The aminoindanol core as a key scaffold in bifunctional organocatalysts

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Abstract

The 1,2-aminoindanol scaffold has been found to be very efficient, enhancing the enantioselectivity when present in organocatalysts. This may be explained by its ability to induce a bifunctional activation of the substrates involved in the reaction. Thus, it is easy to find hydrogen-bonding organocatalysts ((thio)ureas, squaramides, quinolinium thioamide, etc.) in the literature containing this favored structural core. They have been successfully employed in reactions such as Friedel–Crafts alkylation, Michael addition, Diels–Alder and aza-Henry reactions. However, the 1,2-aminoindanol core incorporated into proline derivatives has been scarcely explored. Herein, the most representative and illustrative examples are compiled and this review will be mainly focused on the cases where the aminoindanol moiety confers bifunctionality to the organocatalysts.

Introduction

The structural and chemical properties of the 1,2-aminoindanol scaffold 1 have transformed aminoindanol derivatives into versatile building blocks for the construction of catalysts and the efficient induction of chirality in asymmetric processes (Figure 1). Some examples of these properties are rigidity, disposition of the two stereogenic centers, ability of the hydroxy and amino groups to coordinate to some metals or to act as hydrogen-bond donors/acceptors, the different catalytic activity of these chemical groups and their possible derivatization. Thus, in the last decade, it has been widely employed in the field of asymmetric catalysis. Regarding the use of aminoindanol derivatives as ligands in organometallic catalytic complexes, the results have been outstanding. Examples are found in (a) the vanadium-catalyzed asymmetric oxidation of disulfides and sulfides, which are involved in the synthesis of ligands and pharmaceutical chiral synthetic precursors [1,2] and in (b) the transfer-hydrogenation reaction catalyzed by bifunctional chiral ruthenium complexes, employed in the synthesis of peptide
Figure 1: Different configurations of 1,2-aminoindanol 1a–d.
In a recent study of this F–C alkylation, Herrera’s group has provided computational evidence of the reaction pathway, which confirms the proposed bifunctional activation mode played by the thiourea catalyst 4 [22]. Remarkably, an interesting hydrogen-bonding interaction between the hydroxy group and the nitro group was detected in this work (Figure 3b). This could explain the low reactivity (18% yield) and selectivity (39% ee) that the silyl ether-protected catalyst 4" exhibited (Figure 2).

Encouraged by the development of more efficient organocatalytic systems, the same research group explored the influence of external acidic additives in this reaction. The authors envisioned that a cooperative effect between the chiral thiourea organocatalyst and a Brønsted acid (AH) could provide better results in terms of reactivity and enantioselectivity. Thus, in 2011, they published an article where it was proved that the synergic system between the thiourea ent-4 and mandelic acid led to the final products 5 with a significant increase of conversion and enantiomeric excess (Scheme 2) [23].

Experimental proofs exploring different catalysts and acids suggested that it is the thiourea which provides the sense of the enantioinduction. Therefore, the authors assumed the bifunctional transition state TS2, similar to the above mentioned TS1, where the external acid (AH) would only coordinate to the thiourea moiety enhancing its acidity and thus forming a more active catalytic species (Figure 4).
Scheme 2: Asymmetric F–C alkylation catalyzed by thiourea ent-4 in the presence of D-mandelic acid as a Brønsted acid additive.

Figure 4: Transition state TS2 proposed for the activation of the thiourea-based catalyst ent-4 by an external Brønsted acid.

Since the pioneering aminindanol-containing organocatalyst 4, reported in 2005 [18], other research groups have studied the possibility of incorporating this scaffold into diverse organocatalysts.

In 2008, Seidel’s group published a new example of an asymmetric addition of indoles to nitroalkenes, employing a novel catalyst design [24]. The authors envisioned that a protonated 2-pyridyl substituent could increase the acidity of the thiourea group through an intramolecular N–H···S hydrogen-bonding interaction (analogous to the C–H···S that exists with the 3,5-bis-trifluoromethylphenyl moiety, commonly used in thiourea-based organocatalysts) [25]. Although this first approach did
not provide a significant increase of the enantioselectivity, further modifications of the catalytic structure led to highly active catalysts. Indeed, the best results were obtained with the quinolinium thioamide 6, where the NH moiety adjacent to the pyridine ring of the analogous thiourea was “removed”. Likely, in this case, the intramolecular hydrogen-bonding interaction described above would yield a negligible stabilization due to the distance between N–H and S moieties. In contrast, it is suspected that both the thioamide N–H as well as the N–H on the quinolinium moiety are engaged in substrate binding, and thus, provide higher yields and selectivity in comparison with the catalyst 4 (up to 96% yield, up to 98% ee) (Scheme 3).

