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Transition-Metal-Free Cascade Synthesis of 4-Quinolones: Umpolung of Michael Acceptors via Ene Reaction with Arynes

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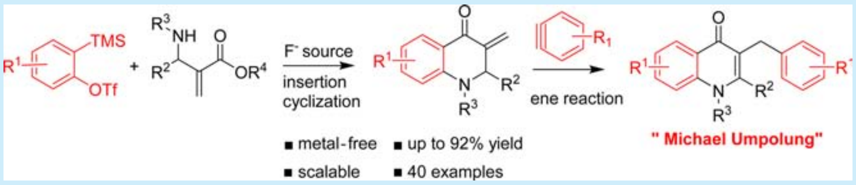
Supporting Information

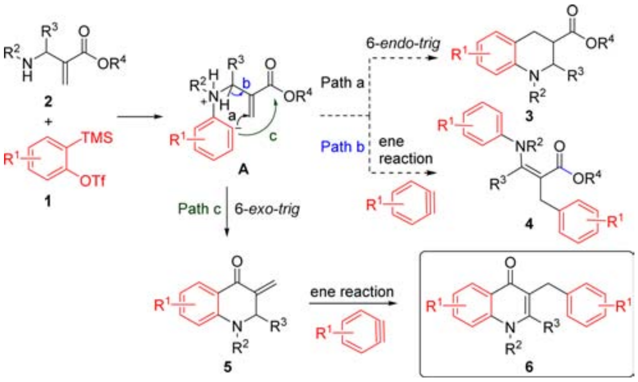


ABSTRACT: A novel "one-pot" aryne transformation is described that affords various 4-quinolone derivatives without recourse to transition-metal catalysis. Arynes react with aza-Morita−Baylis−Hillman (AMBH) adducts through a cascade sequence involving an insertion/cyclization/ene reaction process to afford 4-quinolones in high yields with a broad substrate scope under mild reaction conditions. Essentially, an umpolung of reactivity at the β carbon of α,β-unsaturated ketone has been achieved by an inverse electron demand aryne−ene reaction to provide a C-arylated product.

4-Quinolones are structural components of many bioactive natural products and pharmaceutically important substances, including a large number of marketed antibiotics such as Ciprofloxacin, Levofloxacin, and Moxifloxacin.[1] In addition, 4-quinolones have been studied as potential treatments for a range of diseases, as they exhibit antidiabetic,[2] anticancer,[3] antiviral,[4] antimitotic,[5] antimalarial,[6] and HIV-1 integrase inhibitory activities.[7] Therefore, various synthetic methods have been developed for the synthesis of this valuable scaffold.[8] Unfortunately, these methods often require multistep sequences, laborious isolation of the intermediates, a longer reaction time, or harsh reaction conditions and are also limited by unsatisfactory yields, narrow substrate scope, and poor regioselectivities. All these methods involve one C−C bond formation as a key step starting with an appropriately functionalized aryl group (Supporting Information, Scheme 1). For flexible and rapid synthesis of 4-quinolone libraries for high-throughput screening and further drug discovery research, a one-pot synthesis with multiple bond-forming transformations (MBFTs) and aryl group incorporation would be more practical and desirable.

As part of our continuing efforts[9] on the transition-metal-free synthesis of valuable bioactive scaffolds using arynes,[10] we envisioned that the zwitterionic intermediate **A** from an *in situ* generated aryne[11] and aza-Morita−Baylis−Hillman (AMBH) adduct (**2**)[12] could undergo favorable intramolecular Michael addition (Path a, 6-*endo*-*trig* cyclization) to afford bioactive tetrahydroquinolines **3** (Scheme 1).[13] In addition, intermediate **A** could also undergo an ene reaction (Path b) with an excess of the aryne to provide *C*-arylated compound **4**. Surprisingly, the reaction took a different course during our studies, where aryl anion **A** smoothly added onto the less reactive ester moiety (Path c, 6-*exo*-*trig* cyclization) to afford enone **5**, which subsequently underwent an inverse electron demand ene reaction with an excess of the aryne, to furnish 2,3-substituted 4-quinolones (**6**) exclusively under mild reaction conditions. Notably, the present novel one-pot reaction with MBFTs provides an efficient method for the flexible and rapid synthesis of highly functionalized 4-quinolones.

