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Iron-Catalyzed Directed C2-Alkylation and Alkenylation of Indole with Vinylarenes and Alkynes

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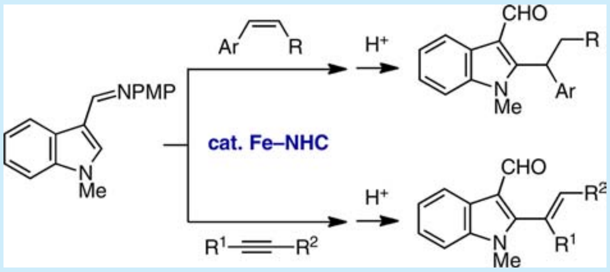
Supporting Information

ABSTRACT: An iron–N-heterocyclic carbene catalyst generated from an iron(III) salt, an imidazolinium salt, and a Grignard reagent promotes alkylation and alkenylation reactions at the indole C2-position with vinylarenes and internal alkynes, respectively, via imine-directed C–H activation. The former reaction affords 1,1-diarylalkane derivatives with exclusive regioselectivity. Deuterium-labeling experiments suggest that these reactions involve oxidative addition of the C–H bond to the iron center, insertion of the unsaturated bond into the Fe–H bond, and C–C reductive elimination.



Insertion of unsaturated hydrocarbon molecules such as alkenes and alkynes into unactivated aromatic C–H bonds (hydroarylation) represents an atom-economical approach for the introduction of alkyl and alkenyl groups onto arenes. In the past few decades, low-valent late transition metal complexes such as ruthenium,[1,2] rhodium,[3,4] iridium,[5] rhenium,[6] nickel,[7] cobalt,[8,9] and manganese[10] complexes have been demonstrated to catalyze a variety of such hydroarylation reactions with or without the assistance of heteroatom directing groups. A typical catalytic cycle of this type of C–H functionalization involves three elementary steps, that is, oxidative addition of the C–H bond to the low-valent metal center (M), migratory insertion of an alkene or alkyne into the M–H bond, and C–C reductive elimination of the resulting diorganometal species.

In light of the above mechanistic framework, we became interested in the potential use of economically and environmentally attractive iron complexes as catalysts for hydroarylation, because each of the three elementary steps appeared feasible. Thus, aromatic C–H bonds are known to undergo oxidative addition to low-valent iron complexes,[11] while migratory insertion of an alkene or alkyne into Fe–H and C–C reductive elimination are common steps in iron-catalyzed reactions such as hydrogenation/hydrosilylation[12] and cross-coupling,[13] respectively. We report herein that an iron–N-heterocyclic carbene (NHC) catalyst generated from an iron(III) salt, an imidazolinium salt, and a Grignard reagent[14] promotes imine-directed insertion of vinylarenes and alkynes into an indole C2–H bond to afford the corresponding alkylation and alkenylation products, respectively. To our knowledge, the reaction represents the first example of iron-catalyzed hydroarylation involving directed C–H activation.[15–17]

The present study began with attempts to perform our previously developed cobalt-catalyzed imine- or pyridine-directed hydroarylation reactions[9] using an iron complex as an alternative catalyst. While simple replacement of the cobalt precatalyst with an iron salt was not effective at all in most of those reactions, the reaction of 1-methyl-3-iminoindole **1** and styrene **2a**[18] was found to be feasible (Table 1). In the presence of $Fe(acac)_3$ (99%, 10 mol %), bis(2,6-dimethylphenyl)-imidazolium chloride (IXyl·HCl, 10 mol %), CyMgCl (100 mol %), and TMEDA (2 equiv), the reaction proceeded in THF at 60 °C to afford 1,1-diarylethane **3a** as the exclusive regioisomer in 72% yield (Table 1, entry 1). The reaction was further improved by using bis(2,6-dimethylphenyl)imidazolinium chloride (SIXyl·HCl) instead of IXyl·HCl, affording **3a** in 90% yield (Table 1, entry 2).

Subsequent screening experiments were performed using less reactive 2-methylstyrene **2b** in place of **2a**. Key findings are summarized as follows: (1) A better yield was achieved in Et_2O than in THF (Table 1, entries 3 and 4). (2) SIXyl·HCl showed the best performance among other common imidazolinium preligands (Table 1, entries 5 and 6). (3) Phosphine and bipyridine ligands as well as ligand-free conditions were almost ineffective (Table 1, entries 7–10). (4) The reaction was shut down in the absence of TMEDA (Table 1, entry 11). (5) No reaction took place when tBuCH$_2$MgBr was used instead of CyMgCl (Table 1, entry 12). Note that high-purity $Fe(acac)_3$ (>99.9%) gave essentially the same result as reagent-grade $Fe(acac)_3$ (Table 1, entry 13). In addition, no reaction was observed when a small amount of $CoBr_2$ (0.5 mol %) was used instead of $Fe(acac)_3$ (Table 1, entry 14). The same observation was made for other metal salts such as $Mn(acac)_3$ and $Ni(acac)_2$. Thus, it is unlikely that trace metal impurity is responsible for the observed reactivity. Note that reduction of the amount of CyMgCl led to diminished catalytic activity.

