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Properties and Reactivity of Conformationally Constrained Bicyclic Diarylprolinol Silyl Ethers as Organocatalysts

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Dedicated to C.I.N.M.P.I.S. on the occasion of its 20th anniversary

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Bicyclic silyl ether derivatives **1**, which are derived from simple chemical manipulations of *trans*-4-L-hydroxyproline, were recently proposed, by us, as conformationally constrained analogues of Jørgensen–Hayashi's catalysts **2**. Despite the structural similarities, **1** displays remarkable performance in iminium chemistry with respect to **2**, but much lower reactivity in enamine chemistry. The peculiar structural features of **1** confer a pattern of reactivity between Jørgensen–Hayashi's catalysts and MacMillan's imidazolidinones.

Introduction

Silylated diarylprolinols (Jørgensen–Hayashi's catalysts),[1] together with proline[2] and MacMillan's imidazolidinones,[3] are the workhorses of enantioselective covalent organocatalysis. They are used in asymmetric versions of most classical organic reactions, such as aldol,[4] Mannich,[5] Michael[6] and many others.[7] In addition, several combinations of some of these reactions in domino processes have been reported for the enantioselective one-pot construction of several stereogenic centers starting from prochiral reagents.[8] However, a few drawbacks affect organocatalytic reactions, such as long reaction times, high catalyst loading and the need to carefully optimize reaction conditions for each specific application.

In the search for organocatalysts that perform better, we recently proposed the introduction of ionic groups covalently installed on the pyrrolidine framework as a strategy to implement calalytic activity. Remarkable improvements were observed in the asymmetric aldol addition by using an ion-tagged proline[9a–9c] and in the Michael addition of aldehydes to nitroalkenes by employing an ion-tagged modified Jørgensen–Hayashi's catalyst.[9d]

By following a different approach to modify the diarylprolinol framework, we recently reported a new family of conformationally constrained bicyclic catalysts (**1**), which are easily prepared in a few synthetic steps from commercially available *N*-Cbz-*trans*-4-L-hydroxyproline.[10] In particular, catalysts **1a** and **1b** (Figure 1) displayed the best overall performances when tested in a few benchmark organocatalyzed asymmetric transformations relative to some Jørgensen–Hayashi's diarylprolinol silyl ethers (**2a–2c**, Figure 1), which are among the best organocatalysts proposed for iminium/enamine activation mode.[11]

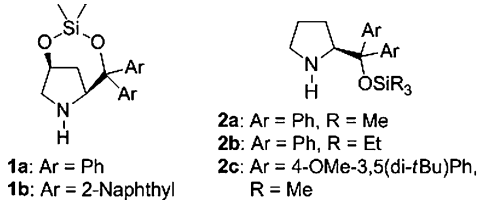

Figure 1. Structures of secondary amine organocatalysts **1** and **2**.

By using **1** we successfully carried out the cyclopropanation reaction of α,β-unsaturated aldehydes with α-bromomalonates,[12] the conjugate Michael addition of nitromethane to (*E*)-cinnamaldehyde,[13] and the Diels–Alder reaction of α,β,γ,δ-unsaturated aldehydes.[14] The activity and selectivity of **1** in the aforementioned reactions were always comparable to, if not superior than, **2**.[10]

The presence of a 2,4-dioxa-3-sila-7-azabicyclo[4.2.1]-nonane scaffold confers to **1** a superior stability towards hydrolytic conditions. Catalysts **1** are indeed bench-stable solids, making their storage and handling extremely practical and convenient. The higher stability towards desilylation, an undesired reaction that compromises catalyst performance,[15] makes their use particularly attractive when acids are needed as co-catalysts and/or when pro-

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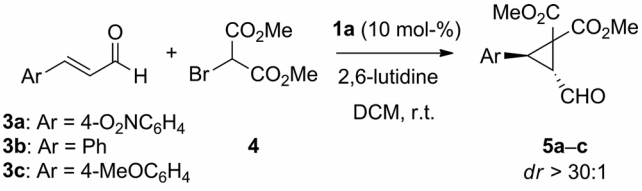
longed reaction times are necessary to achieve good conversions. Herein we wish to report a more detailed study on the organocatalytic activity and on the structural peculiarities of catalyst **1a**.

Results and Discussion

Among previously tested reactions, the cyclopropanation of (*E*)-4-nitrocinnamaldehyde (**3a**) with dimethyl α-bromomalonate (**4**) afforded the best results with catalysts **1a** or **1b**, and gave better yields and slightly enhanced enantioselectivities relative to Jørgensen–Hayashi's catalyst **2a**. We decided to examine this reaction in more detail not only by using **1a** in lower catalytic amounts, but also by employing (*E*)-cinnamaldehyde **3b** and electron-rich (*E*)-4-methoxycinnamaldehyde **3c** (Table 1).

Table 1. Organocatalytic cyclopropanation reaction of α,β-unsaturated aldehydes **3a**–**3c** with dimethyl α-bromomalonate **4** with catalyst **1a** at 10 mol-%.



