Synthesis of Polycyclic Guanidines by Cyclocondensation Reactions of *N*-Amidinyliminium Ions

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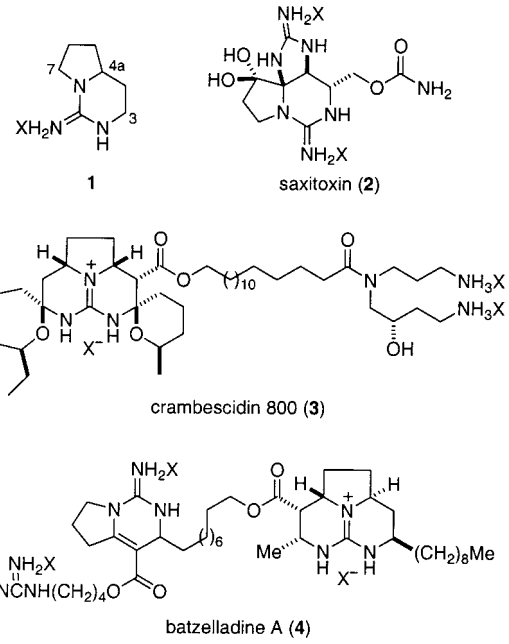
A new method for the synthesis of polycyclic guanidines is described. The *N*-amidinyliminium ion generated from α-(phenylthio)amidine precursor **16** by reaction with $Cu(OTf)_2$ undergoes cyclocondensation with 1,3-dienes, styrenes, and *β*-dicarbonyl compounds to give 1-iminohexahydropyrrolo[1,2-*c*]pyrimidines having side chains at C3 and C7. In all cases, major products have a cis relationship of the C7 side chain and angular C4a hydrogen, whereas C3 side chains are incorporated with lower stereoselectivity (dr = 2−5:1) in cyclocondensations with dienes and styrenes to give stereoisomer **39** as the major product. In contrast to most cycloadditions of alkenes with *N*-acyliminium ions, cyclocondensations of alkenes with *N*-amidinyliminium ions proceed by a stepwise pathway. Cyclocondensation of the cognate ureido aminal **31** with styrene provides the rare 2-imino-5,6-dihydro-4*H*-1,3-oxazine derivative **32**, rather than a pyrimidine as the major product. The high stereoselectivity observed in condensations of **16** with benzyl acetoacetate to afford Biginelli adduct **29** supports the intermediacy of *N*-amidinyliminium ions in related tethered Biginelli condensations of guanidines reported earlier from our laboratories.

Introduction

Guanidine functionality is found in a strikingly high percentage of pharmacologically active natural products, as well as being an important feature of several clinical agents and numerous exploratory drug candidates.[1] The wide occurrence of bioactive guanidines likely reflects the multiple ways that guanidinium cations can participate in noncovalent associations, for example, by electrostatic, hydrogen-bonding, and *π*-stacking interactions. Among the most structurally complex guanidine natural products are those containing a 1-iminohexahydropyrrolo[1,2-*c*]-pyrimidine fragment (**1**). This ring system is found in alkaloids such as saxitoxin (**2**)[2] and in crambescidin and batzelladine alkaloids exemplified by crambescidin 800 (**3**)[3] and batzelladine A (**4**).[4,5] These latter marine natural products display a variety of potentially important pharmacological activities including powerful anticancer activity[3,6] and inhibition of protein−protein interactions.[4,7]



We have previously developed a general synthesis of guanidines **1** and documented procedures whereby a C7 substituent can be incorporated with either a cis or trans relationship to an angular C4a hydrogen.[8] The pivotal step in this synthesis is an intramolecular variant of the Biginelli reaction[9] that we first reported in 1993 (eq 1).[10]

(1) (a) Greenhill, J. V.; Lue, P. *Prog. Med. Chem.* **1993**, *30*, 203−326. (b) Berlinck, R. G. S. *Nat. Prod. Rep.* **1999**, *16*, 339−365. (c) Berlinck, R. G. S. *Nat. Prod. Rep.* **1996**, *13*, 377−409. (d) Berlinck, R. G. S. *Prog. Chem. Org. Nat. Prod.* **1995**, *66*, 119−295.

(2) Structure: (a) Schantz, E. J.; Ghazarossian, V. E.; Schnoes, H. K.; Strong, F. M.; Springer, J. P.; Pezzanite, J. O.; Clardy, J. *J. Am. Chem. Soc.* **1975**, *97*, 1238−1239. (b) Bordner, J.; Thiessen, W. E.; Bates, H. A.; Rapoport, H. Ibid. **1975**, *97*, 6008−6012. Total synthesis: (c) Tanino, H.; Nakata, T.; Kaneko, T. Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 2818−2819. (d) Hannick, S. M.; Kishi, Y. *J. Org. Chem.* **1983**, *48*, 3833−3835. (e) Jacobi, P. A.; Martinelli, M. J.; Polanc, S. *J. Am. Chem. Soc.* **1984**, *106*, 5594−5598.

(3) Structure: (a) Jares-Erijman, E. A.; Sakai, R.; Rinehart, K. L. *J. Org. Chem.* **1991**, *56*, 5712−5715. Total synthesis: (b) Coffey, D. S.; McDonald, A. I.; Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. *J. Am. Chem. Soc.* **2000**, *122*, 4893−4903.

(4) For recent reviews of guanidine alkaloids, see: Faulkner, D. J. *Natl. Prod. Rep.* **1999**, *16*, 155−198, and earlier reviews in this series; see also refs 1b−d.

(5) (a) Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; De Brosse, C.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Potts, B. C. M. *J. Org. Chem.* **1995**, *60*, 1182−1188. (b) Snider, B. B.; Chen, J.; Patil, A. D.; Freyer, A. J. *Tetrahedron Lett.* **1996**, *37*, 6977−6980.

(6) For a recent summary, see ref 3b.

(7) Patil, A. D.; Freyer, A. J.; Taylor, P. B.; Carte, B.; Zuber, G.; Johnson, R. K.; Faulkner, D. J. *J. Org. Chem.* **1997**, *62*, 1814−1819.

(8) McDonald, A. I.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 1520−1528.

(9) For a review of the Biginelli reaction, see: Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937−6963.

(10) Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1993**, *58*, 3235−3237.

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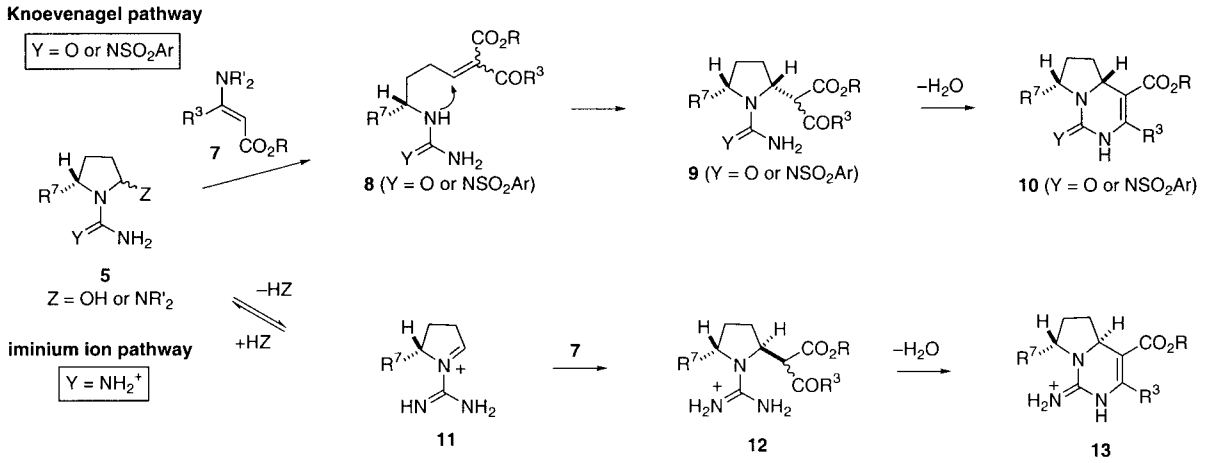
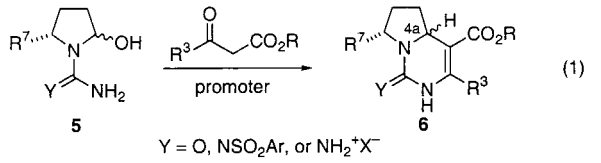


Figure 1. Two mechanistic possibilities for tethered Biginelli condensations under Knoevenagel conditions.

