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Ni(II)/Cr(II)-Mediated Coupling Reaction: Beneficial Effects of 4-*tert*-Butylpyridine as an Additive and Development of New and Improved Workup Procedures

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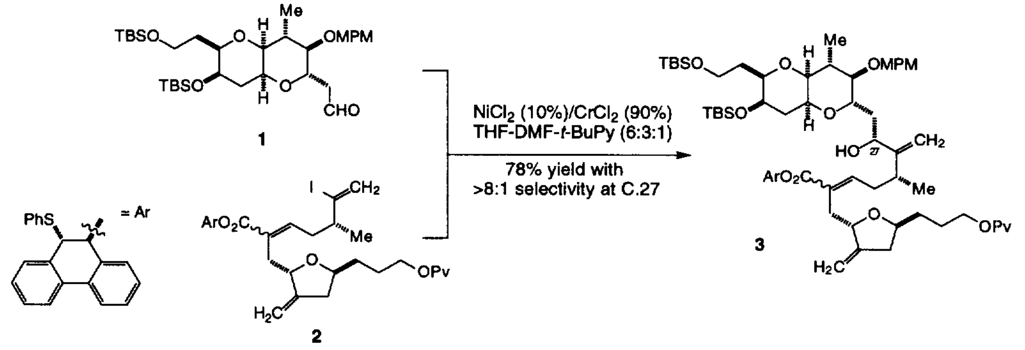
Abstract: 4-tert-Butylpyridine has been shown to be a beneficial additive in the Ni(II)/Cr(II)-mediated coupling reaction. This additive allows for homogeneous reactions, improves reproducibility, and inhibits homo-coupling of vinyl iodides or triflates. Improved workup procedures using chromium ion chelators (ethylenediamine or sodium or potassium serinate) allow for a better mass recovery. © 1997 Elsevier Science Ltd.

The development of new methods for carbon-carbon bond-formation has played a central role in organic synthesis. Of the many such methods, the unique synthetic potential of the Ni(II)/Cr(II)-mediated coupling of vinyl iodides or triflates to aldehydes has been demonstrated in the synthesis of complex natural products including palytoxin, halichondrin, and ophiobolin C.[1,2] Nevertheless, improvements in some of the reaction characteristics may further expand its synthetic practicality. Such improvements include: (1) minimizing homo-coupling of the vinyl iodides or triflates when a high content of Ni(II) is necessary, (2) avoiding heterogeneous reaction conditions which often lead to variably extended reaction times, and (3) achieving a high mass recovery of products. In this communication, we report the beneficial effects of 4-*tert*-butylpyridine (4-*t*-BuPy) as a ligand for the Ni(II)/Cr(II)-mediated coupling as well as improved workup procedures.

Related to our continued efforts to develop a practical synthesis of halichondrin B,[3,4] we were interested in improving the stereoselectivity and reproducibility of the Ni(II)/Cr(II)-mediated coupling reaction of **1** and **2** to yield **3** (Scheme 1).[5,6] However, the heterogeneous nature of this reaction presented technical difficulties. Our earlier observation[7] that the coupling smoothly progressed in the presence of pyridine hinted at a way to overcome this problem. In particular, 4-*t*-BuPy appeared to possess appealing characteristics such as high lipophilicity and commercial availability. Indeed, addition of excess 4-*t*-BuPy (>5 eq. of 4-*t*-BuPy to Cr(II) in $NiCl_2$ (10%)/$CrCl_2$ (90%)) homogenized the reaction to yield the desired product **3** in 78% yield with excellent reproducibility and stereoselectivity.

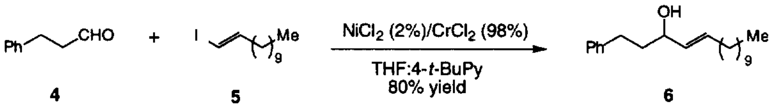
Intrigued by this result, we tested the reaction using a mixture of $NiCl_2$ (33%)/$CrCl_2$ (67%) and made two stunning observations: (1) no homo-coupling was observed[8] even in the presence of 33% of $NiCl_2$ and (2) the reaction mixture appeared (visual analysis) to consist of dissolved $CrCl_2$ and suspended solid $NiCl_2$. Solutions (ca. 0.15 M) of $NiCl_2$ (2~33%)/$CrCl_2$ (98~67%) in THF/4-*t*-BuPy (4/1 v/v) were prepared by simply stirring at room temperature for 5~15 minutes. Alternatively, a mixture of DMF/4-*t*-BuPy (3/1 v/v) allowed for the preparation of ca. 1.0 M solutions of $NiCl_2$ (2~33%)/$CrCl_2$ (98~67%). In both solvent systems, a suspention of solid $NiCl_2$ was observed. The exact role 4-*t*-BuPy plays in inhibiting homo-coupling is not clear but may be related to the selective solublization of chromium ion over nickel ion.[9]

