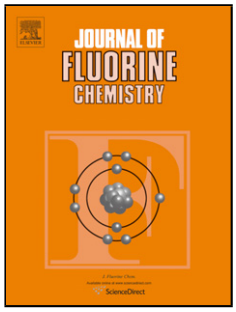

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Diastereoselectivity of cyclopropanation of substituted α-fluorostyrenes versus styrenes by different methods

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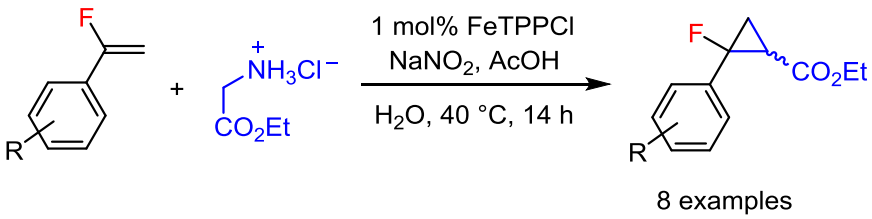
Dedicated to Professor Antonio Togni, the 2017 recipient of the ACS award for Creativity in Fluorine Chemistry

Graphical Abstract



Highlights

- Metal catalyzed cyclopropanations of substituted α-fluorostyrenes with diazoacetate provide mixtures of *cis*/*trans*-isomeric 2-aryl-2-fluorocyclopropane carboxylates.
- *In situ* generation of diazoacetate in aqueous solution with subsequent iron porphyrin catalyzed cyclopropanation is safe.
- $Cu(acac)_2$ catalyzed cyclopropanation α-fluorostyrene proceeds slower than with styrene.
- The *trans*-diastereoselectivity of α-fluorostyrene is lower compared to styrene.

Abstract

The diastereoselectivity of cyclopropanations of styrene and α-fluorostyrene with diazoacetate depends on the catalyst used and the presence or absence of the fluorine substituent. The $Cu(acac)_2$ catalyzed reaction of styrene with diazoacetate led to 3:1 selectivity in favor of *trans*-2-phenylcyclopropane carboxylate, while α-fluorostyrene gave a 1:1 mixture of *cis/trans*-isomers. A competition experiment proved that α-fluorostyrene reacted slower compared to styrene itself. With the bulkier tetraphenyl-iron(III)-porphyrin chloride as catalyst, 10:1 or 3:1 mixture, respectively, were obtained. An advantage of the latter protocol is the *in situ* formation of ethyl diazoacetate from ethyl glycinate hydrochloride in aqueous solution by diazotation avoiding the in-substance application of the potentially explosive ethyl diazoacetate. Accordingly, a series of diastereoisomeric ethyl 2-aryl-2-fluoro-cyclopropane carboxylates was synthesized from *p*- or *m*-substituted α-fluorostyrenes.

1. Introduction

For the synthesis of both fluorinated and non-fluorinated cyclopropanes plenty of methods do exist, which were reviewed in recent years. Most frequently used methods involve the intermediate formation of carbenes or metal carbenoides, which are generated by metal mediated decomposition of diazo compounds and addition of the corresponding carbenes across non-fluorinated [1] or fluorinated double bonds [2]. All these reactions can proceed enantioselectively applying chiral, non-racemic auxiliaries in the substrates or in the respective ligands of catalysts [1f,1h,2b,3].

Alternative to the photochemical reaction of diazomethane with fluoroacrylic carboxylates [4], the $Cu(acac)_2$ catalyzed reaction of diazoacetates with α-fluorostyrene has a couple of advantages in safety and toxicity aspects. Accordingly, a series of mixtures of *cis*- and *trans*-2-fluoro-2-phenylcyclopropane carboxylates were prepared in good yields, however, with low diastereoselectivity in case of application of ethyl diazoacetate. Higher diastereoselectivity was obtained applying *tert*-butyl diazoacetate [5]. The formed diastereomers were separated either chromatographically or by recrystallization of the corresponding carboxylic acids. The latter compounds [6] were shown to be versatile starting materials for the preparation of corresponding fluorinated phenylcyclopropyl amines, which are highly potent monoamine oxidase inhibitors [7,8] exhibiting better selectivity compared to the lead compound tranylcypromine®, a potent drug used, for instance, for treatment of chronic depression [9].

However, the copper- or rhodium catalyzed cyclopropanations do have a general disadvantage, which is connected to the application of low molecular weight, potentially explosive, diazocarbonyl compounds. Therefore, several attempts were made to produce such diazo compounds *in situ* and to couple its formation with a transition metal catalyzed cyclopropanation. In 2001, Barrett et al. described a series of experiments with a rhodium-porphyrin catalyst. Thus, ethyl diazoacetate formed *in situ* by diazotation of ethyl glycinate hydrochloride was used subsequently in Rh-catalyzed cyclopropanation in a two-phase-system of water and methylene chloride at room temperature [10]. No diastereoselectivity was observed and the products were isolated in moderate yields after long reaction time of 4 days. A year later Wurz and Charette used a rhodium catalyst in aqueous medium to generate a 3:2 mixture of *cis*- and *trans*-2-phenyl-cyclopropanecarboxylic acid ethyl ester in 70% yield [11]. More efficient approach was the iron(III)-porphyrin-catalyzed cyclopropanation of a series of styrenes substituted in aromatic positions with diazoacetate generated *in situ* from ethyl glycinate hydrochloride in aqueous acetic acid [12]. This approach was based on earlier investigations on iron-catalyzed cyclopropanations with *in situ* generated diazomethane [13,14]. Very recently Arnold et al. reported on asymmetric olefin-cyclopropanation reactions via carben transfer, catalyzed by engineered Cytochrome P_{450} enzymes giving mixtures of optically active ethyl or *tert*-butyl 2-arylcyclopropane carboxylates with moderate yields and moderate to high diastereo- and enantioselectivities [15]. Similar examples were highlighted by Roiban and Reetz recently [16].

For a couple of years, we have been involved in stereoselective syntheses of 2-aryl-2-fluoro-cyclopropane carboxylates from α- and β-fluorostyrenes substituted in the aryl ring and alkyl diazoacetates [5,17], its transformation to fluorinated arylcyclopropyl amines and investigation of their potency and selectivity to inhibit monoamine oxidases [18] or lysine-specific demethylase 1 (LSD1) [19]. A recent paper of Carreira et al. [12] aroused our interests to investigate the tandem diazotation/cyclopropanation reactions of substituted in the aryl ring α-fluorostyrenes in the presence of tetraphenyl-iron(III)-porphyrin chloride (FeTPPCl).

