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A highly enantioselective [4+2] cycloaddition involving aldehydes and β,γ-unsaturated-α-keto esters

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ABSTRACT

A stereoselective inverse electron demand oxo-Diels-Alder reaction involving electron poor dienes (γ-aryl-β,γ-unsaturated-α-keto ester) and electron rich dienophiles has been studied. These cycloaddition reactions are extremely useful for the construction of *O*-, *N*-, *S*-centered heterocyclic compounds, which are routinely used in both synthetic organic and medicinal chemistry. The [4+2] hetero cycloaddition reactions involving various aldehydes and β,γ-unsaturated-α-keto esters were carried out in which three different types of substituted proline catalysts were examined. For these reactions, high selectivities (enantiomeric excess 93–98%) were obtained using catalyst **3**. Due to the bulkiness of catalyst **3**, compared to the other catalysts tested, it is more efficient at catalyzing these type reactions.

1. Introduction

Ever since the discovery of the Diels-Alder reaction,[1] it has become a cornerstone reaction in organic chemistry for the synthesis of carbon–carbon bonds. Researchers over the years have been inspired to develop different catalysts to effectively catalyze these reactions.[2] Catalytic asymmetric Diels-Alder reactions have emerged as a powerful methodology for the stereoselective construction of functionalized six membered rings with control of regio-, diastereo-, and enantioselectivity.[3] The inverse-electron demand hetero Diels-Alder reactions, which involve the incorporation of heteroatoms, such as oxygen or nitrogen, have given rise to the construction of heterocyclic compounds that are of extreme importance in medicinal chemistry.[4] A number of different Lewis-acid catalysts and chiral Lewis acid complexes[5] have been used to catalyze asymmetric hetero Diels-Alder reactions.[6] It was discovered that chiral Brønsted acids could be used to promote a highly enantioselective hetero Diels-Alder reaction via hydrogen-bonding interactions.[7] According to frontier orbital theory,[8] most of these catalysts employ a LUMO-activation strategy to activate electron-deficient dienophiles, and there have been only a few chiral catalysts that take advantage of an alternative strategy that activates the HOMO. A large percentage of the studies that involve catalytic asymmetric hetero Diels-Alder reactions are carried out using organometallic catalysts, which normally require harsh reaction conditions. As a result, a major disadvantage of this approach is that the catalysts are typically not recyclable.[9] In contrast, the use of organocatalysts for asymmetric hetero Diels-Alder has many advantages, such as mild reaction conditions, tolerance of a diverse range of functional groups, and the easy construction of carbon–heteroatom bonds. A major advantage is the facile stereospecific introduction of functionalized ring systems with up to four stereocenters in the products.[10] Herein, the effectiveness of a series of proline derived organocatalysts in promoting the enantioselective outcomes of the hetero Diels-Alder reactions of aldehydes with electron-deficient enones are analyzed.

2. Results and discussion

Amines, including proline and different proline derivatives, have emerged as very effective organocatalysts for various reactions, including aldol, Mannich, and Michael reactions.[11] Hayashi research et al. have successfully utilized diarylprolinol silyl ether salts to catalyze an asymmetric Diels-Alder reaction.[12] Figure 1 shows the organocatalysts that were considered herein.

List et al. and Hayashi et al. developed catalyst **1** and independently reported its success in catalyzing the asymmetric Michael addition involving acetaldehyde.[13] Catalyst **2** was synthesized in our lab and tested owing to possible hydrogen bond donor capability of the hydroxyl hydrogen. In 2009, our research group reported the design, synthesis and application of a new type of highly active di(*N*,*N*-dimethylbenzylamine)prolinol silyl ether organocatalyst (catalyst **3** in Fig. 1). This organocatalyst was shown to be a highly water-soluble organocatalyst for the asymmetric Michael addition

