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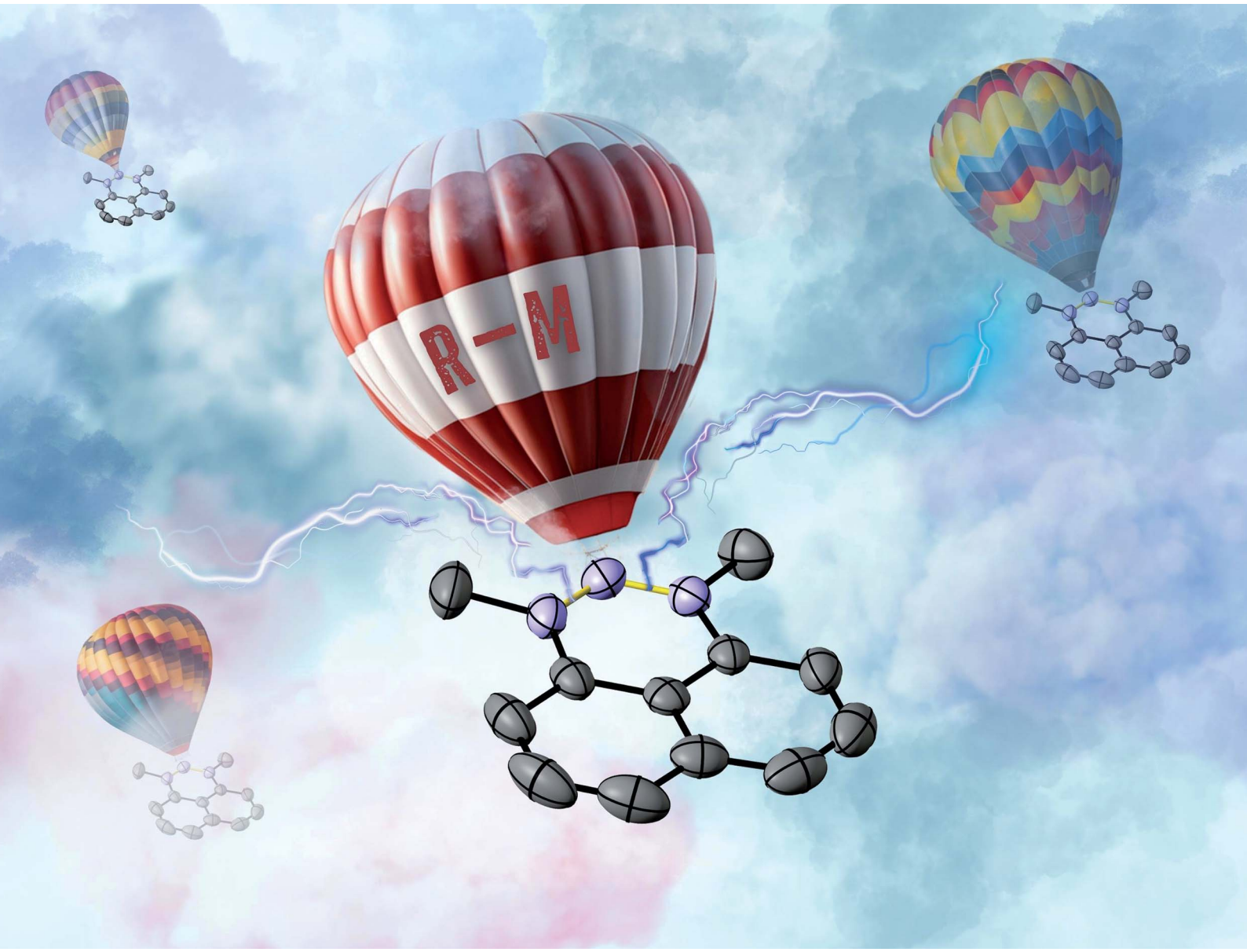

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Nitrenium ions as new versatile reagents for electrophilic amination†

