DOI: 10.1002/adsc.201700120

Advanced Synthesis & Catalysis

Very Important Publication

# *cis*-4-Alkoxydialkyl- and *cis*-4-Alkoxydiarylprolinol Organocatalysts: High Throughput Experimentation (HTE)-Based and Design of Experiments (DoE)-Guided Development of a Highly Enantioselective *aza*-Michael Addition of Cyclic Imides to α,β-Unsaturated Aldehydes

Ismael Arenas,[+a] Alessandro Ferrali,[+a] Carles Rodríguez-Escrich,[a] Fernando Bravo,[a,*] and Miquel A. Pericàs[a,b,*]

[a] Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, Av. Països Catalans 16, 43007 Tarragona, Spain
Fax: (+34)-977-920-224; phone: (+34)-977-920-200; e-mail: fbravo@iciq.cat or mapericas@iciq.es

[b] Departament de Química Orgànica i Inorgànica, Universitat de Barcelona (UB), 08028 Barcelona, Spain

[+] These authors contributed equally to this work.

Received: January 31, 2017; Revised: February 1, 2017; Published online: ■■ ■■, 0000

*Dedicated to Professor Sergio Castillón on the occasion of his 65th birthday.*

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201700120.

**Abstract:** A diverse family (37 compounds) of *cis*-4-alkoxydiorganylprolinol derivatives has been prepared and evaluated in organocatalysis for the first time. The combined use of high throughput experimentation (HTE) techniques with efficient analytical methods has led to the identification of two superior catalysts for the enantioselective addition of succinimide to α,β-unsaturated aldehydes. Further optimization of the reaction conditions with design of experiments (DoE) techniques established the catalyst of choice for the considered *aza*-Michael reaction, the corresponding adducts (12 examples) being obtained in good yields and excellent enantioselectivities (succinimide and maleimide donors). The synthetic versatility of these Michael adducts is illustrated by a two-step sequence leading to enantiopure 1,3-amino alcohols.

**Keywords:** design of experiments; diarylprolinol catalysts; high throughput experimentation; organocatalysis

## Introduction

Organocatalysis has become one of the fundamental pillars in the preparation of enantioenriched compounds, as it has provided elegant methods which are complementary to biocatalytic and metal-catalyzed reactions. In contrast to enzymes, organocatalysts are ideally small, inexpensive and highly-tunable molecules and their use has overcome the problem of heavy metals that may contaminate the final products. In the realm of organocatalysis,[1] diarylprolinols[2] are considered as privileged catalysts due to their outstanding levels of enantiodiscrimination by steric effects and high catalytic activity in a wide range of organic transformations under enamine/iminium activation modes, including α-sulfenylation,[3] α-fluorination,[4] α-bromination and α-amination,[5] Michael,[6] Diels–Alder,[7] epoxidation,[8] and aziridination[9] reactions, among many other examples.

In a continuous effort to improve the level of diastereo- and enantioselectivity in organocatalyzed transformations, several modifications of the basic pyrrolidine scaffold have been described. Regarding the functionalization of the quaternary carbon adjacent to C-2, Gilmour et al. described the use of (fluorodiphenylmethyl)pyrrolidine (Figure 1, **I**) in epoxidation and aziridination reactions, in which the fluorine atom proved to be very efficient for controlling the conformation of the catalyst along the catalytic cycle.[10]

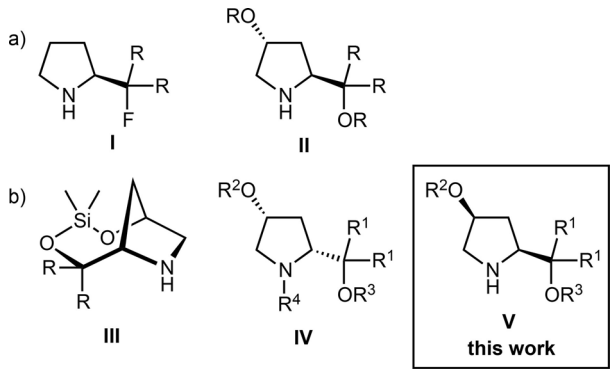



**Figure 1.** a) Selected examples of functionalized diarylprolinols. b) *cis*-4-Substituted diarylprolinols.

Another structural modification was described by Oriyama et al., where bulky silyloxy groups at the C-4 position (Figure 1, **II**) led to good levels of enantioselectivity in conjugate additions of thiols[11] and malonates[12] to α,β-unsaturated aldehydes. Similarly, Chen et al. described the use of these catalysts for the Diels–Alder reaction between electron-deficient β-substituted 2,4-dienes and 2,4-dienals.[13] Related C-4 substituted diarylprolinols (Figure 1, **II**) were used by Jørgensen et al. in the enamine activation of cyclopropanes, yielding tetrasubstituted cyclobutanes,[14] as well as in the α-alkylation of aldehydes, where the approach of the electrophile was conveniently directed by the bulky OTIPS group in this position.[15] 4-Hydroxypyrrolidine derivatives have also proven to be an excellent choice for catalyst immobilization, leading to functionalized materials able to mediate aldol,[16] Mannich,[17] Michael[18] and α-amination[19] reactions, both in batch and in flow processes.

Nonetheless, there are still unresolved challenges regarding the functionalization of the pyrrolidine backbone in proline-derived catalysts. Of note, most of the C-4 substituted analogues are synthesized starting from *trans*-4-hydroxy-L-proline and the introduction of protecting groups at the secondary alcohol is often plagued by variable degrees of epimerization in the C-2 center in the presence of strong bases.[20] To avoid this, careful control of the reaction conditions is required. Therefore, it would be useful to develop an efficient approach to C-4 substituted diarylprolinols that avoids by design the possibility of erosion in the optical purity of the final catalysts.

A salient structural feature of *trans*-4-substituted diarylprolinols is the simultaneous steric blocking of both the upper and the lower face of the pyrrolidine ring. Considering the iminium/enamine manifold that is usually invoked for these catalysts, the face-shielding created by these groups is of paramount importance, being involved in the origin of the stereoselectivity exhibited by these catalytic reactions. In spite of the good levels of stereocontrol that are frequently achieved with Jørgensen–Hayashi catalysts, we considered that *cis*-4-substituted diorganylprolinols could exhibit, as a result of steric repulsion caused by the C-2 and C-4 substituents, an even more efficient shielding of one of the pyrrolidine faces in the putative iminium/enamine intermediates, which could lead to better enantioselectivities in the catalytic processes.

Despite these considerations, there are scarcely any examples in the scientific literature regarding the use of these *cis*-4-substituted diorganylprolinols as organocatalysts. For example, Lombardo et al. described the synthesis of 2,4-dioxa-7-aza-3-silabibyclo[4.2.1]nonanes (Figure 1, **III**), which can be considered as constrained *cis*-4-silyloxydiarylprolinol silyl ethers, and studied their catalytic potential in cyclopropanation, Michael and Diels–Alder reactions. Remarkably, catalytic properties of these species were comparable and in some cases superior to those of Jørgensen–Hayashi catalysts.[21] Zhao reported the use of diarylprolinols such as **IV** in Figure 1 for the epoxidation of enones[22] and Diels–Alder[23] reactions. The group of Zlotin prepared ionic liquids from both *trans*- (Figure 1, **II**) and *cis*-4-substituted (Figure 1, **IV**) diphenylprolinols and studied their use as organocatalysts in the addition of nitromethane to enals.[24] To the best of our knowledge, there are no further examples describing the use of *cis*-4-substituted diorganylprolinols in organocatalysis.[25]

In order to systematically address the impact of the substitution pattern and to assess the potential of these scaffolds in organocatalysis, we have rationally designed a completely new set of *cis*-4-substituted dialkyl- or diarylprolinol derivatives (Figure 1, **V**), introducing diversity in three different positions:

(i) the diorganyl moiety; $R^1$ = 3,5-$(CF_3)_2$-$C_6H_3$, Ph or *n*-hexyl,

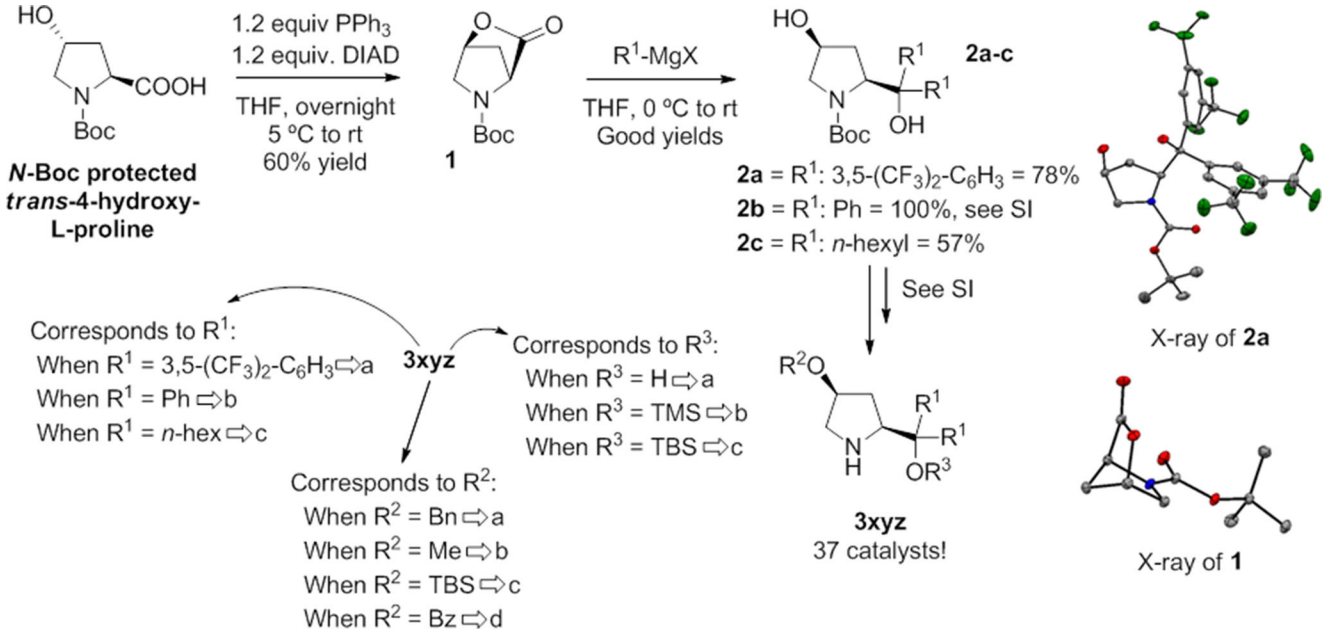
(ii) the alkoxy group at C-4; $R^2$ = Bn, Me, TBS or Bz,

(iii) the protecting group of the diorganylcarbinol moiety at C-2; $R^3$ = H, TMS or TBS.

## Results and Discussion

We embarked on the synthesis of these new catalysts, starting from the commercially available *N*-Boc-protected *trans*-4-hydroxy-L-proline. The synthetic protocols have been streamlined to give multi-gram amounts of the intermediates in very high yields while avoiding chromatographic purifications for most steps (see the Supporting Information for details). *trans*-4-Hydroxy-L-proline underwent an intramolecular Mitsunobu reaction in good yield (Scheme 1) to afford lactone **1**.[26] This compound was envisaged as




**Scheme 1.** Synthesis of *cis*-4-substituted dialkyl- and diarylprolinol catalysts.

the relay intermediate for the synthesis of the new *cis*-4-substituted dialkyl- or diarylprolinol catalysts; thus, large amounts of this material were required. Gratifyingly, the reaction could be scaled-up to 10 g with complete avoidance of column chromatography purification. Moreover, X-ray analysis of a single crystal confirmed the inversion of the configuration at the C-4 stereocenter. Then, reaction with the corresponding Grignard reagent ($R^1MgX$) under Knochel conditions[27] afforded the unprotected diol intermediates **2a–c**, which were further protected by standard procedures (see the Supporting Information for details). Considering the possible combinations, thirty-six catalysts were synthesized in good to excellent yields. Additionally, when the 3,5-bis(trifluoromethyl)phenyl derivative (**2a**) was synthesized and further protected employing MeI, the dimethyl-protected scaffold was obtained as a by-product (**3abd**), and it was finally incorporated into the set of catalysts. In order to classify the catalysts, we created a code of three letters (**xyz**). The first letter (**x**) corresponds to the $R^1$ group, the second one (**y**) to the protecting group of the secondary alcohol ($R^2$) and the third letter (**z**) corresponds to the $R^3$ group (Scheme 1).

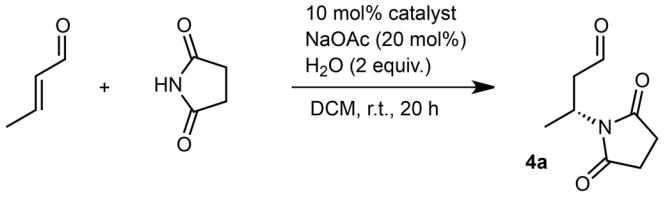
Having established a powerful strategy to synthesize the catalysts, we faced the challenge of testing such a large number of catalysts in a selected benchmark reaction. To this end, we searched the literature to identify potentially useful transformations mediated by a diarylprolinol derivative that were currently underexploited due to unsatisfactory levels of enantioselectivity. During this screening, we identified the *aza*-Michael reaction[28] between α,β-unsaturated aldehydes and imides as a proper candidate to put our set of catalysts to the test. This reaction was first described by Jørgensen et al.,[29] achieving good yields with a wide range of substrates although moderate *ee* values (78%) and yields (65%) were obtained when crotonaldehyde was used.

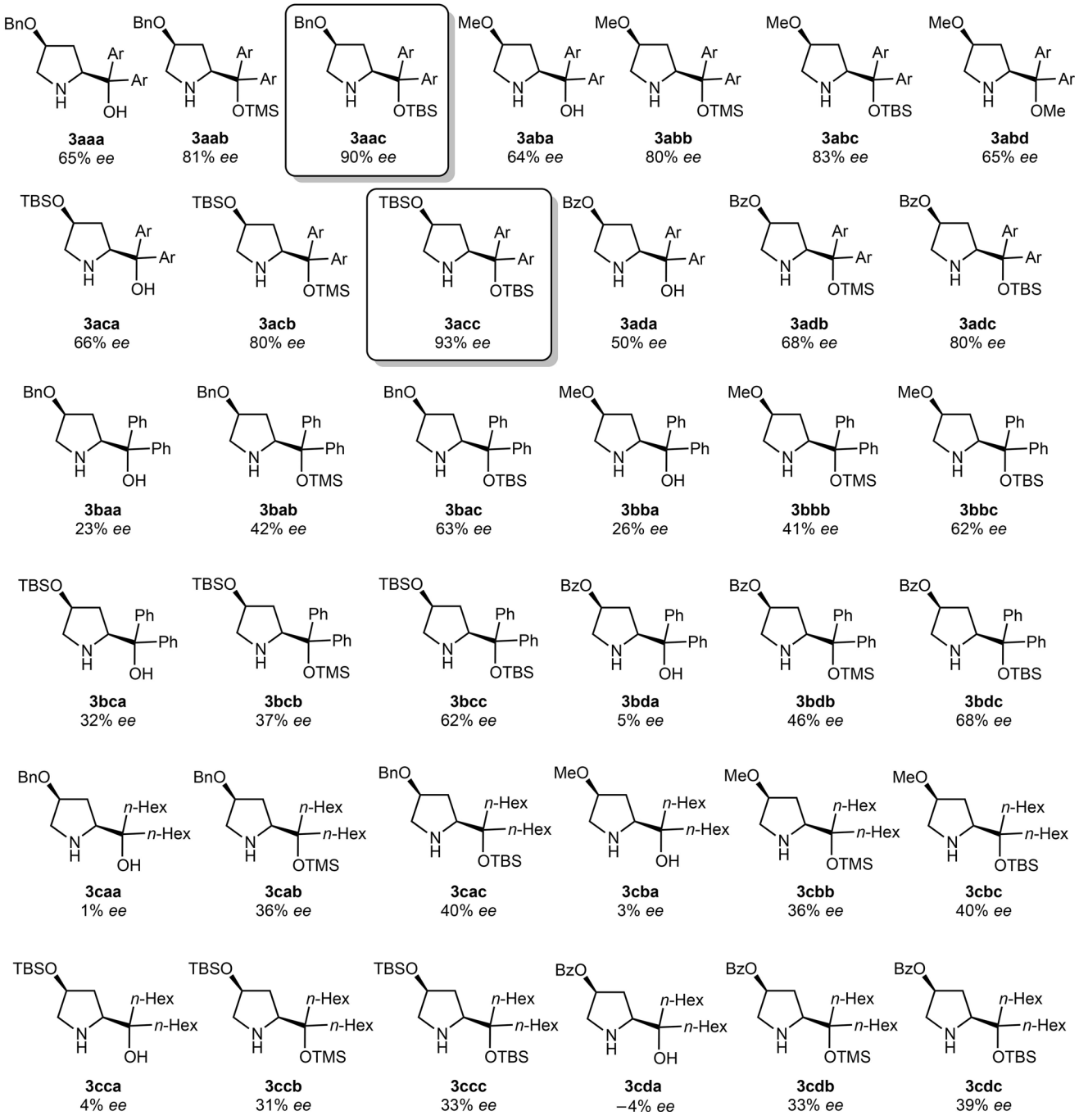
As one can imagine, it is possible to deal with a large number of experiments at a relatively small-scale, but several drawbacks may arise from treating this new set of catalysts in a "conventional" approach, especially when considering that different variables will need some optimization. The most evident difficulty would be to handle hundreds of reactions with their generated samples, as well as the time needed to analyze them. Unless careful design is undertaken, one might end up with a considerable bottleneck along the process of catalyst evaluation. At this stage, we relied on high throughput experimentation (HTE),[30] which has been proven as a powerful methodology for carrying out rapid screenings.[31] To date, advantages of this technique are very attractive: (i) a single researcher may run hundreds of simultaneous reactions per day, (ii) analysis of these reactions by means of HPLC or GC takes a few hours and can be automatized (generally carried out overnight), (iii) every single experiment needs a very small amount of reagents (around 1–4 mg per reaction), thus maximizing the number of possible reactions carried out per mg of catalyst synthesized, (iv) it allows the researcher to discover unexpected products, by means of an "accelerated serendipity", as conceptualized by MacMillan.[32]

We conveniently prepared an initial HTE screening on a μmol scale by using the already described conditions in the seminal work of Jørgensen et al.,[29] where

**Table 1.** Screening of *aza*-Michael reaction using *cis*-4-substituted dialkyl- and diarylprolinol ethers.[a]




[a] The diorganyl moiety $R^1$ = 3,5-$(CF_3)_2$-$C_6H_3$, Ph or *n*-hexyl, the alkoxy group at C-4 $R^2$ = Bn, Me, TBS or Bz, the protecting group of the diorganylcarbinol moiety at C-2 $R^3$ = H, TMS or TBS.

