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Cu/Pd-Catalyzed, Three-Component Click Reaction of Azide, Alkyne, and Aryl Halide: One-Pot Strategy toward Trisubstituted Triazoles

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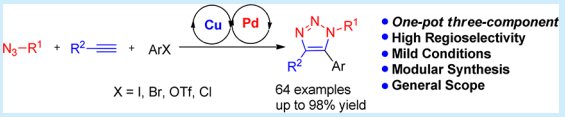
Supporting Information

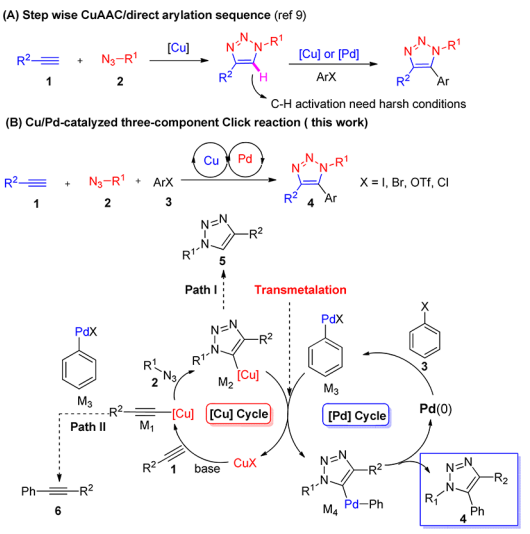
ABSTRACT: A Cu/Pd-catalyzed, three-component click reaction of azide, alkyne, and aryl halide has been developed. By using this Cu/Pd transmetalation relay catalysis, a variety of 1,4,5-trisubstituted 1,2,3-triazoles were quickly assembled in one step in high yields with complete regioselectivity, just like assembling Lego bricks. Notably, different from the well-established CuAAC click reactions only working on terminal alkynes, this reaction offers an alternative solution for the problem of the click reaction of internal alkynes.



1,2,3-Triazoles are privileged heterocycles, serving as key functional groups in many bioactive molecules and pharmaceuticals.[1] Recently, they are widely used as ligands for catalysis,[2a] directing groups for transition-metal-catalyzed C−H activation,[2b,c] and versatile building blocks in organic synthesis.[3] The copper-catalyzed azide−alkyne cycloaddition (CuAAC)[4] is the major approach to this heterocycle and has been widely extended into various research fields, such as chemical biology and materials science.[5] In the CuAAC reaction, the copper(I) catalyst forming copper(I) acetylide complexes with terminal alkynes is crucial to accelerate this cycloaddition reaction and also deliver region selectivity. Consequently, the CuAAC is limited to terminal alkynes. Internal alkynes are far more difficult to react with azides to synthesize fully substituted triazoles due to their weak reactivity and difficulty in regiocontrol. This becomes a fundamental problem of current click reactions.[6−8]

To access trisubstituted triazoles, a CuAAC reaction and subsequent transition-metal-catalyzed direct arylation sequence has been developed (Scheme 1A).[9] In 2008, the Ackermann group reported a copper-catalyzed, two-step, one-pot coupling reaction of alkyne, azide, and aryl iodide at 140 °C for 20 h.[9c] However, to cleave the inert C−H bond of the triazole ring, usually very harsh conditions, such as very high temperature or microwave, were required. To address this issue, we proposed a new Cu/Pd transmetalation step to trap the vinylcopper intermediate $\mathbf{M_2}$;[10] thus, direct C−H bond cleavage was avoided and very mild reaction conditions were possible (Scheme 1B). By using this unprecedented Cu/Pd transmetalation relay catalysis,[11] a modular synthesis of trisubstitued triazoles[12,13] from easily available materials was developed. This

Scheme 1. Cu/Pd-Catalyzed Three-Component Click Reaction



reaction makes it possible to freely install three different substituents onto the triazole ring in one step.

