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Phosphine-mediated partial reduction of alkynes to form both (*E*)- and (*Z*)- alkenes

Brett M. Pierce, Brittany F. Simpson, Kane H. Ferguson and Rachel E. Whittaker*

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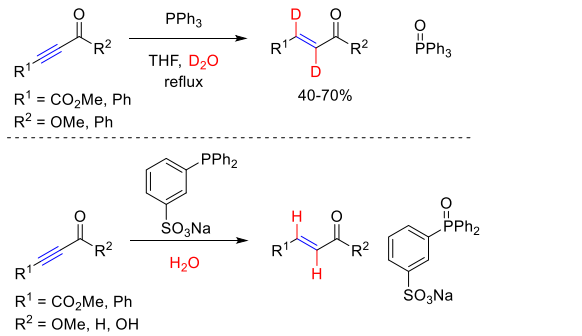
A mild, phosphine-mediated partial reduction of alkynyl carbonyls to the corresponding alkenes was developed. Tuning of the reaction conditions led to either the (*E*)- or (*Z*)- diasetereomer with high selectivity. A range of alkynyl esters, amides, and ketones were reduced to form alkenes in good to high yields and with excellent functional group tolerance.

The partial hydrogenation of alkynes to produce alkenes is a useful and important synthetic transformation. Mild and selective methods remain scarce, however; typical procedures utilize transition metal-catalysts or harsh reagents and conditions.[1,2] In particular, the reduction of ynones and ynoates is limited. Furthermore, vastly different methods and conditions must be applied to obtain either (*E*)- or (*Z*)- alkenes stereoselectively. Typical methods to form (*Z*)-enones selectively rely on transition metal catalysts, such as Lindlar's catalyst or, more recently, on metal nanoparticle catalysts.[3] Selective formation of (*E*)-enones can be accessed via harsh hydride reagents (with additives)[4] or enzyme catalysis.[5] The resulting α, β-unsaturated carbonyls are important synthetic building blocks, as well as being found in numerous natural products, so a mild and convenient synthesis of (*E*)- and (*Z*)-alkenes selectively through a common method would be an important development.

Nucleophilic addition of phosphines to alkynyl carbonyl-containing compounds has been well reported.[6] The resulting zwitterionic phosphonium intermediate can undergo a diverse array of transformations. Typically, the phosphine is regenerated in the final step, allowing for it to be used in catalytic amounts. An interesting, but underexplored, example of this reactivity is the partial reduction of ynones to form primarily (*E*)-alkenes under aqueous conditions (Scheme 1).[7,8] Though not catalytic in nature, this process is phosphine-mediated and results in phosphine oxide by-products. Richards and Williams's seminal study examined the formation of di-deuterated alkenes from alkynyl carbonyls with D_2O in refluxing THF.[7] This transformation showed the potential for a mild reduction of alkynes, but the scope was limited to only a few examples and (*E*):(*Z*) selectivity was not well controlled. Later, Larpent and Meignan performed the reduction of alkynyl carbonyls in water by utilizing a water-soluble tri-aryl phosphine.[8] The scope of this reaction was also limited and water was required as the solvent in order to achieve high yields and selectivity of the (*E*)-isomer.



Scheme 1. Initial Studies of Phosphine-Mediated Reductions

Based on these early studies, we hypothesized that this method could be made more general for a wide variety of alkynyl carbonyls by employing the inexpensive and readily available triphenylphosphine and a mixed solvent system with water to maximize the solubility of organic molecules. Additionally, since the (*E*)-/(*Z*)- isomerization of alkenes by nucleophilic phosphine addition had been established,[8] it was hypothesized that by tuning the reaction conditions, the stereoselective formation of both *(Z)*- and (*E*)- alkenes could be achieved.

To examine our hypothesis, an alkynyl ester was chosen 1) because it should be intermediate in reactivity towards the

Murray State University, Department of Chemistry, 1201 Jesse D. Jones Hall, Murray, Kentucky 42071. Email: rwhittaker1@murraystate.edu

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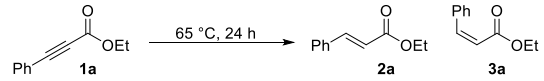
phosphine between ketones and amides and 2) in order to avoid the possibility of 1,3-hydrogen transfer,[9] which could interfere with the reactivity or selectivity of the reaction. With these considerations in mind, ynoate **1a** was chosen as the standard substrate to obtain optimal conditions (Table 1). First, using ethanol as the solvent, the equivalents of triphenylphosphine was explored. Slightly greater than a stoichiometric amount (1.5 equivalents) was found to be optimal for increased yield, though the (*E*):(*Z*) selectivity was poor (Entry 2). Next, effects of the solvent were explored and it was found to play a crucial role in the diastereoselectivity. By switching from ethanol to THF the yield was slightly lowered, but the selectivity was inverted to greatly favour the (*Z*)-alkene (Entry 4). Use of other solvents showed decreased yield, likely due to lack of miscibility with water (Entries 5 and 6). Slightly increasing the amount of water to 40 equivalents increased the yield while only marginally reducing the selectivity for the (*Z*)-enoate (Entry 7).

