Ni(II)/Cr(II)-Mediated Coupling Reaction: An Asymmetric Process

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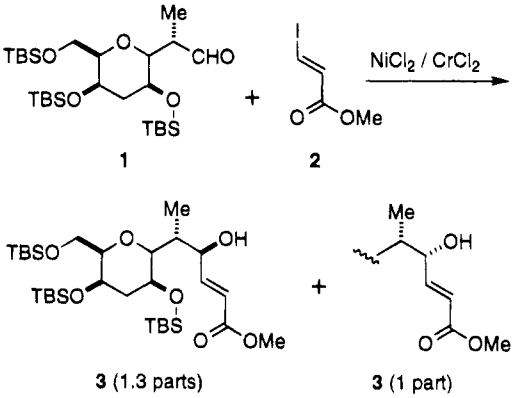
During the synthetic studies of palytoxin, we have recognized the unique potential that the Ni(II)/Cr(II)-mediated coupling reaction offers.[1] In our view, this reaction has most demonstrated its versatility for coupling multifunctional substrates, to which conventional organometallic reagents are difficult to apply. Indeed, it has successfully been used for the key bond-forming steps in various syntheses of natural and non-natural products.[2] However, there is an unsolved problem. The example chosen from the halichondrin area illustrates this: coupling of **1** with **2** in THF:DMF (4:1) at room temperature yielded the two possible diastereomers **3** and **4** in a 1.3:1 ratio (Scheme 1).[3] There is a possibility that the stereochemical course inherent to this type of process could be overridden by using a suitable chiral ligand, and we report our efforts along this line.

This process appears to involve the activation of the carbon–iodine bond via Ni(0) or Ni(I), the transmetalation of Ni to Cr, and the carbon–carbon bond formation via the organochromium reagent.[1] A catalytic cycle of Ni is required for this process to function efficiently, suggesting that a chiral ligand for the current purpose must meet with the condition that its capacity to form metal complexes should not be too strong with Ni but should be sufficiently strong with Cr. Several ligands known in the literature illustrate the difficulty of meeting this condition; for example, the coupling reaction did not progress in the presence of 2,2′-dipyridyl, 1,10-phenanthroline, CHIRAPHOS, or 4,4′-disubstituted bis(oxazolines).[4] Interestingly, we observed that in contrast to 2,2′-dipyridyl, the coupling smoothly took place in the presence of pyridine.[5] This observation hinted that tuning the complexation capacity of 2,2′-dipyridyl might be one of the ways to accomplish our goal. For this reason, we synthesized dipyridyls with one or both pyridine rings modified, as well as a pyridine with a second heterocycle, and tested their effect on the coupling reaction shown in Scheme 1. Some of these ligands are listed in Table 1

Scheme 1



along with an approximate ratio of the diastereomers formed. Generally, the coupling reaction proceeded smoothly in the presence of dipyridyls with a substituent at the 6-position, whereas no reaction was observed in the presence of dipyridyls unsubstituted at the both 6- and 6′-positions. The best ligand thus far identified was **5d**. Using this ligand, we then sought an optimal solvent and temperature (Table 2). Interestingly, the homocoupling reaction[1] was completely suppressed in the presence of these ligands. Therefore, even a 1:2 mixture of $NiCl_2$ and $CrCl_2$ could be used for synthetic purposes. With a 1:2 mixture of $NiCl_2$ and $CrCl_2$, the rate of coupling was dramatically enhanced, and reactions even at −20 °C became practical (Table 2).[6] Thus, the asymmetric induction reached an acceptable level for practical use, although the current method requires a stoichiometric amount of dipyridyl.[7,8]

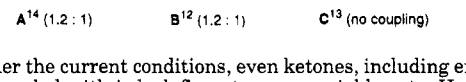
The results summarized may suggest that the stability and/or reactivity of the Cr- vs Ni-complexes correlates to the tendency for the ligands to adopt a nonplanar vs coplanar conformation so that the substrate is not trapped as an organonickel species. This view appears to be consistent with the observation that coupling did not progress in the presence of CHIRAPHOS whereas it

