

# Air-Stable Heterobimetallic Catalysts to Effect Ni/Cr-Mediated Couplings with a ca. 1:1 Molar Ratio of Coupling Partners at Low Catalyst Loadings

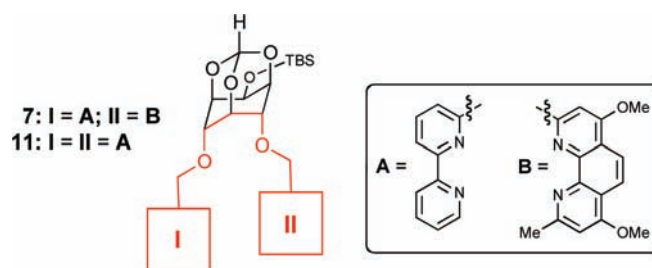
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Received October 25, 2011

## ABSTRACT



Two air-stable Ni,Cr-heterobimetallic catalysts have been prepared from ligands 7 and 11, obtained from *scyllo*-inositol in four and three steps, respectively. Both catalysts smoothly promote Ni/Cr-mediated coupling reactions with a ca. 1:1 molar ratio of coupling partners. The catalyst derived from 11 exhibits a better catalytic profile, thereby allowing Ni/Cr-mediated coupling reactions to be achieved with a wide range of substrates at a low catalyst loading in an operationally simple manner.

The Ni/Cr-mediated addition of vinyl halides or triflates to aldehydes exhibits several unique characteristics. Among them, it is worthwhile to note its exceptional compatibility with a wide range of functional groups. Because of this characteristic, the Ni/Cr-mediated bond-forming process can be applied to the coupling of polyfunctional substrates; indeed, there are numerous examples in which this reaction has been successfully used at a late stage in a multistep synthesis.<sup>1,2</sup>

This bond-forming reaction is known to involve at least three discrete steps (Scheme 1): (1) oxidative addition of Ni(0) to a vinyl iodide (**i**→**ii**), (2) transmetalation of the resultant vinyl-Ni(II)-species to Cr(II) (**ii**→**iii**), and (3)

C–C bond formation through the resultant vinyl-Cr(III) species (**iii**→**iv**). Fürstner and Shi reported a catalytic version in which TMS-Cl and Mn(0) are used as the dissociating agent of chromium alkoxides and the reducing agent of chromium, respectively.<sup>3</sup> Later, we found that Zr(cp)<sub>2</sub>Cl<sub>2</sub> is also an effective dissociating agent.<sup>4</sup> In spite of its cost, Zr(cp)<sub>2</sub>Cl<sub>2</sub> has two attractive properties. First, because of silyl enol ether formation, enolizable aldehydes are not completely consumed in the coupling with TMS-Cl, which is not the case for Zr(cp)<sub>2</sub>Cl<sub>2</sub>. Second, the coupling rate with Zr(cp)<sub>2</sub>Cl<sub>2</sub> is noticeably faster than that with TMS-Cl.

With these developments, Ni/Cr-mediated couplings can be achieved in a catalytic manner. We reported the air-stable Cr(III)- and Ni(II)-catalysts prepared from 3,3'-dimethyl-2,2'-dipyridyl or 4,4'-di-*tert*-butyl-2,2'-dipyridyl.<sup>5</sup> These catalysts smoothly promote the Ni/Cr-mediated

(1) (a) Jin, H.; Uenishi, J.-I.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (b) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.

(2) For reviews on Cr-mediated carbon-carbon bond-forming reactions, see: (a) Saccomano, N. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, p 173. (b) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991. (c) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1. (d) Takai, K.; Nozaki, H. *Proc. Jpn. Acad. Ser. B* **2000**, *76*, 123. (e) Hargaden, G. C.; Guiry, P. J. *Adv. Synth. Catal.* **2007**, *349*, 2407.

(3) (a) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 2533.

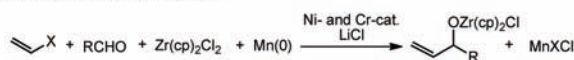
(b) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349.

(4) Namba, K.; Kishi, Y. *Org. Lett.* **2004**, *6*, 5031.

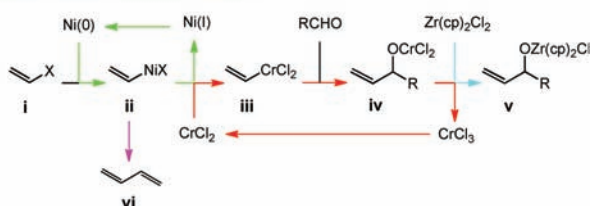
(5) Namba, K.; Wang, J.; Cui, S.; Kishi, Y. *Org. Lett.* **2005**, *7*, 5421.

