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Photoinduced Olefin Diamination with Alkylamines

Sebastian Govaerts,‡ Lucrezia Angelini,‡ Charlotte Hampton, Laia Malet-Sanz, Alessandro Ruffoni* and Daniele Leonori*

Abstract: Vicinal diamines are ubiquitous materials in organic and medicinal chemistry, and methods for their preparation are of relevance to a broad range of chemical applications. The direct coupling of olefin and amine building blocks would represent an ideal approach to construct these motifs. However, alkene diamination remains a long-standing challenge in organic synthesis, especially when two different amine components need to be introduced. Here we report a general strategy for the direct and selective assembly of vicinal 1,2-diamines using readily available olefin and amine building blocks. This mild and straightforward approach exploits the *in situ* formation and photoinduced activation of *N*-chloroamines leading to aminium radicals that enable efficient alkene aminochlorination. Owing to the ambiphilic nature of the β-chloroamines accessed, conversion into tetra-alkyl aziridinium ions was possible, thus enabling diamination by regioselective ring-opening with both primary and secondary amines. Overall, this strategy streamlines the preparation of vicinal diamines from current multi-step sequences to a single chemical transformation. This operationally simple process has broad functional group compatibility and enables the use of advanced building blocks for the preparation of drug-like small molecules.

Introduction.

Vicinal diamines are important building blocks in organic chemistry with applications as commercial medicines and ligands in transition metal catalysis, as well as organocatalysts (Scheme 1A).[1] Despite their importance, the preparation of these high-value materials is still very challenging.

Olefin diamination would represent a very attractive approach for their assembly, especially owing to the large availability of alkenes as commercial materials coming from petroleum feedstocks.[2] Indeed, several strategies have been developed to directly introduce two *N*-containing functionalities across an olefin. The most general approach involves olefin di-azidation, which can be promoted by a broad range of systems spanning Mn/Fe/Pd/photoredox catalysis as well as electrochemistry (Scheme 1B, path a).[3] Alternatively, hypervalent iodine reagents have been applied to the preparation of 1,2-bis-sulfonamides[4] while Pd/Rh/Cu-catalytic systems[5] and electrochemistry[6] have enabled the reaction of sulfonamides and symmetrical ureas with olefins (Scheme 1B, path b and c respectively).

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While successful, these strategies do not enable the direct introduction of alkylamine substituents, which are a prominent class of nitrogenated motifs frequently found in the high-value materials mentioned above. As a result, multi-step synthetic sequences are still required to elaborate any of these nitrogenated intermediates into the corresponding alkylamine targets. Pioneering studies that attempted to solve this challenge involved the use of stoichiometric Os(VIII)-imido-complexes for the introduction of *t*-BuNH_2 units (Scheme 1B, path c),[7] while a restricted number of anilines have been added across alkenes with the aid of equimolar HgO[8] or $Tl(OAc)_3$[9] under acidic conditions (Scheme 1B, path d). In an isolated example, Bäckvall demonstrated the stoichiometric reaction between olefins, Me_2NH and a Pd(II) species to produce a dimethylamino-palladate complexes that, upon oxidation, yielded the diaminated products (Scheme 1B, path e).[10]

Overall, despite the success and applicability of all these methods, the construction of vicinal diamines is still synthetically very demanding. The development of a general strategy able to directly engage amines and olefins would be very desirable, especially considering the direct construction of unsymmetrically substituted substrates has thus far been elusive (e.g. **A,** Scheme 1C). Currently, the preparation of this class of substrates is still based on lengthy synthetic sequences, relying on functional group manipulation around epoxides,[11] α-Br-ketones[12], or α-hydroxy-acids.[13] In this article, we report the development of a general process for the direct and selective construction of unsymmetrical diamines wherein readily available primary and secondary amines are sequentially added with complete site-selectivity across olefin building blocks.

Design Plan.

We have recently demonstrated how primary and secondary amines can be converted into the corresponding aminium radicals by *in situ* activation with *N*-chlorosuccinimide (NCS), protonation, and photoinduced SET (single-electron transfer) reduction.[14]

We have explored the ability of these highly electrophilic open-shell intermediates to react selectively with a wide range of aromatic coupling partners, thus offering a platform for direct aromatic C–H amination. We recently questioned if this reactivity profile for amine activation could be exploited in order to enable intermolecular reaction of aminium radicals with alkenes leading to an olefin aminochlorination that would serve as stepping stone to achieve a general and direct strategy leading to olefin diamination. Pioneering work of Minisci[15] and Neale[16] demonstrated the ability of preformed *N*-chloroamines to engage in aminochlorination reactions with olefins. However, the requirement for harsh reaction conditions (sulfuric acid as solvent and highly-energy UV light) as well as the known chemical instability of these reagents have limited the adoption of this approach as well as its applicability in complex molecular assembly.

