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Selective Propargylation of Diaryl Azo Compounds Using Metallic Barium

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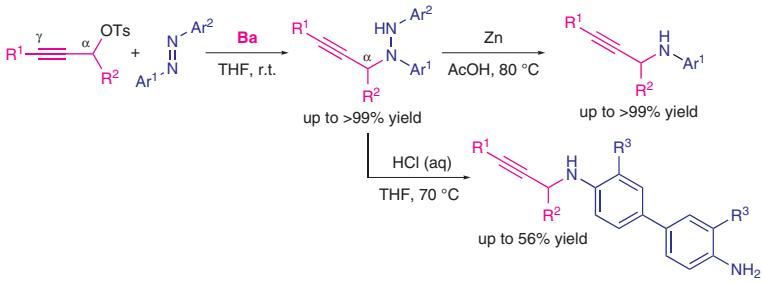

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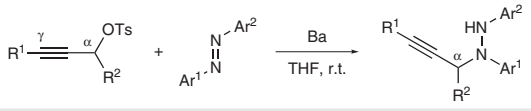
Abstract The Barbier-type propargylation of azo compounds with α,γ-disubstituted propargylic tosylates was achieved by using metallic barium as the promoter. Various propargylated hydrazines (α-adducts) were exclusively synthesized from the corresponding propargylic tosylates and azobenzenes (diaryldiazenes). The thus-obtained propargylic hydrazines were further efficiently converted into propargylic amines by reductive N–N bond cleavage. Benzidine rearrangement of the propargylic hydrazines was also attempted.

Key words azo compounds, barium, hydrazines, propargylation, propargylic tosylates

Propargylic/allenylic barium compounds, which are generated from Rieke barium[1] and propargylic halides, are useful reagents for the synthesis of organic molecules having a carbon–carbon triple bond and high α-regioselectivity.[2] We have previously reported that a propargylation of azo compounds with propargylic halides occurs via a Barbier-type procedure using reactive barium as the low-valent metal to yield propargylic hydrazines (α-product).[3] In addition, a Grignard-type α-allylation of azo compounds with allylic barium reagents[4] and a Barbier-type benzylation of azo compounds with benzylic chlorides[5] have been achieved. We report herein a metallic-barium-promoted Barbier-type propargylation of azo compounds with propargylic tosylates (Scheme 1). The results of reductive N–N bond cleavage of the products, propargylic hydrazines, to form the corresponding propargylic amines as well as benzidine rearrangement of the propargylic hydrazines are also disclosed. The propargylic amine structure is often seen as a key framework in pharmaceutical compounds, such as rasagiline mesylate[6] and selegiline hydrochloride.[7] Therefore, the development of useful methods for the synthesis



Scheme 1 Barbier-type propargylation of azobenzenes using metallic barium

of such propargylic amines has captivated the interest of researchers in the field of organic synthesis.

We have found that allylic barium reagents can be prepared from metallic barium and allylic chlorides and show high reactivity toward isatin imines with α-selectivity.[8] We envisioned that if a propargylic or an allenylic barium reagent could be generated from metallic barium[9] and the corresponding propargylic halide under mild reaction conditions and displayed α-selectivity in the reaction with an azo compound, the propargylation would provide a practical synthetic procedure for propargylated hydrazines. Thus, we first selected (3-chloroprop-1-ynyl)trimethylsilane (**1a**) and azobenzene (**2a**) as the precursor of propargylic or allenylic barium reagent and the electrophile, respectively, and attempted to perform a Barbier-type reaction due to the simplicity of the experimental procedure. When a 3:1 mixture of propargylic chloride **1a** (3 equiv) and azobenzene (**2a**, 1 equiv) was treated with metallic barium (3 equiv) in THF at room temperature for 14 h, the reaction did not proceed and targeted propargylated hydrazine **3aa** (α-adduct) was not observed at all (Table 1, entry 1). In contrast, α-methylated trimethylsilyl-substituted propargylic chloride **1b** showed remarkable reactivity toward **2a** and the desired product was obtained in 49% yield without formation of the corresponding allenylated hydrazine under similar reaction conditions (entry 2). However, the reaction of α-dimethylated propargylic chloride **1c** with **2a** resulted in a low yield (entry 3). α-Methylated *tert*-butyl-substitut-

