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Z-Selective phosphine promoted 1,4-reduction of ynoates and propynoic amides in the presence of water†

Fabian Seifert,[a] Denis Drikermann,[a] Johannes Steinmetzer,[b] You Zi,[a] Stephan Kupfer[b] and Ivan Vilotijevic*[a]

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Phosphine-mediated reductions of substituted propynoic esters and amides in the presence of water yield the partially reduced α,β-unsaturated esters and amides with high *Z*-selectivity. The competitive *in situ Z* to *E*-isomerization of the product in some cases lowers the *Z* to *E* ratios of the isolated α,β-unsaturated carbonyl products. Reaction time and the amounts of phosphine and water in the reaction mixture are the key experimental factors which control the selectivity by preventing or reducing the rates of *Z*- to *E*-product isomerization. Close reaction monitoring enables isolation of the *Z*-alkenes with high selectivities. The computational results suggest that the reactions could be highly *Z*-selective owing to the stereoselective formation of the *E*-*P*-hydroxyphosphorane intermediate.

Introduction

Reduction of electron deficient alkynes is a straightforward path for synthesis of α,β-unsaturated carbonyl compounds. Numerous methods have been developed for selective partial reduction of such alkynes to the corresponding alkenes. Most of these methods preferentially produce the more stable, *E*-alkenes.[1] Methods to selectively produce *Z*-alkenes from the corresponding alkyne are still in high demand. The existing methods that typically rely on transition metal catalyzed hydrogenations[2] and catalysis by frustrated Lewis pairs[3] leave space for further development of more general and mild reduction methods that avoid the use of hydrogen gas or expensive catalysts.

In our work on phosphine catalyzed *trans*-hydroboration of alkynes, we observed a competitive 1,4-reduction of electron deficient alkynes under forcing conditions with substrates that do not undergo the desired hydroboration reaction.[4] The origin of the 1,4-reduction products was attributed to the ability of the phosphine to promote alkyne reduction in the presence of water. The recent reports of stereoselective difunctionalizations of alkynes promoted by phosphines compelled us to conduct a more detailed study of the selectivity in these 1,4-reduction reactions (Scheme 1).[5]

Phosphine mediated reduction of alkynes in the presence of water has been reported as a metal-free alternative to reductions of electron deficient alkynes using transition metal catalysts.[1a–d] Almost uniformly, these reactions have been reported to preferentially produce *E*-alkenes. A recent study by Whittaker disclosed for the first time that these reactions, depending on the reaction conditions, can produce the *Z*-alkene preferentially when ynoates are used as starting materials.[1e] Here, we report that phosphine-promoted reductions of ynoates and propynoic amides in the presence of water can be highly *Z*-selective and we present a mechanistic analysis of these reactions with a focus on factors that determine stereochemical outcome of the reaction supported by quantum chemical simulations "pysisyphus",[6] a recently introduced efficient external optimizer written in Python which can also be used to describe excited states.

Results and discussion

Reduction of methyl 3-phenylpropiolate **P-3** was taken as a model for optimization of the reaction conditions (Table 1). A brief survey of solvents identified that the reactions in ethereal solvents mixable with water gave highest yields when used in 1 : 5 v/v mixtures with water in the presence of 1.0 equiv. of PBu_3. Further optimization was focused on reactions in 1,4-dioxane. The use of higher amount of phosphine resulted in reduced selectivity. The amount of water in the reaction mixture proved to be an important determinant of the *E* : *Z* product ratio.

[a]*Institute of Organic Chemistry and Macromolecular Chemistry, Friedrich Schiller University Jena, Humboldtstr. 10, 07743 Jena, Germany. E-mail: ivan.vilotijevic@uni-jena.de*
[b]*Institute for Physical Chemistry and Abbe Center of Photonics, Friedrich Schiller University Jena, Helmholtzweg 4, 07743 Jena, Germany*

