Site-Selective Allylic C-H Amination with Aliphatic Amines

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Article

Abstract

The direct coupling of olefins and alkyl amines represents the most efficient and atom-economical approach to prepare aliphatic allylamines which are fundamental building blocks. However, the method that achieves this goal while exhibiting exquisite control over the site at which the amine is introduced remains elusive. Herein, we report that the combination of a photocatalyst and a cobaloxime enables site-selective allylic C−H amination of olefins with secondary alkyl amines to afford allylic amines, eliminating the need for oxidants. This reaction proceeds by a radical-based mechanism distinct from those of existing allylic amination reactions. It affords the product resulting from cleavage of the stronger, primary allylic C−H bonds over other weaker allylic C−H bond options. DFT calculations reveal that this selectivity originates from a cobaloxime-promoted hydrogen atom transfer (HAT) process. Our method is compatible with a broad scope of alkenes, and can be extended to achieve a site- and diastereoselective amination of natural terpenes.

Main Text

The physiological properties of aliphatic allylamines have rendered them highly effective pharmaceutical agents[1,2], ranging from antifungal regents[3] (such as terbinafine[4], included in WHO Model List of Essential Medicines[5]) to B-cell lymphoma-2 inhibitor[6] (such as venetoclax[7]). One of the most efficient and atom-economical route to synthesize allylic amines is the catalytic allylic C−H amination[8]. To date, several synthetic strategies have been employed for the allylic amination, which is often based on ene-type reactions[9,10] or transition-metal-catalyzed reactions *via* either nitrene insertion[11,12] or π-allyl formation[13-17] (Fig. 1a). However, these reactions require pre-functionalized electrophilic nitrogen-based reagents, stoichiometric oxidants, use of amides or sulfonamides as the nucleophile, or a combination of several of these components, undermining the overall efficiency and atom-economy of the process. Thus, methods that prepare allylic amines directly from aliphatic amines, as the starting material, represents an ideal approach, that is yet to be developed.

Significant challenges impede the direct utilization of alkyl amines in allylic amination. Alkyl amines coordinate much more strongly to transition metals than olefins, thus substantially reducing their catalytic activity[18,19]. Furthermore, electron-rich, alkyl amines are typically incompatible with the oxidants needed to promote the reaction[20,21]. The direct coupling of olefins and amines under thermal conditions is a thermodynamically uphill method in the absence of external oxidants[22]. Therefore, we seek an alternative pathway for the allylic amination that could address these limitations, represents the scope of current work. Aminium radical cations (ARCs) have emerged as a versatile intermediate that can be accessed by photoredox catalysis and can readily be added to a wide range of double bonds in olefins and arenes[23-26]. We considered that a new mode of allylic amination could be achieved based on the addition of ARCs to olefins, where the subsequent conversion of the resulting carbon-centered radical to the product could proceed in a regioselective manner (Fig. 1b). This radical-based process would offer a solution to avoid issues associated with catalyst inhibition by alkyl amines and the use of light could

have the potential to drive the endergonic coupling of olefins and amines[22], thereby making possible allylic amination that utilizes alkyl amines directly as the reactant and circumvents the use of external oxidants.

To achieve a site-selective allylic amination, the catalyst needs to distinguish several, often similar, allylic C−H bonds[9,11,16]. However, known radical systems that succeed in doing so have been limited. A rare example was a site- and enantioselective allylic C−H cyanation enabled by a Cu(II)-bound N-centered radical[27]. We envisioned that in the case of radical allylic amination, site-selectivity could originate from a selective hydrogen atom transfer (HAT) at the adjacent position of the carbon-centered radical (Fig. 1b) to reconstruct the alkene, rather than an alternative pathway involving single-electron oxidation and proton elimination, which could form a mixture of alkene isomers[25]. This HAT step tunable through metal catalysts[28], together with the known *anti*-Markovnikov addition of ARCs to olefins[23], could introduce high site-selectivity. Herein, we report that combining a photoredox catalyst and a cobaloxime complex (Fig. 1c) enables an oxidant-free allylic amination with alkyl amines to occur with high site selectivity (H_2 as a sole byproduct). The use of cobaloxime is crucial to forming allylic amine products in high site-selectivity that preferentially cleaves the stronger, primary allylic C−H bond.

