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Broad Scope Hydrofunctionalization of Styrene Derivatives Using Iron-Catalyzed Hydromagnesiation

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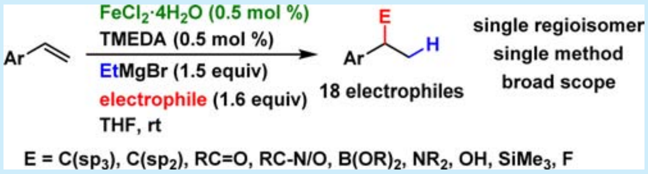
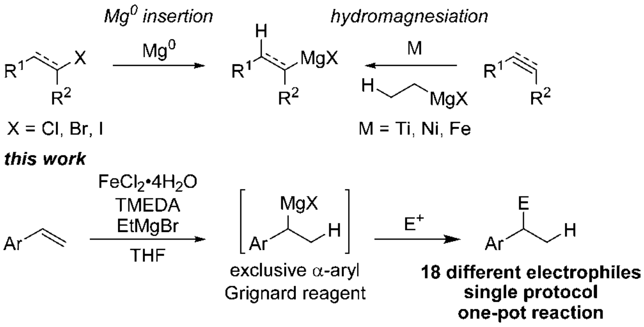
S *Supporting Information*

ABSTRACT: The highly regioselective iron-catalyzed formal hydrofunctionalization of styrene derivatives with a diverse range of electrophiles has been developed using a single, operationally simple hydromagnesiation procedure and only commercially available, bench-stable reagents. Using just 0.5 mol % FeCl$_2$·4H$_2$O and *N,N,N′,N′*-tetramethylethylenediamine, hydromagnesiation and electrophilic trapping have been used to form new carbon−carbon bonds (13 examples) and carbon−heteroatom bonds (5 examples) including the products of formal cross-coupling reactions, hydroboration, hydroamination, hydrosilylation, and hydrofluorination.



The controlled synthesis of new molecular architectures is a fundamental goal of chemical synthesis. Key to the widespread adoption of any synthetic method is operational simplicity, reliability, and generality. Ideally, a single method should enable the formation of both carbon−carbon and carbon−heteroatom bonds. Currently, few methods meet this criteria, with cross-coupling reactions being a notable exception.[1] In the search to develop a reaction that uses bench-stable feedstock chemicals, the hydrofunctionalization of olefins is an attractive alternative.[2] Such addition reactions have the potential to be highly atom economic,[3] and a wide range of functionalized alkenes and alkynes are readily available.[4] Additionally, olefins offer orthogonal reactivity to organohalides and allow late-stage functionalization.[5] The majority of hydrofunctionalization reactions reported to date require the use of precious metals,[2] and although powerful, these methods suffer from the inherent toxicity and environmental impact of the catalysts used.[6] The development of more sustainable and environmentally benign methods is therefore paramount, and iron is quickly becoming recognized as a viable alternative.[2e−s,6,7]

Scheme 1. Preparation of Grignard Reagents



To develop a general, iron-catalyzed hydrofunctionalization procedure, it is necessary to proceed through a common reactive intermediate. Grignard reagents are highly reactive species that are commonly used in organic syntheses.[8] A plethora of conditions currently exist for both the preparation and, particularly, the reaction of Grignard reagents with electrophiles. Additionally, competitive Wurtz homocoupling and the presence of sensitive functional groups can make the formation of Grignard reagents challenging.[9] The hydromagnesiation of alkenes and alkynes (Scheme 1) provides an alternative *in situ* route to alkyl, vinyl, and benzylic Grignard reagents.[10] We recently reported the iron-catalyzed formal hydrocarboxylation of a range of electronically differentiated styrene derivatives.[10l] The reaction was proposed to proceed by iron-catalyzed hydromagnesiation to give a benzylic Grignard reagent intermediate, which was confirmed using NMR spectroscopy.[10m] Herein we report a one-pot, operationally simple procedure for the synthesis and reaction of benzylic Grignard reagents with a wide variety of electrophiles. Significantly, a single set of reaction conditions were used for both the preparation of the *α*-aryl Grignard reagent and reaction with electrophiles, thus providing a facile route to the products of a formal hydrofunctionalization.

