

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 70

www.rsc.org/obc

PAPER

# Indolizinones as synthetic scaffolds: fundamental reactivity and the relay of stereochemical information†

Alison R. Hardin Narayan and Richmond Sarpong\*

Received 19th August 2011, Accepted 20th September 2011

DOI: 10.1039/c1ob06423a

Indolizinones are under-explored *N*-heterocycles that react with exquisite chemo- and stereoselectivity. An exploration of the fundamental reactivity of these azabicycles demonstrates the potential to relay stereochemical information from the ring-fusion to newly formed stereocenters on the bicyclic core. The indolizinone diene undergoes selective hydrogenation and readily participates in Diels–Alder cycloadditions as well as ene reactions. The vinylogous amide embedded in the five-membered ring is resistant to reaction when the diene is in place. However, removal of the diene allows for diastereoselective hydrogenation of, and 1,4-additions to, the vinylogous amide. These fundamental reactions with indolizinones have provided a structurally diverse array of products that hold promise in the context of natural product synthesis.

## Introduction

Indolizinones are *N*-heterocycles that have only recently appeared in the chemical literature.<sup>1–5</sup> These 6,5-*N*-fused bicycles contain eight contiguous sp<sup>2</sup>-hybridized atoms and a single sp<sup>3</sup>-carbon atom, which resides at the ring-fusion (see C9 of **1**, Fig. 1). Both the dienamine contained within the six-membered ring and the vinylogous amide moiety in the five-membered ring could serve as functional handles, rendering indolizinones as useful precursors to indolizidine natural products, pharmaceutical agents and new materials.

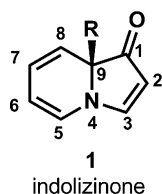


Fig. 1 Indolizinone.

Methods for the synthesis of indolizinones were pioneered in our laboratories with platinum(II) and indium(III) salts<sup>1,3</sup> and have been further developed by others with salts or complexes of copper,<sup>2</sup> silver,<sup>6</sup> gold<sup>6</sup> and iodine.<sup>4</sup> This transformation is proposed to proceed by cyclization of the pyridine moiety (see **2**, Fig. 2A) onto a metal-activated alkyne to form an intermediate

such as **3** followed by a stereoretentive Wagner–Meerwein shift of the propargylic substituent with concomitant proton transfer to afford the indolizinone product (**4**). Indolizinones are also accessible from propargylic alcohols using a greener protocol. Both our group<sup>7</sup> and the Kim group<sup>5</sup> discovered that heating tertiary alcohols such as **5** in a polar protic solvent (*e.g.*, water or ethanol) affords indolizinone products in excellent yields (Fig. 2B).

Although several protocols for the synthesis of indolizinones have recently emerged, little is known about their innate reactivity. Only two examples of reactions of indolizinones have appeared in the literature. In 2008, Paquette and co-workers described the dimerization of benzannulated indolizinones (see **7**, Fig. 3A) *via* a light promoted [4+2] cyclization between the diene component of one indolizinone molecule and a double bond of the diene from another molecule of the indolizinone.<sup>8</sup> The second disclosure of indolizinone chemistry came in 2010 from Kim and co-workers on the palladium-catalyzed cross-coupling of 2-iodoindolizinones (Fig. 3B).<sup>9</sup> They demonstrated the competence of 2-iodoindolizinones as the halide component in Heck, Sonogoshira, and Suzuki–Miyaura reactions.

The relative lack of knowledge regarding indolizinone reactivity compared to other nitrogen-heterocycles (*e.g.*, indoles<sup>10</sup> and indolizines), coupled with our desire to use indolizinones as building blocks in the synthesis of complex molecules, spurred our investigation of these bicycles. In addition to understanding the types of reactions indolizinones would participate in, we were intrigued by the potential to relay the stereochemistry of the ring-fusion position (*i.e.*, C9, Fig. 4) to the installation of additional stereocenters. Our studies have revealed the exquisite chemo- and stereoselectivity of several reactions that transform indolizinones into structurally diverse products with high diastereoselectivity in the formation of bonds at C3, C5, C6 and C8 (see asterisked

Department of Chemistry, University of California, Berkeley, CA 94720, USA. E-mail: rsarpong@berkeley.edu; Web: <http://www.cchem.berkeley.edu/rsgrp/>; Fax: (+1) 0-510-642-8369

† Electronic supplementary information (ESI) available. CCDC reference numbers 834076 and 834077. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob06423a

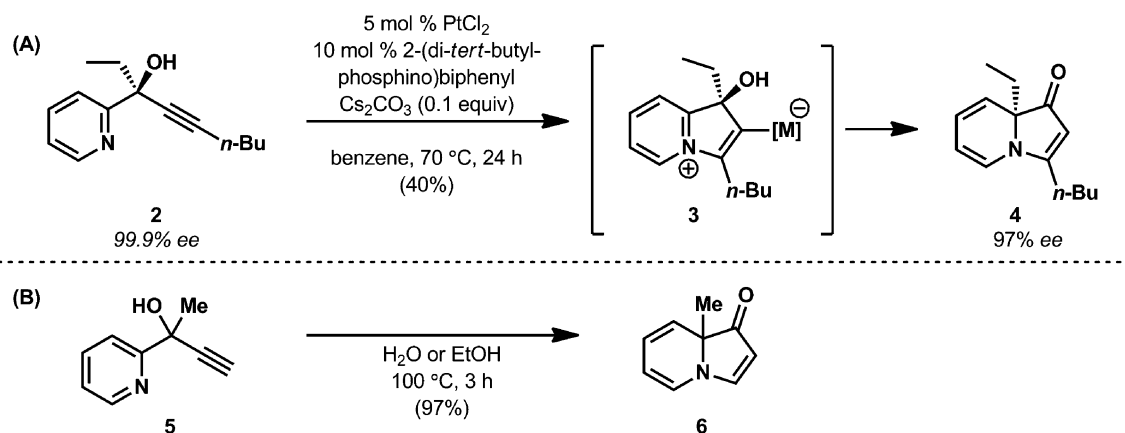


Fig. 2 Cyclization of tertiary alcohols to form indolizones (A) metal-catalyzed cyclization and (B) metal-free cyclization.

