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Dramatic Improvement on Catalyst Loadings and Molar Ratios of Coupling Partners for Ni/Cr-Mediated Coupling Reactions: Heterobimetallic Catalysts

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Abstract

Two new ligands **1a,b** have been reported. Upon treatment with one equivalent of $\text{NiCl}_2 \cdot (\text{MeOCH}_2)_2$, **1a,b** give the corresponding Ni-complexes. X-ray analysis of **1a**· NiCl_2 has established that the NiCl_2 is selectively coordinated to the phenanthroline nitrogens. Ni/Cr-heterobimetallic catalysts **1a,b**· $\text{CrCl}_2/\text{NiCl}_2$, prepared from **1a,b**· NiCl_2 , have been shown to behave exceptionally well for the catalytic asymmetric Ni/Cr-mediated couplings, with the highlights including: (1) 1~2 mol % catalysts are sufficient to complete the coupling, (2) only a negligible amount of the dimers, by-products formed through the alkenyl Ni-species, is observed, (3) the coupling completes even with a 1:1 molar ratio of the coupling partners, and (4) the asymmetric induction is practically identical with that obtained in the coupling with the Cr-catalyst prepared from (S)-sulfonamide **2a,b**. Using 4 additional aldehydes, a scope of the new Ni/Cr-heterobimetallic catalysts is briefly studied. Applicability of new catalysts to polyfunctional substrates has been demonstrated, with use of two C-C bond-formations chosen from the halichondrin/E7389 synthesis as examples.

CrCl_2 -mediated Grignard-type addition of an alkenyl halide to an aldehyde was first reported by Takai, Hiyama, Nozaki and coworkers in 1978, cf., eq. 1 in Scheme 1.¹ Since then, it was shown that the addition is initiated by a catalytic amount of NiCl_2 .² It is now known that this coupling involves: (1) oxidative addition of $\text{Ni}(0)$, formed from NiCl_2 via reduction with CrCl_2 *in situ*, to an alkenyl halide to form the alkenyl $\text{Ni}(\text{II})$ -halide, (2) transmetalation of the resultant $\text{Ni}(\text{II})$ -species to the $\text{Cr}(\text{II})\text{Cl}_2$ to form the alkenyl $\text{Cr}(\text{III})$ -halide, and (3) carbonyl addition of the resultant $\text{Cr}(\text{III})$ -species to an aldehyde to form the product $\text{Cr}(\text{III})$ -alkoxide (Scheme 1).³ One of the by-products commonly found under both stoichiometric and catalytic conditions is **iv**, the dimer of **i** formed through the alkenyl Ni -halide.^{4,5} In order to suppress formation of this by-product, it is critically important to keep a low ratio of Ni- over Cr-salts. For example, the catalytic asymmetric couplings recently reported typically uses 10~20 mol

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

% of the Cr-catalyst and 1~5 mol % of Ni-catalyst.⁶ Under this condition, **iv** is observed only in a negligible amount. However, to ensure complete consumption of an aldehyde, the coupling reaction is performed with a slight excess (typically 1.5 equiv) of an alkenyl halide. It is noteworthy that the coupling rate observed is roughly proportional to the amount of Ni(II)-catalyst and, in this respect, the catalyst loading in the Ni/Cr-mediated coupling is already low, *i.e.*, 1~5 mol %. In this communication, we report a solution to improve not only the catalyst loading, but also the molar ratio of coupling partners.

Both problems mentioned above are connected with the efficiency in the alkenyl-group transfer from nickel to chromium, *cf.*, alkenyl Ni(II)-halide $\leq$ alkenyl Cr(III)-halide *vs.* $\leq$ **iv**. To enhance the transmetalation, we have been curious about the possibility of placing Ni- and Cr-metals in close proximity. Specifically, we have been interested in a ligand bearing two ligation sites, each of which is complexed specifically to Cr- and Ni-metals, respectively.⁷ Two observations have encouraged us to study ligands represented by **1a,b** in which a sulfonamide is tethered with 2,9-dimethylphenanthroline (DMP). First, upon addition of NiCl₂·(MeOCH₂)₂ (1.05 equiv) to a 1:1 mixture of sulfonamide **2a** (1.0 equiv) and DMP (1.0 equiv) in CD₃CN at rt, DMP is selectively precipitated out as yellow crystalline solid (>95%), leaving the almost colorless solution containing only **2a** (¹H NMR). Second, NiCl₂·DMP **3** is the best Ni-catalyst to achieve the catalytic asymmetric Ni/Cr-mediated couplings.⁸ Under the coupling condition, **3** is stable and exhibits no ability to facilitate carbonyl addition; in other words, the C-C bond formation takes place through the Cr-sulfonamide catalyst.⁹

