A Novel C−C Single Bond Formation by Use of Ketones, Alkylmagnesium Bromide, and Low-Valent Vanadium in the Presence of a Catalytic Amount of Molecular Oxygen

Yasutaka Kataoka,* Hiroaki Akiyama,
Isamu Makihira, and Kazuhide Tani*

*Department of Chemistry, Faculty of Engineering Science,
Osaka University, Toyonaka, Osaka 560, Japan*

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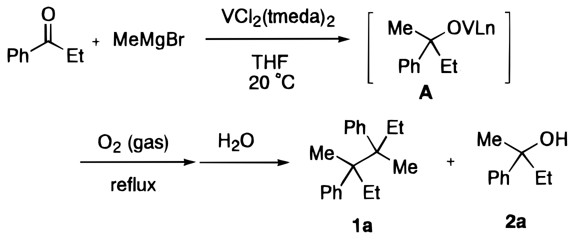
New methodologies for C−C bond formation mediated by transition metal complexes are of considerable interest in the fields of both organic synthesis and organometallic chemistry.[1] The pinacol coupling reaction is one of the most useful C−C bond-forming reactions, based on carbonyl compounds and mediated by low-valent early transition metals.[2] Although the reductive dehydroxy coupling of alcohols has also proven to be an efficient method for forming C−C bonds,[3,4] examples of this reaction beyond those using low-valent titanium[3] and niobium[4] are rare. Different from pinacol coupling, this reaction makes a C−C single bond with accompanying C−O bond cleavage. In order to remove oxygen from a C−O single bond without an accompanying dehydration, the strong oxophilicity of low-valent early transition metals is utilized. Herein we report a new C−C single bond-forming reaction by reductive coupling mediated by a system comprised of MeMgBr, low-valent vanadium, and a catalytic amount of O_2.



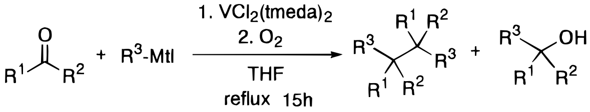
(1)

1a **2a**

O_2 (gas)	**1a**	**2a**
none	trace	92 %
0.2 equiv	89 %	11 %
under O_2 atmosphere	trace	89 %

We have established that the combination of an alkylating reagent, $VCl_2(tmeda)_2$ [tmeda = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine],[5] and a catalytic amount of O_2 does indeed efficiently induce the reductive dimerization of alcoholates, derived from ketones and an alkylating reagent, with accompanying C−O bond cleavage, providing a coupling product with a C−C single bond. For example, propiophenone was first reacted with methylmagnesium bromide (1.0 equiv) in THF and then treated with $VCl_2(tmeda)_2$ (1.0 equiv) at 20 °C for 1 h. The resulting reaction mixture was heated under reflux in the presence of O_2 (0.2 equiv) to give a coupling product **1a** in 89% isolated yield along with tertiary alcohol **2a** in 11% isolated yield. The coupling product **1a** can be considered to be obtained by homocoupling of an intermediate, alkoxyvanadium species **A**, with accompanying C−O bond cleavage, while the alcohol **2a** was derived from the hydrolysis of **A** or by the Grignard reaction. A catalytic amount of O_2 is essential for the reductive coupling. Without O_2 (under Ar atmosphere) the reductive coupling did not proceed at all. An excessive amount of O_2 also prevented the coupling reaction.

