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New Regio- and Stereoselective Cascades via Unstabilized Azomethine Ylide Cycloadditions for the Synthesis of Highly Substituted Tropane and Indolizidine Frameworks

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Supporting Information

ABSTRACT: Multisubstituted tropanes and indolizidines have been prepared with high regio- and stereoselectivity by the [3+2] cycloaddition of unstabilized azomethine ylides generated from readily prepared trimethylsilyl-substituted 1,2-dihydropyridines via protonation or alkylation followed by desilylation. Starting from 1,2-dihydropyridines bearing a ring trimethylsilyl substituent at the 6-position, an intermolecular alkylation/desilylation provides endocyclic unstabilized ylides that successfully undergo cycloaddition with a range of symmetrical and unsymmetrical alkyne and alkene dipolarophiles to afford densely substituted tropanes incorporating quaternary carbons in good yields and with high regio- and stereoselectivity. Additionally, an intramolecular alkylation/desilylation/cycloaddition sequence provides convenient and rapid entry to bridged tricyclic tropane skeletons, allowing for five contiguous carbon stereocenters to be set in a single experimental operation and under mild conditions. Starting from 1,2-dihydropyridines with trimethylsilylmethyl groups on nitrogen, protonation followed by desilylation generates exocyclic unstabilized ylides that undergo cycloaddition with unsymmetrical alkynes to give indolizidines with good regio- and stereoselectivity. *N*-Trimethylsilylmethyl-1,2-dihydropyridines can also be alkylated and subsequently desilylated to give endocyclic unstabilized ylides that undergo intermolecular cycloadditions with carbonyl compounds to give bicyclic oxazolidine products in good overall yields. Moreover, an intramolecular alkylation/desilylation/cycloaddition sequence with the *N*-trimethylsilylmethyl-1,2-dihydropyridines affords tricyclic indolizidines that incorporate quaternary carbons and up to five stereocenters with good to excellent regio- and diastereoselectivity.

INTRODUCTION

Two classes of bicyclic pyrrolidines, the tropanes and indolizidines, have long attracted considerable interest due to their high frequency of occurrence in alkaloids and drugs.[1] However, few examples of tropane or indolizidine synthesis by [3+2] cycloaddition between an azomethine ylide and a dipolarophile have been reported, and this is particularly true for unstabilized ylides.[2] While azomethine ylide cycloadditions represent a powerful strategy for the convergent assembly of five-membered nitrogen heterocycles,[3,4] only simple unstabilized ylides have primarily been used due to the challenges associated with generating more complex and highly substituted derivatives.

We recently developed an efficient and very high yielding one-step synthesis of 6-trimethylsilyl-substituted 1,2-dihydropyridines **1** from readily available α,β-unsaturated imines and trimethylsilyl alkynes by a tandem Rh(I)-catalyzed C−H alkenylation/electrocyclization cascade (eq 1).[5] Upon exploring methods for the reductive protodesilylation of **1** to obtain piperidines, we discovered that these silyl-substituted dihydropyridines provide a powerful and versatile new entry into 6-membered endocyclic unstabilized azomethine ylides, of which very few examples have been reported.[6] Protonation of **1** followed by desilylation generates endocyclic unstabilized azomethine ylides **2**, which were then shown to undergo [3+2] cycloaddition with electron deficient alkyne dipolarophiles (Figure 1, eq 2).[7]

This new approach for the generation of highly substituted unstabilized ylides should provide an opportunity for performing [3+2] cycloadditions to prepare a variety of highly substituted, multicyclic pyrrolidines. Herein, we demonstrate the versatility of this approach for the rapid and stereoselective preparation of additional classes of tropanes, and for the first

