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Rh-Catalyzed N–O Bond Cleavage of Anthranil: A C–H Amination Reagent for Simultaneous Incorporation of Amine and a Functional Group

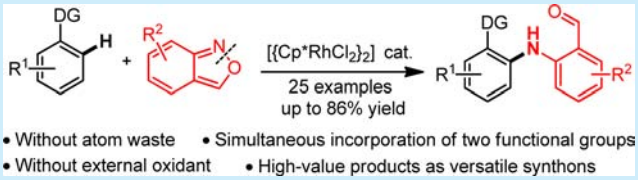
Miancheng Zou,[†] Jianzhong Liu,[†] Conghui Tang,[†] and Ning Jiao*[,†,‡]

[†]State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Beijing 100191, China

[‡]State Key Laboratory of Organometallic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

Supporting Information

ABSTRACT: A novel Rh(III)-catalyzed C–H bond amination with the simultaneous release of a formyl group at distal positions is realized employing anthranil as a new type of C–H amination reagent. This chemistry provides an efficient protocol for the synthesis of 2-acyl diarylamines, which are important structural motifs in many bioactive compounds. This new type of C–H amination reagent possesses the advantages of high atom economy, avoids the use of external oxidants, and enables further transformation of the amination products.



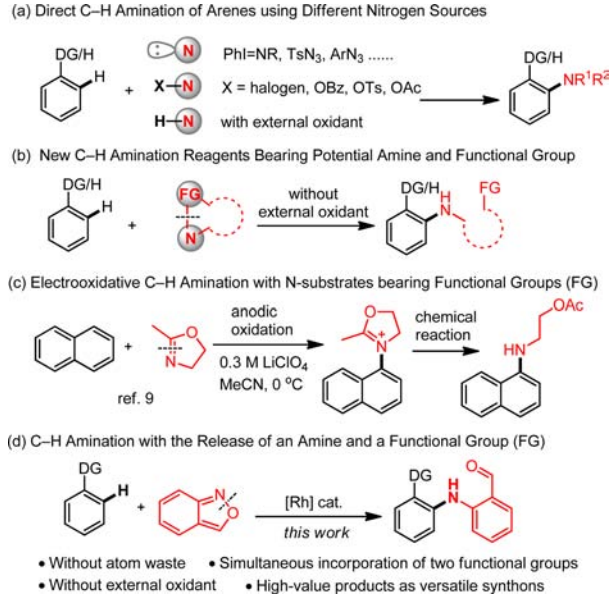
Arylamines are frequently found in numerous natural products, pharmaceuticals, and functional materials.[1] Significant methodologies toward arylamine preparation have been developed through C–N bond formation.[2] In recent years, considerable improvements have been achieved via direct C–H amination.[3] Among them, the nitrogen sources could be generally categorized into three parts (Scheme 1a). C–H activation with nitrenes has been widely used in C–N bond formations employing iminoiodinanes or relative precursors[4] and azide reagents.[5] In addition, by using the umpolung strategy, aryl aminations can be achieved with N-halo-substituted amine and *N*-alkyl hydroxylamines.[6] This protocol is also suitable for amidation with *N*-fluorobenzenesulfonimides and *N*-acetoxycarbamates.[7] From the view of atom economy, commercially available amines are ideal partners to form a C–N bond by dual C–H and N–H bond cleavage in the presence of external oxidants (Scheme 1a).[8]

Despite the significance of these protocols, amination precursors that could enable the generation of amine with the release of a functional group are rarely reported[9] but are very attractive because they offer the feasibility for further various transformations using simultaneously incorporated amine and functional groups (Scheme 1b). An elegant example was recently disclosed by Yoshida and co-workers with an electro-oxidative coupling process (Scheme 1c).[9]

Herein, we report a novel transition-metal-catalyzed C–H amination protocol for the synthesis of 2-acyl diarylamines, which are important structural motifs and useful building blocks (Scheme 1d). Various important bioactive compounds could be prepared from 2-acyl diarylamine products (Figure 1). For instance, transformation of aldehyde to an acid or amide group could afford important drugs or inhibitors (Figure 1).[10] Moreover, 2-(phenylamino)benzaldehyde could serve as a precursor for the synthesis of various heterocycles, such as indoles, indazoles, and acridines (Figure 1).[11]

