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Short communication

Synthesis of novel chiral guanidine catalyst and its application in the asymmetric Pictet-Spengler reaction

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ABSTRACT

A new chiral guanidine catalyst has been synthesized by the reaction of (*R*)-1-(1-phenylethyl)guanidine and 2,3-diphenylcycloprop-2-enone. The catalyst was evaluated for the Pictet-Spengler reaction in which tetrahydro-β-carbolines were obtained in good yields with up to 64% ee.

1. Introduction

Guanidine containing compounds have been used in various organic reactions as strong organic bases. Various chiral guanidine derivatives comprising from acyclic to polycyclic systems have been reported in the literature and have been used in a variety of asymmetric reactions e.g., Michael, Henry, Mannich, Strecker [1]. They activate the substrates by unique mode of dual hydrogen bonding thus providing high catalytic as well as high enantioselective activities. Several effective organocatalysts possessing the guanidinium functional group have been introduced to organic synthetic methodology. For example, chiral guanidine based on (*R*)-(+)-1-phenylethylamine was first developed by Nájera as the catalyst for asymmetric addition of nitroalkanes to aldehydes [2]. In the following years, many other scaffolds were introduced as effective and enantioselective chiral guanidine catalysts. These include Lipton's dipeptide guanidine [3] and Corey's bicyclic guanidine [4], useful for asymmetric Strecker reaction. Selected other chiral guanidine catalysts like Ishikawa's bifunctional guanidine [5,6], Terada's binaphthyl-based guanidine [7–9], and Tan's modified Corey-type bicyclic guanidine [10–15]. Finally, Dixon has developed a class of chiral bifunctional thiourea imininophosphoranes as effective catalysts for asymmetric nitro-Mannich reaction [16]. Also recently, Wang introduced a very effective tartrate-derived guanidine for diastereoselective Michael addition of 3-subtituted oxindoles to nitroolefins [17]. The introduction of an electron-withdrawing group attached to the guanidine moiety increases the acidity of the N—H bonds thus allowing the construction of new effective organocatalysts acting as strong hydrogen bond donors [18].

Our idea was to develop a new chiral guanidine catalyst with the core skeleton easily accessible by the reaction of (*R*)-1-(1-phenylethyl)guanidine and aryl-substituted cyclopropenone. This type of reaction has already been reported in the literature [19] but neither its application to catalysis nor its chiral version was elaborated. We therefore expected that the reaction of (*R*)-1-(1-phenylethyl)guanidine with 2,3-diphenylcycloprop-2-enone would afford new chiral guanidine able to catalyze useful organic transformations. Herein, we report on the synthesis of such organocatalyst and its application in the asymmetric Pictet-Spengler reaction.

2. Experimental

2.1. Synthesis of guanidine 3

To a cooled 15–20 °C solution of (*R*)-(+)-1-phenylethylamine **1** (2.4 g, 19.8 mmol) in dioxane (3 mL) conc. HCl (2.1 mL) was added dropwise over a period of 10 min and then the solution was stirred for 15 min at the same temperature. Then, all volatiles were removed under reduced pressure till dryness. The white crystalline solid was washed with Et_2O (3 × 10 mL) to get compound **2** (3.1 g, 99%) as

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white crystals. Compound **2** (3.1 g, 19.8 mmol) was dissolved in water (12 mL) and then cyanamide (NH_2CN, 0.82 g, 19.5 mmol) was added, and the solution was adjusted to pH 8–9 by the addition of (*R*)-(+)-1-phenylethylamine (few drops). After 5 h of reflux, the reaction mixture was allowed to cool and then all volatiles were removed under reduced pressure. The resulted sticky mass was triturated with Et_2O to get white solid which was dissolved in a minimum volume of water and was passed through Amberlite IRA-401 column (hydroxide ion, eluted with water) to get guanidine **3** as a colourless oil (2.31 g, 72%). $[\alpha]^{22}_D$ + 28.9 (*c* 1.0, EtOH); {For enantiomer lit. [20] $[\alpha]^{22}_D$ − 29.3 (*c* 3.52, EtOH), 99% ee}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.33–7.25 (m, 4H), 7.21–7.16 (m, 1H), 5.09 (br s, 4H), 4.58 (q, *J* = 6.8 Hz, 1H), 1.28 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.5, 156.9, 143.8, 128.9, 127.7, 126.2, 50.5, 23.5; LRMS (ESI): $[M + H]^+$ (100%) 164.2. HRMS (ESI+): *m/z* calcd for $C_9H_{14}N_3$ $[M + H]^+$ 164.1188; found 164.1197.