Figure 1c summarizes selected experiments to examine the effect of cobaloxime on the reaction yield and site-selectivity. With morpholine and 2,3-dimethyl-1-butene as model reactants, we found that the combination of [Ir(dFCF$_3$ppy)$_2$(dtbpy)]PF$_6$ and [Co(dmgH)$_2$(py)$_2$]PF$_6$ led to the highest yield and exclusive site-selectivity for formation of **3** (entry 1). The use of other cobaloxime complexes either lowered the site-selectivity (entries 2 and 3) or the reaction yield (entry 4). The reaction catalyzed by metal salts other than cobalt did not afford any allylic amine product (see Table S1 for the detailed optimization).

After the initial optimization, we screened the scope of alkenes with a focus to investigate the site-selectivity. Figure 2a shows that the reaction of 1,1-disubstituted and trisubstituted alkenes bearing a methyl group and a secondary alkyl group on one of the two olefin carbons proceeded to form products from cleavage of the methyl C−H bond with consistently high site-selectivity (**3** to **8**). The site-selectivity of allylic amination of alkenes containing a methyl and a primary alkyl substituent ranged from 2.5:1 to >20:1 (**9** to **19**). The low selectivity (2.5:1) was observed in the case of 2-methyl-1-pentene, which carries a methyl and an ethyl substituent, presumably due to a small difference in steric property of the two substituents (Fig. S7). Our allylic amination method is compatible with a wide range of unactivated olefins (**20** to **37**), including various trisubstituted olefins and even a tetrasubstituted olefin (Fig. 2). Notably, numerous natural terpenes all underwent allylic amination with >20:1 diastereoselectivity (**8**, **16**, **18** and **19b**).

Next, we turned our attention to evaluate the scope of aliphatic amines in the allylic amination. Since hindered amines are valuable targets in medicinal chemistry tetramethylethylene was first chosen as the model substrate[29] (Fig. 3). The allylic amination of a wide range of functionalized secondary aliphatic amines occurred in good to high yields (**38** to **59**). This result demonstrates that our method provides a simple and rapid access to various hindered amines which are often difficult to prepare by existing

methods[18]. To show that the high site-selectivity can be achieved consistently, (-)-isopulegol was selected for subsequent evaluation of the amine scope. Both cyclic and acyclic amines underwent allylic amination with high site-selectivity (**60** to **69**). Finally, we demonstrate that our method is suitable for the late-stage amination of structurally complex and biologically active amines (**70** to **76**).

This unique mode of radical allylic amination can be extended to achieve a site- and diastereoselective amination to afford aminated limonene products via the remote primary C−H bond cleavage[30]. These compounds are of potential value considered that limonene displays unique physiological activity[31]. As shown in Fig. 4a, this amination process comprises a sequence of an *anti*-Markovnikov ARC addition to olefin, selective C−C bond cleavage, and a HAT event, ultimately leading to amination at an olefinic carbon and desaturation at a remote site. In the presence of $[Ir(dFCF_3ppy)_2(dtbpy)]PF_6$ and $Co(dmgBF_2)_2(H_2O)_2$, both a- and b-pinene were modified with various amines in high yields to afford the corresponding limonene derivatives (Fig. 4b). Since $Co(dmgBF_2)_2(H_2O)_2$ led to the highest selectivity toward the oxidative amination pathway over a redox-neutral amination pathway, it was employed in the place of $[Co(dmgH)_2(py)_2]PF_6$ (Table S3). Due to the different location of the double bond in a- and b-pinene, the reactions installed the amine at different sites (Fig. 4a&4b, **82** to **94**). Despite the radical nature of this process, the amine products were formed with excellent diastereoselectivity and complete retention of the optical purity of the starting pinene (**83**).

