Asymmetric Formation of Quaternary Centers through Aza-Annulation of Chiral β-Enamino Esters with Acrylate Derivatives

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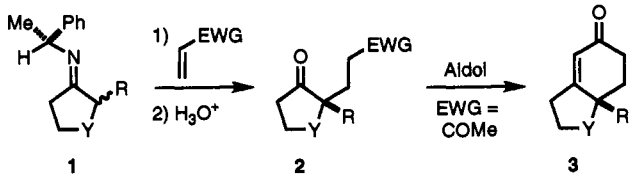
Abstract: The aza-annulation of β-enamino ester substrates with acrylate derivatives was used for the stereoselective formation of quaternary carbon centers. Tetrasubstituted secondary enamines, in which the enamine tautomer was stabilized through conjugation with an ester carbonyl, were generated from the optically active primary amine (*R*)-α-phenethylamine and the α-amino esters of L-valine and (*R*)-phenylglycine. Treatment of the enamine with either acryloyl chloride or sodium acrylate/ethyl chloroformate resulted in aza-annulation to give the corresponding δ-lactam with high diastereoselectivity (>84% de). The effects of reaction temperature, solvent, and acrylate reagent on the stereoselectivity of this reaction were examined. Aza-annulation with crotonyl chloride resulted in concomitant formation of two vicinal stereogenic centers with >97% stereoselectivity. Quaternary carbon centers were formed stereoselectively during aza-annulation with α-substituted acrylate derivatives, but poor selectivity was observed for generation of the stereogenic center α to the lactam carbonyl.

Introduction

Quaternary carbon centers are found in a wide range of naturally occurring compounds, and this structural feature presents a number of synthetic challenges.[1] A variety of methods have been established to prepare these species, and the enantioselective formation of quaternary stereogenic centers has led to a higher level of synthetic accomplishment.[2] One method commonly employed for carbon–carbon bond formation, the Michael addition, has been investigated for this purpose.

Conjugate addition of chiral imines to electron-deficient alkenes has produced excellent results in the stereoselective generation of quaternary centers, in which this "deracemizing alkylation" occurred through the more substituted enamine tautomer of **1** (Scheme 1).[3] Substrate studies have included carbocyclic (**1**: Y = CH_2,[4] $(CH_2)_2$,[5] and Ar[6]) and heterocyclic imines (**1**: Y = O,[7] CH_2NMe,[8] and CH_2S[9]) in which R = Me, Et, OMe, or CH_2CO_2R'. Excellent stereoselectivity in the formation of **2** resulted from this sequence of reactions (typically 85–97% ee), and the electron-deficient alkenes used for this reaction have included methyl acrylate,[4,5b,8] vinyl ketones,[5,6,8,9] acrylonitrile,[8] and phenyl vinyl sulfone.[4a] In the case of methyl vinyl ketone, subsequent condensation resulted in formation of the Robinson annulation product **3**.[5,6] Similarly, asymmetric formation of heterocyclic lactams has been reported for the reaction of **1** (R = Me, Y = $(CH_2)_2$) with crotonyl cyanide[10] and a β-tetralone substrate with acryloyl chloride.[11]

Scheme 1. Asymmetric Michael Addition Reactions



When the chiral secondary enamine was stabilized through further conjugation with an electron-withdrawing group (**1**: R = CO_2R' or COR'), the substrate was significantly less reactive toward conjugate addition. Although the use of alkylidene malonates resulted in stereoselective product formation in good yields, typical Michael acceptors required extended reaction times or the addition of activating agents.[12] As a result, the asymmetric Michael addition of β-enamino esters to alkyl acrylates,[13] methyl vinyl ketone,[13] acrylonitrile,[14] and phenyl vinyl sulfone[15] has been accelerated through the use of high pressure, Lewis acids ($MgBr_2$, $ZnCl_2$, $SnCl_4$, or $Et_2O{\cdot}BF_3$), or TMSCl.

A general synthesis of δ-lactam products (**6**) with stereoselective introduction of asymmetry at C-5 is described. In these studies, deracemization of the β-keto ester substrate **4** was accomplished through asymmetric β-enamino ester formation (**5**) and aza-

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Scheme 2. General Strategy for Asymmetric Aza-Annulation Reactions

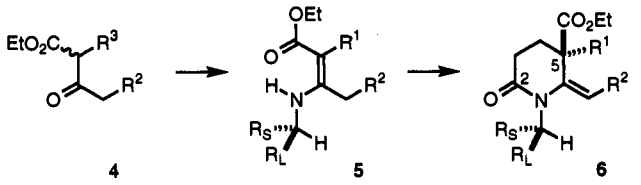
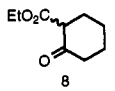
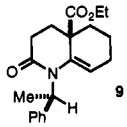
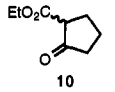
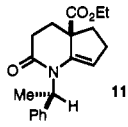
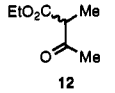
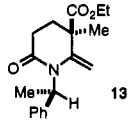
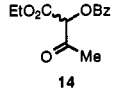
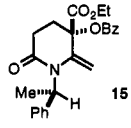
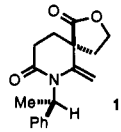


Table 1. Effect of Substrate Variation on Asymmetric Induction[a]

substrate	product	diastereomer ratio[b]	yield[c]
 8	 9	>97:3	85
 10	 11	97:3	76
 12	 13	97:3	92
 14	 15	92:8	58
 16	 17	94:6	80

