Synthetic Methods

DOI: 10.1002/anie.201207746

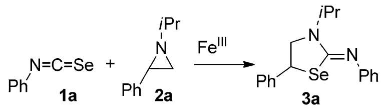
# "On Water": Efficient Iron-Catalyzed Cycloaddition of Aziridines with Heterocumulenes**

*Mani Sengoden and Tharmalingam Punniyamurthy**

The use of water as a reaction medium for organic synthesis has attracted much interest in recent years,[1–3] because water is the most abundant liquid on the planet, cheap, readily available, nontoxic, and nonflammable. The [3+2] cycloaddition reaction of aziridines with heterocumulenes provides a powerful tool to access a wide range of functionalized five-membered heterocycles that exhibit interesting biological and medicinal properties.[4] Thus, the cycloaddition of aziridines with carbodiimides,[5] isocyanates,[5–8] and isothiocyanates[5,7,9–11] has been studied employing Pd,[5] Ni,[6] $HBF_4$,[7] Mg–MeOH,[8] $PBu_3$,[9] NaI[10] or $Ph_4SbBr$[11]-based systems as either the catalyst or stoichiometric reagent. These reactions are effective in an organic medium and generally involve an inert atmosphere. In continuation of our studies on heterocycle synthesis,[13] we wish to herein report the first example of iron(III)-catalyzed cycloaddition of aziridines with heterocumulenes that takes place in aqueous suspension at moderate temperature. The protocol is simple and utilizes environmentally benign nontoxic and cheap iron(III) salt as the catalyst[14] and water as a reaction medium in air.

Firstly, the optimization of the reaction conditions was carried out by using phenyl isoselenocyanate (**1a**) and 1-isopropyl-2-phenylaziridine (**2a**) as model substrates in the presence of $Fe(NO_3)_3{\cdot}9\,H_2O$ (10 mol%) and water as the solvent at various temperatures (Table 1). Gratifyingly, the reaction proceeded to afford selectively the target iminoazoselenolidine[12] **3a** after five hours in 80% conversion at room temperature when the suspension of the soluble $Fe(NO_3)_3{\cdot}9\,H_2O$ and the insoluble substrates **1a** and **2a** in water was stirred (Table 1, entry 1). Increase of the reaction temperature to 60 °C led to completion of the process in one hour with 100% conversion (Table 1, entry 3). In a set of iron(III) salts screened, $Fe(NO_3)_3{\cdot}9\,H_2O$, $Fe_2(SO_4)_3{\cdot}5\,H_2O$, $FeCl_3{\cdot}6\,H_2O$, and $[Fe(acac)_3]$, all were active, and the former afforded the best results (Table 1, entries 5–8). The effect of an organic medium, such as toluene, $CH_2Cl_2$, and $(CH_2Cl)_2$, was examined, but no reaction was observed, and the starting material was recovered intact (Table 1, entries 9–11). Lowering the amount of the iron(III) catalyst (5 mol%) or the quantity of the aziridine (1 equiv) led to the formation of **3a** in less than 91% conversion (Table 1, entries 4 and 5). Control experiments confirmed that without the iron(III) catalyst the reaction produced **3a** after eight hours in 12% conversion (Table 1, entry 12).

***Table 1:*** Optimization of the reaction conditions.[a]



| Entry | Catalyst | Solvent | $T$ [°C] | $t$ [h] | Conversion **3a** [%][b] |
|---|---|---|---|---|---|
| 1 | $Fe(NO_3)_3{\cdot}9\,H_2O$ | $H_2O$ | 25 | 5 | 80 |
| 2 | $Fe(NO_3)_3{\cdot}9\,H_2O$ | $H_2O$ | 40 | 3 | 87 |
| 3 | $Fe(NO_3)_3{\cdot}9\,H_2O$ | $H_2O$ | 60 | 1 | 100 |
| 4 | $Fe(NO_3)_3{\cdot}9\,H_2O$ | $H_2O$ | 60 | 2 | 82[c] |
| 5 | $Fe(NO_3)_3{\cdot}9\,H_2O$ | $H_2O$ | 60 | 1 | 91[d] |
| 6 | $FeCl_3{\cdot}6\,H_2O$ | $H_2O$ | 60 | 1 | 87 |
| 7 | $Fe_2(SO_4)_3{\cdot}5\,H_2O$ | $H_2O$ | 60 | 1 | 58 |
| 8 | $[Fe(acac)_3]$ | $H_2O$ | 60 | 1 | 47 |
| 9 | $Fe(NO_3)_3{\cdot}9\,H_2O$ | toluene | 60 | 1 | n.d. |
| 10 | $Fe(NO_3)_3{\cdot}9\,H_2O$ | $CH_2Cl_2$ | 40 | 1 | n.d. |
| 11 | $Fe(NO_3)_3{\cdot}9\,H_2O$ | $(CH_2Cl)_2$ | 60 | 1 | n.d. |
| 12 | – | $H_2O$ | 60 | 8 | 12 |