Results and discussion

Our interest was to extend the scope of Carreira's tandem diazotation/cyclopropanation protocol of styrenes [12] to corresponding reactions of α-fluorostyrenes as an alternative approach to copper- and rhodium-catalyzed cyclopropanations using diazoacetate [5,17-20]. Moreover, the diastereoselectivity and the yields of these reactions will be compared.

Thus we reacted substituted styrenes **1** with ethyl glycinate hydrochloride and sodium nitrite in the presence of 1 mol% of FeTPPCl in aqueous acetic acid (Scheme 1). The results of these reactions are listed in Table 1 (column 5) and compared to results obtained by Carreira with the corresponding non-fluorinated compounds. For comparison the results of similar cyclopropanation reactions of the same fluorinated or non-fluorinated styrenes **1** with ethyl diazoacetate catalyzed by $Cu(acac)_2$ or $Rh(OAc)_4$ in organic solvents are also included in Table 1 (column 7 and 9).

[a] Yield of the mixture of diastereomers; [b] 1 mol% FeTPPCl, $NaNO_2$, AcOH, H_2O, 40 °C, 14 h; [c] 5 mol% $Cu(acac)_2$, CH_2Cl_2, 40 °C, 10 h; [d] 2 mol% $Rh_2(OAc)_4$, CH_2Cl_2, 40 °C, 6 h.

In most of the cases (except column 5, entries 8/9), the yields of the fluorinated products were lower compared to the non-fluorinated parent compounds, and the diastereoselectivity was also reduced. The cyclopropane carboxylates were formed as 1:3 mixtures of *cis*/*trans*-isomers, while the ratio of the fluorine free counterparts was approximately 1:8 or even better (column 5). This trend was observed already in our earlier studies of the copper-catalyzed cyclopropanations with ethyl diazoacetate [5,7] (column 7) and a similar effect was observed also in some rhodium-catalyzed cyclopropanations (column 9) [17,25].

We also investigated the relative reaction rates of $Cu(acac)_2$ catalyzed cyclopropanation of styrene and α-fluorostyrene with ethyl diazoacetate in methylene chloride using a competition experiment with a 1:1 mixture of the alkenes. The progress of the reaction was monitored by gas chromatography. Figure 1 shows the consumption of the styrenes and the formation of the *cis*/*trans*-isomeric fluorinated and non-fluorinated ethyl 2-phenyl-cyclopropylcarboxylates **2**.

Due to its higher HOMO (**H**ighest **O**ccupied **M**olecular **O**rbital) energy [26], styrene (**1a**) reacted slightly faster than α-fluorostyrene (**2b**). The relative rate constant in this competition reaction was

calculated to be approximately 1.3 in favor of styrene using the equation (1). This equation was applied already by Shell and Garner for the determination of the relative rate constant (k_x/k_y) for the dibromocarbene addition across different alkenes [27].

$$\frac{K_x}{K_y} = \frac{\log(nx)/n(x,0)}{\log(ny)/n(y,0)} \qquad (1)$$

[n(x,0) or n(y,0) mean the molar amount of compounds X or Y at the starting point (t = 0); n(x)/n(y) means the molar amount of compound X or Y at the end of the measurement]

From styrene the *cis*- and *trans*-diastereoisomers were formed in a 1:3 ratio, which is in agreement with earlier results by Kaiser et al. for the uncatalyzed thermal reaction of styrene with diazoacetate [28] and Ahuja et al. for different Cu-catalyzed cyclopropanations [29].

The *trans*-selectivity of transition metal-catalyzed cyclopropanations of alkenes with different diazoacetates was investigated by Doyle et al. [30].

The bulkier the substituent Z of the diazoacetate, favors the *trans*-configured transition state leading to the *trans*-product. We observed similar results also for the $Cu(acac)_2$ catalyzed reactions of α-fluorostyrenes [5]. Doyle et al. obtained a diastereoselectivity as high as 2:98 in favor of the *trans*-isomer using the extremely bulky 2,6-di-*tert*-butyl-4-methylphenyl diazoacetate in a Rh-catalyzed cyclopropanation of styrene [31]. The maximum we achieved for the Cu-catalyzed reaction of α-fluorostyrene with *tert*-butyl diazoacetate was 1:4 [5].

Doyle et al. also investigated electronic effects of double bonds on the diastereoselectivity of cyclopropanation and found out that electron deficient double bonds exhibited higher *trans*-diastereoselectivity because electron poor double bonds have to be arranged closer to the carbenoid center, which causes increased steric repulsion in the *cis*-transition state and hence favors the *trans*-arrangement [30].

In the above mentioned competition experiment the 2-fluoro-2-phenylcyclopropane carboxylates were formed in 1:1 ratio, which is in agreement with earlier results [5] and also with Doyle's results on the electronic effects of the double bond. Due to the electron donating ($+I_\pi$) effect of fluorine on π-systems [32], the double bond of α-fluorostyrene is more electron-rich compared to styrene. Therefore, the distance of the carbenoid center to the double bond is bigger and consequently there is less steric congestion in the *cis*-transition state. Also the bigger van der Waals radius of fluorine compared to hydrogen contributes to the lower diastereoselectivity in case of α-fluorostyrene. Moreover, repulsion of the ester carbonyl group and the vinylic fluorine disfavors the formation of the *trans*-transition state.

In addition to these effects also electronic interactions of the carbonyl oxygen with the forming electrophilic center at the β-carbon in the alternative *cis*- and *trans*-transition states were discussed [17,25]. In the *trans*-transition state of styrene an n-electron pair of the carbonyl oxygen of the diazo compound interacts with the forming electrophilic β-carbon of styrene. This leads to a stabilization, which is not possible in the *cis*-transition state. In the corresponding transition state starting from α-fluorostyrene, the interaction of the forming electrophilic center of the *trans*-transition state is also possible, but less efficient due to the stabilizing effect of a positive charge by α-fluorine [32]. Consequently, the diastereoselectivity is lower (Figure 3).

