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Letter

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The "Fully Catalytic System" in Mitsunobu Reaction Has Not Been Realized Yet

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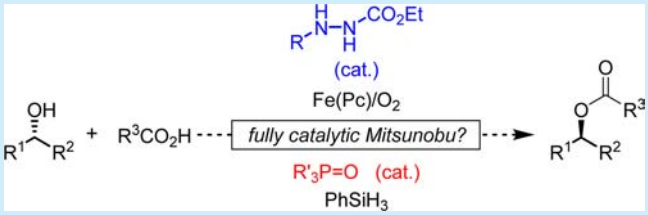
Supporting Information

ABSTRACT: An investigation of the recently reported "fully catalytic Mitsunobu reaction" using catalytic amounts of a phosphine reagent and an azo reagent has shown that although benzyl 4-nitrobenzoate is formed under the fully catalytic conditions, the same result is obtained if the hydrazine catalyst is omitted, indicating that this is not a Mitsunobu reaction. In addition, when the reaction between (−)-ethyl lactate and 4-nitrobenzoic acid was carried out using the "fully catalytic" method, the corresponding ester was formed but in very low yield and with predominant retention of configuration. Unfortunately, the system catalytic in phosphine reagent is incompatible with that in the azo reagent.



There are myriad methods for the esterification of carboxylic acids with alcohols. Most of these do not affect the stereochemistry potentially present at the chiral secondary alcohol substrate, providing esters with retention of configuration.[1] In contrast, an oxidation−reduction condensation protocol using azo and phosphine reagents, well-known as the Mitsunobu reaction, is a remarkable exception. The stereochemistry of a chiral secondary alcohol that is combined with a carboxylic acid in the Mitsunobu reaction is typically inverted in the resulting ester product.[2] The stereochemical outcome is rationalized by the Walden inversion via alkoxyphosphonium intermediates. This is the most important feature of the Mitsunobu reaction and is utilized as the method for inversion of stereochemistry of secondary alcohols as well as stereocontrolled substitution of the hydroxy groups with other nucleophiles.

Despite overt features that make the Mitsunobu reaction so attractive, it is associated with serious drawbacks. Typical azo reagents, such as diethyl azodicarboxylate, are toxic as well as light and shock sensitive, posing a considerable health and safety threat. In addition, massive amounts of waste are produced, including hydrazinedicarboxylates and triphenylphosphine oxide, often making purification of desired products troublesome.

Creative modifications in reagents and methods have been realized to circumvent the above-mentioned disadvantages. Most of them rely on removal of hydrazine and phosphine oxide byproducts.[3] Ultimately, development of catalytic systems in the Mitsunobu reaction should be a substantial improvement.

From the standpoint of azo reagents, Toy and co-workers reported the first example of the catalytic Mitsunobu reaction using iodobenzene diacetate as a sacrificial oxidizer in 2006.[4] We reported another catalytic Mitsunobu reaction with azo reagents recyclable by aerobic oxidation in 2013.[5] Ethyl 2-(3,4-dichlorophenyl)azocarboxylate has been identified as an efficient catalyst, enabling the reactions in the presence of a stoichiometric amount of triphenylphosphine, a catalytic amount of iron phthalocyanine [Fe(Pc)], and atmospheric oxygen. Recently, we reported the substantial improvement of this methodology.[6]

From the standpoint of phosphine reagents, Buonomo and Aldrich reported the catalytic Mitsunobu reaction with recyclable phosphine reagents in 2015.[7] The catalytic concept is based on *in situ* reduction of phosphine oxides with phenylsilane, which has been developed by O'Brien and co-workers in their catalytic Wittig reactions.[8] The authors succeeded in showing that the catalytic system in phosphines worked in the Mitsunobu reaction with a stoichiometric amount of diisopropyl azodicarboxylate (DIAD). Much earlier, O'Brien and co-workers disclosed the concept of the Mitsunobu reactions catalytic in phosphines in their patent report.[8c]

In their publication, Buonomo and Aldrich proposed a "fully catalytic system" of the Mitsunobu reaction combining their catalytic system in phosphines with ours of the azo reagents recyclable by aerobic oxidation (Scheme 1).[7] If realized, this is without doubt an outstanding idea, completely resolving the major drawback of the Mitsunobu protocol, i.e., generation of the large amounts of problematic wastes, hydrazides, and phosphine oxides. Under the "fully catalytic system" conditions,

