How to cite: *Angew. Chem. Int. Ed.* **2021**, *60*, 13089–13097
International Edition: doi.org/10.1002/anie.202101511
German Edition: doi.org/10.1002/ange.202101511

Synthetic Methods

Nitrone and Alkyne Cascade Reactions for Regio- and Diastereoselective 1-Pyrroline Synthesis

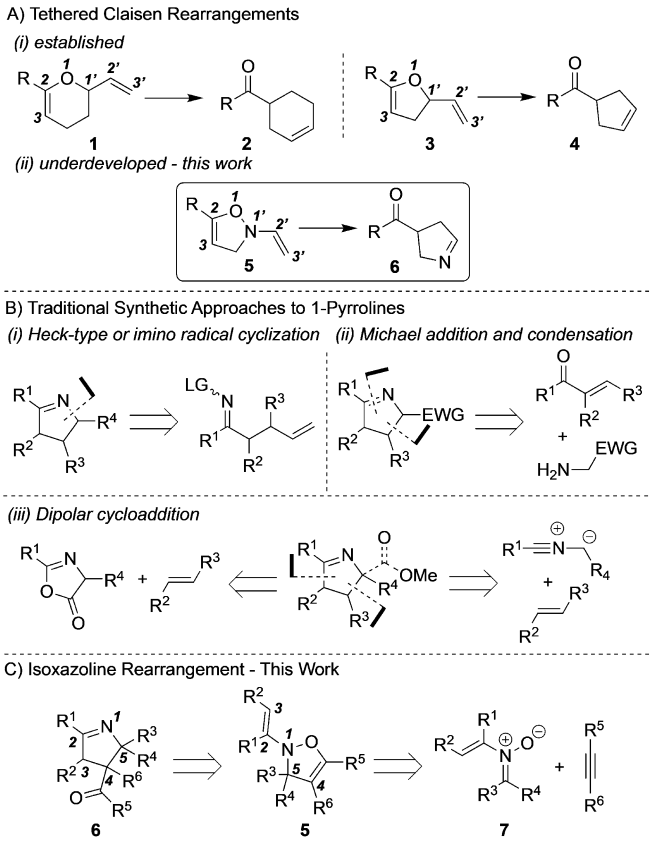
*Guanqun Zhang[+], Abdullah S. Alshreimi[+], Laura Alonso, Alan Antar, Hsien-Cheng Yu, Shahidul M. Islam, and Laura L. Anderson**

Abstract: *The synthesis of 1-pyrrolines from N-alkenylnitrones and alkynes has been explored as a retrosynthetic alternative to traditional approaches. These cascade reactions are formal [4+1] cycloadditions that proceed through a proposed dipolar cycloaddition and N-alkenylisoxazoline [3,3′]-sigmatropic rearrangement. A variety of cyclic alkynes and terminal alkynes have been shown to undergo the transformation with N-alkenylnitrones under mild conditions to provide the corresponding spirocyclic and densely substituted 1-pyrrolines with high regio- and diastereoselectivity. Mechanistic studies provide insight into the balance of steric and electronic effects that promote the cascade process and control the diastereo- and regioisomeric preferences of the 1-pyrroline products. Diastereoselective derivatization of the 1-pyrrolines prepared by the cascade reaction demonstrate the divergent synthetic utility of the new method.*

Introduction

Cascade reactions that pair two fragments to form reactive intermediates and undergo subsequent transformations to form more complex products are important processes in synthetic chemistry.[1] These reactions facilitate modular access to sophisticated scaffolds from simple reagents. Pericyclic reactions have featured prominently in a variety of fragment coupling and domino processes.[2] While pyranyl and furanyl substrates such as **1** and **3** are well-known to undergo [3,3′]-sigmatropic rearrangements to carbocycles **2** and **4**, the analogous transformation of *N*-alkenylisoxazoline **5** to 1-pyrroline **6** is underdeveloped due to the challenges involved in accessing this heterocycle (Scheme 1 A).[3–5] Identification of new modular routes to *N*-alkenylisoxazoline **5** represent an opportunity for the design of new cascade processes.

1-Pyrrolines are prominent scaffolds in a variety of biologically active molecules.[6] Traditionally, these compounds are prepared by Heck-type or imino radical cyclizations, Michael addition and condensation processes, or dipolar cycloadditions of nitrile ylides or munchnones (Scheme 1 B).[7–11] While several elegant catalytic systems have been designed to control the reactivity and selectivity of these reactions, they still have fundamental limitations due to the specific C–N and C–C bond forming events involved in each synthetic approach. We were curious if 1-pyrrolines **6** could be constructed from readily accessible *N*-alkenylnitrone **7** and an alkyne through the [3,3′]-sigmatropic rearrangement of *N*-alkenylisoxazoline **5** (Scheme 1 C). If successful, this approach would enable access to this important heterocyclic scaffold through a formal [4+1] process and assembly of the two sterically congested C–C bonds tethering the carbon atom at the 4-position of the ring. This transformation would facilitate the incorporation of a ring-fusion at the 2- and 3-positions, which is challenging to achieve with dipolar cycloadditions of nitrile ylides and munchnones. In addition, when paired with an *N*-alkenylisoxazoline synthesis



Scheme 1. *N*-Alkenylisoxazoline approach to 1-pyrroline synthesis. LG = leaving group. EWG = electron-withdrawing group.

