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Highly Diastereoselective Mannich-Type Reactions of Chiral *N*-Acylhydrazones

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The Lewis acid-mediated addition of silyl enolates to easily accessible homochiral *N*-acylhydrazones derived from 3-amino-2-oxazolidinones proceeded in yields up to 71% and diastereomeric ratios of 99:1. In most cases, optimal reaction conditions entailed the simple use of $ZnCl_2$ in acetonitrile at room temperature. Hydrazones derived from phenyl-, isopropyl-, and benzyl-substituted 2-oxazolidinones were examined in the reaction in terms of yield and diastereoselectivity. The facile SmI_2-mediated N−N bond cleavage of the formed hydrazines was demonstrated yielding a β-amino acid derivative. Hence, the overall reaction sequence constitutes an efficient asymmetric Mannich-type reaction. The sense of diastereoselectivity was explained by a preferential attack on the less shielded *Si* face of the chiral hydrazones and confirmed by means of X-ray crystallography.

Introduction

The Lewis acid-mediated reactions of imines with silyl enolates are among the most efficient for the synthesis of β-amino acids. The unique conformational and biological properties of β-amino acids in β-peptides[1] incorporating such monomers and their use as building blocks for many nitrogen-containing biological compounds[2] has prompted a tremendous amount of effort in the development of asymmetric variants.[3] However, many imines tend to be unstable during purification by chromatography, distillation, or prolonged storage, especially aliphatic imines. Our previous work on the SmI_2-mediated diastereoselective construction of highly functionalized proline derivatives demonstrated that key stereocontrol in the reaction could be traced to the C4-stereocenter of the β-lactam precursors.[4] In our pursuit of simple and novel methods for the asymmetric synthesis of such C4-functionalized precursors, we have recently reported on the asymmetric Mannich-type reaction of ketene acetals **4** and sulfinimines of the structure **3** derived from chiral *N-tert*-butanesulfinamide.[5] These sulfinimines are stable imine equivalents. The aspartic acid derivatives **2** obtained are excellent precursors for the access to β-lactams **1** (Scheme 1).

Another stable class of imine equivalents is represented by the hydrazones since a variety of protocols exist for efficient N−N cleavage of hydrazones.[6] On the other hand, their lack of reactivity toward nucleophiles has resulted in few reports on addition reactions compared to imines,[6b−f,7] except those involving organometallic reagents.[8] While the use of basic organometallic reagents for C−C bond formation limits the functional group tolerance and can result in competitive metalloenamine formation,[9] the Lewis acid-mediated Mannich-type reactions of silyl enolates are usually highly chemoselective and can be performed under relatively mild conditions.

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(7) For Lewis acid-mediated nucleophilic additions to hydrazones, see: (a) Kobayashi, S.; Hamada, T.; Manabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 5640 and references therein. (b) Manabe, K.; Oyamada, H.; Sugita, K.; Kobayashi, S. *J. Org. Chem.* **1999**, *64*, 8054. (c) Friestad, G. K.; Ding, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 4491.

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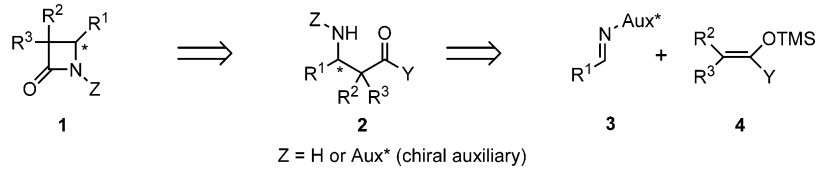
SCHEME 1



Recently, Friestad introduced *N*-acylhydrazones derived from *N*-amino 2-oxazolidinones in asymmetric synthesis, most prominently in stereoselective allylation and radical addition reactions.[7c,10] We envisioned that the right choice of Lewis acid and aldehyde precursor of the hydrazone would yield a sufficiently potent species capable of reacting with many different silyl enolates. Thus, glyoxylates emerged as obvious aldehyde candidates for the condensation with *N*-amino 2-oxazolidinones. The neighboring ester functionality should increase the reactivity toward nucleophiles by lowering the LUMO of the C═N bond.

