Migrative Reductive Amination of Ketones Enabled by Multitasking Reagents

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Abstract

Skeletal editing and "single-atom logic" are emerging strategies that accelerate compound synthesis and open new chemical space by modifying organic molecules using unconventional bond forming processes. These new strategies are particularly attractive to access important biologically active classes of compounds, such as secondary amines, which are key synthetic intermediates and components found in numerous pharmaceutical agents. Herein, a practical modification of the classical reductive amination of ketones and aldehydes, a staple reaction in drug discovery research, was developed to provide isomeric amines by way of a migratory reductive amination (MRA). This one-pot method combines three distinct chemical reactions in a single flask, without solvent changes, via the orchestrated addition of two inexpensive and non-toxic multitasking reagents: Zn(II) salts and a hydrosilane. Both reagents display exceptional orthogonality with a synergetic role in all three stages of the process, lending a procedure that embodies many of the ideals of green chemistry. This MRA method demonstrates a wide scope of acyclic and cyclic ketones and aldehydes with aliphatic or aromatic groups, including complex molecules such as drug intermediates and natural products with an exceptionally low E factor compared to established methods. Remarkably, MRA enables the expeditious preparation of cyclic secondary amines of varying ring size, including a cyclopentanone-to-piperidine ring-edit that provides a direct access to the most common saturated heterocycle in drug discovery.

Introduction

Amines are a ubiquitous functional group present on the structure of a large number of natural products (e.g., alkaloids) and other biologically occurring compounds such as amino acids. Countless synthetic commodity chemicals and as many as 62% of bioactive molecules embed an amine-containing substructure (Figure 1A).[1] Although other methods exist to prepare amines, the process of reductive amination (RA) of carbonyl compounds stands out as one of the staple reactions of organic chemistry that ranks amongst the top-ten most employed chemical reactions in medicinal chemistry.[2,3] Reductive amination is a two-stage transformation involving first, a condensation between the carbonyl compound and the amine, followed by reduction of the imine or iminium intermediate typically with a hydride reagent.[4] It can often be achieved in "one-pot",[5] enabling the predictable formation of primary, secondary, and tertiary amines without altering the skeleton of the starting ketone or aldehyde (Figure 1B). As exemplified by recent advances in "skeletal editing" or "single atom logic", transformations that provide a rearrangement of the existing carbon framework are rare and highly desirable tools to accelerate organic synthesis and expand chemical space.[6-9] By providing isomeric amine products with a rearranged carbon skeleton featuring the formal insertion of a nitrogen atom into a C–C bond, the process of migrative reductive amination (MRA) would provide a powerful complement to the classical reductive amination. The resulting secondary amines are particularly attractive products that can be readily transformed into a tertiary amine or other functional groups (amide, sulfonamide, etc.). With cyclic ketones, MRA would enable a unique ring expansion to afford medium- and large-sized cyclic amines, including the cyclopentanone-to-piperidine ring edit affording, in a single operation, the most utilized non-aromatic heterocycle in drug development.[10]

The design of a MRA reaction requires the insertion of a nitrogen atom into a carbon–carbon sigma bond. This type of 1,2-carbon-to-nitrogen electrophilic migration can be achieved by way of a Beckmann rearrangement of oximes to amides.[11,12] The latter can subsequently be reduced to the desired amines. However, starting from ketones, this entire sequence requires three distinct reactions that usually necessitate individual isolations and purifications of the respective oxime and amide intermediates (Figure 1C). The first two steps of oxime formation and rearrangement are rarely performed in a one-pot protocol.[13-18] Likewise, few examples exist of the one-pot reductive Beckmann rearrangement wherein the amide product of an oxime substrate is reduced in situ to an amine, and typically employ harsh reductants and air-sensitive Lewis acid activators.[19-22] Although

an elegant procedure was recently described, it resorts to the use of an air-sensitive catalyst and its demonstrated scope is limited to the preparation of tertiary aromatic amines.[23] There is currently no practical and general MRA method enabling access to a wide scope of secondary amines from ketones that can circumvent solvent exchange and intermediary purification operations.

Despite innovations in green chemistry enabling technologies such as continuous-flow synthesis,[24] electrosynthesis,[25,26] and solid-state (mechanochemical) synthesis,[27] the multi-step synthesis of an organic molecule is commonly executed by repeating a series of three consecutive operations consisting of: reaction, workup, purification. This approach can be time- and energy-consuming. Moreover, solvents used in reactions, filtrations, and purifications are responsible for the largest mass contribution to the unfavorable E-factor in pharmaceutical processes.[28] Excessive or unnecessary purification of intermediates results in significant solvent waste, thus deviating from the principles of green chemistry.[29] To address this quandary, the concept of "one-pot" synthesis provides an opportunity for telescoping the above operations while reducing time and solvent consumption by avoiding filtrations and solvent exchanges.[30,31] In addition to embracing the notions of green chemistry, an ideal one-pot reaction would employ the sequential addition of minimal non-toxic reagents that are not only mutually compatible, but also active and even synergetic in all stages of the process – "multitasking reagents". The step-economical telescoping of intermolecular reactions is challenging as it requires the successive addition of various reagents that may prove detrimental to subsequent operations owing to incompatibilities between other reagents, intermediates, or with the universal solvent employed. Key issues involve the selection of a non-reactive solvent capable of maintaining a homogenous solution throughout the sequence of reactions, the selection of safe and non-toxic reagents, and the possible need to eliminate by-products or excess reagents that are incompatible with subsequent reagents. In this scenario, a multitasking reagent can perform multiple roles; when added at the initial stage of a telescoped reaction, it can serve a specific task as an activator or a neutralizer, and play similar or different task in subsequent stages of the process. Herein, we describe a general synthesis of secondary amines by an operationally simple and practical one-pot migrative reductive amination of ketones and aldehydes enabled by the exceptional efficiency and concerted action of mutually compatible, multitasking reagents.

