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Exploitation of Cyclopropane Carbaldehydes to Prins Cyclization: Quick Access to (*E*)-Hexahydrooxonine and Octahydrocyclopenta[*b*]pyran

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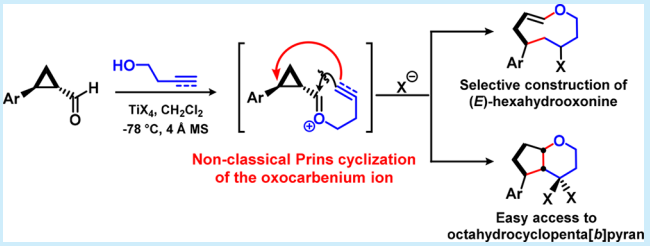
Supporting Information

ABSTRACT: A single-step TiX_4-mediated Prins-type cyclization of cyclopropane carbaldehydes with 3-buten-1-ol for the highly stereoselective construction of relatively strained (*E*)-hexahydrooxonines is reported. Switching the alcohol to 3-butyn-1-ol prompted a similar route, augmented by another cyclization within a nine-membered ring to afford a bicyclized product (4,4-dihalo-5-aryloctahydrocyclopenta[*b*]pyran). Easy transformation of the resulting geminal dihalide to a vinyl halide and a ketone further supplemented the substance of this approach.



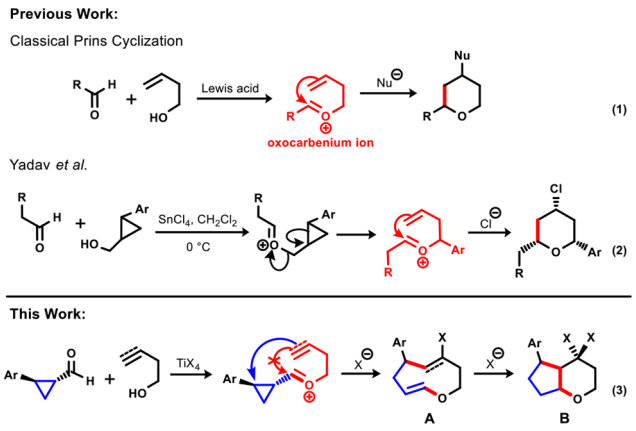
Over the years, Prins cyclization[1] has extensively been used as a facile tool for the synthesis of various tetrahydropyran, tetrahydrofuran, piperidine, and many carbocyclic derivatives which are useful structural motifs of various complex natural products and bioactive molecules[2] like calyxin F,[3] zampanolide,[4] and clavosolide A.[5] The process necessitates the formation of an oxocarbenium ion (an iminium ion in the case of aza-Prins cyclization) that undergoes a nucleophilic attack on its carbon center by an alkene/alkyne, followed by capturing the carbocation with a nucleophile.

Prins reaction has been thoroughly studied with a variety of substrates, and the literature is full of reports on the synthesis of the tetrahydropyran skeleton employing a variety of alkenols with the carbonyl compounds[6] (Scheme 1, eq 1). However, there are insignificant reports on cyclopropanes being an active participant in the Prins cyclization. One interesting approach, which engaged the cyclopropyl methanol in the synthesis of (±)-centrolobine, using the Prins chemistry was reported by Yadav et al.[7] (Scheme 1, eq 2). Although, in its proposed mechanism, cyclopropane is not directly involved in the Prins cyclization, it helps in the generation of benzylic carbocation, which gets captured by the aldehyde to form the active oxocarbenium ion that ultimately undergoes Prins cyclization. Similarly, in most of the reports on cyclopropanes in the Prins reaction, a cyclopropane ring opens up to generate the carbocation or promote nucleophilic attack on the carbonyl carbon.[8] The donor−acceptor cyclopropane ring opening was yet to be associated with the Prins cyclization in a direct fashion.

Our group has also been working on the reactivity of donor−acceptor cyclopropanes,[9] and in this regard, a Lewis acid catalyzed annulation of cyclopropane carbaldehydes with aryl hydrazines was reported.[10a] The captivating reactivity of the cyclopropane carbaldehyde[10] is built on the inceptive attack of a nucleophilic functionality on its carbonyl center. This makes it an intriguing reactant for possible Prins-type processes. We took this opportunity and designed a scheme that would implicate the aryl-substituted cyclopropane carbaldehyde (ACC) and an alkenol in the synthesis of strained medium-sized ring systems[11] via an extended Prins-type cyclization process (Scheme 1, eq 3).

