

# New Catalytic Cycle for Couplings of Aldehydes with Organochromium Reagents

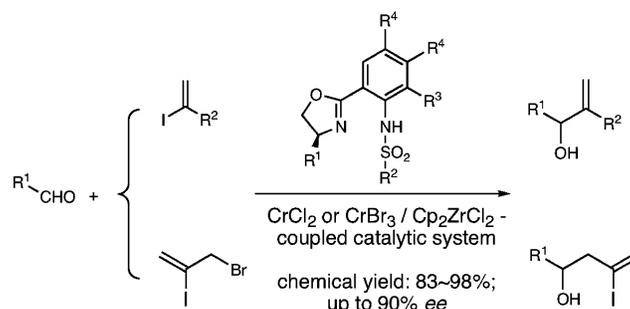
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Received November 12, 2004

## ABSTRACT



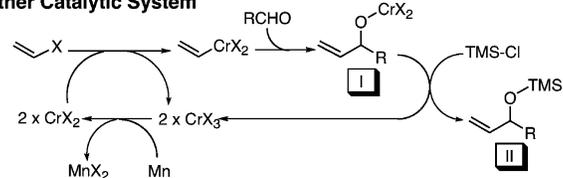
A new catalytic cycle has been developed to effect all three subgroups of Cr-mediated couplings, i.e., (1) Ni/Cr-mediated alkenylation, alkynylation, and arylation, (2) Co/Cr-mediated 2-haloallylation, alkylation, and propargylation, and (3) Cr-mediated allylation. In the presence of chiral sulfonamide ligands, good asymmetric inductions can be achieved for some of the Ni/Cr-mediated alkenylation, Co/Cr-mediated 2-haloallylation and propargylation, and Cr-mediated allylation.

As demonstrated in a number of examples, the Ni/Cr-mediated coupling reaction has shown its unique potential most when applied to a polyfunctional molecule.<sup>1</sup> Thus, this reaction has successfully been used at a late-stage in a multiple-step synthesis where scalability and practicability are not necessarily the priority. For application of this process to a practical synthesis, however, it is highly desirable to develop a catalytic process for the Ni/Cr-mediated reactions. In 1996, Fürstner and Shi reported seminal work on a catalytic process of the Ni/Cr-mediated coupling reaction, in which TMS–Cl and Mn(0) are used as a dissociating agent of chromium-alkoxides (I→II in panel A, Scheme 1) and a reducing agent of chromium, respectively.<sup>2</sup> Electrochemically driven Cr(II)-mediated couplings were also reported.<sup>3</sup>

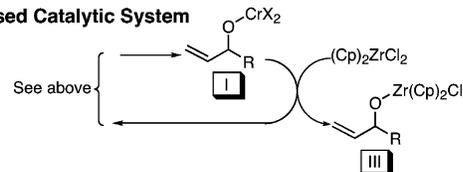
(1) For reviews on Cr-mediated reactions, see: (a) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991–1046. (b) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1–36. (c) Nozaki, H.; Takai, K. *Proc. Japan Acad.* **2000**, *76*, 123–131. (d) Saccomano, N. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, p 173.

## Scheme 1

### A : Fürstner Catalytic System



### B : Zr(Cp)<sub>2</sub>Cl<sub>2</sub>-Based Catalytic System

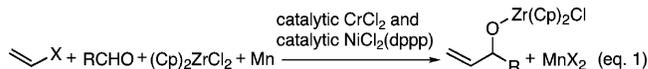


The Fürstner protocol works well also with chiral ligands, permitting carbon–carbon bond formation in a catalytic asymmetric manner.<sup>4,5</sup> Nevertheless, we wished to make

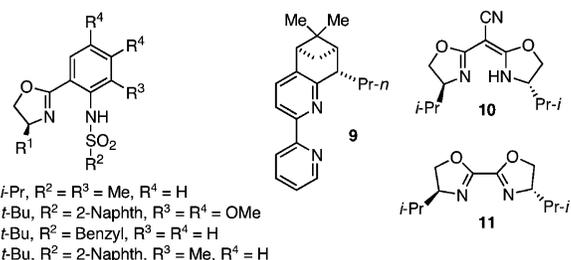
some improvements on the catalytic process for Cr-mediated coupling reactions. In particular, it has been often observed that, with low catalyst-loading, asymmetric catalytic couplings smoothly progress only to a certain degree but not to completion. Not surprisingly, it was found that this was due to the formation of TMS-enol ethers of aldehydes. Thus, we were interested in developing a new catalytic cycle for the Cr-mediated couplings without use of TMS-Cl or an equivalent reagent. Apparently, formation of a strong O-Cr(III) bond is a driving force for addition of an organochromium nucleophile to an aldehyde. Therefore, to establish a catalytic cycle for the Cr-based reagent, a special means is required to cleave the resultant strong O-Cr(III) bond. We were curious about the possibility of transferring the alkoxy group to a second metal. Provided that the second metal has a higher oxophilicity but a lower halophilicity than chromium, this proposed step should be thermodynamically feasible (I→III in panel B, Scheme 1). Extrapolating the oxophilicity and halophilicity estimated through combustion of a solid metal propellant,<sup>6</sup> we speculated that Be, Al, Zr, and Mg might meet this condition. Consistent with this speculation, we found that zirconocene indeed smoothly exchanges its chloride ligand(s) with an alkoxy group(s),<sup>7,8</sup> suggesting that zirconocene might fulfill our needs both thermodynamically and kinetically.

