X. Xia et al.

Letter

Triphenylphosphine Oxide-Catalyzed Selective α , β -Reduction of Conjugated Polyunsaturated Ketones

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Xuanshu Xia Zhiqi Lao Patrick H. Toy* [©]

Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, P. R. of China phtoy@hku.hk



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Abstract The scope of the triphenylphosphine oxide-catalyzed reduction of conjugated polyunsaturated ketones using trichlorosilane as the reducing reagent has been examined. In all cases studied, the α , β -C=C double bond was selectively reduced to a C–C single bond while all other reducible functional groups remained unchanged. This reaction was applied to a large variety of conjugated dienones, a trienone, and a tetraenone. Additionally, a tandem one-pot Wittig/conjugate-reduction reaction sequence was developed to produce γ , δ -unsaturated ketones directly from simple building blocks. In these reactions the byproduct of the Wittig reaction served as the catalyst for the reduction reaction. This strategy was then used in the synthesis of natural-product synthesis.

Key words triphenylphosphine oxide, trichlorosilane, reduction, Lewis base, organocatalysis, pheromones

Several years ago, Nakajima and co-workers reported the selective 1,4-conjugate reduction of α , β -unsaturated ketones catalyzed by Lewis bases such as HMPA or triphenylphosphine oxide (1) with $HSiCl_3$ as the reducing reagent.¹ Interestingly, one of the examples they reported was the selective reduction of conjugated dienone 2a to unsaturated ketone **3a** (Scheme 1). Because the γ , δ -unsaturated ketone structural motif appears in a variety of natural products, we were intrigued by this reaction and curious about its substrate scope. This exact transformation had been previously reported by others using different reaction conditions $[Pd(PPh_3)_4/ZnCl_2/Ph_2SiH_2^2 \text{ or Hantzsch ester/SiO}_2^3]$ that were found not to be generally selective across a range of conjugated dienone substrates; we therefore thought that the selective conversion of 2a into 3a might simply be due to steric interference by the methyl groups. To our knowledge, the only reported general methods for the selective α,β -reduction of conjugated polyunsaturated ketones involve the use of catecholborane,⁴ Stryker's reagent,⁵ or a catalytic InCl₃/NaBH₄ reaction system.⁶ Additionally, a $B(C_6F_5)_3$ /poly(methylhydrosiloxane) reaction system that might be highly selective has been reported, but it was applied to only a single polyunsaturated ketone substrate and a related ester-nitrile substrate.⁷ Finally, a Ru-catalyzed process was found to be relatively unselective in the single example studied.8 Consequently, whereas methods for selective metal-catalyzed 1,4-9 and 1,6-conjugate additions¹⁰ of carbon nucleophiles to conjugated polyunsaturated ketones are relatively widely known, highly selective organocatalytic methods for 1,4-conjugate hydride addition for double-bond reduction are virtually unknown. Here we report a study of the substrate scope of the HSiCl₃-mediated reduction of conjugated polyunsaturated ketones catalyzed by oxide **1** and its application to the synthesis of a series of naturally occurring moth pheromones.



Scheme 1 Selective reduction of conjugated dienone 2a to 3a

The conjugated diene substrates for our study **2b–p** were prepared in a straightforward manner as outlined in Scheme 2,¹¹ with the phosphine-catalyzed isomerization of alkynones to *trans,trans*-dienones as the key transformation.¹² Specifically, terminal alkynes **4** were deprotonated with BuLi and then treated with an aldehyde to produce the corresponding secondary alcohols **5** after workup. These alcohols were oxidized with MnO₂ to afford the alkynone

isomerization products **6**, which, in turn, were treated with catalytic amounts of Ph_3P in toluene at elevated temperature to afford **2b**-**p** with high stereochemical purity.



Trieneone **2q** was synthesized by a similar route, except that methyl chloroformate was used instead of an aldehyde to convert the deprotonated alkyne **4** into the alkynoate **7** (Scheme 3). This product was isomerized, reduced, and then oxidized to give the corresponding dienal **8**. Finally, dienal **8** was treated with phosphorane **9** to afford **2q**. The synthesis of tetraenone **2r** involved the reaction of dienal **8** with phosphorane **10** to afford trienoate **11**. This, in turn, was reduced and oxidized to afford trienal **12**. Finally, treatment of **12** with phosphorane **9** afforded **2r**.



