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# Organocatalytic Mitsunobu Reactions

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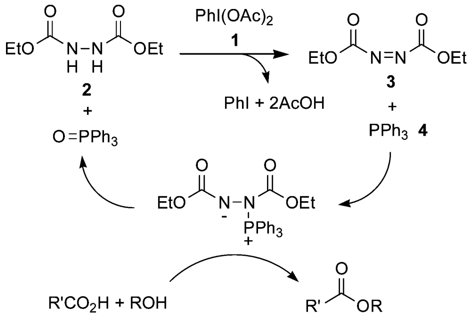
The Mitsunobu reaction is a powerful and widely used procedure for the synthesis of a range of acid derivatives.[1] This reaction involves the dehydrative coupling of an alcohol with an acidic component to form esters, ethers, imides, and so on, using a combination of a reducing (phosphine) and an oxidizing (azo) reagent. One of the major attractions of this reaction is that it inverts the stereochemistry of the alcohol starting material.[2] However, a significant drawback is that these reactions require four reagents and starting materials (an alcohol, an acid/pro-nucleophile, a phosphine, and an azo reagent) and, thus, the desired product can be difficult to separate from the excess starting materials and reagents and the reaction byproducts (a phosphine oxide and a hydrazine derivative). Thus, numerous modified reagents and separation techniques have been developed with the aim of facilitating isolation of the desired product from these reactions.[3]

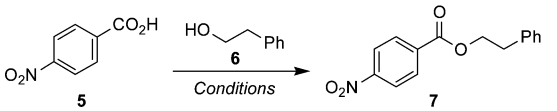
In this area, we have had an interest in the development of polymeric phosphine reagents for use in Mitsunobu reactions[4] and have recently reported a reaction system in which both the required phosphine and azo reagents are attached to individual polymers.[5] We have also described an organocatalytic dual polymer system for selective nitroxyl radical mediated alcohol oxidation in which the stoichiometric oxidant is a polystyrene-supported analogue of iodosobenzene diacetate (**1**).[6] In the course of investigating the latter reaction system, it occurred to us that since **1** is known to oxidize 1,2-dicarbethoxyhydrazine (**2**) to diethyl azodicarboxylate (**3**),[7] it might be possible to use **1** as the stoichiometric oxidant in Mitsunobu reactions and, thus, allow **3** to be used as a catalyst (Scheme 1). Despite the large volume of research dedicated to improving the Mitsunobu reaction, to our knowledge no system has yet been reported in which product recovery is facilitated by using one of the reagents that produces a difficult to remove byproduct as a catalyst rather than as a stoichiometric reagent. Herein we report the development of such an organocatalytic Mitsunobu reaction system that uses **3** as a catalyst and **1** as the stoichiometric oxidant.[8,9]

***Scheme 1.*** Proposed Catalytic Mitsunobu Reaction Cycle



To test the feasibility of the concept outlined in Scheme 1, we first examined the reaction of 4-nitrobenzoic acid (**5**)[10] with 2-phenylethanol (**6**) under various conditions. Gratifyingly, the desired ester **7** was formed in good yield using the initial conditions of 0.2 equiv of catalyst **3** in conjunction with 1.5 equiv of oxidant **1** and 1.2 equiv of **4**. Eventually, optimal conditions were determined to be the use of 0.1 equiv of **3** and 2.0 equiv of both **1** and **4** (Table 1, entry 1). This combination of reagents allowed for excellent yield of product to be formed that could be separated from the reaction byproducts in an efficient manner. However, it should be noted that a control reaction in which **3**, but not **4**, was omitted afforded 18% yield of the **7** (Table 1, entry 2), and omission of both **3** and **4** resulted in no formation of **7** (Table 1, entry 3). Regardless of this background reaction and the details of its mechanism, our isolated yields clearly indicate that a process catalytic in **3** is occurring because the isolated yield of **7** (90%) is greater than the sum of the background yield (18%) and the amount of **3** (10%) used. Importantly, when primary alcohols are used as the electrophile, the background reaction provides the same product as the organocatalytic reaction and, thus, it actually increases the overall yield of the desired product.

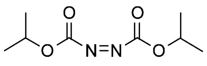
***Table 1.*** Catalytic Mitsunobu Esterification of 4-Nitrobenzoic Acid



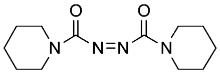
| entry | reaction conditions | yield[a] (%) |
|---|---|---|
| 1 | **5** (1.1 eq.), **6** (1.0 eq.), **4** (2.0 eq.), **3** (0.1 eq.), and **1** (2.0 eq.), THF, rt, 16 h | 90 |
| 2 | **5** (1.1 eq.), **6** (1.0 eq.), **4** (2.0 eq.), and **1** (2.0 eq.), THF, rt, 16 h | 18 |
| 3 | **5** (1.1 eq.), **6** (1.0 eq.), and **1** (2.0 eq.), THF, rt, 16 h | 0 |
| 4 | **5** (1.1 eq.), **6** (1.0 eq.), **4** (2.0 eq.), **8** (0.1 eq.), and **1** (2.0 eq.), THF, rt, 16 h | 69 |
| 5 | **5** (1.1 eq.), **6** (1.0 eq.), **4** (2.0 eq.), **9** (0.1 eq.), and **1** (2.0 eq.), THF, rt, 16 h | 41 |

[a] Average isolated yield of at least two 1.8 mmol scale experiments.

