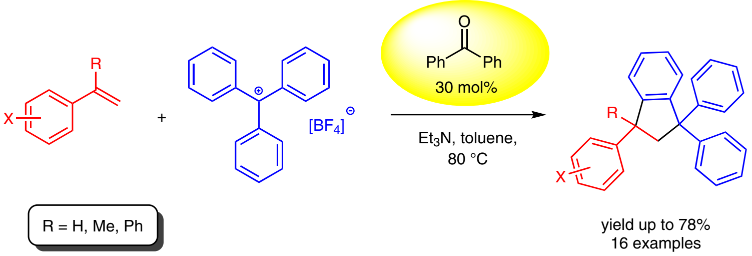
Organopromoted Direct Synthesis of 1,1-Diphenyl-3-arylindanes via Formal [3+2] Cycloadditions of Triphenylcarbenium Tetrafluoroborate with Styrenes

Nakin Surapanich*[a]
Patcharin Chaisuwan[b]
Chutima Kuhakarn[c]
Vichai Reutrakul[c]

[a] Department of Chemistry, Faculty of Science and Technology, Rajabhat Rajanagarindra University, 422 Marupong Road, Tombon Na Muang, Amphoe Muang, Chachoengsao 24000, Thailand
nakin_s@hotmail.com
[b] School of Chemistry, Suranaree University of Technology, 111 University Avenue, Muang District, Nakhon Ratchasima 30000, Thailand
[c] Department of Chemistry and Center of Excellence for Innovation in Chemistry (PERCH-CIC), Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand



Received: 12.06.2016
Accepted after revision: 05.08.2016

DOI: 10.1055/s-0036-1588302; Art ID: st-2016-d0383-l

Abstract A formal [3+2] cycloaddition of triphenylcarbenium tetrafluoroborate with structurally different styrene derivatives has been developed. A combination of benzophenone and Et$_3$N is key for promoting a formal [3+2] cycloaddition of triphenylcarbenium tetrafluoroborate with styrenes affording 1,1-diphenyl-3-arylindanes in moderate to good yields. The reaction mechanism of this transformation is also discussed.

Key words styrenes, triphenylcarbenium tetrafluoroborate, indanes, formal [3+2] cycloaddition, organocatalyst

The indane ring system is an important structural motif found in many naturally occurring compounds. In addition, a large number of them have significant biological activities,[1] such as the antihypertensive drug (+)-indacrinone,[1a] the antidepressant indatraline,[1b] the HIV protease inhibitor indinavir,[1c] and the acetylcholinesterase inhibitor donepezil.[1d] Moreover, compounds **1**, **2**, and **3** were developed and used as precursors of polymers of intrinsic microporosity materials (PIM), which display enhanced solubility and microporosity in the solid state (Figure 1).[2] Additionally, such PIM have been developed for potential applications as heterogeneous catalysts,[3] hydrogen storage materials,[4] and polymer membranes for gases.[5]

There is a large number of methods to access the indane framework, including intermolecular [3+2] cycloaddition of benzylic cations with alkenes,[6] intramolecular Friedel–Crafts reactions of alkanols,[7] cyclodimerization of alkenes,[8] and other approaches.[9]

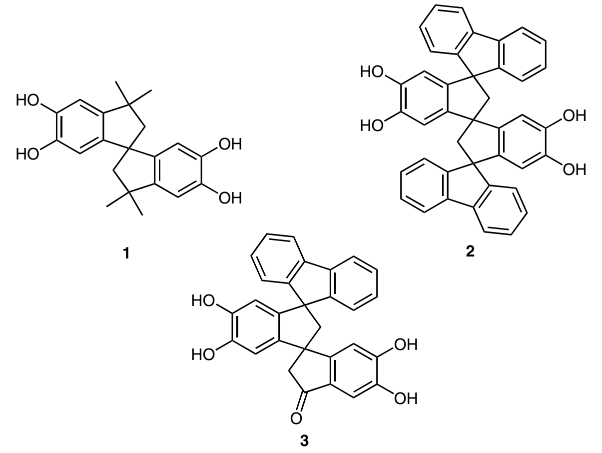
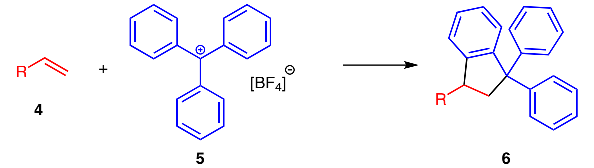


