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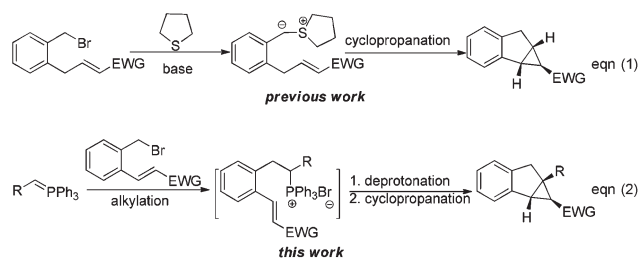
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Stereospecific synthesis of highly functionalized benzo[3.1.0]bicycloalkanes *via* multistep cascade reactions†

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rsc.li/frontiers-organicA facile approach for the synthesis of benzo[3.1.0]bicycloalkanes *via* alkylation/cyclopropanation cascade reactions of benzyl bromide with triphenylphosphonium bromide has been developed. By elaborate designing of starting materials, this multistep cyclization proceeded smoothly with a wide range of substrates, providing the benzo[3.1.0]bicycloalkanes in 52–90% yields with exclusive diastereoselectivity.

The benzo[3.1.0]carbocycles are widely distributed as key skeletons in a variety of natural products and biologically active compounds,^{1,2} as well as versatile building blocks in organic synthesis.³ Considerable efforts have been devoted to forge this core structure.⁴ Cyclopropanation of cyclic alkenes with metal carbenes is one of the most direct protocols and has been intensively studied.⁵ However, current limitations of this process include the difficulty associated with the cyclopropanation of trisubstituted olefins, alongside the paucity of stereocontrol of the cyclopropanation, probably because the metal carbene might be very sensitive to the steric hindrance of the alkene.⁶ An alternative strategy of tandem Michael addition/nucleophilic substitution of ylides, including sulfur, nitrogen and phosphorus, *etc.*, to α,β -unsaturated compounds has been developed to produce cyclopropanes in impressive elegance.^{7,8} In the construction of trisubstituted benzo[3.1.0]carbocycles, intramolecular reactions of chalcone derived benzyl bromides in terms of sulfur ylide methods have presented powerful potential (53% yield, Scheme 1, eqn (1)).^{8f} However, in the cases of tetrasubstituted benzo[3.1.0]carbocycles, relevant studies become difficult because the corresponding secondary benzyl bromides are unstable. Recently, we developed a cascade strategy and found that alkylation of phosphorus ylide provided a facile access to stereo hindered phosphonium salts,⁹ which could be easily deprotonated to *in situ* generate the corresponding phosphorus ylide. Followed by typical tandem Michael addition/nucleophilic substitution, a tetrasubstituted benzo[3.1.0]carbocycle was constructed



Scheme 1 Ylide mediated cyclopropanation.

(Scheme 1, eqn (2)). Herein, we wish to report this reaction in detail.

Initial studies focused upon synthesis of benzo[3.1.0]bicycloalkanes *via* alkylation/cyclopropanation cascade reactions of chalcone-derived benzyl bromide **1a** and benzyltriphenylphosphonium bromide **2a** (Table 1). Treatment of **2a** with Cs_2CO_3 and **1a** at 80 °C in DME (dimethyl ether) led to the alkylation of the *in situ* generated phosphorus ylide, with subsequent intramolecular cyclization giving **3a** in 58% yield with an exclusive *cis*¹⁰ diastereoselectivity (entry 1). Using toluene and ethyl acetate as solvents, the reaction could also proceed in moderate yields (entries 2 and 3). The effect of using a protic solvent was explored, and 55% yield was obtained (entry 4). Both 1,2-dichloroethane and DMF could raise the yield to 70% (entries 5 and 6). When acetonitrile was employed as the solvent, an obvious acceleration of the reaction was observed, and the yield was increased to 82% after 13 hours (entry 7). Alternative inorganic bases such as Na_2CO_3 , K_2CO_3 , and NaOH were also examined, and typically a stronger base led to a higher reactivity (entries 8–10). However, when a much stronger base like *t*-BuOK was used, the reaction becomes complicated, only 6% of the desired product was obtained (entry 11). In addition, an organic base such as DBU resulted in rather low yield after 20 hours (4% yield, entry 12).