This tethered Biginelli reaction has played a central role in stereocontrolled total syntheses of crambescidin[3b,11] and batzelladine[12] alkaloids accomplished recently in our laboratories.



(1)

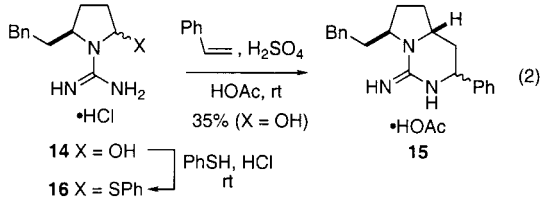
The stereochemical outcome of tethered Biginelli reactions is dependent upon both the nature of Y and the reaction conditions.[8] Substrates containing a urea (Y = O) or a *N*-arylsulfonylguanidine (Y = NSO_2Ar) unit yield products having cis stereochemistry around the pyrrolidine ring when the cyclocondensation is promoted with morpholinium acetate. In contrast, substrates containing an unprotected guanidine (Y = NH_2^+) provide the trans stereoisomer under identical conditions. To explain these results, we postulated that cis stereoisomer **10** arises from stereochemistry-determining cyclization of Knoevenagel adduct **8**, whereas trans stereoisomer **13** results from stereochemistry-determining addition of the β-ketoester-derived nucleophile **7** to *N*-amidinyliminium ion **11** from the face opposite the alkyl chain (Figure 1).[8] This latter mechanistic scenario was consistent with the observation that tethered Biginelli reactions promoted by the strong dehydrating reagent polyphosphate ester give trans products regardless of the nature of Y.[13]

To probe mechanism and stereochemical control elements in tethered Biginelli reactions further, we set out to unambiguously generate *N*-amidinyliminium ions **11** under conditions that would eliminate the possibility of a precursor reacting with a β-ketoester, or its enamine derivative, by a Knoevenagel pathway. In addition to these mechanistic objectives, we were interested to see if *N*-amidinyliminium ions could be trapped with other nucleophiles such as alkenes to provide a new method for constructing complex guanidines containing substructure **1**.[14] The results of these studies are described herein.

Results

Generation of *N*-Amidinyliminium Ions. Iminium ions having an amidine substituent on nitrogen have previously been implicated as reactive intermediates in Pictet–Spengler and other electrophilic aromatic substitution reactions.[15] In these cases, the *N*-amidinyliminium cation was generated by dehydrative condensation of guanidines with aldehydes or ketones, by dehydration of *N*-(1-hydroxyalkyl)guanidines, or by protonation of *N*-alkenylguanidines with strong acids.[15]

To test the viability of utilizing *N*-amidinyliminium ions in cyclocondensation processes, we first examined the reaction of guanidine hemiaminal **14**[8] with styrene in the presence of a stoichiometric amount of sulfuric acid (eq 2). One major product, 3-phenylhexahydropyrrolo[1,2-*c*]pyrimidine **15**, was isolated in ~35% yield as a 4:1 mixture of C3 epimers when this reaction was carried out in acetic acid at room temperature.



(2)

Although this initial result was promising, we felt that these strongly acidic conditions would be too harsh for

(11) (a) Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 2657–2658. (b) Coffey, D. S.; McDonald, A. I.; Overman, L. E.; Stappenbeck, F. *J. Am. Chem. Soc.* **1999**, *121*, 6944–6945. (c) Coffey, D. S.; McDonald, A. I.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 8741–8742. (d) Coffey, D. S.; Overman, L. E.; Stappenbeck, F. *J. Am. Chem. Soc.* **2000**, *122*, 4904–4914.

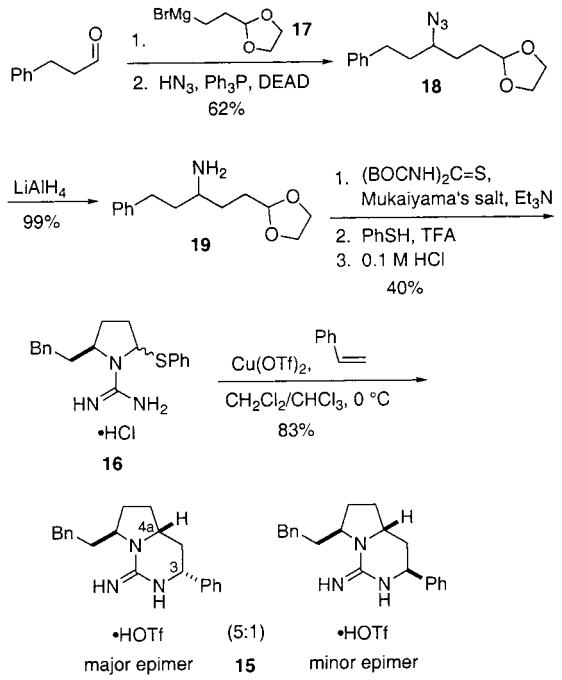
(12) (a) Franklin, A. S.; Ly, S. K.; Mackin, G. H.; Overman, L. E.; Shaka, A. J. *J. Org. Chem.* **1999**, *64*, 1512–1519. (b) Cohen, F.; Overman, L. E.; Sakata, S. K. L. *Org. Lett.* **1999**, *1*, 2169–2172.

(13) Studies by Kappe indicate the intermediacy of *N*-amidinyliminium ions in classical Biginelli condensations carried out in the presence of mineral acids; see: Kappe, C. O. *J. Org. Chem.* **1997**, *62*, 7201–7204.

(14) For reviews of the chemistry of *N*-acyliminium ions, see: (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856. (b) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 2, pp 1047–1082. (c) Zaugg, H. E. *Synthesis* **1984**, 181–212. (c) Weinreb, S. M.; Scola, P. M. *Chem. Rev.* **1989**, *89*, 1525–1534. (d) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367–4416.

(15) For representative reactions where *N*-amidinyliminium ions are believed to be intermediates, see: (a) Esser, F.; Pook, K.-H.; Carpy, A. *Synthesis* **1990**, 72–78. (b) Esser, F.; Pook, K.-H.; Carpy, A.; Leger, J.-M. *Synthesis* **1994**, 77–82. (c) Lyssikatos, J. P.; Chang, S.-P.; Clancy, J.; Dirlam, J. P.; Finegan, S. M.; Girard, A. E.; Hayashi, S. F.; Larson, D. P.; Lee, A. S.; Linde, R. G., II; MacLelland, C. P.; Petitpas, J. W.; Seibel, S. B.; Vu, C. B. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1145–1148.

Scheme 1



more complex molecules. Moreover, guanidine aminal **14** and related species previously employed by us in tethered Biginelli condensations are complex mixtures that resist purification and are prone to oligomerization.[8,10,11] We sought an alternative iminium ion precursor that would be synthesized and purified easily. To this end, the corresponding α-phenylthioguanidine was prepared by reaction of guanidine hemiaminal **14** with thiophenol in the presence of anhydrous HCl. These conditions provided a mixture of the desired thioaminal **16** and the corresponding acyclic guanidine dithioacetal. In contrast to **14**,[8] thioaminal **16** is easily purified by flash chromatography and is a stable solid at room temperature.

An improved synthesis of **16** was subsequently developed (Scheme 1). Treatment of hydrocinnamaldehyde with Grignard reagent **17**[16] followed by Mitsunobu reaction of the resulting alcohol with HN_3 provided azide **18**.[17] This intermediate was reduced with $LiAlH_4$ to give amine **19**. Guanylation of **19** with bis(BOC)thiourea[18] followed by reaction of the resulting BOC-protected guanidine with 1 equiv of thiophenol in 1:1 TFA−CH_2Cl_2 yielded the trifluoroacetate salt of **16**. Under these conditions, formation of the undesired dithioacetal was minimized. Because preliminary scouting experiments had shown that cyclocondensations with this trifluoroacetate salt led to the generation of a substantial amount of the enamide resulting from deprotonation of the *N*-amidinyliminium ion, the trifluoroacetate salt was converted to the hydrochloride salt by treatment with aqueous HCl.[19] Thiophenylguanidine hydrochloride **16** prepared in this way was a 9:1 mixture of epimers.

