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Copper-Catalyzed Synthesis of Polysubstituted Pyrroles through [3+1+1] Cycloaddition Reaction of Nitrones and Isocyanides

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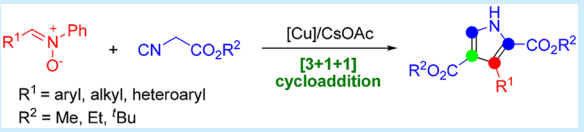
Supporting Information

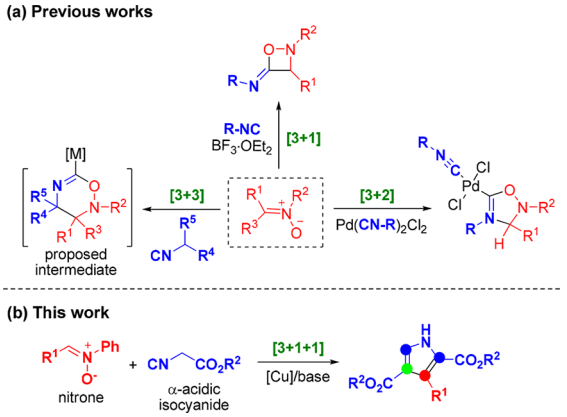
ABSTRACT: An efficient, copper-catalyzed [3+1+1] cycloaddition reaction was developed for the expedient synthesis of pharmacologically interesting polysubstituted pyrroles from easily available nitrones and α-acidic isocyanides. The given approach features a new mode of cycloaddition between nitrones and isocyanides with wide substrate scope, good functional group tolerance, and operational simplicity. The operando infrared spectroscopy was used for the characterization of reaction intermediates.



Isocyanides have attracted tremendous attention in organic synthesis due to their unique reactivity toward electrophiles, nucleophiles, and radicals.[1] Meanwhile, isocyanides also act as "CN" sources[2] or ligands for transitional metals[1c,3] in many transformations. The [3+2] cycloaddition reaction of α-acidic isocyanides with multiple bonds has provided a wide range of nitrogen-containing heterocycles, such as pyrroles,[4] pyrrolines,[5] oxazoles,[6] and imidazoles.[7] As a typical α-acidic isocyanide bearing both an isocyanide group and an acidic α-carbon fragment, isocyanoacetates occur as one of the most useful building blocks with respect to their exceptionally rich synthetic possibilities.[8]

Nitrones, readily available dipoles for 1,3-dipolar cycloadditions, have been widely utilized for the construction of numerous nitrogen-containing heterocycles with activated alkenes or alkynes.[9,10] However, few reports have been documented on the reactions of nitrones with isocyanides. In 2012, Soeta and co-workers demonstrated the chlorosilane-promoted addition reaction of isocyanides to 3,4-dihydroisoquinoline *N*-oxides, affording 1,2,3,4-tetrahydroisoquinoline-1-carboxylamides in moderate to high yields.[11] Several cycloaddition reactions of nitrones with isocyanides were also reported (Scheme 1a). For example, Zeeh, Lorke, and Zhu have independently reported the synthesis of four-membered 4-imino-1,2-oxazetidines by a [3+1] cycloaddition of isocyanides to nitrones with internal octet stabilization, respectively.[12] In a [3+2] cycloaddition manner, nitrones react with palladium-bound isocyanides to provide the carbene complexes.[13] In addition, α-acidic isocyanides were reported to react with nitrones through a proposed [3+3] cycloaddition to give five-membered 2-imidazolidinones.[14] As a part of our interest in exploring isocyanides in the synthesis of heterocycles,[2a,b,3a,e,f,15] we herein report a copper-catalyzed, unprecedented [3+1+1] cycloaddition of nitrones and isocyanoacetates for the expedient synthesis of polysubstituted pyrroles, whereby three sequential C−C bonds

Scheme 1. Cycloaddition of Nitrones with Isocyanides



are formed (Scheme 1b). The prepared polysubstituted pyrroles are prevalent five-membered heterocycles, which are the basic constituents of natural products, pharmaceuticals, functional materials, and agrochemicals.[16] To our knowledge, the given approach features a new mode of cycloaddition between nitrones and isocyanides in the presence of a copper catalyst.