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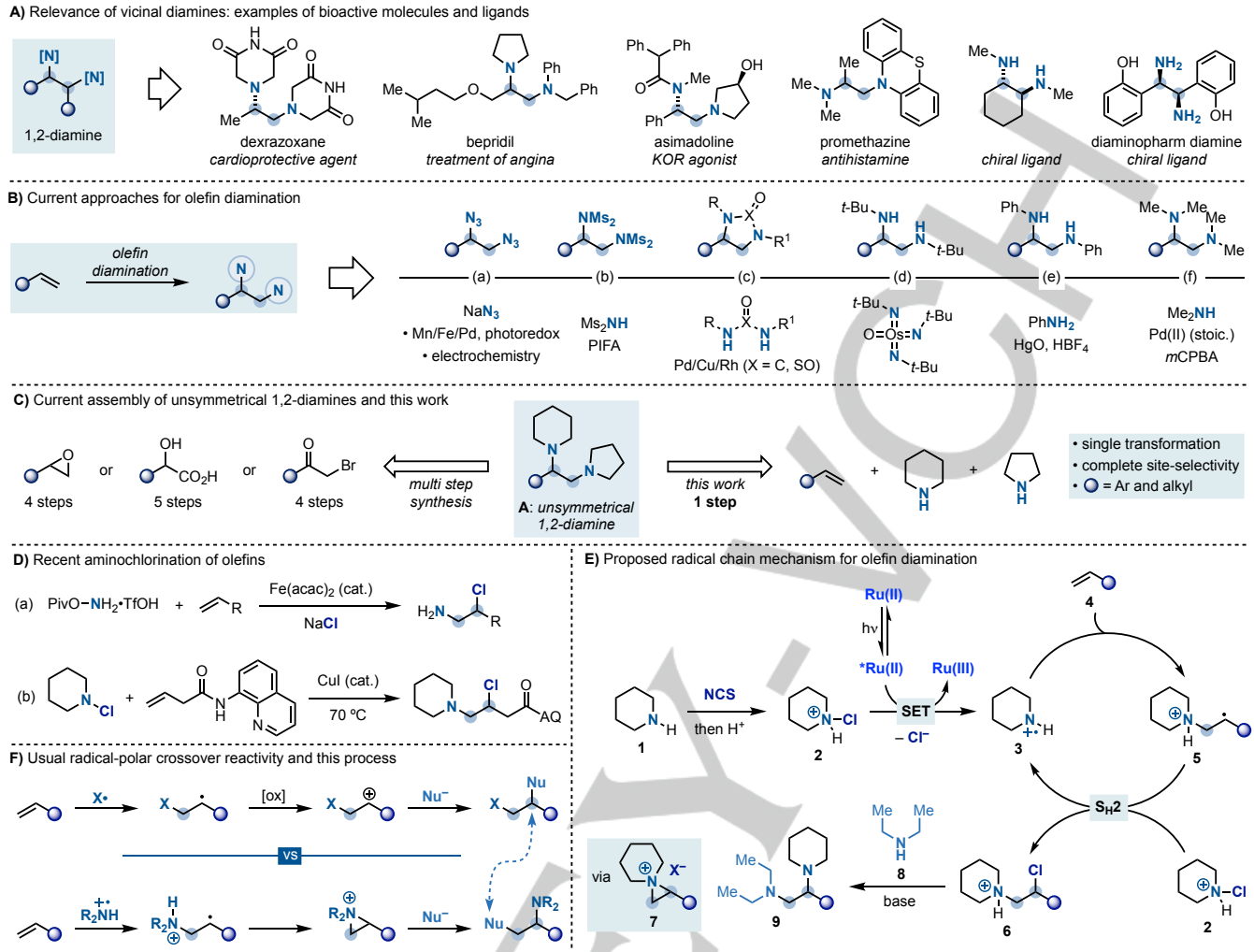

Scheme 1. (A) Vicinal diamines are high-value materials impacting many chemical sciences. **(B)** Current olefin diamination strategies do not enable the direct use of alkylamines. **(C)** The construction of unsymmetrical diamines requires multi-step syntheses while the strategy reported here assembles them in a single step. **(D)** Recent developments for olefin aminochlorination. **(E)** The proposed mechanism for olefin diamination involves the generation of an aminium radical to achieve an aminochlorination reaction which is followed by aziridinium formation and regioselective ring-opening. **(F)** This radical-polar crossover strategy offers a different disconnection to classical approaches.

More recently Morandi has developed an Fe-catalysed aminochlorination of olefins using *O*-Piv hydroxylamine and NaCl as the chlorine source (Scheme 1D, reaction a).[17] This strategy enables the addition of a free amino group across the olefin, which requires further multi-step manipulation to access any desired alkylamine. During the execution of this project, Fu has used preformed secondary *N*-chloroamines under Cu-catalysis to enable aminochlorination of 3-butenoic derivatives containing an 8-aminoquinoline (AQ) directing group required for binding and activation of the metal catalyst (Scheme 2C, reaction b).[18] In both reports, the isolated β-chloroamines have been modified to yield various β-functionalised amines. Overall, despite these advances, the direct construction of β-chloroamines using unfunctionalized alkylamines and alkenes is still not possible and still prepared by multi-step sequences from the corresponding epoxides.[19] We were hopeful that addressing this synthetic gap might provide a powerful entry for olefin diamination where complex alkylamines can be sequentially introduced across non-activated olefins in a programmable manner.

As shown in Scheme 1E, we envisioned a process where initial chlorination of an alkylamine (e.g. piperidine **1**) with NCS, followed by the addition of a strong Brønsted acid would form a highly activated *N*-chloroammonium salt **2**. This species has a very high reduction potential (E_{red} = +0.43 V vs SCE)[14] and should undergo exothermic SET reduction from the photoexcited state of a $Ru(bpy)_3^{2+}$ photocatalyst ($^*E_{ox}$ = –0.81 V vs SCE).[20] This event ought to trigger a radical chain propagation where the incipient aminium radical **3** would react with an olefin coupling partner **4** with complete *anti*-Markovnikov selectivity.[21] At this point S_H2 functionalization of the β-ammonium radical **5** with another molecule of **2** would regenerate the chain-carrying aminium radical **3** and provide the protonated β-chloroamine **6** that can undergo further ionic reactivity. Indeed, as β-chloroamines are ambiphilic building blocks, we speculated that upon addition of a base, a transient aziridinium ion **7** could be accessed.[19a] The high electrophilicity of this species should ensure a facile ring-opening reaction by a second alkylamine (e.g.

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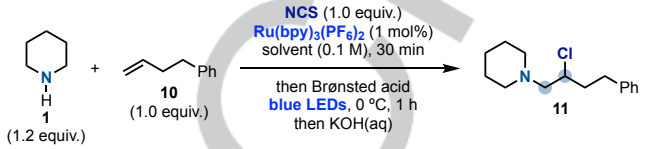
Et_2NH **8**) to give the desired product **9**. The high selectivity of this reaction for the less substituted site[22] should ensure full regioselectivity in our proposal for vicinal dialkylamine synthesis. Mechanistically, it is interesting to note that we would explore umpolung radical chemistry to assemble the first C–N bond by ATRA (atom-transfer radical reaction) reactivity and natural ionic polarity to forge the second one. Furthermore, radical chemistry would initially deliver the first amine at the most reactive terminal carbon of the olefin, to then rearrange it to the internal one upon addition of the second nucleophilic building block. This strategy therefore offers the opposite disconnectivity to what is normally observed in olefin difunctionalization via radical-polar crossover strategies (Scheme 1F).[23]

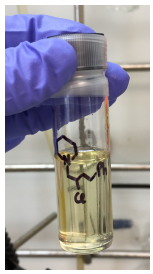
Development and Scope of Olefin Aminochlorination