Figure 1 Structures of synthetic indane monomers

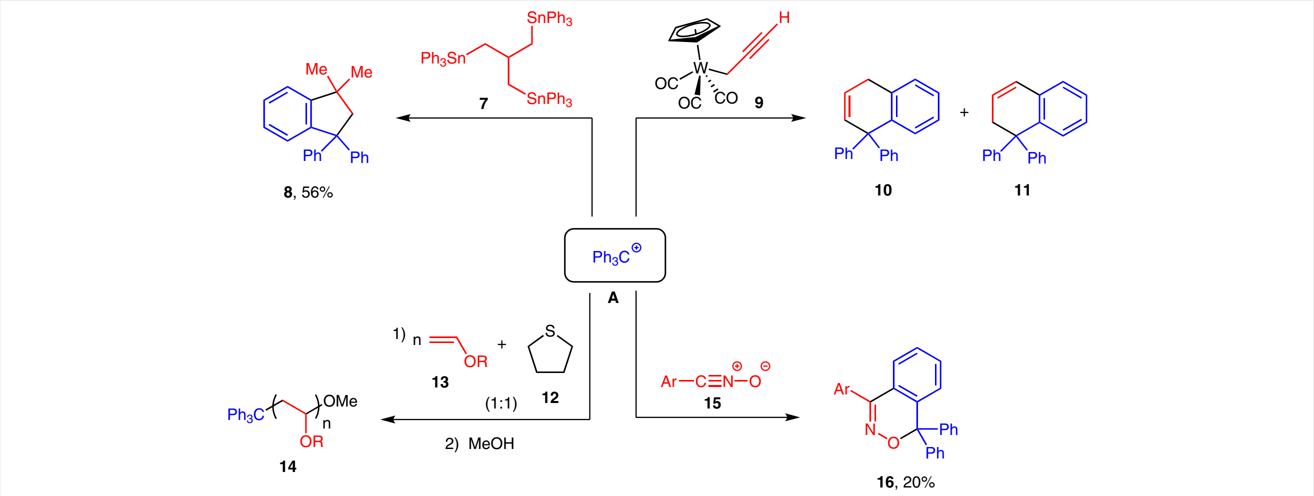
In the course of our investigation on the formal [3+2] cycloaddition of benzylic cations with alkenes, we envisaged that with commercially available triphenylcarbenium tetrafluoroborate (**5**), a stable triphenylmethyl cation intermediate Ph$_3$C$^+$, could be possible, initiating a formal [3+2] cycloaddition with alkenes **4** to give indane products **6** (Scheme 1).



Scheme 1 Synthetic strategy to access the indane framework **6**

A literature search revealed that a formal [3+2] cycloaddition of triphenylmethyl cation with alkenes is rare and has limitations. For instance, in 1984, Ducharme and coworkers[10] demonstrated the transfer of hydrogen from the carbon–hydrogen bond of tris[(triphenylstannyl)methyl]methane (**7**) to triphenylcarbenium hexafluorophosphate, in which isobutylene was generated in situ under the reaction conditions followed by a formal [3+2] cycloaddition with the triphenylmethyl cation Ph_3C^+ (**A**) to give 1,1-dimethyl-3,3-diphenylindane (**8**) in 56% yield (Scheme 2). In 1993, Wu and co-workers[11] reported a study of carbon–carbon bond formation and its subsequent cyclization in the reaction of triphenylmethyl cation (**A**) with the tungsten propargyl complex **9** for the synthesis of two polyaromatic compounds; each of which contain a new six-membered ring (Scheme 2). In 1997, Acar and co-workers[12] reported the use of triphenylcarbenium tetrafluoroborate as a cationic initiator for vinyl ether polymerization affording trityl-terminated poly(butyl vinyl ether) (**14**, Scheme 2). This trityl-terminated polymer **14** was further used to initiate free radical polymerization of methyl methacrylate for the preparation of a block copolymer. In 2002, Auricchio and co-workers[13] reported their study on the cycloaddition reaction between the stable nitrile oxide **15**, used as 1,3-dipole, and triphenylcarbenium tetrafluoroborate to give benzoxazine **16** in 20% yield (Scheme 2). In addition, the 2π electrons of the triphenylmethyl cation and the 4π electrons of nitrile oxide **15** participate in a stepwise cycloaddition process. Herein, we report a successful synthesis of 1,1-diphenyl-3-arylindanes via a formal [3+2] cycloaddition of triphenylcarbenium tetrafluoroborate **5** with structurally different styrene derivatives promoted by a combination of benzophenone and Et_3N. To the best of our knowledge, this is the first example for the synthesis of 1,1-diphenyl-3-arylindanes via a formal [3+2] cycloaddition of triphenylcarbenium tetrafluoroborate with styrenes.

