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Communication

Novel Tartrate-Based Guanidines for Enantioselective Fluorination of 1,3-Dicarbonyl and α-Cyano Carbonyl Compounds

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A novel library of chiral guanidines featuring the tartaric acid skeleton is easily accessed with tunable steric and electronic properties. A guanidine molecule of this library with an incorporated 2,6-diisoaniline fragment was identified as a suitable promoter for the enantioselective fluorination of 1,3-dicarbonyl and α-cyano carbonyl compounds to furnish the fluorinated product with up to 84 % *ee* and 99 % yield using *N*-fluorobenzenesulfonimide (NFSI) as the fluorinating agent.

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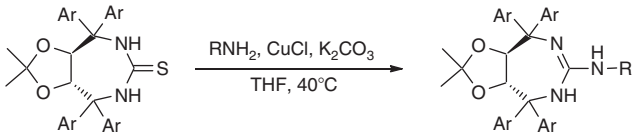
Within the domain of asymmetric organocatalysis, chiral guanidines constitute a prominent catalyst class.[1] Generally, their catalytic property arises from the combination of the strong basicity of the guanidine moiety and the notable hydrogen-bond donor capacity of its conjugate acid. To date, a broad spectrum of asymmetric organic reactions have been effected by chiral guanidine catalysis. Meanwhile, a diverse range of guanidine catalysts have been designed with varying chiral sources. Of particular note are the chiral scaffolds of amino acids[2] and binaphthols,[3] which produced some leading guanidine molecules that exhibit prominent catalytic activities and stereoselectivities. Despite these advances, however, privileged[4] guanidine catalysts are very rare and the full evolvement of this area is still hampered by the lack of a skeleton that is both easily accessible and readily tunable in terms of steric and electronic properties. Hence, the development of chiral guanidines from simple precursors with readily tunable steric and electronic factors for more asymmetric applications is highly desirable.

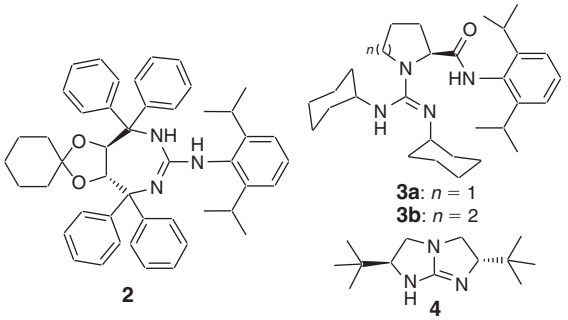
Given the abundant availability and ready diversification of tartaric acid and derivatives thereof, we have very recently developed a novel library of chiral guanidines with ethyl tartrate as the chiral source (Scheme 1).[5] The advantageous features of this library of guanidines include the following points. First, these guanidines are easily accessible, as can be seen from the synthetic route; even though seven steps are needed, all are routine, high-yielding operations. Second, the steric and electronic property of the guanidines can be readily tuned by varying the changeable substituents Ar and R. Third, since any primary or secondary amine can theoretically be incorporated in a modular manner at the final stage of the guanidine synthesis, the volume of this guanidine library can be exceptionally huge, thereby ensuring the possibility of a high-throughput screening for the best guanidine for a given reaction.

In a preliminary catalytic performance survey, we disclosed that this library of guanidines showed remarkable catalytic activity and enantioselectivity towards the asymmetric α-hydroxylation of β-dicarbonyl compounds.[5a] In a further



1: Yield: 60–93 %

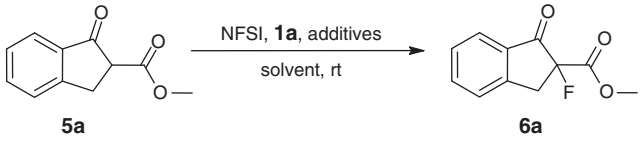
1a: Ar = Ph, R = Bn
1b: Ar = Ph, R = 4-*tert*-butylbenzyl
1c: Ar = Ph, R = 9-anthracenylmethyl
1d: Ar = Ph, R = diphenylmethyl
1e: Ar = Ph, R = (*S*)-hydroxymethyl-*tert*-butylmethyl
1f: Ar = Ph, R = Cy
1g: Ar = Ph, R = 4-methylphenyl
1h: Ar = Ph, R = 2,6-dimethylphenyl
1i: Ar = Ph, R = 2,6-di-*iso*-propylphenyl
1j: Ar = Ph, R = 3,5-di-*tert*-butylphenyl
1k: Ar = *p*-bisphenyl, R = 2,6-di-*iso*-propylphenyl



2 **3a**: *n* = 1 **3b**: *n* = 2 **4**

Scheme 1. Catalysts used in this work.

