A Metal-free Multicomponent Strategy for Amidine Synthesis

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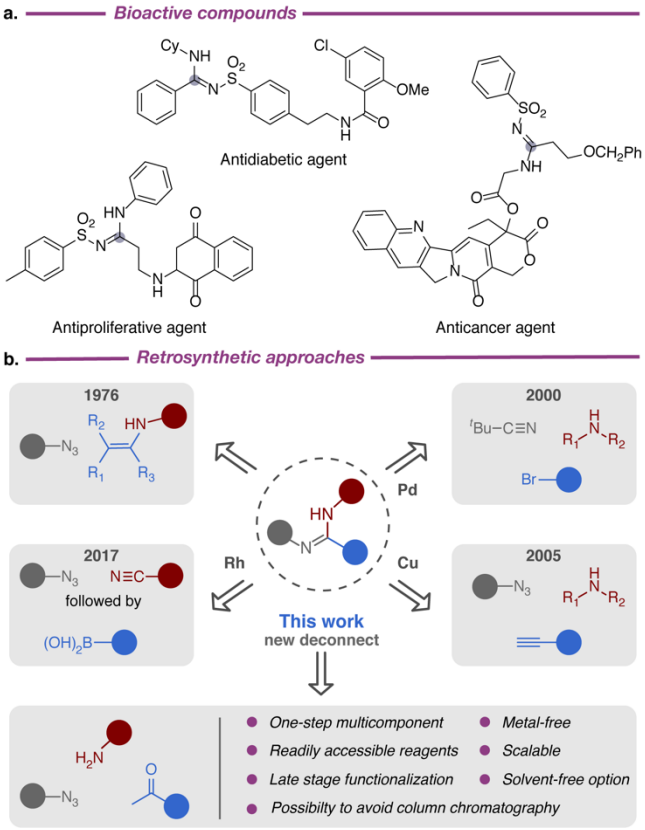
ABSTRACT: Amidines are a ubiquitous class of bioactive compounds found in a wide variety of natural products; thus, efficient strategies for their preparation are in great demand. Specifically, their common structural core decorated with three substituents, set amidines as perfect candidates for multicomponent synthesis. Herein, we present a highly modular metal-free multicomponent strategy for the synthesis of sulfonyl amidines. This work was focused on selecting readily accessible reagents to facilitate the *in situ* formation of enamines by the addition of amines to ketones. These components were coupled with azides to provide a broad reaction scope with respect to all three coupling partners. Aromatic and aliphatic amines and ketones were tolerated under our reaction conditions. Likewise, the presence of a methyl group on the ketone was critical to reactivity, which was leveraged for the design of a highly regioselective reaction with aliphatic ketones. A biologically active compound was successfully synthesized in one step, demonstrating the practical utility of our methodology. Finally, the postulated mechanism was investigated and supported both experimentally and by means of a multivariate statistical model.

Introduction

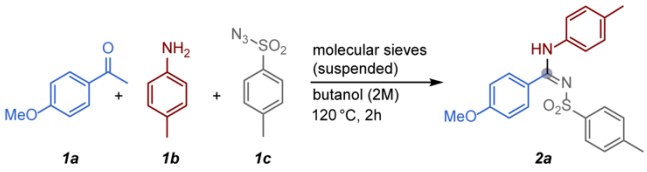
Multicomponent reactions are arguably one of the most powerful methods for diversity-oriented synthesis.[1–5] These step-economical strategies have been embraced by medicinal chemists to expand the chemical space evaluated in biological screening and drug discovery, and are predicated on constructing a common structural core from easily diversified building blocks.[6,7] These reactions commonly proceed *via* a cascade of elementary chemical steps. Nevertheless, orthogonal functionality and undesirable cross-reactivity between reaction components are key limiting factors when designing appropriate synthons and conditions. Amidines are a prominent class of bioactive compounds found in a wide variety of natural products (scheme 1.a).[8–10] Due to their common structural core decorated with three substituents, amidines are perfect candidates for multicomponent synthesis.[11] Their unique structural features, stemming from a conjugated amine core, are at the root of numerous applications.[10,11] In addition to their broad use as bioactive pharmacophores, amidines are synthetic intermediates for heterocyclic compounds and useful ligands for metal complexes.[11] Nevertheless, none of the existing synthetic methodologies afford amidines with three aromatic substituents. Thus, the design of a multicomponent , single-step reaction to afford a diverse array of amidines, especially those with three aromatic substituents decorating the conjugated amine core, is both synthetically challenging and appealing as a gateway to numerous untapped applications.



