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Regioselective Ring Expansion of 2,4-Diiminoazetidines via Cleavage of C−N and C(sp^3)−H Bonds: Efficient Construction of 2,3-Dihydropyrimidinesulfonamides

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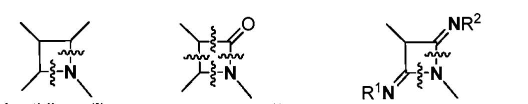
Supporting Information

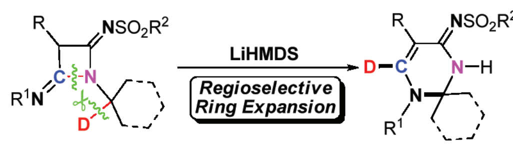
ABSTRACT: A highly regioselective base-mediated ring expansion of 2,4-diiminoazetidines via cleavage of C−N and C(sp^3)−H bonds is achieved for the first time to afford efficiently 2,3-dihydropyrimidinesulfonamides. The mechanism of the ring expansion via tandem 4π electrocyclic ring-opening/1,5-H shift/6π electrocyclic ring-closing is well confirmed by the trapping experiments of two key intermediates and deuterium labeling studies.

Aza-heterocycles, such as azetidines (**I**) and azetidinones (**II**), have been extensively studied in the past three decades because of their great importance not only as biologically relevant compounds but also in synthetic applications for the construction of N-containing heterocycles.[1−5] The ring-opening of four-membered aza-heterocycles is a fundamental process for the initiation of their further synthetic transformation. Azetidines usually undergo the cleavage of two C−N bonds; however, any of the four single bonds of azetidinones can be broken in chemical transformation. In contrast, studies on iminoazetidine chemistry are very limited, probably due to lack of efficient synthetic methods.[6] Until recently, Xu et al reported an efficient copper-catalyzed three-component coupling of terminal alkynes, sulfonyl azides, and carbodiimides to give functionalized diiminoazetidines (**III**).[7] Up to now, the reaction chemistry of iminoazetidines still remains unexplored.



We have been interested in metal-promoted reaction chemistry of carbodiimides.[8−10] Various diiminoazetidines were prepared by the CuI-catalyzed coupling of terminal alkynes, sulfonyl azides, and carbodiimides for our research.[11] Herein, we report a highly regioselective base-mediated ring-expansion of 2,4-diiminoazetidines to afford exclusively 2,3-dihydropyrimidinesulfonamides in excellent yields (Scheme 1). In this process the highly regioselective cleavage of a C−N bond and 1,5-hydride shift are observed.[12] The mechanism of the ring expansion via tandem 4π electrocyclic ring-opening/1,5-H shift/6π electrocyclic ring-closing is well confirmed by the trapping experiments of two key intermediates and deuterium labeling studies.

Scheme 1. Ring Expansion of 2,4-Diiminoazetidines via Cleavage of C−N and C(sp^3)−H Bonds



Initially, **1a** (R = 3-ClC_6H_4, R^1 = Cy, R^2 = 4-MeC_6H_4, n = 3) was treated with different bases, such as n-BuLi, lithium diisopropylamide (LDA), and lithium bis(trimethylsilyl)amide (LiHMDS), in THF at −78 °C for 1 h, and then at room temperature for 3 h. After the reaction mixture was quenched with water, a N-containing compound **2a** was obtained in 49%, 25%, and 98% yield, respectively (Table 1). LiHMDS seemed to be the best choice for the present reaction. The X-ray structure of **2a** revealed the product was 2,3-dihydropyrimidinesulfonamide with a 6,6-spiro skeleton (Figure 1).