Optimization of the aminochlorination process started by using piperidine **1** as the amine, 4-phenylbutene **10** as the olefin building block, and NCS (Scheme 2). We were pleased to find out that this reactivity could be immediately achieved in high yield by using $HClO_4$ (pK_a = –10) (6.0 equiv.) as the Brønsted acid and $Ru(bpy)_3(PF_6)_2$ (1 mol%) as the photocatalyst in CH_2Cl_2 solvent under blue light irradiation at 0 °C (entry 1). Interestingly, while HFIP proved to be a powerful solvent to achieve aromatic C–H amination, its use in these settings completely suppressed the desired reactivity and led to complex reaction mixtures (entry 2). Weaker acids were evaluated and while TFA (pK_a = –0.25) was found optimum (96% yield, entry 3), AcOH (pK_a = 4.76) did not lead to product formation (entry 4). In this case, as AcOH is not strong enough to promote *N*-chloroamine protonation, we believe that the radical chain propagation cannot be initiated due to an endothermic SET between *Ru(II) ($^*E_{ox}$ = –0.81 V vs SCE) and *N*-chloropiperidine (E_{red} = –1.80 V vs SCE).[24] The equivalents of TFA could be reduced to 3.0 without affecting the overall productivity of the reaction (entry 5 and 6). However, during the substrate scope evaluation better and more consistent results were obtained with 6.0 equiv. of the acid. Evidence for the efficiency of the radical chain propagation was obtained by measuring the quantum yield for the reaction, which gave $\Phi > 200$. We then decided to make use of the fast nature of the aminochlorination radical chain to scale-up the process. Using a custom-made batch-to-flow reactor developed at Eli Lilly, **11** was prepared on multi-gram scale by slightly changing the reaction conditions (higher concentration: 0.6 M, reduced photocatalyst loading: 0.5 mol%). The flow process proved to be a very effective solution for the scale-up of the original reaction (0.1 mmol, 96%, 1 hour), as it provided similar yield and excellent productivity in a much shorter time (70 mmol, 87%, 3.75 min – productivity = 16.7 mmol min^{-1} – residence time = 8.7 sec), which could not be achieved in batch.[24]

The scope of the aminochlorination reaction proved to be general and enabled the direct installation of a broad range of secondary as well as primary amines across **10** (Scheme 3A). We started by evaluating the use of differentially substituted piperidines and found that a variety of substituents across the *N*-heterocycle core were tolerated. This included sterically encumbering methyl groups at C-2 and C-6 (**12** and **13**), and a C-3 free alcohol (**14**). C-4 substituted piperidines are commonly found in the core structure of many opioid analgesics and antipsychotic agents such as pethidine and haloperidol. Pleasingly, we were able to engage advanced building blocks containing C-4 azide (**15**) useful in click chemistry ligation, benzylic quaternary centre (**16**), sulfonamide (**17**), tertiary benzylic alcohol (**18**), and *O*-aryl ether units (**19**). The amine leading to product **20** is the direct precursor in the synthesis of the anti-Alzheimer drug donepezil.



Entry	Brønsted acid	(equiv.)	solvent	yield (%)
1	$HClO_4$	(6.0)	CH_2Cl_2	89
2	$HClO_4$	(6.0)	HFIP	–
3	**TFA**	**(6.0)**	**CH_2Cl_2**	**96**
4	AcOH	(6.0)	CH_2Cl_2	–
5	TFA	(3.0)	CH_2Cl_2	92
6	TFA	(1.0)	CH_2Cl_2	48
7	TFA	(6.0)	CH_2Cl_2	87%
batch-to-flow: 4 g min^{-1} [70 mmol scale]				



Scheme 2. Development of the aminochlorination reaction using piperidine **1** and olefin **10**.

Other saturated *N*-heterocycles were tolerated and we successfully extended this chemistry to the introduction of morpholines (**21** and **22**), *N*-Cbz-piperazine (**23**), pyrrolidine (**24**), and azepane (**25**), as well as azetidine (**26**) and a spirocyclic derivative which has application as morpholine bioisostere (**27**). Non-cyclic secondary amines were tested next and they efficiently delivered the desired products in high yields (**28**–**30**). Finally, we evaluated the use of primary amines. While $MeNH_2$ gave the desired product **31** in low yield, sterically more demanding substrates reacted smoothly providing **32**–**34** in high conversions. The chemistry was also extended to olefin functionalization using (+)-norephedrine (**35**) and (–)-*cis*-myrtanylamine (**36**).

Evaluation of the olefin scope was performed using piperidine as the amine and it revealed that a wide range of alkyl substituents could be present. Alkyl groups containing activated C–H bonds for H-atom abstraction (HAT) by aminium radicals were tolerated (**37** and **38**), as well as substrates containing inductively electron withdrawing ester (**39**), nitrile (**40**), and Weinreb amide (**41**) groups. Protected amine and alcohol functionalities were also compatible and provided the desired products **42** and **43** in high yields. Disubstituted olefins may be employed as demonstrated by the formation of **44** and **45**.

The number of functional groups tolerated by this process meant that we were able to successfully use it for the late-stage aminochlorination of a protected L-allyl glycine residue (**46**), a protected cinchonidine alkaloid (**47**), and the terpene (–)-carvone (**48**). In this last example, the two olefins are electronically different, which ensured complete chemoselectivity for the functionalization of the electron rich one.

