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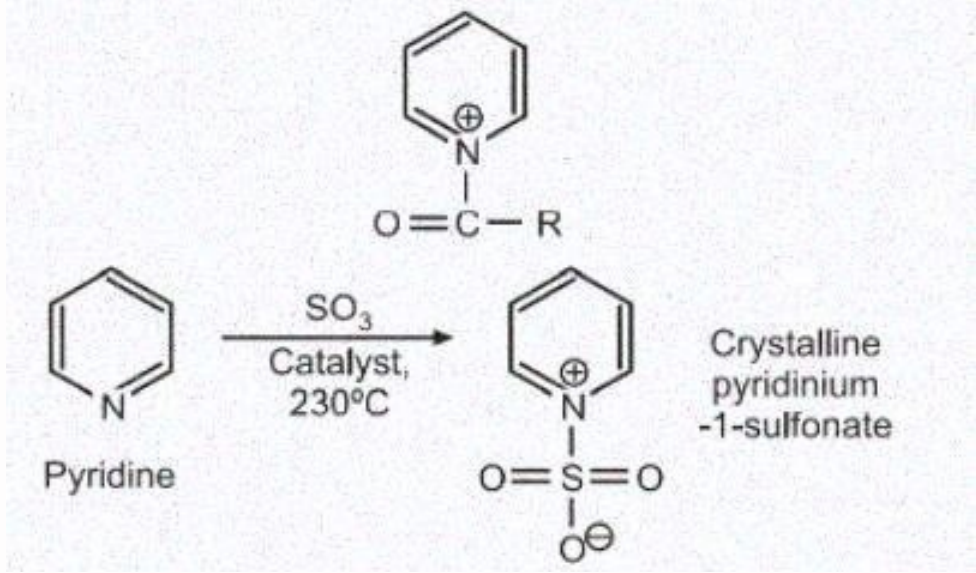
  
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## Synthesis of pyridine derivatives. Pyridine synthesis. Synthesis of pyridine pdf.

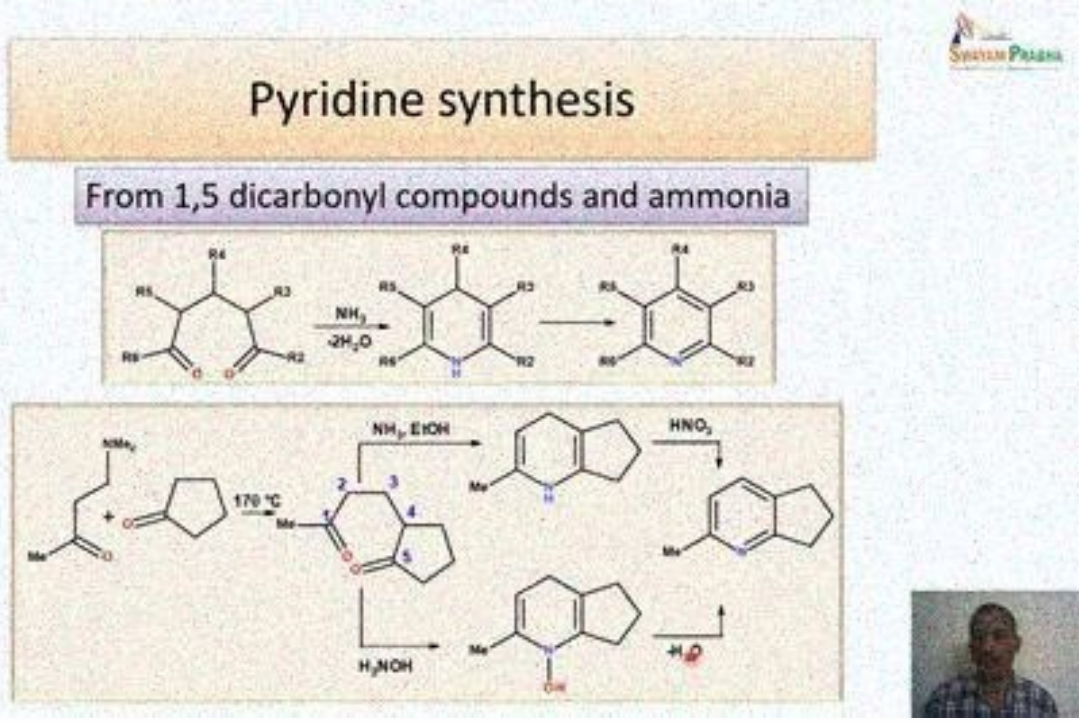
Author links open overlay panel, rights and contentView full textCopyright © 2023 Elsevier Inc. All rights reserved. Chemical reaction Hantzsch pyridine synthesis Named after Arthur Rudolf Hantzsch Reaction type Ring forming reaction Identifiers Organic Chemistry Portal hantzsch-dihydropyridine-synthesis RSC ontology ID RXNO:0000268 The Hantzsch pyridine synthesis or Hantzsch dihydropyridine synthesis is a multi-component organic reaction between an aldehyde such as formaldehyde, 2 equivalents of a  $\beta$ -keto ester such as ethyl acetoacetate and a nitrogen donor such as ammonium acetate or ammonia.[1][2] The initial reaction product is a dihydropyridine which can be oxidized in a subsequent step to a pyridine.[3] The driving force for this second reaction step is aromatization. This reaction was reported in 1881 by Arthur Rudolf Hantzsch. A 1,4-dihydropyridine dicarboxylate is also called a 1,4-DHP compound or a Hantzsch ester. These compounds are an important class of calcium channel blockers[2] and as such commercialized in for instance nifedipine, amlodipine or nimodipine. The reaction has been demonstrated to proceed in water as reaction solvent and with direct aromatization by ferric chloride, manganese dioxide or potassium permanganate in a one-pot synthesis.[4] Hantzsch reaction with ammonium acetate, ethyl acetoacetate, formaldehyde and ferric chloride The Hantzsch dihydropyridine synthesis has been effected by microwave chemistry.[5] Mechanism At least five significant pathways have been proposed for the Hantzch reaction synthesis of 1,4-dihydropyridine. Low yield and unexpected products may arise under varying reactants and reaction conditions. 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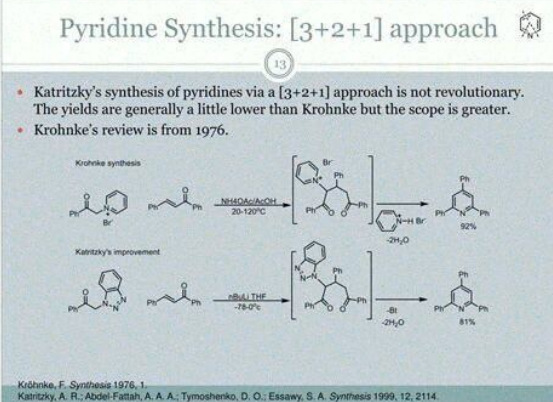
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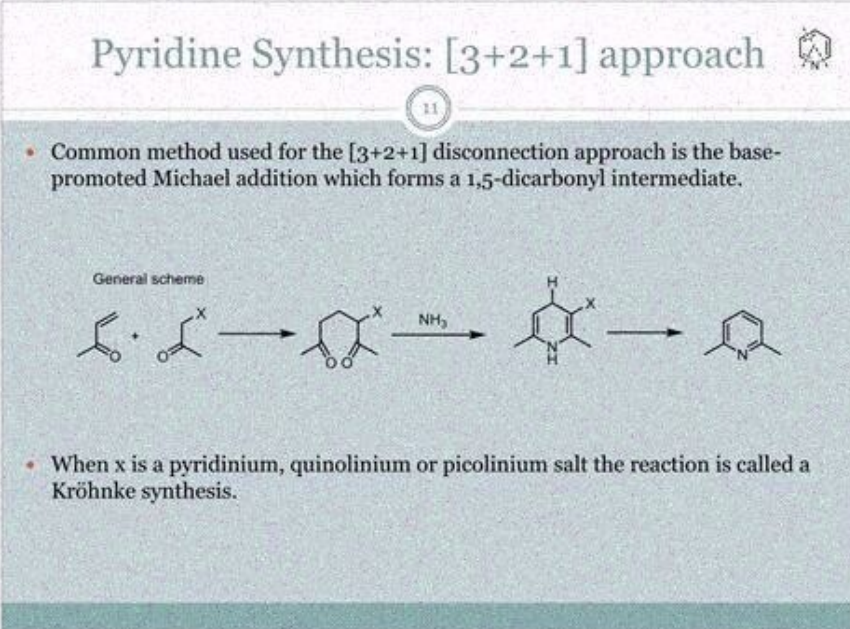
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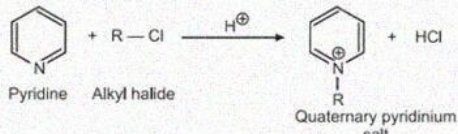




