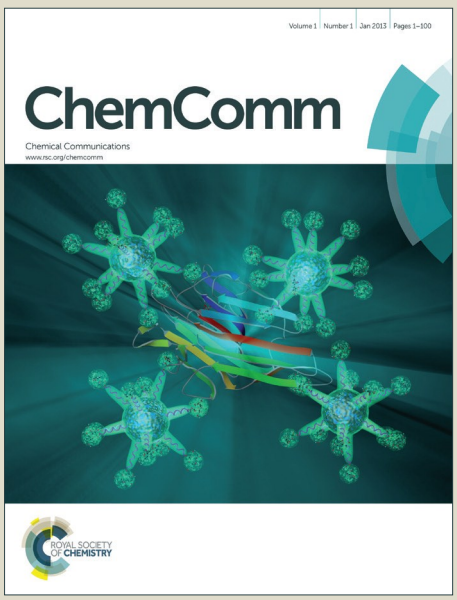
ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: X. Zhu and S. Chiba, *Chem. Commun.*, 2016, DOI: 10.1039/C5CC10299E.



View Article Online
DOI: 10.1039/C5CC10299E

Journal Name

COMMUNICATION

Construction of 1-Pyrroline Skeletons by Lewis Acid-Mediated Conjugate Addition of Vinyl Azides

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

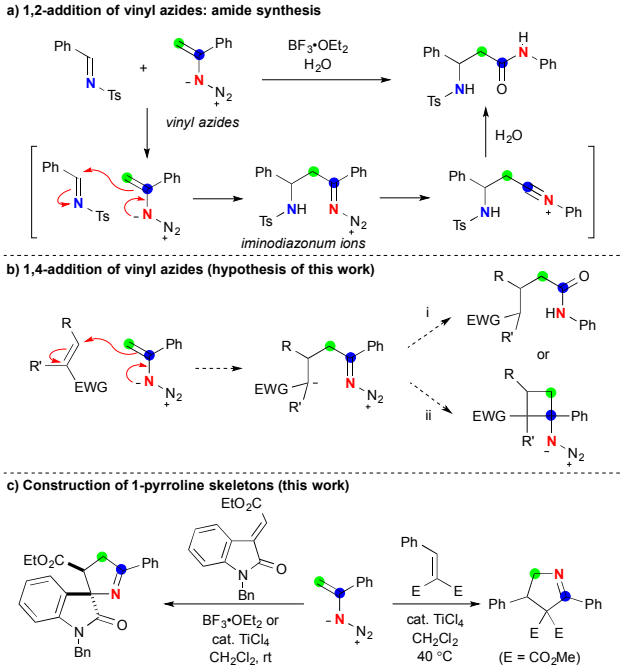
www.rsc.org/

Xu Zhu[a] and Shunsuke Chiba*[a]

Lewis acid-mediated conjugate addition of vinyl azides to electron-deficient alkenes led to the efficient construction of 1-pyrroline skeletons. The reactions of vinyl azides with 3-alkylidene-2-oxoindolines afford 3',4'-dihydrospiro[indoline-3,2'-pyrrol]-2-ones in diastereoselective fashion, whereas those with dimethyl 2-alkylidenemalonates provide 4,5-dihydro-3*H*-pyrroles.

In seeking to develop new and efficient methods for nitrogen-containing molecules, vinyl azides have been recently employed as the source of three-atom unit including one nitrogen.[1] As one of their unique chemical reactivities, of particular interest to us is that they perform as an enamine-type nucleophile to various carbon electrophiles such as imines, aldehydes, and carbocations derived from alcohols, constructing the new C-C bond in the presence of Lewis/Brønsted acid activators.[2] Unlike the Stork enamine reaction that concurrently forms an iminium ion,[3] the C-C bond formation with vinyl azides generates a distinct reactive intermediate, namely, an iminodiazonium ion. For example, the reactions of vinyl azides with *N*-Ts imines proceed smoothly in the presence of BF_3•OEt_2 to form β-amino amides via the Schmidt type rearrangement[4] of iminodiazonium ion intermediates (Scheme 1-a).[2a,5]

