Published in final edited form as:
J Am Chem Soc. 2019 June 05; 141(22): 8778–8782. doi:10.1021/jacs.9b04325.

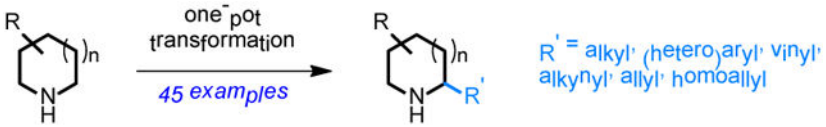
α-Functionalization of Cyclic Secondary Amines: Lewis Acid Promoted Addition of Organometallics to Transient Imines

Anirudra Paul, **Daniel Seidel***
Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida, 32611, United States

Abstract

Cyclic imines, generated in situ from their corresponding *N*-lithiated amines and a ketone hydride acceptor, undergo reactions with a range of organometallic nucleophiles to generate α-functionalized amines in a single operation. Activation of the transient imines by Lewis acids that are compatible with the presence of lithium alkoxides was found to be crucial to accommodate a broad range of nucleophiles including lithium acetylides, Grignard reagents, and aryllithiums with attenuated reactivities.

Graphical Abstract



Saturated nitrogen heterocycles remain one of the most important classes of compounds in drug discovery.[1] C—H bond functionalization of the parent heterocyclic frameworks represents an attractive strategy for accessing more complex saturated amines from simple ones, and remains a topic of widespread interest.[2] Particularly well-studied are α-C—H bond functionalizations of cyclic amines (Scheme 1).[3] However, despite considerable advances, the vast majority of the various activation modes developed to date are incompatible with the presence of an N—H bond, limiting their utility to 3° (often *N*-aryl) or protected 2° amines. Directing groups are frequently required and can be difficult to remove, hampering the use of the underlying methods. As an alternative, condensation-based methods involving α-C—H bond functionalization of 2° cyclic amines have recently emerged.[2m,2o] While attractive for a number of reasons, the products of these transformations are necessarily 3° amines. Methods for the direct synthesis of α-functionalized 2° cyclic amines from their corresponding parent amines remain limited. Hydroaminoalkylation enables the introduction of α-branched aliphatic substituents and is

*Corresponding Author seidel@chem.ufl.edu.

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures and characterization data (PDF)

The authors declare no competing financial interests.

relatively well-developed for acyclic amines.[4] However, applications to the functionalization of 2° cyclic amines remain underdeveloped and typically require elevated temperatures and prolonged reaction times (Scheme 1, eq 1).[5] An interesting recent advance is the electrochemical α-cyanation of *N*H-piperidines (Scheme 1, eq 2).[6] Here we report a generalizable method for the α-C—H bond functionalization of 2° cyclic amines, utilizing a broad range of easily accessible organometallic nucleophiles (Scheme 1, eq 3).

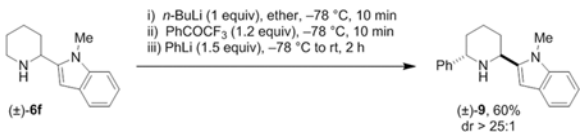
Inspired by seminal studies on the hydride donor ability of lithium amides by Wittig et al.,[7] we recently developed a new strategy for amine α-C—H bond functionalization (Scheme 1, eq 3).[8] In the process, an *N*-lithiated amine **1** reduces a ketone to form a lithium alkoxide and cyclic imine **3**, presumably via a transition state related to **2**.[9] Imine **3** subsequently engages an organolithium reagent, providing an α-functionalized amine **4**.[10] While applicable to a relatively broad range of amines, our original procedure is limited to the use of highly reactive organolithium nucleophiles. Organolithiums with attenuated reactivities (e.g., lithium acetylides) and, importantly, Grignard reagents, failed to effectively engage the transient imine species. We hypothesized that a Lewis acid may serve to activate cyclic imines towards nucleophilic addition. While there is precedent showing that such a strategy can be successful with acyclic imines and nonenolizable cyclic imines,[11–13] it was not obvious whether previously developed methods would be applicable to enolizable cyclic imines such as 1-pyrroline and 1-piperideine. These species are known to be unstable and prone to trimerization,[14] a process that could potentially be accelerated by Lewis acids. Imine trimers tend to be stable under basic conditions and don't react with organolithium compounds even at elevated temperatures. Conversion of the imine trimers to the corresponding monomers is possible but requires protic conditions and/or heating, conditions that are incompatible with strong nucleophiles.[15] Further, while Lewis acid activation of an enolizable cyclic imine should serve to increase its electrophilicity, it also increases the acidity of the β-proton and may thus further enhance the known propensity of these imines to undergo deprotonation.[7] Finally, it was unclear whether any Lewis acid with sufficient activity would be compatible with the lithium alkoxide produced in the imine-generating step. Needless to say, having to first remove said alkoxide from the reaction mixture would diminish the attractiveness of the method.

