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Synthesis of Inherently Chiral Calix[4]arenes: Stereocontrol through Ligand Choice

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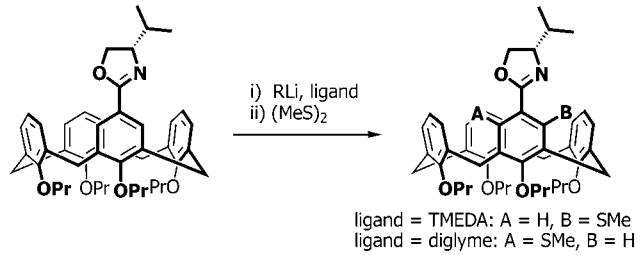
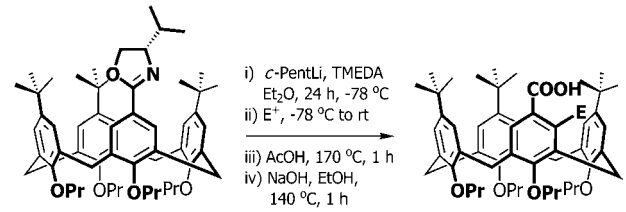
ABSTRACT



Employing a chiral oxazoline as an ortholithiation directing group allows the synthesis of inherently chiral calix[4]arenes suitable for elaboration into planar chiral molecules. An important finding has been that the diastereoselectivity of the reaction can be tuned by the choice of additive. These results have bearing on the elucidation of the general mechanism of oxazoline-directed ortholithiation.

As a methodology, asymmetric ortholithiation using chiral directing (DoM) groups has been well established, particularly in the ferrocene field where it has been extensively used to generate planar chiral ligands.[1,2] We recently reported the first asymmetric synthesis of inherently chiral calix[4]arenes using a chiral oxazoline derived from L-valine as the DoM group (Scheme 1).[3,4] During the course of that study, we observed a slight reversal in the diastereoselectivity when using THF as the solvent (25% de for opposite diastereomer).[5] Little work has been published on solvent/ligand effects reversing diastereoselectivity in ortholithiations,[6] although the choice of solvent is well-known to have

Scheme 1. Ortholithiation Approach to Inherently Chiral Calix[4]arenes[3]



(1) For a review on planar chiral ferrocenes, see: Atkinson, R. C. J.; Gibson, V. C.; Long, N. J. *Chem. Soc. Rev.* **2004**, *33*, 313–328.

(2) For an overview of directed metalations of aromatic compounds, see: Clayden, J. In *The Chemistry of Organolithium Compounds*, 1st ed.; Rappopart, Z., Marek, I., Eds.; John Wiley & Sons: New York, 2004; pp 495−646.

(3) Herbert, S. A.; Arnott, G. E. *Org. Lett.* **2009**, *11*, 4986–4989.

(4) Selected resolution methods to inherently chiral calix[4]arenes: (a) Yakovenko, A. V.; Boyko, V. I.; Danylyuk, O.; Suwinska, K.; Lipkowski, J.; Kalchenko, V. I. *Org. Lett.* **2007**, *9*, 1183–1185. (b) Kliachyna, M. A.; Yesypenko, O. A.; Pirozhenko, V. V.; Shishkina, S. V.; Shishkin, O. V.; Boyko, V. I.; Kalchenko, V. I. *Tetrahedron* **2009**, *65*, 7085–7091. (c) Xu, Z. X.; Zhang, C.; Zheng, Q. Y.; Chen, C. F.; Huang, Z. T. *Org. Lett.* **2007**, *9*, 5331–5331. (d) Xu, Z.-X.; Zhang, C.; Yang, Y.; Chen, C.-F.; Huang, Z.-T. *Org. Lett.* **2008**, *10*, 477–479. (e) Shirakawa, S.; Shimizu, S. *New J. Chem.* **2010**, *34*, 1217–1222.

(5) Unpublished results.