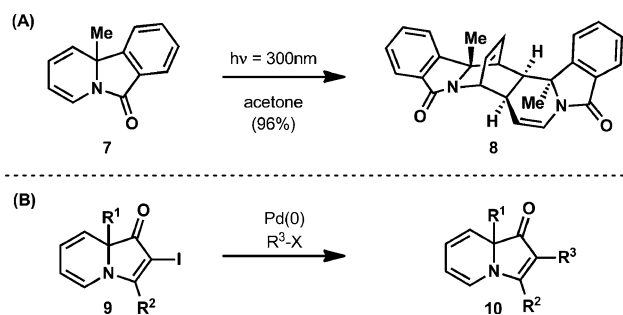


Fig. 3 (A) Paquette's photodimerization of pyrido[2,1-*a*]isoindol-6(4*H*)-one (7); (B) palladium-catalyzed cross couplings of 2-iodoindolizone (9).

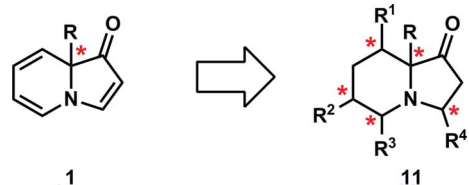


Fig. 4 The relay of stereochemistry from the ring-fusion to positions on the indolizone core.

positions in **11**). The potential application of these products to the synthesis of indolizidine alkaloids is also discussed.

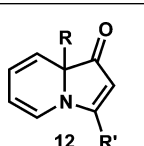
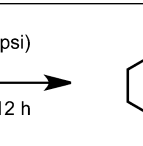
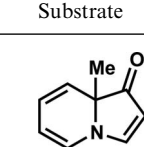
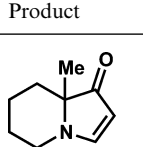
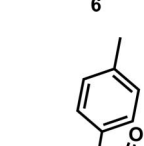
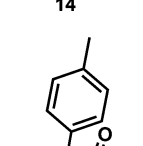
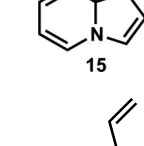
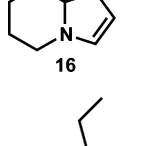
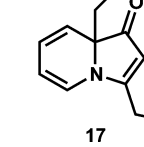
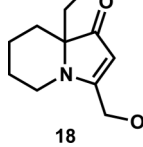
## Results and discussion

### 1. Hydrogenation

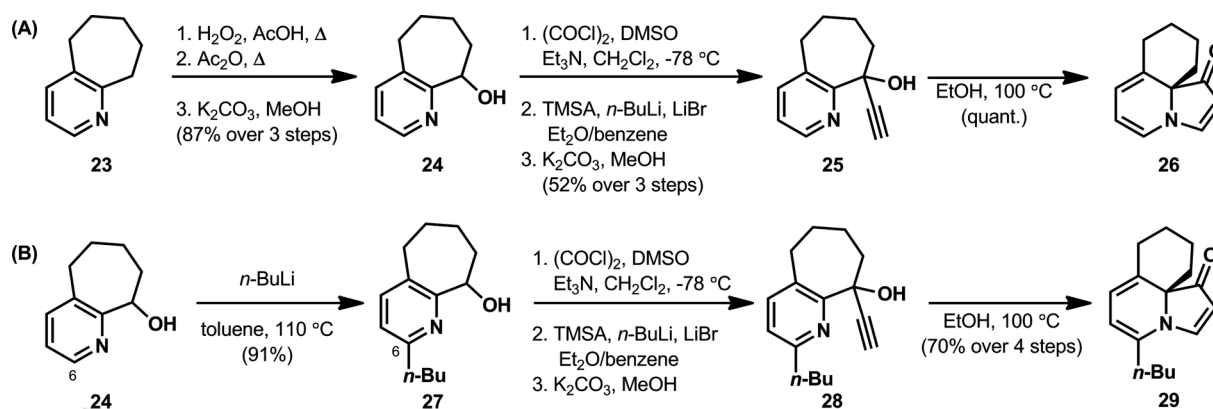
Indolizones undergo regio- and diastereoselective hydrogenation under a variety of conditions. The electron-rich diene component is selectively reduced in the presence of the relatively electron-poor vinylogous amide double bond. Heterogeneous catalysts, such as Pd/C and RANEY® nickel, reduce only the indolizone diene using pressures of hydrogen ranging from 1 to 15 atm.

Exposing several indolizones to Pd/C in methanol under hydrogen (150 psi) for 12 h led to high yields of the corresponding piperidine products (Table 1). Shorter reaction times and lower pressures of hydrogen led to incomplete conversion in some cases. Ethyl acetate and ethanol are also competent solvents for this transformation; however, the use of these solvents also led to

Table 1 Hydrogenation of the indolizone diene

Entry	Substrate	Product	Yield
1			98%
2			94%
3			78%
4			93%
5			99%

incomplete conversion of starting material in some cases. The hydrogenation of indolizones with alkyl or aryl substituents



Scheme 1 Synthesis of (A) tricyclic indolizinone **26** and (B) alkylated indolizinone **29**.

at C9 (entries 1–2) proceeded without event. Substitution on the vinylogous amide component is also tolerated and does not qualitatively affect the course of the reaction (entries 3–5).

