Asymmetric Catalysis

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Construction of Tropane Derivatives by the Organocatalytic Asymmetric Dearomatization of Isoquinolines

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Abstract: *A chiral-NHC-catalyzed highly diastereo- and enantioselective dearomatizing double Mannich reaction of isoquinolines was developed that provides a powerful and straightforward synthetic route toward substituted tropane derivatives with four contiguous stereocenters. A unique feature of this strategy is the use of readily available isoquinolines to provide two reactive sites for dearomatization, thus opening up an unprecedented approach to tropane derivatives with excellent stereoselectivity. The four-component reactions proceeded smoothly with good results. Thus, the present method is suitable for the diversity-oriented synthesis of useful tropane derivatives with high efficiency.*

The tropane (8-azabicyclo[3.2.1]octane) skeleton is widespread in both natural products and synthetic compounds with a wide range of biological activity.[1] Many tropane derivatives play a key role in a large number of neurological and psychiatric diseases, such as Parkinson's disease, depression, and panic disorder (Scheme 1, left).[2] Maraviroc, with a tropane structural core, has been used in the treatment of HIV infection and deserves considerable attention.[3] Benzotropane, containing a phenyl ring in the tropane moiety, also occurs in numerous lead compounds and pharmaceuticals for the treatment of type 2 diabetes and antitumor drug candidates (Scheme 1, right).[4] The medicinal relevance of tropane derivatives has stimulated considerable interest among synthetic chemists, and several catalytic methods have been developed for the construction of optically pure tropane frameworks.[5] In contrast, only one route has been presented for the enantioselective synthesis of benzotropane scaffolds.[6] In their pioneering study, the groups of Waldmann and Antonchick developed a very efficient copper-catalyzed highly stereoselective [3+2] cycloaddition reaction of 1,3-fused cyclic azomethine ylides and nitroalkenes for the synthesis of functionalized benzotropane scaffolds (Scheme 2a). The development of further highly efficient routes to enantiomerically enriched tropanes from readily available starting materials is highly desirable.

The catalytic asymmetric dearomatization (CADA) reaction has emerged as a powerful organic transformation for the construction of complex molecules from relatively simple aromatic compounds, such as indoles, pyrroles, and phenols.[7] Although isoquinolines are readily available, cheap, and versatile feedstocks for the synthesis of chiral multifunctionalized alkaloids, and frequently appear as a structural core in natural products, the catalytic asymmetric dearomatization of isoquinoline and its derivatives remains underdeveloped.[8,9] In the context of CADA reactions of isoquinoline derivatives, the main focus has been on Reissert-type reactions. The elegant examples reported by Shibasaki,[9a,b] Jørgensen,[9c] Jacobsen,[9d] Seidel,[9e] Cozzi,[9f] and Glorius[9g] all involved nucleophilic attack at the C1 position (Scheme 3a), which restricted their application for the construction of complex molecules. It is well-known that α,β-unsaturated aldehydes (enals) can behave as nucleophiles with two nucleophilic centers for enantioselective annulation reactions[10] through polarity inversion by means of organocatalysis by chiral N-heterocyclic carbenes (NHCs).[11] Inspired by Robinson's classic total synthesis of tropinone on the basis of the strategy of a double Mannich reaction,[12] we envisioned that isoquinoline derivatives may provide two reactive sites at the C1 and C2 positions for a double Mannich reaction with the above-mentioned two nucleophilic centers (Scheme 3b) to enable the construction of the tropane skeleton in an asymmetric manner (Scheme 2b).

In this scenario, several challenges were identified: 1) The dearomatization reaction of isoquinolines has never been investigated in enantioselective double Mannich reactions for difunctionalization; 2) appropriate reaction conditions had to be found to increase the reaction efficiency, control reactivity at sites C1 and C2, and inhibit most undesirable side reactions; 3) we needed to find a suitable chiral NHC organocatalyst to efficiently induce the desired stereoselectivity; and 4) the formation of four contiguous stereocenters in multisubstituted tropane derivatives with bridged ring systems was a particularly challenging task. As part of our ongoing interest in asymmetric organocatalysis on core-structure-motivated reactions,[13] we describe herein a chiral-NHC-catalyzed highly diastereo- and enantioselective dearomatizing double Mannich reaction of isoquinolines. This reaction provides a powerful and straightforward synthetic route to substituted tropane derivatives with four contiguous stereocenters. Such structural motifs are important components of various biologically active natural products and pharmaceutical compounds.[1–3]