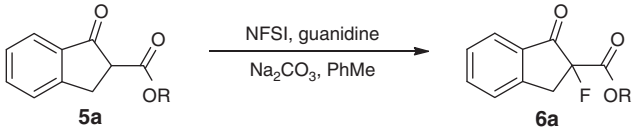
Table 1. Survey of the base additives and solvent effect



Entry[A]	Additive	Solvent [mL]	Time [h]	Yield [%][B]	*ee* [%][C]
1	Na_2CO_3	Toluene	6	99	47
2	K_2CO_3	Toluene	3 d	99	42
3[D]	Li_2CO_3	Toluene	4 d	45	32
4	Cs_2CO_3	Toluene	5	99	34
5	$K_3PO_4{\cdot}3H_2O$	Toluene	11	99	29
6[D]	$K_2HPO_4{\cdot}3H_2O$	Toluene	5 d	50	40
7	KF	Toluene	55	99	33
8	KOAc	Toluene	20	99	32
9[E]	Na_2CO_3	Toluene	6	99	47
10	Na_2CO_3	$PhCF_3$	4	99	36
11	Na_2CO_3	CH_2Cl_2	24	99	26
12	Na_2CO_3	$CHCl_3$	12	99	28
13	Na_2CO_3	Et_2O	3	99	34
14	Na_2CO_3	THF	0.5	99	14
15	Na_2CO_3	Dioxane	0.5	99	16
16	Na_2CO_3	Methyl *tert*-butyl ether	5	99	35
17	Na_2CO_3	Ethyl acetate	1.5	99	32
18	Na_2CO_3	Acetone	0.5	99	11
19	Na_2CO_3	CH_3CN	1	99	11
20[F]	Na_2CO_3	Toluene	3.5	95	4

[A]Unless otherwise noted, reactions were conducted with **5a** (0.1 mmol), **1a** (10 mol-%), NFSI (0.12 mmol), and additive (0.1 mmol) in 1 mL of solvent at room temperature.
[B]Isolated yields.
[C]The *ee* values were determined by HPLC (Chiralcel OD-H).
[D]Not completely reacted.
[E]Finely ground Na_2CO_3 powder was used.
[F]Selectfluor was used in place of NFSI.

Table 2. Further optimization of reaction conditions



Entry[A]	R	Cat.	Na_2CO_3 [equiv.]	Time [h]	Yield [%][B]	*ee* [%][C]
1	Me	**1a**	1.0	6	99	47
2	Me	**1b**	1.0	5.5	99	47
3	Me	**1c**	1.0	2	99	4
4	Me	**1d**	1.0	8.5	99	1
5	Me	**1e**	1.0	4	98	−10
6	Me	**1f**	1.0	19	99	10
7	Me	**1g**	1.0	4.5	99	31
8	Me	**1h**	1.0	3	99	37
9	Me	**1i**	1.0	8.5	99	60
10	Me	**1j**	1.0	4	99	12
11	Me	**1k**	1.0	2	99	55
12	Me	**2**	1.0	7	99	50
13	Me	**3a**	1.0	3	99	−17
14	Me	**3b**	1.0	8	99	−9
15	Me	**4**	1.0	4	76	20
16[D]	Me	**1i**	1.0	24	99	65
17[D]	Me	**1i**	1.1	11.5	99	64
18[D]	Me	**1i**	1.5	10	99	61
19[D]	Et	**1i**	1.1	14	99	40
20[D]	*iso*-Pr	**1i**	1.1	15	99	34
21[D]	*tert*-Bu	**1i**	1.1	18	95	43
22[D]	Bn	**1i**	1.1	15	96	44
23[E]	Me	**1i**	1.1	25	99	73
24[F]	Me	**1i**	1.1	116	99	81

[A]Unless otherwise noted, all reactions were carried out with **5a** (0.1 mmol), catalyst (10 mol-%), NFSI (0.12 mmol), and additive (0.1–0.15 mmol) in 1 mL of toluene at room temperature.
[B]Isolated yields.
[C]The *ee* values were determined by HPLC (Chiralcel OD-H).
[D]0°C.
[E]–20°C.
[F]–40°C.

study, we found that this guanidine library can catalyze the Michael addition of oxindoles to nitroolefins in high yields with excellent diastereo- and enantioselectivities over an extraordinarily broad substrate scope.[5b] To further expand the catalytic application of this chiral guanidine library, herein we report the asymmetric fluorination of 1,3-dicarbonyl and α-cyano carbonyl compounds under the catalysis of the tartrate-based guanidines. Since the initial report by Hintermann and Togni on the catalytic asymmetric fluorination of β-ketoesters with chiral titanium TADDOLate (TADDOL = α,α,α′,α′-tetraaryl-1,3-dioxolan-4,5-dimethanol) complexes and Selectfluor,[6] both chiral metal complexes[7] and organocatalysts[8] have been investigated for this transformation. But, to our knowledge, no guanidine catalyst has been documented for this reaction.