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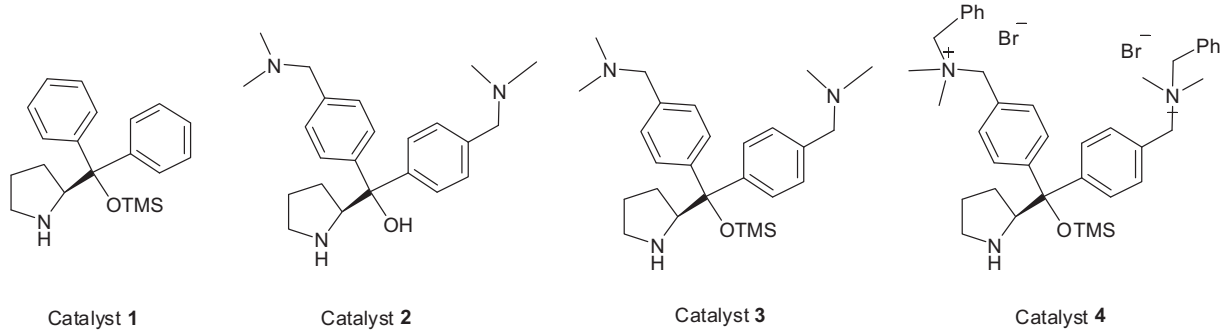
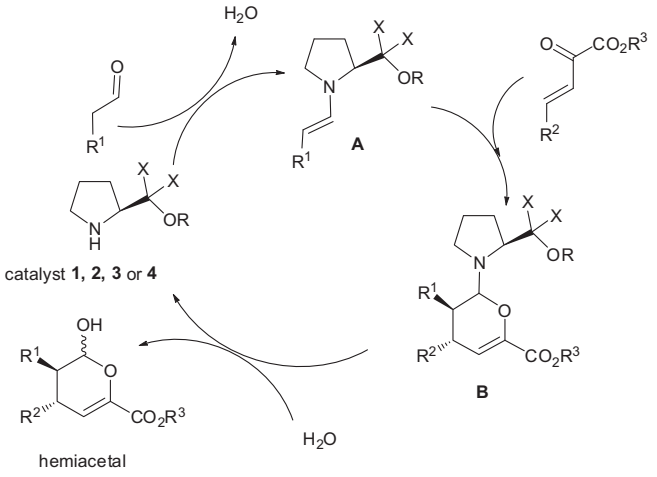


Figure 1. Organocatalysts screened for the oxo-Diels-Alder reaction.

of aldehydes to nitroolefins in which high diastereo- and enantioselectivities were obtained.[14]

Recently, our research efforts have focused on the development of water-soluble organocatalysts that are effective in aqueous media. In addition to the obvious advantages of carrying out reactions in aqueous media, including ease of product isolation, water has the unique advantage of being an environmentally benign economical solvent. As a result, it is a desirable medium to carry out asymmetric organocatalysis.[15] Catalyst **4**, which was developed in our research group, was found to be very effective for the asymmetric Michael reactions in aqueous media. Its effectiveness is primarily due to the presence of the ionic ammonium functionality, which when combined with the presence of the bulky OTMS group, serves as an effective organocatalyst for asymmetric reactions.[16] These bulky groups serve to selectively block one side of the reactant so that a stereoselective reaction can take place from the less sterically hindered side to afford the stereoselective products. The development of water-compatible asymmetric organocatalysts is a growing area of research and many have been developed and applied to a wide range of organic transformations, in which asymmetric products are obtained with high stereoselectivities.[17,18] In the use of these catalysts, bulky tags and effective hydrogen bonding capabilities selectively serve to give enantiospecific products.

For the reaction studied herein, the electron rich dienophile intermediate **A** is generated in situ from the aldehyde with either organocatalyst **1**, **2**, **3** or **4** as shown in the general catalytic cycle in Scheme 1.[19] The electron-rich alkene then undergoes the stereoselective hetero Diels-Alder reactions with the enone to give the intermediate **B**, which after hydrolysis gives the hemiacetal product. The hemiacetal is then oxidized further to give the products shown in Table 2. Similar hetero Diels-Alder reactions involving β,γ-unsaturated-α-keto-esters[20] and β,γ-unsaturated-α-ketophosphonates[21] have been studied and are shown to have a similar reaction cycle.



