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Efficient Catalytic, Oxidative Lactonization for the Synthesis of Benzodioxepinones Using Thiazolium-Derived Carbene Catalysts

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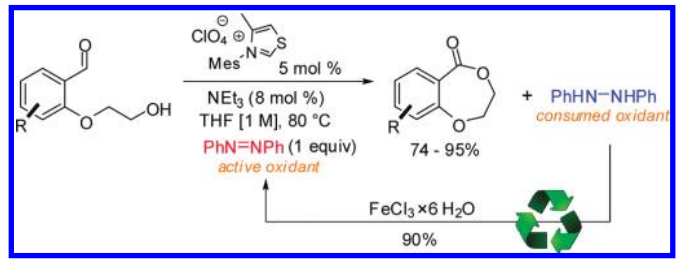
ABSTRACT



An efficient, oxidative carbene-catalyzed lactonization reaction has been developed. Using thiazolium precatalysts, a variety of benzodioxepinone products are accessible in good to excellent yields under mild and operationally simple conditions. The reaction does not require high dilution conditions and proceeds via mild and selective oxidation with azobenzene, which can easily be recovered and reused applying inexpensive $FeCl_3$ as a formal terminal oxidant.

Lactones are ubiquitous motifs in organic chemistry and constitute the core of many biologically active compounds and natural products. As a consequence, the mild and efficient preparation of these cyclic systems, particularly via new strategies, remains an important objective. Thus, a variety of powerful methods for the "carbonyl-centered"[1] ring closure has been developed, including numerous approaches of coupling preformed or in situ activated acyl species, such as mixed anhydrides, thioesters, acyl halides, or activated esters, amenable for the subsequent C−O bond formation with the nucleophilic alcohol species.[2] However, such classical lactonization protocols starting from the parent acid (Scheme 1, path A) require the (super)stoichiometric use of an activation reagent and often depend on non-"step-economical"[3] protection/deprotection sequences to ensure chemoselectivity and to avoid potential side reactions. In contrast, there are only few catalytic reactions to achieve the desired ring closure. On the basis of Cannizzaro-type, respectively, Tishchenko-type, disproportionation of dialdehydes, only recently a number of elegant transition-metal-catalyzed intramolecular ketone hydroacylation processes[4,5] have been developed; general organocatalytic lactonization approaches are rather rare.[6] Additionally, in the context of valuable alternative transformations, oxidative

(1) Especially for the synthesis of macrolides, alternative methods targeting other positions to achieve ring closure, such as ring closing metathesis or (Suzuki) cross coupling, have gained in importance during the last years; for corresponding reviews, see, for RCM: (a) Rouge dos Santos, A.; Kaiser, C. R.; Férézou, J.-P. *Quim. Nova* **2008**, *31*, 655. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490. For cross coupling: (c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442.

(2) (a) Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911. (b) Shiina, I.; Fukui, H.; Sasaki, A. *Nat. Protoc.* **2007**, *2*, 2312, and references cited therein.

(3) (a) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40. (b) Young, I. S.; Baran, P. S. *Nat. Chem.* **2009**, *1*, 193. (c) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010.

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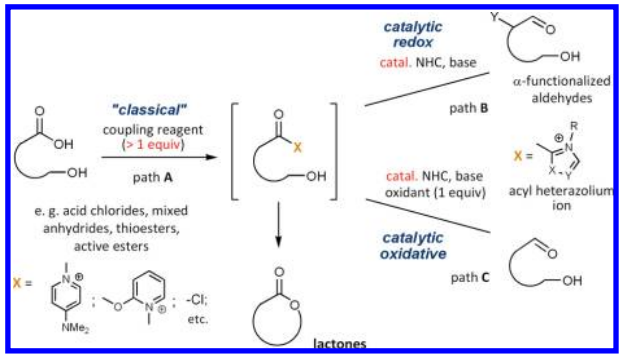
Scheme 1. Overview of Stoichiometric and (NHC) Catalytic Lactonization Approaches via Activated Acyl Species



