

A Novel Palladium-Catalyzed
Intramolecular Redox Reaction

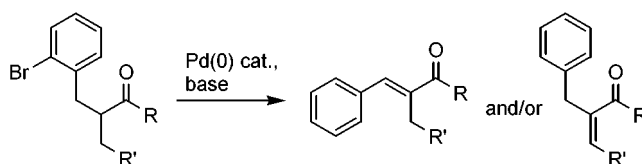
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Received March 8, 2001

ABSTRACT



A new type of palladium-catalyzed redox reaction is described, forming enones from 2-(2-bromobenzyl)-ketones with an overall loss of HBr. The scope and limitations of the reaction are demonstrated by a series of cyclic and acyclic substrates. The mechanism most probably involves the formation of an intramolecular arylpalladium enolate and is related to the oxidation of silyl enol ethers with palladium acetate.

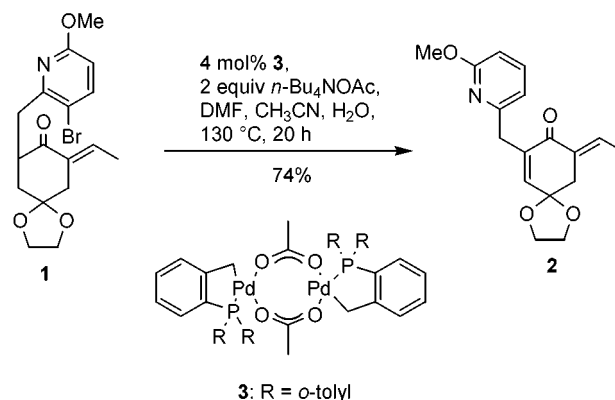
Palladium has found widespread use in modern organic synthesis because of the important carbon–carbon bond forming reactions catalyzed by Pd(0) complexes, as well as the unique oxidative properties of Pd(II) salts.¹ The reaction of a silyl enol ether with palladium acetate developed by Ito² is one of the most convenient methods of forming α,β -unsaturated ketones.³ However, stoichiometric quantities of the reagent are usually required. A catalytic variant of this reaction using Pd(0) and diallylcarbonate via a π -allyl palladium enolate⁴ has not found widespread application.

In the course of our program to develop a new synthetic strategy toward the molecular skeleton of the *Lycopodium* alkaloid huperzine A,⁵ we planned an intramolecular Heck cyclization of aryl bromide **1** as a key step (Scheme 1).

However, the reaction of **1** with a catalytic amount of the Herrmann–Beller palladacycle **3**⁶ resulted in the unexpected formation of dienone **2** as the main product.

To test the generality of this yet unprecedented overall dehydrobromination reaction, we prepared cyclic and acyclic 2-(2-bromobenzyl)-ketones as model compounds. In the course of the following palladium-catalyzed reactions, the conditions were optimized. A catalyst load of 5 mol % proved to give the best yields. Other bases, such as NaOAc or KOAc, and alternative solvent systems (omitting water

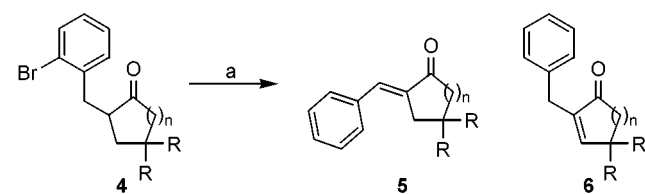
Scheme 1



- (1) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: Chichester, 1995.
- (2) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
- (3) For a review of forming α,β -unsaturated ketones, see: Buckle, D. R.; Pinto, I. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 7, p 119. An efficient method using IBX has recently been developed: Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596.
- (4) (a) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 5635.
- (b) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 5639.
- (c) Minami, I.; Takahashi, K.; Shimizu, I.; Kimura, T.; Tsuji, J. *Tetrahedron* **1986**, *42*, 2971.
- (5) Kozikowski, A. P.; Tückmantel, W. *Acc. Chem. Res.* **1999**, *32*, 641.
- (6) (a) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C.-P.; Priemeier, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844.
- (b) Herrmann, W. A.; Böhm, V. P. W.; Reisinger, C.-P. *J. Organomet. Chem.* **1999**, *576*, 23.

and/or acetonitrile) resulted in less satisfactory results. In addition, the temperature also proved to be critical. To maintain a reflux temperature of at least 130 °C, the proportions of both water and acetonitrile were kept fairly low. The results for the reaction of the cyclopentanone and cyclohexanone derivatives **4a–c** with Pd(0) are summarized in Table 1. Indeed, all substrates gave the corresponding