Scheme 1



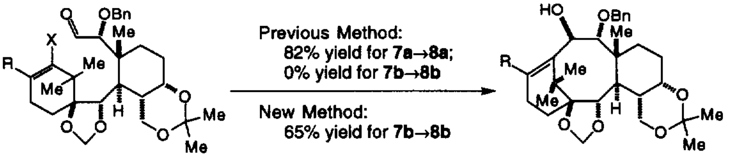
To further investigate the nature of the 4-*t*-BuPy effect, a series of coupling reactions of hydrocinnimaldehyde (**4**) with *trans*-1-iodo-1-dodecene (**5**) in the presence of $NiCl_2$ (2%)/$CrCl_2$ (98%) were performed with varying amounts of 4-*t*-BuPy relative to $CrCl_2$ (Scheme 2).[10] The coupling was complete in approximately 4 hours when 2 and 3 equivalents of 4-*t*-BuPy against $CrCl_2$ were added, whereas in approximately 12 hours when 1 equivalent of 4-*t*-BuPy was added or in approximately 13 hours when 4 and 5 equivalents of 4-*t*-BuPy were added. In all cases, no homo-coupling of the vinyl iodide was observed. Interestingly, the optimum ratio of 4-*t*-BuPy to $CrCl_2$ in terms of reaction rate was 2~3:1 even though homogeneity was not obtained until the fourth equivalent of 4-*t*-BuPy was added.

Scheme 2



An example from our efforts towards the taxane class of natural products[11,12] further illustrates the power of the new method. The Ni(II)/Cr(II)-mediated cyclization was demonstrated to be remarkably effective for the transformation of **7a** to **8a**. While all attempted cyclizations of the tetrasubstituted vinyl iodide aldehyde **7b** under the previous conditions failed,[13] the cyclization of **7b** to **8b** was realized surprisingly smoothly under the new conditions ($NiCl_2$ (10%)/$CrCl_2$ (90%)/THF-DMF-4-*t*-BuPy (6:3:1)/r.t.). Obviously, there are two distinct steps involved in this transformation, i.e., activation of the C-I bond and carbon-carbon bond formation. Under the previous conditions, no activation of the C-I bond was observed. However, under the new conditions, fast activation of the C-I bond (<24 h at r.t.) was observed, which was followed by slow cyclization (3~4 days at r.t.) to yield the desired product **8b**. It is worth noting that activation/cyclization of the corresponding vinyl triflate was as facile as that of the vinyl iodide.

Scheme 3

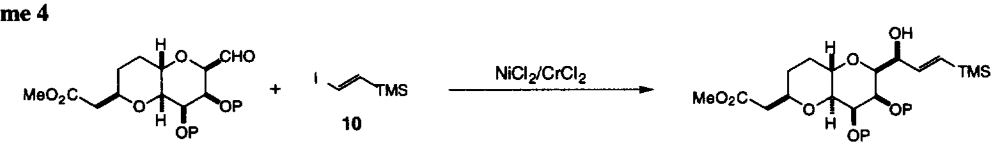


7a : R=H, X=I
7b : R=Me, X=I or OTf

8a : R=H
8b : R=Me

Early in its development, the Ni(II)/Cr(II)-mediated coupling of highly oxygenated substrates, except polysilyl-protected, often suffered from poor mass recoveries.[2] This phenomenon was also observed for the case of **9**+**10**→**11** (Scheme 4).[3] Under standard workup conditions, i.e., aq. NH_4Cl quench followed by ethyl acetate extraction (Method A), coupling product **11** (P, P = cyclohexylidene) was isolated only in 45% yield. However, using a more potent metal sequestering agent in the workup such as aqueous ethylenediamine, followed by partitioning between ethyl acetate and aqueous HCl (Method B), the isolated yield of **11** improved to 75%.

