# Catalytic synthesis of azoarenes via metal-mediated nitrene coupling

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# Catalytic synthesis of azoarenes via metal-mediated nitrene coupling

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## Abstract

Various valuable properties of azoarenes ("azo dyes"), including their vivid colors and their facile *cis-trans* photoisomerization, lead to their wide use in the chemical industry. As a result, ~700,000 metric tons of azo dyes are produced each year. Most currently utilized synthetic methods towards azoarenes involve harsh reaction conditions and/or toxic reagents in stoichiometric amounts, which may affect selectivity and produce significant amounts of waste. An efficient alternative method towards this functional group includes transition metal catalyzed nitrene coupling. This method is generally more sustainable compared with most stoichiometric methods as it uses only catalytic amounts of co-reactants (metal catalysts), requires easily synthesizable organoazide precursors, and forms only dinitrogen as a by-product of catalysis. During the last decade, several catalytic systems were reported, and their reactivity was investigated. This perspective article will review these systems, focusing on various nitrene coupling mechanisms, and the substrate scope for each system. A particular attention will be devoted to the iron-alkoxide catalytic systems investigated in the PI's laboratory. A design and structural features of several generations of iron bis(alkoxide) complexes will be discussed, followed by the structure-activity studies of these catalysts in nitrene homo- and heterocoupling.

## Introduction

Azoarenes (azo compounds) are organic compounds containing ArN=NAr functional group bearing aryl (or related) substituents (see **Fig. 1** for selected examples of azoarenes). Azoarenes are brightly colored and are commonly used as dyes.[1,2] The presence of the N=N double bond allows azoarenes to exhibit *cis-trans* isomerism in the presence of light and/or at elevated temperatures.[3-7] While the *trans* isomer is generally more stable, the *cis* isomer exhibits varying stability (from seconds to years) as a function of azoarene substituents.[8] The change in geometry is usually accompanied by a change in color and the overall 3D structure of the molecule. The photo- or thermoswitchable isomerism can be manipulated by choosing different aryl substituents.[9-12] The ability to fine-tune the *cis-trans* isomerism makes the azoarene functionality an excellent candidate in the field of photoswitches.[13, 14] Azobenzene-based photoswitches are used in many applications including polymers, biomolecules, light-gated glutamate receptors (MAG), photoactive Brønsted bases, energy storage materials, and liquid crystals.[15-26] Additionally, azobenzene derivatives such as Congo Red and Sulfasalazine have been used for various biomedical applications.[27] Selected examples of azoarene derivatives are provided in **Fig. 1**.[19, 23, 27]

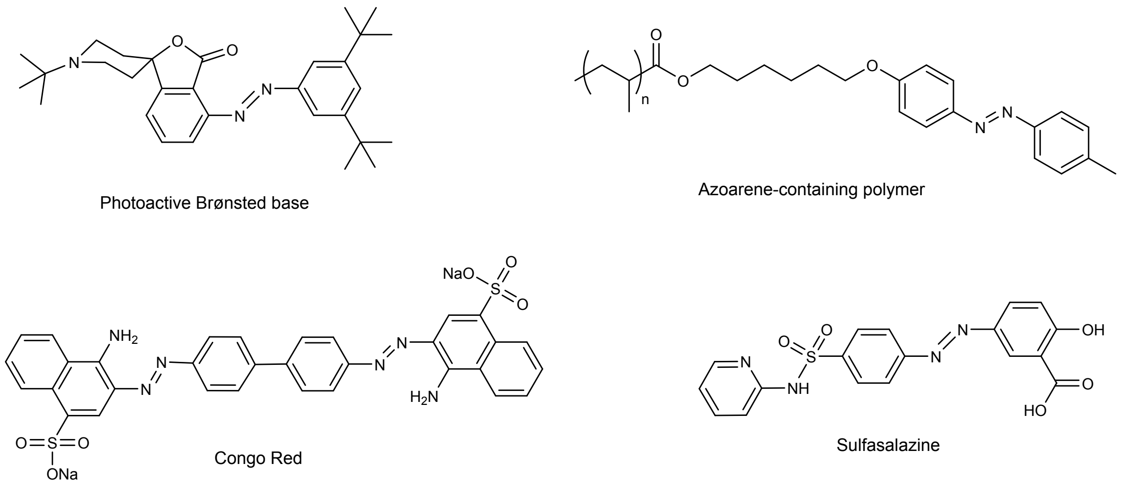

**Fig. 1** Examples of compounds containing an azo functional group.

Many different synthetic routes to azoarenes have been reported in the literature.[28] Azo coupling reaction, Mills and Wallach methods, oxidative coupling of anilines and reductive dimerization of nitro compounds are among the most commonly used routes towards azoarenes (see **Fig. 2** for selected examples of the methods described above).[28] Azo coupling reaction proceeds via an electrophilic aromatic substitution between a previously diazotized aniline (electrophile) and an electron-rich aromatic ring (nucleophile).[28] This reaction generally takes place at the *para* position of the electron-rich ring. Mills method involves the synthesis of nitroso arenes from methylhydroxyl amines.[28, 29] The nitroso derivative is then coupled with aromatic amines to obtain the desired azoarene. In the Wallach reaction, azoxybenzene is converted to azoarene using sulphuric acid.[28, 30] Oxidative dimerization (coupling) of anilines is a general and commonly used method that typically employs a stoichiometric amount of oxidant (such as AgO, $HgO/I_2$, $H_2O_2$, $KO_2$, $Pb(OAc)_4$ and many other reagents).[28] Different mechanistic pathways have been proposed for this reaction. For example, the oxidative coupling involving $HgO/I_2$ is proposed to undergo via initial one-electron oxidation of aniline to give cation radical, which undergoes dimerization to give diphenylhydrazine and subsequent oxidation to give azobenezene.[28] Reductive coupling of nitro compounds is another relatively general method that requires stoichiometric amounts (excess) of a reducing reagent (such as $LiAlH_4$, Zn/NaOH, $Pb/HCO_2NH_4$ etc).[28] Reductive coupling of nitro compounds was postulated to proceed via the initial formation of nitroso, followed by the formation of radical anion, dimerization and dehydration.[28] The formation of azobenzene is also possible through a direct thermolysis of azides, albeit this reaction is generally not very efficient, producing azoarenes in relatively low yields.[28, 31] Many other stoichiometric methods towards azoarenes exist; this field has been recently reviewed by Merino.[28]

