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Revisit to the reduction of allylic chlorides to less substituted olefins by a low-valent chromium species in the presence of a proton source

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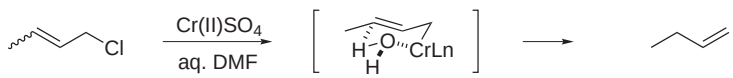
Abstract—Allylic chlorides have been reduced to afford less substituted olefins by a low-valent chromium species in the presence of an alcoholic proton source. This process certainly has synthetic benefits since the regio-selectivity of the reduction is high and the reaction conditions are mild and nearly neutral.

In 1977, a procedure for the in situ preparation of a low-valent chromium species (Cr(II)) in an aprotic medium was reported by Hiyama et al.[1] Since then, Cr(II) has been widely used in organic synthesis especially in the C–C bond formation reactions of allylic (Nozaki–Hiyama reaction) or vinylic halides (Nozaki–Hiyama–Kishi reaction) with aldehydes.[2]

Prior to these studies, Cr(II) was generated in an aqueous medium and utilized mainly for the reductive cleavage of the carbon–halogen bond.[3] Among these earlier investigations, the reduction of allylic halides is noteworthy. Castro et al. reported that both *cis*- and *trans*-crotyl chloride are reduced by chromous sulfate in an aqueous DMF to afford 1-butene in high selectivity.[4] This result suggests that the protonation of the allylchromium species must be faster than the radical homo-coupling reaction, affording dimeric products as are obtained in the absence of a proton source.[5] And more importantly from the synthetic aspect, similarly to C–C bond formation with aldehydes, protonation occurs at the γ-position of the allylchromium species to give a less substituted olefin, i.e. a thermodynamically less stable olefin, through the six-membered transition state (Scheme 1). Furthermore, the reaction proceeds under nearly neutral conditions. Despite the advantageous aspects of this synthetic procedure, applications have been limited in comparison with other more common methods, such as the acid hydrolysis of allylstanannes[6] or allyltosylhydrazides[7] and the hydride reduction of allyltriphenylphosphonium halides.[8] Here, we revisit the double bond migrative reduction of allylic halides by the Cr(II) species to report the synthetic utility.

At first, we re-checked the regio-selectivity of this reaction with the use of geranyl chloride (**1a**) as a substrate. The allylchromium species was generated by Hiyama's conditions.[1] Similar to the originally reported results in an aqueous medium,[4] the reduction proceeds quantitatively even in the presence of a limited amount of an alcoholic proton source in an aprotic solvent system, a mixture of THF and DMF. However, a mixture of dimeric products arising from the radical homo-coupling reaction[5] was obtained when bulky *t*-BuOH was used as a proton source. The regio-selectivity of the reduction is high enough as shown in Table 1 to give 3,7-dimethylocta-1,6-diene (**2a**) exclusively.



Scheme 1. Double bond migrative reduction of crotyl chlorides by $Cr(II)SO_4$ in an aqueous medium.[4]

Keywords: Hiyama reactions; olefins; protonation; reduction; regioselection.
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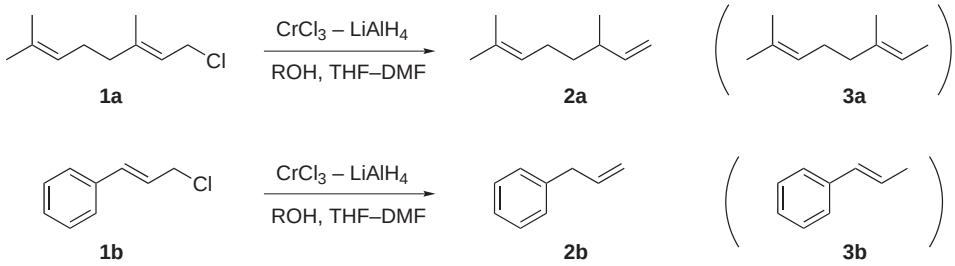


Scheme 2. Double bond migrative reduction of allylic chlorides by Cr(II) species in the presence of alcoholic proton sources.