Idan Avigdori, ‡ Kuldeep Singh, ‡ Natalia Fridman and Mark Gandelman *

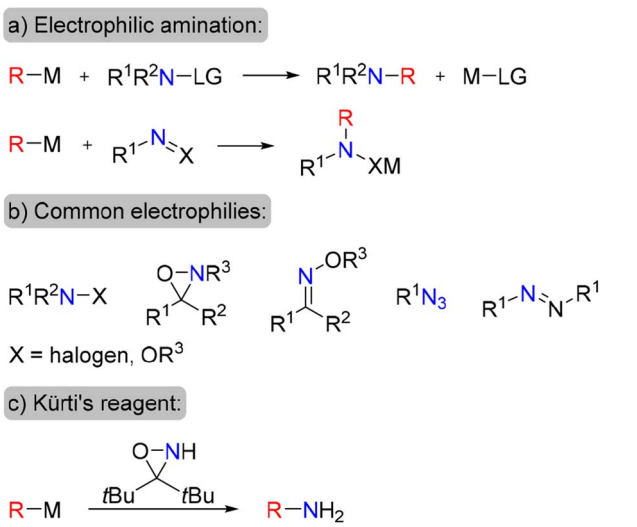
Herein we report the utilization of N-heterocyclic nitrenium ions – easily prepared, bench-stable and non-oxidating nitrogen sources for the efficient electrophilic amination of aliphatic and aromatic organometallic nucleophiles, towards the facile and general preparation of primary amines. To this end, a plethora of abundant organolithium and organomagnesium reagents were combined with nitrenium salts to generate a variety of previously unexplored *N*-alkyl and *N*-aryl triazanes. Through the simple hydrogenolysis of these relatively stable triazanes, we have prepared a diverse scope of primary amines, including linear and branched aliphatic as well as (hetero)aromatic amines possessing various stereo-electronic substituents. Furthermore, we present the facile synthesis of valuable ^{15}N-labelled primary amines from easily prepared ^{15}N-labelled nitrenium salts, as well as a one-pot approach to biologically relevant primary amines. Finally, a recyclable variant of the nitrenium precursor was prepared and a simple recovery protocol was developed to improve the atom-economy of this procedure.

Introduction

Amines in general, and primary amines in particular, play a crucial role in chemical enterprise due to a plethora of valuable applications. They are found in a wide range of natural products and synthetic materials, and have diverse employment in pharmaceuticals, agrochemicals, polymers, and materials science.[1] The unique chemical properties of organic amines, such as their ability to form relatively strong hydrogen bonds and to act as nucleophiles in chemical reactions, make them essential building blocks in many chemical processes. Therefore, development of new selective and versatile methods for the synthesis of primary amines represents a highly important yet challenging goal.

Representative classical methods include alkylation of ammonia with alkyl halides, reduction of nitriles, the Gabriel synthesis, and reductive amination.[2] All these nucleophilic amination approaches are restricted to aliphatic amines and have their own well-known limitations, *e.g.*, overalkylation and/or limitation to sterically non-congested alkyl halides. Aromatic primary amines can be prepared, for example, *via* reduction of nitroarenes.[3] Modern methods encompass the Buchwald–Hartwig transition metal catalyzed amination[4,5] of aryl electrophiles with ammonia-equivalent reagents.[6,7] This highly useful reaction usually employs an expensive ligand–metal catalyst and is challenging for the amination of sterically congested organic skeletons.[8]

An attractive alternative approach to the synthesis of amines is electrophilic amination, in which organometallic nucleophilic precursors undergo C–N bond formation *via* their reaction with electrophilic N-species (Scheme 1a). This approach has attracted the continuous interest of chemists, thus several types of electrophilic aminating reagents have been developed, such as haloamines, *O*-substituted hydroxylamines, oxaziridines, oximes, organic azides and diazonium salts (Scheme 1b).[9–15] Nonetheless, many of these reagents are only moderately



Scheme 1 Electrophilic amination reactions and reagents.

