ORGANIC LETTERS

2009
Vol. 11, No. 21
4986−4989

An Asymmetric Ortholithiation Approach to Inherently Chiral Calix[4]arenes

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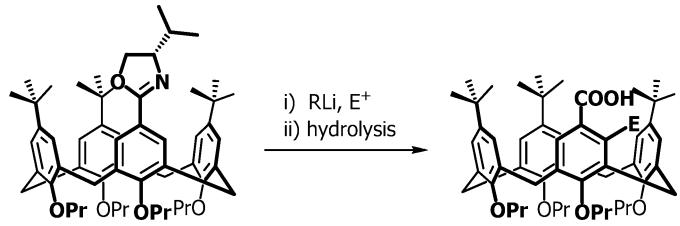
Received September 28, 2009

ABSTRACT



A general asymmetric synthesis of inherently chiral calix[4]arenes is described: using a chiral oxazoline derived from L-valine, an ortholithiation strategy is employed to give inherently chiral calix[4]arenes with high (93%) enantiomeric excesses. A crystal structure of a phosphine oxide intermediate has been obtained, unambiguously assigning the major diastereomer in the reaction; a mechanism explaining this result is proposed.

Calix[4]arenes are large bowl-shaped molecules that have been well studied for their properties in host−guest chemistry.[1] Since calix[4]arenes are nonplanar, it is possible to functionalize them in such a way as to produce an inherently chiral framework; the first example of this was published more than 25 years ago by Gutsche.[2] Although there are potentially many exciting applications of inherently chiral calix[4]arenes as ligands for asymmetric reactions,[3] their study has been severely hampered by the difficulty in obtaining them in an enantiomerically pure form.[4] Recently, there have been reports on methods for obtaining nonracemic inherently chiral calix[4]arenes via resolution techniques,[5] but none of these demonstrates the use of an asymmetric synthetic methodology. Intrigued by this, we considered whether the asymmetric ortholithiation approaches used to introduce planar chirality in ferrocenes[6] and chromium−arenes[7] would translate to the realm of calix[4]arenes. We reasoned that the shape of the calixarene allows for facial differentiation of the aromatic rings (i.e., "inside bowl" or "outside-bowl") which may be comparable to the metal−arene complex's "metal-side" and "open-side". To test this hypothesis, we envisaged employing a chiral oxazoline as an ortholithiation directing group,[8] which would allow for asymmetric functionalization of the upper rim of the calixarene. Herein we report our findings.

(1) Gutsche, C. D., Ed. *Calixarenes: An Introduction*, 2nd ed.; RSC: Cambridge, 2008; 276 pp.

(2) No, K. H.; Gutsche, C. D. *J. Org. Chem.* **1982**, *47*, 2713–2719.

(3) Examples of inherently chiral calix[4]arenes in asymmetric catalysis: (a) Shirakawa, S.; Moriyama, A.; Shimizu, S. *Org. Lett.* **2007**, *9*, 3117–3119. (b) Shirakawa, S.; Moriyama, A.; Shimizu, S. *Eur. J. Org. Chem.* **2008**, 5957–5964. (c) Shirakawa, S.; Kimura, T.; Murata, S.; Shimizu, S. *J. Org. Chem.* **2009**, *74*, 1288–1296. (d) Shirakawa, S.; Shimizu, S. *Eur. J. Org. Chem.* **2009**, 1916–1924.

(4) First asymmetric synthesis of a calix[4]resorcinarene:Page, P. C. B.; Heaney, H.; Sampler, E. P. *J. Am. Chem. Soc.* **1999**, *121*, 6751–6752.

(5) Lower-rim lipase transesterification: (a) Browne, J. K.; McKervey, M. A.; Pitarch, M.; Russell, J. A.; Millership, J. S. *Tetrahedron Lett.* **1998**, *39*, 1787–1790. Lower-rim resolution: (b) Yakovenko, A. V.; Boyko, V. I.; Danylyuk, O.; Suwinska, K.; Lipkowski, J.; Kalchenko, V. I. *Org. Lett.* **2007**, *9*, 1183–1185. (c) Boyko, V. I.; Yakovenko, A. V.; Matvieiev, Y. I.; Kalchenko, O. I.; Shishkin, O. V.; Shishkina, S. V.; Kalchenko, V. I. *Tetrahedron* **2008**, *64*, 7567–7573. (d) 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. Upper-rim resolution: (e) Xu, Z. X.; Zhang, C.; Zheng, Q. Y.; Chen, C. F.; Huang, Z. T. *Org. Lett.* **2007**, *9*, 5331–5331. (f) Xu, Z.-X.; Li, G.-K.; Chen, C.-F.; Huang, Z.-T. *Tetrahedron* **2008**, *64*, 8668–8675. (g) Xu, Z.-X.; Zhang, C.; Yang, Y.; Chen, C.-F.; Huang, Z.-T. *Org. Lett.* **2008**, *10*, 477–479.