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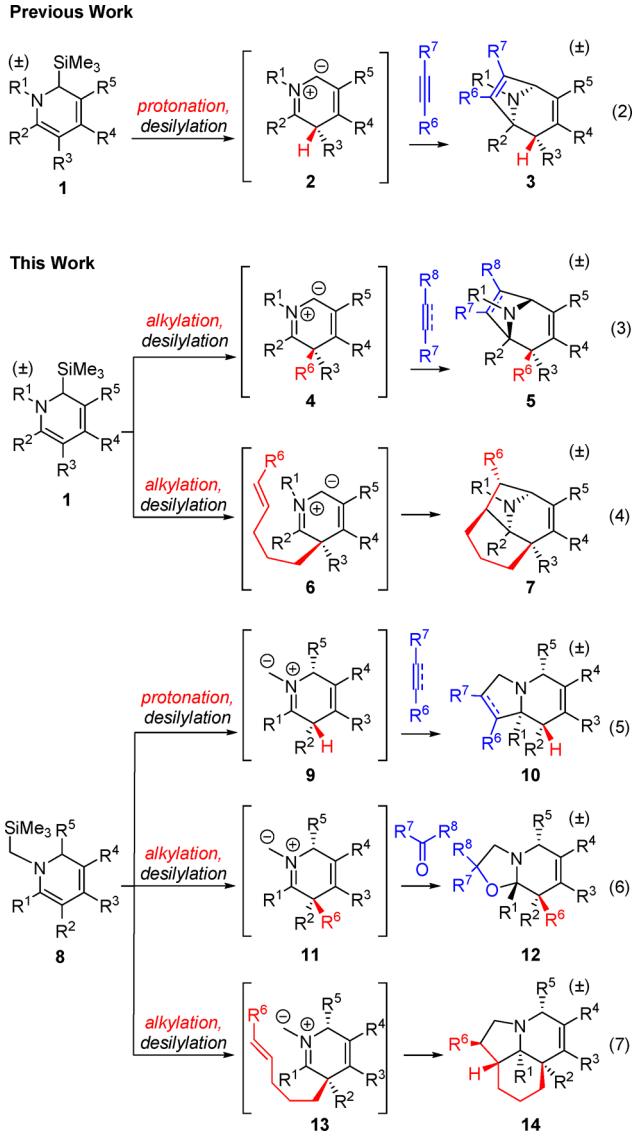


Figure 1. Endo- and exocyclic [3+2] cycloadditions via TMS dihydropyridines for the rapid synthesis of tropanes (eq 2–4), indolizidines (eqs 5 and 7), and fused oxazolidines (eq 6).

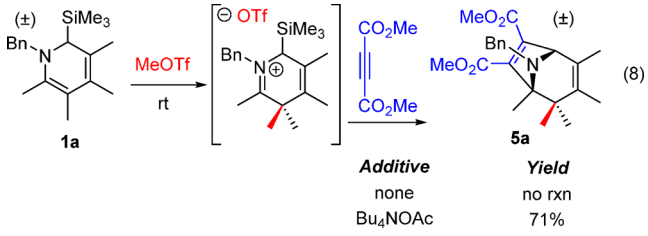
time indolizidines, through inter- and intramolecular cycloadditions of complex, unstabilized ylides.

First, we demonstrate that endocyclic azomethine ylides **4** can be generated from silyl-substituted dihydropyridines **1** by alkylation instead of protonation (Figure 1, eq 3). Subsequent cycloaddition gives tropanes **5** that contain quaternary carbon centers. Both electron deficient alkenes and alkynes proved to be effective dipolarophiles. Moreover, when the alkylating agent is tethered to an electron-deficient alkene, alkylation followed by intramolecular [3+2] cycloaddition proceeds with high regio- and stereoselectivity to afford novel multicyclic products **7** with an embedded tropane framework with five contiguous stereocenters (Figure 1, eq 4).

We further demonstrate for the first time that exocyclic azomethine ylides can be generated from *N*-trimethylsilylmethyl-1,2-dihydropyridines **8** (Figure 1, eqs 5–7). Notably, dihydropyridines **8** are readily prepared in one step and in high yield by a Rh(I)-catalyzed C–H alkenylation/electrocyclization cascade using *N*-trimethylsilylmethyl α,β-unsaturated imines and internal alkynes (*vide infra*). Protonation of **8** with subsequent desilylation provides ylides **9**, which undergo intermolecular cycloadditions to give highly substituted indolizidine products **10** (Figure 1, eq 5). Alternatively, alkylation followed by reaction with carbonyl compounds give bicyclic oxazolidines **12** (Figure 1, eq 6). Finally, when the alkylating agent is tethered to an electron-deficient alkene, intramolecular [3+2] cycloaddition proceeds with high regio- and stereoselectivity to give highly substituted tricyclic derivatives **14** with five stereocenters (Figure 1, eq 7).

RESULTS AND DISCUSSION

Intermolecular Endocyclic Cycloaddition. In our initial studies (Figure 1, eq 2), diphenyl phosphoric acid proved effective for C-protonation of TMS dihydropyridines **1** with subsequent phosphate attack upon the silyl group to generate azomethine ylides **2**, which underwent cycloaddition in the presence of alkyne dipolarophiles. This overall process was sufficiently facile that it could even be performed at −78 °C.[7] While alkyl triflates do alkylate dihydropyridines **1**, this approach for generating the iminiums has a much higher activation energy than that for protonation, making it necessary for alkylations to be performed at ambient temperature (eq 8).[8]



Additionally, because the triflate counterion is non-nucleophilic, spontaneous desilylation to generate the ylide does not occur. However, addition of Bu_4NOAc rapidly generated the ylide to enable cycloaddition to give tropane **5a**, which incorporates contiguous tetrasubstituted carbons, in good yield.

