Oxidative Arylation

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Titanium-Mediated Oxidative Arylation of Homoallylic Alcohols**

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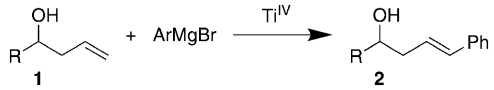
The addition of aryl groups to unactivated olefins represents a direct approach to C–C bond construction. Pd-catalyzed coupling of aryl halides with alkenes, the Heck reaction, offers a viable approach to arylation.[1] However, terminal unactivated olefins often display low reactivity in Heck reactions and can yield mixtures of styrenes and allyl arenes owing to poor regiocontrol in the β-hydride elimination.[2] High selectivity for styrene products has been observed with oxidative couplings between aryl boronic acids and terminal olefins.[3] In this context, we wondered if inexpensive Group 4 transition metals could promote oxidative couplings between olefins and aryl organometallic reagents. Indeed zirconocene and titanocene catalysts as well as stoichiometric titanium(IV) reagents are capable of effecting the carbometalation of terminal alkenes with a variety of nucleophilic partners, including alkylaluminum species[4] and alkyl Grignard reagents.[5] However these methodologies are limited to the addition of simple alkyl groups and cyclization reactions.[6] More recently, titanacyclopropanes and titanacyclopropenes[7] have been shown to effect alkylation and vinylation of alkenols and alkynols.[8] These methods involved the generation of low-valent titanium complexes through β-hydride elimination/reductive elimination pathways. Therefore, we were uncertain if substrates lacking this ability, for example, aryl groups, would participate in addition reactions. Here we report an oxidative coupling of homoallylic alcohols and aryl Grignards [Eq. (1)]. This work demonstrates the ability of aryl titanium complexes to add to unactivated olefins and therefore reveals a new reaction manifold for Group 4 transition metals.



Initial experiments revealed that $Ti(OiPr)_4$ and $ClTi(OiPr)_3$ promote the addition of PhMgBr to homoallylic alcohol **1a** to provide mixtures of products arising from oxidative arylation (**2**) and carbometalation (**3**).[9] $Ti(OiPr)_4$ and $ClTi(OiPr)_3$ could be used interchangeably with comparable results, but the order of addition of reaction components proved essential for reproducibility. Optimally, the Mg-alkoxide was formed by treating **1a** in CH_2Cl_2 with PhMgBr (1 equiv, solution in Et_2O) prior to the addition of Ti^{IV}. Subsequent addition of stoichiometric ArMgBr initiated arylation. Use of THF as the reaction medium or Grignard solvent greatly decreased conversion.[10] The product ratio is also heavily dependent on the titanium and Grignard stoichiometry: a 1:1:1 ratio of **1a**:Ti:ArMgBr yielded a ca. 1:1 ratio of **2a** and **3a** (Table 1, entry 1) while a 1:2:2 ratio improved selectivity to 18:1 (entry 2). Ultimately, the optimized conditions employed 2 equiv $Ti(OiPr)_4$ and 3 equiv PhMgBr and provided **2a** in 91% yield (entry 3; **2a**:**3a** > 99:1).[11]

Several homoallylic alcohols were subjected to the oxidative arylation. Silyl ethers, acids, amides, amines, and heterocycles were stable to the standard conditions. Substrates with an additional acidic proton required an extra equivalent of base prior to addition of titanium and the remaining Grignard reagent (Table 1, entries 6, 8, 10–11). A *tert*-butyl ester was partially hydrolyzed under the reaction conditions, but arylation efficiency was still high (entry 9). Notably, only alkenes with a proximal alcohol reacted,[12] diene **2b** was isolated in good yield, and no arylation of the remote olefin was observed (entry 4).

The oxidative arylation proved sensitive to the steric environment of both the olefin and the alcohol. A substrate containing a geminal dimethyl group (**1k**) yielded a 1.7:1 mixture of **2k**:**3k** (Table 1, entry 13). Tertiary alcohol **1l** reacted with similarly poor selectivity at room temperature, but the product ratio could be favorably increased to a 4.8:1 mixture of **2l**:**3l** at 40 °C (entry 14). Moderately hindered substrates *syn*- and *anti*-**1m** both reacted with high selectivity (entries 15 and 16). In contrast, 1,1-disubstituted alkenes were unreactive under these reaction conditions. However, the method was successfully expanded to accommodate substrates containing disubstituted olefins. For example, *trans*-1,2-disubstituted alkene **1n** was successfully arylated in good yield at a slightly elevated temperature (entry 17). A single regio- and stereoisomeric trisubstituted olefin was isolated in good yield. In contrast, *cis*-**1n** failed to react at room temperature; higher temperatures resulted in a complex mixture of products. In all cases, only (*E*)-olefins were observed. Finally, allylic alcohols provided intractable mixtures of regioisomeric and stereoisomeric substitution and addition products when submitted to the reaction conditions.

