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Organocatalytic Strategies for the Construction of Optically Active Imidazoles, Oxazoles, and Thiazoles

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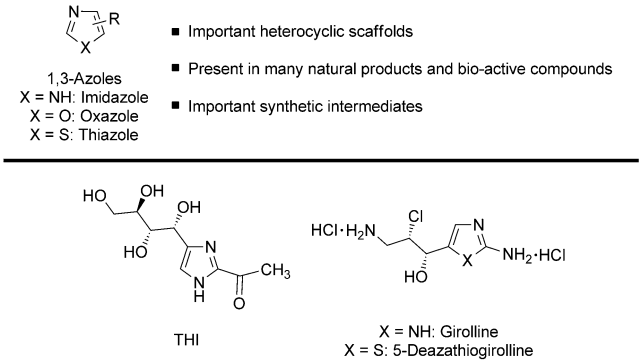
Abstract: This study demonstrates the first enantioselective synthesis of hydroxyalkyl- and aminoalkyl-substituted imidazoles, oxazoles, and thiazoles. The approach developed utilizes a highly effective one-pot reaction cascade that consists of either an organocatalytic epoxidation or aziridination of α,β-unsaturated aldehydes coupled with a [3+2]-annulation, in which amidines, ureas, or thioureas act as effective 1,3-dinucleophilic species. The methodology described benefits from low catalyst loadings, commercially and readily available starting materials, and mild reaction conditions.

Keywords: annulation · asymmetric catalysis · azoles · heterocycles · one-pot reactions

Introduction

The increasing demand from the chemical community for the development of cost- and time-effective, environmentally benign synthetic methodologies has resulted in tremendous expansion of the field of asymmetric catalysis.[1] Since the turn of the millennium, the application of small, chiral molecules as catalysts for a variety of enantioselective transformations—termed organocatalysis—has attracted much attention and has become a complementary method to the classical approaches utilized in asymmetric synthesis.[2] In particular, organocatalytic asymmetric one-pot strategies have recently emerged as a very rapidly developing research area and allow for facile and stereoselective assembly of molecular and stereochemical complexity.[3]

Heteroaromatic compounds occupy a prominent position among biologically relevant molecules.[4] The extraordinary abundance of heteroaromatic frameworks, their remarkable structural diversity, and specific chemical behavior, as well as wide occurrence in nature, gives them a privileged position in modern medicinal and synthetic organic chemistry. 1,3-Azoles, namely imidazoles, oxazoles, and thiazoles, constitute a particularly important class of heteroaromatic framework that occurs in many biologically active compounds and natural products (Scheme 1).[5–7] For instance, the imidazole ring is a constituent of the amino acid histidine. 2-Acetyl-4-tetrahydroxybutylimidazole (THI) is a component of caramel color III, a colorant commonly used in foods and beverages.[8] It was also found to produce lymphopenia without toxic effects in rats and mice.[8c,d] Girolline, a natural isolate from *Cymbastela cantharella* collected around New Caledonian, exhibits strong cytotoxicity and antitumor activity.[6a,g] Furthermore, 1,3-azoles constitute important synthetic intermediates that have found widespread applications in target-oriented synthesis[9] and are also commonly utilized as precursors of N-heterocyclic carbenes[10] and ionic liquids.[11]



Scheme 1. Importance of 1,3-azole structural unit.

Traditionally, the predominant strategy for the synthesis of 1,3-azoles utilizes a condensation reaction between α-halogenated carbonyl compounds and thioamides (Hantzsch synthesis) or amidines (Scheme 2).[12] Alternatively, oxiranes with a suitable leaving group on the epoxide ring can be applied instead of α-halogenated carbonyls in such annulation strategies.[13] However, the utilization of 2,3-epoxy or 2,3-aziridne aldehydes for the construction of 5-hydroxyalkyl- or 5-aminoalkyl-substituted 1,3-azoles is, to the best of our knowledge, unknown. So far, the only report on similar

