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Microwave-Assisted Synthesis of Guanidine Organocatalysts Bearing a Tetrahydroisoquinoline Framework and Their Evaluation in Michael Addition Reactions

Tricia Naicker,[a] Per I. Arvidsson,[a,b,c] Hendrik G. Kruger,[d] Glenn E. M. Maguire,[d] and Thavendran Govender*[a]

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The simple and practical syntheses of chiral guanidine organocatalysts and their evaluation in the asymmetric Michael addition reaction of malonates and β-keto esters with nitro-olefins is reported. These organocatalysts are the first of their kind based on a tetrahydroisoquinoline framework. In addition, a microwave-assisted procedure for introducing the guanidine unit onto amino amide derivatives is reported. The chiral products were obtained with quantitative chemical efficiency (up to 99 % yield) and excellent enantioselectivity (up to 97 % *ee*).

Introduction

The guanidine moiety has become well known in both chemistry and biology for its characteristic high pK_a value and its ability to form dual hydrogen bonds.[1] Therefore, this functional group has been an attractive target that has been incorporated into several chiral catalysts used for both metal–ligand[2] and organocatalysis.[3] It has been successfully employed as both Brønsted base/acid and phase-transfer catalysts for several important asymmetric reactions such as the Henry,[4] Strecker,[5] Mannich, Diels–Alder, and Michael reaction and Claisen rearrangement.[6] As a result, the roles of guanidine-based catalysts are steadily increasing in asymmetric synthesis. Some excellent reviews on guanidine chemistry have emerged during the last decade.[1b,1c,2b,3,6,7]

Amino acid based organocatalysts have arisen as versatile and efficient candidates that promote a wide range of enantioselective transformations.[8] The incorporation of naturally occurring α-amino acids as a source for chirality into guanidine organocatalysts, however, has not been widely investigated.[9] As illustrated in Figure 1, only a few organocatalysts have taken advantage of including guanidines into readily available amino acids.

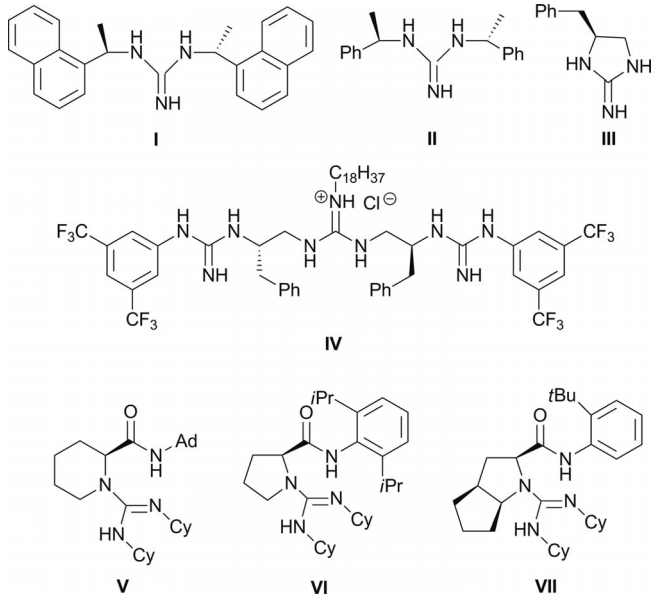

Figure 1. Examples of chiral guanidine organocatalysts derived from α-amino acids (**I** and **II**,[9a] **IV**,[9b] and **V**–**VII**[9c]).

Furthermore, the amino acid based guanidine catalysts developed thus far are molecules that are prepared through nontrivial syntheses. Hence the development of a simple route to prepare other chiral guanidines is still of great interest. We have set out to introduce a new class of easily accessible amino acid based guanidine organocatalysts bearing a tetrahydroisoquinoline (TIQ) backbone (Figure 2).

[a] School of Pharmacy and Pharmacology, University of KwaZulu-Natal,
Durban Private Bag 4000, South Africa
Fax: +27-72603091
E-mail: govenderthav@ukzn.ac.za
[b] Organic Pharmaceutical Chemistry, Department of Medicinal Chemistry, Uppsala Biomedical Centre, Uppsala University, Box 574, 75123 Uppsala, Sweden
[c] Innovative Medicines, CNSP iMed, AstraZeneca R&D Sodertalje,
15185 Sodertalje, Sweden
[d] School of Chemistry, University of KwaZulu-Natal, Westville, Durban, South Africa
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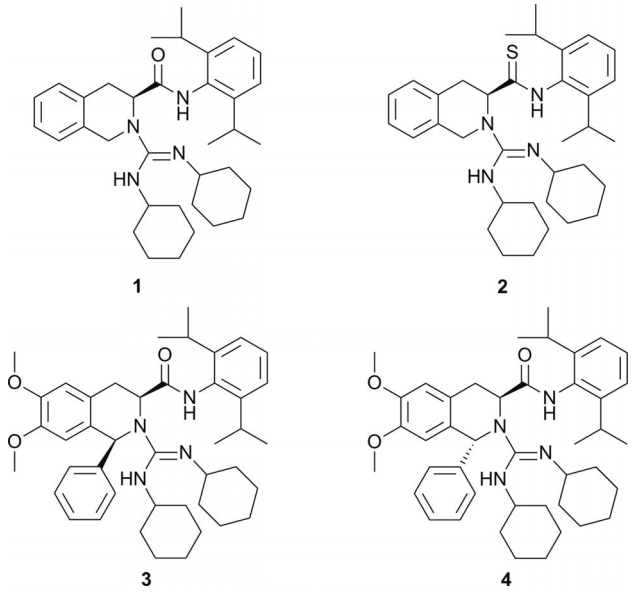
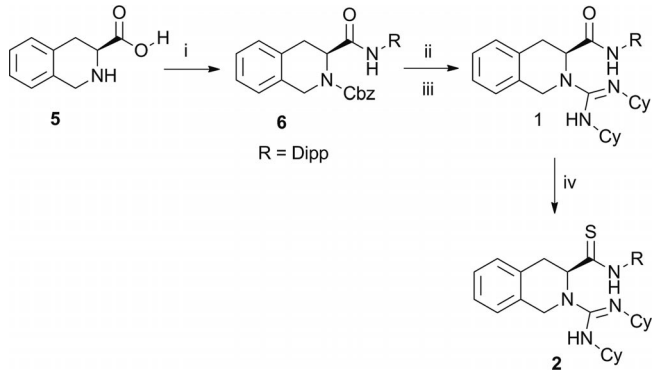


Figure 2. TIQ guanidine organocatalysts evaluated in this study.



