New Synthesis of –α,αDisubstituted –βAmino Acid –^{2,2}β(Amino Acid) *N*-Carboxy Anhydrides Relying on Sequential Brønsted Base Catalyzed Enantioselective C(4)-Functionalization of Pyrrolidin-2,3-diones and Regioselective Baeyer-Villiger Oxidation

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Abstract: A catalytic enantioselective entry to β^{2,2}-amino acids enabling their direct coupling with nucleophiles is described. The approach is based upon an effective bifunctional Brønsted base catalyzed construction of a quaternary carbon stereocenter at C_4 position of pyrrolidin-2,3-diones. Subsequent regioselective Baeyer-Villiger rearrangement of the resultant adducts gives β^{2,2}-amino acid *N*-carboxy anhydrides as the reactive species, which can further react with nucleophiles. Following this strategy both, β^{2,2}-amino acid derivatives with different functionalities at the newly created stereocenter, and spirocyclic structures can be efficiently prepared.

Introduction

Construction of tetrasubstituted carbon stereocenters, particularly all carbon quaternary stereogenic centers is an important challenging goal within the domain of asymmetric synthesis.[1] A representative example is the catalytic enantioselective synthesis of α.α-disubstituted α-amino acids. Given their stability and conformational properties when incorporated into peptides, their synthesis has focused much attention over the years.[2] β-Amino acids, on the other hand, constitute another example of this interest, not only they are important building blocks for a wide variety of natural products and pharmaceutical agents, but also mimics of protein structural motifs.[3] They are also precursors of β-lactams, structural key units of the most significant class of antibiotics.[4] β-Amino acids may be classified, Figure 1, into β^2-, β^3- and β^{2,3}-amino acids depending upon the position of the R substituent. To date several methods to synthesize these types of β-amino acids with different substitution patterns exist.[5] However, despite their interest, catalytic enantioselective entries to β^{2,2}-amino acids, the homologous of α.α-disubstituted α-amino acids, are currently

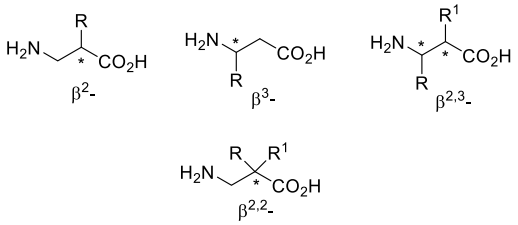
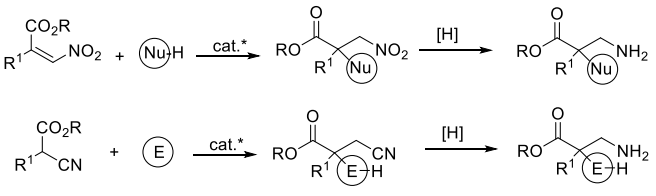


Figure 1. Different types of β-amino acids.

very limited.[6] The most frequently employed methods to synthesize β-amino acids involve the catalytic asymmetric hydrogenation of β-dehydroamino acids, the Mannich reaction and the conjugate addition of carbon nucleophiles to α,β-unsaturated systems. However, only the latter has proven to be effective for the catalytic enantioselective construction of β^{2,2}-amino acids with an all carbon quaternary streocenter. Whilst the former approach cannot be used to synthesize β^{2,2}-amino acids, catalytic Mannich reactions have been hampered by the usual unstability of formaldehyde derived imines.[7] A literature search indicates that conjugate addition of nucleophiles to β-nitroacrylates,[8,9] and the reaction of α-cyanoacetates with Michael acceptors,[10] are effective catalytic enantioselective methods for the production of β^{2,2}-amino acids with a quaternary carbon stereocenter (Scheme 1). Several other reaction types have also been reported for the synthesis of β^{2,2}-amino acids. For instance, the Henry reaction of nitromethane with α-keto esters,[11] the catalytic asymmetric acylation of (silyloxy) nitrile



Scheme 1. Catalytic enantioselective approaches to β^{2,2}-amino acid derivatives through conjugate addition reactions.

anions[12] and Sharpless dihydroxylation of α,α-disubstituted acrylates and subsequent amino group installation.[13] However, in these cases, α-hydroxy β^{2,2}-amino acids may be produced only. Besides this narrow range of enantioselective methods,[14] there is the fact that they are generally accompanied by two general drawbacks, i) the need for functional nitro and cyano group reductions to get the corresponding β-amino acid derivative, and ii) the need for several protection/deprotection/activation steps for the incorporation of the resultant β^{2,2}-amino esters into a peptide segment and/or transformation into a more complex product, thus

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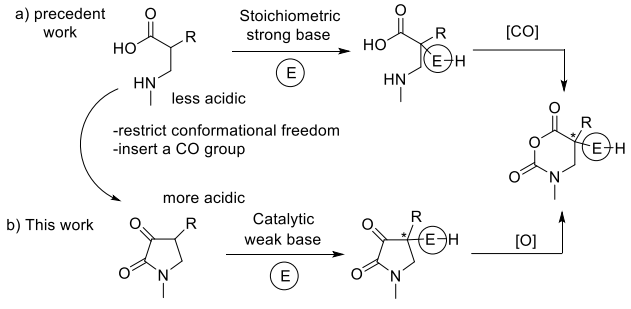
complicating somewhat the process. In this respect, while there is much room for improvement, new approaches to quaternary $\beta^{2,2}$-amino acids are clearly needed. We have addressed these issues and we report here a concise novel entry for the catalytic asymmetric synthesis of $\beta^{2,2}$-amino acid derivatives that may directly be combined with a nucleophile coupling step.

The approach is very simple and is founded upon two key elements, the design and identification of pyrrolidin-2,3-diones, *vide infra*, enabling catalytic enantioselective generation of an all-carbon quaternary stereocenter at C(4) position of the heterocycle and their subsequent ring enlargement through a regioselective oxygen insertion between both carbonyl groups to produce β-amino acid *N*-carboxy anhydrides (β-NCAs).That is, for the first time, these activated forms of β-amino acids may be produced from a non β-amino acid precursor.[15]

Results and Discussion

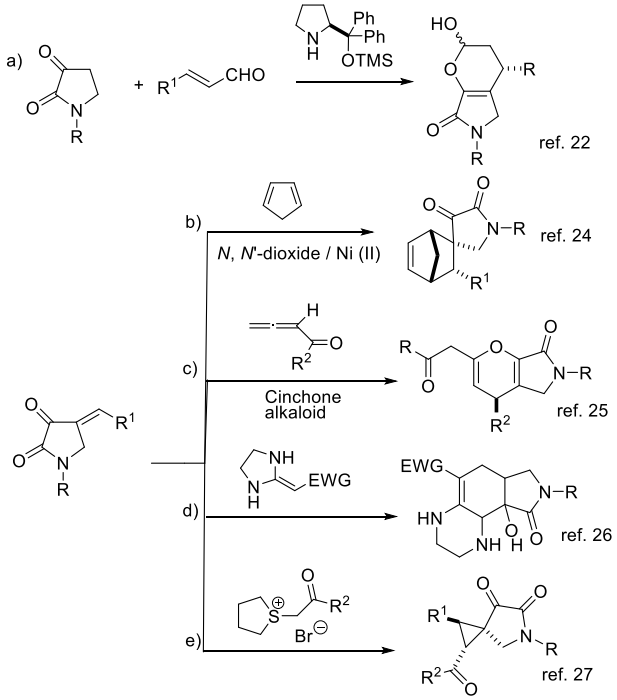
Background and working plan: Probably, one of the most direct access to $\beta^{2,2}$-amino acids would be the catalytic enantioselective nucleophilic α-functionalization of α-branched β-amino acids, Scheme 2a. However, enolization of a β–amino acid derivative by a soft Brønsted base is difficult owing to the low acidity of the α–carbon and generally a stoichiometric (or more) amount of strong base is required. Although only efficient with reactive alkyl halides (ie, benzylic halides), an attractive approach, in this context, is the phase-transfer catalytic alkylation of 2-phenyl-2-imidazoline-4-carboxylic acid esters.[16] However, only α,β–diamino acids may be obtained using this approach. In fact, given the literature precedents noted above, the catalytic enantioselective synthesis of $\beta^{2,2}$-amino acids is still underdeveloped.