Scheme 1. Reaction of Aryne with AMBH Adduct



This metal-free aryne−ene reaction attracted our attention and aroused curiosity, as intermolecular aryne−ene reactions[14] (with electron-rich ene component) have received only scant attention in the realm of ene reactions (Supporting Information, Scheme 2), and the inverse electron demand[15] aryne−ene reaction with electron deficient ene component remains elusive.[14c] Herein we report a mild and novel "one-pot" aryne transformation for the construction of various substituted

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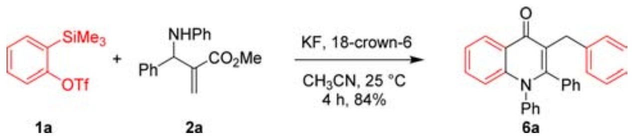
4-quinolones through a cascade insertion−cyclization followed by a rare inverse electron demand ene reaction.

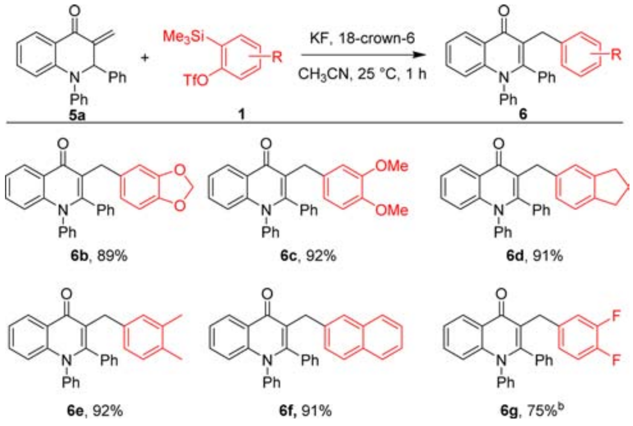
Our exploration was commenced by treating AMBH adduct **2a** with the aryne generated *in situ* from 2-(trimethylsilyl)aryl triflate **1a** using KF and 18-crown-6 at ambient temperature (Scheme 2). Either enone **5a** or 4-quinolone **6a** could be obtained by varying the equivalents of **1a** in the cascade reaction. The reaction afforded **5a** (49%) as the major product when 1.2 equiv of **1a** was used, whereas the use of 2.5 equiv of **1a** resulted in the formation of **6a** (84%) (Supporting Information, Table 1).[16]

Scheme 2. Cascade Reaction of Aryne and AMBH Adduct



Encouraged by these results, the versatility of an aryne−ene reaction as an effective strategy in C−C bond formation was examined by treating a wide range of β-trimethylsilyl triflates **1** with electron-deficient alkene intermediate **5a**, and the results are summarized in Scheme 3. Initially, the reaction was conducted with the parent aryne derived from **1a** (1.2 equiv) in CH$_3$CN, where the β-carbon of α,β-unsaturated cyclic ketone **5a** reacted with "polarity inversion" (via ene reaction) and provided *C*-arylated umpolung product **6a** in 91% yield. To further demonstrate the potential expandability and flexibility of this method in the formation of molecularly diverse 4-quinolone derivatives, different 4,5-disubstituted symmetrical aryne precursors, including benzodioxole, dimethoxy, Indane, and dimethyl derivatives were examined. In all the cases studied, the corresponding umpolung products (**6b**−**e**) were obtained in excellent yields. Most notably, the extended π conjugate naphthalene derived benzyne also afforded the desired 4-quinolone **6f** in high yield. Gratifyingly, the 4,5-difluoro aryne reacted under the optimized reaction conditions to provide 4-quinolone **6g** in 75% yield, albeit at a slower rate. These results suggest that the reaction proceeds through an inverse electron demand ene reaction, as electron-rich arynes reacted faster and gave higher yields than the electron-deficient aryne.