Scheme 1. Synthetic route to catalysts **1**. Reagents and conditions: (i) $KHCO_3$, CbzCl, dioxane/water in situ solvent evaporation, DIPEA, ethyl chloroformate, 2,6-diisopropylphenylamine, dichloromethane, 0 °C to r.t, 12 h; (ii) Pd/C (10 wt.-%), H_2 (1 atm), methanol, r.t, 1 h; (iii) $Yb(OTf)_3$, DCC, microwave irradiation, toluene, 120 °C, 3 h; (iv) Lawesson's reagent, toluene, reflux, 12 h.

This initiative was also partly encouraged by the observation that chiral pipecolic and pyrrole acid derived guanidines (Figure 1) with an amide functional group (i.e., **V**–**VII**) have been shown to promote synthetically useful transformations such as the Michael addition[9c] and domino reactions.[10] The TIQ molecule and its derivatives have been extensively studied due to their biological and pharmaceutical properties.[11] However, it has been sparsely used a source for chirality in asymmetric catalysis. Recently, we have made much progress with TIQ-based ligands for catalytic asymmetric reactions, including the transfer hydrogenation of prochiral ketones,[12] Henry reaction,[13] hydrogenation of olefins,[14] and we have expanded the potential of these TIQ derivatives as organocatalysts for the Diels–Alder reaction[15] and allylation of aldehydes.[16]

Herein, we report the microwave-assisted synthesis and catalytic activity of TIQ-based guanidines that promote the asymmetric 1,4-addition of β-keto esters or malonates to nitro-olefins in up to 97%*ee*. The catalysts are insensitive to moisture and oxygen and are easily prepared from commercially available starting materials in three straightforward steps with isolated yields of 90–95%.

Results and Discussion

Catalyst Synthesis

As a preliminary study we chose the 2,6-diisopropylphenylamine (dipp) amide and dicyclohexylcarbodiimide (DCC) functional groups to be used on the TIQ skeleton. These moieties proved to be optimal when used by Feng et al. on pipecolic acid for application as an organocatalyst for Michael addition reactions.[9c] Catalyst **1** (Scheme 1) was synthesized in 95% overall yield from commercially available tetrahydroisoquinoline amino acid **5** (phenylalanine derived).

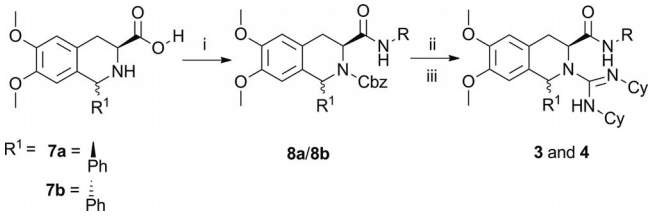
Secondary amine **5** was protected by performing an in situ reaction with benzyl chloroformate (Cbz)[12] followed by amide bond formation with diisopropylphenylamine to yield compound **6**. Thereafter, the amide was deprotected through hydrogenation. Upon filtration of Pd/C and evaporation of the solvent, the product was used directly for the next step. To synthesize the guanidine unit, we applied the lithiation and subsequent addition of DCC procedure as done with pipecolic and pyrrole acid derivatives.[9c] However, even after several attempts, the reaction resulted in many side products and the crude mixture proved difficult to purify. Next, we attempted the one-pot procedure by Shen et al., who reported the catalytic use of $Yb(OTf)_3$ for the addition of carbodiimides to non-chiral amines under solvent-free conditions utilizing conventional heating.[17] However, low product yields (40% isolated) and long reaction times (>24 h) led us to modify this procedure by using microwave irradiation. Initially, the reaction was carried out under neat conditions in the microwave (Table 1, Entries 1–3). An increase in temperature resulted in higher yields of the product; however, for reactions performed at temperatures greater than 100 °C charring of the reagents occurred. Next, we investigated adding a solvent to the reaction mixture (Table 1, Entries 4–6). Toluene proved to be optimal in the microwave at 120 °C for 3 h (Table 1, Entry 8) with a 95% isolated yield. This is one of only few procedures employing microwave irradiation for guanidine attachment to chiral auxiliaries.[18]

A similar synthetic route (as that of catalyst **1**) was followed for **2** except that the triflate salt of final product **1** was treated with Lawesson's reagent to yield the TIQ thioamide guanidine organocatalyst. We have previously reported the synthesis of both *cis*-/*trans*-substituted TIQ acids **7a/7b**.[13,16] The *N*-Cbz protected acid was treated with 2,6-diisopropylphenylamine to furnish amides **8a/8b**. The protecting group was then removed, and the guanidine moiety was attached following the same microwave procedure as that for the unsubstituted organocatalysts to furnish compounds **3** and **4**.

Table 1. Optimization of microwave conditions for guanidine formation on TIQ derivatives.

