Organic LETTERS

Letter

pubs.acs.org/OrgLett

Base-Catalyzed Selective Synthesis of 2-Azabicyclo[3.2.0]hept-2-enes and Sulfonyl Vinyl-Substituted Pyrroles from 3-Aza-1,5-enynes

Xiaoyi Xin, Haolong Wang, Xincheng Li, Dongping Wang, and Boshun Wan*

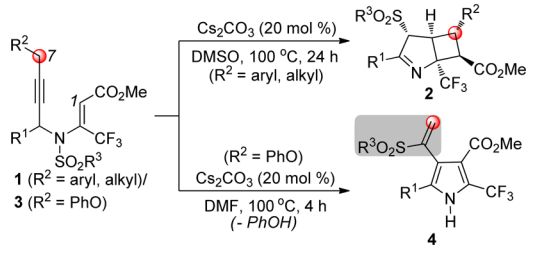
Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, China

Supporting Information

ABSTRACT: A base-catalyzed selective cycloisomerization of 3-aza-1,5-enynes is developed. This transformation provides a facile access to highly functionalized 2-azabicyclo[3.2.0]hept-2-enes and sulfonyl vinyl-substituted pyrroles. The chemoselectivity was controlled by the substituent pattern of the substrates.

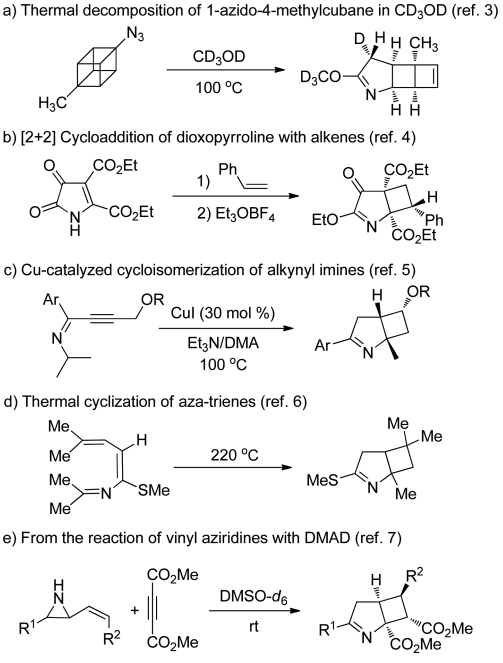
Cycloisomerization of enynes has emerged as a powerful strategy for the synthesis of heterocycles and carbocycles.[1] Higher levels of molecular complexity and better functional group compatibilities can be achieved from relatively simple and readily accessible starting materials. In most cases, transition-metal catalysts were usually essential. In terms of the product patterns, five- or six-membered monocyclic and cyclopropane-bridged bicyclic compounds were the most common products.[1] Herein, we report a transition-metal-free synthesis of densely functionalized 2-azabicyclo[3.2.0]hept-2-enes and sulfonyl vinyl-substituted pyrroles from 3-aza-1,5-enynes (Scheme 1).

Scheme 1. Cycloisomerization of 3-Aza-1,5-enynes



2-Azabicyclo[3.2.0]hept-2-ene is a unique kind of bicyclic heterocycle.[2] The limited reports on their synthesis are divided into the following five methods: (1) thermal decomposition of 1-azido-4-methylcubane in CD_3OD (Scheme 2a);[3] (2) [2 + 2] cycloaddition of dioxopyrroline with alkenes (Scheme 2b);[4] (3) Cu-catalyzed cycloisomerization of alkynyl imines (Scheme 2c);[5] (4) thermal cyclization of aza-trienes at 220 °C (Scheme 2d);[6] and (5) reaction of vinyl aziridines with dimethyl acetylenedicarboxylate (DMAD) (Scheme 2e).[7] Meanwhile, vinyl sulfones are important sulfur-containing functional groups and have found widespread applications in biological research and drug design.[8] The synthetic procedures for the construction of vinyl sulfones often require toxic or unstable

Scheme 2. Summary for Approaches



starting materials and several steps.[9] The method in this work provides a straightforward strategy where α-substituted vinyl sulfone functional groups and pyrrole rings[10] are built simultaneously in one step.