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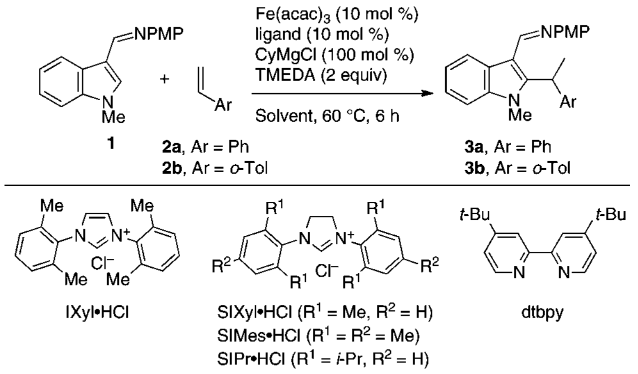
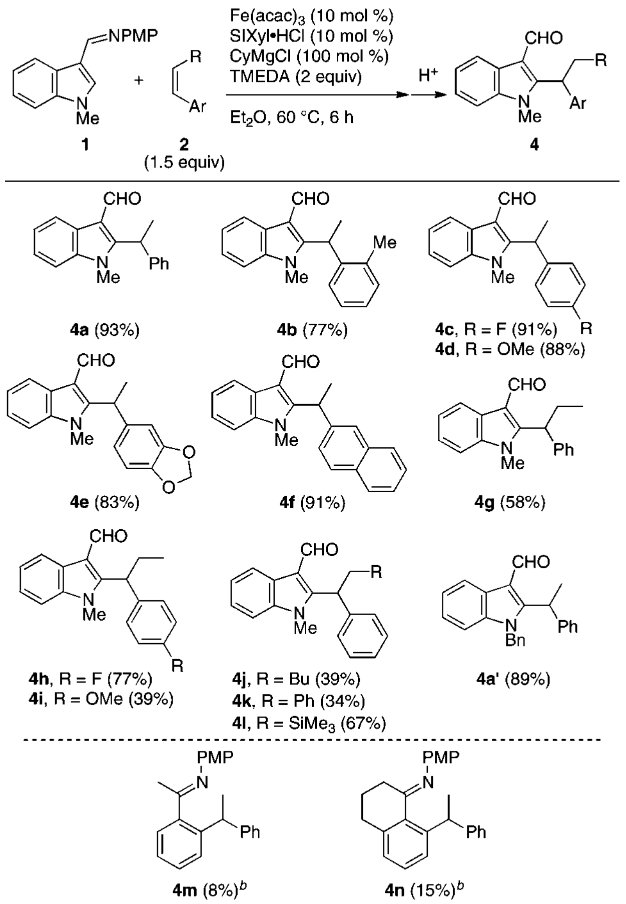
Table 1. Screening of Reaction Conditions[a]



entry	olefin	ligand	solvent	yield (%)[b]
1	**2a**	IXyl·HCl	THF	72
2	**2a**	SIXyl·HCl	THF	90
3	**2b**	SIXyl·HCl	THF	59
4	**2b**	SIXyl·HCl	Et_2O	65
5	**2b**	SIMes·HCl	Et_2O	57
6	**2b**	SIPr·HCl	Et_2O	20
7	**2b**	PCy_3	Et_2O	4
8[c]	**2b**	PPh_3	Et_2O	2
9	**2b**	dtbpy	Et_2O	0
10	**2b**	none	Et_2O	6
11[d]	**2b**	SIXyl·HCl	Et_2O	0
12[e]	**2b**	SIXyl·HCl	Et_2O	0
13[f]	**2b**	SIXyl·HCl	Et_2O	67
14[g]	**2b**	SIXyl·HCl	Et_2O	0

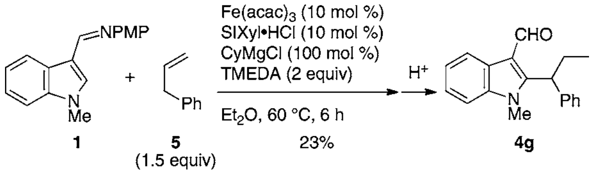
[a] The reaction was performed using **1a** (0.2 mmol), **2a** or **2b** (0.3 mmol). $Fe(acac)_3$ (99%) was used. PMP = *p*-methoxyphenyl. [b] Determined by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [c] 20 mol % of PPh_3 was used. [d] TMEDA was omitted. [e] *t*-$BuCH_2MgBr$ was used instead of CyMgBr. [f] $Fe(acac)_3$ (≥99.9%) was used. [g] $CoBr_2$ (0.5 mol %) was used instead of $Fe(acac)_3$.

