C–C coupling

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Z-Selective (Cross-)Dimerization of Terminal Alkynes Catalyzed by an Iron Complex

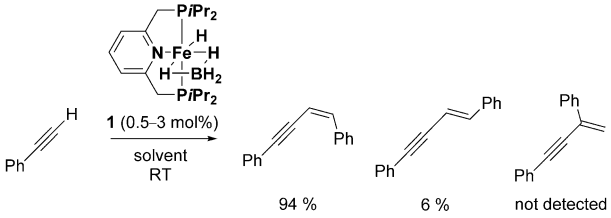
*Orestes Rivada-Wheelaghan, Subrata Chakraborty, Linda J. W. Shimon, Yehoshoa Ben-David, and David Milstein**

In memory of Alex Nerush

Abstract: *Efficient iron-catalyzed homocoupling of terminal alkynes and cross-dimerization of aryl acetylenes with trimethylsilylacetylene is reported. The complex [Fe(H)(BH$_4$)(iPr-PNP)] (**1**) catalyzed the (cross-)dimerization of alkynes at room temperature, with no need for a base or other additives, to give the corresponding dimerized products with Z selectivity in excellent yields (79–99 %).*

Conjugated 1,3-enynes are important building blocks in organic synthesis for the preparation of polysubstituted aromatic rings and natural products, and key units found in a variety of biologically active molecules, drug intermediates, and organic materials.[1] Several methods for their synthesis are known, such as Sonogashira coupling between terminal alkynes and vinyl halides, cross-coupling of terminal alkynes with preactivated alkenes, Wittig olefination of conjugated alkynals, and dehydration of propargylic alcohols.[2] Direct hydroalkynylation across the carbon–carbon triple bond or alkyne dimerization to form conjugated enynes is the most attractive method as it is fully atom economical.[3] However, this process has resulted in relatively few applications owing to issues of chemo-, regio-, and stereoselectivity. The dimerization of terminal alkynes has been investigated with a large number of transition-metal-based catalysts, mostly based on precious metals.[3,4] Since iron salts are readily available, inexpensive, and environmentally benign, the development of iron-based catalysts for organic transformations is currently a very active area of research.[5] We are aware of only a marginally catalytic (maximum 3 turnovers) *E*-selective alkyne dimerization involving iron to give enyne products,[6] with $FeCl_3$, a ligand, and KO*t*Bu (300 mol %) at high temperatures.[6a] Following our studies on iron pincer complexes of the Fe–PNP and Fe–PNN types,[5b,7] we describe herein the first iron-catalyzed *Z*-selective homo- and cross-coupling of terminal alkynes in the absence of additives under mild conditions. Mechanistic insight, including isolation of the likely actual catalyst, is provided.

When a solution of phenylacetylene and [Fe(H)(BH$_4$)(*i*Pr-PNP)] (**1**; 1 mol %)[7a] in THF was stirred at room temperature for 24 h, 1,4-diphenyl-1-buten-3-yne was formed quantitatively (94 % *Z* and 6 % *E*; Scheme 1). An increase in the catalyst loading to 3 mol % resulted in complete conversion after 15 h into the *Z* dimerized product as the only product (Table 1, entry 1). Significantly, the catalyst remained fully active after completion of the reaction. Thus, at a catalyst loading of 3 mol %, the addition of the same amount of phenylacetylene after the dimerization reaction was completed yielded the homocoupling product again with no substantial change in the catalytic activity.



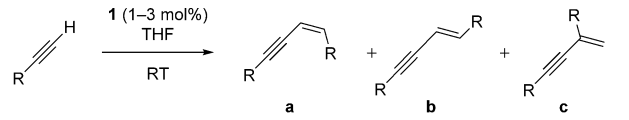
Scheme 1. Dimerization of phenylacetylene as catalyzed by complex **1** in THF or C_6H_6.

