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Silver-Mediated Direct C–H Cyanation of Terminal Alkynes with *N*-Isocyanoiminotriphenylphosphorane

Hannan Wang,[†,∥] Pengbing Mi,[†,∥] Wanjun Zhao,[†] Ravi Kumar,[§] and Xihe Bi*[,†,‡]

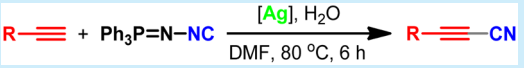
[†]Jilin Province Key Laboratory of Organic Functional Molecular Design & Synthesis, Department of Chemistry, Northeast Normal University, Changchun 130024, China

[‡]State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China

[§]Medicinal and Process Chemistry, CSIR-Central Drug Research Institute, Lucknow 226031, India

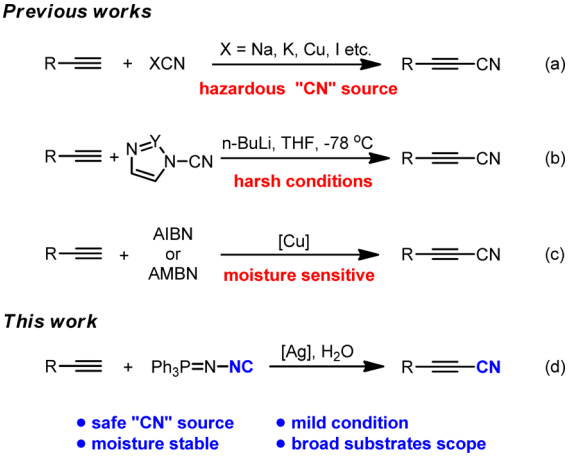
Supporting Information

ABSTRACT: A direct cyanation of terminal alkynes for the synthesis of propionitrile derivatives, with the aid of silver salt using water additive, has been achieved. The cyano source used is *N*-isocyanoiminotriphenylphosphorane, which is nontoxic, safe, and easy to handle. This protocol is characterized by its operational simplicity, high efficiency with excellent yields, broad substrate scope, and greater functional group tolerance.



Nitrile functionality represents one of the most promising active units, which is not only present in natural products from plant/animal sources but is also present in a large number of clinically used drugs and polymers and serves as a valuable synthetic precursor in organic chemistry.[1] One of the most important nitrile compounds is propiolonitrile, which is characterized by assembly of two important functionalities, alkyne and nitrile, and has been identified as a versatile building block for decades.[2] Molecules obtained from derivatizing these two functional units possess great importance both in chemical and biological aspects.[3] Therefore, the development of practical methods for its preparation is of great importance. In this line, few groups have converted propargylic systems to propionitrile under metal or metal-free conditions.[4] Direct cyanation[5] of terminal alkynes, however, opens a new avenue to approach propionitrile using both organic and inorganic cynating reagents (Scheme 1). The methodologies, however, suffer from the limitations to use toxic cyanide salts, moisture sensitive reagents, or harsh conditions. Therefore, safe, moisture stable, convenient approaches to propiolonitriles from simple starting materials is of great interest in modern organic synthesis.

Scheme 1. Preparation of Propiolonitriles



Over the past few decades isocyanide has shown spectacular rise in its application as reactive intermediate in organic synthesis because of its ability to act as one carbon unit in the insertion reaction and as the coupling partner.[6] Among innumerable applications of isocyanide, the most striking feature is to acts as "cyano" source and have advantages over others being nontoxic, commercially available, easy to handle, and environmentally benign. Accordingly, a plethora of examples has been reported for the introduction of nitrile unit using isocyanides into heteroarenes,[7] imines,[8] aldehydes,[9] alkyl halogens,[10] and *N N*-dimethyl-2-alkynylaniline.[11] One of the bench stable isocyanides, *N*-isocyanoiminotriphenylphosphorane (NIITP), was reported by Fehlhammer and Weinberger in 1980, which opened the door for extensive use of isocyanides as these are bench-stable, safe, easy-to-handle, and odorless solids.[12] Since its inception, the synthetic potency has been extensively explored, but they are restricted to act as a "CNN" building block in base-mediated heterocyclic synthesis.[13] However, from the first application of NIITP for converting acid chloride to α-diazoketone, NIITP is still a great choice due to safety and ease of handling.[14] As our journey is to explore the silver-catalyzed σ-activation of isocyanides[15] and alkynes,[16] herein we reported a silver-promoted intermolecular direct cyanation of terminal alkynes with NIITP via cleavage of its N–NC bond, thereby providing a safe, moisture-stable, and convenient method for the synthesis of propiolonitriles.