To provide mechanistic insights into this radical allylic amination, we first studied the interaction of cobaloxime $[Co(dmgH)_2py_2]PF_6$ with morpholine and tetramethylethylene by X-ray absorption fine structure (XAFS) spectroscopy (Fig. S1). The XAFS spectra showed that the metal center of the cobaloxime was not coordinated by either the amine or alkene. In addition, we carried out in-situ electron paramagnetic resonance (EPR) experiments to investigate whether a single electron transfer (SET) process between the photocatalyst $[Ir(dFCF_3ppy)_2(dtbpy)]PF_6$ and morpholine occurs. Under blue LED irradiation, a radical signal was observed, confirming the SET process (Fig. S2). Further spin-trapping experiments suggest that the ARC, generated from single-electron oxidation of morpholine by the photocatalyst, reacts with tetramethylethylene to yield the corresponding carbon-centered radical (Fig. S3). These sets of experiments altogether support that an amine is oxidized by the excited-state Ir(III), followed by the addition of the ARC with an alkene to generate a carbon-centered radical.

Density functional theory (DFT) calculations were conducted to reveal the origin of the site- and diastereoselectivity of the a-pinene amination process. The computed free energy profile of this process is shown in Fig. 4c, which is consistent with the proposed mechanism in Fig. 4A. The calculation shows that the radical ring-opening of the cyclobutene ring in a-pinene determines the diastereoselectivity of the overall process, and that the ARC addition to the trisubstituted olefin, though thermodynamically favored, is reversible. A close examination of the relevant transition states reveals that the steric interaction between the morpholine moiety and the axial methyl on the incipient isopropyl group caused the free energy of **TS-2b** to be much higher than that of **TS-2** ($\Delta\Delta G^{\ddagger}$ =5.0 kcal/mol), thereby leading to the high diastereoselectivity. In addition, it should be noted that the ARC addition to a-pinene olefin from the top

face (**TS-1**) is preferred over that from the bottom face (**TS-1b**), again due to the steric interaction between the amine and the same methyl group.

The high selectivity toward the cleavage of the strong, primary C−H bond in the radical intermediate **81** originates from a cobaloxime-assisted HAT process. Our computations show that the transition state (**TS-3**) for direct transfer of a methyl hydrogen to the cobaloxime is much lower in energy than that for the transfer of the methine hydrogen (**TS-4**), leading to the formation of a terminal alkene over a tetrasubstituted alkene ($\Delta\Delta G^{\ddagger}$ =7.1 kcal/mol). The bulky framework of limonene in **TS-4** is placed at the conformationally disfavored axial position of the morpholine ring due to the steric hindrance caused by the planar ligands of cobalt. Severe steric repulsion between the cobaloxime and the isopropyl group was also observed. In addition, an alternative mechanism involving β-hydride elimination from a tertiary alkyl cobaloxime complex is kinetically disfavored due to a highly distorted transition state in which the planar ligands of the cobaloxime have to accommodate the β-hydrogen. Collectively, our experimental and computational studies indicate that the site-selectivity for C−H bond cleavage, promoted by cobaloxime, is kinetically controlled and favors the formation of terminal alkene products.

We have demonstrated that a radical allylic amination process consisting of the addition of aminium radical cations to olefins and a metal-promoted HAT process, has led to the first direct coupling of alkyl amines and a remarkably wide range of olefins to prepare allylic amines with H_2 as the only byproduct. This process features a selective olefin transposition with an unusual preference to cleave primary allylic C−H bonds over other allylic C−H bonds, which is imparted by a cobaloxime complex. We believe that this method not only addresses a longstanding synthetic challenge in allylic amination of unactivated alkenes with aliphatic amines, but also should inspire advances in other, selective allylic C−H functionalizations based on the concept outlined here.

Methods

A solution of amines (0.2 mmol), unactivated olefins (0.5 mL) or aryl olefins (0.8 mmol), Ir-catalyst (1 mol%) and cobaloxime (2.5 - 5 mol%) in degased toluene (6 mL) were stirred under nitrogen atmosphere and irradiated by 3W blue LEDs at 25 °C for 9 h. After completion of the reaction, the solvent was removed under reduced pressure by rotary evaporation. Then, the solvent was extracted twice with 0.5 M HCl (20 mL). And the water phase was collected and excess sodium carbonate were added to slightly basic conditions. The resulting solution was extracted three times with CH_2Cl_2 (20 mL x 3). Then the organic phase was dried over sodium sulfate and concentrated to obtain the target product.