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Ionic liquids are an easy to handle and non-toxic option to replace traditional catalysts. Additionally, this catalyst lead to a high yield at room temperature, reducing the impact of heating the reaction for an extended time. A second study used ceric ammonium nitrate (CAN) as an alternate catalyst and achieved a solvent-free room temperature reaction.[16] Knoevenagel-Fries modification The Knoevenagel-Fries modification allows for the synthesis of unsymmetrical pyridine compounds.[17] See also Hantzsch pyrrole synthesis References ^ Hantzsch, A. (1881). "Condensationprodukte aus Aldehydammoniak und Ketonartigen Verbindungen". *Chemische Berichte*. 14 (2): 1637–8. doi:10.1002/cber.18810140214. ^ a b Li, Jie Jack (19 July 2006). Name Reactions (3rd ed.). ISBN 3-540-30030-9. ^ Li, Jie Jack (11 October 2004). Name reactions in heterocyclic chemistry. p. 304. ISBN 0-471-30215-5. ^ Xia, J. J.; Mayence, A. (2003). "Synthesis and Aromatization of Hantzsch 1,4-Dihydropyridines under Microwave Irradiation. An Overview" (PDF). *Molecules*. 8 (4): 381–91. doi:10.3390/80400381. S2CID 98443099. ^ a b Santos, Vanessa G. (2014). "The Multicomponent Hantzsch Reaction: Comprehensive Mass Spectrometry Monitoring Using Charge-Tagged Reagents". *Chemistry Letters*. 43 (10): 1690–1. doi:10.1002/chem.201303065. PMID 25179028. ^ Katrinsky, Alan R.; Ostercamp, Daryl L.; Yousaf, Taher I. (1986). "The mechanism of the hantzsch pyridine synthesis: A study by 15N and 13C NMR spectroscopy". *Tetrahedron*. 42 (20): 5729–5738. doi:10.1016/S0040-4020(01)88178-3. ^ Saini, Anil (February 2008). "Hantzsch reaction: Recent advances in Hantzsch 1,4-dihydropyridines" (PDF). *Journal of Scientific and Industrial Research*. 67: 95–111. ^ Kumar, Atul (5 August 2008). "ChemInform Abstract: Efficient Synthesis of Hantzsch Esters and Polyhydroquinoline Derivatives in Aqueous Micelles". *ChemInform*. 39 (32). doi:10.1002/chin.200832145. ^ Mashraqui, Sabir H. (1998). "Bismuth Nitrate Pentahydrate: A Convenient Reagent for the Oxidation of Hantzsch 1,4-Dihydropyridines". *Synthesis*. 1998 (5): 713–714. doi:10.1055/s-1998-4516. ^ a b c Yadav, Jhillsu S. (2000). "Aromatization of Hantzsch 1,4-Dihydropyridines with 12-MeOH". *Synthesis*. 2000 (11): 1532–1534. doi:10.1055/s-2000-7613. ^ a b Ko, Kwang-Youn (1999). "Aromatization of Hantzsch 1,4-Dihydropyridines with Magtrieve". *Tetrahedron Letters*. 40: 3207–3208. doi:10.1016/S0040-4039(99)00467-0. ^ a b Liao, Xiali (2010). "Oxidative aromatization of Hantzsch 1,4-dihydropyridines by sodium chlorite". *Tetrahedron Letters*. 51 (29): 3859–3861. doi:10.1016/j.tetlet.2010.05.091. S2CID 94650170. ^ Wei, Xiaojing (2014). "Metal-Free-Mediated Oxidation Aromatization of 1,4-Dihydropyridines to Pyridines Using Visible Light and Air". *Chinese Journal of Chemistry*. 32 (12): 1245–1250. doi:10.1002/cjoc.201400521. ^ Jassem, Ahmed Majeed; Almashal, Faeza Abdul Kareem; Mohammed, Mohammed Qasim; Jabir, Hadi Abdal Samad (2 February 2020). "A catalytic and green method for one-pot synthesis of new Hantzsch 1,4-dihydropyridines". *SN Applied Sciences*. 2 (3). doi:10.1007/s42452-020-2165-x. ^ Sharma, M.G; Rajani, D.P.; Patel, H.M. (14 June 2017). "Green approach for synthesis of bioactive Hantzsch 1,4-dihydropyridine derivatives based on thiophene moiety via multicomponent reaction". *Royal Society Open Science*. 4 (6): 170006. Bibcode:2017RSOS...470006S. doi:10.1098/rsos.170006. PMC 5493906. PMID 28680664. ^ Knoevenagel, E.; Fries, A. (1898). "Synthesen in der Pyridinreihe. Ueber eine Erweiterung der Hantzsch'schen Dihydropyridinsynthese". *Berichte der Deutschen Chemischen Gesellschaft*. 31 (1): 761–7. doi:10.1002/cber.1898011157. ^ Daly, J. W.; Gassoff, M. & Spande, T. F. Alkaloids from amphibian skins. In *Alkaloids: chemical and biological perspectives* (ed. Pelletier, S. W.) 13, 1–161 (Pergamon), (1999).De, S. S. et al. Pyridine: the scaffolds with significant clinical diversity. *RSC Adv* 12, 15385–15406 (2022).Article CAS PubMed PubMed Central Google Scholar Hamada, Y. Role of pyridines in medicinal chemistry and design of BACE1 inhibitors possessing a pyridine scaffold, in *Pyridine* (ed. Pandey, P. P.) (Intech), (2018).Ling, Y. et al. The expanding role of pyridine and dihydropyridine scaffolds in drug design. *Drug Des. Devel. Ther.* 15, 4289–4338 (2021).Article CAS PubMed PubMed Central Google Scholar Altaf, A. A. et al. A review on the medicinal importance of pyridine derivatives. *J. Drug Des. Med. Chem.* 1, 1–11 (2015).Google Scholar Lou, X.-Y. & Yang, Y.-W. Pyridine-conjugated pillar[5]arene: from molecular crystals of blue luminescence to red-emissive coordination nanocrystals. *J. Am. Chem. Soc.* 143, 11976–11981 (2021).Article CAS PubMed Google Scholar Blatchford, J. et al. Photoluminescence in pyridine-based polymers: Role of aggregates. *Phys. Rev. B* 54, 9180–9189 (1996).Article CAS Google Scholar Tahir, T. et al. Pyridine scaffolds, phenols and derivatives of azo moiety: Current therapeutic perspectives. *Molecules* 26, 4872 (2021).Article CAS PubMed PubMed Central Google Scholar Lin, S. X., Curtis, M. A. & Sperry, J. Pyridine alkaloids with activity in the central nervous system. *Bioorg. Med. Chem.* 28, 115820 (2020).Article CAS PubMed PubMed Central Google Scholar Abdel-Raheem, S. A. A. et al. Synthesis and biological activity of 2-(4-(3-Cyano-4,6-diisopropylpyridin-2-yl)thio) acetamide and its cyclized form. *Alger. J. Sci.* 16, 3432–3435 (2014).Article CAS PubMed Google Scholar Zhou, Y., Tang, Z. & Song, Q. Lewis acid-mediated [3+3] annulation for the construction of substituted pyrimidine and pyridine derivatives. *Adv. Synth. Catal.* 359, 952–958 (2017).Article CAS Google Scholar Allais, C., Grassot, J.-M., Rodriguez, J. & Constantieux, T. Metal-free multicomponent syntheses of pyridines. *Chem. Rev.* 114, 10829–10868 (2014).Article CAS PubMed Google Scholar Liu, N. W. et al. Nickel-catalyzed synthesis of diaryl sulfones from aryl halides and sodium sulfonates. *Eur. J. Org. Chem.* 2018, 1208–1210 (2018).Article CAS Google Scholar Liu, N. W., Hofman, K., Herbert, A. & Manolikakes, G. Visible-light photoredox/nickel dual catalysis for the cross-coupling of sulfonic acid salts with aryl iodides. *Org. Lett.