



Room temperature chromium(0)-catalyzed higher-order cycloaddition reactions

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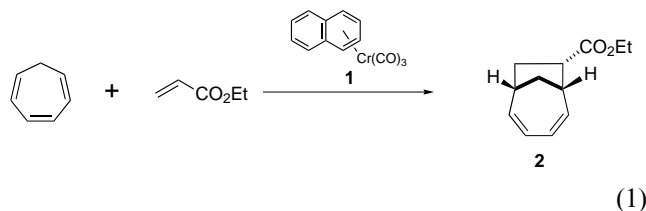
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Abstract—Room temperature thermal and photochemical chromium(0)-catalyzed higher-order cycloaddition processes are described. A novel photoactivated reaction employing a substoichiometric amount of a chromium(0) pre-catalyst has also been demonstrated in a multi-component $[6\pi+2\pi+2\pi]$ cycloaddition. These chromium-mediated cycloaddition reactions can also be conducted in aqueous media. © 2001 Elsevier Science Ltd. All rights reserved.

Chromium-promoted higher-order cycloaddition reactions have been previously demonstrated to be powerful synthetic methods for the rapid, stereocontrolled assembly of polycyclic systems.¹ Recently, conditions have been developed that employ substoichiometric amounts of a chromium(0) pre-catalyst to promote thermal $[6\pi+2\pi]$ and $[6\pi+4\pi]$ cycloaddition reactions.² Furthermore, the use of a polymer-bound chromium catalyst for performing $[6\pi+2\pi]$ cycloaddition reactions has been described.³ In each case, the transformation has required elevated temperatures ($>140^\circ\text{C}$, sealed tube) and long reaction times. We now describe an unprecedented *room temperature* chromium(0)-catalyzed $[6\pi+2\pi]$ cycloaddition reaction that delivers the desired products with excellent efficiency.⁴

At the outset of these investigations, the possibility of performing chromium-catalyzed higher-order cycloaddition reactions in an aqueous medium was considered.⁵ Gratifyingly, it was found that the desired bicyclic compound **2**⁶ could be prepared in 58% yield using complex **1** (15 mol%)⁷ as the catalyst precursor by refluxing cycloheptatriene and ethyl acrylate in water in the presence of magnesium metal (Eq. (1)).⁸



While monitoring this reaction by TLC, it was noted that cycloadduct **2** was present in some quantity after only 15 min, suggesting the reaction may proceed under conditions milder than those originally envisioned. To test this notion, an identical reaction mixture was stirred for 3 days at room temperature, at which time, TLC and ^1H NMR analysis indicated formation of the desired cycloadduct **2** (Eq. (1)[‡]) albeit in low yield (13%), indicating that the process was not catalytic in chromium; however, the reaction had proceeded at room temperature, an unprecedented observation in chromium(0) cycloaddition chemistry. Therefore, the parameters of this ambient temperature cycloaddition reaction were examined in greater detail. In a significant development, it was found that when water was replaced with an equal volume of methanol, ethanol, or THF catalyst turnover at room temperature ensued (Eq. (1)[§]); whereas the addition of diethyl ether, dimethyl formamide (DMF) or trifluoroethanol was ineffective at promoting catalyst turnover. Although we routinely observed formation of tricarbonyl(cycloheptatriene)chromium(0) (**3**)⁹ under these reaction condi-

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[†] Conditions: (a) complex **1** (15 mol%), Mg^0 (3.5 equiv.) ethyl acrylate (10 equiv., 10 mL), and water (12 equiv., 1 mL) at reflux, 24 h, 58%.

[‡] Same conditions but at room temperature (13%).

[§] Complex **1** (10 mol%), Mg^0 (3.5 equiv.) ethyl acrylate (10 equiv., 10 mL), and ethanol (10 equiv., 1 mL) at room temperature, 24 h, 61% yield.