Comparing the diastereoselectivity of the iron porphyrin-catalyzed reactions (Table 1, column 5) the *trans*-diastereoselectivity is much more pronounced, in the styrene case, but also in the α-fluorostyrene case a 1:3 selectivity was observed. The sterically more demanding iron-porphyrin catalyst seems to favor the *trans*-transition states and the *trans*-configured 2-arylcyclopropane carboxylates are the main products.

3. Conclusions

The iron(III)-porphyrin catalyzed cyclopropanation of α-fluorostyrene and several of its *p*- and *m*-substituted derivatives with *in situ* generated ethyl diazoacetate in acidic aqueous medium has advantages in spite of safety and economic issues compared to corresponding copper- or rhodium catalyzed reactions using the potentially explosive ethyl diazoacetate in organic media. While the diastereoselectivity is higher for the iron-porphyrin catalyzed reactions in favor of the *trans*-products (3:1), the yields are lower compared to the $Cu(acac)_2$ catalyzed reactions. Moreover, the latter reaction with styrene is faster by a factor of 1.3 compared to that of α-fluorostyrene. Here the ratio of *trans*- to *cis*-diastereomeric products is 3:1 from styrene and 1:1 for the α-fluorostyrene reactions.

4. Experimental

4.1 General remarks

NMR spectra were recorded on Bruker Avance II at 300 and 400 MHz, (^{1}H), at 25 °C. TMS (^{1}H and ^{13}C NMR) and CCl_3F (^{19}F NMR) were used as internal standards. Mass spectra (ESI-MS) were measured on a MicroTof Bruker Daltonics. The reaction progress was monitored gas-chromatographically using a gas-chromatograph Hewlett-Packard “HP 6890” with an FID, an auto-sampler and data registration and reporting with the program “GC ChemStation Rev. B 02.01-SR1”. A 30 m quartz capillary “HP-1” with inner diameter of 0.32 mm and a film thickness of 0.25 μm was used. The same system was used to monitor the reaction progress and to determine the *cis*/*trans* ratio of products in the competition experiment. Column chromatography was carried out using silica gel 60 (Merck, particle size 0.040–0.063 mm). The used eluent is mentioned in the respective experiment.

4.2 Syntheses

4.2.1 Cyclopropanation of styrene and α-fluorostyrene derivatives with FeTPPCl (General procedure)

Analogously to the protocol by Carreira et al. [12], FeTPPCl (7 mg, 0.01 mmol) was dissolved in the corresponding styrene (1 mmol) and ethyl glycinate hydrochloride (419 mg, 3 mmol, 3 equiv), water (10 mL) and acetic acid (9 mg, 0.15 mmol, 0.15 equiv) were added. To this heterogenic mixture sodium nitrite (497 mg, 7.2 mmol, 2.4 equiv) was added in one portion under stirring at 40 °C. Stirring was continued at this temperature for 15 hours. Then water (15 mL) was added and the mixture was extracted with dichloromethane (3 × 15 mL). The combined organic phase was washed with 5% bicarbonate solution (5 mL), water (10 mL) and dried with magnesium sulfate. After evaporation of the solvent, the crude product mixture was analyzed by GC and separated by column chromatography (*n*-pentane/diethyl ether).

*4.2.1.1 Ethyl 2-phenylcyclopropanecarboxylate (**2a**)*

From styrene (100 mg, 0.96 mmol), ethyl glycinate hydrochloride (268 mg, 1.92 mmol) and sodium nitrite (159 mg, 2.3 mmol) in acidified water (4.5 mL) in the presence of FeTPPCl (7 mg, 0.01 mmol) a 1:10 mixture of *cis*-**2a** and *trans*-**2a** was formed as colorless oil. Yield: 133 mg (73%). The stereoisomers were separated chromatographically (*n*-pentane/diethyl ether, 20:1). The spectroscopic data of both diastereoisomers agree with published values [33].

*4.2.1.2 Ethyl 2-fluoro-2-phenylcyclopropanecarboxylate (**2b**)*

From α-fluorostyrene (50 mg, 0.41 mmol), ethyl glycinate hydrochloride (127 mg, 1.23 mmol) and sodium nitrite (69 mg, 1.0 mmol) in acidified water (2 mL) in the presence of FeTPPCl (3 mg, 0.004 mmol) a 1:3-mixture of *cis*-**2b** and *trans*-**2b** was formed as colorless oil. Yield: 45 mg (53%). The stereoisomers were separated chromatographically (*n*-pentane/diethyl ether, 20:1). The spectroscopic data of both diastereoisomers agree with published values [5].

*4.2.1.3 Ethyl 2-fluoro-2-(4-methoxyphenyl)cyclopropanecarboxylate (**2c**)*

From *p*-methoxy-α-fluorostyrene (50 mg, 0.33 mmol), ethyl glycinate hydrochloride (138 mg, 0.99 mmol) and sodium nitrite (55 mg, 0.79 mmol) in the presence of FeTPPCl (3 mg, 0.004 mmol) in acidified water (2 mL) a 1:3 mixture of *cis*-**2c** and *trans*-**2c** was formed as colorless oil. Yield: 55 mg (70%). The stereoisomers were separated chromatographically (cyclohexane/ethyl acetate, 15:1). The spectroscopic data of both diastereoisomers agree with published values [18b].

*4.2.1.4 Ethyl 2-fluoro-2-(3-methoxyphenyl)cyclopropanecarboxylate (**2d**)*

From *m*-methoxy-α-fluorostyrene (50 mg, 0.33 mmol), ethyl glycinate hydrochloride (138 mg, 0.99 mmol) and sodium nitrite (55 mg, 0.79 mmol) in the presence of FeTPPCl (3 mg, 0.004 mmol) in

acidified water (2 mL) a 1:3 mixture of *cis*-**2c** and *trans*-**2c** was formed as colorless oil. Yield: 42 mg (55%). The stereoisomers were separated chromatographically (cyclohexane/ethyl acetate, 15:1).