We started our investigations by studying the reaction of 1-ethynyl-4-methoxybenzene (**1a**) with NIITP (**2**) in the presence of a quantitative amount of silver carbonate (Table 1). To our delight we get our desired 3-(4-methoxyphenyl)propiolonitrile (**3a**) in 24% yield using MeCN as solvent (entry 1). A solvent

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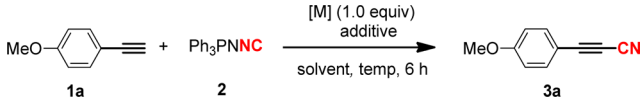
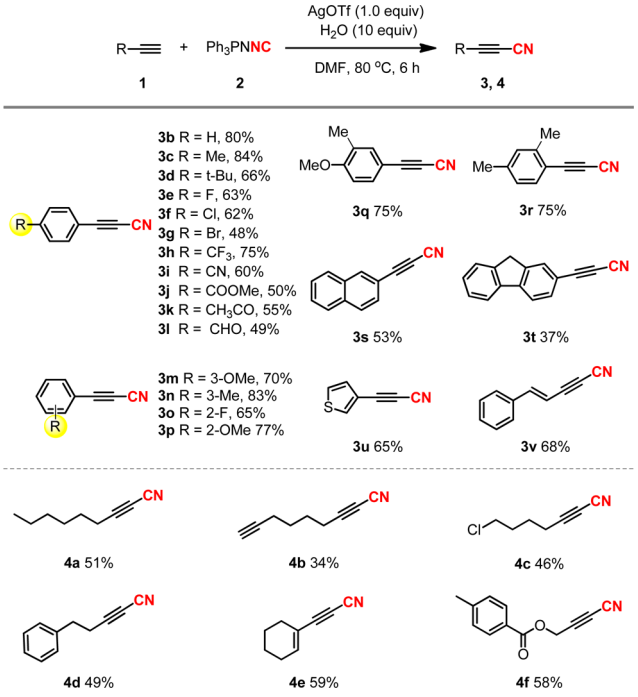
Table 1. Optimization of the Reaction Conditions[a,b]



entry	[M] cat.	additive	solvent	temp	yield (%)[b]
1	Ag_2CO_3	H_2O	CH_3CN	80	24
2	Ag_2CO_3	H_2O	PhCl	80	17
3	Ag_2CO_3	H_2O	DCE	80	12
4	Ag_2CO_3	H_2O	THF	80	6
5	Ag_2CO_3	H_2O	DMF	80	26
6	AgOTf	H_2O	DMF	80	76
7	$AgNO_2$	H_2O	DMF	80	18
8	Ag_3PO_4	H_2O	DMF	80	25
9	$AgNO_3$	H_2O	DMF	80	50
10	$Sc(OTf)_3$	H_2O	DMF	80	0
11	$Bi(OTf)_3$	H_2O	DMF	80	24
12	$Ga(OTf)_3$	H_2O	DMF	80	35
13[c]	AgOTf	H_2O	DMF	80	16
14	AgOTf		DMF	80	np
15	AgOTf	CH_3OH	DMF	80	67
16	AgOTf	H_2O	DMF	100	58
17	AgOTf	H_2O	DMF	60	67

[a]Reaction conditions: **1a** (0.5 mmol), **2** (1.0 mmol), and additive (10 equiv) for 6 h, under Ar. [b]Isolated yield. [c]AgOTf (30 mol %).