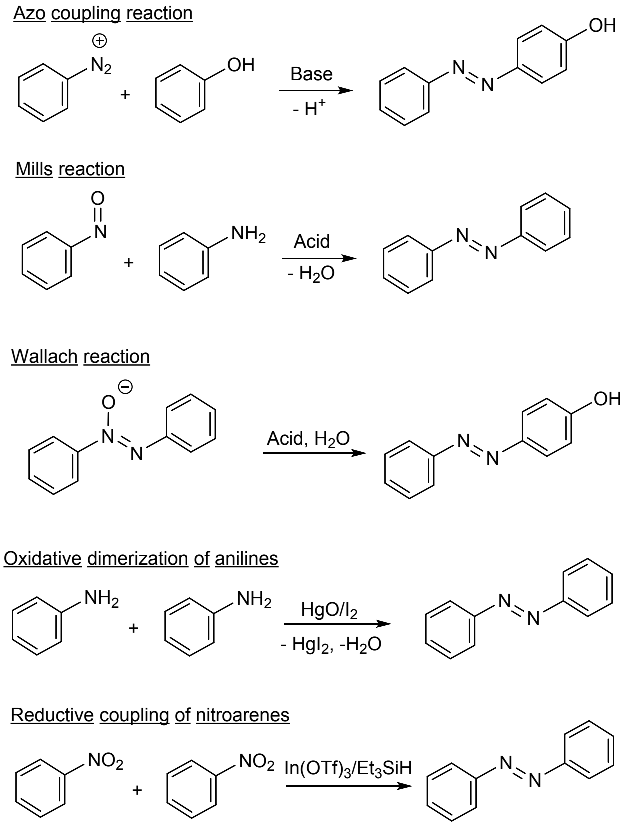

**Fig. 2**. Selected examples of the common synthetic routes towards azoarenes.

As described above, azoarenes are widely used in the chemical industry and have even more potential large-scale applications. However, the existing synthetic routes towards this functional group are often wasteful, commonly require harsh reaction conditions, and produce significant amounts of harmful by-products. Furthermore, these methods often require specific combinations of electron-rich/electron-poor aromatic rings, and take place only in very specific (*ortho*/*para*) positions, thus producing limited types of azoarenes. An alternative and more general route involves transition metal-mediated nitrene-transfer (coupling) catalysis (**Fig. 3**). For the combination of inexpensive base transition metals (Mn, Fe, Ni) with conveniently obtained "green" precursors (most notably, organoazides), this route offers the advantage of sustainability that is of paramount importance in the contemporary chemical synthesis.

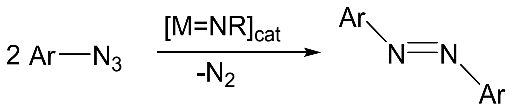

**Fig. 3** Azide-derive nitrene homocoupling to produce azoarenes.

This perspective article will present the emerging field of nitrene coupling catalysis. The focus will be on the catalytic synthesis of azoarenes using organoazide-derived metal-nitrenes (metal-imidos), the nature of the reaction intermediates, and the substrate scope of various catalysts. We will begin by discussing general requirements for a successful nitrene transfer/coupling catalyst. The presentation of the initial (stoichiometric) discoveries in the field will be followed by the discussion of structure/activity relationships and mechanisms of various catalytic systems. As this is a personal perspective, particular emphasis will be put on the iron-alkoxide nitrene coupling catalysis pursued by the authors' lab.

## Nitrene transfer via metal-imido intermediacy: Metal-imido formation, bonding, and reactivity

Transition-metal-mediated nitrene homocoupling requires prior synthesis of a reactive transition metal-nitrene (imido) complex. Therefore, some elaboration of metal-nitrene/imido chemistry is necessary prior to focusing on nitrene homocoupling. Transition-metal nitrene complexes are a convenient instrument for the transfer of nitrenes [NR] to various substrates under mild reaction conditions. A general route towards metal-nitrene (metal-imido) functionality involves the reaction of a metal precursor [M] with a nitrene precursor [X=NR] to form [M=NR] intermediate (**Fig. 4**).[32-34] Of the different nitrene precursors that had been developed over the years, organoazides are most commonly used due to their ease of synthesis and their sustainable nature, as they produce only $N_2$ as a by-product.[35-37] The reaction is formally an oxidation of the metal center, thus generally requiring formally reduced metal precursors. Upon formation, a reactive metal-imido can undergo a nitrene-transfer reaction with substrates such as alkenes, alkynes, isocyanides, CO, and C-H bonds to form the corresponding products and to restore the formally reduced metal catalyst as shown in **Fig. 4**. One of the possible nitrene acceptors is another nitrene functionality (Y = [NR]), which leads to formal nitrene homocoupling to produce azoarene.

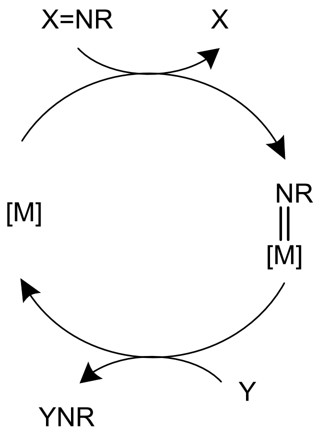

**Fig. 4** Catalytic cycle of nitrene transfer employing formally metal-imido intermediate. X = $N_2$, IPh; Y = CNR, CO, $R_2C=CR_2$, C-H, [NR]

The electronic structure and the reactivity of the metal-imido functional group depend on the combination of a transition metal, complex geometry, and an ancillary ligand. As a diverging focus of this article does not permit us to go into details of the electronic structure of metal-nitrene/imido complexes, it must suffice to notice here that the more reactive metal-nitrene complexes involve middle and late transition metals in medium and low oxidation states. Interested reader is referred to several excellent reviews discussing the electronic structure and the reactivity of transition metal imidos/nitrenes as a function of the transition metal and the complex geometry.[38-41] The nature of ancillary ligands also plays a significant role in the stability of metal-imidos. Strong-field soft ligands (e.g., phosphines or unsaturated ligands) demonstrate σ donating and π accepting properties, compatible with the π-donating nature of the imido. When installed at the late metals, these ligands often yield more stable low-spin metal-imidos, many representatives of which have been isolated and structurally and spectroscopically characterized.[38-41] In contrast, weak-field hard ligands (e.g., alkoxides, amides, and related ligands) are π-donors; their π-donation further competes with π-donation from the imido.[37, 42] As a result, these ligands are likely to destabilize metal-nitrene functionality and yield less stable complexes but more reactive nitrene-transfer catalysts.

## Formation of azoarenes (and related products) via nitrene coupling: stoichiometric examples

Azoarene formation via nitrene homocoupling is a relatively common minor side reaction in the chemistry of reactive metal-nitrene complexes. However, it is relatively uncommon to observe high-yielding nitrene homocoupling, particularly in systems that demonstrate other reactivity pathways for the nitrenes. In an early example, Decker and Knox reported that treatment of $Fe_2(CO)_9$ with phenyl azide leads to the formation of $[Fe_2(CO)_4(\mu_2\text{-}N_2Ph_2)]$, among other products.[43] Conducting a mechanistic study, Hansert and Vahrenkamp demonstrated that the reaction proceeded via a 1,4-tetrazene intermediate $[Fe(CO)_3(N_4Ph_2)]$ that underwent subsequent reaction with another equivalent of $Fe_2(CO)_9$ (under UV) to produce $[Fe_2(CO)_4(\mu_2\text{-}N_2Ph_2)]$ and $N_2$ (**Fig. 5, top**).[44] In a related example, Hillhouse and coworkers have reported that [(dtbpe)Ni(=NR)] (R = Mes, Ad) reacts with $N_3R$ to produce RN=NR.[45] Computational and mechanistic studies suggested that the reaction proceeded via an initial 1,3-dipolar addition to give a 1,2-tetrazene intermediate $[(dtbpe)Ni(N(R)N(R)N_2)]$ that produced diazene RN=NR and $N_2$ upon decomposition (**Fig. 5, middle**). Albeit the diazene was produced in a high yield, the reaction was not catalytic due to the coordination of the diazene to the Ni(0) product. Heyduk and coworkers reported that a dinuclear bis(imido) Ta(V) complex $[ONO]_2Ta_2(\mu_2\text{-}NAr)_2py_2$ formed the corresponding azoarene ArN=NAr (Ar = 4-$MeC_6H_4$) upon oxidation with $PhICl_2$ (**Fig. 5, bottom**).[46] The reaction is accompanied by the formation of Ta(V) by-product $[ONO]_2Ta_2Cl_4(py)_2$ and is likely facilitated by the redox-active nature of [ONO] ligand. Same system was found later to serve as a catalyst for the formation of azobenzene from phenyl azide (5 equivalents of azobenzene over 7 days at 55 °C).[47] Mansuy and coworkers reported that treatment of the formally Fe(IV) porphyrin complex (TPP)Fe(=N-NR) (TPP = tetraphenylporphyrin, NR = 2,2,6,6-tetramethylpiperidyl) with pyridine forms the corresponding tetrazene RN-N=N-NR and (TPP)$Fe^{II}(pyridine)_2$.[48]

