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Rhodium(II)-Catalyzed Formal [3 + 2] Cycloaddition of *N*-Sulfonyl-1,2,3-triazoles with Isoxazoles: Entry to Polysubstituted 3-Aminopyrroles

Xiaoqiang Lei,[†,‡] Longbo Li,[‡] Yu-Peng He,[*,†] and Yefeng Tang[*,‡,§]

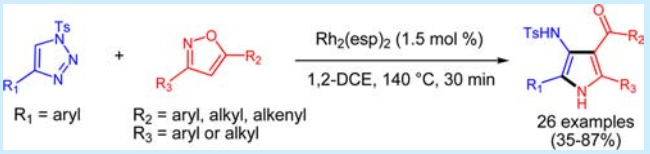
[†]College of Chemistry, Chemical Engineering and Environmental Engineering, Liaoning Shihua University, Dandong Lu West 1, Fushun 113001, China

[‡]Comprehensive AIDS Research Center, Department of Pharmacology & Pharmaceutical Sciences, School of Medicine, Tsinghua University, Beijing 100084, China

[§]Collaborative Innovation Center for Biotherapy, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, West China Medical School, Sichuan University, Chengdu 610041, China

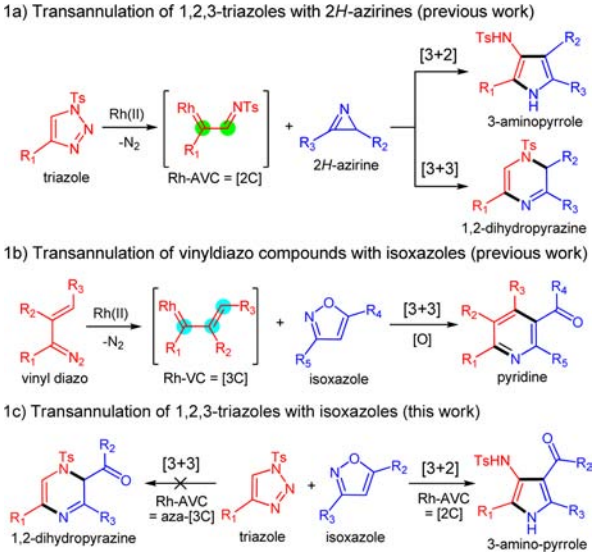
Supporting Information

ABSTRACT: A novel rhodium(II)-catalyzed formal [3 + 2] cycloaddition of *N*-sulfonyl-1,2,3-triazoles with isoxazoles has been achieved that provides an efficient method for the synthesis of polysubstituted 3-aminopyrrole derivatives. An operationally simple one-pot synthesis of the titled compounds from terminal alkynes, tosyl azide, and isoxazoles was also developed. The presented reaction affords an illustrative example of employing 1,2,3-triazoles as the [2C]-component in relevant cycloaddition reactions.



N-Sulfonyl 1,2,3-triazoles have recently emerged as capable precursors for the synthesis of various nitrogen heterocycles.[1] Upon treatment with rhodium(II) catalysts, *N*-sulfonyl 1,2,3-triazoles readily undergo denitrogenative reaction to form Rh(II)−azavinylcarbene (Rh−AVC, Scheme 1a), a versatile intermediate that could promote a wide range of transformations. Thus far, the applications of Rh−AVC as [1C]- or aza-[3C]-synthons in cycloaddition reactions have been well explored.[2,3] However, its potential as a [2C]-synthon remains underdeveloped. In early 2015, we disclosed a novel Rh(II)-catalyzed transannulation of *N*-sulfonyl 1,2,3-triazoles with 2*H*-azirines, which allowed the divergent synthesis of polysubstituted 3-aminopyrroles and 1,2-dihydropyrazines, respectively, via formal [3 + 2] and [3 + 3] cycloadditions (Scheme 1a).[4] Notably, two highly relevant works were independently reported by Shi and Lee.[5] The above studies[4,5a] represent the first two examples of the application of Rh−AVC as a [2C]-synthon in cycloaddition reactions, thus opening new prospects for the emerging area of research.

