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Cyclotrimerization

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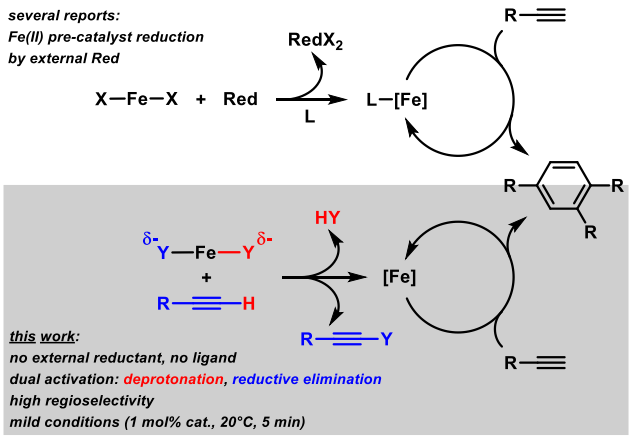
Iron-Catalyzed Cyclotrimerization of Terminal Alkynes by Dual Catalyst Activation in the Absence of Reductants

*Davide Brenna,[a] Matteo Villa,[a] Tim N. Gieshoff,[a] Fabian Fischer,[b] Marko Hapke,[b] and Axel Jacobi von Wangelin[a],**

***Abstract**: Catalysis of C-C bond forming reactions by earth abundant metals under mild conditions is at the heart of sustainable synthesis. The cyclotrimerization of alkynes is a valuable atom-efficient tool of organic synthesis which operates with several metal catalysts, including iron. This study reports an effective iron-catalyzed cyclotrimerization for the regioselective synthesis of 1,2,4-substituted benzenes (1 mol% cat., toluene, 20°C, 5 min). A dual activation mechanism (substrate deprotonation, reductive elimination) enables high catalytic activity of a simple Fe(II) pre-catalyst in the absence of any reductant.*

Metal-catalyzed cyclotrimerizations of alkynes constitute a key technology for the construction of substituted aromatics and have been developed to great maturity since its first discovery in the mid-19th century and the early studies of Reppe in 1948.[1] Today, several transition metals display good catalytic activity in this highly atom-efficient, redox-neutral, complexity-generating reaction.[2] The search for sustainable base metal technologies has recently prompted the development of iron-catalyzed protocols.[3] High activities were especially observed with low-valent iron catalysts which can be generated from iron(0) precursors or by reactions of Fe(II) complexes with suitable reductants. The first report utilized iron carbonyl catalysts at high temperatures.[4] Recently, various combinations of iron complexes, ligands, and zinc were shown to exhibit high catalytic activity and wide applicability.[5] Alternatively, elaborate iron complexes in low oxidation states (+1, 0) were also applied.[6] The majority of catalyst developments was fueled by the notion that a low-valent iron species would engage in coordinative activation of the softly Lewis basic alkyne, facilitate the iron-centered oxidative cyclization step, and is regenerated upon reductive elimination. However, these protocols require the preparation and handling of highly reactive iron complexes or the presence of suitable reductants. The conceptual relation between reductants and bases led us to postulate a mechanistically distinct approach to the design of effective iron(II) pre-catalysts in which a simple internal base would mimic the role of an external reductant. With one equivalent of a terminal alkyne, a dual activation mechanism of the inactive FeX_2 involving sequential alkyne deprotonation and reductive alkyne elimination would result in an overall reduction in the absence of an actual reductant (Scheme 1). We believed that FeX_2 complexes constitute most simple pre-catalysts with cheap, easily accessible ligands X that are bulky (facile dissociation), strongly basic (alkyne deprotonation), lipophilic (solubility in organic solvents). With these framework conditions, we investigated various ferrous salts and identified $Fe(hmds)_2$, iron(II) bis(1,1,1,3,3,3-hexamethyldisilazan-2-ide), a active catalyst. Documented herein are the benefits of this simpl catalytic system that presents tangible advances over the currer state-of-the-art: The pre-catalyst is activated by the substrate; n reductant is required. Instantaneous and highly regio-selectiv cyclotrimerization of terminal alkynes proceeds under very mil conditions. A most user-friendly protocol can be adopted b preparing the catalyst from the simple salts $FeCl_2$ and Li(hmds).



