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Stereocontrolled Synthesis of Functionalized *cis*-Cyclopentapyrazolidines by 1,3-Dipolar Cycloaddition Reactions of Azomethine Imines

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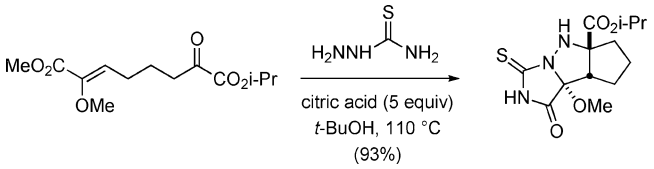

The reaction of alkene-tethered α-ketocarboxylic acid derivatives with monosubstituted hydrazines allows highly substituted *cis*-cyclopentapyrazolidine ring systems **4** to be constructed rapidly. Successful cyclocondensations are realized under thermal reaction conditions; in some cases, protic or Lewis acids accelerate these reactions. α-Methoxy-α,*β*-unsaturated esters are suitable alkene components, as are alkenes having either electron-withdrawing or electron-donating substituents at the terminal alkene carbon. α-Ketoesters, α-ketoamides, and α-ketothioesters can be employed. Various hydrazines substituted with *N*-acyl, *N*-carboalkoxy, or *N*-carbamothioyl protecting groups are tolerated in these transformations. The rate of intramolecular cycloaddition is found to reflect not only the reactivity and equilibrium concentration of the azomethine imine intermediate, but, also in some cases, the rate at which hydrazone stereoisomers interconvert under the reaction conditions.

Introduction

Transformations that rapidly introduce molecular complexity are essential for the efficient chemical synthesis of complex natural products and other fine chemicals. 1,3-Dipolar cycloadditions are one such class of reactions that provide rapid access to structurally complex five-membered heterocycles.[1] Since the initial reports by Oppolzer and co-workers in the early 1970s,[2] intramolecular 1,3-dipolar cycloadditions of azomethine imines have been used to construct a variety of complex heterocyclic structures containing pyrazolidine rings.[3]

Various methods to generate azomethine imines are available. A commonly employed approach generates this dipole in situ from the condensation of 1,2-disubstituted hydrazines with aldehydes, acetals, or hemiacetals.[2] This strategy has been used widely, for example, by Jacobi and co-workers in their incisive total synthesis of (±)-saxitoxin.[4] Azomethine imines can also be generated from hydrazones by thermal[5] or acid-induced[6] 1,2-prototropy from the terminal nitrogen atom to the central nitrogen atom. In our studies to prepare potential precursors of the complex diguanidine alkaloid palau'amine (**1**, Figure 1), we employed this latter approach to assemble pentacyclic pentaamine **3** (Scheme 1).[7,8]

In the context of a program in our laboratories to synthesize the diguanidine alkaloid massadine (**2**),[9,10] we sought to expand

(1) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products;* Padwa, A., Pearson, W. H., Eds.; Chemistry of Heterocyclic Compounds Series 59; Wiley: Chichester, 2002.

(2) (a) Oppolzer, W. *Tetrahedron Lett.* **1970**, *11*, 3091−3094. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10−23.

(3) (a) Schantl, J. G. Azomethine Imines. *Science of Synthesis*; Georg Thieme Verlag: Stuttgart, 2004; Vol. 27, pp 731−824. (b) Padwa, A. Intermolecular 1,3-Dipolar Cycloadditions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: London, 1991; Vol. 4, pp 1069−1109. (c) Wade, P. A. Intramolecular 1,3-Dipolar Cycloadditions: Azomethine Imine Cyclizations. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: London, 1991; Vol. 4, pp 1144−49.

(4) (a) Jacobi, P. A.; Martinelli, M. J.; Polanc, S. *J. Am. Chem. Soc.* **1984**, *106*, 5594−5598. (b) Jacobi, P. A.; Brownstein, A.; Martinelli, M.; Grozinger, K. *J. Am. Chem. Soc.* **1981**, *103*, 239−241. (c) Martinelli, M. J.; Brownstein, A. D.; Jacobi, P. A.; Polanc, S. *Croat. Chem. Acta* **1986**, *59*, 267−295.

(5) Grigg, R.; Kemp, J.; Thompson, N. *Tetrahedron Lett.* **1978**, *31*, 2827−2830.

(6) Le Fevre, G.; Sinbandhit, S.; Hamelin, J. *Tetrahedron* **1979**, *35*, 1821−1824.

(7) Katz, J. D.; Overman, L. E. *Tetrahedron* **2004**, *60*, 9559−9568.

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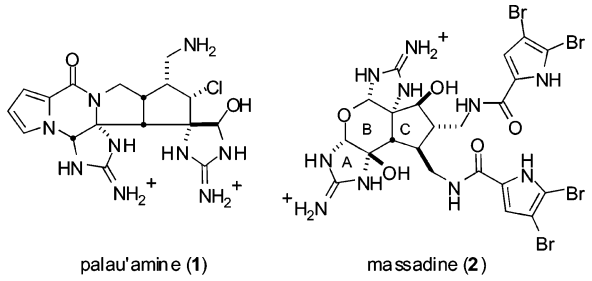
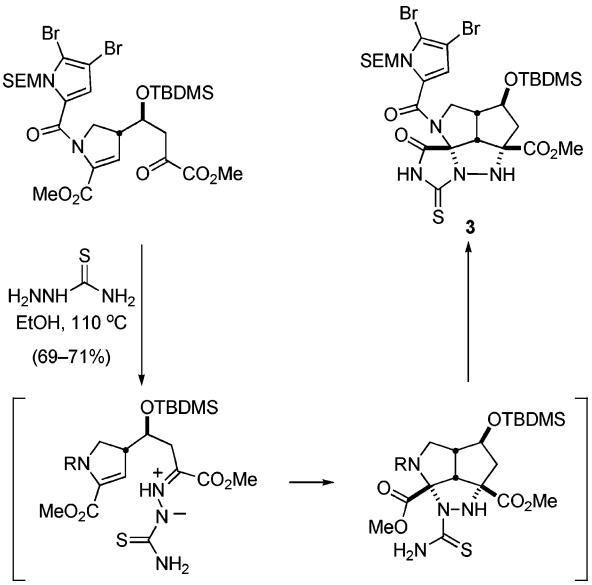
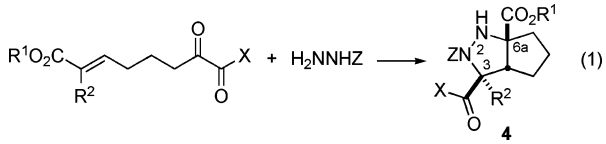


FIGURE 1. Palau'amine and massadine.

