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Iron-catalyzed kinetic resolution of *N*-sulfonyl oxaziridines†

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We have developed a highly selective kinetic resolution of *N*-sulfonyl oxaziridines. This reaction utilizes an inexpensive and easily synthesized iron bis(oxazoline) catalyst to promote the efficient rearrangement of oxaziridines to the corresponding *N*-sulfonyl imides; no sacrificial reagents are required to effect this resolution. This process is readily translated to gram scale, which provides a practical method for the preparation of structurally diverse, enantiopure *N*-sulfonyl oxaziridines for use as reagents in organic synthesis.

Introduction

Oxaziridines, first prepared by Emmons in 1957,[1] are fascinating three-membered heterocycles composed of nitrogen, oxygen, and carbon. Much of the early work on the chemistry of oxaziridines focused upon the unusual physical properties that arise from the presence of two adjacent heteroatoms in a strained three-membered ring.[2] For example, the rate of pyramidal inversion in oxaziridines is slow enough to allow the isolation of enantioenriched oxaziridines chiral only at nitrogen.[3] From a synthetic perspective, oxaziridines have long been recognized as useful oxidants: they are generally air-stable crystalline materials that mediate a wide variety of powerful oxidative functional group transformations.[4] Our laboratory has a long-standing interest in developing catalytic methods that exploit the unique reactivity of *N*-sulfonyl oxaziridines to perform oxyamination, dipolar cycloaddition, and C–H amination reactions.[5] We are particularly interested in investigating stereocontrolled versions of these reactions,[6] but our studies have often been hampered by the fact that only a few highly enantioselective methods for the synthesis of chiral oxaziridines have been reported to date.

Our on-going investigations of structure-activity relationships in stereoselective reactions of *N*-sulfonyl oxaziridines require access to gram quantities of a wide variety of structurally diversified oxaziridines in enantiopure form, but each of the previously known methods have proven to be problematic for our needs. Stoichiometric oxidations using chiral peracids[7] generally afford low ee's. The organocatalytic phase-transfer reactions recently reported by Jorgensen[8] and Jin[9] scaled up poorly in our hands, which we attributed to the heterogeneity of these reaction conditions. Catalytic imine oxidations using a chiral Lewis acid or hydrogen-bonding catalyst developed by Yamamoto[10] and Ooi,[11] respectively, provide high ee's only with *N*-tosyl or *N*-mesityl imines. This presents a significant limitation in the context of our studies because of the large influence of the *N*-substituent on the reactivity of oxaziridines. Finally, Feng and Liu recently reported a quite general kinetic resolution of racemic oxaziridines,[12,13] but the need for a nontrivial azlactone as a stoichiometric nucleophilic reagent renders this method impractical for preparation of oxaziridines on gram scale. Given the recent renewed interest in the chemistry of these reactive heterocycles,[14] we sought to develop a more general approach to the preparation of enantiopure *N*-sulfonyl oxaziridines that would tolerate a broad range of structural variation and would be amenable to scale-up.

Results and discussion

Two well-established features of oxaziridine chemistry guided our reaction design. First, the racemic synthesis of *N*-sulfonyl oxaziridines by oxidation of the corresponding imines is robust, tolerant of great structural diversity, and is scalable to hundreds of grams.[15] Thus, the racemates of a diverse range of oxaziridines are readily prepared in substantial quantities. Second, oxaziridines are rapidly isomerized to the corresponding amides in the presence of redox-active transition metal catalysts.[16] We speculated that an appropriate chiral Fe(II) complex[17] might catalyze the kinetic resolution of racemic oxaziridines. Such a process would satisfy the criteria for an ideal kinetic resolution as delineated by Jacobsen:[18] the resolution would begin with an easily accessible racemate, it would involve an inexpensive chiral catalyst, the products would be easily separated by chromatography, and the rearrangement would rely on the intrinsic reactivity of oxaziridines and thus require no additional stoichiometric reagents.

