Organic LETTERS

Letter

pubs.acs.org/OrgLett

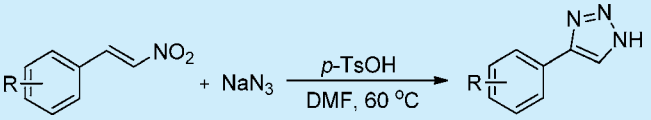
# *p*-Toluenesulfonic Acid Mediated 1,3-Dipolar Cycloaddition of Nitroolefins with $NaN_3$ for Synthesis of 4-Aryl-*NH*-1,2,3-triazoles

Xue-Jing Quan, Zhi-Hui Ren, Yao-Yu Wang, and Zheng-Hui Guan*

Key Laboratory of Synthetic and Natural Functional Molecule Chemistry of Ministry of Education, Department of Chemistry & Materials Science, Northwest University, Xi'an, 710127, P. R. China

Supporting Information

**ABSTRACT:** A *p*-TsOH-mediated 1,3-dipolar cycloaddition of nitroolefins and sodium azide for the synthesis of 4-aryl-*NH*-1,2,3-triazoles has been developed. *p*-TsOH was discovered as a vital additive in this type of 1,3-dipolar cycloaddition. This novel cycloaddition reaction is a good method for the rapid synthesis of valuable 4-aryl-*NH*-1,2,3-triazoles in high yields.




1,2,3-Triazoles are one of the most valuable compounds and have been widely applied in diverse areas of chemistry such as

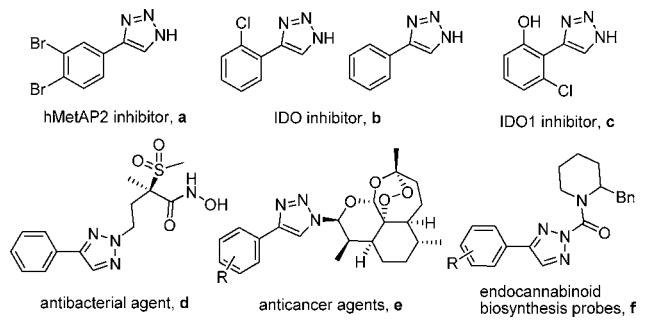
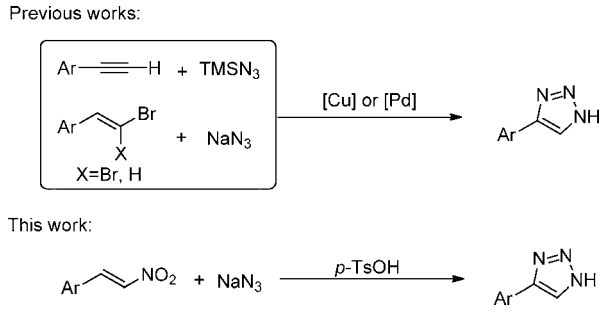