2.2. Synthesis of catalyst 5 ((5S,6R)-5,6-diphenyl-2-((R)-1-phenylethylamino)-5,6-dihydropyrimidin-4(1H)-one)

To a solution of (*R*)-1-(1-phenylethyl)guanidine **3** (1.15 g, 7.0 mmol) in benzene:EtOH (1:1) (70 mL) 2,3-diphenylcycloprop-2-enone **4** (1.44 g, 7.0 mmol) was added at room temperature and the mixture was stirred for 18 h. All volatiles were then removed under reduced pressure and the residue was purified by silica gel column chromatography (10–80% EtOAc/hexane) to get oily product, which was recrystallized from EtOH to get compound **5** (1.40 g, 55%) as a white solid. Mp 230–233 °C; $[\alpha]^{25}_D$ + 25.8 (*c* 1.0, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$:DMSO-d_6 (10:1)) δ 7.42–7.30 (m, 5H), 7.25–7.04 (m, 11H), 6.78 (br s, 1H), 5.31 (br s, 1H), 4.62 (d, *J* = 9.0 Hz, 1H), 3.60 (d, *J* = 9.0 Hz, 1H), 3.13 (br s, 1H), 1.44 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$:DMSO-d_6 (10:1)) δ 143.2, 140.1, 137.7, 133.6, 128.8, 128.0, 127.90, 127.87, 127.7, 127.4, 127.3, 127.0, 126.5, 126.3, 126.0, 125.5, 59.1, 53.9, 48.9, 22.5; IR (KBr) 3249, 3060, 2939, 2775, 1640, 1358, 1065, 860, 681 cm − 1; HRMS (ESI+): *m/z* calcd for $C_{24}H_{24}N_3O$ $[M + H]^+$ 370.1919; found 370.1927. The deposit number CCDC 1498781 [21].

2.3. Representative procedure for the Pictet-Spengler reaction (compound 8e, Table 2, entry 4)

To a suspension of catalyst **5** (3.7 mg, 0.01 mmol, 10 mol%), in THF (1.5 mL) *N*-(4-nitrobenzyl) tryptamine **6b** (29.5 mg, 0.1 mmol), malonic acid (1.0 mg, 0.01 mmol, 10 mol%), $BF_3 \cdot Et_2O$ (1.4 mg, 1.2 μL, 0.01 mmol, 10 mol%), and 3 Å molecular sieves (200 mg, powdered) were added at room temperature and stirred for 5 min. Then *p*-nitrobenzaldehyde **7c** (45.3 mg, 0.3 mmol) was added and stirred at room temperature for 120 h. Then the reaction was quenched by the addition of saturated aqueous Na_2CO_3 (3 mL) and extracted with EtOAc (3 × 6 mL). Organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. Compound **8e** was purified by silica gel column chromatography (1–20% EtOAc/hexane).

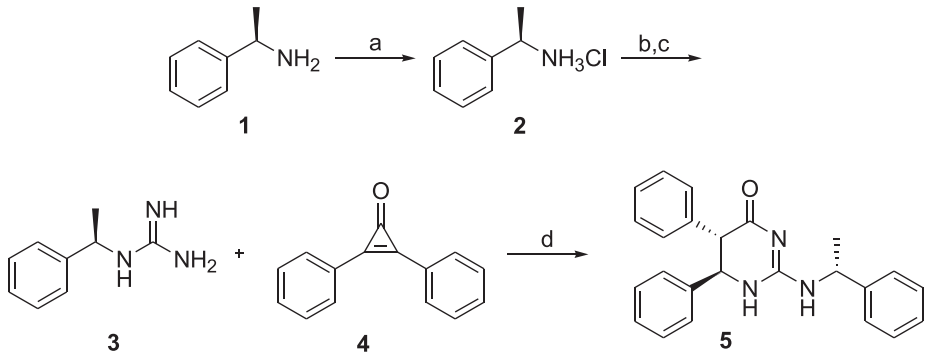
2.4. 2-(4-nitrobenzyl)-1-(4-nitrophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (8e)

