

## Cr-waste free catalytic carbonyl addition reactions with polymer-immobilized $\text{CrF}_2$

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Received 1 March 2006; accepted 10 March 2006  
Available online 31 March 2006

**Abstract**—A monomeric  $[\text{Cr}(\text{pyridine})_4\text{F}_2]^+\text{Br}^-$  is immobilized onto the dipyridyl-TentaGel resin. Allylations of aldehydes with 5–10 mol % of the  $\text{CrF}_2$ -dipyridyl-TentaGel resin **2**/Mn/TMSCl in THF provide the corresponding homoallylic alcohols in excellent yields after TMS-desilylations with a polymer-supported ammonium fluoride **3**. The recovered  $\text{CrF}_2$ -dipyridyl-TentaGel resins can be utilized multiple times without a decrease of reactivity.

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Chromium-mediated carbonyl addition reactions have been recognized as very powerful methods for the syntheses of complex natural products and their analogues.<sup>1</sup> These reactions take advantage of sufficient reduction potential of Cr(II) species that oxidatively insert into allyl, alkynyl, vinyl, aryl, and alkyl halides in the absence or presence of co-catalysts and high-oxophilicity of Cr(III) species. Chromium alkanes, alkynes, and allyl species are extremely mild alkylating reagents for aldehydes and electronically activated ketones. The usefulness of Cr-mediated vinylations has been demonstrated in the late stage (segment couplings) of the syntheses of complex natural products by a large number of groups.<sup>2</sup> On the other hand, allylation reactions are often utilized at the start in constructing 1,3-polyol units of natural products of polyketide origin.<sup>3</sup> Catalytic process of Cr-mediated carbonyl addition reactions can be achieved by using a Cr–O bond dissociating reagent and an external reducing reagent. One of the established catalytic cycles is the use of TMSCl as a Cr-regenerating reagent and Mn(0) as a reducing reagent.<sup>4</sup> However, it has been observed in allylations of aldehydes with 1–2.5 mol % of  $\text{CrCl}_3$ -ligand complexes/Mn (200 mol %)/TMSCl (150 mol %) system at 0.2 M concentrations that the reaction rate is dramatically decreased after 30–40% conversion and usually end up 50–65% conversion after 36 h. Although utility of Cr-mediated carbonyl addition reactions has been demonstrated experimentally, there

are several fundamental reaction mechanisms that have not been addressed in these reactions: (1) the identification and generation mechanism of an electrolyte (electron transporter) in the reaction mixture, (2) aging process of Cr species. Nonetheless, catalytic allylations with 5–10 mol % of Cr complexes/Mn/TMSCl proceed with relatively fast-reaction rate (complete within 3–12 h) and provide the corresponding TMS-protected homoallylic alcohols in good yields (85–95%).

Although highly toxic Cr(VI) species are not generated throughout the reactions, recent studies, however, showed that Cr(III) induced DNA–DNA interstrand crosslinks.<sup>5</sup> The ecological and environmental problems associated with total Cr (Cr(VI) and Cr(III))-contamination issues render useful Cr-mediated coupling reaction less attractive. One may suggest that polymer-bound Cr species are environmentally benign reagents and utilize them as non-toxic and non-hazardous reagents.<sup>6</sup> However, the replacement of Cr–ligand complexes for carbonyl addition reactions developed in solution with a immobilized-Cr(III) species that can be reduced to an active polymer-bound Cr(II) species is a remaining subject that has not been achieved. So far no data are available on (1) whether the electrons flow efficiently from Mn(0) to a polymer-bound Cr(III) complex to reduce to its Cr(II) species in organic solvents, (2) the hydrolytic stability of Cr(III)- and Cr(II)-ligand complexes and their reactivity in Barbier-type reactions, (3) an immobilization method of Cr species onto a polymer-support. Ideally, the polymer-bound Cr species can

