Heterocycles

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Synthesis of Pyridines by Carbenoid-Mediated Ring Opening of 2*H*-Azirines**

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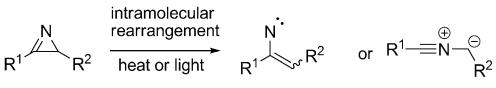
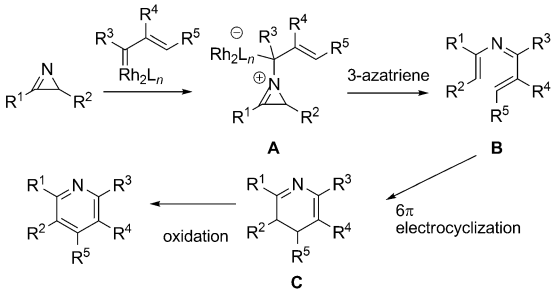
Dedicated to Professor Sunggak Kim

Pyridines are an important class of compounds because of their prevalence in a myriad of natural products, pharmaceuticals, agrochemicals, and functional materials.[1] Driven by the demands, diverse approaches to pyridine synthesis have been developed.[2] Traditionally, they have been prepared by condensation of amine and carbonyl compounds.[3] More recently, synthesis of pyridines based on cycloaddition and transition-metal catalysis has been reported.[4] Also, direct functionalization of pyridine cores also allows access to elaborate pyridine derivatives.[5] Despite these progress, a flexible synthesis of pyridines allowing access to diverse substitution patterns continues to draw a great deal of interest from the synthetic community.

Strain-driven ring expansion has proven a powerful strategy for construction of various types of carbocycles and heterocycles.[6] This approach has been utilized in a broad range of transformations by employing cyclopropane and cyclobutane derivatives as the key components.[7] In this regard, 2*H*-azirines have also been exploited as useful precursors for reactive intermediates such as vinyl nitrenes and nitrile ylides. These species have been employed in the synthesis of various N-heterocycles[8] including indoles, pyrroles, isoxazoles, and pyrazolo[1,5-a]pyridines by reactions such as C–H insertion and cycloaddition. However, the synthesis of pyridines based on carbenoid-mediated ring opening of 2*H*-azirines remains to be explored. Unlike the reactions based on 2*H*-azirines where reactive species are generated by intramolecular rearrangements initiated by either heat or light [Eq. (1)], this carbenoid-mediated reaction is unique in that intermolecular activation of 2*H*-azirine leads to the formation of pyridines [Eq. (2)].



(1)



(2)

The remarkable versatility of metal carbenoids renders them valuable intermediates in the synthesis of various heterocycles.[9] Given our interest in the ring-strain-driven synthesis of heterocycles,[8a,10] we envisioned that activation of 2*H*-azirines, which are readily accessible through the Neber reaction[11] in two steps from ketones may lead to the formation of pyridines upon reaction with vinyl carbenoids through a cascade of rearrangements as outlined in Equation (2). Thus, the reaction initiated by the formation of the ylide **A** triggers ring opening of 2*H*-azirine to afford the 3-azatriene **B**. Subsequent 6π electrocyclization leads to the formation of the 3,4-dihydropyridine **C**, which could be readily oxidized to pyridine. Herein, we describe the successful development of a flexible synthesis of pyridines by formal [3+3] cycloaddition of 2*H*-azirines with vinyl carbenoids which enables the introduction of a broad range of substitution and its application in the synthesis of highly conjugated poly-arylpyridine systems.

Our initial efforts to realize the transformation commenced with the reaction of **1a** with the vinyl diazoacetate **2a** in the presence of $[Rh_2(OAc)_4]$ in 1,2-dichloroethane (DCE) at 90°C. The reaction proceeded smoothly to give 1,4-dihydropyridine **3aa** in 46% yield. We surmise that rapid tautomerization of the corresponding 3,4-dihydropyridine accounts for the formation of **3aa**. The structure of **3aa** was unambiguously assigned based on comprehensive NMR experiments and the X-ray structure of the analogue **4ba**.[12]