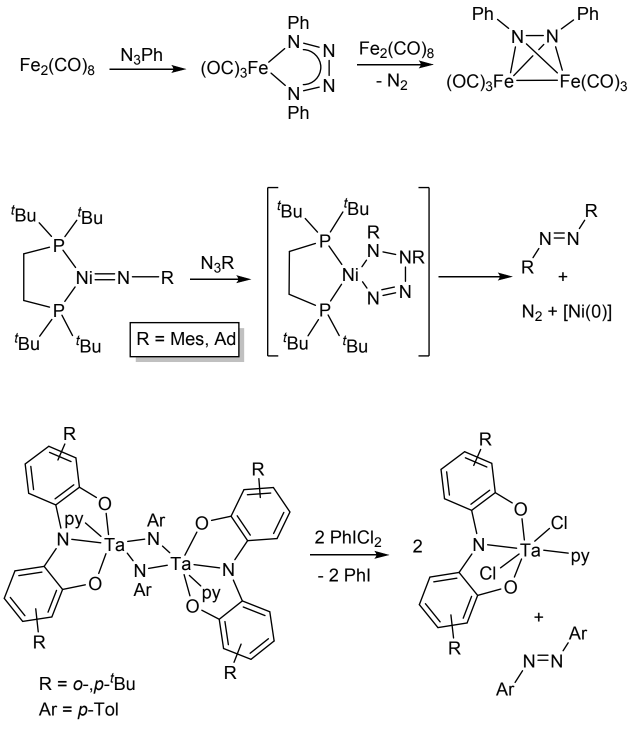

**Fig. 5** Selected examples of nitrene homocoupling.

## Nitrene homocoupling: development of the catalytic systems

An early example of catalytic azoarene formation using transition metal catalysis was described by Cenini and coworkers as part of their studies on Co-porphyrin-mediated C-H activation.[49] Cenini and coworkers reported that various Co(II) porphyrin complexes (1 mol%) catalyzed amination of benzylic C-H bonds, with aryl azides as nitrene precursors. Along the expected benzylic amine and imine products, they also detected the formation of the corresponding azoarene as a significant by-product. For some of the azides (for example, 4-$FC_6H_4N_3$), azoarenes were the major product. Catalysis in the absence of benzylic substrates led to the formation of azoarenes only, in varying yields. Interestingly, kinetic study led the authors to conclude that while the amination proceeds directly via the organoazide adduct, azoarene formation requires first $N_2$ extrusion and the formation of the Co-nitrene complex, which reacts with an azide to form an azoarene (**Fig. 6**).

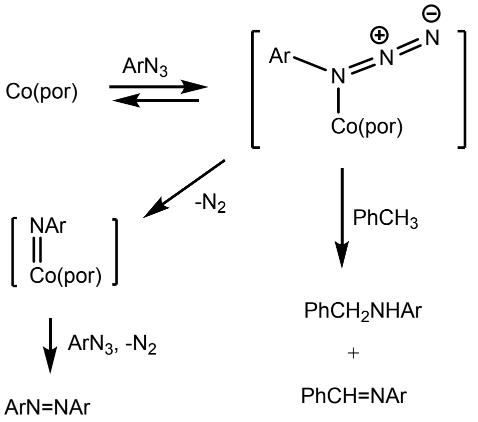

**Fig. 6** Reactivity of cobalt-porphyrin catalysts in the amination of benzylic C-H bonds and nitrene homocoupling. Por = tetraphenylporphyrin (and its derivatives) and octaethylporphyrin.

Peters and coworkers discovered that trigonal bipyramidal iron and ruthenium complexes in triphosphinosilyl ligand $[SiP_3]$ environment catalyzed nitrene homocoupling. Upon reaction with adamantyl azide, iron(I) precursor $[SiP^{iPr}_3]Fe(N_2)$ formed structurally characterized complex $[SiP^{iPr}_3]Fe(N_3Ad)$ in which the azide was bound $\eta^1$ through $N_\gamma$ (**Fig. 7**).[50] The reaction of $[SiP^{iPr}_3]Fe(N_2)$ with aryl azides (Ar = Ph, 4-$MeC_6H_4$, 4-$MeOC_6H_4$, Mes) led to the formation of azoarenes. Using catalytic amounts of $[SiP^{iPr}_3]Fe(N_2)$ (5 mol%), these aryl azides were converted into the corresponding azoarenes at 70 °C in moderate yields (44-57%). The reaction was proposed to proceed via the initial coordination of azides to the metal (similar to $N_3Ad$). The azide subsequently underwent $N_2$ extrusion to form reactive transient Fe(III) imido $[SiP^{iPr}_3]Fe(NAr)$ (**Fig. 7**). The reactive nature of the iron(III)-imido functionality in $[SiP^{iPr}_3]Fe(NAr)$ was ascribed to the trigonal bipyramidal geometry, which diminishes its multiple bond character. As a result, it undergoes bimolecular coupling to form azoarene.

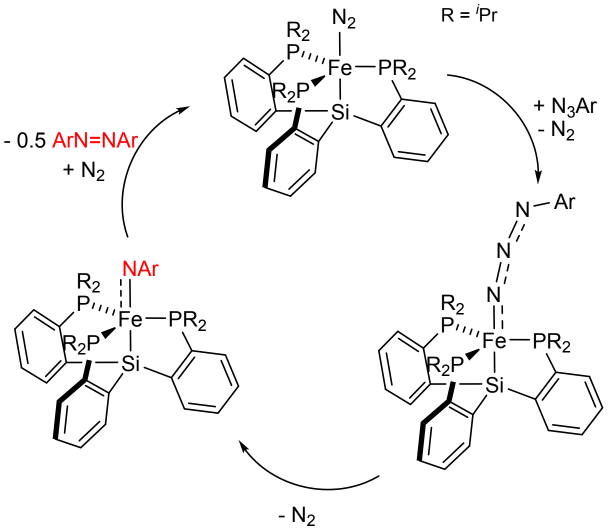

**Fig. 7** Mechanism for the formation of azoarene using $[SiP^{iPr}_3]Fe(N_2)$ precatalyst.

The Ru analogue was also found to catalyze nitrene homocoupling efficiently for the electron-rich azide precursors (4-$MeOC_6H_4N_3$ and 4-$EtOC_6H_4N_3$).[51] However, a different mechanism was proposed for the ruthenium system (**Fig. 8**). In contrast to the reactive transient Fe(III) imidos $[SiP^{iPr}_3]Fe(NAr)$, which undergo four-electron reductive coupling to give azoarenes, Ru(III) imidos $[SiP^{iPr}_3]Ru(NAr)$ were found to be stable and did not produce azoarenes. Following the series of mechanistic experiments, the authors concluded that azoarene production in the ruthenium system proceeded via the formation of free (triplet) aryl nitrene, which underwent direct coupling with itself or with a corresponding azide. It should be noted that the authors have also ruled out coupling mechanism involving the reaction between a coordinated nitrene and an azide, as described above for the Co-porphyrin system.[49] Related nitrene formation from an $\eta^1$-bound (electron-rich) azide and subsequent capture to give azoarene or V(V)-imido was observed by Chang and coworkers.[52]