Satisfied with the formation of (*Z*)-alkenes, focus was returned to the (*E*)-isomer. It was hypothesized that an acidic additive could help the stereoselectivity of the reaction.[10] Indeed, the addition of benzoic acid was found to invert the stereoselectivity once again and led to the (*E*)-enoate in high yield and with high distereoselectivity (Entry 9). Addition of a Lewis acid, such as $ZnCl_2$, did not show any improvement over benzoic acid (Entry 10).

Table 1. Selected Optimization Studies[a]



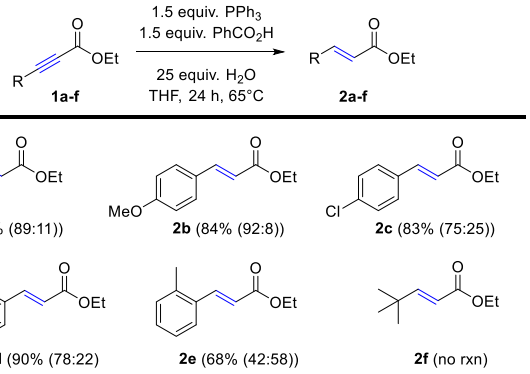
Entry	PPh_3 (Equiv.)	H_2O (Equiv.)	Solvent	Additive	Yield (E:Z)[b]
1	0.8	55	EtOH	-	43% (58:42)
2	1.5	55	EtOH	-	51% (69:31)
3	2	55	EtOH	-	42% (70:30)
4	1.5	25	THF	-	46% (10:90)
5	1.5	25	Toluene	-	<5% (6:94)
6	1.5	25	DCE	-	30% (12:88)
7	**1.5**	**40**	**THF**	**-**	**68%[c] (15:85)**
8	1.5	100	THF	-	45% (17:83)
9	**1.5**	**25**	**THF**	**1.5 equiv $PhCO_2H$**	**91%[c] (89:11)**
10	1.5	40	THF	1 equiv. $ZnCl_2$	44% (68:32)

[a] The reactions were run with ynoate **1a** (0.10 mmol). [b] Yield and (*E*):(*Z*) ratio were determined via ^1H NMR using 1,3,5-trimethoxy benzene as the internal standard. [C] Isolated yield.

With both sets of optimized conditions in hand, the substrate scope for (*E*)-enoates was initially explored. First, electronic effects were explored on the aryl ring (**2b-2d**). The electron-donating methoxy **1b** gave excellent yield and (*E*)-selectivity of the alkene. Electron withdrawing groups such as chloro- and nitro- (**1c, 1d**) also gave excellent yield, though the (*E*)- to (*Z*)- ratio was slightly diminished. Notably, no reduction of the nitro group was observed. To test if steric bulk would be tolerated, *o*-tolyl- subtrate **1e** was subjected to the reaction conditions. The yield was lowered (68%), while also severely reducing (and inverting) the diastereoselectivity ((*E*):(*Z*), 42:58).[11]

One inherent limitation of the alkyne scope was that substrates needed to be blocked alpha to the alkyne to avoid the competing phosphine-catalyzed isomerization to the conjugated diene.[6a] To avoid this, the tertiary, aliphatic *tert*-butyl alkyne **1f** was used. Unfortunately, it showed no reaction under the standard conditions.

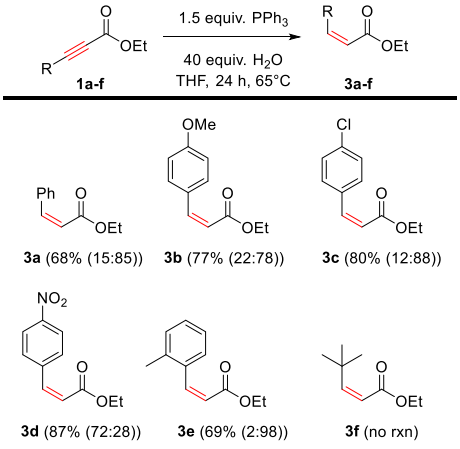
Table 2. Reduction of Ynoates to Form (*E*)-Enoates[a, b]



[a] Reactions run on a 0.10 mmol scale; all yields are isolated. [b] Number in parentheses is the (*E*):(*Z*) ratio.