Using the method outlined in Supporting Information, we synthesized ligands **1a,b** and studied their behaviors in Ni-complexation. Upon treatment of **1a** (150 mg) with 0.95 equiv of NiCl₂·(MeOCH₂)₂ in MeCN (2 mL) at rt, light violet crystalline powder (168 mg, 94% yield based on **1a**; 99% yield based on NiCl₂·(MeOCH₂)₂) precipitated out. In a ¹H NMR study (CDCl₃), this substance caused severe signal-broadenings for the protons on the phenanthroline moiety, but little signal-broadenings for the protons on the sulfonamide moiety. This NMR experiment suggested that the paramagnetic nickel is coordinated to the phenanthroline nitrogens and also that **1a**·NiCl₂ likely exists in an extended conformation. The structure of **1a**·NiCl₂ was ultimately established by X-ray analysis (Figure 1). Similarly, upon treatment with 0.95 equiv of NiCl₂·(MeOCH₂)₂ in MeCN at rt, **1b** also gave light violet crystalline powder in ~95% yield.

Taking into account the relative rate of ligand exchange on Cr(II)- *vs.* Cr(III)-species,¹⁰ we routinely use the following protocol for preparation of a Cr-sulfonamide complex. A sulfonamide anion, generated from a given sulfonamide (proton sponge), is treated with

CrCl₂ in MeCN at rt for 1 h. Upon addition of NiCl₂·DMP **3**, an alkenyl halide, an aldehyde, and additives (Mn, ZrCl₂(cp)₂), and LiCl), the resultant Cr(II)-complex enters into the Cr(II) ⇌ Cr(III) catalytic cycle and catalyzes the coupling. Notably, the color of sulfonamide Cr(II)-complex is deep-green, but turns into deep-brown, once the catalytic reaction begins. Based on the X-ray structure of three Cr-complexes, we proposed the octahedral structures for those Cr-complexes (Scheme 2).¹¹

We applied this protocol for preparation of the Cr-catalysts in the tethered series and observed that **1a,b**·NiCl₂ exhibit behavior identical to that of **2a,b**. Primarily based on three reasons, we assume that the MeCN-solution thus prepared contains the heterobimetallic catalysts, with Cr and Ni coordinated to the sulfonamide and phenanthroline moieties, respectively, cf., **1a**·CrCl₂/NiCl₂ in Scheme 2. First, the color of MeCN-solution is deep-green as found for the MeCN-solution of **2a,b**·CrCl₂. Second, our previous work suggests no metal-exchange between **2a,b**·CrCl₂ and NiCl₂·DMP.⁸ Third, the degree of asymmetric induction by **1a,b**·CrCl₂/NiCl₂ is virtually identical with that by the corresponding **2a,b**·CrCl₂ (*vide infra*). Structurally, we speculate that the Ni-phenanthroline and Cr-sulfonamide adopt tetrahedral and octahedral coordinations, respectively, and that C-C bond-formation takes place at these catalyst-surfaces.

To reveal their catalytic capacity of promoting the Ni/Cr-mediated couplings, we first tested **1a,b**·CrCl₂/NiCl₂ for the standard model system, i.e., **5** + **6** **7** (Table 1). To our delight, both **1a,b**·CrCl₂/NiCl₂ were found to behave exactly as we hoped, with the following highlights. First, even with 1 mol % catalyst loading, the coupling progressed to completion in MeCN, to furnish the coupled product in >90% yield (entries 1–3). Second, only a small amount of dimer **8** (≤3%) was observed; thus, the coupling completed even with a 1:1 molar ratio of **5** and **6** (entries 1, 2, 4, 6).¹² Third, the asymmetric induction by **1a,b**·CrCl₂/NiCl₂ was practically identical with that by the corresponding previous Cr-catalysts derived from (S)-sulfonamide **2a,b** (entries 1–5 vs. entry 9).¹³ Fourth, the coupling rate was slightly faster at substrate-concentration of 0.8 M than that of 0.4 M, but no significant difference was noticed in the coupling yield (entries 1 vs. 2).

