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# A Versatile, Functional Group-Tolerant, and Bench-Stable Iron Precatalyst for Building Arene and Triazine Rings by [2+2+2] Cycloadditions

William Parisot,<sup>[a]</sup> Mansour Haddad,<sup>[a]</sup> Phannarath Phansavath,<sup>\*[a]</sup> Guillaume Lefèvre<sup>\*[a]</sup> and Virginie Ratovelomanana-Vidal<sup>\*[a]</sup>

[a] W. Parisot, Dr. M. Haddad, Dr. P. Phansavath, Dr. G. Lefèvre, Dr. V. Ratovelomanana-Vidal, PSL University, Chimie ParisTech, CNRS UMR 8060, Institute of Chemistry for Life and Health Sciences, CSB2D Team, 75005 Paris, France  
E-mail: phannarath.phansavath@chimieparistech.psl.eu; guillaume.lefevre@chimieparistech.psl.eu; virginie.vidal@chimieparistech.psl.eu

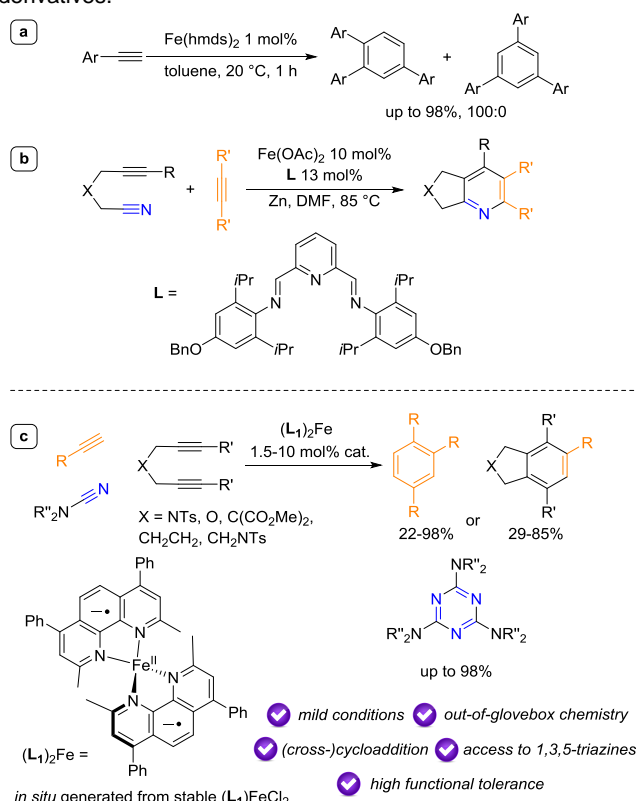
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**Abstract:** We report an efficient iron-catalyzed cycloaddition procedure leading to the construction of (hetero)aromatic rings by alkyne [2+2+2] cycloisomerization. This method relies on the use of an air-stable (*N,N*)Fe(II) precursor easily prepared from a commercially available ligand derived from 1,10-phenanthroline, reduced *in situ* into a catalytically active non-innocent (*N,N'*)<sub>2</sub>Fe(II) species. This system displays a large scope application, operates under mild conditions and at low catalytic charges (25 cycloadducts formed, up to 1.5 mol% catalyst). Moreover, this method also enables access to 29 cycloadducts by cross-cycloisomerization between 1,6- or 1,7-diynes and alkynes in near-equimolar conditions. 1,3,5-Triazines can also be prepared with this procedure starting from the corresponding cyanamides. Scale-up reactions and post-functionalization of several cycloadducts also show that this [2+2+2] cycloaddition can be used in multistep sequences.

## Introduction

Construction of (hetero)aromatic rings by alkyne [2+2+2] cycloadditions is a particularly appealing synthetic tool because it allows access to an important variety of organic compounds in a single, atom-economical step. The field of alkyne [2+2+2] cycloadditions, including the construction of aromatic carbocycles as well as the extension to heterocycles using *N*-containing partners such as nitriles or cyanamides<sup>[1,2]</sup> is however, strongly dominated by the use of noble metal-based catalysts.<sup>[3,4,5]</sup> Rh- or Ru-catalysts predominate in this area, displaying high catalytic activities encompassing a large scope of cycloaddition transformations. As an alternative to the use of such metals, the chemistry of Co- and Ni-mediated cycloadditions is also of particularly high interest, and has witnessed numerous developments during the last decades.<sup>[3,6,7,8,9,10]</sup> Among the 3rd-row metals, iron is a good candidate to overcome cost and toxicity issues associated with other transition metals.<sup>[11]</sup> Iron-mediated cycloadditions remain exceedingly rare,<sup>[12]</sup> however, this field has witnessed recent breakthroughs. Jacobi von Wangelin described highly efficient cycloaddition systems involving Fe<sup>II</sup>[N(SiMe<sub>3</sub>)<sub>2</sub>]<sub>2</sub> as a precursor, activated in the absence of an external reductant (Scheme 1a).<sup>[13]</sup> The same group also reported that the *in situ* generation of reduced active species could be performed under photoredox conditions.<sup>[14]</sup> Webster reported an air-stable salen-stabilized iron(III) precursor activated by pinacol borane, which also efficiently promotes the trimerization of terminal alkynes under mild conditions, the salen ligand being readily accessible in a one-step synthetic procedure.<sup>[15]</sup> Tailor-made multidentate *N*-based pincer ligands derived from pyridine<sup>[16]</sup> or pyrimidine<sup>[17]</sup> have also been reported, the latter example enabling selective

