DOI: 10.1002/ejoc.200600664

# Benzimidazole-pyrrolidine/$H^+$ (BIP/$H^+$), a Highly Reactive Organocatalyst for Asymmetric Processes

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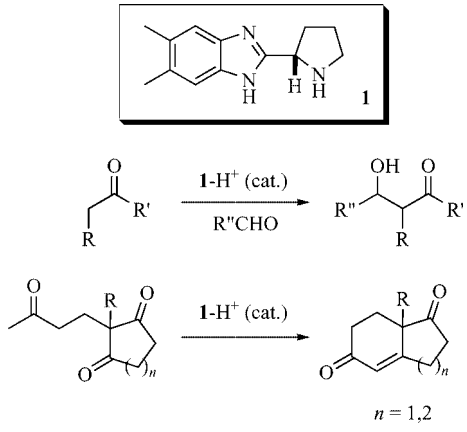
**Keywords:** Organocatalysis / Aldol reactions / Amination / Robinson annelation / Proline / 1-Silacyclohexan-4-one

A new chiral benzimidazole-pyrrolidine has been devised, which exhibits excellent activities in aminocatalyzed aldol reactions, leading to aldol products in high yields and enantioselectivities in the presence of an equimolar amount of a Brönsted acid. This organocatalyst has demonstrated remarkable reactivities in aldol processes even with equimolar amounts of aldehyde and ketone in THF. A discussion of the role of the Brönsted acid as a co-catalyst is provided along with some applications of this new class of organocatalyst in Robinson annelation and α-amination processes.


## Introduction

Organocatalyzed reactions have been the subject of renewed interest[1] over the last six years and are now part of the organic chemistry armoury, as demonstrated by some recent applications in the total synthesis of natural products.[2] The aldol process was at the origin of this revival and is still the subject of intense research, as it represents an effective methodology for the formation of carbon–carbon bonds and a useful test reaction for the design of new catalysts. Proline was soon recognized as an attractive catalyst in this context and may be used in a number of cases.[3] However, the tendency of proline to form unreactive oxazolidinone[4] in significant amounts by reaction with the aldehyde or the ketone often led to the utilization of substoichiometric amounts of catalyst (20–30 mol-%). Moreover, due to slow reaction rates, a large amount of ketone is generally used (20–27 equiv. or neat), which renders the method unsuitable for an extension of the methodology to functionalized and/or costly ketones. Finally, although proline provides satisfactory results in terms of regio- and enantioselectivity in a number of processes including aldol and Michael addition reactions, there are still transformations and substrates where it leads to disappointing results. This suggested the need for more efficient catalysts possessing a tuneable structure. Most of the strategies developed so far to improve the catalytic activity of proline derivatives were based on the assumption that the hydrogen bond formed at the transition state between the acidic moiety of the catalyst and the developing alkoxide plays a crucial role in the stabilisation of the transition state.[5] Consequently, proline-based catalysts with more acidic groups or capable of multiple hydrogen-bond interactions with the aldehyde have been prepared and were shown to exhibit significant rate accelerations and improved enantioselectivities.[6] However, these approaches, which mainly focus on acceptor activation, did not succeed in reducing the amount of ketone used in the aldol process. Thus, other strategies should be envisioned that will not only focus on aldehyde activation but on the ketone activation as well to favour the formation of the iminium/enamine intermediates.

We recently reported on the design, synthesis and application of a new and simple proline surrogate, the benzimidazole-pyrrolidine (= BIP) (**1**) in asymmetric, organocatalyzed, aldol reactions (Scheme 1).[7] Preliminary results showed that **1**, when activated by one equiv. of a Brönsted




Scheme 1.

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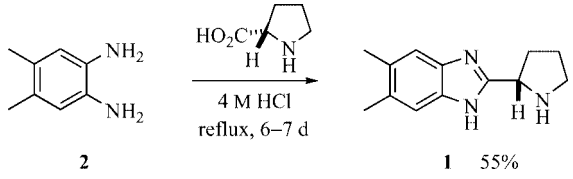
acid such as trifluoroacetic acid (TFA), affords aldol products in high enantioselectivity under real catalytic conditions (2–5 mol-%), with a stoichiometric amount of the ketone.[8] We provide here a full account of this work, including further examples of applications of **1**/$H^+$ as a catalyst in the aldol reaction and Robinson annelation as well as mechanistic insights accounting for the increased reactivity observed.

## Results and Discussion

### Synthesis of BIP (1)

Proline, which has been used with success in a number of cases, is a readily available catalyst whose cyclic structure has a strong influence on the stereochemical outcome of the aldol process.[3a–3b] It is also a bifunctional catalyst, which acts both as a Lewis base and Brönsted acid. Thus, we envisioned that both points should be taken into account in the design of a catalyst. BIP was prepared in 55% yield by a simple condensation of proline with a bisaniline **2** under acidic conditions (Scheme 2). High conversion was achieved within 6–7 d, and the condensation occurs without racemisation. It is also worth noting that the methyl groups probably enhance the nucleophilicity of the aromatic amino groups and also improve the solubility of the catalyst in organic solvents. X-ray structure determination confirmed the structure of **1** and provided useful information.[7] For instance, it was observed that two molecules of **1** crystallize in the presence of one molecule of water with the electron lone pairs of the oxygen atom linked to **1** through two hydrogen bonds involving pyrrolidine and benzimidazole N–H bonds with bond lengths of 1.87 Å and 2.71 Å, respectively. This suggests a possible pathway for activation of the electrophile by the formation of hydrogen bonds.




**2** **1** 55%

Scheme 2.

### Aldol Reactions Catalyzed by BIP

Preliminary investigations were carried out with acetone as a donor and *p*-nitrobenzaldehyde as the acceptor. The aldol reaction with 30 mol-% of **1** in DMSO led to a modest enantioselectivity as compared to that obtained with proline under similar conditions (Table 1, Entries 1–2).[3a] We attributed this poor result to the absence of an acidic proton in **1**. Indeed, while **1** can be considered a nitrogenated analogue of L-proline, a major difference is that the benzimidazole proton ($pK_a \approx 12.3$)[9] is much less acidic than that of the carboxylic acid of proline ($pK_a \approx 4.75$), leading to a less stabilized transition state. The addition of a proton source (AcOH, Table 1, Entry 3) effectively enhanced the rate of the reaction, in good agreement with recent studies by Barbas,[8a] who emphasized the role of an added Brönsted acid to accelerate the formation of the enamine in pyrrolidine-catalyzed aldol processes between aldehydes.[8] Interestingly, in our case, a significant improvement of the enantioselectivity was also observed. We soon found that the strength of the acid had a major impact on both the yield and enantioselectivity, as shown by the results observed with TFA, triflic acid and heptadecafluorononanoic acid (Table 1, Entries 4–6). In neat acetone, the aldol product **4**, possessing the (*R*) configuration similar to that obtained with L-proline,[3a] was obtained in 87% yield and 82% *ee* in 24 h with a catalyst loading of only 2 mol-% (Table 1, Entry 7). More importantly, under optimized conditions, the reaction was carried out in THF at 10 °C (to avoid the formation of the corresponding α,β-unsaturated ketone) with only one equiv. of acetone and 5 mol-% of the catalyst to afford **4** in good yield and enantioselectivity (Table 1, Entry 8). This result clearly demonstrates the high reactivity of the **1**/$H^+$ couple, which allowed a significant decrease in the quantity of both the catalyst and ketone. Lewis acids such as $Cu(OAc)_2$ or $Zn(OTf)_2$ (Table 1, Entries 9 and 10) were also tested with success, with higher enantioselectivity and yield observed with the more Lewis-acidic Zn salt,[10] demonstrating that **1** might also be a useful catalyst for enantioselective metal-catalyzed processes other than aldol reactions. Finally, the use of acidic hexafluoro-2-propanol[11] (HFIP, Table 1, Entry 11) led to a relatively slow reaction and poor yield, indicating that such a solvent likely disrupts hydrogen bonds necessary for the aminocatalysis.

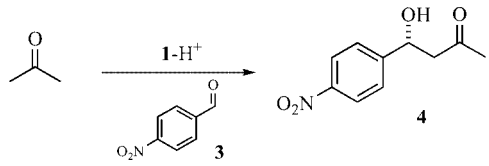
### Mechanistic Considerations

The results on aldol processes gathered in Table 1 clearly show the prominent role of added Brönsted acid with our organocatalyst **1**. Rather unexpectedly and in marked contrast with **1**, we have also observed that addition of a proton source (TFA) in the aldol reaction catalyzed by L-proline led to no aldol adduct, even after a prolonged reaction period (Table 1, Entry 12), pointing to a specific behaviour of the less acidic pyrrolidine-benzimidazole precatalyst. In line with these results and those previously reported by Barbas et al.[8a] and more recently by Peng et al.,[12] we have proposed the following mechanism to account for the high reactivity of **1**/$H^+$ (Figure 1). We also believe that according to a wealth of literature data,[3,5] this mechanism is likely to be applicable to other aminocatalyzed processes (such as α-amination, vide infra).

