
# Facile *N*-Arylation of Amidines and *N*,*N*-Disubstituted Amidines

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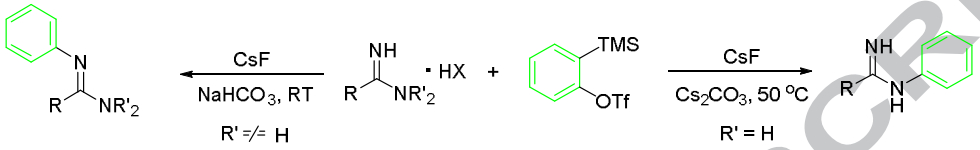

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# Facile *N*-Arylation of Amidines and *N*,*N*-Disubstituted Amidines

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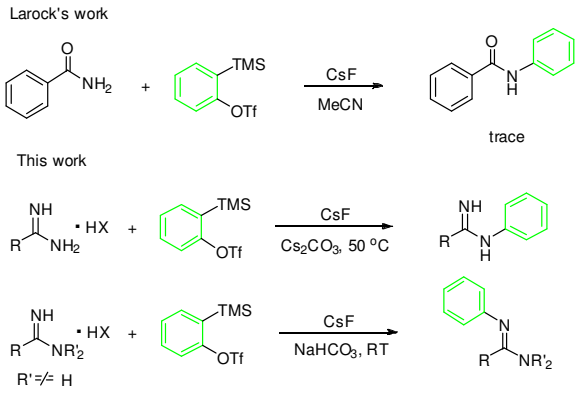
ABSTRACT

A metal-free method for the N-arylation of amidines and N,N-disubstituted amidines using o-silylaryl triflate under very mild reaction conditions is developed. The reactions are compatible with a variety of functional groups. Imines can also be N-arylated by this method. Preparation of substituted phenanthridines via a Pd catayzed intramolecular cyclization of the iodine containing N-arylation product is demonstrated



Amidines are fundamental entity in modern drug discovery.[1] They exist as a structural part not only in various drugs[1a-c] and agrochemicals,[2] but also in a variety of natural products.[3] Amidines have also been shown to act as organocatalysts,[4] important precursors in the synthesis of heterocycles,[5] and *N*-based donor ligands in coordination chemistry.[6] Thus, developing efficient process for the synthesis of substituted amidines has been a subject of enduring interest. *N*-Arylamidines have been prepared by reaction of aniline with corresponding thioimidic esters,[7a] activated nitrile,[7a-d] and trihaloethyl imidates.[8] Recently, application of transition-metal catalyzed C-N cross-coupling to *N*-arylation of amidines has been advanced.[9] On the other hand, tertiary amidines are generally prepared from monosubstituted amides or thioamides.[10] Application of transition-mental catalyzed C-N cross-coupling in preparation of tertiary amidines remain challenging, since the basic tertiary amidines can coordinate strongly with the metal center.[6] Several intramolecular *N*-arylation of *N*,*N*-disubstituted amindines have been reported recently.[11] Nontheless, these methods have certain limitations such as strongly acidic or basic conditions, high temperature, using stoichiometric or catalytic amounts of transition metals, or the preparation of activated intermediates. A simple and general metal-free *N*-arylation procedure to directly generate *N*-arylated amidines from amidines and *N*,*N*-disubstituted amidines, or their salts under mild reaction conditions should be very attractive, since it offers efficient access to a variety of such compounds.

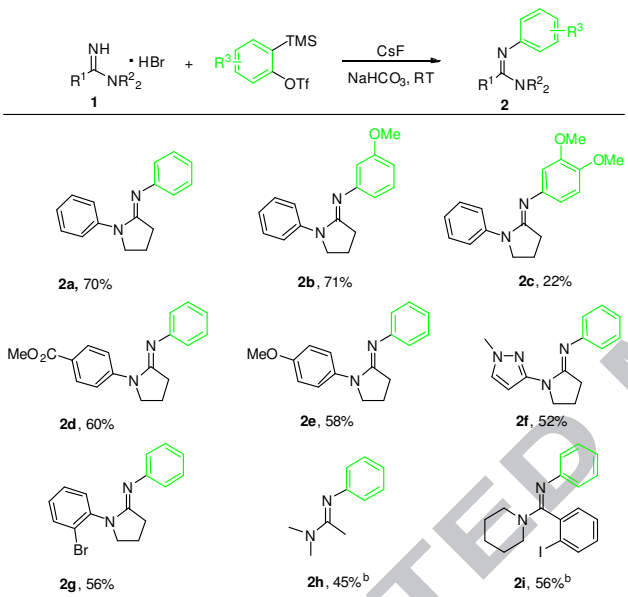
Arynes generated from *o*-silylaryl triflate[12] and a fluoride source have been applied in various useful synthetic methodologies.[13] Facile arylation of amines,[14a,c] sulfonamides,[14a,c], carbamates[14c], acetanilides,[15] phosphite, phosphonite and phosphinite,[14d] and sodium sulfinates[14e] using *o*-silylaryl triflates have been reported. Unfortunately, arylation of carboxamides only afford trace of the corresponding *N*-arylamide product, since simple amides are apparently neither nucleophilic enough to directly attack the aryne nor acidic enough to form the corresponding anion.[14c] We envisaged that amidines which are much more nucleophilic than amides, might be able to react with the aryne intermediates (Scheme 1). Herein we report a facile, transition-metal free method for the *N*-monoarylation of amidines and *N*,*N*-disubstituted amidines using *o*-silylaryl triflates under very mild reaction conditions.