To demonstrate the difference between the new and previous catalysts, we ran the (**5**+**6** **7**)-coupling side by side in MeCN (entries 5 and 8). In the coupling employing **1a**·CrCl₂/NiCl₂ (2 mol %), both **5** (1.0 equiv) and **6** (1.1 equiv) were consumed within 1.5 h, to furnish **7** (>95%, *er* = 10:1) and **8** (~3%).¹² On the other hand, in the coupling employing the Cr-catalyst from **2a** (2 mol %) with NiCl₂·DMP **3** (2 mol %), vinyl iodide **6** (1.1 equiv) was consumed in 4 h, to give a mixture of **7** (~45%, *er* = 8.6:1), **8** (~55%) and recovered **5** (55%). Their difference is further illuminated by the comparison of the result under entry 9 (the optimized condition for the previous catalysts^{6a}) over the result under entry 5.

The Cr-catalyst (2 mol %) derived from the antipode of **1a**·NiCl₂ was tested for additional aldehydes **9**–**12**, thereby demonstrating that the new catalyst matches well with all of them (Table 2).

Encouraged by these results, we chose two C-C bond-forming reactions from the synthesis of halichondrin/E7389, to show the applicability of new catalysts for polyfunctional substrates.

¹⁴ The first example is the C26-C27 bond-formation employing aldehyde **13** (1.0 eq) and vinyl iodide **14** (1.2 eq) (Scheme 3).^{6c} Employing the previous Cr-catalyst (20 mol %) derived from **2a**, the desired allylic alcohol was obtained in ~90% yield with *dr* = 19:1.¹⁵ The new Cr-catalyst, prepared from **1a**·NiCl₂, was found to effect this coupling well, to furnish the desired allylic alcohol in 86% yield with *dr* = 19:1. We should note, however, that 3 mol % catalyst loading was required to complete the coupling with an acceptable rate. As reported previously, reductive cyclization of the allylic alcohol stereoselectively gave **15** in 95% yield.^{6c}

The second example is the C19-C20 bond-formation employing aldehyde **16** (1.0 eq) and vinyl iodide **17** (1.1 eq) (Scheme 3).^{6c} With the previous Cr-catalyst (20 mol %) derived from the *antipode* of **2a**, the desired allylic alcohol **18** was obtained in ~90% yield with *dr* = 20:1.¹⁵ Again, the new Cr-catalyst, prepared from the *antipode* of **1a-NiCl₂**, was found to work well for this bond formation, to furnish **18** in 91% yield with *dr* = 19:1. It is noteworthy that 2 mol % catalyst loading was sufficient to complete the coupling with an acceptable rate. As previously reported, the allylic alcohol was converted to **18** in 88% yield.^{6c}

In conclusion, we have reported two new ligands **1a,b**. Upon treatment with one equivalent of NiCl₂·(MeOCH₂)₂, **1a,b** give the corresponding Ni-complexes. X-Ray analysis of **1a-NiCl₂** has established that the NiCl₂ is selectively coordinated to the phenanthroline nitrogens. Ni/Cr-heterobimetallic catalysts **1a,b-CrCl₂/NiCl₂**, prepared from **1a,b-NiCl₂**, behave exceptionally well for the catalytic asymmetric Ni/Cr-mediated couplings, with the highlights including: (1) 1~2 mol % **1a,b-CrCl₂/NiCl₂** are sufficient to complete the coupling, (2) only a negligible amount of the dimers, by-products formed through the alkenyl Ni-species, is observed, (3) the coupling completes even with a 1:1 molar ratio of the coupling partners, and (4) the asymmetric induction is practically identical with that obtained in the coupling with the Cr-catalyst prepared from (S)-sulfonamide **2a,b**. Applicability of these catalysts to polyfunctional substrates has been demonstrated, with use of two C-C bond formations chosen from the halichondrin/E7389 synthesis as examples. We are currently engaged with further refinements of the tethered ligands as well as preparation of other tethered heterobimetallic catalysts, including tethered Co/Cr-catalysts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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9. Phenanthroline also forms the NiCl_2 -complex selectively. However, this Ni-complex causes a significant reduction in the asymmetric induction in translating the stoichiometric to the catalytic conditions; see ref. 8.
10. Ligand-exchange rates on Cr(II) are known to be up to ca. 15~16 orders of magnitude faster than that on Cr(III); see ref. 3c.
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12. It is not clear whether 8 formed after the complete consumption of 5 or through a leakage of the alkenyl-Ni-complex. However, the latter seems to be more likely, because a trace amount of 8 was observed even in the coupling of 5 (1.1 equiv) and 6 (1.0 equiv).
13. For the coupling of 5 with 6, the Cr-catalysts derived from 2a and 2b gave *er* = 9.8:1 and 5.1:1 asymmetric inductions, respectively.
14. For halichondrins and E7389, see ref. 1–3 in ref. 6b.
15. Using the toolbox strategy for a ligand search, we have recently identified two sulfonamides, which allow us to form the C26–C27 and C19–C20 bonds with *dr* = ca. 50:1 and ca. 26:1, respectively: see ref. 6a,c.

