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SUPPLEMENTARY MATERIALS

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ORGANIC CHEMISTRY

Iron-catalyzed intermolecular [2+2] cycloadditions of unactivated alkenes

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Cycloadditions, such as the [4+2] Diels-Alder reaction to form six-membered rings, are among the most powerful and widely used methods in synthetic chemistry. The analogous [2+2] alkene cycloaddition to synthesize cyclobutanes is kinetically accessible by photochemical methods, but the substrate scope and functional group tolerance are limited. Here, we report iron-catalyzed intermolecular [2+2] cycloaddition of unactivated alkenes and cross cycloaddition of alkenes and dienes as regio- and stereoselective routes to cyclobutanes. Through rational ligand design, development of this base metal–catalyzed method expands the chemical space accessible from abundant hydrocarbon feedstocks.

Cycloaddition reactions as exemplified by the venerable [4+2] Diels-Alder reaction are among the most powerful in organic chemistry, providing an atom-economical method for the synthesis of six-membered rings (*1*). Despite their widespred utility and applications, these reactions require the use of activated substrates and are often ineffective for unactivated alkene coupling partners. Pure hydrocarbons are the principal feedstocks of the chemical industry, serving as essential precursors to fuels, films, liquid crystal displays, materials, and medicines (*2*). Among these, ethylene and propylene are the most abundant and are produced in 130 and 85 million metric tons annually, respectively, serving principally as monomers for the multibillion-dollar polyolefins industry (*3*, *4*). Ethylene is also selectively trimerized and tetramerized on large scale rendering 1-hexene and 1-octene commodity alkenes (*5*), motivating the development of new cycloaddition methods that incorporate these fundamental industrial building blocks.

Although analogous [2+2] cycloadditions to prepare cyclobutanes are thermodynamically favorable and could be similarly transformative in synthesis, the exploration of the chemical space of four-membered carbocycles has been substantially hindered by the lack of selective methods for their synthesis (*6*). One challenge in realizing a practical method is overcoming the high kinetic barrier imparted by the thermal constraints of orbital symmetry (*7*). The use of activated alkenes (*8*) and substrates that have the appropriate redox potentials to interact with photocatalysts (*9*, *10*) have been described that overcome these challenges, and examples with high degrees of regio- and stereoselectivity have recently been reported (*11*, *12*). Unactivated alkenes, such as those available in vast excess from shale gas reserves and biorenewable sources, are currently outside the scope of these methods (*13*). Although theoretical methods predict the photochemical feasibility of such cycloadditions (*7*), photodimerization of unactivated alkenes, typically conducted in the presence of copper catalysts, is limited to selected cyclic alkenes and often yields mixtures of products, highlighting the potential utility of alternative methods for cyclobutane synthesis (*14*).

Transition metal catalysis offers the prospect of promoting the [2+2] cycloaddition of unactivated alkenes by virtue of valence d-orbitals and low-energy pathways to metallacyclic intermediates (*15*). Nickel-phosphine combinations have been reported for the synthesis of cyclobutanes from dienes and unactivated alkenes, although both yields and selectivities are not synthetically useful (*8*). Related examples with Ti, Mn, and Fe have also been described and suffer from the same limitations in yield and selectivity (*8*). Examples of more-selective alkene [2+2] cycloadditions with stoichiometric Mg, allyl chloride, and an Al reagent in the presence of Zr and Pd additives have also been reported (*16*).

Our group has found that iron and cobalt complexes bearing redox-active pyridine(diimine) ligands, which undergo reversible one-electron transfer with the transition metal, promote the intramolecular [2+2] cycloadditions of α,ω-dienes to yield the corresponding bicyclo[2.3.0]heptanes (Fig. 1A) (*17*–*19*). These base metal–catalyzed reactions proceed with unactivated dienes at ambient temperature, and mechanistic studies support reductive elimination from metallacyclic intermediates as the key C–C bond–forming step. In both iron (*18*) and cobalt (*19*) examples, the redox active pyridine(diimine) adopts its one-electron-reduced form, resulting in a more-oxidized metal center, and likely facilitates the directional, cyclobutane-forming $C(sp^3)$-$C(sp^3)$ reductive elimination.