The authors do not comment on whether the catalyst 6 acts in a bifunctional fashion or not, but it is reasonable to assume that the OH group is again involved in the transition state by a possible interaction with the indole derivatives 2. Indeed, as discussed below, other authors proposed the compound 6 as a plausible bifunctional catalyst. The Enders’ group used its enantiomer (ent-6) to develop a pioneering scalable one-pot multicatalytic method for the C2/C3-annulation of the indoles 2 (Scheme 4) [26]. In this work, an efficient enantioselective and sequential double Friedel–Crafts alkylation provided direct access to the tetracyclic seven-membered ring containing indoles 8. These pharmaceutically intriguing compounds exhibit anticancer [27] and antiproliferative activity [28].

In the first catalytic cycle of the authors’ mechanistic hypothesis, the β-nitroalkene derivatives 7 are proposed to react with the indoles 2 in the presence of the organocatalyst ent-6 to afford the intermediates 9 with excellent enantioselectivity (Scheme 5). Furthermore, a bifunctional activation mode through the transition state TS3 was proposed. Herein, the NH from the thioamide and the protonated quinoline moiety would activate and fix the nitroalkene framework through hydrogen-bonding interactions. Simultaneously, the oxygen atom of the

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**Scheme 3:** Friedel–Crafts alkylation of indoles catalyzed by the chiral thioamide 6.

**Scheme 4:** Scalable tandem C2/C3-annulation of indoles, catalyzed by the thioamide ent-6.
hydroxy group would orientate the attack of the indole by the Si face through the formation of a hydrogen bond with the indolic proton. In the second catalytic cycle, the intermediates 9 would react to give an intramolecular Friedel–Crafts alkylation. The alkyne moiety of 9 would be previously activated by a gold complex in the presence of p-toluenesulfonic acid hydrate as the additive. The final tetracyclic indoles 8 are released from the spirocyclic intermediates 11, following a ring-expansion and rearomatization/final protodeauration cascade process (Scheme 5) [26].

In 2012, the same group reported an additional example of a one-pot multisequence reaction following a similar mode of activation. This method provided a route to access the enantiomerically enriched tetrahydrocarbazole scaffold-containing compounds 14 (Scheme 6 and Scheme 7) [29]. One of these valu-
able products is a synthetic precursor of the pharmacologically active compound 15, used to treat Alzheimer and other central nervous system diseases [30-34].

In the proposed reaction pathway, the nucleophilic addition of the indole derivatives 2 to the nitroalkene 13 progresses in a stereocontrolled manner due to the creation of a ternary complex with the chiral bifunctional thioamide ent-6 (TS4, Scheme 7). Herein, the catalyst activates both substrates simultaneously through hydrogen-bonding interactions between the thioamidic NH and the nitro group, and between the hydroxy group and the indolic proton. In the presence of AgSbF$_6$, a soft Lewis acid, the stereogenic center-containing intermediates 16 are activated. This triggers an SN$_2$-type attack/Ciamician–Plancher rearrangement [35]/rearomatization cascade process, affording the final products 14 (Scheme 7).

More recently, the same authors also provided an elegant and efficient solution to give direct access to cis-vicinal-substituted indane scaffolds through an organocatalyzed asymmetric domino-Michael addition/Henry reaction (Scheme 8) [36]. These heterocyclic products are important chiral building
Scheme 9: Asymmetric domino procedure (Michael addition/Henry cyclization), catalyzed by the thioamide ent-6 which involves a cis-matched transition state (TS6) that allows a kinetic control of the second reaction.
Scheme 10: The enantioselective addition of indoles 2 to α,β-unsaturated acyl phosphonates 24, a) screening of different catalysts and b) optimized conditions using catalyst ent-4.

Based on the experimental results, the authors proposed a bifunctional mode of activation (TS7), where the electrophile is fixed and activated by the thiourea framework through several hydrogen bonds. At the same time, the indole is oriented to attack the Re face of the Michael-type acceptor, by weak hydrogen-bonding interaction between the oxygen atom of the hydroxy group and the indolic proton (Figure 5).

Recently, the conjugated addition of indole derivatives to β,γ-unsaturated α-ketoesters was explored [40]. To this end, the catalytic activity of several chiral thioureas was studied, revealing the aminooindanol-based thiourea ent-4 as the most suitable catalyst for this process. The authors studied aliphatic derivatives because for this reaction these compounds had been much less explored than the aromatic ones. Thus, the different aliphatic β,γ-unsaturated α-ketoesters 26a–f reacted with the substituted indoles 2 in the presence of ent-4 to achieve the corresponding adducts 27 with good yields and enantioselectivities (up to 88% yield, up to 76% ee) (Scheme 11).