We started our investigation by exploring the reaction of (*Z*)-*N*-benzylideneaniline oxide **1a** with isocyanide **2a** in the presence of copper acetate monohydrate and $KHCO_3$ in dioxane at 80 °C under a nitrogen atmosphere. Intriguingly, trisubstituted pyrrole **3aa** was isolated in 62% yield. The identity of **3aa** was determined by spectral analysis and further confirmed by X-ray crystallographic analysis.[17] A screening of Cu(II) catalysts showed that $Cu(OAc)_2·H_2O$ was the most effective catalyst (Table 1, entries 1−4). Subsequently, examination of different solvents revealed

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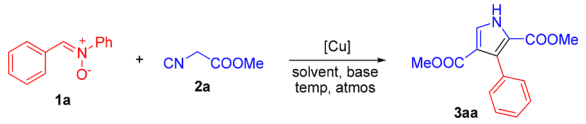
Table 1. Optimization of the Reaction Conditions[a]



entry	Cu source	solvent	base	atmos	temp (°C)	yield[b](%)
1	$Cu(OAc)_2·H_2O$	dioxane	$KHCO_3$	N_2	80	62
2	$CuCl_2$	dioxane	$KHCO_3$	N_2	80	/
3	$Cu(acac)_2$	dioxane	$KHCO_3$	N_2	80	/
4	$CuBr_2$	dioxane	$KHCO_3$	N_2	80	/
5	$Cu(OAc)_2·H_2O$	CH_3CN	$KHCO_3$	N_2	80	60
6	$Cu(OAc)_2·H_2O$	PhCN	$KHCO_3$	N_2	80	64
7	$Cu(OAc)_2·H_2O$	toluene	$KHCO_3$	N_2	80	41
8	$Cu(OAc)_2·H_2O$	DCE	$KHCO_3$	N_2	80	72
9	$Cu(OAc)_2·H_2O$	DMF	$KHCO_3$	N_2	80	52
10	$Cu(OAc)_2·H_2O$	NMP	$KHCO_3$	N_2	80	76
11	$Cu(OAc)_2·H_2O$	NMP	K_3PO_4	N_2	80	55
12	$Cu(OAc)_2·H_2O$	NMP	NaOAc	N_2	80	44
13	$Cu(OAc)_2·H_2O$	NMP	DBU	N_2	80	61
14	$Cu(OAc)_2·H_2O$	NMP	Cs_2CO_3	N_2	80	80
15	**$Cu(OAc)_2·H_2O$**	**NMP**	**CsOAc**	**N_2**	**80**	**86**
16	/	NMP	CsOAc	N_2	80	38
17	$Cu(OAc)_2·H_2O$	NMP	/	N_2	80	48
18	$Cu(OAc)_2·H_2O$	NMP	CsOAc	N_2	70	76
19	$Cu(OAc)_2·H_2O$	NMP	CsOAc	N_2	90	73
20	$Cu(OAc)_2·H_2O$	NMP	CsOAc	O_2	80	71
21	$Cu(OAc)_2·H_2O$	NMP	CsOAc	air	80	47
22	$Cu(OAc)_2·H_2O$	NMP	CsOAc	N_2	80	46[c]
23	$Cu(OAc)_2·H_2O$	NMP	CsOAc	N_2	80	69[d]
24	$Cu(OAc)_2·H_2O$	NMP	CsOAc	N_2	80	48[e]

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.9 mmol), [Cu] (0.09 mmol), base (0.6 mmol), solvent (1 mL), 20 h. [b]Isolated yields. [c]10 mol % $Cu(OAc)_2·H_2O$ was used. [d]20 mol % $Cu(OAc)_2·H_2O$ was used. [e](*Z*)-*N*-Benzylidenemethanamine oxide was used instead of **1a**.