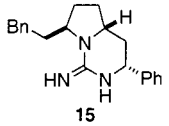
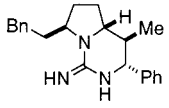
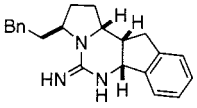
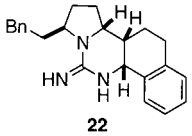
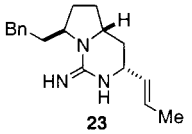
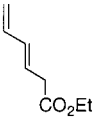
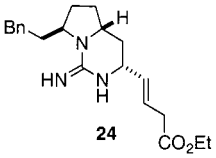
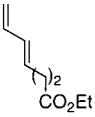
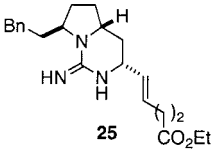
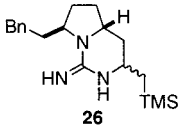
A variety of Lewis acids and thiophilic reagents such as methylthiodimethylsulfonium tetrafluoroborate were examined for effecting the reaction of **16** with styrene. Use of stoichiometric $Cu(OTf)_2$ in 3:1 CH_2Cl_2−$CHCl_3$[20] at 0 °C was found to promote the desired cyclocondensation in highest yield and diastereoselectivity.[21] Utilizing these conditions, **16** reacted with 2 equiv of styrene to give cycloadduct **15** in 83% yield as a 5:1 mixture of C3 epimers. No products having a trans relationship of the phenethyl side chain and the angular C4a hydrogen were observed. The epimers of **15** could be separated by flash chromatography, and detailed ^{1}H NMR NOE studies on the pure isomers showed that the phenyl substituent was equatorial (trans to the angular C4a hydrogen) in the major epimer.

Cyclocondensations of *N*-Amidinyliminium Ions with Alkenes, 1,3-Dienes, and *β*-Ketoesters. To ascertain the scope of *N*-amidinyliminium ion cyclocondensations, a number of π-nucleophiles were allowed to react with **16** under the conditions optimized with styrene. Results of these studies are summarized in Table 1. Styrenes and 1,3-dienes reacted in useful yields to provide cycloadducts as mixtures of C3 epimers. With but one exception, the product of endo addition having the C3 side chain equatorial predominated. Only products having a cis relationship of the phenethyl side chain and angular C4a hydrogen were observed. Reaction of **16** with styrenes afforded a 4−5:1 mixture of endo and exo cycloadducts as judged by ^{1}H NMR analysis of the crude reaction mixtures. Lower endo/exo selectivities (∼2−3:1) were observed with 1,3-dienes, whereas a 1:1 mixture of C3 epimers was formed in the reaction of **16** with allyltrimethylsilane. Stereochemical assignments for the products summarized in Table 1 were based on extensive ^{1}H NMR NOE experiments. Particularly diagnostic were NOE enhancements of 2−3% observed between the methine hydrogens at C3 and C4a in the major epimer and the corresponding lack of these enhancements in the minor epimer. The trans relationship between H7 and H4a was established by evaluation of NOE enhancements resulting from sequential irradiation of all hydrogens on the five-membered ring. Full details of these ^{1}H NMR NOE studies are provided in the Supporting Information.

Cyclocondensations of **16** with styrenes, or 1,3-dienes containing a terminal vinyl group, generally proceeded smoothly; however, reactions of other alkenes and dienes were problematic. For example, styrenes or 1,3-dienes having 1,1-disubstitution gave complex product mixtures containing adducts that incorporated more than one diene or styrene unit. Simple terminal alkenes did not undergo cyclocondensation with **16**. Reaction of allyltrimethylsilane and **16** gave a ∼2.6:1 mixture of cycloadducts **26** (isolated in 37% yield) and the corresponding 2-allyl *N*-guanylpyrrolidine.[22] Electron-rich alkenes such as vinyl ethers and enamines decomposed prior to cyclocondensation; the major products observed in these reactions were ethoxy aminals or *N*,*N*-acetals resulting from replacement of the phenylthio group by the alkoxy or amino group of the nucleophile. Similarly, attempted reaction of **16** with (*E*)-4-methoxy-3-buten-2-one or (*E*)-4-(dimethylamino)-3-buten-2-one[23] resulted in decomposi-

(16) Büchi, G.; Wuest, H. *J. Org. Chem.* **1969**, *34*, 1122−1123.
(17) Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1976**, *59*, 2100−2113.
(18) Yong, Y. F.; Kowalski, J. A.; Lipton, M. A. *J. Org. Chem.* **1997**, *62*, 1540−1542.
(19) Greater than 95% exchange of the counterion was obtained as judged by ^{19}F NMR analysis.
(20) Chloroform was added to improve the solubility of the substrate.
(21) At −15 °C, no reaction was observed.
(22) Similar mixtures were observed in reactions of allyltrimethylsilane with iminium ions derived from BOC-protected α-methoxy pyrrolidine or piperidine. Brocherieux-Lanoy, S.; Dhimane, H.; Poupon, J.-C.; Vanucci, C.; Lhommet, G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2163−2165.
(23) Burgi, D.; Sterchi, A.; Neuenschwander, M. *Helv. Chim. Acta* **1977**, *60*, 2195−2207.

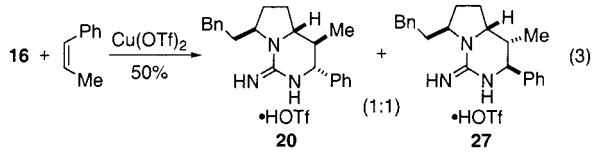
Table 1. Cyclocondensation of Alkenes and Dienes with 16[a]

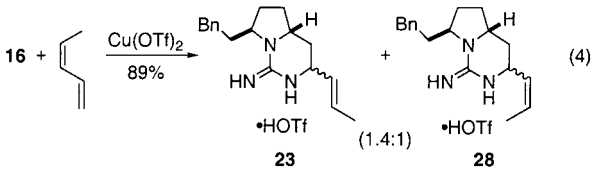
entry	alkene/diene	product (major isomer)	yield (dr)[b]
1		 **15**	83% (5:1)
2		 **20**	82% (2:1)[c]
3		 **21**	70% (>20:1)
4		 **22**	82% (6:1)
5		 **23**	76% (4:1)
6		 **24**	67% (13:1)
7		 **25**	69% (7:1)
8		 **26**	37% (1:1)[d]

[a] Reaction conditions: **16** (1.0 equiv, 0.25 M), alkene/diene (2.0 equiv), $Cu(OTf)_2$ (1.0 equiv), 3:1 CH_2Cl_2−$CHCl_3$, 0 ° C. [b] Isolated yields and diastereomer ratios of the mixture of stereoisomeric products after purification on silica gel. Diastereomer ratios in the crude reaction product were typically 2:1−5:1; chromatographic purification often led to enrichment in the major stereoisomer. See the Supporting Information for full details. [c] The minor product is epimeric at both C3 and C4. [d] The 2-allyl-*N*-guanylpyrrolidine was isolated in 14% yield.

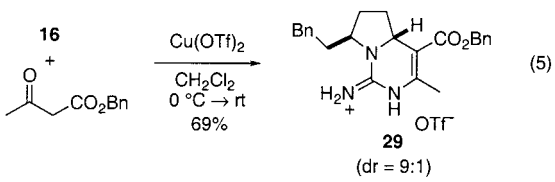
tion of the heterosubstituted alkene prior to cyclocondensation.[24] Due to the acid-sensitive nature of vinyl ethers and enamines, attempts were made to buffer their cyclocondensations with **16**. However, reactions conducted in the presence of amine bases also failed to provide the desired products; typically, either no reaction or slow hydrolysis of the substrate was observed. Attempts to employ the guanidine free base in these cyclocondensations by treating **16** with NaH prior to the addition of the alkene and $Cu(OTf)_2$ also failed to provide cycloadducts.

