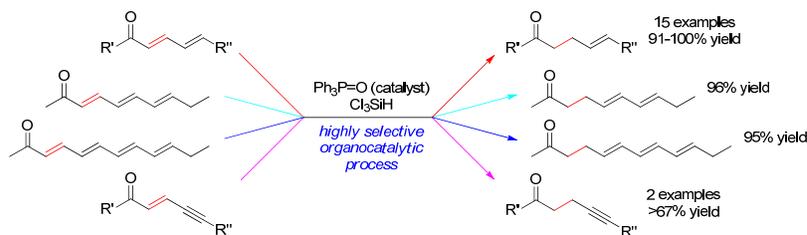


Triphenylphosphine Oxide-Catalyzed Selective α,β -Reduction of Conjugated Polyunsaturated Ketones

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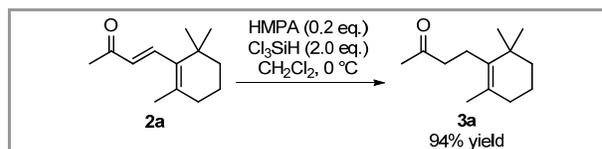
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Abstract The scope of the triphenylphosphine oxide-catalyzed reduction of conjugated polyunsaturated ketones using trichlorosilane as the reducing reagent has been examined. In all cases studied the α,β -carbon-carbon double bond was selectively reduced to a carbon-carbon single bond, and 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 by-product of the Wittig reaction served as the catalyst for the reduction reaction. This strategy was then used in the synthesis of naturally occurring moth pheromones in order to demonstrate its utility in the context of natural product synthesis.

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

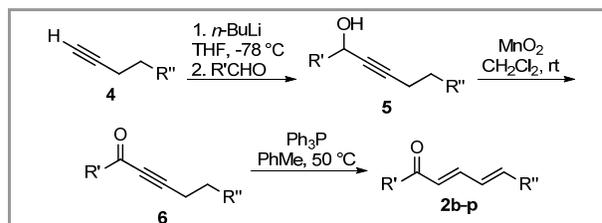
Several years ago Nakajima and co-workers reported the selective 1,4-conjugate reduction of α,β -unsaturated ketones catalyzed by Lewis bases such as HMPA and triphenylphosphine oxide (**1**), with HSiCl_3 as the reducing reagent.¹ Interestingly, one of the examples they reported showed the selective reduction of conjugated dienone **2a** to unsaturated ketone **3a** (Scheme 1). Since 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 ($\text{Pd}(\text{PPh}_3)_4/\text{ZnCl}_2/\text{Ph}_2\text{SiH}_2$ ² and Hantzsch ester/ SiO_2 ³) that were found not to be generally selective across a range of conjugated dienone substrates, so we thought the selective conversion of **2a** into **3a** could be simply due to steric interference by the methyl groups. To our knowledge the only reported general methods for selective α,β -reduction of conjugated polyunsaturated ketones involve the use of catechol borane,⁴ Stryker's reagent,⁵ or a catalytic $\text{InCl}_3/\text{NaBH}_4$ reaction system.⁶ Additionally, a $\text{B}(\text{C}_6\text{F}_5)_3/\text{PMHS}$ 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 relatively unselective in the single example studied.⁸ Thus, it seems that while methods for selective

metal-catalyzed 1,4-⁹ and 1,6-conjugate addition¹⁰ 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. Herein we report a study of the substrate scope of the Cl_3SiH -mediated reduction of conjugated polyunsaturated ketones catalyzed by **1** and its application to the synthesis of a series of naturally occurring moth pheromones.



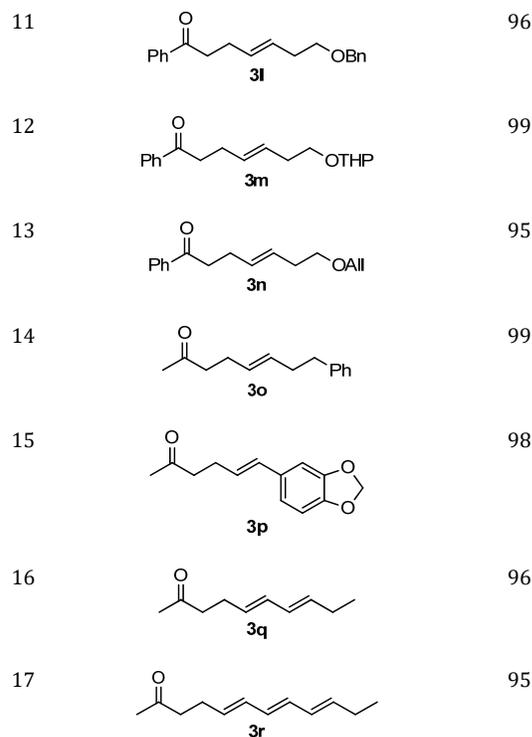
Scheme 1 Selective reduction of conjugated dienone **2a** to **3a**.

