Advanced Synthesis & Catalysis

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Title: Phosphine Catalyzed [3+2] or [4+2] Cycloaddition/ SN2 Substitution Domino Reaction of ortho-Amino Trifluoroacetophenone Derivatives with Hex-3-yn-2-one: Preparation of Functionalized 1-Benzazepine Compounds

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201700778

Link to VoR: http://dx.doi.org/10.1002/adsc.201700778

10.1002/adsc.201700778

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FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Phosphine Catalyzed [3+2] or [4+2] Cycloaddition/S_N2 Substitution Domino Reaction of *ortho*-Amino Trifluoroacetophenone Derivatives with Hex-3-yn-2-one: Preparation of Functionalized 1-Benzazepine Compounds

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. In this paper, we disclosed a novel strategy for the phosphine catalyzed cycloaddition/S_N2 substitution domino reaction, giving functionalized O-bridged benzoazepine and benzoxazepine derivatives in moderate to good yields. Changing the N-H protecting group of ***ortho***-amino trifluoroacetophenone derivatives gave different bridged-ring products in one step.

Keywords: phosphine catalysis, alkyone, domino reaction, bridged-ring compound.

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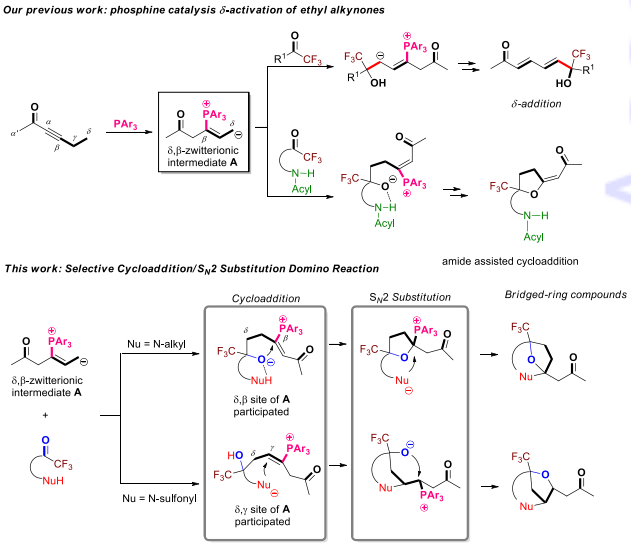
Introduction

Recently, nucleophilic phosphine organocatalysis[1] has made remarkable and continuous progress due to its wide applicability in the construction of carbo- and heterocyclic systems,[2] which have potential applications for the synthesis of crucial moieties in important drug leads.[3] On the basis of the pioneering work of Lu,[4a, 4b, 2j, 4c, 4d] Kwon,[5] Huang[6] and Marinetti,[7] several novel strategies on the phosphine catalyzed cycloadditions have been established, that could be widely used in the synthesis of functionalized nitrogen- and oxygen-containing heterocyclic compounds.[8] Following these pioneering reports, complex molecules such as fused aromatic rings,[9] polycyclic compounds[10] and bridged-ring structures[11] could be directly and efficiently constructed.

Alkynones can be activated by tertiary phosphine as a nucleophilic catalyst to generate zwitterionic intermediates, which can undergo nucleophilic additions[12] or annulations with other electrophiles in different pathways.[13, 10d] However, domino annulations of alkynones with other electrophiles are scarcely reported. Recently, our group has focused on the development of alkynone chemistry upon phosphine catalysis and found that a novel δ,β-zwitterionic intermediate **A** could be generated from the addition of P(4-FC_6H_4)$_3$ to ethyl alkynone,[14] which could efficiently react with trifluoroacetyl compounds to afford δ-addition products. Moreover, with the assistance of intramolecular hydrogen bonding, cycloaddition of zwitterionic intermediate **A** with trifluoroacetyl compounds was also possible upon phosphine catalysis (Scheme 1, previous work).[15]

We envisaged that zwitterionic intermediate **A** could undergo a cycloaddition/S_N2 substitution domino process with an additional nucleophile tethered with trifluoroacetyl compounds. Herein, we wish to report the first example of cycloaddition/S_N2 substitution domino reaction of *ortho*-amino trifluoroacetophenone derivatives with 3-hex-2-one to form two kinds of CF_3-containing[16] O-bridged benzoazepine[17] and benzoxazepine derivatives[18] (Scheme 1, this work).



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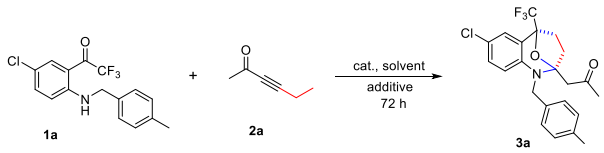
Scheme 1. Our strategies of phosphine catalyzed activation of alkynones *via* vinyl phosphoniums.