**Scheme 1.** *N*-Arylation of amides and amidines with *o*-silylaryl triflate

*N*-Arylation of *N*,*N*-disubstituted amidines was examined first (Scheme 2). HBr salt of 1-phenylpyrrolidin-2-imine was treated with 2.0 eq. of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate, 1.0 eq. of $NaHCO_3$ and 3.0 eq. of CsF in acetonitrile (3 mL) at room temperature. We were gratified to find that a 51% yield of the desired *N*-arylation product **2a** was isolated after 16h. The yield was further improved to 74% when using 3.0 eq. of *o*-silylaryl triflate. To investigate the scope and

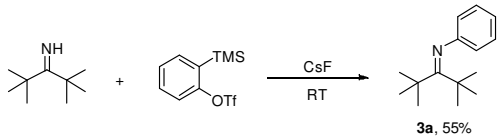
limitation of this procedure, varieties of *o*-silylaryl triflates and amidines were examined. Substituted *o*-silylaryl triflates reacted readily with aminides under our reaction conditions. The reaction of 4-methoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate showed excellent selectivity and generated a single isomer **2b** in a 72% yield. When using dimethoxy-substituted *o*-silylaryl triflate, the aryaltion product **2c** was generated in a lower yield. Amidines containing an electron-withdrawing group or electron-donating group generated the corresponding arylation products **2d** and **2e** in moderate yield. Heterocycle was also well tolerated in the reaction. Significantly, steric hindered amidines bearing *o*-bromo or *o*-iodo produced the arylation product **2g** and **2i** smoothly. The high reactivity of aryne intermediates generated *in situ* made the arylation possible under increased steric hindrance. Non-cyclic alkyl and aryl amidines also worked well in this procedure, generating the corresponding aryaltion products **2h** and **2i** in moderate yields. For the free base amidines, only 1.5 eq. of *o*-silylaryl triflate was required for arylation.




[a]Reaction conditions: 0.2 mmol of amidine is allowed to react with silylaryl triflate (3.0 eq.), CsF (3.0 eq.) and $NaHCO_3$ (1.0 eq.) in MeCN (0.07 M) at RT for 10 h. [b]Free base amidine and 1.5 eq. of silylaryl triflate used; no $NaHCO_3$.

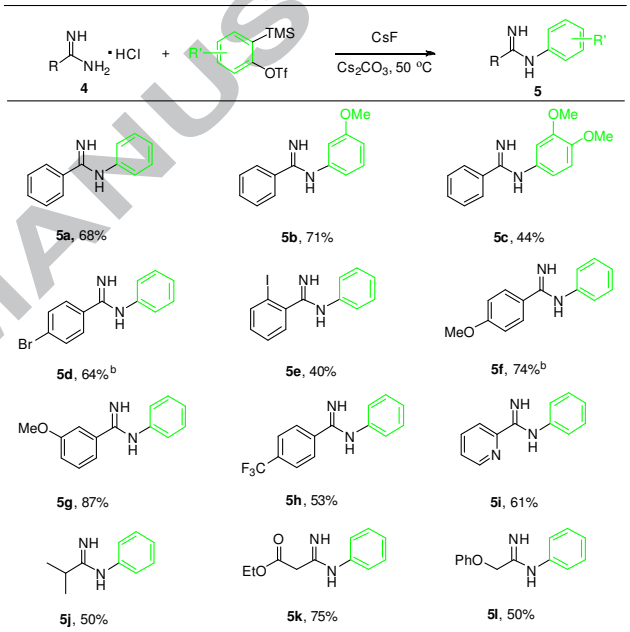
**Scheme 2.** *N*-Arylation of *N*,*N*-disubstituted amidines[a]

