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Benzene construction *via* Pd-catalyzed cyclization of 2,7-alkadiynylic carbonates in the presence of alkynes†

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A palladium-catalyzed highly regio- and chemo-selective cyclization of 2,7-alkadiynylic carbonates with functionalized alkynes to construct 1,3-dihydroisobenzofuran and isoindoline derivatives under mild conditions has been developed. Functional groups such as alcohol, sulfonamide, and indoles could be well tolerated. After careful mechanistic studies, a mechanism involving oxidative addition and regioselectivity-defined double alkyne insertions has been proposed.

Introduction

Benzocyclopentane derivatives, especially those containing oxygen and nitrogen heterocycles, exist widely in natural products and biologically active molecules:[1] the phthalan (1,3-dihydroisobenzofuran) and isoindoline skeletons are representative examples (Fig. 1),[2] which are also important building blocks in organic synthesis.[3] Common approaches for the construction of phthalan and isoindoline structures include: (1) [2 + 2 + 2] cycloaddition reactions of 1,6-diynes with alkynes;[4–11] (2) tetradehydro-Diels–Alder reaction of eneynes and alkynes or hexadehydro-Diels–Alder reaction of 1,3,8-triynes and electrophiles;[12] (3) domino reaction consisting of Heck couplings and consecutive 6π-electrocyclizations or Sonogashira couplings and sequenced Garratt–Braverman cyclization of alkenyl halides and 1,6-diynes.[13]

Among all these methods, transition metal-catalyzed [2 + 2 + 2] cyclization of 1,6-diynes and alkynes is the most straightforward one.[4–11] However, there is an issue of regioselectivity when non-symmetric 1,6-diynes and non-symmetric alkynes were applied (Scheme 1, eqn (1)).[4–11] Based on our previous explorations in the tandem reactions between 2,7-alkadiynyl carbonates **3** and various allenes to construct fused tricycles,[14] we envisioned a new approach to benzocyclopentanes by applying Pd-catalyzed tandem reaction of 2,7-alkadiynyl carbonates **3** with functionalized terminal or non-terminal alkynes **4**, in which the selectivity issue may be addressed by starting the cyclization from the oxidative addition of the propargylic carbonate unit to afford allenylpalladium intermediate **A**. Then the defined exo-insertion of the intramolecular alkyne and the

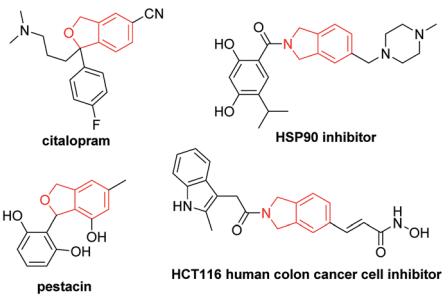
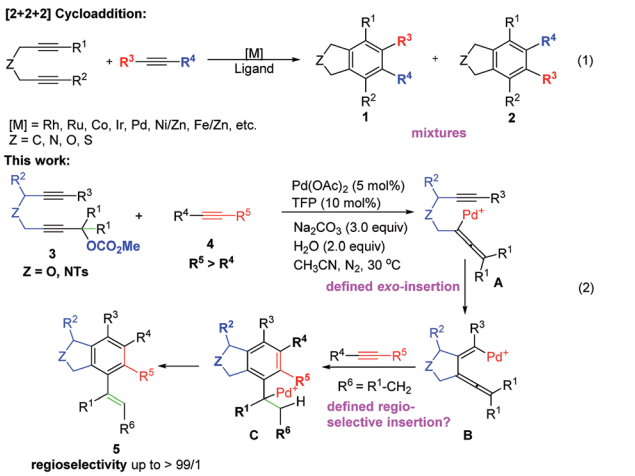


Fig. 1 Some typical natural or bioactive phthalans and isoindolines compounds.



Scheme 1 The transition metal-catalyzed [2 + 2 + 2] cyclotrimerization and cyclization of 2,7-alkadiynyl carbonate **3** in the presence of functionalized alkynes **4**.

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subsequent regio-selective insertion of the intermolecular alkyne would produce benzylpalladium intermediate **C**, which underwent β-H elimination to give the final alkenyl benzene product (Scheme 1, eqn (2)). Here we wish to report the realization of such a concept.