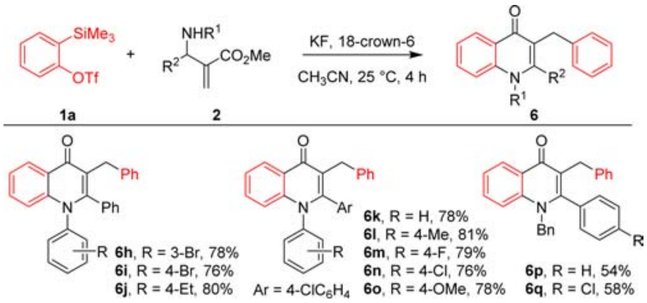
Scheme 3. Substrate Scope of the Inverse Electron Demand Ene Reaction[a,b]



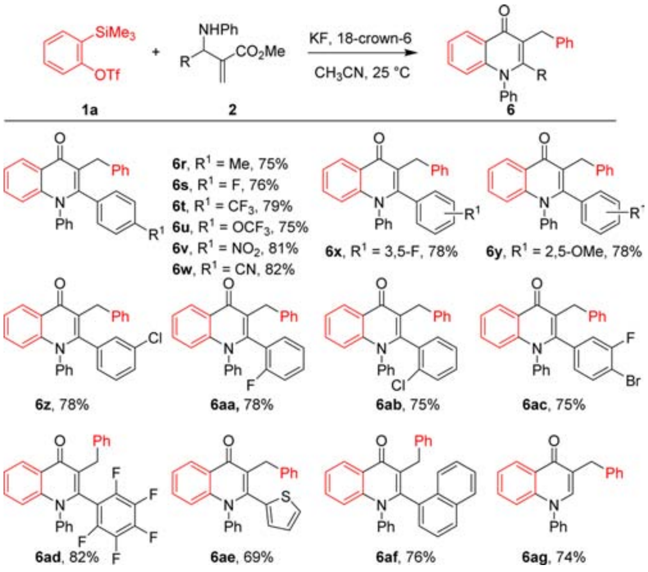
[a] Reaction conditions: **5a** (0.15 mmol), **1** (0.18 mmol), KF (0.36 mmol), 18-crown-6 (0.36 mmol), CH$_3$CN (3.0 mL), 25 °C, and 1 h. Yields of the isolated products with respect to **5a**. [b] 12 h.

The scope and generality of the cascade reaction was then explored under the optimized reaction conditions (AMBH adduct (1 equiv), aryne (2.5 equiv), KF (5.0 equiv), 18-crown-6 (5.0 equiv), CH$_3$CN, 25 °C, 4 h), and the results are summarized in Schemes 4, 5, and 6. Initially, to test the effect of an aryl group on amines in the formation of 4-quinolone derivatives, various arylamine adducts **2** were examined (Scheme 4). *N*-Arylamines bearing a Br, Cl, F, ethyl, or methoxy group on an aromatic nucleus were well tolerated to furnish 4-quinolone derivatives (**6h**−**o**) in high yields. Benzyl capped amine with an unsubstituted and p-Cl aryl ring also underwent an efficient cascade reaction with arynes, leading to the formation of 4-quinolone derivatives (**6p** and **6q**) in moderate yields. It is noteworthy that various halo quinolones could allow further functionalization to afford libraries of 4-quinolones.

Scheme 4. Substrate Scope of the Cascade Reaction: Variation of Aryl Amines of Aza MBH Adducts



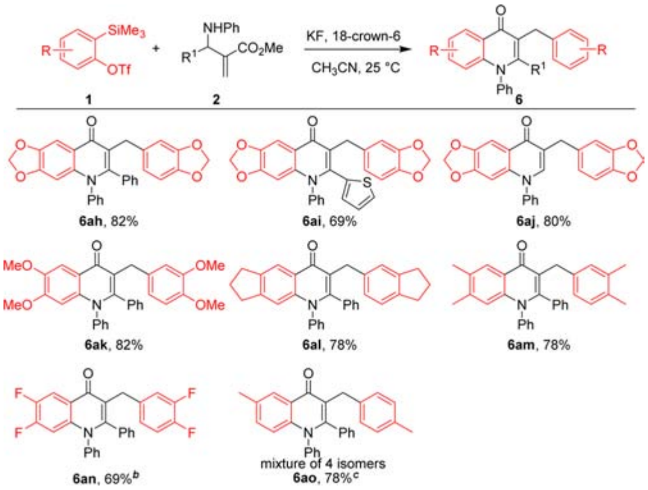
Scheme 5. Substrate Scope of the Cascade Reaction: Variation of AMBH Adducts[a]



[a] Reaction conditions: **1a** (0.50 mmol), **2** (0.20 mmol), KF (1.00 mmol), 18-crown-6 (1.00 mmol), CH$_3$CN (4.0 mL), 25 °C, and 4 h. Yields of the isolated products with respect to **2**.