3a: Ar = 4-$O_2NC_6H_4$
3b: Ar = Ph
3c: Ar = 4-$MeOC_6H_4$

4

5a–c
dr > 30:1

Entry[a]	**3**	*t* [h]	Conv. [%] [b]	Y [%][c]	*ee* [%][d]
1	**3a**	0.5	65	92	94
2		1	77		
3		2	88		
4		4	99		
5	**3b**	1	68	84	96
6		2	80		
7		4	90		
8	**3c**	2	71	80	95
9		4	86		

[a] Reactions run with **3** (0.12 mmol), **4** (1.1 equiv.), **1a** (10 mol-%) and 2,6-lutidine (1.2 equiv.) in dichloromethane (0.5 mL) at room temp. [b] Conversion calculated with respect to the starting aldehyde was checked by ^{1}H NMR spectroscopy (400 MHz) by taking samples (20 μL) at different time intervals and diluting them in $CDCl_3$ (0.5 mL) in a standard 5 mm NMR tube. [c] Isolated yields after purification by flash chromatography on silica. [d] Determined by chiral HPLC on purified products.

In all cases examined, under the same experimental conditions and catalyst loading, **1a** gave comparable yields with respect to catalyst **2a**, but in a shorter reaction time.

Wang and co-workers reported that by using **2a**, **5a** was obtained in 92% yield (94% *ee*) after 5.5 h (relative to Table 1, Entries 1–4,), **5b** in 88% yield (96% *ee*) after 21 h (Table 1, Entries 5–7), and **5c** in 85% yield (94% *ee*) after 24 h (Table 1, Entries 8–9).[12a] In terms of enantiocontrol, **1a** and **2a** provided the same results. The higher activity of catalyst **1a** prompted us to explore the reaction with more reactive aldehyde **3a** at lower catalytic loadings. The results obtained are reported in Table 2.

Table 2. Organocatalytic cyclopropanation reaction of (*E*)-4-nitrocinnamaldehyde **3a** with dimethyl α-bromomalonate **4** with catalyst **1a** in different catalytic amounts.

Entry[a]	**1a** [mol-%]	*t* [h]	Conv.[b]	*ee* [%][c]
1	5	12	99	94
2	1	21	90	95
3	0.1	24	20	94

[a] Reactions run with **3a** (0.12 mmol), **4** (1.1 equiv.), reported amounts of **1a** and 2,6-lutidine (1.2 equiv.) in dichloromethane (0.5 mL) at room temp. [b] Conversion calculated with respect to the starting aldehyde was checked by ^{1}H NMR spectroscopy (400 MHz) by taking samples (20 μL) at different time intervals and diluting them in $CDCl_3$ (0.5 mL) in a standard 5 mm NMR tube. [c] Determined by chiral HPLC on crude products.

The reaction conversion was virtually complete after 12 h by employing **1a** at 5 mol-% (Table 2, Entry 1), whereas 90% conversion was obtained after 21 h when lowering the catalyst loading to 1 mol-% (Table 2, Entry 2). A very interesting result was obtained when the reaction was tested by using **1a** at 0.1 mol-%, a catalytic loading seldom used in asymmetric organocatalyzed transformations,[16] providing an appreciable 20% conversion after 24 h and retaining the same high level of stereocontrol (Table 2, Entry 3).

One of the most frequent criticisms regarding organocatalytic protocols is that a relatively large amount of catalyst is typically required to obtain the desired product at a useful reaction rate. To better elucidate the potential of catalyst **1a**, we decided to explore its activity relative to **2a** in the cyclopropanation reaction of **3a** at 0.1 mol-% catalytic loading, and followed the conversion at different time intervals. The results obtained are reported in Table 3 and plotted in Figure 2.

Table 3. Organocatalytic cyclopropanation reaction of (*E*)-4-nitrocinnamaldehyde **3a** with dimethyl α-bromomalonate with catalyst **1a** or catalyst **2a** at 0.1 mol-%.

Entry[a]	*t* [d]	Conv. [%] (**1a**)[b]	Conv. [%] (**2a**)[b]
1	1	21	11
2	2	45	19
3	3	56	24
4	4	62	30
5	5	66	34
6	6	71	39
7	7	73	42
8	8	76	44
9	10	80	47
10	11	81	47

[a] Reactions run with **3a** (0.1 mmol), **4** (1.1 equiv.), catalyst (0.1 mol-%) and 2,6-lutidine (1.2 equiv.) in dichloromethane (0.4 mL) at room temp. [b] Conversion calculated with respect to the starting aldehyde was checked by ^{1}H NMR spectroscopy (400 MHz) by taking samples (20 μL) at different time intervals and diluting them in $CDCl_3$ (0.5 mL) in a standard 5 mm NMR tube.

Catalyst **1a** was significantly more active than **2a**, and reached 56% conversion after 3 d and a notable 76% conversion after 8 d. A value of 94% *ee* was obtained by analyzing the crude reaction mixture after 11 d, without any significant difference from the results obtained employing

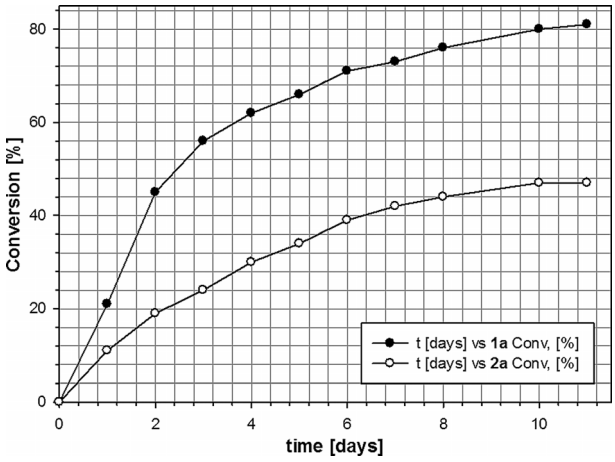
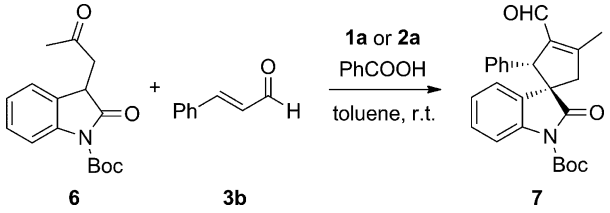


Figure 2. Activities of **1a** and **2a** in the cyclopropanation reaction of (*E*)-4-nitrocinnamaldehyde **3a** with dimethyl α-bromomalonate **4** in dichloromethane at room temp., with 0.1 mol-% catalyst loading.