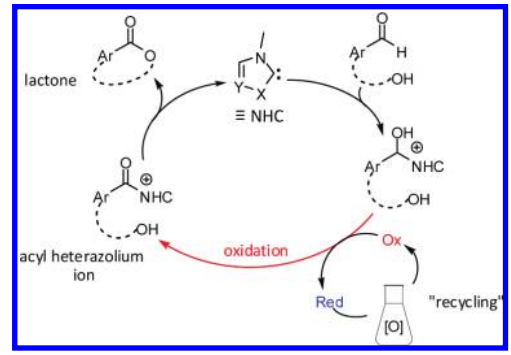
lactonization reactions[7] have recently attracted a revived interest.[8]

Apart from the versatile chemistry of N-heterocyclic carbene (NHC)-catalyzed C−C bond formations,[9] NHCs also allow for the catalytic generation of activated acyl azolium species which can undergo subsequent C−O or C−N bond formation.[10] In general, these activated carboxylates are not only accessible via *internal* redox reactions employing α-functionalized aldehyde precursors (Scheme 1, path B)[11] but can, in principle, also be obtained from unfunctionalized aldehydes upon carbene attack via *external* oxidation (Scheme 1, path C)[12,13] of the corresponding initial intermediate.

Recently, we reported on the NHC-mediated synthesis of 3,4-dihydrocoumarins following the intramolecular redox strategy starting from *o*-hydroxycinnamaldehydes.[14]

The obvious benefits of a related oxidation/esterification sequence using heterazolium-derived carbenes as *catalytic acyl transfer agents* for the synthesis of lactones and the significant potential of merging this approach with an operationally trivial recycling method for the oxidant prompted us to evaluate the feasibility of this concept (Scheme 2).

Scheme 2. Catalytic Oxidative Lactonization Using NHCs



Herein, we disclose the successful development of a simple carbene-catalyzed oxidative lactonization protocol for the efficient synthesis of benzodioxepinone derivatives.

Macrocyclic benzolactones such as the marine salicylihalamides and structurally related salicylic acid lactones exhibit attractive biological properties;[15] also, the lichen and endophytic fungi-derived class of depsidones with their characteristic seven-membered benzo[*e*]1,4-dioxepan-5-one

(4) For selected examples, see, for aldehyde C−H activation with Rh catalysts: (a) Phan, D. H. T.; Kim, B.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 15608. (b) Shen, Z.; Khan, H. A.; Dong, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 2916. (c) Shen, Z.; Dornan, P. K.; Khan, H. A.; Woo, T. K.; Dong, V M. *J. Am. Chem. Soc.* **2009**, *131*, 1077. Rh-catalyzed oxidative process: (d) Ye, Z.; Lv, G.; Wang, W.; Zhang, M.; Cheng, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 3671. Pd catalysts: (e) Ye, Z.; Qian, P.; Lv, G.; Luo, F.; Cheng, J. *J. Org. Chem.* **2010**, *75*, 6043. (f) Li, Y.; Jardine, K. J.; Tan R.; Song, D.; Dong, V. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 9690. (g) Fraunhoffer, K. J.; Prabagaran, N.; Sirois, L. E.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 9032. Ru catalysts: (h) Omura, S.; Fukuyama, T.; Murakami, Y.; Okamoto, H.; Ryu, I. *Chem. Commun.* **2009**, 6741, and references cited therein.

(5) For an NHC-catalyzed intramolecular hydroacylation yielding a phthalide scaffold, see: Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4558.

(6) For selected recent examples, see: (a) Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *J. Am. Chem. Soc.* **2010**, *132*, 3298. (b) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. *J. Am. Chem. Soc.* **2010**, *132*, 3664. (c) Zhang, H.; Zhang, S.; Liu, L.; Luo, G.; Duan, W.; Wang, W. *J. Org. Chem.* **2010**, *75*, 368.

(7) Potential complications arise from overoxidation, especially in the case of electron-rich substrates and as well from missing selectivity if non-*meso*-diols are used. For a general review on oxidative esterifications, see: Ekoue-Kove, K.; Wolf, C. *Chem.—Eur. J.* **2008**, *14*, 6302.