Ethyl *cis*-2-fluoro-2-(3-methoxyphenyl)cyclopropanecarboxylate (*cis*-**2d**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (t, $^{3}J_{H,H}$ = 7.1 Hz, 3 H, 12-CH_3), 1.81 (ddd, $^{2}J_{H,H(B)}$ = 7.1, $^{3}J_{H,H(X)}$ = 10.3, $^{3}J_{H,F(cis)}$ = 19.3 Hz, 1 H, H_A), 1.97 (ddd, $^{2}J_{H,H(A)}$ = 7.1, $^{3}J_{H,H(X)}$ = 7.7, $^{3}J_{H,F(trans)}$ = 12.4 Hz, 1 H, H_B), 2.54 (ddd, $^{3}J_{H,H(B)}$ = 7.7, $^{3}J_{H,H(A)}$ = 10.3, $^{3}J_{H,F(cis)}$ = 18.1 Hz, 1 H, H_X), 3.81 (s, 3 H, 13-CH_3), 3.94 (qd, $^{2}J_{H,H}$ = 1.6, $^{3}J_{H,H}$ = 7.1 Hz, 2 H, 11-CH_2), 6.91 (ddd, $^{4}J_{H,H}$ = 1.4, $^{4}J_{H,H}$ = 2.5, $^{3}J_{H,H}$ = 8.3 Hz, 1 H, 6-CH), 7.02 (dt, $^{4}J_{H,H}$ = 1.5, $^{4}J_{H,H}$ = 2.8 Hz, 1 H, 10-CH), 7.03 (dtd, $^{4}J_{H,H}$ = 0.9, $^{4}J_{H,H}$ = 1.6, $^{3}J_{H,H}$ = 7.6 Hz, 1 H, 8-CH), 7.27 (m, 1 H, 7-CH). ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.0 (q, C-12), 16.6 (d, $^{2}J_{C,F}$ = 10.4 Hz, C-3), 28.0 (d, $^{2}J_{C,F}$ = 16.4 Hz, C-2), 55.4 (q, C-13), 60.8 (t, C-11), 83.1 (d, $^{1}J_{C,F}$ = 221.4 Hz, C-4), 113.9 (d, $^{3}J_{C,F}$ = 4.1 Hz, C-10), 115.2 (d, $^{3}J_{C,F}$ = 2.6 Hz, C-6), 120.5 (s, C-8), 129.3 (d, $^{4}J_{C,F}$ = 1.3 Hz, C-7), 134.4 (d, $^{2}J_{C,F}$ = 19.9 Hz, C-5), 159.4 (d, $^{4}J_{C,F}$ = 1.2 Hz, C-9), 168.9 (d, $^{3}J_{C,F}$ = 1.7 Hz, C-1). ^{19}F NMR (282 MHz, $CDCl_3$): δ -154.12 (ddd, $^{3}J_{H,F(trans)}$ = 12.4, $^{3}J_{H,F(cis)}$ = 18.1, $^{3}J_{H,F(cis)}$ = 19.5 Hz, 1 F, 4-CF). MS (GC/EI): *m/z* (%) 238.1 (45) $[M]^+$, 193.1 (30) $[M\text{-}C_2H_5O]^+$, 165.1 (100) $[M\text{-}COOC_2H_5]^+$, 115.1 (40) $[C_9H_8F\text{-}HF]^+$. MS (ESI^+, exact mass): *m/z* 261.0902 $[M+Na]^+$, calcd for $C_{13}H_{15}FO_3Na^+$: 261.0897.

Ethyl trans-2-fluoro-2-(3-methoxyphenyl)-cyclopropanecarboxylate (*trans*-**2d**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (t, $^{3}J_{H,H}$ = 7.1 Hz, 3 H, 12-CH_3), 1.63 (ddd, $^{2}J_{H,H(A)}$ = 6.8, $^{3}J_{H,H(X)}$ = 8.9, $^{3}J_{H,F(trans)}$ = 10.7 Hz, 1 H, H_B), 2.18 (ddd, $^{3}J_{H,F(trans)}$ = 3.2, $^{3}J_{H,H(A)}$ = 7.8, $^{3}J_{H,H(B)}$ = 8.9 Hz, 1 H, H_X), 2.31 (ddd, $^{2}J_{H,H(B)}$ = 6.8, $^{3}J_{H,H(X)}$ = 7.8, $^{3}J_{H,F(cis)}$ = 19.9 Hz, 1 H, H_A), 3.83 (s, 3 H, 13-CH_3), 4.23 (qd, $^{2}J_{H,H}$ = 1.8, $^{3}J_{H,H}$ = 7.2 Hz, 2 H, 11-CH_2), 6.80-6.85 (m, 1 H, 6-CH), 6.87-6.90 (m, 2 H, 8/10-CH), 7.29 (dt, $^{4}J_{H,H}$ = 0.9, $^{3}J_{H,H}$ = 7.9 Hz, 1 H, 7-CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 (q, C-12), 19.2 (d, $^{2}J_{C,F}$ = 12.3 Hz, C-3), 29.2 (d, $^{2}J_{C,F}$ = 11.6 Hz, C-2), 55.3 (q, C-13), 61.2 (t, C-11), 80.5 (d, $^{1}J_{C,F}$ = 228.3 Hz, C-4), 110.7 (d, $^{3}J_{C,F}$ = 7.3 Hz, C-10), 113.6 (d, $^{4}J_{C,F}$ = 1.4 Hz, C-7), 116.5 (d, $^{3}J_{C,F}$ = 6.5 Hz, C-6), 129.7 (d, C-8), 139.3 (d, $^{2}J_{C,F}$ = 21.3 Hz, C-5), 159.8 (s, C-9), 167.7 (d, $^{3}J_{C,F}$ = 2.3 Hz, C-1). ^{19}F NMR (282 MHz, $CDCl_3$): δ -188.36 (ddd, $^{3}J_{H,F(trans)}$ = 3.2, $^{3}J_{H,F(trans)}$ = 10.7, $^{3}J_{H,F(cis)}$ = 20.4 Hz, 1 F, 4-CF). MS (GC/EI): *m/z* (%) 238.1 (40) $[M]^+$, 193.1 (25) $[M\text{-}C_2H_5O]^+$, 165.1 (100) $[M\text{-}COOC_2H_5]^+$, 115.1 (40) $[C_9H_8F\text{-}HF]^+$. MS (ESI^+, exact mass): *m/z* 261.0902 $[M+Na]^+$, calcd for $C_{13}H_{15}FO_3Na^+$: 261.0897.