1a at higher catalytic loadings. The same level of enantiocontrol was displayed by **2a**, but Jørgensen–Hayashi's catalyst afforded lower conversions in the same reaction time.

This difference was particularly noticeable in the earlier stages of the cyclopropanation reaction, in which conversions with **1a** were always more than twofold those obtained with **2a**.

To expand the study on the activity of **1a** in organocatalytic transformations, we decided to test it in a different enantioselective iminium/enamine cascade reaction. The reaction chosen was between 3-substituted oxindoles and α,β-unsaturated aldehydes catalyzed by **2a** in the presence of an equimolar amount of benzoic acid as co-catalyst, which was recently reported by Barbas III and co-workers.[17] In particular we chose to examine the reaction of *N*-Boc-3-(2-oxopropyl)-oxindole **6**[18] with **3b** (Scheme 1), a reaction that affords complex spiro-cyclopenteneoxindole **7** in 95% *ee* and 9:1 *dr* after 24 h at 37 °C with catalyst **2a** at 10 mol-%.



Scheme 1. Organocatalytic iminium/enamine cascade reaction of *N*-Boc-3-(2-oxopropyl)oxindole **6** with (*E*)-cinnamaldehyde **3b**.

We initially performed the reaction under similar conditions reported by Barbas III, but at a temperature of 20 °C instead of 37 °C. In this case we observed that both catalyst **1a** and **2a** at 10 mol-% quantitatively afforded desired product **7** after 24 h, with 94% *ee*. A better diastereomeric ratio (*dr* > 95:5) was observed by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures obtained at room temp.

Encouraged by these results we lowered the catalyst loading to 5 mol-%, and again we observed complete consumption of limiting oxindole **6** after 24 h. Under these conditions, besides the signals of **7**, we identified in the ^{1}H NMR spectrum of samples (taken from the reaction mixture and diluted in $CDCl_3$ without any work-up) some new signals, probably a result of aldol intermediate **8** (Figure 3). The relative *trans* configuration between the C2–C3 substituents was tentatively assigned by analysis of the ^{1}H NMR spectroscopic coupling constant (*J* H2-H3 = 13.6 Hz), but we did not define the relative C3–C4 stereochemistry.

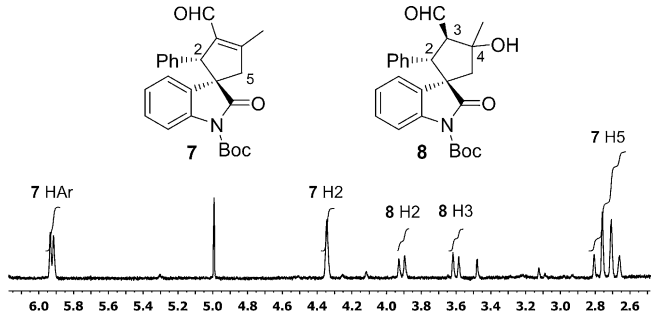


Figure 3. Structures of intermediate **8** and product **7** and the ^{1}H NMR spectrum (400 MHz) inset relative to the reaction between **6** and **3b** catalyzed by **2a** at 5 mol-% in toluene at room temp. in the presence of benzoic acid (5 mol-%), after 24 h.

Although practically the same rate of conversion relative to **6** was achieved after 24 h, catalyst **1a** and **2a** behave differently with respect to the relative ratios between **7** and **8** at different time intervals. By using **2a** the **7**/**8** ratio was 67:33 after 24 h, 80:20 after 48 h, 85:15 after 4 d and finally 95:5 after 7 d. However, by using catalyst **1a** the **7**/**8** ratio was 20:80 after 24 h, 25:75 after 48 h, 37:63 after 4 d and only 45:55 after 7 d (Figure 4). It should be noted we were not able to isolate intermediate **8** because, after reaction work-up and/or purification by flash chromatography on silica, only dehydrated product **7** was quantitatively recovered from the reaction mixture.

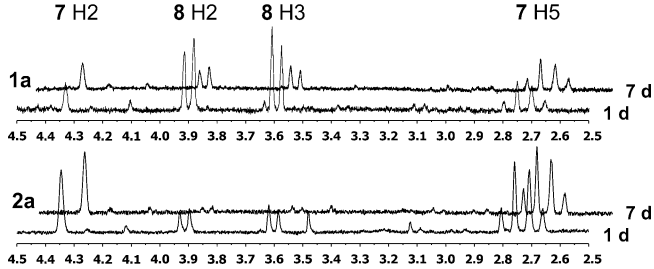


Figure 4. ^{1}H NMR spectroscopy (400 MHz) insets relative to the reaction between **6** and **3b** catalyzed by **1a** (upper traces) and **2a** (bottom traces) at 5 mol-% in toluene at room temp. in the presence of benzoic acid (5 mol-%), after 1 and 7 d.

