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Preparation and Asymmetric Induction Evaluation of the First Ephedrine-Based Ligands Immobilized on Magnetic Nanoparticles

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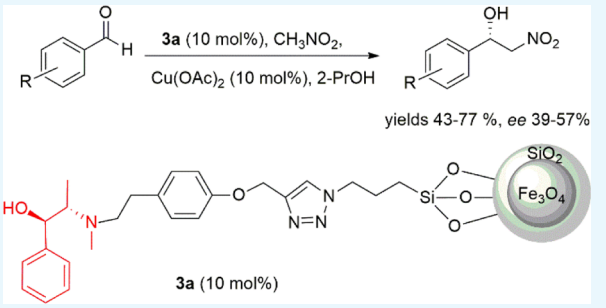
ABSTRACT: Herein, the synthesis and catalytic activity of two ephedrine-based catalysts and two ephedrine-based magnetic nanoparticle-supported catalysts are reported. All catalysts developed were tested in the addition of diethylzinc to aromatic aldehydes and in the Henry reaction. The homogeneous catalysts showed moderate catalytic activity in the organozinc addition and good activity in the Henry reaction, whereas in the case of the nanocatalyst, it was not effective in the addition of diethylzinc to aldehydes and gave reasonable results in the Henry reaction. Moreover, the nanocatalyst remained unchanged over the course of up to three catalytic cycles. To the best of our knowledge, the proposed system is the first recyclable ephedrine-based magnetic nanocatalyst employed in an enantioselective reaction.



1. INTRODUCTION

In recent times, the need for sustainable development inspired and directed the path of research, and chemistry, among all sciences, has the duty to make sustainable the processes now essential for human modern life.

Asymmetric catalysis, one of the most powerful strategies for the synthesis of precious optically active compounds, embodies many of the Green Chemistry principles,[1] making it possible to work under very mild conditions and with little waste. The large industrial use, however, is seriously hampered by the high production costs of the chiral catalysts and by their difficult recovery from the reaction mixture. These issues actually cancel out the benefits derived from the catalytic approach.[2]

The immobilization of the catalyst on solid supports is an intuitive solution to the problem of catalyst recovery and reuse; papers addressing these issues have been growing in the last decades, exploring various materials and immobilization strategies.[3] Unfortunately, the activity and enantioselectivity of supported chiral catalysts are usually lower compared to the unsupported ones due to their scarce dispersibility. The use of nanoparticles could overcome this problem since their small size has advantages of dispersion. Moreover, the high surface area/volume ratio of the nanoparticles results in an activity close to the homogeneous catalysts. In this contest, our attention has been drawn to the opportunity to anchor catalysts on magnetic materials, so as to overcome the recovery step by means of agile magnetic decantation.[4] Specifically, nanoparticles of magnetite (Fe_3O_4) with size up to roughly 20 nm exhibit a special form of magnetism called superparamagnetism that makes them extremely dispersible in solvents in the absence of an external magnetic field.[5]

2. RESULTS AND DISCUSSION

In the last years, our group has investigated the catalytic efficiency of β-aminoalcohols and their immobilization on nanomaterials. The new aminoalcohol ligand **A** was developed,[6] suitably modified to be anchored on superparamagnetic nanoparticle **B** and employed in the asymmetric catalysis, that is, the addition of organozinc to aldehydes[7] and the addition of nitroalkanes to carbonyl compounds (Henry reaction)[8] (Scheme 1).

Herein, we describe the catalytic activity of a new magnetic nanocatalyst derived from the immobilization of a well-known β-aminoalcohol catalyst, ephedrine (Figure 1). Since its successful employment in the asymmetric addition of alkylzinc reagents to aldehydes reported by Soai, it has been widely studied as a chiral catalyst in various asymmetric transformations.[9] Although ephedrine has been studied extensively as a chiral catalyst, only a few examples of immobilization onto mesoporous silica nanoparticles have been reported.[10] To the best of our knowledge, no superparamagnetic ephedrine-type catalyst has been developed for asymmetric reactions.[11]

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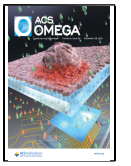

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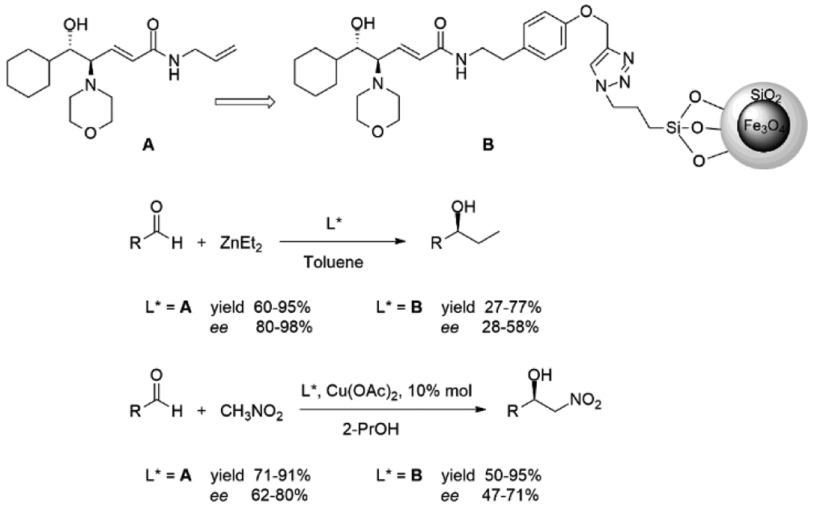
Scheme 1. Asymmetric ZnR_2 and CH_3NO_2 Addition to Aldehydes Catalyzed by Ligands A and B



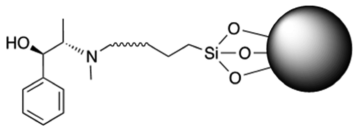


Figure 1. Ephedrine-based nanocatalyst.

2.1. Development of the Catalysts. Since the hydroxyl group must remain free to carry out the catalytic activity, we decided to use the amino group for the immobilization. Moreover, several examples in the literature prove that the dialkylation of the amino group is beneficial for the catalytic efficiency. First, we thought about building a catalyst following a strategy based on a nucleophilic substitution between the ephedrine and the nanoparticles functionalized with iodosilane (Scheme 2).

Core−shell Fe_3O_4@SiO_2 nanoparticles[7] were treated with iodopropyltrimethoxysilane in anhydrous toluene, obtaining the iodo-functionalized nanoparticles **1**. Then, the reaction with ephedrine was performed in the presence of DIPEA as a base, leading to the immobilized chiral catalyst **2**. Catalyst **2** was evaluated in the addition of diethylzinc to *o*-methoxy benzaldehyde in the conditions optimized in our previous work. Very poor results were observed with yield and enantioselectivity comparable to the uncatalyzed reaction.

Trying to rationalize the bad results obtained, we reconsidered the structure of the synthesized linker, questioning whether the catalytic site was too close to the oxide surface to be adequately free to coordinate the reagents. In analogy to the strategy adopted in our previous work, we decided to immobilize ephedrine through a copper(I)-catalyzed azide alkyne cycloaddition (CuAAC) and introduce a longer spacer between the catalytic active moiety and the nanoparticles. With this in mind, catalysts **3a** and **3b** were devised (Figure 2).

