Nitrile, Imine and Amide Reduction Using Tropylium Catalyst

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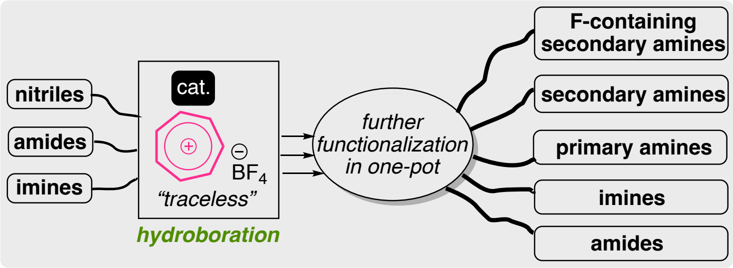
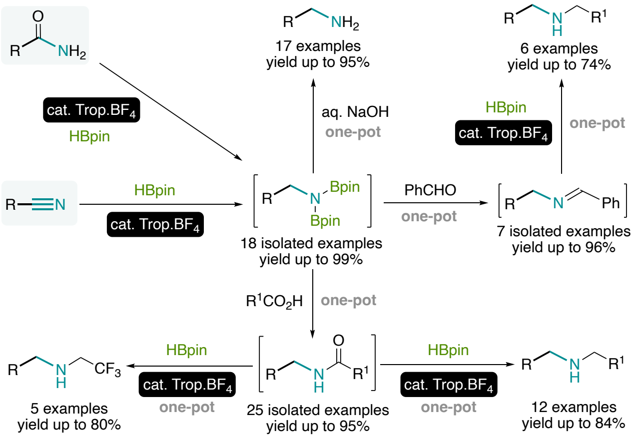


ABSTRACT: We report a new method for the hydroboration reactions of nitriles, imines and amides.

The conversions of nitriles, readily available synthetic precursors, into other *N*-containing derivatives (Scheme 1) such as amines, imines or amides are important chemical transformation in both synthetic laboratories and industrial chemistry.[1] This process can be realized by direct hydrogenation or reduction with organometallic or organic hydride donors such as boranes.[1] The former often requires precious metal catalysts and complicated reaction setups and controls to deliver desirable efficiency and selectivity. The latter, while being milder and more selective, generally involves specifically designed catalysts and laborious product purification processes. However, it is still being use predominantly in synthetic laboratories to discover new synthetically useful approaches to access important *N*-containing organic compounds.[2]

Based on our recent works on tropylium-promoted hydroboration chemistry[3] and Ritter reaction,[4] we believed that the simple and commercially available tropylium tetrafluoroborate ($TropBF_4$) salt[5] could act as a traceless reaction promoter for the hydroboration of nitriles. Our previous experimental and computational mechanistic studies revealed that $TropBF_4$ facilitated hydroboration with pinacolatoborane (HBpin) via a hydride abstraction of pinacolborane with tropylium ion, followed by a series of *in situ* substituent exchanges to generate boron intermediate BH_2F that was the active catalyst for the reaction.[3] $TropBF_4$ turned itself into cycloheptatriene[5i, 6] and BH_2F and possibly some other borane by-products during the course of the reaction.[3] All of these are volatile compounds and can be removed under reduce pressure at the end of the reaction,[3] making $TropBF_4$ a traceless reaction promoter and reducing the complication of product purification. This in addition to the transition metal-free nature of this process offer an attractive synthetic toolbox for the hydroborative reduction of nitriles and further functionalization reactions to produce a broad range of amines and amides in one-pot fashion (Scheme 1).