To test our hypothesis, our preliminary investigations commenced by considering a formal [3+2] cycloaddition reaction between triphenylcarbenium tetrafluoroborate **5** (1.5 equiv) and styrene **4a** (1 equiv) in toluene at room temperature for 48 hours (Table 1, entry 1). Unfortunately, the desired cycloaddition product **6a** was not observed; only styrene polymerization products were detected. Serendipitously, we observed that a formal [3+2] cycloaddition of triphenylcarbenium tetrafluoroborate **5** with styrene **4a** could be achieved by using benzophenone as an additive. The results showed that the desired product **6a** was obtained in 40% yield when 30 mol% of benzophenone were employed as the additive (Table 1, entry 2). Further screening revealed that : decreasing the loading of benzophenone to 20 mol% or increasing the loading of benzophenone to 40 mol% did not significantly affect the reaction (Table 1, entry 3); neither did increasing the amount of triphenylcarbenium tetrafluoroborate **5** from 1.5 equivalents to 3 equivalents significantly improve the yield of the desired product **6a** (40% yield, Table 1, entry 2). A number of solvents, such as benzene, CH_2Cl_2, EtOAc, THF, DMF, DMSO, and MeCN was examined, but they gave inferior results (Table 1, entries 4–10), except for benzene, affording **6a** in a comparable yield (40% yield, Table 1, entry 5). Subsequently, the effects of other heteroatom-containing additives such as methylphenylsulfide, EtOAc, acetone, DMSO, DMF, and Et_3N were investigated, yielding the desired product **6a** ranging from 13–36% yield (Table 1, entries 11–16). Increasing the amount of Et_3N from 0.3 equivalents to 1 equivalent was found to be effective to produce the desired product **6a** in 46% yield (Table 1, entry 16). No reaction was observed when an inorganic base such as K_2CO_3 was employed (Table 1, entry 17). To our satisfaction, when a combination of benzophenone (0.3 equiv) and Et_3N (1.0 equiv) was used, the desired product **6a** was obtained in 58% yield (Table 1, entry 18). The effect of the reaction temperature was fur-

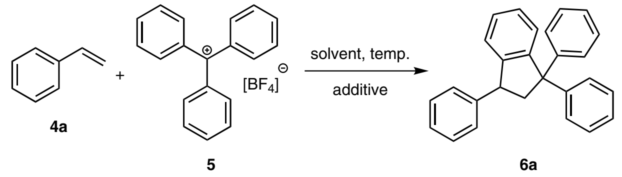


Scheme 2 Reported reactions of Ph_3C^+ (**A**) under different conditions

ther investigated, and the best result was achieved when the reaction was performed at 80 °C for 48 hours to give the cycloaddition product **6a** in 77% yield (Table 1, entry 20). Inferior yields were observed when the reaction was performed at 100 °C for three hours affording the cycloaddition product **6a** in 49% yield (Table 1, entry 21). Finally, a mixture of styrene **4a** (1.0 equiv), triphenylcarbenium tetrafluoroborate (**5**, 1.5 equiv), benzophenone (0.3 equiv), and Et_3N (1.0 equiv) in toluene at 80 °C for 48 hours was established as the optimal conditions (Table 1, entry 20).

