

Recent applications of imines as key intermediates in the synthesis of alkaloids and novel nitrogen heterocycles*

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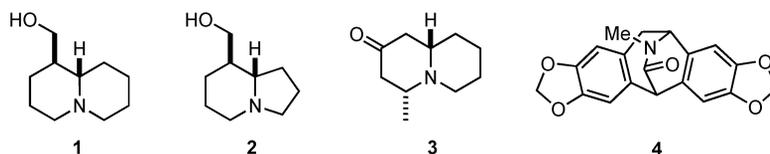
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Abstract: One of the major challenges in contemporary synthetic organic chemistry is the design and development of new tactics and strategies and their application to concise and efficient syntheses of biologically active natural products. Strategies that utilize reactions that enable the rapid assembly of the skeletal framework of such targets are thus especially attractive. In this context, we have developed novel applications of imine chemistry in Mannich and related reactions, cascade processes, and multicomponent reactions (MCRs) to rapidly assemble structural subunits common to diverse families of alkaloids. The practical utility of these chemistries is evidenced by their use in the execution of facile total syntheses of (\pm)-epilupinine (**1**), (\pm)-tashiromine (**2**), (–)-epimyrtine (**3**), and (\pm)-roelactamine (**4**) as well as other nitrogen heterocycles of potential biological interest.

Keywords: imines; Mannich reaction; multicomponent reactions; cascade reactions; alkaloid synthesis; diversity-oriented synthesis.

INTRODUCTION

Imines and their derivatives have long been recognized as key intermediates for the synthesis of nitrogen heterocycles, especially in the arena of alkaloid synthesis [1]. Over the years, we have had a keen interest in developing new applications of imine chemistry that enable the facile construction of the nitrogen heterocyclic frameworks found in alkaloids and other biologically active nitrogen heterocycles [1]. We have recently reported two novel strategies for the rapid synthesis of bicyclic and tricyclic nitrogen heterocycles that feature cascade and multicomponent reactions (MCRs) involving imines. In designing the first, we were guided by an interest to combine the reactivity modes of imines as both electrophiles and nucleophiles with the nucleophilic reactivity of allylsilanes to provide access to nitrogen heterocycles with nitrogen atoms at one of the bridgehead positions [3]. In the second, we sought to develop MCRs that would provide suitably functionalized intermediates that could undergo cyclization via a number of reaction manifolds [4]. Recognizing that the test of any new methodology lies in its application to practical problems, we successfully applied these processes to the concise syntheses of (\pm)-epilupinine (**1**), (\pm)-tashiromine (**2**), (–)-epimyrtine (**3**), and (\pm)-roelactamine (**4**).