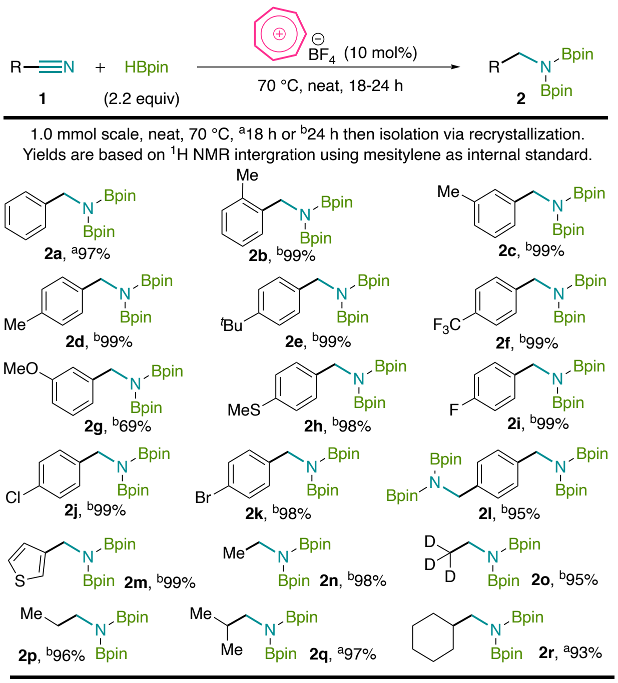
Scheme 1. One-pot synthesis of amines and amides via traceless hydroboration of nitriles, amides and imines.



We were delighted to see that $TropBF_4$ could indeed efficiently promote the hydroboration reaction of nitriles. A standard optimization study (see page S3 in the experimental SI for detail)[7] led us to the optimal conditions depicted in Scheme 1, where a wide range of nitriles **1** were converted to their corresponding *N*,*N*-diborylamines **2** in excellent efficiencies (Scheme 2) using 10 mol% TropBF$_4$ at 70 ºC for 18-24 h. As predicted, ^{1}H, ^{13}C, ^{11}B and ^{19}F NMR of the crude reaction mixture after evaporation under reduced pressure showed no evidence of the catalyst or its byproducts. The "traceless" nature of TropBF$_4$ allowed for a simple product purification process via recrystalization, which enable us to isolate these *N*,*N*-diborylamines with exceptional purity in comparison to previously reported protocols in literature, based on reported NMR spectra. Functional groups tolerated in this reaction included halogens, alkoxy, thioether and heterocyclic systems (Scheme 2).

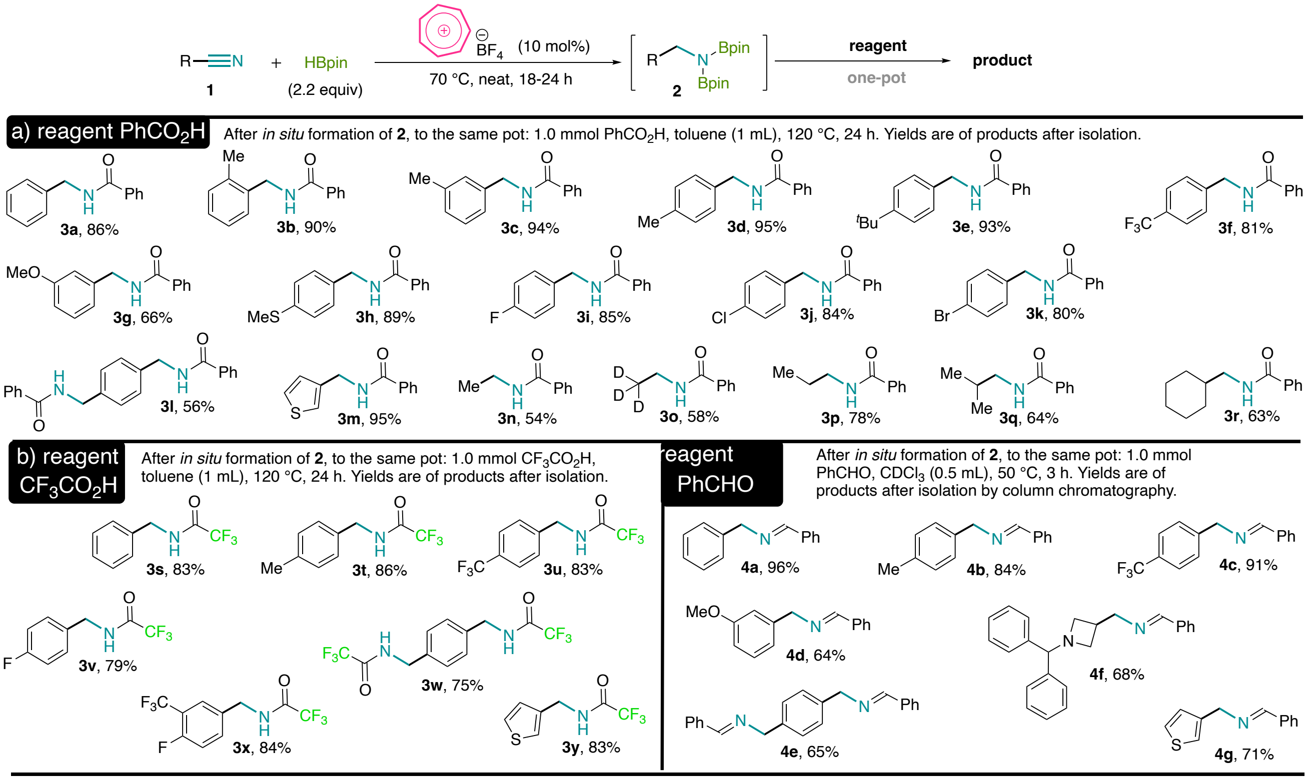
However, the key significance of this "traceless" catalytic method was that we could directly submit new reagents to the crude hydroboration reaction mixtures to perform sequential one-pot functionalization chemistry. Such one-pot sequence might not always be feasible using traditional catalytic hydroboration approaches, as the efficiency of the first step might not be adequate or the catalysts might not be compatible with further chemical transformations.[1b] Our developed catalytic method satisfies both criteria, offering a pathway to conveniently access downstream *N*-containing derivatives (Scheme 3).