As illustrated in Scheme 1, the cycloaddition of copper(I) acetylide $\mathbf{M_1}$ with azide **2** generates cuprate−triazole intermediate $\mathbf{M_2}$. At the same time, oxidative addition of aryl halide **3** to Pd(0) catalyst forms the palladium intermediate $\mathbf{M_3}$. The transmetalation reaction between $\mathbf{M_2}$ and $\mathbf{M_3}$ followed by

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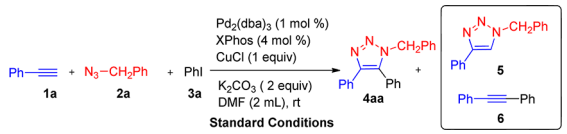
reductive elimination would produce the target trisubstituted triazole **4** and regenerate Pd(0) catalyst. However, to achieve this ideal catalytic cycle is an extremely challenging task because of the two inevitable competing reactions: (1) Protonation of the cuprate-triazole intermediate $\mathbf{M_2}$ produces the undesired 1,4-disubstituted 1,2,3-triazole **5** (path I). (2) Transmetalation between copper(I) acetylide $\mathbf{M_1}$ and palladium intermediate $\mathbf{M_3}$ forms another byproduct **6**, which is the traditional Sonogashira coupling reaction (path II). To inhibit path I, we need to reduce all of the possible proton sources and increase the reaction rate of transmetalation. However, the facility of transmetalation would also increase the amount of the undesired Sonogashira coupling product (path II). This is the most challenging issue of the proposed three-component cycloaddition coupling reaction.

To validate this concept, phenylacetylene **1a**, benzylazide **2a**, and iodobenzene **3a** were chosen as the model substrates to optimize the reaction conditions. When a catalytic amount of copper catalyst was used, two major byproducts, the normal click product **5** and diphenylacetylene **6** were the major products, together with trace trisubstituted triazole **4aa**. The Lei group recently discovered that the Sonogashira coupling is a first-order kinetic dependence on both [Cu] catalyst and [Pd] catalyst;[14a] however, the Fokin group demonstrated the CuAAC reaction is a second-order kinetic dependence on [Cu] catalyst.[14b,c] Thus, increasing the concentration of [Cu] would favor the designed click reaction pathway. We then decided to screen the reaction conditions using 1 equiv of copper catalyst (Table 1).

After a variety of reaction parameters were screened (for details, see the Supporting Information), the desired three-component cycloaddition coupling product **4aa** was achieved in 93% yield under standard conditions: a mixture of CuCl (1 equiv), $Pd_2(dba)_3$ (1 mol %), XPhos (4 mol %) in DMF (2 mL) was stirred at room temperature under N_2 atmosphere overnight (Table 1, entry 1). The ligand XPhos greatly accelerates the [Pd] cycle, which is very crucial for the success of this reaction. When XPhos was replaced by PPh_3, the yield of **4aa** was low, and large amounts of byproduct **6** were observed (entry 2). Base plays a very important role in this reaction, and the use of Et_3N or $LiOBu^t$ in place of K_2CO_3 was not effective (entries 6 and 7). Increasing the loading of palladium catalyst led to decreased yield and selectivity, indicating the ratio of Cu/Pd is highly important to realize this challenging reaction (entry 11). We then tried to lower the loading of copper catalyst (entries 12 and 13). The yield slightly dropped to 78% with 50 mol % of copper. When CuCl (25 mol %) was employed, the yield of **4aa** further decreased to 62%. Even though reduced yield was obtained when a catalytic amount of copper catalyst was used, these results clearly demonstrated the feasibility of the copper-catalyzed cycles.

Bromobenzene **3a′** is a cheaper aryl source but much less reactive than iodobenzene. Thus, the application of bromobenzene instead of iodobenzene in the above three-component coupling reaction is highly desirable but also very challenging. After a detailed optimization of reaction conditions (see the Supporting Information), the reaction of bromobenzene at 70 °C could also deliver the triazole **4aa** in 86% yield (entry 14). Notably, by using 20 mol % CuCl together with 0.5 mol % of $Pd_2(dba)_3$ as catalysts, the desired triazoles could be isolated in 73% yield (entry 15). The reaction of disubstituted triazole **5** with iodobenzene or bromobenzene under standard conditions could not afford any desired products **4aa**, indicating **5** is not

