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Brønsted Acid Catalyzed Oxocarbenium-Olefin Metathesis/Rearrangements of 1*H*-Isochromene Acetals with Vinyl Diazo Compounds

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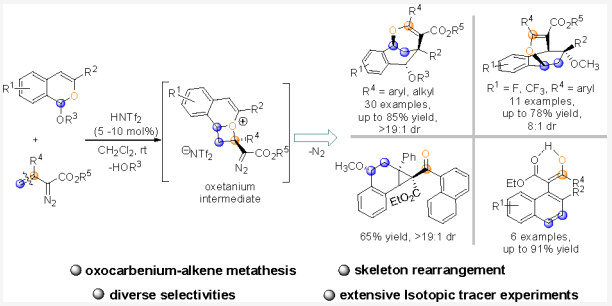
ABSTRACT: An oxocarbenium-olefin cross metathesis occurs during Brønsted acid catalyzed reactions of 1*H*-isochromene acetals with vinyl diazo compounds. Formally a carbonyl-alkene [2 + 2]-cyclization between isobenzopyrylium ions and the vinyl group of vinyl diazoesters, the retro-[2 + 2] cycloaddition produces a tethered alkene and a vinyl diazonium ion that, upon loss of dinitrogen, undergoes a highly selective carbocationic cascade rearrangements to diverse products whose formation is controlled by reactant substituents. Polysubstituted benzobicyclo[3.3.1]oxocines, benzobicyclo[3.2.2]oxepines, benzobicyclopropane, and naphthalenes are obtained in good to excellent yields and selectivities. Furthermore, isotopic tracer and control experiments shed light on the oxocarbenium-olefin metathesis/rearrangement process as well as on the origin of the interesting substituent-dependent selectivity.



INTRODUCTION

Vinyl diazo compounds, especially vinyl α-diazoacetates, are easily accessible versatile reagents that have provided an attractive platform for a variety of metal carbene transformations (Scheme 1a-left), including C−H insertion, C−C bond formation, and cycloaddition.[1] The site of electrophilic attack by the transition metal catalyst on the vinyl diazo group in all of these cases is the diazo carbon rather than the vinyl group, although subsequent nucleophilic attack on the metallovinylcarbene often occurs at the vinylogous position.[2] In contrast, synthetically effective cationic addition reactions with vinyl diazo compounds that could realize new transformations via the formation of vinyl diazonium ion or vinyl carbocation[3] intermediates have rarely been explored (Scheme 1a-right). We recently reported that bis(trifluoromethanesulfonyl)imide ($HNTf_2$) serves as a uniquely efficient Brønsted acid that selectively protonates the vinylogous position of vinyl diazo compounds forming reactive vinyl diazonium ions.[4] Brewer has developed the Lewis acid mediated dehydroxylation of β-hydroxy-α-diazo carbonyl compounds that also forms vinyl diazonium ion intermediates,[5] and they are also accessed from *N*-nitrosoamides[6] and, possibly, vinyl triazines.[7] For reactions with diazo compounds, the vinyl diazonium ion is formed either by elimination of a leaving group α to a diazo functional group[5,6] or by proton addition to a vinyl diazo compound.[4] In each process, synthetically viable electrophilic reactions of the vinyl diazonium ion or the vinyl cation formed by dinitrogen extrusion have been reported. With access to vinyl diazonium ions through proton addition validated, could alternative electrophiles undergo similar vinylogous addition to vinyl diazo compounds and, thereby, produce vinyl diazonium ion intermediates that dissociate dinitrogen to form highly reactive vinyl cations?[4]

Isobenzopyrylium species, which are generated by metal or acid catalysis,[8] are examples of alternative electrophiles that could undergo reactions with vinyl diazo compounds. Generally, metal catalyzed [4 + 2]-cycloadditions occur between isobenzopyrilium salts and alkenes, affording 1-ketonyl-1,2-dihydronaphthalenes.[8] Very recently, Liu and coworkers reported gold-catalyzed bicyclic annulations or formal [4 + 3]-cycloadditions of 2-alkynyl-1-carbonylbenzenes with vinyl diazo ketones that serve as five- or three- atom building units (Scheme 1b).[9] These intriguing transformations are initiated by concerted [5 + 4]- or [4 + 2]-cycloadditions of vinyl diazo compounds with gold complex-stabilized isobenzopyrylium intermediates, followed by ring opening and rearrangement. Instead of gold catalysis with ortho-alkynylbenzaldehydes, we surmised that the reaction of 1*H*-isochromene acetal with Brønsted acid catalysts would give ionic isobenzopyrylium salts[10] that could also undergo vinylogous addition to vinyl diazo compounds with overall

