Dualistic Reactivity of Lithium and Zinc Dienolates with Imines: Effects of Counterion, Temperature, and Substituents on α- and γ-Coupling

Hendrik L. van Maanen,† Henk Kleijn,† Johann T. B. H. Jastrzebski,† Miles T. Lakin,‡ Anthony L. Spek,‡,§ and Gerard van Koten*,†

Debye Institute, Department of Metal-Mediated Synthesis, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands, and Bijvoet Center for Biomolecular Research, Department of Crystal and Structural Chemistry, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands

Received July 11, 1994®

Lithium and zinc dienolates of 3-butenoic, 3-methyl-2-butenoic, 3-pentenoic, and 4-phenyl-3-butenoic methyl esters are reacted with imines $R^1C(H)=NR^2$[**3a**: R^1 = 2-pyridyl, R^2 = Ph; **3b**: R^1 = $Me_3SiC\equiv C$; R^2 = Ph; **3c**: R^1 = 2-pyridyl, R^2 = (*R*)-PhCH(CH_3); **3d**: R^1 = $Me_3SiC\equiv C$; R^2 = (*R*)-PhCH(CH_3)]. Depending on metal counterion, temperature, and substituents, the C–C coupling occurs either at the 2-position (α-coupling) or at the 4-position (γ-coupling) of the dienolate, giving β-amino esters and α,β-unsaturated esters, respectively. The α-coupling occurs at −78 °C and is reversible, whereas γ-coupling products are formed upon warming to −20 °C. The C–C coupled products may undergo irreversible ring closure to β-lactams (from β-amino esters) or 5,6-dihydropyridin-2-ones (from Z)-α,β-unsaturated esters). Starting from enantiomerically pure imine **3c**, high (71–92%) asymmetric inductions were realized in both β-lactams and 5,6-dihydropyridin-2-ones; γ-coupling of enolate **2a** and chiral imine **3d** occurred with low diastereoselectivity (15%). Four factors favor the formation of β-lactams: (i) the use of zinc dienolates, (ii) 4-substitution of the dienolates, (iii) nonaromatic imine N-substituents, and (iv) a low reaction temperature (−78 °C). The product formation is discussed in terms of six-membered cyclic transition states, involving either zinc enolates (α-coupling) or isomeric allylzinc species (γ-coupling).

Introduction

The β-lactam function is a common structural feature of an important class of antibiotics.[1] In the past decades, several routes for the synthesis of β-lactams have been published.[2,3] Since generally only one enantiomer displays biological activity, the development of synthetic methodologies that allow control of the diastereoselectivity is an important topic in β-lactam chemistry. The condensation reaction of ester enolates with imines constitutes a versatile route to synthetic β-lactams.[3] The *cis–trans*-selectivity of this reaction is determined primarily by the metal. We have shown recently, that zinc enolates afford *trans* β-lactams almost exclusively.[4] Moreover, zinc enolates display a high reactivity toward imines, both in the C–C coupling reaction and in the subsequent ring closure. A convenient one-pot procedure for the synthesis of β-lactams from zinc enolates and imines has been developed.[4a] Asymmetric synthesis employing chiral imines was accomplished with excellent diastereoselectivity.[4e,f]

Biologically active bicyclic *trans*-β-lactams are found among the carbapenems.[5] Generally, they possess a 3-alkyl substituent, *e.g.* PS-5, PS-6, and thienamycins, having an ethyl, isopropyl, and (*R*)-1-hydroxyethyl side chain at the 3-position, respectively. This class of compounds is a potential target for the zinc-mediated ester enolate–imine condensation reaction. The (formal) total synthesis of carbapenems is well documented. By employing 3-hydroxybutyric esters[6] in the lithium ester enolate–imine condensation, the hydroxyethyl function was directly introduced. However, our results with the corresponding chlorozinc enolate were not very promising.[7] It was considered to be advantageous to introduce a latent hydroxy function, to be activated at a later stage of the synthesis. For this reason, we selected 3-alkeno-

* To whom correspondence should be addressed.
† Debye Institute.
‡ Bijvoet Center for Biomolecular Research.
§ To whom correspondence pertaining to crystal structural data should be addressed.

® Abstract published in *Advance ACS Abstracts,* November 1, 1994.

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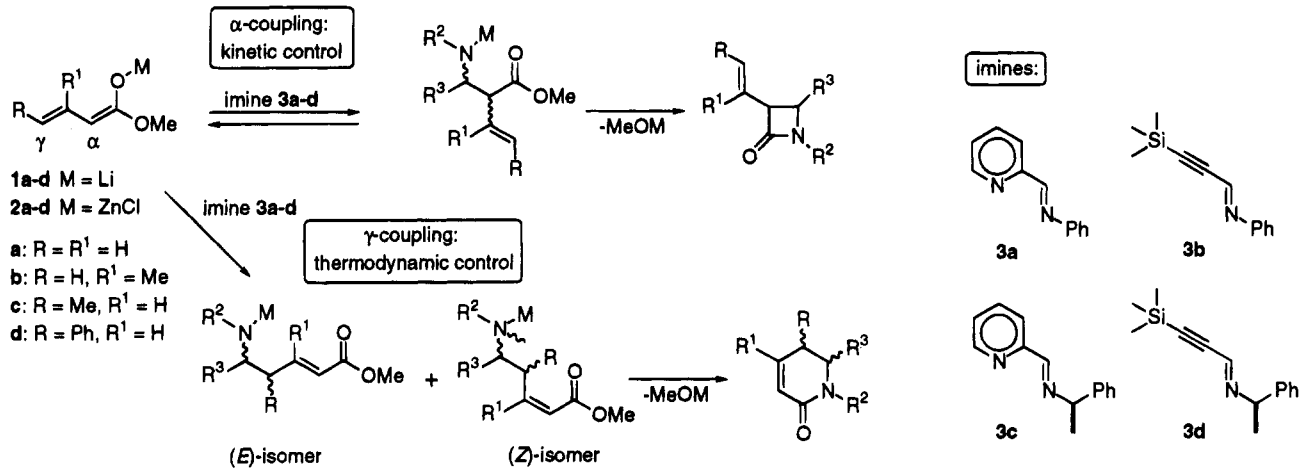
0022-3263/94/1959-7839$04.50/0

Scheme 1



ates as the starting esters, to produce 3-(1-alkenyl)-2-azetidinones,[8] that can be transformed to an aldehyde or ketone function by ozonolysis,[8e,9] or to a 3-alkyl substituent by hydrogenation (Pd/C).[8e]

Several research groups have already employed dienolates in C−C coupling reactions with electrophiles, and the regiochemistry of lithium[10] and zinc[11] dienolates in the related aldol reaction has been the subject of a number of synthetic and mechanistic studies. The formation of α- and γ-coupled products was interpreted in terms of solvent, temperature, and substituent effects. Usually, the α-coupled product is the kinetic product of the reaction, which is isolated by quenching at −78 °C. Upon raising the temperature, the thermodynamically more stable γ-coupled products are formed. Retroaldolization has been established in several cases.[10] However, to our knowledge, only one communication on the direct condensation of a dienolate with imines has appeared in print.[12,13] It is noteworthy that Lewis acid-mediated coupling of vinylketene silyl acetals with imines leads to the exclusive formation of γ-coupled products (5-amino-2-alkenoates and 5,6-dihydropyridin-2-ones).[14]

Results

Under the previously described reaction and workup conditions[4c−e] (see Experimental Section), lithium (**1a−d**) and chlorozinc dienolates (**2a−d**) of methyl 3-alkenoates were reacted with *N*-(2-pyridylmethylidene)-aniline (**3a**), *N*-(3-(trimethylsilyl)-2-propynylidene)aniline (**3b**), (*R*)-[1-(*N*-[2-pyridylmethylidene]amino)ethyl]benzene (**3c**), and (*R*)-[1-(*N*-[3-(trimethylsilyl)-2-propynylidene]-amino)ethyl]benzene (**3d**). In a typical one-pot procedure, the dienolates were generated by deprotonation of the ester[15] with 1 equiv of LDA in THF at −78 °C,[16] followed by transmetalation with $ZnCl_2$ (Scheme 1). After addition of the appropriate imine and reacting for 1 h at −78 °C, the kinetic products were obtained by quenching the reaction mixture with saturated aqueous NH_4Cl. Alternatively, the reaction mixture was stirred for 1 h at −20 °C, in order to obtain the thermodynamic products. Two reaction pathways were operative (Scheme 1): coupling at the α-position, affording β-amino esters as the kinetic products, and γ-coupling, leading to both (*Z*)- and (*E*)-5-aminoalkenoates as the thermodynamic products. Depending on the reaction conditions, the β-amino esters and the (*Z*)-alkenoates may undergo cyclization to β-lactams and 5,6-dihydropyridin-2-ones, respectively. The influence of the metal, the temperature (−78 or −20 °C) and the substituents (at the 3- and 4-position of the dienolate) on the outcome of the reactions were investigated. The lithium enolates reacted only with *N*-phenyl imines **3a** and **3b**.

The reactions were monitored by quenching small samples and analyzing their composition by ^1H NMR and GCMS (EI, 70 eV). Products were purified after quench-

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(13) We have attempted to perform the reactions with *N*-alkyl imines described in ref 12 *via* our standard procedure. However, no reaction occurred at −20 °C; the zinc dienolate decomposed above room temperature. Clearly, the generation of short-lived, reactive zinc dienolates using Reformatsky-type reaction conditions (refluxing benzene or toluene) is not comparable to our methods. Moreover, the thermal stability of many imines is a problem at such high temperatures.

