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Further enhancement of the clickability of doubly sterically-hindered aryl azides by *para*-amino substitution

The sterically-hindered aromatic azide further activated by the *para*-amino group is attacking the cyclooctyne hell-for-leather.

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Further enhancement of the clickability of doubly sterically-hindered aryl azides by para-amino substitution*

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Introduction of an amino group at the para position of doubly sterically-hindered aryl azides significantly enhances the reactivity with cyclooctynes. The distortability of the azido group is synergistically enhanced by the para-electron-donating group and two bulky ortho substituents, which increases the HOMO energy level and provoke the steric inhibition of resonance, respectively.

The click reaction,^{1,2} particularly the catalyst-free, strain-promoted azide-cycloalkyne cycloaddition (SPAAC),^{3,4} is one of the most reliable methods for conjugating molecules, having wide applications in broad research fields such as materials chemistry⁵ and chemical biology.6 To make the method more practical, a wide variety of useful cyclic alkynes with improved properties such as higher azidophilicity, lower hydrophobicity, and synthetic easiness have been developed.⁴ In contrast, little attention has been paid to increase the reactivity of the azide.⁷

In the course of our studies on azide chemistry,⁸ we found that 2,6-disubstituted phenyl azides show remarkably enhanced clickability in the reaction with strained alkynes such as Sondheimer diyne (1),^{9,10} despite the steric hindrance.^{8d} From experimental and computational studies, we concluded that this seemingly contradictory phenomenon could be attributed to the increased distortability of the azido group elicited by the steric inhibition of resonance with the aromatic ring (Fig. 1). Compared to the electronic effects observed for the clickability of para-substituted phenyl azides (e.g., 2a versus 2b), doubly sterically-hindered substrates such as 2,6-diisopropylphenyl azide (2c), in which the resonance is canceled to some extent, showed remarkably high reactivity. This finding enabled the facile preparation of trifunctional molecules by three sequential

2a 2b 2c This work 8.8 x 10⁻³ 3.3 x 10⁻² 0.67 3.8 Fig. 1 Double-click reaction of Sondheimer diyne (1) with aryl azides 2.^{8d} k: second-order rate constant.

azido-type-selective triazole forming reactions using a triazido platform molecule bearing three different types of azido groups.^{8g} In this study, with the aim of enhancing the selectivity of the click conjugation, the effect of para substituents on the clickability of 2,6-diisopropylphenyl azides was examined.

We firstly examined the reactivity of 2,6-diisopropylphenyl azides 2d-f bearing para-bromo, -iodo, and -pinacolatoboryl group, respectively, with divne 1 (Table 1). Despite the different electronegativity of the three groups, little difference in clickability was observed between these azides (entries 2-4) and 2,6-diisopropylphenyl azide (2c) (entry 1).

We then turned our attention to the resonance effect that would be induced by the para substituent. For an efficient comparison, we prepared two types of 2,6-diisopropylphenyl azides 2g-k and 2l-o bearing a variety of para-aryl¹¹ or -amino¹² groups by the palladium-catalyzed cross-coupling reactions of 4-bromo-2,6-diisopropylaniline (4), followed by azidation of the resulting anilines via diazotization (Scheme 1). In addition, by means of the azido-type-selective cycloaddition^{8g} of diazide 5 with acetylacetone catalyzed by potassium carbonate,¹³ paratriazolyl-substituted 2,6-diisopropylphenyl azide 2p was prepared (Scheme 2).

The effect of para-aryl substituents on the clickability of 2,6-diisopropylphenyl azides was found quite limited in the reaction with diyne 1 (Table 2, entries 2-6). The reaction rates

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 Table 1
 Clickability of para-halogenated or -borylated 2,6-diisopropylphenyl azides









for azides **2g–j**, bearing different aryl groups, *i.e.*, phenyl, 2,6-xylyl, 4-(trifluoromethyl)phenyl, and 4-methoxyphenyl, respectively, were almost the same or smaller than that for azide **2c** (entries 2–5), whereas **2k**, which has an electron-rich 4-(dimethylamino)phenyl group, reacted slightly faster than **2c** (entry 6).

In marked contrast to the limited effect of the aryl, halogeno, and boryl groups, introduction of an amino group at the *para* position of 2,6-diisopropylphenyl azide significantly enhanced the clickability (Table 2, entries 7–11). For example, azides **2l–o** bearing the *para*-amino groups reacted with **1** more than twice faster than **2c** (entries 7–10). In particular, 2,6-diisopropyl-4-pyrrolidinophenyl azide (**2o**) showed the highest clickability, reacting more than five times faster than **2c** (entry 10) and approximately 400 times faster than phenyl azide (**2a**). The enhanced clickability of azide **2o** was also observed in the reaction with diyne **1** in acetonitrile, although the reaction rate decreased slightly compared to that in methanol (entry 10 *versus* entry 1). The reaction of azide **2p** with **1** was rather slower than that of **2c**, indicating that the triazolyl group was not effective in accelerating the reaction (entry 11).

