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Optically Active Thiophenes via an Organocatalytic One-Pot Methodology

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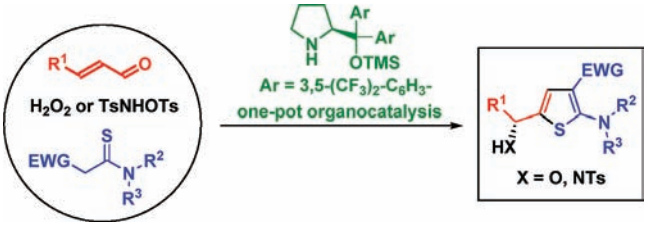
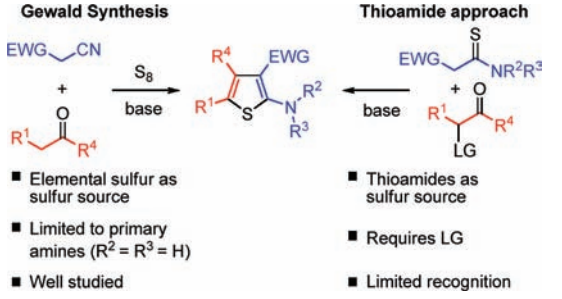
ABSTRACT



A general methodology for the synthesis of trisubstituted, optically active thiophenes by an organocatalytic one-pot reaction cascade is presented. The target products are synthesized in good yields (up to 92%) and with excellent enantioselectivities (up to 98% ee). Importantly, based on practical and easily available starting materials, the presented methodology can be conducted under mild reaction conditions. To further elucidate the generality, the synthesis of optically active thienoindoles, as well as selenophenes, is also demonstrated.

Heteroaromatic compounds constitute an important class of molecules which are widespread in nature as well as among synthetically obtained products.[1] Their structural rigidity and distinct electronic properties allow for considerable fine-tuning of molecular properties. Among the heteroaromatic frameworks, thiophenes occupy a prominent position.[2] While polysubstituted thiophenes are well studied, their synthesis often relies on the functionalization of simpler thiophenes, whereas methods for their construction from acyclic precursors are scarce. An example of major importance is the Gewald synthesis, which affords 2-aminothiophenes.[3] This well-studied multicomponent reaction utilizes elemental sulfur for the introduction of the thiophene sulfur atom and benefits from mild reaction conditions, high efficiency, and easily available starting materials (Scheme 1, left). An alternative methodology for the preparation of thiophenes has been reported,[4] in which the sulfur atom is introduced by thioamides, a class of practical and easily available molecules that have found wide applications for the construction of heterocyclic scaffolds (Scheme 1, right).[5]

Scheme 1. 2-Aminothiophene Annulation Strategies



(1) (a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 5th ed.; Blackwell: Oxford, U.K., 2010. (b) *Comprehensive Heterocyclic Chemistry: The Structure, Reactions, Synthesis, and Uses of Heterocyclic Compounds*, Vols. 1–8; Katrizky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, U.K., 1984. (c) *Hetarenes and Related Ring Systems, Science of Synthesis, Category 2*, Vol. 10; Thomas, E. J., Ed.; Georg Thieme Verlag: Stuttgart, 2000. (d) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491.

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(3) For recent reviews, see: (a) Puterová, Z.; Krutošíková, A.; Végh, D. *ARKIVOC* **2010**, No. i, 209. (b) Huang, Y.; Dömling, A. *Mol. Diversity* **2011**, *15*, 3.

(4) For examples, see: (a) Moghaddam, F. M.; Boinee, H. Z. *Tetrahedron* **2004**, *60*, 6085. (b) Reddy, K. V.; Rajappa, S. *Heterocycles* **1994**, *1*, 347.

(5) For a review, see: Jagodziński, T. S. *Chem. Rev.* **2003**, *103*, 197.

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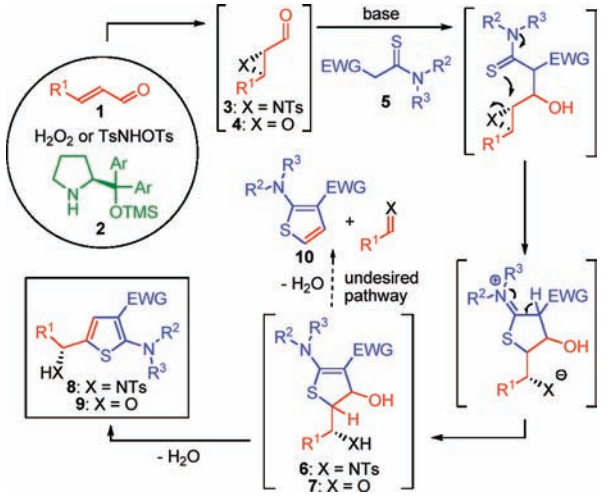
As a result of the limited availability of annulative strategies, investigations on formation of optically active thiophenes rely predominantly on functionalization of prochiral heteroaromatic starting materials.[6] Consequently, access to polysubstituted products is limited by the availability of the parent thiophenes. A direct strategy for the formation of optically active polysubstituted thiophenes from acyclic precursors is therefore of intriguing interest.