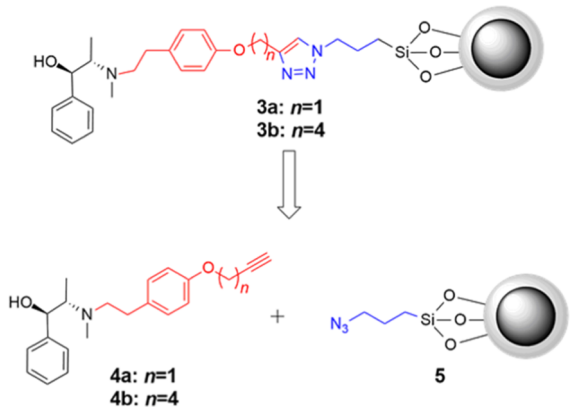
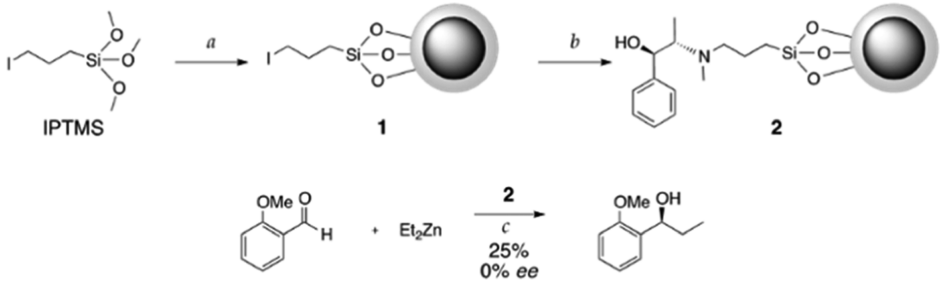


Figure 2. Immobilization strategy to obtain catalysts **3**

The terminal alkynes **4a** and **4b** were easily obtained in a few steps starting from ephedrine and tyrosol (Scheme 3). First, tyrosol was selectively alkylated with propargyl bromide or with 6-iodo-1-hexyne on the phenolic position to give ethers

Scheme 2. Preparation of Nanocatalyst 2 and Its Catalytic Evaluation[a]



[a](a) Fe_3O_4@SiO_2, toluene, 105 °C, 12 h; (b) ephedrine, DIPEA, toluene, 105 °C, 48 h, loading: 0.22 mmol/g; (c) toluene, 6 mol % of **2**, 0 °C, 6 h, 25% yield, 0% ee.

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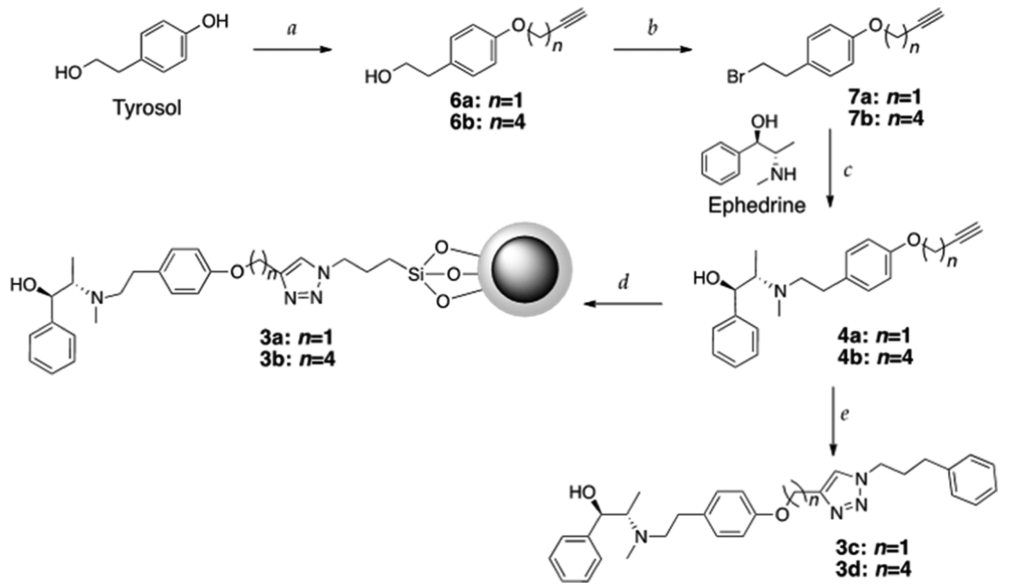
Scheme 3. Preparation of Catalysts 3[a]



[a](a) Propargyl bromide, K_2CO_3, acetonitrile, reflux, 12 h, 93% (**6a**) or 6-iodo-1-hexyne, K_2CO_3, acetonitrile, reflux, 12 h, 64% (**6b**); (b) CBr_4, PPh_3, CH_2Cl_2, 0 °C—r.t., 12 h, 94 (**7a**), 94% (**7b**); (c) K_2CO_3, acetonitrile dry, reflux, 12 h, 86 (**4a**), 82% (**4b**); (d) **5**, CuI, DIPEA, THF, r.t, 48 h, 0.33 mmol/g loading (**3a**), 0.26 mmol/g loading (**3b**); (e) (3-azidopropyl)benzene, CuI, DIPEA, THF, r.t, 12 h, 79% (**3c**), 82% (**3d**).

6a and **6b**. The primary alcohol was then halogenated with the CBr_4/PPh_3 system affording bromides **7a** and **7b** in a high yield.

Finally, the anchorable ligands **4a** and **4b** were obtained by nucleophilic substitution of ephedrine on substrates **7a** and **7b**; the subsequent immobilization onto azido-functionalized nanoparticles **5** was realized in the usual CuAAC conditions. Catalysts **3a** and **3b** were obtained with 0.33 and 0.26 mmol/g loadings, respectively.[6] In parallel, we synthesized the corresponding catalysts **3c** and **3d** with the aim to use them in homogeneous conditions in order to compare the catalytic efficiencies of structures as similar as possible.

Scanning electron microscopy (SEM) image of **3a** shows nanoparticles with diameters in the range of 10−15 nm (Figure 3).

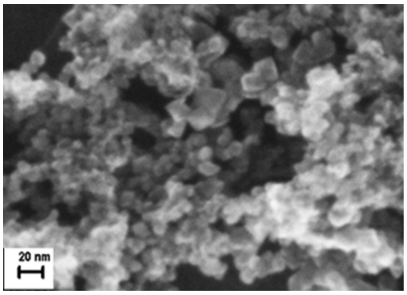
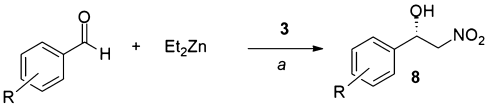


Figure 3. SEM image of functionalized silica-coated magnetite nanoparticles **3a**.

2.2. Enantioselective Catalysis. First, the developed catalysts were evaluated in the addition of diethylzinc to aldehydes in the usual conditions (Table 1).

