JOC Article
pubs.acs.org/joc

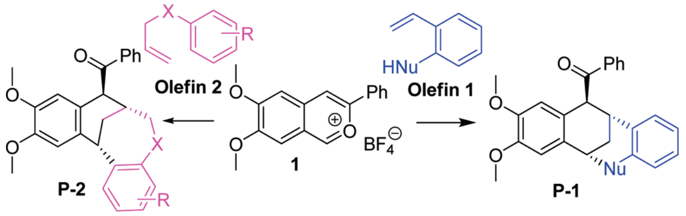
Construction of Multiring Frameworks by Metal-Free Cascade Reactions of Stable Isochromenylium Tetrafluoroborate

Zhi-Long Hu,[†] Wen-Jian Qian,[†] Sheng Wang,[‡] Shaozhong Wang,[‡] and Zhu-Jun Yao*,[†]

[†] *State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China, and*
[‡] *Nanjing National Laboratory of Microstructures, School of Chemistry and Chemical Engineering, Nanjing University, 22 Hankou Road, Nanjing, Jiangsu 210093, China*

yaoz@mail.sioc.ac.cn; yaoz@nju.edu.cn

Received September 23, 2009



Efficient methodologies for constructing several multiring frameworks have been developed utilizing the cascade reactions of air-stable isochromenylium tetrafluoroborates with olefins. Successive additions of two equivalents of styrene-type olefins to isochromenylium tetrafluoroborate (ICTB) **1** have been observed and their mechanisms were proposed and discussed. Intramolecular capture of the early stage cationic intermediates by predevised heteroatoms or Friedel−Crafts donors provided two different types of bridged-ring systems.

Introduction

Isochromenylium cations, a type of reactive intermediates, have attracted great attention from organic chemists in recent years.[1−3] They have been reported to be involved in many cascade transformations in constructing complex multiring frameworks.[4] Previously, isochromenyliums were commonly produced in situ as inseparable intermediates by treatment of *o*-alkynylbenzaldehyde precursors with metal catalyst or promoters (AuX$_3$,[5] AgX,[6] CuX$_2$,[7] PdX$_2$,[8] W,[9] PtX$_2$,[10] etc.) or other electrophiles (IPy$_2$BF$_4$,[11a−d] I$_2$,[11e−g] TfOH,[12] etc.). The catalysts or promoters are thought to activate the alkyne functionality and then to initiate the subsequent intramolecular cyclization by the oxygen of the carbonyl group. Such in situ produced isochromenylium intermediates are very reactive to olefins, giving 1,2-dihydronaphthalenes[5d,7a] (reaction a in Scheme 1) and oxa-bridged

---

(1) (a) Zhang, Y.-C.; Lebeau, E.; Gillard, J. W.; Attardo, G. *Tetrahedron Lett.* **1993**, *34*, 3841–3844. (b) Mutter, R.; Campbell, I. B.; Martin de la Nava, E. M.; Merritt, A. T.; Wills, M. *J. Org. Chem.* **2001**, *66*, 3284–3290. (c) Kueny-Stotz, M.; Isorez, G.; Chassaing, S.; Brouillard, R. *Synlett* **2007**, 1067–1070. (d) Peter, L. *Synlett* **2007**, 1016–1025.

(2) (a) Zhu, J. L.; Germain, A. R.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2004**, *43*, 1239–1243. (b) Qian, W.-J.; Wei, W.-G.; Zhang, Y.-X.; Yao, Z.-J. *J. Am. Chem. Soc.* **2007**, *129*, 6400–6401. (c) Wei, W.-G.; Zhang, Y.-X.; Yao, Z.-J. *Tetrahedron* **2005**, *61*, 11882–11886. (d) Marsini, M. A.; Gowin, K. M.; Pettus, T. R. *Org. Lett.* **2006**, *8*, 3481–3483. (e) Zhu, J. L.; Grigoriadis, N. P.; Lee, J. P.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 9342–9343.

(3) (a) Wei, W.-G.; Yao, Z.-J. *J. Org. Chem.* **2005**, *70*, 4585–4590. (b) Yao, Y.-S.; Yao, Z.-J. *J. Org. Chem.* **2008**, *73*, 5221–5225.

(4) (a) Asao, N.; Sato, K.; Yamamoto, Y. *J. Org, Chem.* **2005**, *70*, 3682–3685. (b) Dyker, G.; Hildebrandt, D. *J. Org. Chem.* **2005**, *70*, 6093–6096. (c) Sato, K.; Asao, N.; Yamamoto, Y. *J. Org, Chem.* **2005**, *70*, 8977–8981. (d) Hildebrandt, D.; Dyker, G. *J. Org. Chem.* **2006**, *71*, 6728–6733.

