DOI: 10.1002/ejoc.201100017

Chemoselective Reduction of Isatin-Derived Electron-Deficient Alkenes Using Alkylphosphanes as Reduction Reagents

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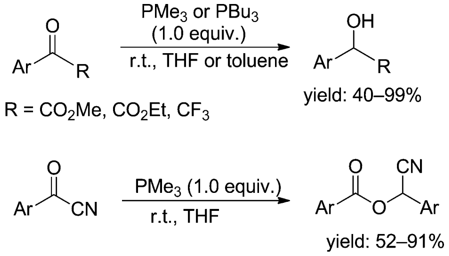
Keywords: Reduction / Alkenes / Chemoselectivity / Phosphanes

Under mild reaction conditions, the C=C double bond in isatin-derived electron-deficient alkenes has been exclusively reduced in the presence of alkylphosphanes and water to afford the corresponding reduction products in good to excellent yields. A plausible mechanism is proposed on the basis of deuterium-labeling experiments.

Introduction

Organophosphorus compounds have proven to be particularly versatile as catalysts or reagents in many types of organic reactions, and phosphanes in particular have been widely used as nucleophilic organocatalysts in recent decades.[1] One interesting organocatalytic reaction is the hydration and hydroalkoxylation of activated olefins catalyzed by nucleophilic phosphanes.[2] However, the use of phosphanes as reducing agents accompanied by a proton transfer is rare. To the best of our knowledge, the Staudinger reaction is the first report of the reduction of azides to amines promoted by PPh_3/H_2O.[3] In 2006, our group reported an interesting reduction of activated carbonyl groups promoted by alkylphosphanes, which is a convenient method for producing the corresponding α-hydroxylated derivatives (Scheme 1).[4] Subsequently, the scope of this reduction process was extended to other compounds including activated carbonyl groups such as 1-aryl-2,2,2-trifluoroethanones,[5] and the reductive coupling of acyl cyanides was also achieved (Scheme 1).[6] On the basis of our previous work, we have attempted to extend the range of substrates used in the reduction reaction promoted by alkylphosphanes. Thus, we investigated the reduction reactions of activated alkenes such as isatin-derived electron-deficient alkenes due to their easy preparation and various applications in the synthesis of natural products, drugs, and related analogues.[7] Herein, we report an interesting, highly chemoselective reduction reaction of isatin-derived electron-deficient alkenes promoted by alkylphosphanes.



Scheme 1. Reduction reactions promoted by alkylphosphanes.

Results and Discussion

An initial examination was carried out by treating (*E*)-1-benzyl-3-(2-oxopropylidene)indolin-2-one (**1a**) with PBu_3 in toluene at 80 °C. We observed that the C=C double bond was exclusively reduced to afford the corresponding reduction product 1-benzyl-3-(2-oxopropyl)indolin-2-one (**2a**) in only 18% yield (Table 1, Entry 1). We assumed that an additional proton source should be added to improve the yield of the desired product. Thus, water was chosen as an additive, which indeed increased the yield of **2a** to >99% (Table 1, Entry 2). Decreasing the amount of phosphane reduced the yield of the desired product (Table 1, Entries 3 and 4). Lowering the reaction temperature to room temperature and increasing the amount of PBu_3 to 1.2 equiv. still produced the corresponding product **2a** in good yield (86%, Table 1, Entry 5). With PMe_3 as promoter, this reduction reaction also proceeded smoothly to give the corresponding product **2a** in 86% yield (Table 1, Entry 6). We also investigated this reaction in tetrahydrofuran (THF) with PBu_3 and PMe_3 as promoters, because THF was a good solvent in our previous studies. It turned out that we could obtain the corresponding product **2a** almost quantitatively when PMe_3 was used as promoter in the presence of THF and water (Table 1, Entry 7). With PMe_3 as promoter, we screened other solvents (Table 1, Entries 9–11), which demonstrated that THF was the best solvent. This reduction reaction also proceeded smoothly by using other

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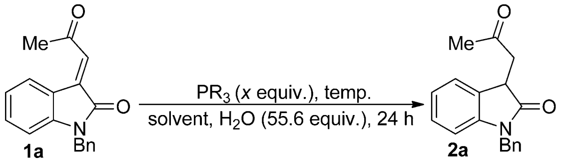
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201100017.

phosphanes with at least one alkyl substituent, such as $PPhMe_2$ or PPh_2Me, to afford the corresponding product **2a** in moderate to good yields (Table 1, Entries 12 and 13). However, a sterically hindered alkylphosphane such as $P\textit{t}Bu_3$ and the aromatic phosphane PPh_3 did not promote this reaction under the same reaction conditions (Table 1, Entries 14 and 15).

