Synthetic Methods

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A Tandem Isomerization/Prins Strategy: Iridium(III)/Brønsted Acid Cooperative Catalysis**

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Tetrahydropyrans (THPs) are important heterocycles found in biologically active natural products and small molecules.[1] There are several established methods to construct THPs including hetero-Diels–Alder cycloadditions,[2] intramolecular conjugate additions,[3] and ring-closing metathesis.[4] A major approach for pyran synthesis involves the condensation of an aldehyde with a homoallylic partner and subsequent C–C bond formation (Prins cyclization, Figure 1).[5] This general Prins strategy has been proven to be efficient for the synthesis of biologically active small molecules,[6] as well as a key tactic in the construction of complex natural products.[7] Yet while the Prins reaction is convergent in nature, recognized drawbacks to the typical reaction conditions for this transformation include: a) the use of strong Lewis or Brønsted acids to generate the requisite oxocarbenium ion **1**, b) the need for reactive carbonyl compounds (e.g., aldehydes) and elevated temperatures to drive the reaction to completion, and c) the control of the stereochemical outcome and exchange of reaction substituents from potentially competing oxonia-Cope pathways.[8]

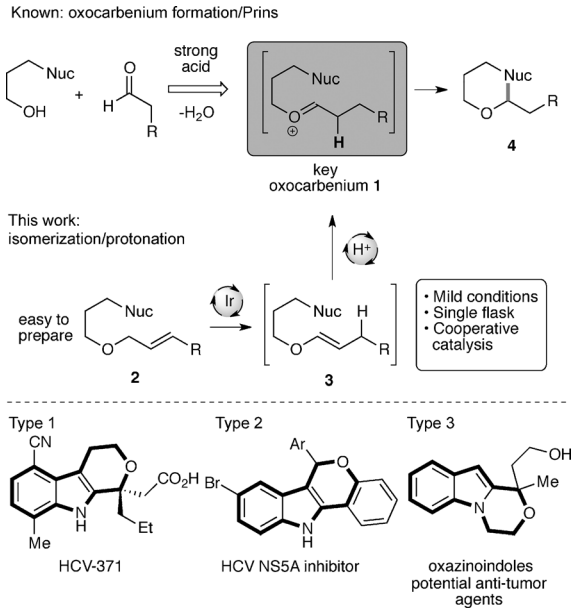

Figure 1. Tandem isomerization cyclization.

An alternative approach to the Prins manifold that potentially circumvents these issues associated with promoting dehydration and subsequent oxocarbenium formation is a transition-metal-catalyzed isomerization/protonation sequence involving an appropriately functionalized precursor (Figure 1). Efficient single-flask operations involving alkene isomerization steps have been utilized in Friedel–Crafts reactions,[9] as well as asymmetric Claisen rearrangements.[10] Our strategy to access Prins-type oxocarbenium intermediates without the need for strong dehydrating conditions involves the isomerization of the allyl ether **2** to the enol ether **3**. The enol ether can then be protonated under mild acidic conditions to provide the oxocarbenium **1** in the presence of a suitable alkene nucleophile with subsequent C–C bond formation. Protonations of enol ethers have also been used independently by the groups of Rychnovsky and Dobbs to promote Prins cyclizations with vinyl and allyl silanes.[11] Notably, the construction of the pyran **4** would be possible at ambient temperatures and without the use of carbonyl functional groups.

As a proof of concept for this Prins process, we crafted our approach around the indole core as the requisite nucleophilic alkene component (Figure 1, Nuc). Utilizing indoles in this process would intersect intermediates in the oxa-Pictet–Spengler reaction,[12] which has been used to generate many biologically relevant oxacycles,[13] but can often suffer from the same limitations as the Prins cyclization. To leverage our substrate design and maximize potential compound library synthesis, the appendage of an allyl group on the N-, C2-, and C3-position of the indole enables the synthesis of three different types of pyran-fused indole scaffolds (Figure 1).[14]

Substituted indoles are abundant in biologically active compounds and promising pharmaceuticals[15] For example, the core structure of the Type 1 class (Figure 1) is found in the anti-inflammatory drug etodolac.[16] The lead compound HCV-371, a potent hepatitis C NS5A polymerase inhibitor discovered by high-throughput screening and chemical optimization, also contains this substitution.[17] Indoles of Type 2 have also been studied for their inhibition of NS5A polymerase.[18] Finally, the heterocycles of the Type 3 variant have been studied for their potential antidepressant and antitumor properties.[19] Despite the significant interest in these compounds for biological applications, an efficient and unified approach to obtain these products is lacking.[20] Herein, we

