Facile β-OR and β-SR Elimination in the Nickel-Catalyzed Cross-Coupling Reactions of Dithioacetals and Related Compounds with Grignard Reagents

Lung-Lin Shiu,[1a] Chun-Chi Yu, Ken-Tsung Wong,[1b] Bi-Ling Chen,
Wen-Lung Cheng, Tien-Min Yuan, and Tien-Yau Luh*

Department of Chemistry, National Taiwan University, Taipei, Taiwan 106, Republic of China

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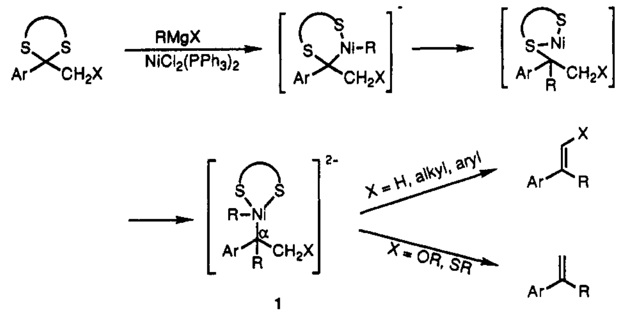
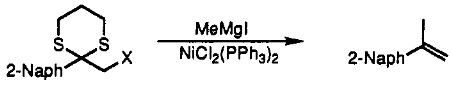
Summary: The $NiCl_2(PPh_3)_2$-catalyzed cross-coupling reactions of Grignard reagents with dithioacetals having a β-OR or β-SR group lead to the regioselective formation of the double bond via a β-heteroatom elimination process. The alkoxy leaving group can also arise from the Grignard reagent. The reaction of benzophenone dithioacetal with the 2-butoxymethyl-substituted cyclopropylmagnesium bromides under the same conditions afforded 1,1-diphenylpenta-1,4-diene derivatives. The extension of this β-heteroatom elimination to the synthesis of conjugated dienes from the corresponding monosaccharide derivative has been executed.

Whereas β-hydride elimination of an organometallic species is facile in transition-metal-catalyzed reactions,[2] elimination of a β-heteroatom has not been well explored.[3–5] Although such β-heteroatom elimination of a main-group organometallic compound is common,[6] the corresponding transition-metal analogues are rare. Most of these reactions are stoichiometric reactions,[4] and forcing conditions (e.g. acid[4a] or heavy-metal catalysts[5a]) are occasionally required. Although a few catalytic processes have been reported,[5] the generality of this process is still limited. We felt that the elimination of a β-OR or a β-SR group of an electron-rich transition organometallic species should occur facilely. Our recent discovery of the nickel-catalyzed olefination of dithioacetals with Grignard reagents may provide a useful model to test this conjecture.[7] The association of the second equivalent of the Grignard reagent with the nickel leading to the anionic intermediate 1 is essential to promote the final β-hydride elimination step (eq 1).[7,8] Accordingly, the α-carbon in 1 is relatively electron rich; when a β-OR or a β-SR group is present in such an anionic intermediate, elimination of this group would result in carbon–carbon double-bond formation (eq 1). We now wish to report facile chemoselective β-OR and β-SR elimination processes under the conditions of the nickel-catalyzed cross-coupling reactions with Grignard reagents.



(1)

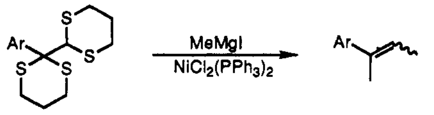
The prototype of such an elimination was observed when dithioacetals 2 and 4 were treated with 4–6 equiv of MeMgI in the presence of $NiCl_2(PPh_3)_2$ (5 mol %) in refluxing benzene–ether to give alkenes 3 and 5, respectively (eqs 2 and 3). Intermediates 6 (*E*/*Z* = 8/92) and 7 (*E*/*Z* = 72/28) were isolated in 6% and 35% yield, respectively, from the partial reaction of 4b with MeMgI at room temperature under similar conditions. Further reaction



(2)

2a X = OMe
b SMe

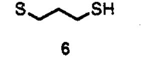
3 75%
73%



(3)

4a Ar=4-MeC_6H_4
b 4-PhC_6H_4
c 2-Naphthyl

5a 81%, E/Z 7/93
b 83%, E/Z 8/92
c 72%, E/Z 10/90



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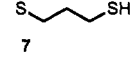

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[1] (a) NSC summer undergraduate research participant, 1991. (b) Recipient of Li-Ching Foundation Scholarship, 1991–1992.