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We began our investigation by examining the rearrangement of racemic oxaziridine **3** in the presence of series of chiral Fe(II) bis(oxazoline) complexes (Table 1). This class of catalysts was selected because our previous studies had shown that they provide an excellent stereocontrolling environment for oxaziridine-mediated alkene oxyaminations.[6b] We observed that the $FeCl_2$ complex of isopropyl bis(oxazoline) ligand **6a** catalysed the efficient rearrangement of **3** to imide **4** in a variety of solvents (entries 1–4), and we were delighted to find that the remaining oxaziridine could be recovered in good to excellent ee. The determination of the relative rate (*s* factor) of rearrangement for the enantiomeric oxaziridines proved to be challenging; normally, *s* factor is calculated from the ee of the recovered reactant and the conversion according to the following relationship,[19] where *c* is the conversion and ee is the enantiomeric excess of the unreacted chiral substrate:

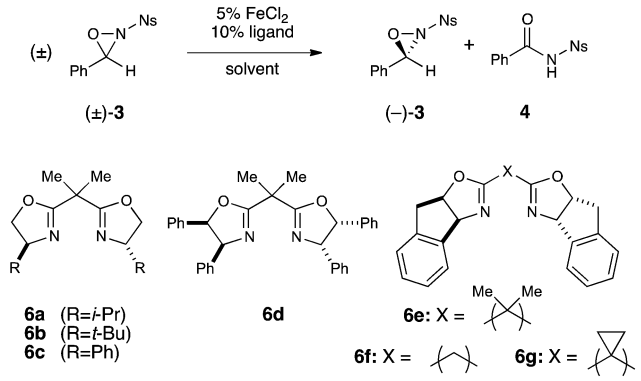
$$s = \frac{\ln[(1-c)(1-\mathrm{ee})]}{\ln[(1-c)(1+\mathrm{ee})]}$$

However, several oxaziridines examined in our study undergo slow, uncatalyzed decomposition in solution, which renders accurate determination of the catalyst-mediated conversion difficult. Instead, apparent *s* values for the resolution were determined based upon the isolated yield of chromatographically purified oxaziridine. We felt that this would be a reasonable approximation because any errors arising from mechanical loss or uncatalyzed decomposition would result in a net decrease in the apparent *s* value; the calculated figure would thus provide a conservative lower limit for the genuine relative rate.[20]

Guided by this calculation, we performed a screen of other bis(oxazoline) ligands in this reaction (entries 5–10) and observed optimal *s* factors using cyclopropane-bridged indanyl ligand **6g**.[21] We were interested in increasing the reaction concentration and lowering the ligand loading of this process to minimize the use of chiral material and solvent waste on larger scale; we found that these factors had little impact on selectivity (entry 11). Finally, we observed that the initial addition of catalyst to oxaziridine resulted in a modest but noticeable evolution of heat. Controlling the temperature by beginning the reaction at −78 °C and then warming the solution to 0 °C as the reaction progressed improved the reproducibility and the selectivity of the reaction (entry 12). Using this protocol, we consistently observed good ee's of recovered oxaziridine after just 5 min of treatment with 5 mol% of the Fe(II) catalyst.

Table 2 summarizes experiments designed to probe the effect of the oxaziridine *N*-substituent on the efficiency of the kinetic resolution under these conditions. As we had hoped, the reaction is relatively insensitive to the structure of the *N*-sulfonyl moiety. A variety of substituted *N*-benzensulfonyl groups were tolerated, and similar *s* values were obtained in each case (entries 1–5), regardless of the electronic or steric properties of the aryl group.[22] *N*-*t*-Butylsulfonyl oxaziridines, however, afforded somewhat more modest selectivity (entry 6), and a resolution of an *N*-alkyl oxaziridine was essentially unselective (entry 7).