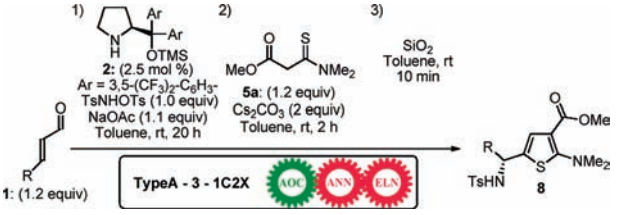
Scheme 2. Organocatalytic One-Pot Methodology for the Synthesis of Optically Active Thiophenes



Pursuing this challenge, it was envisioned that readily available α,β-unsaturated aldehydes **1** could serve as a starting point for an organocatalytic one-pot approach (Scheme 2).[7] After transformation of **1** to the aziridine- or epoxy-aldehyde **3** or **4**, subsequent reaction with a thioamide **5** under basic conditions followed by aromatization would form the desired thiophene **8** or **9**. One major challenge to this strategy would be to overcome the undesired elimination pathway leading from the intermediate **6** or **7** to the achiral disubstituted thiophene **10**. Herein, the efficient enantioselective synthesis of polysubstituted thiophenes, as well as related heteroaromatic structures, is reported.

Optimization studies were conducted using nonenal **1a** and methyl 3-(dimethylamino)-3-thioxopropanoate **5a** as substrates. A selection of bases and solvents were screened (see Supporting Information for details), with Cs_2CO_3 in toluene at 60 °C proving superior, providing the desired thiophene **8a** in 72% yield, with excellent enantioselectivity. Importantly, an alternative elimination pathway leading to the achiral thiophene **10** was identified, resulting in yield deterioration. Therefore, investigations on the aromatization step were undertaken. When the annulation reaction was performed at room temperature, clean conversion to dihydrothiophene **6a** was observed. Delightfully, subsequent addition of acid promoted clean product formation, and while other acids gave similar results, silica was found to be the most convenient, affording **8a** in 91% yield and 96% ee (Table 1, entry 1).

Table 1. Aldehyde Scope for the Formation of Aminoalkylthiophenes **8**[a]



entry	R	product	yield [%]	ee[b] [%]
1	Hex	**8a**	91	96
2	Pr	**8b**	83	95
3	*i*Pr	**8c**	92	93
4[c]	Me	**8d**	80	89
5	(*E*)-Hex-3-enyl	**8e**	81	95
6	(*Z*)-Hex-3-enyl	**8f**	60	94
7	$CH_2OTBDMS$	**8g**	82	96
8	CH_2CH_2Ph	**8h**	83	92

[a] Reactions performed on a 0.1 mmol scale in 0.5 mL toluene (see Supporting Information for details). Nomenclature legend: Type A: the position of the enantio-differentiating manual operation (at the start); 3: the number of manual operations; 1C2X: the number of C−C bonds (*m*C) and C−X bonds (*n*X) formed; AOC: asymmetric organocatalysis; ANN: annulation; ELN: elimination reaction. [b] Determined by chiral stationary phase HPLC. [c] Crotonaldehyde was utilized as a 97:3 *E*/*Z* mixture.

With the optimized reaction conditions established, the scope of this TypeA-3-1C2X cascade[7f] was investigated (Table 1). A selection of α,β-unsaturated aldehydes carrying primary and secondary alkyl substituents were successfully employed, all giving rise to the target thiophenes in excellent yields and enantioselectivities (Table 1, entries 1−4). Moreover, side chain functional groups were successfully introduced, providing equally good results (Table 1, entries 5−8). Ethyl 4-oxobut-2-enoate was also tested but disappointingly resulted in a complex reaction mixture.