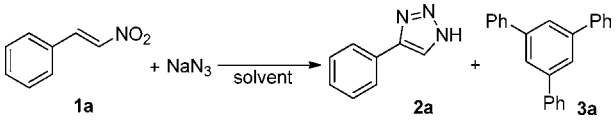

**Figure 1.** Several 4-aryl-*NH*-1,2,3-triazoles and their derivatives.

**Scheme 1. Strategies for the Synthesis of 4-Aryl-*NH*-1,2,3-triazoles**




medicinal chemistry, agrochemistry, and materials chemistry.[1] Therefore, methods for the synthesis of 1,2,3-triazoles have gained much attention in the past decades.[2] The Huisgen azide–alkyne 1,3-dipolar cycloaddition (AAC)[3] and later developed Cu-[4] or Ru-catalyzed[5] azide–alkyne cycloadditions (CuAAC, RuAAC) are the most commonly utilized methods for the synthesis of *N*-substituted 1,2,3-triazoles. However, most of these protocols employ alkynes and organic azides as the substrates, thus restricting the synthesis of N1-substituted 1,2,3-triazoles. And the employed transition-metal catalysts are not compatible with some biological applications. Recently, complementary methods, such as organocatalyzed azide–ketone cycloaddition,[6] the three-component reaction,[7] thermodynamic cycloaddition of $\alpha,\beta$-disubstituted nitroolefins and sodium azide,[8] Cu-catalyzed cyclization of *N*-tosylhydrazones and anilines,[9] Ir-catalyzed azide–alkyne cycloaddition (IrAAC),[10] and functionalization of simple 1,2,3-triazoles,[11]

**Table 1. Optimization of the Reaction Conditions**[a]



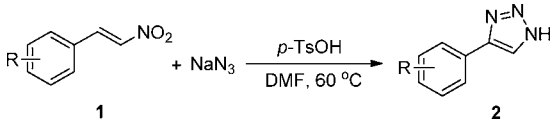

| entry | acid (equiv) | solvent | temp (°C) | yield (%)[b] |
|---|---|---|---|---|
| 1 | | DMSO | 110 | 30[c] |
| 2 | $FeCl_3$ (0.1) | DMSO | 110 | 66 |
| 3 | $ZnBr_2$ (0.1) | DMSO | 110 | 52 |
| 4 | HOAc (0.1) | DMSO | 110 | 56 |
| 5 | PivOH (0.1) | DMSO | 110 | 55 |
| 6 | TFA (0.1) | DMSO | 110 | 76 |
| 7 | *p*-TsOH (0.1) | DMSO | 110 | 83 |
| 8 | *p*-TsOH (0.3) | DMSO | 110 | 86 |
| 9 | *p*-TsOH (0.5) | DMSO | 110 | 90 |
| 10 | *p*-TsOH (0.5) | DMSO | 60 | 92 |
| 11 | *p*-TsOH (0.5) | DMSO | rt | 80 |
| 12 | *p*-TsOH (0.5) | DMF | 60 | 93 |
| 13 | *p*-TsOH (0.5) | $CH_3OH$ | 60 | 24 |
| 14 | *p*-TsOH (0.5) | $CH_3CN$ | 60 | 7 |
| 15 | *p*-TsOH (0.5) | $H_2O$ | 60 | trace |

[a]Reaction conditions: **1a** (0.3 mmol), $NaN_3$ (1.5 equiv), and acid (indicated amount), in solvent (3 mL) in air. [b]Isolated yield. [c]48% of **3a** was isolated

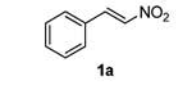
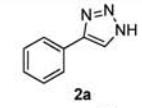
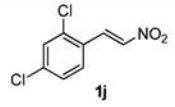
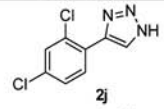
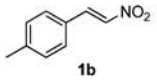
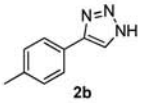
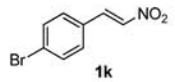
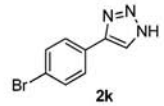
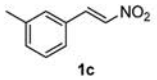
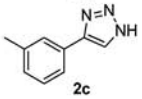
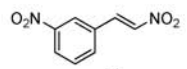
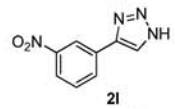
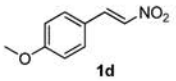
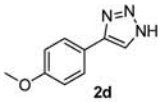
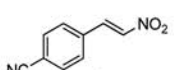
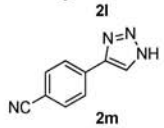
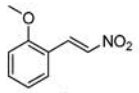
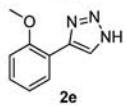
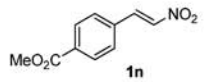
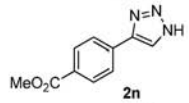
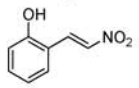
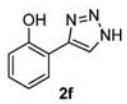
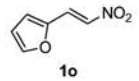
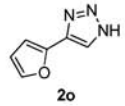
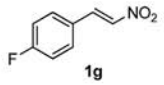
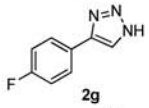
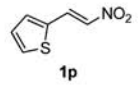
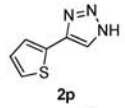
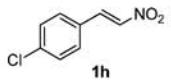
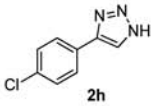
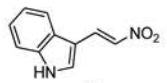
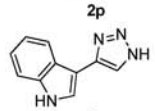
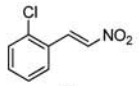
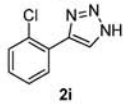
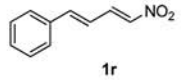
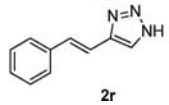
**Received:** September 22, 2014
**Published:** October 24, 2014