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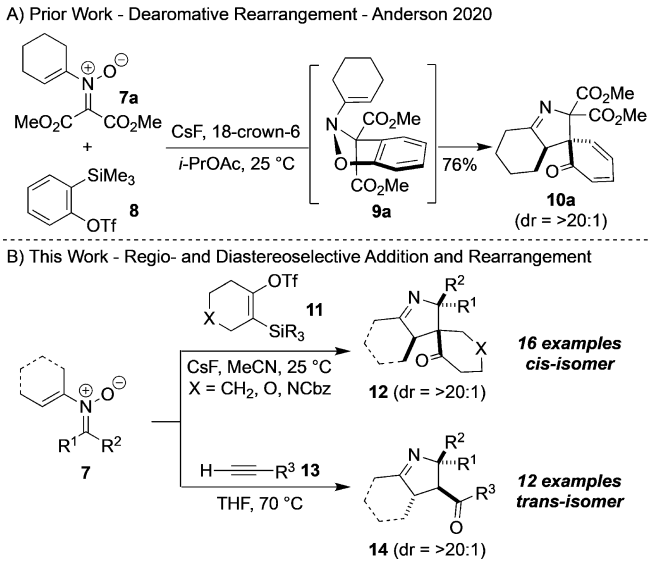
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.202101511.

via dipolar cycloaddition, this approach achieves the benefit of modularity that is lacking from many cyclization strategies.

Recently, we communicated a dipolar cycloaddition and dearomative rearrangement cascade reaction for the synthesis of spirocyclic 1-pyrrolines (Scheme 2 A).[12] This transformation is proposed to proceed via a [3 + 2]-dipolar cycloaddition of an *N*-alkenylnitrone and an aryne to give *N*-alkenylbenzisoxazoline intermediate **9**, which spontaneously undergoes a formal dearomative [3,3′]-sigmatropic rearrangement to give the corresponding spirocyclic 1-pyrrolines **10**.[13] These studies provided proof of principle for the utility of *N*-alkenylisoxazoline cascade intermediates as retrosynthetic alternatives for 1-pyrroline synthesis and were facilitated by our previous discovery of the use of the Chan-Lam reaction for preparing *N*-alkenylnitrones from oximes.[14] We surmised that this reactivity pattern could be advanced beyond highly reactive benzyne reagents and that further investigation would improve our understanding of the generation and reactivity of *N*-alkenylisoxazolines. Herein we describe the development of dipolar cycloaddition and [3,3′]-sigmatropic rearrangement cascade reactions of *N*-alkenylnitrones with cycloalkynes and terminal alkynes to give a broad range of spirocyclic and densely substituted 1-pyrrolines (Scheme 2 B). These transformations are regioselective, diastereoselective, and access 1-pyrrolines through an unusual formal [4 + 1]-process, which allows for consideration of alternative retrosynthetic strategies in comparison to traditional approaches (Scheme 1 B). Mechanistic studies are included, which describe the regiochemical preferences of the initial dipolar cycloaddition, consider the relationship between cycloaddition synchronicity and reaction scope, and explore the diastereomeric preference of the products. Functionalization studies further showcase the utility of this method for synthetic applications.[15]



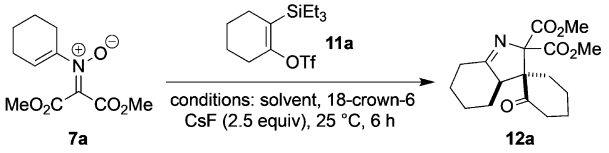
Scheme 2. 1-Pyrroline synthesis via fragment coupling of *N*-alkenylnitrones and alkynes.

Results and Discussion

Cascade Synthesis of Spirocyclic 1-Pyrrolines from N-Alkenylnitrones and Cyclic Alkynes

To initially explore the tolerance of the cascade reaction for spirocyclic 1-pyrroline formation beyond aryne reagents, the reactivity of cyclohexyne was investigated with *N*-alkenylnitrone **7a** (Table 1).[16,17] As shown in Table 1, when cyclohexyne was generated in the presence of nitrone **7a** under the optimal conditions reported for the formation of **10**, pyrroline **12a** was observed in 64% yield (entry 1). Further screening indicated that this transformation is sensitive to solvent effects and increased yields of **12a** were obtained in THF and MeCN (entries 1–5). While the polarity of MeCN could mediate the need for a crown-ether additive, it was observed that at least one equivalent of 18-crown-6 increases the yield of the desired product (entries 5–7). This requirement is likely associated with the activation of **11a**. The ratio of **7a** to **11a** could be reduced to 1:1 but a slight reduction in yield was observed under these conditions (entry 8). Variation of the reaction time and decreasing the reaction temperature to 0 °C showed little effect on the yield of **12a** and concentration studies indicated cleaner reactivity with less concentrated mixtures (entries 9–12). With the optimal conditions of Table 1, entry 5 in hand, the scope of the cycloalkyne and *N*-alkenylnitrone cascade reaction was explored for the synthesis of 1-pyrroline spirocycles.