Table 1. Optimization of Reaction Conditions[a]



entry	variation from "standard conditions"	yield[b] (%) 4aa	5
1	none	**93 (90)**	3
2	PPh_3 instead of XPhos	52	5
3	SPhos instead of XPhos	87	9
4	BrettPhos instead of XPhos	89	10
5	$PdCl_2(PPh_3)_2$ instead of $Pd_2(dba)_3$ and XPhos	76	8
6	Et_3N instead of K_2CO_3	15	44
7	*t*-BuOLi instead of K_2CO_3	5	6
8	toluene instead of DMF	0	23
9	dioxane instead of DMF	2	29
10	THF instead of DMF	7	17
11	$Pd_2(dba)_3$ (2.5 mol %)	71	6
12	CuCl (50 mol %), DMF (1 mL)	78	10
13	CuCl (25 mol %), DMF (0.5 mL)	62	13
14[c]	PhBr **3a′** instead of PhI	**87 (86)**	11
15[d]	PhBr **3a′** instead of PhI	73	15

[a]Reaction conditions: a mixture of **1a** (0.2 mmol), **2a** (0.3 mmol), and **3a** (0.3 mmol) in DMF (2 mL) was stirred at room temperature under N_2 atmosphere. [b]Determined by ^1H NMR using trimethoxybenzene as the internal standard. The number in parentheses is the isolated yield. [c]CuCl (1 equiv), $Pd_2(dba)_3$ (2.5 mol %), XPhos (10 mol %), 70 °C, 5 h. [d]CuCl (20 mol %), $Pd_2(dba)_3$ (0.5 mol %), XPhos (2 mol %), DMF (0.6 mL), $MgSO_4$ (30 mg), 70 °C. XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl, SPhos =2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, BrettPhos =2-(dicyclohexylphosphino)-3,6-dimethoxy-2′-4′-6′-triisopropyl-1,1′-biphenyl.

the reaction intermediate. Thus, a stepwise reaction is not likely, and vinylcopper to palladium transmetalation mechanism is very possible.

We then started to investigate the scope of alkynes of this reaction. To achieve better yields, we used the conditions using 1 equiv of cheap copper catalyst with very low precious palladium catalyst loading. Both iodobenzene **3a** and bromobenzene **3a′** were used to react with benzyl azide and various terminal alkynes under their optimized conditions (Scheme 2). Both aromatic and aliphatic alkynes were suitable substrates for this reaction, and a large variety of trisubstituted triazoles were synthesized in good yields as the single regioisomer. It was observed that the electron-withdrawing or electron-donating groups at the para position of the aromatic ring did not affect the reaction (entries 1−8). Notably, thiophene- or ferrocene-substituted acetylenes were also applicable in this transformation and gave the corresponding trisubstituted triazoles in good yields, and the structure of product **4ha** was confirmed by single-crystal X-ray analysis (entries 9−14). The reaction of aliphatic alkyne with iodobenzene at room temperature was not successful. Raising the reaction temperature to 60 °C could furnish the expected three-component coupling products in very good yields (conditions C). A series of functional groups such as hydroxyl, cyclopropyl, and phenoxyl groups were well tolerated under these conditions (entries 19−24). Electron-deficient alkynes were similarly transformed into the corresponding products in 73−98% yields (entries 25−28).

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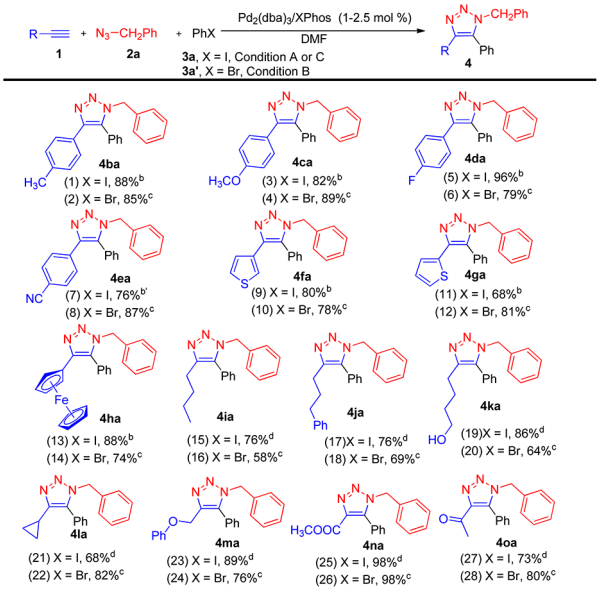
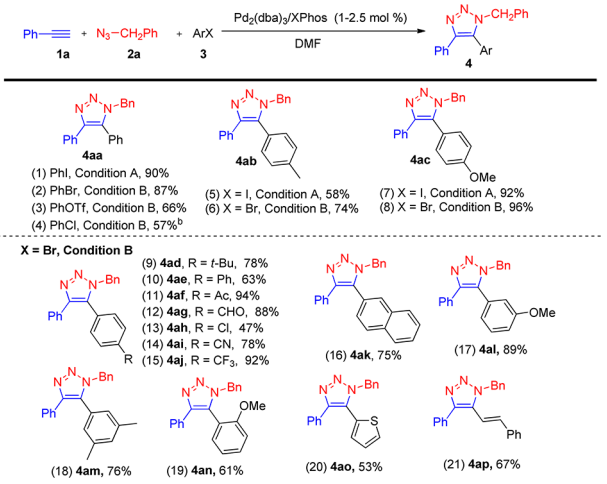
Scheme 2. Substrate Scope of Alkynes[a]



