Ir-catalyzed C–H activation in the synthesis of borylated ferrocenes and half sandwich compounds†

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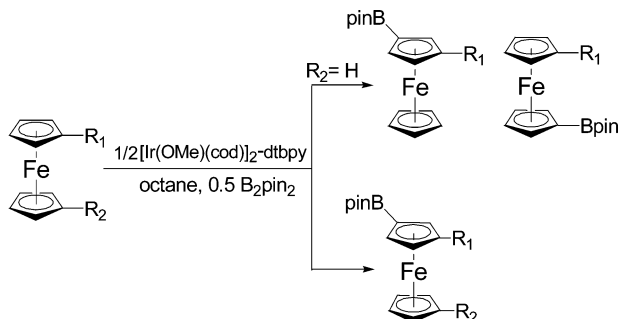E-mail: plenio@tu-darmstadt.de*

The complex generated from $\frac{1}{2}$ [Ir(OMe)(cod)]$_2$ and 4,4′-di-*tert*-butyl-2,2′-bipyridine catalyzes the regioselective borylation of ferrocenes, CpMn(CO)$_3$ and CpMo(CO)$_3$CH$_3$ with a stoichiometric amount of B$_2$pin$_2$.

Functionalized ferrocenes are of interest due to their use as chiral ligands in catalysis[1] and as components of polymers,[2] molecular switches,[3] drugs,[4] and sensors.[5] Most applications involve the use of di-, tri- or even higher substituted ferrocenes. Consequently, there is a permanent interest in new tools for the derivatization of ferrocene.[6] The most common method of functionalization is the deprotonation with bases such as *n*-BuLi, to generate a potent nucleophile followed by substitution reactions with various electrophiles. A significant advantage of this approach is the presence of *ortho*-directing groups for the metallation, which allows the precise control of regioselectivity (or stereoselectivity) for the synthesis of 1,2-disubstituted ferrocenes. On the downside, organolithium reagents are highly reactive and impose restrictions related to functional group tolerance. The chemistry of 1,3-disubstituted ferrocenes is much less explored even though they were used by Deschenaux *et al.* for the preparation of organometallic liquid crystals[7] and by Plenio *et al.* for the synthesis of alternating ferrocene acetylene polymers.[8]

The Ir-based complex prepared *in situ* from [IrCl(cod)]$_2$ or [Ir(OMe)(cod)]$_2$ and 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) was shown to be an excellent catalyst for the direct functionalization of unreactive hydrocarbons by C–H activation with bis(pinacolato)diboron (B$_2$pin$_2$).[9]

This methodology of aromatic C–H activation prompted us to extend it to the chemistry of ferrocene, its derivatives and related half sandwich compounds, to demonstrate the utility of Ir-catalyst based CH-activation reactions in organometallic chemistry.

The coupling between ferrocene and stoichiometric amounts of B$_2$pin$_2$ is catalyzed by 1/2[Ir(OMe)(cod)]$_2$ and 4,4′-di-*tert*-butyl-2,2′-bipyridine (dbtpy) in an inert solvent at elevated temperatures. As noted by Ishiyama *et al.*,[10] the reactions are fast in nonpolar solvents (alkanes), as compared to coordinating solvents like DMF or DME.

The reaction of ferrocene with B$_2$pin$_2$ in the presence of the aforementioned Ir-complex was carried out at 126 °C for 24 h in octane.‡ At this point the reaction mixture primarily consists of the monoborylated product FcBpin formed in 60% yield, unreacted ferrocene and 1,1′-Fc(Bpin)$_2$, formed in a yield of less than 5%. 1,2-Fc(Bpin)$_2$ and 1,3-Fc(Bpin)$_2$ were not observed. More forcing conditions did not lead to an appreciable increase in the yield of the diborylated ferrocene, even when using a significant excess of B$_2$pin$_2$. Similarly, isolated FcBpin could not be further functionalized with B$_2$pin$_2$. Even at this early stage it has to be conceded that the reactivity of ferrocene is significantly reduced as compared to that of benzene; probably due to the much higher electron density and steric hindrance of the former.

