

On Ni Catalysts for Catalytic, Asymmetric Ni/Cr-Mediated Coupling Reactions

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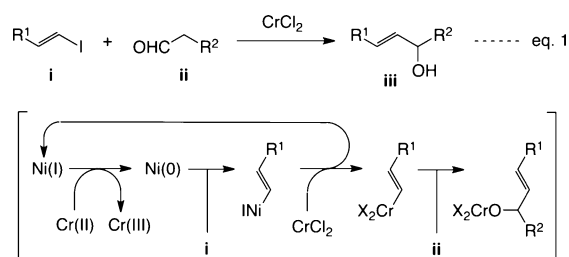
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Supporting Information

ABSTRACT: The importance of the Ni catalyst in achieving catalytic asymmetric Ni/Cr-mediated coupling reactions effectively is demonstrated. Six phenanthroline–NiCl₂ complexes **1a–c** and **2a–c** and five types of alkenyl iodides **A–E** were chosen for the study, thereby demonstrating that these Ni catalysts display a wide range of overall reactivity profiles in terms of the degree of asymmetric induction, geometrical isomerization, and coupling rate. For three types of alkenyl iodides **A–C**, a satisfactory Ni catalyst(s) was found within **1a–c** and **2a–c**. For disubstituted (*Z*)-alkenyl iodide **D**, **2c** was identified as an acceptable Ni catalyst in terms of the absence of *Z* → *E* isomerization and the degree of asymmetric induction but not in terms of the coupling rate. Two phosphine-based Ni catalysts, [(Me)₃P]₂·NiCl₂ and [(cy)₃P]₂·NiCl₂, were found to meet all three criteria for **D**. The bond-forming reaction at the C16–C17 position of palytoxin was used to demonstrate the usefulness of the Ni catalysts thus identified.

Coupling of an alkenyl halide/triflate with an aldehyde mediated by CrCl₂ was reported by Takai, Hiyama, Nozaki and co-workers¹ in 1983 (eq 1 in Scheme 1).

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



Subsequently, it was revealed that the coupling is initiated by a catalytic amount of NiCl₂.² It is now generally accepted that this coupling involves (1) oxidative addition of Ni(0), formed from NiCl₂ via reduction with CrCl₂ in situ, to an alkenyl halide/triflate to form an alkenylnickel(II) species; (2) transmetalation of the resultant Ni(II) species to CrCl₂ to form alkenylchromium(III) and nickel(I) halides; and (3) carbonyl addition of the resultant Cr(III) species to an aldehyde to form the chromium(III) alkoxide product (Scheme 1).³ The chemistry was developed to achieve this coupling

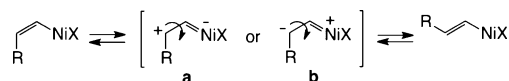
under catalytic conditions.⁴ Several chiral ligands⁵ and a ligand-optimization strategy⁶ were introduced. Thus, the Ni/Cr-mediated coupling reactions give chiral allylic alcohols at a synthetically useful level.⁷

Overall, this bond-forming process is a Grignard-type carbonyl addition reaction. However, it is noteworthy that this reaction displays a remarkable selectivity toward aldehydes over other carbonyl compounds. Activation of halides/triflates in the presence of aldehydes provides not only an experimental convenience but also an opportunity to achieve chemical transformations in an unconventional manner (e.g., cyclization). Undoubtedly, the most valuable feature of this coupling is its exceptional compatibility with a wide range of functional groups. This unique potential is appreciated most when applied to polyfunctional molecules. There are numerous examples in which this bond-forming process has been used at a late stage in a multistep synthesis.⁸

In an earlier study of the catalytic asymmetric version of Ni/Cr-mediated coupling, we focused on the chromium chemistry, as the C–C bond formation takes place through the alkenylchromium(III) species.⁹ However, we gradually realized that the Ni catalyst plays an equally important role.¹⁰ In this communication, we report three areas in which Ni catalysts play important roles in achieving catalytic asymmetric Ni/Cr-mediated couplings effectively: (1) geometrical isomerization of (*Z*)-alkenyl halides, (2) the degree of asymmetric induction, and (3) the coupling rate.

