Synthesis of Multisubstituted Pyridines

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ABSTRACT

By utilizing amino allenes, aldehydes, and aryl iodides as readily available building blocks, a simple and modular synthesis of multisubstituted pyridines with flexible control over the substitution pattern has been achieved. The method employs a two-step procedure involving the preparation of "skipped" allenyl imines and a subsequent palladium-catalyzed cyclization.

Pyridines have a range of applications in many areas of chemistry.¹ They are not only found in the structural cores of numerous pharmaceutical compounds² and natural products³ but are also widely used as building blocks in the preparation of chiral ligands⁴ and new materials with important photo- or electrochemical properties.⁵ Consequently,

(4) For examples, see: (a) Durola, F.; Sauvage, J. P.; Wenger, O. S. *Chem. Commun.* **2006**, 171. (b) Sweetman, B. A.; Müller-Bunz, H.; Guiry, P. J. *Tetrahedron Lett.* **2005**, *46*, 4643. (c) Kozhevnikov, V. N.; Kozhevnikov, D. N.; Nikitina, T. V.; Rusinov, V. L.; Chupakhin, O. N.; Zabel, M.; Koenig, B. J. Org. Chem. **2003**, *68*, 2882.

efficient preparation of highly substituted pyridine derivatives represents a worthwhile goal of organic synthesis. The majority of synthetic routes to pyridine rings are based on either reactions between amines and carbonyl compounds,⁶ metal-catalyzed multicomponent formal cycloadditions,^{7,8} or cycloisomerisation reactions.⁹ Despite the numerous studies and applications that have appeared in the literature, most of the protocols still suffer from one or more important limitations. New or improved synthetic methods to gain easy access to pyridine structures, particularly with flexible control of substitution pattern, are therefore much sought-after. Herein, we describe an efficient and modular synthesis of highly substituted pyridines from readily available α -amino allenes, aldehydes, and aryl halides.

⁽¹⁾ Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 5th ed.; Wiley-Blackwell: Oxford, UK, 2010.

⁽²⁾ For examples, see: (a) *Pharmaceutical Chemistry, Drug Synthesis*; Roth, H. J., Kleemann, A., Eds.; Prentice Hall Europe: London, 1988; Vol. 1, p 407. (b) Kletsas, D.; Li, W.; Han, Z.; Papadopoulos, V. *Biochem. Pharmacol.* **2004**, *67*, 1927. (c) Basnet, A.; Thapa, P.; Karki, R.; Na, Y.; Jahng, Y.; Jeong, B.-S.; Jeong, T. C.; Lee, C.-S.; Lee, E.-S. *Bioorg. Med. Chem.* **2007**, *15*, 4351.

^{(3) (}a) *The Chemistry of Heterocyclic Compounds*; Coppola, G. M., Schuster, H. F., Eds.: Wiley-VCH: New York, 1981. (b) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627. (c) Plunkett, A. O. *Nat. Prod. Rep.* **1994**, *11*, 581. (d) Daly, J. W.; Pinder, A. R. *Nat. Prod. Rep.* **1992**, *9*, 491. (e) Spande, T. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 31.

⁽⁵⁾ For examples, see: (a) Tang, B.; Yu, F.; Li, P.; Tong, L.; Duan, X.; Xie, T.; Wang, X. J. Am. Chem. Soc. **2009**, *131*, 3016. (b) Havas, F.; Leygue, N.; Danel, M.; Mestre, B.; Galaup, C.; Picard, C. Tetrahedron **2009**, *65*, 7673. (c) Yan, B.-P.; Cheung, C. C. C.; Kui, S. C. F.; Xiang, H. F.; Roy, V. A. L.; Xu, S.-J.; Che, C.-M. Adv. Mater. **2007**, *19*, 3599. For a review, see: (d) Kaes, C.; Katz, A.; Hosseini, M. W. Chem. Rev. **2000**, *100*, 3553.