Discovery of new N-containing reagents for C–H amination has received much attention in recent years.[12] Ideally, the new amination reagents should be readily available, enabling high atom economy[13] and also serving as an internal oxidant.[14] Given the significance of the 2-acyl diarylamine skeleton (Figure 1), we

Scheme 1. Reagents for Direct C–H Amination



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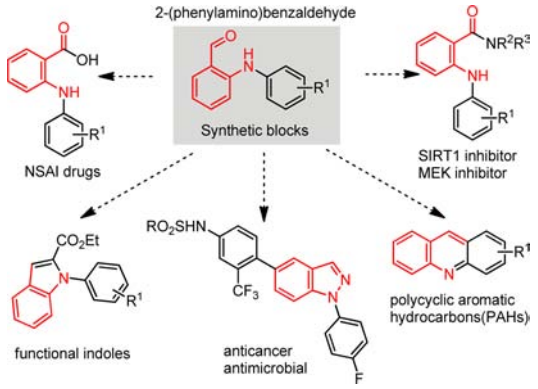
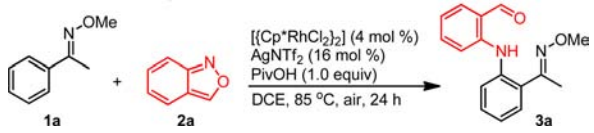


Figure 1. Transformation of 2-aminobenzaldehydes.

were eager to develop direct C(sp^2)−H amination by installing 2-amino benzaldehyde in one step, but it is a challenging issue because the aldehyde group either is oxidized or undergoes side reactions in conventional methods.[15] Anthranil is a N,O-containing heterocyclic compound and is commercially available. It has been used in ring-opening reactions with organozinc reagents and ring expansion reactions with aryldiazoacetates.[16] Recently, Hashmi and co-workers reported a Au-catalyzed cyclization of anthranil with alkyne to form 7-acyl indoles.[17] However, it was not used in a direct C−H bond amination reaction until Li's work[18] and this work (Scheme 1c). Employing anthranil as an amination reagent would have the following advantages: (1) 100% atom efficiency without atom waste, (2) no requirement for an external oxidant, (3) direct C−H amination with simultaneous release of amine and a formyl group, and (4) production of high-value products as versatile building blocks for further transformation, especially for heterocycle synthesis.

Based on the above assumptions, we commenced our investigation using acetophenone *O*-methyl oxime (**1a**) as the model substrate. After screening, we found that when **1a** and **2a** were treated with [{Cp*RhCl$_2$}$_2$], AgNTf$_2$, PivOH at 85 °C in DCE, target product **3a** was obtained in 77% yield (Table 1, entry 1). Controlled experiments revealed that the Rh/Ag catalyst system and the PivOH additive are indispensable in this transformation (entries 2−4). **3a** was obtained in slightly lower yield when the loading of PivOH, **2a**, or catalyst was decreased (entries 5−7). Further, we found that the reaction did not proceed at all under other transition metal catalysts such as Pd, Ru, Co, and Ir (entries 8−11).

Table 1. Rh-Catalyzed Amination of Oxime 1a[a]

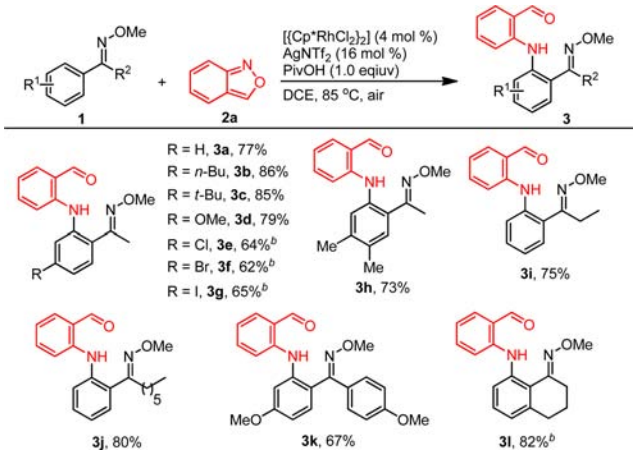


entry	change from the standard conditions	yield (%)[b]
1	none	77
2	no [{Cp*RhCl$_2$}$_2$]	NR
3	no AgNTf$_2$	NR
4	no PivOH	<5
5	60 mol % of PivOH	64
6	2.0 equiv of **2a**	70
7	[{Cp*RhCl$_2$}$_2$] (2.5 mol %), AgNTf$_2$ (10 mol %)	60
8	Pd(OAc)$_2$ instead of [{Cp*RhCl$_2$}$_2$]	NR
9	[Ru(p-cym)Cl$_2$]$_2$ instead of [{Cp*RhCl$_2$}$_2$]	NR
10	[Cp*Co(CO)I$_2$ instead of [{Cp*RhCl$_2$}$_2$]	NR
11	[Cp*IrCl$_2$]$_2$ instead of [{Cp*RhCl$_2$}$_2$]	NR

