Sustainable Chemistry

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Improving the Atom Efficiency of the Wittig Reaction by a "Waste as Catalyst/Co-catalyst" Strategy**

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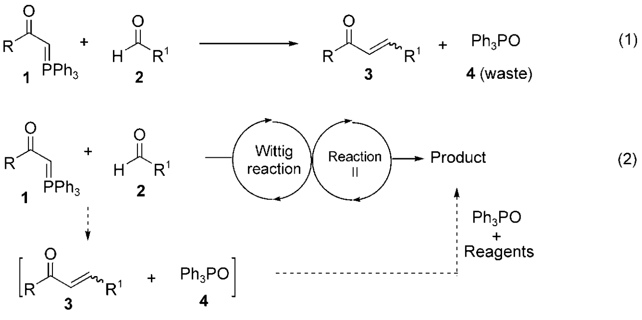
Maximizing synthetic efficiency and minimizing waste generation is a very important but challenging task in organic chemistry.[1] Much progress has been achieved in making synthetic chemistry more sustainable using strategies such as the replacement of classical "stoichiometric" methods with atom-efficient, catalytic, and selective processes,[2] the substitution of toxic organic solvents with novel media (e.g., ionic liquids and supercritical fluids),[3] and the combination of multi-step syntheses into one-pot tandem reactions.[4]

Nevertheless, many reactions still suffer from low atom efficiency because a large amount of waste is generated simultaneously with the desired product. For instance, the Wittig,[5] aza-Wittig,[6] Mitsunobu,[7] and Staudinger reactions,[8] and some Ph_3P-triggered reactions[9] stoichiometrically produce Ph_3PO as waste. Considering the high molecular weight of Ph_3PO (278), the atom efficiency of these reactions is relatively low. Although much effort has been devoted to improving the atom efficiency of these transformations, for example in the development of a catalytic Wittig reaction,[10] the development of new strategies to improve the atom efficiency of such reactions is still urgent and very important.

In nature, a practical strategy to improve atom utilization is the use of waste from one species by another species. Urea, for example, whilst being a waste produced in the metabolism of animals, is a nitrogen-release fertilizer for plants. Inspired by this, and together with our interest in tandem reactions,[4l] we considered a "waste as catalyst/co-catalyst" approach to improving the atom economy of a reaction by coupling it into a tandem reaction and directly using its generated waste as a catalyst/co-catalyst for the next step.

Surprisingly, the employment of this strategy to improve synthetic efficiency has been rarely explored in organic chemistry. In 2008, Alaimo et al. reported a tandem nitroarene reduction/imine formation/aza Diels–Alder reaction,[11] which utilized the In^{III} byproducts produced from the reduction step to catalyze the aza-Diels–Alder reaction. However, the use of two equivalents of In^0 as the reducing agent and five equivalents of aldehyde to achieve high overall yield, together with the fact that the same aza-Diels–Alder reaction was reported to work well in methanol without any catalyst,[12] made the whole transformation less atom-economical. Most recently, Tian and co-workers reported an indirect method for utilization of the TMSCl byproduct that was generated in a tandem nitrogen protection/imine formation/imine addition reaction.[13] That process needed the addition of water to hydrolyze the TMSCl byproduct from the reaction of hexamethyldisilazane (HMDS) and chloroformate to produce the active catalyst, HCl, for the following two steps. To the best of our knowledge, only the two examples are reported in the literature that utilize the byproduct of an upstream step to catalyze the downstream reaction in a tandem reaction, and the use of waste generated in the first step of a catalystic asymmetric reaction as catalyst/co-catalyst in the enantioselective reaction step has not yet been reported.

The Wittig reaction (Scheme 1) is an ideal testing ground for demonstrating the power and potential of this "waste as catalyst/co-catalyst" strategy, for the following reasons: 1) in spite of the low atom efficiency, the Wittig reaction is one of the most powerful tools for the construction of carbon–carbon double bonds,[5] including the synthesis of α,β-unsaturated carbonyl compounds,[14] which are widely used substrates for the design of tandem reactions; 2) though being a "notorious" waste in the aforementioned reactions, Ph_3PO is a powerful Lewis base catalyst for an array of transformations.[15] In addition, Ph_3PO is a useful additive in some chiral Lewis acid catalyzed reactions for improving reactivity and selectivity,[16] which makes it possible to use Ph_3PO that is generated in situ to improve the selectivity of tandem reactions that involve a chiral Lewis acid catalyzed reaction. In light of these two facts, we considered that the combination of the Wittig reaction with Ph_3PO chemistry might allow for the development of tandem reactions with improved atom economy. As shown in Scheme 1, if the Wittig reaction is run independ-



Scheme 1. A tandem Wittig/conjugate-reduction reaction.