(8) Representative recent examples: (a) Ebine, M.; Suga, Y.; Fuwa, H.; Sasaki, M. *Org. Biomol. Chem.* **2010**, *8*, 39. (b) Ito, M.; Osaku, A.; Shiibashi, A.; Ikariya, T. *Org. Lett.* **2007**, *9*, 1821. (c) Hansen, T. M.; Florence, G. J.; Lugo-Mas, P.; Chen, J.; Abrams, J. N.; Forsyth, C. J. *Tetrahedron Lett.* **2003**, *44*, 57. (d) Suzuki, T.; Morita, K.; Tsuchida, M.; Hiroi, K. *Org. Lett.* **2002**, *4*, 2361.

(9) For recent reviews, see: (a) Phillips, E. M.; Chan, A.; Scheidt, K. A. *Aldrichimica Acta* **2010**, *42*, 55. (b) Moore, J. L.; Rovis, T. *Top. Curr. Chem.* **2010**, *291*, 77. (c) Zeitler, K. *E. Schering Found. Symp. Proc.* **2007**, *2*, 183. (d) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (e) Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506.

(10) For selected related, recent preparations of lactones via NHC catalysis, see: (a) Kaeobamrung, J.; Mahatthananchai, J.; Zheng, P.; Bode, J. W. *J. Am. Chem. Soc.* **2010**, *132*, 8810. (b) Ryan, S. J.; Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 14176. (c) Phillips, E. M.; Wadamoto, M.; Roth, H. S.; Ott, A. W.; Scheidt, K. A. *Org. Lett.* **2009**, *11*, 105. (d) Wang, L.; Thai, K.; Gravel, M. *Org. Lett.* **2009**, *11*, 891. (e) Wang, X.-N.; Shao, P.-L.; Lv, H.; Ye, S. *Org. Lett.* **2009**, *11*, 4029. (f) Li, G.-Q.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2009**, *11*, 1623. (g) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370. (h) Glorius, F.; Burstein, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205. (i) See also references cited in ref 14.

(11) Representative recent examples: (a) Reynolds, N. T.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518. (b) Chow, K. Y.-K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126. (c) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905. (d) Sohn, S. S.; Bode, J. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 6021. (e) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 2860. (f) Zeitler, K. *Org. Lett.* **2006**, *8*, 637.

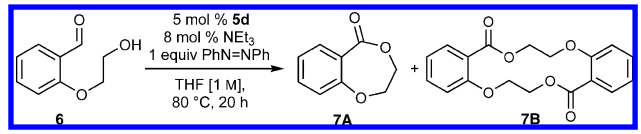
(12) Representative recent examples using MnO_2: (a) Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Tetrahedron* **2009**, *65*, 3102. (b) Maki, B. E.; Scheidt, K. A. *Org. Lett.* **2008**, *10*, 4331. (c) Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Org. Lett.* **2007**, *9*, 371.

(13) Representative examples using organic oxidants: (a) De Sarkar, S.; Studer, A. *Org. Lett.* **2010**, *12*, 1992. (b) De Sarkar, S.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2010**, *132*, 1190. (c) Noonan, C.; Baragwanath, L.; Connon, S. J. *Tetrahedron Lett.* **2008**, *49*, 4003. (d) Guin, J.; De Sarkar, S.; Grimme, S.; Studer, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8727. (e) Miyashita, A.; Suzuki, Y.; Nagasaki, I.; Ishiguro, C.; Iwamoto, K.-I.; Higashino, T. *Chem. Pharm. Bull.* **1997**, *45*, 1254. (f) Tam, S. W.; Jimenez, L.; Diederich, F. *J. Am. Chem. Soc.* **1992**, *114*, 1503. (g) Inoue, H.; Higashiura, K. *J. Chem. Soc., Chem. Commun.* **1980**, 549. (h) Shinkai, S.; Yamashita, T.; Kusano, Y.; Manabe, O. *J. Org. Chem.* **1980**, *45*, 4947. (i) Castells, J.; Pujol, F.; Llitjós, H.; Moreno-Mañas, M. *Tetrahedron* **1982**, *38*, 337. (j) Castells, J.; Llitjós, H.; Moreno-Mañas, M. *Tetrahedron Lett.* **1977**, *18*, 205, and references cited therein.