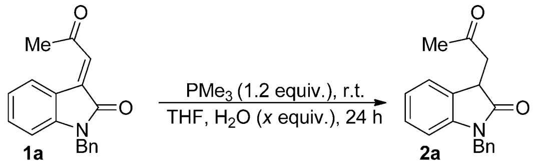
Table 1. Reduction of **1a** under various conditions.[a]



Entry	PR_3	*x*	Solvent	*T* [°C]	Yield [%][b]
1[c]	PBu_3	1.0	toluene	80	18
2	PBu_3	1.0	toluene	80	>99
3	PBu_3	0.2	toluene	80	18
4	PBu_3	0.5	toluene	80	48
5	PBu_3	1.2	toluene	r.t.	86
6	PMe_3	1.2	toluene	r.t.	86
7	PMe_3	1.2	THF	r.t.	>99
8	PBu_3	1.2	THF	r.t.	>84
9	PMe_3	1.2	CH_3CN	r.t.	54
10	PMe_3	1.2	DCM	r.t.	99
11	PMe_3	1.2	Et_2O	r.t.	43
12	PPh_2Me	1.2	THF	r.t.	39
13	$PPhMe_2$	1.2	THF	r.t.	86
14	$P\textit{t}Bu_3$	1.2	THF	r.t.	–[d]
15	PPh_3	1.2	THF	r.t.	–[d]

[a] Reaction conditions: **1a** (0.10 mmol), solvent (1.0 mL), 24 h. [b] Isolated yield. [c] H_2O was not added to the reaction mixture. [d] The desired product was not detected.

Table 2. Screening of water loading in the reduction reaction.[a]



Entry	H_2O [equiv.]	Yield [%][b]
1	2.5	39
2	5.0	86
3	10.0	99
4	55.6	>99

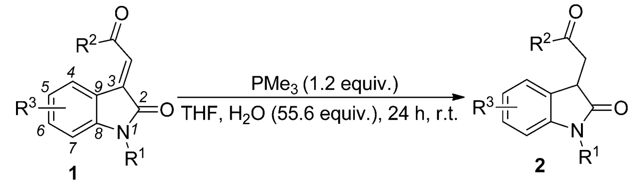
[a] Reaction conditions: **1a** (0.10 mmol), PMe_3 (0.12 mmol), THF (1.0 mL), H_2O, r.t., 24 h. [b] Isolated yield.

We noticed that the addition of water significantly increased the yield of the desired product in this reduction reaction (Table 1, Entry 2). We thus carried out a series of reactions under the standard conditions with various amounts of water. The results are summarized in Table 2. The addition of 2.5 equiv. of water to the reaction mixture led to the formation of the corresponding product **2a** in low yield (39 %, Table 2, Entry 1). Increasing the amount of water to 5 and 10 equiv. improved the yield of **2a** to 86 and 99 %, respectively (Table 2, Entries 2 and 3). Continually increasing the amount of water up to 55.6 equiv. still afforded **2a** in excellent yield (Table 2, Entry 4). For substrate **1a**, at least 10 equiv. of water was required to maximize this reduction reaction. For substrates that react slowly, more than 10 equiv. of water would be required for this reduction reaction. To guarantee complete conversion of the reactant, we chose to add 55.6 equiv. of water in the following experiments.

