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"*Syn-effect*" in asymmetric vinylogous alkylation of 3-[4-(*N*-phthalimide)-but-2-enoyl]oxazolidinone

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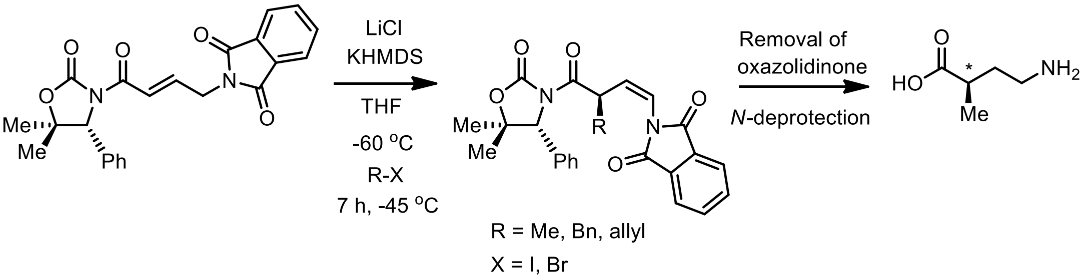
Abstract

An asymmetric vinylogous alkylation reaction of a *N*-enoyl oxazolidinone where an *N*-protected γ-nitrogen atom is linked to the α,β–unsaturated system is described. This reaction gave α-alkylated products in moderate yields and moderate diastereomeric ratios regarding the newly formed stereogenic center. Concomitantly, a deconjugated double bond was formed with a high *Z*-selectivity, thus representing a strong "*syn-effect*". The removal of chiral oxazolidinone moiety and *N*-deprotection of amino group furnished a chiral α-substituted γ-amino acid.



Keywords: *Syn-effect*, vinylogous alkylation, asymmetric alkylation, γ-amino acid

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Introduction

α,β-unsaturated carboxylic derivatives are suitable molecules to carry out a vinylogous reaction wherein a strong base extracts a hydrogen atom at the γ-position generating the respective anion which can extend its conjugation until the formation of the enolate. The enolate has both α and γ positions to react with electrophiles; however, the reaction is highly regioselective in α-position. An isomerization is carried out on the vinylogous reaction product to afford a deconjugated β,γ-unsaturated carboxylic derivative. Surprisingly, the configuration of this alkene corresponds to the sterically unfavoured *Z*-alkene with a high stereoselectivity. This preferential stereochemistry has been rationalized in terms of the "*syn-effect*".[1, 2] Nakai et al. described an asymmetric vinylogous alkylation of a *N*-enoyl oxazolidinone to provide an α-alkylated product and form a double bond with high *Z*-selectivity (*Z,E*) (96:4).[3] Our group also described an asymmetric vinylogous alkylation of a *N*-enoyl oxazolidinone, where a γ-OBn group is connected to the α,β-unsaturated system, to afford the α-alkylated product with a high *Z*-selectivity. Removal of the chiral auxiliary with sodium borohydride gave chiral alcohols bearing electron rich *cis*-alkenes as substituent (Figure 1).[4, 5] On the other hand, the enamides have been the subject of synthetic interest, because of their importance as building blocks used in a wide range of different transformations such as cycloadditions, cross coupling reactions or asymmetric C-C bond formations and asymmetric hydrogenation reactions. Therefore, different protocols for its synthesis have been described, such as, *N*-allylamides isomerization, acylation of imines, condensation of amides and carbonyl compounds or addition of amides to terminal alkynes. Some protocols are carried out under harsh reaction conditions, giving as reaction products mixtures of *Z/E*-enamides.[6-14] We report herein, the first asymmetric vinylogous alkylation of a chiral *N*-enoyl oxazolidinone, where the nitrogen atom is linked to the α,β-unsaturated system as phthalimide group. This compound was treated under alkylation reaction conditions to give chiral *Z*-enamides, α-alkylated compounds bearing a double bond with a high *Z*-selectivity (> 98%). Despite the volume of the phthalimide group, the *syn-effect* was predominant to achieve the *Z*-alkene. Removal of chiral oxazolidinone and *N*-deprotection of amino group gave the α-substituted γ-amino acid.[15-22]

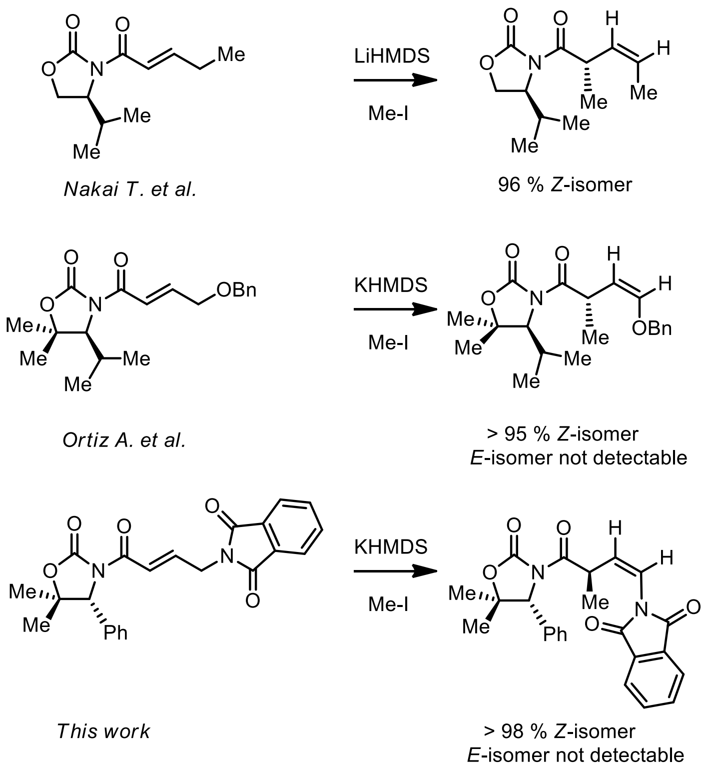
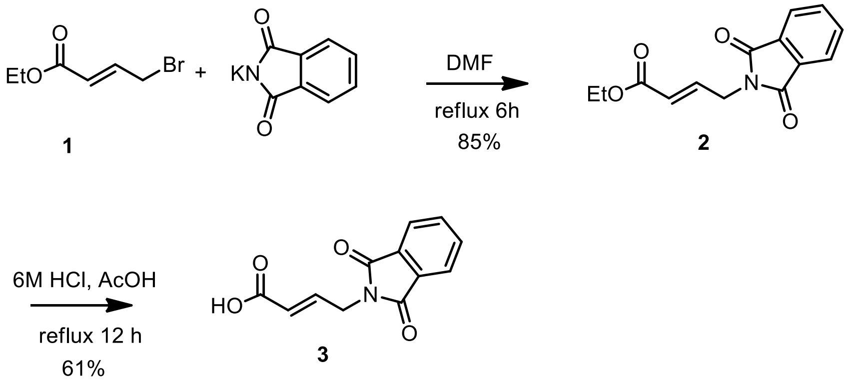