Interestingly, imine itself was a good substrate, undergoing *N*-aryaltion under our reaction conditions (Scheme 3.). It's utility in the preparation of extremely sterically hindered imines should be emphasized, since this kind of imines only can be prepared by the twofold extrusion reaction of selones or thiones with aromatic azides before.[16]




**Scheme 3.** *N*-Arylation of imine

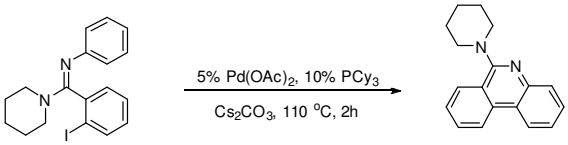
We next examined the *N*-monoarylation of amidines. (Scheme 4). The reaction of amidine HCl salts was examined first, since many of these salts are commercial available. When HCl salt of benzimidamide reacted with 1.5 equiv of 2-(trimethylsilyl)phenyl triflate, 2.0 equiv of CsF and 1.5 equiv of $Cs_2CO_3$ in acetonitrile at 50 °C for 5 h, monoarylation product **5a** was isolated in a 68% yield. The methoxy-substituted *o*-silylaryl triflate again showed excellent selectivity and furnished only the *meta* substituted amidine **5b** in good yield. The more electron-rich dimethoxy-substituted *o*-silyaryl triflate afforded the desired product **5c** in a lower yield. The *para* bromo substituted amidine furnished the *N*-arylated product **5d** in only 46% yield after 5 h at 50 °C. The yield of **5d** was improved to 64% when extending the reaction time to 14 h. The *ortho* iodo substituted amidine also produced the desired iodine-containing product **5e.** Thus, halides are readily accommodated by our reaction conditions. Aryl amidines bearing an electron-withdrawing or donating group furnished the expected *N*-monoarylated amidines in good to excellent yields. Heterocyclic amidine worked well to furnish the desired product **5i** in good yield. This method was not limited to aryl amidines, as *N*-monoarylated alkyl amidines **5j**, **5k** and **5l** were also prepared in good yields.




[a]Reaction conditions: 0.2 mmol of amidine salt is allowed to react with *o*-silylaryl triflate (1.5 equiv), CsF (2.0 equiv) and $Cs_2CO_3$ (1.5 equiv) in MeCN (0.07 M) at 50 ºC for 5 h. [b]Reaction time is 16 h.

**Scheme 4.** *N*-Monoarylation of amidine salts[a]

To demostrate the utility of this method, the iodine containing




product **2i** was converted to 6-aminophenanthridine **6a** in an excellent yield through Pd catalyzed intramolecular coupling reaction (Scheme 5).[17]

**Scheme 5.** Synthesis of 6-Aminophenanthridine

In summary, we have developed a metal-free method for the *N*-arylation of amidines and *N*,*N*-disubstituted Amidines under

very mild reaction conditions. The reactions are compatible with a variety of functional groups. Imines can be *N*-arylated by this method. We also demonstrated the preparation of substituted phenanthridines via a Pd cataylzed intramolecular cyclization of the iodine containing *N*-arylation product.

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## Spplementary data

Supplementary data (experimental procedures, characterization data, as well as $^{1}H$ and $^{13}C$ NMR spectra) associated with this article can be found, in the on line version, at http://dx.doi.org/.