Having identified the optimal reaction conditions, we next set out to examine the scope and limitations of this reduction reaction with PMe_3 using various isatin derivatives **1**. The results are summarized in Table 3. Substrate **1b** having a methyl group at the 5-position of the benzene ring of *N*-benzylisatin gave the corresponding product **2b** in a lower yield (52 %, Table 3, Entry 1). Varying the R^2 substituent from methyl to phenyl or ethyl afforded the corresponding products **2c**–**2e** in high yields (Table 3, Entries 2–4). Irrespective of whether electron-withdrawing or -donating groups were present at the 4-, 5-, or 6-position of the *N*-benzylisatins **1**, the reactions proceeded smoothly to give the corresponding products **2f**–**2l** in good to excellent yields when R^2 was an OEt group and R^3 a Bn group (Table 3, Entries 5–11). Substrates with a substituent at the 7-position of the *N*-benzylisatins (R^2 = OEt and R^1 = Bn) furnished the corresponding products **2m** and **2n** in low to moderate yields (Table 3, Entries 12 and 13). Varying the *N*-substituent in substrates **1** (R^2 = OEt and R^1 = H) afforded the corresponding products **2o**–**2r** in moderate to excellent yields (Table 3, Entries 14–17). We also used this reduction system in reactions with other α,β-unsaturated compounds (Scheme 2). Unfortunately, no reduction took place.

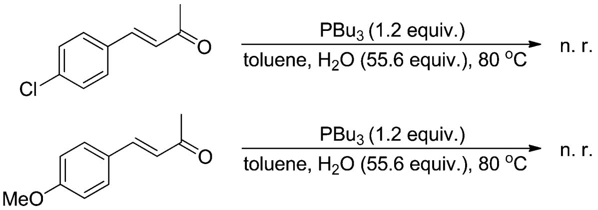
To clarify the reaction mechanism, several deuterium-labeling experiments were conducted, and the results are summarized in Scheme 3. The first experiment was carried out with D_2O under the standard reaction conditions to afford the crude product **2a** in 99 % yield with 56, 85, 85, and 62 % D content[8] at the D^1, D^2, $D^{2'}$, and D^3 positions, respectively [Scheme 3, Equation (1)]. After silica gel column chromatography, the D contents of the isolated product **2a** were measured again, and it was found that the D contents at the D^1, D^2, $D^{2'}$, and D^3 positions were 49, 77, 77, and 10 %, respectively. This indicates that water is the proton source for this reduction reaction and that the workup procedure leads to changes in the D content, especially at the D^3 position. Performing the same reaction with a different workup method, that is, by recrystallization in THF/D_2O, gave **2a** in 90 % yield with 65, 63, 63, and 36 % D content at the D^1, D^2, $D^{2'}$, and D^3 positions, respectively [Scheme 3, Equation (2)]. The recrystallization was conducted in THF/D_2O, which led to a higher amount of D at C-1 than in the crude product. The recrystallization procedure was rather long (5 d) and H/D exchange occurred more easily at the D^2, $D^{2'}$, and D^3 positions, and thus the amount of D on C-2 and C-3 is lower than in the crude product.

Table 3. Scope of the reduction reactions promoted by PMe_3.[a]