[2] (a) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; Chapter 7. (b) Hegedus, L. S. In *The Chemistry of the Metal-Carbon Bond*; Hartley, F. R., Ed.; Wiley: Chichester, U.K., 1985; Vol. 2, p 401. (c) Henningsen, M.; Jeropoulos, S.; Smith, E. H. *J. Org. Chem.* **1989**, *54*, 3015.

[3] Yamamoto, A. *Organotransition Metal Chemistry*; Wiley: New York, 1986; p 268.

[4] For stoichiometric reactions, see: (a) Rosenblum, M. *Pure Appl. Chem.* **1984**, *56*, 129. (b) Daves, G. D., Jr. *Acc. Chem. Res.* **1990**, *23*, 201. (c) Cohen, H.; Feldman, A.; Ish-Shalom, R.; Meyerstein, D. *J. Am. Chem. Soc.* **1991**, *113*, 5292. (d) Osakada, K.; Matsumoto, K.; Yamamoto, T.; Yamamoto, A. *Organometallics* **1985**, *4*, 857.

[5] For catalytic reactions, see the following. (a) Hg-promoted β-S elimination: Trost, B. M.; Tanigawa, Y. *J. Am. Chem. Soc.* **1979**, *101*, 4745. (b) β-OR elimination: Sen, A.; Lin, M.; Kao, L.-C.; Hutson, A. C. *J. Am. Chem. Soc.* **1992**, *114*, 6385. (c) β-Si elimination: Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1986**, *51*, 5286. (d) β-Sn elimination: Shi, X.; Luh, T.-Y. *Organometallics* **1990**, *9*, 3019.

[6] Cf.: Reeve, W.; Brown, R.; Steckel, T. F. *J. Am. Chem. Soc.* **1971**, *93*, 4607 and references cited therein.

[7] For a review on this coupling reaction, see: Luh, T.-Y. *Acc. Chem. Res.* **1991**, *24*, 257.

[8] Ni, Z.-J.; Mei, N.-W.; Shi, X.; Tzeng, Y.-L.; Wang, M. C.; Luh, T.-Y. *J. Org. Chem.* **1991**, *56*, 4035.

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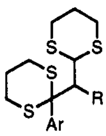
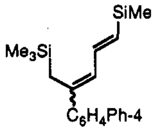
of (*Z*)-**7** under the same conditions afforded (*E*)-**5b** in 99% yield. It is noteworthy that, because of the double-bond formation by β-heteroatom elimination, one of the C–S bonds of the aliphatic dithioacetal moiety in **3** became a vinylic one and was hence "activated" such that a further coupling process[9,10] occurred, leading to **5**. This reaction provided an intriguing procedure to activate in situ the aliphatic carbon–sulfur bond, which is otherwise unreactive under these cross-coupling reaction conditions.

The nickel-catalyzed cross-coupling reactions of allylic dithioacetals are particularly useful for the synthesis of silyl-substituted butadienes[11] and for the introduction of a geminal dimethyl group at the allylic position.[12] Our previous approach of coupling bis(dithioacetal) **8a** with Me_3SiCH_2MgCl in the presence of the nickel catalyst, in the hope of generating the allylic intermediate **11a**, which will further react to give **9**, was partially successful.[13] Because the β-hydride elimination of intermediate **12a** is nonselective, the undesired product **10**, which will not undergo further coupling, was also obtained. However, when **8b** was treated under similar conditions, diene **9** (*E*/*Z* = 25/75) was isolated regioselectively in 64% yield, the methoxy group being eliminated. Similarly, the $NiCl_2$(dppe)-catalyzed reaction[12] of **8b,c** with MeMgI under similar conditions afforded the isopropylstyrenes **13a,b** in 71% (*E*/*Z* = 75/25) and 76% (*E*/*Z* = 80/20) yields, respectively. The preferential elimination of a β-methoxy group in these reactions furnishes a regioselective path, leading to the allylic intermediate **11** exclusively.