Results and discussion

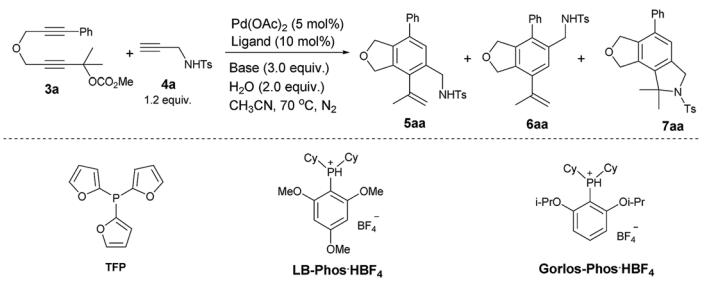
Initially we conducted the reaction of 2,7-alkadiynylic carbonate **3a** (0.3 mmol) and 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide **4a** (1.2 equiv.) under the catalysis of $Pd(OAc)_2$ (5 mol%) and TFP (10 mol%) in the presence of K_2CO_3 (3.0 equiv.) and H_2O (2.0 equiv.) at 70 °C in CH_3CN. Interestingly, a pair of regioisomers **5aa** and **6aa** were observed in 81% and 3% yields, respectively, demonstrating a high regioselectivity. In addition, 2% yield of the cyclization product **7aa** was obtained (entry 1, Table 1). Encouraged by this exciting observation, the influence of the critical reaction parameters was investigated. Firstly, considering of our previous works,[14b,15] an appropriate amount of water may increase the solubility of K_2CO_3 in CH_3CN, the effect of water was tested: the reaction failed to give better results when more water or no water were added (entries 2 and 3, Table 1). After screening a series of mono-phosphine ligand such as PPh_3, LB-Phos·HBF_4,[16] and Gorlos-Phos·HBF_4,[17] it was found that TFP was still the best (entries 4–6, Table 1). The effect of base was also investigated: the reactions using NaOH or NEt_3 as the base produced **5aa** in lower yields with a poorer selectivity (entries 7 and 8, Table 1). Na_2CO_3 was slightly better than K_2CO_3, resulting in 82% yield of **5aa** (entry 9, Table 1).

Further solvent screening showed that the reactions in dioxane, DMSO, DMF, or DCE all delivered poorer results than those in CH_3CN (entries 1–4, Table 2). It is worth mentioning that the efficiency, yield, and selectivity could be kept at the same level when the reaction was conducted at a lower temperature of 30 °C (entries 5–7, Table 2). The reaction at 10 °C is sluggish (entry 8, Table 2). Based on these studies, the optimal mild conditions have been defined as follows: $Pd(OAc)_2$ (5 mol%), TFP (10 mol%), Na_2CO_3 (3.0 equiv.), and H_2O (2.0 equiv.) in CH_3CN at 30 °C.

The scope of the terminal alkynes was examined by using methyl (2-methyl-5-((3-phenylprop-2-yn-1-yl)oxy)pent-3-yn-2-yl) carbonate (**3a**) as the model substrate on a 1 mmol scale (Table 3). The reaction of **3a** with propargyl tosylamide **4a** afforded **5aa**/**6aa** in 78% yield with a selectivity of 97/3. When propargyl alcohol **4b** was used, **5ab**/**6ab** was obtained in 72% yield with the same selectivity. In light of the fact that the indole skeletons are very common in natural products and biologically active molecules,[18] it is interesting to note that the reactions with a series of *N*-propargyl indole derivatives (**4c–4f**) also worked, affording the phthalan derivatives bearing an indole ring **5ac**/**6ac**–**5af**/**6af** in 66–69% yields with a ratio of 95/5 ~> 99/1. Synthetically useful groups such as methyl, formyl, bromo could be introduced at different positions in the indole ring. The structure of product was unambiguously established by the X-ray single crystal diffraction analysis of **5ae** (Fig. 2).[19]

Next, the reactivity of various oxygen- or nitrogen-tethered 2,7-alkadiynylic carbonates was examined with different functionalized terminal alkynes (Table 4). In addition to being methyl groups, the two R^1 groups could be a five- or six-membered ring. The corresponding products **5ba**/**6ba** and **5ja**/**6ja** were isolated in 79% yield with a selectivity of 98/2 and 53% yield with a selectivity of 90/10, respectively. The substrates with the Ar group bearing either electron-rich or electron-deficient