Entry	Solvent	Time [h]	Temperature [°C]	Yield [%]
1	neat	3	80	20
2	neat	6	80	34
3	neat	1	100	41
4	THF	1	80	35
5	CH_3CN	1	80	32
6	toluene	1	80	40
7	toluene	1	100	55
8	toluene	3	120	95

Notably, all compounds in Scheme 2 have a second chiral center and could not be synthesized from a phenylalanine derivative, as it was essential to employ activated aromatic groups **7a/7b** (derived from L-DOPA) to facilitate the cyclization and to introduce the additional chiral group. Moreover, for catalysts **3** and **4**, a single diastereomer was observed by ^{1}H NMR spectroscopy after both coupling of the amide and carbodiimide groups.



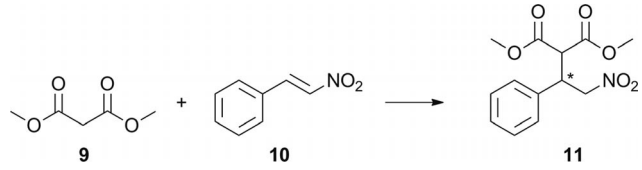
Scheme 2. Synthetic route to catalyst **3** and **4**. Reagents and conditions: (i) $KHCO_3$, CbzCl, dioxane/water in situ solvent evaporation, DIPEA, ethylchloroformate, 2,6-diisopropylphenylamine dichloromethane, 0 °C to r.t, 12 h; (ii) Pd/C (10 wt.-%), H_2 (1 atm), methanol, r.t, 1 h; (iii) $Yb(OTf)_3$, DCC, microwave irradiation, toluene, 120 °C, 3 h.

Catalyst Evaluation

The TIQ guanidine organocatalysts was evaluated on the asymmetric 1,4-addition reaction between dimethyl malonate (**9**) and nitrostyrene (**10**). It has been shown in the literature that the appropriate choice of solvent was crucial for asymmetric induction.[7h,9c,19] Therefore, catalyst **1** was tested in the most common solvents used for this type of asymmetric reaction (Table 2). The change in solvent had a noteworthy effect on the enantiomeric excess of reaction product **11** (Table 2, Entry 6).

Although moderate selectivity was observed, there was excellent reactivity to Michael addition product **11**. Encouraged by these results we set out to modify our catalyst in the hope of increasing the enantiomeric excess. Feng and co-workers have reported that the amide hydrogen was imperative for both selectivity and conversion with their pipecolic organocatalysts.[9c] It has been shown in the literature, for some organocatalysts in which the amide group played a significant role, that replacement of this group with a more acidic thioamide functionality could be beneficial.[20] Hence, catalyst **2** was synthesized; however, this change decreased both the selectivity and yield of the reaction product (Table 3, Entry 2). This result indicated that the amide hydrogen was also important in our system for conversion and asymmetric induction.

Table 2. Michael addition between dimethyl malonate (**9**) and nitrostyrene (**10**) with catalyst **1** at 0 °C.



Entry	Solvent[a]	Yield [%][b]	*ee* [%][c,d]
1	Et_2O	93	21 (*S*)
2	EtOAc	90	22 (*S*)
3	THF	92	23 (*S*)
4	DCM	90	5 (*S*)
5	MeOH	99	2 (*S*)
6	Toluene	99	45 (*S*)
7	CH_3CN	95	3 (*S*)

[a] Reactions were carried out by using 10 mol-% of organocatalyst **1** for 12 h. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC. [d] The configuration of the chiral product was established by comparison of its HPLC retention time with that obtained from the literature.

Table 3. Michael addition between dimethyl malonate (**9**) and nitrostyrene (**10**) with catalysts **1**–**4** in toluene at 0 °C.

Entry	Catalyst[a]	Yield [%][b]	*ee* [%][c,d]
1	**1**	99	45
2	**2**	90	20
3	**3**	91	2
4	**4**	95	31

[a] Reactions were carried out by using 10 mol-% of the organocatalyst for 12 h. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC. [d] The configuration of the chiral product was established by comparison of its HPLC retention time with that obtained from the literature.

Next, we looked at the X-ray crystal structure of catalyst **1** for further information on how the catalyst could be modified to enhance the enantiomeric excess as illustrated from OLEX2-generated Figure 3.

It is evident from the crystal structures that the N-containing six-membered ring assumes a half-boat conformation with the guanidine moiety tilted downwards. It is synthetically possible to introduce a phenyl ring at the C1 atom in either the *cis* or *trans* position in hope that this would have an effect on the chiral induction of the catalyst. Derivatives **3** and **4** were synthesized and tested; however, a marginal difference in enantiomeric excess was observed (Table 3, Entries 3 and 4). It was optimal to proceed with catalyst **1** and toluene as the solvent of choice.

TIQ-based organocatalyst **1** was extended by applying it to other malonates or β-keto esters and nitrostyrene (Table 4, Entries 1–6).

All of the reactions proceeded with quantitative yields and reasonable increases in selectivities were observed. This illustrated that catalyst **1** could be applied to both linear

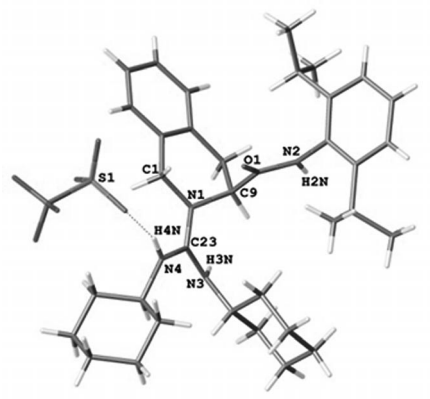
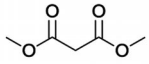
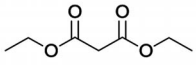
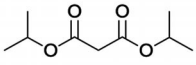
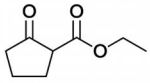
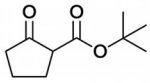
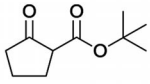


Figure 3. OLEX2-generated[21] drawing of the X-ray structure of catalyst **1** as the triflate salt.