that the reaction in *N*-methyl-pyrrolidone (NMP) afforded the best result (entries 5−10). After an extensive screening of the bases (entries 10−15), CsOAc was found to be the best choice, affording the pyrrole **3aa** in 86% yield (entry 15). The synergetic effect of the copper catalyst and base was justified, as the absence of either led to a significant decrease of the yields (entries 16−17). The temperature, atmosphere, and loadings of the catalyst also have dramatic effects on the yields (entries 18−23). When (*Z*)-*N*-benzylidenemethanamine oxide was used instead of **1a**, the desired pyrrole product was obtained in only 48% yield (entry 24), indicating the crucial substituent effect of the nitrones.

With the optimized conditions in hand, we next examined the substrate scope of nitrones and isocyanides. As shown in Scheme 2, the reaction showed good functional group tolerance. Aryl nitrones bearing either electron-withdrawing or electron-donating groups in the *para* position were smoothly converted to the corresponding products in moderate to excellent yields (**3ba**−**3ha**). The *ortho*-, *meta*-substituted, or disubstituted aryl nitrones also afforded the desired products in good yields (**3ia**−**3na**). The present protocol is not only compatible with simple benzene-based substrates: nitrones with naphthyl (**3oa** and **3pa**) or heteroaromatic substituents bearing indolyl (**3qa**), thienyl (**3ra** and **3sa**), and furyl (**3ta**) groups afforded the corresponding products in moderate to good yields. Notably, a variety of alkyl nitrones all gave pyrroles in moderate to good yields (**3ua**−**3wa**). The ester groups of isocyanoacetates were also investigated with the final pyrrole products obtained smoothly (**3ab**, **3vb**, **3ac**). However, attempts to use methyl 2-isocyanopropanoate[18] as substrate failed under the same conditions, which gave a complicated mixture and was hard to identify.

The prepared polysubstituted pyrroles are important starting materials for the synthesis of biologically active compounds and organic functional materials.[16] As an example, postfunctionalization of pyrrole **3aa** was performed to afford pyrrolo[1,2-*a*]-quinoxalines **5** in 52% yield through CuI/L-proline-catalyzed intermolecular coupling with 2-iodotrifluoroacetanilide **4**,[19] followed by hydrolysis and a spontaneous intramolecular cyclization reaction (Scheme 3). The cyclic product **5** was a key intermediate for the synthesis of nonpeptide inhibitors of platelet aggregation.[20]

To define the possible intermediates and pathway, several control experiments were carried out, as shown in Scheme 4. Only a trace amount of the desired product **3aa** was obtained when benzaldehyde was used instead of nitrone **1a** under the standard reaction conditions (Scheme 4a). The reason for the low yield of **3aa** may be due to the formation of other byproducts through different pathways.[21] This result suggested that the aldehyde was not the key intermediate in this reaction, and the use of nitrone as substrate is superior to aldehyde for the cycloaddition reaction. However, a high yield could be achieved when vinyl isocyanide **6**[22] was used instead of nitrone **1a** (Scheme 4b), which indicated that it might be a possible intermediate for this reaction. Furthermore, the addition of 2,2,6,6-tetramethyl-1-piperidinyl-oxy (TEMPO) or 1,4-dinitrobenzene as radical scavengers had no significant effect on this reaction (Scheme 4c,d), which might rule out a radical pathway.

