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Nitromethane as a nitrogen donor in Schmidt-type formation of amides and nitriles

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The Schmidt reaction has been an efficient and widely used synthetic approach to amides and nitriles since its discovery in 1923. However, its application often entails the use the of volatile, potentially explosive and highly toxic azide reagents. Here we report a sequence whereby triflic anhydride, formic and acetic acids activate the bulk chemical nitromethane to serve as a nitrogen donor in place of azides in Schmidt-like reactions. This protocol further expands the substrate scope to alkynes and simple alkyl benzenes for the preparation of amides and nitriles.

Amides and nitriles are broadly important compounds for the synthesis of materials, agrochemicals and pharmaceuticals (*1*, *2*). The Schmidt reaction is one of the most efficient nitrogenation approaches to access amides and nitriles from aldehydes and ketones with HN_3 or alkyl azides (*3–12*). Discovered in 1923, it has been used extensively by synthetic chemists for almost a century. However, its reliance on volatile, highly toxic and potentially explosive azide reagents leaves room for further development (*13–15*) (Fig. 1A). Despite the long-standing search for hydrazoic acid replacements, the use of azide remains prevalent (*16–18*). The Beckmann rearrangement starting from oxime substrates is a well-known alternative approach to secondary amides (*19*, *20*). However, mild Beckmann rearrangements are still rare (*21*). Some specialized active oxime substrates, strong protic acid promotion, or preactivation of the hydroxyl (eg by tosylation) were usually required in classical catalytic Beckmann rearrangements (*22–25*). Moreover, traditionally, aldoximes are rarely transformed into the corresponding nitriles and *N*-unsubstituted amides (*25*).

Ideally, if one bulk and common chemical could be activated and endowed with new reactivity (*26–35*), it would promote synthetic innovation and industrial development. Due to the strongly electron-withdrawing properties of the nitro group, nitromethane has often been employed as a carbon pronucleophile in transformations such as the traditional Henry or nitroaldol reactions (*36*, *37*), cross dehydrogenative coupling (CDC) reactions (*38*) and Michael addition reactions (*39*) (Fig. 1B). In contrast, the reactivity of nitromethane as a nitrogen-donor has been scarcely developed (*40*). It was reported that the electrophilic nitroxyl species (HNO) could be generated via the *Nef* process (*41*, *42*) (Fig. 1C); however, it is rather unstable due to its quick dimerization ($k = 8\times10^6$ M^{-1} s^{-1}) to produce inert N_2O, and oxidation by O_2 ($k = 3\times10^3$ M^{-1} s^{-1}) (*43*), which therefore limit its broad application. We hypothesized that a cascade reductive activation sequence could reduce the nitroxyl species (HNO) to a hydroxylamine-derivative (NH_2OR) which would be more reductive than HNO to facilitate the condensation and the subsequent rearrangement processes for Schmidt-type reactions (Fig. 1C). Thus this cascade activation strategy would render simple bulk nitromethane a nitrogen–donor akin to azides, but with considerably less associated hazard. We report here that nitromethane can in fact donate its nitrogen to aldehydes, ketones, alkynes, and even simple alkylbenzenes, for the preparation of valuable amides or nitriles (Fig. 1D).

As a proof-of-principle study, we began our investigation by evaluating the Schmidt reaction with isobutyrophenone (**S1**) as substrate. After extensive screening (see tables S1, S2), we realized the targeted reactivity by tandem activation of the nitromethane with triflic anhydride (Tf_2O) and formic acid (HCOOH), and the desired amide product (**1**) was observed in 70% yield based on integration of nuclear magnetic resonance (NMR) spectra with HCHO and TfOH as the by-products (Fig. 2A). Four equivalents of nitromethane were sufficient to complete this transformation, while lower loading of nitromethane decreased the efficiency. Acetic acid was also crucial for the high efficiency of this transformation (see table S3).