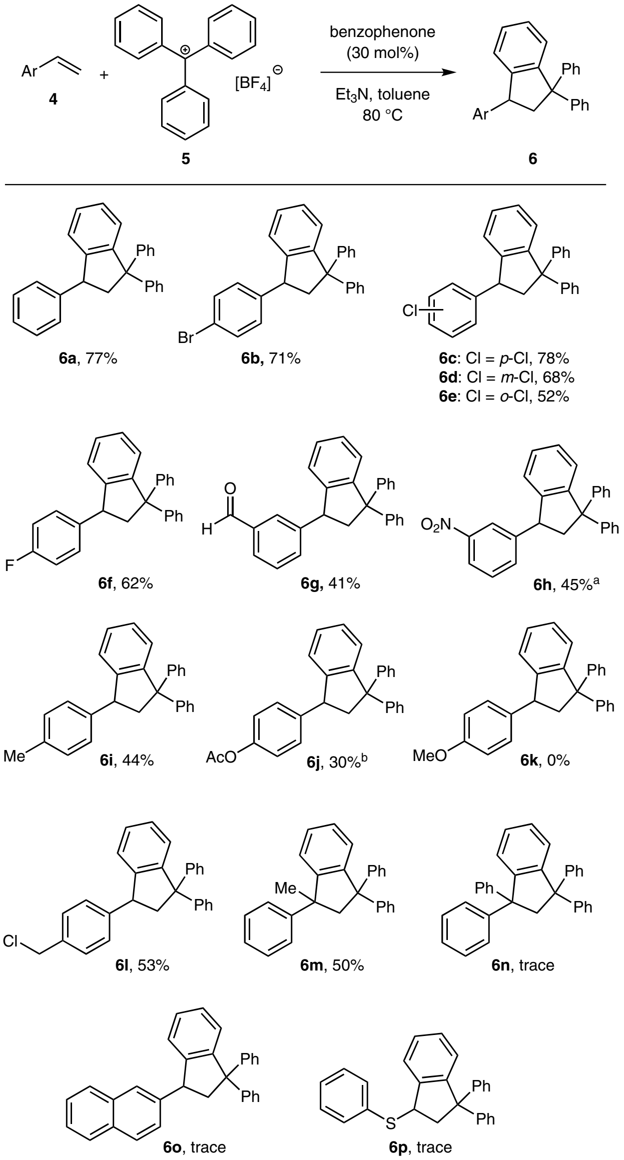
After established the optimal conditions, we next evaluated the scope and limitations of this transformation, and the results are summarized in Scheme 3. Firstly, a variety of styrene derivatives was investigated. Good results were obtained when styrene derivatives bearing an electron-withdrawing substituent at the *para* position including *p*-bromostyrene (**4b**), *p*-chlorosytrene (**4c**), and *p*-fluorostyrene (**4f**) were employed as substrates. The cycloaddition products **6b**, **6c**, and **6f** were obtained in high yields ranging from 62–78% yield. In comparison, *ortho*-substituted chlo-

Table 1 Optimization of Reaction Conditions[a]



Entry	Additive (0.3 equiv)	Base (1 equiv)	Solvent (2.5 mL)	Temp (°C)	Yield (%)[b]
1	-	–	toluene	r.t.	0
2	Ph_2CO	–	toluene	r.t.	40, 40[c]
3	Ph_2CO	–	toluene	r.t.	32[d], 40[e]
4	Ph_2CO	–	hexanes	r.t.	27
5	Ph_2CO	–	benzene	r.t.	40
6	Ph_2CO	–	CH_2Cl_2	r.t.	24
7	Ph_2CO	–	MeCN	r.t.	26
8	Ph_2CO	–	DMF	r.t.	0
9	Ph_2CO	–	DMSO	r.t.	0
10	Ph_2CO	–	THF	r.t.	0
11	PhSMe	–	toluene	r.t.	13
12	EtOAc	–	toluene	r.t.	28
13	Me_2CO	–	toluene	r.t.	34
14	DMSO	–	toluene	r.t.	30
15	DMF	–	toluene	r.t.	26
16	–	Et_3N	toluene	r.t.	46, 36[f]
17	–	K_2CO_3	toluene	r.t.	0
18	Ph_2CO	Et_3N	toluene	r.t.	58
19	Ph_2CO	Et_3N	toluene	60	73, 67[g]
20	Ph_2CO	Et_3N	toluene	80	77
21	Ph_2CO	Et_3N	toluene	100	49[h]