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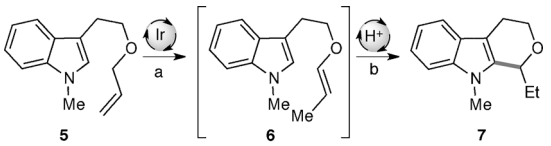
describe the development of a tandem catalytic isomerization/Prins-type cyclization for the efficient construction of three types of pyran-fused indoles geared toward bioactive compound library development.[6a,21]

We initially sought to achieve this reaction in a stepwise manner by first isomerizing the allyl ether **5** into enol ether **6** and subsequently adding an acid source to facilitate cyclization to the pyran **7** (Table 1). We began our studies by first exploring reaction conditions for the isomerization of **5** into **6**. After examining several different reaction conditions, the iridium catalyst $[IrH_2(THF)_2(PPh_2Me)_2)]PF_6$, used previously by Miyaura and co-workers to convert allyl ethers into *E*-vinyl ethers, was determined to be the most effective catalyst for the isomerization.[22] With the isomerization conditions identified, both Brønsted acids and metal triflates were evaluated for their ability to catalyze the efficient cyclization of **5** to **7** (Table 1). Metal triflates can be employed as hidden acid catalysts which circumvent the difficulties of using small amounts of strong Brønsted acids.[23] Acids such as TMSOTf, camphorsulfonic acid (CSA), $MeSO_3H$, and $Yb(OTf)_3$ did not completely promote cyclization to **7**. Lewis acids such as $InCl_3$ and $FeCl_3$ were tested with $FeCl_3$ promoting nearly full conversion into **7** (90:10, entry 5).[24] In contrast, the addition of $Bi(OTf)_3$ to the reaction after the isomerization resulted in full conversion into **7** in high yield (70%, entry 7). In particular, $Bi(OTf)_3$ has been used as a convenient and mild source of triflic acid in the presence of water[25] and has been proven to be effective in catalyzing Prins-type cyclizations.[26] To assess whether $Bi(OTf)_3$ is a TfOH source in this process, a control experiment with 2,6-di-*tert*-butyl pyridine (DTBP) as an additive was performed. With the addition of this hindered base, only low conversion into the pyran and mostly enol ether was observed (entry 10).

Table 1: Screening of acid sources.



>95:5 *E/Z*

Entry	Acid source	**6**/**7**	Yield [%][c]
1	TMSOTf	40:60	n.a.
2	CSA	73:27	n.a.
3	$MeSO_3H$	54:46	n.a.
4	$InCl_3$	94:6	n.a.
5	$FeCl_3$	10:90	n.a.
6	$Yb(OTf)_3$	35:65	n.a.
7	$Bi(OTf)_3$	0:100	70
8	$Bi(OTf)_3$[d]	0:100	70
9	TfOH	0:100	65
10	$Bi(OTf)_3$[e]	90:10	n.a.

[a] 1 mol% $[IrH_2(THF)_2(PPh_2Me)_2)]PF_6$ in THF (0.1 M). [b] 1 mol% acid source. [c] Yield of product isolated after column chromatography. [d] Simultaneous addition of both catalysts: reaction time decreased from 12 h to 2 h. [e] 2,6-di-*tert*-butylpyridine (10 mol%) added. CSA = camphorsulfonic acid, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran, TMS = trimethylsilyl. n.a. = yield not determined.

