ABSTRACT: A highly efficient enantioselective α-nitrogenation method of α,α-di-substituted aldehydes with azodicarboxylates promoted by a chiral carbamate-monoprotected cyclohexa-1,2-diamine as organocatalyst has been developed. The process was carried out without any solvent, and the corresponding α,α-di-substituted α-nitrogenated aldehydes were obtained with excellent yields and enantioselectivities up to 99% ee. The sustainability of the procedure was established through the calculation of green metrics, such as EcoScale and E-factor. In addition, theoretical calculations have been used to justify the obtained enantioselectivity sense.

INTRODUCTION

Enantioenriched α-nitrogenated aldehydes are important building blocks in chemical synthesis, with many applications in medicinal chemistry and the pharmaceutical industry.1-5 The aldehyde functionality can be transformed into various functional groups, leading to substituted chiral amines in natural products and bioactive substances.6 Particularly interesting is the synthesis of quaternary α-amino aldehydes as they can be transformed into quaternary α-amino acids, which are building blocks for constructing peptidomimetics or valuable as pharmaceuticals.7-11 An example of the latter is α-aryl-α-alkyl α-amino acid derivatives, which have shown strong inhibitory effects on aldose reductases, a potential target for treating various diabetes-related diseases.12

Although not too extensively explored, organocatalysis has been found as a direct and convenient method for the asymmetric synthesis of quaternary α-amino aldehydes through the conjugate addition reaction of α,α-di-substituted aldehydes with azodicarboxylates as the electrophilic nitrogen source. Chiral amine-containing species, suitable to generate an enamine nucleophile and, at the same time, coordinate with the electrophile to get a close transition state, have been used as organocatalysts (Figure 1).

Thus, l-proline (1) has been the pioneering and mainly employed organocatalyst in this reaction.13-18 In addition, the secondary amine in l-proline has also been the enamine-forming moiety in the case of the l-proline-derived tetrazole 2, employed in the synthesis of cell adhesion inhibitor BIRT-37719 or prolinamide-derived thiourea 3.20 Moreover, chiral primary amines have also been used as organocatalysts for this enamine-driven transformation, as is the case of the amino acids 3-(1-naphthyl) alanine hydrochloride (4)21 and l-β-tert-butyl aspartate (5).22 Other organocatalysts containing primary amines have been naphthylethanamine 6,23 chiral benzoisoquinoline-1,3-dione 7,24 and 9-amino-(9-deoxy)-epi-quinine (8), alone25-27 or combined with (−)-camphorsulfonic acid as a chiral counteranion28 or even magnetically supported.29

These mentioned organocatalysts 1-8 only afforded good enantioselectivities starting from α-alkyl–α-aryl aldehydes. In addition, as is usual, an organic solvent is always present. Thus, environmentally unfriendly halogenated media13,15,20,24,25,28 or highly volatile and flammable or toxic solvents have been employed. As the solvent is one of the key elements for naming a chemical process as sustainable, we have taken seriously into consideration the aphorism “the best solvent is no solvent”30-34 and have developed a highly efficient and greener enantioselective solvent-free α-nitrogenation of α,α-di-substituted aldehydes with azodicarboxylates, using a simple mono-N-Boc-protected cyclohexa-1,2-diamine 935 as a chiral organocatalyst.

RESULTS AND DISCUSSION

The conjugate addition reaction between 2-phenylpropanal (10a) and diisopropyl azodicarboxylate (DIAD, 11a), in the presence of the monocarbamate derived from (1R,2R)-cyclohexa-1,2-diamine 935 as an organocatalyst (20 mol%), was chosen as a model reaction to optimize the reaction

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conditions (see Table 1). Initially, we were interested in the behavior of organocatalyst 9 in conventional, solvent-present reaction conditions. Thus, the reaction of 10a (2 equiv) with 11a organocatalyzed by 9 (20 mol%) in several organic solvents at room temperature for 48 h afforded the α-nitrogenated α,α-disubstituted aldehyde 12aa in up to 71% ee (Table 1, entries 1–6). The absolute stereochemistry of 12aa was determined according to the order of elution of the corresponding enantiomers in chiral HPLC reported in the literature (see the Supporting Information).

However, when the same reaction was carried out under solvent-free conditions, the reaction was completed in 24 h, observing similar enantioselectivity for 12aa to the one obtained when the best solvent was used (Table 1, compare entry 7 with entries 5 and 6). In addition, when the molar ratio of the reagents was modified and 1.2 equiv of 11a were used under solvent-free conditions, the conversion remained unaltered in 24 h, and the enantioselectivity for 12aa increased slightly to 75% (Table 1, entry 8). This change in the molar ratio is important as the usual excess of the most expensive or not commercially available aldehyde is avoided. Therefore, as solvent-free conditions resulted in a superior methodology, we further optimize this environmentally friendlier procedure.