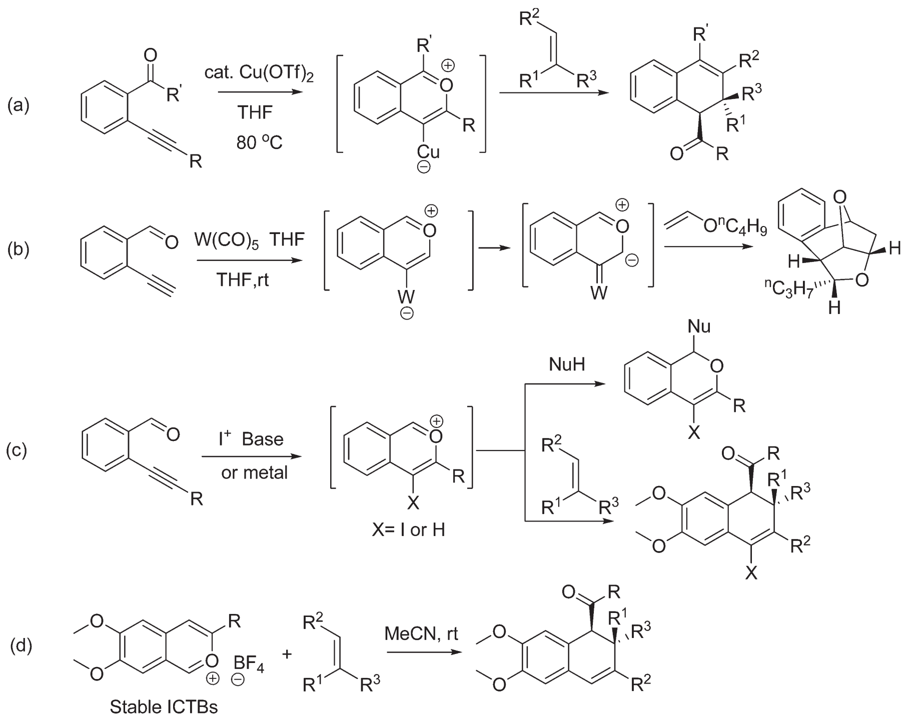
(5) (a) Asao, N.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650–12651. (b) Asao, N.; Nogami, T.; Lee, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10921–10925. (c) Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7458–7459. (d) Dyker, G.; Hildebrandt, D.; Liu, J. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4399–4402. (e) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395–3442. (f) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266–3325. (g) Li, Z. G.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239–3265. (h) Jin, T. N.; Yamamoto, Y. *Org. Lett.* **2007**, *9*, 5259–5262. (i) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847–7870. (j) Li, G. T.; Huang, X. G.; Zhang, L. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 346–349. (k) Kim, N.; Kim, Y.; Park, W.; Sung, D.; Gupta, A. K.; Oh, C. H. *Org. Lett.* **2005**, *7*, 5289–5291.

(6) (a) Beeler, A. B.; Su, S.; Singleton, C. A.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 1413–1419. (b) Ogawa, Y.; Maruno, M.; Wakamatsu, T. *Synlett* **1995**, 871–872. (c) Rossi, R.; Bellina, F.; Biagetti, M.; Mannina, L. *Tetrahedron Lett.* **1998**, *39*, 7799–7802. (d) Xu, C.; Negishi, E. *Tetrahedron Lett.* **1999**, *40*, 431–434. (e) Anastasia, L.; Xu, C.; Negishi, E. *Tetrahedron Lett.* **2002**, *43*, 5673–5676. (f) Ogawa, Y.; Maruno, M.; Wakamatsu, T. *Heterocycles* **1995**, *41*, 2587–2599. (g) Pale, P.; Chuche, J. *Tetrahedron Lett.* **1987**, *28*, 6447–6450. (h) Dalla, V.; Pale, P. *Tetrahedron Lett.* **1994**, *35*, 3525–3528. (i) Pale, P.; Chuche, J. *Eur. J. Org. Chem.* **2000**, 1019–1025. (j) Patil, N. T.; Pahadi, N. K.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 4564–4565.

(7) (a) Asao, N.; Kasahara, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 3504–3506. (b) Ezquerra, J.; Pedregal, C.; Lamas, C. *J. Org. Chem.* **1996**, *61*, 5804–5812. (c) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126–1136.

DOI: 10.1021/jo902051g
Published on Web 10/28/2009

SCHEME 1. Representative Reactions of Isochromenyliums with Olefins and Nucleophiles



frameworks[9a−e] (reaction b in Scheme 1) through a [4+2]- or a [3+2]-cycloaddition process, respectively. In addition, they are able to react with a variety of nucleophiles, affording the corresponding 1*H*-isochromene products[6a,11a,d,f] (reaction c in Scheme 1). Among these recent methodologies, due to the excellent alkynophilicity, the gold-based alkyne activation has attracted special attention as a flexible catalytic strategy for various efficient cascade transformations.[13,14] However, optimization of those unsatisfactory cases is rather difficult in the protocols using the in situ generated isochromenylium intermediates for many unknown factors associated with inaccurate stoichiometry of reactants and reagents. For the first time, we successfully prepared and characterized a number of air- and moisture-stable and storable isochromenylium tetrafluoroborates (ICTBs) without using any metals.[15] Furthermore, these stable ICTBs could be used as a regular reagent and retain the high reactivity with various olefins (reaction d in Scheme 1).[15] Unambiguously, the isolation and application of the air- and moisture-stable isochromenylium salts would greatly facilitate the discovery of novel transformations and show the versatility of future methodologies.