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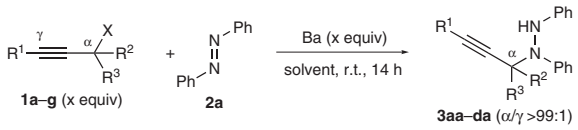
Table 1 Optimization of Metallic-Barium-Promoted Barbier-Type Propargylation of Azobenzene (**2a**)[a]



1a–g (x equiv) **2a** **3aa–da** (α/γ >99:1)

Entry	R^1	R^2	R^3	X	x	Solvent	Product	Yield (%)[b]
1	Me_3Si	H	H	Cl **1a**	3	THF	**3aa**	<1
2	Me_3Si	Me	H	Cl **1b**	3	THF	**3ba**	49
3	Me_3Si	Me	Me	Cl **1c**	3	THF	**3ca**	23
4	*t*-Bu	Me	H	Cl **1d**	3	THF	**3da**	46
5	*t*-Bu	Me	H	Cl **1d**	3	DMF	**3da**	38
6	*t*-Bu	Me	H	Cl **1d**	3	THF–DMF (4:1)	**3da**	60
7	*t*-Bu	Me	H	OTs **1e**	3	THF–DMF (4:1)	**3da**	72
8	*t*-Bu	Me	H	$OPO(OPh)_2$ **1f**	3	THF–DMF (4:1)	**3da**	46
9	*t*-Bu	Me	H	$OCOCF_3$ **1g**	3	THF–DMF (4:1)	**3da**	<1
10	*t*-Bu	Me	H	OTs **1e**	2	THF–DMF (4:1)	**3da**	47
11	*t*-Bu	Me	H	OTs **1e**	4	THF–DMF (4:1)	**3da**	47
12	*t*-Bu	Me	H	OTs **1e**	3	THF	**3da**	69

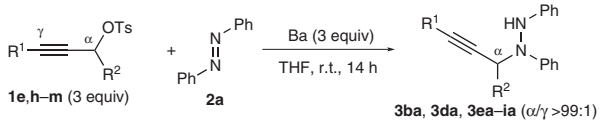
[a] The Barbier-type reaction was carried out using propargylic compounds **1a–g** (x equiv), metallic barium (x equiv), and azobenzene (**2a**, 1 equiv) in the specified solvent at room temperature for 14 h.
[b] The chemical yield was determined by ^{1}H NMR spectroscopy using 1,4-bis(trimethylsilyl)benzene as the internal standard.

ed propargylic chloride **1d** showed similar reactivity toward **1b** and target adduct **3da** was formed in 46% yield (entry 4). Subsequently, we examined solvent effect (entries 4–6) and found that a 4:1 mixture of THF and DMF was the most suitable solvent from the point of view of chemical yield (entry 6). We further focused on electron-withdrawing group X of substrate **1** and when propargylic tosylate **1e** was employed, the highest chemical yield (72%) was attained (entry 7). Diphenyl phosphate was also a promising X group (entry 8); in contrast, trifluoroacetate gave unsatisfactory results and desired adduct **3da** was not obtained in the reaction (entry 9). The chemical yield of **3da** shown in entry 7 was not improved when the amounts of propargylic tosylate **1e** and metallic barium were decreased or increased (entries 10 and 11). THF was also a suitable solvent in the reaction of **1e**, and 69% yield of product **3da** was obtained under the optimized reaction conditions (entry 12).

With the optimum reaction conditions in hand, we examined the propargylation of azobenzene (**2a**) with propargylic tosylates **1e** and **1h–m** derived from various propargylic alcohols (Table 2). Higher reactivity was observed for the reaction of propargylic tosylate **1h**, which has an ethyl group as the R^2 group (entry 2). In contrast, propargylic tosylate **1i**, which has an isopropyl group, afforded product **3fa** in a lower yield than propargylic tosylate **1e** probably due to its steric hindrance (entry 3 vs. entry 1). Employment of phenyl-substituted propargylic tosylate **1k** caused a significant decrease in the yield (31%) of its product **3ha** (entry 5). Trialkylsilyl-substituted propargylic tosylates **1l** and **1m** furnished products in satisfactory yields (entries 6 and 7).