With these considerations, we tested a catalytic Ni/Cr-mediated coupling of dihydrocinnamaldehyde (**1**, 1.0 equiv) with 2-iodo-1-hexene (**2a**, 2.0 equiv)<sup>9</sup> using CrCl<sub>2</sub> (20 mol %), NiCl<sub>2</sub>(dppp) (2 mol %), Cp<sub>2</sub>ZrCl<sub>2</sub> (1.0 equiv), Mn (2.0 equiv), and LiCl (2.0 equiv) at room-temperature overnight and were delighted to find that the coupling reaction did proceed smoothly to furnish the expected allylic alcohol **3a** in 71% yield. It is noteworthy that, even with 0.5 equiv of Cp<sub>2</sub>ZrCl<sub>2</sub> against aldehyde **1**, this catalytic process led to

almost complete conversion, but with a lower efficiency (57% yield). Overall, this chemical transformation is described by eq 1 and, upon aqueous workup, unprotected secondary alcohols are obtained.



It was equally exciting to find that the catalytic Ni/Cr-mediated coupling proceeded in the presence of the chiral sulfonamide **8a** (Figure 1), thereby demonstrating the pos-



**Figure 1.** Chiral ligands for Ni/Cr-mediated couplings.

sibility of extending this catalytic cycle to a catalytic asymmetric process (vide infra). Encouraged with these results, we then optimized the coupling conditions (Scheme 2).

Several comments are in order. First, with small modifications, this catalytic process is effective for all three subgroups of Cr-mediated couplings,<sup>4,10,11</sup> i.e., (1) Ni/Cr-mediated alkenylation, (2) Co/Cr- and Fe/Cr-mediated 2-haloallylation and alkylation, and (3) Cr-mediated allylation. Second, the catalyst loading can be lowered to 5 mol % without significant losses in chemical yields. Importantly, even under these conditions, aldehydes were completely consumed. Third, among the tested zirconium salts,<sup>12</sup> Cp<sub>2</sub>ZrCl<sub>2</sub> was found to be best by far. Fourth, among the tested reducing agents,<sup>13</sup> manganese metal (powder) was found to give the best result. Last, we would suggest the catalytic cycle depicted in Scheme 3.

Sulfonamide ligands have been shown to effect an asymmetric induction for the Cr-mediated couplings under both stoichiometric and catalytic conditions.<sup>4</sup> A similar trend is observed for the new catalytic process. Good asymmetric inductions were observed for the Ni/Cr-mediated alkenylation (86% ee for **1** + **2a** with **8b**<sup>14</sup>), Co/Cr-mediated 2-haloallylation (90% ee for **1** + **4a** with **8c**<sup>10</sup>) and propargylation (82% ee for **1** + **4c** with **8c**<sup>10</sup>), and Cr-mediated allylation (>90% ee for **1** + **6b** with **8c**<sup>10</sup>). However, a ligand optimization is still needed for the Ni/Cr-mediated alkeny-

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(5) (a) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umami-Ronchi, A. *Angew Chem., Int. Ed.* **1999**, *38*, 3357–3359. Bandini, M.; Cozzi, P. G.; Umami-Ronchi, A. *Chem. Commun.* **2002**, 919–927 and references therein. Jacobsen's Cr complex was used for these studies. (b) Lombardo, M.; Licciulli, S.; Morganti, S.; Trombini, C. *Chem. Commun.* **2003**, 1762–1763. Jacobsen's Cr complex was used for these studies. (c) Berkessel, A.; Menche, D.; Sklorz, C. A.; Schroder, M.; Paterson, I. *Angew Chem., Int. Ed.* **2003**, *42*, 1032–1035. Paterson, I.; Bergmann, H.; Menche, D.; Berkessel, A. *Org. Lett.* **2004**, *6*, 1293–1295. (d) Inoue, M.; Suzuki, T.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 1140–1141. Inoue, M.; Nakada, M. *Org. Lett.* **2004**, 2977–2980.