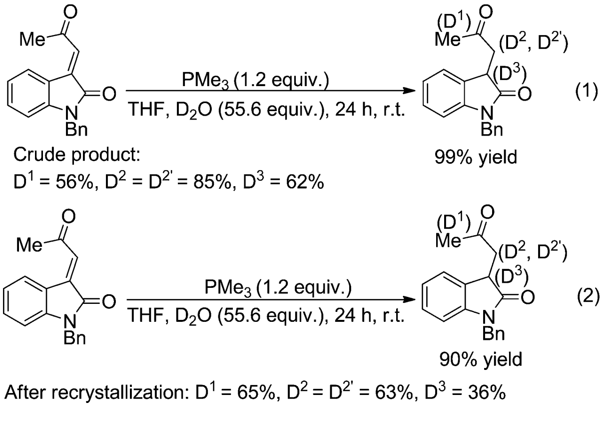


Entry	R^1	R^2	R^3	Yield [%][b]
1	Bn	Me	5-Me (**1b**)	52 (**2b**)
2	Bn	Ph	H (**1c**)	94 (**2c**)
3	Bn	Ph	5-Me (**1d**)	86 (**2d**)
4	Bn	Et	H (**1e**)	99 (**2e**)
5	Bn	OEt	H (**1f**)	99 (**2f**)
6	Bn	OEt	4-Cl (**1g**)	99 (**2g**)
7	Bn	OEt	4-Br (**1h**)	92 (**2h**)
8	Bn	OEt	5-F (**1i**)	94 (**2i**)
9	Bn	OEt	5-Br (**1j**)	74 (**2j**)
10	Bn	OEt	5-Me (**1k**)	99 (**2k**)
11	Bn	OEt	6-Br (**1l**)	92 (**2l**)
12	Bn	OEt	7-Br (**1m**)	58 (**2m**)
13	Bn	OEt	7-CF_3 (**1n**)	16 (**2n**)
14	Me	OEt	H (**1o**)	70 (**2o**)
15	allyl	OEt	H (**1p**)	99 (**2p**)
16	H	OEt	H (**1q**)	99 (**2q**)
17	Boc	OEt	H (**1r**)	53 (**2r**)

[a] Reaction conditions: **1** (0.10 mmol), PMe_3 (0.12 mmol), THF (1.0 mL), r.t., 24 h. [b] Isolated yield.

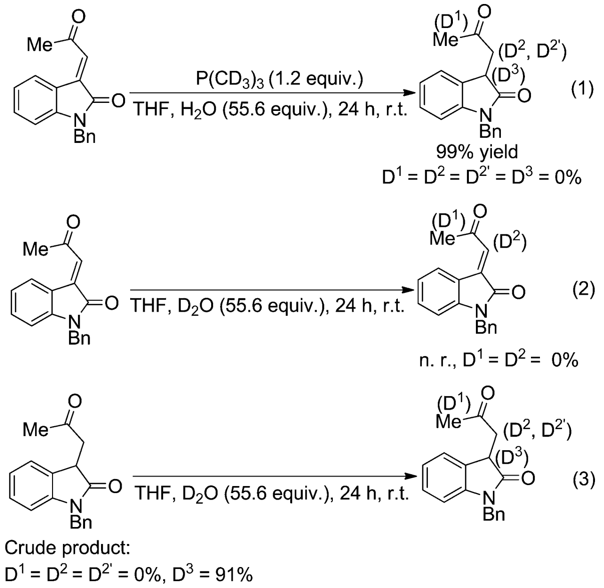


Scheme 2. Attempted reduction reactions of α,β-unsaturated compounds.



Scheme 3. Deuterium-labeling experiments.

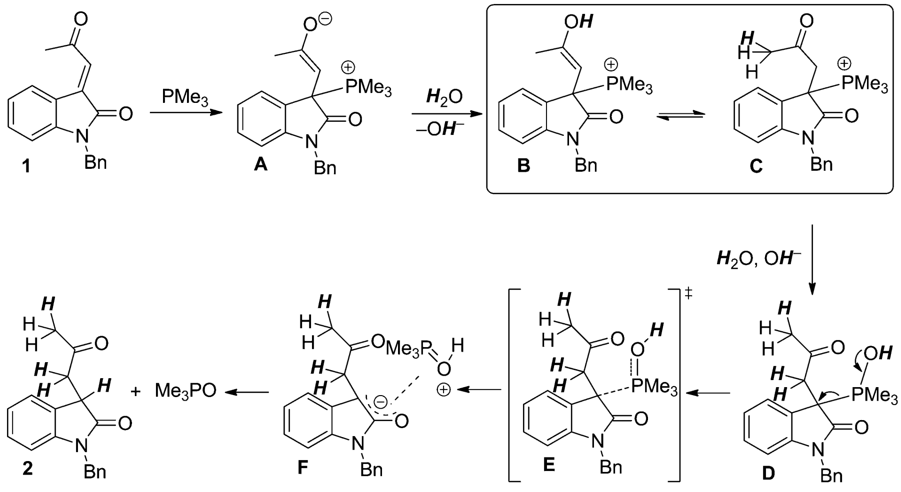
Subsequently, several control experiments were carried out, and the results are summarized in Scheme 4.



