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Aromatic Azido-selective Reduction via the Staudinger Reaction Using Tri-*n*-butylphosphonium Tetrafluoroborate with Triethylamine

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Aromatic Azido-selective Reduction via the Staudinger Reaction Using Tri-*n*-butylphosphonium Tetrafluoroborate with Triethylamine

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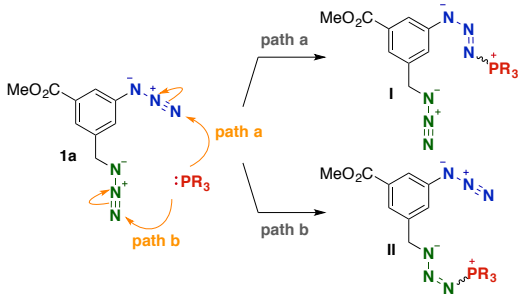
An efficient method for the reduction of aromatic azides to anilines via the Staudinger reaction using tri-*n*-butylphosphonium tetrafluoroborate with triethylamine in aqueous tetrahydrofuran solution is reported. The method enables aromatic azido-selective reduction of 3-azido-5-(azidomethyl)benzene derivatives to efficiently afford anilines bearing an azidomethyl group.

Keywords: Azide | Staudinger reaction | Reduction | Aniline

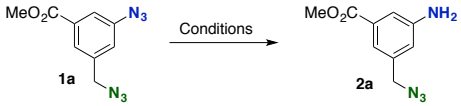
The Staudinger reaction,[1] the reaction between organic azides and trivalent phosphorus compounds, affords iminophosphoranes (aza-ylides), which are useful intermediates for preparing various nitrogen-containing compounds. In particular, the reaction of azides with triphenylphosphine in an aqueous solution, which allows for the subsequent hydrolysis of aza-ylide intermediates, has been widely used to prepare a variety of amines. However, the reduction of aromatic azides via the Staudinger reaction using triphenylphosphine often requires harsh conditions for the hydrolysis step owing to the high stability of aza-ylides.[2]



Scheme 1. Possible reactions between diazide **1a** and a phosphine.

In the course of our recent studies on azide chemistry,[3] we also faced a problem in achieving the selective reduction of the aromatic azido group of methyl 3-azido-5-(azidomethyl)benzoate (**1a**) via the Staudinger reaction using triphenylphosphine (Scheme 1). We assumed that a nucleophilic attack by the phosphine on the aromatic azido group of diazide **1a** (path a) would be more favored than that on the aliphatic azido group (path b) because the phosphazide intermediate **I** would be more stabilized than **II** by the direct resonance between the triazenide and the benzene ring.[1b,4] As we expected, the reaction of **1a** with triphenylphosphine in aqueous tetrahydrofuran (THF) at room temperature selectively occurred at the aromatic azido group to form the corresponding aza-ylide. However, desired aniline **2a** was not obtained probably due to the stability of the formed aza-ylide (Table 1, Entry 1). An attempt to hydrolyze the aza-ylide according to a reported method,[2a] heating under acidic conditions, afforded **2a**, albeit in low yield (Entry 2). Several other attempts to prepare **2a** by the reduction of **1a** based on reported conditions[5] were totally unsuccessful (Entries 3–6).

Table 1. Attempts for selective reduction of diazide **1a**.



Entry	Conditions	Conversion/%[a]	Yield/%[a]
1	PPh_3 (1.0 equiv) THF/H_2O (10:1, v/v), rt, 24 h	100	0
2	PPh_3 (1.0 equiv), THF, rt, 2 h; then 5 M aq. HCl, MeOH, 100 °C, 48 h	100	37
3	BH_3·THF (1.0 equiv), THF, rt, 24 h	26	0
4	NaI (50 mol %), BF_3·OEt_2 (2.0 equiv) MeCN, rt, 24 h	19	0
5	Al(OTf)$_3$ (20 mol %), NaI (3.0 equiv) MeCN, rt, 24 h	20	0
6	Gd(OTf)$_3$ (20 mol %), NaI (3.0 equiv) MeCN, rt, 24 h	6	0

[a]Yields determined by ^{1}H NMR analysis.