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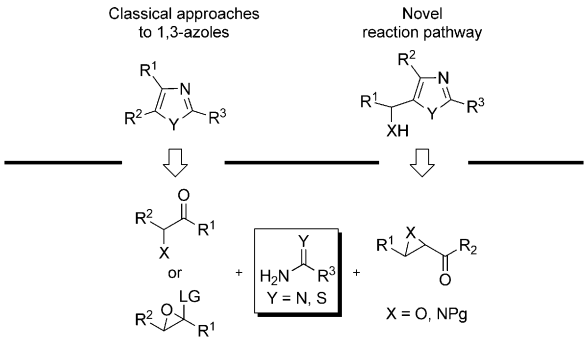
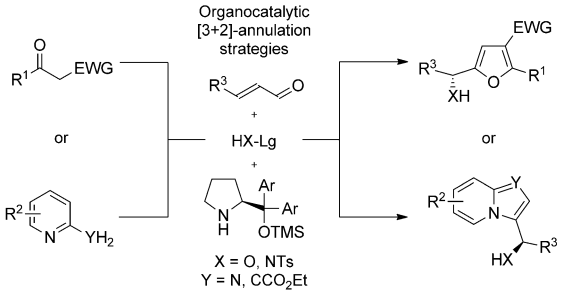


Scheme 2. Synthetic strategies for the synthesis of polysubstituted 1,3-azoles.

methodology deals with the application of 2,3-epoxy ketones for the preparation of fully substituted racemic thiazoles from the reaction with thiourea or thioamides.[14] Moreover, methods for the preparation of hydroxyalkyl- or aminoalkyl-substituted 1,3-azoles are scarcely recognized,[15] and no enantioselective method for the preparation of 5-substituted derivatives exists in the literature. Therefore, the development of synthetic methods that lead to these essential structural motifs is of particular importance.

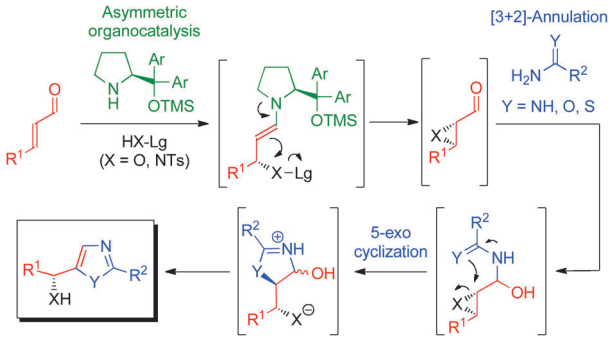
Recently we have developed new synthetic strategies to provide optically active hydroxyalkyl- and aminoalkyl-substituted heteroaromatic compounds: electron-poor furans, imidazo[1,2-*a*]pyridines, and indolizines (Scheme 3).[16] This



Scheme 3. Enantioselective organocatalytic [3+2]-annulation strategies for the synthesis of electron-poor furans, imidazo[1,2-*a*]pyridines, and indolizines.

approach is based on an efficient and highly enantioselective one-pot reaction sequence that consists of asymmetric organocatalytic epoxidation or aziridination of α,β-unsaturated aldehydes, followed by annulation with a 1,3-dinucleophilc species, such as a 1,3-dicarbonyl compound, 2-aminopyridine, or pyridylacetate.

Given the importance of functionalized imidazoles, oxazoles, and thiazoles, as well as the absence of a general enantioselective methodology for the preparation of hydroxyalkyl- or aminoalkyl-substituted 1,3-azoles, we envisioned that a strategy utilizing amidines, ureas, or thioureas as 1,3-dinucleophilic species in the annulation step could be feasible (Scheme 4). It was anticipated that 2,3-epoxy- or



Scheme 4. Asymmetric organocatalytic strategy for the synthesis of imidazoles, oxazoles, and thiazoles.