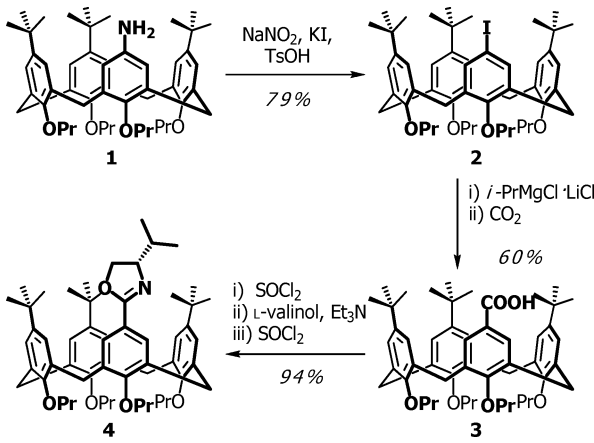
(6) Atkinson, R. C. J.; Gibson, V. C.; Long, N. J. *Chem. Soc. Rev.* **2004**, *33*, 313–328.

(7) Rosillo, M.; Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2007**, *36*, 1589–1604.

(8) For an overview of directed metalations of aromatic compounds, see: Clayden, J. *Chem. Organolithium Compd.* **2004**, *1*, 495–646.

10.1021/ol902238p CCC: $40.75
Published on Web 10/08/2009

Scheme 1. Synthesis of Isopropyloxazoline Calix[4]arene **4**



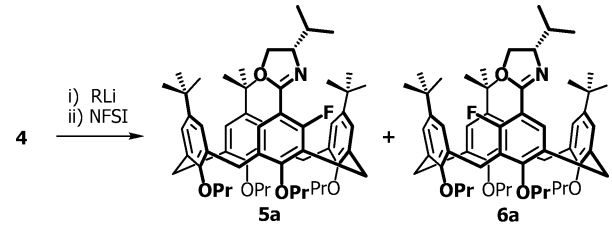
Chiral oxazoline calix[4]arene **4** was targeted as a model to study this reaction (Scheme 1); starting from known amino calix[4]arene **1**,[9] the desired oxazoline calix[4]arene was readily obtained in three steps. Knochel's recent version of the Sandmeyer reaction converted arylamine **1** to the aryl iodide **2** in 79% yield.[10] Introduction of the carboxyl group proved to be capricious when using a lithium−halogen exchange protocol (followed by CO_2 quench), often returning up to 70% of the protonated byproduct. Various methods and conditions were explored with the greatest success coming from Knochel's modified Grignard reagent,[11] which afforded the desired carboxyl calix[4]arene **3** in at least 60% yield. The oxazoline could then be introduced using standard conditions with L-valinol in 94% yield.

With the desired oxazoline calix[4]arene **4** in hand, our attention turned to the feasibility of ortholithiation. Competing benzylic lithiation of the calix[4]arene was considered in light of a report from Bennet et al.[12] which demonstrated this on a calix[4]arene; however, the relatively harsh conditions (10-fold excess of *n*-butyllithium at room temperature) suggested that this would not present any problems in our studies.

For the electrophile it was decided to use an F^+ reagent since the diastereomeric ratio of the products could then be determined by ^{19}F NMR spectroscopy. Selectfluor was unsuitable due to its poor solubility under the reaction conditions, but *N*-fluorobenzenesulfonimide (NFSI) proved to give good yields.[13]

Our preliminary attempts to ortholithiate **4** using *n*-butyllithium, with or without the addition of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), failed to produce any product on quenching with NFSI, even at temperatures up to 0 °C (Table 1, entry 1). No benzylic lithiation was observed, with only starting material being recovered. However the use of *tert*-butyllithium with TMEDA at −78 °C (entry 2) resulted in trace quantities of product with a modest de of 17% (diastereomer signals found at −113.29 ppm and −114.25 ppm in the ^{19}F NMR spectrum, Figure 1). Attempts to improve the yield by performing the reaction at higher temperatures resulted in the major product arising from the addition of *tert*-butyllithium onto the oxazoline.[14] The use of *sec*-butyllithium, however, returned up to 66% of the product with a de of 75% (entry 3). At higher temperatures, the diastereoselectivity dropped off, e.g., at −45 °C the reaction returned a lower de of 68%. It was also found that TMEDA was essential for product formation when the reactions were performed in diethyl ether.