We investigated the feasibility of this approach by evaluating the reaction between cinnamaldehyde (**1a**) and isoquinolinium bromide **2a** in dichloromethane at room temperature in the presence of the chiral triazolium-salt catalyst **C1**, first reported by Rovis and co-workers[14] (Table 1). The desired tropane product **3a** was isolated in 39 % yield with complete diastereomeric control (d.r. > 20:1)

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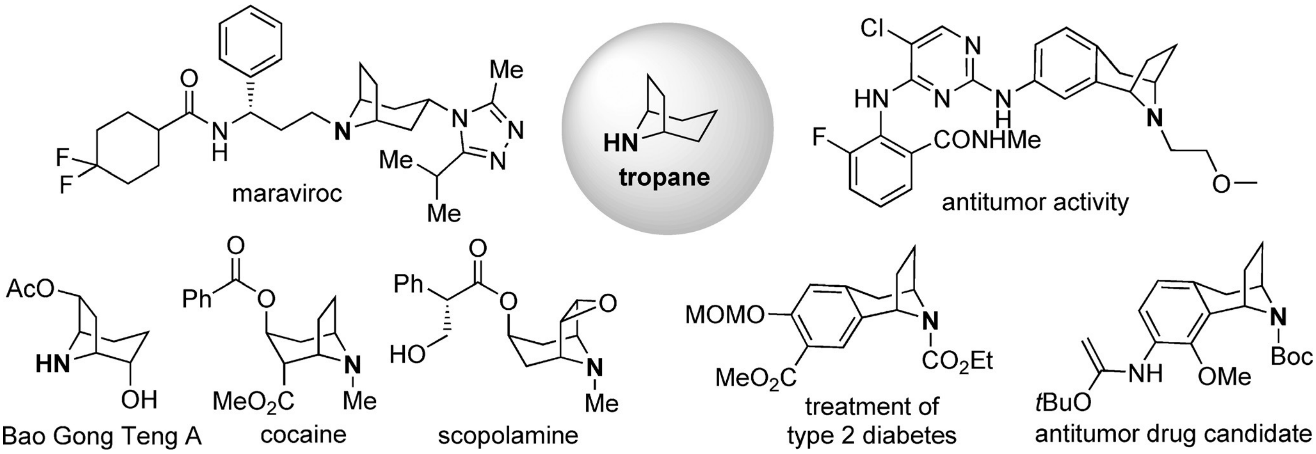
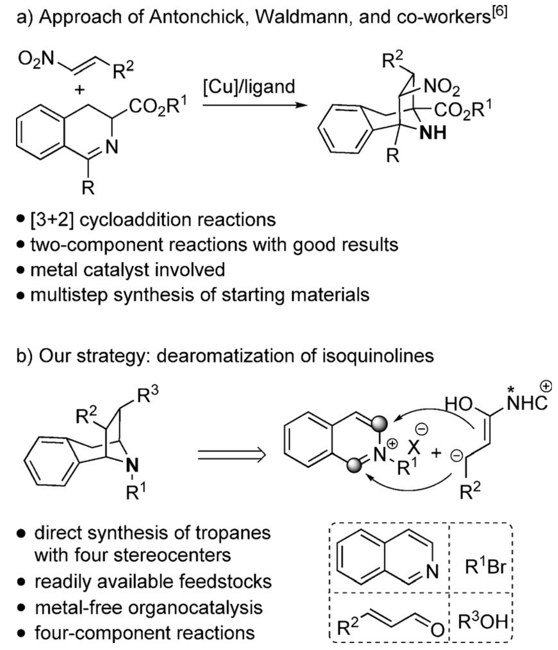
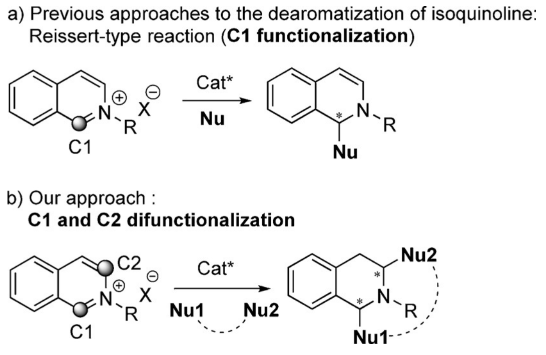


Scheme 1. Representative natural products and biological active compounds with tropane frameworks. Boc = *tert*-butoxycarbonyl.

