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Formal [4+2]-Annulation of Vinyl Azides with N-Unsaturated Aldimines

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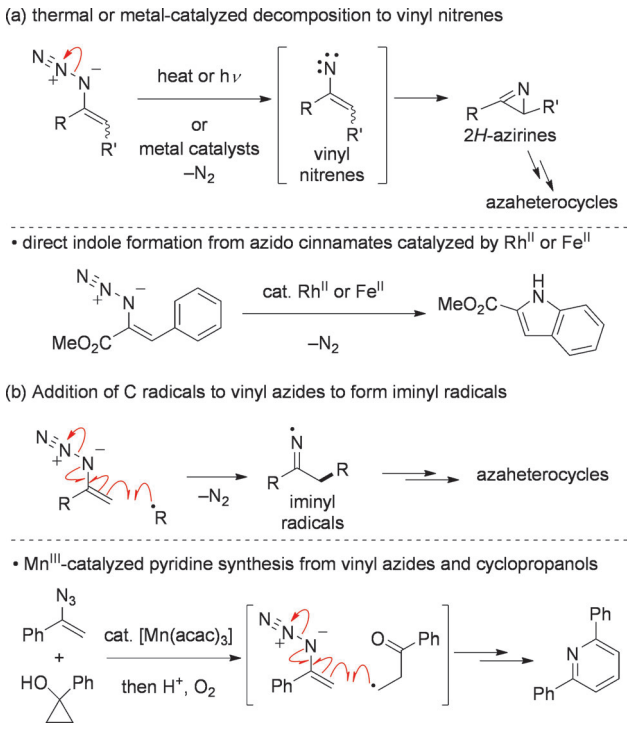
Abstract: Highly functionalized quinolines and pyridines could be synthesized by $BF_3{\cdot}OEt_2$-mediated reactions of vinyl azides with *N*-aryl and *N*-alkenyl aldimines, respectively. The reaction mechanism could be characterized as formal [4+2]-annulation, including unprecedented enamine-type nucleophilic attack of vinyl azides to aldimines and subsequent nucleophilic cyclization onto the resulting iminodiazonium ion moieties.

Design and development of new methods to assemble nitrogen heterocycles (azaheterocycles) is one of the most intense subjects in the area of synthetic organic chemistry, as these classes of molecules are particularly important in pharmaceutical and materials sciences.[1,2] Among available nitrogen sources for construction of azaheterocycles, vinyl azides have shown unprecedented chemical reactivity for synthesis of azaheterocycles (Scheme 1).[3] The thermolysis or photolysis of vinyl azides result in elimination of dinitrogen to generate vinyl nitrenes that undergo ring closure to 2*H*-azirines (Scheme 1 a).[4] The 2*H*-azirines having adjacent aryl or vinyl tethers are further converted into the corresponding indole or pyrrole derivatives via sp^2 C–H amination. More recently, the groups of Driver and Bolm have reported that these transformation can be catalyzed by transition-metals such as Rh^{II} carboxylates, ZnI_2, and $Fe(OTf)_2$ under much milder reaction conditions.[5–7] Vinyl azides can function as radical acceptors, and various carbon radicals add to the C=C bond of vinyl azides to form iminyl radicals that can be used for azaheterocycle synthesis (Scheme 1 b). Our group has reported synthesis of azaheterocycles based on the oxidative radical reactions of vinyl azides.[8]

Our recent interest in reaction design using vinyl azides relies on their potential nucleophilicity as enamine equivalents (Scheme 2). Indeed, we have reported amide synthesis by $BF_3{\cdot}OEt_2$-mediated nucleophilic attack of vinyl azides onto various carbon electrophiles (E^+) such as *N*-Ts imines (Scheme 2 a).[9,10] The reactions were initiated by nucleophilic attack of vinyl azides to E^+ to form iminodiazonium ion intermediates **I**, which undergo substituent-1,2-migration to form nitrilium ions **II**. Subsequent hydrolysis of **II** affords the corresponding amides. We wondered whether, if the electrophile is tethered with another nucleophilic part (Nu) that can trap the resulting iminodiazonium ion intermediate, it would be possible to construct a new cyclic structure prior to the substituent migration (Scheme 2 b). Herein, we report a realization of this concept by $BF_3{\cdot}OEt_2$-mediated reactions of vinyl azides with N-unsaturated imines, enabling efficient and robust synthesis of highly functionalized quinolines and pyridines.