**Scheme 1.** Catalytic Ni/Cr-Mediated Coupling Reaction with  $\text{Zr}(\text{cp})_2\text{Cl}_2$  and  $\text{Mn}(\text{O})^a$

**A: Overall Transformation**



**B: Ni- and Cr-Catalytic Cycles**



<sup>a</sup> A: overall transformation; B: Ni- and Cr-catalytic cycles.

couplings even at 1 mol % catalyst loading, yet we wish to make one additional improvement. Namely, to consume the electrophile completely, 1.5–2.0 equiv of the nucleophile are typically required, because some portion of the vinyl-Ni(II) species leaks out via homodimerization (ii→vi, Scheme 1). In order to overcome this difficulty, we recently introduced a heterobimetallic catalyst prepared from a tethered sulfonamide/phenanthroline ligand.<sup>6</sup> In this paper, we report air-stable Ni,Cr-heterobimetallic catalysts prepared from tethered dipyriddy/dipyriddy and dipyriddy/phenanthroline ligands, which allows us to effect the Ni/Cr-mediated coupling reactions with a *ca.* 1:1 molar ratio of coupling partners at 1–2 mol % catalyst loadings.

Based on our previous work,<sup>5</sup> we were interested in a tethered ligand containing a dipyriddy and a phenanthroline, which should serve as a ligand for chromium and nickel, respectively. To select a suitable dipyriddy, we screened several dipyriddy-Cr(III) complexes, showing that the Cr-complex prepared from 6-methyl-2,2'-dipyriddy is most effective for the Ni/Cr-mediated couplings.<sup>7</sup> On the other hand, our previous work suggested that 4,7-dimethoxy-2,9-dimethyl-1,10-phenanthroline is a Ni-selective ligand.<sup>6,8</sup> We planned to use the methyl group present in these ligands for tethering, *cf.*, **A** and **B** in Scheme 2.

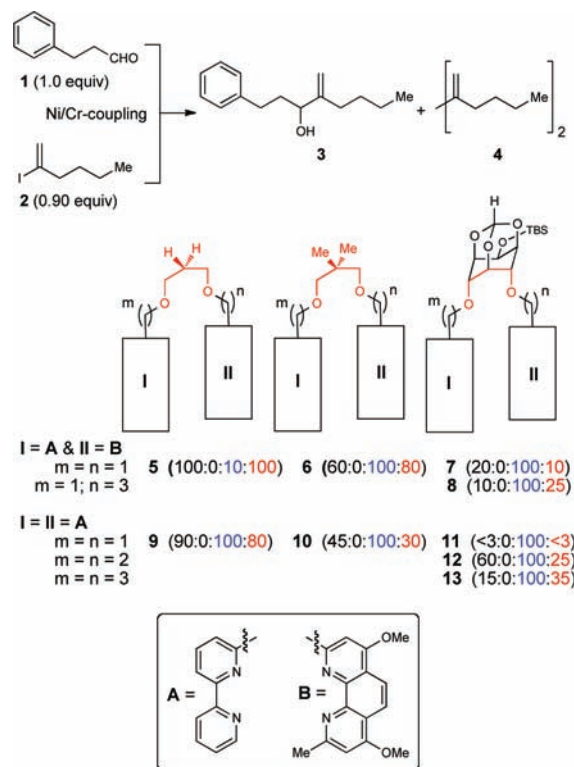
With these ligands selected, we then searched for a suitable tether and prepared two Ni,Cr-heterobimetallic catalysts from **5** and **6**, respectively (Scheme 2). Both catalysts promoted the transformation of **1** + **2**→**3**. However, we noticed that some portion of nucleophile **2** still leaked out via homodimerization of the Ni(II)-species. To evaluate the efficiency of catalysts, we used the following protocol: (1) coupling was conducted with **1** (1.0 equiv) and **2** (0.90 equiv) with 1 mol % catalyst and (2) the ratio of **3** and **4** was estimated from <sup>1</sup>H NMR spectra of crude

(6) Liu, X.; Henderson, J. A.; Sasaki, T.; Kishi, Y. *J. Am. Chem. Soc.* **2009**, *131*, 16678.

(7) Tested 2,2'-dipyriddy and relative reactivity are as follows: 6-methyl-2,2'-dipyriddy > 4,4'-di-*tert*-butyl-2,2'-dipyriddy ≈ 3,3'-dimethyl-2,2'-dipyriddy > 6,6'-dimethyl-2,2'-dipyriddy ≈ 2,2'-dipyriddy.