   dx.doi.org/10.1021/ol5027975 | *Org. Lett.* 2014, 16, 5728–5731

Table 2. *p*-TsOH-Mediated 1,3-Dipolar Cycloaddition of Nitroolefins with $NaN_3$ for Synthesis of 4-Aryl-*NH*-1,2,3-triazoles[a]




1 2

| entry | substrate, 1 | product, 2 | yield (%)[b] | entry | substrate, 1 | product, 2 | yield (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 |  1a |  2a | 93 | 10 |  1j |  2j | 90 |
| 2 |  1b |  2b | 94 | 11 |  1k |  2k | 66 |
| 3 |  1c |  2c | 94 | 12 |  1l |  2l | 70 |
| 4 |  1d |  2d | 97 | 13 |  1m |  2m | 66[c] |
| 5 |  1e |  2e | 95 | 14 |  1n |  2n | 71[c] |
| 6 |  1f |  2f | 73 | 15 |  1o |  2o | 85 |
| 7 |  1g |  2g | 96 | 16 |  1p |  2p | 87 |
| 8 |  1h |  2h | 84 | 17 |  1q |  2q | 85[c] |
| 9 |  1i |  2i | 93 | 18 |  1r |  2r | 74[c] |

[a]Reaction conditions: **1** (0.3 mmol), $NaN_3$ (1.5 equiv), *p*-TsOH (0.5 equiv), DMF (3 mL) at 60 °C for 1−3 h, in air. [b]Isolated yield. [c]The reaction was performed at 100 °C.

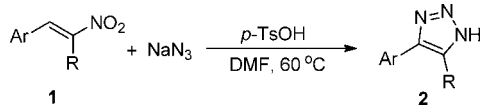
have emerged. However, versatile and practical methods for the synthesis of substituted 1,2,3-triazoles are still desirable.

4-Aryl-*NH*-1,2,3-triazoles are a class of important triazoles, which were discovered to be potent inhibitors of cobalt-activated human methionine aminopeptidase type 2 (hMetAP2) **a** and indoleamine 2,3-dioxygenase (IDO) **b**−**c**; thus, they have great potential to become anticancer drugs.[12] They are also important precursors to synthesize bioactive *N*-substituted triazoles, such as antibacterial agent **d**, anticancer agents **e**, and endocannabinoid biosynthesis probes **f** (Figure 1).[13] However, the preparation of this class of simple molecules (4-aryl-*NH*-1,2,3-triazoles) is still a challenging task. Methods for the synthesis of 4-aryl-*NH*-1,2,3-triazoles are still mainly limited to cycloaddition of $TMSN_3$ (trimethylsilyl azide)-alkynes followed by deprotection of the TMS (trimethylsilyl) group,[14] and palladium-catalyzed cyclization of vinyl bromides and sodium azide.[15] In this paper, we describe the development of a *p*-TsOH-mediated 1,3-dipolar cycloaddition of nitroolefins with $NaN_3$ for the synthesis of 4-aryl-*NH*-1,2,3-triazoles (Scheme 1).

