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Article

Palladium-Catalyzed Arylation of Enoates with Iodobenzene: Stereoselective Synthesis of Trisubstituted Olefins

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A reação de Heck entre enoatos de configuração *Z* e *E* e o iodobenzeno foi estudada na presença de $Pd(OAc)_2$. A estereoquímica nos adutos formados foi dependente da geometria do enoato (reação estereoespecífica). Os melhores rendimentos foram obtidos a partir de enoatos *Z*, em acetona, utilizando Ag_2CO_3 como base. Os principais intermediários catiônicos de paládio possivelmente envolvidos no ciclo catalítico puderam ser interceptados e caracterizados por espectrometria de massas com ionização electrospray (ESI-MS). A estereosseletividade observada pôde ser racionalizada através do mecanismo clássico da reação de Heck.

The Heck reaction between *E*- and *Z*-enoates and iodobenzene was studied in the presence of $Pd(OAc)_2$. The stereochemistry in resulting adducts was dependent on the enoate geometry (stereospecific reaction). Best yields were obtained from *Z*-isomers in acetone using Ag_2CO_3 as base. The main cationic palladium intermediates possibly involved in the catalytic cycle could be intercepted and characterized by electrospray ionization mass spectrometry (ESI-MS). The stereoselectivity observed was rationalized through the classic mechanism of the Heck reaction.

Keywords: Heck reaction, enoates, palladium catalysis, mass spectrometry

Introduction

Heck and collaborators described in 1968 the preparation of methyl cinnamate by the reaction of phenylmercuric chloride with methyl acrylate in the presence of stoichiometric amounts of $PdCl_2/LiCl$.[1] Mizoroki, *et al.* in 1971[2] and Heck and Nolley in 1972[3] reported the arylation of styrene by iodobenzene in the presence of catalytic amounts of palladium salts. Since then, the scope of the Heck reaction has been extensively expanded and new sources of organopalladium species as well as new types of olefins have been incorporated into the set of starting materials suitable for this reaction.[4,5]

Intramolecular Heck reaction allows the preparation of heterocycles and molecules bearing tertiary and quaternary centers, via carbopalladation of 1,2-disubstituted and trisubstituted double bonds.[6] In contrast, we found scattered examples involving the intermolecular Heck reaction of conjugate double bond bearing substituents at the β-position, such as crotonates and cinnamates.[7]

Stereoselective synthesis of 1,2 disubstituted olefins is a well established process and these products can be synthesized via Wittig-type reactions,[8] using organometallics[9] and more recently by metathesis.[10] In contrast, stereocontrol in construction of trisubstituted olefins remains a challenge.[11]

In this article we report stereoselective arylation of a series of enoates with iodobenzene. These reactions were studied under classical Heck conditions,[3] in which the

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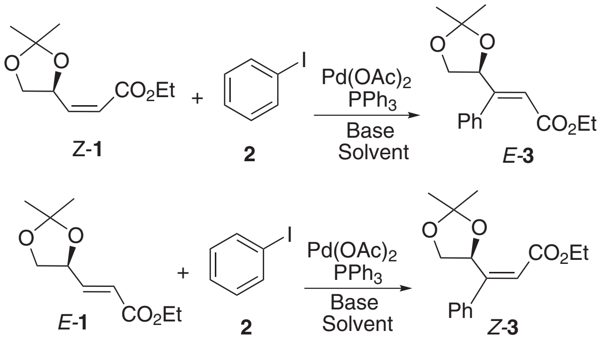
neutral mechanism is favored and the results are compared with those obtained in conditions favoring the cationic mechanism (in the presence of Ag_2CO_3 or using water as solvent).[4,12] A mechanistic rationalization was proposed based on electrospray ionization mass spectrometry (ESI-MS) monitoring.