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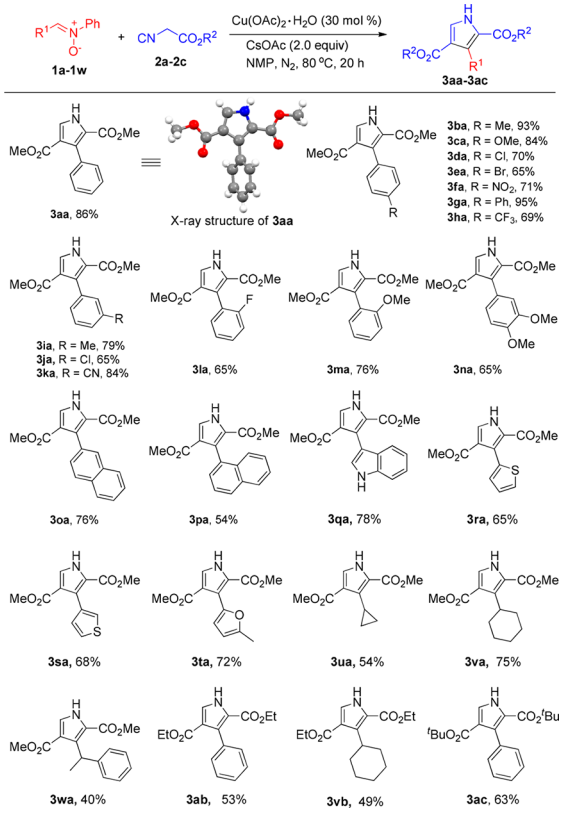
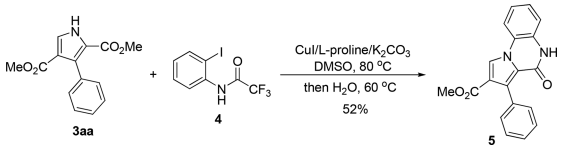
Scheme 2. Substrate Scope of Pyrroles[a,b]

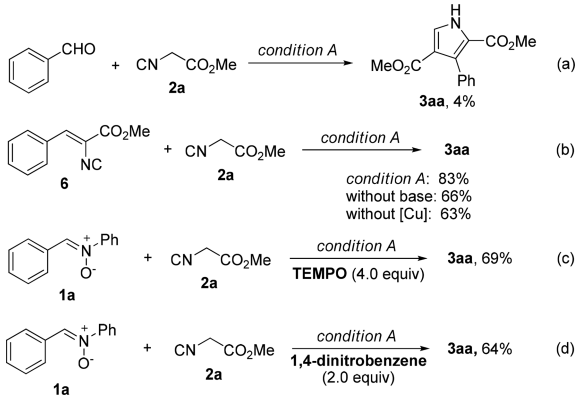


[a]Reaction conditions: **1** (0.3 mmol), **2** (0.9 mmol), $Cu(OAc)_2·H_2O$ (0.09 mmol), CsOAc (0.6 mmol), and NMP (1.0 mL), 80 °C, nitrogen atmosphere. [b]Isolated yield.

Scheme 3. Synthetic Application of the Product



Scheme 4. Mechanistic Studies[a]

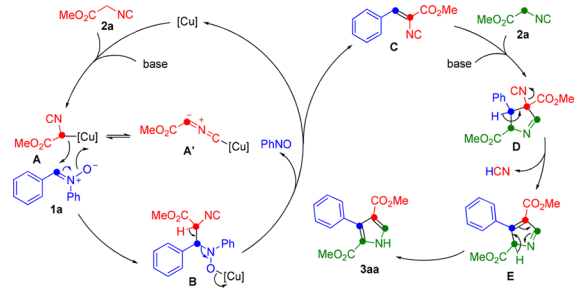


[a]Condition A: $Cu(OAc)_2·H_2O$ (30 mol %), CsOAc (2.0 equiv), NMP, 80 °C, nitrogen atmosphere, 20 h.

The operando infrared spectroscopy has been used as an effective method for the characterization of reaction intermediates, which provides direct evidence for the reaction mechanism.[23] We contemplated that the nitrone fragment may be eliminated as nitrosobenzene during the reaction. To probe the progress of this cascade transformation further, we investigated this reaction using operando IR to monitor the possible existence of nitrosobenzene. During the study, the characteristic absorption of nitrosobenzene at 1505 cm^{-1} was selected for observation to avoid interferences from the reaction system. Finally, the *in situ* generation of nitrosobenzene was proved by the operando infrared spectroscopy (Figures S1−S3, see the SI for more details), indicating that the reaction may undergo the release of nitrosobenzene.