Scheme 2. Hydroboration of nitriles



1.0 mmol scale, neat, 70 °C, ^{a}18 h or ^{b}24 h then isolation via recrystallization. Yields are based on ^{1}H NMR intergration using mesitylene as internal standard.

Scheme 3. Two-step one-pot synthesis of amides and imines from nitriles.



a) reagent PhCO$_2$H: After *in situ* formation of **2**, to the same pot: 1.0 mmol PhCO$_2$H, toluene (1 mL), 120 °C, 24 h. Yields are of products after isolation.

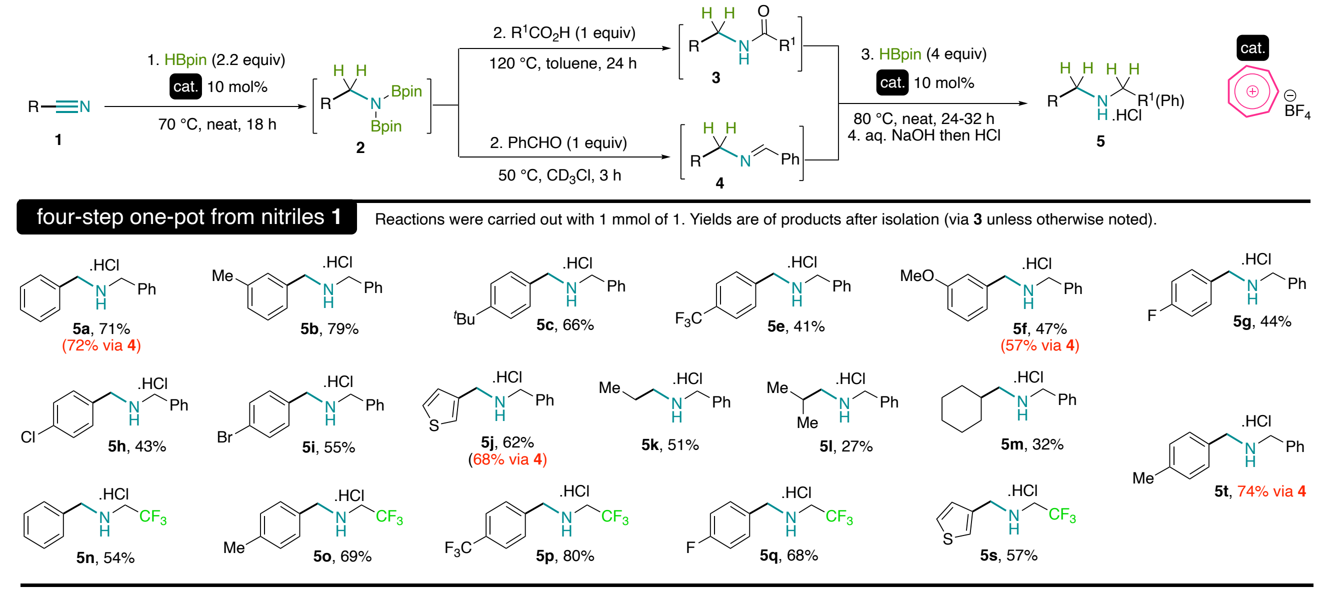
b) reagent CF$_3$CO$_2$H: After *in situ* formation of **2**, to the same pot: 1.0 mmol CF$_3$CO$_2$H, toluene (1 mL), 120 °C, 24 h. Yields are of products after isolation.