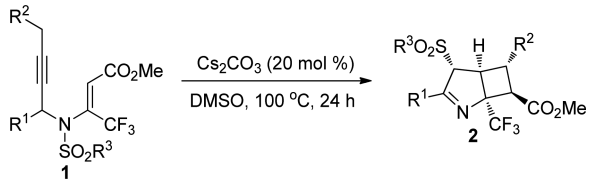
In the course of our continuous transformation of the six-atom skeleton of 3-aza-1,5-enynes to diverse heterocycles and carbocycles,[11] we reasoned that if one additional exploitable CH_2 group (C7 in substrates **1** and **3**, Scheme 1) existed in the previous framework then the newly added carbon atom may be

Received: May 20, 2015
Published: August 7, 2015

DOI: 10.1021/acs.orglett.5b01474
Org. Lett. 2015, 17, 3944–3947

incorporated into the product skeleton, thus leading to more complex heterocycles. We initiated our study with aza-enyne **1a** (see Table 1 for structure) as model substrate to test its

Table 1. Substrate Scope and Limitations[a]



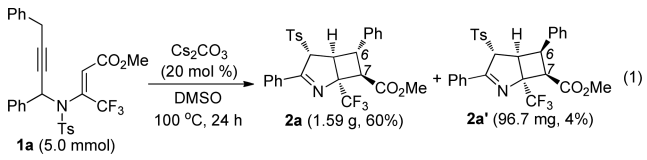
entry	1	R^1	R^2	R^3	2, yield[b] (%)
1	**1a**	Ph	Ph	4-MeC_6H_4	**2a**, 56
2	**1b**	4-MeC_6H_4	Ph	4-MeC_6H_4	**2b**, 41
3	**1c**	2-$MeOC_6H_4$	Ph	4-MeC_6H_4	**2c**, –[c]
4	**1d**	4-FC_6H_4	Ph	4-MeC_6H_4	**2d**, 44
5	**1e**	2-ClC_6H_4	Ph	4-MeC_6H_4	**2e**, 35
6	**1f**	3-ClC_6H_4	Ph	4-MeC_6H_4	**2f**, 45
7	**1g**	4-BrC_6H_4	Ph	4-MeC_6H_4	**2g**, 54
8	**1h**	2-$CF_3C_6H_4$	Ph	4-MeC_6H_4	**2h**, 13[d]
9	**1i**	2-naphthyl	Ph	4-MeC_6H_4	**2i**, 54
10	**1j**	Ph	4-MeC_6H_4	4-MeC_6H_4	**2j**, 45
11	**1k**	Ph	4-$MeOC_6H_4$	4-MeC_6H_4	**2k**, 56
12	**1l**	Ph	4-FC_6H_4	4-MeC_6H_4	**2l**, 40
13	**1m**	^{n}Bu	Ph	4-MeC_6H_4	**2m**, -[e]
14	**1n**	^{n}Bu	^{n}Pr	4-MeC_6H_4	**2n**, -[e]
15	**1o**	Ph	Et	4-MeC_6H_4	**2o**, 52[f]
16	**1p**	Ph	^{n}Pr	4-MeC_6H_4	**2p**, 51
17	**1q**	Ph	Bn	4-MeC_6H_4	**2q**, 34
18	**1r**	Ph	Cl	4-MeC_6H_4	**2r**, -[c]
19	**1s**	4-FC_6H_4	Ph	Ph	**2s**, 50
20	**1t**	2-ClC_6H_4	Ph	Ph	**2t**, 43
21	**1u**	Ph	Ph	4-$NO_2C_6H_4$	**2u**, 25