Catalysts **3c** and **3d** employed in homogeneous conditions led to good-to-excellent yields, proving that the new structures retain the catalytic effect showed by the reference compound, the Soai's DBNE. The asymmetric induction[12] appeared

Table 1. Addition of Et_2Zn to Different Aldehydes Catalyzed by Ligands 3a−3d



entry	R	3	yield (%)[b]	ee (%)[c]	8
1	H	**3c**	80	60	**8a**
2	H	**3d**	80	50	**8a**
3	2-Cl	**3c**	87	61	**8b**
4	2-Cl	**3d**	87	60	**8b**
5	2-MeO	**3c**	>95	74	**8c**
6	2-MeO	**3d**	>95	79	**8c**
7	4-Br	**3c**	>95	77	**8d**
8	4-Br	**3d**	>95	78	**8d**
9	4-CN	**3c**	>95	38	**8e**
10	4-CN	**3d**	>95	38	**8e**
11	H	**3a**	25	10	**8a**
12[d]	H	**3a**	22	18	**8a**
13[e]	H	**3a**	20	3	**8a**
14	H	**3b**	15	0	**8a**

[a]All experiments were performed under identical conditions unless otherwise stated: toluene, 6 mol % of 3, 0 °C, 6 h. [b]Determined by NMR analysis. [c]Determined by chiral HPLC analysis. [d]BuLi (0.72 mmol/g solid) was added. [e]Nanoparticles previously treated with hexamethyldisilazane were used (see Experimental Section).

instead slightly decreased (entries 1−10). Both catalysts **3c** and **3d** showed similar results, implying that the linker moiety is not affecting the reaction. We then tested the magnetic nanocatalyst **3a** (entry 11), but the results obtained suggested no catalytic activity for this system. Following a reported procedure, a second test was performed by adding BuLi to the reaction mixture. The additive is supposed to have a dual action: the inactivation of the vicinal free silanols on the surface of the nanoparticles by lithiation and the formation of an active lithium amino alkoxide species by reaction with

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Et_2Zn.[13] Anyway, the result obtained in this experiment was similar to the previous one (entry 12). As a further test, we decided to convert the surface-free silanols in trimethylsilil-oxides by reacting them with hexamethyldisilazane to obtain a nonpolar surface.[14] Also in this case, however, we obtained poor results (entry 13). The only test carried out using **3b** led to an even worse result.

Nonetheless, considering that ephedrine-based catalysts were successfully employed in the Henry reaction[9e] and that this reaction would not be affected by problems related to the presence of vicinal free silanols, we decided to evaluate the catalysts in this reaction. Nitromethane was added to several aromatic aldehydes in the presence of catalysts **3a**–**3d** and $Cu(OAc)_2$ under the conditions previously optimized by our group. Both catalysts **3c** and **3d** in the homogeneous phase showed similar good catalytic activity, leading to the corresponding nitroalcohols in high yields and good enantioselectivities in almost all cases, mainly using **3c** (Table 2).

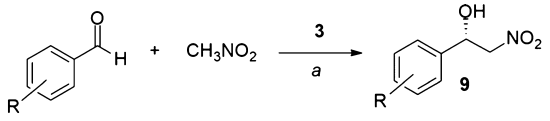
Once the catalytic activity of **3c** and **3d** in the Henry reaction was verified, we decided to study the same reaction in the heterogeneous phase by testing nanocatalysts **3a** and **3b**. This time, quite a difference in the catalytic activity of the two ligands was observed. Ligand **3b** was not able to induce asymmetry in this reaction, leading in all cases to racemic nitroalcohols, often in very poor yields. On the contrary, ligand **3a** catalyzed the addition of nitromethane to benzaldehyde with fairly good results, leading to nitroalcohol **9a** with satisfactory yield and acceptable ee, even if not comparable to those obtained in the homogeneous phase with the corresponding ligand **3c** (entries 1, 4). The flexible chain of ligand **3b** probably causes an undesired folding, thus making its interaction with reagents difficult.

Ligand **3a** confirmed a moderate catalytic efficiency in the addition of nitromethane to other aromatic aldehydes, unfortunately noticeably worse than the homogeneous counterpart. Evidently, working in the heterogeneous phase, the accessibility of catalytic sites from reagents could be considerably decreased.

We also tested the catalytic efficiency of the fully silylated nanoparticles (entry 2), but a negative effect on the enantioselectivity was observed.

Finally, we investigated the recyclability of the superparamagnetic nanocatalyst **3a**. The catalyst was easily recovered by magnetic decantation, washed, and reused up to three times in a new reaction. As showed in Table 3, the catalytic activity remained high in the first three catalytic cycles performed to recycle the functionalized nanoparticles, proving that highly efficient catalysts can be easily recovered and reused by being immobilized on suitable nanosupports. Unfortunately, the fourth cycle resulted in a decrease in efficiency, and the reasons behind this decrease are under investigation.

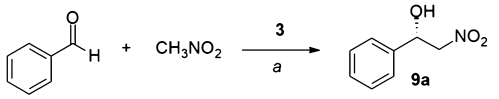
Table 2. Henry Reaction Catalyzed by Ligands 3a–3d



entry	R	3	yield (%)[b]	ee (%)[c]	9
1	H	**3a**	77	57	**9a**
2[d]	H	**3a**	75	56	**9a**
3	H	**3b**	44	0	**9a**
4	H	**3c**	90	75	**9a**
5	H	**3d**	87	91	**9a**
6	2-Cl	**3a**	71	47	**9b**
7	2-Cl	**3c**	90	74	**9b**
8	2-Cl	**3d**	90	70	**9b**
9	2-MeO	**3a**	43	39	**9c**
10[d]	2-MeO	**3c**	85	80	**9c**
11[d]	2-MeO	**3d**	67	84	**9c**
12	2-Me	**3a**	59	49	**9d**
13	2-Me	**3c**	90	89	**9d**
14	2-Me	**3d**	77	79	**9d**
15	4-Me	**3a**	47	47	**9e**
16	4-Me	**3c**	65	88	**9e**
17	4-Me	**3d**	36	84	**9e**
18	3-Me	**3a**	58	44	**9f**
19	3-Me	**3c**	72	84	**9f**
20	3-Me	**3d**	72	84	**9f**
21	4-CN	**3a**	60	36	**9g**
22	4-CN	**3c**	90	50	**9g**
23	4-CN	**3d**	>95	48	**9g**
24	3-NO_2	**3a**	65	37	**9h**
25	3-NO_2	**3c**	>95	53	**9h**
26	3-NO_2	**3d**	83	33	**9h**

[a]All experiments were performed under identical conditions unless otherwise stated: 2-PrOH, 10 mol % of 3, 10 mol % of $Cu(OAc)_2$, rt, 72 h. [b]Determined by NMR analysis. [c]Determined by chiral HPLC analysis. [d]Nanoparticles previously treated with hexamethyldisilazane were used (see Experimental Section).

Table 3. Recyclability of the Superparamagnetic Nanocatalyst 3a in the Addition of Nitromethane to Benzaldehyde



entry	cycle	yield (%)[b]	ee (%)[c]
1	I	77	57
2	II	70	54
3	III	70	50
4	IV	55	25

[a]All experiments were performed under identical conditions: 2-PrOH, 10 mol % of **3a**, 10 mol % of $Cu(OAc)_2$, rt, 72 h. [b]Determined by NMR analysis. [c]Determined by chiral HPLC analysis.