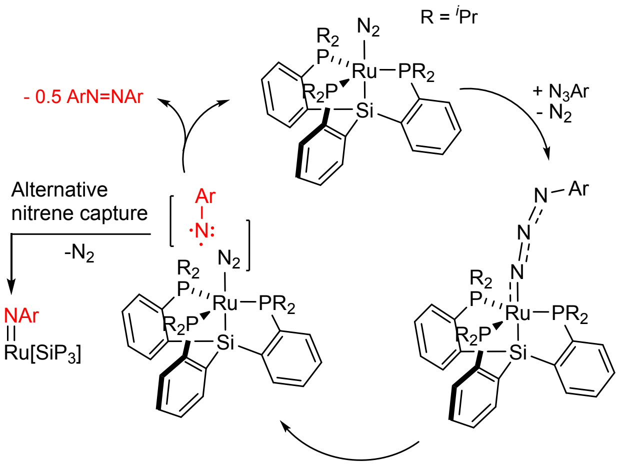

**Fig. 8** Mechanism for the formation of azoarene using $[SiP^{iPr}_3]Ru(N_2)$ precatalyst.

Uyeda's group carried out an extensive investigation on the reactivity of various mononuclear formally nickel(0) complexes in azoarene synthesis.[53] Their experimental results demonstrated that stoichiometric amounts of a precatalyst (for example, an iminopyridine complex of Ni(0), **Fig. 9**) formed azoarenes in good yields but lacked catalytic turnover due to the strong coordination of the *trans* isomer, similarly to the report by Hillhouse and coworkers.

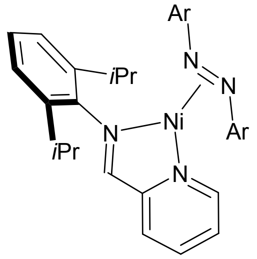

**Fig. 9** Strong coordination by *trans* azoarene to Ni-iminopyridine complex, precluding its catalytic reactivity in azoarene synthesis.

To overcome the challenges associated with mononuclear Ni(0) complexes, a related dinuclear nickel complex incorporating a naphthyridine-diimine ligand, $Ni_2[N4](C_6H_6)$ (**Fig. 10**), was designed.[54] The reaction of $Ni_2[N4](C_6H_6)$ with an organic azide $N_3Ar$ led to the formation of a $Ni_2[N4](\mu_2\text{-NAr})$ imido complex, with the release of $N_2$.[53] Upon reaction with another equivalent of azide, this intermediate forms the corresponding azoarene (**Fig. 10**). Similarly to the mononuclear nickel complexes, azoarene product likely initially coordinates to the metal, causing product inhibition. In contrast to the mononuclear complex, the dinuclear, more congested, nature of the active site necessitates coordination of the *cis* isomer, which is significantly less stable and enables facile turnover. As a result, Uyeda's catalyst was highly efficient and displayed reactivity with a broad range of aryl azides. At 5 mol%, room temperature and relatively short reaction times, $Ni_2[N4](C_6H_6)$ enabled good to excellent reactivity with a variety of electron-rich (for example, 4-$MeOC_6H_4$, 76%, and 4-$^t$Bu-$C_6H_4$, 95%) and electron-deficient (for example, 4-$ClC_6H_4$, 89%, and 3,5-$(CF_3)_2C_6H_3$, 93%) aryl azides (**Fig. 11**). The catalyst was able to couple bulkier *ortho*-substituted aryl nitrenes (up to mesityl), albeit this reactivity required higher temperature and/or longer reaction times. Furthermore, the catalyst exhibited good functional group tolerance (see **Fig. 11** for selected examples) and enabled efficient reactivity with diazides to form azopolymers.[55]

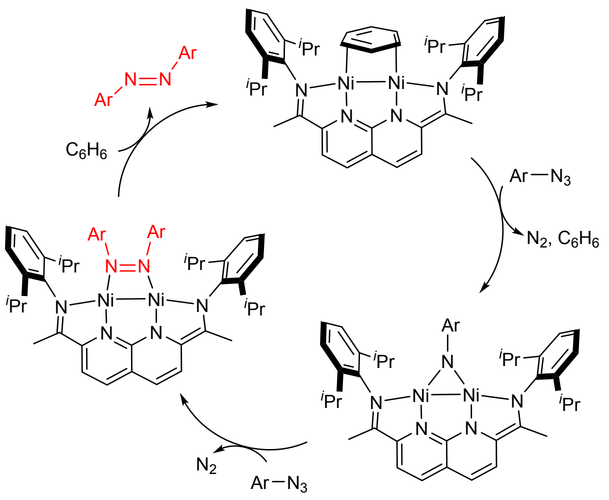

**Fig. 10** Mechanism for the formation of azoarene using $Ni_2[N4](C_6H_6)$.

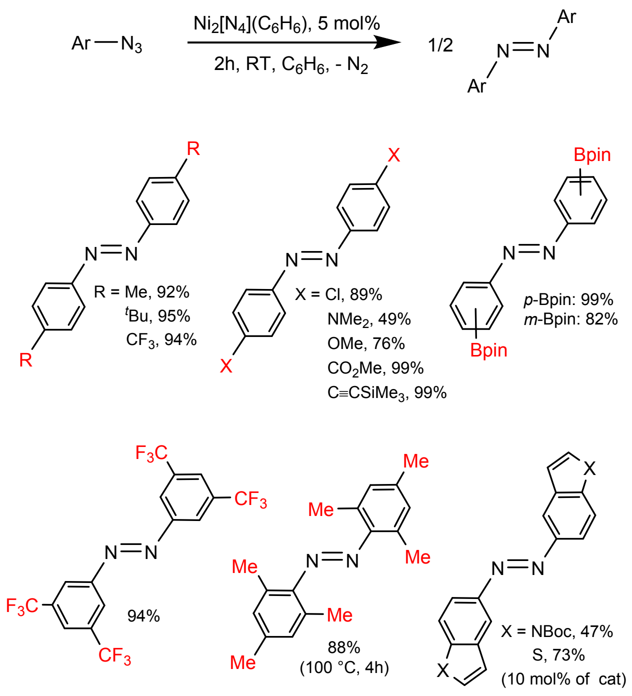

**Fig. 11** Representative selected examples of reactivity of $Ni_2[N4](C_6H_6)$ in nitrene homocoupling.

As indicated above, only few complexes were able to produce azoarenes catalytically via nitrene homocoupling. With the notable exception of the Ueyda's system, most of these catalysts exhibited limited substrate scope, typically operating on phenyl azide or selected electron-rich azides. Furthermore, structure-activity factors controlling the formation of various types of azoarenes were not studied in details. Therefore, there is a significant interest in the pursuit of new sustainable catalysts which (i) exhibit broader reactivity in azoarene formation and (ii) would enable clear understanding of the factors controlling formation of different products.

