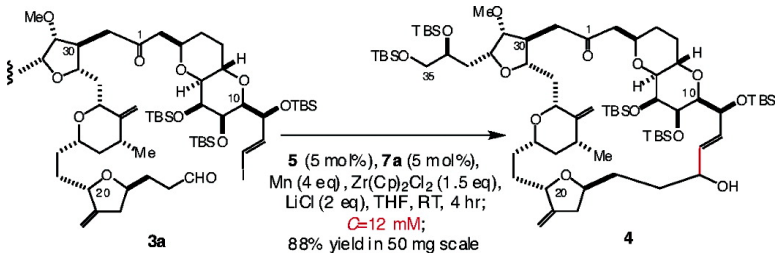
Communication

Catalytic Ni/Cr-Mediated Macrocyclization without Use of High-Dilution Techniques

Kosuke Namba, and Yoshito Kishi

J. Am. Chem. Soc., **2005**, 127 (44), 15382-15383• DOI: 10.1021/ja055966v • Publication Date (Web): 15 October 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 8 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 10/15/2005

Catalytic Ni/Cr-Mediated Macrocyclization without Use of High-Dilution Techniques

Kosuke Namba and Yoshito Kishi*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138

Received September 5, 2005; E-mail: Kishi@chemistry.harvard.edu

We recently reported that the rate of the catalytic Cr-mediated coupling reaction is dramatically accelerated in the presence of 3,3′-dimethyl-2,2′-dipyridyl.[1] This observation immediately suggests several new directions for expanding the scope of Cr-mediated coupling reactions. In this communication, we would like to report a successful extension of this observation to catalytic Ni/Cr-mediated macrocyclization without use of high-dilution techniques.

The catalytic Ni/Cr-mediated coupling reaction involves at least the following four discrete steps: (1) oxidative addition 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**).[2] Related to the present study, it should be noted that the C−C bond formation takes place via a nucleophile−electrophile pairing, where the electrophile aldehyde is activated through coordination to Cr, and the nucleophile vinyl−Cr species is formed through Ni-to-Cr transmetalation of the vinyl−Ni species.[3] With this analysis, the concentration of real electrophile and nucleophile is equal to, or lower than, the concentration of Cr and Ni catalysts, respectively. For example, for the coupling reaction with [substrate] = 20 mM in the presence of 5 and 1 mol % of Cr and Ni catalysts, the maximum concentration of real electrophile and nucleophile is 1 and 0.2 mM, respectively. Interestingly, these concentrations do not significantly differ from the substrate concentration for macrocyclization under high-dilution conditions,[4] thereby suggesting a possibility that catalytic Ni/Cr-mediated coupling reactions can be applied for macrocyclization[5] without use of the high-dilution techniques. Obviously, several additional factors should be considered. First, with the progress of the reaction, manganese dihalide is formed, which might also activate RCHO.[6] Second, the molar ratio of RCHO and Cr catalyst decreases with the progress of the reaction. Third, with the progress of the reaction, Ni and Cr catalysts may lose some catalytic activity.[7] Despite these unclear aspects, we still explored this possibility with two vinyl iodide aldehydes **1** and **3a** chosen from the halichondrin area (Figure 2).[8,9] We should note that an attempted Ni/Cr-mediated macrocyclization of **1** under the traditional stoichiometric conditions did not give **2**,[10] whereas the stoichiometric Ni/Cr-mediated macrocyclization of **3a** via slow addition furnished the desired product **4**.[11] Interestingly, the efficiency of this stoichiometric macrocyclization was dramatically improved in the presence of (*S*)-sulfonamide ligand.[12]

Under conditions optimized for the intermolecular system,[1,13] we attempted the macrocyclization of **3a** and isolated a single product in an almost quantitative yield. However, spectroscopic analysis showed that this product was not the desired product **4**, but the known C14 primary alcohol **3b**.[11,14] On changing the solvent from DME to THF, we observed that formation of the primary alcohol **3b** was significantly suppressed, but activation of the vinyl iodide group was still very sluggish. Therefore, we next screened the Ni source, resulting in a major breakthrough; on replacement the $NiCl_2$ source from **8** to **7a**,[1] **3a** gave the desired macrocycle **4** in ca. 60% yield as a 3:2 mixture of the C14 diastereomers even at the substrate concentration of 20 mM.[15]