Alkylation of dihydropyridines **1** with MeOTf, followed by Bu_4NOAc-induced desilylation and trapping of the transient azomethine ylides with dimethyl acetylenedicarboxylate (DMAD) afforded tropanes **5** with different R^1 nitrogen substituents (**5a**–**5c**, Scheme 1). The unsymmetrical alkyne dipoloraphile methyl propiolate provided the cycloaddition product as a single regioisomer (**5d**). A variety of alkyl (**5a**–**5f**), phenyl (**5g**) and benzyl (**5h**) substituents at the R^5 position were also well-tolerated. Importantly, alkylation with EtOTf followed by desilylation and cycloaddition provided tropanes **5e**–**5g** and **5i** each with a quaternary carbon stereocenter in good yields and with excellent diastereoselectivities. X-ray crystallographic analysis of **5g** establishes that the dipolarophile adds to the face opposite to the more sterically demanding ethyl substituent that was introduced in the alkylation step.

Alkenes were also effective dipolarophiles (Scheme 2), although the cycloadducts were obtained in modestly lower yields than those observed for alkyne dipolarophiles. Cycloaddition with *N*-phenylmaleimide afforded tropane adduct **5j** in good yield and with 87:13 *exo*/*endo* selectivity. Methyl acrylate gave predominately one tropane regio- and stereoisomer **5k**. The cycloaddition with *trans*-β-nitrostyrene afforded cycloadduct **5l** as a single regio- and diastereoisomer, but initially in a disappointing 24% yield as determined by ^1H NMR analysis. However, upon replacing Bu_4NOAc with CsO_2CCF_3 along with addition of 10 mol % of Schreiner's thiourea catalyst,[9]

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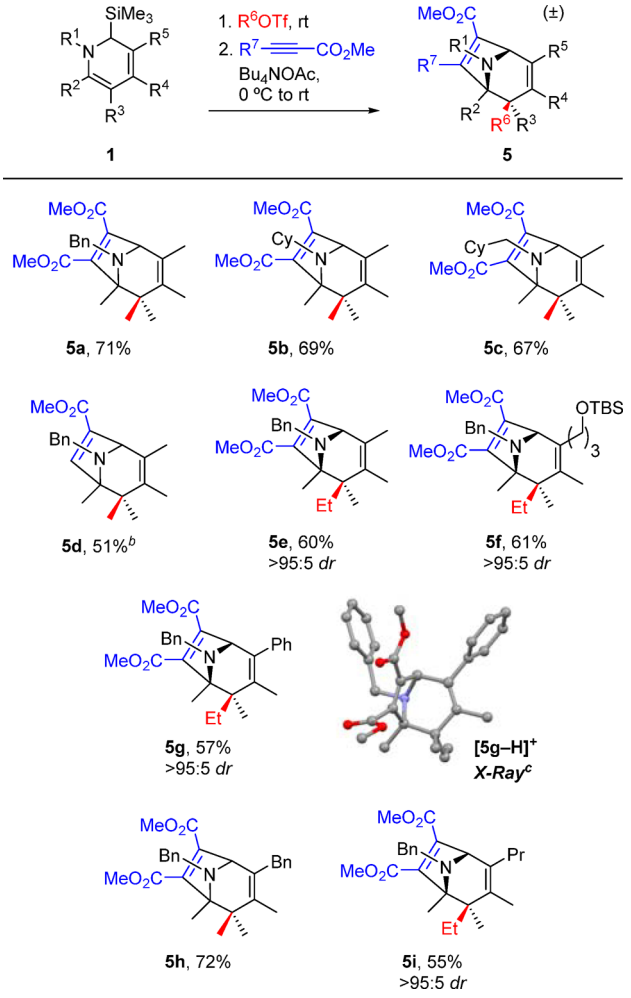
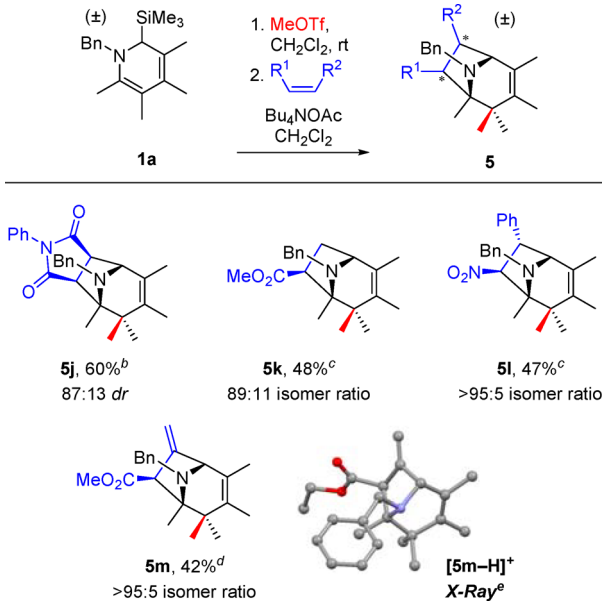
Scheme 1. Tropanes via Intermolecular Cycloaddition of Endocyclic Azomethine Ylides with Alkyne Dipolarophiles[a]