⁽⁶⁾ For examples, see: (a) Allais, C.; Liéby-Muller, F.; Constantieux, T.; Rodriguez, J. Adv. Syn. Catal. 2012, 354, 2537. (b) Tenti, G.; Ramos, M. T.; Menéndez, J. C. ACS Comb. Sci. 2012, 14, 551. (c) Allais, C.; Constantieux, T.; Rodriguez, J. Chem.—Eur. J. 2009, 15, 12945. (d) Liéby-Muller, F.; Allais, C.; Constantieux, T.; Rodriguez, J. Chem. Commun. 2008, 4207. (e) Sausins, A.; Duburs, G. Heterocycles 1988, 27, 269. (f) Stout, D. M.; Meyers, A. I. Chem. Rev. 1982, 82, 223.

⁽⁷⁾ For recent examples, see: (a) Kumar, P.; Prescher, S.; Louie, J. Angew. Chem., Int. Ed. 2011, 50, 10694. (b) Wang, Y.-F.; Toh, K. K.; Ng, E. P. J.; Chiba, S. J. Am. Chem. Soc. 2011, 133, 6411. (c) Ohashi, M.; Takeda, I.; Ikawa, M.; Ogoshi, S. J. Am. Chem. Soc. 2011, 133, 18018. (d) Wang, C.; Li, X.; Wu, F.; Wan, B. Angew. Chem., Int. Ed. 2011, 50, 7162. (e) Ren, Z.-H.; Zhang, Z.-Y.; Yang, B.-Q.; Wang, Y.-Y.; Guan Z.-H. Org. Lett. 2011, 13, 5394. (f) Hyster, T. K.; Rovis, T. Chem. Commun. 2011, 47, 11846. (g) Too, P. C.; Noji, T.; Lim, Y. J.; Li, X.; Chiba, S. Synlett 2011, 2789. (h) Donohoe, T. J.; Basutto, J. A.; Bower, J. F.; Baker, D. B.; Basutto, J. A.; Chan, L. K. M.; Gallagher, P. Chem. Commun. 2011, 47, 10611. (j) Yuan, C.; Chang, C.-T.; Axelrod, A.; Siegel, D. J. Am. Chem. Soc. 2010, 132, 5924.

⁽⁸⁾ For reviews, see: (a) Domínguez, G.; Pérez-Castells, J. Chem. Soc. *Rev.* **2011**, 40, 3430. (b) Varela, J. A.; Saá, C. Synlett **2008**, 2571. (c) Varela, J. A.; Saá, C. Chem. Rev. **2003**, 103, 3787.

⁽⁹⁾ For recent examples, see: (a) Nakamura, I.; Zhang, D.; Terada, M. J. Am. Chem. Soc. **2010**, 132, 7884. (b) Zhu, J. L.; Su, Y. L.; Chan, Y. H.; Chen, I. C.; Liao, C. C. Heterocycles **2009**, 78, 369. (c) Gao, H.; Zhang, J. Adv. Synth. Catal. **2009**, 351, 85. (d) Cacchi, S.; Fabrizi, G.; Filisti, E. Org. Lett. **2008**, 10, 2629. (e) Movassaghi, M.; Hill, M. D. J. Am. Chem. Soc. **2006**, 128, 4592.

While the thermal 6π -electrocyclization of 1-, 2-, and 3-azatrienes has been demonstrated to have great potential in the construction of pyridine rings,¹⁰ synthetic applications of this transformation are still limited due to the lack of efficient ways to access the conjugated azatriene systems. As part of our ongoing program on the use of amphoteric aziridine aldehydes for the synthesis of nitrogen-containing heterocycles.¹¹ we recently disclosed a facile preparation of unprotected α -amino allenes from N-H alkynylaziridines through a 9-BBN-mediated hvdride transfer process.^{11e} We were aware that carbopalladation of allene functionalities regioselectively provides an efficient entry to versatile and reactive π -allylpalladium species¹² that can potentially undergo subsequent β -hydride elimination to form 1,3-dienes (Scheme 1, eq 1).¹³ We sought to apply this cascade process to access conjugated 2-azatrienes from a "skipped" allenyl imine structure obtained via simple condensation of α -amino allenes and aldehydes (Scheme 1, eq 2). Further in situ thermal electrocyclization and oxidative aromatization of the azatriene intermediates were projected to result in straightforward and modular construction of multisubstituted pyridine rings.

