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ARTICLE

Highly efficient organocatalysts for the asymmetric aldol reaction

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A new class of bifunctional organocatalysts containing both thiazolidine/pyrrolidine and imidazole cycles was prepared in a readily available synthetic route. The highly efficient five steps methodology did not require intermediary purification and provided the compounds in high yields. The catalysts were successfully applied in the asymmetric direct aldol reaction between aromatic aldehydes and cyclic ketones in aqueous media. Aldol adducts were obtained in high yields with perfect stereoselectivities (up to >99% *ee* and >19:1 *dr*).

Introduction

Organocatalysis has been used as an important tool in organic synthesis, as a large number of asymmetric organic reactions have been shown to be efficiently performed using this methodology.[1] Since the organocatalysed aldol reaction was published by List, Barbas et al. in 2000,[2] several research groups have been directing their efforts to discover new compounds and methodologies that can be used to improve the yield and selectivity of many products, including those of importance to the pharmaceutical industry.[3]

A significant part of the publications in this area presents L-proline or its derivatives as the organocatalyst.[4] This natural amino acid had been shown to catalyze a number of different asymmetric reactions, inducing high selectivity, and it is now considered one of the most important organocatalysts to be discovered. These results have inspired researchers to study other amino acids in organocatalysis, since they are good sources of chirality and are readily available.[5]

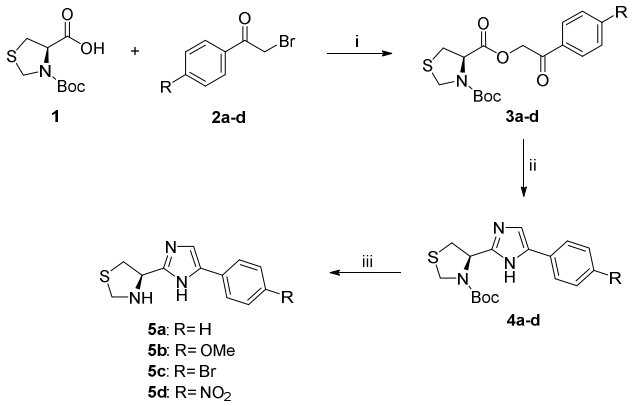
The sulfur analogue of L-proline, (*R*)-thiazolidine-4-carboxylic acid and its derivatives are rarely used in asymmetric synthesis.[6] In spite of this, our group has published several reports using thiazolidines as chiral ligands in organometallic reactions.[7] Recently we also reported the synthesis of a new class of thiazolidine derivatives and their successful application as organocatalysts in asymmetric aldol reactions.[8]

Aromatic heterocycles, especially azoles, have been used as substitutes for carboxylic acids in the structures of bifunctional ligands and catalysts,[9] showing some very relevant results. The imidazole cycle is a promising scaffold for organocatalysis, since in the few reports existing it has been shown to act either as a basic group[10] or as a hydrogen-bond donor in bifunctional catalysis.[11]

Given these considerations, this work presents the synthesis of four new compounds containing both thiazolidine and imidazole cycles. The design of these molecules was carefully planned so they could act as good bifunctional catalysts. The direct asymmetric aldol reaction between different ketones and aldehydes was used as a probe to verify the performance of these organocatalysts, looking to identify those with superior catalytic activity.

Results and Discussion

The organocatalysts **5a-d** were synthesized by a simple and efficient five-step route, using the natural amino acid L-cysteine as starting material (Scheme 1). At first, compound **1** was obtained following a very well-established methodology, in which the thiazolidine ring was obtained by cyclisation of L-cysteine with formaldehyde, and further protected with Boc_2O[12]. The acid was then reacted with different acetophenone derivatives affording esters **3a-d**, which underwent cyclisation with ammonium acetate, generating the



Reaction conditions: i. Et_3N, AcOEt, 24 h, r.t. (79–95%); ii. NH_4OAc, toluene, 20 h, reflux (83–94%); iii. TFA, AcOEt, 1–2 h, r.t. (83–95%).