Table 1. Synthesis of Cyclic Enones^a



| compound | <i>n</i> | R | product(s) (yield) |
|-----------|----------|--------------------------------------|----------------------------------|
| 4a | 1 | H | 6a (72%) |
| 4b | 2 | H | 6b (57%) |
| 4c | 2 | –O(CH ₂) ₂ O– | 5c (23%), 6c (73%) |

^a (a) Reagents and conditions: 5 mol % **3**, 2 equiv of *n*-Bu₄NOAc, DMF/CH₃CN/H₂O = 5/1/1, 130 °C, 16 h

enones, although the reaction of 2-(2-bromobenzyl)-cyclohexanone (**4b**) additionally gave a range of unidentified byproducts. Blocking C4 of the cyclohexanone with a cyclic ketal (**4c**) resulted in better yields of the corresponding enone **6c**. In this particular case, the fully conjugated enone **5c** was also formed to a considerable extent. The position and geometry of the double bond in structures **5** and **6** were unambiguously assigned by NOE experiments.⁷ These results are particularly interesting, as substrates **4a** and **4b** have been reported to give a palladium-catalyzed intramolecular α -arylation using PdCl₂(Ph₃P)₂ and CsCO₃ in THF.⁸

Subjecting the acyclic bromoketone **7** to the same reaction conditions resulted in the formation of the dimeric structures **10** and **11** as inseparable diastereomeric mixtures. We assume that the expected enones **8** and **9** are initially formed but undergo additional palladium-catalyzed reactions with the oxidative addition complex of **7** and a Pd(0) species. In particular, this complex could insert into the highly reactive double bond of enone **8** via a Heck reaction to form **10**, whereas **11** might be formed by an intermolecular α -arylation^{8b} of the fully conjugated enone **9** (Scheme 2). Performing the reaction under high dilution did not avoid the dimerization.

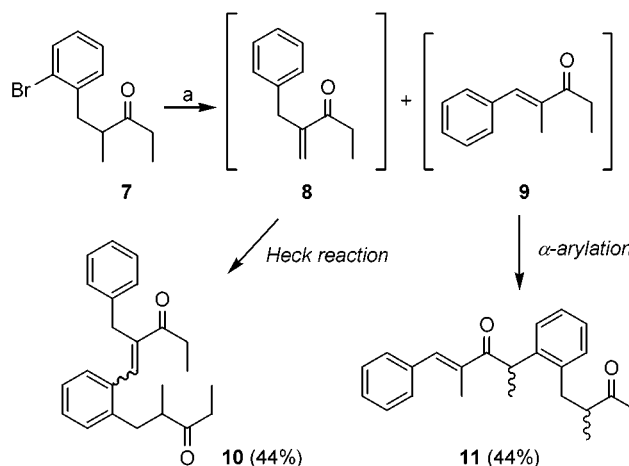
(7) The aromatic *ortho* protons of **5** showed NOE contacts to the olefinic proton and to the endocyclic allylic protons. In **6**, the aromatic *ortho* protons only showed NOE contacts to the benzylic protons, which themselves showed an NOE contact to the olefinic proton.

(8) (a) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, 38, 7581. (b) For comprehensive intermolecular examples, see: Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, 122, 1360.

(9) Triethylammonium formate has been used as a reducing agent for aryl triflates: Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortá, G. *Tetrahedron Lett.* **1986**, 27, 5541.

(10) (a) A similar palladium-catalyzed aryl homocoupling using **3** has recently been published: Hennings, D. D.; Iwama, T.; Rawal, V. H. *Org. Lett.* **1999**, 1, 1205. (b) For other examples, see: de Meijere, A.; Bräse, S. *J. Organomet. Chem.* **1999**, 576, 88.

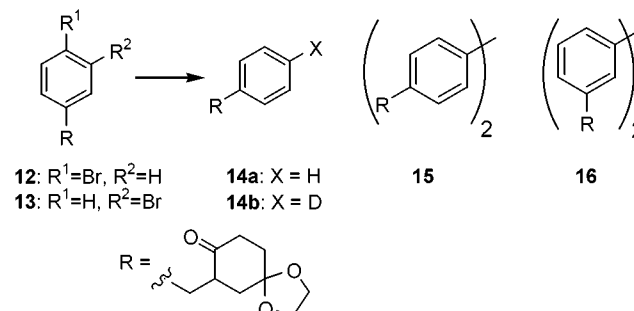
Scheme 2^a



^a (a) Same reaction conditions as in Table 1.

