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Nucleophilic addition of tertiary propargylic amines to arynes followed by a [2,3]-sigmatropic rearrangement

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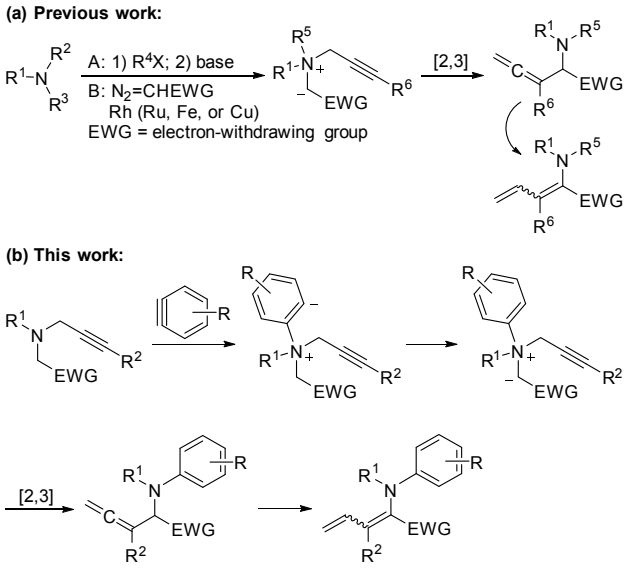
In the presence of 2-(trimethylsilyl)aryl triflates as aryne precursors under mild conditions, a range of tertiary propargylic amines bearing electron-withdrawing groups were converted to quaternary propargylic ammonium ylides followed by a [2,3]-sigmatropic rearrangement to afford structurally diverse amino-substituted allenes or conjugated dienes, depending on their structure, in moderate to good yields.

Owing to charge acceleration, conversion of tertiary propargylic amines to quaternary propargylic ammonium ylides permits a [2,3]-sigmatropic rearrangement under mild conditions to afford amino-substituted allenes and/or conjugated dienes depending on their structure and reaction conditions (Scheme 1, a).[1] It is noteworthy that such type of amino-substituted allenes and conjugated dienes serve as versatile building blocks in chemical synthesis through transformations such as carbonylation and cycloaddition.[2] There are two approaches reported previously to access quaternary propargylic ammonium ylides for the [2,3]-sigmatropic rearrangement: (1) *N*-alkylation of tertiary amines followed by treatment with bases;[3] and (2) metal carbenoid-mediated coupling between tertiary propargylic amines and diazo compounds.[4] These approaches rely on the introduction of alkyl groups to the nitrogen atom of tertiary amines to access quaternary propargylic ammonium ylides. To expand the scope for the [2,3]-sigmatropic rearrangement of quaternary propargylic ammonium ylides, we have developed a new strategy to execute the rearrangement through *N*-arylation of tertiary propargylic amines without the presence of strong bases and metals (Scheme 1, b).



Scheme 1 [2,3]-Sigmatropic rearrangement of quaternary propargylic ammonium ylides.

Recently, we[5] and others[6] reported that arynes and tertiary allylic amines can participate in a [2,3]-sigmatropic rearrangement under mild conditions. Inspired by this discovery, alongside our interest in synthetic exploration of C–N bond cleavage,[7,8] we envisioned that addition of tertiary propargylic amines to arynes[9] followed by proton transfer would lead to the formation of quaternary propargylic ammonium ylides, which would undergo a [2,3]-sigmatropic rearrangement to afford amino-substituted allenes (Scheme 1, b). In exposure to bases, some of the allene products would further isomerize to conjugated dienes.[3]

Using 2-(trimethylsilyl)phenyl triflate (**2a**) as a benzyne precursor,[10] we surveyed a few readily available fluoride sources in the model reaction of tertiary propargylic amine **1a** in acetonitrile at room temperature and found that the combined use of KF and 18-crown-6 afforded conjugated diene **4a** in the best yield, 49%, with >99:1 *Z/E* selectivity (Table 1, entry 5). Allene **3a** was not obtained probably due to its ready