Upon extensive evaluation of a range of reaction parameters, conditions were identified that allowed for the one-pot α-alkynylation of various amines with lithium acetylides (Scheme 2).[16] Briefly, following the generation of the cyclic imine, Li-acetylide was added, immediately followed by addition of BF_3 etherate. The order of addition and the timing was found to be crucial.[16] Regardless of ring size, 2° cyclic amines readily underwent substitutions with Li-phenylacetylide. A range of alkynes participated in this reaction. 4-Methyl piperidine and a bicyclic pyrrolidine derivative underwent alkynylation to provide products in highly diastereoselective fashion. Little or no product formation was observed in the absence of BF_3 etherate.

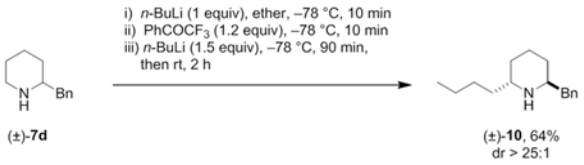
Similar reaction conditions were successfully applied to substitution reactions of amines with aryllithium compounds possessing attenuated nucleophilicities, enabling the introduction of furan, benzofuran, and various substituted indole moieties (Scheme 3). Several of the nucleophiles had previously been evaluated in the absence of a Lewis acid.

For instance, 2-furyllithium failed to provide any product without added BF_3 etherate. Others, such as 2-lithiated *N*-methylindole provided only trace amounts of products in the absence of a Lewis acid.

Grignard reagents, an important class of easily accessible organometallic nucleophiles, failed to provide notable yields in the addition to cyclic imines in the absence of Lewis acids. While BF_3 etherate also enabled the use of these nucleophiles, trimethylsilyl trifluoromethanesulfonate (TMSOTf) provided the best results in the α-substitution of amines with Grignard reagents.[16] The scope of this transformation is summarized in Scheme 4. Phenyl- and benzyl substituents were readily introduced into amines with different ring sizes. To obtain easily isolable nonvolatile products in the introduction of lower molecular weight substituents, these reactions were evaluated with azacyclotridecane. Linear, α-branched, and β-branched alkyl groups, as well as vinyl, allyl, and ethynyl groups were readily introduced. Notably, while methyllithium was previously found to be a poor nucleophile for cyclic imines, methylmagnesium chloride in combination with TMSOTf readily provided product **7g**. High levels of diastereoselectivity were achieved in the α-phenylation of a bicyclic amine (product **7o**), the introduction of an α-homoallyl substituent in 4-benzylpiperidine (product **7p**), and the α-*n*-butylation of an intermediate used in the synthesis of the commercial drug risperidone (product **7q**).[17] Notably, the preparation of **7q** failed with *n*-butyllithium as the nucleophile, presumably due to the incompatibility of this reagent with the benzisoxazole moiety. Further expansion of scope was achieved with active nucleophiles obtained via the turbo Grignard method (Scheme 5).[18]



(4)



(5)

Products derived from the Lewis acid promoted α-C—H bond functionalization of 2° cyclic amines could be further functionalized regioselectively on the α′-position. For instance, piperidine **6f** underwent α′-phenylation to provide product **9** in 60% yield (eq 4), whereas **10** was obtained in 64% yield via the α′-*n*-butylation of **7d** (eq 5).

In summary, we have achieved the α-C—H bond functionalization of 2° cyclic amines with a broad range of organometallic nucleophiles. This method significantly improves the availability of valuable building blocks for synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

Financial support from the NIH–NIGMS (Grant R01GM101389) is gratefully acknowledged.

REFERENCES

(1) a). Rings in Drugs. Taylor RD; MacCoss M; Lawson ADG J. Med. Chem. 2014, 57, 5845–5859; [PubMed: 24471928] b)Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. Vitaku E; Smith DT; Njardarson JT J. Med. Chem. 2014, 57, 10257–10274. [PubMed: 25255204]

