Organocatalysis

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Catalytic Enantioselective Alkylation of Sulfenate Anions to Chiral Heterocyclic Sulfoxides Using Halogenated Pentanidium Salts**

Lili Zong, Xu Ban, Choon Wee Kee, and Choon-Hong Tan**

Abstract: *We report halogenated pentanidiums as phase-transfer catalysts for the asymmetric alkylation of sulfenate anions to various sulfoxides with high enantioselectivities (up to 99 % ee) and yields (up to 99 %). This approach gives access to enantioenriched heterocyclic sulfoxides that might not be compatible with strong oxidants or organometallic reagents. Computational studies have revealed that the multiple non-covalent interactions such as halogen bonds and nonclassical hydrogen bonds are involved.*

Optically active sulfoxides are extensively used as chiral auxiliaries, chiral ligands for metal complexes, and organocatalysts.[1] This unique moiety is also found in several marketed drugs such as esomeprazole (proton pump inhibitor), armodafinil (eugeroic), and sulindac (anti-inflammation).[2] Currently, there are two main strategies to synthesize enantioenriched sulfoxides: the nucleophilic substitution of nonracemic sulfinates using organometallic reagents (Andersen method)[3] and the direct oxidation of prochiral sulfides catalyzed by metal complexes (Kagan and Modena methods).[4] Recently, a metal-free approach using chiral imidodiphosphoric acid catalysts for highly enantioselective sulfide oxidation employing aqueous H_2O_2 was demonstrated by List and co-workers.[5]

Due to the importance of such compounds, the development of catalytic and enantioselective methodologies with broad substrate scope is still highly desirable. In the classical Andersen method and its variants, the reactive sulfur center is electrophilic and a stoichiometric quantity of chiral auxiliary is required (although the recycling of auxiliary is possible in some cases[3b]). Recently, a complementary approach based on sulfenate anions (RSO^-)[6] with a nucleophilic sulfur center has emerged as a viable method for the enantio- and diastereoselective synthesis of sulfoxides.[7] However, reports with sulfenate anions in the catalytic enantioselective synthesis of sulfoxides remain scant.[7a,c] Recent attempts with cinchona alkaloids as phase-transfer catalysts were reported by Perrio and co-workers; despite the high yields, the *ee* values did not exceed 60 %.[8]

Asymmetric phase-transfer catalysis is a convenient, scalable and environmentally benign method to prepare compounds in high enantiopurity.[9] Despite the success of several reported phase-transfer catalysts (PTCs) in the literature, it is still meaningful to design new ones with a high level of stereocontrol.[10] Recently, our group has developed structurally novel pentanidiums[11] based on quaternized sp^2-hybridized N-atoms[12] as PTCs (Figure 1). The pentanidiums are highly amenable to variation due to the ease of changing the R group on the catalyst to vary electronic and steric properties. Herein, we introduce novel pentanidiums with halogenated benzyl R groups (**1b**, **1c**, and **1d**) and their application in the enantioselective synthesis of heterocyclic sulfoxides from sulfenate anions.

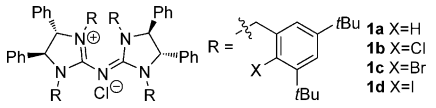

Figure 1. Various chiral pentanidium salts.

Thiophene derivatives[13] are important heteroaromatic compounds, which have been used prevalently in functional materials and pharmaceutical industry due to their distinct electronic and biological activities (see the Supporting Information, SI, Figure S1). Based on currently available methodologies to synthesize optically active sulfoxides, sulfoxides which contain thienyl group pose significant challenges (SI, Scheme S4), such as potential incompatibility with strong oxidants[14] or organometallic reagents.[15] Herein, we report the nucleophilic displacement of alkyl halides by sulfenate anions using pentanidiums as catalysts to synthesize various heterocyclic sulfoxides such as thienyl sulfoxides with high enantioselectivity.