Results and discussion

Our study commenced with 1-(5-chloro-2-((4-methylbenzyl)amino)phenyl)-2,2,2-trifluoroethan-1-one **1a** and hex-3-yn-2-one **2a** as the substrates in the presence of PPh_3 (20 mol%) in toluene (1.0 mL) at room temperature, affording the desired product **3a** in 14% yield after 72 hours (Table 1, entry 1). Other phosphine catalysts also gave **3a** in low yields along with recovery of **1a** (Table 1, entries 2-3). Raising the reaction temperature to 65 °C gave **3a** in 26% yield if using PPh_3 (20 mol%) as the catalyst (Table 1, entry 4). Moreover, **3a** could be produced in 40% yield at 65 °C when $P(4\text{-}FC_6H_4)_3$ (20 mol%) was employed (Table 1, entry 5). The examination of solvent effect revealed that toluene and dioxane were the suitable media (Table 1, entries 6-13). Next, we examined a variety of additives such as phenol, benzoic acid, water and HFIP (1,1,1,3,3,3-hexafluoro-2-propanol) and identified that none of these additives benefited the reaction proceeding (Table 1, entries 10-16). Organic bases could not improve the reaction yields (Table 1, entries 18-22). Using inorganic bases as additives could improve the yield of **3a** and addition of Na_2CO_3 (1.0 equiv) could afford **3a** in 73% NMR yield (72% isolated yield) in toluene at 65 °C (Table 1, entries 23-24). In the absence of phosphine, no reaction occurred (Table 1, entry 25). Thus, the best reaction conditions are using $P(4\text{-}FC_6H_4)_3$ (20 mol%) as the catalyst, Na_2CO_3 (1.0 equiv) as the additive and carrying out the reaction in toluene at 65 °C for 72 hours (see Table S1 in the Supporting Information for the more details).

Table 1. Optimization of the reaction conditions for the synthesis of **3a**.

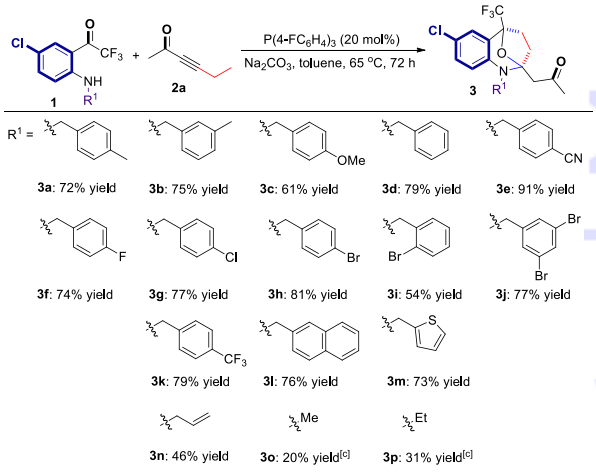


entry[a]	**2a** (equiv)	cat.	additive (equiv)	solvent	temp (°C)	yield (%)[b]
1	2	PPh_3	-	toluene	r.t	14
2	2	$PMePh_2$	-	toluene	r.t	10
3	2	$P(4\text{-}FC_6H_4)_3$	-	toluene	r.t	11
4	4	PPh_3	-	toluene	65	26
5	4	$P(4\text{-}FC_6H_4)_3$	-	toluene	65	40
6	4	$P(4\text{-}FC_6H_4)_3$	-	DCM	65	13
7	4	$P(4\text{-}FC_6H_4)_3$	-	DMSO	65	8
8	4	$P(4\text{-}FC_6H_4)_3$	-	dioxane	65	40
9	4	$P(4\text{-}FC_6H_4)_3$	-	MeOH	65	trace
10	4	$P(4\text{-}FC_6H_4)_3$	-	EtOH	65	12
11	4	$P(4\text{-}FC_6H_4)_3$	-	EA	65	34
12	4	$P(4\text{-}FC_6H_4)_3$	-	THF	65	26
13	4	$P(4\text{-}FC_6H_4)_3$	-	DMF	65	17
14	3	$P(4\text{-}FC_6H_4)_3$	PhOH (1)	toluene	65	9
15	3	$P(4\text{-}FC_6H_4)_3$	PhCOOH (1)	toluene	65	0
16	3	$P(4\text{-}FC_6H_4)_3$	H_2O (1)	toluene	65	34
17	3	$P(4\text{-}FC_6H_4)_3$	HFIP (1)	toluene	65	0
18	3	$P(4\text{-}FC_6H_4)_3$	DBU (1)	toluene	65	0
19	3	$P(4\text{-}FC_6H_4)_3$	DIPEA (1)	toluene	65	21
20	3	$P(4\text{-}FC_6H_4)_3$	TEA (1)	toluene	65	22
21	3	$P(4\text{-}FC_6H_4)_3$	bipy (1)	toluene	65	34
22	3	$P(4\text{-}FC_6H_4)_3$	dtbpy (1)	toluene	65	38
23	3	$P(4\text{-}FC_6H_4)_3$	K_2CO_3 (1)	toluene	65	67
24	***3***	***$P(4\text{-}FC_6H_4)_3$***	***Na_2CO_3 (1)***	***toluene***	***65***	***73 (72[c])***
25	3	-	Na_2CO_3 (1)	toluene	65	-

[a] The reaction was carried out using **1a** (0.2 mmol), **2a** (2 ~ 4 equiv), cat.(0.04 mmol), in the indicated solvent (1 mL) in a Schlenk tube at the indicated temperature.[b] Determined by ^{19}F NMR analysis of the crude reaction mixture. [c] Isolated yield.

