ORGANIC LETTERS

2013
Vol. 15, No. 3
714–717

Iron-Catalyzed Allylic Arylation of Olefins via C(sp^3)–H Activation under Mild Conditions

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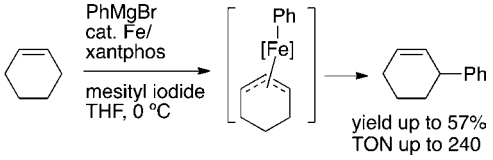
Received January 8, 2013

ABSTRACT



An aryl Grignard reagent in the presence of mesityl iodide converts an allylic C–H bond of a cycloalkene or an allylbenzene derivative into a C–C bond in the presence of a catalytic amount of $Fe(acac)_3$ and a diphosphine ligand at 0 °C. The stereo- and regioselectivity of the reaction, together with deuterium labeling experiments, suggest that C–H bond activation is the slow step in the catalytic cycle preceding the formation of an allyliron intermediate.

Interest in directly substituting the C(sp^3)–H bond[1,2] of an olefin with a nucleophile can be traced back to the Tsuji report on the reaction between a π-allylpalladium complex and a malonate anion.[3] This reaction was first developed into a stoichiometric reaction of an olefin with a stabilized nucleophile in the 1970s,[4] which has long served as a model for the development of catalytic reactions where the catalyst is oxidatively recycled. Several examples of group 9, 10, and 11 metal-catalyzed reactions of a stabilized carbanion[5] and a CF_3Cu reagent[6] are now known in the literature. We report here the coupling of an aryl Grignard reagent with an alkene at 0 °C under iron catalysis[7] (see Scheme 1). The reaction proceeds exclusively through abstraction of an allylic hydrogen atom, and for a cycloalkene used in excess the yield approaches 60% based on the Grignard reagent and with a catalyst turnover number (TON) up to 240. Several lines of evidence suggest that the C–H bond-activation step is the slow step in the catalytic cycle to generate an allyliron intermediate (cf. **C** and **D**). Under similar conditions, PhMgBr can phenylate cyclohexane in 10% yield at 0 °C. These results attest to the extremely high reactivity of organoiron catalytic species[8] and suggest the potential of C–H bond activation of simple hydrocarbons as a synthetically viable tool.

The reaction was designed to take place in the sequence shown in Scheme 1,[9] where PhMgBr first generates a phenyliron species (Ph[Fe]) that reacts with mesityl iodide to give a putative coordinatively unsaturated phenylmesityliron intermediate such as **A**. The use of a bulky mesityl group was considered to be beneficial to create a vacant

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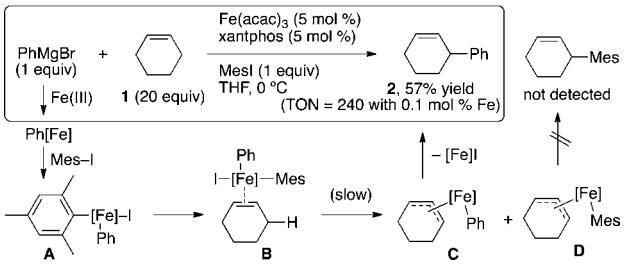
10.1021/ol400056z
Published on Web 01/22/2013

Scheme 1. Iron-Catalyzed Arylation of Cyclohexene (**1**) with PhMgBr in the Presence of Mesityl Iodide (MesI)



coordination site as well as to prevent cross-coupling with PhMgBr.[10] As shown in a deuterium labeling experiment discussed later, both the aryl Grignard reagent and the mesityl iodide participate in the hydrogen abstraction in an olefin complex **B**, probably to generate two π-allylic iron species[11] **C** and **D**. Thus, this hydrogen-abstraction process appears to be insensitive to the steric effects of the mesityl group. However, the subsequent reductive elimination is subject to the steric effects of the mesityl group, as judged by the complete absence of mesitylated cyclohexene via **D** as opposed to the competitive formation of a *p*-tolylated product when *p*-tolyl iodide was used (cf. Table 1, entry 7).