Results and Discussion

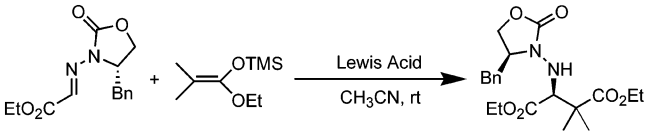
Deprotonation of chiral 2-oxazolidinones **5a**−**c** with NaH in dioxane and subjection to the effective NH_2^+ equivalent *O*-(*p*-nitrobenzoyl)hydroxylamine ($NbzONH_2$) furnished crude *N*-amino 2-oxazolidinones, which were condensed with ethyl glyoxylate in toluene to give the *N*-acylhydrazones **3a**−**c** in moderate to good yields (34−78%).[11]

Our initial studies examined the influence of different Lewis acids on the outcome of the reaction of chiral hydrazone **3a** with ketene acetal **4a** (Table 1).

Indium(III) trifluoromethanesulfonate has proven efficient in the allylations of similar hydrazones with allylsilanes,[7c] but no reaction was observed in either CH_2Cl_2 or CH_3CN (entry 1 and 2). This was surprising since ketene acetals are usually considered more reactive than allylsilanes as nucleophiles. The lanthanide salts Yb(OTf)$_3$ and $CeCl_3$ did not prove successful either, since only a trace of product could be observed.[12]

The use of Sc(OTf)$_3$ in catalytic quantities for the activation of hydrazones has been reported before,[7b,13] and indeed the product **2a** was obtained in a promising 53% yield with almost complete stereocontrol (entry 6). Changing the amount of Sc(OTf)$_3$ seemed to have little influence. Minor amounts (∼5%) of product resulting from the attack of **4a** on the ester moiety of **3a** were also detected by ^{1}H NMR and MS in the case of Sc(OTf)$_3$ (entries 6−8).

TABLE 1. Survey of Lewis Acids for Promotion of Addition to Hydrazone 3a[a,b]



3a **4a** **2a**

entry	Lewis acid (mol %)	yield (%)[c]	dr[d]
1	In(OTf)$_3$ (130%)	0	
2[e]	In(OTf)$_3$ (130%)	0	
3	Yb(OTf)$_3$ (10%)	trace	
4	$CeCl_3$ (110%)	trace	
5	Cu(OTf)$_2$ (100%)	0	
6	Sc(OTf)$_3$ (5%)	53	99:1
7	Sc(OTf)$_3$ (10%)	51	99:1
8	Sc(OTf)$_3$ (20%)	46	98:2
9	Zn(OTf)$_2$ (100%)	66	83:17
10	Zn(OTf)$_2$ (130%)	71	79:21
11[f]	ZnF_2 (130%)	trace	
12	ZnI_2 (130%)	60	98:2
13	$ZnCl_2$ (130%)	64 (54)[g]	97:3 (>99:1)[g]
14	$ZnCl_2$ (250%)	60	97:3

[a] Reaction time was 24 h except for entries 1, 10, 11, and 13 where reaction time was 44 h. [b] The absolute configuration of the major diastereomer of **2a** shown was confirmed by X-ray crystallographic analysis; see the text. [c] Isolated yields of purified diastereomeric mixtures after chromatography. [d] Determined by ^{1}H NMR (400 MHz) analysis of crude product. [e] Reaction was performed in CH_2Cl_2. [f] Very low solubility of ZnF_2 in CH_3CN. [g] Isolated yield after direct recrystallization of crude product from Et_2O/pentanes.

More clean reactions ensued by using Zn^{2+} Lewis acids, and analytically pure samples of virtually complete enantiopurity could be obtained in greater than 50% yield by a single recrystallization of the crude product (entry 13).[14] The optimal conditions involved the use of a slight excess of either ZnI_2 or $ZnCl_2$ in CH_3CN. A larger excess did not improve the yield (entry 14).

Next, we examined the effect of changing the substitution on the 2-oxazolidinones (Table 2). However, little change in yield and diastereoselectivity was observed with the isopropyl derivative **3b** and ketene acetal **4a** compared to **3a** and **4a**. The yields were lowered considerably when other silyl enolates **4b** and **4c** were employed (entry 3 and 4), although high dr values were still attained. Interestingly, extensive formation of byproducts was observed in the reaction of **3b** with **4b** (entry 3, see discussion below). The phenyl derivative **3c** showed similar tendencies as **3a**, but furnished lower dr values (entries 5−6) and yields (entries 6 and 7). Notably, the yield and diastereoselectivity eroded compared to the results for **3b** when $ZnCl_2$ was used.