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (2.5 equiv), catalyst, additives, DCE (1 mL), stirred at 85 °C under air for 24 h. [b]Isolated yields.

The scope of this Rh-catalyzed C−H amination reaction was demonstrated with a series of oxime ether derivatives (Scheme 2). A variety of electron-neutral and electron-rich acetophenone oximes were readily converted to the corresponding products (**3a−d,h**) in excellent yields. Notably, halogen-substituted substrates can be smoothly transformed to the corresponding amination products (**3e−g**), which offer opportunities for further coupling reactions. Oxime ethers derived from phenyl alkyl ketones or diaryl ketones are also suitable substrates to achieve C(sp^2)−H amination products in high yields (**3i−k**). In addition, cyclic oxime ether is well-tolerated in this transformation, producing **3l** in 82% yield.

Scheme 2. Rh-Catalyzed Amination of Oxime Ethers[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (2.5 equiv), [{Cp*RhCl$_2$}$_2$] (4 mol %), AgNTf$_2$ (16 mol %), PivOH (1.0 equiv), DCE (2 mL), stirred at 85 °C under air for 24 h. [b]Reaction was carried out with **2a** (0.2 mmol) and **1** (0.4 mmol) at 100 °C.

Furthermore, other N-containing directing groups were investigated (Scheme 3). Various substituents at the para position of 2-phenylpyridine were tolerated and showed little effect on the efficiency (**5a−d**). A methyl substituent attached to the pyridine ring also showed satisfactory efficiency (**5e**). Other N-containing heterocycles such as quinoline, purine, and pyrazole derivatives could also act as directing groups for this C−H amination reaction with high performance (**5f−h**).

The scope of the anthranils was then examined with oxime ether **1a** (Scheme 4). Several substituted anthranils performed well and delivered the unprotected 2-acyl diarylamines in moderate yields. Some functional groups, such as F (**3m,q**), Cl (**3n**), Br (**3o**), or OAc (**3p**), could be contained in the substrates, leading to various 2-acyl diarylamine products.

As mentioned above, diarylamines are versatile intermediates and flexible scaffolds in organic synthesis. After this pratical intermolecular ortho-functional amination protocol was established, we were eager to apply the products in other transformations. Polycyclic aza-aromatic compounds are basic skeletons in organic molecules, which can be constructed by In(OTf)$_3$ catalysis in 54% yield from **3a** (eq 1). Meanwhile, indoles are important structural motifs in bioactive compounds

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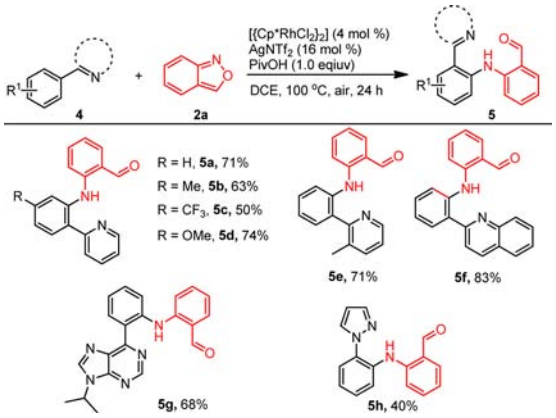
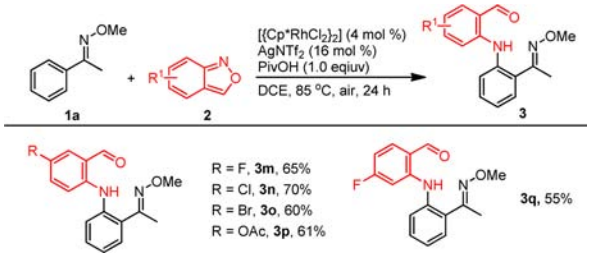
Scheme 3. Scope of Heteroarylarenes[a]

