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Regio- and stereoselective intramolecular hydroalkoxylation of aromatic alkynols: an access to dihydroisobenzofurans under transition-metal-free conditions

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Abstract

An efficient, transition-metal-free method to synthesize dihydroisobenzofuran derivatives via intramolecular hydroalkoxylation of aromatic alkynols with the promotion of cesium carbonate has been developed. The reaction proceeds regioselectively with exclusive formation of *5-exo-dig* product, and only *Z*-isomer of the new generated double bond is observed. This new protocol features with milder reaction conditions, more convenient operation and satisfactory selectivities.

Keywords Cesium carbonate · Intramolecular hydroalkoxylation · Dihydroisobenzofurans · Transition-metal-free

Introduction

Dihydroisobenzofurans skeletons are widespread in both natural products and biologically and pharmaceutically active compounds (Shang et al. 2015; Shishkina et al. 2016; Yang et al. 2017). Moreover, they are useful intermediates for the synthesis of important biomolecules subunits (Alcaide et al. 2011). Therefore, efficient and versatile methods to form such entities from readily available starting materials have been of particular interest (Aronica et al. 2015; Kobayashi et al. 2008; Karmakar et al. 2014; Albano and Aronica 2017,2018; Brinkmann et al. 2012; Fairley et al. 2019). Among these developed methods, intramolecular hydroalkoxylation of aromatic alkynols via *5-exo-dig* annulation pathway represents a straight and atom-economical alternative to construct such oxygenated heterocycles (Scheme 1, path A). Followed the first report on

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Shu-Yan Yu yushuyan_zzuli@163.com exo-cyclization with mercury salt as the catalyst (Riediker and Schwartz 1982), several more transition metal catalysts were later found to work well with dihydroisobenzofuran as main or only product, such as copper (Praveen et al. 2010; Pouy et al. 2012), palladium (Buxaderas et al. 2014) and palladium nanoparticles (Chahdoura et al. 2015; Mandali et al. 2017), silver (Praveen et al. 2012), rhodium (Sarbaina et al. 2017), gold (Dorel and Echavarren 2015) or even lanthanide and actinide complexes (Seo et al. 2009; Wobser and Marks 2013). However, the cyclization regioselectivity has not been fully resolved as many factors affecting the outcome of selectivity, including catalyst choices, ligands, steric environment and even additives (Costello and Ferreira 2019; Doherty et al. 2016; Goodwin and Aponick 2015). Besides, these transition metals-catalyzed reactions suffered some drawbacks such as being expensive, sensitive to oxygen and moisture and mostly violent. Given the prevalence of dihydroisobenzofurans in natural products and bioactive molecules, more practical catalytic system towards the construction of these entities under transition metal-free conditions is still highly required (Krishna Reddy and Satyanarayana 2017; Mancuso et al. 2010).

As interest in the synthesis of heterocyclic compounds through alkynes functionalization (Yu et al. 2018, 2020), we realized that a base-promoted intramolecular cyclization of aromatic alkynols would provide an alternative methodology (Vandavasi et al, 2014). However, base-mediated cyclization is much more difficult owing to the absence of activation of alkyne moiety. The reported reactions are mostly restricted

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Scheme 1 The two regioselective cyclization pathways of aromatic alkynols



to excess use of base or harsh conditions (Berg et al. 2006; Hiroya et al. 2001; Jean et al. 2019; Li et al. 2014; Weingarten and Padwa 1995). Herein we want to report our recent finding that cesium carbonate could serve as an effective catalyst for the intramolecular cyclization of aromatic alkynols, affording the desired dihydroisobenzofuran compounds with satisfactory yields and excellent regioselectivities and stereoselectivities in more flexible reaction conditions.

Experimental

Materials and methods

All reactions were carried out under air atmosphere condition. Aromatic alkynols were prepared according to the published procedure. Solvents were purchased from Alfa Aesar or J&K, which were used directly without purification. Column chromatography was performed on silica gel (300–400 mesh). ¹H and ¹³C NMR were recorded on a 600 or 400 MHz Bruker NMR spectrometer in CDCl₃ or DMSO d_6 using tetramethylsilane (TMS) as the internal standard.

General procedure for the synthesis of aromatic alkynols

Aromatic alkynols were prepared through a two-step procedure including Sonogashira coupling and reduction with the corresponding *o*-bromobenzaldehyde or *o*-bromoacetophenone and alkyne as starting materials. The synthesis of (2-(phenylethynyl) phenyl) methanol **1a** was illustrated as a representative example.