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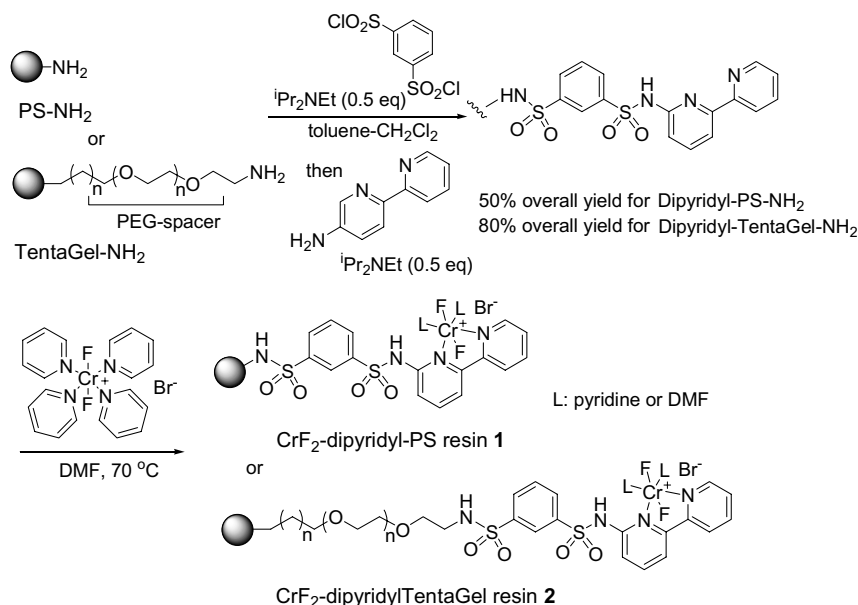
be reused multiple times after activation of the surface of the recovered Cr-resins. Herein, the author describes an efficient immobilization method of a monomeric Cr(III) species onto polystyrene-based polymers and catalytic activities of polymer-bound Cr species in catalytic allylation reactions.

Although a variety of Cr(III) species are commercially available, it was considered that most commonly utilized  $\text{CrCl}_2$ ,  $\text{CrCl}_3$ ,  $\text{CrCl}_3 \cdot 3\text{THF}$ , and  $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$  in Barbier-type reactions would be insufficient to form a hydrolytically stable complex with the ligands that can be utilized in Barbier-type reactions.<sup>7</sup> In addition the polymer nature of Cr(III) halides typically exhibits very poor solubility in organic solvents and hampers the complexation with an insoluble polymer-supported ligand. A stable monomeric  $[\text{Cr}(\text{pyridine})_4\text{F}_2]^+\text{Br}^-$  is readily obtained from  $\text{Cr}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$  and its pyridine ligand can be exchanged with multi-site coordination ligands such as a 2,2'-dipyridyl.<sup>8</sup> It was demonstrated that the  $\text{CrF}_2(\text{III})$  complex could be utilized in catalytic allylation and vinylation (in the presence of  $\text{NiCl}_2$ -dppp complex) reactions.<sup>9</sup> Because of the cationic nature of Cr center of the  $\text{CrF}_2(\text{III})$ -ligand complexes, their 2,2'-dipyridyl complexes are expected to form stronger dative covalent bonds.

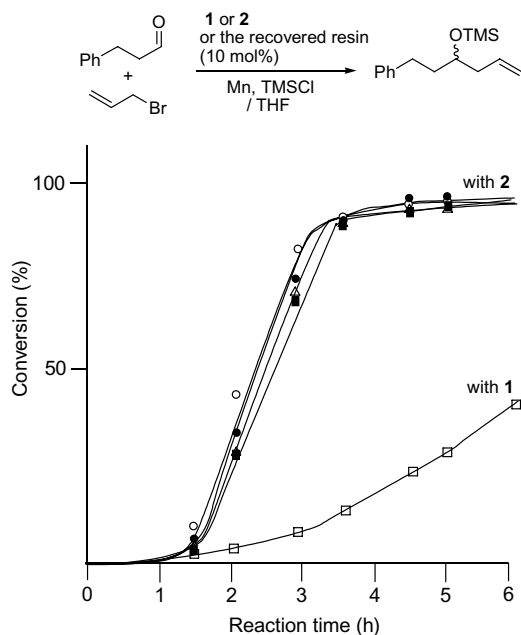
In order to immobilize  $[\text{Cr}(\text{pyridine})_4\text{F}_2]^+\text{Br}^-$  onto a polymer resin, it is necessary to establish an efficient route to graft a functionalized 2,2'-dipyridyl derivative onto a polymer support. As a result of laborious reaction screenings, it was found that a one-pot coupling reaction of (aminomethyl)polystyrene (PS) (1% cross-linked, 1.0 mmol/g), benzene-1,3-disulfonyl dichloride, and 5-amino-2,2'-bipyridine afforded reproducibly the corresponding dipyridyl-PS resin in 50% overall yield, which was determined by elemental analysis of total nitrogen and sulfur (Scheme 1). The unreacted nitrogens on the polymer were capped as their acetylammides using