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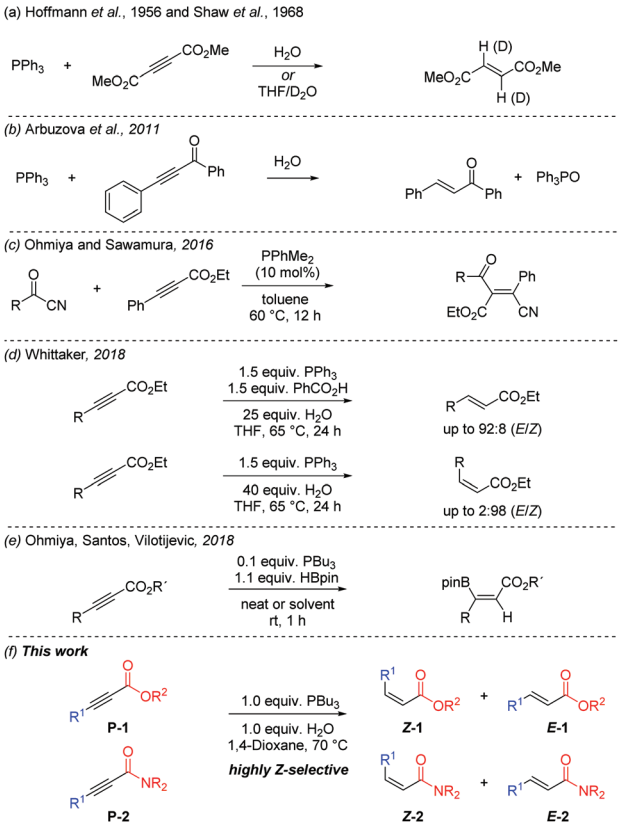
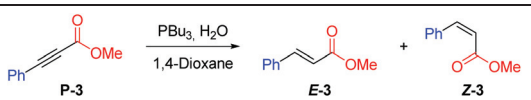


Scheme 1 Previously reported phosphine-mediated and phosphine-catalyzed reductions and difunctionalizations of electron deficient alkynes that produce α,β-unsaturated alkenes and comparison to this work.

Table 1 Reduction of methyl 3-phenylpropiolate **P-3** in 1,4-dioxane and tri-*n*-butylphosphine, [**P-3**] = 125 mmol L^{-1}



Entry	PBu_3 [eq.]	H_2O [eq.]	T [°C]	t [min]	NMR-yield of 3 [%]	E/Z [mol%]	**P-3** [%]
1	1.0	0	70	300	14	1 : 1	11
2	1.0	1.0	70	30	95 (93)[a]	1 : 25 (1 : 25)[a]	5
3	1.0	2.0	70	30	93	1 : 17	2
4	1.0	3.0	70	30	95	1 : 14	2
5	1.0	4.0	70	30	95	1 : 13	2
6	1.0	6.0	70	30	93	1 : 11	2
7	1.0	1.0	40	30	83	1 : 25	3
8	1.0	1.0	50	30	86	1 : 25	4
9	1.0	1.0	60	30	87 (91)[a]	1 : 25 (1 : 25)[a]	4
10	1.0	1.0	80	30	89	1 : 25	4
11	1.0	1.0	90	30	90	1 : 17	3
12	1.0	1.0	100	30	90	1 : 14	4

[a] Yield and *E*/*Z*-ratio after column chromatography. NMR-yields were determined by ^{1}H NMR-spectroscopy with dimethylsulfone as an internal standard.