*4.2.1.5 Ethyl 2-fluoro-2-(4-nitrophenyl)cyclopropanecarboxylate (**2e**)*

From 4-nitro-α-fluorostyrene (500 mg, 3.0 mmol), ethyl glycinate hydrochloride (1,260 mg, 9.0 mmol) and sodium nitrite (500 mg, 7.2 mmol) in the presence of FeTPPCl (20 mg, 0.03 mmol) in acidified water (15 mL) a 1:2 mixture of *cis*-**2e** and *trans*-**2e** was formed as colorless oil. The stereoisomers were separated chromatographically (*n*-pentane/diethyl ether, 20:1).

Ethyl *cis*-2-fluoro-2-(4-nitrophenyl)cyclopropanecarboxylate (*cis*-**2e**). Yield: 114 mg (15%). **^{1}H** NMR (300 MHz, $CDCl_3$): δ 1.06 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, 12-CH_3), 1.95 (ddd, $^2J_{H,H(B)}$ = 7.4, $^3J_{H,H(X)}$ = 10.5, $^3J_{H,F(cis)}$ = 19.5 Hz, 1 H, H_A), 2.07 (dt, $^3J_{H,H(X)}$ = 7.7, $^3J_{H,F(trans)}$ = 13.0 Hz, 1 H, H_B), 2.65 (ddd, $^3J_{H,H(B)}$ = 7.9, $^3J_{H,H(A)}$ = 10.5, $^3J_{H,F(cis)}$ = 18.4 Hz, 1 H, H_X), 3.95 (qd, $^2J_{H,H}$ = 3.7, $^3J_{H,H}$ = 7.2 Hz, 2 H, 11-CH_2), 7.61-7.66 (m, 2 H, 6/10-CH), 8.20-8.25 (m, 2 H, 7/9-CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (q, C-12), 17.3 (d, $^2J_{C,F}$ = 9.8 Hz, C-3), 29.0 (d, $^2J_{C,F}$ = 15.9 Hz, C-2), 61.2 (t, C-11), 81.9 (d, $^1J_{C,F}$ = 221.9 Hz, C-4), 123.3 (d, C-7/9), 128.7 (d, $^3J_{C,F}$ = 5.2 Hz, C-6/10), 140.2 (d, $^2J_{C,F}$ = 20.7 Hz, C-5), 148.1 (s, C-8), 168.3 (d, $^3J_{C,F}$ = 1.8 Hz, C-1). ^{19}F NMR (282 MHz, $CDCl_3$): δ -160.61 (ddd, $^3J_{H,F(trans)}$ = 13.0, $^3J_{H,F(cis)}$ = 18.6, $^3J_{H,F(cis)}$ = 19.6 Hz, 1 F, 4-CF). MS (GC/EI): *m/z* (%) 253.1 (20) $[M]^+$, 225.1 (10) $[M\text{-}C_2H_5]^+$, 208.0 (20) $[M\text{-}C_2H_5O]^+$, 188.0 (40) $[M\text{-}C_{10}H_7FNO_3\text{-}HF]^+$, 180.1 (20) $[M\text{-}COOC_2H_5]^+$, 134.1 (85) $[C_9H_8F]^+$, 133.1 (100) $[C_9H_7F]^+$, 115.1 (12) $[C_9H_7F\text{-}HF]^+$. MS (ESI^+, exact mass): *m/z* 276.0657 $[M+Na]^+$, calcd for $C_{12}H_{12}FNO_4Na^+$: 276.0643.

Ethyl *trans*-2-fluoro-2-(4-nitrophenyl)-cyclopropanecarboxylate (*trans*-**2e**). Yield: 138 mg (0.54 mmol, 18 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, 12-CH_3), 1.72 (ddd, $^2J_{H,H(A)}$ = 7.3, $^3J_{H,H(X)}$ = 9.5, $^3J_{H,F(trans)}$ = 10.5 Hz, 1 H, H_B), 2.28 (ddd, $^3J_{H,F(trans)}$ = 3.1, $^3J_{H,H(A)}$ = 8.0, $^3J_{H,H(B)}$ = 9.4 Hz, 1 H, H_X), 2.42 (ddd, $^2J_{H,H(B)}$ = 7.2, $^3J_{H,H(X)}$ = 8.0, $^3J_{H,F(cis)}$ = 20.2 Hz, 1 H, H_A), 4.19-4.27 (m, 2 H, 11-CH_2), 7.38-7.41 (m, 2 H, 6/10-CH), 8.20-8.25 (m, 2 H, 7/9-CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 (q, C-12), 20.1 (d, $^2J_{C,F}$ = 11.8 Hz, C-3), 30.4 (d, $^2J_{C,F}$ = 11.2 Hz, C-2), 61.6 (t, C-11), 79.8 (d, $^1J_{C,F}$ = 229.8 Hz, C-4), 123.9 (d, $^4J_{C,F}$ = 1.4 Hz, C-7/9), 124.5 (d, $^3J_{C,F}$ = 7.7 Hz, C-6/10), 145.1 (d, $^2J_{C,F}$ = 21.6 Hz, C-5), 147.5 (s, C-8), 166.8 (d, $^3J_{C,F}$ = 2.4 Hz, C-1). ^{19}F NMR (282 MHz, $CDCl_3$): δ -193.22 (ddd, $^3J_{H,F(trans)}$ = 3.0, $^3J_{H,F(trans)}$ = 10.7, $^3J_{H,F(cis)}$ = 20.4 Hz, 1 F, 4-CF). MS (GC/EI): *m/z* (%) 253.1 (15) $[M]^+$, 225.1 (8) $[M\text{-}C_2H_5]^+$, 208.0 (20) $[M\text{-}C_2H_5O]^+$, 188.1 (30) $[M\text{-}C_{10}H_7FNO_3\text{-}HF]^+$, 180.1 (20) $[M\text{-}COOC_2H_5]^+$, 134.1 (80) $[C_9H_8F]^+$, 133.1 (100) $[C_9H_7F]^+$, 115.1 (12) $[C_9H_7F\text{-}HF]^+$. MS (ESI^+, exact mass): *m/z* 276.0657 $[M+Na]^+$, calcd for $C_{12}H_{12}FNO_4Na^+$: 276.0643.

