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Organocatalyzed Three-Component Ugi and Passerini Reactions of 4-Oxoazetidine-2-carbaldehydes and Azetidine-2,3-diones. Application to the Synthesis of γ-Lactams and γ-Lactones

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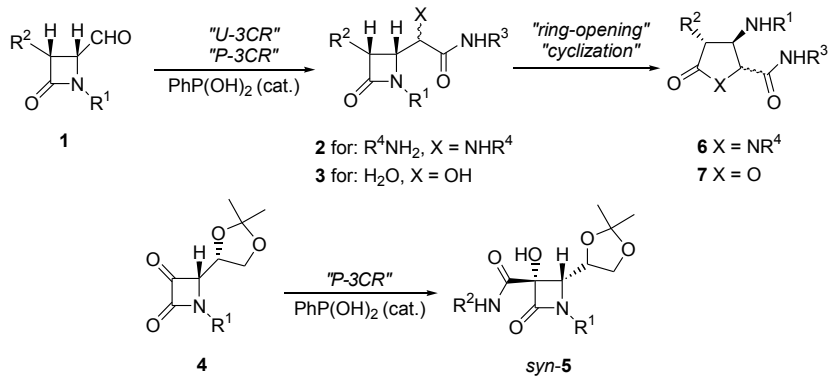
ABSTRACT



Organocatalyzed U-3CR of 4-oxoazetidine-2-carbaldehydes has been studied. Besides, the organocatalyzed P-3CR of 4-oxoazetidine-2-carbaldehydes and azetidine-2,3-diones has been described for the first time. U-3CR and P-3CR adducts have been obtained in good yields and reasonable diastereoselectivities. Phenyl phosphinic acid has been the catalyst of choice to study the scope of both organocatalyzed multicomponent reactions using a variety of β-lactams, isocyanides and amines. Highly

functionalized U-3CR and P-3CR adducts derived from β-lactams have proved to be useful substrates for the preparation of enantiopure γ-lactams and γ-lactones via N1–C2 β-lactam ring opening/cyclization under acidic or basic conditions.

INTRODUCTION

Multicomponent reactions (MCRs) are synthetic processes that combine three or more substrates to afford new compounds in one pot.[1] This powerful methodology allows both complexity and diversity in the final substrates with high atom economy. The advantages and the applications of MCRs have been widely demonstrated in the synthesis of natural products[2,3] and medicinal chemistry.[3,4] In particular, isocyanide-based MCRs (IMCRs) are especially attractive in terms of functional group tolerance and the high levels of chemo-, regio-, and stereoselectivity obtained.[5] Among them, the Passerini three-component reaction (P-3CR) and the Ugi four-component reaction (U-4CR) are the most prominent. In this context, List has reported the first organocatalyzed three-component Ugi reaction (U-3CR) of different aldehydes, *p*-anisidine and a variety of isocyanides using phenyl phosphinic acid as catalyst.[6]

On the other hand, the β-lactam ring has been permanently associated with their potent antibacterial activity and, more recently, with enzyme inhibition, anticancer activity and gene activation.[7] Besides, from the synthetic point of view, this four-membered ring is an excellent substrate to obtain a diverse family of nitrogenated compounds ranging from three-membered skeletons to macrocyclic structures and acyclic compounds.[8] In particular, different methodologies which involves ring opening of the β-lactam nucleus followed by cyclization have been developed.[9]

The γ-lactam ring is present in natural and synthetic products with interesting therapeutic activities.[10] For example, succinimide[11] and pyroglutamic acid[12] cores have significant chemical and medicinal importance as they are implicate in different relevant processes. In addition, the γ-lactone moiety is a substructure present in natural compounds. In particular *N*-acyl homoserine lactones (AHLs)

are involved in the multicellular communication network of most gram-negative bacteria,[13] and sesquiterpene lactones exhibit a variety of biological activities.[14]

Following up our interest in the area of the synthesis of nitrogenated compounds,[15] and the investigation of methodologies based in multicomponent processes,[16] we became interested in the study of the organocatalyzed U-3CR process in β-lactam substrates.

RESULTS AND DISCUSSION

U-3CR of 4-Oxoazetidine-2-carbaldehydes

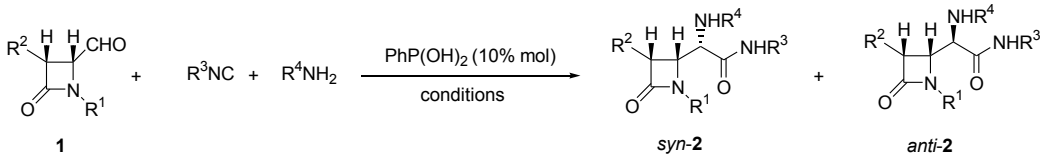
First of all, we decided to investigate the U-3CR catalyzed by phenyl phosphinic acid of 4-oxoazetidine-2-carbaldehydes **1**.

Starting substrates, optically pure 4-oxoazetidine-2-carbaldehydes **1a–e**, were prepared, using standard methodology, as single *cis*-enantiomers from imines of (*R*)-2,3-*O*-isopropylideneglyceraldehyde, through Staudinger reaction with the corresponding alkoxy(aryloxy)acetyl chloride in the presence of Et_3N, followed by sequential acidic acetonide hydrolysis and oxidative cleavage.[17]

In order to show the viability of the organocatalyzed U-3CR of β-lactam aldehydes **1**, our first experiment was the reaction of aldehyde **1a**, allylamine and benzyl isocyanide (BnNC) in presence of a catalytic amount of phenyl phosphinic acid (10% mol), using the same reaction conditions previously described (toluene, 80°C).[6] In the event, α-amino amide **2a** was obtained as a separable mixture of *syn/anti* isomers in 61:39 ratio in 83% yield (Table 1, entry 1). Compound **2a** was also obtained quantitatively within the same *syn/anti* ratio when the reaction was tested under milder conditions, dichloromethane at room temperature (Table 1, entry 2). Thus, the above mild reaction conditions were applied to study the scope of the multicomponent process of β-lactam aldehydes **1**. The reaction of aldehyde **1a**, allylamine and *t*-butyl isocyanide (*t*-BuNC) in presence of phenyl phosphinic acid (10%

mol) afforded product **2b** with similar diastereoselectivity (63:37) and excellent yield (92%) (Table 1, entry 3). When the U-3CR was tested in aldehyde **1b**, with an aliphatic substituent in the nitrogen, compound **2c** was obtained with slightly better diastereoselectivity (72:28) in 66% yield (Table 1, entry 4). Analogously, the reaction of aldehyde **1c**, *t*-BuNC and methyl glycinate, afforded compound **2d** with a comparable diastereoselectivity (70:30) and good yield (74%) (Table 1, entry 5). Unfortunately, α-amino amide **2d** was isolated as an inseparable mixture of *syn/anti* isomers. Next, we decided to explore the multicomponent reaction using aromatic amines. The reactions were performed using aldehydes **1a** and **1d,** benzyl isocyanide and *t*-BuNC, respectively, and an electron rich aromatic amine, *p*-anisidine. Thus, compounds **2e** and **2f** were obtained with comparable values in terms of diastereoselectivity and yield (Table 1, entries 6 and 7). However, α-(*p*-methoxyphenyl)amino amide **2e** was isolated as an inseparable mixture of *syn/anti* isomers. Compound **2g** was obtained without significant changes in terms of diastereoselectivity (68:32) and yield (67%) when the reaction was performed with aldehyde **1b**, *t*-BuNC and an electron poor aromatic amine, such as *p*-nitroaniline (Table 1, entry 8).

Table 1. U-3CR of 4-oxoazetidin-2-carbaldehydes 1, amines, isocyanides and phenyl phosphinic acid as catalyst[a]



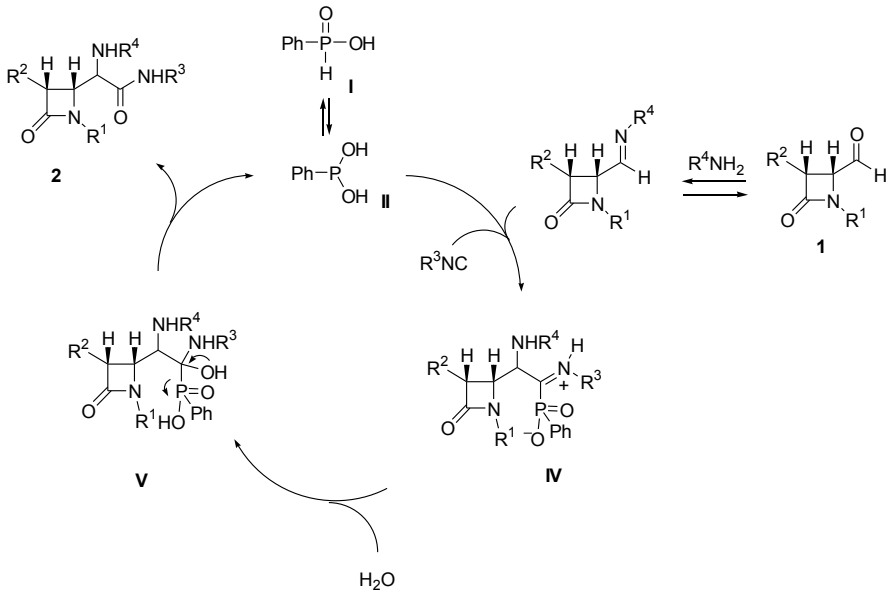
Entry	Aldehyde	R^1	R^2	R^3	R^4	Conditions	t (h)[b]	Product	*syn/anti*[c]	Yield (%)[d]
1	(+)-**1a**	PMP[e]	MeO	Bn	2-propenyl	toluene/80°C	28	**2a**	61:39	51:32
2	(+)-**1a**	PMP[e]	MeO	Bn	2-propenyl	CH_2Cl_2/rt	28	**2a**	61:39	61:39
3	(+)-**1a**	PMP[e]	MeO	*t*-Bu	2-propenyl	CH_2Cl_2/rt	48	**2b**	63:37	58:34

4	(–)-**1b**	2-propenyl	PhO	Bn	2-propenyl	CH_2Cl_2/rt	39	**2c**	72:28	48:18
5	(–)-**1c**	Bn	Pht[f]	*t*-Bu	CH_2CO_2Me[g]	CH_2Cl_2/rt	24	**2d**	70:30	74[h]
6	(+)-**1a**	PMP[e]	MeO	*t*-Bu	PMP[e]	CH_2Cl_2/rt	18	**2e**	64:36	74[h]
7	(+)-**1d**	PMP[e]	PhO	Bn	PMP[e]	CH_2Cl_2/rt	16	**2f**	70:30	62:28
8	(–)-**1b**	2-propenyl	PhO	*t*-Bu	PNP[i]	CH_2Cl_2/rt	22	**2g**	68:32	46:21

[a]All reactions were performed by using an aldehyde/amine/isocyanide ratio of 1.0:1.1:1.1 mmol. [b]Reaction progress was followed by TLC. [c]The *syn/anti* ratio was determined by integration of well-resolved signals in the ^{1}H NMR spectra (300 MHz) of the crude reaction mixtures before purification. [d]Yield of pure, isolated isomers with correct analytical and spectral data. [e]PMP = 4-$MeOC_6H_4$. [f]Pht = Phtalimidoyl. [g]The reaction was carried out by treatment of amine chlorhydrate with triethyl amine in the reaction conditions. [h]Yield of pure, isolated mixture of isomers. [i]PNP = 4-$NO_2C_6H_4$.

Scheme 1 shows the mechanistic proposal for the U-3CR of compounds **1**, which is comparable to List's proposal. Phenyl phosphinic acid **I** can be considered a Brönsted acid and, in the form of its phenylphosphonous acid tautomer **II**, a Lewis base. Both properties could be involved in the catalytic process. The mechanism proposed involves protonation of the in situ generated imine, formed by reaction of aldehyde **1** and the corresponding amine. Next, addition of the isocyanide and subsequent trapping of the nitrilium ion with the phosphinate anion would take place. Finally, a molecule of water, which is released in the imine formation, reacts with intermediate **IV** to generate **V**, which fragments to the α-amino amide **2**, and the catalyst.