We successfully constructed the nine-membered cyclic system[12] with a *trans* geometry about the double bond, (*E*)-4-chloro-6-aryl-2,3,4,5,6,7-hexahydrooxonine (**A**) (Scheme 1, eq 3). The *trans* geometry of the carbon−carbon double bond in the hexahydrooxonine ring, specifically induced in this pathway, is quite troublesome to achieve via any other synthetic route, and the procedures reported for the synthesis of similar systems are

Scheme 1. Classical Prins Cyclization and Its Extension to the Cyclopropane Carbaldehydes



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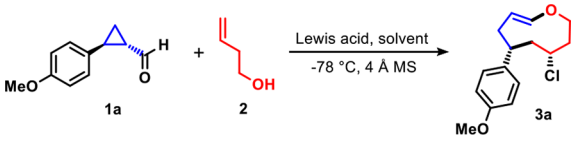
very limited.[13] With these results, we envisioned a bicyclization process subject to the use of alkynols[14] under identical reaction conditions. The second cyclization was expected to involve protonation and an in situ generation of the oxocarbenium ion that would take part in the classical Prins cyclization, all inside a nine-membered ring. Accordingly, with 3-butyn-1-ol (**4**), we successfully synthesized a bicyclic five-six fused ring system, 4,4-dihalo-5-aryloctahydrocyclopenta[*b*]pyran[15] (**B**) (Scheme 1, eq 3).

We took *trans*-2-(4-methoxyphenyl)cyclopropane-1-carbaldehyde (**1a**) as a standard substrate and made various attempts with the alkenols such as allyl alcohol, 3-buten-1-ol, and 4-penten-1-ol. Following the established literature,[16] we screened the process with Lewis acids like $SnCl_4$, $AlCl_3$, $FeCl_3$, and $TiCl_4$ in varying concentrations, but the expected product was not found in any of the prototypes. This could be due to decomposition of cyclopropane carbaldehyde by strong Lewis acids. We tried the reaction at lower temperatures[6,16a] and screened the process with a variety of Lewis acids. We obtained the nine-membered cyclic product **3a** with 3-buten-1-ol (**2**) by treatment with 1 equiv of $TiCl_4$ at −78 °C. The reaction was also carried out in various solvents (Table 1), and it was found that

Table 1. Optimization of the Reaction Conditions[a]



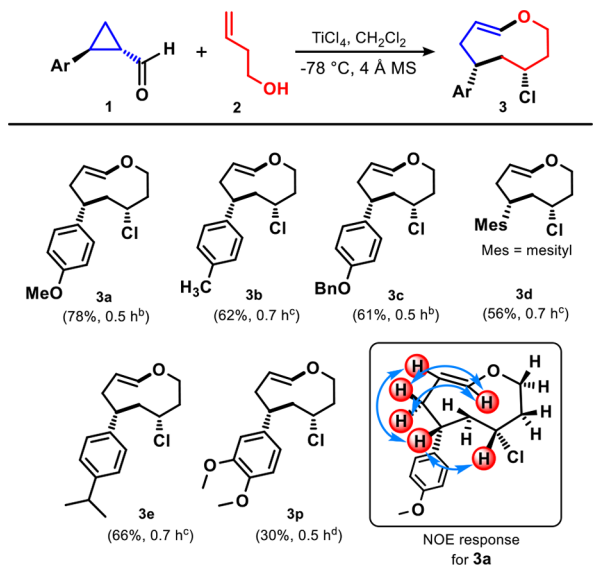
entry	Lewis acid	equiv	solvent	additive (2 equiv)	yield %
1	$TiCl_4$	0.2	CH_2Cl_2		
2	$TiCl_4$	1	CH_2Cl_2		78
3	$TiCl_4$	1.5	CH_2Cl_2		38
4	$AlCl_3$	1	CH_2Cl_2		26
5	$TiCl_4$	1	$CHCl_3$		22
6	$TiCl_4$	1	DCE		52
7	$TiCl_4$	1	toluene		30
8	$TiCl_4$	1	THF		-
9	$TiCl_4$	1	Et_2O		-
10	$TiCl_4$	0.6	CH_2Cl_2	TMSCl	36
11	$TiCl_4$	0.1	CH_2Cl_2	TMSCl	10
12	$BF_3{\cdot}OEt_2$	1	CH_2Cl_2	TMSCl	32

[a]The optimum condition involved using 1 equiv of $TiCl_4$ at −78 °C in CH_2Cl_2 as a solvent.