Addition of a Brönsted acid (AcOH, TFA or triflic acid) to precatalyst **1** should lead to the protonation of the more basic pyrrolidine ring ($pK_a \approx 11–12$)[13] to form intermediate **I** (Figure 1). The $^1H$ NMR spectrum (see the Supporting Information) of a mixture of **1** and TFA clearly exhibits a pronounced deshielding effect of 0.75 ppm for proton H2 of the pyrrolidine ring. In contrast, benzimidazole protons

Table 1. Optimizing the reaction conditions with **1**/acid.




| Entry | Cat./acid | mol-% | Solvent | Acetone [equiv.] | Time [h] | *T* [°C] | Yield [%][a] | *ee* [%] |
|---|---|---|---|---|---|---|---|---|
| 1 | L-proline/– | 30 | DMSO | 25 | 4 | 20 | 58 | 76[b] |
| 2 | **1**/– | 30 | DMSO | 25 | 8 | 20 | 40 | 44[b] |
| 3 | **1**/AcOH | 20 | acetone | – | 4 | –30 | 78 | 62[b] |
| 4 | **1**/TFA | 20 | acetone | – | 24 | –35 | 91 | 78[b] |
| 5 | **1**/$CF_3SO_3H$ | 20 | acetone | – | 24 | –20 | 84 | 80[b] |
| 6 | **1**/$C_8F_{17}CO_2H$ | 20 | acetone | – | 3 | –20 | 97 | 76[b] |
| 7 | **1**/TFA | 2 | acetone | – | 24 | –5 | 87 | 82[b] |
| 8 | **1**/TFA | 5 | THF | 1.1 | 24 | 10 | 85 | 78[c] |
| 9 | **1**/$Cu(OAc)_2$ | 30 | DMSO | 25 | 24 | 20 | 24 | 16[b] |
| 10 | **1**/$Zn(OTf)_2$ | 20 | acetone | – | 17 | 20 | 87 | 74[b] |
| 11 | **1**/TFA | 5 | HFIP | 1.1 | 48 | 15 | 21 | 15[c] |
| 12 | L-proline/TFA | 20 | DMSO | 25 | 24 | 20 | – | – |

[a] Isolated yield of **4**. [b] Enantiomeric excess estimated from $^1$H NMR of the corresponding Mosher's ester of **4**. [c] *ee* determined by HPLC with a Chiralcel AD-H® chiral column.

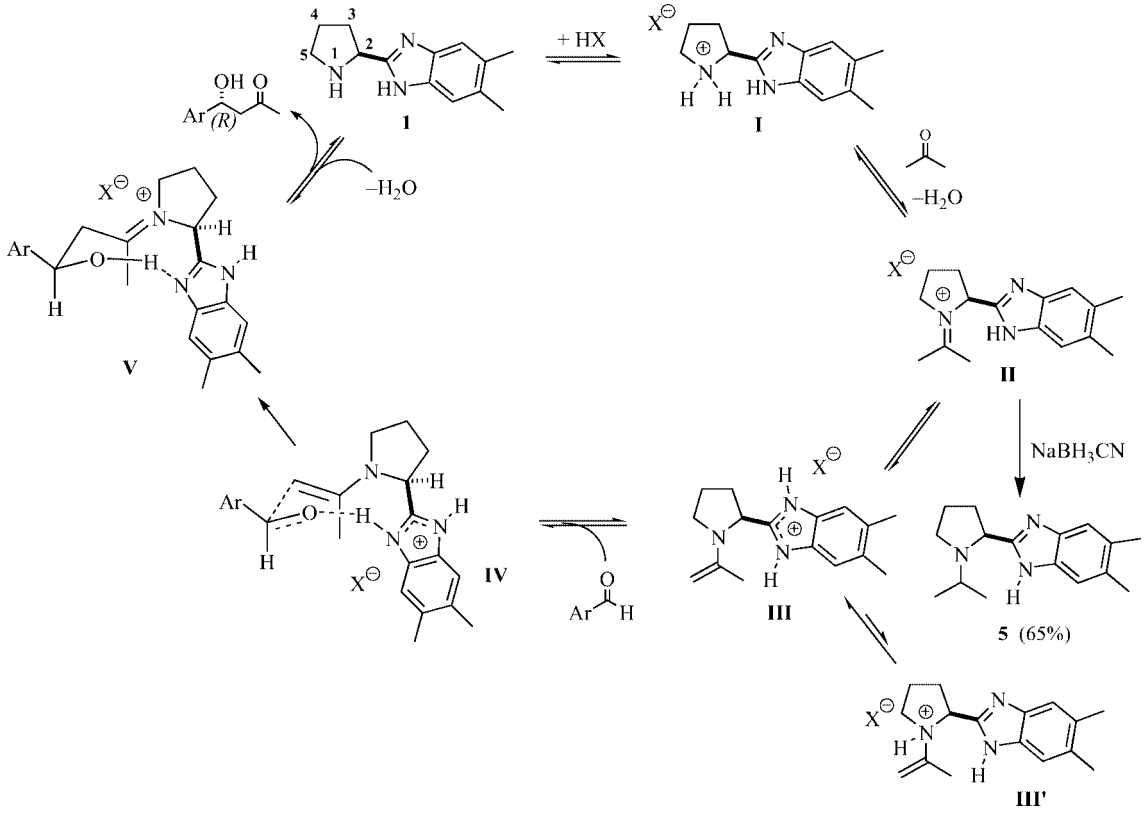
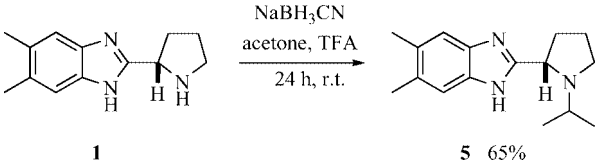



Figure 1. Proposed mechanism for the **1**/acid-catalyzed aldol reaction.

are little affected by the addition of a proton source, supporting the protonation of the pyrrolidine ring to generate **I**. The second step is the formation of the iminium **II** through nucleophilic addition of the pyrrolidine (or the benzimidazole) onto the ketone, which should then lead to the key intermediate enamine **III**. In the second step, the proton source (protonated BIP **I**) activates the ketone toward addition of the secondary amine. In order to rule out the possibility of formation of the enamine on the benzimidazole ring, we carried out the condensation between acetone and **1** in the presence of $NaBH_3CN$ to trap the iminium intermediate.[14] This led exclusively to the forma-

tion of the *N*-isopropylpyrrolidine **5** in 65% isolated yield (Scheme 3),[7] indicating that iminium **II** is an intermediate in the process and that the benzimidazole moiety is not nucleophilic enough to generate an iminium.[15]




**1** **5** 65%

Scheme 3.

Interestingly, the proton generated through sequence **II** → **III** may then protonate either the enamine or the benzimidazole ring to give the corresponding enammonium **III′** ($pK_a \approx 4$) or benzimidazolium **III** ($pK_a \approx 5.4$), which should be in equilibrium. However, we propose that the active intermediate is the benzimidazolium **III** and not the enammonium **III′**, which should not be nucleophilic enough to account for a high reactivity. Additionally, the benzimidazolium ring in **III** can form relatively strong hydrogen bonds with the aldehyde,[16] leading to a more stabilized chair-like transition state **IV** and, consequently, to higher enantioselectivity. Nucleophilic attack of the enamine on the *re*-face of the aldehyde (with the largest aldehyde substituent in a *pseudo*-equatorial arrangement),[5] followed by proton transfer from the benzimidazolium ring would afford the iminium **V**, which upon in situ hydrolysis, would lead to an aldol having predominantly the (*R*) configuration. The strength of the acid added at the beginning of the process is clearly central to this aminocatalysis. The addition of strongly acidic TFA ($pK_a \approx -0.3$) should ensure an efficient protonation of the benzimidazole ring in intermediate **III**. On the contrary, the addition of weak acid such as AcOH ($pK_a \approx 4.8$) provides only a partial protonation of the benzimidazole ring, leading to a less efficient catalysis, as indicated by lower enantioselectivity. It is also interesting to note that the addition of more than one equiv. of TFA was detrimental to the reaction, probably due to the subsequent protonation of enamine nitrogen site of **III** (as in **III′**), which slows down the process. The formation of an inactive enammonium intermediate could also explain the inhibition of the proline activity observed upon addition of one equiv. of TFA (Table 1, Entry 12). With proline, the enamine is the only site available for the "extra" proton. In summary, **1** incorporates two basic/nucleophilic sites that are crucial for the catalysis, and works synergistically in the presence of one equiv. of a proton source.