* 20, 760–763 (2018).Article CAS PubMed Google Scholar Bangdar, B. P., Bettigeri, S. V. & Phopase, J. Unsymmetrical diaryl sulfones through palladium-catalyzed coupling of aryl boronic acids and arylsulfonyl chlorides. *Org. Lett.* 6, 2105–2108 (2004).Article CAS PubMed Google Scholar Trankle, W. G. & Kopach, M. E. Green chemical synthesis of 2-benzenesulfonyl-pyridine and related derivatives. *Org. Process Res. Dev.* 11, 913–917 (2007).Article CAS Google Scholar Guilbaud, J. et al. Palladium-catalyzed heteroaryl thioethers synthesis overcoming palladium dithiolate resting states inertness: practical road to sulfones and NH-sulfoximines. *Catal. Commun.* 111, 52–58 (2018).Article CAS Google Scholar Kim, D. K. et al. Silyloxymethanesulfonate as a sulfonylate equivalent for the modular synthesis of sulfones and sulfonyl derivatives. *Chem. Sci.* 11, 13071–13078 (2020).Article CAS PubMed PubMed Central Google Scholar Margraf, N. & Manolikakes, G. One-pot synthesis of aryl sulfones from organometallic reagents and iodonium salts. *J. Org. Chem.* 80, 2582–2600 (2015).Article CAS PubMed Google Scholar Maloney, K. M., Kuethe, J. T. & Linn, K. A practical, one-pot synthesis of sulfonfylated pyridines. *Org. Lett.* 13, 102–105 (2011).Article CAS PubMed Google Scholar Wang, D., Wang, F., Song, G. & Li, X. Diverse reactivity in a rhodium(III)-catalyzed oxidative coupling of N-allyl arenesulfonamides with alkynes. *Angew. Chem.* Int. Ed. 51, 12348–12352 (2012).Article CAS Google Scholar Scalone, M. & Waldmeier, P. Efficient enantioselective synthesis of the NMDA 2B receptor antagonist Ro 7-8867. *Org. Process Res. Dev.* 7, 418–425 (2003).Article CAS Google Scholar Fu, W. C., So, C. M. & Kwong, F. Y. Palladium-catalyzed phosphorylation of aryl mesylates and tosylates. *Org. Lett.* 17, 5906–5909 (2015).Article CAS PubMed Google Scholar Belabassi, Y., Alzghari, S. & Montchamp, J.-L. Revisiting the Hirao cross-coupling: improved synthesis of aryl and heteroaryl phosphates. *J. Organomet. Chem.* 693, 3171–3178 (2008).Article CAS PubMed PubMed Central Google Scholar Kalek, M., Jezowska, M. & Stawinski, J. Preparation of arylphosphonates by palladium(0)-catalyzed cross-coupling in the presence of acetate additives: synthetic and mechanistic studies. *Adv. Synth. Catal.* 351, 3207–3216 (2009).Article CAS Google Scholar Zhang, Y. et al. Palladium-catalyzed one-pot phosphorylation of phenols mediated by sulfonyl fluoride. *Chem. Commun.* 57, 4588–4591 (2021).Article CAS Google Scholar Kalek, M., Ziadi, A. & Stawinski, J. Microwave-assisted palladium-catalyzed cross-coupling of aryl and vinyl halides with H-phosphonate diesters. *Org. Lett.* 10, 4637–4640 (2008).Article CAS PubMed Google Scholar Petrakis, K. S. & Nagabhushan, T. L. Palladium-catalyzed substitutions of triflates derived from tyrosine-containing peptides and simpler hydroxyarenes forming 4-(diethoxyphenyl)phenylalanines and diethyl arylphosphonates. *J. Am. Chem. Soc.* 109, 2831–2833 (1987).Article CAS Google Scholar Hirao, T., Masunaga, T., Yamada, N., Ohshiro, Y. & Agawa, T. Palladium-catalyzed new carbon-phosphorus bond formation. *Bull. Chem. Soc. Jpn.* 55, 909–913 (1982).Article CAS Google Scholar Hirao, T., Masunaga, T., Ohshiro, Y. & Agawa, T. A novel synthesis of dialkyl arenephosphonates. *Synth* 1981, 56–57 (1981).Article Google Scholar Li, C.-j Nickel-catalyzed phosphorylation of tosylates. *Russ. J. Gen. Chem.* 90, 725–730 (2020).Article CAS Google Scholar Peng, Z. et al. Pd-catalyzed C–P coupling of heteroaryl boronic acid with H-phosphonate diester. *Tetrahedron Lett.* 57, 3063–3066 (2016).Article CAS Google Scholar Qiu, D. et al. Visible light-driven, photocatalyst-free Arbuszov-like reaction via arylazo sulfones. *Adv. Synth. Catal.* 361, 5239–5244 (2019).Article CAS Google Scholar Shaikh, R. S., Düsel, S. J. S. & König, B. Visible-light photo-Arbusov reaction of aryl bromides and trialkyl phosphites yielding aryl phosphonates. *ACS Catal* 6, 8410–8414 (2016).Article CAS Google Scholar Wang, S., Qiu, D., Mo, F., Zhang, Y. & Wang, J. Metal-free aromatic carbon-phosphorus bond formation via a Sandmeyer-type reaction. *J. Org. Chem.* 81, 11603–11611 (2016).Article CAS PubMed Google Scholar Lee, S. & Park, S. B. An efficient one-step synthesis of heterobiaryl pyrazolo[3,4-b] pyridines via indole ring opening. *Org. Lett.* 11, 5214–5217 (2009).Article CAS PubMed Google Scholar Varun, B. V., Vaithegi, K., Yi, S. & Park, S. B. Nature-inspired remodeling of (aza)indoles to meta-aminoaryl nicotines for late-stage conjugation of vitamin B3 to (hetero)arylamines. *Nat. Commun.* 11, 1–9 (2020).Article Google Scholar Leal, A. S. et al. Retinoid X receptor agonist LG100268 modulates the immune microenvironment in preclinical breast cancer models. *npj Breast Cancer* 5, 1–15 (2019).Article CAS Google Scholar Miao, Y. H. et al. Natural source, bioactivity and synthesis of benzofuran derivatives. *RSC Adv.* 9, 27510–27540 (2019).Article CAS PubMed PubMed Central Google Scholar Rahim, M. A., Kristufek, S. L., Pan, S., Richardson, J. J. & Caruso, F. Phenolic building blocks for the assembly of functional materials. *Angew. Chem. Int. Ed.* 58, 1904–1927 (2019).Article CAS PubMed Google Scholar Scott, K. A., Cox, P. B. & Njardarson, J. T. Phenols in pharmaceuticals: analysis of a recurring motif. *J. Med. Chem.* 65, 7044–7072 (2022).Article CAS PubMed Google Scholar Tang, T. T. et al. Fusaric acid and analogues as gram-negative bacterial quorum sensing inhibitors. *Eur. J. Med. Chem.* 126, 1011–1020 (2017).Article CAS PubMed Google Scholar Salehi, B. et al. Epibatidine: a promising natural alkaloid in health. *Biomol.* 9, 6 (2019). Google Scholar Li, W. et al. Antinociceptive effects of novel epibatidine analogs through activation of α4β2 nicotinic receptors. *Sci. China Life Sci.