Organic LETTERS

Letter

pubs.acs.org/OrgLett

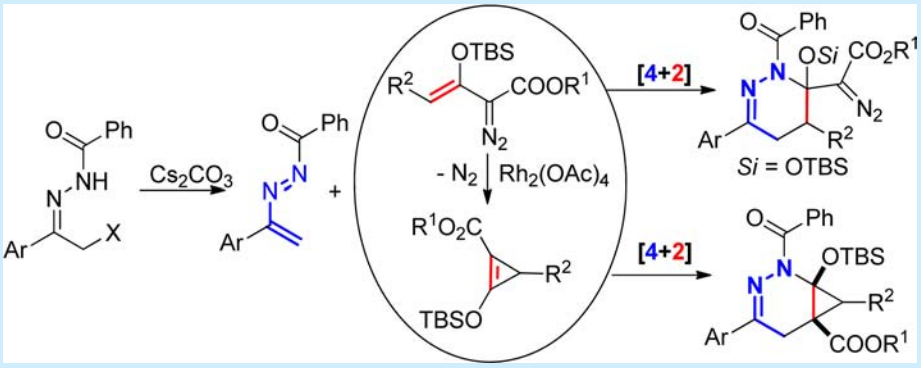
Syntheses of Tetrahydropyridazine and Tetrahydro-1,2-diazepine Scaffolds through Cycloaddition Reactions of Azoalkenes with Enol Diazoacetates

Yongming Deng,[†,§] Chao Pei,[‡,§] Hadi Arman,[†] Kuiyong Dong,[‡] Xinfang Xu,[*,‡] and Michael P. Doyle[*,†]

[†]Department of Chemistry, The University of Texas at San Antonio, San Antonio, Texas 78249, United States

[‡]College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, P. R. China

Supporting Information

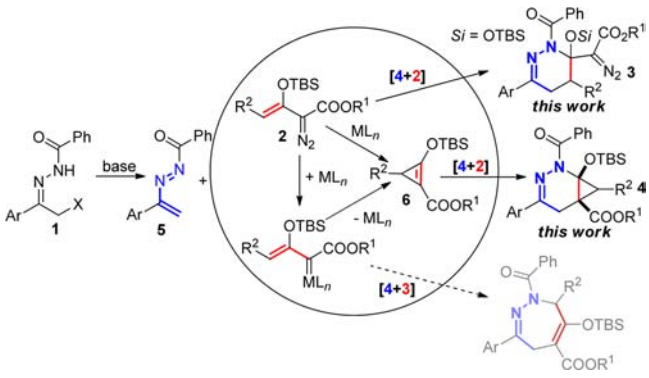


ABSTRACT: Catalyst-dependent [4 + 2]-cycloaddition reactions of azoalkenes from α-halohydrazones with enol diazoacetates have been developed. A [4 + 2]-cycloaddition of enol diazoacetates with in situ formed azoalkenes produces tetrahydropyridazinyl-substituted diazoacetates promoted by only Cs_2CO_3. In contrast, donor−acceptor cyclopropenes, which are formed in situ from enol diazoacetates by $Rh_2(OAc)_4$-catalyzed dinitrogen extrusion, undergo [4 + 2]-cycloaddition with azoalkenes to yield bicyclo[4.1.0]tetrahydropyridazines. These stable cycloaddition products undergo subsequent one-step transformations to form 6-alkylidenetetrahydropyridazines and 4,5,6,7-tetrahydro-1,2-diazepine derivatives in good yields.