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Scheme 2

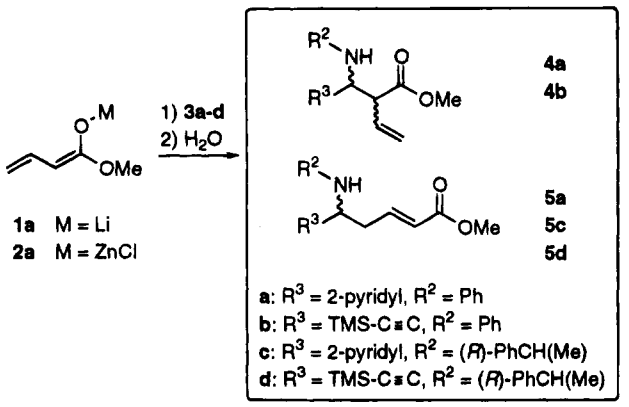


Table 1. Reactions of Unsubstituted Zinc and Lithium Dienolates with Imines 3a–d at −78 °C

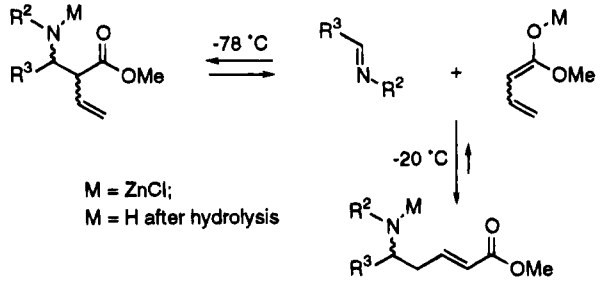
enolate	imine	ester	α-coupling[a]	syn:anti	γ-coupling[a]	de[b]
2a (Zn)	**3a**	Me	**4a** (60)[c]	30:70	**5a** (40)[c]	–
1a (Li)	**3a**	Me	(0)		**5a** (>98)[d]	–
2a (Zn)	**3b**	Me	**4b** (>98)	20:80	(0)[d]	
1a (Li)	**3b**	Me	**4b** (>98)	50:50	(0)[d]	
2a (Zn)	**3c**	Me	(0)	–	**5c** (>98)[e]	92
2a (Zn)	**3d**	Me	(0)	–	**5d** (>98)[d]	15
2e (Zn)[f]	**3a**	(−)-menthyl	(0)	–	**5e** (94)	0
2e (Zn)	**3b**	(−)-menthyl	**4f** (72)	11:89[g]	(0)	

[a] Conversions (%) determined by integration of ^{1}H NMR signals. [b] Asymmetric Induction. [c] After standing overnight at −20 °C, **5a** is obtained quantitatively. [d] Completely polymerized after 1 h at −20 °C. [e] Partially polymerized after 1 h at −20 °C. [f] Stirred for 2 h at −20 °C to complete the reaction. [g] de of *anti*-**4f**: 42%.

ing the reaction mixture by crystallization or HPLC. New compounds were fully characterized by ^{1}H and ^{13}C NMR, IR, GCMS, and elemental analysis. In the mass spectra, the β-amino esters and 5-aminoalkenoates displayed molecular peaks with very low intensity (<0.5%). Their major fragmentation originated from cleavage of the C−C bond that was formed in the reaction, giving the [imine + H]$^+$ ion (*m/z* = 183 [**3a** + H]$^+$, 202 [**3b** + H]$^+$, 211 [**3c** + H]$^+$, and 230 [**3d** + H]$^+$). The β-lactams also display a very low molecular ion peak. The major peaks are due to loss of an isocyanate *via* cleavage of C(2)−C(3) and N−C(4) (**9b** and **13b,c**).[17] 3-Phenylethenyl β-lactam **16c** is not volatile enough to be analyzed by GCMS. Only the 5,6-dihydropyridin-2-ones show significant molecular ion peaks (5−68%).

Unsubstituted Dienolates 2a and 2e. The reaction of zinc dienolate **2a** with imine **3a** resulted in the quantitative formation of a 60:40 mixture of α-coupled product **4a** and γ-coupled product **5a** (Scheme 2, Table 1). By quenching after 1 h at −78 °C, β-amino ester **4a** was obtained as a 30:70 mixture of *syn* and *anti* diastereoisomers, from which the major one was isolated by crystallization. Quenching the reaction after stirring for 1 h at −20 °C afforded no β-lactam. Instead, α,β-unsaturated ester **5a** was obtained as the only product in quantitative yield. The reaction of lithium dienolate **1a** with imine **3a**, when quenched at −78 °C, afforded γ-coupled product **5a** quantitatively. However, warming the reaction mixture to −20 °C before quenching resulted in polymerization of the product.

Scheme 3



Evidently, in the zinc-mediated reaction the β-amino ester **4a** is formed under kinetic control. At higher temperatures it equilibrates to the thermodynamic product **5a**, *via* a retro enolate−imine condensation (Scheme 3). The reversibility of the initial C−C coupling reaction was clearly demonstrated by deprotonation of recrystallized α-coupled product **4a** with LDA and transmetalation with $ZnCl_2$ in THF at −78 °C. After warming to −20 °C, the thermodynamically more stable γ-coupled product **5a** was obtained, together with a small amount of the imine **3a**. Due to the low boiling point, the ester itself was not recovered.

Imine **3b** afforded exclusively the α-coupled product **4b** (*syn:anti* 20:80) in the reaction with zinc dienolate **2a** at −78 °C. However, at −20 °C only polymeric products were observed. Presumably, the retro enolate−imine condensation produces the γ-coupled product **5b** (not observed), which undergoes a rapid (Lewis acid-mediated) polymerization. The analogous reaction of the lithium dienolate **1a** afforded **5b** at −78 °C, and polymeric products at −20 °C.

The reaction of zinc dienolate **2a** with the chiral imines **3c** and **3d** afforded exclusively the γ-coupled products **5c,d** in a quantitative yield at −78 °C. In both cases, warming to −20 °C resulted in polymerization. Whereas the formation of **5c** was highly diastereoselective (de = 92%), **5d** was formed with a poor asymmetric induction (de = 15%). This low diastereoselectivity is consistent with earlier results from reactions of imine **3d** with zinc enolates. Whereas most aldimines exist exclusively in the (*E*)-configuration,[18] imine **3d** is present in solution as an (*E*)−(*Z*) mixture (70:30 by ^{1}H NMR).

An alternative approach to asymmetric synthesis is to use chiral esters in this reaction.[19] Thus, the zinc enolate **2e** of (−)-menthyl 3-butenoate was reacted with imines **3a** and **3b** (Scheme 4, table 1), to study the influence on γ- and α-coupling, respectively. The reaction with imine **3a** was quenched after stirring for 2 h at −20 °C, affording the expected γ-coupled product **5e** in 94%

(15) Recently, a convenient, general synthesis of β,γ-unsubstituted carboxylic acids from allylic barium reagents has been published. Yanagisawa, A.; Yasue, K.; Yamamoto, H. *Synth. Lett.* **1992**, 593–594.

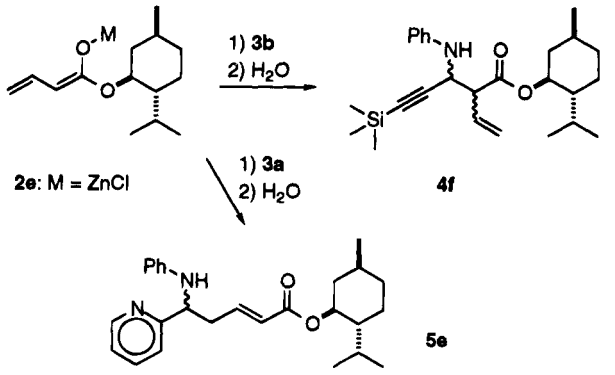
(16) Alternatively, dienolates might be generated by deprotonation of α,β-unsaturated esters with LDA in THF containing 23% (v/v) HMPA.[10a,d] Because of the high toxicity of this additive, we did not consider this possibility. The lithium enolate **2b** was generated from methyl 3-methyl-2-butenoate by deprotonation at the 4-position with LDA in THF. Michael addition of LDA was not observed.

(17) For a more detailed discussion of β-lactam mass spectra, see: Fetter, J.; Giang, L. T.; Czuppon, T.; Lempert, K.; Kajtár-Peredy, M.; Czira, G. *Tetrahedron* **1994**, *50*, 4185–4200.

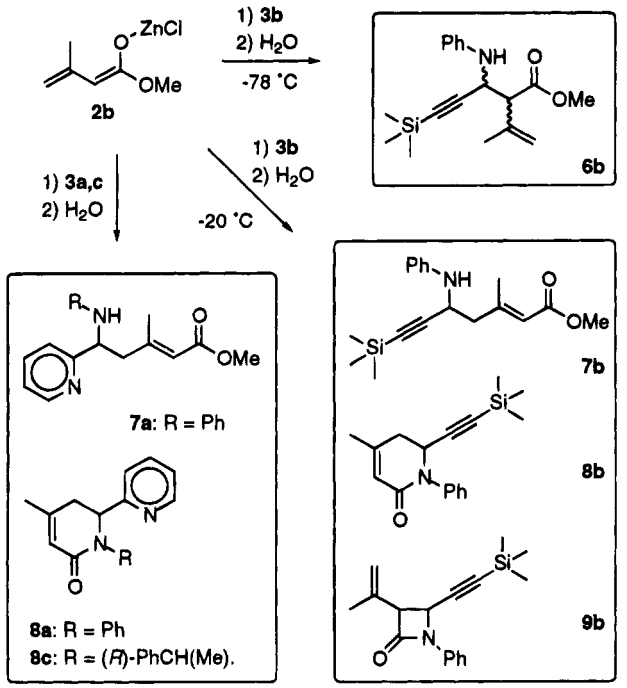
(18) Generally, aldimines are present in the (*E*)-configuration: (a) Fraser, R. R; Banville, J.; Akiyama, F.; Chuaqui-Offermanns, N. *Can. J. Chem.* **1981**, *59*, 705–709. (b) De Kimpe, N.; Verhe, R.; De Buyck, L; Schamp, N. *Can. J. Chem.* **1984**, *62*, 1812–1816.