We became interested in using this enamine-type nucleophilic reactivity of vinyl azides for conjugate addition onto α,β-unsaturated carbonyl compounds.[6] In this case, the iminodiazonium ion bearing the γ-carbanion might be generated (Scheme 1-b). We wondered if this iminodiazonium intermediates might undergo formation of amides via the Schmidt rearrangement (path-i) or azidocyclobutanes through cyclization of the carbanion onto the C=N bond[7] (path-ii). We herein report construction of 1-pyrroline skeletons enabled by



Scheme 1 Enamine-type nucleophilic reactivity of vinyl azides.

sequence of Lewis-acid promoted conjugate addition of vinyl azides and denitrogenative ring-expansion of transient azidocyclobutane intermediates (Scheme 1-c).[8] Changing the conjugate electrophiles uniquely switched the atom composition of the resulting 1-pyrroline skeletons derived from vinyl azides.

To elucidate our hypothesis, 3-alkylidene-2-oxoindoline **1a** was first chosen as the conjugate electrophile for the reactions of vinyl azide **2a**. Extensive screening of acid-promoters and solvents reveled two complementary reaction conditions using BF_3•OEt_2 (2 equiv, conditions **A**) or $TiCl_4$ (10 mol%, conditions **B**) in CH_2Cl_2 are optimal (Scheme 2), providing 3',4'-dihydrospiro[indoline-3,2'-pyrrol]-2-one **3aa** as a single diastereomer in excellent yields.[9,10] The process could

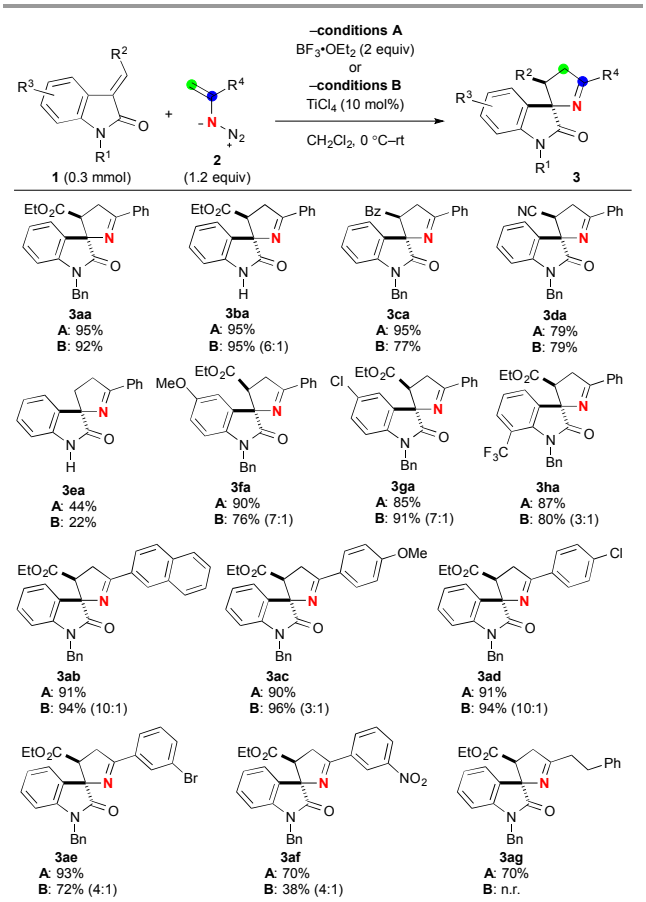
[a] *Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore.*

† Footnotes relating to the title and/or authors should appear here.