[a]Reaction conditions: **1** (0.4 mmol), Cs_2CO_3 (20 mol %), DMSO (8 mL), argon atmosphere, 100 °C, 24 h. [b]Isolated yields. [c]Very complicated mixtures; the desired product was not successfully isolated. [d]0.8 mmol scale. [e]No reaction. [f]1.0 mmol scale.

reactivity. To our delight, 2-azabicyclo[3.2.0]hept-2-ene **2a** was obtained. The structure of **2a** was unambiguously confirmed by X-ray crystal diffraction analysis (see the Supporting Information). Sulfonyl group migration[11a,12] was observed in this reaction. After screening of catalysts, solvents, and reaction temperatures, the following reaction conditions were chose as the optimized reaction conditions: 20 mol % of Cs_2CO_3 as catalyst, DMSO as solvent, under 100 °C for 24 h (see Table S1 in the Supporting Information for details).

With the optimized reaction conditions in hand, we then directly investigated the scope of this transformation (Table 1). Both electron-deficient and electron-rich groups on aromatic groups (R^1) were tolerated in this reaction, giving low to moderate yields (13%–56%, entries 1–8). Unfortunately, 2-MeO-substituted substrate **1c** gave very complicated mixtures, and the desired products were not successfully isolated (entry 3). 2-CF_3-substituted **1h** gave very low yield (entry 8). A fused ring was also suitable in this reaction (entry 9). The alkyl (R^1) substrates did not react under the standard condations with recovery of the starting materials **1m** and **1n** (entries 13 and 14). Aryl and alkyl groups (R^2) were both tolerated (entries 10–12 and 15–17). The Cl-substituted **1r** also yielded a very complicated mixture (entry 18). When R^3 was 4-$NO_2C_6H_4$, a relatively lower yield was obtained (entry 21 versus entry 1).

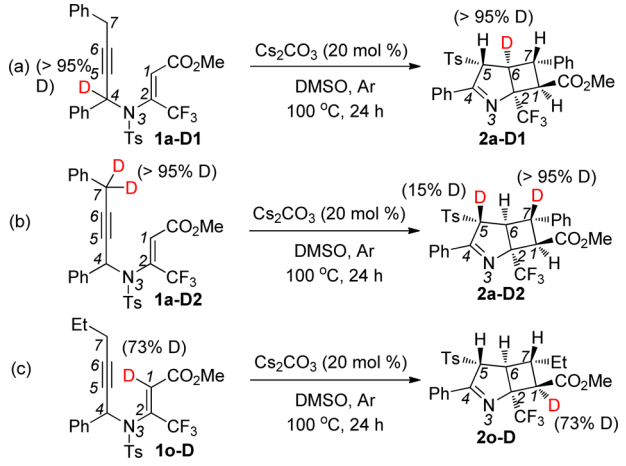
We also carried out the experiment on a larger scale (eq 1). Besides the major product **2a**, its stereoisomer **2a′** (two groups



at the C6 and C7 position are in a *syn* relationship; see the Supporting Information) was also obtained albeit in very low yield (4%).

To probe the reaction mechanism, deuterium-labeling experiments were carried out (Scheme 3). Substrate deuterated