(19) We have previously (ref 4b) used menthyl esters in the reactions of zinc enolates, giving poor diastereoselectivity. However, in reactions of lithium enolates stereogenic ester groups effected good asymmetric induction: Ojima, I.; Habus, L. *Tetrahedron Lett.* **1990**, *31*, 4289–4292.

Scheme 4



Scheme 5



conversion (based on recovered imine), as a 1:1 mixture of the two diastereoisomers. Reaction of **2e** with imine **3b** for 1 h at −78 °C afforded the α-coupled product **4f** in 72% conversion, on the basis of the integrals of ester and imine signals in the ^{1}H NMR spectrum. The diastereoselectivity is slightly better than the corresponding reaction with the methyl ester: an 11:89 mixture of *syn* and *anti* diastereoisomers was obtained. However, the asymmetric induction (de 42%) was poor.

3-Substituted Dienolate 2b. The methyl 3-methyl-3-butenoate zinc dienolate **2b** (Scheme 5, Table 2) reacted with the pyridyl-substituted imine **3a** at the γ-position only. The cyclization to the 5,6-dihydropyridin-2-one **8a** is rapid at −78 °C. By quenching at this temperature only **8a** and the (*E*)-α,β-unsaturated ester **7a** are obtained in a 58:42 ratio. This ratio had not changed significantly when the reaction was performed for 1 h at room temperature. After 14 days at room temperature, a 75:25 ratio of **8a**:**7a** was observed, which demonstrates that the γ-coupling is also reversible, although the retroreaction is very slow. The lithium-mediated reaction afforded the same products in a slightly different ratio, together with 5% of the noncyclized (*Z*)-α,β-unsaturated ester. Apparently the lithium-mediated ring closure is slow.

A diastereoselective γ-coupling (de 80%) was observed in the reaction of the chiral pyridyl-substituted imine **3c** with zinc dienolate **2b** at −78 °C, affording exclusively the 5,6-dihydropyridin-2-one **8c**. However, the (trimethylsilyl)ethynyl imine **3b** afforded the α-coupled product **6b** quantitatively (*syn*:*anti* 18:82). Upon warming to −20 °C, only a minor amount of ring closure to the β-lactam **9b** is observed. Furthermore, the α-coupling is readily reversible, resulting in the formation of γ-coupled products upon warming. The product mixture consisted mainly of four compounds: 5,6-dihydropyridin-2-one **8b**, (*E*)-α,β-unsaturated ester **7b**, β-lactam **9b** (only the *trans*-diastereoisomer was observed), and β-amino ester **6b**, together with some polymeric material. Reaction of lithium dienolate **1b** with imine **3b** resulted in complete polymerization at −78 °C.

4-Substituted Dienolates 2c and 2d. The products of the reactions of zinc dienolates **2c** (R = Me) and **2d** (R = Ph) with the imines **3a**−**c** (Scheme 6, Tables 3 and 4) almost exclusively resulted from coupling at the α-position of the dienolate. Reaction with the *N*-phenyl imines **3a,b** (−78 °C, 1 h) afforded α-coupled products **10a,b** and **14a,b** with low *syn*−*anti*-selectivity. In the reactions of zinc enolate **2c**, double bond isomerization resulted in the formation of β-amino esters with a (*Z*)-1-propenyl side chain ((*Z*)-**10a**: 9%, (*Z*)-**10b**: 21%) with the same de as the (*E*)-isomer. The corresponding reaction of lithium enolate **1c** with imine **3b** afforded only the (*E*)-isomer; no isomerization of the side chain was observed.

Upon warming the reaction mixtures to −20 °C, the initially formed β-amino esters completely disappeared. Zinc dienolate **2c** (R = Me) afforded mainly γ-coupled products. A small amount (11%) of β-lactam **13b** was observed, but determination of the diastereoselectivity was impossible due to the presence of signals of polymeric products. Polymerization products were also found in the reaction of zinc dienolate **2d** with *N*-phenyl imines **3a,b** (1 h at −20 °C), although ^{1}H NMR of the reaction mixture showed that the γ-coupled product **15b** was formed in 80% conversion (de 33%).

The reaction of the chiral *N*-(1-phenylethyl) imine **3c** with zinc dienolates **2c,d** at −78 °C afforded *trans*-β-lactams **13c** (90%, de 88%) and **16c** (97%, de 92%), respectively. Apart from β-lactam **13c**, the reaction of zinc dienolate **2c** with imine **3c** afforded also a small amount of 5,6-dihydropyridin-2-one **12c** (10%, de 80%). These data demonstrate that 4-substitution of the dienolate favors α- over γ-coupling. The ring closure of the intermediate *N*-(1-phenylethyl)-substituted β-amino esters to the *trans*-β-lactams is fast at −78 °C, thus blocking the retroreaction. The *N*-phenyl-substituted β-amino esters are isolated by quenching at −78 °C. Because ring closure to the β-lactam is slow, γ-coupled products (which polymerize slowly under the reaction conditions) are formed upon warming to −20 °C.

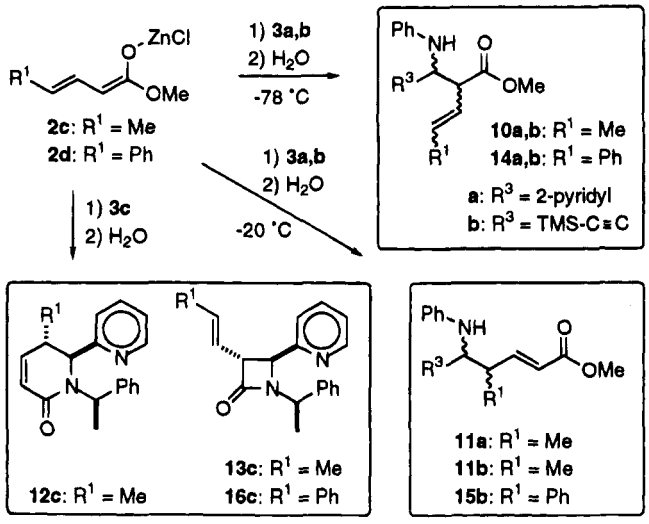
Stereochemistry. To ascertain the relative stereochemistry of the α-coupled products, a crystal structure determination was performed. Both diastereoisomers of **6b** (see Scheme 5) crystallize from Et_2O, the major one as colourless feather-shaped crystals, the minor one as orange disk-shaped crystals. The latter crystals were suitable for X-ray analysis. The molecular structure of the minor diastereoisomer, together with the adopted numbering scheme, is depicted in Figure 1. As the space group ($P2_1/c$) is nonchiral, both enantiomers are present in the unit cell, interrelated by an inversion center. The molecules are arranged in chains of one enantiomer, interconnected *via* an intermolecular C=O···H−N hydrogen bridge. The relative stereochemistry of the minor

Table 2. Reactions of 3-Substituted Lithium (1b) and Zinc (2b) Dienolate with Imines 3a–c

					α-coupling		γ-coupling	
enolate	imine	T (°C)	conv[a]	α:γ-ratio	ester	β-lactam	ester	pyridinone
2b (Zn)	**3a**	*b*	>98	0:100	(0)	(0)	**7a** (42)	**8a** (58)
1b (Li)	**3a**	−20	>98	0:100	(0)	(0)	**7a** (32)	**8a** (68)[c]
2b (Zn)	**3b**	−78	>98	100:0	**6b** (100)[d]	(0)	(0)	(0)
2b (Zn)	**3b**	−20	~85	23:77	**6b** (4)	**9b** (19)[e]	**7b** (25)	**8b** (52)
1b (Li)	**3b**	−78		–	(0)	(0)	(0)[f]	(0)
2b (Zn)	**3c**	*b*	>98	0:100	(0)	(0)	(0)	**8c** (100)[g]

[a] Conversions (%), determined by integration of ^{1}H NMR signals. [b] Identical results at −78 and −20 °C. [c] 5% was present as noncyclized (Z)-α,β-unsaturated ester. [d] *syn*:*anti* 18:82. [e] *cis*:*trans* 18:82. [f] Completely polymerized [g] de 77%.

Scheme 6



diastereoisomer of **6b** is *syn* (relative orientation of the isopropenyl and PhNH group), which upon ring closure affords a *cis*-β-lactam. Thus, the major diastereoisomer has the *anti*-configuration, corresponding to the *trans*-β-lactam.

The formation of *anti*-β-amino esters and *trans*-β-lactams is in accordance with our previous results in the C–C coupling reactions of imines and zinc enolates[4] under kinetic control. The stereochemical interpretation is further substantiated by the coupling constants of the protons attached to C(3) and C(4) ($^3J_{H-H} \sim 2$ Hz) of *trans*-β-lactams **9b**, **13b**, **13c**, and **16c**. In the reactions of enolates **2a–d** with *N*-phenyl substituted imines **3b** at −78 °C both *syn*- and *anti*-β-amino esters were obtained. The ratios of the two diastereoisomers were determined by integration of characteristic ^{1}H NMR signals. The similar ^{1}H NMR spectra of the major and minor diastereoisomers of the β-amino esters strongly suggest that in all cases the same diastereoisomer (*anti*) is the predominant one.

The γ-coupled products derived from 4-substituted enolates **2c** and **2d** did not afford crystals suitable for molecular structure determination. The relative stereochemistry of the 5,6-dihydropyridin-2-one **12c** is deduced from its ^{1}H NMR. The coupling constants of the protons attached to C(5) and C(6) is very small (~0 Hz), indicating a HCCH torsion angle of ~90°, and thus a *trans*-arrangement. Notably, the six-membered ring is not in a chair conformation, since the C=C–C(=O)–N bonds of the α,β-unsaturated amide are nearly coplanar. Rotation around the C(5)–C(6) bond is therefore very limited.

