Involvement of an Oxidation-Reduction Equilibrium in Chromium-Mediated Enantioselective Nozaki–Hiyama Reactions

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Dedicated to Dr. Joe Richmond on the occasion of his 60th birthday.

Abstract: Ligand induced enantioselective versions of the chromium(II)-mediated Nozaki–Hiyama reaction to homoallyl alcohols proved to be very difficult to achieve, especially if any other nucleophile than the parent allylchromium(III) species was applied. Also, the reaction is frequently accompanied by the formation of oxidation side products, predominantly allyl ketones. This can be explained by an Oppenauer–(Meerwein–Ponndorf–Verley) type mechanism (OMPV reaction). The addition of an enantiopure ligand to racemic chromium homoallyl alcoholate intermediates produced enantiomerically enriched homoallyl alcohols with an enantiomeric excess of up to 32%. This observation not only supports that the proposed OMPV oxidation-reduction equilibrium plays a crucial role in Nozaki–Hiyama reactions, but also proves its involvement in enantioselective versions.

Keywords: chromium; enantioselection, Meerwein–Ponndorf–Verley reduction; Nozaki–Hiyama reaction, Oppenauer oxidation; thermodynamic deracemization

Coupling reactions of allyl organometallic reagents with aldehydes have been extensively investigated.[1,2] An elegant method for the synthesis of homoallyl alcohols is the chromium(II)-promoted Nozaki–Hiyama reaction, which allows the coupling of allyl halides with aldehydes in a Barbier-type reaction.[3,4] In our previous studies on the Nozaki–Hiyama reaction we observed that allyl ketones **4** can be common side products, or even the main product, although they are neglected by most authors.[5] This formation can be explained by an Oppenauer-type oxidation mechanism (Scheme 1) and is strongly favoured with sterically unhindered aromatic aldehydes and a substituted allylchromium.[5–8]

The involvement of an Oppenauer–Meerwein–Ponndorf–Verley (OMPV) type oxidation-reduction equilibrium reaction implies dramatic consequences for enantioselective Nozaki–Hiyama reactions.[9] The newly formed stereocentre is scrambled through such an oxidation-reduction process. So far, the development of asymmetric versions of the chromium(II)-mediated Nozaki–Hiyama reaction has proven to be troublesome.[3,10–18] Interestingly, an OMPV-reaction also seems to participate in other chromium(II)-mediated reactions like the Nozaki–Hiyama–Kishi and chromium-Reformatsky reactions.[3,5,8] In accordance with this observation, OMPV equilibria are especially relevant in products from substituted allylchromiums, whereas good enantioselectivities were initially reported for the unsubstituted case only. This prompted us to look more closely into the relationship between enantioselective Nozaki–Hiyama reactions and OMPV transformations. Here, we report the results of this study.

The coupling of benzaldehyde (**1a**) with allyl bromide (**2a**) in the presence of bipyridyl ligand **6** was reported to afford homoallyl alcohol **5a** in an enantiomeric excess of 74% (Scheme 2).[10]

This system was suitable for our investigations, as the chiral modifier, the bipyridyl **6**, is bound non-covalently to the chromium centre. This offers the possibility to add bipyridyl **6** after the formation of the racemic chromium(III) alcoholate. In theory, exchange of THF for chiral ligand **6** should result in the formation of a chiral chromium alcoholate complex. If the proposed OMPV equilibrium is responsible for the formation of allyl ketones **4**, this might result in enantiomerically enriched homoallyl alcohols **5** (Pathway 1, Scheme 3). Deracemization of homoallyl alcohols **5** would not only support