We also initiated an NMR study to get a better understanding of the role of the added proton on the catalyst activation (see the $^1H$ NMR spectra of **1** and **1**/$H^+$ in deuterated acetone, used both as solvent and reactant in Figure 2). **1** alone reacts rapidly with acetone to afford, after 30 min, 60% of the benzimidazolidine **6**,[4] while unreacted **1** constitutes the other 40%. Notably, in **6**, the two protons and methyl groups on the phenyl ring become magnetically non–equivalent, leading to the splitting of their signals. The complete assignment of the resonances of **6** has been achieved through a range of NMR experiments including $^{13}C$, TOCSY, HSQC and HMBC (see the Supporting Information). Thus, the reactivity of **1** is similar to that of proline, which was shown to react with ketones or aldehydes to give the corresponding bicyclic oxazolidinones.[4] It has been proposed that such parasitic consumption of the catalyst was partially responsible for the low reactivity of proline. Interestingly, a different reactivity was observed with the more active **1**/$H^+$ species **I** (Figure 1). As shown in Figure 2, two species are clearly present (≈ 1:1 ratio) after 30 min of reaction, unreacted **I** and another species the NMR ($^{13}C$ DEPT135, TOCSY, HSQC and HMBC) and ES-MS data (see the Supporting Information) of which are in agreement with the structure of iminium **II**. From the $^1H$ NMR spectrum, it is clear that the second species is not the benzimidazolidine **6** (only one resonance is observed for the benzimidazole protons), while the enamine structure can be ruled out, as the characteristic $^{13}C$ resonances of the ethylenic group are not observed in the $^{13}C$ NMR spectrum ($^{13}C$ and DEPT135 spectra are given in the Supporting Information). Instead, the highly deshielded proton resonance at $\delta = 6.24$ ppm was assigned through HSQC and TOCSY experiments to the –C*H*– of the pyrrolidine ring in **II**. Moreover, the quaternary carbon of iminium **II** was observed at $\delta = 160.9$ ppm in the $^{13}C$ spectrum, giving a broad signal due to the couplings with the deuterium and nitrogen atoms (see the Supporting Information). Importantly, the ESI-MS spectrum of an acetone/**1**/$H^+$ solution displayed an intense peak at $m/z = 256.2$ (100%), which corresponds to the molecular weight of **II** (see the Supporting Information). Overall, this preliminary study clearly shows that the addition of one equiv. of protons to **1** favours the formation of reactive intermediates such as the iminium salt **II**.

Having demonstrated the prominent role of acids as co-catalysts, we then investigated the stereochemical issue of an aldol process in which the acid would also be chiral. A series of commercially available (*R*)- and (*S*)-configured chiral acids (1 equiv.) were thus associated with **1** in order to test a putative match and mismatch effect. As summarized in Table 2, the enantioselectivity is slightly improved in the aldol reaction with camphorsulfonic acid (CSA) as compared to that with TFA, but there is no visible match-mismatch effect in this case (Entries 3 and 4, Table 2). A small effect is observed with binapthol phosphoric and Mosher's acids (Δ*ee*: 7% for Table 2, Entries 5 and 6 and Δ*ee*: 6% for Table 2, Entries 1 and 2), while a more important one is detected with tartaric acid (Δ*ee*: 25% for Table 2, Entry 8), indicating that the counter-anion is probably intimately associated with the benzimidazolium transition state **IV**, as proposed in the reaction mechanism (Figure 1).[17] In this case, the enantioselectivity is low so that the effect is more easily detected. Therefore, although the chiral acid effect is weak, double stereodifferentiation with the chiral ligand/chiral acid pair has been demonstrated, which may provide an entry for further improvements. Moreover, the strength

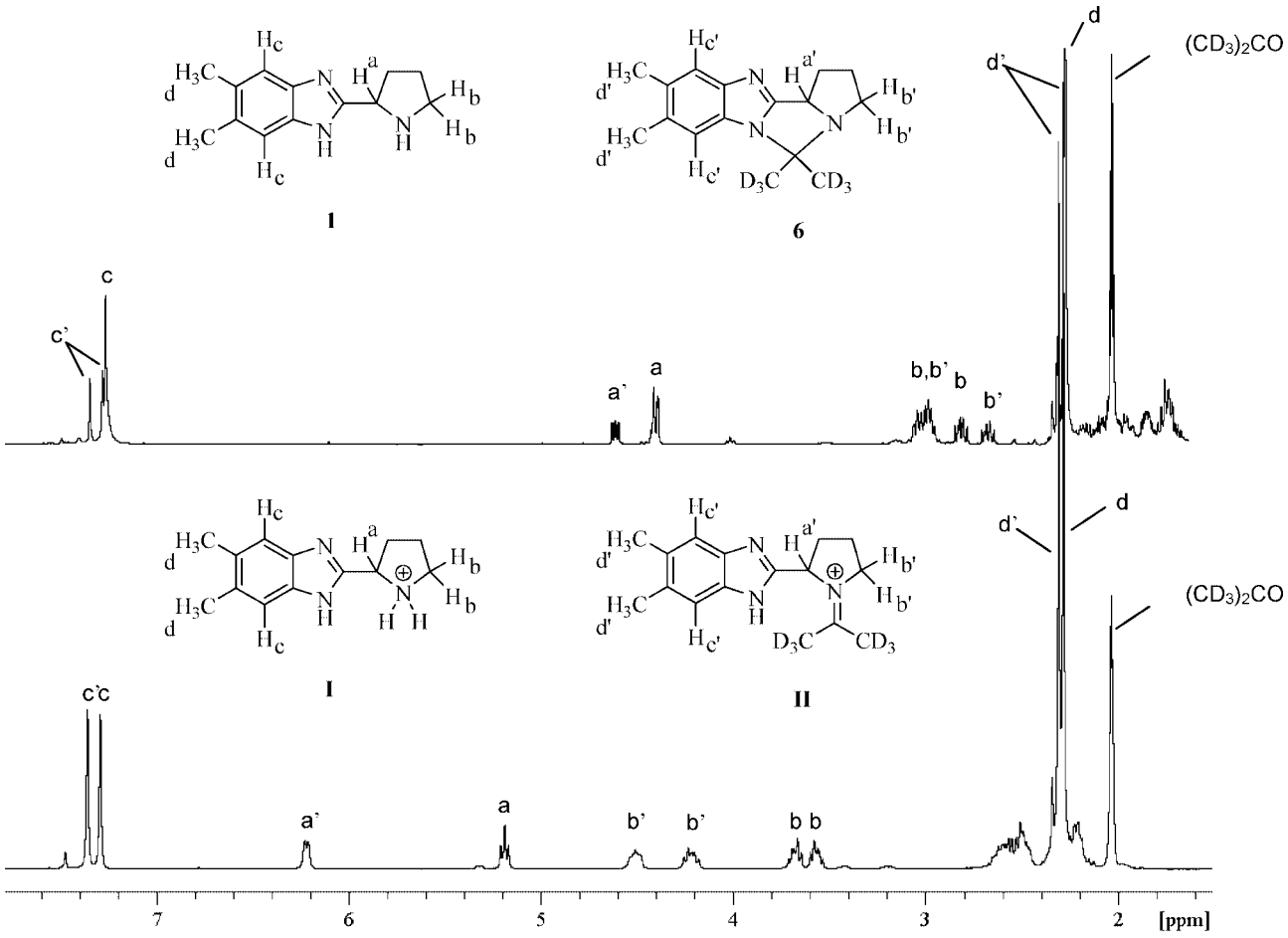
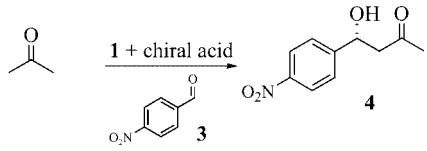



Figure 2. $^1$H NMR analyses of aldol reactions. Upper spectrum: $^1$H NMR spectrum of **1** (25 mg, 4 Å molecular sieves) in [$D_6$]acetone (0.5 mL); Lower spectrum: $^1$H NMR spectrum of **1** (25 mg, 4 Å molecular sieves) in [$D_6$]acetone (0.5 mL)/TFA (1 equiv., 9 μL).

of the acid is crucial for a high enantioselectivity, as shown by the better *ee* obtained with the stronger CSA (Table 2, Entries 3 and 4).