Introduction of an amino group at the *para* position of phenyl azide also enhanced the clickablity of substrates without

 Table 2
 Clickability of para-aryl- and -amino-substituted 2,6-diisopropylphenyl azides

1 + N_3 $MeOH$ bistriazole $i-Pr$ (or MeCN) $25 \degree C$							
Entry	R	2	$k (M^{-1} s^{-1})$	$k_{\rm rel}$	Yield (%)	trans/cis	
1	Н	2c	$0.67^{a} (0.37)^{b}$	$1(1)^{b}$	95 ^{<i>a</i>}	96/4 ^a	
2	Ph	2g	0.74	1.1	Quant	96/4	
3	$2,6-Me_2C_6H_3$	2ĥ	0.75	1.1	81	96/4	
4	$4 - F_3 CC_6 H_4$	2i	0.47	0.70	Quant	95/5	
5	4-MeOC ₆ H ₄	2j	0.72	1.1	Quant	96/4	
6	4-Me ₂ NC ₆ H ₄	2k	0.83	1.2	88	96/4	
7	Ph、N~~~~ Ne	21	1.4	2.1	Quant	95/5	
8	O N - Z	2m	1.6	2.4	77	96/4	
9	N ²	2n	1.7	2.5	Quant	96/4	
10	CN-22	20	$3.5(2.1)^b$	$5.2(5.8)^{b}$	Quant	95/5	
11	Me Me	2р	0.53	0.79	Quant	99/1	
^a From ref. 8 <i>d</i> . ^{<i>b</i>} In acetonitrile.							

ortho substituents, as demonstrated in the reaction with diyne **1** (Table 3). For example, 4-morpholinophenyl azide (**2q**) showed slightly higher clickablity than 4-methoxyphenyl azide (**2b**) (entry 3 *versus* entry 2). The introduction of a morpholino group at the *para* position of phenyl azide elicited a 3.4-fold acceleration of the reaction (entry 3 *versus* entry 1). 4-Azidoaniline (**2r**), which has an unsubstituted amino group, also showed a comparable reactivity to that of the methoxy congener **2b** (Table 3, entry 4 *versus* entry 2). Intriguingly, this accelerating effect was completely canceled by salt formation of the amino group of 4-azidoaniline, which resulted in the deceleration of the reaction (entry 5).

Table 3 Clickability of para-substituted phenyl azides						
	1 +	R	2 N ₃ MeOH (or MeCN) 25 °C	bistriazo rans- 3 +	le cis- 3	
Entry	R	2	$k \left(\mathbf{M}^{-1} \mathbf{s}^{-1} \right)$	k _{rel}	Yield (%)	trans/ cis
1 2	H MeO	2a 2b	$\begin{array}{c} 8.8 \times 10^{-3a} \left(6.4 \times 10^{-3} \right)^{b} \\ 3.3 \times 10^{-2a} \left(1.8 \times 10^{-2} \right)^{b} \end{array}$	${\begin{array}{*{20}c} 1 \ (1)^b \\ 3.8 \ (2.7)^b \end{array}}$	94 ^a 89 ^a	43/57 ^a 36/64 ^a
3		2q	$(2.2 imes 10^{-2})^b$	$(3.4)^{b}$	Quant	37/63
4 5	H ₂ N ClH·H ₂ N	2r 2s	$\begin{array}{c} 2.7 \times 10^{-2} \\ 6.5 \times 10^{-3} \end{array}$	3.1 0.74	Quant Quant	36/64 35/65

^{*a*} From ref. 8*d*. ^{*b*} In acetonitrile.

Table 4 FMO analysis of azides 2c and 2m-o

Entry	ArN ₃	HOMO (eV)	LUMO (eV)	$k^a (\mathrm{M}^{-1} \mathrm{s}^{-1})$	$k_{\rm rel}$
1	2c	-6.19	-0.75	0.67	1
2	2m	-5.29	-0.65	1.6	2.4
3	2n	-5.16	-0.58	1.7	2.5
4	20	-4.85	-0.44	3.5	5.2

^{*a*} Second-order rate constant (*k*) for the reaction of **1** with aryl azides **2** conducted in methanol at 25 $^{\circ}$ C (from Table 2).