[a]Yields were determined by mass balance of isolated products after chromatography and represent yields with respect to the starting dihydropyridine **1**. Isomeric ratios were determined by ^{1}H NMR analysis of crude materials. [b]Cycloaddition performed at −78 °C; regiochemistry assigned by 2D NMR. [c]X-ray structure shown with anisotropic displacement ellipsoids at the 50% probability level. Anion and hydrogen atoms omitted for clarity.

Scheme 2. Tropanes via Intermolecular Cycloaddition of Endocyclic Azomethine Ylides with Alkene Dipolarophiles[a]



[a]Yields were determined by mass balance of isolated products after chromatography and represent yields with respect to the starting dihydropyridine **1a**. Isomeric ratios were determined by ^{1}H NMR analysis of crude materials. [b]Cycloaddition performed at 0 °C to rt. [c]Cycloaddition performed at −78 °C to rt. [d]Cycloaddition performed with CsO_2CCF_3 and 10 mol % of *N,N′*-bis[3,5-bis(trifluoromethyl)-phenyl]thiourea instead of an acetate at 0 °C to rt. [e]X-ray structure shown with anisotropic displacement ellipsoids at the 50% probability level. Anion and hydrogen atoms omitted for clarity.

which is reported to activate nitroalkenes through bidentate hydrogen bonding, the yield of cycloadduct **5l** increased ~2-fold to 47%. Interestingly, the allene dipolarophile, ethyl 2,3-butadienoate, provided tropane **5m** with >95:5 diastereo- and regioselectivity, with the structure of **5m** rigorously confirmed by X-ray structural analysis of the amine salt.

Intramolecular Endocyclic Cycloaddition. Having demonstrated [3+2] cycloadditions with ylides generated by C-alkylation/deslilylation of trimethylsilyl-substituted dihydropyridines **1**, we envisioned that even more complex multicyclic frameworks could potentially be accessed by using an alkylating agent tethered to a dipolarophile (Scheme 3). However, the very limited precedent for intramolecular cycloadditions of unstabilized ylides was a cause for concern.[10] To establish feasibility, 1,2-dihydropyridine **1a** was treated with triflate **15**, and upon heating to 40 °C, without the need for an external desilylation agent, bridged tricyclic tropane **7a** with five contiguous stereocenters was obtained in a reasonable yield as a single diastereoisomer. The relative stereochemistry of **7a** was rigorously assigned by X-ray crystallography.

The viability of this intramolecular alkylation/desilylation/cycloaddition cascade was then evaluated for a range of trimethylsilyl-substituted dihydropyridines **1** (Scheme 3). Adduct **7b** was obtained in comparable yield to that obtained for **7a** and incorporates an aromatic ring in place of the methyl group at R^5. Adducts **7c**−**7h** derived from dihydropyridines **1** with lower substitution levels (R^2, R^4 = H) were also successfully prepared with high diastereoselectivity. For these examples, heating was not required, and desilylation and cycloaddition occurred rapidly at room temperature, presumably due to the reduced stability of the iminium produced upon alkylation when R^2 = H rather than a methyl group. In terms of substrate scope, the *N*-benzyl substituent at R^1 (**7c**) could be replaced with the cyclohexylmethyl group (**7d**) with only a modest reduction in yield. At the R^5 position, alkyl groups (**7c**, **7d**, and **7i**) and electron-poor, -neutral, and -rich phenyl substituents (**7e**−**7g**) could each be incorporated. Significantly, each of these products was isolated as a single regio- and stereoisomer.