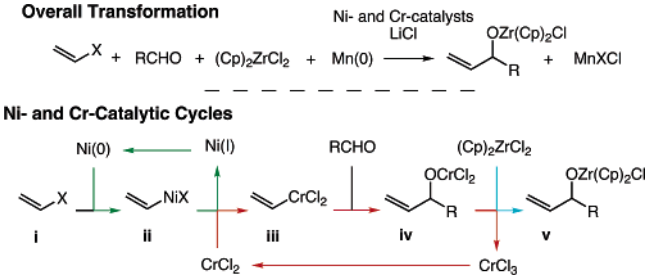


Figure 1. Ni and Cr catalytic cycles involved in the Ni/Cr-mediated coupling. The dissociation step is illustrated with $(Cp)_2ZrCl_2$, which can be replaced with TMSCl.

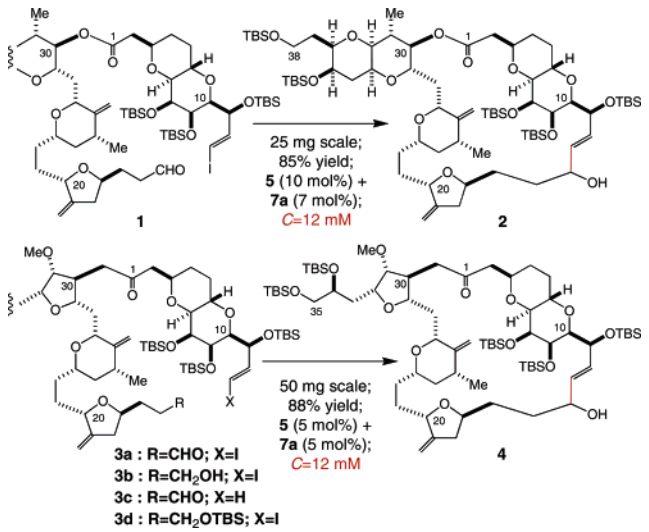


Figure 2. Substrate structures used.

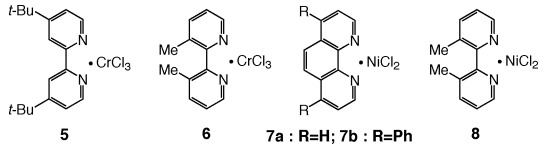


Figure 3. Ni and Cr catalysts used.

One of the byproducts observed was the deiodinated aldehyde **3c**. Formation of this byproduct was almost completely suppressed by use of Baker's anhydrous THF.[16] In previous studies,[1] we noticed that both oxidative addition of Ni(0) to a vinyl iodide and transmetalation of Ni(II) to Cr(II) is very fast, relative to the following steps, but this kinetic profile may not be translated to the present, complex intramolecular system. To address this specific question, the reactivity of the *trans*-iodide **3d** toward the $NiCl_2$ complex **7a** was tested in the absence of the $CrCl_3$ complex **5**; under the catalytic condition [**7a** (10 mol %), none of **5** in THF], **3d** slowly gave the corresponding deiodinated product, but interestingly no detectable amount of the homo-coupled diene. Thus, contrary to the simple system, the first or second step in Figure 1, or both of

10.1021/ja055966v CCC: $30.25

them, appears to be sluggish, which may account for formation of the deiodinated aldehyde **3c**. For this reason, a higher ratio of the Ni catalyst against the Cr catalyst (molar ratio of **7a**:**5** = 1:1−2:3) was used for the macrocyclization. However, we speculate the actual effective concentration of the Ni catalyst is significantly lower.[7]

With use of **7a** as the $NiCl_2$ source, we then screened the best $CrCl_3$ source and found that **5** gave the best result; in the presence of **5** (5 mol %) and **7a** (5 mol %), **3a** smoothly macrocyclized in THF (C = 12 mM) at room temperature in 4 h, and the product was isolated by simple silica gel flash chromatography to furnish **4** as a 3:2 mixture of the diastereomers at C14 in ca. 90% yield. It is worthwhile noting two additional observations. First, under the optimized conditions, formation of the primary alcohol **3b** was almost completely eliminated. Second, the reaction rate was relatively slow for the first 10−15 min and then accelerated. We speculate that this might relate to a time-lag for the catalytic system to be completely established, but currently, there is no direct experimental support for this.