The hydrogenation of more substituted indolizinones provided insight into the facial selectivity of this transformation. We expected hydrogenation to occur from the less sterically hindered face of the bicycle, opposite the ring-fusion substituent. Tricyclic indolizinones **26** and **29** (Scheme 1) were synthesized and subjected to the hydrogenation conditions. The synthesis of indolizinones **26** and **29** began with a Boekelheide sequence on 2,3-cycloheptenopyridine (**23**) to regioselectively install the requisite hydroxyl group, affording alcohol **24** in 87% yield over three steps.<sup>11</sup> Alcohol **24** was oxidized under Swern conditions to the corresponding ketone followed by 1,2-addition of the lithium acetylide of trimethylsilylacetylene. Subsequent removal of the silyl group provided cyclization substrate **25** in 52% yield over three steps. Upon heating in ethanol, **25** underwent ring-contractive cyclization to afford tricyclic indolizinone **26** in quantitative yield. In parallel, alcohol **24** was elaborated to alkylated indolizinone **29** in five steps (Scheme 1B). Several strategies for alkylation of pyridine **24** at C6 were explored, but ultimately, only the Chichibabin-type addition of *n*-butyllithium provided a single isomer of the desired product (**27**) in high yield. Alkylation product **27** was carried forward to indolizinone **29** in a manner analogous to the conversion of alcohol **24** to indolizinone **26**.

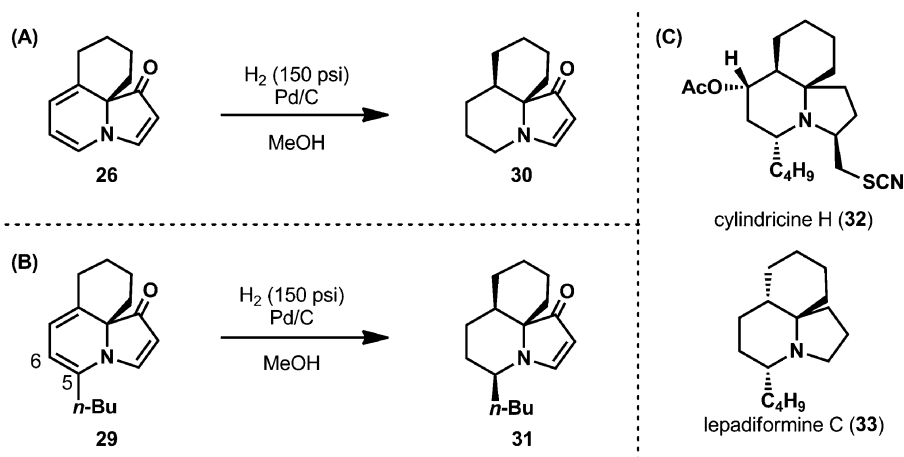
Exposure of 6,6,5-tricycle **26** to Pd/C under 150 psi of hydrogen provided a single diastereomer of the reduction product, which was assigned as **30** (Scheme 2A). The *cis*-ring fused product (**30**) constitutes the tricyclic core conserved throughout several members of the cylindricine family of marine alkaloids (e.g., **32**, Scheme 2C).<sup>12–16</sup> The alternative *trans*-ring fusion of the six-membered rings, which is not accessed by this method, is present in a related family of alkaloids, the lepadiformines (e.g., **33**).<sup>17</sup>

To probe the facial selectivity of the hydrogenation of the dienamine double bond most proximal to the indolizinone nitrogen ( $\Delta^{5,6}$ ), tricyclic indolizinone **29** was exposed to the standard hydrogenation conditions. After 12 h, **29** was converted to **31**, whereby the hydrogenation of both double bonds of the diene took place from the less hindered face, providing an entry to the 9-*epi*-lepadiformine core.

## 2. Diels–Alder cycloaddition

In addition to hydrogenation, the indolizinone dienamine participates in Diels–Alder cycloadditions with high regio- and diastereoselectivity. Using the Diels–Alder reaction, indolizinones are transformed into complex [2.2.2]azabicycles, which can be further processed into a structurally diverse set of products.

Cognizant of the possibility for dimerization of the indolizinone as observed by Paquette and co-workers under photo-irradiation



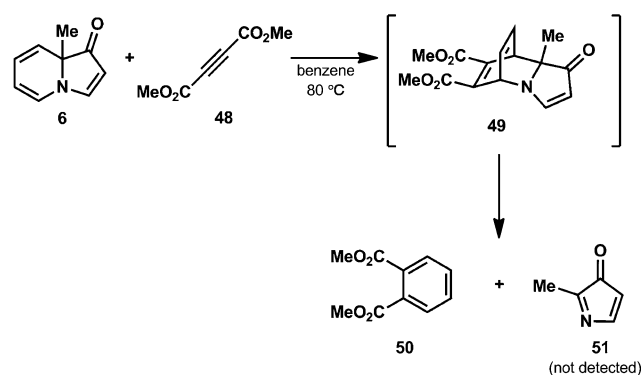
Scheme 2 (A) Hydrogenation of tricyclic indolizinone **26**, (B) hydrogenation of alkylated indolizinone **29**, and (C) select tricyclic marine natural products.

**Table 2** Diels–Alder cycloadditions of methylindolizone (6) with various dienophiles

Entry	Dienophile	Product	Yield
1			96%
2			84%
3			94%
4			91%
6			93%
6			73%

(see Fig. 3A), reactive dienophiles were first investigated. Heating methylindolizone (6) with maleic anhydride (36) in benzene at 80 °C afforded [2.2.2]azabicyclic 37 as a single diastereomer in 96% yield (entry 1, Table 2). Under the same conditions, high yields as well as high diastereoselectivity (>20:1 d.r. by <sup>1</sup>H NMR) were also observed in the reaction of methylindolizone (6) with acrolein (38), methyl acrylate (40), *t*-butyl acrylate (42) and 2-chloroacrylonitrile (44). Methylindolizone (6) reacted with 4-phenyl-1,2,4-triazole-3,5-dione (46) at 0 °C in dichloromethane to provide the hetero-Diels–Alder adduct 47 in 73% yield.

