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Investigations of the Intramolecular Ni(II)/Cr(II)-Mediated Coupling Reaction: Application to the Taxane Ring System

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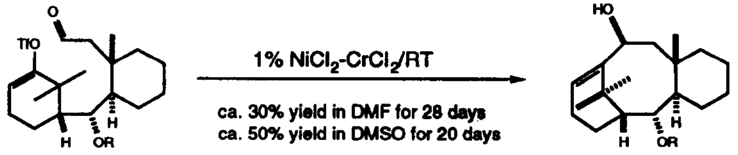
Abstract: The intramolecular Ni(II)/Cr(II)-mediated coupling reaction of activated olefins with aldehydes is studied in order to identify an ideal arrangement of functionality for construction of the taxane ring system.

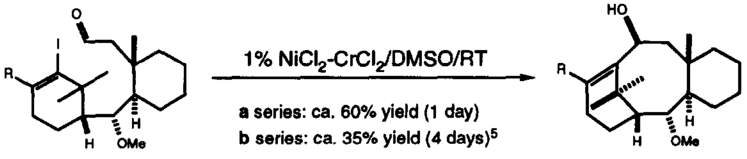
In the preceding paper,[1] we reported a convergent synthetic route to the taxane ring system. During these investigations we had the opportunity to apply the key coupling reaction to a variety of appropriately functionalized substrates. In this communication, we disclose the versatility of this reaction, and some limitations, for construction of the taxane ring system.

In our first model study, we examined the vinyl triflate aldehyde **1**.[2] Treatment of **1** with 1% Ni(II)/Cr(II)-reagent[3] either in DMF or DMSO yielded the desired cylization product **2** as a single diastereomer.[4] However, the rate of the cyclization was exceedingly slow, e.g. the tricyclic compound **2** was isolated in a modest 30% yield after 28 days at room temperature in DMF or in approximately 50% after 20 days in DMSO. The remaining materials consisted of a mixture of alkene and the starting vinyl triflate **1**. Encouraged by this result, and in hope of gaining further insight, we decided to examine the scope and limitations of this reaction.



1 : R=$CH_2OCH_2C_6H_5$ **2** : R=$CH_2OCH_2C_6H_5$

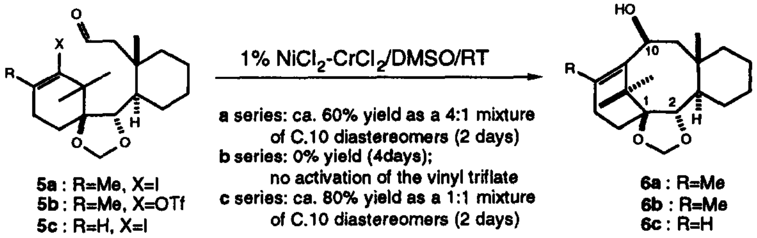
Accordingly, we synthesized the iodoolefins **3a** and **3b** and subjected each to the Ni(II)/Cr(II)-mediated coupling reaction. Under the standard conditions **3a** and **3b**, respectively, afforded **4a** and **4b**, each as a single diastereomer. This set of experiments yielded two important insights. First, the observed rate of product formation for the iodoolefin **3a** was significantly faster than that for the vinyl triflate **1**. Second, the observed rate of product formation for the trisubstituted iodoolefin **3a** was faster than that for the tetrasubstituted iodoolefin **3b**. Furthermore, the crude products obtained from the tetrasubstituted iodoolefin **3b** consisted of the product (ca. 35%), the starting material (ca. 40%), and the reduced olefin (ca. 20%).[5] Whereas the crude products obtained from the trisubstituted iodoolefin **3a** consisted only of the product (ca. 60%) and the reduced olefin (ca. 30%). This observation suggests that the rate determing step of the tetrasubstituted iodoolefin **3b** is the activation of the iodine-carbon bond, whereas the rate determining step of the trisubstituted iodoolefin **3a** is the cyclization of the organometallic intermediate.



3a : R=H
3b : R=Me

4a : R=H
4b : R=Me

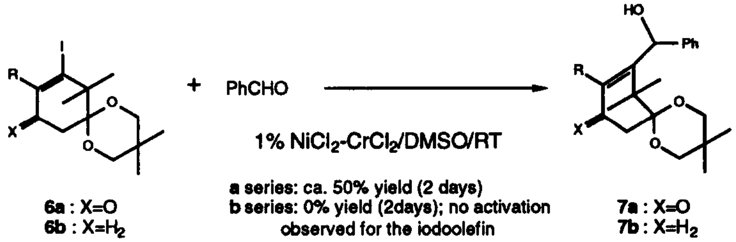
On the basis of geometrical considerations, we envisioned that a cyclic C.1-C.2 diol protecting group would bring the two reactive centers spatially closer, which might affect the rate of cyclization. Thus, three substrates **5a-c** were synthesized and subjected to the Ni(II)/Cr(II)-mediated coupling reaction under the standard conditions. These experiments resulted in several interesting observations. First, the tetrasubstituted iodoolefin **5a** gave **6a** as a 4:1 mixture[6] of the C.10 diastereomers in 60% yield in DMSO, but the corresponding tetrasubstituted vinyl triflate **5b** was recovered unchanged. This supports the conclusion drawn from the first set of experiments, i.e. the activation of iodoolefin to be faster than the corresponding the vinyl triflate. Second, the trisubstituted iodoolefin **5c** gave **6c** as a 1:1 mixture of the C.10 diastereomers in 81% yield. However, the overall rate of reaction for the cyclic acetal **5a** was not significanly improved over the corresponding non-bridged substrate **3b**, which is consistent with the conclusion drawn from the first set of experiments, i.e. the rate determining step of this reaction appears to be the activation of iodine-carbon bond rather than the cyclization of the organometallic intermediate. However, it was intriguing to observe that conformational restriction imposed by the C.1-C.2 methylidene bridge resulted in decreased diastereoselectivity. This may indicate that the C.1-C.2 bridging has affected the transition state geometry of cyclization.



