

Addition of Organochromium Reagents to Aldehydes, Ketones and Enones: a Low-temperature Version of the Nozaki–Hiyama Reaction

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Ph_2Cr -tetramethylethylenediamine-mediated Nozaki–Hiyama reaction of allylic and propynylic halides leads to rapid 1,2-addition to aldehydes, ketones and enones at $-60\text{ }^\circ\text{C}$ in moderate to high yields.


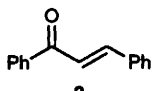
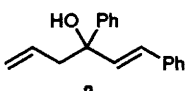
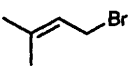
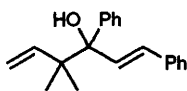
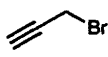
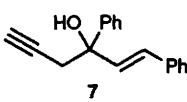
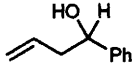
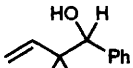
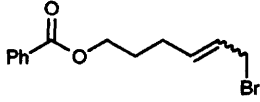
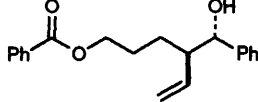
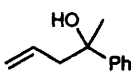
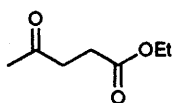
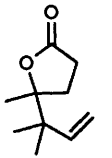
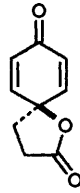
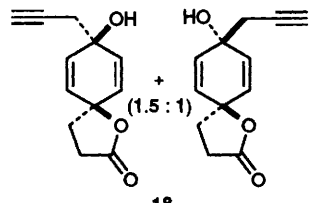
The addition of alkynyl, alkenyl and allyl chromium compounds to aldehydes, known as the Nozaki–Hiyama reaction,¹ is an important method for C–C bond formation in organic synthesis.² The general protocol for this reaction involves treatment of halides with chromium(II) chloride at room temperature for several hours in the presence of aldehydes. Reactions with ketones are generally more sluggish, and α,β -unsaturated ketones fail.³ In the context of our work with low-valent samarium reagents,⁴ we realized that the redox potential of M^{II} salts could be conveniently manipulated by the presence of electron-rich organic ligands. Since a rapid, low-temperature reduction of allylic halides with Cr^{II} complexes would be highly desirable, especially for sensitive substrates, we initiated a programme for the study of the reaction profile of organochromium(II) complexes in the Nozaki–Hiyama coupling. Our preliminary data that highlight the synthetic usefulness of such an approach are summarized in this communication.

Addition of PhMgBr (2 equiv.) to a suspension of commercial anhydrous CrCl_2 in tetrahydrofuran (THF) in the presence of TMEDA⁵ (tetramethylethylenediamine; 1 equiv.) resulted in the formation of a pale brown, homogenous solution. Allyl iodide (0.5 equiv.) was added at $-60\text{ }^\circ\text{C}$, followed by chalcone (0.25 equiv.), and after 15 min the reaction mixture was quenched and chromatographed to give 77% of the 1,2-addition product **3** (Table 1, Entry 1). In control reactions with the unmodified CrCl_2 -allyl iodide system, no reaction with chalcone was observed in the absence of TMEDA. In the presence of TMEDA, which increases the thermal stability of the allylchromium(III) species, 30% of alcohol **3** was isolated after 1.5 h at room temperature; below $0\text{ }^\circ\text{C}$ no reaction occurred. Therefore, the use of the $\text{Ph}_2\text{Cr}(\text{TMEDA})$ complex leads to a unique rate enhancement in the Nozaki–Hiyama coupling.

Further examples in Table 1 illustrate the general scope of this approach. Enones, ketones and aldehydes react rapidly at $-60\text{ }^\circ\text{C}$ and give clean addition products in high yields. Additions of prenyl and propynyl bromides result in highly regioselective attack of the more substituted carbon and exclusive propynyl transfer,⁶ respectively (entries 2 and 3). Functionalization of the allyl halide as well as the carbonyl component is tolerated under the reaction conditions (entries 6, 8, 9). The highly reactive organochromium(II) reagent obtained by addition of phenylmagnesium bromide to CrCl_2 allows the use of very sensitive substrates such as spirodienone **17**. Under regular Nozaki–Hiyama reaction conditions, dienone **17** decomposed rapidly and no addition product could be identified. With $\text{Ph}_2\text{Cr}(\text{TMEDA})$ complex, however, the desired 1,2-addition occurred smoothly at $-60\text{ }^\circ\text{C}$, and bisallylic alcohols **18** were isolated in a ratio of 1.5 : 1 and 57% yield. The structure of the major isomer was assigned based on the previously demonstrated preference of 4,4-disubstituted dienones of type **17** to add organometallic nucleophiles *anti* to the C(4)-oxygen substituent.⁷

