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Lewis acid–catalyzed domino generation/[2,3]-sigmatropic rearrangement of ammonium ylides to access chiral azabicycles

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[2,3]-Sigmatropic rearrangement of ammonium ylides represents a fundamental reaction for stereoselective synthesis of nitrogenous compounds. However, its applicability is limited by the scarcity of efficient, catalytic, and mild methods for generating ammonium ylides. Here, we report silver-catalyzed domino generation/[2,3]-sigmatropic rearrangement of ammonium ylides, furnishing chiral azabicycles with bridgehead quaternary stereogenic centers in high enantiomeric purity (up to 99% *ee*). A combination of density functional theory calculations and experimental studies revealed that residual water in the reaction system is crucial for the mild reaction conditions by functioning as a proton shuttle to assist carbon-silver bond protonation and C2—H deprotonation to generate the ammonium ylide. This reaction has a broad application scope. Besides the diverse substituents, N-fused azabicycles of various ring sizes are also easily accessed. In addition to silver salts, this strategy has also been successfully implemented by using a stoichiometric amount of nonmetallic I_2.

INTRODUCTION

[2,3]-Sigmatropic rearrangement of ammonium ylides is one of the most efficient approaches for synthesizing complex nitrogenous compounds (*1*–*3*). During this rearrangement, a new stereogenic carbon center can be stereoselectively created by chiral induction of the neighboring chiral ammonium nitrogen atom through a concerted five-membered ring transition state (*4*–*6*). The most common method to generate ammonium ylides for rearrangement involves two separate steps: quaternization of a tertiary amine and deprotonation of the resulting quaternary ammonium salt with a strong base (Fig. 1A) (*1*–*3*). However, the harsh reaction conditions usually required for generation and deprotonation of the quaternary ammonium salts and the problems associated with purification of these salts limit the applicability of this type of reaction (*7*). To obviate the requirement of synthesizing and purifying problematic quaternary ammonium salts, protocols have been developed for directly generating ammonium ylides from tertiary amino carbonyl compounds by reacting them with a stoichiometric amount of a strong Lewis acid (e.g., $BF_3{\cdot}Et_2O$ and BBr_3) and a strong Brønsted base (*8*, *9*), or with aryne intermediates formed in situ (Fig. 1A) (*10*, *11*). However, to the best of our knowledge, only two catalytic domino processes for directly generating ammonium ylides from tertiary amines have been reported: (i) metal-catalyzed coupling of tertiary amines with diazo esters (*12*) and (ii) Pd-catalyzed N-allylation of tertiary amines with allylic carbonates (Fig. 1A) (*13*, *14*). The scarcity of catalytic methods for domino generation/rearrangement of ammonium ylides highlights the need for development of new strategies and identification of new catalytic systems, particularly that can be performed under mild reaction conditions.

Inspired by the success of π–Lewis acid catalysis (*15*–*19*), we envisioned that π–Lewis acid–catalyzed *5-endo-dig* cyclization of a tertiary amine to an ynone moiety would generate a quaternary ammonium salt and form an azabicyclic skeleton with various ring systems (5/*X*; *X* = 5, 6, and 7) (Fig. 1B). Upon proton transfer, ammonium ylide **3** would be generated from the bicyclic intermediate **2** for subsequent [2,3]-sigmatropic rearrangement. If this multistep process could be accomplished without a strong acid or base, chirality erosion of the potentially racemization-prone precursors or intermediates could be circumvented, and consequently, the chirality information of **1** would be efficiently transferred to product **4** with an N-fused bicyclic skeleton and a bridgehead quaternary center (Fig. 1B) (*20*, *21*). This type of bicyclic framework with various ring systems is commonly present in therapeutics and natural products, such as the human leukemia cell (HL-60) cell adhesion inhibitor NP25302 (*22*), the immunosuppressant FR901483 (*23*), the lycopodium alkaloid serratinine (*24*), the erythrina alkaloid 8-oxoerythraline oxide (*25*), and the antileukemia drug homoharringtonine (*26*, *27*) (Fig. 2). Owing to the challenges presented by installing quaternary stereogenic centers in bicyclic skeletons (*28*, *29*), most of the existing strategies for constructing this type of bicyclic skeleton involve generation of a bridgehead quaternary stereogenic center and a bicyclic framework in separate and multiple steps (*30*–*33*), or they are limited to one type of bicyclic ring system (*34*–*36*). Successful implementation of this strategy would provide not only a new catalytic method for generating ammonium ylides but also general access to bicycles with various ring sizes.

RESULTS AND DISCUSSION

Preliminary validation

Although the hypothesis described above is feasible in principle, many challenges remain. First, ynone **1** is prone to racemization under the acidic conditions used to activate the ynone moiety, and initial studies revealed that substantial chirality erosion occurs during purification of **1** by silica gel chromatography (<80% *ee* from 98% *ee*). II–Lewis acidic metals are capable of selectively activating

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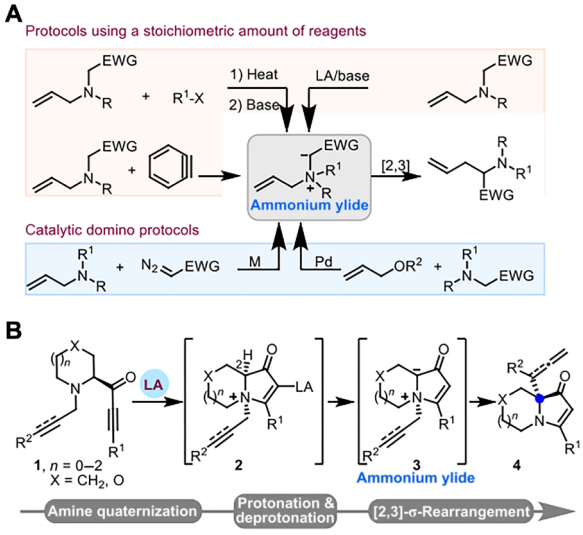


Fig. 1. Research background. (**A**) Known methods for generating ammonium ylides. (**B**) Our strategy: Lewis acid–catalyzed domino generation/[2,3]-sigmatropic rearrangement of ammonium ylides to access chiral azabicycles with bridgehead quaternary stereogenic centers. LA, Lewis acid; EWG, electron-withdrawing group.