We began by investigating the enantioselective benzylation of 2-thienyl sulfenate anion generated in situ with pentanidiums as PTCs by using benzyl bromide as the electrophile. Preliminary variations of reaction parameters such as pentanidiums, sulfenate anion precursors, solvent, inorganic base, and temperature were performed (SI). Representative variations are presented in Table 1. The β-sulfinyl methyl ester **2a** was found to be the appropriate sulfenate anion precursor. Halogenated pentanidiums have significant effects on both the course and enantioselectivity of the reaction. We found that the level of enantioselectivity

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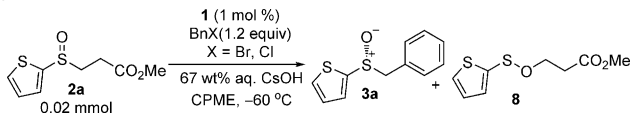
Table 1: Benzylation of the 2-thienyl sulfenate anion catalyzed by pentanidiums.



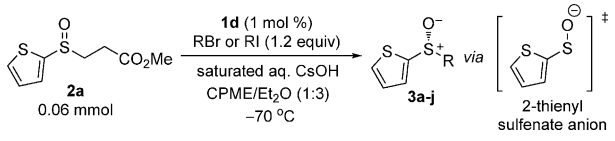
Entry	Catalyst	X	*t* [h]	Product	Yield [%][a]	*ee* [%][b]
1	**1a**	Br	48	**3a**	76	61
2	**1c**	Br	48	**3a**	72	81
3[c]	**1c**	Br	48	**3a**	86	88
4[c]	**1d**	Br	48	**3a**	72	91
5[d,e]	–	Br	1	–	–	–
6[e]	**1a**	–	24	**8**	40	–
7[e]	**1a**	Cl	48	**8**	27	–
8[e]	**1b**	Cl	48	**3a/8 (1:2)**[f]	9	83
9[e]	**1d**	Cl	24	**3a**	29	90

[a] Yield of isolated product. [b] Determined by HPLC analysis. [c] The reaction was conducted at −70 °C with saturated aqueous CsOH solution (24 μL) in a solvent mixture of CPME (0.2 mL)/Et_2O (0.6 mL). [d] **2a** decomposed under basic conditions without PTCs at RT. [e] Saturated aqueous CsOH solution (24 μL) was used. [f] The ratio was determined by ^{1}H NMR analysis. The absolute configuration of **3a** was assigned to be *R* by single-crystal X-ray diffraction of **6q** and DFT-calculated specific optical rotation of **3a** and **6q**.

significantly increases with the introduction of halogen to pentanidiums (entries 1–4). Pentanidium **1d** can promote the reaction with an excellent enantioselectivity of 91 % *ee* (Table 1, entry 4). When a less reactive electrophile benzyl chloride (entries 5–9) was used, the ratio of desired chiral product **3a** to **8** increases as the substituent is varied from H to I (from **1a** to **1d**).

A variety of alkyl halides was examined as electrophile under optimized conditions (Table 2). With 1 mol % of pentanidium **1d**, the alkylation of 2-thienyl sulfenate anion

Table 2: Asymmetric alkylation of 2-thienyl sulfenate anion catalyzed with iodo-pentanidium **1d**.



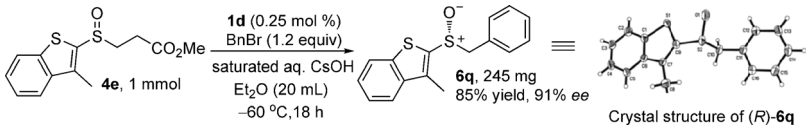
Entry	R	Product	*t* [h]	Yield [%][a]	*ee* [%][b]
1	$PhCH_2$	**3a**	12	87	92
2	4-$MeC_6H_4CH_2$	**3b**	12	88	94
3	4-$ClC_6H_4CH_2$	**3c**	12	84	90[c]
4	4-$CF_3C_6H_4CH_2$	**3d**	12	83	94[c]
5	3-$MeOC_6H_4CH_2$	**3e**	12	84	90
6	2-naphthylCH_2	**3f**	12	84	92
7		**3g**	36	82	92
8		**3h**	21	79	92
9		**3i**	21	77	82
10[d]	Me	**3j**	40	65	77[c]
11[d]	$CH_3CH_2CH_2$	**3k**	28	66	81[c]
12[d]	$CH_3(CH_2)_6CH_2$	**3l**	20	69	81[c]