Scheme 1. Mechanistic proposal for the U-3CR catalyzed by phenyl phosphinic acid



P-3CR of 4-Oxoazetidine-2-carbaldehydes and Azetidine-2,3-diones

Once the U-3CR organocatalyzed by phenyl phosphinic acid was studied, we decided to investigate the analogous process, the Passerini reaction of aldehydes **1**. In fact, to the best of our knowledge, there is no report about organocatalyzed diastereoselective Passerini reaction.[18]

According to the mechanism previously proposed for the organocatalyzed U-3CR, a molecule of water is produced during the formation of the imine. Thus, an external addition of water would be necessary which would act as the acidic component in the Passerini reaction. Taking into account this idea, we decided to study the reaction of aldehyde **1a**, *t*-BuNC, a stoichiometric amount of water and phenyl phosphinic acid (10% mol) in dichloromethane at room temperature. Fortunately, the corresponding α-hydroxy amide **3a** was obtained as a mixture of isomers (60:40) quantitatively (Table 2, entry 1). Next, we decided to test the P-3CR in aqueous media in order to minimize the amount of organic solvent employed. However, adduct **3a** was isolated in lower yield (64 and 67%) when the reaction was performed using mixtures of THF/H_2O (1:1) and MeCN/H_2O (1:1), respectively (Table 2, entries 2 and 3). In addition, the reaction times for both experiments were considerably longer than with

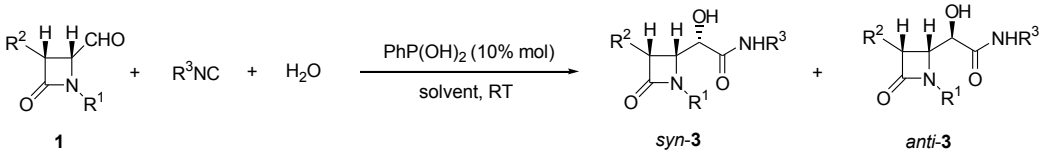
the use of dichloromethane as solvent. In relation with the diastereoselectivity, the use of MeCN/H_2O slightly decreased the *syn/anti* ratio (55:45) (Table 2, entry 3). Thus, we decide to study the scope of the reaction using dichloromethane at room temperature. When the reaction was carried out with β-lactam **1d**, containing a phenoxy instead of a methoxy group at C-3 position of the β-lactam ring, the diastereoselectivity was slightly increased (65:35) in the α-hydroxy amide **3b** (Table 2, entry 4). Next, we decided to investigate the effect of another isocyanide. Thus, the reaction of aldehyde **1a** with BnNC, water and phenyl phosphinic acid, in the above reaction conditions afforded compound **3b** with a comparable diastereoselectivity (60:40) and excellent yield (88%) (Table 2, entry 5).

Taking into consideration that the use of β-lactam aldehydes **1** with aliphatic substituents at nitrogen position increased the diastereoselectivity in the U-3CR, we decided to examine the behaviour of aldehydes **1c** and **1e**. In the event, the reaction of both compounds with *t*-BuNC and phenyl phosphinic acid (10% mol) afforded adducts **3d** and **3e** respectively. Unexpectedly, compound **3d** was isolated in a very low diastereoselectivity (55:45) in 68% yield (Table 2, entry 6). Fortunately, an improved diastereoselectivity (70:30) was observed for compound **3e**, which was isolated in excellent yield (96%) (Table 2, entry 7).

The structure of adducts **2** and **3** was assigned by NMR studies. The relative stereochemistry of compounds **2** has been established in the γ-lactams (see below). However, NMR vicinal coupling constants of the H4 and H4' protons for the *syn*-**3** and *anti*-**3** adducts are very useful information to stablish the relative stereochemistry (see Table S1 in Supporting information). For any pair of diastereomers, the vicinal coupling constant between H4 and H4' is higher for *anti*-isomers ($^3J_{H4,H4'}$ = 5.2–1.6 Hz) than for the *syn*-isomers ($^3J_{H4,H4'}$ = 3.4–1.2 Hz). In addition, the stereochemistry of compounds **3** was finally confirmed by chemical correlation with their corresponding γ-lactones (see

below). Then, by analogy, adducts *syn*-**2** are the major isomers for the previous U-3CR in aldehydes **1**. The observed *syn*-diastereoselectivity for compounds **2** and **3** might be explained by the Felkin-Anh model.[19]

Table 2. P-3CR of 4-oxoazetidine-2-carbaldehydes 1, isocyanides and water in presence of phenyl Phosphinic Acid[a]



Entry	Aldehyde	R^1	R^2	R^3	Solvent	t (h)[b]	Product	*syn/anti*[c]	Yield (%)[d]
1	(+)-**1a**	PMP[e]	MeO	*t*-Bu	CH_2Cl_2	21	**3a**	60:40	60:40
2	(+)-**1a**	PMP[e]	MeO	*t*-Bu	THF/H_2O	48	**3a**	60:40	38:26
3	(+)-**1a**	PMP[e]	MeO	*t*-Bu	MeCN/H_2O	32	**3a**	55:45	37:30
4	(+)-**1d**	PMP[e]	PhO	*t*-Bu	CH_2Cl_2	19	**3b**	65:35	59:32
5	(+)-**1a**	PMP[e]	MeO	Bn	CH_2Cl_2	20	**3c**	60:40	55:35
6	(–)-**1c**	Bn	Pht[f]	*t*-Bu	CH_2Cl_2	21	**3d**	55:45	37:31
7	(+)-**1e**	2-Propynyl	PhO	*t*-Bu	CH_2Cl_2	20	**3e**	70:30	67:29

[a]All reactions were performed by using an aldehyde/isocyanide/water ratio of 1.0:1.1:1.1 mmol. [b]Reaction progress was followed by TLC. [c]The *syn/anti* ratio was determined by integration of well-resolved signals in the ^{1}H NMR spectra (300 MHz) of the crude reaction mixtures before purification. [d]Yield of pure, isolated isomers with correct analytical and spectral data. [e]PMP = 4-$MeOC_6H_4$.

The 3-substituted 3-hydroxy β-lactam scaffold is an efficient carboxylate mimic,[20] showing interesting activity in acyl CoA-cholesterol acyltransferase inhibition assays. In addition, it is found in several monobactams with interesting pharmacological activities such as sulfacezin (A) (Figure 1), and related compounds. Due to the importance of the 3-hydroxy-3-substituted β-lactam skeleton, we have reported the synthesis of these compounds using different synthetic strategies.[16,21]

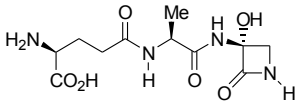


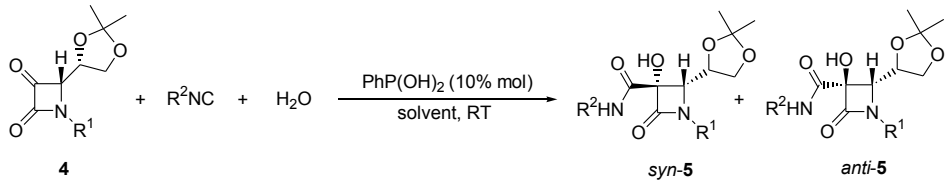
Figure 1. Sulfacezin (A), a representative example of a compound containing the 3-substituted 3-hydroxy β-lactam framework.

The results obtained with oxoazetidine-2-carbaldehydes **1** encouraged us to screen the P-3CR in azetidine-2,3-diones **4**. The starting materials, enantiopure azetidine-2,3-diones **4**, were efficiently prepared from aromatic or aliphatic (*R*)-2,3-*O*-isopropylideneglyceraldehyde-derived imines by Staudinger reaction with acetoxyacetyl chloride in the presence of Et_3N, followed by sequential transesterification and Swern oxidation, as we have previously reported.[22]

First, we examined the reaction of azetidine-2,3-dione **4a** with BnNC, water and phenyl phosphinic acid (10% mol), affording α-hydroxy amide **5a** with complete *syn*-diastereoselectively (with cis configuration between the β-lactam H4 and the amide group on C3) and good yield (78%). Analogously, the reaction of ketene **4b** with BnNC and water, in the above reaction conditions afforded 3-substituted 3-hydroxy-β-lactam **5b** in excellent yield and total diastereoselectivity. The reaction of azetidine-2,3-diones **4a** and **4d** using *t*-BuNC afforded compounds **5c** and **5d** in total diastereoselectivity although, compound **5c** was isolated in low yield. The use of ethyl isocyanoacetate with ketone **4a** gave compound **5e** with 45% yield and total diastereoselectivity.

The diastereoselectivity is controlled by the presence of the substituent placed at C-4 position of the β-lactam ring, which blocks preferentially one face of the carbonyl group. Thus, the nucleophilic addition takes place to the less hindered face of the carbonyl group, affording P-3CR adducts **3** as single isomers.[16a, 23]

Table 3. P-3CR of azetidine-2,3-diones 4, isocyanides and water in presence of phenyl phosphinic acid[a]



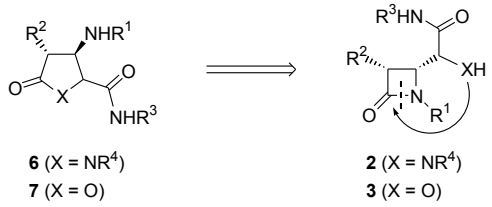
Entry	Ketone	R^1	R^2	t (h)[b]	Product	*syn/anti*[c]	Yield (%)[d]
1	(+)-**4a**	PMP[e]	Bn	45	**(−)-5a**	100:0	78
2	(−)-**4b**	Bn	Bn	27	**(−)-5b**	100:0	80
3	(+)-**4a**	PMP[e]	*t*-Bu	48	**(−)-5c**	100:0	48
4	(−)-**4c**	2-propenyl	*t*-Bu	23	**(−)-5d**	100:0	71
5	(+)-**4a**	PMP[e]	CH_2CO_2Et	72	**(+)-5e**	100:0	45

[a]All reactions were performed by using a ketone/isocyanide/water ratio of 1.0:1.1:1.1 mmol. [b]Reaction progress was followed by TLC. [c]The *syn/anti* ratio was determined by integration of well-resolved signals in the ^{1}H NMR spectra (300 MHz) of the crude reaction mixtures before purification. [d]Yield of pure, isolated isomers with correct analytical and spectral data. [e]PMP = 4-$MeOC_6H_4$.

Synthesis of γ-Lactams and γ-Lactones via N1−C2 Ring Cleavage/Cyclization of U-3CR Adduct 2 and P-3CR Adduct 3, Respectively

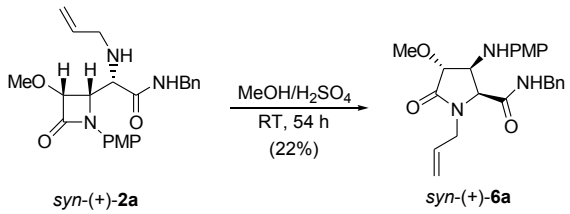
Taking into account the importance of γ-lactam and γ-lactone skeletons, we decide to take advantage of the highly functionalized adducts **2** and **3** to access to these 5-membered rings. In fact, rearrangement reactions of both adduct would result a stereoselective synthetic pathway to functionalized γ-lactams **6** and γ-lactones **7** (Scheme 2).

Scheme 2. Possible N1−C2 β-lactam ring cleavage/cyclization of Ugi adducts 2 and Passerini adducts 3



N1–C2 β-lactam ring cleavage/cyclization usually takes place in acidic or basic conditions. To explore the process, compound *syn*-**2a** containing a *p*-methoxyphenyl group in the nitrogen of the β-lactam was employed. It is well known that this kind of β-lactams undergo easy N1–C2 ring cleavage due to the stabilization of the nitrogen anion, acting as a good leaving group. Treatment of adduct *syn*-**2a** under acidic conditions, using a mixture of methanol and sulphuric acid, afforded γ-lactam *syn*-**6a** in low yield (22%) (Scheme 3).

Scheme 3. Synthesis of γ-lactam *syn*-6a via N1–C2 cleavage/cyclization in acidic conditions

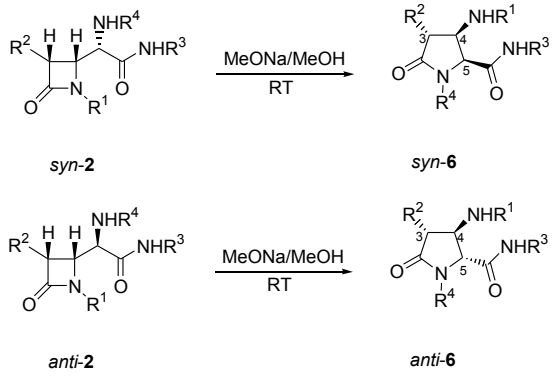


syn-(+)-**2a** *syn*-(+)-**6a**

In order to improve the yield, we decided to carry out the reaction in basic conditions, using a stoichiometric amount of sodium methoxide in methanol. Thus, reaction of compound *syn*-**2a** using one equivalent of sodium methoxide in methanol at room temperature exclusively afforded γ-lactam *syn*-**6a** in excellent yield (84%) after chromatographic purification (Table 1, entry 1). The reaction of isomer *anti*-**2a** under the same reaction conditions gave the expected γ-lactam in 60% yield (Table 1, entry 2). Fortunately, the feasible epimerization of the proton in α position of the amide group was not observed in both experiments. The scope of the reaction was developed using Ugi adducts *syn*-**2b** and *anti*-**2b**, with a *t*-butyl carbamoyl group, affording γ-lactams *syn*-**6b** and *anti*-**6b** in good yields (82 and 71%, respectively). Interestingly, the expansion process took place with Ugi adducts *syn*-**2c** and *anti*-**2c** with a propenyl group substituent in the nitrogen of the β-lactam ring. γ-Lactams *syn*-**6c** and *anti*-**6c** were obtained in excellent yields (81 and 76% respectively) in longer reaction times. It seems reasonable that the expansion reaction of *N*-propenyl substituted β-lactams can be slower than with *N*-PMP substituted

β-lactams, because the negative charge of the nitrogen is not in resonance with the aliphatic group. Next, the influence of an aromatic substituent in the amine group, such as *p*-methoxyphenyl, was studied. Thus, reaction of an inseparable mixture of isomers **2e** (*syn:anti* 64:36) in presence of sodium methoxide and methanol at 35°C, gave β-lactams *syn*-**6d** and *anti*-**6d** as a separable mixture of diastereoisomers by flash chromatography. Isomers *syn*-(+)-**6d** and *anti*-**6d** were isolated in good yields and in the same *syn/anti* ratio (Table 1, entry 7). γ-Lactam *syn*-**6e** was obtained in lower yield (45%) when the reaction was performed using compound *syn*-**2f** with a *p*-nitrophenyl group. It seems reasonable that the nitrogen at this position is less nucleophile than in the rest of the examples.