Although the absolute configuration was unknown at that point, the authors envisioned a plausible reaction pathway based on previously reported transition states (Figure 6). The catalyst ent-4 would activate and fix the electrophile through several
hydrogen-bonding interactions with the NH groups of the thiourea. Simultaneously, the hydroxy group would be involved in the activation of the nucleophile, establishing a hydrogen bond with the indolic proton. This would conduct its attack over the Re face of the \( \beta,\gamma \)-unsaturated \( \alpha \)-ketoesters, producing the addition in a stereocontrolled fashion. Some additional experimental proofs provided in the article supported this hypothesis [40].

**Michael addition to \( \alpha,\beta \)-unsaturated compounds**

Fernández, Lassaleta and co-workers provided an elegant, versatile and mild umpolung strategy, which leads to key synthetic precursors using the thiourea ent-4. In this study, an organocatalytic enantioselective addition of nucleophilic N,N-dialkylhydrazones to electron-deficient \( \beta,\gamma \)-unsaturated \( \alpha \)-ketoesters was reported (Table 1) [41]. In the presence of catalyst ent-4, 1-methyleneaminopyrrolidine (28) reacted with the different \( \beta,\gamma \)-unsaturated \( \alpha \)-ketoesters 26 in dichloromethane at low temperature to give the corresponding products 29, which are useful masked 1,4-dicarbonyl compounds with moderate to high yield and high selectivity, after moderate reaction times (Table 1).

The authors proposed the plausible transition state TS10, where the acidic hydrogen atoms of the thiourea could activate the \( \beta,\gamma \)-unsaturated \( \alpha \)-ketoesters 26. Simultaneously, the hydrogen atom of the hydroxy group of the thiourea would coordinate and direct the hydrazones 28 to the Re face of the esters 26 in order to afford the absolute configuration found in the final products 29 of this process (Figure 7).

Another example of the bifunctional action of the indanol-based thiourea 4 was reported by Sibi’s group. There, 100 mol % of
Table 1: Asymmetric addition of 1-methyleneaminopyrrolidine (28) to β,γ-unsaturated α-ketoesters 26, catalyzed by ent-4.

| Entry | 26 (R) | Temp. (ºC) | Yield 29 (%) | ee 29 (%) |
|-------|--------|------------|--------------|-----------|
| 1     | Me     | 60         | 60           | 80        |
| 2     | iPr    | 45         | 80           | 78        |
| 3     | iBu    | 45         | 75           | 78        |
| 4     | n-C₅H₁₁ | 60         | 61           | 70        |
| 5     | (CH₃)₂CH₂ | 45         | 64           | 58        |
| 6     | Cy     | 45         | 82           | 72        |

Figure 7: Transition state TS₁₀ proposed for the asymmetric addition of dialkylhydrazone 28 to the β,γ-unsaturated α-ketoesters 26 catalyzed by ent-4.

In this work, the authors compared the results achieved by means of 4 with other urea- and thiourea-based organocatalysts in order to understand the effect of the acidity, the structural rigidity, and the bifunctionality of the promoter. These reactions were performed in trifluorotoluene at room temperature.

Table 2: The enantioselective addition of the hydroxylamine derivatives 31 to the enoates 30 promoted by 4.

| Entry | 30 (R¹, R², R³) | 31 (R⁴) | Time (h) | Yield 32 (%) | ee 32 (%) |
|-------|-----------------|---------|----------|--------------|-----------|
| 1ᵃ    | Me, H, Me      | PhCH₂   | 24       | 75 (32a)     | 71        |
| 2ᵃᵇ   | Me, H, Me      | PhCH₂   | 168      | 63 (32a)     | 71        |
| 3     | Me, H, Me      | PhCH₂   | 72       | 82 (32a)     | 87        |
| 4ᵃ    | Me, Br, Me     | PhCH₂   | 24       | 85 (32b)     | 61        |
| 5ᵃ    | Ph, H, Me      | PhCH₂   | 14       | 76 (32c)     | 45        |
Table 2: The enantioselective addition of the hydroxylamine derivatives 31 to the enoates 30 promoted by 4. (continued)

| Entry | R1, R2, R3     | R4          | Yield (%) | ee (%) |
|-------|----------------|-------------|-----------|--------|
| 6a    | Ph, Br, Me     | PhCH₂       | 12        | 72 (32d) |
| 7     | Me, H, Me      | Ph₂CH       | 96        | 86 (32e) |
| 8     | Me, H, CO₂Et   | Ph₂CH       | 96        | 50 (32f) |
| 9     | Me, H, CO₂Et   | TBDMS       | 96        | 42 (32g) |
| 10    | Me, H, Et      | Ph₂CH       | 168       | 92 (32h) |
| 11    | Me, H, n-Pr    | Ph₂CH       | 138       | 84 (32i) |
| 12    | Me, H, iPr     | Ph₂CH       | 216       | 68 (32j) |
| 13    | Me, H, c-C₆H₁₃ | Ph₂CH       | 288       | 59 (32k) |
| 14b   | Me, H, CH₂OPMP | Ph₂CH       | 24        | 98 (32l) |
| 15a   | Me, H, Ph      | PhCH₂       | 72        | 19 (32m) |
| 16    | Me, H, Me      | TBDMS       | 120       | 82 (32n) |