Scheme 1. Imine-Directed C2-Alkylation of Indole with Vinylarenes[a]



[a] The reaction was performed on a 0.2 mmol scale. [b] Determined by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

Scheme 2. Isomerization/Hydroarylation of Allylbenzene[a]

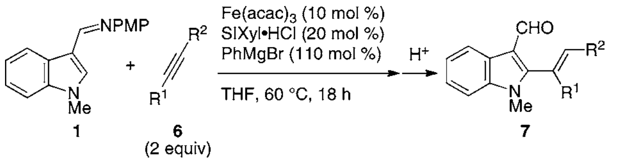


With the optimized reaction conditions (Table 1, entry 4) in hand, we next explored the scope of vinylarenes (Scheme 1). A variety of substituted styrene derivatives participated in the reaction with **1** to afford, upon acidic hydrolysis, 1,1-diarylethane derivatives bearing C3-formyl group **4a**–**4f** in good yields, while the reaction turned out incompatible with functional groups such as bromo, iodo, and cyano groups (see the Supporting Information for detail). *cis*-*β*-Substituted styrenes bearing alkyl, aryl, and silyl substituents were also amenable to the present reaction, thus affording the corresponding 1,1-diarylalkanes **4g**–**4l** in moderate yields. Note that *trans*-*β*-methylstyrene showed much poorer reactivity than the *cis*-isomer. An indole substrate with an N-benzyl protecting group reacted smoothly with styrene to afford the adduct **4a′** in a good yield, while an N-Boc derivative failed to participate in the reaction. Note that imines derived from acetophenone and tetralone also participated in the reaction with styrene under the present iron catalysis, albeit in low yields (Scheme 1, bottom).[9h]

Similarly to the case of the cobalt-catalyzed reaction,[18] the iron-catalyzed reaction of **1** with allylbenzene **5** afforded the 1,1-diarylpropane derivative **4g** albeit in a low yield, presumably through an olefin isomerization[19]–hydroarylation sequence (Scheme 2). Under the present reaction conditions, no reaction took place when another terminal alkene such as 1-octene or vinyltrimethylsilane was employed as the reaction partner.

With some modifications, the Fe–SIXyl catalyst also promotes the imine-directed C2-alkenylation of indole with internal alkynes (Table 2) (see the Supporting Information for the optimization).[20] Thus, with a catalyst generated from $Fe(acac)_3$ (10 mol %), SIXyl·HCl (20 mol %), and PhMgBr (110 mol %) in THF, the reaction of **1** with diphenylacetylene was achieved to afford the hydroarylation product **7a** in a good yield with high *syn*-stereoselectivity (Table 2, entry 1). Di(4-methoxyphenyl)-acetylene also smoothly participated in the reaction (Table 2, entry 2), while the reaction of di(4-fluorophenyl)acetylene was rather sluggish (Table 2, entry 3). The reaction of di(*o*-tolyl)acetylene afforded the alkenylation product **7d** in 40% yield with a modest *E*/*Z* ratio of ca. 3:2 (Table 2, entry 4). An unsymmetrical diarylacetylene bearing phenyl and mesityl groups underwent C–C bond formation regioselectively at the less hindered acetylenic carbon proximal to the phenyl group, thus affording the alkenylation product **7e** in 70% yield with high stereoselectivity (Table 2, entry 5). The regio- and stereochemistry of **7e** was unambiguously confirmed by single crystal X-ray diffraction analysis (see the Supporting Information). The

Table 2. Imine-Directed C2-Alkenylation of Indole with Internal Alkynes[a]



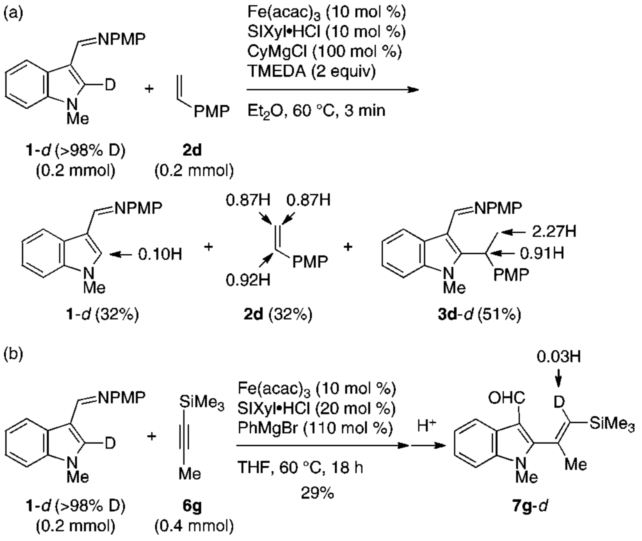
entry	R^1	R^2	7, yield (%)[b]	E/Z[c]
1	Ph	Ph	**7a**, 84	94/6
2	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**7b**, 83	96/4
3	4-FC_6H_4	4-FC_6H_4	**7c**, 25	95/5
4	2-MeC_6H_4	2-MeC_6H_4	**7d**, 40	57/43
5	Ph	Mes	**7e**, 70	>99/1
6	Ph	$SiMe_2Ph$	**7f**, 79	76/24
7	Me	$SiMe_3$	**7g**, 59	>99/1
8	Pr	Pr	**7h**, 18	75/25