Table 4. Synthesis of γ-lactams 6 via N1−C2 ring cleavage/cyclization of Ugi adducts 2[a]



syn-**2** *syn*-**6**

anti-**2** *anti*-**6**

Entry	U-3CR adduct	R^1	R^2	R^3	R^4	t(h)[b]	Product	Yield (%)[c]
1	*syn*-(+)-**2a**	PMP[d]	MeO	Bn	2-propenyl	10	*syn*-(+)-**6a**	84
2	*anti*-(+)-**2a**	PMP[d]	MeO	Bn	2-propenyl	10	*anti*-(−)-**6a**	60
3	*syn*-(+)-**2b**	PMP[d]	MeO	*t*-Bu	2-propenyl	23	*syn*-(+)-**6b**	82
4	*anti*-(+)-**2b**	PMP[d]	MeO	*t*-Bu	2-propenyl	23	*anti*-(−)-**6b**	71
5	*syn*-(+)-**2c**	2-propenyl	PhO	Bn	2-propenyl	24	*syn*-(+)-**6c**	81
6	*anti*-(+)-**2c**	2-propenyl	PhO	Bn	2-propenyl	24	*anti*-(+)-**6c**	76
7[e]	**2e**[f]	PMP[d]	MeO	*t*-Bu	PMP[d]	17	*syn*-(+)-**6d**/*anti*-**(+)-6d**	51:28

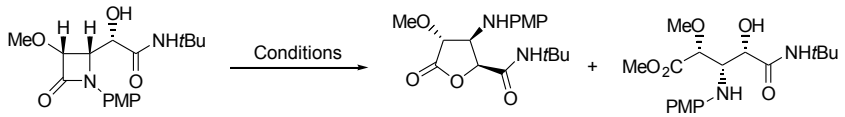
8[e]	*syn*-(+)-**2f**	2-propenyl	PhO	*t*-Bu	PNP[g]	24	*syn*-(+)-**6e**	45

[a]All reactions were performed by using a substrate/MeONa ratio of 1.0:1.0 mmol. [b]Reaction progress was followed by TLC. [c]Yield of pure, isolated isomers with correct analytical and spectral data. [d]PMP = 4-$MeOC_6H_4$. [e]The reaction was performed at 35°C. [f]The starting material was an inseparable mixture of *syn/anti* isomers in 64:36 ratio. [g]PNP = 4-$NO_2C_6H_4$.

Finally, it is important to remark that γ-lactams **6** with an amide group in C5 position, are structurally related to pyroglutamic acid. Thus, compounds **6** are interesting compounds from the chemical and biological point of view.

Satisfied with the above results, we set out to evaluate the N1–C2 ring cleavage/cyclization of Passerini adducts **3**. The application of this methodology would allow access to γ-butyrolactones (Tables 5 and 6). The $FeCl_3$-catalyzed ring expansion reaction of 2-azetidinone-tethered allenic alcohols to give γ-lactones has been recently described in our research group.[24] Thus, we decided to apply the same reaction conditions to substrate *syn*-**3a**. Reaction of α-hydroxy amide *syn*-**3a**, with $FeCl_3 \cdot 6H_2O$ (10 % mol) in dichloroethane at 80 °C, selectively gave γ-lactone *syn*-**7a** in very low yield (23%) (Table 5, entry 1). Then, we decided to try the basic conditions used for the preparation of γ-lactams **6**. Reaction of compound *syn*-**3a** with 1 equivalent of sodium methoxide gave a mixture of γ-lactone *syn*-**7a** (32%) and hydroxyamino ester **8** (47%) (Table 5, entry 2). The use of two equivalents of sodium methoxide at room temperature or under reflux conditions, afforded hydroxyamino ester **8** exclusively (75% and 48% respectively) (Table 5, entries 3 and 4). Unfortunately, the use of excess of sodium methoxide gave compound **8** in lower yield, with partial epimerization after long reaction times. Interestingly, when the reaction was conducted in a mixture of methanol and sulphuric acid gave hydroxyamino ester **8** in good yield (73%) after chromatographic purification (Table 5, entry 5).

Table 5. Reactivity of α-hydroxy amide *syn*-3a



syn-(+)-**3a** *syn*-(+)-**7a** (–)-**8**

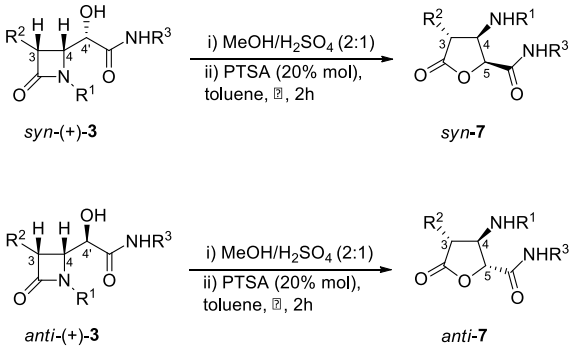
Entry	Conditions	t(h)[a]	*syn*-(+)-**7a**/(–)-**8**[b]	Yield (%)[c]
1	$FeCl_3 \cdot 6H_2O$ (10% mol)/DCE/80 °C	21	100:0	23
2	MeONa (1 equiv.)/MeOH/RT	6	40:60	32:47
3	MeONa (2 equiv.)/MeOH/RT	3	0:100	75
4	MeONa (1 equiv.)/MeOH/reflux	1	0:100	48
5	MeOH (1 equiv.)/H_2SO_4 (2:1)	2	0:100	73

[a]Reaction progress was followed by TLC. [b]The *syn/anti* ratio was determined by integration of well-resolved signals in the ^{1}H NMR spectra (300 MHz) of the crude reaction mixtures before purification. [c]Yield of pure, isolated isomers with correct analytical and spectral data.

Due to the difficulties to obtain γ-lactones in a one pot process from α-hydroxy amides **3**, we decided to prepare these compounds via sequential ring opening followed by lactonization of the α-hydroxy amides **3** in acidic media. Thus, reaction of compound *syn*-**3a** in MeOH/H_2SO_4 (2:1) gave α-hydroxy amide **8**. The cyclization step was carried out using a catalytic amount of *p*-toluenesulfonic acid in toluene at reflux temperature after neutralization and isolation of compound **8**. In the event, enantiomerically pure γ-butyrolactone *syn*-**7a** was isolated in good yield (73%) without epimerization of the α position of the amide group (Table 6, entry 1). However, lactone *anti*-**7a** was obtained in low yield when the reaction was performed with isomer *anti*-**3a**, (Table 6, entry 2). To assess scope, Passerini adducts **3b** and **3c** were tested as precursors. Gratifyingly, compounds **3b** and **3c** were completely and exclusively converted to γ-lactones **7** in moderate yield (Table 6, entries 3–5). Replacement of the *p*-methoxyphenyl group at the nitrogen, by an aliphatic substituent such as 2-propynyl group, in Passerini adduct *syn*-**3d**, also afforded γ-butyrolactone *syn*-**7d** (Table 6, entry 6). However, longer reaction time for the ring opening of the β-lactam was observed.

The structure and stereochemistry of γ-lactams **6** and γ-lactones **7** were assigned by NMR studies. The *cis*-stereochemistry of the four-membered ring was set during the cyclization step. The cyclic structures (by DEPT, HMQC, and COSY) and the stereochemistry (by vicinal proton couplings) of γ-lactams **6** and γ-lactones **7** were established by NMR one- and two-dimensional techniques and NOESY-1D experiments (see Fig 1 in Supporting information). In addition, the vicinal coupling constants between H3, H4 and H4, H5 protons in compounds **6** are higher for *anti,syn*-isomers [(7.0 Hz < $^3J_{3,4}$ < 9.5 Hz); (7.9 Hz < $^3J_{4,5}$< 9.1 Hz)] than for the *anti,anti*-isomers [(7.0 Hz < $^3J_{3,4}$ < 9.5 Hz); (7.9 Hz < $^3J_{4,5}$ < 9.1 Hz)] (see Table S3 in Supporting information). Analogously, for γ-lactones **7**, the vicinal coupling constants between H3, H4 and H5, H4 protons, are higher for *anti,syn*-isomers [(5.7 Hz < $^3J_{3,4}$ < 6.9 Hz); (4.1 Hz < $^3J_{5,4}$< 6.7 Hz)] than for the *anti,anti*-isomers [(4.9 Hz < $^3J_{3,4}$ < 5.1 Hz); (4.7 Hz < $^3J_{5,4}$< 5.4 Hz)] (see Table S4 in Supporting information). Taking into account that U-3CR adducts **2** and P-3CR adducts **3** are converted into γ-lactams **6** and γ-lactones **7**, respectively, the stereochemistries of the carbinolic stereogenic centers for compounds **2** and **3** were confirmed by comparison with well-established five-membered rings **6** and **7**.

Table 6. Synthesis of γ-butyrolactones 7 via sequential ring opening/lactonization of Passerini adducts 3



Entry	P-3CR adduct	R^1	R^2	R^3	t(h)[a]	Product	Yield (%)[b]

1	*syn*-(+)-**3a**	PMP[c]	MeO	*t*-Bu	2	*syn*-(+)-**7a**	73
2	*anti*-(+)-**3a**	PMP[c]	MeO	*t*-Bu	2	*anti*-(−)-**7a**	34
3	*syn*-(+)-**3b**	PMP[c]	MeO	Bn	7	*syn*-(+)-**7b**	47
4	*anti*-(+)-**3b**	PMP[c]	MeO	Bn	7	*anti*-(−)-**7b**	42
5	*syn*-(+)-**3c**	PMP[c]	PhO	*t*-Bu	24	*syn*-(+)-**7c**	57
6	*syn*-(+)-**3d**	2-propynyl	PhO	*t*-Bu	72	*syn*-(+)-**7d**	52

[a]Reaction progress was followed by TLC for the methanolysis step. The reaction time for the lactonization reaction was 2 hours in all cases. [b]Yield of pure, isolated isomers with correct analytical and spectral data. [c]PMP = 4-MeOC$_6$H$_4$

CONCLUSION

In conclusion, firstly, organocatalyzed U-3CR between β-lactam aldehydes, amines, isocyanides and phenyl phosphinic acid has been studied affording the corresponding adducts with moderate diastereoselectivities and good yields. Secondly, organocatalyzed P-3CR between carbonyl β-lactams, isocyanides and water has been described for the fist time. The scope of these multicomponent processes has been investigated and the utility of the resulting products for the selective preparation of highly functionalized γ-lactams and γ-lactones has been demonstrated.

EXPERIMENTAL SECTION[25]

General Methods. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ except otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm) or $CDCl_3$ (^{13}C, 77.0 ppm). Low and high resolution mass spectra were performed on a QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. Specific rotation $[\alpha]_D$ is given in 10^{-1} deg cm^2 g^{-1} at 20 °C, and the concentration (*c*) is expressed in grams per 100 mL. All commercially available compounds were used without further purification. Flash S-2 chromatography was performed by using silica gel 60 (230−400 mesh). Products were identified by TLC. UV light (λ = 254nm) and a

solution of phosphomolibdic acid in EtOH (1 g of phosphomolybdic acid hydrate, 100 mL EtOH) was used to develop the plates.