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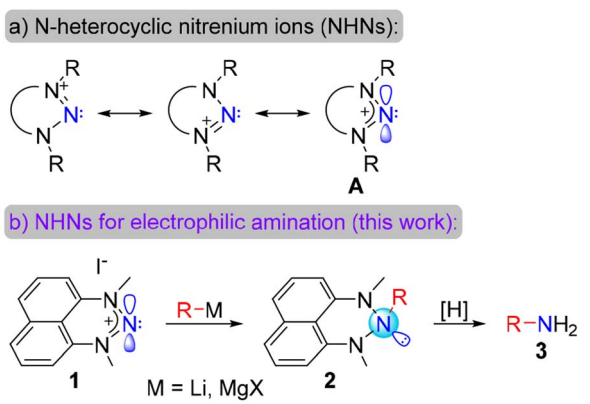
stable, possess oxidizing properties, require tedious preparation protocols or are specific for certain types of nucleophiles.

Moreover, only a few of the available electrophilic amination reagents are suitable for the preparation of primary amines.[16,17] Recently, the electrophilic amination approach has received a boost due to an elegant design of specific bulky oxaziridines for the amination of organic nucleophiles[18,19] (Scheme 1c) as well as development of transition-metal-catalyzed amination procedures.[20–22] Undoubtedly, development of a new robust and stable electrophilic aminating agent, applicable for the synthesis of both aliphatic and aromatic amines is of high value.

We have recently established a program on the chemistry of N-heterocyclic nitrenium ions (NHNs). These ions are N-based isostructural and isoelectronic analogs of the ubiquitous N-heterocyclic carbenes (Scheme 2a).[23] We and others demonstrated that such species can serve as cationic ligands to a plethora of transition metals, being poor σ-donors and considerable π-acceptors.[24–28] This is due to a substantial contribution of the resonance form **A** to the electronic structure of the nitrenium ions. This form demonstrates a nitrogen non-octet character in these ions, which possess a relatively low LUMO and a free p-orbital on the central N-atom. These unique properties of NHNs allowed us and others to demonstrate that NHNs can act as nitrogen-based Lewis acids,[29–33] activators of strong bonds through frustrated Lewis pair chemistry,[30,34] catalytic Lewis acids for several reactions,[35–38] photocatalysts[39–41] and a platform for stable nitrogen-based radicals.[42,43]

Exploring this Lewis acidity, we previously demonstrated that NHN **1** reacts with phenyllithium or *n*-butyllithium to furnish cyclic triazanes **2** (Scheme 2b).[29] While such triazanes possess an unusual molecular structure bearing three saturated nitrogen atoms in row, their intriguing chemistry is previously unexplored. We envision that the N–N bonds in these compounds should be relatively weak and could be cleaved under standard reduction conditions, providing primary amines *via* N-atom deletion from the triazane ring (Scheme 2b). Interestingly, carbon and nitrogen atom deletion from heterocycles for synthetic purposes,[44–47] including carbon atom deletion from N-heterocyclic carbenes,[48] have gained much current interest. If this hypothesis is successful, the NHN would serve as a novel robust and stable electrophilic aminating agent. Moreover, the first step of the nucleophile addition would furnish a protected primary amine. This form is essentially stable (*vide infra*) and can be tolerated during the synthesis.



Scheme 2 Structure of NHNs and their use in amination.