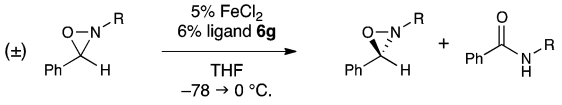
Table 1 Optimization of conditions for kinetic resolution of oxaziridines[a]



Entry	Solvent	Ligand	Time	Yield[b]	ee[c]	*s*[d]
1	Toluene	**6a**	2 h	43%	70%	7
2	CH_2Cl_2	**6a**	2 h	19%	97%	5
3	MeCN	**6a**	2 h	29%	60%	3
4	THF	**6a**	2 h	21%	99%	7
5	THF	**6b**	1 h	95%	4%	8
6	THF	**6c**	1 h	78%	14%	3
7	THF	**6d**	1 h	79%	17%	5
8	THF	**6e**	1 h	32%	98%	11
9	THF	**6f**	30 min	38%	80%	6
10	THF	**6g**	15 min	41%	96%	19
11[e]	THF	**6g**	5 min	36%	98%	15
12[e,f]	THF	**6g**	5 min	38%	99%	17

[a] Unless otherwise noted, reactions performed at 0 °C on 0.5 mmol scale (0.2 M) using 5 mol% $FeCl_2$ and 10 mol% ligand. [b] Isolated yield of recovered oxaziridine. [c] Enantiomeric excess determined by chiral SFC analysis. [d] Calculated based upon yield of recovered oxaziridine according to ref. 17. [e] Reaction conducted at 0.5 M concentration using 6 mol% ligand. [f] Reaction conducted on 1.0 mmol scale starting at −78 °C and warming to 0 °C.

Table 2 Effect of *N*-substituents on the kinetic resolution of oxaziridines[a]

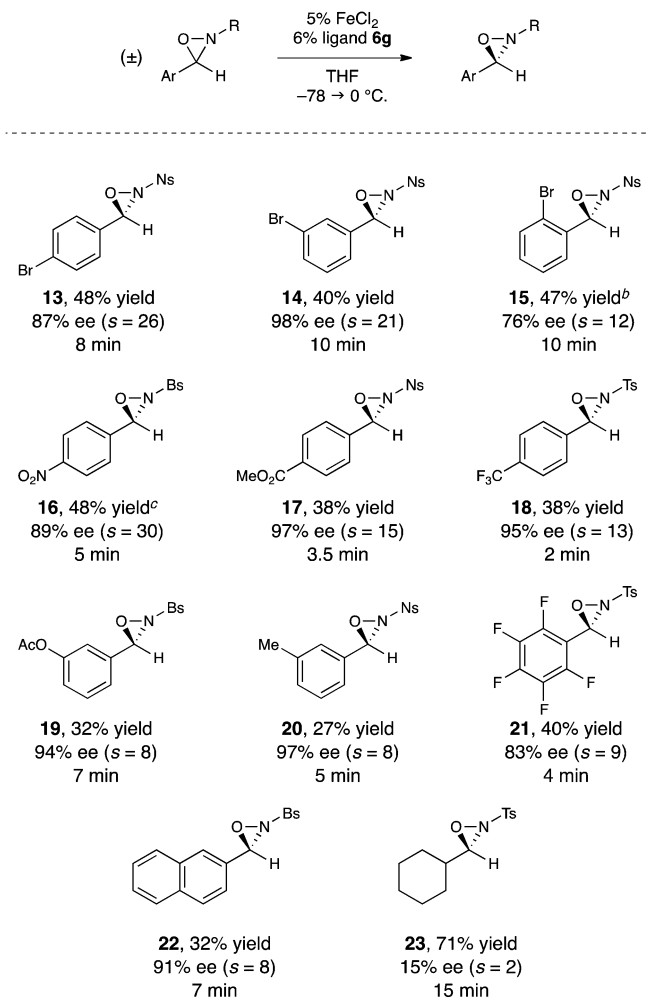


Entry	R	Time	Yield[b]	ee[c]	*s*[d]
1	Ns (**3**)	5 min	38%	99%	17
2	Ts (**7**)	7 min	41%	93%	16
3	Bs (**8**)	6 min	42%	91%	15
4	2 Ns (**9**)	2 min	40%	96%	17
5	SO_2Mes (**10**)	13 min	45%	89%	18
6	Bus (**11**)	5 min	55%	57%	10
7	i-Pr (**12**)	5 min	33%	48%	2

