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Reductive Amination of Carbonyl C−C Bonds Enables Formal Nitrogen Insertion

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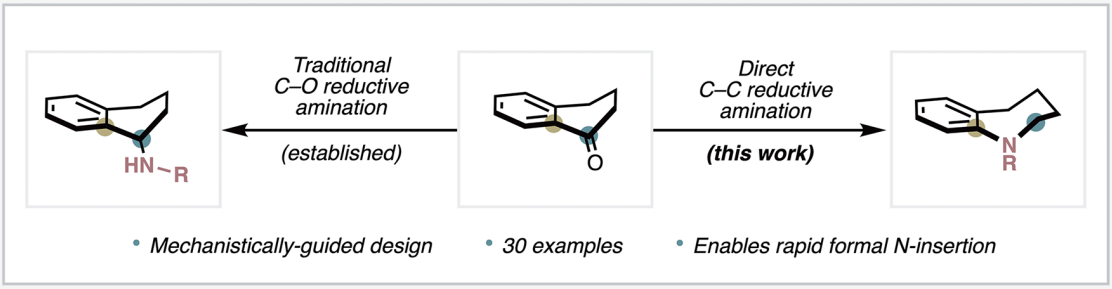

ABSTRACT: Given its relevance across numerous fields, reductive amination is one of the oldest and most widely used methods for amine synthesis. As a cornerstone of synthetic chemistry, it has largely remained unchanged since its discovery over a century ago. Herein, we report the mechanistically driven development of a complementary reaction, which reductively aminates the C−C σ-bond of carbonyls, not the carbonyl C−O π-bond, generating value-added linear and cyclic 3° amines in a modular fashion. Critical to our success were mechanistic insights that enabled us to modulate the resting state of a borane catalyst, minimize deleterious disproportionation of a hydroxylamine nitrogen source, and control the migratory selectivity of a key nitrenoid reactive intermediate. Experiments support the reaction occurring through a reductive amination/reductive Stieglitz cascade, via a ketonitrone, which can be interrupted under catalyst control to generate valuable *N*,*N*-disubstituted hydroxylamines. The method reported herein enables net transformations that would otherwise require lengthy synthetic sequences using pre-existing technologies. This is highlighted by its application to a two-step protocol for the valorization of hydrocarbon feedstocks, the late-stage C−C amination of complex molecules, diversity-oriented synthesis of isomeric amines from a single precursor, and transposition of nitrogen to different positions within a heterocycle.

The direct functionalization of unstrained C−C σ-bonds is a fundamental challenge in organic chemistry. Since C−C σ-bonds comprise most organic frameworks (especially true in hydrocarbon feedstocks and waste stream materials such as polyalkenes), the ability to modify these bonds would provide tremendous value. While the past two decades have seen a surge of methods for the conversion of ubiquitous C−H bonds into new functional groups,[1] there are considerably fewer approaches reported for the conversion of C−C bonds to higher-value products. Many methods for C−C π-bond functionalization are known, enabling powerful disconnections and broad synthetic diversity, and new methods for this purpose continue to emerge. In these cases, the reactive frontier molecular orbitals are energetically and sterically accessible (Scheme 1A).[2] In comparison, C−C σ-bonds are kinetically and thermodynamically inaccessible. Indeed, in the select examples wherein C−C σ-bond functionalization by a transition metal is rendered kinetically feasible by means of a directing group,[3,4] the thermodynamics still largely disfavor C−C activation due to exchange of a strong C−C bond for weak C−M bonds. The latter organometallic species must therefore be trapped, using either aromatization,[5] chelation,[6] or strain-release[7] as a driving force to facilitate the desired C−C functionalization reaction. While bond distortion through the introduction of strain can render the kinetics and thermodynamics of C−C σ-bond activation more favorable, researchers such as Bergman and co-workers,[8,9] Milstein and co-workers,[10] and Jones and Perthuisot[11] (Scheme 1B) have shown that even with a strong driving force for C−C cleavage, C−H activation is kinetically preferred. Upon forming a fleeting C−M−H or σ-complex species, which reversibly brings the metal into proximity to the reacting C−C bond (i.e., a traceless directing group effect), the C−C σ-bond cleavage event is thus facilitated.

It was within this context that we questioned whether the formal insertion of a single nitrogen atom into unstrained C−C