The identification of selective, intermolecular variants of the base metal–catalyzed [2+2] cycloaddition is key to the development of a more broadly useful method compatible with abundant, unactivated alkenes. With the first-generation iron precatalyst, (^{iPr}PDI)Fe(N_2) [^{iPr}PDI = 2,6-(2,6-$^{i}Pr_2$-C_6H_3-N=CMe)$_2$$C_5H_3$N, iPr is an isopropyl group, and Me is a methyl group], addition of common unfunctionalized terminal alkenes, such as propylene or 1-hexene, resulted in formation of a stoichiometric quantity of the corresponding alkane, arising from transfer hydrogenation from one of the isopropyl aryl groups on the iron catalyst (*20*). New approaches to catalyst design were therefore necessary to promote C–C bond formation via an iron metallacycle followed by $C(sp^3)$-$C(sp^3)$ reductive elimination. Here, we report that iron precatalysts attained through rational ligand design enable the regio- and stereochemically controlled synthesis of 1,2- and 1,3-disubstituted cyclobutanes by thermal [2+2] cycloaddition.

In an attempt to prevent transfer dehydrogenation, we synthesized an iron precatalyst lacking β-hydrogens on the aryl substituents, [(^{Me}PDI)Fe(N_2)]$_2$(μ-N_2)], and observed catalytic turnover with propylene to produce a 2:1 mixture of 2,3-dimethylbutene and *trans*-1,2-dimethylcyclobutane. It is likely these products derive from a common iron metallacyclic intermediate, where β-hydrogen elimination followed by C-H reductive elimination yields the "tail-to-tail" dimerization product—a precursor to an

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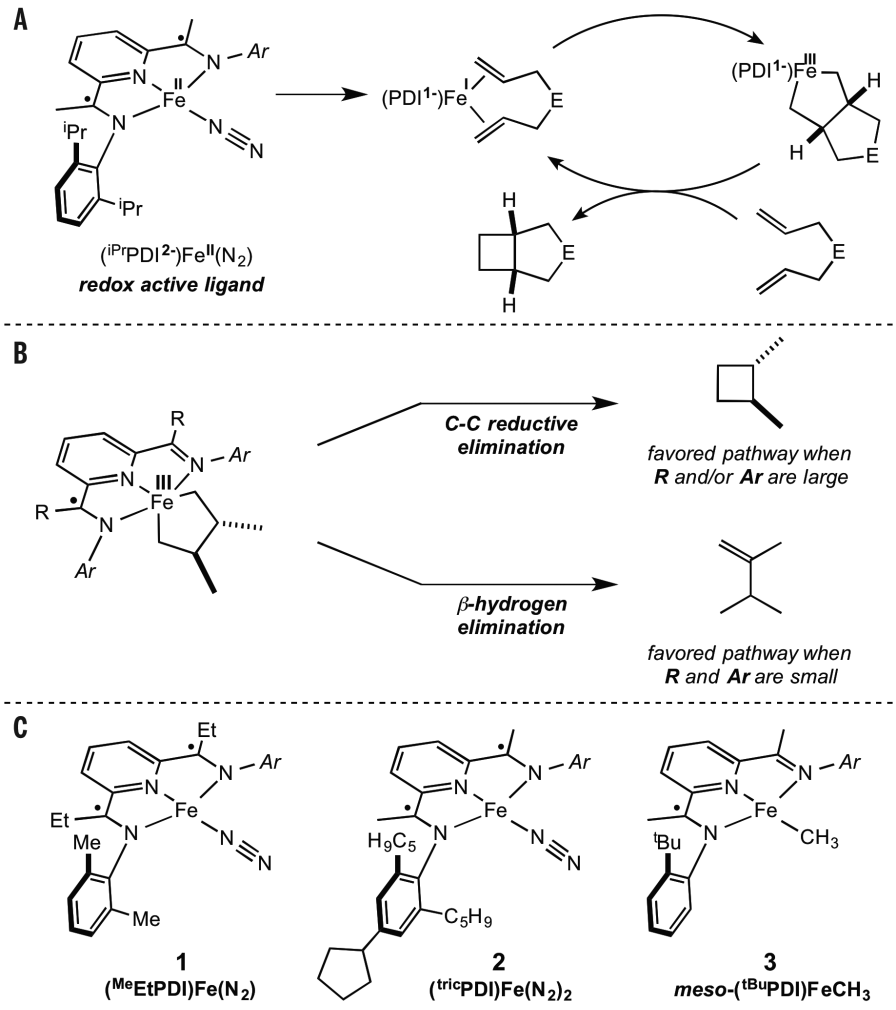
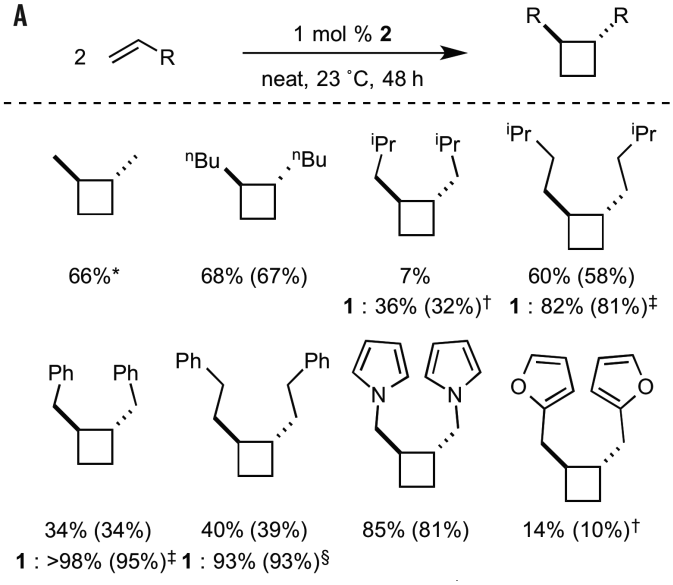


