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Three-Component Reactions of Isochromenylium Tetrafluoroborates via Non-Classical [4+2]-Intermediates: Mild One-Step Metal-Free Synthesis of Functionalized Dihydronaphthalenes and Tetrahydronaphthalenes

Zhi-Long Hu,[a] Zhen-Yu Yang,[a] Shaozhong Wang,[b] and Zhu-Jun Yao*[a, b]

Abstract: Two novel types of elegant three-component reactions of stable isochromenylium tetrafluoroborates (ICTBs) have been developed under mild metal-free conditions in this work. Mechanistically, these reactions are commonly initiated by a [4+2]-cycloaddition between the non-classical isochromenylium diene and the aldehyde–enol, and terminated by the following addition of weak nucleophiles, including nitriles or the second equivalent of aldehydes, in a one-pot fashion. The developed methodologies exhibit excellent chemoselectivity, regioselectivity, and diastereoselectivity, and provide a new convenient access to functionalized dihydronaphthalenes and tetrahydronaphthalenes.

Keywords: aldehydes · cascade reactions · cycloaddition · multicomponent reactions · naphthalenes

Introduction

Isochromenylium tetrafluoroborates (ICTBs) are a type of stabilized reactive intermediate recently developed by our group,[1] and they can be used as regular reagents in the laboratory. These crystalline materials are considerably stable under air and moisture conditions, but retain high reactivities in organic media with various nucleophiles,[1c] olefins, and electron-rich arenes.[1a–b] Many ICTB-based reactions produce cascade reactions and can be carried out under mild conditions without any assistance of metal catalysts and promoters. These properties of ICTBs also make them very useful for the development of new multistep transformations to construct complex frameworks. Rapid synthesis of complex molecules in a single operation without isolation of intermediates is one of the current concerns of the synthetic community.[2] Recently, cascade multicomponent reactions (CMCR) have emerged as powerful and efficient bond-forming tools that allow the preparation of polycyclic targets by connecting several components in one pot by efficient sequential chemical reactions.[3] Compared with reactions that use in situ generated metallic isochromenylium intermediates with metal catalysts or promoters,[4–12] ICTB-based reactions have shown many significant differences in their reaction behavior, products, and mechanisms. Such unique properties of ICTBs definitely provide us with new opportunities to discover novel useful chemical transformations. To further understand the ambiguous mechanisms involving the reactive isochromenylium intermediates, reactions of stable ICTBs with aldehydes (or their enol equivalents) were thus investigated. Several previous studies have shown that metallic isochromenylium-based reactions can produce complex multiring frameworks[9a,10a] (Scheme 1a and b) and naphthalene derivatives[5c–d] (Scheme 1c), but a number of sensitive functional groups could not be tolerated under such strong Lewis acid based conditions.[13] However, up until now, direct reactions of stable ICTBs with electron-rich compounds, as well as their further conversions, have not been much explored. As a new type of stabilized reactive agent, ICTBs are potentially useful for future industrial applications, besides their value in mechanistic studies. ICTB-based reactions usually do not need any metal catalysts or promoters and can be carried out by direct treatment with reaction partners at ambient temperatures. In this article, we wish to report two new types of three-component reactions of ICTBs under mild metal-free conditions

[a] Dr. Z.-L. Hu, Dr. Z.-Y. Yang, Prof. Dr. Z.-J. Yao
State Key Laboratory of Bioorganic and Natural Products Chemistry
EISU Chemical Biology Division, Shanghai Institute of
Organic Chemistry, Chinese Academy of Sciences
345 Lingling Road, Shanghai 200032 (China)
Fax: (+86) 215-492-5123
E-mail: yaoz@sioc.ac.cn

[b] Dr. S. Wang, Prof. Dr. Z.-J. Yao
Nanjing National Laboratory of Microstructures
School of Chemistry and Chemical Engineering
Nanjing University, 22 Hankou Road
Nanjing 210093, Jiangsu (China)