10 mol% of catalyst loading and 1.5 equiv. of succinimide were used, together with NaOAc as a base and 2 equiv. of water. The results of this preliminary catalyst evaluation are shown in Table 1.

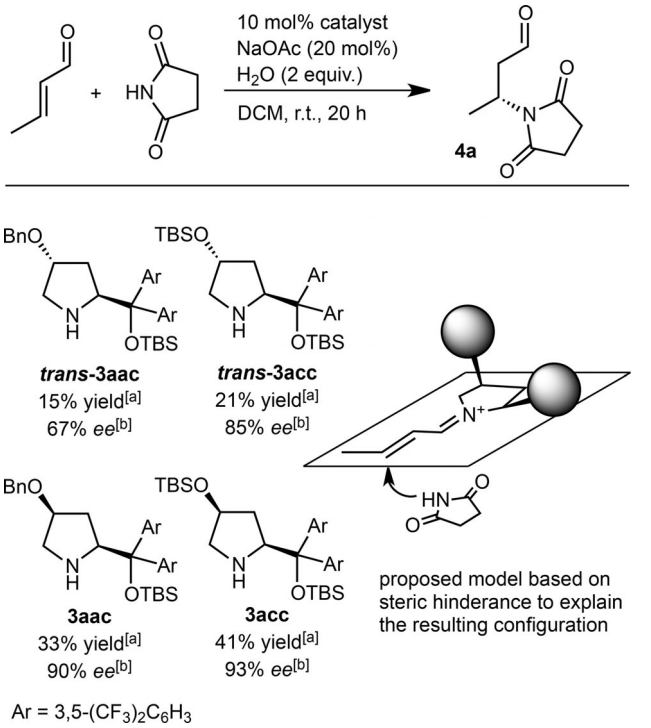
Several conclusions can be extracted from the screening: (i) the use of the 3,5-bis(trifluoromethyl)-phenyl scaffold in $R^1$ afforded the best *ee* values; (ii) a TBS protecting group in $R^3$ enabled better *ee*s than TMS, probably due to its increased bulkiness and stability under reaction conditions; (iii) other things being equal, the bulkiest $OR^2$ group (OTBS) led to slightly higher *ee* values. Overall, these results were in agreement with our initial hypothesis, in which the more sterically crowded catalyst could afford the highest *ee*. Gratifyingly, we found that derivatives **3aac** and **3acc** were suitable catalysts for the iminium activation of crotonaldehyde with excellent enantioselectivities (90 and 93%, respectively), albeit in moderate conversions (41 and 33%). Notably, the range of enantiomeric excesses obtained with this family of organocatalysts (from −4 to 93% *ee*), which are caused by the subtle differences in the protection pattern, would have made it very difficult and tedious to identify suitable catalysts with a strategy different to the employment of the powerful HTE techniques.

At this point we wondered if the *cis*-disposition of substituents was exerting such a difference in the enantioselection, so we decided to synthesize the analogues of **3aac** and **3acc** with the *trans*-configuration to validate the generality of our concept (see the Supporting Information for details). We observed that *trans*-substituted catalysts led to a substantial drop in yield and *ee* values. The results are shown in Table 2.

These results are in agreement with our hypothesis that the *cis* arrangement of substituents results in a more effective shielding of the beta face of the prolinol moiety. This seems to be confirmed by the solid state conformation shown by one of the derivatives, **3bdb**, from which we were able to obtain single crystals suitable for X-ray analysis (Figure 2). This substrate adopts an envelope conformation of the 5-membered ring, with the nitrogen positioned in the upper (beta) face of the plane. As a result, the substituent at C-4 shields effectively this side of the molecule. Interestingly, the coupling constants displayed by **3bdb** are almost identical to those of the best catalysts **3aac** and **3acc**, which indicates that these *cis* organocatalysts adopt the same conformation in solution (NMR and NOE effects are compiled in Section 8 in the Supporting Information).

We then evaluated in depth the reaction conditions with the most promising catalysts (**3aac** and **3acc**). Screening of several solvents ($CH_2Cl_2$, THF, toluene, MeOH, DCE and $CHCl_3$) revealed that $CH_2Cl_2$ and $CHCl_3$ were the most appropriate in terms of conversion and enantioselectivity. Additionally, other bases were tested ($K_2CO_3$, DIPEA), but NaOAc and lutidine provided higher yields. Additionally, the presence or absence of water in the reaction mixture was studied. The final screening (Table 3) was carried out at 40 °C for 48 h, in an attempt to increase the yield

**Table 2.** *aza*-Michael reaction catalyzed by *cis*- and *trans*-4-substituted diarylprolinols.




[a] Yield estimated by GC using 4,4-dimethylbiphenyl as internal standard.
[b] Determined by chiral GC.

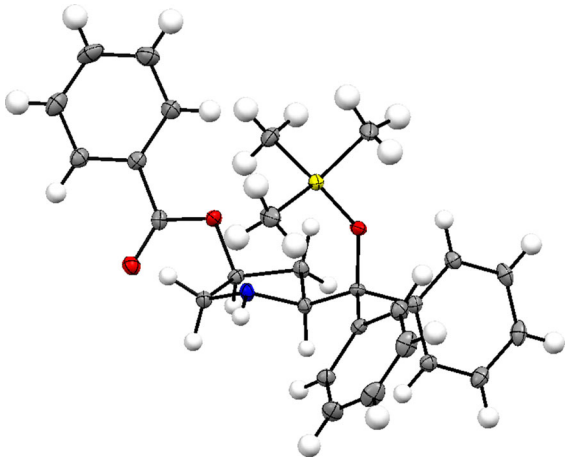
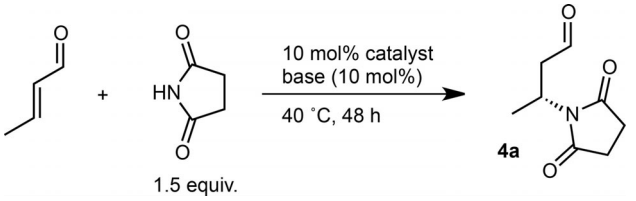


**Figure 2.** X-ray structure of **3bdb**.

of **4a** while maintaining a high *ee*. While reactions at room temperature afforded **4a** in around 35–40% yield, heating up to 40 °C delivered the expected product in the range of 60% yield, without any significant erosion in the *ee*. It was observed again that catalyst **3acc** gave slightly better yields than **3aac** (compare entries 1 and 3, or entries 9 and 11), and all reactions carried out in $CHCl_3$ gave rise to higher yields and *ee* values than those performed in $CH_2Cl_2$. As

**Table 3.** Final screening in the *aza*-Michael reaction.




| Entry | Cat. | Base | Solvent[a] | Yield[b] [%] | *ee*[c] [%] |
|---|---|---|---|---|---|
| 1 | **3aac** | NaOAc | $CH_2Cl_2/H_2O$ | 52 | 87 |
| 2 | **3aac** | NaOAc | $CHCl_3/H_2O$ | 60 | 89 |
| 3 | **3acc** | NaOAc | $CH_2Cl_2/H_2O$ | 61 | 88 |
| 4 | **3acc** | NaOAc | $CHCl_3/H_2O$ | 65 | 89 |
| 5 | **3aac** | NaOAc | $CH_2Cl_2$ | 56 | 88 |
| 6 | **3aac** | NaOAc | $CHCl_3$ | 59 | 89 |
| 7 | **3acc** | NaOAc | $CH_2Cl_2$ | 61 | 88 |
| 8 | **3acc** | NaOAc | $CHCl_3$ | 63 | 89 |
| 9 | **3aac** | lutidine | $CH_2Cl_2/H_2O$ | 57 | 88 |
| 10 | **3aac** | lutidine | $CHCl_3/H_2O$ | 64 | 89 |
| 11 | **3acc** | lutidine | $CH_2Cl_2/H_2O$ | 61 | 87 |
| 12 | **3acc** | lutidine | $CHCl_3/H_2O$ | 66 | 90 |
| 13 | **3aac** | lutidine | $CH_2Cl_2$ | 62 | 89 |
| 14 | **3aac** | lutidine | $CHCl_3$ | 66 | 90 |
| 15 | **3acc** | lutidine | $CH_2Cl_2$ | 66 | 89 |
| 16 | **3acc** | lutidine | $CHCl_3$ | 70 | 90 |

[a] Concentration of the reaction was 0.5 M. When stated, 2 equiv. of water were added to the reaction mixture.
[b] Yield estimated by GC using 4,4-dimethylbiphenyl as internal standard.
[c] Determined by chiral GC analysis.

a summary, we chose lutidine as a base in the absence of water (entry 12 *vs.* 16) and $CHCl_3$ as solvent for the reaction.