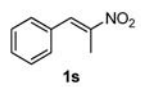
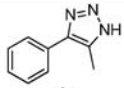
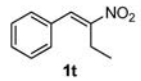
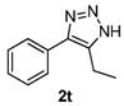
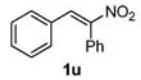
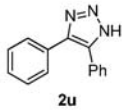
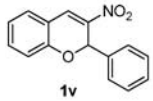
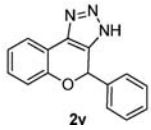
Due to the explosive and toxic nature of hydrazoic acids, Brønsted acids should not be mixed with $NaN_3$. Therefore, the reaction of $NaN_3$ has always been conducted under basic or neutral conditions.[14b] However, the cycloaddition of simple arylnitroolefin and $NaN_3$ resulted in significant cyclotrimerization of nitroolefin under neutral conditions (Table 1, entry 1).[8a] We hypothesized that the undesired cyclotrimerization of nitroolefin **1a** may be inhibited under acidic conditions. Therefore, various Lewis acids and Brønsted acids were screened under careful operation (Table 1, entries 2−7). Indeed, the efficiency of the 1,3-dipolar cycloaddition was dramatically improved in the presence of 10 mol % of a Lewis acid or a Brønsted acid. Especially, *p*-TsOH gives an 83% yield of the 4-phenyl-*NH*-1,2,3-triazole **2a** (Table 1, entry 7). Then, the amount of *p*-TsOH and the reaction temperature were optimized; a 92% yield of **2a** was obtained in the presence of 0.5 equiv of *p*-TsOH at 60 °C (Table 1, entry 10). Furthermore, various solvents were also screened (Table 1, entries 12−15). It was found that the side product **3a** was


dx.doi.org/10.1021/ol5027975 | *Org. Lett.* 2014, 16, 5728−5731

**Table 3. *p*-TsOH-Mediated Cycloaddition of Various Nitroolefins with $NaN_3$[a]**

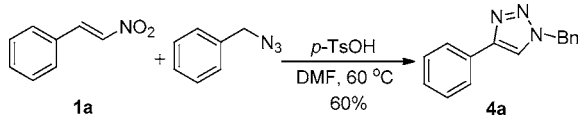



1 2

| entry | substrate, 1 | product, 2 | yield (%)[b] |
|---|---|---|---|
| 1 |  1s |  2s | 94 |
| 2 |  1t |  2t | 98 |
| 3 |  1u |  2u | 95 |
| 4 |  1v |  2v | 95 |

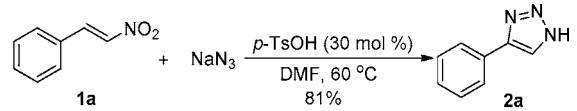
[a]Reaction conditions: **1** (0.3 mmol), $NaN_3$ (1.5 equiv), *p*-TsOH (0.5 equiv), DMF (3 mL), at 60 °C for 1−3 h, in air. [b]Isolated yield.

**Scheme 2. *p*-TsOH-Mediated Cycloaddition of Nitroolefin 1a with Benzyl Azide**




1a 4a

**Scheme 3. A Gram-Scale Preparation of 4-Phenyl-*NH*-1,2,3-triazole**




1a (10.4 g, 70 mmol) (5.4 g, 84 mmol) 2a (8.2 g)

totally suppressed when DMF was used as the solvent and a slightly higher yield (93%) was isolated (Table 1, entry 12).