To optimize the reaction conditions, a variety of metal complexes were screened (Table 1). Reactions with $[Rh_2(OAc)_4]$ at different concentrations and temperatures all provided inferior results (Table 1, entries 4 and 5). While copper catalysts failed to give any 1,4-dihydropyridine (Table 1, entries 1 and 2), electron-deficient dirhodium complexes such as $[Rh_2(TFA)_4]$, $[Rh_2(tfacam)_4]$, and $[Rh_2(pfb)_4]$ gave the desired product albeit in low yield (Table 1,

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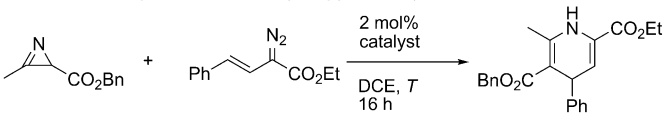
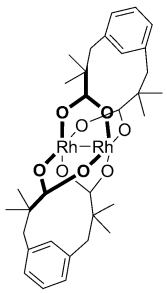
Table 1: Development of 1,4-dihydropyridine synthesis.[a]



1a **2a** **3aa**

Entry	Catalyst	*T* [°C]	Yield [%][b]
1	$Cu(OTf)_2$	90	0
2	$[Cu(hfacac)_2]$	90	0
3	$[Rh_2(OAc)_4]$	90	44
4[c]	$[Rh_2(OAc)_4]$	90	38
5	$[Rh_2(OAc)_4]$	70	38
6	$[Rh_2(TFA)_4]$	90	28
7	$[Rh_2(tfacam)_4]$	90	34
8	$[Rh_2(pfb)_4]$	90	34
9	$[Rh_2(Piv)_4]$	90	71
10	$[Rh_2(esp)_2]$	90	80

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.48 mmol), DCE (0.15 M). [b] Yields determined by NMR vs. standard. [c] Reaction performed in 0.05 M. esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionate, pfb = perfluorobutyrate, Piv = pivaloate, hfacac = hexafluoroacetylacetonate, TFA = trifluoroacetate, tfacam = trifluoroacetamide.

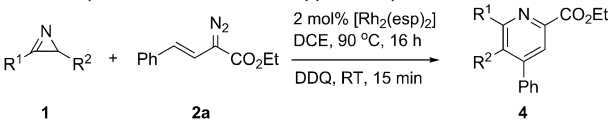


$[Rh_2(esp)_2]$

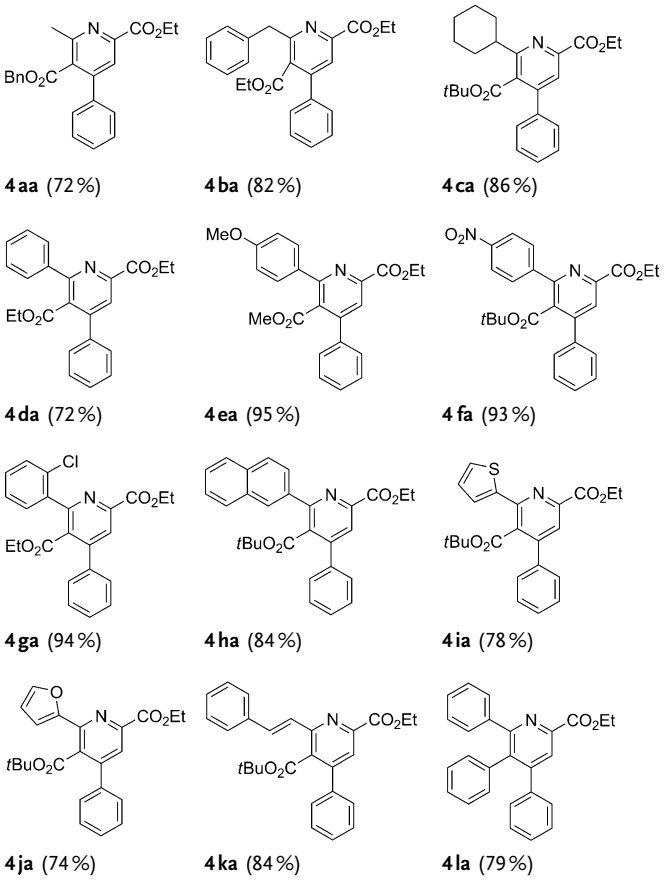
entries 6–8). In contrast, improved yields were achieved by using dirhodium complexes with sterically bulky ligands such as $[Rh_2(Piv)_4]$ and $[Rh_2(esp)_2]$[13] (Table 1, entries 9 and 10), thus suggesting that the steric effect of ligands plays an important role in this reaction. We postulate that the steric demand of catalysts steers the formation of 3-azatriene with the correct configuration necessary for cyclization among potentially multiple isomers. To develop a one-pot synthesis of pyridines, we attempted direct oxidation of **3aa** by exposure to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) at room temperature for 15 minutes after the completion of the reaction with $[Rh_2(esp)_2]$. We were pleased to find that the one-pot protocol provided the pyridine **4aa** in 72% yield.