Table 4. Michael addition between different malonates or β-keto esters and nitrostyrene (**10**) with catalyst **1** at 0 °C in toluene.

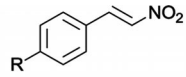
Entry	Substrate[a]	Yield [%][b]	*ee* [%][c,d]	*syn*/*anti*[c]
1		99	45(*S*)	–
2		99	50 (*S*)	–
3		99	68 (*S*)	–
4		99	63	99:1
5		99	78	99:1
6		99	82[e]	99:1

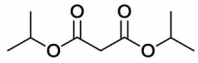
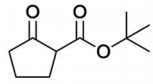
[a] Reactions were carried out by using 10 mol-% of the organocatalyst for 12 h. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC. [d] The configuration of the chiral product was established by comparison of its HPLC retention time with that obtained from the literature. [e] Reaction was carried out at –15 °C after 20 h (further decrease in the temperature did not increase the selectivity).

and cyclic esters. The cyclic esters gave rise to chiral products containing an additional stereogenic center with excellent diastereomeric ratios (Table 4, Entries 4–6). *tert*-Butyl 2-oxocyclopentanecarboxylate ester gave the highest selectivity (Table 4, Entry 6) at –15 °C. It was then decided to vary the nitro-olefin for both diisopropyl malonate and *tert*-butyl 2-oxocyclopentanecarboxyl7ate ester (Table 5).

Nitro-olefins including electron-withdrawing and electron-donating group substituents on the aryl ring of nitrostyrene were employed with both linear and cyclic esters (Table 5). All substrates displayed very good conversions. A decrease in activity for both ester systems was observed when 4-OMe was used as the substituent on the nitro-olefin, suggesting electronics play a role in this substrate's reactivity. For the linear diisopropyl malonate substrate, in general, an increase in electron density from the 4-position of the aryl ring on the nitro-olefin resulted in an increase in stereoselectivity. However, this effect appears less pronounced when *tert*-butyl 2-oxocyclopentanecarboxylate ester was employed. The best result observed from all of the substrates screened was with diisopropyl malonate and 4-methoxynitrosytrene (85% yield, 97%*ee*). These results compare well with those reported for other catalytic systems for the same Michael addition, with cyclic and linear esters and nitro-olefins,[9c,19a,19c,22] demonstrating the utility of these readily available and modular TIQ-based catalysts.

Table 5. Michael addition between diisopropyl malonate or *tert*-butyl 2-oxocyclopentanecarboxylate ester and different nitrostyrene derivatives with catalyst **1** at –15 °C in toluene.



Entry	Substrate[a]	R	Yield [%][b]	*ee* [%][c,d]	*syn*/*anti*[c]
1		H	99	73(*S*)	–
2		Me	94	92(*S*)[e]	–
3		NO_2	92	77(*S*)[e]	–
4		OMe	85	97(*S*)[e]	–
5		H	99	82	99:1
6		Me	99	71	99:1
7		NO_2	95	72	96:4
8		OMe	82	60	97:3

[a] Reactions were carried out by using 10 mol-% of the organocatalyst after 20 h. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC. [d] The configuration of the chiral product was established by comparison of its HPLC retention time with that obtained from the literature. [e] The absolute configuration was arbitrarily assigned based on the sign of the optical rotation for known diisopropyl 2-(2-nitro-1-phenylethyl)malonate (Entry 1).

Conclusions

We have identified a novel class of TIQ-based guanidine organocatalysts that promotes the enantioselective Michael addition of malonates and β-keto esters with nitro-olefins. The catalysts are easily prepared from commercially available substrates and are insensitive to moisture and oxygen. Furthermore, a new microwave-assisted procedure of introducing the guanidine unit onto amino amide derivatives is reported. The chiral products were obtained with quantitative chemical efficiency (up to 99% yield) and excellent enantioselectivity (up to 97%*ee*). Further studies of this class of organocatalysts are ongoing in our laboratory.

Experimental Section

General Methods: Reagents and solvents were purchased from Aldrich, Merck, or Fluka suppliers. All solvents were dried prior to

use according to standard procedures. All NMR spectra were recorded with a Bruker Avance III 400 MHz instrument. Chemical shifts are expressed in ppm relative to $CDCl_3$. NMR spectra were obtained at room temperature. Thin-layer chromatography (TLC) was performed by using Merck Kieselgel 60 F^{254}. Crude compounds were purified by column chromatography by using silica gel 60 mesh. All IR spectra were recorded with a Perkin–Elmer spectrum 100 instrument with a universal ATR attachment. Optical rotations were recorded with a Perkin–Elmer Polarimeter. Microwave-assisted reactions were carried out with a CEM Discover SP system. High-resolution mass spectrometric data was obtained by using a Bruker microTOF-Q II instrument. The enantiomeric excess values of the chiral products were determined with a Shimadzu Prominence HPLC with either a Chiralpak IA or IB column.

Representative Procedure for Cbz Protection and Synthesis of TIQ-Based Amides:[12] To a solution of TIQ carboxylic acid (1.0 g) in dioxane (20 mL) and water (10 mL) at 0 °C was added a solution of potassium hydrogen carbonate (5.0 equiv.) dropwise over 15 min followed by the addition of CbzCl (1.1 equiv.). The solution was stirred for 1.5 h at 0 °C and then at ambient temperature for 1.5 h. The reaction was monitored with LC–MS (by neutralizing the reaction mixture with 10% HCl and extraction with ethyl acetate). The solvent was evaporated under reduced pressure, and the crude was dried under high vacuum. To the solid *N*-Cbz-TIQ acid product (2.0 g) dissolved in dichloromethane (20 mL) was added *N*,*N*-diisopropylethylamine (DIPEA, 1.5 equiv.) and ethyl chloroformate (1.5 equiv.) at 0 °C. After 1 h, diisopropylamine (1.1 equiv.) was added, and the mixture was stirred at ambient temperature for 18 h. Completion of the reaction was monitored by TLC. The reaction mixture was washed with saturated sodium hydrogen carbonate (20 mL) followed by brine (10 mL). The organic layer was separated, dried with anhydrous magnesium sulfate, and purified by silica gel column chromatography (hexane/ethyl acetate).