[a] Yield of isolated product. [b] Determined by HPLC analysis. [c] Data was obtained in the presence of 1 mol % of brominated pentanidium **1c**. [d] 2.5 Equivalents of alkyl iodides was used.

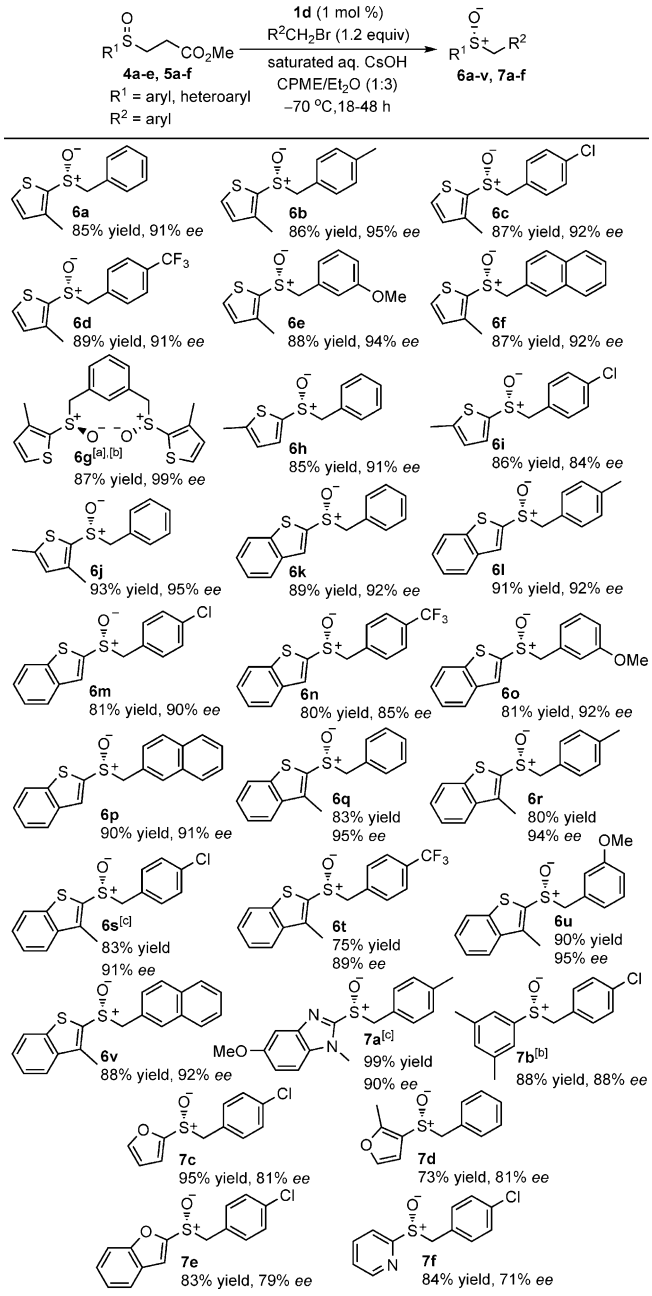
with various alkyl halides produced the corresponding sulfoxides in good yields and excellent enantioselectivities. Benzyl bromides with electron-withdrawing and electron-donating substituents are well tolerated (entries 1–6). It should be noted that benzyl bromides caused an erosion of the enantioselectivity in the previous report of a related reaction by Perrio group.[8] Moreover, commercially available PTCs were also tested and low enantioselectivity was obtained (below 15 % *ee*, SI, Table S5). The construction of stereogenic sulfoxides bearing allylic and propargylic substituents could also be achieved in a similar manner (entries 7–9). Moreover, the alkylation of 2-theinyl sulfenate anion with alkyl iodides provided sulfoxides **3j**–**3l** with good enantioselectivities (77–81 % *ee*, entries 10–12). These results indicated that both alkyl and benzyl groups can be installed using this methodology. For specific benzyl bromide derivatives with electron-withdrawing substituents (entries 3–4) and alkyl iodides (entries 10–12), brominated pentanidium **1c** gave marginally better enantioselectivities.

