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Chiral bicyclic guanidines: a concise and efficient aziridine-based synthesis

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Abstract—A series of chiral bicyclic guanidines, either symmetrical or non-symmetrical, was synthesized using a concise and efficient aziridine-based synthetic methodology. Starting from commercial amino alcohols, five synthetic steps were performed, with only three requiring chromatographic purification, giving the desired guanidines in 43–71% overall yield. Preliminary studies using these guanidines showed moderate enantioselectivity for several Michael reactions.

Arginines are found in the active site of many enzymes and it is likely that their guanidine side-chains are involved in substrate recognition as well as in the catalytic cycle.[1] Guanidinium ions are known to interact with phosphate- and carboxylate-containing biomolecules and the synthesis of artificial bicyclic guanidinium ions as selective anion receptors is of considerable interest in bioorganic chemistry.[2] The bicyclic guanidinium moiety is also found in a large variety of structurally diverse natural products isolated from marine organisms.[3] These natural products have received intense synthetic investigations due to their interesting biological activities.

We recently reported that 1,5,7-triazabicyclo[4.4.0]dec-5-ene (**TBD**), a bicyclic guanidine base, is an excellent catalyst for Michael and Michael-type reactions.[4] The C_2-symmetrical derivatives of the core structures of batzelladine and crambescidin alkaloids have been found to accelerate the Michael addition reaction of pyrrolidine to α,β-unsaturated lactones.[5] These guanidiniums are also excellent phase transfer catalysts, participating in the highly enantioselective alkylation reaction of *tert*-butyl glycinate.[6] On the other hand, as free bases, guanidines are known as superbases due to their high pK_a.[7] Chiral guanidines have been shown to participate in several asymmetric reactions[8] such as epoxidation,[9] Michael addition using glycine imines,[10,11] silylation of secondary alcohols[12] and the Strecker reaction of imines.[13]

Base catalyzed reactions are ubiquitous in organic chemistry. However, there are relatively few examples of organocatalytic reactions utilizing Brønsted bases.[14] We are attracted to the possibility of using chiral bicyclic guanidines as general organobases and are particularly interested in the 1,4,6-triazabicyclo[3.3.0]oct-4-enes. It is a challenge to develop these guanidines into a 'privileged' class of catalysts that is capable of catalyzing a variety of reactions.[15] The current synthetic approaches to these guanidines include the coupling of two amino acid derivatives and reduction of the resulting amide to obtain the triamine backbone.[13,16] Another strategy is to go through a thiourea intermediate, followed by 1,3-dimethylimidazolinium chloride induced step-wise cyclization.[17] However, a more efficient synthetic protocol is needed if this class of catalysts is to gain widespread use. We envisioned that an effective synthesis would take advantage of the C_2-symmetric nature of the catalyst.

Aziridines can undergo regio- and stereoselective ring opening reactions, making them useful synthetic intermediates.[18] *N*-tosyl aziridines **2** (Scheme 1) were readily prepared from their corresponding commercially available amino alcohols.[19] Triamines **3** were easily obtained by treating **2** with 0.5 equiv of benzylamine.[20]

Keywords: Guanidine; Aziridine; Michael reaction; Enantioselectivity; Regioselectivity.
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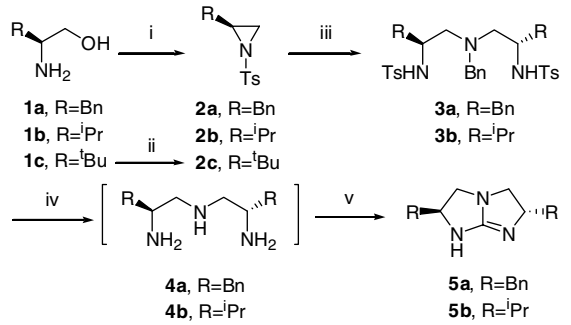
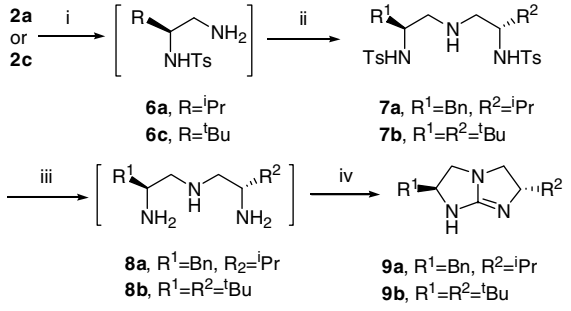


Scheme 1. Reagents and conditions: (i) TsCl, Et_3N, MeCN, 92% for **2a**, 94% for **2b**; (ii) TsCl, Et_3N, MeCN, 4 Å MS, 0 °C then MsCl, Et_3N, DMAP, CH_2Cl_2, rt, 80%; (iii) 0.5 equiv $BnNH_2$, MeOH, 60 °C, 3 days, 92% for **3a**, 75% for **3b**; (iv) (a) Na, NH_3(l), −78 °C, THF; (b) H_2, Pd/C, MeOH; (v) $(MeS)_2C{=}S$ then MeI/AcOH, $MeNO_2$, reflux, 84% for **5a**, 61% for **5b**.