Scheme 1. Chemical reactivity of vinyl azides for synthesis of azaheterocycles. acac = 2,4-pentanedionato.

We began our studies using vinyl azide **1a** with *N*-phenyl benzaldimine (**2a**) in the presence of $BF_3{\cdot}OEt_2$ (Scheme 3). The reaction of **1a** and *N*-phenyl benzaldimine **2a** (1.5 equiv) with $BF_3{\cdot}OEt_2$ (1.5 equiv) in CH_2Cl_2 at room temperature delivered 2,4-diphenylquinoline (**3aa**) in 63% yield along with generation of *N*-benzyl aniline (**4a**) in 57% yield. The reaction is likely initiated by nucleophilic attack

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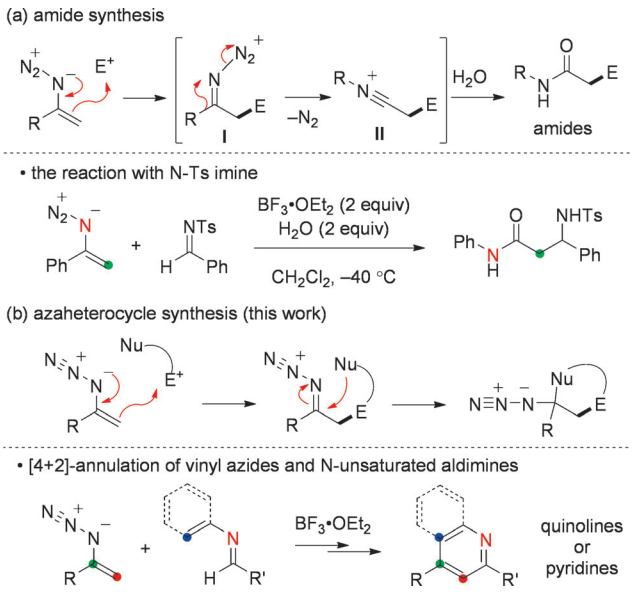
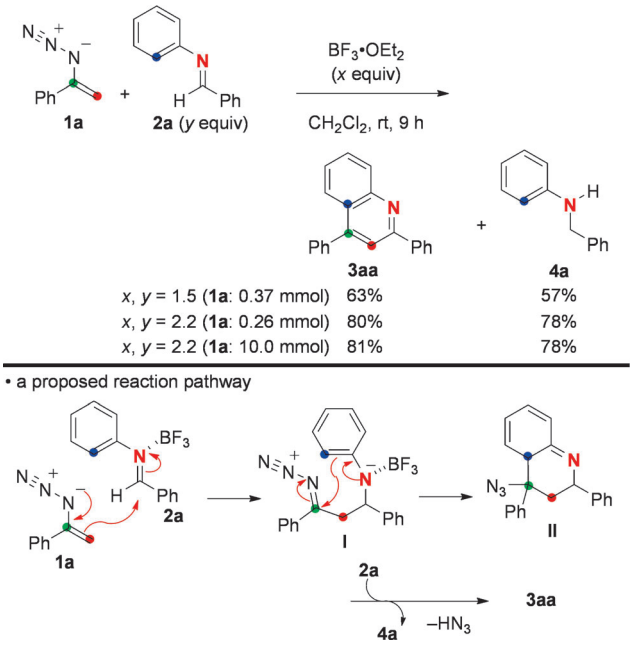


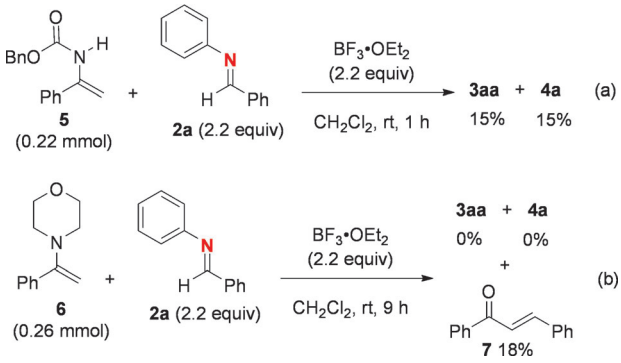
Scheme 2. Chemical reactivity of vinyl azides as nucleophile. Ts = $CH_3C_6H_4SO_2$.