Scheme 1. Rh(II)−Carbene-Promoted Formal [3 + 2] and [3 + 3] Cycloadditions



Isoxazoles represent a class of important heterocycles in organic synthesis.[6] Great efforts have been made to develop new methods for their preparation.[7] In turn, they could also serve as precursors for the synthesis of other valuable scaffolds.[8] Indeed, one of the key structural elements of isoxazoles relies on the fact that they possess a relatively labile N−O bond that could be readily cleaved and then integrated into a new heterocycle.[8a−c] As a paradigm, Davies recently developed an intriguing Rh(II)-catalyzed transannulation of isoxazoles with vinyl diazo compounds.[8a] In this reaction, the isoxazole partner reacts with Rh−vinylcarbene (Rh−VC) to form an isoxazolium ylide intermediate, which then undergoes sequential ring-opening with cleavage of the N−O bond, 6π electrocyclization, and oxidative dehydrogenation to afford polysubstituted pyridine (Scheme 1b). In view of the resemblance between

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the above-mentioned Rh−AVC and Rh−VC species, we assumed that a Rh(II)-catalyzed aza-[3 + 3] cycloaddition between *N*-sulfonyl 1,2,3-triazoles and isoxazoles could be also feasible, which would lead to 1,2-dihydropyrazine derivatives (Scheme 1c). As a part of our continuing interest on the development of novel transformations for the synthesis of heterocycles of biological importance,[4,9] we report herein the progress we have achieved on this subject. Interestingly, while the originally proposed chemistry failed to work as expected, a novel [3 + 2] cycloaddition was discovered in practice, which resulted in highly functionalized 3-aminopyrroles as products (Scheme 1c).

We commenced our studies by treatment of 1-tosyl-1*H*-1,2,3-triazole **1a** (1.5 equiv) and 5-phenyl-3-propylisoxazole **2a**[10] (1.0 equiv) with 1.5 mol % of $Rh_2(oct)_4$ in 1,2-DCE at 140 °C. The starting materials were consumed quickly, providing a major product in 47% isolated yield. However, careful analysis of the NMR spectroscopic data of the product showed that it was not the expected dihydropyrazine product but a 3-amino-4-acylpyrrole derivative, as represented by the structure of **3a** (Table 1). This discovery, despite being unexpected, deserved

Table 1. Optimization of Reaction Conditions[a]

entry	catalyst	temp (°C)	time	yield[b] (%)
1	$Rh_2(oct)_4$	140	30 min	47
2	$Rh_2(OAc)_4$	140	30 min	24
3	Rh_2(*S*-DOSP)$_4$	140	30 min	trace
4	Rh(*S*-PTAD)$_4$	140	30 min	trace
5	$Rh_2(esp)_2$	140	30 min	84
6	$Rh_2(esp)_2$	140	3 h	<10
7	$Rh_2(esp)_2$	120	1 h	65
8	$Rh_2(esp)_2$	160	30 min	41
9[c]	$Rh_2(esp)_2$	140	30 min	81
10	$Rh_2(esp)_2$	140, microwave	10 min	78
11[d]	$Rh_2(esp)_2$	140	30 min	44