access to 1,3,5-trimers. Several heterocycles, in particular substituted pyridines, also proved to be accessible through Fe-based [2+2+2] cycloaddition strategies, as reported by Louie with novel pyridylbisimine ligands (Scheme 1b)<sup>[18]</sup> or by Wan.<sup>[19]</sup> Later, Louie also reported access to 2-aminopyridines using cyanamides and alkynes as cycloaddition partners involving an iron-based redox-active pyridinedialdimine (PDAI) complex.<sup>[20]</sup> Several iron-mediated cross-[2+2+2] cycloadditions were also reported, leading to the formation of pyridine<sup>[19,21,22,23]</sup> or phosphabenzene rings,<sup>[24,25]</sup> or, more rarely, of benzene derivatives.<sup>[26,27,28]</sup>



**Scheme 1.** Representative milestones in Fe-mediated [2+2+2] cycloadditions for the building of a) carbocycles or b) substituted pyridines; c) this work: construction of carbocycles and heterocycles by [2+2+2] cycloadditions mediated by an *in situ* generated non-innocent iron complex stabilized by a commercially available ligand.

The common feature shared by the majority of the iron-mediated [2+2+2] cycloaddition catalysts is that the catalytic cycle is initiated by highly unstable low iron oxidation states, such as iron(0) or iron(I),<sup>[26,29]</sup> often leading to decomposition pathways such as aggregation to non-active clusters, or redox

disproportionation.<sup>[30,31]</sup> From a synthetic standpoint, it is more convenient to handle stable precatalysts that are reduced *in situ* into catalytically active low oxidation states. Thus, numerous methods have been described using a well-defined, stable iron(II) or iron(III) precursor, and with Zn dust<sup>[18,19,20,32,33]</sup> or Grignard reagents<sup>[16,34]</sup> such as EtMgBr used most commonly as reductants. In some rare cases, iron(II) complexes activated by hydride donors such as pinacolborane remain the active species.<sup>[15]</sup> In our quest to develop new, efficient, and robust iron-based catalysts supported by cheap, commercially available, simple ligands that are easily handled in synthetic procedures, we recently reported that phenanthroline-derived scaffolds substituted at the C4 and C7 positions such as bathocuproine (denoted as **L**<sub>1</sub> in this report) stabilize formally reduced iron(0) atoms. The corresponding homoleptic complex (**L**<sub>1</sub>)<sub>2</sub>Fe is easily obtained *in situ* by reduction of the ferrous precursor (**L**<sub>1</sub>)FeCl<sub>2</sub> with two equivalents of a Grignard reagent. (**L**<sub>1</sub>)<sub>2</sub>Fe displays an original non-innocent coordination pattern and is accurately described as an iron(II) center with two reduced, anionic, bathocuproine ligands (Scheme 1c). Substitution at the C4/C7 positions proved to be a crucial parameter, inhibiting the decomposition of the reduced **L**<sub>1</sub><sup>-</sup> moiety by radical pathways. We reported that (**L**<sub>1</sub>)<sub>2</sub>Fe was an efficient alkyne [2+2+2] cycloaddition catalyst, albeit under thorough air-sensitive, glovebox conditions.<sup>[34]</sup>

Because (**L**<sub>1</sub>)FeCl<sub>2</sub> is readily obtained in a single, quantitative step from commercially available ligand **L**<sub>1</sub> and can subsequently be stored with no need of specific air-sensitive procedures, it appears to be a particularly appealing catalyst for synthetic purposes, because the targeted transformations are carried out with no need of glovebox or drastic air- and moisture-free conditions. In this report, we demonstrate that cycloadditions mediated by *in situ* generated (**L**<sub>1</sub>)<sub>2</sub>Fe can be achieved in such user-friendly conditions. A study comprising 25 alkyne trimers has been performed under mild conditions, with remarkably low 1.5 mol% catalytic loads for some of them and a moderate 75 °C temperature. This method successfully incorporated a wide range of functional groups. A large variety of cross-cycloadditions between 1,6- or 1,7-diynes and alkynes (29 examples) has also been achieved under mild conditions (use of near-equimolar quantities of each cycloaddition partner in some cases), with a particularly large functional group tolerance. Twenty-six new cycloadducts were thus prepared for the first time under iron-catalyzed conditions. Importantly, this method was also extended successfully to the synthesis of substituted 1,3,5-triazines, using cyanamides as starting material with some of the cycloadducts being obtained with a near-quantitative yield, such as altretamine, a potent antineoplastic agent (Scheme 1c, R<sup>1</sup> = Me).<sup>[35]</sup> To our knowledge, this is the first time that 1,3,5-triazines have been prepared using a well-defined iron catalyst. Post-functionalization transformations of cycloadducts obtained with this procedure have also been performed, demonstrating that this method can be included as part of a multistep synthetic scheme. Overall, we report a simple catalytic system, involving a commercially available ligand, allowing access to a wide range of (hetero)aromatic rings through [2+2+2] cycloaddition of alkynes or cyanamides operating under green reaction conditions.