Scheme 3. Mechanistic Studies

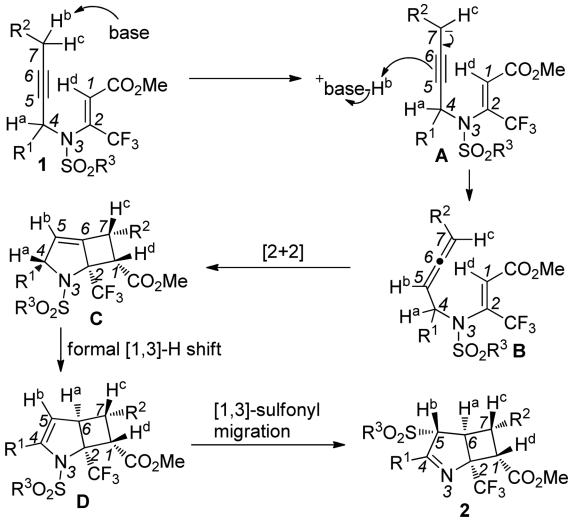


at the C4-position (**1a-D1**) was subjected to the standard reaction conditions, and the D atom was incorporated completely into the C6-position of the product (**2a-D1**) (Scheme 3a). One of the two D atoms at the C7 position (**1a-D2**) appeared at C7 position of the product (**2a-D2**) with no deuterium scrambling, and another D atom at C7 position was incorporated at the C5 position of **2a-D2** with scrambling of the D atom (Scheme 3b). Substrate deuterated at the C1-position (**1o-D**) was also subjected to the standard reaction conditions, and the D atom was incooporated into the C1-position of the product (**2o-D**) without any scrambling (Scheme 3c).

A plausible reaction mechanism for the formation of 2-azabicyclo[3.2.0]hept-2-enes based on the deuterium-labeling experiments is depicted in Scheme 4. The base (Cs_2CO_3) abstracts one of the two protons (marked as H^b) at C7-position of reactant **1** to form the allene intermediate **B**. It is competitive that abstraction of a proton of reactant **1** by the base at C4- and C7-position. The proton at C4-position is more acidic but has more steric hindrance. In contrast, the proton at C7-position is less acidic yet has less steric hindrance. The proton abstraction occurs at the C7-position is favorable probably because steric hindrance factor is dominant. The [2 + 2] cycloaddition between the akene and one of the double bonds in the allene moiety of **B** gives the heterocyclic itermediate **C**. Then [1,3]-shift of the H atom at C4-position (marked as H^a) to form the intermediate **D** (H^a appears at C6-position in **D**). Finally, [1,3]-sulfonyl migration generates the 2-azabicyclo[3.2.0]hept-2-ene **2**. The overall outcome is that H^a at C4-position of the starting material appears at the C6-position of the product, H^b connects

DOI: 10.1021/acs.orglett.5b01474
Org. Lett. 2015, 17, 3944–3947

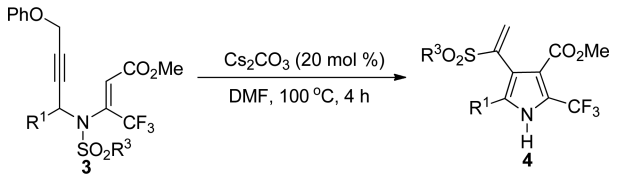
Scheme 4. Proposed Mechanism for the Formation of 2



to the C5, and H^c and H^d remain connected to the same carbon atoms, C7 and C1, respectively. This illustrates well the D-incorporated experiments (Scheme 3).

Along with the study went through, we found that phenoxy-substituted aza-enyne **3** could generate a new kind of heterocycle, 4-(1-sulfonylvinyl)-2-(trifluoromethyl)-1*H*-pyrrole **4**, which contains a vinyl sulfone functional group (see Table 2 for structures). The structure of **4a** was also unambiguously confirmed by X-ray crystal diffraction analysis (see the Supporting Information). And sulfonyl group migration[11a,12] also occurred in this reaction. After screening of solvents and reaction temperatures using Cs_2CO_3 (20 mol %) as catalyst and **3a** as model substrate, the optimal conditions were chose as following: DMF as solvent, under 100 °C for 4 h (see Table S2 in the Supporting Information for details).