(14) Zeitler, K.; Rose, C. A. *J. Org. Chem.* **2009**, *74*, 1759.

(15) Yet, L. *Chem. Rev.* **2003**, *103*, 4283.

Table 1. Optimization of Reaction Conditions for Oxidative Lactonization



entry	variation of standard condition	yield[a] **A** (%)	yield[a] **B** (%)
1	none	95(94)[b]	<5
2	1 equiv of MnO_2 instead of azobenzene	84	<5
3[c]	**1** instead of **5d**, 5 mol % of DMAP instead of NEt_3, toluene (0.5 M) instead of THF	10	<5
4	**2** instead of **5d**	49	<5
5[d]	**3** instead of **5d**, 1.2 equiv of DBU instead of NEt_3, 5 equiv of MnO_2 instead of azobenzene, toluene[e]	41	<5
6	**4** instead of **5d**	93	7
7	**5a** instead of **5d**	27	<5
8	**5b** instead of **5d**	91	<5
9	**5c** instead of **5d**	93	<5
10	0 mol % of **5d**	0	0
11	0 mol % of **5d**; 1 equiv of MnO_2 instead of azobenzene	0	0

[a] Yields determined by ^{1}H NMR using 1,1,2-trichloroethylene as internal standard. [b] Isolated yield. [c] Reaction conditions according to ref 11f. [d] Reaction conditions related to ref 12a. [e] $c = 0.2$ M.

core shows a broad range of interesting biological activities.[16] Moreover, in perfumery, so-called marine notes mainly stem from benzodioxepinone compounds.[17]

Our initial experiments began with simple test substrates, such as **6**, which could be conveniently prepared from salicylaldehyde derivatives.[18] At the outset of our study, we investigated the efficacy and selectivity of various heterazolium salt/base combinations (Table 1). As we envisioned the "reactivation" of the oxidizing agent, we focused on mild organic oxidants, such as azobenzene,[13c,g,i] which previously had proven to also work successfully without the general requirement of being applied in excess.

After examining a number of common NHC precursors (Figure 1 and Table 1), we found that sterically hindered Mes-substituted thiazolium perchlorate **5d** in combination with NEt_3 and azobenzene indeed promotes the desired cyclization, providing lactone **7A** in excellent yield (94%, entry 1).[19] Gratifyingly, our initial concerns centered on a potential concurrent competing dimerization[2a] of the starting material were not confirmed as even at 1 M substrate concentration we could only detect traces of the 14-membered diolide **7B**.[20] In a brief solvent screen, toluene and dichloromethane in addition to THF gave best yields, while the use of chloroform and acetonitrile showed some

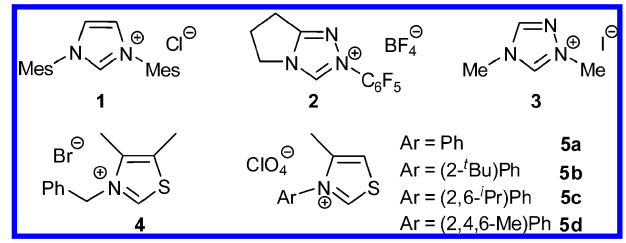


Figure 1. Evaluated heterazolium-derived carbene precursors.

limitations and ethyl acetate proved ineffective. Changing the oxidant to MnO_2 resulted in diminished but still very good yield (entry 2).[21]

This study also revealed marked effects on reactivity and performance of the heterazolium carbene precursors, emphasizing the importance of the employment of thiazolium-derived carbenes for this process (entries 6−9 vs entries 3−5). In the presence of imidazolium precatalyst **1**, lactone **7A** was obtained in poor yield, while triazolium salts **2** and **3** only showed moderate activity for the desired conversion (including versatile conditions developed by Scheidt et al., entry 5). Within the group of thiazolium precatalysts, simple commercially available benzyl-substituted precatalyst **4** demonstrated an excellent performance for this transformation, albeit with a slightly diminished selectivity (entry 6). However, *N*-phenyl thiazolium catalyst **5a** only displayed minor lactonization reactivity, providing further evidence for

