A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

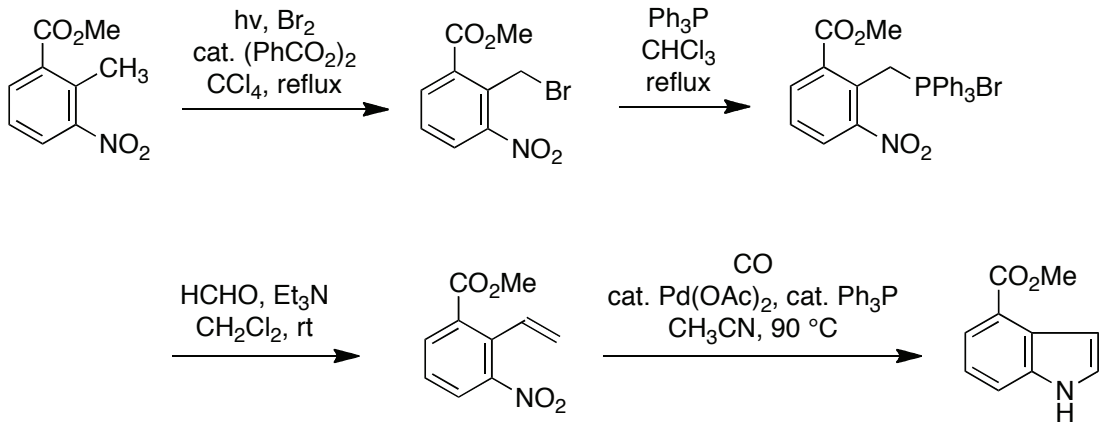
The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Discussion Addendum for:
SYNTHESIS OF INDOLES BY PALLADIUM CATALYZED REDUCTIVE *N*-HETEROANNULATION OF 2-NITROSTYRENES: METHYL INDOLE-4-CARBOXYLATE



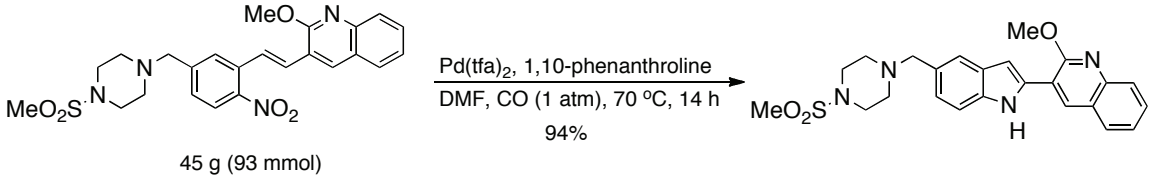
Prepared by Björn C. Söderberg.*[1]
Original article: Söderberg, B.; Shriver, J.; Wallace, J. *Org. Synth.* **2003**, *80*, 75.

Transition metal catalyzed reductive *N*-heterocyclization of 1-(2-nitroaryl)-1-alkenes, using carbon monoxide as the ultimate reducing agent, is emerging as a powerful methodology for the synthesis of a wide variety of functionalized indoles.[2,3,4,5,6,7,8] Palladium complexes have mainly been used as the catalyst of choice but other transition metals including ruthenium ($Ru_3(CO)_{12}$,[8] $RuCl_2(PPh_3)_2$[6]), rhodium ($Rh_6(CO)_{16}$,[8] $RhCl(PPh_3)_3$[6]), iron ($Fe(CO)_5$),[8] nickel ($NiCl_2(PPh_3)_2$),[6] and platinum ($PtCl_2(PPh_3)_2$)[6] also catalyze this transformation. A molybdenum ($MoO_2Cl_2(dmf)_2$) catalyzed reaction in the absence of carbon monoxide has also been described.[9] In addition to transition metals, a catalytic amount of elemental selenium in the presence of carbon monoxide can be used.[10] A direct comparison between all of the different catalysts cannot be made, however in general the palladium diacetate – triphenylphosphine catalyst system usually afford superior yield of product at lower temperature and pressure.

For most substrates, the exclusion of oxygen and water is not required and reagent grade chemicals and solvent can be used with excellent results. The palladium-catalyzed cyclizations are usually free from byproducts derived from the starting material. If observed, byproducts include *N*-

hydroxyindoles, indole dimerization products, and reduction of the nitro-group to an amine. The former impurity can be eliminated or minimized by extending the reaction time or increasing the CO pressure. A potential purification problem is triphenylphosphine and the small amounts of triphenylphosphine oxide formed when using $Pd(OAc)_2$-PPh_3. This can be particularly problematic on a larger reaction scale. Replacing triphenylphosphine with 1,10-phenanthroline or a related bidentate ligand is a convenient solution to this problem although, these ligands are significantly more expensive.