## Iron bis(alkoxide)s in azoarene synthesis

Typically, late metal-nitrene complexes employ soft, strong-field ligand environment, as discussed above. However, recent studies demonstrated that weak-field ligand systems lead to highly reactive 3d late-metal nitrene transfer catalysts.[56-58] Alkoxide ligands are good candidates to develop reactive and sustainable nitrene transfer catalysts incorporating middle and late transition metal centers.[37, 42] Alkoxides are among the oldest and well-studied ligands in the arsenal of a synthetic chemist.[59-64] There are generally well-established efficient routes towards alkoxides.[42, 59-61] Alkoxides are generally considered σ- and π-donors. As a result, protio alkoxides are among the weakest-field ligands that nearly always lead to reactive high-spin complexes.[65] Furthermore, л donation from an alkoxide ligand can compete with the π-donation from the imido group, decreasing the multiple M=NR bond character and increasing its group transfer reactivity.

Groysman, Lord, and coworkers have synthesized series of well-defined Cr(II)-Co(II) transition metal complexes with bulky alkoxide ligand OR (OR = OC$^t$Bu$_2$Ph),[66, 67] and explored their reactivity in group-transfer reactions.[37, 68] Mononuclear M(OR)$_2$(THF)$_2$ precursors (M = Mn, Fe, Co) complexes exhibited geometry intermediate between tetrahedral and seesaw, featuring wide interalkoxide angle (130-139 °), and narrow angle between THF ligands (83-88 °).[67] The steric bulk of the alkoxides, manifesting itself in the seesaw distortion, enables formation of the reactive trigonal planar intermediates upon treatment with a group-transfer reagent.[69-71] The iron(II) complex $Fe(OR)_2(THF)_2$ was found to exhibit reactivity in azoarene formation.[72] Thus, treatment of $Fe(OR)_2(THF)_2$ with *ortho*-substituted aryl azides (mesityl, 2,6-diethylphenyl azide) produced the corresponding azoarenes in nearly quantitative yields, along with the iron(III) by-product $Fe(OR)_3$. Using catalytic amounts of $Fe(OR)_2(THF)_2$ (up to 1 mol%) produced nearly quantitative yields of both azomesitylene and azo(2,6-diethylbenzene) at room temperature (**Fig. 12**). In contrast, the reaction of $Fe(OR)_2(THF)_2$ with azides lacking both *ortho* substituents led to the formation of an iron(III) bis(imido) dimer $Fe_2(\mu_2\text{-}NAr)_2(OR)_2(THF)_2$ and $Fe(OR)_3$ (**Fig. 13**).[72] Conducting the reaction under catalytic conditions and/or at elevated temperature did not result in the formation of the corresponding non-bulky azoarenes (**Fig. 12**). Treatment of $Fe(OR)_2(THF)_2$ with bulky aliphatic (adamantyl) azide led to the formation of the reductively coupled hexazene species $Fe_2(\mu\text{-}\kappa^2\text{:}\kappa^2\text{-}AdN_6Ad)(OR)_4$ (**Fig. 13**).[73] $Fe_2(\mu\text{-}\kappa^2\text{:}\kappa^2\text{-}AdN_6Ad)(OR)_4$ was found to be stable and did not produce azoarene even at elevated temperatures. Similar N-N reductive coupling reactivity with $Fe(OR)_2(THF)_2$ was observed more recently with diazoesters.[80]

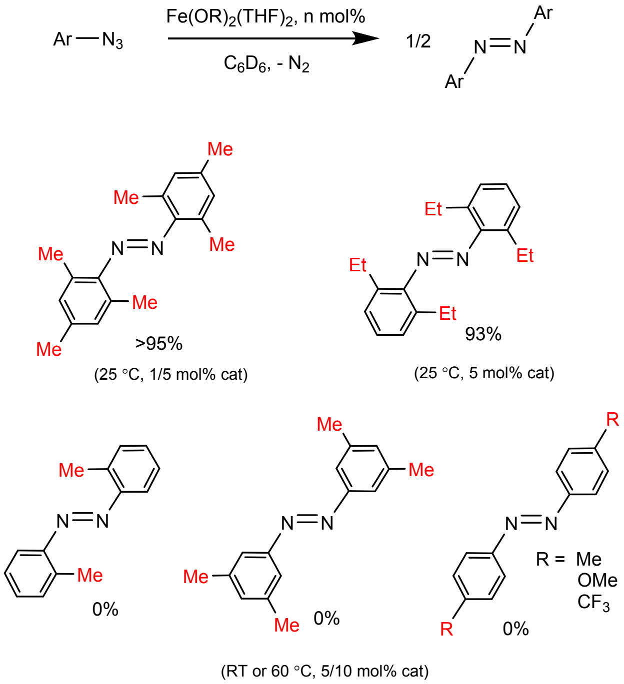

**Fig. 12** Catalytic reactivity of $Fe(OR)_2(THF)_2$ in nitrene homocoupling.

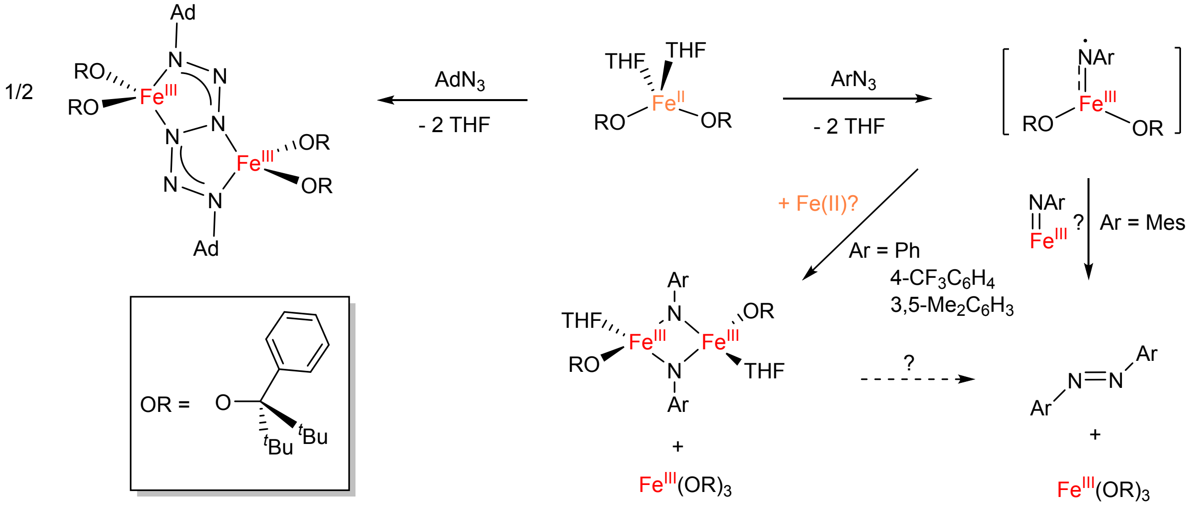

**Fig. 13** Stoichiometric reactivity of $Fe(OR)_2(THF)_2$ with organoazides.

DFT calculations suggested that treatment of $Fe(OR)_2(THF)_2$ with an aryl azide formed a Fe(III) imido radical $Fe(OR)_2(NAr)$ (**Fig. 13**), likely through the intermediacy of the organoazide adduct. It is feasible that, following its formation, the highly reactive imido radical