Ynoates **1a-f** were also subjected to the (*Z*)-enoate-forming optimized conditions. First, substituent effects were explored on the aryl ring (**2b-2e**). For *p*-OMe and *p*-Cl groups, the (*Z*)-enoate was favoured and in good yields. However, for the strongly electron-withdrawing *p*-NO_2 group, the (*E*)-enoate was still favoured ((*E*):(*Z*), 72:28), though the overall yield was slightly higher (87%) compared with other substrates. To test if steric bulk would be tolerated, the *o*-tolyl (**1e**) substrate was subjected to the reaction conditions. The addition of steric bulk did not affect yield greatly, but showed extremely high diastereoselectivity for the (*Z*)-isomer ((*E*):(*Z*), 2:98) (*vide infra*). As for the (*E*)-enoates, the bulky aliphatic *tert*-butyl alkyne **1f** showed no reactivity to the reaction conditions.

Table 3. Reduction of Ynoates to Form (*Z*)-Enoates[a, b]



[a] Reactions run on a 0.10 mmol scale; all yields are isolated. [b] Number in parentheses is the (*E*):(*Z*)ratio.

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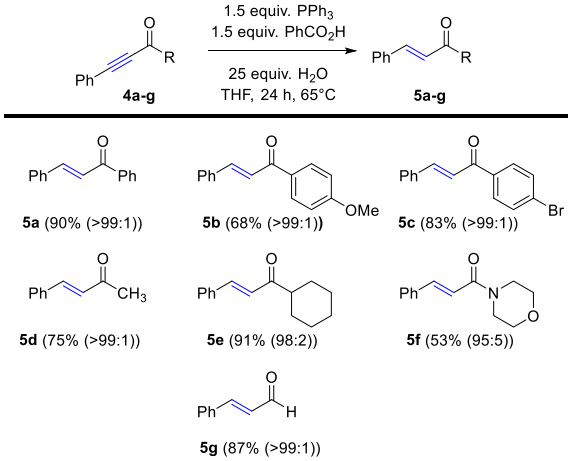
In addition to esters, other alkynyl carbonyls were also examined. First, several ketones were explored (**4a-e**). Both aromatic and aliphatic ketones were well tolerated and almost exclusively favoured the formation of (*E*)-enones, regardless of the reaction conditions used (substrates showed similar yields using either set of conditions (68-91%)). This is presumed to be the result of the increased reactivity of ketones towards nucleophilic attack by the phosphine when compared to esters. An amide was also subjected to the reaction conditions (**4f**). As expected, the morpholino amide's lowered reactivity towards nucleophilic addition resulted in slightly decreased yield (53%), but (*E*)-selectivity was still high ((*E*):(*Z*), 95:5). Finally, aldehyde **4g** was found to give the product in 87% yield and with excellent diastereoselectivity ((*E*):(*Z*), >99:1).

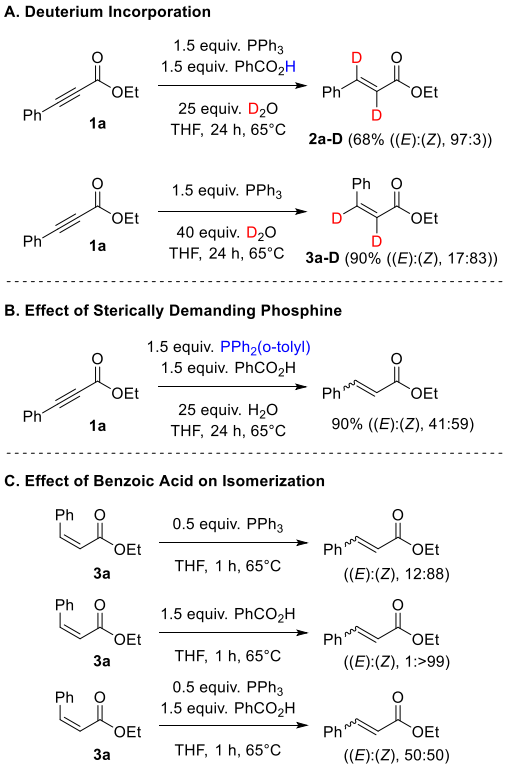
Table 4. Reduction of Other Alkynyl Carbonyls[a, b]



[a] Reactions run on a 0.10 mmol scale; all yields are isolated. [b] Number in parentheses is the (*E*):(*Z*) ratio.