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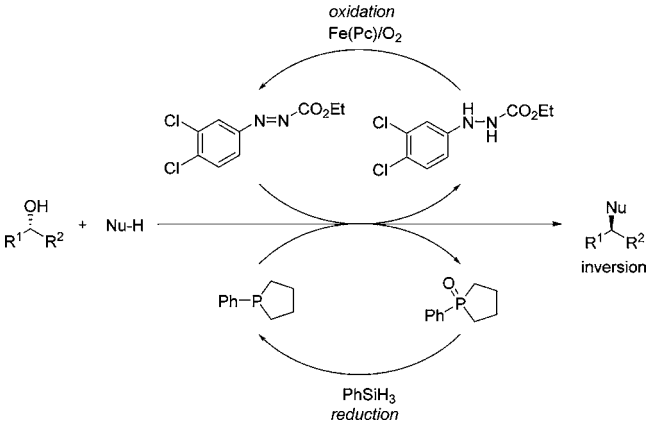
Scheme 1. Proposed Concept of the Fully Catalytic Mitsunobu Reactions

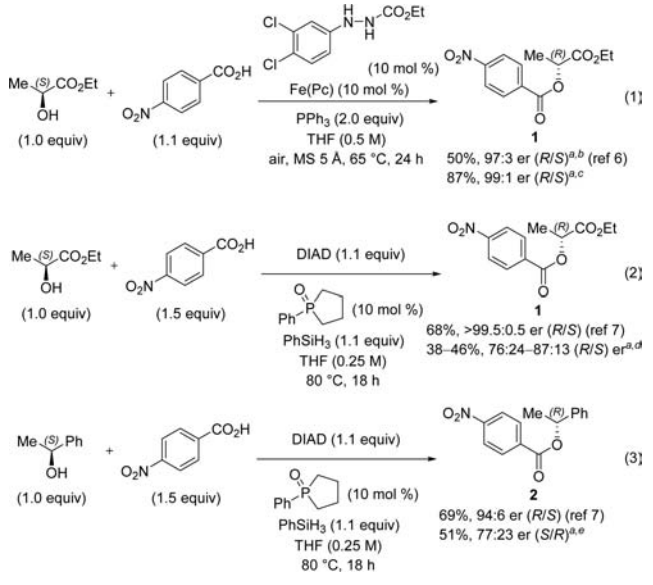


however, the authors provided only a few examples with a limited scope of substrates, demonstrating the condensation of two benzyl alcohols (4-methoxylbenzyl alcohol and benzyl alcohol) with 4-nitrobenzoic acid.

It is essential to investigate the stereochemistry in products of the protocol that is claimed to be the Mitsunobu reaction. In their "fully catalytic system", however, Buonomo and Aldrich have not clarified this point, though the reactions of chiral secondary alcohols have been properly illustrated in the system catalytic in the phosphine reagent.

In this letter, we tentatively decided to adapt a model reaction using (−)-ethyl lactate (>99:1 er) and 4-nitrobenzoic acid to evaluate the "fully catalytic" Mitsunobu reaction. Our system catalytic in the azo reagent provided the corresponding ester **1** in 50% yield and in a 97% inversion ratio (Scheme 2, eq 1).[6] On the other hand, Buonomo and Aldrich reported that

Scheme 2. Results of Catalytic Mitsunobu Reactions in the Azo Reagent or in the Phosphine Reagent



[a]Percent yield of isolated products is given. [b]MS 5 Å was activated by heating using heat gun in vacuo. [c]MS 5 Å was activated by heating using Bunsen burner in vacuo. [d]Three independent reactions were conducted. [e](*R*)-1-Phenylethanol was used instead of (*S*)-1-phenylethanol as a starting material in our trial.

the system catalytic in the phosphine reagent provided the same product in 68% yield and in a greater than 99% inversion ratio (Scheme 2, eq 2).[7] We repeated the reaction of Buonomo and Aldrich three times, but our experiments gave ester **1** in lower yields (38−46%) and moderate inversion (76−87%) than those described by the authors (Scheme 2, eq 2). When the reaction was quenched soon after the start (ca. 3 h), no significant change of the enantiomer ratio (87:13) in ester **1** could be observed (see the Supporting Information (SI)), ruling out a possibility of gradual racemization of the product during the course of the reaction. Similarly, we checked the reaction of chiral 1-phenylethanol (98:2 er) to give the ester product **2** and again obtained the result that was inferior (51% yield, 77% inversion) to the reported one (69% yield, 94% inversion) (Scheme 2, eq 3). It is certain that the "single catalytic system" of Buonomo and Aldrich provides the Mitsunobu product, but our results imply that the present reaction conditions have not been sufficiently optimized as the Mitsunobu reaction.