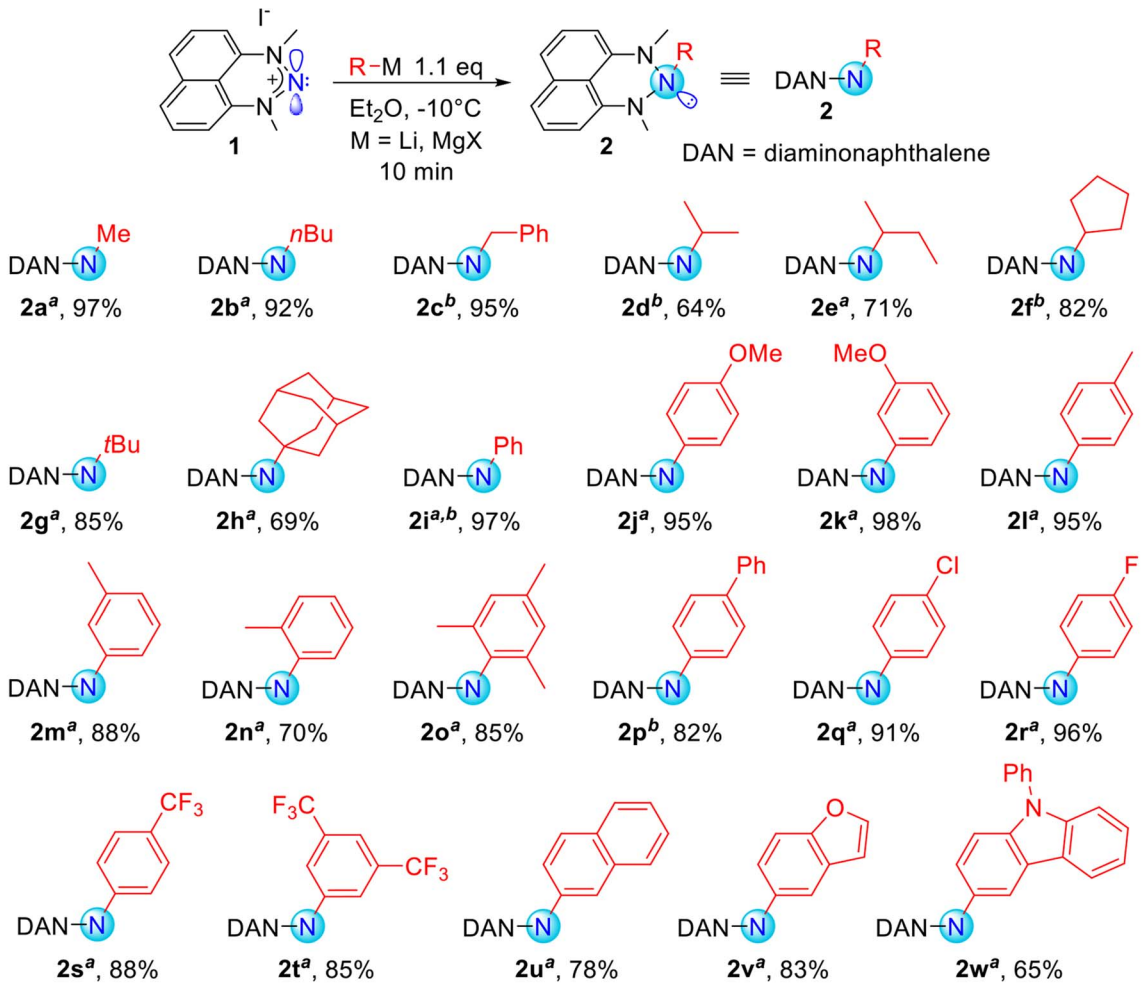
In this article we report on the preparation and full characterization of a broad range of *N*-alkyl and *N*-aryl triazanes, which properties, to the best of our knowledge, were not previously explored. Most importantly, we demonstrate that the nitrenium salt – an air-stable, non-oxidative and easily prepared compound – can serve as a novel efficient electrophilic aminating agent. Utilizing nitrenium, we have prepared a broad range of primary amines. This approach is truly general: linear and branched aliphatic amines as well as aromatic amines bearing substituents with variable stereo-electronic parameters on the aromatic ring can be efficiently prepared by this reaction. Moreover, ^{15}N-labeled amines can be easily prepared by our procedure since we provide a facile approach to the ^{15}N-labeled bench-stable nitrenium salts. We also reveal a straightforward protocol for the recycling of the generated co-product diaminonaphthalene to the starting aminating nitrenium, to address the atom-economy of the method.

