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Selective hydrogenation through phosphazide formation†

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The selective hydrogenation of ketones without any reaction at the azide moiety is disclosed. A key factor in the success of the reaction is the formation of phosphazides and catalyst poisoning. Hydrogenation of various functional groups was achieved in the presence of phosphazide moieties, allowing us to prepare various azides despite their significant reactivity.

Introduction

Catalytic hydrogenation has played an essential role as a fundamental textbook process in synthetic chemistry.[1] In particular, various functional groups, including azido, ethynyl, nitro, bromo, carbonyl, and benzyloxy groups are easily reduced in the presence of a heterogeneous catalyst, such as Pd/C, under a hydrogen atmosphere (Fig. 1A). Although a number of selective hydrogenations have been achieved thus far on the basis of the reactivities of functional groups in hydrogenation, it is not easy to realize the hydrogenation of functional groups without disturbing azide moieties owing to the remarkable reactivity of azides in hydrogenation.[2,3] Thus, hydrogenation with heterogeneous catalysts leaving the azido groups untouched is a challenging issue in synthetic chemistry. Herein, we disclose the selective hydrogenation of functional groups *via* the protection of azido groups.

Azide protection is an emerging method to accomplish a variety of transformations without damaging azido groups (Fig. 1B).[4] The formation of phosphazides *via* the treatment of azides with di-*tert*-butyl(4-dimethylaminophenyl)phosphine (Amphos) allowed us to realize various transformations, and the azides could be recovered through the addition of elemental sulfur.[4a] Phosphazides were significantly stabilized without denitrogenation by bulky *tert*-butyl groups and electron-donating aromatic groups. In contrast, a smooth Staudinger reaction took place when using triphenylphosphine instead of Amphos. We have developed synthetic methods for highly functionalized azides *via* triazole formations,[4a] 1,2-addition of carbanions,[4b] and iodine–magnesium exchange[4c] through azide protection. For example, selective triazole formation was accomplished through phosphazide formation using methyl 3-

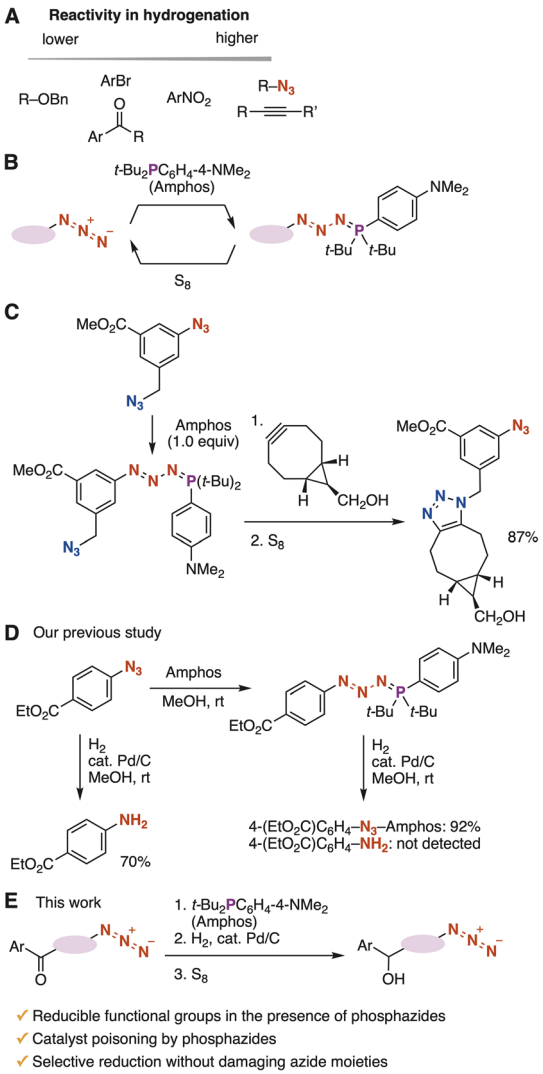

Fig. 1 (A) Reactivities of various functional groups under the hydrogenation conditions. (B) Protection of azides. (C) Selective triazole formation. (D) Hydrogenation in our previous studies. (E) This work.