Only cyclocondensations of *E* alkenes proved to be stereospecific. For example, reaction of **16** with *trans*-*β*-methylstyrene provided 1-iminohexahydropyrrolo[1,2-*c*]-pyrimidine **20** and stereoisomer **27**, both of which have a trans relationship of phenyl and methyl substituents, in a 2:1 ratio (Table 1, entry 2). These stereoisomeric products were formed in equal amounts from an identical reaction of **16** and *cis*-*β*-methylstyrene (eq 3). Similarly, reaction of *trans*-piperylene and **16** gave exclusively epimeric products **23** having (*E*)-propenyl side chains (Table 1, entry 5). However, identical reaction of *cis*-piperylene provided a 1.4:1 mixture of **23** and (*Z*)-propenyl isomers **28** (eq 4). Control experiments conducted in the absence of **16** showed that *cis*-piperylene and *cis*-*β*-methylstyrene were not isomerized by $Cu(OTf)_2$ in the amount of time required for the cyclocondensation reactions to proceed to completion.





To pursue the possible intermediacy of *N*-amidinyliminium ions in tethered Biginelli condensations, guanidine thioaminal **16** was allowed to react with benzyl acetoacetate in the presence of $Cu(OTf)_2$. Under these conditions, the Biginelli products **29** were obtained in 69% yield, with the stereoisomer having a cis relationship of the phenethyl side chain and angular C4a hydrogen predominating to the extent of 9:1 (eq 5).[25]

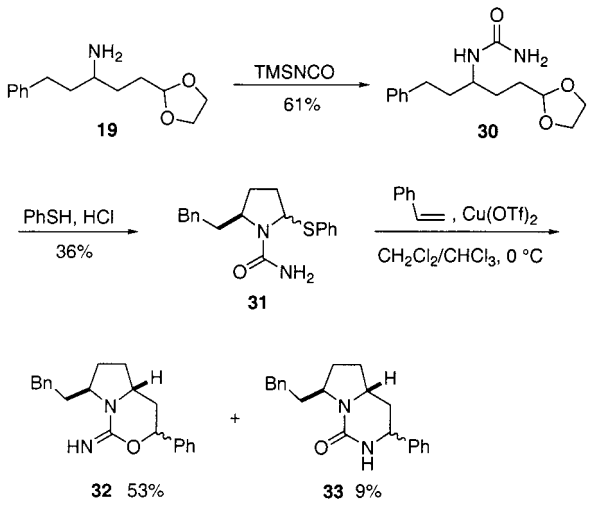


Cyclocondensations of *N*-(Acylamino)iminium Ions with Representative *π*-Nucleophiles. Previous studies in our laboratories suggested that tethered Biginelli condensations of *N*-(acylamino)aminals also proceed through iminium ion intermediates when strong dehydrating reagents were employed as promoters.[8] To probe the validity of this hypothesis, we prepared **31**, the urea analogue of **16**, and examined its reactivity with styrene (Scheme 2). The synthesis of **31** began with amine **19**, which upon reaction with trimethylsilyl isocyanate gave urea **30**. Formation of thioaminal **31** from ureido acetal **30** required more forcing conditions than the correspond-

(24) Side products observed by electrospray MS included hemiaminals and methoxy aminals.

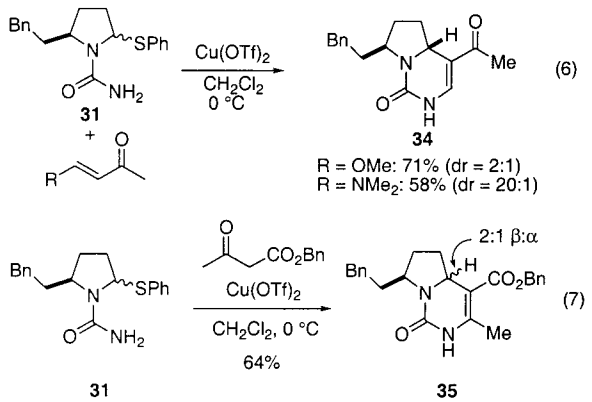
(25) Stereochemical assignments were made by ^{1}H NMR NOE experiments and by comparison of the chemical shifts of the angular methine hydrogens H4a and H7 with those of related compounds previously reported.[8]

Scheme 2

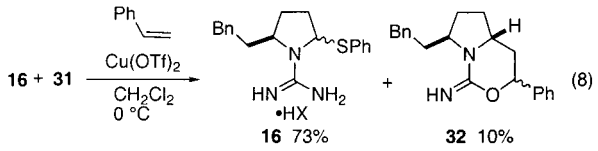


ing conversion in the guanidine series. This transformation could be realized in low yield by reaction of **30** at room temperature with excess PhSH and 4 M HCl. Subsequent reaction of **31** with $Cu(OTf)_2$ and styrene under the conditions developed in the guanidine series provided as the major product (53% yield) iminodihydro-1,3-oxazine derivative **32**. The corresponding cyclic urea **33** was obtained in 9% yield. Both products were isolated as ~4:1 mixtures of endo and exo cycloadducts. As observed for reactions of **16**, all products formed from **31** have the cis relationship of the phenethyl side chain and C4a hydrogen. The structure of **32** was apparent from the diagnostic signal for the C3 methine hydrogen at δ5.16 in its ^{1}H NMR spectrum, whereas the stereochemistry of **32** and **33** was secured by ^{1}H NMR NOE experiments.

In contrast to guanidine thioaminal **16**, **31** reacted with (*E*)-4-methoxy-3-buten-2-one and (*E*)-4-(dimethylamino)-3-buten-2-one to give 4-acyl-1-oxohexahydropyrrolo[1,2-*c*]pyrimidine **34** in 58−70% yield (eq 6). This product undoubtedly arises by cyclocondensation followed by elimination of the β methoxy or dimethylamino groups. Interestingly, reaction of **31** with (*E*)-4-(dimethylamino)-3-buten-2-one was highly stereoselective (dr = 20:1), whereas face selectivity was much lower (dr = 2:1) in the reaction with (*E*)-4-methoxy-3-buten-2-one. Reaction of **31** with benzyl acetoacetate in the presence of $Cu(OTf)_2$ afforded Biginelli adduct **35** in 64% yield as a 2:1 mixture of epimers, with the major isomer having the trans stereochemistry (eq 7).



To pursue whether cycloadducts would be formed more readily from thioaminal precursors in the guanidine or urea series, a 1:1 mixture of **16** and **31** was allowed to react with 1 equiv each of styrene and $Cu(OTf)_2$ (eq 8). The major product obtained from this competition was iminodihydro-1,3-oxazine derivative **32**, which was isolated in 10% yield. No products resulting from ionization of **16** and subsequent cyclocondensation of the *N*-amidinyliminium ion were detected as judged by ^{1}H and ^{13}C NMR analysis of the crude reaction mixture; **16** was recovered in 73% yield.



Discussion

Synthesis of Guanidines from *N*-Amidinyliminium Ions and Alkenes. Reaction of *N*-amidinyl-2-(phenylthio)pyrrolidine **16** with $Cu(OTf)_2$ was found to be a mild method for chemoselectively generating *N*-amidinyliminium ion **37** (Figure 2). Cyclocondensation of this intermediate with alkenes provides a new route for preparing polycyclic guanidines. This method is useful for the synthesis of 1-iminohexahydropyrrolo[1,2-*c*]pyrimidines **39** containing aryl or alkenyl substituents at the C3 position. Cyclocondensation occurs exclusively from the face opposite the preexisting C7 side chain to give products having a trans relationship of the methine hydrogens flanking nitrogen. Mixtures of C3 epimers, typically 2:1−5:1 favoring the endo product **39**, are observed. The scope of this reaction as currently practiced is limited to conjugated alkenes that are not disubstituted at their termini. Cyclocondensations of *N*-amidinyliminium ions with 1,3-dienes could potentially be applied to the synthesis of batzelladine A and related alkaloids; however, further optimization of stereoselectivity would be needed for this to represent a practical entry into these compounds.