eagent PhCHO: After *in situ* formation of **2**, to the same pot: 1.0 mmol PhCHO, CDCl$_3$ (0.5 mL), 50 °C, 3 h. Yields are of products after isolation by column chromatography.

Indeed, by treating the hydroboration crude mixtures with benzoic acid in toluene at reflux for 24 h in the same reaction pot, we could isolate corresponding benzamides in good to excellent yields (**3a**-**r**, Scheme 3a).[7] Similarly, trifluoroacetic acid could also react with the *in situ* generated *N*,*N*-diborylamines to form trifluoroacetamides (**3s**-**y**, Scheme 3b) with good efficiencies. Treatment of the same crude reaction mixtures of **2** with benzaldehyde[1b] in chloroform at 70 ºC for 3 h afforded the corresponding phenylimines (**4a**-**g**, Scheme 3c). The by-product of these reactions was Bpin-O-Bpin (see page S15-16 in the SI).

We subsequently investigated the four-step one-pot synthesis of secondary amines from nitriles via a hydroboration followed by amidation or imination and further hydroborative reduction and acidic workup of the resulting amide or imine, respectively (Scheme 4). This was inspired by common reactivity trend that a catalyst system capable of promoting nitrile hydroboration can also mediate similar reactions on amides and imines. Indeed, after some optimization studies, we were able to carry out such four-step one-pot synthetic sequences to produce a wide range of unsymmetrical secondary amines, including CF_3-containing amines, with good to excellent outcomes (**5a**-**t**, Scheme 4). The reduction of the amide group in this synthetic sequence likely went through a deoxygenative step to the imine intermediate before being further reduced to the *N*-boryl secondary amine, as evidenced by NMR spectroscopy (see page S36 in the SI for more details).

Scheme 4. Four-step one-pot synthesis of secondary amines.

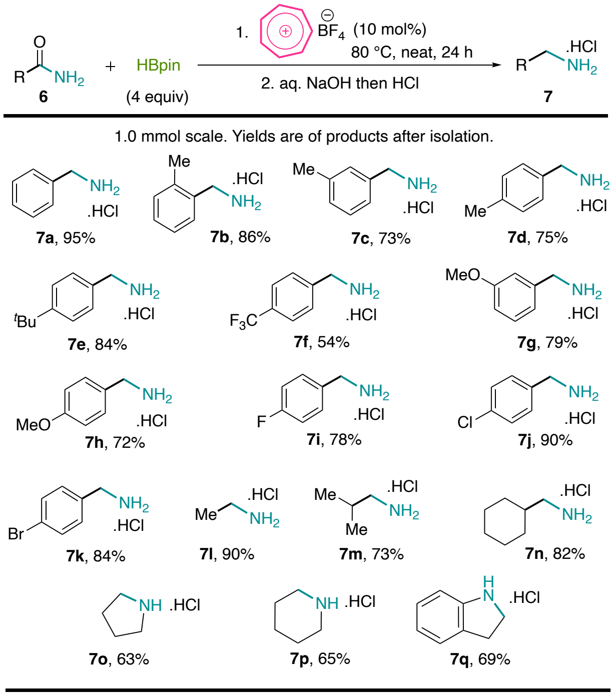


Reactions were carried out with 1 mmol of 1. Yields are of products after isolation (via **3** unless otherwise noted).