Scheme 3. Reactions of vinyl azide **1a** and *N*-phenyl aldimine **2a**.

of vinyl azide **1a** to aldimine **2a** electrophilically activated by $BF_3{\cdot}OEt_2$ as the first C–C bond forming process, giving iminodiazonium ion intermediate **I**. Subsequent intramolecular cyclization to the imine moiety of **I** (the second C–C bond formation) forms 4-azido-tetrahydroquinoline **II**. Aromatization of **II** via hydrogen transfer to another molecule of aldimine **2a**[11] and elimination of HN_3 delivers quinoline **3aa** and *N*-benzyl aniline (**4a**). Therefore, the overall transformation is characterized as formal [4+2]-annulation,[12] and two equivalents of aldimine **2a** is theoretically required to complete the formation of quinoline **3aa**. As expected, to increase the amounts of aldimine **2a** and $BF_3{\cdot}OEt_2$ to 2.2 equivalents improved the yield of **3aa** to 80% (along with formation of **4a** in 78%). The reaction performed equally well on a large scale (10 mmol of **1a**).

To confirm the suitability of vinyl azide **1a** for the present [4+2]-annulation with *N*-phenyl benzaldimine **2a** for synthesis of quinoline **3aa**, we next tested the reactions of analogous enamide **5** and enamine **6** with **2a** in the presence of $BF_3{\cdot}OEt_2$ (Scheme 4). In the case of enamide **5**, the reaction



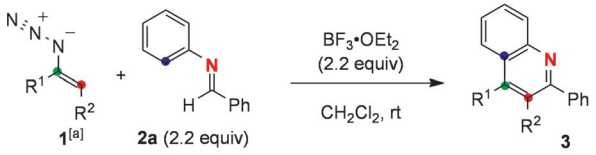
Scheme 4. Chemical reactivity of vinyl azides for synthesis of azaheterocycles.

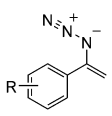
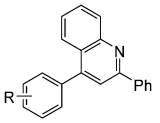
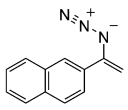
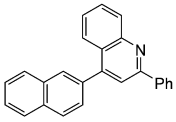
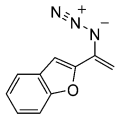
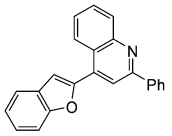
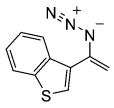
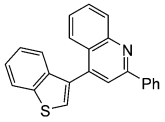
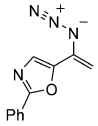
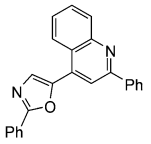
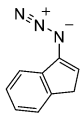
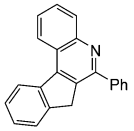
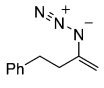
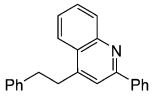
resulted in a complex mixture that included only a small amount of desired quinoline **3aa** (15% yield) along with **4a** in 15% yield (Scheme 4a). The reaction of morpholine enamine **6** afforded chalcone **7** in 18% yield without formation of quinoline **3aa** (Scheme 4b). These results unambiguously showed the special chemical reactivity of vinyl azide **1a** as an enamine-type nucleophile as well as the putative iminodiazonium ion intermediate **I** (Scheme 2a) as an electrophile for the present transformation.[13,14]

Following the established procedure, the generality of this quinoline synthesis[15] was examined using a series of vinyl azides **1**[16] with aldimine **2a** (Table 1). α-Aryl substituted vinyl azides (**1b–g**) reacted smoothly with aldimine **2a** to afford the corresponding quinolines **3ba–3ga** in good yields (Table 1, entries 1–6). Notably, heteroaryl motifs such as 2-benzofuranyl (Table 1, entry 7), 3-benzothienyl (Table 1, entry 8), and 5-oxazolyl motifs (Table 1, entry 9) were compatible under the present reaction conditions, furnishing the desired quinolines **3ha–3ja**. The reaction of 3-azido-1*H*-indene (**1k**) proceeded smoothly to give polycyclic 6-phenyl-7*H*-indeno[2,1-*c*]quinoline **3ka** in 70% yield (Table 1, entry 10). α-Alkyl substituted vinyl azide **1l** was also capable of coupling with aldimine **2a**, while the yield of quinoline **3la** was moderate (40% yield; Table 1, entry 11).