$Fe(OR)_2(NAr)$ (derived from bulky aryl azides) undergoes bimetallic coupling to form an azoarene, similar to the iron catalyst studied by Peters and coworkers.[57] Related postulated formation of a trigonal highly reactive $Fe(OAr)_2(NAd)$ (OAr = $[OC_6H_2\text{-}2,6\text{-}Ad\text{-}4\text{-}R]$, R = Me, $^i$Pr) by Kawaguchi and coworkers is noted.[79] As the *ortho*-adamantyl groups pointed towards the reactive metal-nitrene, it underwent facile intramolecular C-H bond activation to form the corresponding amine–aryloxide product $Fe(OAr^{AdR})(\kappa^2\text{-}OAr^{AdR}\text{–}NHAd)$. In contrast, the alkoxide substituents (in OR) point away from the metal site, preventing ligand C-H functionalization, and enabling selective nitrene homocoupling. For smaller azides, the reactive transient imido possibly undergoes comproportionation reaction with another equivalent of $Fe(OR)_2(THF)_2$ to form $Fe_2(\mu_2\text{-}NAr)_2(OR)_2(THF)_2$ and $Fe(OR)_3$. One can't rule out, however, that the productive "bimetallic" coupling to form an azoarene proceeds via $Fe_2(\mu_2\text{-}NAr)_2(OR)_2(THF)_2$ species as well. It is feasible that $Fe_2(\mu_2\text{-}NAr)_2(OR)_2(THF)_2$ becomes more reactive towards coupling due to the steric effect of the bridging imido for Ar = Mes or 2,6-$Et_2C_6H_3$. As a result, two bridging imidos couple directly, similarly to the Heyduk's system.[46, 47]

While the detailed mechanism of nitrene homocoupling was not established unequivocally for the $Fe(OR)_2(THF)_2$ system, it was clear that the formation of the undesired products $Fe_2(\mu_2\text{-}NAr)_2(OR)_2(THF)_2$ and $Fe(OR)_3$ can be related to the insufficient bulk of $[OC^tBu_2Ph]$ and the well-known lability of monodentate alkoxides. To prevent catalyst decomposition and to improve its performance in azoarene formation, a new sterically bulkier ligand OR' (OR' = $OC^tBu_2(3,5\text{-}Ph_2C_6H_3)$) was designed.[74] OR' featured additional phenyl substituents in the 3,5 positions of the aryl ring. Bulking up the alkoxide ligand had a desirable effect on the stability of the bis(alkoxide) ligation.[75] No tris(alkoxide) or mono(alkoxide) decomposition products were observed; treatment of $FeCl_3$ with three equivalents of

LiOR'/KOR' failed to produce the Fe(OR')$_3$ complex.[75] More robust catalyst structure had a positive effect on the substrate scope in azoarene formation. Similar to Fe(OR)$_2$(THF)$_2$ system, new Fe(OR')$_2$(THF)$_2$ formed azoarene with di-*ortho*-substituted azides in quantitative yields (**Fig. 14**).[75] However, it was also able to engage less bulky (mono-*ortho*-substituted and meta-substituted) aryl azides to afford the corresponding azoarenes in good to moderate yields (**Fig. 14**), although these reactions required heating to 60 °C and higher catalyst loading (10 mol%). *Para*-substituted aryl azides generally formed the resulting products in low yields. No clear trend was observed for the *para* substituents of different electronic nature. While the electron-withdrawing *p*-CF$_3$ group leads to the formation of the azoarene product in low, but detectable, yield (15%), product yields for the electron-rich *p*-Me and *p*-OMe group vary between somewhat higher (33%, Me) and 0% (OMe) yields.

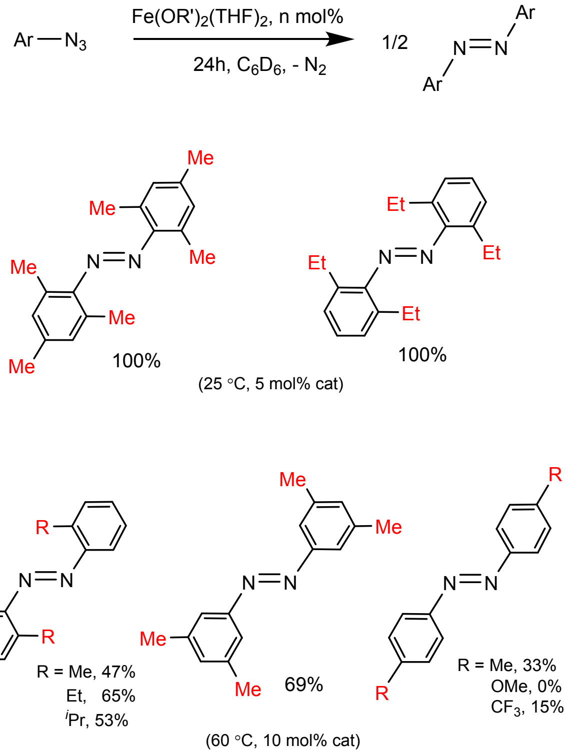

**Fig. 14** Catalytic reactivity of Fe(OR')$_2$(THF)$_2$ in nitrene homocoupling.

Due to its more robust nature, $Fe(OR')_2(THF)_2$ also enabled direct insight into the reaction mechanism.[75] While the reaction of $Fe(OR')_2(THF)_2$ with near stoichiometric amounts of $MesN_3$ (1-2 equiv.) led directly to the formation of azomesitylene, treatment of $Fe(OR')_2(THF)_2$ with *meta*/*para*-substituted organoazides formed the corresponding 1,4-tetrazenes $Fe(OR')_2(ArNNNNAr)$ (**Fig. 15**). Characterization of the tetrazene complexes by X-ray crystallography, Mössbauer spectroscopy, and DFT revealed high-spin Fe(III) antiferromagnetically coupled to the tetrazene radical anion. Upon heating, tetrazene complexes evolved azoarenes. Mixing a tetrazene complex $Fe(OR')_2(ArNNNNAr)$ with a different azide $N_3Ar'$ produced all three possible azoarenes ArN=NAr, Ar'N=NAr'. These experiments, together with computational studies, suggested reaction mechanism outlined in **Fig. 15**. The key intermediate in the mechanism is the reactive nitrene complex $Fe^{III}(OR')_2(^{\bullet}NAr)$, containing again high-spin Fe(III) antiferromagnetically coupled to the nitrene radical. For the non-bulky aryl azides, this intermediate readily undergoes [2+3] cycloaddition to form $Fe(OR')_2(ArNNNNAr)$ tetrazene intermediate, which is more stable compared with nitrene by ~20 kcal/mol. Productive catalysis requires restoration of the nitrene intermediate and takes place via a bimetallic nitrene coupling. Computational studies suggested that the alternative coupling mechanisms (via 1,2-tetrazene or monometallic bis(imido), **Fig. 15**) were less likely in the present system.