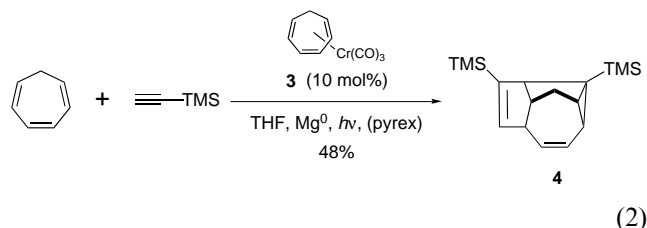
tions, employing this complex as the pre-catalyst at room temperature gave no observable product by ^1H NMR analysis. Thus, it is possible that formation of this complex under these reaction conditions arrests the catalytic cycle.¹⁰ Nevertheless, the ability to run these chromium-promoted cycloaddition reactions at ambient temperature represents a substantial improvement over previous methods, wherein temperatures in excess of 140°C (in sealed tubes) were required to effect reaction.^{2,3}

We speculated that a photochemical chromium-catalyzed process might also prove beneficial for facilitating catalyst turnover.¹¹ To this end, the reaction was conducted in a Pyrex photochemical immersion well apparatus⁹ using chromium complex **3** (10 mol%). The reaction was irradiated at ambient temperature for 2 h, at which time it was placed under a blanket of CO gas and stirred overnight to decomplex the initial adduct complex. Isolation and purification by flash column chromatography provided an 81% yield of the expected cycloadduct (entry 1, Table 1) as a single diastereomer.^{2a} This result represents the first example of a photochemically activated, higher-order cycloaddition process employing *substoichiometric* quantities of chromium(0).¹¹

This process is also applicable to reactions with various acrylate esters (Table 1). For example, when the enantiomerically enriched 8-phenylmenthylacrylate ester is employed in the reaction, an excellent yield of the cycloadduct is obtained with good diastereoselectivity (8:1) in favor of the *endo* product. This represents an improvement over the previous report using a resin-based catalyst under thermal conditions wherein the diastereoselectivity was only 4:1.³

It is noteworthy that these substoichiometric chromium(0) photochemical conditions can be applied to the corresponding multicomponent higher-order cycloaddition process.¹² In the event, cycloheptatriene and trimethylsilylacetylene (2 equiv.) were reacted

together under mediation by a substoichiometric amount of chromium complex **3** (10 mol%) to give a 48% yield of cycloadduct **4** (Eq. (2)).



In this paper, we have demonstrated the use of unusually mild reaction conditions for a number of chromium(0)-catalyzed higher-order cycloaddition reactions. It is anticipated that the superior catalyst turnover and general nature of the catalytic photochemical-promoted process should provide an entry into a viable set reaction conditions for carrying out asymmetric higher-order cycloaddition reactions. Investigations are currently underway in our laboratories to establish the scope and limitations of this reaction with the goal of developing chiral chromium catalysts for use in higher-order cycloaddition reactions.

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Table 1. Room temperature, photochemical, chromium(0)-mediated cycloaddition reactions^a

Entry	R	Yield (%)	de
1	Et	81	—
2	<i>t</i> -Butyl	82	—
3	(–)-Menthyl	78	2:1
4	(–)-8-Phenylmenthyl	89	8:1

^a General conditions: (i) THF (250 mL), cycloheptatriene, acrylate ester (4 equiv.), magnesium metal (3 equiv.), chromium complex **3** (10 mol%), $h\nu$ (Pyrex), ambient temperature, 2 h; (ii) CO gas (1 atm), overnight.

6. The spectroscopic data (NMR, IR, HRMS, TLC) obtained from compounds prepared in this study are identical to those previously published. See Ref. 2a.
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8. This additive presumably serves as a reducing agent that returns oxidized chromium back to the active chromium(0) species, thus promoting effective turnover of the catalyst. See Ref. 2d.
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10. As a control experiment, cycloheptatriene and ethyl acrylate were heated to reflux in water. After 24 h, ^1H NMR indicted that none of the desired $[6\pi+2\pi]$ cycloadduct **2** was present. Also, the chromium-catalyzed, reaction (with ethanol as an additive) proceeded equally well with strict exclusion of light to provide similar yields of cycloadduct **2**.
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