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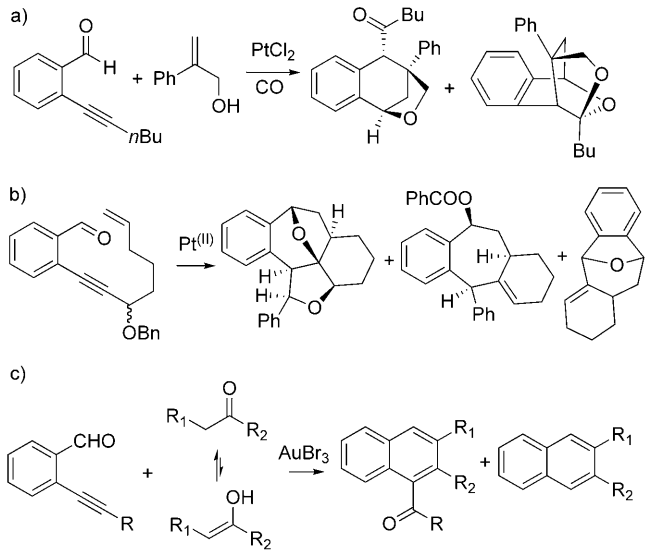
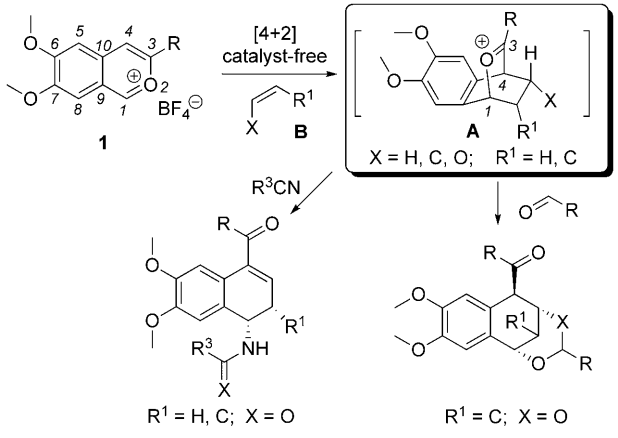


Scheme 1. Several representative reactions with an in situ generated [4+2]-isochromenylium intermediate.

(Scheme 2). These newly developed cascade reactions provide a new convenient one-step entry to functionalized dihydronaphthalenes and tetrahydronaphthalenes, which are widely found as core structures in many bioactive natural products and pharmaceutically important compounds,[14] with high synthetic efficiency and excellent chemo-, regio-, and diastereoselectivity.

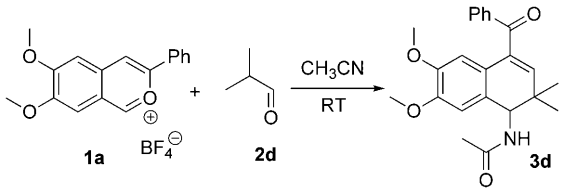


Scheme 2. Outline of the three-component reactions in this work.

Results and Discussion

In our previous investigations, the Huckel aromatic pyrylium part of ICTBs **1** has shown typical properties as a non-classical 2-oxonium 1,3-diene.[1a,b] The reactive [4+2]-adduct (Scheme 2, **A**) was commonly thought to be generated upon treatment with various olefins. We believe that the C1 carbon of this intermediate is the equivalent of a masked carbocation, which should have the capability to receive the attacks from proper nucleophiles inter- or intramolecularly. Such inference prompts us to attempt to introduce some heteroatom-based fucntionalities into the naphthalene skeleton. As a result, a variety of functionalized dihydronaphthalene or tetrahydronaphthalene derivatives could be obtained. Unfortunately, the C1 carbon of ICTBs **1** is highly reactive in solution,[1c] and many regular nucleophiles, such as free amino- and hydroxyl-containing substrates, are not amenable to such one-pot cascade transformations. The determination of suitable nucleophiles applicable to these transformations is thus a crucial challenge in this work. With our previous knowledge of ICTBs, we started our exploration of novel three-component reactions of ICTBs with nitriles, a type of very weakly nucleophilic nitrogen source.

Three-component reactions of ICTBs with aldehydes and nitriles: First, the direct treatment of ICTB **1a** (1.0 equiv) with isobutyraldehyde (**2d**, 1.2 equiv) in dry acetonitrile at room temperature was employed as the assessment and optimization platform. An unusual dihydronaphthalen-acetamide **3d** was isolated in 37% yield after 48 h in our initial experiment (Scheme 3). When the amount of aldehyde **2d**

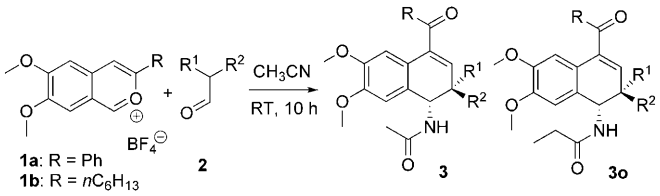


2d	reaction time	yield of 3d
1.2 equiv	48 h	37%
2.0 equiv	48 h	51%
3.0 equiv	48 h	67%
4.0 equiv	24 h	84%
5.0 equiv	10 h	86%