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Table 1 Reaction optimization^a

Entry	Base	Solvent	<i>t</i> (h)	Yield ^b (%)
1	Cs ₂ CO ₃	DME	18	58
2	Cs ₂ CO ₃	Toluene	14	58
3	Cs ₂ CO ₃	EA	18	53
4	Cs ₂ CO ₃	<i>t</i> BuOH	23	55
5	Cs ₂ CO ₃	DCE	14	70
6	Cs ₂ CO ₃	DMF	17	70
7	Cs ₂ CO ₃	CH ₃ CN	13	82
8	Na ₂ CO ₃	CH ₃ CN	13	Trace
9	K ₂ CO ₃	CH ₃ CN	23	64
10	NaOH	CH ₃ CN	13	78
11	<i>t</i> -BuOK	CH ₃ CN	19	6
12	DBU	CH ₃ CN	20	4

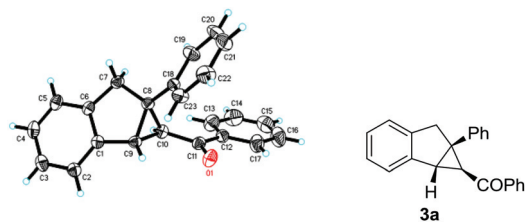
^a Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), base (1.8 mmol), in solvent (4 mL). ^b Isolated yield.

With the optimized reaction conditions in hand, we next investigated the generality of this tandem cyclization reaction, as shown in Table 2. A range of chalcone derivatives **1a–h** with different substituents on the benzoyl group, including 4-*t*Bu-, 4-F-, 3-Br, 2-Br, *etc.*, were reacted with **2a** smoothly to give the corresponding cyclopropanes **3a–h** in good to high yields, and neither electronic changes nor substitution positions on the aryl ring had a significant effect on the reactivities (64–85% yields, entries 1–8). Heterocyclic substrates **1i** and **1j**, contain-