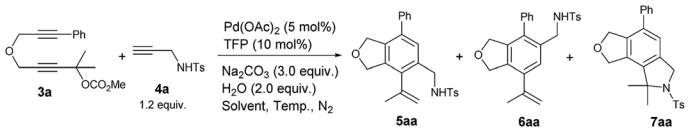
Table 1 The effect of water, ligand, and base[a]



Entry	Ligand	Base	Time (h)	Yield of **5aa**/**6aa**/**7aa**[b] (%)	Recovery of **3a**[b] (%)
1	TFP	K_2CO_3	2	81/3/2	0
2[c]	TFP	K_2CO_3	2	76/3/3	0
3[d]	TFP	K_2CO_3	2	70/4/3	0
4	PPh_3	K_2CO_3	26	37/5/5	14
5	LB-Phos·HBF_4	K_2CO_3	24	19/3/2	43
6	Gorlos-Phos·HBF_4	K_2CO_3	24	31/4/2	27
7	TFP	NaOH	2	64/5/4	0
8	TFP	Et_3N	2	77/4/2	0
9	**TFP**	**Na_2CO_3**	**2**	**82/3/2**	**0**

[a] Reaction condition: **3a** (0.3 mmol), **4a** (1.2 equiv.), $Pd(OAc)_2$ (5 mol%), ligand (10 mol%), base (3.0 equiv.), and H_2O (2.0 equiv.) in CH_3CN (3.0 mL) at 70 °C unless otherwise noted. [b] Determined by the ^1H NMR analysis of the crude product using mesitylene as the internal standard. [c] H_2O (4.0 equiv.) were added. [d] No H_2O was added.

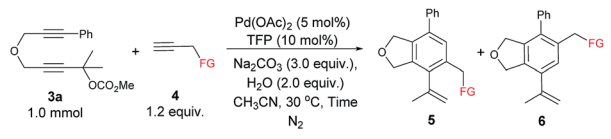
Table 2 The effect of solvent and temperature[a]

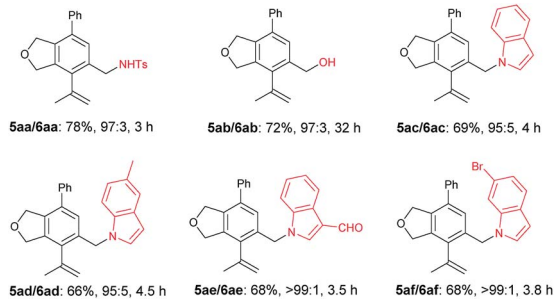


Entry	Solvent	Temp. (°C)	Time (h)	Yield of **5aa**/**6aa**/**7aa**[b] (%)	Recovery of **3a**[b] (%)
1	Dioxane	70	2	72/6/4	0
2	DMSO	70	26	48/3/3	25
3	DMF	70	2	76/3/5	0
4	DCE	70	6	49/7/3	0
5	CH_3CN	80	2	80/3/3	0
6	CH_3CN	60	2	80/3/3	0
7	**CH_3CN**	**30**	**2**	**82/3/2**	**0**
8	CH_3CN	10	26	68/2/4	3

[a] Reaction condition: **3a** (0.3 mmol), **4a** (1.2 equiv.), $Pd(OAc)_2$ (5 mol%), TFP (10 mol%), Na_2CO_3 (3.0 equiv.), and H_2O (2.0 equiv.) in solvent (3.0 mL). [b] Determined by the ^1H NMR analysis of the crude product using mesitylene as the internal standard.

Table 3 Scope of terminal alkynes **4**.[a,b,c]





[a] Reaction conditions: **3a** (1.0 mmol), **4** (1.2 equiv.), $Pd(OAc)_2$ (5 mol%), TFP (10 mol%), Na_2CO_3 (3.0 equiv.), and H_2O (2.0 equiv.) in CH_3CN (10 mL) at 30 °C. [b] Combined isolated yield of **5** and **6**. [c] The ratio of **5** and **6** was determined by ^1H NMR analysis of the isolated product.

groups at the 8-position could also be applied, producing the expected products **5cb**/**6cb**–**5fg**/**6fg** in 59%–85% yields with the ratio of 93/7–97/3. This method could be extended to 8-(3′-thienyl), 8-^{n}Bu, 8-TMS and 6-propyl substituted 2,7-alkadiynylic