Scheme 3. Reactions of ICTB **1a** with isobutyraldehyde **2d** in acetonitrile.

was increased to 4.0 equivalents, the yield of product **3d** could be improved up to 84%. The structure of **3d** was assigned by the use of ^{1}H and ^{13}C NMR spectra and mass spectrometry, and confirmed by comparison with another product **3h** (the structure of which was determined by X-ray crystallographic analysis) in our further study (see Table 1 and Figure 1).[15] With these results, we believed that acetonitrile did participate in this reaction as a nucleophile attacking the C1 carbon of intermediate **A** at the second stage of the cascade transformations (Scheme 2). Mechanistic analysis also showed that the enol derived from aldehyde **2d** was the real reactant with the ICTB oxa-diene in the first step.[5c] This mild one-step three-component procedure is considerably useful for the introduction of nitrogenous functionality into the dihydronaphthalene skeleton, especially for compounds that are labile under metallic Lewis acid based conditions.

Table 1. Reactions of ICTBs **1** with aldehydes **2** in acetonitrile.[a]



Entry	1	2 (R^1, R^2)	3	Yield [%][b]
1[c]	**1a**	**2a** (H, H)	**3a**	69
2[d]	**1a**	**2b** (Me, H)	**3b**	79
3	**1a**	**2c** (Et, H)	**3c**	81
4	**1a**	**2d** (Me, Me)	**3d**	84
5	**1a**	**2e** ($CH_3(CH_2)_3$, H)	**3e**	83
6	**1a**	**2f** (-$(CH_2)_5$-)	**3f**	81
7	**1a**	**2g** ($AcOCH_2CH_2$, H)	**3g**	78
8	**1a**	**2h** ($ClCH_2CH_2$, H)	**3h**	80
9	**1a**	**2i** ($BnOCH_2$, H)	**3i**	64
10	**1a**	**2j** ($BnOOCCH_2$, H)	**3j**	72
11	**1a**	**2k** ($NO_2CH_2CH_2$, H)	**3k**	71
12[e]	**1a**	**2l** (Ph, Me)	**3l**	77 (d.r. 5.4/1)
13	**1a**	**2m** (allyl, H)	**3m**	71
14	**1b**	**2d** (Me, Me)	**3n**	74
15[f]	**1a**	**2o** ($BrCH_2(CH_2)_3$, H)	**3o**	76
16[e]	**1a**	**2p** (allyl, Me)	**3p**	72 (d.r. 3/1)
17	**1a**	**2q** (allyl, allyl)	**3q**	75

[a] A mixture of **1** (0.5 mmol, 1.0 equiv) and **2** (2.0 mmol, 4.0 equiv) in acetonitrile (10 mL) was stirred for 10 h at 25 °C. [b] Yields of the isolated, analytically pure products. [c] 20.0 equiv of **2a** was used in a sealed tube. [d] 10.0 equiv of **2b** was used in a sealed tube. [e] The d.r. value was determined by ^{1}H NMR spectroscopy. [f] Propionitrile was used as the solvent. Bn = benzyl.

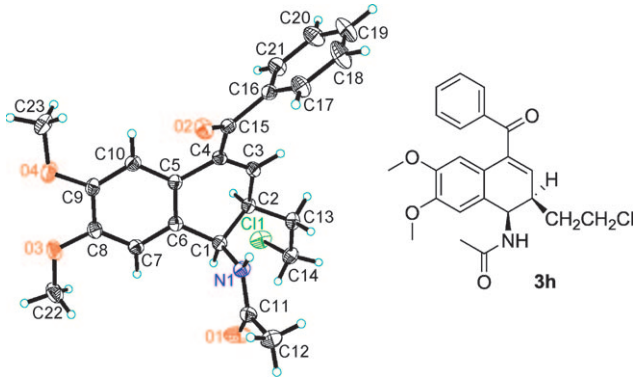
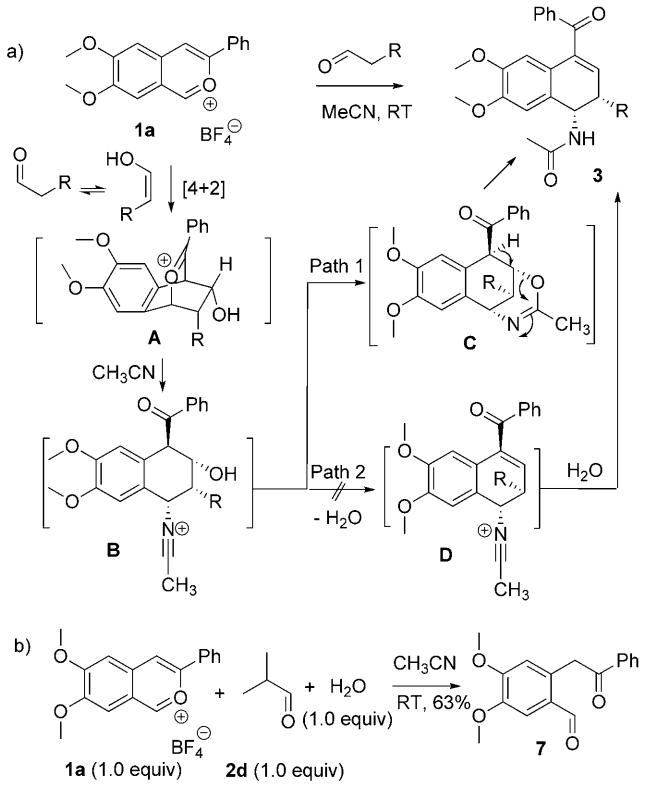


