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Practical olefin hydroamination with nitroarenes

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The formation and functionalization of amines are fundamentally important in a vast range of chemical contexts. We present an amine synthesis that repurposes two simple feedstock building blocks: olefins and nitro(hetero)arenes. Using readily available reactants in an operationally simple procedure, the protocol smoothly yields secondary amines in a formal olefin hydroamination. Because of the presumed radical nature of the process, hindered amines can easily be accessed in a highly chemoselective transformation. A screen of more than 100 substrate combinations showcases tolerance of numerous unprotected functional groups such as alcohols, amines, and even boronic acids. This process is orthogonal to other aryl amine syntheses, such as the Buchwald-Hartwig, Ullmann, and classical amine-carbonyl reductive aminations, as it tolerates aryl halides and carbonyl compounds.

The formation and manipulation of amines represent a large fraction of the daily activity of practicing organic chemists (1). The most useful methods for the synthesis and functionalization of amines currently include alkylation (2, 3), amine-carbonyl reductive amination (4), and C–N cross-coupling (5–8). For example, secondary aromatic and heteroaromatic amines are usually accessed by arylation or alkylation of the parent amine. Given the prevalence of amines in medicinal chemistry (9) and some of the limitations of current amine syntheses, we pursued a distinct pathway for their construction.

The challenges of amine synthesis can be exemplified with conventional retrosynthetic logic applied to a prototypical medicinal chemistry building block 1 (Fig. 1A). The first disconnection, between nitrogen and C-1, results in a C–N cross-coupling transformation and leads to aromatic amine 2 and the hindered primary amine 3 (10). Because of functional group incompatibilities, protecting groups on the alcohol and amino groups of 2 might be required. The second approach involves a disconnection between nitrogen and C-2 and proceeds by way of a Grignard reagent and C-2 and proceeds by way of a Grignard reagent and reduction of a nitro group. To our knowledge, there are no practical methods for direct formation of a C–N bond from a nitroarene that liberate a secondary amine. In this work, the invention of such a reaction is reported that uses simple olefins as the radical source, an inexpensive silane and zinc metal as reductants, and an abundant iron salt as a catalyst.

Reactions development and optimization

There were clues in the literature suggesting the feasibility of this reaction. For example, Russell and Yao demonstrated that tert-buty1 radicals, derived from the photoinitiated decomposition of an organomercury species, could add to both nitroarenes and nitrosamines to give mixtures of N- and N,O-alkylated adducts (11). Numerous reports have shown that radicals react readily with nitro compounds (12–15), as demonstrated by Corey and Gross as a means to generate hindered amines (16). Buchwald and colleagues have also demonstrated that hydroxylamine derivatives can be used in olefin hydroamination under copper catalysis (17), and Lilly and colleagues have used similar hydroxylamine derivatives to aminate allyl boranes in a two-step hydroamination process (18). Additionally, Yu and colleagues have coupled hydroxylamine derivatives with aromatic C–H bonds to generate amines under palladium catalysis (19). Given the widespread availability of nitro(hetero)arenes and their ease of synthesis, it is surprising that they have not been exploited further beyond their reduction to the corresponding aniline (20), the Cadogan carbazole synthesis (21, 22), the Bartoli indole synthesis (23), and a few C–C bond-forming reactions (24, 25).

Our recent work on Fe-catalyzed olefin cross-coupling via allyl radical intermediates (26, 27) led us to attempt the coupling of nitronaphtalene 8 with isoprenyl alcohol A (Fig. 1B). To our delight, useful quantities of the desired amine product were isolated upon initial attempts, along

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PhSiH3 proved to be the most effective at facilitating the transformation (Fig. 1B, entries 8 to 10). With an optimized set of conditions in hand, introducing a Zn-mediated reduction of the corresponding aniline, a process observed with Co(acac)2 and Mn-based (Fig. 1B, entry 7) and Mn-based (32, 33) (Fig. 1B, entry 6) systems delivered only trace amounts of product. In the absence of olefin, Co(acac)2 and Mn(dpm)3 failed to reduce the nitroarene to the corresponding aniline, a process observed with the use of Fe(acac)3; this indicates that there is some interaction of the Fe-based system with the nitroarene prior to presumed radical addition (see figs. S1 and S2). Among the silanes screened, PhSiH3 proved to be the most effective at facilitating the transformation (Fig. 1B, entries 8 to 10).

Exploring substrate scope

With an optimized set of conditions in hand, the scope of the olefin and nitroarene partners was extensively evaluated. We subjected 27 different olefin donors (Fig. 2) to hydrosilation with an array of nitro(hetero)arenes adorned with a variety of functional groups, for a total of 113 examples (Figs. 3 to 7). In accord with known reactivity trends in Fe-based olefin functionalization (34, 35), adducts were formed at the most substituted carbon of the olefin, with olefins A and B delivering the same products. Mono-, di-, tri-, and tetrasubstituted olefins serve as viable substrates ranging in complexity. Iso-butylene (E) can be used to enable facile access to N-tert-butyl aromatic amines. Several of the olefins, such as F, G, and K, permit access to extremely hindered amines that might be challenging to prepare in other ways (10). This is particularly exciting given the documented utility of hindered amines as a method to block metabolism in drug discovery (36).

