Expedient syntheses of N-heterocycles via intermolecular amphoteric diamination of allenes

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Saturated 1,4-diazo heterocycles including piperazines, 1,4-diazepanes, and 1,4-diazocanes, are highly important for therapeutic development, but their syntheses are often tedious. We describe here an amphoteric diamination strategy to unite readily available 1,2-, 1,3- or 1,4-diamine derivatives with electron-deficient allenes via a formal \([n + 2]\) \((n = 4, 5, 6)\) cyclization mode to produce the corresponding 1,4-diazo heterocycles in just one step. This strategy features mild reaction conditions, high functional group tolerance, and scalability (gram scale). The reagents used are cheap and readily available and no transition metal catalysts are needed. More sophisticated products containing trifluoromethyl group or bicyclic ring systems can be accessed via a one-pot procedure as well. Our mechanistic studies support that formation of mono-iodinated or chlorinated diamine intermediates is important for the desired transformation and the commonly proposed chloride-iodide exchange process and a radical \(N−C\) bond formation is unlikely when the combination of NCS/KI is used.
M. More than half of the FDA-approved small-molecule therapeutics contain at least one N-heterocyclic ring. Among these N-heterocycles, saturated N-heterocycles are indispensable in drug discovery. For example, piperidine and piperazine rank the first and third most common N-heterocycles appearing in small-molecule drugs, respectively. Over 60 FDA approved drugs contain a piperazine ring, several of which are within the top 100 best-selling pharmaceutical products. Structurally, piperazine features a six-membered ring with two nitrogen atoms in 1,4-relationship. This structural feature provides large polar surface area and relative structural rigidity. The piperazine moiety can often function as both hydrogen bond acceptor and donor and lead to improved potency, selectivity, water solubility, oral bioavailability, and ADME (absorption, distribution, metabolism, and excretion) properties. Similarly, other 1,4-diazo heterocycles such as 1,4-diazepanes and 1,4-diazocanes are important structural motifs in bioactive molecules. Saturated 1,4-diazepane backbone has already emerged in several important FDA-approved small-molecule drugs. However, most of the 1,4-diazo heterocycle-containing molecules, particularly piperazinyl-containing drugs, only have substitutions on one or both of the nitrogen atoms and the piperazine moiety is used as a linker to connect two portions for target binding or as an appendage to tune physicochemical properties. Only a small percentage of them have substitutions on the carbon atoms of the 1,4-diazo heterocycle and these substitutions are usually limited to methyl, aryl, or carboxylate groups. Therefore, there is lack of carbon-substitution diversity on these 1,4-diazo heterocycle scaffolds in modern drug discovery and this is mainly due to the scarcity of available synthetic methods to efficiently provide carbon-substituted 1,4-diazo heterocycles with high regio-, stereo- and/or enantio-selectivity.

So far, the most commonly used approaches to synthesize piperazines are the reduction of (di)ketopiperazines and stepwise N-alkylation of 1,2-diamines. These methods generally use amino acids and 1,2-diamines as starting materials and require multiple steps. Therefore, the carbon-substitution pattern highly depends on the starting material availability. Recently, transition metal including Pd, Au, Zr, and Ir catalyzed amine cyclization methods have been developed to synthesize piperazines. These methods need to use precious and often air and moisture sensitive heavy metal catalysts and are very substrate dependent. Notably, a series of stannyl amine protocol (SnAP) reagents have been developed by Bode and co-workers to enable efficient and modular access of N-heterocycles including piperazines. One limitation for the SnAP method is the involvement of toxic tin reagents which is partially solved by their development of a series of silicon amine protocol (SLAP) reagents. Zhou and co-workers have developed an asymmetric reduction of pyrazine derivatives to provide substituted piperazine products in high enantioselectivity. In this case, the pyrazine starting materials need to be pre-activated first. An appealing strategy to introduce substituents on piperazine is direct C-H functionalization. Unfortunately, most of the available methods for α-C-H functionalization of amines including piperidines and pyrrolidines failed miserably on piperazine substrates due to the existence of the second nitrogen, which either creates various side reactions including elimination and dehydrogenation or diminishes the reactivity of the α-C-H bond and/or the catalyst used. Progress has been made in direct α-C-H lithiation-trapping protocol of N-Boc-protected piperazines, but the reaction conditions are generally harsh and the results are highly substrate dependent. Recently, pioneered by MacMillan and co-workers, direct α-C-H functionalization of piperazines via photoredox catalysis has emerged as a promising method. In addition to transition metal catalysis, an interesting phosphate-catalyzed umpolung addition and intramolecular conjugative addition strategy has been developed by the Lu group to synthesize piperazines and 1,4-diazepanes. In this case, only symmetrical 1,2- or 1,3-diamine derivatives (tosyl sulfonamides) were explored. In general, the syntheses of 1,4-diazepanes and 1,4-diazocanes are also very limited and far less studied than the piperazines. 1,4-Diazocanes present an even higher level of synthetic challenge due to the existence of a strained eight-membered ring. Overall, there is a strong need for efficient and selective synthesis of substituted piperazines, 1,4-diazepanes and 1,4-diazocanes in order to unleash their full potential in novel therapeutic development.