Results and Discussion

In contrast to acrylates, which under classical Heck conditions (neutral mechanism) are known to react with iodobenzene (**2**) leading to cinnamates in good yields,[3,13] enoate *Z*-**1** furnished only traces of adduct *E*-**3** in the presence of $Pd(OAc)_2$, PPh_3, Et_3N and DMF (Dimethylformamide) at 70 ºC for 40 h (Scheme 1, Table 1, entry 1). Yield of *E*-**3** did not increase when Z-**1** and **2** were allowed to react under reflux in this solvent, leading to extensive isomerization from *Z*-**1** to *E*-**1** (data not showed). Enoate *E*-**1** was completely recovered when allowed to react under these conditions (entry 2). Due to these disappointing results, we decided to try reaction conditions that would favor the cationic mechanism, using silver salts as bases. Indeed, the yield of *E*-**3** obtained from Z-**1** increased to 71% in the presence of Ag_2CO_3, PPh_3 and acetone (entry 3) and higher yield (79%) was obtained in the absence of PPh_3 (entry 4). Reaction times could not be reduced without decrease in yields. An excess of enoate is necessary but it can be recovered in the reaction purification. Enoate *E*-**1** was much less reactive than *Z*-**1** under these same conditions, leading to adduct *Z*-**3** in moderate yield (entry 5). This difference in chemical reactivity between *Z*-**1** and *E*-**1** suggest that the transition state for the carbopalladation step of *Z*-**1** is sterically less hindered. Since it has been accepted that Heck reactions in water also proceed through a cationic mechanism,[4,12] these reactions were also studied in water using $Pd(OAc)_2$ and Et_3N. In contrast with Heck-lactonization reactions with enoate *Z*-**1**, which proceeds quite well in aqueous medium,[12] the yields of Heck reaction between *Z*-**1** and **2** decreased in water. Cinnamate *E*-**3** was obtained in 48% yield from *Z*-**1** (entry 6), while *E*-**1** furnished *Z*-**3** in only 18% yield (entry 7). These reactions were stereospecific and only one geometric isomer was observed in crude spectra.



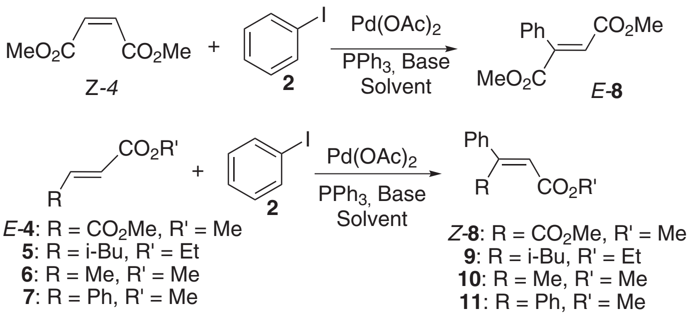
Scheme 1. Palladium catalyzed reaction between iodobenzene **2** and olefins *Z*-**1** and *E*-**1.**

To further evaluate the scope of this Heck reaction, a few other enoates were selected to react with **2** (Scheme 2, Table 2). Methyl maleate (*Z*-**4**) led to adduct *E*-**8** in 63% yield whereas its isomer *Z*-**8** was obtained from *E*-**4** in 35% yield (Scheme 2, Table 2, entries 1 and 2). Kondolff *co-workers*[7] described a mixture of stereoisomers in which the geometry of preferential product was independent on the starting material geometry in the reaction of these olefins with iodobenzene using a tedicyp-palladium complex in DMF.[7] Methyl maleate (*Z*-**4**) produced the corresponding adduct in worse yields than *Z*-**1** but in better yields than its isomer *E*-**4**. Only traces of the corresponding geometric isomers were observed in the purified products (they not appeared in crude mixtures). Adduct **9** was obtained from **5** in 40% yield in the presence of Ag_2CO_3 but only 14% yield was obtained in water (entries 3 and 4). Methyl crotonate (**6**) and methyl cinnamate (**7**) led to the corresponding adducts **10** and **11**, respectively, in poor yields (entries 5, 6 and 7).[14]