We tested reproducibility of the reaction between benzyl alcohol and 4-nitrobenzoic acid under the "fully catalytic system" conditions according to the authors' procedure[7] and obtained the corresponding ester **3** in 38% average yield (Figure 1, entry 1, first and second runs). Although the product

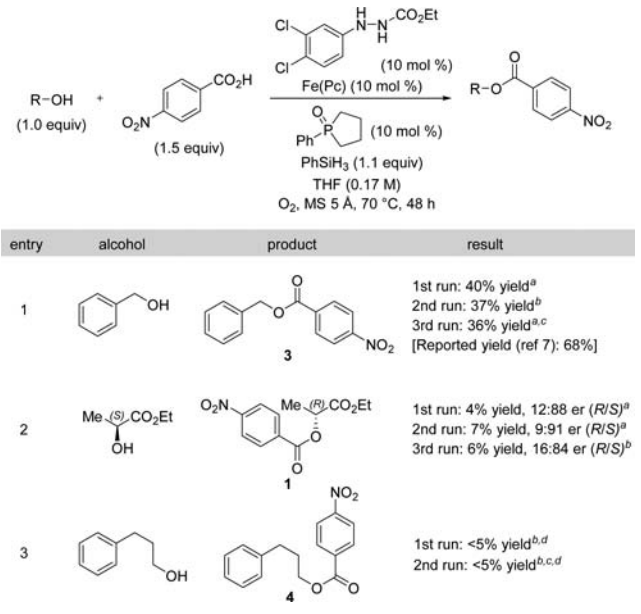


Figure 1. Results of reactions under the "fully catalytic Mitsunobu" conditions. Yields are based on isolated products unless otherwise noted. [a] MS 5 Å was activated by heating using heat gun in vacuo. [b] MS 5 Å was activated by heating using Bunsen burner in vacuo. [c] The reaction was performed in the absence of the hydrazine catalyst. [d] Yield was estimated by ^{1}H NMR analysis of the crude product.

yield is somewhat lower than that reported by the authors (68% yield), we considered that the result was qualitatively reproduced in the reaction of benzyl alcohol.

Next, we applied the "fully catalytic system" to the model substrates, (−)-ethyl lactate and 4-nitrobenzoic acid. The reaction with a chiral alcohol has not been described in the authors' publication.[7] Surprisingly, the corresponding ester product was obtained in only 4% isolated yield, and HPLC analysis showed only a 12% inversion ratio (Figure 1, entry 2, first run). This result indicates that the Mitsunobu product **1**

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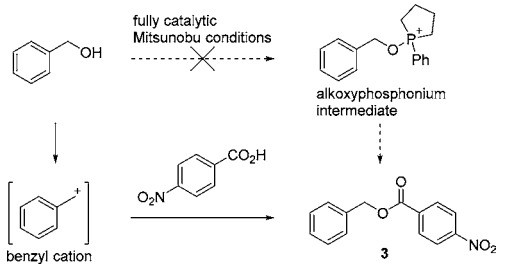
was obtained in only 0.5% yield in this system. The same experiment was repeated twice and almost reproduced the result (6−7% yield, 9−16% inversion). Incidentally, replacing 1-phenylphospholane-1-oxide with another cyclic phosphine oxide (5-phenyldibenzophosphole oxide), described in authors' publication,[7] provided only a trace amount of the product **1** (<5% yield, SI).

Our reaction conditions might partially differ from those of Buonomo and Aldrich. First, suppliers of the reagents and solvents used would not be the same in each case. We tested the reactions using reagents from different suppliers, with no impact to the outcome (see SI for our case). Second, our method for the molecular sieves activation differs from that of the authors'. The authors reported in the Supporting Information that "molecular sieves were activated by heating at 200 °C under reduced pressure",[9a] but we have recently demonstrated that such a method is insufficient for activating molecular sieves in the catalytic Mitsunobu reaction.[6] Therefore, we used molecular sieves activated strictly by heating with a heat gun (ca. 450 °C) or Bunsen burner (>1000 °C) under reduced pressure (0.1−0.9 mbar), and at least this change should work advantageously in our experiments. In the present study, we found out that the impact of molecular sieves was significantly great in reactions conducted in THF. Activating molecular sieves by Bunsen burner instead of a heat gun proved beneficial to our catalytic system in THF (Scheme 2, eq 1). This is somehow different from our recent observation where both methods of activation resulted in comparable yields of the Mitsunobu reaction in toluene and is probably a result of the hygroscopic nature of THF. On the other hand, the difference in the molecular sieves activation method affected the esterification of neither benzyl alcohol (Figure 1, entry 1) nor (−)-ethyl lactate (Figure 1, entry 2). Third, the authors used oxygen generated by sodium hypochlorite (NaClO) and hydrogen peroxide (H_2O_2). Although we typically employed commercially available oxygen filled in a gas cylinder, for comparison reasons, we repeated the reaction from entry 1 in Figure 1 by using oxygen generated from NaClO and H_2O_2, yet, with no change in the result (SI). Therefore, the above-mentioned differences in the reaction conditions are not an essential issue here.