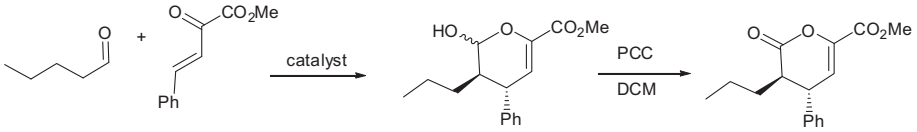
Scheme 1. Catalytic cycle for the hetero Diels-Alder reaction, where X and R are shown in Figure 1 and R^1 and R^2 are shown in Table 2.

The reaction involving valeraldehyde and Y-phenyl-β,Y-unsaturated-α-keto methyl ester served as a model to gain the optimized set of reaction conditions (catalyst, catalyst loading, temperature, and solvent) and the results are shown in Table 1. As mentioned earlier, the initially obtained hemiacetal product was converted to the more stable lactone product by oxidation with pyridinium chlorochromate. The percentage yield and enantiomeric excess were determined from the oxidized product.

First, catalyst **4** was considered since it is ionic and was successfully used as a recyclable catalyst in aqueous solvents for aldol reactions that were previously studied in our laboratory.[16] Unfortunately, it was not successful. As shown in Table 1, (entries 1, 2 and 3), the reaction was tested in three different solvents, including water, but no product was isolated. Next, catalyst **1** was tested since it was shown to be an effective catalyst for the asymmetric synthesis of various compounds.[22] As shown in Table 1, it was not effective in catalyzing the reaction in water (entry 6), probably due to its low solubility, but was most effective in CH_2Cl_2 (entries 4 and 5). As a result, different ratios of reactants were tested in CH_2Cl_2. For this catalyst, these changes did not have a significant effect on the reaction. Due to the polar property of catalyst **2** brought about by the introduction of the dimethylamino groups and the presence of the hydroxyl group, it was tested for this reaction in CH_2Cl_2. As shown in Table 1, this catalyst performed much better, compared to the previously tried catalysts, even though the yields were relatively low. In addition, these results showed that silica gel was needed for this reaction (entries 10 and 11). Silica gel is necessary for the substrates to be converted into the final products and to achieve catalytic turnover.

Encouraged by the results using catalyst **2** and that the dimethylamino group played an important role in the reaction, we envisioned that a catalyst containing the bulky OTMS group should be an improvement over catalyst **2**. As a result, the next catalyst tested was catalyst **3**; this catalyst definitely showed an improvement with shorter reaction times and improved enantioselectivities. These results also indicate that the best results were obtained when there was a slightly higher aldehyde concentration compared to the enone (entries 13 and 14). The reaction was also carried out using different catalyst concentrations as shown in entries 17 and 18. These results confirm that a catalyst concentration of 10 mol % provides the optimum results for this reaction. In order to ensure that CH_2Cl_2 was the best solvent for this reaction, the reaction was carried out in other solvents as shown in Table 1 (entries 19–23). Although a good amount of substrate conversion

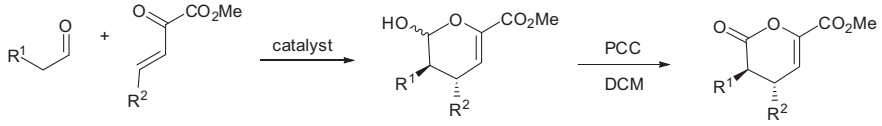
Table 1
Optimization of reaction conditions for the hetero Diels-Alder reaction involving valeraldehyde and γ-phenyl-β,γ-unsaturated-α-keto methyl ester carried out at 23 °C



