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A New Method for Translating the Asymmetric Ni/Cr-Mediated Coupling Reactions from Stoichiometric to Catalytic

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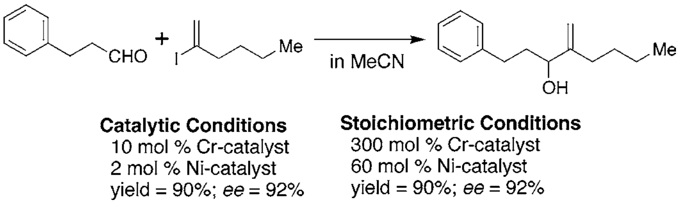
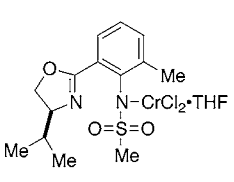
ABSTRACT

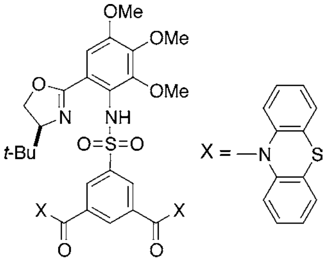


A new method has been developed for effectively translating the degree of asymmetric induction and the chemical yield achieved in the stoichiometric asymmetric Ni/Cr-mediated coupling to a catalytic asymmetric process via a chiral sulfonamide ligand. It has also been shown that the Ni catalyst plays a central role. Among a number of the Ni catalysts, the 2,9-dimethylphenanthroline/NiCl$_2$ complex (7) has been found to be the most effective.

The stable, crystalline Cr(III)/sulfonamide complex **1** (Figure 1) was shown to act as a useful agent for asymmetric Cr-mediated coupling reactions under both stoichiometric and catalytic conditions.[1] In our continued efforts to optimize catalytic asymmetric Ni/Cr-mediated couplings such as **3** + **4** → **5** (Figure 2), we noticed that Ni ligands play a central role. In this paper, we report a new method for effectively translating the asymmetric Ni/Cr-mediated coupling reaction from stoichiometric to catalytic.



1



2

Figure 1. Structure of the Cr(III)/sulfonamide complex **1** and the sulfonamide ligand **2**. The Cr complex derived from **2** is thus far the best asymmetric inducer (92% ee) under the stoichiometric conditions.

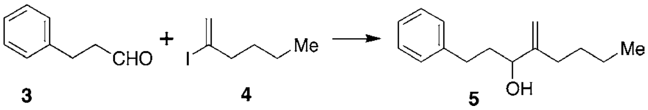


Figure 2. Coupling reaction used for this study.

Catalytic Ni/Cr-mediated coupling reactions involve at least the following four discrete steps: (1) oxidative addition

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(1) (a) Wan, Z.-K.; Choi, H.-W.; Kang, F.-A.; Nakajima, K.; Demeke, D.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4431. (b) Choi, H.-W.; Nakajima, K.; Demeke, D.; Kang, F.-A.; Jun, H.-S.; Wan, Z.-K.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4435. (c) Choi, H.; Demeke, D.; Kang, F.-A.; Kishi, Y.; Nakajima, K.; Nowak, P.; Wan, Z.-K.; Xie. C. *Pure Appl. Chem.* **2003**, *75*, 1.

10.1021/ol052084s CCC: $30.25

of Ni(0) to a vinyl iodide (**i** → **ii**), (2) transmetalation of the resultant vinyl-Ni(II) species to Cr(II) (**ii** → **iii**), (3) C−C bond formation through the resultant vinyl-Cr(III) species (**iii** → **iv**), and (4) dissociation of the resultant product from the Cr(III) species (**iv** → **v**) (Figure 3).[1,2] Thus, the overall efficiency of this catalytic system relies on the efficiency of not only the Cr-catalytic cycle but also Ni-catalytic cycle. At an early phase of the study, we focused primarily on the Cr-catalytic cycle, in particular the optimization of Cr ligands to achieve a high asymmetric induction for the C−C bond-forming step. Among the large number of sulfonamide ligands tested, the Cr complex derived from **2** is thus far the best at inducing asymmetry; under the stoichiometric conditions, this Cr complex gave a 25:1 mixture (92% ee) of *R*- and *S*-allylic alcohols **5** in 90% yield for the coupling of **3** with **4**. However, to achieve this level of overall efficiency under the catalytic conditions, we have gradually realized that the Ni catalyst plays a crucial role.

