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Identification of a tartrate-based modular guanidine towards highly asymmetric Michael addition of 3-aminooxindoles to nitroolefins

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ABSTRACT

A novel tartrate-derived guanidine accessed by a modular approach was identified to be an efficient catalyst for the Michael addition of 3-aminooxindoles to nitroolefins. A range of quaternary 3-aminooxindoles bearing adjacent quaternary–tertiary stereocenters were obtained in good to excellent yields (up to 95%) with good to excellent diastereo- and enantioselectivities (up to >20:1 dr and 98% ee).

Introduction

The modular nature of a synthetic route often has the advantage of providing targeted products with readily tunable steric and electronic properties simply by varying the participating building blocks, thus affording ample space for function exploitation and optimization of the synthetic targets [1]. Particularly, in the field of asymmetric catalysis the development of privileged chiral catalysts/ligands has benefited considerably from modular synthetic approaches, because fine tuning of the steric and electronic factors of the chiral promoters is usually required and modular modification of the catalyst/ligand scaffold, especially at a late stage, can arguably facilitate the optimization process [2].

In this context, in an effort to develop new and efficient chiral guanidine catalysts for asymmetric organic transformations [3], we recently reported the construction of a tartrate-based chiral guanidine library by a practical, modular synthetic route [4]. Of particular note of this route is the final stage guanidine formation between the cyclic thiourea and amine partners in a modular manner (Fig. 1). The huge variability of the amines that can be incorporated together with the facile decagram scale preparation of the cyclic thiourea precursor renders the guanidine library large enough, thus securing the successful search of competent guanidine catalysts for different asymmetric reactions. Indeed, exploration into the asymmetric catalytic activities led to identification of individual guanidine members that can effectively catalyze asymmetric hydroxylation [4a], fluorination [4b], and C—C bond forming Michael addition reactions (Scheme 1a, b) [4c].

Owing to the significant medicinal relevance of chiral quaternary 3-aminooxindole compounds [5], asymmetric synthesis of this structural motif has become a topic of intense research [6]. Among various strategies toward this goal, catalytic asymmetric Michael addition reactions of 3-aminooxindoles represent a straightforward approach [7]. Given our success in the identification of **TG-1** for highly *enantio*- and diastereoselective Michael addition of 3-alkyl/aryl substituted oxindoles to nitroolefins (Scheme 1b) [4c], we turned our attention to 3-aminooxindole substrate. Unfortunately, however, **TG-1** showed reduced reactivity and stereoselectivity in this case. Given the flexible tunability of the tartrate-derived guanidine, we think that an optimal guanidine member might be identified (Scheme 1c). Herein, we report our effort toward this goal.

Results and discussion

To validate this hypothesis, the Michael addition of 3-aminooxindole **1a** to nitroolefin **2a** was investigated as the model reaction for optimization (Table 1). As mentioned above, the guanidine catalyst **TG-1**, the efficient catalyst for Michael addition of 3-alkyl/aryl oxindoles to nitroolenfins [4c], showed significantly decreased reactivity in Et_2O (**entry 1**). But in toluene the reaction can occur smoothly in 72 h to afford the Michael adduct in 95% yield with moderate levels of stereocontrol (**entry 2**). Thus, with

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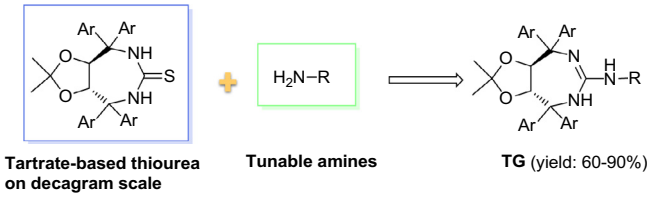
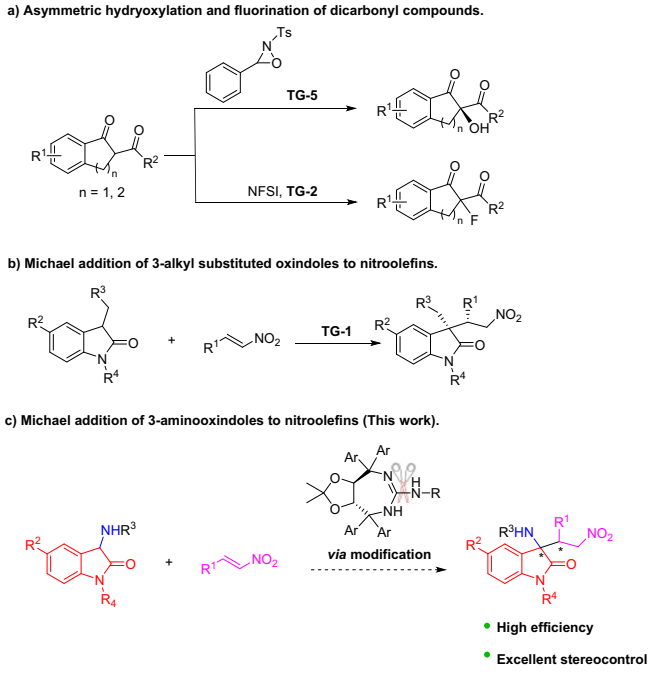