Scheme1 Synthesis of organocatalysts **5a-d**.

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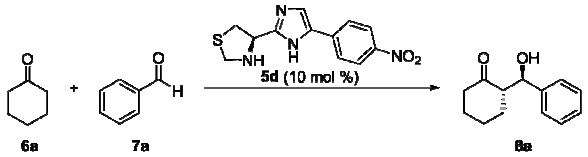
imidazole cycle. Finally, removal of the Boc group in acidic conditions led to compounds **5a-d**. It is important to mention that through this new methodology, the final compounds were obtained without the need for purification of any of the intermediates. This is very important for the rapid development of methodologies for obtaining enantiomerically enriched compounds. All the synthesized organocatalysts were obtained in good overall yields (39 to 54%).

With this easily accessible set of organocatalysts, available in large quantities, our attention turned towards the evaluation of their catalytic activity. The compounds **5a–d** were employed in the direct asymmetric aldol reaction, which is widely applied to evaluate organocatalysts,[13] with the aim of controlling the stereochemistry of the two stereocenters formed during the reaction. In order to determine the best conditions to carry out the aldol reactions, we investigated the effect of several parameters on the yields and the selectivities obtained, using initially the compound **5d** as catalyst and cyclohexanone and benzaldehyde as reactants, as a model reaction (Table 1).

Initially, we tested the reaction at two temperatures, and the best results concerning stereoselectivity were obtained at 0 °C, despite the slight decrease in yield (Table 1, entry 1 vs 2). The other parameter investigated was the reaction media; for that, the reaction was performed in different organic and aqueous solvents. Using cyclohexanone and dichloromethane the results were very similar in terms of yield, enantiomeric excess (*e.e.*) and diastereoisomeric ratio (*d.r.*) (Table 1, entries 2 and 3). However, when performed in DMSO, which is a solvent widely used in organocatalysis,[14] the reaction furnished only traces of the product (entry 4). Based on the literature[15] and our previously published results,[8] in which the direct aldol reaction has been shown to be influenced, in terms of stereoselectivity, by the use of a reaction system with equal amounts of water or brine and ketone, we performed some experiments to evaluate this concept (Table 1, entries 5–8). In water the results were almost the same as those obtained in dichloromethane. However, the use of brine proved to be more interesting, since both yield and stereoselectivity were improved. The product was obtained with 54% yield and almost perfect stereocontrol with 94% *e.e.* and a diastereoisomeric ratio up to 19:1 (Table 1, entry 6). The reaction time was also varied, but any reduction led to a dramatic drop in yield.

After the preliminary investigations of the reaction conditions, we studied the influence on the reaction of the catalyst loading, the amount of ketone and the presence of additives. The decrease of the catalyst loading caused a decrease in yield as well as in stereoselectivity. On the other hand, the increase to 15 mol% did not generate significant improvement in the yield; however the stereoselectivity was seriously affected (Table 2, entries 1–3). As can be seen from Table 2, the concentration of the ketone is also an important feature, as better results were obtained when 10 equivalents were used. Finally, the use of an acidic additive was also investigated, as it is well established in the literature that it could help during the catalytic cycle in the formation of the enamine, as well as on

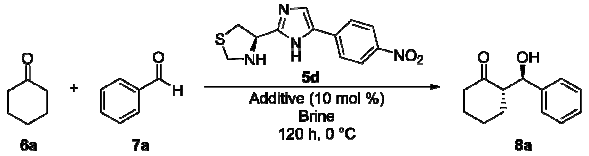
Table1 Optimisation of the reaction conditions[a]



Entry	Temp. (°C)	Solvent	Time (h)	Yield[b] (%)	*e.e.*[c] (%)	*d.r.*[d] (*anti*:*syn*)
1	25	Cyclohexanone	120	47	74	2:1
2	0	Cyclohexanone	120	30	95	6:1
3	0	CH_2Cl_2	120	32	93	5:1
4	0	DMSO	120	Traces	-	-
5	0	H_2O	120	31	94	8:1
6	0	Brine	120	51	97	>19:1
7	0	Brine	72	22	94	>19:1
8	0	Brine	96	30	95	>19:1