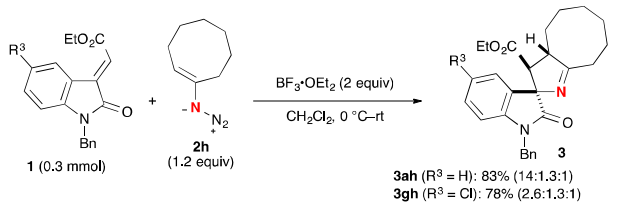
Electronic Supplementary Information (ESI) available: Electronic Supplementary Information (ESI) available: Experimental details, including procedures, syntheses and characterization of new compounds; ^{1}H and ^{13}C NMR spectra. CCDC 1436809 – 1436815. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C5CC10299E

construct a 1-pyrroline scaffold as the part of the spiro structure of **3aa**. As the molecules having 2,3'-pyrrolidinyl spirooxindole skeletons exhibit a wide spectrum of biological activities,[11,12] this finding stimulated us further to investigate the substrate scope. The process did not require protection (R^1) on the nitrogen of 2-oxoindoline **1b**, giving *N*-H product **3ba** in good yields. By changing R^2 on the alkene of **1**, the present method allowed for installation of benzoyl and cyano groups to give the corresponding azaspirocyclic products **3ca** and **3da**, respectively in good yields, whereas the reaction with terminal alkene (**1e**, R^1 = H) resulted in poor yields of **3ea**. Investigation of the substituent compatibility (R^3) on the benzene ring of 2-oxoindoline **1** revealed that methoxy, chloro, and trifluoromethyl groups were well tolerated (for **3fa**-**3ha**). Next, we examined the scope of vinyl azides **2** in the reactions with **1a**. As the substituent R^4, a variety of aromatic groups could be introduced without diminution of the chemical yields for **3ab**-**3af** except for nitro-substituted **3af** under the $TiCl_4$-catalyzed reaction conditions **B**. It is worthy to note that alkyl substituted vinyl azide **2g** was amenable to the present process for synthesis of **3ag** under BF_3-mediated reaction conditions **A**. In the general trend, the reactions under the BF_3-mediated reaction conditions **A** provided single diastereomers of **3**, whereas those under the $TiCl_4$-catalzyed



Scheme 2 Synthesis of 3',4'-dihydrospiro[indoline-3,2'-pyrrol]-2-ones **3**.

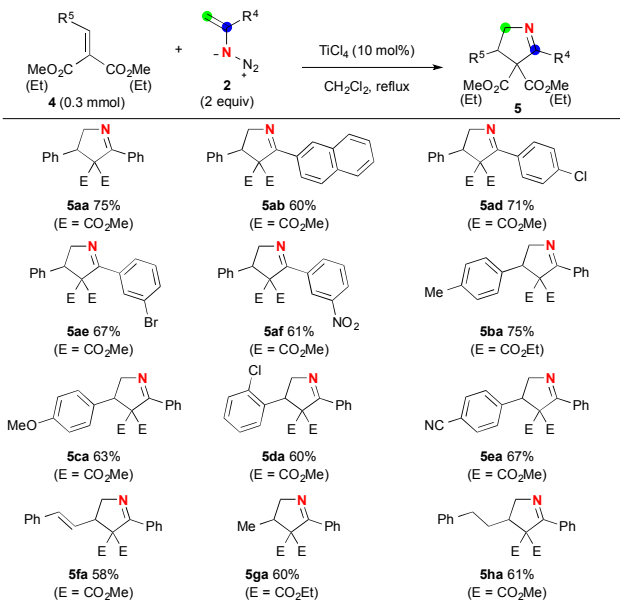


Scheme 3 The reactions with 1-azidocyclooctene **2h**. The chemical structure of the major isomer is shown.

reaction conditions **B** resulted in formation of a mixture of the diastereomers.

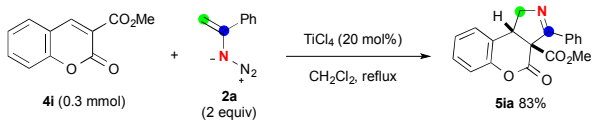
Interestingly, the reaction of 1-azidocyclooctene **2h** with 3-alkylidene-2-oxoindoline **1a** under the BF_3-mediated reaction conditions delivered unique polycyclic system **3ah** in highly diastereoselective manner (Scheme 3), whereas that with chlorine-substituted **1g** somehow lowered the diastereoselectivity of **3gh**.