Having the optimal reaction conditions in hand, we next investigated the substrate scope of the reaction with respect to a variety of 2-(2,2,2-trifluoroacetyl)phenylamides **1** with different N-alkyl groups and the results are outlined in Table 2. As can be seen, various N-benzyl group substituted 2-(2,2,2-trifluoroacetyl)phenylamides **1b-1m** afforded the desired bridged-ring products **3b-3m** in good to excellent yields regardless of whether electron-withdrawing or -donating substituent was introduced on the aromatic ring. Substrate **1i** bearing 2-bromobenzyl group afforded the corresponding product **3i** in 54% yield presumably due to the steric hindrance. Replacing benzyl group by naphthalen-2-ylmethyl group (**1l**) or thiophen-3-ylmethyl (**1m**) did not influence the yield significantly, giving **3l** in 76% yield and **3m** in 73% yield, respectively. As for substrate **1n**, in which R^1 = allyl, **3n** was isolated in 46% yield under the standard conditions similar as N-benzyl derivatives. When R^1 = Me or Et, the reaction mixture became a mess under the standard conditions. The desired products **3o** and **3p** were produced in 20% yield and 31% yield without using Na_2CO_3 as an additive. Probably, the stronger basicity of N-alkyl group influences the S_N2 substitution proceeding and Na_2CO_3 might accelerate the side reactions. In addition, N-Me and N-Et products were found to be unstable at high temperature.

Table 2. Reaction Scope: O-bridged benzoazepine derivatives **3**.[a][b]



[a] The reaction was carried out using **1** (0.2 mmol), **2a** (0.6 mmol), Na_2CO_3 (0.2 mmol) and $P(4\text{-}FC_6H_4)_3$ (0.04 mmol), in toluene (1.0 mL) in a Schlenk tube at 65 °C. [b] Isolated yield. [c] The reaction was carried out without using Na_2CO_3.

Next, the substituents on the benzene ring of **1** were also examined with substrates **1q-1y** as shown in Table 3. If without substituent on the benzene ring or substrates containing electron-deficient aromatic ring, the reactions proceeded smoothly to give the corresponding bicyclic products **3q-3v** in 65-85% yields. Substrates **1w-1y** containing electron-donating groups such as OMe, Me and *i*-Pr groups afforded the corresponding products in moderate yields (33%-65%), suggesting that electron-donating group on the benzene ring would impair the reaction proceeding. Next, the substituent in acyl group was tested. When R = CF_2Cl, the desired product **3z** was obtained in 53% yield. However, using CF_2CF_3 instead of CF_3 failed to give the desired product **3aa**. When R = Me or Ph, no reaction occurred, suggesting that trifluoromethyl group activated acyl group is essential for the reaction with zwitterionic intermediate **A**. (Z)-4-(benzylamino)-1,1,1-trifluorobut-3-en-2-one **1ad** also failed to

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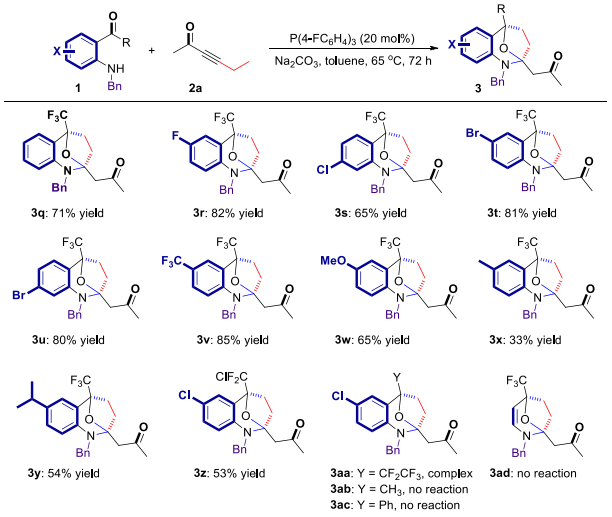
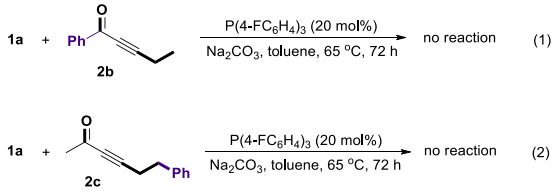
afford the desired product **3ad**. Attempts to synthesize *ortho*-aminobenzoyl formats met with little success; replacement of CF_3 with CO_2R or CN groups made compound **1** unstable and was converted to isatin *in situ*.