In a further exploration of dienophiles for the Diels–Alder cycloaddition with methylindolizone (6), dimethylacetylenedicarboxylate (DMAD, 48) was combined with 6 and heated to 80 °C in benzene for 12 h (Scheme 3). The sole product recovered from this reaction was a highly symmetrical aromatic compound that was identified as dimethyl phthalate (50), which could arise from the retro-Diels–Alder of the anticipated product, [2.2.2]azabicyclic

**Scheme 3** Reaction of methylindolizone (6) with DMAD (48).

49. Attempts to isolate Diels–Alder adduct 49 were not fruitful, but dimethyl phthalate (50) was consistently isolated as the major product. The generation of dimethyl phthalate (50) via a retro [4+2] of 49 would also produce azacyclopentadienone 51, which could not be isolated or trapped with either dienes or dienophiles.

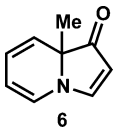
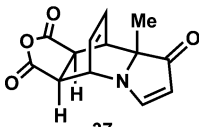
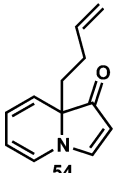
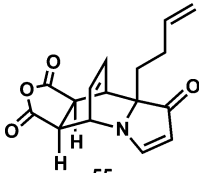
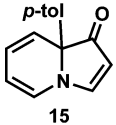
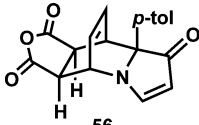
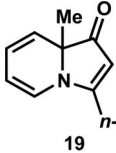
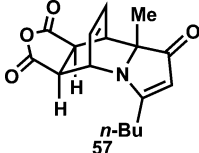
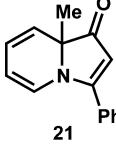
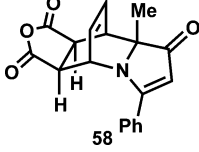
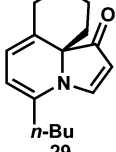
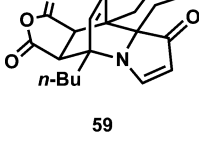
A variety of indolizones bearing different substituents readily participate in Diels–Alder cycloadditions, which have been investigated with maleic anhydride (Table 3). In addition to varied substitution at the ring fusion of the indolizone, alkyl and aryl groups on the vinylogous amide component (see entries 4 and 5) do not qualitatively affect the reaction. Tricyclic indolizone 29 provided an extra challenge in the Diels–Alder reaction, where a productive cycloaddition generates a quaternary and tertiary center in quantitative yield (see 59).

As illustrated (Tables 2 and 3), the Diels–Alder reactions consistently afforded a single diastereomer of the [2.2.2]azabicyclic product (>20:1 d.r. by <sup>1</sup>H NMR). To determine the relative stereochemistry of the Diels–Alder adducts, X-ray diffraction studies of 55 and 64 were undertaken. The crystal structures of 55 and 64 (Fig. 5) confirm the *syn* relationship between the unsaturated two-carbon bridge and the C9 substituent that results from the approach of the dienophile from the face of the indolizone opposite the ring-fusion substituent. Furthermore, the crystal structures of 55 and 64 provide additional information about the Diels–Alder transition states. In 55, the *syn* relationship between the anhydride moiety and the two-carbon unsaturated bridge suggests an *endo*-transition state. The cyano group of 64 is *anti* to the unsaturated bridge providing evidence for a transition state in which the chlorine atom resides in the *endo*-position.

The rapid generation of complexity afforded by indolizones through Diels–Alder cycloadditions presents an intriguing opportunity to assemble highly caged skeletons by employing an intramolecular variant. To this end, two indolizone substrates were investigated which possessed a tethered dienophile: homoallylindolizone 54 and ester 62. Heating homoallylindolizone 54 at temperatures up to 120 °C resulted only in recovery of the starting material (Scheme 4). Presumably, the [4+2] cycloaddition of 54 does not proceed because of poorly matched electronics. To access a substrate with an electron deficient dienophile, homoallylindolizone 54 was converted to  $\alpha,\beta$ -unsaturated ester 62 via cross metathesis with methyl crotonate mediated by the Grubbs II catalyst.

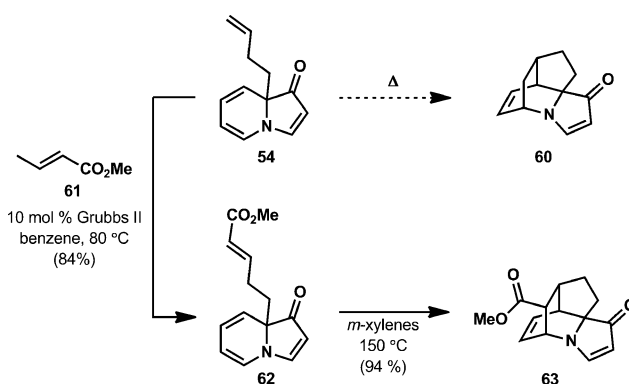
Despite the strain inherent in the desired product, heating 62 in *m*-xylenes at 150 °C for 12 h led to the desired [2.2.2]bicyclic

**Table 3** Diels–Alder cycloadditions of indolizinones and maleic anhydride

Entry	Indolizinone	Product	Yield
1			96%
2			67%
3			89%
4			93%
5			91%
6			88%

**63**, which could be isolated in quantitative yield (Scheme 4). The intramolecular Diels–Alder provides a product with a different stereochemical relationship between the C9 ring-fusion substituent and the unsaturated two-carbon bridge as compared to the intermolecular reaction. The tethered dienophile can only approach the diene from the same face of the molecule, resulting in an *anti* relationship between the unsaturated two-carbon bridge and the ring-fusion substituent. The highly caged skeleton (see **63**) generated in the intramolecular Diels–Alder reaction is unprecedented.

With rapid access to [2.2.2]azabicycles, the potential to convert these complex intermediates to indolizidine natural products and

**Scheme 4** Intramolecular Diels–Alder cycloadditions.

natural product-like structures was investigated. Efforts to synthesize tricyclic marine alkaloids (*e.g.*, cylindricine and lepadiformine alkaloids, see **32** and **33**, respectively, Fig. 2C) from Diels–Alder adducts led to several unanticipated discoveries.