Scheme 1. (a) examples of bioactive compounds bearing an amidine core (b) selected approaches for the preparation of amidines and the methodology presented in this work

In light of the above-mentioned considerations, it is not surprising that amidine synthesis has received attention in recent years. Initial studies were based on the reactivity between enamines and sulfonyl azides; however, this methodology depended on the isolation of stable enamine substrates (Scheme 1.b. top left).[12–14] In the following years, focus shifted to organometallic catalysis. Furber and coworkers developed a palladium-catalyzed multicomponent amidine synthesis from secondary amines, tert-butyl isonitrile, and substituted bromobenzene (Scheme 1.b. top right).[15] However, this transformation required the addition of stoichiometric amounts of base (Cs_2CO_3), and the substrate scope was limited mostly to aliphatic secondary amines and only one example of isonitrile precursor was presented. Chang and coworkers reported a copper-catalyzed multicomponent oxidative amination, which offers practical access to sulfonyl amidines from alkyl amine, azide and alkyne building blocks (Scheme 1.b. bottom right).[16] Zhang and coworkers reported a one-pot two-step rhodium-catalyzed amidine synthesis, wherein isonitriles were reacted with azides forming carbodiimides, to which boronic acids were added to afford amidine products (Scheme 1.b. bottom left).[17] The scope of this reaction was limited to tert-butyl, cyclohexyl and 2,6-dimethylphenyl isonitrile, and only allylic and aromatic boronic acids were used. Overall, despite the great progress these and other metal-catalyzed methodologies represent in the multicomponent synthesis of amidines, they still rely on the preparation of building blocks that are often not readily accessible such as isonitriles, aldoximes, and terminal alkynes.[18,19]

Table 1. Perturbations to optimal reaction conditions



1a *1b* *1c* *2a*

Optimization

entry	*deviation from conditions*	*Yield %[a]*
1	none	62
2	no molecular sieves	44
3	molecular sieves in solution	31
4	Toluene	52
5	DMSO	54
6	solvent-free	49
7	100 °C	10
8	80 °C	<5
9	24 hours	65

[a] *determined by NMR*

Inspired by the metal-free approach for the formation of sulfonyl amidines through a reaction between enamines and azides (Scheme 1.b.),[12,20] we envisioned a new strategy for amidine synthesis. Herein, based on the *in situ* formation of enamines by the addition of amines to ketones, we disclose a three-component, one-step, metal-free strategy to afford sulfonyl amidines from readily accessible reagents. To the best of our knowledge, this is the first transformation in which three aromatic substituents could be connected to the amidine core in a single step.

Methodology Optimization and Scope

To develop and optimize this reaction, three model components that can be tracked by NMR were selected: acetophenone **1a**, aniline **1b**, and azide **1c**. Our starting point was to apply conditions that resemble the aforementioned initial studies;[21,22] thus, alcohols seemed to be an ideal solvent choice. Because conditions that are known to facilitate imine formation between acetophenone and aniline, such as elevated reaction temperatures, were also required, butanol was selected due to its high boiling point. Thus, we placed all three components under reflux in butanol and to our delight 44% of the desired product was obtained (Table1. entry 2). Based on the hypothesized reaction mechanism, we speculated that molecular sieves (MS) could have a positive effect on the conversion by sequestering water released in the formation of the imine intermediate. However, upon the addition of MS to the reaction mixture the yield decreased (Table1. entry 3). We suspected that the basicity of molecular sieves could have negatively affected the conversion. Thus, we suspended MS at the top of the reaction tube with filter paper (see Figure S1 in SI), which led to a significant increase in reaction yield (Table1. entry 1). We then tested toluene and DMSO as solvents because they are commonly used in imine formation reactions,[23,24] yet in both cases the yield was slightly diminished (Table1. entry 4, 5). We also tested a solvent-free reaction and maintained decent yields (Table1. entry 6). When lowering the temperature to 100 ºC we observed a significant decrease in product formation, and lowering the temperature further to 80 ºC was associated with negligible product yield (Table1. entry 7, 8). Finally, we tested the progress of reaction over time and found that the reaction exhibits similar conversions from two hours onward (Table1. entry 9).