When we lowered the catalyst loading to 2.5 mol-% a much slower reaction resulted, with conversions based on starting oxindole **6** of 50% (**7**/**8** = 15:85) for catalyst **1a** and of 44% (**7**/**8** = 57:43) for catalyst **2a** after 24 h. Unfortunately, when we checked the conversions after 48 h, the re-

actions seemed to have stopped, showing again a value of 50% (**7**/**8** = 20:80) for catalyst **1a** and of 46% (**7**/**8** = 59:41) for catalyst **2a**. Further lowering of the catalytic loading gave much slower reactions and with very low conversions even after prolonged reaction times. When the reaction was tested with 0.5 mol-% catalytic loading no product formation was detected by ^{1}H NMR spectroscopy for both **1a** and **2a**, even after 7 d.

Catalysts **1a** and **2a** displayed almost the same activity in this iminium/enamine cascade reaction when benzoic acid was used as an equimolar co-catalyst, but they showed markedly different behavior in the dehydration reaction from **8** to **7**. Because the dehydration reaction should be accelerated by acid-catalysis and because the relative amount of benzoic acid was always the same in the two sets of reactions, this different behavior may be ascribed to different basicity of the catalysts employed. Although no general rule can be simply derived to determine the efficacy of an acid additive on the activity of a determined catalyst and/or reaction, Seebach and Hayashi recently studied in detail the effect of acid co-catalysts in the Michael addition of aliphatic aldehydes to nitroalkenes catalyzed by **2a**.[19] They noted that the best results are obtained when acids in the 4–6 pK_a range are used. The acid additive plays many fundamental roles to foster the organocatalytic cycle by increasing reaction rates, but the use of acids that are too strong (pK_a < 3) inhibit the reaction, probably as a result of a lower concentration of the free amine catalyst left in solution.

To verify the role of the acid in the dehydration reaction, we analyzed the reactions catalyzed by **1a** and **2a** at 5 mol-% in the absence of benzoic acid. Starting oxindole **6** was completely consumed after 24 h and in both cases aldol product **8** was the major component of the reaction mixtures. Again different **7**/**8** ratios were found: 30:70 (versus 67:33 with benzoic acid) for **2a** and 7:93 (versus 20:80 with benzoic acid) by using **1a** (Figure 5).

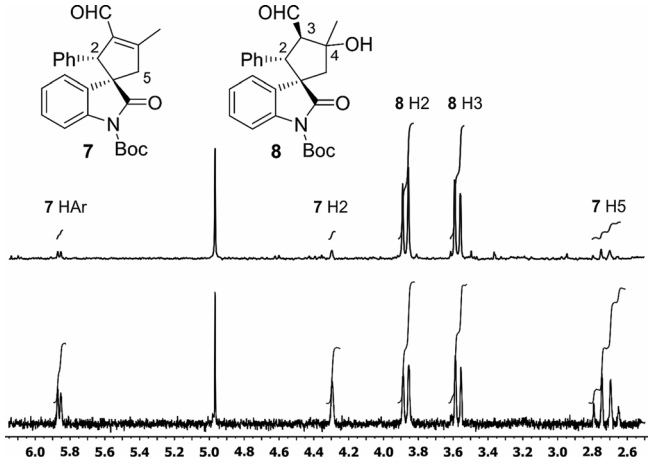


Figure 5. ^{1}H NMR spectra (400 MHz) insets relative to the reaction between **6** and **3b** catalyzed by **1a** (upper trace) and **2a** (bottom trace) at 5 mol-% in toluene at room temp. without benzoic acid, after 24 h.

This different behavior may be explained by considering that the much higher steric encumbrance of amine **1a** decreases its basicity and makes the elimination reaction less efficient, even when catalyzed by weak acids. (Figure 5). Indeed, the apparent conjugate acids pK_a calculated by using ACD/Percepta software resulted 7.9 ± 0.5 for **1a** and 8.5 ± 0.4 for **2a**.[20]

We next expanded the study on the catalytic activity of **1a** to the enantioselective Michael addition of aliphatic aldehydes to nitroalkenes, a classic workbench reaction commonly employed to test the performance of new organocatalysts in enamine chemistry.[21]

We recently employed, for the same reaction, an ion-tagged modified Jørgensen–Hayashi's catalyst[9d] and, following the protocols reported, we tested **1a** in dichloromethane or in water as the solvent with and without benzoic acid as co-catalyst. Invariably the product formed with excellent values of enantio- and diastereoselectivity, but surprisingly in all tested conditions only very low yields of the desired product were obtained in short reaction times.

To better understand the reasons for this poor reactivity, we studied the enamine formation with both catalyst **1a** and **2a** by ^{1}H NMR spectroscopy.[22] We choose phenyl-acetaldehyde (**12**) as the electrophilic reaction partner because the corresponding enamine with **2a** has been extensively studied by the groups of Seebach[23] and Mayr.[24] So by simply mixing equimolar amounts of **12** and **1a**, or **2a** (0.030 mmol) in $CDCl_3$ (0.6 mL) in a standard 5-mm NMR tube we were able to confirm that corresponding enamines **13** and **14** were quantitatively formed almost instantaneously (Figure 6).