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



[a]Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), and AgOTf (0.5 mmol) and H_2O (5 mmol) in DMF (5 mL) at 80 °C for 6 h, under Ar. [b]Isolated yield.

screening then conducted to improve the yield; accordingly, PhCl, DCE, and THF, were tested and found unsuitable for the conversion (entries 2−4). Switching to DMF as solvent marginally raised the yield of **3a** to 26% (entry 5). Interestingly use of AgOTf was particularly propitious affording **3a** in 76% yield (entry 6). Other silver salts were soon tested for further improvement of the product outcome. Likewise $AgNO_2$, Ag_3PO_4, and $AgNO_3$ were chosen and found ineffective in the title conversion and afforded **3a** in 18−50% yield (entries 7−9). We next turned our attention to use Lewis acids as promoter of the reaction. In this context, $Sc(OTf)_3$ totally halted the reaction (entry 10); however, $Bi(OTf)_3$ and $Ga(OTf)_3$ were less effective in direct cyanation process and yielded **3a** in 24% and 35%, respectively (entries 11−12). Interestingly, product yield was totally diminished when silver loading was dropped to 30%, which showed that silver is necessary in stoichiometric amount (entry 13). Either removal of water as additive or replacement with methanol totally resisted the reaction or afforded **3a** in lower yield (entries 14−15). We also probe to test the fate of the reaction temperature by carrying out reaction at 100 or 60 °C, which did not lead to the improvement of the yield (entries 16−17).

We therefore proceeded with the best condition involving stoichiometric the use of AgOTf with 10 equiv of water as additive in DMF solvent. We investigate the scope and limitation of the reaction on aryl acetylenes containing both electron-donating/withdrawing substituents (Scheme 2). Likewise 4-substituted Me (**1c**) and ^{t}Bu (**1d**) aryl acetylene smoothly converted to corresponding propionitrile derivatives (**3c−d**) in 84% and 66% yield, respectively. Halogen-containing acetylenes (**1e−g**) were suitable feedstock for the direct cyanation process but afforded halogen-containing propionitrile derivatives **3e−g** in somewhat lower yields (48−63%). Next electron withdrawing groups like $-CF_3$ and −CN were tested for title conversion, which afforded **3h** and **3i** in good yields. Sensitive functional groups like ester (**1j**), keto (**1k**), and aldehyde (**1l**) were well effective for product formation **3j−l** but in moderate reactivity (49−55%). Similarly 3- and 2-substituted aryl acetylenes did not resist the reaction and gave propionitrile derivative **3m−p** in high yield (65−83%). Reactivity of disubstituted acetylene was equally potent and delivered **3r** and **3q** in 75% yields. Substrate scope was then extended to naphthalene (**1s**) and fluorene (**1t**) derivatives, which afforded corresponding propionitrile derivatives in moderate yields. We were also curious to check the feasibility of reaction on some heterocyclic (**1u**) and olefinic (**1v**) alkynes, which furnished **3u−v** in good yield. In addition, we also tested some aliphatic alkynes, which indeed converted into corresponding propionitrile derivatives, but in moderate to good reactivity, and afforded **4a−f** in 34−59% yields.

Gram-scale synthesis of **3c** was achieved in 75% yield demonstrating the practicability of the transformation. Further, we investigated the follow-up chemistry using propiolonitrile **3c** as a substrate (Scheme 3). The synthetic utility of **3c** was demonstrated by preparation of a series of heterocycles, such as 1,2,3-triazole (**5**), pyrrole (**6**), and benzofuran (**7**), in good to high yields. Additionally, acrylonitriles (**8−9**) were efficiently synthesized from **3c** upon treatment with phenol or 1-methylimidazole under mild conditions.

