JOC
The Journal of Organic Chemistry

VOLUME 67, NUMBER 7 APRIL 5, 2002

Articles

In Situ Formation of Allyl Ketones via Hiyama−Nozaki Reactions Followed by a Chromium-Mediated Oppenauer Oxidation

Henri S. Schrekker,† Martin W. G. de Bolster, Romano V. A. Orru, and Ludger A. Wessjohann*,†

Faculty of Sciences, Chemistry Division, Department of Organic and Inorganic Chemistry, Vrije Universiteit Amsterdam, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands

wessjohann@ipb-halle.de

Received December 15, 2000

In Hiyama−Nozaki reactions of allylchromium with aldehydes the expected products are homoallylalcohols. However, oxidation products derived from these, predominantly allyl ketones, can be common side products. This can be explained by an Oppenauer−(Meerwein−Ponndorf−Verley)-type mechanism (OMPV-reaction). The amount of oxidation is strongly dependent on the substitution pattern of the reaction partners and the reaction conditions. An appropriate choice of these can lead to preferential formation of ketones instead of the alcohols. In addition to its synthetic usefulness, the oxidation−reduction equilibrium is of the utmost importance for the design of enantioselective Hiyama−Nozaki reactions because it is also a potential racemization pathway.

Introduction

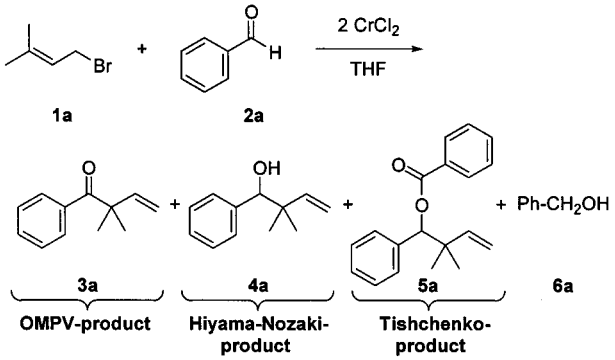
Chromium(II)-mediated reactions such as the Hiyama−Nozaki, the Takai−Utimoto−Kishi, or the chromium-Reformatsky reaction have become popular in total syntheses of natural products due to the mild conditions, excellent chemoselectivity, and predictable stereoselectivity.[1,2] During our studies on the chromium-Reformatsky reaction, we observed that especially 1-halo crotonate esters do not react via the usual enolate intermediate.[3−7] Instead, the reactions of these vinylogous substrates seem to proceed via a typical allylchromium Hiyama−Nozaki pathway.[1,8] The reaction of some allylic halides with chromium(II) and benzaldehyde, especially that of dimethylallyl bromide, resulted in considerable formation of the corresponding allyl ketone instead of the expected homoallyl alcohol (Scheme 1).[8,9] Allyl ketone formation was also observed by Mulzer[10] as a byproduct. He suggested that an Oppenauer-type oxidation of the chromium(III) alkoxide intermediate was responsible for this behavior. The simultaneous presence of an alkoxide, an aldehyde, and a multivalent metal ion (as a potent Lewis acid) together with the exclusion of oxygen suggests optimal conditions for an Oppenauer-type oxidation

* Corresponding author.
† New address: Institute of Plant Biochemistry, Weinberg 3, D-06120 Halle (Saale), Germany. Fax: ++49 (345) 5582-1309.

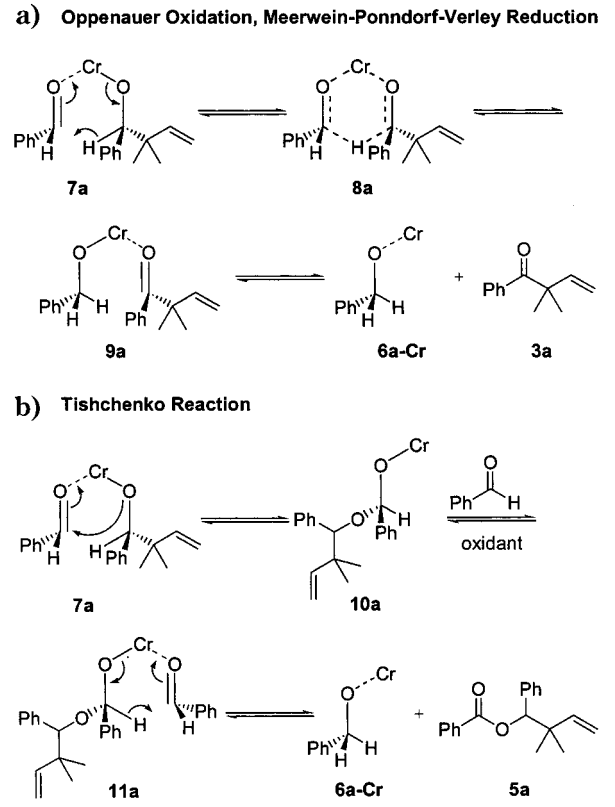
(1) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1−36.
(2) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991−1045.
(3) Gabriel, T.; Wessjohann, L. *Tetrahedron Lett.* **1997**, *38*, 1363−1366.
(4) Wessjohann, L.; Gabriel, T. *J. Org. Chem.* **1997**, *62*, 3772−3774.
(5) Wessjohann, L.; Wild, H. *Synthesis* **1997**, 512−514.
(6) Wessjohann, L.; Wild, H. *Synlett* **1997**, 731−733.
(7) Gabriel, T.; Wessjohann, L. *Tetrahedron Lett.* **1997**, *38*, 4387−4388.
(8) Wessjohann, L.; Mühlbauer, A. In *24. GDCh-Hauptversammlung Hamburg*; GDCh, Ed.; VCH: Weinheim, 1993; p 502.
(9) Wessjohann, L. Habilitation Thesis, Ludwig-Maximilians-Universität München, Germany, 1998.
(10) Maguire, R. J.; Mulzer, J.; Bats, J. W. *Tetrahedron Lett.* **1996**, *37*, 5487−5490.

