J. Org. Chem. **2000,** *65,* 7183−7186

Consequences of Affinity in Heterogeneous Catalytic Reactions: Highly Chemoselective Hydrogenolysis of Iodoarenes

Yves Ambroise,[†] Charles Mioskowski,[†] Gérald Djéga-Mariadassou,[‡] and Bernard Rousseau[*,†]

Service des Molecules Marquées, CEA/Saclay, 91191 Gif sur Yvette, France, and Laboratoire de Réactivité de Surface, Université Pierre et Marie Curie, 4 place Jussieu, 75252 Paris, France

bernard.rousseau@cea.fr

Received August 10, 2000

The catalytic hydrodeiodination reaction using molecular hydrogen and Pd/C has been revisited. It is shown, for the first time, that the chemoselectivity of this reaction is controlled by the high affinity of the iodinated compound for the catalyst. This reaction is compatible with most easily reducible functional groups (nitro, aldehyde, olefin, etc.). Using this reaction, the first general method for tritium labeling of 3-(trifluoromethyl)-3-phenyldiazirine is described.

Introduction

Selectivity in organic chemistry is a major asset during the synthesis of complex molecules, and the development of chemoselective reactions provides a powerful tool for organic chemists. Current chemoselective reactions rely on a simple principle: the selectivity reflects the rate constants for product formation.[1] We report that the selectivity observed in some heterogeneous catalyst transformations is not consistent with this principle.

We revisited the catalytic hydrogenolysis of iodoarenes using hydrogen and Pd/C.[2−5] We determined its chemoselectivity versus a variety of functional groups that are known to be easily reduced (e.g., double bonds). When an iodoaryl compound and an olefin were separately subjected to the reducing conditions, the double bond was transformed faster. When these two groups were reacted together (whether borne by the same molecule or not), the selectivity obtained was unexpected. The less reactive iodoarene was selectively reduced while the more reactive double bond was unaffected. This surprising behavior can be neither explained nor anticipated by the rate constants for product formation and relies only on substrate affinity for the palladium catalyst.

This important result points to new synthetic strategies. We illustrated the utility of this reaction by solving the 3-(trifluoromethyl)-3-phenyldiazirine tritium labeling problem.[6] This template is used for photoaffinity labeling and cross-linking experiments, which are biochemical techniques used to investigate structural and functional properties of biological systems. Tritium incorporation in the 3-(trifluoromethyl)-3-phenyldiazirine template requires the introduction of the radioactive element at an early stage of the synthesis, thus increasing the number of radioactive steps. Under our conditions, we were able to introduce tritium in the final step of the synthesis.

Results and Discussion

Under the following conditions—methanol, 10% Pd/C, triethylamine, 10 equiv, H_2, 1 atm—hydrogenolysis of iodobenzene was complete in 40 min, of bromobenzene in 14 min, and of chlorobenzene in 6 min. Under the same

---

[†] CEA/Saclay.

[‡] Université Pierre et Marie Curie.

(1) (a) Yamakawa, M.; Ito, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 1466−1478. (b) Carreño, M. C.; Ruano, J. L. G.; Urbano, A.; Remor, C. Z.; Arroyo, Y. *J. Org. Chem.* **2000**, *65*, 453−458. (c) Saito, S.; Nakagawa, S.; Koizumi, T.; Hirayama, K.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 3975−3978. (d) Shibata, I.; Moriuchi-Kawagami, T.; Tanizawa, D.; Suwa, T.; Sugiyama, E.; Matsuda, H.; Baba, A. *J. Org. Chem.* **1998**, *63*, 383−385. (e) Yasuda, M.; Hayashi, K.; Katoh, Y.; Shibata, I.; Baba, A. *J. Am. Chem. Soc.* **1998**, *120*, 715−721. (f) Ohkuma, T.; Ooka; H.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 10417−10418. (g)Yanagisawa, A.; Inoue, H.; Morodome, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10356−10357.

(2) Removal of an iodine atom temporarily attached to a molecule in order to modify its reactivity: (a) Ahluwalia, V. K.; Prakash, C.; Gupta, R. *Tetrahedron* **1982**, *38*, 609−611. (b) Ahluwalia, V. K.; Jolly, R. S.; Tehim, A. K. *Tetrahedron* **1982**, *38*, 3673−3677. (c) Kende, A. S.; Ebetino, F. H.; Otha, T. *Tetrahedron Lett.* **1985**, *26*, 3063−3066. (d) Weeratunga, G.; Horne, S.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1988**, 721−722. (e) Nishiyama, S.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1989**, *30*, 379−382. (f) Donnelly, D. M. X.; Molloy, D. J.; Reilly, J. P.; Finet, J. P. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2531−2534. (g) Fukuyama, T.; Liu, G. *J. Am. Chem. Soc.* **1996**, *118*, 7426−7427.