We performed the metallic-barium-promoted Barbier-type propargylation of symmetrical azobenzenes **2b–k** derived from a diversely substituted aniline (Table 3). The ef-

Table 2 Metallic-Barium-Promoted Barbier-Type Propargylation of Azobenzene (**2a**) with Various Propargylic Tosylates **1e** and **1h–m**[a]



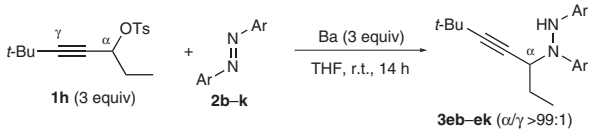
1e,**h–m** (3 equiv) **2a** **3ba**, **3da**, **3ea–ia** (α/γ >99:1)

Entry	R^1	R^2	Product	Yield (%)[b]
1	*t*-Bu	Me (**1e**)	**3da**	69
2	*t*-Bu	Et (**1h**)	**3ea**	85
3	*t*-Bu	*i*-Pr (**1i**)	**3fa**	57
4	Bu	Me (**1j**)	**3ga**	50
5	Ph	Me (**1k**)	**3ha**	31
6	Me_3Si	Me (**1l**)	**3ba**	60
7	*t*-Bu$(Me)_2Si$	Me (**1m**)	**3ia**	89

[a] The Barbier-type reaction was carried out using propargylic tosylates **1e** and **1h–m** (3 equiv), metallic barium (3 equiv), and azobenzene (**2a**, 1 equiv) in THF at room temperature for 14 h.
[b] The chemical yield was determined by ^{1}H NMR spectroscopy using 1,4-bis(trimethylsilyl)benzene as the internal standard.

fect of a substituent on the aromatic ring of azobenzenes **2b–k** on the chemical yield was notable: an electron-withdrawing group (Cl or F) at 4-position of the phenyl group enhanced the electrophilicity of **2e** and **2f** relative to **2d**, which has an electron-donating MeO group (entries 4 and 5 vs. entry 3). A methyl group at 2-position reduced the reactivity of **2i** (entry 8), whereas 2-F substituted azobenzene showed significant reactivity probably due to its electronic effect rather than its steric hindrance (entry 9).

Table 3 Metallic-Barium-Promoted Barbier-Type Propargylation of Symmetrical Azobenzenes **2b–k** with Propargylic Tosylate **1h**[a]

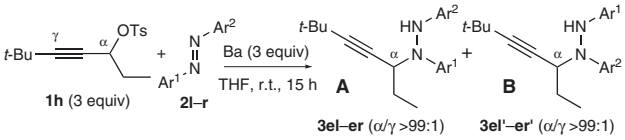


Entry	Ar	Product	Yield (%)[b]
1[c]	4-MeC_6H_4 **2b**	**3eb**	80
2	4-*i*-PrC_6H_4 **2c**	**3ec**	73
3	4-$MeOC_6H_4$ **2d**	**3ed**	27
4	4-ClC_6H_4 **2e**	**3ee**	56
5	4-FC_6H_4 **2f**	**3ef**	60
6[d]	3-MeC_6H_4 **2g**	**3eg**	77
7	3-ClC_6H_4 **2h**	**3eh**	51
8	2-MeC_6H_4 **2i**	**3ei**	10
9[d]	2-FC_6H_4 **2j**	**3ej**	>99
10	2,4-$F_2C_6H_3$ **2k**	**3ek**	51

[a] The Barbier-type reaction was carried out using propargylic tosylate **1h** (3 equiv), metallic barium (3 equiv), and azobenzenes **2b–k** (1 equiv) in THF at room temperature for 14 h.
[b] The chemical yield was determined by ^{1}H NMR spectroscopy using 1,4-bis(trimethylsilyl)benzene as the internal standard.
[c] The reaction was performed for 15 h.
[d] The reaction was performed for 8 h.