[a]The reaction was performed on a 0.3 mmol scale. [b]Isolated yield. [c]Determined by ^1H NMR.

reaction of silyl-substituted alkynes also took place regioselectively, the new C−C bond being formed at the position distal to the silyl group (Table 2, entries 6 and 7). 4-Octyne reacted sluggishly to afford the corresponding alkenylation product **7h** in a low yield with moderate stereoselectivity (Table 2, entry 8). Note that terminal alkynes such as phenylacetylene and 1-octyne failed to participate in the present alkenylation reaction.

To gain mechanistic insights into the present hydroarylation reactions, deuterium-labeling experiments were performed (Scheme 3). The reaction of the C2-deuterated indole substrate **1**-*d* with 4-methoxystyrene **2d**, when quenched at the reaction time of 3 min, afforded the hydroarylation product **3d**-*d* in 51% yield along with recovery of the starting materials both in ca. 30% yields (Scheme 3a). The deuterium content of **1**-*d* decreased only slightly (0.90D), and the deuterium incorporation into the olefinic positions of **2d** was marginal (ca. 0.1D for each). In accordance with these observations, the methyl position of **3d**-*d* was substantially deuterated (>0.7D), while the methine position was not (<0.1D). The reaction of **1**-*d* with 1-trimethylsilylprop-1-yne **6g** afforded the product **7g**-*d* with virtually complete transfer of the C2-deuterium atom to the vinylic position (Scheme 3b). Note that the yield of **7g**-*d* was much lower (29%) compared with that of **7g** obtained from the parent substrate (59%) (Table 2, entry 7).

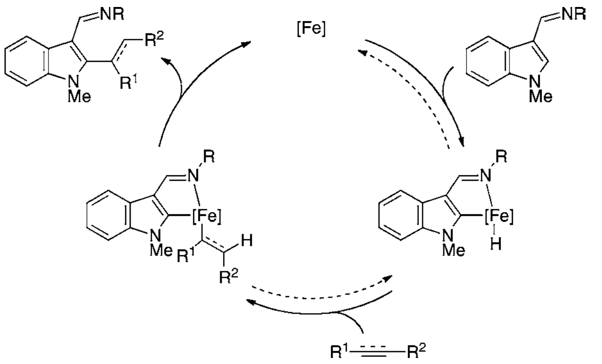
Scheme 3. Deuterium-Labeling Experiments[a]



[a]The yields and the proton contents were determined by ^1H NMR spectroscopy.

We speculate that the present reaction is initiated by the formation of a low-valent iron−NHC complex through reduction of the Fe(III) precatalyst by the Grignard reagent in the presence of the imidazolinium salt. The reason for the necessity of an excess amount of the Grignard reagent is not clear, but might be attributed to the formation of a ferrate species.[21] On the basis of the results of the deuterium-labeling experiments, we propose a catalytic cycle involving chelation-assisted oxidative addition of the C−H bond to iron,[11c,d] migratory insertion of an alkene or alkyne into the Fe−H bond, and reductive elimination of the resulting diorganoiron species (Scheme 4). The observation of H/D scrambling in the reaction of **1**-*d* and **2d** (Scheme 3a) may suggest that the oxidative addition and migratory insertion steps are reversible and that the reaction rate and the regioselectivity are primarily controlled in the reductive elimination step.[9b,g] Note, however, that reductive elimination would not be substantially slower than deinsertion, because the distributions of the deuterium atoms in the recovered starting materials are far from statistical equilibrium (i.e., 0.25D for each position). The poorer reactivity of **1**-*d* in the addition to **6g** suggests that the C−H oxidative addition is rate-limiting in the alkyne hydroarylation.[9e]

Scheme 4. Possible Catalytic Cycle



In summary, we have developed iron−NHC catalytic systems for the directed C2-alkylation and alkenylation of indole with vinylarenes and internal alkynes, respectively. Unlike other iron-catalyzed C−H functionalization reactions developed by Nakamura and others,[16] the present reaction appears to involve C−H oxidative addition rather than deprotonative C−H metalation. Further efforts in the elaboration of the iron−NHC catalytic system to achieve broader-scope hydroarylation are currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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