Scheme 4. Control experiments.

The use of $P(CD_3)_3$[9] and water afforded product **2a** in 99% isolated yield. However, no H/D exchange was observed [Scheme 4, Equation (1)], which suggests that the protons are not derived from $P(CD_3)_3$. Without PMe_3, no reaction occurred, and no H/D exchange was observed either [Scheme 4, Equation (2)]. In the presence of D_2O, H/D exchange only took place at the D^3 position of the crude product **2a** [91% D content, Scheme 4, Equation (3)], which indicates that H/D exchange occurs easily at the D^3 position and may account for why the amount of D at D^3 always varies during workup. In the presence of PMe_3 and D_2O, a similar result was obtained (the D content at the D^3 position was 63%, see the Supporting Information);[8] the isolated product **2a** purified by silica gel column chromatography gave similar results (see the Supporting Information).

Based on the results of the deuterium-labeling experiment and the mechanism previously proposed in the literature,[2–4] we suggest a mechanism for this reduction reaction (Scheme 5). Initially, Michael addition of PMe_3 to compound **1** forms enolate **A**, which abstracts a proton from water to generate intermediate **B**. As a result of keto/enol tautomerization, another intermediate **C** could be formed at this stage. These intermediates could continue to exchange protons with water to furnish intermediate **D**, which gives the complex **F** via transition state **E**.[10] The proton is quickly transferred to the anionic moiety in complex **F** to furnish the corresponding product **2** and to release the phosphane oxide (identified by ^{31}P NMR spectroscopy, see the Supporting Information). Strongly basic reaction intermediates such as **A** and several keto/enol tautomerizations exist in the reaction process, and this might be a reason for the H/D exchange observed at all the "acidic" positions of the final product in deuterium-labeling experiments carried out in D_2O.



Scheme 5. Plausible mechanism for the reduction reaction.

Conclusions

We have demonstrated a novel, highly chemoselective reduction of the C=C double bond in isatin-derived electron-deficient alkenes promoted by alkylphosphanes with water under mild reaction conditions to afford the products in good to excellent yields. Moreover, a plausible mechanism is proposed on the basis of deuterium labeling and control experiments as well as DFT calculations. Research is in progress to elucidate further mechanistic details of these reactions and to understand their scope and limitations.

Experimental Section

General Procedure for the Reduction of Isatin-Derived Electron-Deficient Alkenes 1: In a flame-dried Schlenk flask was placed **1** (0.10 mmol) under argon, and then anhydrous THF (1.0 mL) and H_2O (100 µL) were added slowly. PMe_3 (1.0 M in THF, 0.12 mmol) was then added quickly. The reaction mixture was stirred at room temperature for 24 h. After that, the solvent was removed under reduced pressure and the residue was purified by silica gel flash column chromatography (pentane/EtOAc, 10:1) to give the corresponding product **2**.

Compound 2a: White solid (28 mg, 99% yield); m.p. 119–121 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 2922, 2852, 1691, 1612, 1486, 1463, 1416, 1365, 1343, 1309, 1194, 1180, 1169, 1080, 748, 733, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 2.23 (s, 3 H, CH_3), 2.92 (dd, J = 8.4, 18.4 Hz, 1 H, CH_2), 3.32 (dd, J = 3.2, 18.4 Hz, 1 H, CH_2), 3.95 (dd, J = 3.2, 8.4 Hz, 1 H, CH), 4.91 (d, J = 15.2 Hz, 1 H, CH_2), 4.96 (d, J = 15.2 Hz, 1 H, CH_2), 6.71 (d, J = 8.0 Hz, 1 H, Ar), 6.95–6.99 (m, 1 H, Ar), 7.13–7.19 (m, 2 H, Ar), 7.21–7.35 (m, 5 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 29.9, 41.0, 43.8, 44.4, 109.0, 122.5, 124.1, 127.2, 127.5, 128.0, 128.8, 135.8, 143.3, 177.5, 205.2 ppm. MS (EI): m/z (%) = 279 (18.8) $[M]^+$, 236 (47.4), 158 (25.0), 91 (100.0), 77 (9.1), 65 (16.3), 43 (12.3). HRMS (EI): calcd. for $C_{18}H_{17}NO_2$: 279.1259; found 279.1258.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectroscopic and analytic data for compounds **1** and **2** and deuterium-labeling experiments.