We wondered whether an amphoteric diamination reagent would undergo cyclization with an unsaturated π-system via a formal [n + 2] (n = 4, 5, 6) cyclization process to produce piperazine, 1,4-diazepane, and 1,4-diazocane products in one step (Fig. 1). This amphoteric diamination strategy, once successfully developed, would provide rapid access to these privileged saturated N-heterocyclic structures and significantly enrich the toolbox of both medicinal chemists and synthetic chemists. In principle, 1,N-diamine (n = 2, 3, 4) derivative could be viewed as an amphoteric reagent. In 6, the two nitrogen atoms are electronically differentiated. Deprotonation of the blue nitrogen would generate the nucleophilic nitrogen species and the red halogen-amine (chloro- or iodo-amine) or O-benzoyl hydroxylamine would function as the electrophilic part. Amphoteric reagent could be synthesized or generated in situ readily from the 1,N-diamine (n = 2, 3, 4) via selective halogenation or oxidation of the red nitrogen. Herein, we report our initial discovery in developing a transition-metal-free intermolecular amphoteric diamination of allenes to synthesize a wide range of carbon-substituted piperazines, 1,4-diazepanes, and 1,4-diazocanes in one step. This enabling method features mild reaction conditions and cheap and readily available reagents. The primary cyclization product could be converted to more sophisticated product by exploiting the rich chemistry of its enamine moiety.

Results
Optimization of reaction conditions. Our investigation of the amphoteric diamination of allenes (Fig. 1c) started with chloroamine sulfonamide 11a (Table 1) which was synthesized from selective chlorination of the more electron-rich alkyamine 11 in presence of a more electron deficient sulfonamide. Chloroamine sulfonamide 11a can be purified on silica gel column and stored in refrigerator for several months. Since copper catalyst has often been used in catalyzing electrophilic amination reactions, we first treated a mixture of chloroamine sulfonamide 11a and allenyl ester 12 (1.5 equiv.) with 10% CuI and Cs2CO3 (1.5 equiv.) in THF at room temperature (Table 1, entry 1). To our delight, cyclized vinylogous amide product 13 was obtained in 20% yield surprisingly as a single regioisomer. Since vinylogous amide 13 is not stable on silica gel, a one-pot reduction was conducted to convert it to piperazine 14. No product 13 was observed without CuI (Table 1, entry 2), which indicates the importance of CuI. With this encouraging result, we investigated various copper catalysts, ligands, and other reaction parameters, but failed to improve the reaction yield. We then switched CuI to KI (0.2 equiv.) and desired product 13 was obtained in 35% yield (Table 1, entry 3). It turned out that iodide was catalyzing this transformation, not the copper part. Once we realized this key point, we quickly optimized the reaction conditions by simply increasing the amount of KI (Table 1, entries 4–6) and product 13 was produced in 79% yield with either 1.0 or 2.0 equiv. of KI. Other iodide salts such as NaI and tetrabutylammonium iodide can be used as well and the reaction conditions were found to be similar.
(TBAI) are less effective than KI (Table 1, entries 8, 9). THF was approved to be superior to CH$_3$CN (Table 1, entry 7) and other solvents and increasing the reaction temperature to 40 °C did not improve the reaction yield (Table 1, entry 10). Since chloroamine sulfonamide 11a was produced simply by chlorination of 11 with N-Chlorosuccinimide (NCS), we explored the possibility of in situ generation of 11a (Table 1, entry 11). This approach was effective to produce 13 in 79% yield. We speculated that the role of KI was presumably to generate a more reactive iodoamine via an iodide-chloride exchange$^{42}$, which turned out not to be the