Using styrene **1** and trimethylsilyl chloride as the model reactants, hydrofunctionalization conditions were investigated (Table 1). As a reference, our previously reported system of FeCl$_2$ and bis(imino)pyridine (BIP) ligand **3** gave silane **2** in 84% yield (entry 1).[10l] Using 1 mol % FeCl$_2$ and *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) **4**, silane **2** was obtained in an excellent yield of 92% (entry 2) without any

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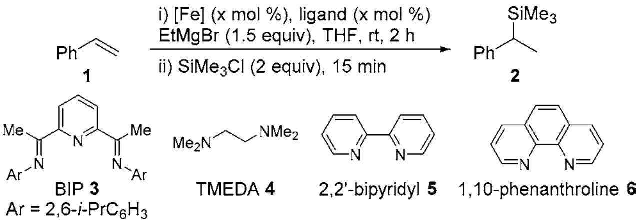
Table 1. Reaction Optimization[a]



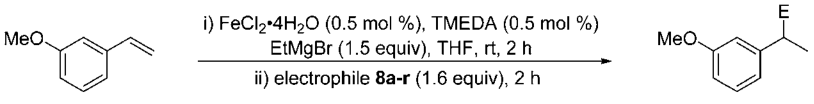
entry	[Fe] (mol %)	ligand (mol %)	yield (%)^{b}
1	$FeCl_2$ (1)	BIP **3** (1)	84
2	$FeCl_2$ (1)	TMEDA **4** (1)	92
3	$FeCl_2{\cdot}4H_2O$ (1)	TMEDA **4** (1)	92
4	$FeCl_3{\cdot}6H_2O$ (1)	TMEDA **4** (1)	89
5	$FeCl_2{\cdot}4H_2O$ (0.5)	TMEDA **4** (0.5)	91
6	$FeCl_2{\cdot}4H_2O$ (0.1)	TMEDA **4** (0.1)	59
7^{c}	$FeCl_2{\cdot}4H_2O$ (0.5)	2,2′-bipy **5** (0.5)	75
8^{c}	$FeCl_2{\cdot}4H_2O$ (0.5)	1,10-phen **6** (0.5)	73
9^{d}	$FeCl_2{\cdot}4H_2O$ (0.5)	TMEDA **4** (0.5)	92^{e}

[a] Conditions: (i) styrene (0.7 mmol), THF (0.14 M). [b] Yield determined by ^1H NMR spectroscopy of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. [c] Me_3SiCl (1.6 equiv). [d] 3-Methoxystyrene and reagent grade THF[12] were used. [e] Product **9n**.

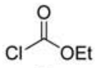
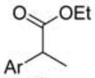
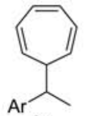
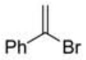
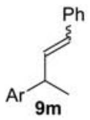
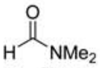
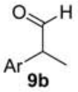
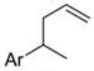
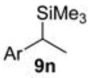
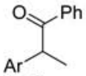
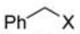
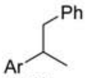
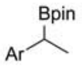
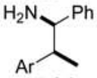
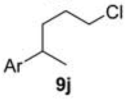
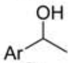
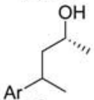
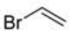
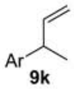
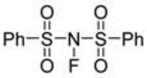
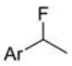
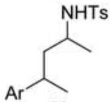
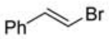
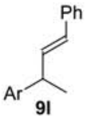
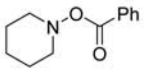
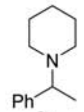
observation of Wurtz homocoupling. $FeCl_2{\cdot}4H_2O$ and $FeCl_3{\cdot}6H_2O$ performed equally to $FeCl_2$ (entries 3 and 4), showing that iron hydrate salts are compatible with the method. $FeCl_2{\cdot}4H_2O$ was selected for further screening due to its low cost and ease of handling. The catalyst loading was then reduced; using 0.5 mol % of iron salt gave the silane product **2** in equally high yield (entry 5), but reducing further to 0.1 mol % resulted in a substantially lower yield (entry 6). 2,2′-Bipyridyl **5** and 1,10-phenanthroline **6** were also tested, but did not prove to be as effective as TMEDA (entries 7 and 8). The operational simplicity of the reaction was further exemplified by equal yields being achieved in both anhydrous[11] and reagent grade THF,[12] with no prior purification of solvent required (entry 9).