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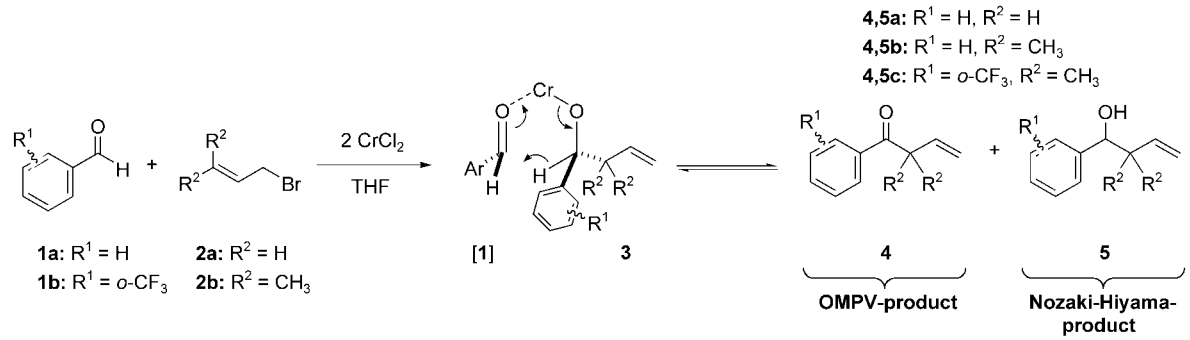
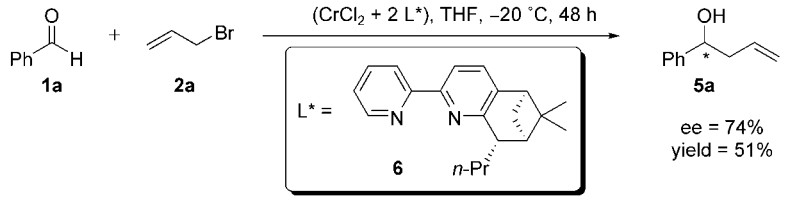
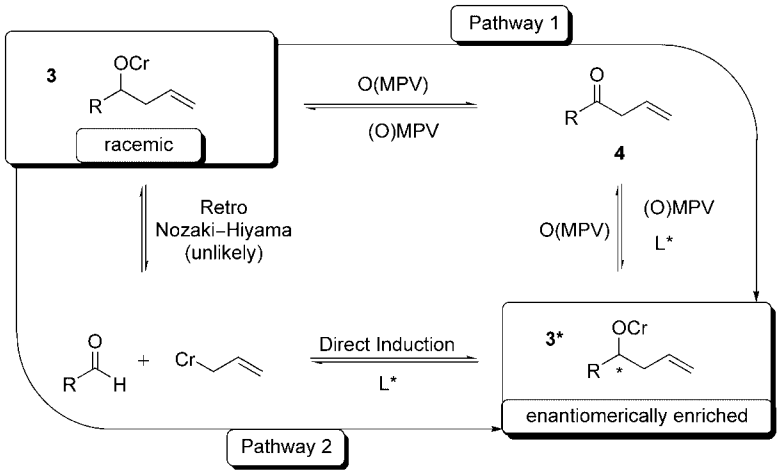


Scheme 1. Oppenauer–(Meerwein–Ponndorf–Verley) oxidation-reduction equilibrium in the Nozaki–Hiyama reaction.



Scheme 2. Enantioselective Nozaki–Hiyama reaction of Kishi et al.[10]

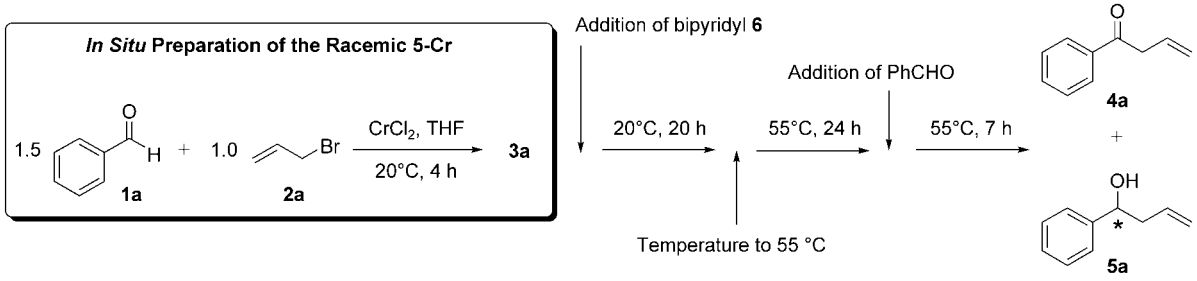


Scheme 3. Possible pathways for deracemization of chromium alcoholate **3**.