Having shown that our catalyst was efficient with acetone, we studied its behaviour toward cyclohexanone, cyclopentanone and diethyl ketone (**7a**–**c**).[8d,18] As summarized in Table 3, catalyst **1** is very efficient with such ketones and provides aldol products **8** and **9** with excellent enantioselectivities, albeit with modest diastereocontrol. Comparison of our results with those obtained with proline, 5,5-dimethylthiazolidinium-4-carboxylate (DMTC),[18] or a pyrrolidinyl-proline derivative showed that improved *de* as well as *ee* were observed.[8d] These results are among the best obtained to date with these substrates. Interestingly, only 2 mol-% of organocatalyst **1** was necessary to mediate the aldol reaction between cycloalkanones **7a** and **b** with only 1.1 equiv. of ketones (Table 3, Entries 1–4), in contrast to the 22–27 equiv. of ketone and 10–20 mol-% of catalysts previously needed.[18] The reaction was faster and more efficient in terms of yield and enantioselectivity with cyclohexanone as compared to cyclopentanone (Entry 4 vs. Entries 1–3, Table 3). Finally, the reaction was also very efficient with the less reactive diethyl ketone **7c**, and provided a 2.5:1 ratio of diastereomeric *anti* aldol **8c** and *syn* aldol **9c** in 98% and >99% *ee*, respectively. Interestingly, using the (*R*) enantiomer of the Mosher's acid instead of TFA provided significantly improved results.

Table 2. Aldolisation reaction with **1**/chiral acids.

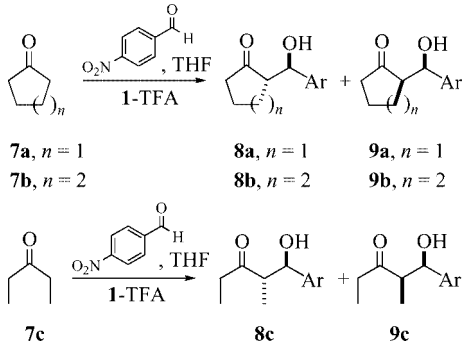



| Entry | Cat./acid[a] | Time [h] | *T* [°C] | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 | **1**/(*R*)-MTPA | 5 | 15 | 87 | 70 |
| 2 | **1**/(*S*)-MTPA | 5 | 15 | 83 | 64 |
| 3 | **1**/(+)-CSA | 24 | 0 | 87 | 83 |
| 4 | **1**/(–)-CSA | 24 | 0 | 63 | 82 |
| 5 | **1**/(*R*)-BINOLPO$_2$H | 24 | 10 | 56 | 75 |
| 6 | **1**/(*S*)-BINOLPO$_2$H | 24 | 10 | 46 | 68 |
| 7 | **1**/D-tartaric acid | 24 | 15 | 81 | 27 |
| 8 | **1**/L-tartaric acid | 24 | 15 | 81 | 52 |

[a] Reaction carried in THF with 1.1 equiv. of acetone and 5 mol-% of **1**/chiral acid. [b] Isolated yields. [c] *ee* determined by HPLC with a Chiralcel AD-H® chiral column.

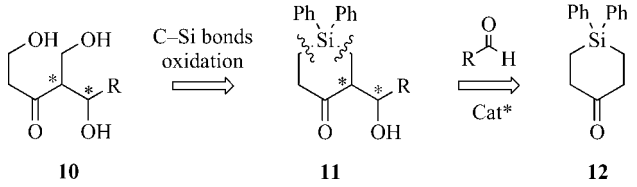
Table 3. Aldolisation reaction with **1**/acids.




| Entry | Ketone [equiv.] | **1**/acid [mol-%] | Time [h] | *T* [°C] | Yield [%][a] | *anti*/*syn*[d] | *ee* (*anti*) [%][e] | *ee* (*syn*) [%][e] |
|---|---|---|---|---|---|---|---|---|
| 1 | **7a** (1.1) | **1**/TFA (10) | 4 | 20 | 78 | 1.5:1 | 79 | 93 |
| 2 | **7a** (1.1) | **1**/TFA (2) | 48 | 20 | 43[b] | 1.2:1 | 75 | 92 |
| 3 | **7a** (1.1) | **1**/TFA (2) | 48 | 40 | 46[c] | 1.6:1 | 66 | 54 |
| 4 | **7b** (1.1) | **1**/TFA (2) | 2 | 20 | 83 | 3.2:1 | 99 | 80 |
| 5 | **7c** (9) | **1**/TFA (10) | 48 | 20 | 91 | 2.2:1 | 92 | >99 |
| 6 | **7c** (9) | **1**/(*R*)-MTPA (10) | 48 | 20 | 88 | 2.5:1 | 98 | >99 |

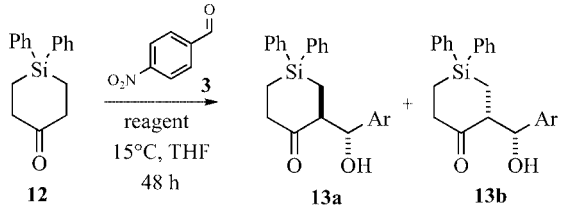
[a] Isolated yield. [b] 48% of recovered aldehyde. [c] 52% of recovered aldehyde. [d] Ratio estimated from $^1$H NMR of the crude reaction mixture. [e] *ee* measured by HPLC with a Chiralcel AD-H® column.

Although the diastereomeric ratio observed in the aldol reaction with diethyl ketone **7c** is modest, this transformation is noteworthy, as it offers a rapid entry to polypropionate fragments with excellent enantioselectivities. In a similar fashion, we tested our catalyst in aldol processes involving 1-silacyclohexan-4-one **12**,[19] which can also be regarded as a potential precursor of polypropionate fragments. Oxidation of the C–Si bond of **11** using the well-known Tamao-Fleming reaction[20] should effectively produce, after the aldol reaction, polypropionate-type fragments such as **10** (Scheme 4).




Scheme 4. 1,1-Diphenyl-1-silacyclohexan-4-one (**12**) as a precursor of polypropionate fragments.

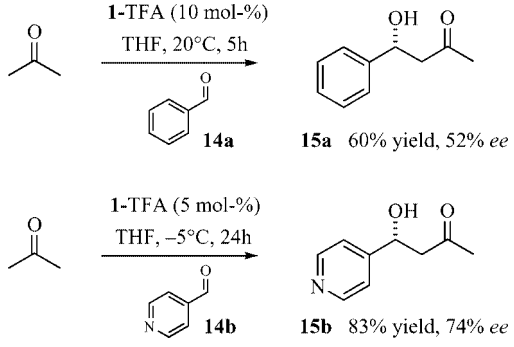
The aldol reaction was thus carried out starting with 1.1 equiv. of ketone **12** and 1 equiv. of our test aldehyde **3** (Scheme 5). A mixture of *anti* and *syn* aldols **13a** and **13b** was obtained with modest *de* but good enantioselectivities. Better enantioselectivities were observed when **1** was associated with (+)-CSA, demonstrating again the match pairing of these chiral reagents. Interestingly, 30 mol-% of proline in DMSO with 2.4 equiv. of **12** led to no reaction, even after 48 h of stirring at room temperature (20 °C), demonstrating the unique reactivity of **1**/acid reagents. The assignment of the relative configurations of **13a** and **13b** was realized by analogy with aldols prepared from cyclohexanone and cyclopentanone.[18] Finally, it can be concluded that **12**, used here for the first time in an aldol reaction, possesses reactivity analogous to that of cyclopentanone and cyclohexanone and leads to similar selectivities.




| | *anti* (*ee*) / *syn* (*ee*) | |
|---|---|---|
| Reagent: **1**-TFA (10 mol-%) | 1.5 (83%) : 1 (67%) | yield: 65% |
| Reagent: **1**-(+)-CSA (5 mol-%) | 2.7 (85%) : 1 (80%) | yield: 49% |

Scheme 5.

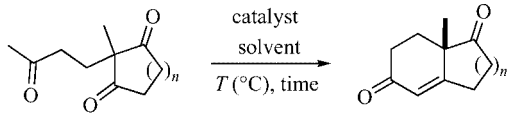
Finally, several aldehydes have been tested in these aldol reactions (Scheme 6). Benzaldehyde (**14a**) and 4-pyridine carbaldehyde (**14b**) were found suitable, leading to aldol products **15a** and **b** in reasonable yield and enantio-




Scheme 6.

Table 4. Robinson annelation of triones **16a** and **b** catalyzed by **1**.