With the optimized reaction conditions established, we have investigated the reaction scope (Table 2). This new *p*-TsOH-mediated 1,3-dipolar cycloaddition reaction displayed good functional-group tolerance and proved to be a general method for the synthesis of 4-aryl-*NH*-1,2,3-triazoles. Nitroolefins with electron-neutral or -donating groups on aryl rings, such as methyl, methoxyl, and hydroxyl, all gave the corresponding 4-aryl-*NH*-1,2,3-triazoles **2b**−**2f** in high to excellent yields (Table 2, entries 2−6). Nitroolefins with electron-withdrawing groups on aryl rings, such as fluoro, chloro, bromo, and nitro, reacted smoothly and resulted in the 1,3-dipolar cycloaddition products **2g**−**2l** in 66−96% yields, thus implying that the electronic nature of the substrates has little influence on the cycloaddition reaction (Table 2, entries 7−12). However, a higher reaction temperature was needed when the strongly electron-poor *p*-cyano-substituted nitroolefin **1m** and (*E*)-methyl 4-(2-nitrovinyl)benzoate **1n** were used as the substrates (Table 2, entries 13−14). In addition, heterocyclic substituted or vinyl substituted nitroolefins such as **1o**−**1r** also proceeded smoothly in the reaction to give the *NH*-1,2,3-triazoles **2o**−**2r** in 74−87% yields (Table 2, entries 15−18). However, aliphatic nitroolefins were inactive in the reaction.

Furthermore, disubstituted nitroolefins were investigated to explore the reaction scope (Table 3). Disubstituted nitroolefins **1s**−**1v** could be used in the 1,3-dipolar cycloaddition reaction and provided the corresponding 4,5-disubstituted-*NH*-1,2,3-triazoles in nearly quantitative yields under the standard conditions.

It should be noted that organic azides were also tolerated in this *p*-TsOH-mediated cycloaddition. As expected, 1-benzyl-4-phenyl-1,2,3-triazole **4a** was obtained in 60% yield when benzyl azide was used as the substrate (Scheme 2).

To demonstrate the synthetic utility of this reaction, a gram-scale (70 mmol) reaction was performed (Scheme 3). The 4-phenyl-*NH*-1,2,3-triazole **2a** was achieved in 81% yield by crystallization of the crude product.

In summary, we have developed a novel and efficient *p*-TsOH-mediated 1,3-dipolar cycloaddition of nitroolefins and inorganic $NaN_3$ for the synthesis of valuable 4-aryl-*NH*-1,2,3-triazoles. *p*-TsOH was discovered as a vital additive in the reaction. This novel cycloaddition reaction tolerates a wide range of functional groups and is a reliable method for the rapid elaboration of readily available nitroolefins and $NaN_3$ into a variety of *NH*-1,2,3-triazoles in high yields under mild conditions. The reaction is complementary for the well-known 1,3-dipolar cycloaddition. Further scope and mechanistic studies of the reaction are underway.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

### Corresponding Author

*E-mail: guanzhh@nwu.edu.cn.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported by generous grants from the National Natural Science Foundation of China (21472147, 21272183), and the Fund of the Rising Stars of Shanxi Province (2012KJXX26).

## ■ REFERENCES

(1) (a) Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. *Chem. Rev.* **2013**, *113*, 4905−4979. (b) Wang, K.; Chen, M.; Wang, Q.; Shi, X.; Lee, J. K. *J. Org. Chem.* **2013**, *78*, 7249−7258. (c) Chen, C.-Y.; Lee, P.-H.; Lin, Y.-Y.; Yu, W.-T.; Hu, W.-P.; Hsu, C.-C.; Lin, Y.-T.; Chang, L.-S.; Hsiao, C.-T.; Wang, J.-J.; Chung, M.-I. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6854−6859. (d) Lau, Y.; Rutledge, P. J.; Watkinson, M.; Todd, M. H. *Chem. Soc. Rev.* **2011**, *40*, 2848−2866. (e) Liu, Y.-H.; Zhang, L.; Xu, X.-N.; Li, Z.-M.; Zhang, D.-W.; Zhao, X.; Li, Z.-T. *Org. Chem. Front.* **2014**, *1*, 494−500.