With the optimized reaction conditions in hand, we sought to investigate the scope of reaction with respect to the ketone, aniline, and sulfonyl azide. First, different substituents on the aniline were examined revealing a broad scope of electron-donating or electron-withdrawing groups at the *ortho*, *meta* and *para* positions (Figure 1. examples **2a**, **2e**-**2n**). Aliphatic amines were also compatible with the reaction conditions (Figure 1. examples **2o** and **2p**). Next, we tested electron-donating and electron-withdrawing sulfonyl azides, which were tolerated under reaction conditions (Figure 1. examples **2b**-**2d**). The ketone scope was also broad, electron-withdrawing and electron-donating substituents provided good yields for *meta* and *para* substituted ketones, whereas substituents at the *ortho* position afforded diminished yields (Figure 1. examples **2q**-**2x**). Finally, aliphatic, and benzylic ketones led to reasonable yields under our reaction conditions (Figure 1. examples **2y** and **2z**). In the following section we discuss several of the trends that appear in the substrate scope.

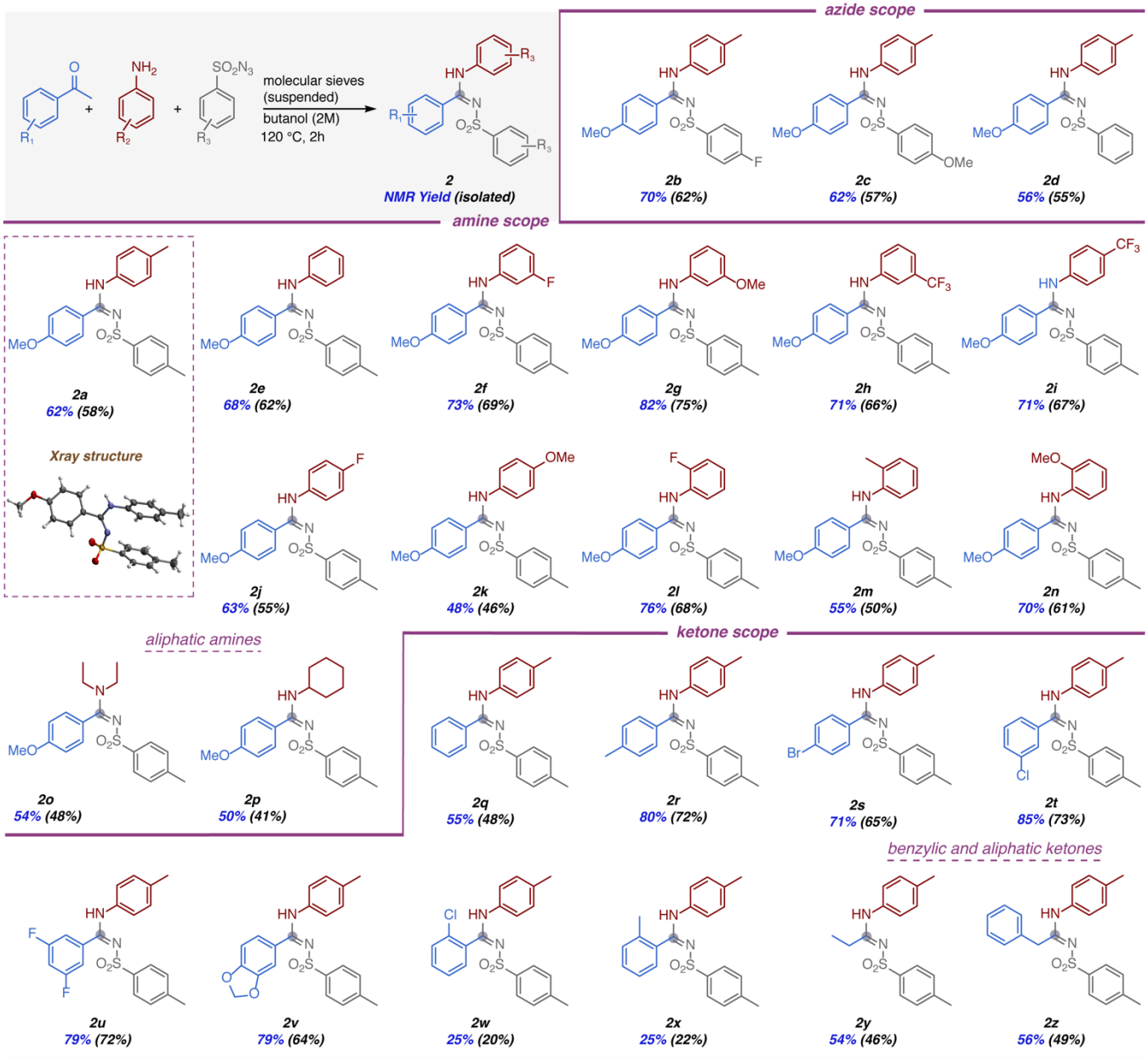


Figure 1. scope of the amidine synthesis, reactions were conducted on a scale of 0.25 mmol (ketone) and 0.35 mmol (amine and azide). All reactions were performed in duplicate and the average yield is reported.