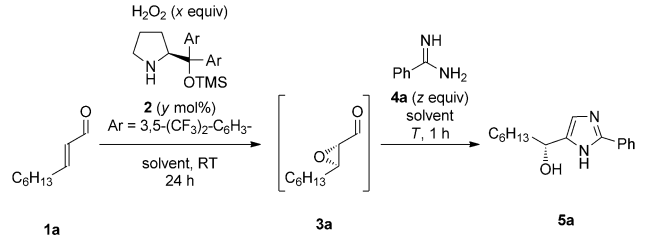
2,3-aziridine aldehydes, easily accessed through enantioselective aminocatalytic epoxidation/aziridination of α,β-unsaturated aldehydes, could undergo nucleophilic 1,2-addition when treated with amidines, ureas, or thioureas. Subsequent cyclization through an epoxide or aziridine ring-opening reaction, followed by dehydrative aromatization, should afford the 1,3-azole framework.

Herein, we report an organocatalytic, enantioselective one-pot strategy for the preparation of hydroxyalkyl- or aminoalkyl-substituted imidazoles, oxazoles, and thiazoles. Practical aspects of the developed strategy are worth noting (low catalyst loadings of 2.5–5 mol%, commercially available starting materials, and no necessity for inert conditions) and may greatly enhance the applicability of the developed protocol.

Results and Discussion

To find the optimal conditions for the preparation of hydroxyalkyl-substituted imidazoles, screening studies were initiated by using *trans*-2-nonenal (**1a**) as a model carbonyl compound and benzamidine (**4a**) as the 1,3-dinucleophilic species in the presence of catalytic α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (**2**).[16,17] Preliminary results revealed that imidazole **5a** can be accessed from a one-pot, two-step epoxidation/annulation reaction sequence. However, a moderate yield of **5a** was obtained when the epoxidation was performed under the conditions previously developed (Table 1, entry 1). Furthermore, it was observed that the amount of **4a** used had no pronounced effect on the reaction outcome (Table 1, entry 2). In both cases the annulation step was performed at 60 °C and was terminated within 1 h. Importantly, it was found that excess H_2O_2 from the epoxidation step has a crucial influence on the reaction outcome. When equimolar amounts of **1a** and H_2O_2 were used, the yield of the one-pot reaction cascade increased to 70% (Table 1, entry 3), which indicates that over-oxidation is a competitive process and results in yield deterioration. The reaction sequence could also be performed at room temperature, however, a longer reaction time (24 h) was required to achieve full conversion (Table 1, entry 4). Gratifyingly, in both cases, **5a** was formed

Table 1. Optimization of the reaction conditions for the synthesis of hydroxyalkyl-substituted imidazoles.[a]



	Solvent	Catalyst loading [mol%]	H_2O_2 [equiv]	**4a** [equiv]	*T* [°C][b]	Yield [%][c]	*ee* [%][d]
1	toluene	5	1.3	1.05	60	52	n.d.[e]
2	toluene	5	1.3	1.5	60	54	n.d.
3	toluene	5	1	1.05	60	70	93
4[f]	toluene	5	1	1.05	RT	70	93
5	CH_2Cl_2	2.5	1	1.05	40	36	n.d.
6[g]	toluene	5	1	1.05	60	64	93
7	toluene	5	1	1.5	60	65	93

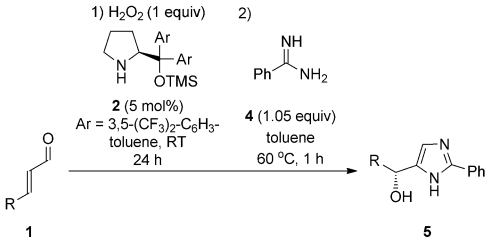
[a] Reactions performed on a 0.2 mmol scale in 0.4 mL of the solvent (see the Supporting Information for details). [b] Reaction temperature for the second step. [c] Overall yield. [d] Determined by chiral stationary phase HPLC. [e] Not determined. [f] Annulation step performed for 24 h. [g] Annulation step performed in the presence of Na_2SO_4.

in a highly enantioselective manner—93% enantiomeric excess (*ee*)—which indicated that the elevated temperature of the annulation step did not lead to racemization of the introduced stereogenic center. Further screening revealed that a change of the solvent to CH_2Cl_2, or the presence of Na_2SO_4 as additive to remove the water present in the reaction mixture from the epoxidation step, did not improve the results (Table 1, entries 5 and 6). Moreover, increasing the amount of **4a** used had no beneficial effect on the cascade yield (Table 1, entry 7).