Figure 1. *Syn-eff*ect promotor of unfavored *Z*-alkenes.

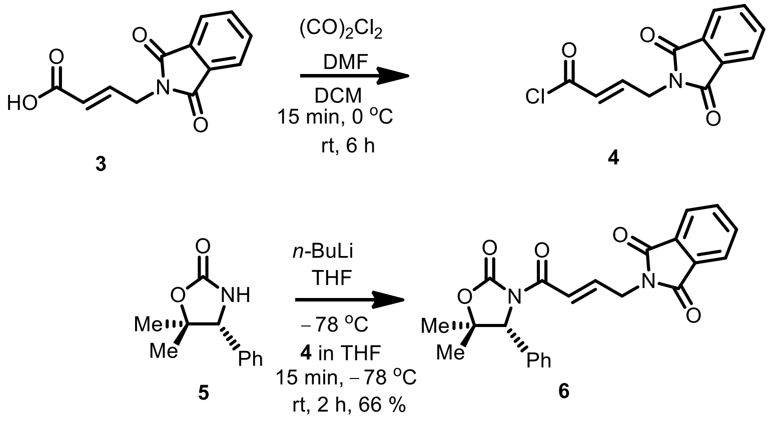
Results and Discussion

The synthesis began with the development of the (*E*)-4-(1, 3-dioxoisoindolin-2-yl)but-2-enoic acid **3**. Ethyl 4-bromocrotonate **1** was treated with phthalimide in DMF at reflux for 6 h to give (*E*)-ethyl-4-(1,3-dioxoisoindolin-2-yl)but-2-enoate **2** in 85%.[23] Ester **2** was hydrolyzed using acetic acid and an aqueous solution of 6M HCl at reflux for 12 h affording the carboxylic acid **3** as a white solid in 61% yield (Scheme 1) . A plausible explanation about this moderate yield is that a partial hydrolysis reaction is carried out at phthalimide group; however, the achievement of carboxylic acid **3** was possible due to a spontaneous precipitation of **3** during the course of the reaction.



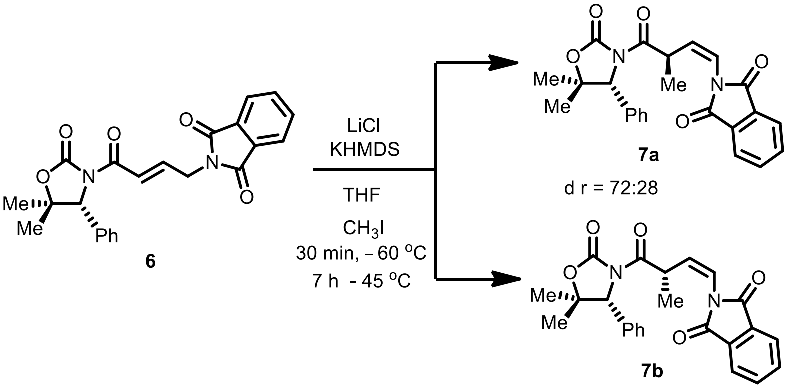
Scheme 1. Incorporation of phthalimide to α.β-unsaturated system.

This compound **3** was transformed to its respective acyl chloride **4** using oxalyl chloride and a catalytic amount of DMF in anhydrous DCM, at 0 °C and subsequent stirring at room temperature for 6 h to give compound **4** in a quantitative yield. This compound **4** was used immediately without further purification since the compound is highly reactive. The chiral oxazolidinone **5** was treated with a solution of *n*-butyllithium (2.5 M, hex.) in anhydrous THF at -78 °C for 15 min followed by the addition of acyl chloride **4** in anhydrous THF. The reaction mixture was stirred at room temperature for 12 h. The reaction crude was purified by a flash column chromatography on silica gel using hex: AcOEt 8:2 to provide a mixture of compounds **6** and **5**. Both compounds were isolated by column chromatography on alumina using hex:AcOEt 9:1 to give *N*-enoyl oxazolidinone **6** as a white solid in 66% yield,[24] (Scheme 2). An increment in eluent polarity (hex:AcOEt 8:2) provides the chiral oxazolidinone **5**.



Scheme 2. Coupling reaction of carboxylic acid **3** and chiral oxazolidinone.

N-Enoyl oxazolidinone **6** was treated under asymmetric vinylogous alkylation reaction conditions. The compound **6** was exposed with LiCl and KHMDS in anhydrous THF at- 60 ^{o}C for 30 min followed by the addition of MeI. This reaction mixture was stirred at -45 ^{o}C for 7 h to provide a mixture of diastereoisomers **7a/7b** in 55% yield and with diastereomeric ratio of 72/28 which was determined by ^{1}H NMR spectrum of crude reaction (Scheme 3). The products **7a** and **7b** were isolated by crystallization using hexane/CH_2Cl_2 (9:1).