As shown in Fig. 2B, numerous acetophenones were well-tolerated in this process and provided the corresponding Schmidt-type amide products in moderate to good yields. In particular, a free amine group (**9**) and unprotected hydroxyl (**10**) proved compatible. The trialkyl-substituted acetophenone **S26** diverged from the reactivity pattern observed with the other substrates, providing the dealkylated free

benzamide **26** in 78% yield. The reactions of unsymmetric diaryl ketones demonstrate that electron-rich aromatic rings are more prone to migrating than electron-deficient aromatic rings (see fig. S4). When we explored aldehyde substrates (Fig. 2C), it was noteworthy that the primary benzamides were obtained under the standard conditions with the formation of trace amount of benzonitriles (see table S6). Considering that a Lewis acid may promote the rearrangement of the oxime intermediate to produce benzonitrile products as in the traditional Schmidt reaction, we explored the transformations in the presence of different Lewis acids (see table S6). The reaction with the synergistic assistance of an iron(III) catalyst and Et_3N base produced the corresponding nitriles in moderate to excellent yields (up to 96%, Fig. 2C). We guess that $Fe(OTf)_3$ and Et_3N serve as a Lewis acid and a base respectively to facilitate the elimination process for the formation of nitriles (see table S6 and fig. S6). The aliphatic aldehyde (**80**) and (hetero)aryl aldehydes (**60-79**) were well-tolerated. In the absence of the Lewis acid catalyst, the reaction afforded benzamide products (Fig. 2C). The competing aromatic nitro group in (**53**, **66, 71**) was not disturbed, highlighting the high chemoselectivity of the nitromethane activation protocol.

To further extend this strategy, simple alkyne substrate which could produce ketones in situ by hydration (*44*) were investigated (Fig. 3A). A broad array of terminal alkynes could be efficiently converted to amide products. Moreover, unsymmetric internal alkynes afforded the corresponding *N*-aryl amide products with high selectivity (**85-87**, **90-92**). The alkyl internal alkyne **84** also performed well. To clarify the nitrogenation chemistry of the alkynes, control experiments and in situ IR experiments were conducted. These results indicate the corresponding ketones are possible intermediates through alkyne hydration (see fig. S5).

As part of an overarching goal of the nitrogenation of simple hydrocarbons (*45–48*), we next explored the tandem oxidative transformation of bulk commodity compounds such as alkylarenes (Fig. 3B). In this case, we tried to use the $Co/NHPI/O_2$ oxidative system (*49*) to produce the corresponding ketones and aldehydes in situ, which might enable the ensuing insertion of nitrogen by the present protocol. A variety of ethylbenzene and methylbenzene derivatives could produce the desired value-added amides by one-pot reaction with O_2 as environmentally benign oxidant and nitromethane as the nitrogen source for the nitrogen incorporation reaction. Neither purification nor isolation of the oxidized intermediate compounds was required, showing the robustness and the potential for industrial applications of this protocol.

Considering that ketone motifs are readily encountered in pharmaceutical compounds, the late-stage modification of such drugs and bioactive molecules would showcase the prospective utility of this protocol. The corresponding valuable amidated derivatives were delivered in moderate to excellent yields from structurally complex substrates containing carbonyl groups, including marketed drugs and their derivatives (**96-98**, **100-107**, **110-111**) (Fig. 3C). Muskolide (**99**), piperonyl aldehyde (**104**), purine derivatives (**109**) and binol ligands (**108**) were also efficiently modified. The methyl group in Metaxalone (**101**) could also be transformed into an amide group through the tandem oxygenation and nitrogenation sequence. The variety of tolerated functional groups further demonstrates the mildness and practicality of this protocol.

