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A mechanistic study of the Hiyama–Nozaki allylation: evidence for radical intermediates

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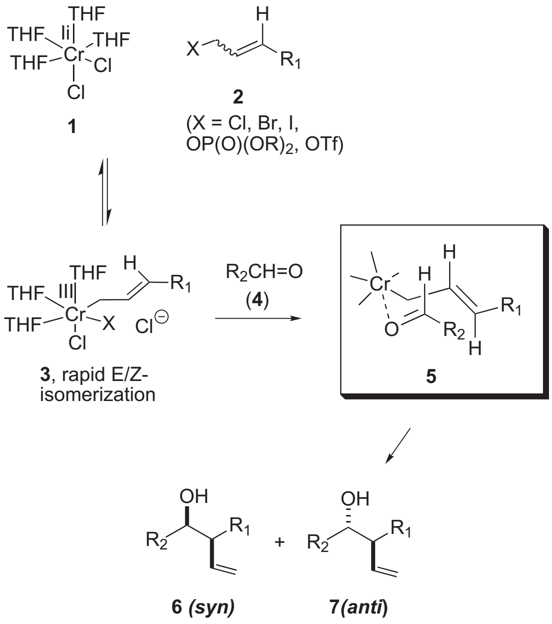
Abstract—In course of chromium(II) mediated additions of relatively complex allylic bromides to aldehydes (Hiyama–Nozaki allylation) radical intermediates have been observed. From these findings a new mechanism of the allylation is derived.

The Hiyama–Nozaki allylation[1] is a well documented reaction of which numerous applications have been reported in natural product synthesis,[2] however the mechanism of this reaction has never been studied in greater detail.

In the early literature[1c] the formation of a covalent Cr–allyl intermediate **3** from the solvated chromium(II) salt (**1**) and the allylic halide (or phosphate or triflate) **2** was postulated, which adds to the aldehyde **4** via a Zimmerman–Traxler like complex **5** from which the homoallylic alcohols **6** and **7** are formed with varying *syn*-stereoselectivity (from ca. 70:30 up to >95:5; in the original literature the *syn*- *anti*-designation is opposite to the one we use here. We do this because it is the easier way to describe linear carbon chains with multiple stereogenic centers). It was also claimed,[1b] that the **6**/**7**-ratio is independent of the *E*/*Z*-geometry of **2**, which indicated that species **3** rapidly isomerizes to the thermodynamically favored *E*-configuration. As these mechanistic conclusions, which are summarized in Scheme 1, were derived from very simple substrates we decided to validate them by using more complex allylic halides and aldehydes. Thus, as shown in Scheme 2, halide **8**[3] and aldehyde **9**[3] under the usual conditions (THF, $CrCl_2$ prepared in situ from $CrCl_3$ and $LiAlH_4$)[1] formed the diastereomeric adducts **10** and **11** in a ratio of 2.5:1.



Scheme 1. Standard mechanism of the Hiyama–Nozaki allylation.

In keeping with our earlier results,[3] the addition proceeded with complete *syn*-stereoselectivity around the 3,4- and with (moderate) Felkin–Anh selectivity around the 4,5-axis. Additionally olefin **12** and di-olefin **13** were isolated. The formation of **12** and, in particular, **13** can be interpreted in terms of an allylic radical intermediate **14**, which is quenched either by hydrogen abstraction or by dimerization.[4] Remarkably, the hydrogen abstraction did not produce regioisomer **12a**, which would come from the most stable radical position in **14**. It

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Keywords: Allylic radicals; Organochromium compounds; SET mechanism; Stereoselective allylation of aldehydes; Homoallylic alcohols.