At this point, we decided to scrutinize the reaction conditions in a systematic manner to further optimize the yield and enantioselectivity. Two general approaches can be followed for systematic reaction optimization: namely modifying one reaction condition whilst keeping the others constant (one factor at a time approach, OFAT), or the multivariate approach, which implies modifying all of them at the same time in a rational way (design of experiments, DoE). The advantages of the latter approach are: (i) despite the initial load of reactions to perform, it generally requires less experimentation to provide the conclusions; (ii) a mathematical model for the reaction conditions explored (design space) will be provided and, if the model is adequate, it is possible to visualize and predict which could be the results at any point within the design space; and (iii) interactions between reaction parameters (factors, in the DoE terminology), which would be overseen with the OFAT approach, can be detected and taken into account in the search for optimal conditions. Moreover, the appearance of computer-aided tools, such as DoE software has greatly facilitated the interpretation of the results. For all these reasons, multivariate optimization guided by the DoE commercially available software Design Expert® v. 8.0.7.1 from StatEase. Inc. was adopted (details of the analysis of the results of the DoE can be found in the Supporting Information).[33]

**Table 4.** Factors and their ranges studied in the DoE.

| Factor | Ranges to study | Central point |
|---|---|---|
| Temperature [°C] | 15–**35** | 25 |
| Reaction time [h] | 30–**66** | 48 |
| Catalyst loading [mol%] | **10**–20 | 15 |
| Equiv. succinimide | 1.1–**1.9** | 1.5 |
| Equiv. lutidine | **0.1**–0.5 | 0.3 |
| Reaction concentration (M) | **0.25**–0.75 | 0.50 |

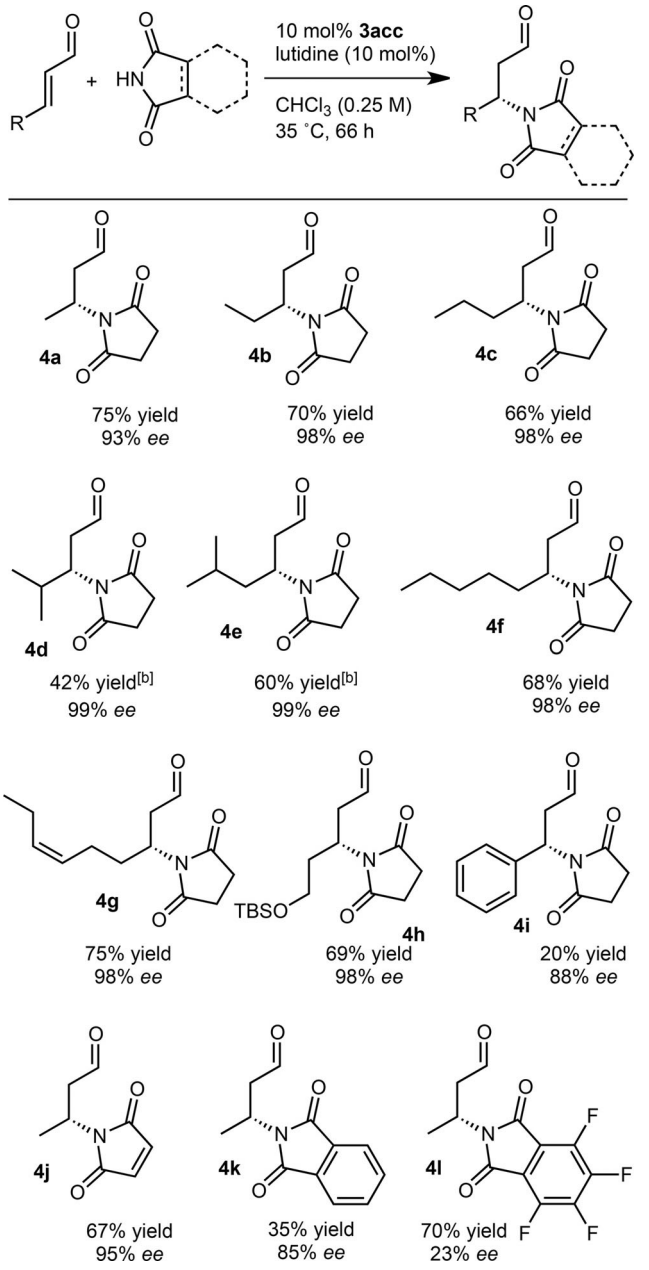
The addition of succinimide to crotonaldehyde catalyzed by diarylprolinols can be impacted by several reaction parameters. We concentrated in optimizing the factors presented in Table 4, and the ranges were selected so that the central conditions were close to those optimized after Table 3.

The optimization focused on two responses, the isolated reaction yield and the enantiomeric excess. In total, 20 experiments were performed, which were run at 1 mmol scale. The results of these experiments showed high variability of the reaction yield depending on the reaction conditions, whereas the results of enantiomeric excesses were always high. In any case, the statistical approach of DoE allows for simultaneously maximizing both responses.

The optimized conditions (highlighted in bold in Table 4) gave rise to **4a** in 75% yield with 93% *ee*. Suitably, these conditions imply that the required amount of the synthesized catalyst **3acc** and of lutidine are at the minimum in the range studied. An additional experiment was performed at a 2 mmol scale and the yield and *ee* were exactly reproduced. An important aspect to take into consideration when working with the DoE approach is that the conclusions are only suitable inside the design space studied, and it is not convenient to extrapolate the trends outside these ranges. For example, seeing that higher amounts of succinimide increased the reaction yield without impacting the *ee*, we decided to add 2.5 equiv. of succinimide to the reaction, keeping all other parameters at their optimal level, but this resulted in a decrease of yield (52%). Remarkably, we have been able to obtain optimal reaction conditions with only 20 experiments out of 64 that would have been required in a full factorial design. Furthermore, we believe that the optimized conditions (lower concentration, minimal amounts of organocatalyst and base, high temperature, etc.) would have been elusive on carrying out the more traditional OFAT approach.

With the optimal conditions in hand, we next evaluated the scope and limitations of **3acc** as a catalyst in the *aza*-Michael reaction (Table 5). Good yields and exquisite *ee* values were recorded when different aliphatic enals were used under the optimized reaction conditions (**4b**, **4c** and **4f**). Branched α,β-unsaturated aldehydes were also tolerated (**4d** and **4e**) as well as aldehydes containing non-conjugated double bonds (**4g**) or other protected functionalities (**4h**). Substrates bearing an α-substituent such as *E*-2,3-dimethylacrolein did not undergo the reaction, probably because steric hindrance precludes the formation of the iminium ion intermediate. Cinnamaldehyde could be employed in the reaction, in contrast with previous studies,[29,34] affording the corresponding product **4i** in modest yield but still good *ee* (88%). Furthermore, other imides such as maleimide (**4j**) and tetrafluorophthalimide were also suitable for the reaction, affording the products in excellent yield although the *ee* value dropped substantially for **4l**. In the case of phthalimide (**4k**), a lower yield was obtained, probably due to its poor solubility in the reaction mixture.

**Table 5.** Scope of the reaction.[a]

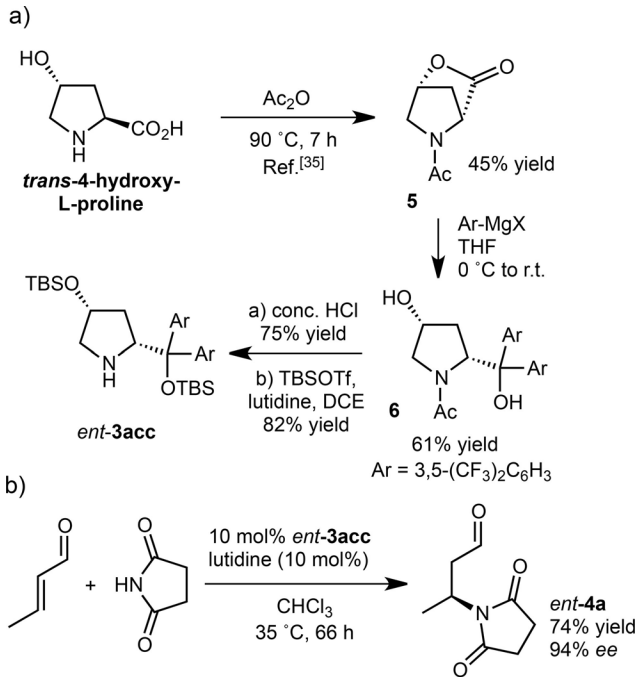



[a] All reactions were carried out at 1 mmol scale; isolated yields were obtained after FCC purification; *ee* values were determined by chiral GC

[b] Reaction time: 7 days.