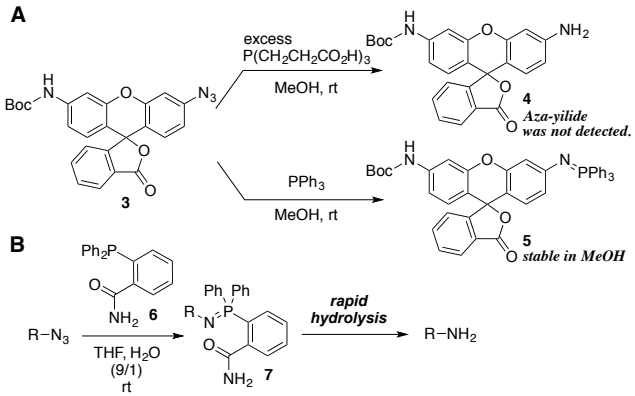


Figure 1. (A) Staudinger reaction of azide **3** with TCEP or triphenylphosphine. (B) Reduction of azides using *o*-(diphenylphosphino)benzamide (**6**).

As there are a few reports of the successful reduction of aromatic azides under mild conditions via the Staudinger reaction,[6] we refocused our attention on this approach. For example, Abe, Ito, and co-workers reported that azide **3** was efficiently reduced by treatment with an excess of tris(2-carboxyethyl)phosphine (TCEP),[7] which is a frequently used reductant in biological studies, to afford a rhodamine derivative **4** exclusively, while treatment with

triphenylphosphine provided the robust aza-ylide **5** (Figure 1A).[6b] The same group also developed a new azide-reducing reagent, *o*-(diphenylphosphino)benzamide (**6**), which was designed and synthesized to accelerate the hydrolysis of the aza-ylide **7** through neighboring group participation (Figure 1B).[6e] In these reports, however, limited reduction of aromatic azides was demonstrated and selectivity between aromatic and aliphatic azides was not examined. In particular, the reactivity of aromatic azides with a wide range of organophosphorus compounds and subsequent hydrolysis of resulting aza-ylides have not been studied systematically. To establish a practical method for aromatic azido-selective reduction of diazides like **1a**, preferably using a commercially available reagent that is easy to handle, we herein revisited the Staudinger reaction of aromatic azides.

We initially monitored the reaction between 4-(ethoxycarbonyl)phenyl azide (**8a**) and triphenylphosphine in THF-d_8 and D_2O (10/1, v/v) at room temperature by ^{1}H NMR (Figure 2). Azide **8a** was completely consumed within 1 h and formation of aza-ylide **10** was observed. Even after 24 h, only a trace amount of aniline **9a** was formed, indicating the high stability of aza-ylide **10** in the aqueous solution.

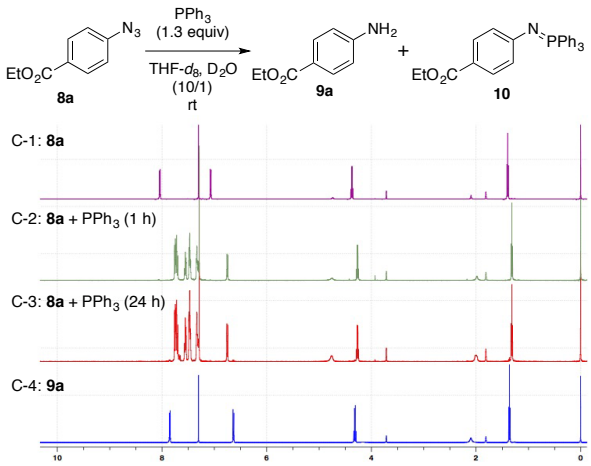
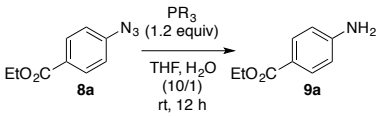


Figure 2. Monitoring the reaction between azide **8a** and triphenylphosphine in THF-d_8 and D_2O (10/1, v/v) at room temperature by ^{1}H NMR.