Figure 1. X-ray crystal structure of **3h**.

Encouraged by the above results, a number of other linear and cyclic aliphatic aldehydes containing halogen, ether (as alcohol protecting groups), carboxylic acid ester, or nitro functionalities were then examined (Table 1). Under the optimized conditions (1.0 equiv of ICTBs **1** and 4.0 equiv of aldehydes **2** in dry acetonitrile at room temperature), all reactions provided the corresponding 1-acetamido-1,2-dihydronaphthalenes **3** in satisfying yields. Excellent *cis*-1,2-selectivities were observed in the products of this type of three-component reaction.[16] Reactions of **1a** with aldehydes **2m**, **2p**, and **2q** (containing a C=C bond) afforded the single products **3m**, **3p**, and **3q**, respectively, and the other possible product resulting from a [4+2]-cycloaddition of **1a** with the non-enol C=C bond was not detected. An explanation is that the enol C=C bond isomerized from aldehyde **2m** is more electron-rich than the regular C=C bond, and the reaction with the enol C=C bond proceeds preferentially through a reverse-electron-demand Diels–Alder reaction.[17] As far as we know, this is the first report of incorporating both an aldehyde and a nitrile into the isochromenylium-intermediate-mediated cascade transformation. Therefore, our findings present a new type of three-component cascade reaction.

Based on our observations, a mechanistic explanation is proposed in Scheme 4. At first, an *endo*-[4+2]-cycloaddition takes place between the isochromenylium oxa-diene **1a** and

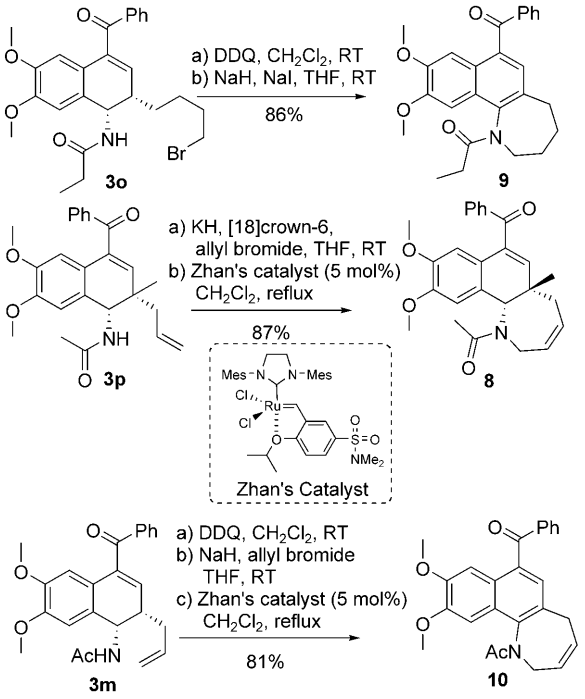


Scheme 4. Proposed mechanisms for the reactions of ICTB **1a** with aldehydes **2** in acetonitrile.

the *cis*-enol (according to the *cis*-configuration of the 1,2-substituents of products **3**) converted from aldehyde **2**, giving a bridged oxonium intermediate, **A** (Scheme 4a, **A**). This bridged [4+2]-adduct is immediately opened by the nitrogen of acetonitrile from the smaller steric direction and converted into a new intermediate, **B**. At this stage, two pathways might compete with each other. Through path 1, an intramolecular nucleophilic addition and cyclization by the free hydroxyl group to the carbocation of intermediate **B** takes place, providing a new bridged intermediate, **C**. Final proton elimination followed by bridge-opening afforded the final product **3**. The other possible pathway