Fig. 1. Catalyst development. (**A**) Intramolecular [(^{iPr}PDI)FeN_2]-catalyzed [2+2] cycloadditions of unactivated olefins. E=CH_2, N-alkyl, aryl, $C(CO_2Et)_2$. (**B**) (PDI)Fe-metallacycle model that allows for control over product distribution. R, methyl or ethyl groups. (**C**) (PDI)Fe compounds used in this study of intermolecular [2+2] alkene cycloadditions. The dots in the chemical structures represent electrons on the ligand.

important fuel additive used to boost octane ratings (*21*). Although selectivity for 2,3-dimethylbutene has been previously observed in nickel catalysis and is used industrially, such reactivity has not been observed previously with iron (*10*).

These observations inspired the catalyst design strategies illustrated in Fig. 1. Two sites of ligand modifications were explored with the goal of promoting reductive elimination over β-hydrogen elimination chemistry. Replacement of the imine methyl groups with ethyl substituents (**1**, Fig. 1C) was explored to prevent imine dissociation, a process that opens a coordination site for β-hydrogen elimination. The second modification installed cyclopentyl in place of isopropyl groups on the aryl rings (**2**, Fig. 1C). The cyclic substituents are constrained to minimize transfer dehydrogenation but remain sufficiently large to promote C-C reductive elimination.

Both **1** and **2** are effective precatalysts for the intermolecular [2+2] cycloaddition of unactivated alkenes. The reactions proceeded efficiently at ambient temperature and in neat substrate, obviating the need for solvent or separations. In each case, the cycloaddition product was identified as the *trans*-1,2-disubstituted cyclobutane, with selectivity resulting from preferential reductive elimination from the metallacycle where the alkyl substituents are distal from the iron (Fig. 1B). As presented in Fig. 2, the cyclopentyl-substituted catalyst **2** proved to be highly selective, forming exclusively cyclobutane products. The commodity terminal alkenes, propylene and 1-hexene, underwent efficient [2+2] cycloaddition over the course of 48 hours at 23°C. Only product and starting alkene were detected during the course of the reactions. The Fe-catalyzed cycloaddition was sensitive to alkene substitution on the allylic position indicated by decreased conversion with 4-methyl-1-pentene and allylbenzene. Improved activity, albeit with slightly reduced



Results of reactions with 1 mol % **1** are shown for select substrates below the standard condition results. *Reaction run in benzene-d_6 (2 M substrate). †9:1 selectivity for cyclobutane product. ‡20:1 selectivity for cyclobutane product. §6:1 selectivity for cyclobutane product.

Fig. 2. Scope of the Fe-catalyzed dimerization. (**A**) Cyclobutanes from variously substituted terminal olefins. Values given are % conversion with isolated yields shown in parentheses. (**B**) "Tail-to-tail" dimerization of propylene using *meso*-(^{tBu}PDI)$FeCH_3$.

selectivity, was observed with **1**; allyl- and 1-butenyl benzene resulted in the formation of their corresponding cyclobutanes in high yields. Consistent with cobalt-catalyzed intramolecular [2+2] cycloadditions (*19*), the reduced steric profile of the methyl (**1**) versus cyclopentyl (**2**) aryl substituents facilitates substrate coordination and metallacycle formation.