**Table 1 Optimization of reaction conditions**

| Entry | X | Reaction conditions (equiv.) | Yield of 13$^a$ (yield of 14$^b$) |
|-------|---|-------------------------------|---------------------------------|
| 1     | Cl| CuI (0.1), Cs$_2$CO$_3$ (1.5), THF, RT, 24 h | 20% |
| 2     | Cl| Cs$_2$CO$_3$ (1.5), THF, RT, 24 h | 0% |
| 3     | Cl| KI (0.2), Cs$_2$CO$_3$ (1.5), THF, RT, 24 h | 35% |
| 4     | Cl| KI (0.5), Cs$_2$CO$_3$ (1.5), THF, RT, 24 h | 75% |
| 5     | Cl| KI (1.0), Cs$_2$CO$_3$ (1.5), THF, RT, 24 h | 79% (65%) |
| 6     | Cl| KI (2.0), Cs$_2$CO$_3$ (1.5), THF, RT, 24 h | 79% |
| 7     | Cl| KI (1.0), Cs$_2$CO$_3$ (1.5), MeCN, RT, 24 h | 63% |
| 8     | Cl| NaI (1.0), Cs$_2$CO$_3$ (1.5), THF, RT, 24 h | 54% |
| 9     | Cl| TBAI (1.0), Cs$_2$CO$_3$ (1.5), THF, RT, 24 h | trace |
| 10    | Cl| KI (1.0), Cs$_2$CO$_3$ (1.5), THF, 40 °C, 24 h | 78% |
| 11    | H | NCS (1.05), THF, 1 h, then 12, KI (1.0), Cs$_2$CO$_3$ (1.5), RT, 24 h | 79% |
| 12    | H | NIS (1.05), THF, 1 h, then 12, Cs$_2$CO$_3$ (1.5), RT, 24 h | 86% (70%) |
| 13    | H | as entry 12, but gram scale | ~% (76%) |

$^a$ NMR yield of 13

$^b$ Isolated yield of 14

Fig. 1 Amphoteric diamination cyclization. a A general design of an amphoteric diamination cyclization to an unsaturated π system. b Potential amphoteric diamination reagents and their syntheses. c This work: a transition-metal-free intermolecular amphoteric diamination of allenes to synthesize piperazines, 1,4-diazepanes, and 1,4-diazocanes
Substrate scope for the synthesis of piperazines. With the optimized reaction conditions in hand, the scope study of both the 1,2-diamines and allenes was subsequently conducted (Table 2). The one-pot amphoteric diamination procedure was approved to be very general in preparing various carbon-substituted piperazine products. Different 1,2-diamine derivatives underwent cyclization with allenyl ester 12 to give the desired piperazine products (19–57) which can also be viewed as β,γ-amino acid derivatives. Functional groups including bromide (28, 29), CF3 (21), NO2 (23), free alcohol (39), Boc-carbamate (40), olefin (44), cyclopropyl group (41), and heteroaromatics (30–35, 45, 51, 58) such as quinoline, pyridine, furan, pyrrole, indole, and thiophene are all well tolerated under the mild reaction conditions. The tosyl group can be switched to other sulfonamide groups (45–52) including the readily removable nosyl group (48–50). In addition to other allenyl esters (53–57), allenyl ketone (58–64), nitrile (65), sulfone (66), phosphine oxide (67), and phosphonate (68) can be used as the unsaturated π-system for the amphoteric diamination cyclization to afford piperazines with a diverse substituents on C2. The introduction of sulfone, phosphate oxide, and phosphonate into the piperazine products offers opportunities for further structural diversifications via various olefination reactions.