Declarations

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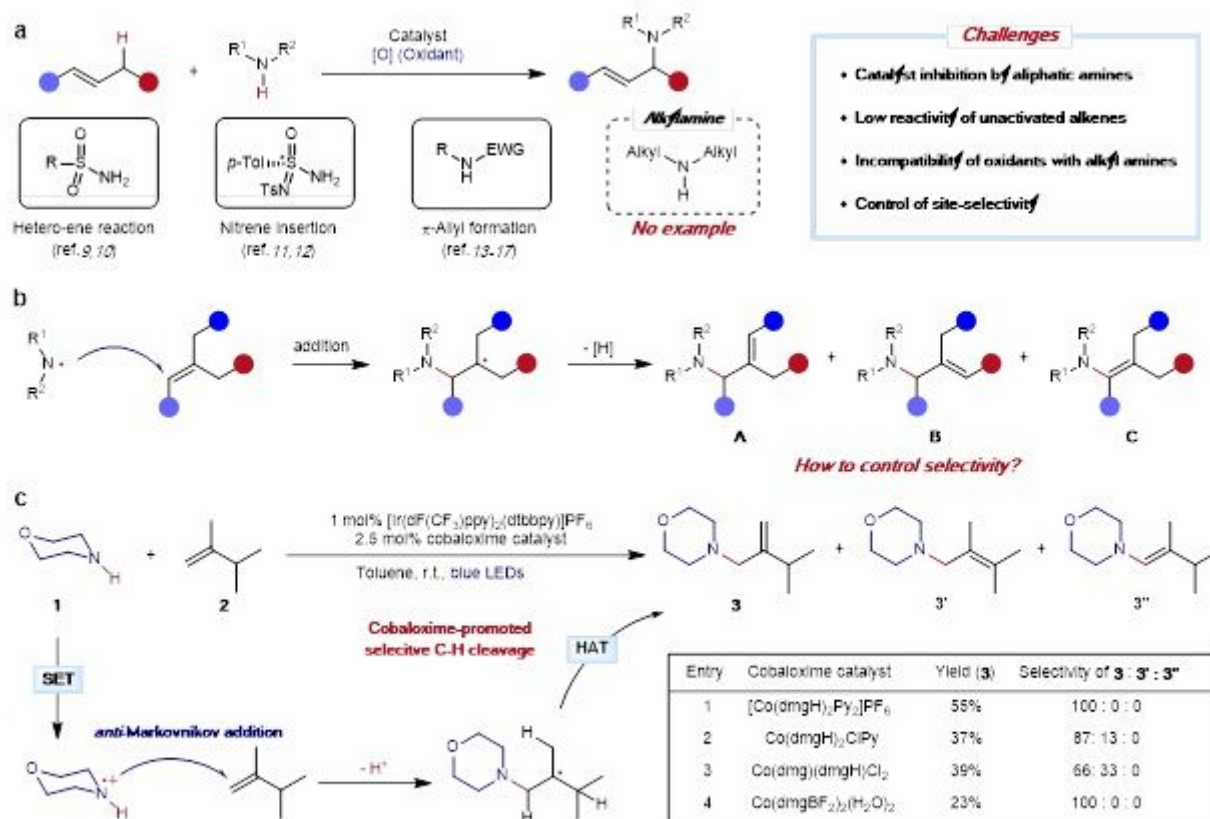
Figures