(6) (a) Overman, L. E.; Owen, C. E.; Zipp, G. G. *Angew. Chem., Int. Ed.* **2002**, *41*, 3884–3887. (b) Park, J.; Lee, S.; Ahn, K. H.; Cho, C.-W. *Tetrahedron Lett.* **1996**, *37*, 6137–6140.

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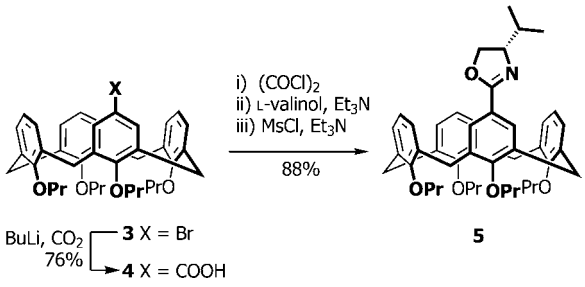
profound stereochemical effects.[7,8] We therefore implemented a study to explore these factors in more detail. We chose here to use calix[4]arene **5**, a debutylated analogue of **1**, since our previous work suggested that the *tert*-butyl groups on the calix[4]arene were hindering the rate of the reaction.

The synthesis of **5** was readily achieved in two steps from monobromocalix[4]arene **3** (Scheme 2),[9] itself easily obtained in three steps from the parent *tert*-butylcalix[4]arene using known literature procedures.[10]

Scheme 2. Synthesis of Oxazoline Calix[4]arene **5**



The ortholithiation studies were initially investigated with *sec*-butyllithium;[11] dimethyl disulfide was used as an electrophile, and the diastereomeric excess (de) of the reactions was determined by integration of the signals for the aromatic singlet *meta* to the methyl thioether group (Figure 1).[12]

We found that the ortholithiation step typically required 5 h at −78 °C,[13] prior to the addition of the electrophile. Using various ethereal solvents (Table 1, entries 1−4), the conversion was found to be generally excellent, albeit with negligible diastereoselectivity. Pentane (entry 5) was unsurprisingly ineffective, confirming the necessity of a coordinating solvent to break down the polymeric structure of *sec*-butyllithium in solution.[14] However, the addition of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) had a profound effect on the diastereoselectivity of the reaction (entries 6−10); the best result arose from the use of a pentane−TMEDA combination which returned an excellent conversion (>95%) and de (90%).[15]

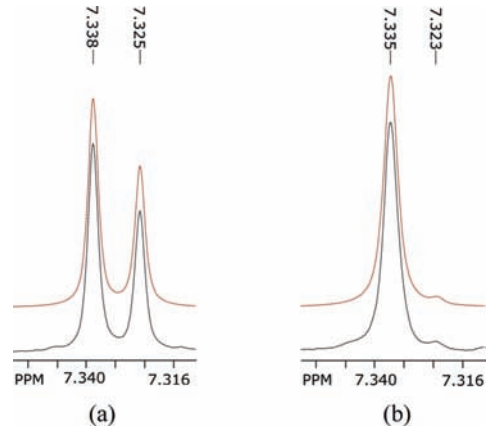
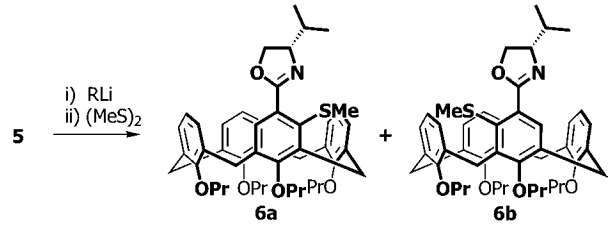


Figure 1. Representative ^{1}H NMR spectra used to determine de's. Offset spectra were derived from best-fit calculations[12] in order to calculate accurate integrals: (a) *s*-BuLi, Et_2O (Table 1, entry 1); (b) *c*-PentLi, pentane/TMEDA (Table 1, entry 19).