The generally poorer performance of **3b** and **3c** compared to **3a** and the more efficient synthesis of **3a** then

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(12) Catalytic amounts of Yb(OTf)$_3$ have been efficient in the activation of imines. For examples, see: (a) Annunziata, R.; Cinquini, M.; Cozzi, F.; Molteni, V.; Schupp, O. *J. Org. Chem.* **1996**, *61*, 8293. (b) Kobayashi, S.; Araki, M.; Ishitani, H.; Nagayama, S.; Hachiya, I. *Synlett* **1995**, 233. (c) Kobayashi, S.; Araki, M.; Yasuda, M. *Tetrahedron Lett.* **1995**, *36*, 5773.

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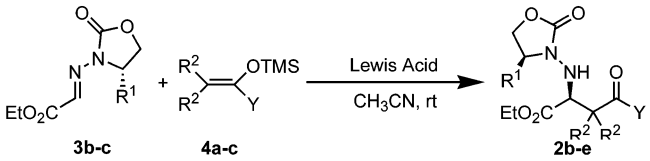
(14) Zn^{2+} Lewis acids have also been employed in the catalytic asymmetric Mannich-type reactions of *N*-acylhydrazones, see ref 7a.

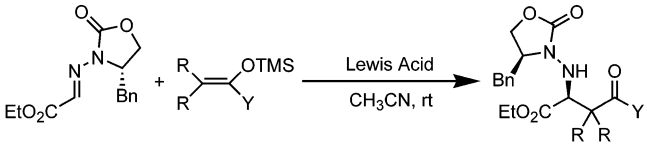
TABLE 2. Effect of Different Chiral 2-Oxazolidinones on the Addition to Hydrazones 3b−c[a,b]



entry	R^1	R^2, Y	Lewis acid (mol %)	product	% yield[c]	dr[d]
1	*i*-Pr (**3b**)	Me, OEt (**4a**)	$Zn(OTf)_2$ (130%)	**2b**	64	86:14
2	*i*-Pr (**3b**)	Me, OEt (**4a**)	$ZnCl_2$ (130%)	**2b**	64	98:2
3[e]	*i*-Pr (**3b**)	H, OEt (**4b**)	$ZnCl_2$ (130%)	**2c**	17	97:3
4	*i*-Pr (**3b**)	H, SPh (**4c**)	$ZnCl_2$ (130%)	**2d**	27	98:2
5	Ph (**3c**)	Me, OEt (**4a**)	$Zn(OTf)_2$ (130%)	**2e**	64	65:35
6	Ph (**3c**)	Me, OEt (**4a**)	$ZnCl_2$ (130%)	**2e**	35	80:20
7	Ph (**3c**)	Me, OEt (**4a**)	$Sc(OTf)_3$ (20%)	**2e**	36	99:1

[a] Reaction time was 24 h. [b] Configurations of **2b−e** shown are assigned by analogy with **2a**; see the text. [c] Isolated yields of purified diastereomeric mixtures after chromatography. [d] Determined by ^{1}H NMR (400 MHz) analysis of crude product. [e] The formation of major amounts of byproducts was observed.

TABLE 3. Mannich-Type Reactions of Hydrazone 3a with Different Ketene Acetals 4b−e[a]



entry	R, Y	Lewis acid (mol %)	product	% yield[b]	dr[c]
1	H, OEt (**4b**)	$Sc(OTf)_3$ (10%)	**2f**	<5[d]	70:30
2	H, OEt (**4b**)	$Zn(OTf)_2$ (130%)	**2f**	trace	
3	H, OEt (**4b**)	$ZnCl_2$ (130%)	**2f**	61	98:2
4	H, SPh (**4c**)	$Sc(OTf)_3$ (10%)	**2g**	27	77:23
5[e]	H, SPh (**4c**)	$ZnCl_2$ (130%)	**2g**	50	87:13
6	H, SPh (**4c**)	$ZnCl_2$ (130%)	**2g**	62	96:4
7	H, SEt (**4d**)	$ZnCl_2$ (130%)	**2h**	30	95:5
8	H, O*t*-Bu (**4e**)	$ZnCl_2$ (130%)	**2i**	56	97:3

[a] Configurations of **2f−i** shown are assigned by analogy with **2a**; see the text. [b] Isolated yields of purified diastereomeric mixtures after chromatography. [c] Determined by ^{1}H NMR (400 MHz) analysis of crude product. [d] NMR yield. [e] The solvent was CH_2Cl_2.

prompted us to use the latter for further investigations of reactions with other silyl enolates (Table 3).