Azoalkenes (1,2-diaza-1,3-butadienes) are highly reactive dienes[1] that undergo cycloaddition reactions with even simple alkenes.[2] They are conveniently generated from α-halohydrazones (**1**), many of which are now commercially available, by treatment with a mild base.[3] Our interest with these dienes originated in their potential uses with enol diazoacetates for cycloaddition,[4] specifically methyl 3-[(*tert*-butyldimethylsilyl)oxy]-2-diazo-3-butenoate (**2**), for which there are three possible outcomes (Scheme 1). One is [4 + 2]-cycloaddition to the enol silyl ether[5] resulting in tetrahydropyridazinyl-substituted diazoacetates. Another, because enol diazoacetates can undergo dinitrogen extrusion to form donor−acceptor cyclopropenes,[6] is [4 + 2]-cycloaddition of the azoalkene with the cyclopropene, which would form a bicyclo[4.1.0]tetrahydropyridazine. If, however, metal carbene formation from the enol diazoacetate is rapid and cyclopropene or enol silyl ether cycloaddition is slow, this system has the potential to undergo [4 + 3]-cycloaddition.[7]

The *N*-benzoyl-α-chlorohydrazone of acetophenone was selected for initial examination. Treatment with a relatively insoluble base is the established procedure for generation of the intermediate azoalkene,[3,8] and copper catalysis has been reported to promote highly efficient cycloaddition reactions with 2-methoxyfurans and 2-(silyloxy)furans.[5a,b] However, with copper catalysis the azoalkene produced from compound **1** gave a relatively low yield of cycloaddition product with methyl 3-[(*tert*-butyldimethylsilyl)oxy]-2-diazo-3-butenoate (**2a**) under conditions comparable to those previously employed. The

Scheme 1. Divergent Cycloaddition Reactions of Enol Diazoacetamides with α-Halohydrazones



Received: September 30, 2016
Published: November 7, 2016

DOI: 10.1021/acs.orglett.6b02965
Org. Lett. 2016, 18, 5884−5887

major product obtained in these investigations (eq 1) was that from [4 + 2]-cycloaddition to the carbon−carbon double bond of **1a**, whose structure was identified spectroscopically and confirmed by X-ray diffraction analysis (**3a**, Figure 1).

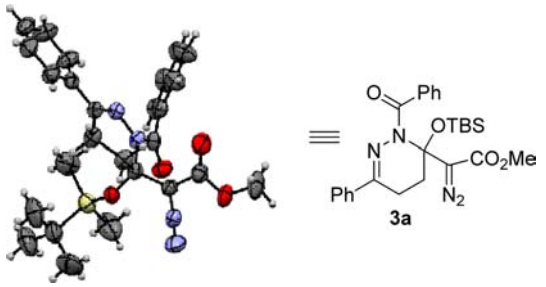


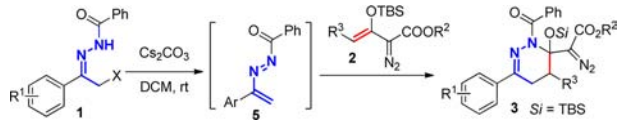
Figure 1. X-ray crystal structure of methyl 2-[2-benzoyl-3-[(*tert*-butyldimethylsilyl)oxy]-6-phenyl-2,3,4,5-tetrahydropyridazin-3-yl]-2-diazoacetate (**3a**).

(1)

Azoalkene **5** was generated by adding *N*-benzoyl-α-chlorohydrazone **1a** over 30 min to dichloromethane containing cesium carbonate, and then the dichloromethane solution of enol diazoacetate **2** was added dropwise at room temperature. Copper catalysts, such as $Cu(MeCN)_4BF_4$ or $Cu(OTf)_2$, were relatively ineffective in producing **3a** (40−50% yields), and the use of scandium(III) triflate (5 mol %) gave an even lower yield of product.[9] Among the competing processes responsible for the low yields of **3** was TBS transfer to the reactant hydrazone amide nitrogen of **1** that occurred in competition with azoalkene formation and cycloaddition between two azoalkenes;[8c,d] an excess of **1a** and moderation of the addition rate was required to balance these two competing processes with the intermolecular cycloaddition of azoalkene **5** with **2**. Further screening of reaction conditions,[9] including solvent, base, and reaction temperature, indicated that the optimal yield of **3a** was obtained from the reaction carried out only in the presence of cesium carbonate at room temperature in dichloromethane (Table 1, entry 1).[2b,10] Variation of the α-halogen (entry 2), aryl substituents (entries 1, 3−7), and the ester R^2 group (entries 8 and 9) had little influence on the yield of product **3**. The reactions of γ-methyl- and γ-phenyl-substituted enol diazoacetates also yielded the desired [4 + 2]-cyclization products but with moderate yield due to steric effects from the γ-substitutions (entries 10 and 11).