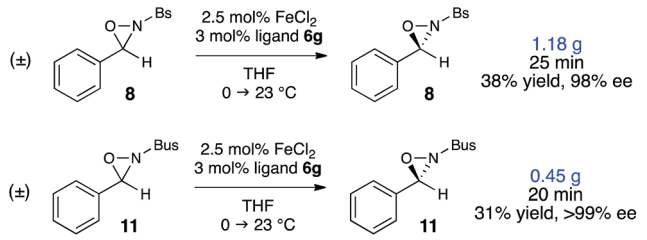
[a] Reactions performed on 1.0 mmol scale (0.5 M). Ns = 4-nitrobenzenesulfonyl; Ts = 4-toluenesulfonyl; Bs = benzenesulfonyl; 2 Ns = 2-nitrobenznesulfonyl; SO_2Mes = 2-mesitylenesulfonyl; Bus = *t*-butylsulfonyl. [b] Isolated yield of recovered oxaziridine. [c] Enantiomeric excess determined by chiral SFC analysis. [d] Calculated based upon yield of recovered oxaziridine according to ref. 19.

Table 3 outlines the scope of the reaction with respect to the *C*-aryl substituent of the oxaziridine. The reaction is tolerant of substitution at the *para*-, *meta*-, and *ortho*- positions of the aryl ring (**13–15**); however, we observed that resolution of oxaziridines bearing *ortho*-substituted *C*-aryl groups required higher catalyst loadings and reacted with slightly lower selectivity. The reaction is tolerant of aryl rings bearing electron-withdrawing groups (**16–18**). In general, we have found *N*-sulfonyl oxaziridines bearing electron-rich *C*-aryl groups to be unstable; those bearing strongly electron-donating *para* substituents can decompose violently at room temperature.[23] Those bearing less strongly electron-donating groups gave lower apparent *s* values, which we rationalize as an artefact of the increased rate of their uncatalyzed decomposition in solution compared to other more stable oxaziridines (**19** and **20**). More extended condensed aromatic groups also afforded somewhat lower selectivity (**22**), as does a *C*-perfluoroaryl oxaziridine (**21**). Finally, *C*-alkyl oxaziridines (**23**) react at much slower rates and with more modest selectivity than *C*-aryl oxaziridines, and this class of oxaziridines represents a limitation of the method.

Table 3 Scope of the kinetic resolution[a]



[a] Unless otherwise noted, all reactions were performed on 1.0 mmol scale using 5 mol% $FeCl_2$ and 6 mol% ligand **6g**, −78 °C to 0 °C. [b] Reaction conducted using 10 mol% $FeCl_2$ and 12 mol% ligand **6g**. [c] Reaction conducted from 0 °C to 23 °C.



Scheme 1 Gram-scale resolutions of *N*-sulfonyl oxaziridines.

A principal motivation for this study was our need for a route to structurally diverse enantiopure oxaziridines on significant scales. Gratifyingly, we found that this protocol for kinetic resolution of oxaziridines is readily scalable (Scheme 1). The gram-scale resolution of *N*-benzenesulfonyloxaziridine (±)-**8** required somewhat higher reaction temperatures (0 °C to ambient temperature), but the enantioselectivity of the process remained excellent even with lower catalyst loading, affording **8** on gram-scale in 98% ee. One of the most important advantages of kinetic resolutions over other forms of asymmetric catalysis is the ability to offset lower intrinsic stereoselectivity by increasing ee at the expense of yield by running the resolution to higher conversion. Thus, we examined the large-scale resolution of racemic *N*-Bus oxaziridine (±)-**11**. Despite the lower *s* factors observed for this oxaziridine compared to analogous *N*-arenesulfonyl oxaziridines in our small-scale studies (Table 2, entry 6), we were able to obtain 0.45 g of enantiomerically pure oxaziridine after a 20 min reaction time. Thus, by taking advantage of a feature inherent to kinetic resolutions, substantial quantities of highly enantioenriched oxaziridines can be obtained even when their small-scale resolutions proceed with moderate *s* factors. These results suggest that this methodology will indeed provide access to a wide range of structurally diverse oxaziridines on synthetically relevant scales, which will enable the investigation of the effect of stereochemistry on a number of oxaziridine-mediated reactions.