(2). a)Selected recent reviews on amine C—H functionalization: Direct sp^3 C-H bond activation adjacent to nitrogen in heterocycles. Campos KR Chem. Soc. Rev. 2007, 36, 1069–1084; [PubMed: 17576475] b)Functionalization of Organic Molecules by Transition-Metal-Catalyzed C(sp^3)-H Activation. Jazzar R; Hitce J; Renaudat A; Sofack-Kreutzer J; Baudoin O Chem. Eur. J. 2010, 16, 2654–2672; [PubMed: 20143359] c)Catalytic Dehydrogenative Cross-Coupling: Forming Carbon-Carbon Bonds by Oxidizing Two Carbon-Hydrogen Bonds. Yeung CS; Dong VM Chem. Rev. 2011, 111, 1215–1292; [PubMed: 21391561] d)Direct alpha-Functionalization of Saturated Cyclic Amines. Mitchell EA; Peschiulli A; Lefevre N; Meerpoel L; Maes BUW Chem. Eur. J. 2012, 18, 10092–10142; [PubMed: 22829434] e)Oxidative Coupling of Tertiary Amines: Scope, Mechanism and Challenges. Jones KM; Klussmann M Synlett 2012, 23, 159–162;f)The Redox-Neutral Approach to C-H Functionalization. Peng B; Maulide N Chem. Eur. J. 2013, 19, 13274–13287; [PubMed: 24027042] g)The Cross-Dehydrogenative Coupling of C sp^3-H Bonds: A Versatile Strategy for C-C Bond Formations. Girard SA; Knauber T; Li C-J Angew. Chem. Int. Ed. 2014, 53, 74–100;h)C-H Bond Functionalization through Intramolecular Hydride Transfer. Haibach MC; Seidel D Angew. Chem. Int. Ed. 2014, 53, 5010–5036;i)Advancement in Cascade [1,n]-Hydrogen Transfer/Cyclization: A Method for Direct Functionalization of Inactive C(sp^3)-H Bonds. Wang L; Xiao J Adv. Synth. Catal. 2014, 356, 1137–1171;j)Synthesis of Saturated N-Heterocycles. Vo C-VT; Bode JW J. Org. Chem 2014, 79, 2809–2815; [PubMed: 24617516] k)The redox-A^3 reaction. Seidel D Org. Chem. Front. 2014, 1, 426–429; [PubMed: 24955245] l)Catalytic asymmetric α-C(sp^3)—H functionalization of amines. Qin Y; Lv J; Luo S Tetrahedron Lett. 2014, 55, 551–558;m)The Azomethine Ylide Route to Amine C—H Functionalization: Redox-Versions of Classic Reactions and a Pathway to New Transformations. Seidel D Acc. Chem. Res. 2015, 48, 317–328; [PubMed: 25560649] n)Amine Functionalization via Oxidative Photoredox Catalysis: Methodology Development and Complex Molecule Synthesis. Beatty JW; Stephenson CRJ Acc. Chem. Res. 2015, 48, 1474–1484; [PubMed: 25951291] o)Classical-Reaction-Driven Stereo- and Regioselective C(sp^3)—H Functionalization of Aliphatic Amines. Mahato S; Jana CK Chem. Rec. 2016, 16, 1477–1488; [PubMed: 27185195] p)Organocatalysis in Inert C—H Bond Functionalization. Qin Y; Zhu L; Luo S Chem. Rev. 2017, 117, 9433–9520; [PubMed: 28697602] q)Recent Advances in the Enantioselective Oxidative α-C—H Functionalization of Amines. Cheng M-X; Yang S-D Synlett 2017, 28, 159–174;r)Transition metal-catalyzed α-alkylation of amines by C(sp^3)–H bond activation. Gonnard L; Guérinot A; Cossy J Tetrahedron 2019, 75, 145–163;s)Construction of N-Heterocycles through Cyclization of Tertiary Amines. Liu S; Zhao Z; Wang Y Chem. Eur. J. 2019, 25, 2423–2441. [PubMed: 30357981]

(3). a)Selected recent reports on amine C—H functionalization: Palladium-catalysed transannular C—H functionalization of alicyclic amines. Topczewski JJ; Cabrera PJ; Saper NI; Sanford MS Nature 2016, 531, 220–224; [PubMed: 26886789] b)Native functionality in triple catalytic cross-coupling: sp^3 C—H bonds as latent nucleophiles. Shaw MH; Shurtleff VW; Terrett JA; Cuthbertson JD; MacMillan DWC Science 2016, 352, 1304–1308; [PubMed: 27127237] c)Enantioselective amine α-functionalization via palladium-catalysed C—H arylation of thioamides. Jain P; Verma P; Xia G; Yu J-Q Nat. Chem. 2017, 9, 140–144; [PubMed: 28282045] d)Palladium-Catalyzed Enantioselective C—H Activation of Aliphatic Amines Using Chiral