Table 2. Scope of the Synthesis of Pyrrole 4[a]



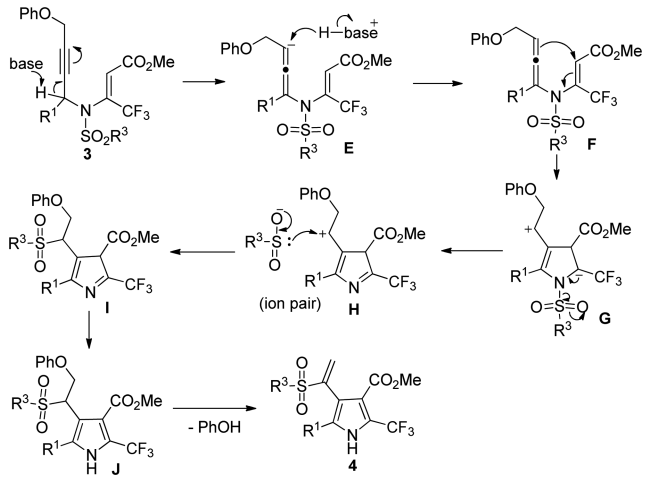
entry	3	R^1	R^3	4	yield[b] (%)
1	**3a**	Ph	4-$CH_3C_6H_4$	**4a**	88
2	**3b**	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	**4b**	69
3	**3c**	2-$CH_3OC_6H_4$	4-$CH_3C_6H_4$	**4c**	53
4	**3d**	4-FC_6H_4	4-$CH_3C_6H_4$	**4d**	86
5	**3e**	2-ClC_6H_4	4-$CH_3C_6H_4$	**4e**	85
6	**3f**	4-BrC_6H_4	4-$CH_3C_6H_4$	**4f**	78
7	**3g**	4-IC_6H_4	4-$CH_3C_6H_4$	**4g**	62
8	**3h**	2-$CF_3C_6H_4$	4-$CH_3C_6H_4$	**4h**	86
9	**3i**	1-naphthyl	4-$CH_3C_6H_4$	**4i**	79
10	**3j**	4-FC_6H_4	C_6H_5	**4j**	85
11	**3k**	4-FC_6H_4	4-ClC_6H_4	**4k**	83

[a]Reaction conditions: **3** (0.4 mmol), Cs_2CO_3 (20 mol %), DMF (4 mL), argon atmosphere, 100 °C, 4 h. [b]Isolated yields.

We directly investigated the scope of this reaction (Table 2). Aryl R^1 groups bearing electron-neutral groups (entry 1), electron-donating groups (entries 2 and 3), and electron-withdrawing groups (entries 4–8) were well tolerated, and the desired products were isolated with moderate to high yields. A fused ring was also suitable for this process (entry 9). The electronic properties of the sulfonyl group (R^3) had a relatively small impact on the yield (entries 4, 10, and 11).

The proposed mechanism for the formation of pyrrole **4** is described in Scheme 5. The propargyl moiety of **3** is transformed into allene **F** first. Cyclization of **F** generates intermediate **G**. An ion pair **H** is formed through N–S bond cleavege. The recombination of the cation and the anion of **H** results in the formation of the C–S bond of **I**, and then **I** aromatized to pyrroles **J**.[11a] Finally, pyrrole **J** eliminates phenol to afford the double bond of product **4**.

Scheme 5. Proposed Mechanism for the Formation of 4



In summary, we have developed diverse transition-metal-free methods to transform the aza-enyne building blocks to 2-azabicyclo[3.2.0]hept-2-enes and sulfonyl vinyl functionalized pyrroles under mild conditions. The chemoselectivity was controlled by the substituent pattern of the substrates. These distinctive reaction pathways and the structural novel products maybe will bring new opportunities to the chemistry of enyne cycloisomerization. Further mechanism research on the formation of 2-azabicyclo[3.2.0]hept-2-enes and sulfonyl vinyl functionalized pyrroles is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01474.

X-ray crystallographic data for **2a** (CIF)
X-ray crystallographic data for **2a′** (CIF)
X-ray crystallographic data for **2o** (CIF)
X-ray crystallographic data for **3a** (CIF)
X-ray crystallographic data for **4a** (CIF)
Experimental procedures, characterization data, copies of NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

* bswan@dicp.ac.cn

DOI: 10.1021/acs.orglett.5b01474
Org. Lett. 2015, 17, 3944–3947

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by NSFC (21172218).