[a]Reactions performed using 0.5 mmol (0.05 mL) of benzaldehyde, 5 mmol (0.52 mL) of cyclohexanone, 0.05 mmol (0.014 g) of organocatalyst **5d** and 0.5 mL of solvent; [b]Isolated yield; [c]Determined by HPLC using chiral stationary phase; [d]Determined by ^{1}H NMR spectroscopy of the crude product.

Table 2 Effect of catalyst loading, ketone amount and additives on the asymmetric aldol reaction[a]



Entry	Catalyst (mol %)	Ketone (eq.)	Additive	Yield (%)	*e.e.* (%)	*d.r.* (*anti*:*syn*)
1	10	10	-	51	97	>19:1
2	5	10	-	37	95	13:1
3	15	10	-	55	92	7:1
4	10	1	-	40	91	>19:1
5	10	5	-	43	94	18:1
6	10	10	HCl	40	>99	14:1
7	10	10	TFA	61	>99	11:1
8	10	10	PhCOOH	81	>99	>19:1

[a]Reactions performed using 0.5 mmol (0.05 mL) of benzaldehyde, 0.5–5 mmol of cyclohexanone, 0.025–0.075 mmol of organocatalyst **5d** and 0.5 mL of brine; [b]Isolated yield; [c]Determined by HPLC using chiral stationary phase; [d]Determined by ^{1}H NMR spectroscopy of the crude product.

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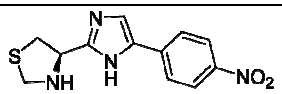
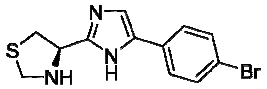
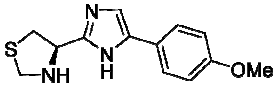
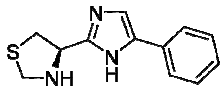
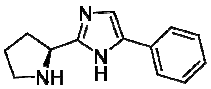
the hydrolysis of the final iminium (Table 2, entries 6–8). Three additives were tested and with 10 mol% of benzoic acid we observed a significant increase in the reaction yield from 51 to 81%, as well as in the steroselectivity (Table 2, compare entries 1 and 8).

Having established the optimized conditions, the synthesized catalysts **5a-d** were applied in the test reaction, in order to investigate how the different electronic and steric characteristics of the compounds would influence their catalytic potential and asymmetric induction power (Table 3). When substituents of the phenyl portion were varied, all the synthesized organocatalysts led to a high stereoselectivity in the aldol reaction. The lowest *e.e.* and *d.r.* were obtained using the nonsubstituted catalyst **5a**, probably because of the diminution of steric hindrance. On the other hand, the reaction yield showed a clear dependence on the acidity of the imidazolic hydrogen. Compounds containing electron-withdrawing groups, which increase the hydrogen acidity, furnished the aldol product in higher yields than did the nonsubstituted catalyst, while a donating group in the phenyl portion led to a dramatic decrease in yield. In order to investigate the role of the thiazolidine ring in the catalytic process, we synthesized the L-proline derivative **5e**, in which the sulfur atom was replaced by carbon. When this compound was applied as catalyst, both yield and stereoselectivity decreased, indicating that the insertion of a heteroatom modifies the conformation of the transition state and influences the course of the reaction.