3. CONCLUSIONS

The focused modification of ephedrine, with a view to developing a nanoparticle-supported form, led to the synthesis of two ephedrine type catalysts **3c** and **3d** and two ephedrine-based magnetic nanoparticle-supported catalytic systems **3a** and **3b**. All catalysts developed were tested in the addition of diethylzinc to aromatic aldehydes and in the Henry reaction. Catalysts **3c** and **3d** used in homogeneous conditions showed moderate catalytic activity in the organozinc addition and good results in the Henry reaction. On the other side, the semiheterogeneous system **3a**, although not effective in the addition of diethylzinc to aldehydes, produced encouraging results in the Henry reaction: The resulting nitroalcohols were collected in high yield and with reasonable ee, and moreover,

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the nanocatalyst remained unchanged over the course of up to three catalytic cycles. To the best of our knowledge, the proposed system **3a** is the first superparamagnetic recyclable ephedrine-based catalyst employed in an enantioselective reaction.

4. EXPERIMENTAL SECTION

All chromatographic purifications, NMR spectra, optical rotation measurement, enantiomeric excess (ee) determination, elemental analysis, and morphological and structural investigations were performed as reported in ref 6. Liquid aldehydes were freshly distilled before use.

The following compounds were synthetized according to reported procedures: (3-azidopropyl)benzene, silica-coated magnetite nanoparticles (Fe_3O_4@SiO_2), 5,5-TMS (obtained by end-capping treatment).[7]

4.1. General Procedure for the Synthesis of 6. 1 mmol tyrosol was dissolved in 5 mL of acetonitrile, 1 mmol alkyl bromide (80 wt % solution in toluene), and 1.5 mmol (207 mg) K_2CO_3 were added under an argon atmosphere. The reaction was refluxed for 12 h. Filtration allowed to eliminate the solid residue, and the reaction mixture was diluted with AcOEt and washed with water. The aqueous layer was extracted with AcOEt. The organic layer was washed with brine and then dried over Na_2SO_4. The solvent was removed in vacuo. The crude product was purified by flash chromatography (Hex/AcOEt 70:30) to obtain product **6** as a yellowish oil.

*4.1.1. 2-[4-(Prop-2-yn-1-yloxy)phenyl]ethanol (**6a**).* Yield 93%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, J = 8.7 Hz, 2H, Ph), 6.92 (d, J = 8.7 Hz, 2H, Ph), 4.65 (d, J = 2.4 Hz, 2H, $OCH_2C{\equiv}CH$), 3.78 (td, J = 6.7, 1.6 Hz, 2H, CH_2OH), 2.79 (t, J = 6.6 Hz, 2H, CH_2Ph), 2.52 (t, J = 2.4 Hz, 1H, C≡CH), 2.1 2−1.95 (m, 1H, OH). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.2, 131.6, 130.0, 115.0, 78.7, 75.6, 63.7, 55.9, 38.3. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.22; H, 7.15.

*4.1.2. 2-[4-(Hex-5-yn-1-yloxy)phenyl]ethanol (**6b**).* Yield 64%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, J = 8.7 Hz, 2H, Ph), 6.85 (d, J = 8.7 Hz, 2H, Ph), 3.97 (t, J = 6.3 Hz, 2H, $PhOCH_2$), 3.82 (t, J = 6.5 Hz, 2H, CH_2OH), 2.81 (t, J = 6.5 Hz, 2H, CH_2Ph), 2.28 (td, J = 7.0, 2.6 Hz, 2H, $CH_2C{\equiv}CH$), 1.97 (t, J = 2.7 Hz, 1H, C≡CH), 1.95−1.85 (m, 2H, OCH_2CH_2), 1.72 (m, 2H, $CH_2CH_2C{\equiv}CH$), 1.51 (bs, 1H, OH). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.0, 130.6, 130.3, 115.0, 84.4, 68.9, 67.6, 64.2, 38.6, 28.6, 25.4, 18.5. Anal. Calcd for $C_{14}H_{17}O_2$: C, 77.39; H, 7.89. Found: C, 77.57; H, 8.18.

4.2. General Procedure for the Synthesis of 7. 1.2 mmol (401 mg) CBr_4 was added to a solution of 1 mmol **6** in 2.5 mL of CH_2Cl_2. The solution is cooled to 0 °C, and 1.88 mmol (493 mg) triphenylphosphine was added in portions. The reaction is stirred at room temperature for 12 h, and then the solvent was evaporated in vacuo. The residue was dissolved in Et_2O, and the insoluble white solid was eliminated by filtration. This operation was repeated several times until the complete removal of the solid. The crude product was purified by flash chromatography (Hex/AcOEt 95:05) to give product **7** as a clear oil.

*4.2.1. 1-(2-Bromoethyl)-4-(prop-2-yn-1-yloxy)benzene (**7a**).* Yield 94%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, J = 8.4 Hz, 2H, Ph), 6.94 (d, J = 8.5 Hz, 2H, Ph), 4.68 (d, J = 2.2 Hz, 2H, $PhOCH_2$), 3.54 (t, J = 7.6 Hz, 2H, CH_2Br), 3.11 (t, J = 7.6 Hz, 2H, CH_2Ph), 2.55−2.50 (m, 1H, C≡CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7, 141.7, 132.1, 129.8, 115.2, 78.7, 75.6, 56.0, 38.7, 33.4. Anal. Calcd for $C_{11}H_{11}BrO$: C, 55.25; H, 4.64. Found: C, 55.57; H, 4.91.

*4.2.2. 1-(2-Bromoethyl)-4-(hex-5-yn-1-yloxy)benzene (**7b**).* Yield 94%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, J = 8.4 Hz, 2H, Ph), 6.86 (d, J = 8.6 Hz, 2H, Ph), 3.98 (t, J = 6.3 Hz, 2H, $PHOCH_2$), 3.53 (t, J = 7.7 Hz, 2H, CH_2Br), 3.10 (t, J = 7.7 Hz, 2H, CH_2Ph), 2.29 (td, J = 7.0, 2.6 Hz, 2H, $CH_2C{\equiv}CH$), 1.99 (t, J = 2.7 Hz, 1H, C≡CH), 1.96−1.86 (m, 2H, OCH_2CH_2), 1.79−1.68 (m, 2H, $CH_2CH_2C{\equiv}CH$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 131.0, 129.7, 114.6, 84.2, 68.8, 67.3, 38.7, 33.5, 28.4, 25.1, 18.2. Anal. Calcd for $C_{14}H_{16}BrO$: C, 60.01; H, 5.76. Found: C, 60.23; H, 5.98.

4.3. General Procedure for the Synthesis of 4. 1 mmol (201 mg) (1*R*,2*S*)-(−)-ephedrine hydrochloride was dissolved in 4 mL of MeOH, and 1 mmol (106 mg) Na_2CO_3 was added. The reaction was stirred for 30 min and then filtered through a pad of celite with methanol. The solvent was evaporated in vacuo, and the residue was dissolved in AcOEt and filtered through a paper. The solvent was evaporated in vacuo to give (1*R*,2*S*)-(−)-ephedrine that was then dissolved in 10 mL of dry CH_3CN under an argon atmosphere. 1.2 mmol bromide **7** and 2 mmol (276 mg) K_2CO_3 were added, and the reaction was refluxed for 12 h. The solid residue was separated by filtration, and the solvent was evaporated at reduced pressure. The crude product was purified by flash chromatography ($CHCl_3$/MeOH 96:04) to give **4** as a light brown oil.