As a powerful methodology, cycloisomerization has been proven an atom-economic and environmentally benign efficient access[16] to a wide spectrum of structural motifs of

---

(8) (a) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764–765. (b) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: New York, 2000. (c) Mondal, S.; Nogami, T.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* **2003**, *68*, 9496–9498. (d) Patil, N. T.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 5139–5142. (e) Wei, L.-M.; Lin, C.-F.; Wu, M.-J. *Tetrahedron Lett.* **2000**, *41*, 1215–1218. (f) Murahashi, S.-I.; Davies, S. G., Eds. *Transition Metal Catalysed Reactions*; Blackwell Science: Cambridge, MA, 1999. (g) Nakamura, H.; Ohtaka, M.; Yamamoto, Y. *Tetrahedron Lett.* **2002**, *43*, 7631–7633.

(9) (a) Iwasawa, N.; Shido, M.; Maeyama, K.; Kusama, H. *J. Am. Chem. Soc.* **2000**, *122*, 10226–10227. (b) Iwasawa, N.; Shido, M.; Kusama, H. *J. Am. Chem. Soc.* **2001**, *123*, 5814–5815. (c) Kusama, H.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2002**, *124*, 11592–11593. (d) Kusama, H.; Funami, H.; Shido, M.; Iwasawa, N. *J. Am. Chem. Soc.* **2005**, *127*, 2709–2716. (e) Miura, T.; Kiyota, K.; Kusama, H.; Lee, K.; Kim, H.; Kim, S.; Lee, P. H.; Iwasawa, N. *Org. Lett.* **2003**, *5*, 1725–1728. (f) Maeyama, K.; Iwasawa, N. *J. Am. Chem. Soc.* **1998**, *120*, 1928–1929. (g) Miura, T.; Iwasawa, N. *J. Am. Chem. Soc.* **2002**, *124*, 518–519. (h) McDonald, F. E. *Chem.—Eur. J.* **1999**, *5*, 3103–3106. (i) Bruneau, C.; Dixneuf, P. H. *Acc. Chem. Res.* **1999**, *32*, 311–323.

(10) (a) Hildebrandt, D.; Hüggenberg, W.; Kanthak, M.; Dyker, G. *Chem. Commun.* **2006**, 2260–2261. (b) Kusama, H.; Funami, H.; Takaya, J.; Iwasawa, N. *Org. lett.* **2004**, *6*, 605–608. (c) Kusama, H.; Ishida, K.; Funami, H.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4903–4905. (d) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167–182. (e) Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328–2334. (f) Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A. M. *Chem.—Eur. J.* **2006**, *12*, 5916–5923. (g) Marco-Contelles, J.; Soriano, E. *Chem.—Eur. J.* **2007**, *13*, 1350–1357.

(11) (a) Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 9028–9029. (b) Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J. M. *Org. Lett.* **2003**, *5*, 4121–4123. (c) Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J. M. *Adv. Synth. Catal.* **2005**, *347*, 526–530. (d) Barluenga, J.; Vázquez-Villa, H.; Merino, I.; Ballesteros, A.; González, J. M. *Chem.—Eur. J.* **2006**, *12*, 5790–5805. (e) Yue, D.; Cá, N. D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1581–1584. (f) Yue, D.; Cá, N. D.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3381–3388. (g) Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 9643–9647.

(12) (a) Singh, V.; Krishna, U. M.; Vikrant, V.; Trivedi, G. K. *Tetrahedron* **2008**, *64*, 3405–3428. (b) Tovar, J. D.; Swager, T. M. *J. Org. Chem.* **1999**, *64*, 6499–6504. (c) Goldfinger, M. B.; Crawford, K. B.; Swager, T. M. *J. Am. Chem. Soc.* **1994**, *116*, 7895–7896.

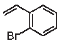
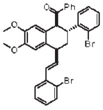
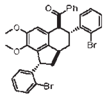
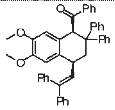
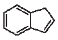
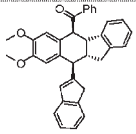
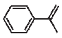
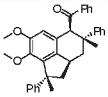
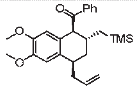
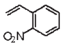
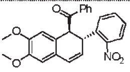
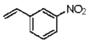
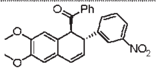
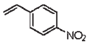
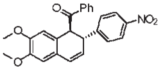
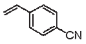
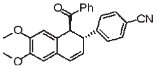
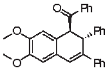
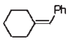
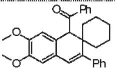
(13) (a) Takaya, J.; Udagawa, S.; Kusama, H.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4906–4909. (b) Kusama, H.; Ishida, K.; Funami, H.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4903–4905. (c) Bhunia, S.; Wang, K.-C.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2008**, *47*, 5063–5066. (d) Hsu, Y.-C.; Ting, C.-M.; Liu, R.-S. *J. Am. Chem. Soc.* **2009**, *131*, 2090–2091. (e) Oh, H. C.; Lee, J. H.; Lee, S. J.; Kim, J. I.; Hong, C. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7505–7507. (f) Oh, H. C.; Lee, J. H.; Lee, S. J.; Yi, H. J.; Hong, C. S. *Chem.—Eur. J.* **2009**, *15*, 71–74.