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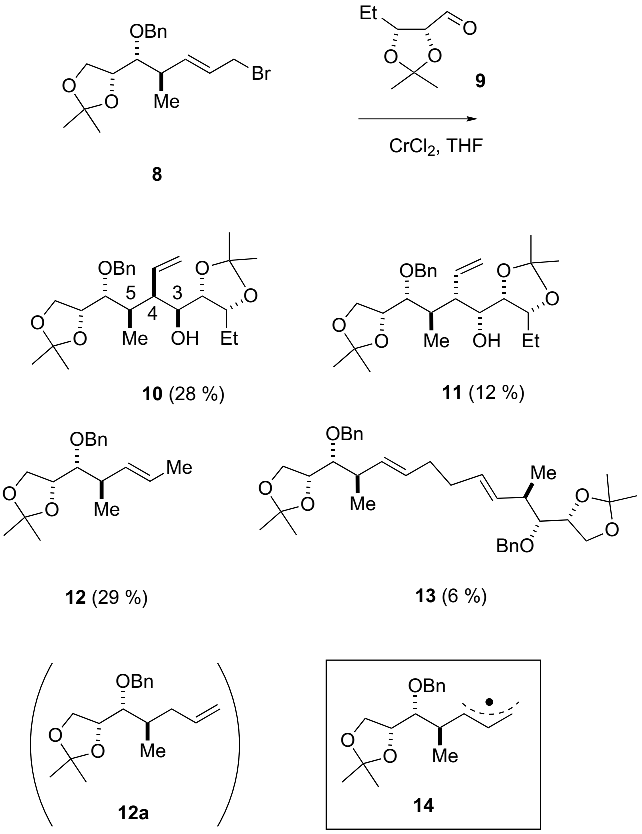
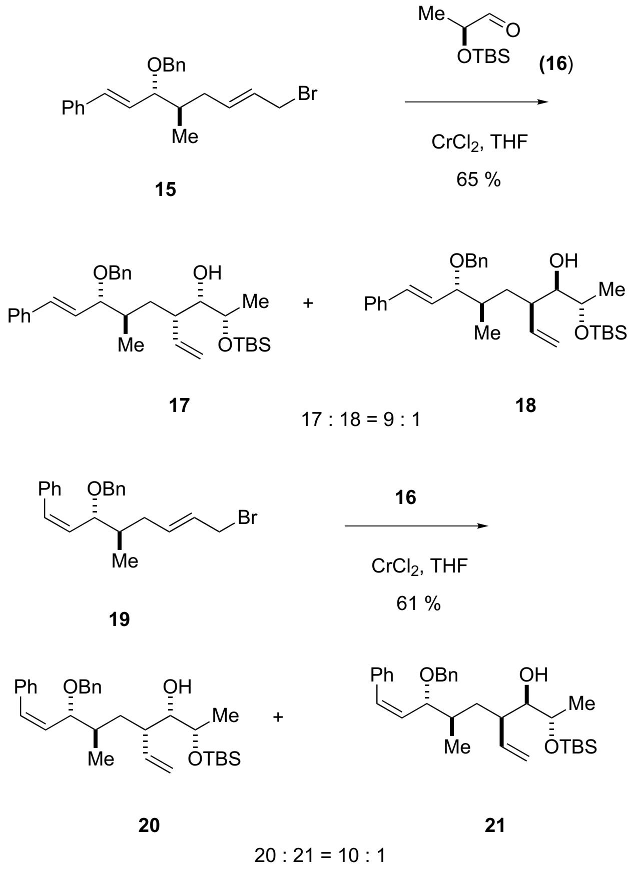


Scheme 2. Dimerization and hydrogen abstraction in the Hiyama–Nozaki allylation.



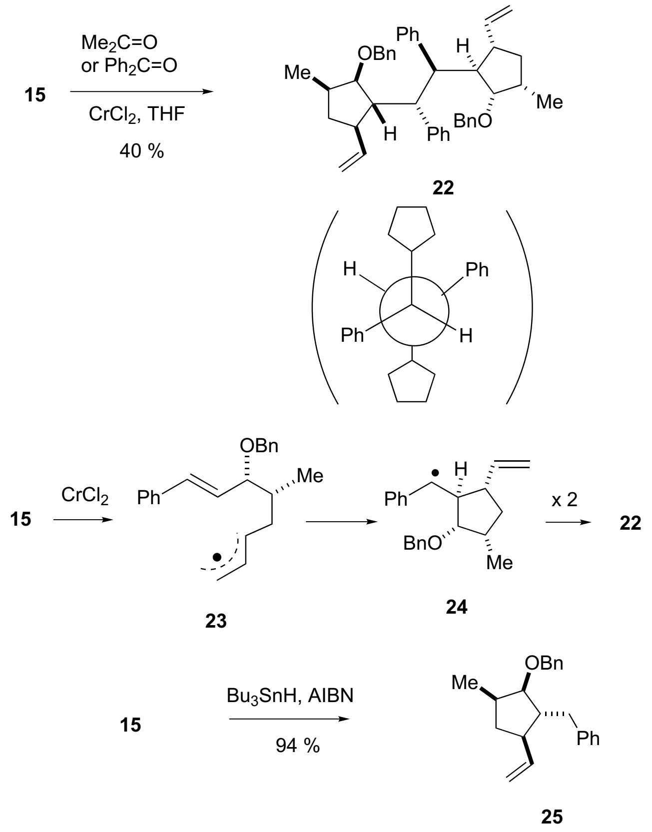
Scheme 3. Stereoselective Hiyama–Nozaki allylation with halides **15** and **19**.