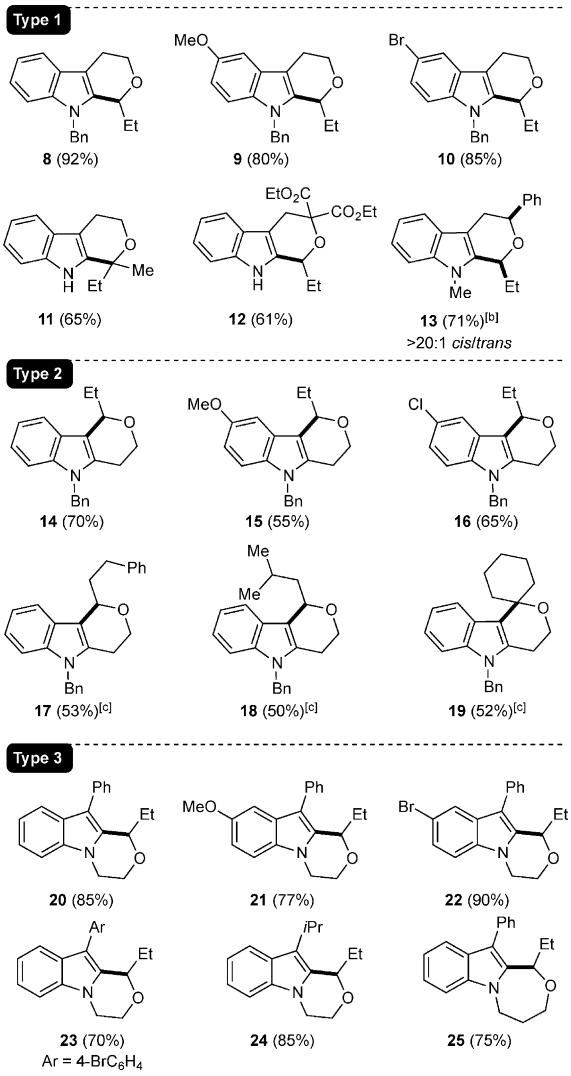
Given our interest in the area of cooperative catalysis,[27] we were interested to see if the simultaneous addition of the metal triflate and the iridium complex directly to the reaction mixture containing **5** would provide a simple protocol for this transformation and possibly increase the activity of either or both catalysts. Cooperative catalysis has been successfully employed with transition metals and Brønsted acids,[28] and recent independent reports by the groups of Rueping and Xiao describe the combination of iridium complexes and Brønsted acids to facilitate reductions of imines.[29] Our cascade isomerization/protonation strategy seemed a prime candidate to apply this catalyst combination for the construction of C–C bonds. To test this hypothesis, **5** was simultaneously subjected to $[IrH_2(THF)_2(PPh_2Me)_2]PF_6$ and $Bi(OTf)_3$ at 1 mol% each (entry 6): the reaction proceeded to 100% conversion within only 2 hours [versus 12 h for initial alkene isomeration with Ir^{III} alone, then $Bi(OTf)_3$]. We attribute the decrease in reaction time to Brønsted acid acceleration of the isomerization, thereby leading to a cooperative or synergistic affect for this system.

We then directed our attention toward the synthesis of various indole-fused heterocycles to investigate if the cooperative or synergistic effect observed could be applied to the three types of indoles discussed above. Beginning with the Type 1 scaffold, in which the allyl ether is appended at the C3-position, the reactions proceeded in high yields with a variety of different products formed (**8**–**13**; Table 2).

The 5-substituted indoles (**9** and **10**) are compatible with the cooperative catalysis conditions, including products such as **10** containing an aryl bromide functionality, which can serve as a handle for additional functionalization through metal-catalyzed coupling reactions. Tertiary ethers (**11**) can be formed in good yield to give the framework found in pharmaceutically relevant compounds such as HCV-371.[18] The geminally disubstituted pyran **12** can be obtained in high yield, and presents the opportunity for functional-group manipulation of the diester.[30] When a secondary allylic ether is employed as a substrate, the corresponding 2,6-substituted pyran **13** is isolated in 71% yield with excellent diastereoselectivity (> 20:1 *cis/trans*).

Moving from the allylic ether at C3 (Type 1) to the the allylic ether at C2 (Type 2) accesses the isosteric tricylic pyrans (Table 2). The C2-substituted allyl ether substrates were efficiently generated through a palladium-catalyzed C–H activation utilizing primary alkyl halides.[31] With each of these substrates, the cyclization reaction provides the pyran products in moderate yields for the overall two-step tandem process. The 5-substituted indoles (**15** and **16**) bearing electron-withdrawing and electron-donating groups are amenable to the reaction conditions but proceed in moderate yields. Allyl groups such as cinnamyl and 3,3-dimethyl allyl (e.g. **17** and **18**) were also explored and found to be compatible, but required a slightly higher iridium catalyst loading to fully isomerize the alkene. The core structure of the spirocyclic indole-fused pyran **19** has been utilized as an antagonist for the μ-opiate receptor.[32]