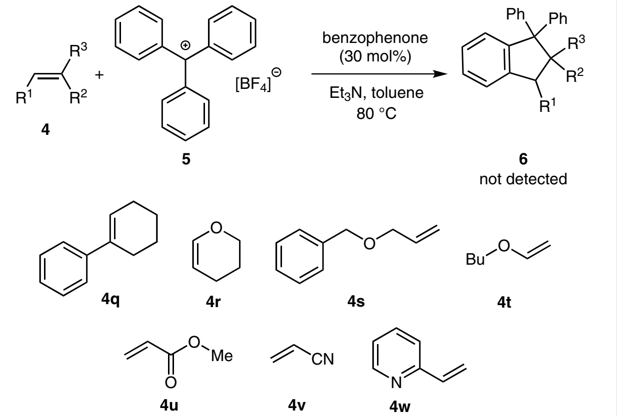
[a] Reaction conditions: **4a** (1.0 mmol), **5** (1.5 mmol), additive (0.3 mmol), and base (1.0 mmol) in toluene (2.5 mL) at 80 °C for 48 h.
[b] Isolated yield.
[c] Conditions: 3 equiv of **5** were used.
[d] Conditions: with 0.2 equiv of benzophenone.
[e] Conditions: with 0.4 equiv of benzophenone.
[f] Conditions: with 0.3 equiv of Et_3N.
[g] Reaction carried out under anhydrous conditions under argon atmosphere.
[h] Reaction was completed in 3 h.



Scheme 3 Synthesis of 1,1-diphenyl-3-arylindanes via a formal [3+2] cycloaddition of triphenylcarbenium tetrafluoroborate with styrenes
[a] Reaction was carried out in the absence of benzophenone and stirred at 80 °C under argon for 144 h. [b] Anhydrous conditions.[c] Reaction was performed at r.t. for 120 h.

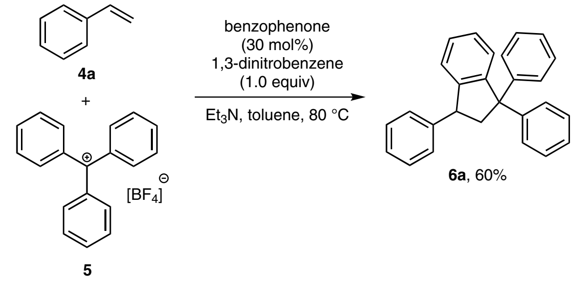
rostyrene (**4e**) gave a relatively lower yield compared with its *meta*- or *para*-substituted analogue, probably due to steric hindrance. 3-Vinyl benzaldehyde (**4g**) was also compatible with the reaction conditions to give the corresponding product **6g** in 41% yield. In the case of *m*-nitrostyrene **4h**, an inseparable mixture of the desired product **6h**, benzophenone, and unidentified products was obtained. To overcome this problem, the modified reaction conditions were carried out in the absence of benzophenone, and the mixture was stirred at 80 °C under an argon atmosphere for 144 hours, providing the cycloaddition product **6h** in 45% yield along with 28% yield of recovered *m*-nitrosyrene **4h**. Lower yields were obtained when styrenes with electron-releasing substituents were subjected to the optimal conditions. For instance, *p*-methylstyrene (**4i**) and *p*-acetoxystyrene (**4j**) were converted into the desired products **6i** and **6j** in 44% and 30% yields, respectively. When *p*-methoxystyrene (**4k**) was employed as a substrate, the desired product **6k** was not obtained. In the case of 1-(chloromethyl)-4-vinylbenzene (**4l**), traces of the desired product **6l** were detected. Gratifyingly, the yield of **6l** was improved to 53% yield when the reaction was conducted at 30 °C for 120 hours. Furthermore, α-methylstyrene (**4m**) was found to undergo the reaction, producing the corresponding product **6m** in 50% yield. Unfortunately, only traces of an inseparable mixture of the corresponding target compounds **6n**, **6o**, and **6p** were produced under these reaction conditions, presumably due to the influence of the steric hindrance of the substrates.