(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 some examples from this laboratory, see the following. (a) Palytoxin: Armstrong, R. W.; Beau, J.-M.; Cheon, S. H.; Christ, W. J.; Fujioka, H.; Ham, W.-H.; Hawkins, L. D.; Jin, H.; Kang, S. H.; Kishi, Y.; Martinelli, M. J.; McWhorter, W. W., Jr.; Mizuno, M.; Nakata, M.; Stutz, A. E.; Talamas, F. X.; Taniguchi, M.; Tino, J. A.; Ueda,K.; Uenishi, J.; White, J. B.; Yonaga, M. *J. Am. Chem. Soc.* **1989**, *111*, 7525. Kishi, Y. *Pure Appl. Chem.* **1989**, *61*, 313 and references cited therein. (b) Halichondrins: Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Materich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K. *J. Am. Chem. Soc.* **1992**, *114*, 3162. Kishi, Y. *Pure Appl. Chem.* **1992**, *64*, 343 and references cited therein. (c) Ophiobolin C: Rowley, M.; Tsukamoto, M.; Kishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2735 and references cited therein. (d) *C*-Glycosides: Dyer, U. C.; Kishi, Y. *J. Org. Chem.* **1988**, *53*, 3383. Goekijian, P. G.; Wu, T.-C.; Kang, H.-Y.; Kishi, Y. *J. Org. Chem.* **1991**, *56*, 6422. Wei, A.; Kishi, Y. *J. Org. Chem.* **1994**, *59*, 88. (e) Taxanes: Kress, M. H.; Ruel, R.; Miller, W. H.; Kishi, Y. *Tetrahedron Lett.* **1993**, *34*, 5999 and 6003) Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Scola, P. M. *Tetrahedron Lett.* **1992**, *33*, 1549. The ratio of **3** and **4** was originally reported to be 2:1, but further studies revealed it to be 1.3:1 at room temperature.

(4) Evans, D. A.; Woerpèl, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. We thank Professor Evans for a generous gift of these ligands.

(5) Coupling in THF containing pyridine at room temperature gave a 1.1:1 ratio of **3** and **4**. The chiral pyridines **A**–**C** were tested for the coupling, and the ratio in parentheses represents that of **3** and **4** formed with $NiCl_2$:$CrCl_2$ (1:2) in THF at room temperature. The results currently available do not necessarily establish that both the pyridine rings of ligands, cf. **5d**, are required for a good asymmetric induction.



A[14] (1.2 : 1) **B**[12] (1.2 : 1) **C**[13] (no coupling)

(6) Under the current conditions, even ketones, including enolizable ketones, coupled with iodoolefins at an appreciable rate. However, it should be emphasized that because of significant differences in the coupling rates between aldehydes and ketones, the selectivity of aldehydes over ketones was exclusive even under the new conditions.

(7) The ligand can be recovered almost quantitatively (see ref 8).

(8) A representative procedure for the coupling is as follows. A mixture of (−)-**5d** (817 mg, 2.8 mmol) and $NiCl_2/CrCl_2$ (155 mg/309 mg) in tetrahydrofuran (40 mL) was stirred for 1 h at room temperature and then cooled to −20 °C. To this mixture was added a solution of **1** (343 mg, 629 μmol) and **2** (533 mg, 2.5 mmol) in tetrahydrofuran (40 mL) and stirred for 66 h at −20 °C. The reaction was quenched by adding saturated NH_4Cl (100 mL) and H_2O (100 mL) and then diluted with CH_2Cl_2 (300 mL). Ethylenediamine (5 mL) was added, and the mixture was stirred at room temperature for 30 min. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (4 × 100 mL). The combined extracts were dried over Mg_2SO_4, filtered, and concentrated to give an oil which was subjected to silica gel column chromatography (chloroform:toluene: ethyl acetate = 25:25:1) to give **3** (325 mg, 82% yield) and **4** (43.3 mg, 11% yield) in addition to (−)-**5d** (775 mg).

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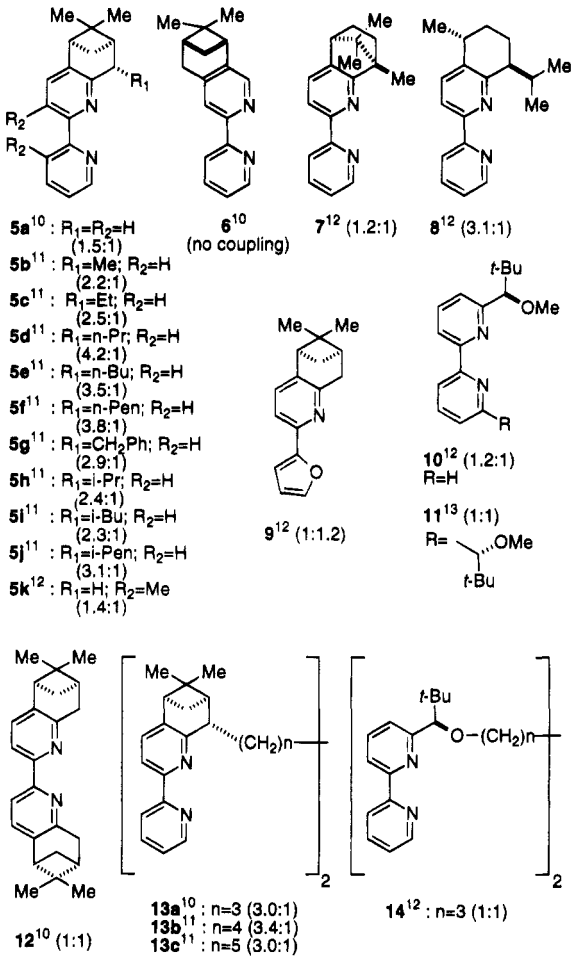
Table 1. Ligands Tested for the Ni(II)/Cr(II)-Mediated Coupling[a]



[a] The ratio in parentheses represents a product ratio (3:4) at room temperature. The product ratio was estimated from PNMR.