(3) Preparation of monoiodinated compounds from their dihalogenated analogues: (a) Numazawa, M.; Kimura, K.; Ogata, M.; Nagaoka, M. *J. Org. Chem.* **1985**, *50*, 5421−5423. (b) Horne, S.; Weeratunga, G.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1990**, 39−41.

(4) Synthesis of new molecules of biological interest: (a) Li, T.; Zeng, Z.; Estevez, V. A.; Baldenius, K. U.; Nicolaou, K. C. Joyce, G. F. *J. Am. Chem. Soc.* **1994**, *116*, 3709−3715. (b) Ishiwata, H.; Sone, H.; Kigoshi, H.; Yamada, K. *Tetrahedron* **1994**, *50*, 12853−12882.

(5) Tritium and deuterium labeling: (a) Chauvière, G.; Rousseau, B.; Pillon, F.; Périé, J. *J. Labeled Compd. Radiopharm.* **1998**, *41*, 47−51. (b) Darula, Z.; Peter, A.; Toth, G. *J. Labeled Compd. Radiopharm.* **1997**, *39*, 817−826. (c) Kalindjian, S. B.; Harper, E. A.; Pether, M. J. *Bioorg. Med. Chem. Lett.* **1996**, *6*(10), 1171−1174. (d) Alcaraz, M. L.; Peng, L.; Klotz, P.; Goeldner, M. *J. Org. Chem.* **1996**, *61*, 192−201. (e) Seltzman, H. H.; Carroll, F. I.; Burgess, J. P.; Wyrick, D.; Burch, D. F. *J. Chem. Soc., Chem. Commun.* **1995**, 1549−1550. (f) Latli, B.; Casida, J. E. *J. Labeled Compd. Radiopharm.* **1995**, *36*, 147−156. (g) Fukazawa, Y.; Usui, S.; Tanimoto, K.; Hirai, Y. *J. Am. Chem. Soc.* **1994**, *116*, 8169−8175. (h) Vader, J.; Kaspersen, F.; Sperling, E.; Schlachter, I.; Terpstra, A. *J. Labeled Compd. Radiopharm.* **1994**, *34*, 845−870. (i) Yamamoto, M.; Dolle, V.; Warnock, W.; Diyizou, Y.; Yamada, M.; Nakatani, Y.; Ourisson, G. *Bull. Soc. Chim. Fr.* **1994**, *131*, 317−329.

(6) (a) Hori, N.; Iwai, S.; Inoue, H.; Ohtsuka, E. *J. Biol. Chem.* **1992**, *267*, 15591−15594. (b) Brunner, J. *Annu. Rev. Biochem.* **1993**, *62*, 483−514. (c) Delfino, J. M.; Schreiber, S. L.; Richards, F. M. *J. Am. Chem. Soc.* **1993**, *115*, 3458−3474. (d) Kotzyba-Hibert, F.; Kapfer, I.; Goeldner, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1296−1312. (e) Hesterkamp, T.; Hauser, S.; Luetcke, H.; Bukau, B. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 4437−4441. (f) Grassi, D.; Lippuner, V.; Aebi, M.; Brunner, J.; Vasella, A. *J. Am. Chem. Soc.* **1997**, *119*, 10992−10999. (g) Hatanaka, Y.; Hashimoto, M.; Kanaoka, Y. *J Am. Chem. Soc.* **1998**, *120*, 453−454. (h) Weber, T.; Brunner, J. *J. Am. Chem. Soc.* **1995**, *117*, 3084−3095.

10.1021/jo0012243 CCC: $19.00

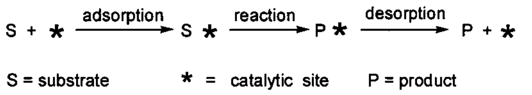


Figure 1. Schematic overview of the different steps in a surface reaction.

conditions, *trans*-1-phenylstyrene was completely reduced in 3 min. These results suggest that selective hydrogenolysis of a carbon−halogen bond in the presence of a double bond is unlikely. To solve this problem, we focused our attention on the mechanism of this catalytic hydrogenation. The substrate is first adsorbed on the palladium surface (Figure 1).[7] Then, the adsorbed substrate reacts with the adsorbed hydrogen to give the product, which is subsequently released from the catalyst surface.