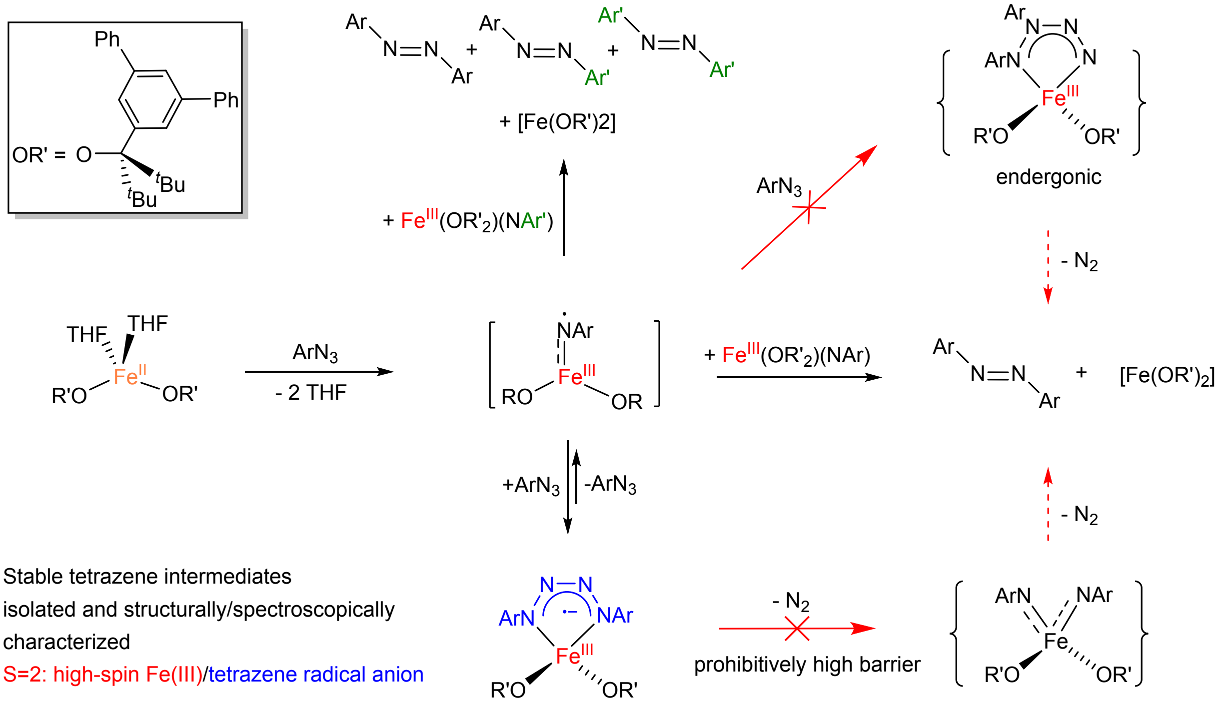

**Fig. 15** Mechanistic studies on the reactivity of Fe(OR')$_2$(THF)$_2$ with aryl azides.

To further improve catalyst stability and reactivity in nitrene formation, we have designed a new chelating bis(alkoxide ligand) H$_2$[OO]$^{Ph}$. Two bulky alkoxide donors in H$_2$[OO]$^{Ph}$ were linked together with a terphenyl linker.[76, 77] The resulting Fe(II) complex Fe[OO]$^{Ph}$(THF)$_2$ (**Fig. 16**) replicated key structural features of the complexes with monodentate alkoxides Fe(OR)$_2$(THF)$_2$ and Fe(OR')$_2$(THF)$_2$, featuring overall seesaw geometry. Notably, the seesaw distortion in Fe[OO]$^{Ph}$(THF)$_2$ was even more significant, with the corresponding interalkoxide angle being 155 ° (vs. 139 ° and 142 ° for Fe(OR)$_2$(THF)$_2$ and Fe(OR')$_2$(THF)$_2$, respectively) (**Fig. 16**).

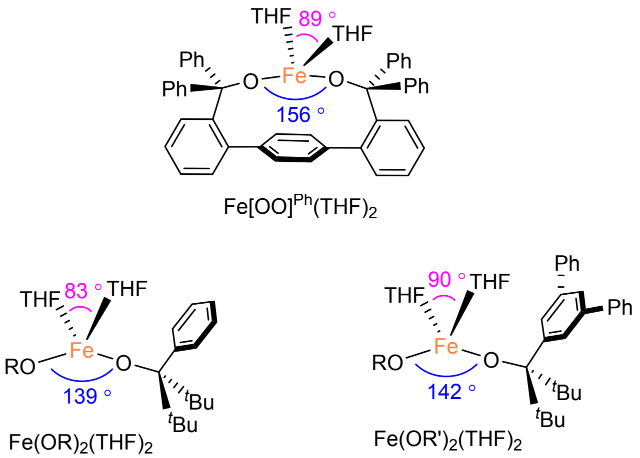

**Fig. 16** Comparison of the key structural parameters of Fe[OO]$^{Ph}$(THF)$_2$ with Fe(OR)$_2$(THF)$_2$ and Fe(OR')$_2$(THF)$_2$.

As anticipated, the chelating bis(alkoxide) system Fe[OO]$^{Ph}$(THF)$_2$ also exhibited reactivity in nitrene coupling.[76] However, the reactivity trend of Fe[OO]$^{Ph}$(THF)$_2$ was complimentary to the previous iron-alkoxide systems. In contrast to Fe(OR)$_2$(THF)$_2$ and Fe(OR')$_2$(THF)$_2$, Fe[OO]$^{Ph}$(THF)$_2$ catalyzed selective coupling of non-bulky aryl nitrenes to obtain the corresponding azoarenes in high yields (**Fig. 17**). Phenyl azide undergoes quantitative conversion to azobenzene, and the *para*-substituted 4-MeC$_6$H$_4$N$_3$ and 4-EtC$_6$H$_4$N$_3$ form the corresponding azoarenes in 85% and 80% yields, respectively. Lower yield (45%) is observed for the somewhat bulkier 4-$^i$PrC$_6$H$_4$N$_3$. Furthermore, Fe[OO]$^{Ph}$(THF)$_2$ is capable of coupling nitrenes bearing functional groups, including *para*-halo-substituted azoarenes (good to moderate yields), *para*-nitro- and *para*-acetyl-substituted azoarenes (moderate to low yields). *Meta*-substituted aryl azides undergo relatively efficient coupling (**Fig. 17**). In contrast, no reactivity was observed for the *ortho*-substituted substrates. The computational study attributed the inability of Fe[OO]$^{Ph}$(THF)$_2$ to couple bulky aryl nitrenes to the more substantial steric shielding of the active site, which is likely also evidenced by the more profound seesaw distortion discussed above (**Fig. 17**). While the "OCPh$_3$" group in Fe[OO]$^{Ph}$(THF)$_2$ is not larger than the "OC$^t$Bu$_2$Ar" group in the earlier complexes, the chelating nature of the ligand results in the formation of the more rigid complex, in which a nitrene group is more efficiently shielded by the phenyl substituents. Similarly to the case of Fe(OR')$_2$(THF)$_2$ catalysis, no clear electronic effect was observed for Fe[OO]$^{Ph}$(THF)$_2$ as well.