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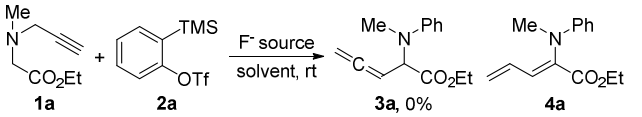
isomerization to diene **4a** in exposure to the remaining fluoride source, a basic salt. We then examined a number of solvents, and to our delight, found that performing the reaction in ethylene glycol diethyl ether enhanced the yield to 65% without erosion of stereoselectivity (Table 1, entry 10). Increasing the reaction scale from 0.20 mmol to 11.6 mmol gave a slightly lower yield (58%). When the temperature was elevated to 60 °C, the reaction gave a comparable yield, 66% (Table 1, entry 15).

Table 1 Optimization of the reaction conditions[a]



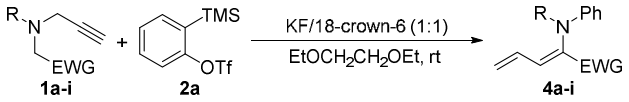
1a **2a** **3a**, 0% **4a**

Entry	F⁻ source	Solvent	Yield[b] (%)	*Z*/*E*[c]
1	Bu_4NF[d]	MeCN	47	>99:1
2	CsF	MeCN	Trace	-
3	CsF/18-crown-6	MeCN	38	>99:1
4	KF	MeCN	0	-
5	KF/18-crown-6	MeCN	49	>99:1
6	KF/18-crown-6	DMF	28	>99:1
7	KF/18-crown-6	THF	55	>99:1
8	KF/18-crown-6	Dioxane	46	>99:1
9	KF/18-crown-6	Et_2O	10	>99:1
10	KF/18-crown-6	$EtOCH_2CH_2OEt$	65	>99:1
11	KF/18-crown-6	Diglyme	56	>99:1
12	KF/18-crown-6	CH_2Cl_2	42	>99:1
13	KF/18-crown-6	$ClCH_2CH_2Cl$	17	>99:1
14	KF/18-crown-6	PhMe	0	-
15[e]	KF/18-crown-6	$EtOCH_2CH_2OEt$	66	>99:1

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.24 mmol), F⁻ source (0.40 mmol), 18-crown-6 (if any, 0.40 mmol), solvent (1.0 mL), rt, 6 h. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] A solution of Bu_4NF (1.0 M) in THF was used. [e] The reaction was run at 60 °C.

A range of tertiary terminal propargylic amines bearing various electron-withdrawing groups were examined in the reaction with 2-(trimethylsilyl)phenyl triflate (**2a**) in the presence of KF/18-crown-6 at room temperature, and the corresponding conjugated dienes were obtained in moderate to good yields (Table 2, entries 1-6). While excellent stereoselectivity was observed for a substrate having an ester group, a ketone group, or a benzoxazole group, the reaction with a substrate having a cyano group exhibited low stereoselectivity. We also examined the reaction with a substrate having an amide group but observed a complex mixture. Other than a simple alkyl group, a propargyl group or an ethoxycarbonylmethyl group was also successfully introduced as a functionalized *N*-substituent, which did not participate in the rearrangement (Table 2, entries 8 and 9).

Table 2 Benzyne-mediated [2,3]-sigmatropic rearrangement of tertiary terminal propargylic amines[a]



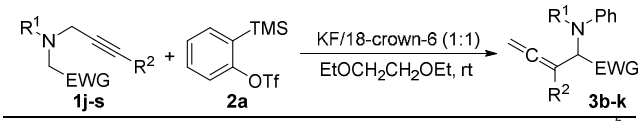
1a-i **2a** **4a-i**

Entry	**1**	R	EWG	**4**	Yield[b] (%)	*Z*/*E*[c]
1	**1a**	Me	CO_2Et	**4a**	65	>99:1
2	**1b**	Me	CO_2Bn	**4b**	61	>99:1
3[d]	**1c**	Me	$CO_2{}^tBu$	**4c**	62	>99:1
4	**1d**	Me	COPh	**4d**	60	>99:1
5	**1e**	Me	CN	**4e**	52	70:30[e]
6	**1f**	Me		**4f**	49	>99:1
7	**1g**	^{n}Bu	CO_2Et	**4g**	70	>99:1
8	**1h**	propargyl	CO_2Et	**4h**	62	95:5
9	**1i**	CH_2CO_2Et	CO_2Et	**4i**	43	96:4