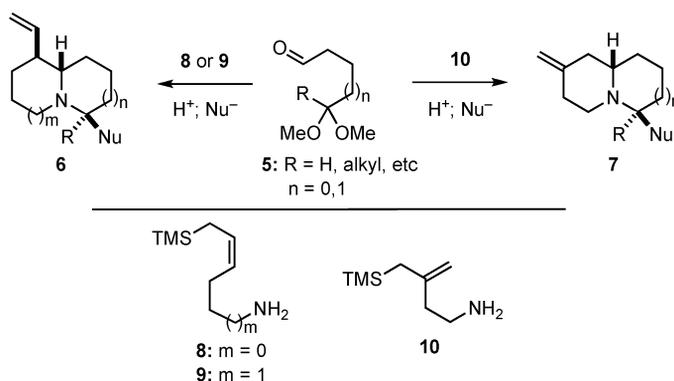


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RESULTS AND DISCUSSION

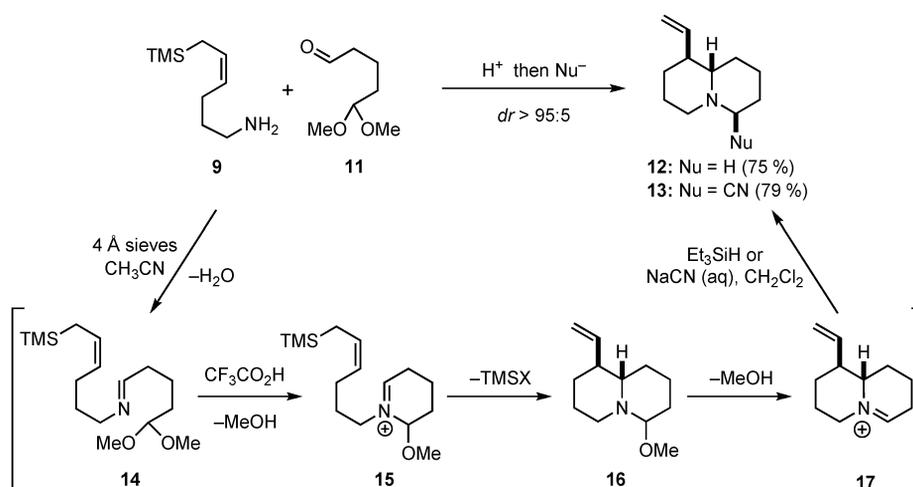
Facile route to quinolizidines and indolizidines via cascade reactions of imines

Drawing on the common knowledge that imines may serve as either electrophiles or nucleophiles in chemical reactions and that allylsilanes act as nucleophiles to add to iminium ions, we developed a plan for the synthesis of quinolizidines and indolizidines that is outlined in general terms in Scheme 1. Namely, we envisioned that monoprotected dicarbonyl compounds of the general form **5** might undergo a cascade of reactions with allylsilanes **8** or **9** in which the penultimate intermediate iminium ion is trapped with another nucleophile to give the bicyclic nitrogen heterocycles **6**. Similarly, the branched allylsilane **10** could react with **5** leading to **7**. The ring sizes of the products could be varied by simply altering the number of carbon atoms in the starting materials. A noteworthy feature of this approach to quinolizidines and indolizidines is that the process is convergent, allowing for the incorporation of two acyclic starting materials into a bicyclic product in one chemical operation.



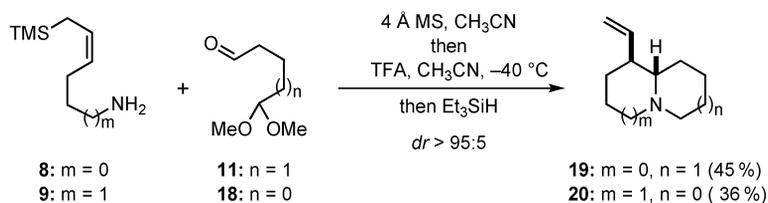
Scheme 1

In order to probe the viability of this approach to the synthesis of quinolizidines, we first condensed the known amino allylsilane **9** [5] with the known monoprotected dialdehyde **11** [6] to provide the imine **14** (Scheme 2). Further transformation of **14** into the putative iminium ion **17**, which pre-



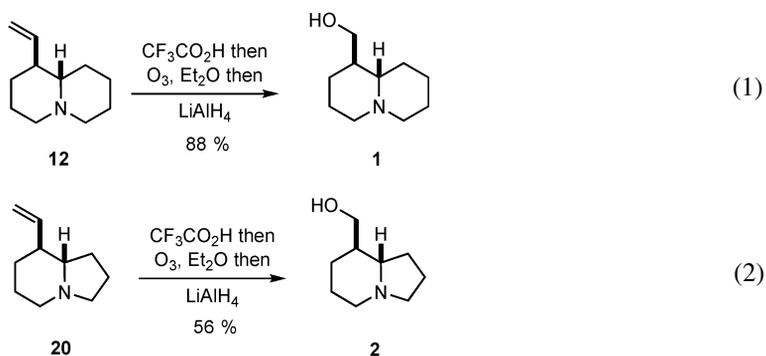
Scheme 2

sumably proceeded via **15** and **16**, was best achieved by the action of trifluoroacetic acid (TFA) at $-40\text{ }^{\circ}\text{C}$. Termination of the cascade using triethylsilane or cyanide ion as a trapping agent for **17** furnished **12** or **13**, respectively, in excellent overall yield. In order to explore the scope of this chemistry, the monoprotected dialdehyde **11** and the linear amino allylsilane **8** [7] were allowed to react, and the reaction was quenched with triethylsilane to give **19** (Scheme 3). Similarly, application of this sequence to **9** and the dialdehyde monoacetal **18** [6] led to **20**. These later two reactions were not optimized. Several preliminary experiments to extend this cascade sequence to the synthesis of pyrrolizidines were not successful.