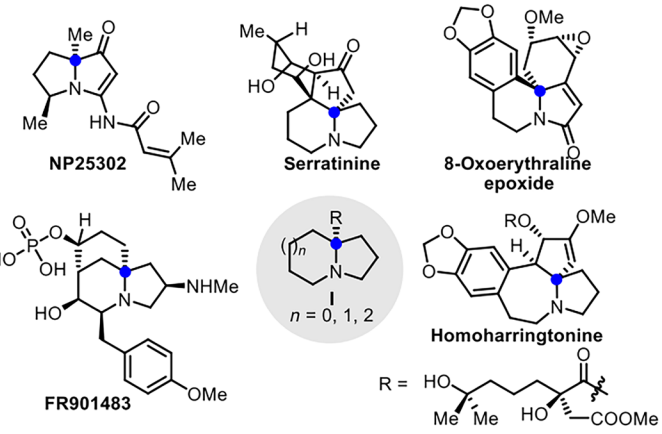


Fig. 2. Representative therapeutics and natural products containing an N-fused bicyclic skeleton with a bridgehead quaternary stereogenic center.

alkynes in complex settings toward a variety of nucleophiles under mild conditions (*15*–*19*). Therefore, we speculated that an appropriate π–Lewis acid would facilitate nucleophilic addition of a tertiary amine to the ynone moiety to form the quaternary ammonium salt without scrambling the chiral center. Second, deprotonation of the quaternary ammonium salts to generate the ammonium ylides often requires a strong base, which can also erode the chirality (*1*–*3*). Regarding this issue, several reactive intermediates have been proposed. The pK_a values of the C2—H moieties of the quaternary ammonium salts were calculated at the start of the present study (Fig. 3). The calculated pK_a of salt **A**, which is generated by nucleophilic addition of a tertiary amine to an enone, is 20.2, indicating that C2—H is weakly acidic. Salt **B** has an endocyclic carbon-carbon double bond that could be formed by nucleophilic addition to an ynone, and it has a C2—H moiety with a pK_a of 16.7. This moiety could donate a proton to a moderate base, theoretically validating the feasibility of our hypothesis. In contrast, the corresponding precursors **C** and **D**, which have carbon-silver bonds, have much higher pK_a values. This indicates that protonation of the carbon-metal bond in **C** or **D** would further enhance the acidity of C2—H. Last, owing to the congested nature of the formed bridgehead quaternary stereogenic carbon center, [1,2]-sigmatropic rearrangement of the ammonium ylide (Stevens rearrangement)—which presumably proceeds by a diradical pathway and could result in racemization—may compete with [2,3]-sigmatropic rearrangement (*1*–*3*).

Reaction optimization

To test the hypothesis described above, as a model study, chiral ynone **1a** was prepared by alkynylation of Weinreb amide **5a**, which was synthesized in three steps from commercially available L-pipecolinic acid (Table 1). We first evaluated Brønsted acids and hard Lewis acids (Table 1), which associate with the carbonyl oxygen atom to activate the ynone group. However, under these conditions, mixtures of unknown composition were produced along with a negligible amount of the expected product **4a** with a versatile allene group installed (entries 1 to 4) (*37*). Because gold salts are widely used to activate alkynes and thus facilitate nucleophilic attack (*15*–*18*), we screened various gold salts in the presence or absence of silver salts. The gold salts alone did not improve the reaction performance (entries 5 to 7). However, (*t*Bu)$_2$(*o*-biphenyl)PAuCl together with AgOTf or $AgBF_4$ gave a promising yield of rearrangement product **4a** with an excellent level of chirality transfer (97% *ee*) (entries 8 and 9). Although the cationic gold salt formed in situ can be considered to be the active catalyst for this reaction, the possibility that the residual trace amount of the silver salt promoted the transformation cannot be ruled out (*19*). Therefore, we evaluated a series of silver salts. To our delight, among the silver salts screened, $AgSbF_6$ was the optimal choice, giving a substantially improved yield of **4a** with high enantiopurity in a much shorter reaction time (entry 12). To further improve the reaction efficiency, we screened a variety of ligands using $AgSbF_6$ as the silver salt (entries 13 to 15). Among these ligands, the phen ligand gave the best results. By further investigating other reaction parameters (see the Supplementary Materials for details), we determined that $AgSbF_6$, phen, CH_3CN, and room temperature were the optimal conditions, giving **4a** in 80% nuclear magnetic resonance (NMR) yield with almost complete chirality transfer (98% *ee*).

Mechanistic study

The M11 density functional (*38*–*41*) with the standard 6-311+G(d,p) basis set [Stuttgart–Dresden electron core potential (*42*, *43*) basis set for Ag and I] was used to gain insight into the possible reaction mechanism (*44*). The free energy profiles are shown in Fig. 4A. The free energy of cation silver species **IM1** and reactant **1a** were chosen as the relative zero in the free energy profiles. Coordination of the C—C triple bond in ynone **1a** to cationic silver species **IM1** forms π-complex **IM2** through an endoergic process (4.0 kcal/mol). Intramolecular nucleophilic attack by the tertiary amine to the silver-activated C—C triple bond occurs via transition state **TS3** with a barrier of only 8.5 kcal/mol to form bicyclic N-chiral alkenyl oxopyrrolyl–silver intermediate **IM4**. A subsequent intramolecular 1,3-H shift generates ammonium ylide intermediate **IM8**. However, the activation barrier of this step was determined to be 70.6 kcal/mol (**TS11**), indicating that the intramolecular 1,3-H shift is kinetically unfavorable. Inspired by Yu's pioneering work (*45*, *46*), we postulated that residual water in the reaction system might assist proton transfer. Therefore, water-assisted