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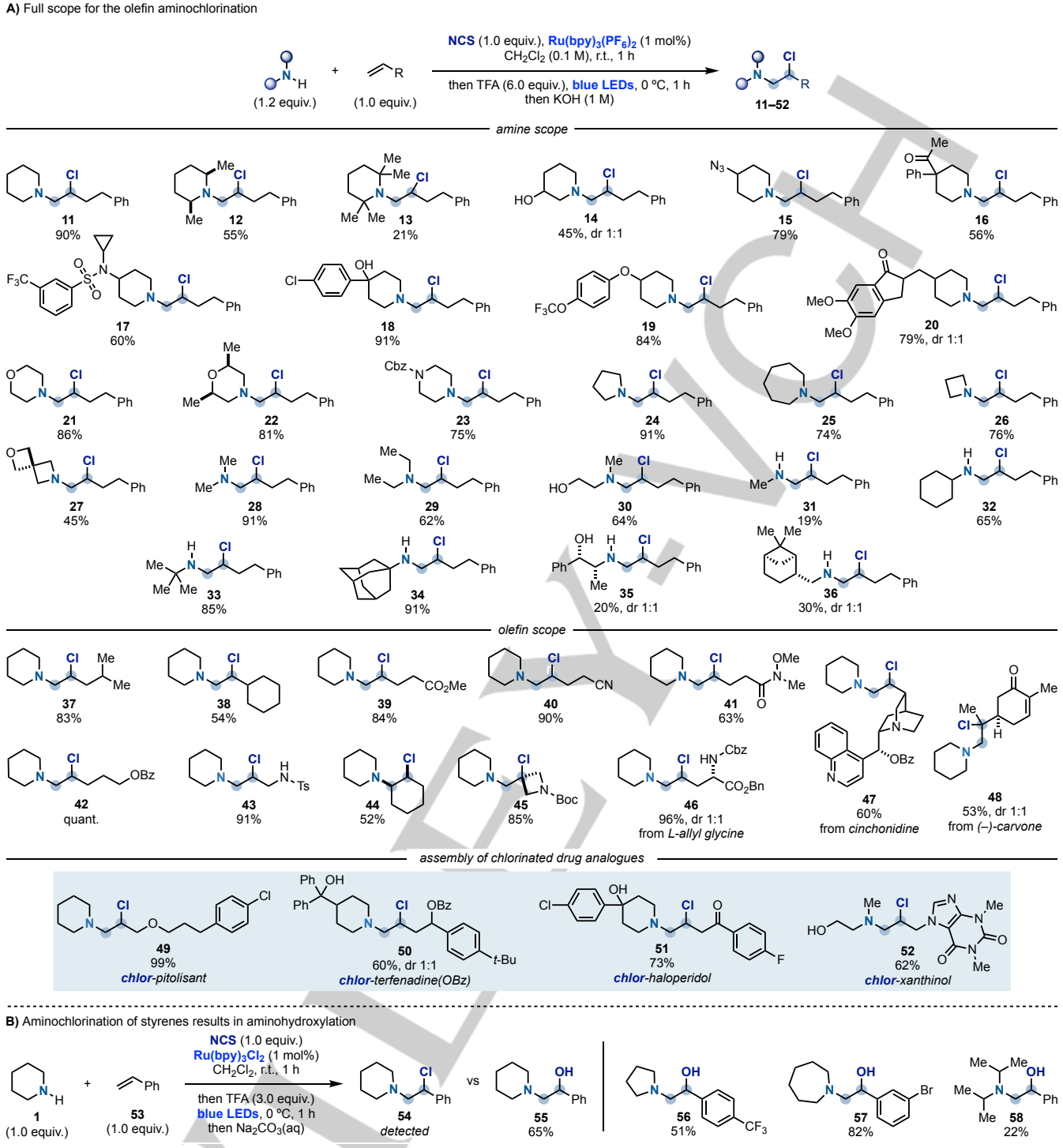

Scheme 3. (A) Substrate scope for the aminochlorination of olefins with different amine and olefin building blocks and its use to assemble chlorinated drug analogues. **(B)** Aminochlorination of styrenes results in aminohydroxylation products.

To further demonstrate the utility of this amination strategy, we sought to adapt it to the direct assembly of sp^3 chlorinated drug analogues. Using readily available and inexpensive amines and olefin building blocks we were able to rapidly access a representative selection of potentially interesting analogues of pitolisant (treatment of narcolepsy) (**49**), terfenadine (antiallergic) (**50**), haloperidol (antipsychotic) (**51**) and xanthinol (vasodilator) (**52**). This reactivity enabled the direct construction of the drug cores in one step and also the installation of a chlorine atom at a specific sp^3 site, which can be then used as handle for further modification.

When evaluating the olefin scope, we realized that styrene **54** displayed a slightly different reactivity profile (Scheme 3B). While aminochlorination (**54**) could be achieved as demonstrated by crude LC-MS analysis, the more activated nature of the benzylic chloride meant that, upon basic work up, full hydrolysis to the

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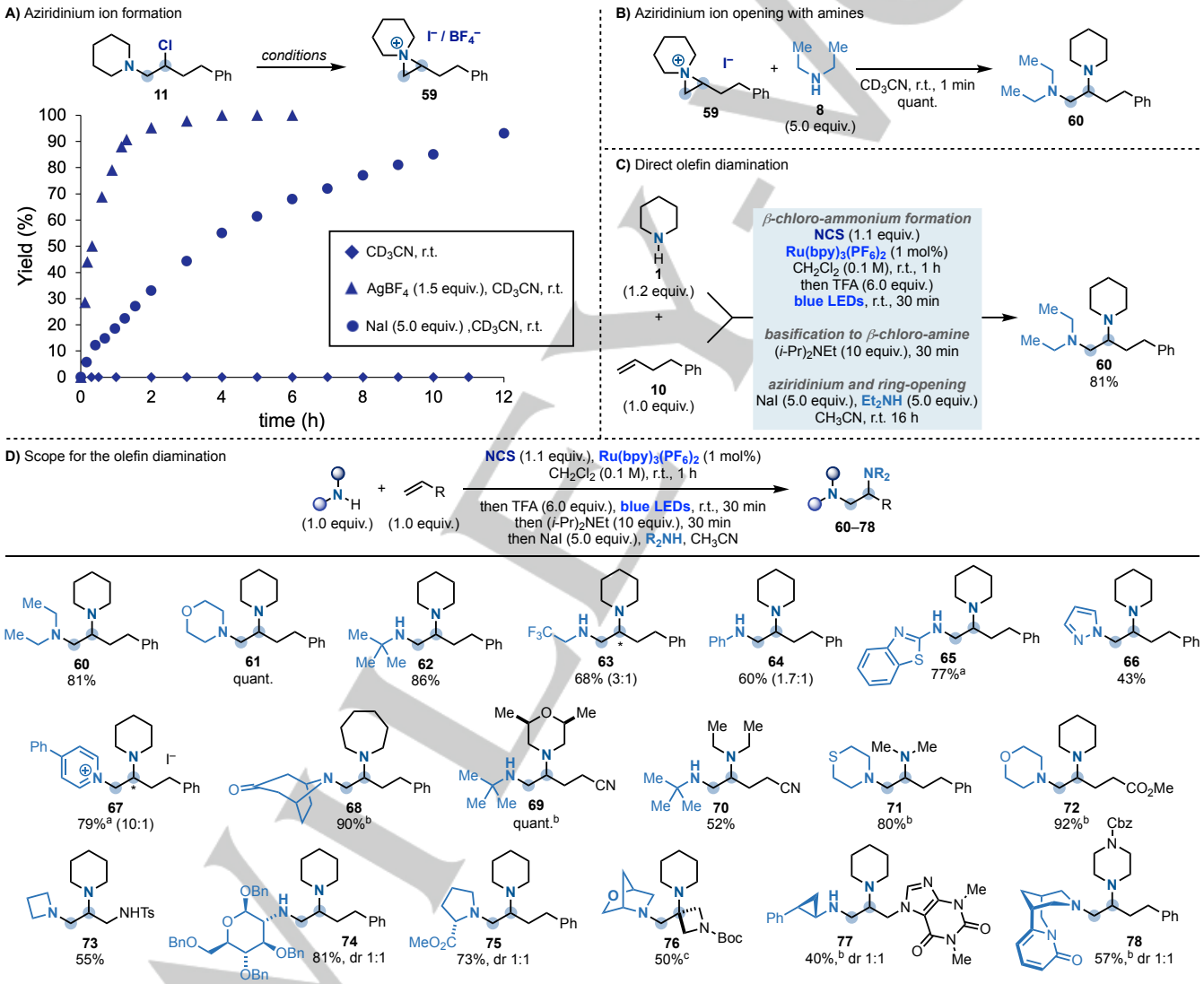
amino-alcohol **55** took place.[25] The process was extended to both cyclic and acyclic amines with differentially substituted styrene partners to give amino-alcohols **56**–**58**. Overall, this reactivity provides a direct access to aminohydroxylated building blocks that are otherwise still prepared via olefin epoxidation followed by nucleophilic substitution.