[a] Reaction conditions: (i) (*R*)-PhCHMeNH$_2$ ((*R*)-**7**), Et$_2$O·BF$_3$, benzene, reflux; (ii) acryloyl chloride, THF, reflux. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Yield (%) of the diastereomeric mixture after chromatography.

annulation to generate the corresponding δ-lactam product **6** (Scheme 2). On the basis of our studies with achiral imine[16] and β-enamino carbonyl substrates,[17] as well as the use of this methodology in the synthesis of natural products,[18] three different classes of acrylate derivatives were utilized. Acryloyl chloride, acrylic acid anhydride, and mixed acrylic anhydride reagents were employed for aza-annulation with asymmetric β-enamino esters. Through this process, the heterocyclic framework for more complex bioactive compounds such as natural product targets or synthetic peptide mimetics is established.

Results and Discussion

Acrylate Derivatives. Efficient formation of δ-lactam products resulted from annulation of enamines derived from a variety of β-keto esters and (*R*)-phenethylamine (**7**) (Table 1). Optimum results were obtained with the use of Et$_2$O·BF$_3$ to promote enamine formation without the generation of amide byproducts.[12] Following enamine formation, the Et$_2$O·BF$_3$ was quenched through aqueous workup. Subsequent treatment of the enamine with acryloyl chloride resulted in the stereoselective formation of δ-lactam products.

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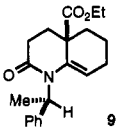
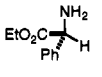
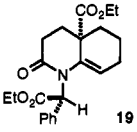
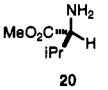
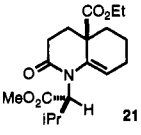
Table 2. Effects of the Chiral Auxiliary on Asymmetric Induction upon Condensation and Aza-Annulation with **8**[a]

amine	product	diastereomer ratio[b]	yield[c]
 7	 9	>97:3	85
 18	 19	79:21	63
 20	 21	57:43	43

[a] Reaction conditions: (i) 1° amine, Et$_2$O·BF$_3$, benzene, reflux; (ii) acryloyl chloride, THF, reflux. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Yield (%) of the diastereomeric mixture after chromatography.

The cyclic β-keto ester substrate **8** was converted to diastereomer **9** in 85% yield for the two-step enamine formation/aza-annulation procedure. The quaternary center was generated with >97:3 diastereoselectivity, and stereochemical assignment was based on comparison with the analogous Michael addition reaction products.[13-15] Similarly, aza-annulation with the five-membered ring analog **10** gave **11** with excellent stereoselectivity. In contrast to analogous Michael addition reactions, aza-annulation reactions with β-enamino esters did not require the use of Lewis acid catalysts or elevated pressure. Heterocycle formation was typically complete within 4–6 h with comparable product selectivity.

An important feature for effective 1,4 asymmetric induction during the annulation reaction is the geometry of the intermediate β-enamino ester. Although substrates **8** and **10** were restricted to a single enamine geometry, the acyclic substrates **12**, **14**, and **16** could form either of two possible geometric isomers. However, in these examples, the intramolecular hydrogen bonding of the enamine hydrogen with the ester carbonyl served to produce selective formation of the *Z* enamine isomer **5**. As a result, annulation was highly stereoselective for each substrate studied. With the exception of **15**, in which the tertiary allylic ester displayed sensitivity to reaction conditions and isolation procedures, product yields were an accurate reflection of reaction efficiency.

As found in the asymmetric Michael addition studies, phenyl and isopropyl groups have been optimum substituents for effective chiral auxiliaries. However, in this study, any variation from the use of **7** led to significant losses in the stereoselectivity of product formation (Table 2). Product selectivity decreased (79:21) with the use of **18**, and asymmetric induction was even lower when the valine derivative **20** was employed as the chiral auxiliary. Although the initial results obtained for the reaction of **18** with **8** were not outstanding, this system was well suited for study of the relationship between reaction conditions and product distribution.

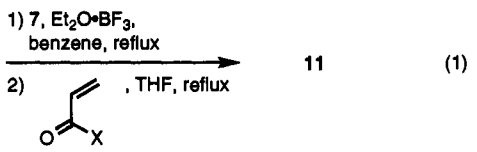
Whereas the stereoselectivity of the asymmetric Michael additions was unaffected by reaction temperature,[4a] the ratio of diastereomers obtained for the conversion of **8** to **19** was temperature dependent (Table 3). The product ratio increased to 93:7 when the aza-annulation reaction was performed at 0 °C, and a ratio of 98:2 was obtained at a reaction temperature of −33 °C. In each case, a decrease in reaction temperature also resulted

Table 3. Temperature Effects on Asymmetric Induction and Reaction Yield for Conversion of **8** to **19**[a]

solvent	*T*, °C	diastereomer ratio[b]	yield[c]
THF	−33	98:2	77
THF	0	93:7	68
dioxane	0	92:8	24
THF	66	79:21	63
dioxane	66	82:18	43
dioxane	101	36:64	28

[a] Reaction conditions: (i) (*R*)-**18**, **8**, $Et_2O{\cdot}BF_3$, benzene, reflux; (ii) acryloyl chloride. [b] Determined by ^1H NMR of the crude reaction mixture. [c] Yield (%) of the diastereomeric mixture **19** after chromatography.