Based on the above preliminary results, a plausible mechanism for this copper-catalyzed [3+1+1] cycloaddition is proposed in Scheme 5. We envisaged that C−H metalation of isocyanide **2a** would occur to generate the intermediate α-cuprio-isocyanide **A** in the presence of $Cu(OAc)_2·H_2O$ and a base.[22b,24] Then, a nucleophilic addition between nitrone **1a** and intermediate **A** took place to produce the copper intermediate **B**.[22b] Intermediate **B** was presumably converted into a more stable vinyl isocyanide intermediate **C**[22] through an elimination process with the expulsion of nitrosobenzene and the regeneration of the copper catalyst. Finally, the olefinic intermediate **C** underwent cycloaddition with the second molecule of isocyanide **2a** to yield pyrrole **3aa** via intermediates **D** and **E**.[4a]

Scheme 5. Plausible Mechanism



In summary, we have developed a novel, copper-catalyzed [3+1+1] cycloaddition reaction for the expedient synthesis of polysubstituted pyrroles from easily available nitrones and isocyanoacetates with operational simplicity, mild reaction conditions, good functional group tolerance, and wide substrate scope. Operando infrared spectroscopy was used for the characterization of reaction intermediates. This approach represents a unique synthetic strategy of nitrones and isocyanides through the formation of three sequential C−C bonds and offers an alternative route for the preparation of polysubstituted pyrroles. Further insight into the mechanism, reaction scope, and biological applications is under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00798.

Experimental procedures and characterization data for all compounds and X-ray structures of compounds **3aa** (PDF)

Accession Codes

CCDC 1813419 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_

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request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For recent reviews on isocyanide, see: (a) Song, B.; Xu, B. *Chem. Soc. Rev.* **2017**, *46*, 1103. (b) Giustiniano, M.; Basso, A.; Mercalli, V.; Massarotti, A.; Novellino, E.; Tron, G. C.; Zhu, J. *Chem. Soc. Rev.* **2017**, *46*, 1295. (c) Boyarskiy, V. P.; Bokach, N. A.; Luzyanin, K. V.; Kukushkin, V. Y. *Chem. Rev.* **2015**, *115*, 2698. (d) Zhang, B.; Studer, A. *Chem. Soc. Rev.* **2015**, *44*, 3505. (e) Wang, H.; Xu, B. *Youji Huaxue* **2015**, *35*, 588. (f) Lang, S. *Chem. Soc. Rev.* **2013**, *42*, 4867. (g) Qiu, G.; Ding, Q.; Wu, J. *Chem. Soc. Rev.* **2013**, *42*, 5257. (h) Vlaar, T.; Ruijter, E.; Maes, B. U. W.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 7084.

(2) (a) Hong, X.; Wang, H.; Qian, G.; Tan, Q.; Xu, B. *J. Org. Chem.* **2014**, *79*, 3228. (b) Xu, S.; Huang, X.; Hong, X.; Xu, B. *Org. Lett.* **2012**, *14*, 4614. (c) Peng, J.; Zhao, J.; Hu, Z.; Liang, D.; Huang, J.; Zhu, Q. *Org. Lett.* **2012**, *14*, 4966.