Table 3. Reaction Scope: Synthesis of O-bridged benzoazepine derivatives **3**.[a][b]



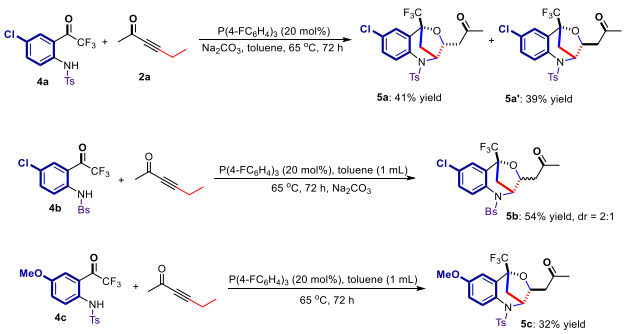
[a] The reaction was carried out using **1** (0.2 mmol), **2a** (0.6 mmol), Na_2CO_3 (0.2 mmol) and $P(4\text{-}FC_6H_4)_3$ (0.04 mmol) in toluene (1 mL) in a Schlenk tube at 65 °C and the solvent was treated by sodium. [b] Isolated yield.

Subsequently, we turned our attention to substrate scope with respect to the alkynones. As shown in Scheme 2, the use of 1-phenylpent-2-yn-1-one **2b** instead of **2a** did not afford the desired product (Scheme 2, eq. 1). When the δ-position of hex-3-yn-2-one **1a** was substituted by a phenyl group, no reaction occurred (Scheme 2, eq. 2). These results suggested that the steric effect in both α'-position and δ-position could significantly influence the generation of key zwitterionic intermediate **A** and defer the reaction proceeding.



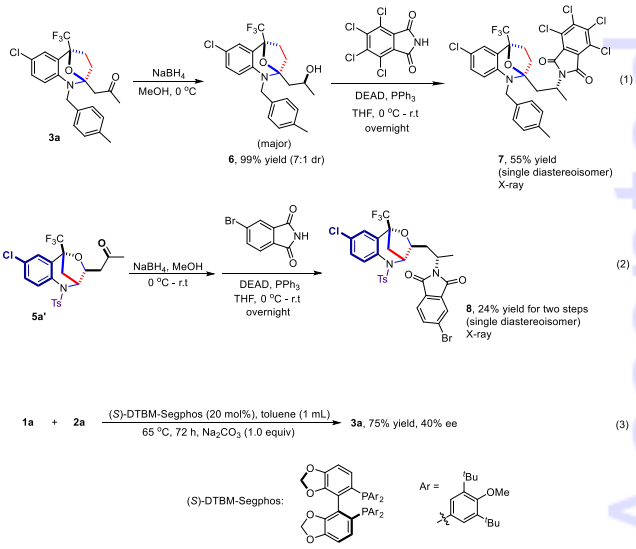
Scheme 2. The substituent effect of alkynones.

As compared with N-alkyl substrates **1**, sulfonated substrates **4** produced different bridged-ring compounds. For example, tosylated substrate **4a** gave **5a** and **5a'** as a pair of diastereoisomers in 80% total yield under the standard conditions (Scheme 3). For substrate **4b** bearing a *para*-bromobenzenesulfonyl group, **5b** was given in 54% yield (2:1 dr). However, in the case of substrate **4c**, the desired product **5c** were only isolated in 32% yield as a single diastereoisomer in the absence of Na_2CO_3. In our unpublished results, a considerable amount of N-acyl substrates were also examined, but only the corresponding cycloaddition products were isolated without domino reaction took place under the standard conditions. The more acidic N-H group of N-sulfonated substrates **4** plays a key role in the production of different bridged-ring compounds (see Scheme 6).



Scheme 3. Synthesis of polycyclic product **5.**

The derivatizations of these functionalized O-bridged benzoazepine and benzoxazepine derivatives were performed as shown in Scheme 4. Treatment of **3a** with $NaBH_4$ provided **6** in 99% yield (7:1 dr), which could be transformed into **7** as a single diastereoisomer in 55% yield via Mitsunobu reaction (Scheme 4, eq. 1). In this case, another diastereoisomer was only isolated in trace. Similarly, phthalimide substituted product **8** was obtained in 24% yield from **5a'** as a single diastereoisomer after two steps (Scheme 4, eq. 2). The structures of **7** and **8** have been unambiguously assigned by X-ray diffraction and their ORTEP drawings are shown in Figure 1 and the CIF data are summarized in the Supporting Information. The asymmetric variant of **1a** and **2a** has been attempted using several chiral phosphines as catalysts, but no satisfactory results were achieved, presumably due to that the chiral phosphine center is far away from the reaction site (see Table S2 in the Supporting Information). Using (*S*)-DTBM-SegPhos (20 mol%) as the catalyst afforded **3a** in 75% yield along with 40% *ee* value (Scheme 4, eq. 3).