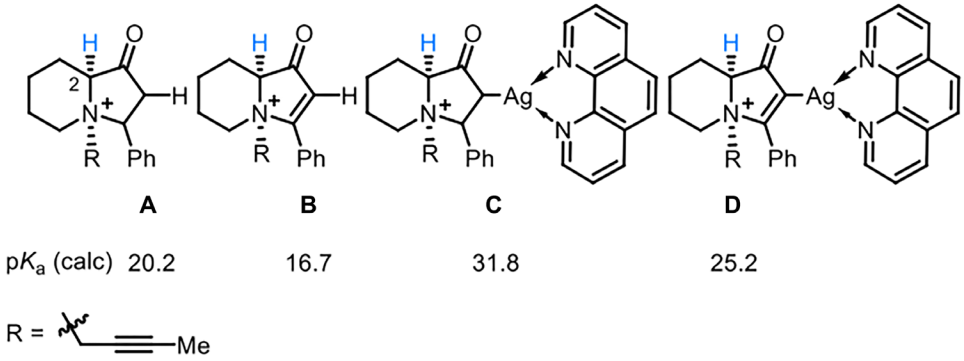
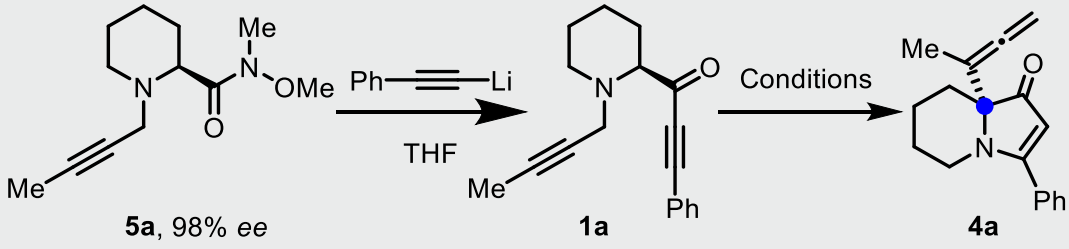


Fig. 3. Calculated pK_a values of the proposed reaction intermediates.

Table 1. Reaction optimization. Conditions: **5a** (0.1 mmol), PhC≡CLi (0.3 mmol), THF (2 ml), −78° to 0°C, 1 hour, followed by aqueous workup; catalyst (0.02 mmol), CH_3CN (1.5 ml), room temperature, 2 to 48 hours. HFIP, hexafluoroisopropanol; IPr, 1,3-bis(diisopropylphenyl)imidazole-2-ylidene); bpy, 2,2-bispyridine; dtbpy, 4,4′-di-tert-butyl bipyridine; phen, 1,10-phenanthroline.



Entry	Catalyst	Time (hours)	% Yield*	% *ee*†
1	*p*-TsOH	48	<5	–
2	HFIP	12	<5	–
3	$Zn(OTf)_2$	12	<5	–
4	$In(OTf)_3$	48	<5	–
5	$Ph_3PAuN(Tf)_2$	36	<5	–
6	IPrAuCl	36	<5	–
7	(*t*Bu)$_2$(*o*-biphenyl)PAuCl	36	<5	–
8	(*t*Bu)$_2$(*o*-biphenyl)PAuCl/ AgOTf	36	14	97
9	(*t*Bu)$_2$(*o*-biphenyl)PAuCl/ $AgBF_4$	36	17	97
10	AgOAc	2	30	97
11	AgOTf	2	43	98
12	$AgSbF_6$	2	47	98
13‡	$AgSbF_6$/bpy	2	72	98
14‡	$AgSbF_6$/dtbpy	2	69	98
15‡	$AgSbF_6$/phen	2	80	98

*NMR yield of **4a** from **5a**. †Determined by chiral HPLC analysis. ‡0.025 mmol of ligand.

proton transfer was also considered. Regrettably, the calculated activation barrier for this step via six-membered ring-type transition state **TS12** is 63.9 kcal/mol. The calculated high energy barrier of the hydrogen shift indicates that concerted proton transfer can be excluded, even with the assistance of water. The pK_a calculations shown in Fig. 3 reveal that the acidity of C2—H substantially increases when the carbon-silver bond of the quaternary ammonium salt intermediate undergoes protonolysis. Therefore, a stepwise pathway involving sequential water-assisted C4—Ag protonation and C2—H deprotonation was considered. Oxopyrrol species **IM6** is generated from intermediate **IM4** via four-membered ring metathesis transition state **TS5**. The calculated activation free energy of this process, which is considered to be the