*Reaction carried out at room temperature. b30 mol % of catalyst 4.

with the Michael acceptor 30 (R₁, R₂, R₃ = Me, H, Me) and O-benzylhydroxylamine (31, R₄ = PhCH₂), using a stoichiometric amount of the chiral activator and MS 4 Å as an additive. Some of the reported experiments supported the ability of the cis-2-aminindanol structure to provide an adequate scaffold to induce chirality. In contrast, the catalysts ent-22 (with the trans-2-aminindanol) or 4′′ (with the aminoadane motif) and the flexible analogues 33–35, provided lower enantioselectivities or led to nearly racemic mixtures (Scheme 12). In the proposed transition state TS11, the α,β-unsaturated substrate is activated by an acidic thiourea template. Moreover, the hydroxylamine derivative is simultaneously oriented to attack the Si face of the Michael acceptor, through its interaction with the hydroxy group of the aminindanol framework. In this case, a pyrazole moiety presents additional H-bond acceptor sites. These could play an important role in fixing the substrate to the catalyst and favoring

Scheme 12: Different β-hydroxylamino-based catalysts tested in a Michael addition, and the transition state TS11 proposed for this reaction catalyzed by 4.
Later, He and co-workers reported the use of several chiral multiple hydrogen-bond donating tertiary amine-based organocatalysts in the asymmetric addition of acetylacetone (36a) to the β-nitroalkenes 3. They found thiourea 37 as a highly suitable catalytic structure to induce chirality in this process (Scheme 13) [43]. Under optimal conditions, this method provided highly enantioenriched γ-nitrocobonyl compounds 38, which are versatile synthetic intermediates for the preparation of diverse chiral scaffolds.

Once again, a bifunctional activation mode as the origin of the asymmetric induction was proposed. In the plausible transition state TS12, acidic hydrogen atoms from both hydroxy and thiourea moieties would activate and fix the nitroalkene. Simultaneously, the tertiary amine of the cinchona framework would deprotonate the acidic proton of acetylacetone (36a), driving the attack of the nucleophile. The chiral environment present in the resulting ternary complex would confer the proper facial selectivity to afford the observed absolute configuration in the final products 38.

At the same time, Yuan and co-workers developed an interesting example of a scalable asymmetric Michael addition of 3-substituted oxindoles 39 to the protected 2-amino-1-nitroethenes 40, using the bifunctional tertiary amine aminodanol-based organocatalyst 41 (Scheme 14) [44]. This catalytic study provides a straightforward synthetic route of the highly functionalized α,β-diamino-3,3′-disubstituted-oxindoles 42. These are key intermediates for the preparation of biologically and pharmacologically attractive compounds, such as (+)-alantrypinone [45], (-)-serantrypinone [46] and (-)-lapatin [47]. In the presence of the catalyst 41 (10 mol %), a broad scope of the oxindoles 39 reacted to give the quaternary stereocenters-containing products 42 with high diastereoselectivity (up to > 99:1 dr) and enantioselectivity (up to 90% ee).

A bifunctional role played by the catalyst was again envisioned by the authors. In the transition state TS13 the tertiary amine group of the catalyst would activate the resulting enolized oxindole reagent 39 via deprotonation. Thus, 39 would be disposed to attack by its Re face to the Si face of the nitroethene derivative 40. Simultaneously, the latter would be fixed and activated by a hydrogen-bonding interaction with the hydroxy moiety of the catalyst, in its Z form, which is stabilized due to an intramolecular hydrogen bond (Scheme 14).

In 2012, Dong and co-workers studied the catalytic activity of several β-amino alcohol-based squaramide organocatalysts involved in the Michael addition of acetylacetone (36a) to β-nitrostyrene (3a) in dichloromethane at 15 °C (Scheme 15) [48]. Although high yields were obtained in all cases, the best enantioselectivity was provided by the bifunctional cis-aminodanol-based squaramide 43. Under these conditions, several
Scheme 14: Addition of 3-oxindoles 39 to 2-amino-1-nitroethenes 40, catalyzed by 41.

Scheme 15: Michael addition of 1,3-dicarbonyl compounds 36 to the nitroalkenes 3 catalyzed by the squaramide 43.