SCHEME 1



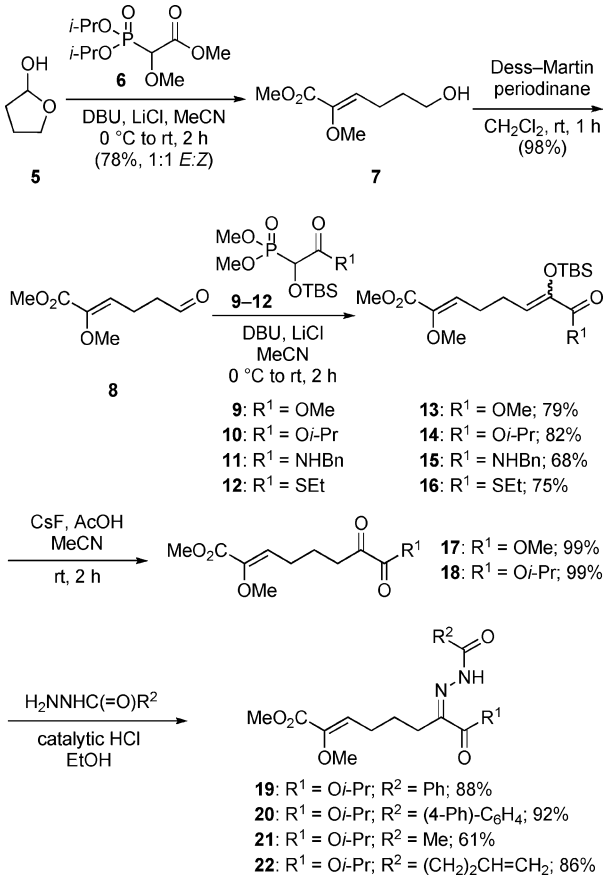
the scope of intramolecular cycloaddition reactions of azomethine imine dipoles generated from the condensation of α-ketoesters and monosubstituted hydrazines. As massadine (**2**) lacks the pyrrolidine ring of palau'amine (**1**), we wanted to define whether the C ring of massadine and the elements of the A and B rings could be assembled by a cycloaddition sequence analogous to the one depicted in Scheme 1, in which the α-hetero-substituted α,β-unsaturated ester dipolarophile was acyclic. In this Article, we report the results of such an investigation of the transformation depicted in eq 1. We demonstrate several useful strategies for forming *cis*-cyclopentapyrazolidines **4** having a variety of substituents at the 2, 3, and 6a positions. We also report the discovery of several new reaction conditions that accelerate the cycloaddition reaction and allow otherwise unreactive substrates to participate in this useful transformation.



Results

Synthesis of Cycloaddition Substrates. Flexible synthetic strategies to access a variety of cycloaddition precursors were

SCHEME 2



developed. The synthesis of acyclic substrates in which the double bond is substituted with both an electron-withdrawing and an electron-donating substituent began with Horner–Wadsworth–Emmons olefination of 2-hydroxytetrahydrofuran (**5**) with phosphonate **6**[11] in the presence of LiCl and DBU to provide a separable mixture of (*Z*)-alkene **7** and the corresponding *E* stereoisomer in a ~1:1 ratio (Scheme 2).[12] Oxidation of **7** with Dess–Martin periodinane furnished aldehyde **8** in 98% yield.[13] Reaction of this intermediate with phosphonates **9**–**12**[14] provided α-siloxy α,β-unsaturated acid derivatives **13**–**16** as inconsequential mixtures of stereoisomers in yields ranging from 68% to 82%. Desilylation of esters **13** and **14** was accomplished by reaction with CsF and acetic acid at room temperature to cleanly give α-ketodiesters **17** and **18**. As these intermediates partially decomposed during silica gel chromatography, they were used directly without purification. Reaction of isopropyl α-ketodiester **18** with monosubstituted hydrazines and catalytic

(8) For our earlier studies in this area, see: (a) Bélanger, G.; Hong, F.-T.; Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Org. Chem.* **2002**, *67*, 7880–7883. (b) Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7159–7160.

(9) Nishimura, S.; Matsunaga, S.; Shibazaki, M.; Suzuki, K.; Furihata, K.; van Soest, R. W. M.; Fusetani, N. *Org. Lett.* **2003**, *5*, 2255–2257.

(10) For reviews of guanidine-containing natural products, see: (a) Berlinck, R. G. S.; Kossuga, M. H. *Nat. Prod. Rep.* **2005**, *22*, 516–550. (b) Berlinck, R. G. S. *Nat. Prod. Rep.* **2002**, *19*, 617–649. (c) Berlinck, R. G. S. *Nat. Prod. Rep.* **1999**, *16*, 339–365. (d) Berlinck, R. G. S. *Nat. Prod. Rep.* **1996**, *13*, 377–409.

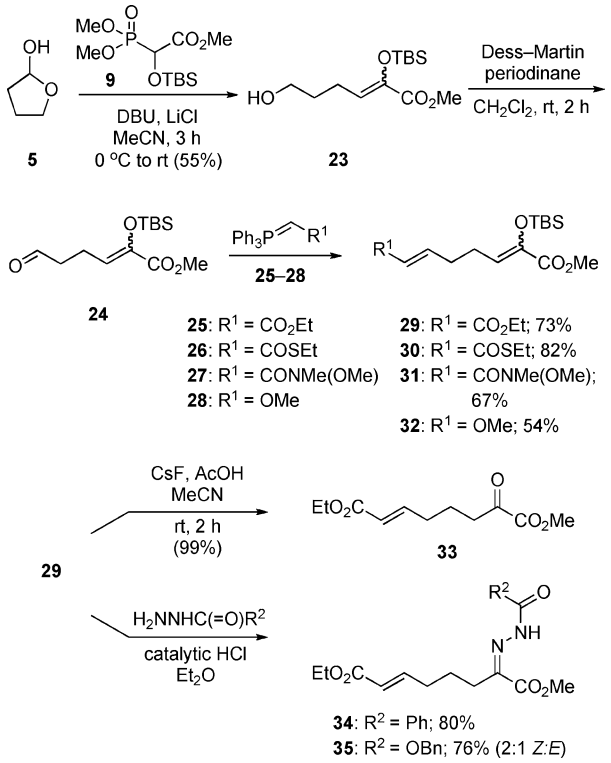
(11) Scheidt, K. A.; Bannister, T. D.; Tasaka, A.; Wendt, M. D.; Savall, B. M.; Fegley, G. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 6981–6990.

(12) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186.

(13) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.

(14) (a) Nakamura, E. *Tetrahedron Lett.* **1981**, *22*, 663–666. (b) Horne, D.; Gaudino, J.; Thompson, W. J. *Tetrahedron Lett.* **1984**, *25*, 3529–3532.

SCHEME 3

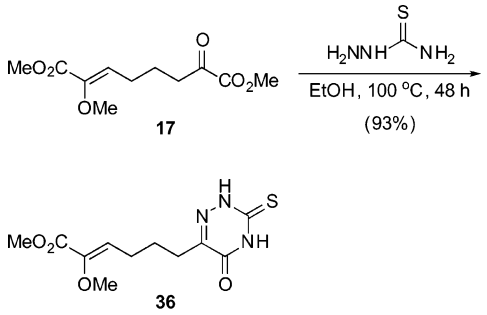


HCl in ethanol at room temperature provided hydrazones **19**−**22**, which were formed as single stereoisomers in yields of 61−92%. The observation of the N−H hydrogen of these products at δ 11−12 ppm in their ^{1}H NMR spectra indicates that the *Z* stereoisomer was formed (vide infra).

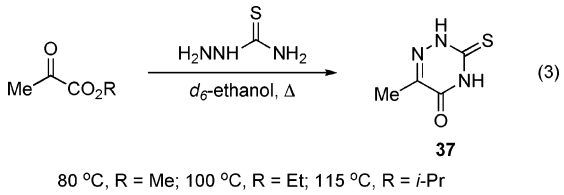
A similar flexible strategy was employed to prepare cycloaddition substrates that contain double bonds having various terminal substituents (Scheme 3). The synthesis began with Horner−Wadsworth−Emmons reaction of lactol **5** with phosphonate **9**[14] to afford siloxy α,β-unsaturated ester **23** as an 8:1 mixture of stereoisomers in 55% yield. Oxidation of this product with Dess−Martin periodinane provided the unstable aldehyde **24**, which was used immediately in Wittig reactions to furnish alkenes **29**−**32** in yields ranging from 54% to 82% over two steps. Cleavage of the enoxysilane substituent of product **29** with CsF and acetic acid quantitatively yielded α-ketoester **33**, which was used without further purification. Hydrazones **34** and **35** were also prepared directly from α-ketoester **29** by HCl-catalyzed condensation with the appropriate hydrazine.

Intramolecular Cycloaddition: Preliminary Optimization Studies. Initially, the reaction of α-ketoester **17** and thiosemicarbazide was studied under thermal conditions similar to those previously employed in our laboratories for related intramolecular azomethine imine cycloaddition reactions.[7] To our surprise, dipolar cycloaddition was not observed, and thioxotriazinone **36** was formed exclusively (eq 2). Varying the solvent and the reaction temperature had little effect on the outcome of this reaction. Because thioxotriazinone **36** could conceivably undergo prototropy to generate an azomethine imine and participate in a subsequent intramolecular cycloaddition, this compound was heated at elevated temperatures (130−200 °C), but no reaction was observed.