Development and Scope of Olefin Diamination

Having developed a versatile and general process for olefin aminochlorination using a broad range of alkylamines, we decided to validate its implementation as part of a strategy leading to an overall diamination. Key to the success of this proposal is the ability of the β-chloroamine intermediates to undergo aziridinium ion formation followed by regioselective nucleophilic ring-opening. As the β-chloroamine substrates were found to be stable at room temperature, we performed initial experiments to identify conditions that could then be adapted for an *in situ* aziridinium ion formation. As shown in Scheme 4A, while **11** was stable in CD_3CN at room temperature, efficient aziridinium **59** formation was achieved by either addition of $AgBF_4$[26] (1.5 equiv.) or NaI (5.0 equiv.). In the case of NaI, the reaction presented a slightly slower profile but complete conversion could be achieved in a 18 h time window. With **59** in hand, we initially evaluated the ability of a secondary amine to undergo regioselective ring-opening at the less substituted carbon (Scheme 4B). Pleasingly, upon addition of Et_2NH **8** (5.0 equiv.) immediate formation of the desired product **60** as a single regioisomer was observed.[24]



Scheme 4. (A) Reaction profiles for the formation of aziridinium **59** from **11**. **(B)** Aziridinium ring opening with Et_2NH **8** is immediate. **(C)** Development of a procedure for direct olefin diamination. **(D)** Substrate scope for the direct olefin diamination using a range of different amine and olefin building blocks. * Denotes the minor constitutional isomer.

Having validated the conversion of the β-chloroamine **11** into the corresponding aziridinium ion **59** and its following nucleophilic ring-opening with a secondary amine (**59**+**8**→**60**), we were keen to adapt this approach to a one-pot procedure. As shown in

Scheme 4C, we identified an optimum protocol starting with the initial aminochlorination step (see Scheme 3, entry 3), followed by basification with (*i*-Pr)$_2$NEt (10 equiv.) and final *in situ* aziridinium formation–ring opening reaction by addition of NaI (5.0 equiv.) and Et$_2$NH (5.0 equiv.) as a solution in CH$_3$CN. This procedure provided **60** in excellent yield, and importantly, streamlined its preparation from a current 5 step synthesis to a single chemical operation that took overall 19 h.[27]

With this optimized procedure in hand, we focused our efforts on establishing the scope for the olefin diamination reaction (Scheme 4D). Using piperidine as the aminium radical precursor and 4-phenyl-butene **10** as the olefin, we then evaluated several other *N*-nucleophiles. Pleasingly, we were able to use secondary cyclic (**61**) as well as primary amines of both high steric hindrance (**62**) and decreased nucleophilicity (**63** and **64**). In just these two cases over the entire scope, the products were respectively obtained as a 3:1 and 1.7:1 mixtures of isomers resulting from an unselective aziridinium ring-opening, while benzothiazole-2-amine gave selectively **65**. Pleasingly, we could also introduce aromatic *N*-heterocycles like pyrazole and 4-Ph-pyridine that gave the desired product **66** and **67** in good yield. In the case of **65** and **67**, a basic work-up at the end of the aminochlorination step before aziridinium formation was crucial in obtaining high reaction yield.

Other unsymmetrical 1,2-diamines were assembled by generating the aminium radical from various *N*-heterocycles like azepane and *syn*-2,6-dimethylmorpholine, that, following aziridinium ring–opening with nortropinone and *t*-BuNH$_2$, gave **68** and **69** in excellent yields. Acyclic amines were also amenable to this reactivity as demonstrated by the sequential introduction of Et$_2$NH and *t*-BuNH$_2$ on 4-pentenenitrile (**70**), whilst Me$_2$NH and thiomorpholine gave **71** also in high yields. Ester containing olefins were compatible with the reactivity (**72**) and by using *N*-Ts-allylamine as the alkene we prepared **73** in high yield that represents a completely differentiated 1,2,3-triamine.