We next examined compatibility of *N*-aryl aldimines **2** in this quinoline synthesis with vinyl azide **1a** (Scheme 5). Installation of a methoxy group as the substituent R^3 did not affect the reactions to deliver quinolines **3ab** and **3ac** in good yields. In the reaction of aldimine **2c** having a 3-methoxy group as R^3, the second C–C bond forming process took place exclusively at the less hindered carbon atom

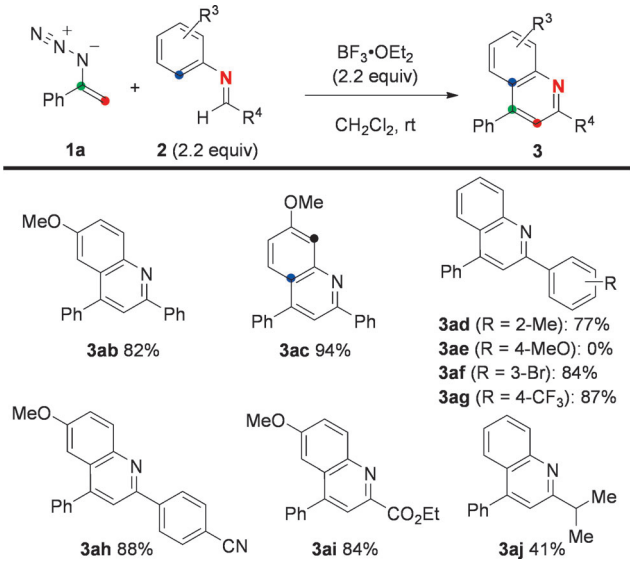
Table 1. Synthesis of quinolines **3**: scope of vinyl azides **1**.[a]



Entry	Vinyl azide **1**	Quinoline **3**, yield[b]
		
1	**1b**: R = 4-Me	**3ba** 68 %
2	**1c**: R = 4-MeO	**3ca** 69 %
3	**1d**: R = 4-Br	**3da** 78 %
4	**1e**: R = 4-CO_2Me	**3ea** 80 %
5	**1f**: R = 3-NO_2	**3fa** 71 %
6		
	1g	**3ga** 79 %
7		
	1h	**3ha** 80 %
8		
	1i	**3ia** 56 %
9		
	1j	**3ja** 85 %
10		
	1k	**3ka** 70 %
11		
	1l	**3la** 40 %

[a] The reaction was conducted using 0.26–0.41 mmol of vinyl azides **1**. [b] Yields of isolated product were recorded.

(marked in blue). The present methods allowed introduction of sterically hindered 2-methylphenyl group (for **3ad**) as the substituent R^4, as well as electron-deficient benzene rings (for **3af**–**3ah**). However, the reaction with electron-rich aldimine **2e** having a 4-methoxybenzene ring as R^4 resulted in no formation of the desired quinoline **3ae**. Synthesis of 2-



Scheme 5. Synthesis of quinolines **3**: scope of aldimines **2**. The reaction was conducted using 0.28–0.33 mmol vinyl azide **1a**.

ethoxy carbonyl quinoline **3ai** could be realized in good yield, while that of 2-isopropyl quinoline **3aj** resulted in moderate yield.

