Synthesis of Lactones and Lactams from Vinylcyclopropane by Palladium-Catalyzed Nucleophilic Allylation

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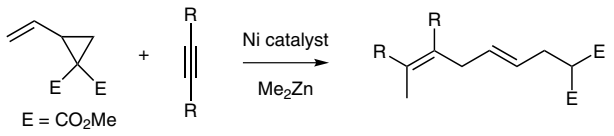
Abstract: A palladium-catalyzed nucleophilic allylation of aldehydes with vinylcyclopropane in the presence of diethylzinc proceeded to provide homoallyl alcohols with *anti* stereoselectivity. Aldimines prepared from aldehyde and primary amines in situ underwent a similar nucleophilic allylation to give homoallylamines with *syn* stereoselectivity. The resulting homoallyl alcohols and homoallylamines could be converted by treatment with a tetranuclear zinc cluster into γ-vinyl-δ-valerolactones and γ-vinyl-δ-valerolactams, respectively.

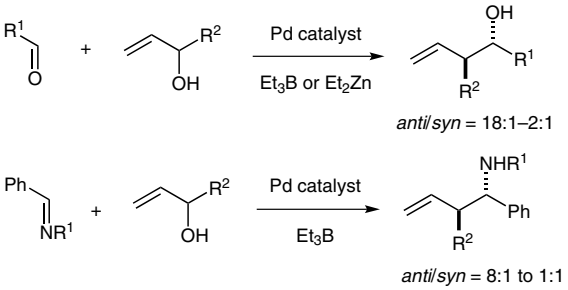
Key words: palladium, vinylcyclopropane, nucleophilic allylation, aldehyde, aldimine

Activated cyclopropanes are important and efficient key intermediates in modern organic synthesis.[1] In particular, cycloaddition and ring expansion reactions of vinylcyclopropanes are powerful tools for the construction of highly functionalized heterocycles and unsaturated hydrocarbons.[2] Recently, we developed a multicomponent coupling reaction of alkynes and dimethylzinc with vinylcyclopropane promoted by a Ni catalyst (Scheme 1).[3] In this case, vinylcyclopropane served as an allylnickel species, undergoing insertion of alkynes followed by transmetalation with dimethylzinc to construct octadiene frameworks with high regio- and stereoselectivity.



Scheme 1 Ni-catalyzed multicomponent coupling of vinylcyclopropane, alkyne, and Me_2Zn

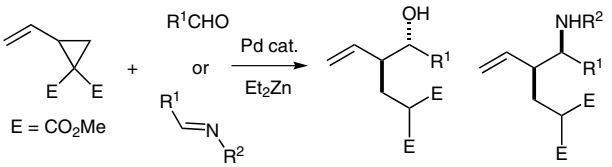
Pd-catalyzed allylation is one of the most useful and convenient methods for the synthesis of important complex molecules containing physiologically active scaffolds.[4] We previously demonstrated that a combination of a Pd(0) catalyst and diethylzinc or triethylborane effectively promotes oxidative addition of allyl alcohols to form a π-allylpalladium intermediate.[5] Interestingly, π-allylpalladium can undergo umpolung upon addition of diethylzinc and triethylborane to serve as an allyl anion equivalent in situ, allowing nucleophilic allylation of aldehydes and aldimines to afford homoallyl alcohols and homoallylamines, respectively (Scheme 2).[6]



Scheme 2 Pd-catalyzed nucleophilic allylation of aldehydes or aldimines with allyl alcohols

The combination of Pd(0) catalyst and diethylzinc or triethylborane accelerates amphiphilic allylations with allyl alcohols as allyl cation and allyl anion equivalents, depending on the nucleophiles and electrophiles in situ.

Herein, we demonstrate a successful extension of the Pd(0) catalyst and diethylzinc system to nucleophilic allylation of aldehydes and aldimines with vinylcyclopropane derived from dimethyl malonate and 1,4-dihalo-2-butene to form homoallyl alcohols and homoallylamines (Scheme 3). Furthermore, these products can be converted into γ-vinyl-δ-valerolactones and γ-vinyl-δ-valerolactams by treatment with a tetranuclear zinc cluster.