Intermolecular Exocyclic Cycloaddition. The previously explored cycloadditions employed endocylic, unstabilized ylides generated from 1,2-dihydropyridines with the trimethylsilyl group at the 6-position. We envisioned that it might be possible to generate exocyclic unstabilized ylides from *N*-trimethylsilyl-methyl-1,2-dihydropyridines **8** (eq 9). Inter- or intramolecular cycloaddtions of these exocyclic azomethine ylides would then provide entry into indolizidine scaffolds found in a wide range of natural products. The *N*-trimethylsilylmethyl-1,2-dihydro-

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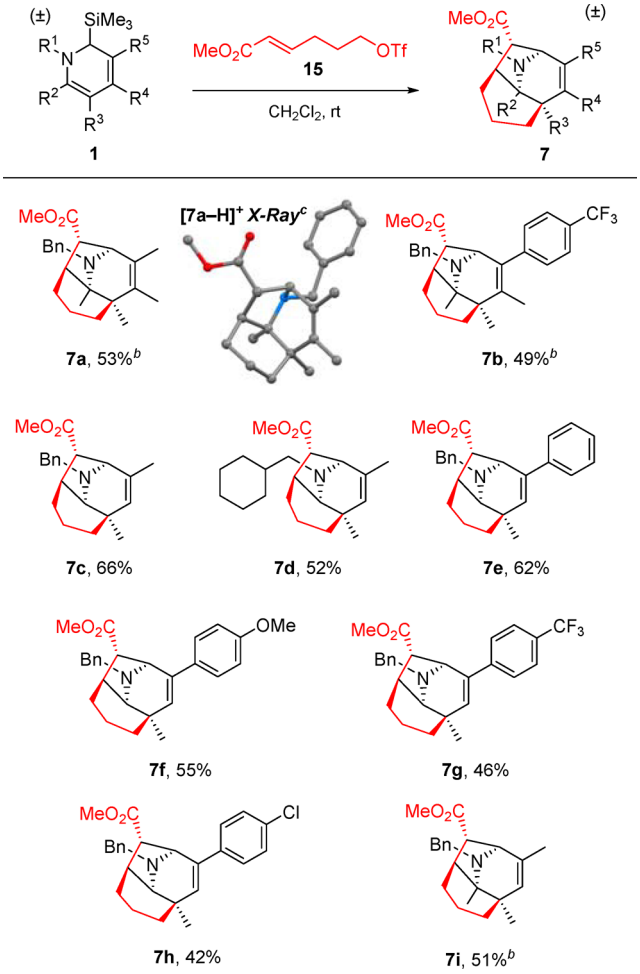
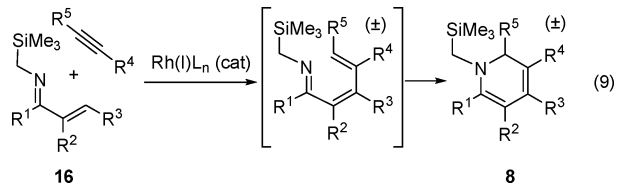
Scheme 3. Bridged Tropanes via Intramolecular Cycloaddition of Endocyclic Azomethine Ylides with Tethered Dipolarophiles[a]



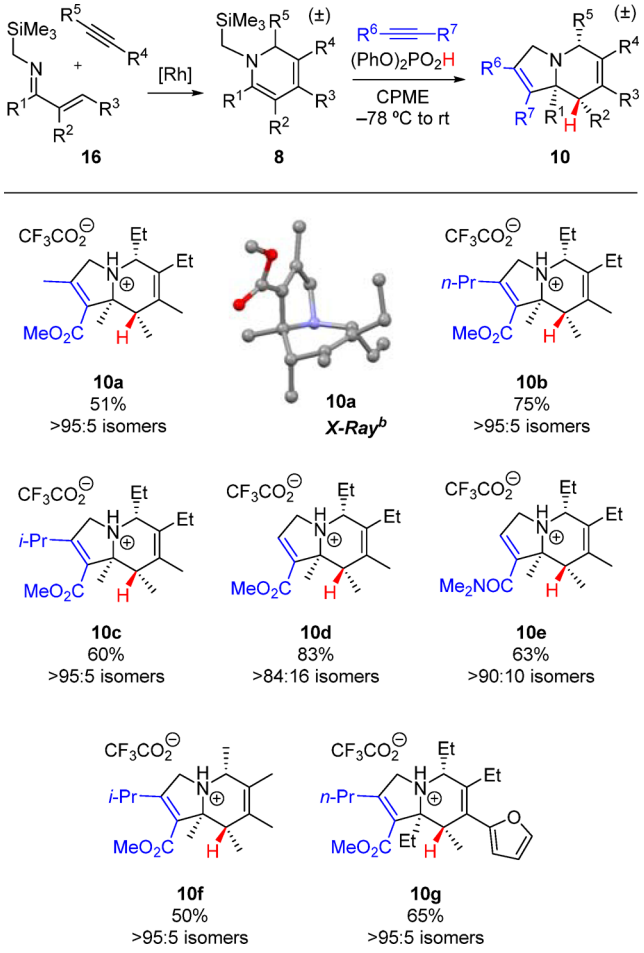
[a]Yields were determined by mass balance of isolated products after chromatography and represent yields with respect to the starting dihydropyridine **1**. [b]Reaction performed at 40 °C. [c]X-ray structure shown with anisotropic displacement ellipsoids at the 50% probability level. Anion and hydrogen atoms omitted for clarity.



