A Long Journey to the Unknown Chemical Space: Synthesis of Ferrocene 1,3–Derivatives by Distal C–H Activation by a Template Approach

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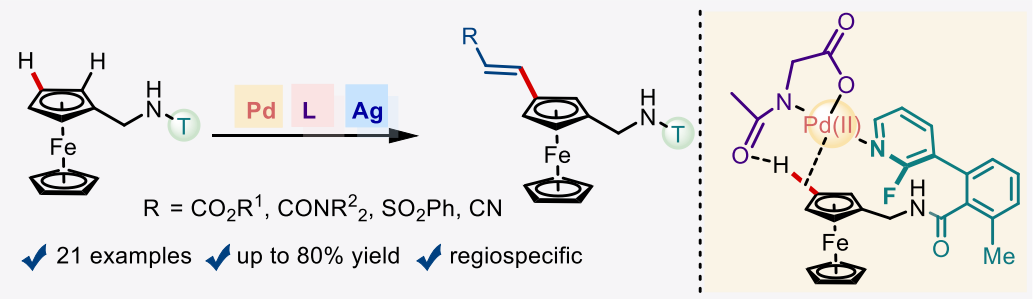
Abstract

Reaching the unreachable! Ferrocene derivatives have found wide applications as ligands, catalysts, functionalized materials, fuel additives, agrochemicals, drugs and many bioorganometallic compounds. Planar chiral ferrocene derivatives are bench-mark ligands used in asymmetric catalysis both in bulk chemical industry and fine chemical synthesis. Traditionally, ferrocene-1,2-derivatives were prepared by lithiation-electrophilic quenching protocol, which is still being pursued, until recently when transition-metal catalyzed C–H activation came into play. But till date, the third position of Cp ring of ferrocene remained as hitherto inaccessible chemical space for the direct functionalization in the ferrocene and bypassing the active second position is most challenging task and beyond common comprehension. Here we report the regiospecific 1,3–functionalization of ferrocene *via* covalently bound pyridine containing template directed approach with precise selectivity under Pd(II)/MPAA catalytic system. The process shows broad scope in olefins with ferrocenylmethylamine in moderate to good yields *via* highly strained 12-membered macrocyclophane-like pre-transition state with appended ferrocene. We believe that this result will pave the way towards the development of novel class of ferrocene pincer ligands that would be an addition to the repertoire of toolbox of ligands available for synthetic organic chemist.



1. Introduction

Ferrocene, the fascinating organometallic sandwich compound, has enjoyed enormous attention since its accidental discovery in 1951,[1] mainly because of its extensive application in catalysis, medicinal chemistry, electrochemistry and materials science (Figure 1).[2] It is considered as a `privileged` scaffold for ligand and

catalyst design in asymmetric synthesis mainly because of the three elements of chirality-central, planar and axial chirality present in ferrocene derivatives by virtue of their unique structure. These benchmark ligands have played a key role in the development of metal-catalyzed organic synthesis as evidenced by the commercial availability of variety of ferrocenyl ligands from various chemical suppliers for synthetic organic chemistry practitioners across the globe. Design and synthesis of novel chiral and achiral ferrocenyl ligands and exploring their catalytic efficiency in various reactions is at the heart of metal-catalyzed synthetic chemistry, relevant to both, academia and industry. A wide range of substituted ferrocene derivatives are known mainly, 1-substituted, 1,1'-disubstituted, 1,2-disubstituted, 1,3-disubstituted, along with polysubstituted ferrocenes (Figure 1). For example, for the industrial production of (*S*)-metolachlor (DUAL Magnum®), a chiral herbicide, Ir/(*R,Sp*)-Xyliphos catalyst is used for the key imine hydrogenation reaction.[3] Another valuable member in the ligand toolbox is *bis*-(diphenylphosphino)ferrocene (dppf) which is exemplified by its powerful ability in Pd-catalyzed cross coupling reactions.[4] Ferroquine, an organometallic analog of chloroquine, is a proven antimalarial agent which is in the Phase II clinical trials for the treatment of malaria in a combination therapy.[5]