Scheme 4. Derivatization and asymmetric variant

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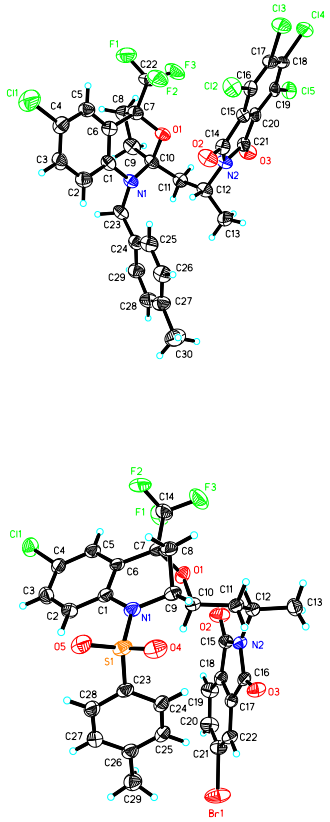
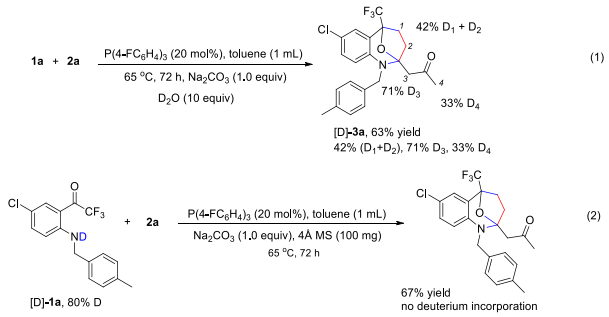


Figure 1. X-ray crystal structures of products **7** and **8**.

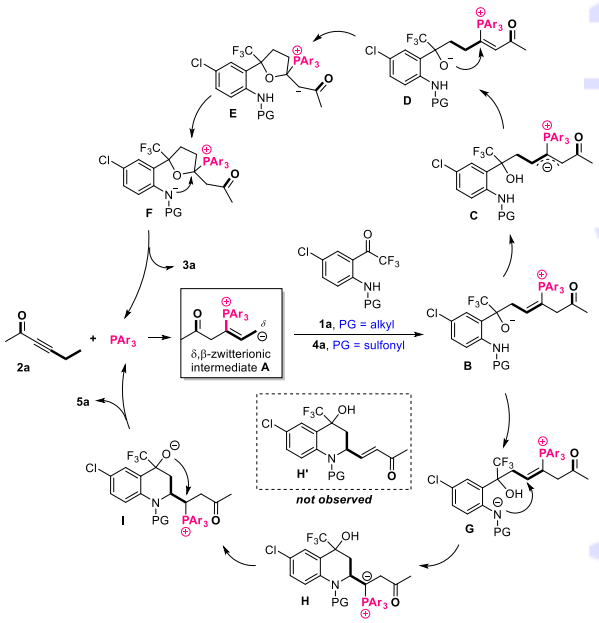
To clarify the reaction mechanism, two deuterium-labeling experiments were conducted under the standard conditions. The reaction of **1a** with **2a** was first carried out in the presence of D_2O (10 equiv) under the standard reaction conditions. The reaction proceeded smoothly to give the corresponding partially deuterated product [D]-**3a** in 63% yield along with the deuterium incorporation at C1~C4 positions (Scheme 5, eq. 1), suggesting the generation of these carbon anionic sites during the catalytic cycle. Using 80% deuterated [D]-**1a** as substrate produced no deuterium incorporated product **3a** in 67% yield, probably due to the scrambling by excess amounts of alkynone **2a** in toluene (Scheme 5, eq. 2).



Scheme 5. Deuterium-labeling experiments

According to the above experimental results and pervious reports, a plausible reaction mechanism for phosphine catalyzed cycloaddition/S_N2 substitution domino process has been outlined in Scheme 6. The reaction is initiated with the *in situ* generated zwitterion **A** derived from the addition of tertiary phosphine to the β-carbon of hex-3-yn-2-one **2a**. Intermediate **A** can attack trifluoroacetyl group of **1a** to afford vinyl phosphonium species **B**. As aforementioned, N-H moieties of N-sulfonated substrates **4** are more acidic than those of N-benzyl substrates **1**,[19] the proton abstraction of N-H moieties of N-benzyl substrates **1** should be more difficult than those of N-sulfonated substrates **4**. The different pK_a values between sulfoamides and amines changed the sequence of proton migration, leading to divergent reaction pathways. When the N-protecting group is an alkyl group, oxygen anion of intermediate **B** prefers to abstract the proton of more acidic carbonyl's α site rather than the proton of amino group, giving zwitterionic intermediate **C**. Zwitterionic intermediate **C** abstracts the proton of hydroxyl group again to afford intermediate **D**. Cyclization of intermediate **D** provides intermediate **E**. The proton shift takes place again to deliver intermediate **F**, which undergoes S_N2 substitution to furnish product **3a** and the phosphine catalyst. When the N-protecting group is a sulfonyl group, the oxygen anion of intermediate **B** directly abstracts the proton of N-H group to give intermediate **G**, which undergoes cyclization to give intermediate **H**. This intermediate **H** produces intermediate **I** via a proton abstraction, which produces **5a** through a subsequent intramolecular S_N2 substitution. Previously, Huang and co-workers reported a PPh_3 catalyzed aza-MBH/aza-Michael domino reaction between salicyl N-tosylimines and allenoates. Unlike Huang's work, we did not detect any product **H'** during the reaction, suggesting that this domino process may not proceed via a stepwise pathway.