Scheme 3. Reaction conditions of conjugate addition.

In ^{1}H NMR spectrum of the major diastereomer **7a**, it is observed a doublet of doublets in 6.23 ppm that corresponds to the olefinic hydrogen H(γ) with coupling constants of (^{3}J 8.5 Hz, ^{4}J 0.5 Hz) and a doublet of doublets in 5.81 ppm that corresponds to the olefinic hydrogen H(β) with coupling constants of (^{3}J 10.3 Hz) and (^{3}J 8.5 Hz) assigned to the other olefinic hydrogen H(β). These values of coupling constants reveal a *cis* relative configuration in the compound **7a**, as shown in Figure 2.

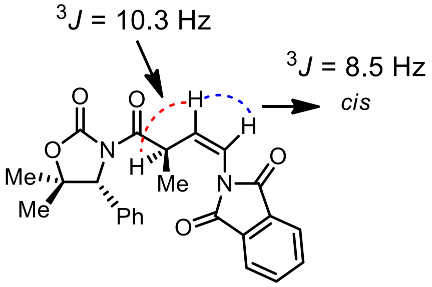


Figure 2. Coupling constants of major product **7a**.

The stereochemistry of the major product **7a** was possible to confirm and establish from the structure obtained by X-ray diffraction being (*R*) absolute configuration at newly formed chiral center and *cis* the relative configuration for the olefin group,[25] as shown in Figure 3.

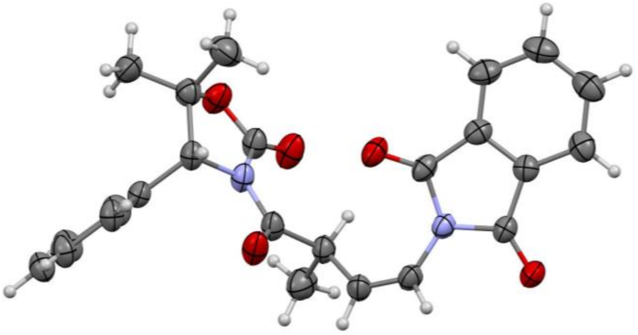
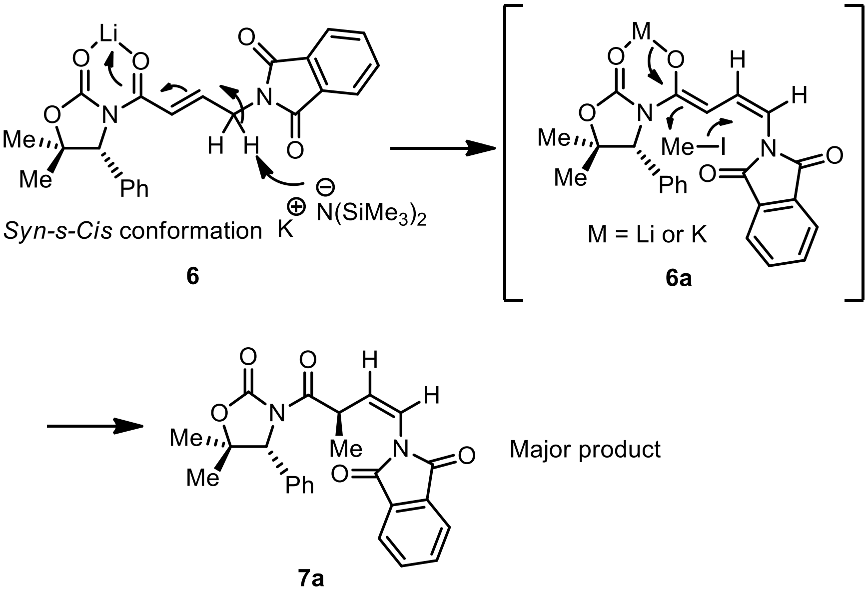


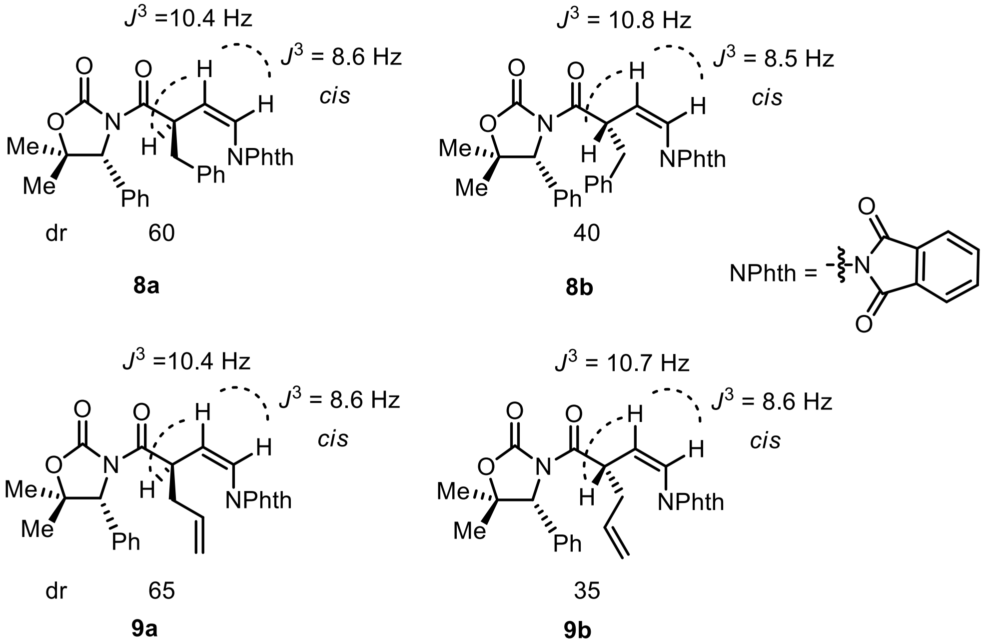
Figure 3. Molecular structure of the compound **7a**.