(2) (a) Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1302−1315. (b) Kappe, C. O.; Eycken, E. V. D. *Chem. Soc. Rev.* **2010**, *39*, 1280−1290. (c) Wang, Y.-C.; Xie, Y.-Y.; Qu, H.-E.; Wang, H.-S.; Pan, Y.-M.; Huang, F.-P. *J. Org. Chem.* **2014**, *79*, 4463−4469. (d) Sahu, D.; Dey, S.; Pathak, T.; Ganguly, B. *Org. Lett.* **2014**, *16*, 2100−2103. (e) Wu, L.;



dx.doi.org/10.1021/ol5027975 | *Org. Lett.* 2014, 16, 5728−5731

Chen, Y.; Luo, J.; Sun, Q.; Peng, M.; Lin, Q. *Tetrahedron Lett.* **2014**, *55*, 3847−3850. (f) Hong, L.; Lin, W.; Zhang, F.; Liu, R.; Zhou, X. *Chem. Commun.* **2013**, *49*, 5589−5591. (g) Li, J.; Wang, D.; Zhang, Y.; Li, J.; Chen, B. *Org. Lett.* **2009**, *11*, 3024−3027.

(3) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984.

(4) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599. (c) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057−3064. (d) Kamata, K.; Nakagawa, Y.; Yamaguchi, K.; Mizuno, N. *J. Am. Chem. Soc.* **2008**, *130*, 15304−15310. (e) Hein, J. E.; Tripp, J. C.; Krasnova, L. B.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2009**, *48*, 8018−8021.

(5) (a) Zhang, L.; Chen, X. G.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 15998−15999. (b) Majireck, M. M.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 8680−8683. (c) Tam, A.; Arnold, U.; Soellner, M. B.; Raines, R. T. *J. Am. Chem. Soc.* **2007**, *129*, 12670−12671.

(6) (a) Li, W.; Du, Z.; Huang, J.; Jia, Q.; Zhang, K.; Wang, J. *Green Chem.* **2014**, *16*, 3003−3006. (b) Ramachary, D. B.; Shashank, A. B. *Chem.—Eur. J.* **2013**, *19*, 13175−13181. (c) Wang, L.; Peng, S. Y.; Danence, L. J. T.; Gao, Y.; Wang, J. *Chem.—Eur. J.* **2012**, *18*, 6088−6093. (d) Belkheira, M.; Abed, D.; Pons, J.-M.; Bressy, C. *Chem.—Eur. J.* **2011**, *17*, 12917−12921. (e) Danence, L.; Gao, Y.; Li, M.; Huang, Y.; Wang, J. *Chem.—Eur. J.* **2011**, *17*, 3584−3587. (f) Ramachary, D. B.; Ramakumar, K.; Narayana, V. V. *Chem.—Eur. J.* **2008**, *14*, 9143−9147.

(7) Thomas, J.; John, J.; Parekh, N.; Dehaen, W. *Angew. Chem., Int. Ed.* **2014**, *53*, 10155−10159.

(8) (a) Zefirov, N. S.; Chapovskaya, N. K.; Kolesnikov, V. V. *J. Chem. Soc. D* **1971**, 1001. (b) Quiclet-Sire, B.; Zard, S. Z. *Synthesis* **2005**, 3319−3326. (c) Guan, Z.-H.; Li, L.; Ren, Z.-H.; Li, J.; Zhao, M.-N. *Green Chem.* **2011**, *13*, 1664−1668. (d) Zhao, M.-N.; Liang, H.; Ren, Z.-H.; Guan, Z.-H. *Adv. Synth. Catal.* **2013**, *355*, 221−226.

(9) Chen, Z.; Yan, Q.; Liu, Z.; Xu, Y.; Zhang, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 13324−13328.

(10) (a) Ding, S.; Jia, G.; Sun, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 1877−1880. (b) Rasolofonjatovo, E.; Theeramunkong, S.; Bouriaud, A.; Kolodych, S.; Chaumontet, M.; Taran, F. *Org. Lett.* **2013**, *15*, 4698−4701.