Results and discussion

Exploring organometallic nucleophiles in reaction with NHN **1**, we were pleased to observe that a broad scope of both organolithium and organomagnesium reagents selectively react with the nitrenium cation to provide the corresponding triazanes **2** (Scheme 3). Moreover, the generality of this reaction is substantial since the reaction was accomplished using numerous alkyl and aryl nucleophiles possessing various stereo-electronic characteristics. We were able to produce triazanes comprising primary (**2a–c**), secondary (**2d–f**), and tertiary (**2g–h**) alkyl groups bonded to the central N-atom, including cyclic alkyl motifs (**2f**, **2h**). Furthermore, triazanes resulting from the combination of **1** with variously substituted aryl-M (M = Li or MgX), including electron-donating and electron-withdrawing groups in the *para*-, *meta*- and *ortho*-positions (**2i–w**), were successfully generated. Most of these triazanes were sufficiently stable at room temperature to be isolated and characterized by multinuclear NMR.

The molecular structures of these triazanes were confirmed, for the first time, by single-crystal X-ray crystallography. Some representative structures (**2a**, **2d**, **2i**, **2p**) are shown in Fig. 1. Contrary to the planar nitrenium species, the central N-atoms in all the triazanes are located outside the plane of the naphthalene moiety. This occurs since the central nitrogen atoms undergo pyramidalization as they transform from the sp^2 hybridization in the nitrenium precursor to the sp^3 hybridization in the triazane product, upon occupation of the vacant p_π orbital on the central N-atom by the σ-donation from the corresponding nucleophile.

Having a wide range of triazanes in hand, we envisioned that the formal reduction of these structures would lead to the N–N bonds cleavage and deletion of the central nitrogen atom from the triazane ring, generating the desired primary amine



[a] Prepared using an organolithium reagent. [b] Prepared using an organomagnesium reagent. PhLi and PhMgBr each gave 97% yield for **2i**.

Scheme 3 Scope of triazanes; reaction scale: 0.3 mmol (0.08 M); yields are of isolated products.

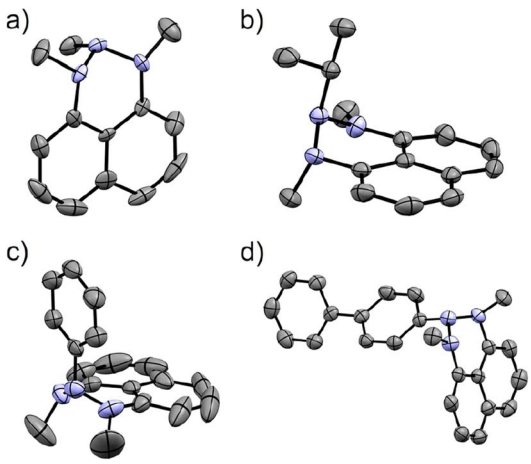
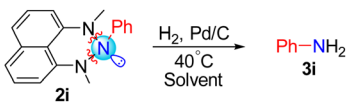


Fig. 1 POV-ray depictions of the X-ray structures of selected triazanes. (a) **2a**; (b) **2d**; (c) **2i**; (d) **2p**. Anisotropic displacement ellipsoids are set at 50% probability. H atoms are omitted for clarity.

Table 1 Optimization of triazane hydrogenolysis



Entry	Solvent	Time (h)	Yield[a] (%)
1	Toluene-d_8[b]	6	100
2	Toluene-d_8	2	100
3	Toluene-d_8	1	92
4	Methanol-d_4	2	36
5	Methanol-d_4[c]	2	100
6	Benzene-d_6	2	100
7	Acetonitrile-d_3	2	50
8	Chloroform-d	2	25
9	DCM-d_2	2	100
10	DMSO-d_6	2	45