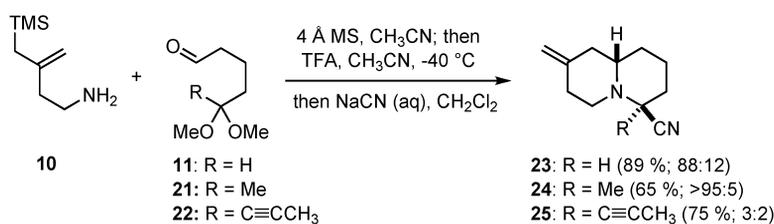


Scheme 3

As noted previously, the true test of any new strategy or methodology is whether it may be applied to preparing targets of interest, and it did not escape attention that compounds **12** and **20** might be readily transformed into naturally occurring quinolizidines and indolizidines. Indeed, compound **12** was a known intermediate in a previous synthesis of (\pm) -epilupinine (**1**) [8,9], but we developed an improved protocol for effecting this conversion that involved the ozonolysis of the trifluoroacetate salt of **12** followed by hydride reduction of the intermediate ozonide (eq. 1). Similarly, compound **20** was converted into the natural product (\pm) -tashiromine (**2**) (eq. 2) [10].

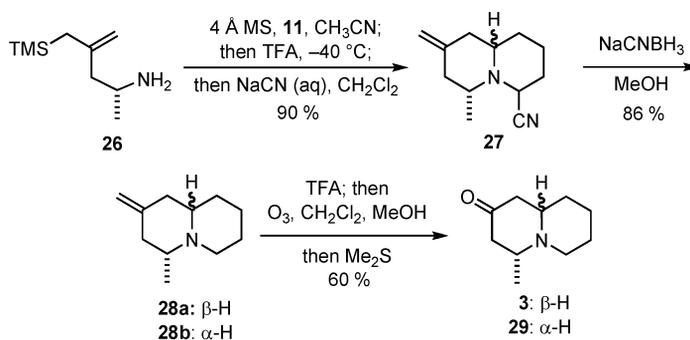


We then wished to explore cascade processes involving branched amino allylsilanes and keto aldehyde monoacetals. In the event, condensation of the known branched amino allylsilane **10** [11] with the monoprotected dialdehyde **11** followed by sequential treatment of the imine thus generated in situ with TFA and then aqueous NaCN furnished an epimeric mixture (88:12) of the aminonitriles **23** in excellent yield (Scheme 4). We were also pleased to discover that keto aldehyde monoacetals were also suitable reaction partners. For example, **21** and **22** were each condensed with the allylsilane **10**, and the intermediate imines were treated with TFA to initiate cyclization; termination of the cascade by the addition of cyanide ion afforded the aminonitriles **24** and **25**.



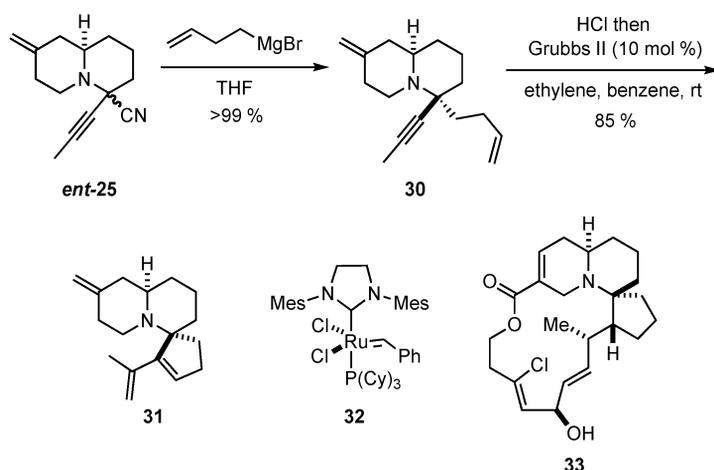
Scheme 4

In order to illustrate the utility of this process, it was applied to a concise, enantioselective synthesis of the quinolizidine alkaloid (–)-epimyrtiline (**3**) (Scheme 5). Thus, the known amino allylsilane **26** [12] was condensed with the dialdehyde monoacetal **11** to give an imine that was then treated sequentially with TFA and aqueous NaCN to give **27**, reduction of which with NaCNBH₃ provided a mixture (95:5) of epimeric quinolizidines **28a,b**. Ozonolysis of the exocyclic olefin in the trifluoroacetate salt of **28a,b** gave an inseparable mixture (95:5) of (–)-epimyrtiline (**3**) and (+)-myrtiline (**29**) [13].