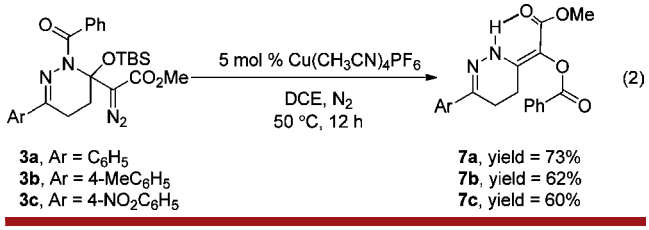
These tetrahydropyridazinyl-substituted diazoacetates **3** provided a structural framework for examination of potential metal carbene transformations. We anticipated that dinitrogen extrusion from **3** would form an electrophilic metal carbene intermediate that would undergo TBSO → carbene migration in a rearrangement process not unlike recently reported examples.[11] Instead, a different product was formed in good yield by treatment of **3a** with $Cu(CH_3CN)_4PF_6$ under mild conditions (eq 2), and its structure was elucidated spectroscopically and verified as tetrahydropyridazine **7a** by X-ray structural analysis (Figure 2). This surprising result was reproduced with

Table 1. Substrate Scope for Synthesis of Tetrahydropyridazinyl-substituted Diazoacetate Product 3[a]



entry	**1**, R^1 =	X =	**2**, R^2 =	**2**, R^3 =	yield[b] (%) (**3**)
1	H	Cl	Me	H	83 (**3a**)
2	H	Br	Me	H	81 (**3a**)
3	4-Me	Cl	Me	H	76 (**3b**)
4	4-NO_2	Cl	Me	H	72 (**3c**)
5	4-Br	Cl	Me	H	81 (**3d**)
6	2-Br	Cl	Me	H	52 (**3e**)
7	3-Br	Cl	Me	H	85 (**3f**)
8	H	Cl	Et	H	80 (**3g**)
9	H	Cl	Bn	H	77 (**3h**)
10	H	Cl	Me	Me	58 (**3i**)
11	H	Cl	Bn	Ph	31 (**3j**)

[a]Standard reaction conditions: **2** (0.20 mmol, 1.0 equiv) in dry dichloromethane (2.0 mL) was added to a 2.0 mL dichloromethane solution of **1** (0.30 mmol, 1.5 equiv), Cs_2CO_3 (0.40 mmol, 2 equiv), and 4 Å MS (100 mg) under N_2 within 30 min at room temperature. [b]Isolated yield.



(2)

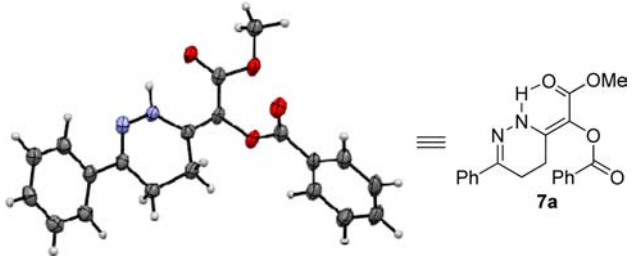


Figure 2. X-ray crystal structure of (*E*)-2-methoxy-2-oxo-1-[6-phenyl-4,5-dihydropyridazin-3(2*H*)-ylidene]ethyl benzoate (**7a**).

