Synthetic Methods

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Tandem Ring Opening/Cyclization of Vinylcyclopropanes: A Facile Synthesis of Chiral Bicyclic Amidines**

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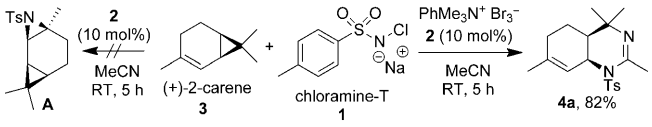
Vinylcyclopropanes (VCP) are important synthons in organic synthesis because of the presence of a highly strained ring system in conjugation with a carbon–carbon double bond, thus enabling these compounds to participate in a wide range of reactions. This structural motif is found in numerous naturally occurring optically active compounds that are important intermediates in the biosynthesis of terpenes.[1] Furthermore, these compounds are prone to pyrolysis, electrophilic ring opening, and acid-catalyzed rearrangement, thus leading to structurally interesting compounds.[2,3]

Herein, a one-pot synthesis of enantiomerically pure bicyclic amidines from bicyclic vinylcyclopropanes is reported (Scheme 1). Amidines have attracted considerable interest owing to their diverse applications in the fields of chemistry



Scheme 1. Reaction of VCP **3** with chloramine-T. Ts = *p*-toluenesulfonyl.

and biology.[4] Chiral amidine scaffolds are efficient organocatalysts and excellent ligands for transition-metal-based asymmetric catalysis, thus providing good enantioselectivity.[5]

However, only a few methods are available for the synthesis of amidines with a wide range of structures.[6] Shibasaki and co-workers reported an interesting intramolecular cyclization for the efficient synthesis of bicyclic amidines[6a] and highlighted the challenge in synthesizing chiral bicyclic amidines. The present study focuses on a ring opening of the VCP, a Ritter-type reaction, and a subsequent cyclization in one pot to obtain enantiomerically pure amidines. In our preliminary studies, we investigated the reaction of (+)-2-carene (**3**) with chloramine-T (**1**) in the presence of a catalytic amount of phenyltrimethylammonium tribromide (**2**; PTAB) using acetonitrile as the solvent (Scheme 1). It resulted in the serendipitous formation of the optically pure [4.4.0] bicyclic amidine **4a** in good yield, rather than the expected aziridine derivative **A**.[7,8] The structure of **4a** was confirmed unambiguously by X-ray crystallography (see Scheme 4). Although, VCP derivatives have been shown to undergo a Ritter-type reaction under strongly acidic conditions,[8] the reaction has not been utilized as an approach for the synthesis of amidines. The reaction was optimized by varying the electrophilic halogen source, which was used as the catalyst, to get the bicyclic amidine **4a** as the exclusive product.

With iodine[7] and other electrophilic halogen sources, such as *N*-bromosuccinimide and *N*-iodosuccinimide, the reaction afforded the product in only a moderate yield. When the reaction was carried out with 10 mol% of pyridinium hydrobromide perbromide,[9a] the yield of **4a** went up to 73% and further improvement in yield (82%) was achieved when PTAB[9b] was used as the catalyst (see the Supporting Information).

To demonstrate the versatility of the reaction as a general method towards the synthesis of chiral bicyclic amidine derivatives, it was carried out using various nitriles as the solvent. In all cases, the reaction proceeded smoothly leading to the corresponding nitrile-inserted compounds (**4b–d**) in good yields (Table 1, entries 2–4).

Even with the electron-deficient nitrile pentafluorobenzonitrile (Table 1, entry 5), the reaction afforded **4e**, albeit in low yield (25%). *Cis*- and *trans*-4-carene (**5** and **7**, respectively), when treated under similar reaction conditions, underwent rearrangement readily in acetonitrile to yield the corresponding amidines **6** and **8** in good yields (Table 1, entries 6 and 7). The study was then extended to other VCP derivatives, such as (*S*)-(+)-caren-5-ol (**9**) and 5-acetylcarene (**11**),[10] which yielded the corresponding amidines **10** (83%) and **12** (76%) in good yields (Table 1, entries 8 and 9).