Having developed an operationally simple reaction, which uses only commercially available and bench-stable reagents, the range of functional groups that could be introduced was investigated. Carbonyl derivatives proved competent electrophiles, as the reaction with ethyl chloroformate **8a** and *N,N*-dimethylformamide **8b** gave ethyl ester **9a** and aldehyde **9b** in 75% and 64% yield, respectively, without over-reduction of the carbonyl (Table 2, entries 1 and 2). Ketone **9c** could be accessed using benzonitrile **8c** in 65% yield (entry 3). The intermediate imine of this reaction could also be reduced with sodium borohydride to give amine (±)-**9d** as a single diastereomer in 55% yield (entry 4). Epoxides and aziridines

Table 2. Electrophile Scope[a]



7 **9a-r**

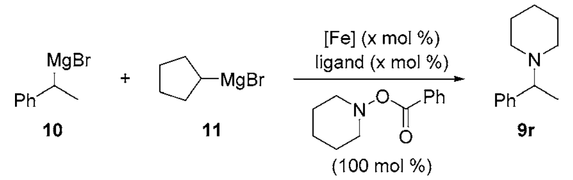
entry	electrophile	product^{b}	yield (%)^{c}	entry	electrophile	product^{b}	yield (%)^{c}	entry	electrophile	product^{b}	yield (%)^{c}
1	 **8a**	 **9a**	75	7^{e}	 **8f**	 **9g**	84	13	 **8m**	 **9m**	64^{g}
2	 **8b**	 **9b**	64	8	 **8g**	 **9h**	81	14	Me_3SiCl **8n**	 **9n**	97
3	PhCN **8c**	 **9c**	65	9^{f}	 X = Br, Cl **8h or 8i**	 **9i**	85, 91	15	HBpin^{h} **8o**	 **9o**	45^{i} (78)^{j}
4	PhCN then MeOH, $NaBH_4$ **8c**	 (±)-**9d**	55	10	 **8j**	 **9j**	62	16	Air^{k} **8p**	 **9p**	83
5	 **8d**	 **9e**	71^{d}	11	 **8k**	 **9k**	76	17^{l,m}	 $PhSO_2N(F)SO_2Ph$ **8q**	 **9q**	43 (53)^{j}
6	 **8e**	 **9f**	78	12	 **8l**	 **9l**	78	18^{n,o}	 **8r**	 **9r**	46

[a] Conditions: (i) 3-methoxystyrene (1.0 mmol), THF (0.14 M). [b] Ar = 3-MeO-C_6H_4. [c] Isolated yield. [d] 1:1 diastereomeric ratio. [e] Hydromagnesiated intermediate added to a solution of tropylium tetrafluoroborate in THF (1 M) due to low solubility of the electrophile. [f] Electrophile added at −78 °C. [g] 1:1 *E*/*Z* ratio. [h] 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane. [i] Product unstable on silica gel. [j] Yield determined by ^1H NMR spectroscopy of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. [k] Reaction open to atmosphere. [l] Electrophile added as a solution in THF (1 M) at −78 °C. [m] Performed on a 2.0 mmol scale. [n] Styrene used in place of 3-methoxystyrene. [o] Electrophile added as a solution in THF (0.7 M) at 0 °C over 1 h.

proved excellent electrophiles for the introduction of alcohol and amine functional groups (entries 5 and 6). The enantioenriched epoxide **8d** reacted with retention of enantiopurity to give alcohol **9e**, albeit as a 1:1 mixture of diastereoisomers at the benzylic position (entry 5). Carbocations could also be trapped, with tropylium tetrafluoroborate **8f** reacting to give the substituted cycloheptatriene **9g** in an excellent 84% yield (entry 7). Allyl bromide **8g** gave the allyl substituted alkane **9h** in excellent yield (entry 8). Benzyl bromide **8h** and benzyl chloride **8i** both gave alkane **9i** in an 85% and 91% isolated yield, respectively (entry 9). In this case, the reaction was cooled to −78 °C before the addition of the mildly oxidizing electrophile, to prevent competitive homocoupling of the benzylic Grignard reagent. The reaction with 1-iodo-3-chloropropane **8j** was chemoselective for substitution at the alkyl iodide to give the chloroalkane **9j** (entry 10). Significantly, the products of formal cross-coupling reactions were obtained when using vinyl halides as electrophiles. The use of vinyl bromide **8k** resulted in the formal cross-coupling reaction product **9k** in 76% yield (entry 11). Stereospecific reaction with *β*-bromostyrene **8l** gave alkene **9l** in 78% yield, with complete retention of regio- and diastereomeric purity (entry 12). However, use of *α*-bromostyrene **8m** resulted in the same product as that using *β*-bromostyrene, as a 1:1 mixture of diastereomers (entry 13), indicating that an addition−elimination reaction is operative, not a cross-coupling reaction.[13]