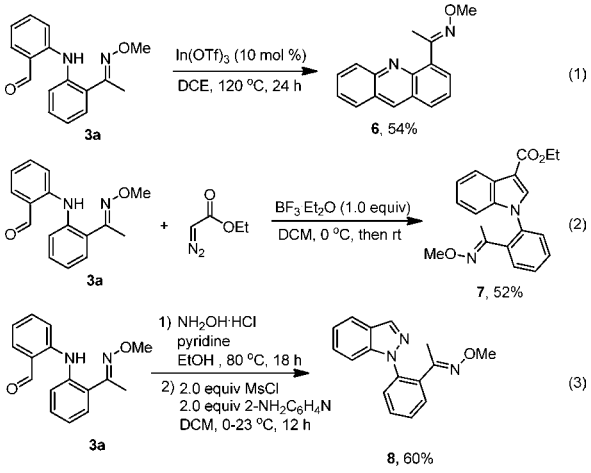


[a]Reaction conditions: **4** (0.2 mmol), **2a** (2.5 equiv), [{Cp*RhCl$_2$}$_2$] (4 mol %), AgNTf$_2$ (16 mol %), PivOH (1.0 equiv), DCE (2 mL), stirred at 100 °C under air for 24 h.

Scheme 4. Substrate Scope of Anthranils[a]



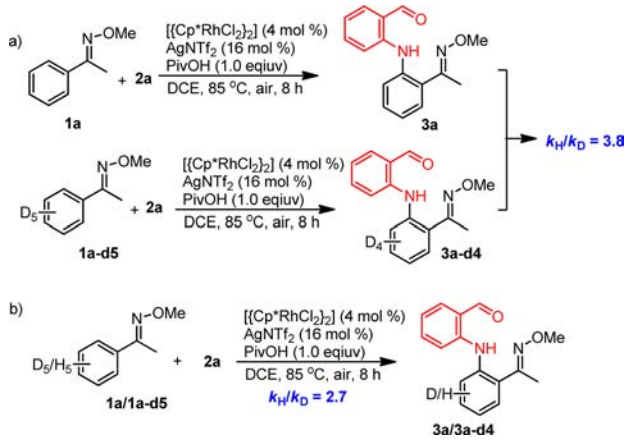
[a]Reaction conditions: **1a** (0.2 mmol), **2** (2.5 equiv), [{Cp*RhCl$_2$}$_2$] (4 mol %), AgNTf$_2$ (16 mol %), PivOH (1.0 equiv), DCE (2 mL), stirred at 85 °C under air for 24 h.



and alkaloids. When **3a** was treated with ethyl diazoacetate, *N*-aryl indole **7** was produced in 52% yield (eq 2). Notably, **3a** could undergo a one-pot reaction to generate *N*-aryl indazole **8** in 60% yield (eq 3), which is the core structure of anti-inflammatory drugs and Hedgehog pathway antagonists.[19]

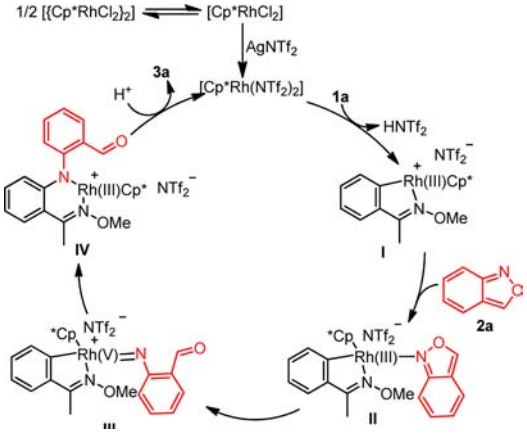
To further understand the mechanism, intermolecular kinetic isotope effect (KIE) experiments were conducted in both parallel and one-pot measurement (Scheme 5a,b), and large KIE values of 3.8 and 2.7 indicated that the C−H/C−D dissociation might be involved in the rate-determining step.