To further broaden the scope of the present 1-pyrroline synthesis, we turned our attention to use 2-alkylidenemalonates **4** (Scheme 4). It was found that the reaction of dimethyl 2-benzylidenemalonate **4a** with vinyl azide **2a** was enabled only by $TiCl_4$-catalyzed reaction conditions in CH_2Cl_2 at 40 °C, providing 1-pyrroline **5aa** in 75% yield (see ESI for optimization of the reaction conditions).[13,14] Elucidation of the chemical structure of **5aa** revealed that the reaction process unambiguously involves C-C bond fission of the vinyl moiety of **2a** (marked in blue and green), which is distinct from the formation of azaspirocycle **3**. By varying the substituent R^4 on vinyl azides **2**, various aryl motifs could be introduced for efficient construction of 1-pyrrolines **5aa**-**5af**.[15] On the other hand, as substituents R^5 on alklidenemalonates **4**, the process



Scheme 4 Synthesis of 1-pyrrolines **5**.

View Article Online
DOI: 10.1039/C5CC10299E



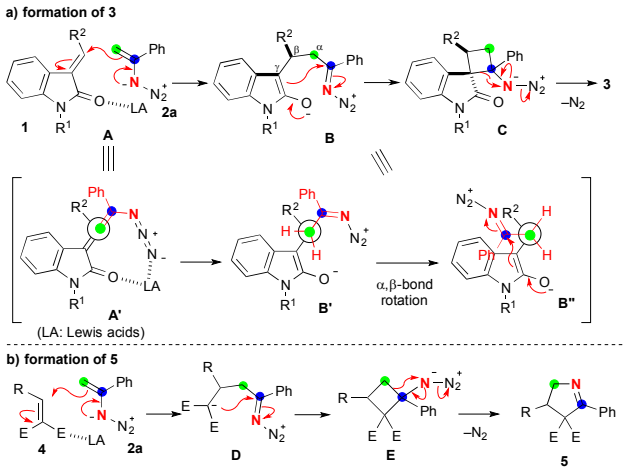
Scheme 5 The reaction with 2-oxo-2*H*-chromene-3-carboxylate (**4i**).

allowed for installing not only aryl (for **5ba**-**5ea**) and alkenyl (for **5fa**) groups but also alkyl groups (for **5ga** and **5ha**).

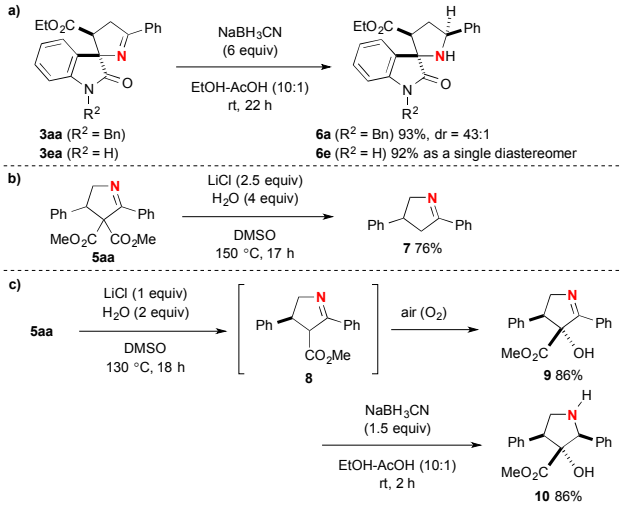
The reaction of methyl 2-oxo-2*H*-chromene-3-carboxylate (**4i**) with vinyl azide **2a** also proceeded well to give 2-chromanone-1-pyrroline hybrid **5ia** in good yield (Scheme 5).