Scheme 5

The potential utility of the α-aminonitriles formed in sequences depicted in Scheme 4 did not escape our attention. For example, α-aminonitriles may be deprotonated with strong bases to generate stabilized carbanions that may undergo reactions with a number of different electrophiles, and they may also serve as iminium ion equivalents in Bruylants and related processes [14]. For example, the utility of the α-aminonitrile **25** is exemplified by its facile conversion to **31**, which possess the tricyclic core of halichlorine (**33**) [15]. Accordingly, *ent*-**25** was allowed to react with 3-butenylmagnesium bromide to deliver quinolizidine **30** as a single diastereomer in virtually quantitative yield (Scheme 6). The hydrochloride salt of **30** underwent facile enyne ring-closing metathesis (RCM) in the presence of Grubbs II catalyst (**32**) to provide **31**. The synthesis of **31** is remarkable for its brevity, only three steps from acyclic starting materials, and its efficiency (64 % overall yield).

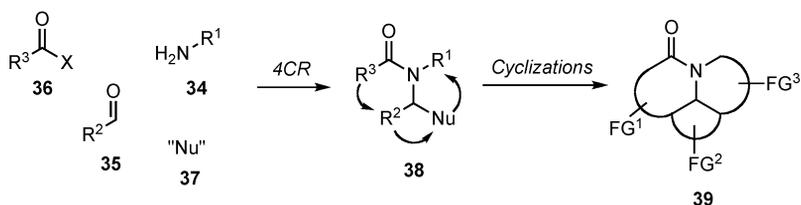


Scheme 6

Imines and diversity-oriented synthesis (DOS)

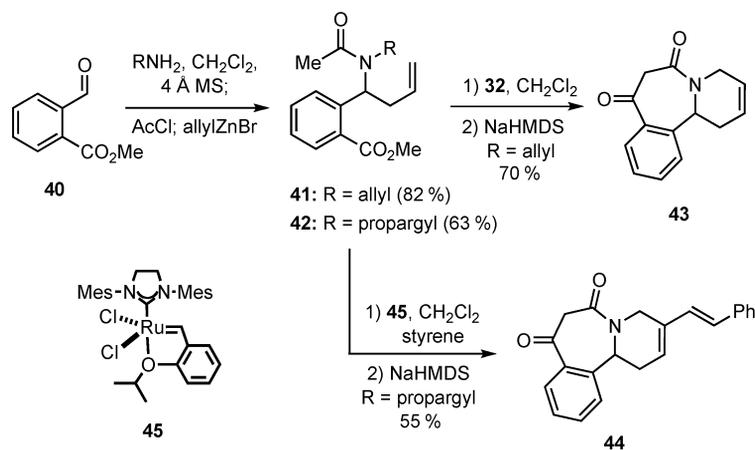
DOS and various manifestations thereof constitute areas of considerable importance at the interface of the fields of organic synthesis and chemical biology [16]. One of the critical challenges in DOS is the efficient generation of collections of functionally and stereochemically diverse small molecules, especially those possessing skeletons found in natural products or drug-like molecules. One attractive and powerful method that has recently emerged for generating such collections of molecules comprises using MCRs [17] to create suitably substituted intermediates that may be readily transformed by cyclizations and refunctionalizations that lead to further increases in molecular complexity and diversity [4].

Some years ago, we discovered an MCR that featured vinylogous Mannich reactions of electron-rich dienes with *N*-acyl iminium ions generated in situ by *N*-acylation of imines to give adducts that were readily transformed into a number of complex alkaloids representing different families [1f]. In the context of DOS, we envisioned that a related four-component process involving combination of an amine **34**, an aldehyde **35**, and an acylating agent **36** might generate a reactive *N*-acyl iminium ion that could be subsequently trapped with a nucleophile **37** to give a functionalized amide **38** (Scheme 7). A variant of this protocol would entail addition of the nucleophile to an intermediate imine, followed by *N*-acylation to furnish **38** [18]. This experimental flexibility together with the ready availability of numerous reactants **34–37** allows for the incorporation of high levels of functional and structural diversity in the products **38**, so that a number of different cyclizations might be subsequently performed to generate an array of heterocyclic scaffolds in only a few steps from commercially available starting materials.