We considered the possibility to address this deficiency by installing a carbonyl moiety adjacent to the carboxyl group in the



Scheme 2. Common (a) and designed (b) approaches to $\beta^{2,2}$-amino amino acid *N*-carboxy anhydrides.

starting β-amino acid, Scheme 2b, which would result in a more reactive 1,2-dicarbonyl compound.[17] Moreover, forming and intramolecular amide bond would result in an even more acidic compound, a pyrrolidin-2,3-dione. Actually, C(4)-substituted pyrrolidin-2,3-diones have a pronounced tendency to enolization,[18] and therefore a weak Brønsted base might be sufficient for enolate generation to promote the reaction with an electrophile under catalytic conditions and, moreover, the resultant 4,4-disubstituted adducts could be transformed, on the basis of previous work from this laboratory,[19] into *N*-carboxy anhydrides, thereby enabling subsequent couplings with nucleophiles. Nonetheless, even assuming these reasonable hypotheses, successful implementation of the idea would require effective control of reaction stereochemistry during the key C-C bond catalytic forming event. Whilst pyrrolidin-2,3-diones are the core of several natural products and drugs[20] and are excellent building-blocks of α–alkylidene γ-lactams and derived products,[21] their general use is hampered by the paucity of existing methodology to build up chiral products by asymmetric catalysis. In this context, Xu et al.[22] reported the reaction of 4-unsubstituted pyrrolidin-2,3-diones with α,β-enals via iminium catalysis but spontaneous hemiketal formation makes this method unsuitable for generation of quaternary stereogenic centers at C(4) (Scheme 3a). To date, methodology for the stereoselective construction of 4,4-disubstituted pyrrolidin-2,3- diones either from 4-unsubstituted or 4-alkyl pyrrolidin-2,3- diones has not been yet described. The most probable reason of this gap is the tendency of pyrrolidin-2,3-diones to undoergo self aldol condensation under basic or acid catalysis.[23] Not surprisingly, pyrrolidin-2,3-diones have been mainly employed in a few cycloaddition reactions, either racemic or asymmetric, through their C(4)-alkylidene derivatives. Ling and Feng[24]

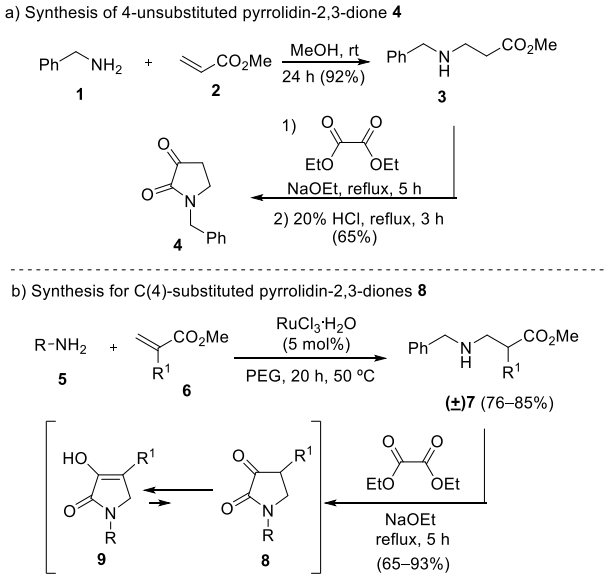


Scheme 3. Catalytic reactions of pyrrolidin-2,3-diones.

described a Diels-Alder reaction of C(4)-alkylidene pyrrolidin-2,3-diones with cyclopentadiene promoted by a chiral *N*,*N*'-dioxide/Ni(II) complex to furnish bridged C(4)-spiro pyrrolidin-2,3-diones (Scheme 3b) and the group of Xu[25] reported the reaction with allene ketones catalyzed by a cinchona alkaloid (Scheme 3c).

This latter method, however, cannot be employed to generate a quaternary stereocenter at C4 of the pyrrolidin-2,3-dione ring. In this regard, two further examples starting from C(4)-alkylidene pyrrolidin-2,3-diones have also been reported, although in racemic form[26,27] (Scheme 3d and 3e). We questioned whether an enantioselective catalytic Brønsted base mediated C(4)-functionalization of pyrrolidin-2,3-diones could be accomplished to remediate the above deficiencies whilst broadening the product scope.

Synthesis of pyrrolidin-2,3-diones: For this study C(4)-unsubstituted *N*-benzyl pyrrolidin-2,3-dione **4** and C(4)-substituted pyrrolidin-2,3-diones **8** were selected (Scheme 4). Pyrrolidin-2,3-dione **4** was prepared following the protocol[28] shown in Scheme 4a, which implies first the aza-Michael addition of benzylamine **1** to methyl acrylate **2**, followed by cyclization with ethyl oxalate and further decarboxylation. For the preparation of C(4)-substituted pyrrrolidin-2,3-diones **8** the same protocol was adapted (Scheme 4b). Thus, α-substituted acrylates **6**, obtained following literature procedures,[29] were reacted with the corresponding amine **5** in the presence of $RuCl_3{\cdot}H_20$ and PEG (polyethylene glycol).[30] The resulting racemic β-amino esters **7** upon treatment with ethyl oxalate cyclisized and *in situ* decarboxylated to provide compounds **8** in good yields. These compounds, in contrast to pyrrolidin-2,3-dione **4**, are essentially in their enolic form **9** as shown by ^{1}H-NMR spectra.