3a was obtained in CH_2Cl_2, $CHCl_3$, $(CH_2)_2Cl_2$ (DCE), and toluene. Among these, CH_2Cl_2 emerged as the solvent of choice. However, ethereal solvents such as diethyl ether (Et_2O) and THF could not afford the desired product. With 1 equiv of $BF_3{\cdot}OEt_2$, we could not obtain the fluorinated hexahydrooxinine derivative because it is difficult to get the fluoride ion from BF_3 at −78 °C, but addition of chlorotrimethylsilane (TMSCl) as an additive, under the same reaction conditions, afforded the chlorinated product **3a** in 32% yield (Table 1).

With this optimized condition in hand, we investigated the scope of cyclopropane carbaldehydes consistent with this protocol (Scheme 2). The results demonstrated that the process was compatible with cyclopropane carbaldehydes having moderately electron-releasing groups such as *p*-methyl, *p*-methoxy, *p*-isopropyl, etc. on the phenyl ring in its vicinal position. Prominent results were obtained with **1a**, affording **3a** in 78% yield. The process was not reconcilable with 3,4-

Scheme 2. Prins-Type Annulation between ACC (1) and 3-Buten-1-ol (2)[a]



[a]Isolated yields and reaction time are illustrated. [b]With 1 equiv of $TiCl_4$. [c]With 1.5 equiv of $TiCl_4$. [d]With 0.1 equiv of $TiCl_4$ and 2 equiv of TMSCl as an additive (for details, see SI).

dimethoxyphenyl and furan-2-yl-substituted ACCs. In such cases, the higher electron-releasing effect of the aryl substituent was expected to promote decomposition of the cyclopropane with higher concentrations of $TiCl_4$. It was also interesting that the yield decreased drastically for **1a** with increased $TiCl_4$ loading to 1.5 equiv. Again, some decomposition of the ACC with elevated concentration of $TiCl_4$ could be the possible reason behind the loss in yield. We also attempted the reaction in the presence of an external chloride source such as TMSCl,[17] using lower concentrations of $TiCl_4$, and successfully obtained product **3p** out of an electron-rich ACC **1p**, though the yield was not satisfactory (Table 1). The geometry of the product was confirmed from the coupling constant values (J = 15−16 Hz, suggesting the *trans* geometry of the double bond) and the 2D-NOE data for **3a** (Scheme 2; also see the Supporting Information (SI)).

To investigate the scope of this approach with the alkynols, the reaction was screened with propargyl alcohol, 3-butyn-1-ol, 4-pentyn-1-ol, and 3-pentyn-1-ol under the optimized reaction conditions. Only **4** with **1a** underwent the proposed route to produce the desired bicyclic product **5a** in 58% overall yield. It appeared to be an excellent method for the one-step synthesis of geminal dichloro-substituted octahydrocyclopenta[*b*]pyran (Scheme 3). It was observed that the overall yield increased with increased $TiCl_4$ loading, and the process was optimized at 1.5 equiv of $TiCl_4$ in CH_2Cl_2 solvent at −78 °C, except for **1c**, which underwent decomposition upon increased $TiCl_4$ loading. Screening the process with a variety of ACCs revealed that the reaction would progress only with the electron-deficient (**1g**−**1i**) cyclopropanes or with those cyclopropane carbaldehydes that were slightly electron-rich (Scheme 3). Electron-rich cyclopropanes like those substituted with 3,4-dimethoxyphenyl **1p** and furan-2-yl failed to afford the desired bicyclic product. Among ACCs, **1i** offered the maximum yield for the bicyclized product and afforded **5i** in an excellent yield of 80%. Both diastereomers (**5ha**/**5hb**) were isolated in the case of **5h**, and their geometries were determined by the NOE experiment (for