*4.3.1. (1R,2S)-2-{Methyl[4-(prop-2-yn-1-yloxy)phenethyl]-amino}-1-phenylpropan-1-ol (**4a**).* Yield 86%. $[\alpha]_D^{25}$: −11.4 (c 6.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.21 (m, 5H, Ph), 7.10 (d, J = 8.6 Hz, 2H, Ph), 6.92 (d, J = 8.7 Hz, 2H, Ph), 4.79 (d, J = 4.2 Hz, 1H, CHOH), 4.67 (d, J = 2.4 Hz, 2H, $PhOCH_2$), 3.39 (bs, 1H, OH), 2.93−2.82 (m, 1H, CHN), 2.78−2.66 (m, 4H, NCH_2CH_2), 2.52 (t, J = 2.4 Hz, 1H, C≡CH), 2.35 (s, 3H, NCH_3), 0.89 (d, J = 6.9 Hz, 3H, $CHCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3, 142.5, 133.5, 130.0, 128.3, 127.2, 126.4, 115.2, 79.1, 75.8, 73.3, 64.0, 57.1, 56.2, 39.4, 33.4, 10.4. Anal. Calcd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 78.35; H, 7.98; N, 4.72.

*4.3.2. (1R,2S)-2-{[4-(Hex-5-yn-1-yloxy)phenethyl](methyl)-amino]-1-phenylpropan-1-ol (**4b**).* Yield 82%. $[\alpha]_D^{25}$ − 14.5 (c 2.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34−7.22 (m, 5H, Ph), 7.08 (d, J = 8.6 Hz, 2H, Ph), 6.82 (d, J = 8.6 Hz, 2H, Ph), 4.85 (d, J = 2.9 Hz, 1H, CHOH), 3.96 (t, J = 6.3 Hz, 2H, $PhOCH_2$), 3.71 (bs, 1H, OH), 2.95−2.85 (m, 1H, CHN), 2.79−2.70 (m, 4H, NCH_2CH_2), 2.39 (s, 3H, CH_3N), 2.27 (td, J = 7.0, 2.6 Hz, 2H, $CH_2C{\equiv}CH$), 1.97 (t, J = 2.6 Hz, 1H, C≡CH), 1.94−1.84 (m, 2H, OCH_2CH_2), 1.78−1.67 (m, 2H, $CH_2CH_2C{\equiv}CH$), 0.89 (d, J = 6.9 Hz, 3H, $CHCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 142.2, 132.0, 129.7, 128.1, 127.0, 126.2, 114.6, 84.3, 72.9, 68.7, 67.4, 63.9, 57.0, 39.2, 33.0, 28.5, 25.2, 18.3, 9.9. Anal. Calcd for $C_{24}H_{30}NO_2$: C, 79.08; H, 8.30; N, 3.84. Found: C, 79.39; H, 8.61; N, 4.12.

4.4. Synthesis of 3a and 3b. Synthesis of **3a** and **3b** were performed as reported in ref 7.

*4.4.1. **3a**.* Obtained 186 mg. Loading: 0.33 mmol/g calculated by elemental analysis: N 1.89% C 8.84%. Fourier transform infrared (FTIR) (neat/ν cm^{-1}): 3329, 2934, 2856, 1510, 1181, 1043, 813, 551.

*4.4.2. **3a-TMS** (End-Capped).* Obtained 280 mg. Loading: 0.46 mmol/g calculated by elemental analysis: N 2.62% C 10.58%. FTIR (neat/ν cm^{-1}): 2934, 1608, 1510, 1207, 1043, 840, 551.

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*4.4.3. **3b**.* Obtained 296 mg. Loading: 0.26 mmol/g calculated by elemental analysis: N 1.46% C 2.98% FTIR (neat/ν cm^{-1}): 3282, 2934, 2869, 1511, 1128, 1037, 711, 557.

4.5. Synthesis of 3c and 3d. 1 mmol terminal alkyne **4** (**4a** or **4b**) and 1.1 mmol (177 mg) (3-azidopropyl)benzene were treated as reported in ref 7.

*4.5.1. (1R,2S)-2-{methyl[4-(1-(3-phenylpropyl)-1H-1,2,3-triazol-4-yl)methoxyphenethyl]}amino-1-phenylpropan-1-ol (**3c**).* Yield 79%. $[\alpha]_D^{25}$: −8.1 (c 4.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (s, 1H, CHN−N═N), 7.33−7.19 (m, 8H, Ph), 7.14 (d, J = 7.3 Hz, 2H, Ph), 7.09 (d, J = 8.5 Hz, 2H, Ph), 6.92 (d, J = 8.6 Hz, 2H, Ph), 5.20 (s, 2H, CH_2OPh), 4.74 (d, J = 4.2 Hz, 1H, CHOH), 4.30 (t, J = 7.1 Hz, 2H, N−N═NCH_2), 3.28 (bs, 1H, OH), 2.89−2.81 (m, 1H, CHN), 2.74−2.66 (m, 4H, $CHNCH_2CH_2$), 2.62 (t, J = 7.5 Hz, 2H, $NCH_2CH_2CH_2Ph$), 2.33 (s, 3H, $CHNCH_3$), 2.27−2.17 (m, 2H, $NCH_2CH_2CH_2Ph$), 0.87 (d, J = 6.9 Hz, 3H, $NCHCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7, 144.4, 142.2, 140.2, 133.0, 129.8, 128.7, 128.5, 128.0, 126.9, 126.4, 126.2, 122.7, 115.0, 73.0, 63.8, 62.3, 56.9, 49.6, 39.1, 33.1, 32.5, 31.6, 10.2. Anal. Calcd for $C_{30}H_{36}N_4O_2$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.71; H, 7.78; N, 11.88.

*4.5.2. (1R,2S)-2-{Methyl[4-(3-(1-(3-phenylpropyl)-1H-1,2,3-triazol-4-yl)propoxy)phenethyl]}amino-1-phenylpropan-1-ol (**3d**).* Yield 82%. $[\alpha]_D^{25}$: −10.3 (c 7.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.15 (m, 11H, CHN−N═N, Ph), 7.09 (d, J = 8.6 Hz, 2H, Ph), 6.84 (d, J = 8.6 Hz, 2H, Ph), 4.82 (d, J = 4.1 Hz, 1H, CHOH), 4.32 (t, J = 7.1 Hz, 2H, N−N═NCH_2), 3.99 (t, J = 5.7 Hz, 2H, $PhOCH_2$), 3.61 (bs, 1H, OH), 2.94−2.87 (m, 1H, CHN), 2.81 (t, J = 7.0 Hz, 2H, CH_2CHN−N═N), 2.78−2.69 (m, 4H, NCH_2CH_2Ph), 2.66 (t, J = 7.5 Hz, 2H, $NCH_2CH_2CH_2Ph$), 2.38 (s, 3H, $CHNCH_3$), 2.30−2.20 (m, 2H, $NCH_2CH_2CH_2Ph$), 1.94−1.82 (m, 4H, $PhOCH_2CH_2CH_2$), 0.91 (d, J = 6.9 Hz, 3H, $NCHCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.5, 148.0, 142.3, 140.3, 132.1, 129.7, 128.7, 128.5, 128.0, 126.9, 126.4, 126.2, 120.7, 114.5, 72.9, 67.6, 63.8, 57.0, 49.4, 39.1, 33.1, 32.6, 31.8, 28.9, 26.1, 25.4, 10.1. Anal. Calcd for $C_{33}H_{42}N_4O_2$: C, 75.25; H, 8.04; N, 10.64. Found: C, 75.56; H, 8.38; N, 10.92.