[a] Isoselenocyanate **1a** (0.5 mmol), aziridine **2a** (0.6 mmol), $Fe(NO_3)_3{\cdot}9\,H_2O$ (10 mol%) and solvent (1 mL) were stirred in air. [b] Determined by 400 MHz $^1H$ NMR spectroscopy. [c] 5 mol% of catalyst used. [d] 1 equiv of aziridine **2a** used. n.d. = not detected; acac = acetylacetonate.

Next, the scope of the procedure was studied for the reactions of the substituted isoselenocyanates (Table 2). A series of substrates **1a–l** having both the electron-withdrawing and -donating groups on the phenyl ring readily reacted with aziridine **2a** to give the target products in one hour with good to high yields.[12] For example, aryl isoselenocyanates containing 2-methoxy, 3-methyl, 4-chloro, 4-iodo, 4-methoxy, 4-methyl, and 4-nitro substituents on the phenyl ring reacted to the target products **3b–h** in 61–90% yield. Recrystallization of **3b** in hexane gave crystals, the structure of which was confirmed by single-crystal X-ray analysis (Figure 1). Aryl isoselenocyanate bearing 3,4-dimethyl substituents on the phenyl ring proceeded to give **3i** in 93% yield. Naphthyl **1j** and fluorene **1k** isoselenocyanates underwent reactions to afford **3j** and **3k** in 85% and 75% yield, respectively. A similar result was observed with cyclohexyl isoselenocyanate **1l** affording **3l** in 72% yield.

The reactions of a series of aziridines were further studied with phenyl isoselenocyanate (Table 3). As above, the reactions took place efficiently to afford the target molecules in good to high yield. For example, aryl aziridines **2b–o** having

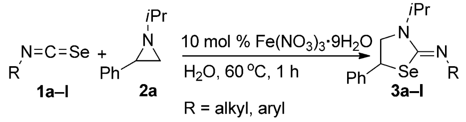
---

[*] M. Sengoden, Prof. T. Punniyamurthy
Department of Chemistry
Indian Institute of Technology Guwahati
Guwahati-781039 (India)
E-mail: tpunni@iitg.ernet.in

[**] We thank Department of Science and Technology, New Delhi and Council of Scientific and Industrial Research, New Delhi for financial Support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201207746.

*Table 2:* Reaction of substituted isoselenocyanates with aziridine.[a]



| Entry | Isoselenocyanates | R | Product (Yield [%])[b] |
|---|---|---|---|
| 1 | **1a** | Ph | **3a** (88) |
| 2 | **1b** | 2-$MeOC_6H_4$ | **3b** (90) |
| 3 | **1c** | 3-$MeC_6H_4$ | **3c** (85) |
| 4 | **1d** | 4-$ClC_6H_4$ | **3d** (86) |
| 5 | **1e** | 4-$IC_6H_4$ | **3e** (89) |
| 6 | **1f** | 4-$MeOC_6H_4$ | **3f** (82) |
| 7 | **1g** | 4-$MeC_6H_4$ | **3g** (79) |
| 8 | **1h** | 4-$NO_2C_6H_4$ | **3h** (61) |
| 9 | **1i** | 3,4-$Me_2C_6H_3$ | **3i** (93) |
| 10 | **1j** | 1-naphthyl | **3j** (85) |
| 11 | **1k** | 2-fluorene | **3k** (75) |
| 12 | **1l** | cyclohexyl | **3l** (72) |

[a] Reaction conditions: Isoselenocyanate **1a–l** (0.5 mmol), aziridine **2a** (0.6 mmol), $Fe(NO_3)_3 \cdot 9H_2O$ (10 mol%) and water (1 mL) were stirred at 60 °C for 1 h in air. [b] Yield of isolated product.