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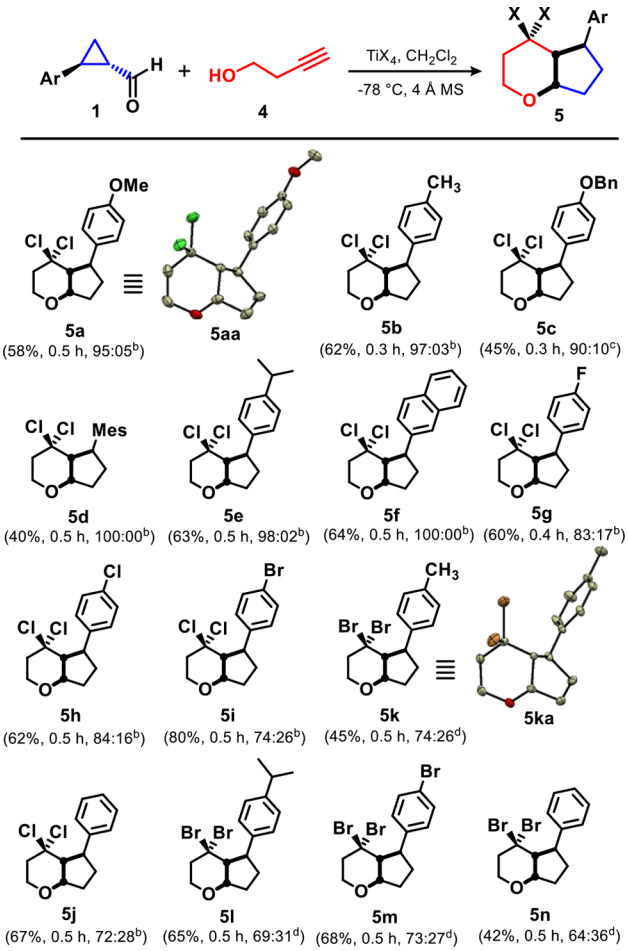
Scheme 3. Reaction of ACC (1) with 3-Butyn-1-ol (4)[a]

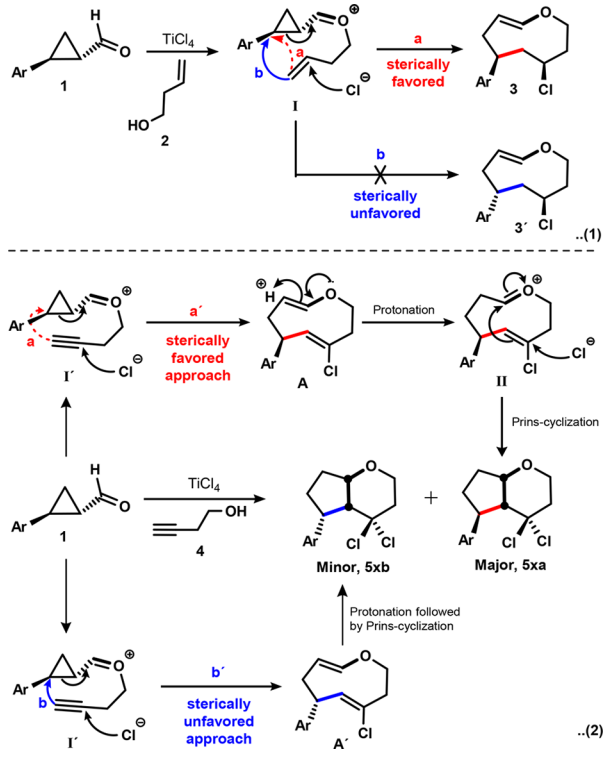


[a]Isolated yields, reaction time, and diastereomeric ratios (**5xa**/**5xb**) are illustrated. Hydrogen atoms are omitted in the single-crystal X-ray structures of **5aa** and **5ka** for the sake of clarity. [b]With 1.5 equiv of $TiCl_4$. [c]With 1 equiv of $TiCl_4$. [d]With 1.5 equiv of $TiBr_4$ (for details, see SI).

details, see SI). The structure of major isomer **5aa** was also ascertained by single-crystal X-ray analysis (Scheme 3). We also explored the reaction with $TiBr_4$ to obtain a geminal dibromo product. With the optimized conditions, we successfully synthesized dibromo derivatives **5k**–**5n** but could not separate the individual diastereomers as they seem to have exactly the same polarity. The X-ray crystal structure for the major diastereomer of **5k** enabled us to ascertain its stereochemistry (Scheme 3).