## Results and Discussion

Our investigations started by reacting phenylacetylene **1a** in the presence of 5 mol% precursor (**L**<sub>1</sub>)FeCl<sub>2</sub>, synthesized from commercially available bathocuproine and ferrous chloride in THF (see SI). The catalyst precursor was reduced by reaction with two equiv. of Me<sub>2</sub>C=CHMgBr (**3**) in the presence of one equivalent of **L**<sub>1</sub>, followed by addition of **1a** after 10 minutes at

20 °C. Importantly, the cycloaddition of **1a** was performed outside of the glovebox under a classic argon atmosphere with a perfectly degassed solvent without impacting the yield, and a 95% yield with a 98:2 1,2,4:1,3,5 selectivity was observed for cycloadducts **2a** and **2a'** after 6 h at 60 °C (Table 1, Entry 1). The study was continued on the bench and the catalyst loading was decreased to 3% then 1.5% (Table 1, Entries 2-5). A complete conversion was observed with this lower catalytic charge.

**Table 1.** Optimization of the reaction conditions for the iron-catalyzed [2+2+2] cycloaddition of phenylacetylene

**L**<sub>1</sub> R<sup>1</sup> = R<sup>2</sup> = Me  
**L**<sub>2</sub> R<sup>1</sup> = R<sup>2</sup> = Ph  
**L**<sub>3</sub> R<sup>1</sup> = R<sup>2</sup> = 4-MeOC<sub>6</sub>H<sub>4</sub>  
**L**<sub>4</sub> R<sup>1</sup> = Mesityl R<sup>2</sup> = H  
**L**<sub>5</sub> R<sup>1</sup> = 9-Anthracenyl R<sup>2</sup> = H  
**L**<sub>6</sub> R<sup>1</sup> = Mesityl R<sup>2</sup> = 4-MeOC<sub>6</sub>H<sub>4</sub>

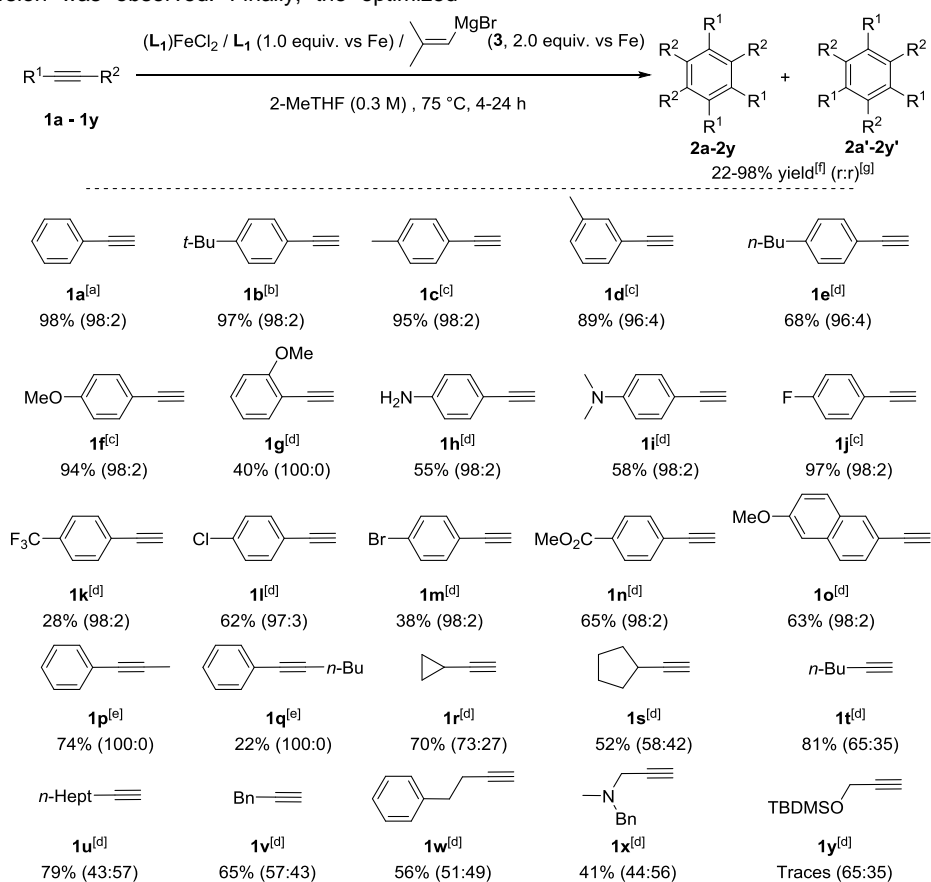
Entry	Solvent	<b>L</b> <sub>x</sub>	Cat. (mol%)	T (°C)	Time (h)	Yield <sup>[a]</sup> (%)	Ratio <sup>[b]</sup> <b>2a</b> : <b>2a'</b>
1	THF	<b>L</b> <sub>1</sub>	5	60	6	95	98 : 2
2	THF	<b>L</b> <sub>1</sub>	3	60	6	92	98 : 2
3	THF	<b>L</b> <sub>1</sub>	3	40	6	85	98 : 2
4	THF	<b>L</b> <sub>1</sub>	1.5	60	8	90	98 : 2
5	THF	<b>L</b> <sub>1</sub>	1.5	80	8	99	98 : 2
6	THF	<b>L</b> <sub>1</sub>	1	60	8	84	98 : 2
7	No solvent	<b>L</b> <sub>1</sub>	1	60	6	21	98 : 2
8	Dioxane	<b>L</b> <sub>1</sub>	1	90	8	86	98 : 2
9	Toluene	<b>L</b> <sub>1</sub>	1	100	8	61	94 : 6
10	2-MeTHF	<b>L</b> <sub>1</sub>	1.5	80	4	98	98 : 2
11	<i>N</i> -Methyl caprolactam	<b>L</b> <sub>1</sub>	1.5	80	4	0	/
12	Anisole	<b>L</b> <sub>1</sub>	1.5	80	4	80	98 : 2
13	1,8-Cineole	<b>L</b> <sub>1</sub>	1.5	80	4	0	/
14	THF	<b>L</b> <sub>2</sub>	5	100	16	35	98 : 2
15	THF	<b>L</b> <sub>3</sub>	5	100	16	72	96 : 4
16	THF	<b>L</b> <sub>4</sub>	5	100	16	98	98 : 2
17	THF	<b>L</b> <sub>5</sub>	5	100	16	97	97 : 3
18	THF	<b>L</b> <sub>6</sub>	5	100	16	0	/