As thioxotriazinone **36** is likely formed from the intermediate thiosemicarbazone by intramolecular acylation of the terminal nitrogen, increasing the steric bulk of the ester substituent should



slow this side reaction. A model study was performed in which pyruvate esters of various sizes were heated with thiosemicarbazide in d_6-ethanol with the formation of thioxotriazinone **37** being monitored by ^{1}H NMR analysis (eq 3). As we suspected, formation of **37** occurred at a higher temperature with isopropyl pyruvate and ethyl pyruvate than with methyl pyruvate (at 115, 100, and 80 °C, respectively). The even bulkier *tert*-butyl pyruvate rapidly decarboxylated in the presence of thiosemicarbazide to produce thiourea, acetamide, and isobutene.



80 °C, R = Me; 100 °C, R = Et; 115 °C, R = *i*-Pr

With this knowledge in hand, isopropyl α-ketodiester **18** was chosen for further study. Heating this substrate in ethanol with 1.1 equiv of thiosemicarbazide at 100 °C for 60 h provided *cis*-cyclopentapyrazolidine **38** as a single stereoisomer in variable yields with thioxotriazinone **36** being a major byproduct (Scheme 4). Cycloadduct **38** was converted into tricyclic thiohydantion **39** by further heating the reaction mixture at 135 °C for an additional 24 h. The relative configuration of triazatricycle **39** was obtained by single-crystal X-ray analysis and is consistent with the cycloaddition proceeding by a chairlike transition structure (vide infra).[15]

We hypothesized that the irreproducibility observed during the cycloaddition reaction to form cyclopentapyrazolidine **38** might be caused by basic impurities, as crude α-ketoester **18** was used without purification. Therefore, the effect of adding various acids and bases was investigated (Table 1). Although the rate of formation of cycloadduct **38** from the reaction of α-ketoester **18** and thiosemicarbazide was not significantly affected by the presence of triethylamine, ammonium acetate, acetic acid, or citric acid, the rate of formation of thioxotriazinone **36** decreased markedly with increasing acidity of the reaction medium. Additionally, in the presence of acids, the initially formed *cis*-cyclopentapyrazolidine **38** cyclized at 100 °C to form tricyclic product **39**. The optimal additive was found to be citric acid. With ethanol as solvent, byproducts resulting from Fischer esterification of citric acid hindered product purification. Employing *tert*-butyl alcohol avoided this complication (entry 5).

Scope of Thermal Intramolecular Cycloadditions. After developing a reliable procedure for forming cycloadduct **39**, we turned to explore the scope of related thermal intramolecular

(15) Crystallographic data for this compound were deposited at the Cambridge Crystallographic Data Centre: CCDC 614479.

SCHEME 4

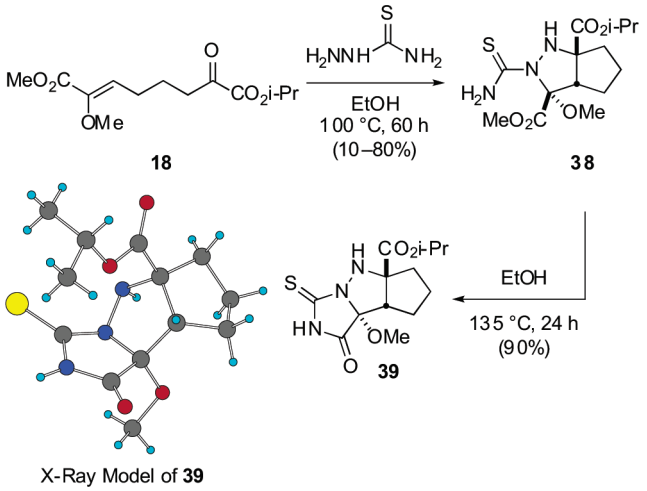
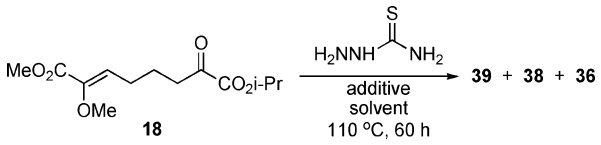


TABLE 1. Reaction of α-Ketoester 18 and Thiosemicarbazide in the Presence of Additives



entry[a]	additive	solvent	**39**:**38**:**36**[c]	yield of **39**, %[d]
1	Et_3N	EtOH	0:0:100	
2	NH_4OAc	EtOH	2:2:3	
3	AcOH	EtOH	3:0:2	54
4	citric acid	EtOH	>20:0:1	89
5[b]	citric acid	*t*-BuOH	>20:0:1	93

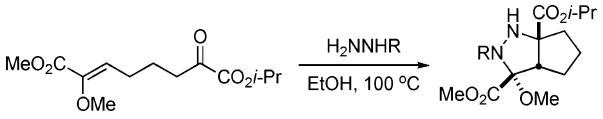
[a] Conditions: **18** (1.0 equiv), thiosemicarbazide (1.05 equiv), and additive (10 equiv) in solvent (0.05 M) at 110 °C for 60 h. [b] Five equivalents of citric acid was used. [c] Determined by ^{1}H NMR. [d] Yield of purified product.

azomethine imine dipolar cycloaddition reactions. Initially, we examined the effect of substituents on the dipole component. Using different monoprotected hydrazines in the reaction with α-ketoester **18** allowed the dipole N-terminus substituent to be easily varied. The optimal conditions identified for these reactions employ 1.0 equiv of α-ketoester **18** and 1.1 equiv of the monoprotected hydrazine in an alcohol solvent (EtOH, *t*-BuOH, or *s*-BuOH). The use of nonpolar solvents, polar aprotic solvents, or acetic acid as solvent resulted in increased reaction times and decreased product yields.[16] Increasing the equivalents of hydrazine led to the formation of polar byproducts and ultimately to lower yields of cycloadducts.

Results obtained from the reaction of five *N*-acyl or *N*-carboalkoxyhydrazines with α-ketoester **18** in ethanol at 100 °C in a sealed reaction vessel are summarized in Table 2. Nicotinic hydrazide (entry 1) and benzoic hydrazide (entry 2) gave the highest yields of cycloadducts (92% and 88%, respectively), with reaction times of 18 h. Acetic hydrazide (entry 3) also reacted under these conditions; however, cycloadduct **42** was isolated in only 56% yield. Hydrazines having *N*-carboalkoxy substituents also performed well, with benzyl carbazate providing cycloadduct **43** in 82% yield after 60 h (entry 4). The reaction of α-ketodiester **18** with 2,2,2-trichloroethyl (Troc) carbazate proceeded more rapidly (18 h), but the yield of cycloadduct **44** was reduced because of product decomposition under the reaction conditions (entry 5). Several other monoprotected hydrazines were also examined. Both *tert*-butyl carbazate and trifluoroacetic hydrazide were unstable to the reaction conditions, resulting in complex product mixtures. Phenylhydrazine, benzylhydrazine, and *para*-toluenesulfonylhydrazide produced only the corresponding hydrazones upon reaction with α-ketodiester **18** under these conditions.

(16) Other solvents examined: toluene, 1,2-dichloroethane, acetic acid, acetonitrile, 2,2,2-trifluoroethanol, and *N*,*N*-dimethylformamide.