Mechanism Evaluation

According to the proposed reaction mechanism (see Figure 2.a.), imine (**IM1**) is first formed by a nucleophilic addition of an amine to the carbonyl group of a ketone under reaction conditions.[24] The newly formed imine can then undergo an imine-enamine tautomerization to form an enamine intermediate (**IM2**).[25,26] Sulfonyl azide reacts with the enamine *via* a dipolar cycloaddition to form a triazoline intermediate (**IM3**).[12,27,28] Finally, the product is formed in a ring opening reaction together with the release of diazomethane gas. We first set out to verify the likelihood of the ring closing and opening steps by identifying the release of diazomethane. Based on literature precedents,[28,29] we aimed to intercept diazomethane *in situ* by reacting it with benzoic acid, which was added to the reaction mixture to afford the corresponding ester (See Figure 2.b. and Scheme S4 in SI for further details). Methyl benzoate was indeed detected under these modified reaction conditions and amidine formation was not affected by the presence of benzoic acid leading to similar yields, which indicated that the cyclization/de-cyclization steps in the mechanism were plausible.

Examination of the reaction scope reveals that structural features of the aniline component greatly impact the reaction yield. Thus, we wished to identify which of the reaction steps is influenced by the aniline substitution pattern. The role of aniline in the mechanism is unique, it first behaves as a nucleophile that adds to ketone to form imine; thus, anilines bearing electron-donating groups should increase reactivity in this step. However, electron-donating aniline-derived intermediates would not facilitate the following tautomerization and cycloaddition steps. Based on this dichotomy, aniline served as an ideal probe for exploring the proposed reaction mechanism and identifying which steps are associated with reactivity. We first attempted to correlate Hammett parameters to the yield of reaction using *meta*- and *para*-substituted anilines.[30–32]