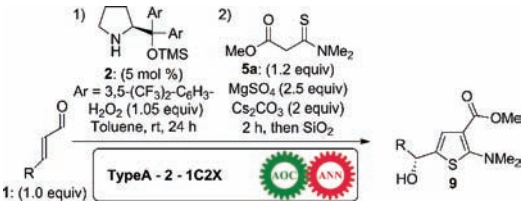
In an attempt to broaden the scope of the reaction for inclusion of hydroxyalkyl substituted thiophenes, the

(6) For selected recent examples, see: (a) Bonini, C.; Chiummiento, L.; De Bonis, M.; Funicello, M. *Tetrahedron: Asymmetry* **2006**, *17*, 2919. (b) Skucas, E.; Kong, J. R.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 7242. (c) Salvi, L.; Kim, J. G.; Walsh, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 12483. (d) Majer, J.; Kwiatkowski, P.; Jurczak, J. *Org. Lett.* **2009**, *11*, 4636. (e) Shimizu, H.; Nagano, T.; Sayo, N.; Saito, T.; Ohshima, T.; Mashima, K. *Synlett* **2009**, 3143. (f) Huang, Z.; Zhang, J.; Zhou, Y.; Wang, N.-X. *Eur. J. Org. Chem.* **2011**, 843.

(7) For recent reviews on organocatalysis, see: (a) *Chem. Rev.* 2007, *107*, 5413 (special issue on organocatalysis). (b) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638. (c) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (d) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (e) Xu, L.-W.; Li, L.; Shi, Z.-H. *Adv. Synth. Catal.* **2010**, *352*, 243. (f) Albrecht, Ł.; Jiang, H.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8492. (g) Weiss, K. M.; Tsogoeva, S. B. *Chem. Rec.* **2011**, *11*, 18. (h) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, 4410.1021/ar200149w.

ability of epoxy-aldehyde intermediates to take part in the developed reaction sequence was investigated (Table 2).

Table 2. Aldehyde Scope for the Formation of Hydroxyalkylthiophenes **9**[a]



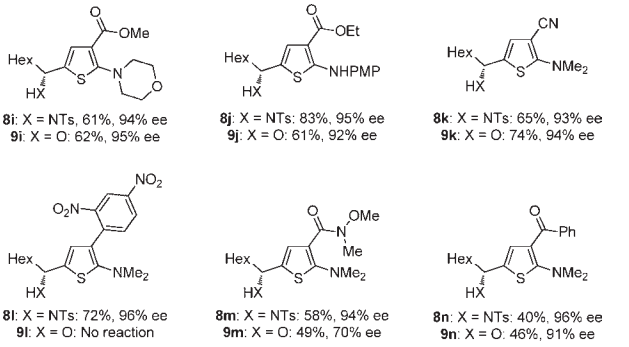
entry	R	product	yield [%]	ee[b] [%]
1	Hex	**9a**	75	94
2	Pr	**9b**	74	94
3	*i*Pr	**9c**	61	98
4[c]	Ph	**9d**	33	86
5	(*E*)-Hex-3-enyl	**9e**	73	96
6	(*Z*)-Hex-3-enyl	**9f**	40	92
7	$CH_2OTBDMS$	**9g**	71	96
8	CH_2CH_2Ph	**9h**	72	94

[a] Reactions performed on a 0.1 mmol scale in toluene (see Supporting Information for details). [b] Determined by chiral stationary phase HPLC. [c] 10 mol % catalyst applied.

Satisfyingly, the previously developed methodology for epoxidation of α,*β*-unsaturated aldehydes in toluene[8] proved compatible with the optimized thioamide approach, resulting in a TypeA-2-1C2X reation cascade. As for the aziridine scope, linear and *γ*-branched α,*β*-unsaturated aldehydes gave rise to the desired thiophenes with excellent enantioselectivities and good yields (Table 2, entries 1−3). Cinnamaldehyde was also tested, resulting in the desired aryl substituted product **9d**, albeit in moderate yield and slightly reduced enantiomeric excess (Table 2, entry 4). Furthermore, incorporation of a range of functionalities in the side chain was demonstrated, with little influence on the efficiency of the cascade (Table 2, entries 5−8). As observed for the aminoalkyl thiophene scope, the application of ethyl 4-oxobut-2-enoate in the reaction gave unsatisfactory results, which was also found for crotonaldehyde.

In the interest of achieving higher substituent diversity, investigations on the application of other nucleophiles were conducted (Scheme 3). The dimethyl thioamide motif was successfully replaced with a cyclic morpholine derivative, leading to the formation of **8i** and **9i**. A secondary thioamide group, carrying a *para*-methoxyphenyl *N*-protecting group, was also tolerated (**8j**, **9j**), principally allowing access to a Gewald-type primary amine substitution pattern. Application of a phenyl ring as an electron-withdrawing group was unsuccessful, and furthermore, it was demonstrated that the application of nucleophiles **5** carrying inductively electron-withdrawing groups, e.g. trifluoromethyl and pentafluorophenyl, did not lead to product formation. Studies were therefore limited to electron-withdrawing groups allowing for mesomerical stabilization (Scheme 3). Introduction of nitrile (**8k**, **9k**) or ketone (**8n**, **9n**) substituents was compatible with both epoxide and aziridine intermediates. Contrarily, a nucleophile carrying a 2,4-dinitrophenyl substituent resulted in good yield and excellent enantioselectivity for the aminoalkyl thiophene **8l**, whereas no reaction occurred when applied to the epoxide intermediate. The incorporation of a Weinreb amide was also demonstrated; however, while satisfying results were obtained for **8m**, the hydroxyalkyl substituted thiophene **9m** was highly prone to racemization.