Scheme 3 Pd-catalyzed nucleophilic allylation of aldehydes or aldimines with vinylcyclopropane

Table 1 shows the results of nucleophilic allylation of aldehydes with dimethyl 2-ethenylcyclopropane-1,1-dicarboxylate in the presence of a Pd(0) catalyst promoted by diethylzinc at room temperature under a nitrogen atmosphere.[7] Among the various Pd catalysts, and using diethylzinc and triethylborane as promoters, the combination of $Pd(acac)_2$ and PPh_3 with diethylzinc gave the best results. Table 1 shows the results of allylation of various aldehydes, such as aromatic, α,β-unsaturated, and aliphatic aldehydes. Benzaldehyde underwent nucleophilic allyla-

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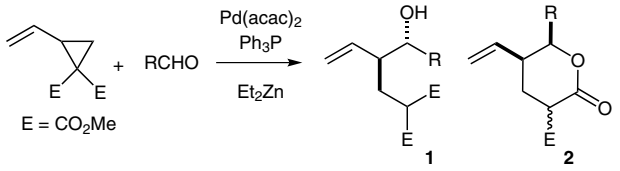
tion with dimethyl 2-ethenylcyclopropane-1,1-dicarboxylate to provide homoallyl alcohol **1a** in 72% yield as a single isomer with *anti* stereoselectivity along with the cyclized product **2a** as a by-product in a 2:1 ratio (entry 1, Table 1). *p*-Chlorobenzaldehyde participated in nucleophilic allylation to afford the homoallyl alcohol **1b** in excellent yield with high stereoselectivity (entry 2, Table 1). *p*-Tolualdehyde and 2-naphthylaldehyde showed similar results and gave the desired products in good to reasonable yields (entries 3 and 4, Table 1). Dihydrocinnamaldehyde gave the desired product **1e** in 39% yield, but lactone **2e** was obtained in 60% yield as a major product. *sec*-Alkylaldehyde participated in the similar nucleophilic allylation to afford homoallyl alcohol **1f** in 54% yield along with lactone **2f** in 36% yield. Pivalaldehyde provided a trace amount of homoallyl alcohol **1g**, instead, lactone **2g** was obtained in 62%, exclusively (entry 7, Table 1). The nucleophilicity of the alkoxides of homoallyl alcohols derived from aliphatic aldehydes seems to enhance the intramolecular esterification leading to γ-vinyl-δ-lactones **2**.

Table 1 Pd/Et_2Zn-Promoted Nucleophilic Allylation of Aldehyde with Vinylcyclopropane[a]

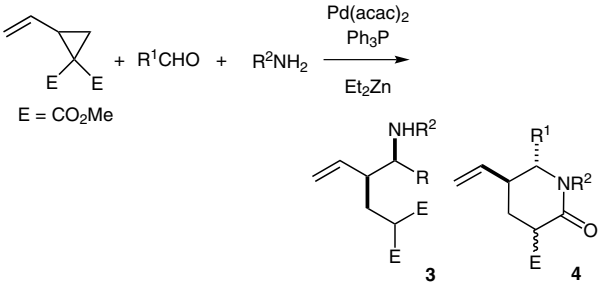


Entry	R	Time (h)	Yield (%) [ratio]
1	Ph	48	**1a**: 72, **2a**: 21 [1:1]
2	*p*-ClC_6H_4	18	**1b**: 78, **2b**: 21 [1:1]
3	*p*-MeC_6H_4	3	**1c**: 71, **2c**: 28 [1:1]
4	2-naphthyl	48	**1d**: 69, **2d**: 17 [1:1]
5	$PhCH_2CH_2$	48	**1e**: 39, **2e**: 60 [2:1]
6	*c*-C_6H_{11}	48	**1f**: 54, **2f**: 36 [1:1]
7	*t*-Bu	24	**1g**: trace, **2g**: 62 [1:1]

[a] The reaction was carried out in the presence of aldehyde (1 mmol), vinylcyclopropane (1.2 mmol), $Pd(acac)_2$ (0.05 mmol), Ph_3P (0.1 mmol), and Et_2Zn (2.4 mmol; 1 M hexane solution) in anhyd THF (1 mL) at r.t. for 48 h under nitrogen. All of the homoallyl alcohols **1** were obtained as a single isomer, whereas lactones **2** were obtained as diastereomeric mixture in 1:1 to 2:1 ratios.