To demonstrate the scalability of the method, we conducted the cyclodimerization of allylbenzene on a 3.0-g scale with 1 mole % (mol %) of **1** and produced *trans*-1,2-dibenzylcyclobutane in 93% isolated yield. Catalytic cycloaddition was also explored with air-stable iron precursors by using in situ activation methods as described previously (*17*). Stirring neat allylbenzene in the presence of 5 mol % of (^{Me}EtPDI)FeCl$_2$ (Et, ethyl group) activated with 10 mol % NaBEt$_3$H produced 97% conversion of the alkene over the course of 48 hours. The product mixture contained 62% of the desired 1,2-*trans*-dibenzylcyclobutane product along with 4% hydrovinylation product and 31% *trans*-β-methyl styrene arising from alkene isomerization. These results highlight the improved catalytic performance associated with the isolated iron dinitrogen precatalysts.

Further support for the selectivity model presented in Fig. 1B was provided by the dimerization of propylene to 2,3-dimethylbutene with more open iron catalysts designed to promote β-hydrogen elimination. Because of the synthetic inaccessibility of the corresponding iron dinitrogen complex, we explored *meso*-(^{tBu}PDI)FeCH$_3$ (**3**) (tBu, *tert*-butyl group) (Fig. 2B). Stirring a benezene-d_6 solution of propylene and 1 mol % of **3** resulted in exclusive formation of 2,3-dimethylbutene in 67% conversion over the course of 48 hours at 23°C. Monitoring the catalytic reaction by ^{1}H nuclear magnetic resonance (NMR) spectroscopy revealed formation of small amounts of methane and ethane, likely resulting from Fe-CH$_3$ homolysis ensuing from catalyst activation en route to the intermediate metallacycle that undergoes preferential β-hydrogen elimination.

The success of iron-catalyzed [2+2] cycloaddition of unactivated alkenes prompted investigation into a more-general method for the heterodimerization of abundant dienes and alkenes to value-added cyclobutanes containing alkene substituents available for further elaboration. Iron-catalyzed cycloaddition of 1,3-butadiene and ethylene with 5 mol % (^{Me}PDI)Fe(N$_2$) to yield vinyl cyclobutane has been reported (*22*) and produced no evidence for six-membered ring products arising from competing Diels-Alder chemistry (*23*). We have since found that, in the presence of 5 mol % of (^{Me}PDI)Fe(N$_2$), [2+2] cycloaddition of butadiene with propylene resulted in >98% conversion to 1-methyl-3-vinylcyclobutane as a 67:33 mix of cis:trans diastereomers (Fig. 3A). As reported previously (*22*), this specific iron catalyst loses selectivity for [2+2] cycloaddition upon introduction of a substitution on the diene component. For example, addition of ethylene or propylene to isoprene preferentially formed hydrovinylation products arising from β-hydrogen elimination over cyclobutane products.