To achieve efficient transformation of aromatic azides into anilines under mild conditions, we screened for an organophosphorus compound that afforded aniline **9a** from azide **8a** in aqueous THF at room temperature (Table 2). Similar to the result described above, the desired aniline **9a** was not obtained by using triphenylphosphine, although azide **8a** was completely consumed (Entry 1). Successful transformation of azide **8a** into aniline **9a** took place using tri(2-furyl)phosphine, which is a more electron-deficient phosphine than triphenylphosphine (Entry 2). However, highly electron-deficient tris(pentafluorophenyl)phosphine did not react with azide **8a** (Entry 3). Smooth consumption of azide **8a** was observed when tris(dimethylamino)phosphine or trimethyl phosphite was used, but aniline **9a** was not obtained (Entries 4 and 5).[8] Various trialkylphosphines reacted with azide **8a** efficiently, while the reaction rate of the hydrolysis step varied depending on the bulkiness of the phosphines (Entries 6–8). In particular, tri-*n*-butylphosphine smoothly reduced azide **8a** to quantitatively afford aniline **9a** (Entry 6), whereas the hydrolysis was sluggish when tricyclohexylphosphine or tri-*t*-butylphosphine were used (Entries 7 and 8).[8] Furthermore, the reduction of azide **8a** to aniline **9a** was also promoted efficiently using air-stable tri-*n*-butylphosphonium tetrafluoroborate or TCEP·HCl in combination with triethylamine, which was added to regenerate the salt-free phosphine in situ (Entries 9 and 10). Considering the availability of the reagent and ease of handling, we used tri-*n*-butylphosphonium tetrafluoroborate as the phosphine source in further studies.

Table 2. Screen of organophosphorus compounds for reduction of azide **8a**.



Entry	PR_3	Conversion/%[a]	Yield/%[b]
1	PPh_3	100	0
2	$P(2\text{-furyl})_3$	100	quant.
3	$P(C_6F_5)_3$	0	0
4	$P(NMe_2)_3$	100	0[c]
5	$P(OMe)_3$	100	0[d]
6	$P(n\text{-Bu})_3$	100	quant.
7	$P(c\text{-Hex})_3$	100	26[e]
8	$P(t\text{-Bu})_3$	100	0[c]
9	$P(n\text{-Bu})_3\cdot HBF_4$, NEt_3[f]	100	94
10	$P(CH_2CH_2COOH)_3\cdot HCl$, NEt_3[f]	100	quant.

[a]Conversion of **8a** determined by ^{1}H NMR analysis. [b]Yields of **9a** determined by ^{1}H NMR analysis. [c]Phosphazide was obtained. [d]A mixture of aza-ylide and phosphonamide (48:52) was obtained. [e]Aza-ylide was obtained. [f]1.2 equiv. of NEt_3 was added.

The conditions using tri-*n*-butylphosphonium tetrafluoroborate with triethylamine (Table 2, Entry 9) were applicable to the reduction of various aromatic azides (Figure 3). A variety of substrates, bearing electron-deficient or electron-rich groups such as halogeno, nitro, ethoxycarbonyl, or methoxy groups at either the *ortho*-, *meta*-, or *para*-positions, were reduced to afford the corresponding anilines **9b–g** in high yields. Even the reduction of 2,6-diisopropylphenyl azide (**8h**), which has bulky substituents at both *ortho*-positions, proceeded smoothly to afford the desired product **9h** efficiently. Unexpectedly, treatment of benzyl azide (**8i**) with tri-*n*-butylphosphonium tetrafluoroborate and triethylamine resulted in a complex mixture,[9] while treatment with triphenylphosphine afforded benzylamine (**9i**) in 98% yield.[10]

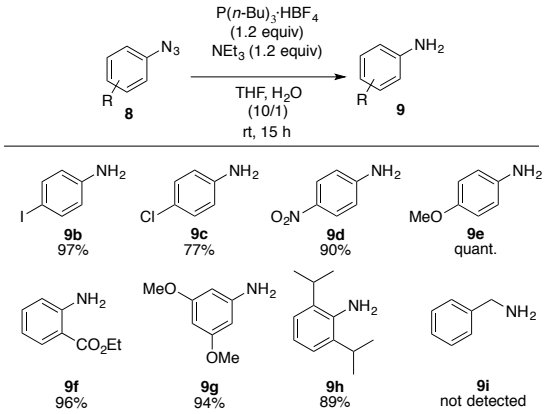
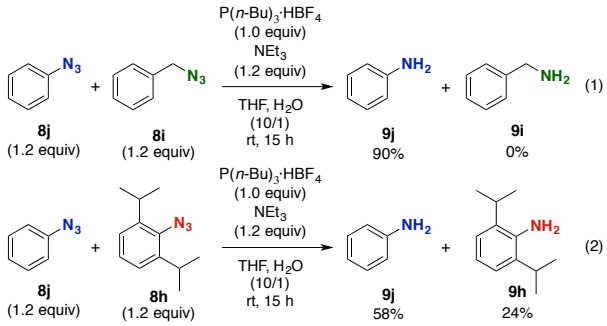


Figure 3. Reduction of various azides **8**.