More complex building blocks were accessed by using a protected glucosamine and L-proline methyl ester in the ring-opening event that gave **74** and **75** respectively (1:1 mixture of epimers). Implementation of 3-methylene-*N*-Boc-azetidine as the olefin, piperidine as the aminium radical precursor, and 2-oxa-5-azobicyclo[2.2.1]heptane as the final nucleophile gave **76** in good yield, demonstrating that aziridinium formation at tertiary centres is possible. A theophylline-containing olefin was reacted with piperidine and the MAO inhibitor tranylcypromine to give **77** in good yield (1:1 mixture of epimers). Finally, by sequentially using *N*-Cbz-piperazine (aminium radical) and the biologically active alkaloid cytisine (nucleophilic amine) we prepared **78** in high yield (1:1 mixture of epimers).

We also found that the diamination could be applied to a broad range of styrene building blocks (Scheme 5A). In this case however, addition of NaI to aid aziridinium ion formation was not required due to the more activated nature of the analogous benzylic β-chloroamine.[28] In line with the observed aminohydroxylation reactivity, we found out that the addition of the second amine nucleophile in the presence of Na$_2$CO$_3$ at the end of the aminochlorination step immediately provided the corresponding 1,2-diamines. Importantly, in this case the substitution occurred at the more activated benzylic position, which is in line with the known reactivity of aryl-substituted aziridiniums. This process was compatible with the use of secondary (**79**–**81**) and primary amines (**82**) as well as pyridine that led to the isolation of the corresponding salt **83** in moderate yield. More advanced amine building blocks were easily introduced and the chemistry was also expanded to both electron rich (**84** and **85**) and electron poor (**86** and **89**) styrenes and tolerated *ortho* (**87**) as well as *meta* (**88**) substituents.

When primary amines were used, the aminochlorination occurred smoothly and upon basification a cyclization occurred leading to the corresponding and stable aziridine, that could not be ring-opened *in situ* (Scheme 6C). This procedure allowed the introduction of amines of increasing steric hindrance (**90**–**92**) and also worked well on disubstituted olefins (**93**). Overall, this reactivity enabled a one-step access to all-alkyl substituted aziridines, which are an underrepresented class of building blocks currently elusive by nitrene-based approaches requiring multi-step sequences.[29]

The initial aminochlorination process represents an interesting gateway to expand the number of potential products of amino-functionalization. As aziridinium ions support a rich array of chemistry, we have been able to engage **11** in several other processes (Scheme 5B). Oxygen nucleophiles were competent partners as demonstrated by the use of NaOMe and NaOH that led to aminohydroxylated products **94** and **95** with opposite selectivity in the ring-opening step. NaN$_3$ could be used to access the vicinal amino-azide **96** albeit as a mixture of isomers (unselective aziridinium ion ring-opening). NaCN enabled selective ring-opening resulting in the formation of a C–C bond which delivered **97** with potential application to the synthesis of β-aminoacids. Vicinal fluoro-amines are important and highly sought-after building blocks in medicinal chemistry[19b, 30] but we did not succeed in identifying reaction conditions for aziridinium ring-opening with fluoride sources. Nevertheless, we found out that direct addition of Et$_3$N•3HF to **11** provided **98** in moderate yield and as a single isomer. Finally, addition of LiAlH$_4$ at 0 ºC enabled efficient reduction (**99**), which gives direct access to challenging products of Markovnikov hydroamination currently prepared by reductive amination on ketones.[31] We have showcased the potential utilization of this reactivity in the preparation of the cough suppressant benproperine (**103**). In this case, the commercial phenol **100** was allylated to give **101**, which underwent efficient aminochlorination with piperidine (**102**, quant.). Aziridinium ion formation and selective LiAlH$_4$ reduction gave benproperine in just 3 steps.

Conclusions

Direct synthesis of vicinal alkyl diamines from olefins has been a long-standing challenge and still requires multi-step synthesis. In this article we have reported the development of a photoinduced protocol for their efficient and selective assembly. This strategy exploits the generation of aminium radicals from *in situ* generated *N*-chloroamines and their ability to react with a broad range of olefins with *anti*-Markovnikov selectivity. The resulting β-chloroamines are powerful ambiphilic building blocks for further elaboration as demonstrated by their direct conversion into the corresponding aziridinium ions. The following *in situ* ring-opening reaction with primary, secondary and aromatic amine nucleophiles allowed regioselective diamination.

Overall, this reactivity enables, for the first time, the direct and selective introduction of advanced amine building blocks across olefins in a single chemical operation. The process tolerated a broad range of functionalities, does not require the presence of

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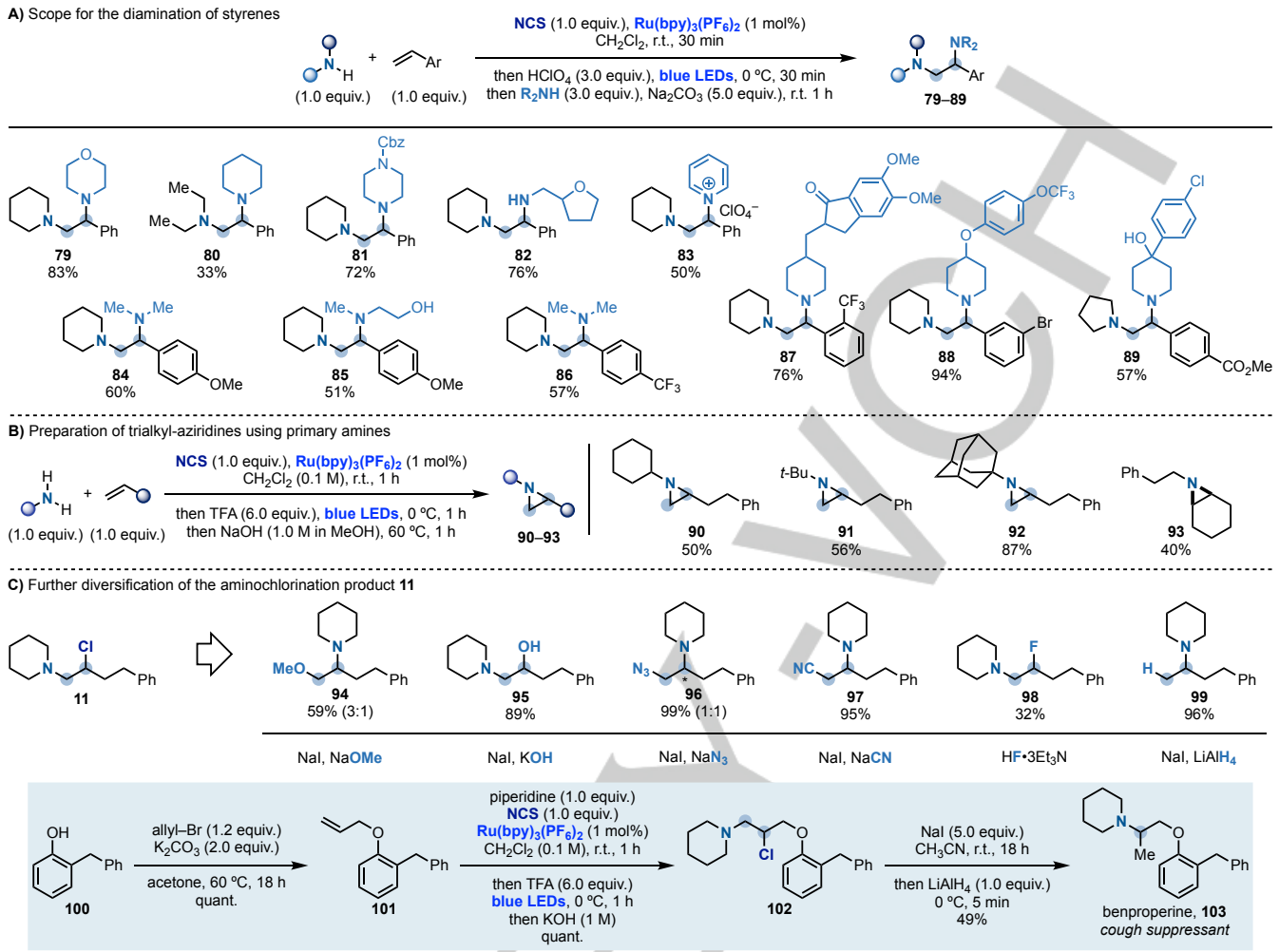