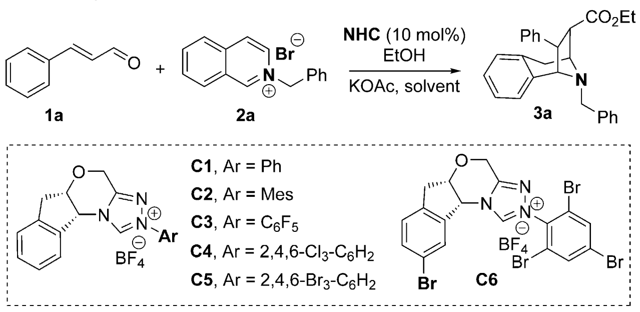


Scheme 2. a) A reported strategy and b) our strategy for the construction of functionalized tropane derivatives.



Scheme 3. Strategies for the dearomatization of isoquinoline.

Table 1: Optimization of the reaction conditions.[a]



Entry	NHC	T [°C]	Solvent	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**C1**	RT	CH_2Cl_2	39	> 20:1	48
2	**C2**	RT	CH_2Cl_2	6	> 20:1	27
3	**C3**	RT	CH_2Cl_2	18	> 20:1	60
4	**C4**	RT	CH_2Cl_2	39	> 20:1	88
5	**C5**	RT	CH_2Cl_2	30	> 20:1	91
6	**C6**	RT	CH_2Cl_2	42	> 20:1	90
7	**C6**	−20	CH_2Cl_2	57	> 20:1	93
8	**C6**	−20	EtOH	58	> 20:1	89
9[e]	**C6**	−20	CH_2Cl_2	66	> 20:1	93
10[f]	**C6**	−20	CH_2Cl_2	67	> 20:1	93

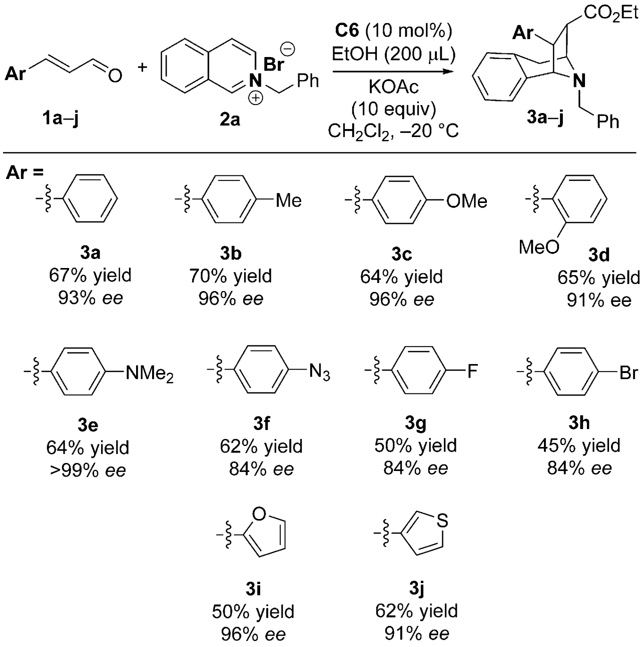
[a] Unless otherwise specified, the reaction was conducted on a 0.1 mmol scale with **1a** (0.2 mmol, 2.0 equiv), **2a** (0.1 mmol, 1.0 equiv), KOAc (2.0 equiv), and the catalyst (10 mol%) in 2 mL of solvent with EtOH (100 μL) at room temperature for 1 day or at −20 °C for 4 days. [b] Yield of the isolated product. [c] The diastereomeric ratio was determined by ^1H NMR spectroscopy of the crude reaction mixture. [d] The *ee* value was determined by HPLC analysis on a chiral stationary phase. [e] The reaction was carried out with 10 equivalents of KOAc. [f] The reaction was conducted on a 0.2 mmol scale in 4 mL of CH_2Cl_2 with 200 μL of EtOH.

and moderate enantioselectivity (48% *ee*). This proof-of-principle result clearly suggested that the dearomatizing double functionalization of isoquinolines with an NHC organocatalyst was feasible. Having thus proven the efficiency of the Rovis-type catalyst in our system, we moved on to investigate catalyst substituent effects[11c] (Table 1, entries 2–6) and found that the newly synthesized organocatalyst **C6** displayed the best results in term of the chemical yield and enantioselectivity. We varied the base, solvent, reaction temperature, catalyst loading, and the number of equivalents of KOAc (Table 1, entries 7–10; see also Table S1 in the Supporting Information) and identified the following protocol as optimal: When **1a** (0.4 mmol) was treated with **2a** (0.2 mmol) in the presence of catalyst **C6** (10 mol %) in CH_2Cl_2 at −20 °C for 4 days, the benzotrapone derivative **3a** was isolated in 67 % yield with 93 % *ee* and d.r. > 20:1 (Table 1, entry 10).