(16) (a) Pittayakhajonwut, P.; Dramae, A.; Madla, S.; Lartpornmatulee, N.; Boonyuen, N.; Tanticharoen, M. *J. Nat. Prod.* **2006**, *69*, 1361. (b) Khumkomkhet, P.; Kanokmedhakul, S.; Kanokmedhakul, K.; Hahnvajanawong, C.; Soytong, K. *J. Nat. Prod.* **2009**, *72*, 1487. (c) Zheng, Y.; Zhao, B.; Lu, C.; Lin, X.; Zvheng, Z.; Su, W. *Nat. Prod. Commun.* **2009**, *4*, 501.

(17) (a) Kraft, P.; Popaj, K.; Müller, P.; Schär, M. *Synthesis* **2010**, 3029. (b) Hügel, H. M.; Drevermann, B.; Lingham, A. R.; Marriott, P. J. *Chem. Biodiv.* **2008**, *5*, 1034.

(18) He, J.; Zheng, J.; Liu, J.; She, X.; Pan, X. *Org. Lett.* **2006**, *8*, 4637.

(19) In addition, benzimidazolium and *N*-Mes triazolium salts were evaluated, but provided much lower yields than **5d**.

(20) We could observe a concentration effect: at 3 M, the ratio of **7A** to **7B** was determined to be ca. 9:1.

(21) Attempts to use air or O_2 (balloon) as terminal oxidant did not provide satisfactory yields (11 resp. 21%); however, for reports on strongly electron-deficient substrates that could be converted to their corresponding esters/acids without additional oxidant, see: (a) Goswami, S.; Hazra, A. *Chem. Lett.* **2009**, *38*, 484. (b) Yoshida, M.; Katagiri, Y.; Zhu, W.-B.; Shishido, K. *Org. Biomol. Chem.* **2009**, *7*, 4062.

the need of a distinct steric environment. We also performed control experiments in order to verify the essential catalytic role of the NHCs for this transformation and to exclude a conceivable hemiacetal oxidation/lactonization process.[22] In the absence of a NHC catalyst, no conversion could be observed (entries 10 and 11).

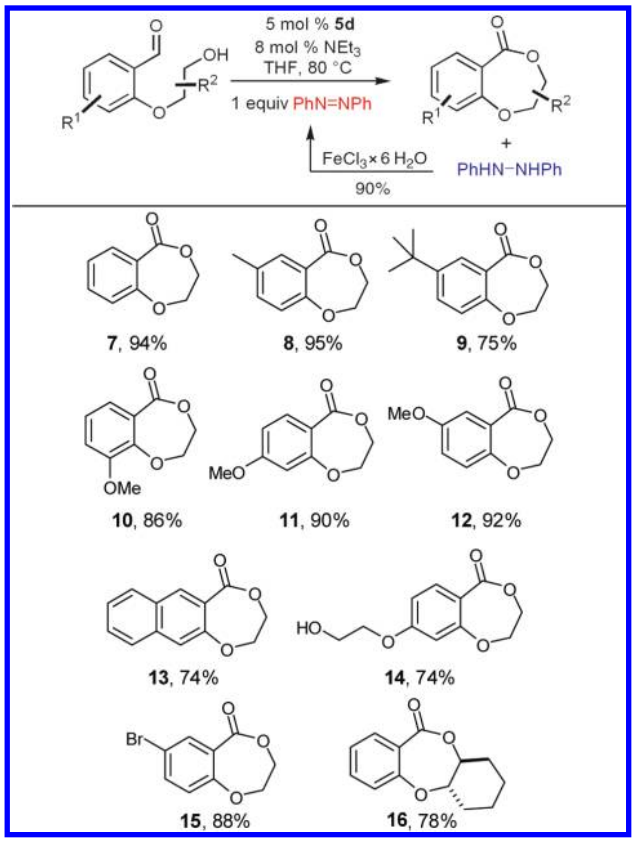
In an effort to further improve our conditions with respect to the terminal oxidant, also being aware of the potential drawbacks of the stoichiometric use of azobenzene, which could significantly curtail the attractivity of our method, we turned our attention to finding a useful, operationally trivial recycling procedure. After separation of the reduced hydrazobenzene from the product via simple filtration over SiO_2, it was treated with $FeCl_3 \times 6H_2O$ in aqueous acetone under reflux.[23] After 5 min, the reoxidized, active oxidant azobenzene can be isolated by filtration, thus rendering this process more attractive by employing $FeCl_3$ as an inexpensive formal oxidant.[24]