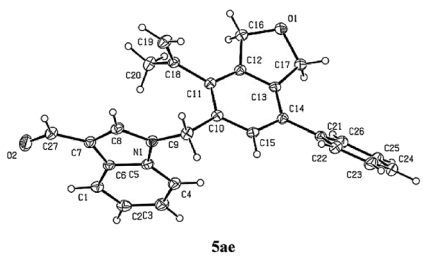
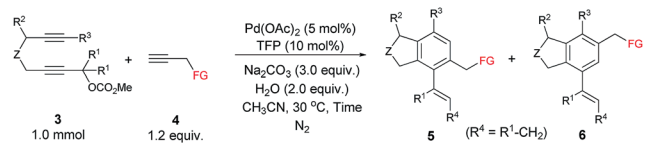
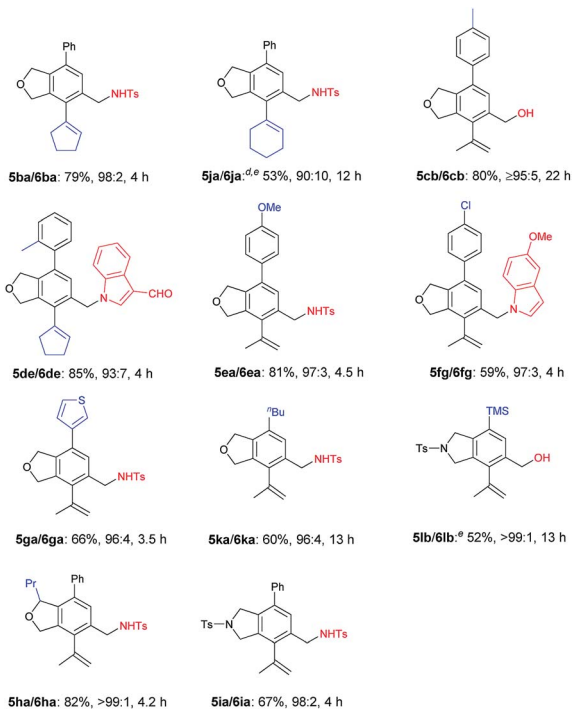


Fig. 2 ORTEP representation of **5ae**.

Table 4 The reaction of 2,7-alkadiynylic carbonates **3** with functionalized terminal alkynes **4**[a,b,c]

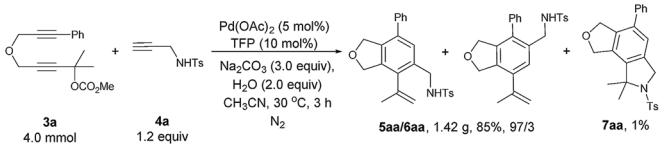




[a] Reaction conditions: **3** (1.0 mmol), **4** (1.2 equiv.), $Pd(OAc)_2$ (5 mol%), TFP (10 mol%), Na_2CO_3 (3.0 equiv.), H_2O (2.0 equiv.) in CH_3CN (10 mL) at 30 °C. [b] Combined yield of **5** and **6**. [c] The ratio of **5** and **6** was determined by ^1H NMR analysis of the isolated product. [d] The reaction was conducted at 50 °C and 11% of **3j** was recovered. [e] 0.5 mmol scale.

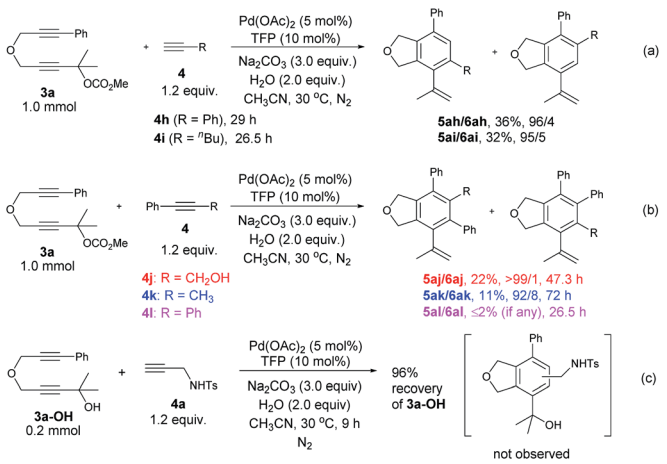
carbonates to afford **5ga**/**6ga**–**5ha**/**6ha** in moderate to good yields with the selectivity of 96/4 to >99/1. Nitrogen-tethered 2,7-alkadiynylic carbonate **3i** also worked and the isoindoline derivatives **5ia**/**6ia** were obtained in 67% yield with a selectivity of 98/2.

