C–H Activation

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Iridium-Catalyzed Enantioselective C–H Alkylation of Ferrocenes with Alkenes Using Chiral Diene Ligands**

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Abstract: *The first catalytic and enantioselective C–H alkylation of ferrocene derivatives with various alkenes was achieved. A cationic iridium complex, having a chiral diene ligand, and an isoquinolyl moiety as a directing group are essential for regioselective and enantioselective C–H bond activation.*

Transition metal catalyzed C–C bond formation initiated by C–H bond cleavage is an ideal synthetic protocol because preactivation of the substrate is unnecessary, and thus makes possible a shorter and more atom-economical synthesis.[1] Since monumental work of Murai et al. on the ruthenium-catalyzed C–H alkylation,[2] various transition-metal catalysts have been reported for C–H bond activation using directing groups such as carbonyl and imino groups.[3] Some reactions have been used as key steps in natural product synthesis.[4] However, catalytic and asymmetric C–C bond formation initiated by enantioselective C(sp^3)–H bond cleavage is still a challenging topic. Secondary C–H bond cleavage induces a chiral center, but the C(sp^3)–H bond is intrinsically more difficult to cleave than the C(sp^2)–H bond. The first successful example was a chiral copper-catalyzed alkynylation at the benzylic position.[5] Yu and co-workers reported an enantioselective palladium-catalyzed arylation of cyclopropane rings.[6] Chiral rhodium-catalyzed intramolecular alkylation at the allylic position is another successful example.[7] We also reported enantioselective C(sp^3)–H alkylation using a chiral iridium catalyst.[8] Another approach to the creation of a chiral center is desymmetrization initiated by C(sp^2)–H bond cleavage. Yu and co-workers reported the asymmetric synthesis of chiral diarylmethane compounds initiated by enantioselective C(sp^2)–H bond cleavage.[9] The generation of planar chirality by enantioselective C(sp^2)–H bond cleavage is also fascinating. In the first elegant work on the enantioselective C–H bond activation of ferrocene, You and co-workers reported a palladium-catalyzed enantioselective arylation, alkenylation, and annulation of aminomethylferrocene.[10] Described herein is the iridium-catalyzed enantioseletive alkylation of (isoqunolin-1-yl)ferrocene (**1a**) using chiral diene ligands, and it serves as the first example of an asymmetric reaction initiated by enantioselective C–H bond cleavage using chiral diene ligands.[11]

Ferrocene is a historically important organometallic compound, and the application of its derivatives in medicinal chemistry and material science has attracted much attention.[12] With regard to organic synthesis, the planar chirality of ferrocene having two different substituents is utilized.[13] In fact, a chiral diphosphine, xyliphos, which has a planar-chiral ferrocene scaffold, is used in iridium-catalyzed hydrogenation on a scale of 10000 ton per year.[14] However, the preparation of planar-chiral ferrocenes has relied on optical resolution or diastereoselective approaches.[15] With respect to enantioselective synthesis, *ortho* lithiation using chiral diamines has been the most successful example.[16] Recently, Ogasawara reported a molybdenum-catalyzed asymmetric olefin metathesis for the creation of planar chirality in ferrocene.[17] In contrast, we recently reported the [Ir(cod)$_2$]BARF-catalyzed C–H alkenylation and alkylation of ferrocenes possessing a directing group.[18] A mechanistic study revealed that cycloocta-1,5-diene (cod) coordinated to the metal center throughout the entire catalytic cycle, and phosphine ligands deactivated the catalytic activity. The results were quite different from those in other iridium-catalyzed C–H bond activations, where phosphine ligands were considered to be critical for efficient transformation.[19] Against this background, we investigated the enantioselective C–H bond activation of ferrocene by using an iridium/chiral diene catalyst.

We chose (isoquinolin-1-yl)ferrocene (**1a**) as a model substrate and examined the reaction with ethyl acrylate (**2a**) (Table 1). As representative diene ligands, Hayashi's diene **L1**[20] and Carreira's diene **L2**[21,22] were used in combination with [{Ir(coe)$_2$Cl}$_2$] and sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) in toluene (entries 1 and 2).[23] The monoalkylated product **3aa** was obtained in good yield in both cases, but the enantioselectivities differed. In this transformation, the rhodium counterpart was completely ineffective (entry 3). We additionally examined various analogues of **L2** derived from carvone (entries 4–7).[24] A *p*-tolyl group gave the best results, and the *ee* value exceeded 90% (entry 5).