When cumene, a feedstock material of the Hock reaction for industrial phenol production, was subjected to the current protocol, amide **2** was obtained via oxidative β-scission (*50*) in 50% yield at gram-scale (Fig. 3D). Moreover, a similar reaction of cyclohexylbenzene produced amide **114** which could be further transformed to the nylon 6.6 precursor adipic acid (**115**) as well as aniline (**116**) (Fig. 3D). ε-Caprolactam (CPL), the monomer of nylon 6, could also be efficiently synthesized from cyclohexanone using this developed method. The products were isolated by direct recrystallization after a routine work-up procedure without column chromatography (Fig. 3E). The synthetically challenging macrocyclic lactam **84** was also easily prepared by this protocol. Moreover, long-chain aliphatic ketone **120** and 7-membered cycloketone **122** were also compatible with this transformation.

The alkyl substituent of the nitro group is necessary to this transformation, as shown in Fig. 4A: when the nitromethane was replaced with nitrobenzene, the reaction did not proceed. The reactivity dependence on alkyl groups was ordered as follows: primary carbon > tertiary carbon > secondary carbon (fig. S2). A measured kinetic isotope effect (KIE) of K_H/K_D = 3.6 suggests that the C(sp^3)-H bond cleavage of nitromethane might be involved in the rate-determining step of the reaction (Fig. 4B, fig. S3). Further study by ^1H NMR spectroscopy indicated that HCOOH is required for the second activation step (see fig. S7). In order to identify the actual active N donor species in this protocol, a HRMS capture experiment was carried out. Excitingly, an acetylated hydroxylamine (NH_2OAc) intermediate and its salt (NH_2OAc·HOTf) were detected by HRMS (fig. S8). Further control experiments suggest that these serve as the actual nitrogen-donor of this system (see supplementary materials). Meanwhile, these results demonstrate that the AcOH is also crucial in this transformation playing a role not only a solvent but also a reagent. Inspired by the traditional *Nef* reaction and our findings, we propose the mechanism in Fig. 4C. Initially, nitromethane is activated by Tf_2O, forming the high electrophilic imine species **II**. Subsequently, the reaction of intermediate **II** with H_2O forms hemiacetal intermediate **III**, which then undergoes intramolecular C-N bond cleavage to liberate HCHO (*41*, *42*) and **IV.** The active HNO species **V** forms after

the elimination of HOTf from **IV**. Finally, the high oxidation state of HNO species **V** is selectively reduced by HCOOH to give an active *N*-donor species **VI** (NH_2OAc·HOTf or NH_2OAc) which was detected by HRMS. Over-reduction is suppressed by the use of HCOOH as a reductant with moderate reducing capacity (*51*). The starting materials then react with active **VI** to form the final products probably through the fast Beckmann-type rearrangement of the corresponding oximes **VII** (Fig. 4C).

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SUPPLEMENTARY MATERIALS

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Materials and Methods
Supplementary Text
Figs. S1 to S8
Tables S1 to S6
Spectral Data
References (*52–109*)