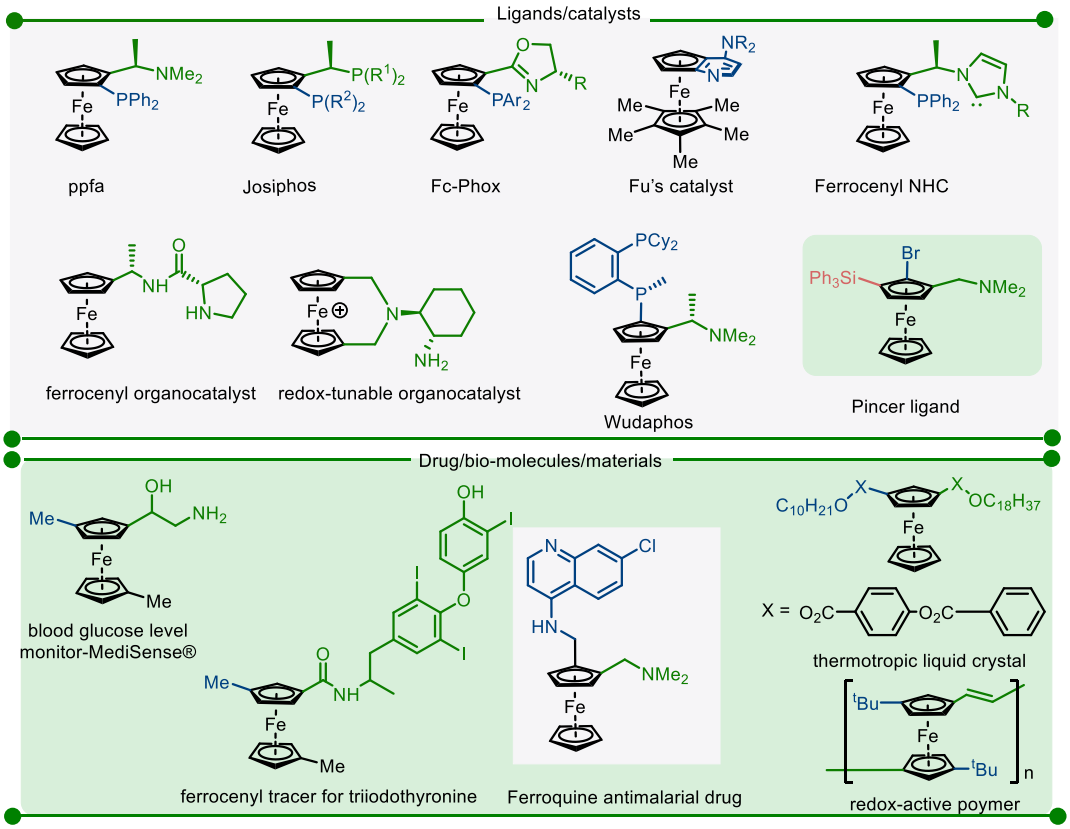


Figure 1. Ferrocenyl 1,2- and 1,3-derivatives as ligands/catalysts/drug/biomolecules

Traditionally, ferrocene functionalization has been achieved by mainly following two approaches. Most widely used one is the direct functionalization of the ferrocene scaffold by making use of electron-rich cyclopentadienyl ring either by Friedel–Crafts electrophilic substitution reaction or by a lithiation followed by intercepting with suitable electrophiles. The lithiation protocol has been a proven method for the synthesis

of 1,2-disubstituted ferrocene derivatives especially for chirality induction *via* pre-installed chiral auxiliary or a chiral base. Despite the wide applications of these exemplary methodologies, several limitations still exist, such as the lengthy synthetic steps, and the low functional group tolerance caused due to usage of a large excess of Lewis acid or organometallic reagent. An alternative method is the pre-functionalization of cyclopentadienyl ring preceding the formation of the metallocene core and is largely exploited for the synthesis of 1,1` di-substituted ferrocene derivatives. This method still falls short in functional group tolerance and reactivity. Kinetic resolution is another practical method to access enantiopure ferrocene derivatives from their planar chiral racemates.[6]

1,3-disubstituted ferrocene derivatives are a singular class of compounds in this repertoire, with large untapped potential, and are less explored due to the lack of efficient synthetic approaches for their selective synthesis. Though, 1,3-disubstituted ferrocene derivatives have been used as redox sensors in commercial blood glucose level monitors, efficient pincer ligands in catalysis, ferrocenyl tracers for triiodothyronine, and materials with liquid crystalline properties,[7] the exploration of these valuable products were retarded by their notorious synthetic unviability. Mostly, ferrocene-1,3 derivatives were prepared from ferrocene 1,2,3-trisubstituted derivatives prepared by two sequential organometallic base mediated *ortho*-deprotonation-electrophilic quenching followed by removing of the central substituent to yield ferrocene-1,3 derivatives.[6,8a] Brown and co-workers synthesized racemic 1,3-disubstituted derivatives by a selective *meta*-lithiation of ferrocenyl-tolyl sulfide.[8b] Also, synthesis of 1,3-disubstituted ferrocene derivatives *via* a base-induced halogen-metal-exchange (HME) reaction, called the *halogen dance* from 1,2 disubstituted derivatives were also tried.[8c] But these reactions are not general, difficult to control and involve multistep synthesis and tedious separation of side products. Hence a direct catalytic synthetic protocol is urgently required for the synthesis of these valuable ferrocene derivatives.