Table 1. The regio-selectivity of the Cr(II)–ROH reduction of geranyl chloride (**1a**) and cinnamyl chloride (**1b**)[a]

Substrate	Proton source	Ratio of **2**:**3**
Geranyl chloride (**1a**)	H_2O	>99.5:<0.5
1a	MeOH	>99.5:<0.5
1a	EtOH	>99.5:<0.5
1a	*i*-PrOH	98.5:1.5
1a	*t*-BuOH	85:15[b]
Cinnamyl chloride (**1b**)	EtOH	95.5:4.5
1b	*i*-PrOH	97.5:2.5

[a] Cr(II) was generated from 5 mmol of $CrCl_3$ and 2.5 mmol of $LiAlH_4$ in THF (5 ml) and the resultant was diluted with 10 ml of DMF. Into the resulted suspension were added 10 mmol of the indicated protone source and a DMF (5 ml) solution of 2 mmol of the substrate and 2 mmol of decane as a analytical standard. After stirring under an inert atmosphere for 15–24 h at room temperature, the reaction mixture was extracted with hexane and the organic phase was directly analyzed by GC-MS. The combined chemical yield of the reductates is quantitaive within an experimental error except the case when *t*-BuOH was used as a proton source.

[b] The combined chemical yield of **2a** and **3a** is estimated to be ~20% based on the isolated yield (77%) of non-volatile dimeric products.

The regio-selectivity is maintained in the conjugated system. As shown also in Table 1, cinnamyl chloride (**1b**) was converted into allylbenzene (**2b**) predominantly even though the reaction involves a thermodynamically unfavorable deconjugation process (Scheme 2).

Taking advantage of the nearly neutral conditions, the synthetic utility of this procedure is emphasized in the formation of acid-labile compounds, which are difficult to obtain by alternative methods involving acid hydrolysis. For example, the Cr(II)–ROH (*i*-PrOH was used) reduction of 2-chloromethylbenzo[*b*]furan (**1c**)[9] successfully afforded 2,3-dihydro-2-methylenebenzo[*b*]furan (**2c**),[10] which is extremely labile toward both acidic and basic conditions, in moderate yield together with the regio-isomer **3c** after chromatographic purification (Scheme 3).†

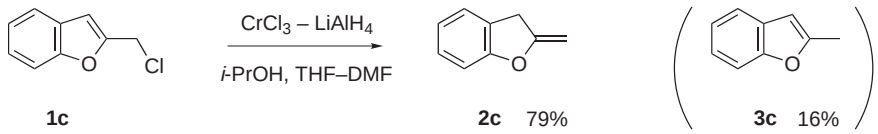
† Since it has been known that **2c** isomerizes into **3c** during a chromatographic (SiO_2) purification,[10] the ratio of the isolated reductates does not directly reflect the regio-selectivity of the reduction process. ^{1}H NMR of the crude product showed the predominant formation of **2c**.

The authors then focused their attention on the stereoselectivity. If this reduction actually involves the six-membered transition state as shown in Scheme 1, then the stereo-structure of the substrate should direct a diastereoselective protonation. In fact, the protonation of the allylchromium species generated from (3*R*,8*S*)-7-chloro-1-iridene derivative (**1d**)[11] occurs on the less hindered face to afford (1*R*,3*R*,8*S*)-irid-2(7)-ene derivative (**2d**)‡ predominantly. The stereochemistry of the newly formed stereogenic center was confirmed by an NOE experiment indicated in Scheme 4 and a further conversion of **2d** into all-*cis*-iridodiol (**4**)[12] through hydroboration on the exocyclic olefin.