Table 4. Dependence of the Aza-Annulation of **10** to **11** on the Acrylate Reagent



(1)

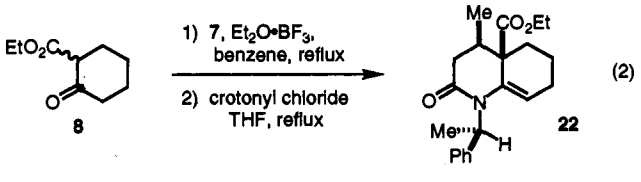
reagent -X	diastereomer ratio[a]	yield[b]
-Cl	97:3	64
$-O_2CCH{=}CH_2$	90:10	75
$-OCO_2Et$	90:10	87

[a] Determined by ^1H NMR of the crude reaction mixture. [b] Yield (%) of the diastereomeric mixture **11** after chromatography.

in increased product yields. In order to examine the reaction at a higher temperature, dioxane was used as the solvent. Although only minor solvent effects on the diastereomer ratio were observed at 66 °C, the use of dioxane produced a substantial decrease in product yield. Even lower yields were observed with dioxane at both room temperature and reflux. The reversed product ratio at high temperatures could have resulted from either diastereoselective product decomposition or epimerization of the chiral auxiliary due to the HCl generated as a reaction product.

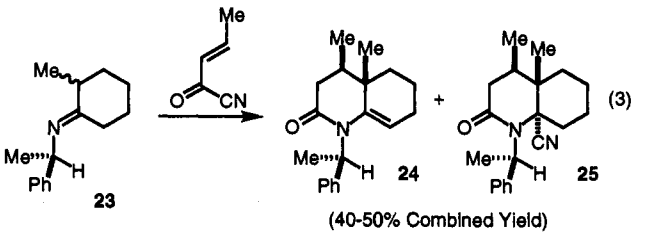
The efficiency of aza-annulation can also be improved through reagent selection (eq 1, Table 4). Although acryloyl chloride was the most convenient reagent, HCl generated during the reaction can adversely affect product yields or selectivity in some cases. In the two-step condensation/aza-annulation of **10** to **11**, a moderate yield was obtained with acryloyl chloride (eq 1). However, through the use of anhydride reagents, which produced optimum results for aza-annulation with imine substrates,[16] significant improvements in the yield of **11** were obtained. The use of acrylic anhydride increased the yield to 75%. Similarly, annulation with the mixed anhydride, formed by activation of sodium acrylate with $EtCO_2Cl$, gave an 87% yield of **11**. Interestingly, a decrease in diastereoselectivity accompanied the use of these anhydride reagents.

Substituted Acrylate Derivatives. Annulation with substituted acrylate derivatives was utilized for examination of the concomitant formation of two stereogenic centers. Due to increased steric hindrance at the β-position, aza-annulation of the enamine derived from **8** with crotonyl chloride was significantly slower than the reaction observed with acryloyl chloride (eq 2).



(2)

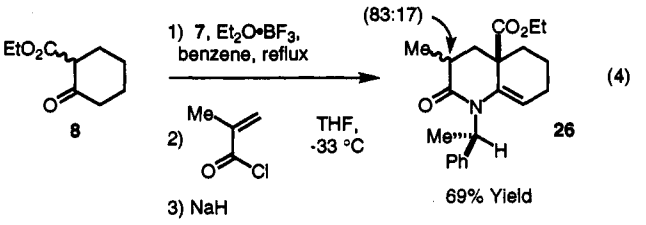
Condensation of **8** with **7**, followed by treatment with 6.0 equiv of crotonyl chloride in THF, required 48 h at reflux for complete consumption of **8** and resulted in only 45% yield (≈90% pure) of the corresponding aza-annulation product **22**. The primary impurities in the reaction mixture were crotonate-derived byproducts, including MeHC=CHCONHCHMePh. Further purification of the reaction mixture gave a 30% yield of products in a 94:4:2 ratio of stereoisomers. The major product was assigned the stereochemistry of **22** on the basis of comparison of spectral data reported for **24**, formed by the analogous aza-annulation reaction with **23** (eq 3).[10]



(3)
(40-50% Combined Yield)

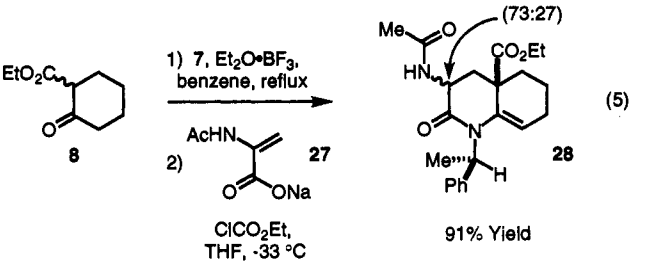
Chemical shifts and coupling constants for the protons α to the lactam carbonyl in **22** (2.25 ppm (dd, J = 18.1, 12.7 Hz), 2.65 ppm (dd, J = 18.1, 5.7 Hz)) were in complete agreement with those of **24** (2.28 ppm (dd, J = 18.5, 12.3 Hz), 2.66 ppm (dd, J = 18.5, 6.4 Hz)). The use of sodium crotonate/EtO_2CCl for annulation did not result in measurable product formation.