Under nitrogen conditions, 2-bromobenzaldehyde (10 mmol), phenylacetylene (12 mmol), $Pd(PPh_3)_2Cl_2$ (0.2 mmol) and CuI (0.1 mmol) were successively introduced into a 100-mL two-neck flask equipped with Et₃N (40 mL). The resulting mixture was stirred at 50 °C for 12 h and monitored with TLC. After completion, the crude mixture was filtered through celite and Et₃N was removed under vacuum. The residue was diluted with EtOAc (60 mL) and washed with water (2×50 mL). The organic layer was dried over Na₂SO₄, which was further purified via column chromatography on silica gel (the mixture of petroleum ether and EtOAc was used as elute) to give 2-(phenylethynyl)benzaldehyde (1.83 g) in 89% yield.

2-(phenylethynyl)benzaldehyde was dissolved in methanol (30 mL), and the resulting mixture was cooled to 0 $^{\circ}$ C.

NaBH₄ (5 mmol) was added in portions, and the solution was stirred for additional 20 min. The reaction was quenched with saturated ammonium chloride solution (30 mL). Methanol was removed under vacuum, and the residue was extracted by EtOAc (2×30 mL). The combined organic layer was dried over anhydrous Na₂SO₄. After the solvent was removed under reduced pressure, (2-(phenylethynyl)phenyl) methanol **1a** was obtained (1.76 g) in 95% yield, which was used directly for the next cyclization without purification.

General procedure for intramolecular hydroalkoxylation of aromatic alkynols

To a solution of aromatic alkynol 1 (1 mmol) in DMF (4 mL) was added cesium carbonate (20 mol%) at room temperature. The mixture was heated to 80 °C and stirred for 12 h. After completion, the reaction mixture was diluted with EtOAc (15 mL) and washed with water (3×20 mL). The organic layer was dried over Na₂SO₄, which was further purified via column chromatography on silica gel with the mixture of petroleum ether and EtOAc as elute to afford the corresponding dihydroisobenzofuran **2**.

Characterization of products

Compounds **2a–2j**, **2l** and **2n** are known compounds, only ¹HNMR spectra and melting points were collected which were consistent with previous studies. Unknown compounds **2k** and **2m** were fully characterized.

(Z)-1-benzylidene-1, 3-dihydroisobenzofuran (2a)

Yield: 97%; Light yellow solid; M.p.:103–105 °C (Reported 100–102 °C, Li et al. 2014); ¹HNMR (600 MHz, CDCl₃): δ 7.78 (d, *J*=7.4 Hz, 2H), 7.60 (d, *J*=6.4 Hz, 1H), 7.37 (t, *J*=8.7 Hz, 5H), 7.18 (t, *J*=7.4 Hz, 1H), 5.98 (s, 1H), 5.54 (s, 2H) ppm.

(Z)-1-(4-methoxybenzylidene)-1, 3-dihydroisobenzofuran (2b)

Yield: 95%; White solid; M.p.:118–120 °C (Reported 118–129 °C, Li et al. 2014); ¹HNMR (600 MHz, CDCl₃): δ 7.61 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 7.2 Hz, 1H), 7.24–7.29 (m, 3H), 6.82 (d, J = 8.8 Hz, 2H), 5.83 (s, 1H), 5.43 (s, 2H), 3.75 (s, 3H) ppm.

(Z)-1-(4-methylbenzylidene)-1, 3-dihydroisobenzofuran (2c)

Yield: 96%; Light yellow solid; M.p.: 95–97 °C (Reported 95–97 °C, Li et al. 2014); ¹HNMR (600 MHz, DMSO- d_{δ}): δ 7.72–7.74 (m, 1H), 7.59 (d, J=7.8 Hz, 2H), 7.47–7.49 (m, 1H), 7.40–7.42 (m, 2H), 7.14 (d, J=7.8 Hz, 2H), 6.09 (s, 1H), 5.55 (s, 2H), 2.28 (s, 3H) ppm.

(Z)-1-(4-chlorobenzylidene)-1, 3-dihydroisobenzofuran (2d)

Yield: 87%; Light yellow solid; M.p.:105–107 °C (Reported 102–104 °C, Li et al. 2014); ¹HNMR (400 MHz, CDCl₃): δ 7.68 (d, J = 8.6 Hz, 2H), 7.55–7.57 (m, 1H), 7.38 (dd, J = 9.2, 3.3 Hz, 3H), 7.28 (dd, J = 10.5, 3.9 Hz, 2H), 5.90 (s, 1H), 5.52 (s, 2H) ppm.

