# Iron-Catalysed Regio- and Stereoselective Head-to-Tail Dimerisation of Styrenes

Jose R. Cabrero-Antonino,<sup>a</sup> Antonio Leyva-Pérez,<sup>a</sup> and Avelino Corma<sup>a,\*</sup>

 <sup>a</sup> Instituto de Tecnología Química (UPV-CSIC), Universidad Politécnica de Valencia, Consejo Superior de Investigaciones Científicas, Avda. de los Naranjos s/n, 46022 Valencia, Spain Fax: (+34)-9638-77809; phone: (+34)-9638-77800; e-mail: acorma@itq.upv.es

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**Abstract:** Cationic iron salts and complexes catalyse the head-to-tail dimerisation of styrene derivatives to form the corresponding dimers with good to excellent yields and stereoselectivities. In particular, the use of a phosphine-iron(III) complex allows the recovery and reuse of the catalyst. The counteranion plays an important role in both the activity and selectivity. These catalysts constitute an alternative to those based on toxic and expensive late-transition metals.

**Keywords:** dimerisation of styrenes; homogeneous catalysis; iron; recoverable catalyst; triflates; triflimide iron salts

The dimerisation of alkenes is a 100% atom-economical reaction that gives access to useful intermediates.<sup>[1]</sup> Traditionally, this reaction has been performed in the presence of Brønsted acids or late-transition metals as catalysts.<sup>[2-4]</sup> The regioselectivity of the reaction follows three different pathways (Scheme 1).

Both the regio- and stereoselectivity of the reaction vary depending on the catalyst employed and the reaction conditions. On the one hand, the head-to-head dimerisation of alkenes has been achieved with cobalt



phosphines complexes/Zn metal<sup>[5]</sup> and iron pyridinebisimine complex<sup>[6]</sup> as catalytic systems, given access to α-linear alkanes. Meanwhile, the tail-to-tail dimerisation is less common, although a typical example of this kind can be found in the Pd-catalysed cycloisomerisation of 1,6-dienes.<sup>[7]</sup> Finally, the head-to-tail dimerisation can be considered the more attractive transformation since a new allylic carbon stereogenic centre is formed. In fact, several natural products containing this chemical structure can be found.<sup>[8a]</sup> For instance, the chiral carbon of enantiomerically-enriched non-steroidal anti-inflammatories such as Naproxen<sup>TM</sup> has been accomplished by head-to-tail vinylation of styrene derivatives.<sup>[8b]</sup> Several catalytic systems have been reported for the head-to-tail dimerisation of alkenes: the above-commented cobalt-phosphines/Zn metal mixture,<sup>[5]</sup> a combination of palladium/indium triflate/phosphines<sup>[9]</sup> and a palladium complex/  $BF_3 \cdot OEt_2$ <sup>[2]</sup> the three of them giving preferentially the E-isomer, cationic palladium complexes that lead to the Z-isomer<sup>[10]</sup> and nickel-diphosphine complexes that give the *E*-isomer under basic conditions.<sup>[11]</sup> Curiously, a Rh(I) catalyst activates instead the ortho-position of styrene.<sup>[12]</sup>

Iron catalysis has attracted again the interest of chemists mainly due to its beneficial environmental and economical aspects compared to late transition metals.<sup>[13]</sup> As a consequence, new iron-catalyzed reactions have appeared in the last years, opening new avenues in the substitution of pollutant metals by iron salts and complexes.<sup>[13]</sup> Iron(III) is a harder Lewis acid compared to late-transition metal cations, allowing better activation of C=C double bonds. In fact, several new iron-catalysed transformations of alkenes have been recently reported, including arylations,<sup>[14-16]</sup> 1,4 additions to dienes<sup>[17]</sup> and hydroaminations.<sup>[18]</sup> FeCl<sub>3</sub> is the usual catalyst for these transformations.<sup>[14,15,18]</sup>