Aza-annulation of **8** with α-substituted acrylate derivatives gave a mixture of products. Condensation of **8** with **7** followed by treatment of the resulting enamine with methacryloyl chloride gave **26**, an inseparable mixture (52:48) of diastereomers (eq 4). This isomeric mixture represented the diastereomeric ratio of products epimeric at the position α to the lactam carbonyl. Treatment of **26** with NaH in THF at ambient temperature produced an equilibrium mixture of stereoisomers (83:17).



(4)

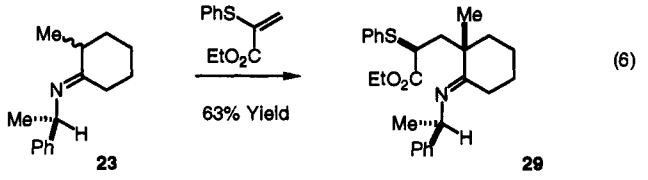
A somewhat more complex product mixture was obtained when the enamine prepared from **8** was treated with the mixed anhydride generated from **27** and $ClCO_2Et$ (eq 5).



(5)

In this case, a 64:23:9:4 mixture of products (**28**) was obtained, which could be separated by silica gel chromatography to give a pair of two-isomer mixtures. The first fraction contained the isomers which were present as 64 and 9% of the original mixture, while the second fraction was composed of the isomers that contributed to 23 and 4% of the initial product mixture. The mixture of stereoisomers was believed to reflect (1) the epimers at C-2 ([64 + 9]:[23 + 4] or 73:27), similar to the selectivity observed for formation of **26** (83:17), and (2) incomplete asymmetric induction at the quaternary center ([64 + 23]:[9 + 4] or 87:13). The 87:13 ratio obtained for stereoselective generation of the quaternary center was comparable to the 90:10 selectivity observed for aza-annulation of **10** with the mixed

anhydride method (Table 4). Treatment of the original mixture of four isomers with NaH under the conditions used to epimerize **26** resulted primarily in the slow disappearance of all four isomers. The results observed for formation of **26** and **28** are in contrast to the high selectivity at the α position obtained for Michael addition of α-(phenylthio)acrylate with **23** to give **29** (eq 6).[10]



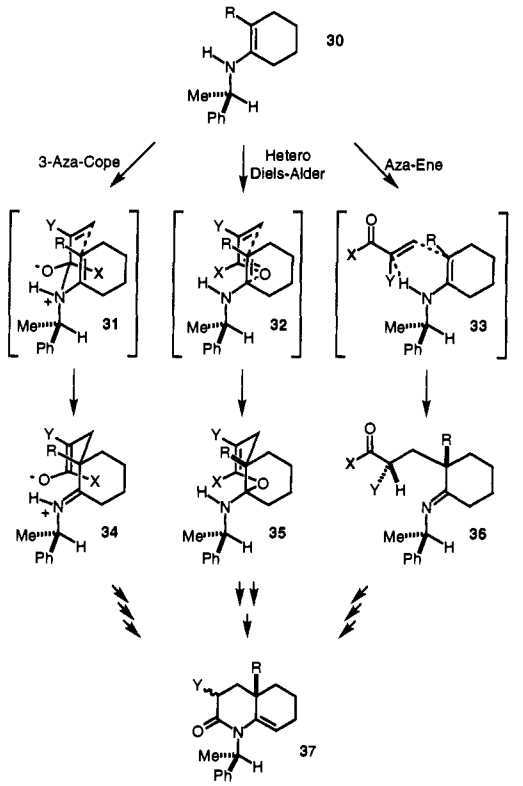
(6)

Mechanistic Implications. There are several possible explanations for the high stereoselectivity obtained for the Michael addition of acrylate derivatives to imine **1** (Scheme 1). Of initial importance is the facial selectivity at the asymmetric β-enamino ester. The favored rotational isomer is illustrated as **5**, in which the H–N is syn to the enamine and the H of the stereogenic center is oriented toward the CH_2 unit of the ketone substrate.[3,8,19] In this conformation, the larger phenyl substituent (R_L) blocks one face of the β-enamino ester, and selective approach of the acrylate occurs from the least hindered face of the enamine.

In order explain the magnitude of the asymmetric induction and the high stereochemical control of the Michael addition to imine substrate **30**, a variety of concerted six-membered ring transition states have been proposed. These mechanistic pathways include (1) a 3-aza-Cope-type rearrangement, in which there is an initial interaction with the carbonyl carbon (**31**) to control facial selectivity followed by formation of the Michael adduct **34** or the corresponding ketene,[10,19,20] (2) a hetero Diels–Alder reaction that involves an interaction of the carbonyl oxygen (**32**) to provide stereochemical control through formation of intermediate **35**, which would eventually break down and cyclize to **37**,[9] or (3) an aza-ene reaction for carbon–carbon bond formation concomitant with stereoselective hydrogen transfer (**33**) to give **36**.[4a,8,10,12b] The ene mechanism has been particularly useful in rationalizing the high asymmetric induction of a substituent α to the acrylate derivative obtained for generation of the Michael addition adduct **29** (eq 6).