## References and notes


1. (a) Ilaš, J.; Jakopin, Z.; Broštnar, T.; Stegnar, M.; Kikelj, D. *J. Med. Chem.* **2008**, *51*, 5617-5629. (b) Kort, M. E.; Drizin, I.; Gregg, R. J.; Scanio, M. J. C.; Shi, L.; Gross, M. F.; Atkinson, R. N.; Johnson, M.; Pacofsky, G. J.; Thomas, J. B.; Carroll, W. A.; Krambis, M. J.; Liu, D.; Shieh, C.-C.; Zhang, X.; Hernandez, G.; Mikusa, J. P.; Zhong, C.; Joshi, S.; Honore, P.; Roeloffs, R.; Marsh, K. C.; Murray, B. P.; Liu, J.; Werness, S.; Faltynek, C. R.; Krafte, D. S.; Jarvis, M. F.; Chapman, M. L.; Marron, B. E. *J. Med. Chem.* **2008**, *51*, 407-416. (c) Grienke, U.; Schmidtke, M.; Kirchmair, J.; Pfarr, K.; Wutzler, P.; Dürrwarld, R.; Wolber, G.; Liedl, K. R.; Stuppner, H.; Rollinger, J. M. *J. Med. Chem.* **2010**, *53*, 778-786.
2. Hollingworth, R. M.; Lund, A. E. In *Insecticide Mode of Action*; Coats, J. R., Ed.; Academic Press: New York, 1982; pp 189-227.
3. Kumamoto, T. In Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organoctalysts; Ishikawa, I., Ed.; John Wiley & Sons: West Sussex, U.K., 2009; pp 295–313.
4. (a) Nagasawa, K.; Sohtome, Y. In *Science of Synthesis, Asymmetric Organocatalysis*; List, B., Maruoka, K., Eds.; Georg Thieme Verlag: Stuttgart, Ger., 2012; Vol. 2, pp 1-40. (b) ) Li, X.; Jiang, H.; Uffman, E. W.; Guo, L.; Zhang, Y.; Yang, X.; Birman, V. B. *J. Org. Chem.* **2012**, *77*, 1722-1737. (c) Taylor, J. E.; Bull, S. D.; Williams, J. M. *J. Chem. Soc. Rev.* **2012**, *41*, 2109-2121.
5. (a) Boyd,G. V. In *The chemistry of Amidines and imidates*; Patai, S.; Rappoport, Z., Ed; Wiley: Chichester, U.K., 1991; Vol. 2, pp 367-424. (b) Tisler, M. *Heterocycles* **1983**, *20* 1591-1614. (c) Miocque, M.; Fauran, C.; Le Cloaree, A. Y. *Ann Chim.* **1972**, *7*, 89-102. (c) Sheng, J.; Chao, B.; Chen, H.; Hu, Y. H. *Org. Lett.* **2013**, *15*, 4508-4511. (d) Li, S.; Li, Z.; Yuan, Y.; Li, Y.; Zhang, L.; Wu Y. *Chem. Eur. J.* **2013**, *19*, 1496-1501. (e) Alla, S. K.; Kumar, R. K.; Sadhu, P.; Punniyamurthy, T. *Org. Lett.* **2013**, *15*, 1334-1337. (f) McGowan, M. A.; McAvoy, C. Z.; Buchwald, S. L. *Org. Lett.* **2012**, *14*, 3800-3803. (g) Wang, Y.-F.; Chen, H.; Zhu, X.; Chiba, S. *J. Am. Chem. Soc.* **2012**, *134*, 11980-11983. (h) Wang, Y.-F.; Zhu, X.; Chiba, S. *J. Am. Chem. Soc.* **2012**, *134*, 3679-3682. (i) Liu, X.; Fu, H.; Jiang, Y.; Zhao, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 348-351. (j) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932-1934. (h) Wiglenda, T.; Ott, I.; Kircher, B.; Schumacher, P.; Schuster, D.; Langer, T.; Gust, R. *J. Med. Chem.* **2005**, *48*, 6516-6521. (i) Li, J.; Neuville, L. *Org. Lett.* **2013**, *15*, 1752-1755. (k) He, Y.; Huang, J.; Liang, D.; Liu, L.; Zhu, Q. *Chem. Commun.* **2013**, *49*, 7352-7354. (l) Huang, J.; He, Y.; Wang, Y.; Zhu, Q. *Chem. Eur. J.* **2012**, *18*, 13964-13967. (m) Ma, B.; Wang, Y.; Peng, J.; Zhu, Q. *J. Org. Chem.* **2011**, *76*, 6362-6366. (n) Wang, Y.; Wang, H.; Peng, J.; Zhu, Q. *Org. Lett.* **2011**, *13*, 4604-4607. (o) Lv, Y.; Li, Y.; Xiong, T.; Pu, W.; Zhang, H.; Sun, K.; Liu, Q.; Zhang, Q. *Chem. Commun.* **2013**, *49*, 6439-6441. Isoquinolines: (p) Wei, X.; Zhao, M.; Du, Z.; Li, X. *Org. Lett.* **2011**, *13*, 4636-4639. (q) Qu, Y.; Pan, L.; Wu, Z.; Zhou, X. *Tetrahedron* **2013**, *69*, 1717-1719. (r) Kumar, V.; Mohan, C.; Gupta, M.; Mahajan, M. P. *Tetrahedron* **2005**, *61*, 3533-3538.