In the last few decades, transition-metal (TM) catalysis emerged as a game changer that revitalize synthetic organic chemistry *via* atom- and step-economical C–C and C–heteroatom bond forming reactions.[9] Very recently, TM-catalyzed C–H activation came up as a milder and step-and atom economical protocol for the proximal functionalization of ferrocene with the assistance of coordinating DGs leading to the synthesis of both racemic and planar chiral ferrocene 1,2-derivatives, by following the pioneering work of Siegel and Schmalz on a copper-catalyzed intramolecular enantioselective carbene C–H insertion reaction to functionalize ferrocenes.[10] After a dormant period, recently, efficient palladium-, iridium-, rhodium, cobalt copper and iron-based catalytic systems have been successfully developed for the functionalization of this prototypical metallocene providing ferrocene–1,2 derivatives.[11] However, in spite of tremendous progress in metal catalyzed C–H activation reactions, functionalizing the third position of monosubstituted ferrocene derivatives, bypassing the second position which is predominantly active, is strategically challenging.

Distal C–H activation in arenes by utilizing covalently attached remote-directing templates has come up as a powerful tool for the distal C–H activation of arenes where the directing group is linked with the substrate

by long molecular bridge, which facilitates the agostic interaction between the metal catalyst and the distal C–H bond *via* 12-13 membered metallacycle intermediate.[12] Pioneering efforts by Yu and co-workers in 2012 using weakly coordinating nitrile group in the directing template were successful in delivering the palladium catalyst to the vicinity of *meta*-C-H bond resulting into selective *meta*-olefination of toluene derivatives and hydrocinnamic acid derivatives.[13] This work paved the way towards the development of a genre of diverse templates and catalytic systems for the selective *meta*-and *para*-C–H functionalization by overriding the inherent steric and electronic biases in (hetero)arenes. Recently, the Yu group reported a strongly coordinating pyridine-based template, which helped them to overcome the weakly-coordinating nature and hence incompatibility of cyano-based templates with harsh reaction conditions, for *meta*-C–H bond functionalization of benzylic alcohols with excellent regioselectivity.[14]

We hypothesized that the hitherto inaccessible chemical space of ferrocene could be operated by remote C–H activation using a carefully engineered template containing a robust DG to selectively release the reactive metal center within the proximity of the desired remote C–H bond in ferrocene and would give rise to ferrocene-1,3 disubstituted derivatives, which are challenging though highly rewarding.

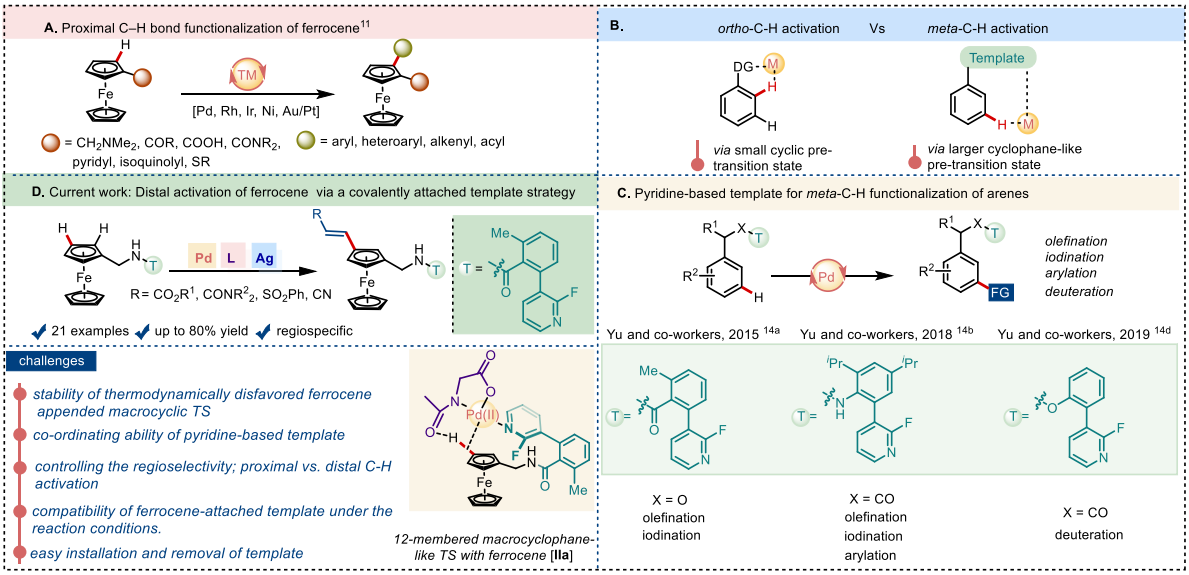


Figure 2: **Transition-metal catalyzed template-assisted distal C–H functionalization of ferrocenes. a**: proximal C–H functionalization of ferrocene; **b**: *ortho vs*. *meta*-C–H activation of benzenoid aromatics; **c**: pyridine-based template development for the *meta*-C-H activation of arenes, **d**: current work: template mediated strategy for the distal C–H functionalization of ferrocene.