**Scheme 1.** Possible reaction pathways for the dimerisation of alkenes.

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As far as we know, the iron-catalysed head-to-tail dimerisation of alkenes has not been reported yet.<sup>[19]</sup> Considering the proposed mechanisms for this reaction,<sup>[20]</sup> it was envisaged that simple Fe(III) salts could play the catalytic role of the toxic and expensive metal complexes used previously. In the one hand, In-(III)  $[4d^{10}, \text{ compare with Fe(III) } 3d^5]$  has been used to form stabilised benzylic carbocations<sup>[20]</sup> of styrene derivatives and, on the other hand, activation of the soft C=C double bond nucleophile is also required.<sup>[2,5,11]</sup> Given that Fe(III) activates similarly styrene derivatives and can add soft carbon nucleophiles,<sup>[14,21]</sup> a catalytic activity could be expected. Indeed, we will see that the head-to-tail dimerisation of styrenes proceeds regio- and stereoselectively under iron catalysis, leading to E-styryl derivatives. It can be anticipated that FeCl<sub>3</sub> does not present enough Lewis acidity to catalyse this reaction, which explains why the dimerisation of styrene derivatives was not detected in the previously reported FeCl<sub>3</sub>-catalysed processes. Higher acidic species such as  $Fe(OTf)_n$  or  $Fe(NTf_2)_n$  (n=2,3)are needed.<sup>[22,23]</sup> To our surprise,  $Fe(NTf_2)_2$  and Fe(NTf<sub>2</sub>)<sub>3</sub> salts have rarely been employed as catalysts,<sup>[21,24]</sup> although their high Lewis acidities makes them suitable catalytic entities.

The dimerisation of styrene **1** was chosen as a test reaction (Scheme 2). In accordance with Bedford,<sup>[9]</sup> 1,4-dioxane was the best solvent found. A screening of possible catalysts including metal salts (Supporting Information, Table S1) and metal complexes (Supporting Information, Table S2) was carried out. A summary of the more relevant results obtained is depicted in Figure 1.

Concerning the metal salts, the corresponding chlorides of Cu(II), Co(II), Pd(II), Fe(II) and Fe(III) do not work as catalysts (Supporting Information, Table S1, entries 2-6). HCl (conc.) does not work either (entry 7). However triflic and triflimidic acids worked well in catalytic amounts (entries 8-12). The corresponding in situ generated triflate salts of Cu(II) (entry 13) and Fe(II) (entry 14) and the Co(II) triflimide salt (entry 15) did not work, but the triflimidic salt of Fe(II) (entries 18 and 19) and the triflate and triflimidic salts of Ag(I) (entries 16 and 17) and Fe(III) (entries 20-22) gave good to excellent conversions and selectivities for 2. Compared with corrosive and unstable organic acids, the in-situ generated iron-(III) catalytic system is more convenient and easy-tohandle, while effective. As expected, the Fe(III) cata-



Figure 1. Comparison of the catalytic activity of different metal salts and complexes for the dimerisation of 1 to 2: A) conversion of 1 (%) and B) yield of 2 (%).

lysts were more active that the corresponding Fe(II) counterparts (compare entries 18 and 21 and entries 15 and 20). The *in-situ* generated triflimide catalysts are as active as the isolated compounds<sup>[23]</sup> (compare entries 18 and 19). The activity of the iron catalyst does not come from copper impurities,<sup>[25]</sup> since the copper catalysts are less active that the corresponding iron salts (compare entries 21 and 23).

From these results it can be claimed that Fe(III) salts are effective catalysts for the head-to-tail dimerisation of styrene. In general, the use of -NTf<sub>2</sub> as counteranion instead of "OTf increases the reaction rate but decreased slightly the selectivity for 2. This counteranion effect was studied by kinetics experiments (Supporting Information, Figure S1 and Table S3). It could be observed that, indeed,  $Fe(NTf_2)_3$  shows the better catalytic activity and, as the <sup>-</sup>NTf<sub>2</sub> groups are replaced by the <sup>-</sup>OTf groups, the activity decreases and the selectivity increases. Nevertheless,  $Fe(NTf_2)_3$  gives an optimum conversion with a good yield of 2. Moreover, triflimide salts are less prone to hydrolysis than triflates and can be recovered by precipitation in hexane.<sup>[26]</sup> In fact, the  $Fe(NTf_2)_3$  catalyst could be recovered by precipitation with hexane (20:1 respect to dioxane) although the activity decreased from 85% conversion to 21% conversion in a second use.

With this result in hand and taking in account our previous work on the use of highly cationic phosphine complexes as reusable catalyst in alkyne transforma-



Scheme 2. Metal-catalysed dimerisation of styrene 1.