While the deoxygenative reduction of secondary amides similar to the third reaction step in Scheme 4 is generally straightforward, the reduction of primary amides is more challenging due to catalyst poisoning and unwanted side processes.[8] Therefore, we subsequently set out to investigate the applicability of our Trop.BF_4 promoted reduction protocol on primary amides (Scheme 5). Gratifyingly, it was shown to efficiently reduce a range of primary amides to the corresponding amines in good to excellent yields. Lactams could also be reduced under the same conditions to afford cyclic amines in high yieds (Scheme 5).

In conclusion, we have developed a new hydroborative method employing tropylium tetrafluoroborate as a traceless reaction promoter. It is amenable to the reduction of nitriles, amides and imines to give convenient access to their corresponding products with excellent efficiencies.

Scheme 5. Reduction of primary amides



1.0 mmol scale. Yields are of products after isolation.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website: general experimental procedures, characterization data of all compounds and NMR spectra.

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Author Contributions

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References

1. a) Garduño, J. A.; García, J. J., Toward Amines, Imines, and Imidazoles: A Viewpoint on the 3d Transition-Metal-Catalyzed Homogeneous Hydrogenation of Nitriles. *ACS Catal.* **2020,** *10* (14), 8012-8022; b) Hayrapetyan, D.; Khalimon, A. Y., Catalytic Nitrile Hydroboration: A Route to N,N-Diborylamines and Uses Thereof. *Chem. Asian J.* **2020,** *15* (17), 2575-2587.

