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Catalytic Enantioselective Synthesis of Tetrahydroisoquinolines and Their Analogues Bearing a C4 Stereocenter: Formal Synthesis of (+)-(8*S*,13*R*)-Cyclocelabenzine

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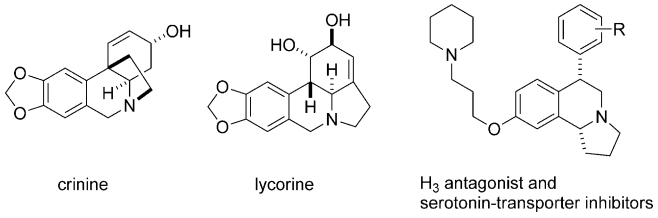
1,2,3,4-Tetrahydroisoquinoline (THIQ) is a ubiquitous subunit found in numerous alkaloids and therapeutic agents with significant biological activities, such as antitumor and antimicrobial activities.[1] Thus, intensive efforts have been directed to the development of methods for the stereoselective incorporation of this important unit. Among the various strategies that have been developed, the majority are focused on the incorporation of THIQs with a C1 stereocenter.[2] In contrast, direct and general asymmetric methods for the preparation of a THIQ skeleton with concomitant formation of the C4 stereocenter are scarce.[3–5] However, THIQs of this type are by no means less important. For example, many natural products and drug leads, such as crinine, lycorine, and a type of H_3 antagonist/serotonin-transporter inhibitors (Scheme 1) have a stereogenic center at



Scheme 1. Selected natural products and drug leads containing THIQs with a C4 stereogenic center.

the C4 position.[6] As a result of the limited availability of such methods, current approaches for the synthesis of these core structures typically involve multistep sequences, for example, initial installation of the C4 stereocenter followed by ring closure at the C1 position (Scheme 2).[7] Herein, we report the first multicomponent strategy to address this unmet challenge by establishing the THIQ skeleton as well as the C-4 stereogenic center in one step.

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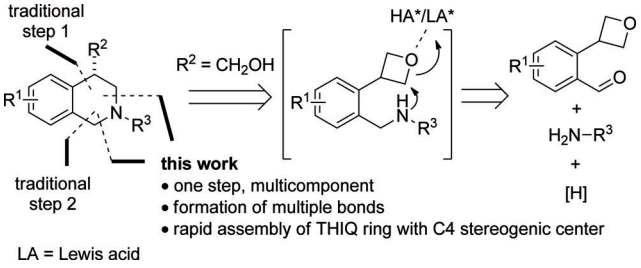
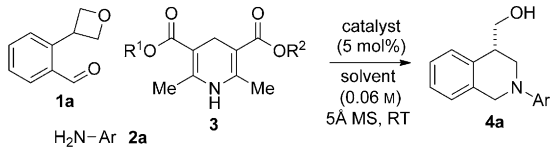


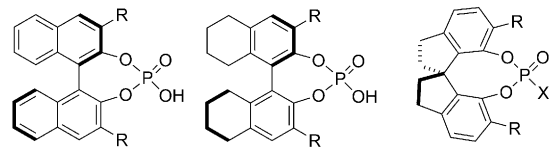
Scheme 2. Synthesis of THIQs bearing a C4 stereocenter.

Intrigued by the versatility of the oxetane functional group in organic synthesis and medicinal chemistry[8] as well as our initial success in employing it for ring-expansion and oxetane-directed aza-Diels–Alder reactions,[9] we envisioned that a benzylamine tethered with an *ortho*-oxetane moiety could undergo ring formation leading to THIQ (Scheme 2). The intramolecular oxetane ring opening by the nitrogen atom could be enantioselective in the presence of a chiral catalyst, thus furnishing the C4 stereocenter. The benzylamine could be generated in situ by reductive amination of the corresponding aldehyde. In this multicomponent cascade process, the proper choice of chiral catalyst is crucial not only for the efficient bond formation in both steps, but also for the chiral induction in the oxetane desymmetrization.[10] In view of the known difficulty in oxetane ring opening by amine nucleophiles,[11] and the high enantioselectivity that can be achieved with Lewis acid catalysis,[11c] we planned to examine the use of chiral Brønsted acid catalysts.[12,13]

We began the evaluation of our hypothesis with aldehyde **1a** and 3,4,5-trimethoxyaniline **2a** as the reaction partners and Hantzsch ester **3a** as the reductant.[14] In the presence of 5 mol% of racemic phosphoric acid **A1**, we were pleased to find that the desired THIQ, **4a**, formed in quantitative yield (Table 1, entry 1). This result prompted us to screen various enantiopure chiral phosphoric acids with different chiral backbones and substituents at the 3- and 3′-positions. Although all of the evaluated catalysts are capable of promoting the desired formation of **4a** in essentially quantitative yield, SPINOL-derived phosphoric acid **C1** gives the highest enantioselectivity (Table 1, entry 6).[15] In the absence of molecular sieves, a slight decrease in enantioselectivity was observed (Table 1, entry 8). Further solvent screening revealed that etherate solvents are superior, with cyclopentyl methyl ether (CPME) being the best (94:6 er;