For example, efforts to remove the chlorine and nitrile groups from [2.2.2]azabicyclo **64**<sup>18</sup> provided an example of the anomalous reactivity of the Diels–Alder adducts (Scheme 5). Exposure of **64** to dissolving metal conditions afforded a single disubstituted aromatic compound, which was identified (by <sup>1</sup>H NMR and mass spectral analysis) as **66**. Arene **66** could arise from an initial reductive C–Cl bond cleavage to afford anion **65**. Subsequent fragmentation to cleave the C–N bond of the [2.2.2]bicyclo (see arrows, **65**) would form a cyclohexadiene intermediate, which upon oxidation in air, would give arene **66**. Although fragmentation of the [2.2.2]azabicyclo was unproductive in the synthesis of indolizidine alkaloids, the potential exists for transforming products such as **66** into biologically relevant classes of molecules, such as protease inhibitors.<sup>19</sup>

The carbon framework of the [2.2.2]azabicyclo can be manipulated to afford a functionalized piperidine ring *via* oxidative cleavage of the unsaturated two-carbon bridge. The oxidative cleavage substrate **70** was accessed in two steps from indolizinone **29** *via* Diels–Alder cycloaddition with acryloyl chloride and a subsequent Barton decarboxylation (Scheme 6). Attempts to dihydroxylate the unsaturated two-carbon bridge of **70** were accompanied by oxidation of the vinylogous amide moiety. Over-oxidation was avoided by first reducing the double bond of the vinylogous amide, then subjecting the tertiary amine product to catalytic osmium tetroxide followed by sodium periodate. This protocol provided dialdehyde **71** as a mixture with its hydrate forms. Conversion of [2.2.2]azabicyclo **70** to functionalized piperidine **71** could be useful in the context of natural product total synthesis. For example, stereoretentive decarbonylation of **71** would afford tricycle **72**, which could lead to marine alkaloids such as lepadiformine C (**73**). Our efforts in this regard have thus far led only to complex mixtures from which **72** could not be isolated.

Alternatively, the unsaturated two-carbon bridge of [2.2.2]azabicyclo **64** (Scheme 7) can be engaged in olefin metathesis reactions. Treatment of [2.2.2]azabicyclo **64** with Grubbs second generation catalyst **81** in refluxing benzene effected a ring-opening/ring-closing metathesis to afford tricycle **79** in 73% yield. The *syn* relationship between the homoallyl group and the two-carbon unsaturated bridge of **64** enforces the



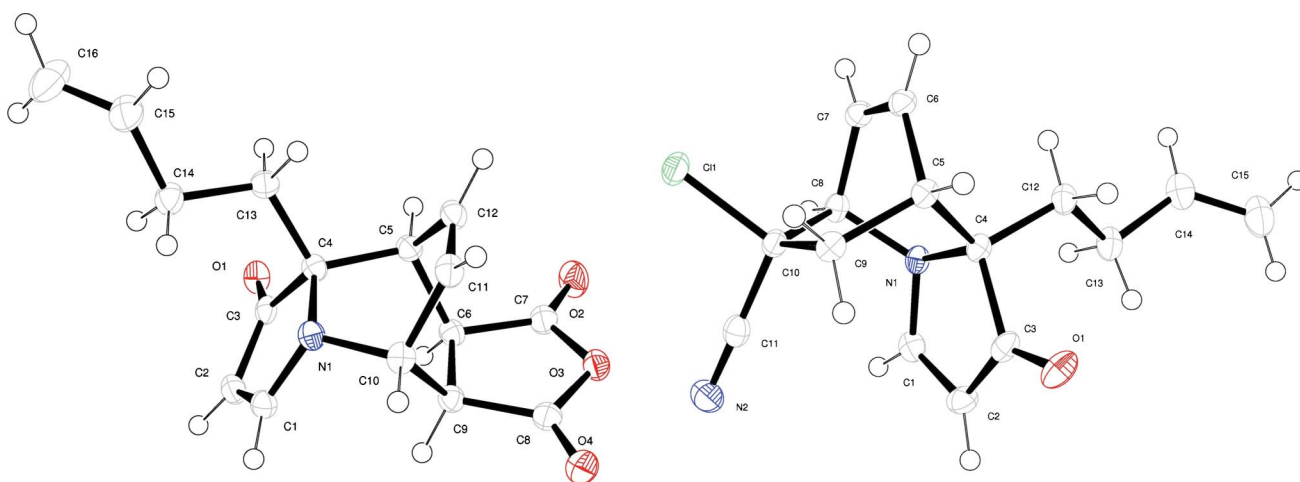
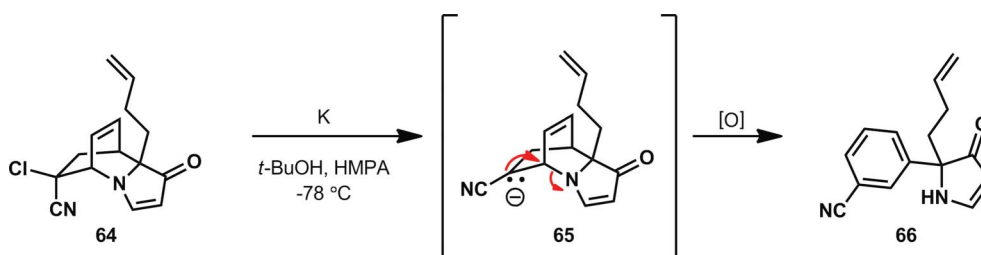
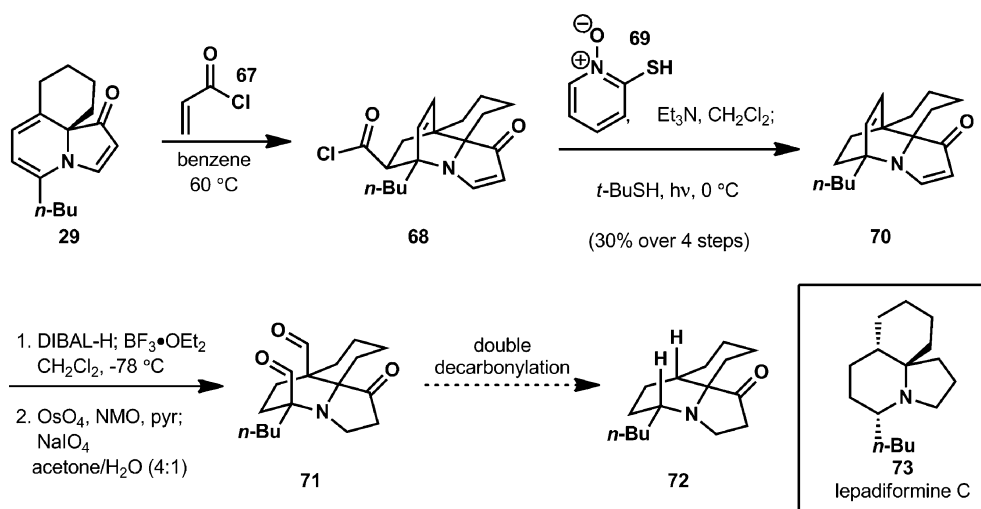