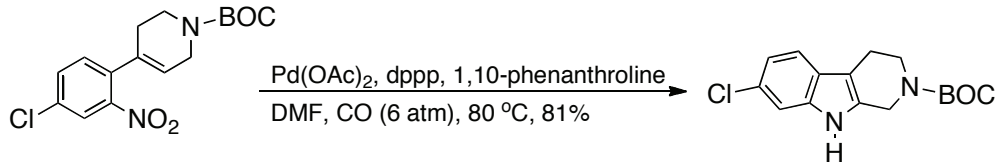
Davies and Smitrovich *et al.* have more recently found, after extensive optimization using a Parallel Pressure Reactor (PPR®), conditions wherein indoles are formed at a low catalyst loading (1 mol% $Pd(OAc)_2$, 2 mol% 1,10-phenanthroline) under 1 atm of CO at 80 °C in DMF (Scheme 1).[11] To our knowledge, this reaction represents the largest scale used to date for this type of cyclization. An even lower catalyst loading was realized for a specific target substrate employing 0.1 mol% of palladium ditrifluoroacetate, 0.7 mol% of 3,4,7,8-tetramethyl-1,10-phenanthroline under the same CO pressure, solvent, and reaction temperature. Rigorous exclusion of oxygen is necessary for reproducibility using the latter conditions.



45 g (93 mmol)

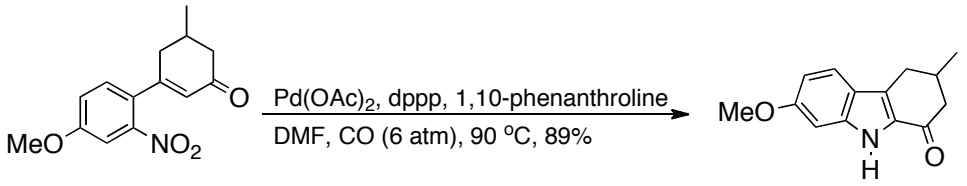
Scheme 1

A wide range of functional groups are compatible with the reaction conditions. Recent applications of the palladium-catalyzed *N*-heterocyclization include the synthesis of tryptophane derivatives,[12] bicyclic pyrrolo-fused heteroaromatic compounds,[13] a synthesis and revision of the structure of fistulosin,[14] koniamborine,[15] tjipanazoles,[16] 1*H*-indole-2-yl-1*H*-quinolin-2-ones,[17] murrayaquinone,[18] bauerine A (Scheme 2),[19] carbazole

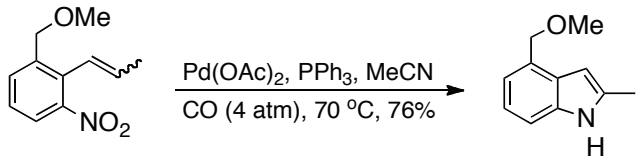


Scheme 2

alkaloids (Scheme 3),[20] and mushroom metabolites (Scheme 4).[21] Enhanced reactivity is observed in some cases when two bidentate ligands, bis(diphenylphosphino)propane and 1,10-phenanthroline, are employed. The reason for this is presently unknown.

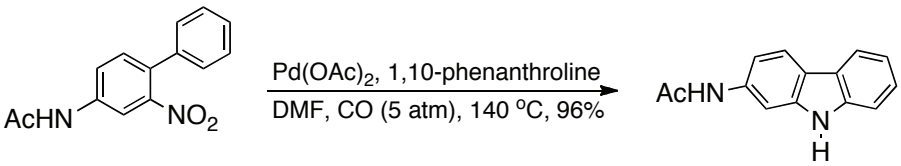


Scheme 3

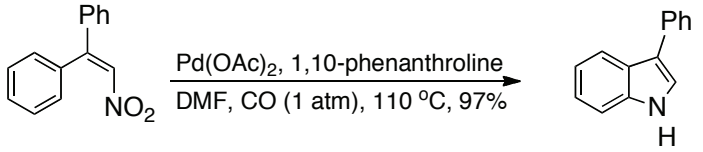


Scheme 4

The reductive *N*-heterocyclization of 1-(2-nitroaryl)-1-alkenes to give indoles is relatively insensitive to the catalyst system used. In contrast, cyclization onto an aromatic ring forming carbazoles and related compounds from 1-aryl-2-nitroaryls is not universal. For example, the $Pd(OAc)_2$-PPh_3 catalyst system and reaction conditions used to prepare methyl indole-4-carboxylate do not affect the cyclization of 2-nitrobiphenyl to give carbazole. $Ru_3(CO)_{12}$,[22] $Fe(CO)_5$,[23] and $MoO_2Cl_2(dmf)_2$[9] have been used to prepare carbazoles and related compounds but to date the best results are obtained using $Pd(OAc)_2$-1,10-phenanthroline in DMF at 140 °C and 5 atm of CO (Scheme 5).[24] 1-(2-Nitroaryl)-1-alkenes can also be cyclized to form 3-arylindoles via a cyclization onto an aromatic ring (Scheme 6).[25]



Scheme 5



Scheme 6

The transition-metal catalyzed reductive *N*-heterocyclization reaction forming indoles is mechanistically related to reductive cyclizations of nitroaryls using trivalent phosphorous compounds, usually triethylphosphite, at elevated temperatures. However, the palladium-catalyzed reaction offers advantages such as lower reaction temperatures, wide functional group compatibility, and few if any byproducts.