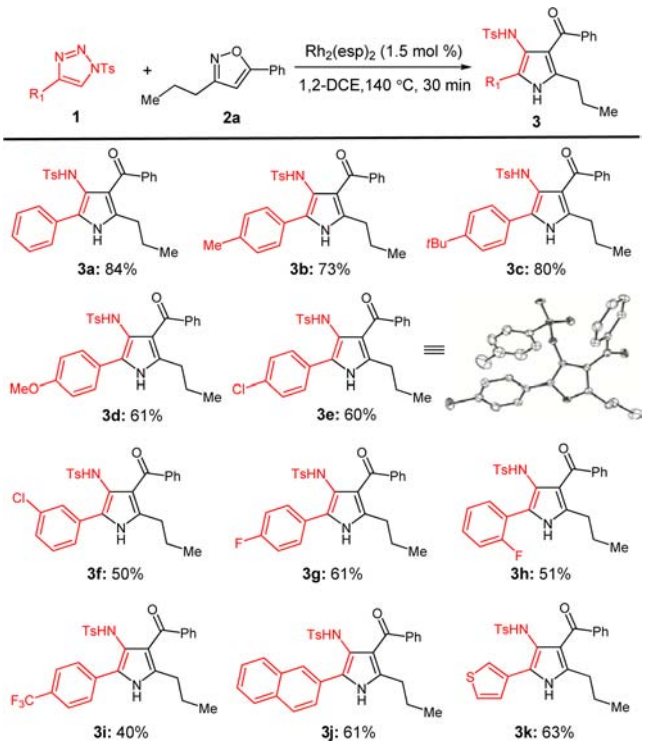
[a]Reaction conditions: **1a** (0.30 mmol), **2a** (0.20 mmol), and Rh(II) cat. (3.0 μmol) in DCE (1.0 mL). [b]Isolated yield. [c]4 Å molecular sieves was used. [d]1:1 ratio of **1a**/**2a** was employed. DCE = dichloroethane, oct = octanoate, (*S*)-DOSP = 4-(dodecylphenyl)-sulfonyl-(2*S*)-prolinate, (*S*)-PTAD = *N*-phthaloyl-(*S*)-adamantylglycine, esp = α,α,α,α-tetramethyl-1,3-benzenedipropanoate.

further investigation, since the resulting polysubstituted 3-aminopyrroles represent a class of unique structural element distributed in various natural products and bioactive molecules,[11] and thus, the development of new methods for their synthesis has been a subject of significant interest.[12] Moreover, the *N*-sulfonyl 1,2,3-triazole **1a** involved in this reaction serves as a [2C]- rather than commonly seen aza-[3C]-component, which showcases the great potential of Rh−AVC as a versatile synthon.

To improve the efficiency of the above transformation, we conducted a systematic condition screening with **1a** and **2a** as standard substrates. First, the effect of Rh(II) catalyst was examined. It was shown that while $Rh_2(oct)_4$, Rh_2(*S*-DOSP)$_4$, and Rh(*S*-PTAD)$_4$ led to poor conversion (entries 2−4), $Rh_2(esp)_2$[13] displayed superior reactivity to afford an excellent yield of **3a** (84%, entry 5). This observation was in agreement with our previous results.[4] We also found that the reaction temperature had a notable influence on the outcomes. Both lower and higher temperatures than 140 °C gave inferior results (entries 6−8). In addition, we attempted to conduct the reaction in the presence of 4 Å molecular sieves or microwave irradiation; however, no improvement could be made (entries 9 and 10). Finally, it turned out that the use of 1.5 equiv of 1,2,3-triazole was required to ensure satisfactory results since a decreased yield was obtained when a 1:1 ratio of **1a**/**2a** was employed in the reaction (entry 11).

Having the optimal conditions in hands, we sought to evaluate the generality of the reaction. First of all, a broad range of 4-aryltriazoles were evaluated with **2a** as the reactant partner (Scheme 2). It was shown that all of the examined reactions

Scheme 2. Scope of 1,2,3-Triazoles[a,b]



[a]Reaction conditions: **1** (0.30 mmol), **2a** (0.20 mmol), and $Rh_2(esp)_2$ (3.0 μmol) in DCE (1.0 mL) at 140 °C. [b]Isolated yield.

worked smoothly to provide the corresponding products in good to acceptable yields. The substrates bearing electron-donating or -withdrawing substituents were well tolerated, although the former generally gave a slightly higher yields than the latter. The orientation of the substitute also showed some impact on the efficacy, while the *para*- and *meta*-substituted substrates gave better results than the *ortho*-substituted ones (**3e** vs **3f**; **3g** vs **3h**). Moreover, the reaction could be applied to the triazoles bearing other aromatic rings, as shown by the case of **3i** and **3j**. However, when some 4-alkyltriazoles were submitted to the current conditions, they failed to give satisfying results (structures not shown). Of note, the structure of **3e** was unambiguously determined by X-ray crystallography.[14]