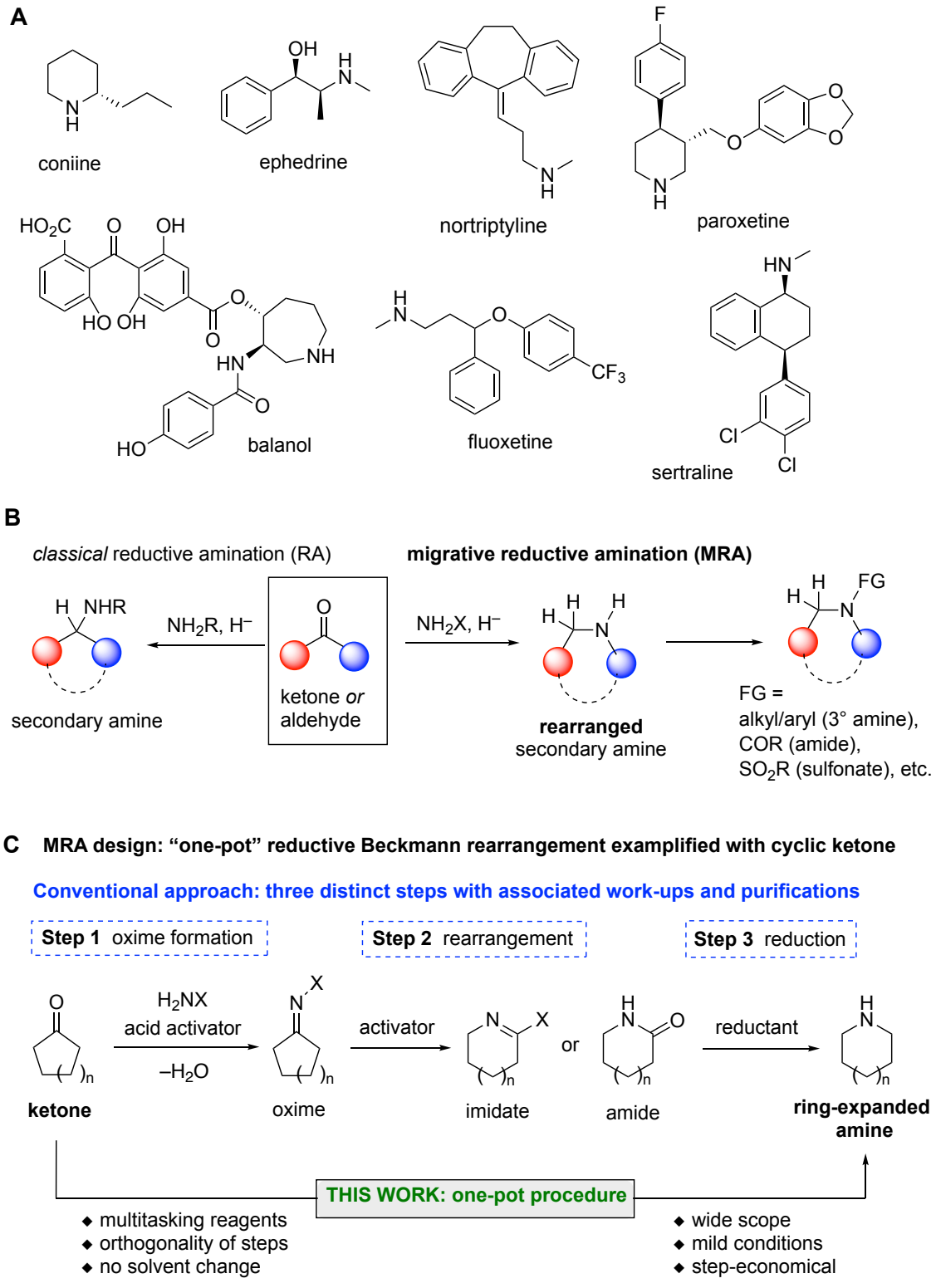

Figure 1. Synthesis of secondary amines. **A**. Examples of biologically relevant natural products and therapeutic drugs containing a secondary amine. **B**. Representation of classical reductive amination (RA) and the migrative variant (MRA). **C**. Design of a one-pot MRA of ketones.