A similar nucleophilic allylation reaction could be used for the synthesis of homoallylamines and δ-lactams. The result of reactions using various kinds of aromatic and aliphatic aldimines prepared from aldehydes and primary amines are summarized in Table 2. The reaction was conducted as follows: in situ formation of aldimines from primary amines and aldehyde by two azeotropic distillations of a mixture of THF–water (30 min reflux in 1 mL of THF), exposure of the aldimines to a mixture of $Pd(acac)_2$, Ph_3P, and vinylcyclopropane, and addition of diethylzinc with stirring at room temperature. As was the case for aldimines prepared from benzaldehyde and aromatic amines, the reaction was compatible with both electron-donating and electron-withdrawing aromatic rings of primary amines.

Table 2 Pd/Et_2Zn-Promoted Nucleophilic Allylation of Aldimines with Vinylcyclopropane[a]



Entry	Aldehyde R^1	Amine R^2	Yield (%) [ratio] **3** [*syn*/*anti*]	**4**
1	Ph	PMP	**3a**: 42 [4:1]	**4a**: 47
2	Ph	Ph	**3b**: 44 [3:1]	**4b**: 27
3	Ph	*p*-ClC_6H_4	**3c**: 36 [2:1]	**4c**: 21
4	Ph	Bn	none	**4d**: 62
5	Ph	*n*-C_6H_{13}	none	**4e**: 50
6	*p*-ClC_6H_4	PMP	**3f**: 27 [3:1]	**4f**: 51
7	*n*-C_5H_{11}	PMP	**3g**: 32 [single]	none

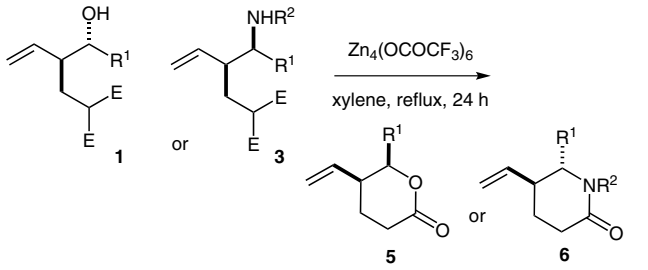
[a] The reaction was carried out in the presence of aldimine which was prepared from aldehyde (1 mmol) and amine (1.05 mmol) in THF (1 mL) at reflux (removal of H_2O by azeotropic distillation), 2-vinylcyclopropane (1.2 mmol), $Pd(acac)_2$ (0.05 mmol), Ph_3P (0.1 mmol), and Et_2Zn (2.4 mmol; 1 M hexane solution) in anhyd THF (1 mL) at r.t. for 48 h under nitrogen. All of the lactams **4** were obtained as a diastereoisomeric mixture in a 2:1 ratio.

Homoallylamines **3a**–**3c** were produced with *syn* stereoselectivity along with lactams **4a**–**4c** in a 2:1 ratio (entries 1–3, Table 2). Aldimines from aliphatic amines such as benzylamine and *n*-hexylamine could be used as substrates for a similar nucleophilic allylation reaction. However, homoallylamines **3** were not obtained at all; instead, lactams **4d** and **4e** were produced exclusively (entries 4 and 5, Table 2). Homoallylamines derived from aliphatic amines could be readily converted into lactams **4** by intramolecular lactamization under the reaction conditions owing to the greater nucleophilicity of the amino groups. Although *p*-chlorobenzaldehyde and aliphatic aldehyde could be also used as aldehydes for nucleophilic allylation, aldimine prepared from *n*-hexanal and *p*-anisidine selectively afforded homoallylamine **3g** as a sole product (entries 6 and 7, Table 2).