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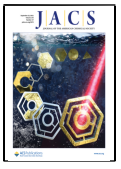
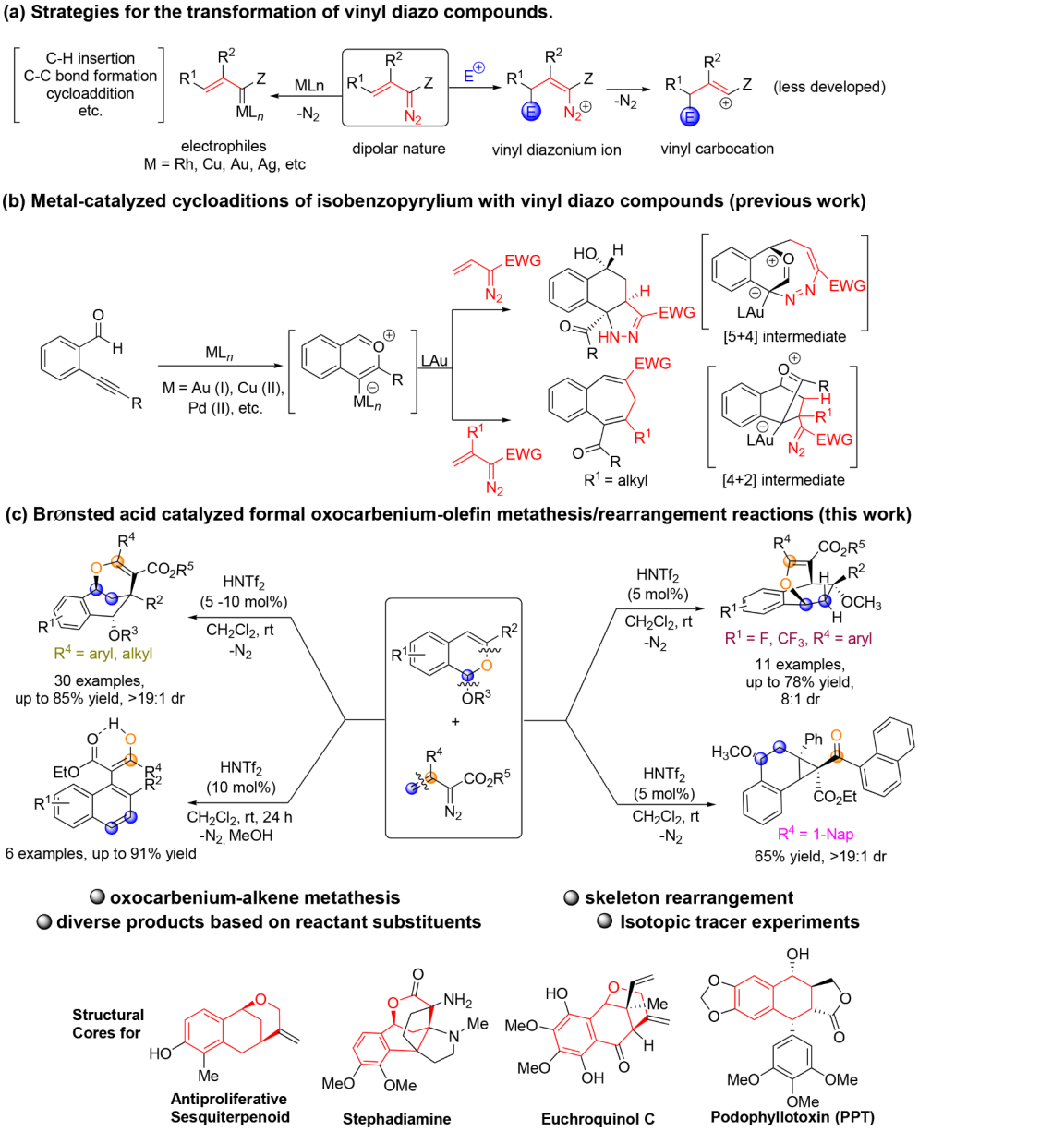


Scheme 1. Research Background for Reactions of Vinyl Diazo Compounds with Isobenzopyrylium Ions and This Work



[4 + 3]-cycloaddition like that of Scheme 1b through vinyl diazonium and vinyl carbocation intermediates. Instead, we discovered a metathesis transformation that forms tunable rearranged products in high yields and diastereoselectivities.

Herein, we report the oxocarbenium-olefin metathesis/rearrangement reactions of 1*H*-isochromene acetals with vinyl diazo compounds induced by bis(trifluoromethanesulfonyl)imide ($HNTf_2$) catalysis[11] (Scheme 1c). Polysubstituted benzobicyclo[3.3.1]oxocines, benzobicyclo[3.2.2]oxepines, benzobicyclopropane, and naphthalenes that form the structural cores of various bioactive molecules, such as an antiproliferative sesquiterpenoid, the alkaloid stephadiamine, the hydroquinone terpenoid euchroquinol C, and the anticancer agent podophyllotoxin,[12] are produced in good to excellent yields and selectivities.

RESULTS AND DISCUSSION

To effect selective protonation of 1*H*-isochromene acetal **1a** in the presence of ethyl 3-methyl-2-diazo-3-butenoate **2a**, several Lewis and Brønsted acids were surveyed to determine the most suitable reaction conditions for isobenzopyrylium ion addition to the vinyl diazo compound (Table 1). Use of 10 mol % of triflimide catalyzed an immediate reaction that converted **1a** to its benzopyrylium ion and methanol but, instead of the anticipated [4 + 3]-cycloaddition product (**3**), rearrangement product **4aa** was formed in 83% yield with high diastereocontrol. Other acids were also effective in forming this rearrangement product (>19:1 dr), with common Lewis acids giving variable reaction efficiency but less acidic Brønsted acids, including trifluoroacetic acid, showing no product formation. Superacid $HNTf_2$ applied with short reaction times gave **4aa** in the highest yield. Longer reaction times and larger amounts of $HNTf_2$ caused the loss of **4aa**.

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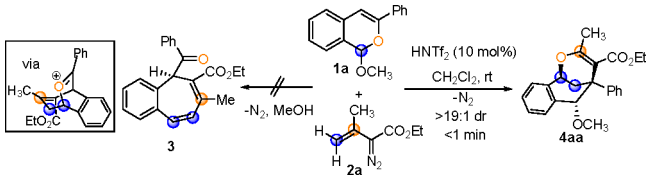
Table 1. Optimization of Reaction Conditions[a]



entry	variation from the standard reaction conditions	yield of **4aa**[b] (%)
1	none	83
2	$B(C_6F_5)_3$, 10 mol %, 10 min	44
3	$BF_3{\cdot}Et_2O$, 10 mol %, 10 min	64
4	$Sc(OTf)_3$, 10 mol %, 10 min	77
5	$In(OTf)_3$, 10 mol %, 10 min	67
6	CF_3COOH, 10 mol %, 24 h	no reaction
7	TfOH, 10 mol %, 10 min	60

[a]Reactions were performed with **1a** (0.1 mmol), catalyst (10 mol %), and **2a** (0.12 mmol) in CH_2Cl_2 at rt for 1 min to 24 h; the dr values were determined by ^{1}H NMR. [b]Isolated yield.