(3) For selected examples, see: (a) Hong, X.; Tan, Q.; Liu, B.; Xu, B. *Angew. Chem., Int. Ed.* **2017**, *56*, 3961. (b) Tšupova, S.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Adv. Synth. Catal.* **2016**, *358*, 3999. (c) Riedel, D.; Wurm, T.; Graf, K.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Adv. Synth. Catal.* **2015**, *357*, 1515. (d) Zeiler, A.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Chem. - Eur. J.* **2015**, *21*, 11065. (e) Gao, M.; Li, Y.; Gan, Y.; Xu, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 8795. (f) Qian, G.; Hong, X.; Liu, B.; Mao, H.; Xu, B. *Org. Lett.* **2014**, *16*, 5294. (g) Hubbert, C.; Breunig, M.; Carroll, K. J.; Rominger, F.; Hashmi, A. S. K. *Aust. J. Chem.* **2014**, *67*, 469. (h) Manzano, R.; Rominger, F.; Hashmi, A. S. K. *Organometallics* **2013**, *32*, 2199. (i) Hashmi, A. S. K.; Riedel, D.; Rudolph, M.; Rominger, F.; Oeser, T. *Chem. - Eur. J.* **2012**, *18*, 3827. (j) Hashmi, A. S. K.; Lothschütz, C.; Böhling, C.; Rominger, F. *Organometallics* **2011**, *30*, 2411. (k) Bartolomé, C.; Ramiro, Z.; García-Cuadrado, D.; Pérez-Galán, P.; Raducan, M.; Bour, C.; Echavarren, A. M.; Espinet, P. *Organometallics* **2010**, *29*, 951. (l) Michelin, R. A.; Pombeiro, A. J. L.; Guedes da Silva, M. F. C. *Coord. Chem. Rev.* **2001**, *218*, 75.

(4) (a) Tiwari, D. K.; Phanindrudu, M.; Aravilli, V. K.; Sridhar, B.; Likhar, P. R.; Tiwari, D. K. *Chem. Commun.* **2016**, *52*, 4675. (b) Liu, J.; Fang, Z.; Zhang, Q.; Liu, Q.; Bi, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 6953. (c) Gao, M.; He, C.; Chen, H.; Bai, R.; Cheng, B.; Lei, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 6958. (d) Larionov, O. V.; de Meijere, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5664.

(5) (a) Arróniz, C.; Gil-González, A.; Semak, V.; Escolano, C.; Bosch, J.; Amat, M. *Eur. J. Org. Chem.* **2011**, *2011*, 3755. (b) Guo, C.; Xue, M.; Zhu, M.; Gong, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 3414.

(6) (a) Shao, P.; Liao, J.; Ho, Y. A.; Zhao, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 5435. (b) Mossetti, R.; Pirali, T.; Tron, G. C.; Zhu, J. *Org. Lett.* **2010**, *12*, 820. (c) Wang, Q.; Xia, Q.; Ganem, B. *Tetrahedron Lett.* **2003**, *44*, 6825. (d) Tang, J.; Verkade, J. G. *J. Org. Chem.* **1994**, *59*, 7793.

(7) Kanazawa, C.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2006**, *128*, 10662.

(8) Gulevich, A. V.; Zhdanko, A. G.; Orru, R. V. A.; Nenajdenko, V. G. *Chem. Rev.* **2010**, *110*, 5235.

(9) For reviews, see: (a) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887. (b) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235.

(10) For selected examples, see: (a) Morse, P. D.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2017**, *56*, 13999. (b) Barber, J. S.; Styduhar, E. D.; Pham, H. V.; McMahon, T. C.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2016**, *138*, 2512. (c) Jiao, P.; Nakashima, D.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2411. (d) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 718. (e) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874. (f) Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 4999. (g) Kinugasa, M.; Hashimoto, S. *J. Chem. Soc., Chem. Commun.* **1972**, 466.

(11) Soeta, T.; Fujinami, S.; Ukaji, Y. *J. Org. Chem.* **2012**, *77*, 9878.

(12) (a) Grassot, J. M.; Masson, G.; Zhu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 947. (b) Moderhack, D.; Lorke, M. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 45. (c) Zeeh, B. *Synthesis* **1969**, *1969*, 37.

(13) Luzyanin, K. V.; Tskhovrebov, A. G.; Guedes da Silva, M. F. C.; Haukka, M.; Pombeiro, A. J. L.; Kukushkin, V. Y. *Chem. - Eur. J.* **2009**, *15*, 5969.

(14) Schöllkopf, U. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 339.