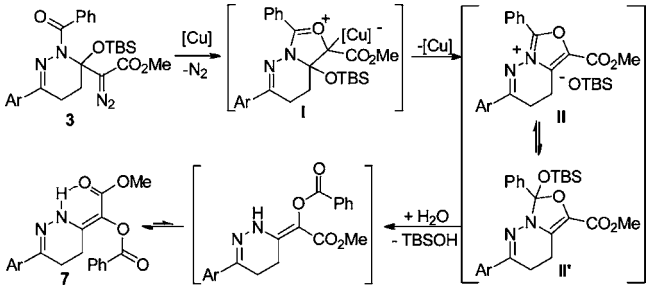
substituted reactants **3b** and **3c** without significant diminution in product yield. Other transition-metal catalysts, including $Rh_2(OAc)_4$, $Rh_2(cap)_4$, and $Cu(CH_3CN)_4BF_4$, also generated **7** as the sole product, but in lower yield.[9]

The formation of **7** is inconsistent with an initial TBSO → carbene migration but can be rationalized through a process involving carbonyl ylide formation (Scheme 2). The α-diazo-δ-amide carbonyl in **3** provides an ideal framework for the generation of carbonyl ylide **I**[12] that, following removal of the catalyst to form oxazolium salt **II**[13] with subsequent hydrolysis and enamine isomerization, completes the transformation. The formation of oxazolium salt **II** intermediate is supported by a LC−mass spectral detection of this reaction intermediate that is on the pathway to **7**.[14]

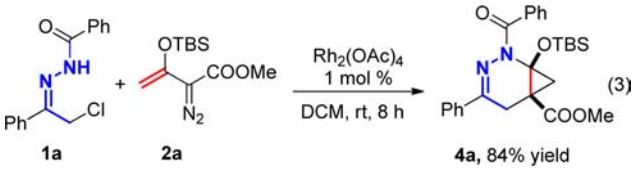
Although copper catalysts were ineffective in causing cycloaddition reactions between azaalkene **5** and enol diazoacetate **2**, reactions catalyzed by dirhodium(II) acetate

DOI: 10.1021/acs.orglett.6b02965
Org. Lett. 2016, 18, 5884−5887

Scheme 2. Proposed Mechanism for the Formation of Tetrahydropyridazine 7 from $CuPF_6(CH_3CN)_4$ Catalyzed Dinitrogen Extrusion of 3



generated bicyclo[4.1.0]tetrahydropyridazines (**4**) that were anticipated from the cycloaddition reaction between **5** and the donor−acceptor cyclopropenes **6** formed in situ from enol diazoacetate **2** (Scheme 1). Reactions were performed at room temperature by adding the enol diazoacetate over 3 h to a solution containing rhodium acetate and the α-chloro-*N*-benzoylhydrazone of acetophenone (**1a**) with cesium carbonate (eq 3). The cycloaddition adduct **4a** was obtained as the sole product in 84% yield. The structure of **4a** was confirmed by X-ray diffraction (Figure 3).



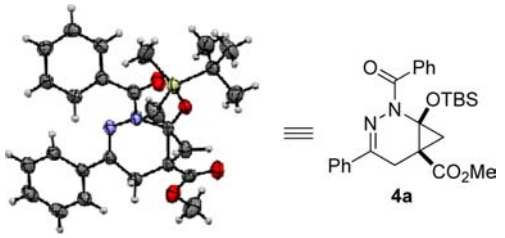
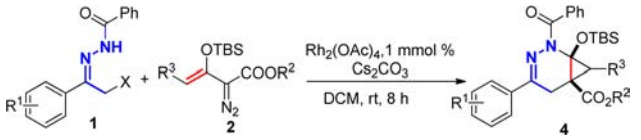


Figure 3. X-ray crystal structure of methyl 2-benzoyl-1-[(*tert*-butyldimethylsilyl)oxy]-4-phenyl-2,3-diazabicyclo[4.1.0]hept-3-ene-6-carboxylate (**4a**).