Acknowledgments

We thank the Shanghai Municipal Committee of Science and Technology (08dj1400100-2), the National Basic Research Program of China (973-2009CB825300), the Fundamental Research Funds for the Central Universities, and the National Natural Science Foundation of China (21072206, 20872162, 20672127, 20732008, 20821002, and 20702013) for financial support.

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[1] For selected reviews on phosphane-catalyzed reactions, see: a) X. Lu, C. Zhang, Z. Xu, *Acc. Chem. Res.* **2001**, *34*, 535–544; b) J. L. Methot, W. R. Roush, *Adv. Synth. Catal.* **2004**, *346*, 1035–1050; c) L.-W. Ye, J. Zhou, Y. Tang, *Chem. Soc. Rev.* **2008**, *37*, 1140–1152; d) D. S. Glueck, *Chem. Eur. J.* **2008**, *14*, 7108–7117; e) B. J. Cowen, S. J. Miller, *Chem. Soc. Rev.* **2009**, *38*, 3102–3116; f) A. Marinetti, A. Voituriez, *Synlett* **2010**, 174; g) Y. Wei, M. Shi, *Acc. Chem. Res.* **2010**, *43*, 1005–1018; for other related reactions, see: h) X.-F. Zhu, C. E. Henry, J. Wang, T. Dudding, O. Kwon, *Org. Lett.* **2005**, *7*, 1387–1390; i) X.-F. Zhu, A.-P. Schaffner, R. C. Li, O. Kwon, *Org. Lett.* **2005**, *7*, 2977–2980; j) X.-F. Zhu, C. E. Henry, O. Kwon, *J. Am. Chem. Soc.* **2007**, *129*, 6722–6723; k) X.-F. Zhu, C. E. Henry, O. Kwon, *Tetrahedron* **2005**, *61*, 6276–6282; l) X.-F. Zhu, J. Lan, O. Kwon, *J. Am. Chem. Soc.* **2003**, *125*, 4716–4717.

[2] I. C. Stewart, R. G. Bergman, D. F. Toste, *J. Am. Chem. Soc.* **2003**, *125*, 8696–8697.

[3] a) H. Staudinger, J. Meyer, *Helv. Chim. Acta* **1919**, *2*, 635–646; for some selected references on the application of the Staudinger reaction, see: b) E. C. Lee, B. L. Hodous, E. Bergin, C. Shih, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 11586–11587; c) Y. Liang, L. Jiao, S. Zhang, J. Xu, *J. Org. Chem.* **2005**, *70*, 334–337; d) J. Li, H.-N. Chen, H. Chang, J. Wang, C.-W. T. Chang, *Org. Lett.* **2005**, *7*, 3061–3064; e) P. T. Nyffeler, C.-H. Liang, K. M. Koeller, C.-H. Wong, *J. Am. Chem. Soc.* **2002**, *124*, 10773–10778.

[4] W. Zhang, M. Shi, *Chem. Commun.* **2006**, 1218–1220.

[5] M. Shi, X.-G. Liu, Y.-W. Guo, W. Zhang, *Tetrahedron* **2007**, *63*, 12731–12734.

[6] W. Zhang, M. Shi, *Tetrahedron* **2006**, *62*, 8715–8719.

[7] F. Zhou, Y.-L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 1381–1407.

[8] These are average values based on two deuterium-labeling experiments. For details, see the Supporting Information.

[9] Prepared according to the procedure by: R. T. Li, S. T. Nguyen, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1994**, *116*, 10032–10040. CD_3MgI was prepared from CD_3I (D content >90%) with magnesium.

[10] This step was investigated theoretically, and the transition state **F** was located at the HF/3-21G* level of theory. Attempts to locate other transition states involving simultaneous proton transfer were unsuccessful at the HF/3-21G* and B3LYP/6-31G(d) levels of theory. For details, see the Supporting Information.

Received: January 7, 2011