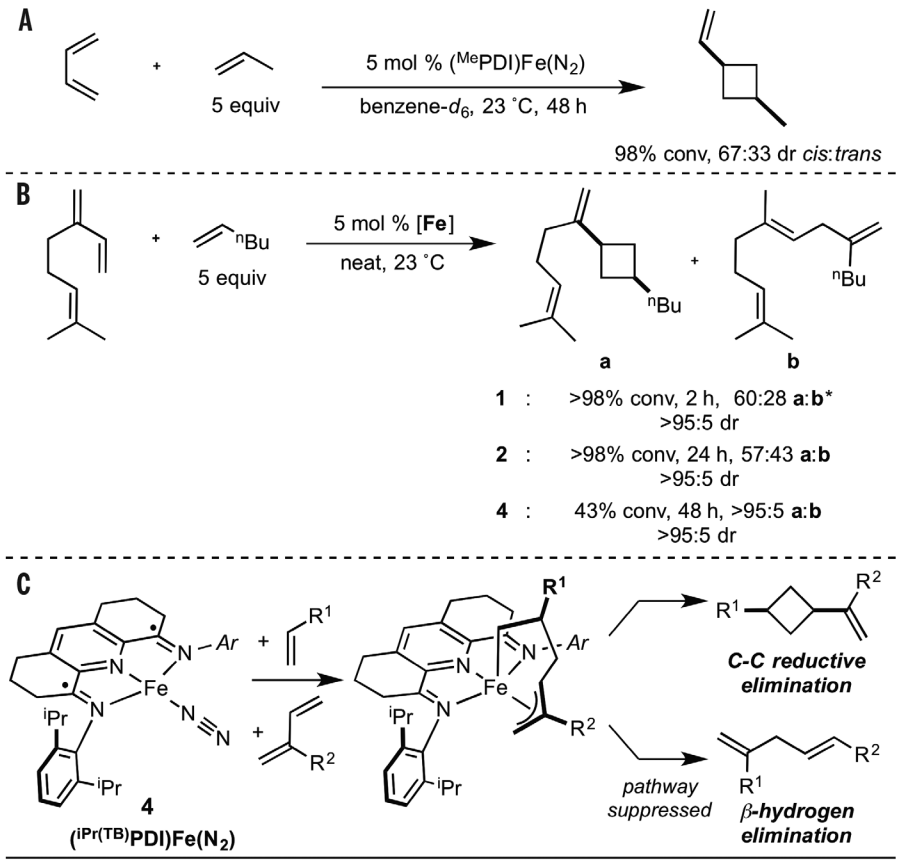


Fig. 3. Expanding from homodimerization to heterocoupling. (**A**) Single-step, Fe-catalyzed 3-methyl-1-vinylcyclobutane synthesis from commodity chemicals. (**B**) Catalyst effects on the [2+2] cycloaddition of myrcene and 1-hexene. (**C**) Fe-alkyl-allyl intermediate en route to 1,3-disubstituted cyclobutanes.

To overcome this limitation, we explored the catalyst design strategies described for alkene [2+2] cycloaddition to increase the cyclization selectivity of diene-alkene reactions. Myrcene, a naturally occurring terpene found as an essential oil in bay, cannabis, parsley, and hops (*24*), was used as a representative diene for reaction discovery. Control experiments wherein neat myrcene was stirred at 23°C with 1 mol % of **1** or **2** resulted in [2+2] homodimerization to yield 46 and 74% of the 1,3-disubstituted cyclobutane product, respectively. Complex mixtures of unidentified organic products account for the mass balance of the reaction or material. The 1,3-disubstituted product was obtained with both catalysts, demonstrating preference for iron alkyl-allyl type metallacycle formation from diene coordination-insertion (*22*).

Evaluation of cross diene-alkene [2+2] cycloadditions were conducted with myrcene and 1-hexene—two liquid substrates that are abundant bio- and fossil hydrocarbon resources, respectively (Fig. 3B). A 1:5 ratio of diene to alkene was used in all catalytic experiments to suppress diene homodimerization. Unfortunately with both **1** and **2**, only slight excesses (1.4:1 and 1.3:1, respectively) of the desired cyclobutane products were observed, demonstrating that the strategy used to supress β-hydrogen elimination and favor C–C bond formation in terminal alkene [2+2] cycloaddition does not translate into diene-alkene chemistry.

A more-rigid catalyst design feature was therefore introduced to favor reductive elimination and suppress hydrovinylation chemistry (Fig. 3C). An iron dinitrogen precatalyst was used in which the imine substituents were covalently attached to the central pyridine, preventing formation of an open coordination site for β-hydrogen elimination (*18*). This approach proved successful, because stirring a 1:5 mixture of myrcene:1-hexene in the presence of 5 mol % of **4** resulted in exclusive (>20:1) selectivity for *cis*-1,3-disubstituted cyclobutane product (Fig. 3B).