(14) (a) Dyker, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 4237–4239. (b) Hashmi, A. S. K. *Gold Bull.* **2003**, *36*, 3. (c) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858–10859. (d) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962–6963.

(15) Hu, Z.-L.; Qian, W.-J.; Wang, S.; Wang, S.-Z.; Yao, Z.-J. *Org. Lett.* **2009**, *11*, 4676–4679.

(16) (a) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1–16. (b) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813–834. (c) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431–436.

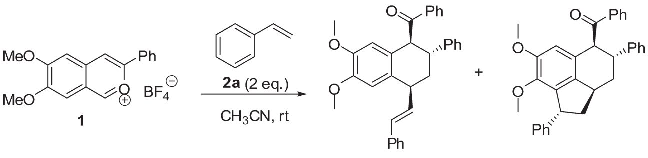
TABLE 1. Reactions of Isochromenylium Tetrafluoroborate 1 with Styrenes and Allylsilane[a]

entry	olefins **2**	products **3/4**	yields [%]
1	**2a**	**3a** and **3a'**	51 (**3a**) 20 (**3a'**)
2	 **2b**	 **3b**  **3b'**	39 (**3b**) 32 (**3b'**)
3	 **2c**	 **3c**	68
4[b]	 **2d**	 **3d**	68
5[c]	 **2e**	 **3e**	48
6[d]	 **2f**	 **3f**	97
7[e]	 **2n**	 **4a**	83
8[e]	 **2o**	 **4b**	75
9[e]	 **2p**	 **4c**	71
10	 **2q**	 **4d**	62
11[e]	 **2r**	 **4e**	80
12[e]	 **2s**	 **4f**	56

[a] A mixture of ICTB **1** (0.1 mmol) and olefin **2** (0.2 mmol) in anhydrous MeCN (5 mL) was stirred at 25 °C for 1 h. [b] 25 °C, 8 h. [c] Other double-olefin-addition products were also isolated as an inseparable mixture of *E*- and *Z*-olefin isomers (~30% yield based on **1**, detected by MS). [d] The reaction time was 10 min. [e] 60 °C, 1 h.

natural and unnatural functional molecules and useful building blocks of multiple-ring systems in organic synthesis. Encouraged by our recent achievement in stable ICTBs,[15] we extended our further methodology exploration to the new cascade transformations building multiple ring-containing frameworks of biologically important natural products.[17] In this article, we wish to report our results in the development of novel metal-free efficient cascade reactions suitable for constructing polycyclic frameworks with the stable ICTBs.

SCHEME 2. Direct Reaction of ICTB 1 with Styrene 2a



1

3a (51%) (x-ray)

3a' (20%) (x-ray)

Results and Discussion

Using the representative stable isochromenylium tetrafluoroborate **1** as the discovery platform, a wide range of olefins were examined. More differently from our previous observation,[15] successive additions of 2 equiv of styrene-type olefins and allylsilane to ICTB **1** were first observed in our study (Table 1). For instance, reaction of **1** with styrene **2a** (2 equiv) afforded two products **3a** (51%) and **3a'** (20%) (Scheme 2), whose structures and relative configurations were determined by the corresponding 2D NMR studies and further confirmed by their X-ray crystallographic analyses (see the Supporting Information). Reducing the amount of styrene **2a** to 1.0 equiv did not significantly affect the ratio of products **3a** (21% yield of **3a** basis on **1**) and **3a'** (12%), except their relatively lower yields.

Similar results were also observed in other reactions with styrenes **2b**−**e** without strong electron-withdrawing substituent(s) (Table 1, entries 2−5), as well as allyltrimethylsilane **2f** (entry 6). In the latter case, two molecules of allylsilane **2f** were incorporated into the final product, and one molecule of trimethylsilane, instead of a proton, was eliminated at the final stage of the cascade process. Exceptionally, reactions with four styrenes **2n**−**q** bearing a strong electron-withdrawing group gave the monoadducts **4a**−**d** (entries 7−10), which were thought to follow our previously proposed pathway.[15] In addition, reactions with disubstituted or trisubstituted styrenes **2r** and **2s** also stopped at the single-olefin-addition stage, affording 1,2-dihydronaphthalenes **4e** and **4f** (entries 11 and 12).