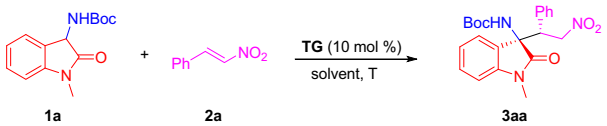
TG-1: Ar = Ph, R = 3,5-di-*tert*-butylphenyl;
TG-2: Ar = Ph, R = 2,6-di-*iso*-propylphenyl;
TG-3: Ar = Ph, R = Bn;
TG-4: Ar = Ph, R = 4-methylbenzyl;
TG-5: Ar = *p*-bisphenyl, R = 4-methylbenzyl;
TG-6: Ar = Ph, R = 4-chlorobenzyl;
TG-7: Ar = Ph, R = (*S*)-phenylethy;
TG-8: Ar = Ph, R = (*R*)-phenylethy;
TG-9: Ar = *p*-bisphenyl, R = (*S*)-phenylethy;

Fig. 1. Modular synthesis of tartrate-based guanidines.



Scheme 1. The application of tartrate-based guanidines in asymmetric reactions.

Table 1
Optimization of the reaction conditions.



Entry[a]	TG	Solvent	t (h)	Yield[b] (%)	Dr[c]	Ee[d] (%)
1	**TG-1**	Et_2O	72	trace	—	—
2	**TG-1**	toluene	72	95	5:1	75
3	**TG-2**	toluene	12	trace	—	—
4	**TG-3**	toluene	1.5	95	8:1	70
5	**TG-4**	toluene	0.5	95	7:1	69
6	**TG-6**	toluene	1.0	95	7:1	64
7	**TG-7**	toluene	1.5	95	7:1	75
8	**TG-8**	toluene	3.0	95	6:1	57
9	**TG-9**	toluene	2.0	95	12:1	86
10	**TG-9**	DCM	3.0	95	4:1	57
11	**TG-9**	mesitylene	1.0	95	11:1	86
12	**TG-9**	Et_2O	4.0	95	10:1	82
13[e]	**TG-9**	toluene	48	95	>20:1	94
14[e]	**TG-9**	mesitylene	54	95	>20:1	94

[a] Unless otherwise noted, reactions were conducted with **1a** (0.1 mmol), **2a** (0.15 mmol), and **TG** (0.01 mmol) in toluene (2.0 mL) at 25 °C.
[b] Isolated yield.
[c] Determined by ^{1}H NMR of the crude reaction mixture.
[d] Determined by chiral HPLC analysis.
[e] Run at −20 °C.