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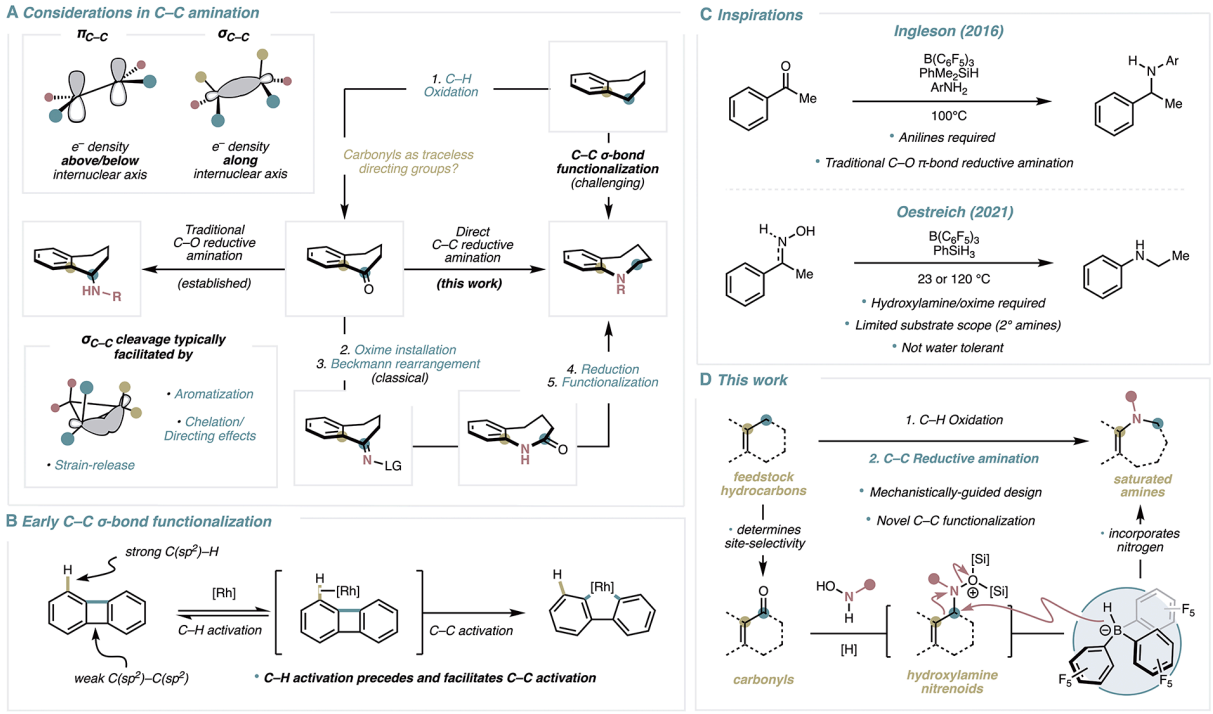
Scheme 1. Challenges of Direct C−C σ-Bond Functionalization[a]



[a]While C−H oxidation could be utilized to facilitate formal nitrogen insertion, existing methods require numerous steps and limit versatility (A). Transition metal-mediated C−C activation reactions are facilitated by reversible C−H activation (B). Water-tolerant borane-mediated reductive amination, as well as a borane-mediated reductive Beckmann rearrangement by Ingleson and Oestreich, respectively (C). This work: formal *N*-insertion into C(sp^3)−C(sp^2) bonds using a C−H oxidation/C−C reductive amination sequence through a key *N*,*N*-disubstituted hydroxylamine nitrenoid reactive intermediate (D).

σ-bonds could be achieved. Specifically, a selectivity-determining C−H oxidation could install a ketone or aldehyde as a traceless "directing" group, setting the stage for a site-selective C−C σ-bond amination event. Crucially, to serve the role of a traceless directing group,[12] the carbonyl that facilitates the C−C σ-bond amination must be concomitantly and exhaustively reduced, a transformation unknown prior to this work. Although classical synthetic approaches can effect the conversion of carbonyl C−C σ-bonds to the corresponding saturated 3° amines, numerous steps are required, resulting in lengthy synthetic sequences[13] (Scheme 1A). During the review of this manuscript, a complementary method for the formal insertion of nitrogen into C−C bonds was disclosed by Jiao and co-workers,[14] leveraging a one-pot oxidation, Stieglitz rearrangement, and subsequent borohydride reduction.

Encouraged by studies from Ingleson and co-workers[15] (Scheme 1C), we hypothesized that reactive *N*,*N*-disubstituted hydroxylamines could be generated in situ from the corresponding ketone and a suitable nucleophile using borane-mediated reductive amination (Scheme 1D).

Additionally, supported by mechanistic studies from Oestreich and co-workers[16] (Scheme 1C) demonstrating that related monosubstituted hydroxylamines are competent rearrangement precursors, we hypothesized that generation of *N*,*N*-disubstituted *O*-bissiloxonium hydroxylamine nitrenoids under borane-mediated reductive amination conditions might trigger a subsequent reductive Stieglitz rearrangement,[17] providing direct access to the saturated 3° amines (Scheme 1D). The development of a "C−C reductive amination" would be significant, as it would be orthogonal to traditional reductive amination, one of the oldest methods for amine synthesis,[18,20,21] and one of the most widely used reactions in medicinal chemistry programs,[22] providing a complementary retrosynthetic disconnection for amine synthesis (Scheme 1A), and facilitate rapid access to diverse structural space through late-stage diversification. Moreover, taken together with the rich existing body of literature for site-selective C−H oxidation, the development of such a method would uniquely enable an expeditious two-step protocol for the formal insertion of a single nitrogen atom into the core framework of organic scaffolds, without a reliance on strain-release or aromatization, enabling the rapid conversion of coal tar-derived feedstock hydrocarbons into value added amines, valorizing these abundant but underutilized materials for chemical synthesis.

With this goal in mind, there were several key challenges to consider at the outset of our studies: First, mechanistic work from Ingleson and co-workers showed that a strongly Brønsted-acidic[23] oxonium-borate species (**B1**), which forms upon exposure of tris(pentafluorophenyl)borane (BCF) to water, can be irreversibly deprotonated in the presence of a Brønsted-base, leading to catalyst death (Scheme 2B). This is a challenge that is relevant only when water is produced stoichiometrically, such as is the case in reductive aminations. Notably, this deleterious effect of water is a nonfactor when classical oximes or hydroxylamines are used as starting materials (as in the studies reported by Oestreich). Second, *N*-substituted hydroxylamine freebases often decompose in Brønsted- and Lewis-acidic media[24,25] (Scheme 2C), and hydroxylamine hydrochloride salts would require aqueous