10.1021/jo001750u CCC: $22.00
Published on Web 03/13/2002

Scheme 1



Scheme 2



reaction, which is based on a hydride transfer from the alkoxide ion to a carbonyl compound.[11] The reaction is reversible, and thus, depending on the conditions, the backward reaction, the Meerwein−Ponndorf−Verley reduction, should also be possible (Scheme 2a).[12] Indeed, such a reduction of aldehydes and ketones to alcohols in a similar chromium-mediated reaction, using *sec*-Bu-$CrCl_2$, was reported.[13] This reduction was explained by assuming a transition state quite similar to that accepted for the Oppenauer−Meerwein−Ponndorf−Verley (OMPV) equilibrium reaction.[14]

The implications of an OMPV oxidation−reduction equilibrium of the chromium alcoholate formed in Hiyama−Nozaki reactions are quite dramatic. The newly formed stereocenter is scrambled through such a process, and the development of asymmetric versions of the Hiyama−Nozaki reaction would be severely hampered. So far, the development of asymmetric versions has proven to be troublesome, and only a few examples have been reported.[1,15−17] On the other hand, OMPV equilibria would provide evidence for significant ligand exchange, which may occur either at Cr(III) or equally well at Cr(II) centers as was discussed previously and which is a prerequisite for catalytic versions of Hiyama−Nozaki reactions.[1,2,18] In addition, the possible formation of the ketone instead of the expected alcohol has consequences for the strategic planning of complex total syntheses. These considerations prompted us to look more closely into the relationship between Hiyama−Nozaki reactions and OMPV transformations. Here, we wish to report the results of this study and discuss the merits of this potentially useful reaction.

Table 1. Optimization of the Hiyama−Nozaki Reaction with Subsequent (in Situ) Oppenauer Oxidation of Prenylbromide 1a ($R^1 = CH_3$, $R^2 = CH_3$, X = Br) with Benzaldehyde 2a ($R^3 = H$)[f]

entry	ratio **1a**:**2a**	LiI (mol %)	*t* (h)	rel yield ketone **3a** (%)	rel yield alcohol **4a** (%)	rel yield ester **5a** (%)[a]	conv. (%)[b]
1	1.1:1.0	0	3	37	37	0[c]	78
2	1.1:1.0	25	3	34	49	0[c]	65
3	1.0:2.0	0	3	82	13	5	78
4	1.0:2.0	10	3	81	15	4	79
5	1.0:2.0	0	6	81	14	5	78
6	1.0:2.0	10	6	79	13	8	66
7	1.0:3.0	0	3	83	8	9	85
8[d]	1.0:3.0	0	3	67[d]	23	10	95[d]
9[e]	1.0[e]:3.0	0	3	69[e]	19	12	71[e]

[a] The MS degradation pattern of **5a** is in accordance with that of other Tishchenko products such as **5j**. [b] Conversion to products based on **2a** (entries 1 and 2) or **1a** (entries 3−8). The ratio of oxidized products to benzyl alcohol [(**3a** + **5a**):**6a**] was in all cases (1.0−1.8):1.0. [c] Formation of small amounts of an unidentified alcohol. [d] Reaction at 55 °C, cooled to 0 °C, then quenched at 0 °C. [e] Dimethylallyl chloride **1b** was used instead of dimethylallyl bromide **1a**. [f] *T* = 55 °C, quenched at 55 °C [except entry 8, quenched at 0 °C, and entry 9, **1b** ($R^1 = CH_3$, $R^2 = CH_3$, X = Cl) instead of **1a**.

Results and Discussion

To test if an OMPV equilibrium (Scheme 2a) is responsible for the formation of allyl ketones in Hiyama−Nozaki reactions, the reaction of dimethylallyl bromide (prenylbromide) **1a** with benzaldehyde **2a** was studied in more detail (Scheme 1). All reactions were performed under similar conditions (55 °C, THF) using 2.5 equiv of chromium(II) chloride. Only the relative amount of the hydrogen acceptor, benzaldehyde **2a**, and the reaction time and lithium iodide as the modifier were varied. The results are summarized in Table 1. They clearly show the formation of up to 83% (relative) of allyl ketone **3a** and a minor amount of homoallyl ester **5a** next to the Hiyama−Nozaki product **4a.** When the molar ratio of allylbromide **1a** to aldehyde **2a** is decreased (entries 1

(11) Hudlický, M. *Oxidations in Organic Chemistry*; American Chemical Society: Washington, DC, 1990.
(12) de Graauw, C. F.; Peters, J. A.; van Bekkum, H.; Huskens, J. *Synthesis* **1994**, 1007−1017.
(13) Kauffmann, T.; Beirich, C.; Hamsen, A.; Möller, T.; Philipp, C.; Wingbermühle, D. *Chem. Ber.* **1992**, *125*, 157−162.
(14) A CH_2−Cr(III) intermediate is present instead of an O−Cr(III) intermediate; see ref 13.
(15) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. *Angew. Chem.* **1999**, *111*, 3558−3561.
(16) Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Angew. Chem.* **2000**, *112*, 2417−2420.
(17) Sugimoto, K.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 2322−2323.
(18) Parris, M.; Ashbrook, A. W. *Can. J. Chem.* **1979**, *57*, 1233−1237.

vs 3 and 7), more of the oxidized products, allyl ketone **3a** and homoallyl ester **5a**, relative to the homoallyl alcohol **4a** were formed. As expected from OMPV equilibrium reactions, higher concentrations of the hydrogen acceptor (aldehyde) give more of the oxidized products (**3a** + **5a**), up to 92% (relative). The formation of homoallyl ester **5a** as a byproduct can be explained by assuming a Tishchenko reaction (Scheme 2b), known to accompany Oppenauer oxidations.[12]

In most cases, a nearly 1:1 relationship of oxidized products (**3a** + **5a**) to benzyl alcohol **6a** was observed, as expected from theory.[19] The OMPV mechanism (Scheme 2a) nicely accounts for these observations. Finally, it should be mentioned that extension of the reaction time (3 → 6h) at 55 °C (entries 3−6) did not result in more of the OMPV product **3a** or the Tishchenko product **5a**. On the other hand, when the reaction was performed as usual at 55 °C but cooled to 0 °C for quenching (entry 8 vs entry 7), significantly less oxidation product was formed. These experiments demonstrate the temperature dependence of the oxidation reaction and its reversibility, and they also suggest that an equilibrium is reached already within 3 h. All this is in accordance with the suggested mechanisms of Scheme 2.