Next, the scope of the isoxazole partner was also systematically evaluated, as shown in Scheme 3. Not surprisingly, an array of 3-alkyl-5-arylisoxazoles exhibited reactivity similar to that of **2a** and provided the corresponding products **3l−o** in

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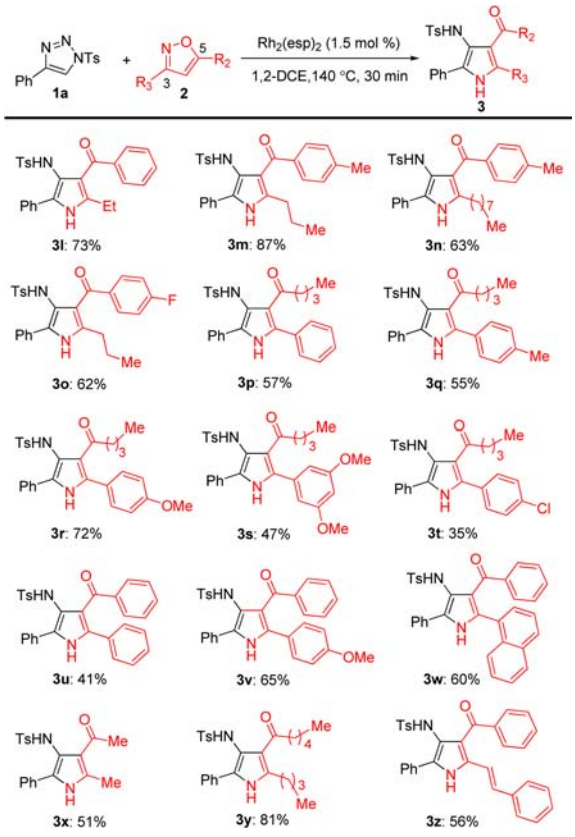
Scheme 3. Scope of Isoxazoles[a,b]



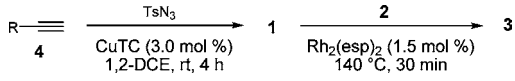
[a]Reaction conditions: **1a** (0.30 mmol), **2** (0.20 mmol), and $Rh_2(esp)_2$ (3.0 μmol) in DCE (1.0 mL) at 140 °C. [b]Isolated yield.

good yields. Moreover, 3-aryl-5-alkylisoxazoles also proved to be suitable substrates for the transformation, although in some cases the yields were moderate (e.g., **3s** and **3t**). This transformation could also be extended to 3,5-diarylisoxazoles and 3,5-dialkylisoxazoles, as shown by the cases of **3u**–**y**. Notably, the substrate bearing an alkenyl substituent on the C-5 position of **2** was also tolerated, which further extended the substrate scope of the method. However, both monosubstituted (e.g., 5-methylisoxazole) and trisubstituted isoxazoles (e.g., 3,5-dimethyl-4-phenylisoxazole) failed to give promising results under the present conditions (results not shown).

To simplify the operation of above transformations, we also developed a one-pot protocol for the synthesis of *N*-aminopyrrole derivatives from terminal alkynes, tosyl azide, and isoxazoles. As a proof of concept, phenylacetylene **4** was treated with TsN_3 in the presence of CuTC (3.0 mol %) in 1,2-DCE at room temperature for 4 h. The resulting mixtures, without isolation, were further treated with isoxazole **2a** (0.7 equiv) and $Rh_2(esp)_2$ (1.5 mol %) at 140 °C for 30 min, which afforded **3a** in 77% yield (entry 1, Table 2). This one-pot protocol was also applied to some other terminal alkynes (**4b** and **4c**) and isoxazoles (**2h**, **2n**, and **2o**). Gratifyingly, all of them gave satisfying yields that are comparable to those obtained in the stepwise reactions (entries 2–6).