Cyclocondensation of ureido aminal **31** with styrene provides 2-imino-5,6-dihydro-4*H*-1,3-oxazine derivative **32** rather than a pyrimidine as the major product (Scheme 2). Although vinylogous esters or amides decompose prior to cyclocondensation with the guanidine substrate, they form 4-acyl-1-oxohexahydropyrrolo[1,2-*c*]pyrimidines under identical conditions in reactions with ureido aminal **31** (eq 6).

The observed loss of stereochemistry of the disubstituted double bond in the reaction of *cis*-piperylene with **16** strongly suggests that cyclocondensations with *N*-amidinyliminium ion **37** proceed by a stepwise mechanism involving an intermediate allylic or benzylic cation **38**. In the case of *cis*-piperylene, stereomutation of the initially formed allylic cation **38**, R = (*Z*)-1-propenyl, is competitive with trapping by the neighboring guanidine. The formation of the same products from *trans*- and *cis*-β-methylstyrene is also consistent with a stepwise pathway. The stepwise nature of cyclocondensations of *N*-amidinyliminium ion **37** with styrenes and 1,3-dienes contrasts to what has previously been observed in related hetero Diels−Alder reactions of *N*-acyliminium ions.[26]

(26) (a) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 602. (b) Schmidt, R. R. *Chem. Ber.* **1970**, *103*, 3242−3251. (c) Schmidt, R. R.; Hoffmann, A. R. *Chem. Ber.* **1974**, *107*, 78−92. (d) Bradsher, C. K. *Adv. Heterocycl. Chem.* **1974**, *16*, 289−324.

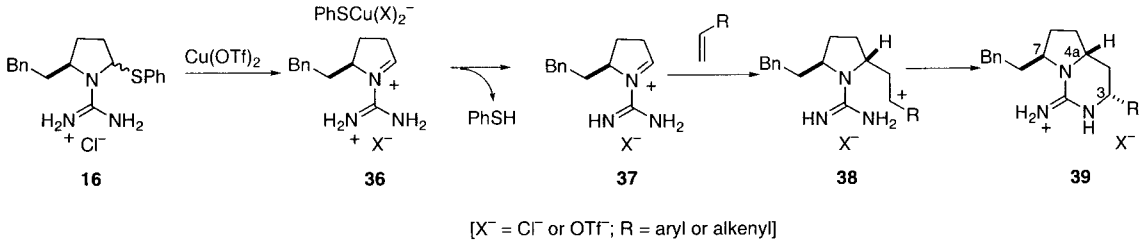


Figure 2. Proposed mechanism of the cyclocondensation.

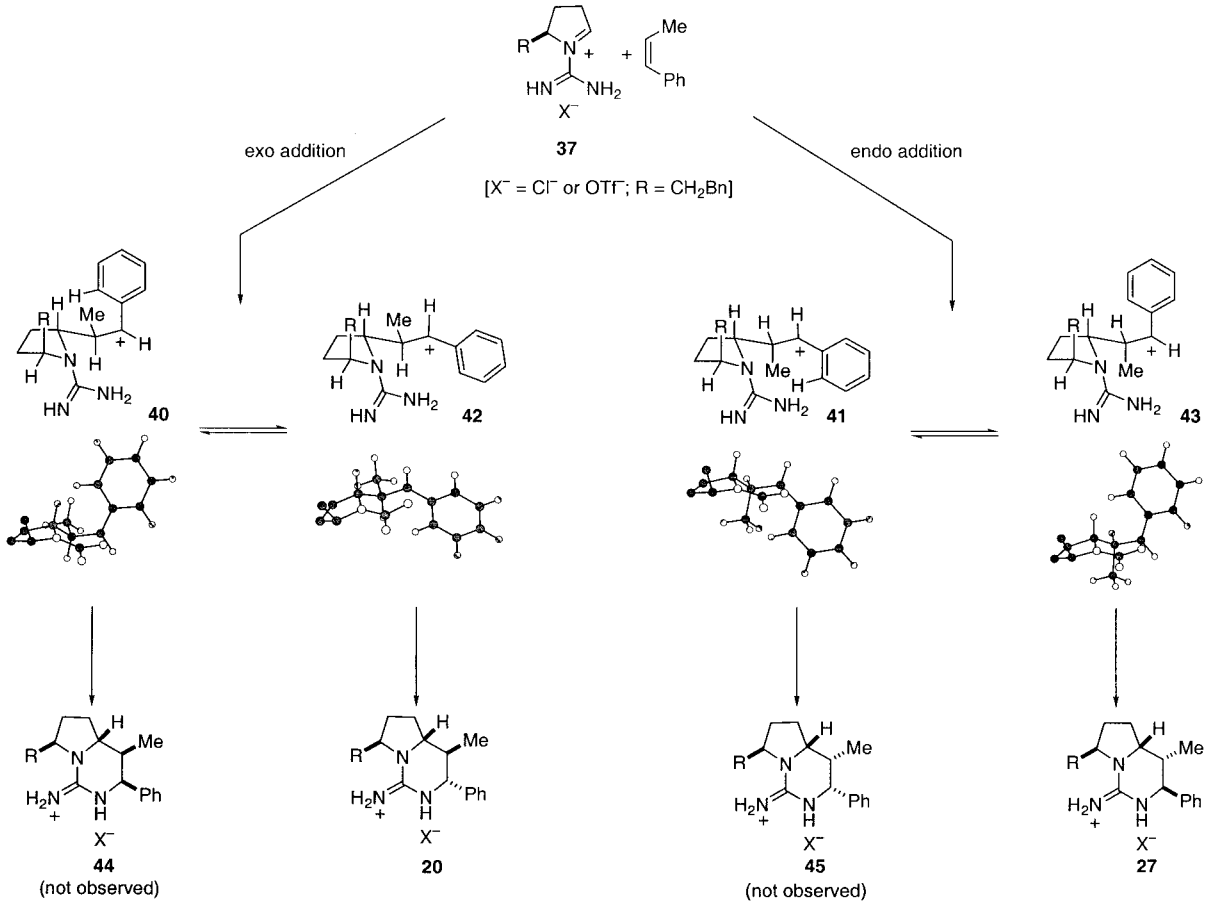


Figure 3. Cyclocondensation of **16** with *cis*-*β*-methyl styrene.

These latter reactions are believed to proceed by concerted [4 + 2]-cycloaddition mechanisms.

On the basis of these observations, the mechanism we postulate for the cyclocondensation of alkenes with **16** involves initial activation of the thiophenyl group by Cu(OTf)$_2$ to form the protonated amidinyl iminium ion **36** (Figure 2). This species most likely transfers a proton to the copper thiophenylate to form iminium ion **37** prior to trapping by a styrene or 1,3-diene, although no experimental evidence precludes direct reaction of these *π*-nucleophiles with **36**. Preferential formation of cycloadducts containing an α C3 side chain from cyclocondensations of styrenes and 1,3-dienes having a terminal vinyl group presumably arises from preferred pseudoequatorial orientation of the side chain in **38** during intramolecular trapping of the benzylic cation. In a similar vein, only two of the four possible stereoisomers are formed in the cyclocondensation of **16** with *trans*- or *cis*-*β*-methylstyrene, one of which, **27**, contains the C3 phenyl group in an axial orientation. As shown in Figure 3, initial addition of *cis*-*β*-methyl styrene to **16** in an exo fashion would lead to two limiting reactive conformers of the intermediate benzylic cation, **40** and **42**, in which the empty p-orbital was oriented toward the nucleophilic guanidine. Conformer **40** suffers from an unfavorable steric interaction between the C3 phenyl group and the C4 methyl group, as well as a 1,3-diaxial interaction between the phenyl group and the angular C4a hydrogen. These steric effects presumably lead to the preferential formation of **20** rather than **44**. Similarly, endo addition of *cis*-*β*-methyl styrene to **16** would lead to reactive intermediate cation conformers **41** and **43**; the severe steric interaction between the methyl and phenyl groups disfavors reaction via **41**, and the observed product **27** arises from trapping of cation **43**. Although isomer **43** places the phenyl group in an axial orientation, examination of molecular models[27] suggests that the steric interaction of the phenyl and methyl groups is more

(27) Bond angles and bond lengths used in models depicted in Figure 3 were obtained from previously described theoretical studies of benzylic cations; see: Nakata, K.; Fujio, M.; Saeki, Y.; Mishima, M.; Tsuno, Y.; Nishimoto, K. *J. Phys. Org. Chem.* **1996**, *9*, 561−572.

severe than the developing 1,3-diaxial interaction between the phenyl group and the angular C4a hydrogen. An identical analysis predicts formation of **20** and **27** in the reaction of **16** with *trans*-*β*-methyl styrene, which is consistent with our experimental observations.