We explored if the presence of additives was beneficial for the reaction. The addition of an organic base such as 1,4-diazabicyclo[2.2.2]octane (DABCO, 10 mol%) gave full conversion in only 8 h, although it was disastrous for the enantioselectivity, obtaining 12aa as a racemic mixture (Table 1, entry 9). However, the use of acids as additives (10 mol%) also gave full conversions in 8 h while keeping the enantioselectivity (Table 1, entries 10–14), with the best ee (83%) being achieved using the economic acetic acid as an additive (Table 1, entry 14). Lowering the loading of the organocatalyst 9 down to 10 mol% diminished the enantioselectivity slightly for 12aa (Table 1, entry 15), while keeping the loading of 9 in 20 mol% and increasing the loading of the acid additive up to 20 mol% raised the enantioselectivity of 12aa (87%) (Table 1, entry 16). A further increase in the amount of acetic acid up to 30 mol% was detrimental to the enantioselectivity (Table 1, entry 17).

Using these conditions, we employed di-tert-butyl azodicarboxylate (11b) as a bulkier electrophilic nitrogen source, although the corresponding nitrogenated aldehyde 12ab was obtained in lower enantioselectivity (Table 1, entry 18). The use of diethyl azodicarboxylate (DEAD) was discarded because it is commercially available in solution due to its explosive potential.

Finally, we lowered the reaction temperature. Thus, when the reaction was carried out at −10 °C, the ee observed for 12aa raised slightly (Table 1, entry 19), increasing to 94% when working at −20 °C (Table 1, entry 20). A lower reaction temperature (−30 °C) did not increase the enantioselectivity (Table 1, entry 21). Diminishing the catalyst loading to 10 mol% at −20 °C gave only 70% ee of 12aa (Table 1, entry 22). This change in enantioselectivity with catalyst loading has been previously observed when using this organocatalyst in other enantioselective reactions.25 This could suggest that when the catalyst concentration reaches a certain value, other species (even combined with the cocatalyst), such as aggregates, could also be present, modifying the enantioselectivity of the process upward. Moreover, in the absence of organocatalyst 9 and in the presence of 20 mol% of AcOH as a cocatalyst, almost no reaction was observed (Table 1, entry 23). In the absence of a background reaction, enantioselectivity should not vary with catalyst loading unless some other processes, such as described above, are occurring.

Once the optimized reaction conditions were established [9 (20 mol%), AcOH (20 mol%), 11a (1.2 equiv), solvent-free, −20 °C, 24 h], we proceeded to extend the application of this organocatalytic methodology to other α,α-disubstituted aldehydes 10 (see Table 2). Thus, we explored a series of α-arylated propanals 10b–k, bearing different substituents on the aromatic ring (Table 2, entries 2–11).

In all cases, high isolated yields and high enantioselectivities of the corresponding α-aminated aldehydes 12ba-ja were obtained, although in the case of the 4-nitro-containing aldehyde 10k, the corresponding adduct 12ka was obtained in a lower 77% ee (Table 2, entry 11). In addition, a 2-naphthyl in the aldehyde 10l gave the corresponding adduct 12la in an 80% ee (Table 2, entry 12). Moreover, changing the α-methyl in the aldehyde 10a by ethyl (10m) allowed us to obtain the corresponding final nitrogenated aldehyde 12ma in 97% ee (Table 2, entry 13). Furthermore, when 1,2,3,4-tetrahydro-naphthalene-1-carbaldehyde (10n) was employed as the starting aldehyde, the final adduct 12na was obtained in a 90% ee (Table 2, entry 14).

When using an α-benzylated-α-methyl aldehyde, such as cyclamen aldehyde (10o), the reaction gave the corresponding nitrogenated adduct 12oa with an enantioselectivity of 89% (Table 2, entry 15). Interestingly, when several α,α-dialkylated aldehydes 10p–s were used as starting materials, the final adducts 12pa-sa were obtained with excellent yields and enantioselectivities ranging from 82 to 95% (Table 2, entries 16–19). These high enantioselections are remarkable as low or...
Table 1. Enantioselective Organocatalytic α-Amination of Aldehyde 10a with Azodicarboxylates: Optimization Experiments

