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Expeditious Synthesis of Enantioenriched Tetrahydropyrans via Chemoselective C–N bond Cleavage of Aza-Oxa-Bicyclo[3.2.1] Octanes

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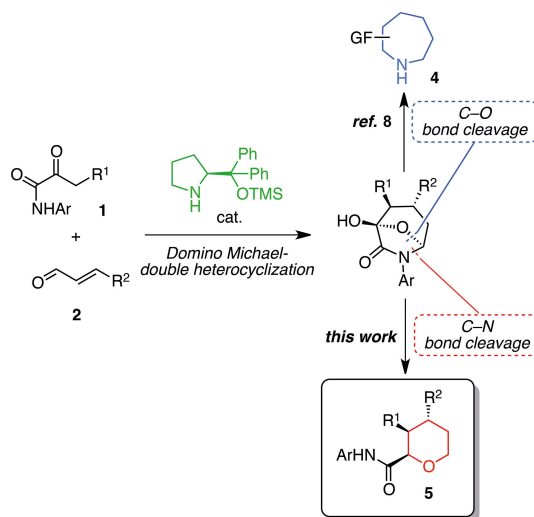
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Abstract: A rapid synthesis of enantioenriched 2,3,4-trisubstituted tetrahydropyrans in good yields and stereoselectivities is reported. The first step is a domino organocatalytic reaction between ambident electrophilic and 1,4-bis-nucleophilic 1,2-ketoamides and 1,3-bis-electrophilic enals, leading to aza-oxa-bicyclo[3.2.1]octane. Then, the TiCl₄/Et₃SiH system ensures a chemoselective cleavage of the C–N bond and affords the desired trisubstituted tetrahydropyran in good yield and with conservation of the precursors optical purity. This final synthetic operation includes two consecutive oxocarbenium ion formation and reductions.

Keywords: Tetrahydropyrans; Azepanes; Organocatalysis; Multiple bond-forming transformations; Oxocarbenium ions

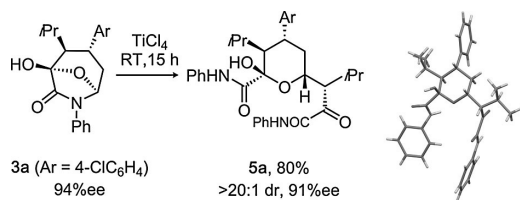
The tetrahydropyran (THP) core constitutes a central structural subunit found in many natural and unnatural products displaying a wide range of biological activities.^[1] For this reason, the stereoselective preparation of such heterocycles has been the center of many efforts.^[2] The most common strategies are based on the inter- and intramolecular C–O^[3] or C–C^[4] bond formations of the oxacycle. Other developed methodologies exploit the C–C bond fragmentations of the dihydrofuran ring in strained 8-oxabicyclo[3.2.1]octene intermediates,^[5a–e] including enantioselective reactions.^[5f,g] As a matter of fact, the implementation of straightforward enantioselective approaches for heterocycle syntheses is an attractive field of research and constitutes an important challenge of modern organic synthesis.^[6] Recently, our group studied the

chiral amine-catalyzed synthesis of optically active aza-oxa-bicyclo[3.2.1]octane **3** from simple achiral α -ketoamides **1** and enals **2**.^[7] These valuable synthetic platforms allowed us to further access functionalized azepanes **4** exploiting the lability of the C–O bond (Scheme 1).^[8] In this context, we disclose a new temporary-bridge strategy^[9] based on a chemoselective C–N bond cleavage leading to the formation of highly diastereo- and enantioselective construction of new functionalized tetrahydropyrans **5**, bearing three consecutive stereogenic centers.



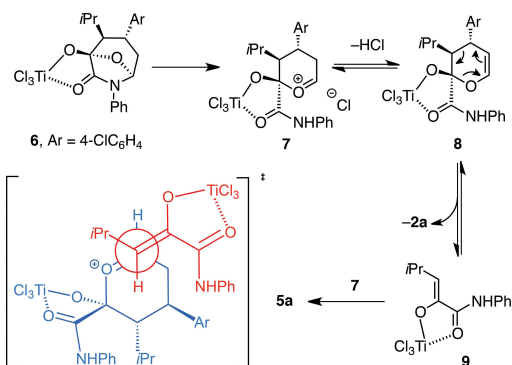
Scheme 1. C–N vs C–O bond cleavage accessing to azepanes **4** or THPs **5** from bicyclic precursors **3**.