The generality of the oxidative arylation was further demonstrated by the incorporation of substituted aryl Grignards, which were freshly prepared in Et_2O prior to use. Methyl-substitution had little electronic effect on the overall yield, but the increased steric hindrance of an *o*-

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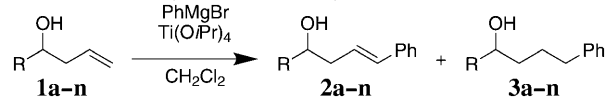
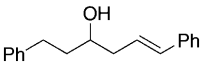
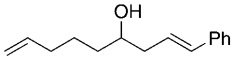
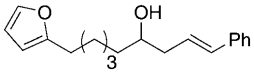
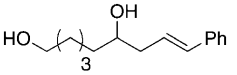
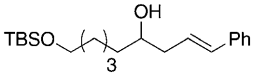
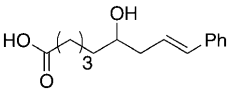
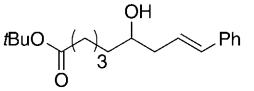
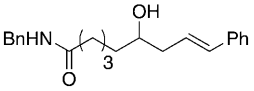
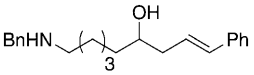
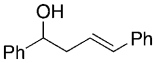
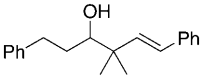
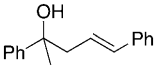
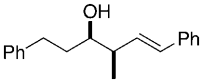
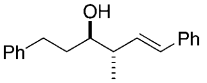
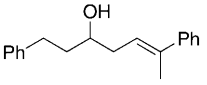
Table 1: Oxidative arylation of homoallylic alcohols.[a]

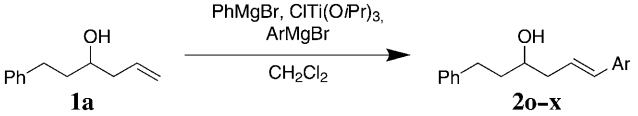


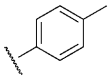
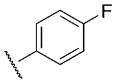
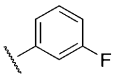
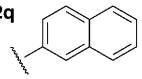
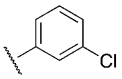
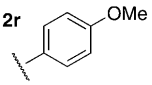
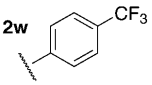
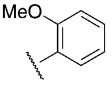
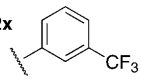
Entry	Substrate	Major product	2:3	Yield [%][b]
	1a			
		1a:Ti:Mg		
1		1:1:1	1:1	(32)
2		1:2:2	18:1	(82)
3		1:2:3	>99:1	91
4	**1b**		>99:1	74
5	**1c**		>99:1	69
6	**1d**		>99:1	80[c]
7	**1e**		>99:1	83
8	**1f**		4:1	74[c]
9	**1g**		>99:1	**2g**: 38 **2f**: 36
10	**1h**		>99:1	78[c]
11	**1i**		>99:1	94[c]
12	**1j**		>99:1	91
13	**1k**		1.7:1	85
14	**1l**		4.8:1	75[d]
15	*syn*-**1m**		17:1[e]	68[d]
16	*anti*-**1m**		>99:1	81
17	**1n**		>99:1	75[d]

[a] 1 Equiv PhMgBr as base, 2 equiv $Ti(OiPr)_4$, 3 equiv PhMgBr, 0.17 M in CH_2Cl_2, RT overnight. [b] Combined yields of **2** and **3** after product isolation. GC yields of **2** in parenthesis. [c] Used 2 equiv PhMgBr as base. [d] Overnight at 40 °C. [e] Ratio of crude product 6:1.

methyl substituent resulted in a 1:2 mixture of **2p**:**3p** (Table 2, entries 1 and 2). Reactions with electron-rich Grignards were complete within 3 h (entries 4 and 5); longer reaction times resulted in arylation of **2**. Lower yields were observed for

Table 2: Scope of substituted aryl Grignard reagents.[a]

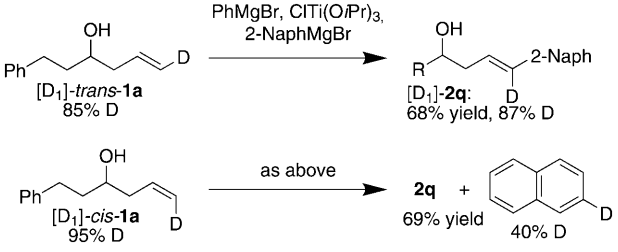


Entry	Ar	Yield [%][b]	Entry	Ar	Yield [%]
1	**2o** 	89	6	**2t** 	73[f]
2	**2p** 	89[c]	7	**2u** 	60 (74)
3	**2q** 	69	8	**2v** 	66 (75)
4	**2r** 	83[d,e]	9	**2w** 	50 (78)
5	**2s** 	75[d]	10	**2x** 	55 (74)

[a] 1 Equiv PhMgBr as base, 2 equiv $Ti(OiPr)_4$, 3 equiv ArMgBr, 0.17 M in CH_2Cl_2, RT overnight. [b] Yields of isolated product. Yields based on recovered starting material in parenthesis. [c] Isolated as a 1:2 mixture of **2p**:**3p**. [d] Reaction time was 3 h. [e] Isolated as a 1:1 mixture of **2r**:**3r**. [f] Isolated as a 5.3:1 mixture of **2t**:**3t**.

electron-poor Grignards due to incomplete conversion (entries 7–10). Neither longer reaction times nor excess reagents were able to bring the reaction to completion. Of the electron-poor Grignards, *p*-fluorophenylmagnesium bromide alone resulted in a mixture of oxidative arylation and carbometalation products under the standard conditions (entry 6).