On the basis of previous results,[15b,d] and our experimental observations, we have proposed a plausible mechanism shown in Scheme 4. Initially, the alkyne **1b** reacts with AgOTf to generate the silver acetylide **I**. In the next step, insertion of isonitrile **2** (NIITP) into the silver−carbon bond of **I** produced an acetylinic imido complex **II**. Finally, the complex **II** give the target compound **2b** with the release of AgOH and triphenylphosphine azaylide.

In summary, we have developed a safe, efficient approach for the synthesis of propiolonitriles derivatives starting from simple terminal alkynes via a direct C−H cyanation process. In the

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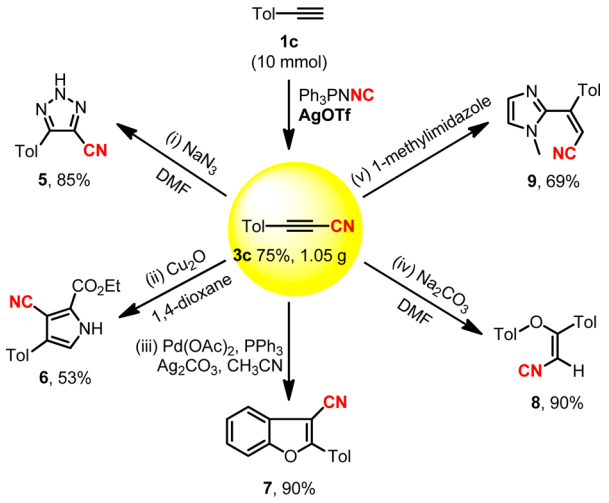
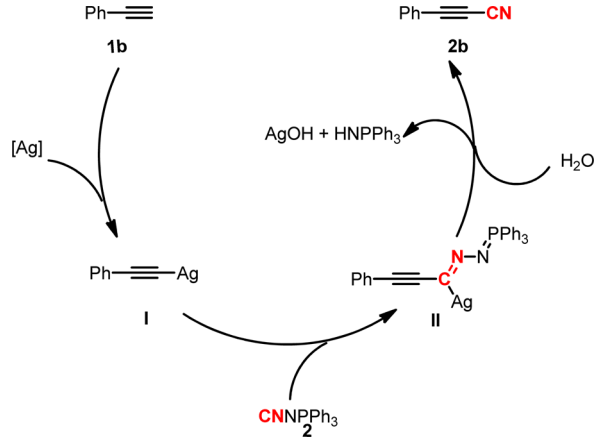
Scheme 3. Gram-Scale Synthesis and Applications



Scheme 4. Plausible Mechanism



reaction, NIITP served as a nontoxic, facile "CN" source. The synthetic value of this compound was evaluated by utilizing them in various organic transformations. Further studies on the utilization of NIITP are ongoing in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02743.

Experimental procedures and spectra copies (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: bixh507@nenu.edu.cn.

ORCID

Xihe Bi: 0000-0002-6694-6742

Author Contributions

‖These authors contributed equally to this work.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Kleemann, J. E.; Kutscher, B.; Reichert, D. *Pharmaceutical Substance: Synthesis, Patents, Applications*, 4th ed.; Georg Thieme: Stuttgart, 2001. (b) Miller, J. S.; Manson, J. L. *Acc. Chem. Res.* **2001**, *34*, 563. (c) Fleming, F. F.; Wang, Q. *Chem. Rev.* **2003**, *103*, 2035.