1,3-dicarbonyl compounds 36 reacted with many different nitrostyrene derivatives 3 with very low catalytic charge (1 mol %), affording a broad scope of the enantiomerically enriched β-nitroalkyl products 38. A possible drawback of the method would be the low diastereoselectivity generally achieved for the nonsymmetrical 1,3-dicarbonyl compounds 36.
In order to understand the role of the catalyst, the hydroxy group of the squaramide 43 was methylated (43'). Its catalytic activity was tested in the reaction of acetylacetone (36a) and β-nitrostyrene (3a), leading to very low enantiomeric excess (24% ee). This fact suggested the important role played by the hydroxy group in the activation and in the chiral induction of the process. The authors proposed the transition state TS14, where the NH groups and the OH group of the squaramide would coordinate to the nitroalkene through hydrogen-bonding interactions with the nitro group. Simultaneously, the amine in the cinchona alkaloid would activate the 1,3-dicarbonyl compound 36 (Scheme 15). We would like to remark that although the authors indicated that the S enantiomer is obtained in their final products, they depicted the R configuration, as is drawn in the Scheme 15.

Aza-Henry reaction

Ellman’s group designed a set of pioneering (thio)urea scaffold-containing hydrogen-bonding organocatalysts with an N-sulfinyl moiety. As previously demonstrated, this chemical group increased the acidity of the catalyst and also served as a chiral controller [49-54]. Hence, in the presence of the catalyst 50 and diisopropylethylamine, a wide scope of the N-Boc-protected imines 48, including aliphatic ones, reacted with an excess of the nitroalkanes 49 at low temperature. This afforded the corresponding products 51 with high yield, diastereomeric ratio and excellent enantioselectivity (Scheme 16) [55].

Some experimental results using the differently substituted aminoindane-derived sulfanyl ureas 50–50'' showed the important effect of the indanol framework in the diastereo- and enantio-selectivity of the process. The catalysts 50' (with the TBS-protected hydroxy group (TBS, tert-butyldimethylsilyl)) and 50'' (without the hydroxy group) exhibited poorenantioselectivity. These effects may suggest and support the bifunctional role played by the catalyst (Figure 8).

![Figure 8: Results for the aza-Henry reaction carried out with the structurally modified catalysts 50–50''](image)

**Scheme 16: Asymmetric aza-Henry reaction catalyzed by the aminoindanol-derived sulfanyl urea 50.**
**Diels–Alder reaction**

An important contribution in the construction of highly substituted carbo cyclic compounds was disclosed by Tan’s group in 2009. In this work, the asymmetric Diels–Alder (D–A) reaction between the N-sulfonamide-3-hydroxy-2-pyridone-based dienes 52 and different dienophile substrates was developed using the bifunctional cis-2-trialkylaminoindanol organocatalyst ent-41 [56]. We show herein the reactivity of this family of dienes with several substituted maleimides 53, which in the presence of the above mentioned catalyst, afforded the highly substituted endo adducts 54 with high yield and enantiomeric excess (Scheme 17). In this approach, the cis orientation of the hydroxy and cyclopentylamine groups of the catalyst was crucial to achieve high enantioselectivity.

**Aminocatalysis**

Although aminoindanol-derived catalysts have been scarcely used in aminocatalysis, some relevant examples have been found in the literature, especially in the enantioselective addition of ketones to nitroalkene compounds. In this context, Alonso, Nájera and co-workers designed different alcohol-amino-derived prolinamide organocatalysts and in 2006 published an organocatalyzed direct asymmetric Michael addition of 3-pentanone (55a) to the nitrostyrenes 3 [57]. The corresponding syn-adducts 57 were obtained with excellent conversion, diastereomeric ratio and high enantiomeric excess when the cis-aminoindanol-based prolinamide 56, acting as bifunctional recyclable catalyst, was used (Scheme 18).

Later, based on this previous work, the same research group extended the methodology to different ketones 55, rendering the syn-products 57 with excellent yield and high selectivity (Scheme 19) [58].

In this case, the hydroxy group seems again to play an important role in the activation of the substrates, as well as in the selectivity of the process. The rigidity of the hydroxylamino moiety represents another important factor, where aminoindanol was the most appropriate scaffold for this asymmetric methodology among the catalysts tested. Based on the experi-

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**Scheme 17:** Diels–Alder reaction catalyzed by the aminooindanol derivative ent-41.

**Scheme 18:** Asymmetric Michael addition of 3-pentanone (55a) to the nitroalkenes 3 through aminocatalysis.
Scheme 19: Substrate scope extension for the asymmetric Michael addition between the ketones 55 and the nitroalkenes 3 through aminocatalysis.