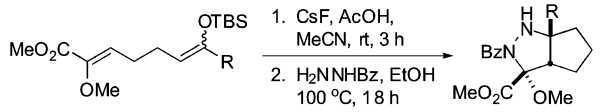
TABLE 2. Reaction of α-Ketoester 18 with Various Monosubstituted Hydrazines



entry[a]	R	time, h	product	yield, %[b]
1	3-pyridylcarbonyl	18	**40**	92
2	Bz	18	**41**	88
3	Ac	18	**42**	56
4	Cbz	60	**43**	82
5	Troc	18	**44**	64

[a] Conditions: crude **18** (1.0 equiv) and hydrazine (1.1 equiv) in EtOH (0.05 M) at 100 °C. [b] Mean yield of purified product from duplicate experiments.

TABLE 3. Reaction of Various α-Ketocarbonyls with Benzoic Hydrazide



entry[a]	precursor	R	product	yield, %[b]
1	**13**	CO_2Me	**45**	81
2	**14**	CO_2i-Pr	**41**	87
3	**15**	C(=O)NHBn	**46**	89
4	**16**	C(=O)SEt	**47**	50

[a] Conditions: Step 1, silyl enol ether (1.0 equiv), CsF (3.2 equiv), and AcOH (6.0 equiv) in MeCN (0.07 M) at rt for 3 h. Step 2, crude α-ketoester (1.0 equiv) and benzoic hyrazide (1.1 equiv) in EtOH (0.05 M) at 100 °C for 18 h. [b] Mean yield of purified product from duplicate experiments.

Next, we examined a series of substrates in which the dipole C-terminus substituent was varied. To minimize differences in product yield resulting from the instability of the α-ketoester component, the reactions were performed as a two-step sequence starting with enoxysilane derivatives **13**−**16**. The precursors were treated with CsF and acetic acid at room temperature for 3 h, and the resulting crude *β*-ketoesters were immediately allowed to react with benzoic hydrazide in ethanol at 100 °C for 18 h in a sealed reaction vessel (Table 3). In general, the nature of the substituent at the dipole C-terminus was found to have little effect on reaction rate or yield. The α-ketoester intermediates (entries 1 and 2) and α-ketoamide intermediate (entry 3) provided cycloadducts **45**, **41**, and **46** in >80% yield for the two-step sequence. The α-ketothioester intermediate (entry 4) reacted at a similar rate, but the yield of cycloadduct **47** was lower because of the instability of the thioester functionality under the reaction conditions.

We also examined the reaction of the related aldehyde substrate **48**, which was available from **8** by a standard one-

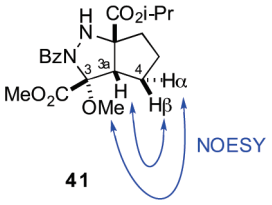
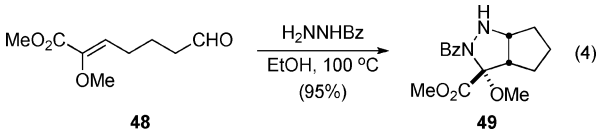


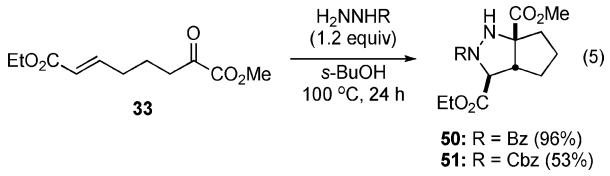
FIGURE 2. Observed NOESY correlations for cycloadduct **41**.

carbon homologation sequence.[17] In this case, *cis*-cyclopentapyrazolidine **49** was formed in nearly quantitative yield (eq 4).



The relative configuration of the C3 and C3a stereocenters of cycloadduct **41** was assigned using ^{1}H−^{1}H COSY and NOESY correlations (Figure 2). The trans relationship between the methoxy substituent and the angular hydrogen at C3a demonstrates, as expected, that the alkene participated in suprafacial fashion. The ring fusion is assigned as cis, because molecular mechanics calculations find this isomer to be ~8.5 kcal/mol lower in energy than the isomer having a trans ring fusion (i.e., the C3,C3a epimer of **41**).[18−20] This assignment of relative configuration of **41** is supported by the similarity of ^{1}H NMR spectra of cycloadducts **41** and **39**, with the signal for the C3a hydrogen being particularly diagnostic: δ 3.40 ppm (dd, J = 9, 3 Hz) for cycloadduct **39** and δ 3.53 ppm (dd, J = 9, 3 Hz) for cycloadduct **41**. This diagnostic signal also is observed at δ 3.45−3.65 ppm in the ^{1}H NMR spectra of cycloadducts **40**, **42**−**44**, **45**−**47**, and **49**, whose relative configurations are assigned by analogy to cycloadduct **41**.

Next, we turned our attention to the dipolarophile component. Initially, α-ketodiester **33** was condensed with benzoic hydrazide and benzyl carbazate at 100 °C in *sec*-butanol (eq 5). When benzoic hydrazide was employed, cycloadduct **50** formed in nearly quantitative yield after 24 h, whereas with benzyl carbazate, *cis*-cyclopentapyrazolidine **51** was produced in only 53% yield after 24 h. In the latter case, the (*Z*)-hydrazone **35a** (vide infra) constituted the majority of the remaining material.



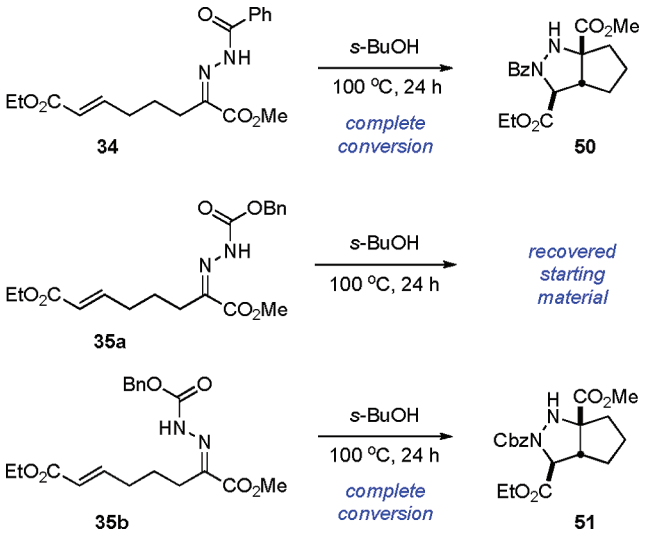
(17) Wittig reaction of aldehyde **8** with methoxymethyltriphenylphosphonium chloride and potassium hexamethyldisilazane (KHMDS) in THF, followed by hydrolysis of the resulting enol ether with aqueous hydrochloric acid in THF, gave aldehyde **48** in 85% yield over two steps.

(18) A Monte Carlo conformational search was performed using the MMFF force field as implemented in Spartan 2005.

(19) The cis cycloadduct **41** was calculated to have a conformational energy of 163.4 kcal/mol, whereas the cycloadduct (epimeric at C3 and C3a) had a conformational energy of 171.9 kcal/mol.

(20) *cis*-Diquinanes are known to be lower in energy than the corresponding trans stereoisomers; see: Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry-Synthesis and Reactions*; Springer-Verlag: New York, 1987.