Table 1. Selected Results of Ortholithiation of **4** with Different Alkyllithiums



entry[a]	RLi[b] (equiv)	time (h)	yield[c] (%)	de[d] (%)
1	*n*-BuLi (3)	4	0	
2	*t*-BuLi (6)	4.5	<5	17
3	*s*-BuLi (3)	4.5	66	75
4	*c*-HexLi (6)	4.5	<5	82
5	*i*-PrLi (3)	4	17	86
6	*i*-PrLi (3)	18	65	84
7	*c*-PentLi(6)	4.5	30	93
8	*c*-PentLi(5)	30	78	93

[a] Reactions performed in Et_2O at −78 °C with 2 equiv of TMEDA per equivalent of alkyllithium. [b] Number of equivalents of alkyllithium used. [c] Determined by ^1H NMR. [d] Determined by ^{19}F-NMR. *c*-Hex = cyclohexyl; *c*-Pent = cyclopentyl.

Although others have observed dramatic variations in de's obtained using different alkyllithiums with chiral oxazoline ortholithiation groups, no explanation for this has been forthcoming. We were curious as to whether other *sec*-alkyllithiums would return results similar to those obtained using *sec*-butyllithium. We found that cyclohexyllithium (entry 4) and isopropyllithium[15] (entry 5) gave slightly better de's, although the yields were significantly lower (no side product from alkyllithium addition onto the oxazoline was observed). The low yield was presumably due to these alkyllithium−TMEDA complexes being less reactive than the *sec*-butyllithium−TMEDA complex with calix[4]arene **4**. By extending the reaction with isopropyllithium to 18 h the yield could be improved to a reasonable 65% (entry 6).

(9) Alemi, A. A.; Shaabani, B.; Dilmaghani, K. A.; Ganjali, S. T. *Molecules* **2001**, *6*, 417–423.
(10) Krasnokutskaya, E. A.; Semenischeva, N. I.; Filimonov, V. D.; Knochel, P. *Synthesis* **2007**, 81–84.
(11) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333–3336.
(12) Scully, P. A.; Hamilton, T. M.; Bennett, J. L. *Org. Lett.* **2001**, *3*, 2741–2744.
(13) Differding, E.; Ofner, H. *Synlett* **1991**, 187–189.
(14) Addition of the base to the oxazoline has been observed previously: Beak, P.; Kerrick, S. T.; Gallagher, D. J. *J. Am. Chem. Soc.* **1993**, *115*, 10628–10636.
(15) Surry, D. S.; Fox, D. J.; Macdonald, S. J. F.; Spring, D. R. *Chem. Commun.* **2005**, 2589–2590.

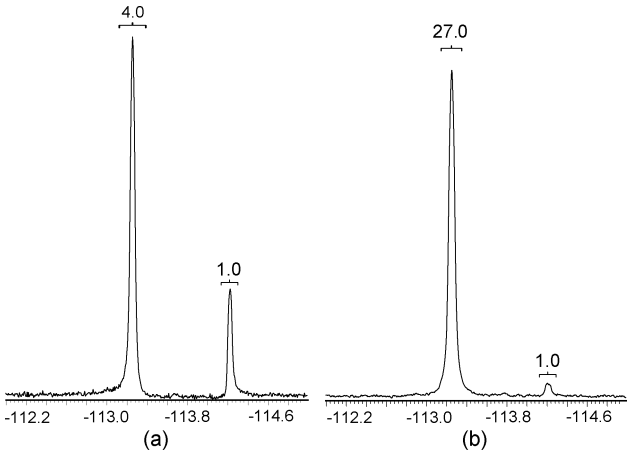


Figure 1. Selected ^{19}F NMR spectra: (a) representative from a poorly selective *s*-BuLi reaction at −45 °C; (b) representative from *c*-PentLi reaction.