Piperazines with more than one carbon-substitutions can be produced as well (69–81). Notably, for the case of 2,6-disubstituted piperazines, after the one-pot NaBH3CN reduction, instead of getting the 2,6-cis products with two equatorial substituents, which are often produced as the predominant products especially with nitrogen-protected cases43, the more challenging 2,6-trans substituted products were obtained as the major products (69, 70; dr > 15:1). The trans-selectivity observed in the above reduction is presumably due to an axial hydride attack on the iminium ion intermediate formed under acidic conditions. Iminium ion conformer 70a is favored over 70b because the latter suffers from strong steric interaction between the C-Me and N-Me groups (A1,2 type interaction)44. An axial hydride attack on 70a delivers the 2,6-trans substituted product as the major stereoisomer. For the case of 2,5-substituted piperazines, instead of getting the 2,5-trans substitution patterns where the two substituents are equatorially oriented, 2,5-cis substituted products were obtained in our cases (71–76, 79, 80). Based on the crystal structures of 71 and 75, an intermediate we isolated before NaBH3CN reduction (the corresponding primary amphoteric cyclization product isomerized to 75’ on silica gel column), we hypothesized that the phenyl group in iminium ion intermediate 75a prefers to occupy the axial position to avoid strong steric repulsion with the tosyl group and an axial delivery of the hydride provides the 2,5-cis product as the dominant stereoisomer. These results enable ready access of 2,6-trans or 2,5-cis substituted piperazines, which are otherwise challenging to synthesize. Interestingly, for the cases of bicyclic piperazine products 77, 78 and 81, the major products (dr > 15:1) turned out to have a 2,6-cis and/or 2,5-trans stereochemical relationship. In these cases, the bicyclic ring systems locked the conformation and an axial hydride attack gave the major product. The relative stereochemistry of 70, 71, 76, 77, and 81 were unambiguously established by X-ray crystallography of themselves (70, 71, 77) or their derivatives (76, 81, see the Supplementary Figs. 1 and 2).

Scope for the synthesis of 1,4-diazepanes and 1,4-diazocanes. We then explored the possibility of expanding the amphoteric diamination cyclization strategy to synthesize 1,4-diazepanes and 1,4-diazocanes with readily available 1,3- or 1,4-diamine derivatives (Table 3). With the NIS reaction conditions at an elevated reaction temperature (60 °C; Conditions A), 1,4-diazepane products 86–102 were produced smoothly in modest to good yield. For the products containing an all-carbon quaternary center (103–106), the combination of NCS (1.05 equiv.) and KI (2.0 equiv.) at 60 °C (Conditions C) is superior to the NIS conditions. For the case of 1,4-diazocane synthesis, a highly strained eight-membered ring needs to be constructed and it has been a long standing synthetic challenge. It turned out that the amphoteric diamination cyclization strategy is highly efficient for this task. Simply heating the mixture of mono-N-iodinated 1,4-diamines generated in situ with NIS treatment and the corresponding allene substrates at 100 °C followed by one-pot reduction, desired 1,4-diazocanes were produced in modest to good yield (107–116). For the syntheses of 1,4-diazepanes and 1,4-diazocanes, like the case of piperazine synthesis, allenyl ester (86–97, 103–107, 112–115), ketone (100), nitro (98, 116), sulfone (102, 108–111), phosphine oxide (99), and phosphonate (101) are all effective substrates. Despite the elevated reaction temperatures, a broad range of functional groups are tolerated. The necessity of an elevated reaction temperature is presumably due to the difficulties involved in closing the seven- or eight-membered ring systems. The amphoteric iodoamine intermediates derived from 1,4-diamines are believed to have lower reactivity in comparison to the ones derived from 1,2- and 1,3-diamines presumably due to the weakened or lack of intramolecular hydrogen bonding interaction between the sulfonamide hydrogen atom and the iodoamine nitrogen atom.