Due to the similar nature of the Michael addition reaction and aza-annulation, the generalized mechanistic pathways illustrated in Scheme 3 are also applicable for explanation of the high degree of stereoselectivity observed for the aza-annulation reaction. However, there are a number of differences in the features of the aza-annulation reaction with β-enamino esters that suggest possible formation of intermediates other than those produced through Michael addition. One observation is the significantly lower reactivity of the β-enamino ester substrates[12] toward acrylate ester, sulfonyl, and nitrile derivatives relative to the rapid and efficient aza-annulation observed with these same substrates. Another obvious deviation from the results reported for Michael addition of the imine substrates (eq 6) was the lack of stereoselectivity obtained at a stereogenic center α to the acrylate derivative in the formation of **26** (eq 4) and **28** (eq 5). In addition, the stereoselectivity observed for carbon–carbon bond formation is dependent on both temperature[4a] and acrylate reagent[21] in the case of the aza-annulation reaction, which is in direct contrast to the Michael addition reactions. As a result of these observations, strong evidence for an ene-type transition state does not exist in the case of the aza-annulation reaction, and the distinctive features of the annulation reaction provide additional support for

Scheme 3. Potential Transition States for Asymmetric Induction in the Aza-Annulation of Enamines with Electron-Deficient Alkenes



mechanisms which differ from the aza-ene-type carbon–carbon bond formation.

Due to the differences observed between Michael addition and aza-annulation reactions, the 3-aza-Cope (**31**) and hetero Diels–Alder (**32**) type pathways are plausible mechanistic alternatives. Such models can be used to account for the greater overall reactivity, temperature dependence, and slight acrylate dependence observed in these aza-annulation studies. In addition, pathways in which equilibration occurs α to the lactam carbonyl can be used to explain the generation of epimeric products.

The aza-annulation reaction exhibits a number of synthetically valuable features for the formation of carbon–carbon bonds. The use of activated acrylic acid reagents significantly accelerated bond formation at the β carbon of the acrylate derivative for aza-annulation with β-enamino ester substrates. When chiral tetrasubstituted enamines were treated with the acryloyl chloride, high asymmetric induction was observed (84–96% de) in the generation of a quaternary stereogenic center. These products are potentially valuable intermediates for the synthesis of a variety of naturally occurring alkaloids. In addition, the δ-lactam products of this aza-annulation reaction are conformationally restricted β-amino esters,[17] and we are currently exploring their potential as peptidomimetic molecules.

Experimental Section

General Methods. All reactions were carried out by performing standard inert atmosphere techniques to exclude moisture and oxygen, and reactions were performed under an atmosphere of nitrogen. Acryloyl chloride was purchased from Fluka and used without purification. Azeotropic removal of H_2O was assisted by the use of 4-Å molecular sieves.[22] Concentration of solutions after workup was performed by rotary evaporation.

(19) Hickmott, P. W.; Sheppard, G. *J. Chem. Soc. C* **1971**, 2112.
(20) Sevin, A.; Tortajada, J.; Pfau, M. *J. Org. Chem.* **1986**, *51*, 2671.
(21) The stereoselectivity of the Michael addition with imine substrates **1** was independent of the type of electron-deficient alkene used (vinyl sulfone, methyl acrylate, and *tert*-butyl acrylate).[4a]

(22) Dehydration of condensation reactions was performed with the use of a modified Dean–Stark apparatus in which the cooled distillate was passed through 4-Å molecular sieves prior to return of the solvent to the reaction mixture. Barta, N. S.; Paulvannan, K.; Schwarz, J. B.; Stille, J. R. *Synth. Commun.* **1994**, *24*, 583.

NMR spectra were obtained on a Varian Gemini 300 instrument with $CDCl_3$ as the solvent. ^1H NMR spectral data are reported as follows: chemical shifts relative to residual $CHCl_3$ (7.24 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, b = broad), coupling, and integration. ^{13}C signals are reported in ppm relative to $CDCl_3$ (77.0 ppm).

General Procedure for Et_2O-BF_3-Catalyzed Enamine Formation ((*R*)-7).[12,23] The β-keto ester (3.0 mmol) was combined with **7** (3.3 mmol) in benzene (23 mL), and Et_2O-BF_3 (0.15 mmol) was added at room temperature. The flask was fitted with a modified Dean–Stark trap filled with 4-Å molecular sieves, and the mixture was heated at reflux until the reaction was complete as determined by NMR analysis (6–18 h). The enamino ester was then washed with saturated aqueous $NaHCO_3$ (15 mL), the aqueous layer was extracted with Et_2O (15 mL), and the combined organic layers were washed with saturated aqueous NaCl. The organic fractions were then dried ($MgSO_4$), concentrated, taken up in THF[24] (20 mL), and carried on without further purification.

General Procedure for Et_2O-BF_3-Catalyzed Enamine Formation (Amino Acid Ester Salts).[12,23] The amino acid ester salt (9.0 mmol) was suspended in benzene (13 mL) and washed with saturated aqueous $NaHCO_3$. After the aqueous layer was washed with benzene (10 mL), the benzene layers were combined, washed with saturated aqueous NaCl, and dried ($MgSO_4$). The benzene solution was then decanted into the flask containing the β-keto ester (3.0 mmol), and Et_2O-BF_3 (0.2 mL) was then added. Enamine formation was carried out as described for **7**.

General Procedure for Aza-Annulation of Enamines (Acid Chloride Method). The acid chloride (3.9 mmol) was added to a solution of the corresponding enamine in THF (20 mL, *vide supra*). The reaction was stirred at the appropriate temperature until complete as indicated by NMR analysis of a sample quenched with saturated aqueous $NaHCO_3$ and dried with $MgSO_4$. When the reaction was complete, the mixture was stirred with 10 mL of 10% NaOH and then extracted with Et_2O (3 × 10 mL). The organic extracts were combined and washed with saturated aqueous NaCl, dried ($MgSO_4$), concentrated, and purified by column chromatography.