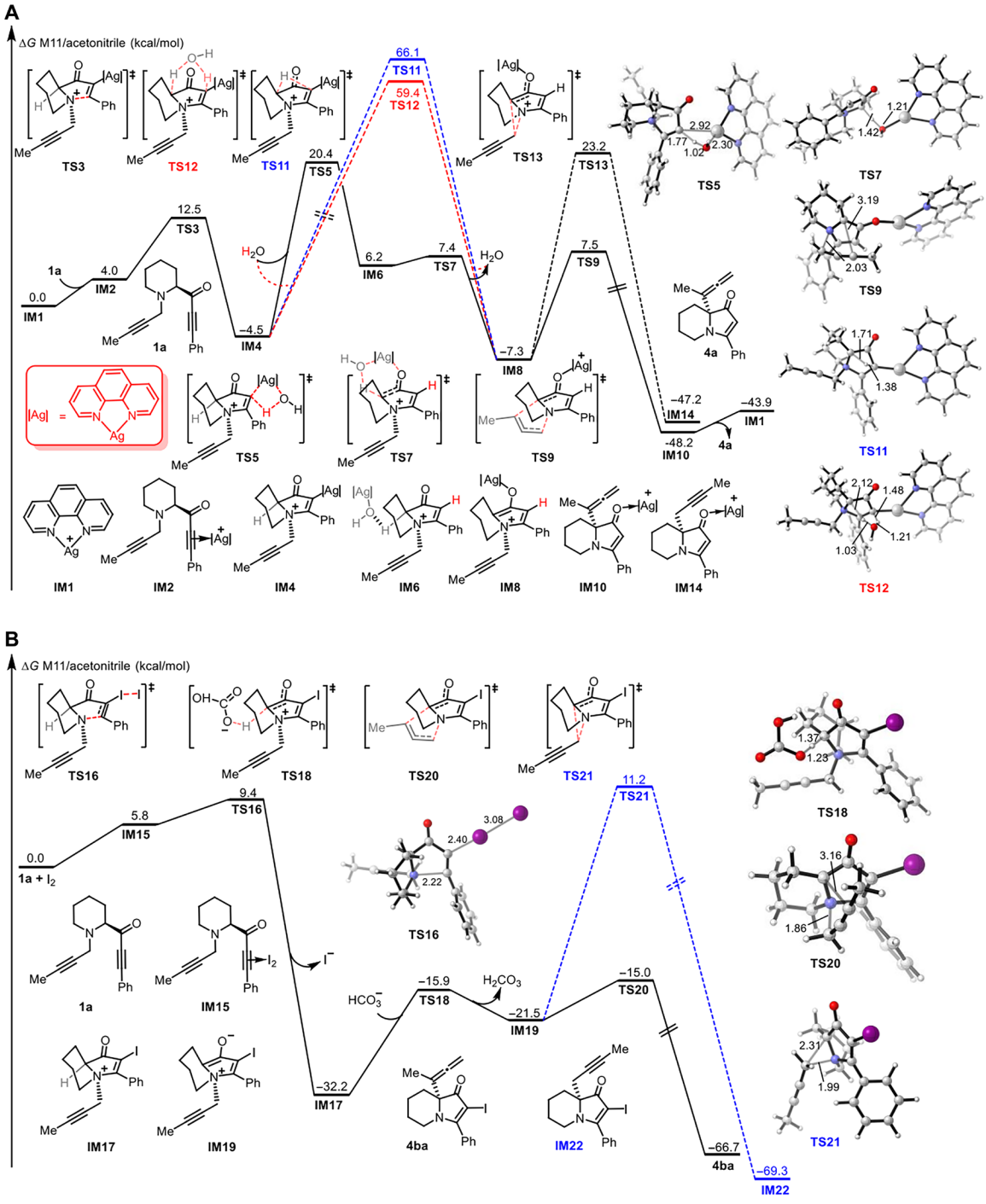


Fig. 4. Computational investigation. (**A**) Free energy profiles of Ag-catalyzed domino generation/[2,3]-sigmatropic rearrangement of ammonium ylides. (**B**) Free energy profiles of I_2-assisted domino generation/[2,3]-sigmatropic rearrangement of ammonium ylides. The favored pathways are shown by solid lines. The values are the relative free energies calculated by the M11 method in acetonitrile solvent (kcal/mol).

rate-determining step for the whole transformation, is 24.9 kcal/mol. With regard to the geometry of **TS5**, the lengths of the formed C—H bond and broken C4—Ag bond are 1.77 and 2.92 Å, respectively, indicating a concerted process. Subsequent irreversible and rapid deprotonation by silver hydroxide produces ammonium ylide **IM8** via transition state **TS7** with a free energy barrier of only 1.2 kcal/mol. Subsequent [2,3]-sigmatropic rearrangement occurs via concerted five-membered ring transition state **TS9** with a free energy barrier of 14.8 kcal/mol to form N-fused azabicycle **IM10**. During this process, the chirality information efficiently transfers from the nitrogen atom in **IM8** to the bridgehead carbon atom in N-fused azabicycle **IM10**. [1,2]-Sigmatropic rearrangement was also considered. The calculated free energy barrier via transition state **TS13** is 30.5 kcal/mol, which is 15.7 kcal/mol higher than that of [2,3]-sigmatropic rearrangement

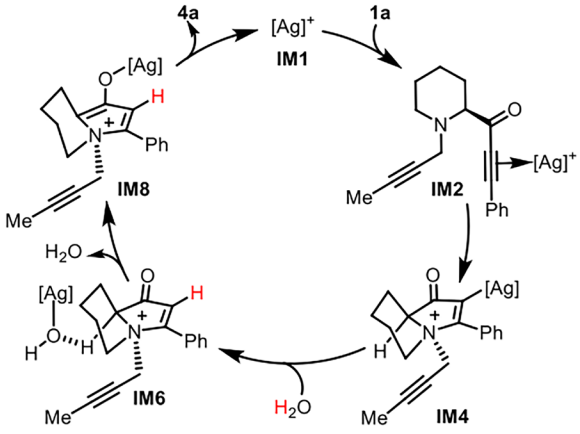


Fig. 5. Proposed mechanism.

via **TS9**. Therefore, [1,2]-sigmatropic rearrangement can be excluded because of the high energy barrier.

The reaction mechanism from our theoretical calculation is summarized in Fig. 5. Coordination of an ynone to cationic silver complex **IM1** leads to intramolecular nucleophilic addition of the neighboring amino group to form oxopyrrolyl-silver intermediate **IM4**. Water-assisted C4—Ag protonation and C2—H deprotonation produce ammonium ylide **IM8**, and subsequent [2,3]-sigmatropic rearrangement gives the azabicyclic product **4a** with regeneration of active catalyst **IM1**. During this reaction, the chirality of the carbon center in **1a** transfers to the ammonium nitrogen atom and subsequently reverts to the bridgehead carbon atom, resulting in complete chirality transfer.

Mechanism verification

The calculated results show that the residual water in the reaction system plays a crucial role in this transformation. We performed deuterium labeling experiments to experimentally elucidate the source of C4—H (i.e., from the internal C2—H or the external solvent) (Fig. 6A). When the reaction was performed with **5a–D** in CH_3CN or with **5a** in CD_3CN, the approximate ratios of the deuterated product **4a–D** were 5 and 6%, and the reaction of **5a** in CD_3CN/D_2O resulted in a 60% ratio of the deuterated **4a–D** product. These results indicate that the residual water in the reaction system is the main source of C4—H. Kinetic studies were carried out to further elucidate the role of water in terms of the rate of generation and [2,3]-sigmatropic rearrangement of the ammonium ylides (Fig. 6B). Rigorous removal of water followed by addition of molecular sieves to the reaction system resulted in a substantially reduced reaction rate (Fig. 6Ba), whereas adding water to the reaction mixture resulted in an increased reaction rate (Fig. 6Bb). The above results suggest that the residual water in the reaction system is critical for catalyst turnover and affects the reaction rate.