The scope of this reaction was further examined under the optimized conditions with various β-heteroaryl and aryl sulfinyl methyl esters (**4a**–**e**, **5a**–**f**) as sulfenate anion precursors (Scheme 2). They participated in the reaction efficiently to provide the anticipated sulfoxides in high yields with good to excellent enantioselectivities. The methyl substituted 2-thienyl sulfinyl ester **4a** was transformed to the corresponding highly enantioenriched sulfoxides **6a**–**f**. Interestingly, the reaction between the sulfenate anion generated from β-sulfinyl ester **4a** and *m*-xylene dibromide produced the bis-sulfoxide **6g** in good yield (87 %, *dl*/*meso* = 4.75:1) and excellent enantioselectivity (> 99 % *ee*). Sulfoxides **6k**–**v** containing benzothiophene were also obtained with excellent enantioselectivities. Benzimidazole sulfoxide **7a**, a reminiscence to the drug esomeprazole, was obtained in high enantioselectivity (90 % *ee*). Sulfenate anions containing furyl, benzofuryl, and pyridyl moieties can be tolerated and converted into the corresponding sulfoxides **7c**–**f** with a slight decrease of the enantioselectivity. To the best of our knowledge, this methodology allows the widest range of heterocyclic sulfoxides to be obtained in high optical purity and yield.[16] The efficiency of pentanidium **1d** was further tested by reducing the catalyst loading to 0.25 mol % in a 1 mmol scale reaction (Scheme 1).The sulfoxide **6q** was obtained in 85 % yield with an excellent enantioselectivity of 91 % *ee*.

Based on experiments that were conducted to provide more insight into the reaction mechanism (Table 1, entries 5–9), a working model was proposed (Scheme 3).[17] The inorganic base promotes the deprotonation of β-sulfinyl methyl ester **2a** to give the corresponding cesium enolate, which leads to the generation of the sulfenate anion and the release of methyl acrylate through a retro-Michael process even without PTC. However, the sulfenate anion will undergo alkaline hydrolysis under basic conditions in the absence of PTC (Table 1, entry 5).[6b] In the presence of the chiral PTC, cationic exchange and retro-Michael processes lead to a chiral ion pair **A**, which can readily react with electrophile RX (X = Br) to afford the product **3a** (Scheme 3, path a). When the reaction was performed in the presence of PTC but not the alkyl halides, **2a** produced thiophene sulfenate **8** through

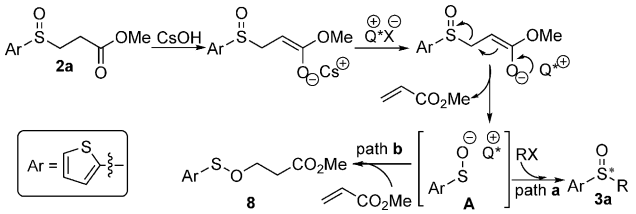


Scheme 1. Further reduction of catalyst loading of pentanidium **1d**.