With the optimized conditions for the enantioselective formation of hydroxyalkyl-substituted imidazoles in hand, attention was turned to the scope of the methodology (Table 2). A range of optically active 2,5-disubstituted imidazoles were readily and efficiently prepared in moderate to good yields (44–76%) with excellent enantioselectivities (92–97% *ee*). Linear and γ-branched aldehydes **1a–d** participated smoothly in the one-pot reaction sequence to afford imidazoles **5a–d** in good yields and with excellent *ee* values (Table 2, entries 1–4). Furthermore, functional groups, such as a double bond (**1e**), protected alcohol (**1f**), and phenyl ring (**1g**), present in the side-chain of the starting α,β-unsaturated aldehyde were well tolerated (Table 2, entries 5–7). Notably, cinnamaldehyde and ethyl 4-oxobutenoate were also applied in the reaction sequence under the optimized reaction conditions. However, unsatisfactory results were obtained in these instances.

Having accomplished the synthesis of the hydroxyalkyl-substituted imidazoles **5**, screening of the complementary aziridination/annulation strategy was initiated (Table 3). Preliminary experiments revealed that the amount of **4a** used is crucial to achieve full conversion of the intermediary aziridine **6a** into **7a** in the annulation step, with 1.5 equiv of

Table 2. Aldehyde scope of the enantioselective synthesis of optically active hydroxyalkyl-substituted imidazoles.[a]

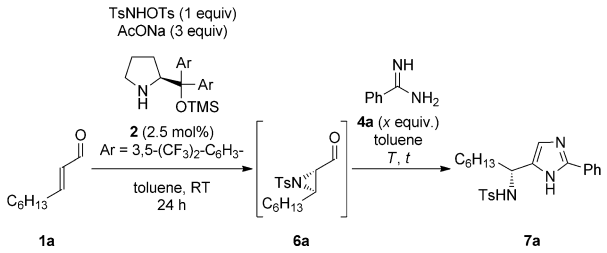


	1	R	Product	Yield [%][b]	*ee* [%][c]
1	**1a**	hexyl	**5a**	70	93
2	**1b**	Pr	**5b**	68	94
3	**1c**	*i*Pr	**5c**	64	97
4[d]	**1d**	Me	**5d**	52	92
5	**1e**	(*E*)-hex-3-enyl	**5e**	76	96
6	**1f**	CH_2OBn	**5f**	44	92
7	**1g**	CH_2CH_2Ph	**5g**	58	93

[a] Reactions performed on a 0.2 mmol scale in toluene (0.4 mL); see the Supporting Information for details. [b] Overall yield. [c] Determined by chiral stationary phase HPLC. [d] Epoxidation performed with catalyst **2** (10 mol%).

4a being optimal (Table 3, entry 3). Again, the annulation step could be performed at elevated temperature (60°C) without detriment to the enantioselectivity of the one-pot reaction cascade.

Table 3. Optimization of the reaction conditions for the synthesis of aminoalkyl-substituted imidazoles.[a]

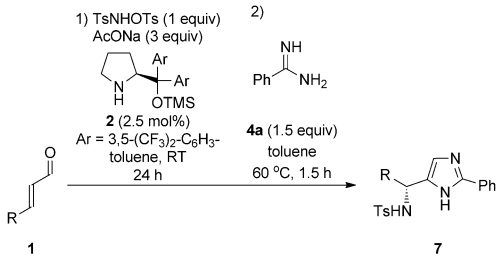


	4a [equiv]	*T* [°C][b]	*t* [h][c]	Yield [%][d]	Conv. [%][e]	*ee* [%][f]
1	1.05	RT	24	n.d.[g]	50	n.d.
2	1.05	60	1	44	53	n.d.
3	1.50	60	1.5	66	>95	96
4	2.00	60	1	57	>95	n.d.
5	1.60	60	1.5	65	>95	96

