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

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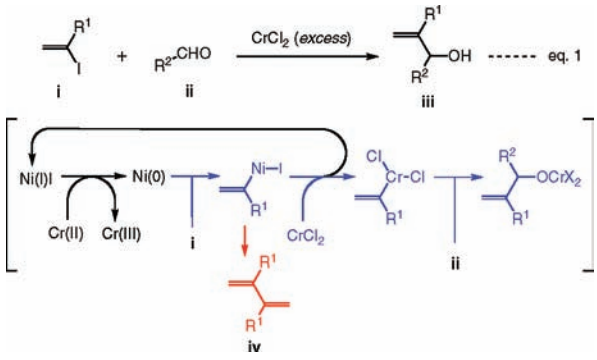
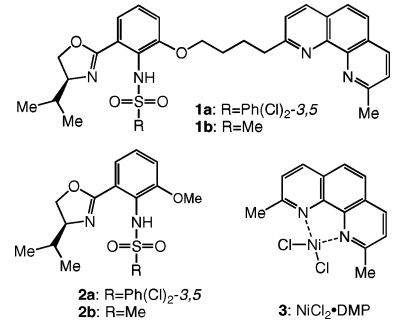
$CrCl_2$-mediated Grignard-type addition of an alkenyl halide to an aldehyde was first reported by Takai et al. in 1978 (eq 1 in Scheme 1).[1] Since then, it has been shown that the addition is initiated by a catalytic amount of $NiCl_2$.[2] It is now known that this coupling involves (1) oxidative addition of Ni(0), formed from $NiCl_2$ via reduction with $CrCl_2$ in situ, to an alkenyl halide to form the alkenyl Ni(II) halide, (2) transmetalation of the resultant Ni(II) species to the $Cr(II)Cl_2$ to form the alkenyl Cr(III) halide, and (3) carbonyl addition of the resultant Cr(III) species to an aldehyde to form the product Cr(III) alkoxide (Scheme 1).[3] One of the byproducts 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 byproduct, it is critically important to keep a low ratio of Ni to Cr salts. For example, the catalytic asymmetric couplings recently reported typically use 10−20 mol % Cr catalyst and 1−5 mol % Ni catalyst.[6] Under these conditions, **iv** is observed in only 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 observed coupling rate 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.

Scheme 1. Ni/Cr-Mediated Coupling Reaction and Probable Reactive Intermediates



Both problems mentioned above are connected with the efficiency of the alkenyl-group transfer from nickel to chromium, i.e., reaction of alkenyl Ni(II) halide to give alkenyl Cr(III) halide rather than **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, one complexed specifically to Cr and the other to Ni.[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 $NiCl_2 \cdot (MeOCH_2)_2$ (1.05 equiv) to a 1:1 mixture of sulfonamide **2a** (1.0 equiv) and DMP (1.0 equiv) in CD_3CN at room temperature (rt), DMP selectively precipitates out as a yellow crystalline solid (>95%), leaving an almost colorless solution containing only **2a** (^{1}H NMR analysis). Second, $NiCl_2 \cdot$DMP (**3**) is the best Ni catalyst for achieving catalytic asymmetric Ni/Cr-mediated couplings.[8] Under the coupling conditions, **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 the Supporting Information, we synthesized ligands **1a,b** and studied their behavior with respect to Ni complexation. Upon treatment of **1a** (150 mg) with 0.95 equiv of $NiCl_2 \cdot (MeOCH_2)_2$ in MeCN (2 mL) at rt, a light-violet crystalline powder [168 mg; 94% yield based on **1a**, 99% yield based on $NiCl_2 \cdot (MeOCH_2)_2$] precipitated out. In an ^{1}H NMR study ($CDCl_3$), this substance caused severe signal broadening for the protons on the phenanthroline moiety but little signal broadening 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·NiCl$_2$** likely exists in an extended conformation. The structure of **1a·NiCl$_2$** was ultimately established by X-ray analysis (Figure 1). Similarly, upon treatment with 0.95 equiv of $NiCl_2 \cdot (MeOCH_2)_2$ in MeCN at rt, **1b** also gave a light-violet crystalline powder in ∼95% yield.