To direct the chemoselectivity of the chromium(II)-mediated reaction toward either the OMPV product **3a** or the Hiyama−Nozaki product **4a**, optimal conditions for each case were explored. The oxidation processes (Oppenauer and Tishchenko, Scheme 2) are highly favored using excess benzaldehyde. In this way, more than 90% of oxidized products (**3a** + **5a**; 83% of **3a**) could be formed when 3 equiv of benzaldehyde **2a** was employed (Table 1, entry 7). The addition of LiI, which enhances the solubility of the chromium(II) complex and increases the reaction rate in THF, showed no significant effect on the chemoselectivity toward allyl ketone **3a** (Table 1, entries 2, 4, and 6).[1,4,9] The use of the cheaper allyl chloride **1b** (Table 1, entry 9) instead of allyl bromide **1a** resulted in a lower chemoselectivity toward allyl ketone **3b** (**3b** = **3a**) and a lower conversion. Because allylbromides suffer some bromine−chlorine exchange with the chloride counterion of chromium(II), the amount of OMPV oxidation can probably be increased further by using chromium(II) bromide instead of chromium(II) chloride.[9]

Because the Hiyama−Nozaki reaction is frequently used for the diastereoselective synthesis of homoallyl alcohols in total syntheses of complex products, it is important to establish reliable conditions for a chemoselective reaction toward the expected homoallyl alcohol **4a**. Table 2 summarizes some experiments toward this goal, which proved to be less straightforward than the rather automatic formation of ketone **3a**. However, with a slight excess of dimethylallyl bromide **1a**, a reduced reaction temperature (0 °C, entries 9−14), and reaction time (30 min, entries 13−14), more than 95% (relative) of the products comprised homoallyl alcohol **4a** (entry 13). Unfortunately, this chemoselectivity could only be achieved at the expense of a rather low conversion level of 36% of **2a** (entry 13). Fortunately, under these conditions, the addition of a catalytic amount of lithium iodide resulted in the desired effect and gave some 90% (relative) of the Hiyama−Nozaki product **4a** at an improved conversion of 70% (entry 14). In general, addition of lithium iodide (entries 2, 6, 8, 10, 12, and 14) resulted in higher conversion levels and improved chemoselectivities toward homoallyl alcohols when the reaction was run for a shorter time and at a lower temperature.

Table 2. Optimization of the Hiyama−Nozaki Reaction of Prenylbromide 1a ($R^1 = CH_3$, $R^2 = CH_3$, X = Br) with Benzaldehyde 2a (R^3 = H, 1a:2a = 1.1:1.0) toward a Minimization of Oppenauer Oxidation Products

entry	LiI (mol %)	*t* (h)	*T* (°C)	rel yield ketone **3a** (%)	rel yield alcohol **4a** (%)	rel yield ester **5a** (%)[a]	conv. (%)[b]
1	0	3	55	37	37	0[c]	78
2	25	3	55	34	49	0[c]	65
3[d]	$CrCl_3$/$LiAlH_4$[d]	2	22	4	84	0[c]	86
4[d,e]	$CrCl_3$/$LiAlH_4$[d,e]	2	22	78[e]	16[e]	6	99
5	0	1.5	22	23	71	2[c]	78
6	25	1.5	22	9	85	0[c]	80
7	0	0.5	22	20	78	2	79
8	25	0.5	22	9	89	0[c]	91
9	0	3	0	16	79	5	74
10	10	3	0	9	89	2	80
11	0	1.5	0	9	85	6	49
12	10	1.5	0	9	84	5[c]	76
13	0	0.5	0	1	97	2	36
14	10	0.5	0	5	90	0[c]	70

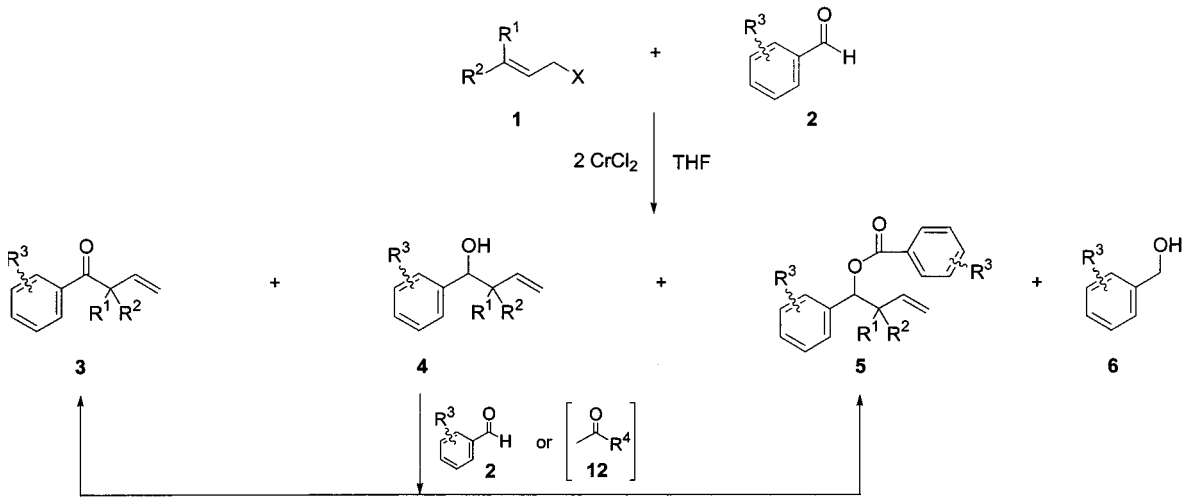
[a] The MS degradation pattern of **5a** is in accordance with that of other Tishchenko products such as **5j**. [b] Conversion based on **2a**. Conversion of **1a** is quantitative. The ratio of oxidized products to benzyl alcohol [(**3** + **5**):**6**] was in all cases (1.0−2.2):1.0 except for entry 3 (1:5). [c] Formation of traces of an unidentified alcohol. [d] No LiI addition. $CrCl_2$ substituted by $CrCl_3$/$LiAlH_4$ (2:1) according to ref 21. [e] Preincubation with benzaldehyde (4 equiv) to remove residual active aluminum hydride, followed by dimethylallyl bromide after 15 min.

At this point, it is important to note that the original Hiyama−Nozaki procedure employs chromium(III) chloride and lithium aluminum hydride (LAH) in a 2:1 ratio to generate, in situ, the low-valent chromium reagent.[20,21] This reagent should behave similar to commercially available pure chromium(II) chloride. But when the reagent was applied, oxidation products were almost completely absent (<5% of **3a** + **5a**, entry 3). Because $CrCl_3$ and LAH were used in a 2:1 molar ratio instead of the stoichiometric 4:1 ratio, active aluminum hydride species should still be present as a reductant in the reaction mixture. This was also indicated by the low ratio of oxidation products (**3a** + **5a**) to benzyl alcohol **6a** of approximately 1:5. Thus, the "in situ"-generated Cr(II) species was allowed to stir first with a 4-fold excess of benzaldehyde **2a** for 15 min in order to destroy excess active hydride, before the coupling partner **1a** was added. This resulted in a complete switch in chemoselectivity (entry 4) compared to the reaction without prior elimination of reductive residues. Now, the oxidation products were formed preferentially and the OMPV pathway dominates again. These observations nicely demonstrate that the OMPV equilibria in the original Hiyama−Nozaki reactions were masked by the only partially reduced LAH, which either removed excess benzaldehyde as an oxidant directly or indirectly re-reduced the OMPV product **3a** to **4a**. Another explanation for the reduction

(19) Ratios of oxidized product to benzyl alcohols were typically between (1.0−1.8):1.0. The higher ratios are probably due to the volatility and loss of benzyl alcohol **6a** during workup.