For a catalytic, enantioselective method to be considered useful, the access to both enantiomers of the final product must be secured at a reasonable cost. This concept has posed some problems in the field of organocatalysis, since various catalyst scaffolds come directly from the chiral pool, with little or no availability of the corresponding enantiomer. Therefore, and as a proof-of-concept, we decided to synthesize the enantiomer of catalyst **3acc**, taking advantage from the elegant work described by La Rosa et al.,[35] in which epimerization of the C-2 center of natural *trans*-4-hydroxy-L-proline[36] was carried out in the presence of acetic anhydride at 90 °C. After opening of the lactone, followed by cleavage of the acetyl group and TBS protection, *ent*-**3acc** (Scheme 2, a) was obtained in good yield (see the Supporting Information).

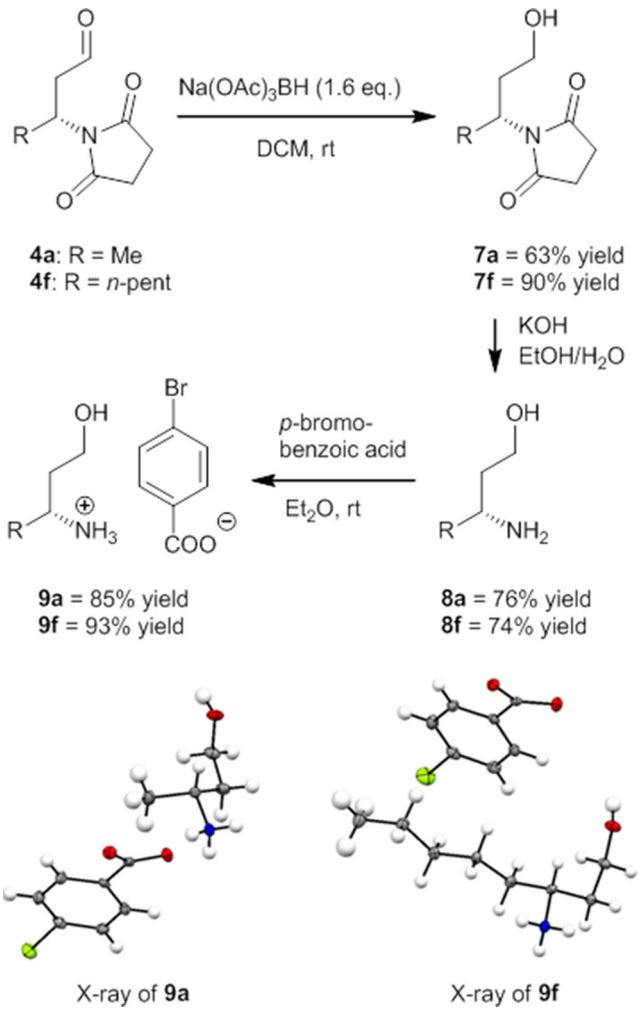
We believe that this synthetic protocol could be further applied to the synthesis of the corresponding enantiomers of the new set of *cis*-4-substituted di-




**Scheme 2.** Synthesis of *ent*-**3acc** and *ent*-**4a**.

alkyl- and diarylprolinols, since the generated lactone can act as a common intermediate for them. When *ent*-**3acc** was used under optimized reaction conditions, *ent*-**4a** was obtained in good yield and excellent *ee* value, displaying the opposite value of optical rotation than that measured for **4a** (Scheme 2, b).

The *aza*-Michael reaction is a useful tool to obtain a wide range of β-amino aldehydes, which can be manipulated conveniently to yield 1,3-amino alcohols (Scheme 3). In the case of **4a**, we found that reduction of the aldehyde functionality with $NaBH_4$ led to complex mixtures, probably as a result of a partial reduction of the imide moiety as well as an intramolecular attack of the resulting alcohol to the imide. This was suppressed by using a milder reducing agent, such as sodium triacetoxyborohydride. In this case, **7a** was obtained in 62% and **7f** in 90% yield. Further cleavage of the succinimide group by a reported protocol[29] gave access to enantiopure 3-amino 1-alcohols **8a** and **8f**. The absolute configuration of these materials was determined through the formation of the corresponding salts with *p*-bromobenzoic acid. In both cases, the




**Scheme 3.** Synthesis of **9a** and **9f**.

X-ray structures confirmed the *R*-configuration of the stereocenter at C-3, in agreement with the proposed model (see Table 2) as well as by comparison with the reported optical rotations. 1,3-Amino alcohols are useful synthetic intermediates and, for example, both **8a**[37] and **8f**[38] or their derivatives have been used in the synthesis of natural products and non-natural alkaloids.

## Conclusions

In summary, we have developed an efficient synthetic route towards *cis*-4-substituted dialkyl- and diarylprolinols, which relies on a scalable Mitsunobu lactonization followed by ring-opening with the corresponding Grignard reagent. A library of 37 members involving three points of diversity has been generated and, by means of a rapid screening performed by HTE, we have been able to identify optimal catalysts for the *aza*-Michael addition of cyclic imides to enals. Remarkably, the *cis*-array of substituents in the pyrrolidine backbone proved to be crucial for high enantioselectivity in the considered reactions. Thus, the highest values of enantioselectivity ever reported for *aza*-Michael reactions between aliphatic α,β-unsaturated aldehydes and succinimide as a nitrogen nucleophile are achieved with the optimal catalyst **3acc**. In view of future practical applications, we have developed a rational design of experiments (DoE) approach which has enabled the localization of a chemical space where yield and enantioselectivity of the *aza*-Michael reactions are simultaneously maximized. According to these findings, *cis*-4-silyloxydiarylprolinols stand as a most promising new type of organocatalysts that further expand the potential of the Jørgensen–Hayashi class. Applications of these species in either homogeneous or immobilized form to other processes involving iminium catalysis are currently under study and will be reported in due course.

## Experimental Section

### General Procedure for the Conjugate Addition of Succinimide to α,β-Unsaturated Aldehydes

Catalyst **3acc** (77 mg, 0.1 mmol), succinimide (188 mg, 1.9 mmol), $CHCl_3$ (4 mL) and 2,6-lutidine (12 μL, 0.1 mmol) were added to a 10-mL vial equipped with a stirring bar. The mixture was stirred at room temperature for 10 min and then the corresponding aldehyde (1 mmol) was added in one portion. The mixture was then stirred at 35 °C for 66 h. Chloroform was evaporated under reduced pressure and the crude reaction mixture was purified by column chromatography on silica gel, eluting with mixtures of $CH_2Cl_2/Et_2O$. The *ee* was determined by GC using chiral columns. **Method A:** β-Dex 120 column, 30×0.25 mm, 0.25 μm, $T = 140$ °C

(hold for 40 min), then rate 20 °C min$^{-1}$ to 230 °C and hold for 20 min. **Method B:** β-Dex 225 column, 30×0.25 mm, 0.25 μm, $T$=140 °C (hold for 60 min), then rate 20 °C min$^{-1}$ to 230 °C and hold for 5 min.

**(*R*)-3-(2,5-Dioxopyrrolidin-1-yl)butanal (4a):** $^1$H NMR (500 MHz, chloroform-*d*): $\delta$=9.69 (t, $J$=1.2 Hz, 1H), 4.76–4.49 (m, 1H), 3.24 (ddd, $J$=18.1, 8.5, 1.4 Hz, 1H), 2.89 (ddd, $J$=18.1, 5.9, 1.0 Hz, 1H), 2.65 (s, 4H), 1.38 (d, $J$=7.0 Hz, 3H); $^{13}$C NMR (125 MHz, chloroform-*d*): $\delta$=199.36, 177.15, 46.43, 42.14, 28.09, 18.02. The *ee* was determined by GC analysis, **Method A** (*R*-isomer=30.1 min, *S*-isomer=30.9 min); $[\alpha]_D^{25}$: +4.8 ($c$=0.5, $CH_2Cl_2$). The spectroscopic data of this compound are consistent with the data available in the literature.[29]

**(*R*)-3-(2,5-Dioxopyrrolidin-1-yl)pentanal (4b):** $^1$H NMR (500 MHz, chloroform-*d*): $\delta$=9.70 (d, $J$=1.3 Hz, 1H), 4.55–4.49 (m, 1H), 3.25 (ddt, $J$=17.9, 9.3, 1.2 Hz, 1H), 2.86 (ddd, $J$=17.9, 5.2, 1.0 Hz, 1H), 2.67 (s, 4H), 1.93 (ddt, $J$=14.6, 9.1, 7.2 Hz, 1H), 1.76–1.66 (m, 1H), 0.85 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (125 MHz, chloroform-*d*): $\delta$=199.56, 177.43, 48.04, 45.12, 28.01, 24.84, 10.79. The *ee* was determined by GC analysis, **Method B** (*R*-isomer=35.5 min, *S*-isomer=39.5 min). $[\alpha]_D^{25}$: +17.5 ($c$=0.5, $CH_2Cl_2$). The spectroscopic data of this compound are consistent with the data available in the literature.[29]