Prompted by these interesting results, a range of differently substituted AMBH adducts (**2**) were examined to afford substituted 4-quinolones (Scheme 5). Various aryl moieties

Scheme 6. Substrate Scope of the Cascade Reaction: Variation of Aryne Precursors[a]

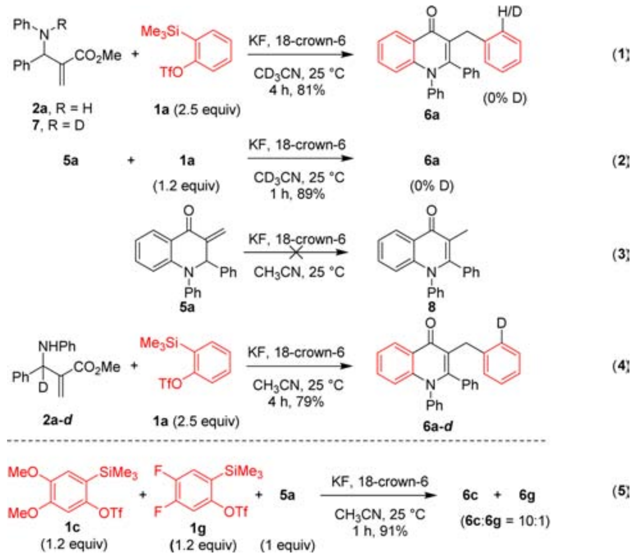


[a] Reaction conditions: **1** (0.50 mmol), **2** (0.20 mmol), KF (1.00 mmol), 18-crown-6 (1.00 mmol), CH_3CN (4.0 mL), 25 °C, and 4 h. Yields of the isolated products with respect to **2**. [b] Reaction time 12 h. [c] Inseparable mixture of regioisomers (1:1:1:1) as determined by ^1H NMR.

with electronically dissimilar groups at the 4-position of the aromatic ring were well tolerated, and their reactions furnished 4-quinolone derivatives (**6r**−**w**) in high yields. Moreover, substitution of a halo or an alkoxy is tolerated at the 2-, 3-, and 5-position of the aromatic ring in **2**, resulting in the desired products (**6x**−**ab**). Intriguingly, 3,4-fluorobromo and pentafluoro substituents on the aromatic ring also afforded 4-quinolones **6ac** and **6ad**. Systems containing thiophene and naphthalene moieties furnished the desired products (**6ae** and **6af**), thereby further expanding the scope of this cascade reaction. In a similar fashion, a substrate lacking an aromatic ring afforded 3-substituted 4-quinolone **6ag** in 74% yield. In general, AMBH adduct **2** bearing an electron-withdrawing group on the aromatic ring usually afforded slightly higher yields, suggesting that an electron-deficient aromatic ring favors the labile proton transfer in the inverse electron demand ene reaction.

In an attempt to further widen the scope and generality, various substituted 2-(trimethylsilyl)aryl triflates **1** were examined. Scheme 6 summarizes the result of this investigation, further demonstrating the power of this method to construct molecular diversity and complexity from simple building blocks. Symmetrical aryne precursor 4,5-benzodioxolebenzyne reacted with AMBH adducts to give the corresponding 4-quinolones **6ah**−**aj** in high yields. Electronically diverse 4,5 disubstituted symmetrical aryne precursors including dimethoxy, Indane, dimethyl, and difluoro derivatives all reacted smoothly to provide the corresponding products (**6ak**−**an**) in good to high yields. Notably, fluorinated 4-quinolones are known to have potential applications in the synthesis of analogues for drug discovery.[17] Remarkably, the reaction of unsymmetrical 4-methylbenzyne furnished almost equal amounts of all four possible regioisomeric products (**6ao**) in 78% yield, suggesting that steric effects of aryne in this reaction are negligible. Significantly, electron-rich arynes gave higher yields than the electron-deficient arynes, which may be attributed to the fact that electron-rich arynes favor cyclization onto ester. More interestingly, the reaction can be easily scaled up without losing the reaction yield (Supporting Information).