Anionic BINOL-Phosphoric Acid Ligands. Smalley AP; Cuthbertson JD; Gaunt MJ J. Am. Chem. Soc. 2017, 139, 1412–1415; [PubMed: 28064488] e)Synthesis of Ring-Fused 1-Benzazepines via [1,5]-Hydride Shift/7-Endo Cyclization Sequences. Suh CW; Kwon SJ; Kim DY Org. Lett. 2017, 19, 1334–1337; [PubMed: 28234485] f)Direct Intermolecular C—H Functionalization Triggered by 1,5-Hydride Shift: Access to N-Arylprolinamides via Ugi-Type Reaction. Zhen L; Wang J; Xu Q-L; Sun H; Wen X; Wang G Org. Lett. 2017, 19, 1566–1569; [PubMed: 28290693] g)Synthesis of Spirooxindoles via the tert-Amino Effect. Ramakumar K; Maji T; Partridge JJ; Tunge JA Org. Lett. 2017, 19, 4014–4017; [PubMed: 28737400] h)Construction of the tetrahydroquinoline spiro skeleton via cascade [1,5]-hydride transfer-involved C(sp^3)-H functionalization “on water”. Zhu S; Chen C; Xiao M; Yu L; Wang L; Xiao J Green Chem. 2017, 19, 5653–5658;i)Organocatalytic C(sp^3)—H Functionalization via Carbocation-Initiated Cascade [1,5]-Hydride Transfer/Cyclization: Synthesis of Dihydrodibenzo[b,e]azepines. Li S-S; Zhou L; Wang L; Zhao H; Yu L; Xiao J Org. Lett. 2018, 20, 138–141; [PubMed: 29239184] j)Intramolecular hydride transfer onto arynes: redox-neutral and transition metal-free C(sp^3)-H functionalization of amines. Idiris FIM; Majeste CE; Craven GB; Jones CR Chem. Sci. 2018, 9, 2873–2878; [PubMed: 29732071] k)Redox-triggered cascade dearomative cyclizations enabled by hexafluoroisopropanol. Li S-S; Lv X; Ren D; Shao C-L; Liu Q; Xiao J Chem. Sci. 2018, 9, 8253–8259; [PubMed: 30542574] l)Second-Generation Palladium Catalyst System for Transannular C—H Functionalization of Azabicycloalkanes. Cabrera PJ; Lee M; Sanford MS J. Am. Chem. Soc. 2018, 140, 5599–5606; [PubMed: 29652497] m)Chiral Magnesium Bisphosphate-Catalyzed Asymmetric Double C(sp^3)—H Bond Functionalization Based on Sequential Hydride Shift/Cyclization Process. Mori K; Isogai R; Kamei Y; Yamanaka M; Akiyama T J. Am. Chem. Soc. 2018, 140, 6203–6207; [PubMed: 29741877] n)C—H Functionalization of Amines via Alkene-Derived Nucleophiles through Cooperative Action of Chiral and Achiral Lewis Acid Catalysts: Applications in Enantioselective Synthesis. Shang M; Chan JZ; Cao M; Chang Y; Wang Q; Cook B; Torker S; Wasa M J. Am. Chem. Soc. 2018, 140, 10593–10601; [PubMed: 30045617] o)Borane-Catalyzed Synthesis of Quinolines Bearing Tetrasubstituted Stereocenters by Hydride Abstraction-Induced Electrocyclization. Maier AFG; Tussing S; Zhu H; Wicker G; Tzvetkova P; Flörke U; Daniliuc CG; Grimme S; Paradies J Chem. Eur. J. 2018, 24, 16287–16291. [PubMed: 30230618]

(4). Early transition metal-catalyzed C—H alkylation: hydroaminoalkylation for Csp^3–Csp^3 bond formation in the synthesis of selectively substituted amines. Edwards PM; Schafer LL Chem. Commun. 2018, 54, 12543–12560.

(5). Tantalum Catalyzed Hydroaminoalkylation for the Synthesis of α- and β-Substituted N-Heterocycles. Payne PR; Garcia P; Eisenberger P; Yim JCH; Schafer LL Org. Lett. 2013, 15, 2182–2185. [PubMed: 23600625]

(6). Electrochemical Aminoxyl-Mediated α-Cyanation of Secondary Piperidines for Pharmaceutical Building Block Diversification. Lennox AJJ; Goes SL; Webster MP; Koolman HF; Djuric SW; Stahl SS J. Am. Chem. Soc. 2018, 140, 11227–11231. [PubMed: 30141925]

(7) a). Über Lithium diäthylamid als Hydrid Donator. Wittig G; Schmidt HJ; Renner H Chem. Ber. 1962, 95, 2377–2383;b)Zur Reaktionsweise N-metallierter acyclischer und cyclischer sekundärer Amine. Wittig G; Hesse A Liebigs Ann. Chem. 1971, 746, 149–173;c)Hydrid-Übertragung von Lithium-pyrrolidid auf Azomethine. Wittig G; Hesse A Liebigs Ann. Chem. 1971, 746, 174–184;d)Über die Reaktivität von metallierten Aminen als Hydrid-Donatoren. Wittig G; Häusler G Liebigs Ann. Chem. 1971, 746, 185–199.