(20) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179−3181.
(21) Hiyama, T.; Okude, Y.; Kimura, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 561−568.

Scheme 3



1-6, 12	R^1	R^2	X	R^3	R^4
a	CH_3	CH_3	Br	H	-
b	CH_3	CH_3	Cl	H	-
c	H	H	Br	H	-
d	H	CH_3	Br	H	-
e	CH_3	$(CH_2)_2CH{=}C(CH_3)_2$	Br	H	-
f	CH_3	CH_3	Br	*o*-OCH_3	-
g	CH_3	CH_3	Br	*m*-OCH_3	-
h	CH_3	CH_3	Br	*p*-OCH_3	-
i	CH_3	CH_3	Br	*o*-CF_3	-
j	CH_3	CH_3	Br	*m*-CF_3	-
k	CH_3	CH_3	Br	*p*-CF_3	-
l	CH_3	CH_3	Br	H	CH_3
m	CH_3	CH_3	Br	H	Ph

may also be the presence of excess or re-formed reductive Cr(II) complexes.[22]

After studying the easily modifiable physical parameters and the influence of additives that guide the reaction toward alcohol or ketone products, it seemed useful to explore the steric and electronic effects of substituents and reagents.

First, the influence of substituents at the γ-position (R^1 and R^2, **1a** and **1c**−**e**) of allylic bromide upon the chromium(II)-mediated coupling with benzaldehyde **2a**, was studied (Scheme 3, Table 3). All reactions were performed under similar conditions (55 °C, THF, 3 h) using allyl bromides **1** and benzaldehyde **2a** in a molar ratio of 1:3 and 2.5 equiv of chromium(II) chloride. The results are summarized in Table 3. Only traces of oxidation products **3c** and **5c**, compared to Hiyama−Nozaki product **4c**, were detected when unsubstituted allylbromide **1c** ($R^1 = R^2 = H$, entry 1) was used. Reaction of the crotylbromide **1d** ($R^1 = H$, $R^2 = CH_3$, entry 2) resulted in a dramatic increase in oxidation toward allyl ketone **3d** relative to the Hiyama−Nozaki product **4d**. The relative yield of allyl ketone **3** could be further improved by the use of the sterically even more demanding allylbromides **1a** ($R^1 = R^2 = CH_3$, prenylbromide, entry 3) and **1e** (geranylbromide, entry 5), but the effect of the second substituent was less dramatic. Thus, it is likely that steric bulk is required, either at the γ-position as shown here or at the β-position as observed by Mulzer,[10] to promote oxidation to allyl ketones **3**. On a speculative basis, two explanations can be given for this steric effect. First, the coordination strength of the alcoholate to chromium(III) might be important and reduced due to steric strain, thus allowing a faster ligand exchange for the OMPV reaction to proceed. Second, stabilization of transition state **8** (Scheme 2a, with a developing π-orbital at the homoallylic position) might play a role, either through hyperconjugative effects or by Cr chelation of the vinyl group, brought into the right position through a Thorpe−Ingold effect of the substituents R^1 and R^2 (i.e., CH_3, CH_3 in **8a**). With 1-phenylethynylbromide as a substrate that is lacking the vinyl group altogether, no ketone formation was observed.

These results are not only important for the scope of the Hiyama−OMPV reaction but also give a better insight into the development of enantioselective Hiyama−Nozaki reactions. Interestingly, enantioselective transfer

Table 3. Influence of Substituents R^1 and R^2 of the Allylic Bromide 1 on the Extent of Allyl Ketone Formation (R^3 = H, 1:2a = 1.0:3.0, T = 55 °C, t = 3 h)

entry	substrate **1**	rel yield ketone **3** (%)	rel yield alcohol **4** (%)	rel yield ester **5** (%) [a]	conv. (%) [b]
1	**c**: $R^1 = H$, $R^2 = H$	<2	>98	<2	quant.
2	**d**: $R^1 = CH_3$, $R^2 = H$	74	24[c]	2	85
3	**a**: $R^1 = CH_3$, $R^2 = CH_3$	83	8	9	85
4	**e**: geranyl bromide	89	11	0	72

[a] The MS degradation pattern is in accordance with that of other Tishchenko products such as **5j**. [b] Conversion to products based on **1a**. The ratio of oxidized products to benzyl alcohol [(**3** + **5**):**6**] was in all cases (1.0−1.1): 1.0. [c] Exclusive formation of the anti-diastereomer (*anti*-**4d**).

(22) Gyarmati, J.; Hajdu, C.; Dinya, Z.; Micskei, K.; Zucchi, C.; Palyi, G. *J. Organomet. Chem.* **1999**, *586*, 106−109.

Table 4. R^3-Substituent Effects of the Benzaldehyde Reactant and Oxidant 2 on the Extent of Allyl Ketone Formation ($R^1 = CH_3$, $R^2 = CH_3$, X = Br, 1a:2 = 1.0:3.0, T = 55 °C, t = 3 h)

entry	substrate 2	rel yield ketone 3 (%)	rel yield alcohol 4 (%)	rel yield ester 5 (%)[a]	conv. (%)[b]
1	**a**: R^3 = H	83	8	9	85
2	**f**: R^3 = *o*-OCH_3	22	78	0	94
3[c]	**f**: R^3 = *o*-OCH_3	47[c]	53	0	n.d.[d]
4	**g**: R^3 = *m*-OCH_3	58	37	5	90
5	**h**: R^3 = *p*-OCH_3	80	19	1	73
6	**i**: R^3 = *o*-CF_3	5	95	0	95
7	**j**: R^3 = *m*-CF_3	43	21	36	93
8	**k**: R^3 = *p*-CF_3	54	22	24	78

[a] The MS degradation pattern is in accordance with that of other Tishchenko products such as **5j**. [b] Conversion based on **1a**. The ratio of oxidized products to benzyl alcohol [(**3** + **5**):**6**] was in all cases (1.0−1.5):1.0. [c] One equivalent of **2f** added, followed by three equivalents of benzaldehyde after 30 min. [d] Not determined.

from chromium allyl was only possible with the unsubstituted allyl when chiral Cr(II) alkoxides were used as catalysts.[17] When the substituted substrates were used, the *enantiomeric excesses* of the easily oxidizable products were negligible. A potential reason may have been the OMPV scrambling of stereochemistry in the substituted substrates or, alternatively, induction in the unsubstituted case may have resulted from OMPV equilibria mediated by the asymmetric alkoxide catalyst, with the equilibrium being at the homoallylic alcohols side only in the unsubstituted case.