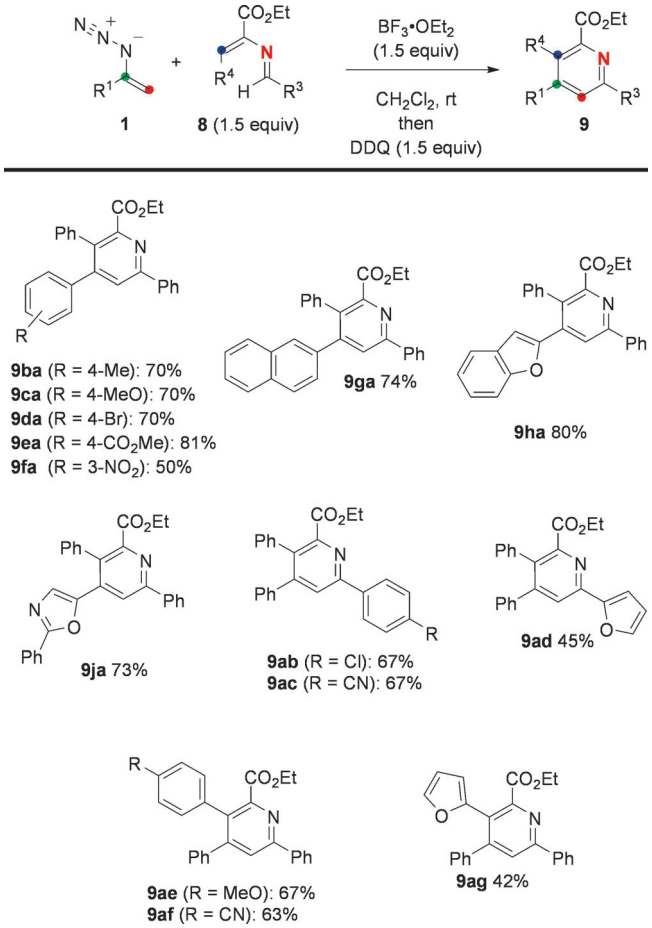
We explored the further potential of the present strategy using vinyl azides **1** for synthesis of pyridines.[17] In that respect, *N*-alkenyl aldimines (2-aza-diene) **8**[18] (1.5 equiv) were utilized as annulation partners with vinyl azides **1** (Scheme 6). Treatment of α-4-tolyl vinyl azide **1b** and *N*-alkenyl aldimine **8a** with BF_3·OEt_2 (1.5 equiv) proceeded smoothly at room temperature and subsequent addition of 2,3-dicyano-5,6-dichloro-1,4-benzoquinone (DDQ, 1.5 equiv) completed the aromatization to afford the corresponding pyridine **9ba** in 70 % yield. Similarly, by varying the substituent R^1 on vinyl azides **1**, various aromatic motifs could be installed for construction of the pyridine scaffold (for **9ca**–**9ha**, **9ja**).The present method allowed installation of various aromatic moieties as substituents R^3 and R^4 to provide the corresponding tetrasubstituted pyridines **9ab**–**9ag** in good to moderate yields.

In summary, we have developed a concise and robust method for synthesis of highly substituted quinolines and pyridines by BF_3·OEt_2-mediated formal [4+2]-annulation of vinyl azides and *N*-unsaturated aldimines. We anticipate that the present annulation strategy with vinyl azides is capable of supplying various azaheterocycles that are important in medicinal and materials application.

Experimental Section

*Typical Procedure: Synthesis of 2,4-diphenylquinoline (**3aa**, Scheme 3).*

To a solution of vinyl azide **1a** (1.45 g, 10.0 mmol) and *N*-phenyl benzaldimine **2a** (3.99 g, 22.0 mmol) in dichloromethane (0.2 M) was added dropwise BF_3·Et_2O (2.7 mL, 22.0 mmol) at 0 °C. After the addition, the reaction mixture was allowed to warm up to room temperature and was stirred for another 12 h. The reaction mixture was quenched with saturat-



Scheme 6. Synthesis of pyridines **9** by the reactions of vinyl azides **1** with azadienes **8**. The reaction was conducted using 0.22–0.42 mmol of vinyl azides **1**.

ed aqueous $NaHCO_3$ and diluted with water. The aqueous layer was extracted with dichloromethane. The combined extracts were washed with brine, dried over $MgSO_4$, and volatile components were evaporated. Purification of the crude product by flash chromatography (silica gel; hexane:ethyl acetate = 99: 1) afforded quinoline **3aa** (2.28 g, 8.10 mmol) in 81% yield and aniline **4a** (1.43 g, 7.80 mmol) in 78% yield.