Entry	Enone (mmol)	RCHO (mmol)	Cat (mol %)	Solvent	Time (h) [d]	% Yield[e]	% ee[f]
1	0.5	1.5	**4** (10)	CH_2Cl_2	96	Trace	nd
2	0.5	1.5	**4** (10)	*i*-PrOH	96	Trace	nd
3	0.5	1.5	**4** (10)	H_2O	96	Trace	nd
4	1.0	1.0	**1** (10)	DCM	20	65	96
5	0.5	1.5	**1** (10)	DCM	26	64	95
6	1.0	0.5	**1** (10)	H_2O	168	nd	nd
7	0.5	3.0	**2** (10)	CH_2Cl_2	34	26	85
8	0.5	1.5	**2** (10)	CH_2Cl_2	34	21	82
9	1.0	0.5	**2** (10)	CH_2Cl_2	10	24	84
10[a]	1.0	1.0	**2** (30)	CH_2Cl_2	32	Trace	nd
11[a]	1.0	0.5	**2** (10)	CH_2Cl_2	32	Trace	nd
12	0.25	1.0	**3** (20)	CH_2Cl_2	18	68	96
13	0.5	1.0	**3** (10)	CH_2Cl_2	20	76	95
14	**0.5**	**1.5**	**3 (10)**	**CH_2Cl_2**	**19**	**78**	**98**
15[b]	0.5	1.5	**3** (10)	CH_2Cl_2	24	44	80
16[c]	0.5	1.5	**3** (10)	CH_2Cl_2	96	29	88
17	0.5	1.5	**3** (5)	CH_2Cl_2	20	61	91
18	0.5	1.5	**3** (20)	CH_2Cl_2	36	44	87
19	0.5	1.5	**3** (10)	Toluene	20	34	98
20	0.5	1.5	**3** (10)	MeCN	32	46	84
21	0.5	1.5	**3** (10)	DMF	24	Trace	nd
22	0.5	1.5	**3** (10)	THF	96	Trace	nd
23	0.5	1.5	**3** (10)	*i*-PrOH	96	Trace	nd

[a] Reaction carried out without using silica.
[b] Reaction carried out at 35 °C.
[c] Reaction carried out at 0 °C.
[d] Time to form cycloadduct.
[e] Determined for oxidized derivative; and nd = not determined.
[f] Determined for oxidized derivative; and nd = not determined.

Table 2
Reaction scope for the oxo-Diels-Alder reaction involving various γ-aryl-β,γ-unsaturated-α-keto esters and substituted aldehydes



Entry	R^1	R^2	Time (h)	% Yield	% ee
1	$CH_3CH_2CH_2$	C_6H_5	19	78	98
2	CH_3	C_6H_5	15	51	93
3	$(CH_3)_2CH$	C_6H_5	26	64	98
4	$CH_3(CH_2)_3CH_2$	C_6H_5	12	86	98
5	$CH_3(CH_2)_3CH_2$	C_6H_5	16	80	98
6	$CH_3(CH_2)_3CH_2$	4-MeC_6H_4	15	76	97
7	$CH_3(CH_2)_3CH_2$	3-$MeOC_6H_4$	13	94	98
8	$CH_3(CH_2)_3CH_2$	4-$MeOC_6H_4$	14	77	98
9	$CH_3(CH_2)_3CH_2$	4-BrC_6H_4	20	76	98
10	$CH_3(CH_2)_3CH_2$	4-FC_6H_4	21	74	98
11	$C_6H_5CH_2$	C_6H_5	12	85	95

to product was observed in acetonitrile (yield 46%), the ee value was only 84% (entry 20). The low yields observed in THF and *iso*-propanol are probably due to the partial solubility of the enone in these solvents. The reaction was carried out at different temperatures; at a higher temperature (35 °C, entry 15), it is observed that even though the reaction time was reduced, the yield and enantioselectivity were lower than those obtained at 23 °C. At a lower temperature of 0 °C, it was observed that the reaction time was greatly increased, and with no real improvement in % yield or % ee (entry 16). These results show that the optimum set of reaction conditions are those shown in entry 14 and were used to carry out a study of the reaction scope; the results are shown in Table 2.