2. a) Geri, J. B.; Szymczak, N. K., A Proton-Switchable Bifunctional Ruthenium Complex That Catalyzes Nitrile Hydroboration. *J. Am. Chem. Soc.* **2015,** *137* (40), 12808-12814; b) Dai, H.; Guan, H., Switching the Selectivity of Cobalt-Catalyzed Hydrogenation of Nitriles. *ACS Catal.* **2018,** *8* (10), 9125-9130; c) Ghosh, C.; Kim, S.; Mena, M. R.; Kim, J.-H.; Pal, R.; Rock, C. L.; Groy, T. L.; Baik, M.-H.; Trovitch, R. J., Efficient Cobalt Catalyst for Ambient-Temperature Nitrile Dihydroboration, the Elucidation of a Chelate-Assisted Borylation Mechanism, and a New Synthetic Route to Amides. *J. Am. Chem. Soc.* **2019,** *141* (38), 15327-15337; d) Harinath, A.; Bhattacharjee, J.; Panda, T. K., Catalytic Hydroboration of Organic Nitriles Promoted by Aluminum Complex. *Adv. Synth. Catal.* **2019,** *361* (4), 850-857; e) Liu, W.; Ding, Y.; Jin, D.; Shen, Q.; Yan, B.; Ma, X.; Yang, Z., Organic aluminum hydrides catalyze nitrile hydroboration. *Green Chem.* **2019,** *21* (14), 3812-3815; f) Saha, S.; Eisen, M. S., Catalytic Recycling of a Th–H Bond via Single or Double Hydroboration of Inactivated Imines or Nitriles. *ACS Catal.* **2019,** *9* (7), 5947-5956; g) Babón, J. C.; Esteruelas, M. A.; Fernández, I.; López, A. M.; Oñate, E., Dihydroboration of Alkyl Nitriles Catalyzed by an Osmium-Polyhydride: Scope, Kinetics, and Mechanism. *Organometallics* **2020,** *39* (21), 3864-3872; h) Babón, J. C.; Esteruelas, M. A.; López, A. M.; Oñate, E., Osmium-Promoted Transformation of Alkyl Nitriles to Secondary Aliphatic Amines: Scope and Mechanism. *Organometallics* **2020,** *39* (11), 2177-2188; i) Barger, C. J.; Dicken, R. D.; Weidner, V. L.; Motta, A.; Lohr, T. L.; Marks, T. J., La[N(SiMe3)2]3-Catalyzed Deoxygenative Reduction of Amides with Pinacolborane. Scope and Mechanism. *J. Am. Chem. Soc.* **2020,** *142* (17), 8019-8028; j) Bedi, D.; Brar, A.; Findlater, M., Transition metal- and solvent-free double hydroboration of nitriles. *Green Chem.* **2020,** *22* (4), 1125-1128; k) Bhattacharjee, J.; Harinath, A.; Bano, K.; Panda, T. K., Highly Chemoselective Hydroboration of Alkynes and Nitriles Catalyzed by Group 4 Metal Amidophosphine–Borane Complexes. *ACS Omega* **2020,** *5* (3), 1595-1606; l) Ghosh, P.; Jacobi von Wangelin, A., Lithium amide catalyzed hydroboration of nitriles. *Org. Chem. Front.* **2020,** *7* (7), 960-966; m) Gudun, K. A.; Slamova, A.; Hayrapetyan, D.; Khalimon, A. Y., Efficient Co-Catalyzed Double Hydroboration of Nitriles: Application to One-Pot Conversion of Nitriles to Aldimines. *Chem. Eur. J.* **2020,** *26* (22), 4963-4968; n) Saha, S.; Eisen, M. S., Mild catalytic deoxygenation of amides promoted by thorium metallocene. *Dalton Trans.* **2020,** *49* (36), 12835-12841; o) Tamang, S. R.; Singh, A.; Bedi, D.; Bazkiaei, A. R.; Warner, A. A.; Glogau, K.; McDonald, C.; Unruh, D. K.; Findlater, M., Polynuclear lanthanide–diketonato clusters for the catalytic hydroboration of carboxamides and esters. *Nature Catal.* **2020,** *3* (2), 154-162; p) Yao, W.; Wang, J.; Zhong, A.; Wang, S.; Shao, Y., Transition-metal-free catalytic hydroboration reduction of amides to amines. *Org. Chem. Front.* **2020,** *7* (21), 3515-3520; q) Ye, P.; Shao, Y.; Ye, X.; Zhang, F.; Li, R.; Sun, J.; Xu, B.; Chen, J., Homoleptic Bis(trimethylsilyl)amides of Yttrium Complexes Catalyzed Hydroboration Reduction of Amides to Amines. *Org. Lett.* **2020,** *22* (4), 1306-1310; r) Bazkiaei, A. R.; Wiseman, M.; Findlater, M., Iron-catalysed hydroboration of non-activated imines and nitriles: kinetic and mechanistic studies. *RSC Adv.* **2021,** *11* (25), 15284-15289; s) Bisai, M. K.; Gour, K.; Das, T.; Vanka, K.; Sen, S. S., Lithium compound catalyzed deoxygenative hydroboration of primary, secondary and tertiary amides. *Dalton Trans.* **2021,** *50* (7), 2354-2358; t) Dicken, R. D.; Motta, A.; Marks, T. J., Homoleptic Lanthanide Amide Catalysts for Organic Synthesis: Experiment and Theory. *ACS Catal.* **2021,** *11* (5), 2715-2734; u) Ghosh, P.; Jacobi von Wangelin, A., Manganese-Catalyzed Hydroborations with Broad Scope. *Angew. Chem. Int. Ed.* **2021,** *60* (29), 16035-16043; v) Guo, C.; Zhang, F.; Yu, C.; Luo, Y., Reduction of Amides to Amines with Pinacolborane Catalyzed by Heterogeneous Lanthanum Catalyst La(CH2C6H4NMe2-o)3@SBA-15. *Inorg. Chem.* **2021**; w) Li, C.; Song, S.; Li, Y.; Xu, C.; Luo, Q.; Guo, Y.; Wang, X., Selective hydroboration of unsaturated bonds by an easily accessible heterotopic cobalt catalyst. *Nature Commun.* **2021,** *12* (1), 3813; x) Li, X.-G.; Zhou, Q.-L., Manganese-Catalyzed Selective Hydrogenative Cross-Coupling of Nitriles and Amines to Form Secondary Imines. *Adv. Synth. Catal.* **2021,** *363* (14), 3471-3475; y) Pandey, V. K.; Tiwari, C. S.; Rit, A., Silver-Catalyzed Hydroboration of C–X (X = C, O, N) Multiple Bonds. *Org. Lett.* **2021,** *23* (5),