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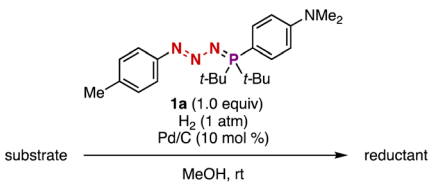
azido-5-(azidomethyl)benzoate with an equimolar amount of Amphos followed by strain-promoted azide–alkyne cycloaddition[5] and the recovery of the azide moiety (Fig. 1C).[4a] In our previous study, we found that phosphazide was stable under hydrogenation conditions with Pd/C (Fig. 1D).[4b] This result suggests that the selective hydrogenation of functional groups can take place, keeping azide moieties intact despite the significant reactivity of azides under hydrogenation conditions. Thus, we decided to examine the selective reduction of functional groups under hydrogenation conditions *via* azide protection, as well as catalyst poisoning by phosphazides for the reduction (Fig. 1E).

Results and discussion

First, we found that the hydrogenation of various functional groups can proceed with a catalytic amount of Pd/C in the presence of phosphazide **1a** under a hydrogen atmosphere (Table 1).[6] For example, the hydrogenation of alkyne **2** catalyzed by Pd/C was accomplished uneventfully at room temperature under a hydrogen atmosphere in the presence of phosphazide **1a**, in which 1,2-diphenylethane (**3**) was quantitatively prepared along with the recovery of phosphazide **1a** (entry 1). When methyl 3-nitrobenzoate was reduced under hydrogenation conditions in the presence of phosphazide **1a**, the quantitative formation of aniline **5** took place (entry 2). The treatment of benzyl azide **6** under a hydrogen atmosphere in the presence of phosphazide **1a** and a catalytic amount of Pd/C provided benzylamine **7** in high yields, where 4-methylaniline was not observed (entry 3). This result clearly indicates that the reduction of the aromatic azido group *via* equilibrium formation of a phosphazide from benzyl azide **6** did not proceed. In the case of the reduction of aryl bromide **8**, phosphazide **1a** was decomposed owing to the production of acids along with reductant **9** (entry 4). When this reaction was performed in the presence of potassium carbonate, efficient reduction took place, in which phosphazide **1a** was recovered in 98% yield (entry 5). In addition, we revealed that the hydrogenative removal of the benzyl group did not proceed because of the catalyst poisoning with basic phosphazide **1a** when using benzyl ether **10** (entry 6).

Modulating the catalytic activity by phosphazide **1a** allowed the selective hydrogenation of α-phenylacetophenone (**12**) (Fig. 2A).[7] The stepwise reduction of the aromatic ketone **12** proceeded to afford 1,2-diphenyl-1-ethanol (**13**) and 1,2-diphenylethane (**3**), in which the complete formation of **3** was observed after 24 h through the gradual reduction of the intermediate alcohol **13** (Fig. 2A, upper).[8] In contrast, the selective formation of **13** was accomplished in the presence of phosphazide **1a** under otherwise identical hydrogenation conditions for the ketone **12**, where the over-reduced alkane **3** was not detected (Fig. 2A, lower). In addition, while **13** was obtained in good yield after 2 h without phosphazide **1a**, the reaction rate was decreased *via* the addition of **1a**. These results clearly show that the catalyst poisoning of Pd/C by phosphazide **1a** inhibited the hydrogenation of **13**, probably because of the coordination of highly basic phosphazide **1a** to palladium.[9] At this stage, the coordination of phosphazide **1a** at the basic nitrogens would lead to catalyst poisoning by decreasing the active sites of palladium on carbon.