Finally, a plausible mechanism for the title reaction is depicted in Scheme 4. Thus, Rh–AVC **A**, once generated from 1,2,3-triazole **1**, could react **2** to form isoxazolium ylide **B**, which then underwent ring opening with cleavage of the N–O bond to form azatriene **C**. At this point, there are two possibilities for **C** to evolve into different products. In the path

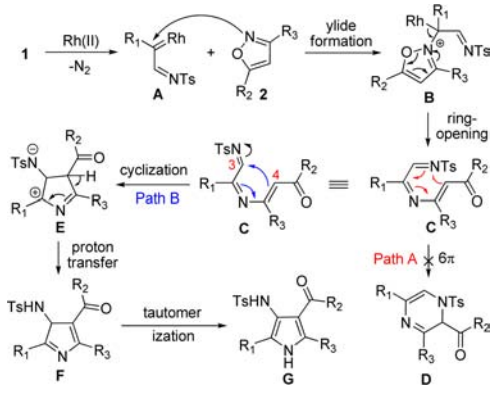
Table 2. One-Pot Synthesis of 3-Aminopyrroles[a]



entry	alkyne	isoxazole	product: yield[b] (%)
1	**4a**: R = Ph	**2a**: R_2 = *n*-C_3H_7; R_3 = Ph	**3a**: 77
2	**4b**: R = 4-Me-Ph	**2a**	**3b**: 72
3	**4c**: R = 4-*t*Bu-Ph	**2a**	**3c**: 82
4	**4a**	**2h**: R_3 = 4-MeO-Ph; R_2 = *n*-C_4H_9	**3r**: 63
5	**4a**	**2n**: R_3 = R_2 = Me	**3x**: 54
6	**4a**	**2o**: R_3 = *n*-C_5H_{11}; R_2 = *n*-C_4H_9	**3y**: 80

[a]Reaction conditions: **4** (0.50 mmol), TsN_3 (0.50 mmol), and CuTc (15.0 μmol) in DCE (1.5 mL); then **2** (0.33 mmol), Rh(II) catalyst (5.0 μmol). [b]Isolated yield.

Scheme 4. Plausible Mechanisms



A, it may convert into 1,2-dihydropyrazine **D** via a 6 π electrocyclization, as we have originally imagined. Alternatively, **C** could undergo a 5-*exo*-*trig* cyclization between the nucleophilic C-4 and electrophilic C-3, thus affording zwitterionic intermediate **E**.[15] After proton transfer followed by tautomerization, **E** could advance to the final product **G**. Interestingly, while path A takes place predominantly in the reaction reported by Davies (Scheme 1b),[8a] path B appears favorable in the current scenario, most likely attributed to the presence of a highly electrophilic imine moiety in the intermediate **C**. In this context, the inherent nature of Rh–AVC endows it some unique reactivity distinct from its all-carbon counterpart, that is, the Rh–VC species.

In summary, we have developed a novel Rh(II)-catalyzed formal [3 + 2] cycloaddition of *N*-sulfonyl-1,2,3-triazoles with isoxazoles, which enables the rapid access of polysubstituted *N*-aminopyrroles from the readily available precursors. The presented chemistry, in conjunction with the precedent,[4,5a] clearly illustrates the attractive potential of Rh–AVC as [2C]-synthon in cycloaddition reactions. Efforts to develop new reactions following this direction are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, spectral data, and spectra of all new compounds (PDF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: yupeng.he@aliyun.com.
*E-mail: yefengtang@tsinghua.edu.cn.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For leading reviews, see: (a) Chattopadhyay, B.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 862. (b) Gulevich, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2013**, *52*, 1371. (c) Davies, H. M. L.; Alford, J. S. *Chem. Soc. Rev.* **2014**, *43*, 5151.