The mental results and computational calculations (DFT and B3LYP76-31G*), the authors proposed a reaction mechanism in which the catalyst 56 acts in a bifunctional way following the route depicted in Scheme 20. Thus, Michael addition of the enamine 58, formed from 3-pentanone (55a) and the catalyst 56, to the nitroalkene 3a takes place leading to the intermediate 59. The last step of the catalytic cycle involves the regeneration of the catalyst by hydrolysis, enabled by the small amount of water present in the solvent.

The transition state TS15 based upon Seebach’s model [59] was envisioned as a plausible activation mode to explain the high asymmetric induction observed and the syn-diastereoselectivity exhibited by the catalyst 56. First, the activation of the ketone via enamine formation is produced. Furthermore, the acidic hydrogen atoms of the amide and the hydroxy groups present in the catalyst would activate and orientate the nitroalkene by hydrogen-bond formation. Thus, the attack of the formed enamine to the Re face of the nitroalkene is favored (Scheme 20). In this way, this example shows an efficient combination of covalent and non-covalent interactions in an interesting bifunctional activation mode.

Conclusion
The design, synthesis and application of catalysts acting in a bifunctional manner is a hot topic in the field of organocatal-
ysis and thus widely investigated. Generally, this particular mode of activation allows the enhancement of both the reactivity and the selectivity of the processes, due to the generation of a more rigid transition state. Among the different ways of conferring this bifunctional character to the catalysts, the incorporation of the aminoindanol core into their structure has shown to be a very suitable method. In most of the examples gathered herein, this can be explained due to the presence of a hydroxy group in the catalyst that normally is able to interact with at least one of the substrates of the reaction, hence facilitating the approach of the reactants in a selective fashion. In many cases, this bifunctional role of the catalyst has been supported with experimental results and sometimes with computational calculations. This smart strategy has allowed the preparation of highly efficient organocatalysts, ranging from very simple structures to more complex ones. These are mainly hydrogen-bonding catalysts, but there is also an example of an aminoindanol-containing aminocatalyst. A broad variety of reactivities has been successfully covered, such as Friedel–Crafts alkylation, Michael addition, Diels–Alder and aza-Henry reactions. However, further exploration into the development of new bifunctional organocatalysts using aminoindanol or another appropriate scaffold and their application in different chemical processes still needs to be performed.

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References

1. Weix, D. J.; Elman, J. A. Org. Lett. 2003, 5, 1317–1320. doi:10.1021/ol030245b

2. Lazar, A.; Sharma, P.; Singh, A. P. Microporous Mesoporous Mater. 2013, 170, 331–339. doi:10.1016/j.micromeso.2012.12.014

3. Dai, X.; Cahard, D. Adv. Synth. Catal. 2014, 356, 1317–1328. doi:10.1002/adsc.201301115

4. Sani, M.; Volontero, A.; Zanda, M. ChemMedChem 2007, 2, 1693–1700. doi:10.1002/cmdc.200700156

5. Piras, M.; Fleming, I. N.; Harrison, W. T. A.; Zanda, M. Synlett 2012, 23, 2899–2902. doi:10.1055/s-0032-1317557

6. Berkessel, A.; Gröger, H. Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis; Wiley-VCH: Weinheim, 2005. doi:10.1002/3527604677

7. Dalko, P. I.; Ed. Enantioselective Organocatalysis: Reactions and Experimental Procedures; Wiley-VCH: Weinheim, 2007. doi:10.1002/9783527610045

8. Dalko, P. I.; Ed. Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions and Applications; Wiley-VCH: Weinheim, 2013. doi:10.1002/9783527658862

9. Sibi, M. P.; Cook, G. R.; Liu, P. Tetrahedron Lett. 1999, 40, 2477–2480. doi:10.1016/S0040-4039(99)00281-6

10. Turgut, Y.; Azizoglu, M.; Ergogan, A.; Arslan, N.; Hossorgen, H. Tetrahedron: Asymmetry 2013, 24, 853–859. doi:10.1016/j.tetasy.2013.05.016

11. Probat, N.; Madarasz, Á.; Valkonen, A.; Pápai, I.; Rissanan, K.; Neuvonen, A.; Pilko, P. M. Angew. Chem., Int. Ed. 2012, 51, 8495–8499. doi:10.1002/anie.201203852

12. Kohno, J.; Koguchi, Y.; Nishio, M.; Nakao, K.; Kuroda, M.; Shimizu, R.; Ohnuki, T.; Komatsubara, S. J. Org. Chem. 2000, 65, 990–995. doi:10.1021/jo991375+ 13. Coste, A.; Couty, F.; Evano, G. C. R. Chim. 2008, 11, 1544–1573. doi:10.1016/j.crci.2008.06.003