Scheme 1. Modes of catalyst formation in iron-catalyzed cyclotrimerization

We commenced our studies with the employment of various simpl ferrous salts in the cyclotrimerization of phenylacetylene at roor temperature (Table 1). $FeCl_2$, $FeCl_2(thf)_{1.5}$, $Fe(OAc)_2$, $Fe(OTf)_2$ an $Fe(acac)_2$ gave no turnover; the starting material was recovere (entries 1-5). The postulated catalyst activation by alkyne deprotc nation (pK_a (PhC≡CH): 28, DMSO)[7a] would require a sufficientl basic substituent Y in the pre-catalyst FeY_2 for attaining hig catalytic activity. Indeed, excellent yields and exclusive formatio of 1,2,4-triphenylbenzene was observed with $Fe(hmds)_2$ (entry 6 The even more basic $Fe_2(mes)_4$ (mes = mesityl) gave lower regic selectivity (entry 8). Reactions in THF and diethylether gav identical yields; hexane as solvent was slightly inferior (90%, 95/5 The optimized set of conditions involved reaction of a 1 M solution of phenylacetylene in toluene at 20°C for 1 min under argon with 1 mol% $Fe(hmds)_2$ and afforded 1,2,4-triphenylbenzene as a single regio-isomer in >99% yield. Importantly, a mixture of the simple salts $FeCl_2$ and Li(hmds) (ratio 1/2) exhibited nearly identical activity (entry 9); other transition metal salts proved inactive (entries 10-12). After 2 sec reaction with 1 mol% catalyst loading, an impressive turnover frequency (TOF) of 180,000 h^{-1} was recorded. To the best of our knowledge, this is the most active catalyst system that operates under such mild conditions. This protocol constitutes the first application of an Fe(II) catalyst to the cyclotrimerization of alkynes in the absence of a common reducing reagent.

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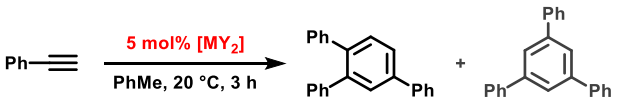
Table 1. Evaluation of MY_2 pre-catalysts.

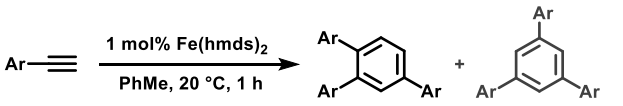


Entry	Pre-catalyst MY_2	pK_a (HY) [a]	Yield [%] [b]	Selectivity [c]
1	$Fe(OTf)_2$	0	0	-
2	$FeCl_2$	2	0	-
4	$FeCl_2(thf)_{1.5}$	2	0	-
3	$Fe(OAc)_2$	11	0	-
5	$Fe(acac)_2$	13	0	-
6	$Fe(hmds)_2$	30/26 [d]	96	100/0
7 [e]	**$Fe(hmds)_2$**		**99**	**100/0**
8	½ $Fe_2(mes)_4$	44	90	94/6
9 [f]	$FeCl_2$ / 2 Li(hmds)		98	99/1
10 [f,g]	MCl_2 / 2 Li(hmds)		0	-
11 [f]	$CuCl_2$ / 2 Li(hmds)		<5	-
12 [f]	$CoBr_2$ / 2 Li(hmds)		<5	-

Conditions: 5 mol % cat., 0.48 mmol alkyne (1 M), toluene, 20 °C, 3 h, Ar. [a] in DMSO.[7b] [b] Combined isolated yields of regioisomers. [c] Ratio 1,2,4/1,3,5-regioisomer (GC-FID). [d] in THF[8]. [e] 1 mol% $Fe(hmds)_2$, 5 mmol scale, 1 min. [f] MX_2 and Li(hmds) in toluene were stirred for 12 h at 20 °C prior to alkyne addition. [g] M = Zn, Mn, Pd, respectively.