(8). Direct α-C—H bond functionalization of unprotected cyclic amines. Chen W; Ma L; Paul A; Seidel D Nat. Chem. 2018, 10, 165. [PubMed: 29359746]

(9). For a review on the hydricity of lithium amides, see: Reduction with lithium dialkylamides. Majewski M; Gleave DM J. Organomet. Chem. 1994, 470, 1–16.

(10) Precedent for these types of reactions is limited: a). Regioselective 2-alkylation and 2-arylation of piperidine and pyrrolidine via organolithiation of cyclic imines. Scully FE J. Org. Chem. 1980, 45, 1515–1517;b)A Convenient Preparation of 3-Aza-2-phenyl Bicyclo[3.2.2]nonane and Related 2-Substituted Cyclic Amines. Healy MAM; Smith SA; Stemp G Synth. Commun. 1995, 25, 3789–3797.

(11) Examples of imine activation with BF3 etherate or TMS triflate: a). 1. Boron trifluoride activated 3-thiazolines. An efficient preparation of functionalized thiazolidines. Meltz CN; Volkmann RA

Tetrahedron Lett. 1983, 24, 4503–4506;b)Addition of alkynyl anions to aldimines containing α-hydrogens: a novel synthesis of β-aminoacetylenes. Wada M; Sakurai Y; Akiba K.-y. Tetrahedron Lett. 1984, 25, 1083–1084;c)The Activation of Imines to Nucleophilic Attack by Grignard Reagents. Brook MA; Jahangir Synth. Commun. 1988, 18, 893–898;d)Alkylation of 3,4-Dihydro-beta-carboline. Kawate T; Nakagawa M; Yamazaki H; Hirayama M; Hino T Chem. Pharm. Bull. 1993, 41, 287–291;e)BF_3-Mediated Addition of Lithium Phenylacetylide to an Imine: Correlations of Structures and Reactivities. $BF_3{\cdot}R_3N$ Derivatives as Substitutes for $BF_3{\cdot}Et_2O$. Aubrecht KB; Winemiller MD; Collum DB J. Am. Chem. Soc. 2000, 122, 11084–11089;f)BF_3-Mediated Additions of Organolithiums to Ketimines: X-ray Crystal Structures of BF_3–Ketimine Complexes. Ma Y; Lobkovsky E; Collum DB J. Org. Chem. 2005, 70, 2335–2337. [PubMed: 15760225]

(12). For the activation of imines with TMS benzotriazole see: 1-(Trimethylsilyl)benzotriazole-Assisted Addition of Grignard Reagents to Imines: A Versatile Approach to Aliphatic Secondary Amines. Katritzky AR; Hong Q; Yang Z J. Org. Chem. 1994, 59, 7947–7948.

(13) For the addition of organometallics to BF3-activated pyridines, see: a). Transition-Metal-Free BF_3-Mediated Regioselective Direct Alkylation and Arylation of Functionalized Pyridines Using Grignard or Organozinc Reagents. Chen Q; du Jourdin XM; Knochel P J. Am. Chem. Soc. 2013, 135, 4958–4961; [PubMed: 23506449] b)Transition-Metal-Free BF_3-Mediated Oxidative and Non-Oxidative Cross-Coupling of Pyridines. Chen Q; León T; Knochel P Angew. Chem. Int. Ed. 2014, 53, 8746–8750.

