

Aza-annulation reactions extend π -conjugated systems

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Iron-catalysed C–H activation enables the aza-annulation of extended π -conjugated systems to access N-doped polycyclic aromatics with outstanding optoelectronic properties.

Polycyclic aromatic hydrocarbons (PAHs) are well-known players in the fields of organic optoelectronics and semiconductors, however, new materials with better tailored properties are always in demand for applications. The incorporation of heteroatoms into extended π -conjugated polycyclic systems is an attractive skeletal manipulation for tuning molecular properties through changing the type of heteroatom used, doping position and concentration¹. The development of robust, high-yielding, and sustainable synthetic methods to precisely control these structural features is key for advancing organic optoelectronics towards real-world applications. Many transformations that satisfy these requirements in the synthesis of heteroatom-doped larger aromatics rely on the use of efficient annulative ring-forming reactions on extended π -systems. Among these, C–H-activation pathways are increasingly preferred, as they eliminate the need for highly pre-functionalized arenes providing atom- and step-economic processes². However, C–H activation reactions involving extended aromatic systems present some obstacles. These reactions often require expensive noble metal catalysts, so face sustainability challenges. Furthermore, aromatic polycycles can readily coordinate to metal centres^{3,4} that may suppress catalytic efficiency. This effect could decrease selectivity and yield, which limits practicality, and could be restrictive regarding the size of the accessible heteroatom-doped PAHs, which sets a limit to accessible properties.

Now, writing in *Nature Synthesis*, Rui Shang, Eiichi Nakamura and co-workers report an iron-catalysed aza-annulation π -extension reaction between aromatic oxime ethers and alkynes (Fig. 1a) that addresses the challenges above. This C–H activation-based method enables the expansion of the chemical space of N-doped PAHs facilitating discoveries in organic optoelectronics⁵.

The success of this method is a result of the optimal interplay of design features: the structure of the starting material, and choice of catalyst and base. The key functional group in the substrate is an oxime methyl ether, which serves multiple roles: a nitrogen source in the reaction, a directing group in the catalytic C–H activation step, and as an internal oxidant for catalyst turnover^{6,7}. Their simple preparation via condensation of N-methoxy amine with commercial or easily accessible aromatic carbonyl compounds, in the presence of a Lewis acid, is a notable advantage.

An important consideration in C–H activation reactions on extended π -systems is the often strong bonding and back-bonding interaction of the PAH substrates and the catalytic metal. Overcoming

this undesired effect is crucial, therefore the catalyst and ligand must act in a way such that the metal–substrate interaction is minimized, while the peripheral C–H site of interest remains accessible for the metal. As a result of extensive optimization efforts^{8,9}, a bulky trisphosphine (TP) ligand was chosen (Fig. 1b) that satisfies these requirements and ensures high catalytic efficiency and selectivity.

The mildly nucleophilic organoaluminium species, isobutyl aluminium(III) catecholate, was identified as an optimal base for the C–H deprotonation step. Due to the catecholate coordination and the bulky alkyl group, C–H alkylation by the organoaluminium reagent is suppressed compared to trialkyl aluminium compounds⁹, allowing for reaction with an external alkyne reagent. Notably, Al(III)-catecholate, apart from acting as a base, may participate in stabilizing interactions with transient organoiron species in the catalytic cycle, which warrants further studies to fully understand the catechol effect on the overall transformation.

Control experiments show all the reaction components are essential for the process to occur and allow a mechanism to be proposed (Fig. 1c) in which the alkyl Al(III)-catecholate facilitates the formation of ferracycle **I** through transmetalation and subsequent C–H deprotonation. The insertion of an alkyne reagent into the Fe–C bond in **I** follows, leading to the seven-membered ferracycle **II**, which upon reductive elimination yields N-methoxy pyridinium **III**. This pyridinium species acts as an oxidant to ensure catalyst turnover.

The method is tolerant of a range of substrates and can provide access to structurally diverse aza-arenes (Fig. 1d), of which several are currently inaccessible with alternative catalytic systems. Amongst others, oxime ethers derived from acridinone, (thio)xanthone, and anthrone provide the aza-annulated products quantitatively, while seven-membered ring containing dibenzosuberone also transformed in high yield. A notable example is the synthesis of a bischromenoisoquinoline type helicene, showcasing that the reaction is also able to access distorted π -frameworks. The use of this method is highlighted through the two-fold and four-fold annulation of (hetero)pentacenone derived oxime ethers. The careful ligand design is especially key here. As is clear from the high overall yields, including gram-scale product synthesis, the polycyclic conjugated substrates do not impede the catalysis through metal-coordination. Furthermore, the bulky ligand provides high regioselectivity, as the C–H bond cleavage occurs on less sterically hindered sites. Regarding the alkyne reagents, both diaryl and dialkyl acetylenes are tolerated. Additionally, unsymmetrically substituted alkynes could be used as substrates, forming the corresponding products with high regioselectivity, dictated by the bulky TP ligand.

Preliminary physico-chemical investigations reveal that the larger aza-arenes comprising the electron-accepting imine-type nitrogens are narrow-band emitters. Notably, the tetraannulated pentacene derivative (R=Ph, Fig. 1d) is a deep blue emitter, which – paired up with its high ambient stability – makes it potentially useful for organic light-emitting diode applications^{10,11}.