The homoallyl alcohols **1** and homoallylamines **3** resulting from Pd-catalyzed nucleophilic allylation with vinylcyclopropane could be converted into lactones and

lactams (Table 3).[8] Mashima and Ohshima reported excellent conversion of esters from a mixture of alcohols and carboxylic acids promoted by a tetranuclear zinc cluster.[9] Under similar conditions for esterification by a zinc cluster, homoallyl alcohols and homoallylamines isolated from the reactions detailed in Tables 1 and 2 could be cyclized to afford lactones and lactams under xylene reflux conditions accompanied by decarboxylation. Homoallyl alcohols as single isomers of **1a** and **1b** led to γ-vinyl-δ-lactones **5a** and **5b** as single isomers (entries 1 and 2, Table 3). Homoallylamines **3a**, **3b**, and **3g** also underwent the intramolecular cyclization to construct lactams **6a**, **6b**, and **6g** in reasonable ways (entries 3–5, Table 3).

Table 3 Decarboxylative Lactonization and Lactamization of Homoallylic Alcohols and Homoallylamines by Tetranuclear Zinc Cluster[a]



Entry	**1** or **3** [ratio]	Yield (%) of **5** or **6** [ratio]
1	**1a**	**5a**: 75
2	**1b**	**5b**: 70
3	**3a**: [4:1]	**6a**: 80 [4:1]
4	**3b**: [3:1]	**6b**: 76 [4:1]
5	**3g**: [single]	**6g**: 89 [single]

[a] The reaction was carried out in the presence of homoallyl alcohol **1** or homoallylamine **3** (0.3 mmol), and $Zn_4(OCOCF_3)_6O$ (0.0038 mmol) in xylene (1 mL) at reflux under nitrogen for 24 h.

The structures of the products were determined based on coupling constants from ^{1}H NMR spectral data and NOE experiments. Selected data for the nOe observed by the irradiation at the protons indicated in bold face are illustrated in Figure 1. The configurations of the lactones **5** and lactams **6** were complementary to each other; that is, the nucleophilic allylation of aldehydes and aldimines with vinylcyclopropane showed the opposite stereoselectivity, providing *anti*-homoallyl alcohols and *syn*-homoallylamines.

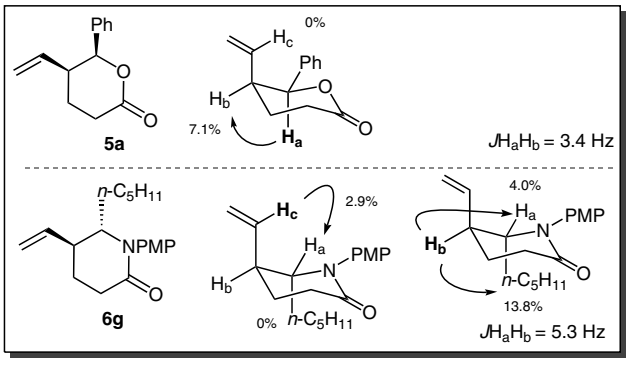
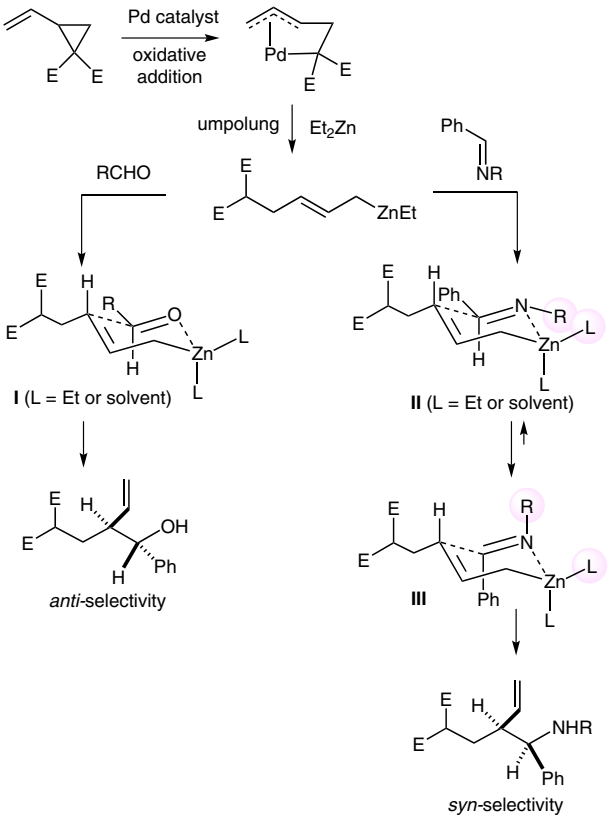