White solid (42.1 mg, 98%) $[\alpha]^{28}_D$ − 15.9 (*c* 1.0, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.34–8.11 (m, 4H), 7.79–7.55 (m, 4H), 7.45 (d, *J* = 7.52 Hz, 1H), 7.23 (d, *J* = 7.70 Hz, 1H), 7.12–6.90 (m, 2H), 4.98 (s, 1H), 3.90–3.67 (m, 2H), 3.05–2.88 (m, 1H), 2.86–2.61 (m, 3H); HPLC (Chiracel OD-H, hexane/*i*-PrOH = 90:10, 1.0 mL/min); t_R (minor) = 24.6 min and t_R (major) = 28.0 min, 64% ee.

3. Results and discussion

The construction of chiral guanidine catalyst **5** is depicted in Scheme 1. The synthesis started with the transformation of (*R*)-(+)-1-phenylethylamine **1** into its hydrochloride salt **2** which was then treated with cyanamide (NH_2CN) at pH 8–9 in water under reflux to afford guanidine hydrochloride [19] which was subsequently converted into the free guanidine **3** by passing through Amberlite IRA-401 column (hydroxide form). Guanidine **3** was then reacted with 2,3-diphenylcycloprop-2-enone **4** in benzene:EtOH (1:1) at room temperature affording compound **5** in 55% yield as a single diastereomer in the form of crystalline solid. Other stereoisomer was not detected. As indicated in the ^{1}H NMR spectrum, phenyl substituents at dihydropyrimidinone ring were in trans disposition to each other having the value of the coupling constant of the adjacent methine protons of 9.0 Hz. The structure and stereochemistry of compound **5** was unambiguously established by X-ray analysis (Fig. 1).

To verify the effectiveness of the newly synthesized guanidine catalysts **5**, we first employed it in the Pictet-Spengler reaction [22] of protected tryptamine **6a** and *p*-bromobenzaldehyde **7a** in dichloromethane (Table 1). The cyclized product **8a** was formed in 28% yield and with 13% ee (Entry 1). Further, we checked the catalytic activity of **5** in different solvents. In less polar solvents (e.g. benzene, toluene and xylene) (Entry 2–4) it gave the product in 8–15% yield and 2–8% ee, while the reaction in $CHCl_3$ (Entry 5) gave 15% yield and 9% ee. In polar solvents, like THF (Entry 6), it gave similar chemical yield (17%) of the product with 17% ee. When the reaction was carried out in protic solvents (like MeOH, *i*-PrOH) (Entry 7, 8), the product was not detected. We then assumed THF as the best solvent for further optimization.



a) Conc. HCl, 1,4-dioxane, 15-20 °C, 15 min, 99%;
b) NH_2CN, pH 8-9, water, reflux, 5 h; **c**) passed through Amberlite IRA-401 (hydroxide form);
d) Benzene:EtOH (1:1), rt, 18 h, **5** 55%;

Scheme 1. Synthesis of chiral guanidine catalyst **5**.

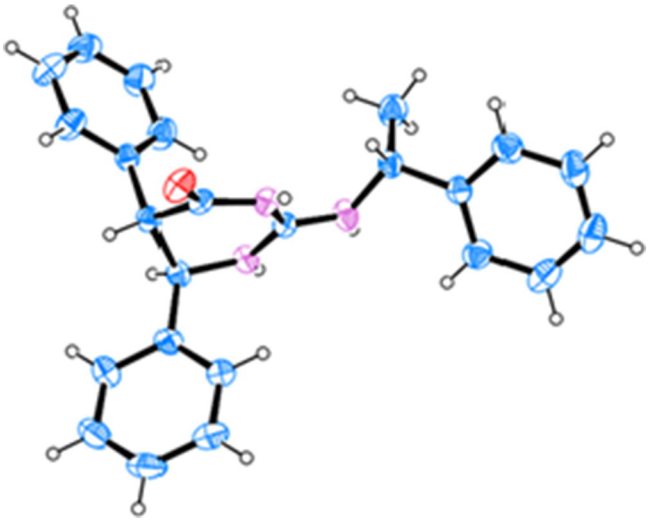


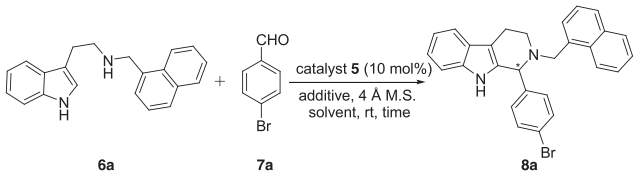
Fig. 1. ORTEP diagram of **5**. The non H-atoms are shown as 30% probability ellipsoids.

