMe_2$	66	11
iv	CS_2	Et_2O, -78°C	2	CS_2H	72	0

[a] The reactions were carried out on a 0.5 mmol scale in the specified solvent (10 mL) and the BuLi added dropwise over *ca.* 5 min

[b] ee determined by NMR method using *S*-1-naphthylethylamine (entries i and iv) and *R*-trifluoroanthranylethanol (ii and iii)

[c] ee confirmed by capillary electrophoresis and optical rotation comparison

[d] A warm-cool regime (-78 -> -10 -> -65 or -94°C) before carboxylation, gave ee's of 24% and 3% respectively

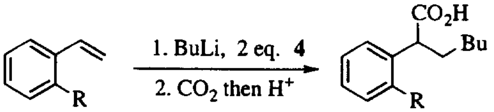
[e] A similar yield and ee were obtained at -94°C

enrichment.[13,14] At −78°C, the highest ee (51%) was obtained using cumene as solvent, with hexane and ether giving lower values. By carrying out the reaction in cumene at −95°C a respectable 72% ee was obtained. A range of electrophiles (see Table 2, footnote d) were employed under these optimum conditions, and satisfactory yields obtained, but we have not yet established the ee's from these reactions. Related 2-alkoxystyrenes also gave products with reasonable ee's (entries ii–iv, 31–50% ee) but the presence of a thiomethyl (entry v) or functionalised 2-methyl substituents (entries vi–viii) did not lead to efficient enantioselectivity. The 2-carboxylate derivative gave a product with 15% ee (entry ix) and the 2-phenyl adduct was obtained in 41% ee (entry x).[15]

Additional work is required before firm mechanistic conclusions can be drawn. However, the reactions of styrene in ether seem to conform to the model proposed by Noyori *et al.*[3] Thus, at −65°C and warmer temperatures, the two diastereomeric benzyllithium–sparteine complexes readily equilibrate and the ee (*ca.* 20%) probably reflects the different rates of the two trapping processes. At lower temperatures it appears that similar amounts of the two diastereomeric complexes are present, and with equilibration slowed with respect to the rate of electrophilic trapping, this distribution is reflected by much lower ee's. Warm–cool experiments[4b] support this rationale: when a −78°C reaction mixture was warmed to −10°C and then cooled down to −65°C before quenching, an ee of 24% was obtained (whereas if it was warmed to −10°C and then cooled to −94°C an ee of 3% resulted). When cumene was employed as solvent high ee's (30%) were obtained at the lower temperatures. Rapid equilibration is unlikely at −95°C and it seems more reasonable that the two benzyllithium–sparteine complexes are present in unequal amounts, as reflected by the enantiomeric ratio of the trapped product (*ca.* 65:35), possibly because of the π-stacking effect.

With 2-methoxystyrene (and related alkoxy derivatives), the highest ee's were again obtained in cumene but with these compounds lowering the reaction temperature resulted in higher enantioselectivity whereas a warm–cool regime (−95°C to −10°C for 0.5 hour, and then quench at −95°C)

Table 2.



	R	Conditions	% Yield	% ee[a]
i	MeO	Et$_2$O, -78°C	79	29[b,c,d]
		Hexane, -78°C	80	40[c]
		Cumene, -78°C	71	51[c]
		Cumene, -95°C	58	72[c,e]
ii	MeOCH$_2$O	Cumene -78°C	70	49
		Cumene, -94°C	67	50
iii	CH$_2$=CHCH$_2$O	Cumene, -94°C	67	50
iv	PhCH$_2$O	Hexane, -78°C	70	31
v	MeS	Ether, -78°C	75	10
vi	MeOCH$_2$	Cumene, -94°C	68	7
vii	Me$_2$NCH$_2$	Hexane, -78°C	80	0
viii[f]	HOCH$_2$	Cumene, -78°C	63	5
ix[f]	HO$_2$C	Hexane-Cumene, -78°C	19	15
x	Ph	Cumene, -78°C	80	41

[a] ee determined by NMR method with *S*-1-naphthylethylamine

[b] When ^{t}BuLi was employed only 7% ee was observed (84% chemical yield)

[c] ee confirmed by capillary electrophoresis

[d] Other electrophiles were also employed (cyclobutanone, MeSSMe, TMSCl, MeI, allylCl)

[e] At -90°C an 87% yield was observed (62% ee); a warm-cool regime (-95 -> -10 -> -95°C) before carboxylation, gave 47% yield (45% ee)

[f] 2 Eq. of BuLi were employed

there was a significant (72 vs. 45%) decrease in ee. These systems contain an auxiliary binding site to stabilise the benzyllithium intermediates and it seems likely that one of the two benzyllithium–sparteine diastereoisomers is formed preferentially during the addition reaction. In these systems, the warm–cool sequence appears to result in partial equilibration of the diastereoisomers.

In summary styrene undergoes organolithium addition–trapping reactions in the presence of sparteine to produce 2-phenylalkanoic acids, and related compounds, in low enantiomeric excess (up to 30%). The presence of a 2-alkoxy substituent enables ee's of up to 72% to be obtained. Although further mechanistic investigations have to be carried out, this process does appear to be of value for the preparation of novel 2-arylalkanoic acids in enantioenriched form. It should be noted that such compounds are of particular value in the non-steroidal anti-inflammatory areas.[16]

Acknowledgements

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11. Pettersson, K.; Willdeck, G. *Ark Kemi*, 1956, **9**, 333. In our study the *R*-adduct predominates {maximum $[\alpha]_D^{20} = -18$ (c=1, EtOH)} as might be expected from related examples (see ref. 4b).
12. The substituted styrenes were prepared by standard procedures such as Wittig homologation of the corresponding aldehyde or by trapping 2-bromomagnesiostyrene.
13. **Experimental procedure for Table 2, entry i**: At −95°C and under a nitrogen atmosphere, BuLi in hexanes (1.6 M, 0.42 mL, 0.67 mmol) was slowly added dropwise to a stirred solution of 2-methoxystyrene (67 mg, 0.5 mmol) and (−)-sparteine (234 mg, 1 mmol) in cumene (10 mL). The orange reaction mixture was stirred for 1 h under these conditions, quenched with excess carbon dioxide gas, and then allowed to warm to room temperature. Ether (50 mL) was added to the now colourless reaction mixture and the resulting solution was washed with 5% hydrochloric acid (3×30 mL), brine (2×30 mL) and then dried (Na_2SO_4). After evaporation of the solvent, the crude product was purified by column chromatography (silica) using diethyl ether–petroleum ether (1:5) as eluent to give *2(2-methoxyphenyl)heptanoic acid* (69 mg, 58%) with consistent spectroscopic data (Found: M^+, 236.1411. $C_{14}O_3H_{20}$ requires 236.1412). The ee (72%) was determined by NMR spectroscopy using *S*-1-naphthylethylamine in $CDCl_3$.[9]
14. We do not yet know the absolute configurations of the predominant enantiomers featured in Table 2.
15. BuLi addition to the 2-$CONMe_2$ and 2-$OCONMe_2$ styrenes were also investigated; amide addition giving a butylketone (*ca.* 60%) occurred in the former case whereas the carbamate gave a complex product mixture.
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