Representative Procedure for Deprotection of the Cbz Group and Guanidine Formation: A solution of the *N*-Cbz protected TIQ amide (1.0 g) in MeOH (20 mL) was added to a suspension of activated Pd/C (10 wt.-%, 250 mg) in MeOH (5 mL). The mixture was supplied with H_2 under atmospheric pressure and stirred at room temperature for 1 h. The reaction was monitored by TLC. The Pd/C was filtered through a Celite pad and washed with methanol (20 mL). The filtrate was then evaporated under reduced pressure to afford the deprotected TIQ amide derivatives. In a 10-mL microwave vessel containing the TIQ amide (300 mg) dissolved in toluene (5 mL) was added $Yb(OTf)_3$ (0.4 equiv.) and DCC (1.1 equiv.). The vessel was then placed in the microwave reactor and heated to 120 °C for 3 h. Toluene was then evaporated under reduced pressure, and the residue was passed through a short plug of silica (hexane/ethyl acetate, 50:50; 100 mL). The solvent was then evaporated under reduced pressure, and the crude material was dissolved in a minimum amount of ethyl acetate and left in the refrigerator overnight. This mixture was then filtered, and the filtrate was evaporated under reduced pressure to yield a residue that was purified by silica gel column chromatography (hexane/ethyl acetate). The white foam product (triflate salt) was dissolved in dichloromethane and an equal amount of saturated aqueous NaOH was added in a separation flask, which was shaken for 2 min. The organic phase was dried with anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure to yield solids for all TIQ guanidine organocatalysts.

(*S*)-Benzyl 3-(2,6–2,6-Diisopropylphenylamine carbamoyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (6): The crude product was purified by column chromatography (EtOAc/hexane, 30:70; R_f = 0.40) to afford the product (51%) as a yellow solid. M.p. 60–62 °C. $[\alpha]_D^{20}$ = –11.32 (c = 0.53, $CHCl_3$). NMR spectra are reported for a mixture of two rotamers due to the Cbz group.[12,23] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52–6.93 (m, 12 H), 5.58–5.00 (m, 3 H), 4.93–4.52 (m, 2 H), 3.53 (m, 1 H), 3.12 (m, 1 H), 1.22 (m, 2 H), 0.88 (m, 12 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.6, 146.1, 132.6, 128.7, 128.4, 127.9, 123.2, 68.2, 56.6, 45.9, 32.2, 28.2, 23.6 ppm. IR (ATR): $\tilde{\nu}$ = 3280, 1643, 1547, 1453, 1222, 1029, 963, 755, 694 cm^{-1}. HRMS: calcd. for $C_{30}H_{35}N_2O_3$ $[M + H]^+$ 471.2642; found 471.2639.

(1*S*,3*S*)-Benzyl 3-(2,6–2,6-Diisopropylphenylamine carbamoyl)-6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2-(1*H*)-carboxylate (8a): The crude product was purified by column chromatography (EtOAc/hexane, 50:50; R_f = 0.55) to afford the product (55%) as a yellow oil. $[\alpha]_D^{20}$ = –5.26 (c = 0.19, $CHCl_3$). NMR spectra are reported for a mixture of two rotamers. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–6.69 (m, 16), 6.63 (s, 1 H), 6.30–6.11 (s, 0.5 H), 5.49 (m, 0.5 H), 5.26–4.85 (m, 2.3 H), 4.52–4.28 (m, 0.5 H), 3.92–3.68 (m, 8 H), 3.32–2.75 (m, 2 H), 1.35–1.01 (m, 12 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.36, 156.13, 148.98, 148.90, 146.40, 141.01, 135.71, 129.46, 128.72, 128.65, 128.58, 127.85, 127.82, 126.95, 125.71, 125.37, 125.21, 123.45, 123.34, 123.26, 110.87,110.01, 110.46, 68.35, 68.02, 60.11, 59.55, 58.45, 57.88, 56.15, 56.09, 55.77, 53.65, 31.00, 27.99, 23.93, 23.58, 22.95 ppm. IR (ATR): $\tilde{\nu}$ = 3298, 2962, 1688, 1513, 1224, 698 cm^{-1}. HRMS: calcd. for $C_{24}H_{25}N_2O$ $[M + H]^+$ 607.3166; found 607.3215.

(1*R*,3*S*)-Benzyl 3-(2,6–2,6-Diisopropylphenylamine carbamoyl)-6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2-(1*H*)-carboxylate (8b): The crude product was purified by column chromatography (EtOAc/hexane, 50:50; R_f = 0.55) to afford the product (58%) as a yellow oil. $[\alpha]_D^{20}$ = +5.26 (c = 0.19, $CHCl_3$). NMR spectra are reported for a mixture of two rotamers. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–6.69 (m, 16), 6.63 (s, 1 H), 6.30–6.11 (s, 0.5 H), 5.49 (m, 0.5 H), 5.26–4.85 (m, 2.3 H), 4.52–4.28 (m, 0.5 H), 3.92–3.68 (m, 8 H), 3.32–2.75 (m, 2 H), 1.35–1.01 (m, 12 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.36, 156.13, 148.98, 148.90, 146.40, 141.01, 135.71, 129.46, 128.72, 128.65, 128.58, 127.85, 127.82, 126.95, 125.71, 125.37, 125.21, 123.45, 123.34, 123.26, 110.87,110.01, 110.46, 68.35, 68.02, 60.11, 59.55, 58.45, 57.88, 56.15, 56.09, 55.77, 53.65, 31.00, 27.99, 23.93, 23.58, 22.95 ppm.