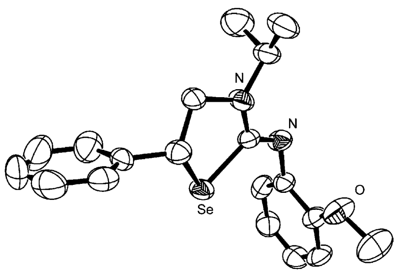
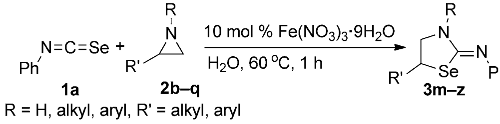


*Figure 1.* ORTEP diagram of ((*Z*)-*N*-(3-isopropyl-5-phenyl-1,3-selenazolidin-2-ylidene)-2-methoxybenzenamine (**3b**). Thermal ellipsoids are drawn at a 40% probability level. Hydrogen atoms have been omitted for clarity.[15]

*Table 3:* Reaction of substituted aziridines with isoselenocyanate.[a]



| Entry | Aziridine | R | R′ | Product (Yield [%])[b] |
|---|---|---|---|---|
| 1 | **2b** | H | Ph | **3m** (81) |
| 2 | **2c** | Bn | Ph | **3n** (75) |
| 3 | **2d** | *n*Bu | Ph | **3o** (91) |
| 4 | **2e** | cyclohexyl | Ph | **3p** (79) |
| 5 | **2f** | Ph | Ph | **3q** (61) |
| 6[c] | **2g** | *i*Pr | 2-$ClC_6H_4$ | **3r** (78) |
| 7 | **2h** | *i*Pr | 3-$NO_2C_6H_4$ | **3s** (66) |
| 8 | **2i** | *i*Pr | 4-$BrC_6H_4$ | **3t** (74) |
| 9 | **2j** | *i*Pr | 4-$ClC_6H_4$ | **3u** (86) |
| 10 | **2k** | *i*Pr | 4-$FC_6H_4$ | **3v** (71) |
| 11 | **2l** | *i*Pr | 4-$MeOC_6H_4$ | **3w** (88) |
| 12 | **2m** | *i*Pr | 4-$MeC_6H_4$ | **3x** (82) |
| 13 | **2n** | *i*Pr | 3,4-$Me_2C_6H_3$ | **3y** (87) |
| 14 | **2o** | *i*Pr | (-$C_6H_4$-4-$CH_2)_2N$(*i*Pr) | **3z** (71) |
| 15 | **2p** | Bz | Ph | **3aa** n.d. |
| 16 | **2q** | Boc | Ph | **3ab** n.d. |

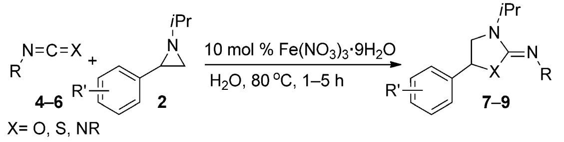
[a] Reaction conditions: Aziridine **2b–q**, isoselenocyanate **1a** (0.5 mmol), $Fe(NO_3)_3 \cdot 9H_2O$ (10 mol%), and water (1 mL) were stirred at 60 °C for one hour in air. [b] Yield of isolated product. [c] Reaction time: 2.5 h. n.d. = not detected.

unsubstituted, benzyl, *n*-butyl, cyclohexyl, and phenyl substituents on the nitrogen atom gave the target iminoazoselenolidines **3m–q** in 61–91% yields. Moreover, both the substrates bearing electron-donating and -withdrawing groups on the phenyl ring of the aziridines were compatible, and the cycloaddition products were obtained in high yields. For example, the substrates having 2-chloro, 3-nitro, 4-bromo, 4-chloro, 4-fluoro, 4-methoxy, and 4-methyl substituents on the phenyl ring reacted to the target molecules **3r–x** in 66–88% yields. Aryl aziridine **2n** having 3,4-dimethyl substituents on the phenyl ring underwent reaction with 87% yield. A similar result was observed with aziridine **2o** giving the target molecule **3z** in 71% yield. Under these conditions, *N*-benzoyl-2-phenyl aziridine (**2p**) proceeded in an intramolecular cyclization to afford 4,5-dihydro-2,5-diphenyloxazole (**10**) in 78% yield as sole product (see the Supporting Information), whereas the aziridine **2q** underwent decomposition and no cycloaddition product was obtained.