As far as we know, few examples have been reported incorporating 2 equiv of olefins in the cascade reactions involving isochromenylium intermediates. According to our above results, a mechanistic explanation is proposed as Figure 1. At first, [4+2]-cycloaddition takes place between the isochromenylium oxa-diene **1** and styrene **2a**, giving a bridged oxonium intermediate A (Figure 1A). This intermediate then counterpoises to the other open form B, which is immediately trapped by the second molecule of styrene **2a** to afford a new intermediate C. At this stage, two pathways compete with each other: In path a, a proton is eliminated to give the olefin product **3a**; while path b undergoes a

---

(17) (a) Don, M.-J.; Shen, C.-C.; Syu, W.-J.; Ding, Y.-H.; Sun, C.-M. *Phytochemistry* **2006**, *67*, 497–503. (b) Xu, J.; Chang, J.; Zhao, M.; Zhang, J.-S. *Phytochemistry* **2006**, *67*, 795–799. (c) Nimgirawath, S.; Udomputtimekakul, P.; Taechowisan, T.; Wanbanjob, A.; Shen, Y. *Chem. Pharm. Bull.* **2009**, *57*, 368–376. (d) Ma, W.; Ma, X.; Lu, Y.; Chen, D. *Helv. Chim. Acta* **2009**, *92*, 709–715. (e) Messiano Gisele, B.; Nascimento Isabele, R.; Lopes Lucia, M. X. *Phytochemistry* **2009**, *70*, 590–596. (f) Clayden, J.; Kenworthy, M. N.; Helliwell, M. *Org. Lett.* **2003**, *5*, 831–834.

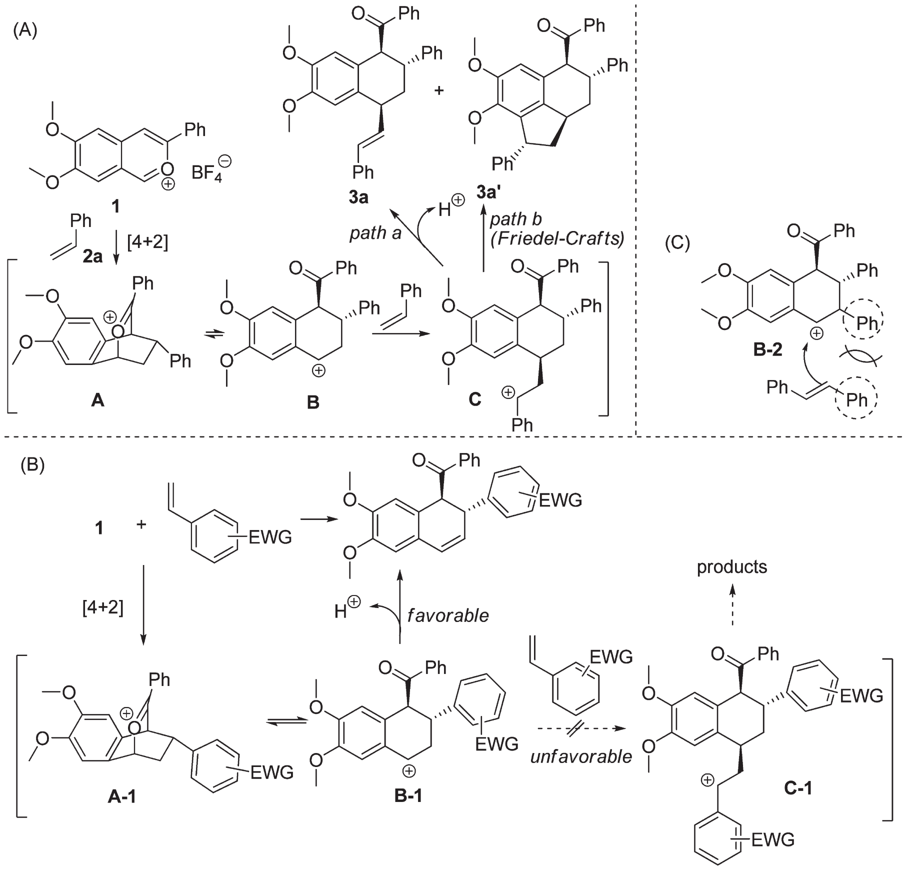
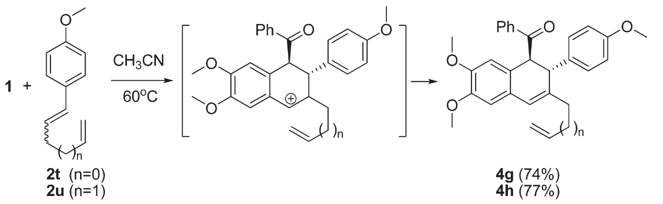


FIGURE 1. Proposed mechanism for reactions of ICTB **1** with various styrenes.

SCHEME 3. Reactions of ICTB 1 with Styrenes 2t and 2u



Friedel−Crafts reaction to afford a more complex tricyclic compound **3a′**. For those styrene substrates having electron-withdrawing group(s) (Table 1, entries 7−10), the further reaction with the second molecule of styrene is electronically unfavorable (to give the less stable carbocation **C-1**, Figure 1B) and thus less competitive in dynamics. In contrast, elimination of a proton from the intermediate **B-1** is a more favorable pathway and results in a fast reaction providing the 1,2-dihydronaphthalene products. In the reaction with (*E*)-1,2-diphenylethene (Table 1, entry 11), approach of the second molecule of (*E*)-1,2-diphenylethene to intermediate **B-2** is spatially unfavorable (Figure 1C). Such explanation is also eligible to the last example in Table 1 (entry 12).