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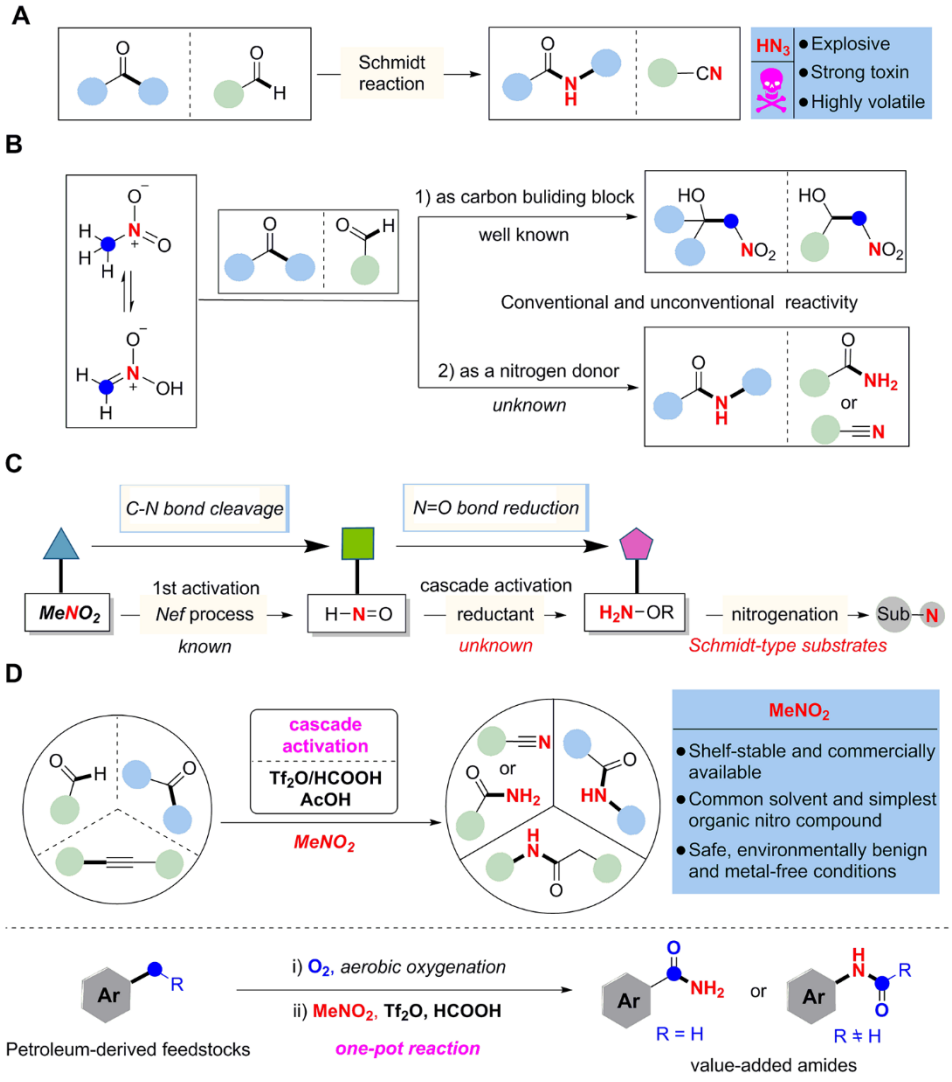

Fig. 1. Nitromethane activation for use in the Schmidt reaction. (A) The long-standing drawback of traditional Schmidt reaction with azide as the limiting reagent. (B) Reactivity patterns of nitromethane. (C) Proposed cascade activation strategy for the discovery of distinct reactivity of nitromethane inspired by the *Nef* process: activation of nitromethane to oxidation-state matchable species endowed with Schmidt-type reactivity. (D) This work: direct nitrogenation of aldehydes, ketones and alkynes, as well as the aerobic oxidative nitrogenation of alkylarenes with nitromethane.