But there are a number of challenges associated with this unprecedented distal C–H functionalization in ferrocene: (1) stability of thermodynamically less favored metallocene-appended macrocyclic pre-transition state (2) remote site-selectivity in functionalizing of unbiased C–H bonds in the Cp ring by careful selection of template (3) coordinating ability of template and compatibility of ferrocene-attached template under the reaction conditions and finally (4) easy installation and removal of suitable directing template with the metallocene backbone (Figure 2). Herein, we report our initial findings regarding remote C–H

functionalization of ferrocenes using covalently attached C3-pyridine containing template leading to the selective synthesis of ferrocene 1,3-derivatives.

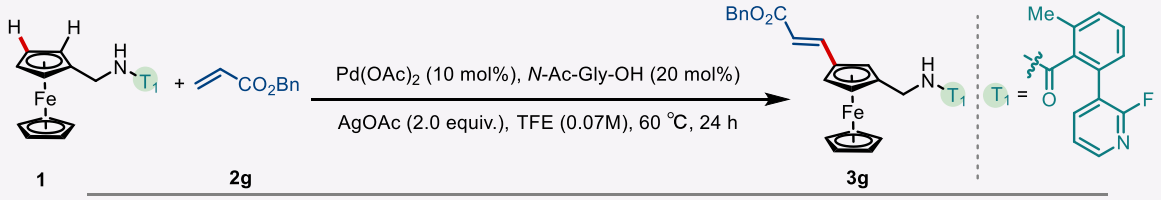
2. Results and Discussion

We chose ferrocenyl methylamine, a versatile and easily available precursor of various ferrocene derivatives, as a model substrate to validate our hypothesis of distal C–H activation in ferrocene *via* a covalently bound template strategy. Inspired by the success of the strongly coordinating U-shaped heterocyclic director developed by Yu and co-workers[14] for the precise *meta*-selectivity in C–H activation of arenes, we chose C3-pyridine containing template (**T1**) for olefination reaction (Table 1).[15] We covalently attached ferrocenyl methylamine backbone with the pyridine containing template (**T1**) by amide bond anticipating the formation of more stabilized cyclophane transition state due to the strong σ-coordination and low angle strain which will ensure the effective delivery of TM-catalyst to the closest proximity of the desired distal-C–H bond to enforce selective C–H activation. Our initial investigation focused on a representative reaction between template (**T1)** bound ferrocenylmethyl amine, **1a** and coupling partner, benzyl acrylate **2j**, in presence of $Pd(OAc)_2$ catalyst with *N*-Ac-glycine ligand combination with $Ag(OAc)_2$ as oxidant in HFIP at 60 ^oC for 24h.

Changing of Pd(II) source from $Pd(OAc)_2$ to $Pd(OPiv)_2$, $Pd(TFA)_2$, $PdCl_2(CH_3CN)_2$ did not seem to be fruitful for increasing yield of the desired product formation (See Table S2, SI, for catalyst optimization studies). Interestingly among various MPAA ligands screened, acetyl protected ones appeared to be superior to Boc, Fmoc or unprotected amino acid ligands. Among the various *N*-acetyl amino acid ligands, N-Ac-glycine worked best, while *N*-(2-hydroxypyridin-3-yl)acetamide) or BINOL ligands were less effective under our reaction conditions (See Table S1, SI, for ligand optimization study). A quick screening for the optimum solvent resulted in TFE as the best compared to HFIP, DCE, DMF, THF and MeCN. (See Table S3, SI, for ligand optimization studies). The distal C–H activation reaction was largely biased by the oxidants used in the reaction and, among the variety of oxidants that were screened, AgOAc was found to be superior to others (See Table S4, SI, for ligand optimization studies). A brief study of the temperature dependence of the reaction revealed that 60 ^oC is optimum for product formation while higher temperature hampered the reactivity (See Table S5, SI, for reaction condition optimization studies). Extended reaction time up to 48 h did not improve the efficiency of the reaction, indicating that the catalytic species was no longer active after 36 h. Detailed screening of various parameters in the reaction (for detailed optimization, see the SI) led us to identify a set of simple and mild reaction condition to yield ferrocene-1,3 derivative **3g** in an isolated yield of 69% (recovered yield 80%): ([$Pd(OAc)_2$] (10 mol%), *N*-Acetylglycine (20 mol%), AgOAc (2.0 equiv.) in TFE at 60 ^oC for 24 h. Most importantly, the competing proximal C–H activation *via* the formation of five membered palladacycle with the assistance of amide chelation resulting into 1,2 functionalized ferrocene derivative was not observed under our optimized condition. This showed the supremacy of C3-pyridine template, which has a strong σ-coordination and lower angle strain, favoring the thermodynamically challenging 12-membered metallocene appended transition state resulting into distal C-H activation in ferrocene. A detailed spectroscopic

characterization and ESI-HRMS inferred the formation of desired ferrocene disubstituted derivative, finally the regioselectivity of the reaction and structure of the product was unambiguously confirmed by single crystal X-ray analysis of compound **3j**.

