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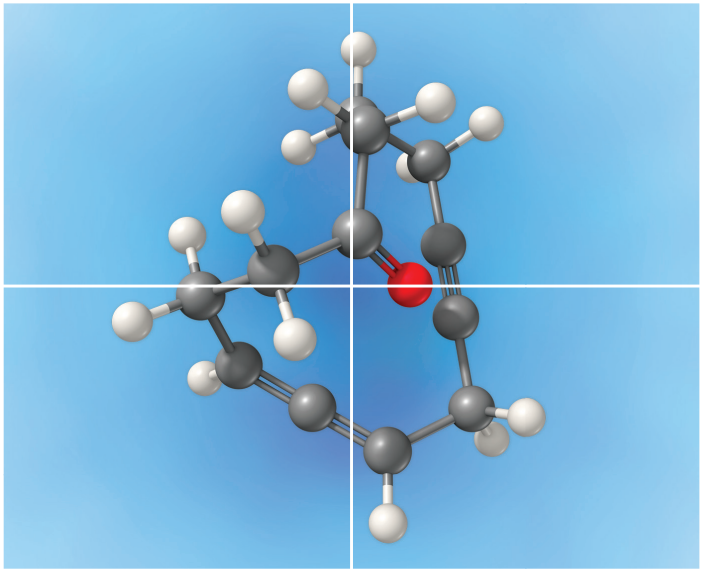

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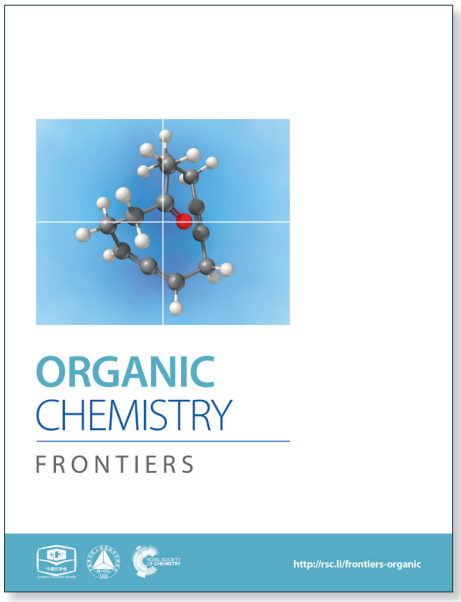

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Stereospecific Synthesis of Highly Functionalized Benzo[3.1.0] Bicycloalkanes via Multistep Casecade Reaction

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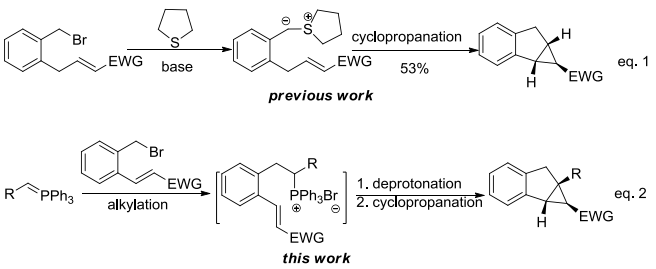
A facile approach in synthesis of benzo[3.1.0] bicycloalkanes via alkylation/cyclopropanation casecade reactions of benzyl bromide with triphenylphosphonium bromide has been developed. By elaborate designing of starting materials, this multistep cyclization proceeded smoothly with a wide range of substrate scope, providing the benzo[3.1.0]bicycloalkanes in 52-90% yields with exclusive diastereoselectivity.

The benzo[3.1.0]carbobicycles 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 carbene 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]carbobicycles, intramolecular reactions of chalcone derived benzyl bromides in terms of sulfur ylide methods have presented powerful potential (53% yield, Scheme 1, eq. 1).[8i] However, in the cases of tetrasubstituted benzo[3.1.0]carbobicycles, 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, tetrasubstituted benzo[3.1.0]carbobicycle was constructed (Scheme 1, eq. 2). Herein, we wish to report this reaction in detail.

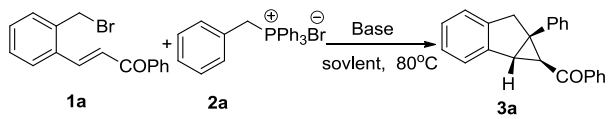
Scheme 1. Ylide mediated cyclopropanation.



Initial studies focused upon synthesis of benzo[3.1.0] bicycloalkanes via alkylation/cyclopropanation casecade 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 much stronger base like *t*-BuOK was used, the reaction become complicated, only 6% of the desired product was obtained (entry 11). In addition, organic base such as DBU resulted in rather low yield after 20 hours (4% yield, entry 12).