Conclusions

To summarize, we have developed a scalable and robust iron-catalyzed kinetic resolution of oxaziridines using an inexpensive and readily available iron bis(oxazoline) catalyst. This process is general for a broad range of *N*-sulfonyl oxaziridines, the racemates are readily accessible *via* a robust and convenient synthetic route, and the resolution is easily translated to the gram scale without loss of selectivity. Importantly, this kinetic resolution requires no sacrificial reagents other than the oxaziridine itself, which renders this a practical method for the preparation of structurally diverse enantiopure oxaziridines as reagents for organic synthesis. The use of these reagents in new oxidative transformations is a continuing theme of research in our laboratory.

Acknowledgements

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Notes and references

1 W. D. Emmons, *J. Am. Chem. Soc.*, 1957, **79**, 5739.
2 (*a*) D. R. Boyd and R. Graham, *J. Chem. Soc. (C)*, 1969, 2648; (*b*) J. Bjørgo and D. R. Boyd, *J. Chem. Soc., Perkin Trans. 2*, 1973, 1575.
3 F. Montanari, I. Moretti and G. Torre, *Chem. Commun.*, 1968, 1694.
4 For reviews, see: (*a*) F. A. Davis and A. C. Sheppard, *Tetrahedron*, 1989, **45**, 5703; (*b*) F. A. Davis and B.-C. Chen, *Chem. Rev.*, 1992, **92**, 919; (*c*) V. A. Petrov and G. Resnati, *Chem. Rev.*, 1996, **96**, 1809; (*d*) S. Andreae and E. Schmitz, *Synthesis*, 1991, 327; (*e*) F. A. Davis and R. T. Reddy, *Comp. Heterocycl. Chem. II*, ed., A. Padwa, Permagon Press, Oxford, 1996, vol. 1, p. 365; (*f*) F. A. Davis, B.-C. Chen and P. Zhou, *Comp. Heterocycl. Chem III*, ed. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K. Taylor, Elsevier, Oxford, 2008, vol. 1, p. 559; (*g*) K. S. Williamson, D. J. Michaelis and T. P. Yoon, *Chem. Rev.*, 2014, DOI: 10.1021/cr400611n.
5 (*a*) D. J. Michaelis, C. J. Shaffer and T. P. Yoon, *J. Am. Chem. Soc.*, 2007, **129**, 1866; (*b*) K. M. Partridge, M. E. Anzovino and T. P. Yoon, *J. Am. Chem. Soc.*, 2008, **130**, 2920; (*c*) C. P. Allen, T. Benkovics, A. K. Turek and T. P. Yoon, *J. Am. Chem. Soc.*, 2009, **131**, 12560; (*d*) K. M. Partridge, I. A. Guzei and T. P. Yoon, *Angew. Chem., Int. Ed.*, 2010, **49**, 930; (*e*) K. S. Williamson and T. P. Yoon, *J. Am. Chem. Soc.*, 2010, **132**, 4570.
6 (*a*) D. J. Michaelis, K. S. Williamson and T. P. Yoon, *Tetrahedron*, 2009, **65**, 5118; (*b*) K. S. Williamson and T. P. Yoon, *J. Am. Chem. Soc.*, 2012, **134**, 12370.
7 M. Bucciarelli, A. Forni, S. Marcaccioli, I. Moretti and G. Torre, *Tetrahedron*, 1983, **39**, 187.
8 L. Lykke, C. Rodríguez-Escrich and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2011, **133**, 14932.
9 T. Zhang, W. He, X. Zhao and Y. Jin, *Tetrahedron*, 2013, **69**, 7416.