Diversification of the vinylogous amide products. Instead of directly reducing the vinylogous amide products generated from the amphoteric diamination cyclization of allenes, we further explored the possibility of harnessing their intrinsic reactivity to introduce other substituents and/or to increase product structural complexity. Due to the importance of trifluoromethyl (CF3) group in medicinal chemistry and the current synthetic challenges of installing CF3 at the α-position of piperazines45, we started to develop a protocol to synthesize α-CF3-substituted piperazines (Fig. 2a). After the formation of the crude primary vinylogous amide product 13, trifluoromethanesulfonic acid (TfOH) was used to isomerize the vinylogous amide to an iminium intermediate, which was then trapped by a nucleophilic addition of trifluoromethyl anion derived from a combination of KH2F and the Ruppert–Prakash reagent TMSCF3. Desired product 117 was obtained in 42% yield from 11. On the other hand, the vinylogous amide products 120 or 121 synthesized from the amphoteric diamination cyclization of 118 or 119 with allen ine 12 can be readily converted to a 6,6- or 6,7-fused bicyclic product (122 or 123) in 54 or 42% yield, respectively, via an intramolecular Mannich-type reaction (Fig. 2b). These two diversification reactions demonstrate the synthetic potential of the amphoteric diamination cyclization of allenes to synthesize complex N-heterocycles and highlight the advantages of using allene substrates.

Removal of tosyl and nosyl groups. While sulfonamides prevalently exist in many drug molecules and other biofunctional molecules, it would significantly enhance the impact of the amphoteric diamination cyclization strategy in medicinal chemistry if the sulfonamide groups such as tosyl and nosyl groups can be removed easily to allow further functionalization of these privileged N-heterocycles. We have successfully demonstrated...
Table 2 Substrate scope for piperazine synthesis

| Substrate | Yield (%) |
|-----------|-----------|
| R = F    | 63% (19)  |
| R = Cl   | 62% (20)  |
| R = CF₃  | 57% (21)  |
| R = Me   | 50% (22)  |
| R = NO₂  | 72% (23)  |
| R = H    | 63% (24)  |
| R = Me   | 47% (31)  |
| R = NO₂  | 67% (26)  |
| R = Br   | 66% (27)  |
| R = Cl   | 64% (29)  |
| R = Me   | 70% (38)  |
| R = OH   | 50% (39)  |
| R = NHBoc| 67% (40)  |
| R = OEt  | 63% (41)  |
| R = NO₂  | 65% (42)  |
| R = Me   | 65% (43)  |
| R = NHBoc| 40% (44)  |
| R = OEt  | 65% (45)  |
| R = NO₂  | 57% (46)  |
| R = Me   | 65% (47)  |
| R = NO₂  | 65% (48)  |
| R = Cl   | 65% (49)  |
| R = Me   | 65% (50)  |
| R = NO₂  | 65% (51)  |
| R = Me   | 61% (52)  |
| R = NO₂  | 33% (53)  |
| R = Me   | 78% (54)  |
| R = nBu  | 50% (55)  |
| R = Me   | 55% (56)  |
| R = OMe  | 81% (57)  |
| R = nBu  | 55% (58)  |
| R = Me   | 43% (59)  |

2.6-trans

2.5-cis

2.5-trans, 2.6-cis

2.5-cis
that both the tosyl and nosyl groups can be removed readily (Fig. 3). For example, upon treatment of piperazine 20 with MeSO₃H in a mixture of trifluoroacetic acid (TFA) and thioanisole, desired product 124 was obtained in 76% yield. The nosyl group of 1,4-diazepane 90 can be removed under basic conditions (Cs₂CO₃) with PhSH as nucleophile and product 125 was obtained in 80% yield. The ease of removing both the tosyl and nosyl group enables the introduction of other functionalities on the nitrogen atoms, which carries important value in applying this method in medicinal chemistry.

