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

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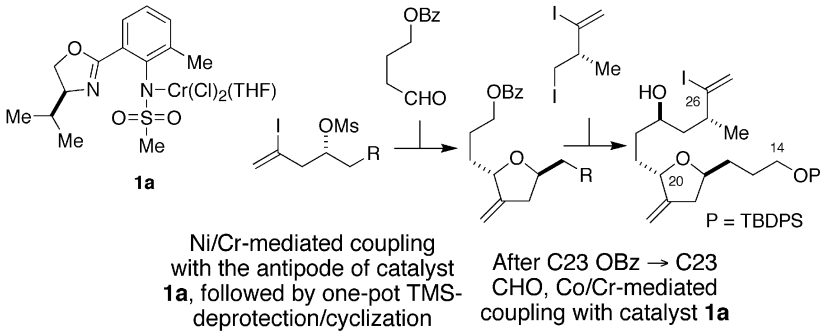
ABSTRACT



The stable, crystalline Cr(III)/sulfonamide complex 1a is shown to be an effective catalyst for the Ni/Cr-mediated coupling reaction. A possible mechanism is suggested for the process. 1a is also effective for other Cr-mediated coupling reactions. With this catalyst, a concise and efficient synthesis of the C14–C26 segment of halichondrins has been developed.

As pointed out in the preceding paper,[1] the Ni/Cr-mediated coupling reaction has shown its unique power, particularly when applied to a polyfunctional substrate. Thus, this reaction has successfully been used at a late stage in a multiple-step synthesis where scalability and practicability are not necessarily the priority.[2,3] For application of this process for a practical synthesis, however, it is highly desirable to develop a catalytic process for the Ni/Cr-mediated reactions. In 1996, Fürstner and Shi reported seminal work on a catalytic process of the Ni/Cr-mediated coupling reaction, in which TMSCl and Mn(0) are used as a dissociating agent of chromium-alkoxides and a reducing agent of chromium, respectively.[4] Electrochemically driven Cr(II)-mediated couplings were also reported.[5]

We were curious to know whether the crystalline Cr(III)/sulfonamide ligand complex **1a** reported in the preceding paper[1] works as a catalyst for the Ni/Cr-mediated coupling. Under the Fürstner conditions in THF at rt, instead of DME/DMF at 50 °C,[4] the Ni/Cr-mediated coupling of **2** with **3** was found to proceed smoothly in the presence of 10 mol % of **1a** with 10 mol % of $NiCl_2$, to give the expected product in an excellent chemical yield with encouraging enantiomeric excess. With the same substrates and catalysts **1a**,**b**, optimization studies were conducted, revealing the following: (1) both **1a** and **b** function as effective catalysts, (2) TMSCl is the best agent to dissociate chromium-alkoxides,[6] (3) Mn(0) is the most effective reducing agent,[6] (4) addition of

(1) Wan, Z.-K.; Choi, H.; Kang, F.-A.; Nakajima, K.; Demeke, D.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4431.

(2) (a) Jin, H.; Uenishi, J.; 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.

(3) For recent reviews on Cr-mediated reactions, see: (a) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991. (b) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1. (c) Saccomano, N. A. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 1, p 173.

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

(5) (a) Grigg, R.; Putnikovic, B.; Urch, C. J. *Tetrahedron Lett.* **1997**, *38*, 6307. (b) Kuroboshi, M.; Tanaka, M.; Kishimoto, S.; Goto, K.; Tanaka, H.; Torii, S. *Tetrahedron Lett.* **1999**, *40*, 2785. Kuroboshi, M.; Tanaka, M.; Kishimoto, S.; Tanaka, H.; Torii, S. *Synlett.* **1999**, 69. (c) Durandetti, M.; Nédélec, J.-Y.; Périchon, J. *Org. Lett.* **2001**, *3*, 2073.

(6) Dissociating and reducing reagents tested include (a) dissociating agents TMS-Cl, TMS-Im, TMS-OTf, TES-Cl, and MeOCOCl and (b) reducing agents Mn, Zn, Al, and Fe.