[a]Isolated yields were reported. [b]A mixture of **1a** (0.2 mmol), **2a** (0.3 mmol), iodobenzene **3a** (0.3 mmol), CuCl (1 equiv), $Pd_2(dba)_3$ (1 mol %), and XPhos (4 mol %) in DMF (2 mL) was stirred at room temperature under N_2 atmosphere overnight (Conditions A). [b]$Pd_2(dba)_3$ (2.5 mol %), X-Phos (10 mol %), other conditions as in Conditions A. [c]Bromobenzene **3a′** (0.3 mmol), CuCl (1 equiv), $Pd_2(dba)_3$ (2.5 mol %), XPhos (10 mol %), 70 °C (Conditions B). [d]Iodobenzene **3a** (0.3 mmol), CuCl (1 equiv), $Pd_2(dba)_3$ (2.5 mol %), XPhos (10 mol %), 60 °C, overnight (Conditions C).

The scope of the various aryl halides was further investigated (Scheme 3). Besides aryl iodides and bromides, phenyl

Scheme 3. Substrate Scope of Aryl Halides[a]

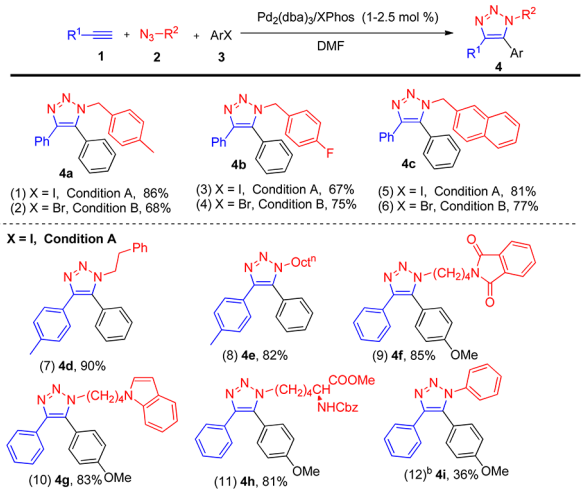


[a]Isolated yields were reported. [b]Chlorobenzene (0.3 mmol), CuCl (1 equiv), $Pd_2(dba)_3$ (5 mol %), XPhos (20 mol %), 110 °C, overnight.

trifluoromethanesulfonate was also applicable for this transformation under standard conditions to afford trisubstituted triazoles in 66% yield (entry 3). The reaction also worked with much less reactive chlorobenzene to produce the desired product in 57% yield, albeit with increased catalyst loading and higher temperature (entry 4). The reaction of various aromatic bromides worked very well, regardless of the electronic nature and position of the substituent groups (entries 5−20). Notably, the styryl group could also be introduced onto the triazole ring efficiently using styryl bromide as the reactant (entry 21).