Finally, the effect of a substituent R^3 on the aromatic ring of aldehydes **2** was studied (Table 4, cf. Scheme 3). Again, all reactions were performed under similar conditions (55 °C, THF, 3 h) using dimethylallyl bromide **1a** and aldehydes **2** in a molar ratio of 1:3 and 2.5 equiv of chromium(II) chloride. Although this substitution alters two parameters at the same time, as the aldehydes are a Hiyama reaction component, and simultaneously can serve as an OMPV oxidant, the cross effects to a great part can be eliminated by a multivariant analysis.

In general, with substituted benzaldehydes **2f**−**k** the products resulting from an oxidative process (**3** + **5**, OMPV + Tishchenko) became less important relative to the Hiyama−Nozaki product **4** (entries 2−8 vs 1). Moreover, for both electron-rich aldehydes ($R^3 = OCH_3$) and electron-poor aldehydes ($R^3 = CF_3$), the substituent position was the crucial factor for the product distribution. A dramatic decrease in the ratio of oxidized products (allyl ketone **3** + homoallyl ester **5**) to homoallyl alcohol **4** was observed, following the order of para > meta ≫ ortho for the substituent position effect on the *oxidation ratio* = (**3** + **5**):**4**. The reactions of para-substituted aldehydes **2h** (*p*-OCH_3) and **2k** (*p*-CF_3) (entries 5 and 8, respectively) resulted in an approximately 4:1 oxidation ratio in both cases; i.e., oxidation is favorable, but a little less compared to the benzaldehyde standard **2a** (R^3 = H, entry 1) with its ∼12:1 oxidation ratio.

For the evaluation of the relative effect of oxidation propensity compared to the benzaldehyde standard, the ratio of oxidation ratios [i.e., of (**3** + **5**):**4**] of benzaldehyde to donor-aldehyde and to acceptor-aldehyde can be used. This is 3:1:1 for **2a** (H, oxidation ratio = 12:1) over **2h** (*p*-OCH_3, oxidation ratio = 4:1) and **2k** (*p*-OCF_3, oxidation ratio = 4:1), respectively. Thus, both an electron-donating as well as an electron-withdrawing substituent in the para position retard the oxidation processes to a similar extent. The effect is so small that it can be concluded that both steric and electronic effects of substituents at the para position of benzaldehyde have only a minor, almost negligible, destabilizing effect on the required transition states (Oppenauer oxidation, transition state **8**, Scheme 2a).

On the other hand, treatment of **2a** (H) and ortho-substituted aldehydes **2f** (*o*-OCH_3) and **2i** (*o*-CF_3) (entries 1, 2, and 6, respectively) in a similar fashion gave a 230:6:1 ratio of oxidation ratios [i.e., of (**3** + **5**):**4**], respectively. Both types of ortho-substituents R^3 now have a strong negative effect on the oxidation processes. The effect is slightly less pronounced for *o*-OCH_3 compared to *o*-CF_3. Because the electronic effects of para and ortho substituents should be similar, the decrease in oxidation products in favor of Hiyama−Nozaki product must be attributed to steric destabilization of the required transition states for oxidation.

Finally, the reactions of **2a** (H), **2g** (*m*-OCH_3), and **2j** (*m*-CF_3) (entries 1, 4, and 7, respectively) resulted in a 7:1:2 ratio of oxidation ratios [of (**3** + **5**): **4**], respectively. As before, both substituents (OCH_3 and CF_3) disfavor the oxidative process compared to the Hiyama−Nozaki process somewhat similar to the para-substitution effect. In this case, the negative effect on oxidation of a meta-electron-donating substituent seems to be more pronounced than that of a meta-electron-withdrawing substituent. A complex interplay between steric and electronic factors must account for this observation.

These results showed that with respect to electronic influences, no really significant advantage toward or against oxidation could be observed with either donor methoxy or acceptor trifluoromethyl substituents. The latter, however, exhibited an interesting effect on the distribution of the oxidized products **3** and **5** (entries 7 and 8) shifting the reaction path more towards the Tishchenko product **5**. The reason for this is likely the increased carbonyl activity in **2i**−**k** shifting the equilibrium toward the hemiacetal intermediate of the Tishchenko pathway (Scheme 2b, cf. formation of **10**).

Further evidence for the dominating steric ortho-effect was obtained by experiments, in which 1 equiv of anisaldehyde **2f** was used and, after 30 min, 3 equiv of benzaldehyde (R^3 = H) was added. Significantly increased oxidation ratios of [(**3** + **5**):**4**] were obtained for *o*-anisaldehyde (47% **3f** + **5f**, 53% **4f**, Table 4, entry 2),[23] *m*-anisaldehyde (69% **3g** + **5g**, 31% **4g**),[23,24] and *p*-anisaldehyde (85% **3h** + **5h**, 15% **4h**).[23,24] OMPV oxidation was increased, as expected most notably in the ortho-substituted derivative, because the negative steric effect in the oxidant was compensated. Oxidation was still lower than with benzaldehyde products (**4a**) as the substrate, probably because of the remaining steric effect of the Hiyama−Nozaki intermediates **4f**−**h**. On the other hand, when ketones **12l** and **12m** (Scheme 3)[24] were used as oxidants instead of benzaldehyde, only very small amounts of oxidation products were detected. Ketones are inefficient as hydrogen acceptors, probably because coordination at the sterically crowded chromium(III) center does not take place easily.[13]

Conclusion

In conclusion, formation of allyl ketones **3** during Hiyama−Nozaki reactions can be explained by an Op-

(23) Less than 1% of compound **5**.
(24) These results are not additionally shown in the table.

penauer-type oxidation (Scheme 1). The following factors, in a rough order of decreasing importance, favor the subsequent formation of allyl ketones **3**: alkyl substitution at the allylic γ- and β-position, excess aldehyde, higher temperatures, aldehydes with electron-donating substituents, unsubstituted benzaldehyde as the oxidant, and allyl bromides instead of allyl chlorides. If a chemoselective reaction toward homoallyl alcohols **4** is required, catalytic amounts of LiI are important at lower temperatures in order to achieve sufficient conversions. With the $CrCl_3$/LAH procedure (in situ generation of $CrCl_2$), the OMPV oxidations may be masked by reduction of the aldehyde substrate **2** or reduction of the formed allyl ketone **3** by the only partially reduced LAH (or from excess or re-formed $CrCl_2$). Thus, reaction conditions should be chosen very carefully, especially when the Hiyama−Nozaki method is applied in total synthesis or when a chemo- and stereoselective reaction is required. Efficient OMPV equilibria suggest themselves as a reason for thwarted enantioselective catalyses in Hiyama−Nozaki reactions.