(2) For selected examples of Rh-AVC as a [1C]-synthon, see: (a) Chuprakov, S.; Kwok, S. W.; Zhang, L.; Lercher, L.; Fokin, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 18034. (b) Grimster, N.; Zhang, L.; Fokin, V. V. *J. Am. Chem. Soc.* **2010**, *132*, 2510. (c) Zibinsky, M.; Fokin, V. V. *Org. Lett.* **2011**, *13*, 4870. (d) Alford, J. S.; Davies, H. M. L. *Org. Lett.* **2012**, *14*, 6020. (e) Miura, T.; Biyajima, T.; Fujii, T.; Murakami, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 194. (f) Miura, T.; Tanaka, T.; Biyajima, T.; Yada, A.; Murakami, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 3883. (g) Chuprakov, S.; Worrell, B. T.; Selander, N.; Sit, R. K.; Fokin, V. V. *J. Am. Chem. Soc.* **2014**, *136*, 195.

(3) For selected examples of Rh-AVC as an aza-[3C]-synthon, see: (a) Horneff, T.; Chuprakov, S.; Chernyak, N.; Gevorgyan, V.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 14972. (b) Miura, T.; Yamauchi, M.; Murakami, M. *Chem. Commun.* **2009**, *45*, 1470. (c) Chattopadhyay, B.; Gevorgyan, V. *Org. Lett.* **2011**, *13*, 3746. (d) Schultz, E. E.; Sarpong, R. *J. Am. Chem. Soc.* **2013**, *135*, 4696. (e) Miura, T.; Hiraga, K.; Biyajima, T.; Nakamuro, T.; Murakami, M. *Org. Lett.* **2013**, *15*, 3298. (f) Chuprakov, S.; Kwok, S. W.; Fokin, V. V. *J. Am. Chem. Soc.* **2013**, *135*, 4652. (g) Parr, B. T.; Green, S. A.; Davies, H. M. J. *J. Am. Chem. Soc.* **2013**, *135*, 4716.

(4) Wang, Y. H.; Lei, X. Q.; Tang, Y. F. *Chem. Commun.* **2015**, *51*, 4507.

(5) For [3 + 2] cycloadditions of 1,2,3-triazoles with 2*H*-azirines, see: (a) Zhao, Y. Z.; Yang, H. B.; Tang, X. Y.; Shi, M. *Chem. - Eur. J.* **2015**, *21*, 3562. For [3 + 3] cycloadditions, see: (b) Ryu, T.; Baek, Y.; Lee, P. H. *J. Org. Chem.* **2015**, *80*, 2376.

(6) For leading reviews on this topic, see: (a) Hu, F.; Szostak, M. *Adv. Synth. Catal.* **2015**, *357*, 2583. (b) Pinho e Melo, T. M. V. D. *Curr. Org. Chem.* **2005**, *9*, 925.

(7) For selected recent examples, see: (a) Schmitt, D. C.; Lam, L.; Johnson, J. S. *Org. Lett.* **2011**, *13*, 5136. (b) Zheng, H.; McDonald, R.; Hall, D. G. *Chem. - Eur. J.* **2010**, *16*, 5454. (c) Jackowski, O.; Lecourt, T.; Micouin, L. *Org. Lett.* **2011**, *13*, 5664. (d) Oakdale, J. S.; Sit, R. K.; Fokin, V. V. *Chem. - Eur. J.* **2014**, *20*, 11101. (e) Kankala, S.; Vadde, R.; Vasam, C. S. *Org. Biomol. Chem.* **2011**, *9*, 7869. (f) Zhu, X.; Wang, Y. F.; Ren, W.; Zhang, F. L.; Chiba, S. *Org. Lett.* **2013**, *15*, 3214.