The scope of the reaction with respect to azides was also investigated (Scheme 4). All of the aliphatic azides tested were

Scheme 4. Substrate Scope of Azides[a]

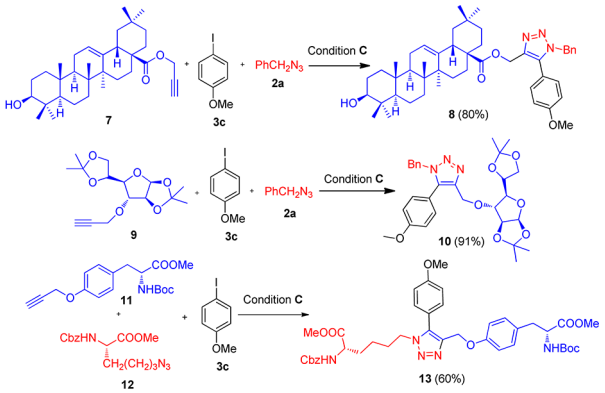


[a]Isolated yields were reported. [b]*p*-Bromoanisole (0.3 mmol), CuCl (1 equiv), $Pd_2(dba)_3$ (5 mol %), XPhos (20 mol %), 80 °C, overnight.

effective substrates, giving the corresponding triazoles in good to excellent yields under standard conditions (entries 1−11). Phthalimide-protected amine and the indole skeleton are both tolerated under these mild conditions (entries 9 and 10). Lysine-derived azide also worked well to give the trisubstituted triazole **4h** in 81% yield (entry 11). However, for the aromatic azide the reaction is less efficient, generating the target trisubstituted triazole in 36% yield (entry 12).

The utility of this chemistry can be featured by the late-stage click reaction on bioactive natural compounds and sugar and amino acid derivatives (Scheme 5). Oleanolic acid, a naturally

Scheme 5. Synthetic Applications



occurring triterpenoid, was found to exhibit anti-HIV and anti-HCV activities, and a recent report indicated that its triazole derivative showed increased potency.[15] Its alkyne derivative **7** could be easily transformed into the trisubstituted triazole **8** in 80% yield, which showed great potential for drug late-stage modification. Sugar derivative **9** bearing sensitive acetal- and acetone-protecting groups was also tolerated and afforded the

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desired product **10** in 91% yield. The three-component click reaction between *p*-iodoanisole, tyrosine, and lysine blocks was also successful and produced the corresponding triazole **13** in 60% yield.

In summary, we have developed a Cu/Pd transmetalation relay catalysis for the construction of trisubstituted triazoles from azide, alkyne, and aryl halide. This method represents a general modular synthesis of trisubstituted triazoles from easily available materials. Application of this protocol led to the bioactive triazole derivatives in a highly efficient and practical manner. Because of the unique structure of the triazoles and the notable features of this protocol, such as high atom and step economy, mild conditions, high efficiency and regioselectivity, and a broad substrate scope, we believe that this method should be useful for drug discovery and development.

■ ASSOCIATED CONTENT

Supporting Information

Experimental detailes, crystal structure of **4ha**, and characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01342.

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Author Contributions

[‖]These authors contributed equally to this work.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews, see: (a) Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. *Chem. Rev.* **2013**, *113*, 4905. (b) Agalave, S. G.; Maujan, S. R.; Pore, V. S. *Chem.—Asian J.* **2011**, *6*, 2696.

(2) (a) Duan, H.; Sengupta, S.; Petersen, J. L.; Akhmedov, N. G.; Shi, X. *J. Am. Chem. Soc.* **2009**, *131*, 12100. (b) Ye, X.; He, Z.; Ahmed, T.; Weise, K.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. *Chem. Sci.* **2013**, *4*, 3712. (c) Gu, Q.; Al Mamari, H. H.; Graczyk, K.; Diers, E.; Ackermann, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 3868.

(3) For reviews, see: (a) Gulevich, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2013**, *52*, 1371. (b) Chattopadhyay, B.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 862.

(4) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) Tornøe, C. W.; Christensen, C.; Medal, M. *J. Org. Chem.* **2002**, *67*, 3057.

(5) (a) Liang, L.; Astruc, D. *Coord. Chem. Rev.* **2011**, *255*, 2933. (b) Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1302. (c) Mamidyala, S. K.; Finn, M. G. *Chem. Soc. Rev.* **2010**, *39*, 1252. (d) Jewett, J. C.; Bertozzi, C. R. *Chem. Soc. Rev.* **2010**, *39*, 1272. (e) Medal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952.

(6) (a) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998. (b) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 8923.