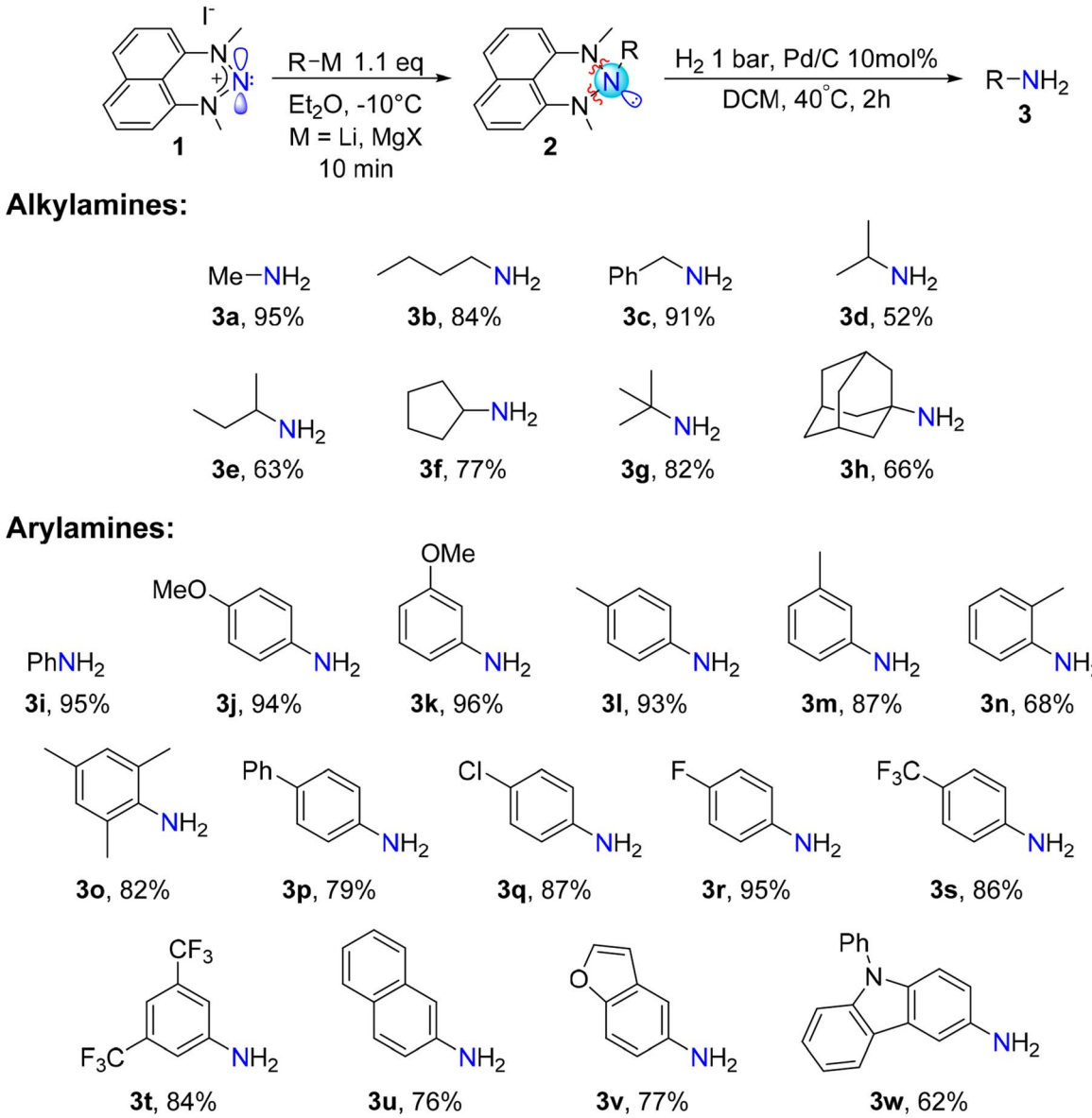
[a] Measured by ^{1}H NMR. [b] Performed at 25 °C. [c] 2 bar of H_2 used.

(Table 1). To investigate this hypothesis, we subjected triazane **2i** to 1 bar of H_2 at 40 °C, in the presence of 10 mol% of Pd/C catalyst, utilizing several different solvents (at room temperature, the reaction was slower – Table 1, entry 1).