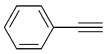
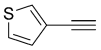
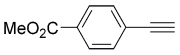
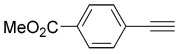
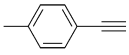
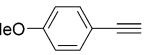
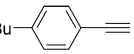
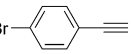
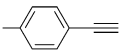
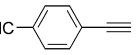
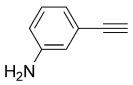
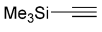
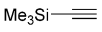
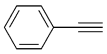
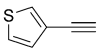
Next, we studied the homodimerization of several types of alkynes under the catalysis of **1**. The complete conversion of several *para*-substituted aryl acetylenes (*p*-CO_2Me, *p*-Me, *p*-OMe, *p*-*t*Bu, *p*-Br, *p*-F, *p*-cyano), *meta*-substituted 3-ethynylaniline, and 3-ethynylthiophene into their corresponding homodimerized products was observed within 15 h at room temperature (Table 1, entries 1–10). The observed reactivity trend of different aryl acetylenes is related to the acidity of the C–H bond of the terminal alkyne. The presence of electron-withdrawing substituents at the *para* position resulted in faster reactions than in the case of electron-donating groups (see Table S1 in the Supporting Information). Although complex **1** is catalytically active towards aryl acetylenes, alkyl acetylenes do not react. Also, *ortho*-substituted aryl acetylenes did not undergo catalysis (see Table S1). On the other hand, a wide range of functional

[*] Dr. O. Rivada-Wheelaghan, Dr. S. Chakraborty, Y. Ben-David, Prof. D. Milstein
Department of Organic Chemistry, Weizmann Institute of Science
76100, Rehovot (Israel)
E-mail: david.milstein@weizmann.ac.il
Dr. L. J. W. Shimon
Chemical Research Support, Weizmann Institute of Science
71600, Rehovot (Israel)

Supporting information, including a detailed description of the synthesis and spectroscopic data of complex **2** as well as NMR spectra of the different crude reaction mixtures and isolated products, and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201601382.

Table 1: Dimerization of terminal alkynes as catalyzed by **1**.[a]



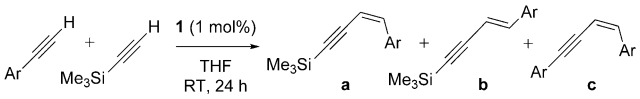
Entry	Substrate	*t* [h]	Conv. [%][b]	Yield [%] (**a**:**b**:**c**)[b]
1		15	> 99	98:0:0
2		15	> 99	94:6:0
3		15	> 99	90:8:0
		15[c]	> 99	74:9:0
4		15	> 99	90:10:0
5		15	> 99	88:10:0
6		15	> 99	88:12:0
7		15	> 99	94:4:0
8		15	> 99	98:0:0
9		15[c]	> 99	73:14:0
10		15[c]	> 99	85:6:0
11[d]		36	> 99	0:0:80
		15	> 99	0:0:40
12[e]		15	> 99	94:6:0
13[f]		12	> 99	95:5:0

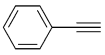
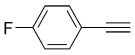
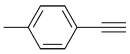
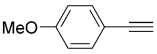
[a] Reaction conditions, unless otherwise noted: substrate (0.1 mmol), **1** (3 mol%), THF (0.5 mL), room temperature. [b] The conversion and yield are based on ^{1}H NMR analysis with mesitylene as an internal standard. [c] The reaction was carried out with 5 mmol of the substrate in 5 mL of THF; the yield of the isolated product is given. [d] The reactions were carried out with 0.25 mmol of the substrate and 1 mol% of **1**. [e] The reaction was carried out with **2** (3 mol%) and 0.13 mmol of the substrate. [f] The reaction was carried out with **2** (5 mol%) and 0.13 mmol of the substrate in C_6D_6 (0.5 mL), without an internal standard.

groups are tolerated, including amines, esters, nitriles, and even aryl halides, which are known to readily oxidize Fe^{II} complexes to Fe^{III}.[5e] The catalytic reaction of ethynyltrimethylsilane led to a different result as compared with aryl-substituted alkynes. The use of 1 mol% of **1** resulted in the geminal product in 80% yield; neither the *Z* nor the *E* coupling product was observed. An increase in the catalyst loading to 3 mol% resulted in a lower yield of the geminal coupling product (Table 1, entry 11).