(8) Namba, K.; Cui, S.; Wang, J.; Kishi, Y. *Org. Lett.* **2005**, *7*, 5417.

**Scheme 2.** Assessment of Ni,Cr-Heterobimetallic Catalysts<sup>a</sup>



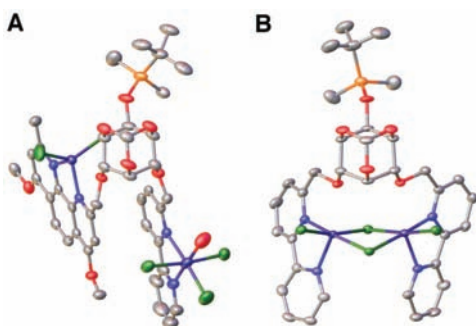
<sup>a</sup> Ni/Cr-coupling conditions: **1** (1.0 equiv), **2** (0.9 equiv), catalyst (1 mol %), Mn (2 equiv),  $\text{Zr}(\text{cp})_2\text{Cl}_2$  (1.2 equiv), LiCl (2 equiv) in DME (C: 0.5 M) at rt. The coupling was followed by TLC, and product distribution (ratio of 1:2:3:4) was estimated from <sup>1</sup>H NMR spectra of crude reaction mixtures. Product distribution at 2 h.

products. With the use of 0.90 equiv of **2**, we reasoned that the ratio of **3** and **4** represents approximately the relative efficiency of ii→iii over ii→iv (Scheme 1). In both couplings with the Ni,Cr-catalysts prepared from **5** and **6**, vinyl iodide **2** was completely consumed within 2 h to furnish a mixture of coupled product **3**, homodimer **4**, and recovered **1**. However, the product distributions were significantly different (Scheme 2): the ratios of **1**, **3**, and **4** were 100:10:100 and 60:100:80 for the catalysts derived from **5** and **6**, respectively, thereby demonstrating that the latter catalyst is superior to the former catalyst. This observation emphasized the conformational rigidity, or preorganization, for efficient Ni→Cr transmetalation and encouraged us to incorporate the two ligands in a conformationally rigid scaffold. To test this notion, we chose the orthoester scaffold derived from *scyllo*-inositol.<sup>9</sup>

As given in the Supporting Information, ligand **7** was prepared from *scyllo*-inositol in four steps. Upon treatment with  $\text{CrCl}_3 \cdot 3\text{THF}$ , followed by  $\text{NiCl}_2 \cdot (\text{MeOCH}_2)_2$ , in THF, tethered ligand **7** gave a green solid which was crystallized by vapor diffusion. An X-ray analysis established the structure of the Ni,Cr-bimetallic complex thus obtained (Figure 1A).

(9) (a) Lee, H. W.; Kishi, Y. *J. Org. Chem.* **1985**, *50*, 4402. (b) Tse, B.; Kishi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 7892.

Using the transformation of **1** + **2** → **3**, we assessed the performance of this catalyst, referred to as catalyst **I**, thereby revealing two outstanding properties (Scheme 2). First, catalyst **I** dramatically suppresses homodimer formation. Second, catalyst **I** promotes the coupling at a faster rate than that with the catalysts derived from **5** and **6**.



**Figure 1.** X-ray structure of (A) **7**•NiCl<sub>2</sub>,CrCl<sub>3</sub> complex and (B) **11**•2×NiCl<sub>2</sub> complex.

Having demonstrated the usefulness of the orthoester scaffold derived from *scyllo*-inositol, we studied the effect of the tether chain length. For this study, we prepared the Ni/Cr-heterobimetallic catalyst from homologous ligand **8**. The catalyst thus obtained was less effective in suppressing homodimerization than catalyst **I**, indicating that the proximity of two catalytic sites is important to achieve efficient Ni → Cr transmetalation.

Being encouraged by the attractive reactivity profile observed for catalyst **I**, we became interested in a tethered ligand containing two 6-methyl-2,2'-dipyridyls. This ligand does not contain differentiated ligation sites for selective complexation with Ni or Cr. Yet, we were interested in this ligand primarily because of the ease of synthesis. Indeed, **11** was straightforwardly prepared from *scyllo*-inositol in three steps.