The first issue concerns geometrical isomerization during the Ni/Cr-mediated couplings. In particular, Ni/Cr-mediated couplings with a (*Z*)-alkenyl iodide give the expected coupling products, but they are formed as a mixture of geometrical isomers. The observed partial *Z* → *E* isomerization apparently takes place via alkenylnickel species, which are known to be prone to geometrical isomerization.¹¹ Two mechanisms were proposed for the isomerization,¹² one via **a** and the other via **b** in Scheme 2, thereby suggesting the possibility that the

Scheme 2. Two Possible Intermediates Suggested for Geometrical Isomerization of Alkenylnickel Species



electronic nature of the Ni ligand might affect the degree of *Z* → *E* isomerization.

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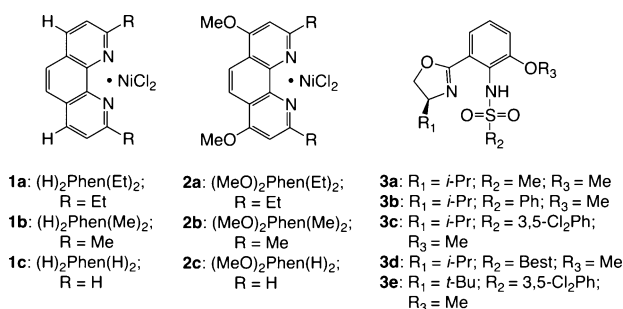
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The second issue is the degree of asymmetric induction. One would assume that the Ni catalyst has no effect on the asymmetric induction, as the C–C bond formation takes place through the Cr complex in the Ni/Cr-mediated couplings. However, the degree of asymmetric induction under catalytic conditions is often lower than that under stoichiometric conditions.¹⁰ For example, 2,9-dimethylphenanthroline–NiCl₂, abbreviated as (H)₂Phen(Me)₂–NiCl₂, is an excellent Ni catalyst for translating the asymmetric induction achieved under stoichiometric conditions to catalytic conditions, as least for exo-type alkenyl iodides (e.g., **A** in Table 1). To the contrary, catalytic asymmetric couplings with some Ni catalysts, represented by 3,3'-dimethyl-2,2'-dipyridyl–NiCl₂, progressed well, but the degree of asymmetric induction was noticeably lower than that observed under stoichiometric conditions. We have suggested that the observed reduction in the asymmetric induction is due to a background reaction, with the C–C bond formation taking place through a Cr complex formed with an *achiral* ligand scrambled from the Ni catalyst.¹³

The third issue is the overall coupling rate. The Ni/Cr-mediated coupling reaction is initiated by oxidative addition of Ni(0) to an alkenyl halide/triflate. Thus, the Ni catalyst has an effect on the overall coupling rate even though it is not directly involved in the C–C bond formation step.

Although (H)₂Phen(Me)₂–NiCl₂ (**1b**) serves well for many cases, we felt that it was important to conduct a thorough study of Ni catalysts for effective use of catalytic asymmetric Ni/Cr-mediated couplings. For this study, we selected six phenanthroline–NiCl₂ complexes **1a–c** and **2a–c**¹⁴ (Scheme 3) and

Scheme 3. Phenanthroline–NiCl₂ Complexes and Chiral Sulfonamide Ligands [Best = 3,5-Di(10*H*-phenothiazine-10-carbonyl)benzene]



studied their behavior in catalytic asymmetric Ni/Cr-mediated coupling reactions in the presence of the Cr catalyst prepared from CrCl₂ and chiral sulfonamide ligand **3a**.