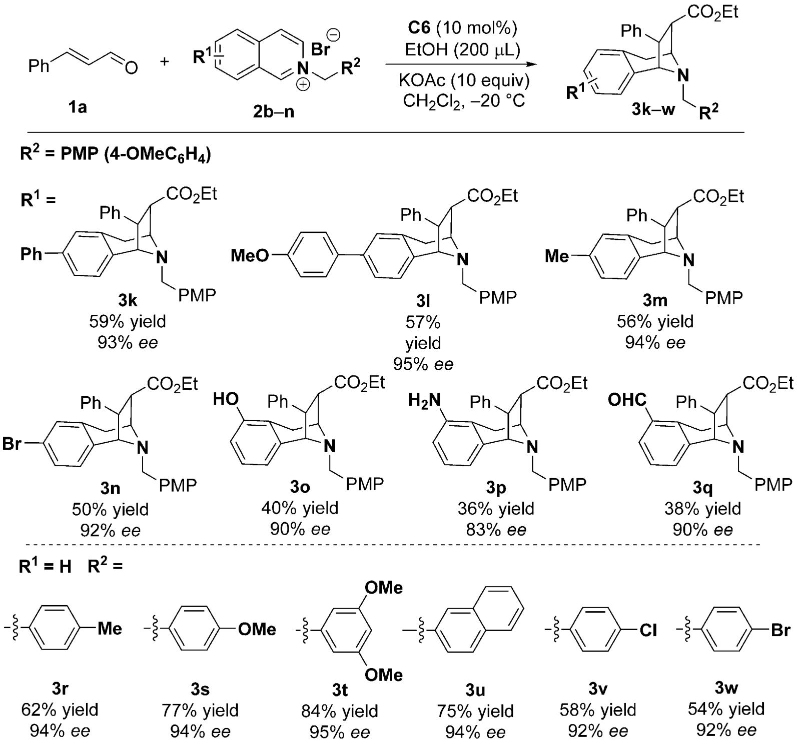
We first examined the scope of the reaction with respect to the enal substrate under the optimized conditions (Scheme 4). Different substituents and substitution patterns on the phenyl ring of the enal substrate were tolerated. Regardless of the type of substituent on the aromatic ring, electron-donating (Me, OMe, NMe_2), electron-neutral, or electron-withdrawing (N_3, F, Br), the corresponding products **3a–h** were obtained in good yield (45–70 %) with 84–> 99 % *ee*. Moreover, the phenyl substituent of substrate **1a** could be replaced with a heteroaryl substituent without any evident effect on the reaction outcome (**3i,j**). Aliphatic enals gave the desired products in poor yield and enantioselectivity (see Scheme S1 in the Supporting Information).

To further explore the scope of this transformation, we next evaluated the use of various isoquinolinium salts as reactants (Scheme 5). Most reactions reached completion within 4 days and gave the desired product in moderate to good yield (36–84 %) with excellent enantioselectivity (83–95 % *ee*) and diastereoselectivity (d.r. > 20:1). The position and electronic properties of substituents (Ph, Me, OMe, Br, OH, NH_2, CHO) on the isoquinoline skeleton appeared to have a very limited effect on stereoselectivity (products **3k–q**). Most importantly, the very reactive free-hydroxy, amine, and aldehyde functional groups were also compatible with the standard reaction conditions (products **3o–q**): These reactions proceeded with good stereoselectivity, albeit in rather low yield. Encouraged by these results, we expanded the generality of the reaction by varying the *N*-benzyl functional group (Scheme 5, products **3r–w**). The desired products were obtained with good stereoselectivity, and the transformation proceeded almost equally well with a range of groups with different electronic properties, thus demonstrating the broad generality of this approach for the synthesis of tropane derivatives. Notably, the presence of a Cl or Br substituent in the obtained tropane derivatives is very important for setting up a compound library in the drug-discovery field because halides are very reactive in many transition-metal-catalyzed reactions,[15] which offer opportunities for further modification at these positions.