The reaction of **3a** with **4a** could be easily conducted on a gram-scale synthesis, resulting in the isolation of 1.42 g (85%) of **5aa**/**6aa** with a selectivity of 97/3 together with a 1% yield of **7aa** (eqn (3)).



(3)

Some control experiments were conducted to obtain further information concerning the regioselectivity (Scheme 2). When phenyl or *n*-butyl substituted terminal alkyne **4h** or **4i** was used, the corresponding bicyclic product could still be formed with a decent regioselectivity, albeit in a much lower yield (Scheme 2a). Furthermore, the reaction of **3a** with internal propargylic alcohol **4j** could give 22% yield of the product **5aj** exclusively (Scheme 2b). X-ray single crystal diffraction analysis of **5aj** showed that the regioselectivity was reversed-the CH_2OH group was at the *ortho*-position of the phenyl group from **3a** (Fig. 3).[20] The reaction of **3a** with 1-phenylpropyne **4k** also gave **5ak**/**6ak** in 11% yield with the same regioselectivity as **4j**, indicating that the hydroxy group should have nothing to do with the regioselectivity (Scheme 2b). The structure of **5ak** was also confirmed by X-ray single crystal diffraction analysis (Fig. 3).[21] However, the reaction did not work with 1,2-diphenylethyne **4l** (Scheme 2b). Thus, the regioselectivity obviously depends on the size of two groups of the alkyne: the larger group of the alkyne was more likely to stay away from the phenyl group originating from **3a**. The failure of the reaction of **3a-OH** with **4a** under the standard conditions indicated that the reaction may not proceed the [2 + 2 + 2] cycloaddition of the diyne unit in **3a** with the C–C triple bond in **4a** (Scheme 2c).



Scheme 2 Control experiments.

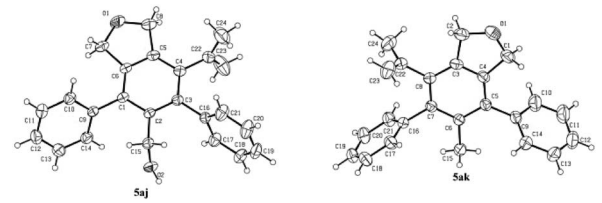
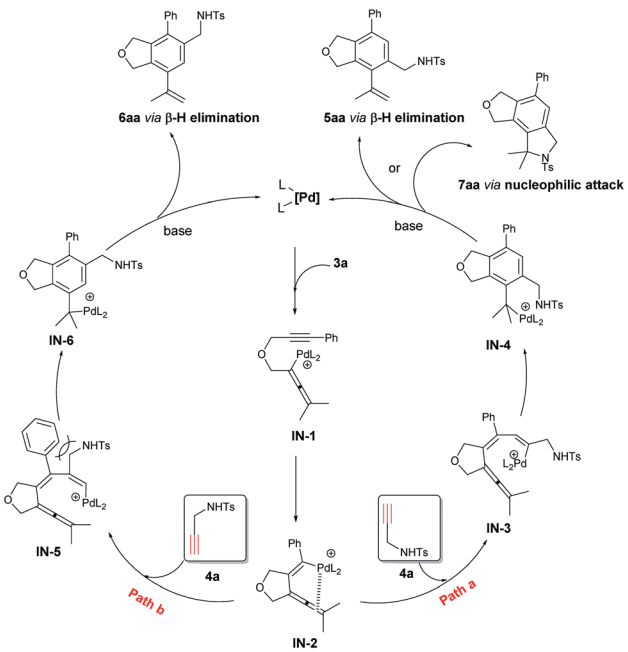


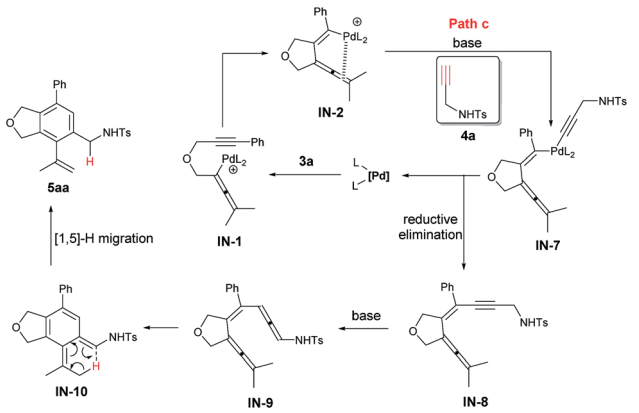
Fig. 3 ORTEP representations of **5aj** and **5ak**.