* 61, 688–695 (2018).Article CAS PubMed Google Scholar Page 2a Bioactive natural products and drug molecules containing substituted pyridines. b Previous synthetic strategies for substituted pyridines. c Proposed synthetic strategy of substituted pyridines with diverse functional groups (esters/sulfones/phosphonates). Reactions > Organic Synthesis Search Categories: Synthesis of N-Heterocycles > Name Reactions Bohlmann-Rahtz Pyridine Synthesis Hantzsch Dihydropyridine (Pyridine) Synthesis Recent Literature Addition of Grignard reagents to C(sp2)-nitriles in THF at room temperature and subsequent treatment with acetic anhydride at 120°C afforded 2-substituted pyridines in good yields. By exchanging acetic anhydride for DMF in the second step, 2-substituted pyridine N-oxides were obtained, enabling the synthesis of 2,6-disubstituted pyridines. H. Andersson, F. Almqvist, R. Olsson, *Org. Lett.*, 2007, 9, 1335-1337. The success of a one-step transformation of heterocyclic N-oxides to 2-alkyl-, aryl-, and alkenyl-substituted N-heterocycles hinges on the combination of copper catalyst and activation by lithium fluoride or magnesium chloride. The utility for the scaffold decoration of a broad range of complex N-heterocycles is exemplified by syntheses of new structural analogues of several antimalarial, antimicrobial, and fungicidal agents. O. V. Larionov, D. Stephens, A. Mfuh, G. Chavez, *Org. Lett.*, 2014, 16, 864-867. Cross-coupling of aryl bromides with 2-thienyl, 3-thienyl, 2-pyridyl, and 3-pyridyl aluminum reagents in the presence of Pd(OAc)2 and (o-tolyl)3P provides useful biaryl building blocks. Additionally, the catalytic system was also suited well for the coupling reaction of benzyl halides with pyridyl aluminum reagents to afford a series of pyridylarylmethanes. X. Chen, L. Zhou, Y. Li, T. Xie, S. Zhou, *J. Org. Chem.*, 2014, 79, 230-239. Mechanochemically activated magnesium(0) metal is a highly active mediator for the direct C-4-H alkylation of pyridines with alkyl halides. The reaction offers excellent regioselectivity and substrate scope, including those containing reducible functionalities, free amines, and alcohols, as well as biologically relevant molecules. C. Wu, T. Ying, H. Fan, C. Hu, W. Su, *J. Org. Lett.*, 2023, 25, 2531-2536. Pyridine derivatives are important building blocks for many biologically active compounds. However, the synthesis of pyridines bearing an all-carbon quaternary center. This strategy features mild conditions, broad substrate scope, and high functional group tolerance. Q. Lin, H. Gong, F. Wu, *Org. Lett.*, 2022, 24, 8996-9006. A simple maleate-derived blocking group for pyridines enables exquisite control for Minisci-type decarboxylative alkylation at C-4 that allows for inexpensive access to a broad range of valuable building blocks. The method is operationally simple and scalable, and is applied to access known structures in a rapid and inexpensive fashion. J. Choi, G. Laudadio, E. Godineau, P. S. Baran, *J. Am. Chem. Soc.*, 2021, 143, 11927-11933. A photochemical cross-coupling between N-amidopyridinium salts and various alkyl bromides under photocatalyst-free conditions provides various C4-alkylated pyridines. The photochemical activity of electron donor-acceptor (EDA) complexes between N-amidopyridinium salts and bromide generates silyl radicals and drives the alkylation process. S. Jung, S. Shin, S. Park, S. Hong, *J. Am. Chem. Soc.*, 2020, 142, 11370-11375. A photoinduced intermolecular charge transfer between 1,4-dihydropyridines and N-amidopyridinium salts induces a single-electron transfer event without requiring a photocatalyst for the facile C4-functionalization of pyridines. Alkyl, acyl, and carbamoyl radicals can be generated from 1,4-dihydropyridines, that provide facile access to synthetically valuable substituted pyridines. I. Kim, S. Park, S. Hong, *Org. Lett.*, 2020, 22, 8730-8734. A Pd-catalyzed decarbonylative Suzuki cross-coupling of widely available heterocyclic carboxylic acids with arylboronic acids enabled the straightforward preparation of >45 heterobiaryl products using pyridines, pyrimidines, pyrazines, and quinolines in very good yields. A. Cervantes-Reyes, A. C. Weissman, S. R. Stauffer, C. S. Burgey, *Org. Lett.*, 2009, 11, 345-347. A nickel-catalyzed reductive cross-coupling between aryl iodides and difluoromethyl 2-pyridyl sulfone provides facile access to biaryls under mild reaction conditions without pregeneration of arylmetal reagents. The new reactivity of the 2-PySO2CF2H reagent enables C(sp2)-C(sp2) bond formation through selective C(sp2)-S bond cleavage. W. Miao, C. Ni, P. Xiao, R. Jia, W. Zhang, J. Hu, *Org. Lett.*, 2021, 23, 711-715. A Suzuki-Miyaura cross-coupling of tetrabutylammonium 2-pyridyltrioborate salts with various aryl and heteroaryl chlorides produces the corresponding desired coupling products with good to excellent yields in the presence of catalytic amounts of PdCl2dppp and CuI/MeNHCH2CH2OH in anhydrous DMF without bases. Tetrabutylammonium 2-pyridyltrioborate salts are more reactive than the corresponding lithium salts. S. Sakashita, M. Takizawa, J. Sugai, H. Ito, Y. Yamamoto, *Org. Lett.*, 2013, 15, 4308-4311. Heteroaromatic tosylates and phosphates are suitable electrophiles in iron-catalyzed cross-coupling reactions with alkyl Grignard reagents. These reactions are performed at low temperature allowing good functional group tolerance with full conversion within minutes. T. M. Gogsis, A. T. Lindhardt, T. Skrydstrup, *Org. Lett.*, 2009, 11, 4886-4888. A simple skeletal editing protocol "inserts" a nitrogen atom into arylcycloalkenes to form the corresponding N-heterocycles. The use of an inexpensive cobalt catalyst under aqueous and open-air conditions makes this protocol very practical. Examples include late-stage modification of compounds of pharmaceutical interest and complex fused ring compounds. J. Wang, H. Lu, Y. He, C. Jing, H. Wei, *J. Am. Chem. Soc.*, 2022, 144, 22433-22439. A visible-light-enabled biomimetic aza-6π electrocyclization provides diverse pyridines. In a subsequent Minisci-type reaction, a broad spectrum of polysubstituted picolinialdehydes were readily constructed with high efficiency and good functional group tolerance under metal- and oxidant-free conditions under visible light irradiation. Q.-L. Zahng, Q.-q. Yu, L. Ma, X. Lu, Q.-T. Fan, T.-S. Duan, Y. Zhou, F.-L. Zhang, *J.*