Scheme 5. Mechanistic Studies



On the basis of the above results and previous reports, a tentative mechanism is depicted as follows (Scheme 6). The

Scheme 6. Proposed Mechanism



active rhodium species reacts with **1a** via C−H activation to form cyclometalated intermediate **I**.[20] Anthranil **2a** coordinates to **I** due to the nucleophilicity of nitrogen and delivers intermediate **II**. Subsequent ring opening produces a Rh(V)=N intermediate **III**, and the amino group is inserted into the C−Rh bond to get intermediate **IV**. Finally, protonolysis occurs to give the desired product **3a** with regeneration of the Rh catalyst.

In conclusion, a novel Rh-catalyzed *ortho*-C−H amination of arenes was developed with anthranil as a new type of C−H amination reagent. This chemistry provides an efficient protocol to 2-acyl diarylamines, which are important structural motifs in many bioactive compounds and could be used as versatile building blocks for further heterocyclic compound construction. The present C−H amination protocol possesses the advantages of high atom economy without the addition of external oxidants, which shows a bright future in C−H amination reactions. Further studies to clarify the reaction mechanism and the synthetic applications are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, analytical data, and NMR spectra (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: jiaoning@pku.edu.cn.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Dauban, P.; Dodd, R. H. In *Amino Group Chemistry, From Synthesis to the Life Sciences*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2008; p 55. (b) Lawrence, S. A. *Amines: Synthesis Properties and Applications*; Cambridge University Press: Cambridge, UK, 2004.

(2) (a) Ullmann, F.; Bielecki, J. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 2174. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (c) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (d) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933. (e) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941. (f) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450.

(3) For general reviews in C−H amination reactions, see: (a) Louillat, M.-L.; Patureau, F. W. *Chem. Soc. Rev.* **2014**, *43*, 901. (b) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (c) Jiao, J.; Murakami, K.; Itami, K. *ACS Catal.* **2016**, *6*, 610. (d) Subramanian, P.; Rudolf, G. C.; Kaliappan, K. P. *Chem. - Asian J.* **2016**, *11*, 168. (e) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2015**, *2*, 1107. (f) Ding, Z.; Tan, Q.; Liu, B.; Zhang, K.; Xu, B. *Huaxue Xuebao* **2015**, *73*, 1302.

(4) (a) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571. (b) Yamada, Y.; Yamamoto, T.; Okawara, M. *Chem. Lett.* **1975**, *4*, 361. (c) Roizen, J. L.; Harvey, M. E.; Du Bois, J. *Acc. Chem. Res.* **2012**, *45*, 911. (d) Che, C.-M.; Lo, V.; Zhou, C.-Y.; Huang, J.-S. *Chem. Soc. Rev.* **2011**, *40*, 1950.

(5) (a) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297. (b) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188. (c) Driver, T. G. *Org. Biomol. Chem.* **2010**, *8*, 3831. (d) Uchida, T.; Katsuki, T. *Chem. Rec.* **2014**, *14*, 117. (e) Shin, K.; Kim, H.; Chang, S. *Acc. Chem. Res.* **2015**, *48*, 1040. (f) Intrieri, D.; Zardi, P.; Caselli, A.; Gallo, E. *Chem. Commun.* **2014**, *50*, 11440.

(6) (a) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900. (b) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2860. (c) Kim, J. Y.; Cho, S. H.; Joseph, J.; Chang, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9899. (d) Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2012**, *14*, 656. (e) Matsubara, T.; Asako, S.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2014**, *136*, 646. (f) Ng, F.-N.; Zhou, Z.; Yu, W.-Y. *Chem. - Eur. J.* **2014**, *20*, 4474. (g) Yoo, E. J.; Ma, S.; Mei, T. S.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7652. (h) Yu, S.; Wan, B.; Li, X. *Org. Lett.* **2013**, *15*, 3706. (i) Wu, K.; Fan, Z. L.; Xue, Y.; Yao, Q. Z.; Zhang, A. *Org. Lett.* **2014**, *16*, 42. (j) Shang, M.; Zeng, S.-H.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *Org. Lett.* **2013**, *15*, 5286. (k) Ng, K.-H.; Ng, F. N.; Yu, W.-Y. *Chem. Commun.* **2012**, *48*, 11680.