Substrate scope of Ag-catalyzed domino generation/[2,3]-sigmatropic rearrangement of ammonium ylides

Having determined the optimal conditions and elucidated the reaction mechanism, we surveyed the substituent scope of the ynone unit (Fig. 7A). Substrates with both electron-donating and electron-withdrawing groups at the para position of the phenyl group produced the rearrangement products in good yields with excellent chirality transfer (**4b**–**4g**, 96 to 98% *ee* from 98% *ee*). The substitution pattern of the phenyl ring had no effect on the reactivity and efficiency of chirality transfer, and fluoro groups at the ortho, meta, and para positions of the phenyl group were all tolerated in this reaction (**4g**–**4i**). Notably, ynone units containing heteroaryl groups, such as pyrryl and thienyl groups, worked well under the optimal conditions (**4l** and **4m**). The substituent scope of the ynone unit was further expanded to include cyclohexyl, cyclopropyl, *n*-butyl, and alkenyl groups (**4n**–**4q**). Ynone units substituted with alkyl groups bearing chlorine, nitrogen, and oxygen atoms were all tolerated (**4r**–**4t**). The presence of these atoms on **4** provides the opportunity to expand the structural diversity of these frameworks. Notably, ynone with a terminal alkyne group was also a suitable substrate, producing **4u** in 56% yield with 95% *ee*. The scope of the protocol was further expanded by varying the substituent on the N-propargyl group. A series of amino-ynones with electronically and sterically different groups on the propargyl unit was prepared and evaluated (Fig. 7B). Substrates with methyl, alkoxyl, and halogen groups on the phenyl ring of the propargyl unit all produced the rearrangement products in good yields with high enantiopurity (**4aa**–**4ah**). As expected, heteroaryl, alkyl, and silyl groups were also tolerated, producing N-fused bicycles with more diverse substituents on the allene unit (**4ai**–**4am**). The propargyl unit without a substituent at the terminal position produced **4an** in a lower yield. This can be attributed to the fact that the silver salt is prone to interfere with the terminal alkyne group, thereby disrupting the desired domino process. Furthermore, the R^1 and R^2 groups can be changed by design to generate desired products, as exemplified by **4ao** and **4ap** (Fig. 7C). In addition to the six-membered substrates discussed above, substrates with five- and seven-membered ring systems were also tolerated, providing access to chiral bicycles **4aq** and **4ar** with fused 5/*X* (*X* = 5 and 7) ring systems (Fig. 7C) and demonstrating the generality of this domino protocol. Notably, **5** containing a morpholine moiety and **5** fused with a phenyl group were also compatible substrates, generating **4as** and **4at** in good yields with excellent chirality transfer (Fig. 7C). Furthermore, this protocol can be adapted to generate N-allyl ammonium ylides, and it provided **4au** in good yield with high enantiopurity (Fig. 7C). The relative and absolute configuration of **4al** was unambiguously determined by single-crystal x-ray crystallographic analysis, and the same configuration was analogously assigned to other products.

I_2-assisted domino generation/[2,3]-sigmatropic rearrangement of ammonium ylides

Although the methodology provides a highly efficient way to produce a series of chiral N-fused azabicycles with bridgehead quaternary stereogenic centers, a transition metal is required. To develop a transition metal–free protocol and generate more functionalized products, we postulated that π-Lewis acidic I_2 would also facilitate generation and rearrangement of ammonium ylides (*47*–*50*), analogous to the silver catalyst. One expected advantage of such an arrangement is that with a stoichiometric amount of I_2, an iodine atom could be retained in the product after rearrangement, thereby providing azabicycles with extra potential for further elaboration. First, the feasibility of I_2-mediated generation and rearrangement of the ammonium ylide was evaluated by theoretical calculations. The calculated free energy profiles are shown in Fig. 4B. The alkyne moiety of ynone **1a** is activated by the interaction between electrophilic I_2 and the π-electrons of the alkyne moiety. Subsequent intramolecular nucleophilic attack by the amino group rapidly occurs through transition state **TS16** with an energy barrier of only 3.6 kcal/mol, irreversibly forming iodinated ammonium salt **IM17** with release of an