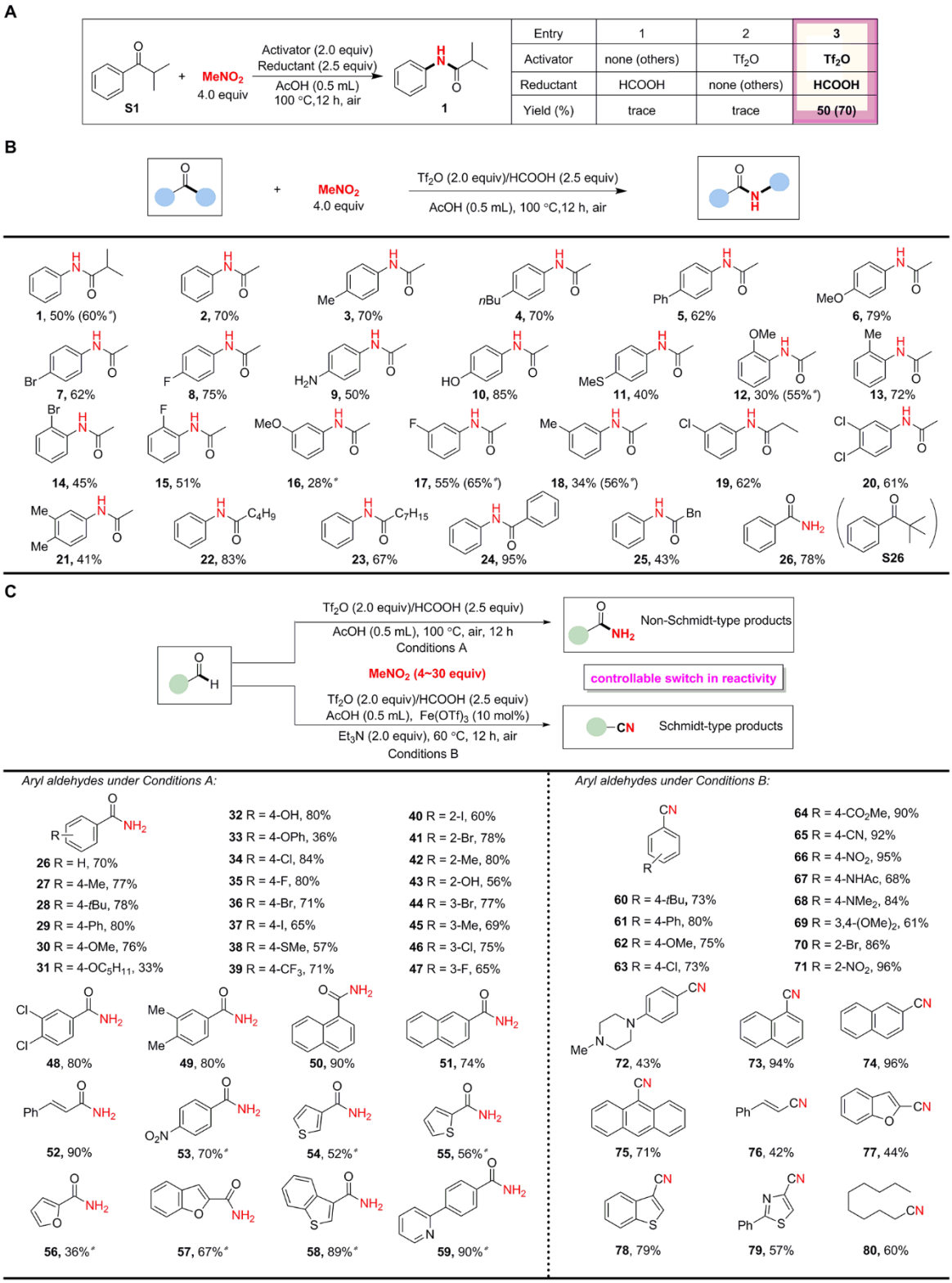

Fig. 2. Substrate scope of ketone and aldehyde derivatives. (**A**) Screening of the activator and reductant for the nitromethane activation. Reaction conditions: **S1** (0.3 mmol), $MeNO_2$ (1.2 mmol), activator (0.6 mmol), reductant (0.75 mmol) in AcOH (0.5 mL) at 100°C for 12 hours under air. The yield of amides in parentheses was determined by ^1H NMR analysis. For details, see supplementary materials: (**B**) Substrate scope of ketones. (**C**) Substrate scope of aldehydes. For details, see supplementary materials. * $MeNO_2$ (9.0 mmol) was used.