Fortunately, the behavior of the **3a**-$ZnCl_2$ system proved different than that of **3b**-$ZnCl_2$, as silyl enolates **4b−e** reacted almost equally well, with the exception of **4d** where the yield was 30%. Again, other Lewis acids tested were overall less efficient than $ZnCl_2$. Surprisingly, almost no reaction with **4b** could be detected by ^{1}H NMR when $Sc(OTf)_3$ or $Zn(OTf)_2$ was employed, contrary to the reaction of **4a**.

The cleavage of the N−N bond of hydrazines is sometimes troublesome, and epimerization is often likely to occur with some hydrogenation protocols, e.g. Raney nickel/H_2.[8] It was pleasing to find though that the published procedure for the mild cleavage of N−N bonds with SmI_2 was efficient.[6b] First, **2a** was subjected to careful benzoylation with *n*-BuLi and BzCl (Scheme 3). The crude product was then reacted with excess freshly prepared SmI_2 in THF-MeOH to afford the desired product **6** in good yield (65%, two steps). Furthermore, the 2-oxazolidinone **5a** could be isolated for recycling.

The sense of diastereoselection in the above Mannich-type reactions was confirmed by single-crystal X-ray

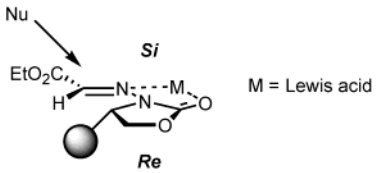
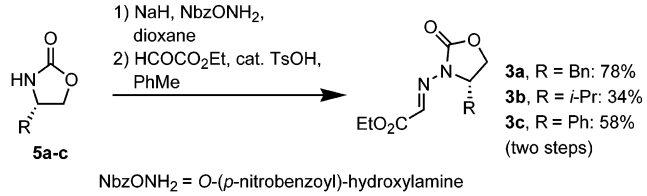
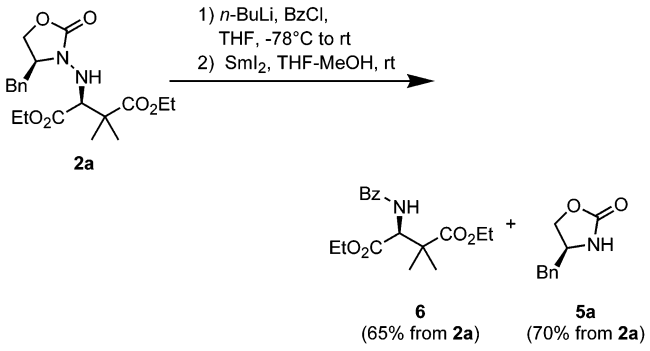


FIGURE 1. A model explaining the stereochemical outcome of the Mannich-type reactions with hydrazones **3a−c**.

SCHEME 2



SCHEME 3

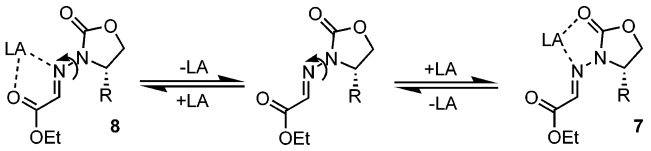


crystallography of **2a**.[15] Stereoregularity was thereafter inferred for **2b−i**. This facial selectivity can be explained by the blocking of the *Re* face of the C=N bond in **2a−i** by the substituent R, hence, the attack is directed to the *Si* face (Figure 1). Similar selectivity was seen in the radical addition and allylations reactions of other *N*-acylhydrazones derived from *N*-amino 2-oxazolidinones.[7c,10]

However, the portrayed bidentate chelation of the Lewis acid may not be the only possible binding mode (Scheme 4, **7**). The chelation of the Lewis acid to the ester moiety and nitrogen atom as in **8** cannot be ruled out. In

(15) See the Supporting Information.