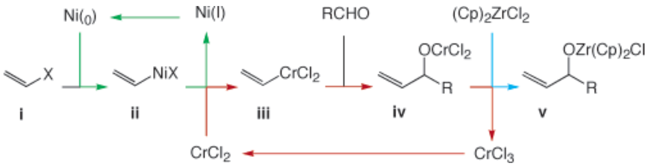

Figure 3. Ni- and Cr-catalytic cycles involved in the Ni/Cr-mediated coupling. The dissociation step is illustrated with Zr(Cp)$_2$Cl$_2$, which can be replaced with TMSCl.

Thus, we studied the catalytic efficiency of Ni-sources. Among a number of the Ni sources tested, their effectiveness can be approximated in the order shown in Figure 4.[3] Employing the Cr complex derived from **2**, we then examined the effect of Ni sources on the asymmetric induction under catalytic conditions. Specifically, with 2 mol % of each Ni catalyst, the coupling reaction was conducted in the presence of 5 and 10 mol % of this Cr complex in MeCN, and the asymmetric induction and chemical yield were determined.

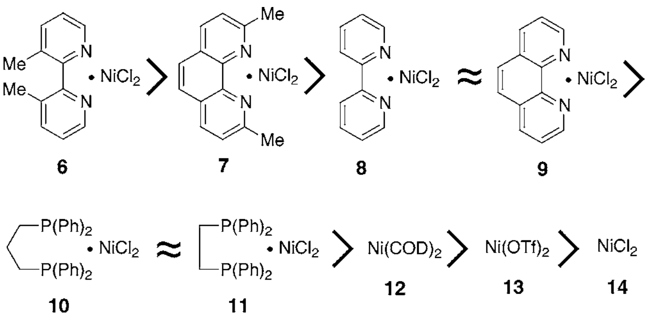

Figure 4. Overall effectiveness of Ni catalysts, estimated from the chemical yields and reaction rates observed for the catalytic coupling of **3** with **4** in the presence of the Cr complex (10 mol %) prepared in situ from **2** and each of the Ni catalysts (2 mol %) in MeCN and DME.

Based on the results summarized in Figure 5, we classified the Ni catalysts into two subgroups; type I Ni catalysts give a high asymmetric induction equal or close to that observed in the stoichiometric reaction, whereas type II Ni catalysts give a significantly lower asymmetric induction.

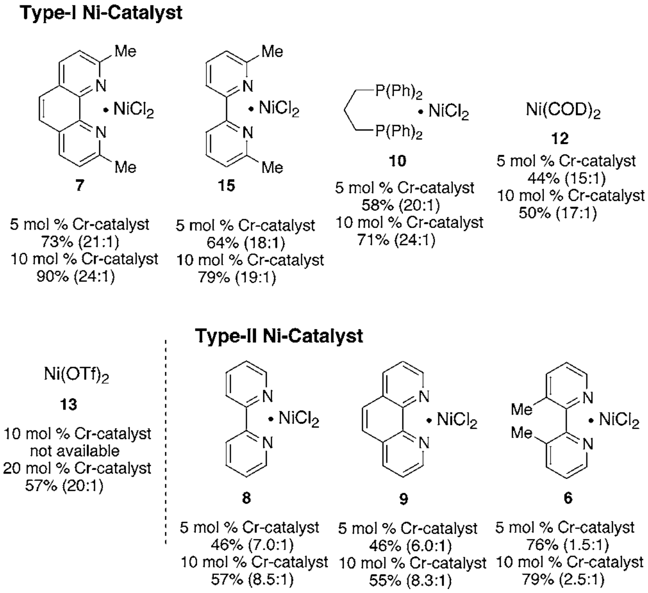

Figure 5. Type I and II Ni catalysts.[5] Catalytic asymmetric Ni/Cr-mediated coupling of **3** with **4** was conducted in the presence of 2 mol % of each Ni catalyst and 5 mol % or 10 mol % of the Cr complex prepared in situ from **2**. Chemical yields and asymmetric inductions (*R*-**5**:*S*-**5**) are given below each Ni catalyst. Three additional aldehydes were tested under the same conditions.[6]