Encouraged by these initial results, we also examined the catalytic use of other azo reagents, such as **8**, which is less expensive and reportedly easier to handle than **3**,[3a] and **9**, which allows for the use of a wider range of nucleophiles than does **3**.[11] With both reagents, the desired product **7** was isolated in slightly lower yield than was obtained with **3** (Table 1, entries 4 and 5).



**8**



**9**

We next examined the range of alcohols that could be used in the reaction system. In addition to primary aliphatic alcohol **6**, other benzylic and aliphatic alcohols all afford the desired product in slightly lower yield in the catalytic reaction than the corresponding reaction that was stoichiometric in **3** (Table 2, entries 1−4). The success with benzylic alcohol substrates is noteworthy because **1**

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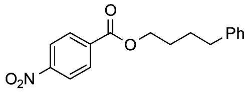
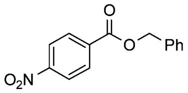
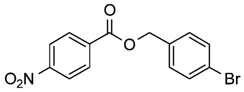
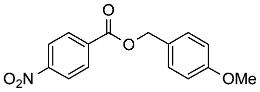
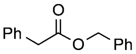
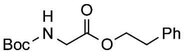
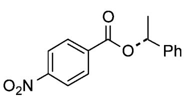
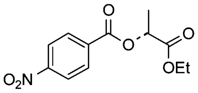
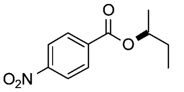
***Table 2.*** Catalytic Mitsunobu Reaction Products[a]

| entry | product | yield (%) | | |
|---|---|---|---|---|
| | | cat.[b] | stoic.[c] | bkgd.[d] |
| 1 |  | 81 | 100 | 10 |
| 2 |  | 76 | 100 | 15 |
| 3 |  | 75 | 98 | 16 |
| 4 |  | 54 | 89 | 23 |
| 5 |  | 88 | 97 | 50 |
| 6 |  | 58 | 58 | 22 |
| 7 |  | 17<br>59[e]<br>er = 84:16 | 100<br>er = 93:7 | 3[e] |
| 8 |  | 65[e]<br>er = 100:0 | 96<br>er = 100:0 | 1[e] |
| 9 |  | 63[e]<br>er = 93:7 | 100<br>er = 94:6 | 0[e] |

[a] Reactions performed with 1.0 equiv of ROH (1.8 mmol), 1.1 equiv of acid, 2.0 equiv of **1**, 0.1 equiv of **3**, and 2.0 equiv of **4** at 25 °C in THF for 16 h. [b] Average isolated yield of at least two experiments. [c] Yield of reaction using 1.0 equiv of **3**. [d] Yield of control reaction analogous to Table 1, entry 2. [e] Reagent **4** was added at a rate of 0.25 equiv/h.

is reported to slowly oxidize such primary benzylic alcohols to the corresponding carboxylic acids under certain conditions.[12]

The aliphatic carboxylic acids phenyl acetic acid and Boc-protected glycine were also examined as pronucleophiles. Again, in these cases, the catalytic reaction afforded similar or slightly lower yield than did the corresponding stoichiometric reaction (Table 2, entries 5 and 6). It should also be noted that reactions using these acids exhibited more of the azo-free background reaction than did reactions with **5** and that the corresponding acetate was a significant byproduct.

The use of secondary alcohols as the electrophile in this catalytic system, when all of the reagents are added at once, affords poor results because the nucleophilic attack by the conjugate base appears to be sluggish enough to allow a significant portion of **4** to be oxidized by **1** so that it cannot participate in subsequent reaction cycles. For example, the use of 1-phenylethanol afforded only 17% yield in the catalytic system (Table 2, entry 7). Therefore, we modified the experimental procedure so that **4** was added slowly to the reaction mixture of **1**, **3**, the alcohol, and the acid. By adding **4** at a rate of 0.25 equiv per hour, the yield of the desired product was increased to 59%.[13] Importantly, in two of the three examples studied, when chiral secondary alcohols were used (Table 2, entries 8 and 9), the products isolated from the catalytic reactions had essentially identical optical rotation and similar enantiomer ratios as did products from stoichiometric reactions (see SI for details). Only the catalytic reaction with chiral 1-phenylethanol afforded a lower enantiomer product ratio than did the corresponding stoichiometric reaction (68% ee vs 86% ee). Furthermore, this slow addition procedure greatly reduced the amount of the azo-free background reaction.

In conclusion, we have developed a Mitsunobu reaction system that is catalytic in the oxidizing azo reagent (**3**, **8**, or **9**) and that uses a hypervalent iodine species as the stoichiometric oxidant. The benefit of using **1** is that its byproducts (iodobenzene and acetic acid) are relatively simple to remove, while at the same time the amount of formed hydrazine byproduct (e.g., **2**) is dramatically reduced. Experiments to further optimize this reaction and to elucidate the mechanism of the background reaction are currently being performed.

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**Supporting Information Available:** Experimental details and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Using this slow addition of $PPh_3$ procedure, **7** was isolated in 87% yield from an 18 mmol scale reaction.

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