General Procedure for the Organocatalyzed U-3CR of aldehydes 1. Synthesis of Compounds 2. Method A. To a solution of aldehyde **1** (1 mmol) in anhydrous dichloromethane (5 mL), the corresponding amine (1.1 mmol), the appropriate isocyanide (1.1 mmol) and phenyl phosphinic acid (0.1 mmol) were sequentially added at room temperature under argon atmosphere. The reaction mixture was stirred until complete disappearances of the starting material (TLC). Then, the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with *n*-hexane/ethyl acetate mixtures. **Method B.** To a solution of aldehyde 1 (1 mmol) in anhydrous dichloromethane (5 mL), methyl glycinate chlorhydrate (1.1 mmol) and triethylamine (1.1 mol) were added at room temperature. The reaction mixture was stirred at room temperature for 1 h. Then, t-butyl isocyanide (1.1 mmol) and phenyl phosphinic acid (0.1 mmol) were added at room temperature and under argon atmosphere. The reaction mixture was stirred at room temperature for 14h. Then, the solvent was removed under reduced pressure. The residue was purified by flash chromatography.

Ugi adduct 2a. **Method A.** From 50 mg (1.19 mmol) of aldehyde (+)-**1a**, compound **2a** was obtained as a mixture of isomers in a *syn/anti* ratio (61:39). After flash chromatography (*n*-hexane/ethyl acetate, 1:1) 53 mg (61%) of the less polar compound *syn*-(+)-**2a** and 34 mg (39%) of the more polar compound *anti*-(+)-**2a** were obtained. ***syn*-(+)-2a**. White solid; Mp: 94–95°C (*n*-hexane/ethyl acetate); $[\alpha]_D$ +66.0 (c 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.88 (t, *J* = 5.3 Hz, 1H), 7.26 (m, 5H), 7.12 (m, 2H), 6.73 (*AA'*XX', 2H), 5.74 (m, 1H), 5.08 (m, 2H), 5.00 (dd, *J* = 5.3 Hz, *J* = 1.3 Hz, 1H), 4.68 (d, *J* = 5.3 Hz, 1H), 4.47 (dd, *J* = 14.8, 6.3 Hz, 1H), 4.19 (dd, *J* = 14.8, 5.5 Hz, 1H), 3.74 (s, 3H), 3.65 (s, 3H), 3.40 (s, 1H), 3.29 (dd, *J* = 13.8, 6.4 Hz, 1H), 3.20 (dd, *J* = 13.7, 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 172.8, 164.8, 156.7, 137.6, 135.7, 130.1, 128.6, 127.6, 127.4, 119.3,

117.0, 114.2, 83.2, 59.9, 59.2, 58.8, 55.4, 51.5, 43.3; IR (KBr): ν = 3340, 1749, 1663 cm^{-1}; HRMS (ES): calcd for $C_{23}H_{28}N_3O_4^+$ $[M+H]^+$: 410.2074; found: 410.2068. ***anti*-(+)-2a**. Colorless oil; $[\alpha]_D$ +123.2 (c 0.4, $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$, 25°C): δ = 8.14 (t, *J* = 5.6 Hz, 1H), 7.40 (AA'*XX'*, 2H), 7.30 (m, 5H), 6.91 (*AA'*XX', 2H), 5.70 (m, 1H), 5.11 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.84 (m, 2H), 4.69 (d, *J* = 5.1 Hz, 1H), 4.57 (dd, *J* = 14.9, 6.7 Hz, 1H), 4.34 (dd, *J* = 15.0, 5.3 Hz, 1H), 3.90 (d, *J* = 3.6 Hz, 1H), 3.81 (s, 3H), 3.47 (s, 3H), 3.24 (dd, *J* = 13.9, 5.4 Hz, 1H), 2.89 (dd, *J* = 13.9, 7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 172.0, 164.4, 156.6, 138.3, 135.9, 130.6, 128.6, 127.5, 127.3, 118.4, 117.3, 114.6, 83.8, 60.0, 58.6, 57.0, 55.4, 51.2, 43.0; IR ($CHCl_3$): ν = 3346, 1748, 1659 cm^{-1}; HRMS (ES): calcd for $C_{23}H_{28}N_3O_4^+$ $[M+H]^+$: 410.2074; found: 410.2076.

Ugi adduct 2b. **Method A.** From 60 mg (0.26 mmol) of aldehyde (+)-**1a**, compound **2b** was obtained as a mixture of isomers in a *syn/anti* ratio (63:37). After flash chromatography (*n*-hexane/ethyl acetate, 1:3) 33 mg (34%) of the less polar compound *syn*-(+)-**2b** and 55 mg (58%) of the more polar compound *anti*-(+)-**2a** were obtained. ***syn*-(+)-2b**. Colorless oil; $[\alpha]_D$ +85.5 (c 0.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.66 (bs, 1H), 7.38 (AA'*XX'*, 2H), 6.88 (*AA'*XX', 2H), 5.63 (m, 1H), 5.02 (dd, *J* = 5.1, 3.6 Hz, 1H), 4.87 (m, 2H), 4.67 (d, *J* = 5.2 Hz, 1H), 3.79 (s, 3H), 3.72 (d, *J* = 3.4 Hz, 1H), 3.55 (s, 3H), 3.23 (ddt, *J* = 14.1, 5.4 Hz, 1.5 Hz, 1H), 2.88 (dd, *J* = 14.2, 6.7 Hz, 1H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 171.1, 164.4, 156.5, 136.1, 130.7, 118.4, 116.8, 114.5, 83.8, 60.1, 58.9, 57.6, 55.4, 51.3, 50.6, 28.6; IR ($CHCl_3$): ν = 3339, 1749, 1666 cm^{-1}; HRMS (ES): calcd for $C_{20}H_{30}N_3O_4^+$ $[M+H]^+$: 376.2231; found: 376.2244. ***anti*-(+)-2b**. Colorless oil; $[\alpha]_D$ +70.7 (c 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.50 (bs, 1H), 7.30 (AA'*XX',* 2H), 6.82 (*AA'*XX', 2H), 5.80 (m, 1H), 5.12 (m, 2H), 4.98 (d, *J* = 5.1 Hz, 1H), 4.66 (d, *J* = 5.2 Hz, 1H), 3.78 (3H, s), 3.65 (s, 3H), 3.36 (dd, *J* = 14.0, 6.2 Hz, 1H), 3.20 (bs, 1H), 3.17 (dd, *J* = 14.3, 6.0 Hz, 1H), 1.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 171.6, 165.1, 156.8, 136.0, 130.4, 119.6, 116.7, 114.3, 83.2, 59.9, 59.5,

58.7, 55.5, 51.4, 28.4, 50.6; IR ($CHCl_3$): ν = 3332, 1750, 1668 cm^{-1}; HRMS (ES): calcd for $C_{20}H_{30}N_3O_4^+$ $[M+H]^+$: 376.2231; found: 376.2234.

Ugi adduct 2c. **Method A.** From 50 mg (0.22 mmol) of aldehyde (–)-**1b**, compound **2c** was obtained as a mixture of isomers in a *syn/anti* ratio (72:28). After flash chromatography (CH_2Cl_2/ethyl acetate, 3:1) 42 mg (48%) of the less polar compound *syn*-(+)-**2c** and 16 mg (18%) of the more polar compound *anti*-(+)-**2c** were obtained. ***syn*-(+)-2c**. White solid. Mp: 108–109°C (*n*-hexane/ethyl acetate); $[\alpha]_D$ +17.4 (c 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.74 (bs, 1H), 7.30 (m, 7H), 7.04 (m, 3H), 5.74 (m, 2H), 5.30 (d, *J* = 4.9 Hz, 1H), 5.12 (m, 4H), 4.54 (dd, *J* = 4.9, 3.0 Hz, 1H), 4.41 (d, *J* = 6.0 Hz, 2H), 4.07 (ddt, *J* = 15.4, 5.6 Hz, 1.4 Hz, 1H), 3.60 (dd, *J* = 15.4, 7.0 Hz, 1H), 3.40 (d, *J* = 2.9 Hz, 1H), 3.25 (d, *J* = 6.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 171.8, 165.6, 157.3, 137.7, 135.5, 130.7, 129.7, 128.7, 127.8, 127.6, 122.6, 119.2, 117.1, 115.4, 80.8, 60.3, 59.0, 51.4, 44.4, 43.4; IR ($CHCl_3$): ν = 3319, 1757, 1656 cm^{-1}; HRMS (ES): calcd for $C_{24}H_{28}N_3O_3^+$ $[M+H]^+$: 406.2125; found: 406.2106. ***anti*-(+)-2c**. White solid. Mp: 125–126°C (*n*-hexane/ethyl acetate); $[\alpha]_D$ +50.7 (c 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.77 (t, *J* = 5.5 Hz, 1H), 7.29 (m, 5H), 7.17 (m, 2H), 7.03 (m, 3H), 5.79 (m, 2H), 5.33 (d, *J* = 4.9 Hz, 1H), 5.21 (m, 4H), 4.61 (t, *J* = 4.9 Hz, 1H), 4.40 (dd, *J* = 14.2, 6.3 Hz, 1H), 4.25 (ddt, *J* = 15.4, 5.4, 1.4 Hz, 1H), 4.11 (dd, *J* = 14.8, 5.6 Hz, 1H), 3.65 (d, *J* = 4.8 Hz, 1H), 3.63 (dd, *J* = 15.2, 7.4 Hz, 1H), 3.38 (dd, *J* = 13.9, 6.0 Hz, 1H), 3.25 (dd. *J* =13.9, 6.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 171.0, 165.7, 157.2, 137.8, 135.7, 130.6, 129.6, 128.6, 127.7, 127.4, 122.7, 119.8, 117.3, 115.6, 81.1, 59.9, 58.9, 51.7, 43.7, 43.2; IR ($CHCl_3$): ν = 3332, 1755, 1658 cm^{-1}; HRMS (ES): calcd for $C_{24}H_{28}N_3O_3^+$ $[M+H]^+$: 406.2125; found: 406.2121.

Ugi adduct 2d. **Method B.** From 89 mg (0.27 mmol) of aldehyde (–)-**1c**, compound **2d** was obtained as a mixture of isomers in a *syn/anti* ratio (70:30). After flash chromatography (*n*-hexane/ethyl acetate, 1:3) 100 mg (74%) of an inseparable mixture of isomers *syn*-**2d** and *anti*-**2d** was obtained. ***syn*-**

2d. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.86 (AA'*BB'*, 2H), 7.74 (*AA'*BB', 2H), 7.33 (m, 5H), 6.24 (bs, 1H), 5.45 (d, *J* = 5.3 Hz, 1H), 4.73 (d, *J* = 15.2 Hz, 1H), 4.60 (d, *J* = 15.2 Hz, 1H), 4.04 (dd, *J* = 7.8, 5.3 Hz, 1H), 3.64 (s, 3H), 3.29 (d, *J* = 7.9 Hz, 1H), 3.09 (d, *J* = 17.2 Hz, 1H), 2.97 (d, *J* = 17.1 Hz, 1H), 2.03 (bs, 1H), 1.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 171.7, 169.4, 164.6, 135.8, 134.5, 131.9, 128.9, 128.2, 127.9, 123.7, 62.9, 59.6, 55.6, 51.8, 51.0, 48.0, 46.1, 28.2; HRMS (ES): calcd for $C_{27}H_{31}N_4O_6^+$ $[M+H]^+$: 507.2238; found: 507.2255. ***anti*-2d**. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.86 (2H, AA'*BB'*), 7.74 (*AA'*BB', 2H), 7.33 (m, 5H), 6.49 (bs, 1H), 5.37 (d, *J* = 5.3 Hz, 1H), 4.68 (d, *J* = 15.2 Hz, 1H), 4.40 (d, *J* = 15.0 Hz, 1H), 4.11 (dd, *J* = 6.9, 5.4 Hz, 1H), 3.45 (s, 3H), 3.26 (d, *J* = 7.2 Hz, 1H), 3.00 (d, *J* = 17.2 Hz, 1H), 2.85 (d, *J* = 17.4 Hz, 1H), 2.03 (bs, 1H), 1.13 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 171.4, 167.4, 164.3, 135.5, 134.4, 131.9, 129.0, 128.3, 128.0, 123.7, 61.8, 58.7, 56.4, 51.6, 51.1, 48.4, 45.6, 28.3.