**(*R*)-3-(2,5-Dioxopyrrolidin-1-yl)hexanal (4c):** $^1$H NMR (500 MHz, chloroform-*d*): $\delta$=9.68 (t, $J$=1.3 Hz, 1H), 4.60 (tt, $J$=9.3, 5.5 Hz, 1H), 3.22 (ddd, $J$=18.0, 9.1, 1.6 Hz, 1H), 2.84 (ddd, $J$=18.0, 5.2, 1.1 Hz, 1H), 2.64 (s, 4H), 1.92 (dtd, $J$=13.7, 9.5, 5.7 Hz, 1H), 1.59 (dddd, $J$=13.7, 9.8, 6.4, 5.6 Hz, 1H), 1.29–1.13 (m, 2H), 0.89 (t, $J$=7.3 Hz, 3H); $^{13}$C NMR (125 MHz, chloroform-*d*): $\delta$=199.55, 177.37, 46.33, 45.39, 33.73, 28.02, 19.53, 13.65. The *ee* was determined by GC analysis, **Method B** (*R*-isomer=44.2 min, *S*-isomer=46.4 min). $[\alpha]_D^{25}$: +17.5 ($c$=0.5, $CH_2Cl_2$). The spectroscopic data of this compound are consistent with the data available in the literature.[29]

**(*S*)-3-(2,5-Dioxopyrrolidin-1-yl)-4-methylpentanal (4d):** $^1$H NMR (500 MHz, chloroform-*d*): $\delta$=9.68 (dd, $J$=1.9, 0.9 Hz, 1H), 4.22 (td, $J$=10.2, 4.0 Hz, 1H), 3.33 (ddd, $J$=17.8, 10.5, 1.9 Hz, 1H), 2.83 (ddd, $J$=17.8, 4.0, 0.9 Hz, 1H), 2.65 (s, 4H), 2.27 (dp, $J$=9.7, 6.7 Hz, 1H), 0.96 (d, $J$=6.7 Hz, 3H), 0.80 (d, $J$=6.7 Hz, 3H); $^{13}$C NMR (125 MHz, chloroform-*d*): $\delta$=199.88, 177.51, 52.63, 43.09, 29.60, 27.95, 19.98, 19.58. The *ee* was determined by GC analysis, **Method B** (*R*-isomer=190.8 min, *S*-isomer=200.5 min). $[\alpha]_D^{25}$: +15.5 ($c$=0.5, $CH_2Cl_2$); HR-MS: $m/z$=220.0940, calcd. for $C_{10}H_{15}NNaO_3$: 220.0944 $[M+Na]^+$; FT-IR (neat): $\nu$=2966, 2876, 1771, 1692, 1390, 1369, 1182 cm$^{-1}$.

**(*R*)-3-(2,5-Dioxopyrrolidin-1-yl)-5-methylhexanal (4e):** $^1$H NMR (500 MHz, chloroform-*d*): $\delta$=9.67 (t, $J$=1.4 Hz, 1H), 4.68 (ddt, $J$=10.0, 9.0, 5.0 Hz, 1H), 3.19 (ddd, $J$=17.8, 9.1, 1.7 Hz, 1H), 2.80 (ddd, $J$=17.8, 5.3, 1.1 Hz, 1H), 2.64 (s, 4H), 2.01–1.90 (m, 1H), 1.42–1.33 (m, 2H), 0.91 (d, $J$=6.1 Hz, 3H), 0.87 (d, $J$=6.3 Hz, 3H); $^{13}$C NMR (125 MHz, chloroform-*d*): $\delta$=199.56, 177.34, 45.69, 44.78, 40.46, 28.04, 25.12, 23.00, 21.93. The *ee* was determined by GC analysis, **Method B** (*R*-isomer=46.4 min, *S*-isomer=47.9 min). $[\alpha]_D^{25}$: +30.0 ($c$=0.5, $CH_2Cl_2$); HR-MS: $m/z$=234.1102, calcd. for $C_{11}H_{17}NNaO_3$: 234.1101 $[M+Na]^+$; FT-IR (neat): $\nu$=2961, 2872, 1770, 1689, 1367, 1176 cm$^{-1}$.

**(*R*)-3-(2,5-Dioxopyrrolidin-1-yl)octanal (4f):** $^1$H NMR (400 MHz, chloroform-*d*): $\delta$=9.69 (t, $J$=1.3 Hz, 1H), 4.58 (tt, $J$=9.3, 5.5 Hz, 1H), 3.23 (ddd, $J$=17.9, 9.2, 1.6 Hz, 1H), 2.84 (ddd, $J$=17.9, 5.2, 1.0 Hz, 1H), 2.65 (s, 4H), 1.92 (dtd, $J$=13.7, 9.6, 5.2 Hz, 1H), 1.62 (ddt, $J$=13.6, 10.9, 5.5 Hz, 1H), 1.31–1.11 (m, 6H), 0.88–0.81 (m, 3H); $^{13}$C NMR (100 MHz, chloroform-*d*): $\delta$=199.56, 177.37, 46.63, 45.42, 31.63, 31.35, 28.04, 25.97, 22.55, 14.06. The *ee* was determined by GC analysis, **Method B** (*R*-isomer=104.9 min, *S*-isomer=109.5 min). $[\alpha]_D^{25}$: +26.3 ($c$=0.5, $CH_2Cl_2$); HR-MS: $m/z$=248.1245, calcd. for $C_{12}H_{19}NNaO_3$: 248.1257 $[M+Na]^+$; FT-IR (neat): $\nu$=2930, 2860, 1772, 1694, 1396, 1369, 1176 cm$^{-1}$.

**(*R*)-(*Z*)-3-(2,5-Dioxopyrrolidin-1-yl)non-6-enal (4g):** $^1$H NMR (500 MHz, chloroform-*d*): $\delta$=9.69 (t, $J$=1.3 Hz, 1H), 5.42–5.33 (m, 1H), 5.24 (dtt, $J$=10.4, 6.9, 1.6 Hz, 1H), 4.62 (tt, $J$=9.2, 5.4 Hz, 1H), 3.22 (ddd, $J$=17.9, 9.1, 1.7 Hz, 1H), 2.85 (ddd, $J$=17.9, 5.3, 1.0 Hz, 1H), 2.65 (s, 4H), 2.10–1.93 (m, 5H), 1.75–1.66 (m, 1H), 0.93 (t, $J$=7.6 Hz, 3H); $^{13}$C NMR (125 MHz, chloroform-*d*): $\delta$=199.37, 177.32, 133.03, 127.21, 46.48, 45.45, 31.54, 28.05, 24.11, 20.68, 14.34. The *ee* was determined by GC analysis, **Method B** (*R*-isomer=165.9 min, *S*-isomer=173.9 min). $[\alpha]_D^{25}$: +27.3 ($c$=0.5, $CH_2Cl_2$). The spectroscopic data of this compound are consistent with the data available in the literature.[29]

**(*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-3-(2,5-dioxopyrrolidin-1-yl)pentanal (4h):** $^1$H NMR (500 MHz, chloroform-*d*): $\delta$=9.69 (dd, $J$=1.8, 1.2 Hz, 1H), 4.79 (tt, $J$=9.0, 5.6 Hz, 1H), 3.60 (qdd, $J$=10.7, 6.8, 4.9 Hz, 2H), 3.19 (ddd, $J$=17.7, 9.1, 1.8 Hz, 1H), 2.90 (ddd, $J$=17.7, 5.3, 1.1 Hz, 1H), 2.63 (s, 4H), 2.14 (dddd, $J$=13.9, 9.0, 6.5, 4.8 Hz, 1H), 1.89 (dddd, $J$=14.1, 7.0, 5.8, 5.0 Hz, 1H), 0.87 (s, 9H), 0.01 (s, 6H); $^{13}$C NMR (125 MHz, chloroform-*d*): $\delta$=199.56, 177.22, 60.35, 45.50, 44.45, 34.41, 28.08, 26.00, 18.41, −5.33, −5.37. The *ee* was determined by GC analysis, **Method B** (*R*-isomer=105.6 min, *S*-isomer=107.7 min). $[\alpha]_D^{25}$: +19.0 ($c$=0.5, $CH_2Cl_2$). The spectroscopic data of this compound are consistent with the data available in the literature.[29]

**(*S*)-3-(2,5-Dioxopyrrolidin-1-yl)-3-phenylpropanal (4i):** $^1$H NMR (500 MHz, chloroform-*d*): $\delta$=9.74 (t, $J$=0.8 Hz, 1H), 7.48–7.45 (m, 2H), 7.35–7.27 (m, 4H), 5.72 (dd, $J$=9.9, 5.5 Hz, 1H), 3.93 (ddd, $J$=18.5, 9.9, 1.1 Hz, 1H), 3.26 (ddd, $J$=18.6, 5.5, 0.7 Hz, 1H), 2.64 (s, 4H); $^{13}$C NMR (125 MHz, chloroform-*d*): $\delta$=198.81, 177.15, 138.12, 128.93, 128.53, 128.03, 49.69, 44.42, 28.10. The *ee* was determined by UPC$^2$, using an IC column with $CO_2$/*i*-PrOH=90:10, P=1500 psi, flow=3 mL min$^{-1}$ (*R*-isomer=2.4 min, *S*-isomer=2.6 min). $[\alpha]_D^{25}$: −5.1 ($c$=0.5, $CH_2Cl_2$); HR-MS: $m/z$=254.0784, calcd. for $C_{13}H_{13}NNaO_3$: 254.0788 $[M+Na]^+$; FT-IR (neat): $\nu$=3402, 1772, 1694, 1391, 1363, 1173 cm$^{-1}$.