the proposed OMPV equilibrium as such, but at the same time indicate the involvement of an oxidation-reduction equilibrium in the enantioselective formation of Nozaki–Hiyama products. Another possible explanation for the deracemization of racemic chromium alcoholate **3** might be, although unlikely, a retro-Nozaki–Hiyama reaction, which is followed by a Nozaki–Hiyama reaction with "normal" direct induction (Pathway 2, Scheme 3). This retro-reaction is unlikely because the driving force of this and other chromium(II)-mediated reactions is the high stability of the formed chromium(III)-oxygen bond, and was confirmed by a reference experiment (Table 1, entry 0).[19–21] No chiral induction was observed when the conditions were chosen as such that the OMPV equilibrium should be inactive. Also, in crossover experiments, in which anisaldehydes were used to form the Hiyama–Nozaki-intermediates **3**, followed by excess benzaldehyde as oxidant, only the anisaldehyde-derived products were detected and not a mixture reflecting the proportions of the two aldehydes applied.[5] More extensive studies on the inhibition of retro-reactivity in Cr(III) complexes[3] will be published elsewhere.

The involvement of the OMPV equilibrium was studied using benzaldehyde (**1a**) and allyl bromide (**2a**) in a 1.5:1 ratio (Table 1). The racemic chromium alcoholate **3a** was formed in the presence of excess oxidant **1** allowing its participation in the OMPV equilibrium. The reac-

Table 1. The *in situ* formation of racemic chromium alcoholate **3** followed by the addition of enantiopure bipyridyl **6** in the presence of oxidant **1a**.[a]



Entry	Time [h]	**4a**:**5a**[b]	**5a** [%][c]	ee [%][d]	Remarks
0	4.0–18.0	0:100	n.d.[e]	0	Reference expt. without excess **1a**[f]
1	4.0	10:90	60	0	racemic **3a**
2	5.0	40:60	36	13	1 h after addn. of chiral ligand **6**
3	24.0	20:80	35	14	after 20 h at 20 °C with **6**
4	48.0	02:98	34	14	after 24 h at 55 °C with **6**
5	55.0	25:75	2	32	after addn. of more oxidant **1a**

[a] $CrCl_2$ (2.00 equivs.), **6** (4.35 equivs.), and additional PhCHO (1.5 equivs.).
[b] Determined by GC analysis.
[c] Determined by GC analysis with naphthalene as internal standard.
[d] Determined by chiral HPLC.
[e] Not determined.
[f] PhCHO (0.5 equiv.), bromide **2a** (1.0 equiv.); addition of **6** after 4 h; reaction for 1 h at 20 °C; temperature to 55 °C; reaction for 13 h at 55 °C.

tion was complete after 4 h at 20 °C, and afforded racemic chromium alcoholate **3a** together with a small amount of ketone **4a** (Table 1, entry 1). After addition of ligand **6**, an interesting change not only of the enantiomeric excess but also of the ratio of ketone **4a** to alcohol **5a** was observed (Figure 1). Indicative for the coordination of bipyridyl **6** to chromium alcoholate **3a** was the immediate colour change of the reaction mixture. The ratio of alcohol **5a** to ketone **4a** decreased significantly within one hour after the addition of **6** (entry 2). Only