10 J. L. Olivares-Romero, Z. Li and H. Yamamoto, *J. Am. Chem. Soc.*, 2012, **134**, 5440.
11 (*a*) D. Uraguchi, R. Tsutsumi and T. Ooi, *J. Am. Chem. Soc.*, 2013, **135**, 8161; (*b*) D. Uraguchi, R. Tsutsumi and T. Ooi, *Tetrahedron*, 2014, **70**, 1691–1701.
12 S. Dong, X. Liu, Y. Zhu, P. He, L. Lin and X. Feng, *J. Am. Chem. Soc.*, 2013, **135**, 10026.
13 Kinetic resolution of an *N*-sulfonyl oxaziridine was also observed during an enantioselective formal [3+2] cycloaddition with ketenes. See: P.-L. Shao, X.-Y. Chen and S. Ye, *Angew. Chem., Int. Ed.*, 2010, **49**, 8412.
14 For selected investigations of oxaziridine chemistry recently reported by other laboratories, see: (*a*) A. M. Adams and J. Du Bois, *Chem. Sci.*, 2014, **5**, 656; (*b*) H. F. Motiwala, B. Gülgeze and J. Aubé, *J. Org. Chem.*, 2012, **77**, 7005; (*c*) X. G. Peng, Y. G. Zhu, T. A. Ramirez, B. G. Zhao and Y. Shi, *Org. Lett.*, 2011, **13**, 5244; (*d*) A. Armstrong and R. S. Cooke, *Chem. Commun.*, 2002, 904.
15 L. C. Vishwakarma, O. D. Stringer and F. A. Davis, *Org. Synth.*, 1988, **66**, 203.
16 (*a*) F. Minisci, R. Galli, V. Malatesta and T. Caronna, *Tetrahedron*, 1970, **26**, 4083; (*b*) K. Suda, M. Sashima, M. Izutsu and F. Hino, *J. Chem. Soc., Chem. Commun.*, 1994, 949.
17 For a recent comprehensive review of chiral iron catalysts, see: K. Gopalaiah, *Chem. Rev.*, 2013, **113**, 3248.
18 J. M. Keith, J. F. Larrow and E. N. Jacobsen, *Adv. Synth. Catal.*, 2001, **343**, 5.
19 For leading references on kinetic resolutions, see: (*a*) E. L. Eliel, S. H. Wilen and L. M. Mander, *Stereochemistry of Organic Compounds*, Wiley-Interscience, New York, 1994, p. 395; (*b*) H. B. Kagan and J. C. Fiaud, in *Topics in Stereochemistry*, ed. N. L. Allinger and E. L. Eliel, Interscience, New York, 1987, vol. 14, p. 249.
20 Jacobsen has also used isolated yield to calculate a lower limit for *s* value. See: J. F. Larrow, S. E. Schaus and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1996, **118**, 7420.
21 A two-step, 26 kg scale synthesis of ligand **6g** has been reported. See: D. M. Barnes, J. Ji, M. G. Fickes, M. A. Fitzgerald, S. A. King, H. E. Morton, F. A. Plagge, M. Preskill, S. H. Wagaw, S. J. Wittenberger and J. Zhang, *J. Am. Chem. Soc.*, 2002, **124**, 13097.
22 The absolute configurations of oxaziridines **7** and **8** were determined by comparison of their optical rotation to values reported in ref 8 and 7, respectively. The configurations of all other enantioenriched oxaziridines in this study were assigned by analogy.
23 F. A. Davis, J. Lamendola Jr, U. Nadir, E. W. Kluger, T. C. Sedergran, T. W. Panunto, R. Billmers, R. Jenkins Jr, I. J. Turchi, W. H. Watson, J. S. Chen and M. Kimura, *J. Am. Chem. Soc.*, 1980, **102**, 2000.