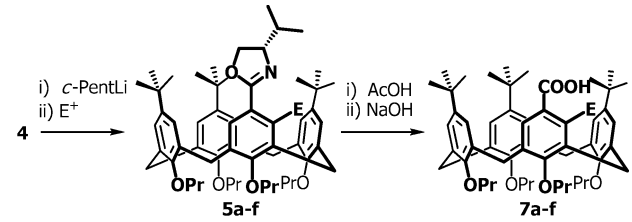
The use of cyclopentyllithium gratifyingly gave a much improved de of 93% and conversion of 78% after 30 h (entries 7 + 8).[16]

We then turned our attention to the removal of the oxazoline chiral auxiliary, which is known to be a stable group and resistant to hydrolysis. We examined a number of procedures but found that a two-step microwave reaction was the most efficient in our hands. Thus, heating the oxazoline in aqueous acetic acid at 170 °C for 1 h afforded the amide intermediate which was transferred to ethanolic sodium hydroxide and heated to 140 °C for a further 1 h. In this way, we obtained the inherently chiral calixarene acid **7a** in 78% yield. Without microwave heating, the reaction was incomplete after 3 days of reflux.

In order to demonstrate the generality of the reaction, we performed a series of electrophilic quenches, followed by hydrolysis of the chiral oxazoline (Table 2). It was found that the enantiomer of oxazoline calix[4]arene **4** resulted in the same de (93%) being observed, giving the enantiomer of **5a**. Using chlorotrimethylsilane as an electrophile afforded the expected product **5b**; however, the hydrolysis of the oxazoline resulted in decomposition of the starting material (entry 3). Quenching with diphenylphosphine chloride (entry 4) resulted in a product that rapidly oxidized to phosphine oxide **5c** on workup. This product was crystalline and was obtained as a single diastereomer as judged by the ^{1}H, ^{13}C, and ^{31}P NMR spectra. Using ethyl chloroformate as an electrophile afforded the diacid **7d** after hydrolysis. This compound proved to be sparingly soluable in most organic solvents (DMSO, $CHCl_3$, EtOH, MeCN, acetone, and benzene), and its NMR spectra exhibited broad signals even at elevated temperatures. It was found to be soluble in acetic acid, and its NMR spectra (recorded in d_4-acetic acid) displayed sharp signals consistent with the proposed structure. Quenches with dimethyl disulfide and ethylene dibromide afforded the expected products, though hydrolysis of the methyl thioether calix[4]arene **5e** returned a very poor yield with concomitant degradation products being observed.

(16) A 93% de represents the lowest value we have measured over a number of reactions.

Table 2. Various Electrophilic Quenches and Oxazoline Removal



entry[a]	electrophile	E	**5** (yield, %)[b]	**7** (yield, %)[c]
1	NFSI	F	**5a** (73)	**7a** (78)
2	NFSI	F	*ent*-**5a** (63)	*ent*-**7a** (88)
3	TMS-Cl	TMS	**5b** (62)	**7b** (0)[d]
4	Ph_2P-Cl	$P(O)Ph_2$ [e]	**5c** (70)	**7c** (99)
5	Cl-CO_2Et	CO_2Et [f]	**5d** (73)	**7d** (72)
6	Me_2S_2	SMe	**5e** (73)	**7e** (41)
7	$Br(CH_2)_2Br$	Br	**5f** (72)	**7f** (72)

[a] Conditions: −78 °C, 6 equiv of *c*-PentLi, 12 equiv of TMEDA, 18−24 h. [b] Isolated yields; de >92% as judged by ^{1}H NMR. [c] Conditions: (i) AcOH, 170 °C, 1 h; (ii) NaOH, ethanol, 140 °C, 1 h. [d] Starting material decomposition. [e] Isolated as a single diastereomer. [f] Ester hydrolysis concomitant with removal of oxazoline.

We then turned our attention to elucidating the structure of the major diastereomer in this reaction. It was found that phosphine oxide calix[4]arene **5c** gave diffraction-quality crystals when grown by slow evaporation of dichloromethane from ethanol. The X-ray crystal structure (Figure 2) unambiguously revealed calix[4]arene **5** to be the major diastereomer in this reaction.

We next considered the origin of this diastereoselectivity. The mechanism of ortholithiation is generally accepted to occur via two steps: a fast reversible coordination of the alkyllithium−TMEDA complex to the nitrogen of the oxazoline followed by a slower deprotonation step.[17] It is therefore reasonable to suggest that aryllithium **5** (E = Li) is the major reaction intermediate and that calix[4]arene **5** is the major diastereomer for all reactions. The formation of calix[4]arene **5** allows us to propose a likely transition state for this reaction (Figure 3). For this the conformation of the oxazoline is such that the bulky isopropyl group faces toward the calix[4]arene cavity, allowing for an unobstructed approach of the alkyllithium from the calix[4]arene outer face.[18] Current work is focused on gaining a better understanding of the mechanism of this reaction, i.e., whether it is governed by thermodynamic (i.e., conformational control of the oxazoline or reactive intermediate) or kinetic factors (reaction faster when isopropyl group facing toward cavity). For

(17) For a recent investigation into the mechanism, see: Chadwick, S. T.; Ramirez, A.; Gupta, L.; Collum, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 2259–2268.