*4.2.1.6 Ethyl 2-fluoro-2-(3-nitrophenyl)cyclopropanecarboxylate (**2f**)*

From 3-nitro-α-fluorostyrene (50 mg, 0.3 mmol), ethyl glycinate hydrochloride (126 mg, 0.9 mmol) and sodium nitrite (50 mg, 0.72 mmol) in the presence of FeTPPCl (3 mg, 0.004 mmol) in acidified water (2 mL) a 1:2 mixture of *cis*-**2f** and *trans*-**2f** was formed as colorless oil. Yield: 65 mg (86%). The stereoisomers were separated chromatographically (*n*-pentane/diethyl ether, 30:1 → 10:1).

Ethyl *cis*-2-fluoro-2-(3-nitrophenyl)cyclopropanecarboxylate (*cis*-**2f**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (t $^3J_{H,H}$ = 7.1 Hz, 1 H, 12-CH_3), 1.94 (ddd, $^2J_{H,H(B)}$ = 7.0, $^3J_{H,H(X)}$ = 10.5, $^3J_{H,F(cis)}$ = 19.5 Hz, 1 H, H_A), 2.06 (ddd, $^2J_{H,H(A)}$ = 7.3, $^3J_{H,H(X)}$ = 7.4, $^3J_{H,F(trans)}$ = 12.3 Hz, 1 H, H_B), 2.63 (ddd, $^3J_{H,H(B)}$ = 7.7, $^3J_{H,H(A)}$ = 10.5, $^3J_{H,F(cis)}$ = 18.1 Hz, 1 H, H_X), 3.96 (q, $^3J_{H,H}$ = 7.5 Hz, 2 H,

11-CH_2), 7.55-7.67 (m, 1 H, 7-CH), 7.79-7.83 (m, 1 H, 6-CH), 8.19-8.26 (m, 1 H, 8-CH), 8.35-8.37 (dt, $^3J_{H,H}$ = 1.5, $^4J_{H,F}$ = 2.8 Hz, 1 H, 10-CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (q, C-12), 17.1 (d, $^2J_{C,F}$ = 9.9 Hz, C-3), 28.3 (d, $^2J_{C,F}$ = 16.0 Hz, C-2), 61.3 (t, C-11), 81.1 (d, $^1J_{C,F}$ = 221.4 Hz, C-4), 123.1 (d, C-7), 124.1 (d, C-8), 129.3 (d, C-6), 129.8 (d, C-10), 134.1 (d, $^3J_{C,F}$ = 4.2 Hz, C-9), 135.3 (d, $^2J_{C,F}$ = 21.1 Hz, C-5), 165.3 (s, C-1). ^{19}F NMR (282 MHz, $CDCl_3$): δ -158.78 (m, 1 F, 4-CF). MS (GC/EI): *m/z* (%) 253.1 (10) $[M]^+$, 208.1 (20) $[M\text{-}C_2H_5O]^+$, 188.1 (40) $[208.1\text{-}HF]^+$, 180.1 (15) $[M\text{-}C_3H_5O_2]^+$, 134.1 (60) $[C_9H_7F]^+$, 133.1 (100) $[C_9H_6F]^+$. MS (ESI^+, exact mass): *m/z* 276.0642 $[M+Na]^+$, calcd for $C_{12}H_{12}FNO_4Na^+$: 276.0643.

Ethyl *trans*-2-fluoro-2-(3-nitrophenyl)-cyclopropanecarboxylate (*trans*-**2f**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, 12-CH_3), 1.72 (ddd, $^2J_{H,H(A)}$ = 7.3, $^3J_{H,H(X)}$ = 9.4, $^3J_{H,F(trans)}$ = 10.4 Hz, 1 H, H_B), 2.28 (ddd, $^3J_{H,F(trans)}$ = 3.0, $^3J_{H,H(A)}$ = 7.9, $^3J_{H,H(B)}$ = 9.4 Hz, 1 H, H_X), 2.42 (ddd, $^2J_{H,H(B)}$ = 7.2, $^3J_{H,H(X)}$ = 8.0, $^3J_{H,F(cis)}$ = 20.2 Hz, 1 H, H_A), 4.26 (qd, $^2J_{H,H}$ = 3.1, $^3J_{H,H}$ = 7.1 Hz, 2 H, 11-CH_2), 7.55-7.67 (m, 1 H, 7-CH), 8.12-8.13 (m, 3 H, 6/8/10-CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 (q, C-12), 19.4 (d, $^2J_{C,F}$ = 12.0 Hz, C-3), 29.7 (d, $^2J_{C,F}$ = 11.4 Hz, C-2), 61.6 (t, C-11), 79.8 (d, $^1J_{C,F}$ = 229.4 Hz, C-4), 119.2 (d, $^3J_{C,F}$ = 7.7 Hz, C-10), 123.1 (d, C-8), 129.8 (d, C-7), 130.2 (d, $^3J_{C,F}$ = 6.9 Hz, C-6), 148.5 (s, C-9), 167.0 (d, $^3J_{C,F}$ = 2.4 Hz, C-1). ^{19}F NMR (282 MHz, $CDCl_3$): δ -191.26 (ddd, $^3J_{H,F(trans)}$ = 3.1, $^3J_{H,F(trans)}$ = 10.6, $^3J_{H,F(cis)}$ = 20.4 Hz, 1 F, 4-CF). MS (GC/EI): *m/z* (%) 253.1 (10) $[M]^+$, 208.1 (20) $[M\text{-}C_2H_5O]^+$, 188.1 (40) $[208.1\text{-}HF]^+$, 180.1 (15) $[M\text{-}C_3H_5O_2]^+$, 134.1 (60) $[C_9H_7F]^+$, 133.1 (100) $[C_9H_6F]^+$. MS (ESI^+, exact mass): *m/z* 276.0642 $[M+Na]^+$, calcd for $C_{12}H_{12}FNO_4Na^+$: 276.0643.

*4.2.1.7 Ethyl 2-fluoro-2-(4-acetoxyphenyl)cyclopropanecarboxylate (**2g**)*

From 3-nitro-α-fluorostyrene (50 mg, 0.28 mmol), ethyl glycinate hydrochloride (117 mg, 0.84 mmol) and sodium nitrite (46 mg, 0.67 mmol) in the presence of FeTPPCl (3 mg, 0.004 mmol) in acidified water (3 mL) a 1:3 mixture of *cis*-**2g** and *trans*-**2g** was formed as colorless oil. Yield: 63 mg (47%). The stereoisomers were separated chromatographically (*n*-pentane/diethyl ether, 10:1).