A competition experiment clearly showed that the reaction conditions allowed for the selective reduction of phenyl azide (**8j**) in the presence of benzyl azide (**8i**); treatment of a mixture of **8j** (1.2 equiv) and **8i** (1.2 equiv) with tri-*n*-butylphosphonium tetrafluoroborate (1.0 equiv) in the presence of triethylamine (1.2 equiv) afforded aniline (**9j**) exclusively (eq 1).[8,11] When an equimolar mixture of **8j** and 2,6-diisopropylphenyl azide (**8h**) was treated with the reagents in a similar manner, preferential reduction of sterically unhindered **8j** was observed (eq 2).[8] This selectivity was opposite to that which we previously observed in the concerted click reaction with a cyclooctyne derivative, in which the clickability of doubly sterically-hindered phenyl azide **8h** was significantly enhanced by the steric inhibition of resonance.[3h] These results demonstrating the reaction-dependent selective reactivity of different types of azides such as **8h**–**8j** would be useful information to achieve sequential molecular conjugations based on orthogonal click chemistry.



Based on the optimized conditions, the aromatic azido-selective Staudinger reactions of 3-azido-5-(azidomethyl)benzene derivatives **1a**–**1d**,[3i] bearing an methoxycarbonyl, iodo, cyano group, or hydroxy group respectively, were successfully achieved to afford 3-(azidomethyl)anilines **2a**–**2d** in excellent yields (Figure 4). Furthermore, aromatic azido-selective reduction of triazide **1e**[3a] also took place uneventfully to afford aniline **2e** leaving two aliphatic azido groups untouched.

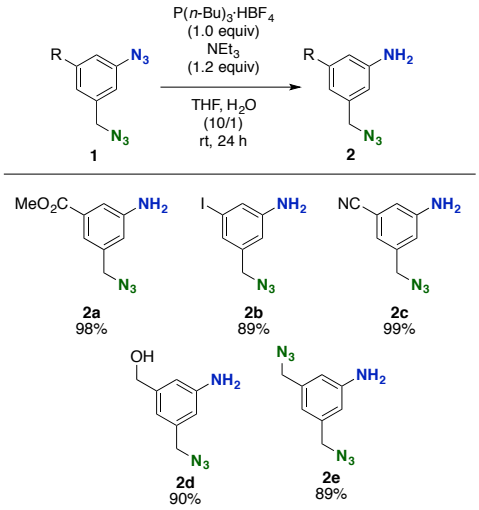


Figure 4. Aromatic azido-selective reduction of di- and triazides **1**.

In summary, we have revisited the Staudinger reaction of aromatic azides and found that the use of commercially available and air-stable tri-*n*-butylphosphonium tetrafluoroborate with triethylamine in aqueous THF solution efficiently promoted their transformation into anilines. The method was applicable to the reduction of a wide range of aromatic azides, including those substituted with an azidomethyl group, in which the aromatic azido-selective reduction proceeded efficiently.

This work was supported by Platform for Drug Discovery, Informatics, and Structural Life Science from MEXT and AMED, Japan; JSPS KAKENHI grant numbers 15H03118 (B; T.H.), 16H01133 (Middle Molecular Strategy; T.H.), and 26350971 (C; S.Y.); Suntory Foundation for Life Sciences (S.Y.); and Naito Foundation (S.Y.).

Supporting Information for characterization of new compounds is available electronically on J-STAGE.

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8 See Supporting Information for details.

9 Treatment of phenethyl azide with $P(n\text{-}Bu)_3 \cdot HBF_4$ and triethylamine also afforded a complex mixture. Currently, the reason why the reduction of alkyl azides failed is unclear.

10 Treatment of benzyl azide (**8i**) with triphenylphosphine in THF-d_8 and D_2O (10/1, v/v) for 15 h afforded benzylamine (**9i**) in 98% yield, which was determined based on ^1H NMR analysis by using 1,1,2,2-tetrachloroethane as an internal standard.

11 Benzyl azide (**8i**) was recovered quantitatively.