Figure 1 Structure determination for NOE data of lactone **5a** and lactam **6g**

A plausible reaction mechanism for Pd-catalyzed nucleophilic allylation of aldehydes and aldimines with vinylcyclopropane is illustrated in Scheme 4. An allyl anion equivalent generated from vinylcyclopropane and diethylzinc via umpolung of π-allylpalladium intermediate reacts with the aldehyde via the six-membered transition state **I** to avoid steric repulsion between the aldehyde substituents and the Et group or ligands on the Zn atom. Thus, homoallyl alcohols **1** are obtained with *anti* stereoselectivity. In contrast to the results obtained for aldehydes, aldimines undergo nucleophilic allylation through the intermediate **II** to avoid steric repulsion between substituents on the nitrogen atom and the Et group or the ligands on the zinc atom, resulting predominantly in the selective formation of *syn*-isomer **3**. An alternative structural feature associated with the six-membered allylzinc species which affects its interaction with aldehydes and aldimines is likely to rationalize the opposite stereoselectivity as well as the nucleophilic allylation of aldehydes and aldimines with allylmetal species.[10]



Scheme 4 Plausible reaction mechanism for Pd/Et_2Zn-promoted nucleophilic allylation of aldehyde and aldimine with vinylcyclopropane

In summary, we have demonstrated the Pd-catalyzed nucleophilic allylation of aldehydes and aldimines with dimethyl 2-ethenylcyclopropane-1,1-dicarboxylate promoted by diethylzinc to form homoallyl alcohols and homoallylamines, respectively.[11] Furthermore, these products were converted into γ-vinyl-δ-valerolactones and γ-vinyl-δ-valerolactams, accelerated by condensation with a tetranuclear zinc cluster as a Lewis acid. This transformation is useful for efficient medicinal synthesis of physiologically active molecules such as hydroxy acids, amino acids, δ-valerolactones, and δ-valerolactams.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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(7) See the Supporting Information.

(8) In the absence of Zn cluster catalyst, no lactonization and lactamization proceeded at all. These cyclizations required Zn cluster catalyst as a promoter to provide lactones and lactams from homoallyl alcohols and homoallylamines, respectively. Simple lactonization or lactamization conditions using acid catalysts and dehydration–condensation agents were ineffective.

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(11) **General Procedure for the Nucleophilic Allylation of Aldehyde with Vinylcyclopropane (Entry 1, Table 1)**: To a solution of $Pd(acac)_2$ (15.2 mg, 0.05 mmol), and Ph_3P (26.2 mg, 0.1 mmol) in anhyd THF (2 mL) were successively added vinylcyclopropane (221.0 mg, 1.2 mmol), benzaldehyde (106.1 mg, 1 mmol), and diethylzinc (2.4 mmol, 1.0 M hexane solution) via syringe under a nitrogen atmosphere. The mixture was stirred at r.t. for 48 h. The mixture was diluted with EtOAc (30 mL) and washed with 2 M HCl, and then brine. The extract was dried ($MgSO_4$) and concentrated in vacuo and the residual oil was subjected to column chromatography over silica gel (hexane–EtOAc, 2:1) to give **1a** (210.5 mg, 72%; R_f 0.63; hexane–EtOAc, 2:1) and **2a** (54.8 mg, 21%; R_f 0.5; hexane–EtOAc, 2:1). **Dimethyl 2-[2-(Hydroxyphenylmethyl)but-3-en-1-yl]malonate (1a)**: IR (neat): 3524 (br), 3064 (m), 3030 (m),