Once the reaction conditions were optimized and the best catalyst was chosen, the versatility of the catalytic system was evaluated by extending this methodology to different aldehydes and ketones, and the results can be seen in Table 4. All the aldehydes employed led to the product with excellent stereoselectivity, showing a decrease in yield only when electron-donating substituents were present, but with quantitative yields when employing substrates with electron-withdrawing groups in their structures. The scope was also extended to *meta*- and *ortho*-substituted benzaldehydes with excellent yields and stereoselectivities, proving that steric hindrance in the aldehydes does not affect the reaction. When a smaller ketone was used, good yield and selectivity were still obtained with three different aldehydes, which is not commonly observed in organocatalysis and evidence the importance of this class of catalysts. When using cycloheptanone the product was not observed, probably due to the difficulty in forming the enamine. These results proved that we have developed a robust catalytic system, which can be applied to a variety of substrates.

The stereoselectivity obtained can be explained analyzing the proposed transition states for this reaction (Chart 1). The hydrogen of the imidazole group coordinates with the aldehyde, improving the reactivity of the carbonyl group and orienting its approach, having a crucial role in the transition state. This way, the enamine attack occurs on the *re*-face of the aldehyde, since the attack to the *si*-face is disfavored by the steric hindrance between the aryl group of the substrate

Table3 Application of synthesized compounds as catalysts in the asymmetric aldol reaction[a]

Entry	Catalyst	Yield (%)	*e.e.* (%)	*d.r.* (*anti*:*syn*)
1	 **5d**	81	>99	>19:1
2	 **5c**	70	>99	18:1
3	 **5b**	34	97	>19:1
4	 **5a**	45	96	8:1
5	 **5e**	20	77	5:1

[a]Reactions performed using 0.5 mmol (0.05 mL) of benzaldehyde, 5 mmol (0.52 mL) of cyclohexanone, 0.05 mmol of the specified organocatalyst, 0.05 mmol (0.006 g) of benzoic acid and 0.5 mL of brine; [b]Isolated yield; [c]Determined by HPLC using chiral stationary phase; [d]Determined by ^{1}H NMR spectroscopy of the crude product.

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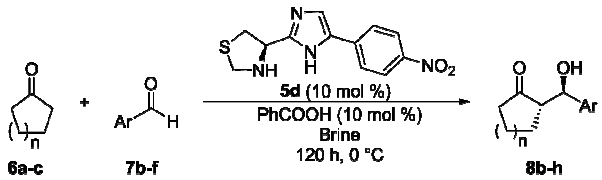
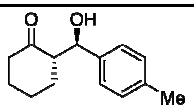
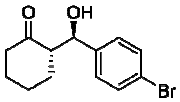
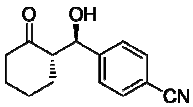
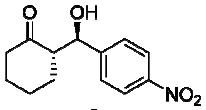
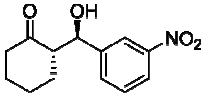
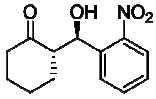
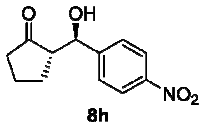
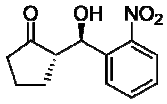
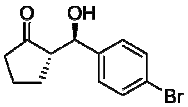
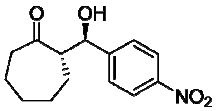
Table4 Extension of reaction scope to other aldehydes and ketones[a]



6a-c 7b-f 8b-h

Entry	Product	Yield (%)	*e.e.* (%)	*d.r.* (*anti*:*syn*)
1	 **8b**	42	>99	>19:1
2	 **8c**	99	98	>19:1
3	 **8d**	92	99	8:1
4	 **8e**	98	96	>19:1
5	 **8f**	93	>99	>19:1
6	 **8g**	99	>99	>19:1
7	 **8h**	81	>99	3:1
8	 **8i**	99	99	3:1
9	 **8j**	99	>99	5:1
10	 **8k**	-	-	-

[a]Reactions performed using 0.5 mmol of aldehyde, 5 mmol of ketone, 0.05 mmol (0.014 g) of organocatalyst **5d**, 0.05 mmol (0.006 g) of benzoic acid and 0.5 mL of brine; [b]Isolated yield; [c]Determined by HPLC using chiral stationary phase; [d]Determined by ^{1}H NMR spectroscopy of the crude product.