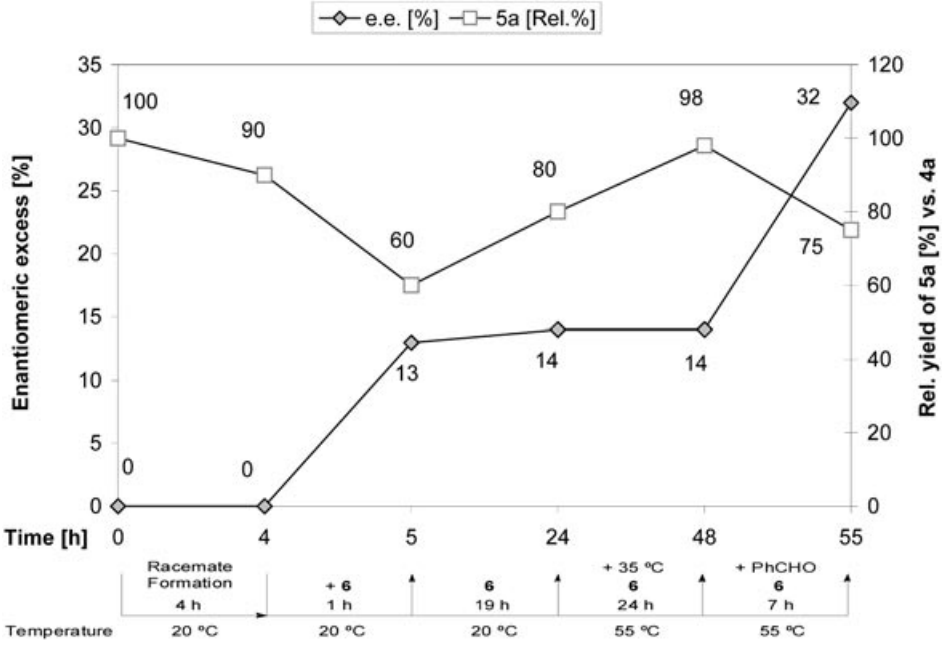


Figure 1. Development of enantiomeric excess and relative yield of alcohol **5a** *vs.* ketone **4a** under the influence of chiral ligand **6** for the experiment presented in Table 1.

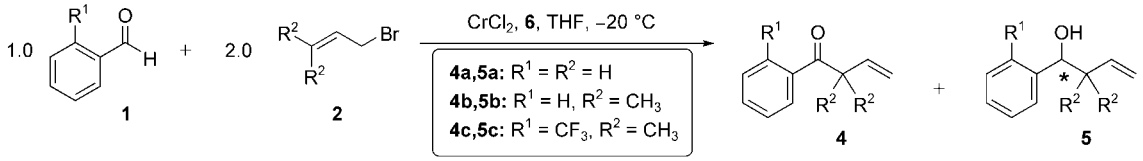
a trace of benzaldehyde **1a** was left, which indicates its consumption as oxidant in the OMPV reaction. This was confirmed by an increase of the amount of benzyl alcohol, and accordingly the equilibrium was shifted as far as possible towards ketone **4a**. Even more important, deracemization of chromium alcoholate **3a** confirms our proposed OMPV equilibrium and its involvement in enantioselective Nozaki–Hiyama reactions. Extended reaction times and elevated temperatures did not effect the enantiomeric excess and conversion of alcohol **5a** and benzyl alcohol (entries 3–4). However, the amount of ketone **4a** decreased with time, probably from decomposition (see below), whereas that of alcohol **5a** remained roughly constant (Table 1 and Figure 1: relative increase of **5a** from 5 h to 48 h).

Additional oxidant **1a** was added after 48 hours to promote the OMPV reaction and again shift the equilibrium. This resulted in a high consumption of alcohol **5a** leaving only 2% of it in the mixture, but with an increased enantiomeric excess of 32% (entry 5). Obviously ketone **4a** is rapidly formed under these conditions but also decomposes rapidly. The addition of oxidant **1a** shifted the reaction further to ketone **4a**, which was confirmed by the increased amount of benzyl alcohol. A new, defined decomposition product derived from ketone **4a** was not observed, which might suggest a polymerization. A change in ee as a consequence of a newly shifted equilibrium upon renewed oxidant (aldehyde) addition is not surprising. Forward and backward reactions may have different kinetics, i.e., the MPV reduction is solely dependent on the chirality induction of Ligand L*, whereas the Oppenauer oxidation of **3** with L* results in a matched/mismatched situation, where one diastereomeric pairing will react preferentially and hence a shift to oxidation as in this case will lead to an enhancement (or decrease) in ee until equilibrium is reached again.

As the reaction of benzaldehyde **1a** with allyl bromide **2a** was the standard reaction to screen the potential of chiral ligands for the enantioselective Nozaki–Hiyama reaction, it is not a surprise that its development was troublesome.

These results support that the OMPV reaction is involved in enantioselective Nozaki–Hiyama reactions, and that the finally obtained chiral induction might be the result of this oxidation-reduction equilibrium. To test this, we performed the same reaction under the conditions published by Kishi ($-20\,^{\circ}C$, THF) using benzaldehyde (**1a**) and allyl bromide (**2a**) in a 1:2 ratio, 2.0 equivs. chromium(II) chloride, and 4.0 equivs. of ligand **6** (Table 2, entries 1–4).[10] The reactions resulted in high enantioselectivities (62–68%) and small fluctuations in enantiomeric excess at different time points (4, 24, 48, and 72 h). The presence of ketone **4a** supports the involvement of the OMPV equilibrium in this reaction. The decreasing ratio of ketone **4a** to alcohol **5a** is probably caused by the previously discussed instability and thus consumption of ketone **4a**. High enantiomeric excesses were also obtained in the reactions of benzaldehyde (**1a**) or *ortho*-substituted aldehyde **1b** ($R^1 = CF_3$) with dimethylallyl bromide (**2b**; $R^2 = CH_3$, entries 5–6). Also in these reactions, the enantiomeric excesses did not change significantly with time. Although it is difficult to give a conclusive explanation for the origin of the extent of the observed asymmetric induction, it is likely that it originates at least to a significant extent from the OMPV equilibrium.