For this study, we used the coupling of dihydrocinnamaldehyde with five types of alkenyl iodides **A–E** and focused on (1) the degree of geometrical isomerization, if relevant; (2) the degree of asymmetric induction; and (3) the time for completion of the coupling (Table 1). This experiment revealed that the six Ni catalysts exhibited a wide range of reactivity profiles. Nonetheless, we recognized three general trends: (1) substitution of 2,9-hydrogens with methyl or ethyl groups resulted in an enhancement of the asymmetric induction and coupling rate; (2) substitution of 2,9-hydrogens with methyl or ethyl groups resulted in an enhancement of *Z* → *E* isomerization; and (3) substitution of 4,7-hydrogens with methoxy groups resulted in a suppression of the *Z* → *E* isomerization.

Table 1. Catalytic Asymmetric Ni/Cr-Mediated Couplings To Assess the Performance of Phenanthroline–NiCl₂ Complexes^a

		1a	1b	1c	2a	2b	2c
A		time <2 h <i>er</i> 9.7:1	time <2 h <i>er</i> 9.7:1	time <5 h <i>er</i> 8.8:1	time <2 h <i>er</i> 9.7:1	time <2 h <i>er</i> 9.7:1	time >>10 h ^c <i>er</i> 7.1:1
B		time <1 h <i>er</i> 3.0:1 <i>E/Z</i> 60/1	time <1.5 h <i>er</i> 3.3:1 <i>E/Z</i> 34/1	time <2 h <i>er</i> 3.0:1 <i>E</i> only	time <3 h <i>er</i> 2.9:1 <i>E</i> only	time <45 m <i>er</i> 3.5:1 <i>E</i> only	time <1 h <i>er</i> 3.3:1 <i>E</i> only
C		time <3 h <i>er</i> 4.6:1 <i>E/Z</i> 43/1	time <4 h <i>er</i> 4.7:1 <i>E/Z</i> 32/1	time <4 h <i>er</i> 3.7:1 <i>E</i> only	time <4 h <i>er</i> 4.4:1 <i>E</i> only	time <2 h <i>er</i> 5.4:1 <i>E</i> only	time <12 h <i>er</i> 3.9:1 <i>E</i> only
D		time <3 h <i>er</i> 3.9:1 <i>Z/E</i> 2.8/1	time <3 h <i>er</i> 3.8:1 <i>Z/E</i> 3.4/1	time <6 h <i>er</i> 3.2:1 <i>Z/E</i> 50/1	time <3 h <i>er</i> 3.9:1 <i>Z/E</i> 4.8/1	time <1 h <i>er</i> 3.9:1 <i>Z</i> only	time <6 h <i>er</i> 3.9:1 <i>Z</i> only
E		time >>16 h ^d <i>er</i> 1.7:1 <i>Z/E</i> 1.1/1	time >>20 h ^d <i>er</i> ND <i>Z/E</i> 1/1	time >>12 h ^d <i>er</i> 1.6:1 <i>Z/E</i> 2.0/1	time >>16 h ^d <i>er</i> 1.8:1 <i>Z/E</i> 1.1/1	time >>16 h ^d <i>er</i> ND <i>Z/E</i> 1/1	time >>15 h ^d <i>er</i> ND <i>Z/E</i> 2.0/1

^aCouplings were done with 10 mol % Cr catalyst prepared from sulfonamide **3a** and 2 mol % Ni catalyst at rt in MeCN (*c* = 0.4 M) in the presence of Mn metal (2 equiv), Zr(cp)₂Cl₂ (1.2 equiv), and LiCl (2 equiv); *E/Z* and *er* were estimated from ¹H NMR spectra of crude products and Mosher esters of coupling products, respectively. ^b1.5 equiv of **A** was used, as homodimerization was more significant for **A** than for the other alkenyl iodides. ^cConversion was ~70%. ^dCouplings were very sluggish with 10 mol % Cr catalyst and 2 mol % Ni catalyst; the conversion was ~20, 55, 60, 70, 65, and 60% at the indicated times.