On treatment with CrCl<sub>3</sub>·3THF (1.0 equiv) for 6 h in THF,<sup>10,11</sup> then with NiCl<sub>2</sub>·(MeOCH<sub>2</sub>)<sub>2</sub> (1.0 equiv), **11** gave green amorphous solid, referred to as catalyst **II**. This catalyst was found to exhibit the excellent catalytic property (Scheme 2). Interestingly, catalyst **II** shares the overall profile of catalyst **I**, yet the performance of catalyst **II** is clearly superior to catalyst **I** in two respects: suppression of homodimerization and a faster coupling rate.

Catalyst **II** (green amorphous solid) can be prepared with excellent reproducibility. It is air-stable and can be

(10) TLC analyses showed only a trace amount of free ligand **11** present.

(11) Four different methods were tested for preparation of Ni,Cr-catalyst from **11**. For details, see Supporting Information.

(12) There was no noticeable loss of activity observed for the catalyst kept on benchtop for several months.

stored on the benchtop at rt without noticeable loss of catalytic activity.<sup>12</sup> Importantly, catalyst **II** allows us to utilize ~95% of nucleophile **2** for the carbonyl addition, with an operationally simple procedure.<sup>13</sup>

Despite extensive efforts, we were not successful in crystallizing catalyst **II**. At present, we have no direct evidence to prove that catalyst **II** is a Ni,Cr-heterobimetallic catalyst. However, the observation that the overall reactivity profile of catalyst **II** is similar to that of catalyst **I** supports that catalyst **II** is a Ni, Cr-heterobimetallic catalyst, although it is undoubtedly contaminated with bis-Ni- and bis-Cr-complexes.

During this study, we obtained a single crystal of the bis-Ni-complex derived from **11**. An X-ray analysis of this complex (Figure 1B) revealed an interesting structural feature, in connection with the Ni ↔ Cr proximity required for the transmetalation.

We then conducted two structural modifications of **11**. First, we examined the effect of the tether chain length and found, once again, that **11** is the best catalyst among **11**–**13** (Scheme 2).

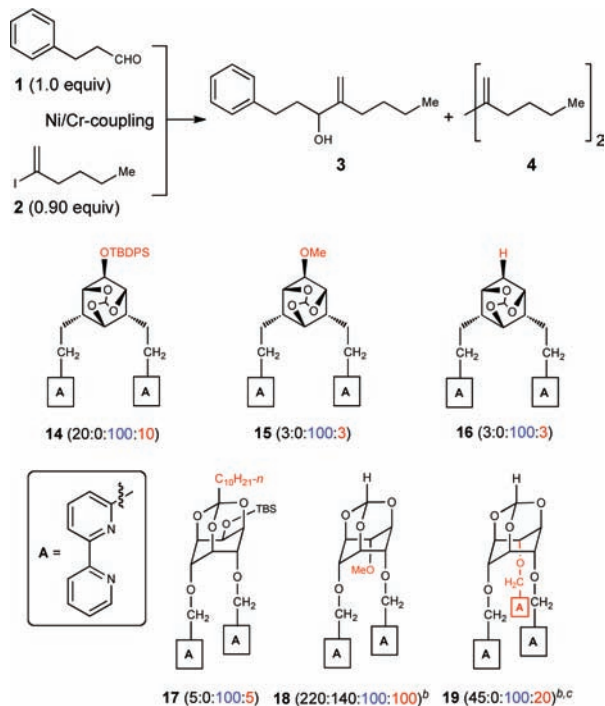
Second, the *scyllo*-inositol orthoester scaffold offers several sites for structural modification. To explore whether such a structural modification might result in a change in the overall reactivity profile of the Ni, Cr-heterobimetallic catalysts, we studied the coupling reaction in the presence of six orthoesters (Scheme 3). Overall, these structural modifications resulted in more or less anticipated effects on the catalyst activity. For example, catalysts derived from **15**, **16**, and **17** exhibited reactivity almost identical to that of **11**, except for better organic solvent solubility of the catalyst derived from **17**. The performance of the catalyst prepared from **18**, which bears an axial methoxy group, was poor, suggesting the importance of the space to accommodate substrates at the catalytic sites. In addition, we prepared ligand **19** bearing three dipyridyls in close proximity, with the hope of exploring the potential that a Ni/Cr-heterometallic catalyst with a Ni/Cr = 1/2 or 2/1 ratio might offer. However, a preliminary study indicated that the coupling rate with this catalyst was slow.