Discussion

In the past decades, reactions of metal enolates with electrophiles have been the subject of many mechanistic studies. Especially for the aldol condensation the reaction mechanism has been well established.[20] The stereochemistry of the products has been described in terms of six-membered cyclic transition states. The results of the closely related enolate–imine condensation reaction has been rationalized *via* analogous cyclic transition states.[21] Moreover, this mechanistic interpretation is also applicable to the reactions of allylmetal reagents[22] with aldehydes and imines.

Zinc enolates are not present in solution as well-defined species. Apart from aggregation equilibria, O- and C-metalated species are in equilibrium.[23] This has been clearly demonstrated in the crystal structure of the Reformatsky reagent $[BrZnCH_2COOR]_2$,[23b] which is an intermediate between O- and C-metalation. Moreover, we have recently observed (*E*)–(*Z*) isomerization of zinc enolates in the absence of a proton source, suggesting the intermediacy of C-metalated species in solution. In the reactions of the zinc dienolates, the C-metalated isomer actually is an allylzinc species, that also reacts with the substrate.

Previously, we have demonstrated[4d] that the excellent *trans*-selectivity of the zinc-mediated ester enolate–imine condensation is accounted for by a six-membered chair transition state **17**, involving an (*E*)-imine and a (*Z*)-enolate (Scheme 7). Transition state **18**, involving an (*E*)-enolate and an (*E*)-imine, is destabilized by a gauche interaction of R^1 and R^3. Products resulting from (*E*)-enolates have only been observed when R^1 or R^3 are small, or when the reactions were performed in polar solvents (*e.g.* mixtures of THF and HMPA). Since the asymmetric induction using a menthyl ester is poor, the 1,3-diaxial interaction of the ester group with R^3 is not substantial.

α-Coupling. The outcome of the α-coupling reactions of zinc dienolates and imines is determined by the relative stabilities of transition states **17** and **18** (Scheme 7). Although their conformation has not been established, the preferential formation of *trans*-β-lactams suggests that zinc dienolates also react mainly in the (Z)-

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Table 3. Reactions of 4-Methyl-Substituted Lithium (1c) and Zinc (2c) Dienolate with Imines 3a–c

				α-coupled products			γ-coupled products		
enolate	imine	T (°C)	conv[a]	α:γ-ratio		ester	β-lactam	ester	pyridinone
2c (Zn)	**3a**	−78	>98	91	9	**10a** (91)[b,c]	(0)	**11a** (9)	(0)
2c (Zn)	**3a**	−20	>98	0	100	(0)	(0)	**11a** (97)[d]	**12a** (3)
1c (Li)[e]	**3a**	−78	83	0	100	(0)	(0)	**11a** (100)[f]	(0)
2c (Zn)	**3b**	−78	>98	96	4	**10b** (96)[g,h]	(0)	**11b** (4)	(0)
2c (Zn)	**3b**	−20	51	29	71	**10b** (18)[g]	**13b** (11)	**11b** (71)[i]	(0)
1c (Li)[d]	**3b**	−78	96	100	0	**10b** (100)[j]	(0)	(0)	(0)
2c (Zn)	**3c**	*k*	>98	90	10	0	**13c** (90)[l]	(0)	**12c** (10)[m]
1c (Li)	**3c**	*k*	0	–	–	0	(0)	(0)	(0)

[a] Conversions (%), determined by integration of ^{1}H NMR signals. [b] Me(CH)=C(H)– fragment was present in (*E*)- (82%) and (*Z*)-(9%) conformation. [c] *syn*:*anti* 43:57. [d] *syn*:*anti* 30:70. [e] Completely polymerized at −20 °C. [f] *syn*:*anti* 50:50. [g] MeC(H)=C(H)- fragment was present in (*E*)- (75%) and (*Z*)- (21%) conformation. [h] *syn*:*anti* 45:55. [i] Partially polymerized. [j] *syn*:*anti* 59:41. [k] Identical results at −78 and −20 °C. [l] Exclusively *trans*, de 88%. [m] de 80%.

Table 4. Reactions of 4-Phenyl-Substituted Lithium (1d) and Zinc (2d) Dienolate with Imines 3a–c

enolate	imine	T (°C)	conv[a]	α:γ-ratio	β-amino ester	syn:anti	*trans*-β-lactam	de[b]
2d (Zn)[c]	**3a**	−78	96	100:0	**14a** (100)	39:61	(0)	
1d (Li)	**3a**	−78	10	100:0	**14a** (100)	–	(0)	
1d (Li)	**3a**	−20	90	100:0	**14a** (100)	55:45	(0)	
2d (Zn)	**3b**	−78	90	100:0	**14b** (100)	45:55	(0)	
2d (Zn)	**3b**	−20	80	0:100[d]	(0)		(0)	
1d (Li)	**3b**	−78	12	100:0	**14b** (100)	nd	(0)	
2d (Zn)	**3c**	e	97	100:0	(0)		**16c** (100)	92
1d (Li)	**3c**	e	0	–	(0)		(0)	

[a] Conversions (%), determined by integration of ^{1}H NMR signals. [b] Asymmetric induction. [c] Completely polymerized at −20 °C. [d] (*E*)-α,β-Unsaturated ester **15b** formed with 33% de. [e] Identical results at −78 and −20 °C.

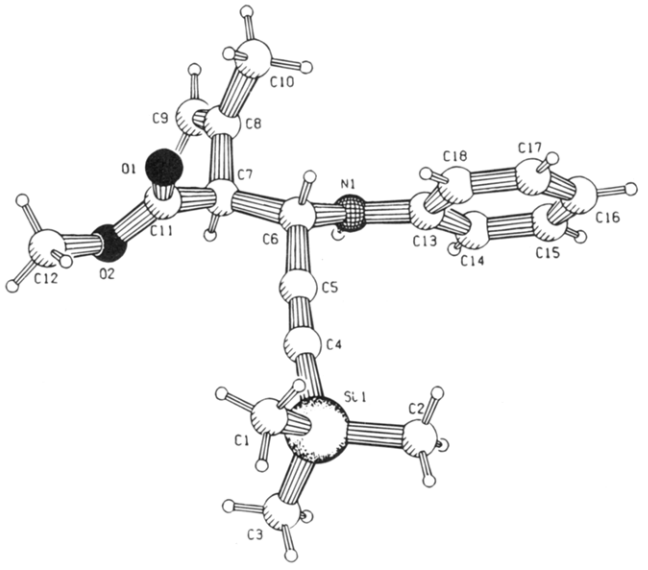
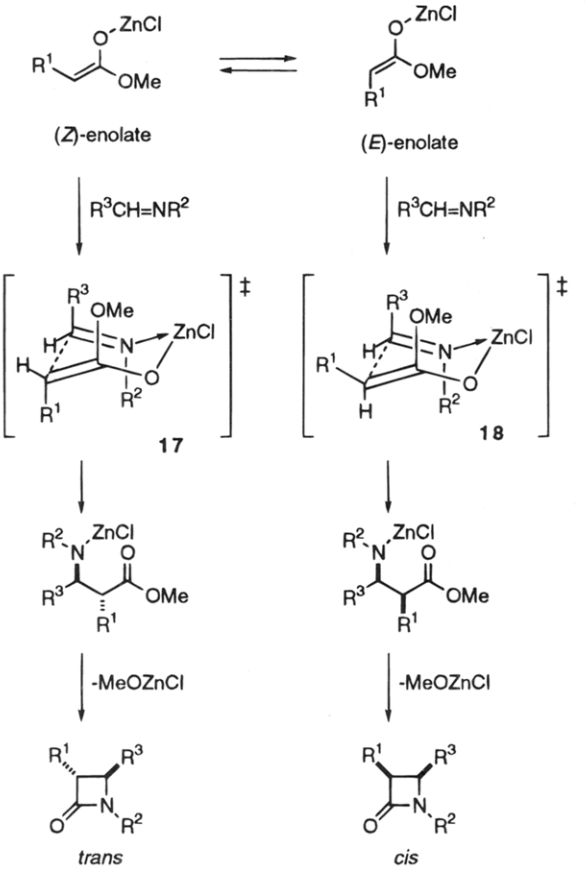


Figure 1. Molecular structure of *syn*-**6b**.

conformation. The alkenyl substituents (vinyl, isopropenyl, 1-propenyl, and styryl) are coplanar with the enolate double bond and thus sterically not very demanding. Therefore, the energy differences of competing transition states **17** and **18**, leading to *anti*- and *syn*-β-amino esters respectively, are relatively small.