The mechanism we proposed (Scheme 4) is in accordance with the earlier reports,[1,6,14] except that the oxocarbenium ion ring closing here is coupled with the cyclopropane ring opening. The mechanism also justified the *trans* geometry of the carbon–carbon double bond in **3**. It involved a $TiCl_4$-induced nucleophilic attack of the alcohol on the aldehyde, resulting in the formation of the oxocarbenium ion **I**. As demonstrated in the plausible mechanism (Scheme 4, eq 1), the *trans* geometry of ACC is conserved as such in the oxocarbenium ion **I**. Intermediate **I** then encountered an intramolecular nucleophilic attack by the carbon–carbon double bond on the cyclopropane, shifting the cyclopropane carbon–carbon bond toward the oxocarbenium carbon and shaping a *trans* double bond inside a nine-membered ring. The resulting cation was then captured by

Scheme 4. Plausible Mechanism for Prins-Type Annulation of 1 with 3-Buten-1-ol (2) and 3-Butyn-1-ol (4)



the chloride ion from $TiCl_4$. The nucleophilic cyclopropane ring opening may take place either via a less hindered approach (a) of the double bond (i.e., from the back side of the aryl substituent), resulting in the formation of **3**, or from the sterically hindered aryl side approach (b) of the double bond, which would afford **3′**. However, the sterically unfavored approach (b) was not feasible here, as only a single isomer **3** was obtained in the process.

With **4**, the reaction did not cease at the nine-membered cyclic product (**A** or **A′**) and underwent protonation to give the oxocarbenium ion **II**. Intermediate **II** then encountered the classical Prins cyclization within the nine-membered ring to give the fused product **5x** (Scheme 4, eq 2). The diastereoselectivity of this process depends on the approach of the carbon–carbon triple bond in the initial cyclization. Major isomer **5xa** was obtained by the sterically facile attack of the alkyne on ACC (a′), and minor isomer **5xb** was obtained by the sterically hindered aryl side attack of the alkyne on the ACC (b′). The sterically unfavorable approach (b′) was possible here, as the attacking moiety in this case was less bulky (an alkyne having a linear geometry). Thus, bicyclization followed a double Prins-type pathway, involving first the extended Prins cyclization, followed by the classical Prins cyclization within a nine-membered ring. As depicted by the stereochemistry of the product, formation of a stable fused tetrahydropyran derivative **5x** (a well-studied pathway for the classical Prins cyclization), rather than a highly strained fused THF derivative with a chlorine atom at the ring fusion, controls the regioselectivity of the second chloride attack.

To showcase the scope of the developed approach, we carried out some simple transformations with the molecules we isolated. To examine the possibility of dehydrochlorination[18] for the geminal dichloride, we subjected **5ha** to elimination with ^{t}BuOK in methanol, which afforded the vinyl chloride **6** in an excellent yield of 99% (Scheme 5). When treated with MgO, **5ha** also

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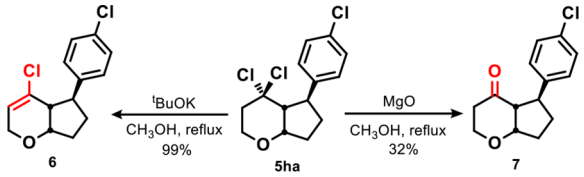
Scheme 5. Derivatization of 5ha



underwent methanolysis[19] to give the keto derivative **7**; however, the yield was restricted only to 32% (Scheme 5). These derivatizations illustrate the potential reactivity of the geminal dihalides produced by this approach.

In summary, a versatile technique was developed, where one can deliberately direct the route to a nine-membered ring or a fused bicyclic system, simply by picking up an appropriate alcohol. The protocol provides an excellent method for the single-step time-efficient construction of (*E*)-hexahydrooxonines and the octahydrocyclopenta[*b*]pyrans. The geminal dichloride was successfully transformed to a vinyl chloride and a pyranone derivative. Cyclic halides, geminal dihalides, vinyl halides, and pyranones formulated in this process possess a great scope for further transformations, and the approach shows promise in the synthetic chemistry sector. Development of the asymmetric variant of the present methodology and its further application are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02094.

Experimental procedures, ^{1}H NMR, ^{13}C NMR, IR spectra, and mass data of all new compounds, single-crystal X-ray data (PDF)

Accession Codes

CCDC 1845296 and 1845299 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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