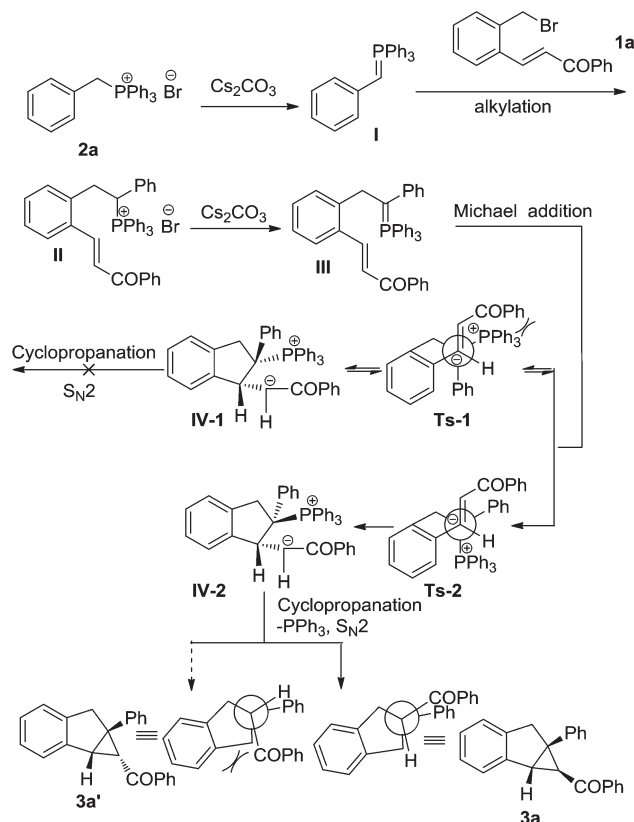
Table 2 Reaction scope^a

Entry	R	Ar	Product	<i>t</i> (h)	Yield ^b (%)
1	Ph	Ph	3a	14	82
2	4- <i>t</i> BuC ₆ H ₄	Ph	3b	16	78
3	4-MeOC ₆ H ₄	Ph	3c	16	85
4	4-FC ₆ H ₄	Ph	3d	12	82
5	4-ClC ₆ H ₄	Ph	3e	14	65
6	4-BrC ₆ H ₄	Ph	3f	12	65
7	3-BrC ₆ H ₄	Ph	3g	16	64
8	2-BrC ₆ H ₄	Ph	3h	16	73
9	2-Furyl	Ph	3i	10	70
10	2-Thienyl	Ph	3j	10	81
11	Me	Ph	3k	12	71
12	<i>t</i> Bu	Ph	3l	12	83
13	Styryl	Ph	3m	13	57
14	Ph	4-BrC ₆ H ₄	3n	18	82
15	Ph	3-MeOC ₆ H ₄	3o	18	90
16 ^c	Ph	2-Furyl	3p	20	75
17 ^d	Ph	2-Thienyl	3q	22	52
18	Ph	2-Naphthyl	3r	13	81

^a Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), Cs₂CO₃ (1.8 mmol), CH₃CN (4 mL). ^b Isolated yield. ^c 20 °C. ^d 40 °C.

Fig. 1 X-Ray crystal structures of **3a**.

ing 2-furyl and 2-thienyl, both can be converted to the desired products in 70% and 81% yields, respectively (entries 9 and 10). Acetyl and pivaloyl products **3k** and **3l** could be accomplished facilely in good yields (71% and 83% yields, entries 11 and 12). When cinnamoyl substrate **1m** was examined, the indanyl cyclopropane **3m** was furnished in moderate yield (entry 13). Remarkably, the current catalytic system is also compatible with a series of phosphonium salts, bearing aryl, heteroaryl and fused-aryl groups. For example, in the case of 4-Br and 3-MeO substituted benzyltriphenylphosphoniums, the reactions showed good to high reactivity (entries 14 and 15). 2-Furyl and 2-thienyl phosphoniums were well tolerated in this tandem cyclization reaction at mild reaction temperatures (entries 16 and 17). With 2-naphthyl phosphonium salt, **3r** was afforded in 81% yield after 13 hours (entry 18). Remarkably, in all cases, the diastereoselectivity of these reactions was excellent, only one diastereomer **3a–r** was observed. The stereo-



Scheme 2 Mechanistic and stereochemical proposal.

chemistry of **3a** was identified by X-ray analysis. As shown in Fig. 1, the torsion angle of C(18)–C(8)–C(10)–C(11) in **3a** is 8.2°, and the torsion angle of C(1)–C(9)–C(10)–C(11) in **3a** is –124.5°, which indicate that the relative configuration of **3a** is *cis*.¹¹

A possible mechanism for the tandem cyclization reactions is proposed as shown in Scheme 2. The benzyltriphenylphosphonium bromide **2a** was initially treated with Cs₂CO₃ to *in situ* generate phosphorus ylide, followed by alkylation with **1a** to give the corresponding phosphonium salt. In the presence of Cs₂CO₃, the phosphonium salt **II** was deprotonated, followed by an intramolecular conjugate addition of ylide **III** and a S_N2 nucleophilic cyclopropanation, furnishing bicycloalkane **3a** and releasing Ph₃P. The reaction is stereospecific in all cases that we have studied. It was proposed that the transition-state **TS-2** might be more stable than the transition-state **TS-1** due to the steric effects between the triphenylphosphine group and the benzoyl group in **TS-2**. Thus, the formation of an intermediate **IV-2** is favored over that of an intermediate **IV-1**. Furthermore, because of the repulsion between the indanyl group and the benzoyl group, compound **3a** was furnished as the major product.

Conclusions

In summary, we have developed a facile approach for the synthesis of benzo[3.1.0]bicycloalkanes *via* alkylation/cyclopropanation cascade reactions of benzyl bromides with triphenylphosphonium bromide. By elaborate designing of starting materials, this multistep cyclization proceeded smoothly with a wide range of substrate scopes, providing the benzo[3.1.0]bicycloalkanes in 52–90% yields with exclusive diastereoselectivity. Further investigations into this process are currently ongoing in our laboratory.

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- 10 The *cis* isomer is defined by the phenyl group and the benzoyl group substituted on cyclopropane, which are on the same side of the cyclopropane ring.
- 11 CCDC 962017 (**3a**) contains the supplementary crystallographic data for this paper.