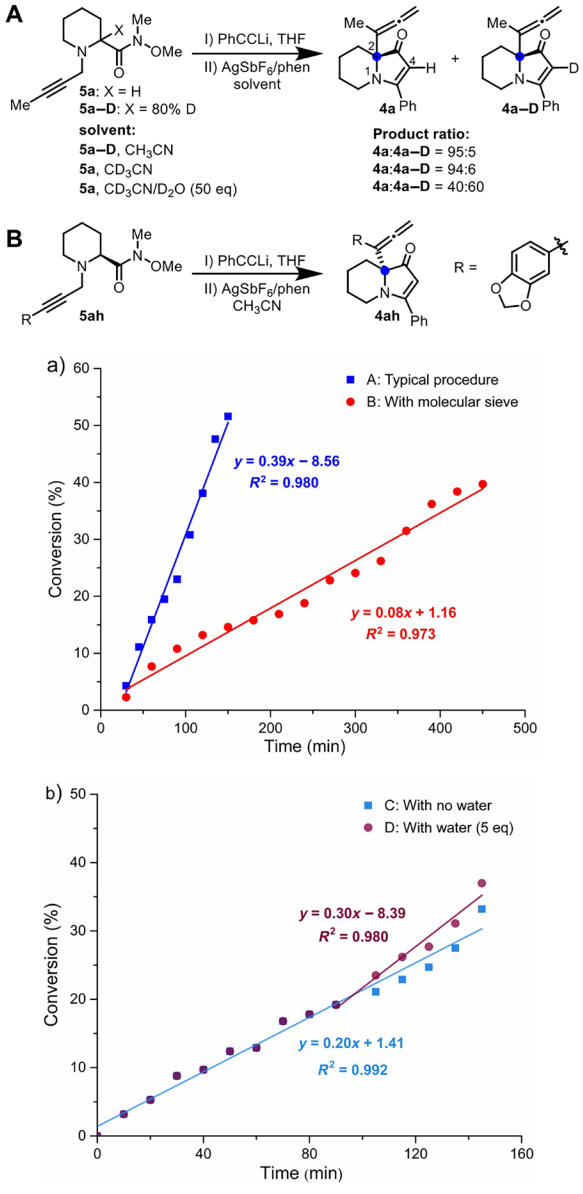


Fig. 6. Mechanism study. (**A**) Deuterium labeling study. Reaction conditions: (I) **5** (0.2 mmol), PhC≡CLi (0.6 mmol), THF (4 ml), –78° to 0°C, 1 hour, followed by aqueous workup; (II) $AgSbF_6$ (0.04 mmol), phen (0.05 mmol), solvent (3 ml), room temperature, 6 hours, the product ratio was determined by NMR. (**B**) Rate dependence on the water amount. Typical reaction conditions: (I) **5ah** (0.2 mmol), PhC≡CLi (0.6 mmol), THF (4 ml), –78° to 0°C, 1 hour, followed by aqueous workup; (II) $AgSbF_6$ (0.04 mmol), phen (0.05 mmol), CH_3CN (3 ml), room temperature. The conversion ratio was determined by ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard. A: Typical conditions. B: With 4-Å molecular sieve (100 mg) as the additive in step II. C: Co-evaporation of the ynone with toluene to remove the residual water in step II (carried out three times). D: With five equivalents of water added at 90 min in step II.

iodide anion. With regard to the geometry of transition state **TS16**, the lengths of the formed C—N bond and broken I—I bond are 2.22 and 3.08 Å, respectively. Bicarbonate-assisted deprotonation via transition state **TS18** generates ylide **IM19** with release of one molecule of carbonic acid. The calculated activation free energy of this step is 16.3 kcal/mol. After the formation of ylide **IM19**, subsequent [2,3]- and [1,2]-sigmatropic rearrangements were taken into consideration. [2,3]-Sigmatropic rearrangement, which is considered to be the rate-determining step of the whole transformation, can occur via transition state **TS20** with an activation free energy of 17.2 kcal/mol. With regard to the geometry of **TS20**, the lengths of the formed C—C bond and broken C—N bond are 3.16 and 1.86 Å, respectively. An intrinsic reaction coordinate calculation revealed a concerted process. In contrast, the calculated activation free energy of [1,2]-sigmatropic rearrangement via **TS21** is 43.4 kcal/mol. Therefore, this pathway can be excluded. On the basis of the theoretical calculation described above, we predict that π-Lewis acidic I_2 would also promote generation and rearrangement of ammonium ylide under mild conditions.

To confirm our hypothesis, we used chiral N-propargyl ynone **1a** as a model substrate, which was also prepared from **5a**. We surveyed various reaction parameters and determined that I_2/$NaHCO_3$/4-Å molecular sieve/CH_3CN were the optimum reaction conditions, providing **4ba** in good yields with high enantiopurity (see the Supplementary Materials for detailed screening of the reaction conditions). Thereafter, the application scope was briefly examined (Fig. 8). The substrate with a five-membered ring system reacted smoothly to produce **4bb** in 46% yield with 90% *ee*. N-allyl substrates, irrespective of the fused ring size (5 or 6/5) or substituents of the ynone units (R^1 = H, Ph, cyclopropyl), were all well tolerated, giving iodinated azabicycles **4bc**–**4bg** in good yields with high enantiopurity. Notably, substrates with α-monosubstituted N-allyl groups successfully generated the corresponding products **4bh** and **4bi** with high enantiopurity and excellent diastereoselectivity (>20:1 diastereomeric ratio). The relative and absolute configuration of **4bi** was unambiguously determined by single-crystal x-ray crystallographic analysis. The substrates with α-disubstituted and β-substituted N-allyl groups were also successfully transformed to **4bj** and **4bk** under the optimal reaction conditions.

Product derivation

The broad application scope of the present protocol allows diverse elaboration of the rearrangement product (Fig. 9). 1,4-Reduction of the enone unit of **4ap** produced **6** with high chemo- and diastereoselectivity (>20:1 diastereomeric ratio) by treatment with DIBAL-H. The stereochemistry of **6** was confirmed by single-crystal x-ray crystallographic analysis. Highly selective 1,4-reduction of the enone unit of **4r** followed by intramolecular ketone α-alkylation using ^{t}BuOK as the base generated tricyclic product **7** in good yield. Hydration of the allenyl group of **4ao** with $Hg(OTFA)_2$ generated a ketone, which underwent intramolecular aldol condensation to produce tricyclic product **8** in good yield. DIBAL-H reduction of **4p** and subsequent Fisher indole synthesis gave highly functionalized tetrahydropyrrolo[3,4-b] indole **9**, which is of potential biological interest. Suzuki coupling of iodinated **4bf** gave **10** with a rapid increase in molecular complexity. These convenient conversions of the rearrangement products demonstrate the wide potential in structural modification, and this method could be used to synthesize more complex molecules.

In conclusion, we have developed a new method for domino generation/[2,3]-sigmatropic rearrangement of ammonium ylides using a π–Lewis acid as the reaction promoter. A wide range of substrates is tolerated by this method, providing access to a series of N-fused azabicycles of various ring sizes containing allenyl- or allyl-substituted bridgehead quaternary stereogenic centers with high enantiomeric purity (up to 99% *ee*). A combination of density functional theory (DFT) calculations and experimental results revealed the reaction mechanism. When an Ag^I salt is used as the catalyst, the reaction process