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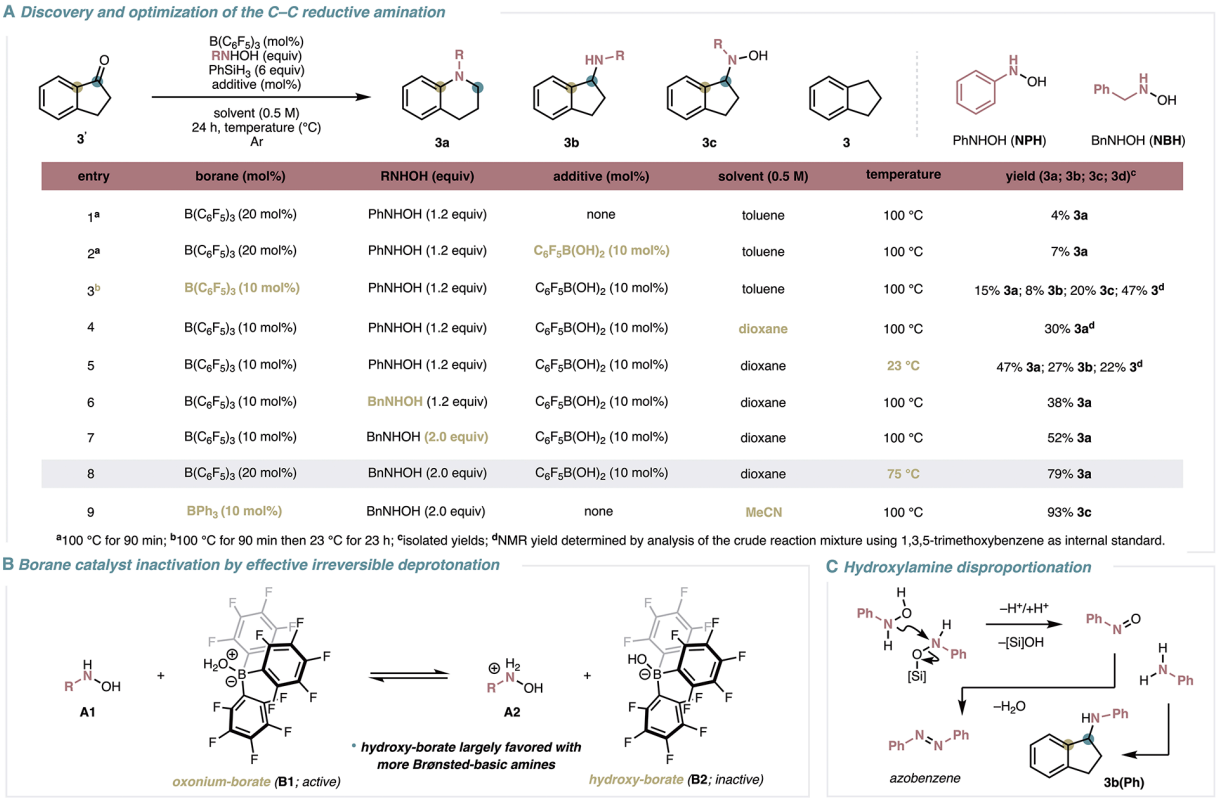
Scheme 2. Discovery and Optimization of the C−C Reductive Amination, Borane Catalyst Inactivation by Effective Irreversible Deprotonation, and Hydroxylamine Disproportionation[a]



entry	borane (mol%)	RNHOH (equiv)	additive (mol%)	solvent (0.5 M)	temperature	yield (3a; 3b; 3c; 3d)[c]
1[a]	$B(C_6F_5)_3$ (20 mol%)	PhNHOH (1.2 equiv)	none	toluene	100 °C	4% **3a**
2[a]	$B(C_6F_5)_3$ (20 mol%)	PhNHOH (1.2 equiv)	$C_6F_5B(OH)_2$ (10 mol%)	toluene	100 °C	7% **3a**
3[b]	$B(C_6F_5)_3$ (10 mol%)	PhNHOH (1.2 equiv)	$C_6F_5B(OH)_2$ (10 mol%)	toluene	100 °C	15% **3a**; 8% **3b**; 20% **3c**; 47% **3**[d]
4	$B(C_6F_5)_3$ (10 mol%)	PhNHOH (1.2 equiv)	$C_6F_5B(OH)_2$ (10 mol%)	dioxane	100 °C	30% **3a**[d]
5	$B(C_6F_5)_3$ (10 mol%)	PhNHOH (1.2 equiv)	$C_6F_5B(OH)_2$ (10 mol%)	dioxane	23 °C	47% **3a**; 27% **3b**; 22% **3**[d]
6	$B(C_6F_5)_3$ (10 mol%)	BnNHOH (1.2 equiv)	$C_6F_5B(OH)_2$ (10 mol%)	dioxane	100 °C	38% **3a**
7	$B(C_6F_5)_3$ (10 mol%)	BnNHOH (2.0 equiv)	$C_6F_5B(OH)_2$ (10 mol%)	dioxane	100 °C	52% **3a**
8	$B(C_6F_5)_3$ (20 mol%)	BnNHOH (2.0 equiv)	$C_6F_5B(OH)_2$ (10 mol%)	dioxane	75 °C	79% **3a**
9	BPh_3 (10 mol%)	BnNHOH (2.0 equiv)	none	MeCN	100 °C	93% **3c**

[a]100 °C for 90 min; [b]100 °C for 90 min then 23 °C for 23 h; [c]isolated yields; [d]NMR yield determined by analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard.