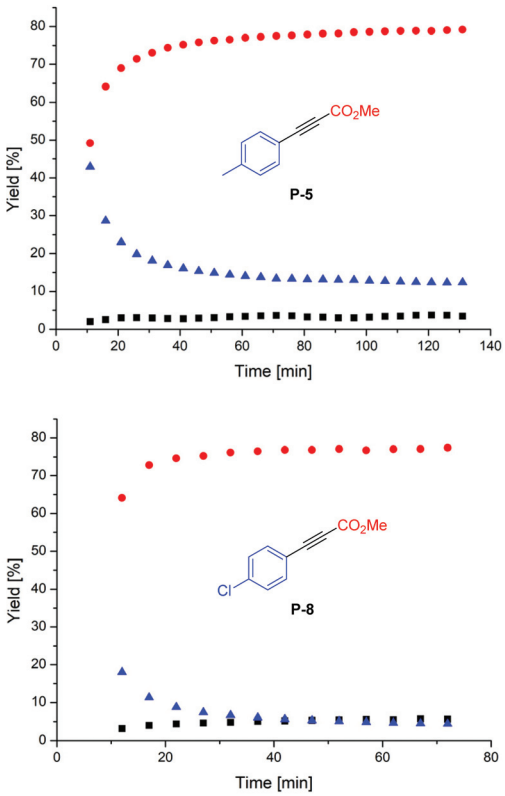
When the water content in the reaction mixture was varied between 1 and 6 equivalents, a clear trend emerged showing that the minimum amount of water should be used if isolation of the *Z*-products is the goal (Table 1, entries 2–6). When water was completely left out, the reaction proceeded with only 14% yield and resulted in equal amounts of the reduced species (Table 1, entry 1). Final optimization effort focused on temperature and overall concentration of the reaction mixture. While increased temperature and increased concentration strongly influenced the reaction rates, the effects on the yield and selectivity remained modest (Table 1, entries 7–12).

Reactions using tertiary triarylphosphines, alkylarylphosphines and other trialkyl phosphines followed similar selectivity trends. Tri-*n*-butylphosphine, a commonly used inexpensive nucleophilic phosphine, was chosen for evaluation of the reaction scope due to the favorable reaction kinetic profile over a range of substrates.

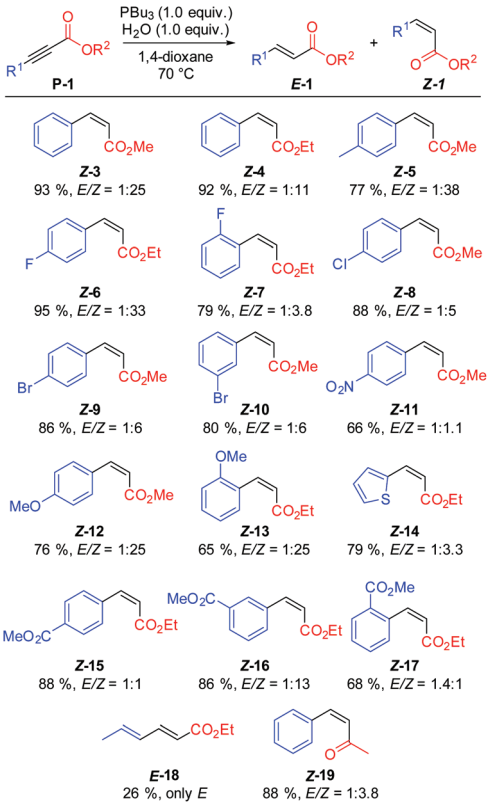
The scope of the reactions for ynoates has been tested under the optimized conditions with a range of diversely substituted aryl ynoates. The influence of substituents on reaction rates required close monitoring of the reaction course for each substrate. These studies led to the conclusion that the selectivity for the *Z*-product significantly decreases with extended reaction times. This was attributed to a competitive isomerization of the initially produced *Z*-enone to the thermodynamically more stable *E*-enone in the presence of phosphine. Such isomerization in the presence of a nucleophilic catalyst is well documented and our experiments corroborated previous reports.[7] The previous reports of related reduction reactions being *E*-selective were likely a consequence of rapid isomerization that can occur under the conditions employed in previous studies.[1d,e] In contrast to previous reports, the conditions employed in our study served a purpose of suppressing the *Z* to *E* isomerization. Namely, minimal amount of the nucleophilic phosphine (1 equiv.) was used in the reaction together with the minimal amount of water (1 equiv.). With increased amount of phosphine and increased amount of water, the competitive isomerization occurs at higher rates leading to diminished selectivities.