4.6. Addition of Diethylzinc to Aldehydes Catalyzed by Free Catalysts 3c and 3d in Homogeneous Phase. The reaction was carried out as reported in ref 7 obtaining the products **8a**−**8e**.

4.7. Addition of Diethylzinc to Aldehydes Catalyzed by Functionalized Nanoparticles 3a and 3b. The reaction was carried out as reported in ref 7 obtaining **8a**.

Absolute configurations of the final alcohols were assigned by comparing the retention time on high-performance liquid chromatography (HPLC) chromatograms with the literature value. The data reported are related to the use of ligand **3c** or **3d**. For the results obtained with other catalysts, refer to the data reported in Table 1.

*4.7.1. (R)-1-Phenylpropan-1-ol (**8a**).*[15] Yield 80%, ee = 60% (HPLC: Column Chiralpak IB, Hex/i-PrOH = 98:2, 1 mL/min, 258 nm, major 9.8 min and minor 10.7 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.24 (m, 5H, Ph), 4.60 (t, J = 6.6 Hz, 1H, CHOH), 1.90−1.69 (m, 3H, OH, CH_2), 0.92 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.7, 128.6, 127.7, 126.1, 76.2, 32.0, 10.3.

*4.7.2. (R)-1-(2-Chlorophenyl)propan-1-ol (**8b**).*[16] Yield 87%, ee = 61% (HPLC: Column Chiralpak IA, Hex/i-PrOH = 99.5:0.5, 1 mL/min, 225 nm, major 30.0 min and minor 33.6 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (dd, J = 7.7, 1.7 Hz, 1H, Ph), 7.35−7.26 (m, 2H, Ph), 7.23−7.16 (m, 1H, Ph), 5.07 (dd, J = 7.6, 4.8 Hz, 1H, CHOH), 1.91−1.68 (m, 3H, OH, CH_2), 0.99 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.1, 132.1, 129.5, 128.5, 127.3, 127.2, 72.1, 30.6, 10.2.

*4.7.3. (R)-1-(2-Methoxyphenyl)propan-1-ol (**8c**).*[6] Yield > 95%, ee = 78% (HPLC: Column Chiralpak IB, Hex/i-PrOH = 97:3, 0.8 mL/min, 220 nm, minor 10.0 min and major 10.6 min) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33−7.21 (m, 2H, Ph), 6.96 (td, J = 7.5, 1.0 Hz, 1H, Ph), 6.88 (dd, J = 8.2, 0.8 Hz, 1H, Ph), 4.79 (t, J = 6.6 Hz, 1H, CHOH), 3.85 (s, 3H, OMe), 2.43 (s, 1H, OH), 1.87−1.76 (m, 2H, CH_2), 0.96 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 132.5, 128.3, 127.2, 120.8, 110.6, 72.6, 55.4, 30.3, 10.6.

*4.7.4. (R)-1-(4-Bromophenyl)propan-1-ol (**8d**).*[17] Yield > 95%, ee = 78% (HPLC: Column Chiralpak IC, Hex/i-PrOH = 99/1, 1.5 mL/min, 220 nm, major 7.5 min and minor 8.7 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, J = 8.4 Hz, 2H, Ph), 7.18 (d, J = 8.2 Hz, 2H, Ph), 4.53 (t, J = 6.6 Hz, 1H, CHOH), 2.18 (bs, 1H, OH), 1.82−1.63 (m, 2H, CH_2), 0.88 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8, 131.8, 128.0, 121.5, 75.6, 32.2, 10.3.

*4.7.5. (R)-4-(1-Hydroxypropyl)benzonitrile (**8e**).*[18] Yield > 95%, ee = 38% (HPLC: Column Chiralpak IA, Hex/i-PrOH = 95:5, 0.8 mL/min, 220 nm, major 17.3 min and minor 18.7 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 8.3 Hz, 2H, Ph), 7.43 (d, J = 8.1 Hz, 2H, Ph), 4.64 (t, J = 6.4 Hz, 1H, CHOH), 2.39 (bs, 1H, OH), 1.80−1.67 (m, 2H, CH_2), 0.89 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 132.2, 126.7, 119.0, 110.9, 75.0, 32.1, 9.8.

4.8. General Procedure for the Addition of Nitromethane to Aldehydes Catalyzed by Free Catalysts 3c and 3d in Homogeneous Phase. The reaction was carried out as reported in ref 6 obtaining products **9a**−**9h**.

4.9. General Procedure for the Addition of Nitromethane to Aldehydes Catalyzed by Functionalized Nanoparticles 3a and 3b. The reaction was carried out as reported in ref 6 obtaining products **9a**−**9e**.

Absolute configurations of the final alcohols were assigned by comparing the retention time on HPLC chromatograms with the literature value. The data reported are related to the use of ligand **3c** or **3d**. For the results obtained with other catalysts, refer to the data reported in Table 2.

*4.9.1. (S)-2-Nitro-1-phenylethanol (**9a**).*[19] Yield 90%, ee = 91% (HPLC: Column Chiralpak IB, Hex/i-PrOH = 95:5, 1 mL/min, 220 nm, minor 16.7 min and major 18.4 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44−7.34 (m, 5H, Ph), 5.47 (dd, J = 9.5, 3.0 Hz, 1H, CHOH), 4.62 (dd, J = 13.4, 9.6 Hz, 1H, CH$\alpha$$NO_2$), 4.52 (dd, J = 13.4, 3.0 Hz, 1H, CH$\beta$$NO_2$), 1.99 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 129.2, 129.1, 126.1, 81.4, 71.2.

*4.9.2. (S)-1-(2-Chlorophenyl)-2-nitroethanol (**9b**).*[7] Yield 90%, ee = 74% (HPLC: Column Chiralpak IB, Hex/i-PrOH = 99:1, 1.3 mL/min, 220 nm, minor 23.4 min and major 24.5 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (dd, J = 7.6, 1.8 Hz, 1H, Ph), 7.41−7.27 (m, 3H, Ph), 5.84 (dd, J = 9.6, 2.3 Hz, 1H, CHOH), 4.67 (dd, J = 13.6, 2.4 Hz, 1H, CH$\alpha$$NO_2$), 4.45 (dd, J = 13.6, 9.6 Hz, 1H, CH$\beta$$NO_2$), 3.07 (bs, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.6, 131.6, 130.0, 129.8, 127.7, 127.6, 79.4, 67.9.