SCHEME 5



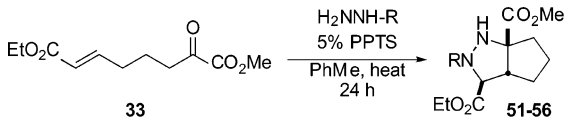
As a carbamate-protecting group is more synthetically useful than an amide-protecting group, we further explored the difference in reactivity between the intermediate hydrazone derivatives **34** and **35** (Scheme 5). First, the hydrazone intermediates were isolated, and their configurations were determined by single-crystal X-ray analysis. Hydrazone **34**, the sole product of the reaction of benzoic hydrazide with α-ketodiester **33**, has the *Z* configuration.[21] An intramolecular hydrogen bond between the hydrazone and the carbonyl group of the methyl ester of **34** is apparent both in the solid state and in solution where this hydrogen is observed at a diagnostic ^{1}H NMR chemical shift of δ 13.38. The Cbz-protected hydrazone, on the other hand, was generated as a separable 2:1 mixture of geometric isomers from the reaction of α-ketodiester **33** with benzyl carbazate. The major hydrazone stereoisomer **35a** has the *Z* configuration with an intramolecular hydrogen bond between the hydrazone N−H and the carbonyl group being suggested by the single-crystal X-ray model.[22] Hydrazone stereoisomers **35a** and **35b** show diagnostic ^{1}H NMR signals for the N−H hydrogen at δ 11.85 and 8.20 ($CDCl_3$), respectively. As summarized in Scheme 5, a dramatic and surprising difference in reactivity was observed between hydrazone stereoisomers: (*Z*)-hydrazone **34** and (*E*)-hydrazone **35b** were converted completely (by NMR analysis) to their respective cycloadducts when heated in *sec*-butanol at 100 °C for 24 h, whereas (*Z*)-hydrazone **35a** was recovered unchanged under these conditions.

The development of new reaction conditions was necessary to circumvent the reactivity difference between the benzyl carbazate-derived hydrazone stereoisomers. We hypothesized that establishing rapid equilibrium between hydrazone isomers **35a** and **35b** would allow reaction of the stereoisomeric mixture through the reactive *E* stereoisomer. Toward this end, (*Z*)-hydrazone **35a** was exposed to various Bronsted or Lewis acids at temperatures ranging from 25 to 115 °C, or to nucleophiles such as chloride ion, acetate ion, or excess hydrazine. This survey identified catalytic pyridinium *p*-toluenesulfonate (PPTS, 5%) in refluxing toluene as a useful reaction condition. Under

(21) Crystallographic data for this compound were deposited at the Cambridge Crystallographic Data Centre: CCDC 614481.

(22) Crystallographic data for this compound were deposited at the Cambridge Crystallographic Data Centre: CCDC 614480.

TABLE 4. Cycloaddition Reactions with an α,β-Unsaturated Ester Dipolarophile

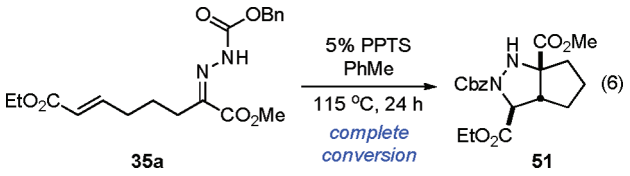


33 51-56

entry[a]	R	temp, °C	product	yield, %[b]
1	Cbz	115	**51**	85
2	CO_2Me	115	**52**	85
3	Troc	110	**53**	63
4	Teoc	110	**54**	71
5	C(=S)NHBn	115	**55**	66
6	(4-Ph)-C_6H_4	100	**56**	94

[a] Conditions: crude **33** (1.0 equiv), benzyl carbazide (1.2 equiv), and PPTS (0.05 equiv) in toluene (0.25 M) at a specified temperature for 24 h. [b] Mean yield of purified product from duplicate experiments.

these conditions, (*Z*)-hydrazone **35a** was transformed completely to cycloadduct **51** within 24 h at 115 °C (eq 6).[23]



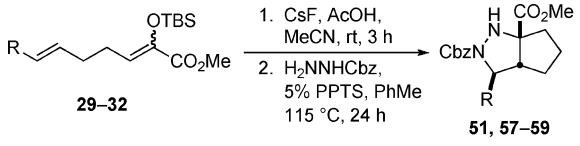
35a 51

After identifying improved reaction conditions for forming cycloadduct **51**, we explored further the scope of the thermal intramolecular azomethine imine dipolar cycloaddition reaction. Initially, we reexamined the effect of the dipole N-terminus substituent by using different monoprotected hydrazines in the reaction with α-ketodiester **33** in the presence of 5% PPTS (Table 4). Under these conditions, benzyl carbazate (entry 1) and methyl carbazate (entry 2) provided cycloadducts in 85% yield. Cycloadditions with carbazates bearing 2,2,2-trichloroethyl (Troc) or 2-(trimethylsilyl)ethyl (Teoc) substituents were complicated by competitive formation of decomposition products (entries 3 and 4). Optimal yields of cycloadducts derived from these latter substrates (63% and 71%, respectively) were obtained at a slightly lower temperature (110 °C). *N*-(Carbamothioyl)hydrazines and *N*-acylhydrazines also reacted under these mildly acidic conditions. *N*-Benzylthiosemicarbazide provided cycloadduct **55** in moderate yield (entry 5), whereas *p*-phenylbenzoic hydrazide gave the highest yield of cycloadduct (94%, entry 6). In all cases, the cycloadducts were isolated as single stereoisomers. Monosubstituted hydrazines such as *tert*-butyl carbazate and trifluoroacetic hydrazide were found to be unstable to these reaction conditions, giving low yields of cycloadducts.

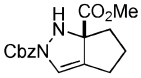
Next, we investigated the role of substituents on the dipolarophile (Table 5). As in our earlier study, crude α-ketoester intermediates were generated from enoxysilane precursors **29**−**32** by reaction with CsF and acetic acid and were combined immediately with benzyl carbazate and PPTS in toluene and heated at 115 °C for 24 h. Precursors containing dipolarophile fragments bearing various electron-withdrawing groups reacted well under these conditions: α,β-unsaturated ester **29**, α,β-unsaturated thioester **30**, and α,β-unsaturated amide **31** provided

(23) The toluene/PPTS conditions were also examined with substrates that contained α-methoxy, α,β-unsaturated esters dipolarophile fragments. In these cases, the cycloaddition substrates decomposed to give intractable mixtures.

TABLE 5. Cycloaddition Reactions Varying the Dipolarophile Component



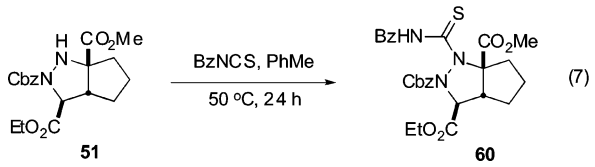
29–32 51, 57–59

entry[a]	precursor	R	product	yield, %[b]
1	**29**	CO_2Et	**51**	85
2	**30**	C(=O)SEt	**57**	73
3	**31**	C(=O)NMeOMe	**58**	72
4	**32**[c]	OMe	 **59**	59

[a] Conditions: (1) Silyl enol ether (1.0 equiv), CsF (3.2 equiv), and AcOH (6.0 equiv) in MeCN (0.07 M) at rt for 3 h. (2) Crude α-ketoester (1.0 equiv), benzyl carbazate (1.2 equiv), and PPTS (0.05 equiv) in toluene (0.25 M) at 115 °C for 24 h. [b] Mean yield of purified product from duplicate experiments. [c] Mixture of four alkene isomers.

cycloadducts as single stereoisomers in good yields (entries 1−3). The electron-rich enol ether **32** was also a suitable substrate. In this case, intramolecular cycloaddition was followed by elimination of methanol to deliver hexahydrocyclopentapyrazole **59** in 59% yield (entry 4). In contrast, reaction of the analogous substrate having an unfunctionalized alkene unit (R = H, not shown) yielded largely the hydrazone intermediate with only trace amounts (<10%) of a cycloadduct after 24 h.

The relative configuration of a representative cyclopentapyrazolidine formed by intramolecular dipolar cycloaddition in the presence of PPTS was confirmed by single-crystal X-ray analysis. Although diester **51** was not crystalline, reaction with benzoylisothiocyanate provided the corresponding thiourea **60**, which gave single crystals suitable for X-ray analysis (eq 7). The cis ring junction and cis relationship of the ester substituents are apparent in the X-ray model (see Supporting Information).[24] This relative configuration is the same as that observed in cycloadducts formed in the absence of PPTS. Diagnostic angular hydrogen signals appear between δ 2.96−3.20 ppm for cyclopentapyrazolidines **51**−**58**, allowing their relative configuration to be assigned by analogy to thiourea **60**.