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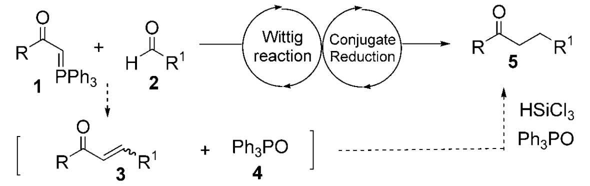
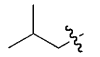
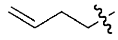
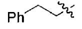
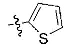
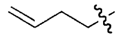
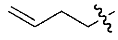
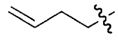
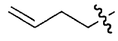
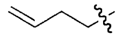
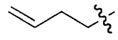
ently, the atom economy is low because of the generation of a stoichiometric amount of Ph_3PO [Eq. (1)]. In contrast, the atom efficiency might be significantly improved in a tandem reaction, if the Ph_3PO that is generated from the Wittig reaction step could serve as a catalyst or co-catalyst for the next step [Eq. (2)]. If this strategy is successful, it might be further applied to improve the atom economy of reactions which generate Ph_3PO or its analogues as by-products. Herein, we report our preliminary results towards such reactions.

First, we attempted a tandem Wittig/conjugate-reduction reaction, with the aim of providing an organocatalytic method for the synthesis of saturated ketones from easily available aldehydes in a one-pot operation. As shown in Table 1, the tandem reaction directly employed the in-situ-generated Ph_3PO as the catalyst for the conjugate reduction step.[17] It should be noted that the preparation of α,β-unsaturated ketones using the Wittig reaction was straightforward when side-reactions involving the direct coupling of ketones and labile aldehydes were observed,[14] because the generation of Ph_3PO was then unavoidable.

After careful screening, the optimal conditions were determined to be performing the reaction under an atmosphere of nitrogen using 1,2-dichloroethane as the solvent, with addition of $HSiCl_3$ after completion of the Wittig reaction step (see the Supporting Information). The substrate scope is shown in Table 1. To obtain accurate yields of the isolated products, aldehydes with low boiling point were chosen to react with phosphorane **1a**, and the desired saturated ketones **5a–d** were obtained in good to excellent yield (Table 1, entries 1–4). Other aldehydes reacted with phosphorane **1b** to afford their corresponding ketone **5e–l** in excellent yield (Table 1, entries 5–12). In the case of aryl aldehydes, the substituent on the *ortho* position of the phenyl ring influenced the reactivity, and slightly lower yield was obtained (Table 1, entry 6–8). A serial of functional groups such as ketones, nitro groups, halogen atoms, and terminal alkene groups tolerated the reaction conditions of the conjugate reduction step, thus illustrating the excellent chemoselectivity of this novel organocatalytic transformation.[18]

Table 1: The substrate scope of the tandem reaction.[a]



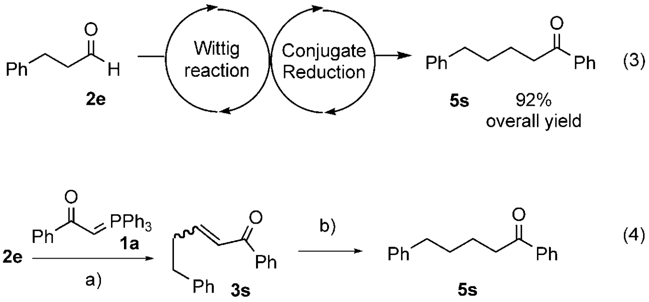
Entry[b]	R	R^1		5	Yield[c] [%]
1	Ph (**1a**)	*n*Pr	(**2a**)	**5a**	87
2	Ph (**1a**)		(**2b**)	**5b**	98
3	Ph (**1a**)		(**2c**)	**5c**	90
4	Ph (**1a**)	*c*-hexyl	(**2d**)	**5d**	79
5	Me (**1b**)		(**2e**)	**5e**	92
6	Me (**1b**)	*o*-$NO_2C_6H_4$	(**2f**)	**5f**	88
7	Me (**1b**)	*m*-$NO_2C_6H_4$	(**2g**)	**5g**	96
8	Me (**1b**)	*p*-$NO_2C_6H_4$	(**2h**)	**5h**	98
9	Me (**1b**)	*p*-BrC_6H_4	(**2i**)	**5i**	89
10	Me (**1b**)	*p*-ClC_6H_4	(**2j**)	**5j**	92
11	Me (**1b**)	2,4-$Cl_2C_6H_3$	(**2k**)	**5k**	98
12	Me (**1b**)		(**2l**)	**5l**	86
13	Me (**1b**)		(**2c**)	**5m**	73
14	*p*-$NO_2C_6H_4$ (**1c**)		(**2c**)	**5n**	70
15	*o*-ClC_6H_4 (**1d**)		(**2c**)	**5o**	76
16	*m*-ClC_6H_4 (**1e**)		(**2c**)	**5p**	81
17	*p*-ClC_6H_4 (**1f**)		(**2c**)	**5q**	87
18	COOEt (**1g**)		(**2c**)	**5r**	–