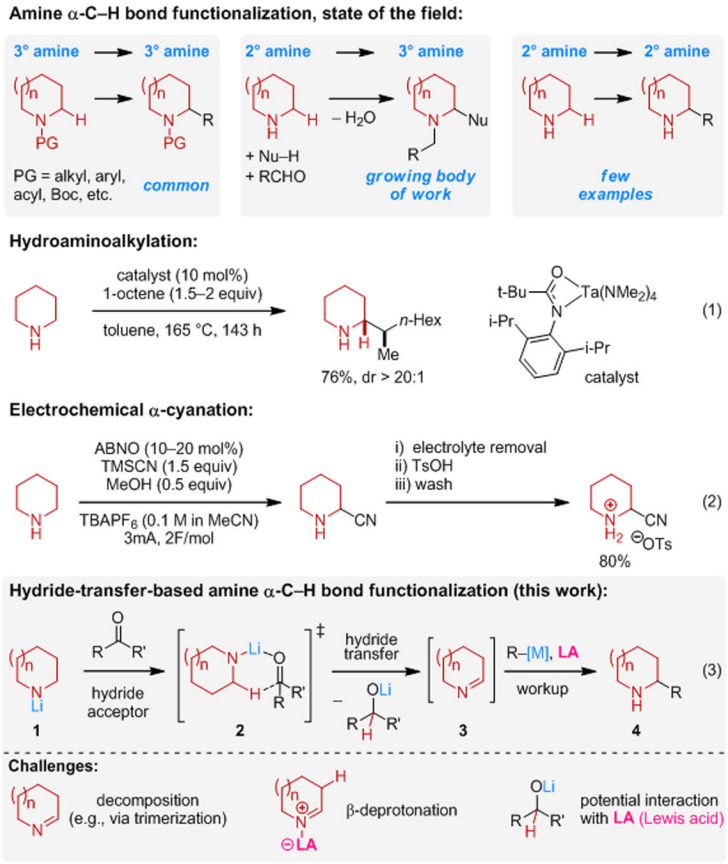
(14). For instance, 1-piperideine has a strong propensity to trimerize: Copper-Catalyzed Asymmetric Propargylation of Cyclic Aldimines. Fandrick DR; Hart CA; Okafor IS; Mercadante MA; Sanyal S; Masters JT; Sarvestani M; Fandrick KR; Stockdill JL; Grinberg N; Gonnella N; Lee H; Senanayake CH Org. Lett. 2016, 18, 6192–6195. [PubMed: 27934338]

(15) Selected applications of imine trimers: a). Facile synthesis of *N*-acyl-2-pyrrolines. Kraus GA; Neuenschwander K J. Org. Chem. 1981, 46, 4791–4792;b)Introduction of carbon unit at the alpha-position of alicyclic amines utilizing a decarboxylative reaction with malonic acid derivatives. Fukawa H; Terao Y; Achiwa K; Sekiya M Chem. Lett. 1982, 11, 231–232;c)A New Method for the Introduction of Arylthio Groups at the alpha-Position of Alicyclic Amines. Terao Y; Yasumoto Y; Ikeda K; Sekiya M Chem. Pharm. Bull. 1986, 34, 105–108;d)A new route to ene carbamates, precursors to benzoindolizinones through sequential asymmetric hydrogenation and cyclization. Couture A; Deniau E; Lebrun S; Grandclaudon P; Carpentier J-F J. Chem. Soc., Perkin Trans 1 1998, 1403–1408;e)Design and Photochemical Characterization of a Biomimetic Light-Driven Z/E Switcher. Sampedro D; Migani A; Pepi A; Busi E; Basosi R; Latterini L; Elisei F; Fusi S; Ponticelli F; Zanirato V; Olivucci M J. Am. Chem. Soc. 2004, 126, 9349–9359; [PubMed: 15281826] f)The reaction of cyclic imines with the Ruppert–Prakash reagent. Facile approach to α-trifluoromethylated nornicotine, anabazine, and homoanabazine. Shevchenko NE; Vlasov K; Nenajdenko VG; Röschenthaler G-V Tetrahedron 2011, 67, 69–74.

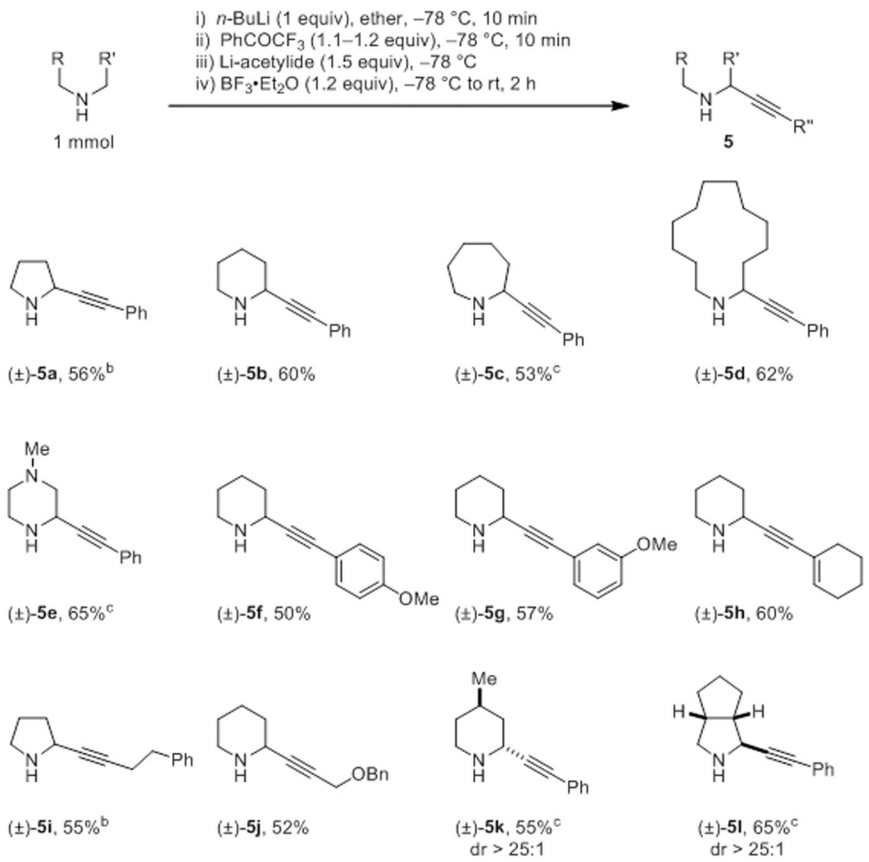
(16). See the Supporting Information for details.