Figure 1

Evolution of strategies for allylic amination. a, State-of-the-art: representative amine sources for allylic amination of alkenes. b, Illustration of the radical allylic functionalization approach. c, This work: site-selective allylic amination via cobaloxime promoted HAT with secondary aliphatic amines.
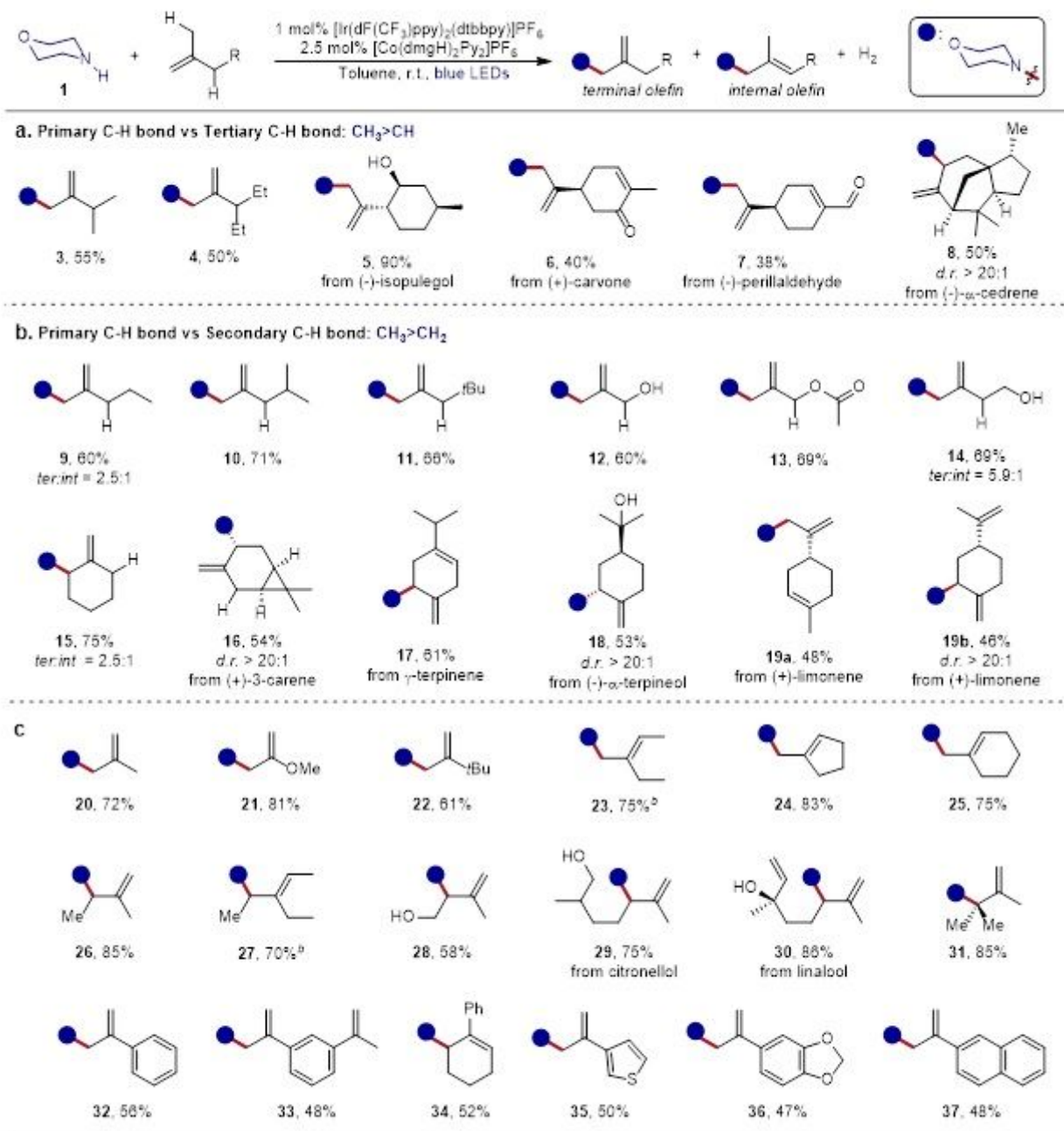
Figure 2