tions,<sup>[26]</sup> we envisaged phosphine triflimide iron complexes as possible reusable active catalysts. For that reason a second screening, where different triflate and triflimide phosphine iron (and cobalt) complexes were used as catalysts for the head-to-tail dimerisation of styrene, was carried out (see Supporting Information, Table S2). As previously, the triflate complexes were less active as catalyst that the corresponding triflimide complexes, regardless the metal employed [compare entries 1 and 2 for Co and entries 3 and 4 for Fe(III)]. Good yields of **2** were achieved by using Fe(III) and even Fe(II) complexes in catalytic amounts (entries 5–8). The number of PPh<sub>3</sub> units in the coordination sphere has a moderate effect in the catalytic activity, observing that the higher the number of phosphines, the lesser the activity is (compare entries 4 and 8 and entry 21 in Table 1). Remarkably, the triflate complex (Ph<sub>3</sub>P)<sub>2</sub>Fe(OTf)<sub>3</sub> showed an excellent conversion (92%) and selectivity for **2** (>98%, entry 5). Thus, we examined again the counteranion effect for the Fe(III) bis(triphenylphosphine) complex (Supporting Information, Figure S2 and Table S4). The counteranion exchange effect is even more pronounced in this case than for the simple salt (compare with Figure S1 and Table S3, Supporting Information), the activity decreases and the selectivity of **2** increases as  $^{-}NTf_{2}$  ions are replaced by  $^{-}OTf$  in the complex. An abrupt loss of activity is observed

Table 1. Head-to-tail dimerisation of styrene derivatives catalysed by cationic iron(III) salts.

		$R^{2}$ $R^{3}$ $R^{3}$ $R^{1}$ $R^{3}$ $R^{3$	st → Dimer	
Entry	Substrate	Catalyst (mol%)	Main Product	Yield [%] <sup>[a]</sup>
1		FeCl <sub>3</sub> +3AgOTf (5)		[95]
2		$FeCl_3 + 3AgNTf_2$ (2)		94, [60]
3	F 5	FeCl <sub>3</sub> +3AgNTf <sub>2</sub> (5)		97
4	7	$FeCl_3 + 3AgNTf_2$ (2)	8	51
5	9	FeCl <sub>3</sub> +3AgNTf <sub>2</sub> (5)	10	61
6	F <sub>3</sub> C 11	$FeCl_3 + 3AgNTf_2$ (10)	F <sub>3</sub> C 12 CF <sub>3</sub>	[75] <sup>[b]</sup>
7	MeO 13	$\operatorname{FeCl}_{3}(2)$	polymerisation	_[c]

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Table 1. (Continued)

Entry	Substrate	Catalyst (mol%)	Main Product	Yield [%] <sup>[a]</sup>
8	N 14	FeCl <sub>3</sub> (2)	polymerisation	_[c]
9	15	$FeCl_3 + 3AgNTf_2$ (2)		54
10	17	$FeCl_3 + 3AgNTf_2$ (10)	mixture of isomers	>95 <sup>[d]</sup>
11	18	$FeCl_3 + 3AgNTf_2$ (2)	N.D.	-
12	19	$FeCl_3 + 3AgNTf_2$ (2)	N.D.	_
13	20	$FeCl_3 + 3AgNTf_2$ (2)	N.D.	_

<sup>[a]</sup> GC or <sup>1</sup>H NMR yield. In square brackets, isolated yield.

<sup>[b]</sup> 7 days reaction time.

<sup>[c]</sup> Room temperature.

<sup>[d]</sup> At least six different dimers were found (GC-MS m/z = 236, intensity pattern 1:3:2:3:1:3).

for the full triflate complex. Nevertheless,  $(PPh_3)_2Fe-(NTf_2)_3$  could be used as a recoverable and reusable catalyst for the head-to-tail dimerisation of **1** to **2** and only a moderate decrease throughout the reuses was observed while a good selectivity was maintained (Figure 2).

In view of the catalytic results obtained (see Figure 1 above), we selected the catalytic system  $FeCl_3+3AgNTf_2$  to explore the scope of the reaction (Table 1).

Styrene derivatives **1**, **3** and **5** gave excellent yields after isolation (entries 1–3). Substrates having a methyl substituent were reactive as well, although, partial polimerisation was observed (entries 4 and 5). Gratifyingly, the electron-poor styrene derivative **11** could form the corresponding dimer in good isolated



**Figure 2.** Reusability study for the head-to-tail dimerisation of **1** catalysed by  $(PPh_3)_2Fe(NTf_2)_3$ . (C=conversion).

yield after a prolonged reaction time (entry 6). In contrast, electron-rich substrates **13** and **14** did not stop at the dimer but polymerised even when using FeCl<sub>3</sub> as catalyst at room temperature (entries 7 and 8). Substitution across the double bond also modifies the catalytic activity.  $\alpha$ -Methylstyrene **15** reacted well (entry 9). However,  $\beta$ -methylstyrene **17** needed 5 times more catalyst to achieve complete conversion (entry 10). When both  $\alpha$ - and  $\beta$ -positions were substituted (entry 11) no reaction was observed. Stilbene did not react either (entry 12). Alkylalkenes were not reactive (entry 13).