Encouraged by these results, we turned our attention to the substrate scope of the reaction. To develop a synthetic protocol which provides pyridines with a wide range of substitution, we first surveyed various 2*H*-azirines by reacting with vinyl diazoacetate **2a** (Table 2). Generally, reactions proceeded smoothly to give pyridines in good to excellent yields. 3-Alkyl-substituted 2*H*-azirines reacted well, including those with primary and secondary alkyl groups, thus providing 6-alkylpyridines (**4aa**–**4ca**). Reactions with 3-aryl-substituted 2*H*-azirines also proceeded smoothly to afford 6-arylpyridines, and those with both electron-rich and electron-deficient aryl groups gave the corresponding products in good yields (**4da**–**4fa**). The 2*H*-azirine having an *ortho*-chlorophenyl group reacted smoothly to afford the corresponding pyridine **4ga** in 94% yield, thus suggesting that steric hinderance is tolerated well. In addition, the substrate **1h**, having a fused aryl substituent, also provided **4ha** in 84% yield. Extension of the reaction to heteroaryl-substituted 2*H*-azirines proved successful to afford 6-(2-thienyl) and 6-(2-furanyl)pyridines in 78% and 74%, respectively. Furthermore, 6-vinyl-substituted pyridines such as **4ka** were readily accessed by using 3-vinyl-2*H*-azirine as the reaction partner. To examine the necessity of an ester group at the 2-position of 2*H*-azirine for successful transformation, the 2,3-diphenyl-2*H*-azirine **1l** was subjected to the optimized reaction conditions. Gratifyingly, the substrate also smoothly reacted to provide the pyridine **4la** in 79% yield.

Table 2: Scope of 2*H*-azirines in the pyridine synthesis.[a]



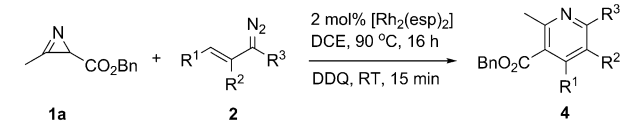
1 **2a** **4**



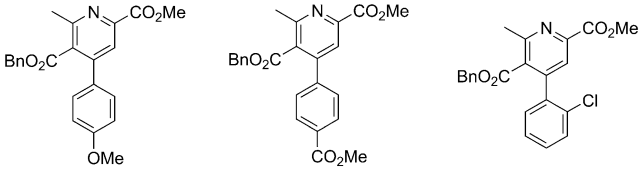
[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.48 mmol), DCE (0.15 M). The reported yields in parentheses are of the isolated products.

Next, we turned our attention to examine the scope of the other reaction partner. Survey of vinyl diazo compounds with various substitutions revealed that the transformation is also generally well tolerated and provides pyridines in good yields (Table 3). Examination of the electronic effect by substitution of the phenyl group of **2a** with electron-donating and electron-withdrawing groups showed that the reaction efficiency is marginally affected: 4-$MeOC_6H_4$ (**4ab**, 76%), Ph (**4aa**, 72%), and 4-$MeO_2CC_6H_4$ (**4ac**, 67%). The reaction with **2d**, bearing a sterically more demanding 2-chlorophenyl group, led to a moderate decrease in yield, which is in contrast to the result of the steric effect examined on 2*H*-azirine **1g**

Table 3: Scope of vinyl diazo compounds in pyridine synthesis.[a]