Finally, to reveal the generality of the protocol, the reactions of aziridines **2** with carbodiimides **4**, isocyanates **5**, and isothiocyanates **6** were studied as representative examples (Table 4). The reactions occurred efficiently at 80 °C to provide the target molecules **7–9** in 65–79% yields. Isothiocyanates **6** exhibited greater reactivity compared to carbodiimides **4** and isocyanates **5**. These observed results suggest that the procedure affords a general method for the cycloaddition of aziridines with heterocumulenes to give the target heterocycles in good to high yield.

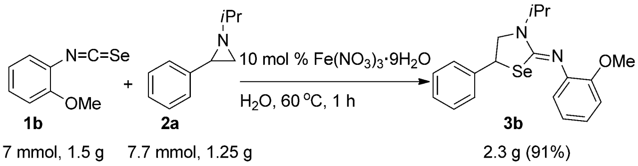
To investigate if the protocol can be applied to a larger scale, the reaction of **1b** with **2a** was examined on gram scale (Scheme 1). As above, the reaction readily proceeded to afford **3b** in 91% yield. This result clearly suggests that the

*Table 4:* Reaction of heterocumulene with isoselenocyanate.[a]



| Entry | Heterocumulene | X | R | R′ | *t* [h] | Product (Yield [%])[b] |
|---|---|---|---|---|---|---|
| 1 | **4a** | N | Ph | H | 2 | **7a** (79) |
| 2 | **4b** | N | 4-$ClC_6H_4$ | H | 3 | **7b** (75) |
| 3 | **4a** | N | Ph | 4-Me | 1.5 | **7c** (68) |
| 4 | **5a** | O | Ph | H | 3.5 | **8a** (65) |
| 5 | **5b** | O | Ph | 4-MeO | 3 | **8b** (71) |
| 6 | **5c** | O | Ph | 4-Me | 5 | **8c** (67) |
| 7 | **6a** | S | Ph | 4-Cl | 1 | **9a** (76) |
| 8 | **6b** | S | Ph | 4-MeO | 1 | **9b** (78) |
| 9 | **6c** | S | Ph | 4-Me | 1 | **9c** (71) |
| 10 | **6d** | S | Ph | 3,5-$Me_2$ | 1 | **9d** (74) |

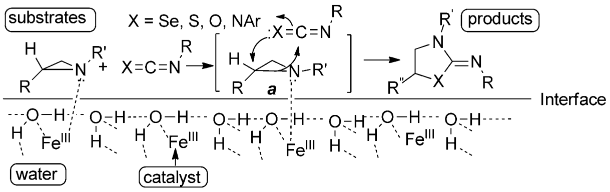
[a] Reaction condition: Heterocumulene **4–6** (0.5 mmol), aziridine **2** (0.6 mmol), $Fe(NO_3)_3 \cdot 9H_2O$ (10 mol%) and water (1 mL) were stirred at 80 °C. [b] Yield of isolated product.



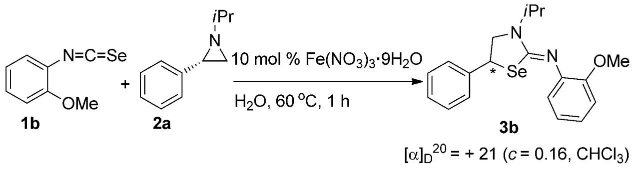
*Scheme 1.*

protocol may be used for the gram-scale synthesis of the target heterocycles.

The proposed catalytic cycle is shown in Scheme 2. Iron salts are soluble in water, while the aziridines and heterocumulenes float on the surface of water as either oil or a mixture of oil and solid. The resulting suspension proceeds to react on stirring to give the target molecules as water-insoluble oil or solid. These results suggest that the reaction may take place on the water–oil interface. Furthermore, (*S*)-**2a** reacted with **1b** to give optically active **3b**, thus suggesting that the reaction may not involve a carbocation intermediate (Scheme 3, see the Supporting Information). Thus, chelation of the iron species with nitrogen of the aziridines may lead to the formation of the intermediate ***a*** (see Scheme 2) that could cyclize to complete the catalytic cycle giving the target products.