**(*R*)-3-(2,5-Dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)butanal (4j):** $^1$H NMR (500 MHz, chloroform-*d*): $\delta$=9.70 (t, $J$=1.2 Hz, 1H), 6.64 (s, 2H), 4.78–4.61 (m, 1H), 3.18 (ddd, $J$=17.9, 8.4, 1.4 Hz, 1H), 2.89 (ddd, $J$=18.0, 6.1, 1.1 Hz, 1H), 1.39 (d, $J$=6.9 Hz, 3H); $^{13}$C NMR (125 MHz, chloroform-*d*): $\delta$=199.26, 170.57, 134.16, 47.36, 41.41, 19.00. The *ee* was determined by GC analysis, **Method B** (*R*-isomer=12.7 min, *S*-isomer=13.3 min). $[\alpha]_D^{25}$: +12.6 ($c$=0.5, $CH_2Cl_2$); HR-MS: $m/z$=190.0475, calcd. for $C_8H_9NNaO_3$: 190.0475 $[M+Na]^+$; FT-IR (neat): $\nu$=3102, 2941, 1696, 1404, 1367, 1173, 829, 694 cm$^{-1}$.

**(*R*)-3-(1,3-Dioxoisoindolin-2-yl)butanal (4k):** $^1$H NMR (500 MHz, chloroform-*d*): $\delta$=9.75 (t, $J$=1.3 Hz, 1H), 7.82

(dd, $J$ = 5.4, 3.1 Hz, 2H), 7.74–7.67 (m, 2H), 4.91 (dqd, $J$ = 8.1, 6.9, 6.1 Hz, 1H), 3.30 (ddd, $J$ = 18.0, 8.2, 1.4 Hz, 1H), 3.01 (ddd, $J$ = 18.0, 6.2, 1.1 Hz, 1H), 1.50 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, chloroform-*d*): $\delta$ = 199.45, 168.22, 134.16, 131.97, 123.39, 47.50, 41.53, 18.99. The *ee* was determined by GC analysis, **Method B** (*R*-isomer = 112.6 min, *S*-isomer = 116.2 min). $[\alpha]_D^{25}$: +3.4 ($c$ = 0.5, $CH_2Cl_2$); HR-MS: $m/z$ = 240.0633, calcd. for $C_{12}H_{11}NNaO_3$: 240.0631 $[M+Na]^+$; FT-IR (neat): $\nu$ = 3046, 2991, 2862, 1769, 1718, 1703, 1390, 1375, 1359, 1334, 1032, 719 cm$^{-1}$.

**(*R*)-3-(4,5,6,7-Tetrafluoro-1,3-dioxoisoindolin-2-yl)butanal (4l):** $^1$H NMR (500 MHz, chloroform-*d*): $\delta$ = 9.73 (t, $J$ = 0.9 Hz, 1H), 4.84 (dqd, $J$ = 8.9, 6.9, 5.6 Hz, 1H), 3.35 (ddd, $J$ = 18.5, 8.8, 1.1 Hz, 1H), 2.97 (ddd, $J$ = 18.5, 5.7, 0.8 Hz, 1H), 1.47 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, chloroform-*d*): $\delta$ = 198.82, 162.31, 145.2 (m, C-F), 143.58 (m, C-F), 113.67 (m), 46.78, 42.41, 18.79; $^{19}$F NMR (376 MHz, chloroform-*d*): $\delta$ = −136.02 (q, $J$ = 9.4 Hz), −142.40 (q, $J$ = 9.4 Hz). The *ee* was determined by GC analysis, **Method B** (*R*-isomer = 96.2 min, *S*-isomer = 112.4 min). $[\alpha]_D^{25}$: +4.0 ($c$ = 0.5, $CH_2Cl_2$); HR-MS: $m/z$ = 312.0269, calcd. for $C_{12}H_7F_4NNaO_3$: 312.0254 $[M+Na]^+$; FT-IR (neat): $\nu$ = 2914, 2848, 1789, 1707, 1497, 1410, 1362, 1038, 939 cm$^{-1}$.

**(*S*)-3-(2,5-Dioxopyrrolidin-1-yl)butanal (*ent*-4a):** The spectroscopic data match those of its enantiomer; $^1$H NMR (500 MHz, chloroform-*d*): $\delta$ = 9.69 (t, $J$ = 1.2 Hz, 1H), 4.76–4.49 (m, 1H), 3.24 (ddd, $J$ = 18.1, 8.5, 1.4 Hz, 1H), 2.89 (ddd, $J$ = 18.1, 5.9, 1.0 Hz, 1H), 2.65 (s, 4H), 1.38 (d, $J$ = 7.0 Hz, 3H). The *ee* was determined by GC analysis, **Method A** (*R*-isomer = 31.1 min, *S*-isomer = 32.1 min); $[\alpha]_D^{25}$: −6.0 ($c$ = 0.5, $CH_2Cl_2$).

### Crystal Data

CCDC 1528369 (**1**), CCDC 1528367 (**2a**), CCDC 1528368 (**3bdb**) CCDC 1528365 (**9a**) and CCDC 1528366 (**9f**) contain 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.

### Supporting Information

Synthetic procedures, characterization data, copies of NMR spectra, GC chromatograms, ANOVA analysis, graphics and predictions from the DoE are presented in the Supporting Information.

## Acknowledgements

*We are grateful to Àlex Cristòfol and Dídac Salvadó for testing the scalability of the preferred catalyst. The authors want to acknowledge the help provided by the Research Support Unit at ICIQ, with particular mention to HTE and Dr. Xisco Caldentey, Chromatography, X-Ray, Mass Spectrometry and NMR units. We thank CERCA Programme/Generalitat de Catalunya and the CELLEX foundation for financial support. We also thank MINECO for a Severo Ochoa Excellence Accreditation 2014–2018 (SEV-2013–0319) and for the Grant CTQ2015- 69136-R. AF thanks the CELLEX foundation for a post-doctoral fellowship.*

## References

[1] For recent reviews on organocatalysis state-of-the-art, see: a) J. Burés, A. Armstrong, D. G. Blackmond, *Acc. Chem. Res.* **2016**, *49*, 214–222; b) M. Holland, R. Gilmour, *Angew. Chem.* **2015**, *127*, 3934–3943; *Angew. Chem. Int. Ed.* **2015**, *54*, 3862–3871; c) P. Chauchan, S. Mahajan, U. Kaya, D. Hacki, D. Enders, *Adv. Synth. Catal.* **2015**, *357*, 253–281; d) X. Fang, C.-J. Wang, *Chem. Commun.* **2015**, *51*, 1185–1197; e) Y. Wang, H. Lu, P.-F. Xu, *Acc. Chem. Res.* **2015**, *48*, 1832–1844; f) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9047–9153; g) C. M. R. Volla, I. Atodiresei, M. Rueping, *Chem. Rev.* **2014**, *114*, 2390–2431.

[2] For a selection of recent representative reviews about diarylprolinol catalysts, see: a) B. S. Donslund, T. K. Johansen, P. H. Poulsen, K. S. Halskov, K. A. Jørgensen, *Angew. Chem.* **2015**, *127*, 14066–14081; *Angew. Chem. Int. Ed.* **2015**, *54*, 13860–13874; b) H. Gotoh, Y. Hayashi, in: *Sustainable Catalysis: Challenges and Practices for the Pharmaceutical and Fine Chemical Industries*, (Eds.: P. J. Dunn, K. K. Hii, M. J. Krische, M. T. Williams), John Wiley & Sons, Inc., **2013**, pp 287–316; c) K. L. Jensen, G. Dickmeiss, H. Jiang, Ł. Albrecht, K. A. Jørgensen, *Acc. Chem. Res.* **2012**, *45*, 248–264.

[3] M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804–807; *Angew. Chem. Int. Ed.* **2005**, *44*, 794–797.

[4] M. Marigo, D. Fielenbach, A. Brauton, A. Kjærsgaard, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 3769–3772; *Angew. Chem. Int. Ed.* **2005**, *44*, 3703–3706.

[5] J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304.

[6] a) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284–4287; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215; For an example on the use of dialkylprolinols in Michael reactions, see: b) C. Palomo, A. Landa, A. Mielgo, M. Oiarbide, A. Puente, S. Vera, *Angew. Chem.* **2007**, *119*, 8583–8587; *Angew. Chem. Int. Ed.* **2007**, *46*, 8431–8435.