In the presence of 1.1 equiv of LiHMDS, a wide range of 2,4-diiminoazetidines having a cyclic group attached to the nitrogen atom of the azetidine ring could afford the corresponding spiro-2,3-dihydropyrimidinesulfonamides **2a**−**q** in good to excellent isolated yields (Table 1). This ring expansion reaction was compatible with halo substituents (F, Cl, Br, and I) on the aromatic ring (**2a**,**c**−**e**). The substitution pattern (*ortho*-, *meta*-, or *para*-) did not affect the reaction yields. Notably, 2,4-diiminoazetidine with a cyano group on the phenyl ring (**2g**) was also tolerated. Biphenyl (**2h**) and 6-methoxynaphthalenyl (**2i**)-substituted 2,4-diiminoazetidines were both suitable substrates for this reaction. 2,4-Diiminoazetidines having heteroaromatic substituents afforded high yields of **2j** and **2k**, respectively. The reaction of four different substituted diiminoazetidines with LiHMDS provided smoothly **2m** in moderate yields. In addition to cyclohexyl group, five- or four-membered ring-substituted diiminoazetidines in similar conditions provided smoothly **2o** and **2p**, respectively. Moreover, the reaction is not only limited to the tosyl 2,4-diiminoazetidine. 2,4-Diiminoazetidine with a 4-acetamidophenylsulfonyl

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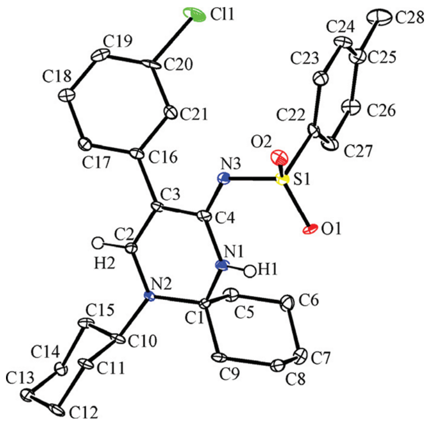


Figure 1. ORTEP drawing of **2a** with 30% thermal ellipsoids. Hydrogen atoms except those on C2 and N1 atoms are omitted for clarity. Selected bond length (Å): C1−N1 1.465(4), C1−N2 1.482(4), C2−N2 1.345(4), C4−N1 1.354(4), C4−N3 1.340(4), C2−C3 1.375(4), C3−C4 1.439(5), C1−C5 1.546(5), C1−C9 1.542(4), N3−S1 1.589(3), O1−S1 1.465(2), O2−S1 1.456(2), C20−Cl1 1.759(4).

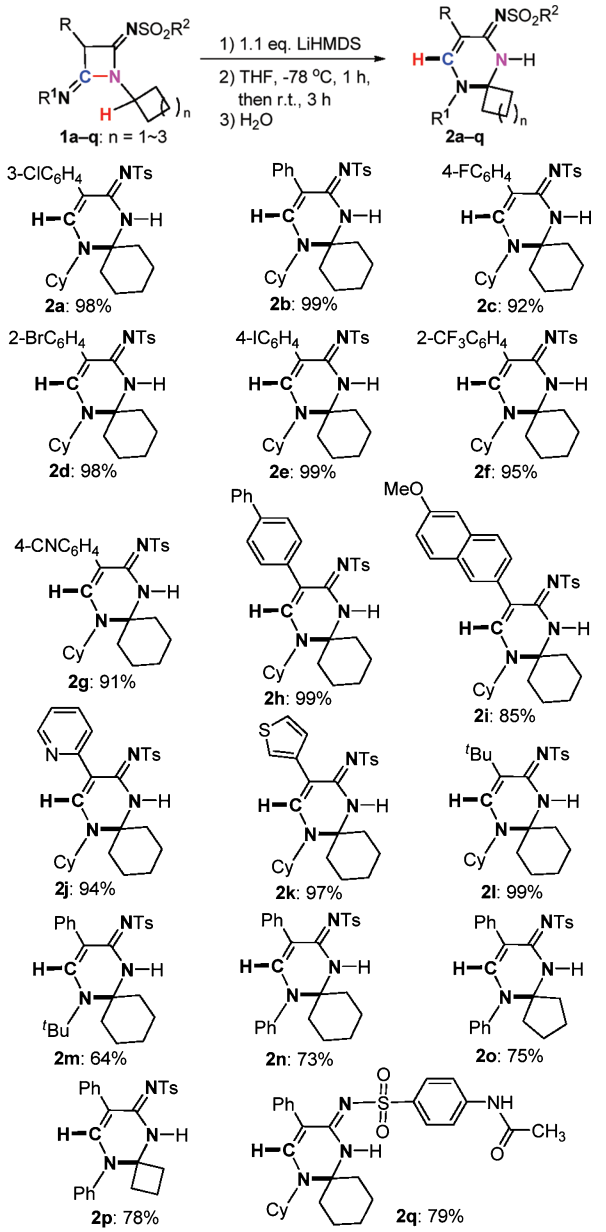
group reacted with LiHMDS to give the desired product **2q** as well.