[a] Order of addition: **2e** and **1a** in 1,2-dichloroethane, 50 °C; then $HSiCl_3$ (2.0 equiv), 0 °C. [b] Reaction scale: 1.0 mmol. [c] Yield of isolated product.

Different phosphoranes **1** were also evaluated using aldehyde **2c** (Table 1, entries 13–18). Generally, the more stable the phosphorane **1**, the slower the reaction rate in the Wittig reaction step. As a result, phosphoranes **1c–f**, which contained electron-withdrawing groups on the phenyl ring, afforded lower yields. The regioselectivity of this reaction was excellent, and only the conjugated C=C double bond was reduced, affording the desired ketones **5c** and **5m–q**, leaving terminal double bond intact. Ketones **5c** and **5m–q**, which all contained a terminal alkene functional group, are useful building blocks in organic synthesis.[19] Multistep syntheses were previously required to obtain this type of saturated ketones;[20] however, using this method, such compounds can be readily prepared via a one-pot tandem reaction from commercially available starting materials with high tolerance of functional groups. Ethyl-pyruvate-derived Wittig reagent **1g** afforded a complex mixture of products under the reaction conditions, and the desired product could not be isolated cleanly (Table 1, entry 18).

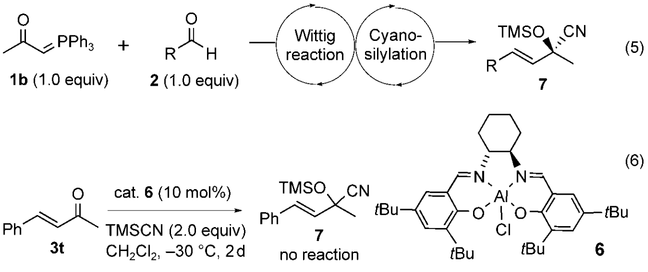
The tandem reaction had an advantage that the conjugate reduction step proceeded very efficiently because Ph_3PO was generated stoichiometrically. For example, the reduction step of the tandem reaction [Scheme 2, Eq. (3)] was finished within one hour, affording product **5s** in 92 % overall yield over two steps. If the two steps were operated independently and only 10 mol % of Ph_3PO was used for the conjugate reduction step [Eq. (4)], the reduction of enone **3s** was noticeably slower, affording **5s** in only 52 % yield, even the reaction time was twice as long as that for Eq. (3). Although one might think it is unsuitable to regard Ph_3PO as a catalyst because it is present in stoichiometric quantities in the reaction system, catalytic amounts of Ph_3PO worked successfully in the conjugate reduction [Eq. (4)], and the conjugate reduction could not take place in the absence of Ph_3PO.

A catalytic asymmetric tandem Wittig–cyanosilylation reaction was also investigated to demonstrate the potential of this "waste as catalyst/co-catalyst" strategy [Eq. (5)], which utilized the Ph_3PO generated in the Wittig reaction step as a Lewis base catalyst to activate TMSCN for facilitating cyanide transfer in the asymmetric cyanosilylation[21] step. For the catalytic asymmetric cyanosilylation step, chiral salen aluminium catalyst **6**[22] was found to be highly enantioselective, and dichloromethane turned out to be the best solvent.



Scheme 2. Control experiments. Order of addition for Eq. (3): **2e** and **1a** in 1,2-dichloroethane, 70 °C, 17 h; then $HSiCl_3$ (2.0 equiv), 0 °C, 1 h. a) 1,2-dichloroethane, 70 °C, 17 h, 88 % yield; b) Ph_3PO (10 mol %), $HSiCl_3$ (2.0 equiv), 0 °C, 2 h, 52 % yield.