[a] Reaction conditions: **1** (0.20 mmol), **2a** (0.24 mmol), KF (0.40 mmol), 18-crown-6 (0.40 mmol), $EtOCH_2CH_2OEt$ (1.0 mL), rt, 6 h. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] KF/18-crown-6 (0.60 mmol) was used and the reaction was run for 12 h. [e] The two stereoisomers are separable on silica gel chromatography.

In sharp contrast, allenes rather than conjugated dienes were obtained from the reaction of tertiary internal propargylic amines with 2-(trimethylsilyl)phenyl triflate (**2a**) under the same conditions (Table 3). In these cases, the allene products were stable under the standard reaction conditions and obviated isomerization to conjugated dienes. The electron-withdrawing group in a suitable internal tertiary propargylic amine could be an ester group, an amide group or a benzoxazole group. Although amides were reported previously to undergo addition[11] or insertion[12] to arynes, in our case they were well tolerated due to their much lower nucleophilicity relative to tertiary amines. We also examined the reaction with the corresponding substrate having a ketone group or a cyano group, but unfortunately, observed a complex mixture. Interestingly, very high site selectivity was observed in the reaction with amine **1n**, wherein the *N*-(3-phenylprop-2-yn-1-yl) group participated in the [2,3]-sigmatropic rearrangement and the *N*-(prop-2-yn-1-yl) group was kept untouched (Table 3, entry 5).

Table 3 Benzyne-mediated [2,3]-sigmatropic rearrangement of tertiary internal propargylic amines[a]



1j-s **2a** **3b-k**

Entry	**1**	R^1	R^2	EWG	**3**	Yield[b] (%)
1	**1j**	Me	Ph	CO_2Et	**3b**	70
2[c]	**1k**	Me	Ph		**3c**	62
3	**1l**	Me	Ph		**3d**	47
4	**1m**	^{n}Bu	Ph	CO_2Et	**3e**	75
5	**1n**	propargyl	Ph	CO_2Et	**3f**	64

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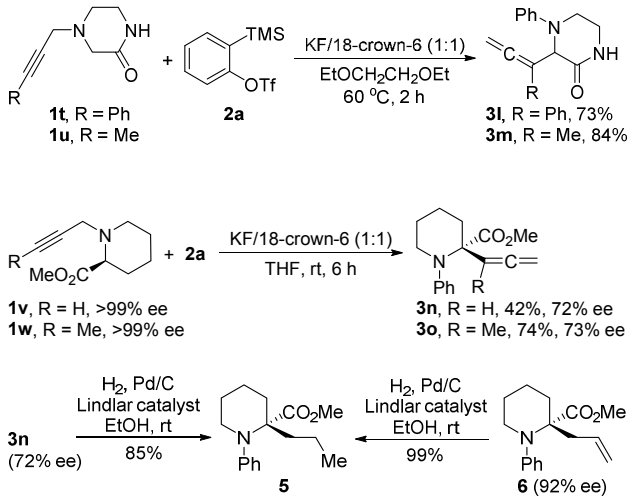
6	**1o**	CH_2CO_2Et	Ph	CO_2Et	**3g**	63
7	**1p**	Me	4-$MeOC_6H_4$	CO_2Et	**3h**	75
8	**1q**	Me	4-$EtO_2CC_6H_4$	CO_2Et	**3i**	72
9	**1r**	Me	2-MeC_6H_4	CO_2Et	**3j**	70
10	**1s**	Me	Me	CO_2Me	**3k**	43

[a] Reaction conditions: **1** (0.20 mmol), **2a** (0.24 mmol), KF (0.40 mmol), 18-crown-6 (0.40 mmol), $EtOCH_2CH_2OEt$ (1.0 mL), rt, 6 h. [b] Isolated yield. [c] The structure of compound **3c** was confirmed by single crystal X-ray analysis (CCDC 1534313).