Other amino ligands were found to be less successful in promoting this reaction; *N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine (PMDTA) and (−)-sparteine[16] both returned unreacted starting material (entries 11 and 12), even though they are recognized as being very effective coordinating ligands.[17] Steric factors were thought to play a part, though in the case of (−)-sparteine we considered the possibility of

Table 1. Results for the Optimization of Asymmetric Ortholithiation of Oxazoline Calix[4]arene **5**



entry[a]	RLi[b]	solvent	ligand[c]	yield[d] (%)	de[e] (%)
1	*s*-BuLi	Et_2O		92	19
2	*s*-BuLi	THF		>95	5
3	*s*-BuLi	*t*-BuOMe		>95	2
4	*s*-BuLi	*i*-Pr_2O		55	22
5	*s*-BuLi	pentane		0[f]	
6	*s*-BuLi	Et_2O	TMEDA	>95	87
7	*s*-BuLi	THF	TMEDA	93	52
8	*s*-BuLi	*t*-BuOMe	TMEDA	>95	84
9	*s*-BuLi	*i*-Pr_2O	TMEDA	>95	89
10	*s*-BuLi	pentane	TMEDA	>95	90
11	*s*-BuLi	pentane	PMDTA	0[f]	
12	*s*-BuLi	pentane	(−)-sparteine	0[f]	
13	*s*-BuLi	pentane	DMM	53	5
14	*s*-BuLi	pentane	DMPU	0[f]	
15	*s*-BuLi	pentane	HMPA	58	−30
16	*s*-BuLi	pentane	glyme	45	−26
17	*s*-BuLi	pentane	diglyme	>95	−56
18	*i*-PrLi	pentane	TMEDA	>95	94
19	*c*-PentLi	pentane	TMEDA	>95	94
20	*i*-PrLi	pentane	diglyme	24	−28

[a] Ortholithiations performed at −78 °C for 5 h. [b] 5 equiv of alkyllithium used. [c] 2 equiv per equivalent of alkyllithium. [d] Conversion determined by ^{1}H NMR. [e] Determined by ^{1}H NMR [**6a** (major) − 7.34 ppm; **6b** (minor) − 7.32 ppm]. [f] Starting material recovered.

(7) For solvent effects on stereoselectivity, see: Cainelli, G.; Galletti, P.; Giacomini, D. *Chem. Soc. Rev.* **2009**, *38*, 990–1001.

(8) For some examples where this is important in asymmetric ortholithiations, see: (a) Siwek, M. J.; Green, J. R. *Chem. Commun.* **1996**, 2359–2360. (b) Sammakia, T.; Latham, H. A. *J. Org. Chem.* **1995**, *60*, 6002–6003.

(9) Ikeda, A.; Yoshimura, M.; Lhotak, P.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, *16*, 1945–1950.

(10) Arduini, A. Casnati, A. *Macrocycle Synthesis: A Practical Approach*; Parker, D., Ed.; Oxford University Press: Oxford, 1996; pp 145−172.

(11) In our previous work, *n*-BuLi returned starting material **1** while *t*-BuLi gave very poor yields; see ref 3.

(12) Deconvolution performed using Kirk Marat's *SPINWORKS* 3.1.6 Software, University of Manitoba. Available from http://www.umanitoba.ca/chemistry/nmr/spinworks.

(13) Much longer reaction times (>24 h) were needed with calixarene **1**; see ref 3.

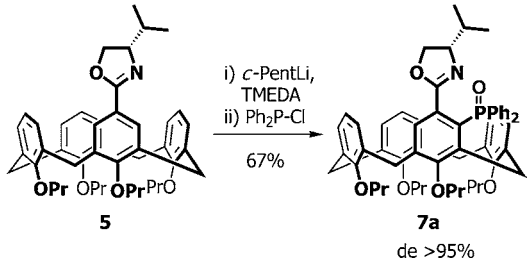
(14) Tetrameric and hexameric mixtures have been reported in cyclopentane; see: Fraenkel, G.; Henrichs, M.; Hewitt, M.; Su, B. M. *J. Am. Chem. Soc.* **1984**, *106*, 255–256.

a mismatch pairing with **5**. We found, however, that the enantiomer of **5** was also resistant to ortholithiation under these conditions.