Results and Discussions

Identification and optimization of reaction conditions with two model ketones

To achieve the challenging objective of telescoping three chemical reactions into a one pot MRA, we sought to identify a solvent and a set of reaction conditions with reagents that would be mutually compatible and possibly display synergetic effects. Mechanistically, some of the challenges include: the possible detrimental effect of water released in the first stage of oxime condensation; heterogeneous reaction mixtures; competitive reduction of the unreacted ketone or oxime intermediates; catalyst poisoning, or reaction of the amine product with electrophilic activators used in the rearrangement. Thus, without any intermediate purification operations or change of solvent, we systematically combined some of the most common and mildest reported procedures for each of the individual stages of dehydrative oxime formation, Beckmann rearrangement, and reduction (Figure 2, see Supporting Information for details). In order to afford a practical benchtop procedure, conditions employing highly air- or water-sensitive reagents and catalysts were disregarded. Possible solvents that are deemed to be attractive on the standpoint of green chemistry were selected.[32] Two representative substrates were designated: cyclopentanone serves as a model cyclic ketone, and 4-fluoroacetophenone as a representative acyclic aromatic ketone. The respective subclasses of products, a cyclic amine and a *N*-alkyl aniline, are prominent and valued in drug discovery.[1] After setting up the initial stage of oxime formation, reagents and additives for the second and third stage were added successively using temperatures and reaction times commensurate with reported conditions (see Supporting Information for details).

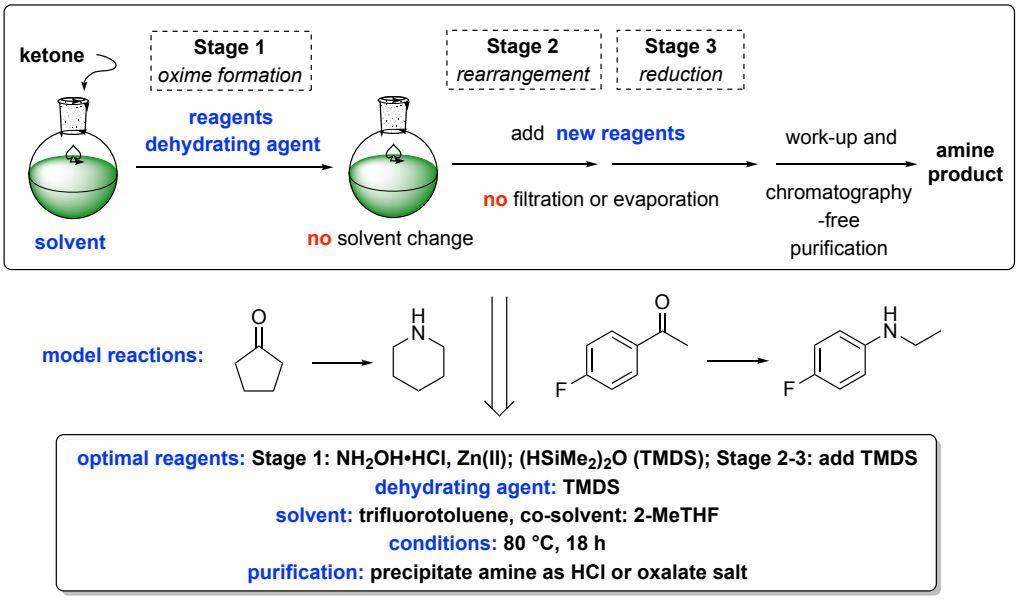

Figure 2. Discovery strategy and optimization outcome for a one-pot MRA procedure.

The first round of screening unveiled Zn(II) salts and hydrosilane reagents in trifluorotoluene as the most promising set of conditions providing good yields with both model substrates. Further fine-tuning of the identity of both the Zn(II) salt and hydrosilane was accompanied by a study of various reaction parameters such as reagent stoichiometry, time, order of addition, additives (e.g., dehydrating agent), co-solvent, and finally, workup and isolation procedures (see Supporting Information for details). The optimal procedure shown in Figure 2 consists in forming the ketoxime by the *in situ* generation of Crismer's salt (dichlorobis(hydroxylamine)zinc(II),[33] a source of neutral hydroxylamine generated through the combined action of ZnO, a basic Zn(II) salt), and NH_2OH•HCl in trifluorotoluene. $ZnCl_2$ was chosen as a Lewis acid accelerant for the oximation because it is amongst the cheapest, mildest, and most commercially accessible zinc salts. Additionally, it is easily prepared and handled as a 2 M $ZnCl_2$·$(2MeTHF)_3$ solution in trifluorotoluene that can be employed as is for the first stage of oxime formation. One challenging aspect of the one-pot procedure was to eliminate the deleterious stoichiometric amount of water from the *in situ* formation of the Crismer's salt and its ensuing condensation with the ketone prior to the second stage (rearrangement). Addition of conventional drying agents (molecular sieves, $CaCl_2$, etc.) and distillation procedures (Dean-Stark) were not effective (see Supporting Information for details). Since a hydrosilane reagent would be needed to promote the reduction stage and possibly participate in the rearrangement stage, we tested the use of a sacrificial amount of hydrosilane as an irreversible dehydrating agent. Indeed, it is known but seemingly underexploited that hydrosilane reagents readily hydrolyze under acidic and basic conditions to form hydrogen gas and inert polymeric side-products.[34] Satisfactorily, the addition of 1,1,3,3-tetramethyldisiloxane (TMDS) successfully purged the water in the reaction mixture within an hour in the presence of Zn(II) salt. Gas evolution was observed upon addition of the hydrosilane, and the cyclic siloxane by-product was formed (observed by LC-MS and GC-MS). Notably, both TMDS[35] and trifluorotoluene[36] are viewed as safe alternatives compared to other reductants and solvents. The following two stages of the optimal procedure are executed simply through adding more TMDS (3 equiv). Both of these stages (rearrangement and reduction) are accelerated in the presence of Zn(II) (*vide infra*). It is especially noteworthy that the overall benchtop reaction procedure is operationally simple and neither a distilled solvent or inert atmosphere is required. Since the reaction by-products include hydrogen gas, zinc chloride salt, and siloxane polymers, the reaction workup is straightforward and does not require any chromatographic purification. While zinc salts and any unreacted oxime can be