Figure 1.
X-ray structure of 1a·NiCl₂

Scheme 1.

Ni/Cr-mediated coupling reaction and probable reactive intermediates

“Panel **A**: Cr(II)- and Cr(III)-complexes derived from sulfonamides **2a** ($\text{R}=\text{PhCl}_2\text{-3,5}$). Panel **B**: Cr(III)-complex derived from tethered sulfonamide **1a** ($\text{R}=\text{PhCl}_2\text{-3,5}$). Solv represents the fifth and sixth neutral ligand for the Cr(II)- and Cr(III)-complexes, respectively.

Scheme 2.

Proposed structure of the catalyst **1a·CrCl₂/NiCl₂**

C26-C27 Bond Formation **C19-C20 Bond Formation**

Scheme 3.
 C26–C27 and C19–C20 bond formations

Table 1

Catalytic asymmetric Ni/Cr-mediated coupling reactions with **1a,b**-CrCl₂/NiCl₂^a

entry	cat.	CL(%) ^b	5/6 ^c	[Cl][M]	t(h) ^d	prod. dist. (%) ^e			e ^g
						7	8	5	
1	1a	1	1/1	0.4	1/20/28	>97	<3	~0	10.2:1
2	1a	1	1/1	0.8	1/20/24	>96	<4	~0	10.2:1
3	1a	1	1/1.1	0.8	1/14/20	>97	<3	~0	10.1:1
4	1a	2	1/1	0.8	1/4/6	>97	<3	~0	10.0:1
5	1a	2	1/1.1	0.8	0.5/1/1.5	~97	~3	~0	10.3:1
6	1b	1	1/1	0.8	1/14/20	>96	<4	~0	5.1:1
7	1b	1	1/1.1	0.8	1/14/18	>95	<5	~0	5.2:1
8 ^h	2a/3	2/2	1/1.1	0.8	~5 ⁱ	45	55	55	8.6:1
9 ^j	2a/3	10/2	1/1.5	0.4	1/2/4	90	10	~0	9.8:1

^a Coupling conditions employed for entries 1–7: catalyst/Mn (2 eq)/ZrCl₂(cp)₂ (1.2 eq)/LiCl (0.5 or 2.0 eq)/MeCN/rt. Couplings under entries 8 and 9 were conducted under the previously established conditions. ^{6a} Chromatographically homogeneous **7** was isolated in >90% yields for entries 1–7, in 90% for entry 9, and 43% for entry 8. For details, see Supporting Information.

^b CL: catalyst loading (mol %).

^c **5/6**: molar ratio of **5** and **6**.

^d t: 50%/90%/100% conversion-time estimated by TLC.

^e prod. dist.: product distribution estimated from ¹H spectra in crude products.

^g *ee*: enantiomer ratio estimated from ¹H spectra of Mosher esters derived from **7**.

^h because **3** was not completely soluble in MeCN at this concentration, a 5:1 mixture of MeCN and THF was used.

ⁱ prod. dist. was studied when **5** was completely consumed (~5 h).

^j coupling was stopped when **5** was completely consumed (~4 h).

Table 2

Catalytic asymmetric Ni/Cr-mediated couplings of **6** with representative aldehydes with antipode of **1a**-CrCl₂/NiCl₂^a

9 (0.8/4; 80% yield; <i>dr</i> = 7.8:1)	10 (<0.2/<2; 85% yield; <i>er</i> = 18.5:1)	11 (nd/4~5; ca 60 yield; <i>er</i> = 14.5:1)	12 (0.8/3.5; 85% yield; <i>er</i> = 2.6:1)

^a Coupling conditions: see Table 1. Numbers in parentheses indicate: 1. ~50%/~100% conversion-time (hr) with 2 mol % catalyst loading, except for **10** (1 mol %); 2. isolated yield; 3. Stereoselectivity, respectively. Because of the high volatility of **11**, it was technically difficult to estimate ~50% conversion-time and yield.