To modify the selectivity of the hydrogenation reaction, we focused on the adsorption step rather than on the reaction step. If two substrates S1 and S2 are competitively reduced, the selectivity could result from the preferential adsorption of S1 or S2 on the catalyst surface. If the affinity of S1 for the catalyst is sufficiently greater than that of S2, then S1 will predominantly cover the catalyst and prevent the adsorption of S2. In this case, hydrogenation of S1 will preferentially occur. Recently, Tundo et al. showed that iodobenzene has a greater affinity for Pd/C than bromo- and chlorobenzene.[8] We imagined that this property could be advantageous in obtaining high selectivities. This hypothesis was tested using the iodobenzene and *trans*-1-phenylpropene templates (Figure 2).

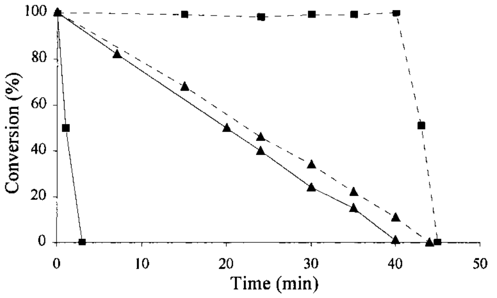
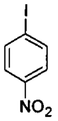
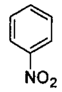
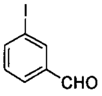
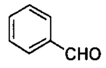
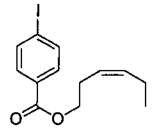
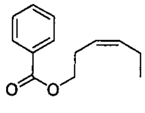


Figure 2. Hydrogenation of PhI and *trans*-1-phenyl-1-propene with hydrogen and Pd/C catalyst. Full line noncompetitive reactions of *trans*-1-phenyl-1-propene (■) and PhI (■). Dotted line: competitive reactions between *trans*-1-phenyl-1-propene (■) and PhI (▲).

We first verified that the stirring speed was sufficiently high (1400 rpm) to ensure that the reduction occurred under kinetic conditions. *trans*-1-Phenyl-1-propene and iodobenzene were hydrogenated separately under the reaction conditions mentioned above. The double bond reduction was complete within 3 min, and iodobenzene was converted into benzene within 40 min (full line ■ and ▲, respectively). When these two substrates were reacted competitively, the reduction of *trans*-1-phenyl-1-propene was delayed and iodobenzene reacted first (dotted line ▲). The reduction of the olefin only occurred when the iodo compound had completely disappeared from the reaction mixture (dotted line ■). The same competitive reaction was carried out with bromobenzene versus *trans*-1-phenyl-1-propene. In this case, no selectivity was observed. The olefin reduction and the bromobenzene hydrogenolysis took place simultaneously. These experiments showed that the iodobenzene delayed the double-bond reduction. As a matter of fact, if the iodobenzene is highly adsorbed on the catalyst surface, its reduction kinetics will not depend on its concentration in solution but rather on its concentration on the palladium surface. The number of catalytic sites being constant, the transformation rate of iodobenzene would also be constant throughout the reaction. The graphical representation of its time-dependent conversion would then be a straight line, and this is indeed what is seen in Figure 2. These experiments show that the selectivity can be explained by a marked adsorption of the aryl iodide on the catalyst. The catalytic sites would then be totally occupied, thereby preventing access by the olefin and hence explaining the selectivity.

Deiodination of Bifunctional Compounds. In the previous experiments, the competitive hydrogenation was carried out on two different molecules. We tried to determine whether the same selectivity could be obtained when both an aryl iodide and an easily reducible function are borne by the same molecule (Table 1).

Table 1. Hydrodeiodination of Bifunctional Compounds[a]

Entry	Time of reduction (min)	Substrate	Product	Yield (%)
1	600			>97
2	60			>97
3	240			>97

[a] Same conditions as described in the text.

The chemoselectivity that we previously noted was confirmed. The hydrogenolysis of the carbon−iodine bond occurred before the reduction of nitro (entry 1) or aldehyde (entry 2) groups. The selectivity again was excellent for the double bond (entry 3), and to the best of our knowledge this is the first report of the selective hydrogenolysis of a carbon−iodine bond in the presence of a double bond. These experiments show that the selectivity observed with iodobenzene can be generalized to other substrates.