Ugi adduct 2e. **Method A.** From 50 mg (0.21 mmol) of aldehyde (+)-**1a**, compound **2e** was obtained as a mixture of isomers in a *syn/anti* ratio (64:36). After flash chromatography (*n*-hexane/ethyl acetate, 1:1) 70 mg (74%) of an inseparable mixture of isomers *syn*-**2e** and *anti*-**2e** was obtained. ***syn*-2e**. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.12 (m, 2H), 7.09 (AA'*XX'*, 2H), 6.68 (*AA'*XX', 2H), 6.58 (m, 2H), 5.19 (bs, 1H), 4.76 (d, *J* = 5.1 Hz, 1H), 4.44 (d, *J* = 2.6 Hz, 1H), 3.74 (s, 3H), 3.671 (s, 3H), 3.669 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 170.0, 163.6, 156.2, 153.1, 140.2, 130.0, 118.5, 115.9, 114.5, 113.9, 83.7, 60.3, 58.9, 57.9, 55.6, 55.3, 51.0, 28.6. HRMS (ES): calcd for $C_{24}H_{32}N_3O_5^+$ $[M+H]^+$: 442.2336; found: 442.2336. ***anti*-2e**. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.38 (AA'*XX'*, 2H), 6.85 (*AA'*XX', 2H), 6.77 (AA'*XX'*, 2H), 6.58 (m, 2H), 5.09 (dd, *J* = 5.2, 1.7 Hz, 1H), 4.68 (d, *J* = 5.3 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.67 (m, 1H), 3.43 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 171.0, 165.1, 156.8, 153.3, 140.6, 130.1, 119.5, 115.8, 114.5, 114.3, 82.9, 59.5, 58.2, 59.0, 55.5, 55.4, 51.0, 28.3.

Ugi adduct 2f. **Method A.** From 53 mg (0.14 mmol) of aldehyde (+)-**1d**, compound **2f** was obtained as a mixture of isomers in a *syn/anti* ratio (70:30). After flash chromatography (*n*-hexane/ethyl acetate, 1:1) 21 mg (28%) of the less polar compound *anti*-(+)-**2f** and 50 mg (64%) of the more polar compound *syn*-(+)-**2f** were obtained. ***syn*-(+)-2f**. White solid. Mp: 141–143°C (*n*-hexane/ethyl acetate); $[\alpha]_D$ +82.7 (c 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.55 (t, *J* = 5.6 Hz, 1H), 7.30 (m, 5H), 7.08 (m, 7H), 6.69 (*AA'*XX', 2H), 6.51 (AA'*XX'*, 2H), 6.47 (*AA'*XX', 2H), 5.51 (d, *J* = 5.0 Hz, 1H), 5.40 (dd, *J* = 4.8, 3.5 Hz, 1H), 4.72 (d, *J* = 3.4 Hz, 1H), 4.34 (dd, *J* = 14.5, 5.6 Hz, 1H), 4.34 (dd, *J* = 14.5, 5.6 Hz, 1H), 4.20 (dd, *J* = 14.6, 6.0 Hz, 1H), 3.65 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 170.6, 162.2, 157.2, 156.6, 153.4, 140.1, 137.6, 129.7, 129.6, 128.7, 127.8, 127.5, 123.1, 118.8, 116.2, 116.1, 114.6, 114.2, 81.1, 58.2, 59.0, 55.6, 55.4, 43.4; IR (KBr): ν = 3374, 1750, 1661 cm^{-1}; HRMS (ES): calcd for $C_{32}H_{32}N_3O_5^+$ $[M+H]^+$: 538.2336; found: 538.2311. ***anti*-(+)-2f**. White solid. Mp: 150–151°C (*n*-hexane/ethyl acetate); $[\alpha]_D$ +66.2 (c 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.59 (t, *J* = 5.6 Hz, 1H), 7.36 (AA'*XX'*, 2H), 7.25 (m, 3H), 7.19 (t, *J* = 8.0 Hz, 2H), 7.08 (m, 2H), 6.96 (t, *J* = 7.3 Hz, 1H), 6.77 (d, *J* = 8.8 Hz, 2H), 6.74 (AA'*XX'*, 2H), 6.65 (*AA'*XX', 2H), 6.57 (*AA'*XX', 2H), 5.53 (d, *J* = 5.1 Hz, 1H), 5.43 (d, *J* = 5.3 Hz, 1H), 4.44 (dd, *J* = 14.8, 6.3 Hz, 1H), 4.36 (dd, *J* = 14.9, 5.7 Hz, 1H), 4.08 (s, 1H), 3.77 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 172.1, 163.4, 157.1, 156.8, 153.7, 140.5, 137.4, 129.9, 129.5, 128.6, 127.8, 127.5, 122.3, 119.3, 116.1, 115.1, 114.8, 114.6, 79.3, 58.44, 58.42, 55.8, 55.5, 43.6; IR (KBr): ν = 3350, 1754, 1664 cm^{-1}; HRMS (ES): calcd for $C_{32}H_{32}N_3O_5^+$ $[M+H]^+$: 538.2336; found: 538.2317.

Ugi adduct 2g. **Method A.** From 58 mg (0.25 mmol) of aldehyde (–)-**1b**, compound **2g** was obtained as a mixture of isomers in a *syn/anti* ratio (68:32). After flash chromatography (diethyl ether) 24 mg (21%) of the less polar compound *anti*-(+)-**2g** and 52 mg (46%) of the more polar compound *syn*-(+)-**2g** were obtained. ***syn*-(+)-2g**. Yellowish solid. Mp: 193–194°C (*n*-hexane/ethyl acetate); $[\alpha]_D$ +5.8

(c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25°C): δ = 8.11 (AA'*XX'*, 2H), 7.25 (m, 2H), 7.02 (m, 1H), 6.88 (m, 2H), 6.67 (*AA'*XX', 2H), 6.51 (bs, 1H), 5.77 (m, 1H), 5.39 (d, *J* = 5.1 Hz, 1H), 5.25 (m, 3H), 4.56 (t, *J* = 5.0 Hz, 1H), 4.21(dd, *J* = 6.3, 5.3 Hz, 1H), 4.15 (ddt, *J* = 15.3, 5.6, 1.2 Hz, 1H), 3.51 (dd, *J* = 15.3, 7.2 Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 168.1, 165.9, 156.5, 152.0, 139.8, 130.4, 129.7, 126.1, 122.8, 120.1, 115.1, 112.8, 80.1, 58.0, 57.1, 51.8, 44.5, 28.5; IR (KBr): ν = 3301, 1755 cm^{-1}; HRMS (ES): calcd for $C_{24}H_{29}N_4O_5^+$ $[M+H]^+$: 453.2132; found: 453.2133.

***anti*-(+)-2g**. Yellowish solid. Mp: 189–190°C (*n*-hexane/ethyl acetate); $[\alpha]_D$ +63.4 (c 0.1, $CHCl_3$) ^1H NMR (300 MHz, $CDCl_3$, 25°C): δ = 8.15 (AA'*XX'*, 2H), 7.39 (m, 2H), 7.14 (m, 3H), 6.62 (*AA'*XX', 2H), 6.58 (bs, 1H), 5.60 (m, 2H), 5.43 (d, *J* = 5.0 Hz, 1H), 5.19 (m, 2H), 4.59 (dd, *J* = 5.0, 2.6 Hz, 1H), 4.43 (dd, *J* = 7.8, 2.6 Hz, 1H), 4.03 (ddt, *J* = 15.4, 5.7, 1.3 Hz, 1H), 3.55 (dd, *J* = 15.3, 7.2 Hz, 1H), 1.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 166.7, 165.0, 156.6, 151.2, 139.8, 130.4, 130.0, 126.5, 123.6, 120.2, 115.8, 112.2, 81.0, 58.3, 56.3, 51.8, 43.8, 28.5; IR (KBr): ν = 3300, 1761 cm^{-1}; HRMS (ES): calcd for $C_{24}H_{29}N_4O_5^+$ $[M+H]^+$: 453.2132; found: 453.2126.

General Procedure for the Organocatalyzed P-3CR of aldehydes 1. Synthesis of Compounds 3. To a solution of aldehyde **1** (1 mmol) in anhydrous dichloromethane (5 mL), water (1.1 mmol), the appropriate isocyanide (1.1 mmol) and phenyl phosphinic acid (0.1 mmol) were sequentially added at room temperature under argon atmosphere. The reaction mixture was stirred until complete disappearances of the starting material (TLC). Then, the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with n-hexane/ethyl acetate mixtures.

Passerini adduct 3a. From 100 mg (0.42 mmol) of aldehyde (+)-**1a**, compound **3a** was obtained as a mixture of isomers in a *syn/anti* ratio (60:40). After flash chromatography (*n*-hexane/ethyl acetate, 1:2) 57 mg (40%) of the less polar compound *anti*-(+)-**3a** and 86 mg (60%) of the more polar compound *syn*-(+)-**3a** were obtained. ***syn*-(+)-3a**. White solid. Mp: 116–117°C (*n*-hexane/ethyl acetate); $[\alpha]_D$ +45.2

(c 0.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.40 (AA'*XX,* 2H,), 6.80 (*AA'*XX', 2H), 6.59 (bs, 1H), 4.94 (dd, *J* = 5.2, 1.2 Hz, 1H), 4.71 (d, *J* = 5.2 Hz, 1H), 4.27 (d, *J* = 1.2 Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 1.22 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 169.2, 164.2, 156.7, 130.2, 120.0, 114.2, 82.8, 69.2, 60.0, 58.2, 55.4, 50.9, 28.4; IR (KBr): ν = 3394, 1747 cm^{-1}; HRMS (ES): calcd for $C_{17}H_{25}N_2O_5^+$ $[M+H]^+$: 337.1758; found: 337.1765. ***anti*-(+)-3a**. White solid. Mp: 158–159°C (*n*-hexane/ethyl acetate); $[\alpha]_D$ +83.9 (c 0.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.41 (AA'*XX'*, 2H), 6.83 (m, 1H), 6.85 (*AA'*XX', 2H), 4.80 (dd, *J* = 5.2, 1.6 Hz, 1H), 4.73 (d, *J* = 5.2 Hz, 1H), 4.48 (d, *J* = 1.1 Hz, 1H), 3.87 (bs, 1H), 3.78 (s, 3H), 3.69 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 169.4, 163.5, 156.6, 130.2, 118.9, 114.4, 83.2, 68.8, 60.0, 59.5, 55.4, 51.4, 28.6; IR (KBr): ν = 3393, 1747, 1664 cm^{-1}; HRMS (ES): calcd for $C_{17}H_{25}N_2O_5^+$ $[M+H]^+$: 337.1758; found: 337.1757.

Passerini adduct 3b. From 67 mg (0.22 mmol) of aldehyde (+)-**1a**, compound **3b** was obtained as a mixture of isomers in a *syn/anti* ratio (65:35). After flash chromatography (*n*-hexane/ethyl acetate, 1:1) 53 mg (59%) of the less polar compound *syn*-(+)-**3b** and 29 mg (32%) of the more polar compound *anti*-(+)-**3b** were obtained. ***syn*-(+)-3b**. White solid; Mp: 167–169°C (*n*-hexane/ethyl acetate); $[\alpha]_D$ +72.5 (c 1.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.45 (AA'*XX'*, 2H), 7.34 (m, 2H), 7.06 (m, 3H), 6.83 (*AA'*XX', 2H), 6.64 (bs, 1H), 5.45 (d, *J* = 5.1 Hz, 1H), 5.20 (d, *J* = 5.6 Hz, 1H), 4.41 (d, *J* = 4.0 Hz, 1H), 3.78 (s, 3H), 3.13 (d, *J* = 4.2 Hz, 1H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 169.2, 162.7, 156.9, 156.8, 130.2, 129.9, 123.2, 120.0, 115.9, 114.3, 80.1, 68.8, 58.5, 55.4, 51.0, 28.4; IR (KBr): ν = 3390, 1751, 1664 cm^{-1}; HRMS (ES): calcd for $C_{22}H_{27}N_2O_5^+$ $[M+H]^+$: 399.1914; found: 399.1927. ***anti*-(+)-3b**. White solid; Mp: 127–128°C (*n*-hexane/ethyl acetate); $[\alpha]_D$ +108.2 (c 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.47 (AA'*XX'*, 2H), 7.35 (m, 2H), 7.12 (m, 3H), 6.88 (*AA'*XX', 2H), 6.76 (bs, 1H), 5.48 (d, *J* = 5.3 Hz, 1H), 5.00 (dd, *J* = 5.3, 1.8 Hz, 1H), 4.61 (s, 1H), 3.79 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 168.8, 162.2, 156.8, 156.7, 130.0, 129.9,

123.5, 119.0, 116.0, 114.4, 80.4, 68.8, 59.9, 55.4, 51.5, 28.5; IR (KBr): ν = 3384, 1752, 1656 cm^{-1}; HRMS (ES): calcd for $C_{22}H_{27}N_2O_5^+$ $[M+H]^+$: 399.1914; found: 399.1897.