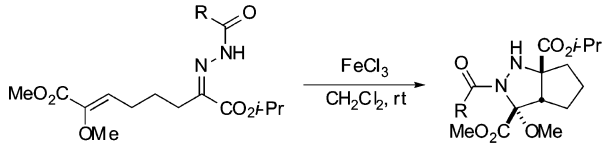
51 60

Alternative Cycloaddition Conditions. Lewis acids have been shown to promote the cycloaddition reaction between hydrazones and alkenes.[25,26] Hydrazone **19** was chosen as a suitable substrate to screen in the presence of a broad selection

(24) Crystallographic data for this compound were deposited at the Cambridge Crystallographic Data Centre: CCDC 614482.

(25) (a) Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 11279−11282. (b) Chung, F.; Chauveau, A.; Seltki, M.; Bonin, M.; Micouin, L. *Tetrahedron Lett.* **2004**, *45*, 3127−3130. (c) Kobayashi, S.; Hirabayashi, R.; Shimizu, H.; Ishitani, H.; Yamashita, Y. *Tetrahedron Lett.* **2003**, *44*, 3351−3354. (d) Kobayashi, S.; Shimizu, H.; Yamashita, Y.; Ishitani, H.;

TABLE 6. $FeCl_3$-Promoted Cycloadditions of Hydrazones 19−22

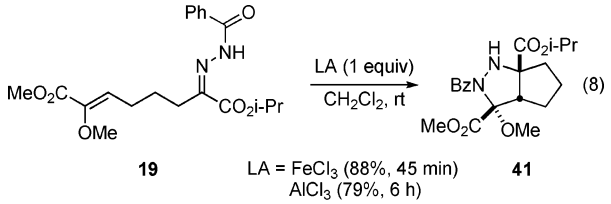


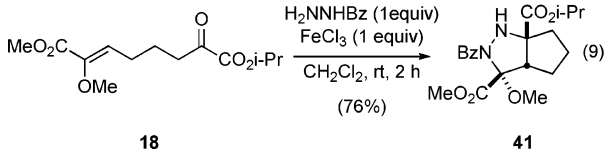
19–22 **41–42, 61–62**

entry[a]	hydrazone	R	product	time, h	yield, %[b]
1	**19**	Ph	**41**	0.75	88
2	**20**	(4-Ph)-C_6H_4	**61**	0.75	86
3	**21**	Me	**42**	6	64
4	**22**	CH_2═$CH(CH_2)_2$	**62**	6	56

[a] Conditions: hydrazone (1.0 equiv) and $FeCl_3$ (1.0 equiv) in CH_2Cl_2 (0.05 M) at rt. [b] Mean yield of purified product from duplicate experiments.

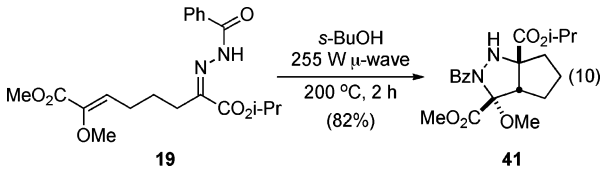
of Lewis acids.[27,28] Two Lewis acids were found to promote cycloaddition. Hydrazone **19** was converted into cycloadduct **41** in 88% yield after 45 min at room temperature in the presence of 1 equiv of $FeCl_3$ and in 79% yield after 6 h in the presence of 1 equiv of $AlCl_3$ (eq 8). Hydrazone **19** was recovered unchanged when treated with either aqueous or anhydrous hydrochloric acid under identical conditions. The cycloaddition promoted by $FeCl_3$ was found to be quite tolerant of water. Employing $FeCl_3 \cdot 6H_2O$ instead of anhydrous $FeCl_3$ gave nearly identical results; 1 equiv of $FeCl_3 \cdot 6H_2O$ provided **41** in 89% yield after 45 min. Cycloadduct **41** was also produced in 76% yield by the direct reaction of α-ketoester **18** with benzoic hydrazide in the presence of 1 equiv of $FeCl_3$ at room temperature (eq 9).





To examine the scope of the $FeCl_3$-promoted cycloaddition, monoprotected hydrazones **19**−**22** were exposed to 1 equiv of this Lewis acid in dichloromethane at room temperature (Table 6). Both benzoyl hydrazone **19** (entry 1) and *p*-phenylbenzoyl hydrazone **20** (entry 2) underwent cycloaddition in >80% yield after 45 min at room temperature. Reactions with acetyl hydrazone **21** (entry 3) and 4-pentenoyl hydrazone **22** (entry 4) required 6 h. In these cases, some polar side products were observed, thereby diminishing the yields of cycloadducts. A variety of other hydrazones (trifluoroacetyl, Cbz, 3-pyridylcarbonyl, formyl) were either unreactive or unstable to the reaction conditions.

Finally, we briefly examined the use of microwave irradiation to shorten the reaction times of a representative thermal intramolecular azomethine imine cycloaddition reaction.[29,30] A *sec*-butanol solution of hydrazone **19** was converted to cycloadduct **41** in 82% yield when heated at 200 °C for 2 h in a 255 W microwave reactor (eq 10). However, directly treating α-ketoester **18** with a variety of monosubstituted hydrazines under identical conditions led to intractable mixtures.



Discussion

The results described herein demonstrate the broad utility of intramolecular azomethine imine dipolar cycloaddition reactions in forming highly substituted *cis*-cyclopentapyrazolidines from simple starting materials. This systematic investigation of a range of substrates and reaction conditions revealed reactivity trends that will allow more general application of this powerful transformation.

Several trends concerning the hydrazine component of the cycloaddition reaction are evident. For instance, only *N*-acyl, *N*-carboalkoxy, and *N*-carbamothioylhydrazines give high-yielding reactions. Moreover, this hydrazine substituent must be compatible with the temperatures and additives required for the cycloaddition to take place at a practical rate. For example, *tert*-butoxycarbonyl, trifluoroacetyl, and formyl protecting groups performed poorly in the cycloaddition reactions surveyed in this study. Reactivity generally increases as the electron-withdrawing ability of the hydrazine protecting group increases; thus, acylhydrazines perform better than carbazates. This trend may reflect the stability of the azomethine imine tautomer of the hydrazone. As the dipole's negative charge is more localized on the N-terminus than on the C-terminus, a better electron-withdrawing group (acyl rather than carboalkoxy) attached to the N-terminus should better stabilize the reactive dipole, increasing the equilibrium concentration of this reactive tautomer.

Interpretation of reactivity trends arising from the hydrazine component is complicated by the different reactivity of hydrazone stereoisomers derived from α-ketoesters. In the case of the *N*-benzyloxycarbonyl hydrazone stereoisomers **35a** and **35b**, only *E* isomer **35b** underwent cycloaddition at 100 °C; *Z* stereoisomer **35a** was recovered unchanged under these conditions (Scheme 5). The (*Z*)-hydrazone stereoisomer is stabilized by an intramolecular hydrogen bond between the hydrazone

Kobayashi, J. *J. Am. Chem. Soc.* **2002**, *124*, 13678−13679. (e) Norman, M. H.; Heathcock, C. H. *J. Org. Chem.* **1987**, *52*, 226−235. (f) Padwa, A.; Ku, H. *J. Am. Chem. Soc.* **1980**, *45*, 3756−3766. (g) Wilson, R. M.; Rekers, J. W. *J. Am. Chem. Soc.* **1979**, *101*, 4005−4007.

(26) Lewis acids have also been used to promote related azomethine ylide cycloadditions: (a) Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174−10175. (b) Nyerges, M.; Rudas, M.; Toth, G.; Herenyi, B.; Kadas, I.; Bitter, I.; Toke, L. *Tetrahedron* **1995**, *48*, 13321−13330.