8a Ar = 4-PhC_6H_4, R = H
b Ar = 4-PhC_6H_4, R = OMe
c Ar = 2-Naph, R = OMe



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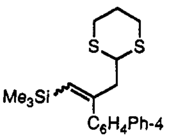

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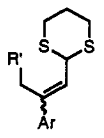
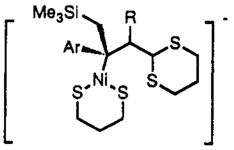
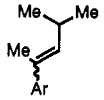


11a Ar = 4-PhC_6H_4, R' = Me_3Si
b Ar = 4-PhC_6H_4, R' = H
c Ar = 2-Naph, R' = H

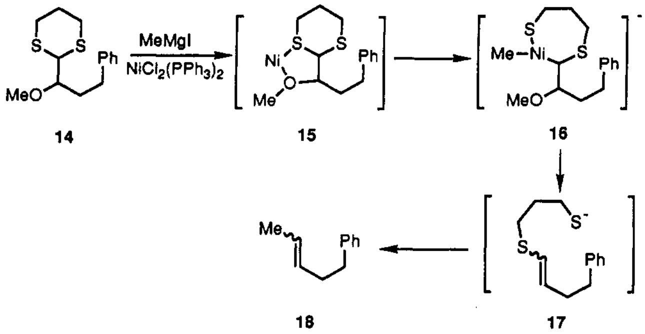


12a R = H
b R = OMe



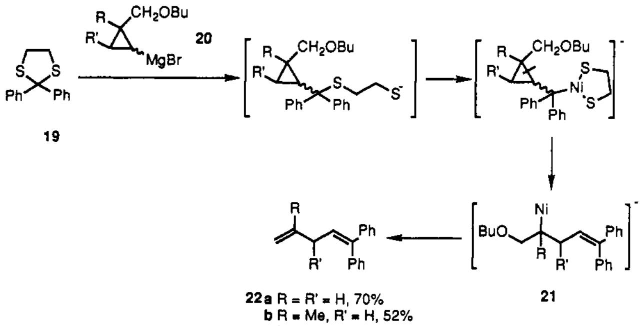
13 a Ar = 4-PhC_6H_4
b Ar = 2-Naph

We recently demonstrated that the aliphatic bis(dithioacetals) can advance the nickel-catalyzed cross-coupling reaction by means of chelation.[14] Accordingly, the presence of a β-methoxy group on the aliphatic dithioacetal moiety (such as in **14**, eq 4) can serve two purposes. First, it can activate the dithioacetal group because the chelation complex **15** might be formed. Second, the organonickel intermediate **16** may undergo elimination of the β-methoxy group to give **17**. Indeed, the reaction of **14** with MeMgI under the nickel-catalyzed coupling conditions afforded alkene **18** in 67% (*E*/*Z* = 72/28) yield.



(4)

The alkoxy leaving group can also arise from the Grignard reagent. Thus, the reaction of **19** with cyclopropyl Grignard reagents **20** under the $NiCl_2(PPh_3)_2$-catalyzed reaction conditions afforded the corresponding nonconjugated pentadienes **22**. A plausible pathway for this transformation is outlined in eq 5.[15a] It is noted that the butoxy group was eliminated from the corresponding intermediates **21**. It is particularly noteworthy that the ring-opening process in these reactions appeared to be regioselective.[15]



(5)

The extension of this β-heteroatom elimination to the synthesis of conjugated dienes from the corresponding monosaccharide derivatives has been executed. Thus, ketene dithioacetal **23** treated with PhMgBr and with *t*-$BuCH_2MgBr$ under the usual conditions afforded diene **24** (41%) and triene **25** (52%), respectively. In addition to the conventional coupling of vinylic carbon–sulfur bonds,[9,10] the allylic carbon–oxygen bond also underwent oxidative addition[16] followed by β-heteroatom elimination and/or a coupling process, leading to the formation of **24** and **25** (eq 6).