Scheme 2. Scope of pentanidium-catalyzed alkylation to enantioenriched heterocyclic sulfoxides. [a] Ratio of *dl*/*meso* = 4.75:1, determined by ^{1}H NMR analysis. [b] The reaction was conducted at −40 °C. [c] Data was obtained in the presence of brominated pentanidium **1c**. The absolute configuration was assigned as *R* by analogy to **6q**. CPME = cyclopentyl methyl ether.

oxygen-Michael addition of the sulfenate anion to methyl acrylate released during the retro-Michael process (Table 1, entry 6; Scheme 3, path b).[18] Moreover, using nonhalogenated pentanidium **1a** and benzyl chloride, a less active electrophile, only sulfenate **8** instead of sulfoxide **3a** was observed (Table 1, entry 7; Scheme 3, path b).[7a] However, it is noteworthy that sulfoxide **3a** can be formed



Scheme 3. Working model of sulfenate anion intermediate.

when halogenated pentanidiums were used as catalysts (Table 1, entry 9; Scheme 3, path a). These results demonstrate the ability of halogenated pentanidiums to activate both the electrophile and the sulfenate anion nucleophile.

To obtain structural features of relevant transition state (TS) structures, we performed theoretical studies with the ONIOM method[19] as implemented in Gaussian 09.[20] M06[21] was used as the high level and UFF molecular mechanics method[22] as the low level (*tert*-butyl group and phenyl ring of catalyst).

The most stable TS structure for the *R*- and *S*-sets of the TS, in terms of the Gibbs free energy, is shown in Figure 2. The *R*-TS is more stable than the *S*-TS by 1.2 kcal mol^{-1},

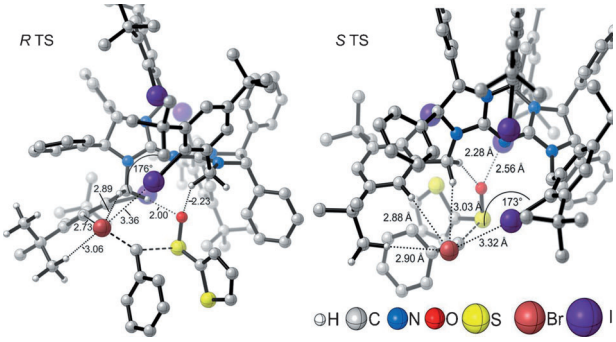


Figure 2. Optimized most stable (in terms of G) *R*- and *S*-TS at M06/BS1:UFF calculated with ONIOM method in Gaussian 09 A2 (see SI for ONIOM partition and definition of BS1). Most of the hydrogen atoms at carbon are hidden. CYLview was used for preparation of the graphics.[23]

which is in good agreement with the experimental e.r. of 95.5:4.5 (*R*/*S*). The Br–I halogen bond (XB)[24] between the leaving Br and the aryl iodide donor of the side chain of the iodinated pentanidium catalyst **1d** is evident in both *R*- and *S*-TS structures (Figure 2). We also applied the noncovalent interaction (NCI) index[25] to analyze the NCI between catalyst **1d** and the substrates leading to product **3a** (see SI). This computational study revealed that the halogen bonds and nonclassical hydrogen bonds (NCHB)[26] stabilize the substrates in the TS.

In summary, we have described a highly enantioselective alkylation of sulfenate anions to prepare enantioenriched sulfoxides using halogenated pentanidiums. These heterocyclic sulfoxides could potentially be used as chiral ligands or organocatalyst and bioactive molecules.[27] Moreover, this work demonstrates the possibility of incorporating halogen bonding as primary noncovalent interaction in catalyst design.

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[1] a) I. Fernández, N. Khiar, *Chem. Rev.* **2003**, *103*, 3651 – 3705; b) J. Legros, J. R. Dehli, C. Bolm, *Adv. Synth. Catal.* **2005**, *347*, 19 – 31; c) H. B. Kagan in *Organosulfur Chemistry in Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2009**, pp. 1 – 29; d) G. E. O'Mahony, P. Kelly, S. E. Lawrence, A. R. Maguire, *Arkivoc* **2011**, 1 – 110.