The ability of the reaction to tolerate sensitive functional groups in the nitroarene component is remarkable (Fig. 3). Simple aliphatic functionalization (12–15), thioethers (16–19), ethers (20–33), and amides (34–40) emerge unsathed. Although this is a reductive process, ketones (41–49) are not reduced, as opposed to the classic carbonylamine reductive amination that would require ketones to be protected. Free alcohols and amines are well tolerated (9, 50–62), including the showcased example in Fig. 1A, delivering target 1 in 70% isolated yield without the need for protecting group chemistry. Unprotected boronic acids (63–65), ary1 triflates (66–70), and aryl halides (71–81; F, Cl, Br, and I) are also tolerated, allowing for downstream C–C, C–O, and C–N cross-coupling chemistry. Most important, nitro-heteroarenes can be used to deliver medically relevant building blocks containing pyrrole (82–84), benzothiazolone (85, 86), indole (87–89), pyrazole (90, 91), indazole (108, 109; Fig. 5), triazole (126; Fig. 6), and pyridine (92–105) ring systems. The reaction was also performed on a decagram scale by Kemxtree, a contract research organization responsible for the commercialization of these amine building blocks, to provide dozens of adducts, five of which (26, 27, 39, 78, and 80) are shown in Figs. 3 and 4. Although tert-butylated amines similar to 13 and 24 have been previously made via aminations of
Fig. 3. Scope of the olefin hydroamination. Isolated yields are shown in parentheses along with the donor olefin used. Standard conditions: nitro(hetero)arene (1 equiv), olefin (3 equiv), Fe(acac)₃ (30 mol %), PhSiH₃ (2 equiv), EtOH, 60°C, 1 hour; Zn (20 equiv), HCl(aq), 60°C, 1 hour. Bu, butyl; Pr, propyl.

*Without Zn/HCl reduction procedure. †Olefin (5 equiv), PhSiH₃ (3 equiv). ‡Olefin (2 equiv), PhSiH₃ (3 equiv). §Olefin (2 equiv), PhSiH₃ (2 equiv).
Fig. 4. Scope of the olefin hydroamination, continued. Isolated yields are shown in parentheses along with the donor olefin used. Standard conditions: nitro(hetero)arene (1 equiv), olefin (3 equiv), Fe(acac)₃ (30 mol %), PhSiH₃ (2 equiv), EtOH, 60°C, 1 hour; Zn (20 equiv), HCl(aq), 60°C, 1 hour.

*Without Zn/HCl reduction procedure. †Olefin (5 equiv). PhSiH₃ (3 equiv). ‡Olefin (2 equiv), PhSiH₃ (3 equiv). §Olefin (2 equiv), PhSiH₃ (2 equiv).

††Performed on decagram scale with no additional optimization.

9: Ar = 1-naphthyl (A, 63%) 57: Ar = 2-fluorenyl (A, 55%)
58: (A, 69%)
59: (A, 60%)
60: (A, 60%)
61: (K, 57%)
62: (S, 72%)

63: (M, 55%)
64: R = CH₂OBn (J, 45%)
65: R = Ph (T, 42%)
66: R = Me (E, 50%)
67: R = "Pr (H, 49%)
68: (Q, 61%)
69: (J, 61%)
70: (K, 80%)

71: R = H (A, 75%)
72: R = Me (K, 58%)
73: (A, 60%)
74: R = Me (E, 42%)
75: R = CH₂OBn (J, 50%)
76: R = H (A, 60%)
77: R = Me (K, 61%)
78: (A, 58%) (B, 31%)
79: (J, 45%)

80: (T, 41, 30%) †
81: (I, 44% †)
82: (P, 54%) †
83: R = Bn (I, 56%) †
84: R = "Pr (H, 53%) †
85: R = Me (E, 54%)
86: R = Ph (T, 50%)
87: (I, 60%) †
88: R = H (P, 46%) †
89: R = Bn (P, 50%) †
90: (J, 63%) †
91: (I, 24%) †
92: R = Et (H, 62%)
93: R = CMe₂OH (K, 58%)
94: n = 1 (M, 54%)
95: n = 2 (Q, 63%)
96: R = Ph (I, 60%)
97: R = OOBn (J, 75%)
98: R = Me (E, 47%)
99: R = "Pr (H, 45%)
100: R = Bn (I, 43%)
101: (A, 64%)
102: R = Cl (Q, 42%)
103: R = OMe (Q, 66%)
104: R = H (A, 68%)
105: R = Me (K, 44%)
carbocations, these processes require either specialized reagents (37) or lack the chemoselectivity of the nitroarene-based approach (38). Finally, the reaction could also be used to construct adducts that, upon initial inspection, might be accessed using conventional amine-carbonyl reductive amination (48, 49, and 53–56). However, the presence of unprotected carbonyl groups, alcohols, and amines would impede such an approach, thus demonstrating the orthogonal nature of the hydroamination process to the classical method.