pyridines **8** could readily be prepared in a single step and in high yield by the Rh(I)-catalyzed C–H activation/alkenylation/electrocyclization cascade utilizing *N*-trimethylsilylmethyl α,β-unsaturated imines **16** and internal alkynes (eq 9) and were often used for ylide generation and cycloaddition without isolation (*vide infra*).

When subjected to diphenyl phosphoric acid in the presence of alkyne dipolarophiles, dihydropyridines **8** underwent the desired protonation/desilylation/cycloaddition reaction sequence to yield indolizidine products **10** in reasonable to good yields (Scheme 4). Internal alkyne dipolarophiles bearing ester groups generally gave excellent selectivity for one out of multiple possible regio- and stereoisomers (**10a**–**10c**), with the

Scheme 4. Indolizidines via Intramolecular Cycloaddition of Exocyclic Azomethine Ylides with Alkyne Dipolarophiles[a]



[a]Yields were determined by mass balance of isolated products after chromatography and represent yields with respect to the starting imine **16**. Isomeric ratios were determined by ^{1}H NMR analysis of crude materials. [b]X-ray structure shown with anisotropic displacement ellipsoids at the 50% probability level. Anion and hydrogen atoms omitted for clarity.

high selectivity maintained even when dihydropyridines with different substitution patterns were employed (**10f**, **10g**). Terminal alkyne dipolarophiles bearing ester or amide groups gave cycloadducts as primarily one isomer but with somewhat attenuated selectivities (**10d**, **10e**). When exposed to air at rt for several days, cycloadducts **10** in free amine form decomposed to an intractable mixture. However, the trifluoroacetate salts of **10a**–**10g** isolated by reverse-phase chromatography were indefinitely stable under benchtop conditions. The relative stereochemistry was rigorously determined for **10a** by X-ray crystallographic analysis. The regiochemistry for **10b**–**10g** was assigned by 2D NMR analysis. Alkene dipolarophiles were also investigated, but gave mixtures of isomeric products (data not shown).

We proceeded to investigate the generation of exocyclic azomethine ylides by C3-alkylation and desilylation of *N*-trimethylsilylmethyl dihydropyridines **8** (Scheme 5). Treatment of **8a** with MeOTf or EtOTf resulted in complete conversion to the desired C3-alkylated iminium ions **17** within 15 min, while the 6-trimethylsilylmethyl dihydropyridines **1** typically required hours to undergo complete alkylation. The higher electron-

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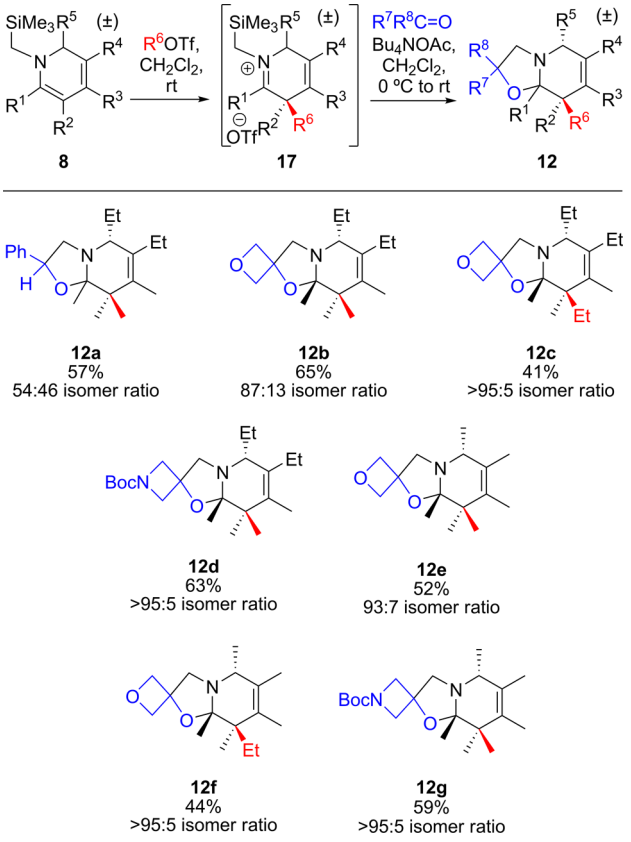
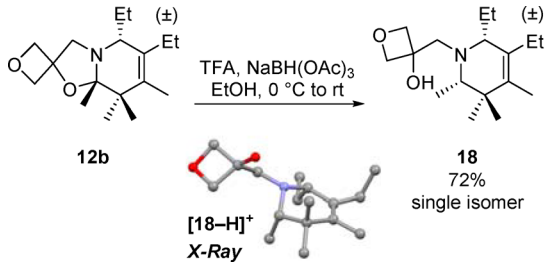
Scheme 5. Oxazolidines via Intermolecular Cycloaddition of Exocyclic Azomethine Ylides with Carbonyl Compounds[a]