A wide range of 1*H*-isochromene acetal substrates with varied substituents reacted with **2a** using $HNTf_2$ catalysis to form rearrangement products **4aa-4sa** (Scheme 2) in good yields and high diastereocontrol. Alkoxy groups, specifically OCH_3, O^{i}Pr, OBn, and the acid-sensitive Oallyl, were tolerated in the reaction, furnishing the corresponding products (**4aa-4da**) with their component alkoxy groups intact in 65%−83% yields. Both electron-donating (**1e** and **1f**) and electron-withdrawing (**1g**−**1k**) substituents on the phenyl ring of the isobenzopyrylium ions had little influence on the product, forming **4ea-4ka** in 57%−85% isolated yields. 2-Thienyl substituted 1*H*-isochromene acetal (**1l**) was a suitable substrate and so were 3-alkyl substituted 1*H*-isochromene acetals (**1m** and **1o**). However, when 3-*H* substituted 1*H*-isochromene acetal (**1n**, R^2 = H) was reacted under the optimized condition, a complex mixture was obtained; but this problem was overcome by adding 2.0 equiv of CH_3OH to accelerate the reaction process, providing desired product **4na** in 71% isolated yield with low diastereocontrol (1.3:1 dr). Furthermore, 1*H*-isochromene acetals bearing functional groups (OAc and OTBS) and natural product units (*s*-naproxen and gemfibrozil acid) also underwent metathesis/rearrangement with **2a** in 30%−37% yields with excellent selectivities.

The outcomes from structural variations in the vinyl diazoacetate were also examined (Scheme 2). Analogous *β*-alkyl substituted vinyl diazo compounds (**2b**−**2d**) reacted with the oxonium ion generated from acetal **1a** to produce corresponding products **4ab-4ad** in moderate yields. For *β*-aryl substituted vinyl diazo compounds (**2e**−**2l**), both electron-withdrawing (**2g, 2h** and **2l**) and electron-donating (**2e** and **2f**) substituents on the para-position of the phenyl ring of vinyl diazo esters were compatible with the formation of products **4ae-4al** in good yields and selectivities, and a methoxy substituent at the meta-position did not influence the reaction outcome (**4ai**). The structure of **4ae** was confirmed by X-ray diffraction.[13] Benzyl ester **2j** also reacted with **1a** to form **4aj** in good yield and diastereoselectivity, and without debenzylation. The *β*-2-naphthyl substituted vinyl diazo compound **2k** underwent reaction with **1a**, and its product (**4ak**) was isolated in only 50% yield.

The generality of this unexpected rearrangement process necessitated our speculation about its origin. We had anticipated cycloaddition reactions, not unlike those previously reported[8,9] for vinyl diazo compounds with isobenzopyrylium ions (Scheme 1b), but no trace of such compounds could be found in thorough analyses of reaction product mixtures. That **4** could not have arisen from initial protonation of the vinyl diazo ester that results in a vinyl diazonium ion is established in the formation of a C−C bond to the vinylic carbon of the carbon−carbon double bond of the vinyl diazo ester.[4] However, in the formation of **4** the reaction pathway must account for the apparent cleavage of the C=C bond of the reactant vinyl diazo ester and the apparent cleavage of a C−O bond of the isobenzopyrylium ion intermediate. Recent identification and elaboration of carbonyl-olefin metathesis reactions[14−16] pointed to a solution to the mechanistic dilemma. They are catalytic and have shown considerable generality with Lewis acids,[14] notably $FeCl_3$,[14c] but they are limited in scope using trityl cation salts[15] or Brønsted acids.[16] With triflimide-catalyzed reactions between 1*H*-isochromene acetals and *β*-aryl/alkyl vinyl diazo esters [2 + 2]-cyclization between the activated carbonyl group (oxonium ion) of the isobenzopyrylium ion and the C=C of the vinyl diazoesters to form a diazo activated oxetanium intermediate that undergoes retro-[2 + 2] cycloaddition (Scheme 3), accounts for bond connections that are evident in the product.

Reactions with deuterium-labeled reactants were performed to certify atomic positions in the rearranged product (Scheme 4). Deuterium labeled substrates **2a**-d_5 (99% D) and **2e**-d_2 (96% D) were prepared and, together with 1*H*-isochromene acetal **1a**, were treated with Tf_2NH under the standard reaction conditions, and products **4aa**-d_5 and **4aa**-d_2 were isolated in 81% yield (>19:1 dr) and 78% yield (>19:1 dr), respectively. ^{1}H NMR analysis of these products (**4aa**-d_5 and **4aa**-d_2) located the terminal vinyl carbon in **2a**-d_5 and **2e**-d_2 at the C11-position of benzobicyclo[3.3.1]oxocine products, and the oxygen at the 2-position of the acetal became attached to the *β*-carbon position of the reactant vinyl diazoacetate (eq 1 and 2). Labeling of 1*H*-isochromene acetal **1a** at the 1- and 4-positions (**1a**-d_1, 80% D at C1, and **1a**-d_4, 90% D at C4 with 99% D at the methoxy group) was also performed, and their reactions with vinyl diazo ester **2a** were run under standard conditions. ^{1}H NMR analysis of the product (**4aa**-d_1) suggested that the C1(SM) ended up at C1(P) and that it was still attached to oxygen (eq 3). Also, ^{1}H NMR analysis of the product (**4aa**-d_4) located the C4(SM) at the C6(P) attached the methoxy group (eq 4). These labeling studies are consistent with the linkage of atoms brought about by metathesis in Scheme 3, but they do not reveal the mechanistic steps that take **int-III** to the observed product 4.