Table 1: **Selective examples of optimization study for the distal C–H functionalization of ferrocene *via* covalently bound template.**



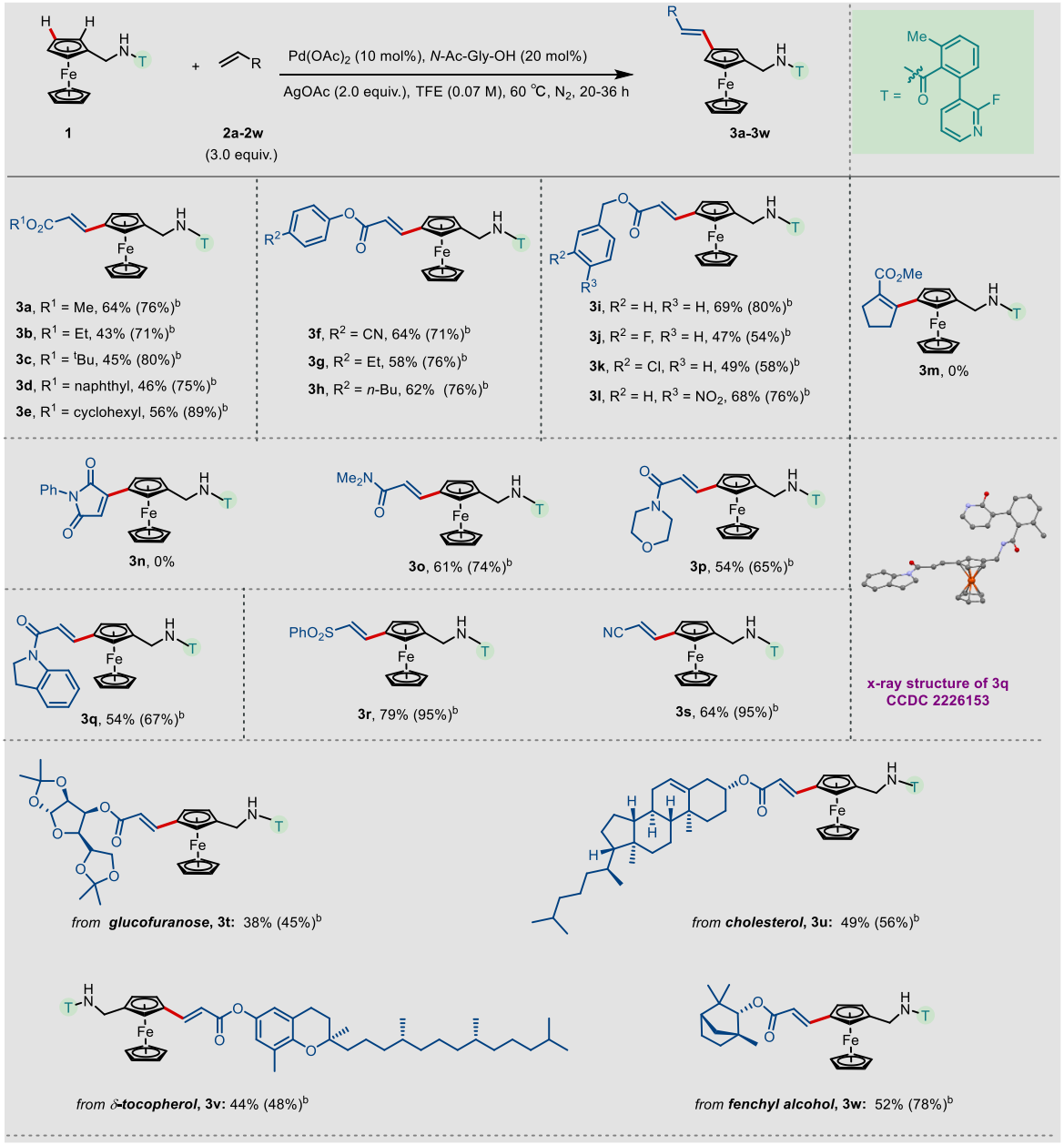
1 **2g** **3g**

entry	variation from optimized condition					yield (%)[a]
	catalyst	ligand	oxidant	temp (°C)	solvent	
1	none	none	1.5 equiv.	none	HFIP	54%
2	$Pd(TFA)_2$	none	1.5 equiv.	none	HFIP	40%
3	$Pd(OPiv)_2$	none	1.5 equiv.	none	HFIP	trace
4	none	N-(2-hydroxypyridin-3-yl) acetamide)	1.5 equiv.	none	HFIP	29%
5	none	N-Ac-Leu-OH	1.5 equiv.	none	HFIP	52%
6	none	N-Boc-Val-OH	1.5 equiv.	none	HFIP	15%
7	none	Glycine	1.5 equiv.	none	HFIP	NR
8	none	R-BINOL	1.5 equiv.	none	HFIP	25%
9	none	none	1.5 equiv.	none	TFE	56%
10	none	none	Ag_2CO_3[b]	none	none	23%
11	none	none	AgTFA[b]	none	none	NR
12	none	none	AgOTf[b]	none	none	NR
13	none	none	$Cu(OAc)_2.H_2O$[b]	none	none	40%
14	none	none	$Cu(OAc)_2$[b]	none	none	44%
15	none	none	none	none	none	69%

[a]Unless otherwise specified, all reactions were carried out using **1** (0.05 mmol), **2g** (0.15 mmol), $Pd(OAc)_2$ (0.005 mmol), N-Ac-Gly-OH d (0.01 mmol), AgOAc (0.10 mmol) with TFE (0.07 M) at 60 °C for 24 h under N_2; [b] 1.5 equiv. of oxidant is used instead of 2.0 equiv.