■ REFERENCES

(1) For selected reviews on enyne cycloisomerization, see: (a) Fensterbank, L.; Malacria, M. *Acc. Chem. Res.* **2014**, *47*, 953. (b) Obradors, C.; Echavarren, A. M. *Acc. Chem. Res.* **2014**, *47*, 902. (c) Marinetti, A.; Jullien, H.; Voituriez, A. *Chem. Soc. Rev.* **2012**, *41*, 4884. (d) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. (e) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (f) Zhang, Z.; Zhu, G.; Tong, X.; Wang, F.; Xie, X.; Wang, J.; Jiang, L. *Curr. Org. Chem.* **2006**, *10*, 1457. (g) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (h) Añorbe, L.; Domínguez, G.; Pérez-Castells, J. *Chem. - Eur. J.* **2004**, *10*, 4938. (i) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813.

(2) The analogies of 2-azabicyclo[3.2.0]hept-2-enes were found in several natural products and biologically active compounds; see: (a) Fitch, R. W.; Spande, T. F.; Garraffo, H. M.; Yeh, H. J. C.; Daly, J. W. *J. Nat. Prod.* **2010**, *73*, 331. (b) Attia, M. I.; Güclü, D.; Hertlein, B.; Julius, J.; Witt-Enderby, P. A.; Zlotos, D. P. *Org. Biomol. Chem.* **2007**, *5*, 2129. (c) Hata, K.; Masuda, M.; Nakai, H.; Taniyama, D.; Tobinaga, H.; Hato, Y.; Fujiu, M. WO 2013/061977A1, 2013. (d) Smith, M.; Dick, S.; Baker, J.; WO 2011/018613A1, 2011. (e) Yet, S.; Ying, L.; Wang, C.; Long, J.; Qui, Y.-L. WO 2009/003009A1, 2009. (f) Tang, P.; Lin, Z.; Yang, J.; Zhao, F.; Wang, Y.; Wang, Q.; WO 2008/148279A1, 2008.

(3) Eaton, P. E.; Hormann, R. E. *J. Am. Chem. Soc.* **1987**, *109*, 1268.

(4) (a) Sano, T.; Enomoto, H.; Kurebayashi, Y.; Horiguchi, Y.; Tsuda, Y. *Chem. Pharm. Bull.* **1993**, *41*, 471. (b) Sano, T.; Horiguchi, Y.; Kambe, S.; Tsuda, Y. *Heterocycles* **1981**, *16*, 363.

(5) (a) Zhou, Y.; Chi, Y.; Zhao, F.; Zhang, W.-X.; Xi, Z. *Chem. - Eur. J.* **2014**, *20*, 2463. (b) Sromek, A. W.; Rheingold, A. L.; Wink, D. J.; Gevorgyan, V. *Synlett* **2006**, *2006*, 2325.

(6) (a) Brandsma, L.; Nedolya, N. A. *Synthesis* **2004**, *2004*, 735. (b) Nedolya, N. A.; Brandsma, L.; Trofimov, B. A. *Chem. Heterocycl. Compd.* **2002**, *38*, 1230. (c) Brandsma, L.; Nedolya, N. A.; Verkruijsse, H. D.; Owen, N. L.; Du, L.; Trofimov, B. A. *Tetrahedron Lett.* **1997**, *38*, 6905.

(7) Baktharaman, S.; Afagh, N.; Vandersteen, A.; Yudin, A. K. *Org. Lett.* **2010**, *12*, 240.

(8) (a) Morales-Sanfrutos, J.; Lopez-Jaramillo, J.; Ortega-Muñoz, M.; Megia-Fernandez, A.; Perez-Balderas, F.; Hernandez-Mateo, F.; Santoyo-Gonzalez, F. *Org. Biomol. Chem.* **2010**, *8*, 667. (b) Kerr, I. D.; Lee, J. H.; Farady, C. J.; Marion, R.; Rickert, M.; Sajid, M.; Pandey, K. C.; Caffrey, C. R.; Legac, J.; Hansell, E.; McKerrow, J. H.; Craik, C. S.; Rosenthal, P. J.; Brinen, L. S. *J. Biol. Chem.* **2009**, *284*, 25697. (c) Meadows, D. C.; Gervay-Hague, J. *Med. Res. Rev.* **2006**, *26*, 793.