*Scheme 2.* Proposed catalytic cycle.



*Scheme 3.*

In summary, an efficient, simple, and general route for the [3+2] cycloaddition reaction of aziridines with heterocumulenes on water has been described using iron(III) catalysis in air. The procedure will be attractive from economical and environmental points of view to access the target heterocycles in good to high yields.

## Experimental Section

General procedure for the cycloaddition reaction of aziridines with heterocumulenes: A mixture of heterocumulene (0.5 mmol), aziridine **2** (0.6 mmol), Fe(NO$_3$)$_3$·9H$_2$O (0.05 mmol), and water (1 mL) was stirred at 60–80 °C for 1–5 h. The progress of reaction was monitored by TLC using ethyl acetate and hexane. The reaction mixture was then cooled to room temperature and extracted with diethyl ether (3 × 10 mL). The organic layer was washed with water (5 mL). Drying (Na$_2$SO$_4$) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate (19:1) as eluent.

Received: September 25, 2012
Revised: October 30, 2012

**Keywords:** aziridine · cycloaddition · heterocumulene · iron · water

---

[1] a) *Handbook of Green Chemistry, Vol. 5* (Ed: P. T. Anastas), Wiley-VCH, Weinheim, **2010**; b) *Organic Reactions in Water* (Ed.: U. M. Lindstroem), Blackwell, Oxford, UK, **2007**; c) H. C. Hailes, *Org. Process Res. Dev.* **2007**, *11*, 114; d) *Clean Solvents: Alternative Media for Chemical Reactions and Processing: ACS Symp. Ser.* (Eds.: M. A. Abraham, L. Moens), American Chemistry Society, New York, **2002**, p. 819; e) *Organic Synthesis in Water* (Ed.: P. A. Grieco), Springer, New York, **1997**.

[2] For examples of aqueous organic reactions, see: a) R. Breslow, *Acc. Chem. Res.* **1991**, *24*, 159; b) M.-O. Simon, C.-J. Li, *Chem. Soc. Rev.* **2012**, *41*, 1415; c) L. Rout, P. Saha, S. Jammi, T. Punniyamurthy, *Eur. J. Org. Chem.* **2008**, 640; d) I. Vilotijevic, T. F. Jamison, *Science* **2007**, *317*, 1189; e) U. M. Lindström, *Chem. Rev.* **2002**, *102*, 2751; f) W. Blokzijl, J. B. F. N. Engberts, *J. Am. Chem. Soc.* **1992**, *114*, 5440; g) A. Lubineau, *J. Org. Chem.* **1986**, *51*, 2142.

[3] For examples of reactions "on water", see: a) S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, K. B. Sharpless, *Angew. Chem.* **2005**, *117*, 3339; *Angew. Chem. Int. Ed.* **2005**, *44*, 3275; b) S. Mellouli, L. Bousekkine, A. B. Theberge, W. T. S. Huck, *Angew. Chem.* **2012**, *124*, 8105; *Angew. Chem. Int. Ed.* **2012**, *51*, 7981; c) N. Shapiro, A. Vigalok, *Angew. Chem.* **2008**, *120*, 2891; *Angew. Chem. Int. Ed.* **2008**, *47*, 2849; d) D. González-Cruz, D. Tejedo, P. de Armas, F. García-Tellado, *Chem. Eur. J.* **2007**, *13*, 4823; e) J. E. Klijn, J. B. F. N. Engberts, *Nature* **2005**, *435*, 746; f) Y. S. Jung, R. A. Marcus, *J. Am. Chem. Soc.* **2007**, *129*, 5492; g) M. C. Pirrung, K. D. Sarma, J. M. Wang, *J. Org. Chem.* **2008**, *73*, 8723; h) S. Jammi, M. A. Ali, S. Sakthivel, L. Rout, T. Punniyamurthy, *Chem. Asian J.* **2009**, *4*, 314; i) D. C. Rideout, R. Breslow, *J. Am. Chem. Soc.* **1980**, *102*, 7816; j) S. Jammi, T. Punniyamurthy, *Eur. J. Inorg. Chem.* **2009**, 2508; k) P. G. Cozzi, L. Zoli, *Angew. Chem.* **2008**, *120*, 4230; *Angew. Chem. Int. Ed.* **2008**, *47*, 4162.