We reasoned that Lewis acid activation on the amide moiety of oxabridged azepanes **3** should weaken the C–N bond triggering its chemoselective cleavage with concomitant revelation of the pyran nucleus.^[10] To this end, we screened various Lewis acids such as InCl₃, BF₃·OEt₂, SnCl₄ or Cu(OTf)₂ but all these reagents left the starting azepane **3a** untouched or partially decomposed in some cases. The use of oxophilic TiCl₄ resulted in the expected C–N bond cleavage, with the formation of densely functionalized tetrahydropyran **5a**, bearing four stereogenic centers and incorporating a second ketoamide moiety, in 80% yield (Scheme 2). This compound was isolated as a single diastereomer with conservation of enantiopurity, as shown by the X-ray structural determination of **5a**.^[11]



Scheme 2. TiCl₄ mediated C–N bond cleavage of **3a**.

A mechanistic rationale coherent with the results above is proposed in Scheme 3. The formation of **5a** (Scheme 3) initiates with chelate **6** triggering the chemoselective C–N bond cleavage to form the reactive dihydropyran **8** via the corresponding oxocarbenium ion intermediate **7**. Then, a retro-Diels–Alder reaction delivers the (*Z*)-titanium enolate intermediate **9**^[12] with expulsion of *p*-chlorocinnamaldehyde (**2a**) which has been detected by ¹H NMR of the crude reaction (see supporting information). Finally, addition of the *Re* face of enolate **9** to the *Si* face of the



Scheme 3. Proposed Mechanism for the formation of **5a**.

oxocarbenium ion **7** via an antiperiplanar transition state rationalizes the high diastereoselectivity observed for this reaction.

As depicted in Scheme 3, the formation of the THP **5** relies on the chelation of oxa-bridged azepanes **3** with titanium(IV) chloride decreasing the electron density of C–N bond and rendering its cleavage possible. The good yield obtained for **5a** (80%) showed that oxocarbenium ion intermediate **7** is relatively stable under the reaction conditions and that the slow generation of titanium enolate **9** from **8** enables the stereoselective formation of the C–C bond. Inspired by this interesting result, we hypothesized that oxocarbenium ions of types such as **7** could be trapped by other nucleophiles.

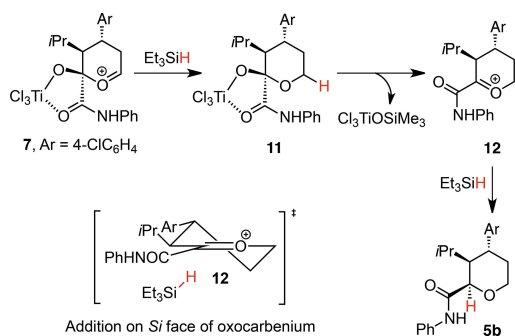
Initial experiments using allyltrimethylsilane or 1,3-dimethoxybenzene resulted in the decomposition of the starting material even at –78 °C. Pleasingly, running the reaction with triethylsilane as a hydride source afforded the 2,3,4-trisubstituted THP **5b** in 78% yield, as a single diastereomer with slight erosion of enantiomeric excess (92% ee starting from 94% ee in **3a**, Table 1, entry 1). More hindered silanes gave poorer yields (entries 2 and 3). When using triphenylsilane, partial isomerization, rather than reduction of the oxocarbenium intermediate, took place (*vide supra*), leading to the formation of dihydropyran **10** in 37% yield. Less reactive siloxanes (entries 4–6) were not effective for this reaction.

Table 1. Optimization of the TiCl₄-mediated reduction.

Entry	Silane	Yield of 5b (%) ^[b]	dr ^[c]
1 ^[d]	Et ₃ SiH	78	>20:1
2	Ph ₂ SiH ₂	39	>20:1
3 ^[e]	Ph ₃ SiH	46	>20:1
4	(EtO) ₂ MeSiH	complex mixture	–
5	(EtO) ₃ SiH	No reaction	–
6	PMHS ^e	No reaction	–

^[a] Reaction conditions: a solution of **3a** (0.2 mmol, 1.0 equiv) was stirred at –78 °C. The silane (0.8 mmol, 4.0 equiv) and TiCl₄ (0.4 mmol, 2 equiv) were added successively. Then, the reaction temperature was increased slowly to 0 °C during 2 h. Then, the reaction was stirred at RT for 18 h. ^[b] Isolated yield. ^[c] Determined by ¹H NMR of crude reaction. ^[d] ee = 92%, determined by chiral HPLC. ^[e] 37% of **10** was isolated (dr >20:1, ee = 92%). ^ePMHS = polymethylhydrosiloxane.