(15) (a) Fang, T.; Tan, Q.; Ding, Z.; Liu, B.; Xu, B. *Org. Lett.* **2014**, *16*, 2342. (b) Huang, X.; Xu, S.; Tan, Q.; Gao, M.; Li, M.; Xu, B. *Chem. Commun.* **2014**, *50*, 1465.

(16) For reviews, see: (a) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J. *Chem. Rev.* **2008**, *108*, 264. (b) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213. For selected examples, see: (c) Desplat, V.; Vincenzi, M.; Lucas, R.; Moreau, S.; Savrimoutou, S.; Pinaud, N.; Lesbordes, J.; Peyrilles, E.; Marchivie, M.; Routier, S.; Sonnet, P.; Rossi, F.; Ronga, L.; Guillon, J. *Eur. J. Med. Chem.* **2016**, *113*, 214. (d) Wang, M.; Gao, M.; Zheng, Q. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3700. (e) Brenner, W.; Malig, J.; Costa, R. D.; Guldi, D. M.; Jux, N. *Adv. Mater.* **2013**, *25*, 2314. (f) Kuzuhara, D.; Mack, J.; Yamada, H.; Okujima, T.; Ono, N.; Kobayashi, N. *Chem. - Eur. J.* **2009**, *15*, 10060. (g) Freel Meyers, C. L.; Oberthür, M.; Heide, L.; Kahne, D.; Walsh, C. T. *Biochemistry* **2004**, *43*, 15022.

(17) For crystallographic data of compound **3aa**, see the Supporting Information.

(18) Elders, N.; Schmitz, R. F.; de Kanter, F. J. J.; Ruijter, E.; Groen, M. B.; Orru, R. V. A. *J. Org. Chem.* **2007**, *72*, 6135.

(19) (a) Yuan, Q.; Ma, D. *J. Org. Chem.* **2008**, *73*, 5159. (b) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164.

(20) Grande, F.; Aiello, F.; Grazia, O. D.; Brizzi, A.; Garofalo, A.; Neamati, N. *Bioorg. Med. Chem.* **2007**, *15*, 288.

(21) (a) Nunami, K.; Hiramatsu, K.; Hayashi, K.; Matsumoto, K. *Tetrahedron* **1988**, *44*, 5467. (b) Suzuki, M.; Miyoshi, M.; Matsumoto, K. *J. Org. Chem.* **1974**, *39*, 1980. (c) Schöllkopf, U.; Gerhart, F.; Schröder, R.; Hoppe, D. *Jusfus Liebig Ann. Chem.* **1972**, *766*, 116.

(22) (a) Mao, H.; Gao, M.; Liu, B.; Xu, B. *Org. Chem. Front.* **2016**, *3*, 516. (b) Du, J.; Xu, X.; Li, Y.; Pan, L.; Liu, Q. *Org. Lett.* **2014**, *16*, 4004. (c) Wang, H.; Yu, Y.; Hong, X.; Xu, B. *Chem. Commun.* **2014**, *50*, 13485. (d) Jiang, H.; Cheng, Y.; Wang, R.; Zhang, Y.; Yu, S. *Chem. Commun.* **2014**, *50*, 6164. (e) Cheng, Y.; Yuan, X.; Jiang, H.; Wang, R.; Ma, J.; Zhang, Y.; Yu, S. *Adv. Synth. Catal.* **2014**, *356*, 2859.

(23) (a) Lu, Q.; Zhang, J.; Zhao, G.; Qi, Y.; Wang, H.; Lei, A. *J. Am. Chem. Soc.* **2013**, *135*, 11481. (b) Hoover, J. M.; Ryland, B. L.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 2357.

(24) (a) Qiu, G.; Wu, J. *Chem. Commun.* **2012**, *48*, 6046. (b) Lygin, A. V.; Larionov, O. V.; Korotkov, V. S.; de Meijere, A. *Chem. - Eur. J.* **2009**, *15*, 227. (c) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260.

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