Oxygen-based ligands were then evaluated:[18] Dimethoxymethane (DMM) returned a moderate conversion (entry 13) with effectively no impact on diastereoselectivity, much like the monodentate ethers.[19] Using *N*,*N*′-dimethylpropylideneurea (DMPU) returned unreacted starting material,[20] but *N*,*N*,*N*′,*N*′,*N*″,*N*″-hexamethylphosphoramide (HMPA, entry 15) resulted in a moderate conversion of product with *reversal* of the observed diastereoselectivity (a ratio of slightly less than 1:2).[21,22] Dimethoxyethane (glyme), a structural analogue of TMEDA, also resulted in partial reversal of the product diastereoselectivity,[23] and the tridentate ligand diethylene glycol dimethyl ether (diglyme) gave both excellent conversions and an appreciable reversal in the diastereoselectivity (almost 1:4).

Lastly, we explored other secondary alkyllithiums, a concept that is not well studied in the literature. By this we imply that most studies compare *n*-, *sec*-, or *tert*-butyllithium, but few look at other homologous alkyllithium reagents. We found that using isopropyllithium or cyclopentyllithium, under the same conditions as those optimized for *sec*-butyllithium, resulted in the diastereoselectivity increasing to 94% (entries 18 and 19), which represents a 70% improvement in selectivity over *sec*-butyllithium.[24] However, an isopropyllithium and diglyme combination (entry 20) was found to give a lower reversed de than with *sec*-butyllithium (entry 17).

Scheme 3. Synthesis of Phosphine Oxide



The major diastereomer of the reaction was determined by the single-crystal structure solution of the product from a quench with diphenylphosphine chloride (Scheme 3). The phosphine oxide **7a** was the only product obtained, and its structure confirmed that the major diastereomer had *cR* chirality (Figure 2).[25]

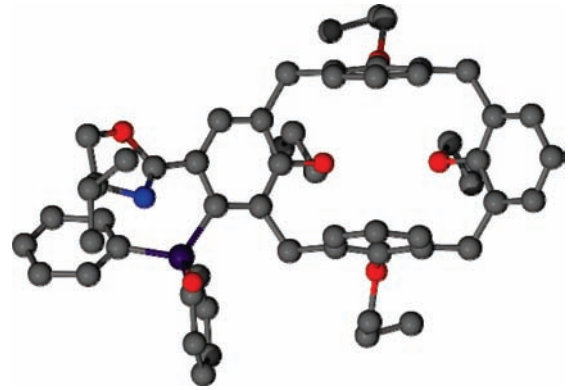


Figure 2. Crystal structure of **7a**, viewed from above.

We also performed an experiment to determine the thermodynamic stability of the aryllithium intermediate: oxazoline calixarene **5** was ortholithiated in pentane with 1.2 equiv of *sec*-butyllithium in the presence of 2.4 equiv of TMEDA at −78 °C. The reaction was held at −78 °C for 7 h and then warmed to 0 °C for 3 h. On quenching with dimethyl disulfide, the diastereoselectivity was found to be the same as a control reaction held at −78 °C for a total of 10 h, confirming that the reaction must be under kinetic control.

Mechanistically speaking, the oxazoline-directed ortholithiation of aromatic rings is not well understood. In one example, evidence for an *N*-directed pathway has been experimentally shown,[26] but others have, however, found little theoretical support for a purely *N*-directed mechanism.[27] To date, no physical evidence for an *O*-directed mechanism has been reported. Our results, however, imply that the stereocontrol we have observed in these ortholithiations must be under more than one competing pathway, particularly in terms of the reversal of diastereoselectivity observed when HMPA, glyme, or diglyme are used.