(Z)-methyl4-(isobenzofuran-1(3H)-ylidenemethyl)benzoate (2e)

Yield: 79%; Light yellow solid; M.p.:111–114 °C (Reported 113–115 °C, Li et al. 2014); ¹HNMR (600 MHz, CDCl₃): δ 8.00 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 7.61 (s, 1H), 7.38 (m, 3H), 5.98(s, 1H), 5.56 (s, 2H), 3.91 (s, 3H) ppm.

(Z)-1-(4-nitrobenzylidene)-1, 3-dihydroisobenzofuran (2f)

Yield: 65%; Orange solid; M.p.:156–158 °C (Reported 156–158 °C, Tomás-Mendivil et al. 2015); ¹HNMR (600 MHz, CDCl₃): δ 8.21 (d, J = 8.7 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.35–7.39(m, 3H), 7.21 (t, J = 7.5 Hz, 1H), 6.21 (s, 1H), 5.38 (s, 2H) ppm.

(Z)-1-(3-methylbenzylidene)-1, 3-dihydroisobenzofuran (2 g)

Yield: 87%; Yellow oil; ¹HNMR (600 MHz, CDCl₃): δ 7.55 (m, 3H), 7.34 (m, 3H), 7.23 (t, J = 7.6 Hz, 1H), 6.98 (d, J = 7.5 Hz, 1H), 5.93 (s, 1H), 5.53 (s, 2H), 2.38 (s, 3H) ppm.

(Z)-2-(isobenzofuran-1(3H)-ylidenemethyl)benzaldehyde (2 h)

Yield: 84%; Light yellow oil; ¹HNMR (600 MHz, CDCl₃): δ 10.26 (s, 1H), 8.27 (d, *J*=7.8 Hz, 1H), 7.79 (d, *J*=6.6 Hz, 1H), 7.71–7.73 (m, 1H), 7.55 (t, *J*=8.3 Hz, 1H), 7.41 (dd,

J=6.0 Hz, 2.6 Hz, 2H), 7.36 (d, *J*=4.8 Hz, 1H), 7.29 (t, *J*=7.9 Hz, 1H), 7.13 (s, 1H), 5.52 (s, 2H) ppm.

(Z)-(2-(isobenzofuran-1(3H)-ylidenemethyl)phenyl) methanol(2i)

Yield: 83%; Light yellow solid; M.p.:128–130 °C (Reported 120–122 °C, Mandali et al. 2017); ¹HNMR (600 MHz, DMSO- d_6): δ 8.09 (d, J=7.8 Hz, 1H), 7.78 (d, J=4.5 Hz, 1H), 7.47–7.51(m, 1H), 7.43 (dd, J=5.1 Hz, 3.5 Hz, 2H), 7.38 (d, J=7.5 Hz, 1H), 7.23 (t, J=7.2 Hz, 1H), 7.12 (t, J=7.1 Hz, 1H), 6.21 (s, 1H), 5.54 (s, 2H), 5.16 (t, J=5.6 Hz, 1H), 4.64 (d, J=5.5 Hz, 2H) ppm.

(Z)-1-benzylidene-5,6-dimethoxy-1,3-dihydroisobenzofur an(2j)

Yield: 80%; Light yellow solid; M.p.:115–117 °C (Reported 115–117 °C, Li et al. 2014); ¹HNMR (600 MHz, CDCl₃): δ 7.71 (d, *J*=7.3 Hz, 2H), 7.32 (t, *J*=7.7 Hz, 2H), 7.12 (t, *J*=7.4 Hz, 1H), 7.01 (s, 1H), 6.81 (s, 1H), 5.77 (s, 1H), 5.45 (s, 2H), 3.96 (s, 3H), 3.92 (s, 3H) ppm.

(Z)-1-benzylidene-6-methoxy-1, 3-dihydroisobenzofuran (2 k)

Yield: 73%; White solid; M.p.:118–120 °C; ¹HNMR (600 MHz, DMSO- d_6): δ 7.65 (t, J=7.5 Hz, 3H), 7.30 (t, J=7.8 Hz, 2H), 7.08 (t, J=7.8 Hz, 2H), 7.00 (dd, J=8.5 Hz, 2.2 Hz, 1H), 5.96 (s, 1H), 5.51 (s, 2H), 3.81 (s, 3H) ppm; ¹³CNMR (150 MHz, DMSO- d_6): δ 161.0, 156.8, 141.8, 137.0, 128.8, 127.6, 126.9, 125.1, 121.8, 115.8, 106.4, 94.5, 74.7, 56.1 ppm.