Scheme 1



In order to test the feasibility of this transformation in pyridine synthesis, the "skipped" allenyl imine 2a was first prepared quantitatively by the condensation of α -amino

(10) For recent examples of pyridine synthesis involving electrocyclization of azatrienes, see: (a) Liu, S.; Liebeskind, L. S. J. Am. Chem. Soc. 2008, 130, 6918. (b) Parthasarathy, K.; Jeganmohan, M.; Cheng, C.-H. Org. Lett. 2008, 10, 325. (c) Movassaghi, M.; Hill, M. D.; Ahmad,
 O. K. J. Am. Chem. Soc. 2007, 129, 10096. (d) Trost, B. M.; Gutierrez, A. C. Org. Lett. 2007, 9, 1473. (e) Meketa, M. L.; Weinreb, S. M.; Nakao, Y.; Fusetani, N. J. Org. Chem. 2007, 72, 4892. (f) Also see refs 9a and 9e. (11) (a) Rotstein, B. H.; Winternheimer, D. J.; Yin, L. M.; Deber, C. M.; Yudin, A. K. Chem. Commun. 2012, 48, 3775. (b) Rotstein, B. H.; Yudin, A. K. Synthesis 2012, 44, 2851. (c) Cheung, L. L. W.; He, Z. Decker, S. M.; Yudin, A. K. Angew. Chem., Int. Ed. 2011, 50, 11798. (d) Botstein, B. H.; Mourtada, R.; Kelley, S. O.; Yudin, A. K. Chem.—Eur.
 J. 2011, 17, 12257. (e) He, Z.; Yudin, A. K. Angew. Chem., Int. Ed. 2010, 49, 1607. (f) Hili, R.; Rai, V.; Yudin, A. K. J. Am. Chem. Soc. 2010, 132, 2889. (g) Rotstein, B. H.; Rai, V.; Hili, R.; Yudin, A. K. Nat. Protoc. 2010, 5, 1813. (h) Baktharaman, S.; Afagh, N.; Vandersteen, A.; Yudin, A. K. Org. Lett. 2010, 12, 240. (i) Assem, N.; Natarajan, A.; Yudin, A. K. J. Am. Chem. Soc. 2010, 132, 10986. (j) Hili, R.; Yudin, A. K. J. Am. Chem. Soc. 2009, 131, 16404. (k) Hili, R.; Yudin, A. K. Angew. Chem., Int. Ed. 2008, 47, 4188. (l) Hili, R.; Yudin, A. K. J. Am. Chem. Soc. 2006, 128, 14772

(12) For reviews about carbopalladation of allenes, see: (a) Mandai, T. In *Modern Allene Chemistry*; Krause, N., Hashmi, S. K., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 2, Ch.16, pp 925. (b) Ma, S. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002; Vol. 1, Ch. IV.7, pp 1491. (c) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067. allene **1a** and benzaldehyde in the presence of MgSO₄ in DCM. Using **2a** as the testing substrate, we initially carried out a trial reaction with phenyl iodide in the presence of Pd(OAc)₂ (10 mol %), LiCl (1.0 equiv), and Na₂CO₃ (2.5 equiv) in DMF under N₂ atmosphere. Gratifyingly, after heating the reaction mixture at 100 °C for 12 h, the desired 2,4,6-triphenylpyridine product **3a** was observed by TLC and crude ¹H NMR analysis (Scheme 2). Not surprisingly, a considerable amount of the dihydropyridine **3a**' was also detected.

Scheme 2. Preliminary Result for Pyridine Synthesis



A simple and straightforward catalytic cycle for the dihydropyridine/pyridine formation is suggested in Scheme 3. It is reasonable to assume that the η^3 -allyl complex **A**, generated via the carbopalladation of allenyl imine **2a**, should isomerize to the η^1 -allyl complex **B** in order to reach the fourcentered transition state needed for the β -hydride elimination (Scheme 2, Path a).^{13a} The conjugated 2-azatriene intermediates are most likely formed as a mixture of *E*- and *Z*-geometric isomers that equilibrate under the reaction conditions. Ultimately, the (*Z*)-2-azatriene undergoes the thermal electrocyclization to afford the dihydropyridine **3a**'. Rapid oxidative aromatization, possibly catalyzed by palladium,¹⁴ completes the formation of pyridine **3a**.