Scheme 4



9

10

11

P = TBS; 85% yield by workup Method A
P, P = cyclohexylidene; 45% yield by workup Method A
P, P = cyclohexylidene; 75% yield by workup Method B

For more delicate substrates, e.g. the acid-labile **3** (Scheme 1), a milder workup method was desired. Replacement of aqueous ethylenediamine for an aqueous solution of sodium or potassium *d,l*-serinate was found to be exceptionally effective for sequestering chromium ion.[14] Presumably, the primary amino and hydroxyl groups of serine are involved in chelation with chromium ion, while the presence of the carboxylate salt renders this complex water soluble leading to easy extractive separation. In this way, the yield of **3** was improved from 50% to 78%.

In conclusion, 4-*t*-BuPy has been shown to be a beneficial additive in the Ni(II)/Cr(II)-mediated coupling reaction leading to homogeneity, more consistent reactivity, and inhibition of homo-coupling. The use of sodium or potassium serinate in the workup allows for an improved mass recovery under mildly basic conditions. These two modifications improve the practicality of the Ni(II)/Cr(II)-mediated coupling reaction.

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2. For some representative examples, see: Kishi, Y. *Pure and Appl. Chem.* **1989**, *61*, 313-324 and references cited therein.

3. For more recent synthetic efforts on halichondrins from this laboratory, see: (a) Stamos, D. P.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8643-8646; Stamos, D. P.; Taylor, A. G.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8647-8650 and references cited therein. (b) Stamos, D. P., Harvard Dissertation, February, 1997.

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5. For a new synthetic route to the C.14-C.38 segment of halichondrin through this type of intermediates, see the reference 3b.

6. The vinyl iodide **2** was used as a 3:2 mixture of *E*- and *Z*-unsaturated esters. In the corresponding methyl ester series, both *E*- and *Z*-unsaturated esters were shown to give the same stereoselectivity in the Ni(II)/Cr(II)-mediated coupling.

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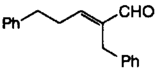
8. Under the original Ni(II)/Cr(II)-mediated coupling condition, it is necessary to keep the Ni(II)-content in Cr(II) low to avoid homo-coupling of vinyl halides or triflates.[1,2]

9. Using 4-*t*-BuPy alone does not provide a homogeneous solution of $CrCl_2$.

10. This coupling was done by dissolving **4** and **5** in THF, followed by addition of 4-*t*-BuPy and then a pre-mixed mixture of $NiCl_2$ (2%)/$CrCl_2$ (98%) in one portion, and being stirred in the drybox at room temperature. The aldol/dehydration product **i** was the only detectable by-product. This by-product was formed only when chromium ion was present, implying that the Lewis acidic nature of chromium ion was necessary to promote enolization. Interestingly, formation of **i** was most prevalent with lower amounts of 4-*t*-BuPy.



i

11. For synthetic work from this laboratory, see: Kress, M. H.; Kishi, Y. *Tetrahedron Lett.* **1995**, *36*, 4583-4584 and references cited therein.

12. For completed total syntheses of taxol, see: (a) Holton, R. A.; Kim, H-B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994,** *116*, 1599-1600 and references cited therein. (b) Nicolaou, K. C.; Ueno, H.; Liu, J-J.; Nantermet, P. G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *J. Am. Chem. Soc.* **1995**, *117*, 653-659 and references cited therein. (c) Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843-2859 and references cited therein. (d) Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T.E.; Houze, J. B.; Krauss, N. E.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Natchus, M. G.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E. *J. Am. Chem. Soc.* **1997**, *119*, 2757-2758 and references cited therein. For a total synthesis of (±)-taxusin, see: Hara, R.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **1996**, *118*, 9186-9187.

13. Kress, M. H., Harvard Dissertation, January, 1995.

14. In a typical workup, the crude reaction mixture is diluted with a 1/1 (v/v) mixture of hexanes and ethyl acetate, treated with a 1.0 M solution of sodium or potassium serinate (pH adjusted around 8 by mixing aq. sodium or potassium bicarbonate and *d,l*-serine), and vigorously stirred for 15~20 minutes. Separation and washing of the aqueous phase once more with hexanes/ethyl acetate provides a clear organic phase and a deep purple aqueous phase. In the case that 4-*t*-BuPy is used as an additive, the combined organic phases are then washed with 3.5 M $NaHSO_4$ (aq.) to remove 4-*t*-BuPy.

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