[2] a) H. Cotton, T. Elebring, M. Larsson, L. Li, H. Sorensen, S. von Unge, *Tetrahedron: Asymmetry* **2000**, *11*, 3819 – 3825; b) M. Darwish, M. Kirby, E. T. Hellriegel, P. Robertson, Jr., *Clin. Drug Invest.* **2009**, *29*, 613 – 623; c) M. A. Scheper, N. G. Nikitakis, R. Chaisuparat, S. Montaner, J. J. Sauk, *Neoplasia* **2007**, *9*, 192 – 199.

[3] a) K. K. Andersen, W. Gaffield, N. E. Papanikolaou, J. W. Foley, R. I. Perkins, *J. Am. Chem. Soc.* **1964**, *86*, 5637 – 5646; b) C. H. Senanayake, D. Krishnamurthy, Z. H. Lu, Z. X. Han, I. Gallou, *Aldrichimica Acta* **2005**, *38*, 93 – 104.

[4] a) P. Pitchen, E. Dunach, M. N. Deshmukh, H. B. Kagan, *J. Am. Chem. Soc.* **1984**, *106*, 8188 – 8193; b) F. Di Furia, G. Modena, R. Seraglia, *Synthesis* **1984**, 325 – 326.

[5] a) S. Liao, I. Čorić, Q. Wang, B. List, *J. Am. Chem. Soc.* **2012**, *134*, 10765 – 10768; b) Z.-M. Liu, H. Zhao, M.-Q. Li, Y.-B. Lan, Q.-B. Yao, J.-C. Tao, X.-W. Wang, *Adv. Synth. Catal.* **2012**, *354*, 1012 – 1022.

[6] a) N. Kharasch, S. J. Potempa, H. L. Wehrmeister, *Chem. Rev.* **1946**, *39*, 269 – 332; b) J. S. O'Donnell, A. L. Schwan, *J. Sulfur Chem.* **2004**, *25*, 183 – 211; c) G. Maitro, G. Prestat, D. Madec, G. Poli, *Tetrahedron: Asymmetry* **2010**, *21*, 1075 – 1084.

[7] a) C. Caupène, C. Boudou, S. Perrio, P. Metzner, *J. Org. Chem.* **2005**, *70*, 2812 – 2815; b) S. C. Soderman, A. L. Schwan, *Org. Lett.* **2011**, *13*, 4192 – 4195; c) G. Maitro, S. Vogel, M. Sadaoul, G. Prestat, D. Madec, G. Poli, *Org. Lett.* **2007**, *9*, 5493 – 5496.

[8] a) F. Gelat, J. Jayashankaran, J. F. Lohier, A. C. Gaumont, S. Perrio, *Org. Lett.* **2011**, *13*, 3170 – 3173; b) F. Gelat, A.-C. Gaumont, S. Perrio, *J. Sulfur Chem.* **2013**, *34*, 596 – 605.

[9] a) K. Maruoka, *Asymmetric Phase Transfer Catalysis*, Wiley-VCH, Weinheim, **2008**; b) S. Shirakawa, K. Maruoka, *Angew. Chem. Int. Ed.* **2013**, *52*, 4312 – 4348; *Angew. Chem.* **2013**, *125*, 4408 – 4445; c) K. Brak, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2013**, *52*, 534 – 561; *Angew. Chem.* **2013**, *125*, 558 – 588; d) J. Novacek, M. Waser, *Eur. J. Org. Chem.* **2013**, 637 – 648.

[10] a) T. Ooi, D. Ohara, M. Tamura, K. Maruoka, *J. Am. Chem. Soc.* **2004**, *126*, 6844 – 6845; b) M. Q. Hua, H. F. Cui, L. Wang, J. Nie, J. A. Ma, *Angew. Chem. Int. Ed.* **2010**, *49*, 2772 – 2776; *Angew. Chem.* **2010**, *122*, 2832 – 2836; c) L. J. Wang, S. Shirakawa, K. Maruoka, *Angew. Chem. Int. Ed.* **2011**, *50*, 5327 – 5330; *Angew. Chem.* **2011**, *123*, 5439 – 5442; d) D. Uraguchi, K. Koshimoto, T. Ooi, *J. Am. Chem. Soc.* **2012**, *134*, 6972 – 6975; e) W. Q. Zhang, L. F. Cheng, J. Yu, L. Z. Gong, *Angew. Chem. Int. Ed.* **2012**, *51*, 4085 – 4088; *Angew. Chem.* **2012**, *124*, 4161 – 4164; f) K. M. Johnson, M. S. Rattley, F. Sladojevich, D. M. Barber, M. G. Nunez, A. M. Goldys, D. J. Dixon, *Org. Lett.* **2012**, *14*, 2492 – 2495.