Mechanism of Tethered Biginelli Condensation of Guanidine Precursors. In addition to providing a new method for the synthesis of 1-iminohexahydropyrrolo[1,2-*c*]pyrimidines, these studies provide further support for our earlier speculation on the origin of stereoselection in tethered Biginelli condensations of guanidines (Figure 1).[8] We originally posited the intermediacy of an *N*-amidinyliminium ion to explain preferential formation of trans iminopyrrolopyrimidine stereoisomer **13** in condensations promoted by morpholinium acetate.[8] The current study demonstrates that *N*-amidinyliminium ion **37** does indeed add nucleophiles preferentially from the face opposite the phenethyl side chain. In the reaction of direct relevance to tethered Biginelli condensations, the putative *N*-amidinyliminium ion generated from **16** and $Cu(OTf)_2$ reacts at room temperature with benzyl acetoacetate with 9:1 facial selectivity from the face opposite the phenylethyl group. Under the conditions employed for this cyclocondensation, a sequence analogous to the Knoevenagel pathway outlined in Figure 1 is highly unlikely.[28]

At first glance, the relative reactivity of **16** and **31** in cyclocondensations with styrene appears to be inconsistent with our earlier analysis of stereoselection in tethered Biginelli reaction.[8] In that discussion, we suggested that an iminium ion bearing a less electron-withdrawing *N*-amidinyl substituent should form more readily by loss of HY from precursor **5** than the corresponding intermediate having *N*-aminocarbonyl functionality (Figure 1). However, the first species generated from **16** upon reaction with $Cu(OTf)_2$ is undoubtedly the *protonated* *N*-amidinyliminium ion **36** (Figure 2), a species that would be considerably higher in energy than an *N*-amidinyliminium ion or an *N*-(acylamino)iminium ion. In contrast, tethered Biginelli reactions employing morpholinium acetate as the promoter would avoid the formation of **36** by transferring a proton from the guanidinium functionality to morpholine as the C−Y bond undergoes heterolytic cleavage.[29] Unfortunately, attempts to directly probe this hypothesis by examining the relative rates of reactions of the free base of **16** were unsuccessful. Presumably, the free guanidine is basic enough to coordinate to the Cu(II) and prevent activation of the phenylthio leaving group.

Conclusion

Our efforts to further explore the mechanism of tethered Biginelli condensations have led to a new method for the synthesis of 1-iminohexahydropyrrolo[1,2-*c*]pyrimidines by formal [4 + 2]-cycloaddition of *N*-amidinyliminium ions with alkenes. This cyclocondensation allows 1-iminohexahydropyrrolo[1,2-*c*]pyrimidines containing side chains at C3 and C7 to be readily prepared. Although the scope of these reactions is currently limited to 1,3-dienes and styrene derivatives, cycloadducts are obtained in good yields with complete control of relative stereochemistry at C4a and C7, whereas C3 side chains are incorporated with lower stereoselectivity (dr = 2−5:1). Stereochemical evidence demonstrates that cyclocondensations of the *N*-amidinyliminium ion derived from **16** proceed by a stepwise mechanism rather than by a concerted [4 + 2]-cycloaddition pathway.

The Biginelli product **29** was formed in 9:1 stereoselectivity from $Cu(OTf)_2$-promoted condensation of **16** with benzyl acetoacetate. This result supports the iminium ion pathway outlined in Figure 1 for tethered Biginelli condensations of guanidines we described earlier from our laboratories.[8]

Experimental Section[30]

2-(3-Azido-5-phenylpentyl)-1,3-dioxolane (18). An oven-dried flask was cooled under a stream of nitrogen and charged with magnesium turnings (2.33 g, 96 mmol). To the flask was added THF (80 mL), followed by one small crystal of iodine. The mixture was cooled to 0 °C, and 2-(2-bromoethyl)-1,3-dioxolane (9.4 mL, 80 mmol) was added in one portion. The mixture was stirred at 0 °C for 3 h, and then 3-phenylpropionaldehyde (5.3 mL, 40 mmol) was added dropwise. The mixture was stirred at 0 °C for 20 min, and then aqueous ammonium chloride (80 mL) was added and the mixture was allowed to warm to room temperature. The mixture was diluted with ether (100 mL), and the layers were separated. The aqueous layer was extracted with ether (3 × 50 mL), and the combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using 30% ethyl acetate/hexanes as the eluant to afford 7.37 g (78%) of 1-[1,3]-dioxolan-2-yl-5-phenylpentan-3-ol as a colorless oil. This material was judged to be ∼80% pure by ^{1}H NMR analysis and was used without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−7.26 (m, 2 H), 7.22−7.17 (m, 3 H), 4.89 (t, J = 4.5 Hz, 1 H), 3.97−3.82 (m, 4 H), 3.67−3.62 (m, 1 H), 2.83−2.78 (m, 1 H), 2.70−2.65 (m, 2 H), 1.85−1.75 (m, 4 H), 1.70−1.64 (m, 1 H), 1.59−1.52 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.1, 128.3, 128.2, 125.6, 104.3, 70.6, 64.8, 64.7, 39.0, 32.0, 31.3, 29.8; IR (film) 3425, 1040 cm^{-1}.

An oven-dried flask was cooled under a stream of nitrogen and charged with triphenylphosphine (9.65 g, 36.8 mmol), 1-[1,3]-dioxolan-2-yl-5-phenylpentan-3-ol (7.25 g, 30.7 mmol), and THF (307 mL). The mixture was cooled to 0 °C, and HN_3 (17.7 mL, 2.08 M in toluene) was added. Diethyl azodicarboxylate (5.8 mL) was added dropwise over 30 min, and the mixture was stirred at 0 °C for 15 min, warmed to room temperature, and stirred for 2 h. The mixture was concentrated in vacuo to 100 mL and then diluted with hexanes (400 mL), filtered, and concentrated. The crude product was purified by flash chromatography on silica gel using 10% ethyl acetate/hexanes as the eluant to afford 6.48 g (80%) of **18** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.3−7.29 (m, 2 H), 7.22−7.19 (m, 3 H), 4.89 (t, J = 4.2 Hz, 1 H), 3.98−3.85 (m, 4 H), 3.33 (p, J = 7.4 Hz, 1 H), 2.82−2.79 (m, 1 H), 2.71−2.67 (m, 1 H), 1.87−1.84 (m, 3 H), 1.73−1.53 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.1, 128.44, 128.35, 126.0, 103.9, 64.90, 64.86, 61.9, 36.1, 32.2, 30.2, 28.5; IR (film) 2096, 1031 cm^{-1}; MS (CI) m/z 262.1553 (262.1555 calcd for $C_{14}H_{20}N_3O_2$, M + H$^+$).

1-(2-[1,3]-Dioxolan-2-ylethyl-3-phenylpropylamine (19). An oven-dried flask was cooled under a stream of nitrogen and charged with a solution of LAH in ether (28 mL, 28 mmol, 1.0 M) and additional ether (170 mL). The solution was cooled to 0 °C, and a solution of 2-(3-azido-5-phenylpentyl)-1,3-dioxolane (6.14 g, 23.2 mmol) in ether (34 mL) was added dropwise. The mixture was stirred at 0 °C for 15 min, warmed to room

(28) Such a sequence would require $Cu(OTf)_2$-promoted ring opening of **16** to give an α-thiocarbenium ion, which then adds the acetoacetate.