Scope of olefins. a, Allylic aminations of di- and trisubstituted olefins leading to selective cleavage of primary allylic C−H bonds over tertiary allylic C−H bonds. b, Allylic aminations of di- and trisubstituted olefins leading to selective cleavage of primary allylic C−H bonds over seconday allylic C−H bonds. c, Additional scope of unactivated olefins. Unless noted, single isomer was obtained. ter : int refers to the ratio of terminal alkene and internal alkene products. aE and Z mixture.
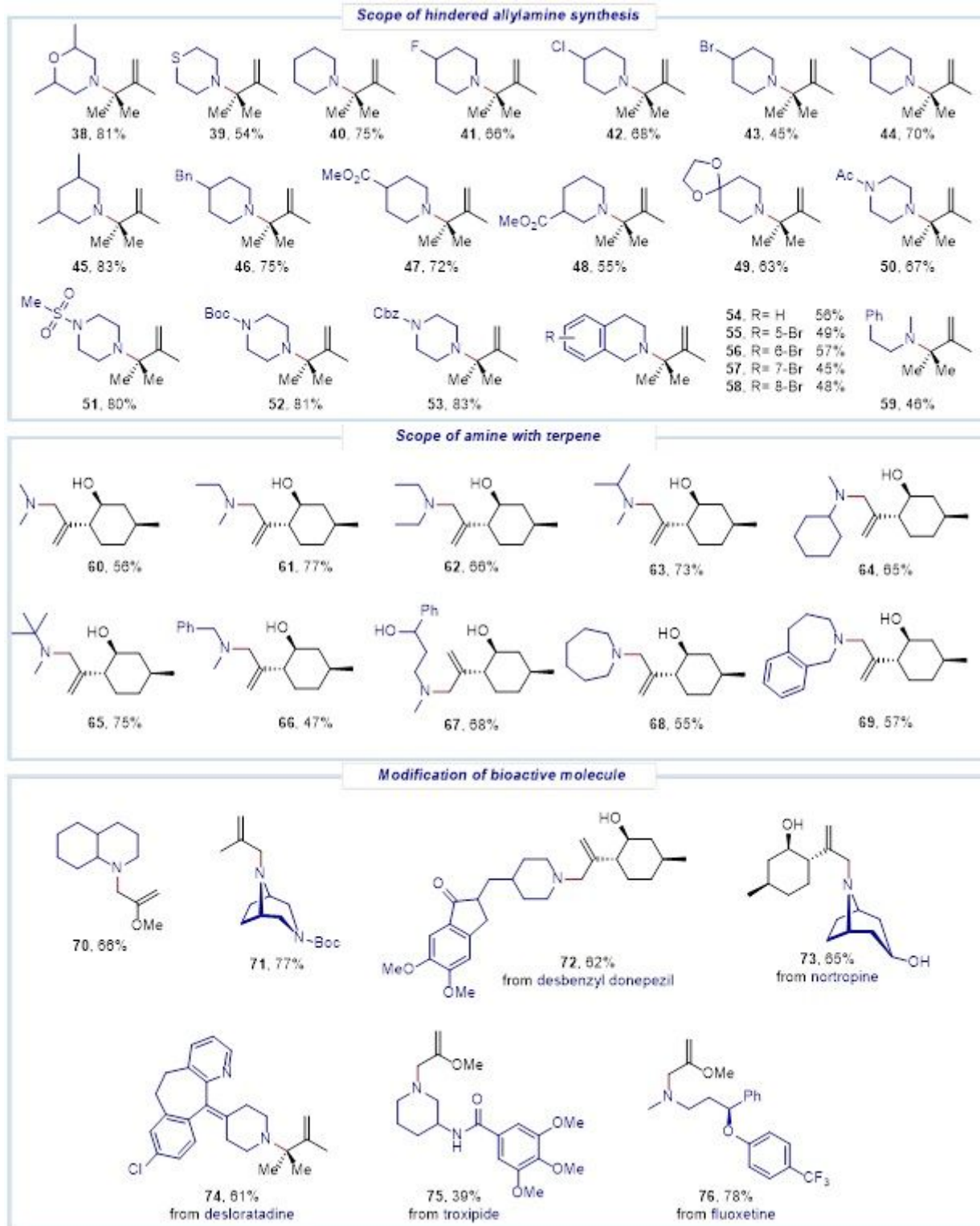
Figure 3