The reduction in the asymmetric induction observed for type II Ni catalysts may be explained by the assumption that the C−C bond formation takes place, at least partially,

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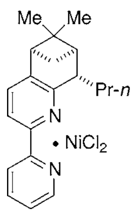
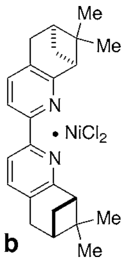
(2) For selected reviews on Cr-mediated reactions, see: (a) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991. (b) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1. (c) Nozaki, H.; Takai, K. *Proc. Jpn. Acad.* **2000**, *76*, 123. (d) Saccomano, N. A. In *Comprehensive Organic Synthesis*; Trost, B.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

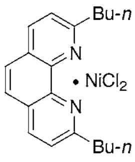
(3) Four additional NiCl$_2$ complexes **a**−**d** were tested. Their effectiveness was approximately in the following order: **a** ≈ **6** > **7** ≈ **b** ≈ **c** > **8** ≈ **9** > **10** ≈ **11** > **d** > **12** > **13** > **14**. For the preparation of the dipyridyls composing **a** and **b**, see: Chen, C.; Tagami, K.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 5386. Malkov, A. V.; Baxendale, I. R.; Bella, M.; Langer, V.; Fawcett, J.; Russell, D. R.; Mansfield, D. J.; Valko, M.; Kocovsky, P. *Organometallics* **2001**, *20*, 673. 2,9-Di-*n*-butylphenanthroline was prepared from 1,10-phenanthroline, adopting the method reported by: Dietrich-Buchecker, C. O.; Marnot, P. A.; Sauvage, J. P. *Tetrahedron Lett.* **1982**, *23*, 5291. **d** was purchased from Tokyo Kasei Kogyo.



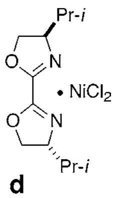
a



b



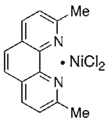
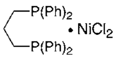
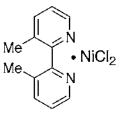
c



d

through the Cr complex formed with an achiral ligand scrambled from the Ni catalyst. To test the possibility, i.e., that asymmetric induction is reduced via a background coupling, we examined the catalytic Ni/Cr-mediated coupling of **3** and **4** in MeCN in the presence of *free* $CrCl_3$ (5 mol %) and Ni catalysts (2 mol %). As anticipated, virtually no couplings were detected in the presence of type I Ni catalysts **7** and **10**, whereas facile couplings were observed in the presence of type II Ni catalyst **6** (Table 1). In DME, however, facile couplings were seen in the presence of both type I and II Ni catalysts. These results support the above assumption and demonstrate that, to avoid the background coupling reaction that reduces the degree of asymmetric induction, it is important to use a type I Ni catalyst in MeCN.

Table 1. Coupling Tests of the Catalytic Ni/Cr-Mediated Coupling of **3** with **4** in the Presence of *Free* $CrCl_3$ (5 mol %) and Ni Catalysts (2 mol %)[a]

Ni-Source	 **7**	 **10**	$Ni(OTf)_2$ **13**	 **6**
MeCN	No	No	No	Yes
DME	Yes	Yes	Yes	Yes

[a] In MeCN, only Ni catalyst **6** was found to promote the coupling, whereas all Ni catalysts were found to promote the coupling in DME.

To further support this conclusion, we studied the ligand exchange between the crystalline Cr(III)/sulfonamide complex **1** and Ni ligands of **6** (type II) and **7** (type I) by NMR spectroscopy. The Cr(III)/sulfonamide complex **1** was found to be stable in CD_3CN containing a Ni ligand (1 equiv) of **6** and LiCl (2 equiv). However, on addition of Mn(0), a rapid ligand-exchange was observed.[4] In contrast, no obvious ligand-exchange was detected between **1** and the Ni ligand of **7** even in the presence of Mn(0).

Among type I Ni catalysts, **7** and **10** gave equally good results in terms of the degree of asymmetric induction; in the presence of 10 mol % of Cr complex, both gave asymmetric induction virtually identical to that achieved under the stoichiometric conditions. However, in terms of chemical yields, the Ni catalyst **7** was found to be far superior. Thus, **7** was selected as the Ni catalyst for the final optimization (Figure 5). In this optimization study, both TMSCl and $Zr(Cp)_2Cl_2$ were tested as a dissociation agent[7,8] (cf. the step of **iv** → **v** in Figure 3). Tests showed that both of the dissociating agents are effective, but the overall efficiency is significantly better with $Zr(Cp)_2Cl_2$.