The reaction scope was further extended by the study of the fused five-membered bicyclic VCP **17** to achieve the synthesis of chiral [4.3.0] bicyclic amidines (see Table 2). Therefore, **17** was synthesized starting with the dihydroxylation of 2-carene (**3**) using OsO_4 and NMMO in *t*BuOH to give the corresponding *cis*-diol **13** in 86% yield (Scheme 2).[11a] The diol was subsequently treated with $NaIO_4$/silica gel[11b] to furnish the keto aldehyde **14** (97% yield), which after an intramolecular Aldol reaction gave the corresponding five-membered α,β-unsaturated ketone **15**.[11c] The ketone **15** was reduced with $NaBH_4/CeCl_3$ under Luche conditions to yield the alcohol **16** as a diastereomeric mixture (85:15). The diastereomers were separated after conversion into the benzyl ether (NaH, BnBr and DMF) and the major isomer **17** was used for further studies.

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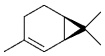
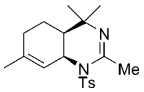
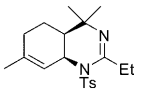
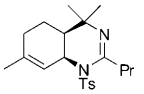
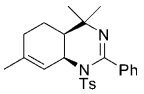
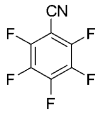
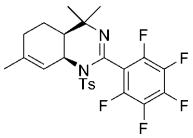
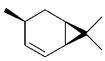
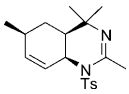
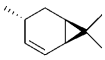
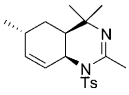
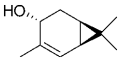
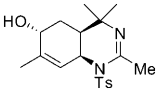
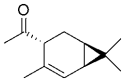
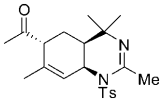
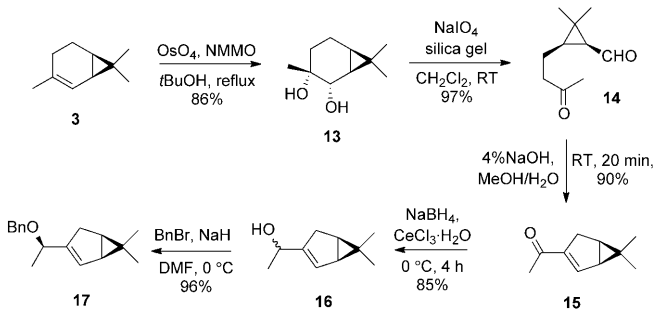
Table 1: Synthesis of [4.4.0] bicyclic amidines from carene derivatives.[a]

Entry	Reactant	Solvent	*t* [h]	Product	Yield [%][b]
1	 **3**	CH_3CN	5	 **4a**	82
2	**3**	EtCN	5	 **4b**	78
3	**3**	PrCN	5	 **4c**	74
4	**3**	PhCN	8	 **4d**	62
5	**3**		15	 **4e**	25
6	 **5**	CH_3CN	5	 **6**	73
7	 **7**	CH_3CN	5	 **8**	82
8	 **9**	CH_3CN	7	 **10**	83
9	 **11**	CH_3CN	7	 **12**	76

[a] Reaction conditions: VCP (3 mmol), chloramine-T (3.3 mmol), PTAB (0.3 mmol), solvent (15 mL), 5-15 h, RT. [b] Yield is of the isolated product.

Compound **17** was subjected to the rearrangement reaction with chloramine-T and PTAB in acetonitrile at room temperature for 5 hours to yield the corresponding amidine **17a** in excellent yield (92%; Table 2, entry 1). To show the general applicability of the method, compound **17** was treated with chloramine-T and PTAB using a variety of nitriles as the solvent to furnish the corresponding bicyclic amidines **17b–f** in good yield (Table 2, entries 2–6).