Scheme 6. A plausible reaction mechanism.



Conclusion

In conclusion, a novel phosphine catalyzed cycloaddition/S_N2 substitution domino reaction to synthesize substituted functionalized O-bridged benzoazepine and benzoxazepine derivatives has been developed for the first time. Among these domino processes, the [3+2] or [4+2] annulation in the first step can be simply adjusted by changing the intramolecular N-H

nucleophilic group to afford the corresponding products in moderated to excellent yields. Plausible mechanisms have been proposed on the basis of deuterium-labeling and control experiments. Further efforts are in progress to utilize these reactions in the synthesis of biologically active molecules.

Experimental Section

General Procedure for Synthesis of 3

A Schlenk tube was heated under vacuum to remove ambient moisture, and then filled with argon. After the Schlenk tube was returned to room temperature, *ortho*-amino trifluoroacetophenone derivative **1** (0.2 mmol), P(4-FC_6H_4)$_3$ (13 mg, 0.04 mmol) and Na_2CO_3 (21.0 mg, 0.2 mmol) was added. Then, hex-3-yn-2-one **2a** (0.6 mmol) was added to the reaction mixture at room temperature. After that, the resulting mixture was heated to 65 ^oC and was stirred at 65 ^oC until the reaction completed upon monitoring by TLC. Then the solvent was removed under reduced pressure and the residue was purified by a silica gel column flash chromatography (eluent: petroleum ether / ethyl acetate = 30 / 1) to afford the product **3**.

General Procedure for Synthesis of 5

A Schlenk tube was heated under vacuum to remove ambient moisture, and then filled with argon. After the Schlenk tube was returned to room temperature, ortho-amino trifluoroacetophenone derivative **4** (0.2 mmol), P(4-FC_6H_4)$_3$ (13 mg, 0.04 mmol) and Na_2CO_3 (21mg, 0.2 mmol) was added. Then, hex-3-yn-2-one **2a** (0.6 mmol) was added to the reaction mixture at room temperature. After that, the resulting mixture was heated to 65 ^oC and was stirred at 65 ^oC until the reaction completed by monitoring by TLC. Then the solvent was removed under reduced pressure and the residue was purified by a silica gel column flash chromatography (eluent: petroleum ether / ethyl acetate = 6 / 1) to afford the product **5**.

Supporting Information Available

Detailed descriptions of experimental procedures and their spectroscopic data as well as the crystal structures are presented in the Supporting Information. CCDC 1445084 (**7**) and CCDC 1540603 (**8**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

We are grateful for the financial support from the National Basic Research Program of China (973)-2015CB856603, the Strategic Priority Research Program of the Chinese Academy of Sciences, Grant No. XDB20000000, the National Natural Science Foundation of China (20472096, 21372241, 21572052, 20672127, 21421091, 21372250, 21121062, 21302203, and 20732008), and the Fundamental Research Funds for the Central Universities 222201717003.

References

[1] X. Lu, C. Zhang, Z. Xu, *Acc. Chem. Res.* **2001**, *34*, 535-544.

[2] a) L.-W. Ye, J. Zhou, Y. Tang, *Chem. Soc. Rev.* **2008**, *37*, 1140-1152; b) A. Marinetti, A. Voituriez, *Synlett* **2010**, *2010*, 174-194; c) Y. Wei, M. Shi, *Acc. Chem. Res.* **2010**, *43*, 1005-1018; d) Y. C. Fan, O. Kwon, *Chem. Commun.* **2013**, *49*, 11588-11619; e) C. Gomez, J.-F. Betzer, A. Voituriez, A. Marinetti, *ChemCatChem* **2013**, *5*, 1055-1065; f) Y. Wei, M. Shi, *Chem. Rev.* **2013**, *113*, 6659-6690; g) Z. Wang, X. Xu, O. Kwon, *Chem. Soc. Rev.* **2014**, *43*, 2927-2940; h) Y. Wei, M. Shi, *Chem. - Asian. J.* **2014**, *9*, 2720-2734; i) W. Li, J. Zhang, *Chem. Soc. Rev.* **2016**, *45*, 1657-1677; j) T. Wang, X. Han, F. Zhong, W. Yao, Y. Lu, *Acc. Chem. Res.* **2016**, *49*, 1369-1378; k) R. Zhou, Z. He, *Eur. J. Org. Chem.* **2016**, *2016*, 1937-1954.