Fig. 5 X-ray crystal structures of Diels–Alder adducts **55** and **64**.



Scheme 5 Fragmentation of [2.2.2]azabicyclic compound under dissolving metal conditions.



Scheme 6 Oxidative cleavage of [2.2.2]azabicyclic compound **70**.

stereochemistry in **79**, which possesses appropriate functional handles for elaboration to cylindricine K (**80**).

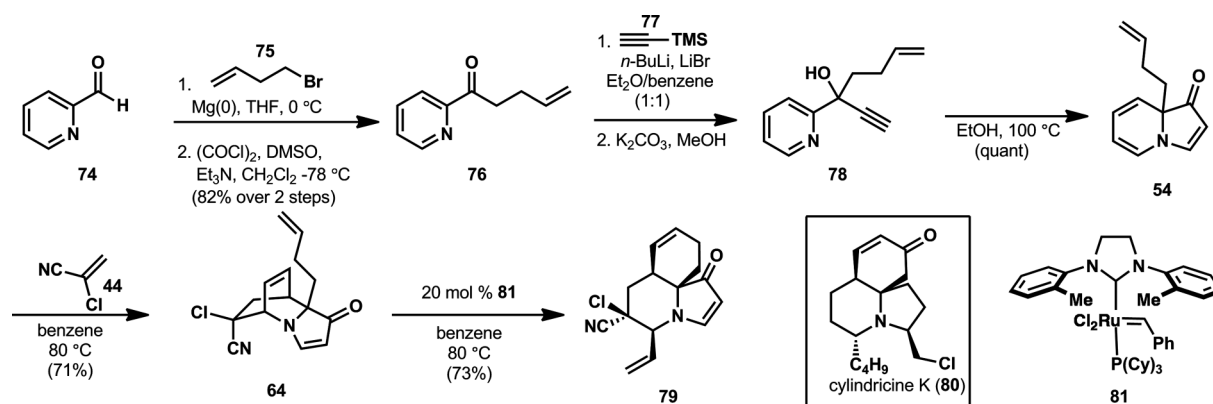
### 3. Ene reaction

As previously illustrated (Table 2, entry 6), indolizone dienes can readily engage in Diels–Alder cycloadditions; however, with an appropriate substituent on the diene (e.g., **29**, Scheme 8), the ene reaction can be a competing pathway. For example, although cycloaddition of methyl indolizone **6** with PTAD (**46**) provided the Diels–Alder adduct **47** (entry 6, Table 2), treatment of tricyclic

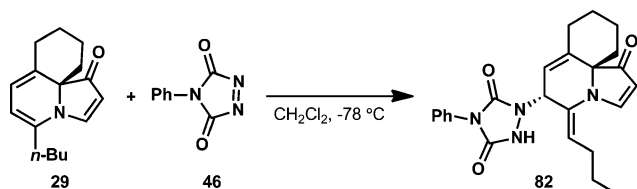
indolizone **29** with PTAD (**46**) gave rise to the ene product (**82**) as a single diastereomer (Scheme 8).

### 4. Chemistry of the vinylogous amide

In our exploration of the reactivity of the dienamine moiety of indolizones, the vinylogous amide was left untouched under the vast majority of the reaction conditions. We, therefore, were interested in learning (1) the identity of nucleophiles and conditions necessary for successful additions to the vinylogous amide and (2) to which position nucleophiles would add. To



**Scheme 7** Synthesis of the tricyclic cylindricine core *via* ring-opening/ring-closing metathesis of **64**.

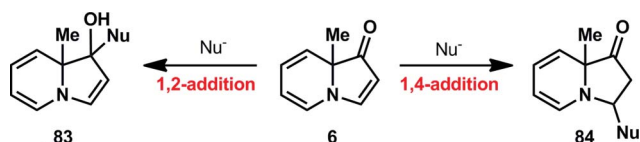


**Scheme 8** Ene reaction of indolizone **29** with PTAD.

answer these questions, we first focused our efforts on two classes of nucleophiles: Grignard reagents and hydride sources.

A series of experiments wherein methylindolizone (**6**) was treated with Grignard reagents in THF or diethyl ether at temperatures ranging from  $-78$  to  $-42$  °C resulted in the recovery of the indolizone starting material. At temperatures above  $-42$  °C, only complex mixtures of extremely polar products were obtained. Likewise, treatment of **6** with a variety of hydride sources including sodium borohydride, diisobutylaluminum hydride, and triethylsilane did not accomplish clean reduction and led only to recovery of starting material or the isolation of an unidentifiable mixture of products.