Nucleophilic attack occurs preferentially at the sterically least hindered carbon atom. Subsequent removal of the tosyl group was achieved using sodium in liquid ammonia and the crude product was immediately subjected to catalytic hydrogenolysis without further purification. The crude triamine **4** was subjected to the final cyclization step, leading to the expected guanidines **5a** and **5b** in 71% and 43% overall yields, respectively, from their amino alcohols. Out of the five synthetic steps used, only three required chromatographic purification.

The formation of aziridine **2c** (Scheme 1) did not proceed as expected via the usual protocol. Tosylation of the hydroxyl group proceeded poorly after the formation of the *N*-sulfonamide intermediate. We found that if methanesulfonyl chloride was added, the *O*-sulfonate was formed more easily and it also facilitated the S_N2 ring-closing reaction.

In our attempt to prepare guanidine **9b** (Scheme 2), we were faced with another obstacle; the aziridine double ring-opening reaction of **2c** with benzylamine turned out to be slow and low yielding, giving mainly the mono-opened product. The problem was circumvented by treating aziridine **2c** with NH_3 to form the diamine **6c**, which was used without purification to open another



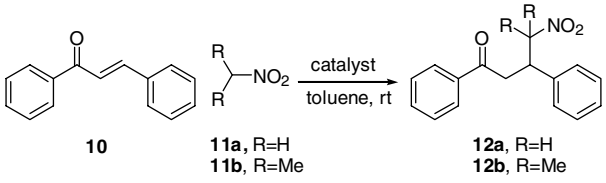
Scheme 2. Reagents and conditions: (i) NH_3/MeOH, 0 °C to rt; (ii) MeCN, 95 °C, 3 days, **2b** or **2c**, 80% for **7a** from **2a**, 84% for **7b** from **2c**; (iii) Na, NH_3(l), −78 °C, THF; (iv) $(MeS)_2C{=}S$ then MeI/AcOH, $MeNO_2$, reflux, 89% for **9a** from **7a**, 75% for **9b** from **7b**.

equivalent of aziridine **2c**, leading to the triamine backbone **7b** in 84% yield (from **2c**). Detosylation and cyclization resulted in the guanidine **9b** (overall yield of 50% from amino alcohol **1c**). A step-wise approach to construct the triamine backbone provided an opportunity to prepare non-symmetrical chiral bicyclic guanidines such as **9a** through the use of two different aziridines. By stirring aziridine **2a** in MeOH saturated with NH_3 gas in a sealed vessel, a single ring-opening product **6a** was obtained. Diamine **6a** was used as the nucleophile for the ring-opening of a second aziridine, **2b**, leading to **7a** in 80% yield (based on **2a**). After removal of the tosyl group and cyclization, guanidine **9a** was obtained in 71% yield (from **2a**).

With efficient syntheses of the chiral bicyclic guanidines in hand, we embarked on a preliminary evaluation of these catalysts in several Michael reactions. It is known that amidine and guanidine bases can interact with nitroalkanes in non-polar solvents and form tightly bound ion pair complexes.[21] Nitroalkanes are a valuable source of stabilized carbanions and are widely used as carbon nucleophiles for conjugate addition to enones.[22] The Michael adducts retaining a nitro group can then undergo a variety of transformations, making them versatile building blocks for organic synthesis.[22] Chiral spirocyclic guanidines have been shown to catalyze the Michael reaction of nitroalkanes to chalcone with modest enantioselectivity.[6a] In general, there are relatively few examples of catalytic Michael reactions of nitroalkanes to chalcone derivatives with satisfactory enantioselectivities.[23] Thus, as a reasonable and reliable starting point, the chiral bicyclic guanidines **5a**, **5b**, **9a** and **9b** were tested as catalysts in the Michael reactions between nitroalkanes and *trans*-chalcone **10** (Scheme 3).

With 20 mol % **TBD**, a non-chiral guanidine base, the conjugate addition of nitromethane **11a** to chalcone **10** was complete within 1.5 h, giving **12a** in 99% yield (Table 1, entry 1). In the presence of 10–20 mol % of **5a**, **5b** and **9b**, 13%, 32% and 56% ee (entries 2, 3 and 4) were obtained, respectively. As the appendage of the catalyst became bulkier, the enantioselectivity improved while both the reaction rate and yield decreased. The enantioselectivity was also affected by the nature of the nitroalkanes. With 2-nitropropane **11b** and **5b** as catalyst (entry 5), a higher enantioselectivity (61% ee) was obtained than with nitromethane **11a** (entry 3).