6. (a) Barker, J.; Kilner, M. Coord. *Chem. Rev.* **1994**, *133*, 219-300. (b) Yu, B.; Liu, H.; Yao, M.; Deng, Y. *Huanxue Tongbao* **2011**, *74*, 225. (b) Dunn, P. J. In Amidines and N-Substituted Amidines. In Comprehensive Organic Functional Group Transformations II; Katritzky, A. R., Taylor, R. J. K., Eds.; Elsevier: New York, 2005; Vol. 5, pp 655–699.
7. (a) Dunn, P. J. Amidines and N-Aryl Amidines. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, I., Taylor, R., Eds.; Elsevier: Oxford, U.K., 2005; Vol. 5, pp 655-699. (b) Forsberg, J. H.; Spaziano, V. T.; Balasubramanian, T. M.; Liu, G. K.; Kinsley, S. A.; Duckworth, C. A.; Poteruca, J. J.; Brown, P. S.; Miller, J. L. *J. Org. Chem.* **1987**, *52*, 1017-1021. (c) Xu, F.; Sun, J.; Shen, Q. *Tetrahedron Lett.* **2002**, *43*, 1867-1869. (d) Wang, J.; Xu, F.; Cai, T.; Shen, Q. *Org. Lett.* **2008**,*10*, 445-448.
8. Caron, S.; Wei, L.; Douville, J.; Ghosh, A. *J. Org. Chem.* **2010**, *75*, 945-947.
9. (a) Rauws, T. R. M.; Maes, B. U. W. *Chem. Soc. Rev.* **2012**, *41* , 2463-2497. (b) Cortes-Salva, M.; Garvin, C.; Antilla, J. C. *J. Org. Chem.* **2011**, *76*, 1456-1459. (c) McGowan, M. A.; McAvoy, C. Z.; Buchwald, S. L. *Org. Lett.* **2012**, *14*, 3800-3803.
10. (a) Yakovenko, M. V.; Cherkasov, A. V.; Fukin, G. K.; Cui, D.; Trifonov, A. A. *Eur. J. Inorg. Chem.*, **2010**, 3290-3298. (b) Stippich, K.; Kretschmer, R.; Beckert, R.; Goerls, H. *Synthesis*, **2010**, 1311-1314. (c) Ursini, A.; Delpogetto, M.; Guercio, G.; Perboni, A.; Rossi, T. *Synlett*, **2001**, 388-390. (d) Avalos, M.; Babiano, R.; Cintas, P.; Dura´n, C. J.; Jiménez, J. L.; Palacios, J. C. *Tetrahedron*, **1995**, *51*, 8043-8056.
11. (a) Blanchot, M.; Candito, D. A.; Larnaud, F.; Lautens, M. *Org. Lett.* **2011**, *13*, 1486-1489. (b) Matsuda, Y.; Kitajima, M.; Takayama, H. *Org. Lett.* **2008**, *10*, 125-128. (c) Petigara, R. B.; Yale, H. L. *J. Heterocycl. Chem.* **1974**, *11*, 331–337.
12. Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211-1214.
13. For reviews of aryne chemistry, see: (a) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701-730. (b) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502-527. (c) Yoshida, H.; Ohshita, J.; Kunai, A. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 199-219. (d) Bhunia, A.; Yetra, S. R.; Biju, A. T. *Chem. Soc. Rev.* **2012**, *41*, 3140-3152. (e) Wu, C.-R.; Shi, F. *Asian J. Org. Chem.* **2013**, *2*, 116-125. (f) Dubrovskiy, A. V.; Markina, N. A.; Larock, R. C. *Org. Biomol. Chem.* **2013**, *11*, 191-218. (g) Gampe, C. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3766-3778. (h) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550-3577. (i) Pena, D.; Perez, D.; Guitian, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579-3581. (j) Yoshida, H.; Takaki, K. *Synlett* **2012**, 1725-1732.
14. (a) Liu, Z.; Larock, R. C. *Org. Lett.* **2003**, *5*, 4673-4675. (b) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 99-102. (c) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198-3209. (d) Dhokale, R. A.; Mhaske, S. B. *Org. Lett.* **2013**, *15*, 2218-2221. (e) Pandya, V. G.; Mhaske, S. B. *Org. Lett.* **2014**, *16*, 3836-3839.
15. Haber, J. C.; Lynch, M. A.; Spring, S. L.; Pechulis, A. D.; Raker, J.; Wang, Y. *Tetrahedron Lett.* **2011**, *52*, 5847-5850.
16. (a) Guziec, F. S. Jr.; Moustakis, C.A. *J. Chem. Soc. Chem. Cummun.* **1984**, 63-64. (b) Guziec, F. S. Jr.; SanFilippo, L. J.; Murphy, C. J.; Moustakis, C. A.; Cullen, E. R. *Tetrahedron* **1985**, *41*, 4843-4852.
17. For a similar synthesis of phenanthridine, see: Peng, J.; Chen, T.; Chen, C.; Li, B. *J. Org. Chem.* **2011**, *76*, 9507-9513.