**16a**, $n = 1$ **17a**, $n = 1$
**16b**, $n = 2$ **17b**, $n = 2$

| Entry | Cat./acid | mol-% | Solvent | Product | Time [h] | $T$ [°C] | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|---|---|
| 1 | L-proline/– | 47[a] | $CH_3CN$ | **17a** | 24 | 80 | 87 | 84 |
| 2 | **1**/TFA | 10 | THF | **17a** | 48 | 0 | quant. | 86 |
| 3 | **1**/(+)-CSA | 10 | THF | **17a** | 48 | 15 | 64 | 88 |
| 4 | L-proline/– | 47[a] | $CH_3CN$ | **17b** | 24 | 80 | 83 | 71 |
| 5 | **1**/TFA | 10 | THF | **17b** | 48 | 0 | 82 | 68 |
| 6 | **1**/(+)-CSA | 10 | THF | **17b** | 72 | 20 | 90 | 64 |

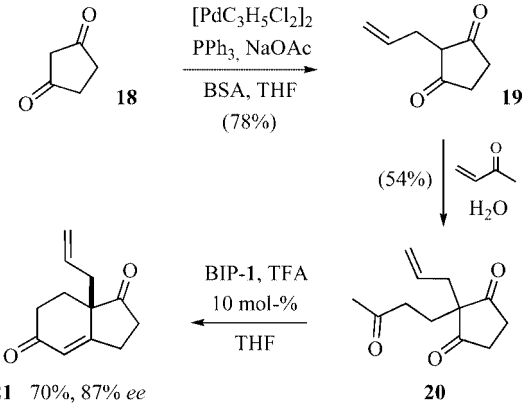
[a] 1 M $HClO_4$ was present in the medium. [b] Isolated yield. [c] *ee* measured by HPLC with a Chiralcel AD-H® column.

selectivities. Equimolar amounts of **14b** and acetone were used to provide **15b**, while benzaldehyde (**14a**) was treated with acetone in excess to minimize the amount of elimination product formed during the aldol process.[21]

### Robinson Annelation Catalyzed by 1/H$^+$

As a continuation of our investigation on the potential of the **1**/H$^+$ reagent, we extended the study to the Robinson annelation of diones **16a** and **b** (Table 4).[22,23] The entire aldol reaction-elimination process could be carried out in one pot, as we observed that the dehydration step was smoothly catalyzed by the **1**/TFA. This is in contrast with proline catalysis, for which the reaction has to be performed at elevated temperature in the presence of 1 M $HClO_4$ to achieve this elimination step. The results are summarized in Table 4. A comparison with the results obtained with L-proline shows that a better yield of **17a**[24] and similar enantioselectivity was obtained with **1**/TFA under milder conditions (Table 4, Entry 2 vs. 1). As already noticed in the aldol reactions, only 10 mol-% of **1**/TFA was needed, as compared with 47 mol-% of L-proline (Table 4, Entry 1). A similar conclusion was reached with the homologous trione **16b**. A better yield of bicyclic ketone **17b** was obtained with **1**/TFA, albeit with slightly lower enantioselectivity (Table 4, Entry 5). Finally, the reagent **1**/(+)-CSA catalyzed the annelation of trione **16a** with slightly better enantioselectivity but lower yield (Entry 3), while the contrary was observed upon annelation of **16b** (Table 4, Entry 6).

The approach was then extended to the Robinson annelation of an analogue of **16a** possessing a more useful allyl substituent on the quaternary centre (Scheme 7). Such an allyl group can be functionalized further to generate valuable intermediates for the synthesis of polycyclic systems. Thus, symmetrical dione **20** was prepared in two steps from cyclopentane-1,3-dione (**18**) through a palladium-catalyzed allylation, followed by Michael addition of **19**[25] onto methylvinyl ketone. Robinson annelation of **20**, catalyzed by **1**/TFA (10 mol-%) finally led to the desired bicyclic ketone **21**[26] in excellent yield and good enantioselectivity (87% *ee*). A single recrystallization in diethyl ether led to **21** with an improved 93% *ee* value. It is noteworthy that when the reaction was performed in DMF instead of THF, **21** was formed along with the aldol product in a 1:1 ratio. In contrast, L-proline in DMSO provided only the aldol product, indicating again that **1**/TFA catalyzes not only the aldol reaction but also the elimination process to provide, in a single operation, the annelation product **21**. The absolute configuration of **21** was assigned based on the known configuration of **17a** and **b** above.[22b,22c]




Scheme 7.

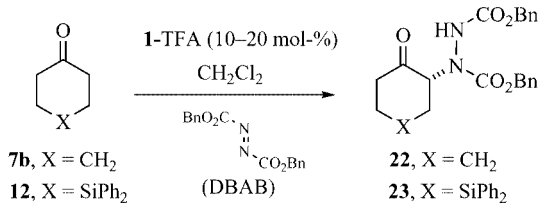
**1**-mediated elimination was supported by an experiment carried out on the racemic aldol product **15a**. Treatment of racemic **15a** in THF in the presence of 10 mol-% of **1**/TFA led, after about 80% conversion into the corresponding chalcone (the reaction was followed by HPLC), to an enantioenriched aldol product **15a** [39% *ee*, major isomer (*S*)] as a result of a kinetic resolution.

### α-Amination of Ketones Catalyzed by 1

The α-amination of ketones is a synthetically relevant transformation which has received a great deal of attention in the context of aminocatalysis.[27] We have tested our organocatalytic system on this reaction and found that the

Table 5. α-Amination of ketones catalyzed by **1**.




**7b**, X = $CH_2$
**12**, X = $SiPh_2$
**22**, X = $CH_2$
**23**, X = $SiPh_2$

| Entry | Cat./acid | mol-% | Solvent | Product | Time [h] | *T* [°C] | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|---|---|---|---|
| 1 | L-proline/– | 15 | $CH_2Cl_2$ | **22** | 24 | 20 | 88 | 84 |
| 2 | **1**/TFA | 10 | $CH_2Cl_2$ | **22** | 24 | 20 | 92 | 66 |
| 3 | **1**/TFA | 10 | THF | – | 24 | 20 | 0 | – |
| 4 | L-proline/– | 20 | $CH_2Cl_2$ | **23** | 24 | 20 | 85 | 60 |
| 5 | **1**/TFA | 20 | $CH_2Cl_2$ | **23** | 24 | 20 | 65 | 71 |

[a] Isolated yield. [b] *ee* was measured by HPLC with a Chiralcel AD-H® column.

reaction occurred smoothly in $CH_2Cl_2$ leading to the α-aminoketones **22** and **23** in good yield and reasonable enantioselectivity (Table 5). **1**/TFA was less efficient than L-proline in terms of enantioselectivity when cyclohexanone **7b** was used but led to better results with 1-silacyclohexan-4-one **12**.[28]

## Conclusions

In summary, we have developed a new organocatalyst, which is available in one step from L-proline. As demonstrated by $^1$H NMR and mass spectrometry studies, this organocatalyst exhibits an enhanced reactivity toward ketones, accelerating significantly the formation of the key iminium and the enamine intermediates in aminocatalyzed aldol and amination reactions. Excellent levels of enantioselectivity have been attained in several cases, with low catalyst loading (<5–10%) and as little as 1.1. equiv. of ketone. Modifications of the basic core of the benzimidazole and that of pyrrolidine should provide analogues of BIP that might exhibit higher reactivity and selectivity. Extension of these aldol processes to various types of ketone donors and application of our catalyst to the synthesis of enantioenriched intermediates and biologically relevant targets is currently under way in our laboratory.

## Acknowledgments

This work was supported by the Ministère de la Recherche et de la Technologie through a PhD grant to E.L. We gratefully acknowledge the Institut Universitaire de France and the CNRS for financial support. We thank Prof. Petri Pihko (University of Helsinki) for a generous gift of DBAB.

## Experimental Section

**General Remarks:** NMR analysis were carried out on Bruker AC-200 FT (200 MHz for $^1$H and 50.4 MHz for $^{13}$C), Bruker AC-250 FT (250 MHz for $^1$H and 63 MHz for $^{13}$C) and Bruker DPX-300 (300 MHz for $^1$H and 75.5 MHz for $^{13}$C) spectrometers with deuterated chloroform as the solvent. The chemical shifts ($\delta$) for $^{13}$C and $^1$H signals are given compared to the internal reference (TMS) and are expressed in ppm. Some mass spectra (low resolution) were obtained with a Thermo Quest Finnigan Trace GC-MS apparatus. Ionization was carried out by electronic impact (potential of ionization: 70 eV). Other mass spectra (low and high resolution) were obtained on a Micromass autospec-Q spectrometer. Ionization employed was the electronic impact mode (potential of ionization: 70 eV), and the LSIMS mode [potential of ionization: 35 keV, matrix: (3-nitrophenyl)methanol]. IR spectra were obtained on a Perkin–Elmer Paragon 1000 FT-IR spectrometer. The wavelengths ($\tilde{\nu}$) are expressed in $cm^{-1}$.