(8) For selected examples, see: (a) Manning, J. R.; Davies, H. M. *J. Am. Chem. Soc.* **2008**, *130*, 8602. (b) Coffman, K. C.; Palazzo, T. A.; Hartley, T. P.; Fettinger, J. C.; Tantillo, D. J.; Kurth, M. J. *Org. Lett.* **2013**, *15*, 2062. (c) Zhou, A. H.; He, Q.; Shu, C.; Yu, Y. F.; Liu, S.; Zhao, T.; Zhang, W.; Lu, X.; Ye, L. W. *Chem. Sci.* **2015**, *6*, 1265. (d) Kawai, H.; Tachi, K.; Tokunaga, E.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 7803. (e) Liu, X. L.; Han, W. Y.; Zhang, X. M.; Yuan, W. C. *Org. Lett.* **2013**, *15*, 1246. (f) Takikawa, H.; Takada, A.; Hikita, K.; Suzuki, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 7446.

(9) (a) Shang, H.; Wang, Y.; Tian, Y.; Feng, J.; Tang, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 5662. (b) Tian, Y.; Wang, Y. H.; Shang, H.; Xu, X. D.; Tang, Y. F. *Org. Biomol. Chem.* **2015**, *13*, 612. (c) Feng, J.; Wang, Y. H.; Li, Q. G.; Jiang, R. W.; Tang, Y. F. *Tetrahedron Lett.* **2014**, *55*, 6455. (d) Wang, Y. H.; Lei, X. Q.; Tang, Y. F. *Synlett* **2015**, *26*, 2051.

(10) Hansen, T. V.; Wu, P.; Fokin, V. V. *J. Org. Chem.* **2005**, *70*, 7761. For details of the preparation of other isoxazoles presented in this study, see the Supporting Information.

(11) For selected reviews, see: (a) Baraldi, P. G.; Preti, D.; Fruttarolo, F.; Tabrizi, M. A.; Romagnoli, R. *Bioorg. Med. Chem.* **2007**, *15*, 17. (b) Bando, T.; Sugiyama, H. *Acc. Chem. Res.* **2006**, *39*, 935. For selected examples, see: (c) De Rosa, M.; Arnold, D.; Hartline, D. *J. Org. Chem.* **2013**, *78*, 8614. (d) Kanakis, A. A.; Sarli, V. *Org. Lett.* **2010**, *12*, 4872. (e) Dose, C.; Farkas, M. E.; Chenoweth, D. M.; Dervan, P. B. *J. Am. Chem. Soc.* **2008**, *130*, 6859. (f) Schneider, K.; Keller, S.; Wolter, F. E.; Roeglin, L.; Beil, W.; Seitz, O.; Nicholson, G.; Bruntner, C.; Riedlinger, J.; Fiedler, H. P.; Süessmuth, R. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 3258. (g) LoVerme, J.; Duranti, A.; Tontini, A.; Spadoni, G.; Mor, M.; Rivara, S.; Stella, N.; Xu, C.; Tarzia, G.; Piomelli, D. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 639.

(12) For selected examples, see: (a) Marcotte, F. A.; Lubell, W. D. *Org. Lett.* **2002**, *4*, 2601−2603. (b) Attanasi, O. A.; Favi, G.; Filippone, P.; Golobic, A.; Stanovnik, B.; Svete, J. *J. Org. Chem.* **2005**, *70*, 4307. (c) Sasada, T.; Sawada, T.; Ikeda, R.; Sakai, N. *Eur. J. Org. Chem.* **2010**, 4237. (d) Zanatta, N.; Schneider, J. M. F. M.; Schneider, P. H.; Wouters, A. D.; Bonacorso, H. G.; Martins, M. A. P.; Wessjohann, L. A. *J. Org. Chem.* **2006**, *71*, 6996.

(13) (a) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378. (b) Zalatan, D. N.; Du Bois, J. *J. Am. Chem. Soc.* **2009**, *131*, 7558.

(14) CCDC 1421308 (**3e**) 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.

(15) Some other processes might also account for the conversion of **C** to **E**, such as a 4π conrotory electrocyclization followed by ring expansion.

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