Other nucleophiles, including amine, indole, phenol, 1,3,5-trimethoxybenzene, and thiophenol, were used in attempts to trap carbocationic intermediates (for detail, see Supporting Information). The amine quenched the reaction, as expected, and neither indole, phenol, or trimethoxybenzene caused formation of any product attributable to the combination of the nucleophile with the reactants. However, the reaction of acetal **1a**, ethyl 3-methyl-2-diazo-3-butenoate **2a**, and thiophenol gave product **4aaS** in 66% yield with >19:1 dr (eq 5). This nucleophilic outcome is consistent with competition between the thiol and methanol for capture of the carbocation that is the penultimate product.[17]

To obtain additional information about this metathesis/rearrangement reaction, we surveyed reactions of 1*H*-isochromene acetals with *β*-phenyl substituted vinyl diazo

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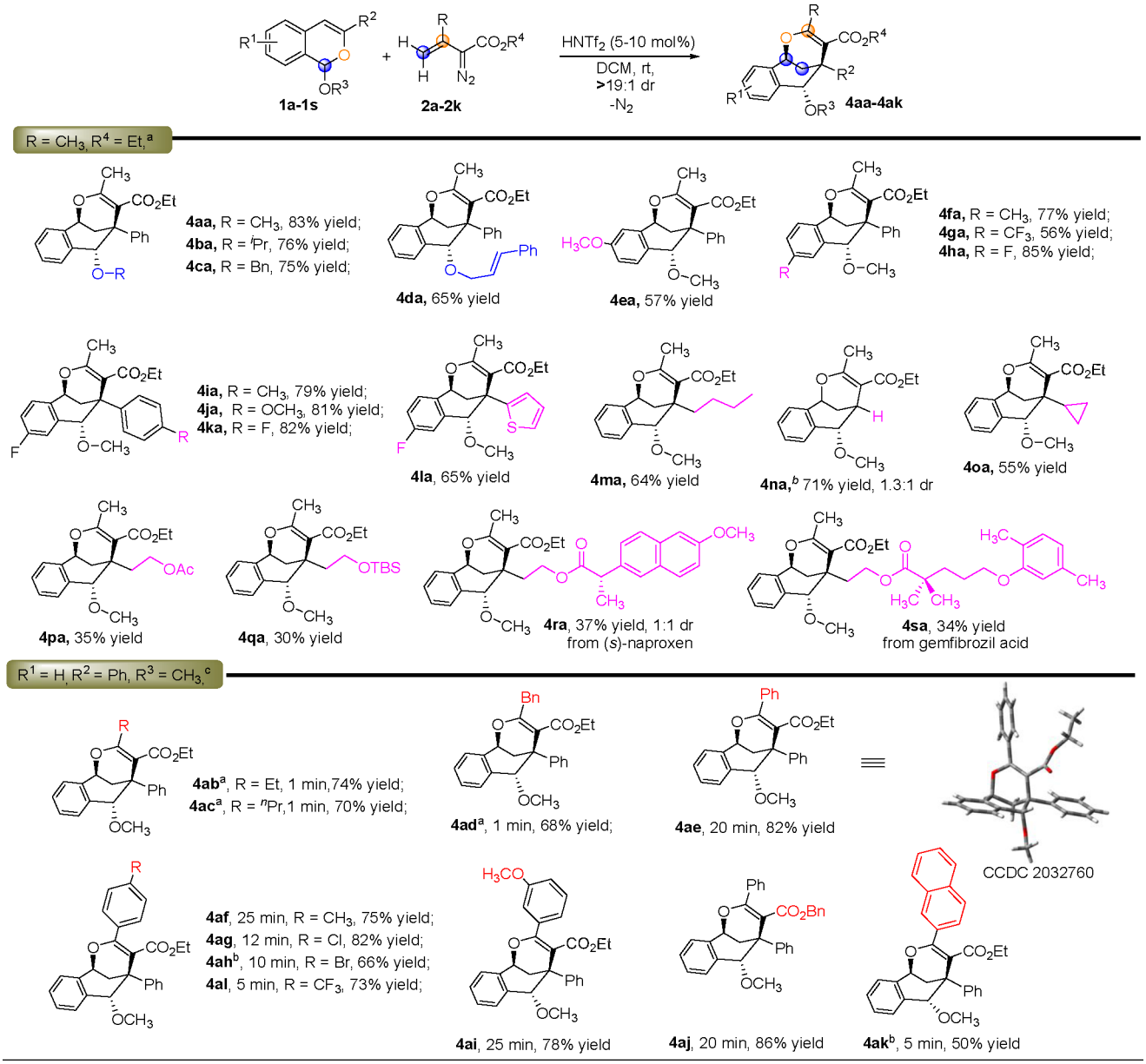
Scheme 2. Substrate Scope of Vinyl Diazoacetates with 1*H*-isochromene Acetals[a]