[a]Initial finding and reaction optimization of the borane-mediated C−C reductive amination (A). Challenges associated with this reactivity paradigm are two-fold: Borane catalyst poisoning through irreversible deprotonation of a oxonium-borate complex (B1), formed on exposure to water resulting from condensation, to give a catalytically inactive hydroxy-borate complex (B2) (B); *N*-Arylhydroxylamines disproportionate via nitrenoid intermediates in Lewis- and Brønsted-acidic media to the corresponding nitroso and amine, the latter of which is competent in a standard C−O π-bond reductive amination (C).

alcoholic solvent mixtures for solubility, complicating the choice of nitrogen source. Finally, the synthesis of 3° amines through the reductive Stieglitz rearrangement of nonsymmetric *N*,*N*-disubstituted hydroxylamine nitrenoids requires migratory selectivity between each of the substituents (Scheme 3B), a challenge not addressed prior to this work.[26,27] Additionally, it was unknown at the outset of our studies whether the hypothesized nitrone intermediates, which are known to be fleeting and reactive,[28] could participate in such a BCF-mediated reduction amination.

■ RESULTS AND DISCUSSION

We first subjected 1-indanone (**3′**) to borane-mediated reductive amination conditions using phenylsilane as reductant (6 equiv), BCF (20 mol %) as catalyst, and *N*-phenyl hydroxylamine (NPH) (1.2 equiv) as the nitrogen source, at 100 °C for 90 min in toluene. The desired *N*-phenyl tetrahydroquinoline [**3a(Ph)**] was isolated in 4% yield after preparative-thin layer chromatography (PTLC) (Scheme 2A, entry 1).

Considering the first of our anticipated challenges, i.e., catalyst death due to hydroxy-borate formation (Scheme 2B), we hypothesized that the equilibrium position of the catalyst resting state could be shifted toward the oxonium-borate upon addition of a Brønsted-acid.[15] Indeed, addition of a Brønsted-acid cocatalyst (pentafluorophenylboronic acid; 10 mol %), boosted the yield of **3a(Ph)** to 7% by NMR (Scheme 2A, entry 2). Additionally, we found that longer reaction times (i.e., an additional 23 h at 23 °C) were beneficial, resulting in 15% yield of **3a(Ph)** by NMR, with complete consumption of the starting material, along with 8% of *N*-indanyl aniline **3b(Ph)**, 20% of hydroxylamine **3c(Ph)**, as well as indane (**3**) in 47% (Scheme 2A, entry 3). 1,4-Dioxane emerged as the optimal solvent,[29] providing **3a(Ph)** in 30% NMR yield with no observable **3c(Ph)** (Scheme 2A, entry 4). This observation suggests **3c(Ph)** is likely an intermediate along the reaction path from **3′** to **3a(Ph)**, a hypothesis which is supported by mechanistic experiments (Scheme 5B). Upon lowering the temperature to 23 °C, we isolated the desired rearrangement product in 47% yield, along with 27% isolated yield of aniline product **3b(Ph)**, and a 22% NMR yield of **3** (Scheme 2A, entry 5). Varying the time, temperature, concentration, stoichiometry, additives (*such as desiccants*), order of addition, or identity of silane (see the Supporting Information for an extensive list of conditions screened) did not lead to any additional improvements in yield.

Considering the second of our anticipated challenges, namely the poor kinetic persistence of hydroxylamine free-bases, we hypothesized that competing formation of **3b(Ph)** occurs due to disproportionation of the NPH through the intermediacy of a phenyl nitrenoid or nitrenium intermediate to form nitrosobenzene and aniline—a process known to occur under Brønsted[24] or Lewis-acidic conditions[25] (Scheme 2C).

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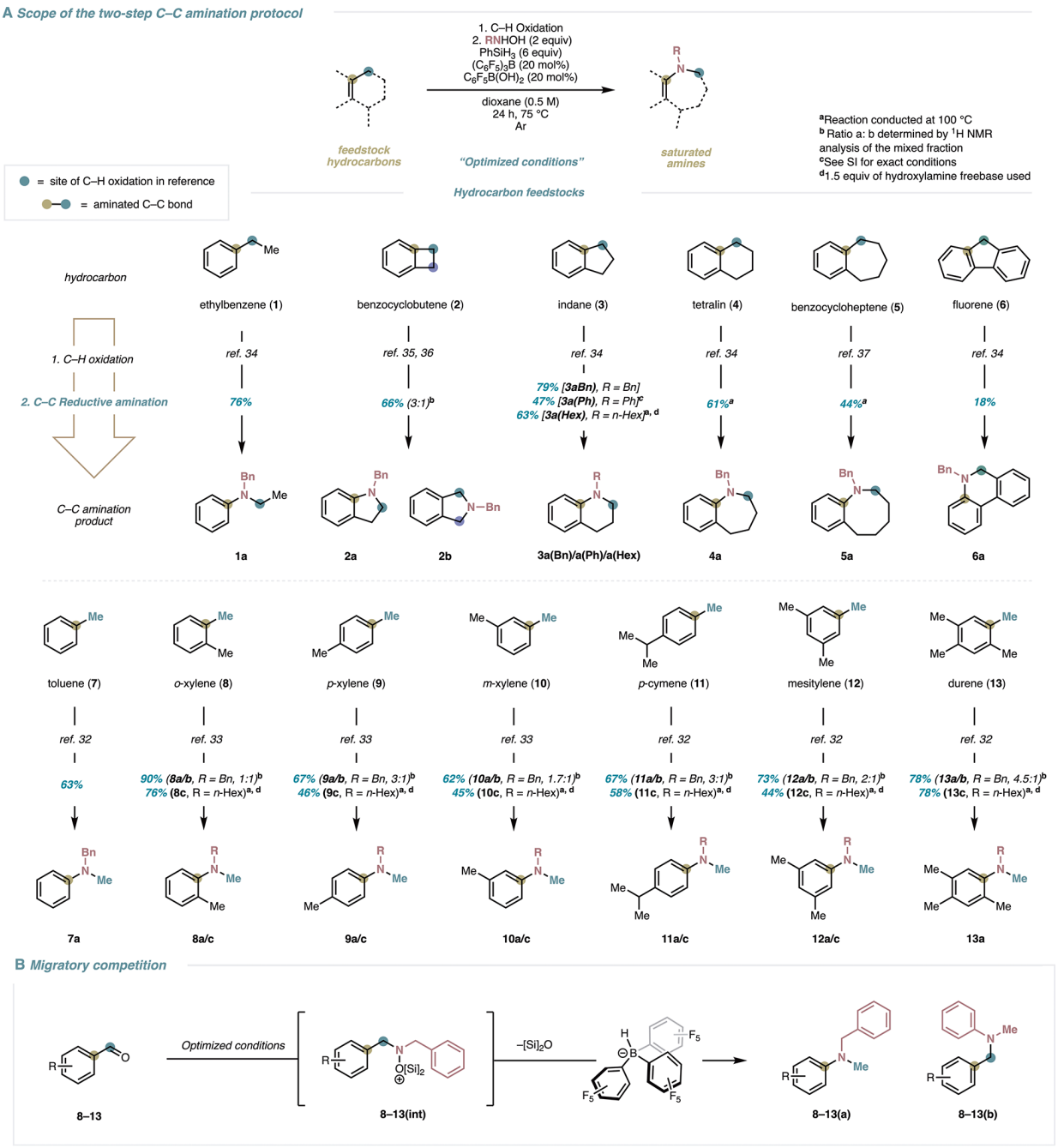
Scheme 3. Scope of the Two-Step C−C Amination Protocol and Migratory Competition[a]