[a]Yields were determined by mass balance of isolated products after chromatography and represent yields with respect to the starting dihydropyridine **8**. Isomeric ratios were determined by ^{1}H NMR analysis of crude materials.

donating ability of the trimethylsilylmethyl substituent compared to the *N*-alkyl group in **1** may account for this heightened nucleophilicity observed for dihydropyridines **8**.[11]

Few examples have been reported for the participation of electron-deficient carbonyl compounds as dipolarophiles in azomethine ylide cycloadditions.[12] Treatment of the iminium ions **17** with an acetate salt provided the exocyclic azomethine ylides, which underwent cycloaddition with carbonyl compounds in moderate to good yields. The ylide generated from **8a** reacted with benzaldehyde to give oxazolidine **12a** in an approximately equal ratio of two diastereomers out of multiple possible regio- and stereoisomers. By instead employing symmetrical activated ketone dipolarophiles, cycloadducts **12b**–**12g** were obtained in moderate to good overall yields and with good to excellent regio- and diastereoselectivities (Scheme 5).[13] Products **12b**, **12c**, **12e**, and **12f** were obtained via cycloaddition with strained carbonyl dipolarophile 3-oxetanone and adducts **12d** and **12g** by cycloaddition with 1-Boc-3-azetidinone. As shown for **12c** and **12f**, the reaction sequence proceeded with high diastereoselectivity when the alkylation step introduced a quaternary carbon stereocenter, although the overall yield was somewhat lower. Although alkene and alkyne dipolarophiles also underwent cycloaddition, mixtures of product isomers were obtained (data not shown). Regiochemistry was determined for **12b** and **12d** by 2D NMR and also for **12b** by ring opening (see eq 10). The regiochemistry for the other adducts **12** were assigned by analogy. Relative stereochemistry was determined for **12e**–**12g** by 2D NMR and NOE characterization, and assigned by analogy for the other products.



(10)

Cycloaddition products **12** contain acid-labile oxazolidine rings that enable further elaboration as exemplified by the reduction of **12b**, which furnished aminoalcohol **18** under acidic conditions in good yield and as a single diastereoisomer (eq 10). X-ray crystallographic analysis of **18** showed relative stereochemistry consistent with its formation by hydride attack upon the iminium intermediate from the less sterically hindered face opposite the ethyl group.[14]

Intramolecular Exocyclic Cycloaddition. Intramolecular cycloadditions of exocyclic azomethine ylides have a number of desirable features (Scheme 6). The constraint provided by intramolecular cycloaddition overcomes the poor regio- and stereoselectivity that had previously been observed for intermolecular cycloadditions between exocyclic azomethine ylides and alkene dipolarophiles (*vide supra*). Successful intramolecular cycloaddition also rapidly introduces a high level of complexity by providing tricyclic frameworks with embedded indolizidine motifs containing five stereocenters. Alkylation of dihydropyridines **8** with triflate **15** proceeded smoothly to afford the corresponding C3-alkylated iminium ions **19**, with the time required for complete alkylation varying from 30 min to 40 h, depending on the substitution of the starting dihydropyridine. Upon addition of CsOAc,[15] desilylation of the *N*-(trimethylsilylmethyl) group and subsequent intramolecular cycloaddition afforded multicyclic indolizidine-containing products **14** in reasonable overall yields and with good diastereoselectivities. Dihydropyridines incorporating a range of different substitution patterns underwent this alkylation/desilylation/intramolecular cycloaddition sequence to afford multicyclic indolizidine-containing products **14a**–**14f**. Methyl (**14a**), ethyl (**14b**), phenyl (**14d**), and even sterically demanding *tert*-butyl (**14c**) was tolerated at the R^5 position. Aldimine-derived dihydropyridines were compatible with the chemistry (**14e**), as was the electron-rich furyl substituent (**14f**). The relative stereochemistry was rigorously determined for cycloadduct **14c** by X-ray crystallographic analysis.