In a pioneering study, Ozawa and co-workers observed the Z-selective cross-dimerization of aryl acetylenes with excess silylacetylenes in the presence of a ruthenium–vinylidene complex and a base.[4d] It was of interest to us to study this cross-dimerization with the Fe catalyst **1**. Interestingly, when a solution of phenylacetylene (1 mmol), trimethylsilylacetylene (3 mmol), and **1** (0.01 mmol) in THF was stirred at room temperature, complete conversion of phenylacetylene into a mixture of the *Z* and *E* isomeric cross-dimerized products **a**,**b** and the phenylacetylene homodimerization product **c** was observed (by GC–MS) after 17 h. This mixture was isolated in 85% yield and showed a *Z* cross-selectivity of 66% (Table 2, entry 1). Higher selectivity for the *Z* cross-

Table 2: Cross-dimerization of aryl acetylenes with trimethylsilylacetylene as catalyzed by **1**.[a]



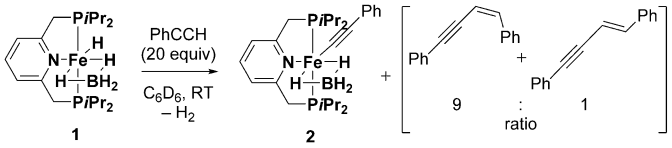
Entry	Aryl acetylene	Conv. [%][b]	Yield [%][c]	Selectivity (**a**:**b**:**c**) [%][d]
1[e]		> 99	85	66:9:26
2[e]		> 99	79	75:7:18
3		> 99	84	79:9:12
4[f]		> 99	88	84:8:8
5		> 99	80	98:2:0

[a] Reaction conditions: aryl acetylene (1 mmol), trimethylsilylacetylene (3 mmol), **1** (0.01 mmol), THF (3 mL), room temperature, 24 h. [b] Conversion was determined by GC–MS as based on consumption of the aryl acetylene. [c] Yield of the mixture of **a**, **b**, and **c** after column chromatography (elution with hexane). [d] Selectivity was determined by integration of the ^{1}H NMR spectrum of the isolated mixture. [e] The reaction was complete after 17 h. [f] The reaction was carried out with 0.5 mmol of 3-ethynylthiophene, 1.5 mmol of trimethylsilylacetylene, and 0.005 mmol of **1**.

coupling products **a** was observed with 4-fluorophenylacetylene (75%), 4-tolylacetylene (79%), and 3-thienylacetylene (84%; Table 2, entries 2–4). However, when 4-ethynylanisole was used, the cross-dimerization products were obtained with 98% *Z* and 2% *E* selectivity (Table 2, entry 5), although a small amount of the homodimerized product **c** of 4-ethynylanisole was observed by GC–MS. In all cases, a 1:3 aryl acetylene/silylacetylene molar ratio was used. These good to excellent yields show the high *Z* selectivity of complex **1** in the cross-dimerization reaction. Thus, complex **1** is the first effective iron catalyst reported to date for the cross-dimerization of terminal alkynes. The regio- and stereoselectivity of the reaction, together with its high activity, make complex **1** comparable to catalysts based on precious-metal complexes.[4a–c,8] As compared to the procedure reported by Ozawa and co-workers for the cross-dimerization catalyzed by ruthenium,[4d] a lower catalyst loading (1 vs. 5 mol%) and a lower excess of ethynyltrimethylsilane were required, under neutral conditions (a base is needed in the case of Ru), for similar catalytic results. Significantly, these reactions are performed at room temperature under base-free conditions and with no extra additives, with earth-abundant

iron and commercially available substrates, with no need for further purification.