1681-1686; z) Sahoo, R. K.; Sarkar, N.; Nembenna, S., Zinc Hydride Catalyzed Chemoselective Hydroboration of Isocyanates: Amide Bond Formation and C=O Bond Cleavage. *Angew. Chem. Int. Ed.* **2021,** *60* (21), 11991-12000; aa) Sarkar, K.; Das, K.; Kundu, A.; Adhikari, D.; Maji, B., Phosphine-Free Manganese Catalyst Enables Selective Transfer Hydrogenation of Nitriles to Primary and Secondary Amines Using Ammonia–Borane. *ACS Catal.* **2021,** *11* (5), 2786-2794; ab) Thenarukandiyil, R.; Satheesh, V.; Shimon, L. J. W.; de Ruiter, G., Hydroboration of Nitriles, Esters, and Carbonates Catalyzed by Simple Earth-Abundant Metal Triflate Salts. *Chem. Asian J.* **2021,** *16* (8), 999-1006; ac) Vermaak, V.; Vosloo, H. C. M.; Swarts, A. J., Chemoselective transfer hydrogenation of nitriles to secondary amines with nickel(II) catalysts. *Mol. Catal.* **2021,** *511*, 111738; ad) Yan, B.; He, X.; Ni, C.; Yang, Z.; Ma, X., n-Butyllithium Catalyzed Hydroboration of Nitriles and Carbodiimides. *ChemCatChem* **2021,** *13* (3), 851-854; ae) Yu, C.; Guo, C.; Jiang, L.; Gong, M.; Luo, Y., Deoxygenation of Primary Amides to Amines with Pinacolborane Catalyzed by Ca[N(SiMe3)2]2(THF)2. *Organometallics* **2021,** *40* (9), 1201-1206; af) Zhang, S.; Xia, Z.; Zou, Y.; Zhang, M.; Qu, Y., Spatial intimacy of binary active-sites for selective sequential hydrogenation-condensation of nitriles into secondary imines. *Nature Commun.* **2021,** *12* (1), 3382.

3. Ton, N. N. H.; Mai, B. K.; Nguyen, T. V., Tropylium-Promoted Hydroboration Reactions: Mechanistic Insights Via Experimental and Computational Studies. *J. Org. Chem.* **2021,** *86* (13), 9117-9133.

4. Doan, S. H.; Hussein, M. A.; Nguyen, T. V., Tropylium-promoted Ritter reactions. *Chem. Commun.* **2021,** *57* (71), 8901-8904.