Scope of aliphatic amines. a, Scope for hindered allylamine synthesis. b, Scope of amine with terpenes. c, Modification of bioactive molecule.
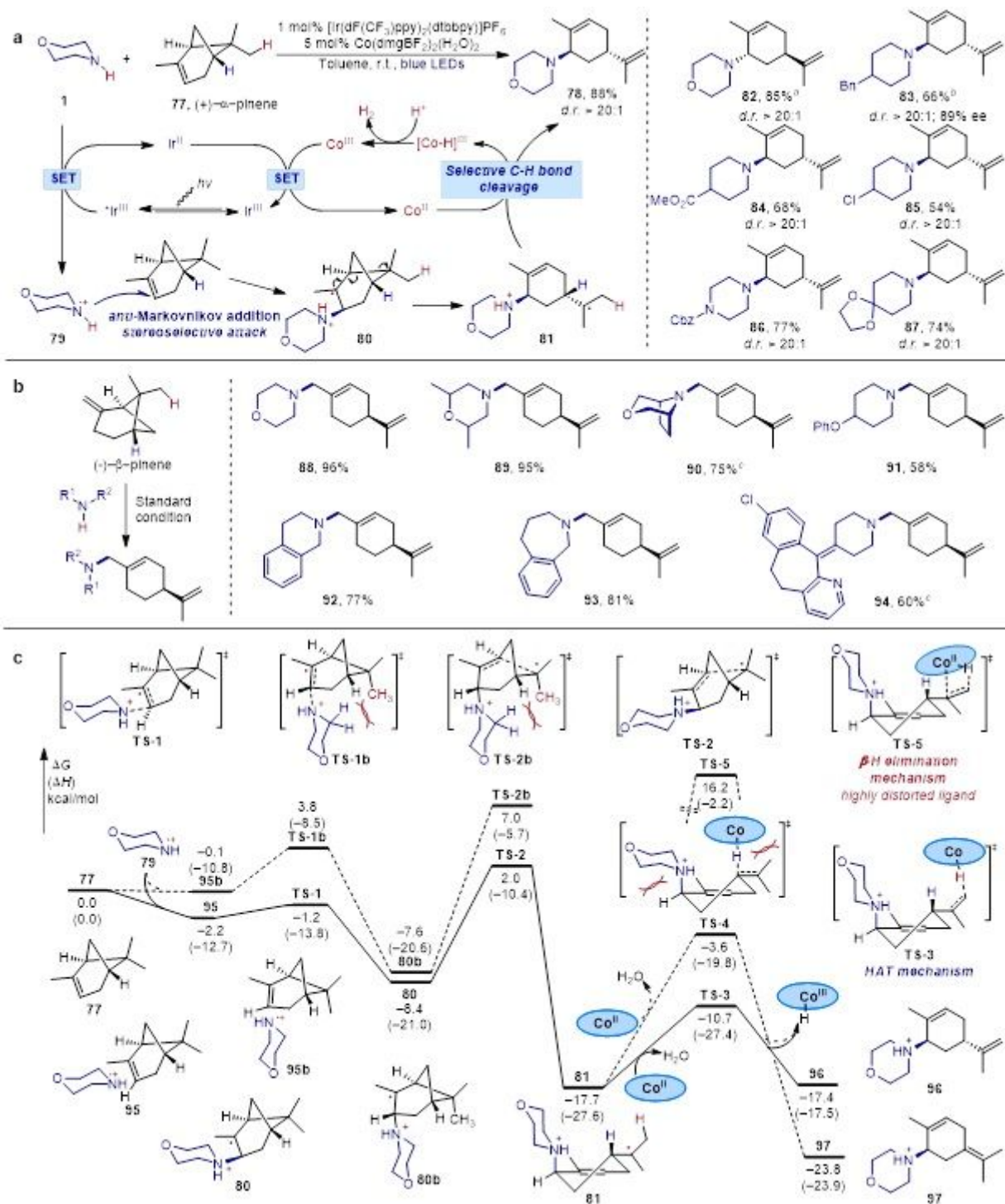
Figure 4

Site- and diastereoselective amination and remote desaturation of nature terpene. a, Reaction design and amine scope with (+)-α-pinene. a(-)-α-pinene was used. b(+)-α-pinene with 89% ee was used. b, The scope of amines with β-pinene. cIncluding 10% redox-neutral amination product. c, DFT computational profiles. Co = Co(dmgBF2)2(H2O)2.

Supplementary Files

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