**Application to medicinal chemistry targets**

Figure 5 depicts three representative examples of how this reaction can simplify the preparation of hindered amine drug candidates: (i) Glucocorticoid receptor modulator intermediate 108 has previously been prepared from nitroindazole 106 in two steps (Fe-mediated reduction followed by ring opening of aziridine 107) in 24% isolated yield (39). Alternatively, direct hydroamination of the same starting material using readily available olefin U affords the same target in a single operation (52% isolated yield). (ii) The HIV-1 reverse transcriptase inhibitor intermediate 111 is known to be accessible from nitropyridine 109 using three different transition metals and an expensive, water-sensitive alkylation agent (110) in 43% yield over three steps (40). The same adduct can be obtained in a single step from the same starting material using a feedstock olefin donor, 2-methyl-2-butenone (R). (iii) The ORL1 (opioid receptor–like) receptor inhibitor intermediate 113 has previously been prepared by a three-step route involving condensation with ketone 112, alkyl lithium addition, and deprotection in 37% overall yield (41). Alternatively, olefin 114 can react directly with nitrobenzene to deliver the same adduct in similar isolated yield in only 2 hours.

As shown in Fig. 6, there are many opportunities for this reaction to be applied in unusual ways. Cascade amine annulation can be accomplished in the case of olefin V, wherein a tandem olefin hydroamination takes place followed by an intramolecular amine-carbonyl reductive amination to deliver the highly substituted N-arylpyperidine 116 in 43% isolated yield (Fig. 6A). Electron-deficient olefins can also be used in instances where conjugate addition fails, as exemplified by the synthesis of β-amine derivatives 118 and 120–123, key intermediates in a current medicinal chemistry program at Bristol-Myers Squibb that were otherwise inaccessible via hetero–Michael addition of 2-chloroaniline (119) to enone W (Fig. 6B). Additionally, this transformation also holds great appeal for isotopic labeling efforts (Fig. 6C). The use of deuterated isobutylene (AA) provides deuterated tert-butyl intermediate 124, which can be used as an internal standard for liquid chromatography–mass spectrometry analysis in an ongoing program at Bristol-Myers Squibb. Simple deuterated building blocks of potential interest in medicine (42) can also be accessed, such as amine 125 in 77% yield. This single-step procedure obviates the need for costly and time-consuming multistep processes to access these labeled compounds. It could also be applied to the synthesis of radiolabeled products using appropriately labeled 3H or 14C alkenes. Finally, we examined the suitability of this reaction for use in a process setting (Fig. 6D). Because nitroarenes are potentially energetic materials, the temperature profile of the hydroamination to form 126 was studied at 20°C by heat flow calorimetry. No temperature spikes were observed when the catalyst was added; however, there was a 2°C internal temperature rise upon addition of the PhSiH₃ that slowly dissipated over 2 hours as the reaction reached completion. These results indicate the absence of an induction period that could lead to a possible runaway thermal event during large-scale hydroaminations and serve to alleviate some of the concerns when performing the reaction in a process setting.

**Substrate limitations**

Although this reaction is exceedingly general in its current form, it is not without limitations. For example, nitroalkanes (127–130; Fig. 7) routinely give low yields of amines; however, it is worth noting that diamines 129 and 130 might not be trivial to directly make in other ways. Products arising from the use of tertiary nitroalkanes were not isolable. During the course of exploring substrate scope (Figs. 3 and 4), we found that esters and amides would impede such an approach, thus demonstrating the orthogonal nature of the hydroamination process to the classical method.

Fig. 5. Olefin hydroamination applied to shorter syntheses of known pharmaceutical targets. (A) Glucocorticoid receptor modulator intermediate 108. (B) HIV-1 reverse transcriptase inhibitor intermediate 111. Boc, tert-butyloxycarbonyl. (C) ORL1 receptor inhibitor intermediate 113.
Fig. 6. Creative uses of the olefin hydroamination technique. (A) Cascade reductive aminations for amine annulation. (B) An efficient method to access hindered Michael adducts. (C) Application to deuterium labeling using isobutylene-\(d_8\) (AA). (D) Temperature profile of the formation of a current intermediate in process chemistry over 6 hours shows the absence of an induction period.

Fig. 7. Limitations of the hydroamination. (A) Nitroalkanes give low yields. (B) Limitations of functional group tolerance.

REFERENCES AND NOTES


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SUPPLEMENTARY MATERIALS

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Materials and Methods

Supplementary Text

Figs. S1 to S20

Tables S1 to S4

Supplementary Text

References (45–50)

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Stitching C-N bonds from nitro groups
Numerous compounds in pharmaceutical research have carbon-nitrogen bonds, and chemists are always looking for ways to make them more efficiently. Gui et al. present a method that links the carbon in an olefin to the nitrogen in a nitroaromatic compound (see the Perspective by Kürti). Nitroaromatics are readily available, and the method tolerates a wide range of other chemical groups present on either reacting partner.

Science, this issue p. 886; see also p. 863

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