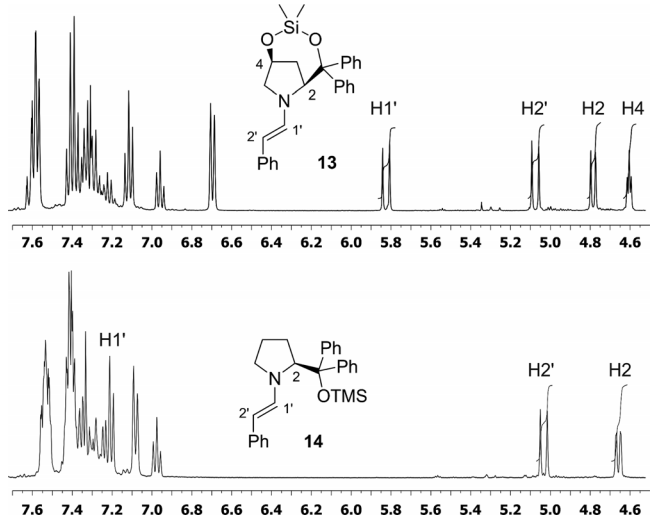


Figure 6. ^{1}H NMR spectra (400 MHz) insets relative to enamines **13** and **14** in $CDCl_3$.

The (*E*)-configuration of the double bond for both enamines was confirmed by inspection of the H1′-H2′ coupling constants (*J* = 14.0 Hz for **13**, and 13.9 Hz for **14**). The preferred *s-trans* conformation of sterically constrained *sc-endo* enamine **13** was supported by a strong anisotropic shielding of the H1′ proton, upfield-shifted to 5.80 ppm, in

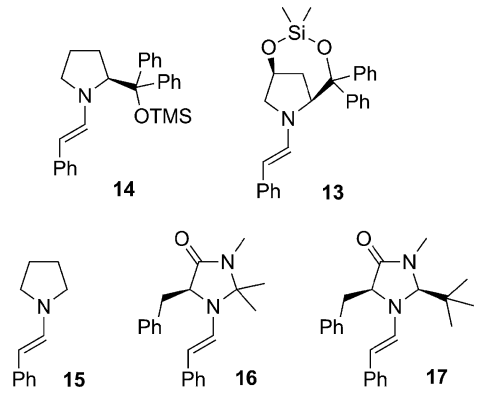
accordance with the studies made by Zeitler and Gschwind on the preferential conformations of **2a**-derived enamines in solution.[22] The ^{1}H NMR spectrum of enamine **14** was in complete agreement with the one reported in the literature for the isolated compound.[23]

Once the quantitative formation of both the enamines in solution was confirmed, we added a stoichiometric amount of β-(*E*)-nitrostyrene **10** to each one and recorded the ^{1}H NMR spectrum again after 24 h. Although enamine **14** and **10** were completely consumed, enamine **13** was left completely untouched.

Mayr recently determined the relative reactivity towards carbocations of several secondary amines derived enamines of phenylacetaldehyde **12**, such as simple pyrrolidine enamine **15** and MacMillan 1st and 2nd generation imidazolidinones derivatives **16** and **17**. The relative reactivity order (**15** > **14** >> **16** > **17**) roughly correlated to the ^{13}C NMR spectroscopic chemical shifts of the C2′ carbon. The more C2′ is downfield-shifted, the lower its electron density and, as a consequence, its nucleophilicity. On this basis, **16** and **17** are up to 100 times less nucleophilic than **14**.

In catalyst **1a** derived enamine **13**, the C2′ carbon resonates at δ = 100.0 ppm, exactly in between enamines **14** and **17** (Δ = –2.9 ppm; Table 4).

Table 4. ^{13}C NMR spectroscopic chemical shifts ($CDCl_3$) of enamines **13**–**17**.



Entry	Enamine	δ(C2′) [ppm]
1	**15**	97.4[a]
2	**14**	97.2[b]
3	**13**	100.0
4	**16**	101.9[a]
5	**17**	102.9[a]

[a] Data taken from ref.[24] [b] Data taken from ref.[23] and confirmed by ^{13}C NMR spectroscopy (100 MHz).

The relative reactivity of enamines can be also related to the sp^n character of the nitrogen atom, because the higher the sp^2 character, the more efficient the *p*-π orbital interaction results thus raising the electron density on C2′. To quantitatively define this interaction, Dunitz introduced the pyramidalization parameter Δ, which is defined as the distance between the nitrogen atom and the plane formed by the three attached carbons.[25] An almost planar sp^2 nitrogen was found in enamine **14** (Δ = 0.037 Å),[23] whereas increasing sp^3 character was determined for less reactive enamine **17** (Δ = 0.293 Å).[24]

To verify the pyramidalization degree of the nitrogen atom in enamine **13**, we calculated the M06–2x/6-311G(d,p) optimized geometries of enamines **13**, **14** and **17**. From the Cartesian coordinates of nitrogen atom and of the three attached carbons, the pyramidalization parameter (Δ) was easily calculated (Figure 7).[26,27]

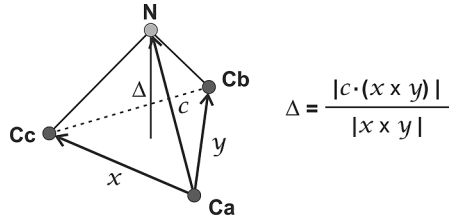


Figure 7. Vector notation and formula used to calculate the altitude Δ of the trigonal pyramid defined by the nitrogen atom (N) and by the three attached carbons (Ca–Cc).

Again an almost planar sp^2 nitrogen was calculated for enamine **14** (Δ = 0.022 Å), in very good accordance with the value derived by Seebach from X-ray crystal structure data.[23] However, increased sp^3 character was determined for enamine **17** (Δ = 0.221 Å), in very good accordance with the values determined from X-ray crystal structure data of MacMillan's catalyst-derived enamines.[24] The calculated Δ value for enamine **13** derived from **1a** (Δ = 0.159 Å) was intermediate between the values of **14** and **17**, in agreement with the trend of the ^{13}C NMR spectroscopic chemical shifts.