Scheme 4. Preparation of the starting pyrrolidin-2,3-diones. pyrrrolidin-2,3-diones **8**

α-Amination of pyrrolidin-2,3-diones: Considering their significant advantages in the realm of cooperative asymmetric catalysis,[31] several bifunctional Brønsted bases[32] were initially evaluated[33] (Figure 2) for the reaction of the pyrrolidin-2,3-dione enolic form **9A** with *tert*-butyl azodicarboxylate **10**, a highly reactive acceptor that should provide rapid information about the feasibility of this plan. Actually, in each case examined, it was

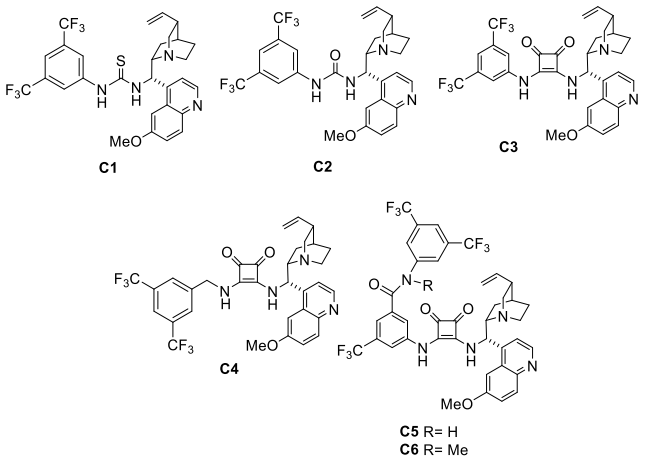
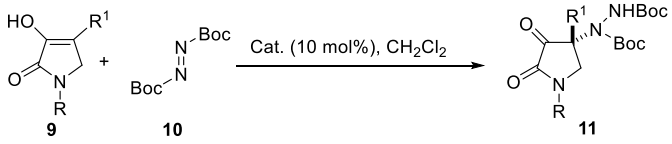


Figure 2. Catalysts employed in this study.

observed that the reaction proceeded cleanly, albeit in variable levels of enantioselectivity. As the results in Table 1 show, whilst thiourea (urea)-catalysts **C1** and **C2** were quite unfruitful, the squaramides pioneered by Rawal[34,35] were the most consistent catalysts. For example, using catalysts **C3**[36] and **C4**,[34] product **11Aa** was formed in enantioselectivities of 80% *ee* and 78% *ee*, respectively. To improve the enantioselectivity of the reaction we screened the recently developed new catalyst **C5**,[37] which was prepared upon the assumption that an additional hydrogen bond donor might be beneficial for stereocontrol.[38] Actually, with this catalyst, product **11Aa** was produced essentially as a single enantiomer. When the *N*-methylated catalyst **C6** was examined a little loss in enantioselectivity was observed. In general, the amination reaction of **9Aa**–**9Ad** with **10** promoted by **C5** proceeded at low temperature (–20 ºC, –40 ºC and/or 0 ºC) to give products **11Aa–d**, with very good yields and enantioselectivities between 95–99% range. The reaction also seems to be independent on the *N*-substituent of the starting pyrrolidin-2,3-dione enol form **9**, as each **9Ba**, **9Ca** and **9Da** led to the respective aminated products **11Ba**, **11Ca** and **11Da** with good yields and *ee´*s up to 99%.

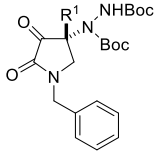
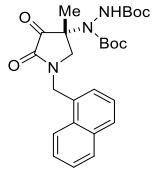
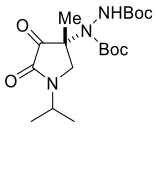
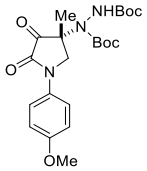
Conjugate addition to enones: We next examined the reaction with the α-silyloxy enone **15** (Table 2), an acrylate equivalent recently documented by us.[39] For these reactions, as Table 2 illustrates, the *N*-methylated catalyst **C6** was found to be the best in comparison with catalyst **C5** as well as catalysts **C1**-**C4** giving products **16** with *ee´*s up to 96%. Whilst these results suggest a strong catalyst/substrate dependence for these reactions, the advantages of this new modular subfamily of

Table 1. Catalytic α-amination of the enols **9**.[a]



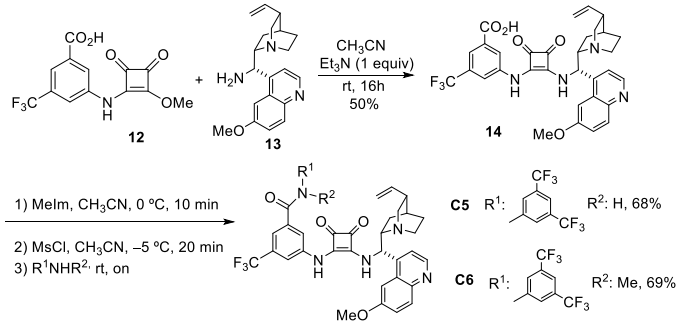
9 **10** **11**

A R: Bn; **B** R: CH_2-1-Naph; **C** R: *i*Pr; **D** R: 4-$MeOC_6H_4$
a R^1: Me; **b** R^1: Bn; **c** R^1: Ph; **d** R^1: Et

Product		Cat	T	t(h)[b]	Yield [%][c]	*ee* [%][d]
	**11Aa** R^1:Me	**C1**	0	2	85	16
		C2	0	2	95	20
		C3	0	1	92	80
		C4	0	1	97	78
		C5	0	1	93	99
		C6	0	1	92	90
	11Ab R^1:Bn	**C5**	–40	1	86	96
	11Ac R^1:Ph	**C5**	–20	1	81	92
			–40	1	77	95
	11Ad R^1:Et	**C5**	0	1	90	99
 **11Ba**[e]		**C5** 95%, 99% *ee*				
 **11Ca**[e,f]		**C5** 80%, 99% *ee*				
 **11Da**[e]		**C5** 95%, 96% *ee*				

[a] The reactions were performed on a 0.20 mmol scale in 0.4 mL of CH_2Cl_2 (mol ratio **9** /*tert*-butyl azodicarboxylate **10**: 1 / 1.5. [b] Time needed for total conversion. [c] Yield of isolated product after chromatography. [d] Determined by chiral HPLC. [e] Reactions conducted with **C5** catalyst at –40 ºC for 1 h otherwise stated. [f] 16 h were needed for complete conversion.

squaramide catalysts when compared with common catalysts such as **C3** are evident, as several options for better catalyst/ substrate adaptation are easily generated by simple fine tuning



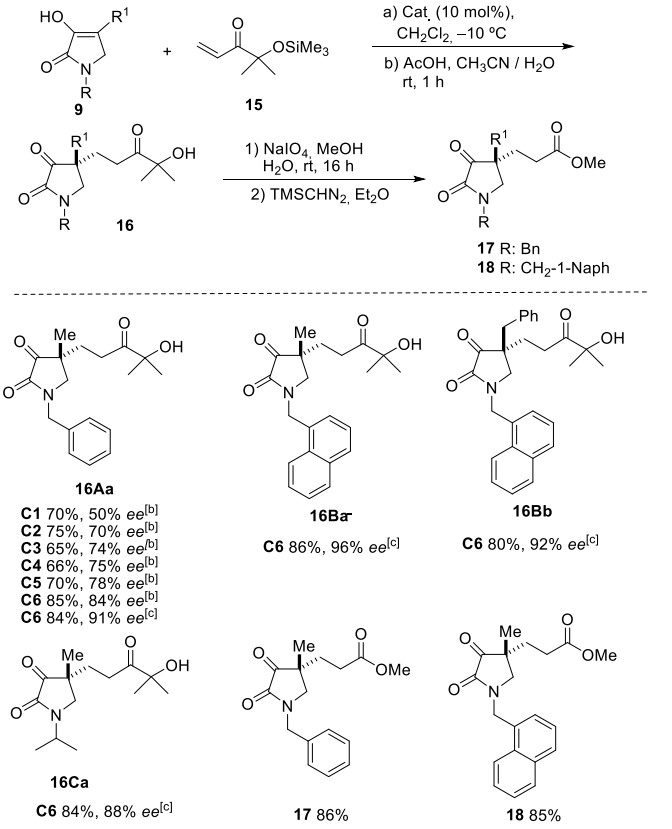
12 **13** **14**

Scheme 5. Preparation of catalysts **C5** and **C6**.

the carboxamide function. As Scheme 5 illustrates, these catalysts may be prepared by coupling of **12** with (R,R)-9-deoxy-9-epiaminoquinine **13** to provide intermediate **14**. Subsequent treatment of this squaramide carboxylic acid with *N*-methyl imidiazol,[40] mesyl chloride and the corresponding amine provides catalyst **C5** and **C6** in acceptable yields.