Scheme 5. (A) Styrene diamination provides a different regioselectivity. **(B)** The use of primary amines in the methodology enables the preparation of trialkyl aziridines. **(C)** Further diversification of β-chloroamine and use of the reduction process for the 3-step synthesis of benproperine. [a] A basic work-up was performed before addition of NaI and the amine. [b] Upon addition of NaI and the amine the mixture was warmed to 60 °C. [c] In this case the aziridinium was formed using $Ag(BF_4)$. * Denotes the minor constitutional isomer.

any directing group, and is scalable using batch-to-flow technology. We believe that these results can substantially broaden the construction of valuable nitrogenated small-molecule building blocks that are central to pharmaceutical, agrochemical and chemical sciences.

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Keywords: diamination • aminochlorination • nitrogen radicals • alkylamines • olefin functionalization

[1] (a) A. Ricci, **2008**, Wiley-VCH, Weinheim, Germany; bD. Lucet, T. L. Gall, C. Mioskowski, *Angew. Chem. Int. Ed.* **1998**, *37*, 2580-2627.

[2] G. R. Lappin, J. D. Sauer, *Marcel Dekker, New York* **1989**.

[3] (a) W. E. Fristad, T. A. Brandvold, J. R. Peterson, S. R. Thompson, *J. Org. Chem.* **1985**, *50*, 3647-3649; (b) Y. A. Yuan, D.-F. Lu, Y. R. Chen, H. Xu, *Angew. Chem. Int. Ed.* **2016**, *55*, 534; (c) G. Fumagalli, P. T. G. Rabet, S. Boyd, M. F. Greaney, *Angew. Chem. Int. Ed.* **2015**, *54*, 11481-11484; (d) M.-Z. Lu, C.-Q. Wang, T.-P. Loh, *Org. Lett.* **2015**, *17*, 6110; (e) S.-J. Shen, C.-L. Zhu, D.-F. Lu, H. Xu, *ACS Catal.* **2018**, *8*, 4473-4482; (f) N. Fu, G. S. Sauer, A. Saha, A. Loo, S. Lin, *Science* **2017**, *357*, 575-579.

[4] (a) K. Muñiz, L. Barreiro, R. M. Romero, C. Martínez, *J. Am. Chem. Soc.* **2017**, *139*, 4354-4357; (b) Muñiz, *Acc. Chem. Res.* **2018**, *51*.

[5] (a) Y. Zhu, R. G. Cornwall, H. Du, B. Zhao, Y. Shi, *Acc. Chem. Res.* **2014**, *47*, 3665-3678; (b) G. L. J. Bar, G. C. Lloyd-Jones, K. I. Booker-Milburn, *J. Am. Chem. Soc.* **2005**, *127*, 7308-7309; (c) K. Shen, Q. Wang, *Chem. Sci.* **2015**, *6*, 4279-4283; (d) K. Muñiz, C. Martínez, A. Iglesias, *Chem. Rec.* **2016**, *16*, 2561-2572; (e) K. Muñiz, C. Martínez, *J. Org. Chem.* **2013**, *78*, 2168-2174; (f) D. E. Olson, J. Y. Su, D. A. Roberts, J. D. Bois, *J. Am. Chem. Soc.* **2014**, *136*, 13506-13509.

[6] C.-Y. Cai, X.-M. Shu, H.-C. Xu, *Nature Comm.* **2019**, *10*, 4953-.

[7] (a) K. Muñiz, *New J. Chem.* **2005**, *29*, 1371-1385; (b) K. Muñiz, M. Nieger, H. Mansikkamäki, *Angew. Chem. Int. Ed.* **2019**, *42*, 5958-5961.

[8] J. Barluenga, F. Aznar, M. C. S. D. Mattos, W. B. Kover, S. Garcia-Granda, E. Perez-Carreno, *J. Org. Chem.* **1991**, *56*, 2930-2932.

[9] V. G. Aranda, J. Barluenga, F. Aznar, *Synthesis* **1974**, 504-505.

[10] J.-E. Backvall, *Tetrahedron Lett.* **1978**.

[11] F. Durrenberger, S. Burckhardt, W. Buhr, P. O. Geisser, F. Funk, V. A. Corden, S. M. Courtney, M. Stephen, T. Fryatt, S. Jaeger, M. P. Rdgill,

M. Slack, C. J. Yarnold, T. W. Yau, in *WO 2011/026959 AI* (Ed.: V. International), Switzerland, **2010**.

[12] R. Lan, B. R. Huck, X. Chen, L. C. Deselm, Y. Xiao, H. Qiu, C. Neagu, I. Mochalkin, T. L. Johnson*, Vol. WO 2013/040044 Al* (Ed.: M. GmbH), Germany, **2013**.