To investigate the electronic effect on the site selectivity of the nitrogen atoms, we carried out the propargylation of unsymmetrical azobenzene derivatives having an electron-deficient group on one aromatic ring and/or an electron-rich group on the other aromatic ring. As a result, a 44:56 mixture of two regioisomers **A** and **B** was obtained as product **3el** + **3el′** in the reaction of 1-(4-tolyl)-2-phenyldiazene (**2l**) with 6,6-dimethylhept-4-yn-3-yl 4-methylbenzenesulfonate (**1h**) almost quantitatively (Table 4, entry 1). In contrast, the reaction of unsymmetrical diaryl azo compounds **2m** and **2n**, which have a 4-halophenyl group as the Ar^2 group, resulted in the formation of regioisomer **A** selectively (entries 2 and 3). Similar site selectivities were observed in the cases of 1-(4-fluorophenyl)-2-(4-tolyl)diazene (**2o**) and 1-(4-fluorophenyl)-2-(4-isopropylphenyl)diazene (**2p**), but with unsatisfactory isolated yields (entries 4 and 5). The highest site selectivity was realized with a 2-tolyl group as the Ar^1 group and a 2-fluorophenyl group as the Ar^2 group (entry 6). A similar site selectivity was achieved by using 1-(2,4-difluorophenyl)-2-(3-tolyl)diazene (**2r**) as the substrate: a 64:36 mixture of propargylic hydrazines **A** and **B** was obtained in 40% combined yield (entry 7).

Table 4 Metallic-Barium-Promoted Barbier-Type Propargylation of Unsymmetrical Azobenzenes **2l–r** with Propargylic Tosylate **1h**[a]



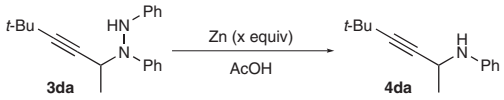
Entry	Ar^1	Ar^2	Product	Yield (%)[b]	**A**/**B**[c]
1	Ph	4-MeC_6H_4 **2l**	**3el** + **3el′**	>99	44:56
2	Ph	4-FC_6H_4 **2m**	**3em** + **3em′**	78	57:43
3	Ph	4-ClC_6H_4 **2n**	**3en** + **3en′**	92	55:45
4	4-MeC_6H_4	4-FC_6H_4 **2o**	**3eo** + **3eo′**	57	58:42
5	4-*i*-PrC_6H_4	4-FC_6H_4 **2p**	**3ep** + **3ep′**	39	56:44
6	2-MeC_6H_4	2-FC_6H_4 **2q**	**3eq** + **3eq′**	>99	66:34
7	3-MeC_6H_4	2,4-$F_2C_6H_3$ **2r**	**3er** + **3er′**	40	64:36

[a] The Barbier-type reaction was carried out using propargylic tosylate **1h** (3 equiv), metallic barium (3 equiv), and azobenzenes **2l–r** (1 equiv) in THF at room temperature for 15 h.
[b] The chemical yield was determined by ^{1}H NMR spectroscopy using 1,4-bis(trimethylsilyl)benzene as the internal standard.
[c] The ratio was determined by ^{1}H NMR spectroscopy or ^{19}F NMR spectroscopy. The structure of the major isomer was determined by N–N bond cleavage.

The thus-obtained propargylic hydrazines can be further converted into propargylic amines through reductive N–N bond cleavage.[10] For example, treatment of propargylic hydrazine derivative **3da** with an excess of Zn in acetic acid[11] at room temperature for 15 h afforded corresponding propargylic amine **4da** in 32% yield (Table 5, entry 1). Elevating the reaction temperature was effective in acquiring a higher yield and when the reaction was performed at 80 °C, a satisfactory isolated yield of **4da** was obtained (entry 3). Decreasing the amount of zinc (entry 4), shortening the reaction time (entry 5), diluting the reaction solution (entries 6 and 7), and employing trifluoroacetic acid instead of acetic acid (entry 8) did not improve the yield.