[3] a) J. Luo, H. Wang, X. Han, L.-W. Xu, J. Kwiatkowski, K.-W. Huang, Y. Lu, *Angew. Chem.* **2011**, 123, 1901–1904; *Angew. Chem. Int. Ed.* **2011**, *50*, 1861-1864; b) X. Han, F. Zhong, Y. Wang, Y. Lu, *Angew. Chem.* **2012**, 124, 791–794; *Angew. Chem. Int. Ed.* **2012**, *51*, 767-770; c) X. Han, W. Yao, T. Wang, Y. R. Tan, Z. Yan, J. Kwiatkowski, Y. Lu, *Angew. Chem.* **2014**, 126, 5749–5753; *Angew. Chem. Int. Ed.* **2014**, *53*, 5643-5647; d) T. Wang, W. Yao, F. Zhong, G. H. Pang, Y. Lu, *Angew. Chem.* **2014**, 126, 3008–3012; *Angew. Chem. Int. Ed.* **2014**, *53*, 2964-2968; e) L. Cai, K. Zhang, O. Kwon, *J. Am. Chem. Soc.* **2016**, *138*, 3298-3301.

[4] a) F. Zhong, J. Luo, G.-Y. Chen, X. Dou, Y. Lu, *J. Am. Chem. Soc.* **2012**, *134*, 10222-10227; b) T. Wang, Z. Yu, D. L. Hoon, K.-W. Huang, Y. Lan, Y. Lu, *Chem. Sci.* **2015**, *6*, 4912-4922; c) T. Wang, Z. Yu, D. L. Hoon, C. Y. Phee, Y. Lan, Y. Lu, *J. Am. Chem. Soc.* **2016**, *138*, 265-271; d) W. Yao, X. Dou, S. Wen, J. e. Wu, J. J. Vittal, Y. Lu, *Nat. Commun.* **2016**, *7*, 13024.

[5] X.-F. Zhu, J. Lan, O. Kwon, *J. Am. Chem. Soc.* **2003**, *125*, 4716-4717.

[6] a) X. Meng, Y. Huang, H. Zhao, P. Xie, J. Ma, R. Chen, *Org. Lett.* **2009**, *11*, 991-994; b) J. Zheng, Y. Huang, Z. Li, *Org. Lett.* **2013**, *15*, 5064-5067.

[7] M. Gicquel, C. Gomez, P. Retailleau, A. Voituriez, A. Marinetti, *Org. Lett.* **2013**, *15*, 4002-4005.

[8] a) T. Wang, S. Ye, *Org. Lett.* **2010**, *12*, 4168-4171; b) R. Na, C. Jing, Q. Xu, H. Jiang, X. Wu, J. Shi, J. Zhong, M. Wang, D. Benitez, E. Tkatchouk, W. A. Goddard, H. Guo, O. Kwon, *J. Am. Chem. Soc.* **2011**, *133*, 13337-13348; c) L. B. Saunders, S. J. Miller, *ACS Catal.* **2011**, *1*, 1347-1350; d) T. Wang, X.-Y. Chen, S. Ye, *Tetrahedron Lett.* **2011**, *52*, 5488-5490; e) T. Wang, S. Ye, *Org. Biomol. Chem.* **2011**, *9*, 5260-5265; f) J. Tian, Z. He, *Chem. Commun.* **2013**, *49*, 2058-2060; g) C. T. Mbofana, S. J. Miller, *ACS Catal.* **2014**, *4*, 3671-3674.

[9] K. Zhang, L. Cai, X. Jiang, M. A. Garcia-Garibay, O. Kwon, *J. Am. Chem. Soc.* **2015**, *137*, 11258-11261.

[10] a) L.-J. Yang, S. Wang, J. Nie, S. Li, J.-A. Ma, *Org. Lett.* **2013**, *15*, 5214-5217; b) E. Li, Y. Huang, *Chem. Commun.* **2014**, *50*, 948-950; c) J. Zheng, Y. Huang, Z. Li, *Chem. Commun.* **2014**, *50*, 5710-5713; d) L. Liang, Y. Huang, *Org. Lett.* **2016**, *18*, 2604-2607.

[11] a) H. Zhao, X. Meng, Y. Huang, *Chem. Commun.* **2013**, *49*, 10513-10515; b) Y. Gu, P. Hu, C. Ni, X. Tong, *J. Am. Chem. Soc.* **2015**, *137*, 6400-6406.

[12] a) I. Junji, B. Yoshiyasu, H. Takeshi, *Chem. Lett.* **1993**, *22*, 241-244; b) B. M. Trost, C.-J. Li, *J. Am. Chem. Soc.* **1994**, *116*, 3167-3168; c) B. M. Trost, C.-J. Li, *J. Am. Chem. Soc.* **1994**, *116*, 10819-10820; d) B. M. Trost, G. R. Dake, *J. Am. Chem. Soc.* **1997**, *119*, 7595-7596; e) C. Lu, X. Lu, *Org. Lett.* **2002**, *4*, 4677-4679; f) R. B. Grossman, S. Comesse, R. M. Rasne, K. Hattori, M. N. Delong, *J. Org. Chem.* **2003**, *68*, 871-874; g) V. Sriramurthy, G. A. Barcan, O. Kwon, *J. Am. Chem. Soc.* **2007**, *129*, 12928-12929; h) V. Sriramurthy, O. Kwon, *Org. Lett.* **2010**, *12*, 1084-1087; i) L. Zhu, Y. Xiong, C. Li, *J. Org. Chem.* **2015**, *80*, 628-633; j) D. T. Ziegler, G. C. Fu, *J. Am. Chem. Soc.* **2016**, *138*, 12069-12072.