General Procedure for Aza-Annulation of Enamines (Anhydride Method). Sodium acrylate (5.1 mmol) was suspended in THF (10 mL) and was treated with acryloyl chloride (0.31 mL, 3.9 mmol) or ethyl chloroformate (3.9 mmol), and the mixture was stirred at room temperature for 1 h. The mixture containing the anhydride was then transferred *via* cannula to a solution of the β-enamino ester in THF (10 mL), and the mixture was stirred at the appropriate temperature until the reaction was complete. Workup conditions were as described for the acid chloride reactions.

9: 60:40 Et_2O:petroleum ether, 0.83 g, 2.55 mmol, 85% yield; $[\alpha]_D$ = −115.2° (*c* = 1.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ1.28 (t, *J* = 7.1 Hz, 3 H), 1.45–1.65 (m, 2 H), 1.70–1.82 (m, 2 H), 1.72 (d, *J* = 7.1 Hz, 3 H), 1.93 (m, 1 H), 2.11 (m, 1 H), 2.22 (m, 1 H), 2.34 (ddd, *J* = 13.1, 6.5, 2.1 Hz, 1 H), 2.53 (ddd, *J* = 18.4, 12.3, 6.4 Hz, 1 H), 2.68 (ddd, *J* = 18.4, 6.5, 2.1 Hz, 1 H), 4.13–4.28 (m, 2 H), 5.02 (dd, *J* = 5.4, 3.0 Hz, 1 H), 6.35 (q, *J* = 6.9 Hz, 1 H), 7.17–7.36 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 14.7, 18.4, 24.4, 30.3, 30.9, 35.4, 46.5, 50.5, 61.2, 112.2, 125.5, 126.2, 128.4, 133.7, 142.3, 168.8, 174.3; IR (film) 3056, 2986, 2920, 1725, 1669, 1636, 1285, 741 cm^{-1}; HRMS calcd for $C_{20}H_{25}NO_3$ *m/z* 327.1834, obsd *m/z* 327.1833.

11: 70:30 Et_2O:petroleum ether, 0.71 g, 2.28 mmol, 76% yield; $[\alpha]_D$ = −15.8° (*c* = 5.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, *J* = 7.1 Hz, 3 H), 1.60–1.78 (m, 2 H), 1.62 (d, *J* = 7.1 Hz, 3 H), 2.12 (ddt, *J* = 15.3, 9.0, 3.2 Hz, 1 H), 2.24 (dd, *J* = 12.9, 7.6 Hz, 1 H), 2.34 (m, 1 H), 2.44 (m, 1 H), 2.51–2.69 (m, 3 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 4.63 (t, *J* = 2.8 Hz, 1 H), 6.22 (q, *J* = 7.1 Hz, 1 H), 7.12–7.30 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 14.2, 29.5, 30.3, 30.6, 35.7, 50.0, 55.2, 61.2, 110.4, 126.0, 126.6, 128.3, 137.9, 141.0, 169.0, 174.2; IR (film) 3056, 2986, 2942, 2857, 1725, 1667, 1636, 1379, 1265, 741, 704 cm^{-1}; HRMS calcd for $C_{19}H_{23}NO_3$ *m/z* 313.1677, obsd *m/z* 313.1662.

13: 60:40 Et_2O:petroleum ether, 0.84 g, 2.76 mmol, 92% yield; $[\alpha]_D$ = −55.2° (*c* = 3.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.1 Hz, 3 H), 1.40 (s, 3 H), 1.43 (s, 3 H, minor isomer), 1.67 (d, *J* = 7.1 Hz, 3 H), 1.67–1.76 (m, 1 H), 2.34 (ddd, *J* = 13.4, 6.9, 4.4, Hz, 1 H), 2.60 (ddd, *J* = 18.3, 6.9, 4.1 Hz, 1 H), 2.73 (ddd, *J* = 18.3, 10.2, 6.9 Hz, 1 H), 4.09–4.20 (m, 2 H), 4.36 (d, *J* = 1.9 Hz, 1 H), 4.43 (d, *J* = 1.9 Hz, 1 H, minor isomer), 4.46 (d, *J* = 1.9 Hz, 1 H, minor isomer), 4.51 (d, *J* = 1.9 Hz, 1 H), 6.22 (q, *J* = 7.1 Hz, 1 H), 7.15–7.35 (m, 5 H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 13.6, 14.1, 23.6, 29.7, 29.8, 46.8, 50.8, 60.9, 98.1, 125.4, 126.0, 127.9, 141.4, 143.7, 169.2, 173.5; IR (film) 3063, 3032, 2982, 2942, 1728, 1667, 1628, 1449, 1381, 1356, 911, 734, 700 cm^{-1}; HRMS calcd for $C_{18}H_{23}NO_3$ *m/z* 301.1678, obsd *m/z* 301.1686.