Org. Chem., 2021, 86, 17244-17248. A reaction sequence involving a Wittig reaction, a Staudinger reaction, an aza-Wittig reaction, a 6n-3-azatriene electrocyclozation, and a 1,3-H shift enables a quick one-pot synthesis of polysubstituted pyridines in very good yields from aldehydes, phosphorus ylides, and propargyl azide. H. Wei, Y. Li, K. Xiao, B. Cheng, H.

Wang, L. Hu, H. Zhai, Org. Lett., 2015, 17, 5974-5977.

An efficient cyclization of readily available  $\alpha,\beta,\gamma,\delta$ -unsaturated ketones with ammonium formate under air atmosphere provides asymmetrical 2,6-diarylpyridines. The reaction is metal-free and operationally convenient. Y. Gao, R. Chen, Y. Ma, Synthesis, 2019, 51, 3875-3882. The combination of iodine and triethylamine triggers an oxime-based synthesis of 2-aryl-substituted pyridines with high chemo-selectivity and wide functional group tolerance. A broad range of functional pyridines were prepared in good yields using this metal-free protocol. While neither iodine nor triethylamine could trigger this transformation, mechanistic experiments indicated a radical pathway for the reaction. H. Huang, J. Cai, L. Tang, Z. Wang, F. Li, G.-J. Deng, J. Org. Chem., 2016, 81, 1499-1505. A redox-neutral, [3+3]-type condensation of O-acetyl ketoximes and  $\alpha,\beta$ -unsaturated aldehydes, that is synergistically catalyzed by a copper(I) salt and a secondary ammonium salt (or amine), allows modular synthesis of a variety of substituted pyridines under mild conditions with tolerance of a broad range of functional groups. The reaction is driven by a merger of iminium catalysis and redox activity of the copper catalyst.

Y.

Wasi, N. Yoshikai, J.

Am. Chem. Soc., 2013, 135, 3756-3759.

Cationic half-sandwich rare-earth catalysts provide an efficient, general and atom-economical method for the synthesis of 2-alkylated pyridine derivatives via C-H addition to olefins. A wide range of pyridine and olefin substrates including  $\alpha$ -olefins, styrenes, and conjugated dienes are compatible with the catalysts. B.-T. Guan, Z. Hou, J. Am. Chem. Soc., 2011, 133, 18066-18089. The use of Pd2(dba)3 and X-Phos as a ligand enables a mild Negishi cross-coupling of 2-heterocyclic organozinc reagents and aryl chlorides providing 2-aryl-substituted pyridines and thiophenes in high yields. An efficient method to generate the organozinc reagents at room temperature is also demonstrated. M. R. Luzung, J. S.

Patel, J. Yin, J. Org. Chem., 2010, 75, 8330-8332. An efficient lithiation/isomerization/intramolecular carbolithiation sequence provides a divergent and straightforward entry to a wide range of polysubstituted dihydropyridines and pyridines starting from readily available N-allyl-ynamides.

W. Gati, M. M. Rammah, M. B. Rammah, F. Couty, G. Evano, J. Am. Chem. Soc., 2012, 134, 9078-9081. The olefin cross-metathesis reaction provides a rapid and efficient method for the synthesis of  $\alpha,\beta$ -unsaturated 1,5-dicarbonyl derivatives which then serve as effective precursors to pyridines with a wide range of substitution patterns. High levels of regiocontrol, short reaction sequences, and facile substrate variation are all notable aspects of this methodology. T. J. Donohoe, J. A.

Basutto, J. F. Bower, A. Rathi, Org. Lett., 2011, 13, 1036-1039. Regioselective hydrominoration of alkynes with N-silylamine using a bis(amide)bis(amido)titanium(IV) precatalyst, addition of  $\alpha,\beta$ -unsaturated carbonyls to the crude mixture followed by oxidation affords 47 examples of pyridines in good yields containing variable substitution patterns, including pharmaceutically relevant 2,4,5-trisubstituted pyridines. E. K. J. Lui, D. Hergesell, L.

L.

Schafer, Org. Lett., 2018, 20, 6663-6667. A very sterically hindered N-heterocyclic carbene ligand promotes cross-coupling at C4 of 2,4-dichloropyridines with high selectivity (~10:1). Under optimized conditions, diverse substituted 2,4-dichloropyridines and related compounds undergo cross-coupling to form C4-C(sp2) and C4-C(sp3) bonds using organoboron, -zinc, and -magnesium reagents.