[13] a) C. Zhang, X. Lu, *J. Org. Chem.* **1995**, *60*, 2906-2908; b) H. Kuroda, I. Tomita, T. Endo, *Org. Lett.* **2003**, *5*, 129-131; c) J.-C. Wang, M. J. Krische, *Angew. Chem.* **2003**, 115, 6035-6037; *Angew. Chem., Int. Ed.* **2003**, *42*, 5855-5857; d) J.-C. Wang, S.-S. Ng, M. J. Krische, *J. Am. Chem. Soc.* **2003**, *125*, 3682-3683; e) J. E. Wilson, J. Sun, G. C. Fu, *Angew. Chem.* **2010**, 122, 165-167; *Angew. Chem. Int. Ed.* **2010**, *49*, 161-163; f) Z. Lian, M. Shi, *Eur. J. Org. Chem.* **2012**, *2012*, 581-586; g)

10.1002/adsc.201700778

Z. Lian, M. Shi, *Org. Biomol. Chem.* **2012**, *10*, 8048-8050; h) L. Yang, P. Xie, E. Li, X. Li, Y. Huang, R. Chen, *Org. Biomol. Chem.* **2012**, *10*, 7628-7634; i) L. Liang, E. Li, P. Xie, Y. Huang, *Chem. - Asian. J.* **2014**, *9*, 1270-1273.

[14] Y.-L. Sun, X.-N. Zhang, Y. Wei, M. Shi, *ChemCatChem* **2016**, *8*, 3112-3117.

[15] Unpublished result.

[16] a) M. Shimizu, T. Hiyama, *Angew. Chem.* **2005**, 117, 218-234; *Angew. Chem. Int. Ed.* **2005**, *44*, 214-231; b) M. Schlosser, *Angew. Chem.* **2006**, 118, 5558-5572; *Angew. Chem. Int. Ed.* **2006**, *45*, 5432-5446; c) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320-330; d) J. Choi, D. Y. Wang, S. Kundu, Y. Choliy, T. J. Emge, K. Krogh-Jespersen, A. S. Goldman, *Science* **2011**, *332*, 1545-1548.

[17] a) E. Kada, T. Tomifuji, H. Tone, H. Takeuchi, M. Hojo, *Heterocycles* **1998**, *47*, 143-148; b) R. G. Brinson, P. B. Jones, *Org. Lett.* **2004**, *45*, 6155-6158; c) C. Moutrille, S. Z. Zard, *Org. Lett.* **2004**, *45*, 4631-4634; d) S. Saubern, J. M. Macdonald, J. H. Ryan, R. C. J. Woodgate, T. S. Louie, M. J. Fuchter, J. M. White, A. B. Holmes, *Tetrahedron* **2010**, *66*, 2761-2767; e) M. G. Lauer, M. K. Thompson, K. H. Shaughnessy, *J. Org. Chem.* **2014**, *79*, 10837-10848; f) Y. Zhang, F. Yang, L. Zheng, Q. Dang, X. Bai, *Org. Lett.* **2014**, *16*, 6041-6043; g) C. W. Suh, S. J. Kwon, D. Y. Kim, *Org. Lett.* **2017**, *19*, 1334-1337.

[18] a) I. Tapia, V. Alcazar, M. Grande, J. R. Moran, *Tetrahedron* **1988**, *44*, 5113-5116; b) I. Tapia, V. Alcazar, J. R. Moran, M. Grande, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2408-2413; c) M. J. Jedrzejas, R. J. Baker, F. A. Sheibley, F. K. Oplinger, R. L. R. Towns, *J. Heterocycl. Chem.* **1993**, *30*, 65-69; d) Z. Li, J. Zhang, C.-J. Li, *Tetrahedron Lett.* **2003**, *44*, 153-156; e) J. S. Yadav, B. V. S. Reddy, S. Meraj, P. Vishnumurthy, K. Narsimulu, A. C. Kunwar, *Synthesis* **2006**, 2923-2926; f) S. Yamazaki, S. Morikawa, K. Miyazaki, M. Takebayashi, Y. Yamamoto, T. Morimoto, K. Kakiuchi, Y. Mikata, *Org. Lett.* **2009**, *11*, 2796-2799; g) S. Yamazaki, M. Takebayashi, K. Miyazaki, *J. Org. Chem.* **2010**, *75*, 1188-1196; h) C. Du, F. Li, X. Zhang, W. Hu, Q. Yao, A. Zhang, *J. Org. Chem.* **2011**, *76*, 8833-8839.

[19] In general, sulfoamides have smaller pKa values than amines. See: Bordwell pKa values on http://www.chem.wisc.edu/areas/reich/pkatable/index.htm and references therein.

10.1002/adsc.201700778

FULL PAPER

Phosphine Catalyzed [3+2] or [4+2] Cycloaddition/S_N2 Substitution Domino Reaction of *ortho*-Amino Trifluoroacetophenone Derivatives with Hex-3-yn-2-one: Preparation of Functionalized 1-Benzazepine Compounds

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