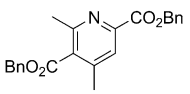
1a **2** **4**



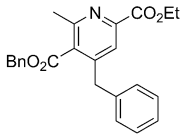
4ab (76%)

4ac (67%)

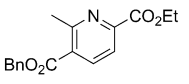
4ad (55%)



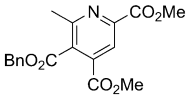
4ae (80%)



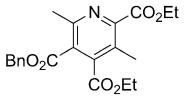
4af (44%)



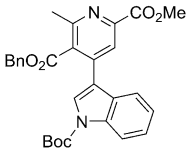
4ag (61%)



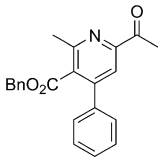
4ah (77%)[b,c]



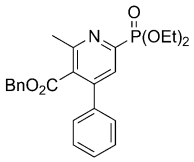
4ai (65%)[b,c]



4aj (81%)



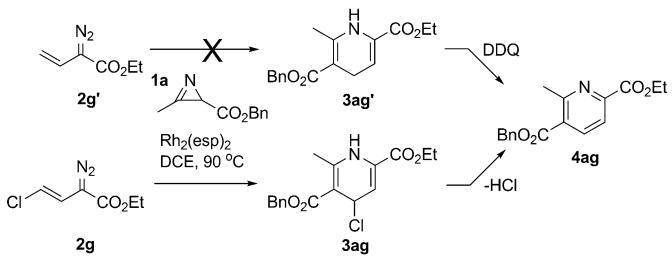
4ak (72%)



4al (71%)

[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.48 mmol), DCE (0.15 M). The reported yields in parentheses are of the isolated products. [b] Reaction performed in 1,2-dichlorobenzene at 90°C for 6 h, then heated at 170°C overnight. [c] Spontaneous oxidation without DDQ.

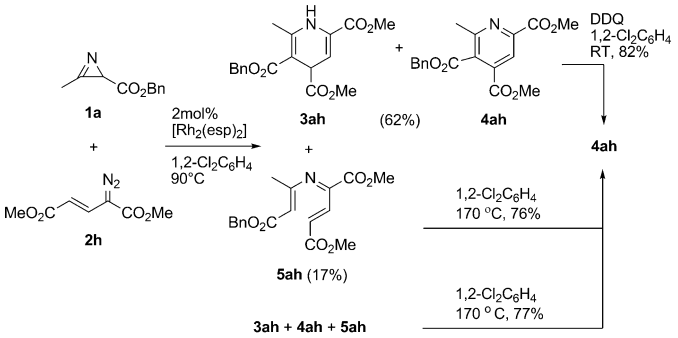
(55% versus 94%). 4-Alkyl-substituted vinyl diazoacetates smoothly reacted to afford the corresponding pyridines **4ae** and **4af**. In an attempt to access 4-unsubstitued pyridines, we performed the reaction with the requisite unsubstituted vinyl diazoacetate **2g′**, which turned out to be sluggish and provided a complex mixture (Scheme 1). We reasoned that no substitution at C4 of **2g′** might cause complication in the reaction and that introduction of a chloro group as a temporary removable substituent may help overcome the problem



Scheme 1. Synthesis of the 4-unsubstituted pyridine **4ag**.

by imposing some steric hindrance. In addition, elimination of the chloro group from the corresponding 1,4-dihydropyridine **3ag** would obviate the need for a separate oxidation. To our delight, the reaction with **2g** smoothly produced 4-unsubstituted pyridine **4ag** in 61% yield after spontaneous elimination of chloride from **3ag**.