Malonates and β-dicarbonyl compounds are another important source of stabilized carbanions.[22] In our report on TBD-catalyzed Michael reactions, fumarate



Scheme 3. Bicyclic guanidines-catalyzed Michael reaction of nitroalkanes with *trans*-chalcone **10**.

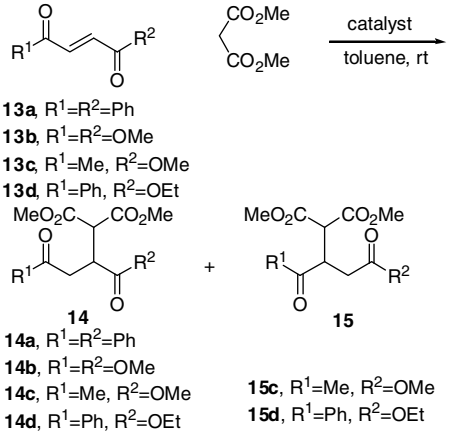
Table 1. The influence of different guanidine catalysts on the reaction in Scheme 3

Entry	Donor	Catalyst/mol %	Time/h	Yield[a]/%	ee[b]/%
1	**11a**	**TBD** (20)	1.5	99	NA
2	**11a**	**5a** (10)	168	60[c]	13
3	**11a**	**5b** (20)	90	42[c]	32
4	**11a**	**9b** (20)	168	35[c]	56
5	**11b**	**5b** (20)	96	23[c]	61
6	**11b**	**9b** (20)	120	20[c]	54

[a] Isolated yield.
[b] Chiral HPLC.
[c] Reaction did not go to completion.

and fumaric derivatives were good substrates for the reactions with dimethyl malonate.[4] Using either **5a** or **5b** as catalyst, poor enantioselectivities (12% ee or less) were observed when 1,2-dibenzoylethylene **13a** or dimethyl fumarate **13b** were reacted with dimethyl malonate (Scheme 4). It was observed that the reaction of **13a** gave a much higher yield and occurred at a much faster rate than **13b**. This implies that α,β-unsaturated ketones are more electrophilic than α,β-unsaturated esters.

The observed difference in reactivity prompted us to investigate the regioselectivity of unsymmetrical conjugated compounds such as methyl *trans*-4-oxo-2-pentenoate **13c** and ethyl *trans*-3-benzoylacrylate **13d** (Scheme 4). With various bicyclic guanidine catalysts, only one regioisomer was observed for both substrates.



Scheme 4. Bicyclic guanidines-catalyzed Michael reaction of dimethyl malonate with fumaric derivatives.

NOE experiments confirmed the structures as **14c** and **14d** (see Supplementary data). The formation of the product is directed by preferential attack of the malonate towards the α,β-unsaturated ketone portion of the substrates. To the best of our knowledge, this is the first example of regioselective Michael reaction of such unsymmetrical olefins.[24] The enantioselectivity of this reaction was determined to be 41%, 33% and 35% ee when catalysts **5a**, **5b** and **9a** (entries 2, 3 and 4, Table 2) were used, respectively. When substrate **13d** was used, the yield was improved to 86% but the enantioselectivity decreased (entry 5).

In summary, a concise and efficient aziridine-based method has been developed for the preparation of a series of chiral bicyclic guanidines. It consists of five chemical steps, with only three requiring chromatographic purification. The overall yields were good, ranging from 43% to 71%. The synthesized guanidines catalyzed the Michael addition of nitroalkanes to *trans*-chalcone with moderate enantioselectivity. Similarly, they catalyzed the Michael reactions of dimethyl malonate with fumaric derivatives, providing excellent regioselectivity but with only moderate enantioselectivity. Based on these preliminary results, further work on asymmetric Michael reactions catalyzed by the synthesized guanidines will be carried out.

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Table 2. The influence of different guanidine catalysts on the reaction in Scheme 4

Entry	Substrate	Catalyst/mol %	Time/h	**14**:**15**	Yield[a]/%	ee[b]/%
1	**13c**	**TBD** (20)	0.5	100:0	90	NA
2	**13c**	**5a** (20)	120	100:0	40[c]	41
3	**13c**	**5b** (10)	90	100:0	41[c]	33
4	**13c**	**9a** (10)	93	100:0	46[c]	35
5	**13d**	**5b** (20)	120	100:0	86	23

[a] Isolated yield.
[b] Chiral HPLC.
[c] Reaction did not go to completion.

Supplementary data

Experimental procedures, characterization of products and NOE experiment results are presented. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.11.133.

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