From Table 2, it is obvious that the best set of results in terms of reaction time, enantioselectivity and yield, is shown in entry 4. It appears that when the larger *iso*-propyl group is removed from the reaction center by a methylene unit, the best yield is obtained. From entry 3, even though the *iso*-propyl group is present, it is closer to the reaction center and results in a lower combination of

enantioselectivity, yield and slightly longer time. It also appears that electron-withdrawing and electron donating substituents on the phenyl ring do not have a major effect on this reaction. From entry 10, in which a very effective electron-withdrawing group on the phenyl ring is used, it can be seen that there is only a slight improvement of the reaction, compared to reactions with other substituents.

3. Conclusions

Of the four catalysts considered for the stereoselective inverse electron demand oxo-Diels-Alder reaction, we have shown that catalysts **3** can be used to effectively carry out this reaction, in which high enantiomeric excess was obtained. The key step in this reaction cycle involves the reaction of the bulky catalyst with the aldehyde to form an enamine intermediate which is a key step in the formation of the six-membered cyclic adduct. A previously proposed transition state model for similar reactions can be used to explain the stereochemical outcomes of these reactions.[19] The effectiveness of the catalyst herein is due to the presence of the bulky OTMS group, combined with the presence of two benzyl dimethyl amino groups.

4. Experimental section

4.1. General procedure for enantioselective hetero Diels-Alder reactions

The synthesis of the catalysts used are described elsewhere: catalyst **1**;[22a] catalyst **2** and catalyst **3**;[23] catalyst **4**.[16] The syntheses of the enones are described elsewhere.[24] For the hetero Diels-Alder reactions, the enone (0.5 mmol) was dissolved in 0.5 mL of dichloromethane and kept in an ice bath, then the aldehyde (1.5 mL), catalyst (0.05 mmol), silica (50 mg of silica) were added separately to the reaction solution, which was allowed to stir until TLC analysis indicated that the reaction was complete. Spots were visualized under UV light (λ = 254 nm) using TLC silica gel 60 F_{254} plates coated with aluminum. The cycloadduct formed was purified by column chromatography to give the hemiacetal, which is dissolved in 2 mL of dichloromethane and oxidized adding 1 equiv of pyridinium chlorochromate (PCC). After the oxidation was complete, the crude product was purified by column chromatography using silica gel (porosity 60 Å, particle size 40–63 μm) and 8/2 hexanes and ethyl acetate. ^{1}H and ^{13}C NMR spectra were obtained using a Varian 400 MHz instrument with TMS as the internal standard. Enantiomeric ratios were determined using a Shimadzu LC solution Chromatography Data System, in which Diacel chiral OD-H or AD-H columns with hexane/isopropanol (90:10) used as the eluent and flow rate 1.0 mL/min; UV = 240 nm were used. Racemates were synthesized using morpholine as an achiral catalyst. Enantiomeric excess determinations were made based on comparisons with previously reported literature determinations.[19] Similar HPLC conditions were used for the separation of the enantiomers for each reaction and based on the retention times, NMR and IR data, the identity of each enantiomer was determined.

4.1.1. (*S,R*)-α-Propyl-β-phenyl-γ,δ-unsaturated-δ-methylester lactone[19]

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.35–7.27 (m, 3H), 7.15–7.11 (m, 2H), 6.52 (d, 1H), 3.85 (s, 3H), 3.64 (m, 1H), 2.78–2.72 (m, 1H), 1.70–1.34 (m, 4H), 0.86 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 168.23, 160.90, 141.49, 139.59, 129.28 (2C), 127.92, 127.38 (2C), 117.34, 52.74, 45.55, 42.97, 31.98, 20.04, 13.93. Enantiomeric excess ratio was determined using Diacel OD-H column and t_{major} = 13.617 min, t_{minor} = 10.528 min.