Table 2. The enantioselective Nozaki–Hiyama reaction with bipyridyl ligand **6**.[a]



Entry	R^1	R^2	Time [h]	**4a**:**5a**[b, c]	ee [%] of **5a**[d]
1	H	H	4.0	42:58	68
2	H	H	24.0	20:80	65
3	H	H	48.0	13:87	62
4	H	H	72.0	12:88	62
				4b:**5b**	
5	H	CH_3	48.0	35:65	70
				4c:**5c**	
6	CF_3	CH_3	48.0	0:100	79

[a] $CrCl_2$ (2.00 equivs.), and **6** (4.00 equivs.).[10]
[b] Determined by GC analysis.
[c] Conversion determined by GC analysis with naphthalene as internal standard. A conversion of 15–25% was observed for **5a** (entries 1–4). A conversion of 22–36% was observed for **5b** at different time points (entry 5). A conversion of 9–20% was observed for **5c** (entry 6). [d] Determined by chiral HPLC.

Explanations for the observed difference in enantiomeric excess between initial (Table 2) and late (Table 1) addition of chiral ligand **6** can only be speculative. In order to obtain high enantiomeric excesses, non-equilibrium conditions without excess aldehyde were chosen and thus the kinetic parameters of the initial reaction become crucial. Also, the complexation of chromium ions by **6** will be better if chiral ligand is added before the reaction starts, because ligand binding (ligand exchange) is up to 10^{15} times faster for the initially present Cr(II) ions than for chromium(III) – hence the exchange stability of Cr(III) alcoholates, e.g., in crossover experiments.[3] However, also qualitative differences of the intermediate complexes have to be considered. Complex **[Cr(II) + 6]** reacting with **1** and **2** to give intermediate **[3 + Cr(III) + 6]** (type 2) may vary to some extent from those generated by reacting **[3 + Cr(III)]** with **6** to obtain **[3 + Cr(III) + 6]** (type 1). Although formally the same, the real nature of the intermediate chromium-alkyl and chromium alcoholate complexes is not understood at all, and it is well known that the complex formed[22] as well as the OMPV equilibrium[5] is strongly influenced by slight variations, e.g., of pH and aldehyde concentration. Thus, if the order of addition or ratio of the components is changed, cluster formation, incorporation of the second Cr(III) ion present, or binding of **6** or other ligands like aldehyde or THF in the active intermediate may be different. We made similar observations with reactions of other chromium(III) alkyls and enolates, formed either by reaction of Cr(II) with alkyl halide (+lithium halide), or by metal exchange of lithium alkyl with Cr(III) halide.[3] Reactivity and yields obtained from these intermediates were significantly different, although again, the complexes were formally the same, the identical product was eventually formed, and the general behaviour, e.g., chemoselectivity, was comparable.

In conclusion, the proposed OMPV equilibrium for the formation of allyl ketones **4** has been confirmed by the deracemization experiments with enantiopure ligand **6**. Its involvement in enantioselective chromium(II)-mediated Nozaki–Hiyama reactions was demonstrated. Likely the observed chiral inductions are the result of this oxidation-reduction equilibrium. These results might be seen in a broader perspective as the formation of ketones as by-products has also been observed in other chromium(II)-mediated reactions like in the Nozaki–Hiyama–Kishi and to a minor extent in chromium-Reformatsky reactions with unsaturated 4-haloenoates.

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 **1b**, **2a**, **b**, and chromium(II) chloride (99.9% from Strem Chemicals) were used as purchased. Bipyridyl ligand **6** was synthesized according to a literature procedure.[10] Tetrahydrofuran was distilled from potassium/benzophenone. Absolute dimethylformamide was purchased from Fluka. Benzaldehyde (**1a**) was distilled from potassium hydride. Spectral data of the known compounds **4a**,[23] **4b**,[24] **5a**,[23] **5b**,[25] and **5c**[5] were in accordance with the literature data. Benzyl alcohol was characterized by comparison with a commercially available sample. Thin-layer chromatography was carried out on Merck silica 60/F-254 aluminium-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). Gas chromatographic analyses were run on a Carl Erba Instruments apparatus (HRGC 5160 Mega Series, Ultra 1 column, 50 m, i.d. 0.2 mm, film thickness 0.33 μm, FID detector). HPLC analyses were carried out on an Agilent 1100 chromatograph using a Chiralcel OD-column (4.6 × 250 mm); solvent: 98:2 hexane:isopropanol; flow rate = 0.5 mL × min^{-1}; T = 25 °C (**5a**, **b**), T = 1 °C (**5c**); UV detection: 220 nm.