(Scheme 4a, path 2) proceeds with dehydration at first to afford the intermediate, **D**, the carbocation of which is immediately attacked by water to give the final product **3**. To determine the most likely pathway (path 1 or path 2), a mixture of salt **1a** (1.0 equiv), aldehyde **2d** (1.0 equiv), and H_2O (1.0 equiv) in acetonitrile was treated for 24 h at room temperature (Scheme 4b). Instead of the previously observed product **3d**, only the hydrolysis product **7** was observed. With this evidence, we believe that dehydration did not happen in this type of cascade reaction and that path 1 is the more plausible route to give the products **3**.

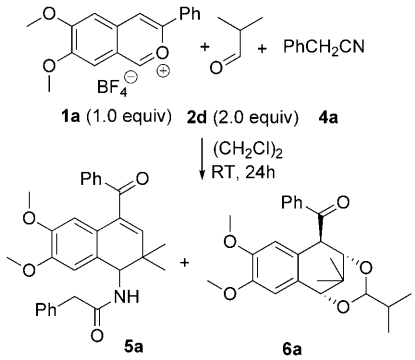
The so-formed products **3** could be applied to further syntheses. For example, a fused tricyclic compound **9** could be synthesized from dihydronaphthalene **3o** by oxidative aromatization and intramolecular nucleophilic substitution (2 steps, 86% yield). Using ring-closing metathesis (RCM) as the cyclization method, tricyclic compounds **8** and **10** could be smoothly prepared in good overall yields from dihydronaphthalenes **3p** and **3m** (87% yield in 2 steps; and 81% yield in 3 steps), respectively (Scheme 5).



Scheme 5. Several applications of 1-amino-1,2-dihydronaphthalenes **3**; DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone.

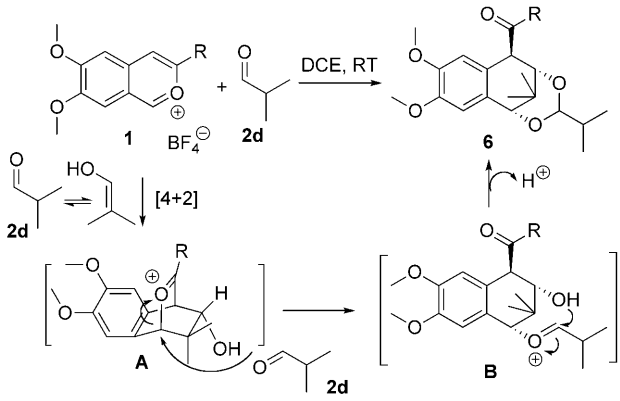
In the above reactions, acetonitrile takes part not only as a reactant, but also as the solvent. To further understand the stoichiometric relationship of the reactants, reactions with stoichiometric amounts of nitriles in a non-nucleophilic solvent 1,2-dichloroethane (DCE)[1b] were thus investigated. The reaction of ICTB **1a** (1.0 equiv) with isobutyraldehyde (**2d**, 2.0 equiv), and 2-phenylacetonitrile (**4a**, 1.0 to 5.0 equiv) at room temperature for 24 h afforded the expected dihydronaphthalene **5a** and an *O*,*O*-acetal byproduct **6a**. When 5.0 equivalents of aldehyde **2d** were used, the yield of product **5a** could be improved to 78%, and the byproduct **6a** decreased to 9% yield (Table 2). The use of 4.0 equivalents of nitrile **4a** is necessary to reach a satisfactory yield of product **5a**. These results mention that the aldehyde (through its carbonyl group) could compete with the nitrile in the nucleophilic opening of bridged oxonium intermediate **A** (Scheme 4a) during the reaction. This finding also prompted us to discover another type of three-component reaction of ICTBs (see text below and Scheme 6 for the details).

Table 2. Reaction of ICTB **1a** with isobutyraldehyde (**2d**) and 2-phenylacetonitrile (**4a**).[a]



Entry	**4a** [equiv]	Yield of **5a** [%][b]	Yield of **6a** [%][b]
1	1.0	29	44
2	2.0	39	38
3	3.0	58	25
4	4.0	76	11
5	5.0	78	9

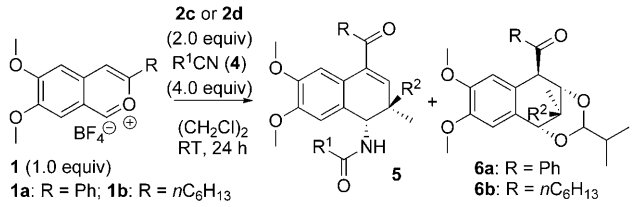
[a] See the Supporting Information for details. [b] Yield of the isolated product.