SCHEME 4



support of this, the isolation of minor amounts (~5%) of byproduct resulting from the attack of **4a** on the ester moiety of hydrazones **3a** and **3b** in the case of $Sc(OTf)_3$ could be the result of an enhanced activation of the ester as in **8** (Table 1, entries 6−8 and Table 2, entry 6). The catalytic use of rare earth triflates has been rationalized by the equilibrium of the coordination of the Lewis acids to the nitrogen of the C=N bond.[13a,16] Therefore, one could speculate that an equilibrium between differently chelated species exists, which is responsible for the decreased regioselectivity in the reactions with $Sc(OTf)_3$ (Scheme 4). Such regioisomers were not detected in the clean reactions with stoichiometric amounts of Zn^{2+} Lewis acids, indicating that chelation of the ester moiety as in **8** may not be of importance, or that the reactivity difference between the two Zn-coordinated species is sufficiently large.

An unexpected and interesting feature of the $ZnCl_2$-mediated reaction of **3b** with **4b** (Table 2, entry 3) was the isolation of major amounts of 2-oxazolidinone **5c** and the unsaturated ester **9**.[17,18] Obviously, this must be the result of N−N bond cleavage. A possible explanation for this observation is outlined below (Scheme 5). Initially, the intermediate **10** is formed from addition to the chelated hydrazone **7**. If silylation of the basic zinc amide moiety in **10** is sufficiently slow, intermolecular deprotonation of **11** can occur, although the reasons for this slow silylation step are not fully understood. This creates the zinc carbanion **12** which in turn can undergo β-elimination to yield the *N*-silylated imine **13** and **14**. Upon aqueous workup **5c** and **9** ensue.

Conclusions

In summary, a simple and useful methodology has been devised for the synthesis of β-amino acid derivatives via Mannich-type reactions of chiral *N*-acylhydrazones and silyl enolates followed by a subsequent removal of the 2-oxazolidinone chiral auxiliary with SmI_2. Consistently high diastereoselectivities were observed in these clean room-temperature reactions with $ZnCl_2$, and moderate to good yields of the products were obtained.

Experimental Section

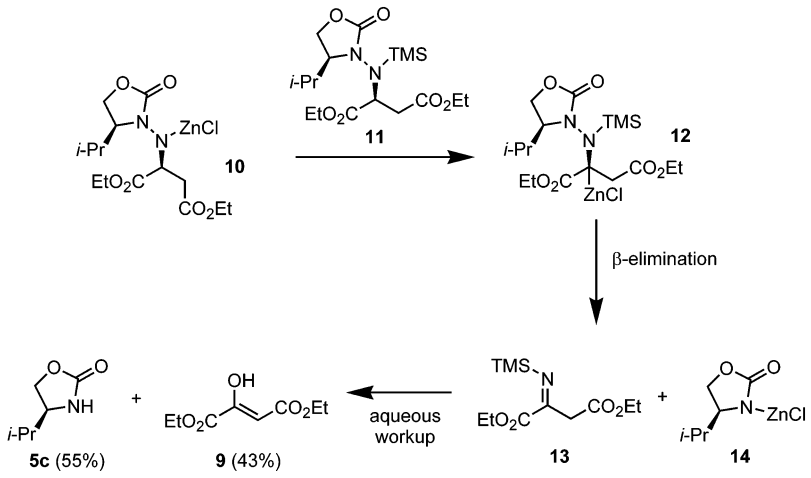
General Procedure for Mannich-Type Reactions of *N*-Acylhydrazones 3a−c. To a solution of the hydrazone in CH_3CN (0.1 M) was added the Lewis acid at room temperature. The resulting solution was stirred for 15 min, after which the ketene acetal or ketene thioacetal (2.0 equiv) was added. The reaction mixture was stirred for the time indicated (Tables 1 and 2) or until no further progress could be detected by TLC (Table 3). Saturated aqueous NH_4Cl solution (0.3 mL/mL of reaction mixture) was added, and the organic phase was diluted with CH_2Cl_2. The aqueous phase was extracted several times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and evaporated to dryness in vacuo. Diastereoselectivity was determined by NMR integration of the crude product (Tables 1−3). Flash chromatography (pentanes/EtOAc, gradient elution) on silica gel afforded the products.