In order to evaluate the usefulness of C–H-activation for the synthesis of substituted ferrocenes, a range of mono- and disubstituted ferrocene derivatives were examined (Table 1). Several borylated ferrocenes can be synthesized, but the reactions are most effective with electron-deficient metallocenes. The influence of electronic effects becomes quite clear when comparing the reactivity of 1,1′-FcBr$_2$ and 1,1′-Fc(CH$_3$)$_2$, with substituents of comparable steric bulk. The borylation of the former compound is facile (yield 81%), while 1,1′-Fc(CH$_3$)$_2$ is converted only in modest 12% yield. In both cases the respective 1,3,1′-isomers are formed exclusively.

Oxygen containing functional groups at the ferrocene, like FcCOOCH$_3$, where reaction with the carbonyl groups could possibly compete with borylation was found to be stable towards B$_2$pin$_2$. The borylation of FcCOOMe and 1,1′-Fc(COOMe)$_2$ resulted in monoborylated products in very good yields, again suggesting that the presence of electron withdrawing groups on the cyclopentadienyl ring results in a marked increase in the reactivity

Scheme 1 Borylation of ferrocenes

Table 1 Borylation of ferrocenes and half-sandwich complexes

Reactant	B$_2$pin$_2$ (equiv.)	Product[a]	Yield (%)
Ferrocene	1.0	FcBpin	60
Ferrocene	3.0	FcBpin	61
		1,1′-Fc(Bpin)$_2$	8
FcCOOCH$_3$	1.5	1,3-FcBpin(COOCH$_3$)	42
		1,1′-FcBpin(COOCH$_3$)	31
1,1′-Fc(COOCH$_3$)$_2$	1.5	1,1′,3-FcBpin(COOCH$_3$)$_2$	83
FcBr	1.5	1,1′-FcBpin(Br)	28
		1,3-FcBpin(Br)	35
1,1′-Fc(Br)$_2$	1.5	1,1′,3-FcBpin(Br)$_2$	81
1,1′-Fc(COCH$_3$)$_2$	1.0	1,1,3′-FcBpin(COCH$_3$)$_2$	15
1,1-Fc(CH$_2$OCH$_3$)$_2$	1.0	1,1,3′-FcBpin(CH$_2$OCH$_3$)$_2$	15
1,1′-Fc(CH$_3$)$_2$	1.0	1,1,3′-FcBpin(CH$_3$)$_2$	12
CpMn(CO)$_3$	1.0	(C$_5$H$_4$Bpin)Mn(CO)$_3$	79
CpMo(CO)$_3$Me	1.0	(C$_5$H$_4$Bpin)Mo(CO)$_3$Me	82
FcBpin	[b]	FcI	55
FcBpin	[c]	1-Fc, 4-COMe-C$_6$H$_4$	55

[a] Reactions were carried out at octane reflux (126 °C) for 24 h unless otherwise noted, 3 mol% catalyst [Ir(OMe)(cod)]$_2$ + dtbpy. [b] Reaction with *N*-iodosuccinimide, time 4 h, room temperature. [c] Suzuki coupling (1-Ad)$_2$PBn, Na$_2$PdCl$_4$ 24 h, 65 °C, THF. The abbreviation Fc is used indiscriminately for ferrocenyl, -diyl and -triyl. All compounds exist as racemates. Yields of the products refer to isolated material after chromatographic purification.

of the respective ferrocene. As a typical example of mono-substituted ferrocenes, methoxycarbonylferrocene, FcCOOMe, gave two borylated products with Bpin substituted at the 3- and the 1′-position. The 1,3-borylated product is preferentially formed and its yield was 1.3 times higher than that of the 1,1′-borylated product.