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Keywords: annulation · azides · heterocycles · Lewis acids

[1] For general reviews, see: a) L. D. Quin, J. Tyrell, *Fundamentals of Heterocyclic Chemistry: Importance in Nature and in the Synthesis of Pharmaceuticals*, Wiley, New York, **2010**; b) *Comprehensive Heterocyclic Chemistry III* (Eds.: A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor), Pergamon, Oxford, **2008**; c) *Comprehensive Heterocyclic Chemistry II* (Eds.: A. R. Katritzky, E. F. V. Scriven, C. W. Rees), Pergamon, Oxford, **1996**; d) *Comprehensive Heterocyclic Chemistry* (Eds.: A. R. Katritzky, C. W. Rees), Pergamon, Oxford, **1984**; e) T. Eicher, S. Hauptmann, *The Chemistry of Heterocycles*, Wiley-VCH, Weinheim, **2003**.

[2] For selected reviews, see: a) G. L. Thomas, C. W. Johannes, *Curr. Opin. Chem. Biol.* **2011**, *15*, 516; b) R. Tohme, N. Darwiche, H. Gali-Muhtasib, *Molecules* **2011**, *16*, 9665; c) S. Dandapani, L. A. Marcaurelle, *Curr. Opin. Chem. Biol.* **2010**, *14*, 362; d) M. E. Welsch, S. A. Snyder, B. R. Stockwell, *Curr. Opin. Chem. Biol.* **2010**, *14*, 347; e) J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337.

[3] For reviews, see: a) N. Jung, S. Bräse, *Angew. Chem. Int. Ed.* **2012**, *51*, 12169; *Angew. Chem.* **2012**, *124*, 12335; b) S. Chiba, *Chimia* **2012**, *66*, 377; c) S. Chiba, *Synlett* **2011**, *23*, 21; d) K. Banert in *Organic Azides: Syntheses and Applications* (Eds.: S. Bräse, K. Banert), Wiley, **2010**, p. 115.

[4] For reviews, see: a) C. J. Moody in *Comprehensive Organic Synthesis*, *Vol. 7* (Eds.: B. M. Trost, I. Fleming, S. Ley), Pergamon, Oxford, **1991**, p. 21; b) B. C. G. Söderberg, *Curr. Org. Chem.* **2000**, *4*, 727.

[5] a) J. Bonnamour, C. Bolm, *Org. Lett.* **2011**, *13*, 2012; b) B. J. Stokes, H. Dong, B. E. Leslie, A. L. Pumphrey, T. G. Driver, *J. Am. Chem. Soc.* **2007**, *129*, 7500; c) H. Dong, M. Shen, J. E. Redford, B. J. Stokes, A. L. Pumphrey, T. G. Driver, *Org. Lett.* **2007**, *9*, 5191.

[6] For related reviews, see: a) B. J. Stokes, T. G. Driver, *Eur. J. Org. Chem.* **2011**, 4071; b) T. G. Driver, *Org. Biomol. Chem.* **2010**, *8*, 3831.

[7] Very recently, Yoon and Farney disclosed visible-light sensitization of vinyl azides using a transition-metal photocatalyst, see: E. P. Farney, T. P. Yoon, *Angew. Chem. Int. Ed.* **2014**, *53*, 793; *Angew. Chem.* **2014**, *126*, 812.

[8] a) Y.-F. Wang, G. H. Lonca, S. Chiba, *Angew. Chem. Int. Ed.* **2014**, *53*, 1067; *Angew. Chem.* **2014**, *126*, 1085; b) Y.-F. Wang, K. K. Toh, E. P. J. Ng, S. Chiba, *J. Am. Chem. Soc.* **2011**, *133*, 6411; c) E. P. J. Ng, Y.-F. Wang, S. Chiba, *Synlett* **2011**, 783; d) Y.-F. Wang, S. Chiba, *J. Am. Chem. Soc.* **2009**, *131*, 12570; e) Y.-F. Wang, K. K. Toh, S. Chiba, K. Narasaka, *Org. Lett.* **2008**, *10*, 5019.

[9] F.-L. Zhang, Y.-F. Wang, G. H. Lonca, X. Zhu, S. Chiba, *Angew. Chem. Int. Ed.* **2014**, *53*, 4390; *Angew. Chem.* **2014**, *126*, 4479.