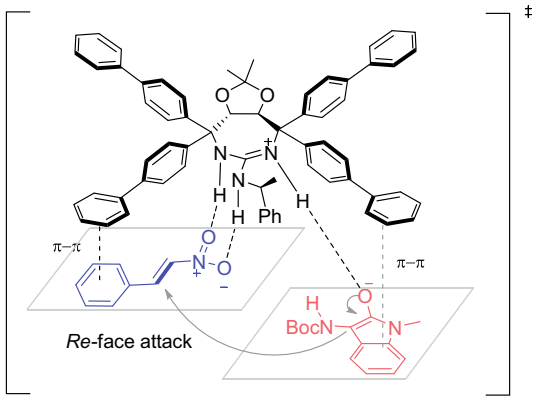
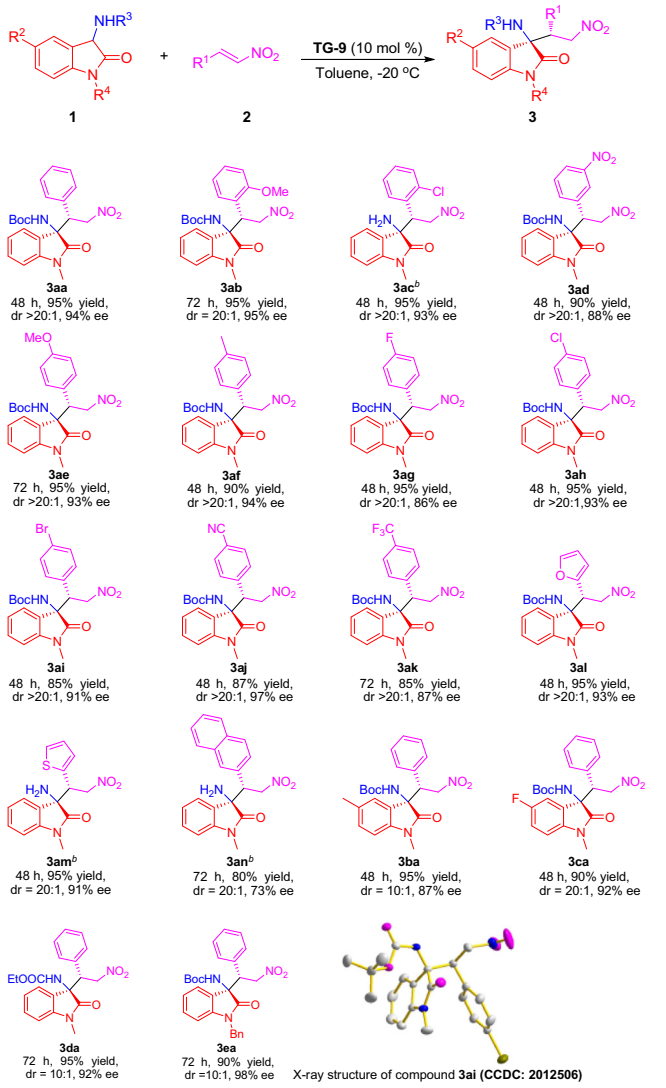


Fig. 2. The transition state working model of the tartrate-derived guanidine promoted Michael addition.

toluene as the solvent, guanidine catalysts were initially screened. Interestingly, the more bulky 2,6-diisopropylaniline-derived guanidine **TG-2** could not promote this reaction (**entry 3**). That further compelled us to investigate our guanidine library to find a more efficient catalyst. To our delight, the guanidine **TG-3** with R being a benzyl group, promoted this reaction to completion in 1.5 h, affording the product in 8:1 dr with a slight decrease of the enantioselectivity to 70% ee (**entry 4**). These results indicated that the steric hindrance of the guanidine dramatically influenced the reactivity of this transformation. Then we performed a survey of the modification at the 4-position of the benzyl moiety of the guanidine. Both electron-donating and electron-withdrawing substituents at the 4-position of the benzyl group gave moderate ee values (**entries 5–6**). To further improve the enantioselectivity, L-1-phenylethylamine was incorporated into the guanidine catalyst, and to our delight, it worked efficiently to give 75% ee within 1.5 h, but D-1-phenylethylamine-based **TG-8** gave poor ee (**entries 7–8**). Notably, the catalyst displaying a *p*-bisphenyl moiety on the guanidine backbone markedly raised the enantioselectivity to 86% ee and diastereoselectivity to 12:1 dr (**entry 9**). This effect was probably due to the weak interaction of phenyl group between guanidine and substrates (Fig. 2). Based on the above results, we chose guanidine **TG-9** to further screen other conditions. Examination of different solvents indicated that toluene and mesitylene had better performance among others (**entries 9–12**). Dropping the temperature to −20 °C, toluene and mesitylene showed the same excellent *enantio*- and diastereoselectivity (94% ee, >20:1 dr), but the latter needed longer reaction time (**entries 13–14**).

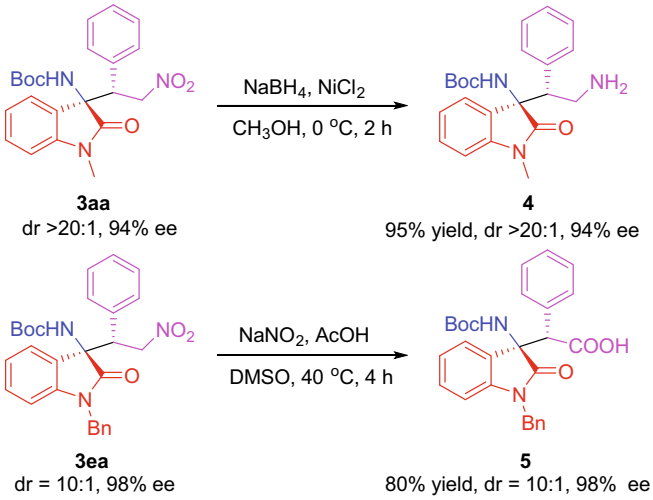
With the optimal conditions being identified, the generality of the substrate scope with respect to nitroolefins and 3-aminooxindoles was investigated (Scheme 2). The nitroolefin component was evaluated first. In general, a variety of substituents on the nitroolefins were well accommodated in this reaction, delivering Michael adducts in uniformly high yields with excellent diastereo- and enantioselectivities (**3aa-3an**). The investigation of the electronic properties of substituents at different positions on the benzene