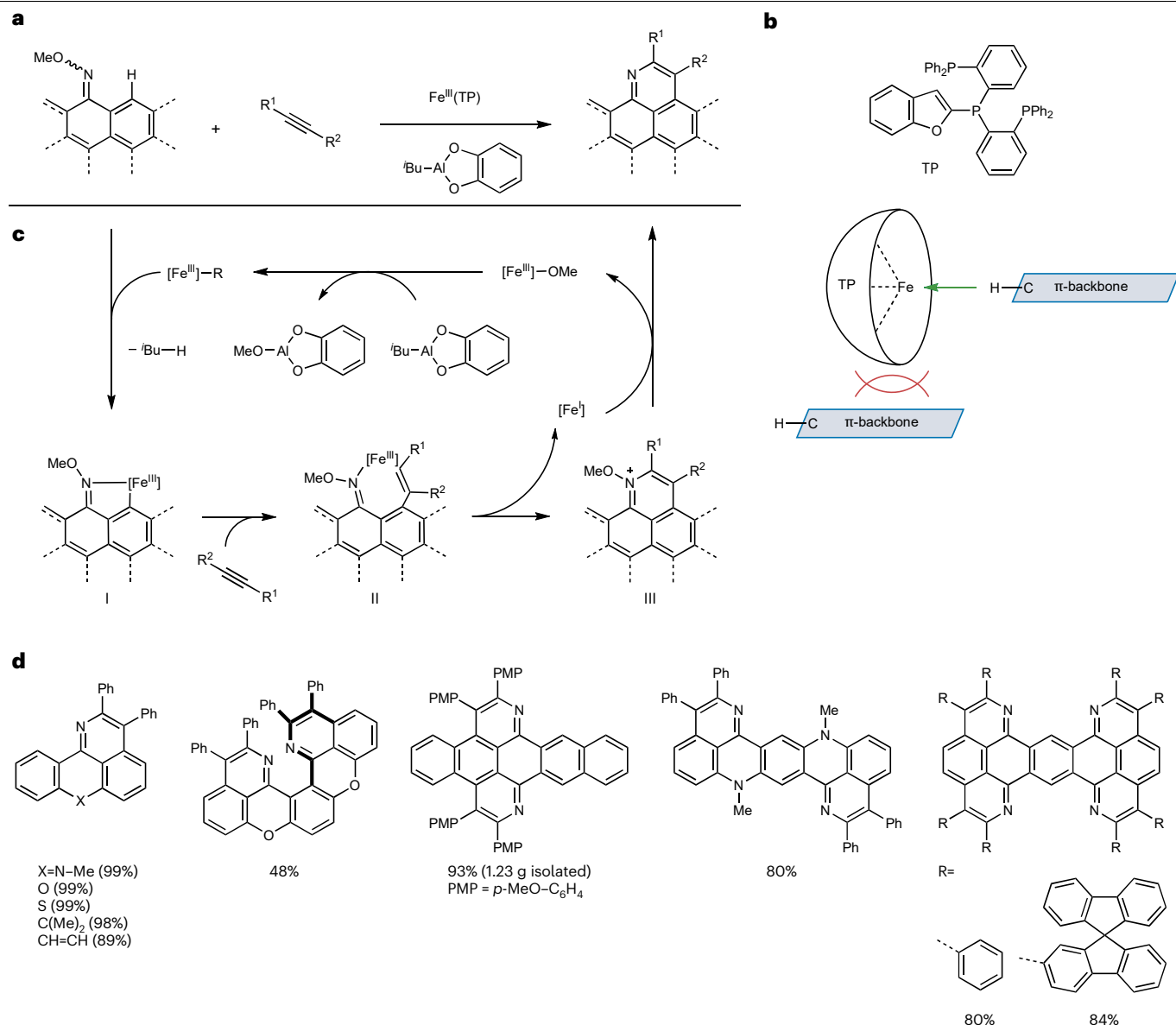


Fig. 1 | Aza-annulation through iron-catalysed C–H activation. **a**, Key components for the iron-catalysed, oxime-directed aza-annulation reaction between oxime methyl ethers and alkynes. **b**, Ligand design for the transformation. The Fe/TP catalyst protects the metal from arene coordination

and facilitates the activation of peripheral C–H sites. **c**, Proposed mechanism of the catalytic cycle. **d**, Examples of accessible products that showcase the structural diversity enabled by the reported methodology.

While this reaction provides a considerable structural diversity and distinct optoelectronic properties, there are some limitations. Along with relatively high catalyst loading, 10 mol%, the reactions require harsh conditions to proceed, 140 °C and 24 h, which might be incompatible with more sensitive functional groups. Furthermore, the low ambient stability of organoaluminium compounds could technically complicate the transformations. On a more conceptual level, the understanding of the described catechol effect and the systematic description of metal–arene interactions in iron catalysis warrants further studies.

Overall, this iron-catalysed aza-annulation reaction reported by Shang, Nakamura and co-workers is a valuable addition to the synthetic

toolbox of organic materials chemistry. Research areas that will benefit from a short and high-yielding synthesis of aza-arenes span supramolecular chemistry, optoelectronic materials, and aromaticity. Additionally, the general catalysis and ligand design concepts learned here will serve as a ground for the development of new and sustainable synthetic methodologies.

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Competing interests

The authors declare no competing interests.