Scheme 6. Proposed mechanism for the reactions of ICTBs **1** with two equivalents of aldehyde **2d**.

The reaction conditions were optimized again during the examination of substrate scope (Table 3). Mixing ICTB **1a**

Table 3. Reaction of ICTBs **1** with propionaldehyde **2c** or isobutyraldehyde **2d** and nitriles **4**.[a]



Entry	1	4 (R^1)	2	5 (%, R^2)[b]	6 (%, R^2)[b]
1	**1a**	**4a** ($PhCH_2$)	**2d**	**5a** (76, Me)	**6a** (11, Me)
2[c]	**1a**	**4b** (Ph)	**2c**	**5b** (71, H)	**6a** (8, H)
3	**1a**	**4c** (Me)	**2d**	**5c** (57, Me)	**6a** (15, Me)
4	**1a**	**4d** (Et)	**2d**	**5d** (51, Me)	**6a** (19, Me)
5	**1a**	**4e** (PhCH=CH)	**2d**	**5e** (77, Me)	**6a** (6, Me)
6	**1a**	**4f** ($NCCH_2$)	**2d**	**5f** (68, Me)	**6a** (12, Me)
7	**1a**	**4g** ($Cl(CH_2)_3$)	**2d**	**5g** (81, Me)	**6a** (6, Me)
8	**1a**	**4h** (EtO_2CCH_2)	**2d**	**5h** (73, Me)	**6a** (6, Me)
9	**1a**	**4i** ($mNO_2C_6H_4$)	**2d**	**5i** (57, Me)	**6a** (32, Me)
10	**1b**	**4d** (Et)	**2d**	**5j** (75, Me)	**6b** (8, Me)

[a] A mixture of isochromenylium tetrafluoroborate **1** (1.0 mmol), nitrile **4** (4.0 mmol), and isobutyraldehyde **2d** (2.0 mmol) in anhydrous DCE (20 mL) was stirred at −78 °C to room temperature for 24 h (See the Supporting Information for details). [b] Yield of the isolated product. [c] Propionaldehyde **2c** was used.

(1.0 equiv), isobutyraldehyde (**2d**, 2.0 equiv), or propionaldehyde **(2c**, 2.0 equiv) and nitriles **4** (4.0 equiv) in DCE at room temperature afforded the best results. All nitriles **4** could react smoothly with **1** and **2c** or **2d**, affording 1-amido-1,2-dihydronaphthalenes **5** predominately. This type of three-component reaction can tolerate a variety of functional groups, including a double bond (Table 3, entry 5), a halogen atom (entry 7), an ester (entry 8), and a nitro group (entry 9). However, our attempt at a double-reaction with the bis-nitrile **4f** failed. It stopped at the mono-reaction stage under the above conditions, affording **5f** in 68% yield (entry 6).

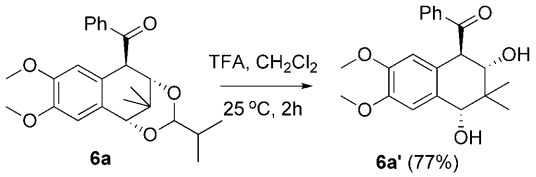
Three-component reactions of ICTBs with two molecules of aldehydes (enol and aldehyde): As motioned above, the cyclic *O*,*O*-acetals **6** were commonly identified as the minor byproducts in the reactions carried out in dry DCE (Table 3). The structure of the representative compound **6a** was first assigned by the use of ^1H and ^{13}C NMR spectroscopy and mass spectrometry, and further confirmed by 2D NMR experiments (1H–1H COSY, NOESY, HMQC, and HMBC).[19] According to the mechanisms of the above three-component reactions, byproducts **6** might be generated from the reaction of one equivalent of ICTB and two equivalents of aldehyde (Scheme 6). After the [4+2]-cycloaddition between the isochromenylium oxa-diene **1** and the enol (derived from the first molecule of aldehyde **2d**), the C1 carbon of the resulting bridged oxonium intermediate **A** is then attacked by the carbonyl oxygen of the second molecule of aldehyde **2d**, affording intermediate **B**. Finally, an intramolecular addition of the exposed hydroxyl to the carbonyl equivalent of **B** gives the 1,3-*syn*-cyclic *O*,*O*-acetal **6**.