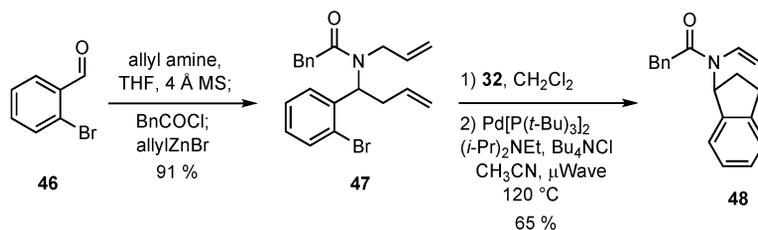
Scheme 7

The question at this juncture was whether we could in fact marshal such reactions to rapidly assemble heterocyclic systems that would be of interest for DOS. Toward this end, we focused on combining unsaturated amines, aryl aldehydes, simple acid chlorides, and allylic and *p*-nucleophiles to prepare adducts that could be further transformed by cyclizations involving RCM, Dieckmann and Heck reactions, and Diels–Alder and dipolar cycloadditions. For example, condensation of methyl 2-formylbenzoate (**40**) with allyl and propargylamine provided intermediate imines that were treated sequentially with acetyl chloride and allylzinc bromide to furnish adducts **41** and **42** in a one-pot operation (Scheme 8). Compound **41** was converted into the benzazepine **43** via an RCM using Grubbs catalyst **32** followed by a Dieckmann cyclization. In a related process, **42** and styrene, which served as a fifth component in the process, underwent an enyne RCM/CM cascade upon treatment with the Hoveyda–Grubbs catalyst (**45**) to give an intermediate that was cyclized by a Dieckmann condensation to give **44**. These two examples nicely illustrate how simply changing one of the inputs in the initial multicomponent process allows for differential processing of the adducts into targets of varying complexity and structure.



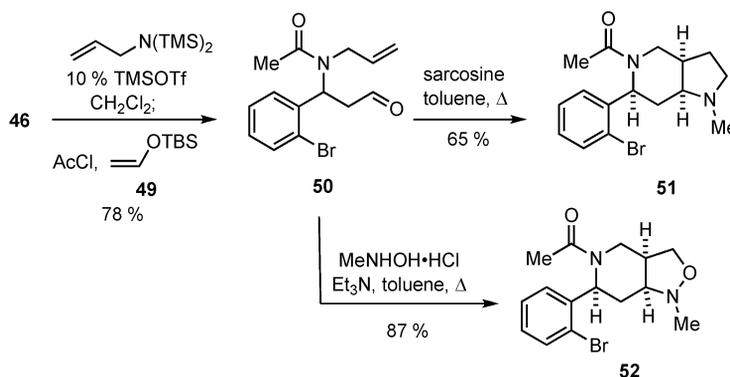
Scheme 8

Varying the functionality on the aldehyde component enables access to other cyclization manifolds and hence other heterocyclic systems. Illustrative of this feature is the use of 2-bromobenzaldehyde (**48**) in a four-component process to furnish substrates that are amenable to Heck cyclizations (Scheme 9). The tertiary amide **47** thus formed was subjected to a two-step sequence of cyclizations involving an RCM followed by a Heck reaction to give **46**.