Most significantly, interest in this enone stems by the fact that attempted formation of these adducts by reaction of the corresponding pyrrolidin-2,3-dione with methyl acrylate failed regardless the catalyst employed.

Table 2. Conjugate additions to α'-silyloxy enone **15**.[a]



9 **15** **16** **17** R: Bn **18** R: CH_2-1-Naph

16Aa
C1 70%, 50% *ee*[b]
C2 75%, 70% *ee*[b]
C3 65%, 74% *ee*[b]
C4 66%, 75% *ee*[b]
C5 70%, 78% *ee*[b]
C6 85%, 84% *ee*[b]
C6 84%, 91% *ee*[c]

16Ba **C6** 86%, 96% *ee*[c]

16Bb **C6** 80%, 92% *ee*[c]

16Ca **C6** 84%, 88% *ee*[c]

17 86%

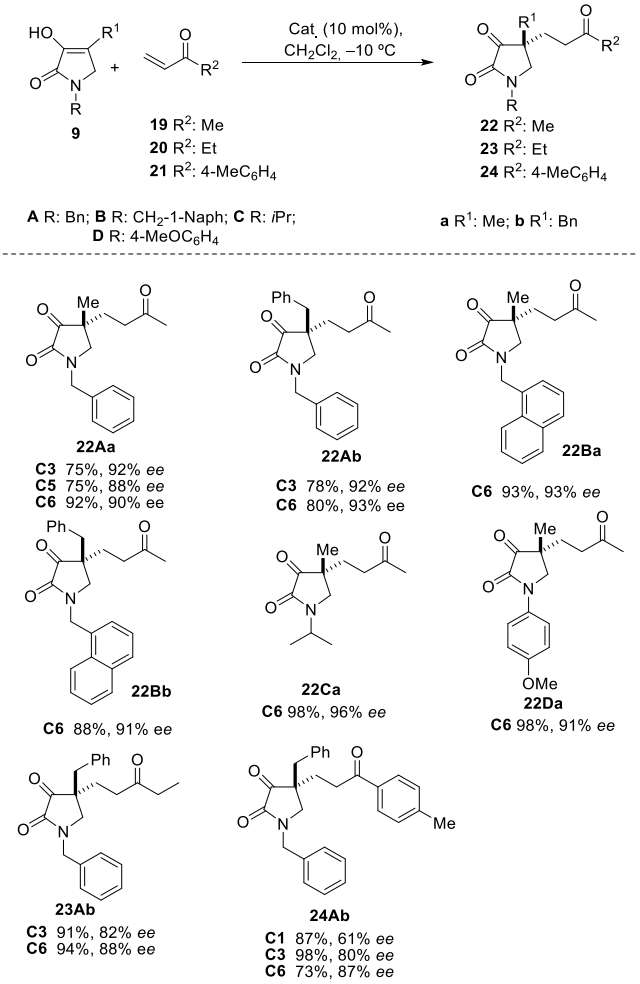
18 85%

a] The reactions were performed on a 0.20 mmol scale in 0.4 mL of CH_2Cl_2 by using 2 equiv. of silyloxy enone. Isolation of **16** was effected by desilylation with AcOH in CH_3CN/H_2O; see S.I. for details. Yield of isolated product after chromatography. Enantioselectivity determined by chiral HPLC. [b] Reactions carried out at rt. [c] Reactions carried out at 0 ºC.

The reaction with other carbon-centered Michael acceptors further illustrates the feasibility of the proposal. Thus, the reaction of **9Aa** with methyl vinyl ketone (MVK) **19** carried out at –10 ºC using catalyst **C5** led to the product **22Aa** in 75% yield and 88% *ee* (Table 3). For this reaction, however, both **C3** and **C6** were found to be equally effective giving the adduct **22Aa** in 92% *ee* and 90% *ee* respectively. Likewise, **22Ab** was obtained from **9Ab** and MVK in good yield and 93% *ee* using catalyst **C6** whilst catalyst **C3** led to the adduct with almost same *ee*. Further experiments revealed that with both catalysts the stereochemical outcome of the reaction appears to be independent upon the *N*-substitution pattern of the pyrrolidin-2,3-dione employed. The *N*-

naphthyl, *N*-isopropyl and *N*-*p*-methoxyphenyl derivatives **9Ba**, **9Bb**, **9Ca** and **9Da** respectively reacted with MVK to afford the corresponding adducts **22Ba**, **22Bb**, **22Ca** and **22Da** with *ee´s* between 91–96% range. Furthermore, the reaction seems to be general with respect to the enone component. For example, pyrrolidin-2,3-dione enol form **9Ab** reacted with ethyl vinyl ketone **20**, Table 3, in the presence of catalysts **C3** and **C6** to afford product **23Ab** in 82% *ee* and 80% *ee*, respectively. Under same conditions, 4-methylphenyl vinyl ketone **21** provided in the presence of **C6** adduct **24Ab** in 87% *ee*. In this instance, catalysts, **C1** and **C3**, led to **24Ab** in 61% *ee* and 80% *ee* respectively.

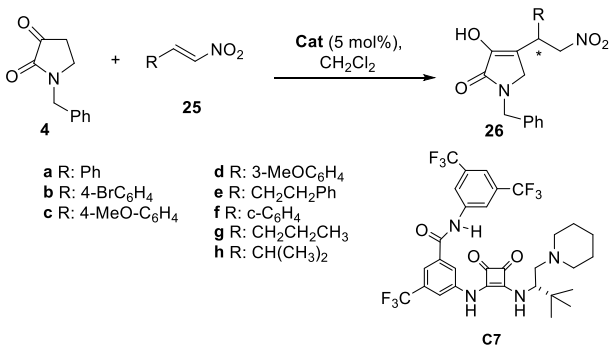
Table 3. Catalytic conjugate addition of pyrrolidin-2,3-dione derived enol **9** to enones **19**–**21**.[a]



[a] The reactions were performed on a 0.20 mmol scale in 0.4 mL of CH_2Cl_2 by using 2 equiv. of enone. Yield of isolated product after chromatography. Enantioselectivity determined by chiral HPLC.

The absolute configuration of the products from these reactions was determined for compounds **11Ad** and **16Ba** by X-ray single crystal structure analysis[41] and that of the remaining adducts was established by assuming an uniform reaction mechanism.