[a]Two-step C−C amination of feedstock hydrocarbons (A). When NBH is used as a nitrogen source, pseudo-symmetric *N*,*N*-dibenzyl hydroxylamine intermediates [**8−13(int)**] are formed and can undergo a reductive Stieglitz rearrangement from either aryl group, kinetically favoring the migration of the more electron-rich arene (B).

The aniline would then react through a traditional reductive amination of the carbonyl to yield **3b(Ph)**. To address this competing reactivity, we synthesized a library of electronically and sterically differentiated *N*-aryl hydroxylamines (see the Supporting Information for more details). Unfortunately, none of the *N*-aryl hydroxylamines synthesized were competent in the reaction: they either prevented reactivity, resulted in decomposition of the hydroxylamine partner, or led to ionic reduction of 1-indanone (**3′**) to give indane (**3**).

Several other designed and commercial nitrogen sources were investigated, including *O*-alkyl/silyl/sulfonyl hydroxylamines. However, these also resulted only in the formation of the corresponding oximes under the optimized conditions, underscoring the fact that a simple telescoping of condensation/reductive rearrangement reactions is not a feasible strategy to effect the reductive amination of carbonyl C−C σ-bonds developed here. This outcome may be attributed to the greater Brønsted-basicity of these hydroxylamines relative to *N*-aryl hydroxylamines, again resulting in the poisoning of the borane catalyst by forming the inactive hydroxy-borate (**B2**) following irreversible deprotonation (Scheme 2b). Despite this challenge, we found that at elevated temperatures

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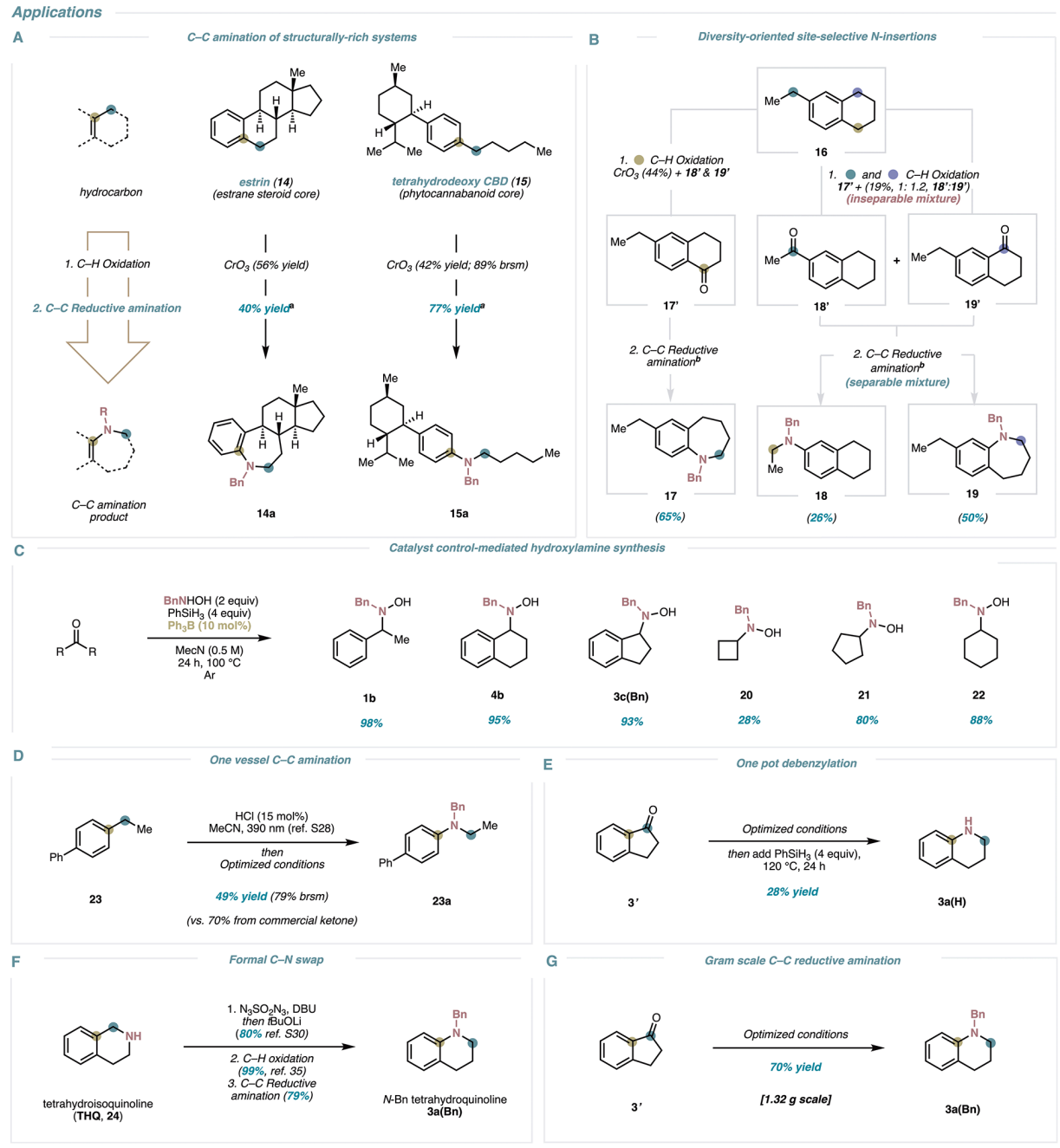
Scheme 4. Applications[a]