Also, introduction of an additional ester group on the pyridine ring was made possible by employing the 4-alkoxycarbonyl vinyl diazoacetate **2h**, thus resulting in the formation of the highly deactivated trialkoxycarbonylpyridine **4ah** in 77% yield (Scheme 2). Under the standard



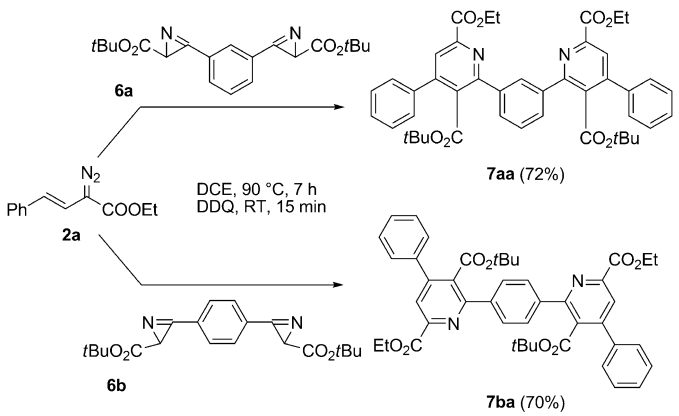
Scheme 2. Mechanistic evidence of 3-azatriene intermediacy.

reaction conditions, the reaction provided an inseparable mixture of the expected 1,4-dihydropyridine **3ah** and pyridine **4ah** in 62% along with 3-azatriene **5ah** in 17%. This 3-azatriene **5ah** smoothly underwent cyclization when heated at 170°C in 1,2-dichlorobenzene to give the pyridine **4ah** in 76% after spontaneous oxidation. This observation suggests that the pyridine formation is likely to involve 6π electrocyclization of 3-azatrienes. Alternatively, **4ah** was obtained in higher yield by directly heating the mixture of **3ah**, **4ah**, and **5ah** at 170°C when the starting materials were consumed.

Furthermore, pentasubstituted pyridines could be prepared by employing 3,4-disubstituted vinyl diazoacetates. Thus, the reaction with **2i** bearing a 3-methyl substitutent proceeded smoothly to afford **4ai** in 65% yield. The indole-substituted pyridine **4aj** could be prepared in excellent yield by employing the corresponding diazo compound. To further expand the scope of functional groups that could be installed on pyridines, we examined the reaction with the diazoketone **2k** and diazophosphonate **2l**. Gratifyingly, the reactions provided the pyridines **4ak** (72%) and **4al** (71%) bearing these useful functional groups.

Molecules with extended conjugation have found broad applications in the area of functional materials.[14] We envisioned that double annulation of *bis*-2*H*-azirines would offer a powerful means for the synthesis of such polyarylpyridine systems. Indeed, the annulation reaction of **6a** and **6b** with vinyl diazoacetate **2a** proceeded remarkably well, providing extended aryl-heteroaryl systems **7aa** and **7ba** in 72% and 70%, respectively (Scheme 3).

In summary, we have developed a novel strategy of activation of 2*H*-azirines with carbenoids for the synthesis of



Scheme 3. Double cyclization for polyarylpyridines.

pyridines. This method allows the formation of pyridines bearing a broad range of substitution in good to excellent yields and requires a low catalyst loading. We have also demonstrated the utility of this transformation in the synthesis of highly conjugated polyarylpyridine systems.

Experimental Section

An oven dried Schlenk tube charged with $[Rh_2(esp)_2]$ (0.02 equiv) was purged with nitrogen, and a solution of azirine (0.3 mmol, 1 equiv) in DCE (1 mL) was added. A solution of the freshly prepared diazo compound (1.6 equiv) in DCE (1 mL) was added dropwise to the suspension under nitrogen. The reaction mixture was then heated to 90 °C for 3–20 h. The solution was cooled to RT and treated with DDQ (1 equiv). The suspension was stirred at RT for 15 min and filtered through a plug of silica gel. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography using hexanes/ethyl acetate (4:1) as the eluent to give the desired product.

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[1] a) A. F. Pozharskii, A. Soldatenkov, A. R. Katritzky, *Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry, Biochemistry and Applications*, Wiley, Hoboken, **2011**; b) J. P. Michael, *Nat. Prod. Rep.* **2005**, *22*, 627 – 646; c) D. O'Hagan, *Nat. Prod. Rep.* **2000**, *17*, 435 – 446.