[11] a) T. Ma, X. Fu, C. W. Kee, L. Zong, Y. Pan, K.-W. Huang, C.-H. Tan, *J. Am. Chem. Soc.* **2011**, *133*, 2828 – 2831; b) Y. Y. Yang, F. Moinodeen, W. Chin, T. Ma, Z. Y. Jiang, C.-H. Tan, *Org. Lett.* **2012**, *14*, 4762 – 4765.

[12] a) T. Kita, A. Georgieva, Y. Hashimoto, T. Nakata, K. Nagasawa, *Angew. Chem. Int. Ed.* **2002**, *41*, 2832 – 2834; *Angew. Chem.* **2002**, *114*, 2956 – 2958; b) K. Ohmatsu, M. Kiyokawa, T. Ooi, *J. Am. Chem. Soc.* **2011**, *133*, 1307 – 1309; c) C. Uyeda, E. N. Jacobsen, *J. Am. Chem. Soc.* **2011**, *133*, 5062 – 5075; d) A. E. Sheshenev, E. V. Boltukhina, A. J. P. White, K. K. Hii, *Angew. Chem. Int. Ed.* **2013**, *52*, 6988 – 6991; *Angew. Chem.* **2013**, *125*, 7126 – 7129; e) J. S. Bandar, T. H. Lambert, *J. Am. Chem. Soc.* **2013**, *135*, 11799 – 11802.

[13] S. Gronowitz, A. B. Hörnfeldt, *Thiophenes*, Elsevier, Oxford, UK, **2004**.

[14] T. Thiemann, D. J. Walton, A. O. Brett, J. Iniesta, F. Marken, Y. Q. Li, *Arkivoc* **2009**, 96 – 113.

[15] L. Melzig, C. B. Rauhut, P. Knochel, *Chem. Commun.* **2009**, 3536 – 3538.

[16] a) W. Du, C. Hardouin, H. Cheng, I. Hwang, D. L. Boger, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 103 – 106; b) T. Z. Jia, A. Bellomo, S. Montel, M. N. Zhang, K. E. L. Baina, B. Zheng, P. J. Walsh, *Angew. Chem. Int. Ed.* **2014**, *53*, 260 – 264; *Angew. Chem.* **2014**, *126*, 264 – 268; c) F. Colobert, R. Ballesteros-Garrido, F. R. Leroux, R. Ballesteros, B. Abarca, *Tetrahedron Lett.* **2007**, *48*, 6896 – 6899.

[17] a) M. Rabinovitz, Y. Cohen, M. Halpern, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 960 – 970; *Angew. Chem.* **1986**, *98*, 958 – 968; b) S. E. Denmark, R. C. Weintraub, N. D. Gould, *J. Am. Chem. Soc.* **2012**, *134*, 13415 – 13429.

[18] a) D. R. Hogg, A. Robertson, *J. Chem. Soc. Perkin Trans. 1* **1979**, 1125 – 1128; b) P. Kiełbasiński, R. Żurawiński, J. Orabowicz, M. Mikołajczyk, *Tetrahedron* **1988**, *44*, 6687 – 6692; c) D. Enders, K. Lüttgen, A. A. Narine, *Synthesis* **2007**, 959 – 980.