A possible mechanism for the Fe(III)-catalyzed head-to-tail dimerisation of styrenes is depicted in Scheme 3. This mechanistic proposal is based on the well-known capability of iron(III) to activate the benzylic position of double bonds<sup>[14]</sup> and the also reported iron(III) activation of soft nucleophiles.<sup>[21]</sup> Thus, the cationic Fe(III) species would form the corresponding benzylic cation and would also activate the double bond. After formation of the new C–C bond, the catalyst would be regenerated for a new cycle. The marked counteranion effect observed on the reaction rate and selectivity suggest that X<sup>-</sup> plays an active role, probably stabilising the different cationic species during the catalytic cycle.

Different experiments were carried out to check this reaction pathway (see Supporting Information). For instance, ethyl triflate was added to the reaction mixture in order to trap any hypothetic nucleophilic



**Scheme 3.** Plausible mechanism of the iron(III)-catalysed head-to-tail dimerisation of styrene **1**.

Fe-C species during the cycle [Supporting Information, Eq. (S1)]. Unfortunately, no ethyl groups were incorporated in the products but instead oxygen was added on the benzylic positions, obtaining the corresponding ketones, which confirms the presence of benzylic carbocations. In a second experiment, the styrene derivative 11 was added together with 1 [Supporting Information, Eqs. (S2) and (S3)] and, curiously, the dimerisation reaction was inhibited. This suggests that the stabilisation of the benzylic carbocation is the key step during the cycle, since the electronwithdrawing nature of the ring in 11 retards and even inhibits the reaction. Furthermore, this also explains the high reactivity observed for electron-donor aryl rings such as substrates 13 and 14, which stabilise better the benzylic carbocation.

In summary, the Fe-catalysed head-to-tail dimerisation of styrene derivatives has been accomplished. Fe(III) is a better catalyst compared to late-transition metals. The corresponding dimers of different substituted substrates have been obtained in good to excellent yields by using simple cationic salts. The use of a phosphine iron(III) complex allows recovering and reusing the catalyst. Since a new stereogenic center is formed in the dimerisation, the use of a chiral phosphine might allow enantioselective induction on the product. Studies in this sense are currently underway.

## **Experimental Section**

### Typical Reaction Procedure for 1,3-Diphenyl-1butene (2) (Table 1, entry 1)

 $FeCl_3$  (16.3 mg, 5 mol%) and AgOTf (77 mg, 15 mol%) were placed in a 10-mL round-bottomed flask. A rubber

septum was fitted. Then, 1,4-dioxane (1,5 mL) was added. The mixture was magnetically stirred at room temperature for 30 min. Then, styrene (230 µL, 2.0 mmol) was added and the mixture was magnetically stirred at 80 °C for 18 h. After cooling, *n*-hexane (30 mL) was added, observing the precipitation of the catalyst. The liquid was passed through a filter containing a Celite<sup>TM</sup> layer on top. The solid was washed with *n*-hexane and filtered again. The filtrates were concentrated under reduced pressure and, after drying under vacuum, the resulting residue 1,3-diphenyl-1-butene was obtained as an clear oil; yield: 189 mg (95%). Further purification was performed by flash column chromatography on silica using neat *n*-hexane as eluent. The spectroscopic data match those previously reported.<sup>2</sup>

# Typical Reaction Procedure for Reusing (PPh<sub>3</sub>)<sub>2</sub>Fe(NTf<sub>2</sub>)<sub>3</sub> (Figure 2)

(PPh<sub>3</sub>)<sub>2</sub>FeCl<sub>3</sub> (68.6 mg, 10 mol%) and AgNTf<sub>2</sub> (116.5 mg, 30 mol%) were placed in a 10-mL round-bottomed flask. A rubber septum was fitted. Then, 1,4-dioxane (0.75 mL) was added. The mixture was magnetically stirred at room temperature for 30 min. Then, styrene (115  $\mu$ L, 1.0 mmol) was added and the mixture was magnetically stirred at 80 °C for 18 h. After cooling, *n*-hexane (30 mL) was added, observing the precipitation of the catalyst. The liquid was decanted, the remaining catalyst was washed with hexane and the liquid was decanted again. The combined organic phases were analysed by GC. The catalyst was dried and used in a next run.

#### **Supporting Information**

Supporting information for this article including synthesis of catalysts, reaction procedures, compound characterization, additional reaction schemes and NMR spectra, is available.

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