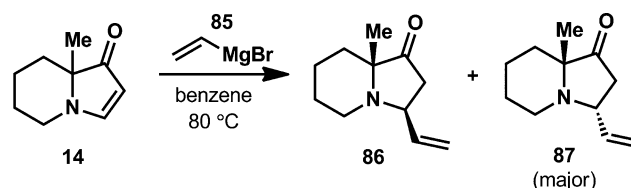
These unfruitful attempts to add nucleophiles to the indolizone vinylogous amide led us to consider the potential outcomes of nucleophilic addition. In one scenario, the nucleophile could add in a 1,2-fashion to the vinylogous amide to generate an allylic alcohol such as **83** (Fig. 6). This product is a trienamine (**83**), which was expected to be highly reactive. The alternative reaction pathway, 1,4-addition to the vinylogous amide, would result in dienamine **84**. Although dienamine **84** might be slightly more stable than trienamine **83**, similar undesired reactions would likely ensue from this product as well.



**Fig. 6** Potential products of nucleophilic addition to the vinylogous amide.

With this insight into the challenges associated with nucleophilic additions to indolizones, we sought to isolate the vinylogous amide in order to study its chemistry. Methylindolizone (**6**) was hydrogenated to provide vinylogous amide **14**. Upon treatment

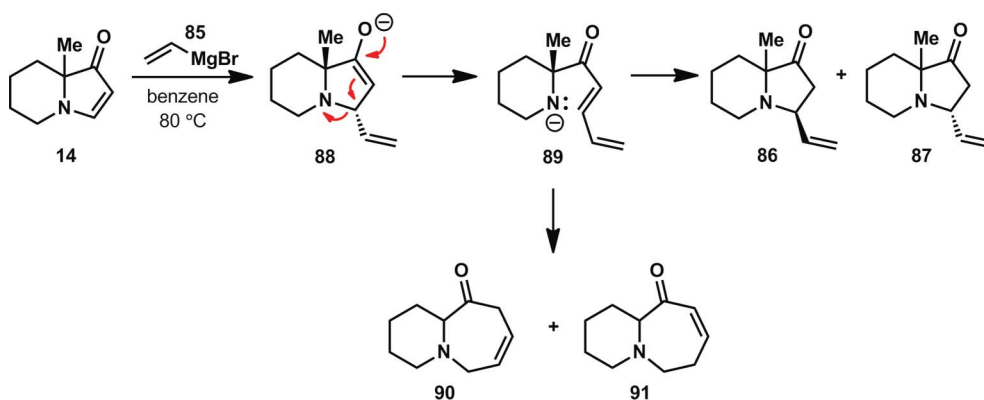
of **14** with vinylmagnesium bromide at temperatures ranging from  $-78$  °C to ambient temperature, the starting material was recovered. However, when several equivalents of Grignard reagent were employed in conjunction with increased reaction temperatures, the 1,4-addition product was obtained as a 3 : 1 mixture of diastereomers **87**:**86** (Scheme 9). The major diastereomer possesses a *trans* relationship between the ring-fusion methyl group and the newly added vinyl substituent as established through *n*Oe experiments.



**Scheme 9** Grignard addition to vinylogous amide **14**.

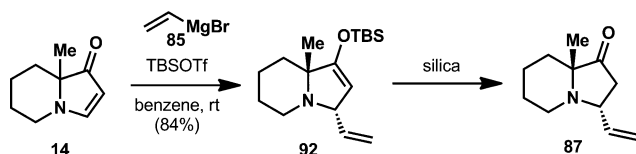
It was expected that addition from the more sterically accessible face of the vinylogous amide, opposite the methyl group at C9, would provide a single diastereomer. However, the mixture of diastereomers implied one of the following scenarios: (1) the vinylmagnesium bromide was adding from both faces of the five-membered ring or (2) the enolate, formed as a direct result of 1,4-addition, could collapse to eliminate the nitrogen group (Scheme 10, see **88**  $\rightarrow$  **89**). In addition to isolating a mixture of diastereomers of the ketone product (**86** and **87**), a trace amount of product was obtained that did not possess a terminal vinyl group, yet contained two more carbon atoms than vinylogous amide **14**.  $^1\text{H}$  NMR data for this minor product suggests a mixture of similar products, which were assigned as 6,7-bicycles **90** and **91** that differ only in the position of the double bond contained within the seven-membered ring. Mechanistically, the seven-membered ring could form from the ring-opened intermediate (**89**) by 1,6-addition of the amide to form the seven-membered ring.

In order to gain insight into the poor diastereoselectivity observed in the addition of vinyl Grignard to the vinylogous amide, we sought to trap the enolate intermediate (**88**). In the event the enolate was leading to fragmentation of the five-membered ring, trapping the enolate could avoid racemization of the stereocenter created upon conjugate addition. If instead the lack of diastereoselectivity stemmed from a lack of facial selectivity



**Scheme 10** Potential mechanism for erosion of diastereoselectivity in conjugate addition.

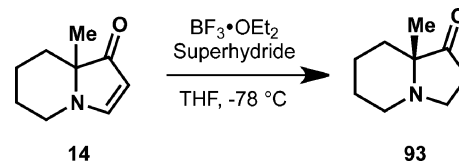
in the addition, the same mixture of diastereomers should be obtained when the enolate is trapped. In practice, the addition of TBSOTf to the reaction mixture successfully intercepted the enolate and led to a single diastereomer of silyl enol ether **92**, which hydrolyzed to afford ketone **87** (Scheme 11). The TBSOTf had two effects on this transformation: (1) a single diastereomer of the product could be obtained and (2) the activation of the vinylogous amide by the TBSOTf made it possible for the nucleophile to add at lower temperatures.



