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Cross-Coupling of Alkenyl/Aryl Carboxylates with Grignard Reagent via Fe-Catalyzed C−O Bond Activation

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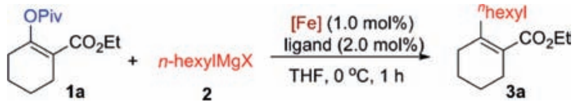
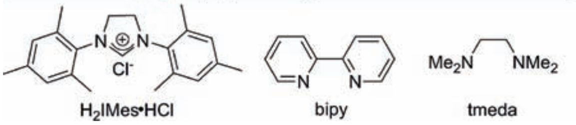
Transition metal catalyzed cross-coupling reactions are indispensable tools for forging C−C bonds.[1] The search for novel electrophiles and efficient catalysts continues to capture significant interest.[2] Recently, Garg's and our group independently reported the examples of Ni-catalyzed Suzuki and Negishi coupling of aryl/alkenyl carboxylates.[3] Compared with traditional cross-coupling reactions of aryl (pseudo)halides, such cross-couplings showed some advantages: (1) aryl/alkenyl carboxylates are easily available and are less expensive than the corresponding halides and sulfonates; (2) the use of halides was avoided, which pollute the environment; (3) aryl/alkenyl carboxylates may exhibit orthogonal reactivity to organohalides. However, several problems still remain, such as a high catalyst loading and elevated temperature. Therefore, we set out to search for alternative coupling partners and novel catalytic systems.

Grignard reagents emerged as an attractive candidate due to its high reactivity. For the catalyst selection, iron has drawn our attention since it is cheap, nontoxic, and environmentally benign. According to the previous work by Kochi, Cahiez, Fürstner, Nakamura and others, iron exhibits remarkable reactivity in the cross-coupling of alkenyl, aryl, and alkyl (pseudo)halides with Grignard reagents.[4−7] Notably, Fürstner's report indicated that iron-catalyzed coupling of aryl tosylate and triflate was even more efficient than the corresponding aryl bromide and iodide.[6a] These interesting findings led us to assume that iron favors activating oxygen-based electrophiles, for example, carboxylates as leaving groups.

Table 1. Optimization Study[a]



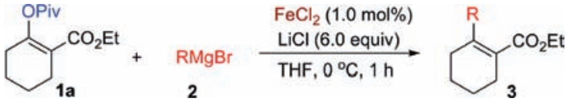
Entry	2	[Fe]	Ligand	Yield(%)[b]
1	*n*-hexylMgCl (**2a**)	$FeCl_2$	–	79
2	*n*-hexylMgCl (**2a**)	$FeCl_2$	PPh_3	77
3	*n*-hexylMgCl (**2a**)	$FeCl_2$	PCy_3	83
4	*n*-hexylMgCl (**2a**)	$FeCl_2$	bipy	75
5	*n*-hexylMgCl (**2a**)	$FeCl_2$	tmeda	< 5
6	*n*-hexylMgCl (**2a**)	**$FeCl_2$**	**H_2IMes•HCl**	**93**
7	*n*-hexylMgCl (**2a**)	–	H_2IMes•HCl	< 5
8	*n*-hexylMgCl (**2a**)	$FeBr_2$	H_2IMes•HCl	86
9	*n*-hexylMgCl (**2a**)	$FeCl_3$	H_2IMes•HCl	83
10	*n*-hexylMgCl (**2a**)	$Fe(acac)_3$	H_2IMes•HCl	78
11	*n*-hexylMgBr (**2a'**)	$FeCl_2$	H_2IMes•HCl	< 5
12[c]	*n*-hexylMgBr (**2a'**)	$FeCl_2$	–	94



[a] Reaction condition: 0.5 mmol of **1a**, 1.0 mmol of **2**, 0.005 mmol of iron catalyst, 0.01 mmol of ligand. [b] Isolated yields. [c] 6 equiv of LiCl were added.

To test the feasibility of such a hypothesis, alkenyl pivalate **1a** was chosen as the model substrate to react with *n*-hexylmagnesium chloride **2a**. To our delight, the desired cross-coupling proceeded smoothly in the presence of iron catalyst (entry 1, Table 1). Screening of the ligands revealed that heterocyclic carbene (NHC) improved the yield, while other mono- or bidentated phosphine and nitrogen ligands gave either lower yields or no product (entry 2−6). Obviously, the reaction could not proceed without iron catalyst (entry 7). Several iron catalyst precursors showed similar efficiencies, presumably due to their *in situ* reduction by the Grignard reagent to generate the active low-valent catalyst (entry 8−10).[8] Finally, we chose $FeCl_2$ as the catalyst since it is air-stable and easy to handle. Interestingly, the counteranion of the Grignard reagent was highly important. *n*-HexylMgCl reacted well, while *n*-hexylMgBr completely failed (entry 11). The reason for this result is still unclear at present. This problem could be solved by the addition of an excess amount of LiCl (entry 12). Under this modified condition, no ligand was required.