With the conjugated polyunsaturated ketone substrates **2b-r** in hand, we began our studies of the selective reduction reaction by using the originally reported reaction conditions as a starting point.¹ Whereas the original report described the use of HMPA as the nucleophilic Lewis base catalyst at 0 °C, we chose to use 1 as the catalyst at -78 °C, on the basis of our previous research on related reductive aldol reactions.¹³ Gratifyingly, by using these conditions for the reduction of **2b** in CH₂Cl₂we obtained **3b** in 95% yield after purification (Table 1, entry 1).¹⁴ Application of the same reduction conditions to aryl ketones **2c-i**, including some with potentially acid-sensitive and/or reducible groups, afforded the corresponding ketones **3c-i** in excellent yields (entries 2–8). Heteroaromatic ketones 2j and 2k were also selectively reduced (entries 9 and 10). Phenyl ketones **21–n**. containing potentially acid-sensitive and/or reducible groups, also proved to be good substrates, affording ketones **31-n** in excellent yields (entries 11–13). Methyl ketones **20** and **2p** were cleanly converted into **3o** and **3p**, respectively (entries 14 and 15). Finally, trienone 2q and tetraenone 2r were selectively reduced to **3a** and **3r**, respectively (entries 16 and 17). In all cases the selectivity of the reactions permitted very simple purification of the products by silica gel chromatography. Therefore, overall, it seems that the Cl₃SiH-mediated reduction of conjugated polyunsaturated ketones catalyzed by 1 is a highly selective and efficient method for reduction of α,β -C=C double bonds.



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Synlett

X. Xia et al.

С

Table 1 (continued)





Letter



Having established the general applicability of the reduction reaction, we next examined the possibility of using it in a one-pot multistep reaction system for the direct synthesis of γ . δ -unsaturated ketones from simple building blocks. This idea was based on the work reported by Zhou and co-workers, in which they performed Wittig reactions to form enones, followed directly by a Cl₂SiH-mediated reduction reactions catalyzed by oxide 1, formed as a byproduct of the first reaction.^{15,16} Our idea is summarized in Scheme 4. Specifically, we planned to mix an α -halo ketone **13** with an α , β -unsaturated aldehyde **14** in the presence of Ph₃P and DIPEA to generate a phosphorane intermediate 15 in situ, which would, in turn, react with 14 to generate a dienone 2 and oxide 1. Once the formation of 2 was complete, Cl₃SiH would be added and **1** would catalyze the reduction of **2** to form γ , δ -unsaturated ketone **3**. Gratifyingly, by using α -halo ketones **13a–c** and α , β -unsaturated aldehydes **14a** and **14b**, we were able to synthesize γ , δ -unsaturated ketones **3s-u** directly in one-pot procedures with good overall yield, especially considering the number of sequential reactions involved (Figure 1).¹⁷



Synlett

X. Xia et al.

Finally, to showcase the utility of the reduction reaction in the context of natural-product synthesis, we targeted the moth pheromones **16a** and **16b** (Scheme 5).¹⁸ The common starting material for both syntheses was phosphorane 9, which was deprotonated and treated with an 1-bromoheptane (17a) or 1-bromooctane (17b) to introduce what would eventually become the fully saturated side chains of 16a and 16b, respectively. The resulting phosphoranes 18a and **18b** were not purified and were treated directly with non-2-ynal (**19**)¹⁹ to perform a Wittig reaction. In a manner similar to the procedure used for the synthesis of **3s-u**, the resulting alkene products were not isolated but, instead, Cl₃SiH was added directly to the reaction mixture to reduce the newly formed C=C double bonds in situ to form unsaturated ketones **20a** and **20b**. Finally, reduction of the alkyne groups to the corresponding (Z)-alkene groups completed the syntheses of 16a and 16b in excellent overall yields from **9**.¹¹



With regards to the mechanism of this selective reduction reaction, the sum total of our results with a wide variety of reaction substrates supports the notion originally proposed by Nakajima and co-workers that a six-membered cyclic transition state might be involved. Specifically, they proposed that the silicon atom of the reducing reagent simultaneously interacts with the oxygen atom of the substrate and the Lewis base catalyst, thereby permitting delivery of hydride selectively at the β -position (Figure 2).