Table 1. Reaction optimization. [a]

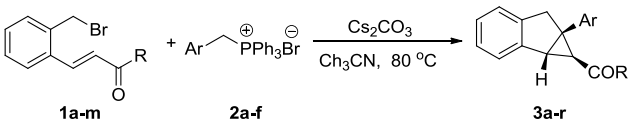


Entry	Base	Solvent	t (h)	Yield (%)[b]
1	$CsCO_3$	DME	18	58
2	$CsCO_3$	toluene	14	58
3	$CsCO_3$	EA	18	53
4	$CsCO_3$	^{t}BuOH	23	55
5	$CsCO_3$	DCE	14	70
6	$CsCO_3$	DMF	17	70
7	$CsCO_3$	CH_3CN	13	82
8	Na_2CO_3	CH_3CN	13	trace
9	K_2CO_3	CH_3CN	23	64
10	NaOH	CH_3CN	13	78
11	*t*-BuOK	CH_3CN	19	6
12	DBU	CH_3CN	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). Containing 2-furyl and 2-thienyl, heterocyclic substrates **1i** and **1j** 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 stereochemistry of the **3a** was identified by X-ray analysis. As shown in Figure 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 configurations of **3a** is *cis*.[11]

Table 2. Reaction scope. [a]



Entry	R	Ar	Product	t (h)	Yield (%)[b]
1	Ph	Ph	**3a**	14	82
2	4-*t*BuC_6H_4	Ph	**3b**	16	78
3	4-MeOC_6H_4	Ph	**3c**	16	85
4	4-FC_6H_4	Ph	**3d**	12	82
5	4-ClC_6H_4	Ph	**3e**	14	65
6	4-BrC_6H_4	Ph	**3f**	12	65
7	3-BrC_6H_4	Ph	**3g**	16	64
8	2-BrC_6H_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	^{t}Bu	Ph	**3l**	12	83
13	styryl	Ph	**3m**	13	57
14	Ph	4-BrC_6H_4	**3n**	18	82
15	Ph	3-MeOC_6H_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), Cs_2CO_3 (1.8 mmol), CH_3CN (4 mL). [b] Isolated yield. [c] 20 °C. [d] 40 °C.

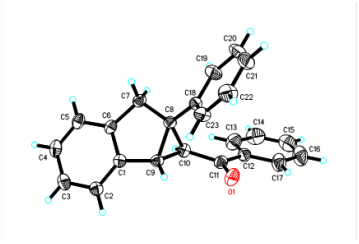
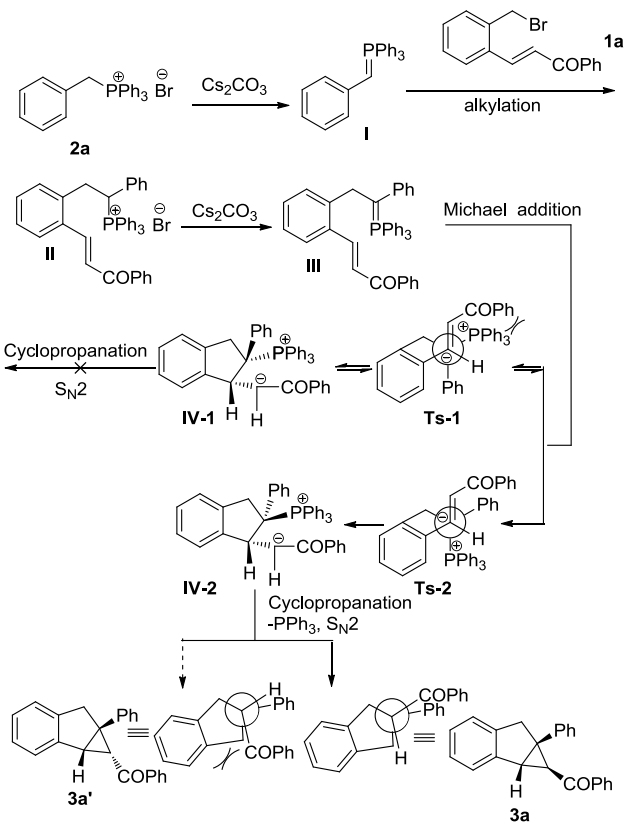


Figure 1. X-Ray crystal structures of 3a.

A possible mechanism for the tandem cyclization reactions is proposed as shown in Scheme 2. The benzyltriphenylphosphonium bromide **2a** was initially treated with Cs_2CO_3 to *in-situ* generate phosphorus ylide, followed by the alkylation with **1a** to give the corresponding phosphonium salt. In the presence of Cs_2CO_3, the phosphonium salt **II** was deprotonated, followed by an intramolecular conjugate addition of ylide **III** and a S_N2 nucleophilic cyclopropanation, furnished bicycloalkane **3a** and released Ph_3P. The reaction is stereospecific in all cases we have studied. It was proposed that transition-state **TS-2** might be more stable than transition-state **TS-1** due to the steric effects between triphenylphosphine group and benzoyl group in **TS-2**. Thus, the formation of intermediate **IV-2** is favored over that of intermediate **IV** . Furthermore, because of the repulsion between indanyl group and benzoyl group, compound **3a** was furnished as the major product.

Scheme 2. Mechanistic and Stereochemical Proposal.



Conclusions

In summary, we have developed a facile approach in synthesis of benzo[3.1.0]bicycloalkanes via alkylation/ cyclopropanation casecade reactions of benzyl bromides with triphenylphosphonium bromide. By elaborate designing of starting materials, this multistep cyclization proceeded smoothly with a wide range of substrate scope, 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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Notes and references

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Electronic Supplementary Information (ESI) available: Experimental procedures and the characterization data of new compounds. See DOI: 10.1039/c000000x/

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10. The *cis* isomer is defined by phenyl group and benzoyl group substituted on cycloprpane which are on the same side of the cyclopropane ring.

11. CCDC 962017 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