Table 1. Yields and major conditions for the reactions shown in Scheme 1

Entry	Olefin	Base	PPh_3	Solvent	Product	%**3**[a]
1[b]	*Z*-**1**	Et_3N	20 mol%	DMF	*E*-**3**	Traces
2[b]	*E*-**1**	Et_3N	20 mol%	DMF	no reaction	
3[c]	*Z*-**1**	Ag_2CO_3	20 mol%	Acetone	*E*-**3**	71
4[c]	*Z*-**1**	Ag_2CO_3	absence	Acetone	*E*-**3**	79
5[c]	*E*-**1**	Ag_2CO_3	20 mol%	Acetone	*Z*-**3**	44
6[d]	*Z*-**1**	Et_3N	absence	H_2O	*E*-**3**	48
7[d]	*E*-**1**	Et_3N	absence	H_2O	*Z*-**3**	18

Reaction mixtures were heated for 40 h in the presence of 10 mol% of $Pd(OAc)_2$, 20 mol% PPh_3 and 3 equiv of base. [a]Isolated yields; [b]Reactions in DMF were heated to 70 ºC; [c]Reactions in acetone were heated to 70 ºC (bath temperature); [d]Reactions in water were heated to 80 ºC in the absence of PPh_3.



Scheme 2. Palladium catalyzed reaction between iodobenzene **2** and olefins **4** to **7**.

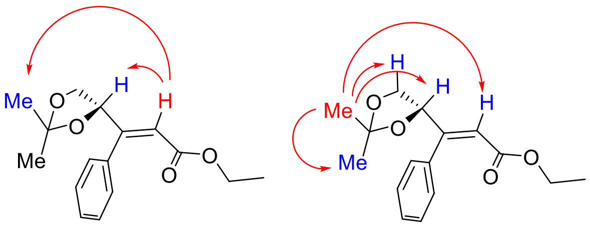
Table 2. Yields and conditions for the reactions shown in Scheme 2

Entry	Olefin	Base	PPh_3	Solvent	Product	%[a]
1	*Z*-**4**	Ag_2CO_3	20 mol%	Acetone	E-**8**	63
2	*E*-**4**	Ag_2CO_3	20 mol%	Acetone	Z-**8**	35
3	**5**	Ag_2CO_3	20 mol%	Acetone	**9**	40
4[b,c]	**5**	Et_3N	absence	H_2O	**9**	14
5	**6**	Ag_2CO_3	20 mol%	Acetone	**10**	26
6	**7**	Ag_2CO_3	20 mol%	Acetone	**11**	33
7[a]	**7**	Et_3N	absence	H_2O	**11**	19

Reaction mixtures were heated to 70 °C for 40 h in the presence of 10 mol% of $Pd(OAc)_2$, 20 mol% PPh_3 and 3 equiv of base. [a]Isolated yields; [b]Reactions in water were heated to 80 °C; [c]$PdCl_2$ used as catalyst.

a) Adduct *E*-**3**, irradiation at 6.29 ppm

b) Adduct *E*-**3**, irradiation at 1.46 ppm



c) Adduct *Z*-**3**, irradiation at 1.37 ppm

d) Adduct *Z*-**3**, irradiation at 1.21 ppm

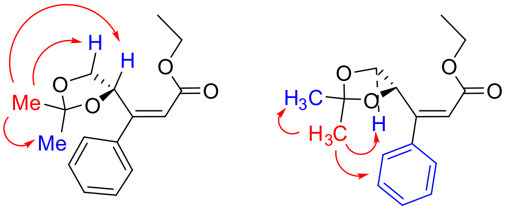


Figure 1. Stereochemistry assignments by NOE experiments; (a) adduct *E*-**3**, (b) adduct *E*-**3**, (c) adduct *Z*-**3**, (d) adduct *Z*-**3**.