Table 1 Hydrogenation of various substrates in the presence of phosphazide **1a**



Entry	Substrate	Reductant	[a]Yield/%
1	Ph—≡—Ph **2**	Ph Ph **3**	Quant. [86]
2	MeO_2C NO_2 **4**	MeO_2C NH_2 **5**	Quant. [97]
3	OMe MeO N_3 **6**	OMe MeO NH_2 **7**	85 [quant.]
4	MeO_2C Br CO_2Me **8**	MeO_2C CO_2Me **9**	93 [11]
5[b]	MeO_2C Br CO_2Me **8**	MeO_2C CO_2Me **9**	98 [98]
6	Ph OBn **10**	Ph OH **11**	0 [79]

[a] Yields based on ^{1}H NMR analysis. The recovery yields of **1a** are shown in brackets. [b] The reaction was conducted in the presence of K_2CO_3 (1.0 equiv.).

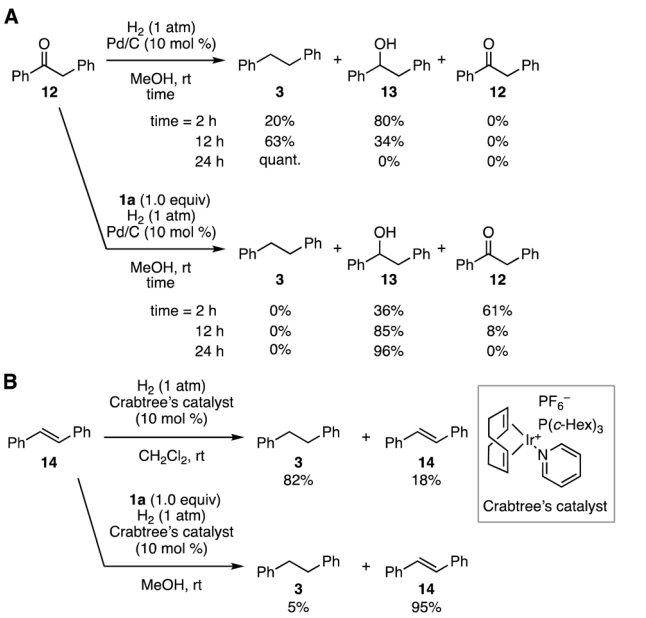


Fig. 2 (A) Hydrogenation of ketone **12**. (B) Hydrogenation of alkene **14**.

The activity of the homogeneous catalyst also decreased upon the addition of phosphazides (Fig. 2B).[10] For instance, the hydrogenation of *trans*-1,2-diphenylethene (**14**) with Crabtree's catalyst under a hydrogen atmosphere was significantly retarded by phosphazide **1a**.

We then examined the hydrogenation of azide **6** and ketone **12** with various heterogeneous catalysts under a hydrogen atmosphere in the presence of phosphazide **1a** (Fig. 3). The efficient reduction of **6** smoothly proceeded in the presence of phosphazide **1a** when using Pt/C, PtO_2, or $Pd(OH)_2$ as a catalyst (Fig. 3A).[11] In the case of the hydrogenation of ketone **12**, the catalytic activities of Pt/C, PtO_2, and $Pd(OH)_2$ were significantly lowered through the addition of phosphazide **1a** (Fig. 3B). Hydrogenation of ketone **12** did not proceed when using Pt/C or PtO_2 in the presence of **1a**, while the gradual formation of alcohol **13** was observed without **1a** (Fig. 3B, upper). The selective formation of alcohol **13** was realized when using $Pd(OH)_2$ as a catalyst in the presence of **1a** owing to catalyst poisoning (Fig. 3B, lower).