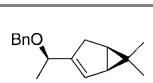
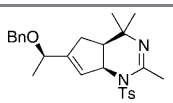
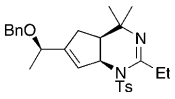
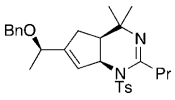
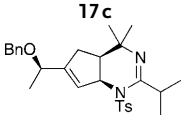
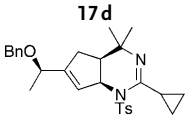
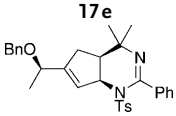
While the present method has been shown to be effective for the synthesis of chiral bicyclic amidines from vinylcyclopropanes that bear *gem* dimethyl groups, it was of interest to study the reactivity of phenyl-substituted vinylcyclopropane **19** (Scheme 3). Accordingly, compound **19** was synthesized



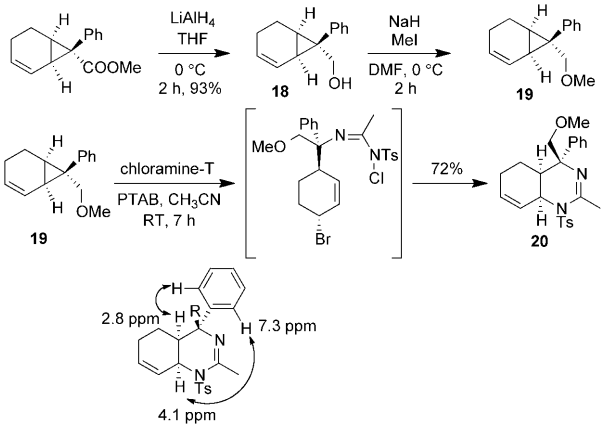
Scheme 2. Synthesis of five-membered bicyclic VCP **17**. Bn = benzyl, DMF = *N*,*N*′-dimethylformamide, NMMO = *N*-methylmorpholine-*N*-oxide.

starting from 1,3-cyclohexadiene and α-phenyl diazoacetate using a $AgSbF_6$-catalyzed cyclopropanation.[12] The cyclopropyl ester was reduced to the corresponding alcohol **18** using $LiAlH_4$ in THF, and a subsequent reaction with NaH and MeI at 0 °C furnished **19**. Compound **19** was subjected to Sharpless aziridination reaction conditions in acetonitrile to afford exclusively the desired bicyclic amidine **20** in good yield (72%). The stereochemistry of compound **20** was confirmed by analysis of ^1H-^1H COSY, HMQC, and NOESY spectra (nOe of the bridgehead protons and the phenyl ring protons; Scheme 3). We observed a complete inversion at the phenyl-substituted cyclopropane carbon

Table 2: Synthesis of [4.3.0] bicyclic amidines from **17**.[a]

Entry	Reactant	Solvent	*t* [h]	Product	Yield [%][b]
1	 **17**	CH_3CN	5	 **17a**	92
2	**17**	EtCN	5	 **17b**	90
3	**17**	PrCN	5	 **17c**	85
4	**17**	*i*PrCN	8	 **17d**	83
5	**17**		5	 **17e**	91
6	**17**	PhCN	5	 **17f**	81

[a] Reaction conditions: **17** (1 mmol), chloramine-T (1.1 mmol), PTAB (0.1 mmol), solvent (5 mL), 5-8 h, RT. [b] Yield is of the isolated product.



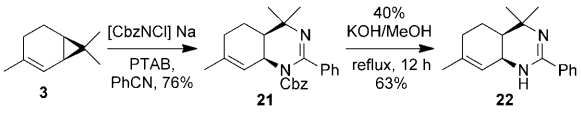
Scheme 3. Rearrangement of the phenyl-substituted VCP **19** with inversion of the phenyl substituent, thus supporting an intimate ion pair pathway. THF = tetrahydrofuran.

center, thus providing support to the intermediacy of an intimate ion pair (or delocalized charge), rather than a free-carbocation pathway with the subsequent attack of acetonitrile in a concerted fashion. This observation is supported by the pioneering work of Cram and Ratajczak[13a] on the stereochemical course of solvolysis in strained ring systems,[13] and that of others reported recently.[13c,d]

Based on the extensive work of Komastu and co-workers[7] and Sharpless and co-workers,[9b] on the chloramine-T/halogen-mediated aziridination of olefins, a plausible mechanism has been proposed for the formation of **4a** from **3** (Scheme 4). It is reasonable to visualize the in situ generation of BrX during the reaction of chloramine-T with PTAB, thus catalyzing the reaction further. BrX thus formed can add to the alkene double bond of **3** to form a π-complex intermediate **Ia,** and subsequent polarization of the cyclopropane C–C bond gives the intimate ion pair **Ib**. This intermediate **Ib** gets trapped in a concerted fashion by the nitrile, which approaches from the direction opposite to the polarized C–C bond of the cyclopropane,[13] thus following a Ritter-type reaction pathway to provide the intermediate **Ic**. A subsequent reaction with chloramine-T generates the intermediate **Id**, which after the abstraction of chlorine facilitates an intramolecular cyclization through an allylic-substitution pathway to form **4a** (path a). Compound **4a** was thus obtained without any compromise to the enantiomeric purity.