With the optimized conditions in hand, we studied the concentration effect. As mentioned above, we were curious about testing the concentration effect on the intra- versus intermolecular Cr-mediated C−C bond-forming events. Thus, the catalytic Ni/Cr-mediated macrocyclization was conducted in THF at [**3a**] = 10, 20, and 40 mM to furnish the desired macrocycle **4** (as a 3:2 diastereomeric mixture at C14) in decreasing yields of ca. 90, ca. 80, and ca. 65%, respectively. MALDI-mass analysis demonstrated that the major byproducts formed in all the cases were mixtures of primarily dimeric and trimeric products.[17] The combined mass recovery of **4** and these byproducts accounted for virtually all the vinyl iodide aldehyde used. It is noteworthy that the byproduct formation was less significant in the early stage of reaction than in the late stage, which is consistent with the analysis given above.

We also anticipated that, by lowering the loading of catalysts with the substrate concentration kept the same, formation of these byproducts should be suppressed. Considering the reaction rate, we feel confident that this catalytic system should be effective even at lower catalyst loadings. However, it is not a practical option for us to test lower loadings of catalysts.[18] Therefore, we tested the catalytic macrocyclization with a higher loading of catalysts (10 mol % of **5** and 10 mol % of **7a**) in THF at the same concentration, yielding a decreased 80% yield of **4**, along with an increased 20% yield of a mixture of dimers and trimers. This result once again supports the analysis given above.

The optimized conditions were also applied to the vinyl iodide aldehyde **1** in the halichondrin B series [25 mg scale with **5** (10 mol %) and **7a** (7 mol %)] to furnish the desired macrocycle **2** in 85% yield.[15] The overall profile of reaction from **1** to **2** was parallel to that from **3a** to **4**, except that the macrocycle **2** was isolated as a single diastereomer at C14.

Last, we should comment on the macrocyclization in MeCN, an effective solvent for catalytic Ni/Cr-mediated couplings.[1,3] The catalytic macrocyclization of **3a** nicely progressed in MeCN to furnish the desired macrocycle **4**. However, there were three distinct differences noticed between MeCN and THF. First, the most effective Cr and Ni catalysts in MeCN were **6** and **7b**, whereas those in THF were **5** and **7a**. Second, the rate of macrocyclization was significantly slower in MeCN than in THF. Third, the macrocycle formed in MeCN was almost a single diastereomer at C14, whereas the product in THF was a 3:2 mixture of the diastereomers at C14. Under the optimized conditions, the macrocyclization of **3a** in MeCN furnished the desired macrocycle **4** in 80% yield. The byproducts formed under this condition were once again mixtures of primarily dimeric and trimeric products.

In conclusion, the feasibility of catalytic Ni/Cr-mediated macrocyclization was demonstrated for the two substrates chosen from the halichondrin area. With 5 mol % of Ni and Cr catalysts, the macrocyclization was realized without use of high-dilution techniques. The reported method has a number of appealing features, including user-friendliness, easy workup, apparent scalability, and cost-effectiveness. In addition, all the required reagents are commercially available or obtainable in one or two steps from commercially available chemicals. Finally, we are currently engaged with the study of extending this method to other types of catalytic Cr-mediated coupling reactions.

