

azido-5-(azidomethyl)benzoate with an equimolar amount of Amphos followed by strain-promoted azide-alkyne cycloaddition⁵ 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			Quant. [86]
2			Quant. [97]
3			85 [quant.]
4			93 [11]
5 ^b			98 [98]
6			0 [79]

^a Yields based on ¹H NMR analysis. The recovery yields of **1a** are shown in brackets. ^b The reaction was conducted in the presence of K₂CO₃ (1.0 equiv.).

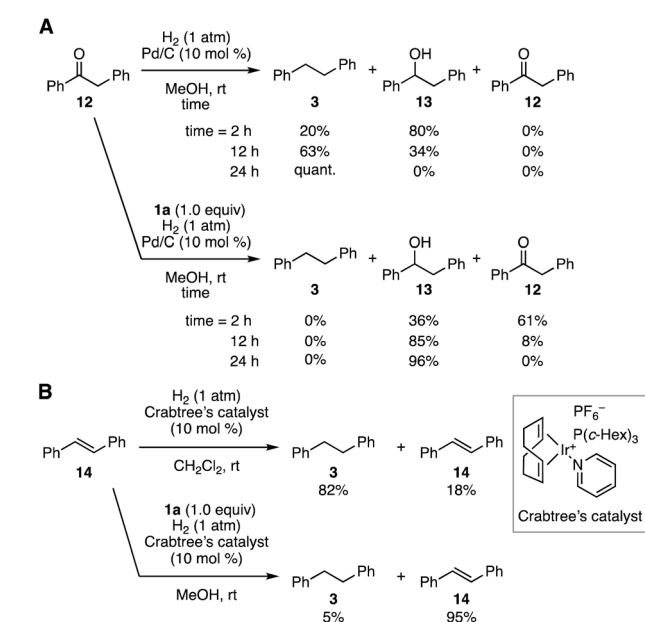


Fig. 2 (A) Hydrogenation of ketone **12**. (B) Hydrogenation of alkene **14**.



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, PtO₂, 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, PtO₂, 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 PtO₂ 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 (Boc₂O) 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 S₈, and the following reaction with Boc₂O 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 ¹H NMR

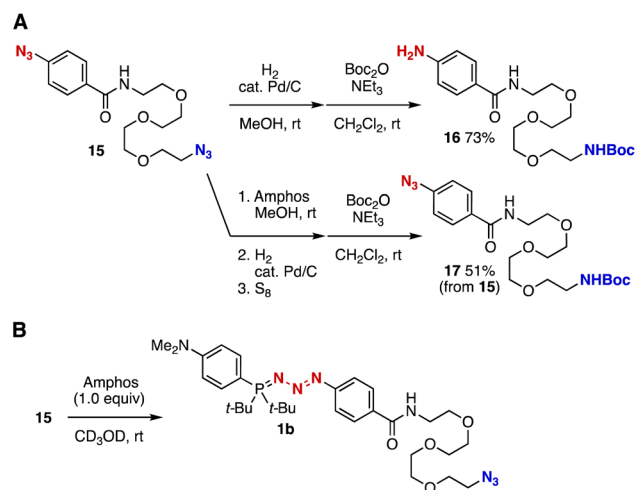


Fig. 4 (A) Reduction of **15**. (B) Formation of phosphazide **1b**. See ESI† for details.

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

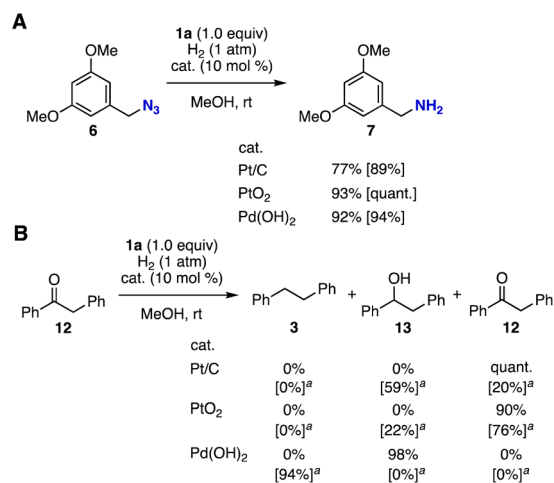


Fig. 3 Hydrogenation of (A) azide **6** and (B) ketone **12** using various catalysts with or without phosphazide **1a**. ^aYields for reactions performed without **1a**.