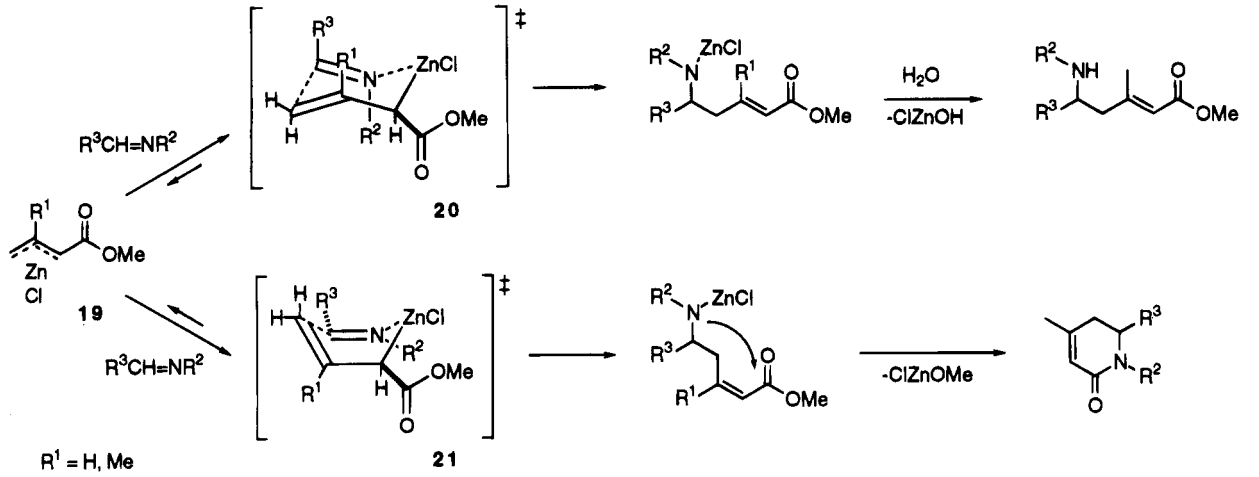
In the reactions of methyl 3-pentenoate enolate **2c** with *N*-phenyl imines **3a,b** significant amounts of α-coupled products having a (*Z*)-1-propenyl side chain were formed, which cannot be explained by this mechanism. However, an equilibrium between the zinc dienolate **2c** and isomeric allylzinc species (*vide infra*) accounts for this unexpected double bond isomerization. As only minor amounts of γ-coupled products are observed in the reactions of 4-substituted zinc dienolates with imines at −78 °C, the O-metalated intermediate is the kinetically active species.

Scheme 7

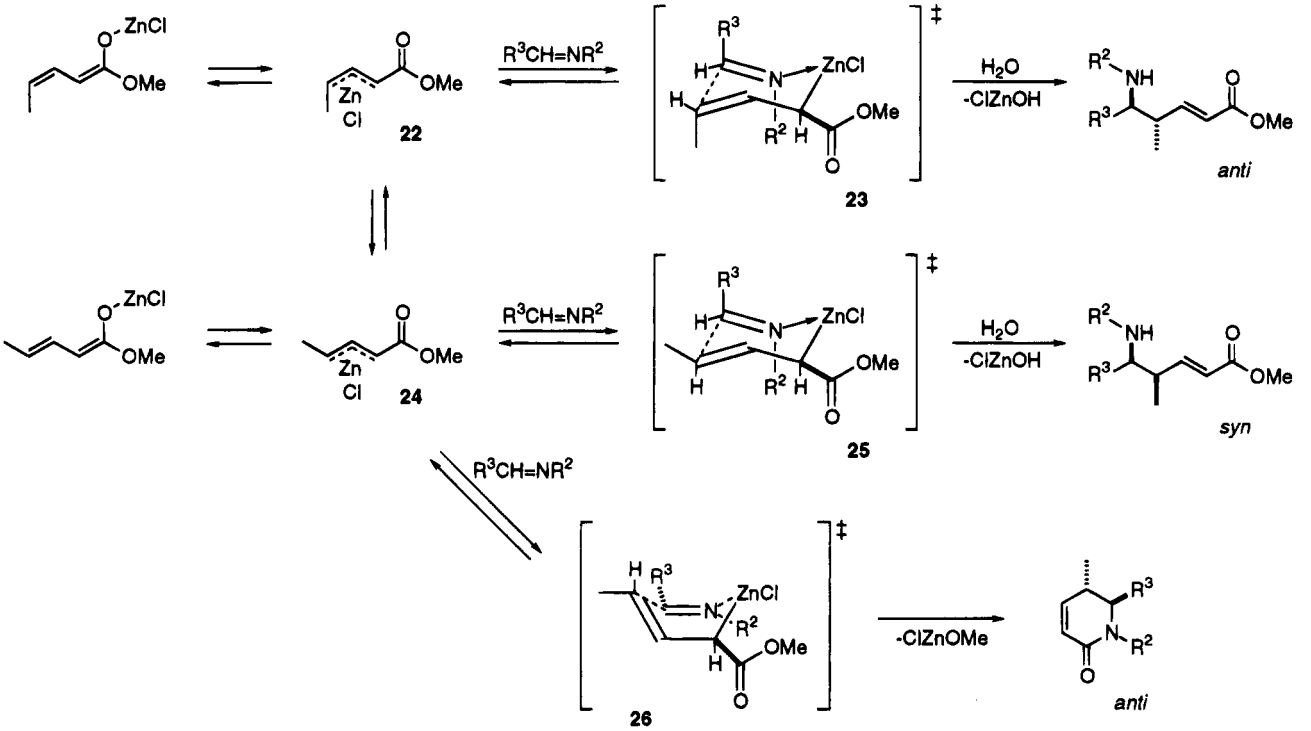


γ-Coupling. The diastereoselective γ-C–C coupling reactions of the dienolates with the chiral *N*-(phenylethyl) imine **3c** suggest that a highly ordered transition state is operative. The formation of γ-coupled products is rationalized *via* a six-membered cyclic transition state involving an allylzinc species **19**, which is in equilibrium with the zinc enolate. The stereochemistry of the products is determined by the conformation of the allylzinc

Scheme 8



Scheme 9



intermediate and the spatial arrangement of the reagents in the transition state complex.

The reactions of allylic organometallic compounds with aldehydes generally involve open or cyclic chair transition states.[22] However, the (*E*)-conformation of the imine forces both R^2 and R^3 in an axial position, introducing 1,3-diaxial interactions. Under such circumstances, a boat transition state may be more stable.[22] In both the chair and the boat transition state (Scheme 8), the ester function will be in an equatorial position to minimize the steric interaction with R^2. Unsubstituted dienolates **2a** and **2e**, which afforded the (*E*)-5-aminoalkenoates (see Table 1) as the only γ-coupling product, react exclusively *via* the chair transition state **20**. However, 3-substituted dienolate **2b** afforded both (*E*)-5-aminoalkenoates and 5,6-dihydropyridin-2-ones (see Table 2). As chair transition state **20** is destabilized by the 1,3-diaxial interaction of the dienolate substituent and imine C-substituent R^3, the reaction proceeds primarily *via* boat transition state **21**. The resulting (*Z*)-5-aminoalkenoate undergoes ring closure to the 5,6-dihydropyridin-2-one. The relative energies of the transition states are reflected in the product distribution, as equilibration *via* the reverse reaction is very slow ($t_{1/2}$ > 14 days).

The situation for the 4-substituted dienolates **2c,d** is more complicated. Evidently, the preferential formation of α-coupling products (especially for **2d**) is due to steric hindrance of the 4-substituent in the γ-coupling transition states. However, under thermodynamic control γ-coupling is observed. Reaction of allylzinc intermediate **24** (Scheme 9) *via* boat transition state **26** results in the formation of *trans*-5,6-dihydropyridin-2-ones, whereas chair transition state **25** affords α,β-unsaturated esters, having a *syn*-relationship between the C(4)-substituent and the amine. The low diastereoselectivity in the formation of the α,β-unsaturated esters requires that an alternative reaction path is available. Isomerization around the C(3)–C(4) bond of the allylzinc intermediate generates **22**, which reacts *via* chair transition state **23** to the *anti*-α,β-unsaturated ester. In the reaction of dienolate **2c** with imines **3a** and **3b**, α-coupled products having a *cis*-1-propenyl side chain were formed in sig-

nificant amounts (*vide supra*), which strongly suggests the intermediacy of the isomerized allylzinc species **22**. A boat transition state involving this intermediate is unlikely, as this would place the 4-substituent in an axial position. Therefore, the 5,6-dihydropyridin-2-ones are formed with excellent diastereoselectivity.

Analogous to the 3-substituted allylzinc species, the product distribution reflects the relative stabilities of the transition states **23**, **25**, and **26**. In the reactions of dienolates **2c** and **2d** with imines **3a,b** at −20 °C the major products are α,β-unsaturated esters. Thus, for the 4-substituted dienolates the γ-C−C coupling reaction proceeds mainly *via* the chair transition states **23** and **25**, affording α,β-unsaturated esters, whereas the 3-substituted dienolate **2b** reacts mainly *via* boat transition state **21**, giving 5,6-dihydropyridin-2-ones, because the alternative chair transition state **20** is destabilized by a 1,3-diaxial interaction involving R^3.

Conclusions

Zinc dienolates derived from 3-alkenoates react with imines to yield α- and γ-coupled products, depending on temperature and substituents. The C−C coupling reaction at the 2-position of the dienolate was shown to be reversible, leading to γ-coupled products upon warming to −20 °C. *N*-Phenyl imines **3a** and **3b** afforded no synthetically useful amounts of β-lactams. Whereas 3-substituted dienolate **2b** reacted primarily at the γ-position, the 4-substituted dienolates **2c** and **2d** afforded mainly α-coupled products. In the reaction of **2c** and **2d** with *N*-phenyl imines, the intermediate (metalated) β-amino esters do not cyclize at −78 °C, leading to γ-coupling products (and polymers) upon warming to −20 °C. The analogous reactions with *N*-(1-phenylethyl)-substituted imine **3c** afforded *trans*-β-lactams **13c** and **16c** in excellent yields and with good asymmetric induction. Lithium enolates **1a−d** reacted with activated *N*-phenyl imines **3a,b** to α- or γ-coupled products, but with low diastereoselectivity. Unactivated imines **3c,d** did not react with lithium enolates.

Whereas the lithium-mediated C−C coupling reaction of dienolates and imines often results in the formation of polymeric materials, the zinc-mediated reaction enables the synthesis of 5-amino-2-pentenoates without polymerization. These compounds are promising precursors for functionalized polymers. The diastereoselective synthesis of 5-amino-2-pentenoate **5c** might give access to chiral polymers.