Aiming to gain mechanistic insight regarding the homocoupling of terminal alkynes, we monitored the reaction of complex **1** with phenylacetylene (20 equiv) in C_6D_6 in a sealed NMR tube by NMR spectroscopy. At the beginning of the reaction, the formation of H_2 was observed by ^1H NMR spectroscopy (singlet at 4.5 ppm) while complex **1** was being consumed. Focusing on the catalyst, the reaction with PhCC–H yielded the novel alkynyl complex [Fe(PhCC)(BH_4)(*i*Pr-PNP)] (**2**) as the major complex, which was formed before all the substrate was consumed (Scheme 2). In contrast to **1**, complex **2** did not exhibit the triplet hydride signal at −18.18 ppm in the ^1H NMR spectrum, and the two broad hydride signals at −9.63 and −28.67 ppm arising from BH_4^- were shifted to −14.28 and −27.26 ppm, thus indicating a change in the σ donation of the ligand bound *trans* to a hydride of BH_4.



Scheme 2. Formation of the iron–alkynyl complex **2**.

The $^{31}P\{^1H\}$ NMR spectrum exhibited a new singlet at $\delta =$ 86.8 ppm, and the Fe–C(sp) peak appeared in the DEPTQ NMR spectrum as a triplet at 122.4 ppm ($J = 30$ Hz).[9] Cooling of a solution of **2** in pentane resulted in the formation of small black crystals suitable for X-ray diffraction. As anticipated, the Fe^{II} center exhibits octahedral geometry, which includes the *i*Pr-PNP ligand, the BH_4 ligand, and the phenylacetylide; the Fe1–C20 bond length of 1.911(3) Å is in agreement with previously reported values (Figure 1).[9,10]

Since **2** is the only complex observed upon the reaction of **1** with excess phenylacetylene, it is probably an actual intermediate (or resting state). Indeed, when the isolated complex **2** was used as the catalyst, the results were similar to those obtained with complex **1** (Table 1, entries 12 and 13). Complex **2** could be stored at −40 °C in the solid state, but in the absence of an alkyne substrate it underwent complete decomposition within 18 h in solution at room temperature.

Since pincer complexes are capable of metal–ligand cooperation (MLC) by aromatization–dearomatization of the N-heterocyclic ring,[11] we explored this possibility by treating deuterated phenylacetylene (PhCC–D) with **1**. No D incorporation at the benzylic position was observed, thus suggesting that MLC does not take place in this case. A signal corresponding to H–D at 4.5 ppm with $^2J_{H-D} = 43$ Hz, indicating HD formation, was detected at the beginning of the reaction, while **1** was consumed to give **2**. Furthermore, the integration of the BH_4 ligand signals remained unchanged after the conversion was complete, thus indicating its spectator behavior during the reaction.

To explore whether insertion of the alkyne triple bond into the iron–alkynyl fragment takes place, we carried out reactions of phenylacetylene with internal alkynes (1:1) in the presence of **1** (1 mol%). With 2-butyne or diphenylacetylene as the internal alkyne, only 1,4-diphenyl-1-buten-3-yne was observed by ^1H NMR spectroscopy. In the case of 2-butyne, traces of other products were observed by GC–MS (see the Supporting Information). The treatment of **2** with the same internal alkynes gave no product of alkyne insertion, nor a possible intermediate that could arise from alkyne insertion. Complex **1** does not react with internal alkynes, thus suggesting, together with the spectroscopic results of monitoring the reaction with PhCC–H(D), that initially coupling of the C–H bond of the terminal alkyne with Fe–H takes place to liberate H_2 and generate the actual catalyst, complex **2**. Moreover the lack of insertion of the internal alkyne into phenylacetylene, plus the minor formation of the *E* enyne coupling product when terminal alkynes are used, is in line with a predominant vinylidene-based mechanism, rather than alkyne insertion into an iron–alkynyl bond (Scheme 3).[13]