1750 (s), 1732 (s), 1640 (m), 921 (m), 765 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.80 (ddd, *J* = 14.3, 11.8, 5.0 Hz, 1 H), 1.94 (ddd, *J* = 14.3, 10.0, 3.7 Hz, 1 H), 2.11 (d, *J* = 2.5 Hz, 1 H), 2.38 (dddd, *J* = 11.8, 9.3, 7.1, 3.7 Hz, 1 H), 3.38 (dd, *J* = 10.0, 5.0 Hz, 1 H), 3.67 (s, 6 H), 4.50 (d, *J* = 7.1 Hz, 1 H), 5.13 (dd, *J* = 17.5, 1.7 Hz, 1 H), 5.26 (dd, *J* = 10.2, 1.7 Hz, 1 H), 5.63 (ddd, *J* = 17.5, 10.2, 9.3 Hz, 1 H), 7.27–7.34 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.7, 30.9, 49.6, 50.3, 52.4, 52.5, 120.0, 126.8, 127.9, 128.4, 137.2, 141.7, 169.4, 169.9. HRMS: *m*/*z* [M] calcd for $C_{16}H_{20}O_5$: 292.1311; found: 292.1311.

Methyl Tetrahydro-2-oxo-6-phenyl-5-vinyl-2*H*-pyran-3-carboxylate (2a): obtained as a mixture of diastereomers in a 2:1 ratio. IR (neat): 3035 (w), 2954 (m), 1732 (s), 1643 (m), 1263 (m), 1070 (m), 1002 (m), 925 (m), 702 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (major isomer) = 2.15 (ddd, *J* = 13.9, 9.8, 7.3 Hz, 1 H), 2.44 (ddd, *J* = 13.9, 11.3, 5.9 Hz, 1 H), 2.80–2.89 (m, 1 H), 3.80 (dd, *J* = 7.3, 5.9 Hz, 1 H), 3.83 (s, 3 H), 4.99 (d, *J* = 17.2 Hz, 1 H), 5.08 (d, *J* = 10.5 Hz, 1 H), 5.09 (d, *J* = 3.7 Hz, 1 H), 5.56 (ddd, *J* = 17.2, 10.5, 7.0 Hz, 1 H) 7.26–7.36 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (2:1 mixture of diastereomers) = 28.2, 29.4, 41.7, 43.6, 45.8, 47.8, 52.9, 85.9, 86.5, 118.2, 118.3, 127.1, 127.3, 128.5, 128.8, 128.9, 134.9, 135.1, 137.3, 137.6, 166.2, 166.7, 169.4, 169.5. HRMS: *m*/*z* [M] calcd for $C_{15}H_{16}O_4$: 260.1049; found: 260.1047.

Nucleophilic Allylation of Aldimine with Vinylcyclopropane (Entry 1, Table 2): A solution of benzaldehyde (106.1 mg, 1 mmol) and *p*-anisidine (129.3 mg, 1.05 mmol) in anhyd THF (1 mL) was refluxed for 30 min under nitrogen. The solvent was removed by distillation under atmospheric pressure of nitrogen (azeotropic removal of H_2O). The azeotropic distillation of THF (1 mL)/H_2O was repeated twice. A mixture of $Pd(acac)_2$ (15.2 mg, 0.05 mmol) and triphenylphoshine (26.2 mg, 0.1 mmol) in anhyd THF (2 mL) and vinylcyclopropane (221.0 mg, 1.2 mmol) dissolved in THF (1 mL) and diethylzinc (2.4 mmol, 1.0 M hexane solution) were successively added to the aldimine residue. The mixture was stirred at r.t. for 48 h. The reaction mixture was diluted with EtOAc (30 mL) and washed with sat. $NaHCO_3$, and brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to give a brown oil, which was subjected to column chromatography over silica gel (hexane–EtOAc, 70:30) to give **3a** (167 mg, 42%; R_f 0.5; hexane–EtOAc, 2:1) and **4a** (172 mg, 47%; R_f 0.27; hexane–EtOAc, 2:1).