[a] Reactions performed on a 0.1 mmol scale in toluene (0.5 mL); see the Supporting Information for details. [b] Reaction temperature for the second step. [c] Reaction time for the second step. [d] Overall yield. [e] Conversion of **6a** in the second step, determined by ^1H NMR spectroscopy. [f] Determined by chiral stationary phase HPLC. [g] Not determined.

The generality of the aziridination/annulation one-pot reaction cascade was next evaluated. As presented in Table 4, the established reaction conditions could be successfully applied with various α,β-unsaturated aldehydes **1**, an indication of the high versatility of the reaction. Good yields and

Table 4. Aldehyde scope in the enantioselective synthesis of optically active aminoalkyl-substituted imidazoles.[a]



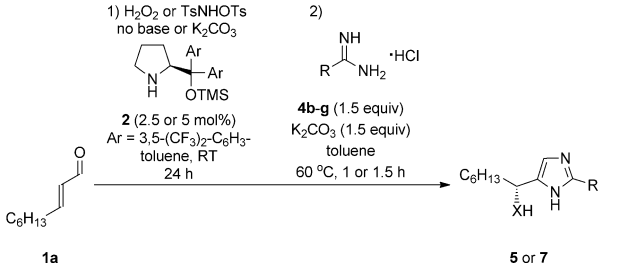
	1	R	Product	Yield [%][b]	*ee* [%][c]
1	**1a**	hexyl	**7a**	66	96
2	**1b**	Pr	**7b**	52	96
3	**1c**	*i*Pr	**7c**	51	95
4	**1d**	Me	**7d**	56	93
5	**1e**	(*E*)-hex-3-enyl	**7e**	70	96
6	**1f**	CH_2OBn	**7f**	60	96
7	**1g**	CH_2CH_2Ph	**7g**	65	92

[a] Reactions performed on a 0.1 mmol scale in toluene (0.5 mL); see the Supporting Information for details. [b] Overall yield. [c] Determined by chiral stationary phase HPLC.

enantioselectivities of **7a–d** were obtained in the case of linear and γ-branched aldehydes **1a–d**. Furthermore, the reaction cascade proved to be unbiased towards additional functional groups in the side chain of the starting α,β-unsaturated aldehyde. Aldehydes **1e–g** afforded imidazoles **7e–g** in good yields and with excellent enantioselectivities. 6-Oxohept-2-enal was also reacted under optimized reaction conditions, but the target imidazole was obtained in only 28% yield, probably due to side reactions taking place at the carbonyl side-chain functionality.

With an established efficient and enantioselective methodology for the preparation of hydroxyalkyl- or aminoalkyl-substituted imidazoles **5** and **7** in place, the possibility of introducing various substituents at the 2-position of the target imidazole derivative was evaluated (Table 5). Therefore, differently functionalized aliphatic, aromatic, and heteroaromatic amidines were employed. However, because commercial amidines are available as hydrochloride or hydroiodide salts, additional base had to be employed in the annulation step. Initial experiments allowed us to identify K_2CO_3 as the most suitable base for liberation of amidines from their salts. Moreover, in the case of the aziridination/annulation sequences it was found that the use of K_2CO_3 as a base in both processes is beneficial for the overall reaction outcome. To our delight aliphatic amidines **4b** and **c** participated smoothly in the reaction cascade, which allowed for facile introduction of cyclic or acyclic aliphatic side chains in the target imidazoles **5** or **7** (Table 5, entries 1–4). Various aromatic and heteroaromatic amidines were also evaluated (Table 5, entries 5–12). Pleasingly, the nature and position of the substituents on the aromatic ring of amidines **4** had no major influence on the outcome of the one-pot cascade and both electron-rich and electron-poor systems could be successfully applied (Table 5, entries 5–10). The use of heteroaromatic 3-pyridyl-substituted amidine **4g** is also worth mentioning; imidazoles **5m** or **7m** were afforded in high yields, in an enantioselective manner (Table 5, entries 11 and 12). Importantly, in all of the cases, excellent enantioselectivities (92–96% *ee*) were obtained despite basic reaction conditions and elevated temperatures.