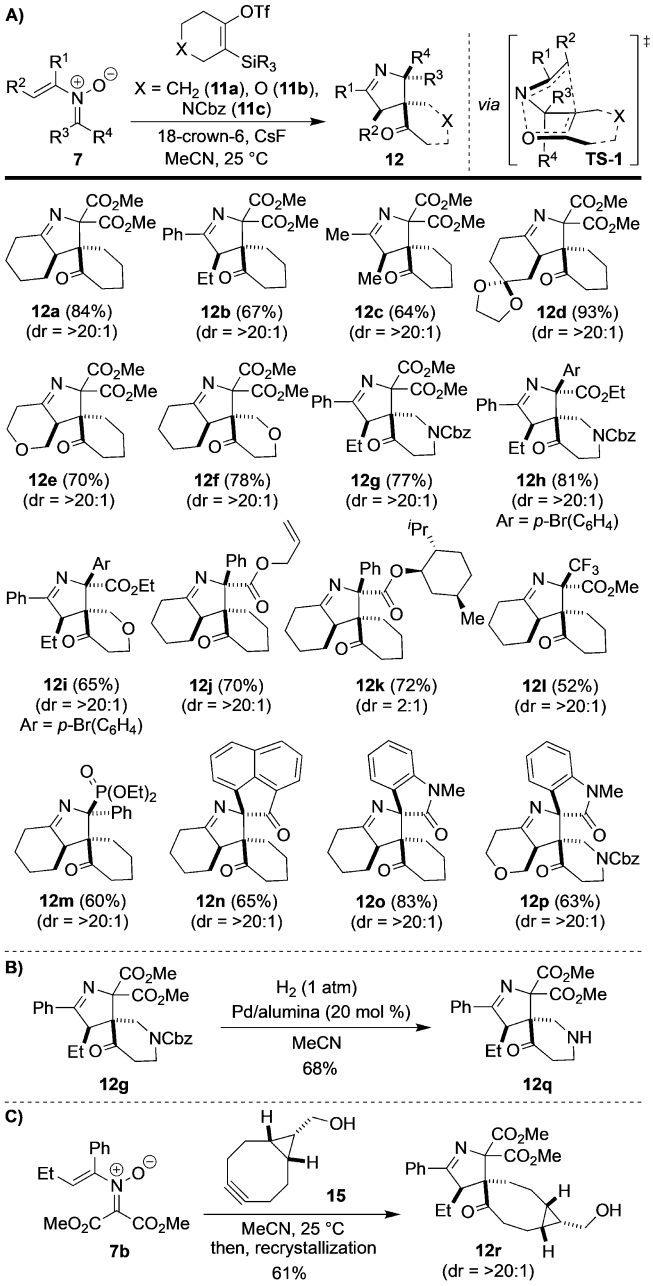
Table 1: Optimization of cascade synthesis of 1-pyrroline **12a** from nitrone **7a** and cyclohexyne precursor **11a**.



Entry[a]	Solvent	**11a** [equiv]	18-crown-6 [equiv]	**7a** [M]	Yield [%][b]
1	*i*-PrOAc	2	2	0.1	64
2	DCE	2	2	0.1	66
3	PhMe	2	2	0.1	22
4	THF	2	2	0.1	78
5	MeCN	2	2	0.1	84[c]
6	MeCN	2	0	0.1	12
7	MeCN	2	1	0.1	78
8	MeCN	1	2	0.1	77
9[d]	MeCN	2	2	0.1	74
10[e]	MeCN	2	2	0.1	87
11	MeCN	2	2	0.05	86
12	MeCN	2	2	0.5	69

[a] Conditions: **7a** (0.05 mmol). [b] Yield determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal reference. [c] Isolated yield. [d] Reaction performed at 0 °C. [e] Reaction run for 48 h. DCE = 1,2-dichloroethane, *i*-PrOAc = isopropyl acetate.

Investigation of the scope of the dipolar cycloaddition and rearrangement reaction for the synthesis of spirocyclic 1-pyrrolines **12** included variation of both the *N*-alkenylnitrone and cycloalkyne components as illustrated in Scheme 3. When cyclohexyne was generated in the presence of malonate-



Scheme 3. Scope of the synthesis of spirocyclic 1-pyrrolines from nitrones **7** and cycloalkynes (R = Et for **11a** and **11b**, R = Me for **11c**).

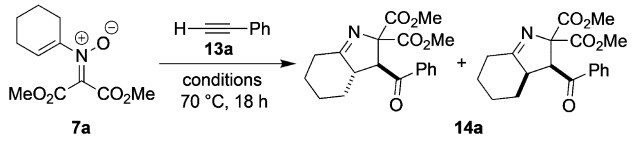
derived nitrones with cyclic, styrenyl, linear, and heterocyclic *N*-alkenyl substituents, pyrrolines **12a**–**12e** were formed in good yield with high diastereoselectivity. The *cis*-relationship between the alkyl substituent at the 3-position and the ketone at the 4-position was initially assumed in analogy to benzyne cascade products **10** but later confirmed by X-ray crystallography (see **12i**).[18] Similarly, when the cyclohexyne precursor was exchanged for pyranyne precursor **11b** and piperidyne precusor **11c**, spirocyclic pyrrolines **12f** and **12g** were generated smoothly. These single regioisomeric products corresponded to the preferred dipolar cycloaddition regioselectivity predicted by the torsion-distortion model previously reported by Garg and Houk.[19] The synthesis of **12g** could also be combined with a deprotection process to give **12q** over two steps (Scheme 3B). Investigation of nitrones derived from unsymmetrical ketones introduced a third stereocenter to the 1-pyrroline ring with consistently high diastereoselectivity (see **12h**–**12m**). The stereochemical relationship of the three stereocenters was confirmed by an X-ray crystal structure of **12i** and is consistent with the cascade reaction being a stereospecific process dependent on the stereochemistry of **7**.[18] The isolation of **12h**–**12j** are noteworthy since analogous cascade reactions between *N*-alkenylnitrones derived from benzoylformate esters and benzyne give dihydrobenzofurans through a proposed spontaneous rearomatization process.[12] Further attempts at controlling stereochemical information using a chiral non-racemic ester substituent on the nitrone showed only moderate selectivity (**12k**) suggesting that the stereochemical information is likely too far removed from the initial C–C bond forming event to be influential. To the best of our knowledge, spirocyclic 1-pyrrolines **12** are new compounds that have not previously been reported in the literature. The only exception is **12b**, which was reported by our group via the hydrogenation of **10**.[12] These novel 1-pyrroline scaffolds highlight the expanded chemical space can be accessed by moving beyond the retrosynthetic limitations of traditional methods.