A DFT calculation[29] on calix[4]arene oxazoline **5** revealed two minimum energy conformations of the oxazoline ring, one with the isopropyl group facing away from the calix[4]arene cavity and the other pointing inward. The energy difference of 0.015 kJ mol^{-1}, favoring the *outward* conformation, was too small to have any role in determining the diastereoselectivity of the reaction. The high de observed here must arise from transition states that have a $\Delta\Delta G$ of approximately 5.6 kJ mol^{-1},[30] which must therefore occur on coordination of the alkyllithium−ligand complex. It is known that the oxazoline isopropyl group will have a steric demand that competes with the alkyllithium complex; thus, these will prefer to occupy opposite "faces" of the oxazoline.[31] Transition state **[A]**‡ (Figure 3) is accepted as giving rise to the major diastereomer with *cR* chirality.[32] Keeping

(15) Using fewer equivalents of *s*-BuLi (1.5 equiv) with TMEDA (3 equiv) in pentane at −78 °C for 5 h returned a slightly lower yield of 80% but identical de (90%).

(16) This is more often used in asymmetric deprotonations; see: Kizirian, J.-C. *Chem. Rev.* **2008**, *108*, 140–205.

(17) Clayden, J. *Organolithiums: Selectivity for Synthesis*, 1st ed.; Pergamon: Amsterdam, 2002.

(18) The ethers used as solvents in entries 1−4 were not reevaluated as stoichiometric ligand additives in pentane.

(19) Known to behave as a monodentate ether ligand (cf. Table 1, entries 1−4); see: Bergander, K.; He, R.; Chandrakumar, N.; Eppers, O.; Günther, H. *Tetrahedron* **1994**, *50*, 5861–5868.

(20) DMPU often facilitates dearomatization, but it was not observed under these conditions; it was tentatively observed though in crude reaction mixtures when THF used as solvent. For an example, see: Clayden, J.; Parris, S.; Cabedo, N.; Payne, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5060–5062. For a theoretical treatment, see: Ramalla, A. M.; Fernández, I.; Ortiz, F. L.; González, J. *Chem.—Eur. J.* **2005**, *11*, 3022–3031.

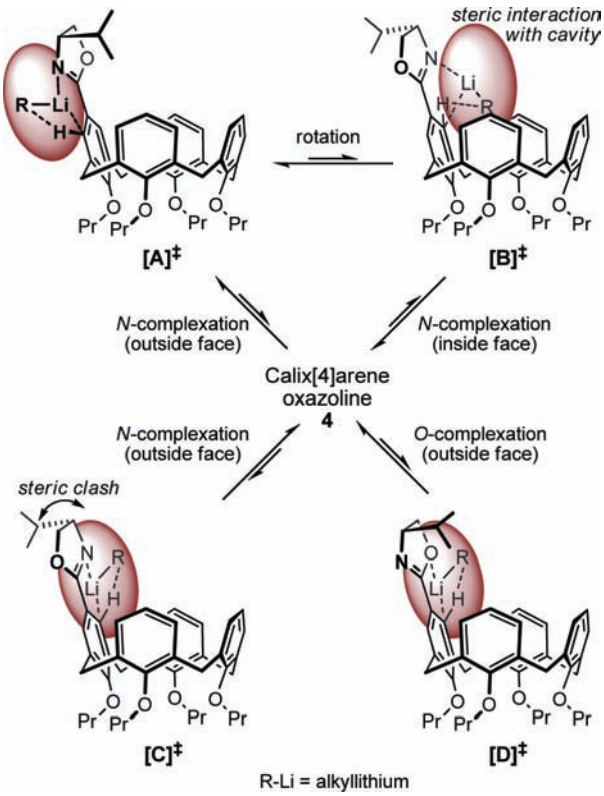


Figure 3. Possible transition states. Ellipsoids represent the unknown complex involving the ligands.[28]

in line with an *N*-coordinated mechanism, poor diastereoselectivity might therefore be attributed to transition states **[B]**‡ or **[C]**‡,[33] both of which have unfavorable steric demands and are unlikely to result in *reversal* of diastereoselectivity. In the cases of reversed stereochemical outcome, an *O*-directed transition state such as **[D]**‡ is more likely. This shift in mechanism is thought to be due to a reduced Lewis acidity of lithium on coordination to HMPA, glyme or diglyme, coupled to steric factors disfavoring an *N*-coordination mechanism.