(*S*)-Diethyl 3-((*S*)-4-Benzyl-2-oxooxazolidin-3-ylamino)-2,2-dimethylsuccinate (2a). Data for major diastereomer: Mp 93−94 °C (CH_2Cl_2/pentanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H), 1.30 (t, J = 6.8 Hz, 3H), 1.36 (s, 3H), 2.60 (dd, J = 10.0, 13.6 Hz, 1H), 3.40 (dd, J = 2.8, 13.6 Hz, 1H), 3.94 (t, J = 7.2 Hz, 2H), 3.98 (t, J = 6.4 Hz, 1H), 4.05 (t, J = 8.0 Hz, 1H), 4.15−4.23 (m, 2H), 4.23 (q, J = 7.2 Hz, 2H), 4.81 (d, J = 6.8 Hz, 1H), 7.16−7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 14.3, 21.3, 22.8, 37.5, 45.2, 59.6, 61.3, 61.5, 66.5, 69.1, 127.2, 129.1 (4C), 135.9, 171.6, 175.5; MS (electrospray) *m*/*z* 415.2 (M + Na); HRMS *m*/*e* calcd for $C_{20}H_{28}N_2NaO_6$ (M + Na) 415.1845, found 415.1843.

(*S*)-Diethyl 3-((*S*)-4-Isopropyl-2-oxooxazolidin-3-ylamino)-2,2-dimethylsuccinate (2b). Data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, J = 7.2 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 1.20 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.29 (s, 3H), 2.18−2.30 (m, 1H), 3.68 (ddd, J = 3.2, 5.6, 8.8 Hz, 1H), 3.86 (br s, 1H), 4.00 (dd, J = 6.0, 8.8 Hz, 1H), 4.11−4.19 (m, 5H), 4.62 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.2, 14.8, 18.0, 21.3, 22.5, 26.9, 45.0, 61.2, 61.3, 61.9, 62.5, 68.3, 158.6, 171.5, 175, 4; MS (electrospray) *m*/*z* 367.2 (M + Na); HRMS *m*/*e* calcd for $C_{16}H_{28}N_2NaO_6$ (M + Na) 367.1845, found 367.1852.

(*S*)-Diethyl 2-((*S*)-4-Isopropyl-2-oxooxazolidin-3-ylamino)succinate (2c). Data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 7.1 Hz, 3H), 1.26 (t, J = 7.6 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 2.20−2.32 (m, 1H), 2.72 (dd, J = 7.2, 16.4 Hz, 1H), 2.80 (dd, J

SCHEME 5



= 5.6, 16.4 Hz, 1H), 3.76−3.80 (m, 1H), 4.04−4.09 (m, 2H), 4.13−4.23 (m, 5H), 4.62 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (2C), 15.0, 18.0, 27.3, 36.1, 58.8, 61.2, 61.6, 61.7, 62.9, 158.9, 170.6, 171.3; MS (electrospray) *m/z* 339.2 (M + Na); HRMS *m/e* calcd for $C_{14}H_{24}N_2NaO_6$ (M + Na) 339.1532, found 339.1537.

(*S*)-Ethyl 2-((*S*)-4-Isopropyl-2-oxooxazolidin-3-ylamino)-4-oxo-4-(phenylthio)butanoate (2d). Data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, J = 7.2 Hz, 3H), 0.89 (d, J = 7.2 Hz, 3H), 1.29 (t, J = 6.8 Hz, 3H), 2.21−2.30 (m, 1H), 3.08 (dd, J = 7.2, 16.0 Hz, 1H), 3.15 (dd, J = 5.2, 16.0 Hz, 1H), 3.72−3.76 (m, 1H), 4.04 (dd, J = 4.4, 8.8 Hz, 1H), 4.09−4.24 (m, 4H), 4.62 (br s, 1H), 7.39−7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 15.0, 17.9, 27.2, 44.5, 58.7, 61.1, 61.2, 62.9, 127.2, 129.4 (2C), 129.8 (2C), 134.6, 158.8, 170.8, 194.8; MS (electrospray) *m/z* 403.2 (M + Na); HRMS *m/e* calcd for $C_{18}H_{24}N_2NaO_5S$ (M + Na) 403.1304, found 403.1303.