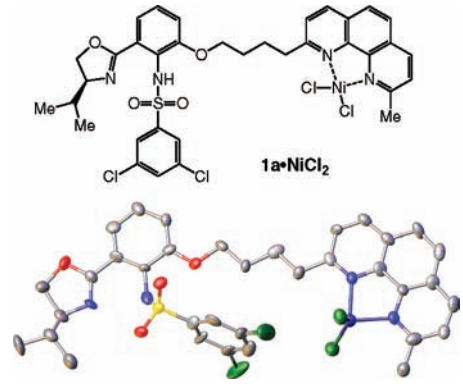


Figure 1. X-ray structure of **1a·NiCl$_2$**.

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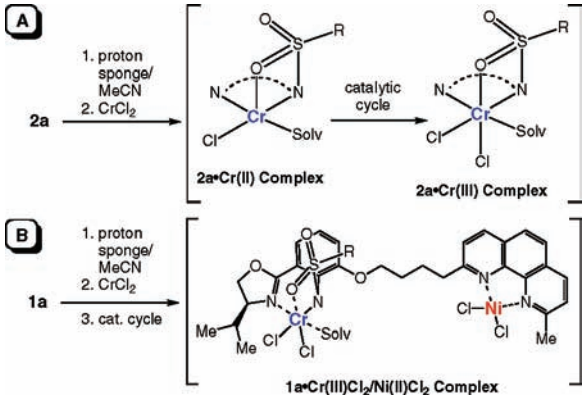
Taking into account the relative rates of ligand exchange in Cr(II) versus Cr(III) species,[10] we routinely use the following protocol for preparation of a Cr sulfonamide complex. A sulfonamide anion, generated from a given sulfonamide (proton sponge), is treated with $CrCl_2$ in MeCN at rt for 1 h. Upon addition of **3**, an alkenyl halide, an aldehyde, and additives [Mn, $ZrCl_2(cp)_2$, and LiCl], the resultant Cr(II) complex enters into the Cr(II) $\rightleftarrows$ Cr(III) catalytic cycle and catalyzes the coupling. Notably, the color of the Cr(II) sulfonamide complex is deep-green but changes to deep-brown once the catalytic reaction begins. On the basis of the X-ray structure of three Cr complexes, we proposed octahedral structures for those Cr complexes (Scheme 2).[11]

Scheme 2. Proposed Structure of the Catalyst **1a·CrCl₂/NiCl₂**[a]

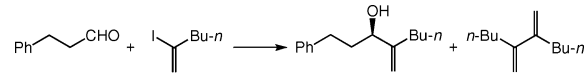


[a] (A) Cr(II) and Cr(III) complexes derived from sulfonamide **2a** (R = $PhCl_2$-3,5). (B) Cr(III) complex derived from tethered sulfonamide **1a** (R = $PhCl_2$-3,5). Solv represents the fifth and sixth neutral ligands for the Cr(II) and Cr(III) complexes, respectively.

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 on the basis of three reasons, we assumed that the MeCN solution thus prepared contained the heterobimetallic catalysts, with Cr and Ni coordinated to the sulfonamide and phenanthroline moieties, respectively (see **1a·CrCl₂/NiCl₂** in Scheme 2). First, the color of the MeCN solution is deep-green, as found for MeCN solutions of **2a,b·CrCl₂**. Second, our previous work suggests that no metal exchange between **2a,b·CrCl₂** and **NiCl₂·DMP** occurs.[8] Third, the degree of asymmetric induction by **1a,b·CrCl₂/NiCl₂** is virtually identical with that by the corresponding catalysts**2a,b·CrCl₂** (see below). Structurally, we speculate that the Ni phenanthroline and Cr sulfonamide adopt tetrahedral and octahedral coordination, respectively, and that C−C bond formation takes place at these catalyst surfaces.