We next examined the effect of the directing group (DG) on ferrocene on the enantioselectivity and regioselectivity using exactly one equivalent of ethyl acrylate (Table 2). Even a simple pyridyl group induced excellent enantioselectivity,

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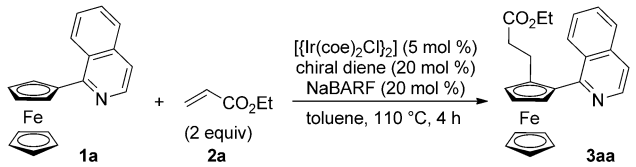
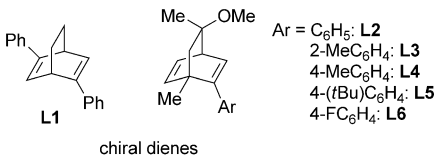
Table 1: Screening of chiral dienes in the iridium-catalyzed C–H alkylation of **1a**.



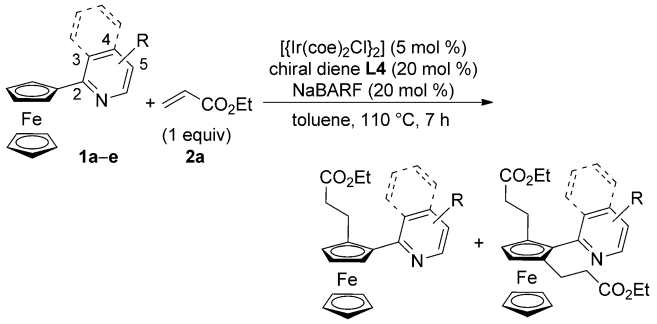


chiral dienes

Entry	Chiral diene	Yield [%][a]	*ee* [%][b]
1	**L1**	80	<2
2	**L2**	91	84
3[c]	**L2**	n.r.	–
4	**L3**	72	22
5[d]	**L4**	90	91
6	**L5**	60	85
7	**L6**	85	59

[a] Yield of the isolated product. [b] The *ee* value was determined by HPLC analysis using a chiral stationary phase. [c] In place of [{Ir(coe)$_2$Cl}$_2$], [{Rh(coe)$_2$Cl}$_2$] was used. [d] The reaction time was 7 h. n.r. = no reaction. coe = cyclooctene.

Table 2: Effect of directing group on the enantioselectivity and regioselectivity.

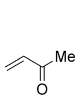
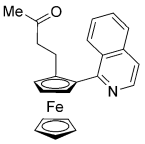
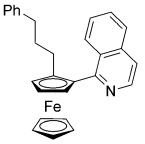
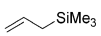
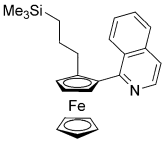
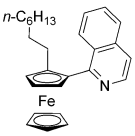
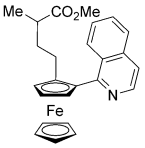
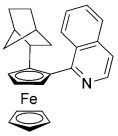


Entry	Directing group		**3** Yield [%][a]	**3** *ee* [%][b]	**4** Yield [%][a]
1	pyridin-2-yl	**1b**	33 (**3ba**)	97	ca. 30[c]
2	5-Me-pyridin-2-yl	**1c**	32 (**3ca**)	98	ca. 30[c]
3	4-Me-pyridin-2-yl	**1d**	45 (**3da**)	96	ca. 25[c]
4	3-Me-pyridin-2-yl	**1e**	77 (**3ea**)	93	trace
5	isoquinolin-1-yl	**1a**	88 (**3aa**)	90	trace
6	pyrimidin-2-yl	**1f**	trace	–	ca. 35[c]
7	pyrimidin-4-yl	**1g**	n.r.	–	–

[a] Yield of the isolated product. [b] The *ee* value was determined by HPLC analysis using a chiral stationary phase. [c] Inseparable impurities were included.