$\text{Ac}_2\text{O}/\text{pyridine}/\text{CH}_2\text{Cl}_2$ .<sup>10</sup> The complexation of the dipyridyl-PS resin with  $[\text{Cr}(\text{pyridine})_4\text{F}_2]^+\text{Br}^-$  in DMF at 70 °C provided the  $\text{CrF}_2(\text{III})$ -dipyridyl-PS resin **1**. Total Cr deposited on the polymer resin was established to be 0.5 mmol/g by inductively coupled plasma (ICP) atomic emission spectrometry<sup>11</sup> after the Cr metal was cleaved from the polymer support with aq  $\text{HNO}_3$  in MeOH and by elemental analysis of total Br atoms in the  $\text{CrF}_2(\text{III})(\text{ligand})_2\text{Br}$ -dipyridyl-PS resin. In a similar manner, TentaGel-NH<sub>2</sub> (*O*-(2-aminoethyl)polyethylene glycol polystyrene-bound, 0.45 mmol/g) was linked with 5-amino-2,2'-bipyridine by disulfonylation in 80% overall yield and the generated dipyridyl-TentaGel linker was complexed with  $[\text{Cr}(\text{pyridine})_4\text{F}_2]^+\text{Br}^-$  to provide  $\text{CrF}_2$ -dipyridyl-TentaGel resin **2** (incorporated total Cr; 0.3 mmol/g) (Scheme 1).<sup>12</sup> Allylation of hydrocinnamaldehyde with 10 mol % of the **1**/Mn/TMSCl provided TMS-protected 1-phenylhex-5-en-3-ol in 95% yield after 12 h. Significant enhancement of the reaction rate with  $\text{CrF}_2$ -dipyridyl-TentaGel resin **2** was observed. The same reaction with 10 mol % of **2** provided the desired products (a mixture of TMS protected- and free alcohols) in 96% within 4 h, whose reaction rate is faster than that observed in the reaction with  $[\text{Cr}(\text{pyridine})_4\text{F}_2]^+\text{Br}^-$  in THF (Fig. 1).<sup>13</sup>

Thus, polyethylene glycol (PEG)-spacer in the polymer-bound Cr resins dramatically increased the reaction rate in the catalytic allylation reactions. As expected the product could very easily be isolated from the Cr-resins and generated salts including  $\text{MnCl}_2$  in the reaction mixtures by the simple filtration through a glass-filter, and the Cr-dipyridyl resins, **1** and **2**, could be recovered quantitatively by washing with water and THF. It is worthwhile noting that the color of recovered Cr-dipyridyl resins turned brownish-yellow from yellow-colored **1** and **2**. This might indicate that Cr ligands and a counter ion in the original  $\text{CrF}_2(\text{ligand})_2\text{Br}$ -dipyridyl resins **1** and **2** were replaced during the reaction, probably by the



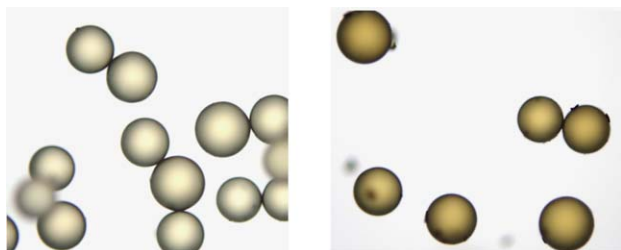
**Scheme 1.** A one-pot procedure for the grafting of 5-amino-2,2'-bipyridine on the polymer resins and their complexations with  $\text{CrF}_2(\text{pyridine})_4\text{Br}$ .