(17). Discovering risperidone: the LSD model of psychopathology. Colpaert FC Nat. Rev. Drug Discov. 2003, 2, 315–320. [PubMed: 12669030]

(18) a). A LiCl-Mediated Br/Mg Exchange Reaction for the Preparation of Functionalized Aryl- and Heteroarylmagnesium Compounds from Organic Bromides. Krasovskiy A; Knochel P Angew. Chem. Int. Ed. 2004, 43, 3333–3336;b)Progress and developments in the turbo Grignard reagent *i*-PrMgCl·LiCl: a ten-year journey. Li-Yuan Bao R; Zhao R; Shi L Chem. Commun. 2015, 51, 6884–6900;c)Improving the Halogen–Magnesium Exchange by using New Turbo-Grignard Reagents. Ziegler DS; Wei B; Knochel P Chem. Eur. J. 2019, 25, 2695–2703. [PubMed: 30230067]

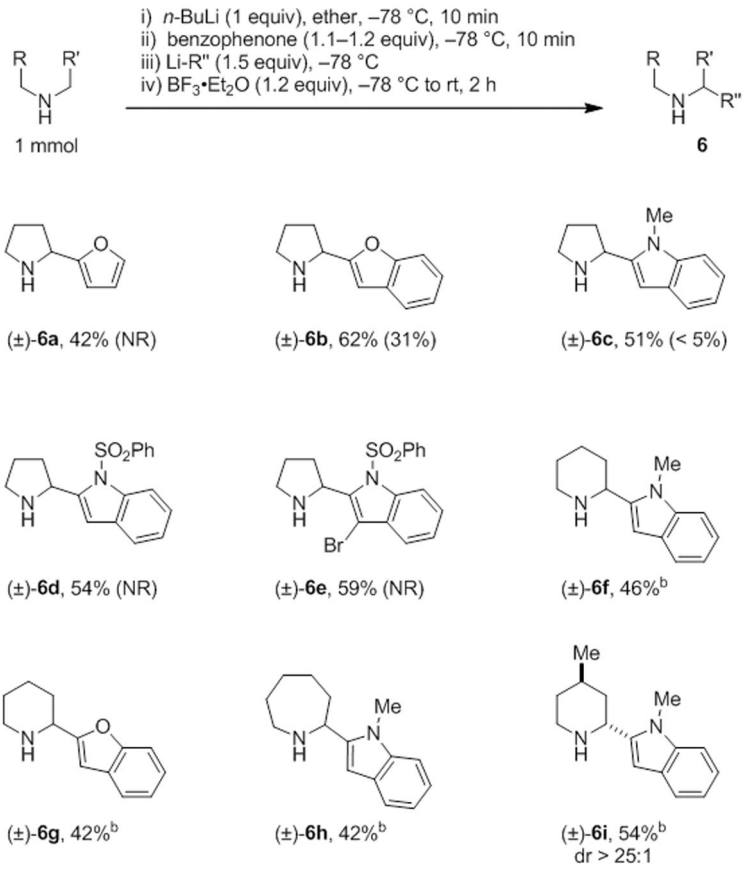


Scheme 1.
Overview and Strategy



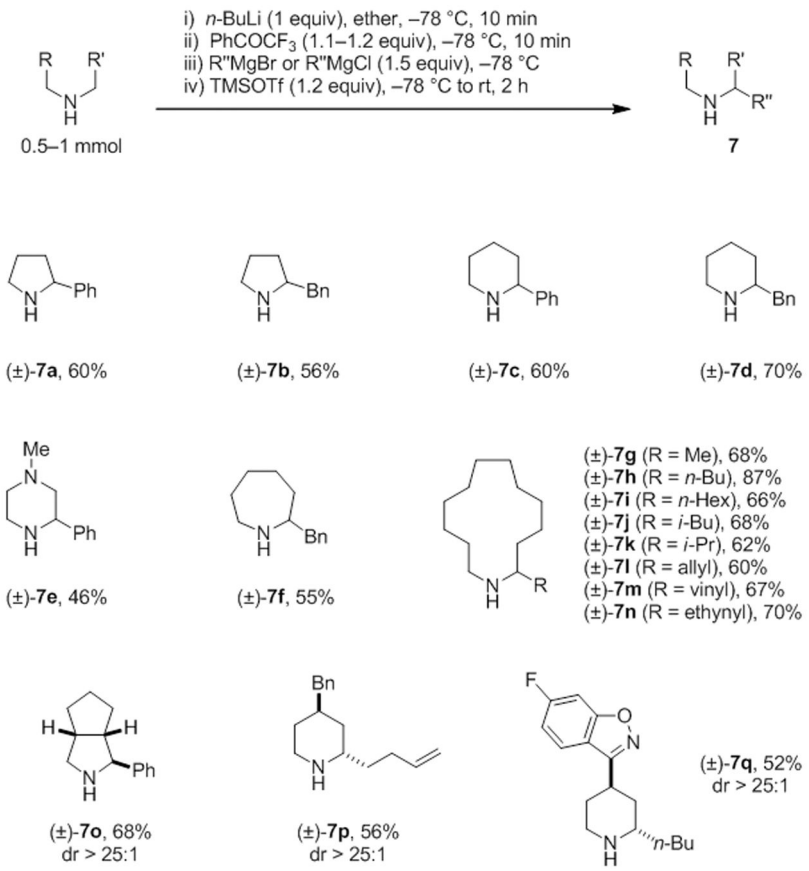
Scheme 2. α-Alkynylation of Amines[a]