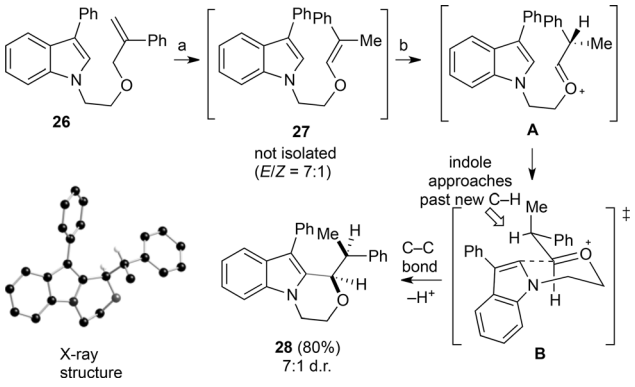
Table 2: Substrate scope.[a]



[a] 1 mol% $[IrH_2(THF)_2(PPh_2Me)_2)]PF_6$ in THF (0.1 M) 1 mol% $Bi(OTf)_3$ added simultaneously. [b] Diastereomeric ratios determined by ^1H NMR spectroscopy (500 MHz). [c] 6 mol% of iridium catalyst was needed for full conversion.

The placement of the ether group on the nitrogen atom of the indole (Type 3) provides increased substrate diversity compared Types 1 and 2 because of the ease of synthesizing different allyl ether precursors from readily available aldehydes.[33] As with Types 1 and 2, 5-substituted indoles were tolerant to the reaction conditions, thus generating the pyrans **21** and **22** in excellent yield. In addition to aromatic substituents, products such as **24**, which have alkyl substitution at the C3-position, can be obtained in high yields. Interestingly, in addition to six-membered pyrans, cyclization to afford the seven-membered oxepane **25** could also be achieved in this Type 3 approach, and was not possible for Types 1 and 2 analogues.

Internal substitution of the allyl ether substituent provides the opportunity to introduce stereochemical complexity to the overall isomerization/cyclization process. Hence, a 1,1-disubstituted-styrene ether substrate (**26**) was subjected to the



Scheme 1. Diastereoselective example. a) 8 mol% $[IrH_2(THF)_2(PPh_2Me)_2)]PF_6$ in THF (0.1 M); b) 10 mol% $Bi(OTf)_3$ added directly to flask. Thermal ellipsoids shown at 50% probability.[37]

$Ir^{III}/Bi(OTf)_3$ conditions (Scheme 1), thus generating **28** as a 7:1 mixture of diastereomers via the intermediate oxocarbenium **A**. The major product is attributed to a chairlike transition state (**B**) with the indole approaching past the newly added C–H bond. A crystal structure of the major diastereomer proved the *syn* relative stereochemistry of **28**. In contrast to simpler substrates, simultaneous addition of $Ir^{III}/Bi(OTf)_3$ did not fully facilitate the cyclization of substrate **26**, which is presumably a result of the known attenuated activity of the iridium catalyst towards internally substituted olefins.[9a] Consequently, a single-flask, sequential approach was employed in which $Bi(OTf)_3$ was added after isomerization to the enol ether using increased catalyst loadings of Ir^{III}.[34] Overall, this Type 3 process offers the highest yields with the ability to easily access different pyrans and oxepane products, and the opportunity to incorporate additional stereocenters with high levels of diastereoselectivity.

Our current understanding of the cascade sequence is shown in Figure 2. The catalytic cycle begins with in situ generation of an active cationic iridium complex (**D**) by