It became apparent that the reaction time is of crucial interest if the *Z*-product was to be isolated with high selectivity. Each reaction should be quenched at an opportune time point to allow isolation of the desired *Z*-alkene in high yields (as a consequence of high conversion of starting material) while preventing significant isomerization to the *E*-product. Monitoring the reactions by NMR spectroscopy allowed us to decide on when to quench the reaction for each substrate. The reactions are highly *Z*-selective, but the observed ratios of *Z*- and *E*-products depends on the rate of isomerization which was higher for the more electrophilic enones that undergo the reversible conjugate addition of the nucleophilic catalysts at higher rates resulting in faster isomerization. Consequently, the reductions of *p*-methyl substituted ynone **P-5** provide a large window of reactions times where the product mixtures feature high ratios of *Z*-and *E*-products ***Z*-5** and ***E*-5**. In contrast to this, *p*-chloro substituted ynone **P-8** featured lower selectivity for the *Z*-product because of the fast isomerization (Scheme 2).

Further evaluation of the reaction scope established that this trend is general. Electron rich ynones such as **P-12** and



Scheme 2 ^{1}H NMR monitoring of the partial reductions of 2-ynoates to corresponding 2-enoates. Conditions: 2-ynoate (1.00 equiv.), PBu_3 (1.00 equiv.), H_2O (1.00 equiv.), 60 °C, 0.60 mL 1,4-dioxane-d_8. ● NMR-yield of 2-enoate in (*Z*)-configuration. ■ NMR yield of 2-enoate in (*E*)-configuration. ▲ Unconsumed 2-ynoate. *E*/*Z*-Ratios were determined based on the intensity of integrals in relationship to internal standard (dimethylsulfone).

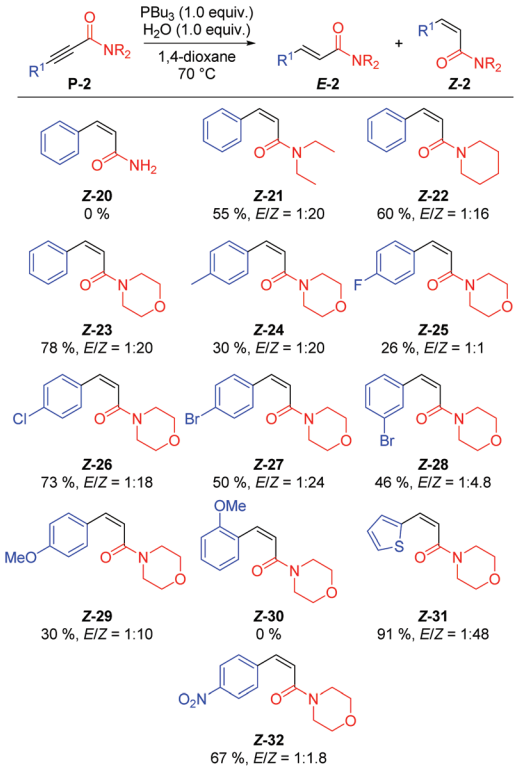


Scheme 3 Scope of the reaction for various ynoates under the optimized conditions. Isolated yields for *Z*-product are listed together with the *E*/*Z* selectivities.

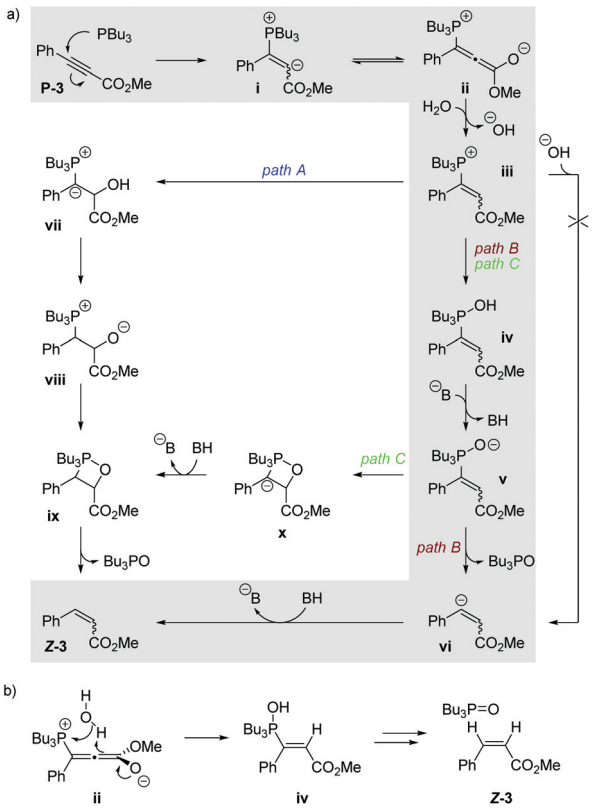
P-13 provided the *Z*-product with high selectivity and in good yields. Electron poor substrates **P-11**, **P-15**, **P-16** and **P-17** were converted to the corresponding alkenes in good yields but with diminished selectivities. The reactions of alkyl substituted ynoates led to competitive isomerization to the corresponding all-*E*-diene. Ynone **P-19** also proved to be a competent substrate for the *Z*-selective reductions giving an 88% combined yield of *Z*- and *E*-products and ratio of 3.8 : 1 (Scheme 3).