The reaction mechanism can be rationalized as follows. The strong and sterically hindered base removes a γ-proton from *N*-enoyl oxazolidinone generating a nucleophilic enolate ion by delocalization of negative charge to oxygen atom. The enolate ion attacks to alkyl halide via a nucleophilic substitution to provide α-alkylation which is carried out by the less hindered side to furnish the major product **7a** with (*R*) configuration. In addition, a double bond with a high *Z*-selectivity was formed being "*syn-effect*" the responsible for this stereoselectivity. It should be noted that the use of LiCl as an additive was important since when the reaction takes places in its absence, it is possible to obtain the same mixture of diastereoisomers **7a/7b** in almost same diasteromeric ratio (70/30), but with a lower yield (40%). The solubility of LiCl and *N*-enoyl oxazolidinone **6** in anhydrous THF at room temperature leads to the assumption that firstly, a prior coordination of the lithium atom with the carbonyl groups of **6** takes place, favoring a *Syn-s-Cis* conformation wherein an acid-base reaction is carried out promoted by KHMDS to form the intermediate **6a**. It is not possible to determine whether in this reaction intermediate **6a** a transmetallation can be carried out exchanging the lithium metal for potassium, as shown in Scheme 4.



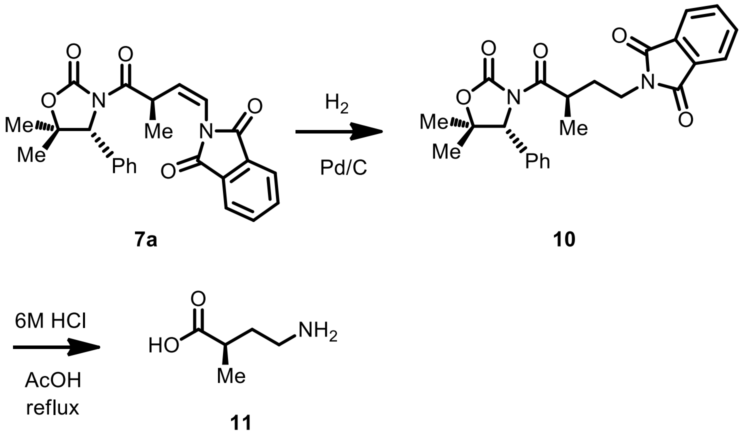
Scheme 4. A plausible reaction mechanism of asymmetric vinylogous alkylation.

N-Enoyl oxazolidinone **6** was treated under the same reaction conditions described above. The enolate ion of compound **6** was exposed with BnBr and this reaction mixture was stirred at -45 °C for 12 h to provide a mixture of diastereoisomers **8a/8b** in 40% yield and with diastereomeric ratio of 60/40 which was determined by ^{1}H NMR spectrum of crude reaction. The products **8a** and **8b** were isolated by column chromatography using silica gel and hexane/AcOEt (75:25) as eluent. In ^{1}H NMR spectrum of the major diastereomer **8a**, it is observed a doublet of doublets in 6.18 ppm that corresponds to the olefinic hydrogen H(γ) with coupling constants of (^3J 8.6 Hz, ^4J 0.6 Hz) and a doublet of doublets in 5.80 ppm that corresponds to the olefinic hydrogen H(β) with coupling constants of (^3J 10.4 Hz) and (^3J 8.6 Hz) assigned to the other olefinic hydrogen H(β). In ^{1}H NMR spectrum of the minor diastereomer **8b**, it is observed a doublet of doublets in 6.23 ppm (H(γ), ^3J 8.5, ^4J 0.5 Hz) and a doublet of doublets in 5.71 ppm (H(β) ^3J 10.8, ^3J 8.5Hz). In the same way, the enolate ion of compound **6** was exposed with allylBr to provide a mixture of diastereoisomers **9a/9b** in 48% yield and with diastereomeric ratio of 65/35 which was determined by ^{1}H NMR spectrum of crude reaction. The products **9a** and **9b** were isolated by column chromatography using silica gel and hexane/AcOEt (70:30) as eluent (Scheme 5). In ^{1}H NMR spectrum of the major diastereomer **9a**, it is observed a doublet in 6.27 ppm that corresponds to the olefinic hydrogen H(γ) with a coupling constant of (^3J 8.6 Hz) and a doublet of doublets in 5.80 ppm that corresponds to the olefinic hydrogen H(β) with coupling constants of (^3J 10.4 Hz) and (^3J 8.6 Hz) assigned to the other olefinic hydrogen H(β). In ^{1}H NMR spectrum of the minor diastereomer **9b**, it is observed a doublet in 6.23 ppm (H(γ), ^3J 8.6 Hz) and a doublet of doublets in 5.65 ppm (H(β) ^3J 10.8, ^3J 8.6Hz), as shown in Scheme 5. The values of the coupling constants confirm a *cis* relative configuration for all compounds (**7a**, **8a**,**8b**, **9a** and **9b**).



Scheme 5. Asymmetric vinylogous alkylation products and their coupling constants.