Table 2: A tandem Wittig-cyanosilylation reaction.[a]



Entry[b]	R	7	Yield [%][c]	*ee* [%][d]
1[e]	Ph	**7a**	84	88
2[f]	*p*-ClC_6H_4	**7b**	93	93
3[f]	*m*-ClC_6H_4	**7c**	96	92
4[e]	*o*-ClC_6H_4	**7d**	71	68
5[f]	*p*-$NO_2C_6H_4$	**7e**	93	90
6[e]	*m*-$NO_2C_6H_4$	**7f**	86	90
7[e]	*p*-$CF_3C_6H_4$	**7g**	89	92
8[e]	*m*-MeC_6H_4	**7h**	97	90
9[e]	*p*-BrC_6H_4	**7i**	86	90
10[e]	2-thienyl	**7j**	97	65
11[e]	1-naphthyl	**7k**	90	86
12[e,g]	*n*Pr	**7l**	66	75

[a] Order of addition: **2** and **1b** in CH_2Cl_2, 80 °C; then catalyst **6** (5–10 mol %) and TMSCN (2.0 equiv), −30 °C. [b] Reaction scale: 0.5 mmol. [c] Yield of isolated product. [d] Determined by chiral HPLC or GC analysis. [e] 10 mol % of catalyst **6**; [f] 5 mol % of catalyst **6**; [g] 1.0 mmol scale.

To speed up the initial Wittig reaction between aldehyde **2** and phosphorane **1b**, the reaction was carried out in a screw-capped pressure tube using dichloromethane as the solvent at 80 °C, and chiral catalyst **6** and TMSCN were added after the completion of the Wittig step (see the Supporting Information). As the subsequent cyanosilylation reaction was run at −30 °C, 5 or 10 mol % chiral catalyst **6** was needed to ensure reasonable reactivity.

A variety of aldehydes worked well under these reaction conditions to afford the desired quaternary cyanohydrins in good to excellent yields and enantioselectivities (Table 2). Generally, *para*- or *meta*-substituted benzaldehydes worked well to provide the corresponding product **7** in excellent yield and enantioselectivity (Table 2, entries 1–3 and 5–9). However, the substituent at the *ortho* position of benzaldehyde had a negative effect on the reactivity and enantioselectivity; for example, 2-chlorobenzaldehyde afforded product **7d** in noticeably lower yield and *ee* value (Table 2, entry 4). 2-Thenaldehyde worked well, but the corresponding product **7j** was obtained in only 65 % *ee* (Table 2, entry 10). In the case of 1-naphthaldehyde, product **7k** was synthesized in 90 % yield and 86 % *ee* (Table 2, entry 11). Aliphatic aldehyde also worked well under these reaction conditions and, for example, *n*-butyraldehyde-derived product **7l** could be obtained in 75 % *ee* (Table 2, entry 12). The absolute configuration of **7a** was determined to be *S* from comparison of the optical rotation with the literature value.[21j]

To demonstrate the pivotal role of Ph_3PO in the cyanosilylation step, a control experiment was conducted starting from the corresponding enone **3t** in the absence of Ph_3PO at −30 °C, and no desired product **7a** was observed by TLC analysis [Eq. (6)]; this result was in accordance with a literature report, which concluded that the cyanosilylation reaction of ketones could not take place without Ph_3PO, even at room temperature, when using chiral catalyst **6**.[21j] This result unambiguously demonstrated the importance of Ph_3PO as a Lewis base catalyst to activate TMSCN in the subsequent cyanosilylation reaction. The high yield and enantioselectivity of this tandem Wittig–cyanosilylation reaction further exhibited the potential of the "waste as catalyst/co-catalyst" strategy in the development of new catalytic asymmetric tandem reactions with improved atom economy.

In conclusion, we have demonstrated that a "waste as catalyst/co-catalyst" strategy has promise for improving the atom economy of a reaction that has poor atom economy, by modular integration of it into a tandem reaction sequence and the direct utilization of its waste as a catalyst or co-catalyst for the next step. Using this strategy, we successfully developed a novel tandem Wittig–conjugate-reduction reaction in which the in-situ-generated Ph_3PO from the Wittig reaction step served as the catalyst for the following conjugate reduction step without any treatment, providing a facile method for the preparation of saturated ketones from easily available substrates with excellent chemo- and regioselectivity. This strategy was also useful in the development of asymmetric catalytic tandem reactions with improved atom efficiency. A tandem Wittig/cyanosilylation reaction was also developed, which provided a facile method for the synthesis of quaternary cyanohydrins in good to excellent yield and enantioselectivity, and the Ph_3PO generated in the Wittig step serves as Lewis base catalyst to activate TMSCN for the following enantioselective cyanosilylation reaction of enones. Considering that Ph_3PO, its analogues, or other Lewis bases could be stoichiometrically generated in a number of widely used reactions, the "waste as catalyst/co-catalyst" strategy might have wide potential application in organic synthesis. Experiments are now underway in our lab to evaluate this strategy in other tandem reactions, and especially to develop catalytic asymmetric tandem reactions which utilize the internally generated by-product for improving reactivity and selectivity.

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