(2) (a) Xu, Y.; Zhao, J.; Chen, H.; Wu, W.; Jiang, H. *Chem. Commun.* **2014**, *50*, 2488. (b) Sahner, J. H.; Groh, M.; Negri, M.; Haupenthal, J.; Hartmann, R. W. *Eur. J. Med. Chem.* **2013**, *65*, 223. (c) Chen, Y. R.; Duan, W. L. *J. Am. Chem. Soc.* **2013**, *135*, 16754. (d) Duckert, H.; Khedkar, V.; Waldmann, H.; Kumar, K. *Chem. - Eur. J.* **2011**, *17*, 5130. (e) Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4572. (f) Kirsch, G.; Thomae, D.; Seck, P. *Synthesis* **2008**, *2008*, 1600. (g) Romagnoli, R. P.; Remusat, G.; Carrion, V. M.; Cara, D.; Preti, C. L.; Baraldi, D.; Fruttarolo, F.; Pavani, M. G.; Tabrizi, M. A.; Tolomeo, M.; Grimaudo, S.; Balzarini, J.; Jordan, M. A.; Hamel, E. *J. Med. Chem.* **2006**, *49*, 6425. (h) Wender, P. A.; Paxton, T. J.; Williams, T. J. *J. Am. Chem. Soc.* **2006**, *128*, 14814. (i) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260. (j) Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. *Tetrahedron Lett.* **2002**, *43*, 9707. (k) McCauley, J. A.; Theberge, C. R.; Liverton, N. J. *Org. Lett.* **2000**, *2*, 3389. (l) Norman, M. H.; Chen, N.; Chen, Z.; Fotsch, C.; Hale, C.; Han, N.; Hurt, R.; Jenkins, T.; Kincaid, J.; Liu, L.; Lu, Y.; Moreno, O.; Santora, V. J.; Sonnenberg, J. D.; Karbon, W. *J. Med. Chem.* **2000**, *43*, 4288. (m) Liu, Y.; Shen, B.; Kotora, M.; Takahashi, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 949. (n) Ren, W. Y.; Rao, K. V. B.; Klein, R. S. *J. Heterocycl. Chem.* **1986**, *23*, 1757. (o) Hartmann, H.; Liebscher, J. *Synthesis* **1984**, *1984*, 275.

(3) (a) Iwai, I.; Nakamura, N. *Chem. Pharm. Bull.* **1966**, *14*, 1277. (b) Cheng, Z. Y.; Li, W. J.; He, F.; Zhou, J. M.; Zhu, X. F. *Bioorg. Med. Chem.* **2007**, *15*, 1533. (c) Lazennec, M. *Bull. Soc. Chim. Fr.* **1906**, *3*, 526. (d) Heard, N. E.; Turner, J. *J. Org. Chem.* **1995**, *60*, 4302. (e) Rama Rao, V. V. V. N. S.; Lingaiah, B. P. V.; Ezikiel, G.; Yadla, R.; Rao, P. S. *Heterocycl. Commun.* **2006**, *12*, 275.

(4) For selected examples, see: (a) Wang, T.; Yin, H.; Jiao, N. *Adv. Synth. Catal.* **2013**, *355*, 1207. (b) Sharma, P. K.; Ram, S.; Chandak, N. *Adv. Synth. Catal.* **2016**, *358*, 894. (c) Murray, R. E.; Zweifel, G. *Synthesis* **1980**, *1980*, 150. (d) Merah, B.; Texier, F. *Bull. Soc. Chim. Fr.* **1980**, 552. (e) Beccalli, E. M.; Manfredi, A.; Marchesini, A. *J. Org. Chem.* **1985**, *50*, 2372. (f) Wu, Y.-Q.; Limburg, D. C.; Wilkinson, D. E.; Hamilton, G. S. *Org. Lett.* **2000**, *2*, 795.