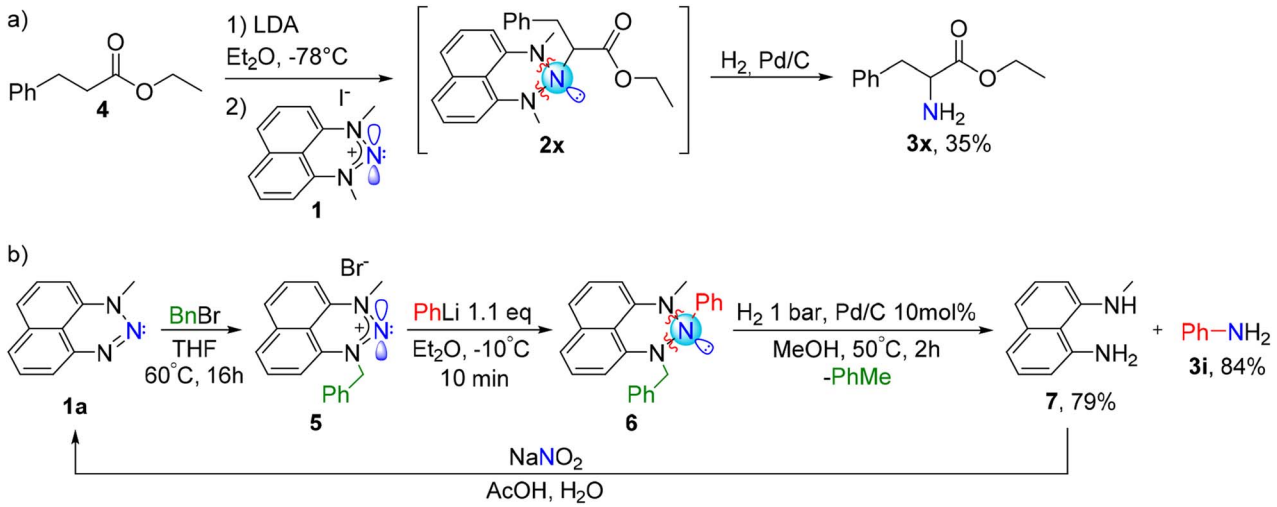
Gratifyingly, many of the examined solvents were suitable for this hydrogenolysis reaction, generating the desired aniline in quantitative yield (Table 1). Applying these conditions for all the triazanes we synthesized, using DCM as the solvent (CD_2Cl_2 was used for amines **2a-b**, **2d–g**), generated the corresponding primary amines in good to excellent yields (Scheme 4).

As can be seen on Scheme 4, primary amines featuring linear and branched alkyl skeletons were successfully synthesized. This includes the installment of the NH_2 unit on primary (**3a–c**), secondary (**3d–f**) and tertiary (**3g-h**) alkyl groups. Examples of primary amines incorporating cyclic (**3f**) and polycyclic (**3h**) alkyl groups were also attained. In addition, our electrophilic amination method proved suitable for the synthesis of primary arylamines featuring electron-withdrawing and electron-donating groups on the rings. This includes various substituents at the *para-*, *meta-*, and *ortho* positions of the aromatic ring. Even a bulky arylamine bearing methyl substituents at two *ortho* positions (**3o**) can be prepared with an isolated yield of 82%. Such sterically congested arylamines are challenging to prepare by the Buchwald–Hartwig cross-coupling reaction and require specific conditions.[8] We were also able to synthesize primary amines comprising heterocyclic aryl groups such as benzofuran (**3v**) and 9-phenylcarbazole (**3w**).

Markedly, ^{15}N-labelled primary amines are easily accessible *via* our protocol since the ^{15}N-labelled NHN precursor **1′** is selectively and facilely prepared using the commercially



Scheme 4 Scope of amines produced by the hydrogenolysis of triazanes. Reaction scale: 0.3 mmol (0.08 M); for **3i**, the reaction was scaled up to 0.2 g of **1** (92% yield). Yields are from **1** to **3**; yields of **2a-b**, **2d–g** were calculated by ^{1}HNMR; all other yields are for the isolated product.