HRMS: $C_{16}H_{15}O_2$ for $[M + H]^+$, calculated 239.1073, found 239.1070.

(Z)-1-benzylidene-5-methyl-1, 3-dihydroisobenzofuran (2 l)

Yield: 84%; White solid; M.p.:106–108 °C (Reported 104–106 °C, Li et al. 2014); ¹HNMR (600 MHz, DMSO- d_6): δ 7.68 (d, J=7.3 Hz, 2H), 7.57 (s, 1H), 7.37 (d, J=7.7 Hz, 1H), 7.32 (t, J=7.8 Hz, 2H), 7.24 (d, J=7.7 Hz, 1H), 7.12 (t, J=7.3 Hz, 1H), 6.09 (s, 1H), 5.51 (s, 2H), 2.39 (s, 3H) ppm.

(Z)-1-benzylidene-5-chloro-1, 3-dihydroisobenzofuran (2 m)

Yield: 90%; Light yellow solid; M.p.:117–119 °C; ¹HNMR (600 MHz, DMSO- d_6): δ 7.04 (d, J = 1.7 Hz, 1H), 6.82 (d, J = 7.3 Hz, 2H), 6.65 (d, J = 8.1 Hz, 1H), 6.60 (dd, J = 8.1 Hz, 1.8 Hz, 1H), 6.49 (t, J = 7.8 Hz, 2H), 6.30 (t, J = 7.4 Hz, 1H), 5.40 (s, 1H), 4.69 (s, 2H) ppm; ¹³CNMR (151 MHz, DMSO-*d*₆): δ 155.2, 138.6, 136.8, 136.4, 133.6, 129.3, 128.8, 128.1, 125.9, 124.1, 120.4, 97.4, 75.2 ppm;

HRMS: $C_{15}H_{12}ClO$ for $[M + H]^+$, calculated 243.0576, found 243.0571.

(Z)-1-benzylidene-3-methyl-1, 3-dihydroisobenzofuran (2n)

Yield: 94%; Yellow oil; ¹HNMR (600 MHz, DMSO- d_6): δ 7.73 (dd, J = 6.0 Hz, 2.7 Hz, 1H), 7.70 (d, J = 7.3 Hz, 2H), 7.47 (dd, J = 5.2 Hz, 3.4 Hz, 1H), 7.42 (dd, J = 5.6 Hz, 3.1 Hz, 2H), 7.33 (t, J = 7.8 Hz, 2H), 7.12 (t, J = 6.8 Hz, 1H), 6.10 (s, 1H), 5.83 (q, J = 6.5 Hz, 1H), 1.57 (t, J = 7.2 Hz, 3H) ppm.

Results and discussion

Our investigation began with o-alkynylbenzynol **1a** as the model substrate, and the key results are briefly summarized in Table 1. A range of bases were screened first with *N*, *N*-dimethylformamide (DMF) as solvent at 60 °C. Gratifyingly, when **1a** was treated with 50 mol% cesium carbonate, the desired cyclization product dihydroisobenzofuran **2a** was isolated in 70% yield, whose structure was firstly characterized by NMR spectrum and then confirmed by X-ray diffraction analysis of its analogous **2d**. Inferior results were displayed when other organic bases or inorganic bases were employed in this reaction, which indicated the degree of alkalinity or the homogeneity of the reaction mixture is not the key factor. (Table 1, Entry 1–9). The nature

Table 1 Optimization of reaction conditions for intramolecular hydroalkoxylation



Entry	Base	Solvent	Temp (°C)	Time (h)	Yield of 2a (%) ^a
1	K ₂ CO ₃	DMF	60	24	NR
2	Cs_2CO_3	DMF	60	15	70
3	NEt ₃	DMF	60	24	NR
4	DBU	DMF	60	15	28
5	DABCO	DMF	60	24	NR
6	Pyridine	DMF	60	24	NR
7	t-BuOK	DMF	60	15	45
8	KOH	DMF	60	24	26
9	CsF	DMF	60	15	35
10	Cs ₂ CO ₃	Toluene	60	24	30
11	Cs ₂ CO ₃	CH ₃ CN	60	24	40
12	Cs ₂ CO ₃	DCM	Reflux	24	25
13	Cs ₂ CO ₃	1,4-dioxane	60	15	36
14	Cs ₂ CO ₃	THF	60	24	NR
15	Cs ₂ CO ₃	MeOH	60	24	Complex
16	Cs ₂ CO ₃	DMSO	60	15	67
17	Cs ₂ CO ₃	DMF	80	10	93
18	Cs ₂ CO ₃	DMF	100	6	65
19 ^b	Cs ₂ CO ₃	DMF	80	12	97
20 ^c	Cs ₂ CO ₃	DMF	80	24	62