Because the cyclic *O*,*O*-acetals **6** represent a category of useful tetrahydronaphthalene-1,3-diol building blocks,[20] optimization of this side reaction to a synthetically applicable methodology was then attempted under nitrile-free conditions. Again, dichloroethane was found to be the most suitable solvent for this type of reaction (Table 4). Increasing the amount of aldehyde **2d** from 2.4 equivalents to 3.6 equivalents did not further improve the yield of the product (Table 4, entries 4 and 6). Treatment of ICTB **1a** (1.0 equiv) with aldehyde **2d** (2.4 equiv) in dry DCE at room temperature afforded the best results. Under such conditions, reaction of ICTB **1b** and isobutyraldehyde **2d** also gave a satisfying yield of cyclic acetal **6b** (Table 4, entry 7). Further treatment of the representative acetal **6a** with trifluoroacetic acid (TFA) in dichloromethane at room temperature[21] gave the corresponding 1,3-*syn*-diol **6a′** in a satisfactory yield (Scheme 7).

Table 4. Optimization of the reaction of ICTB **1** with isobutyraldehyde **2d**.[a]

Entry	Solvent	1	2d [equiv]	6 [%][b]
1	THF	**1a**	2.4	**6a** (22)
2	toluene	**1a**	2.4	**6a** (17)
3	CH_2Cl_2	**1a**	2.4	**6a** (25)
4	DCE	**1a**	2.4	**6a** (73)
5	DCE	**1a**	1.2	**6a** (33)
6	DCE	**1a**	3.6	**6a** (76)
7	DCE	**1b**	2.4	**6b** (69)

[a] Reactions were stirred in the solvent at 25 °C for 48 h. [b] Yield of the isolated product.



Scheme 7. Transformation of acetal **6a** to 1,3-*syn*-diol **6a′**.

Conclusion

Two types of novel three-component reaction of stable isochromenylium tetrafluoroborates have been developed in this work. These mild cascade reactions commonly begin with a [4+2]-cycloaddition between the non-classic isochromenylium diene and the aldehyde–enol and is terminated by the C1 addition of nitriles or aldehydes. Nitriles and aldehyde carbonyls were utilized as the nitrogen, and oxygen sources in these reactions, respectively. The developed methodology provides a convenient way to introduce new functionality into dihydro- or tetrahydronaphthalene skeletons in an atom- and step-economical way. Advantages of such metal-free three-component cascade reactions also include high diastereoselectivity and ease of operation in the synthe-

sis of several functionalized dihydro- and tetrahydronaphthalene frameworks. In addition, the combinative use of readily available reactants (aldehydes and nitriles) will allow the incorporation of high levels of skeletal, functional, and stereochemical diversity in dihydro- and tetrahydronaphthalene synthesis with principles of diversity-oriented organic synthesis. Further application of these reactions to natural or unnatural product synthesis is currently underway in our laboratories.

Experimental Section

General methods: All reactions were conducted using oven-dried glassware. Acetonitrile, dichloromethane, and 1,2-dichloroethane were distilled from CaH_2, and tetrahydrofuran and toluene were distilled from Na prior to use. Petroleum ether and ethyl acetate were obtained from commercial suppliers and used without further distillation. IR spectra were recorded on an FTIR instrument. ^{1}H NMR spectra were recorded at 300 or 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz, and assigned in parts per million (δ). Reference peaks for chloroform in the ^{1}H NMR and ^{13}C NMR spectra were set at $\delta = 7.27$ and 77.0 ppm, respectively. For [D_6]DMSO, the reference peaks in the ^{1}H NMR and ^{13}C NMR spectra were set at $\delta = 2.50$ and 40.0 ppm, respectively. Crystallographic structures were determined on a 1000 diffractometer, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), at 120 K. Flash column chromatography was performed on silica gel H (10–40 μ).