The increased diastereoselectivity on using isopropyllithium or cyclopentyllithium is a conundrum; it is possible though that these are less sterically demanding then *sec*-butyllithium and have a better "fit" near the isopropyl group of the oxazoline. Indeed, the result with isopropyllithium−diglyme (entry 20) suggests a shift toward an *N*-coordination mechanism compared to entry 17 employing *sec*-butyllithium. Furthermore, subjecting calix[4]arene **5** to *tert*-butyllithium in pentane−TMEDA returned a lower 72% de (>95% conversion), seemingly also supporting this point, but we acknowledge that more theoretical and experimental work is needed.

In conclusion, we present the first evidence that an oxazoline *O*-directed mechanism for ortholithiation is likely a result which answers questions posed from the theoretical studies.[27] We have also demonstrated that the diastereoselectivity of this reaction is in fine balance between ligand and alkyllithium choice. We also believe it is critical that researchers working with asymmetric lithiations not ignore the role that structural homologues of conventional alkyllithiums may play. Lastly, we have demonstrated that inherently chiral calixarenes can be obtained in good yields without employing resolution techniques and, to a lesser extent, that both enantiomers[34] may be obtained via the same starting material.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds, including spectra; diastereomeric excess calculations, DFT calculations, and crystallographic data (CIF) for **7a**.This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) The use of ethoxyvinyllithium−HMPA mixtures has led to unusual regioselectivities; see: (a) Shimano, M.; Meyers, A. I. *J. Am. Chem. Soc.* **1994**, *116*, 10815–10816.

(22) HMPA is known to strongly coordinate lithium and alter organolithium transition structures; see: (a) Romesberg, F. E.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5751. (b) Romesberg, F. E.; Bernstein, M. P.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 3475. (c) Riggs, J. C.; Singh, K. J.; Yun, M.; Collum, D. B. *J. Am. Chem. Soc.* **2008**, *130*, 13709–13717.

(23) Dimethoxyethane (glyme) is known to be unstable in *sec*-BuLi ($t_{1/2}$ = 120 min at −70 °C), explaining the low yield; see :Fitt, J. J.; Gschwend, H. W. *J. Org. Chem.* **1984**, *49*, 209–210.

(24) Diastereomer ratios of ~31:1 vs 18:1 when using *s*-BuLi.

(25) Cort, A. D.; Mandolini, L.; Pasquini, C.; Schiaffino, L. *New J. Chem.* **2004**, *28*, 1198–1199.

(26) Using a conformationally restricted ferrocene oxazoline: Sammakia, T.; Latham, H. A. *J. Org. Chem.* **1996**, *61*, 1629–1635.

(27) For a physical and theoretical investigation into the mechanism using *n*-BuLi and TMEDA, see: Chadwick, S. T.; Ramirez, A.; Gupta, L.; Collum, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 2259–2268.

(28) Monomer or triple ion transition states have been explored but seem to be dependent on the oxazoline used and the ligand's role; see ref 27.

(29) At the RB3LYP/6-311G level of theory.

(30) $\Delta\Delta G = -RT \ln([\mathbf{6a}]/[\mathbf{6b}])$.

(31) Substituents α to the nitrogen are known to dramatically slow down the ortholithiation step and have been shown to clash with ancillary (nonreacting) alkyllithium fragments or TMEDA in triple ion or monomer-based transition states respectively; see ref 27.

(32) This is analogous to our previous work (ref 3) and to that of ref 26.

(33) **[B]**‡ might form directly from **4** or through rotation from **[A]**‡.

(34) After hydrolysis of the oxazoline; see ref 3.