Based on these experimental results, a possible mechanism is shown in Scheme 3 by taking the reaction of **3a** and **4a** as an example: oxidative addition of **3a** with the catalytically active species Pd(0) would give the allenylpalladium intermediate **IN-1**,[22] which undergoes intramolecular exo-mode insertion of the C–C triple bond to generate the alkenylpalladium species **IN-2**.[23] The species **IN-2** would undergo intermolecular carbopalladation of the C≡C bond of **4a** to generate a new alkenylpalladium intermediate **IN-3** (path a) or **IN-5** (path b). Then intramolecular carbopalladation of allene would form a new benzylpalladium intermediate **IN-4** or **IN-6**. In the presence of a base, the key intermediate **IN-4** could undergo the intramolecular nucleophilic attack or β-H elimination forming tricyclic product **7aa** or the phthalan derivative **5aa** and regenerating the catalytically active Pd(0). As a comparison, the key intermediate **IN-6** could only go through the β-H elimination to deliver the phthalan derivative isomer **6aa**. Obviously, there is a strong steric interaction between the phenyl group and $-CH_2NHTs$ moiety in **IN-5**, which make the reaction more likely to go through path a.

An alternative mechanism involving a Sonogashira coupling (path c) of **IN-2** has been presented in Scheme 4. The resulted intermediate **IN-8** could go through the Garratt–Braverman cyclization to deliver **5aa**.[24]

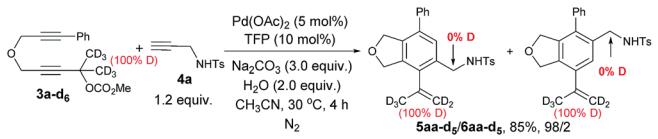


Scheme 3 The proposed mechanistic pathways.



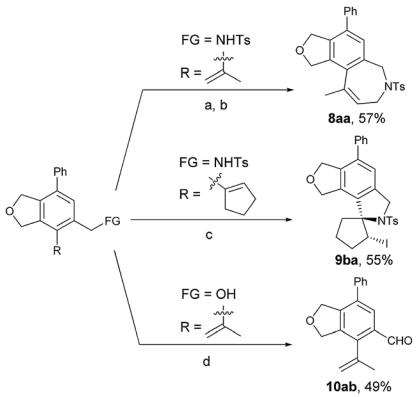
Scheme 4 An alternative mechanism involving a Sonogashira coupling of IN-2.

There should be a possibility of [1,5]-H migration process in path c. Thus, the reaction of **3a-d$_6$** and **4a** was conducted and a mixture of **5aa-d$_5$** and **6aa-d$_5$** with a ratio 98/2 with no deuteration at the α-position of the NHTs group was afforded in 85% yield (eqn (4)), indicating that there is no H-migration process, thus, path c is not viable for the formation of **5aa**.

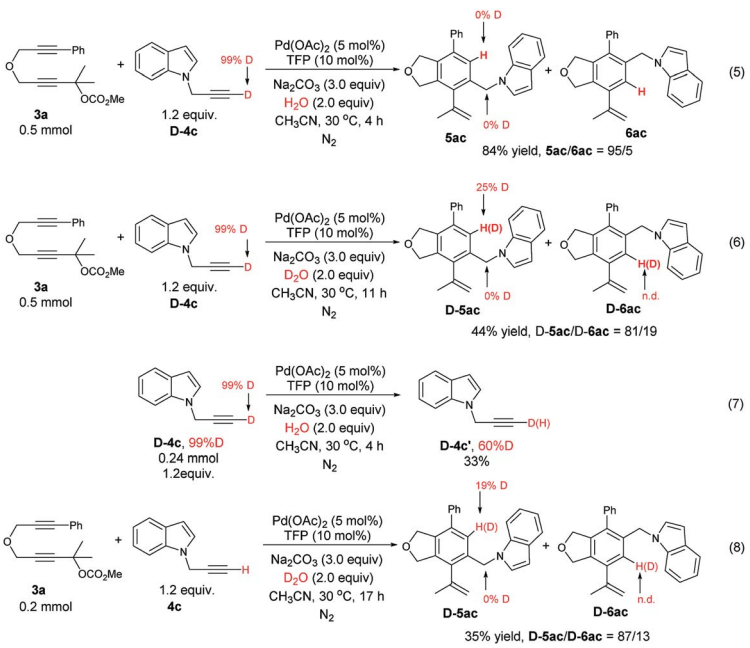


(4)