Conjugate addition to nitroolefins: The conjugate addition was next extended to nitroolefins with the aim to broaden the pool of available β[2,2]-amino acids. In particular, we studied the reaction of pyrrolidin-2,3-dione **4** with nitroolefins **25**, Scheme 6, wherein the resulting adducts would be attractive intermediates or precursors of unprecedented spirocyclic β–amino acid *N*-carboxy-anhydrides, *vide infra*. In a first instance, we explored the reaction of pyrrolidin-2,3-dione **4** with nitrostyrene **25a** (Scheme 6, Table 4) and found that whilst thiourea based catalyst **C1** afforded after 40 h at 0 ºC the Michael adduct **26a** in poor enantioselectivity (58% *ee*), the squaramide-type catalysts **C3**, **C5**, **C6** and **C7** were more effective. For instance, catalyst **C3** provided adduct **26a** in 75% *ee* after 3 h reaction at rt, and lowering the temperature to –20 ºC led to an improvement of enantioselectivity up to only 84% *ee*. Similarly, with both **C5** and **C6** the *ee*s could be improved up to 87%, being **C5** slightly superior to **C6**. Thus, we then replaced the cinchona portion in **C5** by another diamine scaffold[42] and envisaged catalyst **C7**.[29] It was gratifying to observe that this catalyst provided the product in 98% *ee*.



Scheme 6. Conjugate additions to nitroolefins.

Table 4. Catalyst screening for the reaction of **4** with **25a** (R = Ph) to give **26a**.[a]

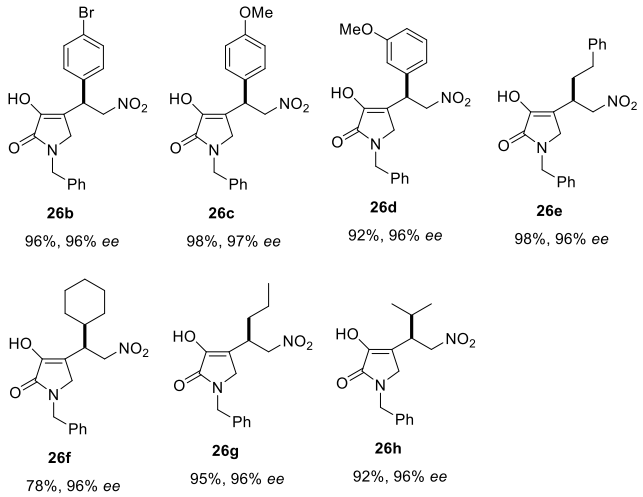
Cat (%)	T(ºC)	t(h)[b]	Conv. (%)[c]	Yield [%][d]	*ee* [%][e]
C1 (5 mol%)	0	40	100	82	58
C3 (5 mol%)	rt	3	100	77	75
C3 (5 mol%)	–10	40	85	59	80
C3 (5 mol%)	–20	40	89	62	84
C5 (5 mol%)	0	16	100	83	87
C6 (10 mol%)	0	16	100	86	82
C6 (10 mol%)	–10	16	100	89	84
C6 (10 mol%)	–20	16	100	83	87
C7(5 mol%)	0	16	100	88	98

[a] The reactions were performed on a 0.20 mmol scale in 0.4 mL of CH_2Cl_2 by using 1.1 equiv. of the nitroalkene. [b] Reaction time. [c] Conversion determined in the reaction crude by ^{1}H-NMR analysis. [d] Yield of isolated product after chromatography. [e] Enantioselectivity determined by chiral HPLC.

We next focused on the reaction scope of the nitroalkene counterpart using **C7**. As the results in Table 5 show, the reaction was equally effective with nitrostyrenes bearing either electron-poor or electron-rich substituents which afforded the corresponding Michael adducts in 96% *ee*. Significantly, the reaction was also efficient with the more recalcitrant β-alkyl nitroalkenes **25e-h**, as in these cases the corresponding adducts were obtained in very good yields (78–98%) and excellent enantioselectivity (96–98% *ee*).

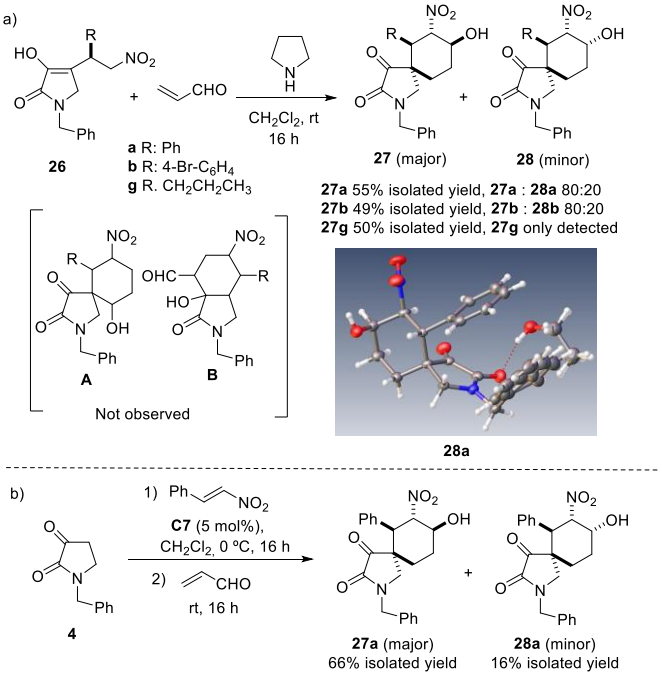
With these results in hand, we next investigated the transformation of the previous Michael adducts in spirocyclic derivatives by treating them with acrolein in the presence of

Table 5. Reaction scope of **4** with different nitroalkenes **25** catalyzed by **C7**.[a]



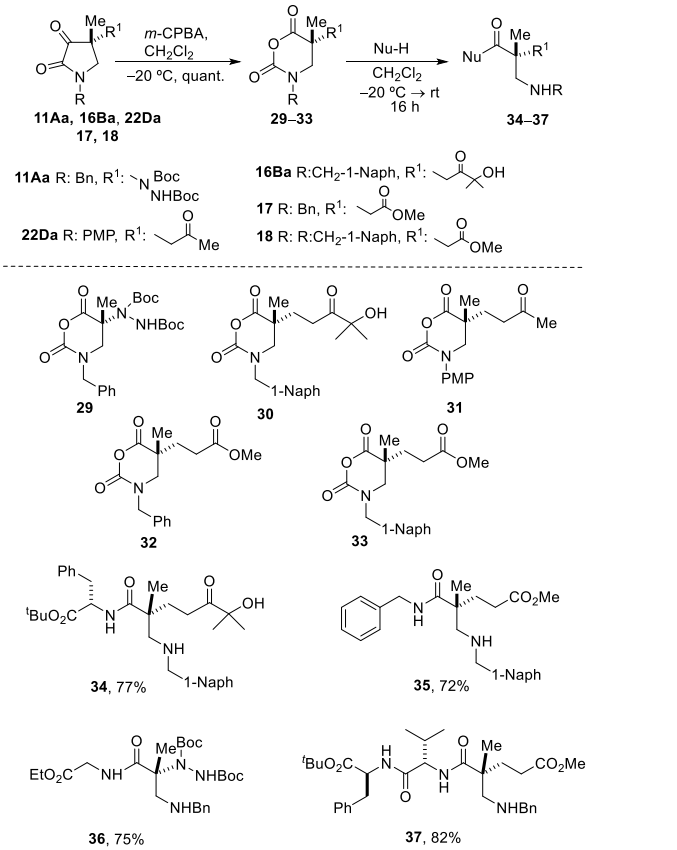
[a] The reactions were performed at 0 ºC on a 0.20 mmol scale in 0.4 mL of CH_2Cl_2 by using 1.1 equiv. of the nitroalkene and catalyst **C7** (5 mol%). The resulting mixture was stirred at 0 ºC until total comsuption of the starting α-ketoamide (monitored by ^{1}H-NMR). Yield of isolated product after chromatography. Enantioselectivity determined by chiral HPLC.