Experimental Section

General Methods. All reactions were carried out under an argon atmosphere in flame-dried glassware using standard syringe and septa techniques. The commercial reagents **1a**−**e**, **2f**−**k**, **12l**−**m**, and chromium(II) chloride (99.9% from Strem Chemicals) were used as purchased. Tetrahydrofuran was distilled from potassium/benzophenone. Benzaldehydes (**2a**−**e**,**l**,**m**) were distilled from potassium hydride. Spectral data of the known compounds (**3a**,**b**,**l**,**m**),[25] **3c**,[26] **3d**,[27] **3g**,[28] (**4a**,**b**,**l**,**m**),[29] **4c**,[26] **4d**−**e**,[30] **4h**,[31] **6f**,[32] **6g**,[33] **6h**,[33] and **6j**[34] were in accordance with the literature data. The known compounds (**6a**−**e**,**l**,**m**), **6i**, and **6k** were characterized by comparison to commercially available samples. Thin-layer chromatography was carried out on Merck silica 60/F-254 aluminum-backed plates. Flash chromatography was performed using Merck silica gel 60 (40−60 μm). NMR spectra were recorded in $CDCl_3$. Chemical shifts δ are quoted in parts per million (ppm), and coupling constants J are given in Hertz (Hz).

General Procedure for the Hiyama−Nozaki Reactions. To chromium(II) chloride (2.5 equiv, 200 mg, 1.63 mmol) and lithium iodide (0.1 equiv, 8.7 mg, 65 μmol) was added THF (2.5 mL) under vigorous stirring. After a few minutes, the aldehyde (1.0 equiv, 0.65 mmol) and the allyl halide (1.1 equiv, 0.72 mmol) were added in this order. The resulting mixture was stirred for 30 min at 0 °C, and the reaction was quenched with a saturated aqueous NaCl solution. The water layer was extracted three times with diethyl ether, and the combined organic fractions were washed twice with a saturated aqueous NaCl solution. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The residue was filtered over a short silica column with diethyl ether and concentrated in vacuo. Conversions were determined from ^{1}H NMR spectra of the crude product. Purification was done by column chromatography on silica or by preparative GC.

General Procedure for the Hiyama OMPV Reactions. To chromium(II) chloride (2.5 equiv, 200 mg, 1.63 mmol) was added THF (2.5 mL) under vigorous stirring. After a few minutes, the aldehyde (3.0 equiv, 2.16 mmol) and the allyl halide (1.0 equiv, 0.72 mmol) were added in this order. The resulting mixture was stirred for 3 h at 55 °C, and the reaction was quenched with a saturated aqueous NaCl solution. The water layer was extracted three times with diethyl ether, and the combined organic fractions were washed twice with a saturated aqueous NaCl solution. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The residue was filtered over a short silica column with diethyl ether and concentrated in vacuo. Conversions were determined from ^{1}H NMR spectra of the crude product. Purification was done by column chromatography on silica or by preparative GC.

Data of New Compounds:

2,6-Dimethyl-1-phenyl-2-vinyl-hept-5-en-1-one (3e). Conversion of 64% based on geranyl bromide **1e**: R_f = 0.64 (hexane:ethyl acetate = 98:2); colorless oil; ^{1}H NMR δ 7.84−7.82 (m, 1H), 7.46−7.43 (m, 1H), 7.38−7.34 (m, 2H), 6.16 (dd, J = 17.6, 10.8, 1H), 5.23 (d, J = 10.8, 1H), 5.20 (d, J = 17.6, 1H), 5.01 (m, 1H), 1.96−1.72 (m, 4H), 1.62 (s, 3H), 1.44 (s, 3H), 1.37 (s, 3H); ^{13}C NMR δ 204.7 (C=O), 143.2 (CH), 137.8 (quart. C), 131.9 (quart. C), 131.4 (CH), 129.0 (CH), 127.9 (CH), 124.0 (CH), 113.2 (CH_2), 53.6 (quart. C), 39.0 (CH_2), 25.6 (CH_3), 23.0 (CH_2 + CH_3), 17.4 (CH_3); IR (neat) 3082 (w), 3059 (w), 3021 (w), 2969 (m), 2928 (m), 2882 (m), 2859 (m), 1678 (s), 719 (m), 696 (m) cm^{-1}; HRMS-EI (70 eV) m/z calcd for $C_{24}H_{28}O_2$ ($M^+ - C_6H_{11}$) 159.0809, found 159.0800.

1-(2-Methoxy-phenyl)-2,2-dimethyl-but-3-en-1-one (3f). Conversion of 21% based on dimethylallyl bromide: R_f = 0.23 (hexane:ethyl acetate = 9:1); colorless oil; ^{1}H NMR δ 7.25 (m, 1H), 6.97 (dd, J = 7.4, 1.7, 1H), 6.86−6.81 (m, 2H), 5.94 (dd, J = 17.4, 10.7, 1H), 5.05−5.00 (m, 2H), 3.71 (s, 3H), 1.24 (s, 6H); ^{13}C NMR δ 210.7 (C=O), 155.8 (quart. C), 143.0 (CH), 131.2 (quart. C), 130.5 (CH), 127.2 (CH), 120.4 (CH), 114.0 (CH_2), 111.3 (CH), 55.7 (CH_3), 51.7 (quart. C), 24.4 (CH_3); IR (neat) 3086 (w), 2974 (m), 2934 (m), 2874 (w), 2837 (w), 1697 (s), 754 (s) cm^{-1}; HRMS-EI (70 eV) m/z calcd for $C_{13}H_{16}O_2$ 204.1150, found 204.1163.

1-(4-Methoxy-phenyl)-2,2-dimethyl-but-3-en-1-one (3h). Conversion of 52% based on dimethylallyl bromide: R_f = 0.66 (hexane:ethyl acetate = 4:1); colorless oil; ^{1}H NMR δ 7.88 (d, J = 9.0, 2H), 6.78 (d, J = 9.0, 2H), 6.12 (dd, J = 17.6, 10.6, 1H), 5.14 (dd, J = 17.6, 0.66, 1H), 5.10 (dd, J = 10.6, 0.66, 1H), 3.75 (s, 3H), 1.31 (s, 6H); ^{13}C NMR δ 202.8 (C=O), 162.8 (quart. C), 144.8 (CH), 132.4 (CH), 129.6 (quart. C), 114.0 (CH_2), 113.5 (CH), 55.7 (CH_3), 50.2 (quart. C), 26.7 (CH_3); IR (neat) 3082 (w), 2974 (m), 2934 (m), 2874 (w), 2839 (w), 1670 (s), 843 (m); HRMS-EI (70 eV) m/z calcd for $C_{13}H_{16}O_2$ 204.1150, found 204.1156. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.32; H, 7.96.