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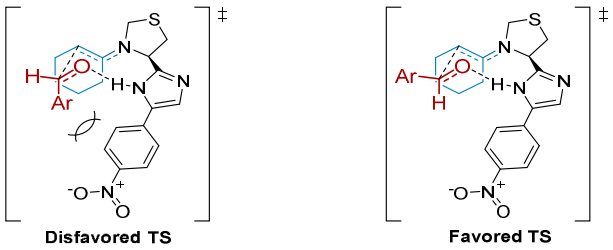
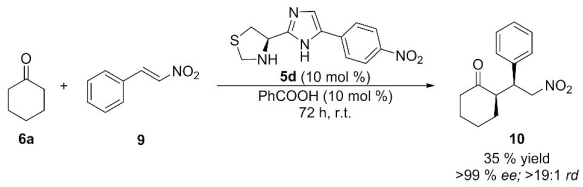


Chart 1 Proposed transition states for the organocatalysed reaction.

and the catalyst, in addition to the interaction with the ketone in *pseudo*-axial position.

The catalytic system was successfully extended to the asymmetric Michael reaction. When 10 mol % of catalyst **5d** was used in the addition of cyclohexanone to *trans*-β-nitrostyrene, the product was obtained as a single stereoisomer (Scheme 2).



Scheme 2 Organocatalysed Michael addition.

Conclusions

Five new organocatalysts containing both imidazole and thiazolidine/pyrrolidine rings were synthesized by a highly efficient route and without the necessity for purification of any intermediate. This work showed the potential of this type of structure in organocatalysis, since aldol reactions were performed with near-perfect yields and stereoselectivities, generating only one of four possible products. This class of compounds also presented great modulability, as different substituents caused substantial changes in the catalytic activity. In this way, further exploration would demonstrate a variety of applications for these molecules and their derivatives.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Experimental Section

General procedure for the synthesis of compounds 5a-e

Ammonium acetate (1.54 g, 20 mmol) was added to a solution of the corresponding phenacyl ester (2 mmol) in toluene (20 mL). The mixture was refluxed with a Dean-Stark trap for 19 h. Then the reaction was cooled to room temperature and poured into water (20 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ solution (20 mL) and water (20 mL), dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (2 mL) and a solution of TFA (4 mL) in ethyl acetate (4 mL) was added. The mixture was stirred at room temperature and the reaction was monitored by TLC. After 1-2 h, the mixture was neutralized with K_2CO_3 and the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The organic extracts were combined, washed with water, dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The product was purified with flash column cromatography on silica gel using ethyl acetate.

(*R*)-4-(5-phenyl-1*H*-imidazol-2-yl)thiazolidine (5a)

The product was obtained as a yellow solid. Yield: 91 %. Mp 178-182 °C. $[\alpha]_D^{20}$= -19 (*c* 0.3, CH_2Cl_2). IR (KBr): 3042, 2979, 2945, 1684, 1441, 1208, 1140. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.3 (bs, 1H), 7.74 (d, *J* = 7.2 Hz, 2H), 7.48 (s, 1H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 4.40 (t, *J* = 6.4 Hz, 1H), 4.17 (s, 2H), 3.23 (dd, *J* = 9.8; 6.4 Hz, 1H), 3.16 (dd, *J* = 9.8; 6.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 147.1, 133.9, 128.5, 126.0, 124.2, 113.9, 61.9, 53.9, 37.4. HRMS calculated for $[C_{12}H_{13}N_3S+H]^+$: 232.0909, obtained: 232.0986.