(6) Kuehl, D. K. U.S. Patent 3133841 19640519, 1964.

(7) (a) Gray, D. R.; Brubaker, C. H., Jr. *Inorg. Chem.* **1971**, *10*, 2143–2146. (b) Femece, D. A.; Silver, M. E.; Fay, R. C. *Inorg. Chem.* **1989**, *28*, 2789–2796 and references therein.

(8) On treatment with 2-PrOH (1.0 equiv) and TEA (1.0 equiv) in CD<sub>3</sub>CN, a clean and complete ligand exchange was observed between the Cl of Cp<sub>2</sub>ZrCl<sub>2</sub> and 2-PrOH (NMR).

(9) Corresponding triflate was also a good substrate.

(10) Kurosu, M.; Lin, M.-H.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 12248–12249.

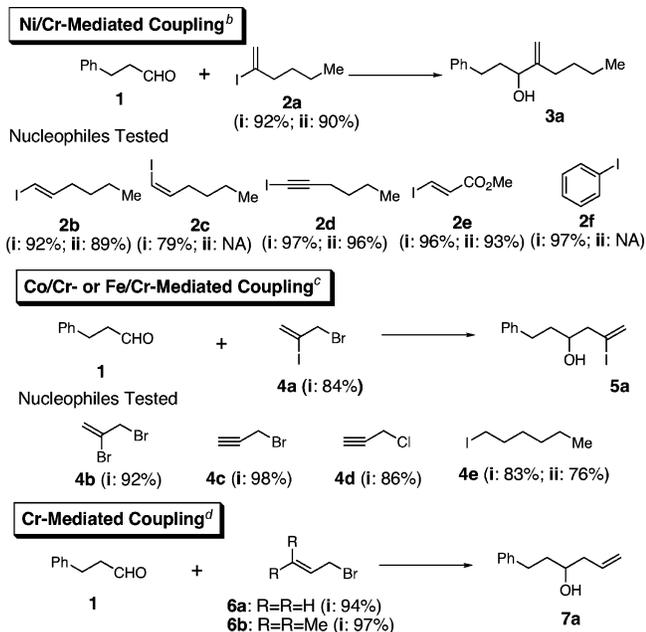
(11) CrCl<sub>3</sub> and CrBr<sub>3</sub> are as effective as CrCl<sub>2</sub> and CrBr<sub>2</sub>. In consideration of the commercial availability and cost, anhydrous CrCl<sub>2</sub> and CrBr<sub>3</sub> have been used for this study.

(12) These included Zr(OPr-*i*)<sub>4</sub>, Zr(acac)<sub>4</sub>, and ZrCl<sub>4</sub>.

(13) Among metals tested, Zn was effective, but the reaction with Zn was not as clean as with Mn.

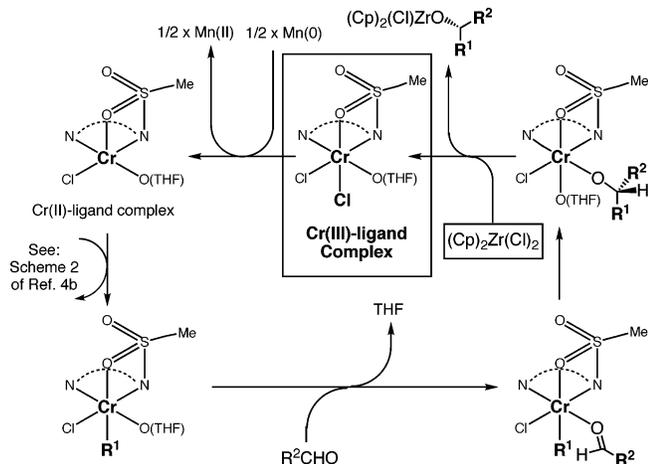
(14) Shi, B.; Cui, S.; Kishi, Y. Unpublished work.