The formation of γ-coupled products is rationalized *via* competing chair and boat transition states involving (*E*)-imines and allylzinc intermediates **19**, **22**, and **24**. For the 4-substituted dienolates, the major pathway at −78 °C is α-coupling, because the presence of a substituent at the 4-position destabilizes the γ-coupling transition states **23**, **25**, and **26**. Rapid, irreversible ring closure leads to *trans*-β-lactams. The formation of β-lactams is favored by four factors: (i) zinc as the counterion, (ii) 4-substitution of the dienolates, (iii) nonaromatic imine-N substituents, and (iv) a low reaction temperature (−78 °C).

The β-lactams **13c** and **16c** possess promising 3-substituents, that might be functionalized by oxidative cleavage (O_3), epoxidation, or reduction. The synthesis of useful intermediates for carbapenems *via* this approach requires the use of imine substituents[4g] that can later be used for formation of the fused ring system.

Experimental Section[24]

Standard Procedure for the C−C Coupling Reaction of Dienolates and Imines. To a solution of 5.0 mmol of diisopropylamine in 50 mL THF, cooled to −78 °C, was added 5.0 mmol of *n*-butyllithium (3.2 mL of a 1.6 M solution in hexanes). After 5 min the appropriate ester was added, and 10 min later the enolate was transmetalated by addition of 5.0 mmol of $ZnCl_2$ (4.1 mL of a 1.23 M solution in Et_2O), followed by another 10 min stirring. Next, 5.0 mmol of the appropriate imine **3a−d** was added. Stirring was continued for 1 h at −78 °C and optionally for 1 h at −20 °C. The reaction was quenched by addition of 10 mL of a saturated aqueous NH_4Cl solution. After filtration, the organic layer was separated. The aqueous layer was extracted twice with 10 mL of Et_2O, and the combined organic layers were dried on $MgSO_4$, filtered, and carefully evaporated to yield the products.

Methyl 2-[(Phenylamino)(2-pyridyl)methyl]-3-butenoate (4a). The product was obtained as a white crystalline solid by recrystallization from Et_2O. Mp 124 °C. Yield: 0.55 g (39%) ^{1}H NMR ($CDCl_3$): δ 8.58 (m, 1H); 7.56 (m, 1H); 7.24 (m, 1H); 7.1−7.2 (m, 3H); 6.7 (m, 3H); 5.86 (m, 1H); 5.1 (m, 3H); 4.94 (br d, *J* = 6.6, 1H); 3.80 (dd, *J* = 6.7, 8.6, 1H); 3.66 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 172.8, 159.4, 149.4, 146.8, 136.4, 129.2, 122.4, 122.2, 118.0, 114.0, 132.6, 119.5, 60.6, 55.2, 52.0. IR (KBr, cm^{-1}): 3277 (NH); 1727 (C=O); 3089, 997 (HC=CH_2). Anal. Calcd for $C_{17}H_{18}N_2O_2$: C 72.32, H 6.43, N 9.92. Found: C 72.22, H 6.46, N 9.86. GCMS: *m/z* 282 (<0.5), 183 (100).

Methyl 3-(phenylamino)-5-(trimethylsilyl)-2-vinyl-4-pentynoate (4b). The product was obtained as a pale yellow solid (80:20 *anti:syn* mixture). Yield: 1.13 g (82%). The major diastereoisomer was enriched up to 84% de by recrystallization from pentane. ^{1}H NMR ($CDCl_3$): δ 7.22 (m, 2H); 6.7−6.8 (m, 3H); 6.04 (m, 1H); 5.2−5.4 (m, 2H); 4.63 (d, 1H, *J* = 6.1); 4.02 (br s, 1H); 3.74 (s, 3H); 3.44 (dd, 1H, *J* = 6.1, 8.9); 0.12 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 171.6, 145.8, 129.2, 119.0, 114.7, 131.6, 120.2, 103.1, 89.7, 54.5, 52.2, 48.2, −0.14. IR (KBr, cm^{-1}): 3357 (NH); 2163 (C≡C); 1727 (C=O); 3083, 1002, 918 (HC=CH_2). Anal. Calcd for $C_{17}H_{23}NO_2Si$: C 67.73, H 7.69, N 4.65, Si 9.32. Found: C 67.83, H 7.74, N 4.73, Si 9.22. GCMS: *m/z* 301 (<0.5), 202 (100).

Methyl (*E*)-5-(Phenylamino)-5-(2-pyridyl)-2-pentenoate (5a). Compound **5a** was obtained as a pale yellow solid after recrystallization from Et_2O. Mp 79.5 °C. Yield: 1.40 g (99%). ^{1}H NMR ($CDCl_3$): δ 8.59 (m, 1H); 7.62 (m, 1H); 7.29 (m, 1H); 7.1−7.2 (m, 3H); 6.92 (dt, *J* = 6.5, 15.6, 1H); 6.69 (m, 1H); 6.57 (d, 2H, *J* = 3.8); 5.88 (d, *J* = 15.6 1H); 4.66 (br t, *J* = 6.5, 1H); 4.43 (br s, 1H); 3.70 (s, 3H); 2.7−2.9 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 166.5, 161.0, 149.5, 146.6, 136.9, 129.2, 123.8, 121.3, 117.9, 113.6, 144.7, 122.4, 57.9, 51.5, 39.1. IR (KBr, cm^{-1}): 3284 (NH); 1715 (C=O); 1603, 989 (*trans* HC=CH). Anal. Calcd for $C_{17}H_{18}N_2O_2$: C 72.32, H 6.43, N 9.92. Found: C 72.18, H 6.53, N 9.83. GCMS: *m/z* 282 (<0.5), 183 (100).

Methyl (*E*)-5-[(*R*)-[(1-Phenylethyl)amino]]-5-(2-pyridyl)-2-pentenoate (5c). The product was obtained as a colorless oil. The ^{1}H NMR spectrum revealed that the product was a mixture of two diastereoisomers (de 92%, $[\alpha]^{20}_D$ = +28.1 (*c* = 0.6, EtOH)). Yield: 1.25 g (95%). All data refer to the major diastereoisomer. ^{1}H NMR ($CDCl_3$): δ 8.52 (m, 1H); 7.52 (m, 1H); 7.1−7.3 (M, 7H); 6.84 (dt, 1H, *J* = 7.3, 15.6); 5.77 (d, 1H, *J* = 15.6); 3.87 (t, 1H, *J* = 6.5); 3.74 (q, 1H, *J* = 6.5);

(24) All synthetic manipulations with air-sensitive reagents were carried out under a dry, inert N_2 atmosphere using standard Schlenk techniques. Solvents were dried and distilled from sodium/benzophenone prior to use. Diisopropylamine was distilled at atmospheric pressure and stored over molecular sieves (3 Å). Dry zinc chloride,[4c] esters, and imines **3a−d**[25] were prepared according to literature procedures. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WP 200 and a Bruker WP 300 spectrometer in chloroform-*d* or benzene-d_6. All coupling constants are presented in hertz (Hz). IR spectra were recorded on a Mattson Galaxy FTIR 5000 spectrometer. Mass spectra were recorded on a Unicam 610 Automass GCMS system. Melting points and boiling points are uncorrected. Elemental analyses were performed by Dornis und Kolbe Mikroanalytisches Laboratorium, Mülheim a/d Ruhr, Germany.

(25) Dayagi, S.; Degani, Y. In *The Chemistry of the Carbon-Nitrogen Double Bond*, Patai, S., Ed., Interscience: London, **1970**; pp 61−148.

3.65 (s, 3H); 2.5–2.7 (m, 2H); 2.18 (br s, 1H); 1.34 (s, 3H, J = 6.5). ^{13}C NMR ($CDCl_3$): δ 166.6, 162.0, 149.4, 136.2, 128.3, 126.9, 126.7, 123.0, 122.1, 145.9, 122.7, 60.2, 55.4, 51.3, 38.7, 23.3. IR (KBr, cm^{-1}): 3316 (NH); 1723 (C=O); 3026, 1656 (*trans* HC=CH). Anal. Calcd for $C_{19}H_{22}N_2O_2$: C 73.52, H 7.14, N 9.03. Found: C 73.36, H 7.10, N 9.10. GCMS (*m/z*): 295 (1), 211 (100), 107 (81), 105 (62).

Methyl (*E*)-5-[(*R*)-[(1-Phenylethyl)amino]]-7-(trimethylsilyl)hept-2-en-6-ynoate (5d). The product, obtained as a yellow oil, was a 1:1 mixture of diastereoisomers. Yield: 1.23 g (100%). ^{1}H NMR ($CDCl_3$): δ 7.28 (m, 5H); 6.96 (m, 1H); 5.91/5.89 (d, J = 15.8, 1H); 4.10/4.04 (q, 1H, J = 6.6/6.5); 3.72 (s, 3H); 3.62 (m, 1H); 2.47 (m, 2H); 1.34/1.32 (d, J = 6.6/6.5); 0.19/0.17 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 166.7, 144.9, 144.5/145.5, 128.5/128.4, 127.1/127.2, 127.0/126.8, 123.5, 106.2/106.5, 88.9, 55.2/55.7, 51.5, 47.4/47.2, 38.4/38.8, 22.4/25.0, 0.1. IR (KBr, cm^{-1}): 3325 (NH); 2160 (C≡C); 1726 (C=O); 1603, 984 (C=C). GCMS: 314 (<1), 230 (100), 126 (80), 105 (93).

Methyl 2-Isopropenyl-3-(phenylamino)-5-(trimethylsilyl)-4-pentynoate (6b). The crude material was an 82:18 *anti-syn* mixture. The major isomer was obtained as white feather-shaped crystals by crystallization from pentane. Mp 73 °C. Yield: 1.20 g (95%). ^{1}H NMR ($CDCl_3$): δ 7.2 (m, 2H); 6.8 (m, 3H); 5.05 (br s, 2H); 4.62 (d, 1H, J = 8.7); 3.70 (s, 3H); 3.43 (d, J = 8.7, 1H); 1.90 (s, 3H); 0.10 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 171.7, 146.4, 129.1, 119.1, 115.1, 139.4, 116.4, 104.1, 89.2, 58.1, 52.1, 47.9, 21.1, −0.2. IR (KBr, cm^{-1}): 3368 (NH); 2164 (C≡C); 1734 (C=O); 1643, 898 (C=C). GCMS: *m/z* 315 (<0.5), 202 (100).