Longer reaction time (Entry 9, 10) allowed for better chemical yield (up to 65%), but very low ee. The change of the type of molecular sieves from 4 Å to 3 Å (Entry 11) gave better yield (69%) and improved ee (36% ee).

The use of $MgSO_4$ (Entry 12) or Na_2SO_4 (Entry 13) as dehydrating agents instead of molecular sieves caused a substantial decrease of the yield (5% and 2%, respectively).

In further investigation of the Pictet-Spengler reaction, we applied certain additives (acidic or basic; Table 1). First, we screened organic acids like trifluoroacetic acid, benzoic acid, acetic acid, *p*-toluenesulfonic acid and isophthalic acid (Entry 14–18) in equimolar ratio, and these all gave the product in yields up to 99%, but unfortunately no acceptable enantioenrichment was observed. Lowering the temperature to 0 °C (Entry 20) and −30 °C (Entry 21) considerably slowed down the reaction but employing an equimolar amount of malonic acid at room temperature (Entry 19) we obtained the product in almost quantitative yield and in 18% ee. When simple Lewis acid ($BF_3 \cdot Et_2O$, 10 mol %) (Entry 23) was employed as an additive, more encouraging results were obtained. The chemical yield was almost quantitative with 31% ee of enantiomeric enrichment. Surprisingly, we found that the combination of malonic acid with $BF_3 \cdot Et_2O$ (both 10%mol) (Entry 24) resulted in a non-linear cooperative effect. With the same excellent chemical yield, we were able to obtain the desired product with 58% ee. The mechanism of the above cooperative effect is unclear to us at the moment and obviously requires further investigation. It might be speculated, however, that the Brønsted acid facilitates the Pictet-Spengler reaction by protonation of the imine intermediate, whereas the Lewis acid, by coordination to the carbonyl group of compound **5**, makes N—H bonds in the catalyst even more acidic.

Table 1
Optimization of the Pictet-Spengler reaction[a].

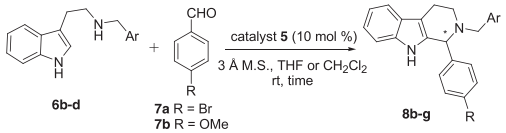


6a **7a** **8a**

Entry	Solvent	Additive (mol%)	Time (h)	Yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	–	48	28	13 (*R*)
2	Benzene	–	48	8	2 (*R*)
3	Toluene	–	48	15	8 (*R*)
4	Xylene	–	48	10	5 (*R*)
5	$CHCl_3$	–	48	15	9 (*R*)
6	THF	–	48	17	17 (*R*)
7	MeOH	–	48	nd	–
8	*i*-PrOH	–	48	nd	–
9	THF	–	72	65	3 (*S*)
10	THF	–	120	72	1 (*S*)
11	THF	–	48	69[d]	36 (*S*)
12	THF	–	48	5[e]	<1
13	THF	–	48	2[f]	<1
14	THF	Trifluoroacetic acid (100)	48	65	1 (*S*)
15	THF	Benzoic acid (100)	48	84	<1
16	THF	Acetic acid (100)	48	91	1 (*S*)
17	THF	TsOH (100)	48	33	<1
18	THF	Isophthalic acid (100)	48	82	<2
19	THF	Malonic acid (100)	48	99	18 (*S*)
20	THF	Malonic acid (10)	72[g]	36	8
21	THF	Malonic acid (10)	72[h]	22	14
22	THF	Citric acid (100)	48	78	3 (*S*)
23	THF	$BF_3 \cdot Et_2O$ (10)	48	99	31
24	THF	Malonic acid (10), $BF_3 \cdot Et_2O$ (10)	48	99	58
25	THF	Et_3N (100)	48	Traces	–
26	THF	*i*-Pr_2NEt (100)	48	Traces	–
27	THF	Pyridine (100)	48	22	9 (*S*)