In an attempt to extend the scope of this transformation, cyclohexenylbenzene (**4q**), 3,4-dihydro-2*H*-pyran (**4r**), allyl benzylether (**4s**), *n*-butyl vinylether (**4t**), methyl acrylate (**4u**), acrylonitrile (**4v**), and 2-vinylpyridine (**4w**) were screened under the standard reaction conditions (Scheme 4). Unfortunately, the desired cycloaddition products were not observed.



Scheme 4 A formal [3+2] cycloaddition of triphenylcarbenium tetrafluoroborate with alkenes

In order to gain more insight into the reaction mechanism of this transformation, a possible electron-transfer process induced by the triphenylmethyl cation Ph_3C^+ as reported by Morkovnik and co-workers in 1995[14] was investigated. To probe the possible electron-transfer process, a radical-scavenging experiment was carried out. Addition of single-electron-transfer inhibitor 1,3-dinitrobenzene[15] (1.0 equiv) to the reaction of triphenylcarbenium tetrafluoroborate and styrene under standard reaction conditions led to slightly lower yield of **6a** (from 77% yield to 60% yield) (Scheme 5). This result implies that the mechanistic pathway of the present reaction is ionic and that it is not an electron-transfer process.



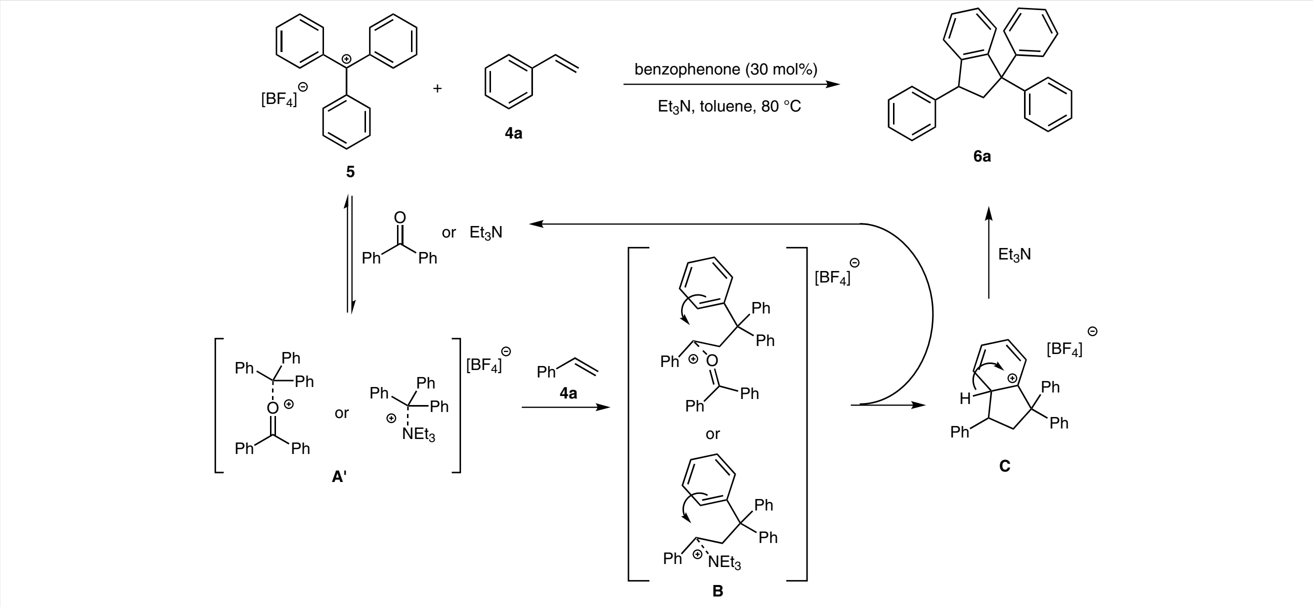
Scheme 5 A formal [3+2] cycloaddition reaction of triphenylcarbenium tetrafluoroborate with styrenes in the present of a single-electron-transfer (SET) inhibitor

Based on the experimental results, the reaction mechanism of this transformation is proposed to proceed via a cation-induced formal [3+2] cycloaddition of triphenylcarbenium tetrafluoroborate with styrene. A key step of this transformation involves an unshared electron pair from a heteroatom, such as oxygen or nitrogen, coordinating to the triphenylmethyl cation resulting an intermediate **A′**. The intermediate **A′** could then be trapped by styrene to afford a new benzylic cation providing intermediate **B**, that would benefit carbocation stabilization, slowing down polymerization, and facilitating ring closure by intramolecular Friedel–Crafts reaction. Finally, aromatization by proton abstraction provides the corresponding product **6a** (Scheme 6).