[19] a) X. Zhang, H. Du, Z. Wang, Y.-D. Wu, K. Ding, *J. Org. Chem.* **2006**, *71*, 2862 – 2869; b) C. D. Anderson, T. Dudding, R. Gordillo, K. N. Houk, *Org. Lett.* **2008**, *10*, 2749 – 2752; c) L. Simón, J. M. Goodman, *J. Am. Chem. Soc.* **2012**, *134*, 16869 – 16876.

[20] a) M. J. Frisch, et al., in Gaussian 09, Revision A.02, Wallingford CT, **2009**; b) S. Dapprich, I. Komáromi, K. S. Byun, K. Morokuma, M. J. Frisch, *J. Mol. Struct.: THEOCHEM* **1999**, *461 – 462*, 1 – 21; c) T. Vreven, K. Morokuma, Ö. Farkas, H. B. Schlegel, M. J. Frisch, *J. Comput. Chem.* **2003**, *24*, 760 – 769.

[21] Y. Zhao, D. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215 – 241.

[22] A. K. Rappe, C. J. Casewit, K. S. Colwell, W. A. Goddard, W. M. Skiff, *J. Am. Chem. Soc.* **1992**, *114*, 10024 – 10035.

[23] C. Y. Legault, 1.0.562 BETA ed., Université de Sherbrooke, **2012**.

[24] a) H. Yan, H. B. Jang, J. W. Lee, H. K. Kim, S. W. Lee, J. W. Yang, C. E. Song, *Angew. Chem. Int. Ed.* **2010**, *49*, 8915 – 8917; *Angew. Chem.* **2010**, *122*, 9099 – 9101; b) A. Vargas Jentzsch, D. Emery, J. Mareda, P. Metrangolo, G. Resnati, S. Matile, *Angew. Chem. Int. Ed.* **2011**, *50*, 11675 – 11678; *Angew. Chem.* **2011**, *123*, 11879 – 11882; c) F. Kniep, S. H. Jungbauer, Q. Zhang, S. M. Walter, S. Schindler, I. Schnapperelle, E. Herdtweck, S. M. Huber, *Angew. Chem. Int. Ed.* **2013**, *52*, 7028 – 7032; *Angew. Chem.* **2013**, *125*, 7166 – 7170; d) L. C. Gilday, T. Lang, A. Caballero, P. J. Costa, V. Felix, P. D. Beer, *Angew. Chem. Int. Ed.* **2013**, *52*, 4356 – 4360; *Angew. Chem.* **2013**, *125*, 4452 – 4456.

[25] a) E. R. Johnson, S. Keinan, P. Mori-Sánchez, J. Contreras-García, A. J. Cohen, W. Yang, *J. Am. Chem. Soc.* **2010**, *132*, 6498 – 6506; b) J. Contreras-García, E. R. Johnson, S. Keinan, R. Chaudret, J.-P. Piquemal, D. N. Beratan, W. Yang, *J. Chem. Theory Comput.* **2011**, *7*, 625 – 632.

[26] a) H. Yang, M. W. Wong, *J. Am. Chem. Soc.* **2013**, *135*, 5808 – 5818; b) X.-S. Xue, X. Li, A. Yu, C. Yang, C. Song, J.-P. Cheng, *J.*

Am. Chem. Soc. **2013**, *135*, 7462 – 7473; c) R. C. Johnston, P. H.-Y. Cheong, *Org. Biomol. Chem.* **2013**, *11*, 5057 – 5064.

[27] a) N. Furukawa, S. Ogawa, T. Kawai, S. Oae, *J. Chem. Soc. Perkin Trans. 1* **1984**, 1833 – 1838; b) S. Kobayashi, C. Ogawa, H. Konishi, M. Sugiura, *J. Am. Chem. Soc.* **2003**, *125*, 6610 – 6611; c) E. Ichikawa, M. Suzuki, K. Yabu, M. Albert, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 11808 – 11809; d) R. S. Kathayat, N. S. Finney, *J. Am. Chem. Soc.* **2013**, *135*, 12612 – 12614.