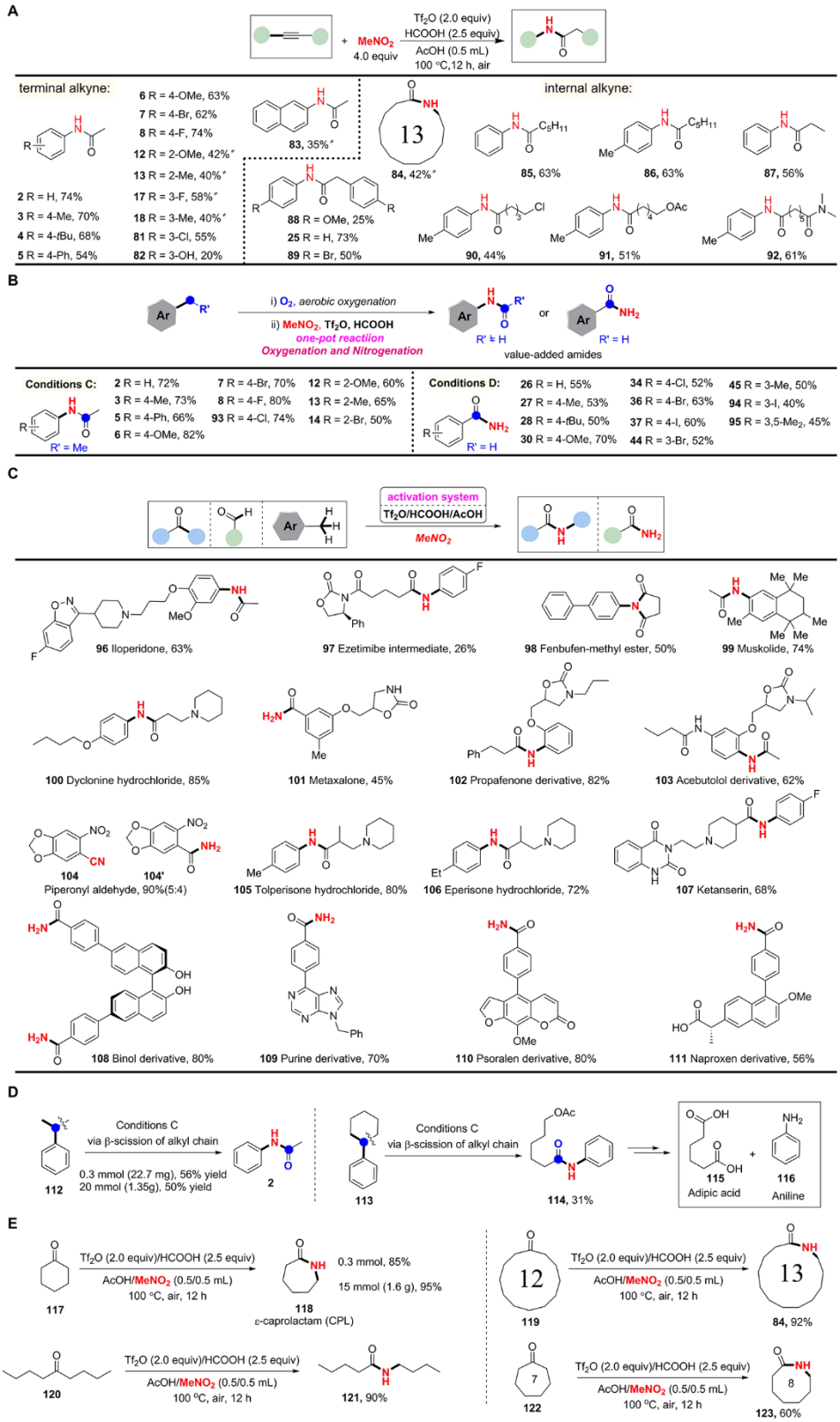

Fig. 3. Further synthetic applications. (**A**) Substrate scope of alkynes. (**B**) Nitrogenation of simple alkylarenes: Conditions C: ethylbenzene (0.3 mmol), $Co(OAc)_2•4H_2O$ (0.015 mmol), N-Hydroxyphthalimide (0.03 mmol) in AcOH (0.5 mL) were stirred at 80°C for 12 hours under 1atm O_2, then $MeNO_2$ (9.0 mmol), Tf_2O (0.6 mmol), HCOOH (0.75 mmol) were added and stirred at 100°C for 12 hours under air. Conditions D: methylbenzene (0.3 mmol), $Co(OAc)_2•4H_2O$ (0.006 mmol), N-Hydroxyphthalimide (0.03 mmol) in Hexafluoroisopropanol (0.6 mL) were stirred at room temperature for 12 hours under 1 atm O_2, then $MeNO_2$ (9.0 