**Figure 1.** Allylation reactions of hydrocinnamaldehyde with CrF<sub>2</sub>-dipyridyl-PS resin **1** and CrF<sub>2</sub>-dipyridyl-TentaGel resin **2** and recycling experiments with the recovered CrF<sub>2</sub>-dipyridyl-TentaGel resins. Squares represent time course experiment with 10 mol % of **1**; open circles represent reaction with 10 mol % of **2**; closed circles represent first recycling experiment with the recovered CrF<sub>2</sub>-dipyridyl-TentaGel resin; triangles represent second recycling experiment; closed squares represent third recycling experiment.

other ligands such as Cl, which is particularly abundant in the reaction mixtures. Total Cr analyses in the reaction mixtures and washing solvents utilized for the regeneration of polymer-bound Cr resins were determined to be less than 0.01 ppm (undetectable amount by ICP atomic emission spectrometry). Microscopic analyses of surface of the recovered Cr-polymer resins revealed that the CrF<sub>2</sub>-dipyridyl-PS resins were sectioned and some of them were fragmented through stirring with Mn powders. On the other hand, the spheres of CrF<sub>2</sub>-dipyridyl-TentaGel resins **2** were unchanged as shown in Figure 2. Because of (1) mechanical stability and (2) enhancement of the reaction rate, the CrF<sub>2</sub>-dipyridyl-TentaGel resin **2** was utilized for further studies.

In order to examine catalytic activity of the recovered CrF<sub>2</sub>-dipyridyl-TentaGel resin, recycling experiments

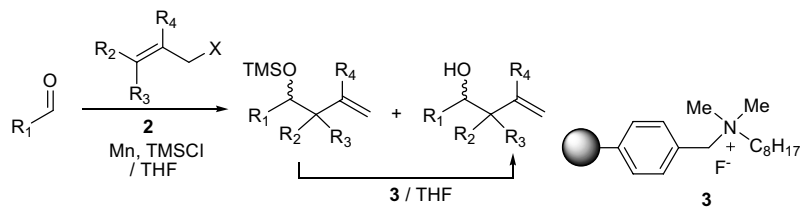


**Figure 2.** Microscopic analyses of spheres of **2** and the recovered CrF<sub>2</sub>-dipyridyl-TentaGel resin after third recycling experiments.

were performed. As shown in Figure 1, the recovered resins could be reused for three times without loss of reactivity. Total Cr analyses by ICP atomic emission spectrometry showed that detectable level of leaching of Cr species into the solution has not been identified in these recycling experiments. Thus, a recyclable and an activatable CrF<sub>2</sub>(III)-dipyridyl resin for a Barbier-type reaction was developed for the first time.

To explore the scope and limitations of the CrF<sub>2</sub>-dipyridyl-TentaGel resin mediated catalytic allylation reactions, a variety of allylic halides were tested against representative aldehydes. Under the conditions of 5 mol % of **2**/Mn (200 mol %)/TMSCl (150 mol %) in THF (0.2 M) allylation reactions of a variety of aldehydes with allyl bromide (200 mol %) were first investigated.<sup>14</sup> The yields were determined by <sup>1</sup>H NMR analysis of total free alcohols obtained by the treatment of a mixture of products with the polymer-supported ammonium fluoride **3**.<sup>15</sup> As summarized in Table 1, alkanals, alkynal, and cinnamaldehyde were converted to the corresponding homoallylic alcohols in 90–97% yields.<sup>16</sup> Cinnamaldehyde showed lower reactivity compared to that of alkanals. 2-Hexenal was not efficiently allylated due to its instability under these conditions. Allylation of benzaldehyde did not afford the desired product in satisfactory yield (20–30% conversion after 24 h), but 98% conversion was achieved in 6 h with 20 mol % of **2**. The CrF<sub>2</sub>-dipyridyl-TentaGel resin **2** could be applied to β-substituted allyl bromides (1-bromobut-2-ene, 1-bromo-3-methylbut-2-ene, 1,3-dibromopropene). On the other hand, **2** exhibited very poor reactivity against α-substituted allyl bromide. Although 3-bromo-2-chloroprop-1-ene was effectively allylated to the aldehydes, allylation with 2,3-dibromopropene and 3-bromo-2-methylprop-1-ene did not afford the desired products at all even after 6 h. These results clearly indicate that the reactivities of α-substituted allyl bromides are electronically and sterically attenuated.<sup>7d</sup> The metallylation of aldehydes was, however, accomplished with 3-iodo-2-methylprop-1-ene.