Table 1. Optimization of reaction conditions.[a]



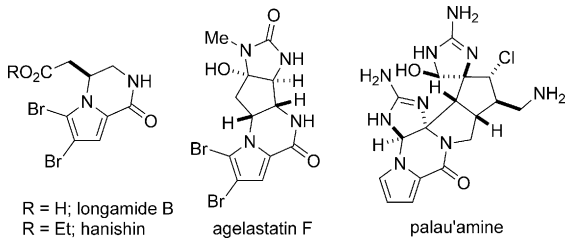


Entry	Catalyst	Solvent	**3** (R^1,R^2)	er (**4a**)
1	(±)-**A1**	toluene	**3a** (Et,Et)	–
2	(*R*)-**A2**	toluene	**3a**	73:27
3	(*R*)-**A3**	toluene	**3a**	64:36
4	(*R*)-**A4**	toluene	**3a**	88:12
5	(*R*)-**B**	toluene	**3a**	70:30
6	(*S*)-**C1**	toluene	**3a**	92:8
7	(*S*)-**C2**	toluene	**3a**	84:16
8[b]	(*S*)-**C1**	toluene	**3a**	91:9
9	(*S*)-**C1**	DCM	**3a**	70:30
10	(*S*)-**C1**	THF	**3a**	91:9
11	(*S*)-**C1**	Et_2O	**3a**	93:7
12	(*S*)-**C1**	CPME	**3a**	94:6
13	(*S*)-**C1**	CPME	**3b** (*t*Bu,*t*Bu)	90:10
14	(*S*)-**C1**	CPME	**3c** (*t*Bu,Me)	92:8
15	(*S*)-**C1**	CPME	**3d** (Me,Me)	95:5
16[c]	(*S*)-**C1**	CPME	**3d**	97:3

[a] The ratio, **1**/**2**/**3**, is 1:1:1.2; GC analysis using an internal standard showed that all products were obtained in quantitative yield. [b] Without 5 Å MS. [c] Run at −20 °C. CPME = cyclopentyl methyl ether, Tf = trifluoromethanesulfonyl.

Table 1, entry 12). The steric bulk of the Hantzsch ester also has an effect on enantioselectivity. When the relatively small dimethyl ester, **3d**, is used, a slight increase in enantiomeric ratio was observed. Finally, at a lower temperature (−20 °C), the reaction proceeds with both high efficiency and excellent enantioselectivity (Table 1, entry 16).

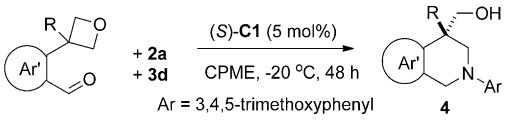
With standard reaction conditions established, we next examined the scope of the multicomponent reaction (Table 2). A range of THIQ products with electron-withdrawing and electron-donating groups can be formed with high efficiency and good to excellent enantioselectivity (**4a**–**e**). A gram-scale reaction was also carried out, and no erosion in efficiency and enantioselectivity were observed (**4a**), relative to the smaller scale reactions, thus suggesting that our protocol is amenable to large-scale multistep synthesis. THIQs with a stereogenic quaternary center at the C4 position can also be obtained in high yield, albeit with moderate enantioselectivity (**4f**). Substrates having oxetanes tethered on a heterocyclic aryl ring, for example, on thiophene (**4g**), pyrrole (**4h-i**), and indole (**4j**) ring can also participate in the enantioselective cascade process to furnish a diverse set of heterocyclic compounds. Notably, pyrrolopiperazine and indolopiperazine are both key subunits of a range of important drug leads and bioactive natural products, such as longamide B, agelastatin F, and palau' amine (Scheme 3).[16] In addition, as shown in Table 3, a range of aryl amines are suitable reaction partners. The mild reaction conditions are compatible with typical functional groups, such as ethers, esters, halides, and free alcohols. Finally, the hydroxymethyl group in the 4-position of the products is poised for further functionalizations, such as oxidation and coupling reactions.