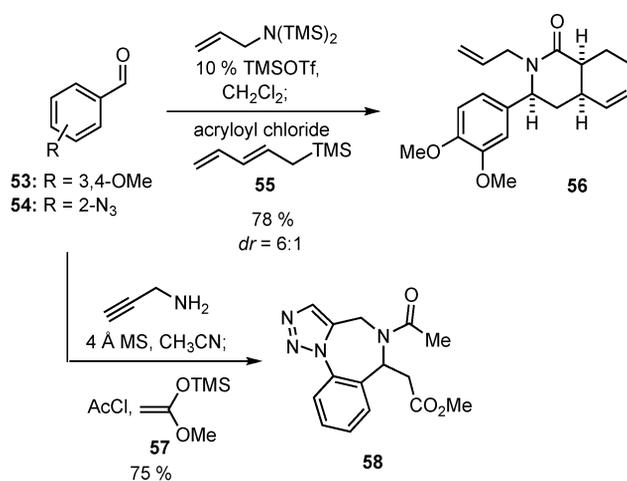
Scheme 9

Another aspect of this strategy for DOS involves the use of silyl enol ethers as inputs in the initial four-component process to generate aldehydes that can then be employed as precursors of 1,3-dipoles that may undergo intramolecular [3+2] dipolar cycloadditions with proximal double or triple bonds to generate diverse heterocyclic scaffolds. For example, reaction of the bromoaldehyde **46** with bis(trimethylsilyl)allylamine in the presence of catalytic amounts of TMSOTf, followed by treatment of the thus obtained imine in situ with acetyl chloride and the enol ether **49** delivered the adduct **50** (Scheme 10). When **50** was condensed with sarcosine in refluxing toluene, the intermediate azomethine ylide readily underwent a [3+2] cycloaddition to give **51**. Similarly, reaction of **50** with *N*-methylhydroxylamine under the same conditions generated a nitron that underwent facile [3+2] cycloaddition to provide **52**.



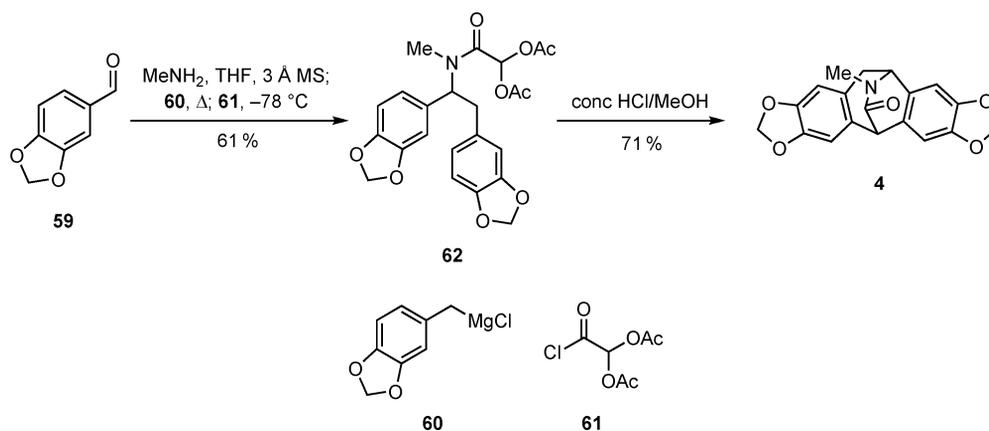
Scheme 10

The intramolecular Diels–Alder (IMDA) reaction is another powerful reaction for the synthesis of complex molecules. Hence, we turned our attention to using inputs in the four-component process that would provide substrates capable of undergoing such transformations. In the event, we found that when the pentadienylsilane **55** and acryloyl chloride were added to the imine generated in situ upon condensation of the benzaldehyde **53** with bis(trimethylsilyl)allylamine in the presence of TMSOTf, the resulting product underwent spontaneous [4+2] cyclization to give **56** (Scheme 11). In a related cascade reaction, condensation of 2-azidobenzaldehyde (**54**) with propargyl amine followed by treatment of the intermediate imine with acetyl chloride and the ketene acetal **57** delivered the triazole **58** via a [3+2] dipolar cycloaddition. A noteworthy aspect of these constructions is that complex heterocyclic systems are rapidly generated in simple one-pot operations.



Scheme 11

Inasmuch as we are always interested in applications of novel strategies for heterocycle synthesis to natural products, we queried whether this novel strategy for DOS might be exploited to prepare complex alkaloids. We thus envisioned that a four-component reaction might be exploited to assemble **62** and analogs thereof, which would nicely serve as precursors of the benzanulated azabicyclo[3.2.2]nonane core present in the isopavine alkaloids [19]. Gratifyingly, we discovered that condensation of piperonal (**59**) with methylamine gave an intermediate imine that was sequentially treated in situ with the Grignard reagent **60** and then the acid chloride **61** to provide **62** (Scheme 12). When **62** was treated with aqueous acid, it underwent facile cyclization to give (\pm)-roelactamine (**4**), an alkaloid that was isolated in 1992 from *Roemeria refracta* DC [20].