A survey of biologically active spirocyclic pyrrolidines encouraged us to further explore 1-pyrroline scaffolds that incorporate isatin- and acenapthylenedione-derived functionalities.[20–23] Conversion of *N*-methyl isatin and acenapthylenedione to *N*-cyclohexenylnitrones and treatment with **11a** or **11c** under the optimized cascade reaction conditions showed that these compounds are well-tolerated for the synthesis of 1-pyrrolines **12n**–**12p** (Scheme 3A). These new heterocycles contain two adjacent spirocyclic functionalities and are consistently formed in high diastereoselectivity. Due to the importance of cyclooctyne cycloadditions in biorthogonal transformations, cyclooctyne **15** was also prepared and tested in the cascade process.[24] As shown in Scheme 3C, the reaction tolerated this less strained cyclic alkyne and the remote cyclopropyl functional group resulted in the formation of a (5:1) mixture of diastereomeric products. Subsequent crystallization gave the major isomer **12r** in 61% yield. The results illustrated in Scheme 3 show the breadth of the cascade reaction for the synthesis of a range of new spirocyclic 1-pyrrolines through a unique retrosynthetic disconnection.

Cascade Reaction of Nitrones and Terminal Alkynes

Having established that *N*-alkenylnitrones **7** undergo the addition and rearrangement cascade process with minimally strained cycloalkynes such as cyclooctyne **15**, the transformation was tested with terminal alkynes.[25] Gratifyingly, when nitrone **7a** was treated with phenylacetylene **13a** at 70 °C in MeCN, formation of pyrroline **14a** was observed in 59% yield as a single regioisomer with moderate diastereoselectivity (Table 2, entry 1).[17] Further optimization showed that this reaction is sensitive to solvent effects and an increase in yield was observed for *i*-PrOAc, toluene, and THF, with THF giving the highest yield of 1-pyrroline **14a** with excellent

Table 2: Optimization of cascade synthesis of 1-pyrroline **14a** from nitrone **7a** and phenylacetylene.

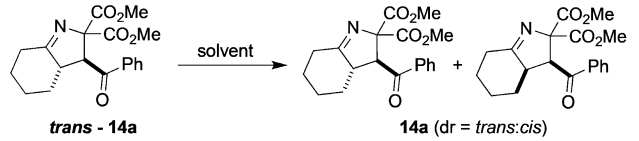


Entry[a]	Solvent	**7a** [M]	*T* [°C]	dr (*trans*:*cis*)	Yield [%][b]
1	MeCN	0.1	70	7:1	59
2	*i*-PrOAc	0.1	70	14:1	71
3	DCE	0.1	70	5:1	49
4	PhMe	0.1	70	15:1	78
5	THF	0.1	70	20:1	80
6	THF	0.2	70	20:1	87
7	THF	0.2	25	20:1	25
8[c]	THF	0.2	70	20:1	79
9[d]	THF	0.2	70	14:1	71
10[e]	THF	0.2	70	13:1	60

[a] Conditions: **7a** (0.05 mmol), **13a** (3 equiv). [b] Yield determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal reference. [c] Time = 9 h. [d] Time = 36 h. [e] **13a** (1 equiv). DCE = 1,2-dichloroethane, *i*-PrOAc = isopropyl acetate.

diastereoselectivity (entries 2–5). Increasing the concentration of the reaction mixture further increased the yield of **14a** and decreasing the reaction temperature and time inhibited the conversion (entries 6–8). Increasing the reaction time led to a decrease in diastereoselectivity (entry 9). The major diastereomer of the product was identified by X-ray crystallography and has a *trans*-relationship between the substituents at the 3- and 4-positions of the 1-pyrroline ring.[18] The *trans*/*cis*-diastereomeric ratio between these two positions was shown to be dependent on the selection of the reaction medium as well as the concentration of phenylacetylene (entries 1–5 and 10). While **14a** can be purified by column chromatography, isolated as a single *trans*-diastereomer, and crystallized as a single *trans*-diastereomer, solutions of **14a** in $CDCl_3$ and [D_4]MeOH isomerize over time to mixtures of *trans*-**14a** and *cis*-**14a** as illustrated in Table 3.[26] With optimal

Table 3: Isomerization of 1-pyrroline ***trans*-14a** in $CDCl_3$ and [D_4]MeOH.