[a]Two-step C−C amination of structurally-rich scaffolds (A). Diversity-oriented amine synthesis (B). Use of triphenylborane as Lewis acid yields pharmacologically and synthetically privileged hydroxylamines (C). One-vessel procedure for conversion of hydrocarbons to the corresponding C−C amination product using mild C−H oxidation conditions (D). One-pot procedure to the free amine by adding additional silane reductant (E). Net transposition of the nitrogen of tetrahydroisoquinoline to the benzylic position (F). The method proved to be scalable and worked in good yield on gram scale (G). (a) Reaction run at 100 °C for 48 h. (b) Reaction run at 100 °C.

(100 °C) deprotonation of the oxonium-borate adduct is reversible, providing the C−C reductive amination product [*N*-benzyl tetrahydroquinoline, **3a(Bn)**] in 38% isolated yield when *N*-benzyl hydroxylamine (NBH) was used as the nitrogen source (Scheme 2A, entry 6). In this case, the mass balance was accounted for by the indane side product (**3**) resulting from ionic reduction, and importantly, no appreciable disproportionation products were observed.

While it is known that BCF is incapable of catalyzing the reductive amination of aldehydes and ketones using alkylamines, even at elevated temperatures (120 °C),[15,30] we propose that in our studies this is only possible because of the increased thermodynamic acidity of the conjugate acid of hydroxylamines as compared to amines,[31] allowing for a more reversible exchange between the *N*-substituted hydroxylammonium (**A2**) and the hydroxy-borate (**B2**) species. Importantly, due to the increased kinetic persistence of NBH,[28] 2 equiv of this reagent could be used without significant disproportionation, resulting in an improved 52% isolated yield of **3a(Bn)** (Scheme 2A, entry 8). Attempts to further increase the loading

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of NBH resulted in poor conversion of intermediate **3c**(**Bn**) to product **3a**(**Bn**), as well as significant competing formation of the traditional reductive amination product **3b**(**Bn**) due to enhanced disproportionation. Finally, by conducting the reaction at a lower temperature (75 °C), the desired C−C reductive amination product **3a**(**Bn**) was isolated in 79% yield after PTLC (Scheme 2A, entry 10). While the less Lewis-acidic triphenylborane[19] could effect the traditional reductive amination, furnishing hydroxylamine **3c**(**Bn**) in high yield (93%) (Scheme 2A, entry 10), this and all other borane catalysts screened were unable to effect the subsequent reductive Stieglitz rearrangement (see the Supporting Information), emphasizing the unique nature of BCF in this system. With optimized reaction conditions in hand, we applied this chemistry in a two-step protocol for the formal insertion of a single nitrogen atom into the core of hydrocarbon frameworks, exploiting known site-selective benzylic oxidation methods for the installation of ketones or aldehydes,[32−37] here leveraged as traceless "directing" groups.

The C−C reductive amination of the corresponding carbonyl compounds proved to be general, enabling a facile two-step synthesis of 3° azacycles (**2a**−**5a**) from coal tar-derived feedstock hydrocarbons in synthetically useful yields (44−79%) with various *N*-substituents [**3a**(**Bn**)−**3a**(**Hex**)] (Scheme 3A). Additionally, the pharmaceutically relevant[38] 5,6-dihydrophenanthridine core was accessed in short order from fluorene (**6**), albeit in modest yield (18%). Interestingly, expansion of tetralin (**4**) and benzocycloheptene (**5**) to the corresponding azacycles required elevated temperatures (100 °C) in the C−C reductive amination step, presumably due to higher transition state barriers[39] for migration, owing to the introduction of ring strain when going from a 6- to 7- or from a 7- to 8-membered ring.[40] In contrast, a strained system such as benzocyclobutene (**2**) is activated to such an extent that competitive formal C(sp^3)−C(sp^3) amination also occurs, yielding a mixture of indoline and isoindoline products (**2a** and **2b**) as a 3:1 mixture (66% combined yield). Significantly, a net C(sp^3)−C(sp^2) amination of linear systems could be achieved in good yields, as observed for ethylbenzene (**1a**; 76% yield) and toluene (**7a**; 63% yield), as well as various other hydrocarbon feedstocks including the xylenes (**8**−**10a**; 62−90% yield), cymene (**11a**; 67% yield), mesitylene (**12a**; 73% yield), and durene (**13a**; 78% yield), highlighting the applicability of this two-step transformation even in inherently unstrained substrates. Notably, the overall transformations shown would otherwise require four to six steps from hydrocarbon to 3° amine using pre-existing technologies, which has thus far limited the use of these abundant feedstocks for value-added chemical synthesis.