The typical conditions that convert cyclohexene (**1**) to 3-phenylcyclohex-1-ene (**2**) are described first. A solution of PhMgBr in THF (1.08 M, 18.5 mL, 20.0 mmol) was added over 10 min to a solution of $Fe(acac)_3$ (353 mg, 1.00 mmol, 5.0 mol %,), xantphos[12] (579 mg, 1.00 mmol, 5.0 mol %), and mesityl iodide (4.92 g, 20.0 mmol, 1 equiv) in degassed cyclohexene (**1**, 40.0 mL, 20 equiv), and the resulting mixture was stirred for 20 min at 0 °C. After aqueous workup, GC analysis indicated the formation of **2** in 52% yield based on PhMgBr, together with a small amount of biphenyl (15%) that was formed by iron-catalyzed homocoupling of the organometallic reagent.[13] Analytically pure **2** was obtained in 42% yield after column chromatography and distillation. When the reaction was performed on a 0.3 mmol scale, **2** was isolated in 57% yield. While the reaction in the presence of 20 equiv of cyclohexene was homogeneous, the use of 3−5 equiv resulted in black precipitates and a lower yield. Neither here nor for the other examples of olefin arylation illustrated in Table 2 did we observe products from other potentially competing side reactions, such as mesitylation (from **D**, vide supra), cross-coupling between PhMgBr and mesityl iodide,[10] addition of a phenyl or mesityl group across the double bond, and arylation of THF,[9,14] and polyarylated products.

Table 1. Effect of Several Reaction Parameters on the Iron-Catalyzed Arylation of **1** with PhMgBr[a]

entry	modification to conditions in Scheme *1*	**2** (%)[b]	Ph_2 (%)[b,c]
1	none	57	10
2	no $Fe(acac)_3$	0	trace
3	$FeCl_3$ instead of $Fe(acac)_3$	42	10
4	$Fe(acac)_2$ instead of $Fe(acac)_3$	28	14
5	no xantphos	14	46
6	no MesI	0	trace
7	*p*-Tol-I instead of MesI	39[d](+8)[e]	36
8	*c*-$C_6H_{11}I$ instead of MesI	0	32
9	no THF	trace	trace
10	Et_2O instead of THF	trace[f]	44

[a] Reaction conditions: A solution of PhMgBr in THF (1.0 M, 0.3 mmol) was slowly added over 5 min to a mixture of cyclohexene (6 mmol), MesI (0.3 mmol), $Fe(acac)_3$ (0.015 mmol), and xantphos (0.015 mmol), and the reaction mixture was stirred for 30 min at 0 °C. [b] Yield based on PhMgBr, determined by GC in the presence of undecane as an internal standard. [c] Yield based on the consumption of PhMgBr. [d] 4-Methyl-1,1′-biphenyl and 1-cyclohexyl-4-methylbenzene were also obtained. [e] The amount of 1-(cyclohex-2-enyl)-4-methylbenzene in parentheses. [f] 1,1′-Bis(cyclohex-2-ene) was mainly obtained.

The effect of the key reaction parameters on the reaction of cyclohexene is summarized in Table 1 and detailed in the Supporting Information (SI). In the absence of the iron catalyst (entry 2), the reaction did not proceed at all. Both Fe(III) (entry 3) and Fe(II) (entry 4) salts gave similar results. The absence of the ligand (entry 5) resulted in a lower yield and the formation of black precipitates, suggesting that the phosphine ligand stabilized the catalytic system. To obtain the best yield of 57% (entry 6), 1 equiv of mesityl iodide was essential. While a fraction of the mesityl iodide (30−40%) was recovered at the end of the reaction, the use of 0.5 equiv resulted in a decrease in the yield by 5 to 10%. The use of tolyl iodide instead of mesityl iodide resulted in a comparable combined yield of 47% (entry 7) including partial tolylation of cyclohexene, as well as cross-coupling between PhMgBr and tolyl iodide. The use of an aliphatic halide gave neither the desired product nor any cyclohexene derivatives (entry 8). Removal of THF as much as possible at the beginning of the reaction suppressed both the formation of **2** and the homocoupling (entry 9). The use of diethyl ether instead of THF resulted in the formation of a cyclohexene dimer (1,1′-bis(cyclohex-2-ene)) instead of the arylated product **2** (entry 10).