To reveal their catalytic capacity in promoting 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, **1a,b·CrCl₂/NiCl₂** were both found to behave exactly as we had hoped, with the following highlights. First, even with 1 mol % catalyst loading, the coupling progressed to completion in MeCN, furnishing the coupled product in >90% yield (entries 1−3). Second, only a small amount of dimer **8** (≤3%) was observed; thus, the coupling reached completion even with a 1:1 molar ratio of **5** and **6** (entries 1, 2, 4, and 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*)-sulfonamides **2a,b** (entries 1−5 vs entry 9).[13] Fourth, the coupling rate was slightly higher at a substrate concentration of 0.8 M than at 0.4 M, but no significant difference was noticed in the coupling yields (entry 1 vs entry 2).

Table 1. Catalytic Asymmetric Ni/Cr-Mediated Coupling Reactions with **1a,b·CrCl₂/NiCl₂**[a]



5 **6** **7** **8**

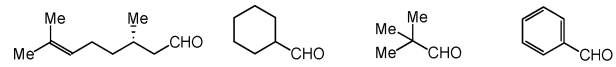
entry	cat.	CL (%)[b]	5/6[c]	[C] (M)	t (h)[d]	Prod. dist. (%)[e] 7	8	5	er[f]
1	**1a**	1	1/1	0.4	1/20/28	>97	<3	~0	10.2:1
2	**1a**	1	1/1	0.8	1/20/24	>96	<4	~0	10.2:1
3	**1a**	1	1/1.1	0.8	1/14/20	>97	<3	~0	10.1:1
4	**1a**	2	1/1	0.8	1/4/6	>97	<3	~0	10.0:1
5	**1a**	2	1/1.1	0.8	0.5/1/1.5	~97	~3	~0	10.3:1
6	**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[g]	**2a/3**	2/2	1/1.1	0.8	~5[h]	45	55	55	8.6:1
9[i]	**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 equiv)/$ZrCl_2(cp)_2$ (1.2 equiv)/LiCl (0.5 or 2.0 equiv)/MeCN/rt. Couplings in entries 8 and 9 were conducted under the previously established conditions.[6a] Chromatographically homogeneous **7** was isolated in >90% yield for entries 1−7, 90% for entry 9, and 43% for entry 8. For details, see the Supporting Information. [b] Catalyst loading (mol %). [c] Molar ratio of **5** and **6**. [d] Times for 50/90/100% conversion, as estimated by TLC. [e] Product distribution estimated from ^{1}H NMR spectra of crude products. [f] Enantiomeric ratio estimated from ^{1}H NMR spectra of Mosher esters derived from **7**. [g] Because **3** was not completely soluble in MeCN at this concentration, a 5:1 mixture of MeCN and THF was used. [h] The product distribution was studied when **5** was completely consumed (~5 h). [i] Coupling was stopped when **5** was completely consumed (~4 h).

To demonstrate the difference between the new and previous catalysts, we ran the corresponding **5** + **6** → **7** couplings side-by-side in MeCN (entries 5 and 8). In the coupling reaction employing **1a·CrCl₂/NiCl₂** (2 mol %), both **5** (1.0 equiv) and **6** (1.1 equiv) were consumed within 1.5 h, furnishing **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 **3** (2 mol %), vinyl iodide **6** (1.1 equiv) was consumed in 4 h, giving a mixture of **7** (~45%, er = 8.6:1), **8** (~55%), and recovered **5** (55%). The difference is further illuminated by a comparison of the result in entry 9 (the optimized conditions for the previous catalysts[6a]) with the result in entry 5.

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

Table 2. Catalytic Asymmetric Ni/Cr-Mediated Couplings of **6** with Representative Aldehydes Using the Antipode of **1a·CrCl₂/NiCl₂**[a]