Passerini adduct 3c. From 103 mg (0.44 mmol) of aldehyde (+)-**1a**, compound **3c** was obtained as a mixture of isomers in a *syn/anti* ratio (60:40). After flash chromatography (*n*-hexane/ethyl acetate, 1:2) 57 mg (35%) of the less polar compound *anti*-(+)-**3c** and 86 mg (53%) of the more polar compound *syn*-(+)-**3c** were obtained. ***syn*-(+)-3c**. White solid; Mp: 157–159°C (*n*-hexane/ethyl acetate); $[\alpha]_D$ +67.3 (c 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.45 (AA'*XX'*, 2H), 7.34 (m, 2H), 7.06 (m, 3H), 6.83 (*AA'*XX', 2H), 6.64 (bs, 1H), 5.45 (d, *J* = 5.1 Hz, 1H), 5.20 (d, *J* = 5.6 Hz, 1H), 4.41 (d, *J* = 4.0 Hz, 1H), 3.78 (s, 3H), 3.13 (d, *J* = 4.2 Hz, 1H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 169.2, 162.7, 156.9, 156.8, 130.2, 129.9, 123.2, 120.0, 115.9, 114.3, 68.8, 58.5, 55.4, 51.0, 28.4; IR (KBr): ν = 3295, 1732, 1652 cm^{-1}; HRMS (ES): calcd for $C_{20}H_{23}N_2O_5^+$ $[M+H]^+$: 371.1601; found: 371.1608. ***anti*-(+)-3c**. White solid; Mp: 135–136°C (*n*-hexane/ethyl acetate); $[\alpha]_D$ +107.6 (c 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.39 (AA'*XX'*, 2H), 7.30 (m, 5H), 7.20 (t, *J* = 5.6 Hz, 1H), 6.88 (*AA'*XX', 2H), 4.95 (dd, *J* = 5.0, 2.6 Hz, 1H), 4.75 (d, *J* = 5.1 Hz, 1H), 4.69 (s, 1H), 4.58 (dd, *J* = 14.8, 6.4 Hz, 1H), 4.38 (dd, *J* = 14.8, 5.4 Hz, 1H), 3.79 (s 3H), 3.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 171.0, 163.5, 156.7, 137.7, 129.8, 128.6, 127.7, 127.6, 118.9, 114.5, 83.7, 68.8, 60.0, 58.3, 55.4, 43.2; IR (KBr): ν = 3354, 1746, 1656 cm^{-1}; HRMS (ES): calcd for $C_{20}H_{23}N_2O_5^+$ $[M+H]^+$: 371.1601; found: 371.1583.

Passerini adduct 3d. From 51 mg (0.15 mmol) of aldehyde (–)-**1c**, compound **3d** was obtained as a mixture of isomers in a *syn/anti* ratio (55:45). After flash chromatography (diethyl ether) 25 mg (37%) of the less polar compound *syn*-(+)-**3d** and 20 mg (31%) of the more polar compound *anti*-(+)-**3d** were obtained. ***syn*-(–)-3d**. Colorless oil; $[\alpha]_D$ –6.5 (c 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.88 (AA'*BB'*, 2H), 7.77 (*AA'*BB', 2H), 7.35 (m, 5H), 6.54 (bs, 1H), 5.50 (d, *J* = 5.4 Hz, 1H), 4.72 (d, *J* =

15.2 Hz, 1H), 4.64 (dd, *J* = 5.5, 3.4 Hz, 1H), 4.31 (d, *J* = 15.1 Hz, 1H), 4.03 (t, *J* = 3.9 Hz, 1H), 3.81 (d, *J* = 4.5 Hz, 1H), 1.27 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 169.3, 167.9, 164.1, 135.5, 134.7, 131.5, 129.0, 128.2, 128.0, 124.0, 68.9, 59.3, 56.0, 51.0, 46.4, 28.5; IR ($CHCl_3$): ν = 3384, 1760, 1720, 1670 cm^{-1}; HRMS (ES): calcd for $C_{24}H_{26}N_3O_5^+$ $[M+H]^+$: 436.1867; found: 436.1867. ***anti*-(+)-3d**. Colorless oil; $[\alpha]_D$ +18.2 (c 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.87 (AA'*BB'*, 2H), 7.78 (*AA'*BB', 2H), 7.36 (m, 5H), 6.21 (bs, 1H), 5.50 (d, *J* = 5.3 Hz, 1H), 4.75 (d, *J* = 14.9 Hz, 1H), 4.40 (t, *J* = 5.2 Hz, 1H), 4.39 (d, *J* = 15.3 Hz, 1H), 4.17 (dd, *J* = 7.8, 5.5 Hz, 1H), 3.76 (d, *J* = 7.8 Hz, 1H), 0.95 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 169.3, 163.7, 134.8, 134.7, 131.6, 129.2, 128.3, 128.3, 123.9, 68.5, 58.6, 55.5, 50.8, 45.7, 28.1; IR ($CHCl_3$): ν = 3382, 1761, 1722, 1668 cm^{-1}; HRMS (ES): calcd for $C_{24}H_{26}N_3O_5^+$ $[M+H]^+$: 436.1867; found: 436.1872.

Passerini adduct 3e. From 81 mg (0.36 mmol) of aldehyde (+)-**1e**, compound **3e** was obtained as a mixture of isomers in a *syn/anti* ratio (70:30). After flash chromatography (*n*-hexane/ethyl acetate, 3:2) 78 mg (67%) of the less polar compound *syn*-(+)-**3e** and 34 mg (29%) of the more polar compound *anti*-(+)-**3e** were obtained. ***syn*-(+)-3e**. White solid; Mp: 137–138°C (*n*-hexane/ethyl acetate); $[\alpha]_D$ +39.6 (c 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.34 (m, 2H), 7.10 (m, 3H), 6.70 (bs, 1H), 5.35 (d, *J* = 5.0 Hz, 1H), 4.59 (dd, *J* = 5.0, 3.1 Hz, 1H), 4.40 (d, *J* = 3.1 Hz, 1H), 4.36 (dd, *J* = 17.8, 2.6 Hz, 1H), 3.85 (dd, *J* = 17.7, *J* = 2.5 Hz, 1H), 2.31 (t, *J* = 2.5 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 168.7, 164.7, 156.6, 129.9, 123.3, 115.8, 80.8, 76.1, 73.1, 69.4, 58.6, 51.3, 30.9, 28.6; IR (KBr): ν = 3297, 3384, 1763, 1666 cm^{-1}; HRMS (ES): calcd for $C_{18}H_{23}N_2O_4^+$ $[M+H]^+$: 331.1652; found: 331.1652. ***anti*-(+)-3e**. White solid; Mp: 88–90°C (*n*-hexane/ethyl acetate); $[\alpha]_D$ +86.4 (c 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.33 (m, 2H), 7.09 (m, 3H), 6.72 (bs, 1H), 5.37 (d, *J* = 5.0 Hz, 1H), 4.60 (dd, *J* = 4.8, 3.4 Hz, 1H), 4.50 (d, *J* = 3.1 Hz, 1H), 4.36 (dd, *J* = 17.8, 2.6 Hz, 1H), 4.01 (dd, *J* = 17.7, 2.5 Hz, 1H), 2.33 (t, *J* = 2.5 Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$,

25°C): δ = 169.2, 164.8, 156.7, 129.8, 123.3, 115.9, 81.5, 75.9, 73.3, 69.7, 59.1, 51.4, 30.4, 28.5; IR (KBr): ν = 3295, 3388, 1761, 1660 cm^{-1}; HRMS (ES): calcd for $C_{18}H_{23}N_2O_4^+$ $[M+H]^+$: 331.1652; found: 331.1665.

General Procedure for the Organocatalyzed P-3CR of ketones 4. Synthesis of Compounds 5. To a solution of ketone **4** (1 mmol) in anhydrous dichloromethane (5 mL), water (1.1 mmol), the appropriate isocyanide (1.1 mmol) and phenyl phosphinic acid (0.1 mmol) were sequentially added at room temperature under argon atmosphere. The reaction mixture was stirred until complete disappearances of the starting material (TLC). Then, the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with n-hexane/ethyl acetate mixtures.

Passerini adduct *syn*-(−)-5a. From 44 mg (0.15 mmmol) of azetidine-2,3-dione (+)-**4a**, 50 mg (78%) of compound *syn*-(−)-**5a** was obtained as a white solid after purification by flash chromatography (*n*-hexane/ethyl acetate, 2:1).[26]

Passerini adduct *syn*-(−)-5b. From 60 mg (0.22 mmmol) of azetidine-2,3-dione (−)-**4b**, 66 mg (80%) of compound *syn*-(−)-**5b** was obtained as a white solid after purification by flash chromatography (*n*-hexane/ethyl acetate, 1:1). Mp: 148−149°C (*n*-hexane/ethyl acetate); $[\alpha]_D$ −79.7 (c 2.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.44 (m, 2H), 7.30 (m, 8H), 6.89 (t, *J* = 5.8 Hz, 1H), 5.47 (bs, 1H), 5.02 (d, *J* = 15.2 Hz, 1H), 4.48 (dd, *J* =14.8, 6.1 Hz, 1H), 4.36 (m, 2H), 4.24 (d, *J* = 15.1 Hz, 1H), 4.10 (dd, *J* = 9.1, 7.2 Hz, 1H), 3.94 (d, *J* = 5.3 Hz, 1H), 3.64 (dd, *J* =9.1, 4.4 Hz, 1H), 1.41 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 167.4, 167.3, 137.4, 134.3, 128.74, 128.69, 128.4, 127.8, 127.6, 127.5, 110.3, 85.2, 75.1, 66.3, 63.6, 45.5, 43.3, 26.3, 24.9; IR (KBr): ν = 3315, 1745, 1671 cm^{-1}; HRMS (ES): calcd for $C_{23}H_{27}N_2O_5^+$ $[M+H]^+$: 411.1914; found: 411.1930.

Passerini adduct *syn*-(−)-5c. From 32 mg (0.11 mmmol) of azetidine-2,3-dione (+)-**4a**, 21 mg (48%) of compound *syn*-(−)-**5c** was obtained as a white solid after purification by flash chromatography (*n*-hexane/ethyl acetate, 1:1). Mp: 154−156°C (*n*-hexane/ethyl acetate); $[\alpha]_D$ −7.0 (c 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.49 (AA'*XX'*, 2H), 6.86 (*AA'*XX', 2H), 6.56 (bs, 1H), 5.08 (bs, 1H), 4.60 (d, *J* = 4.8 Hz, 1H), 4.43 (td, *J* = 6.7, 4.9 Hz, 1H), 4.20 (dd, *J* =8.9, 6.7 Hz, 1H), 3.79 (s, 3H), 3.80 (dd, *J* = 8.8, 6.9 Hz, 1H), 1.41 (s, 3H), 1.39 (s, 9H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 166.0, 164.7, 157.1, 130.0, 120.6, 114.0, 110.2, 84.9, 75.7, 66.5, 64.9, 55.4, 51.7, 28.6, 26.3, 25.2; IR (KBr): ν = 3243, 1759, 1658 cm^{-1}; HRMS (ES): calcd for $C_{20}H_{29}N_2O_6^+$ $[M+H]^+$: 393.2020; found: 393.2034.

Passerini adduct *syn*-(−)-5d. From 55 mg (0.24 mmmol) of azetidine-2,3-dione (−)-**4c**, 56 mg (71%) of compound *syn*-(−)-**5d** was obtained as a white solid after purification by flash chromatography (*n*-hexane/ethyl acetate, 1:1). Mp: 130−132°C (*n*-hexane/ethyl acetate) $[\alpha]_D$ −106.8 (c 0.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25°C): δ = 6.57 (bs, 1H), 5.85 (m, 1H), 5.36 (m, 2H), 4.96 (bs, 1H), 4.34 (m, 2H), 4.17 (dd, *J* = 8.9, 7.2 Hz, 1H), 4.05 (d, *J* = 4.5 Hz, 1H), 3.82 (dd, *J* = 9.1, 4.5 Hz, 1H), 3.70 (dd, *J* =15.7, 7.5 Hz, 1H), 1.39 (s, 9H), 1.38 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 167.4, 166.1, 130.9, 119.1, 110.2, 85.3, 75.2, 66.4, 63.7, 51.4, 44.1, 28.6, 26.5, 25.0; IR (KBr): ν = 3403, 1746, 1679 cm^{-1}; HRMS (ES): calcd for $C_{16}H_{27}N_2O_5^+$ $[M+H]^+$: 327.1914; found: 327.1914.

Passerini adduct *syn*-(+)-5e. From 42 mg (0.14 mmmol) of azetidine-2,3-dione (+)-**4a**, 27 mg (45%) of compound *syn*-(+)-**5e** was obtained as a white solid after purification by flash chromatography (*n*-hexane/ethyl acetate, 1:1). Mp: 123−124°C (*n*-hexane/ethyl acetate); $[\alpha]_D$ +5.8 (c 0.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.57 (AA'*XX'*, 2H), 6.87 (*AA'*XX', 2H), 6.37 (bs, 1H), 4.56 (d, *J* = 6.6 Hz, 1H), 4.45 (q, *J* = 6.6 Hz, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 4.22 (m, 2H), 3.96 (dd, *J* = 18.0, 5.0 Hz, 1H), 3.80 (s, 3H), 3.79 (m, 1H), 1.46 (s, 3H), 1.38 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$, 25°C): δ = 170.1, 167.9, 164.5, 157.2, 130.0, 120.7, 114.0, 110.1, 84.1, 76.3, 66.7, 66.3, 61.7, 55.4, 41.1, 26.5, 25.1, 14.0; IR (KBr): ν = 3346, 1750, 1680 cm^{-1}; HRMS (ES): calcd for $C_{20}H_{30}N_3O_8^+$ $[M+NH_4]^+$: 440.2027; found: 440.2045.