(7) (a) Sun, K.; Li, Y.; Xiong, T.; Zhang, J. P.; Zhang, Q. *J. Am. Chem. Soc.* **2011**, *133*, 1694. (b) Tang, R. J.; Luo, C. P.; Yang, L.; Li, C.-J. *Adv. Synth. Catal.* **2013**, *355*, 869. (c) Ng, K. H.; Chan, A. S. C.; Yu, W. Y. *J. Am. Chem. Soc.* **2010**, *132*, 12862. (d) Patel, P.; Chang, S. *Org. Lett.* **2014**, *16*, 3328. (e) Ali, M. A.; Yao, X. Y.; Sun, H.; Lu, H. J. *Org. Lett.* **2015**, *17*, 1513. (f) Kawakami, T.; Murakami, K.; Itami, K. *J. Am. Chem. Soc.* **2015**, *137*, 2460.

(8) (a) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (b) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (c) Uemura, T.; Imoto, S.; Chatani, N. *Chem. Lett.* **2006**, *35*, 842. (d) Thu, H. Y.; Yu, W. Y.; Che, C. M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (e) Shang, M.; Sun, S. Z.; Dai, H. X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 3354. (f) Kim, H.; Shin, K.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 5904. (g) Xiao, B.; Gong, T. J.; Xu, J.; Liu, Z. J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 1466.

(9) Morofuji, T.; Shimizu, A.; Yoshida, J. *J. Am. Chem. Soc.* **2015**, *137*, 9816.

(10) (a) Adeniji, A. O.; Twenter, B. M.; Byrns, M. C.; Jin, Y.; Chen, M.; Winkler, J. D.; Penning, T. M. *J. Med. Chem.* **2012**, *55*, 2311. (b) Congiu, C.; Cocco, M. T.; Lilliu, V.; Onnis, V. *J. Med. Chem.* **2005**, *48*, 8245.

(11) (a) Kuninobu, Y.; Tatsuzaki, T.; Matsuki, T.; Takai, K. *J. Org. Chem.* **2011**, *76*, 7005. (b) Levesque, P.; Fournier, P.-A. *J. Org. Chem.* **2010**, *75*, 7033. (c) Wray, B. C.; Stambuli, J. P. *Org. Lett.* **2010**, *12*, 4576.

(12) (a) Jat, J. L.; Paudyal, M. P.; Gao, H.; Xu, Q.-L.; Yousufuddin, M.; Devarajan, D.; Ess, D. H.; Kürti, L.; Falck, J. R. *Science* **2014**, *343*, 61. (b) Park, Y.; Park, K. T.; Kim, J. G.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 4534. (c) Shu, Z.; Ye, Y.; Deng, Y.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 10573. (d) Morofuji, T.; Shimizu, A.; Yoshida, J. *J. Am. Chem. Soc.* **2013**, *135*, 5000.

(13) Trost, B. M. *Science* **1991**, *254*, 1471.

(14) (a) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449. (b) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350. (c) Zhao, D.; Shi, Z.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 12426.

(15) In amination reactions, the aldehyde group easily undergoes a Schmidt reaction when using azide as the nitrogen source and prefers to be oxidized when using the combination of amine and oxidants.

(16) (a) Baum, J. S.; Condon, M. E.; Shook, D. A. *J. Org. Chem.* **1987**, *52*, 2983. (b) Manning, J. R.; Davies, H. M. *Tetrahedron* **2008**, *64*, 6901.

(17) Jin, H.; Huang, L.; Xie, J.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2016**, *55*, 794.

(18) During the revision, a similar work was published: Yu, S.; Tang, G.; Li, Y.; Zhou, X.; Lan, Y.; Li, X. *Angew. Chem., Int. Ed.* **2016**, DOI: 10.1002/anie.201602224.

(19) (a) Yates, C. M.; Brown, P. J.; Stewart, E. L.; Patten, C.; Austin, R. J. H.; Holt, J. A.; Maglich, J. M.; Angell, D. C.; Sasse, R. Z.; Taylor, S. J.; Uings, I. J.; Trump, R. P. *J. Med. Chem.* **2010**, *53*, 4531. (b) Dessole, G.; Branca, D.; Ferrigno, F.; Kinzel, O.; Muraglia, E.; Palumbi, M. C.; Rowley, M.; Serafini, S.; Steinkuhler, C.; Jones, P. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4191.

(20) (a) Ryu, J.; Shin, K.; Park, S. H.; Kim, J. Y.; Chang, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 9904. (b) Park, S. H.; Kwak, J.; Shin, K.; Ryu, J.; Park, Y.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 2492.

DOI: 10.1021/acs.orglett.6b01459
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