Summarized in Table 2 are representative results for the synthesis of various 2,3-dihydropyrimidinesulfonamides **4a−l** showing excellent functional group compatibility as well. Electron-withdrawing (Table 1, **2f** and **2g**) or electron-donating substituents (Table 2, **4a** and **4b**) on the aromatic ring were both tolerated. In addition to phenyl groups, naphthalenyl- or benzothiophenyl-substituted diiminoazetidines also smoothly underwent this reaction to generate the corresponding products **4c** and **4d**. This ring expansion reaction was applicable to a wide variety of aliphatic substituents in **2l** (Table 1) and **4e−h** (Table 2). The keto and ester groups in **4i−k** survived the present conditions. 2,4-Diiminoazetidine having two α-H atoms adjacent to the nitrogen atom of the azetidine ring underwent similar reaction to furnish **4l**.

2,3-Dihydropyrimidinesulfonamides possessing a pyrimidine ring and "CN_2" amidine unit in this skeleton might show unique biological activity.[13] As far as we are aware, our result is the first example of efficient preparation of well-defined 2,3-dihydropyrimidinesulfonamides. They are a new type of N-containing heterocyclic compounds, which cannot be accessed by other means.

In order to better understand this ring expansion, isolation and trapping experiments of four- or six-membered intermediates were carried out. 2,4-Diiminoazetidine **1b** was treated with LiHMDS in THF at −78 °C for 1 h, which provided the four-membered anionic intermediate **A**. We failed to isolate **A** because it was only stable at low temperature and quantitatively rearranged to six-membered anionic intermediate **B** when the temperature was increased from −78 °C to room temperature. The intermediate **A** was confirmed by trapping with various electrophiles such as D_2O, iodomethane, and benzoyl chloride (Scheme 2), yielding the deuterated 2,4-diiminoazetidine **5** and all-substituted 2,4-diiminoazetidines **6** and **7**, respectively. The D, Me, and PhCO groups were regioselectively attached to the carbon atom of the azetidine ring. **B** was trapped with D_2O to quantitatively yield **2b-D**. In contrast, trapping **B** with iodomethane furnished the product **8**. An X-ray analysis of **8** revealed the methyl group was bonded to the exocyclic nitrogen atom.

Table 1. Formation of Spiro-2,3-dihydropyrimidinesulfonamides[a]