The above cascade chemistry of stable ICTBs unambiguously provides us new insights into their potential applications in constructing novel multiring frameworks. To further explore the kinetically favorable type of C−C double bond between the terminal olefin and styrene, as well as the possible prolonged cationic cascade with the second olefin, two additional styrenes **2t** and **2u** were then designed and examined (Scheme 3). Under the same conditions, the terminal olefin functionality in both cases did not participate in the reactions, and no further extended cascades were observed. Obviously, styrene-type olefins are the preferred reaction partner for ICTB **1**, providing 1,2-dihydronaphthalenes **4g** and **4h** in 74% and 77% yield, respectively.

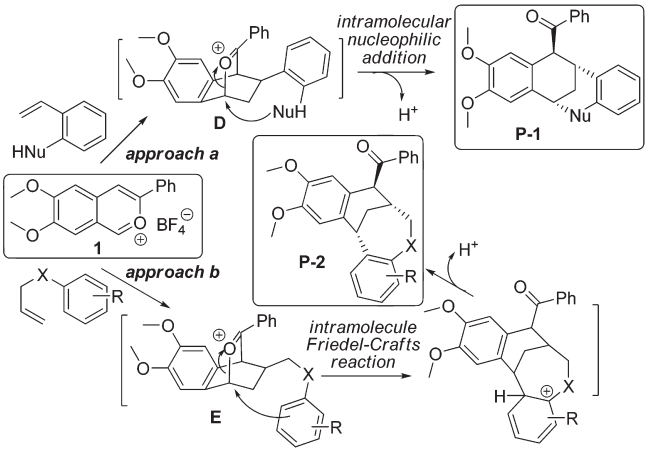
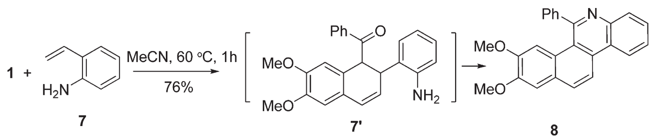


FIGURE 2. Design of cascade reactions for bridged-ring frameworks **P-1** and **P-2**.

Because intramolecular capture of the carbocation intermediates by additional C−C double bonds failed (Scheme 3), devising alternative suitable C-, O-, or N-based functionalities was considered to intramolecularly receive the carbocation

SCHEME 4. Reaction of ICTB 1 with *o*-Vinylaniline 7

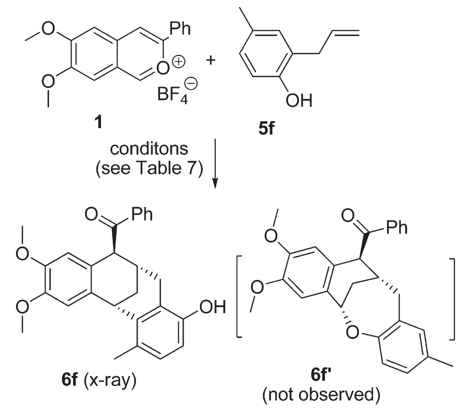


intermediates at the stage of intermediates D and E (Figure 2). If this new design works, two different types of bridged-ring frameworks would be furnished after the corresponding cascade reactions.

o-Vinylaniline **7** was first examined to react with ICTB **1** in MeCN. After treatment for 24 h at room temperature, the reaction became very complicated and did not afford any expected products. When the reaction temperature was raised to 60 °C, after 1 h, a single benzophenanthridine derivative **8** was afforded instead of the expected bridged product (**P-1**, Figure 2) (Scheme 4). Undoubtedly, benzophenanthridine **8** was produced via a [4+2]-cycloaddition of ICTB **1** with styrene **7** followed by a dehydrative imine-cyclization and an auto-oxidative aromatization.

To dismiss the undesired intramolecular imine-cyclization, olefin substrate **5f** containing a phenol hydroxyl group was then examined under the same conditions. Theoretically, reaction of **1** with olefin-phenol **5f** would give two possible products **6f** and **6f′** according to the analysis in Figure 2. However, only [4.1.4]-bicyclic product **6f** was afforded in this reaction (Table 2). The structure and relative chemistries of **6f** were confirmed by its X-ray single crystallographic study. Optimization of the reaction conditions showed that MeCN was the most suitable solvent for this type of cascade reaction (Table 2), and increasing the amount of olefin **5f** (to 2.4 equiv) could not further accelerate the reaction and improve the yield of product (entry 8). It is speculated that the transition state(s) leading to [4.1.4]-bicyclic framework **6f** might be more favorable in energy than that for the other theoretically possible [4.1.5]-bicyclic product **6f′**.

TABLE 2. Reaction of ICTB 1 with 2-Allylphenol 5f[a]



entry	solvent	temp [°C]	time [h]	product	yield [%]
1	MeCN	60	5	**6f**	66
2	THF	60	24	**6f**	27
3	toluene	60	24	**6f**	18
4	1,2-DCE	60	24	**6f**	43
5[b]	DCM	40	24	**6f**	15
6	MeCN	25	24	**6f**	24
7[b]	MeCN	80	5	**6f**	62
8[c]	MeCN	60	5	**6f**	68
9	MeCN	60	24	**6f**	61

[a] A mixture of ICTB **1** (0.1 mmol) and olefin **5f** (0.12 mmol) in anhydrous solvent (5 mL) was stirred for the indicated times. [b] The reaction was carried out under reflux. [c] Olefin **5f** (0.24 mmol) was used.