Scheme 3. Nucleophile Scope for the Formation of Thiophenes **8** and **9**[a]



[a] See Supporting Information for details.

To further elucidate the versatility of the developed cascade, the synthesis of compounds closely related to thiophenes was studied. Thieno[2,3-*b*]indoles are structures consisting of a fused aromatic three-ring system containing a nitrogen and a sulfur heteroatom. Interesting biological properties of these systems have been described,[9] but few methods for their preparation exist.[10] It was envisioned that the application of 2-thioindole **11** as a nucleophile in the developed reaction sequence would allow for the synthesis of unprecedented optically active thieno[2,3-*b*]indoles **12** (Scheme 4, right). Preliminary results indicated that the direct application of the optimized

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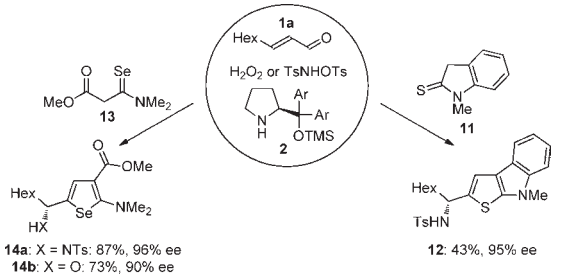
TypeA-3-1C2X cascade was unsuccessful, leading to fast decomposition of the reactants. However, under base-free conditions, 1-methylindoline-2-thione **11** could be reacted with the intermediate aziridine-aldehyde resulting in formation of the desired aminoalkyl thieno[2,3-*b*]-indole **12** with excellent enantioselectivity and acceptable yield, thus proving the concept of this pathway. In contrast, the application of epoxy-aldehydes in the reaction sequence led to the formation of the desired product in low yields when dichloromethane was used as solvent. Furthermore, fast racemization of the product was observed.

Scheme 4. Synthesis of Thienoindoles **12** and Selenophenes **14**[a]



[a] See Supporting Information for details.

Selenophenes are closely related to thiophenes and furans, originating from incorporation of the third member of the chalcogen group. Although organoselenium compounds share many properties with their sulfur counterparts, selenophenes have been investigated for their distinct properties.[11] The formation of an optically active selenophene through coupling to a chiral starting material has also been reported.[12] As is, an efficient methodology for the formation of the selenophene motif in an asymmetric fashion would be of major interest. Studies to identify a suited nucleophile were therefore initiated, with the directly analogous and easily obtainable selenoamide **13** as a prime candidate. The reaction cascades proceeded with excellent stereoselectivities, giving rise to the target selenophenes **14a** and **14b** in 87% and 73% yield, respectively (Scheme 4, left). The close resemblance to the results obtained for thiophenes indicates that the developed strategy can be directly applied as a general method for the preparation of selenophenes.

The assignment of the absolute configuration of the obtained products **8**, **9**, **12**, and **14** is based on studies on the organocatalytic epoxidation and aziridination of α, *β*-unsaturated aldehydes and their application in target oriented one-pot reaction cascades.[8b,13] To support these assignments, the crystal structure of **8b** was obtained by X-ray analysis, unambiguously confirming the *R*-configuration.[14]

In conclusion, an efficient and highly stereoselective one-pot methodology for the synthesis of optically active thiophenes, thieno[2,3-*b*]indoles, and selenophenes has been described. The developed cascades rely on a highly enantioselective amino-catalyzed epoxidation or aziridination reaction, combined with a ring annulation, to afford the target compounds. These reactions can be carried out under mild reaction conditions and are based on the application of convenient, easily obtainable reagents. The scope of the thiophene formation has been thoroughly investigated, demonstrating wide functional group tolerance resulting in the high substitution diversity of the final aromatic framework.

Acknowledgment. This work was made possible by grants from FNU, OChemSchool, and the Carlsberg Foundation. Thanks are expressed to Dr. Jacob Overgaard (Department of Chemistry, Aarhus University) for performing X-ray analysis.

Supporting Information Available. Complete experimental procedures and characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) See Supporting Information for the crystal structure. CCDC 854647 (**8b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.