extracted into the basic aqueous layer, the non-polar siloxane impurities and unreacted ketone remain in the organic solvent from which the amine product is precipitated as a highly pure salt.

Reaction scope

The optimized MRA conditions were applied to a range of structurally diverse ketones with different types of groups flanking the carbonyl. As shown in Figure 3, a series of acetophenones and other aryl-alkyl ketones (products **1**–**16**) bearing various substituents on the aryl ring provided the expected amine products, with most examples isolated in good to excellent yields. Naphthyl and heterocycle-containing ketones afforded the expected amines **17**–**20**. In the few low-yielding examples, such as product **8**, losses are caused by incomplete oxime formation or rearrangement, as well as difficult purification by salt formation. The position of the substituent on the aryl ring did not significantly influence the reaction outcome (e.g., **2** vs **4, 9** vs **11**). Furthermore, methoxy (**2**), thioether (**6**), and trifluoromethyl (**8**) substituents and a sulfone (**7**) functional group are tolerated, and no dehalogenation product was observed with either 4-fluoro- or 4-iodoacetophenones (**3**, **5**). Indanones provided the desired tetrahydroquinoline products (**21**–**25**) in high yields. In all cases, the major migration product is the *N*-alkylaniline regioisomer, with tetrahydroisoquinoline being the only side-product. Larger ring systems are also amenable to this MRA method (**26**, **27**). Benzophenones (**28**–**31**) react smoothly to afford the corresponding amine salts in 51–78% yields, albeit unsymmetrical examples are subject to the intrinsically modest regioselectivity of the rearrangement stage.

The MRA is compatible with aliphatic (alkyl-alkyl) ketones, with acyclic substrates affording products **32**–**39** in moderate to good yields. In the few cases where a minor regioisomer is observed, the predominant isomer is rationalized based on established migratory aptitudes.[11,12] As shown with product **39**, the preferential migration of a bulky tertiary alkyl group may lead to reduced yields. Surprisingly, benzylacetone (**36**) resulted in a crude mixture containing the rearranged amines (13 % and 63 %) along with a primary amine (24%), the non-rearranged side-product of a normal reductive amination arising from oxime reduction and N–O bond hydrogenolysis. To avoid a challenging and solvent-wasting chromatographic separation that would increase the reaction's E-factor, an operationally simple and novel method for the separation of primary and secondary amines was developed. It involves scavenging the primary amine via Schiff base formation with salicylaldehyde during the extractive workup,[37] followed by precipitation of the unreacted

secondary amines as the oxalate salt (see Supporting Information for details). This purification procedure is possible because of the difference in pK_a values between protonated secondary amines (~10) and the Schiff base (~5–7), enabling a selective salting of the desired amine product.

Alicyclic ketones of all sizes, including the cyclopentanone to piperidine ring-edit (**41**), can be transformed in high yields into the corresponding ring-enlarged cyclic secondary amines **40**-**49**. Medium- and large-ring cyclic amines such as **42**-**47** would be difficult to synthesize in such a straightforward manner using alternative approaches. For example, azacyclohexadecane **47** was previously prepared from cyclopentadecanone in three steps, each requiring isolation of the intermediates.[38] Similarly to the benzylacetone substrate **36**, the primary amine side-product of oxime reduction was observed in varying amounts. Nevertheless, the salicylaldehyde purification procedure was successfully applied to all alicyclic substrates exclusively yielding secondary amine products in good yields. Finally, as shown with product **50**, aldehydes are suitable substrates affording the rearranged methylated amines. This MRA procedure is incompatible with a number of unsaturated functionalities, such as carboxylate, nitrile, and nitro functional groups. Substrates bearing a free amino group resulted in precipitation during the oxime formation step, which caused a low conversion.