[a] Isolated yield [b] Determined by <sup>1</sup>H NMR of the crude product after cycloaddition.

However, lower catalyst loading did not lead to a full conversion of the substrate (Table 1, Entry 6). The optimal temperature was determined to be 80 °C which allows a full conversion of the phenylacetylene in 8 hours. Cycloaddition attempts were then performed in neat conditions, in dioxane or in toluene (Table 1, Entries 7-9), with no improvement as compared to the conditions optimized in THF. The solvent-free reaction probably led to formation of some unreactive iron aggregates during the reaction, leading to a low yield of 21% (Entry 7). To develop sustainable catalytic conditions, we then examined the possibility to use eco-friendly solvents for this transformation.<sup>[36,37]</sup> Greener conditions are indeed major assets for the catalytic reactions of the near-future synthetic chemistry. With this in mind, 2-MeTHF, *N*-methylcaprolactam, anisole and 1,8-cineole (eucalyptol) were used (Table 1, Entries 10-13). 2-MeTHF was the most suitable solvent for the reaction as eucalyptol and *N*-methylcaprolactam were found to be detrimental to the cycloaddition process and anisole hampered the reaction kinetics. To investigate the stereoelectronic effects of the ligand scaffold, a library of C<sub>2</sub>C<sub>9</sub>-disubstituted bathophenanthroline ligands was synthesized according to reported procedures (see SI), and their performances in the cycloaddition of phenylacetylene were examined (Table 1, **L<sub>2</sub>-L<sub>6</sub>**, Entries 14-18). These ligands underwent an *in situ* complexation with ferrous chloride at 60 °C overnight to afford the (L<sub>x</sub>)FeCl<sub>2</sub> precursor, which was used as a precatalyst under the conditions outlined in the Table. No significant modification of the regioselectivity was observed but poorer cycloaddition yields were obtained. A higher 100 °C temperature was also required to reach a near-quantitative conversion in the case of **L<sub>5</sub>** and with **L<sub>6</sub>** no conversion was observed. Finally, the optimized

conditions for the [2+2+2] cycloaddition of phenylacetylene **1a** were determined to be 1.5 mol% of catalyst in 2-MeTHF at 80 °C for 4 hours providing the desired product with a near-quantitative yield and a regioselectivity of 98:2 (Table 1, Entry 10; for the full optimization table see SI). Consequently, the remainder of the study was conducted with the cheaper and commercially available bathocuproine ligand **L<sub>1</sub>**.

With the optimized reaction conditions in hand, the substrate scope of this [2+2+2] cycloaddition was explored with the pre-catalyst (L<sub>1</sub>)FeCl<sub>2</sub>. The pre-established conditions afforded the expected products from terminal aromatic alkynes **1a-1o** with generally good yields and regioselectivities, the 1,2,4-isomer (**2a-2o**, Scheme 2) being almost exclusively formed. Catalytic loads ranging from 1.5 mol% to 5 mol% were used for all terminal alkynes. We first evaluated the scope of the reaction by reacting electron-rich alkynyl arenes (**1a-1i**, Scheme 2). With 4-*tert*-butyl and 4-methyl groups as substituents, the yields were 97% and 95%, respectively (**1b** and **1c**). Modifying the substituent position (3-methyl) slightly decreased the regioselectivity from 98:2 to 96:4 probably because of a lower electronic density on the alkyne moiety (**1d**). A longer *n*-butyl chain in the *para* position led to a lower 68% yield (**1e**). Substitution by a 4-MeO group led to a 94% cycloaddition yield (**1f**), whereas the 2-MeO isomer only afforded 40% of the expected product (**1g**), probably because of the *ortho* hindrance of the starting alkyne. Notably, unprotected aniline was successfully trimerized by the catalyst with a full conversion (**1h**, 55% isolated yield), meaning that there was no apparent catalyst poisoning by the NH<sub>2</sub> group. A similar 58% yield was obtained for the *N,N*-dimethyl analogue **1i**. We then focused on electron-poor aromatics (**1j-1n**).