(5) (a) Zhang, G.; Chen, S.; Fei, H.; Cheng, J.; Chen, F. *Synlett* **2012**, *23*, 2247. (b) Wen, Q.; Jin, J.; Hu, B.; Lu, P.; Wang, Y. *RSC Adv.* **2012**, *2*, 6167. (c) Luo, F.-H.; Chu, C.-I.; Cheng, C.-H. *Organometallics* **1998**, *17*, 1025. (d) Kim, J.; Chang, S. *J. Am. Chem. Soc.* **2010**, *132*, 10272. (e) Xu, H.; Liu, P.-T.; Li, Y.-H.; Han, F.-S. *Org. Lett.* **2013**, *15*, 3354. (f) Teng, F.; Yu, J.-T.; Yang, H.; Cheng, J. *Chem. Commun.* **2014**, *50*, 12139. (g) Teng, F.; Yu, J.-T.; Zhou, Z.; Chu, H.; Cheng, J. *J. Org. Chem.* **2015**, *80*, 2822. (h) Xu, W.; Xu, Q.; Li, J. *Org. Chem. Front.* **2015**, *2*, 231. (i) Pan, C.; Jin, H.; Xu, P.; Liu, X.; Cheng, Y.; Zhu, C. *J. Org. Chem.* **2013**, *78*, 9494. (j) Lin, S.; Wei, Y.; Liang, F. *Chem. Commun.* **2012**, *48*, 9879. (k) Zhang, Y.; Peng, H.; Zhang, M.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2011**, *47*, 2354. (l) Zhu, C.; Xia, J.-B.; Chen, C. *Org. Lett.* **2014**, *16*, 247. (m) Powell, K. J.; Han, L.-C.; Sharma, P.; Moses, J. E. *Org. Lett.* **2014**, *16*, 2158. (n) Shu, Z.; Ji, W.; Wang, X.; Zhou, Y.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 2186. (o) Li, J.; Ackermann, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 3635. (p) Yang, Y.; Liu, P. *ACS Catal.* **2015**, *5*, 2944. (q) Martin Castro, M.-C. *Chem. Rev.* **2004**, *104*, 2939. (r) Rehbein, J.; Hiersemann, M. *Synthesis* **2013**, *45*, 1121.

(6) (a) Ugi, I. *Isonitrile Chemistry*; Academic Press: New York, 1971. (b) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (c) Domling, A. *Chem. Rev.* **2006**, *106*, 17. (d) Lygin, A. V.; de Meijere, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9094. (e) Gulevich, A. V.; Zhdanko, A. G.; Orru, R. V. A.; Nenajdenko, V. G. *Chem. Rev.* **2010**, *110*, 5235. (f) Nenajdenko, V. G. *Isocyanide Chemistry*; Wiley-VCH: Weinheim, 2012.

(7) (a) Xu, S.; Huang, X.; Hong, X.; Xu, B. *Org. Lett.* **2012**, *14*, 4614. (b) Peng, J.; Zhao, J.; Hu, Z.; Liang, D.; Huang, J.; Zhu, Q. *Org. Lett.* **2012**, *14*, 4966. (c) Hong, X.; Wang, H.; Qian, G.; Tan, Q.; Xu, B. *J. Org. Chem.* **2014**, *79*, 3228. (d) Chen, Z.-B.; Zhang, Y.; Yuan, Q.; Zhang, F.-L.; Zhu, Y.-M.; Shen, J.-K. *J. Org. Chem.* **2016**, *81*, 1610.