Procedure for the Nozaki–Hiyama Reaction Followed by the Addition of Bipyridyl Ligand 6 (Table 1)

To chromium(II) chloride (2.0 equivs., 50 mg, 0.41 mmol) was added a solution of naphthalene (as internal reference; 0.5 equiv., 13 mg, 0.10 mmol) in 1.0 mL THF under vigorous stirring. After a few minutes, a solution of the aldehyde in 0.5 mL THF and a solution of allyl halide (1.0 equiv., 0.20 mmol) in 0.5 mL THF were added in this order. The resulting mixture was stirred for 4 h at 20 °C, followed by the addition of bipyridyl **6** [4.83 equivs. (entry 0); 4.35 equivs. (entries 1–5), 238 mg, 0.41 mmol]. Stirring was continued for the given time and temperature. Benzaldehyde (1.5 equivs., 20 μL, 0.20 mmol) was added at the given time. Samples (0.3 mL) were taken after the given intervals. Samples were quenched with water. The water layer was extracted three times with diethyl ether, and the combined organic fractions were washed with a saturated aqueous NaCl solution. The organic layer was dried with $MgSO_4$. Conversions were determined by GC with naphthalene as the internal standard. Enantiomeric excesses were determined by chiral HPLC.

General Procedure for the Enantioselective Nozaki–Hiyama Reactions (Table 2)

To chromium(II) chloride (2.0 equivs., 50 mg, 0.41 mmol) and bipyridyl **6** (4.0 equivs., 238 mg, 0.81 mmol) was added 1 mL of a solution of naphthalene (0.5 equiv., 13 mg, 0.10 mmol) in 1.0 mL THF under vigorous stirring. The solution was stirred for 1 hour at 20 °C, and cooled to −20 °C. The aldehyde (1.0 equiv., 0.20 mmol) in 1.0 mL THF and allyl halide

(2.0 equivs., 0.41 mmol) in 1.0 mL THF were added in this order. The resulting mixture was stirred for 78 h at $-20\,^{\circ}C$, and samples (0.3 mL) were taken at the given time points. The samples were quenched with water. The water layer was extracted three times with diethyl ether, and the combined organic fractions were washed with a saturated aqueous NaCl solution. The organic layer was dried with $MgSO_4$. Conversions were determined by GC with naphthalene as the internal standard. Enantiomeric excesses were determined by chiral HPLC.

2,2-Dimethyl-1-(2-trifluoromethylphenyl)-but-3-en-1-one (4c): Colourless oil; $R_f = 0.52$ (hexane:diethyl ether, 90:10); ^{1}H NMR (400 MHz): $\delta = 7.67$ (m, 1H), 7.51–7.49 (m, 2H), 7.35 (m, 1H), 6.02 (dd, $J = 17.6$, $J = 10.5$ Hz, 1H), 5.20 (d, $J = 17.6$ Hz, 1H), 5.19 (d, $J = 10.5$ Hz, 1H), 1.33 (s, 6H); ^{13}C NMR (100 MHz): $\delta = 208.7$ (C=O), 142.7 (CH), 139.3 (quart. C), 131.0 (CH), 129.0 (CH), 127.0 (q, $J = 32.2$ Hz, quart. C), 126.7 (q, $J = 5.0$, CH), 126.0 (CH), 123.5 (q, $J = 274$ Hz, quart. C), 114.62 (CH_2), 51.12 (quart. C), 24.49 (CH_3); IR (film): $\nu =$ 2974 (w), 1702 (s), 1321 (s), 1064 (m), 1034 (m), 970 (m), 922 (m), 769 (m) cm^{-1}; anal. calcd. for $C_{13}H_{13}F_3O$: C 64.46, H 5.41; found: C 64.86, H 5.44.

Acknowledgements

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