The conjugated diene substrates for our study **2b-p** were prepared in a straightforward manner as outlined in Scheme 2,¹¹ utilizing the phosphine-catalyzed isomerization of alkynones to *trans,trans*-dienones as the key transformation.¹² Specifically, terminal alkynes **4** were deprotonated with *n*-BuLi and then treated with an aldehyde to produce the corresponding secondary alcohol **5** after workup. These alcohols were oxidized using MnO_2 to afford the alkynone isomerization substrates **6**, that were in turn treated with catalytic Ph_3P in toluene at elevated temperature to afford **2b-p** with high stereochemical purity.



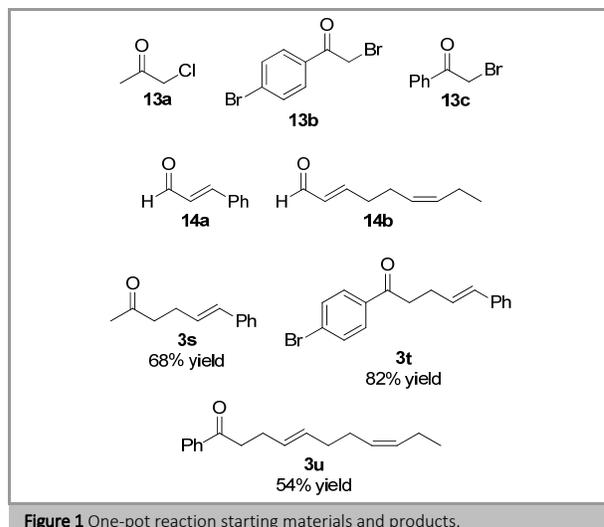
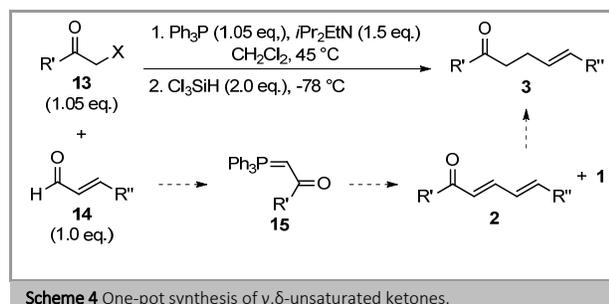
Scheme 2 Synthesis of conjugated polyunsaturated ketone substrates **2a-p**.

Trieneone **2q** was synthesized by a similar route, except that methyl chloroformate was used instead of an aldehyde to react with the deprotonated alkyne **4** to form alkynoate **7**. This was isomerized, reduced and then oxidized to the corresponding dienal **8**. Finally, aldehyde **8** was reacted with

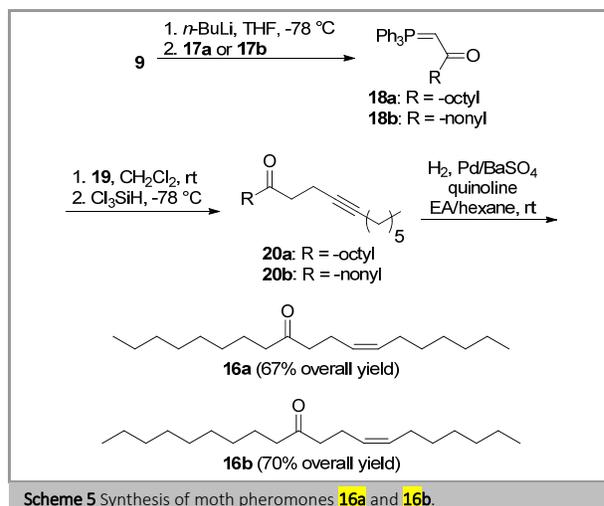


^a Reaction conditions: **1** (0.2 mmol), **2** (1.0 mmol), Cl₃SiH (2.0 mmol), CH₂Cl₂ (5 mL), -78 °C.

Having established the general applicability of the reduction reaction, we next examined the possibility of using it in a one-pot multiple 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 Cl₃SiH-mediated reduction reactions that were catalyzed by **1** that was formed as a by-product in the first reaction.^{15,16} Our idea is summarized in Scheme 4. Specifically we planned to mix an α -halo ketone (**13**) together with an α,β -unsaturated aldehyde (**14**) in the presence of Ph₃P and *i*Pr₂EtN in order to generate a phosphorane intermediate (**15**) in situ that would in turn react with **14** to generate a dienone (**2**) and **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, using α -halo ketones **13a-c** and α,β -unsaturated aldehydes **14a-b**, we were able to synthesize γ,δ -unsaturated ketones **3s-u** directly in one-pot procedures in good overall yield, especially when considering the number of sequential reactions performed (Figure 1).¹⁷