The vinylogous alkylation reaction carried out in 3-[4-(*N*-phthalimide)-but-2-enoil] oxazolidinone can be considered as a new highly stereoselective method to achieve chiral *Z*-enamides **7a**, **8** (**a**,**b**) and **9** (**a**,**b**), which could be applied in cycloaddition reaction. With the purpose to explore the applications of these *Z*-enamides, we realized the synthesis of (*R*)-4-amino-2-methylbutanoic acid **11**. The major compound **7a** was exposed to hydrogenation reaction conditions using a catalytic amount of Pd/C in EtOH at room temperature for 16 h to deliver the saturated compound **10** in quantitative yield (98%)[27, 28] (Scheme 6). The removal of chiral oxazolidinone moiety and *N*-deprotection were carried out using Duke´s protocol, using 6M HCl and AcOH at reflux, for 6 h to give α-substituted γ-amino acid **11** in moderated yield (70%) and moderated chemical purity[23]. The spectral data of the compound **11** is in accordance with literature.[23] The obtaining of γ-amino acid **11** was a difficult task since its high solubility in acid mixture therefore, this protocol was not recommended for the others chiral Z-enamides **8-9**. It is worthy to mention that under these reaction conditions it was possible to carry out the removal of Phthalimide group, possibly due to *Z*-enamide **7a** was highly soluble in the acid mixture until the reaction was over.



7a **10**

11

Scheme 6. Removal of chiral oxazolidinone moiety and *N*-deprotection of amino group to achieve α-substituted γ-amino acid.

Conclusions

We have described an asymmetric vinylogous alkylation reaction carried out in *N*-enoyl oxazolidinone where a γ-nitrogen atom is linked to the α,β-unsaturated system. The reaction furnished α-alkylation and the major products have *R* configuration besides a double bond with a high *Z*-selectivity was formed, thus representing a strong "*syn-effect*". This result does not stop surprising since despite the volume of *N*-substituent, the *Z*-selectivity predominates in the formation of the double bond. The removal of chiral oxazolidinone moiety and *N*-deprotection produced an α-substituted γ-amino acid.

Experimental Section

General. All moisture-sensitive reactions were carried out in oven-dried glassware under argon atmosphere. Reagents were purchased from Aldrich and used without any further purification. Dichloromethane was distilled from CaH_2 under argon. THF was distilled from Na/benzophenone under argon. Optical rotations were measured in Atago AP-300 polarimeter with sodium D-line (589 nm) and are reported on a concentration (*c*) of grams/100 mL of solvent. Nuclear Magnetic Resonance (NMR) spectra were measured with a 500 MHz FTNMR spectrometer. ^{1}H-NMR chemical shifts (δ) are reported in parts per million (ppm) relative to Me_4Si (δ 0.0 ppm) with coupling constants (*J*) reported in Hertz (Hz). Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad singlet (bs). ^{13}C-NMR are reported using 77.0 ppm ($CDCl_3$) as internal reference. High resolution mass spectra were performed with QQHQ mass analyzer type, at the Universidad Autónoma de Puebla (México) Mass Spectrometry Facility.

(*E*)-Ethyl 4-(1,3-dioxoisoindolin-2-yl)but-2-enoate (2). To a solution of potassium phthalimide (0.58 g, 3.1 mmol) in anhydrous DMF (20 mL), ethyl 4-bromocrotonate (0.5 g, 0.36 mL, 2.5 mmol) was added at room temperature. The reaction mixture was refluxed for 6 h, then cooled and filtered. The filtrate was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel with hexane/ethyl acetate 90/10 as eluent to yield **2** as a white solid: 0.55 g, 85%, mp 160 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 7.88 (2H, dd, *J* 5.5, 3.1 Hz, Ph), 7.76 (2H, dd, *J* 5.5, 3.1 Hz, Ph), 6.93 (1H, dt, *J* 15.7, 5.2 Hz, CH=), 5.89 (1H, dt, *J* 15.7, 1.8 Hz, CH=), 4.45 (2H, dd, *J* 5.2, 1.8 Hz, CH_2), 4.17 (2H, q, *J* 7.2 Hz, CH_2), 1.26 (3H, t, *J* 7.2 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 167.5 (C=O), 165.6 (C=O), 140.7 (Ph), 134.2 (CH=), 131.8 (Ph), 123.5 (CH=), 123.0 (Ph), 60.6 (CH_2), 38.1 (CH_2), 14.1 (CH_3); IR_{umax}: 1706, 13934, 1269, 1122, 1039, 933, 715 cm^{-1}. EI-HRMS: calculated for ($C_{14}H_{13}NO_4$), 259.0845; found, 259.0840.

(*E*)-4-(1,3-Dioxoisoindolin-2-yl)but-2-enoic acid (3). To a solution of **2** (0.7 g, 2.7 mmol) in acetic acid (4.35 mL) an aqueous solution of 6M HCl (0.85 mL) was added. The reaction mixture was refluxed for 12 h and then the mixture was crystallized on cooling. The solid was filtered to give **3** as a white solid: 0.37 g, 61%, mp 210 °C; ^{1}H NMR (500 MHz, (DMSO-*d*$_6$) 12.41 (1H, bs, OH), 7.89-7.82 (4H, m, Ph), 6.83 (1H, dt, *J* 15.7, 4.8 Hz, CH=), 5.80 (1H, dt, *J* 15.7, 1.5 Hz, CH=), 4.36 (2H, d, *J* 4.7 Hz, CH2); ^{13}C NMR (125 MHz, (DMSO-*d*$_6$) 169.3 (C=O), 167.5 (C=O), 166.6 (C=O), 142.1 (Ph), 134.5 (CH=), 134.4, 132.6, 131.7 (Ph), 123.2 (CH=), 123.0, 122.4 (Ph), 38.1 (CH_2); IR_{umax}: 3269, 1694, 1323, 1283, 1105, 1036, 947, 721 cm^{-1}. EI-HRMS: calculated for ($C_{12}H_9NO_4$), 231.0532; found, 231.0534.