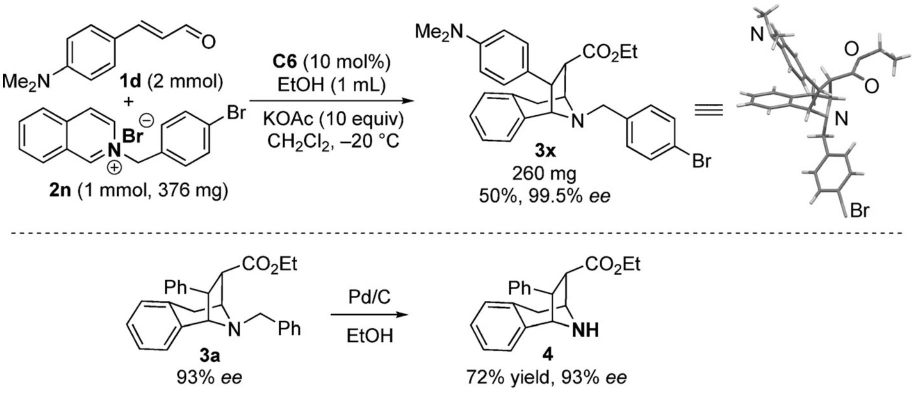
To demonstrate the utility of this transformation, we carried out a preparative-scale synthesis of product **3x** (Scheme 6). The reaction occurred in 50 % yield with high stereoselectivity (99.5 % *ee*, d.r. > 20:1), thus suggesting



Scheme 4. Scope of the reaction for the construction of tropane derivatives with respect to the enal substrate. Under the optimized reaction conditions (Table 1, entry 10), all products were obtained with d.r. > 20:1. Yields are for the isolated product, and *ee* values were determined by HPLC analysis on a chiral stationary phase.



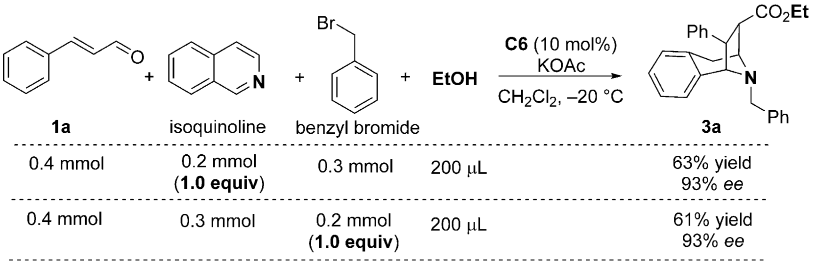
Scheme 5. Scope of the reaction for the construction of tropane derivatives with respect to the isoquinolium salt. Under the optimized reaction conditions (Table 1, entry 10), all products were obtained with d.r. > 20:1. Yields are for the isolated product, and *ee* values were determined by HPLC analysis on a chiral stationary phase.



Scheme 6. Preparative-scale synthesis of product **3x** and further transformation of **3a**.