In conclusion, we have developed an experimentally simple, one-pot synthesis of 1,1-diphenyl-3-arylindanes promoted by benzophenone and Et_3N via formal [3+2] cycloaddition reaction between triphenylcarbenium tetrafluoroborate and structurally diverse styrene derivatives to give 1,1-diphenyl-3-arylindanes in moderate to good yields.[16]

Acknowledgment

We thank Rajabhat Rajanagarindra University Research and Development Institute for financial support.



Scheme 6 Proposed mechanism

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588302.

References and Notes

(1) (a) DeSolms, S. J.; Woltersdorf, O. W. Jr.; Cragoe, E. J. Jr. *J. Med. Chem.* **1978**, *21*, 437. (b) Bøgesø, K. P.; Christensen, A. V.; Hyttel, J.; Liljefors, T. *J. Med. Chem.* **1985**, *28*, 1817. (c) Dorsey, B. D.; Levin, R. B.; McDaniel, S. L.; Vacca, J. P.; Guare, J. P.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Lin, J. H.; Chen, I.-W.; Holloway, M. K.; Fitzgerald, P. M. D.; Axel, M. G.; Ostovic, D.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1994**, *37*, 3443. (d) Sugimoto, H.; Iimura, Y.; Yamanishi, Y.; Yamatsu, K. *J. Med. Chem.* **1995**, *38*, 4821.

(2) Carta, M.; Msayib, K. J.; Budd, P. M.; McKeown, N. B. *Org. Lett.* **2008**, *10*, 2641.

(3) (a) MacKenzie, H.; Budd, P. M.; McKeown, N. B. *J. Mater. Chem.* **2008**, *18*, 573. (b) Budd, P. M.; Ghanem, B.; Msayib, K.; McKeown, N. B.; Tattershall, C. *J. Mater. Chem.* **2003**, *13*, 2721.

(4) (a) McKeown, N. B.; Gahnem, B.; Msayib, K. J.; Budd, P. M.; Tattershall, C. E.; Mahmood, K.; Tan, S.; Book, D.; Langmi, H. W.; Walton, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 1804. (b) Budd, P. M.; Butler, A.; Selbie, J.; Mahmood, K.; McKeown, N. B.; Ghanem, B.; Msayib, K.; Book, D.; Walton, A. *Phys. Chem. Chem. Phys.* **2007**, *9*, 1802. (c) Ghanem, B. S.; Msayid, K. J.; McKeown, N. B.; Harris, K. D. M.; Pan, Z.; Budd, P. M.; Butler, A.; Selbie, J.; Book, D.; Walton, A. *Chem. Commun.* **2007**, 67. (d) McKeown, N. B.; Budd, P. M.; Book, D. *Macromol. Rapid Commun.* **2007**, *28*, 995.

(5) Budd, P. M.; Elabas, E. S.; Ghanem, B. S.; Makhseed, S.; McKeown, N. B.; Msayib, K. J.; Tattershall, C. E.; Wang, D. *Adv. Mater.* **2004**, *16*, 456.

(6) (a) Angle, S. R.; Arnaiz, D. O. *J. Org. Chem.* **1992**, *57*, 5937. (b) Katritzky, A. R.; Zhang, G.; Xie, L. *Synth. Commun.* **1997**, *27*, 2467. (c) Lantaño, B.; Aguirre, J. M.; Finkielsztien, L.; Alesso, E. N.; Brunet, E.; Moltrasio, G. Y. *Synth. Commun.* **2004**, *34*, 625. (d) Lantaño, B.; Aguirre, J. M.; Ugliarolo, E. A.; Benegas, M. L.; Moltrasio, G. Y. *Tetrahedron* **2008**, *64*, 4090.