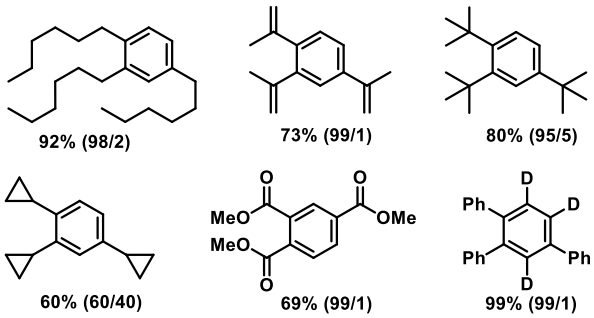
The scope of the cyclotrimerization was then extended to other terminal alkynes. Generally, good to excellent yields and regioselectivities were observed under the standard conditions with 1 mol% $Fe(hmds)_2$ at 20 °C after 1 h (Table 2). The bulky mesityl-acetylene showed very little conversion (entry 10). Alkynes bearing non-aryl substituents were also competent substrates and gave clean conversions to the benzene derivatives (Scheme 2). High regio-selectivities were observed with *t*-butyl, *i*-propenyl, carboxymethyl, and deuterium substituents. Tris(cyclopropyl)benzenes were formed in good yields but low regioselectivity.[9] The deuterium content of d_1-phenylacetylene was fully conserved in the product.

Table 2. Scope of iron-catalyzed cyclotrimerization of terminal alkynes. [a]



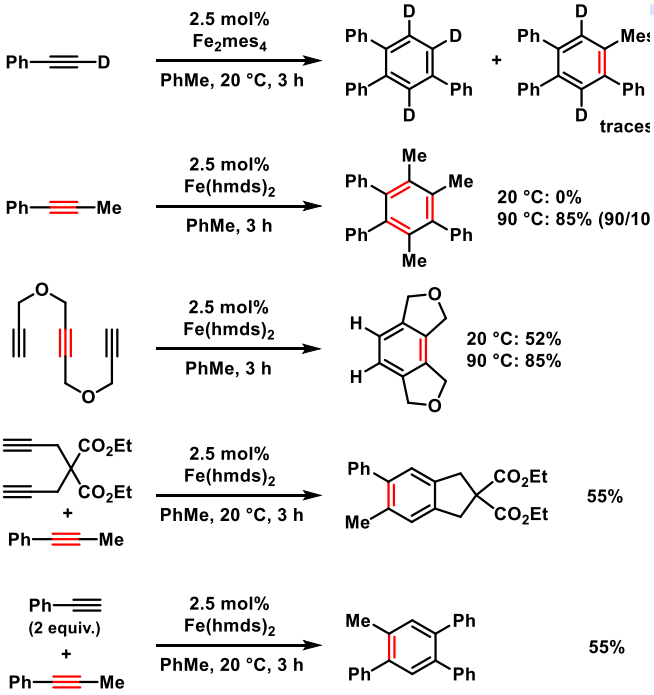
Entry	Aryl substituents	Yield [%] [b]	Selectivity [c]
1	4-NMe_2	95	96/4
2	4-OMe	95	100/0
3	4-OPh	94	n.d.
4	4-Me	98	100/0 [d]
5 [e]	4-Cl	99	99/1
6	4-F	94	96/4
7	4-CF_3	98	100/0 [c]
8	2-Me	90	96/4
9	2,4,5-Me_3	98	100/0 [d]
10	2,4,6-Me_3	<5	n.d.
11	2-Me-4-OMe	95	98/2
12	3-OMe	98	96/4
13	3-OBn	98	98/2
14	3,4-$(OMe)_2$	98	98/2
15	6-Methoxy-2-naphthyl	93	98/2

[a] Conditions: 0.48 mmol alkyne (1 M), toluene, 1 mol% $Fe(hmds)_2$, 20 °C, 1 h, Ar. [b] Combined isolated yields of both regioisomers. [c] Ratio 1,2,4/1,3,5-regioisomer (^{1}H-NMR). [d] Ratio 1,2,4/1,3,5-regioisomer (GC-FID). [e] 5 mol% cat.