(*S*)-Diethyl 2,2-Dimethyl-3-((*S*)-2-oxo-4-phenyloxazolidin-3-ylamino)succinate (2e). Data for diastereomeric mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (s, 3H, minor diastereomer), 1.02 (s, 3H, minor diastereomer), 1.07 (s, 3H, major diastereomer), 1.15 (s, 3H, major diastereomer), 1.19 (t, J = 7.2 Hz, 3H, major diastereomer), 1.20 (t, J = 7.2 Hz, 3H, minor diastereomer), 1.25 (t, J = 7.2 Hz, 3H, minor diastereomer), 1.26 (t, J = 7.2 Hz, 3H, major diastereomer), 3.47 (d, J = 7.6 Hz, 1H, minor diastereomer), 3.85 (s, 1H, major diastereomer), 3.99−4.09 (m, 4H), 4.11−4.19 (m, 6H), 4.53 (t, J = 8.8 Hz, 1H, minor diastereomer), 4.59 (t, J = 8.4 Hz, 1H, major diastereomer), 4.72−4.84 (m, 4H), 7.24−7.27 (m, 2H), 7.34−7.45 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.2, 20.9, 21.8, 22.1, 22.3, 46.2, 60.9, 61.0, 61.4, 61.5, 62.9, 68.4, 68.9 (2C), 69.3, 127.1 (2C), 127.9 (2C), 128.9, 129.1 (2C), 129.2 (2C), 129.4, 136.8, 138.1, 157.9, 158.3, 171.7 (2C), 175.3, 175.8; MS (electrospray) *m/z* 401.2 (M + Na); HRMS *m/e* calcd for $C_{19}H_{26}N_2NaO_6$ (M + Na) 401.1689, found 401.1688.

(*S*)-Diethyl 2-((*S*)-4-Benzyl-2-oxooxazolidin-3-ylamino-)succinate (2f). Data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J = 7.0 Hz, 3H), 1.30 (t, J = 7.0 Hz, 3H), 2.61 (dd, J = 9.4, 13.3 Hz, 1H), 2.78 (dd, J = 7.0, 16.4 Hz, 1H), 2.84 (dd, J = 5.5, 16.4 Hz, 1H), 3.37 (dd, J = 3.6, 12.5 Hz, 1H), 3.97−4.05 (m, 2H), 4.08−4.30 (m, 6H), 4.80 (d, J = 3.9 Hz, 1H), 7.16−7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 14.3, 36.0, 37.3, 59.0, 59.4, 61.2, 61.7, 66.6, 127.2, 129.1 (2C), 129.2 (2C), 135.9, 158.8, 170.6, 171.2; MS (electrospray) *m/z* 387.2 (M + Na); HRMS *m/e* calcd for $C_{18}H_{24}N_2NaO_6$ (M + Na) 387.1532, found 387.1527.

(*S*)-Ethyl 2-((*S*)-4-Benzyl-2-oxooxazolidin-3-ylamino)-4-oxo-4-(phenylthio)butanoate (2g). Data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, J = 7.0 Hz, 3H), 2.61 (dd, J = 9.4, 13.3 Hz, 1H), 3.11 (dd, J = 7.0, 16.4 Hz, 1H), 3.18 (dd, J = 5.5, 16.4 Hz, 1H), 3.35 (dd, J = 3.1, 13.3 Hz, 1H), 3.94−4.11 (m, 3H), 4.18−4.31 (m, 3H), 4.77 (d, J = 4.7 Hz, 1H), 7.15−7.33 (m, 5H), 7.39−7.43 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 37.2, 44.4, 59.0, 59.0, 61.9, 66.5, 127.2 (2C), 129.1 (2C), 129.2 (2C), 129.5 (2C), 129.8 (2C), 134.6, 135.8, 158.7, 170.8, 194.7; MS (electrospray) *m/z* 451.2 (M + Na); HRMS *m/e* calcd for $C_{22}H_{24}N_2NaO_5S$ (M + Na) 451.1304, found 451.1307.