J. P. Norman, N. G. Larson, E. D. Entz, S.

R. Neufeldt, J.

Org. Chem., 2022, 87, 7414-7421. A photoredox coupling of  $\alpha,\alpha$ -difluoro- $\beta$ -iodoketones with silyl enol ethers catalyzed by fac-Ir(ppy)3 under blue LED irradiation with subsequent one-pot condensation with ammonium acetate provides diversely substituted 3-fluoropyridines. S. I. Scherbinina, O. V.

Fedorov, V. V.

Levin, V. A. Kokorekin, M. I. Struchkova, A. D. Dilman, J. Org. Chem., 2017, 82, 12967-12974. A convenient base-promoted reaction of 1-arylethylamines with ynonees gives polysubstituted pyridines via direct  $\beta$ -C(sp3)-H functionalization of enaminoxones under metal-free conditions. This procedure features high regioselectivity, high efficiency, and environmental friendliness. Various polysubstituted pyridines were provided in high yields. J. Shen, D. Cai, C. Kuai, Y. Liu, M. Wei, G. Cheng, X. Cui, J. Org. Chem., 2015, 80, 6584-6589. Ring-closing olefin metathesis (RCM)/elimination and RCM/oxidation/deprotection of nitrogen-containing dienes are the key processes of new synthetic routes to substituted 3-hydroxypyridines. An application of RCM/oxidation/deprotection allows the synthesis of 3-aminopyridine derivatives. K. Yoshida, F. Kawagoe, K. Hayashi, S. Horiuchi, T. Imamoto, A. Yanagisawa, Org. Lett., 2009, 11, 515-518. A visible-light-enabled biomimetic aza-6n electrocyclozation provides diverse pyridines. In a subsequent Minisci-type reaction, a broad spectrum of polysubstituted phtolinaldehydes were readily constructed with high efficacy and good functional group tolerance under metal- and oxidant-free conditions under visible light irradiation. Q.-L. Zahng, Q.-q. Yu, L. Ma, X. Lu, Q.-T. Fan, T.-S. Duan, Y. Zhou, F.-L. Zhang, J. Org. Chem., 2021, 86, 17244-17248. A simple and highly efficient protodecarboxylation of various heteroaromatic carboxylic acids is catalyzed by Ag2CO3 and AcOH in DMSO. This methodology enables also a selective monoprotodecarboxylation of several aromatic dicarboxylic acids. P. Lu, C. Sanchez, J. Cornella, I. Larrosa, Org. Lett., 2009, 11, 5710-5713. Reactions of vinyl azides with monocyclic cyclopropanols provided pyridines in the presence of Mn(acac)3, whereas those with bicyclic cyclopropanols led to the formation of 2-azabicyclo[3.3.1]non-2-en-1-ol derivatives using a catalytic amount of Mn(acac)3. Y.-F. Wang, S. Chiba, J. Am. Chem. Soc., 2009, 131, 12570-12572.

A ruthenium-catalyzed formal dehydrative [4 + 2] cycloaddition of enamides and alkynes enables a mild and economic construction of a broad range of highly substituted pyridines. The reaction tolerates many functional groups and offers excellent regioselectivities. J. Wu, W. Xu, Z.-X. Yu, J. Wang, J. Am. Chem. Soc., 2015, 137, 9489-9495. A DBU-promoted metal-free reaction of 2-allyl-2H-azirines affords 1-azatrienes that in situ electrocyclyze to pyridines in very good yields. The reaction displays a broad substrate scope and tolerates various substituents. In addition, one-pot synthesis of pyridines from oximes via in situ formation of 2H-azirines was achieved. Y. Jiang, C.-M. Park, T.-P. Loh, Org. Lett., 2014, 16, 3432-3435. An iodoxybenzoic acid-mediated selected oxidative cyclization of N-hydroxyalkyl enamines provides a variety of 2,3-disubstituted pyrroles and pyridines in good selectivity. This metal-free method offers use of environmentally friendly reagents, broad substrate scope, mild reaction conditions, and high efficiency.

P. Gao, H.-J. Chen, Z.-J.

Bai, M.-N. Zhao, D. Yang, J. Wang, N. Wang, L.

Du, Z.-H. Guan, J. Org. Chem., 2020, 85, 7939-7951. An efficient and practical visible-light photoredox-catalyzed formal [5 + 1] cycloaddition of N-tosyl vinylaziridines with difluoroalkyl halides as unique C1 synthons provides pyridines in good yields. Y.

Liu, W. Luo, Z. Wang, Y. Zhao, J. Zhao, X. Xu, C. Wang, P. Li, Org. Lett., 2020, 22, 9638-9643. Oxidative one-pot sequential reactions of inactivated saturated ketones with electron-deficient enamines enable an efficient synthesis of 3-acylpyridines and pyridine-3-carboxylates. The reaction involve oxidative dehydrogenation of the saturated ketone substrate, followed by [3+3] annulation with  $\beta$ -enaminone or  $\beta$ -enaminoester via a cascade process, including Michael addition, aldol type condensation, and oxidative aromatization.

G.

Chen, Z. Wang, X. Zhang, X. Fan, J. Org. Chem., 2017, 82, 11230-11237. A 2-fluoro-1,3-dicarbonyl-initiated one-pot Michael addition/[5 + 1] annulation/dehydrofluorinative aromatization reaction sequence enables a transition-metal catalyst-free, regioselective synthesis of di-, tri-, tetra-, and pentasubstituted pyridines as well as fused pyridines from readily available starting materials. Z. Song, X. Huang, W. Yi, W. Zhang, Org. Lett., 2016, 18, 5640-5643.

A one-pot synthesis of substituted pyridines via a domino cyclization-oxidative aromatization approach is based on the use of a new bifunctional noble metal-solid acid catalyst, Pd/C/K-10 montmorillonite and microwave irradiation. The cyclization readily takes place on the strong solid acid while palladium dehydrogenates the dihydropyridine intermediate. O. De Paolis, J. Baffoe, S. M. Landge, B. Török, Synthesis, 2008, 3423-3428. Stable 1,2,3-triazine 1-oxides are remarkably effective substrates for inverse electron demand Diels-Alder reactions. Base-catalyzed reactions with amidines provide pyrimidines, with  $\beta$ -ketocarbonyl compounds and related nitrile derivatives polysubstituted pyridines and with 3/5-aminopyrazoles pyrazolo[1,5-*a*]pyrimidines in high yield at room temperature. S. Biswas, L. De Angelis, G. Rivera, H. Arman, M. P.

Doyle, Org. Lett., 2023, 25, 1104-1108. An efficient copper-mediated cleavage of isoxazoles enables the synthesis of nicotinate derivatives and tetrasubstituted pyridines in DMSO as solvent. DMSO serves as a one-carbon surrogate, that forms two C-C bonds.