DOI: 10.1021/acs.orglett.7b02743
Org. Lett. XXXX, XXX, XXX−XXX

(8) Cioc, R. C.; Preschel, H. D.; van der Heijden, G.; Ruijter, E.; Orru, R. V. A. *Chem. - Eur. J.* **2016**, *22*, 7837.
(9) Cioc, R. C.; Schuckman, P.; Preschel, H. D.; Vlaar, T.; Ruijter, E.; Orru, R. V. A. *Org. Lett.* **2016**, *18*, 3562.
(10) (a) Jiang, X.; Wang, J.-M.; Zhang, Y.; Chen, Z.; Zhu, Y.-M.; Ji, S.-J. *Tetrahedron* **2015**, *71*, 4883. (b) Coppola, A.; Sánchez-Alonso, P.; Sucunza, D.; Burgos, C.; Alajarín, R.; Alvarez-Builla, J.; Mosquera, M. E. G.; Vaquero, J. J. *Org. Lett.* **2013**, *15*, 3388.
(11) Qiu, G.; Qiu, X.; Liu, J.; Wu, J. *Adv. Synth. Catal.* **2013**, *355*, 2441.
(12) Weinberger, B.; Fehlhammer, W. P. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 6.
(13) (a) Giustiniano, M.; Basso, A.; Mercalli, V.; Massarotti, A.; Novellino, E.; Tron, G. C.; Zhu, J. *Chem. Soc. Rev.* **2017**, *46*, 1295. (b) Aller, E.; Molina, P.; Lorenzo, A. *Synlett* **2000**, 526. (c) Bio, M. M.; Javadi, G.; Song, Z. J. *Synthesis* **2005**, *2005*, 19. (d) Souldozi, A.; Ramazani, A. *Tetrahedron Lett.* **2007**, *48*, 1549. (e) Souldozi, A.; Ramazani, A.; Bouslimani, N.; Welter, R. *Tetrahedron Lett.* **2007**, *48*, 2617. (f) Adib, M.; Kesheh, M.; Ansari, S.; Bijanzadeh, H. *Synlett* **2009**, *2009*, 1575. (g) Adib, M.; Ansari, S.; Fatemi, S.; Bijanzadeh, H. R.; Zhu, L. G. *Tetrahedron* **2010**, *66*, 2723. (h) Ramazani, A.; Rezaei, A. *Org. Lett.* **2010**, *12*, 2852. (i) Adib, M.; Ansari, S.; Feizi, S.; Bijanzadeh, H. R. *Synlett* **2010**, *2010*, 921. (j) Adib, M.; Sheikhi, E.; Kavoosi, A.; Bijanzadeh, H. R. *Synthesis* **2010**, *2010*, 4082. (k) Cui, L.; Liu, Q.; Yu, N. C.; Yu, H. *Tetrahedron Lett.* **2011**, *52*, 5530. (l) Nasrabadi, F. Z.; Ramazani, A.; Ahmadi, Y. *Mol. Diversity* **2011**, *15*, 791. (m) Brockmeyer, F.; van Gerven, D.; Saak, W.; Martens, J. *Synthesis* **2014**, *46*, 1603. (n) Rouhani, M.; Ramazani, A.; Joo, S. W. *Ultrason. Sonochem.* **2014**, *21*, 262. (o) Adib, M.; Ansari, S.; Bijanzadeh, H. R. *Synlett* **2011**, *2011*, 619. (p) Adib, M.; Ansari, S.; Zhu, L.-G.; Rahimi-Nasrabadi, M. *Helv. Chim. Acta* **2013**, *96*, 675.
(14) (a) Aller, E.; Molina, P.; Lorenzo, A. *Synlett* **2000**, 526. (b) Bio, M. M.; Javadi, G.; Song, Z. J. *Synthesis* **2005**, *2005*, 19.
(15) For examples, see: (a) Fang, G.; Bi, X. *Chem. Soc. Rev.* **2015**, *44*, 8124. (b) Liu, J.; Fang, Z.; Zhang, Q.; Liu, Q.; Bi, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 6953. (c) Liu, J.; Liu, Z.; Liao, P.; Zhang, L.; Tu, T.; Bi, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 10618. (d) Liu, J.; Liu, Z.; Wu, N.; Liao, P.; Bi, X. *Chem. - Eur. J.* **2014**, *20*, 2154.
(16) For examples, see: (a) Liu, Z.; Liu, J.; Zhang, L.; Liao, P.; Song, J.; Bi, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 5305. (b) Liu, Z.; Liao, P.; Bi, X. *Org. Lett.* **2014**, *16*, 3668. (c) Ning, Y.; Ji, Q.; Liao, P.; Anderson, E. A.; Bi, X. *Angew. Chem., Int. Ed.* **2017**, DOI: 10.1002/anie.201705122.

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