Scheme 7. Control and Crossover Experiments

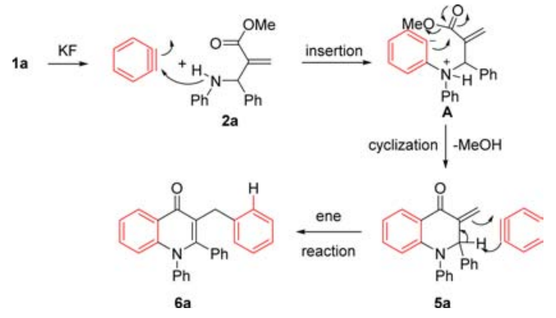


To probe the mechanism of this reaction, the following control experiments were carried out (Scheme 7): (a) when **2a**, **7**, and **5a** were treated separately with **1a** in CD_3CN, the corresponding protonated product **6a** was obtained smoothly (eqs 1 and 2), and no deuterium incorporation product was observed, which sheds light on a concerted ene reaction; (b) in the absence of an aryne, intermediate **5a** remained unchanged under the optimized reaction conditions, and olefin isomerization was not observed (eq 3). These results support that the second aryne addition preferentially follows the ene reaction rather than base mediated deprotonation/nucleophilic addition. Further, the reaction of aryne **1a** with deuterated AMBH adduct **2a-*d*** under the optimized conditions led to deuterated quinolone **6a-*d***. The complete transfer of deuterium onto an aromatic moiety was observed as expected, which confirms the concerted ene reaction (eq 4). To substantiate the inverse electron demand aryne−ene reaction, ene-intermediate **5a** was treated with a mixture of electron-rich and -deficient aryne precursors **1c** and **1g** (1:1 molar ratio) (eq 5), and the study suggests that electron-rich aryne-enophile **1c** reacts almost 10 times faster than the electron-deficient aryne **1g**, providing 4-quinolone **6c** in excellent yield.

Based on the aforementioned results and literature precedence,[10] a probable mechanism for the synthesis of 4-quinolone derivatives is outlined in Scheme 8. The reaction of the AMBH adduct with an aryne leads to the generation of intermediate **5a** through a cascade insertion−cyclization process.[18] Intermediate **5a** subsequently adds to another molecule of electrophilic aryne in a concerted manner proceeding via an inverse electron demand ene reaction to provide product **6a**.

In summary, we have developed a transition-metal-free, mild, general, and efficient method for the flexible synthesis of functionalized 4-quinolones in high yields via a unique cascade reaction of arynes with an AMBH adduct. This one-pot cascade sequence features insertion, cyclization, and an inverse electron demand aryne−ene reaction, involving one C−N and two C−C bond formations. The methodology presented herein is

Scheme 8. Proposed Mechanism of the Cascade Reaction



expected to find applications in the synthesis of 4-quinolone derivatives in drug discovery. Further studies focusing on the extension of the reaction scope and medicinal chemistry are ongoing in our laboratory and shall be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01830.

Experimental procedures and spectral data for all new compounds (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Manfroni, G.; Cannalire, R.; Barreca, M. L.; Kaushik-Basu, N.; Leyssen, P.; Winquist, J.; Iraci, N.; Manvar, D.; Paeshuyse, J.; Guhamazumder, R.; Basu, A.; Sabatini, S.; Tabarrini, O.; Danielson, U. H.; Neyts, J.; Cecchetti, V. *J. Med. Chem.* **2014**, *57*, 1952. (b) Zhi, Y.; Gao, L. X.; Jin, Y.; Tang, C. L.; Li, J. Y.; Li, J.; Long, Y. Q. *Bioorg. Med. Chem.* **2014**, *22*, 3670. (c) Huse, H.; Whiteley, M. *Chem. Rev.* **2011**, *111*, 152. (d) Wiles, J. A.; Bradbury, B. J.; Pucci, M. J. *Expert Opin. Ther. Pat.* **2010**, *20*, 1295. (e) Mugnaini, C.; Pasquini, S.; Corelli, F. *Curr. Med. Chem.* **2009**, *16*, 1746.