mmol), Tf_2O (0.6 mmol), HCOOH (0.75 mmol), AcOH (0.5 mL) were added and stirred at 100°C for 12 hours under air. (**C**) The late-stage modification of drugs or bioactive molecules. (**D**) Gram-scale reaction with cumene and cyclohexylbenzene. (**E**) ε-Caprolactam (CPL) and macrocyclic lactam synthesis from cyclic ketones.

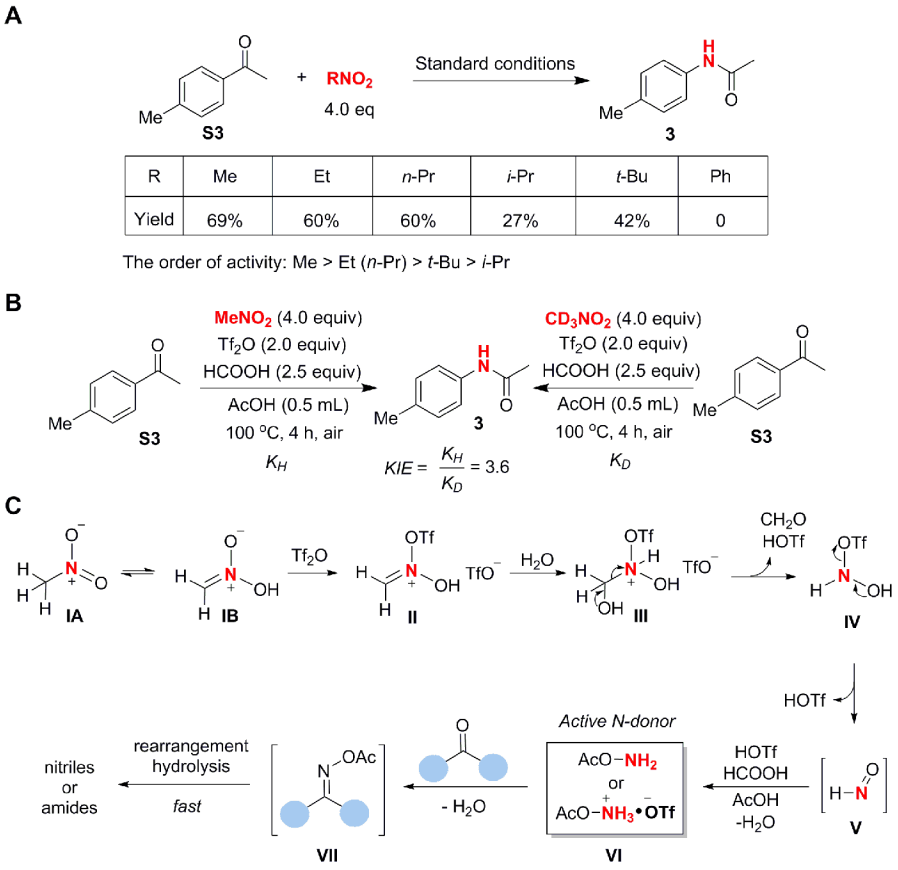

Fig. 4. Mechanistic experiments and proposed mechanism. (A) The structure-reactivity relationship of nitroalkanes. (B) Kinetic isotope effect study. (C) Proposed mechanism.

Nitromethane as a nitrogen donor in Schmidt-type formation of amides and nitriles

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