The configuration at the double bond in **3** was established by nOe experiments (Figure 1). Irradiation at the olefinic hydrogen of *E*-**3** (in red) led to enhanced signals for one of the methyl group at the dioxolane ring and hydrogen at chiral center (Figure 1a). Similarly, irradiation at this methyl group (in red, Figure 1b) led to enhanced signals for the other geminal methyl group, one hydrogen at the dioxolane ring, olefinic hydrogen and hydrogen attached at the chiral center. As expected, for NOE experiments with *Z*-**3** no interference was observed in olefinic proton after irradiation at methyl groups at the dioxolane ring (Figure 1c and 1d). Configuration of *Z*-**8** and *E*-**8** were established by comparison with literature data.[15] Products **9**, **10** and **11** are also described.[16]

DFT (Density Functional Theory) calculations at M06-2X/6-311++G(d,p) level were carried out to confirm the NOE interpretation. Geometries of *Z*-**3** and *E*-**3** were fully optimized at this level and characterized as minimum on the potential energy surface by the absence of imaginary frequencies after vibrational analysis. Figure 2 shows the optimized geometries showing some selected distances. All calculations were made with the Gaussian 09 package.[17] The intermolecular distances shown confirm the assignment made by the nOe experiments.

It was also performed an investigation of the mechanism of enoate arylations *via* direct infusion electrospray ionization mass spectrometry (ESI-MS) monitoring and its tandem version (ESI-MS/MS).[18] This technique has become a major tool for mechanistic studies in organic and inorganic chemistry owing to its outstanding ability to "fish" ionic or ionized intermediates directly from reaction solutions into the gas phase with high sensitivity, speed,

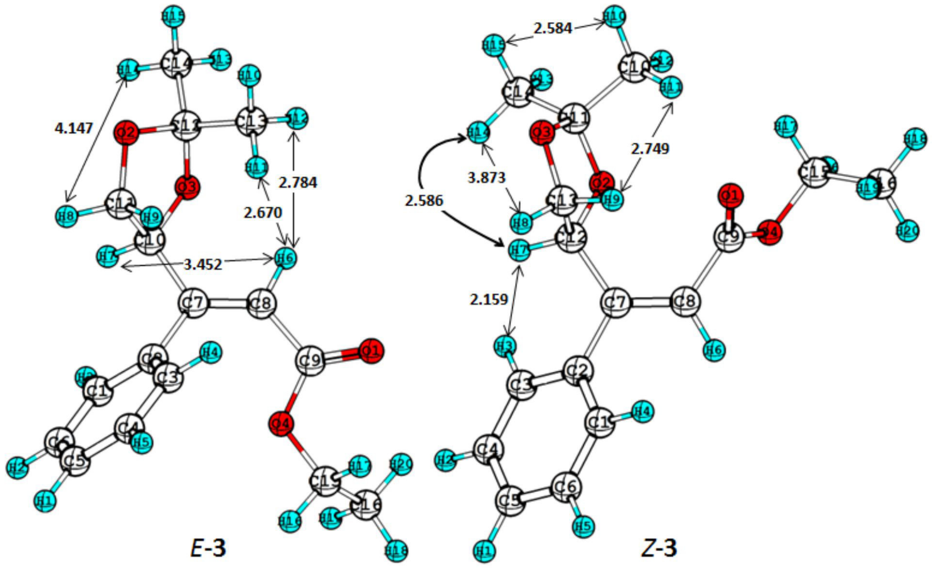


Figure 2. Optimized geometries of the *E* and *Z* forms of the adduct 3.

and gentleness. The mechanism of Heck reactions has also been the subject of extensive investigation via ESI-MS.[12,19] Samples of the reaction solution were diluted in MeCN before recording the MS data.

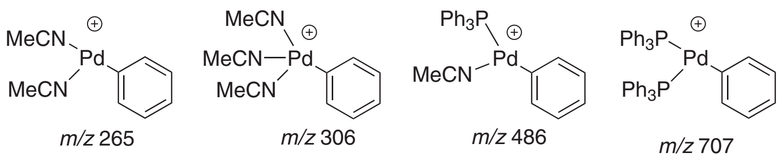
As expected, cationic palladium species could be intercepted in Heck reaction between *Z*-**1** and **2** in presence or absence of phosphines. Figure 3 shows some intermediates formed in oxidative addition and migratory insertion steps. The structures of these cationic species were confirmed by the characteristic Pd multi-isotopic pattern (only the *m/z* of the most abundant isotopologue ion is mentioned) and by ESI-MS/MS (supplementary information).