**(*S*)-5,6-Dimethyl-2-(pyrrolidin-2-yl)-1*H*-benzimidazole (1):** L-proline (3.4 g, 27 mmol) was treated with 4,5-dimethyl-1,2-phenylenediamine **2** (3.1 g, 23 mmol) in aqueous HCl (4 M, 40 mL) at reflux for 6–7 d. The solution was then treated with aqueous NaOH (4 M, until pH = 12), affording a brown sticky residue. After vigorous stirring for 5 h, the precipitate that formed was filtered, washed with water and thoroughly washed with diethyl ether to give **1** as a beige powder (2.7 g, 55% yield). **1** can be recrystallised by slow evaporation of a water/MeOH solution. M.p. 94 °C (beige powder). IR (KBr): $\tilde{\nu}$ = 3280 (NH), 2970, 2871, 2282, 1634, 1444, 1310, 825 $cm^{-1}$. $^1$H NMR ([D$_6$]DMSO): $\delta$ = 7.30 (s, 2 H), 4.46–4.41 (m, 1 H), 3.06–2.98 (m, 2 H), 2.34 (s, 6 H), 2.22–2.13 (m, 1 H), 2.02–1.98 (m, 1 H), 1.85–1.77 (m, 2 H) ppm. $^{13}$C NMR ([D$_6$]DMSO): $\delta$ = 155.2, 136.9, 131.2, 115.1, 56.3, 46.5, 32.2, 25.5, 20.2 ppm. MS (EI): *m*/*z* (%) = 215 (71) $[M]^+$, 187 (53), 186 (37), 173 (100), 160 (75), 147 (26). $C_{13}H_{17}N_3 \cdot 1.5H_2O$ (241.1) calcd. C 64.46, H 8.26, N 17.35; found C 64.50, H 7.85, N 17.25.

**General Procedure for Aldol Reactions with 1:** Compound **1** (4.9 mg, 23 μmol) and TFA (1.8 μL, 23 μmol) were stirred in THF (1 mL) with ketone (1.1 equiv.) for 10 min. *p*-Nitrobenzaldehyde (**3**, 177.6 mg, 1.17 mmol) was added in one portion. The reaction progress was monitored by TLC (hexanes/EtOAc, 7:3). The crude reaction mixture was purified by flash column chromatography on silica gel (hexanes/EtOAc 7:3) to give the aldol adduct. Enantiomeric excess (*ee*) was determined through $^1$H-NMR spectroscopy of the corresponding Mosher's ester or with chiral HPLC. The *anti*/*syn* ratio was estimated from a $^1$H NMR analysis of crude reaction mixture. The enantioselectivities of the *anti* and *syn* isomers were measured by chiral HPLC analysis.

**4-Hydroxy-4-(4-nitrophenyl)butan-2-one (4):** This aldol product was prepared according to the general procedure described above. $R_f$ (hexanes/EtOAc, 7:3) = 0.3. HPLC: Chiralcel AD-H®, hexanes/

MeOH, 96:4, retention time 50.3 min. (*S*) and 51.9 min. (*R*). $^1$H NMR ($CD_2Cl_2$): $\delta$ = 8.18 (d, $J$ = 9 Hz, 2 H), 7.54 (d, $J$ = 8.85 Hz, 2 H), 5.28–5.22 (m, 1 H), 3.58 (broad s, 1 H), 2.87–2.82 (m, 2 H), 2.19 (s, 3 H) ppm. $^{13}$C NMR ($CD_2Cl_2$): $\delta$ = 208.8, 150.8, 147.7, 129.4, 124.0, 69.3, 51.8, 30.8 ppm. MS (FAB+): *m*/*z* (%) = 232 (100) [M + Na]$^+$, 212 (40), 210 (35) [M + H]$^+$. HRMS: calcd. for $C_{10}H_{11}NO_4Na$ [M + Na]$^+$ 232.058578; found 232.053874.

**(*S*)-2-(1-Isopropylpyrrolidin-2-yl)-5,6-dimethyl-1*H*-benzimidazole (5): 1** (50 mg, 0.23 mmol) and TFA (18 μL, 0.23 mmol) were stirred in acetone for 10 min, and $NaBH_3CN$ (30 mg, 0.5 mmol) was added in portions. After 24 h at room temperature, the resulting solution was treated with water and $Na_2CO_3$. The reaction mixture was extracted with EtOAc, and the resulting organic layer was dried with $MgSO_4$. The solvent was evaporated in vacuo to afford **5** as a white powder (39 mg, 65% yield). M.p. 160–178 °C. IR (KBr): $\tilde{\nu}$ = 2966, 1635, 1417, 1309 cm$^{-1}$. $^1$H NMR ($CDCl_3$): $\delta$ = 7.25 (s, 2 H), 4.11–4.08 (m, 1 H), 3.15–3.05 (m, 1 H), 2.85–2.75 (m, 1 H), 2.60–2.40 (m, 1 H), 2.28 (s, 6 H), 2.25–2.15 (m, 1 H), 1.95–1.75 (m, 1 H), 1.73–1.65 (m, 2 H), 0.99 (d, $J$ = 6.4 Hz, 3 H), 0.95 (d, $J$ = 6.4 Hz, 3 H) ppm. $^{13}$C NMR ([D$_6$]DMSO): $\delta$ = 159.2, 131.3, 115.4, 59.7, 53, 50.3, 33.8, 24.7, 22.2, 20.7, 19.4 ppm. MS (FAB+): *m*/*z* (%) = 280 [M + Na]$^+$, 258 (100) [M + H]$^+$, 257 (26), 256 (80), 214 (65), 212 (22). HRMS: calcd. for $C_{16}H_{24}N_3$ [M + H]$^+$ 258.196543; found 258.197023.

**2-[Hydroxy-(4-nitrophenyl)methyl]cyclopentanone (8a and 9a):**[18b] $R_f$ (hexanes/EtOAc, 7:3) = 0.4. HPLC: Chiralcel AD-H®, hexanes/MeOH, 95:5, retention time for *syn*-**9a** 26.7 min and 42 min; *anti*-**8a** 52.6 min and 55.3 min. *anti*-**8a**: $^1$H NMR ($CD_2Cl_2$): $\delta$ = 8.18 (d, $J$ = 10.6 Hz, 2 H), 7.53 (d, $J$ = 10.2 Hz, 2 H), 4.82 (d, $J$ = 9.0 Hz, 1 H), 4.67 (s, 1 H), 2.30–1.50 (m, 7 H) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 240.1, 150.8, 148.0, 126.8, 123.9, 74.8, 55.4, 39.0, 27.2, 20.7 ppm. *syn*-**9a**: $^1$H NMR ($CDCl_3$): $\delta$ = 8.18 (d, $J$ = 7.2 Hz, 2 H), 7.53 (d, $J$ = 7.5 Hz, 2 H), 5.38 (m, 1 H), 2.59 (d, $J$ = 4.9 Hz, 1 H), 2.30–1.50 (m, 7 H) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 220.1, 149.4, 127.8, 123.4, 70.9, 56.3, 39.2, 22.8, 20.7 ppm. MS (FAB+): *m*/*z* (%) = 258 (100) [M + Na]$^+$, 218 (37), 212 (42). HRMS: calcd. for $C_{12}H_{13}NO_4Na$ [M + Na]$^+$ 258.074228; found 258.074435.

**2-[Hydroxy(4-nitrophenyl)methyl]cyclohexanone (8b and 9b):** $R_f$ (hexanes/EtOAc, 7:3, *syn*) = 0.25; $R_f$ (hexanes/EtOAc, 7:3, *anti*) = 0.2. HPLC: Chiralcel AD-H®, hexanes/MeOH, 90:10, retention time *syn*-**9b** 14.6 min and 16.1 min; *anti*-**8b** 17.4 min and 24.2 min. *anti*-**8b**: $^1$H NMR ($CDCl_3$) $\delta$ = 8.19 (d, $J$ = 10.3 Hz, 2 H), 7.50 (d, $J$ = 10.2 Hz, 2 H), 4.88 (dd, $J$ = 6.2 and 3.7 Hz, 1 H), 4.09 (d, $J$ = 4 Hz, 1 H), 2.64–2.28 (m, 3 H), 2.14–2.06 (m, 1 H), 1.83–1.30 (m, 5 H) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 214.7, 148.4, 127.9, 123.6, 74.0, 57.2, 42.7, 30.7, 27.6, 24.7 ppm. *syn*-**9b**: $^1$H NMR ($CDCl_3$): $\delta$ = 8.21 (d, $J$ = 7.5 Hz, 2 H), 7.49 (d, $J$ = 7.5 Hz, 2 H), 5.49 (s, 1 H), 3.20 (d, $J$ = 3 Hz, 1 H), 2.67–2.53 (m, 3 H), 2.16–2.07 (m, 1 H), 1.89–1.45 (m, 5 H) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 213.9, 147.6, 126.6, 123.4, 70.1, 56.8, 42.6, 27.8, 25.9, 24.8 ppm. MS (FAB+): *m*/*z* (%) = 272 (100) [M + Na]$^+$, 232 (30), 212 (49). HRMS: calcd. for $C_{13}H_{15}NO_4Na$ [M + Na]$^+$ 272.089878; found 272.090203.