Having established a viable synthetic protocol for an unprecedented 1,3 derivatization of ferrocene by distal C–H activation, we started to screen the scope and limitation of this methodology. At first, we screened a variety of activated esters as coupling partner for this olefination reaction as shown in Table 2.

Table 2: **Substrate scope for template mediated strategy for the distal C-H functionalization of ferrocene**

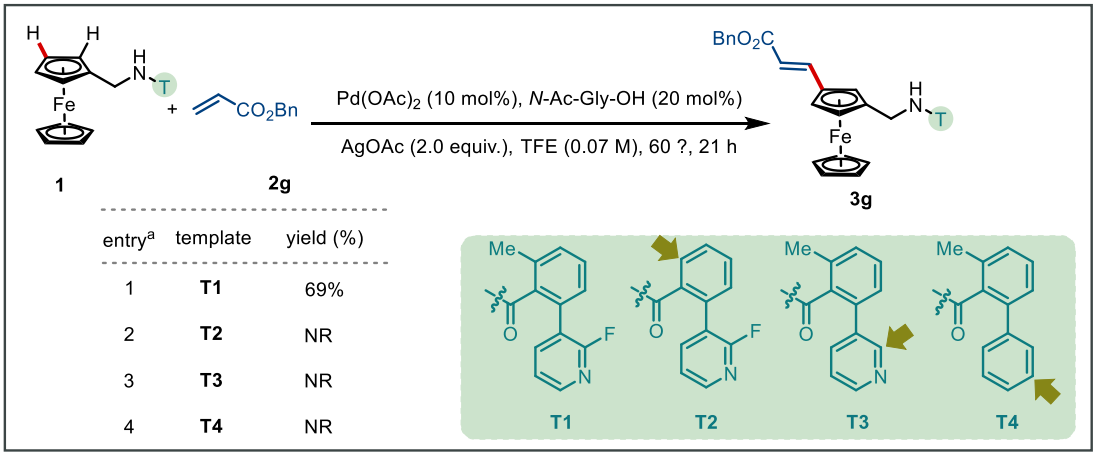


[a]Unless otherwise specified, all reactions were carried out using **1** (0.05 mmol), **2g** (0.15 mmol), $Pd(OAc)_2$ (0.005 mmol), N-Ac-Gly-OH (0.01 mmol), AgOAc (0.10 mmol) with TFE (0.07 M) at 60 °C for 20-36 h under N_2; [b]yield calculated based on recovered starting material.

Generally available acrylic esters like methyl, ethyl, *t*-butyl and acrylates could all be effectively coupled, providing the desired products in good yield under the optimized condition (**3a-3c**). Interestingly naphthyl and cyclohexyl acrylates also participated in this reaction effectively (**3d-3e**). The reaction was found to be general with phenyl acrylates carrying various electron withdrawing and donating groups at the para-position (**3f-3h**). Benzyl acrylates substituted with electron-withdrawing and electron-donating groups including halogens at meta-and para position reacted efficiently (**3i-3l**). The inclusion of halogens at the meta-position of the phenyl ring gave slightly lower yield of the olefinated product while electron-withdrawing group at the *para*-position

improved the efficiency of the reaction (**3m**). Cyclic α,β–unsaturated ester (**3n**) and *N*-phenyl maleimide (**3o**) did not work well in this reaction. To our delight, acrylamides coupled effectively in the olefination reaction to give ferrocene 1,3-derivative (**3o**) in good yield. Interestingly, acryloyl morpholine and 1-indol-1-ylprop-2-en-1-one also underwent effective coupling under the optimized condition (**3p** and **3q**, table 2). Phenyl vinyl sulfone and acrylonitrile also coupled well with ferrocene to give corresponding 1,3-derivatives (**3r** and **3s**, table 2). Various acrylates with complex natural product pendants such as glucofuranose derivative (**3t**), cholesterol (**3u**), δ-tocopherol (**3v**) and fenchyl alcohol (**3w**) underwent regiospecific coupling with ferrocene in moderate yields. It is noteworthy that the library of structurally diverse natural products containing ferrocene at third position not only illustrates the robustness of the developed methodology, but the synthesized products could be used to check for pharmacological and material properties. In all the cases, the regioselectivity of C–H activation in ferrocene remained intact regardless of the different coupling partners (activated olefins) used for the olefination reaction without trace amount of diolefinated product.