Finally, in order to showcase the utility of the reduction reaction in the context of natural product synthesis, we targeted moth pheromones **16a** and **16b** (Scheme 5).¹⁸ The common starting material for both syntheses was phosphorane **9**, which was deprotonated and then treated with an 1-bromoheptane (**17a**) or 1-bromooctane (**17b**) in order to introduce what would eventually become the fully saturated side chains of **16a** and **16b**. The thus formed phosphoranes **18a** and **18b** were both not purified and reacted directly with non-2-ynal (**19**)¹⁹ to perform Wittig reactions, and in a manner similar the procedure used for the synthesis of **3s-u**, the resulting alkene products were not isolated. Instead, Cl₃SiH was added directly to the reaction mixture in order to reduce the newly formed carbon-carbon 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, it seems that the sum total of our results with a wide variety of reaction substrates lends support to the notion originally put forth by Nakajima and co-workers that a 6-membered cyclic transition state could 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, and thereby allowing for hydride delivery selectively to the β -position (Figure 2).

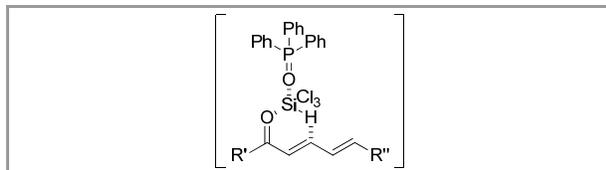


Figure 2 Possible reaction transition state.

In summary we have demonstrated that the previously reported Cl_3SiH -mediated 1,4-reduction of conjugated polyunsaturated enones catalyzed by **1** is applicable to a wide range of reaction substrates to produce γ,δ -unsaturated ketones products. These reaction conditions are compatible with a wide range of potentially reducible functional groups, and even a trienone (**2q**), a tetraenone (**2r**) and alkynoneones generated in situ can be selectively reduced. The reduction of the latter substrates was studied in order 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 will report our results in due course.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

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- General procedure for the synthesis of 3b-r (Table 1)**
A solution of **2b-r** (1.0 mmol) and **1** (0.2 mmol) in dry CH_2Cl_2 (5 mL) was stirred under a N_2 atmosphere and cooled to -78°C . Reducing reagent Cl_3SiH (2.0 mmol) was then added and stirring was continued for 2 h more. At this time the reaction mixture was allowed to warm to room temperature and then the volatiles were removed under a stream of air. Saturated aqueous 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 later was extracted with additional CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (ethyl acetate/hexane = 10/90) to afford **3b-r**.
3b: ^1H NMR (CDCl_3 , 400 MHz) δ 1.61 (d, 3H, $J = 3.8$ Hz), 2.41-2.46 (m, 2H), 3.04 (t, 2H, $J = 7.3$ Hz), 5.46-5.48 (m, 2H), 7.39 (t, 1H, $J = 7.7$ Hz), 7.46 (t, 1H, $J = 7.7$ Hz), 7.53 (t, 1H, $J = 7.7$ Hz), 7.76 (d, 1H, $J = 7.1$ Hz), 7.79 (d, 1H, $J = 8.2$ Hz), 7.88 (d, 1H, $J = 8.2$ Hz), 8.57 (d, 1H, $J = 8.6$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 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 ppm; HRMS m/z calcd for $\text{C}_{16}\text{H}_{16}\text{O}$ 224.1201, found 224.1190.
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- General procedure for the synthesis of 3s-u (Figure 1)**
A mixture of **13a-c** (2.1 mmol), **14a-b** (2.0 mmol), Ph_3P (2.1 mmol) and $i\text{Pr}_2\text{EtN}$ (3.0 mmol) in dry CH_2Cl_2 (10 mL) was stirred under a N_2 atmosphere and refluxed. When TLC analysis indicated that the Wittig reaction was complete, the reaction mixture was cooled to -78°C and Cl_3SiH (4.0 mmol) was then added. Stirring was continued for 2 h more, and then the reaction mixture was allowed to warm to room temperature. After 2 h the volatiles were removed under a stream of air. Saturated aqueous Na_2CO_3 (20 mL) and CH_2Cl_2 (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 CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (ethyl acetate/hexane = 10/90) to afford **3s-u**.
3s: ^1H NMR (CDCl_3 , 400 MHz) δ 2.16 (s, 3H), 2.46-2.51 (m, 2H), 2.58-2.63 (m, 2H), 6.19 (dt, 1H, $J_1 = 15.8$ Hz, $J_2 = 6.7$ Hz), 6.40 (d, 1H, $J = 15.8$ Hz), 7.16-7.21 (m, 1H), 7.24-7.34 (m, 4H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 27.2, 30.2, 43.3, 126.1, 127.2, 128.6, 128.9, 130.9, 137.5, 208.2 ppm; HRMS m/z calcd for $\text{C}_{12}\text{H}_{14}\text{O}$ 174.1045, found 174.1031.
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