[4] For examples, see: a) T. Fujinami, T. Suziki, M. Kamiya, S. Fukuzawa, S. Sakai, *Chem. Lett.* **1985**, 199; b) A. Baba, I. Shibata, M. Fujiwara, H. Matsuda, *Tetrahedron Lett.* **1985**, *26*, 5167; c) H. Kisch, R. Millini, I. Wang, *Chem. Ber.* **1986**, *119*, 1090; d) I. Shibata, A. Baba, H. Iwasaki, H. Matsuda, *J. Org. Chem.* **1986**, *51*, 2177; e) B. M. Trost, A. R. Sudhakar, *J. Am. Chem. Soc.* **1987**, *109*, 3792; f) M. Fujiwara, A. Baba, H. Matsuda, *J. Heterocycl. Chem.* **1988**, *25*, 1351; g) M. Fujiwara, M. Imada, A. Baba, H. Matsuda, *J. Org. Chem.* **1988**, *53*, 5974.

[5] For examples, see: a) C. D. Butler, A. G. Inman, H. Alper, *J. Org. Chem.* **2000**, *65*, 5887; b) B. M. Trost, D. R. Fandrick, *J. Am. Chem. Soc.* **2003**, *125*, 11836; c) A. Okano, S. Oishi, T. Tanaka, N. Fujii, H. Ohno, *J. Org. Chem.* **2010**, *75*, 3396.

[6] T. Munegumi, I. Azumaya, T. Kato, H. Masu, S. Saito, *Org. Lett.* **2006**, *8*, 379.

[7] E. Pfeil, K. Milzner, *Angew. Chem.* **1966**, *78*, 677; *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 667.

[8] U. K. Nadir, R. V. Krishna, A. Singh, *Tetrahedron Lett.* **2005**, *46*, 479.

[9] J.-Y. Wu, Z.-B. Luo, L.-X. Dai, X.-L. Hou, *J. Org. Chem.* **2008**, *73*, 9137.

[10] U. K. Nadir, N. Basu, *J. Org. Chem.* **1995**, *60*, 1458.

[11] R. Nomura, T. Nakano, Y. Nishio, S. Ogawa, A. Ninagawa, H. Matsuda, *Chem. Ber.* **1989**, *122*, 2407.

[12] For biological properties of selenium-containing compounds, see: a) C. W. Nogueira, G. Zeni, J. B. T. Rocha, *Chem. Rev.* **2004**, *104*, 6255; b) G. Mugesh, W. W. du Mont, H. Sies, *Chem. Rev.* **2001**, *101*, 2125; c) V. Jamier, L. A. Ba, C. Jacob, *Chem. Eur. J.* **2010**, *16*, 10920; d) H. J. Amouri, J. Moussa, A. K. Renfrew, P. J. Dyson, M. N. Rager, L.-M. Chamoreau, *Angew. Chem.* **2010**, *122*, 7692; *Angew. Chem. Int. Ed.* **2010**, *49*, 7530.

[13] For examples, see: a) M. M. Guru, T. Punniyamurthy, *J. Org. Chem.* **2012**, *77*, 5063; b) T. Ramana, T. Punniyamurthy, *Chem. Eur. J.* **2012**, *18*, 13279; c) M. Sengoden, T. Punniyamurthy, *RSC Adv.* **2012**, *2*, 2736.

[14] For some recent examples of iron-catalyzed reactions, see: a) C. Wang, X. Li, F. Wu, B. Wan, *Angew. Chem.* **2011**, *123*, 7300; *Angew. Chem. Int. Ed.* **2011**, *50*, 7162; b) O. García Mancheño, *Angew. Chem.* **2011**, *123*, 2264; *Angew. Chem. Int. Ed.* **2011**, *50*, 2216; c) A. Fürstner, *Angew. Chem.* **2009**, *121*, 1390; *Angew. Chem. Int. Ed.* **2009**, *48*, 1364; d) S. Enthaler, K. Junge, M. Beller, *Angew. Chem.* **2008**, *120*, 3363; *Angew. Chem. Int. Ed.* **2008**, *47*, 3317; e) B. D. Sherry, A. Fürstner, *Acc. Chem. Res.* **2008**, *41*, 1500.

[15] CCDC-899302 (**3b**) 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.