Changing the carboxylate ligand of the dirhodium catalyst, including $Rh_2(Oct)_4$ and $Rh_2(pfb)_4$, had only minor influences on product yield, and cesium carbonate remained the optimum base for azoalkene formation without inhibiting catalysis in the formation of the donor−acceptor cyclopropene (Table 2).[9] Additionally, variation of the α-halogen of the halohydrazone (entry 2), aryl substituents (entries 3−7), and the ester R^2 group (entries 8 and 9) are well tolerated, and a series of bicyclo[4.1.0]tetrahydropyridazines **4** were successfully synthesized in good yield. Additionally, the desired [4 + 2]-cycloaddition products were also generated in good yields from γ-methyl- and γ-phenyl-substituted enol diazoacetates (entries 10 and 11).

Diazepines are important heterocycles that are found in many natural products and bioactive compounds.[15] Moreover, the 1,2-diazepine structure is also an important scaffold in organic synthesis.[16] Although diazepine product formation was

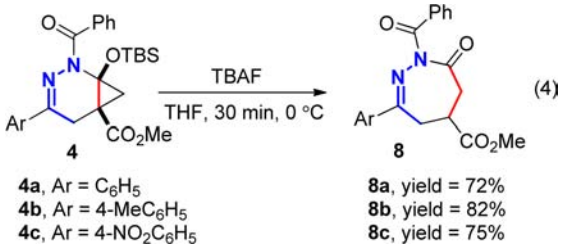
Table 2. Substrate Scope for Synthesis of Bicyclo[4.1.0]-Tetrahydropyridazines Product 4[a]



entry	**1**, R^1 =	X =	**2**, R^2 =	**2**, R^3 =	yield[b] (%) (**4**)
1	H	Cl	Me	H	84 (**4a**)
2	H	Br	Me	H	83 (**4a**)
3	4-Me	Cl	Me	H	77 (**4b**)
4	4-NO_2	Cl	Me	H	70 (**4c**)
5	4-Br	Cl	Me	H	83 (**4d**)
6	2-Br	Cl	Me	H	68 (**4e**)
7	3-B	Cl	Me	H	75 (**4f**)
8	H	Cl	Et	H	72 (**4g**)
9	H	Cl	Bn	H	65 (**4h**)
10	H	Cl	Me	Me	82 (**4i**)
11	H	Cl	Bn	Ph	75 (**4j**)

[a]Standard reaction conditions: **2** (0.20 mmol, 1.0 equiv) in dry dichloromethane (2.0 mL) was added to 2.0 mL of a dry dichloromethane solution of **1** (0.30 mmol, 1.5 equiv), Cs_2CO_3 (0.40 mmol, 2 equiv), $Rh_2(OAc)_4$ (0.002 mmol), and 4 Å MS (100 mg) under N_2 within 3 h at room temperature. [b]Isolated yield.

not observed to occur between **5** and the metal carbene from **2** (Scheme 1), the bicyclo[4.1.0]tetrahydropyridazines **4** from [4 + 2]-cycloaddition with donor−acceptor cyclopropene **6** are suitably constructed for ring opening to 4,5,6,7-tetrahydro-1,2-diazepine derivatives.[17] As expected, simple treatment of **4** with TBAF at 0 °C formed **8** (eq 4), which was isolated in good



yield. This synthetic methodology from α-halohydrazones and enol diazoacetates provides an effective approach to the synthesis of heterocycle-fused lactam-1,2-azepines.

In summary, we have discovered catalyst-dependent cycloaddition reactions of azoalkenes from α-halohydrazones with enol diazoacetates, and although azoalkenes readily dimerize,[8c,d] only a modest excess of α-halohydrazones is required. Tetrahydropyridazinyl-substituted diazoacetates have been prepared by a [4 + 2]-cycloaddition of enol diazoacetates with in situ formed azoalkenes that occurs without a Lewis acid or metal carbene-forming catalyst. Copper or Lewis acid compounds inhibit this cycloaddition process, but the tetrahrdropyridazinyl diazoacetates are effectively transformed subsequently into novel 6-alkylidenetetrahydropyridazines by copper(I) catalysis via an acyl-transfer reaction that occurs through an oxazolium salt intermediate. In contrast, $Rh_2(OAc)_4$ catalyzes dinitrogen extrusion of enol diazoacetates to form donor−acceptor cyclopropenes that undergo [4 + 2]-cycloaddition with azoalkenes yielding bicyclo[4.1.0]-tetrahydropyridazines, and these products readily undergo ring expansion generating 4,5,6,7-tetrahydro-1,2-diazepine