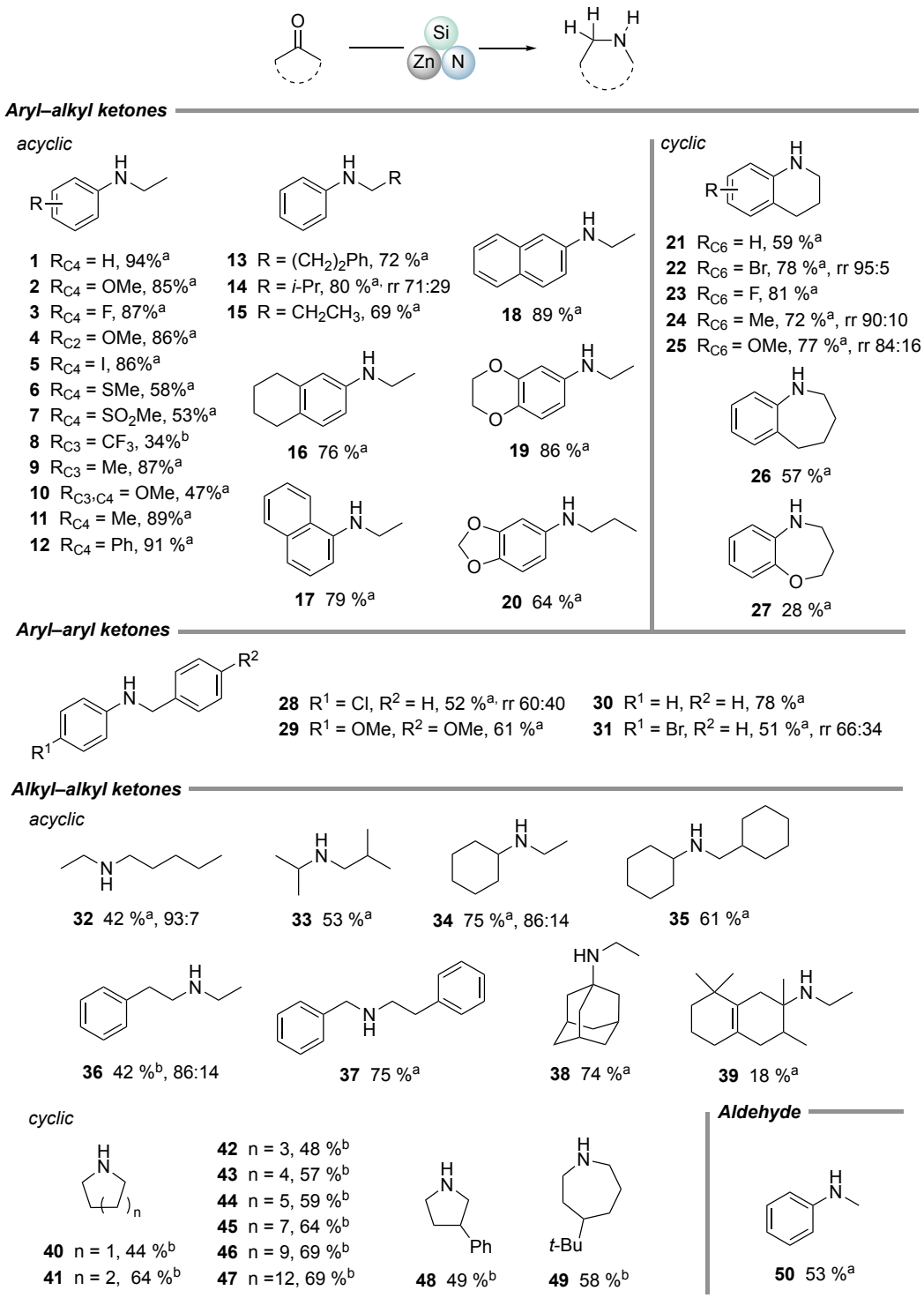

Figure 3. MRA substrate scope (Part 1). All yields are isolated products as hydrochloride[a] or oxalate[b] salts. Unless noted, rr > 95:5 ***i. Oximation stage***: 0.5 mmol ketone (1 equiv), 0.5 mmol $NH_2OH{\cdot}HCl$ (1 equiv), 0.25 mmol ZnO (0.5 equiv), 0.25 mL 2M $ZnCl_2{\cdot}$(2-methyltetrahydrofuran)$_3$ (1 equiv) in trifluorotoluene, 80 °C, 15 minutes — 1 hour; ***ii. Dehydration***: add 0.75 mL trifluorotoluene, 0.18 mL 1,1,3,3-tetramethyldisiloxane (2 equiv), 80 °C, 1 hour; ***iii. Rearrangement and reduction stage***: 0.27 mL 1,1,3,3-tetramethyldisiloxane (3 equiv), 18 hours. Abbreviations: **Si**: $HSiMe_2OSiMe_2H$ (TMDS), **Zn**: ZnO + $ZnCl_2$, **N**: $NH_2OH{\cdot}HCl$. rr: regioisomeric ratio.