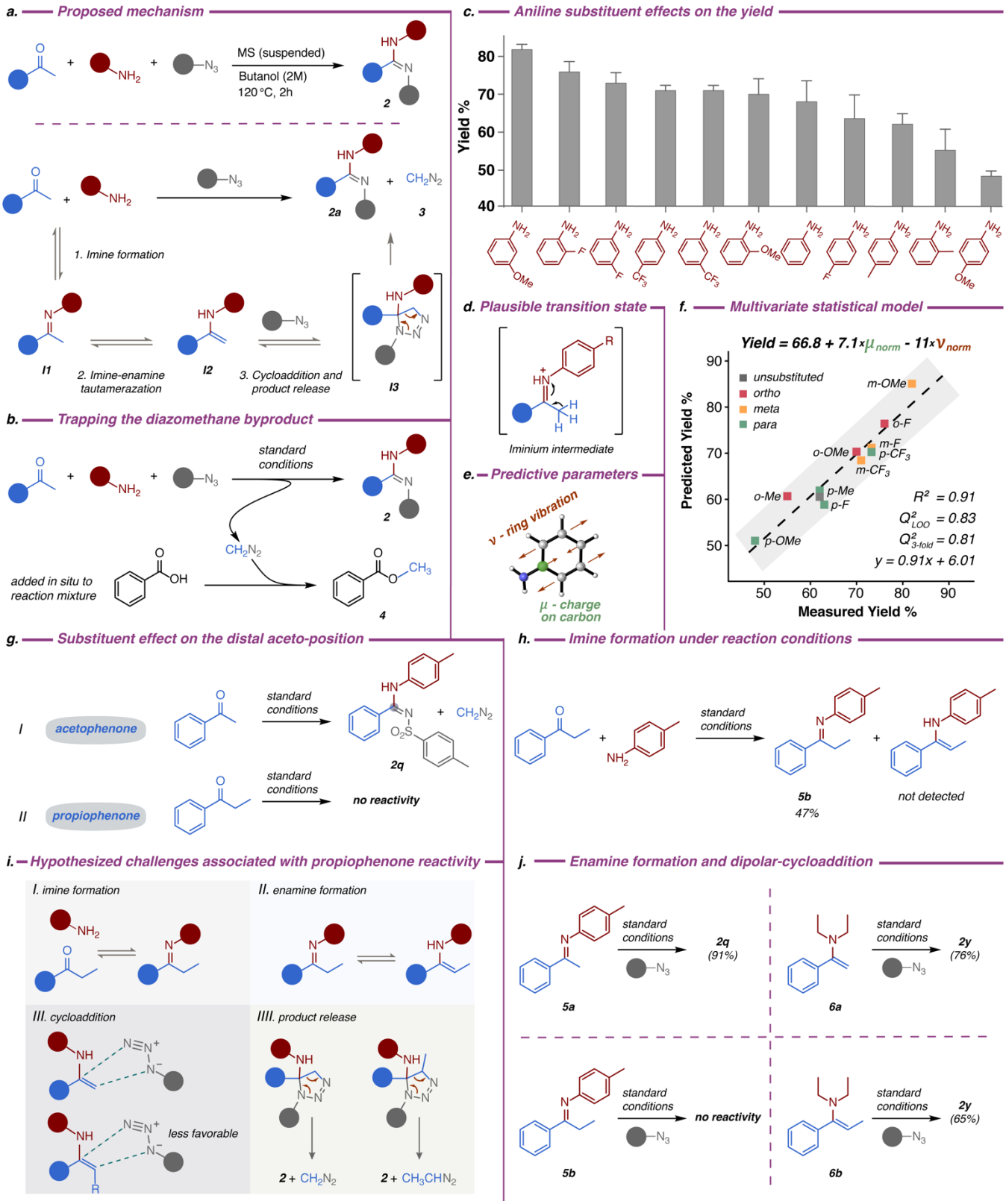


Figure 2. (a) General reaction scheme and proposed mechanism (b) Trapping diazomethane by adding benzoic acid *in situ* (c) The effect of different anilines on the yield (d) Measured versus predicted yield values, the goodness-of-fit is represented by R^2 and Q^2 for leave one-out and 3-fold validation (see SI section 6 for details) (e) Model descriptors: ν, ring vibration, and μ, NPA charge on the carbon adjacent to the amine group (f) Representation of the iminium intermediate (g) The difference between acetophenone and propiophenone in reactivity (h) Investigating imine formation under standard reaction conditions (i) Mechanistic hypotheses for the lack of propiophenone reactivity (j) Investigating imine-enamine tautomerization and cycloaddition steps with acetophenone- and propiophenone-derived intermediates

In the absence of the *m*-anisidine, we identified a good correlation with σ+ values (see SI Figure S5 for details). The slope of the plot was positive, which classically indicates the formation of a negative charge or the collapse of a positive charge at the rate-determining step. This analysis fits well with our observation that electron-withdrawing substituents increase reactivity given a collapse of positive charge at the postulated iminium transition state (Figure 2.d.).[33] Thus, this analysis supports the formation of enamine as being rate-limiting. Moreover, the poor fit with σ values and the reduced correlation with *m*-anisidine included, both support the important contribution of resonance to the rate-determining transition state(s).

Given these limitations of the Hammett correlation and the fact that we also had *ortho*-substituted anilines in our set, we selected to apply a multivariate approach.[34,35] A robust model with two parameters was identified: the natural population analysis (NPA) charge on the ring carbon connected to the nitrogen and a ring vibration aligned with the *para* substituent axis (μ and ν respectively, Figure 2.e.).[36] In this model increased positive charge adjacent to the nitrogen and lower vibration frequencies lead to higher yields. The vibration frequencies are difficult to interpret intuitively because they are influenced by changes to charge and the mass and location of the substituents (see SI Figure S8 for further details). However, the variation in charge confirms the conclusions gained from the Hammett analysis—the ability of substituents to stabilize the iminium transition state, through both resonance and inductive effects, is responsible for the yield of the reaction (See Figure 2.d-f.).