pyrrolidine (Scheme 7,a). At the onset, three possible spirocycles could be generated from this approach. However, fortunately, the reaction of **26a** under these conditions revealed the formation of only the diastereomeric spirocycles **27**/**28** in 80:20 ratio (55% isolated yield for **27**) and neither **A** nor **B** were observed. Similar results were obtained from nitro derivatives **26b** and **26g**, being in this latter case **27g** the only diastereomer observed. Lowering the temperature did not led to any change in diastereoselectivity, but these data show that the reaction occurs through a cascade Michael-Henry sequence,[43] involving first the Michael addition of the C(4) carbon of pyrrolidin-2,3-dione to acrolein. Significantly, treatment of **4** with nitrostyrene at 0 ºC in the presence of **C7** followed by addition of acrolein and further reaction at rt for 16 h provided spirocyclic compounds **27a** and **28a** in the same diastereomeric ratio but better yield (Scheme 7, b), thus showing that it is possible to carry all three reactions (Michael to nitrostyrene/Michael to acrolein/Henry) without isolation of intermediate **26a** and by using only **C7** as catalyst. X-Ray analysis of the minor diastereomer **28a**[44] provided its absolute configuration and that of the major diastereomer **27a** was assigned by *noe* experiments and analysis of coupling constants.[29] The configuration of the remaining adducts was established by assuming an uniform reaction mechanism.



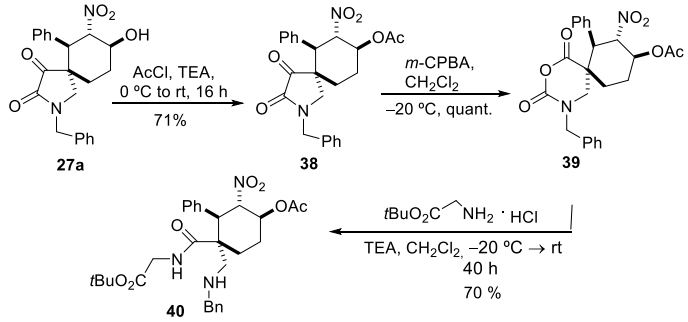
Scheme 7. Synthesis of spirocyclic pyrrolidin-2,3-diones. a) Sequential protocol. b) One-pot protocol.

β^{2,2}-Amino acid *N*-carboxyanhydrides: Given the precedents from this laboratory,[19] we questioned whether these 4,4-disubstituted adducts upon Baeyer-Villiger oxidation could be regioselectively transformed into the respective *N*-carboxy anhydrides, that is, a carboxyl activated form of β^{2,2}-amino acids which would provide the opportunity to perform further couplings, for instance, with α-amino acid esters. We were pleased to find that reaction of pyrrolidin-2,3-diones **11Aa**, **16Ba**, **22Da**, **17** and **18**, with *m*-chloroperbenzoic acid (*m*-CPBA) proceeds with complete regio- and chemoselectivity to give the respective β-amino acid derived *N*-carboxyanhydrides (β^{2,2}-NCAs) **29**-**33**, almost quantitatively and without products from oxidation of the exocyclic carbonyl group (Scheme 8). To the best of our knowledge, this is the first approach to a carboxyl activated form of α,α-disubstituted β-amino acids instead of the most common free acids or esters,[45] and therefore products of relatively more complexity may be made readily feasible by coupling of these NCAs with appropriate nucleophiles. For example, **30**, after treatment with *L*-phenylalanine *tert*-butyl ester, furnished product **34** in 77% yield. Similarly, **33** reacted with benzylamine to provide **35** in 72% yield, and the coupling of β-NCA **29**, prepared from **11Aa** as above, with glycine ethyl ester afforded the α-tetrasubstituted β-amino α-hydrazino acid derived peptide **36** in 75% yield.[46] This coupling reaction also tolerates dipeptides, even with relatively bulky groups, as shown in the preparation of product **37** through coupling of **32** with the corresponding dipeptide H_2N-Val-Phe-O^{t}Bu.



Scheme 8. β[2,2]-amino acid *N*-carboxy anhydrides (β[2,2]-NCAs) from 2,3-dioxopyrrolidines and reaction couplings. PMP: *p*-methoxyphenyl, Naph: Naphthyl.

To further prove the efficiency of this protocol, spirocyclic derivative **38** was subjected to Baeyer-Villiger oxidation under the previous conditions (Scheme 9). For this purpose **27a** was transformed into the acetylated derivative **38**, which upon treatment with *m*-CPBA provided NCA **39**. Subsequent coupling of **39** with glycine *tert*-butyl ester chlorohydrate afforded compound **40** in 70% yield.



Scheme 9. β[2,2]-amino acid *N*-carboxy anhydrides (β[2,2]-NCAs) from spirocyclic derivative **27a** and ring opening with glycine *tert*-butyl ester chlorohydrate.

Conclusions

In summary, we have reported a new subclass of easily tunable squaramide-Brønsted base catalysts that promote the reaction of pyrrolidin-2,3-diones or their enolic form with a survey of different electrophiles generating either quaternary or tetrasubstituted carbon stereocenters with very high enantioselectivity, including enantioenriched unprecedented β[2,2]-spyrocyclic compounds. Smooth ring enlargement of the adducts with *m*-CPBA provides a quick entry to the synthesis of β[2,2]-amino acid *N*-carboxy anhydrides enabling subsequent direct couplings with nucleophiles en route to relatively more complexity. This approach thus may serve to increase not only the chemical space of pyrrolidin-2,3-diones for new bioactive compounds, but also their synthetic applications in asymmetric catalysis and peptidic synthesis.

Experimental Section

General procedure for the synthesis of catalysts C5 and C6.

Synthesis of 14: Squaramide based catalysts **C5** and **C6** were synthesized from 3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzoic acid **12**.[29] Triethylamine (0.67 mL, 4.8 mmol, 1 equiv.) and (*R,R*)-9-deoxy-9-epiaminoquinine **13** (1.55 g, 4.8 mmol, 1 equiv.) were added to a suspension of **12** (1.51 g, 4.8 mmol, 1 equiv.) in CH_3CN (5 mL) at room temperature. The reaction mixture was stirred vigorously at room temperature for 16 h and then was directly purified by flash column chromatography (DCM/ MeOH, 99:1) to give the title product as a yellow solid. Yield: 1.46 g, 2.4 mmol, 50%. ^{1}H NMR (300 MHz, Acetonitrile-*d*3) δ 11.51 (bs, 1H), 10.17 (bs, 1H), 8.85 (d, *J* = 4.5 Hz, 1H), 8.38 (s, 1H), 8.07 – 7.56 (m, 5H), 7.32 (dd, *J* = 9.2, 2.5 Hz, 1H), 6.40 (bs, 1H), 5.86 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.32 – 4.97 (m, 2H), 4.50 (s, 1H), 4.05 – 3.53 (m, 5H), 3.51 – 3.11 (m, 2H), 2.84 (d, *J* = 9.0 Hz, 1H), 2.25 – 1.97 (m, 4H), 1.78 (t, *J* = 12.4 Hz, 1H), 1.22 (d, *J* = 13.9 Hz, 1H). ^{13}C NMR (75 MHz, Acetonitrile-*d*3) δ 185.7, 181.9, 171.9, 169.0, 166.5, 159.5, 149.0, 145.6, 142.4, 140.6, 139.6, 138.4, 132.8, 131.7 (q), 127.9, 127.0, 123.2, 122.7, 120.7, 120.6, 117.38, 117.0, 102.2, 60.4, 56.3, 55.3, 54.3, 42.2, 37.3, 27.6, 24.7, 24.2. UPLC-DAD-QTOF: $C_{40}H_{33}N_5O_4F_9$ $[M+H]^+$ calcd.: 818.2389, found: 818.2398.