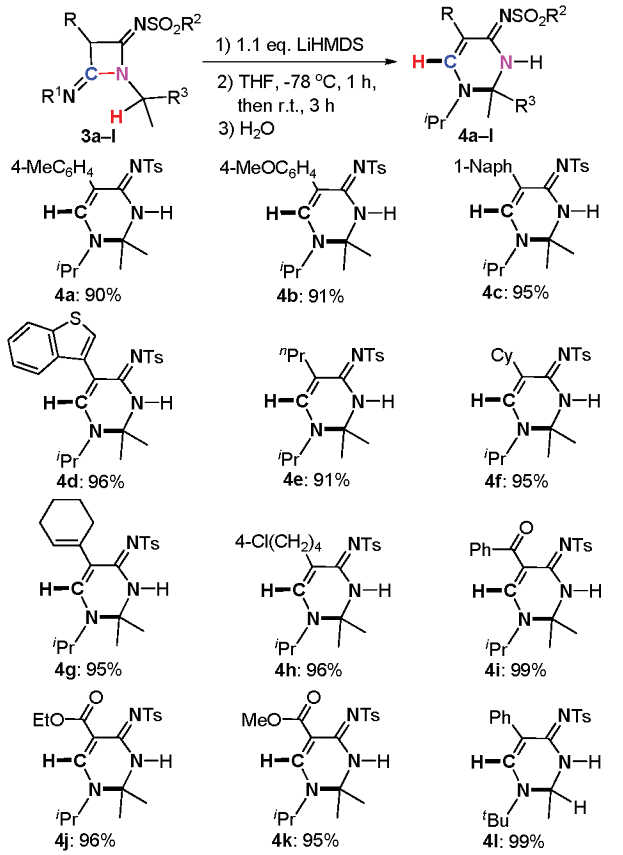


[a]Conditions: 2,4-diiminoazetidines (1 mmol), LiHMDS (1.1 mmol), THF (10 mL), unless otherwise noted. Isolated yields are given.

To gain further mechanistic insight into the origin of the hydrogen attached to the carbon of six-membered C_4N_2 ring, deuterium labeling experiments were conducted (Scheme 3). Deuterated 2,4-diiminoazetidine **1n-D** was prepared (see Supporting Information (SI)). When **1n-D** was used under the above ring-opening conditions, the deuterium was incorporated exclusively to the C-6 position of the product **2n-D**. Deuterium-labeling studies unambiguously indicate that this hydrogen, transferred to the 6-position of 2,3-dihydropyrimidinesulfonamides, originates from the α-hydrogen adjoining to the nitrogen atom of the azetidine ring.

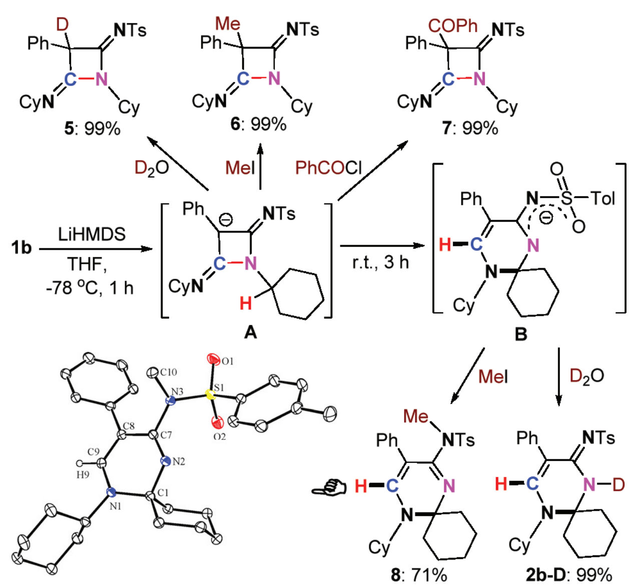
Based on the above observations, a proposed mechanism is shown in Scheme 4. Reaction of diiminoazetidine with

Table 2. Formation of 2,3-Dihydropyrimidinesulfonamides[a]



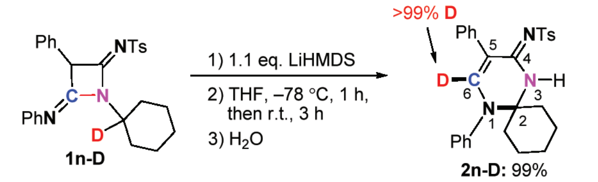
[a]Conditions: 2,4-diiminoazetidines (1 mmol), LiHMDS (1.1 mmol), THF (10 mL), unless otherwise noted. Isolated yields are given.