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14. Coste, A.; Bayle, A.; Marrot, J.; Evano, G. Org. Lett. 2014, 16, 1306–1309. doi:10.1021/ol403675s

15. Miyabe, H.; Takemoto, Y. Bull. Chem. Soc. Jpn. 2008, 81, 785–795. doi:10.1246/bcsj.81.785

16. Connin, S. J. Chem. Commun. 2008, 2499–2510. doi:10.1039/b719249e

17. Liu, X.; Lu, Y. Org. Biomol. Chem. 2010, 8, 4063–4065. doi:10.1039/c0ob00223b

18. Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. Angew. Chem., Int. Ed. 2005, 44, 6576–6579. doi:10.1002/anie.200500227

19. Yevich, J. P.; Yooea, F. D. Curr. Med. Chem. 1997, 4, 295–312.

20. Arendt, J.; Deacon, S. Chronobiol. Int. 1997, 14, 185–204. doi:10.3109/07420529790011155

21. Laine, A. E.; Lood, C.; Koskinen, A. M. P. Molécules 2014, 19, 1544–1567. doi:10.3390/molecules19021544

22. Roca-López, D.; Marqués-López, E.; Alcaine, A.; Merino, P.; Herrera, R. P. Org. Biomol. Chem. 2014, 12, 4503–4510. doi:10.1039/c4ob00348a

23. Marqués-López, E.; Alcaine, A.; Tejero, T.; Herrera, R. P. Eur. J. Org. Chem. 2011, 3700–3705. doi:10.1002/ejoc.201100506

24. Ganesh, M.; Seidel, D. J. Am. Chem. Soc. 2008, 130, 18644–18645. doi:10.1021/ja8063292

25. Wittkopf, A.; Schreiner, P. R. Chem. – Eur. J. 2003, 9, 407–414. doi:10.1002/chem200390042

26. Loh, C. C. J.; Badorrek, J.; Raabe, G.; Enders, D. Chem. – Eur. J. 2011, 17, 13409–13414. doi:10.1002/chem.201102793

27. Joseph, B.; Chapellier, V.; Mérour, J.-Y.; Léonce, S. Heterocycles 1998, 48, 1423–1430. doi:10.3987/COM-98-8178

28. Joseph, B.; Alagille, D.; Mérour, J.-Y.; Léonce, S. Chem. Pharm. Bull. 2000, 48, 1872–1876. doi:10.1248/cpb.48.1872

29. Loh, C. C. J.; Raabe, G.; Enders, D. Chem. – Eur. J. 2012, 18, 13250–13254. doi:10.1002/chem.201202908

30. Glennon, R. A.; Lee, M.; Rangisetty, J. B.; Duckat, M.; Roth, B. L.; Savage, J. E.; MacBride, A.; Raiser, L.; Hufeisen, S.; Lee, D. K. H. J. Med. Chem. 2000, 43, 1011–1018. doi:10.1021/jm990550b

31. Glennon, R. A.; Roth, B. L. Selective 5-HT4 Receptor Ligands. WO Patent WO2000/034242, June 15, 2000.

32. Chang-Fong, J.; Rangisetty, J. B.; Duckat, M.; Setola, V.; Raffay, T.; Roth, B.; Glennon, R. A. Bioorg. Med. Chem. Lett. 2004, 14, 1961–1964. doi:10.1016/j.bmcl.2004.01.071

33. Cole, D. C.; Lennox, W. J.; Stock, J. R.; Ellingboe, J. W.; Mazandarani, H.; Smith, D. L.; Zhang, G.; Tawa, G. J.; Schechter, L. E. Bioorg. Med. Chem. Lett. 2005, 15, 4780–4785. doi:10.1016/j.bmcl.2005.07.028
34. Dukat, M.; Mosier, P. D.; Kolanos, R.; Roth, B. L.; Glennon, R. A. J. Med. Chem. 2008, 51, 603–611. doi:10.1021/jm070910s

35. Ciamician, G.; Plancher, G. Ber. Dtsch. Chem. Ges. 1896, 29, 2475–2482. doi:10.1002/ber.18960290131

36. Loh, C. C. J.; Atodiresei, I.; Enders, D. Chem. – Eur. J. 2013, 19, 10822–10826. doi:10.1002/chem.201302131

37. Vacca, J. P.; Dorsey, B. D.; Schleif, W. A.; Levin, R. B.; McDaniel, S. L.; Darke, P. L.; Zugay, J.; Quintero, J. C.; Blahy, O. M.; Roth, E.; Sardana, V. V.; Schlabach, A. J.; Graham, P. I.; Condra, J. H.; Gollib, L.; Holloway, M. K.; Lin, J.; Chen, I.-W.; Vastag, K.; Ostovic, D.; Anderson, P. S.; Emini, E. A.; Huff, J. R. Proc. Natl. Acad. Sci. U. S. A. 1994, 91, 4096–4100. doi:10.1073/pnas.91.9.4096