**1-Hydroxy-2-methyl-1-(4-nitrophenyl)pentane-3-one (8c and 9c):**[18c] $R_f$ (hexanes/EtOAc, 7:3) = 0.3. HPLC: Chiralcel OD®, hexanes/MeOH, 92:8, retention time for *syn*-**9c** 14.9 min and 15.4 min; *anti*-**8c** 13.8 min and 16.4 min. *anti*-**8c**: $^1$H NMR ($CDCl_3$): $\delta$ = 8.22 (d, $J$ = 8.8 Hz, 2 H), 7.51 (d, $J$ = 8.5 Hz, 2 H), 4.88 (d, $J$ = 7.5 Hz, 1 H), 2.95–2.91 (m, 1 H), 2.55–2.51 (m, 1 H), 2.49–2.43 (m, 1 H), 1.05–0.95 (m, 6 H) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 215.6, 149.6, 127.4, 123.7, 75.6, 52.2, 36.4, 14.5, 7.5 ppm. *syn*-**9c**: $^1$H NMR ($CDCl_3$): $\delta$ = 8.22 (d, $J$ = 8.8 Hz, 2 H), 7.51 (d, $J$ = 8.5 Hz, 2 H), 5.23 (d, $J$ = 3 Hz, 1 H), 2.85–2.75 (m, 1 H), 2.55–2.51 (m, 1 H), 2.49–2.43 (m, 1 H), 1.05–0.95 (m, 6 H). $^{13}$C NMR ($CDCl_3$): $\delta$ = 215.6, 146.6, 126.8, 123.5, 71.9, 51.4, 35.1, 9.9, 7.4 ppm. MS (FAB+): *m*/*z* (%) = 260 (100) [M + Na]$^+$, 238 (20) [M + H]$^+$, 212 (21). HRMS: calcd. for $C_{12}H_{15}NO_4Na$ [M + Na]$^+$ 260.089878; found 260.090584.

**3-[Hydroxy(4-nitrophenyl)methyl]-1,1-diphenylsilinan-4-one (13a and 13b):** $R_f$ (hexanes/EtOAc, 8:2, *syn*) = 0.4, $R_f$ (hexanes/EtOAc, 8:2, *anti*) = 0.35. HPLC: Chiralcel AD-H®, hexanes/MeOH, 96:4, retention time for *syn*-**13b** 34.4 min and 36.7 min; *anti*-**13a** 71.1 min and 96.3 min. *syn*-**13b**: $^1$H NMR ($CDCl_3$): $\delta$ = 8.15 (d, $J$ = 8.7 Hz, 2 H), 7.39 (d, $J$ = 8.7 Hz, 2 H), 7.37–7.29 (m, 10 H), 5.35 (s, 1 H), 3.47 (d, $J$ = 3 Hz, 1 H), 2.88–2.84 (m, 1 H), 2.82–2.64 (m, 2 H), 1.47–1.35 (m, 4 H) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 216.6, 148.9, 147.1, 134.7, 130.7, 128.5, 128.4, 127.1, 123.8, 71.8, 52.8, 39.0, 10.4, 8.2 ppm. *anti*-**13a**: $^1$H NMR ($CDCl_3$): $\delta$ = 8.15 (d, $J$ = 8.7 Hz, 2 H), 7.39 (d, $J$ = 8.7 Hz, 2 H), 7.37–7.29 (m, 10 H), 4.96 (d, $J$ = 8 Hz, 1 H), 3.7 (br., 1 H), 2.96–2.92 (m, 1 H), 2.75–2.69 (m, 2 H), 1.67–1.58 (m 4 H) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 216.6, 148.9, 147.1, 134.7, 130.7, 128.5, 128.4, 127.1, 123.8, 76.3, 53.3, 39.4, 14.3, 10.8 ppm.

**4-Hydroxy-4-(pyridin-4-yl)butan-2-one (15b):**[29] $R_f$ ($CH_2Cl_2$/diethyl ether, 8:2) = 0.5. HPLC: Chiralcel AD-H®, hexanes/MeOH, 90:10, retention time 15.5 min. (*S*) and 16.7 min. (*R*). $^1$H NMR ($CD_2Cl_2$): $\delta$ = 8.49 (d, $J$ = 6 Hz, 2 H), 7.22 (d, $J$ = 6 Hz, 2 H), 5.08 (t, $J$ = 6.4 Hz, 1 H), 3.65 (br., 1 H), 2.76 (d, $J$ = 5.3 Hz, 2 H), 2.15 (s, 3 H) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 208.4, 151.6, 149.9, 120.5, 68.4, 51.2, 30.7 ppm. MS (EI): *m*/*z* (%) = 132 (20), 107,(100), 106,(37), 78(55).

**2-Methyl-2-(3-oxobutyl)cyclopentane-1,3-dione (16a):**[24] 2-Methylcyclopentane-1,3-dione (2 mmol) was placed in $CH_3CN$ (3 mL), and triethylamine (1 mL) was added, followed by methylvinyl ketone (200 μL, 2.4 mmol). The reaction mixture was stirred at room temperature. The reaction progress was monitored by TLC (hexanes/EtOAc, 1:1). The solvents were removed under vacuum, and the residue was purified through chromatography over silica gel to give **16a** as an oil (100% yield); $R_f$ (hexanes/EtOAc, 1:1) = 0.4. $^1$H NMR ($CDCl_3$): $\delta$ = 2.89–2.73 (m, 4 H), 2.47 (t, $J$ = 7 Hz, 2 H), 2.12 (s, 3 H), 1.91 (t, $J$ = 5 Hz, 2 H), 1.12 (s, 3 H) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 215.7, 207.8, 55.1, 37.4, 34.7, 30.0, 27.8, 19.1 ppm. MS (FAB+): *m*/*z* (%) = 183 (100) [M + H]$^+$. HRMS: calcd. for $C_{10}H_{15}O_3$ [M + H]$^+$ 183.102120; found 183.10190.

**2-Methyl-2-(3-oxobutyl)cyclohexane-1,3-dione (16b):**[24] Compound **16b** was prepared following the same procedure as described for **16a** above. $R_f$ (hexanes/EtOAc, 1:1) = 0.4. $^1$H NMR ($CDCl_3$): $\delta$ = 2.79–2.59 (m, 4 H), 2.36 (t, $J$ = 7 Hz, 2 H), 2.13 (s, 3 H), 2.09–2.01 (m, 2 H), 1.99–1.85 (m, 2 H), 1.26 (s, 3 H) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 210.0, 207.5, 64.3, 38.4, 37.8, 29.9, 29.6, 20.0, 17.6 ppm. MS (FAB+): *m*/*z* (%) = 197 (100) [M + H]$^+$. HRMS: cacld. for $C_{11}H_{17}O_3$ [M + H]$^+$ 197.117770; found 197.118217.

**7α-Methyl-2,3,7,7α-tetrahydro-6*H*-indene-1,5-dione (17a):**[22c] In a 2 mL flask, **1** (11 mg, 48 μmol), TFA (3.9 μL, 50 μmol) and **16a** (98 mg, 5 mmol) were mixed in THF (1 mL), and the reaction mixture was stirred at room temperature. The reaction progress was monitored by $^1$H NMR analysis. The crude reaction mixture was purified by flash column chromatography on silica gel (hexanes/EtOAc, 9:1) to give ketone **17a**. HPLC: Chiralcel OD®, hexanes/MeOH, 96:4, retention time 31.9 min and 36.7 min. $^1$H NMR ($CDCl_3$): $\delta$ = 5.98 (s, 1 H), 3.05–2.92 (m, 1 H), 2.85–2.77 (m, 2 H), 2.58–2.47 (m, 2 H), 2.17–2.04 (m, 2 H), 1.98–1.84 (m, 1 H), 1.33 (s, 3 H) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 214.3, 196.0, 167.6, 121.8, 94.4, 32.6, 27.6, 24.7, 18.4 ppm. MS (FAB+): *m*/*z* (%) = 165 (100)

$[M + H]^+$, 147 (31), 141 (54), 135 (33). HRMS: calcd. for $C_{10}H_{13}O_2$ $[M + H]^+$ 165.091555; found 165.091101.