To elucidate the reaction mechanisms for the formation of 1-pyrrolines **3** and **5**, a series of control experiments were conducted (see ESI for more details). These results as well as characterization of the side products[14] implicated that the present processes are composed of step-wise sequence initiated by conjugate addition of vinyl azides **2** to the α,β-unsaturated electrophiles **1** or **4**, that is followed by cyclization to give azidocyclobutane intermediates. For the formation of 3',4'-dihydrospiro[indoline-3,2'-pyrrol]-2-ones **3** (Scheme 6-a), alignment of alkylidene-2-oxoindolines **1** and vinyl azides **2** in the 1st 1,4-addition might be controlled by coordination of the Lewis acids to both **1** and **2** in state **A'** to afford iminodiazonium ions **B**. In prior to the 2nd cyclization, rotation of the Cα-Cβ bond in the states **B'** should be necessary to form **B"**, leading to the formarion of cyclobutane intermediates **C** in diastereoselective manner.[16,17] The quaternary carbon on the 2-oxoindoline core finally migrated to the azide nitrogen atom to give azaspirocycles **3**. On the other hand, as for the formation of 1-pyrrolines **5** from 2-alkylidenemalonates **4** (Scheme 6-b), similarly formed cyclobutane intermediates **E** might undergo ring-expansion to give 1-pyrrolines **5**. In this case, migration of the secondary carbon (marked in green) was predominant over that of the quaternary carbon due to its deactivation by two methoxycarbonyl groups.

Finally, we demonstrated concise chemical conversions of 1-pyrroline products **3aa**, **3ea**, and **5aa** (Scheme 7). Highly diastereoselective reduction of the C=N bond of **3aa** and **3ea**



Scheme 6 Proposed reaction mechanisms for the 1-pyrroline formations.



Scheme 7 Chemical transformations of **3aa**, **3ea** and **5aa**.

could be achieved by $NaBH_3CN$ to give 2,3'-pyrrolidinyl spirooxiindoles **6a** and **6e**, respectively, in which hydride approached from the opposite face from the benzene ring of the 2-oxoindoline moiety (Scheme 7-a). Decarboxylation of **5aa** could be controlled precisely by the reaction temperature.[18] Namely, treatment of **5aa** with LiCl in the presence of H_2O in DMSO at 150 °C resulted in double decarboxylation to give **7** in 76% yield (Scheme 7-b), whereas that at 130 °C gave mono-decarboxylation product to afford **8**, further autooxidation of which under air delivered 3-hydroxy-1-pyrroline **9** in 86% yield as a single diastereomer (Scheme 7-c).[19] Furthermore, $NaBH_3CN$ reduction of the C=N bond of **9** afforded densely functionalized pyrrolidine **10** in 86% yield as a single diastereomer.

We anticipate that the present methods are capable of supplying various pyrrolidine-based azaheterocycles of medicinal importance.[20] Further studies are in progress to elucidate the detailed reaction mechanism and to upgrade the present transformations to catalytic enantioselective variants.

This work was supported by funding from Nanyang Technological University (NTU) and the Singapore Ministry of Education (Academic Research Fund Tier 1: 2015-T1-001-040). We thank Dr. Yongxin Li and Dr. Rakesh Ganguly (Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University) for assistance in X-ray crystallographic analysis.

Notes and references

1 For reviews, see: (a) B. Hu and S. G. DiMagno, *Org. Biomol. Chem*., 2015, **13**, 3844; (b) N. Jung and S. Bräse, *Angew. Chem., Int. Ed*., 2012, **51**, 12169; (c) S. Chiba, *Chimia*,, 2012, *66*, 377; d) S. Chiba, *Synlett,* 2012, **23**, 21; (d) K. Banert, In *Organic Azides: Syntheses and Applications*; S. Bräse and K. Banert, Eds.; Wiley, 2010; p 115; (e) B. J. Stokes and T. G. Driver, *Eur. J. Org. Chem*., 2011, 4071; (f) T. G. Driver, *Org. Biomol. Chem*., 2010, **8**, 3831.

View Article Online
DOI: 10.1039/C5CC10299E

2 (a) F.-L. Zhang, Y.-F. Wang, G. H. Lonca, X. Zhu and S. Chiba, *Angew. Chem., Int. Ed.,* 2014, **53**, 4390; (b) F.-L. Zhang, X. Zhu and S. Chiba, *Org. Lett.,* 2015, **16**, 6136; (c) X. Zhu, Y.-F. Wang, F.-L. Zhang and S. Chiba, *Chem. Asian J*., 2014, **9**, 2458.

3 (a) *The Chemistry of Enamines*; Z. Rappoport, Ed.; Wiley, New York, 1994; (b) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Terrell, *J. Am. Chem. Soc*.,1963, **85**, 207.