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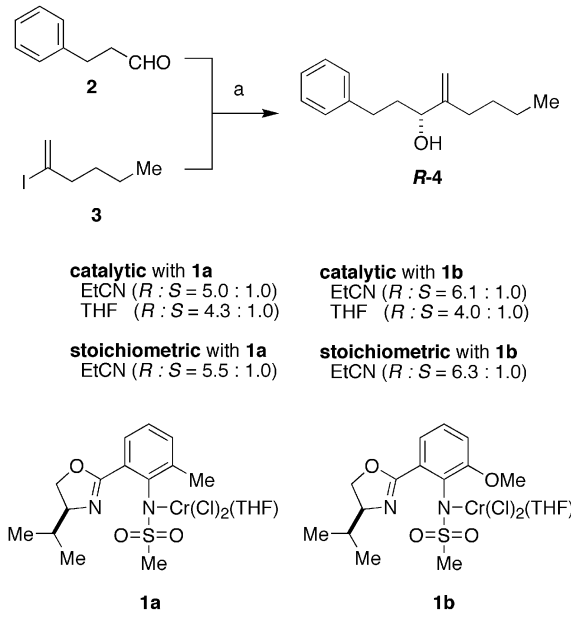
(Bn)(*n*-Bu)$_3$NCl or Et$_3$N·HCl enhances the coupling efficiency,[7] (5) addition of LiCl enhances the coupling rate, (6) EtCN and THF are good solvents,[8] (7) 10 mol % of **1a**,**b** is sufficient to complete the coupling within 24 h at rt, (8) the optimal temperature is around rt but the reaction proceeds at 0 °C, and (9) the optimal range of concentration is 0.5−0.1 M.

The enantiomeric excess observed for the catalytic process in THF was found to be lower than that in the stoichiometric process. With the progress of coupling, a Lewis acid MnX_2 is formed which might have an effect of lowering the enantiomeric excess. However, addition of $MnCl_2$ did not appreciably affect the enantiomeric excess. In addition, a rough time-course study indicated no noticeable change in the enantiomeric excess throughout the coupling reaction. Ultimately, the catalytic reaction in EtCN was found to proceed as efficiently as in THF and give the product in almost quantitative yield. Importantly, the enantiomeric excess obtained in the catalytic process in EtCN was found to be roughly comparable with that obtained in the stoichiometric process (Scheme 1).[8]

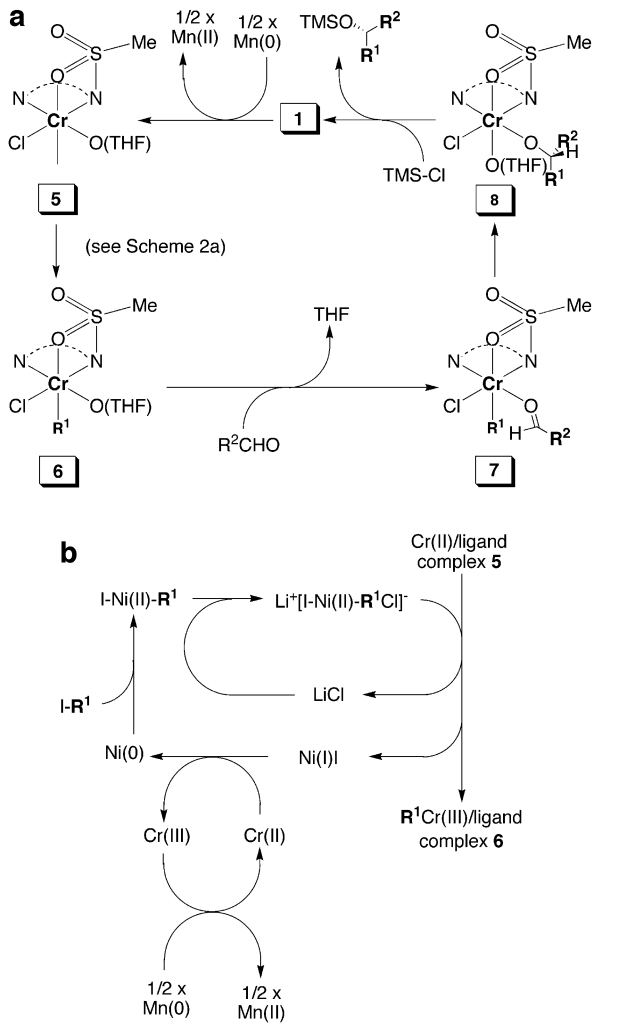
Scheme 1[a]



[a] Reagents and conditions: (a) **2** (1 equiv), **3** (2 equiv), **1** (10 mol %), $NiCl_2$ (10 mol %), Mn (2 equiv), TMSCl (2 equiv), Et$_3$N·HCl or (Bn)(*n*-Bu)$_3$NCl (20 mol %), LiCl (2 equiv), EtCN or THF, rt.