We also performed some deuterium labelling experiments for the investigation of the D–H exchange of the terminal alkyne (Scheme 5). To our surprise, the reaction of **3a** with **D-4c** under the standard conditions afforded **5ac**/**6ac** in 84% yield with a selectivity of 95/5 without any deuterium incorporation (eqn (5)). We conjectured that the deuterium atom may be easily exchanged with the hydrogen atom under the aqueous environment. Thus, H_2O (2.0 equiv.) was replaced with D_2O (2.0 equiv.), which led to the formation of 25% deuterium incorporation in **D-5ac** (eqn (6)). Interestingly, the regioselectivity dropped from 95 : 5 to 81 : 19 (compare eqn (5) with eqn (6)), which might be explained by the steric effect of D *vs.* H at 30 °C.[25] Of course, further attention is obviously needed. The D–H exchange was also proven by the reaction of **D-4c** with H_2O or the reaction of **4c**



Scheme 6 Synthetic applications. Reaction condition: (a) allylbromide (2.0 equiv.), K_2CO_3 (4.0 equiv.), CH_3CN, refluxed (85 °C), 4 h; (b) Grubbs' II catalyst (10 mol%), toluene, 80 °C, 26 h; (c) NIS (1.5 equiv.), CH_3CN/H_2O = 15/1, rt, 27 h. (d) $Fe(NO_3)_3{\cdot}9H_2O$ (10 mol%), TEMPO (10 mol%), NaCl (5 mol%), CH_2Cl_2, rt, 17.5 h.



Scheme 5 Deuterium labeling experiments: investigating of the D–H exchange of the terminal alkyne (n.d. = not able to be determined by ^{1}H NMR analysis).

with **3a** in the presence of D_2O (eqn (7) and (8)). These experimental facts further support the mechanism shown in Scheme 3.

In order to show the potential of the products, some synthetic applications have been conducted (Scheme 6). The bicyclic product **5aa** could be transferred to tricyclic isobenzofuro[5,4-*c*]azepine derivative **8aa** in 57% yield after an allylation-RCM process.[26] The tetracyclic product **9ba** containing a spirocycle skeleton can be easily obtained through an electrophilic cyclization with NIS (1.5 equiv.).[27] The $Fe(NO_3)_3$-$\cdot 9H_2O$–TEMPO–NaCl–catalyzed oxidation of **5ab** proceeded smoothly to give the aryl aldehyde **10ab** in 49% yield.[28]

Conclusions

In summary, we have developed a highly regio- and chemoselective annulation of 2,7-alkadiynylic carbonates in the presence of functionalized alkynes to construct 1,3-dihydroisobenzofuran and isoindoline derivatives under mild conditions. Functional groups such as sulfonamide, alcohol, and indoles could be kept untouched, which provides a chance for many further transformations to more complicated polycycles. Further studies in this area are being pursued in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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150.0 K; Z = 8; reflections collected/unique 23799/3672 (R_{int} = 0.0793); number of observations [>2\s(I)] 2837, parameters: 272. CCDC 1849157 contains the supplementary crystallographic data for this paper.†

20 Crystal data for compound **5aj**: $C_{24}H_{22}O_2$; MW=342.41; monoclinic space group *P* 1 21/*n* 1; final R indices [I > 2\s(I)], R_1 = 0.0602, wR_2 = 0.1251, R indices (all data) R_1 = 0.0921, wR_2 = 0.1457; a = 6.8864(5) Å, b = 33.272(3) Å, c = 8.5011(8) Å; α = 90, β = 104.932(8), γ = 90; V= 1882.0(3) Å3; T = 293.0 K; Z = 4; reflections collected/unique 7378/3441 (R_{int} = 0.0345); number of observations [>2\s(I)] 2370, parameters: 237. CCDC 1849158 contains the supplementary crystallographic data for this paper.†

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