In the first step of our proposed mechanism, the terminal alkyne coordinates to **1** to form complex **A**, in which the acidity of the terminal alkyne C–H atom is enhanced. Subsequent reaction with the hydride of **1** liberates dihydrogen and yields the corresponding iron–alkynyl complex **2**. Coordination of another molecule of the alkyne gives rise to intermediate **B**. It is likely that **B** is transformed into the

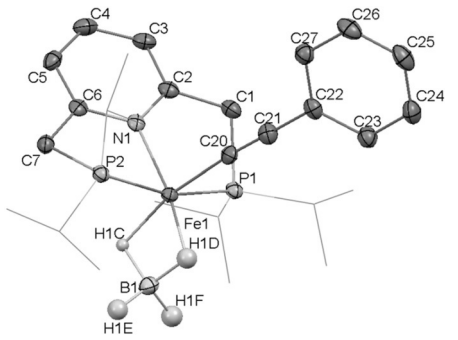
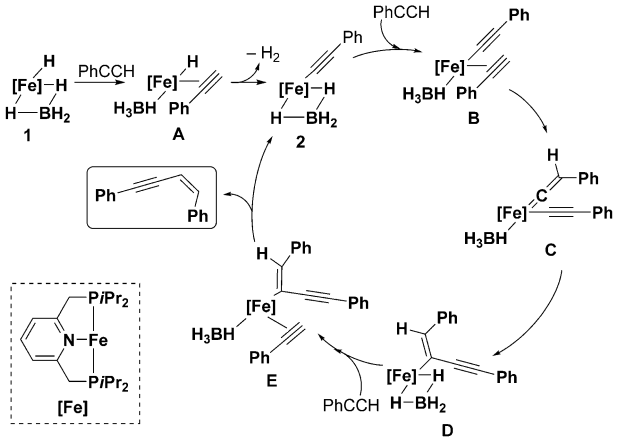


Figure 1. X-ray crystal structure of complex **2** with thermal ellipsoids set at 50% probability. The isopropyl groups are presented in wire-frame style for clarify. See the Supporting Information for selected bond lengths and angles.



Scheme 3. Proposed catalytic cycle for phenylacetylene dimerization.

vinylidene intermediate **C**,[13] in line with the lack of reactivity of internal alkynes with complex **2**, and as observed in alkyne dimerization catalyzed by ruthenium.[4d,8a,12] Intramolecular C–C coupling of the alkynyl fragment with the α-carbon atom of the vinylidene can explain the *Z* isomerization in **D**, considering the steric effects that the pincer ligand and BH_4^- impose on the organic fragments. It is likely that the formation of **B** is reversible, with the equilibrium lying towards **2**, and the reaction step to generate intermediate **C** might be rate-determining, hence **2** accumulates. Coordination of another terminal alkyne to form intermediate **E**, followed by proton transfer from the coordinated alkyne, leads to release of the *Z* enyne product and regeneration of complex **2**, thus completing the catalytic cycle. We believe that the BH_4 group behaves as a spectator ligand, stabilizing the subsequent intermediates and forbidding the coordination of an additional terminal alkyne, which could lead to trimerization products.[14] At the same time, its hemilability allows the coordination of the terminal alkyne for further reactivity.

In conclusion, the homo- and heterocoupling of terminal alkynes to give enynes was efficiently catalyzed by a well-defined iron complex. This reaction exhibits high regio- and stereoselectivity under very mild, neutral conditions at room temperature. Our studies suggest that the reaction proceeds via the alkynyl–iron complex **2**, which was characterized by X-ray diffraction and is likely to be the actual catalyst. Alkyne coordination to **2** may lead to a vinylidene intermediate, followed by C–C coupling and product release upon protonation by an additional alkyne molecule.

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Keywords: C–C coupling · homogeneous catalysis · hydroalkynylation · iron · pincer complexes

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