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TETRAHEDRON: *ASYMMETRY*

Enantioselective 1,4-addition of aryllithium reagents to α,β-unsaturated *tert*-butyl esters in the presence of chiral additives

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Abstract

Reaction of *t*-BuLi with a mixture of aryl bromide and chiral diamine, amino ether or diether, in toluene at −78°C provided chiral aryllithium complexes efficiently. Reaction of these aryllithium complexes with α,β-unsaturated *tert*-butyl esters afforded the 1,4-addition products in up to 88% ee.

Chiral β,β-diaryl propionic acid derivatives are biologically interesting compounds, having reported activities as antiarrhythmics,[1] vasodilators,[1a,2] antidepresssives,[1a,3] and antihistamines.[1a] As such, we are interested in the development of general methods for the synthesis of functionalized β,β-diaryl propanoates, especially in optically enriched form.[3b,4,5] Recently, we described the conjugate addition reactions of aryllithium reagents with α,β-unsaturated *tert*-butyl esters **1** bearing a chiral imidazolidine (**1b**) or oxazolidine (**1c**) auxiliary (Scheme 1).[6] This chemistry takes advantage of the ease of preparation and high reactivity of a wide variety of substituted aryllithium reagents while providing the products **2** with high chemoselectivity (1,4-addition only) and stereoselectivity (chiral auxiliary control). However, this approach requires the use of a chiral auxiliary, which must be attached/removed and is limited to substrates (**1a**) which have an aldehyde function in the *ortho* position relative to the unsaturated *tert*-butyl ester. These factors led us to investigate a non-auxiliary approach to the enantioselective synthesis of β,β-diaryl propionates **4** involving 1,4-addition[7] of aryllithium reagents to α,β-unsaturated *tert*-butyl esters **3** in the presence of chiral additives (Scheme 1).

Our initial studies focussed on the reaction of the α,β-unsaturated *tert*-butyl ester **5** with the aryllithium **6**-(−)-sparteine complex (Eq. 1). While conversion of 2-bromo-5-methoxy toluene **7** into the aryllithium reagent **6** is straightforward in THF using either *n*-BuLi or *t*-BuLi, it does not proceed efficiently in less polar solvents. Reaction of **7** with *t*-BuLi in toluene or hexane provided approximately 7% conversion to the aryllithium reagent **6** (−78 to −50°C, 4 h). Subsequent addition of (−)-sparteine to the reaction

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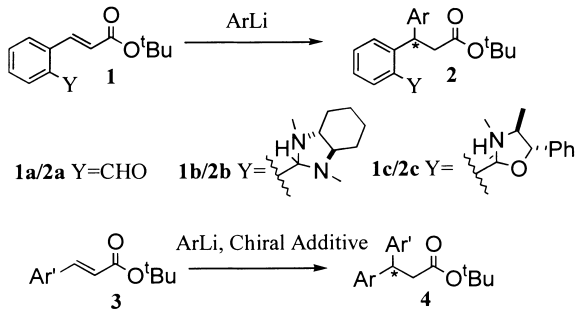
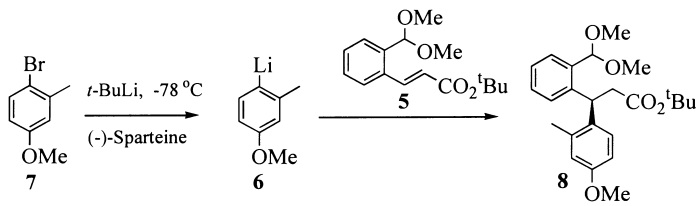


Scheme 1.

mixture effected complete consumption of **7** within 15 min at −78°C. This finding made it possible to study the conjugate addition reactions of the aryllithium **6**-sparteine complex in a range of polar and non-polar aprotic solvents (Table 1). In these reactions the aryllithium, **6**-sparteine complex was generated by addition of *t*-butyllithium (2.2 equiv.) to a mixture of 2-bromo-5-methoxy toluene **7** (1.1 equiv.) and (−)-sparteine (0.5–5.0 equiv.) in the required solvent[8] at −78°C (HPLC analysis indicated >99% conversion to **6** within 15 min). The unsaturated ester **5** (1 equiv.) was then added at −78°C, and after 1 h, the reaction was quenched. The 1,4-addition product **8** was purified by silica gel chromatography, and the optical purity of **8** was determined using chiral SFC.[9]