Interestingly, the use of mesitylmagnesium bromide or methylmagnesium bromide with CrCl_2 provided reagents with a completely different reactivity profile than that of $\text{Ph}_2\text{Cr}(\text{TMEDA})$. Upon addition of allyl halide and chalcone to these reagents, only decomposition products and transfer of methyl and mesityl substituents to the carbonyl group of chalcone could be identified. Since we have not observed any phenyl group transfer in the $\text{Ph}_2\text{Cr}(\text{TMEDA})$ system, the latter observation is especially mechanistically relevant. $\text{Ph}_2\text{Cr}^{\text{II}}$ has been postulated to rearrange to arene complexes, e.g. bis(benzene)chromium(0) and benzene(biphenyl)chromium(0).⁸ Indeed, biphenyl is a major byproduct in our modified Nozaki–Hiyama reaction. Dimesitylchromium(II), however, is isolable and does not rearrange.⁹

Table 1 Ph₂Cr(TMEDA)-mediated low-temperature carbonyl additions of allyl and propynyl halides†

Entry	Halide	Aldehyde or Ketone	Product	Yield (%) ^a
1				77
2		2		83
3		2		92
4	1	PhCHO		86
5	4	8		89
6		8		60 ^b
7	1	PhCOMe		76
8	4			83
9	6			57

^a Yields are not optimized and are based on aldehyde or ketone and chromatographically purified product. All new compounds were characterized by IR, ¹H NMR, ¹³C NMR, and high resolution mass spectrometry. ^b A 94:6 ratio of diastereoisomers was formed. The *anti* configuration for the major isomer was assigned based on the work of Hiyama, Kimura and Nozaki.¹⁰

† A typical procedure: 4,4-dimethyl-1,3-diphenylhexa-1,5-dien-3-ol **5**. To a suspension of 150.3 mg (1.22 mmol) of anhydrous CrCl₂ in 6 ml of THF was added 0.19 ml (1.22 mmol) of TMEDA under an atmosphere of argon. After 1 h, the blue suspension was treated with 2.5 ml (2.5 mmol) of a 1.0 mol l⁻¹ solution of PhMgBr in THF at -25 to -30 °C. After 20 min, the reaction mixture was cooled to -60 °C, and a solution of 70 μl (0.61 mmol) of propargyl bromide in 6 ml of THF was added dropwise over a period of 30 min followed by addition of a solution of 64 mg (0.31 mmol) of chalcone in 6 ml of THF. After 15 min, the mixture was quenched with 10 ml of 5% aqueous HCl and the resulting solution was extracted with Et₂O (3 × 5 ml). The combined organic layers were dried (MgSO₄), filtered (Celite), and concen-

trated *in vacuo*. The residue was chromatographed on SiO₂ (hexanes-EtOAc, 10:1) to yield 71.8 mg (83%) of **5** as a colourless oil: IR (neat) ν/cm^{-1} 3550, 3050, 2973, 1680, 1599, 1495, 1447, 1414, 1163, 974, 916 and 696; ¹H NMR δ 7.58–7.26 (m, 10 H), 7.12 (d, 1 H, *J* = 16 Hz), 6.74 (d, 1 H, *J* = 16 Hz), 6.01 (dd, 1 H, *J* = 11, 19 Hz), 5.19 (d, 1 H, *J* = 11 Hz), 5.14 (d, 1 H, *J* = 19 Hz), 2.22 (s, 1 H), 1.13 (s, 3 H) and 1.08 (s, 3 H); ¹³C NMR δ 144.7, 143.4, 137.2, 133.4, 129.4, 128.6, 127.5, 127.3, 126.8, 126.6, 114.5, 79.4, 45.5, 23.2 and 21.8; MS (EI) *m/z* (rel. intensity) 278 (M⁺, 0.2) 260 (2), 245 (1), 225 (1), 219 (1), 209 (100), 191 (10), 158 (30), 143 (20), 131 (30), 105 (70), 91 (10), 77 (40), 69 (10) and 55 (10); HRMS (EI) calc. for C₂₀H₂₀ [M - H₂O]: 260.1565, found: *m/z* 260.1545.

Advantages of the present method over the standard Nozaki-Hiyama protocol are: (a) the efficient addition to enones, which otherwise result in complex reaction mixtures and low yields; (b) the increased reactivity of the intermediate allyl-chromium species and, consequently, the high reaction rates; (c) the mild reaction conditions that allow the use of extremely sensitive substrates such as **17**. The mechanism of this low-temperature version of the synthetically useful Nozaki-Hiyama reaction and further applications of low-valent organochromium complexes will be the subject of future investigations.

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