The reaction of 1 equiv of an aryl Grignard reagent with 10−20 equiv of an alkene in the presence of 5 mol % of $Fe(acac)_3$ took place in a synthetically acceptable yield with a TON of 5−10 for cycloalkenes, allylbenzenes and *trans*-β-methylstyrene (Table 2). In no case did we observe any diarylated products. The Grignard reagent was consumed partly for hydrogen abstraction (eq 2) and for

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generation of a catalytically reactive iron species, which accounts for the moderate yields based on the Grignard reagent. When the catalyst loading was decreased to 0.2 mol %, the TON was dramatically increased to 100−240 at the expense of the yield dropping to < 50% (SI, Table S5).

Cyclohexene (entry 1) and cyclopentene (entry 6) reacted with PhMgBr in 54−57% yield, while cycloheptene (entry 7) reacted in 21% yield. Grignard reagents bearing electron-donating or -withdrawing groups or those that are modestly bulky reacted with cyclohexene and allylbenzene in 30−40% yields (entries 1−3, 8−12). Alkenyl and alkyl Grignard reagents did not react under these conditions. 4-Methylcyclohexene (**5**, entry 5) gave *trans*-5-methyl-3-phenylcyclohexene (**6t**) as the main product, together with several minor isomers (cf. Scheme 2). Under these conditions, linear alkenes gave only a trace amount of the desired products (data not shown). A benzylic C−H bond in toluene or diphenylmethane was entirely unreactive. Electron-rich (entry 15) and -deficient (entries 16 and 17) allylbenzene derivatives reacted with nearly equal facility. The allylic position of allylbenzene was arylated selectively over a benzylic site (entry 15), the α-C−H of ether (entries 2 and 10), and the α-C−H of amine (entry 11). Fluorine (entries 3 and 12), chlorine (entry 17), and bromine (entry 18) were tolerated under these conditions. 2-Allylthiophene (entry 19) reacted to afford a yield comparable to that of allylbenzene, and a pyridine-containing substrate did not give any of the desired product. Of considerable mechanistic interest is the smooth and stereoretentive reaction of *trans*-*β*-methylstyrene (entry 20) as opposed to the poor-yielding and stereoisomerizing reaction of *cis*-*β*-methylstyrene (entry 21). No allylbenzene or *trans*-*β*-methylstyrene was found in the reaction mixture, indicating neither positional nor stereochemical isomerization,[15] or such isomerized products being arylated in situ.

The iron system showed similar reactivity toward saturated hydrocarbons (entries 22 and 23). When we performed the reaction using cyclohexane as a substrate and PhMgBr in THF as an aryl donor (entry 22), cyclohexylbenzene was obtained as the sole product in 10% yield (TON = 2). Under similar conditions, *n*-hexane was arylated with an organozinc reagent in 6% yield (TON = 1.2) to give a 1:1 mixture of 2- and 3-phenylhexane (entry 23). In these examples, we noted the formation of a small amount of 2-phenylated THF through competitive phenylation of the reactive C_2 position of THF.[9,14]

The reaction of 4-methylcyclohexane in entry 5 of Table 1 is analyzed in more detail because it showed interesting regio- and stereoselectivity. This observation does not support a pure radical mechanism and suggests the involvement of an allylic iron intermediate. Thus, the reaction gave *trans*-5-methyl-3-phenylcyclohexene (**6t**) as the major product through metal coordination to the alkene (**E**) followed by intramolecular abstraction of axial