Synthesis of compound 3d: Isobutyraldehyde **2d** (2.0 mmol) was added to a solution of **1a** (0.5 mmol) in dry CH_3CN (10 mL) at room temperature. After the starting material was consumed, saturated aqueous $NaHCO_3$ (15 mL) was added. The mixture was extracted with ethyl acetate (15 mL × 3). 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 = 1:2) to give pure product **3d**. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.86$ (d, $J = 7.2$ Hz, 2H), 7.63 (t, $J = 7.5$ Hz, 1H), 7.50 (t, $J = 7.5$ Hz, 2H), 6.92 (s, 1H), 6.88 (s, 1H), 6.05 (s, 1H), 5.77 (d, $J = 9.6$ Hz, 1H), 4.94 (d, $J = 9.6$ Hz, 1H), 3.91 (s, 3H), 3.78 (s, 3H), 1.97 (s, 3H), 1.20 (s, 3H), 1.19 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 196.9$, 169.4, 149.2, 148.3, 143.8, 137.9, 135.4, 133.1, 129.9 (×2), 128.5 (×2), 128.3, 122.0, 111.6, 109.4, 56.0, 55.9, 55.2, 36.9, 25.1, 23.4, 23.2 ppm; IR (KBr): $\tilde{\nu}_{max} =$ 3350, 2964, 1654, 1513, 1269, 1058, 733 cm^{-1}; MS (ESI): *m/z*: 402 [M+Na$^+$]; HRMS (ESI) calcd for $C_{23}H_{25}NO_4Na$ [M+Na$^+$]: 402.1681; found: 402.1678.

Synthesis of compound 5a: A solution of isobutyraldehyde **2d** (1.0 mmol) and 2-phenylacetonitrile **4a** (2.0 mmol) at room temperature was added to a solution of **1a** (0.5 mmol) in dry $(CH_2Cl)_2$,725 mL). After the starting material was consumed, saturated aqueous $NaHCO_3$ (20 mL) was added. The mixture was extracted with ethyl acetate (20 mL × 3). 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 = 3:1) to give pure product **5a**. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.73$ (d, $J = 4.8$ Hz, 2H), 7.58 (t, $J = 4.5$ Hz, 1H), 7.44 (t, $J = 4.5$ Hz, 2H), 7.24–7.34 (m, 5H), 6.92 (s, 1H), 6.76 (s, 1H), 5.96 (s, 1H), 5.75 (d, $J = 5.7$ Hz, 1H), 5.00 (d, $J = 6.0$ Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 3.61 (d, $J = 9.6$ Hz, 1H), 3.57 (d, $J = 9.3$ Hz, 1H), 1.13 (s, 3H), 0.99 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 196.5$, 170.3, 149.0, 148.1, 143.2, 137.8, 135.3, 134.8, 132.9, 129.7 (×2), 129.1, 128.9 (×2), 128.4 (×2), 128.0, 127.3 (×2), 122.2, 110.8, 109.5, 55.9, 55.8, 55.3, 43.9, 36.7, 25.2, 22.1 ppm; IR (KBr): $\tilde{\nu}_{max} =$3300, 2935, 1735, 1653, 1513, 1269, 1058, 734 cm^{-1}; MS (ESI): *m/z*: 478 [M+Na$^+$]; HRMS (ESI) Calcd for $C_{29}H_{29}NO_4Na$ [M+Na$^+$]: 478.1994; Found: 478.1988.

Synthesis of compound 6a: A solution of isobutyraldehyde **2d** (1.2 mmol) in dry $(CH_2Cl)_2$ (25 mL) was ,added at room temperature, to a solution of **1**a (0.5 mmol) After the starting material was consumed, saturated aqueous $NaHCO_3$ (20 mL) was added. The mixture was extracted with ethyl acetate (20 mL × 3). 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 product **6a**. ^{1}H NMR (CD_3OD, 500 MHz): $\delta = 8.02$ (d, $J = 7.3$ Hz, 2H), 7.66 (t, $J = 7.4$ Hz, 1H), 7.56 (t, $J = 7.4$ Hz, 2H), 6.90 (s, 1H), 6.72 (s, 1H), 5.24 (d, $J = 5.0$ Hz, 1H), 4.51 (d, $J = 4.3$ Hz, 1H), 4.36 (s, 1H), 4.08 (d, $J = 4.1$ Hz, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 1.44–1.47 (m, 1H), 1.30 (s, 3H), 0.80 (s, 3H), 0.74 (d, $J =$ 6.8 Hz, 3H), 0.64 ppm (d, $J = 6.9$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 199.1$, 148.2, 147.8, 137.2, 132.6, 128.6 (×2), 128.0 (×2), 127.0, 125.6, 113.0, 112.4, 91.7, 77.9, 76.2, 55.5, 55.4, 50.3, 34.3, 31.5, 23.8, 22.1, 16.9, 15.7 ppm; IR (KBr): $\tilde{\nu}_{max} = 3048$, 2253, 1685, 1518, 1272, 1056, 732, 699 cm^{-1}; MS (ESI): *m/z*: 433 [M+Na$^+$]; HRMS (ESI) calcd for $C_{25}H_{30}O_5Na$ [M+Na$^+$]: 433.1991; found: 433.1999.

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