Scheme 5 (a) A one-pot procedure for the synthesis of phenylalanine ethyl ester **3x** (isolated yield); (b) a recyclable variant for improving the atom-economy of the NHN-based electrophilic amination. Yields are for the isolated products, from NHN **5** to products **3i** + **7**.

available, isotopically labelled $Na^{15}NO_2$.[29] As an example, we have prepared aniline-^{15}N **3i′** with a yield as high as 95%. Additionally, the dyskinesia medication amantadine (1-adamantylamine, **3h**)[49] was prepared with 66% isolated yield. These examples demonstrate the potential of this procedure for the synthesis of valuable isotopically labelled and biologically active compounds.

To prepare amines utilizing our approach, it is not necessary to isolate the R-*N*-triazane intermediate. The whole procedure, including the preparation of R-Li, its amination with a nitrenium salt and the final "deprotection" to the desired primary amine can be done in a one-pot process. As an interesting example, we generated *in situ* an enolate of ester **4** by its treatment with lithium diisopropylamide (LDA) at −78 °C and quenched it with the aminating agent **1** (Scheme 5a). The resulting triazane **2x** was directly, without isolation, treated with hydrogen gas in the presence of a catalytic amount of Pd/C to furnish the amino acid precursor phenylalanine ethyl ester **3x**. This further demonstrates the capability of our electrophilic amination procedure to produce compounds of well-established biological importance in a one-pot protocol.

Notably, we have developed this method driven by our fundamental interest in the properties of novel triazanes. NHN **1** can serve not only as a versatile aminating agent, but also, in the triazane form **2**, as a protecting group for primary amines (a masked RNH_2), which can be deprotected at the late stage of the synthesis. However, we recognize that potential scale-up protocols would be concerned by the formation of the diaminonaphthalene co-product. To improve the atom-economy of this procedure, we devised a method enabling the recycling of the residual diaminonaphthalene. To this end, we modified the NHN precursor by replacing one of the flanking methyl groups with a benzyl group, by reacting *N*-methyl-naphthotriazine **1a** with benzyl bromide (Scheme 5b). We combined the newly produced NHN **5** with phenyllithium, using the same conditions as with the precursor **1**, and generated the corresponding triazane **6**. Gratifyingly, the subsequent hydrogenolysis of **6** (using 2 bar of H_2 and 10 mol% of Pd/C, in methanol at 50 °C, over 4 hours) directly results in a clean formation of the desired amine **3i** along with the *N*-methyl-1,8-diaminonaphthalene **7**. Notably, diamine **7** can be utilized as a starting material for the preparation of NHN **5**; therefore, it can be recycled by a reaction with $NaNO_2$ – our standard approach to the synthesis of nitrenium substrates – to regenerate triazine **1a**.

Conclusions

In summary, we demonstrated a new efficient and selective method for the synthesis of primary amines *via* electrophilic amination, utilizing easily prepared, non-oxidative and bench-stable nitrenium salts as the electrophilic nitrogen source. This robust and general procedure makes use of abundant organolithium and organomagnesium reagents as the nucleophilic partners. The method is suitable for the preparation of linear and branched aliphatic and aromatic amines with various stereo-electronic properties. Biologically relevant and ^{15}N-labelled counterparts were easily prepared, displaying the capability and viability of this procedure to obtain these valuable compounds. Moreover, we also produced a recyclable variant of the nitrenium precursor to increase the atom economy of our method. We demonstrated that the *N*-R-triazanes, whose crystallographic characterization and properties were revealed here for the first time, represent isolable intermediates in the amination process. Other nucleophiles (organozinc, organoboron, *etc.*) for electrophilic amination using nitrenium salts are under investigation in our labs.

Data availability

Further experimental details, synthetic procedures, characterization data, copies of NMR spectra and X-ray crystallographic data are available in the ESI.†

Author contributions

I. A. and K. S. preformed the experiments and the NMR characterization. N. F. performed the X-ray crystallography characterization. I. A. and M. G. co-wrote the manuscript with feedback from K. S. and N. F. M. G. conceived the idea and directed the project.

Conflicts of interest

There are no conflicts to declare.

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