The selective reduction of diazide **15** with an aromatic and aliphatic azido group was realized through phosphazide formation with Amphos (Fig. 4). The treatment of diazide **15** with a catalytic amount of Pd/C in methanol at room temperature under a hydrogen atmosphere, followed by the addition of di-*tert*-butyl dicarbonate (Boc_2O) and triethyl amine, furnished diamine **16** in high yields (Fig. 4A, upper). Azide protection allowed us to perform selective hydrogenation of the aliphatic azido group (Fig. 4A, lower). After the pretreatment of **15** with an equimolar amount of Amphos, Pd/C-catalyzed hydrogenation, the removal of Amphos with S_8, and the following reaction with Boc_2O provided azide **17** in good yields through the selective reduction of the aliphatic azido group. A key to the success of the selective reduction of the aliphatic azido group was the selective formation of phosphazide **1b** at the aromatic azido group and subsequent hydrogenation at the aliphatic azido group without equilibrium phosphazide formation. The selective formation of phosphazide **1b** was confirmed using ^{1}H NMR

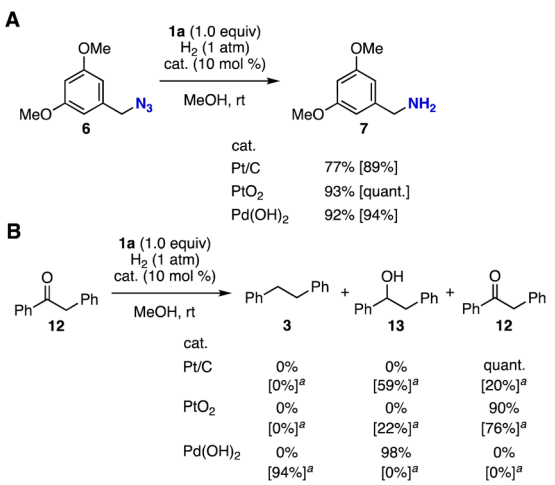


Fig. 3 Hydrogenation of (A) azide **6** and (B) ketone **12** using various catalysts with or without phosphazide **1a**. [a]Yields for reactions performed without **1a**.

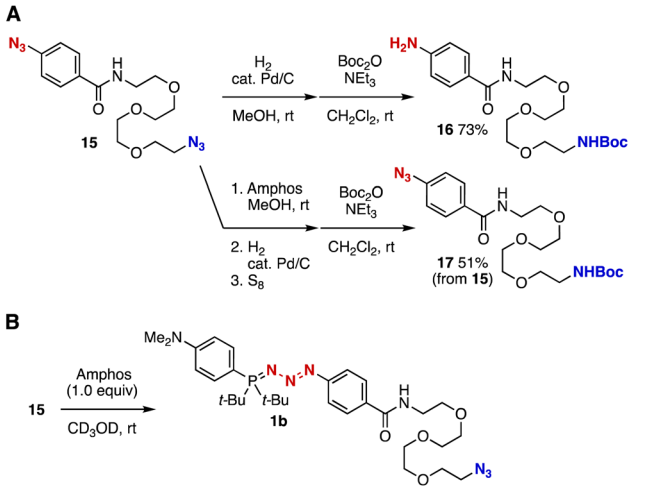


Fig. 4 (A) Reduction of **15**. (B) Formation of phosphazide **1b**. See ESI† for details.

analysis in methanol-d_4 (Fig. 4B). Since aromatic azides serve not only as synthetic intermediates for various transformations, including triazole formations, but also in photo-induced reactions such as photoaffinity labeling and skeletal rearrangement, the selective reduction of diazides would contribute to various disciplines such as pharmaceutical sciences and materials chemistry.[2]

Lastly, we realized the selective reduction of a carbonyl group while keeping the azide moiety unreacted (Fig. 5). When ketones **18** and **20** bearing azido groups were treated with a catalytic amount of Pd/C at room temperature under a hydrogen atmosphere, alcohols **19** and **21** with amino groups