Ethyl *cis*-2-fluoro-2-(4-acetoxyphenyl)cyclopropanecarboxylate (*cis*-**2g**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, 14-CH_3), 1.83 (ddd, $^2J_{H,H(B)}$ = 7.1, $^3J_{H,H(X)}$ = 10.3, $^3J_{H,F(cis)}$ = 19.1 Hz, 1 H, H_A), 1.97 (ddd, $^2J_{H,H(A)}$ = 7.1, $^3J_{H,H(X)}$ = 7.3, $^3J_{H,F(trans)}$ = 12.6 Hz, 1 H, H_B), 2.29 (s, 3 H, 12-CH_3), 2.57 (ddd, $^3J_{H,H(B)}$ = 7.3, $^3J_{H,H(A)}$ = 10.4, $^3J_{H,F(cis)}$ = 17.8 Hz, 1 H, H_X), 3.92 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, 13-CH_2), 7.09-7.12 (m, 2 H, 6/10-CH), 7.45-7.50 (m, 2 H, 7/9-CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (q, C-12), 16.7 (d, $^2J_{C,F}$ = 10.3 Hz, C-3), 21.1 (q, C-14), 28.0 (d, $^2J_{C,F}$ = 16.5 Hz, C-2), 60.8 (t, C-13), 82.4 (d, $^1J_{C,F}$ = 221.9 Hz, C-4), 121.4 (d, $^4J_{C,F}$ = 1.3 Hz, C-7/9), 129.5 (d, $^3J_{C,F}$ = 4.0 Hz, C-6/10), 130.7 (d, $^3J_{C,F}$ = 20.6 Hz, C-5), 151.2 (s, C-8), 168.7 (d, $^3J_{C,F}$ = 1.8 Hz, C-1), 169.1 (s, C-11). ^{19}F NMR (282 MHz, $CDCl_3$): δ -154.3 (ddd, $^3J_{H,F(trans)}$ = 12.3, $^3J_{H,F(cis)}$ = 17.2, $^3J_{H,F(cis)}$ = 19.9 Hz, 1F, 4-CF). MS (GC/EI): *m/z* (%) 266.1 (50)

$[M]^+$, 224.1 (40) $[M\text{-}C_2H_3O]^+$, 195.0 (30) $[224.3\text{-}C_2H_5]^+$, 151.1 (90) $[195.3\text{-}CO_2]^+$, 131.3 (40) $[M\text{-}C_6H_5O]^+$, 103.1 (100) $[C_4H_4FO_2]^+$. MS (ESI^+, exact mass) *m/z* 289.0848 $[M+Na]^+$, calcd for $C_{14}H_{15}FO_4Na^+$: 289.0847.

Ethyl *trans*-2-fluoro-2-(4-acetoxyphenyl)cyclopropanecarboxylate (*trans*-**2g**). ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (ddd, $^2J_{H,H(A)}$ = 7.1, $^3J_{H,H(X)}$ = 9.1, $^3J_{H,F(trans)}$ = 12.7 Hz, 1 H, H_B), 1.30 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, 14-CH_3), 1.61 (ddd, $^3J_{H,F(trans)}$ = 3.1 Hz, $^3J_{H,H(A)}$ = 7.0, $^3J_{H,H(B)}$ = 9.2, 1 H, H_X), 2.20 (ddd, $^2J_{H,H(B)}$ = 7.2, $^3J_{H,H(X)}$ = 7.0, $^3J_{H,F(cis)}$ = 19.5 Hz, 1 H, H_A), 2.31 (s, 3 H, 12-CH_3), 4.08-4.26 (m, 2 H, 13-CH_2), 7.09-7.12 (m, 2 H, 6/10-CH), 7.31-7.34 (m, 2 H, 7/9-CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 (q, C-14), 18.8 (d, $^2J_{C,F}$ = 12.4 Hz, C-3), 21.0 (q, C-12), 28.9 (d, $^2J_{C,F}$ = 11.6 Hz, C-2), 61.2 (t, C-13), 80.5 (d, $^1J_{C,F}$ = 227.2 Hz, C-4), 118.7 (d, C-7), 121.8 (d, C-9), 126.0 (d, $^3J_{C,F}$ = 6.3 Hz, C-6), 129.2 (d, C-10), 135.0 (d, $^3J_{C,F}$ = 22.0 Hz, C-5), 150.5 (s, C-8), 167.6 (d, $^3J_{C,F}$ = 2.2 Hz, C-1), 169.3 (s, C-11). ^{19}F NMR (282 MHz, $CDCl_3$): δ -187.4 (ddd, $^3J_{H,F(trans)}$ = 3.1, $^3J_{H,F(trans)}$ = 10.2, $^3J_{H,F(cis)}$ = 20.6 Hz, 1 F, 4-CF). MS (GC/EI): *m/z* (%) 266.1 (60) $[M]^+$, 224.1 (50) $[M\text{-}C_2H_3O]^+$, 195.0 (30) $[224.3\text{-}C_2H_5]^+$, 151.1 (100) $[195.3\text{-}CO_2]^+$, 131.3 (40) $[M\text{-}C_6H_5O]^+$, 103.1 $[C_4H_4FO_2]^+$. MS (ESI^+, exact mass): *m/z* 289.0848 $[M+Na]^+$, calcd for $C_{14}H_{15}FO_4Na^+$: 289.0847.

*4.2.1.8 Ethyl 2-fluoro-2-(4-methylphenyl)cyclopropanecarboxylate (**2h**)*

From 4-methyl-α-fluorostyrene (50 mg, 0.37 mmol), ethyl glycinate hydrochloride (155 mg, 1.11 mmol) and sodium nitrite (61 mg, 0.89 mmol) in the presence of FeTPPCl (3 mg, 0.004 mmol) in acidified water (2 mL) a 1:4 mixture of *cis*-**2h** and *trans*-**2h** was formed as colorless oil. Yield: 20 mg (24%). The stereoisomers were separated chromatographically (*n*-pentane/diethyl ether, 20:1). The spectroscopic data of both diastereoisomers agree with published values [18b].