## Scheme 2. Catalytic Cr-Mediated Coupling Reactions<sup>a</sup>



<sup>a</sup> **i** and **ii**: isolated yields with 10 and 5 mol % catalyst, respectively. <sup>b</sup> **1** (1.0 equiv), **2a–f** (2.0 equiv), sulfonamide (11 or 6 mol %), CrCl<sub>2</sub> (10 or 5 mol %), proton sponge or (*i*-Pr)<sub>2</sub>(Et)N (11 or 6 mol %), NiCl<sub>2</sub>(dppp) (2 or 1 mol %), Cp<sub>2</sub>ZrCl<sub>2</sub> (1.0 equiv), Mn (2.0 equiv), LiCl (2.0 equiv), MeCN (*c* = 0.2 M), rt. <sup>c</sup> **1** (1.0 equiv), **4a–e** (2.5 equiv), sulfonamide ligand (11 mol %), CrBr<sub>3</sub> (10 mol %), (*i*-Pr)<sub>2</sub>(Et)N or (Et)<sub>3</sub>N (11 mol %), CoPc (0.2 mol %), Cp<sub>2</sub>ZrCl<sub>2</sub> (1.0 equiv), Mn (3.0 equiv), 2,6-lutidine (11 mol %), THF (*c* = 0.2 M), 0 °C. <sup>d</sup> **1** (1.0 equiv), **6a,b** (2.0 equiv), CrCl<sub>3</sub>·3THF (10 mol %), sulfonamide ligand (11 mol %), (*i*-Pr)<sub>2</sub>(Et)N or (Et)<sub>3</sub>N (11 mol %), Mn (3.0 equiv), 2,6-lutidine (11 mol %), THF (*c* = 0.2 M), 0 °C.

## Scheme 3

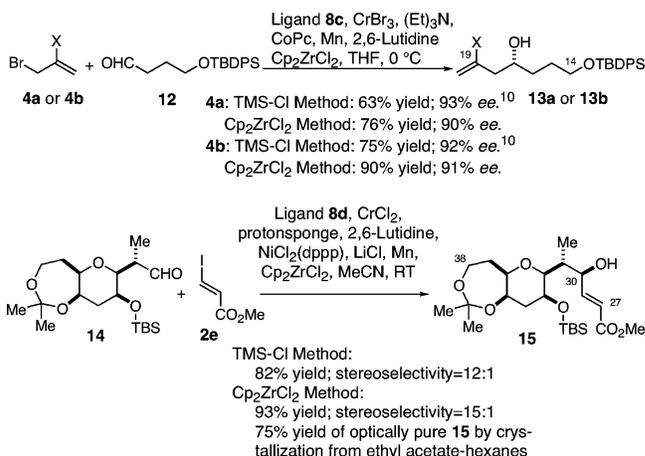


lation with vinyl iodides represented by **2b** and **2c** as well as the Co/Cr-mediated alkylation. Related to this, it is worthwhile noting that the new catalytic cycle was not interrupted by some of the chiral ligands known in this area, including **9**, **10**, and **11**,<sup>4,10,15</sup> (Figure 1) but was, completely or partially, interrupted by those ligands bearing phenolic

or carbazolic groups, cf., the chiral ligands studied by Cozzi and Umami-Ronchi,<sup>5a</sup> Lombardo and Trombini,<sup>5b</sup> Berkessel and Paterson,<sup>5c</sup> and Nakada.<sup>5d</sup> These observations are consistent with the working hypothesis given in the introduction.

The usefulness of the new catalytic system is easily seen from two examples selected from the ongoing halichondrin program in this laboratory (Scheme 4).<sup>4,10</sup> The first example

## Scheme 4



demonstrates that the efficiency of catalytic asymmetric 2-haloallylation is significantly improved with the new catalytic system, cf., **4a,b** + **12** → **13a,b**, respectively. The second example illustrates that the new catalytic asymmetric process is applicable even for polyfunctionalized aldehydes such as **14**. Under the TMS-Cl condition, the coupling of **14** with **2e** did not proceed to completion, due to the TMS-enol ether formation. It is worthwhile noting that, upon aqueous workup, a small amount (10~20%) of **14** was recovered but as a nonrecyclable 1:1 mixture of the C31 diastereomers. Under the new system, the coupling proceeded smoothly to completion to furnish a 15:1 mixture of the C30 diastereomers in 93% yield. A direct crystallization of the crude product from ethyl acetate-hexanes gave the optically pure desired product **15** (mp 137 °C) in 75% yield.

In conclusion, a new catalytic reaction has been developed to achieve Cr-mediated couplings of aldehydes with alkyl, alkenyl, alkynyl, 2-haloallyl and allyl, propargyl, and aryl halides. Good asymmetric inductions can be achieved at least for some of the Ni/Cr-mediated alkenylation, Co/Cr-mediated 2-haloallylation and propargylation, and Cr-mediated allylation.

**Acknowledgment.** We are grateful to the National Institutes of Health (CA 22215) and Eisai Research Institute for financial support.

**Supporting Information Available:** Experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL047661B

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