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Effective Nonenzymatic Kinetic Resolution of Racemic *m*-Nitro-Substituted Inherently Chiral Aminocalix[4]arenes

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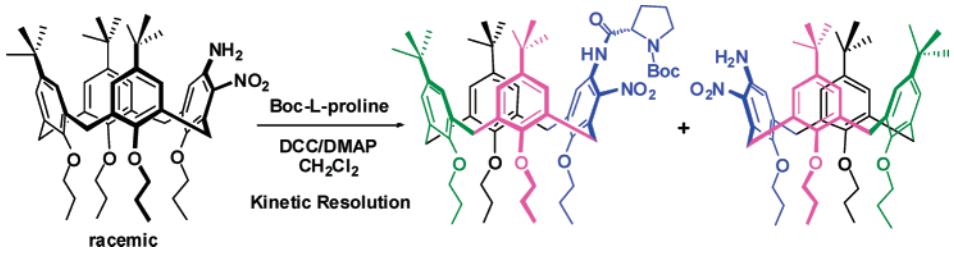
ABSTRACT



Effective nonenzymatic kinetic resolution of racemic *m*-nitro-substituted inherently chiral aminocalix[4]arenes with Boc-L-proline as the acylating reagent is described, which provides an efficient and convenient method for the enantioselective synthesis of meta-substituted aminocalix-[4]arenes.

Nonenzymatic kinetic resolution[1] has proven to be a very efficient method for the preparation of enantiopure compounds. During the past decade, significant progress has been made in the development of effective nonenzymatic acylation catalysts for the kinetic resolution of alcohols.[1,2] However, nonenzymatic kinetic resolution of amines, as one important class of organic compounds, has not been paid great attention.[3] In particular, to the best of our knowledge, there are still no reports on the enantioselective acylation of aromatic chiral amine and nonenzymatic kinetic resolution of racemic inherently chiral aminocalixarenes.

Since Gutsche et al.[4] reported the first example of inherently chiral calix[4]arene in 1982, there has been increasing interest in the synthesis of inherently chiral calixarenes for their unique structures and potential applica-

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(1) (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249−331. (b) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412−420. (c) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542−547. (d) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974−4001.

(2) (a) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985−3012. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138−5175. (c) Jarvo, E. R.; Miller, S. J. Asymmetric Acylation. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Heidelberg, 2004; Supplement 1, Chapter 43.

(3) (a) Kondo, K.; Kurosaki, T.; Murakami, Y. *Synlett* **1998**, 725−726. (b) Al-Sehemi, A. G.; Atkinson, R. S.; Fawcett J.; Russell, D. R. *Tetrahedron Lett.* **2000**, *41*, 2239−2242. (c) Ie, Y.; Fu, G. C. *Chem. Commun.* **2000**, 119−120. (d) Arai, S.; Bellemin-Laponnaz, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 234−236. (e) Arseniyadis, S.; Valleix, A.; Wagner, A.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3314−3317. (f) Arseniyadis, S.; Subhash, P. V.; Valleix, A.; Mathew, S. P.; Blackmond, D. G.; Wagner, A.; Mioskowski, C. *J. Am. Chem. Soc.* **2005**, *127*, 6138−6139. (g) Birman, V. B.; Jiqang, H.; Li, X.-M.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536−6537.

(4) (a) No, K. H.; Gutsche, C. D. *J. Org. Chem.* **1982**, *47*, 2713−2719. (b) Gutsche, C. D. *Calixarenes Revisted, Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, U.K., 1998.

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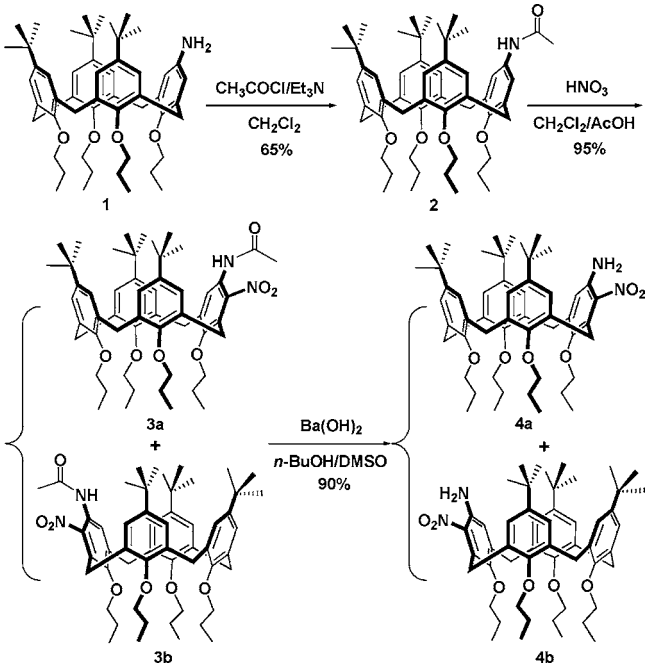
tions in chiral recognition and asymmetric catalysis.[5] However, the optical resolution of racemic inherently chiral calixarenes was usually achieved by using the HPLC method,[4b] which was inappropriate for scale-up and thus impeded their practical applications. Consequently, an effective approach to enantiopure inherently chiral calixarenes was recently developed by introduction of a chiral auxiliary and then separation of subsquent diastereomers via preparative TLC or column chromatography on silica gel.[6,7] More recently, we[8] reported a new approach to the enantiopure meta-substituted inherently chiral aminocalix[4]arenes based on the dual functions of Boc-L-proline auxiliary. Interestingly, we further found that Boc-L-proline could also be used as the chiral acylating reagent for the enantioselective acylation of the racemic *m*-nitro-substituted aminocalix[4]arenes. Herein, we describe the first effective nonenzymatic kinetic resolution of the racemic inherently chiral aminocalix[4]-arenes, which provides an efficient and convenient method for the enantioselective synthesis of meta-substituted inherently chiral aminocalixarenes.