*4.2.1.9 Ethyl 2-fluoro-2-(4-chlorophenyl)cyclopropanecarboxylate (**2i**)*

From 4-methyl-α-fluorostyrene (50 mg, 0.32 mmol), ethyl glycinate hydrochloride (134 mg, 0.96 mmol) and sodium nitrite (53 mg, 0.77 mmol) in the presence of FeTPPCl (3 mg, 0.004 mmol) in acidified water (3 mL) a 1:3 mixture of *cis*-**2i** and *trans*-**2i** was formed as colorless oil. Yield: 16 mg (21%). The stereoisomers were separated chromatographically (*n*-pentane/diethyl ether, 20:1). The spectroscopic data of both diastereoisomers agree with published values [5].

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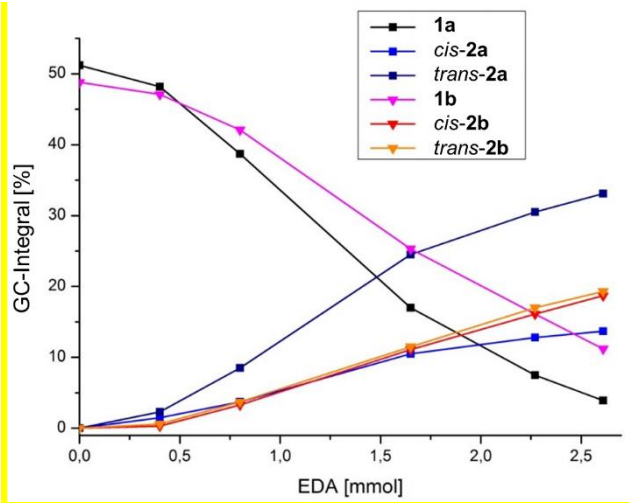


Figure 1. Competition experiment of $Cu(acac)_2$ catalyzed cyclopropanation of styrene (**1a**) and α-fluorostyrene (**1b**) with ethyl diazoacetate (EDA) in methylene chloride at room temperature to form ethyl *cis*- and *trans*-2-phenylcyclopropanecarboxylates (*cis*- and *trans*-**2a**) and ethyl *cis*- and *trans*-2-fluoro-2-phenylcycopropanecarboxylates (*cis*- and *trans*-**2b**), respectively (GC analysis).

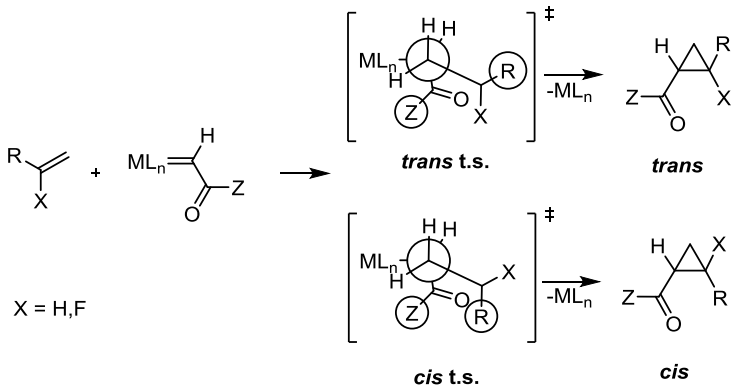


Figure 2. Transition states of the formation of *cis*/*trans*-isomeric cyclopropane carboxylates [30]

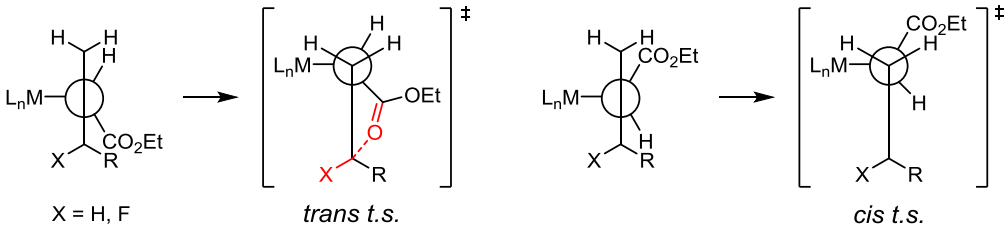
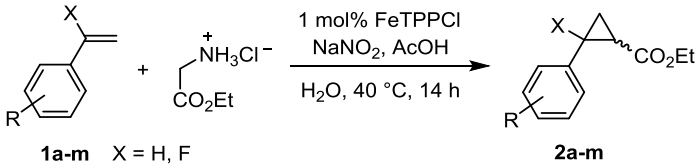


Figure 3. Transition states of the cyclopropanation of styrene and α-fluorostyrene



1a-m X = H, F **2a-m**

Scheme 1. Iron-porphyrin-catalyzed cyclopropanations of styrenes and α-fluorostyrenes

Table 1. Results of iron-porphyrin-catalyzed cyclopropanations of styrenes and α-fluorostyrenes and comparison to alternative copper- or rhodium catalyzed reactions

Entry	Compound	R	X	Yield[a] **2** [%][b] (*c*/*t*-ratio)	Ref.	Yield[a] **2** [%][c] (*c*/*t*-ratio)	Ref.	Yield[a] **2** [%][d] (*c*/*t*-ratio)	Ref.
1	**1a**	H	H	71 (1:10)	12	71 (1:2.6)	21	93 (1:1.6)	21
2	**1a**	H	H	73 (1:10)	this work	65 (1:2)	22	92 (1:1.5)	22
3	**1b**	H	F	53 (1:3)	this work	87 (1:1)	5	25 (1:1)	21
4	**1c**	*p*-OMe	H	79 (1:8)	12			87 (1:7)	23
5	**1d**	*p*-OMe	F	70 (1:3)	this work	89 (1:1)	18e		
6	**1e**	*m*-OMe	F	55 (1:3)	this work	62 (1:1)	24		
7	**1f**	*p*-NO_2	F	33 (1:2)	this work	40 (1:1)	24		
8	**1g**	*m*-NO_2	H	55 (1:6)	12				
9	**1h**	*m*-NO_2	F	86 (1:2)	this work	51 (1:1)	24		
10	**1i**	*p*-OAc	H	68 (1:8)	12			78 (1:5)	23
11	**1j**	*p*-OAc	F	47 (1:3)	this work				
12	**1k**	*p*-Me	H	74 (1:9)	12	90 (1:2)	20	89 (1:8)	23
13	**1l**	*p*-Me	F	24 (1:4)	this work	90 (1:2)	20		
14	**1m**	*p*-Cl	F	21 (1:3)	this work	91 (1:1)	5		