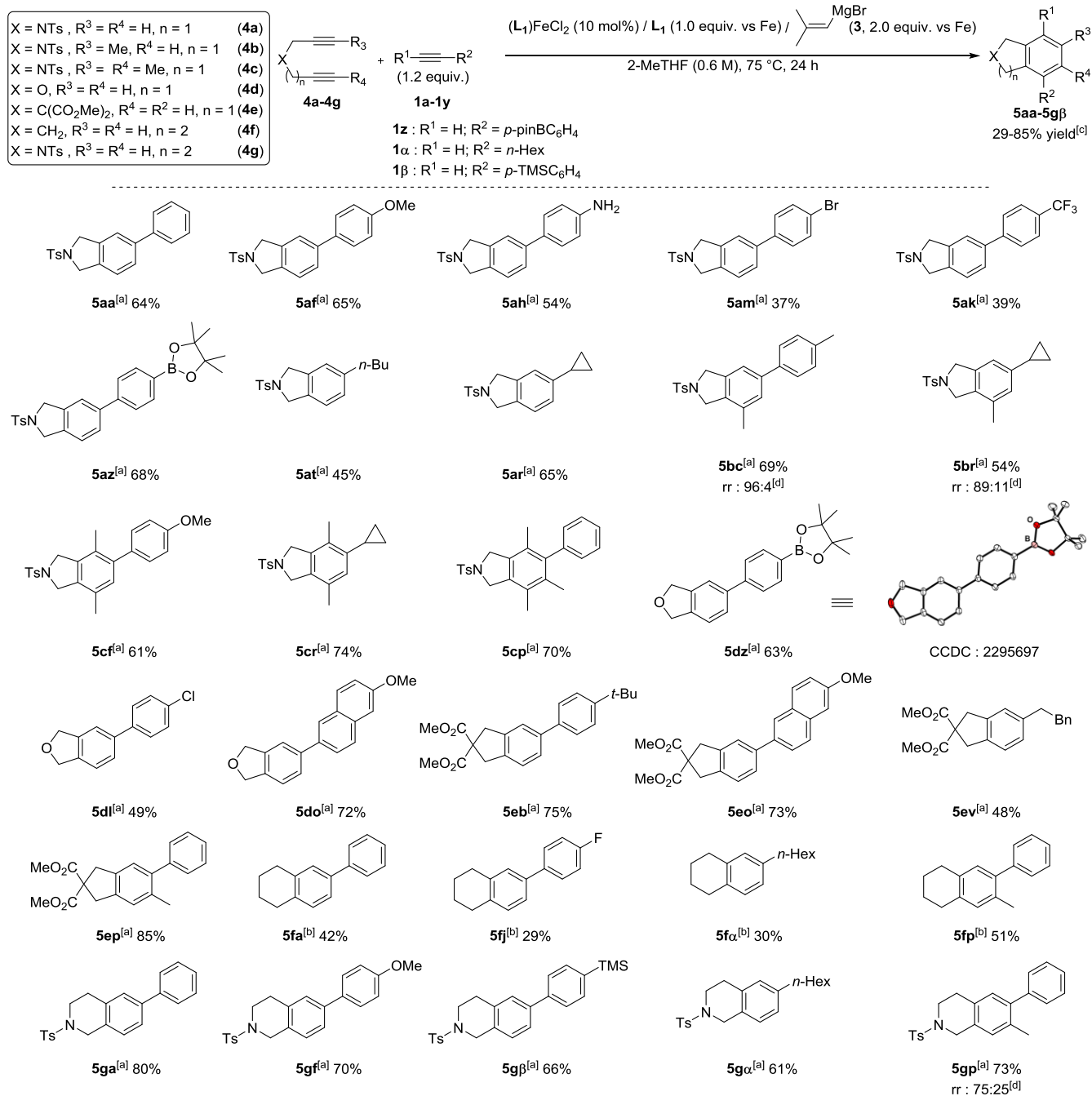
Reaction conditions: [a] (L<sub>1</sub>)FeCl<sub>2</sub> 1.5 mol%, 2-MeTHF (2 mL), 80 °C, 4 h. [b] (L<sub>1</sub>)FeCl<sub>2</sub> 1.5 mol%, 2-MeTHF (2 mL), 80 °C, 8 h. [c] (L<sub>1</sub>)FeCl<sub>2</sub> 2.0 mol%, 2-MeTHF (2 mL), 80 °C, 8 h. [d] (L<sub>1</sub>)FeCl<sub>2</sub> 5.0 mol%, 2-MeTHF (2 mL), 75 °C, 24 h. [e] (L<sub>1</sub>)FeCl<sub>2</sub> 10.0 mol%, 2-MeTHF (2 mL), 75 °C, 24 h. [f] Isolated yield. [g] Determined by quantitative <sup>1</sup>H NMR of the crude product after cycloaddition.

Scheme 2. Scope of the [2+2+2] cycloaddition reaction

Decreasing the electron density of the aromatic ring by substituting a 4-F with a 4-CF<sub>3</sub> group led to a much lower yield and a lower conversion (97% yield for **1j** vs 28% yield for **1k**). The results obtained with the halide substituents showed a correlation between the ease of the C-X bond reduction and the yield. The more easily reduced the C-X bonds (Br > Cl > F), the lower the cycloaddition yield (**1j**, **1l**, **1m**, 38% - 97% yield), which might be attributed to a deactivation of the active reduced catalyst (L<sub>1</sub>)<sub>2</sub>Fe by reduction of the C-X bond. Ester group was also tolerated (**1n**, 65% yield), and hindered aromatic naphthyl derivative was also effectively converted (**1o**, 63% yield). To assess the catalyst limitations further, more sterically hindered

internal alkynes were used. Harsher conditions were required for internal alkynes, and an increase to 10 mol% of catalyst was used (**1p**, 74% yield); however, an incomplete conversion was observed with 1-phenyl-1-hexyne (**1q**, 22% yield). In this case, exclusive formation of the 1,2,4-isomers **2p** and **2q** was observed.