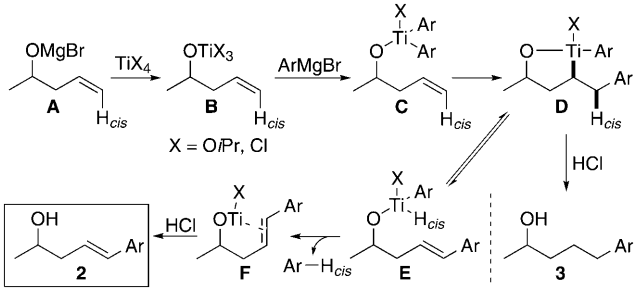
Two sets of experiments revealed aspects of the mechanism of oxidative arylation. First, as foreshadowed by the reactivity of **1n** (Table 1, entry 17), the transformation is stereospecific. Thus, [D_1]-*trans*-**1a** reacted with (2-naphthyl)MgBr to give [D_1]-**2q** which completely retained the deuterium label; in contrast, deuterium was completely eliminated from [D_1]-*cis*-**1a** to provide unlabeled **2q** and [D_1]naphthalene, revealing the final destination of the eliminated hydrogen (Scheme 1).[13] Secondly, time course experiments indicated that the oxidative arylation (**2**) and carbometalation products (**3**) likely arise from a common intermediate. For example, under conditions that provide



Scheme 1. Stereospecificity of oxidative arylation.

mixtures of products, the ratio of **2**:**3** evolved from 0.9:1 at 40 min (100% conversion) to 6.4:1 at 40 h.

Under the reaction conditions, transmetalation of magnesium alkoxide **A** to titanium[14] and addition of aryl Grignard may yield the aryltitanium alkoxide **C** (Scheme 2).[15] The aryltitanation is then directed to the proximal olefin to form



Scheme 2. Mechanistic considerations.

oxatitanacycle **D**,[16] which undergoes a rapid, reversible β-hydride elimination with the exocyclic hydrogen. Quenching at this stage yields mixtures of **2** and **3**. However, upon prolonged reaction times or in the presence of excess ArMgBr this equilibrium is driven toward **2** by the reductive elimination of arene or transmetalation back to Mg (not shown). This scenario accounts for all current information regarding the carbometalation and oxidative arylation including 1) the sensitivity towards order of addition, 2) the stereospecificity, 3) the dependence of the **2**:**3** ratio on the concentrations of Mg and Ti and on time, and 4) the formation of $[D_1]$naphthalene in Scheme 1. The reductive elimination of arene from an $L_2Ti(aryl)H$ intermediate therefore explains a curious feature of the transformation, namely that more of the oxidized product, **2**, is formed when more of a formally reducing reagent (aryl Grignard) is added. The reductive elimination of arene is presumabaly irreversible and drives the reaction to the styrene product.

In conclusion, a highly regioselective and stereospecific oxidative arylation of homoallylic alcohols has been developed. The reaction tolerates a range of widely used functional groups and uses inexpensive reagents. In addition to phenyl Grignard reagents, both electron-poor and electron-rich arylmagnesium bromides are suitable reaction partners. The proposed reaction mechanism suggests that other directing groups may facilitate arylation, that carbometalation could be favored, and that catalytic protocols could be identified. Moreover, these results document the first examples of carbometalations with organotitanium reagents that do not require the intermediacy of a low-valent titanium intermediate. This recognition should provide new opportunities for Group 4 metals in synthesis. Efforts towards those objectives are ongoing.

Experimental Section

PhMgBr (3.0 M in Et_2O, 0.33 mL, 1.0 equiv) was added to a stirred solution of homoallylic alcohol (1.0 mmol) in 6 mL CH_2Cl_2 at 0 °C. After 5 min $Ti(OiPr)_4$ (293 μL, 2.0 equiv) was added and the yellow solution was removed from the ice bath and stirred at room temperature for 1 h. The reaction was then brought to −78 °C, and PhMgBr (3.0 M in Et_2O, 1.0 mL, 3.0 equiv) was added slowly dropwise. When the addition was complete, the reaction was removed from the ice bath and allowed to stir overnight at room temperature. The reaction was quenched with 1 M HCl (15 mL) and stirred until both phases became clear. The aqueous layer was extracted 3 times with Et_2O (20 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure to yield the crude oxidative arylation product.

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