Regioselectivity

Prior to intercepting the diazomethane *in situ*, we speculated that by replacing the methyl group of acetophenone with extended alkyl substituents, we would be able to isolate non-gaseous diazoalkane by-products. Interestingly, upon the addition of propiophenone to the reaction mixture instead of acetophenone (See Figure 2.g.), product was not formed and the ketone remained unreacted. This result does not represent a limitation of our methodology because both substrates lead to the same product with a different by-product. Yet, the origin of this puzzling observation might shed light on the reaction mechanism. We postulated that the lack of propionate reactivity could be associated with one of the following challenges (Figure 2.i.): (a) imine formation might be prohibitive, (b) the tautomerization step to form enamine may be unfavorable, (c) bulkier substituents on the enamine might limit the approach of sulfonyl azides, and (d) the release of bulkier diazoalkanes may be less favorable than the release of diazomethane gas.

To differentiate between these mechanistically distinct options, we tried to intercept the proposed intermediates and submit each of them to our reaction conditions. We first studied the formation of imine and enamine when treating propiophenone with aniline in the absence of azide. Under our reaction conditions, imine was observed while enamine was not detected (Figure 2.h.). We then probed the imine-enamine tautomerization step by synthesizing and purifying the imines of acetophenone and propiophenone, followed by treatment with azide under our standard reaction conditions (Figure 2.j.). Product formation was observed with acetophenone, whereas the propiophenone imine remained unreacted. We then sought to test whether the reaction can proceed upon the addition of azide to enamines. The enamines that were postulated to form under our reaction conditions are not stable, thus we synthesized and isolated stable enamines from secondary amines with acetophenone (**6a**) and propiophenone (**6b**) and submitted them to our reaction conditions (Figure 2.j.).[37,38] In both cases, amidine products were obtained, implying that the cyclization/de-cyclization steps are not limiting to propiophenone reactivity. Overall, this set of experiments strongly suggested that whereas propiophenone can form an imine, it could not proceed to form enamine under our reaction conditions.

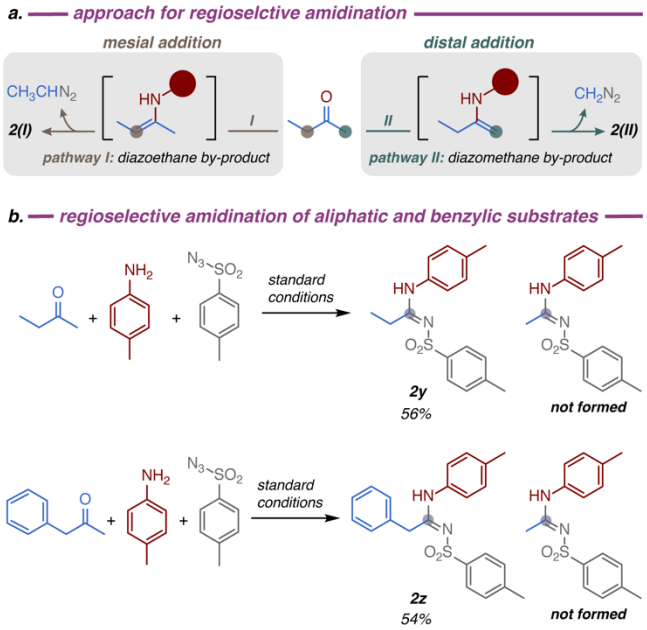


Figure 3. (a) General approach for regioselective amidination (b) Proof-of-concept: aliphatic and benzylic substrates demonstrate regioselectivity

Given these results, we postulated that the sensitivity of the reaction to the nature of the alkyl substituent on the ketone could provide us with a powerful methodology to control regioselective amidine transformations of aliphatic substrates. Upon the addition of aliphatic ketones, theoretically, the reaction may proceed through two possible pathways (see figure 3.a.): *(I)* the imine-enamine tautomerization would occur on the mesial position with the elimination of the corresponding diazoalkane by-product; *(II)* the imine-enamine tautomerization would occur on the distal methyl position with the elimination of diazomethane. As a proof-of-concept we submitted butanone to our reaction conditions to probe its regioselectivity. Indeed, the tautomerization occurs only on the distal methyl position, leaving the mesial position intact and providing a highly regioselective transformation (**2y** Figure3.b.). Similar behavior was observed with phenyl acetone as substrate affording product **2z** exclusively (Figure3.b.).