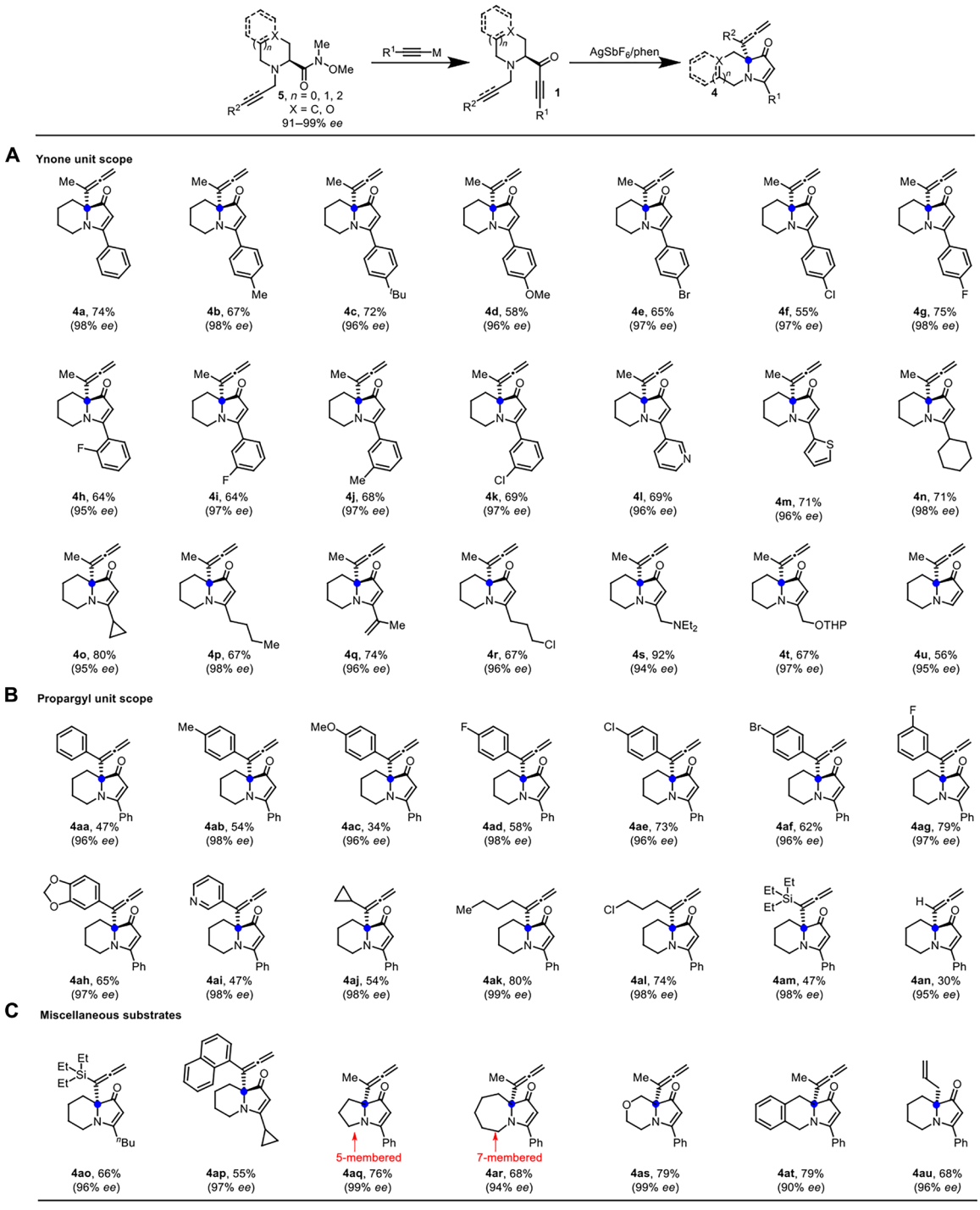


Fig. 7. Substrate scope of Ag-catalyzed domino generation/[2,3]-sigmatropic rearrangement of ammonium ylides. (**A**) Substrate scope with respect to the ynone units. (**B**) Substrate scope with respect to the propargyl units. (**C**) Miscellaneous substrates. Reaction conditions: **5** (0.2 mmol), $R^1C{\equiv}CM$ (M = Li or MgBr, 0.6 mmol), THF (4 ml), −78° to 0°C, 1 hour, followed by aqueous workup; $AgSbF_6$ (0.04 mmol), phen (0.05 mmol), CH_3CN (3 ml), room temperature, 2 to 48 hours. The yields are of the isolated products from **5**. *ee* was determined by chiral high-performance liquid chromatography (HPLC) analysis.

involves four steps: tertiary amine quaternization, water-assisted protonation and deprotonation, and propargylic or allylic [2,3]-sigmatropic rearrangement. Protonation of the C—Ag bond greatly increases the acidity of C2—H and occurs before C2—H deprotonation. Both of these events are assisted by the residual water in the reaction system, which leads to generation of ammonium ylides under mild conditions without the need for a strong base. Therefore, this reaction involves almost no chirality erosion. Furthermore, replacing the silver catalyst with a stoichiometric amount of nonmetallic I_2 generates the corresponding iodinated N-fused azabicycles with greater potential for

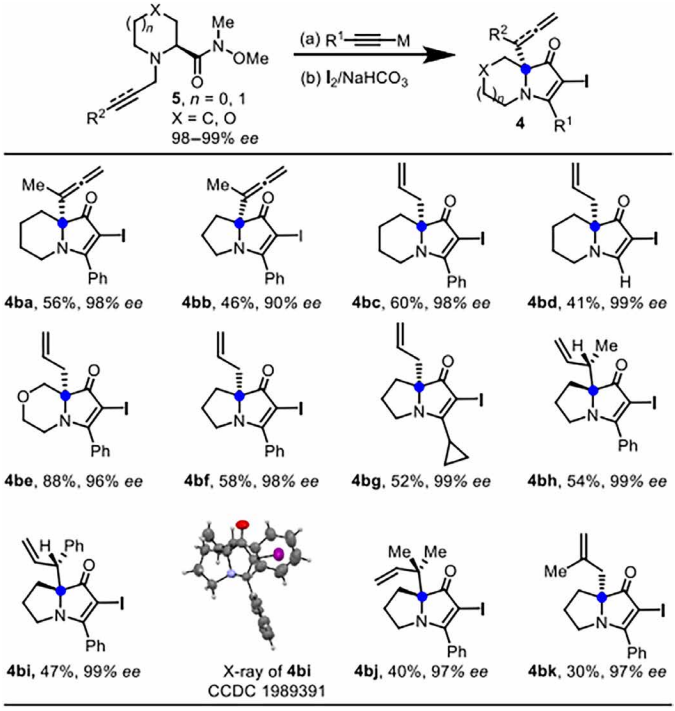


Fig. 8. Substrate scope of I_2-assisted domino generation/[2,3]-sigmatropic rearrangement of ammonium ylides. Reaction conditions: **5** (0.2 mmol), $R^1C{\equiv}CM$ (M = Li or MgBr, 0.6 mmol), THF (4 ml), −78° to 0°C, 1 hour, followed by aqueous workup; I_2 (0.2 mmol), $NaHCO_3$ (0.6 mmol), 4-Å molecular sieve (100 mg), CH_3CN (3 ml), room temperature, 2 to 12 hours. The yields are of the isolated products from **5**. *ee* was determined by chiral HPLC analysis.