It could be that the pathway in which ester **3** is produced in the "fully catalytic system" has been misinterpreted, and it might come from an inappropriate selection of the model alcohol substrates.[7] Namely, these reactions were performed with benzyl alcohols at elevated temperature (70 °C), which might induce the formation of a benzyl cation in the presence of 4-nitrobenzoic acid to provide the ester via the S_N1 mechanism (Scheme 3). Indeed, the authors suggested the possibility of formation of the benzyl cation in the reaction between 4-trifluoromethylbenzyl alcohol and 4-nitrobenzoic acid in the presence of phenylsilane.[9b] Yet, another pathway is possible. For instance, typical dehydrated condensation or Fe(Pc)-catalyzed oxidation−reduction condensation[10] would give ester products.

To shed light on this, we conducted control experiments in the reaction between benzyl alcohol and 4-nitrobenzoic acid. By performing the reaction in the absence of the hydrazine catalyst, product **3** was obtained in almost identical yield (36%) as that of the reaction with the hydrazine catalyst, which indicates that the hydrazine catalyst does not participate in the authors' "fully catalytic system" (Figure 1, entry 1, third run). In addition, we tested the reaction between benzyl alcohol and 4-nitrobenzoic acid solely in the presence of molecular sieves, as well as in the presence of molecular sieves and phenylsilane. No formation of ester **3** could be observed in any of these cases, ruling out S_N1 pathways mediated by the benzoic acid derivative or the silane (SI). The reaction between benzyl alcohol and 4-nitrobenzoic acid in the presence of only Fe(Pc) and molecular sieves resulted in the formation of benzaldehyde (75% yield by ^{1}H NMR) and trace amounts of ester **3** (SI).[11] Similarly, when phenylsilane was added into the reaction mixture, no ester product was detected (SI).

Scheme 3. Outline of the Mechanism of the Reaction between Benzyl Alcohol and 4-Nitrobenzoic Acid under the "Fully Catalytic" Conditions



By replacing benzyl alcohol with 3-phenylpropan-1-ol in the fully catalytic conditions, the corresponding ester **4** was hardly produced (<5% yield, Figure 1, entry 3). The above-mentioned results imply that Fe(Pc)-catalyzed oxidation−reduction condensation might be ruled out in the formation of ester **3**. A remaining possibility is that an intermediate, generated *in situ* from Fe(Pc), the phosphine oxide, and phenylsilane, induces an S_N1 reaction as a Lewis acid. This putative Lewis acid might slightly include Fischer-type esterification in the reaction of (−)-ethyl lactate or 3-phenylpropan-1-ol. Incidentally, another model reaction of benzyl alcohol using Fe(Pc) and tricyclohexylphosphine provided no ester product, supporting that phenylsilane might participate in formation of the intermediate (SI).

We previously reported that our system catalytic in the azo reagent did not work well when a trialkylphosphine, such as tri-*n*-butylphosphine, was used as a stoichiometric phosphine reagent.[6] Probably, the highly nucleophilic phosphines cause structural or functional changes in iron phthalocyanine by strong coordination to the metal center. A green spot having low polarity was observed on TLC analysis of the mixture of tri-*n*-butylphosphine and iron phthalocyanine. It is assumed that this spot belongs to a complex of iron phthalocyanine with the phosphine. Under the conditions of the "fully catalytic system", a similar spot was observed probably because the cyclic phosphine that formed *in situ* also has strong nucleophilicity (SI). Thus, our system catalytic in the azo reagent might be incompatible with the system catalytic in the phosphine when the cyclic phosphine is used.

In conclusion, our preliminary results suggested two problems for the report by Buonomo and Aldrich. First, the protocol of the catalytic Mitsnobu reaction in the phosphine appears insufficiently optimized. Second, the proposed "fully catalytic system" does not work as the catalytic Mitsunobu reaction. The former problem might be solved by strict optimization of the reaction conditions. The latter issue is more significant because the reaction does not seem to undergo the Mitsunobu process. Of course, we do not fully rule out the future feasibility of this ideal concept by further studies. In our

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opinion, however, it is premature at the moment to support the claim that "the concept of a fully catalytic Mitsunobu reaction has finally been realized".

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01894.

Full experimental details and analytical data (PDF)

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Notes

The authors declare no competing financial interest.

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