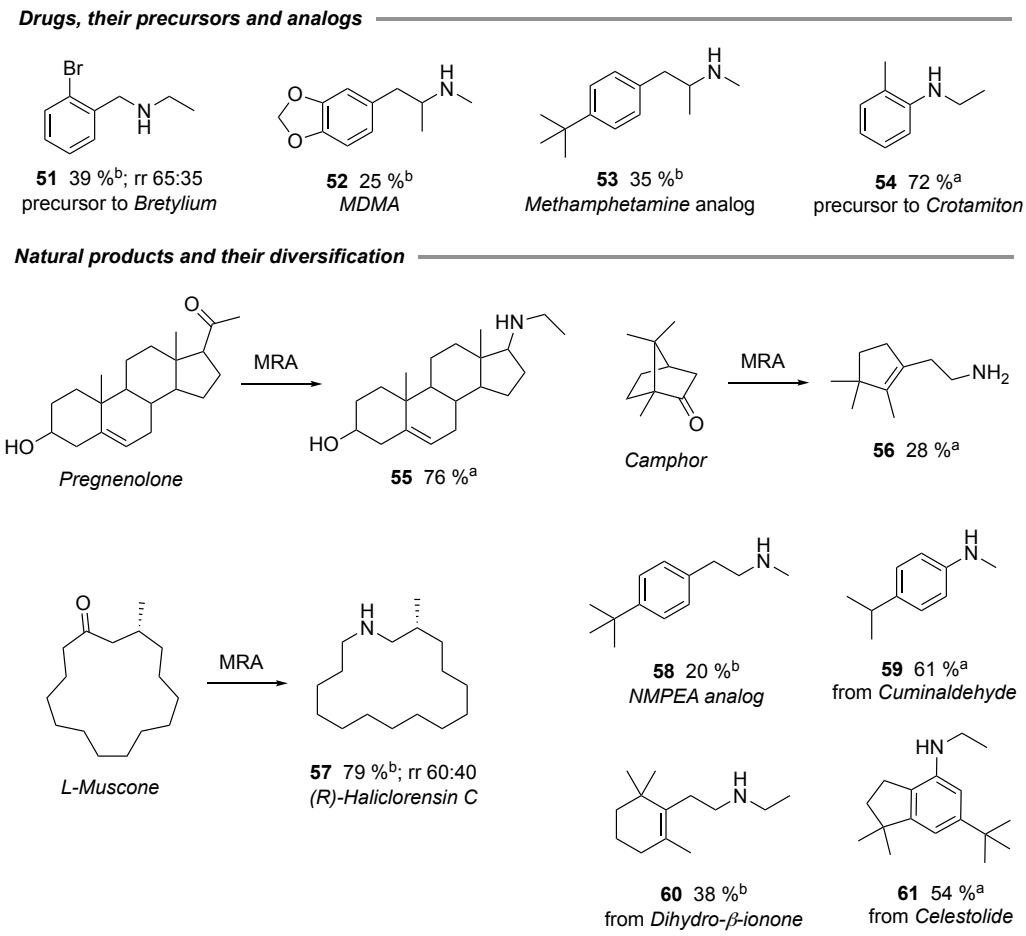

Figure 4. MRA substrate scope (Part 2). See Figure 3 legend for conditions.

The one-pot MRA procedure was successfully extended to more complex substrates, including pharmaceutically relevant ketones and aldehydes (**51**–**54**) and naturally occurring ones (**55**–**61**) (Figure 4). For example, the high-yielding MRA of pregnenolone further confirms the compatibility of functional groups like a secondary hydroxy and a free alkene. Camphor afforded an expected reduced Beckmann fragmentation product, **56**, in low yield.[39] It must be emphasized that many of the amine products herein are novel. In most examples where the products are known, the literature preparation is accomplished via a three-step oximation-rearrangement-reduction sequence often under harsh reaction conditions requiring numerous purification operations.

To demonstrate the practicality and applicability of the one-pot MRA, a saturated 13-membered macrocyclic amine precursor to the anti-invasive marine natural product, motuporamine A[38] was prepared on a gram scale in a flask open to air (Figure 5). Green chemistry metrics[40] of the traditional three-step protocol (oximation, rearrangement, and reduction)[38] and other reported

syntheses of **46**[41,42] were compared with the developed MRA procedure on a gram-scale. Although the three-step and one-pot MRA methodologies provide a similar overall yield, the E-factor and process mass intensity (PMI) metrics are more than six times better for the one-pot procedure. Likewise, the improved atom economy (AE) and the reaction mass efficiency (RME) parameters demonstrate the significant improvement in "greenness" provided by the MRA method.