Unless noted, the reaction was conducted in a flask equipped with alkynol **1a** (1 mmol), base (0.5 equiv.) and solvent (4 mL) under atmospheric condition;

^aIsolated yields after silica gel column chromatography;

^b20 mol% Cs₂CO₃ was used;

^c10 mol% Cs₂CO₃ was used





chromatography.

of the solvent has an important influence on the result of the reaction: DMF proved to be more favorable than others (Table 1, Entry 10–15). By comparison, DMF gave a more clear solution which suggested the good solubility of Cs_2CO_3 in DMF might contribute to the efficiency of cyclization (Cella and Bacon 1984). To test this assumption, the cyclization reaction was operated in DMSO (Table 1, Entry 16). As expected, a parallel result was indeed observed. In

light of the above results, the advantage of cesium carbonate might be derived from suitable basicity, good solubility and weak Lewis acidity of Cs⁺ (Flessner and Doye 1999) (more details, please see the proposed mechanism). Slightly increasing reaction temperature was found to be beneficial. Up to 93% yield of product was obtained within a shortened time (93% yield at 80 °C vs 70% yield at 60 °C vs 75% yield at 100 °C) (Table 1, Entry 16–18). The loading of the base



Scheme 3 The possible reaction pathway

was also investigated. 20 mol% Cs_2CO_3 proved to be suitable for this transformation, affording the desired dihydroisobenzofuran in nearly quantitative yield (Table 1, Entry 19). But further decreasing the amount of catalyst resulted in a slow conversion (Table 1, Entry 20). Notably, all the transformations were carried out under air atmosphere condition without the exclusion of moisture and oxygen.

After establishing the optimal reaction conditions, we examined the generality of the highly regioselective hydroalkoxylation with various substituted alkynols, and the results were summarized in Scheme 2. It was found that this catalytic strategy was applicable to various aromatic alkynols bearing different types of substituents, affording the corresponding dihydroisobenzofuran derivatives in good to satisfactory yields with uniformly excellent regio- and stereoselectivity. This catalytic system was compatible with various substituents. Hydroxyl, ester, formyl, nitro, and halide groups were amenable in this catalytic system. Substitution electron patterns affected the yields of the products to some extent. In generally, alkynols with electron-donating substituents could afford the expected products in better yields compared to those with withdrawing substituents (2a-2c vs 2d-2f). As indicated by the results of the steric hindrance investigation, the reaction of alkynols with a substituent at the para- position proceeded better than the meta- and orthoones (2c vs 2g-2h). The broad generality of the versatile synthetic method was demonstrated by the variation of R^1 (Scheme 2). To our delight, this highly diastereoselective intramolecular cyclization could be compatible for steric benzyl alcohol, the resulting highly functionalized dihydroisobenzofuran 2n could be isolated in 94% yield. It was worth mentioning that only one diastereoisomer generated via exo-dig regioselectivity and anti-addition stereoselectivity was observed in all these substrates. Unfortunately, when we attempted to adopt this catalytic system to other alkyl- or terminal alkyne, no corresponding product could be collected.

A possible reaction pathway was postulated in Scheme 3. Cs_2CO_3 deprotonates the OH bond of the alkynol leading

to the anion intermediate. At this stage, the coordination of weak Lewis acidic Cs^+ with the triple bond enhanced its electrophilicity which facilitated nucleophilic attack of oxygen anion. The intramolecular cyclization proceeds in a totally stereoselective fashion to give the configurationally stable *E*-vinylcesium. Protolysis delivered the desired dihydroisobenzofuran with *Z*-configuration and regenerated the base catalyst. Although we are not clear with the origin of regioselectivity, several theoretical studies indicated that might be substrate-dependant. In the case of electronically unbiased acetylenes, *exo-dig* cyclizations are favored, facilitating the approach path of O–H to the triple bond is at an obtuse angle of 120–127 degrees (Dykstra et al. 1978; Elliott and Richards 1982; Ersenstein et al. 1978; Mellor et al. 1978; Perkins et al. 1981; Strozier et al. 1979).