All these results indicate that the asymmetric reaction developed in the stoichiometric process is translated well into the catalytic, asymmetric process, and we speculate that the critical bond-forming steps involved in the catalytic process are the same as those proposed for the stoichiometric process (Scheme 2a). Taking into account the relative rate

Scheme 2



of ligand exchange on Cr(II) vs Cr(III) species,[3] we assume that the transmetalation takes place at the Cr(II)-oxidation state, which is formed through chemical reduction of **1** by Mn(0). The structural information on the proposed Cr(II)/sulfonamide ligand complex is not available at this time, but an X-ray structure was obtained on Cr(II)(Cl)$_2$(4-*tert*-butylpyridine)$_3$ (**9**) (Figure 1).[9] This Cr(II) complex **9** posseses an unusual square-pyrimidal geometry.[10] Interestingly, this structure can be viewed as an octahedral structure with one vacant ligation site. It is tempting to suggest that

(7) (Bn)(*n*-Bu)$_3$NCl and Et$_3$N·HCl are equally effective in EtCN, whereas (Bn)(*n*-Bu)$_3$NCl is slightly more effective in THF.

(8) The rate of coupling was found significantly faster in MeCN than in EtCN. However, the enantioselectivity was significantly lower in MeCN than in EtCN.

(9) Stamos, D.; Kishi, Y. Unpublished result. Bond lengths: Cr−N(1) = 2.14 Å; Cr−N(2) = 2.15 Å; Cr−N(3) = 2.36 Å; Cr−Cl(1) = 2.37 Å; Cr−Cl(2) = 2.37 Å. Bond angles: N(1)−Cr−N(2) = 173.9°; N(1)−Cr−N(3) = 95.4°; N(2)−Cr−N(3) = 90.7°; N(1)−Cr−Cl(1) = 89.5°; N(2)−Cr−Cl(1) = 90.2°; N(3)−Cr−Cl(1) = 96.4°; N(1)−Cr−Cl(2) = 88.6°; N(2)−Cr−Cl(2) = 90.1°; N(3)−Cr−Cl(2) = 98.2°; Cl(1)−Cr−Cl(2) = 165.3°.

(10) (η^1-C$_4$H$_4$N)$_2$Cr(Py)$_3$ is known to possess an unusual square-pyramidal geometry similar to **9**: Edema, J. J. H.; Gambarotta, S.; Meetsma, A.; van Bolhuis, F.; Spek, A. L.; Smeets, W. J. J. *Inorg. Chem.* **1990**, *29*, 2147.

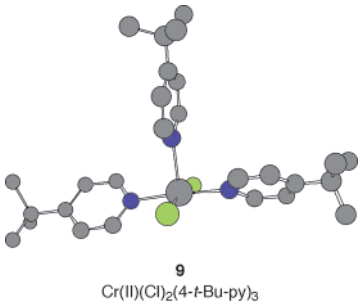


Figure 1.

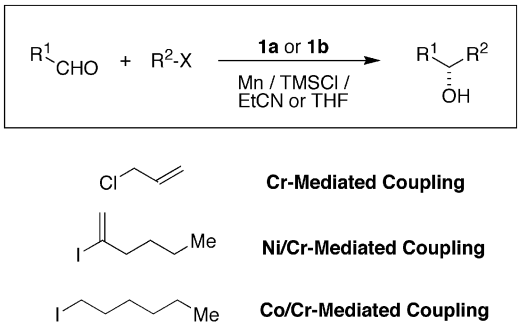
the proposed Cr(II)/sulfonamide ligand complex adopts a similar structure and that the vacant ligation site is involved in the transmetalation with the alkenyl-Ni(II) complex. The Cr(III)/ligand complex thus formed proceeds through the steps suggested for the stoichiometric series, to furnish Cr(III)/ligand alkoxide. As suggested by Fürstner,[4] TMS-Cl dissociates the Cr-alkoxide to give the TMS ether of **4** and regenerates the ligand-Cr(III) complex **1**. Thus, all the chemistry takes place only at the two ligation sites of **1**.

In addition, this process contains a catalytic cycle centered on the Ni salt, which is coupled with the Cr-catalytic cycle and hence with the Mn-redox cycle (Scheme 2b). Lastly, the effect of LiCl on the overall reaction rate may be attributed to formation of the Ni-ate complex from the alkenyl-Ni(II) complex, enhancing the rate of transmetalation.