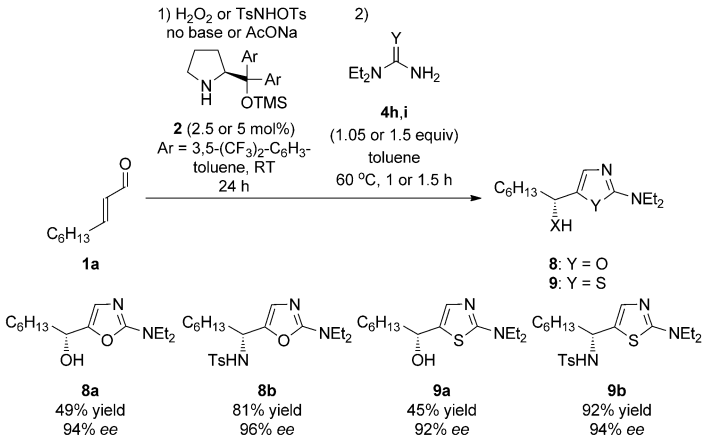
Table 5. Amidine scope in the enantioselective synthesis of optically active imidazoles.



	4	R	X	Product	Yield [%][c]	*ee* [%][d]
1[a]	**4b**	*c*Pr	O	**5h**	63	91[f]
2[b]	**4b**	*c*Pr	NTs	**7h**	69	96
3[a]	**4c**	*t*Bu	O	**5i**	66	n.d.[g]
4[b]	**4c**	*t*Bu	NTs	**7i**	55	94
5[a]	**4d**	4-CH_3-C_6H_4-	O	**5j**	64	94
6[b]	**4d**	4-CH_3-C_6H_4-	NTs	**7j**	68	96
7[a,e]	**4e**	4-Cl-C_6H_4-	O	**5k**	52	93
8[b,e]	**4e**	4-Cl-C_6H_4-	NTs	**7k**	63	95
9[a]	**4f**	3-NO_2-C_6H_4-	O	**5l**	59	93
10[b]	**4f**	3-NO_2-C_6H_4-	NTs	**7l**	64	96
11[a]	**4g**	3-pyridyl	O	**5m**	62	92
12[b]	**4g**	3-pyridyl	NTs	**7m**	75	92

[a] Reactions performed on a 0.2 mmol scale in toluene (0.4 mL); see the Supporting Information for details. [b] Reactions performed on a 0.1 mmol scale in toluene (0.5 mL); see the Supporting Information for details. [c] Overall yield. [d] Determined by chiral stationary phase HPLC. [e] HI salt used. [f] Determined by chiral stationary phase HPLC after the transformation of the products into the corresponding *N*-tritylated derivative (see the Supporting Information for details). [g] Not determined—separation of the enantiomers by chiral stationary phase HPLC could not be achieved. However, because the optical activity of **5i** originates from the same enantiodifferentiating process as for the other imidazoles **5** obtained, it is reasonable to assume that the *ee* also exceeds 90% in this case.