These results encouraged us to investigate an extension of the scope to aliphatic alkynes (**1r-1y**). These non-aromatic substrates ultimately led to lower regioselectivities: the 1,2,4-isomer was still the major compound, but with more balanced selectivities ranging between 73:27 and 51:49; compound **1x** however, led to an inversion of the selectivity, with a 44:56 ratio in favor of the 1,3,5 isomer.

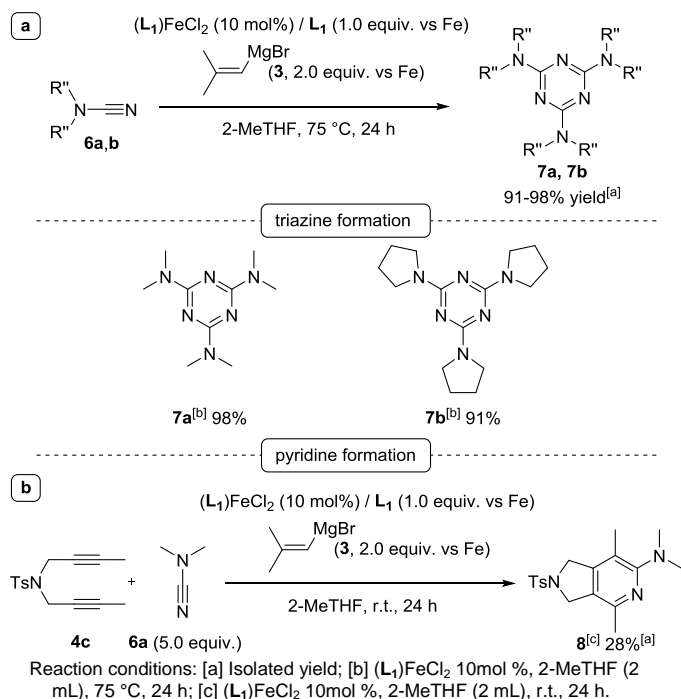


Reaction conditions: [a] (L<sub>1</sub>)FeCl<sub>2</sub> 10 mol%, alkyne (1.2 equiv.), 2-MeTHF (1 mL), 75 °C, 24 h. [b] (L<sub>1</sub>)FeCl<sub>2</sub> 10 mol%, alkyne (3.0 equiv.), 2-MeTHF (1 mL), 75 °C, 24 h. [c] Isolated yield. [d] Determined by quantitative <sup>1</sup>H NMR of the crude product after cycloaddition.

**Scheme 3.** Scope of the cross-cycloaddition [2+2+2] reaction

Aliphatic terminal alkynes provided cycloaddition yields up to ca. 80% (**1t**, 81% yield; **1u**, 79% yield) with a 5 mol% catalytic load. Interestingly, strained cycles such as cyclopropyl and cyclopentyl derivatives were trimerized with 70% and 52% yields, respectively (**1r** and **1s**). Seemingly, a wider (CCC) angle directly linked to the alkyne has a detrimental impact on the yield and regioselectivity. Examples with bulky substituents provided the corresponding product with moderate yields (**2v**, 65% yield, **2w**, 56% yield, and **2x**, 41% yield); however, silylether **1y** only led to traces of the expected cycloadduct.