Synthesis of the racemic *m*-nitro-substituted aminocalixarene is depicted in Scheme 1. Starting from the aminocalix-

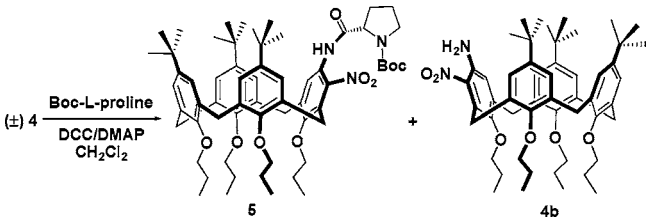
Scheme 1. Synthesis of (±)-**4** (**4a** + **4b**)



arene **1**,[6d] compound **2** was prepared in 65% yield by the reaction of **1** with acetyl chloride.[9] Treatment of **2** with HNO_3 (100%) in CH_2Cl_2 and acetic acid gave racemic inherently chiral calix[4]arene **3** (**3a** + **3b**) in 95% yield, which was then hydrolyzed by $Ba(OH)_2 \cdot 8H_2O$ in *n*-butanol and DMSO to provide the racemic **4** (**4a** + **4b**) in 90% yield.[10]

The *N*-acylation reaction of racemic **4** with Boc-L-proline was first carried out in CH_2Cl_2 in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) at room temperature, which led to a mixture of the corresponding amide **5** and the remaining aminocalix[4]arene **4b** (Scheme 2). The results are summarized in Table 1, which

Scheme 2. Kinetic Resolution of (±)-**4**



showed that the process took place through a kinetic resolution. According to our previous report,[8] the configuration of the recovered substrate aminocalix[4]arene **4b** was determined to be *cR*, and consequently, the corresponding *cS*-isomer **4a** was preferentially acylated to give the product **5**.[10]

Initially, we considered the influence of the ratio of acylating reagent to the substrate on the process. As expected, increasing the ratio resulted in an increase in the enantioselectivity (Table 1, entries 1−4). When 2.0 equiv of Boc-L-proline was employed, we obtained the recovered substrate **4b** in 26% isolated yield and 95% ee, while the selectivity factor (*s*) was determined to be 9.9 (Table 1, entry 5). When we used 1.8 equiv (Table 1, entry 4) or 3.0 equiv (Table 1, entry 6) of Boc-L-proline, it was found that there are no obvious changes in the enantioselectivity, but both the yield and *s* value in two cases are decreased. The results suggested that 2.0 equiv of the acylating reagent could be the optimal condition. Next, the influence of reaction time was investigated. Under otherwise identical conditions, we found that as the reaction time went on, the enantioselectivity gradually increased (entries 7−9). When the acylation reaction was performed for 20 h, the ee value was up to 95% (Table 1, entry 5). However, the enantioselectivity was found to be noticeably decreased when the reaction time was prolonged for 48 h and even 96 h (entries 10 and 11).

(5) (a) Jin, T.; Monde, K. *Chem. Commun.* **1998**, 1357−1358. (b) Dieleman, C.; Steyer, S.; Jeunesse, C.; Matt, D. *J. Chem. Soc., Dalton Trans.* **2001**, 2508−2517. (c) Shirakawa, S.; Moriyama, A.; Shimizu, S. *Org. Lett.* **2007**, *9*, 3117−3119.

(6) (a) Cao, Y.-D.; Luo, J.; Zheng, Q.-Y.; Chen, C.-F.; Wang, M.-X.; Huang, Z.-T. *J. Org. Chem.* **2004**, *69*, 206−208. (b) Li, S.-Y.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Tetrahedron: Asymmetry* **2005**, *16*, 641−645. (c) Luo, J.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Chem. Eur. J.* **2005**, *11*, 5917−5928. (d) Mao, R.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *J. Org. Chem.* **2005**, *70*, 7662−7671. (e) Luo, J.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Tetrahedron* **2005**, *61*, 8517−8528.