The minor isomer was also crystallized from pentane, affording pale orange needles. Mp 100 °C. ^{1}H NMR ($CDCl_3$): δ 5.06 (br s, 2H); 4.46 (d, 1H, J = 9.3); 3.75 (s, 3H); 3.53 (d, 1H, J = 9.3); 1.78 (s, 3H); 0.09 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 171.0, 146.3, 139.4, 129.1, 118.8, 117.3, 114.3, 104.5, 88.6, 58.8, 52.1, 46.4, 19.5, −0.2. Anal. Calcd for $C_{18}H_{25}NSiO_2$: C 68.53, H 7.99, N 4.44. Found: C 68.48, H 8.08, N 4.54. GCMS: *m/z* 315 (<0.5), 202 (100).

X-ray Structure Determination of *syn*-6b.[26] Data were obtained at 150 K using an Enraf-Nonius CAD4-Turbo diffractometer with rotating anode (Mo K_α, $C_{18}H_{25}NO_2Si$, M_w = 315.49, space group $P2_1/c$, a = 10.1370(7) Å, b = 9.4817(7) Å, c = 19.653(2) Å, β = 94.623(8)°, Z = 4, d_x = 1.113 g cm^{-3}, V = 1882.8(3) Å^3. The 5364 reflections collected were corrected for linear decay, Lp, and absorption (DIFABS), and processed to give 4304 unique reflections (R_{int} = 0.08). The structure was solved with DIRDIF-92 and refined on F^2 using SHELXL-93. All reflections were considered observed. Final R_1 = 0.0788 (2210 $F_o > 4\sigma(F_o)$) with hydrogen atoms included at calculated positions. Full details may be obtained from one of the authors (A.L.S.).

Methyl (*E*) 3-Methyl-5-(phenylamino)-5-(2-pyridyl)-2-pentenoate (7a) and 4-Methyl-1-phenyl-6-(2-pyridyl)-5,6-dihydropyridin-2-one (8a). A mixture of α,β-unsaturated ester **7a** (42%) and pyridin-2-one **8a** (58%) was obtained. Yield: 1.30 g (95%). Compound **7a**, contaminated with 6% of the 5,6-dihydropyridin-2-one **8a**, was obtained by crystallization from Et_2O. Mp 95–101 °C. ^{1}H NMR ($CDCl_3$): δ 8.59 (d, J = 3.0, 1H); 7.61 (m, 1H); 6.67 (t, J = 7.2, 1H); 6.55 (d, J = 7.8, 2H); 5.71 (br s, 1H); 4.71 (dd, J = 5.7, 8.6, 1H); 4.42 (br s, 1H); 3.67 (s, 3H); 2.81 (dd, J = 5.7, 13.8, 1H); 2.60 (dd, J = 8.6, 13.8, 1H); 2.19 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 166.6, 161.7, 155.9, 149.4, 146.7, 137.0, 129.2, 121.2, 118.3, 117.9, 113.6, 122.4, 57.1, 50.9, 48.0, 18.5. GCMS: *m/z* 296 (3), 183 (100).

The pyridin-2-one **8a** was purified by recrystallization from Et_2O. Mp: 134 °C. ^{1}H NMR ($CDCl_3$): δ 8.55 (d, J = 4.5, 1H); 7.64 (m, 1H); 7.1–7.3 (m, 6H); 5.90 (br s, 1H); 5.16 (dd, 1H, J = 1.9, 7.0); 3.16 (dd, J = 7.0, 17.6, 1H); 2.85 (dd, J = 1.9, 17.6, 1H); 1.79 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 164.6, 160.2, 149.4, 142.0, 136.8, 128.8, 125.8, 125.1, 122.4, 121.5, 121.1, 63.4, 36.1, 22.9. IR (KBr, cm^{-1}): 1662 (C=O); 1624 (C=C). Anal. Calcd for $C_{17}H_{16}N_2O$: C 77.25, H 6.10, N 10.60. Found: C 77.16, H 6.19, N 10.55. GCMS: *m/z* 264 (37), 186 (100), 144 (42), 77 (80).

4-Methyl-1-[(*R*)-1-phenylethyl]-6-(2-pyridyl)-5,6-dihydropyridin-2-one (8c). The crude material 1.23 g was a mixture of two diastereoisomers (de 77%). The major diastereoisomer was obtained by crystallization from Et_2O/pentane as a white crystalline solid. Mp 86 °C. $[\alpha]^{20}_D$ 90° (*c* 0.17, EtOH). ^{1}H NMR ($CDCl_3$): δ 8.47 (m, 1H); 7.58 (m, 1H); 7.2–7.3 (m, 6H); 7.11 (m, 1H); 6.15 (q, 1H, J = 7.2); 5.84 (br s, 1H); 4.50 (d, 1H, J = 7.0); 2.60 (dd, 1H, J = 7.0, 7.5); 2.32 (d, 1H, J = 7.5); 1.61 (s, 3H); 1.17 (d, 3H, J = 7.2). ^{13}C NMR ($CDCl_3$): δ 164.9, 161.9, 149.3, 147.5, 141.9, 136.2, 128.5, 127.4, 127.1, 122.0, 121.0, 55.7, 50.3, 36.3, 22.7, 16.3. IR: (KBr, cm^{-1}): 1664 (C=O); 1620 (C=C). Anal. Calcd for $C_{19}H_{20}N_2O$: C 78.05, H 6.90, N 9.58. Found: C 78.18, H 6.98, N 9.51. GCMS: *m/z* 292 (9), 173 (100), 144 (78), 105 (61).

Methyl 2-[(Phenylamino)(2-pyridyl)methyl]-3-pentenoate (10a). A 57:43 *anti/syn* mixture was obtained by quenching the reaction mixture at −78 °C. Crystallization from Et_2O/hexane yielded a 1:1 mixture of the two. Major diastereoisomer. ^{1}H NMR ($CDCl_3$): δ 8.57 (d, J = 3.0, 1H); 7.55 (m, 1H); 7.31 (d, J = 7.8, 2H); 7.1 (m, 3H); 6.6–6.7 (m, 3H); 5.5–5.7 (m, 2H); 4.86 (d, 1H, J = 6.4); 4.66 (br s, 1H); 3.64 (m, 1H); 3.58 (s, 3H); 1.66 (d, 3H, J = 5.4). ^{13}C NMR ($CDCl_3$): δ 172.7, 160.2, 149.3, 147.1, 136.4, 130.6, 129.2, 125.1, 122.3, 122.2, 118.0, 114.0, 61.0, 55.0, 51.8, 18.1. GCMS: *m/z* 282 (<0.5), 183 (100).

Minor diastereoisomer. ^{1}H NMR ($CDCl_3$): δ 8.57 (d, J = 3.0, 1H); 7.55 (m, 1H); 7.17 (d, J = 7.8, 2H); 7.1 (m, 3H); 6.6–6.7 (m, 3H); 5.47–5.68 (m, 2H); 5.07 (br s, 1H); 4.86 (d, 1H, J = 6.4); 3.71 (m, 1H); 3.62 (s, 3H); 1.59 (d, 3H, J = 4.5). ^{13}C NMR ($CDCl_3$): δ 173.3, 159.7, 149.1, 147.0, 136.2, 129.1, 125.2, 122.3, 117.8, 114.0, 130.6, 122.3, 61.0, 54.4, 51.8, 18.0. IR (KBr, cm^{-1}): 3287 (NH); 1728 (C=O); 1603, 976 (C=C). GCMS: *m/z* 282 (<0.5), 183 (100).

Methyl (*E*)-2-(1-Propenyl)-3-(phenylamino)-5-(trimethylsilyl)-4-pentynoate (10b). A 55:45 mixture of two diastereoisomers was obtained by quenching the reaction mixture. The major isomer was obtained as a white solid by crystallization from Et_2O/hexane (80:20). Yield: 1.20 g (96%). Mp 80 °C. ^{1}H NMR ($CDCl_3$): δ 7.2–7.3 (m, 2H); 6.7–6.8 (m, 3H); 5.6–5.7 (m, 2H); 4.55 (d, 1H, J = 6.4); 3.72 (s, 3H); 3.38 (m, 1H); 4.0 (br s, 1H); 1.76 (d, 3H, J = 4.4); 0.12 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 172.2, 145.9, 131.8, 129.1, 124.2, 118.9, 114.7, 103.6, 89.4, 53.8, 52.1, 48.5, 18.1, −0.1. IR (KBr, cm^{-1}): 3355 (NH), 2173 (C≡C), 1722 (C=O), 967 (C=C). Anal. Calcd for $C_{18}H_{25}NSiO_2$: C 68.53, H 7.99, N 4.44, Si 8.90. Found: C 68.38, H 8.11, N 4.48, Si 9.04. GCMS: *m/z* 315 (<0.5), 202 (100).

Minor diastereoisomer (not isolated, characteristic data): ^{1}H NMR ($CDCl_3$): δ 5.6–5.7 (m, 2H); 4.40 (d, 1H, J = 6.2); 3.73 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 171.9, 146.3, 129.1, 118.7, 114.5, 131.4, 125.0, 104.0, 89.0, 54.2, 52.1, 49.1, 20.8, −0.1. GCMS: *m/z* 315 (<0.5), 202 (110).