Table 1. Reductive Coupling Reaction Mediated by a $VCl_2(tmeda)_2$−O_2 System[a]



1 **2**

run	R^1	R^2	R^3-Mtl (alkylating reagent)	yield/%[b]	
				1[c]	2
1	Ph	Et	MeMgBr (**a**)	89	11
2			MeLi	74	24
3			EtMgBr	63	24
4			^nBuLi	31[d]	30
5			 MgBr	58	35
6			PhMgBr	0[e]	4
7		Me	MeMgBr	84	0
8			EtMgBr	37	13
9	$Ph(CH_2)_2$	Me	MeMgBr	0	96
10			PhMgBr	69	15
11	$-(CH_2)_3MeC{=}CH-$		MeMgBr	80[f]	0

[a] Ketone (1.0 equiv), R^3MgBr (1.0 equiv), $VCl_2(tmeda)_2$ (1.0 equiv) and O_2 (0.2 equiv) were employed. [b] Isolated yield. [c] *meso*:*dl* = 1:1. [d] The ratio of the diastereomers was not defined. [e] 1,1-Diphenyl-1-propene (47% isolated yield) and 1,1-diphenylpropane (39% isolated yield) were obtained. [f] *meso*:*dl* = 60:40 or *vice versa*.

The representative results of the reductive coupling starting from several ketones are summarized in Table 1. When propiophenone or acetophenone was employed as the starting ketone, the coupling product was obtained in moderate to good yield. Although the easy cleavage of the C−O bond at the benzylic position was observed, aliphatic ketones did not afford the corresponding coupling product at all under similar reaction conditions (run 9). When MeMgBr or MeLi was used as an alkylating reagent, no other product besides the coupling product and the tertiary alcohol was obtained. When EtMgBr, C_3H_5MgBr, or ^nBuLi was used, the isolated yield of the coupling product **1** decreased compared to that obtained with MeMgBr as the alkylating reagent. The coupling product derived from propiophenone and PhMgBr was easily transformed into a mixture of 1,1-diphenyl-1-propene and 1,1-diphenylpropane by homolytic cleavage of the C−C bond having four phenyl groups of the initial product (run 6).[6] In runs 1 and 8, since the same alkoxy magnesium bromide was produced from the combination of propiophenone and MeMgBr or of acetophenone and EtMgBr, it was expected the same alkoxy vanadium would be produced as an intermediate in the reaction

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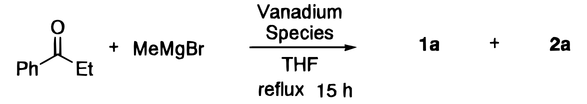
Table 2. Several Vanadium Species Mediated Reductive Coupling Reactions[a]



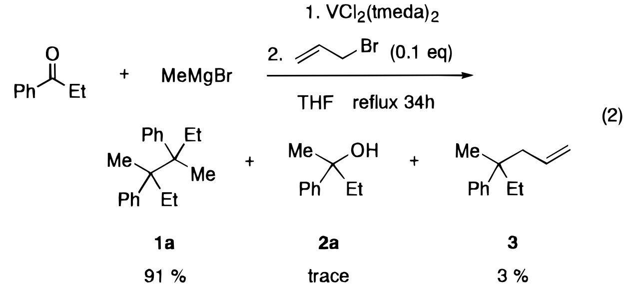
run	vanadium species	yield/%[b] 1a[c]	yield/%[b] 2a
1	$VCl_3(thf)_3$	58	22
2	$VCl_3(thf)_3 + 0.2\ O_2$	56	22
3	VCl_4	0	26[d]
4	$VCl_4 + 0.2\ O_2$	0	58[d]
5	$VCl_2(tmeda)_2 + 0.2\ VCl_3(thf)_3$	91	6
6	$VCl_2(tmeda)_2 + 0.2\ VCl_4$	88	2

[a] Propiophenone (1.0 equiv), MeMgBr (1.0 equiv), and vanadium species (1.0 equiv) were employed. [b] Isolated yield. [c] *meso:dl* = 1:1. [d] A mixture of 2-phenyl-1-butene and 2-phenyl-2-butene was obtained in 20% (run 3) and 23% (run 4) isolated yield.

mixture; however, the yield of the coupling product in run 8 was very poor compared to that in run 1. The reason for the difference in yield is not clear at the moment.