Conclusions

We have developed a straightforward and convenient method for the synthesis of dihydroisobenzofuran derivatives through intramolecular hydroalkoxylation of aromatic alkynols under transition-metal-free conditions. The desired cycloadducts could be obtained with high efficiency and uniformly excellent stereo- and regio-selectivities. No special handling for reagents or reaction conditions was necessary for these transformations. Moreover, the generating double bonds in the dihydroisobenzofuran skeletons provide a wide scope for further structural transformations.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

- Albano G, Aronica LA (2017) Potentiality and synthesis of O- and N-heterocycles: Pd-catalyzed cyclocarbonylative sonogashira coupling as a valuable route to phthalans, isochromans, and isoindolines. Eur J Org Chem 48:7204–7221. https://doi.org/10.1002/ ejoc.201701041
- Albano G, Aronica LA (2018) Cyclization reactions for the synthesis of phthalans and isoindolines. Synthesis 50:1209–1227. https:// doi.org/10.1055/s-0037-1609175
- Alcaide B, Almendros P, Alonso JM (2011) Gold-catalyzed cyclizations of alkynol-based compounds: synthesis of natural products and derivatives. Molecules 16:7815–7843. https://doi. org/10.3390/molecules16097815

- Aronica LA, Giannotti L, Tuci G, Zinna F (2015) Cyclocarbonylative sonogashira reactions of 1-ethynylbenzyl alcohols: synthesis of 1-carbonylmethylene-1,3-dihydroisobenzofurans. Eur J Org Chem 22:4944–4949. https://doi.org/10.1002/ejoc.201500539
- Berg TC, Bakken V, Gundersen LL, Petersen D (2006) Cyclization and rearrangement products from coupling reactions between terminal o-alkynylphenols or o-ethynyl(hydroxymethyl)benzene and 6-halopurines. Tetrahedron 62:6121–6131. https://doi. org/10.1016/j.tet.2006.03.112
- Brinkmann C, Barrett AGM, Hill MS, Procopiou PA, Reid S (2012) Alkaline earth catalysis of alkynyl alcohol hydroalkoxylation/cyclization. Organometallics 31:7287–7297. https://doi. org/10.1021/om3008663
- Buxaderas E, Alonso DA, Nájera C (2014) Synthesis of dihydroisobenzofurans via palladium-catalyzed sequential alkynylation/ annulation of 2-bromobenzyl and 2-chlorobenzyl alcohols under microwave irradiation. Adv Synth Catal 356:3415–3421. https:// doi.org/10.1002/adsc.201400457
- Cella JA, Bacon SW (1984) Preparation of dialkyl carbonates via the phase-transfer-catalyzed alkylation of alkali metal carbonate and bicarbonate salts. J Org Chem 49:1122–1125. https://doi.org/10.1021/jo00180a033
- Chahdoura F, Mallet-Ladeira S, Gómez M (2015) Palladium nanoparticles in glycerol: a clear-cut catalyst for one-pot multi-step processes applied in the synthesis of heterocyclic compounds. Org Chem Front 2:312–318. https://doi.org/10.1039/C4QO00338A
- Costello JP, Ferreira EM (2019) Regioselectivity influences in platinum-catalyzed intramolecular alkyne O-H and N-H additions. Org Lett 21:9934–9939. https://doi.org/10.1021/acs.orglett.9b035 57
- Doherty S, Knight JG, Perry DO, Ward NAB, Bitter DM, McFarlane W, Wills C, Probert MR (2016) Triaryl-Like MONO-, BIS-, and TRISKITPHOS phosphines: synthesis, solution NMR studies, and a comparison in gold-catalyzed carbon-heteroatom bond forming 5-exo-dig and 6-endo-dig cyclizations. Organometallics 35:1265– 1278. https://doi.org/10.1021/acs.organomet.6b00146
- Dorel R, Echavarren AM (2015) Gold(I)-catalyzed activation of alkynes for the construction of molecular complexity. Chem Rev 115:9028–9072. https://doi.org/10.1021/cr500691k
- Dykstra CE, Arduengo AJ, Fukunaga FT (1978) A study of the vinyl anion system. Rearrangements and formation from hydride(1-) ion and acetylene. J Am Chem Soc 100:6007–6009. https://doi. org/10.1021/ja00487a005
- Elliott RJ, Richards WG (1982) Quantitative frontier orbital theory: part II. A theoretical interpretation of the rules for ring closure. J Mol Struct (Theochem) 87:247–254. https://doi. org/10.1016/0166-1280(82)80004-3
- Ersenstein O, Procter G, Dunitz JD (1978) Nucleophilic addition to a triple bond; preliminary *ab initio* study. Helv Chim Acta 61:2538–2541. https://doi.org/10.1002/hlca.19780610725
- Fairley M, Davin L, Hernán-Gómez A, García-Álvarez J, O'Hara CT, Hevia E (2019) s-Block cooperative catalysis: alkali metal magnesiate-catalysed cyclisation of alkynols. Chem Sci 10:5821–5831. https://doi.org/10.1039/C9SC01598A
- Flessner T, Doye S (1999) Cesium carbonate: a powerful inorganic base in organic synthesis. J Prakt Chem 341:186–190
- Goodwin JA, Aponick A (2015) Regioselectivity in the Au-catalyzed hydration and hydroalkoxylation of alkynes. Chem Commun 51:8730–8741. https://doi.org/10.1039/C5CC00120J
- Hiroya K, Jouka R, Kameda M, Yasuhara A, Sakamoto T (2001) Cyclization reactions of 2-alkynylbenzyl alcohol and 2-alkynylbenzylamine derivatives promoted by tetrabutylammonium fluoride. Tetrahedron 57:9697–9710. https://doi.org/10.1016/S0040 -4020(01)00991-7