Methyl (*E*)-4-Methyl-5-(phenylamino)-5-(2-pyridyl)-2-pentenoate (11a). The crude material (1.42 g, 97%) was a 70:30 *anti/syn* mixture. The *anti*-diastereoisomer was purified by crystallization from THF. Mp: 97 °C. ^{1}H NMR ($CDCl_3$): δ 8.60 (m, 1H); 7.62 (m, 1H); 7.27 (d, J = 7.2, 1H); 7.18 (m, 1H); 7.10 (m, 2H); 6.96 (dd, J = 7.4, 15.7, 1H); 6.66 (t, J = 7.3, 2H); 5.88 (dd, J = 1.3, 15.7, 1H); 4.50 (d & br s, J = 6.2, 2H); 3.73 (s, 3H); 3.08 (m, 1H); 1.07 (d, J = 6.8, 3H). ^{13}C NMR: 166.7, 160.3, 150.1, 149.1, 146.9, 136.8, 129.2, 122.5, 122.2, 122.0, 117.8, 113.6, 62.9, 51.5, 41.9, 16.2. IR (KBr, cm^{-1}): 3285 (NH); 1709 (C=O); 989 (C=C). Anal. Calcd for $C_{18}H_{20}N_2O_2$: C 72.95, H 6.80, N 9.45. Found: C 73.06, H 6.88, N 9.41. GCMS: *m/z* 296 (1), 183 (100).

Minor diastereoisomer (not isolated, characteristic data): ^{1}H NMR ($CDCl_3$) δ 5.80 (d, J = 15.7, 1H); 4.56 (d, J = 4.7, 1H); 3.70 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 62.3, 51.5, 41.7, 14.9.

5-Methyl-1-[(*R*)-1-phenylethyl]-6-(2-pyridyl)-5,6-dihydropyridin-2-one (12c) and *trans*-1-[(*R*)-1-Phenylethyl]-3-[(*E*)-1-propenyl]-4-(2-pyridyl)-2-azetidinone (13c). The crude product consisted of 90% 2-azetidinone **13c** and 10% of 5,6-dihydropyridin-2-one **12c**. Yield: 1.41 g (96%). After

(26) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

filtration over Al_2O_3, compound **13c** was separated from **12c** by HPLC (Supelcosil PLC-Si, hexane/iPrOH 80:20) and obtained with 88% de as a pale yellow oil. $[\alpha]^{20}_D$ +100.1 (*c* 0.5, EtOH). ^1H NMR ($CDCl_3$): δ 8.45 (d, J = 4.5, 1H); 7.50 (m, 1H); 7.0–7.3 (m, 7H); 5.54 (dq, J = 6.2, 15.8, 1H); 5.36 (dd, J = 7.8, 15.8, 1H); 4.92 (q, J = 7.1, 1H); 4.12 (d, J = 2.0, 1H); 3.68 (dd, J = 2.0, 7.8, 1H); 1.52 (d, J = 6.2, 3H); 1.18 (d, J = 7.1, 3H). ^{13}C NMR ($CDCl_3$): δ 168.8, 158.2, 149.7, 140.0, 136.6, 130.5, 128.5, 127.6, 127.0, 123.7, 123.1, 62.0, 60.8, 52.1, 18.6, 18.0. IR (KBr, cm^{-1}): 1748 (C=O); 965 (C=C). Anal. Calcd for $C_{19}H_{20}N_2O$: C 78.05, H 6.90, N 9.58. Found: C 77.95, H 6.97, N 9.65. GCMS: *m/z* 292 (1), 145 (30), 130 (100).

5,6-Dihydropyridin-2-one **12c** was obtained as a colorless oil by HPLC. ^1H NMR ($CDCl_3$): δ 8.54 (m, 1H); 7.64 (m, 1H); 6.9–7.4 (m, 7H); 6.31 (q, J = 7.0, 1H); 6.16 (m, 1H); 6.01 (d, J = 9.7, 1H); 4.34 (br s, 1H); 2.57 (dq, J = 6.5, 6.8, 1H); 1.19 (d, J = 7.3, 3H); 0.63 (d, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$): δ 163.4, 162.0, 149.2, 141.8, 136.4, 128.4, 128.0, 127.8, 122.1, 120.9, 118.8, 61.3, 50.2, 36.3, 18.9, 15.8. GCMS: *m/z* 292 (5), 173 (100), 130 (64), 105 (47).

Methyl (*E*)-4-Phenyl-2-[(2-pyridyl)(phenylamino)methyl]-3-butenoate (14a). The crude material had a de of 22%. Yield: 1.59 g (88%). The major diastereoisomer was obtained as an off-white solid by crystallization from THF/Et_2O (40:60). Mp 132 °C. ^1H NMR ($CDCl_3$): δ 8.60 (d, J = 4.2, 1H); 7.56 (m, 1H); 7.1–7.3 (m, 9H); 6.7 (m, 3H); 6.38 (d, J = 15.9, 1H); 5.15 (br s, 1H); 5.04 (d, J = 5.2, 1H); 3.94 (dd, J = 5.2, 6.6, 1H); 3.68 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 172.9, 159.3, 149.4, 146.8, 136.6, 136.4, 134.3, 129.3, 128.5, 127.8, 126.5, 123.9, 122.5, 122.2, 118.1, 114.1, 61.1, 54.6, 52.1. IR (KBr, cm^{-1}): 3273 (NH); 1728 (C=O); 968 (C=C). Anal. Calcd for $C_{23}H_{22}N_2O_2$: C 77.07, H 6.19, N 7.82. Found: C 77.13, H 6.31, N 7.85. GCMS: *m/z* 358 (<0.5), 207 (52), 183 (100).

Minor diastereoisomer: Mp 116 °C. ^1H NMR ($CDCl_3$): δ 6.41 (d, J = 15.8, 1H); 6.33 (dd, J = 8.1, 15.9, 1H); 5.01 (d, J = 7.0, 1H); 3.87 (dd, J = 7.0, 8.1, 1H); 3.63 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 172.4, 159.9, 149.4, 147.0, 136.6, 136.5, 134.7, 129.2, 128.5, 127.9, 126.5, 123.8, 122.5, 122.2, 118.1, 114.1, 114.0, 61.2, 55.1, 52.1. GCMS: *m/z* 358 (<0.5), 207 (7), 183 (100).

Methyl (*E*)-3-(Phenylamino)-2-(2-phenylethenyl)-5-(trimethylsilyl)-4-pentynoate (14b). The crude product was obtained as an off-white solid, yield 1.50 g (99%, de 10%). After crystallization from Et_2O/pentane the de was unchanged. Major diastereoisomer. ^1H NMR ($CDCl_3$): δ 7.2–7.4 (m, 8H); 6.7–6.8 (m, 2H); 6.62 (d, J = 15.7, 1H); 6.27 (dd, J = 9.4, 15.7, 1H); 4.52 (d, J = 6.4, 1H); 3.77 (s, 3H); 3.60 (m, 1H); 0.14 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 172.0, 146.0, 135.4, 135.1, 129.2, 128.6, 128.0, 126.6, 123.3, 119.1, 114.8, 103.5, 89.4, 54.3, 52.2, 49.6, −0.14. IR (KBr, cm^{-1}): 3352 (NH); 2166 (C≡C); 1720 (C=O); 1603, 970 (C=C). Anal. Calcd for $C_{23}H_{27}NO_2Si$: C 73.17, H 7.21, N 3.71, Si 7.44. Found: C 73.20, H 7.28, N 3.16, Si 7.59. GCMS: *m/z* 377 (<0.5), 202 (100), 115 (22).

Minor diastereoisomer. ^1H NMR ($CDCl_3$): δ 7.2–7.4 (m, 8H); 6.7–6.8 (m, 2H; 6.52 (d, J = 16.1, 1H); 6.40 (dd, J = 7.1, 16.1, 1H); 4.70 (d, J = 6.1, 1H); 3.69 (s, 3H); 3.60 (m, 1H); 0.12 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 171.9, 145.8, 134.6, 129.2, 128.6, 128.0, 126.6, 122.8, 119.1, 114.7, 103.2, 89.7, 53.9, 52.0, 48.9, −0.14. GCMS: *m/z* 377 (<0.5), 202 (100).

***trans*-1-[(*R*)-1-Phenylethyl]-3-[(*E*)-phenylethenyl]-4-pyridyl-2-azetidinone (16c).** Compound **16c** was obtained as a pale yellow oil, as a mixture of two *trans*-diastereoisomers with a de of 92%. $[\alpha]^{20}_D$ +208.2 (*c* 0.37, EtOH). ^1H NMR ($CDCl_3$): δ 8.59 (m, 1H); 7.62 (m, 1H); 7.1–7.3 (m, 12H); 6.55 (d, J = 15.9, 1H); 6.20 (dd, J = 8.0, 15.9, 1H); 5.06 (q, J = 7.1, 1H); 4.32 (d, J = 2.2, 1H); 4.02 (dd, J = 2.2, 8.0, 1H); 1.31 (d, J = 7.1, 3H). ^{13}C NMR ($CDCl_3$): δ 168.2, 140.0, 158.0, 149.9, 136.8, 136.5, 134.1, 128.7, 128.5, 127.8, 127.2, 126.4, 123.4, 121.9, 122.1, 62.0, 61.0, 52.4, 18.7. IR (KBr, cm^{-1}): 1743 (C=O); 964 (C=C). Anal. Calcd for $C_{24}H_{22}N_2O$: C 81.33, H 6.26, N 7.90. Found: C 81.19, H 6.21, N 7.84.

Acknowledgment. The authors wish to thank Gistbrocades for financially supporting this research. Dr. Jan Verweij and Dr. Antonius P. G. Kieboom are kindly acknowledged for the stimulating discussions. This work was supported in part (A.L.S.) by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for Advancement of Pure Research (NWO). M.T.L. thanks the EC for the award of a postdoctoral fellowship under the framework of the Human Capital and Mobility Initiative.