(29) The high acidity of **36** may be responsible for the apparent decomposition of 4-methoxy or 4-(dimethylamino)-3-buten-2-one during attempted cyclocondensations with **16**.

(30) General experimental details have been described: Ando, S.; Minor, K. P.; Overman, L. E. *J. Org. Chem.* **1997**, *62*, 6379−6387.

temperature, and stirred for 1.5 h. The mixture was then cooled to 0 °C, and water (4 mL), sodium hydroxide (5 mL, 10 M), and additional water (8 mL) were added dropwise sequentially. The mixture was warmed to room temperature and stirred for 10 min, and then the solution was decanted, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford 5.44 g (99%) of **19** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.25 (m, 2 H), 7.20−7.16 (m, 3 H), 4.87 (t, J = 4.6 Hz, 1 H), 3.95−3.84 (m, 4 H), 2.77−2.70 (m, 2 H), 2.63−2.55 (m, 1 H), 1.77−1.58 (m, 5 H), 1.41−1.33 (m, 1 H), 1.24 (s, br, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.2, 128.3, 125.7, 104.5, 64.84, 64.78, 50.6, 39.8, 32.5, 32.2, 30.4; IR (film) 3365, 1031 cm^{-1}; MS (EI) *m*/*z* 235.1578 (235.1572 calcd for $C_{14}H_{21}NO_2$).

2-Phenethyl-5-phenylsulfanylpyrrolidine-1-carboxamidine HCl (16). An oven-dried flask was cooled under a stream of nitrogen and charged with 1-(2-[1,3]dioxolan-2-ylethyl-3-phenylpropylamine (4.0 g, 17 mmol), bis-BOC-thiourea[31] (5.63 g, 20.4 mmol), triethylamine (5.21 mL, 37.4 mmol), and DMF (4 mL). A suspension of 2-chloro-*N*-methylpyridinium iodide (5.21 g, 20.4 mmol) in DMF (13 mL) was added dropwise, and the resulting mixture was stirred at room temperature for 14 h. The mixture was then diluted with water (20 mL) and extracted with ether (3 × 40 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography on silica gel using ethyl acetate/hexanes as the eluant (10% to 20%) to afford 4.75 g (60%) of *N*,*N*′-bis(*tert*-butoxycarbonyl)-*N*″-[1-(2-[1,3]-dioxolan-2-ylethyl)-3-phenylpropyl]guanidine as a viscous oil. This material was judged to be ∼90% pure by ^{1}H NMR analysis and was used without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 9.2 Hz, 1 H), 7.26−7.24 (m, 2 H), 7.20−7.14 (m, 3 H), 4.87 (t, J = 4.4 Hz, 1 H), 4.27 (s, br, 1 H), 3.96−3.82 (M, 4 H), 2.66 (t, J = 8.0 Hz, 2 H), 1.90−1.59 (m, 7 H), 1.50 (s, 9 H), 1.49 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 156.0, 153.2, 141.8, 128.3, 128.2, 125.7, 104.1, 82.9, 78.9, 64.8, 49.6, 36.5, 31.9, 29.7, 28.8, 28.3, 28.0; IR (film) 3323, 3281, 1718, 1637, 1613, 1054 cm^{-1}; MS (CI) 500.2724 (500.2736 calcd for $C_{25}H_{39}N_3O_6Na$). An oven-dried flask was cooled under a stream of nitrogen and charged with *N*,*N*′-bis(*tert*-butoxycarbonyl)-*N*″-[1-(2-[1,3]-dioxolan-2-ylethyl)-3-phenylpropyl]guanidine (4.75 g, 10.0 mmol), thiophenol (1.03 mL, 10.0 mmol), trifluoroacetic acid (20 mL), and methylene chloride (20 mL). The mixture was stirred at room temperature for 17 h and then was concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford 3.2 g (73%) of a viscous oil which solidified upon standing to give 2-phenethyl-5-phenylsulfanylpyrrolidine-1-carboxamidine hydrotrifluoroacetate as a colorless solid, mp 133−135 °C. This material was determined to be a 10/1 mixture of diastereomers by ^{1}H NMR analysis. Data are for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, br, 2 H), 7.48−7.46 (m, 2 H), 7.38−7.35 (m, 3 H), 7.26−7.24 (m, 3 H), 7.20−7.18 (m, 1 H), 7.12−7.10 (m, 2 H), 5.03 (dd, J = 3.2, 6.8 Hz, 1 H), 4.09−4.06 (m, 1 H), 2.60−2.55 (m, 2 H), 2.33−2.16 (m, 3 H), 2.03−1.55 (m, 2 H), 1.42−1.36 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9 (q, J = 36.5 Hz), 156.0, 140.7, 135.0, 130.7, 129.9, 129.7, 128.4, 128.1, 126.4, 116.2 (q, J = 292 Hz), 68.5, 59.3, 35.1, 32.6, 31.5, 28.9; ^{19}F NMR (375 MHz, $CDCl_3$) δ −76.7; IR (film) 3443, 3343, 1779, 1656, 1590, 1135 cm^{-1}; MS (FAB) *m*/*z* 326.1696 (326.1691 calcd for $C_{19}H_{24}N_3S$).

2-Phenethyl-5-phenylsulfanylpyrrolidine-1-carboxamidine hydrotrifluoroacetate (3.1 g, 7.1 mmol) was dissolved in chloroform (75 mL). The solution was washed with 0.1 M HCl saturated with sodium chloride (5 × 80 mL) and then concentrated in vacuo. The crude material was dried in vacuo on a rotary evaporator by azeotropic removal of water with toluene (2 × 150 mL) to afford 2.32 g (91%) of **16** as a colorless solid, mp 174−177 °C. This material was determined to be a 9/1 mixture of diastereomers by ^{1}H NMR analysis. Data are for the major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60−7.40 (m, 4 H), 7.32−7.30 (m, 3 H), 7.24−7.20 (m, 3 H) 7.16−7.13 (m, 4 H), 5.10 (dd, J = 3.4, 6.9 Hz, 1 H), 4.34−4.32 (m, 1 H), 2.79 (td, J = 5.4, 13.6 Hz, 1 H), 2.47 (td, J = 5.1, 12.0 Hz, 1 H), 2.38−2.33 (m, 1 H), 2.16−2.13 (m, 2 H), 2.04−2.00 (m, 1 H), 1.88−1.84 (m, 1 H), 1.30−1.26 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 141.1, 135.0, 129.6, 129.5, 128.3, 125.9, 68.2, 59.8, 35.1, 32.4, 31.6, 28.9; IR (film) 3300, 1648, 1586 cm^{-1}; MS (FAB) *m*/*z* 326.1692 (326.1691 calcd for $C_{19}H_{24}N_3S$).

[1-(2-[1,3]-Dioxolan-2-ylethyl)-3-phenylpropylurea (30). An oven-dried flask was cooled under a stream of nitrogen and charged with 1-(2-[1,3]-dioxolan-2-yl-ethyl-3-phenylpropylamine (**19**) 1.2 g (5.0 mmol) and 2-propanol (7 mL). Trimethylsilyl isocyanate (0.95 mL, 7.0 mmol) was added, and the mixture was stirred at room temperature for 5 h. The mixture was concentrated in vacuo and purified by flash chromatography on silica gel using 3% methanol/chloroform as the eluant to afford 850 mg (61%) of **30** as a colorless solid: mp 128−130 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25−7.22 (m, 2 H), 7.15−7.13 (m, 3 H), 5.23 (s, br, 1 H), 4.85 (s, br, 2 H), 4.83 (t, J = 4.3 Hz, 1 H), 3.91−3.75 (m, 4 H), 3.66 (s, br, 1 H), 2.71−2.59 (m, 2 H), 1.80−1.63 (m, 5 H), 1.51−1.46 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 141.8, 128.3, 125.7, 104.2, 64.8, 64.7, 49.8, 37.6, 32.2, 29.8, 29.5; IR (film) 3312, 3212, 1648, 1565, 1139, 1034 cm^{-1}; MS (CI)*m*/*z* 278.1631 (278.1630 calcd for $C_{15}H_{22}N_2O_3$).