With the optimized reaction conditions in hand, we then executed the N–N bond cleavage of diverse propargylic hydrazines employing Zn in AcOH. α-Ethylated propargylic hydrazine **3ea** showed higher reactivity than **3da** (Table 6, entry 1 vs. Table 5, entry 3). Not only electron-rich hydrazines but also electron-deficient hydrazines provided the anticipated propargylic amines in satisfactory yields (Table 6, entries 2–5). Regioisomeric mixtures of **3eq** and **3eq′** effectively underwent the N–N bond cleavage (Table 6, entry 6) and as a result, regioisomer **3eq** was unambiguously determined to be the major product of the reaction shown in Table 4, entry 6. Similarly, regioisomer **3er** was

Table 5 Optimization of Reductive N–N Bond Cleavage of Propargylic Hydrazine (**3da**)[a]



Entry	x	Temp (°C)	Time (h)	Yield (%)[b]
1	100	r.t.	15	32
2	100	40	15	57
3	100	80	15	80
4	50	80	15	70
5	100	80	4	78
6[c]	100	80	4	46
7[c]	100	120	4	68
8[d]	100	80	4	33

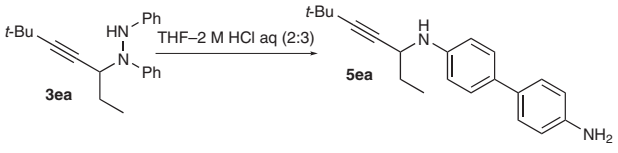
[a] The reaction was carried out using propargylic hydrazine **3da** (1 equiv) and zinc dust (x equiv) in acetic acid (1.5 mL) at the specified temperature for 4 h or 15 h.
[b] Isolated yield.
[c] Acetic acid (3 mL) was used.
[d] Trifluoroacetic acid was used in place of acetic acid.

found to be the major product in the reaction shown in Table 4, entry 7 from the result of the reduction of a mixture of **3er** and **3er′** (Table 6, entry 7).

Subsequently, we investigated the benzidine rearrangement of propargylic hydrazine **3ea**, which afforded corresponding biphenylamine **5ea** through the N–N bond cleavage of **3ea** under acidic conditions.[12] Optimization of the reaction temperature and the reaction time was performed, and the results are shown in Table 7. When **3ea** was exposed to a 2:3 mixture of THF and 2 M HCl (aq) at 50 °C for 20 h, anticipated biphenylamine **5ea** was obtained in 47% yield (Table 7, entry 1). When the reaction temperature was elevated to 70 °C, the yield was improved to 56% (entry 2). Attempts to carry out the rearrangement for a shorter reaction time and/or at a higher reaction temperature were not effective in gaining better results (entries 3 and 4).

A substituent on the aromatic ring of propargylic hydrazines affected the isolated yields of the products. Introduction of a methyl group to 3-position decreased the yield of **5dg** because of steric repulsion between the two methyl groups of product **5dg** (Table 8, entry 2). 2-Methyl-substi-

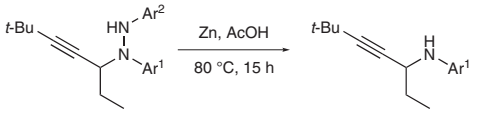
Table 7 Optimization of Benzidine Rearrangement of Propargylic Hydrazine **3ea**[a]



Entry	Temp (°C)	Time (h)	Yield (%)[b]
1	50	20	47
2	70	20	56
3	70	7	51
4	120	7	28

[a] The reaction was carried out using propargylic hydrazine **3ea** in a mixture of THF (1 mL) and 2 M HCl aq (1.5 mL) at the specified temperature for 7 h or 20 h.
[b] Isolated yield.

Table 6 Reductive N–N Bond Cleavage of Various Propargylic Hydrazines **3ea**, **3eb**, **3ef**, **3ej**, **3eq**+**3eq′**, and **3er** + **3er′**[a]



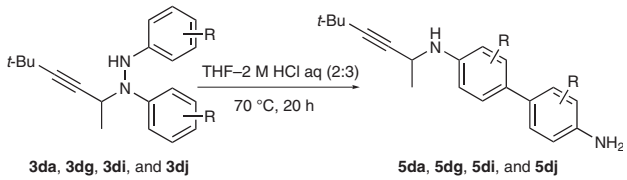
3ea, **3eb**, **3ef**, **3ej**, **3eq+3eq′**, and **3er+3er′** → **4ea**, **4eb**, **4ef**, **4ej**, **4eq+4eq′**, and **4er+4er′**