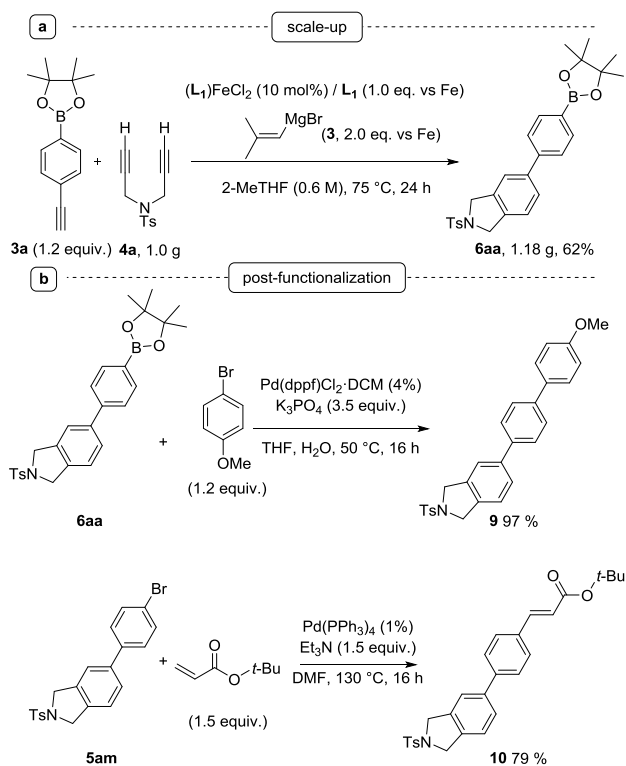
Aiming at introducing more structural diversity using this system, we then explored the [2+2+2] cross-cycloaddition between diynes and alkynes with 10 mol% of catalyst loading (Scheme 3). Starting with the diyne **4a**, homocycloaddition of the latter was observed in the presence of 1.2 equiv. of phenylacetylene as a side reaction. However, operating in a more concentrated medium (0.6 M) led to the formation of the desired isoindoline **5aa** with 64% yield in a 94:6 ratio toward the desired cycloadduct compared to 81:19 at 0.3 M concentration (see SI for the optimization conditions). With those reaction conditions in hand, other alkynyl arenes were tested as cross-cycloaddition partners. Good yields were obtained with electron rich arylated alkynes bearing 4-MeO- and 4-NH<sub>2</sub>- moieties, which provided 65% and 54% yields, respectively (**5af** and **5ah**). Notably, arylated alkynes functionalized with pinacol boronate esters were efficiently converted under those conditions (68%, **5az**), allowing possible Suzuki-Miyaura post-functionalization of the cycloadduct. The formation of **5am** and **5ak** in the presence of electron-poor aromatic alkynes as partners led to lower yields of 37% with the 4-Br and 39% with the 4-CF<sub>3</sub> groups. Use of alkyl alkynes associated with diyne **4a** also led to 45%-65% yields (**5at**, **5ar**). More hindered substrates such as diynes **4b** and **4c** successfully reacted with the alkyne partners. In the case of unsymmetrical diyne **4b**, good regioselectivity was observed, ranging from 89:11 to 96:4 ratios. In the presence of the tolyl moiety, the regioselectivity and the yield were higher compared to the cyclopropyl analogue (69% and 54% yields, **5bc** and **5br**). The disubstituted diyne **4c** provided results comparable to those obtained with the diyne **4a** bearing terminal alkynes. Interestingly, formation of the byproduct arising from the homocycloaddition of the diyne **4c** was not observed because of steric effects (**5cf**, **5cr**, **5cp**, 61% to 74%). This induced an increase of the yield from 65 to 74% (**5ar** and **5cr**) with the cyclopropyl substituent. An internal alkyne was tested to evaluate the method limitations and despite the bulkiness of both diyne and alkyne a remarkable yield of 70% was obtained for **5cp**. Encouraged by these results, we pursued the modification of the diyne scaffold. The proportion of diyne homocycloaddition increased using diyne **4d**. This detrimental effect for the reaction resulted in a decrease of the yield from 68% to 63% (e.g., **5az** and **5dz**, the structure of the latter being confirmed by single-crystal X-Ray diffraction). The chlorinated aryl and sterically hindered naphthyl moieties provided the cycloadducts in 49% (**5dl**) and 72% (**5do**) yields, respectively. Diyne **4e**, whose reactivity is enhanced by a Thorpe-Ingold effect induced by a 3,3'-substitution of the COOMe groups, provided the best yields ranging from 48% to 85% (**5eb**, **5eo**, **5ev**, **5ep**), showing that aliphatic esters were also tolerated by this method. 1,7-Diynes were also successfully tested to produce a new family of 1,2,3,4-tetrahydronaphthalene and 3,4-dihydro-1*H*-2λ<sup>2</sup>-isoquinoline derivatives. Tetrahydronaphthalene derivatives were observed in modest yields from commercially available 1,7-octadiyne. Three equivalents of alkyne were used to attempt to resolve this issue. Despite the use of an excess of the alkyne partner, yields ranging from 29% to 51% were obtained (**5fa**, **5fj**, **5fa**, **5fp**). However, using *N*-Ts substituted 1,7-diyne **4g** led to a significant yield improvement. In all cases only one tetrahydroisoquinoline regioisomer was obtained, using either terminal aromatic or aliphatic alkynes (**5ga**, **5gf**, **5gβ**, **5ga**, 61-80% yield). Internal alkyne PhC≡CMe provided the cycloadduct **5gp** in 73% yield with a regioselectivity of 75:25.



**Scheme 4.** Scope of the cycloaddition with cyanamides

The ability of (L<sub>1</sub>)FeCl<sub>2</sub> to catalyze cycloadditions leading to heterocyclic compounds was further investigated. Promising results were obtained in the presence of dimethylcyanamide **6a** leading to **7a**, a reported potent antineoplastic agent (altretamine)<sup>[35]</sup> in a near-quantitative yield (Scheme 4a). Commercially available pyrrolidine-1-carbonitrile **6b** was also successfully cyclotrimerized in 91% yield (**7b**). Encouraged by these results, the synthesis of a pyridine scaffold using a cross-cycloaddition reaction was explored. Despite our efforts and the use of 5 equiv. of cyanamide per equivalent of diyne, pyridine-2-amine **8** was obtained in a poor 28% yield by slow addition of diyne **4c** at room temperature (Scheme 4b). Alternatively, employing toluene as a solvent as well as a higher temperature promoted the homocycloaddition of the diyne **4c**. On the other hand, using hex-5-ynenitrile (**4h**) was found to be detrimental for the reaction (see SI).