[10] For reports on amide synthesis by protonation of vinyl azides, see: a) C. Qin, P. Feng, Y. Ou, T. Shen, T. Wang, N. Jiao, *Angew. Chem. Int. Ed.* **2013**, *52*, 7850; *Angew. Chem.* **2013**, *125*, 8004; b) A. Hassner, E. S. Ferdinandi, R. J. Isbister, *J. Am. Chem. Soc.* **1970**, *92*, 1672; c) H. W. Moore, H. R. Shelden, W. Weyler, Jr., *Tetrahedron Lett.* **1969**, *10*, 1243.

[11] N. Shindoh, H. Tokuyama, Y. Takemoto, K. Takasu, *J. Org. Chem.* **2008**, *73*, 7451.

[12] Banert reported [4+2]-annulation of 2-azido-1,3-butadienes with various dienophiles, see: a) K. Banert, A. Ihle, A. Kuhtz, E. Penk, B. Saha, E.-U. Würthwein, *Tetrahedron* **2013**, *69*, 2501; b) K. Banert, *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 879; *Angew. Chem.* **1987**, *99*, 932.

[13] The reactions of trimethylsilyl enol ether of acetophenone and styrene with imine **2a** under the present reaction conditions did not form the desired quinoline **3aa** at all. Akiyama reported synthesis of aryl-substituted quinolines from *N*-aryl benzaldimines and silyl enol ethers of acetophenones in a stepwise manner including CF_3SO_3H-mediated attack of silyl enol ethers to imines and cyclization followed by $Mn(OAc)_3$-mediated oxidative aromatization, see: T. Akiyama, S. Nakashima, K. Yokota, K. Fuchibe, *Chem. Lett.* **2004**, *33*, 922.

[14] For reviews on the reaction of *N*-aryl aldimines and electron-rich alkenes for synthesis of quinoline derivatives (the Povarov reaction), see: a) D. Bello, R. Ramon, R. Lavilla, *Curr. Org. Chem.* **2010**, *14*, 332; b) V. V. Kouznetsov, *Tetrahedron* **2009**, *65*, 2721.

[15] For a general review on synthesis of quinolines, see: V. V. Kouznetsov, L. Y. V. Méndez, C. M. M. Gómez, *Curr. Org. Chem.* **2005**, *9*, 141.

[16] Vinyl azides **1** were readily prepared from the corresponding alkenes by following the Hassner method via addition of IN_3 followed by elimination of HI with *t*BuOK, see: a) A. Hassner, F. W. Fowler, *Tetrahedron Lett.* **1967**, *8*, 1545; b) F. W. Fowler, A. Hassner, L. A.

Levy, *J. Am. Chem. Soc.* **1967**, *89*, 2077. Detailed experimental procedures are described in the Supporting Information.

[17] For general reviews on synthesis of pyridines, see: a) M. D. Hill, *Chem. Eur. J.* **2010**, *16*, 12052; b) M. C. Bagley, C. Glover, E. A. Merritt, *Synlett* **2007**, 2459; c) B. Heller, M. Hapke, *Chem. Soc. Rev.* **2007**, *36*, 1085; d) G. D. Henry, *Tetrahedron* **2004**, *60*, 6043; e) J. A. Varela, C. Saá, *Chem. Rev.* **2003**, *103*, 3787.

[18] For a preparation of *N*-alkenyl aldimines (2-aza-diene) **8**, see: a) J. Barluenga, M. Ferrero, F. Palacios, *J. Chem. Soc. Perkin Trans. 1* **1990**, 2193; b) J. Barluenga, M. Ferrero, F. Palacios, *Tetrahedron Lett.* **1988**, *29*, 4863.

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COMMUNICATION

Heterocycles

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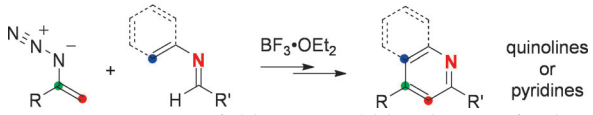
Formal [4+2]-Annulation of Vinyl Azides with N-Unsaturated Aldimines



Brought to you by the letter *N*: Highly functionalized quinolines and pyridines could be synthesized by $BF_3{\cdot}OEt_2$-mediated reactions of vinyl azides with *N*-aryl and *N*-alkenyl aldimines, respectively. The reaction mechanism could be characterized as formal [4+2]-annulation, including unprecedented enamine-type nucleophilic attack of vinyl azides to aldimines with subsequent nucleophilic cyclization of the resulting imine intermediates.