(11) (a) Ueda, S.; Su, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8944−8947. (b) Yan, W.; Liao, T.; Tuguldur, O.; Zhong, C.; Petersen, J. L.; Shi, X. *Chem.—Asian J.* **2011**, *6*, 2720−2724. (c) Yan, W.; Wang, Q.; Chen, Y.; Petersen, J. L.; Shi, X. *Org. Lett.* **2010**, *12*, 3308−3311. (d) Wang, X.-J.; Zhang, L.; Lee, H.; Haddad, N.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2009**, *11*, 5026−5028. (e) Shi, W.; Shi, Z. *Chin. J. Chem.* **2014**, *32*, 974−980. (f) Sengupta, S.; Duan, H.; Lu, W.; Petersen, J. L.; Shi, X. *Org. Lett.* **2008**, *10*, 1493−1496.

(12) (a) Kallander, L. S.; Lu, Q.; Chen, W.; Tomaszek, T.; Yang, G.; Tew, D.; Meek, T. D.; Hofmann, G. A.; Schulz-Pritchard, C. K.; Smith, W. W.; Janson, C. A.; Ryan, M. D.; Zhang, G.; Johanson, K. O.; Kirkpatrick, R. B.; Ho, T. F.; Fisher, P. D.; Mattern, M. R.; Johnson, R. K.; Hansbury, M. J.; Winkler, J. D.; Ward, K. W.; Veber, D. F.; Thompson, S. K. *J. Med. Chem.* **2005**, *48*, 5644−5647. (b) Rohrig, U. F.; Awad, O. L.; Grosdidier, O. A.; Larrieu, P.; Stroobant, V.; Colau, D.; Cerundolo, V.; Simpson, A. J. G.; Vogel, P.; Van den Eynde, B. J.; Zoete, V.; Michielin, O. *J. Med. Chem.* **2010**, *53*, 1172−1189. (c) Huang, Q.; Zheng, M.; Yang, S.; Kuang, C.; Yu, C.; Yang, Q. *Eur. J. Med. Chem.* **2011**, *46*, 5680−5687. (d) Rohrig, U.; Majjigapu, S.; Grosdidier, A.; Bron, S.; Stroobant, V.; Pilotte, L.; Colau, D.; Vogel, P.; Eynde, B. J. V.; Zoete, V.; Michielin, O. *J. Med. Chem.* **2012**, *55*, 5270−5290.

(13) (a) McAllister, L. A.; Montgomery, J. I.; Abramite, J. A.; Reilly, U.; Brown, M. F.; Chen, J. M.; Barham, R. A.; Che, Y.; Chung, S. W.; Menard, C. A.; Mark, M.-F.; Mullins, L. M.; Noe, M. C.; Donnell, J. P.; Oliver, R. M., III; Penzien, J. B.; Plummer, M.; Price, L. M.; Shanmugasundaram, V.; Tomaras, A. P.; Uccello, D. P. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6832−6838. (b) Oh, S.; Shin, W.-S.; Ham, J.; Lee, S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4112−4115. (c) Hsu, K.-L.; Tsuboi, K.; Whitby, L. R.; Speers, A. E.; Pugh, H.; Inloes, J.; Cravatt, B. F. *J. Med. Chem.* **2013**, *56*, 8257−8269.

(14) (a) Jin, T.; Kamijo, S.; Yamamoto, Y. *Eur. J. Org. Chem.* **2004**, 3789−3791. (b) Kalisiak, J.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2008**, *10*, 3171−3174. (c) Cohrt, A. E.; Jensen, J. F.; Nielsen, T. E. *Org. Lett.* **2010**, *12*, 5414−5417.

(15) (a) Barlunga, J.; Valdés, C.; Beltrán, G.; Escribano, M.; Aznar, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 6893−6896. (b) Wang, X.; Kuang, C.; Yang, Q. *Eur. J. Org. Chem.* **2012**, 424−428.