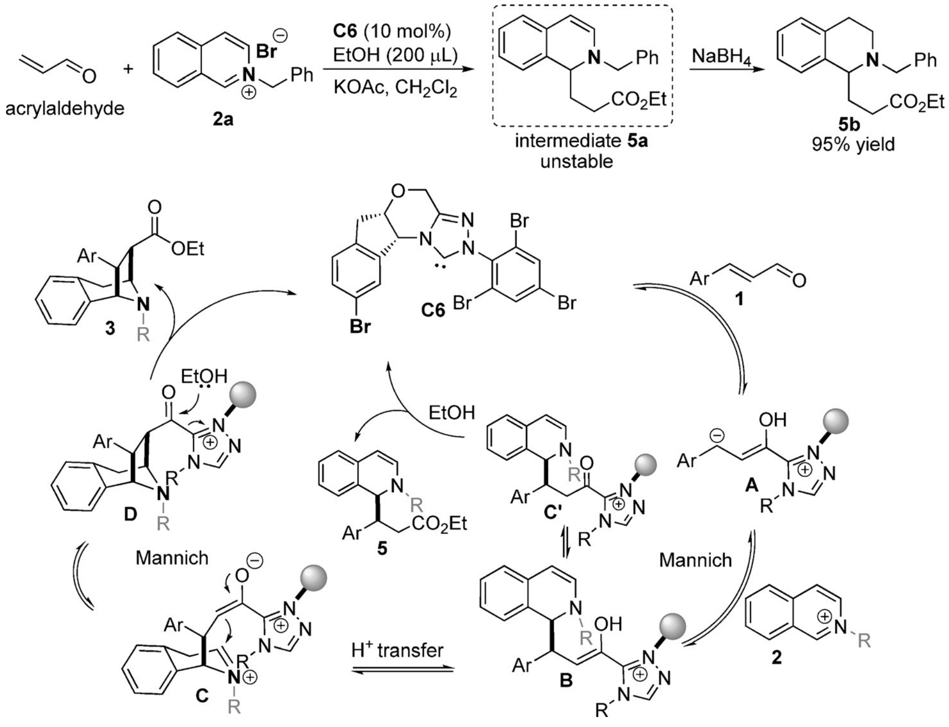
that this method has the potential for large-scale chemical production. The absolute configuration of **3x** was determined by X-ray diffraction analysis[16] (Scheme 6), and that of other products was assigned by analogy. We also found that the benzyl group in **3a** could be readily removed by using Pd/C as the catalyst without any effect on enantioselectivity (Scheme 6).

Multicomponent reactions (MCRs) are a powerful chemical tool for the preparation of complex molecules owing to their atom and step economy, as well as the high efficiency in generating complex molecules through the structural modulation of each component.[17] On the basis of our comprehension of the above-mentioned protocol, we investigated the possibility of performing the reaction as a multicomponent reaction in a one-pot fashion from simple commercially available starting materials. A model four-component reaction proceeded very smoothly to produce the desired tropane product **3a** with almost the same chemical yield and enantioselectivity, regardless of whether isoquinoline or benzyl bromide was used in excess (Scheme 7). The present process is a rather general and straightforward method for the diversity-oriented synthesis of useful tropane derivatives in high efficiency, and clearly complementary to previous synthetic methods.[5,6]



Scheme 7. Successful attempt at a multicomponent reaction with commercially available starting materials.

Since the current reaction could proceed in a stepwise manner or a concerted formal [5+2] mechanism,[18] we carried out a control experiment to rationalize the course and stereoselectivity of the reaction. When the reaction of acrylaldehyde with **2a** was conducted under the otherwise identical conditions, the intermediate product **5a** was formed in almost quantitative yield without the formation of the desired product (Scheme 8). This result provided evidence for a stepwise mechanism. Product **5a** is unstable and could be readily transformed into **5b** by reduction with $NaBH_4$ for further analysis.[19] On the basis of the above observations and previous reports on NHC catalysis,[10,11]



Scheme 8. Proposed mechanism and isolation of a key intermediate.

we propose a catalytic cycle for the double Mannich reaction of an isoquinolinium salt with an enal in Scheme 8. Thus, the addition of the NHC catalyst to enal **1** yields an NHC-bonded homoenolate intermediate **A** containing a nucleophilic β-carbon center. Nucleophilic Mannich attack at the C1 position of isoquinonium **2** results in the formation of enol intermediate **B**, followed by proton transfer to generate the enolate **C** with an active iminium ion moiety, which participates in an intramolecular Mannich reaction to deliver the key tropane skeleton **D**. A final esterification reaction leads to ester formation through attack by ethanol and regenerates the catalyst **C6**. During the course of proton transfer, the side product **5** may be produced if the reaction proceeds via another active intermediate **C′**.

In summary, we have successfully developed the first chiral-NHC-catalyzed asymmetric dearomatizing double Mannich reaction of isoquinolines to enable the straightforward and efficient synthesis of biologically important tropanes bearing four contiguous stereogenic centers with high levels of diastereo- and enantioselectivity. A unique feature of this strategy is the use of readily available isoquinolines to provide two reactive sites for dearomatization reactions. This highly convergent and functional-group-tolerant strategy enables the rapid construction of complex compounds from simple, readily available starting materials. Furthermore, the tropane derivatives can be synthesized through four-component reactions in one-pot fashion with good results, thus indicating that the present process is a rather general and straightforward protocol for diversity-oriented synthesis with high efficiency. We anticipate that this promising strategy will motivate the design of related processes for the efficient synthesis of complex natural products and bioactive molecules.

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