1. C. Eugene Bennett Department of Chemistry, West Virginia University, Morgantown, WV 26506.

2. For an excellent review, see: Ragaini, F.; Cenini, Gallo, E.; Caselli, A.; Fantauzzi, S. *Curr. Org. Chem.* **2006**, *10*, 1479-1510.

3. Clawson Jr., R. W.; Deavers III, R. E.; Akhmedov, N. G.; Söderberg, B. C. G. *Tetrahedron* **2006**, *62*, 10829-10834.

4. Söderberg, B. C. G.; Hubbard, J. W.; Rector, S. R.; O'Neil, S. N. *Tetrahedron* **2005**, *61*, 3637-3649.

5. Söderberg, B. C.; Shriver, J. A. *J. Org. Chem.* **1997**, *62*, 5838-5845.

6. Akazome, M.; Kondo, T.; Watanabe, Y. *J. Org. Chem.* **1994**, *59*, 3375-3380.

7. Tollari, S.; Cenini, S, Crotti, C.; Gianella, E. *J. Mol. Catal.* **1994**, *87*, 203-214.

8. Crotti, C.; Cenini, S.; Rindone, B.; Tollari, S.; Demartin, F. *Chem. Commun.* **1986**, 784-786.

9. Sanz, R.; Escribano, J.; Pedrosa, M. R.; Aguado, R.; Arnaiz, F. J. *Adv. Synth. Catal.* **2007**, *349*, 713-718.

10. Nishiyama, Y.; Maema, R.; Ohno, K.; Hirose, M.; Sonoda, N. *Tetrahedron Lett.* **1999**, *40*, 5717-5720.

11. Davies, I. W.; Smitrovich, J. H.; Sidler, R.; Qu, C.; Gresham, V.; Bazaral, C. *Tetrahedron* **2005**, *61*, 6425-6437.

12. Dacko, C. A.; Akhmedov, N. G.; Söderberg, B. C. G. *Tetrahedron Asymm*. **2008**, *19*, 2775-2783.

13. Gorugantula, S. P.; Carrero-Martinez, G. M.; Dantale, S. W.; Söderberg, B. C. G. *Tetrahedron* **2010**, *66*, 1800-1805.

14. Clawson Jr., R. W.; Dacko, C. A.; Deavers III, R. E.; Akhmedov, N. G.; Söderberg, B. C. G. *Tetrahedron* **2009**, *65*, 8786-8793.
15. Clawson Jr., R. W.; Söderberg, B. C. G. *Tetrahedron Lett*. **2007**, *48*, 6019-6021.
16. Kuethe, J. T.; Wong, A.; Davies, I. W. *Org. Lett.* **2003**, *5*, 3721-3723.
17. Kuethe, J. T.; Wong, A.; Qu, C.; Smitrovich, J.; Davies, I. W.; Hughes, D. L. *J. Org. Chem.* **2005**, *70*, 2555-2567.
18. Scott, T. L.; Söderberg, B. C. G. *Tetrahedron* **2003**, *59*, 6323-6332.
19. Dantale, S. W.; Söderberg, B. C. G. *Tetrahedron* **2003**, *59*, 5507-5514.
20. Scott, T. L.; Yu, X.; Gorunatula, S. P.; Carrero-Martínez, G.; Söderberg, B. C. G. *Tetrahedron* **2006**, *62*, 10835-10842.
21. Söderberg, B. C.; Chisnell, A. C.; O'Neil, S. N.; Shriver, J. A. *J. Org. Chem.* **1999**, *64*, 9731-9734.
22. Crotti, C.; Cenini, S.; Bassoli, A.; Rindone, B.; Demartin, *J. Molec. Catal.* **1991**, *70*, 175-187.
23. Kmiecik, J. E. *J. Org. Chem.* **1965**, *30*, 2014-2020.
24. Smithrowich, J. H.; Davies, I. W. *Org. Lett.* **2004**, *6*, 533-535.
25. Hsieh, T. H. H.; Dong, V. M. *Tetrahedron* **2009**, *65*, 3062-3068.

Björn C. G. Söderberg received his M.S. degree in 1981 and his Ph.D. degree in 1987, both from the Royal Institute of Technology, Stockholm, Sweden. He did postdoctoral research at Colorado State University and started his independent career at the University of South Alabama in 1990. In 1994 he joined the faculty at West Virginia University. Professor Söderberg's research is focused on the discovery, development, and application of transition metal catalyzed or mediated reactions. He has developed palladium-catalyzed reductive cyclization reactions of nitro-aromatic compounds to form indoles, quinoxalines, benzimidazoles, and related systems.