[2] a) K. Kral, M. Hapke, *Angew. Chem.* **2011**, *123*, 2482 – 2483; *Angew. Chem. Int. Ed.* **2011**, *50*, 2434 – 2435; b) J. A. Joule, K. Mills, *Heterocyclic Chemistry*, Wiley, Hoboken, **2010**, pp. 115 – 175; c) M. D. Hill, *Chem. Eur. J.* **2010**, *16*, 12052 – 12062; d) P. A. Keller, in *Comprehensive Heterocyclic Chemistry III*, *Vol. 7* (Eds.: A. R. Katritzky, A. R. Christopher, E. F. V. Scriven, R. J. K. Taylor), Elsevier, Oxford, **2008**, pp. 217 – 308; e) G. D. Henry, *Tetrahedron* **2004**, *60*, 6043 – 6061.

[3] a) C. Simon, T. Constantieux, J. Rodriguez, *Eur. J. Org. Chem.* **2004**, 4957 – 4980; b) A. Sausins, G. Duburs, *Heterocycles* **1988**, *27*, 269 – 289.

[4] a) I. Nakamura, D. Zhang, M. Terada, *J. Am. Chem. Soc.* **2010**, *132*, 7884 – 7886; b) T. Sakai, R. L. Danheiser, *J. Am. Chem. Soc.* **2010**, *132*, 13203 – 13205; c) F. Sha, X. Huang, *Angew. Chem.* **2009**, *121*, 3510 – 3513; *Angew. Chem. Int. Ed.* **2009**, *48*, 3458 – 3461; d) Y.-F. Wang, S. Chiba, *J. Am. Chem. Soc.* **2009**, *131*, 12570 – 12572; e) S. Liu, L. S. Liebeskind, *J. Am. Chem. Soc.* **2008**, *130*, 6918 – 6919; f) D. A. Colby, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2008**, *130*, 3645 – 3651; g) J. Barluenga, M. Á. Fernández-Rodríguez, P. García-García, E. Aguilar, *J. Am. Chem. Soc.* **2008**, *130*, 2764 – 2765; h) J. A. Varela, C. Saá, *Synlett* **2008**, 2571 – 2578; i) M. Movassaghi, M. D. Hill, O. K. Ahmad, *J. Am. Chem. Soc.* **2007**, *129*, 10096 – 10097; j) H.-T. Chang, M. Jeganmohan, C.-H. Cheng, *Org. Lett.* **2007**, *9*, 505 – 508; k) B. Heller, M. Hapke, *Chem. Soc. Rev.* **2007**, *36*, 1085 – 1094; l) M. Movassaghi, M. D. Hill, *J. Am. Chem. Soc.* **2006**, *128*, 4592 – 4593; m) M. M. McCormick, H. A. Duong, G. Zuo, J. Louie, *J. Am. Chem. Soc.* **2005**, *127*, 5030 – 5031; n) D. Suzuki, Y. Nobe, Y. Watai, R. Tanaka, Y. Takayama, F. Sato, H. Urabe, *J. Am. Chem. Soc.* **2005**, *127*, 7474 – 7479; o) J. A. Varela, C. Saá, *Chem. Rev.* **2003**, *103*, 3787 – 3802; p) Y. Yamamoto, R. Ogawa, K. Itoh, *J. Am. Chem. Soc.* **2001**, *123*, 6189 – 6190.

[5] a) B.-T. Guan, Z. Hou, *J. Am. Chem. Soc.* **2011**, *133*, 18086 – 18089; b) S. H. Cho, S. J. Hwang, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 9254 – 9256; c) J. C. Lewis, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2007**, *129*, 5332 – 5333; d) K. Godula, B. Sezen, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 3648 – 3649; e) R. Chinchilla, C. Nájera, M. Yus, *Chem. Rev.* **2004**, *104*, 2667 – 2722.

[6] a) M. Murakami, T. Matsuda, *Chem. Commun.* **2011**, *47*, 1100 – 1105; b) C. A. Carson, M. A. Kerr, *Chem. Soc. Rev.* **2009**, *38*, 3051 – 3060; c) C.-H. Jun, *Chem. Soc. Rev.* **2004**, *33*, 610 – 618.