15: 90:10 Et_2O:petroleum ether, 0.71 g, 1.74 mmol, 58% yield; $[\alpha]_D$ = +74.6° (*c* = 6.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.1 Hz, 3 H), 1.60 (d, *J* = 7.1 Hz, 2 H), 2.45 (tdd, *J* = 13.9, 4.8, 1.1 Hz, 1 H), 2.58 (td, *J* = 10.5, 6.4 Hz, 1 H), 2.73 (tdd, *J* = 1.1, 5.9, 16.0 Hz, 1 H), 2.94 (ddd, *J* = 16.0, 10.2, 5.9 Hz, 1 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 4.63 (m, 1 H, minor isomer), 4.65 (d, *J* = 1.9 Hz, 1 H), 4.81 (d, *J* = 1.9 Hz, 1 H, minor isomer), 5.13 (d, *J* = 1.9 Hz, 1 H), 6.11 (q, *J* = 7.1 Hz, 1 H), 7.21–7.62 (m, 8 H), 8.02 (dd, *J* = 8.4, 1.2 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 15.0, 27.2, 29.5, 51.7, 62.2, 80.5, 102.9, 126.3, 126.9, 128.5, 128.6, 129.3, 129.7, 133.6, 139.5, 141.2, 165.1, 168.6, 170.2; IR (film) 3056, 2988, 1745, 1727, 1680, 1634, 1265, 738, 706 cm^{-1}; HRMS calcd for $C_{24}H_{25}NO_5$ *m/z* 407.1733, obsd *m/z* 407.1736.

17: 70:30 Et_2O:petroleum ether, 0.68 g, 2.40 mmol, 80% yield; $[\alpha]_D$ = +74.4° (*c* = 3.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (d, *J* = 6.9 Hz, 1 H, minor isomer), 1.74 (d, *J* = 7.2 Hz, 3 H), 1.80 (ddd, *J* = 13.3, 6.4, 4.4 Hz, 1 H), 2.17 (ddd, *J* = 12.9, 9.5, 8.2 Hz, 1 H), 2.35 (dtd, *J* = 12.9, 6.5, 2.5 Hz, 2 H), 2.59 (ddd, *J* = 17.5, 10.5, 6.6 Hz, 1 H), 2.83 (ddd, *J* = 17.5, 6.6, 4.5 Hz, 1 H), 3.98 (td, *J* = 9.5, 6.6 Hz, 1 H), 4.28 (d, *J* = 3.0 Hz, 1 H), 4.30 (td, *J* = 9.5, 2.8 Hz, 1 H), 4.51 (d, *J* = 3.0 Hz, 1 H), 5.08 (q, *J* = 7.0 Hz, 1 H, minor isomer), 6.17 (q, *J* = 7.4 Hz, 1 H), 7.20–7.40 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 28.2, 29.5, 34.3, 48.5, 52.4, 65.2, 98.4, 126.5, 127.0, 128.4, 140.2, 140.6, 168.8, 176.6; IR (film) 3056, 2988, 2800, 1717, 1690, 1422, 1265, 739, 706 cm^{-1}; HRMS calcd for $C_{17}H_{19}NO_3$ *m/z* 285.1365, obsd *m/z* 285.1370.

19: 70:30 Et_2O:petroleum ether, 0.73 g, 1.89 mmol, 63% yield; $[\alpha]_D$ = +106.4° (*c* = 3.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (t, *J* = 7.1 Hz, 3 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 1.16–1.32 (m, 1 H), 1.33–1.56 (m, 1 H), 1.57–1.70 (m, 1 H), 1.78 (td, *J* = 12.0, 6.3 Hz, 1 H), 2.05–2.18 (m, 2 H), 2.21–2.33 (m, 2 H), 2.45 (ddd, *J* = 18.1, 11.9, 5.9 Hz, 2 H), 2.56 (ddd, *J* = 18.1, 6.3, 2.7 Hz, 2 H), 3.89–4.11 (m, 2 H), 4.22 (q, *J* = 7.1 Hz, 2 H), 5.05 (m, 1 H, minor isomer), 5.25 (dd, *J* = 4.4, 3.6 Hz, 1 H), 5.45 (s, 1 H, minor isomer), 5.79 (s, 1 H), 7.20–7.40 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 18.3, 24.1, 30.2, 30.5, 34.8, 46.5, 61.1, 61.3, 109.0, 127.4, 127.7, 128.7, 134.5, 136.4, 168.5, 169.1, 173.7; IR (film) 3058, 2982, 2938, 2872, 1727, 1673, 1645, 1453, 1401, 1267, 1202, 1028, 738, 704 cm^{-1}; HRMS calcd for $C_{22}H_{27}NO_5$ *m/z* 385.1889, obsd *m/z* 385.1916.

21: 70:30 Et_2O:petroleum ether, 0.44 g, 1.29 mmol, 43% yield, 57:43 ratio of diastereomers; ^1H NMR (300 MHz, $CDCl_3$) (characteristic peaks for both isomers) δ 0.78 (d, *J* = 7.0 Hz, 3 H, minor), 0.85 (d, *J* = 7.0 Hz, 3 H, major), 1.10 (d, *J* = 6.4 Hz, 3 H, minor), 1.61 (d, *J* = 6.4 Hz, 3 H, major), 3.63 (s, 3 H, major), 3.67 (s, 3 H, minor), 5.17 (dd, *J* = 3.1, 1.5 Hz, 1 H, major), 5.31 (dd, *J* = 3.1, 1.5 Hz, 1 H, minor); ^{13}C NMR (75 MHz, $CDCl_3$) (both isomers) δ 14.0, 14.1, 18.2, 18.4, 18.6, 18.7, 21.9, 22.1, 24.1, 24.3, 26.8, 28.5, 29.9, 30.1, 30.3, 30.5, 35.2, 46.5, 46.6, 51.8, 51.9, 61.1, 61.3, 61.8, 61.9, 76.5, 77.0, 77.1, 77.4, 107.6, 107.8, 136.6, 168.4, 168.7, 171.2, 173.7; IR (film) 3056, 2953, 2874, 2843, 1730, 1669, 1642, 1265, 1215, 1024, 745, 704 cm^{-1}; HRMS calcd for $C_{18}H_{27}NO_5$ *m/z* 337.1888, obsd *m/z* 337.1888.