The chemical and biological properties of the 2-amino-1,3-azole subunit (a very potent pharmacophore, commonly utilized in drug discovery process) have recently gained much attention.[6a,g] Many natural products isolated from marine sponges contain this moiety and have intriguing biological properties. Therefore, we questioned whether the developed strategy could be extended to these structural motifs. In particular, a facile construction of oxazole and thiazole rings seemed appealing. To access these two classes of heteroaromatic compounds, the replacement of amidines with ureas or thioureas in the annulation step was envisioned (Scheme 5). The studies were performed by using **1a** as a model carbonyl compound and 1,1-diethyl-urea (**4h**) or thiourea (**4i**) as the annulating reagent. We were pleased to observe that this approach proved successful. 5-Hydroxyalkyl- and aminoalkyl-substituted oxazoles **8a** and **8b** and



Scheme 5. Enantioselective synthesis of optically active oxazole and thiazole derivatives.

thiazoles **9a** and **9b** were effectively accessed in a highly enantioselective manner. Notably, higher yields were observed for aziridination/annulation sequences relative to the cascades initiated with organocatalytic epoxidations. A particularly remarkable feature of the developed cascades is the complete regioselectivity. In all cases, the formation of oxazoles **8** and thiazoles **9** arises from opening of the epoxide or aziridine ring by the oxygen or sulfur atom of **4h** or **4i**, respectively (see below and Figure 1 for further details).

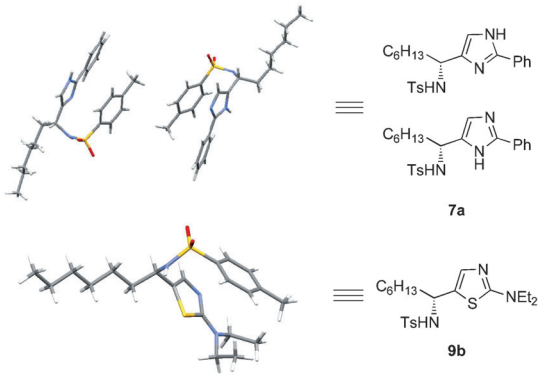


Figure 1. X-ray structures of **7a** and **9b**.

Amides and thioamides were also investigated in the developed synthetic strategy. Benzamide was unreactive under the present reaction conditions. Contrarily, thiobenzamide underwent reaction with the intermediary 2,3-epoxy aldehyde, but the desired thiazole was not obtained.[18]

The absolute configuration of imidazole **7a** was unambiguously assigned as (*R*)-**7a** by X-ray analysis.[19] Interestingly, it was found that in the crystal unit, **7a** exists as a mixture of two tautomers. Notably, one main product was observed by ^{1}H NMR spectroscopy, which indicates that the rate of tautomeric proton shift is similar to, or faster, than the NMR timescale. Therefore, two tautomers of imidazoles **5** or **7** exist in rapid equilibrium and are indistinguishable by this technique. In this context it is worth mentioning that unusual signal broadening, especially pronounced for the C4 and C5 carbon atoms in all obtained imidazoles **5** and **7**, was observed by ^{13}C NMR spectroscopy.

Similarly, the absolute stereochemistry of the thiazole **9b** was established as (*R*)-**9b** by single crystal X-ray analysis.[19] This result also revealed that the sulfur atom is indeed involved in the aziridine ring-opening reaction, which results in a fully regioselective cascade. The absolute configuration of all remaining imidazoles **5b–m** and **7b–m**, oxazoles **8a** and **8b**, and thiazole **9a**, as well as the regioselectivity of the oxazole and thiazole annulations, were assigned by analogy. These assignments are in accordance with the previous results for epoxidation and aziridination of enals **1** catalyzed by **2** and their applications in the synthesis of heteroaromatic compounds.[16,17a–d]

Conclusion

The enantioselective organocatalytic strategy for the synthesis of hydroxyalkyl- and aminoalkyl-substituted imidazoles was established. This efficient one-pot protocol utilizes a highly enantioselective aminocatalytic epoxidation or aziridination of α,β-unsaturated aldehydes, followed by a ring-closing step that uses amidines as 1,3-dinucleophilic species. Various linear, branched, and functionalized α,β-unsaturated aldehydes can be efficiently applied in these cascades. Furthermore, the generality of the process was confirmed by use of aromatic, heteroaromatic, and aliphatic amidines, which allowed for the introduction of various substituents in the 2-position of the target imidazoles. Finally, the established protocol was extended to the synthesis of 2-diethylaminooxazoles and -thiazoles when 1,1-diethylurea and thiourea were employed in the annulation step. In these cases, complete regioselectivity of the reaction was observed and 5-substituted oxazoles and thiazoles were the only products.