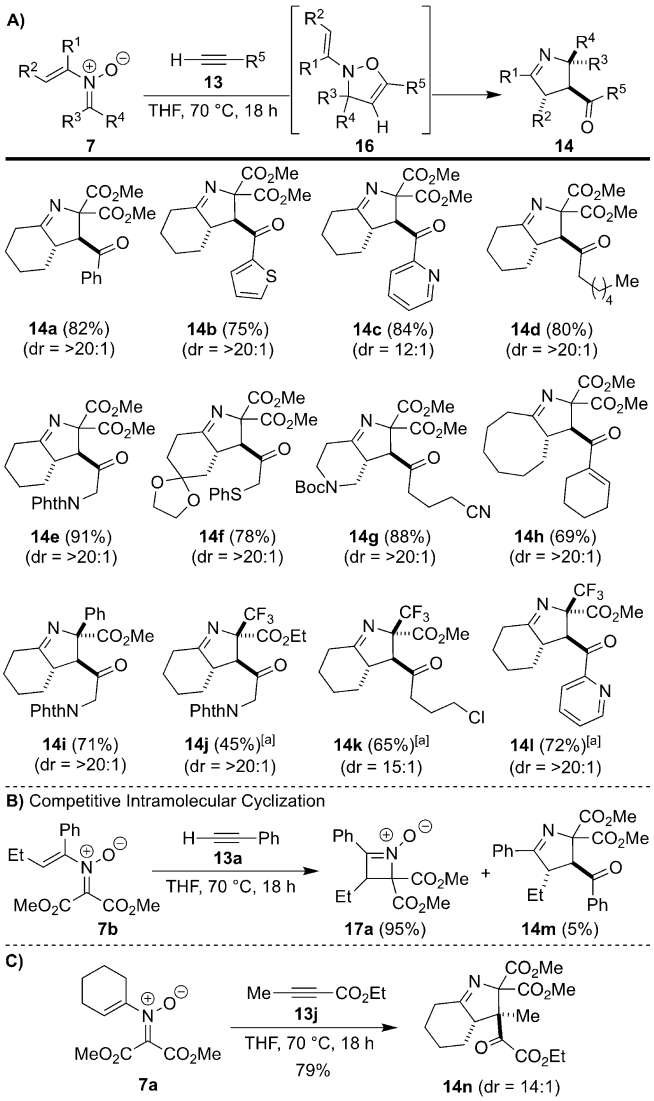


Entry[a]	Solvent	*T* [°C]	*t* [h]	dr
1	$CDCl_3$	25	0	>50:1
2	$CDCl_3$	25	12	13:1
3	$CDCl_3$	60	8	10:1
4	$CDCl_3$	70	18	10:1
5	CD_3OD	25	0	>50:1
6	CD_3OD	25	12	>50:1
7	CD_3OD	60	8	>50:1
8	CD_3OD	70	18	11:1

[a] Conditions: ***trans*-14a** (0.07 mmol), 0.2 M. [b] Yield determined by ^{1}H NMR spectroscopy using 1,4-dimethoxybenzene as an internal standard. No deuterium incorporation was observed at the 3- or 4-positions of **14a**.

conditions in hand for the conversion of nitrone **7a** to 1-pyrroline **14a** (Table 2, entry 6), a broader survey of terminal alkyne reaction partners was undertaken.

Investigation of the scope of the cascade reaction for the synthesis of 1-pyrrolines **14** included variation of both the *N*-alkenylnitrone and terminal alkyne components as illustrated in Scheme 4 A. When nitrone **7a** was treated with aryl, heteroaryl, or alkyl alkynes, pyrrolines **14a**–**14e** were formed in good yield with high regio- and diastereoselectivity corresponding to a sterically controlled dipolar cycloaddition and favoring a *trans*-relationship between the substituents at the 3- and 4-positions of the 1-pyrroline. While pyrrolines **14a**–**14c** converted to diastereomeric mixtures when left in solution, no isomerization was observed for pyrrolines **14d** and **14e** under analogous conditions. Nitrones with substituted *N*-cyclohexenyl, *N*-cyclooctenyl, and *N*-heterocyclic functionalities were also shown to be tolerant of the addition and rearrangement cascade process (see **14f**–**14h**); however, nitrones with linear *N*-alkenyl substituents underwent com-



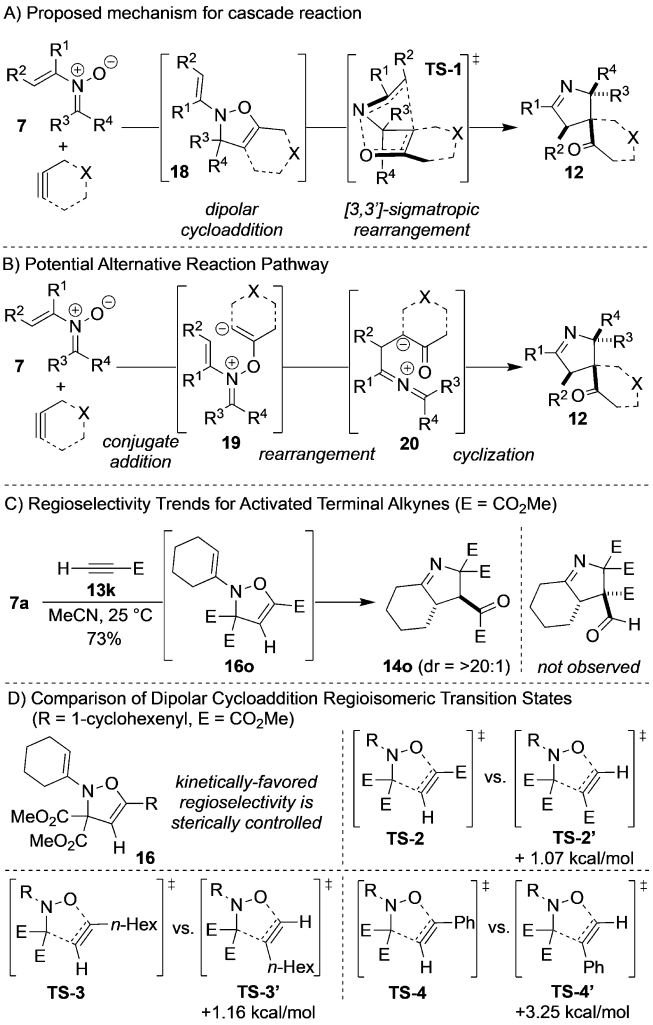
Scheme 4. Scope of cascade synthesis of 1-pyrrolines from nitrones **7** and terminal alkynes **13**. [a] 25 °C.