Scheme 2. Synthesis of other 1,2,4-trisubstituted benzenes: 1 M alkyne, PhMe, 1 mol% $Fe(hmds)_2$, 20 °C, 1 h, Ar. Yields were identical to conversion; no other side products formed. Ratios of 1,2,4/1,3,5-isomer i parentheses.

Internal alkynes did not undergo cyclotrimerizations under standar conditions which is consistent with the postulated mechanism c initiating alkyne deprotonation. However, a competent catalys activation would only require catalytic amounts of terminal alkyn as the cyclotrimerization does not involve alkynyl anions (se deuteration, Scheme 2). Consistent with this hypothesis, th standard reaction of phenylacetylene with catalytic Fe_2mes_4 afforde trace amounts of mesityl-2,4,5-triphenylbenzene (beside the majc homo-cyclotrimer) via co-cyclization with the in situ formed 2 mesityl phenylacetylene. 1-Phenyl-1-propyne showed no reactivit under standard conditions but was converted at elevated temperatur to give 1,2,4-trimethyl-3,5,6-triphenylbenzene in 85% yiel (Scheme 3, top). However, mixtures of internal alkynes and termina alkynes could be cleanly reacted at 20 °C and afforded the cc cyclotrimers in good yields (Scheme 3). Intramolecular and inter molecular reactions were successful.



Scheme 3. $Fe(hmds)_2$-catalyzed co-cyclizations with internal alkynes.

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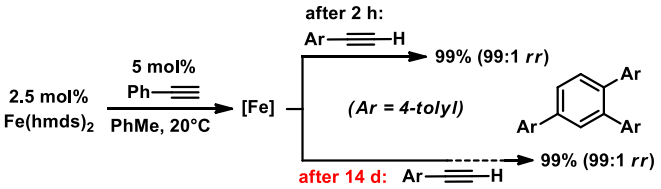
The catalyst solutions prepared by treatment of $Fe(hmds)_2$ with 2 equiv. phenylacetylene in toluene resulted in a rapid colour change to brownish and were highly stable over extended periods of time. Identical yields and selectivities were observed after 1 min and 14 d storage (Scheme 4). Poisoning studies with 0.5 equiv. trimethylphosphine (PMe_3) per Fe unambiguously resulted in inhibition of catalysis (Figure 1).[10] No impact on catalyst activity was observed upon addition of the selective homotopic poison dibenzo[*a*,*e*]cyclooctatetraene (dct) to the reaction mixture (Figure 1).[11] Based on the collected mechanistic data and literature precedents,[2-6] we postulate a reaction mechanism that is initiated by substrate-induced catalyst formation via sequential alkyne deprotonation and reductive elimination (Scheme 5). Both side products were observed by mass spectrometry. The formal reduction event leads to a low-valent catalyst species, presumably an iron(0) particle that is stabilized by labile coordination to the amine, alkyne, or solvent.[12] The mechanism presumably follows that of related protocols via π-alkyne, ferracyclopentadiene, and ferracycloheptatriene intermediates.[5a,6a,6b] The high regioselectivity is determined at the stage of the ferracyclopentadiene which might experience significant steric repulsion in the 2,5-diaryl isomer by bulky ligands (amine, alkyne, solvent) or the catalyst surface.



Scheme 4. Catalyst ageing studies document long-term stability and activity.