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(9) (a) Okamura, H.; Miura, M.; Takei, H. *Tetrahedron Lett.* **1979**, *20*, 43. (b) Wenkert, E.; Ferreira, T. W.; Michelotti, E. L. *J. Chem. Soc., Chem. Commun.* **1979**, 637.

(10) For reviews, see: (a) Luh, T.-Y.; Ni, Z.-J. *Synthesis* **1989**, 89. (b) Naso, F. *Pure Appl. Chem.* **1988**, *60*, 79. (c) Fiandanese, V. *Pure Appl. Chem.* **1990**, *62*, 1987.

(11) (a) Ni, Z.-J.; Luh, T.-Y. *J. Org. Chem.* **1988**, *53*, 5582. (b) Ni, Z.-J.; Yang, P.-F.; Ng, D. K. P.; Tzeng, Y.-L.; Luh, T.-Y. *J. Am. Chem. Soc.* **1990**, *112*, 9356.

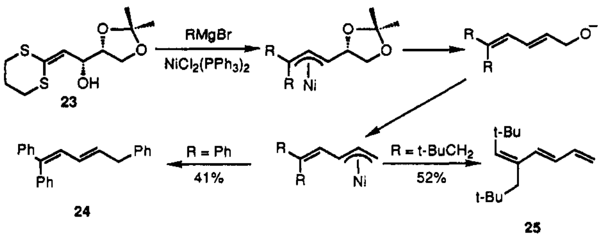
(12) (a) Yang, P.-F.; Ni, Z.-J.; Luh, T.-Y. *J. Org. Chem.* **1989**, *54*, 2261. (b) Tzeng, Y.-L.; Mei, N.-W.; Yang, P.-F.; Yuan, T.-M.; Yu, C. C.; Luh, T.-Y. *J. Org. Chem.* **1991**, *56*, 5289. (c) Yuan, T.-M.; Luh, T.-Y. *J. Org. Chem.* **1992**, *57*, 4550.

(13) Wong, K.-T.; Luh, T.-Y. *J. Chem. Soc., Chem. Commun.* **1992**, 564.

(14) Wong, K.-T.; Luh, T.-Y. *J. Am. Chem. Soc.* **1992**, *114*, 7308.

(15) Cf: (a) Ng, D. K. P.; Luh, T.-Y. *J. Am. Chem. Soc.* **1989**, *111*, 9119. (b) The effect of the nature of the substituent on the regioselectivity of such a rearrangement will be reported shortly: Yu, C. C.; Ng, D. K. P.; Luh, T.-Y. Manuscript in preparation.

(16) For a review, see: Felkin, H.; Swierczewski, G. *Tetrahedron* **1975**, *31*, 2735.



(6)

In summary, we have demonstrated a general reaction of β-heteroatom elimination under the nickel-catalyzed cross-coupling reaction conditions. Substrates having a wide spectrum of structural variety can undergo such a process smoothly. No competitive β-hydride elimination was observed at all in these reactions. Determination of the mechanistic details of such an elimination process, whether it arises directly from the organonickel intermediate or from an organomagnesium species possibly formed by Mg/Ni exchange,[17] and the synthetic applications of this reaction are in progress.

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Supplementary Material Available: Text giving experimental details for the reactions of **2**, **4**, (*Z*)-**7**, **8b**,**c**, **14**, **19**, and **23** with different Grignard reagents (6 pages). Ordering information is given on any current masthead page.

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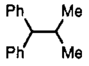
[17] For example, the reaction of **19** with *i*-PrMgBr in the presence of $NiCl_2(PPh_3)_2$ (5 mol %) followed by D_2O workup afforded **26** and **27**.[8]



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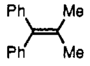

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No deuterium incorporation was found in the reduced product **26**. This result suggested that the concentration of the organomagnesium species formed, if any, by transmetalation of an organonickel species with the Grignard reagent may not be an appreciable amount.