(1)

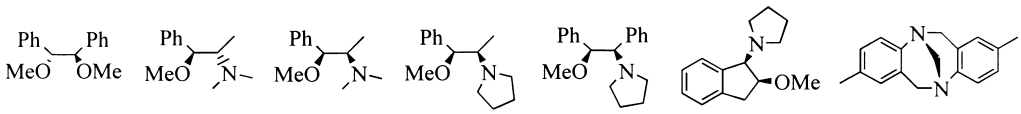
Table 1

Entry	Ratio **6**:(-)sparteine	Solvent	**8** %ee
1	1:2	THF	11
2	1:2	Hexane	54
3	1:2	Ethyl ether	59
4	1:2	DME	0
5	1:2	Toluene	68
6	1:1	Toluene	64
7	1:0.5	Toluene	47
8	1:5	Toluene	68.3
9	1:3	Toluene	65
10	1:2	Toluene	61[a]

a. 1.2 eqiv LiCl was added.

Several comments should be made regarding the data in Table 1. First, in all cases the 1,4-addition product **8** was obtained in high yield (>80%) with minimal amounts (<5%) of the corresponding 1,2-addition products being observed. The absolute configuration of the major enantiomer of **8** formed in these reactions was assigned as *S*, based on conversion of the dimethyl acetal to the corresponding known aldehyde.[5a,6] The reaction enantioselectivity was found to be highly solvent dependent. In good donor solvents such as THF and DME the reactions were non-selective (entries 1 and 4), while better selectivities were obtained in less or non-coordinating solvents such as diethyl ether, hexane and, in particular, toluene (entries 2, 3 and 5). Using toluene as solvent, the optimal ratio of aryllithium

6:(−)-sparteine was established as 1:2 providing the product **8** in 68% ee (entry 5). Use of less (−)-sparteine resulted in lower selectivity (entries 6 and 7) while use of excess (−)-sparteine did not further improve the selectivity (entries 8 and 9). A reaction carried out in the presence of added LiCl caused a slight decrease in selectivity (entry 10). These results indicate the formation of a complex between the aryllithium reagant **6** and (−)-sparteine, which is perturbed by donor solvents and by added Li salts.

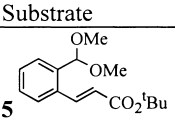
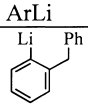
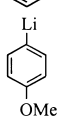
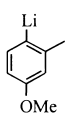
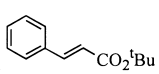
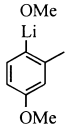
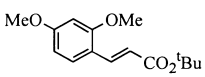
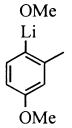
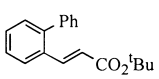
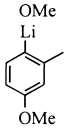
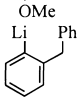


9 88% ee **10** 31%ee **11** 50 % ee **12** 62% ee **13** 34% ee **14** 65% ee **15** 57% ee

Scheme 2.

Next, attempts were made to improve the enantioselectivity of the reaction of aryllithium reagent **6** with unsaturated *tert*-butyl ester **5** by screening a variety of diamine, amino ether, and diether chiral additives (Scheme 2). As before, complete lithiation of 2-bromo-5-methoxy toluene **7** was possible in toluene by reaction with *t*-BuLi in the presence of the chiral additive.[10] Subsequent reaction of the **6**–chiral additive complex with the unsaturated *tert*-butyl ester **5** was rapid at −78°C and provided the 1,4-addition product **8** cleanly and in high yield. It was found that as high as 88% ee could be obtained in this reaction using the C_2-symmetrical diether **9**[11] as an additive.

Table 2

Entry	Substrate	ArLi	Additive	ee%[9]	Yield %
1	 **5**		(-)sparteine	63	92
2	**5**		(-)sparteine	56	89
3	**5**		(-)sparteine **9**	48 59	79 82
4	**5**		(-)sparteine **9**	68 88	91 90
5	 **18**		(-)sparteine	28	78
6	 **16**		(-)sparteine **9**	42 61	90 92
7	 **17**		(-)sparteine **9**	78 60	88 82
8	**17**		(-)sparteine **9**	74 59	91 84