Discussion

To provide insights about the reaction mechanism of this amphoteric diamination cyclization, we first used ESI-MS to monitor the reaction process. The reaction between 11 and 12 was studied under both the NIS and NCS/KI reaction conditions (Fig. 4 and Supplementary Figs. 3–6). Upon the treatment of 11 with NIS, we observed the formation of iodoamine 11b ([M+H]+: 397.1), but it cannot be isolated due to its instability under light and heat and on silica gel column. After introduction of allene 12 and Cs₂CO₃ to 11b, the formation of an iodide intermediate with molecular weight of 508.1 was observed. This iodide intermediate was tentatively assigned as 126 or 127, which cannot be differentiated by the ESI MS data. We also tried to isolate these two proposed allylic iodide intermediates, but these attempts were unsuccessful due to their high reactivity despite their clear existence in the ESI-MS systems. Longer reaction time led to the formation of 13, observed at 381.3 ([M+H]+) or 513.2 [M+Cs]+, via a substitution process to form the second carbon–nitrogen bond and closed the six-membered ring. An aziridinium ion intermediate is unlikely to be involved in the ring closing process, but cannot be ruled out completely at this stage. Interestingly, when N-chloroamine 11a, which is bench stable and can be isolated as a white solid, was treated with KI, we did not observe the formation of 11b via the ESI-MS study, but 126 or 127 was observed upon the treatment with KI, 12, and Cs₂CO₃. This result suggests that the formation of 126 or 127 from a combination of 11/NIS or 11/NCS/KI might occur via different reaction mechanisms and chloroamine 11a did not undergo a simple chloride-iodide exchange process to form iodoamine 11b while such chloride-iodide exchange process is commonly proposed in literature.