Through this study, a satisfactory Ni catalyst(s) was identified for four types of alkenyl iodides. First, **1a,b** and **2a,b** are satisfactory Ni catalysts for alkenyl iodide **A**, representing 2-iodoolefins. Second, **2b** is a satisfactory Ni catalyst for alkenyl iodides **B** and **C**, representing di- and trisubstituted (*E*)-1-iodoolefins, respectively; no *E* → *Z* isomerization was detected with **1c** and **2b,c**, whereas *E* → *Z* isomerization was observed with **1a,b** and **2a**. However, **2b** is far superior to **1c** and **2c** in terms of (1) the degree of asymmetric induction and (2) the time for coupling completion. Third, **2c** is the only Ni catalyst to avoid *Z* → *E* isomerization of alkenyl iodide **D**, representing disubstituted (*Z*)-1-iodoolefins. Fourth, no Ni catalyst was found completely to suppress *Z* → *E* isomerization of alkenyl iodide **E**, representing trisubstituted (*Z*)-1-iodoolefins.¹⁵ It is noteworthy that under the original stoichiometric coupling conditions, the olefin geometry is retained for disubstituted (*E*)- and (*Z*)-vinyl iodides and trisubstituted (*E*)-vinyl iodides but is lost for trisubstituted (*Z*)-vinyl iodides.¹

As mentioned, the geometrical isomerization takes place through the alkenylnickel species, thereby suggesting the possibility that the geometrical isomerization should be suppressed by lowering the Ni/Cr ratio. This notion was tested by conducting the coupling with two different of Ni/Cr catalyst ratios; the coupling of **D** with 1 mol % Ni catalyst **2b** and 10 mol % Cr catalyst gave only the *Z* product with *er* = 3.8:1, whereas the coupling with 2 mol % Ni catalyst **2b** and 10 mol % Cr catalyst gave a 11:1 *Z/E* product mixture (*er* = 3.9:1).¹⁵ Overall, this approach did help in maintaining the *Z* configuration but significantly slowed the coupling (i.e., the

times for coupling completion were 10 h and <1 h with 1 and 2 mol % **2b**, respectively).

For disubstituted (*Z*)-alkenyl iodides, (MeO)₂Phen-(H)₂NiCl₂ (**2c**) was found to be a satisfactory Ni catalyst in maintaining the olefin geometry, but we wished to enhance the coupling rate. To achieve this goal, we expanded the search area of Ni catalysts and eventually found that some phosphine-based Ni catalysts exhibit an appealing profile (Table 2). For

Table 2. Catalytic Asymmetric Ni/Cr-Mediated Coupling To Assess Performance of Phosphine–NiCl₂ Complexes^a

$\text{Ph-CH}_2\text{-CH}_2\text{-CHO} + \text{I-CH=CH-C}_4\text{H}_9\text{-n} \rightarrow \text{Ph-CH}_2\text{-CH}_2\text{-CH(OH)-CH=CH-C}_4\text{H}_9\text{-n}$		
(1.0 eq)	(1.1 eq)	
4a: [(Me) ₃ P] ₂ •NiCl ₂	4b: [(cy) ₃ P] ₂ •NiCl ₂	4c: DPPP•NiCl ₂
time <2 h	time <5 h	time <12 h
<i>er</i> 3.8:1	<i>er</i> 3.9:1	<i>er</i> 3.3:1
<i>Z/E</i> Z only	<i>Z/E</i> Z only	<i>Z/E</i> Z only

^aFor experimental details, see the footnotes of Table 1.

disubstituted (*Z*)-vinyl olefins, represented by **D**, both [(Me)₃P]₂•NiCl₂ (**4a**) and [(cy)₃P]₂•NiCl₂ (**4b**) meet all the three criteria, i.e., no *Z* → *E* isomerization, a high degree of asymmetric induction, and a high coupling rate. However, for trisubstituted (*Z*)-vinyl olefins, represented by **E**, these Ni catalysts still gave a mixture of *Z* and *E* products.¹⁵ We should also note that these phosphine-based Ni catalysts are not as effective as the phenanthroline-based NiCl₂ catalysts for the vinyl iodides represented by **A**, **B**, and **C** in terms of the coupling rate.