(*E*)-4-(1,3-Dioxoisoindolin-2-yl)but-2-enoyl chloride (4). To a solution of carboxylic acid **3** (0.3 g, 1.30 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 ^{o}C, three drops of DMF followed by oxalyl chloride (0.41 g, 3.24 mmol) were added. The reaction mixture was stirred at the same temperature for 15 min and stirring was continued at room temperature for 16 h. The oxalyl chloride and CH_2Cl_2 were removed under vacuum to give the acyl chloride **4** as a yellow solid.

(*R,E*)-2-(4-(5,5-Dimethyl-2-oxo-4-phenyloxazolidin-3-yl)-4-oxobut-2-en-1-yl)isoindoline-1,3-dione (6). To a solution of carboxylic acid **3** (0.3 g, 1.30 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 ^{o}C, three drops of DMF followed by oxalyl chloride (0.41 g, 3.24 mmol) were added. The reaction mixture was stirred at the same temperature for 15 min and stirring was continued at room temperature for 16 h. The oxalyl chloride and CH_2Cl_2 were removed under vacuum to give the acyl chloride **4** as a yellow solid. In another flask, to a solution of chiral oxazolidinone **5** (0.25 g, 1.30 mmol) in anhydrous THF (15 mL), *n*-BuLi (2.5 M in hexane, 0.62 mL) was added dropwise at –78 ^{o}C. The reaction mixture was stirred for 30 min and then, a solution of acyl chloride **4** in anhydrous THF was added and the reaction mixture was stirred for 15 min at the same temperature and stirring was continued at room temperature for 12h. The mixture reaction was quenched with saturated aqueous NH_4Cl (20 mL), the THF was removed under vacuum and the residue was extracted with ethyl acetate (3 x 30 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel with hexane/ethyl acetate 80/20 as eluent to yield a mixture of **6** and the oxazolidinone **5**. The product **6** and unreacted oxazolidinone **5** were isolated by column chromatography on alumina with hexane/ethyl acetate 9:1 and 8:2 as eluent respectively, to yield the compound **6** as a white solid 0.35 g 66% yield; mp 160 °C, $[\alpha]^{25}_{D}$ -51.06 (*c* 1.41, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 7.88 (2H, dd, *J* 5.5, 3.1 Hz, Ph), 7.74 (2H, dd, *J* 5.5, 3.1 Hz, Ph), 7.47 (1H, dt, *J* 15.4, 1.7 Hz, CH=), 7.33 (3H, m, Ph), 7.13 (2H, d, *J* 6.9 Hz, Ph), 6.98 (1H, dt, *J* 15.4, 5.3 Hz, CH=), 5.09 (1H, s, CH), 4.50 (2H, dd, *J* 5.3, 1.7 Hz, CH_2) 1.59 (3H, s, CH_3), 0.98 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 167.6 (C=O), 163.8 (C=O), 152.9 (C=O), 142.7 (CH=), 136.0, 134.2, 131.9, 128.9, 128.6, 123.5 (Ph), 121.9 (CH=), 82.5 (C), 67.1 (CH), 38.6 (CH_2), 28.9 (CH_3), 23.7 (CH_3); IR_{umax}: 1763, 1717, 1677, 1636, 1324, 1224, 1158, 1103, 931 cm^{-1}. EI-HRMS: calculated for ($C_{23}H_{20}N_2O_5$), 404.1372; found, 404.1370.

General procedure for asymmetric alkylation. 2-((*R,Z*)-4-((*R*)-5,5-Dimethyl-2-oxo-4-phenyloxazolidin-3-yl)-3-methyl-4-oxobut-1-en-1-yl)isoindoline-1,3-dione (7a). To a solution of *N*-enoyl oxazolidinone **6** (0.20 g, 0.50 mmol) and LiCl (25.4 mg, 0.60 mmol) in anhydrous THF (15 mL), KHDMS (0.5 M in toluene, 1.10 mL, 0.55 mmol) was added dropwise at –60 ^{o}C. The reaction mixture was stirred for 30 min and then CH_3I (0.21 g, 1.50 mmol) was added and the reaction mixture was stirred at –45 ^{o}C for 7h. The reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL), the THF was removed under vacuum and the residue was extracted with CH_2Cl_2 (3 x 30 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel with hexane/ethyl acetate 85/15 as eluent to give a diastereomeric mixture of compounds **7a** and **7b**. Their isolation was carried out by crystallization with hexane-CH_2Cl_2 9:1 to give the compound **7a** as a white solid: 82.0 mg, 39.6%, mp 152.5°C, $[\alpha]^{25}_{D}$ -135.3 (*c* 1.17, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 7.86 (2H, dd, *J* 5.5, 3.0 Hz, Ph), 7.75 (2H, dd, *J* 5.5, 3.0 Hz, Ph), 7.39-7.31 (3H, m, Ph), 7.16 (2H, d, *J* 7.0 Hz, Ph), 6.23 (1H, dd, *J* 8.5, 0.5 Hz, =CHN), 5.81 (1H, dd, *J* 10.3, 8.5 Hz, CH=), 5.22 (1H, s, CH-Ph), 4.62 (1H, dq, *J* 10.3, 6.8 Hz, CH-CH_3), 1.82 (3H, s, CH_3), 1.33 (3H, d, *J* 6.8 Hz, CH_3-CH), 1.01 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 174.3 (C=O), 167.0 (C=O), 153.0 (C=O), 136.7, 134.4, 131.9 (Ph), 129.3 (CH=), 128.9, 128.6, 123.7 (Ph), 117.1 (CH=), 82.7 (C), 66.9 (CH), 37.9 (CH), 28.9 (CH_3), 23.7 (CH_3), 18.2 (CH_3); IR$_{\text{umax}}$: 1767, 1706, 1374, 1326, 1223, 1156, 987, 885, 722 cm^{-1}. EI-HRMS: calculated for ($C_{24}H_{22}N_2O_5$), 428.1529; found, 428.1533.