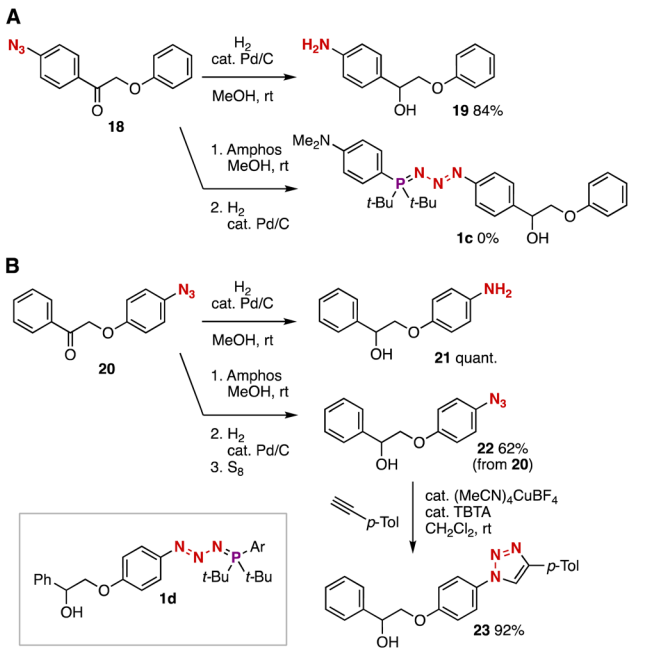


Fig. 5 (A) Reduction of **18**. (B) Transformations of **20**. See ESI† for details.

were synthesized in high yield through the reduction of the carbonyl and azido groups (Fig. 5A and B). Unfortunately, after the treatment of azide **18** with Amphos, alcohol **1c** was not observed through the hydrogenation of the carbonyl group, where hydrogenation at the carbonyl group did not take place owing to significant catalyst poisoning (Fig. 5A, lower). The electron-donating nature of the phosphazide moiety toward the conjugated carbonyl group would decrease the reactivity in the hydrogenation. In contrast, the pretreatment of azide **20** with Amphos, Pd/C-catalyzed hydrogenation under a hydrogen atmosphere, and subsequent removal of the Amphos moiety resulted in the selective synthesis of the azide-containing alcohol **22** in good yield, in which the reduction of the azide moiety was not observed (Fig. 5B, middle). It is worth noting that the selective hydrogenation was achieved to afford **22** *via* the formation of phosphazide **1d**, while azides are one of the most reactive functional groups under hydrogenation conditions. Considering the great importance of azides and Pd/C-catalyzed hydrogenation in synthetic chemistry, this novel approach, enabled by azide protection, would allow us to synthesize diverse organonitrogen compounds such as 2-amino-1-arylethanol analogs.[12] Since a wide range of azide transformations enable us to prepare diverse organonitrogen compounds, carbonyl-selective reduction and subsequent transformation would allow for the facile construction of a chemical library. For example, the copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction of the resulting azide **22** with 4-methylphenylacetylene efficiently proceeded to furnish 1,4-triazole **23** in high yield without the formation of a regioisomer, leaving the triazole, ether, and benzyl alcohol moieties intact (Fig. 5B, bottom).[13] A large chemical library would be constructed *via* selective hydrogenation and subsequent triazole formations in a modular synthetic manner.[12]

Conclusions

In summary, we achieved the Pd/C-catalyzed hydrogenation of various functional groups, leaving the azide moieties untouched through phosphazide formation. In addition, we found that the modulation of Pd/C catalytic activity by the presence of phosphazides enabled the selective synthesis of alcohols from ketones by preventing over-reduction. In particular, the selective transformations of diazide **15** and ketone **20** without damaging aromatic azide moieties were realized through hydrogenation *via* azide protection. Since azides are one of the most reducible molecules under hydrogenation conditions catalyzed by heterogeneous Pd/C, the unique selectivity would allow us to synthesize a wide variety of azides. Further studies such as examination of the detailed substrate scope, mechanistic studies on catalyst poisoning, and applications of this method for synthesizing analogs of bioactive compounds are ongoing in our laboratory.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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