petitive intramolecular 4π-electrocyclization at the elevated reaction temperature to give azetidine nitrones such as **17** (Scheme 4B).[14a,17,27] Nitrones derived from unsymmetrical carbonyl precursors were also shown to participate in the cascade process with alkyl- and aryl-substituted terminal alkynes to give **14i–14l**. The pyrrolines formed in these reactions incorporated an additional tertiary carbon stereocenter with analogous high regio- and diastereoselectivity. The relative stereochemistry of these compounds was confirmed by X-ray crystallographic analysis of **14j**.[18] In contrast to **14c**, 1-pyrroline **14l** was resistant to isomerization in solution. Nitrones prepared from *N*-methylisatin and acenaphthylenedione were unreactive with terminal alkynes suggesting that some amount of strain release is required to initiate the cascade reaction for these substrates.[25] Activated internal alkynes such as **13j** were observed to undergo analogous reactivity to give pyrrolines such as **14n** with a quaternary stereocenter at the 4-position of the pyrroline (Scheme 4C).[17,28] This survey of reaction scope showcased the tolerance of the cascade process beyond strained alkynes, while also highlighting a need for increased reaction temperature, a preference for the *trans*-pyrroline diastereomer, and competition with alternative reaction pathways. In analogy to the spirocyclic compounds presented in Scheme 3, it is worth noting that the 1-pyrrolines illustrated in Scheme 4 are also new compounds that are more easily accessed through the cascade approach than traditional cycloaddition and cyclization methods.

Mechanistic Considerations

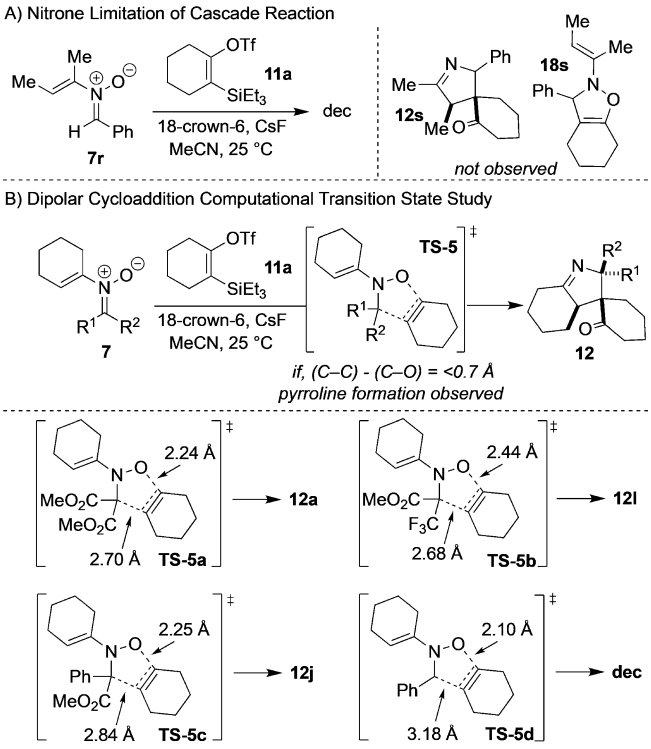
Previously, we proposed that the cascade reaction of *N*-alkenylnitrones and arynes proceeds via an initial dipolar cycloaddition to form **9** followed by a [3,3]-sigmatropic rearrangement to form **10** (Scheme 2A). This reaction pathway is consistent with the stereochemistry observed for the dearomatized spirocyclic pyrroline products and was also supported by the isolation of a dipolar cycloaddition adduct that was deactivated towards the subsequent [3,3′]-sigmatropic rearrangement.[12] We initially proposed that cascade reactions of *N*-alkenylnitrones with cyclic and terminal alkynes likely proceed by an analogous mechanism (see Scheme 5A) but decided to further interrogate this conjecture.

The regioselectivity observed for the cascade synthesis of 1-pyrrolines **12** and **14** supports our mechanistic proposal of a dipolar cycloaddition followed by a [3,3′]-sigmatropic rearrangement. The regioselectivity observed for **12f–12i** is consistent with the torsion-distortion regiochemical model proposed by Garg and Houk but does not rule out an alternative stepwise addition, rearrangement, and cyclization mechanism (Scheme 5B).[19,29,30] The regioselectivity observed for the cascade synthesis of 1-pyrrolines **14** is consistent with a sterically controlled dipolar cycloaddition (Scheme 4 and Scheme 5A). To determine if electronically activated alkynes could reverse this selectivity or indicate an alternative operative mechanism such as the one shown in Scheme 5B, propiolate **13k** was subjected to reaction conditions with nitrone **7a**. As shown in Scheme 5C, pyrroline **14o** was observed as the major product and supports a mechanistic pathway that proceeds through a dipolar cycloaddition instead of a conjugate addition. A computational study was also initiated to interrogate the transition states for the dipolar cycloadditions of nitrone **7a** with methyl propiolate, 1-octyne, and phenylacetylene.[17] As shown in Scheme 5D, all of these transformations kinetically favor the sterically controlled transition state that leads to the observed regiochemically favored product. Therefore, although we have not been able to experimentally observe *N*-alkenylisoxazoline intermediates converting to 1-pyrrolines in these transformations, the above regiochemical data supports the proposed mechanism illustrated in Scheme 5A.[31]