*4.9.3. (S)-1-(2-Methoxyphenyl)-2-nitroethanol (**9c**).*[7] Yield 85%, ee = 84% (HPLC: Column Chiralpak IB, Hex/i-PrOH = 95:5, 0.8 mL/min, 273 nm, minor 16.6 min and major 18.4

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min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (dd, J = 7.6, 1.4 Hz, 1H, Ph), 7.36−7.30 (m, 1H, Ph), 7.01 (td, J = 7.5, 0.9 Hz, 1H, Ph), 6.91 (dd, J = 8.3, 0.7 Hz, 1H, Ph), 5.63 (dd, J = 9.2, 3.2 Hz, 1H, CHOH), 4.65 (dd, J = 13.0, 3.3 Hz, 1H, CH$\alpha$$NO_2$), 4.57 (dd, J = 13.0, 9.2 Hz, 1H, CH$\beta$$NO_2$), 3.88 (s, 3H, CH_3), 2.95 (bs, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1, 129.9, 127.3, 126.1, 121.3, 110.6, 80.0, 67.9, 55.5.

*4.9.4. (S)-2-Nitro-1-(o-tolyl)ethanol (**9d**).*[7] Yield 90%, ee = 89% (HPLC: Column Chiralpak IB, Hex/i-PrOH = 95:5, 0.8 mL/min, 220 nm, minor 16.0 min and major 21.4 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54−7.49 (m, 1H, Ph), 7.31−7.23 (m, 2H, Ph), 7.21−7.16 (m, 1H, Ph), 5.67 (dd, J = 9.7, 2.6 Hz, 1H, CHOH), 4.54 (dd, J = 13.3, 9.7 Hz, 1H, CH$\alpha$$NO_2$), 4.43 (dd, J = 13.3, 2.7 Hz, 1H, CH$\beta$$NO_2$), 2.67 (bs, 1H, OH), 2.39 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.4, 134.6, 131.0, 128.8, 126.9, 125.7, 80.3, 68.0, 19.0.

*4.9.5. (S)-2-Nitro-1-(p-tolyl)ethanol (**9e**).*[7] Yield 65%, ee = 88% (HPLC: Column Chiralpak IB, Hex/i-PrOH = 95:5, 1 mL/min, 220 nm, minor 15.1 min and major 17.9 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, J = 8.1 Hz, 2H, Ph), 7.21 (d, J = 8.0 Hz, 2H, Ph), 5.42 (dd, J = 9.5, 2.9 Hz, 1H, CHOH), 4.60 (dd, J = 13.3, 9.6 Hz, 1H, CH$\alpha$$NO_2$), 4.49 (dd, J = 13.3, 3.1 Hz, 1H, CH$\beta$$NO_2$), 2.79 (bs, 1H, OH), 2.36 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.1, 135.3, 129.8, 126.0, 81.4, 71.0, 21.3.

*4.9.6. (S)-2-Nitro-1-(m-tolyl)ethanol (**9f**).*[7] Yield 72%, ee = 84% (HPLC: Column Chiralpak IB, Hex/i-PrOH = 95:5, 1 mL/min, 220 nm, minor 12.6 min and major 13.5 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (t, J = 7.5 Hz, 1H), 7.23−7.15 (m, 3H), 5.41 (dd, J = 9.6, 3.0 Hz, 1H), 4.59 (dd, J = 13.3, 9.6 Hz, 1H, CH$\alpha$$NO_2$), 4.49 (dd, J = 13.3, 3.1 Hz, 1H, CH$\beta$$NO_2$), 2.90 (bs, 1H, OH), 2.37 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0, 138.2, 129.8, 129.0, 126.7, 123.1, 81.4, 71.2, 21.5.

*4.9.7. (S)-4-(1-Hydroxy-2-nitroethyl)benzonitrile (**9g**).*[7] Yield > 95%, ee = 50% (HPLC: Column Chiralpak IB, Hex/i-PrOH = 90:10, 0.4 mL/min, 220 nm, major 50.7 min and minor 55.2 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 8.4 Hz, 2H, Ph), 7.56 (d, J = 8.1 Hz, 2H, Ph), 5.54 (dd, J = 8.5, 3.8 Hz, 1H, CHOH), 4.63−4.50 (m, 2H, CH_2NO_2), 3.21 (bs, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 132.9, 126.9, 118.4, 112.8, 80.8, 70.2.

*4.9.8. (S)-2-Nitro-1-(3-nitrophenyl)ethanol (**9h**).*[7] Yield > 95%, ee = 53% (HPLC: Column Chiralpak IB, Hex/i-PrOH = 90:10, 1.2 mL/min, 220 nm, minor 15.1 min and major 16.4 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (t, J = 1.9 Hz, 1H, Ph), 8.20 (ddd, J = 8.2, 2.2, 0.9 Hz, 1H, Ph), 7.77 (d, J = 7.7 Hz, 1H, Ph), 7.61 (t, J = 8.0 Hz, 1H, Ph), 5.61 (dd, J = 8.3, 4.1 Hz, 1H, CHOH), 4.68−4.55 (m, 2H, CH_2NO_2), 3.27 (bs, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 140.4, 132.2, 130.3, 123.9, 121.3, 80.8, 70.0.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c05514.

^{1}H and ^{13}C spectra of ligands and intermediates, ^{1}H and ^{13}C spectra of diethylzinc addition products, ^{1}H and ^{13}C spectra of nitromethane addition products, chiral HPLC chromatograms of diethylzinc addition products, HPLC chromatograms of nitromethane addition products, and attenuated total reflection -FTIR spectra of synthetized nanoparticles (PDF)

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L.P. and C.S. have contributed equally to this work. The manuscript was written through contributions of all authors. Conceptualization: L.P., C.S., and G.R.; NMR analyses: L.P. and M.D.; investigation: F.R. and G.L.; validation: M.I. and G.L.; methodology: F.R. and G.L.; HPLC analyses: A.R.; writing—review: A.R. and L.S.; funding acquisition: A.R. and G.R.; supervision: L.S., F.L., and G.R. All authors have read and agreed to the published version of the manuscript.

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Notes

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■ REFERENCES

(1) (a) Anastas, P.; Eghbali, N. Green Chemistry: Principles and Practice. *Chem. Soc. Rev.* **2010**, *39*, 301−12. (b) Anastas, P. T.; Zimmerman, J. B. Design through the Twelve Principles of Green Engineering. *Environ. Sci. Technol.* **2003**, *37*, 94A−101A.

(2) Sheldon, R. A. E factors, green chemistry and catalysis: an odyssey. *Chem. Commun.* **2008**, *29*, 3352−4336.

(3) (a) Baráth, E. Selective Reduction of Carbonyl Compounds via Asymmetric Transfer Hydrogenation on Heterogeneous Catalysts.

Synthesis **2020**, *52*, 504−520. (b) Cozzi, F. Immobilization of Organic Catalysts: When, Why, and How. *Adv. Synth. Catal.* **2006**, *348*, 1367−1390. (c) Li, C. Chiral synthesis on catalysts immobilized in microporous and mesoporous materials. *Catal. Rev.* **2004**, *46*, 419−492. (d) Murzin, D. Y.; Mäki-Arvela, P.; Toukoniitty, E.; Salmi, T. Asymmetric Heterogeneous Catalysis: Science and Engineering. *Catal. Rev.* **2005**, *47*, 175−256.