| entry | R   | 9 (mol %) | 10a/11 molar ratio | additive (mol %) | solvent | T (°C) | t (h) | % conv. | ee | % ee  |
|-------|-----|-----------|---------------------|------------------|---------|--------|-------|---------|----|-------|
| 1     | iPr | 20        | 2/1                 |                  | PhMe    | 25     | 48    | 89      | 52 |       |
| 2     | iPr | 20        | 2/1                 |                  | CH<sub>2</sub>Cl | 25     | 48    | 93      | 54 |       |
| 3     | iPr | 20        | 2/1                 |                  | DMF/H<sub>2</sub>O<sup>d</sup> | 25     | 48    | 100     | 57 |       |
| 4     | iPr | 20        | 2/1                 |                  | THF     | 25     | 48    | 57      | 60 |       |
| 5     | iPr | 20        | 2/1                 |                  | TBME    | 25     | 48    | 73      | 71 |       |
| 6     | iPr | 20        | 2/1                 |                  | Et<sub>2</sub>O | 25     | 48    | 51      | 71 |       |
| 7     | iPr | 20        | 2/1                 |                  |          | 25     | 24    | 100     | 69 |       |
| 8     | iPr | 20        | 1/1.2               |                  |          | 25     | 24    | 100     | 75 |       |
| 9     | iPr | 20        | 1/1.2               | DABCO (10)       |          | 25     | 8     | 100     | 77 |       |
| 10    | iPr | 20        | 1/1.2               | HDA (10)         |          | 25     | 8     | 100     | 77 |       |
| 11    | iPr | 20        | 1/1.2               | PhCO<sub>2</sub>H (10) |          | 25     | 8     | 100     | 71 |       |
| 12    | iPr | 20        | 1/1.2               | 3,4-DMBA (10)    |          | 25     | 8     | 100     | 73 |       |
| 13    | iPr | 20        | 1/1.2               | NBA (10)         |          | 25     | 8     | 100     | 81 |       |
| 14    | iPr | 20        | 1/1.2               | AcOH (10)        |          | 25     | 8     | 100     | 83 |       |
| 15    | iPr | 10        | 1/1.2               | AcOH (10)        |          | 25     | 8     | 100     | 83 |       |
| 16    | iPr | 20        | 1/1.2               | AcOH (20)        |          | 25     | 8     | 100     | 87 |       |
| 17    | iPr | 20        | 1/1.2               | AcOH (30)        |          | 25     | 8     | 100     | 76 |       |
| 18    | iPr | 20        | 1/1.2               | AcOH (20)        |          | 25     | 8     | 100(98) | 84 |       |
| 19    | iPr | 20        | 1/1.2               | AcOH (20)        |          | −10    | 24    | 100     | 88 |       |
| 20    | iPr | 20        | 1/1.2               | AcOH (20)        |          | −20    | 24    | 100(99) | 94 |       |
| 21    | iPr | 20        | 1/1.2               | AcOH (20)        |          | −30    | 24    | 100     | 89 |       |
| 22    | iPr | 10        | 1/1.2               | AcOH (20)        |          | −20    | 24    | 100     | 70 |       |
| 23    | iPr | 10        | 1/1.2               | AcOH (20)        |          | 25     | 8     | 100     | 76 |       |

<sup>a</sup>Abbreviations: DABCO: 1,4-diazabicyclo[2.2.2]octane; 3,4-DMBA: 3,4-dimethoxybenzoic acid; HDA: hexadecanoic acid; NBA: 4-nitrobenzoic acid; TBME: tert-butyl methyl ether. <sup>b</sup>Determined by <sup>1</sup>H NMR from the remaining aldehyde; isolated yield after flash chromatography in parenthesis. <sup>c</sup>Enantioselectivities and absolute stereochemistry determined by chiral HPLC on the reaction crude. <sup>d</sup>2:1 (v/v).

The synthetic usefulness of these enantioenriched nitro-germinated adducts 12 was exemplified by preparing the hydrazide-containing oxazolidin-2-one 13 in a 92% yield after reduction of aldehyde 12aa, obtained in the scaled-up reaction (93% ee), and further cyclization (Scheme 1). The subsequent reaction of 13 with methyl bromoacetate in the presence of cesium carbonate, and additional treatment with this base, gave the (R)-oxazolidinone 14 in a 90% yield and the expected 93% ee.

To get further insight into the behavior of organocatalyst 9 when leading to the observed sense of enantioselectivity, we performed DFT theoretical calculations (see the Supporting Information) on substrates 10a and 11a. Thus, the initial enamine formed between aldehyde 10a and catalyst 9 can adopt two different configurations, and the most stable one...
corresponds to the phenyl group trans to the NH moiety (A-E isomer, Figure 2). The A-Z enamine was found to be 1.4 kcal/mol higher in energy, affording a predicted 10:1 E/Z enamine ratio. This difference is significant but not enough to discard the participation of both enamines in the reaction (see below).