[a]Unless otherwise noted, reactions were performed with **1** (0.2 mmol), $HNTf_2$ (10 mol %), and **2** (1.2 equiv., 0.24 mmol) in CH_2Cl_2 at rt for 1 min; isolated yield; the dr values were determined by ^1H NMR spectral analyses and, unless otherwise noted, dr is >19:1. [b]CH_3OH (0.4 mmol) was added. [c]Reactions were performed with **1a** (0.2 mmol), $HNTf_2$ (5 mol %), and **2** (1.2 equiv., 0.24 mmol) in CH_2Cl_2 at rt for 1−25 min; isolated yield; the dr values were determined by ^1H NMR spectroscopic analysis and, unless otherwise noted, the dr was >19:1.

compound **2e** (Scheme 5). Surprisingly, the substituents on the phenyl ring of acetal **1** (R) had a significant influence on site selectivity for methanol quenching. Two rearranged products are formed. The 1*H*-isochromene acetal with an electron-donating methyl substituent (**1f**) afforded benzobicyclo[3.3.1]oxocine **4fe** in 72% yield with >19:1 dr but also formed a regioisomer, benzobicyclo[3.2.2]oxepine **5fe**, in 9% yield with 11:1 dr (8:1 rr). This byproduct appears to come from a common intermediate whose priority is determined by electronic stabilization afforded to the carbocation intermediate that is the precursor to **4**. Accordingly, fluoro-substituted 1*H*-isochromene acetal **1h** produced benzobicyclo[3.2.2]oxepine **5he** as the major product with only 7% benzobicyclo[3.3.1]oxocine **4he**. However, with strong electron withdrawal,[18] trifluoromethyl substituted acetals **1g** and **1t** showed complete inversion of regioselectivity with the benzobicyclo[3.2.2]oxepine compounds **5ge** and **5te** obtained in 78% yield (8:1 dr) and 72% yield (8:1 dr), respectively. A search for benzobicyclo[3,2,2]-oxepine byproducts in the reactions reported in Scheme 2 discovered these products as minor components (generally <5% and often negligible).[19]

Because of the dominance of **5** when R = CF_3, we synthesized varioustrifluoromethyl substituted 1*H*-isochromene acetals (**1g−1w**) and investigated their reactions with *β*-aryl substituted vinyl diazo compounds (**2e−2j**). In all cases, the reaction proceeded with high efficiency, affording benzobicyclo[3.2.2]oxepines **5** in good yields and diaster-

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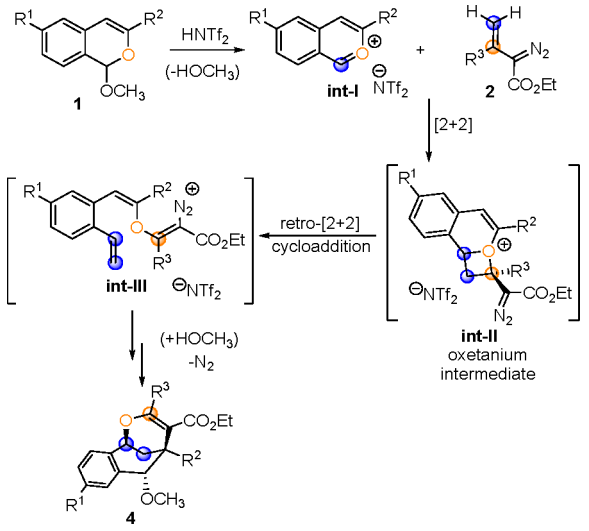
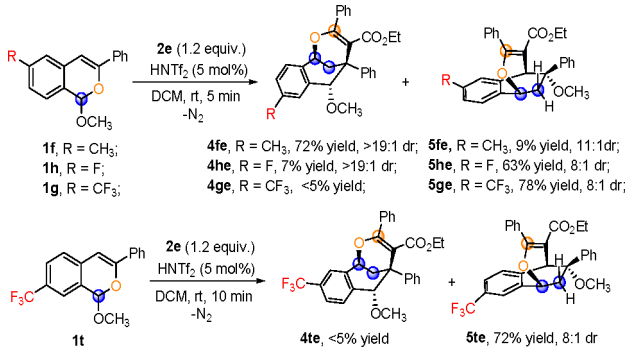
Scheme 3. Isobenzopyrylium Ion Metathesis with Vinyl Diazoesters



Scheme 5. Substituent Effects on Regioselectivity[a]



[a]Unless otherwise noted, reactions were performed with **1g** (0.2 mmol), $HNTf_2$ (5 mol %), CH_3OH (2.0 equiv., 0.4 mmol), and **2** (2 equiv., 0.4 mmol) in CH_2Cl_2 at rt for 5 min; isolated yield; the dr and rr values were determined by ^1H NMR spectroscopic analysis.