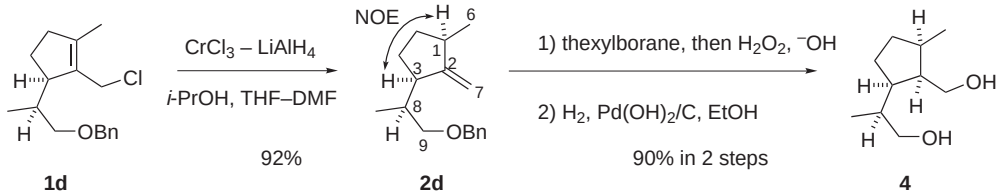
It has been known that the same crotylchromium species is generated from both crotyl chloride (1-chloro-2-butene) and 3-chloro-1-butene in order to locate the metal at the less crowded circumstances of the allylic system.[1] Taking this feature into account, it is possible to isomerize a thermodynamically more stable olefin to a less stable one by a sequence of allylic chlorination and Cr(II)–ROH reduction. Scheme 5 shows an example of this type of transformation. The allylic chlorination of the internal olefin of **5** was achieved by the hypochlorous acid treatment,[13] and then the Cr(II)–ROH reduction of the resulting chloride furnished the isomerization of the double bond to give **6** in good yield.[14]

As realized in this example, the aldehyde-selective nature of the allylchromium species as a nucleophile allows application of this process to substrates carrying functional groups other than aldehydic moieties. Thus, this procedure is certainly an alternative synthetic method to advantageously obtain less substituted olefins from allylic halides.

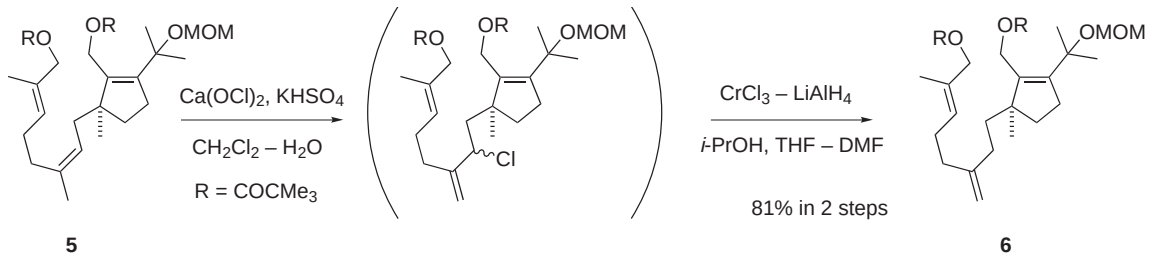
‡ A colorless oil; $[\alpha]_D^{22}$ +60.8 (*c* 1.86, $CHCl_3$); δ_H (C_6D_6) 0.99 (3H, d, *J*=7.1 Hz; H-6), 1.11 (1H, dm, *J*=13.0 Hz; H-5), 1.12 (3H, d, *J*=7.1 Hz; H-10), 1.45 (1H, dm, *J*=12.5 Hz; H-4), 1.52 (1H, dm, *J*=12.5 Hz; H-4), 1.60 (1H, dm, *J*=13.0 Hz; H-5), 2.05 (1H, m; H-8), 2.40 (1H, m; H-1), 2.46 (1H, m; H-3), 3.17 (1H, dd, *J*=8.8, 8.1 Hz; H-9), 3.42 (1H, dd, *J*=8.8, 4.6 Hz; H-9), 4.29 (1H, d, *J*=12.2 Hz; benzyl), 4.33 (1H, d, *J*=12.2 Hz; benzyl), 4.93 (1H, m; H-7), 4.96 (1H, m; H-7), 7.08 (1H, t-like, *J*=~8 Hz; Ph-*para*), 7.17 (2H, t-like, *J*=~8 Hz; Ph-*meta*), and 7.29 (2H, d-like, *J*=~8 Hz; Ph-*ortho*); δ_C (C_6D_6) 17.11 (C-10), 20.08 (C-6), 26.96 (C-4), 33.18 (C-5), 36.47 (C-8), 39.51 (C-1), 47.69 (C-3), 73.11 (benzyl), 73.30 (C-9), 105.19 (C-7), 127.49 (Ph-*para*), 127.62 (2C, Ph-*ortho*), 128.46 (2C, Ph-*meta*), 139.52 (Ph-*ipso*), and 159.49 (C-2).



Scheme 3. Double bond migrative reduction of **1c** to **2c**.



Scheme 4. Double bond migrative reduction of **1d** to **2d** and a further conversion into all-*cis*-iridodiol (**4**).



Scheme 5. Transformation of a more substituted internal double bond to a less substituted external double bond.

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