In addition to carbon−carbon bond formation, a variety of carbon−heteroatom bonds were formed. Using trimethylsilyl chloride as the electrophile gave the silane product **9n** quantitatively (97% yield) (entry 14). Pinacol borane **8o** was used to give boronate ester **9o** in 78% yield (45% isolated yield, the low isolated yield of **9o** being attributed to low product stability during purification on silica gel) (entry 15).[14] Exposing the reaction mixture to air following hydromagnesiation gave benzyl alcohol **9p** in excellent yield (entry 16). *N*-Fluorobenzenesulfonimide (NFSI) **8q** was used to perform a formal hydrofluorination to give the fluorinated alkane **9q** in a moderate 43% yield (entry 17). The addition of *O*-benzoyl-*N*-hydroxypiperidine **8r** at rt gave only trace quantities of the hydroamination product. Yang and co-workers recently introduced a procedure for the formal hydroamination of alkenes[15] using a closely related procedure to our original hydrocarboxylation conditions.[10l] Slow addition of *O*-benzoyl-*N*-hydroxypiperidine **8r** at low temperature, akin to Yang's method, led to the formal hydroamination product **9r** in a moderate 46% yield.

Table 3. Reactivity of Benzylic Grignard Reagent with *O*-Benzoyl-*N*-hydroxypiperidine



10 (mol %)	**11** (mol %)	[Fe] (mol %)	ligand (mol %)	yield (%)
100	–	–	–	61
200	200	–	–	70
100	–	$FeCl_2 \cdot 4H_2O$ (0.5)	TMEDA **4** (0.5)	69
200	200	$FeCl_2$ (10)	BIP **3** (10)	63

Yang reported good yields for the formal hydroamination of styrene derivatives (200 mol %) using $FeCl_2$ (10 mol %), BIP **3** (10 mol %), and H_9C_5MgBr (400 mol %), followed by reaction with the electrophilic amination reagent **8r**. Although using similar reaction conditions, it was proposed that the reaction with the electrophilic amine source proceeded through an organoiron species and not an *α*-aryl Grignard reagent. We therefore sought to clarify the difference between our and Yang's systems, and the nature of the organometallic intermediate. To test the validity of a reaction between our proposed hydromagnesiation intermediate and the amination reagent **8r**, Grignard reagent **10** was independently synthesized[16] and reacted under both sets of reaction conditions (Table 3). The reaction of Grignard reagent **10** with *O*-benzoyl-*N*-hydroxypiperidine **8r** gave amine **9r** in comparable yields to those of Yang, in both the presence and absence of an iron precatalyst (Table 3). This suggests that the reaction of the benzylic Grignard reagent and electrophile takes place without any interaction with the iron species present under the reaction conditions. NMR spectroscopy was used to follow the reaction of styrene[10m] under the conditions reported by Yang and herein.[17] In both cases, complete conversion of styrene to the benzylic Grignard reagent was observed by ^{1}H and ^{13}C NMR spectroscopy, and quantitative conversion to silane **2** was observed, following reaction with Me_3SiCl. Thus, we propose that these hydrofunctionalization reactions proceed by iron-catalyzed hydromagnesiation to give a stoichiometric quantity of a benzylic Grignard reagent which reacts with an electrophile in a standard fashion, including amination.[18] Although the hydromagnesiation of styrene derivatives produces chiral benzylic Grignard reagents, rapid epimerization of the Grignard reagent[16] precludes an enantioselective variant of the reaction through ligand controlled hydromagnesiation. However, the rapid epimerization of benzylic Grignard reagents has been exploited for enantioselective cross-coupling reactions through dynamic kinetic resolution.[19,20]

In summary, using only commercially available reagents, the broad scope formal hydrofunctionalization of alkenes using a bench-stable iron hydrate precatalyst has been developed. This operationally simple procedure has been used to construct a variety of carbon−carbon and carbon−heteroatom bonds using a single reaction protocol for both steps in a one-pot reaction. Chemo- and regioselective reactions were achieved by exploitation of a highly selective iron-catalyzed hydromagnesiation reaction to generate a common benzylic Grignard reagent which could undergo reaction with a diverse array of electrophiles. Significantly, formal cross-coupling, hydroboration (from HBpin directly), hydrosilylation, and hydrofluorination reactions have all been achieved.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental and characterization data of reactions and products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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