We selected 11 representative nucleophiles to test the scope of Ni,Cr-heterobimetallic catalyst **II** (Scheme 4). Overall, the catalyst performed well for all the substrates tested, including a tetrasubstituted iodoolefin.<sup>14</sup> Noteworthy, di- and trisubstituted *trans*-iodoolefins furnished the expected coupled products *without* geometrical isomerization. On the other hand, di- and trisubstituted *cis*-iodoolefins gave the expected coupled products, but *with*

(13) Typical procedure for couplings: A pear-shape flask was charged with a magnetic stir bar, catalyst **II** (0.01–0.02 equiv, solid), Zr(cp)<sub>2</sub>Cl<sub>2</sub> (1.2 equiv, solid, Aldrich), Mn powder (2.0 equiv, solid, Aldrich), and LiCl (2.0 equiv, solid, Aldrich). With stirring, 1,2-dimethoxyethane (Aldrich, sure-sealed) was added up to the final concentration = 0.5 M at rt under nitrogen. To this mixture were added aldehyde (1.0 equiv) and iodide (1.1 equiv) successively. The reaction mixture was stirred at rt under nitrogen, typically for 2 h. For details, see Supporting Information.

(14) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281.

**Scheme 3.** Performance of Ni,Cr-Heterobimetallic Catalysts Resulting from Structure Modification of the *scyllo*-Inositol Scaffold<sup>a</sup>



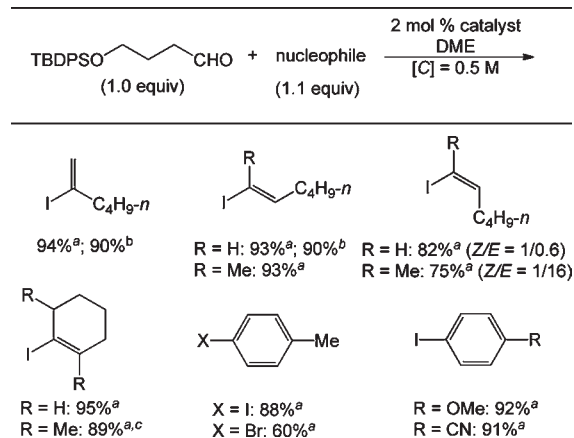
<sup>a</sup>Ni/Cr-coupling conditions: **1** (1.0 equiv), **2** (0.9 equiv), catalyst (1 mol %), Mn (2 equiv), Zr(cp)<sub>2</sub>Cl<sub>2</sub> (1.2 equiv), LiCl (2 equiv) in DME (C: 0.5 M) at rt. The coupling was followed by TLC, and product distribution (ratio of 1:2:3:4) was estimated from <sup>1</sup>H NMR spectra of crude reaction mixtures. <sup>b</sup>Product distribution at 2 h. <sup>c</sup>Catalyst prepared by treatment with CrCl<sub>3</sub>·3THF (2.0 equiv) and NiCl<sub>2</sub>·(MeOCH<sub>2</sub>)<sub>2</sub> (1.0 equiv).

geometrical isomerization, which had been reported in the original stoichiometric Cr-mediated alkenylation.<sup>15</sup>

In conclusion, two air-stable Ni,Cr-heterobimetallic catalysts were prepared from ligands **7** and **11**, obtained from *scyllo*-inositol in four and three steps, respectively. The structure of one of the catalysts was established via

(15) Activation of tetrasubstituted iodoolefins is known to require special conditions; see: Stamos, D. P.; Sheng, X. C.; Chen, S. S.; Kishi, Y. *Tetrahedron Lett.* **1997**, *38*, 6355.

**Scheme 4.** Representative Nucleophiles Tested



<sup>a</sup>Yields are chromatographically isolated product at 0.50 mmol scale. <sup>b</sup>Yields are chromatographically isolated product at 5.0 mmol scale. <sup>c</sup>5 mol % catalyst loading used.

X-ray analysis. Both catalysts smoothly promote Ni/Cr-mediated coupling reactions with a *ca.* 1:1 molar ratio of the coupling partners. Of the two, the catalyst derived from **11** exhibits a significantly better catalytic profile, thereby allowing us to achieve Ni/Cr-mediated coupling reactions with a wide range of substrates at a low catalyst loading. Compared with a Ni,Cr-heterobimetallic catalyst prepared from a tethered chiral sulfonamide/phenanthroline ligand, the Ni/Cr-catalyst reported here has a few appealing profiles, including its air stability and its use with an operationally simple procedure. Our next focus is to translate the reported nonasymmetric process into an asymmetric one.

**Acknowledgment.** Financial support from Eisai Research Institute is gratefully acknowledged. We thank Dr. Shao-Liang Zheng, Department of Chemistry and Chemical Biology, Harvard University, for his help with X-ray data collection and structure determination.

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