General Procedure for the Ring Expansion of Ugi Adducts 2. Synthesis of functionalized γ-lactams 6. **Method A.** To a solution of Ugi adduct **2** (1 mmol) in methanol (23 mL), sodium methoxide (1 mmol), was added in small portions at room temperature under argon atmosphere. The reaction mixture was stirred until complete disappearances of the starting material (TLC). Then, the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with *n*-hexane/ethyl acetate mixtures. **Method B.** To a solution of Ugi adduct *syn*-(+)-**2a** (1 mmol) in methanol (2 mL), sulfuric acid (cc.) (12 mL) was added at room temperature. The reaction mixture was dtirred for 54 h. Then, the mixture was neutralized with $NaHCO_3$ (sat.) (50 mL). The methanol was removed under reduced pressure and the mixture was extracted with ethyl acetate (5 x 100 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with *n*-hexane/ethyl acetate mixtures.

Functionalized γ-lactam *syn*-(+)-6a. **Method A.** From 46 mg (0.11 mmmol) of compound *syn*-(+)-**2a**, 39 mg (84%) of compound *syn*-(+)-**6a** was obtained as a colorless oil after purification by flash chromatography (*n*-hexane/ethyl acetate, 1:3). **Method B.** From 51 mg (0.12 mmmol) of compound *syn*-(+)-**2a**, 11 mg (22%) of compound *syn*-(+)-**6a** was obtained as a colorless oil after purification by flash chromatography (*n*-hexane/ethyl acetate, 1:3). $[\alpha]_D$ +155.8 (c 0.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25°C): δ =7.82 (bs, 1H), 7.22 (m, 3H), 7.11 (m, 2H), 6.79 (AA'*BB'*, 2H), 6.75 (*AA'*BB', 2H), 5.78 (m, 1H), 5.20 (m, 2H), 4.58 (d, *J* = 7.4 Hz, 1H), 4.44 (dd, *J* = 15.2, 6.4 Hz, 1H), 4.32 (d, *J* = 9.1 Hz, 1H), 4.27 (dd, *J* =15.2, 5.3 Hz, 1H), 4.18 (dd, *J* = 9.0, 7.3 Hz, 1H), 4.15 (m, 1H), 3.73 (s, 3H), 3.63 (s, 3H), 3.58 (dd *J* = 15.7, 6.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 171.3, 168.3, 152.8, 140.2,

136.9, 131.7, 128.7, 127.8, 127.7, 119.3, 115.1, 114.4, 81.1, 61.1, 59.2, 57.5, 55.6, 45.0, 43.9; IR ($CHCl_3$): ν = 3317, 1689 cm^{-1}; HRMS (ES): calcd for $C_{23}H_{28}N_3O_4^+$ $[M+H]^+$: 410.2074; found: 410.2067.

Functionalized γ-lactam *anti*-(−)-6a. **Method A.** From 44 mg (0.11 mmmol) of compound *anti*-(+)-**2a**, 27 mg (60%) of compound *anti*-(−)-**6a** was obtained as a white solid after purification by flash chromatography (*n*-hexane/ethyl acetate, 1:3). Mp: 163−165°C (*n*-hexane/ethyl acetate); $[\alpha]_D$ −9.2 (c 0.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25°C): δ = 8.01 (bs, 1H), 7.26 (m, 5H), 6.78 (AA'*BB'*, 2H), 6.73 (*AA'*BB', 2H), 5.74 (m, 1H), 5.15 (m, 2H), 4.49 (dd, *J* = 14.9, 6.1 Hz, 1H), 4.39 (m, 1H), 4.36 (dd, *J* =14.8, 5.9 Hz, 1H), 4.09 (t, *J* = 5.7 Hz, 1H), 4.03 (d, *J* = 5.4 Hz, 1H), 3.94 (d, *J* = 6.1 Hz, 1H), 3.74 (s, 3H), 3.56 (s, 3H), 3.44 (dd, *J* = 15.5, 7.4 Hz, 1H), 2.91 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 171.1, 168.9, 153.5, 138.9, 137.4, 130.8, 128.7, 127.8, 127.7, 119.9, 115.8, 115.0, 83.1, 65.9, 58.7, 58.3, 55.6, 44.5, 43.7; IR (KBr): ν = 3364, 3277, 1699, 1657 cm^{-1}; HRMS (ES): calcd for $C_{23}H_{28}N_3O_4^+$ $[M+H]^+$: 410.2074; found: 410.2077.

Functionalized γ-lactam *syn*-(+)-6b. **Method A.** From 31 mg (0.08 mmmol) of compound *syn*-(+)-**2b**, 25 mg (82%) of compound *syn*-(+)-**6b** was obtained as a colorless oil after purification by flash chromatography (*n*-hexane/ethyl acetate, 1:3). $[\alpha]_D$ +139.6 (c 0.2, $CHCl_3$); ^1H NMR (300 MHz, d^6-acetone, 25°C): δ = 6.80 (AA'*BB'*, 2H), 6.74 (*AA'*BB', 2H), 5.77 (m, 1H), 5.21 (m, 2H), 4.45 (d, *J* = 7.3 Hz, 1H), 4.25 (d, *J* = 8.8 Hz, 1H), 4.11 (m, 1H), 4.07 (ddt, *J* = 15.2, 5.5 Hz, 1.5 Hz, 1H), 3.72 (s, 3H), 3.62 (s, 3H), 3.59 (dd, *J* = 15.6, 6.4 Hz, 1H), 1.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 171.3, 167.3, 152.8, 140.3, 132.1, 119.2, 115.2, 114.4, 81.0, 61.5, 59.2, 57.2, 55.8, 52.0, 45.0, 28.3; IR ($CHCl_3$): ν = 3337, 1689 cm^{-1}; HRMS (ES): calcd for $C_{20}H_{30}N_3O_4^+$ $[M+H]^+$: 376.2231; found: 376.2235.

Functionalized γ-lactam *anti*-(−)-6b. From 21 mg (0.06 mmmol) of compound *anti*-(+)-**2b**, 15 mg (71%) of compound *anti*-(−)-**6b** was obtained as a colorless oil after purification by flash chromatography (*n*-hexane/ethyl acetate, 1:3); $[\alpha]_D$ −14.1 (c 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD, 25°C): δ = 6.77 (AA'*BB'*, 2H), 6.68 (*AA'*BB', 2H), 5.76 (m, 1H), 5.23 (m, 2H), 4.38 (ddt, *J* = 15.4, 4.8 Hz, 1.5 Hz, 1H), 4.04 (m, 2H), 3.84 (d, *J* = 6.0 Hz, 1H), 3.72 (s, 3H), 3.59 (s, 3H), 3.39 (dd, *J* = 15.3, 7.7 Hz, 1H), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 171.0, 168.1, 153.2, 139.7, 131.2, 119.7, 115.6, 115.0, 83.1, 66.6, 58.52, 58.48, 55.7, 51.6, 44.5, 28.4; IR ($CHCl_3$): ν = 3334, 1693 cm^{-1}; HRMS (ES): calcd for $C_{20}H_{30}N_3O_4^+$ $[M+H]^+$: 376.2231; found: 376.2234.

Functionalized γ-lactam *syn*-(+)-6c. From 32 mg (0.08 mmmol) of compound *syn*-(+)-**2c**, 26 mg (81%) of compound *syn*-(+)-**6c** was obtained as a colorless oil after purification by flash chromatography (dichloromethane/ethyl acetate, 5:1); $[\alpha]_D$ +149.7 (c 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.32 (m, 7H), 7.14 (dd, *J* = 8.7, 1.0 Hz, 2H), 7.01 (tt, *J* = 7.2, 1.0 Hz, 1H), 6.52 (t, *J* = 5.3 Hz, 1H), 5.74 (m, 2H), 5.12 (d, *J* = 9.1 Hz, 1H), 5.13 (m, 4H), 4.49 (d, *J* = 5.8 Hz, 2H), 4.31 (ddt, *J* = 15.1, 5.3, 1.4 Hz, 1H), 4.04 (d, *J* = 7.9 Hz, 1H), 3.74 (dd, *J* = 8.6, 8.0 Hz, 1H), 3.58 (dd, *J* = 15.3, 7.9 Hz, 1H), 3.37 (ddt, *J* = 14.0, 5.7, 1.4 Hz, 1H), 3.30 (ddt, *J* = 14.0, 5.7, 1.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 171.0, 168.7, 158.4, 137.4, 135.8, 131.6, 129.4, 128.8, 127.9, 127.8, 122.0, 119.3, 116.5, 80.9, 61.4, 60.7, 50.6, 45.0, 43.8; IR ($CHCl_3$): ν = 3308, 1688 cm^{-1}; HRMS (ES): calcd for $C_{24}H_{28}N_3O_3^+$ $[M+H]^+$: 406.2125; found: 406.2125.

Functionalized γ-lactam *anti*-(+)-6c. From 15 mg (0.04 mmmol) of compound *anti*-(+)-**2c**, 11 mg (76%) of compound *anti*-(+)-**6c** was obtained as a colorless oil after purification by flash chromatography (*n*-hexane/ethyl acetate, 1:2); $[\alpha]_D$ +10.2 (c 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.30 (m, 7H), 7.01 (m, 3H), 6.66 (bs, 1H), 5.75 (m, 2H), 5.16 (m, 4H), 4.62 (d, *J* = 4.3 Hz, 1H), 4.47 (d, *J* = 5.9 Hz, 2H), 4.43 (m, 1H), 3.87 (d, *J* = 4.5 Hz,1H), 3.68 (dd, *J* = 15.2, 7.8 Hz, 1H),

3.58 (t, J = 4.3 Hz, 1H), 3.31 (d, J = 5.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 170.7, 169.0, 157.6, 137.5, 135.2, 130.8, 129.5, 128.8, 127.9, 127.8, 122.3, 119.9, 117.1, 116.2, 81.2, 64.6, 61.4, 49.8, 44.9, 43.6; IR ($CHCl_3$): ν = 3285, 1700, 1660 cm^{-1}; HRMS (ES): calcd for $C_{24}H_{28}N_3O_3^+$ $[M+H]^+$: 406.2125; found: 406.2138.

Functionalized γ-lactams *syn*-(+)-6d and *anti*-(+)-6d. **Method B.** From 72 mg (0.16 mmol) of an inseparable mixture (64:36) of compound **2e**, compound **6d** was obtained as a mixture of isomers in a *syn/anti* ratio (64:36). After flash chromatography (dichloromethane/ethyl acetate, 2:1) 31 mg (51%) of the less polar compound *syn*-(+)-**6d** and 21 mg (28%) of the more polar compound *anti*-(+)-**6d** were obtained. ***syn*-(+)-6d**. Colorless oil; $[\alpha]_D$ +91.9 (c 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.29 (AA'*XX'*, 2H), 6.86 (*AA'*XX', 2H), 6.81 (AA'*BB'*, 2H), 6.65 (*AA'*BB', 2H), 5.29 (bs, 1H), 4.42 (d, J = 7.0 Hz, 1H), 4.39 (d, J = 8.3 Hz, 1H), 4.30 (m, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H), 1.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 170.8, 167.5, 158.0, 152.8, 140.1, 130.7, 124.8, 115.2, 114.4, 114.3, 80.9, 64.5, 59.4, 57.2, 55.8, 55.4, 52.0, 28.2; IR ($CHCl_3$): ν = 3340, 1692 cm^{-1}; HRMS (ES): calcd for $C_{24}H_{32}N_3O_5^+$ $[M+H]^+$: 442.2336; found: 442.2332. ***anti*-(+)-6d**. Brown solid; Mp: 85–87°C (*n*-hexane/ethyl acetate); $[\alpha]_D$ + +22.1 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.38 (AA'*XX'*, 2H), 6.85 (*AA'*XX', 2H), 6.79 (bs, 4H), 6.06 (bs, 1H), 4.30 (d, J = 3.2 Hz, 1H), 4.09 (bs, 1H), 3.90 (d, J = 3.6 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.62 (s 3H), 1.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 170.3, 168.0, 157.7, 153.3, 139.2, 130.0, 123.6, 115.7, 115.0, 114.2, 83.6, 68.4, 58.7, 58.1, 55.6, 55.4, 51.5, 28.3; IR (KBr): ν = 3340, 1696 cm^{-1}; HRMS (ES): calcd for $C_{24}H_{32}N_3O_5^+$ $[M+H]^+$: 442.2336; found: 442.2341.