The M06-2x/6-311G(d,p) optimized geometries of the most stable conformers of enamines **13**, **14** and **17** are displayed in Figure 8.

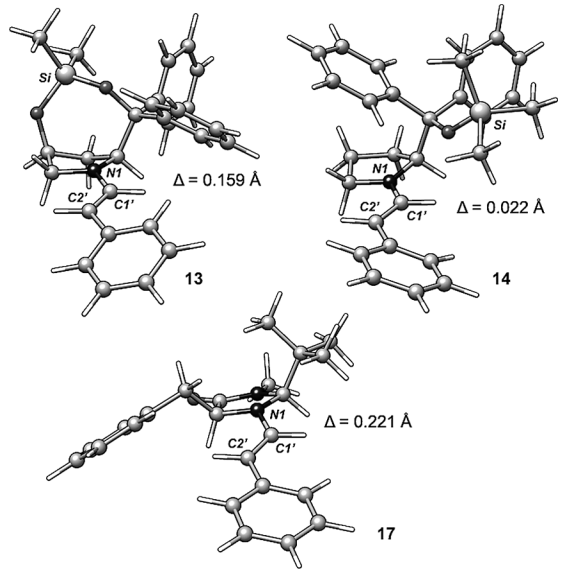
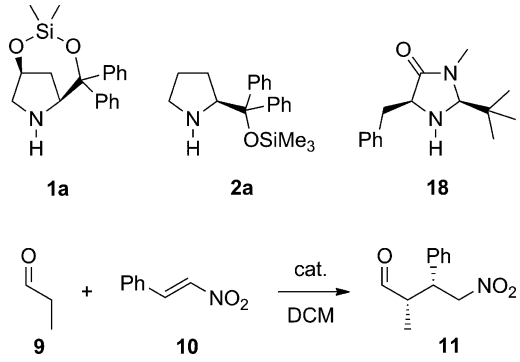


Figure 8. M06-2x/6-311G(d,p) optimized geometries of the most stable conformers of *s-trans*-(*E*)-configured enamines **13**, **14** and **17**.

To confirm this order of reactivity, we studied the addition reaction of propanal (**9**) to nitrostyrene (**10**) in

dichloromethane as the solvent with catalysts **1a**, **2a** and MacMillan's imidazolidinone **18** at 10 mol-%, both with and without an equimolar amount of benzoic acid as the co-catalyst (Scheme 2).



Scheme 2. Organocatalytic Michael addition of propanal **9** to β-(*E*)-nitrostyrene **10** with catalysts **1a**, **2a** and **18**.

Jørgensen–Hayashi's catalyst **2a** was by far the most active one and afforded complete conversion to desired product **11** in less than 1 h both with or without benzoic acid. However, under both conditions tested, MacMillan's imidazolidinone catalysts **18** did not afford any traces of **11**, even after 48 h. As expected, an intermediate reactivity was displayed by catalyst **1a**, which afforded 48% yields of **11** after 48 h, with and without benzoic acid and with the same values of enantioselectivity obtained by using **2a** (*ee* 93% without benzoic acid and *ee* 95% with benzoic acid as the co-catalyst).

Conclusions

Catalyst **1a** was rationally designed with the aim to obtain a more stable analogue under hydrolytic conditions of Jørgensen–Hayashi's catalyst **2a**, with which it shares a strict structural resemblance. From studies that explored its reactivity in classic iminium/enamine activation modes, we noticed remarkably different behavior of the two catalysts, mainly owing to the higher steric encumbrance of **1a**, which results from its conformational rigidity.

A careful study of some recently reported organocatalyzed domino reactions, together with a more detailed structural characterization, allowed us to determine that **1a** is highly efficient in iminium chemistry, but a less powerful enamine catalyst.

Although structurally similar to **2a**, its reactivity seems to be more similar to the first generation MacMillan's imidazolidinone catalyst, able to work efficiently in iminium chemistry, but not completely unreactive when used in enamine activation modes. Investigations to explore the reactivity of **1a** in transformations in which MacMillan's catalysts offer the best performances are underway and will be reported in due course.

Experimental Section

Organocatalytic Cyclopropanation Reaction of (*E*)-4-Nitrocinnamaldehyde 3a with Dimethyl α-Bromomalonate 4: (Table 1, Entry 4 and 5a). **General Procedure:** To a solution of **1a** (3.9 mg, 0.012 mmol, 10%) in CH_2Cl_2 (0.5 mL) was added methyl bromomalonate (0.13 mmol, 0.019 mL, 1.1 equiv.), 2,6-lutidine (0.14 mmol, 0.021 mL, 1.2 equiv.) and finally 4-nitro cinnamaldehyde (0.12 mmol, 21 mg). The reaction was stirred at room temperature for the specified time. Product **5a** was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.59 (d, J = 3.8 Hz, 1 H), 8.19 (d, J = 8.8 Hz, 2 H), 7.44 (d, J = 8.2 Hz, 2 H), 3.88–3.83 (m, 4 H), 3.54 (s, 3 H), 3.47 (dd, J = 7.6, 3.8 Hz, 1 H) ppm. Conversions were determined with ^{1}H NMR spectroscopy by using the doublet at δ = 9.59 ppm of the product and the doublet at δ = 9.79 ppm of the starting aldehyde. The racemic product was synthesized under the same conditions with racemic Jørgensen–Hayashi's catalysts **2a**. The enantiomeric excess was determined by chiral HPLC after derivatization of the product with $Ph_3P{=}CHCO_2Et$. Separation conditions in chiral HPLC: AD 90:10 *n*-Hex/IPA for 15 min then 80:20 in 10 min, 0.5 mL/min, 40 °C, λ = 230 nm; t_r = 32.6 min (major), t_r = 34.7 min (minor).