Scheme 12

CONCLUSIONS

We have thus described several novel applications of imine chemistry. The first of these featured a variety of related cascade reactions in which iminium ions were generated and trapped by allylsilanes and other nucleophiles such as cyanide ion and hydride donors to give functionalized quinolizidines and indolizidines in a one-pot process involving the formation of two rings and four new bonds from simple

acyclic starting materials. The importance and practical utility of this new entry to polycyclic nitrogen heterocycles was demonstrated by its application to the facile syntheses of several quinolizidine and indolizidine alkaloids as well as the tricyclic core of the more complex alkaloid halichlorine. The second advance was the design and development of a novel approach for DOS that features a one-pot process in which four components are combined to give functionalized adducts that may be transformed via various cyclization manifolds into a diverse collection of functionalized heterocyclic scaffolds that may be further diversified. The utility of this strategy for DOS was exemplified by its application to the synthesis of an isopavine alkaloid. Further applications of these processes to the preparation of targets of biological interest are under active investigation, and the results will be reported in due course.

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REFERENCES

1. For reviews of *N*-alkyl iminium ions, see: (a) T. A. Blumenkopf, L. E. Overman. *Chem. Rev.* **86**, 857 (1986); (b) E. F. Kleinman, R. A. Volkmann. In *Comp. Org. Syn.*, B. M. Trost (Ed.), 975 (1991); (c) J. Royer, M. Bonin, L. Micouin. *Chem. Rev.* **104**, 2311 (2004); for reviews of *N*-acyl iminium ions, see: (d) W. N. Speckamp, M. J. Moolenaar. *Tetrahedron* **56**, 3817 (2000); (e) B. E. Maryanoff, H.-C. Zhang, J. H. Cohen, I. J. Turchi, C. A. Maryanoff. *Chem. Rev.* **104**, 1431 (2004); for a review of vinylogous Mannich reactions, see: (f) S. F. Martin. *Acc. Chem. Res.* **35**, 895 (2002).
2. For selected examples, see: (a) S. F. Martin, B. Benage, L. S. Geraci, J. E. Hunter, M. Mortimore. *J. Am. Chem. Soc.* **113**, 6161 (1991); (b) S. F. Martin, C. C. Clark, J. W. Corbett. *J. Org. Chem.* **60**, 3236 (1995); (c) M. Ito, C. C. Clark, M. Mortimore, J. B. Goh, S. F. Martin. *J. Am. Chem. Soc.* **123**, 8003 (2001); (d) S. Liras, C. L. Lynch, A. M. Fryer, B. T. Vu, S. F. Martin. *J. Am. Chem. Soc.* **123**, 5918 (2001); (e) A. Reichelt, S. K. Bur, S. F. Martin. *Tetrahedron* **58**, 6323 (2002); (f) A. Deiters, K. Chen, C. T. Eary, S. F. Martin. *J. Am. Chem. Soc.* **125**, 4541 (2003); (g) S. F. Martin, C. E. Neipp. *J. Org. Chem.* **68**, 8867 (2003); (h) D. G. Washburn, R. W. Heidebrecht Jr., S. F. Martin. *Org. Lett.* **5**, 3523 (2003); (i) A. C. Rudolph, R. Machauer, S. F. Martin. *Tetrahedron Lett.* **45**, 4895 (2004); (j) S. T. M. Simila, S. F. Martin. *J. Org. Chem.* **72**, 5342 (2007).
3. For a preliminary account of this work, see: S. M. Amorde, A. S. Judd, S. F. Martin. *Org. Lett.* **7**, 2031 (2005).
4. For a preliminary account of this work, see: J. D. Sunderhaus, C. Dockendorff, S. F. Martin. *Org. Lett.* **9**, 4223 (2007). See also references therein for related strategies for rapid assembly of functionalized heterocycles.
5. H. H. Wasserman, C. B. Vu, J. D. Cook. *Tetrahedron* **48**, 2101 (1992).
6. S. L. Schreiber, R. E. Claus, J. Reagan. *Tetrahedron Lett.* **23**, 3867 (1982).