4 (a) A. Wrobleski, T. C. Coombs, C. W. Huh, S.-W. Li and J. Aubé, *Org. React*., 2012, **78**, 1; (b) S. Grecian and J. Aubé, In *Organic Azides: Syntheses and Applications*; S. Bräse and K. Banert, Eds.; Wiley: Chichester, U.K., 2010; p 191; (c) S. Lang and J. A. Murphy, *Chem. Soc. Rev*., 2006, **35**, 146; (d) S. Bräse, C. Gil, K. Knepper and V. Zimmermann, *Angew. Chem., Int. Ed*., 2005, **44**, 5188.

5 The Jiao group applied the protonation of vinyl azides for Au-catalzyed synthesis of amides from alkynes and $TMSN_3$, see: C. Qin, P. Feng, Y. Ou, T. Chen, T. Wang and N. Jiao, *Angew. Chem., Int. Ed*., 2013, **52**, 7850.

6 For general reviews on conjugate addition reactions, see: (a) P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992; (b) H.-G. Schmalz, In *Comprehensive Organic Synthesis*; B. M. Trost, I. Fleming, Eds.; Pergamon: Oxford, 1991; Vol. 4, Chapter 1.5.; (c) B. E. Rossiter and N. M. Swingle, *Chem. Rev*., 1992, **92**, 771.

7 (a) H. K. Hall, Jr., M. Abdelkader and M. E. Glogowski, *J. Org. Chem*., 1982, **47**, 3691; (b) K. C. Brannock, A. Bell, R. D. Burpitt and C. A. Kelly, *J. Org. Chem*., 1961, **26**, 625.

8 The reactions of vinyl azides with cyclopentadienones and tri/tetracyanoethylenes were previously reported, while the different types of cycloaddition products from the present works were obtained via distinct reaction pathways, see: (a) A. Hassner, D. J. Anderson and R. H. Reuss, *Tetrahedron Lett*., 1977, **18**, 2463; (b) K. Banert, *Chem. Ber*., 1989, **122**, 123.

9 For reviews on construction of spirooxindole skeletons from 3-alkylidene-2-oxoindolines, see: (a) D. Cheng, Y. Ishihara, B. Tan and C. F. Barbas III, *ACS Catal.,* 2014, **4**, 743; (b) L. Hong and R. Wang, *Adv. Synth. Catal*., 2013, **355**, 1023; (c) N. R. Ball-Jones, J. J. Badillo and A. K. Franz, *Org. Biomol. Chem*., 2012, **10**, 5165.

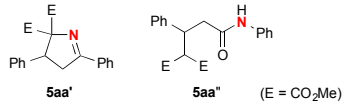
10 The chemical structures of **3aa**, **3ca**, **3da**, **3gh**, **5ia**, **6a**, and **10** were elucidated by X-ray crystallographic analyses. See ESI for more details.

11 For recent reports on synthesis of 3,2'-pyrrolidinylspirooxindole derivatives and their biological activities, see: (a) Y. A. Ivanenkov, S. V. Vasilevski, E. K. Beloglazkina, M. E. Kukushkin, A. E Machulkin, M. S.Veselov, N. V. Chufarova, E. S. Chernyaginab, A. S. Vanzcool, N. V. Zyk, D. A. Skvortsov, A. A. Khutornenko, A. L. Rusanov, A. G. Tonevitsky, O. A. Dontsova, A. G. Majouga, *Bioorg. Med. Chem. Lett*., 2015, **25**, 404; (b) W. Tan, X.-T Zhu, S. Zhang, G.-J. Xing, R.-Y. Zhu and F. Shi, *RSC Adv.,* 2013, **3**, 10875; (c) M. A. Ali,; R. Ismail, T. S. Choon, R. S. Kumar, H. Osman, N. Arumugam, A. I. Almansour, K. Elumalai and A. Singh, *Bioorg. Med. Chem. Lett.,* 2012, **22**, 508; (d) G. Bhaskar, Y. Arun, C. Balachandran, C. Saikumar and P. T. Perumal, *Eur. J. Med. Chem.,* 2012, **51**, 79.