appears, however, that the radical transfer favors the least hindered, that is terminal position of the allylic radical. Workup with D_2O did not lead to deuterium incorporation in **12** or **13**, which excluded the presence of anionic precursors. Halide **8** was inert toward chromium(II) in the absence of aldehyde **9** and could be re-isolated. In a second set of experiments (Scheme 3), (*E*)- and (*Z*)-halides **15**[3] and **19**[3] were first shown to behave 'normally' by giving the Hiyama–Nozaki adducts **17/18** and **20/21** in high diastereoselectivity. However, when **15** (or its (Z)-isomer **19**) was treated with $CrCl_2$ and 1 mol equiv of acetone or benzophenone, no Hiyama–Nozaki allylation was observed. Instead the crystalline dimer **22** was isolated[5] whose structure was elucidated via single crystal diffraction.[12] The formation of **22** can be rationalized (Scheme 4) in terms of a 5-*exo*-*trig*-cyclization of allylic radical **23** to benzyl radical **24** and subsequent radical dimerization to form the least hindered dimer possible (the two phenyl groups on the bridge in **22** are *anti*-periplanar). In the absence of the ketone, no reaction occurred and **15** remained untouched. Similarly, acetone and benzophenone were inert toward chromium(II)chloride and benzophenone could be re-isolated. To probe the stereochemical result of a 'real' free radical cyclization, halide **15** was subjected to a standard 5-hexenyl-cyclization[6] in presence of *n*-Bu_3SnH as a hydrogen donor. In fact, cyclopentane **25** was formed with the same relative configuration as the one found in dimer **22**, according to extensive NOE experiments.

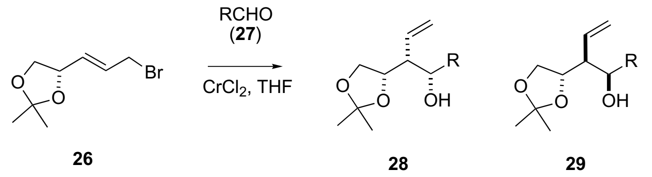
To probe the amount of negative charge that is accumulated in the allylic moiety during the Hiyama–Nozaki allylation, halide **26** was tested, which has an oxygen leaving group in the δ-position (Scheme 5). On treatment with reducing metals such as Zn or Mg such halides undergo elimination to form olefins.[7] Under Hiyama–Nozaki conditions, however, **26** reacted with a variety of aldehydes **27** to give the homoallylic alcohols **28/29** with varying *syn*-selectivity.[8] This result renders the formation of an organometallic species such as **3** with carbanion-like properties unlikely. Similarly, all attempts to quench Cr–allyl intermediates with D_2O did not lead to deuterium incorporation (vide supra).

In conclusion, we suggest an alternative mechanistic pathway for the Hiyama–Nozaki allylation (Scheme 6), which in contrast to the 'standard' mechanism shown in Scheme 1 avoids the formation of **3** and focuses on a primary chromium–carbonyl interaction instead.

Hence, in the first step the reversible formation of a ketyl radical **30** in low concentration is postulated. Another reversible SET to the allylic bromide places bromide into the ligand sphere of the chromium and generates complex **31**, in which the carbonyl species and an allylic radical are coordinated with the metal. It remains a matter of speculation whether the allylic species is coordinated to the chromium in a η^1- or η^3-fashion.[9] The regiochemistry of the ensuing Hiyama–