38. Dorsey, B. D.; Levin, R. B.; McDaniel, S. L.; Vacca, J. P.; Guare, J. P.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Lin, J. H.; Chen, I.-W.; Holloway, M. K.; Fitzgerald, P. M. D.; Axel, M. G.; Ostovic, D.; Anderson, P. S.; Huff, J. R. J. Med. Chem. 1994, 37, 3443–3451. doi:10.1021/jm00047a001

39. Jiang, H.; Paixão, M. W.; Monge, D.; Jørgensen, K. A. J. Am. Chem. Soc. 2010, 132, 2775–2783. doi:10.1021/ja9097803

40. Juste-Navarro, V.; Marqués-López, E.; Herrera, R. P. Asian J. Org. Chem. 2015, 4, 884–889. doi:10.1002/ajoc.201500154

41. Herrera, R. P.; Monge, D.; Martín-Zamora, E.; Fernández, R.; Lassaletta, J. M. Org. Lett. 2007, 9, 3303–3306. doi:10.1021/ol071292c

42. Sibi, M. P.; Itoh, K. J. Am. Chem. Soc. 2007, 129, 8064–8065. doi:10.1021/ja071739c

43. Shichi, H.; Li, H.; Zhang, X.; Zhang, S. Tetrahedron Lett. 2011, 52, 3204–3207. doi:10.1016/j.tetlet.2011.04.043

44. Liu, X.-L.; Wu, Z.-J.; Du, X.-L.; Zhang, X.-M.; Yuan, W.-C. J. Org. Chem. 2011, 76, 4008–4017. doi:10.1021/jo2004378

45. Sartori, M. R.; Larsen, T. O.; Petersen, B. O.; Duus, J. Ø.; Christophersen, C. J. Nat. Prod. 1998, 61, 1154–1157. doi:10.1021/np980056v

46. Ariza, M. R.; Larsen, T. O.; Petersen, B. O.; Duus, J. Ø.; Christophersen, C.; Barrero, A. F. J. Nat. Prod. 2001, 64, 1590–1592. doi:10.1021/np0101550

47. Sartori, M. R.; Larsen, T. O.; Petersen, B. O.; Duus, J. Ø.; Sørensen, D.; Frisvad, J. C.; Hansen, M. E. J. Nat. Prod. 2005, 68, 871–874. doi:10.1021/jp040248s

48. Dong, Z.; Qiu, G.; Zhou, H.-B.; Dong, C. Tetrahedron: Asymmetry 2012, 23, 1550–1556. doi:10.1016/j.tetasy.2012.10.016

49. Owens, T. D.; Hollander, F. J.; Oliver, A. G.; Ellman, J. A. J. Am. Chem. Soc. 2001, 123, 1539–1540. doi:10.1021/ja005635c

50. Owens, T. D.; Souers, A. J.; Ellman, J. A. J. Org. Chem. 2003, 68, 3–10. doi:10.1021/jo020524c

51. Schenkel, L. B.; Ellman, J. A. Org. Lett. 2003, 5, 545–548. doi:10.1021/ol027468m

52. Pei, D.; Zhang, W.; Wei, S.; Zhang, Y.; Sun, J. Org. Lett. 2006, 8, 5913–5915. doi:10.1021/ol062633+

53. Solà, J.; Revés, M.; Riera, A.; Verdaguer, X. Angew. Chem., Int. Ed. 2007, 46, 5020–5023. doi:10.1002/anie.200701040

54. Tan, K. L.; Jacobsen, E. N. Angew. Chem., Int. Ed. 2007, 46, 1315–1317. doi:10.1002/anie.200603354

55. Robak, M. T.; Trincado, M.; Ellman, J. A. J. Am. Chem. Soc. 2007, 129, 15110–15111. doi:10.1021/ja075653v

56. Soh, J. Y.-T.; Tan, C.-H. J. Am. Chem. Soc. 2009, 131, 6904–6905. doi:10.1021/ja900582a

57. Almås, D.; Alonso, D. A.; Nájera, C. Tetrahedron: Asymmetry 2006, 17, 2064–2068. doi:10.1016/j.tetasy.2006.07.023

58. Almås, D.; Alonso, D. A.; Gómez-Bengoa, E.; Nagel, Y.; Nájera, C. Eur. J. Org. Chem. 2007, 2328–2343. doi:10.1002/ejc.200700031

59. Blarer, S. J.; Seebach, D. Chem. Ber. 1983, 116, 2250–2260. doi:10.1002/cber.19831160616

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