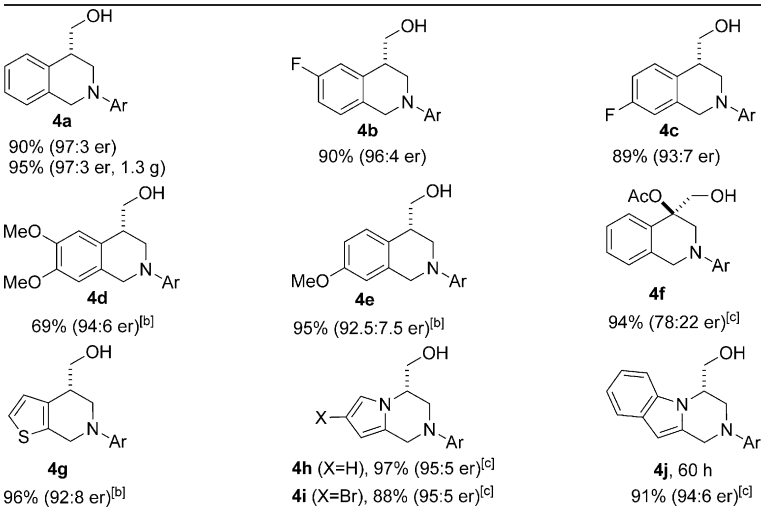


Scheme 3. Representative pyrrolopiperazine-containing alkaloids.

We have carried out several control experiments to probe the reaction mechanism. In the absence of the reductant **3d**, the reaction between **1a** and **2a** affords **5** in quantitative yield as a single diastereomer [Eq. (1)], presumably resulting from formation of the N,O-acetal followed by oxetane ring opening by attack of the nitrogen atom. Because the C4

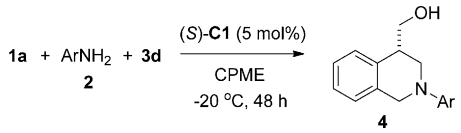
Table 2. Aldehyde scope.[a]





[a] Yield of isolated product. [b] Reaction performed at 0 °C. [c] Reaction performed at room temperature.

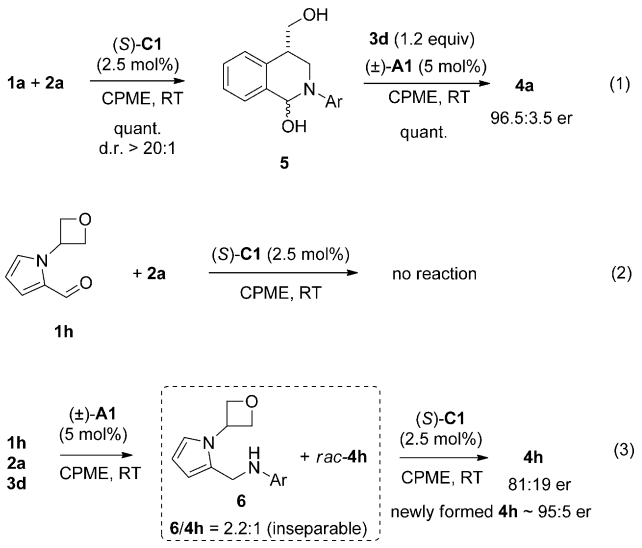
Table 3. Amine scope.[a]

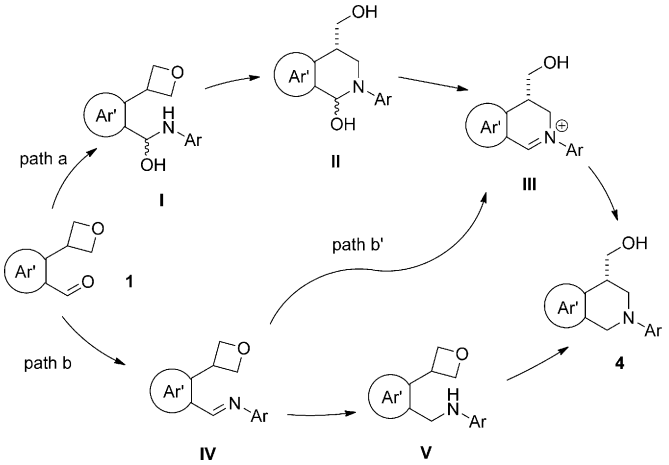


Entry	Ar	Product	Yield [%]	er of **4**
1	3-OH-C_6H_4	**4k**	95	96:4
2	3,5-$(OMe)_2$-C_6H_3	**4l**	96	96:4
3	4-OMe-C_6H_4	**4m**	89	94:6
4	4-SMe-C_6H_4	**4n**	96	93:7
5		**4o**	95	88:12
6	2-napthyl	**4p**	96	90:10

[a] Yield of isolated product.