(2) Edmont, D.; Rocher, R.; Plisson, C.; Chenault, J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1831.

(3) (a) Nakamura, S.; Kozuka, M.; Bastow, K. F.; Tokuda, H.; Nishino, H.; Suzuki, M.; Tatsuzaki, J.; Natschke, S. L. M.; Kuo, S.-C.; Lee, K.-H. *Bioorg. Med. Chem.* **2005**, *13*, 4396. (b) Xia, Y.; Yang, Z.-Y.; Xia, P.; Bastow, K. F.; Nakanishi, Y.; Nampoothiri, P.; Hamel, E.; Brossi, A.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2891.

(4) (a) Wang, S. F.; Lin, J. P.; He, P. L.; Zuo, J. P.; Long, Y. Q. *Huaxue Xuebao* **2014**, *72*, 906. (b) Llinas-Brunet, M.; Bailey, M. D.; Ghiro, E.; Gorys, V.; Halmos, T.; Poirier, M.; Rancourt, J.; Goudreau, N. *J. Med. Chem.* **2004**, *47*, 6584.

(5) (a) Fryknas, M.; Gullbo, J.; Wang, X.; Rickardson, L.; Jarvius, M.; Wickstrom, M.; Hassan, S.; Andersson, C.; Gustafsson, M.; Westman, G.; Nygren, P.; Linder, S.; Larsson, R. *BMC Cancer* **2013**, *13*, 374. (b) Chen, C. T.; Hsu, M. H.; Cheng, Y. Y.; Liu, C. Y.; Chou, L. C.; Huang, L. J.; Wu, T. S.; Yang, X. M.; Lee, K. H.; Kuo, S. C. *Eur. J. Med. Chem.* **2011**, *46*, 6046.

(6) Zhang, Y. Q.; Clark, J. A.; Connelly, M. C.; Zhu, F. Y.; Min, J. K.; Guiguemde, W. A.; Pradhan, A.; Iyer, L.; Furimsky, A.; Gow, J.; Parman, T.; El Mazouni, F.; Phillips, M. A.; Kyle, D. E.; Mirsalis, J.; Guy, R. K. *J. Med. Chem.* **2012**, *55*, 4205.

(7) (a) Di Santo, R.; Costi, R.; Roux, A.; Artico, M.; Lavecchia, A.; Marinelli, L.; Novellino, E.; Palmisano, L.; Andreotti, M.; Amici, R.; Galluzzo, C. M.; Nencioni, L.; Palamara, A. T.; Pommier, Y.; Marchand, C. *J. Med. Chem.* **2006**, *49*, 1939. (b) Moyer, M. P.; Weber, F. H.; Gross, J. L. *J. Med. Chem.* **1992**, *35*, 4595.

(8) (a) Hu, W.; Lin, J. P.; Song, L. R.; Long, Y. Q. *Org. Lett.* **2015**, *17*, 1268. (b) Seppanen, O.; Muuronen, M.; Helaja, J. *Eur. J. Org. Chem.* **2014**, *2014*, 4044. (c) Iaroshenko, V. O.; Mkrtchyan, S.; Villinger, A. *Synthesis* **2013**, *45*, 205. (d) Fei, X. D.; Zhou, Z.; Li, W.; Zhu, Y. M.; Shen, J. K. *Eur. J. Org. Chem.* **2012**, *2012*, 3001. (e) Shao, J.; Huang, X. M.; Hong, X. H.; Liu, B. X.; Xu, B. *Synthesis* **2012**, *44*, 1798. (f) Liu, Q. L.; Li, Q. L.; Fei, X. D.; Zhu, Y. M. *ACS Comb. Sci.* **2011**, *13*, 19. (g) Okamoto, N.; Takeda, K.; Ishikura, M.; Yanada, R. *J. Org. Chem.* **2011**, *76*, 9139. (h) Mphahlele, M. J. *J. Heterocycl. Chem.* **2010**, *47*, 1. (i) Zhao, T. K.; Xu, B. *Org. Lett.* **2010**, *12*, 212. (j) Bernini, R.; Cacchi, S.; Fabrizi, G.; Sferrazza, A. *Synthesis* **2009**, *2009*, 1209. (k) Huang, J.; Chen, Y.; King, A. O.; Dilmeghani, M.; Larsen, R. D.; Faul, M. M. *Org. Lett.* **2008**, *10*, 2609. (l) Jones, C. P.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 7968. (m) Ding, D.; Li, X.; Wang, X.; Du, Y.; Shen, J. *Tetrahedron Lett.* **2006**, *47*, 6997. (n) Heindel, N. D.; Bechara, I. S.; Kennewell, P. D.; Molnar, J.; Ohnmacht, C. J.; Lemke, S. M.; Lemke, T. F. *J. Med. Chem.* **1968**, *11*, 1218.