Based on the ESI-MS data and in the observed stereoselectivity, it was rationalized a mechanism for the Heck reaction between **1** and **2** in the presence of Ag_2CO_3 (Scheme 3). The cationic phenyl palladium **12** is firstly formed, reacting subsequently with *Z*-**1** via a regio and *syn*-stereoselective carbopalladation, to form the key cationic intermediate **13**. *Syn*-elimination of HPd^+ from **13** (conformer C_2) leads stereoselectively to adduct *E*-**3** (Scheme 3a).[4,5] Similarly, *Z*-**3** is formed when *E*-**1** is used as the olefin (Scheme 3b).

Conclusions

This study has shown that *Z*-enoates are better substrates for the Heck reaction than *E*-enoates, which are more sterically hindered. The use of such enoates allowed the stereospecific synthesis of isomeric β-substituted cinnamates. These present results are in contrast with those previously reported for Heck reactions of cinnamates with

(a) Oxidative addition intermediates:



(b) Migratory insertion intermediates:

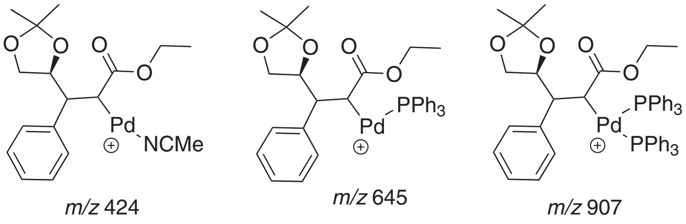
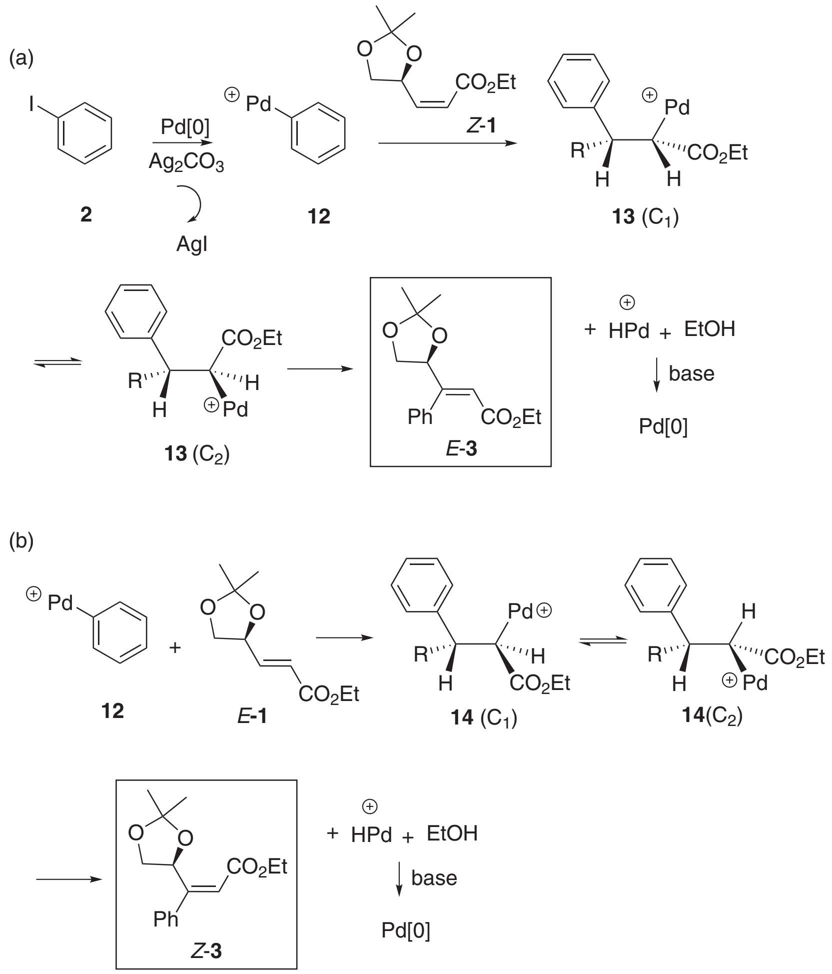