From this initial point, the nucleophilic attack on the azodicarboxylate looks quite straightforward to compute. However, as previously described by our groups in related reactions, the calculations showed a complex mixture of possible conformations and reacting faces of the two substrates. For example, just to indicate some of the varying factors, the enamine can adopt different conformations, that is, A (E and Z) or B (E and Z) (Figure 2). The approach between the enamine and azodicarboxylate can proceed through diastereomeric endo (C) or exo (D) transition states, and both the nucleophile and electrophile present two reacting Si and Re faces. In the case of the azodicarboxylate, these faces do not generate a new stereogenic center but still strongly affect the approach’s selectivity to the enamine. Meanwhile, the two faces of the enamine lead to the R and S enantiomers of product 12aa after forming the corresponding diastereoselective transition states.

Following extensive calculations of all possibilities, structure A-E was found to be the most reactive enamine, where two main factors affect the electrophile’s approach. First, the Re face (upper face in A-E representation), which leads to the minor S enantiomer of the product, is less sterically congested, as computed by the difference between TS2 and TS4 (Figure 3). Meanwhile, an intramolecular hydrogen bond can be formed between the carbamate NH of the catalyst and one of the carbonyl groups in the azodicarboxylate. This H-bond is easier to create and stronger in the lower Si face of the enamine (TS1 vs TS3). Thus, two opposite factors are competing, with the steric one favoring the Re approach and the H-bond leading to the Si face activation. The computed energies of the most preferred structures (TS1–TS4) show the stronger stabilizing effect of the H-bond, which outcompetes the steric destabilization. The lowest transition state in energy and explaining the formation of the experimental R major enantiomer. Related transition states were found for the minor Z enamines, but their activation energies are at least 2.0 kcal/mol higher, indicating that they do not participate in the reaction. It is worth noting that, in the absence of the intermolecular H-bond between the electrophile and enamine, a weaker intramolecular H-bond forms between the NH of the enamine and the carbonyl group of the carbamate, both in the catalyst. Finally, the calculations were repeated with aldehyde 10p, containing methyl and ethyl substituents, and the results were almost identical to the previous ones, reinforcing the agreement between calculations and experiments (see Figure S106 in the Supporting Information).

Scheme 1. Preparation of Enantioenriched Oxazolidinone 14 from α-Nitrogenated Aldehyde 12aa

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**CONCLUSIONS**

α,α-Disubstituted aldehydes have been enantioselectively α-nitrogenated employing disisopropyl azodicarboxylate as the electrophilic nitrogen source and a simple chiral mono-N-Boc-protected cyclohexa-1,2-diamine as the organocatalyst under..."
solvent-free conditions, the presence of acetic acid as an additive improving the results. Contrary to other reported methodologies, high yields and enantioselectivities were obtained from alkyl-α-aryl aldehydes and their α,α-dialkylated counterparts. The obtained adducts can be transformed into valuable compounds, such as enantioenriched oxazolidine-2-ones. Theoretical calculations confirmed the bifunctional behavior of the employed organocatalyst, responsible for the formation of the nucleophilic enamine and the activation of the electrophilic azodicarboxylate through the creation of an intermolecular hydrogen bond with the NH of the carbamate. The stabilizing effect of the H-bond is also responsible for the enantioselective formation of the major R isomer. This procedure is efficient, easily scalable, and environmentally convenient for the enantioselective preparation of synthetically useful α,α-disubstituted α-nitrogenated aldehydes.

**EXPERIMENTAL SECTION**

**General Procedure for the Organocatalytic Enantioselective α-Nitrogenation.** A glass vial (ø 16 mm) was charged with 9 (8.6 mg, 0.04 mmol, 0.2 equiv), aldehyde 10 (0.2 mmol, 1 equiv), and azodicarboxylate 11 (0.24 mmol, 1.2 equiv). The mixture was gently stirred at −20 °C under an argon atmosphere for 24 h. After this time, the reaction crude was purified by column chromatography [silica gel, hexanes/ethyl acetate (85/15, v/v)] to afford product 12. All characterization data of compounds 12 are available in the Supporting Information.

**Scaled-Up Synthesis of 12aa.** A glass vial (ø 16 mm) was charged with 9 (0.6 mmol, 129 mg), acetic acid (0.6 mmol, 36 mg, 34.5 μL), aldehyde 10a (3 mmol, 402 mg, 0.40 mL), and azodicarboxylate 11a (3.6 mmol, 727 mg, 0.73 mL). The mixture was gently stirred at −20 °C under an argon atmosphere for 24 h. After this time, the reaction crude was purified by column chromatography [silica gel, hexanes/ethyl acetate (85/15, v/v)] to afford product 12aa (0.95 g, 95%, 95% ee).

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**Figure 3.** Computed transition states for the reaction between the enamine from 9 and 10a and 11a. Energies are given in kcal/mol (see the Supporting Information).
chromatograms, calculation of sustainability metrics, and computational data (PDF)

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**Author Contributions**

The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

**Notes**

The authors declare no competing financial interest.

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