but the yield of the monoalkylated adduct **3ba** was low and a significant amount of the achiral dialkylated product **4ba** was also obtained (entry 1).[25] A methyl group at the 5- or 4-position could not suppress the second alkylation, but in the case of a 3-methylpyridin-2-yl group, as well as an isoquinolin-2-yl group, only trace amounts of the dialkylated products were detected (entries 4 and 5). These results imply that the substituent adjacent to the ferrocenyl group controls the regioselectivity, and the coordination of the nitrogen atom to the metal center leads to excellent enantioselectivity. The pyrimidyl group was ineffective in this C–H alkylation and the monoalkylated products **3** were not obtained (entries 6 and 7).[26]

Table 3: Substrate of scope with respect to the alkenes.[a]

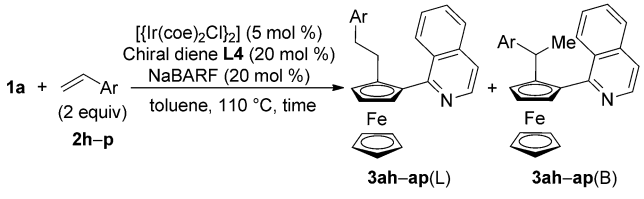
Entry	Alkene	*t* [h]	**3** Yield [%][b]	*ee* [%][c]
1[c]	 **2b**	48	 38 (**3ab**)	75
2	 **2c**	24	 83 (**3ac**)	88
3	 **2d**	24	 73 (**3ad**)	93
4	 **2e**	24	 96 (**3ae**)	79
5[d]	 **2f**	24	 64 (d.r. = 2:1) (**3af**)[e]	83
6	 **2g**	24	 78 (**3ag**)	77

[a] The reaction conditions were the same as those used for the reactions in Table 2 except the reaction time. [b] Yield of the isolated product. [c] The *ee* value was determined by HPLC analysis using a chiral stationary phase. [d] Four equivalent amounts of alkenes were used. [e] The stereostructures of the diastereomers could not be determined. The *ee* value of the minor diastereomer was 85%.

Several alkenes were subjected to the reaction with (isoquinolin-1-yl)ferrocene (**1a**; Table 3). Methyl vinyl ketone (**2b**) was too reactive, and the chiral ketone **3ab** was obtained, albeit in low yield (entry 1). The reactions of allylbenzene and allylsilane gave the corresponding monoalkylated products **3ac** and **3ad** (entries 2 and 3). Notably, a simple alkene, oct-1-ene (**2e**), could be used as a coupling partner (entry 4). The reaction of methyl methacrylate (**2f**) also proceeded, but the products were obtained as a 2:1 diastereomeric mixture (entry 5). Norbornene (**2g**) was also a good alkylating reagent (entry 6).[27]

Table 4 shows the results of the reaction of **1a** with styrene derivatives under the same reaction conditions.[24] In each case, high to excellent yields were achieved, but the branched

Table 4: Substrate scope of with respect to the styrenes.

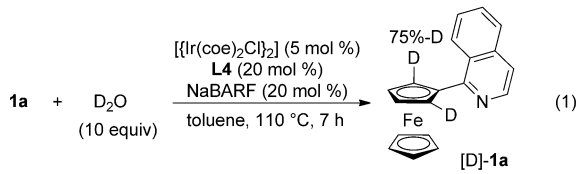


Entry	Ar		*t* [h]	Yield [%][b]	L/B[b]	*ee* [%][c]
1	C_6H_5	**2h**	7	96 (**3ah**)	3:1	89 (91)[d]
2	2-BrC_6H_4	**2i**	7	92 (**3ai**)	>20:1	83
3	3-BrC_6H_4	**2j**	24	96 (**3aj**)	2:1	87
4	4-BrC_6H_4	**2k**	24	95 (**3ak**)	2:1	83
5	4-ClC_6H_4	**2l**	12	99 (**3al**)	2:1	87
6	2-$CF_3C_6H_4$	**2m**	7	99 (**3am**)	>20:1	82
7	3-$CF_3C_6H_4$	**2n**	24	86 (**3an**)	2:1	87 (91)[e]
8	C_6F_5	**2o**	24	69 (**3ao**)	>20:1	51 (95)[f]
9	naphthalen-2-yl	**2p**	7	95 (**3ap**)	1:1	91