In summary, the data described in this letter represent a significant advance in the Cr mediated catalytic carbon-carbon bond forming reactions. The CrF<sub>2</sub>(III)-TentaGel resin **2** are air and moisture stable and can be reduced to the corresponding Cr(II)-resin with Mn powder. Careful monitoring of Cr leaching from the polymer support during the reactions showed less than 0.01 ppm (undetectable by ICP atomic emission spectrometry). The surface of Cr resins can be activated by washing with water and the spheres of the recovered CrF<sub>2</sub>-dipyridyl-TentaGel resins were unchanged. Thus, the CrF<sub>2</sub>(III)-TentaGel resin is reusable. [Cr(pyridine)<sub>4</sub>F<sub>2</sub>]<sup>+</sup>Br<sup>-</sup>, Mn, and TMSCl are an economical Cr-source, external reducing and Cr-regenerating reagents, respectively. Most importantly, it was demonstrated that the CrF<sub>2</sub>(III)-dipyridyl resins are environmentally benign reagents; the reactions developed here do not generate problems associated with highly toxic waste disposal. The CrF<sub>2</sub>(III)-resins may not be restricted to only allylation reactions, and may be applicable to the other Barbier-type reactions

**Table 1.** Catalytic allylations of aldehydes with CrF<sub>2</sub>-dipyridyl-TentaGel resin **2**<sup>a</sup>

Aldehyde	Allylic halide	Cr resin <b>2</b> (mol %)	Time (h)	Product	Yield (%) <sup>b</sup>
Ph-CH <sub>2</sub> -CH <sub>2</sub> -CHO		5	12		93
C <sub>6</sub> H <sub>13</sub> -CH <sub>2</sub> -CHO		5	12		94
Ph-CH=CH-CHO		5	24		90
C <sub>6</sub> H <sub>13</sub> -C≡C-CHO		5	12		97
TBDPSO(CH <sub>2</sub> ) <sub>3</sub> -CHO		5	12		93
Ph-CHO		10	24		90
Ph-CH <sub>2</sub> -CH <sub>2</sub> -CHO		5	12		95
TBDPSO(CH <sub>2</sub> ) <sub>3</sub> -CHO		5	12		96
Ph-CH <sub>2</sub> -CH <sub>2</sub> -CHO		5	12		91
TBDPSO(CH <sub>2</sub> ) <sub>3</sub> -CHO		5	12		95
TBDPSO(CH <sub>2</sub> ) <sub>3</sub> -CHO		5	12		92

<sup>a</sup> All reactions were carried out at room temperatures.<sup>b</sup> Yield was determined by <sup>1</sup>H NMR.

such as alkynylations, vinylations, and alkylations in the absence or presence of promoters such as Ni or Co species.<sup>17</sup>

### Acknowledgements

The author thanks Colorado State University for generous financial support and Dr. James R. Self (Colorado State University) for the measurement of total chromium, and Professor Yoshito Kishi (Harvard University) for useful discussions.