Experimental Section

General procedure for the preparation of hydroxyalkyl-substituted imidazoles (5): A glass vial equipped with a magnetic stirrer bar was charged with aldehyde **1** (0.2 mmol, 1 equiv), aminocatalyst **2** (0.01 mmol, 0.05 equiv), and toluene (0.4 mL). After briefly stirring at RT, H_2O_2 (35% *w*/*w* in water, 0.2 mmol, 1 equiv) was added. The stirring was maintained at ambient temperature for 24 h to achieve full conversion of **1**. Upon completion of the reaction, benzamidine **4a** (0.21 mmol, 1.05 equiv) [or the corresponding amidine salt **4b–g** (0.3 mmol, 1.5 equiv) and K_2CO_3 (0.3 mmol, 1.5 equiv)] was added. The mixture was heated at 60 °C for 1 h and then directly subjected to flash column chromatography on silica gel to afford imidazole **5**.

General procedure for the preparation of aminoalkyl-substituted imidazoles (7): A glass vial equipped with a magnetic stirrer bar was charged with aldehyde **1** (0.12 mmol, 1.2 equiv), catalyst **2** (0.0025 mmol, 0.025 equiv), and toluene (0.5 mL). After briefly stirring at RT, TsNHOTs (0.1 mmol, 1 equiv) was added, followed by NaOAc (0.3 mmol, 3 equiv) or K_2CO_3 (0.3 mmol, 3 equiv). The stirring was maintained at ambient temperature for 24 h to achieve full conversion of the nucleophile. Upon completion of the reaction, benzamidine **4a**

(0.3 mmol, 1.5 equiv) [or the corresponding amidine salt **4b–g** (0.3 mmol, 1.5 equiv) and K_2CO_3 (0.3 mmol, 1.5 equiv)] was added. The resulting mixture was heated at 60 °C for 1.5 h and then directly subjected to flash column chromatography on silica gel to afford imidazole **7**.

General procedure for the preparation of hydroxyalkyl-substituted oxazoles and thiazoles: A glass vial equipped with a magnetic stirrer bar was charged with aldehyde **1** (0.2 mmol, 1 equiv), aminocatalyst **2** (0.01 mmol, 0.05 equiv) and toluene (0.4 mL). After briefly stirring at RT, H_2O_2 (35 % *w*/*w* in water, 0.2 mmol, 1 equiv) was added. The stirring was maintained at ambient temperature for 24 h to achieve full conversion of **1**. Upon completion of the reaction, urea **4h** or thiourea **4i** (0.21 mmol, 1.05 equiv) was added. The resulting mixture was heated at 60 °C for 1 h and then directly subjected to flash column chromatography on silica gel to afford oxazole **8a** or thiazole **9a**.

General procedure for the preparation of aminoalkyl-substituted oxazoles and thiazoles: A glass vial equipped with a magnetic stirrer bar was charged with aldehyde **1** (0.12 mmol, 1.2 equiv), catalyst **2** (0.0025 mmol, 0.025 equiv), and toluene (0.5 mL). After briefly stirring at RT, TsNHOTs (0.1 mmol, 1 equiv) was added followed by NaOAc (0.3 mmol, 3 equiv). The stirring was maintained at ambient temperature for 24 h to achieve full conversion of the nucleophile. Upon completion of the reaction, urea **4h** or thiourea **4i** (0.3 mmol, 1.5 equiv) was added. The resulting mixture was heated at 60 °C for 1.5 h and then directly subjected to flash column chromatography on silica gel to afford oxazole **8b** or thiazole **9b**.

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[19] See the Supporting Information for the crystal structure. CCDC-829245 (**9b**) and 829246 (**7a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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