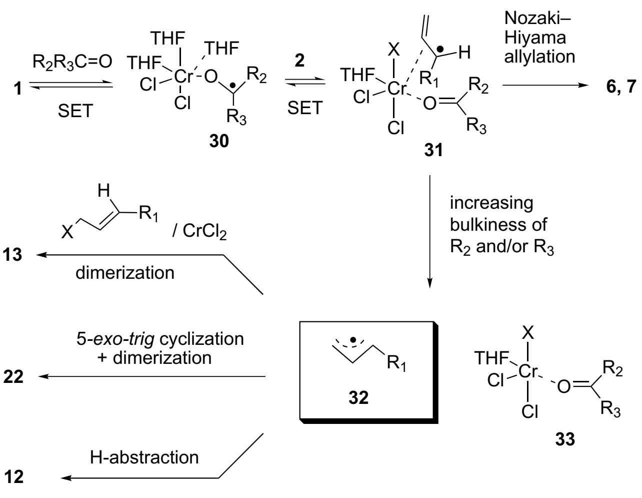


Scheme 4. Radical cyclization and dimerization of allylic halide **15**.



	R	28 : 29	total yield (%)
a	Ph	93 : 7	86
b	naphthyl	92 : 8	84
c	Me	60 : 40	91
d	$C_{13}H_{27}$	60 : 40	88

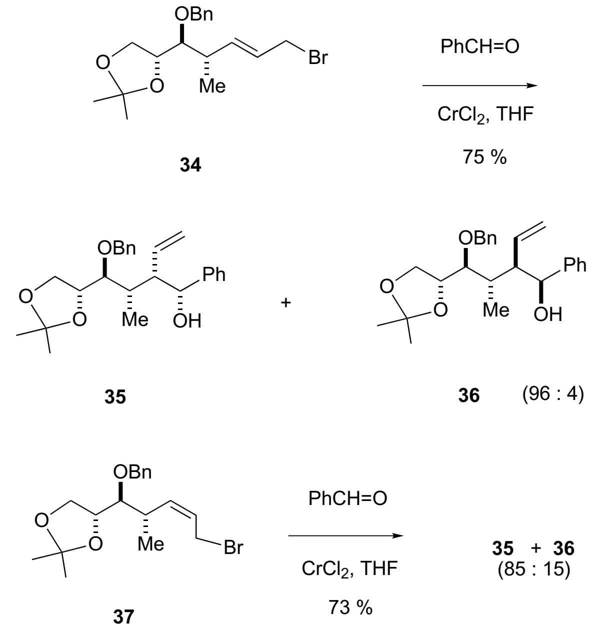
Scheme 5. Hiyama–Nozaki allylation with δ-alkoxy-allylic halides.



Scheme 6. Alternative mechanism for the Hiyama–Nozaki allylation.

Nozaki allylation, however, suggests it is η^1, which means that the geometry of **31** strongly resembles the one of complex **5**. The reversibility of the formation of **31** is necessary to explain the Cl/Br-exchange in the allylic bromides **8**, **15**, and **19**, which was observed as a side reaction. For small substituents R^2 and R^3 **31** may collapse to generate the homoallylic alcohols **6**/**7** after hydrolysis. For bulky residues R^2 and R^3 **31** dissociates into the Cr–carbonyl complex **33** and radical **32**, which either undergoes dimerization to **13** and **22**, or forms **12** via hydrogen abstraction. This dissociation most likely is irreversible, as it is driven by the release of steric repulsion between the residues R^1, R^2, and R^3. If the dissociation were reversible, the allylic species in **31** would be symmetrized and the corresponding Hiyama–Nozaki adducts **6**/**7** would necessarily show allylic transposition. From **30**, a pinacol dimerization of the ketyl radical with unreacted ketone could occur. However, such pinacol dimerizations are slow in the absence of TMSCl.[1g,10]

Allylic radicals such as **32** are known to have a relatively high barrier toward *E*/*Z*-isomerization,[11] which would be in contradiction to the behavior of intermediate **3** (Scheme 1). Thus, the *E*- and *Z*-allylic halides **34**[3] and **37**[3] were treated with benzaldehyde in a standard Hiyama–Nozaki allylation (Scheme 7). Although the *syn*-diastereomer **35** was formed selectively in both experiments, the diastereomeric ratios of **35**:**36** were clearly different. This observation suggests that the allylic intermediates, which have been formed from **34** and **37** are different and do not equilibrate.



Scheme 7. Hiyama–Nozaki allylation of (*E*) and (*Z*)-allylic halides **34** and **37**.