2,2-Dimethyl-1-(3-trifluoromethyl-phenyl)-but-3-en-1-one (3j). Conversion of 40% based on dimethylallyl bromide: R_f = 0.27 (hexane:ethyl acetate = 95:5); colorless oil; ^{1}H NMR δ 8.08 (s, 1H), 7.98 (d, J = 7.8, 1H), 7.64 (d, J = 7.8, 1H), 7.44 (dd, J = 7.8, 7.8, 1H), 6.10, (dd, J = 17.6, 10.6, 1H), 5.19 (d, J = 17.6, 1H), 5.19 (d, J = 10.6, 1H), 1.33 (s, 6H); ^{13}C NMR δ 203.5 (C=O), 143.7 (CH), 138.0 (quart. C), 132.8 (CH), 131.0 (q, J = 50.1, quart. C), 128.5 (CH), 128.4 (CH), 126.5 (CH), 124.1 (q, J = 272, quart. C), 115.2 (CH_2), 50.6 (quart. C), 26.2 (CH_3); IR (neat) 3084 (w), 2982 (m), 2934 (m), 2884 (w), 1686 (s), 1333 (s), 1246 (m), 1169 (s), 1076 (m), 814 (m) cm^{-1}; HRMS-EI (70 eV) m/z calcd for $C_{13}H_{13}F_3O$ 242.0918, found 242.0937.

2,2-Dimethyl-1-(4-trifluoromethyl-phenyl)-but-3-en-1-one (3k). Conversion of 42% based on dimethylallyl bromide: R_f = 0.34 (hexane:ethyl acetate = 95:5); colorless oil, containing a minor impurity of a **2k** derivative (~4%, probably hydrated aldehyde), which could not be removed by preparative GC; ^{1}H NMR δ 7.87 (dd, J = 8.2, 0.68, 2H), 7.56 (dd, J = 8.2, 0.68, 2H), 6.08 (dd, J = 17.6, 10.6, 1H), 5.18 (dd, J = 10.6, 0.54, 1H), 5.17 (dd, J = 17.6, 0.54, 1H), 1.32 (s, 6H); ^{13}C NMR δ 204.4 (C=O), 143.5 (CH), 140.7 (quart. C), 133.5 (q, J = 37.6, quart. C), 129.7 (CH), 125.4 (CH), 122.7 (q, J = 308, quart. C), 115.2 (CH_2), 50.7 (quart. C), 26.1 (CH_3); IR (neat) 3086 (w),

(25) Katritzky, A. R.; Wu, H.; Xie, L. *J. Org. Chem.* **1996**, *61*, 4035−4039.
(26) Jones, P.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 186−195.
(27) Reetz, M. T.; Wenderoth, B.; Urz, R. *Chem. Ber.* **1985**, *118*, 348−353.
(28) Marceau, P.; Gautreau, L.; Beguin, F. *J. Organomet. Chem.* **1991**, *403*, 21−27.
(29) Jubert, C.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 5425−5431.
(30) Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620−6628.
(31) Ahn, Y.; Doubleday, W. W.; Cohen, T. *Synth. Commun.* **1995**, *25*, 33−41.
(32) Yates, P.; Macas, T. S. *Can. J. Chem.* **1988**, *66*, 1−10.
(33) Brown, H. C.; Narasimhan, S.; Choi, Y. M. *J. Org. Chem.* **1982**, *47*, 4702−4708.
(34) Blanco, F. E.; Harris, F. L. *J. Org. Chem.* **1977**, *42*, 868−871.

2980 (m), 2936 (m), 2876 (w), 1686 (s), 1327 (s), 1169 (s), 1131 (s), 1069 (s), 853 (m) cm^{-1}; HRMS-EI (70 eV) *m*/*z* calcd for $C_{13}H_{13}F_3O$ 242.0918, found 242.0912.

1-(2-Methoxy-phenyl)-2,2-dimethyl-but-3-en-1-ol (4f). Conversion of 73% based on dimethylallyl bromide: $R_f = 0.74$ (hexane:ethyl acetate = 2:1); colorless oil; ^{1}H NMR δ 7.22−7.13 (m, 2H), 6.86 (m, 1H), 6.78 (d, $J = 8.3$, 1H), 5.88 (dd, $J = 17.5$, 10.8, 1H), 4.99 (dd, $J = 10.8$, 1.4, 1H), 4.94 (dd, $J = 17.5$, 1.4, 1H), 4.77 (d, $J = 5.64$, 1H), 3.72 (s, 3H), 2.52 (d, $J = 5.64$, 1H), 0.96 (s, 3H), 0.90 (s, 3H); ^{13}C NMR δ 157.4 (quart. C), 145.9 (CH), 129.6 (CH), 129.6 (quart. C), 128.6 (CH), 120.5 (CH), 113.2 (CH_2), 110.9 (CH), 76.0 (CH), 55.5 (CH_3), 43.4 (quart. C), 24.5 (CH_3), 22.2 (CH_3); IR (neat) 3478 (m, br), 3081 (w), 2967 (m), 2934 (m), 2874 (w), 2837 (w), 754 (s) cm^{-1}; HRMS-EI (70 eV) *m*/*z* calcd for $C_{13}H_{18}O_2$ ($M^+ - C_5H_9$) 137.0603, found 137.0601. Anal. Calcd for $C_{13}H_{16}O_2$: C, 75.69; H, 8.80. Found: C, 75.43; H, 8.88.

1-(3-Methoxy-phenyl)-2,2-dimethyl-but-3-en-1-ol (4g). Conversion of 33% based on dimethylallyl bromide: $R_f = 0.17$ (hexane:ethyl acetate = 95:5); colorless oil; ^{1}H NMR δ 7.15 (m, 1H), 6.80−6.72 (m, 3H), 5.84 (dd, $J = 17.5$, 10.8, 1H), 5.06 (dd, $J = 10.8$, 1.24, 1H), 5.00 (dd, $J = 17.5$, 1.24, 1H), 4.33 (s, 1H), 3.72 (s, 3H), 0.95 (s, 3H), 0.90 (s, 3H); ^{13}C NMR δ 159.4 (quart. C), 145.5 (CH), 142.9 (quart. C), 128.8 (CH), 120.8 (CH), 114.2 (CH), 114.0 (CH_2), 113.2 (CH), 81.0 (CH), 53.6 (CH_3), 42.6 (quart. C), 24.9 (CH_3), 21.6 (CH_3); IR (neat) 3538 (s, br), 3084 (w), 2967 (m), 2934 (m), 2874 (w), 2836 (w), 789 (m) cm^{-1}; HRMS-EI (70 eV) *m*/*z* calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.2808. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.50; H, 8.77.