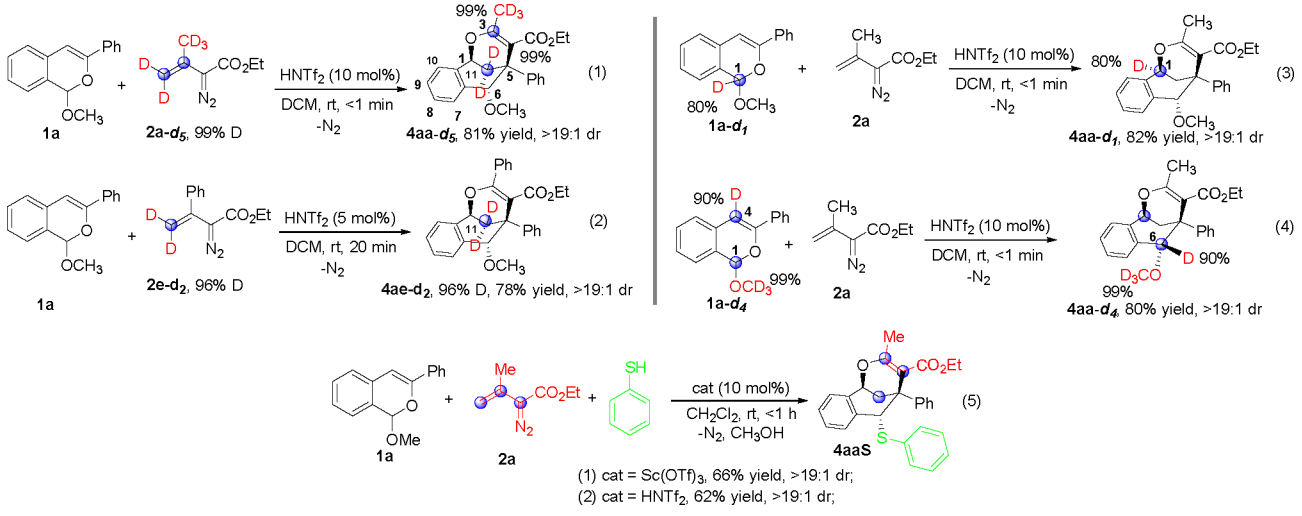
eoselectivities, with high regiocontrol (Scheme 6). Both 3-aryl or 3-alkyl substituted 1*H*-isochromene acetals (**1g**−**1w**) underwent this metathesis/rearrangement (**5ge-5we**), and the structure of **5ge** was confirmed by X-ray diffraction.[13] For *β*-aryl substituted vinyl diazo compounds (**2e**−**2j**), both para-substituted electron-withdrawing (**2g** and **2h**) and electron-donating (**2e** and **2f**) substituents of the *β*-phenyl substituted vinyl diazo ester were compatible with the formation of the benzobicyclo-[3.2.2]oxepine products (**5ge-5gh**) in good yields and selectivities. Furthermore, a meta-methoxy substituent of the phenyl ring of the 1*H*-isochromene acetal or the benzyl ester of the vinyl diazoacetate had little effect on product yield or selectivity.

The formation of benzobicyclo[3.3.1]oxocines **4** and benzobicyclo[3.2.2]oxepine **5** appear to occur through a common intermediate. To explain this, we propose that the vinyl cation produced by dinitrogen extrusion from **int-III** reacts with the proximal C=C to form oxo-stabilized **int-IV** that cyclizes with the styryl double bond, forming **int-V**, which with further cyclization produces a key intermediate **int-VI** that is also an oxo-stabilized carbocation (Scheme 7). Intramolecular vinyl cation addition to alkenes has been reported,[20] and oxonium addition to alkenes is well established.[21] The conversion of a benzyl carbocation to an oxonium ion is classically found in carbocation rearrangements.[22] That nucleophilic attack on **INT-VI** can occur at either positions *a* and *b* forming **4** or **5**, respectively, is consistent with known ring opening reactions of cyclopropylcarbonyl compounds.[23] Product **4** is favored when R^1 = alkyl or aryl with an EDG on phenyl, and **5** is favored when R^1 = aryl and R = EWG.

The deuterium labeling experiment in eq 6 (Scheme 8) is consistent with the proposed mechanism. Acetal **1g** reacting with **2e**-d_2 yields **5ge**-d_2 with deuterium imbedded into the carbons predicted from **int-V** and **int-VI**.

INT-VI also predicts the feasibility of yet another mode of methanol quenching of the intermediate oxonium ion (Scheme 9) and, accordingly, we also found the formation of benzobicyclopropane product 7(65% yield, > 19:1 dr) when the *β*-1-naphthyl substituted vinyl diazo compound was used as the substrate. Naphthalene products **6ae-6re** were obtained via this pathway by performing the reaction in the presence of 10 mol % of $HNTf_2$ for 24 h. Both *β*-alkyl (**2a**) and *β*-phenyl (**2e**) substituted vinyl diazo compounds gave corresponding

Scheme 4. Labeling Experiments to Certify Atomic Positions in Rearranged Products 4



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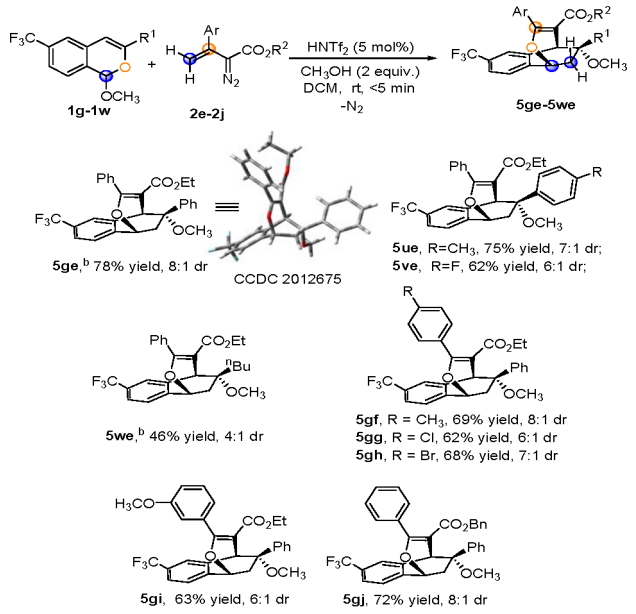
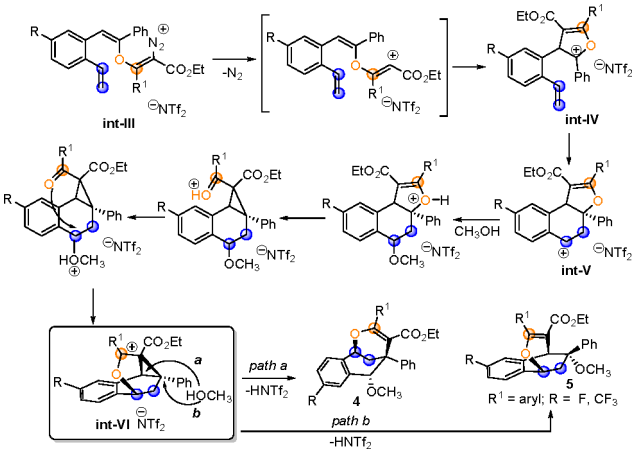
Scheme 6. Substrate Scope of Trifluoromethyl Substituted 1*H*-Isochromene Acetals with *β*-Aryl Substituted Vinyl Diazoacetates[a]