⁽¹³⁾ For recent synthetic examples involving β -hydride elimination of π -allylpalladium species, see: (a) Ogawa, R.; Shigemori, Y.; Uehara, K.; Sano, J.; Nakajima, T.; Shimizu, I. *Chem. Lett.* **2007**, *36*, 1338. (b) Albéniz, A. C.; Espinet, P.; Martín-Ruiz, B. *Dalton Trans.* **2007**, 3710. (c) Franzén, J.; Löfstedt, J.; Falk, J.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2003**, *125*, 14140. (d) Franzén, J.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2003**, *125*, 6056.

⁽¹⁴⁾ For examples of palladium-catalyzed oxidative aromatization, see: (a) Jiang, M.; Wei, Y.; Shi, M. *Eur. J. Org. Chem.* 2010, 3307. (b) Bercaw, J. E.; Hazari, N.; Labinger, J. A. *J. Org. Chem.* 2008, *73*, 8654.
(c) Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Org. Lett.* 2002, *4*, 3955.

⁽¹⁵⁾ For reviews of nucleophilic η^1 -allylpalladium complexes (e.g., η^1 -allylpalladium pincer complexes and η^1, η^3 -bis-allylpalladium complexes), see: (a) Selander, N.; Szabó, K. J. *Chem. Rev.* **2011**, *111*, 2048. (b) Pilarski, L. T.; Szabó, K. J. *Curr. Org. Chem.* **2011**, *15*, 3389. (c) Zanoni, G.; Pontiroli, A.; Marchetti, A.; Vidari, G. *Eur. J. Org. Chem.* **2007**, 3599. (d) Szabó, K. J. *Synlett* **2006**, 811. (e) Szabó, K. J. *Chem. Eur. J.* **2044**, *10*, 5268. (f) Tamaru, Y. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002; Vol. 2, Ch. V.7.3.4, pp 1917.

Scheme 3. Preparation of 2,4,6-Trisubstituted Pyridines^a



^a For detailed experimental procedure, see Supporting Information. All yields in parentheses are isolated yields after silica gel chromatography.

It is noteworthy that the proposed involvement of transient η^1 -allylpalladium intermediate **B** in the reaction also implies the possibility of an intramolecular 6-*endo*-trig nucleophilic allylation of the imine C=N double bond (Scheme 2, Path b).^{15,16} The newly formed *N*-pallado-tetrahydropyridine intermediate **C** would then undergo a β -hydride elimination to release the dihydropyridine **3a**' that is subsequently oxidized to the final pyridine product.

Further condition screenings of the above reaction revealed that a simplified catalytic system containing 10 mol % Pd(PPh₃)₄ and 2.5 equiv of NaOAc was capable of giving optimal yields of the pyridine product. The reaction was carried out with allenyl imine 2a and phenyl iodide at 80 °C in anhydrous DMF for 12 h under N₂ atmosphere, followed by an additional 12 h exposure to air at the same temperature. An 84% yield of 2,4,6-triphenyl pyridine 3a was obtained. It was found that an efficient preformation of the "skipped" allenyl imine, facilitated by anhydrous MgSO₄ in DCM, was necessary prior to the palladiumcatalysis step. Attempts at one-pot reactions using a mixture of α -amino allene **1a**, benzaldehyde, phenyl iodide, Pd- $(PPh_3)_4$, and NaOAc with or without 4 Å molecular sieves all resulted in considerable decomposition and low yields of the pyridine product. This is presumably attributable to side reactions triggered by undesirable interactions between the palladium species and the free amino group of the α -amino allene.