2-Phenethyl-5-phenylsulfanylpyrrolidinecarboxylic Acid Amide (31). An oven-dried flask was cooled under a stream of nitrogen and charged with [1-(2-[1,3]dioxolan-2-ylethyl)-3-phenylpropylurea (1.10 g, 3.96 mmol), thiophenol (1.63 mL, 15.84 mmol), dichloromethane (1 mL), and a solution of anhydrous HCl in dioxane (1 mL, 4.0 mmol, 4 M). The mixture was stirred at room temperature for 16 h, triethylamine (1 mL) was added, and the mixture was concentrated in vacuo. The crude material was purified by flash chromatography on silica gel using 30% ethyl acetate/hexanes as the eluant to afford 470 mg (36%) of **31** as a colorless solid: mp 124−127 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51−7.47 (m, 2 H), 7.33−7.29 (m, 3 H), 7.28−7.25 (m, 2 H), 7.19−7.15 (m, 3 H), 5.10 (dd, J = 3.0, 6.4 Hz, 1 H), 4.96 (s, br, 2 H), 4.02−3.98 (m, 1 H), 2.59 (t, J = 8.15 Hz, 2 H), 2.24−2.15 (m, 3 H), 1.83−1.79 (m, 1 H), 1.45−1.41 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 141.8, 134.4, 132.1, 129.2, 128.6, 128.3, 128.2, 125.7, 68.5, 58.5, 36.4, 33.3, 32.2, 28.9; IR (film) 3408, 1668 cm^{-1}; MS (CI) *m*/*z* 327.1521 (327.1531 calcd for $C_{19}H_{23}N_2OS$, $M + H^+$).

General Procedure for *N*-Amidinyliminium Ion Cyclocondensation Reactions. An oven-dried flask was cooled under a stream of nitrogen and charged with $Cu(OTf)_2$ (145 mg, 0.4 mmol), the alkene (0.8 mmol), and methylene chloride (400 μL). The mixture was cooled to 0 °C, and a solution of 2-phenethyl-5-phenylsulfanylpyrrolidine-1-carboxamidine HCl (**16**) (144 mg, 0.40 mmol) in methylene chloride/chloroform (1.2 mL, 2/1 v/v) was added dropwise. The mixture was stirred at 0 °C until the starting material had been completely consumed as judged by electrospray MS analysis. Reactions were generally complete in 2 h at 0 °C. The mixture was then diluted with methylene chloride (5 mL), filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel using methanol/chloroform as the eluant (0% to 3%). The products were isolated as mixtures of diastereomers; ratios of the diastereomers were determined by ^{1}H NMR analysis. The diastereomers were separated by flash chromatography or preparative HPLC for characterization purposes. Stereochemistry of the products was assigned by NOE experiments.

Reaction of 16 with Styrene. The general procedure afforded 156 mg (83%) of *7*-phenethyl-3-phenylhexahydropyrrolo[1,2-*c*]pyrimidine-1-ylideneamine (**15**) as a 5/1 mixture of diastereomers (the crude reaction mixture was judged to be a 5/1 mixture of diastereomers by ^{1}H NMR analysis).

(3*R*,4a*R*,7*R*)-7-Phenethyl-3-phenylhexahydropyrrolo-[1,2-*c*]pyrimidine-1-ylideneamine Hydrotrifluoromethanesulfonate (15). This material was obtained as a colorless

(31) Iwanowicz, E. J.; Poss, M. A.; Lin, J. *Synth. Commun.* **1993**, *23*, 1443−1445.

solid: mp 66−68 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.15 (m, 11 H), 6.52 (s, 2 H), 4.37 (dd, J = 2.9, 8.6 Hz, 1 H), 4.17−4.12 (m, 1 H), 3.73−3.67 (m, 1 H), 2.89−2.84 (m, 1 H), 2.63−2.55 (m, 1 H), 2.35−2.30 (m, 2 H), 2.26−2.10 (m, 2 H), 1.87−1.70 (m, 2 H), 1.56−1.50 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 141.0, 138.3, 128.9, 128.5, 128.4, 128.3, 126.0, 120.0 (q, J = 318 Hz), 58.1, 56.5, 54.0, 36.3, 35.5, 31.2, 31.1, 29.6; ^{19}F NMR (375 MHz, $CDCl_3$) δ −79.5; IR (film) 3350, 1652, 1027 cm^{-1}; MS (CI) m/z 320.2120 (320.2127 calcd for $C_{21}H_{26}N_3$).

(3*S*,4a*R*,7*R*)-7-Phenethyl-3-phenylhexahydropyrrolo-[1,2-*c*]pyrimidine-1-ylideneamine Hydrotrifluoromethanesulfonate. This material was obtained as a viscous oil and judged to be a 4/1 mixture of diastereomers by ^{1}H NMR analysis after purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 4.9 Hz, 1 H), 7.36−7.34 (m, 2 H), 7.33−7.28 (m, 3 H), 7.23−7.20 (m, 3 H), 7.12 (d, J = 7.5 Hz, 2 H), 6.52 (s, 2 H), 4.82−4.79 (m, 1 H), 4.17−4.10 (m, 1 H), 3.27−3.21 (m, 1 H), 2.73−2.68 (m, 1 H), 2.61−2.55 (m, 1 H), 2.35−2.30 (m, 2 H), 2.22−2.18 (m, 1 H), 2.13−2.07 (m, 1 H), 1.85 (td, J = 5.0, 13.1 Hz, 1 H), 1.72−1.63 (m, 2 H), 1.61−1.50 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1, 140.8, 140.3, 128.9, 128.6, 128.3, 127.8, 126.3, 125.3, 58.3, 52.1, 51.3, 36.1, 33.5, 31.20, 31.17, 29.63; ^{19}F NMR (375 MHz, $CDCl_3$) δ −79.5; IR (film) 3346, 3223, 1652, 1027 cm^{-1}; MS (CI) m/z 320.2116 (320.2127 calcd for $C_{21}H_{26}N_3$).

Control Experiments. *cis*-β-Methyl styrene (26 μL, 0.1 mmol) was treated with $Cu(OTf)_2$ (37 mg, 0.1 mmol) in methylene chloride/chloroform (400 μL, 3/1 v/v) for 2 h at 0 °C. The mixture was then diluted with 2 mL of methylene chloride, filtered, and concentrated in vacuo. Analysis of the crude product by ^{1}H NMR showed no isomerization of the olefin had occurred. In a separate experiment, *cis*-piperylene (20 μL, 0.2 mmol) was treated with $Cu(OTf)_2$ (37 mg, 0.1 mmol) in $CDCl_3$ (400 μL) at 0 °C for 2 h. The mixture was then diluted with $CDCl_3$ (500 μL) and filtered. Analysis of the crude mixture by ^{1}H NMR showed no isomerization of the olefin had occurred.

Competition Experiment. An oven-dried vial was cooled under a stream of nitrogen and charged with $Cu(OTf)_2$ (25 mg, 0.07 mmol), styrene (9 μL, 0.07 mmol), and methylene chloride (70 μL). The mixture was cooled to 0 °C, and a solution of **16** (25 mg, 0.07 mmol) and **31** (23 mg, 0.07 mmol) in methylene chloride/chloroform (210 μL, 2/1 v/v) was added dropwise. The mixture was stirred at 0 °C for 2 h. The mixture was then diluted with methylene chloride (5 mL), filtered, and concentrated in vacuo. Analysis of the crude reaction mixture by ^{1}H and ^{13}C NMR showed that **22** had been completely consumed and **16** remained unreacted. A small amount of **32** was also detected. The crude material was purified by flash chromatography on silica gel using ethyl acetate/hexanes as the eluant (60% to 80%) to afford 2 mg (10%) of **32** and 24 mg (73%) of the hydrotrifluoromethanesulfonate salt of **16**.

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Supporting Information Available: Characterization data for compounds **20**−**29** and **32**−**35**, tables of NOE data, and copies of ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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