Coupling of 14 with the corresponding amine: Obtention of C5 and C6. 1-Methylimidazole (0.2 mL, 2.5 mmol, 2.5 equiv.) was added to a slurry of **14** (606 mg, 1 mmol, 1 equiv.) in CH_3CN (2.5 mL) at 0 °C, and the mixture was stirred for 10 min. MsCl (0.12 mL, 1.5 mmol, 1.5 equiv) in CH_3CN (0.5 mL) was added to the mixture under –5 °C. After stirring at that temperature for 20 min, the corresponding amine (1 mmol, 1 equiv.) was added. The mixture was then stirred at room temperature overnight. H_2O (10 mL) was added to the mixture and a solid precipitated. This solid was solved with EtOAc (10 mL) and the organic layer was washed with brine (3 x 50 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the crude was purified by silica flash column chromatography to afford the desired catalyst.

***N*-(3,5-Bis(trifluoromethyl)phenyl)-3-((2-(((*S*)-(6-methoxyquinolin-4-yl) ((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzamide C5.** The title catalyst was synthethyzed starting from 3,5-bis(trifluoromethyl)aniline (0.16 mL, 1 mmol, 1 equiv.) and following the general procedure. The reaction crude was purified by column chromatography (eluting with CH_2Cl_2:MeOH, 98:2). Yellow solid. Yield: 556 mg, 0.68 mmol, 68%. ^{1}H NMR (300 MHz, DMSO-d_6) 10.94 (s, 1H), 10.16 (s, 1H), 8.80 (d, *J* = 4.5 Hz, 1H), 8.47 (d, *J* = 1.8 Hz, 2H), 8.27 (s, 1H), 8.17 (s, 1H), 7.97 (t, *J* = 4.5 Hz, 3H), 7.84 (s, 1H), 7.76 (s, 1H), 7.67 (d, *J* = 4.6 Hz, 1H), 7.45 (dd, *J* = 9.2, 2.4 Hz, 1H), 6.22 – 5.82 (m, 2H), 5.30 – 4.81 (m, 2H), 3.96 (s, 3H), 3.56 – 3.06 (m, 3H), 2.85 – 2.55 (m, 2H), 2.28 (q, *J* = 8.0, 7.2 Hz, 1H), 1.84 – 1.34 (m, 4H), 0.68 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ184.6, 180.1, 168.5, 164.4, 163.0, 157.9, 147.8, 144.3,

143.1, 142.1, 140.7, 140.3, 136.0, 131.5, 130.9, 130.5, 127.5, 125.1, 121.2, 120.0, 118.0, 117.5, 116.8, 114.3, 101.5, 58.9, 55.8, 55.7,40.2, 39.4, 38.3, 38.0, 27.3, 26.0. UPLC-DAD-QTOF: $C_{40}H_{33}N_5O_4F_9$ $[M+H]^+$ calcd.: 818.2389, found: 818.2398.

3-(2-((*S*)-(2-Methoxynaphthalen-8-yl)(8-vinylquinuclidin-2yl)methylamino)-3,4-dioxocyclobut-1-enylamino)-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoro methyl)-*N*-methylbenzamide C6. The title catalyst was synthethyzed starting from 1-(3,5-bis(trifluoromethyl)phenyl)-*N*-methylmethanamine[29] (257 mg, 1 mmol, 1 equiv.) and following the general procedure. The reaction crude was purified by column chromatography (eluting with CH_2Cl_2:MeOH, 98:2). Yellow solid. Yield: 573 mg, 0.69 mmol, 69%. ^{1}H NMR (300 MHz, Acetone-d_6) δ 8.77 (d, *J* = 4.5 Hz, 1H), 8.01 (d, *J* = 9.6 Hz, 4H), 7.93 (s, 2H), 7.86 (s, 1H), 7.77 (s, 1H), 7.69 (d, *J* = 4.0 Hz, 1H), 7.42 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.23 (s, 1H), 6.31 (s, 1H), 5.87 (m , 1H), 4.97 (m, 2H), 4.04 (s, 3H), 3.59 (s, 3H), 3.36 – 3.20 (m, 1H), 2.82 (d, *J* = 12.4 Hz, 2H), 2.36 (s, 1H), 2.08 (m, 1H), 1.65 (d, *J* = 15.0 Hz, 4H), 0.89 (s, 1H). ^{13}C NMR (75 MHz, Acetone-d_6) δ 185.8, 181.4, 169.7, 169.1, 164.1, 159.3, 148.4, 146.8, 145.8, 143.9, 142.4, 141.1, 138.9, 132.6, 132.4, 131.9, 129.3, 128.8, 128.5, 126.1, 125.7, 123.0, 122.5, 122.1, 120.7, 119.3, 118.4, 116.6, 114.8, 102.2, 60.7, 56.7, 56.3, 54.9, 41.5, 40.4, 38.3, 30.3, 28.5, 28.1, 26.7. UPLC-DAD-QTOF: $C_{42}H_{36}N_4O_4F_9$ $[M+H]^+$ calcd.: 831.2593, found: 831.2596. $[\alpha]_D^{25}$ = – 115.89° (c=1.0, CH_2Cl_2).

Synthesis of catalysts C7. Catalyst **C7** was synthesiszed from 3-amino-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)benzamide and 3,4-dimethoxy-3-cyclobutane-1,2-dione.[29]

***N*-(3,5-Bis(trifluoromethyl)phenyl)-3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzamide.** To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (711 mg, 5.0 mmol, 1 equiv.) in MeOH (10 mL), 3-amino-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoro-methyl)benzamide (2.3 g, 5.5 mmol, 1.1 equiv.) was added at room temperature. The mixture was stirred at room temperature for 15 h. The white precipitate was filtrated, washed with MeOH, dried *in vacuum* and used as such in the next step. Yield: 2.3 g, 4.4 mmol, 88%. ^{1}H NMR (300 MHz, Acetone-d_6) δ 10.71 (s, 1H), 10.52 (s, 1H), 8.03 (s, 2H), 7.73 (s, 1H), 7.64 (s, 1H), 7.59 (s, 1H), 7.39 (s, 1H), 3.96 (s, 3H).