(*S*,*E*)-2-(*N*,*N*′-Dicyclohexylcarbamimidoyl)-*N*-(2,6–2,6-diisopropylphenylamine)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (1): The crude product was purified by column chromatography (EtOAc/hexane, 50:50; R_f = 0.20) to afford the product (95%) as a white solid. M.p. 82–83 °C. $[\alpha]_D^{20}$ = –70.71 (c = 0.66, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.53 (s, 1 H), 7.32–6.72 (m, 8 H), 4.98 (s, 1 H), 4.43 (q, J = 16.5 Hz, 2 H), 3.42 (t, J = 13.3 Hz, 1 H), 2.88 (m, 5 H), 1.92–1.32 (m, 12 H), 1.32–0.55 (m, 20 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.25, 158.55, 145.84, 131.69, 131.31, 130.08, 128.48, 128.36, 127.98, 127.48, 126.04, 123.37, 122.01, 118.83, 77.36, 77.04, 76.72, 57.54, 55.56, 48.89, 33.52, 33.20, 32.43, 29.70, 28.75, 28.49, 25.08, 24.81, 23.62 ppm. IR (ATR): $\tilde{\nu}$ = 2926, 2853, 1613, 799 cm^{-1}. HRMS: calcd. for $C_{35}H_{51}N_4O$ $[M + H]^+$ 543.4059; found 543.4057.

CCDC-860511 (for **1**) 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.

(*S*,*E*)-2-(*N*,*N*′-Dicyclohexylcarbamimidoyl)-*N*-(2,6–2,6-diisopropylphenylamine)-1,2,3,4-tetrahydroisoquinoline-3-carbothioamide (2): To a solution of the triflate salt (white foam) of compound **1** (0.1 g, 0.3 mmol) dissolved in dry toluene (20 mL) was added Lawesson's

reagent (0.5 equiv., 0.06 g) under a nitrogen atmosphere. The mixture was heated gently at reflux under an atmosphere of nitrogen for 12 h. Thereafter, the solvent was evaporated under reduced pressure to yield a residue that was purified by silica gel column chromatography (EtOAc/hexane, 50:50; R_f = 0.15) to afford the product (92%) as a yellow solid. M.p. 100–102 °C. $[\alpha]_D^{20}$ = –100.00 (c = 0.20, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–6.67 (m, 8 H), 5.15 (s, 1 H), 4.37 (s, 2 H), 4.00 (d, J = 16.2 Hz, 1 H), 3.18–2.67 (m, 6 H), 2.32–1.95 (m, 4 H), 1.61 (t, J = 42.6 Hz, 10 H), 1.36–0.84 (m, 18 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.91, 132.77, 128.96, 127.25, 126.92, 125.36, 125.14, 123.40, 123.12, 77.33, 59.73, 54.73, 46.85, 35.35, 34.17, 31.93, 30.93, 28.73, 28.52, 25.42, 25.06, 24.88, 24.43, 24.34, 23.57, 23.13 ppm. IR (ATR): $\tilde{\nu}$ = 3302, 2924, 1651, 1651, 1494, 743, 698 cm^{-1}. HRMS: calcd. for $C_{35}H_{51}N_4S$ $[M + H]^+$ 559.3829; found 559.3840.

(1*S*,3*S*)-2-[(*E*)-*N*,*N*′-Dicyclohexylcarbamimidoyl]-*N*-(2,6–2,6-diisopropylphenylamine)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (3): The crude product was purified by column chromatography (EtOAc/hexane, 50:50; R_f = 0.20) to afford the product (90%) as a white solid. M.p. 100–103 °C. $[\alpha]_D^{20}$ = –44.09 (c = 0.93, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.92 (s, 1 H), 7.29–6.88 (m, 9 H), 6.60 (s, 1 H), 6.33 (s, 1 H), 6.16 (s, 1 H), 4.58 (s, 1 H), 3.85–3.46 (m, 7 H), 3.34 (d, J = 10.0 Hz, 2 H), 3.13 (s, 1 H), 2.80 (d, J = 32.8 Hz, 2 H), 1.70–0.86 (m, 16 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.08, 153.99, 147.87, 147.54, 146.29, 146.13, 145.70, 131.45, 129.59, 129.17, 127.81, 127.69, 126.66, 124.67, 123.12, 111.56, 110.76, 59.94, 58.93, 55.79, 55.68, 53.36, 49.10, 36.34, 34.50, 34.05, 33.96, 32.48, 28.67, 28.09, 25.98, 25.74, 25.63, 25.38, 24.95, 24.78, 24.07, 23.35, 22.74 ppm. IR (ATR): $\tilde{\nu}$ = 3349, 2926, 2852, 1629, 1254, 699 cm^{-1}. HRMS: calcd. for $C_{43}H_{59}N_4O_3$ $[M + H]^+$ 679.4582; found 679.4564.

(1*R*,3*S*)-2-[(*E*)-*N*,*N*′-Dicyclohexylcarbamimidoyl]-*N*-(2,6–2,6-diisopropylphenylamine)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (4): The crude product was purified by column chromatography (EtOAc/hexane, 50:50; R_f = 0.20) to afford the product (95%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.93 (s, 1 H), 7.34–6.82 (m, 9 H), 6.60 (s, 1 H), 6.33 (s, 1 H), 6.18 (s, 1 H), 4.59 (s, 1 H), 3.87–3.43 (m, 7 H), 3.29 (d, J = 63.6 Hz, 2 H), 3.13 (s, 1 H), 2.80 (d, J = 20.6 Hz, 2 H), 1.59–0.86 (m, 17 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.01, 154.06, 147.90, 147.59, 146.30, 146.12, 145.65, 131.44, 129.53, 129.12, 128.23, 127.82, 127.75, 126.72, 124.62, 124.47, 123.98, 123.45, 123.13, 119.09, 111.55, 110.75, 59.99, 58.98, 55.80, 55.71, 53.39, 36.29, 34.47, 34.02, 32.50, 31.93, 31.44, 30.20, 28.66, 28.10, 25.95, 25.70, 25.36, 24.96, 24.75, 24.03, 23.40 ppm.