[13] (a) P. Saravanan, A. Bisai, S. Baktharaman, M. Chandrasekhar, V. K. Singh, *Tetrahedron* **2002**, *58*, 4693-4706; (b) E. Curthbertson, P. O'Brien, T. D. Towers, *Synthesis* **2001**, 693-695.

[14] A. Ruffoni, F. Julia', T. D. Svejstrup, A. McMillan, J. J. Douglas, D. Leonori, *Nat. Chem.* **2019**, *11*, 426.

[15] (a) F. Minisci, R. Galli, *Tetrahedron Lett.* **1964**, 3197-3200; (b) F. Minisci, R. Galli, M. Cecere, *Tetrahedron Lett.* **1966**, 3163-3166.

[16] (a) R. S. Neale, *Tetrahedron Lett.* **1966**, 483-488; (b) R. S. Neale, N. L. Marcus, *J. Org. Chem.* **1967**, *32*, 3273-3284.

[17] C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322-5363.

[18] (a) M. P. Lau, A. J. Cessna, Y. L. Chow, R. W. Yip, *J. Am. Chem. Soc.* **1971**, *93*, 3808-3809; (b) A. J. Musacchio, B. C. Lainhart, X. Zhang, S. G. Naguib, T. C. Sherwood, R. R. Knowles, *Science* **2017**, *355*, 727; (c) R. S. Neale, *Synthesis* **1971**, *1*, 1.

[19] For the preparation of β-N-choloroamines and their use in asymmetric catalysis, see: (a) G. L. Hamilton, T. Kanai, F. D. Toste, *J. Am. Chem. Soc.* **2008**, *130*, 14984-14986; (b) G. Pupo, A. C. Vicini, D. M. H. Ascough, F. Ibba, K. E. Christensen, A. L. Thompson, J. M. Brown, R. S. Paton, V. Gouverneur, *J. Am. Chem. Soc.* **2019**, *141*, 2878-2883.

[20] C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322-5363.

[21] (a) M. P. Lau, A. J. Cessna, Y. L. Chow, R. W. Yip, *J. Am. Chem. Soc.* **1971**, *93*, 3808-3809; (b) A. J. Musacchio, B. C. Lainhart, X. Zhang, S. G. Naguib, T. C. Sherwood, R. R. Knowles, *Science* **2017**, *355*, 727; cR. S. Neale, *Synthesis* **1971**, *1*, 1.

[22] (a) S. S.´, M. D'hooghe, S. Catak, H. Eum, M. Waroquier, V. V. Speybroeck, N. D. Kimpe, H.-J. Ha, *Chem. Soc. Rev.* **2012**, *41*, 643-665; (b) T.-X. Métro, B. Duthion, D. G. Pardo, J. Cossy, *Chem. Soc. Rev.* **2012**, *39*, 89-102. (c) N. De Rycke, O. David, F. Couty, *Org. Lett.* **2011**, *13*, 1836-1839

[23] J. A. Murphy, *Radicals in Organic Synthesis (Chapter 2.7)* **2001**, P. Renaud & M. P. Sibi Ed., *Wiley*.

[24] See SI for more information.

[25] G. Miao, B. E. Rossiter, *J. Org. Chem.* **1995**, *60*, 8424-8427.

[26] P. J. Foley, R. S. Neale, *J. Chem. Eng. Data* **1968**, *13*, 593-595.

[27] We have attempted the one-pot diamination procedure using NBS and NIS in place of NCS as this should have avoid the addition of NaI. However, in both cases no product was formed.

[28] S. E. d. Sousa, P. O'Brien, P. Poumellec, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1483-1492.

[29] (a) J. B. Sweeney, *Chem. Soc. Rev.* **2002**, *31*, 247-258; (b) L. Degennaro, P. Trinchera, R. Luisi, *Chem. Rev.* **2014**, *114*, 7881-7929; (c) B. B. Lohray, Y. Gao, K. B. Sharpless, *Tetrahedron Lett.* **1989**, *30*, 2623; (d) Z. Ma, Z. Zhou, L. Kürti, *Angew. Chem. Int. Ed.* **2017**, *56*, 9886-9890.

[30] (a) G. Pupo, A. C. Vicini, D. M. H. Ascough, F. Ibba, K. E. Christensen, A. L. Thompson, J. M. Brown, R. S. Paton, V. Gouverneur, *J. Am. Chem. Soc.* **2019**, *141*, 2878-2883; (b) M. Morgenthaler, E. Schweizer, F. Hoffmann-Roder, F. Benini, R. E. Martin, G. Jaeschke, B. Wagner, H. Fischer, S. Bendels, D. Zimmerli, J. Schneider, F. Diederich, M. Kansy, K. Muller, *ChemMedChem* **2007**, *2*, 1100.

[31] (a) O. I. Afanasyev, E. Kuchuk, D. L. Usanov, D. Chusov, Chem. Rev. 2019, 119, 11857-11911. For a different approach towards alkylamines from aldehydes and ketones, see: (b) A. Trowbridge, D. Reich, M. J. Gaunt, Nature 2018, 561, 522-527.

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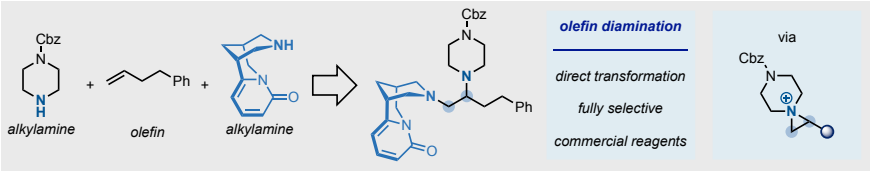

Direct olefin diamination with alkylamines has been achieved using a photoinduced radical-to-polar cross-over strategy. This approach enables the programmable and sequential addition of complex amine building blocks across olefins in a single chemical transformation.

Sebastian Govaerts, Lucrezia Angelini, Charlotte Hampton, Laia Malet-Sanz, Alessandro Ruffoni and Daniele Leonori**

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