Prompted by the above achievement, a variety of olefin substrates **5** were then examined under the above optimized conditions (Table 2). All these reactions provided the corresponding polycyclic structures **6** in excellent regio- and diastereoselectivities and satisfactory yields (Table 3, 57–84%). This unambiguously indicated that all these achieved cascade reactions presented very high efficiency in the whole process. Reactions of **1** with olefins **5b** and **5c** containing a phenol functionality (entries 2 and 3) and olefins **5d** and **5e** having an amide functionality (entries 4 and 5) afforded the **P-1** products (approach a, Figure 2), in which the carbocation intermediates were finally captured by the corresponding intramolecular heteroatoms. Alternatively, the **P-2** products (Figure 2, approach b) were generated in other examples where the cascade pathways were terminated by an intramolecular Friedel–Crafts reaction. In addition, excellent regioselectivities were observed in several examples (Table 3, entries 9, 13, and 15). It is believed that all these regioselectivities were determined by the favorable directions of the corresponding Friedel–Crafts reactions. For the reactions with olefins **5i** (entry 9) and **5m** (entry 13), the less hindered direction was favored in the Friedel–Crafts cyclizations, while the regio selectivity observed in the reaction with olefin **5o** (entry 15) is more likely controlled by the electron factor of the substrate, favorably occurring at the α-position of naphthalene. Unfortunately, our further attempts failed to provide the [4.1.6]-bicyclic frameworks and other larger medium-size rings.

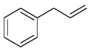
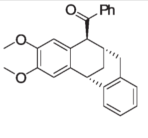
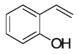
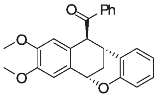
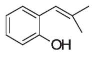
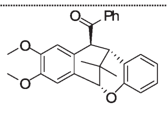
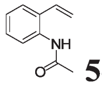
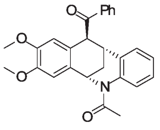
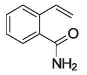
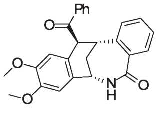
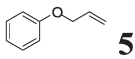
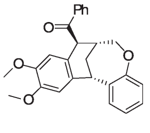
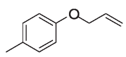
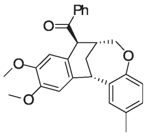
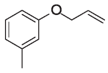
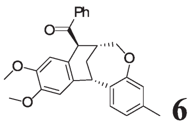
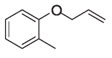
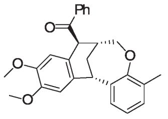
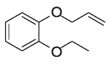
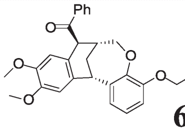
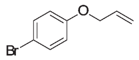
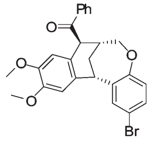
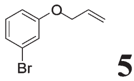
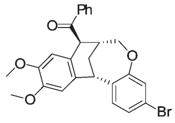
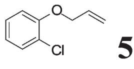
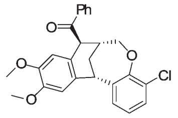
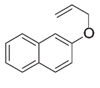
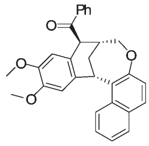
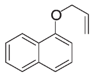
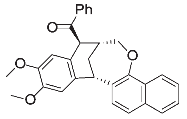
Conclusions

In summary, new metal-free cascade reactions suitable for the synthesis of several multiring frameworks have been developed in this study, utilizing the air- and moisture-stable isochromenylium tetrafluoroborates. Involvement of the successive addition of 2 equiv of olefins was observed, and their mechanisms were accordingly proposed and discussed. New methodologies applying isochromenylium chemistry were designed, explored, and optimized for efficient construction of different bridged-ring frameworks by the intramolecular capture of cationic intermediates with prefunctionalized heteroatoms or Friedel–Crafts donors. Further application of our newly developed methodology to target- and diversity-oriented organic synthesis is currently under investigation in this laboratory.

Experimental Section

Synthesis of Compound 3a. To a solution of **1** (35 mg, 0.1 mmol) in dry CH_3CN (5 mL) was added olefin **2a** (0.2 mmol) at room temperature under N_2 atmosphere. After the starting material was consumed, saturated aqueous $NaHCO_3$ (5 mL) was added. The mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 4:1) to give pure products **3a**. Yellow oil; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.78 (d, $J = 7.8$ Hz, 2H), 7.49

TABLE 3. Reactions of ICTB 1 with Functionalized Alkenes 5[a]

entry	olefin **5**	product **6**	yield [%]
1	 **5a**	 **6a**	61
2	 **5b**	 **6b**	74
3	 **5c**	 **6c**	64
4	 **5d**	 **6d**	83
5	 **5e**	 **6e**	71
6	**5f**	**6f**	66
7	 **5g**	 **6g**	70
8	 **5h**	 **6h**	73
9	 **5i**	 **6i**	83
10	 **5j**	 **6j**	80
11	 **5k**	 **6k**	71
12[b]	 **5*l***	 **6*l***	60
13[b]	 **5m**	 **6m**	62
14[b]	 **5n**	 **6n**	57
15	 **5o**	 **6o**	84
16	 **5p**	 **6p**	71

[a] A mixture of ICTB **1** (0.1 mmol) and olefin **5** (0.12 mmol) in anhydrous MeCN (5 mL) was stirred at 60 °C for 5 h. [b] The reaction time was 10 h.