(*R*)-4-(5-(4-methoxyphenyl)-1*H*-imidazol-2-yl)thiazolidine (5b)

The product was obtained as a brown solid. Yield: 83 %. Mp 166-169 °C. $[\alpha]_D^{20}$= -50 (*c* 0.3, CH_2Cl_2). IR (KBr): 3055, 2946, 2887, 1687, 1208, 1141. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65-7.40 (m, 2H), 7.08 (s, 1H), 6.93-6.65 (m, 2H), 4.32-4.05 (m, 1H), 3.90-3.55 (m, 5H), 3.50-2.95 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 157.9, 130.2, 126.6, 125.6, 114.2, 114.0, 55.2, 55.0. HRMS calculated for $[C_{13}H_{15}N_3OS+H]^+$: 262.1014, obtained: 262.1082.

(*R*)-4-(5-(4-bromophenyl)-1*H*-imidazol-2-yl)thiazolidine (5c)

The product was obtained as a yellow solid. Yield: 93 %. Mp 174-178 °C. $[\alpha]_D^{20}$= -34 (*c* 0.3, CH_2Cl_2). IR (film): 3261, 3035, 2981, 2943, 2893, 1687, 1476, 1435, 1208, 1140. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.54 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.18 (s, 1H), 4.45 (t, *J* = 6.8 Hz, 1H), 4.20 (s, 2H), 3.33 (dd, *J* = 10.3; 6.8 Hz, 1H), 3.28 (dd, *J* = 10.3; 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.7, 147.4, 132.0, 131.8, 126.4, 120.9, 114.6, 61.4, 50.7, 37.4. HRMS calculated for $[C_{12}H_{12}BrN_3S+H]^+$: 310.0013, obtained: 309.9938.

(*R*)-4-(5-(4-nitrophenyl)-1*H*-imidazol-2-yl)thiazolidine (5d)

The product was obtained as a yellow solid. Yield: 95 %. Mp 185-190 °C. $[\alpha]_D^{20}$= -23 (*c* 0.2, CH_2Cl_2). IR (KBr): 3265, 3021,

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2981, 2946, 2885, 1588, 1506, 1333, 1146, 1111. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (d, *J* = 8.9 Hz, 2H), 7.89 (d, *J* = 8.9 Hz, 2H), 7.50 (s, 1H), 4.99-4.92 (m, 1H), 4.34-4.30 (m, 2H), 3.64 (dd, *J* = 11.2; 8.4 Hz, 1H), 3.47 (dd, *J* = 11.1; 6.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 148.5, 145.1, 141.6, 137.8, 124.6, 124.1, 116.8, 61.8, 53.9, 37.2. HRMS calculated for $[C_{12}H_{12}N_4O_2S+H]^+$: 277.0759, obtained: 277.0804.

(*S*)-5-phenyl-2-(pyrrolidin-2-yl)-1*H*-imidazole (5e)

The product was obtained as a brown oil. Yield: 81 %. $[\alpha]_D^{20}$= -38 (*c* 0.2, CH_2Cl_2). IR (film): 3036, 2948, 2913, 1655, 1450, 1402, 1290, 1186. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (s, 1H), 7.70 (d, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 1H), 4.54 (t, *J* = 6.7 Hz, 1H), 3.29-3.19 (m, 1H), 3.17-3.07 (m, 1H), 2.35-2.19 (m, 1H), 2.18-2.07 (m, 1H), 2.03-1.86 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.6, 133.9, 130.9, 128.8, 128.2, 125.6, 55.2, 46.3, 30.9, 25.2. HRMS calculated for $[C_{13}H_{15}N_3+2H]^+$: 215.1422, obtained: 215.1365.

General procedure for organocatalytic asymmetric direct aldol reaction

A solution of organocatalyst 5d (0.014 g, 0.05 mmol), benzoic acid (0.006 g, 0.05 mmol) and the corresponding ketone (5 mmol) was stirred at room temperature for 0.5 h. Then the system was cooled to 0 °C, the aldehyde (0.5 mmol) was added and the reaction mixture was stirred for 120 h. The solution was returned to room temperature, treated with saturated aqueous NH_4Cl solution (1 mL) and extracted with dichloromethane (3 x 2 mL). The organic extracts were combined, dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The product was purified with flash column cromatography on silica gel using ethyl acetate and hexane (20:80).

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