DOI: 10.1021/acs.orglett.6b02965
Org. Lett. 2016, 18, 5884−5887

derivatives in good yields. These transformations provide new methodologies with which to access substituted tetrahydropyridazine and tetrahydro-1,2-diazepine heterocyclic compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02965.

General experimental procedures, X-ray structures of **3a**, **4a**, and **7a**, and spectroscopic data for all new compounds (PDF)
Crystallographic data for **3a** (CIF)
Crystallographic data for **4a** (CIF)
Crystallographic data for **7a** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: xinfangxu@suda.edu.cn.
*E-mail: michael.doyle@utsa.edu.

Author Contributions

§Y.D. and C.P. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support for this research to M.P.D. from the National Science Foundation (CHE-1464690) is gratefully acknowledged. X.X. is thankful for a grant from the National Science Foundation of China (21602148).

■ REFERENCES

(1) For reviews of the chemistry of azoalkenes, see: (a) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, P.; Mantellini, F.; Perrulli, F. R.; Santeusanio, S. *Eur. J. Org. Chem.* **2009**, *2009*, 3109. (b) Attanasi, O. A.; Filippone, P. *Synlett* **1997**, *1997*, 1128. For recent examples, see: (c) Attanasi, O. A.; Favi, G.; Filippone, P.; Mantellini, F.; Moscatelli, G.; Perrulli, F. R. *Org. Lett.* **2010**, *12*, 468. (d) Attanasi, O. A.; Favi, G.; Mantellini, F.; Moscatelli, G.; Santeusanio, S. *Adv. Synth. Catal.* **2011**, *353*, 1519. (e) Lopes, S. M. M.; Brigas, A. F.; Palacios, F.; Lemos, A.; Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2012**, *2012*, 2152. (f) Attanasi, O. A.; Favi, G.; Mantellini, F.; Mantenuto, S.; Moscatelli, G.; Nicolini, S. *Synlett* **2015**, *26*, 193. (g) Attanasi, O. A.; Bianchi, L.; D'Auria, M.; Mantellini, F.; Racioppi, R. *Curr. Org. Synth.* **2013**, *10*, 631. (h) Chen, J.-R.; Dong, W.-R.; Candy, M.; Pan, F.-F.; Jorres, M.; Bolm, C. *J. Am. Chem. Soc.* **2012**, *134*, 6924.

(2) (a) Yang, X.-L.; Peng, X.-X.; Chen, F.; Han, B. *Org. Lett.* **2016**, *18*, 2070. (b) Zhong, X.; Lv, J.; Luo, S. *Org. Lett.* **2015**, *17*, 1561.

(3) (a) Reese, C. B.; Sanders, H. P. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2719.

(4) Xu, X.; Doyle, M. P. *Acc. Chem. Res.* **2014**, *47*, 1396.

(5) (a) Li, J.; Huang, R.; Xing, Y.-K.; Qiu, G.; Tao, H.-T.; Wang, C.-J. *J. Am. Chem. Soc.* **2015**, *137*, 10124. (b) Huang, R.; Chang, X.; Li, J.; Wang, C.-J. *J. Am. Chem. Soc.* **2016**, *138*, 3998. (c) Wei, L.; Wang, C.-J. *Chem. Commun.* **2015**, *51*, 15374. (d) Gao, S.; Chen, J.-R.; Hu, X.-Q.; Cheng, H.-G.; Lu, L.-Q.; Xiao, W.-J. *Adv. Synth. Catal.* **2013**, *355*, 3539.