Scheme 2. Trapping Experiments of Intermediates A and B

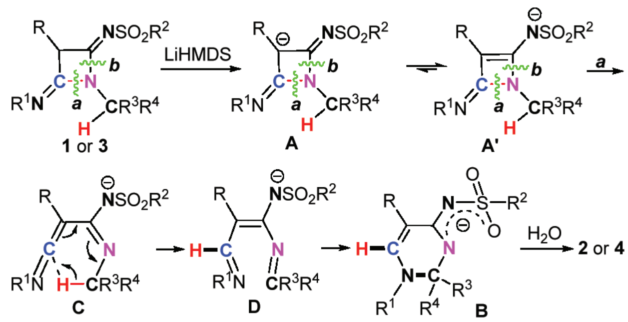


LiHMDS forms the anionic species **A** or **A′** with the cleavage of two potential C–N bonds (*a* or *b*). In fact, only the cleavage C–N bond (*a*) was observed to evolve into intermediate **C** via 4π electrocyclic ring-opening. The highly regioselective C–N cleavage is probably because the alkylimino C–N single bond (*a*) is weaker than the sulfonylimino C–N single bond (*b*), due to the strong electron-withdrawing nature of the sulfonyl group.

Scheme 3. Deuterium Labeling Studies



Scheme 4. A Possible Mechanism



This is in agreement with the bond length of the corresponding C–N bonds. The alkylimino C–N bond (1.427 Å) is much longer than the sulfonylimino C–N bond (1.358 Å) in **1h** (see SI). **C** is then converted into intermediate **D** via 1,5-H shift. The concurrent 6π electrocyclic ring-closing of **D** affords the final products after quenching.

In summary, a highly regioselective base-mediated ring expansion of 2,4-diiminoazetidines via cleavage of C–N and C(sp^3)–H bonds has been achieved to afford exclusively 2,3-dihydropyrimidinesulfonamides in excellent yields. The mechanism involves tandem 4π electrocyclic ring-opening/1,5-H shift/6π electrocyclic ring-closing, which is confirmed by the trapping experiments of two key intermediates and deuterium labeling experiments.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, X-ray data for **1h**, **2a**, and **8** (CIF), and NMR spectra of all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews of azetidines, see: (a) Abbaspour Tehrani, K.; De Kimpe, N. *Curr. Org. Chem.* **2009**, *13*, 854. (b) Couty, F.; Evano, G. *Synlett* **2009**, 3053. (c) Singh, G. S.; D’hooghe, M.; De Kimpe, N. In

Comprehensive Heterocyclic Chemistry III; Katritzky, A., Ramsden, C., Scriven, E., Taylor, R., Eds.; Elsevier: Oxford, 2008; Vol. *2*, p 1. (d) Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, *108*, 3988. (e) Ferraris, D.; Belyakov, S.; Li, W.; Oliver, E.; Ko, Y. S.; Calvin, D.; Lautar, S.; Thomas, B.; Rojas, C. *Curr. Top. Med. Chem.* **2007**, *7*, 597. (f) Couty, F.; Evano, G. *Org. Prep. Proced. Int* **2006**, *38*, 427. (g) De Kimpe, N. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Ed.; Elsevier: Oxford, 1996; Vol. *1B*, p 507. (h) Cromwell, N. H.; Phillips, B. *Chem. Rev.* **1979**, *79*, 331.

(2) For reviews of azetidinones, see: (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437. (b) Dejaegher, Y.; Kuz'menok, N. M.; Zvonok, A. M.; De Kimpe, N. *Chem. Rev.* **2002**, *102*, 29. (c) Alcaide, B.; Almendros, P. *Chem. Soc. Rev.* **2001**, *30*, 226.

(3) Selected examples for azetidines: (a) Denis, J.-B.; Masson, G.; Retailleau, P.; Zhu, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5356. (b) Shindoh, N.; Kitaura, K.; Takemoto, Y.; Takasu, K. *J. Am. Chem. Soc.* **2011**, *133*, 8470. (c) Alcaide, B.; Almendros, P.; Luna, A.; Torres, M. R. *Adv. Synth. Catal.* **2010**, *352*, 621. (d) Feula, A.; Male, L.; Fossey, J. S. *Org. Lett.* **2010**, *12*, 5044. (e) Shindoh, N.; Takemoto, Y.; Takasu, K. *Chem. Eur. J.* **2009**, *15*, 7026. (f) Ungureanu, I.; Klotz, P.; Schoenfelder, A.; Mann, A. *Chem. Commun.* **2001**, 958.