[7] a) S. Wang, C. Rodríguez-Escrich, M. A. Pericàs, *Org. Lett.* **2016**, *18*, 556–559; b) Z.-J. Jia, H. Jiang, J.-L. Li, B. Gschwend, Q. Z. Li, X. Yin, J. Grouleff, Y.-C. Chen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2011**, *133*, 5053–5061.

[8] M. Marigo, J. Franzén, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 6964–6965.

[9] J. Vesely, I. Ibrahem, G.-L. Zhao, R. Rios, A. Córdova, *Angew. Chem.* **2007**, *119*, 792–795; *Angew. Chem. Int. Ed.* **2007**, *46*, 778–781.

[10] a) C. Sparr, W. B. Schweizer, H. M. Senn, R. Gilmour, *Angew. Chem.* **2009**, *121*, 3111–3114; *Angew. Chem. Int. Ed.* **2009**, *48*, 3065–3068; b) I. G. Molnár, E.-M. Tanzer, C. Daniliuc, R. Gilmour, *Chem. Eur. J.* **2014**, *20*, 794–800.

[11] T. Ishino, T. Oriyama, *Chem. Lett.* **2007**, *36*, 550–551.

[12] H. Sato, F. Nagashima, T. Oriyama, *Chem. Lett.* **2010**, *39*, 379–381.

[13] M. Chao, Z.-J. Jia, J.-X. Liu, Q.-Q. Zhou, L. Dong, Y.-C. Chen, *Angew. Chem.* **2013**, *125*, 982–985; *Angew. Chem. Int. Ed.* **2013**, *52*, 948–951.

[14] K. S. Halskov, F. Kniep, V. H. Lauridsen, E. H. Iversen, B. S. Donslund, K. A. Jørgensen, *J. Am. Chem. Soc.* **2015**, *137*, 1685–1691.
[15] L. Caruana, F. Kniep, T. K. Johansen, P. H. Poulsen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2014**, *136*, 15929–15932.
[16] a) C. Ayats, A. H. Henseler, M. A. Pericàs, *ChemSusChem* **2012**, *5*, 320–325; b) P. Llanes, S. Sayalero, C. Rodríguez-Escrich, M. A. Pericàs, *Green Chem.* **2016**, *18*, 3507–3512.
[17] R. Martín-Rapún, S. Sayalero, C. Rodríguez-Escrich, M. A. Pericàs, *Green Chem.* **2013**, *15*, 3295–3301.
[18] a) E. Alza, M. A. Pericàs, *Adv. Synth. Catal.* **2009**, *351*, 3051–3056; b) E. Alza, S. Sayalero, P. Kasaplar, D. Almaşi, M. A. Pericàs, *Chem. Eur. J.* **2011**, *17*, 11585–11595.
[19] X. Fan, S. Sayalero, C. Rodríguez-Escrich, M. A. Pericàs, *Adv. Synth. Catal.* **2012**, *354*, 2971–2976.
[20] For a precedent, see: D. S. Kemp, T. P. Curran, *J. Org. Chem.* **1988**, *53*, 5729–5731.
[21] a) M. Lombardo, E. Montroni, A. Quintavalla, C. Trombini, *Adv. Synth. Catal.* **2012**, *354*, 3428–3434; b) M. Lombardo, L. Cerisoli, E. Manoni, E. Montroni, A. Quintavalla, C. Trombini, *Eur. J. Org. Chem.* **2014**, 5946–5953.
[22] Y. Li, X. Liu, G. Zhao, *J. Org. Chem.* **2007**, *72*, 288–291.
[23] C. Zheng, Y. Lu, J. Zhang, X. Chen, Z. Chai, W. Ma, G. Zhao, *Chem. Eur. J.* **2010**, *16*, 5853–5857.
[24] O. V. Maltsev, A. S. Kucherenko, I. P. Beletskaya, V. A. Tartakovsky, S. G. Zlotin, *Eur. J. Org. Chem.* **2010**, 2927–2933.
[25] There is one example in which *N*-protected diarylprolinols act as ligands in the addition of $Me_2Zn$ to α-keto esters: K. Funabashi, M. Jachmann, M. Kanai, M. Shibasaki, *Angew. Chem.* **2003**, *115*, 5647–5650; *Angew. Chem. Int. Ed.* **2003**, *42*, 5489–5492.
[26] a) M. M. Bowers-Nemia, M. M. Joullié, *Heterocycles* **1983**, *20*, 817–828; b) J. Seo, P. Martásek, L. J. Roman, R. B. Silverman, *Bioorg. Med. Chem.* **2007**, *15*, 1928–1938.
[27] A. Krasovskiy, P. Knochel, *Angew. Chem.* **2004**, *116*, 3396–3399; *Angew. Chem. Int. Ed.* **2004**, *43*, 3333–3336.
[28] For recent reviews on the *aza*-Michael addition reaction, see: a) M. Sánchez-Roselló, J. L. Aceña, A. Simón-Fuentes, C. del Pozo, *Chem. Soc. Rev.* **2014**, *43*, 7430–7453; b) J. Wang, P. Li, P. Y. Choy, A. S. C. Chan, F. Y. Kwong, *ChemCatChem* **2012**, *4*, 917–925; c) E. Enders, C. Wang, J. X. Liebich, *Chem. Eur. J.* **2009**, *15*, 11058–11076.
[29] H. Jiang, J. B. Nielsen, M. Nielsen, K. A. Jørgensen, *Chem. Eur. J.* **2007**, *13*, 9068–9075.
[30] For recent reviews on HTE state-of-the-art, see: a) W. Schafer, X. Bu, X. Gong, L. A. Joyce, C. J. Welch, in: *Comprehensive Organic Synthesis*, 2nd edn., Vol. 9, (Eds. P. Knochel, G. A. Molander), Elsevier, B.V., **2014**, pp 28–53; b) J. R. Schmink, A. Bellomo, S. Berritt, *Aldrichimica Acta* **2013**, *46*, 71–80; c) S. Monfette, J. M. Blacquiere, D. E. Fogg, *Organometallics* **2011**, *30*, 36–42.
[31] Selected examples of HTE screenings: a) A. Bellomo, J. Zhang, N. Trongsiriwat, P. J. Walsh, *Chem. Sci.* **2013**, *4*, 849–857; b) A. Bellomo, N. Celebi-Olcum, X. Bu, N. Rivera, R. T. Ruck, C. J. Welch, K. N. Houk, S. D. Dreher, *Angew. Chem.* **2012**, *124*, 7018–7021; *Angew. Chem. Int. Ed.* **2012**, *51*, 6912–6915.
[32] A. McNally, C. K. Prier, D. W. C. MacMillan, *Science* **2011**, *334*, 1114–1117.
[33] S. A. Weissman, N. G. Anderson, *Org. Process Res. Dev.* **2015**, *19*, 1605–1633.
[34] S. Ma, M. Liu, Y. Huang, Y. Wang, *Chin. J. Chem.* **2013**, *31*, 726–730.
[35] P. Dalla Croce, C. La Rosa, *Tetrahedron: Asymmetry* **2002**, *13*, 197–201.
[36] We decided to use natural (2*S*,4*R*)-*trans*-4-hydroxy-L-proline to prepare both **3acc** and *ent*-**3acc**. Alternatively, *ent*-**3acc** could be prepared from the non-natural enantiomer (2*R*,4*S*)-*trans*-4-hydroxy-D-proline, but its price is much less affordable (5.98 €/g compared to 259 €/g; source: www.sigmaaldrich.com).
[37] For some examples of the use of **8a** and its derivatives in synthesis, see: synthesis of α-methylspermidine: a) N. A. Grigorenko, J. Vepsalainen, A. Jarvinen, T. A. Keinanen, L. Alhonen, J. Janne, A. M. Kritsyn, A. R. Khomutov, *Russ. J. Bioorg. Chem.* **2004**, *30*, 396–399; synthesis of α-methyl- and α,α′-dimethylspermine: b) N. A. Grigorenko, J. Vepsalainen, A. Jarvinen, T. A. Keinanen, L. Alhonen, J. Janne, A. R. Khomutov, *Russ. J. Bioorg. Chem.* **2005**, *31*, 183–188; synthesis of natural alkaloid (*R*)-pipecoline: c) J. Etxebarria, J. L. Vicario, D. Badía, L. Carrillo, *Tetrahedron* **2007**, *63*, 11421–11428; synthesis of natural alkaloids (−)-GB 13 and (+)-GB 16: d) W. Zi, S. Yu, D. Ma, *Angew. Chem.* **2010**, *122*, 6023–6026; *Angew. Chem. Int. Ed.* **2010**, *49*, 5887–5890.
[38] For some examples of the use of **8f** and its derivatives in synthesis see: synthesis of natural alkaloid (−)-indolizidine 209B and isomers: a) J. P. Michael, D. Gravestock, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1919–1928; synthesis of natural alkaloid (−)-indolizidine 209B: b) D. Ma, X. Pu, J. Wang, *Tetrahedron: Asymmetry* **2002**, *13*, 2257–2260; synthesis of non-natural alkaloids: c) G. Cai, W. Zhu, D. Ma, *Tetrahedron* **2006**, *62*, 5697–5708.