(6) Deng, Y.; Jing, C.; Doyle, M. P. *Chem. Commun.* **2015**, *51*, 12924.

(7) (a) Hu, X.-Q.; Chen, J.-R.; Gao, S.; Feng, B.; Lu, L.-Q.; Xiao, W.-J. *Chem. Commun.* **2013**, *49*, 7905−7907. (b) Doyle, M. P.; Hu, W.; Timmons, D. J. *Org. Lett.* **2001**, *3*, 3741.

(8) (a) Tong, M.-C.; Chen, X.; Li, J.; Huang, R.; Tao, H.; Wang, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 4680. (b) Chen, J.-R.; Dong, W.-R.; Candy, M.; Pan, F.-F.; Jörres, M.; Bolm, C. *J. Am. Chem. Soc.* **2012**, *134*, 6924. (c) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Mantellini, F.; Mantenuto, S.; Nicolini, S. *J. Org. Chem.* **2014**, *79*, 8331. (d) Shelke, A. M.; Suryavanshi, G. *Org. Lett.* **2016**, *18*, 3968.

(9) Detailed results from the screening are provided in the Supporting Information.

(10) For examples of only base-promoted reactions of azoalkenes, see: (a) Hu, X.-Q.; Chen, J.-R.; Gao, S.; Feng, B.; Lu, L.-Q.; Xiao, W.-J. *Chem. Commun.* **2013**, *49*, 7905. (b) Zhao, H.-W.; Pang, H.-L.; Li, B.; Tian, T.; Chen, X.-Q.; Song, X.-Q.; Meng, W.; Yang, Z.; Liu, Y.-Y.; Zhao, Y.-D. *RSC Adv.* **2016**, *6*, 25562.

(11) (a) Xu, X.; Qian, Y.; Zavalij, P. Y.; Doyle, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 1244. (b) Cheng, Q.-Q.; Qian, Y.; Zavalij, P. Y.; Doyle, M. P. *Org. Lett.* **2015**, *17*, 3568.

(12) For reviews, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998. (b) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. *Chem. Rev.* **2015**, *115*, 9981. (c) Padwa, A. *Chem. Soc. Rev.* **2009**, *38*, 3072.

(13) (a) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765. (b) Palmer, D. C. *Oxazoles: Synthesis, Reactions, and Spectroscopy*; Wiley: New York, 2003.

(14) (a) Hsieh, C.-H.; Chao, C.-S.; Mong, K.-K. T.; Chen, Y.-C. *J. Mass Spectrom.* **2012**, *47*, 586. (b) Schrader, W.; Handayani, P. P.; Zhou, J.; List, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 1463.

(15) (a) Mendonca, F. B., Jr.; Scotti, L.; Ishiki, H.; Botelho, S. P. S.; Da Silva, M. S.; Scotti, M. T. *Mini-Rev. Med. Chem.* **2015**, *15*, 630. (b) Szucs, T. *Drugs* **1991**, *41*, 18.

(16) (a) Meyer, A. G.; Smith, J. A.; Hyland, C.; Williams, C. C.; Bissember, A. C.; Nicholls, T. P. In *Progress in Heterocyclic Chemistry*; Gordon, W. G., John, A. J., Eds.; Elsevier, 2016; Vol. *28*, p 579. (b) Snieckus, V.; Streith, J. *Acc. Chem. Res.* **1981**, *14*, 348.

(17) (a) Kageshima, Y.; Suzuki, C.; Oshiro, K.; Amii, H. *Synlett* **2014**, *26*, 63. (b) Kantorowski, E. J.; Kurth, M. J. *Tetrahedron* **2000**, *56*, 4317. (c) Hasegawa, E.; Nemoto, K.; Nagumo, R.; Tayama, E.; Iwamoto, H. *J. Org. Chem.* **2016**, *81*, 2692.

DOI: 10.1021/acs.orglett.6b02965
Org. Lett. 2016, 18, 5884−5887