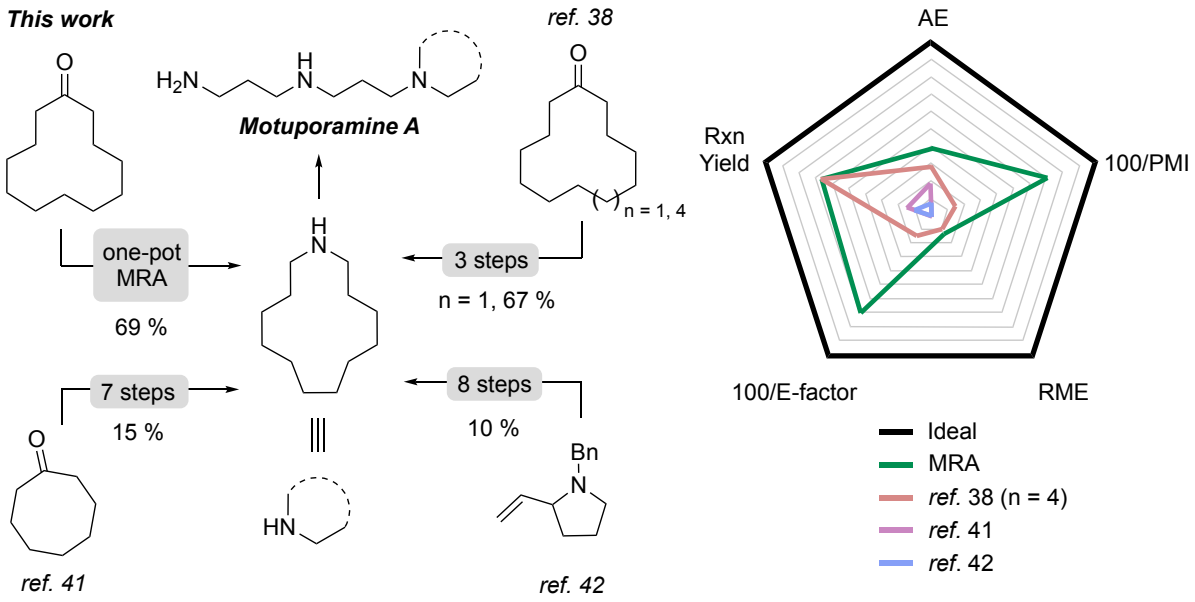

Figure 5. Gram-scale synthesis and green chemistry metrics for a macrocyclic motuporamine A precursor comparing the MRA and other approaches. See Figure 3 legend for MRA conditions.

Mechanistic studies

The combination of Zn(II) salts with a hydrosilane reductant has previously been exploited in the telescoping of two reactions into a one-pot process.[43] In this example, Denton and coworkers elegantly merged the dual-reactivity of hydrosilanes in a reductive amination of carboxylic acids that combines the two formal steps of amidation and amide reduction. To the best of our knowledge the combination of Zn(II)/hydrosilane combination has never been employed in the successful telescoping of molecular rearrangements or any processes merging three distinct reactions.

To gain an insight into the workings of this unique one-pot MRA reaction and the role of each reagent, a series of exclusion experiments were designed using 4-fluoroacetophenone as the substrate (see Figure 6A). As expected, the rearranged amine product cannot be obtained from either a ketone or oxime substrates without $ZnCl_2$ present in the system (***i***). Likewise, without the addition of TMDS for dehydration following the oximation stage, little amine product forms (27%

vs 87%, ***ii***). Furthermore, for full conversion of oxime to amine, two equivalents of TMDS (i.e., 4 equiv. SiH) are necessary, with a single equivalent affording only half of the product (***iii***).

To determine whether the reaction occurred via the proposed Beckmann rearrangement or via a Stieglitz rearrangement (i.e., inverted reduction and migration: oxime reduction followed by rearrangement of the resulting hydroxylamine),[22,44] a comparison of migratory aptitudes was performed on phenyl isopropyl ketone and the corresponding hydroxylamine (Figure 6A). As expected for a classical Beckmann rearrangement,[11] under standard MRA conditions the isolated amine isomer ratio is relatively close to the oxime's E/Z isomeric ratio (***iv***), whereas starting directly from the hydroxylamine intermediate results almost exclusively in a single product regioisomer (***v***). Moreover, silylated oxime, which is suspected to form in the presence of excess TMDS[22] and was observed by DART-HRMS, was shown to undergo the Beckmann rearrangement under standard MRA conditions affording the corresponding amide isomers in the expected ratio (***vi***). In contrast, the free oxime does not react with Zn(II) alone (***vii***), further supporting the essential role of TMDS in the rearrangement stage. Altogether, these experiments favor a mechanistic sequence involving the Beckmann rearrangement of a silyl oxime ether,[45] wherein two multitasking reagents are required in all three stages. The Zn(II) ion is essential as an oxophilic Lewis acid promoting all three stages of oxime formation, rearrangement, and amide reduction. In turn, the hydrosilane TMDS serves an essential role as a dehydrating agent in the stage of oxime formation, as an activator forming a silylated oxime to promote the second stage of rearrangement, and as the reductant in the final stage yielding the rearranged secondary amine product. A similar pathway involving the Stieglitz rearrangement of a silylated hydroxylamine may compete with certain substrates, as hinted in the reaction of alkyl-alkyl ketones that provide unrearranged primary amine as a minor side-product (*vide supra*).