(9) For a review on the synthesis of vinyl sulfones, see: (a) Simpkins, N. S. *Tetrahedron* **1990**, *46*, 6951. For selected reports on the synthesis of α-substituted vinyl sulfones, see: (b) Xi, Y.; Dong, B.; McClain, E. J.; Wang, Q.; Gregg, T. L.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 4657. (c) Chawla, R.; Kapoor, R.; Singh, A. K.; Yadav, L. D. S. *Green Chem.* **2012**, *14*, 1308. (d) Qian, H.; Huang, X. *Synlett* **2001**, *2001*, 1913. (e) Inomata, K.; Sasaoka, S.-i.; Kobayashi, T.; Tanaka, Y.; Igarashi, S.; Ohtani, T.; Kinoshita, H.; Kotake, H. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1767. (f) Inomata, K.; Kobayashi, T.; Sasaoka, S.; Kinoshita, H.; Kotake, H. *Chem. Lett.* **1986**, *15*, 289. (g) Hendrickson, J. B.; Palumbo, P. S. *Tetrahedron Lett.* **1985**, *26*, 2849. (h) Hsiao, C.-N.; Shechter, H. *Tetrahedron Lett.* **1982**, *23*, 3455. (i) Back, T. G.; Collins, S. *J. Org. Chem.* **1981**, *46*, 3249. (j) Kotake, H.; Inomata, K.; Sumita, M. *Chem. Lett.* **1978**, *7*, 717. (k) Chodroff, S.; Whitmore, W. *J. Am. Chem. Soc.* **1950**, *72*, 1073.

(10) For selected reviews on synthesis of pyrroles, see: (a) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2014**, *43*, 4633. (b) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084. (c) Joshi, S. D.; More, U. A.; Kulkarni, V. H.; Aminabhavi, T. M. *Curr. Org. Chem.* **2013**, *17*, 2279. (d) Liu, T.; Fu, H. *Synthesis* **2012**, *44*, 2805. (e) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402.

(11) (a) Xin, X.; Wang, D.; Li, X.; Wan, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 1693. (b) Xin, X.; Wang, D.; Wu, F.; Li, X.; Wan, B. *J. Org. Chem.* **2013**, *78*, 4065. (c) Xin, X.; Wang, D.; Wu, F.; Wang, C.; Wang, H.; Li, X.; Wan, B. *Org. Lett.* **2013**, *15*, 4512.

(12) For a review on functional group migration, see: (a) Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Aldrichchimica Acta* **2010**, *43*, 37. For selected reports on sulfonyl group migration, see: (b) Boominathan, S. S. K.; Senadi, G. C.; Vandavasi, J. K.; Chen, J. Y.-F.; Wang, J.-J. *Chem. - Eur. J.* **2015**, *21*, 3193. (c) Xu, X.-H.; Taniguchi, M.; Wang, X.; Tokunaga, E.; Ozawa, T.; Masuda, H.; Shibata, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 12628. (d) Wang, D.; Wang, F.; Song, G.; Li, X. *Angew. Chem., Int. Ed.* **2012**, *51*, 12348. (e) Zhu, Y.; Lu, W.-T.; Sun, H.-C.; Zhan, Z.-P. *Org. Lett.* **2013**, *15*, 4146. (f) Stokes, B. J.; Liu, S.; Driver, T. G. *J. Am. Chem. Soc.* **2011**, *133*, 4702. (g) Nakamura, I.; Yamagishi, U.; Song, D.; Konta, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 2284.

DOI: 10.1021/acs.orglett.5b01474
Org. Lett. 2015, 17, 3944−3947