Overall, the catalytic Ni/Cr-mediated coupling reaction relies on the two catalytic cycles. Therefore, to achieve this bond-forming process economically in terms of the Cr(III)/sulfonamide ligand complex **1**, it is important to realize an efficient catalytic cycle not only for Cr salt but also for Ni salt. It appeared that the efficiency for the Cr-catalytic cycle is sufficiently good but that of the Ni-catalytic cycle, especially in EtCN, needs improvement. In practice, the catalytic reaction in the presence of 10 mol % of **1** with either 20−40 mol % of $NiCl_2$ or 4−6 mol % $Ni(COD)_2$ gave a significantly improved reproducibility.[11,12] Considering the fact that the stoichiometric coupling is routinely performed in the presence of 3−4 equiv of $CrCl_2$, the current catalytic process represents a reduction of Cr use by a factor of 30−40.

We would like to point out the possibility that the Cr(III)/sulfonamide complexes **1a**,**b** can be potentially applied to any chemistry associated with a Cr species, and we are currently studying the scope that these complexes may offer. Somewhat related to this issue, it should be noted that the Cr-mediated coupling reactions are grouped into three

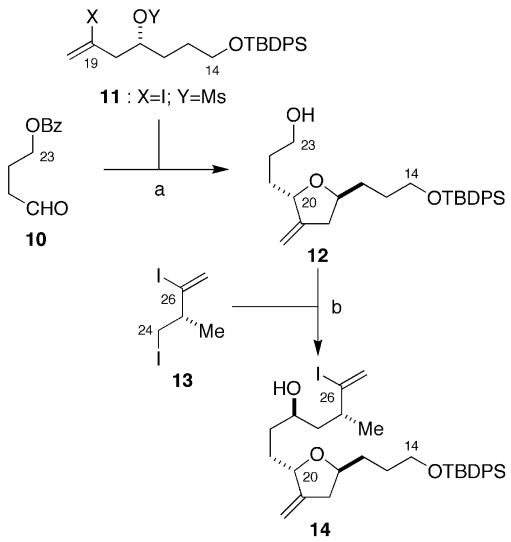
Scheme 3



subgroups (Scheme 3): allyl halides are activated by Cr(II) species alone,[13] whereas alkenyl halides and alkyl halides are activated through Ni(0) and Co(I) species, respectively.[1,14] Gratifyingly, the ligand-Cr(III) complex shows good applicability for all three subgroups of Cr-mediated coupling reactions, which certainly expands the scope of Cr-mediated reactions.

The synthesis of the C14-C26 segment of halichondrins[15] illustrates this point further (Scheme 4). The first bond formation was achieved via a catalytic, asymmetric Ni/Cr-mediated coupling reaction; in the presence of 10 mol % of

Scheme 4[a]



[a] Reagents and conditions: (a) (1) **10** (2 equiv), **11** (1 equiv), the antipode of **1a** (10 mol %), $NiCl_2$ (40 mol %) or $Ni(COD)_2$ (3 × 1 mol %), Mn (2 equiv), TMSCl (2 equiv), Et_3N·HCl or (Bn)(n-Bu)$_3$NCl (20 mol %), LiCl (2 equiv), EtCN or THF, rt. (2) PPTS/Py/i-PrOH/RT. (3) K_2CO_3/MeOH, followed by separation via silica gel chromatography (Biotage medium-pressure unit). The overall yield of **12** from **11** was 70−80%. (b) (1) Dess−Martin oxidation of **12** (90% yield). (2) The aldehyde (1 equiv), **13** (2 equiv), **1a** (50 mol %), Co-phthalocyanine (10 mol %), Mn (2 equiv), TMSCl (2 equiv), Et_3N·HCl (20 mol %), LiCl (2 equiv), DME. (2) aq oxalic acid/THF/rt, followed by silica gel column chromatography. The overall yield of **14** from the aldehyde was 73%, with the 5.3:1.0 stereoselectivity

(11) In the presence of 20∼40 mol % of $NiCl_2$, the coupling reaction with 5 mol % of **1a** gave a satisfactory result, except for the sluggish rate of reaction.

(12) With addition of $Ni(COD)_2$ in several portions (3−4 × 1 mol %), the homocoupling of **11** can be avoided.

(13) (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc*. **1977**, *99*, 3179. (b) Okude, Y.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett*. **1977**, *43*, 3829. (c) Kuroboshi, M.; Tanaka, M.; Kishimoto, S.; Tanaka, H.; Torii, S. *Synlett*. **1999**, 69.

the antipode of **1a** with either 40 mol % of $NiCl_2$ or 5 mol % of $Ni(COD)_2$, the coupling of **10** with **11**[16] furnished the desired product.[17] Treatment of the crude coupled product with PPTS/Py/*i*-PrOH not only removed the resultant C20 TMS-silyl ether but also effected the cyclization.[18] After debenzoylation, the stereochemically homogeneous **12** was isolated by silica gel chromatography[19] in 70−80% overall yield from **11** with ca. 9:1 overall stereoselectivity.