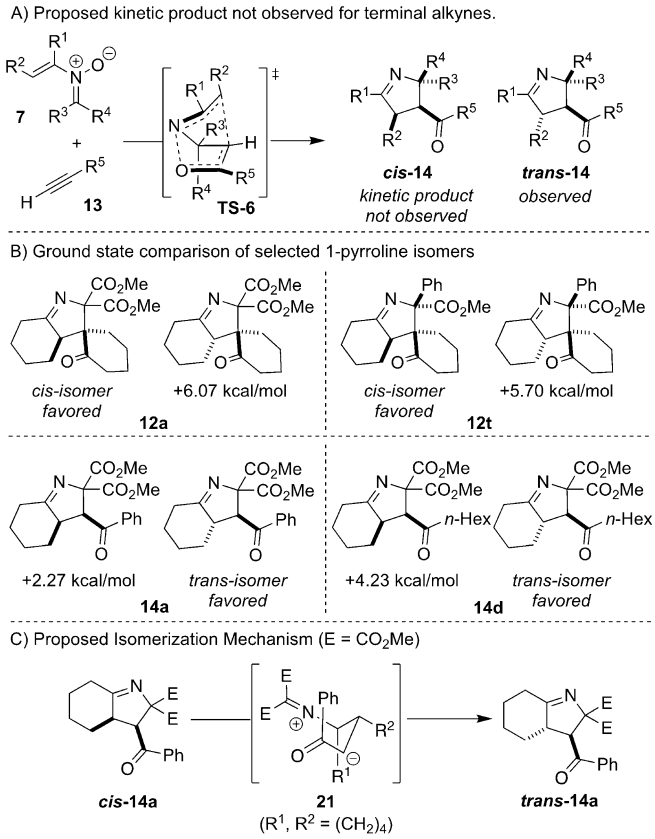


Scheme 5. Correlation of observed regioselectivity and proposed mechanism.

While investigating the tolerance of the cascade reaction for different nitrone substitution patterns, we observed that nitrone **7r** does not form the corresponding 1-pyrroline **12s** or intermediate **18s** when treated with cyclohexyne precursor **11a**.[32] Only starting material decomposition was observed for these reaction mixtures (Scheme 6A). Considering the steric and electronic differences between benzaldehyde-derived nitrone **7r** and the other electron-deficient keto-



Scheme 6. Dipolar cycloaddition transition-state comparisons.



Scheme 7. Isomerization of 1-pyrrolines **14**.

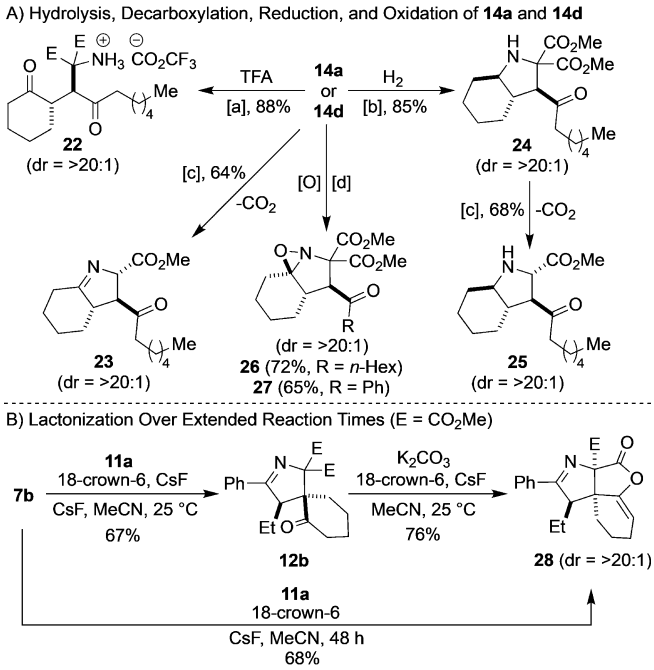
nitrones **7** that successfully form 1-pyrrolines when treated with cyclic and terminal alkynes (Scheme 3 and Scheme 4), we wondered if comparison of these substrates could inform on the mechanism of the cascade process. As shown in Scheme 6B, transition states **TS-5a**, **TS-5b**, and **TS-5c** correspond to substrate mixtures that form spirocyclic pyrrolines **12a**, **12l**, and **12j**, respectively, when subjected to reaction conditions. A computational study indicated that all of three of these dipolar cycloaddition transition states have bond length differences between the forming C–C bond and the forming C–O bond that are less than 0.7 Å.[17,33] In comparison, transition state **TS-5d** corresponds to the experimentally failed conversion of **7r** to **12s** and has a bond length distance difference greater than 1 Å between the two forming bonds. This distinction suggests that reagents that favor more synchronous bond-forming events in the dipolar cycloaddition may be more likely to proceed via the cascade process to form spirocyclic pyrrolines and avoid alternative decomposition pathways.[34]