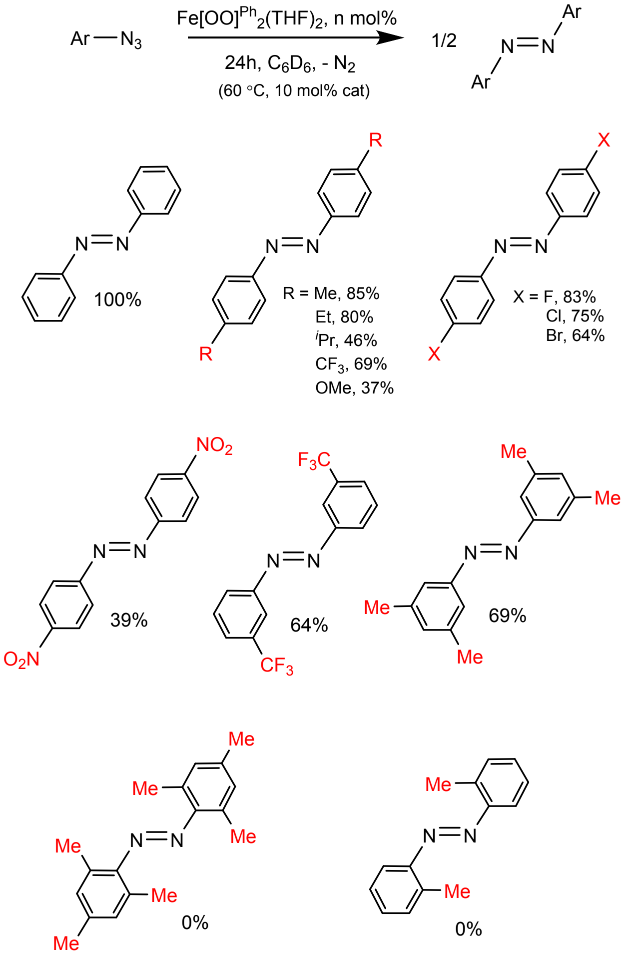

**Fig. 17**. Catalytic reactivity of Fe(OR')$_2$(THF)$_2$ in nitrene homocoupling.

## Formation of asymmetric azoarenes via iron alkoxide catalysis

Some of metal catalysts described above offer an efficient route towards symmetric azoarenes. However, majority of the industrially useful azo compounds are asymmetric, and feature two different aryl groups.[1,2] The formation of asymmetric azoarenes would require nitrene heterocoupling, as opposed to nitrene homocoupling that produces symmetric azoarenes. While stoichiometric examples of nitrene heterocoupling were previously reported, catalytic examples are rare.

Groysman and coworkers have recently reported investigation of nitrene heterocoupling mediated by iron alkoxide catalysts.[78] Two different catalysts were investigated: Fe(OR’)$_2$(THF)$_2$ and Fe[OO]$^{Ph}$(THF)$_2$ (**Fig. 18**). Both catalysts exhibit relatively broad substrate scope, with Fe(OR’)$_2$(THF)$_2$ coupling bulky (*ortho*-substituted) nitrenes more efficiently, while Fe[OO]$^{Ph}$(THF)$_2$ being capable of homocoupling various *meta*- and *para*-substituted azides.[75, 76] When treated with a combination of two different bulky aryl azides ArN$_3$ and Ar’N$_3$, Fe(OR’)$_2$(THF)$_2$ produced nearly statistical distribution of the products (25:50:25 ArN=NAr:ArN=NAr’:Ar’N=NAr’).[78] In contrast, treating Fe[OO]$^{Ph}$(THF)$_2$ with a 1:1 mixture of two different non-bulky aryl azides produced mostly symmetric azoarenes. Several new bulky asymmetric azoarenes (**Fig. 18**) synthesized by Fe(OR’)$_2$(THF)$_2$ were isolated, and their isomerism was investigated. Spectroscopic studies on their cis:trans interconversion revealed relative stable cis isomers ($t_{1/2}$ ~ 10 days), obtained in a high yield (90%) following UV light irradiation (365 nm).

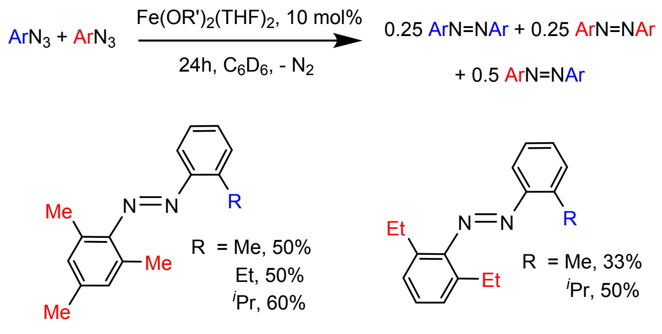

**Fig. 18** Heterocoupling reactivity of Fe(OR')$_2$(THF)$_2$ and the observed yields of the corresponding asymmetric azoarenes.

## Conclusions and future directions

Metal-catalyzed nitrene coupling constitutes an attractive route towards a variety of azo compounds. Several research groups demonstrated efficient nitrene homocoupling producing azoarenes in good to excellent yields. Mechanistic studies revealed a plethora of possible mechanisms, including (i) bimetallic nitrene coupling; (ii) free nitrene coupling; (iii) coupling of metal-nitrene with an azide (possibly via a tetrazene intermediate). Furthermore, structure-activity study carried out on the iron-alkoxide system illustrated how a relatively subtle modification in the ancillary ligand structure can have a profound effect on the substrate selectivity, and can increase significantly the substrate scope. Given the importance of azoarenes in the chemical industry, further research is desirable and should focus on overcoming the following challenges outlined in the next paragraphs.

(1) Most industrially viable azoarenes contain functional groups. However, metal-nitrene chemistry is often incompatible with functional groups. Of the catalysts described so far, only Uyeda's system demonstrated relatively broad tolerance of functional groups. Thus, with an eye towards wider utilization of nitrene coupling catalysts in production of azoarenes, new catalysts should be designed which would be compatible with various functional groups commonly used in azo dyes, including amines, nitro, phenol, and others.

(2) Efficient nitrene coupling catalysts with broad functional group tolerance may also enable extension of this synthetic method into additional fields where azoarenes are of potential interest, including macromolecules or biological systems. Recent studies have demonstrated that

diazides can be polymerized to give azo polymers with azo groups in the main chain. Efficient nitrene coupling catalysts should be also capable of facile post-synthetic modifications of polymers, which can affect their photophysical properties. Additionally, they can serve to easily install switchable linkers in various macromolecules.

(3) Most of the industrially used azo compounds feature two different aryl substituents. However, metal catalysts typically catalyze nitrene homocoupling; nitrene heterocoupling has been less explored. Recent studies have shown that an iron alkoxide catalyst was able to produce asymmetric azoarenes in approximately statistical (~50% theoretical) yield from mixtures of two different organoazides. Design of new catalysts (or exploration of the combination of previously designed catalysts) towards selective heterocoupling is desirable, as it could enable utilization of such catalysts in the production of industrially relevant azo compounds.

## Author contributions

Both authors participated in the writing of the original draft of this manuscript, and in preparing the revised version.

## Conflicts of interest

There are conflicts of interest to declare.

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**Caution!** Organoazides are potentially explosive reagents that can be heat- or shock-sensitive, and should be handled with care. The following references provide additional information regarding the appropriate handling of organoazides.[81, 82]

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