Frontier molecular orbital (FMO) analysis of azide 2c and *para*-amino-substituted 2,6-diisopropylphenyl azides 2m-o revealed a good correlation between the HOMO energy levels and the second-order rate constants (*k*) (Table 4). It was found that the reactivity of azides with diyne 1 increased with the rise of the HOMO energy. This result suggests that the electron-donating amino group at the *para* position reduced the energy gap between the HOMO of the aryl azide and the LUMO of diyne 1, which resulted in the enhancement of the cycloaddition. Indeed, azide 2o, which exhibited the highest HOMO energy due to the presence of the highly electron-donating pyrrolidino group, proved to be the most reactive among the azides examined.¹⁴

To gain further mechanistic insight into the enhanced clickability of *para*-amino-substituted phenyl azides, the transition state (TS) structure for the first cycloaddition of **1** with **20** was obtained by a density functional theory (DFT) (B3LYP/ 6-31G(d)) method¹⁵ and compared with those obtained for the reactions with **2a** and **2c** (Table 5). The activation energy for the reaction of **1** with **20** was lower than that with **2c**, which was in good agreement with the experimental result. The corresponding distortion–interaction analysis¹⁶ indicated that, in accord with our previous report,^{8d} the enhanced clickability of **20** mostly rested on the enhanced distortability of the azido



^{*a*} Distortion, interaction, and activation energies for the first cycloaddition obtained at the B3LYP/6-31G(d) are shown in kcal mol⁻¹. ^{*b*} From ref. 8*d*. ^{*c*} Energy required to distort the geometry of each reactant to the transition state (TS). ^{*d*} Interaction energy between the distorted fragments at the TS. ^{*e*} Energy differences of each fragment between the optimized and the TS geometries.



Fig. 2 Global minima on the potential energy surface of aryl azides 2c and 2o obtained by DFT (B3LYP/6-31G(d)) method. (A) Overhead view of 2c. (B) Side view of 2c. (C) Overhead view of 2o. (D) Side view of 2o. θ indicates the rotational angle of the azido group from the aromatic plane.

group (**2a**: 17.4 kcal mol⁻¹; **2c**: 15.1 kcal mol⁻¹; **2o**: 13.8 kcal mol⁻¹). We previously explained that the higher clickability of 2c compared to that of 2a was elicited by the steric inhibition of resonance: *i.e.*, the two bulky ortho substituents of 2c forced the azido group to twist out of the plane of the benzene ring, which partially released the azido from the strong conjugation. In this case, however, the calculated rotational angle (θ) of the azido group from the aromatic plane for **20** (θ = 61.2°) was similar to that for **2c** (θ = 58.2°) (Fig. 2), indicating that the steric inhibition of resonance alone cannot be invoked to rationalize the higher clickability of 20 compared to that of 2c. Taken together, the FMO and the distortion-interaction analyses suggest that the clickability of doubly sterically-hindered aryl azides bearing an amino group at the para position stemmed from the enhanced distortability of the azido group, which was synergistically provoked by the steric inhibition of resonance and the raised HOMO energy level.

The clickability enhancement by *para*-amino substitution of sterically-hindered aryl azide was also observed in the SPAAC reactions using other cycloalkynes that are widely used for bioconjugation. The most reactive azide **20** in the reaction with diyne **1** also showed significantly higher reactivity in the reactions with a bicyclo[6.1.0]non-4-yne (BCN)⁴ⁱ derivative ($k = 0.92 \text{ M}^{-1} \text{ s}^{-1}$) in MeOH than **2c** ($k = 0.20 \text{ M}^{-1} \text{ s}^{-1}$). The reaction of a **1**:1 mixture of **20** and **2c** with a dibenzoazacyclooctyne (DIBAC)^{4g} derivative afforded **20**- and **2c**-derived cycloadducts at a ratio of **3**.3:1.¹⁷

The enhanced clickability of the aryl azide elicited by the *para*-amino group enabled performing a sequential doubleclick reaction using diazido compound **6** with excellent azidotype selectivity (Scheme 3). Thus, the reaction of **6** with the strained alkyne **7** took place exclusively at the sterically-hindered *para*-amino-substituted aryl azido group, despite the presence of another phenyl azido group with sufficient reactivity, and the subsequent copper-catalyzed azide–alkyne cycloaddition with terminal alkyne **8** afforded bistriazole **9** in high yield.

In summary, we have found that the introduction of an amino group at the *para* position of doubly sterically-hindered aryl azides significantly enhances their clickability in the reaction with strained alkynes. The azide is synergistically activated by the electron-donating *para*-amino group and two bulky *ortho* substituents, with the former increasing the HOMO energy level of the azide, thereby enhancing its ynophilicity, and the latter inhibiting the resonance between azido and phenyl groups, which enhances the distortability of the azido group. This finding



Scheme 3 Azido-type selective double-click reaction of diazide 6.

allowed for the sequential double-click conjugation of a diazido compound with excellent efficiency, which would be useful for the preparation of multifunctionalized molecules using a multiazido platform molecule bearing a *para*-amino-2,6-disubstituted aryl azide unit. Further studies to develop more reactive azides for their application to the preparation of multifunctional molecules are ongoing.

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Conflicts of interest

There are no conflicts to declare.

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