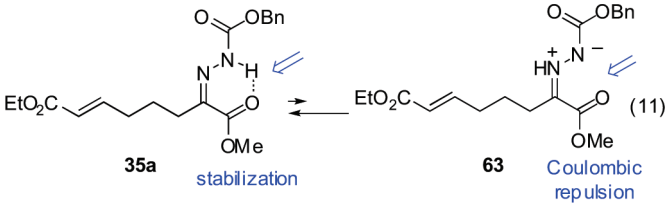
(27) Carlson, R.; Lundstedt, A. N.; Prochazka, M. *Acta Chem. Scand.* **1986**, *40B*, 522−533.

(28) Additional Lewis acids examined: $BF_3 \cdot Et_2O$, $SnCl_4$, $TiCl_4$, TMSOTf, $Sc(OTf)_3$, $Zr(Oi\text{-}Pr)_4$, $TiCl_3$, $CrBr_3$, AgOAc, LiBr, $MgBr \cdot Et_2O$, ZnI_2, $SnCl_2$, $AlBr_3$, and $Cu(OTf)_2$.

(29) For a general review of microwave chemistry, see: Galema, S. A. *Chem. Soc. Rev.* **1997**, *26*, 233−238.

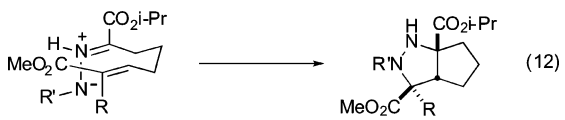
(30) Microwave irradiation has previously been reported to promote intermolecular azomethine imine cycloaddition reactions, see: Arrieta, A.; Carrillo, J. R.; Cossío, F. P.; Díaz-Ortiz, A.; Gómez-Escalonilla, M. J.; de la Hoz, A.; Langa, F.; Moreno, A. *Tetrahedron* **1998**, *54*, 13167−13180.

N−H and the carbonyl oxygen of the ester, whereas the corresponding azomethine imine tautomer **63** should be destabilized by charge repulsion (eq 11). As a result, prototropy to form the reactive azomethine imine tautomer should be much less favorable with the (*Z*)-hydrazone stereoisomer. We suggest that this factor is responsible for the lack of reactivity of the (*Z*)-*N*-carboalkoxy hydrazone stereoisomer. As this trend should be seen also with hydrazones having *N*-acyl substituents, we attribute the successful cycloaddition of the (*Z*)-*N*-benzoyl hydrazone isomer **34** (Scheme 5) to rapid equilibration of these hydrazone steroisomers. One indication that equilibration might be rapid for hydrazone **34** is seen in our isolation of only the (*Z*)-hydrazone stereoisomer in the *N*-benzoyl series (and in acyl hydrazones **19**−**22**). Thus, the rate of intramolecular cycloaddition appears to reflect not only the reactivity and equilibrium concentration of the azomethine imine intermediate, but in some cases also the rate at which hydrazone stereoisomers interconvert under the reaction conditions.



Considerable variation in the dipolarophile fragment of the intramolecular cycloaddition precursors examined in this study was tolerated. Substrates containing electron-donating or electron-withdrawing groups at the alkene terminus underwent intramolecular dipolar cycloaddition efficiently. However, analogous substrates containing a terminal vinyl substituent were converted only slowly to cyclopentapyrazolidines. As HOMO and LUMO energies of azomethine imines and alkenes are fairly similar,[31] either raising the alkene HOMO or lowering the alkene LUMO could increase reaction rate by decreasing the HOMO−LUMO gap between the reacting partners. Such a trend would be consistent with perturbation theory calculations reported previously by Houk and co-workers.[32]

The synthetic value of 1,3-dipolar cycloaddition reactions is directly linked to the ability to predict the reactivity and the regiochemical and stereochemical outcome of these transformations. The regiochemistry of the intramolecular azomethine imine cycloaddition reactions studied here is dictated by the three-carbon tether, which favors the formation of only diazabicyclo[3.3.0]octane products.[33] The high stereoselectivity seen in these cycloadditions is consistent with cycloadditions proceeding by chairlike transition structure **64**, which allows favorable overlap between the π orbitals of the dipole and dipolarophile (eq 12).



Conclusions

Intramolecular dipolar cycloaddition reactions of azomethine imines derived from the condensation of hydrazines bearing an electron-withdrawing substituent and α-ketoesters, α-ketoamides, and α-ketothioesters provide access to a wide variety of cyclopentapyrazolidines having an ester, thioester, or amide substituent at C6a. α-Methoxy-α,*β*-unsaturated esters are suitable alkene components, as are alkenes having either electron-withdrawing or electron-donating substituents at the terminal alkene carbon. Depending upon the specific case, these cyclocondensations are achieved optimally either under thermal conditions or in the presence of protic acids or Lewis acids.

Experimental Section[34]

General Method A for Formation of Cycloadducts. 3-Methoxy-2-(pyridine-3-carbonyl) Hexahydrocyclopentapyrazole-3,-6a-dicarboxylic Acid 6a-Isopropyl Ester 3-Methyl Ester (40). A solution of α-ketoester **18** (54 mg, 0.20 mmol) and 3-pyridylcarbonyl hydrazide (30 mg, 0.22 mmol) in EtOH (3.9 mL) was maintained at 100 °C for 18 h. EtOH was removed in vacuo, and the resulting yellow oil was purified via flash chromatography (40% EtOAc/hexanes) to yield 72 mg (93%) of cycloadduct **40** as a clear glaze: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.35 (br s, 1H), 8.68 (br s, 1H), 8.60 (dt, J = 8.0, 1.9 Hz, 1H), 7.38 (dd, J = 7.9, 4.9 Hz, 1H), 5.05 (sept, J = 6.3 Hz, 1H), 4.35 (s, 3H), 3.77 (s, 3H), 3.58 (s, 3H), 3.50 (dd, J = 9.2, 3.1 Hz, 1H), 2.26−2.21 (m, 1H), 2.12−2.04 (m, 1H), 1.95−1.78 (m, 3H), 1.76−1.68 (m, 1H), 1.18 (d, J = 6.3 Hz, 3H), 1.15 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 168.3, 165.7, 151.2, 150.8, 138.2, 130.2, 122.8, 93.7, 79.8, 69.4, 63.0, 54.4, 52.9, 35.4, 27.7, 27.4, 21.8, 21.7; IR (film) 3250, 1756, 1745, 1723, 1640, 1596 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{25}NaN_3O_6$ (M + Na) 414.1641, found 414.1653. Anal. Calcd for $C_{19}H_{25}N_3O_6$: C, 58.30; H, 6.44; N, 10.74. Found: C, 58.17; H, 6.52; N, 10.61.

General Method B for Formation of Cycloadducts. 2-Benzoyl-3-methoxy Hexahydrocyclopentapyrazole-3,6a-dicarboxylic Acid 6a-Isopropyl Ester 3-Methyl Ester (41). A solution of hydrazone **19** (11 mg, 0.03 mmol) in CH_2Cl_2 (1.0 mL) was added in one portion to a flask containing solid iron(III) chloride (4.6 mg, 0.03 mmol), and the resulting yellow-green solution was maintained at room temperature for 45 min. The solution was directly loaded onto silica gel and purified by flash chromatography (20% EtOAc/hexanes) to give 9.8 mg (88%) of cycloadduct **41** as a clear glaze: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, J = 6.1, 1.5 Hz, 2H), 7.47−7.27 (m, 3H), 5.08 (sept, J = 6.3 Hz, 1H), 4.26 (s, 3H), 3.78 (s, 3H), 3.54 (dd, J = 9.2, 3.0 Hz, 3H), 2.26−2.21 (m, 1H), 2.08−2.01 (m, 1H), 1.92−1.66 (m, 4H), 1.21 (d, J = 6.3 Hz, 3H), 1.17 (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 168.6, 168.0, 134.0, 131.2, 129.9, 127.7, 93.5, 79.7, 69.2, 62.7, 54.2, 52.9, 35.6, 27.7, 27.4, 21.8, 21.7; IR (film) 3256, 1756, 1745, 1719, 1637, 1448, 1384 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{26}NaN_2O_6$ (M + Na) 413.1689, found 413.1671. Anal. Calcd for $C_{20}H_{26}N_2O_6$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.44; H, 6.67; N, 7.05.