General Procedure for Michael Addition Reactions: To a 10-mL microwave vial was added the catalyst (0.02 mmol) followed by toluene(1.0 mL) and the nitro-olefin (0.20 mmol); thereafter, the malonate (0.20 mmol) was added. The reaction was kept at the specified temperature while stirring for 12 h (or some cases 20 h). Toluene was directly evaporated under vacuum, and the resulting residue was purified by silica gel chromatography (Et_2O/hexane, 40:60) and analyzed as described below. NMR spectroscopic data and retention times for all chiral products were in agreement to the racemic samples or previously reported literature data. Chiral products are listed in the order of presentation in Tables 2–5.

(*S*)-Dimethyl 2-(2-Nitro-1-phenylethyl)malonate:[22] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.38 (m, 5 H),4.92 (dd, J = 13.0, 5.7 Hz, 1 H), 4.89 (dd, J = 13.0, 8.6 Hz, 1 H), 4.25 (td, J = 8.6, 5.7 Hz, 1 H), 3.87 (d, J = 8.6 Hz, 1 H), 3.77 (s, 3 H), 3.56 (s, 3 H) ppm. HPLC (Chiralpak IA, hexane/2-propanol = 90:10, flow rate = 0.9 mL/min, λ = 210 nm): t_R = 15.2 (major), 20.0 (minor) min.

(*S*)-Diethyl 2-(2-Nitro-1-phenylethyl)malonate:[12,23] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.36 (m, 5 H), 4.95 (dd, J = 13.1, 5.3 Hz, 1 H), 4.87 (dd, J = 13.1, 8.1 Hz, 2 H), 4.17–4.34 (m, 3 H), 4.01 (q, J = 7.2 Hz, 2 H), 3.83 (d, J = 9.5 Hz, 1 H), 1.27 (t, J = 1.2 1.05 Hz, 3 H), (t, J = 72 Hz, 3 H) ppm. HPLC (Chiralpak IA, hexane/2-propanol = 90:10, flow rate = 0.9 mL/min, λ = 210 nm): t_R = 12.8 (major), 16.8 (minor) min.

(*S*)-Diisopropyl 2-(2-Nitro-1-phenylethyl)malonate:[12,23] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.35 (m, 5 H), 5.09 (sept., J = 6.2 Hz, 1 H), 4.93 (dd, J = 12.7, 9.5 Hz, 1 H), 4.84 (dd, J = 12.7, 9.5 Hz, 1 H), 4.82 (sept., J = 6.2 Hz, 1 H), 4.21 (td, J = 9.5, 4.9 Hz, 1 H), 3.76 (d, J = 9.5 Hz, 1 H), 1.24 (d, J = 6.2 Hz, 6 H), 1.07 (d, J = 6.2 Hz, 3 H), 1.02 (d, J = 6.2 Hz, 3 H) ppm. HPLC (Chiralpak IA, hexane/2-propanol = 90:10, flow rate = 0.9 mL/min, λ = 210 nm): t_R = 11.4 (major), 24.0 (minor) min.

Ethyl 1-(2-Nitro-1-phenylethyl)-2-oxocyclopentanecarboxylate: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.32 (m, 5 H), 4.75–4.87 (m, 2 H), 4.11–4.20 (m,3 H), 4.02 (q, J = 6.8 Hz, 1 H), 3.83 (d, J = 9.6 Hz, 1 H), 1.25 (t, J = 7.2 Hz, 3 H), 1.05 (t, J = 7.2 Hz,3 H) ppm. HPLC (Chiralpak IB, hexane/2-propanol = 95:5, flow rate = 0.9 mL/min, λ = 210 nm): t_R = 11.9 (*syn*, major), 24.5 (minor) min.

***tert*-Butyl 1-(2-Nitro-1-phenylethyl)-2-oxocyclopentanecarboxylate:**[12,23] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.24 (m, 5 H), 5.16 (dd, J = 13.44, 3.76 Hz, 1 H), 4.98 (dd, J = 13.28, 11.16 Hz, 1 H), 4.04 (dd, J = 11.12, 3.72 Hz, 1 H), 2.38–2.25 (m, 2 H), 2.02–1.74 (m, 4 H), 1.44 (s, 9 H) ppm. HPLC (Chiralpak IA, hexane/2-propanol = 99:1, flow rate = 0.9 mL/min, λ = 210 nm): t_R = 12.8 (*syn*, major), 15.1 (minor) min.

Diisopropyl 2-(2-Nitro-1-*p*-tolylethyl)malonate: $[\alpha]_D^{20}$ = +863 (c = 0.10, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (s, 1 H), 7.01 (m, 3 H), 5.01 (q, J = 6.64, 12.61 Hz, 1 H), 4.80 (m, 3 H), 4.09 (m, 1 H), 3.66 (d, J = 8.77 Hz, 1 H), 2.10 (s, 3 H), 1.17 (m, 6 H), 0.98 (m, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.1, 133.2, 129.5, 127.9, 78.10, 69.8, 69.4, 55.3, 42.5, 21.6, 21.4, 21.3, 21.2 ppm. IR (ATR): $\tilde{\nu}$ = 2983, 1727, 1553, 1100 cm^{-1}. HRMS: calcd. for $C_{18}H_{25}NO_6$ $[M + Na]^+$ 374.1580; found 374.1677. HPLC (Chiralpak IA, hexane/2-propanol = 90:10, flow rate = 0.9 mL/min, λ = 210 nm): t_R = 24.9 (major), 23.5 (minor) min.