**Scheme 11** Activation and trapping with TBSOTf.

Similar to the addition of carbon nucleophiles, hydrides also add in a conjugate fashion to the vinylogous amide. To achieve synthetically useful yields of the reduced product, it was necessary to first activate the vinylogous amide to increase its electrophilicity. A variety of Lewis acids were screened for this purpose. In addition to silylating reagents such as TBSOTf and TMSOTf that provide silyl enol ether products, boron trifluoride diethyl etherate was also sufficient for amide activation. In parallel with the Lewis acid screen, a variety of hydride sources were evaluated

for the conjugate reduction of the vinylogous amide. DIBAL-H, Superhydride, and L-Selectride were competent in this reduction in the presence of an exogenous Lewis acid. Superhydride provided the highest and most reproducible yields (Scheme 12).

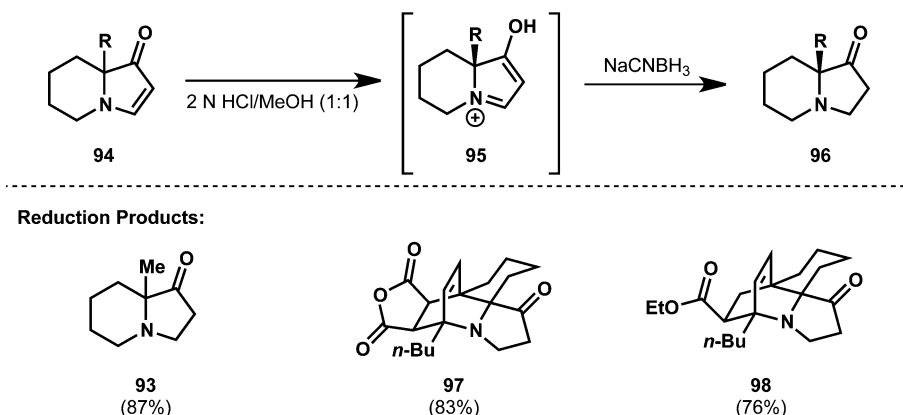


**Scheme 12** Conjugate reduction of the vinylogous amide.

Further experimentation unveiled conditions for the selective reduction of the vinylogous amide in the presence of esters, anhydrides, and ketones. Under strongly acidic conditions, the vinylogous amide was reduced by NaCNBH<sub>3</sub> (Fig. 7). This reagent, famous for its ability to reduce iminium ions formed in reductive amination over carbonyls, can competently deliver a hydride to the iminium ion (**95**) formed upon treatment of the vinylogous amide with 2 N HCl.

## Conclusions

The first in depth exploration of the innate reactivity of indolizinsones has uncovered several regio- and stereoselective reactions. Specifically, the indolizinsonone diene can be hydrogenated,



**Fig. 7** Reduction of the vinylogous amide with sodium cyanoborohydride.



engaged in a Diels–Alder cycloaddition, or participate in an ene reaction. The vinylogous amide has proven to be significantly less reactive, requiring activation for the addition of nucleophiles to occur.

Beyond illuminating the reactivity of indolizinones, we anticipate that the reactions discussed herein, will set the stage for the synthesis of complex molecules from indolizinone building blocks. Our initial endeavors have provided access to the core of tricyclic marine alkaloids such as the cylindricines and lepadiformines. We intend to apply these new discoveries in indolizinone reactivity to the synthesis of indolizidine alkaloids and other complex natural product-like alkaloid structures. Overall, indolizinones are unique molecules that hold promise across a broad range of fields from materials to medicine.

## References

- 1 C. R. Smith, E. M. Bunnelle, A. J. Rhodes and R. Sarpong, *Org. Lett.*, 2007, **9**, 1169–1171.
- 2 B. Yan, Y. B. Zhou, H. Zhang, J. J. Chen and Y. H. Liu, *J. Org. Chem.*, 2007, **72**, 7783–7786.
- 3 E. M. Bunnelle, C. R. Smith, S. K. Lee, S. W. Singaram, A. J. Rhodes and R. Sarpong, *Tetrahedron*, 2008, **64**, 7008–7014.
- 4 J. Choi, G. H. Lee and I. Kim, *Synlett*, 2008, 1243–1249.
- 5 I. Kim, J. Choi, S. Lee and G. H. Lee, *Synlett*, 2008, 2334–2338.
- 6 I. V. Seregin, A. W. Schammel and V. Gevorgyan, *Org. Lett.*, 2007, **9**, 3433–3436.
- 7 The cyclization of tertiary alcohols such as **5** in water to obtain indolizinone products was developed in our laboratories concurrently with Kim and coworkers' (see ref. 5) report of the EtOH version of this metal-free reaction.
- 8 L. A. Paquette, R. D. Dura and J. C. Gallucci, *Heterocycles*, 2008, **76**, 129–132.
- 9 K. Kim and I. Kim, *J. Comb. Chem.*, 2010, **12**, 379–382.
- 10 R. J. Sundberg, *Indoles*, Academic Press, London, 1996.
- 11 K. Gudmundsson, S. D. Boggs, U.S. Patent 11,574,583, 2007.
- 12 A. J. Blackman, C. P. Li, D. C. R. Hockless, B. W. Skelton and A. H. White, *Tetrahedron*, 1993, **49**, 8645–8656.
- 13 C. P. Li and A. J. Blackman, *Aust. J. Chem.*, 1994, **47**, 1355–1361.
- 14 C. P. Li and A. J. Blackman, *Aust. J. Chem.*, 1995, **48**, 955–965.
- 15 P. Schar, S. Cren and P. Renaud, *Chimia*, 2006, **60**, 131–141.
- 16 S. M. Weinreb, *Chem. Rev.*, 2006, **106**, 2531–2549.
- 17 J. F. Biard, S. Guyot, C. Roussakis, J. F. Verbist, J. Vercauteren, J. F. Weber and K. Boukef, *Tetrahedron Lett.*, 1994, **35**, 2691–2694.
- 18 See Supporting Information for details on the preparation of **64**†.
- 19 S. Peukert, Y. C. Sun, R. Zhang, B. Hurley, M. Sabio, X. Y. Shen, C. Gray, J. Dzink-Fox, J. S. Tao, R. Cebula and S. Wattanasin, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 1840–1844.