2-((*R,Z*)-3-Benzyl-4-((*R*)-5,5-dimethyl-2-oxo-4-phenyloxazolidin-3-yl)-4-oxobut-1-en-1-yl)isoindoline-1,3-dione (8a). To a solution of *N*-enoyl oxazolidinone **6** (0.20 g, 0.50 mmol) and LiCl (25.4 mg, 0.60 mmol) in anhydrous THF (15 mL), KHDMS (0.5 M in toluene, 1.10 mL, 0.55 mmol) was added dropwise at –60 ^{o}C. The reaction mixture was stirred for 30 min and then BnBr (0.26 g, 0.18 mL 1.50 mmol) was added and the reaction mixture was stirred at –45 ^{o}C for 7 h. The crude product was purified by flash column chromatography on silica gel with hexane/ethyl acetate 75/25 as eluent to yield **8a** as a white solid: 58.7 mg, 24 %, mp 155.3°C, $[\alpha]^{25.6}_{D}$ -42.18 (*c* 1.92, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 7.86 (2H, dd, *J* 5.5, 3.0 Hz, Ph), 7.75 (2H, dd, *J* 5.5, 3.0 Hz, Ph), 7.29-7.27 (5H, m, Ph), 7.15-7.11 (5H, m, Ph), 6.94 (2H, bs, Ph), 6.18 (1H, dd, *J* 8.6, 0.6 Hz, CH=), 5.80 (1H, dd, *J* 10.4, 8.6 Hz, CH=), 5.15 (1H, s, CH-Ph), 5.13-5.06 (1H, m, CH-CH_2), 3.18 (1H, dd, *J* 13.3, 6.6 Hz, CH_aH_b), 2.84 (1H, dd, *J* 13.3, 8.0 Hz, CH_bH_a), 1.75 (3H, s, CH_3), 0.95 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 172.8 (C=O), 166.7 (C=O), 153.0 (C=O), 137.5, 136.3, 134.3, 131.9, 129.2, 128.8, 128.3, 128.3 (Ph), 127.6 (CH=), 126.4, 123.6 (Ph), 118.5 (CH=), 82.5 (C), 67.1 (CH), 44.4 (CH), 38.7 (CH_2), 28.8 (CH_3), 23.7 (CH_3); IR$_{\text{umax}}$: 1767, 1712, 1374, 1093, 881, 695 cm^{-1}. EI-HRMS: calculated for ($C_{30}H_{26}N_2O_5$), 494.1842; found, 494.1840.

2-((*R,Z*)-3-Benzyl-4-((*R*)-5,5-dimethyl-2-oxo-4-phenyloxazolidin-3-yl)-4-oxobut-1-en-1-yl)isoindoline-1,3-dione (8b). White solid: 39 mg, 16%, mp 56.5 °C, $[\alpha]^{27}_{D}$ +131.07 (*c* 2.06, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 7.93 (2H, dd, *J* 5.5, 3.0 Hz, Ph), 7.76 (2H, dd, *J* 5.5, 3.0 Hz, Ph), 7.39-7.36 (2H, m, Ph), 7.33-7.30 (1H, m, Ph), 7.26-7.20 (4H, m, Ph), 7.15-7.13 (3H, m, Ph), 6.23 (1H, dd, *J* 8.5, 0.5 Hz, NCH=), 5.71 (1H, dd, *J* 10.8, 8.5 Hz, CH=), 5.33-5.28 (1H, m, CH), 4.80 (1H, s, CH), 3.15-3.07 (2H, m, CH_2), 1.11(3H, s, CH_3), 0.85 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 172.5 (C=O), 166.9 (C=O), 152.6 (C=O), 138.3, 135.9, 134.2, 132.2, 129.3, 128.9, 128.5, 128.4 (Ph), 127.8 (CH=), 126.5, 123.7 (Ph), 119.0 (CH=), 82.1 (C-O), 67.0 (CH), 44.9 (CH), 39.0 (CH_2), 28.2 (CH_3), 23.5 (CH_3); IR$_{\text{umax}}$: 2918, 1768, 1715, 1363, 1323, 1216, 1097, 891, 758 cm^{-1}. EI-HRMS: calculated for ($C_{30}H_{26}N_2O_5$), 494.1842; found, 494.1840.

2-((*S,Z*)-3-((*R*)-5,5-Dimethyl-2-oxo-4-phenyloxazolidine-3-carbonyl)hexa-1,5-dien-1-yl)isoindoline-1,3-dione (9a). To a solution of *N*-enoyl oxazolidinone **6** (0.20 g, 0.50 mmol) and LiCl (25.4 mg, 0.60 mmol) in anhydrous THF (15 mL), KHDMS (0.5 M in toluene, 1.10 mL, 0.55 mmol) was added dropwise at –60 ^{o}C. The reaction mixture was stirred for 30 min and then allylBr (0.18 g, 0.13 mL 1.50 mmol) was added and the reaction mixture was stirred at –45 °C for 7h. The crude product was purified by flash column chromatography on silica gel with hexane/ethyl acetate 70/30 as eluent to yield **9a** as a white solid: 68.6 mg, 31.2%, mp 144 °C, $[\alpha]^{22}_{D}$ –116.5 (*c* 1.03, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 7.86 (2H, dd, *J* 5.5, 3.1 Hz, Ph), 7.75 (2H, dd, *J* 5.5, 3.1 Hz, Ph), 7.38-7.32 (3H, m, Ph), 7.16 (2H, d, *J* 6.7 Hz, Ph), 6.27 (1H, d, *J* 8.6 Hz, NCH=), 5.80 (1H, dd, *J* 10.4, 8.6 Hz, CH=), 5.70-5.61 (1H, m, CH), 5.22 (1H, s, CH), 5.04-4.97 (2H, m, CH_2), 4.73 (1H, ddd, *J* 10.4, 7.3, 6.0 Hz, CH), 2.56-2.51 (1H, m, CH_aH_b), 2.41-2.35 (1H, m, CH_bH_a), 1.83 (3H, s, CH_3), 1.02 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 173.0 (C=O), 167.0 (C=O), 153.2 (C=O), 136.6, 134.5 (Ph), 133.7 (CH=), 131.9, 128.8, 128.6 (Ph), 128.0 (CH=), 123.7 (Ph), 118.2 (CH=), 118.0 (CH_2=), 82.7 (C-O), 67.1 (CH), 42.4 (CH), 37.1 (CH_2), 28.9 (CH_3), 23.8 (CH_3); IR$_{\upsilon max}$: 1769, 1719, 1379, 1363, 1324, 1212, 1105, 945, 891 cm^{-1}. EI-HRMS: calculated for ($C_{26}H_{24}N_2O_5$), 444.1685; found, 444.1691.