Table 2. Iron-Catalyzed Reaction of Allylic Compounds with Organomagnesium Compounds[a]

entry	substrate	ArMgBr	product	yield (%)[b]/TON[c]
1	 **1**	*p*-XC_6H_4MgBr	 **2**	X = H 57/11
2				X = OMe 42/8
3				X = F 31/6
4	 **1**	*o*-TolMgBr		39/8
5	 **5**	PhMgBr	 **6t**	27(+18)[d]/9
6		PhMgBr		n = 1 54/11
7		PhMgBr		n = 3 21/4
8		*p*-XC_6H_4MgBr		X = H 40/8
9				X = Me 40/8
10				X = OMe 31/6
11				X = NMe_2 30/6
12				X = F 42/8
13		2-NaphthylMgBr		18/4
14		*o*-TolMgBr		37/7
15		PhMgBr		R = Me 35/7
16				R = F 37/7
17				R = Cl 27/5
18				R = Br 24/5[e]
19		PhMgBr		34/7
20		*p*-TolMgBr		31/6
21		*p*-TolMgBr		5/1[f]
22		PhMgBr		10/2[f]
23		Ph_2Zn[g]		3+3/1.2[f]

[a] Reaction conditions: a solution of ArMgBr in THF (1.0 M, 0.3 mmol) was slowly added over 5 min to a mixture of a cycloalkene (6 mmol) or allylbenzene derivative (3 mmol), MesI (0.3 mmol), Fe(acac)$_3$ (0.015 mmol), and xantphos (0.015 mmol), and the reaction mixture was stirred for for 30 min at 0 °C. See the SI for details. [b] Yield determined by isolation and based on PhMgBr. [c] TON = mol of product/mol of catalyst. [d] The amount of isomers obtained. See also Scheme 2. [e] Allylbenzene was observed in 20% yield (based on PhMgBr). [f] Determined by GC in the presence of undecane as an internal standard. [g] Prepared from $ZnCl_2$•TMEDA and 2PhMgBr.

H^a [16] to give allyliron intermediate **F**. The *cis* isomer **6c** was obtained in a trace amount from the stereoisomer of **F**.[17] Abstraction of H^b is slightly less favored and leads to the formation of allyliron intermediates **G** that produces minor isomers **7** and **8**. Reductive elimination of the allyliron intermediate is sensitive to sterics, as suggested by the fact that **8c** was not formed at all (SI, Figure S1). A similar argument regarding the reactivity of an allyliron species also holds for the regio- and stereoselectivity observed for 3-methylcyclohex-1-ene (SI, Figure S2).

The reactivity of *cis*- and *trans*-methylstyrene and allylbenzene supports the intermediacy of a *π*-allyliron intermediate instead of a Heck-type mechanism (Scheme 3).

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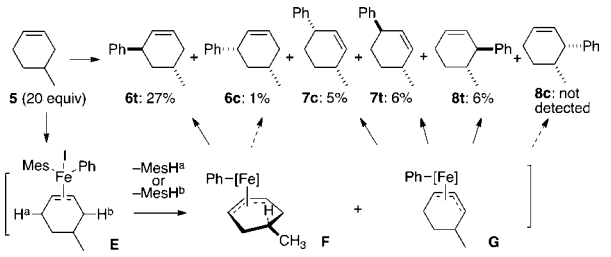
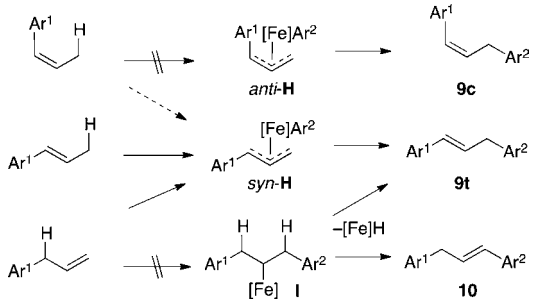
(17) Intermolecular attack of a phenylmetal to an allyliron is less probable.