Scheme 2. Substrate scope of the asymmetric Michael addition of 3-aminooxindoles **1** to nitroolefins **2**. [a]The reactions were conducted with **1** (0.2 mmol) and **TG-9** (10 mol %) in toluene (2.0 mL) at −20 °C for 10 min. Then nitroolefin **2** (0.3 mmol) was added into the reaction mixture. Yields of the isolated products are given. The dr was determined by ^{1}H NMR spectroscopy of the crude products. The ee was determined by chiral HPLC. [b]The free amine products **3** were obtained for chiral HPLC analysis.

ring of the nitroolefins showed that both the electron-donating and electron-withdrawing groups could afford excellent results (**3aa-3ak**). Notably, the chlorine and bromine substitutions on the phenyl ring of the nitroolefins endowed the Michael addition products with useful synthetic handles for further diversifications (**3ah**, **3ai**). Furthermore, heteroaryl nitroolefins were also accommodated, as exemplified by the addition of 3-aminooxindoles to 2-furanyl and 2-thienyl nitroolefins, which furnished the desired products in high yields and excellent diastereoselectivities with 93% ee and 91% ee, respectively (**3al**, **3am**). But the bulky 2-naphthyl substituted nitroolefin underwent the asymmetric Michael addition process smoothly with erosion of the enantioselectivity (**3an**).

After the wide generality of nitroolefins has been established, the variations with respect to 3-aminooxindoles were next investigated. With the *N*-methyl protection on 1-position, both electron-donating and withdrawing substitutions on 5-position underwent the process smoothly. For example, 3-aminooxindoles with 5-Me



Scheme 3. Transformations of the Michael addition products.

and 5-F groups afforded the adducts in high yields and excellent diastereoselectivities with 87% and 92% ee, respectively (**3ba**, **3ca**). In addition, the ethyl 1-methy-2-oxoindole-3-ylcarbamate **1d** was also subjected to this reaction, affording the product with 92% ee and 10:1 dr (**3da**). The *N*-benzyl substitution of the oxindole nitrogen also matched the process, affording the products in 10:1 dr and improved the enantioselectivity to 98% ee (**3ea**). Furthermore, the absolute structure of **3ai** was confirmed by X-ray crystallographic analysis (Scheme 2), and those of other products were assigned by analogy.

To show the synthetic utility of the asymmetric Michael addition process, derivatization of the quaternary 3-aminooxindoles was implemented. To this end, in the presence of $NaBH_4/NiCl_2$, the nitro group of **3aa** could be reduced easily, affording chiral γ-diamine derivative **4** with maintained *enantio*- and diastereoselectivity in 95% yield. Moreover, the α-carbon of the nitro group of **3ea** was oxidized to acid, which gave a novel *β*-amino acid derivative bearing oxindole structure in 80% yield with 98% ee (Scheme 3).

Based on the stereochemical outcome of the Michael adduct together with the activation mode by guanidine catalysis [3b,d], a plausible transition state working model was proposed (Fig. 2). The guanidine as a strong base could abstract proton from 3-aminooxindole and activate the corresponding enolate anion via hydrogen bonding. Meanwhile, the protonated tartrate-derived guanidinium as a chiral hydrogen bond donor activates the nitroolefin by double hydrogen bonds. Moreover, the phenyl group of guanidine probably has π-π interaction with substrates. These stereo-arrangements facilitate the result in the stereodetermining addition of 3-aminooxindole (as its enol tautomer) to the *Re* face of the nitroolefin, delivering the quaternary 3-aminooxindole product with observed stereochemistry.

In conclusion, we have identified a novel efficient tartrate-derived guanidine catalyst for Michael addition of 3-aminooxindoles to nitroolefins. Through the reasonable modification of a chiral tartrate-derived guanidine catalysts, a series of diversified quaternary 3-aminooxindoles containing adjacent quaternary–tertiary stereocenters were achieved in high yield (up to 95%) with good to excellent diastereo- and enantioselectivities (up to >20:1 dr and 98% ee). A possible transition state working model involving multiple hydrogen bonding interactions for this reaction was proposed. Further applications of the chiral tartrate-derived guanidine catalysts in other asymmetric transformations are ongoing in our laboratory.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152741.

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