2-((*R,Z*)-3-((*R*)-5,5-Dimethyl-2-oxo-4-phenyloxazolidine-3-carbonyl)hexa-1,5-dien-1-y) isoindoline-1,3-dione (9b). The crude product was purified by flash column chromatography on silica gel with hexane/ethyl acetate 70/30 as eluent to yield **9b** as a white solid, 37 mg, 16.8%, mp 138.8 °C; $[\alpha]^{28}_{D}$ +109.4 (*c* 1.06, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 7.92 (2H, dd, *J* 5.5, 3.0 Hz, Ph), 7.76 (2H, dd, *J* 5.5, 3.0 Hz, Ph), 7.39-7.36 (2H, m, Ph), 7.33-7.30 (1H, m, Ph), 7.28-7.26 (2H, m, Ph), 6.23 (1H, d, *J* 8.6 Hz, NCH=), 5.81 (1H, m, CH), 5.65 (1H, dd, *J* 10.7, 8.6 Hz, CH=), 5.11 (1H, dd, *J* 17.1, 1.4 Hz, CH=), 5.05 (1H, m, CH=), 5.04 (1H, s, CH), 5.02-4.97 (1H, m, CH), 2.59-2.47 (2H, m, CH_2), 1.54 (3H, s, CH_3), 0.97 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 172.7 (C=O), 166.9 (C=O), 152.8 (C=O), 135.9 (Ph), 134.6 (CH=), 134.3, 132.1, 128.8, 128.5, 127.9, 123.7 (Ph), 118.7 (CH=), 117.6 (CH_2=), 82.2 (C-O), 67.3 (CH), 42.9 (CH), 37.2 (CH_2), 28.9 (CH_3), 23.7 (CH_3). IR$_{\upsilon max}$: 1770, 1720, 1380, 1361, 1324, 1213, 1106, 947, 890 cm^{-1}. EI-HRMS: calculated for ($C_{26}H_{24}N_2O_5$), 444.1685; found, 444.1689.

2-((*R*)-4-((*R*)-5,5-Dimethyl-2-oxo-4-phenyloxazolidine-3-yl)-3-methyl-4-oxobutyl)isoindoline-1,3-dione (10). To a solution of **7a** (50 mg, 0.11 mmol) in anhydrous ethyl acetate (3 mL), Pd/C (9.2 mg, 20 wt%) was added and stirred under ordinary hydrogen pressure (balloon) at 25 °C for 16 h. Then the resulting mixture was diluted with ethyl acetate, filtered through a pad of celite and washed with ethyl acetate (3 x 20 mL). The crude product was purified by flash column chromatography on silica gel with hexane/ethyl acetate 90/10 as eluent to give the compound **10** as a white solid: 45.3 mg, 98%, mp 136.1 °C, $[\alpha]^{25.5}_{D}$ -55.14 (*c* 1.07, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 7.82 (2H, dd, *J* 5.5, 3.1 Hz, Ph), 7.70 (2H, dd, *J* 5.5, 3.1 Hz, Ph), 7.38-7.30 (3H, m, Ph), 7.14 (2H, d, *J* 7.1 Hz, Ph), 5.19 (1H, s, CH), 3.78-3.69 (3H, m, CH and CH_2), 2.12 (1H, m, CH_aH_b), 1.81 (3H, s, CH_3), 1.73 (1H, m, CH_bH_a), 1.18 (3H, d, *J* 6.9 Hz, CH_3), 1.00 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 175.5 (C=O), 168.5 (C=O), 152.8 (C=O), 136.7, 133.9, 132.0, 128.8, 128.4, 123.2 (Ph), 82.3 (C-O), 66.8 (CH), 35.6 (CH_2), 35.2 (CH), 31.5 (CH_2), 28.9 (CH_3), 23.9 (CH_3), 17.9 (CH_3); IR$_{\upsilon max}$: 2978, 1748, 1701, 1323, 1323, 1163, 1090, 964, 751 cm^{-1}. EI-HRMS: calculated for ($C_{24}H_{24}N_2O_5$), 420.1685; found, 420.1675.

(*R*)-4-amino-2-methylbutanoic acid (11). To a solution of compound **10** (40 mg, 0.095 mmol) in glacial acetic acid (1 mL) was added 6M HCl (1.5 mL). The resulting solution was refluxed for 18 h. The reaction mixture was quenched with cold water (1 mL). The resulting aqueous solution was evaporated to dryness by placing it below an incandescent lamp for one week to provide a brown solid. A subsequent crystallization the crude of reaction gave the compound **11** as a less brown powder 8.0 mg, 70%. The γ-amino acid **11** was possible to detect by its ^1H NMR (500 MHz, D_2O) 2.84-2.95 (2H, m, CH_2N), 2.30 (1H, m, Ph), 1.60-1.83 (2H, m, CH_2), 1.00 (3H, d, *J* 7.0 Hz, CH_3).

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Supplementary Material

Copies of spectra of compounds are provided in the supplementary material file available on the Publisher's web site.

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