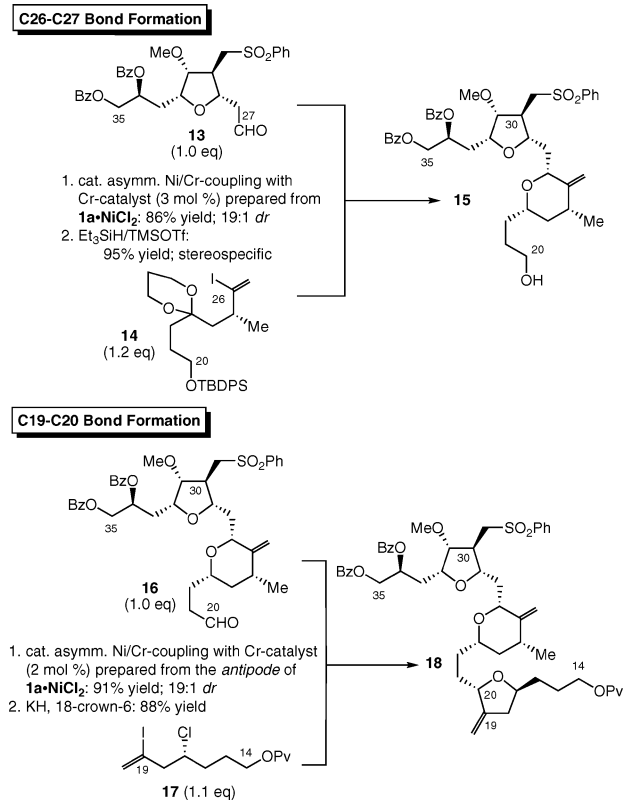


9 (0.8/4; 80% yield; *dr* = 7.8:1) **10** (<0.2/<2; 85% yield; *er* = 18.5:1) **11** (nd/4~5; ca 60 yield; *er* = 14.5:1) **12** (0.8/3.5; 85% yield; *er* = 2.6:1)

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

Encouraged by these results, we chose two C−C bond-forming reactions from the synthesis of halichondrin/E7389 to show the applicability of the new catalysts for polyfunctional substrates.[14] The first example was the C26−C27 bond formation employing aldehyde **13** (1.0 equiv) and vinyl iodide **14** (1.2 equiv) (Scheme 3).[6c] With the previous Cr catalyst (20 mol %) derived from **2a**, the desired allylic alcohol was obtained in ~90% yield with dr =

Scheme 3. C26−C27 and C19−C20 Bond Formations



19:1.[15] The new Cr catalyst prepared from **1a·NiCl$_2$** was found to effect this coupling well, furnishing the desired allylic alcohol in 86% yield with dr = 19:1. We should note, however, that a 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 was the C19−C20 bond formation employing aldehyde **16** (1.0 equiv) and vinyl iodide **17** (1.1 equiv) (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·NiCl$_2$** was found to work well for this bond formation, furnishing **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 1 equiv of $NiCl_2$·$(MeOCH_2)_2$, **1a,b** give the corresponding Ni complexes. X-ray analysis of **1a·NiCl$_2$** established that the $NiCl_2$ is selectively coordinated to the phenanthroline nitrogens. The Ni/Cr heterobimetallic catalysts **1a,b·CrCl$_2$/NiCl$_2$** prepared from **1a,b·NiCl$_2$** behave exceptionally well in catalytic asymmetric Ni/Cr-mediated couplings, with highlights including the following: (1) 1−2 mol % **1a,b·CrCl$_2$/NiCl$_2$** is sufficient to complete the coupling; (2) only negligible amounts of the dimers, which are byproducts formed through the alkenyl Ni species, are observed; (3) the coupling goes to completion 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 catalysts prepared from (*S*)-sulfonamides **2a,b**. The applicability of these catalysts to polyfunctional substrates was demonstrated using two C−C bond formations chosen from the halichondrin/E7389 synthesis as examples. We are currently engaged in further refinements of the tethered ligands as well as preparation of other tethered heterobimetallic catalysts, including tethered Co/Cr catalysts.

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Supporting Information Available: Experimental details, characterization data, and crystallographic data for **1a·NiCl$_2$** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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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 upon translation from stoichiometric to catalytic conditions (see ref 8).
(10) Ligand-exchange rates on Cr(II) are known to be up to 15−16 orders of magnitude faster than those 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, as 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,b** gave er = 9.8:1 and 5.1:1 asymmetric inductions, respectively.
(14) For halichondrins and E7389, see refs 1−3 in ref 6b.
(15) Using the toolbox strategy for a ligand search, we recently identified two sulfonamides that allow us to form the C26−C27 and C19−C20 bonds with dr ≈ 50:1 and 26:1, respectively (see ref 6a, c).

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