To further demonstrate the utility of this method, we investigated the reductions of propynoic amides. While expecting lower reaction rates due to the generally lower electrophilicity of propynoic amides, the focus was directed to how this will influence the reaction selectivity and the rates of *Z* to *E* isomerization. Free propynoic amides did not produce any of the acrylamide products under the optimized reaction conditions. In contrast to this, dialkyl propynoic amides were smoothly reduced to the corresponding acrylamides in moderate yields. The generally lower yields compared to the reaction of ynoates were attributed to the lower reaction rates. Selectivities in the reactions of propynoic amides, on the other hand, proved to be more robust and at the same level or higher than those in the reductions of the corresponding esters. This could be the consequence of the lower rates of isomerization, but it could also be attributed to the higher steric demand of the dialkylamides used in the study. Although electron poor propynoic amides provided the reduction products in higher yield due to the higher reaction rates, the selectivity of the reduction of nitro-substituted **P-32** remained low with 1 : 1.8, yet higher than for the corresponding ynoate (Scheme 4). Lower selectivities observed with electron poor propynoic amides are consistent with the hypothesis that higher rate of isomerization leads to diminished selectivity.

Three possible reaction pathways are presented in Scheme 5. It has been established that electron poor alkynes undergo conjugate addition of nucleophilic phosphines resulting in a zwitterionic enolate intermediate **ii** which can deprotonate sufficiently acidic protic additives, in this case water, to produce intermediate **iii**,[1e,4,8] (see Fig. S1–S3 in the ESI† document for calculated reaction profile). The vinylphosphonium ion features possible electrophilic sites at C1, C2, C3 and the phosphorus atom. Since the ester hydrolysis products are not observed in appreciable amount, nucleophilic attack of the hydroxide at C1 is considered unlikely. This is also the case with attack at C3 as it is not clear how the resulting intermediate would lead to the reaction products. Hydroxide addition at C2 (path A) would result in formation of a phosphonium ylide **vii**. Similar transformations have been proposed in the related



Scheme 4 Scope of the reaction for various propynoic amides under the optimized conditions. Isolated yields for *Z*-product are listed together with the *E*/*Z* selectivities.



Scheme 5 Mechanistic considerations of possible reaction pathways for the partial reduction of ynoates to ynones. Stereochemical assignments for intermediates are omitted for simplicity. (a) Representation of possible pathways A, B and C. (b) Possible explanation for *Z*-selectivity of the partial reduction.

phosphine catalyzed alkyne difunctionalization reactions.[4,5] Upon proton transfer, intermediate **vii** would lead to the betaine **viii** and subsequently to the oxaphosphetane **ix** which, *via* elimination of phosphine oxide, produces the enoate product ***Z*-3**. Such intermediates have been proposed to be involved in Wittig type olefinations.[8a] and are also invoked in phosphine promoted reductions of epoxides that require heating to high temperatures and presumably feature high kinetic barriers.[9] In agreement with the literature,[9] the performed quantum chemical calculations predict high energy barriers to be involved in the formation of ***Z*-3** along path A (see Fig. S11†). Overall, water addition to the zwitterion appears to be the rate-limiting step in this proposed pathway. The computational results are in line with the experimental finding and show that the reduction of **P-3** using tributylphosphine is highly *Z*-selective, as three of four investigated channels yield ***Z*-3**. Detailed information regarding the computational results assessing the thermodynamics of path A are presented in the ESI.†