Figure 3. Some detected intermediates on ESI(+)-MS of the reaction solution of *Z*-**1** and **2**; (a) oxidative addition intermediates, (b) migratory insertion intermediates.



Scheme 3. Proposed mechanism for the Heck reaction between enoates *Z*-**1** (a) and *E*-**1** (b) with **2** in the presence of Ag_2CO_3.

haloarenes, in which the stereochemistry in the adducts is defined by isomerisation of products via thermodynamic control.[4] The results are also in contrast with those previously reported for Heck reactions of maleates and fumarates with iodobenzene, in which a mixture of isomeric products was formed.[7] Although it was used a limited number of variations, further studies with a large set olefins and iodoarens must be accomplished to confirm the suitability of this stereoselective methodology as an important tool to synthesize trisubstituted olefins.

Experimental

General procedure of ESI-MS and ESI-MS/MS

All experiments were performed on a hybrid quadrupole time-of-flight mass spectrometer (Q-TOF, Waters). For typical electrospray ionization (ESI) conditions, the Teflon-sealed microsyringe was put in a pump that delivered the reagent solution into the ESI source at a flow rate of 10 μL min^{-1}. ESI and the mass spectrometer was operated in the positive ion mode. Main conditions were capillary voltage, 3500 eV; cone voltage, 35 eV; source temperature, 100 °C; desolvation temperature, 100 °C. The cationic species were subjected to collision-induced dissociation (CID) with argon by using collision energies ranging from 5 to 45 eV.

Cinnamates 3, 8, 9, 10 and 11; General procedure in organic solvents

A mixture of iodobenzene (**2**, 102 mg, 0.5 mmol), enoate (*Z*-**1**, 300 mg, 1.5 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PPh_3 (26.2 mg, 0.1 mmol), Ag_2CO_3 (414 mg, 1.5 mmol) and acetone (15 mL) was stirred at 70 °C for 40 h under inert atmosphere. It was cooled, filtered through diatomaceous earth, extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed *in vacuum* and the residual mass was purified by column chromatography (hexane/EtOAc, 97:3 v/v) to give *E*-**3** (98 mg, 71%).

Cinnamates 3, 8, 9, 10 and 11; General procedure in water

A mixture of Pd(OAc)$_2$ (11.2 mg, 0.05 mmol), enoate (*Z*-**1**, 300 mg, 1.5 mmol), iodobenzene (**2**, 102 mg, 0.5 mmol) and Et$_3$N (0.208 mL, 1.5 mmol) in H$_2$O (10 mL) was stirred at 80 ºC for 40 h under N$_2$ atmosphere. The mixture was allowed to cool, H$_2$O (10 mL) was added and it was extracted with EtOAc. The organic phase was washed with brine, dried over Na$_2$SO$_4$ and filtered through diatomaceous earth. The solvent was removed *in vacuum* and the residual mass was purified by column chromatography (hexane/EtOAc, 97:3 v/v) to give *E*-**3** (66 mg, 48%).

(S,E)-Ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-phenylacrylate (*E*-3)

Compound *E*-**3** was obtained as a yellow oil after purification by flash chromatography (EtOAc/hex 3:97 v/v); IR (KBr) νmax/cm^{-1} 1727 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40-7.31 (3H, m), 7.19-7.13 (2H, m), 6.29 (1H, d, *J* 1.5 Hz), 4.83 (1H, td, *J* 7.4, 1.5 Hz), 4.06-3.92 (3H, m), 3.67 (1H, dd, *J* 8.1, 7.6 Hz), 1.47 (3H, s), 1.43 (3H, s), 1.06 (3H, t, *J* 7.1 Hz); ^{13}C NMR (101 MHz, CDCl$_3$) δ 165.9, 155.3, 137.0, 128.2, 128.2, 127.6, 117.0, 110.5, 78.8, 68.8, 60.0, 26.3, 25.9, 14.0. MS, *m/z* : 276 [M$^+$]; HRMS (ESI) calcd for C$_{16}$H$_{20}$NaO$_4$ [M + Na] 299.1259, found: 299.1273.