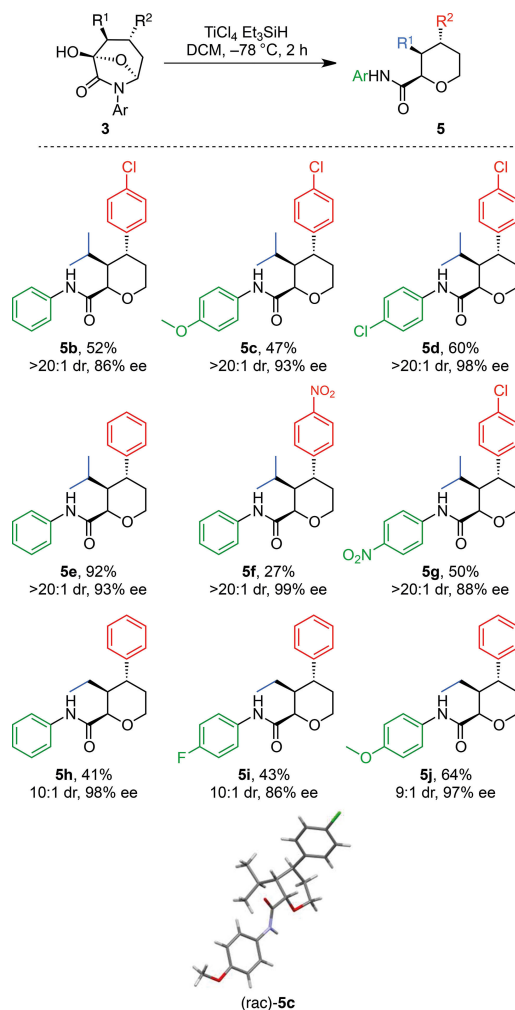
A double reduction of both the *N,O*-mixed acetal and the hemiacetal functions *via* two successive oxocarbenium formations and trappings (intermediates **7** and **12**, Scheme 4) explains the formation of this novel product. The second reduction occurs from the more accessible *Si* face of oxocarbenium **12**, delivering predominantly the *trans-cis* diastereomer **5b** (dr > 20:1, Scheme 4).



Scheme 4. Mechanism for the formation of **5b**.

Having established the best reaction conditions for this two-step enantioselective synthesis of 2,3,4-trisubstituted tetrahydropyran **5**, we examined the reaction scope by varying the nature of R^1 , R^2 and Ar substituents (Scheme 5). With an isopropyl group ($R^1 = iPr$), the bicyclic azepanes **3** were obtained in moderate to good yields as single diastereomers and with generally good to high enantiomeric excesses (see supporting information). Conversion to THPs in these cases was efficient, even if a poor yield was observed in **5f** when $R^2 = 4\text{-NO}_2\text{C}_6\text{H}_4$. Switching to ketoamides with $R^1 = \text{Et}$ resulted in equally good enantioselectivities with still reasonable diastereoselectivities for the synthesis of bicyclic azepanes (see supporting information). Their transformation into corresponding THPs **5h-j** using $\text{TiCl}_4/\text{Et}_3\text{SiH}$ was possible maintaining the enantiomeric excesses even if the yield in some cases was moderate. Finally, in the case of oxa-bridged azepane **3l** ($R^1 = \text{H}$, $R^2, R^3 = \text{Ph}$), the reduction resulted in decomposition of the starting material. Unfortunately, the introduction of an aliphatic group at R^2 was not possible since the domino reaction starting with an aliphatic substituted enal **2** ($R^2 = \text{Me}$ or Et) was not efficient. Similarly, the use of acrolein ($R^2 = \text{H}$) in the domino reaction led to degradation of the starting materials.

Racemic tetrahydrofuran **5c** was crystallized and its relative configuration was identified by X-ray diffraction analysis.^[13] The same configuration was assigned in analogy for all compounds **5**.



Scheme 5. Synthesis of compounds **5b-j**.

In conclusion, we have developed a new expeditious access to enantioenriched 2,3,4-trisubstituted tetrahydropyrans. The bicyclo[3.2.1]octane starting materials, synthesized from 1,2-ketoamides and enals *via* an enantioselective chiral amine-catalyzed domino three bond-forming reaction, are readily available on a gram scale. Then, the formation of the THP core relies on the reductive $\text{TiCl}_4/\text{Et}_3\text{SiH}$ system ensuring a chemoselective cleavage of the oxa-bridge *C-N* bond. This final synthetic operation includes two consecutive oxocarbenium ion formation and reductions. The desired THPs were obtained in good yields with high optical purity.

Experimental Section

General Procedure for the Reduction Step:

A 1 M solution of TiCl_4 in DCM (400 μL , 0.4 mmol, 2.0 equiv) is added to a stirred solution of the bicyclic compound **3** (70 mg, 0.2 mmol, 1.0 equiv) and Et_3SiH (128 μL , 0.8 mmol, 4.0 equiv) in dry CH_2Cl_2 (2 mL) at -78°C , under argon atmosphere. Then, the reaction is allowed to reach 0°C during two hours, then is stirred at room temperature for 18 h. After completion, the reaction mixture is quenched with a saturated solution of NH_4Cl (2 mL). The reaction mixture is extracted with DCM (4×3 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash chromatography over silica gel (eluent: petroleum ether/EtOAc gradient 90:10 to 70:30) affords the desired tetrahydropyran.

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