[a] Reaction conditions: **6a** (0.1 mmol), **7a** (0.3 mmol), catalyst **5** (0.01 mmol, 10 mol%), solvent (1.5 mL), molecular sieves (200 mg) and additive (as given) at the mentioned temperature and time.
[b] Isolated yields of products. nd: product not detected.
[c] Enantiomeric excess was determined by chiral HPLC analysis. The absolute configuration was established on the basis of literature values of the sign of optical rotation.
[d] Freshly activated 3 Å M.S. were used.
[e] $MgSO_4$ was used.
[f] Na_2SO_4 was used.
[g] Reaction was carried out at 0 °C.
[h] Reaction was carried out at −30 °C.

Table 2
Screening of guanidine catalyst **5** in the reaction of protected tryptamines **6b–d** and aldehydes **7a–c**.



Entry	Substrate	Ar	Aldehyde	Product	Solvent	Additives (10 mol% each)	Time (h)[a]	Yield (%)[b]	ee (%)[c]
1	**6b**	*p*-$NO_2C_6H_4$	**7b**	**8b**	THF	Malonic acid, $BF_3\cdot Et_2O$	72	81	58
2	**6c**	*p*-$MeOC_6H_4$	**7b**	**8c**	THF	Malonic acid, $BF_3\cdot Et_2O$	72	33	46
3	**6d**	9-Anthracenyl	**7b**	**8d**	THF	Malonic acid, $BF_3\cdot Et_2O$	72	18	33
4	**6b**	*p*-$NO_2C_6H_4$	**7c**	**8e**	THF	Malonic acid $BF_3\cdot Et_2O$	120	98	64
5	**6c**	*p*-$MeOC_6H_4$	**7c**	**8f**	THF	Malonic acid, $BF_3\cdot Et_2O$	120	96	63
6	**6d**	9-Anthracenyl	**7a**	**8g**	THF	Malonic acid, $BF_3\cdot Et_2O$	72	84	23
7	**6d**	9-Anthracenyl	**7a**	**8g**	CH_2Cl_2	Malonic acid, $BF_3\cdot Et_2O$	72	84	55 (*S*)

[a] Reaction condition: **6** (0.1 mmol), **7** (0.3 mmol), catalyst **5** (0.01 mmol, 10 mol%), THF or CH_2Cl_2 (1.5 mL), additive or no additive, molecular sieves (200 mg) at room temperature and the time as mentioned.
[b] Isolated yields of products.
[c] Enantiomeric excess was determined by chiral HPLC analysis. The absolute configuration was established on the basis of literature values of the sign of optical rotation.

Organic bases like Et_3N (Entry 25) or *i*-Pr_2NEt (Entry 26) gave trace amount of product **8a**, while Pyridine (Entry 27) gave rather poor yield of the product with only 9% ee.

Further, we screened the effect of shielding groups on tryptamine molecule as well as the role of the substituent at benzaldehydes (Table 2). When *p*-methoxybenzaldehyde **7b** reacted with tryptamine **6b** (Entry 1), it gave the cyclized product **8b** in excellent yield, but with moderate ee, while tryptamine **6c** (Entry 2), containing electron donating group, gave poor yield of the product and comparable ee. Tryptamine **6d** (Entry 3), possessing more sterically demanding 9-anthracenyl substituent, gave low yield of product. *p*-Nitrobenzaldehyde **7c** on reaction with tryptamine **6b** (Entry 4) and **6c** (Entry 5) gave the products in excellent yields and with acceptable level of enantioenrichment (up to 64% ee). *p*-Bromobenzaldehyde **7a** on reaction with tryptamine **6d** (Entry 6) gave a good yield of the product and with only 23% ee, when the reaction was carried out in CH_2Cl_2 (Entry 7) it gave the same yield, but with improved ee (55% ee).

4. Conclusion

In summary, we have synthesized a novel chiral guanidine catalyst and we used it in the Pictet-Spengler reaction between protected tryptamine derivatives and aromatic aldehydes. After careful optimization, we selected conditions allowing for good chemical yield and chirality transfer (up to 64% ee). Further study on the described organocatalyst in the asymmetric synthesis is in progress and will be published in due course.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.catcom.2016.10.008. These data include MOL files and InChiKeys of the most important compounds described in this article.

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