P. Kumar, M. Kapur, Org. Lett., 2020, 22, 5855-5860. A simple, modular method to prepare highly substituted pyridines in good isolated yields employs a cascade reaction comprising a novel Cu-catalyzed cross-coupling of alkenylboronic acids with  $\alpha,\beta$ -unsaturated ketoxime O-pentafluorobenzoates, electrocyclozation of the resulting 3-azatriene, and air oxidation. S. Liu, L. S. Liebeskind, J. Am. Chem. Soc., 2008, 130, 6918-6919. A single-step conversion of various N-vinyl and N-aryl amides to the corresponding pyridine and quinoline derivatives involves amide activation with trifluoromethanesulfonic anhydride in the presence of 2-chloropyridine followed by n-nucleophile addition to the activated intermediate and annulation. Compatibility of this chemistry with various functional groups is noteworthy. M. Movassaghi, M. D. Hill, O. K. Ahmad, J. Am. Chem. Soc., 2007, 129, 10096-10097. DABCO promotes an efficient, solvent-free, and eco-friendly domino reaction of various  $\beta,\gamma$ -unsaturated  $\alpha$ -ketocarboxyls with 5/6-membered cyclic sulfamidate

170 $^{\circ}$ C in neat conditions under MW irradiation to provide densely functionalized picolinates in short reaction times. S. Biswas, D.

Majee, S. Guin, S.

Samanta, J. Org. Chem., 2017, 82, 10928-10938. A domino reaction of 5-membered cyclic sulfamidate imines with various Morita-Baylis-Hillman acetates of nitroolefins/nitrodienes provides a series of 4,6-diarylpicolinates in excellent yields in the presence of DABCO as an organic base at 55  $^{\circ}$ C. D. Majee, S.

Biswas, S. M. Mobin, S. Samanta, J. Org. Chem., 2016, 81, 4378-4385. A range of highly functionalised pyridines is prepared from enamino and alkynones in a single synthetic step by the use of acetic acid or amberlyst 15 ion exchange resin at 50 $^{\circ}$ C. M. C. Bagley, J. W. Dale, J. Bower, Synlett, 2001, 1149-1151. N-Propargylic  $\beta$ -enaminones are common intermediates for the synthesis of polysubstituted pyrroles and pyridines. In the presence of Cs2CO3 N-propargylic  $\beta$ -enaminones are cyclized to pyrroles in good to high yields, whereas CuBr leads to pyridines. S. Cacchi, G.

Fabrizi, E. Filisti, Org. Lett., 2008, 10, 2629-2632. Polysubstituted pyridines are prepared in good yield and with total regiocontrol by the one-pot reaction of an alkyne, 1,3-dicarbonyl compound and ammonium acetate in alcoholic solvents. This new three-component heteroannulation reaction proceeds under mild conditions in the absence of an additional acid catalyst. X. Xiong, M. C. Bagley, K. Chapaneri, Tetrahedron Lett., 2004, 45, 6121-6124. Tr- or tetrasubstituted pyridines are prepared by microwave irradiation of ethyl  $\beta$ -aminocrotonate and various alkynones in a single synthetic step and with total control of regiochemistry. This new one-pot Bohlmann-Rahtz procedure conducted at 170 $^{\circ}$ C gives superior yields to similar experiments conducted using conductive-heating techniques in a sealed tube. M. C. Bagley, R.

Lunn, X.

Xiong, Tetrahedron Lett., 2002, 43, 8331-8334. The direct conversion of amides, including sensitive N-vinyl amides, to the corresponding trimethylsilyl alkynyl imines followed by a ruthenium-catalyzed protodesilylation and cycloisomerization gives various substituted pyridines and quinolines. M. Movassaghi, M. D. Hill, J. Am. Chem. Soc., 2006, 128, 4592-4593. A rhodium-catalyzed chelation-assisted C-H activation of  $\alpha,\beta$ -unsaturated ketoximes and the reaction with alkynes affords highly substituted pyridine derivatives. K. Parthasarathy, M. Jegannmohan, C.-H. Cheng, Org. Lett., 2008, 10, 325-328. A convenient one-pot C-H alkenylation/electrocyclization/aromatization sequence allows the synthesis of highly substituted pyridine derivatives from alkynes and  $\alpha,\beta$ -unsaturated N-benzyl aldimines and ketimines. The reaction proceeds through dihydropyridine intermediates.

D. A. Colby, R. G. Berman, J. A. Ellman, J. Am. Chem. Soc., 2008, 130, 3645-3651. The NH4I-triggered formal [4 + 2] annulation of  $\alpha,\beta$ -unsaturated ketoxime acetates with N-acetyl enamides enables an efficient and straightforward construction of polysubstituted pyridines in good yields.

This metal-free protocol employs electron-rich enamides as C2 synthons and tolerates a wide range of functional groups. J. Duan, L. Zhang, G. Xu, H. Chen, X. Ding, Y. Mao, B.

Rong, N. Zhu, K. Guo, J. Org. Chem., 2020, 85, 8157-8165. A concise copper-catalyzed N-O bond cleavage/C-C-N bond formation procedure enables the synthesis of multisubstituted pyridines from various oxime acetates, activated methylene compounds, and a wide range of aldehydes. This method features inexpensive catalysts, no need for extra oxidant, and high step-economy.

H. Jiang, J. Yang, X. Tang, J. Li, W. Wu, J. Org. Chem., 2015, 80, 8763-8771. A concise one-pot synthesis of highly functionalized pyridines involves a formal insertion of rhodium vinylcarbenoids derived from diazo compounds across the N-O bond of isoxazoles. Upon heating, the insertion products undergo a rearrangement to give 1,4-dihydropyridines. DDQ oxidation then affords the corresponding pyridines in good yield. J. R. Manning, H. M. L. Davies, J. Am. Chem. Soc., 2008, 130, 8602-8603. Cationic rhodium(I)/modified-BINAP complexes catalyze a chemo- and regioselective [2+2+2] cycloaddition of a wide variety of alkynes and nitriles leading to highly functionalized pyridines under mild reaction conditions. K. Tanaka, N. Suzuki, G. Nishida, Eur. J. Org. Chem., 2006, 3917-3922. Conversion of unsaturated ketones and aldehydes derived from the cycloisomerization of primary and secondary propargyl diynols in the presence of [CpRu(CH3CN)3]PF6 to 1-azatrienes and a subsequent electrocyclozation-dehydration provides pyridines with excellent regiocontrol. B. M. Trost, A. C. Gutierrez, Org. Lett., 2007, 9, 1473-1476. Coupling of acetylene, nitrile, and a titanium reagent generated new azatitanacyclopentadienes in a highly regioselective manner. The subsequent reaction with sulfonylacetylene and electrophiles gave substituted pyridines virtually as a single isomer. Alternatively, the reaction of azatitanacyclopentadienes with an aldehyde or another nitrile gave furans or pyrroles having four different substituents again in a regioselective manner. D. Suzuki, Y. Nobe, R. Tanaka, Y. Takayama, F. Sato, H. Urabe, J. Am. Chem. Soc., 2005, 127, 7474-7479.