4.1.2. (*S,R*)-α-Methyl-β-phenyl-γ,δ-unsaturated-δ-methylester lactone[19]

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.38–7.30 (m, 3H), 7.18–7.15 (m, 2H), 6.50 (d, 1H), 3.85 (s, 3H), 3.53 (dd, 1H), 2.77–2.68 (m, 1H), 1.19 (d, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 169.40, 161.0, 141.80, 139.90, 129.40 (2C), 128.20, 127.90 (2C), 119.0, 52.90, 44.90, 40.40, 14.30. Enantiomeric excess ratio was determined using Diacel OD-H column and UV = 240 nm; t_{major} = 21.285 min, t_{minor} = 17.750 min.

4.1.3. (*S,R*)-α-Isopropyl-β-phenyl-γ,δ-unsaturated-δ-methylester lactone

[10] ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.34–7.25 (m, 3H), 7.12–7.09 (m, 2H), 6.54 (dd, 1H), 3.86 (s, 3H), 3.79 (dd, 1H), 2.54 (ddd, 1H), 1.96–1.90 (m, 1H), 1.11 (d, 3H), 1.02 (d, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 167.23, 160.85, 141.83, 139.66, 129.34 (2C), 127.85, 127.17 (2C), 116.40, 53.50, 52.75, 41.21, 29.12, 20.97, 19.89. Enantiomeric excess ratio was determined using Diacel OD-H column and t_{major} = 11.687 min, t_{minor} = 9.255 min.

4.1.4. (*S,R*)-α-Pentyl-β-phenyl-γ,δ-unsaturated-δ-methylester lactone[19]

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.35–7.27 (m, 3H), 7.14–7.11 (m, 2H), 6.52 (d, 1H), 3.85 (s, 3H), 3.65 (dd, 1H), 2.76–2.71 (m, 1H), 1.68–1.54 (m, 2H), 1.46–1.32 (m, 2H), 1.27–1.18 (m, 4H), 0.83 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 168.23, 160.90, 141.49, 139.59, 129.28 (2C), 127.92, 127.38 (2C), 117.34, 52.74, 45.82, 42.97, 31.44, 29.81, 26.41, 22.34, 13.93. Enantiomeric excess ratio was determined using Diacel OD-H column and t_{major} = 12.027 min, t_{minor} = 9.513 min.

4.1.5. (*S,R*)-α-Heptyl-β-phenyl-γ,δ-unsaturated-δ-methylester lactone[19]

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.35–7.26 (m, 3H), 7.14–7.11 (m, 2H), 6.51 (d, 1H), 3.84 (s, 3H), 3.66–3.63 (dd, 1H), 2.76–2.70 (m, 1H), 1.69–1.54 (m, 2H), 1.47–1.31 (m, 2H), 1.27–1.16 (m, 8H), 0.84 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 168.35, 160.88, 141.46, 139.56, 129.24 (2C), 127.88, 127.34 (2C), 117.15, 52.65, 45.72, 42.87, 31.74, 29.83, 29.29, 28.88, 26.71, 22.64, 14.08. Enantiomeric excess ratio was determined using Diacel OD-H column and t_{major} = 11.337 min, t_{minor} = 8.577 min.

4.1.6. (*S,R*)-α-Pentyl-β-4-methylphenyl-γ,δ-unsaturated-δ-methylester lactone[19]

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.13 (d, 2H), 7.01 (d, 2H), 6.50 (d, 1H), 3.84 (s, 3H), 3.62–3.59 (m, 1H), 2.74–2.68 (m, 1H), 2.32 (s, 3H), 1.68–1.53 (m, 2H), 1.46–1.31 (m, 2H), 1.28–1.17 (m, 4H), 0.83 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 168.35, 160.88, 141.32, 137.66, 136.57, 129.92 (2C), 127.20 (2C), 117.69, 52.65, 45.86, 42.46, 31.46, 29.70, 26.44, 22.36, 21.14, 13.95. Enantiomeric excess ratio was determined using Diacel OD-H column and t_{major} = 9.408 min, t_{minor} = 7.845 min.