General Method for the Labeling of the 3-(Trifluoromethyl)-3-phenyldiazirine Group. We took advantage of this efficient hydrogenolysis method by solving the 3-(trifluoromethyl)-3-phenyldiazirine tritium labeling problem. This template is known to be easily

---

[7] (a) Boudart, M.; Djéga-Mariadassou, G. *Kinetics of Heterogeneous Catalytic Reactions*; Princeton University Press: Princeton, 1984; pp 38−76. (b) Norskov, J. K.; Stoltze, P. In *Handbook of Heterogeneous Catalysis*; Ertl, G., Knözinger, H., Weitkamp, J., Eds.; VCH: Weinheim, Germany, 1997; Vol. 3, pp 984−991.

[8] Marques, C. A.; Selva, M.; Tundo, P. *J. Org. Chem.* **1993**, *58*, 5256−5260.

reduced by molecular hydrogen and Pd.[9] Consequently, when one designs a photoactivatable probe containing a tritium nucleus as well as a diazirine group, the radioelement needs to be introduced early in the synthesis. This implies several radioactive steps.[10] For example, six radioactive steps were required to label the photoactivatable membrane-spanning phospholipid probe recently introduced by Schreiber and Richards.[6c] This multistep synthesis considerably increases costs, experimental difficulties, and radioactive waste. Furthermore, the lack of an efficient tritium-labeling method for 3-(trifluoromethyl)-3-phenyldiazirine is a major drawback for the use of this photolabeling reagent.

We synthesized compound **1a**, which contains the photoactivatable group and a carbon–iodine bond (Figure 3). Compounds **1a** and **1b** were easily synthesized by means of reported procedures.[6h] For convenience, all tests were first carried out with hydrogen rather than tritium.

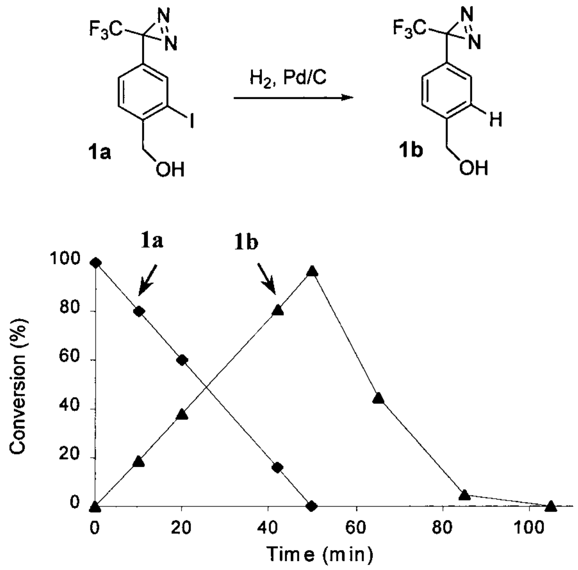
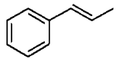
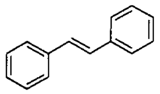
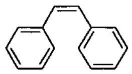
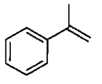
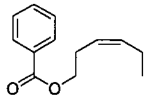
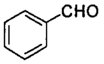
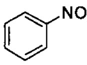
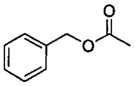
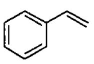
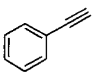
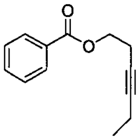


Figure 3. Hydrogenolysis kinetics of **1a**.

For the first 50 min of the reaction, the disappearance of the iodinated compound **1a** (◆) was accompanied by the concomitant appearance of **1b** (▲) in over 97% yield. As expected, the diazirine reduction only began once **1a** had completely disappeared from the reaction medium (after 50 min). This behavior can be explained by a selective adsorption of **1a** on the catalyst via its carbon–iodo bond, as demonstrated above.

We determined the scope and limitations of the deiodination of the photoactivatable probe by studying the competitive hydrogenation of an equimolecular mixture of **1a** and an easily reducible substrate. The method's selectivity was evaluated by HPLC to quantify easily reducible substrate remaining when **1a** was converted into **1b** with the best yield. The compounds used and the results obtained are indicated in Table 2.

Table 2. Chemoselective Hydrogenolysis of Iodinated Compound 1a in the Presence of an Easily Reducible Substrate[a]

Entry	Easily Reducible substrate	Time (min)	Conversion of **1a**^{b} (%)	Yield of **1b**^{b} (%)	Amount of substrate remaining^b (%)
1		50	>99	>97	>97
2		60	>99	>97	>97
3		50	>99	>97	>97
4		30	>99	>97	>95
5		30	95	92	95
6		60	>99	>97	>97
7		40	>99	>97	>97
8		30	>99	>97	>97
9		30	75	73	55
10		10	0	0	0 (95% of styrene)
11		10	55	55	0 (90% of olefin)

[a] The reaction was carried out as described in the text. [b] Determined by HPLC: column Zorbax ODS, mobile phase: H_2O/CH_3CN 1/1, UV detection at 220.