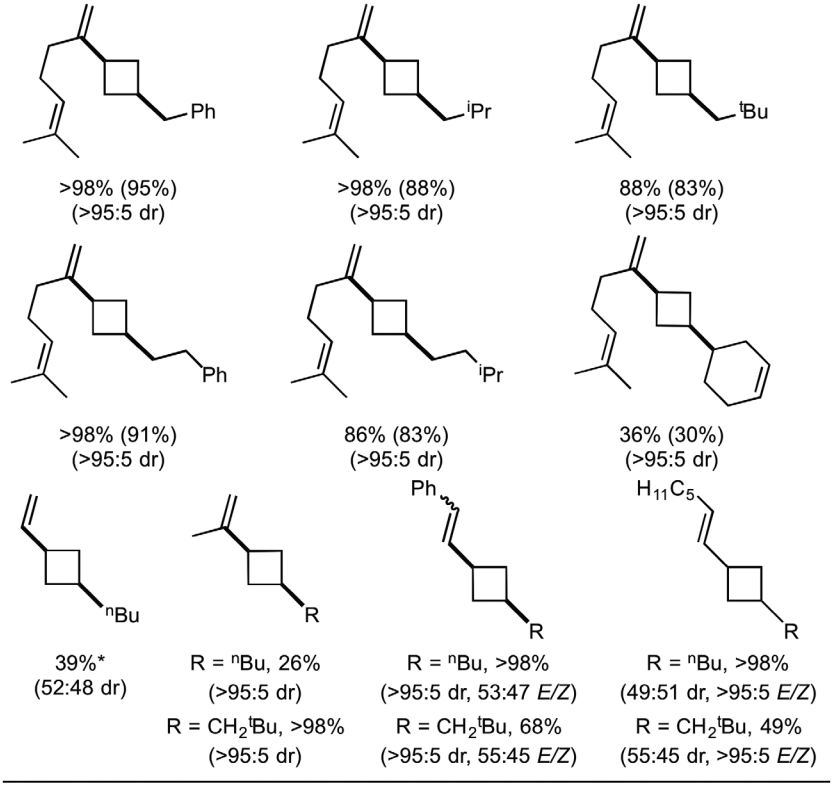


Fig. 4. Scope of the Fe-catalyzed diene-α-olefin cycloaddition. Values reported are % conversion with isolated yields shown in parentheses. Standard conditions were as follows: 5 mol % **4**, 1 equiv diene, 5 equiv olefin, 23°C for 48 hours. The reaction with butadiene and ethylene was conducted with 5 mol % (^{Me}PDI)Fe(N_2) dr is diastereomeric ratio as determined by means of ^{1}H NMR.

With an optimized iron precatalyst structure identified, the scope of the diene-alkene cross [2+2] cycloaddition was evaluated (Fig. 4). By using myrcene as the diene partner, we observed highly regio- and diastereoselective (>95:5) cycloaddition to form *cis*-1,3-disubstituted cyclobutanes with various terminal alkenes, including 1-hexene, allyl benzene, 4-methyl-1-pentene, 4,4-dimethyl-1-pentene, and 4-phenyl-1-butene. Introduction of a cyclohexenyl substituent onto the alkene coupling partner resulted in reduced yields but maintained high selectivity, likely because of the steric inhibition for forming the intermediate metallacycle. In each of these examples, good to excellent conversions and isolated yields were obtained. Products from diene or alkene homodimerization were not observed, demonstrating a highly selective iron-catalyzed regioselective route to stereodefined cyclobutanes with alkenyl substituents. The cross [2+2] cycloaddition of myrcene and 4,4-dimethylpentene was also effective with 5 mol % (^{Me}PDI)Fe(N_2), an iron catalyst precursor more straightforward to prepare than **4** and hence easily obtained in larger quantities. With this precatalyst, the cross cycloaddition was conducted on a 7.0-mmol scale of mycrene and yielded 1.57 g (96% isolated yield) of the *cis*-1,3-disubstituted cyclobutane. Despite the excess of 4,4-dimethylpentene used in the reaction, 83% of this olefin was recovered by vacuum transfer of the volatile components from the crude reaction mixture. The cyclobutane product was then isolated by simple filtration through a short plug of silica and, after rinsing with hexanes, was obtained as an analytically pure material.

Variations in the diene partner were also tolerated, including the use of commodity hydrocarbons (Fig. 4). With butadiene:1-hexene, high 1,3-regioselectivity was maintained with reduction in diastereoselectivity, likely because of reduced steric interactions between the smaller substituents on the alkyl-allyl metallacycle and the supporting pyridine(diimine) ligand. Introduction of a methyl substituent as in isoprene returned the diastereoselectivity to >95:5. Terminal phenyl and pentyl substituents were also well tolerated on the diene partner; efficient cross [2+2] cycloaddition of 1-phenyl-1,3-butadiene and 1,3-nonadiene with 1-hexene and 4,4-dimethyl-1-pentene was observed (Fig. 4).

The iron precatalysts used in this work were ineffective for [2+2] cycloadditions involving more functionalized alkenes, such as 4-bromo-1-butene, trimethylsilyloxypropene, and 2-butenyl-6-methylpyridine. The understanding of how ligand design affects the reactivity of intermediate metallacycles en route to cyclobutane formation provides important insight for the synthesis of the next generation of base metal catalysts to expand the scope of the reaction.

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SUPPLEMENTARY MATERIALS

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Iron-catalyzed intermolecular [2+2] cycloadditions of unactivated alkenes

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