The enantioselective fluorination of indanone derived β-ketoester was selected as a model reaction to identify optimal reaction conditions. Base additives were first screened using the model fluorination reaction of **5a** in toluene with 10 mol-% of **1a** and *N*-fluorobenzenesulfonimide (NFSI) as the fluorinating reagent (Table 1, entries 1–8). When Na_2CO_3 was used as an additive, the reaction was completed in 6 h with full conversion and a promising enantioselectivity of 47 % *ee* (Table 1, entry 1). While the reactions with K_2CO_3 and Li_2CO_3 were very sluggish, Cs_2CO_3 reacted faster but afforded lower enantioselectivity (Table 1, entries 2–4). Further investigation on the use of other inorganic bases afforded inferior *ee* values (Table 1, entries 5–8). The use of Na_2CO_3, which was ground into fine powders, gave the same enantioselectivity (entry 9, 47 % *ee*). With Na_2CO_3 as the additive and **1a** as the catalyst, other solvents were then surveyed and the results indicated that toluene remained the solvent of choice (Table 1, entries 10–19). We also attempted the use of Selectfluor in place of NFSI in the presence of 10 mol-% of **1a** in toluene using Na_2CO_3 (1.0 equiv.) as the additive at room temperature. However, the reaction gave very poor enantioselectivity with 95 % yield (Table 1, entry 20).

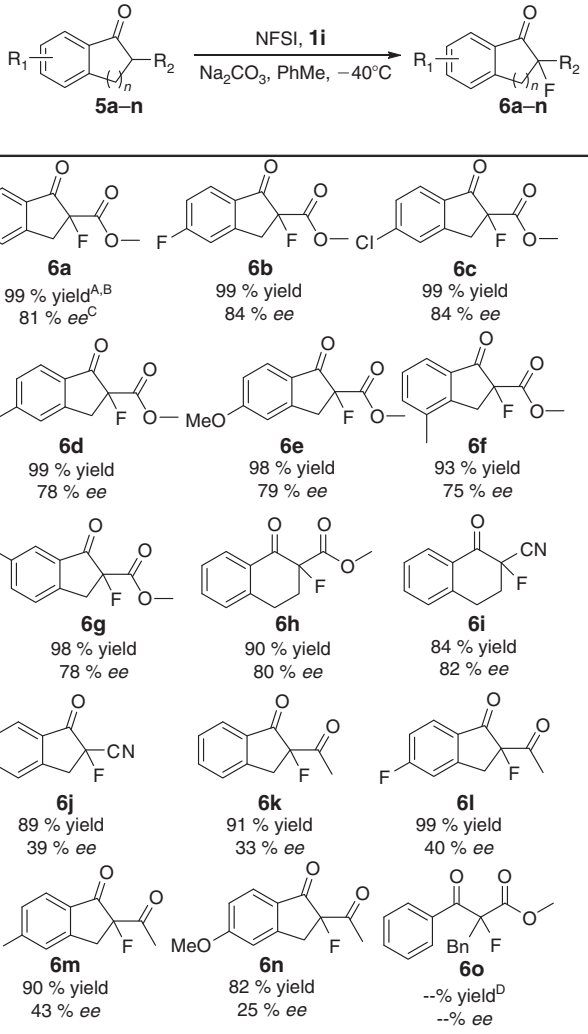
With the optimal base additive and solvent identified, other reaction parameters were then examined. The amine moiety, which was introduced at the final stage as an integral component of the guanidine catalyst, has a marked influence on the enantioselectivity of the hydroxylation reaction.[5a] The same phenomenon was also seen in the fluorination reaction (Table 2, entries 1–10). While benzyl amine derived guanidine **1a** exhibited promising enantioselectivity at room temperature, other