Applications and Conclusion

To demonstrate the applicability of our methodology, we scaled up the reaction using **1a**, **1d**, and **1c** as model substrates. With industrial applications in mind, we selected to run this reaction under solvent-free conditions affording 67% isolated yield (Figure 4.a.). Moreover, as the costs of

large scale columns are prohibitive,[39] we opted to recrystallize the product, which is facilitated by the solvent-free conditions in this reaction set-up. Next, we aimed to apply this methodology in late-stage functionalization to create a specific structural core found in a wide variety of biological active molecules. Namely, we constructed in a single step the amidine core of a glibenclamide-derivative, which is a very commonly prescribed diabetes medication.[40–42] The ketone and amine components were commercially available, and we synthesized the required sulfonyl azide in three steps (See SI section 3.8 for details). We then submitted the three components to our standard reaction conditions to afford the desired product **7** in 52% isolated yield (Figure 4.b.).[43]

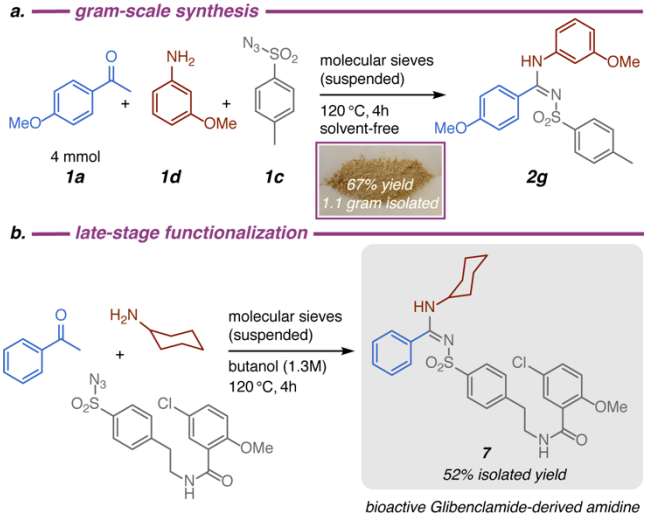


Figure 4. (a) Gram-scale synthesis of **2g** under solvent-free conditions (b) Glibenclamide-derivative synthesis by coupling the three components in a single step

In summary, we have developed a novel methodology for the synthesis of sulfonyl amidines from readily available starting materials in a metal-free one-pot reaction. These reaction conditions afford a broad substrate scope and functional group tolerance. Studies focused on intercepting reaction intermediates and submitting them to our reaction conditions provide insights on the reaction mechanism, which are further supported by Hammett analysis and multivariate linear regression models. Moreover, this mechanistic analysis led to the discovery of a highly regioselective amidination of aliphatic ketones. The one-step, multicomponent synthesis of a bioactive glibenclamide derivative demonstrated the efficacy of this methodology in drug development.

ASSOCIATED CONTENT

Supporting Information. Electronic Supplementary Information (ESI) available free of charge via the Internet at http://pubs.acs.org. All underlying data are available in the article itself and its supplementary materials and include: Detailed experimental and computational procedures, analyses, and characterizations (AmidineSI.pdf); Excel sheet with the results and parameters that were used to identify models (Amidine2022.xlsx); Zip archive with cif and checkcif X-ray files (xray.zip). The raw data and code files are openly available in GitHub at https://github.com/Milo-group/Amidine2022 and include machine readable NMR and HRMS traces, as well as all optimized .xyz files, code and data sets.

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Author Contributions

The manuscript was written through contributions of all authors, who have given approval to the final version of the manuscript.
‡These authors contributed equally.

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Notes

The authors declare no competing financial interest.

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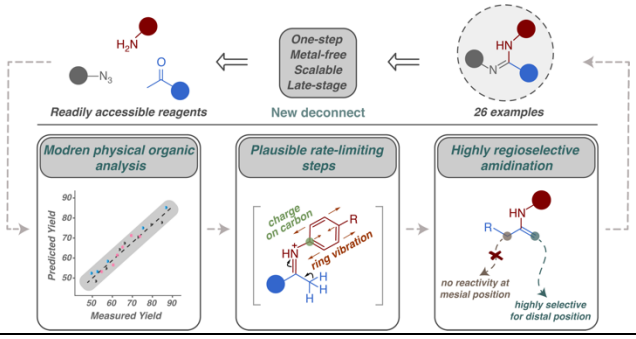
(43) This is the best yield to date compared to the 42% obtained with rhodium catalysis in reference 17.


Readily accessible reagents
One-step
Metal-free
Scalable
Late-stage
New deconnect
26 examples
Modren physical organic analysis
Predicted Yield
Measured Yield
Plausible rate-limiting steps
charge on carbon
ring vibration
Highly regioselective amidination
no reactivity at mesial position
highly selective for distal position