Scheme 2. Pathway for the Phenylation of 4-Methylcyclohexene (**5**)[a]



[a] Conditions: PhMgBr (1 equiv), $Fe(acac)_3$ (5 mol %), xantphos (5 mol %), MesI (1 equiv), THF, rt.

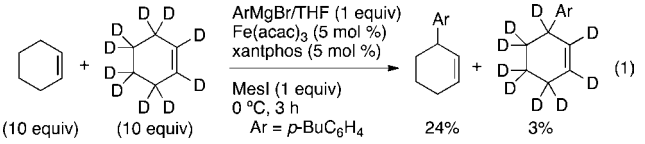
Scheme 3. Dichotomy between the Reactivity of *cis*- and *trans*-β-Methylstyrene and Evidence against a Heck-Type Mechanism[a]



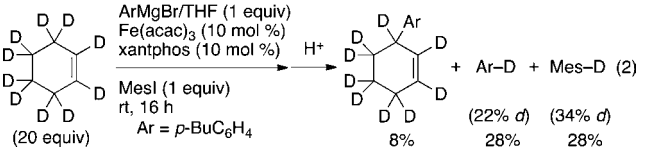
[a] Ar^1 = Ph, Ar^2 = Ph or Tol.

For instance, the much poorer reactivity of *cis*-methylstyrene compared with the *trans* isomer and allylbenzene agrees with this mechanism, because the hydrogen abstraction from the terminal methyl group in the *trans* isomer produces a stable *syn*-π-allyliron (*syn*-**H**) and hence **9t**, while the reaction on the *cis* isomer produces an unacceptably unstable *anti*-π-allyliron intermediate (*anti*-**H**) and does not produce **9c**. Both *trans*-β-methylstyrene and allylbenzene should produce the *syn*-π-allyliron intermediate and hence the *trans*-product. As shown at the bottom of Scheme 3, the product selectivity observed for allylbenzene rules out a Heck-type carbometalation pathway,[18] which places the iron atom in the central carbon atom (cf. **I**), and β-elimination[19] should have produced a mixture of olefinic isomers.

Deuterium labeling experiments indicated that the abstraction of the allylic hydrogen atom is a slow step in the reaction. Intermolecular competition between cyclohexene and cyclohexene-d_{10} showed a large intermolecular kinetic isotope effect value of 8 (eq 1), indicating that the abstraction of the allylic hydrogen atom is slow.



Careful analysis of the reaction of cyclohexene-d_{10} indicated that it is not only slow but results in deuteration of the Grignard reagent. As shown in eq 2, the reaction with 4-*n*-butylphenylmagnesium bromide in THF resulted in recovery of 22% deuterated *n*-butylbenzene and 34% deuterated mesitylene after aqueous quenching. We consider that the comparable degree of deuterium incorporated into both aromatic partners provides support for the formation of a complex of cyclohexene with a diaryliron species, as illustrated in Scheme 1.



In conclusion, we have developed a new reaction that converts the allylic hydrogen of an olefin under mild conditions. The observed regio- and stereoselectivities are consistent with the intermediacy of an allyliron species rather than a free allylic radical. The reaction can be applied to the arylation of saturated hydrocarbons, albeit in poor yield. As has also been found in $C(sp^2)$–H activation reactions,[20] iron-catalyzed $C(sp^3)$–H activation takes place under very mild conditions. The abundance, low cost, and nontoxicity are well-known features of iron catalysis.[21] The lack of selectivity in the hydrogen-abstraction step and the consumption of the Grignard reagent for catalyst generation largely account for the modest yield and arguably represent the synthetic problems to be resolved in the future.

Acknowledgment. We thank MEXT for financial support (KAKENHI Specially Promoted Research No. 22000008 to E.N., and Grant-in-Aid for Young Scientists (B) No. 23750100 to L.I.).

Supporting Information Available. Experimental procedures and physical properties of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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