Next, after establishing the generality and scope of the selective distal C–H functionalization of ferrocene we went on to investigate the role of substituents in the pyridine-template that would help to develop templates for ferrocene functionalization in the future (Figure 3).



entry[a]	template	yield (%)
1	**T1**	69%
2	**T2**	NR
3	**T3**	NR
4	**T4**	NR

[a]Unless otherwise specified, all reactions were carried out using **1** (0.05 mmol), **2g** (0.15 mmol), $Pd(OAc)_2$ (0.005 mmol), N-Ac-Gly-OH (0.01 mmol), AgOAc (0.10 mmol) with TFE (0.07 M) at 60 °C for 24 h under N_2.

Figure 3: **Template tuning for distal C–H functionalization of ferrocene.**

The role of 2-methyl group in the template was expected to give a conformational resistance which would help to keep the Cp ring of ferrocene at an optimum distance to the pyridyl template and hence successfully deliver the catalyst to distal C–H bond. We synthesized template **T2** without methyl group and checked the reaction outcome, but the reaction did not work out. Another important moiety in U-shaped template is the suitably placed fluoro-group into the pyridine ring which is supposed to modulate the coordinating ability of the pyridyl nitrogen for successful distal C–H activation. When we checked the reactivity of ferrocenyl methylamine with template **T3**, without 2`-F group, the reaction failed to give the desired product. Finally, the template without coordinating nitrogen (**T5**) was also tested which would facilitate competing proximal C–H functionalization, but not even a trace amount of ferrocene-1,2 derivative was observed.

The final objective of our hypothesis has been attained by an easy removal of the ferrocene appended template by acid mediated hydrolysis and concomitant protection strategy, as depicted in Figure 4.

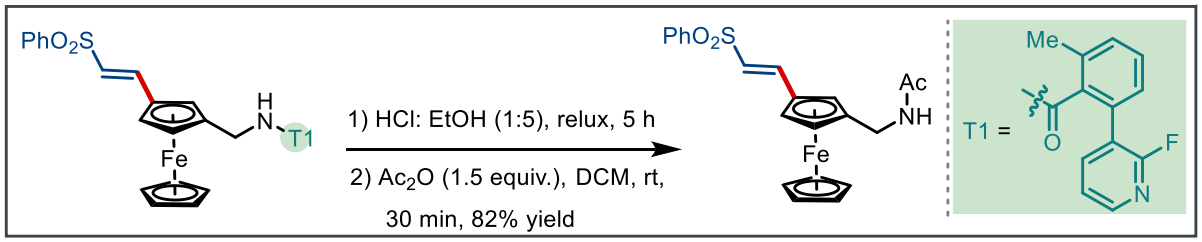


Figure 4: **Selective removal of the pyridine containing template.**

Next, we turned our attention to ESI-HRMS analysis studies to invoke experimental evidence for the unprecedented distal C–H activation in ferrocene. During stoichiometric addition of palladium acetate and *N*-Ac-glycine ligand to the substrate **1a** under the standard reaction condition, the ferrocene appended highly strained 12-membered palladacycles with and without MPAA ligand have been detected by ESI-HRMS analysis, strongly indicating that palladium assisted C–H activation is the initial step in the selective olefination at ferrocene backbone (Figure 5).