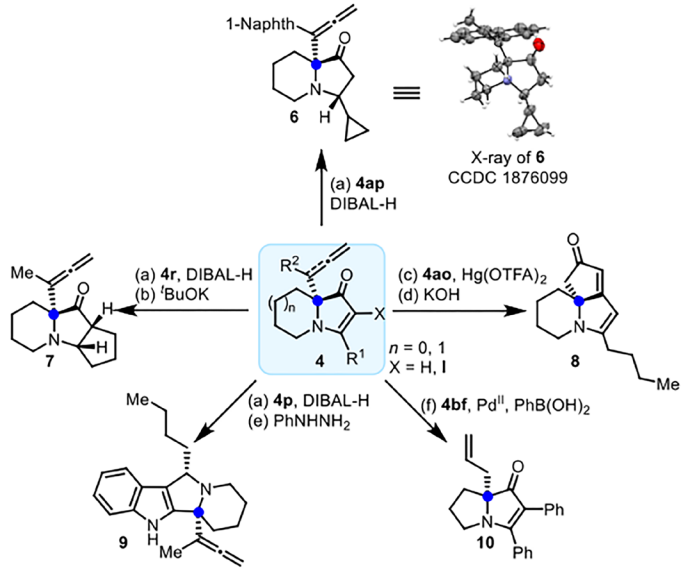


Fig. 9. Product derivation. Reagents and conditions: (a) DIBAL-H, THF, −78°C (from **4ap**, 45% yield; from **4r**, 61% yield; from **4p**, 65% yield); (b) ^{t}BuOK, THF, 0°C, 70% yield; (c) $Hg(OTFA)_2$, AcOH, 50°C, 64% yield; (d) KOH, xylenes, 110°C, 50% yield; (e) $PhNHNH_2$, H_2SO_4, EtOH, 70°C, and then CCl_3COOH, $ZnCl_2$, BHT, toluene, 70°C, 40% yield; (f) $Pd(PPh_3)_2Cl_2$, $PhB(OH)_2$, Cs_2CO_3, dioxane/H_2O, 50°C, 70% yield. DIBAL-H, diisobutylaluminium hydride; BHT, 2,6-di-tert-butyl-4-methylphenol.

further elaboration. The present work provides a new efficient method for domino generation and [2,3]-sigmatropic rearrangement of ammonium ylides and unified access to chiral N-fused bicycles of various ring sizes with bridgehead quaternary stereogenic centers.

MATERIALS AND METHODS

All the reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. All the reactions were carried out under a positive pressure of dry nitrogen gas in oven-dried glassware with magnetic stirring. Unless otherwise stated, all the solvents used in the reactions were distilled from appropriate drying agents before use. The ^{1}H NMR and ^{13}C NMR spectra were obtained with an Agilent 400MR or 600MR DD2 spectrometer at ambient temperature. The infrared (IR) spectra were recorded with a Bruker 100 FT-IR spectrometer. Electrospray ionization–high-resolution mass spectrometry was performed with a Bruker SolariX 7.0T spectrometer or H2Os SYNAPT G2 spectrometer. X-ray crystallography analysis of the single crystals was performed with an Agilent SuperNova-CCD X-Ray diffractometer. The melting points were determined with an SGW X-4A apparatus.

General procedure for preparing the ynone substrates

^{n}BuLi (2.5 M solution in hexane, 1.0 ml, 1 eq) was added dropwise to a solution of the alkyne (2.5 mmol, 1 eq) in tetrahydrofuran (THF) (3.7 ml) at −78°C. The reaction mixture was stirred at −78°C for 1 hour to afford a 0.5 M solution of $R^1C{\equiv}CLi$. $R^1C{\equiv}CLi$ (0.5 M, 1.2 ml, 0.6 mmol) was added dropwise to a solution of Weinreb amide **5** (0.2 mmol) in THF (2.8 ml) at −78°C. The reaction mixture was slowly warmed to 0°C and stirred until complete consumption of **5** (typically in 1 hour). The reaction was quenched with a saturated solution of NH_4Cl (4 ml) at −78°C. The resulting mixture was added with EtOAc (8 ml), washed with brine (4.0 ml × 3), dried over Na_2SO_4, filtered, and concentrated at 0°C. The crude ynone **1** was used in the next step without further purification.

General procedure for silver-catalyzed domino generation/[2,3]-sigmatropic rearrangement of ammonium ylides

A mixture of $AgSbF_6$ (13.7 mg, 0.04 mmol) and 1,10-phenanthroline (9.1 mg, 0.05 mmol) in CH_3CN (1 ml) was stirred at room temperature for 30 min, and then a solution of the above crude ynone **1** in CH_3CN (2 ml) was added. The reaction was stirred until complete consumption of **1** and then concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel to afford pure product **4**.

General procedure for I_2-assisted domino generation/[2,3]-sigmatropic rearrangement of ammonium ylides

A mixture of crude **1** and 4-Å molecular sieve (100 mg) in CH_3CN (3 ml) was stirred at room temperature for 10 min. I_2 (0.2 mmol) and $NaHCO_3$ (0.6 mmol) were then added to the mixture. The reaction was stirred until complete consumption of **1**. The crude reaction mixture was filtered through a pad of celite, and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel to afford pure iodinated product **4**.

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/7/5/eabd5290/DC1

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