5. a) Nguyen, T. V.; Bekensir, A., Aromatic Cation Activation: Nucleophilic Substitution of Alcohols and Carboxylic Acids. *Org. Lett.* **2014,** *16* (6), 1720-1723; b) Nguyen, T. V.; Hall, M., Activation of DMSO for Swern-type oxidation by 1,1-dichlorocycloheptatriene. *Tetrahedron Lett.* **2014,** *55* (50), 6895-6898; c) Nguyen, T. V.; Lyons, D. J. M., A novel aromatic carbocation-based coupling reagent for esterification and amidation reactions. *Chem. Commun.* **2015,** *51* (15), 3131-3134; d) Lyons, D. J. M.; Crocker, R. D.; Blümel, M.; Nguyen, T. V., Promotion of Organic Reactions by Non-Benzenoid Carbocylic Aromatic Ions. *Angew. Chem. Int. Ed.* **2017,** *56*, 1466-1484; e) Lyons, D. J. M.; Crocker, R. D.; Enders, D.; Nguyen, T. V., Tropylium salts as efficient organic Lewis acid catalysts for acetalization and transacetalization reactions in batch and flow. *Green Chem.* **2017**, 3993-3996; f) Hussein, M. A.; Huynh, V. T.; Hommelsheim, R.; Koenigs, R. M.; Nguyen, T. V., An efficient method for retro-Claisen-type C–C bond cleavage of diketones with tropylium catalyst. *Chem. Commun.* **2018,** *54* (92), 12970-12973; g) Lyons, D.; Crocker, R.; Nguyen Thanh, V., Stimuli-Responsive Organic Dyes with Tropylium Chromophore. *Chem. Eur. J.* **2018,** *24* (43), 10959-10965; h) Oss, G.; de Vos, S. D.; Luc, K. N. H.; Harper, J. B.; Nguyen, T. V., Tropylium-Promoted Oxidative Functionalization of Tetrahydroisoquinolines. *J. Org. Chem.* **2018,** *83* (2), 1000-1010; i) Oss, G.; Ho, J.; Nguyen Thanh, V., Tropylium Ion Catalyzes Hydration Reactions of Alkynes. *Eur. J. Org. Chem.* **2018,** (29), 3974-3981; j) Tran, U. P. N.; Oss, G.; Pace, D. P.; Ho, J.; Nguyen, T. V., Tropylium-promoted carbonyl–olefin metathesis reactions. *Chem. Sci.* **2018,** *9*, 5145-5151; k) Hussein, M. A.; Tran, U. P. N.; Huynh, V. T.; Ho, J.; Bhadbhade, M.; Mayr, H.; Nguyen, T. V., Halide Anion Triggered Reactions of Michael Acceptors with Tropylium Ion. *Angew. Chem. Int. Ed.* **2020,** *59* (4), 1455-1459; l) Lyons, D. J. M.; Empel, C.; Pace, D. P.; Dinh, A. H.; Mai, B. K.; Koenigs, R. M.; Nguyen, T. V., Tropolonate Salts as Acyl-Transfer Catalysts under Thermal and Photochemical Conditions: Reaction Scope and Mechanistic Insights. *ACS Catal.* **2020,** *10*, 12596-12606; m) Omoregbee, K.; Luc, K. N. H.; Dinh, A. H.; Nguyen, T. V., Tropylium-promoted prenylation reactions of phenols in continuous flow. *J. Flow Chem.* **2020,** *10* (1), 161-166; n) Empel, C.; Nguyen, T. V.; Koenigs, R. M., Tropylium-Catalyzed O–H Insertion Reactions of Diazoalkanes with Carboxylic Acids. *Org. Lett.* **2021,** *23* (2), 548-553; o) Crocker, R. D.; Pace, D. P.; Zhang, B.; Lyons, D. J. M.; Bhadbhade, M. M.; Wong, W. W. H.; Mai, B. K.; Nguyen, T. V., Unusual Alternating Crystallization-Induced Emission Enhancement Behavior in Nonconjugated ω-Phenylalkyl Tropylium Salts. *J. Am. Chem. Soc.* **2021,** *143* (48), 20384-20394.

6. Allen, J. M.; Lambert, T. H., Tropylium Ion Mediated α-Cyanation of Amines. *J. Am. Chem. Soc.* **2011,** *133* (5), 1260-1262.

7. *See the Supporting Information for more details.*

8. a) Khalimon, A. Y.; Gudun, K. A.; Hayrapetyan, D., Base Metal Catalysts for Deoxygenative Reduction of Amides to Amines. *Catalysts* **2019,** *9* (6), 490; b) Cabrero-Antonino, J. R.; Adam, R.; Papa, V.; Beller, M., Homogeneous and heterogeneous catalytic reduction of amides and related compounds using molecular hydrogen. *Nature Commun.* **2020,** *11* (1), 3893.