2,2-Dimethyl-1-(2-trifluoromethyl-phenyl)-but-3-en-1-ol (4i). Conversion of 91% based on dimethylallyl bromide: $R_f = 0.30$ (hexane:chloroform = 1:1); colorless oil; ^{1}H NMR δ 7.65 (d, $J = 8.0$, 1H), 7.55 (d, $J = 7.8$, 1H), 7.44 (dd, $J = 8.0$, 7.6, 1H), 7.29 (dd, $J = 7.8$, 7.6, 1H), 6.02 (dd, $J = 17.6$, 10.8, 1H), 5.08 (dd, $J = 10.8$, 1.3, 1H), 4.97 (dd, $J = 17.6$, 1.3, 1H), 4.85 (s, 1H), 1.99 (bs, 1H), 1.02 (s, 3H), 0.87 (s, 3H); ^{13}C NMR δ 144.8 (CH), 140.9 (quart. C), 131.6 (CH), 130.0 (CH), 128.9 (q, $J = 48.3$, quart. C), 128.0 (CH), 126.0 (q, $J = 274$, quart. C), 125.9 (CH), 114.3 (CH_2), 75.2 (CH), 42.9 (quart. C), 26.2 (CH_3), 22.3 (CH_3); IR (neat) 3442 (m, br), 3084 (w), 3011 (w), 2972 (m), 2934 (m), 2876 (w), 1310 (s), 1161 (s), 1123 (s), 768 (m) cm^{-1}; HRMS-EI (70 eV) *m*/*z* calcd for $C_{13}H_{15}F_3O$ ($M^+ - C_5H_9$) 175.0371, found 175.0378. Anal. Calcd for $C_{13}H_{15}F_3O$: C, 63.93; H, 6.19. Found: C, 64.16; H, 5.96.

2,2-Dimethyl-1-(3-trifluoromethyl-phenyl)-but-3-en-1-ol (4j). Conversion of 19% based on dimethylallyl bromide: $R_f = 0.32$ (hexane:chloroform = 1:1); colorless oil; ^{1}H NMR δ 7.48−7.32 (m, 4H), 5.80 (dd, $J = 17.5$, 10.8, 1H), 5.09 (dd, $J = 10.8$, 0.9, 1H), 5.00 (dd, $J = 17.5$, 0.9, 1H), 4.39 (d, $J = 2.68$, 1H), 2.09 (d, $J = 2.68$, 1H), 0.93 (s, 3H), 0.87 (s, 3H); ^{13}C NMR δ 144.8 (CH), 142.1 (quart. C), 131.5 (CH), 130.3 (q, $J = 38.3$, quart. C), 128.2 (CH), 124.9 (CH), 124.6 (CH), 124.6 (q, $J = 274$, quart. C), 80.4 (CH), 42.7 (quart. C), 24.6 (CH), 21.2 (CH); IR (neat) 3485 (m, br), 3086 (w), 2974 (m), 2934 (m), 2899 (m), 1329 (s), 1165 (s), 1128 (s), 1074 (s), 806 (m) cm^{-1}; HRMS-EI (70 eV) *m*/*z* calcd for $C_{13}H_{15}F_3O$ ($M^+ - C_5H_9$) 175.0371, found 175.0360.

2,2-Dimethyl-1-(4-trifluoromethyl-phenyl)-but-3-en-1-ol (4k). Conversion of 17% based on dimethylallyl bromide: $R_f = 0.29$ (hexane:chloroform = 1:1); colorless oil; ^{1}H NMR δ 7.48 (d, $J = 8.0$, 2H), 7.33 (d, $J = 8.0$, 2H), 5.80 (dd, $J = 17.5$, 10.8, 1H), 5.09 (dd, $J = 10.8$, 1.2, 1H), 5.00 (dd, $J = 17.5$, 1.2, 1H), 4.39 (d, $J = 2.8$, 1H), 2.08 (d, $J = 2.8$, 1H), 0.93 (s, 3H), 0.87 (s, 3H); ^{13}C NMR δ 145.1 (quart. C), 144.9 (CH), 130.0 (q, $J = 53.8$, quart. C), 128.5 (CH), 124.8 (CH), 124.6 (q, $J = 272$, quart. C), 114.9 (CH_2), 80.4 (CH), 42.7 (quart. C), 24.7 (CH_3), 21.3 (CH_3); IR (neat) 3458 (m, br), 3086 (w), 2974 (m), 2933 (m), 2876 (m), 1327 (s), 1165 (s), 1127 (s), 1069 (s), 851 (m) cm^{-1}; HRMS-EI (70 eV) *m*/*z* calcd for $C_{13}H_{15}F_3O$ ($M^+ - F$) 225.1091, found 225.1098.

3-Trifluoromethyl-benzoic Acid 2,2-Dimethyl-1-(3-trifluoromethyl-phenyl)-but-3-enyl Ester (5j). Conversion of 34% based on dimethylallyl bromide: $R_f = 0.22$ (hexane:ethyl acetate = 95:5); colorless oil; ^{1}H NMR δ 8.31 (s, 1H), 8.25 (d, $J = 7.8$, 1H), 7.84 (m, 1H), 7.62 (dd, $J = 7.8$, 7.8, 1H), 7.57−7.53 (m, 3H), 5.93 (dd, $J = 17.5$, 10.8, 1H), 5.83 (s, 1H), 5.12 (dd, $J = 10.8$, 1.0, 1H), 5.02 (dd, $J = 17.5$, 1.0, 1H), 1.14 (s, 3H), 1.11 (s, 3H); ^{13}C NMR δ 164.6 (C=O), 143.2 (CH), 138.5 (quart. C), 132.7 (CH), 131.4 (q, $J = 36.1$, quart. C), 131.1 (CH), 130.9 (quart. C), 130.2 (q, $J = 38.9$, quart. C), 129.6 (CH), 129.6 (CH), 128.3 (CH), 126.5 (CH), 124.5 (CH), 124.5 (CH), 124.1 (q, $J = 284$, quart. C), 123.6 (q, $J = 269$, quart. C), 114.3 (CH_2), 82.4 CH), 41.35 (quart. C), 23.96 (CH_3), 22.85 (CH_3); IR (neat) 3090 (w), 2974 (m), 2934 (m), 2878 (w), 1730 (s), 1331 (s), 1252 (s), 1169 (s), 1131 (s), 756 (m) cm^{-1}; HRMS-EI (70 eV) *m*/*z* calcd for $C_{21}H_{18}F_5O_2$ ($M^+ - F$) 397.1227, found 397.1235. Anal. Calcd for $C_{21}H_{18}F_6O_2$: C, 60.58; H, 4.36. Found: C, 60.80; H, 4.17.

Supporting Information Available: ^{1}H NMR spectra for **3e**, **3f**, **3j**, **3k**, **4j**, and **4k**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO001750U