The selectivity was excellent for disubstituted conjugated double bonds of *E* (entries 1 and 2) or *Z* (entry 3) stereochemistry and for methylene double bonds (entry 4). Nonconjugated double bonds (entry 5), aldehyde (entry 6), and nitro (entry 7) were left unchanged. The protective *O*-benzyl group is also very stable under these conditions (entry 8). A weaker selectivity was, however, observed for the monosubstituted double bonds (entry 9). The reduction of the monosubstituted triple bonds to double bonds was faster than the hydrogenolysis of the carbon–iodine bond (entry 10). The same was true for the disubstituted triple bonds but with a lower selectivity (entry 11). All these reactions were carried out under simple and fast (<1 h) conditions. When carrying out the reaction with tritium, [^{3}H]-**1b** was obtained with an isotopic purity higher than 95% (determined by mass

---

[9] Schmitz, E.; Ohme, R. *Chem. Ber.* **1961**, *94*, 2166–2173.

[10] (a) Brunner, J.; Spiess, M.; Aggeler, R.; Huber, P.; Semenza, G. *Biochemistry* **1983**, *22*, 3812–3820. (b) Harter, C.; Bächi, T.; Semenza, G.; Brunner, J. *Biochemistry* **1988**, *27*, 1856–1864. (c) Nakayama, T.; Khorana, H. G. *J. Org. Chem.* **1990**, *55*, 4953–4956. (d) Taki, M.; Kuniyasu, A.; Nakayama, H.; Kanaoka, Y. *Chem. Pharm. Bull.* **1991**, *39*, 1860–1862. (e) Resek, J. F.; Bhattacharya, S.; Khorana, H. G. *J. Org. Chem.* **1993**, *58*, 8, 7598–7601. (f) Latli, B.; Morimoto, H.; Williams, P. G.; Casida, J. E. *J. Labeled Compd. Radiopharm.* **1998**, *41*, 191–199.

spectroscopy). ^{3}H NMR of [^{3}H]-**1b** gave a unique singlet in the aromatic region, thus showing that tritium did not exchange under our catalytic conditions. A detailed description of the synthesis and characterization of [^{3}H]-**1b**, and as well as of two other photoactivatable probes, will be reported in due course.

Concluding Remarks

We have shown that the rate constants for product formation neither explain nor allow anticipation of the chemoselectivity that occurs during a catalytic deiodination using H_2 and Pd/C. We have demonstrated, for the first time, that the selectivity of this reaction is controlled by the substrate's affinity for the catalyst. As an application, we developed the first general method for tritium labeling of the 3-(trifluoromethyl)-3-phenyldiazirine photoactivatable template in the final step. Beyond the radiolabeling of fragile molecules, we think that this principle is general, will lead to new chemoselective reactions, and will find wide application in the areas of synthetic organic, mechanistic organic, organometallic, and catalysis chemistry.

Experimental Procedures

The palladium on carbon (10% w/w) used in the experiments was from Aldrich and was used without any treatment.

Typical Experiment: Hydrogenation of 1a (See Figure 3). [2-Iodo-4-(3-trifluoromethyl-3*H*-diazirin-3-yl)phenyl]methanol **1a** (25.6 mg, 1 equiv) was dissolved in MeOH (3 mL) and triethylamine (105 μL, 10 equiv). Pd/C (7.95 mg, 0.1 equiv) was added, and the reaction mixture was vigorously stirred at 20 °C under 1 atm of hydrogen. During the reaction, the pressure of H_2 was maintained constant by a continuous supply of H_2 (checked with an accurate manometer). Aliquots (80 μL) were sampled at 0, 10, 20, 40, 50, 65, 85, and 105 min, filtered, and analyzed by HPLC (H_2O/MeCN = 1/1, 1 mL/min, UV detection at 220 nm). The rates of conversion of **1a** and production of **1b** were derived from the respective areas by correlation with standard curves.

This typical procedure was applied for all the hydrogenations described in this paper, including hydrogenation of PhI versus *trans*-1-phenyl-1-propene (Figure 2), deiodination of bifunctional compounds (Table 1), and competitive hydrogenations versus **1a** (Table 2).

Acknowledgment. We warmly thank Dr. Eric Doris for helpful discussions. We also thank Ms. Florence Pillon and Mr. Alain Valleix for running important control experiments and Dr. L. Pichat for critical reading of this paper.

Supporting Information Available: Experimental procedures, characterization data, and ^{1}H and ^{13}C spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0012243