Finally, the generality of this enantioselective 1,4-addition process with respect to substitution in the aryllithium reagent and in the unsaturated *tert*-butyl ester[12] was briefly examined. All of these experiments were carried out using the diether **9** or (−)-sparteine as additives and under the optimal reaction conditions (toluene, −78°C, 2:1 ratio of additive to aryllithium; Table 2). For the reactions listed in Table 2, the isolated yields of 1,4-addition products were uniformly high, with minimal 1,2-addition (<5%) being observed. In general, the reactions proceeded with moderate enantioselectivities, similar results being obtained using (−)-sparteine and diether **9** as additives for each aryllithium reagent. In the reactions of several substituted aryllithium reagents with unsaturated ester **5** (entries 1–4) there were no obvious trends noted, indicating that the reaction is not highly sensitive to substitution in the aryllithium reagent. However, it is clear that substitution in the acceptor is important. For example, in the reactions of aryllithium reagent **6**-(−)-sparteine complex with the substrates **5**, **16** and **17** (entries 4, 6–8) which have an *ortho* substituent relative to the unsaturated ester portion, improved enantioselectivities were observed relative to the reaction involving the unsubstituted substrate **18** (entry 5). This is, presumably, a result of conformational effects in the unsaturated ester.

In summary, it has been shown that aryllithium–chiral additive complexes are readily generated in non-polar aprotic solvents via an Li–halogen exchange reaction of the corresponding aryl bromides in the presence of a range of chiral additives (diamines, diethers or amino ethers). The complexes generated in this manner undergo efficient and highly chemoselective addition reactions with α,β-unsaturated *tert*-butyl esters to provide substituted β,β-diaryl propionates with moderate enantioselectivity. Optimal enantioselectivities were obtained in the reactions of several aryllithium reagents and α,β-unsaturated *tert*-butyl esters using toluene as solvent and either (−)-sparteine or diether **9** as chiral additive.

References

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6. Frey, L. F.; Tillyer, R. D.; Caille, A.; Tschaen, D. M.; Dolling, U.; Grabowski, E. J. J. *J. Org. Chem*. **1998**, in press.
7. For conjugate addition of organolithium reagents to naphthyl BHA esters and unsaturated imines in the presence of chiral additives see (a) Tomioka, K.; Shindo, M.; Koga, K. *Tetrahedron Lett*. **1993**, 34, 681. (b) Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc*. **1989**, 111, 8266. For carbolithiation of cinnamyl alcohol derivatives by organolithium reagents mediated by (−)-sparteine see Norsikian S.; Marek, I.; Normant, J. *Tetrahedron Lett*. **1997**, 38, 7523 and associated references.
8. The aryllithium–sparteine complex was not completely soluble in both THF and hexane, but formed homogenous solutions in toluene, DME and Et_2O. Analysis of a 1:2 mixture of aryllithium **6** and (−)-sparteine in toluene at −70°C, using ^{6}Li NMR spectroscopy, showed a singlet due to LiBr–sparteine complex and at least seven signals indicating a complex mixture of species.
9. Supercritical fluid chromatography (SFC) conditions: for products of entries 1–4 and 8 in Table 2, Chiracel OD was used as the stationary phase (IPA/supercritical CO_2 as modifier); for products of entries 5–7 in Table 2, Chiracel OJ was used as the stationary phase (IPA/supercritical CO_2 as modifier).

10. Lithium–bromine exchange of **7** in the presence of (−)-Troger's base **10** required 0.4 equiv. of THF to be added to proceed to completion. It was found that trace amounts of THF rapidly accelerated the lithium halogen exchange reaction in non-polar solvents in the presence or absence of chiral additive.
11. Tomioka has very recently reported the conjugate addition reactions of simple organolithium reagents (MeLi, BuLi, PhLi) to α,β-unsaturated BHA esters mediated by sparteine and diether **9**. Asano, Y.; Iida, A; Tomioka, K. *Tetrahedron Lett*. **1997**, 38, 8973.
12. All unsaturated *tert*-butyl esters were prepared via the Heck reaction (5 mol% allylpalladium chloride dimer, 10 mol% tri-*o*-tolylphosphine, 1.5 equiv. NaOAc, 1.5 equiv. *t*-butyl acrylate, 80°C or 5 mol% $Pd(OAc)_2$, 1.0 equiv. Bu_4NCl, 1.1 equiv. $NaHCO_3$, 1.5 equiv. *t*-butyl acrylate, DMF, 120°C) or direct esterification of the corresponding carboxylic acids with N,N′-diisopropyl-O-*tert*-butylisourea (Mathias, L. J. *Synthesis* **1979**, 561).