Organocatalytic Cyclopropanation Reaction of (*E*)-Cinnamaldehyde 3b with Dimethyl α-Bromomalonate 4: (Table 1, Entry and 5b). Following the procedure reported for **5a**, **5b** was isolated by flash chromatography on silica gel (cyclohexane/ethyl acetate, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.53 (d, J = 4.4 Hz, 1 H), 7.88 (t, J = 7.8 Hz, 1 H), 7.35–7.24 (m, 4 H), 3.87–3.84 (m, 4 H), 3.50 (s, 3 H), 3.42 (dd, J = 7.5, 4.4 Hz, 1 H) ppm. Conversions were determined with ^{1}H NMR spectroscopy by using the doublet at δ = 9.53 ppm of the product and the doublet at δ = 9.74 ppm of the starting aldehyde. The racemic product was synthesized under the same conditions with racemic Jørgensen–Hayashi's catalysts **2a**. The enantiomeric excess was determined by chiral HPLC after reduction of the aldehyde to alcohol with $NaBH_4$ in MeOH. Separation conditions in chiral HPLC: IC 70:30 *n*-Hex/IPA, 0.5 mL/min, 40 °C, λ = 230 nm; t_r = 14.4 min (minor), t_r = 20.2 min (major).

Organocatalytic Cyclopropanation Reaction of (*E*)-4-Methoxycinnamaldehyde 3c with Dimethyl α-Bromomalonate 4: (Table 1, Entry 9 and 5c). Following the procedure reported for **5a**, **5c** was isolated by flash chromatography on silica gel (cyclohexane/ethyl acetate, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.48 (d, J = 4.5 Hz, 1 H), 7.16 (d, J = 8.4 Hz, 2 H), 6.84 (d, J = 8.3 Hz, 2 H), 3.85 (s, 3 H), 3.79–3.81 (m, 4 H), 3.51 (s, 3 H), 3.35 (dd, J = 7.5, 4.8 Hz, 1 H) ppm. Conversions were determined with ^{1}H NMR spectroscopy by using the doublet at δ = 9.48 ppm of the product and the doublet at δ = 9.67 ppm of the starting aldehyde. The racemic product was synthesized under the same conditions with racemic Jørgensen–Hayashi's catalysts **2a**. The enantiomeric excess was determined by chiral HPLC after reduction of the aldehyde to alcohol with $NaBH_4$ in MeOH. Separation conditions in chiral HPLC: AD 90:10 *n*-Hex/IPA for 10 min, then 80:20 in 15 min, 0.5 mL/min, 40 °C, λ = 230 nm; t_r = 23.3 min (major), t_r = 26.0 min (minor).

Low-Loading Organocatalytic Cyclopropanation Reaction of (*E*)-4-Nitrocinnamaldehyde 3a with Dimethyl α-Bromomalonate 4: (Table 3). To avoid excessive weighting errors, stocks solutions of reagents were freshly prepared before each run and mixed by using volumetric syringes. Solutions (0.01 M) of each catalyst were prepared by dissolving **1a** or **2a** (3.3 mg) with CH_2Cl_2 in a 1 mL volumetric flask (solutions **A1** and **A2**). A solution of 2,6-lutidine (1 M) was prepared by dissolving the reagent (0.35 mL) with CH_2Cl_2 in a volumetric flask (3 mL; solution **B**). A solution of 2-bromo-dimethylmalonate **4** (1 M) was prepared by dissolving the reagent (0.44 mL) with CH_2Cl_2 in a volumetric flask (3 mL; solution **C**). To **3a** (0.1 mmol, 17.7 mg) in CH_2Cl_2 (0.16 mL) were added solution **C**

(0.11 mL), solution **B** (0.12 mL) and solution **A1** or **A2** (0.01 mL) and the reactions were stirred at room temperature and checked for conversion at the reported time intervals. Conversions were determined with ^{1}H NMR spectroscopy by using the doublet at δ = 9.59 ppm of the product and the doublet at δ = 9.79 ppm of the starting aldehyde.

Organocatalytic Iminium/enamine Cascade Reaction of *N*-Boc-3-(2-oxopropyl)oxindole 6 with (*E*)-Cinnamaldehyde 3b. General Procedure: The catalyst (**1a** or **2a**; 3.3 mg, 0.01 mmol, 10%) and benzoic acid (0.6 mg, 0.01 mmol, 10%) were added to a solution of 3-substituted oxindole **6** (29 mg, 0.1 mmol) and (*E*)-cinnamaldehyde **3b** (0.0126 mL, 0.1 mmol, 1 equiv.) in toluene (0.4 mL, 0.25 M). The reaction was allowed to stir at room temperature and the conversions were determined by ^{1}H NMR spectroscopy. When (*E*)-β-nitrostyrene was completely consumed, the reaction mixture was quenched at 0 °C with HCl (1 M, 2 mL) and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried (Na_2SO_4) and the solvents evaporated under vacuum. The product was purified by flash chromatography on silica by eluting with cyclohexane/ethyl acetate mixtures. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.07 (s, 1 H), 7.73 (d, J = 8.3 Hz, 1 H), 7.12–7.09 (m, 4 H), 6.78–6.76 (m, 2 H), 6.72–6.69 (m, 1 H), 6.20 (d, J = 7.6 Hz, 1 H), 4.60 (s, 1 H), 3.04–2.99 (m, 2 H), 2.42 (s, 3 H), 1.66 (s, 9 H) ppm. The racemic product was synthesized under the same conditions with racemic Jørgensen–Hayashi's catalysts **2a**. The enantiomeric excess was determined by chiral HPLC: IC 80:20 *n*-Hex/IPA, 1.0 mL/min, 40 °C, λ = 214 nm; t_r = 19.8 min (minor), t_r = 39.8 min (major).