Last, we should note that this method has been tested for the nucleophiles listed in Figure 6, thereby demonstrating its applicability to other types of nucleophiles known for the Ni/Cr-mediated coupling reactions.[9]

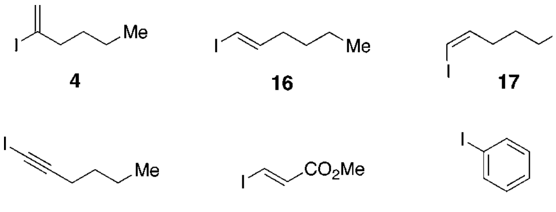


Figure 6. Representative nucleophiles tested under the current method.

In conclusion, the reported method allows us to translate effectively the high asymmetric induction and chemical yield achieved in the stoichiometric asymmetric Ni/Cr-mediated coupling reaction into a catalytic asymmetric process. This method has a number of appealing features, including user-friendliness, easy workup, and apparent scalability. In addition, all the required reagents are available in one or two steps from commercially available chemicals, except the sulfonamide ligand **2** which was prepared in five steps from commercially available methyl 2-nitro-3,4,5-trimethoxybenzoate.

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

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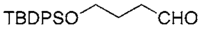
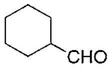
(4) Ligand-exchange rates on Cr(II) species are known to be roughly 15 orders of magnitude faster than those on Cr(III) species. See ref 2.

(5) The $NiCl_2$ complexes were prepared from $NiCl_2$−DME and the corresponding dipyridyls and phenanthrolines in MeCN. Preparation of the catalyst **6**: A mixture of 3,3′-dimethyl-2,2′-dipyridyl (50 mg, 0.27 mmol) and $NiCl_2$−DME (60 mg, 0.27 mmol) in MeCN (5 mL) was shaken until the suspension changed to a deep green clear solution. The mixture was concentrated under reduced pressure. The resultant solid was dried under reduced pressure to give **6** (84 mg, quant) as a deep green powder. For preparations and characterizations of Ni complexes relevant to this study, see also: Brewer, B.; Brooks, N. R.; Abdul-Halim, S.; Sykes, A. G. *J. Chem. Crystallogr.* **2003**, *33*, 651 and references therein. $NiCl_2$(DPPP), $NiCl_2$(DPPE), and $Ni(COD)_2$ were purchased from Strem. $Ni(OTf)_2$ was prepared according to the known procedure; Jansky, M. T.; Yoke, J. T. *J. Inorg. Nucl. Chem.* **1979**, *41*, 1707.

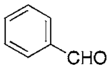
(6) Three additional aldehydes **e**−**g** were tested under 5 mol % of Cr catalyst.



e (*ee* = 91%)



f (*ee* = 93%)



g (*ee* = 72%)

(7) (a) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 2533. (b) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349.

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

(9) A typical experimental procedure is given for the transformation of **3** + **4** → **5**. To a solution of *S*-ligand **2** (60 mg, 0.066 mmol) and Proton Sponge (14.1 mg, 0.066 mmol) in MeCN (1.5 mL) was added $CrCl_2$ (7.5 mg, 0.060 mmol) under nitrogen. The mixture was stirred for 1 h at room temperature under nitrogen. To this mixture were added lithium chloride (51 mg, 1.2 mmol), manganese powder (66 mg, 1.2 mmol), $NiCl_2$ complex **7** (4.2 mg, 0.012 mmol), **3** (81 μL, 0.60 mmol), **4** (252 mg, 1.2 mmol), and $Zr(Cp)_2Cl_2$ (174 mg, 0.60 mmol). The mixture was stirred for 15 h under nitrogen and diluted with ethyl acetate (20 mL). Florisil (ca. 150 mg) was added, and the reaction mixture was stirred for 30 min, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (elution with hexanes/ethyl acetate 19/1 to 9/1) to furnish the coupled product **5** (118 mg, 90%) as colorless oil. The enantiomeric ratio of **5** was determined to be 24:1 from an ^{1}H NMR analysis of its (+)-Mosher ester.