CONCLUSION

In conclusion, we have developed new, highly regio- and diastereoselective cascades via cycloadditions with unstabilized azomethine ylides for the synthesis of multisubstituted tropanes, indolizidines and oxazolidines. Moreover, the starting materials for these reaction cascades are silyl-substituted 1,2-dihydropyridines that are prepared in one step and in high yield from readily available imine and alkyne inputs. For endocyclic azomethine ylides generated via alkylation/desilylation from 6-trimethylsilyl-1,2-dihydropyridines, intermolecular cycloaddition with electron-deficient alkyne and alkene dipolarophiles afforded densely substituted tropanes incorporating a quaternary carbon in good yields and with generally high regio- and

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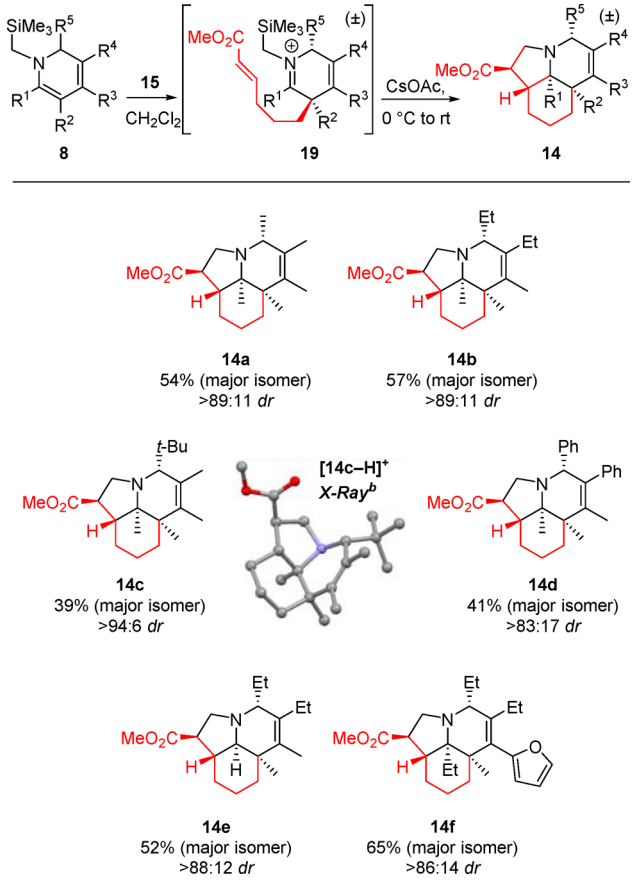
Scheme 6. Multicyclic Indolizidines via Intramolecular Cycloaddition of Exocyclic Azomethine Ylides with Tethered Dipolarophiles[a]



[a]Yields were determined by mass balance of isolated products after chromatography and represent yields with respect to the starting dihydropyridine **8**. [b]X-ray structure shown with anisotropic displacement ellipsoids at the 50% probability level. Anion and hydrogen atoms omitted for clarity.

stereoselectivity. The analogous intramolecular cycloadditions with an alkene dipolarophile tethered to the carbon electrophile provided extremely rapid entry into novel bridged tricyclic tropanes, setting five contiguous carbon stereocenters in a single experimental operation and under mild conditions. Exocyclic azomethine ylides generated from *N*-trimethylsilylmethyl dihydropyridines by protonation followed by desilylation underwent intermolecular cycloadditions with alkyne dipolarophiles to give indolizidines with good selectivities and yields. Correspondingly, alkylation followed by desilylation of *N*-trimethylsilylmethyl dihydropyridines resulted in exocyclic ylides that underwent cycloaddition with carbonyl dipolarophiles to give complex oxazolidine products. Analogous intramolecular cycloadditions with an alkene dipolarophile tethered to the alkylating agent furnished indolizidine-containing multicyclic frameworks with five stereocenters in generally good selectivity for one product isomer.

Together, these cascade strategies represent a powerful approach for the rapid assembly of biologically and pharmaceutically relevant nitrogen heterocycle scaffolds with high degrees of substitution from simple precursors. The multicyclic nitrogen heterocycles prepared in this study would be very difficult to synthesize by other methods. Application of these methods to the efficient synthesis of natural products will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08355.

Full experimental procedures; ^{1}H, ^{13}C, and ^{19}F NMR spectra of new compounds; and X-ray crystallographic data (PDF)

Compilation of CIF files for compounds **5g**, **5m**, **7a**, **10a**, **14c**, and **18** (ZIP)

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Notes

The authors declare no competing financial interest.

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