7. H. H. Mooiweer, H. Hiemstra, H. P. Fortgens, W. N. Speckamp. *Tetrahedron Lett.* **28**, 3285 (1987).
8. G. Pandey, G. D. Reddy, D. Chakrabarti. *J. Chem. Soc., Perkin Trans. 1* 219 (1996).
9. For some other syntheses of epilupinine, see: (a) D. L. Comins, J. D. Brown. *Tetrahedron Lett.* **27**, 2219 (1986); (b) C. Morley, D. W. Knight, A. C. Share. *J. Chem. Soc., Perkin Trans. 1* 2903 (1994); (c) B. N. Naidu, F. G. West. *Tetrahedron* **53**, 16565 (1997); (d) P. Mangeney, L. Hamon, S. Raussou, N. Urbain, A. Alexakis. *Tetrahedron* **54**, 10349 (1998); (e) S. Ma, B. Ni. *Chem.—Eur. J.* **10**, 3286 (2004).
10. For representative syntheses of tashiromine, see: (a) D. Olivier, C. Bellec, M. C. Fargeau-Bellassoued, G. Lhommet. *Heterocycles* **55**, 1689 (2001); (b) R. W. Bates, J. Boonsombat. *J. Chem. Soc., Perkin Trans. 1* 654 (2001); (c) R. K. Dieter, R. Watson. *Tetrahedron Lett.* **43**, 7725 (2002).
11. (a) J. C. Gramain, R. Remuson. *Tetrahedron Lett.* **26**, 327 (1985); (b) J. Burfeindt, M. Patz, M. Mueller, H. Mayr. *J. Am. Chem. Soc.* **120**, 3629 (1998).
12. J. Monfray, Y. Gelas-Mialhe, J.-C. Gramain, R. Remuson. *Tetrahedron Lett.* **44**, 5785 (2003).
13. For syntheses of epimyrtiline, see: (a) P. Slosse, C. Hootele. *Tetrahedron* **37**, 4287 (1981); (b) D. Gardette, Y. Gelas-Mialhe, J.-C. Gramain, B. Perrin, R. Remuson. *Tetrahedron: Asymmetry* **9**, 1823 (1998); (c) F. A. Davis, Y. Zhang, G. Anilkumar. *J. Org. Chem.* **68**, 8061 (2003).
14. D. Enders, J. P. Shilvock. *Chem. Soc. Rev.* **29**, 359 (2000).
15. For representative syntheses of halichlorine, see: (a) D. Trauner, J. B. Schwartz, S. J. Danishefsky. *Angew. Chem., Int. Ed.* **38**, 3542 (1999); (b) H. S. Christie, C. H. Heathcock. *Proc. Natl. Acad. Sci. USA* **101**, 12079 (2004); (c) Y. Matsumura, S. Aoyagi, C. Kibayashi. *Org. Lett.* **6**, 965 (2004); (d) H.-L. Zhang, G. Zhao, Y. Ding, B. Wu. *J. Org. Chem.* **70**, 4954 (2005); (e) R. Andrade, S. F. Martin. *Org. Lett.* **7**, 5733 (2005).
16. (a) M. D. Burke, S. L. Schreiber. *Angew. Chem., Int. Ed.* **43**, 46 (2004); (b) D. R. Spring. *Org. Biomol. Chem.* **1**, 3867 (2003); (c) R. L. Strausberg, S. L. Schreiber. *Science* **300**, 294 (2003).
17. For example, see: (a) S. Marcaccini, T. Torroba. *Multicomponent Reactions*, J. Zhu, H. Bienayme (Eds.), p. 33, Wiley-VCH, Weinheim (2005); (b) A. Dömling. *Chem. Rev.* **106**, 17 (2006).
18. For a related MCR, see: Y. Yin, G. Zhao, G.-L. Li. *Tetrahedron* **61**, 12042 (2005).
19. For selected syntheses of isopavine alkaloids, see: (a) B. Gözler. *The Alkaloids*, Vol. 31, A. Brossi (Ed.), p. 343, Academic Press, New York (1987); (b) L. Gottlieb, A. I. Meyers. *J. Org. Chem.* **55**, 5659 (1990); (c) L. Carrillo, D. Badía, E. Domínguez, J. L. Vicario, I. Tellitu. *J. Org. Chem.* **62**, 6716 (1997); (d) T. Shinohara, A. Takeda, J. Toda, T. Sano. *Heterocycles* **48**, 981 (1998); (e) D. R. Dragoli, M. T. Burdett, J. A. Ellman. *J. Am. Chem. Soc.* **123**, 10127 (2001); (f) U. K. Tambar, D. C. Enber, B. M. Stoltz. *J. Am. Chem. Soc.* **128**, 11752 (2006).
20. B. Gözler, M. A. Öñür, S. Bilir, M. Hesse. *Helv. Chem. Acta* **75**, 260 (1992).