The vinylphosphonium intermediate could also undergo nucleophilic attack of the hydroxide ion on the phosphorus atom resulting in the pentavalent *P*-hydroxyphosphorane **iv** (paths B and C). Interestingly, the quantum chemical simulations reveal a considerable destabilization of the P-C2 single bond upon deprotonation (**iv** to **v**), which is evident from the elongation of this bond from 1.895 (**iv**) to 2.234 Å (**v**). This finding is further supported by the reduction of the Mayer bond-order from 1.05 in the zwitterion – typical for a regular single bond – to merely 0.51. The intermediate **iv** and its deprotonated form **v** could lead to the oxaphosphetane intermediate **x** (path C). We considered this pathway unlikely as it involves 4-*endo-trig* type cyclization. Instead, *P*-oxophosphorane **v** could fragment to produce phosphine oxide and the vinyl anion **vi** which is rapidly protonated to afford the enone ***Z*-3**. Such fragmentation is supported by the simulations which clearly reveal the weakening of the P-C2 (single) bond in **v**, thus initiating the complete cleavage of the P-C2 bond to form **vi** (Fig. S15 in the ESI†). This mechanism has been invoked in recently reported substitutions of phosphonium salts[10] and studied in detail in the pioneering work of Byrne and Gilheany on hydrolysis and alcoholysis of phosphonium ylides.[11] Our preliminary computational results indicate that this fragmentation occurs with a low kinetic barrier which favors path B as a mechanism of the reduction over paths A and C. Direct S_N2-type substitution at the phosphorus atom of intermediate **v** to generate the vinyl anion was excluded in the light of previous studies.[10h,12]

The control of stereoselectivity in these reactions is then reduced to the question of stereoselectivity in the formation of

vinylphosphonium intermediate **iii** or the *P*-hydroxyphosphorane **iv**. There is some evidence that addition of phosphine to ynoates followed by protonation can be highly selective.[13] Alternatively, solvation of allenic intermediate **ii** may be controlled by electrostatic interactions which would bring water molecules in proximity of the phosphonium salt (Scheme 5b). This would set the stage for a fast, consecutive deprotonation of water and the addition of hydroxide into the phosphonium ion. The linear allenic enolate would then be preferentially protonated on the side of the C2–C3 alkene *syn* to the phosphonium substituent which could explain high *Z*-selectivity. In this case, intermediate **ii** would be short-lived and exist as a tight ion pair of phosphonium and hydroxide. The preliminary computational study agrees with this scenario. Formation of *E*-enoate is a consequence of thermodynamically controlled isomerization of the *Z*-enoate that could be catalyzed by any Lewis-basic species in the reaction mixture.

Conclusions

In conclusion, tributylphosphine promotes efficient and selective 1,4-reductions of electron deficient alkynes to the corresponding alkenes, α,β-unsaturated esters and amides. The reduction reactions are highly *Z*-selective. Under conditions that promote isomerization, they are followed by the *Z*- to *E*-isomerization of the product *in situ*. Reaction time and the amounts of phosphine and water in the reaction mixture are the key experimental factors controlling the selectivity by preventing and/or reducing the rates of the *Z*- to *E*-product isomerization. The proposed reaction mechanism involves formation of a vinylphosphonium intermediate that undergoes addition of hydroxide to the phosphonium ion followed by fragmentation of the resulting *P*-hydroxyphosphorane to the phosphine oxide and the vinyl anion. Overall selectivity in these reductions could be determined by the stereoselective formation of the *E*-*P*-hydroxyphosphorane *via* protonation of the enolate ion and a fast consecutive addition of the formed hydroxide to the phosphonium ion which occur with overall *syn* selectivity. The possibility of reducing the phosphine oxide byproduct by other reductants *in situ*,[14] may set the foundation for the development of reduction reactions that are catalytic in phosphine.

Conflicts of interest

There are no conflicts to declare.

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