22: 60:40 Et_2O:petroleum ether, 0.44 g, 1.29 mmol, 43% yield; $[\alpha]_D$ = −70.9° (*c* = 1.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (d, *J* = 6.8 Hz, 3 H), 1.2 (d, *J* = 7.1 Hz, 3 H), 1.60 (d, *J* = 7.1 Hz, 3 H), 1.73–1.89 (m, 2 H), 1.92–2.54 (m, 2 H), 2.25 (dd, *J* = 18.1, 12.7 Hz, 1 H), 2.51 (m, 1 H), 2.65 (dd, *J* = 18.1, 5.7 Hz, 1 H), 4.00–4.20 (m, 2 H), 4.90 (dd, *J* = 5.5, 2.8 Hz, 1 H), 6.44 (q, *J* = 6.8 Hz, 1 H), 7.10–7.30 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 15.3, 18.7, 24.4, 32.8, 36.1, 38.5, 49.2, 49.8, 60.7, 112.2, 125.3, 126.0, 128.0, 128.2, 133.9, 142.2, 168.7, 172.1; IR (film) 3056, 2986, 2944, 1721, 1665, 1634, 1265, 911, 738, 708 cm^{-1}; HRMS calcd for $C_{21}H_{27}NO_3$ *m/z* 341.1991, obsd *m/z* 341.1989.

26: 60:40 Et_2O petroleum ether, 0.65 g, 1.89 mmol, 63% yield; ^1H NMR (300 MHz, $CDCl_3$) (characteristic peaks both isomers) δ 1.61 (d, *J* = 7.3 Hz, 0.96 H), 1.67 (d, *J* = 7.1 Hz, 2.04 H), 4.95 (dd, *J* = 5.4, 2.9 Hz, 0.68 H), 5.17 (t, *J* = 3.9 Hz, 0.32 H), 5.90 (q, *J* = 7.2 Hz, 0.32 H), 6.26 (q, *J* = 7.3 Hz, 0.68 H); ^{13}C NMR (75 MHz, $CDCl_3$) (both isomers) δ 14.0, 14.1, 14.5, 15.4, 16.1, 18.3, 18.6, 23.9, 24.3, 34.5, 34.7, 34.9, 35.4, 38.2, 38.6, 40.0, 46.3, 47.4, 50.7, 52.5, 60.9, 61.1, 110.8, 117.5, 125.6, 125.8, 125.9, 126.1, 128.1, 134.4, 134.6, 142.3, 142.9, 171.9, 173.8, 174.4, 174.8; IR (film) 3056, 2986, 2941, 1725, 1675, 1636, 1448,

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(24) Dioxane was substituted here in the reactions indicated in Table 3.

1265, 748, 704 cm^{-1}; HRMS calcd for $C_{21}H_{27}NO_3$ *m/z* 341.1991, obsd *m/z* 341.1982.

28: solvent gradient, 70:30 EtOAc:CH_2Cl_2–100% EtOAc, 1.01 g, 2.73 mmol, 91% yield; ^1H NMR (300 MHz, $CDCl_3$) (characteristic peaks for four isomers) δ 4.78 (q, J = 7.1 Hz, 0.04 H), 5.08 (dd, J = 2.8, 5.3 Hz, 0.64 H), 5.21 (t, J = 3.8 Hz, 0.09 H), 5.33 (t, J = 4.0 Hz, 0.23 H), 5.40 (q, J = 7.0 Hz, 0.09 H), 5.63 (t, J = 3.7 Hz, 0.04 H), 5.72 (q, J = 7.1 Hz, 0.23 H), 6.00 (q, J = 7.1 Hz, 0.64 H), 6.60 (d, J = 5.6 Hz, 0.09 H), 6.68 (d, J = 5.5 Hz, 0.68 H, two isomers), 6.72 (q, J = 5.8 Hz, 0.23 H); ^{13}C NMR (75 MHz, $CDCl_3$) (all isomers) δ 13.9, 14.0, 14.1, 15.1, 15.2, 16.6, 17.8, 18.0, 18.1, 18.3, 18.9, 19.8, 23.0, 23.1, 24.0, 24.1, 24.3, 33.8, 34.1, 34.8, 35.0, 36.6, 36.9, 37.0, 46.3, 46.6, 46.9, 48.6, 49.9, 52.7, 54.1, 57.5, 61.1, 61.3, 61.5, 110.4, 111.6, 121.1, 125.6, 125.8, 126.2, 126.3, 126.9, 128.2, 128.3, 128.4, 133.3, 133.7, 141.3, 141.6, 142.0, 166.5, 168.0, 169.9, 170.1, 170.3, 173.7, 174.2; IR (film) 3056, 2986, 2944, 1725, 1669, 1644, 1265, 740, 704 cm^{-1}; HRMS calcd for $C_{22}H_{28}NO_4$ *m/z* 370.2019, obsd *m/z* 370.2082.

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Supplementary Material Available: Copies of ^1H spectra of all compounds in the Experimental Section (10 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.