Bicyclic hydrocarbons **2**−**6** exhibited highly selective migration of the hydrocarbon arene over the NBH phenyl group due to the preferential formation of a putative 2° iminium/phenonium ion intermediate (over a 1° intermediate). Presumably, the difference in stability of the incipient cation imparts kinetic selectivity by lowering the corresponding transition state barrier.[39] In contrast, there is little migratory selectivity in the case of hydrocarbons **8**−**13** (isomeric ratios range from 1:1 to 4.5:1). This is likely due to the formation of pseudosymmetric *N*,*N*-dibenzyl hydroxylamine nitrenoids **8**−**13**(**int**), resulting in a mixture of isomeric amine products (Scheme 3B). To address this third challenge, namely the migratory selectivity of *N*,*N*-disubstituted hydroxylamine nitrenoids, we hypothesized that *N*-hexylhydroxylamine (NHH) could be used to impart greater migratory selectivity by increasing the energy difference between the transition states. Ultimately, we found that use of NHH imparted exclusive migratory selectivity for the hydrocarbon arene, giving the desired C−C amination products (**8**−**13c**) in good to moderate yields (44−78%) as single isomers.

With the key challenges successfully addressed and a better understanding of the factors that control the reductive amination of carbonyl C−C σ-bonds in hand, we recognized that the method would enable the rapid generation of highly complex amines that would otherwise require lengthy and laborious synthetic sequences. For example, the estrogenic hormone core estrin (**14**)[41] was converted to the corresponding aza-steroid in only two steps (40% for the C−C reductive amination step) (Scheme 4A). Notably, the site of the nitrogen insertion is dictated by reagent control[42] in the C−H oxidation event, allowing for site-selective amination of the least hindered bond with absolute control, which is complementary to the work of Jiao and Zhang.[14] In alignment with our previous observations (vide supra), the most efficient C−C reductive amination in a complex setting was in the case of the phytocannabanoid core tetrahydrodeoxy-CBD (**15**),[43] a linear system, providing the desired C−C amination product in 77% yield from the corresponding ketone. With the reductive amination of carbonyl C−C σ-bonds, diversity-oriented amine synthesis is also now possible—by effecting various simultaneous undirected C−H oxidations, multiple divergent isomeric amine products (**17**−**19**) can be synthesized from a single precursor (**16**) (Scheme 4B) in rapid fashion. Importantly, inseparable ketones mixtures (i.e., **18′** and **19′**) could be used directly without the need for laborious separation, providing separable amine products (**18** and **19**) in a streamlined workflow.

During our optimization, we found that the reaction conditions can be modified to provide *N*,*N*-disubstituted hydroxylamines under catalyst control. These privileged compounds are often difficult to access in a modular fashion and are highly coveted for their pharmacological and synthetic utility.[44,45] Specifically, using triphenylborane instead of BCF-furnished hydroxylamine products in high yield (Scheme 4C). In this case, it appears the less Lewis-acidic triphenylborane is incapable of the second silylation event, thus hampering the reductive Stieglitz rearrangement, implying that bissiloxonium formation is rate-determining.[46] Using the two-step protocol reported here, conversion of an unstrained C−C σ-bond to the corresponding amine can now be achieved without a workup or purification (Scheme 4D) in 49% yield, when conducted in a single vessel. Additionally, the *des*-benzyl 2° amine **3a**(**H**) can be accessed (28% isolated yield) in a single pot[47] (Scheme 4E). In combination with recently developed methods for the removal of nitrogen from cyclic amines,[48] this C−C amination protocol enables rapid conversion of tetrahydroisoquinoline (THIQ) (**24**) to benzyl-protected tetrahydroquinoline [**3a**(**Bn**)] in only three steps, effectively transposing the nitrogen and the benzylic methylene (Scheme 4F), thus interconverting two distinct saturated azacycles. Lastly, the reductive amination of carbonyl C−C σ-bonds is scalable, providing the product [**3a**(**Bn**)] in 70% yield on a 10 mmol (1.32 g) scale (Scheme 4G).

We have also sought to gain insight into the mechanism of the reductive amination of carbonyl C−C σ-bonds. A substitution via either an S_N1 or S_N2 pathway from a bissiloxonium ether could be envisioned as an alternative