The intermediate **Id** can follow an alternate pathway (path b; Scheme 4), which involves the attack of the alkene at the nitrogen atom of *N*-chlorosulfonamide **Id** with the expulsion of chloride, thus leading to **If**. Decomplexation of **If** leads to the formation of product **4a**.[15]

Chiral amidines with free N–H have a wide scope of applications as organocatalysts and chiral bases,[6] and this feature encouraged us to attempt the removal of the tosyl group. Since the removal of a tosyl group often requires harsh reaction conditions, various attempts were unsuccessful (HBr/phenol, SmI_2/Et_3N). Finally, the use of *N*-sodio-*N*-chloro benzyloxycarbamate (chloramine-Cbz), instead of chloramine-T, for the reaction with **3** (PTAB, PhCN), led to the desired amidine **21** in 76% yield (Scheme 5). The removal the of Cbz group in **21** was carried out successfully using methanolic KOH (40%) under reflux to furnish chiral amidine **22** in 63% yield.

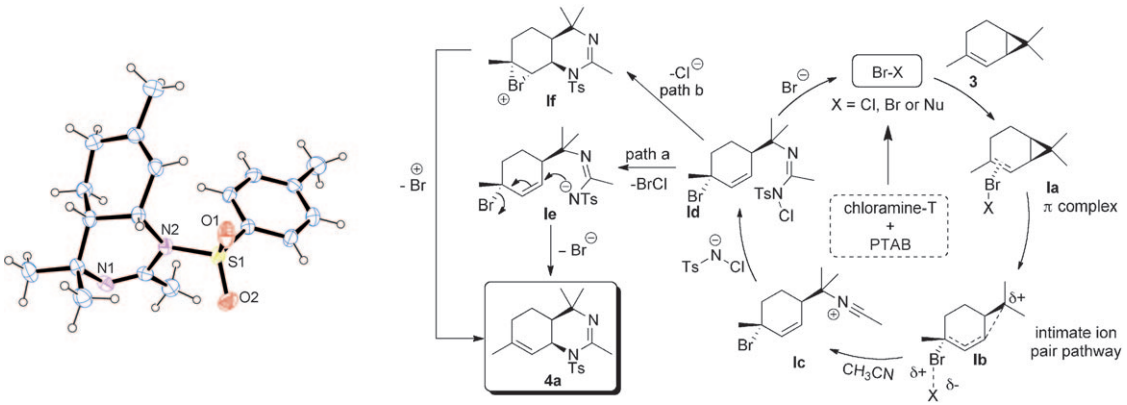


Scheme 5. Chloramine-Cbz-mediated rearrangement and deprotection to give free amidine **22**. Cbz = benzyloxycarbonyl.

In conclusion, we have demonstrated an interesting bromine-catalyzed tandem ring opening/cyclization of vinylcyclopropane derivatives through a Ritter-type rearrangement to give enantiomerically pure [4.4.0] and [4.3.0] bicyclic amidine derivatives in good yield. The use of these easily accessible chiral amidines as organocatalysts and chiral bases is under investigation.

Experimental Section

General procedure for the synthesis of cyclic *N*-sulfonylamidines: Chloramine-T (1.1 equiv) and phenyltrimethylammonium tribromide (PTAB; 10 mol%) were added to the stirred solution of the olefin (1 equiv) in the respective nitrile (ca. 2 M concentration). The mixture was stirred at room temperature (25 °C) until the reaction was



Scheme 4. The X-ray crystal structure of **4a** and the proposed catalytic cycle for its formation.[14]

complete (5–18 h; monitored by TLC). Then the solvent was removed under reduced pressure. The solid residue was directly purified by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate 7:3).

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[14] CCDC 748917 (**4a**) 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.

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