5a : R=Me, X=I
5b : R=Me, X=OTf
5c : R=H, X=I

6a : R=Me
6b : R=Me
6c : R=H

We were also interested in comparing the rate of activation of a β-iodoenone to that of the corresponding iodooloefin. An ideal set of substrates for this purpose might be the tetrasubstituted iodoolefin **5a** and the corresponding tetrasubstituted β-iodoenone. However, because of some technical difficulties in synthesizing a suitable substrate,[7] we addressed this issue by using the reaction of **6a** and **6b** with benzaldehyde. This set of experiments definitively demonstrated the rate of coupling for **6a** to be superior to that of **6b**.

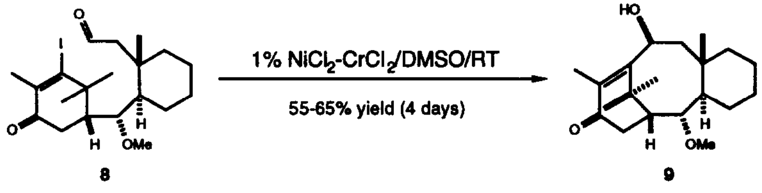

+ PhCHO

1% NiCl$_2$-CrCl$_2$/DMSO/RT

a series: ca. 50% yield (2 days)
b series: 0% yield (2days); no activation observed for the iodoolefin

6a : X=O
6b : X=H$_2$

7a : X=O
7b : X=H$_2$


1% NiCl$_2$-CrCl$_2$/DMSO/RT

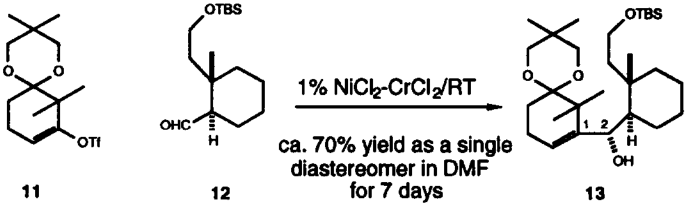
55-65% yield (4 days)

8

9

The results outlined clearly point to an ideal arrangement of functionality for a synthesis of the taxane class of natural products. As reported in the preceding paper,[1] we verified its feasibility by using the model compound **8**. Two observations are worthwhile to note. First, the cyclization of **8** yielded exclusively the desired diastereomer **9**, which is consistent with the conclusion drawn from the cyclizations of **3a** and **3b**. Second, the rate determining step of reaction appears to be the cyclization step rather than the activation of the iodine-carbon bond, as shown by the complete conversion of starting material and the isolation of the enone after quenching the reaction.

Obviously, the the Ni(II)/Cr(II)-mediated coupling can be used for the C.1-C.2 bond formation of the taxane ring system. Indeed, the coupling reaction of the vinyl triflate **11** with the aldehyde **12** gave exclusively the desired product **13** in 71% yield under the standard conditions. We still need to conduct a thorough study on the scope and limitations of this bond-forming process. However, it is intriguing to note that this experiment,


1% NiCl$_2$-CrCl$_2$/RT

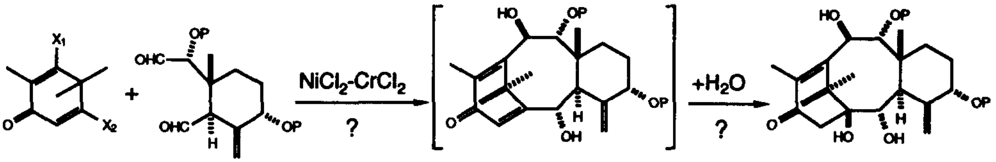
ca. 70% yield as a single diastereomer in DMF for 7 days

11

12

13

combined with the results outlined in this paper, may suggest a possibility to construct the taxane ring system in a one-pot reaction. Namely double Ni(II)/Cr(II)-mediated couplings, followed by hydration on the less hindered C.1-C.14 olefin.



P : a suitable protecting group, but the Ps are not necessarily identical.

Further studies of the intramolecular Ni(II)/Cr(II)-mediated coupling aimed for a synthesis of the taxane class of natural products are in progress in our laboratories.

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References and Footnotes

1. Kress, M. H.; Ruel, R.; Miller, W. H.; Kishi, Y. *Tetrahedron Lett.* **1993**, *34*, 5999-6002.
2. All substrates used in this study were synthesized with necessary modifications of the synthetic sequence disclosed in the preceding paper.
3. Jin, H.; Uenishi, J-i.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644-5646. Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048-6050.
4. The structure of the cyclization products reported in this paper was elucidated by spectroscopic (^{1}H NMR, MS, IR) methods. The C.10 stereochemistry asssignment was based on nOe experiments.
5. The reaction was worked up after 4 days at room temperature, although it appeared still to be progressing.
6. The nOe experiments supported the major product to have the desired stereochemistry at the C.10 position.
7. At the CrO_3 oxidation step, cf. step iv.c. in Scheme 2 in the preceding paper, an eliminative cleavage of the C.1 oxygen was observed.

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