To elucidate the mechanism of the redox reaction, we performed control experiments with 2-(4-bromobenzyl)-ketone **12** and 2-(3-bromobenzyl)-ketone **13** (Table 2). None

Table 2. Control Experiments with 2-(4-bromobenzyl)-ketone **12** and 2-(3-Bromobenzyl)-ketone **13**

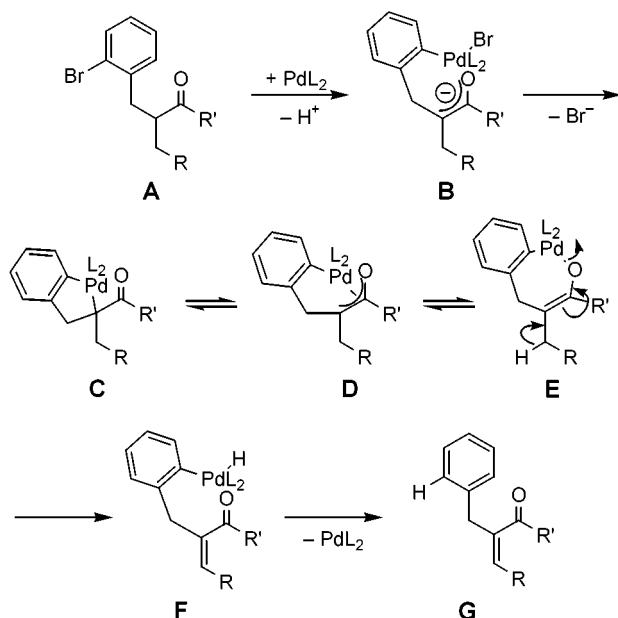


| entry | bromide | method ^a | product(s) (yield) |
|-------|-----------|---------------------|-----------------------------------|
| 1 | 12 | A | 14a (66%), 15 (8%) |
| 2 | 12 | B | 14b (60%) ^b |
| 3 | 13 | A | 14a (55%), 16 (30%) |

^a Method A: 5 mol % **3**, 2 equiv of *n*-Bu₄NOAc, DMF/CH₃CN/H₂O = 5/1/1, 130 °C, 72 h. Method B: 5 mol % **3**, 2 equiv of *n*-Bu₄NOAc, *d*₇-DMF/CH₃CN/H₂O = 5/1/1, 130 °C, 72 h. ^b Only main product isolated.

of these reactions resulted in the formation of the corresponding enones. After extended reaction times (72 h), the dehalogenated aryl ketone **14a** was isolated as the main product in both cases (entries 1 and 3). The nature of the reducing agent became clear when we used deuterated DMF as part of the solvent mixture (entry 2), resulting in the formation of aryl deuteride **14b**. We concluded that DMF is slowly hydrolyzed under the basic, aqueous conditions and the formate thus formed acts as the active hydrogen donor.⁹ The aryl homocoupling products **15** and **16** were also found in both control experiments.¹⁰

Scheme 3



The failure to apply the palladium-catalyzed reaction *intermolecularly* using cyclohexanone and 2 equiv of bromobenzene additionally confirmed the proposed mechanism given in Scheme 3. Thus, the first step would involve an oxidative addition of the aryl bromine of ketone **A** to a Pd(0)

species. Subsequent deprotonation would furnish enolate **B**, which could displace the bromine at palladium in a nucleophilic manner to give an oxo- π -allyl palladium complex.¹¹ This palladium enolate can be formulated using the tautomeric structures **C**, **D**, and **E**. The redox step would then form the palladium-containing enone **F**. Depending on the substitution pattern of the ketone, a benzylic proton can also undergo the elimination. Finally, reductive elimination leads to the enone **G**.

In summary, we have discovered a new type of a palladium-catalyzed redox reaction. Elucidation of the mechanism revealed that the reaction proceeds intramolecularly and forms enones from 2-(2-bromobenzyl)-ketones with an overall loss of HBr. Further studies are underway to apply the reaction in a more general manner.

Acknowledgment. We thank Prof. Dirk Trauner for helpful discussions and the Jubiläumsfonds der Österreichischen Nationalbank for funding.

Supporting Information Available: Experimental procedures and full characterization of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(11) For a similar complex, see ref 2.