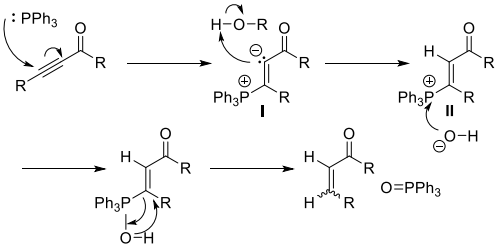
Encouraged by the scope and in order to better understand the mechanism and diastereoselectivity, the following control reactions were performed (Scheme 2). First, **1a** was subjected to both the (*E*)- and (*Z*)- conditions using deuterated water (Scheme 2A). ^{1}H NMR analysis of both **2a-D** and **3a-D** showed deuterium incorporation at both alkene positions with similar (*E*):(*Z*) ratios as with water. Next, the more sterically demanding PPh_2(*o*-tolyl) was used as the phosphine in the (*E*)-enoate reaction (Scheme 2B). This led to a slight preference for the (*Z*)-isomer, though the diastereoselectivity was greatly reduced ((*E*):(*Z*), 41:59, compared with 89:11 under the standard conditions). Interestingly, the yield was not reduced under the bulky phosphine conditions.

Finally, pure samples of the (*Z*)-isomer were subjected to either PPh_3, benzoic acid, or both for one hour under the reaction conditions (Scheme 2C). With only PPh_3 present, the disatereomeric purity was slightly degraded ((*E*):(*Z*), 12:88). This is in agreement with previous mechanistic studies, albeit in water, by Larpent and Meignan.[7] Without PPh_3, but in the presence of benzoic acid, essentially no isomerization was observed after 1 hour. With both PPh_3 and benzoic acid present, however, it was found that the pure (*Z*)-isomer had isomerized to give a 50:50 (*E*):(*Z*) mixture after 1 hour. This supports the theory that the benzoic acid additive is facilitating the (*Z*) to (*E*) isomerization catalysed by PPh_3, though its exact role is still under investigation.



Scheme 2. Control Experiments

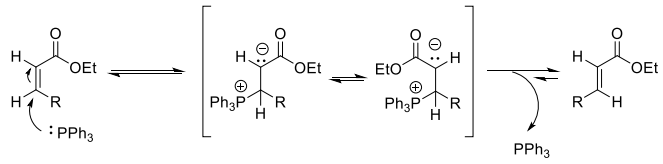
From the results of these experiments, the following mechanism was proposed (Scheme 3). First, the phosphine can nucleophilically add to the alkyne. This results in phosphonium zwitterionic intermediate **I** that can be protonated by either water or benzoic acid (if present in the reaction conditions). The resulting hydroxide can then attack the phosphonium **II**, which after collapse can give the alkene and triphenylphosphine oxide (observed *via* ^{31}P NMR). This results in a mixture of (*Z*)- and (*E*)-alkenes, though the exact diastereomeric ratio depends on the water content of the reaction.



Scheme 3. Proposed Mechanism

After the initial product formation, the (*Z*)-isomer can further undergo a phosphine-catalysed isomerization (Scheme

4). Larpent and Meignan's mechanistic studies suggested this (*Z*)- to (*E*)- isomerization could occur in the presence of excess phosphine, where the phosphine adds into the (*Z*)-alkene to form a zwitterionic intermediate that could undergo free rotation (Scheme 4).[8] Subsequent elimination of the phosphine led to the formation of the more thermodynamically-favoured (*E*)-alkene. This second phosphine addition to the sp^2 carbon is more sensitive to sterics, as evidenced by the diastereoselectivity of the bulky *o*-tolyl ester **1e**. Not only is the yield of this substrate slightly reduced, it exhibits a preference for the (*Z*)-enoate, even under (*E*)-forming conditions. This steric effect is also evidenced when a bulkier phosphine reagent (Scheme 2B) was utilized, leading to a slight excess of the (*Z*)-isomer of the standard substrate.



Scheme 4. Proposed Mechanism for (*Z*)-/(*E*)- Isomerization

Additionally, this isomerization is proposed to not go through a protonation step from water (or other proton sources);[8] no over reduction to the alkane was observed. This is further supported by the isomerization control reactions (Scheme 2C), as the isomerization can take place in the absence of a proton source. Benzoic acid does seem to play a crucial role in the isomerization step, however (Scheme 2C). Though its exact function is still being examined, it is hypothesized to be playing a stabilizing role to the zwitterionic intermediate. The addition of a non-protic Lewis acid also results in an excess of the (*E*)-product, further supporting a lack of protonation during this transformation (Table 1, Entry 10). Further studies are ongoing to more fully understand the exact role of the acid additive.

In conclusion, a metal-free reduction of ynoates and other alkynyl carbonyls is reported. Tuning of the reaction acidity gave (*E*)- and (*Z*)-alkenes selectively and in good to high yields. Other functional groups were not reduced under these chemoselective conditions. Further studies to make this method catalytic in phosphine are ongoing.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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‡ All experimental data and spectral data for all products can be found in the Supporting Information document.

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