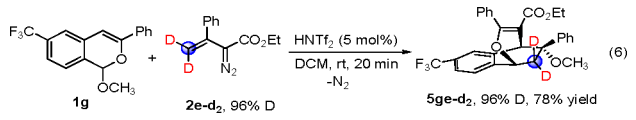


[a]Unless otherwise noted, reactions were performed with **1g** (0.2 mmol), $HNTf_2$ (5 mol %), CH_3OH (2.0 equiv., 0.4 mmol), and 2 (2 equiv., 0.4 mmol) in CH_2Cl_2 at rt for 5 min; isolated yield; the dr and rr values were determined by ^1H NMR spectroscopic analysis. [b]No CH_3OH added.

Scheme 7. Regioselectivity in Methanol Quenching of Int-VI

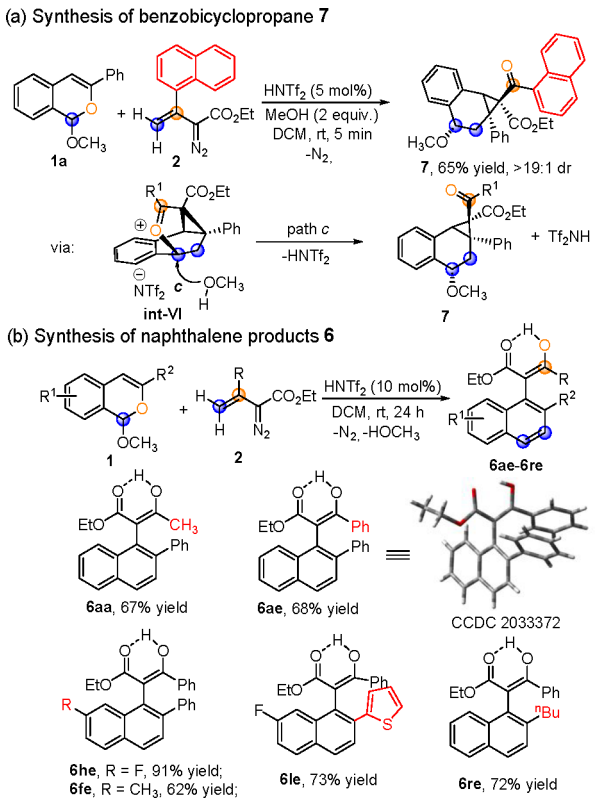


Scheme 8. Labeling Experiment to Certify Atomic Positions in Rearranged Products 5



products (**6aa** and **6ae**) in good yields, and the structure of **6ae** was confirmed by X-ray diffraction.[11] In addition, 4-fluoro (**1h**), 4-methyl (**1f**), 2-thienyl (**1l**), and *n*-butyl (**1r**) substituted 1*H*-isochromene acetals produced naphthalene products **6he-6re** in 62%−91% isolated yields. These results indicated that both benzobicyclo[3.3.1]oxocines (**4**) and

Scheme 9. Catalytic Formation of Benzobicyclopropane and Naphthalene Products



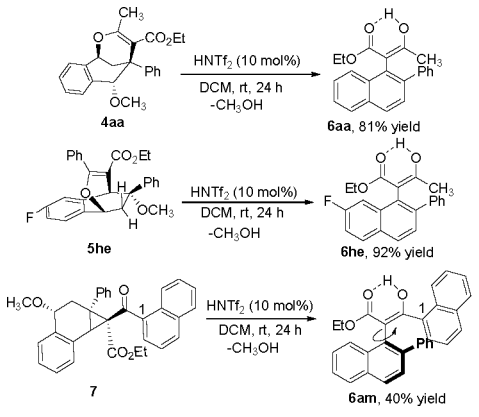
[a]Unless otherwise noted, the reactions were performed with 1 (0.2 mmol), $HNTf_2$ (10 mol %), and 2 (1.2 equiv., 0.24 mmol) in CH_2Cl_2 at rt for 24 h. Isolated yields.

benzobicyclo[3.2.2]oxepines (**5**) products could eliminate methanol, affording naphthalene products (**6**) by prolonging the reaction time to 24 h.

Finally, we also treated products **4aa**, **5he**, and **7** with 10 mol % $HNTf_2$ for 24 h, and the resulting naphthalene products **6aa**, **6he**, and **6am** were obtained in 81%, 92%, and 40% yield, respectively (eqs 7−9 in Scheme 10). In consistency with previous examples with 1-naphthyl derivatives,[24] ^1H NMR evidence for rotamers of **6am** was found.