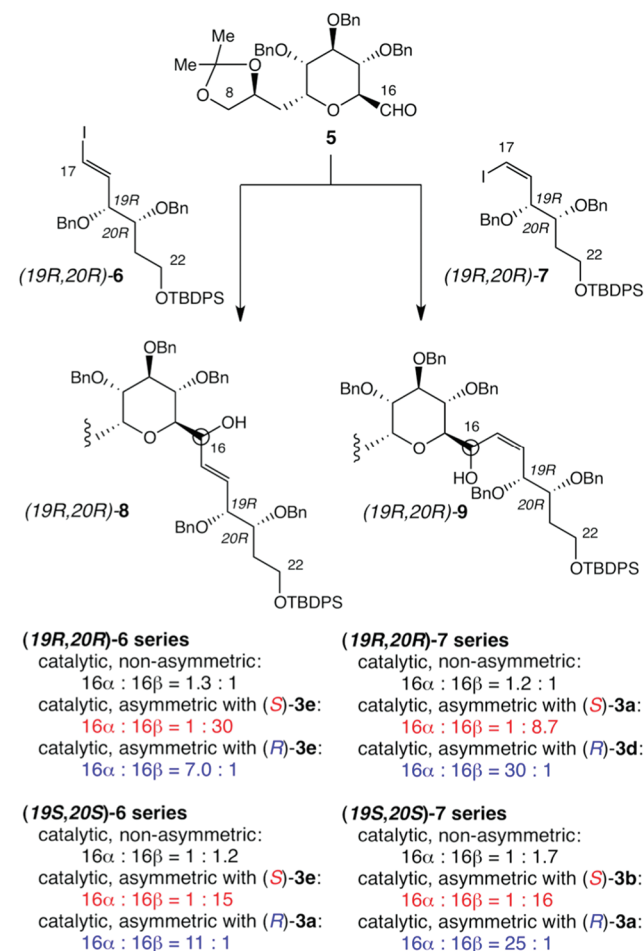
Lastly, it is noteworthy that the effective Ni catalysts **2b**, **2c**, **4a**, and **4b** gave only insignificant amounts of homodimers. This observation probably implies that no significant amounts of alkenylnickel(II) species accumulated in these cases.¹⁶

Naturally, we were interested in testing the performance of these Ni catalysts for catalytic asymmetric Ni/Cr-mediated coupling of polyfunctional substrates. As a demonstration, we chose the C16–C17 bond-forming reaction of palytoxin for three reasons. First, this is the coupling reaction that led us to the discovery of the Ni/Cr-mediated coupling reaction.^{2a} Second, aldehyde **5** is labile and does not agree well with standard organometallic reagents.¹⁷ Third, the original non-asymmetric stoichiometric protocol gave only very modest diastereoselectivity.^{2a}

On the basis of the results outlined in Tables 1 and 2, we chose Ni catalysts **2b** and **4a**¹⁸ for (*E*)- and (*Z*)-vinyl iodides **6** and **7**, respectively. A brief ligand optimization via the toolbox approach⁶ allowed us to find a suitable chiral sulfonamide for each case. Thus, four allylic alcohols, namely, 16 α - and 16 β -**8** and 16 α - and 16 β -**9** in both the (19*R*,20*R*) and (19*S*,20*S*) series, were obtained at a synthetically useful level of stereoselectivity without geometrical isomerization (Scheme 4).¹⁹

In conclusion, we have shown the importance of the Ni catalyst in achieving catalytic asymmetric Ni/Cr-mediated coupling reactions effectively. Six phenanthroline–NiCl₂ complexes **1a–c** and **2a–c** and five types of alkenyl iodides **A–E** were chosen for the study. These Ni catalysts were found to display a wide range of overall reactivity profiles in terms of the degree of asymmetric induction, geometrical isomerization, and coupling rate. For three types of alkenyl iodides **A–C**, a satisfactory Ni catalyst(s) was found within **1a–c** and **2a–c**.