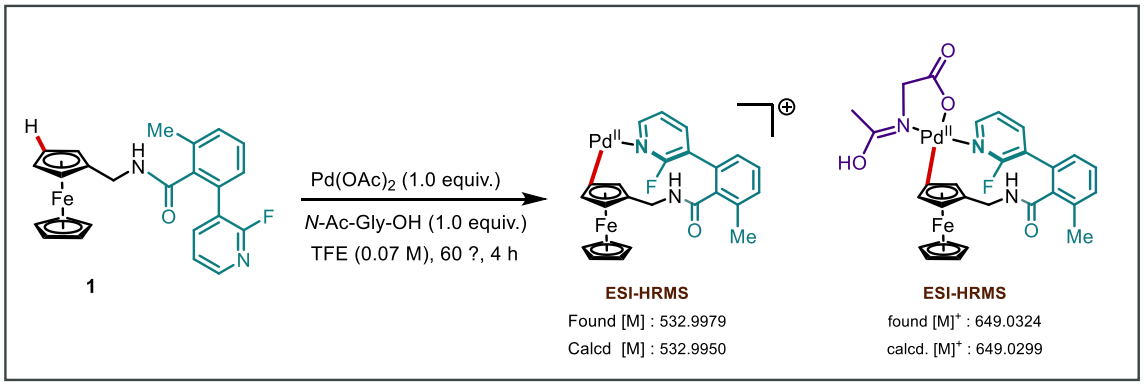


Figure 5: **ESI-HRMS studies for the detecting the intermediates**

Following the aforementioned control experiments and previous literature reports, a plausible mechanism has been suggested as shown in Figure 6. Initially, the catalyst, $Pd(OAc)_2$ after chelation with the *N*-acyl amino acid ligand undergoes ligand exchange with one molecule of TFE to generate active Pd(II) species **I**.[16] Subsequently, catalyst-substrate complex **IIa** (Figure 2) is formed in which the palladium is suitably placed in the vicinity of distal-C–H bond of ferrocene leading to C–H activation, to form the conformationally well-defined ferrocene-appended 12-membered palladacycle **II** aided by chelating with iminol nitrogen of MPAA, as confirmed by ESI-HRMS studies. Coordination followed by 1,2-migratory insertion of olefin to provide intermediate **III**. β-hydride elimination results in the formation of desired 1,3-functionalized ferrocene derivative *via* intermediate **IV**. The resultant Pd(0) complex formed after reductive elimination during the reaction is reoxidized with the help of silver salt, thus regenerating the catalytic Pd(II) species. A detailed study may be required to fully understand the mechanism of this Pd(II)-catalyzed precise distal C–H activation

in ferrocene *via* the strained 12-membered ferrocene appended palladium intermediate, leading to the synthesis of 1,3-disubstituted ferrocenes, assisted specifically by monoprotected amino acid (MPAA) ligands.

In summary, by following this synthetic protocol we were able to achieve hitherto inaccessible chemical space in ferrocene *via* an engineered long molecular bridge. We anticipate that this unprecedented distal C–H functionalization in ferrocene *via* the template approach will give access to elusive positional isomers in this prototypical metallocene which would enable enantioenriched planar chiral ligands by kinetic resolution.[6a] We are sure this will have a major impact in the development new series of ligands, eventually various new reaction gets facilitated by them, also in the synthesis of pharmaceuticals, and functionalized materials. Synthesis of enantiopure ferrocene 1,3-derivatives using a chiral template approach is in progress in our laboratory.

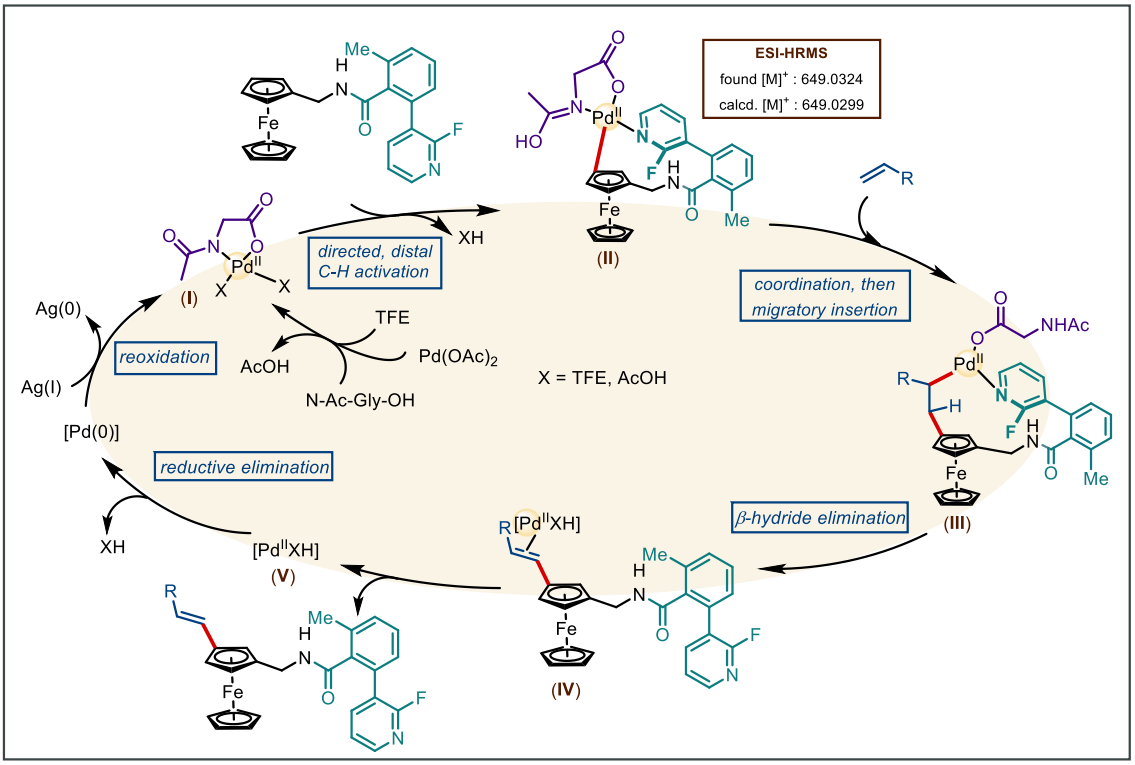


Figure 6: **Plausible reaction mechanism of distal C–H activation of ferrocenyl methylamine**

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Supporting Information

Experimental details and spectral data of all new compounds, X-ray data of **3q** (CCDC 2226153).

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Notes

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