Diisopropyl 2-[2-Nitro-1-(4-nitrophenyl)ethyl]malonate: $[\alpha]_D^{20}$ = +11.6 (c = 0.17, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.75 (d, J = 8.75 Hz, 2 H), 7.48 (d, J = 8.75 Hz, 2 H), 5.10 (q, J = 6.06, 12.12 Hz, 1 H), 4.92 (m, 3 H), 4.35 (m, 1 H), 3.78 (d, J = 9.3 Hz, 1 H), 1.26 (m, 6 H), 1.10 (m, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.0, 143.9, 137.4, 129.5, 124.2, 70.4, 70.2, 54.6, 42.5, 21.5, 21.4, 21.36, 21.33 ppm. IR (ATR): $\tilde{\nu}$ = 2975, 1718, 1522, 1139 cm^{-1}. HRMS: calcd. for $C_{17}H_{22}N_2O_8$ $[M + Na]^+$ 405.1274; found 4051352. HPLC (Chiralpak IA, hexane/2-propanol = 90:10, flow rate = 0.9 mL/min, λ = 210 nm): t_R = 18.6 (major), 17.4 (minor) min.

Diisopropyl 2-[1-(4-Methoxyphenyl)-2-nitroethyl]malonate: $[\alpha]_D^{20}$ = +580 (c = 0.1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08 (d, J = 8.36 Hz, 2 H), 6.75 (d, J = 8.36 Hz, 2 H), 5.10 (q, J = 7.76, 13.5 Hz, 1 H), 4.77 (m, 3 H), 4.08 (m, 1 H), 3.69 (s, 3 H), 3.65 (d, J = 9.52 Hz, 1 H), 1.16 (m, 6 H), 0.99 (m, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.5, 142.1, 136.6, 129.3, 114.26, 78.2, 69.8, 69.5, 55.3, 55.2, 21.6, 21.4, 21.34, 21.32 ppm. IR (ATR): $\tilde{\nu}$ = 2984, 1718, 1555, 1099 cm^{-1}. HRMS: calcd. for $C_{18}H_{25}NO_7$ $[M + Na]^+$ 390.1529; found 390.1533. HPLC (Chiralpak IA, hexane/2-

propanol = 90:10, flow rate = 0.9 mL/min, λ = 210 nm): t_R = 11.1 (major), 9.7 (minor) min.

***tert*-Butyl 1-(2-Nitro-1-*p*-tolylethyl)-2-oxocyclopentanecarboxylate:**[12,23] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.16 (m, 2 H), 7.12–7.10 (m, 2 H), 5.16 (dd, *J* = 13.28, 3.76 Hz, 1 H), 4.97 (dd, *J* = 13.32, 11.20 Hz, 1 H), 4.03 (dd, *J* = 11.16, 3.76 Hz, 1 H), 2.32 (s, 3 H), 2.38–2.29 (m, 3 H), 2.02–1.77 (m, 4 H), 1.47 (s, 9 H) ppm. HPLC (Chiralpak IB, hexane/2-propanol = 98:2, flow rate = 1.0 mL/min, λ = 210 nm): t_R = 12.0 (*syn*, major), 16.9 (minor) min.

***tert*-Butyl 1-[2-Nitro-1-(4-nitrophenyl)ethyl]-2-oxocyclopentanecarboxylate:**[12,23] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19–8.17 (m, 2 H), 7.59–7.55 (m, 2 H), 5.23 (dd, *J* = 13.84, 3.56 Hz, 1 H), 5.02 (dd, *J* = 13.84, 11.20 Hz, 1 H), 4.09 (dd, *J* = 11.20, 3.56 Hz, 1 H), 2.49–2.40 (m, 1 H), 2.34–2.25 (m, 1 H), 2.14–1.84 (m, 4 H), 1.44 (s, 9 H) ppm. HPLC (Chiralpak IB, hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 22.9(*syn*, major), 49.5 (minor) min.

***tert*-Butyl 1-[1-(4-Methoxyphenyl)-2-nitroethyl]-2-oxocyclopentanecarboxylate:**[12,23] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.21 (m, 2 H), 6.86–6.82 (m, 2 H), 5.14 (dd, *J* = 13.20, 3.80 Hz, 1 H), 4.95 (dd, *J* = 13.20, 11.28 Hz, 1 H), 3.93 (dd, *J* = 13.20, 3.80 Hz, 1 H), 3.79 (s, 3 H), 2.39–2.29 (m, 2 H), 2.02–1.77 (m, 4 H), 1.47 (s, 9 H) ppm. HPLC (Chiralpak IB, hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, λ = 210 nm): t_R = 9.2 (*syn*, major), 10.1 (minor) min.

Supporting Information (see footnote on the first page of this article): NMR and high-resolution mass spectra of novel compounds, and crystallographic details.

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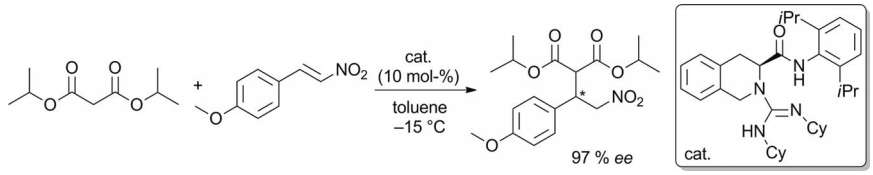
Organocatalysis



The synthesis of chiral guanidine organocatalysts based on a tetrahydroisoquinoline framework and their evaluation in asymmetric Michael additions of malonates and β-keto esters with nitro-olefins is reported. A microwave-assisted procedure for introducing the guanidine unit onto amino amide derivatives is also reported. The chiral products were obtained in up to 99% yield with up to 97%*ee*.

Keywords: Organocatalysis / Michael addition / Microwave chemistry