(t, $J = 7.4$ Hz, 1H), 7.30−7.41 (m, 6H), 7.12−7.25 (m, 6H), 6.76 (s, 1H), 6.41−6.53 (m, 3H), 4.88−4.90 (d, $J = 7.6$ Hz, 1H), 3.83 (s, 3H), 3.67 (s, 3H), 3.60−3.65 (m, 2H), 2.28 (ddd, $J = 5.5$, 9.7, 15.2 Hz, 1H), 2.17 (ddd, $J = 3.5$, 5.3, 13.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.5, 148.1, 148.0, 143.5, 137.5, 137.4, 134.3, 132.8, 131.1, 130.5, 128.7, 128.6, 127.4, 127.3, 126.7, 126.6, 126.3, 112.6, 111.2, 55.9, 55.8, 54.4, 40,8, 40.3, 35.2; IR (KBr) ν_{max} 3057, 2962, 1672, 1515, 1260, 798, 692 cm^{-1}; ESI-MS (*m*/*z*) 497 [M + Na$^+$]; HRMS (ESI) calcd for $C_{33}H_{30}O_3Na$ [M + Na$^+$] 497.2093, found 497.2084.

Syntheses of Compound 6a. To a solution of **1** (35 mg, 0.1 mmol) in dry CH_3CN (5 mL) was added olefin **5a** (0.12 mmol) at room temperature under N_2 atmosphere. The resulting mixture was stirred at 60 °C until the starting material was consumed. Saturated aqueous $NaHCO_3$ (5 mL) was added and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 4:1) to give pure products **6a**. White solid; mp 62−64 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.08−8.11 (m, 2H), 7.53−7.67 (m, 3H), 7.24−7.28 (m, 1H), 7.08−7.11 (m, 3H), 6.79 (s, 1H), 6.30 (s, 1H), 4.66 (s, 1H), 3.93 (s, 1H), 3.88 (s, 3H), 3.65 (s, 3H), 3.44 (dd, $J = 8.1$, 17.7 Hz, 1H), 3.01 (d, $J = 18.0$ Hz, 1H), 2.75−2.78 (m, 1H), 2.30−2.36 (m, 1H), 1.93−1.99 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.3, 148.1, 147.5, 142.4, 136.7, 135.4, 133.5, 133.2, 129.3, 128.9, 128.7, 127.3, 126.2, 125.9, 123.8, 112.8, 110.7, 55.9, 55.8, 53.7, 39.4, 36.6, 29.6, 25.9; IR (KBr) ν_{max} 2931, 1682, 1515, 1448, 1259, 1221, 1124, 738, 699 cm^{-1}; ESI-MS (*m*/*z*) 385 [M + H$^+$]; HRMS (ESI) calcd for $C_{26}H_{25}O_3$ [M + Na$^+$] 385.1800, found 385.1798.

Reaction of ICTB 1 with 2-Vinylaniline 7. To a solution of **1** (35 mg, 0.1 mmol) in dry CH_3CN (5 mL) was added olefin **7** (0.1 mmol) at room temperature under N_2 atmosphere. The resulting mixture was stirred at 60 °C until the starting material was consumed. Saturated aqueous $NaHCO_3$ (5 mL) was added, and the mixture was extracted with ethyl acetate (3×10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 2:1) to give **8** (27 mg, 76%). Yellw solid; mp 150−154 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.65 (d, $J = 7.2$ Hz, 1H), 8.58 (d, $J = 8.7$ Hz, 1H), 8.25 (d, $J = 6.6$ Hz, 1H), 8.08 (d, $J = 8.7$ Hz, 1H), 7.47−7.76 (m, 7H), 7.32 (s, 1H), 7.25 (s, 1H), 4.02 (s, 3H), 3.32 (s, 3H); IR (KBr) ν_{max} 1611, 1515, 1472, 1218, 1047, 863, 796, 761, 516 cm^{-1}; ESI-MS (m/z) 366 [M + H$^+$]. Anal. Calcd for $C_{25}H_{19}NO_2$: C, 82.17; H, 5.24; N, 3.83. Found: C, 82.22; H, 5.19; N, 3.64.

Acknowledgment. This project was financially supported by MOST (2010CB832200), MOH (2009ZX09501), NSFC (20672128), CAS (KJCX2-YW-H08), and SHMCST (08JC1422800). Y.Z.J. is a principal investigator of the e-Institute of Chemical Biology of Shanghai Universities.

Supporting Information Available: Experimental details and characterizations of new compounds, NMR copies of new compounds (PDF), and X-ray crystal data of **3a**, **3a′**, and **6f** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.