It is worthwhile noting the observation made on the C17 leaving group; in the coupling reaction with the substrate with X = I and Y = Ts in **11**, the C17 tosyl group was reductively cleaved in THF slowly.[20] However, this side reaction was not significant in EtCN or could be eliminated by replacing the tosyl group with the corresponding mesyl group even in THF.[21]

A catalytic, asymmetric Co/Cr-mediated coupling reaction was used for the C23−C24 bond formation. Takai and Uchimoto showed that alkyl halides and tosylates are coupled with aldehydes in the presence of $CrCl_2$ and a catalytic amount of vitamin B_{12} or cobalt phthalocyanine. Using a model system,[22] we have first established that **1a** acts as a catalyst for the Co/Cr-mediated coupling reaction. Under the condition established in the model system, selective activation of the alkyl iodide over the vinyl iodide present in **13** was indeed possible, but the coupling reaction was accompanied by a significant amount of byproducts. Screening solvents, Co-sources, additives, and the amount of **1a**, the condition specified in Scheme 4 is most effective to date. In this manner, the desired, stereochemically homogeneous coupling product **14**[23] was isolated in 73% yield, with a 5.3:1 stereoselectivity, and the structure of **14** was confirmed on comparison with the sample available from the previous synthesis.[15]

In summary, we have shown that the stable, crystalline Cr(III)/sulfonamide complex **1** acts as an effective catalyst for the Cr-mediated coupling reactions. We are currently engaged with further improvements on the catalyst, particularly in terms of the degree of asymmetric induction and the catalyst loading.

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Supporting Information Available: Experimental details for the syntheses outlined in Schemes 1 and 4 and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Takai, K.; Nitta, K.; Fujimura, O.; Utimoto. K. *J. Org. Chem.* **1989**, *54*, 4732.

(15) Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Matelich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K. *J. Am. Chem. Soc.* **1992**, *114*, 3162.

(16) **11** was prepared from the (*R*)-5-[(*tert*-butyldiphenylsilyl)oxy]-1,2-epoxypentane obtained by catalytic, kinetic hydrolytic resolution of the corresponding racemic epoxide, in three steps, (1) TMSC≡CH/*n*-BuLi/BF_3·Et_2O/THF/−78 °C, (2) TsCl or MsCl/Py, and (3) NaI/TMSCl/H_2O/MeCN. **13** was prepared from (*R*)-HC≡CCH(Me)CH_2OBn in three steps, (1) *B*-iodo-9-BBN, (2) TsCl/Py, and (3) LiI/acetone.

(17) The C14-C26 segment **14** of halichondrins could be synthesized by consecutive use of all the three subgrouped reactions (Scheme 3). However, an attempted coupling of 2,3-dibromopropene with the TBDPS silyl ether of 4-hydroxybutyraldehyde under the current protocol did not give the satisfactory level of chemical yield nor asymmetric induction for practical application.

(18) C20-TMS deprotection and subsequent cyclization were effected under various conditions, including (1) aq oxalic acid, followed by silica gel treatment/EtOH or hexanes/$CHCl_3$, (2) Montmorillonite clay/*i*-PrOH, (3) PPTS/*i*-PrOH, and (4) Amberlite 15/*i*-PrOH.

(19) Separation of **12** from its C20-diastereomer was carried out in 1−2 g scales by a Biotage medium-pressure chromatographic unit.

(20) This side-product formation was found significantly slower than the Ni/Cr-mediated coupling itself. Nonetheless, when the substrate with X = I and Y = Ts in **11** was completely consumed, this side-product was isolated in ca. 30% yield as a ca. 8:1 mixture of the C20 diastereomers.

(21) Two additional substrates with X = I/Y = Ts and X = Br/Y = Ts in **11** were used for the coupling. In EtCN, both substrates gave the results comparable to **11**. For the details, see the Supporting Information.

(22) The catalytic Co/Cr-mediated coupling of dihydrocinnamaldehyde (**2**) with isobutyl iodide was effected in EtCN (0.3 M), containing **1a** (10 mol %), Co-phthalocyanine (5 mol %), Mn (2 equiv), TMSCl (2 equiv), LiCl (2 equiv), and Et_3N·HCl (20 mol %), at rt for 40 h, to give the expected product in ≥90% yield. The enantioselectivity found was 2.3:1, with the major enantiomer corresponding to (*R*)-**4**.

(23) Separation of **14** from its C23-diastereomer was carried out by gravity column chromatography on silica gel.