Organocatalytic Michael Addition of Propanal 9 to β-(*E*)-Nitrostyrene 10. General Procedure: Propanal (0.0144 mL, 0.2 mmol, 2 equiv.) was added to a solution of catalyst (**1a**, **2a** or **18**, 0.01 mmol, 10%), β-(*E*)-nitrostyrene **10** (14.9 mg, 0.1 mmol) and eventually benzoic acid (0.6 mg, 0.01 mmol, 10%) in CH_2Cl_2 (0.4 mL, 0.25 M). The reaction was allowed to stir at room temperature and the conversions were determined by ^{1}H NMR spectroscopy. When the starting materials were completely consumed, the reaction mixture was quenched with HCl (1 M, 2 mL) and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried (Na_2SO_4) and the solvents evaporated under vacuum. The product was purified by flash chromatography on silica by eluting with cyclohexane/ethyl acetate mixtures. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.72 (d, J = 1.7 Hz, 1 H), 7.37–7.27 (m, 3 H), 7.18–7.13 (m, 2 H), 4.80 (dd, J = 5.5/12.7 Hz, 1 H), 4.68 (dd, J = 9.3/12.7 Hz, 1 H), 3.81 (dt, J = 5.5/9.1 Hz, 1 H), 2.90–2.69 (m, 1 H), 1.00 (d, J = 7.3 Hz, 3 H) ppm. The racemic product was synthesized under the same conditions with racemic Jørgensen–Hayashi's catalysts **2a**. The enantiomeric excess was determined by chiral HPLC: IC 90:10 *n*-Hex/IPA, 1.0 mL/min, 40 °C, λ = 214 nm; t_r = 15.1 min (*anti*, minor), t_r = 22.0 min (*syn*, minor), t_r = 25.6 min (*syn*, major), t_r = 27.4 min (*anti*, major).

Supporting Information (see footnote on the first page of this article): M06-2x/6-311G(d,p)-optimized coordinates of the most stable conformers of *s-trans*-(*E*)-configured enamines **13**, **14** and **17**; copies of ^{1}H and ^{13}C NMR of enamines **13** and **14**; chiral HPLC traces of tested reactions.

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[20] The apparent pK_a values were calculated under standard conditions (25 °C and zero ionic strength) in aqueous solutions for every ionizable group within organic structures by using the ACD/pK_a DB, version 12.00, software (Advanced Chemistry Development Inc., Toronto, Canada, www.acdlabs.com).
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[27] It should be noted that although Dunitz pyramidalization factor is one of the most used crystallographic index for describing the distortion from planarity of a trivalent atom, its value depends on the lengths of the three bonds incident at the central atom and thus can give different values depending the nature of the groups bounded to it. This is not completely correct because, in principle, pyramidalization should be considered simply as the tendency of an atom to deviate from planarity. The nitrogen sp^2 character of enamine **13** relative to enamine **14** and **17** was thus evaluated also by using π-orbital axis vector (POAV) methodology, which considers only the angles formed by δ-orbitals with the central atom π-orbital. a) R. C. Haddon, *J. Am. Chem. Soc.* **1986**, *108*, 2837–2842; b) R. C. Haddon, *Acc. Chem. Res.* **1988**, *21*, 243–249; c) R. C. Haddon, *J. Am. Chem. Soc.* **1990**, *112*, 3385–3389. We determined a pyramidalization angle $\theta_p = 0.93°$ for **14**, which corresponds to an index of hybridization $n = 2.00$ (sp^n), whereas $\theta_p = 5.67°$ with $n = 2.06$ for **13** and $\theta_p = 8.25°$ with $n = 2.13$ for **17**.

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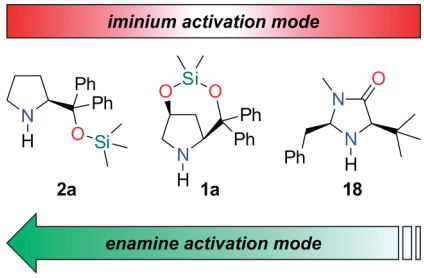
Bicyclic silyl ether derivative **1a**, which is easily prepared from *trans*-4-L-hydroxyproline, is much more stable toward protodesilylation than Jørgensen–Hayashi's catalyst **2a**. Despite their structural analogy, **1a** behaves as a very efficient catalyst in iminium chemistry, but is much less active than **2a** in the enamine activation mode. Here, **1a** exhibits a higher or equivalent level of stereocontrol.



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Properties and Reactivity of Conformationally Constrained Bicyclic Diarylprolinol Silyl Ethers as Organocatalysts

Keywords: Synthetic methods / Organocatalysis / Low-loading catalysis / Nitrogen heterocycles