To strengthen the applicability of our method further, a gram-scale cross-cycloaddition leading to cycloadduct **5az** was performed, affording 1.18 g of the purified product with an overall 62% yield, and a small 6% alteration of the yield compared to the result obtained at a 0.6 mmol scale (Scheme 5a). This result also demonstrates that pinacol boronate esters can be tolerated on a large scale using this strategy. Importantly, given the versatility of the aryl pinacol boronate esters and aryl bromide scaffolds, this also shows that the cross-cycloaddition described herein for arene skeleton building can be included in a multistep complex synthesis. For instance, **5az** was subjected to Pd-catalyzed Suzuki-Miyaura cross-coupling as a nucleophilic partner, and **5am** to a Heck coupling with 97% and 79% yields respectively (**9** and **10**, Scheme 5b).



**Scheme 5.** Gram-scale and post-functionalization reactions

## Conclusion

In summary, we have reported a straightforward and efficient access to benzene, triazine, tetrahydroisoquinoline and isoindoline derivatives through an iron-catalyzed [2+2+2] cycloaddition process. The catalytic system relies on the use of an air-stable ferrous precursor that can easily be reduced *in situ* using a Grignard reagent. Stabilisation of the iron catalyst moreover involves a commercially available ligand, making this method easily adaptable to routine bench synthesis. The low catalyst loading and use of 2-MeTHF as a green, bio-based solvent also contribute to make this method an eco-compatible cycloaddition process. Benzene derivatives as well as several heterocycles were obtained by cycloaddition of a large variety of alkynes, as well as by cross-cycloaddition of 1,6 and 1,7-diyne with alkynes. Application to the synthesis of heterocycles of biological interest such as altretamine was performed. The method described herein is also tolerant of a large range of functional groups and provides rapid access to valuable building blocks. Further possible post-functionalizations can be envisaged at a preparative scale. For example, this method can also lead to promising developments in the synthesis of useful monomers in the COF (Covalent Organic Framework) or CTF (Covalent Triazine Framework) fields at large scales.<sup>[38]</sup>

## Experimental Section

Typical procedure for complex  $(L_1)FeCl_2$  synthesis:

In a 25 mL round bottom two necked flask equipped with a magnetic stirring bar was added  $FeCl_2$  (78 mg, 0.62 mmol, 1.00 equiv.) and bathocuproine (222 mg, 0.62 mmol, 1.00 equiv.). Three vacuum/argon cycles were made (1, 5, 10 min) with a greased glass stopper. Under an argon flux the glass stopper was replaced by a folding skirt stopper, then anhydrous and degassed 2-MeTHF (6 mL) was added. Under an argon flux the rubber stopper was exchanged with a greased glass stopper

and the reaction mixture was stirred at 75 °C overnight. The solution was left at room temperature (~20 °C) and orange crystals were observed. The resulting mixture was concentrated under reduced pressure, affording complex  $(L_1)FeCl_2$  quantitatively as an orange solid which was used without further purification. Spectroscopic data matched with literature.<sup>[34]</sup>

Typical procedure for cycloadditions:

A 10 mL round bottom two-necked flask was charged with  $(L_1)FeCl_2$  (29.2 mg, 0.06 mmol, 1.00 equiv.) and bathocuproine ( $L_1$ ), 22.6 mg, 0.06 mmol, 1.00 equiv.). Three vacuum/argon cycles were performed (1, 5, 10 min) with a greased glass stopper. Under an argon flux the glass stopper was replaced by a folding skirt stopper, then anhydrous and degassed 2-MeTHF (1~2 mL) was added followed by 2-methyl-1-propenylmagnesium bromide (0.5 M in THF, 240  $\mu$ L, 0.12 mmol, 2.00 equiv.). The resulting purple solution was stirred at room temperature for 10 minutes, then the corresponding alkyne (1.20 mmol ~ 3.99 mmol, 20.0 ~ 66.6 equiv.) was added. Under an argon flux the rubber stopper was exchanged with a greased glass stopper, the brown mixture was heated to 75 °C and was stirred for 8 to 24 h. The solution was allowed to reach room temperature (~20 °C) and quenched with 2 mL of water before 10 mL of HCl (1 M) were added. The resulting mixture was extracted with 2-MeTHF (3 x 10 mL). The combined organic layers were washed with brine (1 x 20 mL) then dried over magnesium sulfate, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with an eluent system depending on the polarity of the product, to afford the pure cycloadduct (28-98% yield).

Deposition Number <https://www.ccdc.cam.ac.uk/services/structures?id=doi:10.1002/chem.202400096> CCDC2295697 (for **5dz**) contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe <http://www.ccdc.cam.ac.uk/structures> Access Structures service

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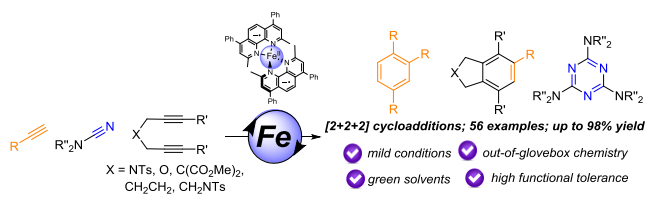
**Keywords:** Cycloaddition • Catalysis • Iron • Alkynes • Diynes • Triazines

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A new [2+2+2] cycloaddition procedure relying on the use of an air-stable iron precatalyst is described, which allows the construction of aromatic and nitrogen-containing heteroaromatic rings in green solvents and mild conditions. Cycloadditions and cross-cycloadditions between 1,6- or 1,7-diynes and alkynes are reported, with a broad functional tolerance, leading to a variety of functionalizable scaffolds.