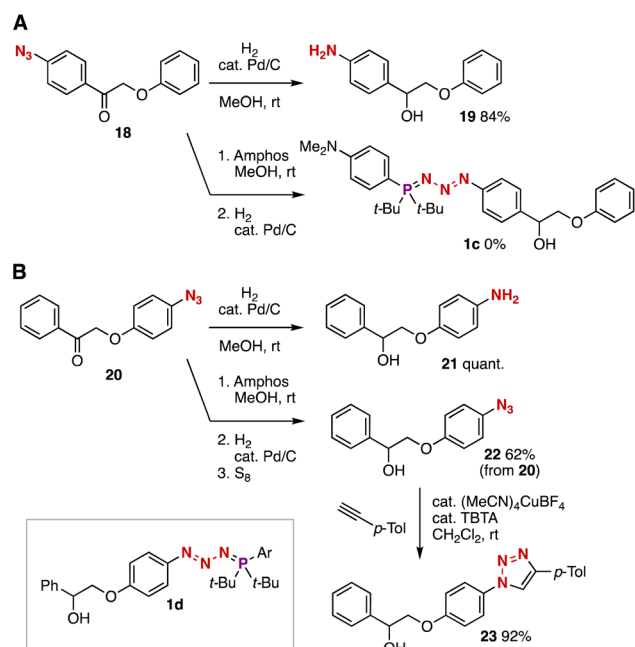


Fig. 5 (A) Reduction of **18**. (B) Transformations of **20**. See ESI† for details.



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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Notes and references

- (a) Y. Yabe, Y. Sawama, Y. Monguchi and H. Sajiki, *Catal. Sci. Technol.*, 2014, **4**, 260; (b) A. O. King, R. D. Larsen and E. Negishi, Palladium-Catalyzed Heterogeneous Hydrogenation, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E. Negishi, John Wiley & Sons, Inc., New York, 2002.
- (a) S. Bräse, C. Gil, K. Knepper and V. Zimmermann, *Angew. Chem., Int. Ed.*, 2005, **44**, 5188; (b) S. Bräse and K. Banert, *Organic Azides: Syntheses and Applications*, John Wiley & Sons, Ltd, Chichester, 2010; (c) H. Tanimoto and K. Kakiuchi, *Nat. Prod. Commun.*, 2013, **8**, 1021; (d) K. Banert, *Synthesis*, 2016, **48**, 2361; (e) D. Huang and G. Yan, *Adv. Synth. Catal.*, 2017, **359**, 1600; (f) S. Yoshida, *Org. Biomol. Chem.*, 2020, **18**, 1550; (g) Z.-K. Liu, Q.-Q. Zhao, Y. Gao, Y.-X. Hou and X.-Q. Hu, *Adv. Synth. Catal.*, 2020, **363**, 411; (h) H. Tanimoto and T. Tomohiro, *Chem. Commun.*, 2024, **60**, 12062.
- (a) F. Rolla, *J. Org. Chem.*, 1982, **47**, 4327; (b) S. N. Maiti, P. Spevak and A. V. N. Reddy, *Synth. Commun.*, 1988, **18**, 1201; (c) G. V. Reddy, G. V. Rao and D. S. Iyengar, *Tetrahedron Lett.*, 1999, **40**, 3937; (d) A. M. Salunkhe, P. V. Ramachandran and H. C. Brown, *Tetrahedron*, 2002, **58**, 10059; (e) A. Kamal, N. Shankaraiah, N. Markandeya and C. S. Reddy, *Synlett*, 2008, 1297; (f) A. Kamal, N. Markandeya, N. Shankaraiah, C. R. Reddy, S. Prabhakar, C. S. Reddy, M. N. Eberlin and L. S. Santos, *Chem.-Eur. J.*, 2009, **15**, 7215; (g) T. Maegawa, T. Takahashi, M. Yoshimura, H. Suzuka, Y. Monguchi and H. Sajiki, *Adv. Synth. Catal.*, 2009, **351**, 2091.
- (a) T. Meguro, S. Yoshida, K. Igawa, K. Tomooka and T. Hosoya, *Org. Lett.*, 2018, **20**, 4126; (b) T. Aimi, T. Meguro, A. Kobayashi, T. Hosoya and S. Yoshida, *Chem. Commun.*, 2021, **57**, 6062; (c) R. Namioka, M. Suzuki and S. Yoshida, *Front. Chem.*, 2023, **11**, 1237878.
- J. C. Jewett and C. R. Bertozzi, *Chem. Soc. Rev.*, 2010, **39**, 1272.
- (a) H. Sajiki, K. Hattori and K. Hirota, *J. Org. Chem.*, 1998, **63**, 7990; (b) D. J. Phillips, R. J. Davenport, T. A. Demaude, F. P. Galleway, M. W. Jones, L. Knerr, B. G. Perry and A. J. Ratcliffe, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4146; (c) X. Li, H. Li, C. Li, M. Wang and Q. Yang, *ChemCatChem*, 2023, **15**, e202300002.
- For example of selective transformations owing to the catalyst poisoning, see: (a) J. R. Weir, B. A. Patel and R. F. Heck, *J. Org. Chem.*, 1980, **45**, 4926; (b) A. Mori, Y. Miyakawa, E. Ohashi, T. Haga, T. Maegawa and H. Sajiki, *Org. Lett.*, 2006, **8**, 3279; (c) S. T. Marshall,