The detailed mechanism for the formation of the first carbon–nitrogen bond has not been well understood yet. This net addition of an iodo/chloroamine to the double bond of an allene substrate might go through a stepwise radical process, a concerted process, or a stepwise ionic process (Fig. 5). Both the radical process and ionic process have been proposed for the reactions of N-iodo/chloroamine with olefins. In our case, a radical process would involve a homolytic cleavage of the N-I/Cl bond of 11b/11a to generate nitrogen radical, which would...
add on the sp carbon of allene 12 to form an allylic radical. The latter would be trapped by iodide to produce allylic iodide 126/127 (Fig. 5a). A concerted mechanism resembling the hydroboration process via a four-membered ring transition state (130 or 131) would give 126/127 as well (Fig. 5b). In this case, the more nucleophilic nitrogen atom would align up with the sp carbon of allene 12 to give the observed regiochemistry. Additionally, stepwise ionic process could be operational (Fig. 5c-e). For example, the iodoamine (11b) or chloroamine (11a) nitrogen could use its electron pair to undergo nucleophilic attack on the sp carbon of allene 12 to form the observed regiochemistry. To probe the addition process of N-iodo/chloroamine to allene substrate such as 12, we prepared 1,2-diamine derivative 135 containing a vinyl cyclopropane moiety, a commonly used radical clock (Fig. 6a). When 135 was treated with the NIS reaction conditions, the reaction turned out to be quite complex and we did not observe the formation of desired piperazine product 136; instead the formation of pyrrolidine product 137 was observed. We then removed the NaBH₄CN reduction step and were able to identify 137 as the major product in 37% yield from a complex mixture (Fig. 6b). The structure of 137 was unambiguously confirmed by X-ray crystallographic analysis. The formation of 137 is presumably via a NIS promoted intramolecular iodination cyclization followed by replacement of the resulting iodide with succinimide. NIS could activate the cis-double bond directly or it could iodinate the secondary alkyl amine first and the resulting iodoamine would activate the double bond via an intramolecular 1⁺ transfer process⁵⁴. Interestingly, when we switched the NIS conditions to the NCS/KI conditions, desired piperazine product 136 was obtained as the major product in 47% yield along with 137 in 15% yield (Fig. 6c). Again, these results indicate that the reaction mechanism for the amphoteric dianion cyclization processes under the NIS conditions is different from the ones under the NCS/KI conditions. The latter might involve the formation of iodine monochloride (ICl, Fig. 5d). Why the NCS/KI conditions are able to produce 136 and suppress the formation of 137 requires further investigation. Similar results were observed when substrate 138 was used. The NIS conditions gave a complex mixture, but the NCS/KI conditions provided desired product 139 in 38% (Fig. 6d). The formation of both 136 and 139 under the NCS/KI conditions suggests that a radical mechanism to form allylic iodide intermediates such as 126/127 observed in ESI-MS is unlikely because the nitrogen radical can be readily intercepted by the intramolecularly tethered olefins via a 5-exo-trig cyclization process. Additionally, in order to explore the roles of NIS and NCS/KI in these transformations, a few more experiments were explored (Fig. 7). First, a reaction between diimine 140 and allene 12 was conducted under basic conditions (Cs₂CO₃) in THF at room temperature. The formation of mono- and bis-nucleophilic addition products 142 and 141 were observed by ¹H NMR analysis of the reaction mixture, which was further confirmed by a one-pot reduction of the corresponding vinylogous amide intermediates to 144 and 143, respectively (Fig. 7a). Further treatment of the reaction mixture of 140 and 12 with NIS or ICl followed by NaBH₄CN reduction did not result in the formation of 20, but 143 in 33 or 27% yield, respectively (Fig. 7b). This result ruled out the possibility of 142 as a potential intermediate for the formation of 20. Since ICl was proposed as a plausible intermediate when the combination of NCS/KI was employed, we used it to replace NIS and NCS/KI for the reaction of 140 with 12 and desired product 20 was formed in 13% yield along with 144 in 31% yield (Fig. 7c), which suggests that ICl is not as good as NIS or NCS to generate the corresponding iodo or chloroamine intermediate. This notion was corroborated by the fact that an unidentified...
Fig. 4 ESI-MS study of the reaction process. Both the NIS and NCS/KI procedures were monitored. The blue numbers are observed ion signals (m/z). MS analysis was performed by nano-electrospray ionization-mass spectrometry (nanoESI-MS), using a 4000 QTRAP mass spectrometer, equipped with a home-built nanoESI source. NanoESI tips (~10 μm o.d.) were pulled from borosilicate glass capillary tips (1.5 mm o.d. and 0.86 mm i.d.) using a micropipette puller.

Fig. 5 Proposed pathways for the first C–N bond formation. a A radical process for the C–N bond formation. b A concerted process for the C–N bond formation. c A stepwise mechanistic mechanism followed by 1+ shift with iodoamine 11b. d A stepwise ionic mechanism with chloroamine 11a followed by ICI formation. e A stepwise ionic mechanism involving the formation of iodonium ion intermediate 134.

mixture was generated when 140 was treated with ICl in THF-d₈, but clear formation of the iodoamine intermediate was observed by ¹H NMR analysis when NIS was used (Supplementary Fig. 7). Additionally, pre-treatment of allene 12 with NIS for 1 h before the addition of 140 or simply adding 12, NIS and 140 at the same time was able to produce 20 in 53 or 56% yield, respectively, which is slightly lower than the yield (62%) of pre-treatment of 140 with NIS for 1 h before the addition of 12 (Table 2 and Fig. 7d). Interestingly, while pre-treatment of 140 with ICl for 1 h before the addition of 12 or pre-treatment of 12 with ICl for 1 h before the addition of 140 could form 20 in 13 or 15% yield, respectively, the operation of simply mixing 12, ICl and 140 at the same time only afforded a trace amount of 20 (~2%). Our ¹H NMR experiments showed that 12 did not react with NIS or ICl in THF-d₈ after 1 h (Fig. 7e and Supplementary Fig. 8) and ICl reacted with THF solvent to produce a new product, which might be a THF polymerization or ring opening product, but need more experiments to elucidate. Overall, these experiments indicate that the successful formation of iodo or chloroamine intermediates is important for the desired amphoteric diamination and whether or not ICl is involved when NCS/KI was used remains unanswered.