Obtention of C7. To a suspension of *N*-(3,5-Bis(trifluoromethyl)phenyl)-3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl) benzamide (1.05 g, 2 mmol, 1 equiv.) in MeOH (10 mL) was added (*S*)-3,3-dimethyl-1-(piperidin-1-yl)butan-2-amine (369 mg, 2 mmol, 1 equiv.) at room temperature. The reaction mixture was stirred vigorously at room temperature for 2 days. The reaction mixture was evaporated and purified by silica column chromatography (CH_2Cl_2:MeOH, 98:2) to give the pure **C7** catalyst as a yellow solid. Yield: 1.17 g, 1.72 mmol, 86%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.99 (s, 1H), 10.06 (s, 1H), 8.50 (t, *J* = 2.1 Hz, 2H), 8.32 (s, 1H), 8.05 (t, *J* = 1.9 Hz, 1H), 7.98 (s, 1H), 7.86 (s, 1H), 7.58 (dd, *J* = 10.4, 5.5 Hz, 1H), 4.02 (d, *J* = 10.4 Hz, 1H), 2.49 – 2.39 (m, 2H), 2.40 – 2.29 (m, 2H), 2.26 – 2.13 (m, 2H), 1.50 – 1.24 (m, 6H), 0.94 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 184.4, 180.1, 170.5, 164.4, 161.8, 140.7, 140.6, 136.1, 130.7 (q), 130.4 (q), 124.3, 122.1, 120.8, 120.1, 117.6, 117.1, 116.86.UPLC-DAD-QTOF: $C_{31}H_{32}N_4O_3F_9$ $[M+H]^+$ calcd.: 679.2331, found: 679.2327. $[\alpha]_D^{25}$ = + 7.8° (c=0.5, MeOH).

General procedure for the α-amination: To a mixture of the corresponding α-ketoamide **9** (0.2 mmol, 1 equiv.) and catalyst **C5** (0.02 mmol, 10 mol%) in dichloromethane (0.4 mL), di-*tert*-butyl azodicarboxylate **10** (69 mg, 0.3 mmol, 1.5 equiv.) was added. The resulting mixture was stirred until consumption of the α-ketoamide **9** (monitored by ^{1}H-NMR). The mixture was then directly purified by flash column chromatography on silica gel (eluent hexane/ ethyl acetate 80/20) without previous work-up to afford the expected adducts.

General procedure for the conjugate addition to α'-silyloxy enones: To a mixture of the corresponding α-ketoamide **9** (0.2 mmol, 1 equiv.) and the α'-silyloxy enone **15** (74 mg, 0.4 mmol, 2 equiv.) in dichloromethane (0.4 mL) catalyst **C6** (0.02 mmol, 10 mol%) was added. The mixture was stirred until consumption of the α-ketoamide **9** (monitored by ^{1}H-NMR). The reaction mixture was then quenched with 1M HCl (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. For the desilylation step, the reaction crude was dissolved in CH_3CN (1 mL) and, H_2O (0.5 mL) and glacial acetic acid (0.3 mL) were added. The reaction mixture was stirred for 1 h at room temperature and it was quenched with $NaHCO_3$ saturated aqueous solution (20 mL). The organic solvent was evaporated under reduced pressure and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude was purified by flash column chromatography on silica gel to afford the expected adducts.

General procedure for the conjugate addition to vinyl ketones: To a mixture of the α-ketoamide enol form **9** (0.2 mmol, 1 equiv.) and the vinyl ketone **19**-**21** (0.4 mmol, 2 equiv.) in dichloromethane (0.4 mL) catalyst **C6** (0.02 mmol, 10 mol%) was added. The mixture was stirred until consumption of the α-ketoamide **9** (monitored by ^{1}H-NMR). The reaction mixture was then quenched with 1M HCl (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude was purified by flash column chromatography on silica gel to afford the expected adducts.

General procedure for the conjugate addition to nitroalkenes: To a mixture of 1-benzylpyrrolidine-2,3-dione **4** (38 mg, 0.2 mmol, 1 equiv.) and the corresponding nitroalkene **25** (0.22 mmol, 1.1 equiv.) in dichloromethane (0.4 mL), catalyst **C7** (5 mg, 0.01 mmol, 5 mol%) was added. The mixture was stirred for 16 h at 0 ºC. The reaction mixture was then directly purified by flash column chromatography on silica gel (eluent hexane/ethyl acetate 70/30) without previous work-up to afford the expected adducts in the enolized form.

General procedure for the synthesis of spirocycles 27 starting from nitroalkanes 26: Pyrrolidine (7 mg, 0.1 mmol, 10 mol%) was added to a solution of acrolein (0.13 mL, 2 mmol, 2 equiv.) and the previously obtained nitroketone **26** (1.0 mmol, 1 equiv.) in dichloromethane (2 mL) and the resulting solution was stirred at room temperature for 16 h. The reaction mixture was directly purified by flash column chromatography (Hex:EtOAc 40:60) separating both diastereomers.

Procedure for the one-pot synthesis of spirocycle 27a: To a mixture of 1-benzylpyrrolidine-2,3-dione **4** (38 mg, 0.2 mmol, 1 equiv.) and the corresponding nitroalkene **25** (0.22 mmol, 1.1 equiv.) in dichloromethane (0.4 mL), catalyst **C7** (5 mg, 0.01 mmol, 5 mol%) was added. The mixture was stirred for 16 h at 0 ºC until completion of the first conjugate addition (monitored by ^{1}H-NMR). Then acrolein (26 μL, 0.4 mmol, 2 equiv.) was *in situ* added at the same temperature and the resulting solution was stirred at room temperature for 16 h. The reaction mixture was directly purified by flash column chromatography (Hex:EtOAc 40:60) separating both diastereomers.

General procedure for NCA synthesis: To a solution of the starting adduct (0.2 mmol, 1 equiv.) in CH_2Cl_2 (1 mL), *m*CPBA (67 mg, 0.3 mmol, 1.5 equiv.) was slowly added at –20 ºC. The reaction mixture was stirred at –20 ºC or warmed up to room temperature. The reaction was quenched with aqueous 10% $NaHSO_3$ and it was extracted with CH_2Cl_2 (x 3). All organic phases were combined, washed with NaOH 1 N, dried over

$MgSO_4$ and evaporated under reduced pressure to afford the corresponding NCAs in quantitative yield.

General procedure for ring opening of the NCAs:

METHOD A: Amino ester hydrochlorides as nucleophiles: A suspension of the amino ester hydrochloride (1.2 equiv.) in CH_2Cl_2 (2 mL/mmol) was treated with TEA (2.0 equiv.) for 30 min. The mixture was then cooled to –20 ºC and the corresponding NCA (1.0 equiv.) solution in CH_2Cl_2 (1 mL/mmol) was added at this temperature. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched with HCl 1N, and the mixture was extracted with CH_2Cl_2 (x 3). The combined organic layers were washed with $NaHCO_3$, dried over $MgSO_4$ and evaporated under reduced pressure.

METHOD B: Amines as nucleophiles: The amine nucleophile (1.2 equiv.) was added to a solution of the crude NCA (1 equiv.) in CH_2Cl_2 (2 mL/mmol) at –20 ºC. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched with HCl 1N, and the mixture was extracted with CH_2Cl_2 (x 3). The combined organic layers were washed with $NaHCO_3$, dried over $MgSO_4$ and evaporated under reduced pressure.

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Keywords: β–amino acids • quaternary centers • organocatalysis • Brønsted bases • synthetic methods

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