Encouraged by the preliminary results, we proceeded to evaluate the generality of this two-step procedure for the synthesis of substituted pyridines. A series of "skipped" allenyl imines 2 was prepared via the condensation of different α -amino allenes and aldehydes. By subjecting the preformed allenyl imine starting materials and a variety of aryl iodides to the palladium catalysis conditions, a wide range of trisubstituted pyridines 3 with flexible combinations of substituents were successfully obtained in moderate to good yields (Scheme 3). This pyridine synthesis methodology has considerable functional group tolerance. Substrates with heterocycles, such as pyridine, furan, and thiophene, were found to work well in the reaction, enabling efficient access to biheteroaryl compounds that can be potentially used as functionalized bidentated ligands (e.g., 31, 3m, and 3p-3s) in transition-metal catalysis.

In addition to fully aryl-substituted pyridine products, 2- or 6-alkyl-substituted ones, 3xa-xf, can also be obtained from the corresponding alkyl-substituted α -amino allene or aldehydes; however, the isolated yields were considerably lower. It is interesting that a trend of decreasing yield was found when the 2-substituent on the pyridine ring 3xa-xc ranged from tertiary to primary alkyl groups. This observation implied that the inefficiency of the preparation of pyridines with alkyl substituents could be attributable to side reactions associated with available α -C-H bonds on the alkyl groups under the basic palladium catalysis conditions.

The successful preparation of 2,4,6-trisubstituted pyridines prompted us to further examine the feasibility of

⁽¹⁶⁾ For synthetic examples involving other nucleophilic η' -allylpalladium species, see: (a) Raikar, S.; Pal, B. K.; Malinakova, H. C. Synthesis **2012**, 1983. (c) Shiota, A.; Malinakova, H. C. J. Organomet. Chem. **2012**, 704, 9. (e) Grote, R. E.; Jarvo, E. R. Org. Lett. **2009**, 11, 485. (g) Hopkins, C. D.; Malinakova, H. C. Synthesis **2007**, 3558. (h) Barczak, N. T.; Grote, R. E.; Jarvo, E. R. Organometallics **2007**, 26, 4863. (i) Hopkins, C. D.; Malinakova, H. C. Org. Lett. **2006**, 8, 5971.

Scheme 4. Preparation of 2,3,4,6-Tetrasubstituted Pyridines^a



^{*a*} For detailed experimental procedure, see Supporting Information. All yields in parentheses are isolated yields after silica gel chromatography.

accessing higher-substituted pyridine derivatives. A series of 2,3,4,6-tetrasusbtituted pyridines **6** were obtained in good to excellent yields via the same two-step pyridine synthesis procedure by using an array of terminal-substituted α -amino allenes **4** (Scheme 4). The steric hindrance introduced by the extra 3-aryl group ($-Ar^1$) did not hamper the formation of the aromatic pyridine system.

Although the two-step pyridine synthesis appears quite general in scope, it is noteworthy that the palladiumcatalyzed transformation of the "skipped" allenyl imine 7 bearing a phenyl group at the 2-position unexpectedly generated a complex product mixture from which only the symmetrical *N*-benzyl pyrrole **8** was isolated in low yield (Scheme 5). Surprisingly, 2,4,5-triphenyl pyridine **9** was not observed in this reaction. It is conceivable that the steric hindrance resulting from an extra substituent at the 2-postion significantly inhibits the isomerization of π -allylpalladium **D** to the energetically uphill η^1 -allylpalladium species **E**, pivotal for the generation of six-membered azacyclic intermediates, thereby completely surpressing the pyridine formation. The π -allylpalladium intermediate **D** presumably Scheme 5. Pyrrole Formation via 5-exo-Trig Cyclization



undergoes the cyclization, initiated by an intramolecular attack of the electrophilic π -allyl moiety by the imine nitrogen and followed by a 1,3-hydrogen shift and deprotonation, to afford the *N*-benzyl pyrrole product. The formation of this pyrrole product supports the hypothesis that an η^1 -allyl structure easily accessible from the π -allylpalladium intermediate is crucial to the generation of pyridine rings.

In summary, we have demonstrated a simple and modular synthesis of multisubstituted pyridines with flexible control over the substitution pattern from readily available α -amino allenes, aldehydes, and aryl halides. The versatility of this chemistry offers a valuable addition to methods of synthesizing of highly substituted pyridines.

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Supporting Information Available. Complete experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.