1. Experimental

A suspension of anhydrous chromium(III)chloride (27 mmol) in THF (100 mL) was treated under vigorous stirring at 0 °C with lithium aluminumhydride (13.5 mmol) in small portions. After the evolution of hydrogen has ceased the mixture was stirred for additional 20 min at ambient temperature. Then the mixture was cooled to 0 °C and the aldehyde (15 mmol) and the allylic bromide (10 mmol) in THF (20 mL each) were added dropwise in succession and the mixture was stirred at room temperature for 36 h. Then the reaction was quenched with saturated aqueous sodium hydroxide (15 mL) and solid sodium sulfate (20 g) was added. The mixture was filtered over Celite, dried over sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (silicagel, hexane–ethylacetate) or HPLC (0.8% 1-propanol in hexane).

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2004.09.179. Some analytical and spectroscopic data of compounds **12**, **13**, **17**, **18**, **20**, **21**, **25**, **28a**, **28b**, **28c**, **29c**, **28d**, **29d**.

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5. Colorless crystals (mp 95 °C). ^{1}H NMR (CDCl$_3$): δ 0.66 and 0.71 (d, 6H, $J = 7.5$ Hz), 0.92 and 0.95 (ddd, 2H, $J = 13$ Hz, $J = 7.5$ Hz, 2H), 1.41 and 1.42 (dddq, 2H, $J = 8$ Hz, $J = 7.5$ Hz), 1.50 and 1.56 (ddd, 2H, $J = 13$ Hz, $J = 9$ Hz, $J = 8$ Hz), 1.87 and 2.01 (mc, 1H), 1.99 and 2.16 (mc, 2H), 3.33 and 3.40 (dd, 2H, $J = 8$ Hz, $J = 7$ Hz), 3.45 and 3.84 (dd, 2H, $J = 13$ Hz, $J = 5$ Hz), AB-system ($\delta_A = 4.21$, $\delta_B = 4.33$, $J_{AB} = 12$ Hz, 2H), AB-system ($\delta_A = 4.35$, $\delta_B = 4.44$, $J_{AB} = 12$ Hz, 2H), 4.90 and 5.00 (dd, 2H, $J = 10$ Hz, $J = 2$ Hz), 5.00 (2dd, 2H, $J = 17$ Hz, $J = 2$ Hz), 5.40 and 5.50 (ddd, 2H, $J = 17$ Hz, $J = 10$ Hz, $J = 9$ Hz), 7.31 (mc, 10H). ^{13}C NMR (CDCl$_3$): δ 15.17, 15.28, 34.26, 34.70, 37.46, 39.84, 42.34, 45.01, 45.79, 48.88, 50.26, 50.62, 71.04, 71.33, 82.88, 84.89, 112.75, 114.23, 125.89, 126.03, 126.13, 127.13, 127.27, 127.40, 127.52, 127.70, 127.83, 128.00, 128.10, 128.18, 128.25, 128.33, 128.61, 133.75, 142.46, 144.98. IR (KBr): ν 3080m, 3065m, 3025s, 3020w, 2955vs, 2920vs, 2865vs, 2855vs, 1945w, 1898w, 1710m, 1635m, 1491m, 1450s, 1421w, 1400m, 1372m, 1350br m, 1295w, 1259m, 1211m, 1176m, 1153m, 1103vs, 1082s,1070s, 1028m, 999m, 906s, 821w, 788w, 753s, 703vs, 682w, 652m cm^{-1}. MS (EI, 80 eV, 90 °C): *m*/*e* 610 (1%, M), 519 (3%, M$-$C$_7$H$_7$), 502 (3%, M$-$C$_7$H$_7$O), 411 (1%, M$-$C$_7$H$_7$$-C_7H_7$O), 394 (3%, M$-$2C$_7H_7$O), 305 (13%, M/2), 287 (5%), 231 (2%), 215 (3%, M/2$-$C$_7$H$_7$), 199 (47%, M/2$-$C$_7$H$_7$O), 143 (10%), 107 (22%, C$_7$H$_7$O), 91 (100%, C$_7$H$_7$). Anal. Calcd for C$_{44}$H$_{50}$O$_2$: C, 86.51; H, 8.25. Found: C, 86.66, H, 8.28.
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12. The crystal data can be obtained free of charge via www from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB21EZ, UK, fax: +44 1223 336 033 or deposit@ccdc.cam.uk under the registration numbers CCDC 241179 (**22**) and 241180 (**28a**).