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

Supporting Information Available: Experimental details (6 pages, print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Namba, K.; Cui, S.; Wang, J.; Kishi, Y. Submitted for publication. (b) Namba, K.; Wang, J.; Cui, S.; Kishi, Y. Submitted for publication.
(2) For reviews on Cr-mediated reactions, see the references cited in: Namba, K.; Kishi, Y. *Org. Lett.* **2004**, *6*, 5031.
(3) For catalytic asymmetric Cr-mediated coupling reactions, see: Namba, K.; Kishi, Y. *Org. Lett.* **2004**, *6*, 5031 and references therein.
(4) In order to avoid intermolecular processes, high-dilution conditions, including slow addition, are commonly used for macrocyclizations. For examples of typical concentrations used for macrocyclizations, see: (a) Ring-closing metathesis: [C] = 0.002 M, Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606. (b) Intramolecular Horner−Wadsworth−Emmons reaction: [C] = 0.001 M or lower and for solid phase synthesis to avoid intermolecular processes: Nicolaou, K. C.; Pastor, J.; Winssinger, N.; Murphy, F. *J. Am. Chem. Soc.* **1998**, *120*, 5132. (c) Suzuki couplings: [C] = 0.003 M or lower, Chemler, S. R.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 2695. Mohr, P. J.; Halcomb, R. L. *J. Am. Chem. Soc.* **2003**, *125*, 1712. Molander, G. A.; Dehmel, F. *J. Am. Chem. Soc.* **2004**, *126*, 10313. (d) Heck macrocyclization: [C] = 0.003 M, Geng, X.; Miller, M. L.; Lin, S.; Ojima, I. *Org. Lett.* **2003**, *5*, 3733. (e) Palladium-catalyzed macrocyclization of ω-haloallenes: [C] = 0.002 M, Ma, S.; Negishi, E. *J. Am. Chem. Soc.* **1995**, *117*, 6345.
(5) For selected examples of stoichiometric Ni/Cr-mediated cyclizations to form medium- and macro-rings, see: (a) Rowley, M.; Kishi, Y. *Tetrahedron Lett.* **1988**, *29*, 4909. Rowley, M.; Tsukamoto, M.; Kishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2735. (b) Kress, M. H.; Ruel, R.; Miller, W. H.; Kishi, Y. *Tetrahedron Lett.* **1993**, *34*, 5999 and 6003. (c) Schreiber, S. L.; Meyers, H. V. *J. Am. Chem. Soc.* **1988**, *110*, 5198. (d) MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391. MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2001**, *123*, 9033. (e) Myers, A, G.; Finney, N. *J. Am. Chem. Soc.* **1992**, *114*, 10986.
(6) $MnCl_2$ and $CrCl_3$ are known as weak Lewis acids. However, considering the bond strengths of Cr−O and Mn−O, we assume that $CrCl_3$ is a stronger Lewis acid than $MnCl_2$.
(7) The lifetime of Ni catalysts appears to be significantly shorter than that of Cr catalysts (ref 1).
(8) For the chemistry of halichondrins, see the references cited in: Namba, K.; Jun, H.-S.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7770.
(9) For a total synthesis of the halichondrins, see: Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Matelich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K.; Kishi, Y. *J. Am. Chem. Soc.* **1992**, *114*, 3162.
(10) In conjunction with the total synthesis of the halichondrins (ref 9), this macrocyclization of **1** was attempted in this laboratory.
(11) Zheng, W. et al. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5551. For the complete list of authors, see Supporting Information.
(12) Fang, F. G. Synthetic Studies on the Halichondrin Analogue E7389. GSK Frontiers in Chemistry and Medicine, ACS, Southeast Regional Meeting, November 9, 2004, RTP, North Carolina. For the structure of (*S*)-sulfonamide ligand, see **1** in ref 1a. We thank Dr. Frank Fang for a generous gift of **3a**.
(13) The conditions were as follows: Cr catalyst **6** (5 mol %), Ni catalyst **8** (0.3 mol %), Mn (4 equiv), $Zr(Cp)_2Cl_2$ (1.5 equiv), LiCl (2 equiv), [C] = 24 mM in DME at room temperature.
(14) On the basis of this observation, we have developed a method to reduce chemoselectively aldehydes into the corresponding primary alcohols.
(15) The structure of this product was established by Dess−Martin oxidation and correlation with the known α,β-enone (refs 9 and 11). Also see Supporting Information.
(16) Baker Sure/Seal inhibitor-free anhydrous THF (water content = <10 ppm). THF distilled from Na−ketyl gave almost equal results.
(17) In a MALDI-mass spectrum (matrix = 2,5-DHB), two strong ion peaks were observed at 2664.5 and 3989.9.
(18) We estimated ca. 250 mg of **3a** was required for one test at 1 mol % catalyst loading.

JA055966V