(9) Guo, J.; Kiran, I. N. C.; Reddy, R. S.; Gao, J.; Tang, M.; Liu, Y.; He, Y. *Org. Lett.* **2016**, *18*, 2499.

(10) (a) Wright, A. C.; Haley, C. K.; Lapointe, G.; Stoltz, B. M. *Org. Lett.* **2016**, *18*, 2793. (b) García-Lopez, J.-A.; Cetin, M.; Greaney, M. F. *Org. Lett.* **2015**, *17*, 2649. For selected reviews on aryne chemistry, see: (c) Yoshida, S.; Hosoya, T. *Chem. Lett.* **2015**, *44*, 1450. (d) Goetz, A. E.; Shah, T. K.; Garg, N. K. *Chem. Commun.* **2015**, *51*, 34. (e) Yoshida, H. Nucleophilic Coupling with Arynes. In *Comprehensive Organic Synthesis*, 2nd ed.; Knochel, P., Molander, G. A., Eds.; Elsevier: Amsterdam, 2014; Vol. 4, p 517. (f) Dubrovskiy, A. V.; Markina, N. A.; Larock, R. C. *Org. Biomol. Chem.* **2013**, *11*, 191. (g) Perez, D.; Peña, D.; Guitiań, E. *Eur. J. Org. Chem.* **2013**, *2013*, 5981. (h) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550. (i) Bhunia, A.; Yetra, S. R.; Biju, A. T. *Chem. Soc. Rev.* **2012**, *41*, 3140.

(11) (a) Peña, D.; Pérez, D.; Cobas, A.; Guitián, E. *Synthesis* **2002**, 1454. (b) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.

(12) For selected reviews on MBH reactions, see: (a) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447. (b) Basavaiah, D.; Rao, A. J.; Satyanarayana, A. *Chem. Rev.* **2003**, *103*, 811.

(13) Sridharan, V.; Suryavanshi, P. A.; Menendez, J. C. *Chem. Rev.* **2011**, *111*, 7157.

(14) Jayanth, T. T.; Jeganmohan, M.; Cheng, M. J.; Chu, S. Y.; Cheng, C. H. *J. Am. Chem. Soc.* **2006**, *128*, 2232. (b) Chen, Z.; Liang, J.; Yin, J.; Yu, G. A.; Liu, S. H. *Tetrahedron Lett.* **2013**, *54*, 5785. (c) Dubrovskiy, A. V.; Larock, R. C. *Tetrahedron* **2013**, *69*, 2789. (d) Aly, A. A.; Mohamed, N. K.; Hassan, A. A.; Mourad, A-F. E. *Tetrahedron* **1999**, *55*, 1111. (e) Nakayama, J.; Yoshimura, k. *Tetrahedron Lett.* **1994**, *35*, 2709. (f) Candito, D. A.; Panteleev, J.; Lautens, M. *J. Am. Chem. Soc.* **2011**, *133*, 14200.

(15) Ofial, A. R.; Mayr, H. *J. Org. Chem.* **1996**, *61*, 5823.

(16) Reported compound was *N*-arylated and matched with the NMR data of **6a**. Cheng, D.; Zhou, J.; Saiah, E.; Beaton, G. *Org. Lett.* **2002**, *4*, 4411.

(17) Asahina, Y.; Araya, I.; Iwase, K.; Iinuma, F.; Hosaka, M.; Ishizaki, T. *J. Med. Chem.* **2005**, *48*, 3443.

(18) (a) Zhao, J.; Larock, R. C. *Org. Lett.* **2005**, *7*, 4273. (b) Zhao, J.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 583.