sterically bulky amine-derived guanidine catalysts generally showed poor enantiocontrol except for the 4-*tert*-butylbenzyl amine derived guanidine which afforded **6a** with the same enantioselectivity as **1a** (Table 2, entries 1–4). When bifunctional catalyst **1e** was used in the reaction, the enantioselectivity of the product was reversed but with a very poor *ee* value (Table 2, entry 5). Guanidine **1f** derived from cyclohexylamine also afforded poor enantiocontrol (Table 2, entry 6). To further improve the enantioselectivity, aryl amine derived guanidines were examined (Table 2, entries 7–10). While 4-methylaniline and 2,6-dimethylaniline derived guanidines gave lower enantioselectivities than **1a** (Table 2, entries 7 and 8), to our delight, 2,6-diisopropylaniline-based guanidine **1i** gave 60 % *ee* (Table 2, entry 9). In sharp contrast, the guanidine derived from 3,5-di-*tert*-butylaniline gave a poor *ee* of 12 % (Table 2, entry 10). Further variation of the aryl groups at the 1,4-positions of the tartaric acid backbone with *p*-bisphenyl functionality decreased the enantioselectivity to 55 % *ee* (Table 2, entry 11). Cyclohexanone ketal catalyst **2** gave the product in good yield but the *ee* value was lower (Table 2, entry 12). For comparison, some amino acid based guanidine catalysts were tested.[2c,d] The results indicated that these guanidines showed inferior asymmetric induction compared with **1i** (Table 2, entries 13–15). Based on the above results, we then focussed on the use of guanidine **1i** for further screening efforts. Dropping the temperature to 0°C appreciably improved the enantioselectivity (Table 2, entry 16), while changing the Na_2CO_3 loading (Table 3, entries 17 and 18) had little effect on *ee* values. A brief survey on the ester moiety of the substrate revealed that the introduction of the sterically bulky group instead of methyl ester group led to reduction of the reactivity and enantioselectivity in the catalytic enantioselective fluorination reaction (Table 2, entries 18–21). Finally, we found that the enantioselectivity of this reaction was sensitive to temperature and lowering the temperature to −40°C gave the product in a reasonable 81 % *ee* and 99 % yield with a prolonged reaction time (Table 2, entry 24).

With the optimized conditions for the guanidine-catalyzed asymmetric fluorination reaction in hand, the scope of the substrate was investigated. The effect of the substituent identity and substitution pattern on the phenyl ring was first studied. Both electron-withdrawing and electron-donating substituents at the 5-position all gave the desired products in quantitative yield with a reasonable level of enantioselectivity (Table 3, **6b**–**e**). It was found that substitution at the 4- or 6-position on the aromatic ring of the substrate did not obviously influence the efffciency of the asymmetric induction. For example, the 4- and 6-methyl substituted substrates afforded slightly decreased enantioselectivities of 75 and 78 % *ee* values (**6f** and **6g**), respectively. Notably, the substrate with a six-membered ring also underwent the fluorination reaction smoothly and a good *ee* value and excellent yield was obtained (**6h**, 80 % *ee*, 90 % yield).

To further expand the utility of our guanidine catalysts, the fluorination procedure was extended to α-cyano carbonyl and β-diketone compounds. Six-membered cyclic α-cyano carbonyl compound **5i** under the same reaction conditions gave a good *ee* value, but the corresponding five-membered product **6j** was obtained with a low *ee* value (Table 3). Cyclic β-diketones **5k**–**n** could be fluorinated smoothly but the enantioselectivity was generally poor in comparison with β-ketoester substrates. When an acyclic β-ketoester **5o** was used, no obvious fluorination reaction occurred after three days under the same reaction conditions.

Table 3. Catalytic asymmetric fluorination of 1,3-dicarbonyl and α-cyano carbonyl compounds



[A]Unless otherwise noted, all reactions were carried out with **5** (0.2 mmol), **1i** (10 mol-%), NFSI (0.24 mmol), and Na_2CO_3 (0.22 mmol) in 2 mL of toluene at −40°C.
[B]Isolated yields.
[C]The *ee* values were determined by HPLC.
[D]Reacted for three days under the same reaction conditions.

In summary, we have developed a tartrate-based guanidine catalyzed asymmetric fluorination reaction for 1,3-dicarbonyl and α-cyano carbonyl compounds with NFSI as the fluorinating agent. A guanidine molecule with an incorporated 2,6-diisoaniline fragment was identified as a suitable catalyst for this reaction to furnish the fluorinated product with up to 84 % enantioselectivity and 99 % yield. Studies towards extending the catalytic applications of this chiral guanidine library for other asymmetric transformations are currently underway in our laboratory.

General Procedure for the Fluorination of 1,3-Dicarbonyl and α-Cyano Carbonyl Compounds

A Schlenk tube equipped with a magnetic stirrer bar was charged with compound **5** (0.2 mmol) and toluene (2 mL),

followed by the guanidine catalyst **1i** (0.02 mmol). The resulting mixture was stirred at room temperature for 5 min before cooling to −40°C. To this mixture was then added NFSI (0.24 mmol). After stirring at −40°C for another 10 min, solid Na_2CO_3 (0.22 mmol) was added to the resulting solution. The resulting solution was stirred at −40°C until complete consumption of **5**. The reaction mixture was allowed to warm to room temperature and the solution of the crude product was concentrated under vacuum. The residue was purified by column chromatography on silica gel (light petroleum/ethyl acetate) to give the product **6**.

Supplementary Material

Characterization data for guanidines **1** and **2**, and compounds **6**, and copies of NMR spectra and HPLC traces are available on the Journal's website.

Acknowledgements

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