Dimethyl 2-[(*p*-Methoxyphenylamino)phenylmethylbut-3-en-1-yl]malonate (3a): obtained as a mixture of diastereomers in a 4:1 ratio. IR (neat): 3404 (m), 3001 (m), 2953 (m), 2833 (m), 1750 (s), 1732 (s), 1508 (s), 1435 (s), 1159 (br), 1038 (s), 925 (m), 704 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (major isomer) = 1.69 (ddd, *J* = 13.7, 11.3, 4.4 Hz, 1 H), 2.32 (ddd, *J* = 13.7, 10.5, 2.9 Hz, 1 H), 2.42–2.49 (m, 1 H), 3.37 (dd, *J* = 10.5, 4.4 Hz, 1 H), 3.67 (s, 6 H), 3.72 (s, 3 H), 4.30 (d, *J* = 5.1 Hz, 1 H), 5.09 (dd, *J* = 17.1, 1.5 Hz, 1 H), 5.17 (dd, *J* = 10.2, 1.5 Hz, 1 H), 5.46 (ddd, *J* = 17.1, 10.2, 9.8 Hz, 1 H), 6.45 (d, *J* = 8.9 Hz, 2 H), 6.65 (d, *J* = 8.9 Hz, 2 H), 7.18–7.31 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (4:1 mixture of diastereomers) = 29.6, 30.4, 48.4, 49.1, 49.4, 49.5, 52.4, 52.5, 52.53, 55.56, 55.59, 51.0, 51.4, 114.6, 114.7, 114.74, 119.6, 127.8, 128.4, 128.6, 128.7, 128.8, 129.0, 132.8, 136.3, 137.2, 139.2, 140.5, 140.7, 141.1, 152.1, 152.3, 169.4, 169.6, 169.7, 169.8. HRMS: *m*/*z* [M] calcd for $C_{23}H_{27}NO_5$: 397.1889; found: 397.1899.

Methyl 1-(*p*-Methoxyphenyl)-2-oxo-6-phenyl-5-vinylpiperidine-3-carboxylate (4a): obtained as a mixture of diastereomers in a 2:1 ratio. IR (neat): 2955 (m), 2839 (m), 1738 (s), 1693 (s), 1514 (s), 1250 (s), 1033 (m), 833 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (major isomer) = 2.09 (dt, *J* = 13.9, 7.0 Hz, 1 H), 2.40–2.47 (m, 1 H), 2.74–2.84 (m, 1 H), 3.70 (s, 3 H), 3.76–3.81 (m, 1 H), 3.84 (s, 3 H), 4.69 (d, *J* = 5.6 Hz, 1 H), 5.18 (dt, *J* = 17.3, 1.2 Hz, 1 H), 5.21 (dd, *J* = 10.5, 1.2 Hz, 1 H), 5.92 (ddd, *J* = 17.3, 10.5, 6.6 Hz, 1 H), 6.72 (d, *J* = 9.0 Hz, 2 H), 6.97 (d, *J* = 9.0 Hz, 2 H), 7.16–7.35 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$; 2:1 mixture of diastereomers): δ = 26.7, 29.1, 42.7, 45.3, 47.2, 49.5, 52.3, 52.5, 55.11, 55.14, 70.0, 70.5, 113.9, 114.1, 117.1, 117.2, 127.6, 127.7, 127.8, 127.9, 128.3, 128.35, 128.43, 128.7, 133.4, 134.3, 137.1, 137.3, 139.5, 140.1, 158.0, 158.1, 166.3, 167.1, 170.7, 171.8. HRMS: *m*/*z* [M] calcd for $C_{22}H_{23}NO_4$: 365.1627; found: 366.1663.