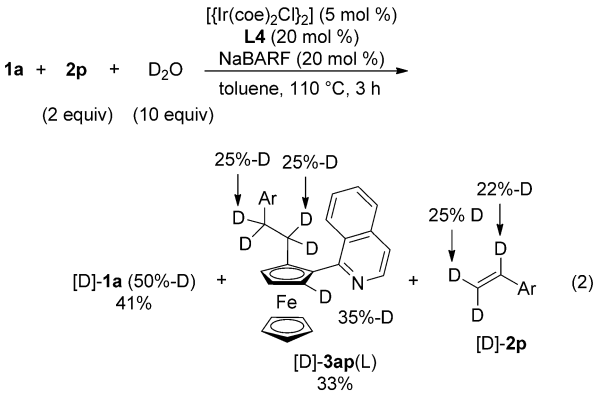
[a] Yield of the isolated product. [b] The ratio of linear and branched adducts was determined by NMR analysis. [c] The *ee* value was determined by HPLC analysis using a chiral stationary phase. The *ee* value of the linear products **3ah**–**ap**(L) was listed, unless otherwise noted. [d] The *ee* value using **L2** as a chiral ligand is described in the parentheses. [e] The *ee* value of the branched adduct **3an**(B) is described within the parentheses. It was obtained as a single diastereomer, but its stereostructure could not be determined. [f] The *ee* value after recrystallization of the obtained **3ao**(L) is described within the parentheses.

alkylated products **3**(B) were also obtained as minor products. In the reaction with *ortho*-substituted styrenes, the linear adducts **3ai**(L) and **3am**(L) were the only detectable products (entries 2 and 6). The reaction of pentafluorostyrene (**2o**) gave only the linear product **3ao**(L) (entry 8). The *ee* value was moderate, but recrystallization of the solid sample drastically improved the enantiomeric purity to 95%, and the structure of the product was determined to be *R* form by X-ray analysis.[28] The *ee* value of the linear products was generally good to high and a comparable *ee* value of the branched product **3an**(B) was ascertained (entry 7).[29]

As a preliminary mechanistic study, we performed labelling experiments. When **1a** was subjected to the reaction conditions in the presence of D_2O and the absence of alkene, deuteration of C–H bond on ferrocene adjacent to the isoquinolin-1-yl moiety was observed [Eq. (1)]. When the reaction was conducted in the presence of both D_2O and 2-vinylnaphthalene (**2p**), and was quenched within 3 hours, deuteration at both the α and β-position of the naphthalene



ring of the product **3ap**(L) was observed [Eq. (2)]. Two vinylic positions of the recovered **2p** ring were also deuterated. These results imply that the C–H bond on ferrocene is cleaved under the present reaction conditions and the alkene insertion pathway is reversible.[8b]



In conclusion, we have developed a catalytic and enantioselective C–H alkylation of (isoquinolin-1-yl)ferrocene with various alkenes. The combination of a cationic iridium complex with a chiral diene ligand is essential for regioselective and enantioselective C–H bond activation. This reaction is the first example of the enantioselective C(sp^2)–H alkylation of ferrocenes. Further studies on the scope of the alkenes and application of the obtained planar-chiral ferrocenes are underway in our laboratory.

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[23] The solvent and counter anion effect were shown in Table S1 in the Supporting Information.

[24] The ligand screening of the reaction with styrene was shown in Table S2.

[25] The kinetic resolution of racemic **3ba** was examined but the *ee* value of recovered **3ba** was low (31% *ee*; see the Supporting Information).

[26] Other directing groups such as acetyl and dimethylaminomethyl groups were ineffective and no reaction proceeded under the same reaction conditions.

[27] The reaction with ynones such as methyl propiolate and methyl 3-phenylpropiolate did not proceed under the same reaction conditions.

[28] The stereostructure of **3ao**(L) is shown in the Supporting Information.

[29] The reaction of diphenylacetylene proceeded to give monoalkenylated product in 66%, but its *ee* value was below 2%.