stereogenic center has been already established, compound **5** was subjected to reduction by Hantzsch ester **3d** in the presence of racemic phosphoric acid **A1**. Product **4a** was obtained in quantitative yield and the enantioselectivity is comparable to that obtained using the one-pot standard reaction conditions. However, we could not observe any intermediate, such as **5**, under our standard one-pot procedure. These results suggest that if compound **5** is an intermediate, the second step might be the faster step. In contrast to **1a**, pyrrole-linked substrate **1h** could not lead to a similar intermediate. Indeed, no reaction was observed between **1h** and **2a** in the presence of catalyst **C1** [Eq. (2)]. However, during the one-pot reaction of **1h** under our standard reaction conditions, we were able to observe one intermediate that is initially generated and then consumed at the end. When racemic catalyst **A1** was used, the same intermediate, which proved to be the reductive amination product **6**, was also observed and isolated at partial conversion of substrate as an inseparable mixture with racemic product **4h** [Eq. (3)]. This mixture was next subjected to the standard reaction conditions, thus forming enantioenriched **4h** (81:19 er). The enantiomeric ratio (er) of **4h** that was formed solely in the second step was calculated as being 95:5, which is similar to





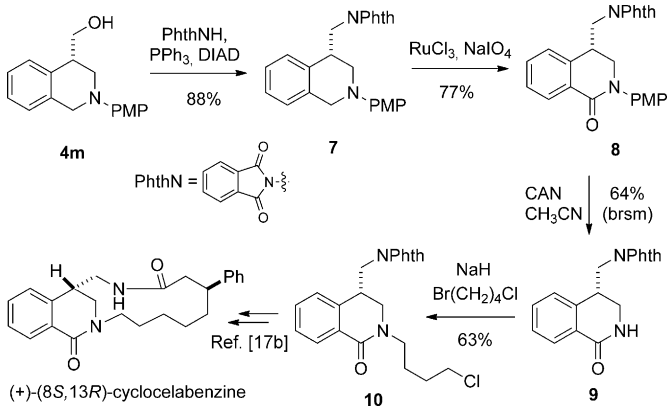
Scheme 4. Plausible mechanisms.

that of the product obtained by using the one-pot standard reaction conditions.

From the above experimental results, we proposed possible mechanisms (Scheme 4). As depicted in path a, through mediation of the acid catalyst, the aldehyde and the amine forms N,O-acetal **I**, an intermediate for imine formation. Rather than undergoing dehydration to form an imine, **I** undergoes intramolecular oxetane ring opening through attack of the amine group, which is more nucleophilic than the alcohol group, to give intermediate **II**. Subsequent reduction of the resulting N,O acetal group, presumably via iminium **III**, affords the desired product, **4**. Alternatively, the aldehyde and the amine may first undergo reductive amination to form amine **V** via the imine intermediate **IV** (path b). Next, enantioselective ring opening of the oxetane delivers product **4**. It is also possible for imine **IV** to undergo enantioselective oxetane ring opening to form iminium **III** (path b′). According to the experimental results, all these mechanisms may function, the one dominating being dependent on the substrate.

To demonstrate the application of our method for THIQ synthesis, we completed a formal asymmetric synthesis of the spermidine alkaloid, (+)-(8*S*,13*R*)-cyclocelabenzine (Scheme 5).[17] The enantioenriched product **4m** obtained from our multicomponent reaction was converted into phthalimide **7** under Mitsunobu conditions. Subsequent oxidation at the C1 position delivered dihydroisoquinolinone **8**. Oxidative cleavage of the *para*-methoxyphenyl (PMP) group followed by alkylation afforded **10**, a known intermediate in a previously completed synthesis of (+)-(8*S*,13*R*)-cyclocelabenzine.[17b]

In summary, we have developed a direct multicomponent method for the efficient assembly of tetrahydroisoquinoline; the transformation involves concomitant formation of a C4 stereocenter by means of enantioselective desymmetrization of oxetanes with amine nucleophiles. Thus, tetrahydroisoquinolines, privileged structures that are typically synthesized by a multistep sequence, can now be prepared using a one-step catalytic asymmetric method with high efficiency and



Scheme 5. A formal synthesis of (+)-(8*S*,13*R*)-cyclocelabenzine. brsm = based on recovered starting material, CAN = cerium ammonium nitrate, DIAD = diisopropylazodicarboxylate.

enantioselectivity. The present method can also be applied to the asymmetric synthesis of other heteroaryl-fused analogs, such as pyrrolopiperazines and indolopiperazines, which are also core structures of many important alkaloids and drug lead compounds. This multicomponent reaction may proceed by two possible mechanisms, either of which could be dominant depending on the substrate. Finally, we have applied our protocol in the formal synthesis of the alkaloid, (+)-(8*S*,13*R*)-cyclocelabenzine. We anticipate that the present method will find more applications in drug discovery and alkaloid synthesis.

Acknowledgements

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Keywords: alkaloids · asymmetric catalysis · nucleophilic addition · organocatalysis · strained molecules

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