Table 2. Solvents and Temperature Effects (for a representative coupling procedure, see ref 8)

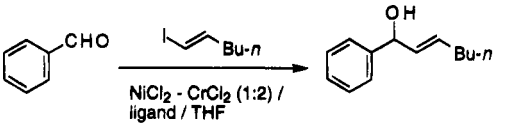
solvent	temp (°C)	time (h)	ratio (**3**:**4**)[a]
THF	30	1	4.2:1
	0	48	6:1
	−20	48	8−10:1
	−40	48	a trace of products
Et_2O	30	38	3.6:1
PhH	30	38	3.9:1
CH_2Cl_2	30	14	2.8:1
MeCN	30	14	3.3:1
DMF	30	24	no reaction
DMSO	30	24	no reaction

[a] The ratio of **3** and **4** was estimated from integrations of the resonances at 6.9 ppm (vinyl-H), 6.2 (vinyl-H), 4.5 (allylic-H), 1.2 (methyl-H) in the ^1H NMR spectrum.

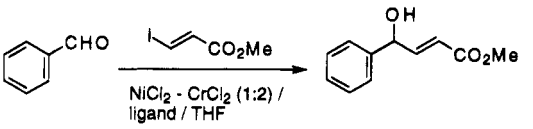
did in the presence of (*S*)-(−)-BINAPH to yield a 1.3:1 mixture of **3** and **4** at room temperature. In addition, the ligand **5k** was found to exhibit a profile almost identical to that of the ligand **5a** in terms of the coupling rate and the product ratio.

For the present work, we used the coupling reaction shown in Scheme 1 for screening chiral ligands. Undoubtedly, the chiral center(s) present in the aldehyde **1** has an effect(s) on the degree of asymmetric induction. Indeed, the asymmetric induction for coupling **1** with **2** in the presence of the antipode of **5d** was approximately 1:1.9 at room temperature. The level of asymmetric induction with simple aldehydes was substantially less

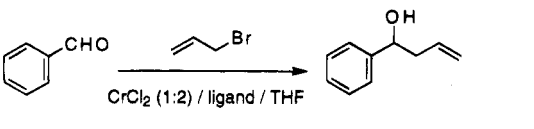
Table 3.



ligand	temp	time	product ratio[a]
5d	30 °C	1 hr	1.8:1
	-20 °C	48	2.5:1



ligand	temp	time	product ratio[a]
5d	30 °C	1 hr	2.2:1
	-20 °C	48	3.1:1



ligand	temp	time	product ratio[a]
5d	30 °C	1 hr	4.9:1
	-20 °C	48	6.7:1
CHIRAPHOS	30 °C	11	1:1
(*S*)-(-)-BINAPH	0 °C	11	1:1

[a] The product ratio was estimated from integrations of the MeO resonances in the ^1H NMR spectrum of their Mosher's esters, prepared by treatment with (*S*)-(−)-MTPA, DMAP, DCC, CH_2Cl_2. The absolute configuration of products is not established.

(Table 3). In this connection, however, it should be emphasized that the synthetic potential of the Ni(II)/Cr-(II)-mediated coupling reaction is its unique versatility with multifunctional substrates, i.e., at an advanced stage of synthesis in a convergent manner. It is also worth noting that these ligands were effective in asymmetric induction for other chromium-based reactions such as Hiyama-type couplings[9] (Table 3).

In summary, a chiral ligand effective for the Ni(II)/Cr-(II)-mediated coupling reaction has been developed for the first time. We are currently engaged in further improvement of the level of asymmetric induction and extension of this process to a catalytic system.

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Supporting Information Available: General procedures for the coupling reactions, synthetic schemes, and general procedures for chiral ligand syntheses and ^1H NMR data of chiral ligands (11 pages).

JO9510651

(9) Okuda, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179.
(10) Hayoz, P.; von Zelewsky, A. *Tetrahedron Lett.* **1992**, *33*, 5165.
(11) This ligand was prepared via alkylation (LDA/THF, then RI or RBr/−40 °C) of **5a**.
(12) The synthetic scheme for this substance is given in the supporting information.
(13) Bolm, C.; Ewald, M.; Felder, M.; Schlingloff, G. *Chem. Ber.* **1992**, *125*, 1169.
(14) Chelucci, G.; Delogu, G.; Gladiali, S.; Soccolini, F. *J. Heterocycl. Chem.* **1986**, *23*, 1395.