On the basis of the experimental results for these reactions, we propose in Figure 1 the probable mechanism of $HNTf_2$

Scheme 10. Formation of Naphthalene Products from Rearranged Product 4aa, 5he, and 7



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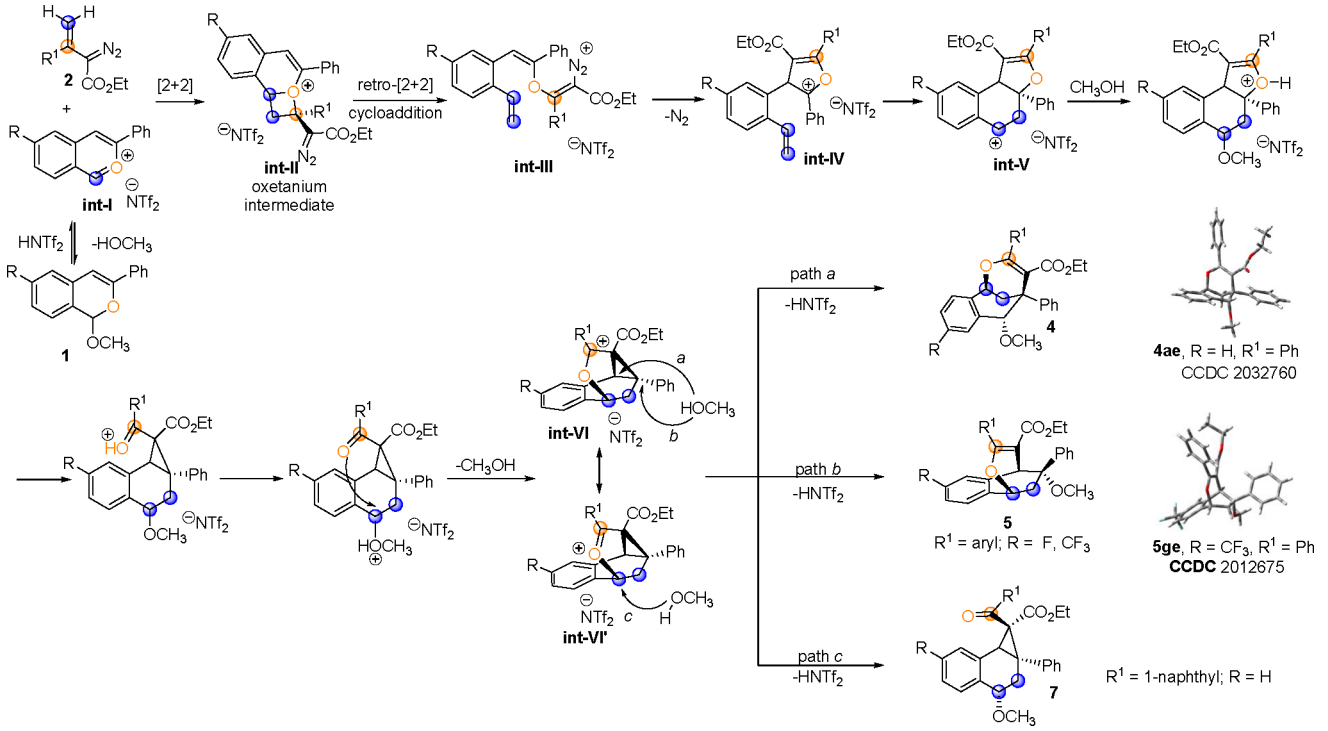

Figure 1. Plausible mechanism for formal oxocarbenium-olefin metathesis/rearrangements of 1*H*-isochromene acetals with vinyl diazo compounds

catalyzed metathesis/rearrangement reactions of vinyl diazo compounds with 1*H*-isochromene acetals. The reaction is initiated by selective protonation of acetal compounds **1** with $HNTf_2$ to give the corresponding bis(trifluoromethanesulfonyl)imide anion (Tf_2N^-) stabilized isobenzopyrylium salt (**int-I**), which is captured by vinyl diazo compounds **2**. Instead of [4 + 2] cycloaddition, cation-induced stepwise [2 + 2]-cyclization occurs, forming the diazo activated oxetanium intermediate **int-II**. Subsequently, the diazo functional group facilitates retro-[2 + 2] cycloaddition to form vinyl diazonium ion **int-III**. Further transformation into carbocation intermediate **int-IV** occurs via loss of dinitrogen and carbocation addition to the carbon−carbon double bond. Carbocation induced cyclization delivers **int-V**, which undergoes oxygen migration/rearrangement cascade processes affording intermediate **int-VI**↔**int-VI′**. Finally, substituent-dependent selective ring-opening gives polysubstituted benzobicyclo[3.3.1]-oxocines **4** (path *a*), benzbicyclo[3.2.2]oxepines **5** (path *b*) and/or benzobicyclopropane **7** (path *c*). After prolonging the reaction time, the thermodynamically stable naphthalene products **6** are obtained in good to excellent yields via loss of methanol and rearrangement (Figure 1).

CONCLUSIONS

In summary, we have reported a Brønsted acid catalyzed oxocarbenium-olefin cross metathesis/rearrangement of 1*H*-isochromene acetals with vinyl diazo compounds. Formally, a carbonyl-alkene [2 + 2]-cyclization between isobenzopyrylium ions and the vinyl group of vinyl diazoesters produces a tethered alkene and a vinyl diazonium ion that, upon the loss of dinitrogen, undergoes a highly selective carbocationic cascade rearrangements to products controlled by reactant substituents. These results demonstrate an intriguing reactivity of vinyl diazo compounds in Brønsted acid catalysis via vinyl cations intermediates and provide a fascinating methodology for the selective synthesis of polysubstituted benzobicyclo[3.3.1]oxocines, benzobicyclo[3.2.2]oxepines, benzobicyclopropane, and naphthalenes. Further studies are ongoing to reveal the scope of oxocarbenium ion-alkene cycloaddition/metathesis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c07271.

Experimental procedures and characterization data (PDF)

Accession Codes

CCDC 2012675, 2032760, and 2033372 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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