**8α-Methyl-3,4,8,8α-tetrahydronaphthalene-1,6(2*H*,7*H*)-dione (17b):**[22c] **17b** was prepared following the same procedure as described for **17a** above. HPLC: Chiralcel OD®, hexanes/MeOH, 95:5, retention time 21.9 min and 24.7 min. $^1H$ NMR ($CDCl_3$): $\delta$ = 5.85 (s, 1 H), 2.85–2.70 (m, 2 H), 2.65–2.40 (m, 4 H), 2.25–2.05 (m, 3 H), 1.85–1.65 (m, 1 H), 1.45 (s, 3 H) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 165.8, 125.9, 50.6, 37.7, 33.6, 31.8, 29.7, 23.3, 23.0 ppm. MS (FAB+): *m*/*z* (%) = 179 (100) $[M + H]^+$. HRMS: calcd. for $C_{11}H_{15}O_2$ $[M + H]^+$ 179.107205; found 179.107743.

**2-Allylcyclopentane-1,3-dione (19):**[25] In a 100 mL flask with a condenser, allyl palladium chloride dimer (68 mg, 0.18 mmol) and dppe (199 mg, 0.50 mmol) were introduced and degassed with $N_2$. Anhydrous THF (30 mL) was added, followed by allyl acetate (0.53 mL, 4.9 mmol). To the solution were added sequentially 1,3-cyclopentanedione (731 g, 7.45 mmol), BSA (1.83 mL, 7.43 mmol) and sodium acetate (24 mg, 0.29 mmol). The reaction mixture was heated to 70 °C, and the reaction progress was monitored by TLC (EtOAc/MeOH, 97:3). The crude reaction mixture was filtered through a celite plug and washed with MeOH (3 × 10 mL). The solvents were removed under vacuum, and the product was purified through column chromatography on silica gel (EtOAc/MeOH, 97:3) to afford a white powder (530 mg, 78% yield). $R_f$ ($CH_2Cl_2$/MeOH, 99.5:0.5) = 0.3. $^1H$ NMR (300 MHz, $CD_3OD$): $\delta$ = 5.85–5.74 (m, 1 H), 4.92–4.82 (m, 3 H), 2.85 (d, *J* = 6 Hz, 2 H), 2.52 (s, 4 H) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 136.4, 116.4, 114.9, 31.3, 25.9 ppm. MS (EI): *m*/*z* (%) = 138 (100), 123 (32), 109 (25), 95 (60), 81 (25), 67 (25), 53 (28), 39 (32), 27 (36). HRMS: calcd. for $C_8H_{10}O_2$ 138.068080; found 138.068106.

**2-Allyl-2-(3-oxobutyl)cyclopentane-1,3-dione (20):**[25] Into a 25 mL flask was introduced **19** (753 mg, 5.8 mmol) and $H_2O$ (2.6 mL), followed by methyl vinyl ketone (1.2 mL, 14.5 mmol). The reaction mixture was stirred at room temperature, and the progress of the reaction was monitored by TLC ($CH_2Cl_2$/MeOH, 97:3). The reaction mixture was diluted with diethyl ether (3 × 10 mL), and the organic layer was washed with a solution of NaCl (3 × 10 mL). The organic layer was dried with $MgSO_4$, and the solvent was removed under vacuum. The crude product was purified through column chromatography on silica gel ($CH_2Cl_2$/MeOH, 97:3) to afford **20** as a yellow oil (649 mg, 54% yield). $R_f$ ($CH_2Cl_2$/MeOH, 96:4) = 0.4. IR (film): $\tilde{\nu}$ = 3464, 1722, 1640 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ = 5.72–5.45 (m, 1 H), 5.09–5.02 (m, 2 H), 2.85–2.55 (m, 4 H), 2.42 (t, *J* = 7.3 Hz, 2 H), 2.31 (d, *J* = 2.3 Hz, 2 H), 2.08 (s, 3 H), 1.88 (t, *J* = 7.3 Hz, 2 H) ppm. MS (FAB+): *m*/*z* (%) = 231.2 (100) $[M + Na]^+$. HRMS: calcd. for $C_{12}H_{16}O_3Na$ $[M + Na]^+$ 231.099309; found 231.099714.

**7α-Allyl-2,3,7,7α-tetrahydro-6*H*-indene-1,5-dione (21):**[26] In a 25 mL flask, 1,3-dione **20** (342 mg, 1.64 mmol) was stirred in THF (5 mL), followed by the addition of **1** (37 mg, 0.16 mmol) and TFA (12 μL, 0.16 mmol). The reaction progress was monitored by TLC (EtOAc/pentane, 4:6). The solvent was removed under vacuum, and the crude reaction mixture was purified through chromatography on silica gel to furnish **21** as a yellow oil (218 mg, 70% yield, 87% *ee*). $R_f$ (EtOAc/pentane, 4:6) = 0.45. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 6.01 (d, *J* = 2 Hz, 1 H), 5.82–5.67 (m, 1 H), 5.18–5.09 (m, 2 H), 2.97–2.16 (m, 8 H), 2.82–2.69 (m, 2 H) ppm. $^{13}C$ NMR (75.47 MHz, $CDCl_3$): $\delta$ = 198.06, 168.89, 131.69, 124.60, 119.73, 52.57, 38.95, 36.07, 32.53, 27.26 ppm. MS (FAB+): *m*/*z* (%) = 191 $[M + H]^+$, 213 $[M + Na]^+$. HRMS: calcd. for $C_{12}H_{14}O_2Na$ $[M + Na]^+$ 213.0891; found 213.0896.

**Dibenzyl 1-(2-Oxocyclohexyl)hydrazine-1,2-dicarboxylate (22): 1** (12 mg, 48 μmol) and TFA (4 μL, 52 μmol) were stirred in $CH_2Cl_2$ (2 mL), and cyclohexanone **7b** (80 μL, 773 μmol) and DBAB (150 mg, 504 μmol) were added. The reaction mixture was stirred at room temperature, and the reaction progress was monitored by TLC (hexanes/EtOAc, 7:3). The crude reaction mixture was purified by flash column chromatography on silica gel (hexanes/EtOAc, 8:2) to give **22**. $R_f$ ($CH_2Cl_2$/diethyl ether, 8:2) = 0.25. HPLC: Chiralcel OD®, hexanes/MeOH, 80:20, retention time 34.8 min and 41.7 min. IR (NaCl): $\tilde{\nu}$ = 3387, 1756, 1727, 1700 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 55 °C): $\delta$ = 7.38–7.33 (m, 10 H), 6.89 (br., 1 H), 5.24–5.17 (m, 4 H), 5.00–4.82 (br., 1 H), 2.54–2.42 (m, 3 H), 1.94–1.59 (m, 5 H) ppm. $^{13}C$ NMR ($CDCl_3$, 55 °C): $\delta$ = 206.9, 156.2, 135.7, 135.6, 128.4, 127.6, 68.5, 67.7, 67.5, 41.1, 30.6, 26.6, 24.2 ppm. MS (EI): *m*/*z* (%) = 396 (0.2), 91 (100). HRMS: calcd. for $C_{22}H_{24}N_2O_5$ 396.168522; found 396.167668.

**Dibenzyl 1-(4-Oxo-1,1-diphenylsilinan-3-yl)hydrazine-1,2-dicarboxylate (23): 23** was prepared following the same procedure as described for **22** above. $R_f$ ($CH_2Cl_2$/diethyl ether, 8:2) = 0.25. HPLC: Chiralcel OD®, hexanes/*i*PrOH, 70:30, retention time 12.5 min and 15.8 min. IR (NaCl): $\tilde{\nu}$ = 3386, 1775, 1727, 1712 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 55 °C): $\delta$ = 7.69–7.30 (m, 20 H), 6.89 (br., 1 H), 5.17–4.98 (m, 5 H), 2.75–2.61 (m, 2 H), 1.77–1.05 (m, 4 H) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 210.5, 156.7, 134.9, 130.8, 130.6, 129.0, 128.9, 128.7, 128.6, 128.5, 127.9, 68.6, 67.9, 64.2, 37.4, 14.9, 9.8 ppm. MS (FAB+): *m*/*z* (%) = $[M + Na]^+$ 587.3 (100). HRMS: calcd. for $C_{33}H_{32}N_2O_5SiNa$ 587.197739; found 587.197821.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Received: July 31, 2006
Published Online: October 10, 2006
Note: Minor modifications have been made to the manuscript at the authors' request since its publication in Early View.

  