Entry	Ar^1	Ar^2	Product	Yield (%)[b]
1	Ph	Ph **3ea**	**4ea**	82
2[c]	4-MeC_6H_4	4-MeC_6H_4 **3eb**	**4eb**	66
3	4-MeC_6H_4	4-MeC_6H_4 **3eb**	**4eb**	96
4[c]	4-FC_6H_4	4-FC_6H_4 **3ef**	**4ef**	55
5	2-FC_6H_4	2-FC_6H_4 **3ej**	**4ej**	75
6[d]	2-MeC_6H_4/2-FC_6H_4	2-FC_6H_4 **3eq**/2-MeC_6H_4 **3eq′**, **3eq** + **3eq′** (66:34)	**4eq** + **4eq′**	82 (74:26)
7[d]	3-MeC_6H_4/2,4-$F_2C_6H_3$	2,4-$F_2C_6H_3$ **3er**/3-MeC_6H_4 **3er′**, **3er** + **3er′** (64:36)	**4er** + **4er′**	>99 (69:31)

[a] The reaction was carried out using propargylic hydrazines **3ea**, **3eb**, **3ef**, **3ej**, **3eq** + **3eq′**, and **3er** + **3er′** (1 equiv) and zinc dust (100 equiv) in acetic acid (1.5 mL) at 80 °C for 15 h.
[b] Isolated yield.
[c] The reaction was performed for 4 h.
[d] The reaction was performed using zinc dust (100 equiv) and MeOH (4 equiv) in acetic acid (1.5 mL) at 80 °C for 15 h.

tuted substrate **3di** displayed comparable reactivity to **3da** (entry 3 vs. entry 1). The existence of an electron-withdrawing group significantly decreased the yield of **5dj** probably due to suppression of protonation of the two amino groups (entry 4).

Table 8 Benzidine Rearrangement of Various Propargylic Hydrazines **3da**, **3dg**, **3di**, and **3dj**[a]



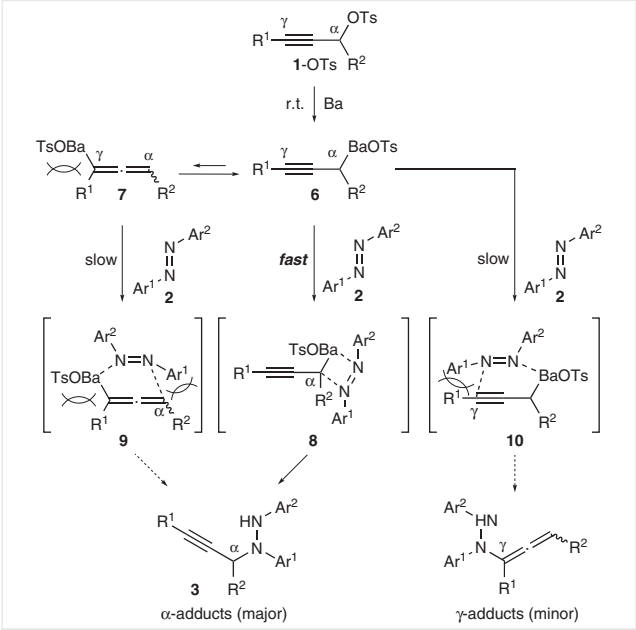
3da, **3dg**, **3di**, and **3dj** **5da**, **5dg**, **5di**, and **5dj**

Entry	R	Product	Yield (%)[b]
1	H **3da**	**5da**	56
2	3-Me **3dg**	**5dg**	30
3	2-Me **3di**	**5di**	54
4	2-F **3dj**	**5dj**	9

[a] The reaction was carried out using propargylic hydrazines **3da**, **3dg**, **3di**, and **3dj** in a mixture of THF (1 mL) and 2 M HCl aq (1.5 mL) at 70 °C for 20 h.
[b] Isolated yield.