A mild, efficient, and general aromatization of Hantzsch 1,4-dihydropyridines with oxygen was realized at room temperature with 5 mol % of 9-phenyl-10-methylacridinium perchlorate as photocatalyst, which could be easily recovered and reused. X. Fang, Y.-C. Liu, C. Li, J. Org. Chem., 2007, 72, 8608-8610. In the presence of activated carbon, Hantzsch 1,4-dihydropyridines and 1,3,5-trisubstituted pyrazolones were aromatized with molecular oxygen to the corresponding pyridines and pyrazoles in excellent yields. N. Nakamichi, Y. Kawashita, M. Hayashi, Synthesis, 2004, 1015-1020. 4-Substituted-1,4-dihydropyridines are readily and efficiently aromatized in only one minute using commercial manganese dioxide in the absence of an inorganic support at 100  $^{\circ}$ C under microwave irradiation. This rapid procedure gives the dehydrogenated or 4-dealkylated product in excellent yield. M.

C. Bagley, M. C.

Lubinu, Synthesis, 2006, 1283-1288. Hantzsch 1,4-dihydropyridines undergo smooth aromatization catalyzed by iodoxybenzoic acid (IBX) to afford the corresponding pyridine derivatives in high yields. All the reactions were carried out in DMSO solvent at 80-85  $^{\circ}$ C for a period of two to four hours to complete conversion of the substrates. J. S. Yadav, B. V. S. Reddy, A. K. Basak, G. Baishya, A. V.

Narsaiah, Synthesis, 2006, 451-454. An intermolecular, Rh(III)-catalyzed cyclization of oximes and diazo compounds involving tandem C-H activation, cyclization, and condensation steps gives multisubstituted isoquinoline and pyridine N-oxides under mild conditions. The reaction obviates the need for oxidants, releases N2 and H2O as the byproducts, and displays a broad substituent scope. Z. Shi, D. C. Koester, M. Bouladakis-Arapinis, F. Glorius, J. Am. Chem. Soc., 2013, 135, 12204-12205. Trapping of in situ generated active intermediate 1,4-oxazepines, formed from base-promoted 7-exo-dig cyclization reaction of N-propargyl enaminones, with alcohols/thiols and aldehydes provides 2-alkoxy/2-sulfonylpyridines and dihydrofuro[2,3-*b*]pyridines in good yields within 30 min at room temperature.

This cascade reaction generates 1 equiv of H2O as the sole byproduct. G. Cheng, L. Xue, Y. Weng, X. Cui, J. Org. Chem., 2017, 82, 9515-9524. A K2CO3-mediated cyclization and rearrangement of  $\gamma,\delta$ -alkynyl oximes for the synthesis of pyridols employs readily accessible starting materials, tolerates a wide range of functional groups, and gives various synthetically challenging pyridols in good yields. The reaction proceeds via an efficient [1,3] rearrangement of an O-vinyl oxime intermediate which is in situ generated by intramolecular nucleophilic addition of  $\gamma,\delta$ -alkynyl oximes. S.

Wang, Y.-Q. Guo, Z.-H. Ren, Y.-Y. Wang, Z.-H.

Guan, Org. Lett., 2017, 19, 1574-1577. Pyridine N-oxides were converted to 2-aminopyridines in a one-pot fashion using Ts2O-tBuNH2 followed by in situ deprotection with TFA. The amination proceeded in high yields, excellent 2/4-selectivity, and with good functional group compatibility.

Yin, B. Xiang, M. H. Huffman, C. E. Raab, I. W. Davies, J.

Org. Chem., 2007, 72, 4554-4557.

A multifunctional reagent enables a direct conversion of pyridines to Boc-protected 2-aminopyridines with exquisite site selectivity and chemoselectivity under mild conditions without precautions toward air or moisture. The reaction tolerates nearly all common functionality. P. S. Fier, S. Kim, R. D. Cohen, J. Am. Chem. Soc., 2020, 142, 8614-8618. In a ligand-free chromium(II)-catalyzed amination reaction of various N-heterocyclic chlorides, CrCl2 regioselectively catalyzes the reaction of chloropyridines, chloroquinolines, chloroisquinolines, and chloroquinoxalines with a broad range of magnesium amides in the presence of lithium chloride as additive. The reactionse provide the desired aminated products in good yield. A. K. Steib, S. Fernandez, O. M. Kuzmina, M. Corpet, C. Gosmini, P. Knochel, Synlett, 2015, 26, 1049-1054. Base-mediated cascade reactions of  $\alpha,\beta$ -unsaturated ketones and 1,1-enediamines, which include Michael addition, intramolecular cyclization, aromatization, and a base-dependent optional loss of HNO2, provide

2-amino-4,6-diarylpyridine derivatives. The methods are suitable for efficient parallel synthesis of pyridines. Q. Luo, R. Huang, Q. Xiao, Y. Yao, J. Lin, S.-J. Yan, J. Org. Chem., 2019, 84, 1999-2011. The use of the commercially available N-fluorobenzenesulfonimide (NFSI) as an amination reagent enables a copper-catalyzed aminative aza-annulation of enynyl azide to provide amino-substituted nicotinate derivatives in a single step in good yield. C. R.

Reddy, S. K. Prajapati, R. Ranjan, Org. Lett., 2018, 20, 3128-3131. Condensation of 2,4-dioxo-carboxylic acid ethyl esters with ethyl 3-amino-3-iminopropionate hydrochloride provides a wide variety of mono- or disubstituted 2-amino isonicotinic acids.

The reaction likely proceeds through an in situ decarboxylation process. X. Jin, L. Xing, D.

D. Deng, Y. Yan, Y. Fu, W. Dong, J. Org. Chem., 2022, 87, 1541-1544. An efficient protecting-group-free two-step route to a broad range of aza- and diazaindoles was established, starting from chloroamino-N-heterocycles. The method involves an optimized Suzuki-Miyaura coupling with (2-ethoxyvinyl)borolane followed by acetic acid-catalyzed cyclization. D. K. Whelligan, D. W. Thomson, D. Taylor, S. Hoelder, J. Org. Chem., 2010, 75, 11-15. Nine azidopyridines bearing a single fluorine, chlorine, or bromine atom were prepared and examined by differential scanning calorimetry (DSC). The utility of these versatile intermediates was demonstrated through their use in a variety of Click reactions and the diversification of the halogen handles. M. D.

Mandler, A. P. Degnan, S. Zhang, D. Aulakh, K. Georges, B. Sandhu, A. Sarjeant, Y. Zhu, S. C. Traeger, P. T. Cheng, B. A.

Ellsworth, A. Requeiro-Ren, Org. Lett., 2022, 24, 799-803. A Gold(I)-catalyzed hetero-tetradehydro-Diels-Alder cycloaddition of enynamides and cyanamides provides diversely substituted 2,6-diaminopyridines in very good yields. This efficient reaction proceeds under very mild conditions with high functional group tolerance. N. V. Shcherbakov, D. V. Dar'in, Y. Y. Kukushkin, Y.

Y. Dubovtsev, J. Org. Chem., 2021, 86, 7218-7228. [bmim]OH, a basic ionic liquid, efficiently promotes a one-pot condensation of aldehydes, malononitrile, and thiophenols to produce highly substituted pyridines in high yields. The ionic liquid can be recovered and recycled. B. C. Ranu, R. Jana, S. Sowmiah, J. Org. Chem., 2007, 72, 3152-3154.