The cleavage of the C−O bond at the allylic position also proceeded similarly (run 11). Although a low-valent titanium[3] or niobium[4] is capable of carrying out the reductive coupling of allyl or benzyl alcohol, neither is effective in our system for the cleavage of the C−O bond of alcoholates. When low-valent titanium or niobium was employed instead of a low-valent vanadium in our system, a tertiary alcohol and/or its dehydrogenated product was mainly obtained.

In order to clarify the effect of the added O_2[7,8] other initiators for this deoxygenative coupling reaction were also examined. In the course of our study on the deoxygenative allylation of ketones mediated by a combination of vanadium(II) and allyl bromide we found a similar coupling product to **1a** was obtained as a byproduct.[9] Thus, at first, a catalytic amount of allyl bromide (0.1 equiv) instead of O_2 in eq 1 was added after the formation of alkoxyvanadium **A**. The same coupling product **1a** was obtained in 91% isolated yield along with a small amount of the allylation product **3** and the alcohol **2a** (eq 2). As the amount of allyl bromide increased, the yield of the coupling product **1a** decreased gradually while the amount of **3** increased. With 4 equiv of allyl bromide, **1a** was obtained in 50% isolated yield along with **3** in 46% isolated yield.



(2)

We have reported that an alkoxy vanadium species, $Ph(Me)(Et)COVL_n'(allyl)$ **B**, is postulated as a reaction intermediate for the allylation.[9] That is, allyl bromide can oxidize vanadium(II) species **A** to a higher-valent vanadium species **B** which may act also as a catalyst for the deoxycoupling.

Next, we examined the effect of several higher-valent vanadium species on the coupling reaction (Table 2). When a vanadium(III) complex, $VCl_3(thf)_3$, was employed instead of the $VCl_2(tmeda)_2{-}O_2$ system, the coupling reaction also occurred to some extent, but the isolated yield was much lower (run 1 of Table 2 vs run 1 of Table 1). Addition of O_2 into the $VCl_3(thf)_3$ system did not affect the result seriously (run 2). In a system employing a vanadium(IV) complex, the VCl_4 or $VCl_4{-}O_2$ system, the β-elimination of the oxometal species from the alkoxy complexes occurred instead of the coupling reaction (run 3, 4). It was found that the vanadium(III) or vanadium(IV) species had a similar effect to that of O_2 or allyl bromide. A combination system of $VCl_2(tmeda)_2$ and a catalytic amount of $VCl_3(thf)_3$ or VCl_4 afforded the coupling product **1a** in good isolated yield just as the $VCl_2(tmeda)_2{-}O_2$ system did (run 5, 6). In a $VCl_2(tmeda)_2{-}O_2$ system, a catalytic amount of the vanadium(III) or vanadium(IV) species[10] should be produced and their collaboration[11] with a low-valent vanadium(II) complex having higher reduction power and oxophilicity[12−14] would induce the C−O cleavage to promote the coupling reaction. The unsuccessful coupling reaction in pure O_2 atmosphere indicated that the vanadium(II) species is requisite for the present deoxygenative coupling. It has been reported that reaction of $VCl_3(thf)_3$ with RMgBr gave the vanadium(II) and vanadium(IV) species by disproportionation.[15] Thus, in the $VCl_3(thf)_3$ system (run 1) some vanadium(II) species would be also produced by disproportionation of the vanadium(III) species, and the coupling product **1a** was obtained in 58% isolated yield.

Different from conventional reductive coupling reactions such as the McMurry coupling, the present method forms a C−C single (instead of a double) bond and yields a product which contains components derived from the ketone and a Grignard reagent in a one-pot reaction. The collaboration of both a low-valent vanadium(II) species and a higher-valent vanadium species produced from vanadium(II) and a catalytic amount of O_2 should induce the removal of oxygen from the C−O bond.

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Supporting Information Available: Experimental procedures and characterization data for all compounds (4 pages).

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