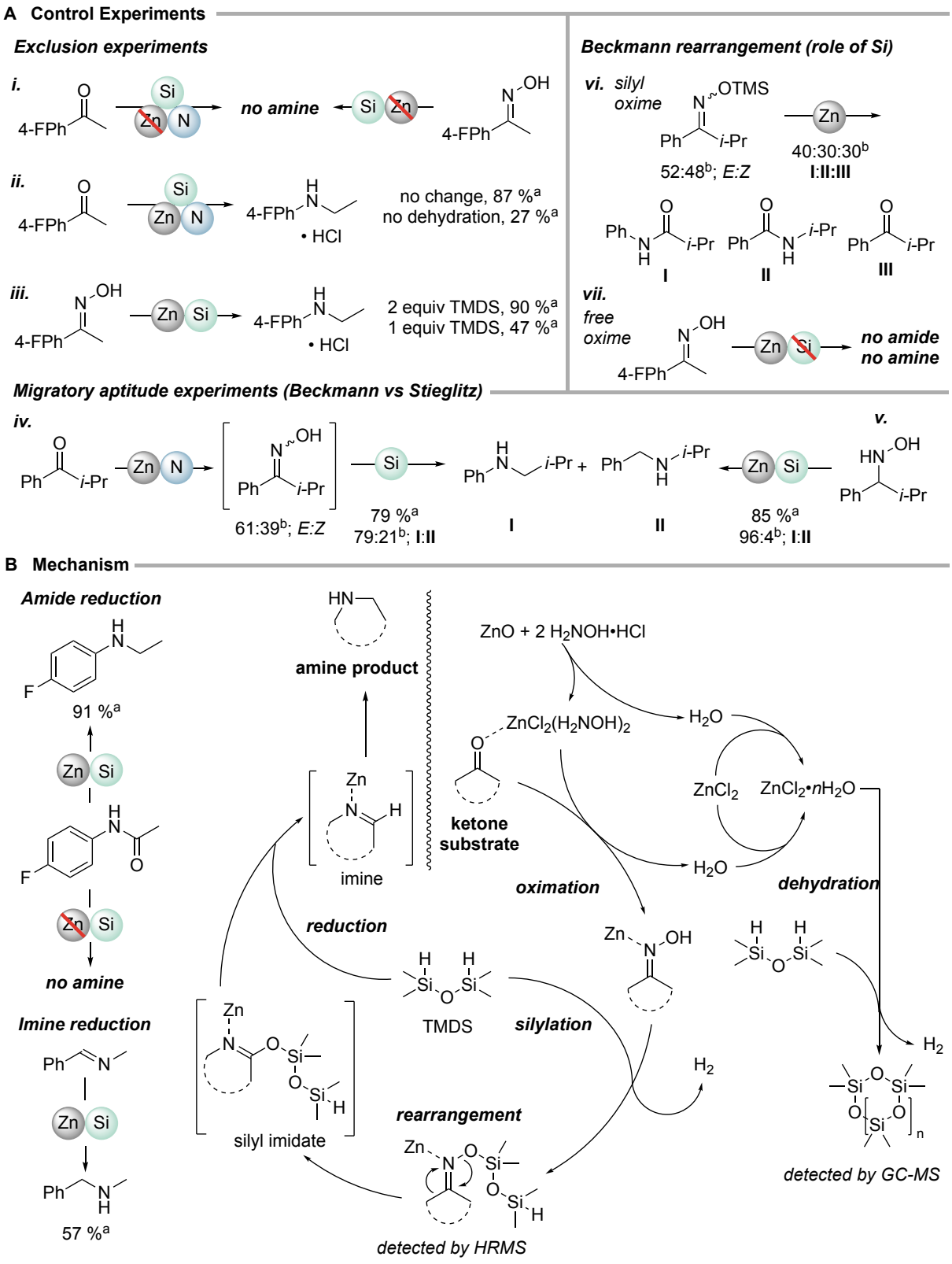

Figure 6. **A.** Mechanistic control experiments to address the role of the reagents and the origin of the migration. **B.** Plausible MRA pathway featuring the multitasking reagents, Zn(II) and hydrosilane (TMDS). See Figure 3 legend for conditions. [a] Isolated yield. [b] ^{1}H NMR ratio.

The likely intermediates formed after the rearrangement stage (amide/imidate, imine) were subjected to the reduction conditions (Figure 6B, left). Both produced the desired amine product, however the amide was not detected by ^{19}F NMR during the standard one-pot reaction from 4-fluoroacetophenone, implying that the reduction stage of this MRA reaction is not rate-limiting or proceeds via a zinc imidate. Summarizing all the data, a plausible pathway can be proposed through which the MRA operates (Figure 6B, right). After the free hydroxylamine is liberated from its hydrochloride salt upon heating in the presence of ZnO (amphoteric base) and $ZnCl_2$ (accelerant and dehydrating agent), the ketone is converted into the oxime intermediate. Then, the addition of two equivalents of TMDS destroys the water by-product from the reaction in the form of hydrogen gas and polymeric siloxane species in a process likely catalyzed by Zn(II) salts. Subsequent addition of an excess of TMDS (3 equiv) leads to silylation of the oxime, followed by Zn(II)-catalyzed rearrangement of the resulting oxime silyl ether. The final Zn(II)-catalyzed reduction stage by the excess TMDS is relatively fast and affords the expected amine product via the imine intermediate.[46]

Conclusions

The effective telescoping of three distinct chemical steps into a single one-pot reaction presents additional challenges in chemoselectivity that lie well beyond the usual concerns of functional group tolerance associated with individual chemical reactions. The migrative reductive amination of ketones developed herein provides a conceptually novel approach to rearranged secondary amines that complements classical reductive amination chemistry. Key to the simple experimental procedure is the use of two mutually compatible multitasking reagents, $ZnCl_2$ and TMDS, which act in concert at each chemical stage to promote oxime formation and dehydrate the reaction medium, rearrange the oxime intermediate, and reduce the rearranged intermediate into the final amine product. The reaction is tolerant to many functional groups and is amenable to acyclic and cyclic aryl-aryl, aryl-alkyl, and alkyl-alkyl ketones, which are transformed in good to high yields into compelling secondary amine products that are isolated as salts, thus allowing a simple chromatography-free isolation and work-up procedure that meets many of the ideals of green chemistry. We anticipate that this work will inspire the design of new and more efficient one-pot reactions exploiting the judicious use and orchestration of multitasking reagents.

Acknowledgments

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