(18) This transition state is an analogous to that proposed for the work on ferrocenes; see: Sammakia, T.; Latham, H. A. *J. Org. Chem.* **1996**, *61*, 1629–1635.

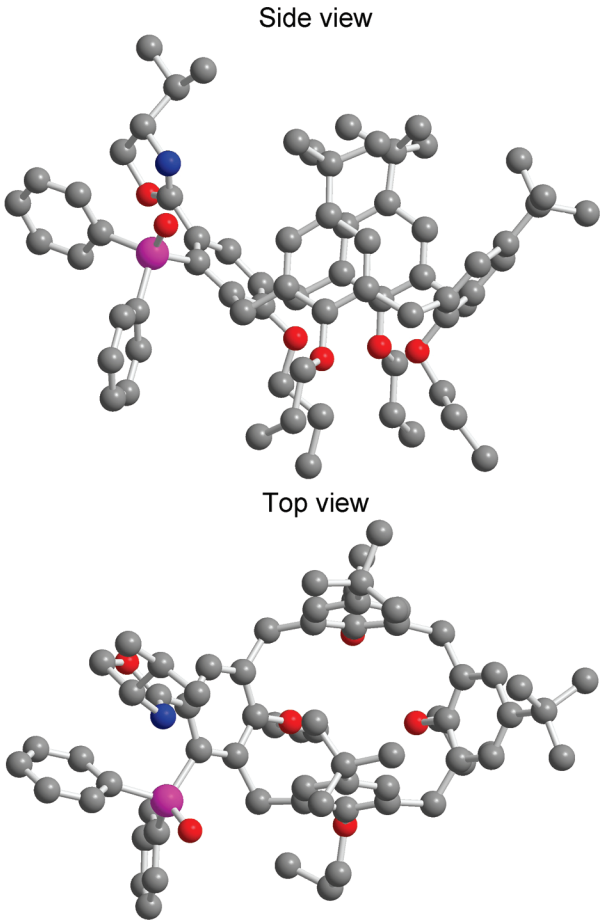


Figure 2. X-ray crystal stucture of phosphine oxide calix[4]arene **5c**.

example, synthesis of a calix[4]arene analogue of **4** without upper rim *tert*-butyl groups would help determine whether they contribute any cooperative effects in determining the diastereoselectivity.

In conclusion, we have demonstrated a practical synthesis of inherently chiral calix[4]arenes with high enantiomeric

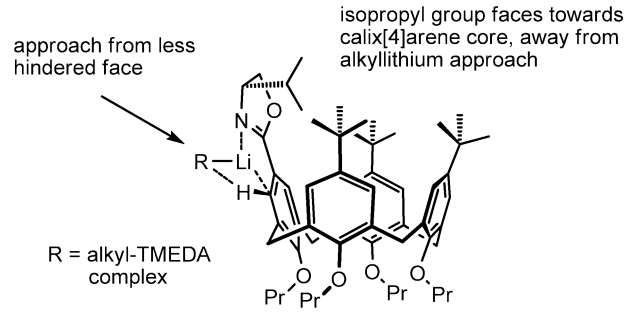


Figure 3. Proposed transition state.

excesses,[19] opening the door for further study into their applications as chiral ligands for asymmetric synthesis. The use of *sec*-butyllithium, which is more readily available from commercial sources, still allows for a diastereoselectivity much higher than that previously shown. This is the first time that cyclopentyllithium (and cyclohexyllithium) have been used as reagents for aromatic lithiation; the results obtained using cyclopentyllithium suggest that this reagent may have been overlooked in the literature and may have an important role to play in other stereoselective lithiations.

Acknowledgment. We thank Dr. T. Jacobs for CIF preparation and the University of Stellenbosch for financial support; S.A.H. thanks the NRF, HB Thom, and Harry Crossley Foundations for funding.

Supporting Information Available: Experimental procedures and characterization data for all new compounds, including spectra; crystallographic data for **5c** (CIF).This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) ee's of **7** are inferred to be the same as de's of precursor **5** since racemization would involve the breaking and formation of aryl−X bonds.