(7) (a) Ding, S.; Jia, G.; Sun, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 1877.

(8) (a) Worrell, B. T.; Ellery, S. P.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2013**, *52*, 13037. (b) Spiteri, C.; Moses, J. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 31. (c) Zhou, Y.; Lecourt, T.; Micouin, L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2607. (d) Hein, J. E.; Tripp, J. C.; Krasnova, L. B.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2009**, *48*, 8018.

(9) (a) Schulman, J. M.; Friedman, A. A.; Panteleev, J.; Lautens, M. *Chem. Commun.* **2012**, *48*, 55. (b) Ackermann, L.; Vicente, R. *Org. Lett.* **2009**, *11*, 4922. (c) Ackermann, L.; Potukuchi, H. K.; Landsberg, D.; Vicente, R. *Org. Lett.* **2008**, *10*, 3081. (d) Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333.

(10) (a) Ackermann, L.; Potukuchi, H. K. *Org. Biomol. Chem.* **2010**, *8*, 4503. (b) Smith, C. D.; Greaney, M. F. *Org. Lett.* **2013**, *15*, 4826. (c) Zhang, X.; Hsung, R. P.; Li, H. *Chem. Commun.* **2007**, 2420. (d) Cai, Q.; Yan, J.; Ding, K. *Org. Lett.* **2012**, *14*, 3332.

(11) (a) Song, C.; Wang, J.; Xu, Z. *Org. Biomol. Chem.* **2014**, *12*, 5802. (b) Song, C.; Ju, L.; Wang, M.; Liu, P.; Zhang, Y.; Wang, J.; Xu, Z. *Chem.—Eur. J.* **2013**, *19*, 3584. (c) Song, C.; Sun, D.; Peng, X.; Bai, J.; Zhang, R.; Hou, S.; Wang, J.; Xu, Z. *Chem. Commun.* **2013**, *49*, 9167. (d) Song, C.; Dong, S.; Feng, L.; Peng, X.; Wang, M.; Wang, J.; Xu, Z. *Org. Biomol. Chem.* **2013**, *11*, 6258.

(12) (a) Li, W.; Wang, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 14186. (b) Thomas, J.; John, J.; Parekh, N.; Dehaen, W. *Angew. Chem., Int. Ed.* **2014**, *53*, 10155. (c) Wang, L.; Peng, S.; Danence, L. J. T.; Gao, Y.; Wang, J. *Chem.—Eur. J.* **2012**, *18*, 6088. (d) Belkheira, M.; Abed, D. E.; Pons, J.-M.; Bressy, C. *Chem.—Eur. J.* **2011**, *17*, 12917. (e) Ramachary, D. B.; Ramakumar, K.; Narayana, V. V. *Chem.—Eur. J.* **2008**, *14*, 9143.

(13) (a) Chen, Z.; Yan, Q.; Liu, Z.; Xu, Y.; Zhang, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 13324. (b) Zhang, H.; Tanimoto, H.; Morimoto, T.; Nishiyama, Y.; Kakiuchi, K. *Org. Lett.* **2013**, *15*, 5222. (c) Sengupta, S.; Duan, H.; Lu, W.; Petersen, J. L.; Shi, X. *Org. Lett.* **2008**, *10*, 1493. (d) Zhou, F.; Tan, C.; Tang, J.; Zhang, Y.-Y.; Gao, W.-M.; Wu, H.-H.; Yu, Y.-H.; Zhou, J. *J. Am. Chem. Soc.* **2013**, *135*, 10994.

(14) (a) He, C.; Ke, J.; Xu, H.; Lei, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 1527. (b) Worrell, B. T.; Malik, J. A.; Fokin, V. V. *Science* **2013**, *340*, 457. (c) Rodionov, V. O.; Fokin, V. V.; Finn, M. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 2210.

(15) Yu, F.; Wang, Q.; Zhang, Z.; Peng, Y.; Qiu, Y.; Shi, Y.; Zheng, Y.; Xiao, S.; Wang, H.; Huang, X.; Zhu, L.; Chen, K.; Zhao, C.; Zhang, C.; Yu, M.; Sun, D.; Zhang, L.; Zhou, D. *J. Med. Chem.* **2013**, *56*, 4300.

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