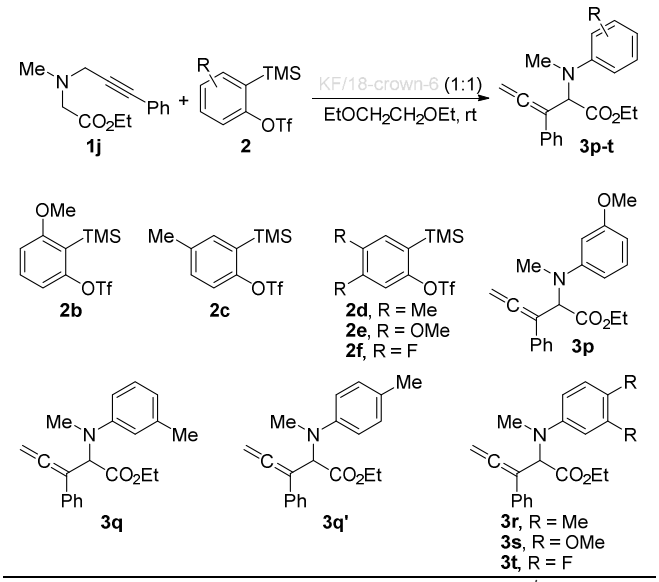
The benzyne-mediated [2,3]-sigmatropic rearrangement was successfully extended to some *N*-propargylic cyclic amines (Scheme 2). Although an elevated temperature (60 °C) was required in the reaction of an *N*-propargylic piperazin-2-one (**1t** or **1u**), the amide group was kept untouched. We further applied the chemistry to optically active tertiary propargylic amines, *L*-pipecolinic acid derivatives **1v** and **1w**, and observed significant erosion of enantiopurity in the construction of nitrogen-substituted quaternary stereocenters. The unsatisfactory efficiency of chirality transfer was attributable to the low diastereoselective attack of the cyclic tertiary amine on the benzyne intermediate, generated in situ from 2-(trimethylsilyl)phenyl triflate (**2a**). The inversion of configuration was determined by catalytic hydrogenation of allene product **3n** to afford α-amino ester **5**, which was also prepared from a known chiral compound, unsaturated α-amino ester **6**.[5]



Scheme 2 *N*-Propargylic cyclic amines.

A few 2-(trimethylsilyl)aryl triflates bearing either electron-donating groups or electron-withdrawing groups were demonstrated to serves as suitable aryne precursors in the reaction of tertiary propargylic amine **1j** (Table 4). The regioselectivity highly depends on the position of substituents in the in situ generated unsymmetrical arynes. While the reaction with 4-methylbenzyne gave poor regioselectivity (Table 4, entry 2), a single regioisomer was obtained from the reaction with 3-methoxybenzyne (Table 4, entry 1).

Table 4 Aryne-mediated [2,3]-sigmatropic rearrangement of amine **1j**[a]



Entry	2	3	Yield[b] (%)
1	**2b**	**3p**	62
2	**2c**	**3q**/**3q'** (56:44)[c]	47
3	**2d**	**3r**	42
4	**2e**	**3s**	57
5	**2f**	**3t**	45

[a] Reaction conditions: **1j** (0.20 mmol), **2** (0.24 mmol), KF (0.40 mmol), 18-crown-6 (0.40 mmol), $EtOCH_2CH_2OEt$ (1.0 mL), rt, 6 h. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopic analysis.

In summary, we have established a new strategy for the [2,3]-sigmatropic rearrangement of quaternary propargylic ammonium ylides via nucleophilic addition of tertiary propargylic amines to arynes under mild conditions. In the presence of 2-(trimethylsilyl)aryl triflates as aryne precursors, a range of tertiary propargylic amines bearing electron-withdrawing groups were converted to quaternary propargylic ammonium ylides followed by a [2,3]-sigmatropic rearrangement to afford structurally diverse amino-substituted allenes or conjugated dienes, depending on their structure, in moderate to good yields. It is noteworthy that the reaction proceeds in the absence of strong bases and metals, is compatible with moisture and air, and tolerates a wide variety of functional groups.

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Conflicts of interest

There are no conflicts to declare.

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