(7) Khalaf, A. A.; El-Khawaga, A. M.; Awad, I. M.; Abd, El-Aal. H. A. K. *Arkivoc* **2009**, *(xiv)*, 314.

(8) (a) Madhavan, D.; Murugalakshmi, M.; Lalitha, A.; Pitchumani, K. *Catal. Lett.* **2001**, *73*, 1. (b) Ciminale, F.; Lopez, L.; Farinola, G. M.; Sportelli, S.; Nacci, A. *Eur. J. Org. Chem.* **2002**, 3850. (c) Peppe, C.; Lang, E. S.; de Andrade, F. M.; de Castro, L. B. *Synlett* **2004**, 1723. (d) Sun, H.-B.; Li, B.; Hua, R.; Yin, Y. *Eur. J. Org. Chem.* **2006**, 4231.

(9) (a) Hixson, S. S.; Franke, L. A. *J. Org. Chem.* **1988**, *53*, 2706. (b) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314. (c) Bailey, W. F.; Longsfaff, S. C. *J. Org. Chem.* **1998**, *63*, 432. (d) Ruan, J.; Iggo, J. A.; Xiao, J. *Org. Lett.* **2011**, *13*, 268.

(10) Ducharme, Y.; Latour, S.; Wuest, J. D. *Organometallics* **1984**, *3*, 208.

(11) Wu, I.-Y.; Tsai, J.-H.; Huang, B.-C.; Chen, S.-C.; Lin, Y.-C. *Organometallics* **1993**, *12*, 3971.

(12) Acar, M. H.; Küçüköner, M. *Polymer* **1997**, *38*, 2829.

(13) Auricchio, S.; Magnani, C.; Truscello, A. M. *Eur. J. Org. Chem.* **2002**, 2411.

(14) Morkovnik, A. S.; Suslov, A. N.; Klimov, E. S.; Morkovnik, Z. S.; Okhlobystin, O. Y. *Chem. Heterocycl. Compd.* **1995**, *31*, 847.

(15) Zhang, X.-M.; Yang, D.-L.; Liu, Y.-C. *J. Org. Chem.* **1993**, *58*, 224.

(16) **General Procedure for the Synthesis of 1,1,3-Triphenylindane (6a)**

A round-bottom flask equipped with a magnetic stirrer bar was charged with styrene (1.0 mmol), benzophene (0.3 mmol), Et$_3$N (1.0 mmol), and toluene (2.5 mL). Triphenylcarbenium tetrafluoroborate (1.5 mmol) was then added, and the resulting mixture was allowed to react at 80 °C for 48 h. After the end of the reaction, the mixture was filtered through a plug of Celite® and eluted with hexane–EtOAc (8:2). The filtrate was concentrated in vacuo and purified by column chromatography on

silica gel. The final product **6a** was obtained in 77% yield as a white solid, mp 111.5–112.5 °C. Analytical TLC on silica gel: R_f = 0.40 (hexanes–EtOAc = 9.9:0.1). IR (KBr): ν_{max} = 3080, 3061, and 3025 (aromatic), 2966, 2928, and 2862 (CH of aliphatic), 1596, and 1491 (aromatic), 1470, 1454, and 1444 (CH of aliphatic) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.16 (m, 17 H), 7.1 (d, *J* = 6.8 Hz, 1 H), 6.92 (d, *J* = 6.8 Hz, 1 H), 4.2 (dd, *J* = 6.4, 11.1 Hz, 1 H), 3.2 (dd. *J* = 6.4, 12.6 Hz, 1 H), 2.90 (dd, 11.1, 12.6 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.41 (C), 148.05 (C), 146.66, (C), 145.83 (C), 143.88 (C), 128.61 (3 CH), 128.54 (3 CH), 128.52 (2 CH), 128.03 (2 CH), 127.99 (2 CH), 127.19 (CH), 126.72 (CH), 126.62 (CH), 126.28 (CH), 126.08 (CH), 126.04 (CH), 125.03 (CH), 60.84 (C), 54.13 (CH_2), 49.01 (CH). HRMS (ESI-TOF): *m/z* [M + Na]$^{+}$ calcd for $C_{27}H_{22}Na$: 369.1619; found: 369.1531.