(7) (a) Narumi, F.; Yamabuki, W.; Hattori, T.; Kameyama, H.; Miyano, S. *Chem. Lett.* **2003**, *32*, 320−321. (b) Narumi, F.; Hattori, T.; Yamabuki, W.; Kabutto, C.; Kameyama, H. *Tetrahedron: Asymmetry* **2005**, *16*, 793−800. (c) Narumi, F.; Hattori, T.; Matsumura, N.; Onodera, T.; Katagiri, C.; Kabutto, C.; Kameyama, H. *Tetrahedron* **2004**, *60*, 7827−7833. (d) Boyko, V. I.; Shivanyuk, A.; Pyrozhenko, V. V.; Zubatyuk, R. I.; Shishkin, O. V.; Kalchenko, V. I. *Tetrahedron Lett.* **2006**, *47*, 7775−7778.

(8) Xu, Z.-X.; Zhang, C.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Org. Lett.* **2007**, *9*, 4447−4450.

(9) Verboom, W.; Bodewes, P. J.; Essen, G. V.; Timmerman, P.; Hummer, G. J. V.; Harkema, S.; Reinhoudt, D. N. *Tetrahedron* **1995**, *51*, 499−512.

(10) See the Supporting Information.

Table 1. Kinetic Resolution of the Racemic **4** with Boc-L-proline as the Chiral Acylating Reagent

				recovered substrate **4b**			**5**		
entry	Boc-L-proline	DCC/DMAP	reaction time (h)	yield[a] (%)	ee[b] (%)	config[d]	yield[a] (%)	de[c] (%)	*s*
1	0.5	1.5/0.5	20	88	4	*cR*	6	84	4.5
2	0.8	1.8/0.5	20	78	17	*cR*	19	84	7.4
3	1.5	1.5/0.5	20	51	56	*cR*	43	74	10.2
4	1.8	1.8/0.6	20	25	95	*cR*	74	35	6.4
5	2.0	2.0/0.7	20	26	95	*cR*	66	46	9.9
6	3.0	3.0/1.0	20	20	96	*cR*	77	24	5.9
7	2.0	2.0/0.7	1	82	14	*cR*	11	80	9.9
8	2.0	2.0/0.7	5	77	21	*cR*	17	85	14.0
9	2.0	2.0/0.7	10	73	28	*cR*	25	86	15.0
10	2.0	2.0/0.7	48	44	69	*cR*	48	67	14.0
11	2.0	2.0/0.7	96	50	55	*cR*	46	71	8.2

[a] Isolated yield. [b] Determined by HPLC analysis using Chiralpak AD-H column. [c] Determined by ^{1}H NMR (600 MHz, $CDCl_3$) spectroscopic analysis. [d] See ref 8.

Furthermore, we examined the effect of solvent on the kinetic resolution process. The results showed that the process could be carried out in different solvents, but the enantioselectivity of the acylation was highly solvent-dependent. Under the optimization reaction conditions (2.0 equiv of Boc-L-proline, 20 h for the reaction time), it was found that lower enantioselectivity of the reaction was observed in Et_2O (13% ee, Table 2, entry 2) and THF (17% ee, entry 3), while higher ee values were achieved in CH_3CN (54%, entry 4) and $CHCl_3$ (48%, entry 6). Compared with other solvents used, the acylation afforded the hightest ee value (98%, entry 5) but lower selectivity (*s* 4.1) in toluene. These observations implied that no evident relationship between the polarity of solvent and the ee value and the *s* value existed.

Table 2. Solvent Effects on the Enantioselectivity

		recovered material		**5a**		
entry	solvent	yield[a] (%)	ee[b] (%)	yield[a] (%)	de[c] (%)	s
1	CH_2Cl_2	26	95	66	46	9.9
2	Et_2O	70	13	13	83	16.0
3	THF	76	17	19	70	1.7
4	CH_3CN	57	54	40	76	16.0
5	$C_6H_5CH_3$	22	98	76	27	4.1
6	$CHCl_3$	60	48	37	76	16.0

[a] Isolated yield. [b] Determined by HPLC analysis using Chiralpak AD-H column. [c] Determined by ^{1}H NMR (600 MHz) spectroscopic analysis.

In conclusion, we have demonstrated that Boc-L-proline could be used as the chiral acylating reagent for the effective nonenzymatic kinetic resolution of the racemic *m*-nitro-substituted inherently chiral aminocalix[4]arenes, which provided an efficient and convenient method for the enantioselective synthesis of meta-substituted inherently chiral aminocalixarenes. Further work will be focused on the nonenzymatic kinetic resolution of other meta-substituted inherently chiral aminocalix[4]arenes and the potential applications of the enantiopure inherently chiral calixarenes in asymmetric catalysis, which are underway in our laboratory.

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Supporting Information Available: Synthesis and characterization data of the new compounds. Copies of ^{1}H and ^{13}C NMR spectra for the new compounds. The HPLC spectra of entries in Tables 1 and 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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