4.1.7. (*S,R*)-α-Pentyl-β-3-methoxyphenyl-γ,δ-unsaturated-δ-methylester lactone[19]

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.26–7.22 (m, 1H), 6.80 (dd, 1H), 6.71 (d, 1H), 6.65 (t, 1H), 6.49 (d, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 3.61 (dd, 1H), 2.73 (dd, 1H), 1.69–1.53 (m, 2H), 1.46–1.31 (m, 2H), 1.27–1.15 (m, 4H), 0.83 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 168.22, 160.90, 160.22, 141.63, 141.22, 130.36, 119.51, 117.20, 113.40, 112.86, 55.32, 52.74, 45.68, 42.83, 31.43, 29.67, 26.41, 22.34, 13.93. Enantiomeric excess ratio was determined using Diacel OD-H column and t_{major} = 18.392 min, t_{minor} = 13.719 min.

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4.1.8. (*S,R*)-α-Pentyl-β-4-methoxyphenyl-γ,δ-unsaturated-δ-methylester lactone[19]

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.04 (d, 2H), 6.84 (d, 2H), 6.5 (d, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 3.59 (dd, 1H), 2.71–2.65 (m, 1H), 1.67–1.52 (m, 2H), 1.45–1.28 (m, 2H), 1.27–1.15 (m, 4H), 0.83 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 168.48, 160.88, 159.25, 141.32, 131.55, 128.42 (2C), 117.70, 114.57 (2C), 55.36, 52.65, 46.13, 42.06, 31.46, 29.70, 26.44, 22.37, 13.95. Enantiomeric excess ratio was determined using Diacel OD-H column and t_{major} = 13.633 min, t_{minor} = 11.031 min.

4.1.9. (*S,R*)-α-Pentyl-β-4-bromophenyl-γ,δ-unsaturated-δ-methylester lactone[19]

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.45 (d, 2H), 7.01 (d, 2H), 6.46 (d, 1H), 3.84 (s, 3H), 3.62 (dd, 1H), 2.68 (dd, 1H), 1.68–1.52 (m, 2H), 1.46–1.30 (m, 2H), 1.28–1.14 (m, 4H), 0.83 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 167.94, 160.74, 141.87, 138.61, 132.50 (2C), 129.10 (2C), 121.90, 116.47, 52.78, 45.72, 42.33, 31.46, 29.70, 26.44, 22.37, 13.95. Enantiomeric excess ratio was determined using Diacel AD-H column and t_{major} = 11.748 min, t_{minor} = 9.092 min.

4.1.10. (*S,R*)-α-Pentyl-β-4-trifluoromethylphenyl-γ,δ-unsaturated-δ-methylester lactone[19]

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.60 (d, 2H), 7.27 (d, 2H), 6.48 (d, 1H), 3.85 (s, 3H), 3.73 (dd, 1H), 2.73 (dd, 1H), 1.69–1.54 (m, 2H), 1.46–1.32 (m, 2H), 1.28–1.15 (m, 4H), 0.83 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 167.68, 160.63, 143.66, 142.04, 127.79 (2C), 126.29 (2C), 115.98, 52.88, 45.55, 42.70, 31.44, 29.67, 26.41, 22.34, 13.93; ^{19}F NMR (400 MHz, $CDCl_3$): δ (ppm) = −62.70 (s, 3F). Enantiomeric excess ratio was determined using Diacel AD-H column and t_{major} = 9.553 min, t_{minor} = 7.081 min.

4.1.11. (*S,R*)-α-Benzyl-β-4-phenyl-γ,δ-unsaturated-δ-methyl-ester lactone[19]

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.33–7.17 (m, 6H), 7.14 (d, 2H), 7.01 (d, 2H), 6.51 (d, 1H), 3.87 (s, 3H), 3.59 (t, 1H), 3.12–2.96 (m, 2H), 2.88 (dd, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 167.95, 160.76, 141.63, 139.19, 137.29, 129.30 (2C), 129.18 (2C), 128.73 (2C), 127.98, 127.31 (2C), 127.07, 116.55, 52.84, 47.75, 41.47, 35.71. Enantiomeric excess ratio was determined using Diacel OD-H column and t_{major} = 20.269 min, t_{minor} = 31.372 min.

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