Table 2. Substrate Scope of Alkyl Grignard Reagent[a]



Entry	RMgBr	Product	Yield(%)[b]
1	*n*-hexylMgBr (**2a'**)	**3a**	94
2	MeMgBr (**2b**)	**3b**	<5
3[c]	^{i}PrMgCl (**2c**)	**3c**	<5
4	EtMgBr (**2d**)	**3d**	69
5	 Ph MgBr (**2e**)	**3e**	51
6	 Ph MgBr (**2f**)	**3f**	85
7	*n*-$C_{12}H_{25}$MgBr (**2g**)	**3g**	81
8	 MgBr 9 (**2h**)	**3h**	90
9	 RO MgBr R = Me (**2i**)	**3i**	73
10	R = MOM (**2j**)	**3j**	76
11	R = Bn (**2k**)	**3k**	74
12	 O O MgBr (**2l**)	**3l**	74
13	 O O MgBr (**2m**)	**3m**	72

[a] Reaction condition: 0.5 mmol of **1a**, 1.0 mmol of Grignard reagent, 0.005 mmol of $FeCl_2$, 3.0 mmol of LiCl. [b] Isolated yields. [c] 2 mol % of NHC ligand instead of LiCl.

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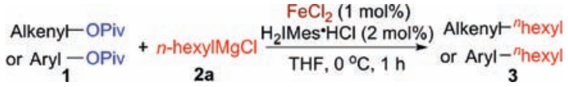
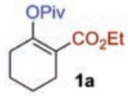
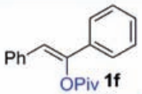
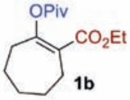
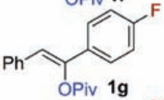
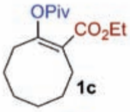
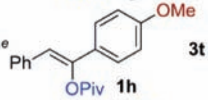
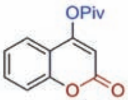
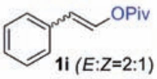
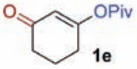
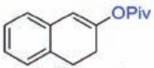
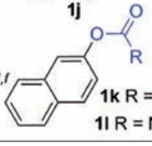
With this efficient catalytic system, we next studied the scope of Grignard reagents (Table 2). Primary alkyl Grignard reagents with different chain lengths proceeded efficiently to give the desired products in high yields (entry 4−13). Functional groups such olefin, ether, and acetal were well tolerated. It is important to note that methyl Grignard reagents were unreactive (entry 2), which may be implied that low valent iron species might be generated through β-H elimination as reported.[6b,8] Secondary and tertiary Grignard reagents did not react either (entry 3).

The functional group tolerance was further demonstrated by the successful reactions of different alkenyl pivalates (Table 3). For example, substrates **1a**−**1c** with various ring sizes reacted to afford the corresponding products in high yields. Alkenyl pivalate (**1d**) derived from 4-hydroxycoumarin was exclusively cleaved in the presence of an aryl carboxylate moiety. Furthermore, the conjugated ketone functionality in the six-membered ring survived in the reaction, demonstrating the high reactivity of the catalyst toward alkenyl carboxylate (entry 5). 1,2-Diarylvinyl pivalates were also suitable substrates (entries 6−8), affording two products with similar ratios (E/Z = 2:1). Such stereoisomerization is relatively rare in other related metal-catalyzed, especially iron-catalyzed, cross-couplings of alkenyl electrophiles,[5,9] which might suggest that a different mechanism is operating. Acyclic and cyclic stryryl carboxylates also resulted in high yields (entries 9 and 10). However, attempts to couple inactivated alkenyl carboxylates such as 1-cyclohexenyl pivalate were unsuccessful. In addition to alkenyl pivalates, the reaction of 2-naphthyl pivalate gave a moderate yield. However, the yield was dramatically improved by using a more stable carbamate, which has rarely been reported as electrophiles (entry 11).[10]

Table 3. Substrate Scope of Alkenvl/Arvl Carboxvlates[a]



Entry	1	3(%)[b]	Entry	1	3(%)[b]
1	 **1a**	**3a** (93)	6[d,e]	 **1f**	**3r** (91)
2	 **1b**	**3n** (78)	7[d,e]	 **1g**	**3s** (85)
3	 **1c**	**3o** (87)	8[d,e]	 **1h**	**3t** (70)
4	 **1d**	**3p** (90)	9[e]	 **1i** (E:Z=2:1)	**3u** (71)
5[c]	 **1e**	**3q** (65)	10	 **1j**	**3v** (87)
			11[d,f]	 **1k** R = ^{t}Bu **1l** R = NMe$_2$	**3w** (40) (80)

[a] Reaction condition: 0.5 mmol of **1**, 1.0 mmol of **2a**, 0.005 mmol of FeCl$_2$, 0.01 mmol of ligand. [b] Isolated yields. [c] 10 min. [d] 25 °C, 2 h. [e] Product was obtained as E/Z = 2:1 isomers. [f] 4 mol % of ligand.

To probe the origin of the double bond isomerization process, 30 mol % of TEMPO (2,2,6,6-tetramethyl-1-piperidinoxy), a radical scavenger, was added to the reaction of **1f**. Indeed, the coupling reaction was dramatically inhibited (<5% product) with 80% of **1f** recovered. Therefore, it is very likely that a vinyl radical was generated, since an aryl substituted vinyl radical possesses a linear structure to some extent.[6f,11,12] Alternatively, the loss of stereochemistry could be explained by the addition of an alkyl radical, generated from an alkyl Grignard reagent, to the double bond to produce a benzylic radical. The subsequent elimination of a pivaloxy radical would afford the product. However, this mechanism seems less feasible based on the good reactivity of aryl carboxylate, since the addition of an alkyl radical to an aryl carboxylate is relatively difficult.

In conclusion, we reported an efficient iron-catalyzed cross-coupling reaction of alkenyl/aryl pivalate with a Grignard reagent under mild conditions. The combination of an inexpensive and stable carboxylate electrophile and an iron catalyst would generate ample advantages. Further studies to clearly understand the detailed mechanism as well as application in natural product synthesis are currently underway.

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

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