Functionalized γ-lactam *syn*-(+)-6e. From 38 mg (0.08 mmmol) of compound *syn*-(+)-**2f**, 17 mg (45%) of compound *syn*-(+)-**6e** was obtained as a yellow oil after purification by flash chromatography (*n*-hexane/ethyl acetate, 1:1); $[\alpha]_D$ +151.1 (c 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 8.24

(AA'*XX'*, 2H), 7.78 (*AA'*XX', 2H), 7.32 (m, 2H), 7.16 (d, *J* = 7.8 Hz, 2H), 7.05 (t, *J* = 7.3 Hz, 1H), 6.04 (bs, 1H), 5.88 (m, 1H), 5.23 (d, *J* = 9.5 Hz, 1H), 5.21 (m, 2H), 4.46 (d, *J* = 7.9 Hz, 1H), 3.86 (dd, *J* = 9.4, 7.9 Hz, 1H), 3.50 (dd, *J* = 14.3, 5.7 Hz, 1H), 3.41 (dd, *J* = 14.3, 5.7 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 171.1, 167.0, 158.2, 144.2, 143.7, 135.7, 129.5, 124.7, 122.4, 120.2, 116.6, 116.3, 80.6, 63.4, 60.2, 52.6, 50.7, 28.6; IR ($CHCl_3$): ν = 3347, 1718 cm^{-1}; HRMS (ES): calcd for $C_{24}H_{29}N_4O_5^+$ $[M+H]^+$: 453.2132; found: 453.2149.

Reaction of α-hydroxy amide *syn*-(+)-3a with $FeCl_3 \cdot 6H_2O$. To a solution of α-hydroxy amide *syn*-(+)-**3a** (51 mg, 0.15 mmol) in anhydrous 1,2-dichloroethane (1.5 mL), $FeCl_3$ (0.10 mmol) was added. The resulting mixture was heated at 85°C for 21 h. The reaction mixture was allowed to cool to room temperature, and then quenched with NH_4Cl sat. (0.15 mL). The mixture was extracted with ethyl acetate (3 x 4 mL), and the combined extracts were washed with brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with *n*-hexane/ethyl acetate (1:1) affording 12 mg (23%) of γ-lactone *syn*-(+)-**7a** as a colorless solid.

Reaction of α-hydroxy amide *syn*-(+)-3a in acidic conditions. To a solution of α-hydroxy amide *syn*-(+)-**3a** (39 mg, 0.12 mmol) in methanol (2.7 mL), sulphuric acid cc. (1.4 mL) was slowly added. The resulting mixture was stirred at room temperature for 2 hours. Then, $NaHCO_3$ (cc.) (6 mL) was added until pH = 7. The methanol was removed under reduced pressure and the mixture was extracted with ethyl acetate (5 x 12 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatogaphy of the residue eluting with *n*-hexane/ethyl acetate (1:1) gave analytically pure amino ester (–)-**8** (32 mg, 73%).

Reaction of α-hydroxy amide *syn*-(+)-3a in basic conditions. To a solution of α-hydroxy amide *syn*-(+)-**3a** (21 mg, 0.06 mmol) in methanol (1.43 mL), sodium methoxide (3 mg, 0.06 mmol) was

added in small portions at room temperature and under argon atmosphere. The reaction mixture was stirred for 6h. After disappearance of the starting material (TLC) the solvent was removed under reduced pressure. Chromatography of the residue gave analytically eluting with *n*-hexane/ethyl acetate (1:1) gave analytically pure amino ester (–)-**8** (11 mg, 47%) and γ-lactone *syn*-(+)-**7a** (7 mg, 32%).

General Procedure for the Synthesis of functionalized γ-lactones 7. To a solution of α-hydroxy amide **3** (1 mmol) in methanol (23 mL), sulphuric acid cc (12 mL) was slowly added. The resulting mixture was stirred at room temperature until complete disappearance (TLC) of the starting material. Then, $NaHCO_3$ (cc.) (50 mL) was added until pH = 7. The methanol was removed under reduced pressure and the mixture was extracted with ethyl acetate (5 x 100 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. To a stirred solution of the crude mixture in anhydrous toluene (25 mL), *p*-toluensulfonic acid (0.2 mmol) was added. The reaction mixture was stirred at reflux temperature for 2h. Then, $NaHCO_3$ (cc.) (10 mL) was added and was extracted with ethyl acetate (3 x 20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue gave analytically pure compounds **7**.

Functionalized γ-lactone, *syn*-(+)-7a. From 31 mg (0.09 mmmol) of compound *syn*-(+)-**3a**, 23 mg (73%) of compound *syn*-(+)-**7a** was obtained as a colorless solid after purification by flash chromatography (*n*-hexane/ethyl acetate, 1:1); Mp: 143–145°C (*n*-hexane/ethyl acetate); $[\alpha]_D$ +51.1 (c 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 6.84 (AA'*XX'*, 2H), 6.75 (*AA'*XX', 2H), 5.92 (bs, 1H), 4.95 (d, *J* = 6.7 Hz, 1H), 4.30 (t, *J* = 6.5 Hz, 1H), 4.20 (d, *J* = 6.4 Hz, 1H), 3.77 (s, 3H), 3.63 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 172.1, 165.8, 153.5, 139.6, 115.6, 115.0, 79.2, 77.2, 59.1, 58.8, 55.7, 52.3, 28.5; IR (KBr): ν = 3363, 1790, 1679 cm^{-1}; HRMS (ES): calcd for $C_{17}H_{25}N_2O_5^+$ $[M+H]^+$: 337.1758; found: 337.1752.

Functionalized γ-lactone, *anti*-(+)-7a. From 29 mg (0.09 mmmol) of compound *anti*-(+)-**3a**, 10 mg (34%) of compound *anti*-(+)-**7a** was obtained as a colorless oil after purification by flash chromatography (*n*-hexane/ethyl acetate, 1:1); $[\alpha]_D$ +20.6 (c 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 6.87 (AA'*XX'*, 2H), 6.82 (*AA'*XX', 2H), 6.10 (bs, 1H), 4.55 (d, *J* = 5.4 Hz, 1H), 4.15 (t, *J* = 5.1 Hz, 1H), 3.93 (d, *J* = 5.1 Hz, 1H), 3.77 (s, 3H), 3.62 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 171.9, 166.6, 154.0, 139.0, 117.0, 114.8, 81.3, 78.2, 61.0, 58.9, 55.6, 51.8, 28.6; IR ($CHCl_3$): ν = 3344, 1792, 1672 cm^{-1}; HRMS (ES): calcd for $C_{17}H_{25}N_2O_5^+$ $[M+H]^+$: 337.1758; found: 337.1758.

Functionalized γ-lactone, *syn*-(+)-7b. From 28 mg (0.08 mmmol) of compound *syn*-(+)-**3b**, 13 mg (47%) of compound *syn*-(+)-**7b** was obtained as a colorless oil after purification by flash chromatography (*n*-hexane/ethyl acetate, 1:2); $[\alpha]_D$ +70.5 (c 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.33 (m, 3H), 7.19 (m, 2H), 6.79 (AA'*XX'*, 2H), 6.62 (*AA'*XX', 2H), 6.54 (t, *J* = 5.6 Hz, 1H), 5.06 (d, *J* = 6.6 Hz, 1H), 4.46 (d, *J* = 5.8 Hz, 2H), 4.33 (t, *J* = 6.3 Hz, 1H), 4.12 (d, *J* = 6.0 Hz, 1H), 3.76 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 171.9, 166.5, 153.5, 139.3, 136.8, 128.9, 127.9, 127.8, 115.7, 115.0, 79.2, 77.3, 59.1, 58.9, 55.6, 43.6; IR ($CHCl_3$): ν = 3358, 1790, 1673 cm^{-1}; HRMS (ES): calcd for $C_{20}H_{23}N_2O_5^+$ $[M+H]^+$: 371.1601; found: 371.1598.

Functionalized γ-lactone, *anti*-(−)-7b. From 40 mg (0.11 mmmol) of compound *anti*-(+)-**3b**, 17 mg (42%) of compound *anti*-(+)-**3b** was obtained as a white solid after purification by flash chromatography (*n*-hexane/ethyl acetate, 1:1); Mp: 161–163°C (*n*-hexane/ethyl acetate); $[\alpha]_D$ −10.6 (c 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.31 (m, 5H), 6.86 (AA'*XX'*, 2H), 6.83 (*AA'*XX', 2H), 6.70 (t, *J* = 5.4 Hz, 1H), 4.71 (d, *J* = 4.9 Hz, 1H), 4.55 (dd, *J* = 14.8, 6.2 Hz, 1H), 4.42 (dd, *J* = 14.7, 5.7 Hz, 1H), 4.24 (t, *J* = 4.7 Hz, 1H), 3.90 (d, *J* = 4.7 Hz, 1H), 3.77 (s, 3H), 3.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 171.8, 167.4, 154.0, 138.9, 137.0, 128.8, 127.81, 127.77, 116.9, 114.9,

81.0, 78.8, 60.9, 58.9, 55.6, 43.2; IR (KBr): ν = 3341, 1793, 1667 cm^{-1}; HRMS (ES): calcd for $C_{20}H_{23}N_2O_5^+$ $[M+H]^+$: 371.1601; found: 371.1598.

Functionalized γ-lactone, *syn*-(+)-7c. From 26 mg (0.07 mmmol) of compound *syn*-(+)-**3c**, 15 mg (57%) of compound *syn*-(+)-**7c** was obtained as a colorless oil after purification by flash chromatography (*n*-hexane/ethyl acetate, 1:1); $[\alpha]_D$ +87.1 (c 0.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.30 (m, 2H), 7.06 (m, 3H), 6.80 (AA'*XX'*, 2H), 6.67 (*AA'*XX', 2H), 5.86 (bs, 1H), 5.11 (d, *J* = 6.9 Hz, 1H), 5.03 (d, *J* = 6.6 Hz, 1H), 4.57 (t, *J* = 6.7 Hz, 1H), 4.06 (bs, 1H), 3.76 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 171.2, 165.7, 157.6, 153.6, 139.3, 129.6, 122.9, 116.6, 115.7, 115.0, 77.2, 77.3, 59.0, 55.7, 52.4, 28.4; IR ($CHCl_3$): ν = 3371, 1791, 1680 cm^{-1}; HRMS (ES): calcd for $C_{22}H_{27}N_2O_5^+$ $[M+H]^+$: 399.1914; found: 399.1922.

Functionalized γ-lactone, *syn*-(+)-7d. From 35 mg (0.11 mmmol) of compound *syn*-(+)-**3d**, 18 mg (52%) of compound *syn*-(+)-**7d** was obtained as a colorless oil after purification by flash chromatography (*n*-hexane/ethyl acetate, 1:1); $[\alpha]_D$ +73.3 (c 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.32 (m, 2H), 7.08 (m, 3H), 6.22 (bs, 1H), 5.05 (d, *J* = 5.7 Hz, 1H), 4.95 (d, *J* = 4.1 Hz, 1H), 4.12 (dd, *J* = 5.7, 4.1 Hz, 1H), 3.60 (dd, *J* = 17.5, 2.4 Hz, 1H), 3.46 (dd, *J* = 17.5, 2.4 Hz, 1H), 2.28 (t, *J* = 2.4 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 171.1, 165.6, 157.1, 129.6, 116.2, 80.7, 78.8, 77.0, 73.0, 60.5, 52.3, 36.5, 28.6; IR ($CHCl_3$): ν = 3301, 1789, 1674 cm^{-1}; HRMS (ES): calcd for $C_{18}H_{23}N_2O_4^+$ $[M+H]^+$: 331.1652; found: 331.1643.

Hydroxy amino ester (–)-8. Colorless oil. $[\alpha]_D$ –6.0 (c 2.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25°C): δ = 6.75 (AA'*XX'*, 2H), 6.68 (*AA'*XX', 2H), 6.44 (bs, 1H), 4.29 (d, *J* = 2.3 Hz, 1H), 4.21 (d, *J* = 4.2 Hz, 1H), 4.17 (dd, *J* = 4.1, 2.5 Hz, 1H,), 3.73 (s, 3H), 3.51 (s, 3H), 3.50 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 170.8, 170.2, 153.2, 140.3, 116.3, 114.6, 80.2, 71.1, 59.7, 58.9, 55.6,

51.9, 51.0, 28.5; IR ($CHCl_3$): ν = 3391, 1746, 1659 cm^{-1}; HRMS (ES): calcd for $C_{18}H_{29}N_2O_6^+$ $[M+H]^+$: 369.2020; found: 369.2012.

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Supporting Information

Representative chemical shifts and vicinal coupling constants of ^1H and ^{13}C NMR of compounds **3** (Table S1), selected vicinal coupling constants for γ-lactams **6** and γ-lactones **7** (Table S2 and S3, respectively), observed NOE for compounds **6** and **7** and copies of NMR spectra (^1H, ^{13}C) for compounds **2**, **3** and **5–8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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