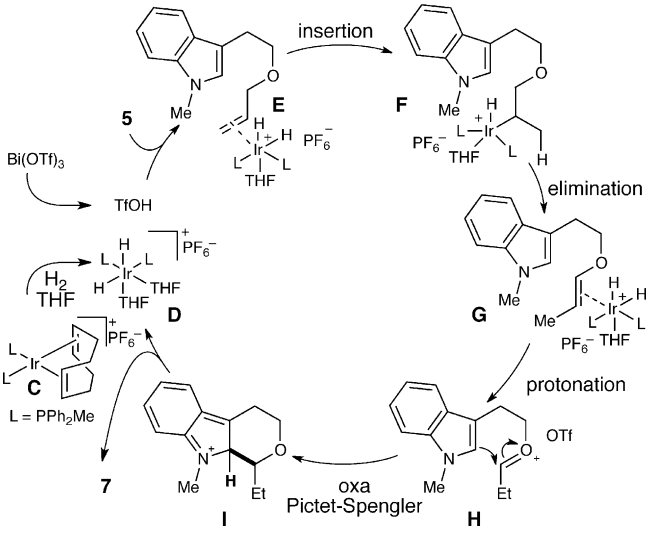
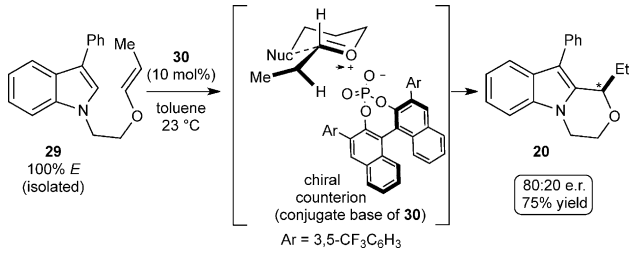


Figure 2. Catalytic cycle.

sparging hydrogen gas (from a balloon) into a suspension of **C** in THF. After association with the substrate **5** to form the complex **E**, a migratory insertion takes place and adds Ir–H across the olefin, thus generating the iridium complex **F**. A β-hydride elimination of the iridium complex subsequently furnishes the vinyl ether **G** which is equipped to be protonated. The triflic acid produced from $Bi(OTf)_3$ effectively protonates **G**, thereby generating the key oxocarbenium ion **H** which then can undergo an oxa-Pictet–Spengler reaction to generate the cyclized iminium ion **I**. The aromatization of **I** regenerates the Brønsted acid (TfOH) and ultimately furnishes the pyran-fused indole **7**.

Based on this reaction pathway, the tandem isomerization/cyclization provides a test platform for an enantioselective variant with chiral Brønsted acids. Chiral phosphoric acid (CPA) catalysis has emerged as a powerful strategy to promote various asymmetric transformations.[35] While the addition of nucleophiles to imines activated by CPAs is well developed, the generation of oxocarbenium ions and subsequent additions are far less advanced with only recent highly enantioselective ketalizations and aldol-type reactions being described.[36] Outside of these examples however, there are few cases of oxocarbenium/chiral counterion catalysis utilizing CPAs in instances of carbon nucleophile addition.[36a] Given the process described in Figure 2, chiral phosphoric acid **30** could protonate the enol ether and the subsequent conjugate base would form a contact ion-pair to generate enantioenriched heterocyclic-fused indoles (Scheme 2).



Scheme 2. Enantioselective oxa-Pictet–Spengler.

While the use of known chiral phosphoric acids instead of $Bi(OTf)_3$ in the one-pot isomerization/cyclization procedure from Table 2 afforded the pyran products with minimal levels of enantioselectivity (not shown), the purification of the intermediate enol ether **29** prior to addition of the phosphoric acid resulted in promising and measurable levels of enantioselectivity. For example, in the presence of 10 mol% of **30**, **29** provided the oxazinoindole **20** with encouraging levels of enantioselectivity (Scheme 2). Through an extensive screening of various phosphoric acids (not shown) it was found that **30** at room temperature gave the highest enantioselectivity (80:20 e.r.). Lowering the temperature did not improve enantioselectivity regardless of catalyst structure. This positive result marks the first example of an enantioselective method to generate oxazinoindoles and is only the second example of an enantioselective oxa-Pictet–Spengler reaction.[11]

In summary, a mild and efficient process to generate a wide variety of heterocycle-fused indoles has been developed utilizing cooperative catalysis between an iridium(III) catalyst and $Bi(OTf)_3$. Three distinct cyclization manifolds (Types 1–3) lead to bioactive scaffolds which can be obtained in good yields through a one-pot reaction with low catalyst loadings while avoiding the traditional harsh reaction conditions of Prins-type reactions. In addition, N-substituted indoles can be synthesized enantioselectively by an oxocarbenium/chiral phosphate counterion approach which provides a clear roadmap for further study of this asymmetric variant. The creation of focused pyran indole libraries through this method and subsequent biological evaluation are currently underway.

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[37] CCDC 950337 (**28**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