- Jean A, Rouden J, Maddaluno J, De Paolis M, Blanchet J (2019) Catalytic and metal-free intramolecular hydroalkoxylation of alkynes. Tetrahedron Lett 60:534–537. https://doi.org/10.1016/j.tetle t.2019.01.0200040-4039
- Karmakar R, Pahari P, Mal D (2014) Phthalides and phthalans: synthetic methodologies and their applications in the total synthesis. Chem Rev 114:6213–6284. https://doi.org/10.1021/cr400524q
- Kobayashi K, Shikata K, Fukamachi S, Konishi H (2008) A facile synthesis of 1, 3-dihydroisobenzofurans using iodocylization of 2-vinylbenzyl alcohols. Heterocycles 75:599–609. https://doi. org/10.3987/COM-07-11244
- Krishna Reddy AG, Satyanarayana G (2017) Palladium-catalyzed copper-free sonogashira coupling of 2-bromoarylcarbonyls: synthesis of isobenzofurans via one-pot reductive cyclization. Synthesis 49:5149–5158. https://doi.org/10.1055/s-0036-1588513
- Li Y, Shi DKJ, Mao XF, Zhao ZL, Wu XY, Liu PN (2014) Selective cyclization of alkynols and alkynylamines catalyzed by potassium tert-butoxide. Tetrahedron 70:7022–7031. https://doi. org/10.1016/j.tet.2014.06.078
- Mancuso R, Mehta S, Gabriele B, Salerno G, Jenks WS, Larock RC (2010) A simple and mild synthesis of 1H-isochromenes and (Z)-1-alkylidene-1,3-dihydroisobenzofurans by the Iodocyclization of 2-(1-alkynyl)benzylic alcohols. J Org Chem 75:897–901. https:// doi.org/10.1021/jo902333y
- Mandali PK, Pati AK, Mishra AK, Chand DK (2017) Fluorescent 1-arylidene-1,3-dihydroisobenzofuran: ligand-free palladium nanoparticles, catalyzed domino synthesis and photophysical studies. ChemistrySelect 2:5259–5265. https://doi.org/10.1002/ slct.201700730
- Mellor M, Santos A, Swrell EG, Sutherland JK (1978) Some epoxyacetylene cyclisations. J Chem Soc Chem Commun 13:528–529. https://doi.org/10.1039/C39780000528
- Perkins MJ, Wong PC, Barrett J, Shalival G (1981) Formation of dioxolanes from carbonyl compounds: favored 5-trigonal cyclizations. J Org Chem 46:2196–2199. https://doi.org/10.1021/jo00323a051
- Pouy MJ, Delp SA, Uddin J, Ramdeen VM, Cochrane NA, Fortman GC, Gunnoe TB, Cundari TR, Sabat M, Myers WH (2012) Intramolecular hydroalkoxylation and hydroamination of alkynes catalyzed by Cu(I) complexes supported by N-heterocyclic carbene ligands. ACS Catal 2:2182–2193. https://doi.org/10.1021/cs300 544w
- Praveen C, Iyyappan C, Perumal PT (2010) Regioselective synthesis of phthalans via Cu(OTf)₂-catalyzed 5-exo-dig intramolecular hydroalkoxylation of 2-(ethynyl)benzyl alcohols. Tetrahedron Lett 51:4667–4771. https://doi.org/10.1016/j.tetlet.2010.07.030
- Praveen C, Iyyappan C, Perumal PT, Girija K (2012) AgOTf as an alternative catalyst for the regioselective cyclization of 2-(alkynyl) benzyl alcohols: synthesis and biological evaluation of phthalans. Indian J Chem 51B:498–507
- Riediker M, Schwartz J (1982) Mercury(II)-induced cyclization of acetylenic alcohols: a new route to enol ethers and substituted enol ethers. J Am Chem Soc 104:5842–5844. https://doi.org/10.1021/ ja00385a074
- Sarbajna A, Pandey P, Rahaman SMW, Singh K, Tyagi A, Dixneuf PH (2017) A triflamide-tethered n-heterocyclic carbene-rhodium(i) catalyst for hydroalkoxylation reactions: ligand-promoted nucleo-philic activation of alcohols. ChemCatChem 9:1397–1401. https://doi.org/10.1002/cctc.201601667
- Seo SY, Yu XH, Marks T (2009) Intramolecular hydroalkoxylation/ cyclization of alkynyl alcohols mediated by lanthanide catalysts. Scope and reaction mechanism. J Am Chem Soc 131:263–276. https://doi.org/10.1021/ja8072462
- Shang XS, Li DY, Li NT, Liu PN (2015) A concise synthesis of tunable fluorescent 1,3-dihydroisobenzofuran derivatives as new