(*S*)-Ethyl 2-((*S*)-4-Benzyl-2-oxooxazolidin-3-ylamino)-4-(ethylthio)-4-oxobutanoate (2h). Data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J = 7.0 Hz, 3H), 1.30 (t, J = 7.0 Hz, 3H), 2.61 (dd, J = 10.2, 13.3 Hz, 1H), 2.92 (q, J = 7.0 Hz, 2H), 3.00 (dd, J = 7.0, 16.4 Hz, 1H), 3.06 (dd, J = 5.5, 16.4 Hz, 1H), 3.36 (dd, J = 3.2, 16.4 Hz, 1H), 3.96−4.03 (m, 2H), 4.07−4.12 (m, 1H), 4.18−4.28 (m, 3H), 4.76 (d, J = 5.5 Hz, 1H), 7.16−7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 14.8, 23.8, 44.7, 59.2, 59.3, 61.8, 66.5, 127.2, 129.1 (2C), 129.2 (2C), 135.9, 158.7, 171.1, 196.3; MS (electrospray) *m/z* 403.2 (M + Na); HRMS *m/e* calcd for $C_{18}H_{24}N_2NaO_5S$ (M + Na) 403.1304, found 403.1304.

(*S*)-Ethyl 2-((*S*)-4-Benzyl-2-oxooxazolidin-3-ylamino)-5,5-dimethyl-4-oxohexanoate (2i). Data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, J = 7.1 Hz, 3H), 1.47 (s, 9H), 2.58−2.64 (m, 1H), 2.71 (dd, J = 4.0, 16.4 Hz, 1H), 2.76 (dd, J = 6.0, 16.4 Hz, 1H), 3.38 (dd, J = 3.2, 13.2 Hz, 1H), 3.99−4.06 (m, 2H), 4.07−4.14 (m, 2H), 4.19−4.29 (m, 2H), 4.79 (d, J = 4.4 Hz, 1H), 7.17−7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 28.2 (3C), 37.1, 37.2, 59.0, 59.4, 61.6, 66.5, 81.7, 127.2, 129.0 (2C), 129.2 (2C), 135.9, 158.8, 169.7, 171.3; MS (electrospray) *m/z* 415.2 (M + Na); HRMS *m/e* calcd for $C_{20}H_{28}N_2NaO_6$ (M + Na) 415.1845, found 415.1832.

(*S*)-Diethyl 3-Benzamido-2,2-dimethylsuccinate (6). To a solution of the hydrazine **2a** (91 mg, 0.23 mmol) in THF (2.0 mL) was added dropwise *n*-BuLi (158 μL, 1.6 M in hexanes, 0.25 mmol) at −78 °C. The resulting mixture was stirred for 40 min at −78 °C. Benzoyl chloride (35 μL, 0.30 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature. Saturated aqueous NH_4Cl (2.0 mL) was added and the aqueous phase was extracted several times with CH_2Cl_2. The combined organics were dried over $MgSO_4$ and evaporated to dryness in vacuo. The crude product was redissolved in MeOH (2.5 mL) and SmI_2 solution was added dropwise (6.0 mL, 0.60 mmol, 0.1 M in THF) at room temperature. The resulting solution was stirred for 5 min and saturated aqueous NH_4Cl (2.0 mL) was added. The organic solvents were removed by evaporation in vacuo and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and evaporated to dryness in vacuo. The residue was subjected to column chromatography (pentanes/EtOAc, gradient elution) on silica gel. This afforded 35 mg (65%) of **6**, followed by 29 mg (70%) of **5a**.[19] Data for **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J = 6.8 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.37 (s, 6H), 4.16−4.26 (m, 4H), 5.04 (d, J = 9.2 Hz, 1H), 7.23 (d, J = 9.2 Hz, 1H), 7.44−7.48 (m, 2H), 7.51−7.55 (m, 1H), 7.82−7.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.9, 23.2, 45.5, 58.5, 61.4, 61.8, 127.2 (2C), 128.8 (2C), 132.0, 134.1, 167.3, 170.6, 175.8; MS (electrospray) *m/z* 344.2 (M + Na); HRMS *m/e* calcd for $C_{17}H_{23}NNaO_5$ (M + Na) 344.1474, found 344.1469.

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Supporting Information Available: General experimental methods, spectroscopic data for **3a**−**c**, copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **2a**−**i** and **6**, and single-crystal X-ray structure and crystallographic data for **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Minor amounts of the 2-oxazolidinone and the corresponding unsaturated ester were also detected (^{1}H NMR) in the case of the $ZnCl_2$-mediated reaction of **4b** and **3a** (Table 3, entry 3). The exact reasons for this apparent deviation of **4b** from the other silyl enolates are unknown.

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