[a] All yields correspond to isolated yields of purified products. The Li-acetylide was prepared in a 4:1 mixture of PhMe and THF. [b] Benzophenone was used as the hydride acceptor [c] The Li-acetylide was prepared in THF.



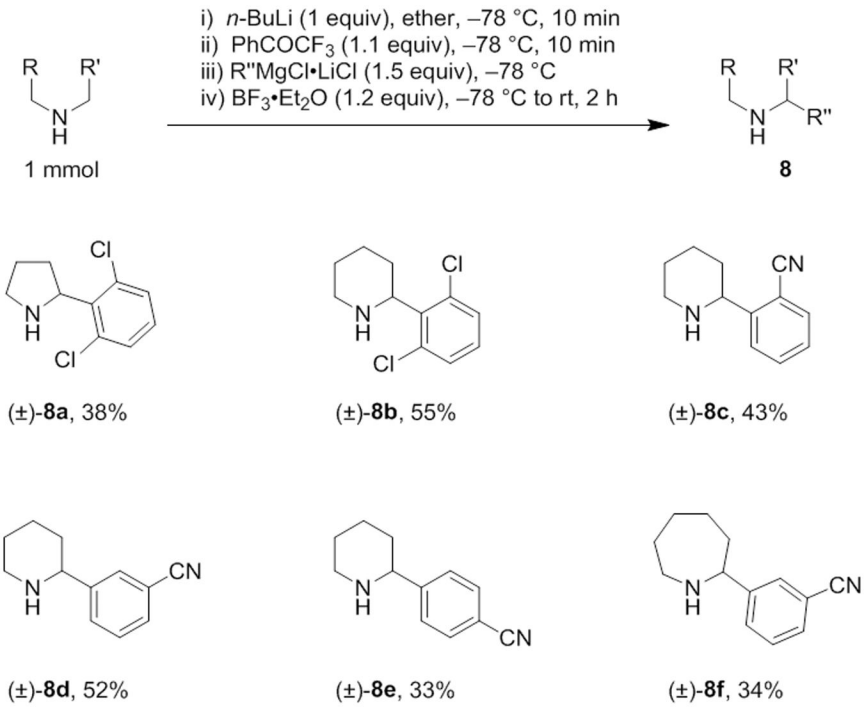
Scheme 3. α-Arylation of Amines With Heteroaryllithiums[a]

[a] All yields correspond to isolated yields of purified products. Yields in parenthesis correspond to results obtained in the absence of BF_3 etherate. [b] Trifluoroacetophenone was used as the hydride acceptor.



Scheme 4. α-Functionalization of Amines With Grignard Reagents[a]

[a] All yields correspond to isolated yields of purified products.



Scheme 5. α-Functionalization of Amines With Activated Grignard Reagents[a]

[a] All yields correspond to isolated yields of purified products.