A proposed reaction mechanism is illustrated in Scheme 2. Two pathways are possible for propargylic hydrazines **3** (α-adducts). A barium reagent generated from propargylic tosylate **1**-OTs and metallic barium is supposed to be present in equilibrium between propargylic isomer **6** and allenylic isomer **7**.[13] Thus, α-adducts are accessible from both isomers **6** and **7** by treating them with azo compound **2** via transition-state models **8** and **9**, respectively, although former structure **8** is more favorable due to minimal steric repulsion. Meanwhile, allenylic hydrazines (γ-adducts) can be formed from **6** by an S_E2'-type reaction of **6** with azo compound **2** through six-membered cyclic transition state **10**. However, **10** is unstable due to steric repulsion between the R^1 group of the barium reagent and an aryl group of the azo compound. As a consequence, propargylic barium species **6** is anticipated to react preferentially at the α-carbon with azo compound **2** via four-membered cyclic transition state **8**,[14] yielding the α-adduct selectively. Furthermore, in the case of unsymmetrical azobenzene (Ar^1 = electron-rich Ar group; Ar^2 = electron-deficient Ar group), the propargylation occurs selectively at the nitrogen atom which bonds to Ar^1 group, because the nitrogen atom is considered to be relatively electron-deficient probably due to resonance effect. In contrast, another relatively electron-rich nitrogen atom is allowed to coordinate to barium atom.

In conclusion, we have achieved a novel Barbier-type propargylation of azo compounds with barium reagents that are prepared from propargylic tosylates and metallic barium. The employment of metallic barium as the source of barium reagents has enabled the synthesis of various propargylic hydrazines in a regioselective manner.[15] In addition, the site-selective propargylation of unsymmetrical azo compounds has been realized, giving isomeric ratios of up to 66:34. The utility of the propargylated product has been further demonstrated by their transformation into propargylated amines and propargylated biphenylamines through two types of N–N bond cleavage. Further studies of related reactions promoted by metallic barium are under way.



Scheme 2 Proposed reaction pathways to α-adducts and γ-adducts

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1706414.

References and Notes

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(15) **Typical Experimental Procedure for the Barbier-Type Selective Propargylation of Diaryl Azo Compounds: Synthesis of 1-(6,6-Dimethylhept-4-yn-3-yl)-1,2-diphenylhydrazine (3ea, Table 2, Entry 2)**

Freshly cut barium (small pieces, 103.0 mg, 0.75 mmol), propargylic tosylate **1h** (220.8 mg, 0.75 mmol), and azobenzene (45.6 mg, 0.25 mmol) were placed in a Schlenk tube (25 mL) under an argon atmosphere and covered with dry THF (1 mL). The mixture was stirred for 14 h at room temperature. The mixture was treated with sat. aq NH_4Cl (10 mL), and the aqueous layer was extracted three times with Et_2O (10 mL each). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo after filtration. The residual crude product was purified by column chromatography on silica gel (hexane–MeOH, 50:1) to afford propargylic hydrazine **3ea** (65.5 mg, 85% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.15 (m, 4 H, Ar–H), 7.05–7.03 (d, 2 H, *J* = 8.2 Hz, Ar–H), 6.91–6.85 (m, 3 H, Ar–H), 6.77–6.74 (t, 1 H, *J* = 7.3 Hz, Ar–H), 5.67 (br, 1 H, NH), 4.43–4.39 (t, 1 H, *J* = 7.5 Hz, CH), 1.89–1.66 (m, 2 H, CH_2), 1.16 (s, 9 H, 3 CH_3), 1.04–1.00 (t, 3 H, *J* = 7.4 Hz, CH_3). ^{13}C NMR (99.5 MHz, $CDCl_3$): δ = 150.8, 149.0, 129.1, 128.9, 120.7, 118.9, 116.2, 112.1, 94.9, 75.1, 58.1, 31.4, 31.1, 27.4, 11.4. IR (neat): 3311, 2965, 2359, 1600, 1496, 1362, 1308, 1239, 1170, 1092, 1025, 992, 857, 819, 745, 691, 628 cm^{-1}. MS (ESI): *m/z* calcd for $[C_{21}H_{27}N_2]^+$ $[M + H]^+$: 307.2169; found: 307.2170; mp 57–60 °C..