- M. O'Brien, B. Oetter, A. Corpuz, R. M. Richards, D. K. Schwartz and J. W. Medlin, *Nat. Mag.*, 2010, **9**, 853; (d) J. C. Moore, R. A. Howie, S. L. Bourne, G. N. Jenkins, P. Licence, M. Poliakoff and M. W. George, *ACS Sustainable Chem. Eng.*, 2019, **7**, 16814; (e) Q. Luo, Z. Wang, Y. Chen, S. Mao, K. Wu, K. Zhang, Q. Li, G. Lv, G. Huang, H. Li and Y. Wang, *ACS Appl. Mater. Interfaces*, 2021, **13**, 31775.
- 8 (a) H. Sajiki, K. Hattori and K. Hirota, *J. Chem. Soc., Perkin Trans. 1*, 1998, 4043; (b) T. Yamada, Y. Kobayashi, N. Ito, T. Ichikawa, K. Park, K. Kunishima, S. Ueda, M. Mizuno, T. Adachi, Y. Sawama, Y. Monguchi and H. Sajiki, *ACS Omega*, 2019, **4**, 10243; (c) R. Li, Y. Wang, Y. Zhao, F. Zhang, W. Zeng, M. Tang, J. Xiang, X. Zhang, B. Han and Z. Liu, *ACS Sustainable Chem. Eng.*, 2021, **9**, 14216.
- 9 A. Sarkar, P. Ilankumaran, P. Kisanga and J. G. Verkade, *Adv. Synth. Catal.*, 2004, **346**, 1093.
- 10 R. H. Crabtree and M. W. Davis, *J. Org. Chem.*, 1986, **51**, 2655.
- 11 (a) J. Hu and D. L. Mattern, *J. Org. Chem.*, 2000, **65**, 2279; (b) Y. Inaba, T. Fujimoto, H. Ono, M. Obata, S. Yano and Y. Mikata, *Carbohydr. Res.*, 2008, **343**, 941; (c) J. B. Santella III, D. S. Gardner, W. Yao, C. Shi, P. Reddy, A. J. Tebben, G. V. DeLuca, D. A. Wacker, P. S. Watson, P. K. Welch, E. A. Wadman, P. Davies, K. A. Solomon, D. M. Graden, S. Yeleswaram, S. Mandlekar, I. Kariv, C. P. Decicco, S. S. Ko, P. H. Carter and J. V. Duncia, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 576.
- 12 N. Mahmoodi, R. K. Harijan and V. L. Schramm, *J. Am. Chem. Soc.*, 2020, **142**, 14222; and references therein.
- 13 (a) C. W. Tornøe, C. Christensen and M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057; (b) V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596; (c) M. Meldal and C. W. Tornøe, *Chem. Rev.*, 2008, **108**, 2952; (d) A. Mandoli, *Molecules*, 2016, **21**, 1174.