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10. A general procedure for the grafting of 5-amino-2,2'-bipyridine on PS-NH<sub>2</sub> resin. To a gently stirred suspension of PS-NH<sub>2</sub> (1 mmol/g) in toluene-CH<sub>2</sub>Cl<sub>2</sub> (1/1, 20 mL) was added benzene-1,3-disulfonyl dichloride (1.1 equiv). After 30 min at rt, <sup>t</sup>PrNEt (0.5 equiv) was added into the reaction mixture. The reaction was stirred for 6 h and 5-amino-2,2'-bipyridine (1.1 equiv) was added. After 1 h, <sup>t</sup>PrNEt (0.5 equiv) was added into the reaction mixture and stirred for an additional 6 h. The resins were washed with water, THF-water (3/1), THF, and EtOAc, and dried under high vacuum. The resins were placed in a flask and CH<sub>2</sub>Cl<sub>2</sub> (10 mL), pyridine (1 mL), and Ac<sub>2</sub>O (1 mL) were added. After 6 h, the resins were washed with water, THF-water (3/1), THF, and EtOAc, and dried under high vacuum for 12 h.
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12. CrF<sub>2</sub>-dipyridyl-TentaGel resin **2**. To a gently stirred suspension of TentaGel-NH<sub>2</sub> (0.45 mmol/g, 1 g) in toluene-CH<sub>2</sub>Cl<sub>2</sub> (1/1, 20 mL) was added benzene-1,3-disulfonyl dichloride (1.1 equiv). After 30 min at rt, <sup>t</sup>PrNEt (0.5 equiv) was added into the reaction mixture. The reaction was stirred for 6 h and 5-amino-2,2'-bipyridine (1.1 equiv) was added. After 1 h, <sup>t</sup>PrNEt (0.5 equiv) was added into the reaction mixture and stirred for an additional 6 h. The resins were washed with water, THF-water (3/1), THF, and EtOAc, and dried under high vacuum. The resins were placed in a flask and CH<sub>2</sub>Cl<sub>2</sub> (10 mL), pyridine (1 mL), and Ac<sub>2</sub>O (1 mL) were added. After 6 h, the resins were washed with water, THF-water (3/1), THF, and EtOAc, and dried under high vacuum for 12 h to give the dipyridyl-TentaGel resins (1.16 g). Overall yield was established to be 80% based on the elemental analysis of total nitrogen of CrF<sub>2</sub>-dipyridyl-entaGel (1.51%N). The dipyridyl-TentaGel resins (0.36 mmol/g, 1 g) and CrF<sub>2</sub>(Pyridine)<sub>4</sub>Br (1.2 equiv) were placed in a flask and DMF (4 mL) was added. The reaction mixture was warmed to 70 °C for 2 h; the reaction color (wine red) in the solution faded into light purple. The resins were washed with DMF, water, THF-water (3/1), THF, and EtOAc, and dried under high vacuum for 12 h to give the CrF<sub>2</sub>-dipyridyl-TentaGel resins (1.17 g). Total Cr incorporated onto the dipyridyl-TentaGel resins was established as ~0.3 mmol/g by elemental analysis of Br.
13. Due to poor solubility of [Cr(pyridine)<sub>4</sub>F<sub>2</sub>]<sup>+</sup>Br<sup>-</sup> in THF, the reaction rate with [Cr(pyridine)<sub>4</sub>F<sub>2</sub>]<sup>+</sup>Br<sup>-</sup> is slower than that with **2**.
14. Experimental procedure for allylation of 2-octynal. To a stirred suspension of **2** (0.3 mmol/g, 1.0 g), Mn (12 mmol) in degassed-THF (12 mL) was added allyl bromide (12 mmol), 2-octynal (6 mmol), and TMSCl (9 mmol). The reaction mixture was stirred at rt for 12 h under N<sub>2</sub>. The reaction mixture was filtrated through a glass-filter funnel. The filtrate was evaporated in vacuo to provide a mixture of TMS-protected and free alcohols. The remains were washed with water, THF-water (3/1), THF, and EtOAc; Cr-resins were separated from unreacted Mn and dried under high vacuum for reusing. The obtained products were dissolved in THF (40 mL), and **3** (1.7 mmol/g, 4.2 g) was added. After 3 h, the reaction mixture was filtered and evaporated in vacuo to give undec-1-en-5-yn-4-ol in 97% yield based on <sup>1</sup>H NMR analysis.
15. Among a variety of polymer-supported ammonium fluorides synthesized from the chloromethylated polystyrene, **3** exhibited excellent reactivities in the cleavage of TMS ethers of secondary alcohols. TBDPS group was not cleaved with **3**.
16. Total Cr contaminated in the isolated products was less than 0.01 ppm.
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