[7] a) A. T. Parsons, J. S. Johnson, *J. Am. Chem. Soc.* **2009**, *131*, 3122 – 3123; b) D. C. Moebius, J. S. Kingsbury, *J. Am. Chem. Soc.* **2009**, *131*, 878 – 879; c) H. Xu, W. Zhang, D. Shu, J. B. Werness, W. Tang, *Angew. Chem.* **2008**, *120*, 9065 – 9068; *Angew. Chem. Int. Ed.* **2008**, *47*, 8933 – 8936; d) T. Seiser, N. Cramer, *Angew. Chem.* **2008**, *120*, 9435 – 9438; *Angew. Chem. Int. Ed.* **2008**, *47*, 9294 – 9297; e) T. Matsuda, T. Tsuboi, M. Murakami, *J. Am. Chem. Soc.* **2007**, *129*, 12596 – 12597; f) J. P. Markham, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 9708 – 9709.

[8] a) Y. Jiang, W. C. Chan, C.-M. Park, *J. Am. Chem. Soc.* **2012**, *134*, 4104 – 4107; b) D. A. Candito, M. Lautens, *Org. Lett.* **2010**, *12*, 3312 – 3315; c) S. Jana, M. D. Clements, B. K. Sharp, N. Zheng, *Org. Lett.* **2010**, *12*, 3736 – 3739; d) S. Brahma, J. K. Ray, *J. Heterocycl. Chem.* **2008**, *45*, 311 – 317; e) D. F. Taber, W. Tian, *J. Am. Chem. Soc.* **2006**, *128*, 1058 – 1059; f) K. L. Stevens, D. K. Jung, M. J. Alberti, J. G. Badiang, G. E. Peckham, J. M. Veal, M. Cheung, P. A. Harris, S. D. Chamberlain, M. R. Peel, *Org. Lett.* **2005**, *7*, 4753 – 4756; g) A. Padwa, T. Stengel, *Tetrahedron Lett.* **2004**, *45*, 5991 – 5993.

[9] a) X. Zhao, Y. Zhang, J. Wang, *Chem. Commun.* **2012**, *48*, 10162 – 10173; b) F. de C. da Silva, A. K. Jordao, D. R. da Rocha, S. B. Ferreira, A. C. Cunha, V. F. Ferreira, *Curr. Org. Chem.* **2012**, *16*, 224 – 251; c) X. Wang, X. Xu, P. Y. Zavalij, M. P. Doyle, *J. Am. Chem. Soc.* **2011**, *133*, 16402 – 16405; d) S. Muthusamy, J. Krishnamurthi in *Synthesis of Heterocycles via Cycloadditions I*, *Vol. 12* (Ed.: A. Hassner), Springer, Berlin, **2008**, pp. 147 – 192; e) J. R. Manning, H. M. L. Davies, *J. Am. Chem. Soc.* **2008**, *130*, 8602 – 8603; f) A. Padwa, S. K. Bur, *Tetrahedron* **2007**, *63*, 5341 – 5378; g) R. P. Reddy, H. M. L. Davies, *J. Am. Chem. Soc.* **2007**, *129*, 10312 – 10313; h) V. F. Ferreira, *Curr. Org. Chem.* **2007**, *11*, 177 – 193; i) M. P. Doyle, M. Yan, W. Hu, L. S. Gronenberg, *J. Am. Chem. Soc.* **2003**, *125*, 4692 – 4693.

[10] a) X. Qi, X. Xu, C.-M. Park, *Chem. Commun.* **2012**, *48*, 3996 – 3998; b) E. Lourdusamy, L. Yao, C.-M. Park, *Angew. Chem.* **2010**, *122*, 8135 – 8139; *Angew. Chem. Int. Ed.* **2010**, *49*, 7963 – 7967.

[11] Z. Rappoport, J. F. Liebman, *The chemistry of hydroxylamines, oximes and hydroxamic acids*, *Vol. 2*, Wiley, Hoboken, **2008**.

[12] CCDC 911613 (**4ba**) 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.

[13] C. G. Espino, K. W. Fiori, M. Kim, J. Du Bois, *J. Am. Chem. Soc.* **2004**, *126*, 15378 – 15379.

[14] a) Y. Shirota, H. Kageyama, *Chem. Rev.* **2007**, *107*, 953 – 1010; b) R. L. Carroll, C. B. Gorman, *Angew. Chem.* **2002**, *114*, 4556 – 4579; *Angew. Chem. Int. Ed.* **2002**, *41*, 4378 – 4400.