Having developed optimal conditions for the oxidative lactonization, we next examined the substrate scope of this transformation. As shown in Scheme 3, a wide range of differently substituted electron-rich as well as electron-deficient aromatic hydroxyaldehydes can undergo catalytic lactonization with good to excellent yields. Due to the mild reaction conditions and the chemoselective oxidant, additional hydroxy groups are tolerated without further protection (**14**, 74% yield). This method is also applicable to secondary alcohol precursors, for example, providing access to tricyclic lactone **16** with 78% isolated yield. Interestingly, an illustrative survey of the olfactory properties of lactones **8**, **9**, and **10** evidenced their quite remarkable high intensity as odorants (threshold values = 250, 0.050, and 0.99 ng/L air, respectively).

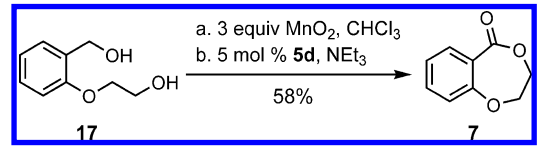
Taking advantage of MnO_2's[12] ability to effectively oxidize allylic and benzylic alcohols and having its usability as alternative oxidant for the oxidative lactonization in mind, we envisioned its application for a tandem sequence combining benzylic oxidation with subsequent oxidative lactonization.

As depicted in Scheme 4, this two-step transformation could be performed as a single-flask procedure without the need of intermediate purification, providing lactone **7** in an overall isolated yield of 58%.

Scheme 3. Substrate Scope of the Catalytic Lactonization



Scheme 4. Tandem One-Pot Oxidation/Lactonization Process



In conclusion, we have developed an NHC-catalyzed mild oxidative lactonization protocol under non-high-dilution conditions. Application of $FeCl_3$ as recycling agent and thus as formal terminal oxidant provides an efficient access to interesting benzodioxepinone derivatives. Future studies will explore the full scope of this method[25] and its application.

Acknowledgment. Generous support from the DFG (priority program "Organocatalysis" SPP1179) is gratefully acknowledged. We also thank Dr. Philip Kraft (Givaudan, Switzerland) for the olfactory evaluation and the determination of the corresponding odor threshold values of compounds **8**, **9**, and **10**.

Supporting Information Available: Experimental details and spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101854R

(22) Foot, J. S.; Kanno, H.; Giblin, G. M. P.; Taylor, R. J. K. *Synthesis* **2003**, 1055.

(23) See Supporting Information for details: Wang, C.-L.; Wang, X.-X.; Wang, X.-Y.; Xiao, J.-P.; Wang, Y.-L. *Synth. Commun.* **1999**, *29*, 3435. Efforts for the concurrent use of $FeCl_3$ for an in situ recycling process of azobenzene have not proven successful so far.

(24) For a recent application of NHC−Fe complexes for an aerobic esterification with boronic acids, see: Rosa, J. N.; Reddy, R. S.; Candeias, N. R.; Cal, P. M. S. D.; Gois, P. M. P. *Org. Lett.* **2010**, *12*, 2686.

(25) Initial attempts to apply this methodology to the synthesis of the most challenging eight-membered ring system[2a] affords the desired lactone in only 14% yield. However, this is remarkable as a related Ru-catalyzed approach only yielded 7% of the envisaged 8-ring. See ref 4h.