fluorophores. Dyes Pigm 114:8–17. https://doi.org/10.1016/j. dyepig.2014.10.013

- Shishkina IN, Sokolovskava EY, Demynovich VM (2016) Stereoselective synthesis of 1,3-disubstituted phthalans by cyclization of (1S)-1-{2-[hydroxy(diaryl)methyl]phenyl}ethanols. Russ Chem Bull 65:2229–2232. https://doi.org/10.1007/s11172-016-1573-y
- Strozier RW, Caramella P, Houk KN (1979) Influence of molecular distortions upon reactivity and stereochemistry in nucleophilic additions to acetylenes. J Am Chem Soc 101:1340–1343. https:// doi.org/10.1021/ja00499a078
- Tomás-Mendivil E, Starck J, Ortuno JC, Michelet V (2015) Synthesis of functionalized 1H-isochromene derivatives via a Au-catalyzed domino cycloisomerization/reduction approach. Org Lett 17:6126–6129. https://doi.org/10.1021/acs.orglett.5b03146
- Vandavasi JK, Hu WP, Senadi GC, Bominathan SSK, Chen HY, Wang JJ (2014) A K₂CO₃-mediated regioselective synthesis of indole/ pyrrole-fused 1,4-oxazines: an unexpected indole-fused azlactone synthesis. Eur J Org Chem 28:6219–6226. https://doi.org/10.1002/ ejoc.201402818
- Weingarten MD, Padwa A (1995) Intramolecular addition to an unactivated carbon-carbon triple bond via an apparent 6-endo digonal pathway. Tetrahedron Lett 36:4717–4720. https://doi. org/10.1016/0040-4039(95)00891-F
- Wobser SD, Marks TJ (2013) Organothorium-catalyzed hydroalkoxylation/cyclization of alkynyl alcohols. scope, mechanism, and

ancillary ligand effects. Organometallics 32:2517–2628. https://doi.org/10.1021/om300881b

- Yang X, Pan S, Cheng F, Lin YW, Yuan Q, Zhang FL, Huang YY (2017) Enantioselective synthesis of 1,3-disubstituted 1,3-dihydroisobenzofurans via a cascade allylboration/oxo-michael reaction of o-formyl chalcones catalyzed by a chiral phosphoric acid. J Org Chem 82:10388–10397. https://doi.org/10.1021/acs. joc.7b01856
- Yu SY, Wu JX, Lan HB, Xu HW, Shi XF, Zhu XW, Yin ZG (2018) Transition metal/Brønsted acid cooperative catalysis enabled facile synthesis of 8-hydroxyquinolines through one-pot reactions of ortho-aminophenol, aldehydes and alkynes. RSC Adv 8:33968– 33971. https://doi.org/10.1039/C8RA07212D
- Yu SY, Wu JX, Lan HB, Gao LH, Qian HY, Fan KQ, Yin ZG (2020) Palladium and brønsted acid Co-catalyzed Biginelli-like multicomponent reactions via in situ-generated cyclic enol ether: access to spirofuran-hydropyrimidinones. Org Lett 22:102–105. https:// doi.org/10.1021/acs.orglett.9b04015

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