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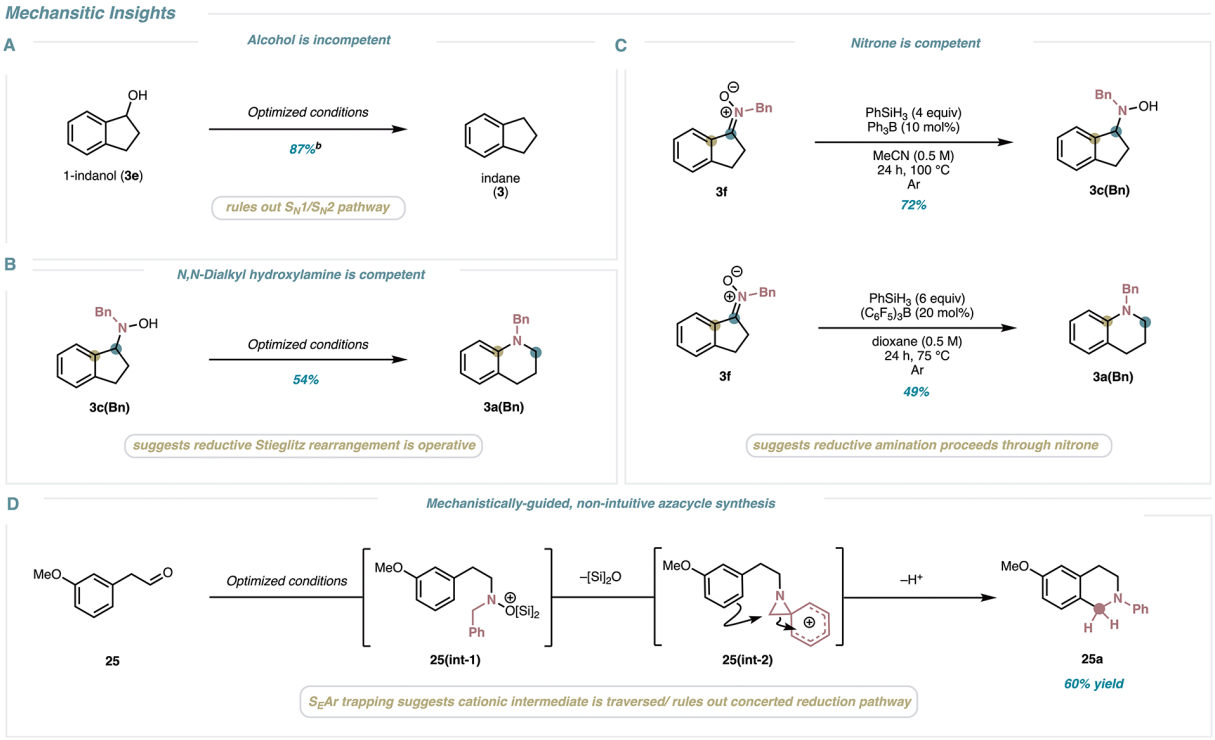
Scheme 5. Mechanistic insights into the C−C reductive amination[a]



[a]Our findings support the hypothesis that the C−C reductive amination of ketones and aldehydes occurs via a reductive amination mechanism, and not a substitution pathway (A), through the intermediacy of nitrone **3f**, which is converted to hydroxylamine **3c(Bn)** (B/C), and then to the product. Intramolecular trapping experiment (D) suggests an iminium/phenonium ion intermediate, as opposed to a concerted reductive rearrangement mechanism, elucidating novel retrosynthetic disconnections for amine synthesis.

pathway to products **3a**,[49] following ionic reduction of the carbonyl to the corresponding alcohol. However, we only observed the ionic reduction product (i.e., indane, **3**) upon subjection of 1-indanol (**3e**) to the reaction conditions (Scheme 5A). In contrast, subjection of either *N*-benzyl-*N*-indan-1-yl nitrone (**3f**) or the corresponding hydroxylamine [**3c(Bn)**] provided the cyclic amine product, suggesting these species are intermediates along the reaction path (Scheme 5B/C). Moreover, subjection of nitrone **3f** to triphenylborane-mediated reductive amination conditions yielded the same hydroxylamine intermediate [**3c(Bn)**], suggesting the hydroxylamine is a reactive intermediate between the nitrone and the product. Taken together, these data support the hypothesis that the reductive amination of carbonyl C−C σ-bonds to the corresponding 3°saturated amines occurs through a cascade process: reductive amination of the carbonyl C−O π-bond, through the intermediacy of a ketonitrone (**3f**), generates an *N*,*N*-disubstituted hydroxylamine **3c(Bn)**, which undergoes a migration-selective reductive Stieglitz rearrangement (Scheme 1D) to furnish the product **3a(Bn)**.

To understand the nature of the reductive Stieglitz rearrangement of intermediate **3c(Bn)** to product **3a(Bn)**, we synthesized aryl acetaldehyde **25** in anticipation of trapping an iminium/phenonium ion intermediate, ruling out a concerted process. In the event, the THIQ product **25a** could be isolated in 60% yield. Not only does this transformation showcase the utility of the reductive amination of carbonyl C−C σ-bonds for new means of amine synthesis through counterintuitive disconnections, but it also provides valuable insight into the stepwise nature of the mechanism, providing direct evidence for the intermediacy of a relatively long-lived iminium/phenonium ion species (vide supra).

CONCLUSIONS

The reductive amination of carbonyl C−C σ-bonds, which yields 3° saturated amines in a modular fashion, presents a complementary approach for amine synthesis. Along with established site-selective C−H oxidation technologies, the formal insertion of a single nitrogen atom into the core of hydrocarbon frameworks can be realized through a two-step protocol, without a reliance on strain-release. The method enables complex amine synthesis through late-stage nitrogen insertion, facilitates the divergent synthesis of various isomeric amines from a single precursor, and enables the translocation of nitrogen to different positions in a cyclic system through a deletion/insertion sequence, significantly expediting the exploration of chemical space. This reductive amination of carbonyl C−C σ-bonds should enable new strategies in natural product, pharmaceutical, and agrochemical synthesis, starting from cheap and abundant feedstock materials.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c02400.

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Supporting Information including all relevant experimental information is included with the manuscript (PDF)

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Author Contributions

†These authors contributed equally. C.A. developed the reaction and designed the experiments. C.A., L.T.G., R.T.S., and T.M.P. ran the experiments. R.S. directed the project. C.A. and R.S. wrote the manuscript.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

(NBH) *N*-benzylhydroxylamine
(NPH) *N*-phenylhydroxylamine
(BCF) tris(pentafluorophenyl)borane

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