(S,Z)-Ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-phenylacrylate (*Z*-3)

Compound *E*-**3** was obtained as a pale yellow oil after purification by flash chromatography (EtOAc/hex 2:98 v/v); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43 – 7.28 (5H, m), 6.00 – 5.96 (1H, m), 5.95 (1H, d, *J* 1.2 Hz), 4.49 (1H, t, *J* 8.0 Hz), 4.21 (2H, q, *J* 7.1 Hz), 3.83 (1H, dd, *J* 8.2, 6.8 Hz), 1.37 (3H, s), 1.31 (3H, t, *J* 7.1 Hz), 1.21 (3H, s); ^{13}C NMR (101 MHz, CDCl$_3$) δ 165.9, 159.2, 138.2, 128.7, 128.5, 127.8, 120.7, 110.2, 74.0, 69.7, 60.5, 25.6, 24.8, 14.4; HRMS (ESI) calcd for C$_{16}$H$_{20}$NaO$_4$ [M + Na] 299.1259, found:299.1242.

Dimethyl 2-phenylfumarate (*E*-8)[15]

Compound *E*-**8** was obtained as a pale yellow oil after purification by flash chromatography (EtOAc/hex 3:97 v/v); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.39-7.35 (3H, m), 7.26-7.22 (2H, m), 7.02 (1H, s), 3.80 (3H, s), 3.60 (3H, s); ^{13}C NMR (101 MHz, CDCl$_3$) δ 166.8, 165.6, 144.3, 133.8, 128.8, 128.7, 128.6, 127.9, 52.9, 51.9.

Dimethyl 2-phenylmaleate (*Z*-8)[15]

Compound *Z*-**8** was obtained as a pale yellow oil after purification by flash chromatography (EtOAc/hex 5:95 v/v). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.50-7.46 (2H, m), 7.44-7.36 (3H, m), 6.32 (1H, s), 3.95 (3H, s), 3.79 (3H, s). ^{13}C NMR (126 MHz, CDCl$_3$) δ 168.3, 165.4, 149.0, 133.1, 130.6, 129.0, 126.7, 126.7, 117.1, 117.0, 52.7, 52.7, 52.1, 52.0.

(E)-Ethyl 5-methyl-3-phenylhex-2-enoate (9)[16]

Compound **9** was obtained as a pale yellow oil after purification by flash chromatography (hexane). NMR (400 MHz, CDCl$_3$) δ 7.46-7.31 (5H, m), 6.04 (1H, s), 4.20 (2H, q, *J* 7.1 Hz), 3.07 (2H, d, *J* 7.3 Hz), 1.71-1.58 (1H, m), 1.31 (3H, t, *J* 7.1 Hz), 0.87 (6H, d, *J* 6.7 Hz).

(E)-Methyl 3-phenylbut-2-enoate (10)[16]

Compound **10** was obtained as a pale yellow oil after purification by flash chromatography (EtOAc/hex 1:99 v/v). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.51-7.42 (2H, m), 7.41-7.33 (3H, m), 6.14 (1H, d, *J* 1.3 Hz), 3.75 (3H, s), 2.58 (3H, d, *J* 1.3 Hz).

Methyl 3,3-diphenylacrylate (11)[16]

Compound **11** was obtained as a pale yellow oil after purification by flash chromatography (EtOAc/hex 1:99 v/v). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.42-7.27 (8H, m), 7.23-7.18 (2H, m), 6.37 (1H, s), 3.61 (3H, s).

Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgments

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