In summary, an amphoteric diamination strategy has been developed to rapidly synthesize medicinally important carbon-substituted 1,4-diazo heterocycles including piperezines, 1,4-diazepanes, and 1,4-diazocanes. These N-heterocycles are otherwise difficult to access. This highly modular and convergent strategy utilizes readily available 1,2-, 1,3- or 1,4-diamine derivatives and electron-deficient allenes as the two coupling partners, which are assembled into saturated 1,4-diazo heterocycles via a formal [n + 2] (n = 4, 5, 6) cyclization mode. It does not require any precious transition metal catalysts. The reagents used are cheap and the reaction features mild reaction conditions, high functional group tolerance, and scalability (gram scale). In addition to a direct one-pot reduction of vinylogous amide products, the transformations reported here are expected to have broad applications in novel therapeutic discovery and development processes. Our current mechanistic studies showed that the formation of mono-iodinated or chlorinated amphoteric diame intermediates is important for the success of the desired cyclization and a commonly proposed chloride-iodide exchange process and a radical N–C bond formation is unlikely when the combination of NCS/KI is used. Further detailed mechanistic studies and developing an enantioselective version of this reaction are currently undergoing in our laboratory.
**Fig. 6** Probe reaction mechanism via 135 and 138. a Using vinyl cyclopropane-containing substrate 135 to probe the radical mechanism for the first C–N bond formation under the NIS conditions. b Synthesis of 137 from 135 without the NaBH₃CN reduction step and a crystal structure of 137. c Using 135 to probe the radical mechanism for the first C–N bond formation under the NCS/KI conditions. d Using 138 to probe the radical mechanism for the first C–N bond formation under the NCS/KI conditions.

**Fig. 7** Probe reaction mechanism with 140 and 12 with NIS and ICl. a Reaction of 140 and 12 under Cs₂CO₃ conditions without NIS. b Reaction of 140 and 12 under Cs₂CO₃ conditions followed by addition of NIS or ICl. c Reaction of 140 and 12 under ICl conditions instead of the NIS conditions. d Pre-treatment of 12 with NIS or ICl before the addition of 140. e Reaction of 12 with NIS or ICl in THF-d₈.
Methods

General procedure for piperazine synthesis. To a 2-dram vial wrapped with aluminium foil was added a 1,2-diamine substrate (0.1 mmol), NIS (0.105 mmol), and dry THF (1 mL). The reaction mixture was stirred for 1 h under argon after an allene substrate (0.15 mmol) and CaCO₃ (0.15 mmol) was added. After the reaction mixture was stirred for 24 h, Na₂H₂CN (0.2 mmol) and a co-solvent of MeOH/ACOH (pH = 4, 1 mL) were added to the reaction mixture. After 3 h, the reaction was quenched with a saturated aqueous solution of NaHCO₃, extracted with CH₂Cl₂ for three times. The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo. The crude mixture was purified on silica gel column with hexane/EtOAc as eluents to give the desired piperazine product.

Data availability

The X-ray crystallographic coordinates for the structures of 70 (CCDC 1561430), 71 (CCDC 1561427), 77 (CCDC 1561428), 75' (CCDC 1583717), 137 (CCDC 1582122), a derivative of 76 (CCDC 1561429), and a derivative of 81 (CCDC 1561431) reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC). The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/org/quest/cif. The authors declare that the data supporting the findings of this study are available within the article and its Supplementary Information Files. All other data are available from the authors upon reasonable request.

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**Author contributions**

Z.Y. and M.D. conceived and designed the experiments. Z.Y. performed the synthesis experiments and S.A. and Z.Y. conducted the ESI/MS studies. Z.Y., S.A., Y.X. and M.D. analyzed the data and wrote the manuscript together.

**Additional information**

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**Competing interests:** The authors declare no competing financial interests.

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