12 Several methods for asymmetric construction of 2,3'-pyrrolidinyl spirooxyindoles have been recently developed, see: (a) J. P. Macdonald, B. H. Shupe, J. D. Schreiber and A. K. Franz, *Chem. Commun*., 2014, **50**, 5242; (b) Y.-M. Cao, F.-F. Shen, F.-T. Zhang and R. Wang, *Chem. Eur. J*., 2013, **19**, 1184; (c) F. Shi, Z.-L. Tao, S.-W. Luo, S.-J. Tu and L.-Z. Gong, *Chem. Eur. J*., 2012, **18**, 6885.

13 For recent selected reports on synthesis of 1-pyrrolines, see: (a) A. Faulkner, J. S. Scott and J. F. Bower, *J. Am. Chem. Soc*., 2015, **137**, 7224; (b) H. Sun, W. Li, Z. Xuan and W. Yu, *Adv. Synth. Catal*., 2015, **357**, 64; (c) A. Faulkner, N. J. Race, J. S. Scott and J. F. Bower, *Chem. Sci*., 2014, **5**, 2416; (d) J. J. Badillo, C. J. A. Ribeiro, M. M. Olmstead and A. K. Franz, *Org. Lett*., 2014, **16**, 6270; (e) M. Bingham, C. Moutrille and S. Z. Zard, *Heterocycles,* 2014, **88**, 953; (f) K. K. Toh, A. Biswas, Y.-F. Wang, Y. Y. Tan and S. Chiba, *J. Am. Chem. Soc*., 2014, **136**, 6011; (g) A. Faulkner, J. S. Scott and J. F. Bower, *Angew. Chem., Int. Ed*., 2012, **51**, 1675; (h) N. Chandan, A. L. Thompson and M. G. Moloney, *Org. Biomol. Chem*., 2012, **10**, 7863; (i) D.-S. Wang, Z.-S. Ye, Q.-A. Chen, Y.-G. Zhou, C.-B. Yu, H.-J. Fan and Y. Duan, *J. Am. Chem. Soc*., 2011, **133**, 8866; (j) A. D. Melhado, G. W. Amarante, Z. J. Wang, M. Luparia and F. D. Toste, *J. Am. Chem. Soc*. 2011, **133**, 3517; (k) M. Strohmeier, K. Leach and M. A. Zajac, *Angew. Chem., Int. Ed*., 2011, **50**, 12335. (l) K. Narasaka and M. Kitamura, *Eur. J. Org. Chem*., 2005, 4505.

14 From the reaction of **2a** and **4a** in 2 mmol scale, in addition to the formation of **5aa** (73% yield), we could isolate and characterize another 1-pyrroline **5aa'** and acylic amide **5aa''** (>1% yields) as shown below. See ESI for the reaction mechanisms for the formation of **5aa'** and **5aa".**



15 The reaction with alkyl-substituted vinyl azide **2g** did not provide the corresponding 1-pyrroline **5ag** at all.

16 Similar diastereochemical outcomes have been observed in Lewis acid-catalyzed carboannulation of 3-alkylidene-2-oxoindolines with allylsilanes, see: N. R. Ball-Jones, J. J. Badillo, N. T. Tran and A. K. Franz, *Angew. Chem., Int. Ed*., 2014, **53**, 9462.

17 Presumably, rotation of the C(β)-C(γ) bond in the iminodiazonium ion **B** is prevented by the steric hindrance.

18 S. S. More, T. K. Mohan, Y. S. Kumar, U. K. S. Kumar and N. B. Patel, *Beilstein J. Org. Chem*., 2011, **7**, 831.

19 (a) A. Dehnel, J. M. Kanabus-Kaminska and G. Lavielle, *Can. J. Chem*., 1988, *66*, 310; (b) O. Tsuge, K. Ueno, S. Kanemasa and K. Yorozu, *Bull. Chem. Soc. Jpn*., 1986, **59**, 1809.

20 (a) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem*., 2014, **57**, 10257; (b) L. D. Quin and J. Tyrell, *Fundamentals of Heterocyclic Chemistry: Importance in Nature and in Synthesis of Pharmaceuticals*; Wiley-Interscience: Hoboken, NJ, 2010.