In summary we have demonstrated that the previously reported Cl₃SiH-mediated 1,4-reduction of conjugated polyunsaturated enones catalyzed by oxide **1** is applicable to a wide range of substrates to produce γ , δ -unsaturated ketone products. These reaction conditions are compatible with a wide range of potentially reducible functional groups, and even a trienone (**2q**), a tetraenone (**2r**), and alkynenones generated in situ were selectively reduced. The reduction of

Letter



Figure 2 Possible reaction transition state

the latter substrates was studied to demonstrate the utility of this synthetic method in the context of natural-product synthesis through the synthesis of moth pheromones **16a** and **16b**. We are currently exploring the utility of this method in other contexts for the selective synthesis of interesting organic molecules, and we will report our results in due course.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611527.

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- (14) Enones 3b-r (Table 1); General Procedure

A solution of the appropriate diene **2b-r** (1.0 mmol) and $Ph_3P=O(1)(0.2 \text{ mmol})$ in anhyd $CH_2Cl_2(5 \text{ mL})$ was stirred under N_2 and cooled to -78 °C. $Cl_3SiH(2.0 \text{ mmol})$ was added, and stirring was continued for 2 h more. The mixture was then allowed to warm to rt and the volatiles were removed under a stream of air. Sat. aq Na_2CO_3 (20 mL) and CH_2Cl_2 were added, and the resulting suspension was stirred for 30 min. The layers were

separated and the aqueous layer was extracted with additional CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by chromatography [silica gel, EtOAc–hexane (10:90)].

(4E)-1-(2-Naphthyl)hex-4-en-1-one (3b)

Clear oil; yield: 213 mg (95%). ¹H NMR (400 MHz, CDCl₃): $\delta = 1.61$ (d, J = 3.8 Hz, 3 H), 2.41–2.46 (m, 2 H), 3.04 (t, J = 7.3 Hz, 2 H), 5.46–5.48 (m, 2 H), 7.39 (t, J = 7.7 Hz, 1 H), 7.46 (t, J = 7.7 Hz, 1 H), 7.53 (t, J = 7.7 Hz, 1 H), 7.76 (d, J = 7.1 Hz, 1 H), 7.79 (d, J = 8.2 Hz, 1 H), 7.88 (d, J = 8.2 Hz, 1 H), 8.57 (d, J = 8.6 Hz, 1 H). ¹³C NMR (100 MHz, CDCl₃): $\delta = 17.9$, 27.6, 41.9, 124.3, 125.8, 126.1, 126.6, 127.3, 127.7, 128.4, 129.6, 130.1, 132.3, 133.9, 136.1, 204.2. HRMS (EI-MS): m/z calcd for C₁₆H₁₆O: 224.1201; found: 224.1190.

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(17) Aryl Enones 3s-u; General Procedure

A mixture of the appropriate aryl ketone **13a–c** (2.1 mmol), enone **14a** or **14b** (2.0 mmol), Ph₃P (2.1 mmol), and DIPEA (3.0 mmol) in anhyd CH₂Cl₂ (10 mL) was stirred under N₂ and refluxed. When the Wittig reaction was completed (TLC), the mixture was cooled to -78 °C and Cl₃SiH (4.0 mmol was added. The mixture was stirred for 2 h more and then warmed to rt. After 2 h, the volatiles were removed under a stream of air. Sat. aq Na₂CO₃ (20 mL) and CH₂Cl₂ (20 mL) were added, and the resulting suspension was stirred for 30 min. The layers were separated and the aqueous later was extracted with additional CH₂Cl₂ (3 × 20 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The crude product was purified by chromatography [silica gel, EtOAc–hexane (10:90)].

(5E)-6-Phenylhex-5-en-2-one (3s)

Clear oil; yield: 237 mg (68%). ¹H NMR (400 MHz, CDCl₃): δ = 2.16 (s, 3 H), 2.46–2.51 (m, 2 H), 2.58–2.63 (m, 2 H), 6.19 (dt, *J*₁ = 15.8, *J*₂ = 6.7 Hz, 1 H), 6.40 (d, *J* = 15.8 Hz, 1 H), 7.16–7.21 (m, 1 H), 7.24–7.34 (m, 4 H). ¹³C NMR (100 MHz, CDCl₃): δ = 27.2, 30.2, 43.3, 126.1, 127.2, 128.6, 128.9, 130.9, 137.5, 208.2. HRMS (El-MS): *m/z* calcd for C₁₂H₁₄O: 174.1045; found: 174.1031.

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