(4) Selected examples for azetidinones: (a) Li, G.-Q.; Li, Y.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2007**, *9*, 3519. (b) Zhao, L.; Li, C.-J. *Chem. Asian J.* **2006**, *1−2*, 203. (c) Vargas-Sanchez, M.; Couty, F.; Evano, G.; Prim, D.; Marrot, J. *Org. Lett.* **2005**, *7*, 5861. (d) Alcaide, B.; Almendros, P.; Cabrero, G.; Ruiz, M. P. *Org. Lett.* **2005**, *7*, 3981. (e) Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 4572. (f) Durst, T.; Elzen, R. V. D.; LeBelle, M. J. *J. Am. Chem. Soc.* **1972**, *94*, 9261.

(5) For biological activity of azetidines or azetidinones, see: (a) Clader, J. W. *Curr. Top. Med. Chem.* **2005**, *5*, 243. (b) Setti, E. L.; Micetich, R. G. *Curr. Med. Chem.* **1998**, *5*, 101. (c) *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1993. (d) Neuhaus, F. C.; Georgeopapadakou, N. H. In *Emerging Targets in Antibacterial and Antifungal Chemoterapy*; Sutcliffe, J., Georgeopapadakou, N. H., Eds.; Chapman and Hall: New York, 1992.

(6) For the synthesis of diiminoazetidines, see: (a) Chen, C. T.; Chan, Y. S.; Tzeng, Y. R.; Chen, M. T. *Dalton Trans.* **2004**, 2691. (b) Schaffer, P.; Morel, P.; Britten, J. F.; Valliant, J. F. *Inorg. Chem.* **2002**, *41*, 6493. (c) Marchand, E.; Morel, G.; Sinbandhit, S. *Eur. J. Org. Chem.* **1999**, 1729. (d) Aumann, R.; Heinen, H. *Chem. Ber.* **1986**, *119*, 2289. (e) L'abbé, G.; Sorgeloos, D.; Toppet, S. *Tetrahedron Lett.* **1982**, *23*, 2909. (f) Deyrup, J. A.; Vestling, M. M.; Hagan, W. V.; Yun, H. Y. *Tetrahedron* **1969**, *25*, 1467.

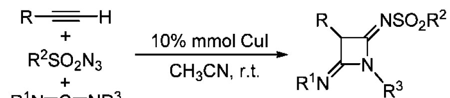
(7) (a) Xu, X.; Cheng, D.; Li, J.; Guo, H.; Yan, J. *Org. Lett.* **2007**, *9*, 1585. See also a review: (b) Kim, S. H.; Park, S. H; Choi, J. H.; Chang, S. *Chem. Asian J.* **2011**, *6*, 2618.

(8) Selected reviews of carbodiimide chemistry: (a) Nishiura, M.; Hou, Z. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 595. (b) Suzuki, T.; Zhang, W.-X.; Nishiura, M.; Hou, Z. *J. Synth. Org. Chem. Jpn.* **2009**, *67*, 451. (c) Shen, H.; Xie, Z. *J. Organomet. Chem.* **2009**, *694*, 1652. (d) Zhang, W.-X.; Hou, Z. *Org. Biomol. Chem.* **2008**, *6*, 1720. (e) Edelmann, F. T. *Adv. Organomet. Chem.* **2008**, *57*, 183. (f) Williams, A.; Ibrahim, I. T. *Chem. Rev.* **1981**, *81*, 589.