General Method C for Formation of Cycloadducts. 2-Benzoyl-3-methoxy Hexahydrocyclopentapyrazole-3,6a-dicarboxylic Acid Dimethyl Ester (45). Following the previously described procedure to prepare α-ketoester **17**, enoxysilane **13** (52 mg, 0.15 mmol) gave 40 mg (99%) of α-ketoester **17** as a clear glaze. Next, a solution of α-ketoester **17** (40 mg, 0.15 mmol) and benzoic

(31) Sustmann, R. *Pure Appl. Chem.* **1974**, *40*, 569−593.

(32) (a) Houk, K. N.; Sims, J.; Duke, R. E., Jr.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287−7301. (b) Houk, K. N.; Sims, J.; Watts, C. R.; Kuskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301−7315.

(33) Although bicyclo[3.3.0]octane ring systems are generally observed in intermolecular dipolar cycloadditions in which a dipole is connected to an alkene through a three-carbon tether, bicyclo[3.2.1]octane ring systems have been observed, see: Koumbis, A. E.; Gallos, J. K. *Curr. Org. Chem.* **2003**, *7*, 585−628.

(34) All cycloaddition reactions were performed in thick-walled sealed tubes for reaction volumes greater than 2 mL and in screw-cap vials with Teflon caps for reaction volumes of 2 mL or less. Other general experimental details have been described: MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2001**, *123*, 9033−9044.

hydrazide (22 mg, 0.16 mmol) in EtOH (2.9 mL) was maintained at 100 °C for 18 h. The reaction was cooled and concentrated in vacuo, and the resulting light yellow oil was further purified by silica gel chromatography (20% EtOAc/hexanes) to give 43 mg (82%) of cycloadduct **45** as a clear glaze: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (dt, J = 7.0, 1.6 Hz, 2H), 7.47 (tt, J = 7.2, 1.4 Hz, 1H), 7.41 (app t, J = 7.0 Hz, 2H), 3.78 (s, 3H), 3.73 (s, 3H), 3.59 (s, 3H), 3.56 (dd, J = 9.1, 3.5 Hz, 1H), 2.26−2.20 (m, 1H), 2.09−2.02 (m, 1H), 1.94−1.70 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 168.8, 168.6, 134.5, 131.0, 129.2, 127.8, 93.6, 79.6, 62.9, 54.3, 53.0, 52.7, 35.6, 29.9, 27.6, 27.3; IR (film) 3252, 1750, 1735, 1642, 1448 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{22}NaN_2O_6$ (M + Na) 385.1375, found 385.1372. Anal. Calcd for $C_{18}H_{22}N_2O_6$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.66; H, 6.03; N, 7.68.

General Method D for Formation of Cycloadducts. 3-Ethyl-6a-methyl-2-benzoyloctahydrocyclopenta[*c*]pyrazole-3,6a-dicarboxylate (50). A solution of hydrazone **34** (6.9 mg, 0.02 mmol) in *sec*-butanol (0.2 mL) was heated at 100 °C for 24 h under an inert atmosphere. The solvent was then removed in vacuo. ^{1}H NMR of the residue indicated complete conversion to cyclopentapyrazolidine **50**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87−7.74 (m, 2H), 7.47−7.36 (m, 3H), 5.64 (br s, 1H), 5.12 (br s, 1H), 4.29−4.18 (m, 2H), 3.75 (s, 3H), 3.08 (br s, 1H), 2.30−2.12 (m, 2H), 1.82−1.72 (m, 3H), 1.63−1.53 (m, 1H), 1.30 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 170.6, 170.2, 134.2, 130.7, 129.2, 127.6, 65.0, 61.6, 56.5, 52.8, 37.2, 33.4, 29.6, 26.5, 14.1; IR (film) 3272, 2960, 1734, 1647, 1447, 1388, 1283, 1198 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{22}NaN_2O_5$ (M + Na)$^+$ 369.1426, found 369.1424.

General Method E for Formation of Cycloadducts. 2-Benzyl-3-ethyl-6a-methylhexahydrocyclopenta[*c*]pyrazole-2,3,6a(1*H*)-tricarboxylate (51). A suspension of α-keto ester **33** (39 mg, 0.17 mmol), benzyl carbazate (34 mg, 0.20 mmol), and pyridinium *p*-toluenesulfonic acid (2.1 mg, 0.0085 mmol) in toluene (0.68 mL) was heated at 115 °C for 24 h under an inert atmosphere. After this time, the solvent was removed by rotary evaporation. The residue was purified by silica gel chromatography (2:1 hexanes/ethyl acetate) to give 55 mg (85%) of **51** as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$ @ 348 K) δ 7.40−7.27 (m, 5H), 5.41 (br s, 1H), 5.23 (d, J = 20.0 Hz, 1H), 5.20 (d, J = 20.0 Hz, 1H), 4.58 (d, J = 1.5 Hz, 1H), 4.23−4.13 (m, 2H), 3.76 (s, 3H), 3.09 (ddd, J = 8.0, 4.5, 2.0 Hz, 1H), 2.30 (dt, J = 13.0, 6.5 Hz, 1H), 2.18−2.09 (m, 1H), 1.86−1.78 (m, 1H), 1.78−1.70 (m, 2H), 1.70−1.60 (m, 1H), 1.25 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 170.7, 156.3 (br), 136.3, 128.5, 128.4, 128.2, 77.3, 67.9, 67.0, 61.7, 57.1, 52.9, 38.1, 33.4, 26.6, 14.1; IR (film) 2958, 1733, 1698, 1456, 1395, 1288, 1199 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{24}NaN_2O_6$ (M + Na)$^+$ 399.1532, found 399.1540.

General Method F for Formation of Cycloadducts. 2-Benzyl-6a-methyl-3-(ethylthiocarbonyl)hexahydrocyclopenta[*c*]pyrazole-2,6a(1*H*)-dicarboxylate (57). Following the procedure to prepare **33**, enoxysilane **30** (0.2 mmol) was converted to the corresponding α-ketoester. A suspension of crude α-keto ester, benzyl carbazate (40 mg, 0.24 mmol), and pyridinium *p*-toluenesulfonic acid (2.5 mg, 0.01 mmol) in toluene (0.8 mL) was then heated at 115 °C for 24 h under an inert atmosphere. Solvent was then removed in vacuo, and the residue was purified by silica gel chromatography (3:1 hexanes/ethyl acetate) to give 58 mg (74%) of **57** as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$ @ 328 K) δ 7.42−7.27 (m, 5H), 5.37 (s, 1H), 5.25 (d, J = 24.0 Hz, 1H), 5.23 (d, J = 24.0 Hz, 1H), 4.67 (br s, 1H), 3.74 (s, 3H), 3.20 (ddd, J = 8.1, 5.0, 1.9 Hz, 1H), 2.90−2.81 (m, 2H), 2.32−2.24 (m, 1H), 2.15−2.05 (m, 1H), 1.79−1.55 (m, 4H), 1.24 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.6, 173.8, 157.0 (br), 136.1, 128.5, 128.3, 128.2, 74.4, 68.2, 56.8, 52.9, 38.1, 33.2, 29.7, 26.5, 23.4, 14.4; IR (film) 2960, 1734, 1685, 1466, 1388, 1298, 1113 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{24}NaN_2O_5S$ (M + Na)$^+$ 415.1304, found 415.1313.

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Supporting Information Available: Experimental procedures and tabulated characterization data for new compounds not reported in the Experimental Section, X-ray models of compounds **34**, **35a**, and **60**, copies of ^{1}H and ^{13}C NMR spectra for all new compounds, and X-ray crystallographic files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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