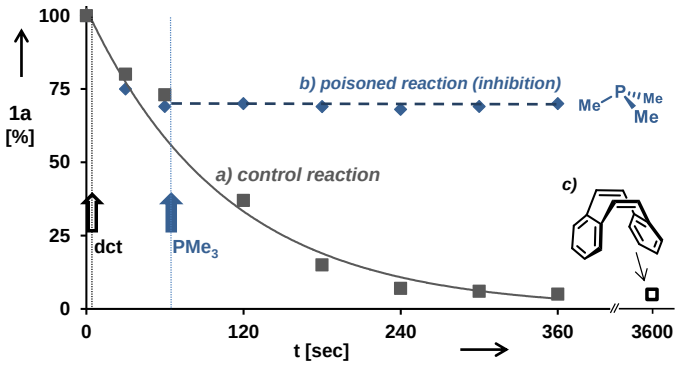
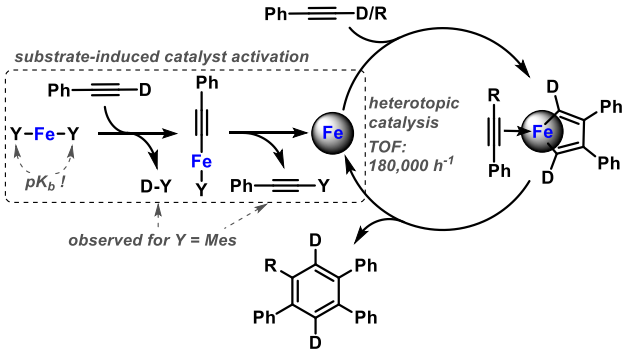


Figure 1. Catalyst poisoning. 4.8 mmol phenylacetylene (1 M in toluene), 1 mol% $Fe(hmds)_2$, -30 °C. *a)* Control reaction; *b)* with 0.5 mol% trimethylphosphine (PMe_3); *c)* with 6 mol% dibenzo[*a*,*e*]cyclooctatetraene (dct).



Scheme 5. Postulated mechanism involving dual catalyst activation and heterotopic cyclotrimerization catalysis.

In summary, we have developed an iron-catalyzed cyclotrimerization protocol that displays unprecedented activity for terminal alkynes under very mild reaction conditions with turnover frequencies reaching 180,000 h^{-1}. The pre-catalyst $Fe(hmds)_2$ does not require the addition of a dedicated reductant but undergoes rapid substrate-induced activation. With such catalyst system, highly regioselective cyclotrimerizations of alkynes to 1,2,4-trisubstituted benzenes proceeded within short reaction times (<2 min) at 20°C in 1 M substrate solution. A most user-friendly procedure can be adopted by simply mixing cheap $FeCl_2$ with the base Li(hmds). Mechanistic studies are indicative of a dual catalyst activation which involves alkyne deprotonation and reductive elimination to a low-valent heterotopic iron catalyst that exhibits long-term stability.

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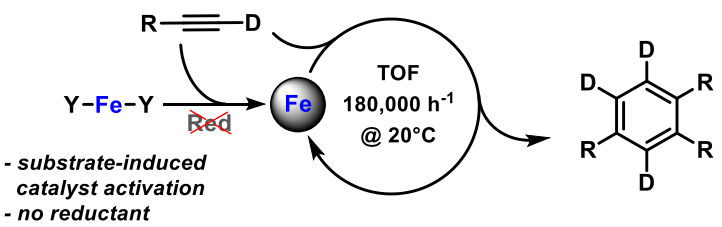
Iron-Catalyzed Cyclotrimerization of Terminal Alkynes by Dual Catalyst Activation in the Absence of Reductants



A new iron-catalyzed cyclotrimerization protocol has been developed. The simple pre-catalyst $Fe(hmds)_2$ does not require the addition of a dedicated reductant but undergoes rapid substrate-induced activation. With such catalyst system, highly regioselective cyclotrimerizations of alkynes to 1,2,4-tri-substituted benzenes proceeded within a few min reaction times at 20°C in 1 M solution. A most user-friendly procedure can be adopted by using $FeCl_2$/$LiN(SiMe_3)_2$. Mechanistic studies are indicative of a dual catalyst activation which involves alkyne deprotonation and reductive elimination to a low-valent heterotopic iron catalyst.

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