The different rates for the borylation of $FcCOOCH_3$ and $1,1'$-$Fc(COOCH_3)_2$ were studied by performing a competition reaction with an equimolar mixture of mono- and disubstituted ferrocene and B_2pin_2. The ratio of the yields of the corresponding borylated products was 35 : 65, demonstrating the roughly twofold speed at which the disubstituted product undergoes CH-activation. Similarly, bromoferrocene derivatives were also tested. FcBr and disubstituted $1,1'$-$Fc(Br)_2$ both show good reactivity towards B_2pin_2. Again, FcBr gave two products with $1,3$-$Fc(Br)(Bpin)$ dominating over $1,1'$-$Fc(Br)(Bpin)$, while $1,1'$-$Fc(Br)_2$ gave $1,1',3$-$Fc(Br)_2(Bpin)$ in more than 85% yield.

Since electron deficient ferrocene derivatives were found to be reactive towards CH-activation we were intrigued to study the reactivity of $Fc^+PF_6^-$. However, no borylation took place in octane, DMF, DMA or DME solvent at 150 °C/48 h.

When studying $CpMn(CO)_3$ and $CpMo(CO)_3Me$ as examples of more electron-deficient half sandwich complexes, both compounds can be reacted to result in the respective borylated products in excellent yields of 79% and 82% respectively.

At this point it has to be mentioned that the direct borylation of ferrocene is also possible using BCl_3 or BBr_3 as pioneered by Siebert et al. in the mid seventies.[11] Nonetheless, the significant advantages of the present approach are obvious: a) quite in contrast to boron halides the present Ir-catalyzed reaction is highly tolerant of various functional groups, and b) monosubstitution is possible with high selectivity.

Successful borylation of arenes and heteroarenes with pinBH in the presence of $[Ir(OMe)(cod)]_2$ and dtbpy has been reported by Ishiyama and Miyaura et al.[12] Our attempts to use pinBH instead of B_2pin_2 for the borylation of ferrocene and FcCOOCH under the conditions mentioned for B_2pin_2 led to the corresponding borylated products in modest yields of 10 and 15%, respectively.

To demonstrate the synthetic value of the borylated ferrocenes we have studied the conversion of FcBpin. On treatment with N-iodosuccinimide in acetonitrile FcBpin is converted into FcI in a 55% yield. Such halogenated ferrocenes are useful materials for cross-coupling reactions. Similarly, FcBpin can be used in the Suzuki-Miyaura cross coupling and the reaction with 4-bromoace-tophenone results in formation of 1-Fc, 4-COMe-C_6H_4 in 55% yield.

The results presented here raise some interesting questions with respect to the mechanism of Ir-catalyzed CH-activation reactions. Very recently both Periana, Goddard et al.[13] and Sakaki et al.[14] proposed in two independent publications that Ir(III) and Ir(V) are the relevant oxidation states of the metal in the catalytic cycle. However, there can be little doubt that Ir(V) has considerable oxidative power and should oxidize even electron-deficient ferrocenes.[15] On the other hand, the successful transformation of ferrocenes demonstrates that metallocenes do not inhibit the active Ir-complex.

In conclusion, CH-activation reaction involving ferrocenes and related half-sandwich compounds are powerful tools for the synthesis of functionalized ferrocenes (preferentially electron-deficient ones), which are complementary to existing techniques. This method appears to be especially useful with half sandwich complexes and it remains to be explored whether it can also be applied to other π-perimeters. Notable is the functional group tolerance of the present process, the 1,3-selective substitution and the highly selective formation of the monosubstituted product.

Notes and references

‡ **General.** All reactions and experiments were performed under an atmosphere of dry argon using standard Schlenk techniques. For gas chromatography, Perkin-Elmer Autosystem with a Varian CP-SIL-8 column was used.

General procedure for the Ir-catalyzed CH-activation: To a Schlenk tube equipped with a reflux condenser, $[Ir(OMe)(cod)]_2$ (0.015 mmol, 10.0 mg), dtbpy (0.03 mmol, 4.7 mg), and B_2pin_2 (1.0 mmol, 254.0 mg) were added. Octane (7 ml) and the respective ferrocene or half sandwich complex (2.0 mmol) were added, and the mixture was stirred at the given temperature for the given period of time (typically at reflux for 24 h). The reaction mixture was analyzed with GC and the pure product was isolated by column chromatography (silica gel, cyclohexane/ethyl acetate) and the purity checked by GC and NMR. Isomers were separated by chromatography.

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