Scheme 4. Palytoxin C16–C17 Bond-Forming Examples^a



^aCouplings were done with 20 mol % Cr catalyst prepared from sulfonamide **3a** and 4 mol % Ni catalyst at rt in MeCN (*c* = 0.4 M), in the presence of Mn metal (2 equiv), Zr(cp)₂Cl₂ (1.2 equiv), and LiCl (2 equiv); *E/Z* and *er* were estimated from HPLC or ¹H NMR analysis, respectively.

For disubstituted (*Z*)-alkenyl iodide **D**, **2b** was identified as an acceptable Ni catalyst in terms of the absence of *Z* → *E* isomerization and the degree of asymmetric induction but not in terms of the coupling rate. Two phosphine-based Ni catalysts, [(Me)₃P]₂•NiCl₂ and [(cy)₃P]₂•NiCl₂, were found to meet all three criteria for **D**. The C16–C17 bond-forming reaction of palytoxin was used to demonstrate the usefulness of the Ni catalysts thus identified.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and ¹H and ¹³C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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- (11) In our work in 1986,^{2a} we observed the coupling reaction with CrCl₂ doped with Pd(OAc)₂. In connection with the current work, this observation is interesting because alkenylpalladium species are known to be configurationally more stable. In spite of extensive efforts, we were unable to activate CrCl₂ by doping with Pd salts. We now speculate that the Pd(OAc)₂ used in the original work might have been contaminated with some metal salt.
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- (13) In the presence of some Ni complexes, the coupling reaction slowly progresses in MeCN with only free CrCl₂, roughly corresponding to the background coupling.
- (14) The colors of the NiCl₂ complexes are violet (**1a**, **2a**, and **2b**), yellow (**1b**), green (**1c**), and blue (**2c**). The yellow and violet complexes are known to be the α - and β -forms of **1b**. See: Preston, H. S.; Kennard, C. H. L. *J. Chem. Soc. A* **1969**, 2682.
- (15) With a lower Ni/Cr-ratio, the degree of $Z \rightarrow E$ isomerization can be suppressed even for the trisubstituted (Z)-olefin **E**: in the presence of 20 mol % Cr catalyst and (2 + 2) mol % Ni catalyst (the second 2 mol % was added at 4 h), the coupling of trisubstituted (Z)-vinyl olefin **E** was complete within 16 h, giving the product with $Z/E = 3.2/1$.
- (16) An alkenylnickel(I) species was suggested to play a key role in homodimerization. See: Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, 101, 7547. Also see: Semmelhack, M. F.; Helquist, P. M.; Gorzynski, J. D. *J. Am. Chem. Soc.* **1972**, 94, 9234. Colon, I.; Kelsey, D. R. *J. Org. Chem.* **1986**, 51, 2627. Amatore, C.; Jutand, A. *Organometallics* **1988**, 7, 2203.
- (17) Aldehyde **5** readily eliminates benzyl alcohol even under weakly basic conditions, yielding the corresponding α,β -unsaturated aldehyde. This instability limited the choices and reaction conditions. Experimentally, it was found that only simple organocuprates gave the desired adduct in satisfactory yields.
- (18) **4a** was chosen because it gave a higher coupling rate than **4b**.
- (19) $Z \rightarrow E$ isomerization was observed in the catalytic asymmetric Ni/Cr-mediated coupling with the Cr catalyst derived from sulfonamide **3b** and Ni catalyst **1b**.