(9) (a) Wang, Y.; Zhang, W.-X.; Wang, Z.; Xi, Z. *Angew. Chem., Int. Ed.* **2011**, *50*, 8122. (b) Li, D.; Wang, Y.; Zhang, W.-X.; Zhang, S.; Guang, J.; Xi, Z. *Organometallics* **2011**, *30*, 5278. (c) Li, D.; Guang, J.; Zhang, W.-X.; Wang, Y.; Xi, Z. *Org. Biomol. Chem.* **2010**, *8*, 1816. (d) Wang, Z.; Wang, Y.; Zhang, W.-X.; Hou, Z.; Xi, Z. *J. Am. Chem. Soc.* **2009**, *131*, 15108. (e) Zhang, W.-X.; Li, D.; Wang, Z.; Xi, Z. *Organometallics* **2009**, *28*, 882.

(10) (a) Zhang, W.-X.; Nishiura, M.; Mashiko, T.; Hou, Z. *Chem. Eur. J.* **2008**, *14*, 2167. (b) Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 3262. (c) Xu, X.; Gao, J.; Cheng, D.; Li, J.; Qiang, G.; Guo, H. *Adv. Synth. Catal.* **2008**, *350*, 61. (d) Volonterio, A.; Zanda, M. *J. Org. Chem.* **2008**, *73*, 7486. (e) Zhang, W.-X.; Nishiura, M.; Hou, Z. *Chem. Eur. J.* **2007**, *13*, 4037. (f) Zhang, W.-X.; Nishiura, M.; Hou, Z. *Chem. Commun.* **2006**, 3812. (g) Zhang, W.-X.; Nishiura, M.; Hou, Z. *Synlett* **2006**, 1213. (h) Zhang, W.-X.; Nishiura, M.; Hou, Z. *J. Am. Chem. Soc.* **2005**, *127*, 16788. (i) Ong, T.-G.; Yap, G. P. A; Richeson, D. S. *J. Am. Chem. Soc.* **2003**, *125*, 8100.

(11) Diiminoazetidines **1a−q** and **3a−l** were prepared by Xu's procedure (ref 7a and eq 1). **1b−q** and **3a−l** were new compounds. In addition to symmetric carbodiimides $R^1N{=}C{=}NR^3$ ($R^1 = R^3$ = Cy, ^{i}Pr), asymmetric carbodiimides $^tBuN{=}C{=}NR^3$ (R^3 = Cy, Et), and $PhN{=}C{=}NR^3$ (R^3 = Cy, cyclopentyl, and cyclobutyl) were also appropriate substrates for the preparation of diiminoazetidines, in which R^3 group (R^3 = Cy, Et, cyclopentyl, and cyclobutyl) was regioselectively attached on the nitrogen atom of the azetidine ring. Furthermore, 4-acetamidophenylsulfonyl azide could be utilized to yield the desired **1q**. See SI for more details.



1b–q and 3a–l (1)

(12) (a) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (b) Yoo, W.-J.; Li, C.-J. *Top. Curr. Chem.* **2010**, *292*, 281. (c) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949. (d) Ren, H.; Li, Z.; Knochel, P. *Chem. Asian J.* **2007**, *2*, 416. (e) Deng, K.; Bensari, A.; Cohen, T. *J. Am. Chem. Soc.* **2002**, *124*, 12106.

(13) (a) Wittine, K.; Benci, K.; Pavelić, S. K.; Pavelić, K.; Bratulić, S.; Hock, K.; Balzarini, J.; Mintas, M. *Med. Chem. Res.* **2011**, *20*, 280. (b) Noll, S.; Kralj, M.; Šuman, L.; Stephan, H.; Piantanida, I. *Eur. J. Med. Chem.* **2009**, *44*, 1172. (c) Peng, X.; Hong, I. S.; Li, H.; Seidman, M. M.; Greenberg, M. M. *J. Am. Chem. Soc.* **2008**, *130*, 10299. (d) Beauchamp, L. M.; Serling, B. L.; Kelsey, J. E.; Biron, K. K.; Collins, P.; Selway, J.; Lin, J.-C.; Schaeffer, H. J. *J. Med. Chem.* **1988**, *31*, 144.