1-Pyrroline Isomers

Upon isolation of pyrrolines **14**, we were initially surprised to observe a *trans*-relationship between the substituents at the 3- and 4-positions of the ring because an analogous cascade reaction mechanism to the one proposed for the aryne and cycloalkyne cascade processes would kinetically favor a *cis*-relationship between these substituents (Scheme 5A and Scheme 7A). We surmised that isomerization of **14** under the elevated reaction temperatures of the cascade reaction for terminal alkynes could be responsible for the observed isolation of *trans*-**14**. The data in Tables 2 and 3 provide evidence of isomerization of **14a** after completion of the cascade reaction. Ground state computational studies indicated that the *trans*-isomers of **14a** and **14d** are thermodynamically favored over the *cis*-isomers; in contrast, spirocyclic 1-pyrrolines **12a** and **12t** thermodynamically favor their *cis*-isomers (Scheme 7B).[17] As described in Table 3, while the isomerization of **14a** was monitored in [D_4]MeOH at elevated temperature, no incorporation of deuterium was observed at any of the acidic hydrogens. This observation suggests that the isomerization of **14a** is unlikely to be occurring by epimerization.[26] Alternatively, isomerization could be occurring via the mechanism illustrated in Scheme 7C. This type of 1-pyrroline ring-opening was previously proposed to explain rearomatization pathways observed for **10**.[12]

1-Pyrroline Functionalization Studies

Opportunities for derivatization of 1-pyrrolines **12** and **14** were explored to assess the synthetic utility of the modular cascade method presented above (Scheme 8). Simple acidic hydrolysis of **14d** gave the dione ammonium salt **22**. Although this compound readily cyclizes back to the corresponding 1-pyrroline when subjected to mild base, the salt can be isolated cleanly.[35] Decarboalkoxylation and hydrogenation were also tested to determine if the relative stereochemistry installed by the cascade reaction could further direct the formation of new



Scheme 8. Functionalization of 1-pyrrolines **12** and **14**. Conditions: [a] TFA, MeOH:H_2O (1:1); [b] H_2 (1 atm), cat. Pd/C, MeOH; [c] KI, Py:MeOH (1:1), 110 °C; [d] *m*-CPBA, CH_2Cl_2, 0 °C. TFA = trifluoroacetic acid. *m*-CPBA = *meta*-chloroperbenzoic acid.

stereocenters. As shown in Scheme 8 A, when **14 d** was subjected to Krapcho decarboxylation conditions 1-pyrroline **23** was isolated in good yield and high selectivity with three contiguous stereocenters at the 3-, 4-, and 5-positions of the 1-pyrroline ring.[36] Similarly, when **14 d** was reduced with H_2 in the presence of Pd/C, pyrrolidine **24** was isolated in good yield and high diastereoselectivity with three contiguous stereocenters at the 2-, 3-, and 4-positions of the heterocycle. Pyrrolidine **24** was subsequently subjected to decarboxylation conditions and pyrrolidine **25** was obtained with high selectivity and 4-contiguous stereocenters at each carbon of the pyrrolidine ring. Beyond, hydrolysis, decarboalkoxylation, and hydrogenation, oxidation with *m*-chloroperbenzoic acid was tested with **14 a** and **14 d**, and gave the unusual strained oxaziridines **26** and **27**, respectively.[37] This reactivity pattern was not accessible for **12 a**. The connectivity and stereochemistry of **26** and **27** were confirmed by X-ray crystallographic analysis of **27**.[18] Finally, an interesting transformation was observed with extended reaction times for the formation of **12 b**. As shown in Scheme 8 B, lactone **28** is formed in good yield and high diastereoselectivity. Further experimentation showed that **28** could also be obtained directly from **12 b** by treatment with K_2CO_3 under the cascade reaction conditions. The transformations illustrated in Scheme 8 showcase the utility of cascade reaction for accessing highly substituted and stereodefined pyrrolines that can be easily converted into a variety of molecules with increased complexity using simple procedures.

Conclusion

1-Pyrrolines are common motifs in synthetic targets. Due to the demand for these molecules, a variety of methods have been developed for their synthesis; however, even with these advances, there are still examples of 1-pyrrolines that are difficult to access due to the limitations of retrosynthetic approaches using known transformations. The new cascade route to 1-pyrrolines described above broadens the chemical space around these important heterocycles and includes the opportunity to consider retrosynthetic disconnections that formally involve a [4 + 1] process via insertion of the carbon atom at the 4-position using an alkyne. This transformation is enabled by access to unusual *N*-alkenylisoxazolines via the dipolar cycloadditions of *N*-alkenylnitrones, which are accessible via the Chan-Lam *N*-alkenylation of oximes. Not only does this modular method provide access to spirocyclic and densely functionalized 1-pyrrolines but it also supports opportunities for the divergent derivatization of these new heterocyclic structures. Ongoing efforts are focused on using the mechanistic lessons learned in the above studies to leverage this reactivity in new directions.

Acknowledgements

We acknowledge generous funding from the National Science Foundation (NSF-CHE 1855833) and the University of Illinois at Chicago. We thank Mr. Furong Sun (UIUC) for high resolution mass spectroscopy data and Professor Donald J. Wink (UIC) for X-ray crystallographic data preparation. X-Ray crystallography data was obtained by H.-C. Yu on an instrument purchased with partial funding from NIH-R01 GM116820 (PI: Professor Neal P. Mankad, UIC).

Conflict of interest

The authors declare no conflict of interest.

Keywords: 1-pyrroline · cycloalkynes · dipolar cycloaddition · nitrones · sigmatropic rearrangement cascade

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Manuscript received: January 31, 2021
Revised manuscript received: March 6, 2021
Accepted manuscript online: March 24, 2021
Version of record online: April 28, 2021