(4) (a) Rossi, L. M.; Costa, N. J. S.; Silva, F. P.; Wojcieszak, R. Magnetic nanomaterials in catalysis: advanced catalysts for magnetic separation and beyond. *Green Chem.* **2014**, *16*, 2906−2933. (b) Dalpozzo, R. Magnetic nanoparticle supports for asymmetric catalysts. *Green Chem.* **2015**, *17*, 3671−3686. (c) Hu, A.; Liu, S.; Lin, W. Immobilization of chiral catalysts on magnetite nanoparticles for highly enantioselective asymmetric hydrogenation of aromatic ketones. *RSC Adv.* **2012**, *2*, 2576−2580. (d) Sun, Y.; Liu, G.; Gu, H.; Huang, T.; Zhang, Y.; Li, H. Magnetically recoverable SiO2-coated Fe3O4 nanoparticles: a new platform for asymmetric transfer hydrogenation of aromatic ketones in aqueous medium. *Chem. Commun.* **2011**, *47*, 2583−2585. (e) Mondini, S.; Puglisi, A.; Benaglia, M.; Ramella, D.; Drago, C.; Ferretti, A. M.; Ponti, A. Magnetic nanoparticles conjugated to chiral imidazolidinone as recoverable catalyst. *J. Nanopart. Res.* **2013**, *15*, 2025−2036.

(5) Shylesh, S.; Schünemann, V.; Thiel, W. R. Magnetically separable nanocatalysts: bridges between homogeneous and heterogeneous catalysis. *Angew. Chem., Int. Ed.* **2010**, *49*, 3428−3459.

(6) Sappino, C.; Mari, A.; Mantineo, A.; Moliterno, M.; Palagri, M.; Tatangelo, C.; Suber, L.; Bovicelli, P.; Ricelli, A.; Righi, G. New chiral amino alcohol ligands for catalytic enantioselective addition of diethylzincs to aldehydes. *Org. Biomol. Chem.* **2018**, *16*, 1860−1870.

(7) Sappino, C.; Primitivo, L.; De Angelis, M.; Righi, F.; Di Pietro, F.; Iannoni, M.; Pilloni, L.; Ciprioti, S. V.; Suber, L.; Ricelli, A.; Righi, G. Linear -amino alcohol catalyst anchored on functionalized magnetite nanoparticles for enantioselective addition of dialkylzinc to aromatic aldehydes. *RSC Adv.* **2020**, *10*, 29688−29695.

(8) Sappino, C.; Primitivo, L.; De Angelis, M.; Domenici, M. O.; Mastrodonato, A.; Romdan, I. B.; Tatangelo, C.; Suber, L.; Pilloni, L.; Ricelli, A.; Righi, G. Functionalized Magnetic Nanoparticles as Catalysts for Enantioselective Henry Reaction. *ACS Omega* **2019**, *4*, 21809−21817.

(9) (a) Cruz, A.; Padilla-Martínez, I. I.; Bautista-Ramírez, M. E. N-Substituted Ephedrines as Chiral Auxiliaries in Enantioselective Alkylation Reactions of Carbonyl Compounds. *Curr. Org. Synth.* **2016**, *13*, 2−40. (b) Takehara, J.; Hashiguchi, S.; Fujii, A.; Inoue, S.-i.; Ikariya, T.; Noyori, R. Amino alcohol effects on the ruthenium(II)-catalysed asymmetric transfer hydrogenation of ketones in propan-2-ol. *Chem. Commun.* **1996**, 233−234. (c) Petra, D. G. I.; Reek, J. N. H.; Handgraaf, J.-W.; Meijer, E. J.; Dierkes, P.; Kamer, P. C. J.; Brussee, J.; Schoemaker, H. E.; Van Leeuwen, P. W. N. M. Chiral induction effects in ruthenium(II)-amino alcohol catalysed asymmetric transfer hydrogenation of ketones: An experimental and theoretical approach. *Chem.—Eur. J.* **2000**, *6*, 2818−2829. (d) Soai, K.; Yokoyama, S.; Hayasaka, T. Chiral N,N-dialkylnorephedrines as catalysts of the highly enantioselective addition of dialkylzincs to aliphatic and aromatic aldehydes. The asymmetric synthesis of secondary aliphatic and aromatic alcohols of high optical purity. *J. Org. Chem.* **1991**, *56*, 4264−4268. (e) Palomo, C.; Oiarbide, M.; Laso, A. Enantioselective Henry Reactions under Dual Lewis Acid/Amine Catalysis Using Chiral Amino Alcohol Ligands. *Angew. Chem., Int. Ed.* **2005**, *44*, 3881−3884. (f) Banerjee, S.; Camodeca, A. J.; Griffin, G. G.; Hamaker, C. G.; Hitchcock, S. R. Aromatic motifs in the design of Ephedra ligands for application in the asymmetric addition of diethylzinc to aldehydes and diphenylphosphinoylimines. *Tetrahedron: Asymmetry* **2010**, *21*, 549−557.

(10) (a) Sarkar, S. M.; Ali, M. E.; Rahman, M. L.; Mohd Yusoff, M. Preparation of Mesoporous Silica-Supported Chiral Amino Alcohols for the Enantioselective Addition of Diethylzinc to Aldehyde and Asymmetric Transfer Hydrogenation to Ketones. *J. Nanomater.* **2015**, *2015*, 1−6. (b) Abramson, S.; Laspéras, M.; Brunel, D. Design of mesoporous aluminosilicates supported (1R,2S)-(−)-ephedrine: evidence for the main factors influencing catalytic activity in the enantioselective alkylation of benzaldehyde with diethylzinc. *Tetrahedron: Asymmetry* **2002**, *13*, 357−367. (c) Soai, K.; Watanabe, M.; Yamamoto, A. Enantioselective Addition of Dialkylzincs to Aldehydes Using Heterogeneous Chiral Catalysts Immobilized on Alumina and Silica Gel. *J. Org. Chem.* **1990**, *55*, 4832−4835.

(11) A recyclable magnetic core-shell nanoparticle-supported oxo-vanadium ephedrine complex has been used for oxidations of alcohols:, Rostami, A.; Pourshiani, O.; Darvishi, N.; Atashkar, B. Efficient and green oxidation of alcohols with tert -butyl hydrogenperoxide catalyzed by a recyclable magnetic core-shell nanoparticle-supported oxo-vanadium ephedrine complex. *Compt. Rendus Chem.* **2017**, *20*, 435−439.

(12) Yamakawa, M.; Noyori, R. An ab initio molecular orbital study on the amino alcohol-promoted reaction of dialkylzincs to aldehydes. *J. Am. Chem. Soc.* **1995**, *117*, 6327−6335.

(13) Fraile, J. M.; Mayoral, J. A.; Serrano, J.; Pericàs, M. A.; Solà, L.; Castellnou, D. New Silica-Immobilized Chiral Amino Alcohol for the Enantioselective Addition of Diethylzinc to Benzaldehyde. *Org. Lett.* **2003**, *5*, 4333−4335.

(14) Slavov, S. V.; Sanger, A. R.; Chuang, K. T. Mechanism of Silation of Silica with Hexamethyldisilazane. *J. Phys. Chem. B* **2000**, *104*, 983−989.

(15) Asami, M.; Inoue, S. Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by (S)-2-(N,N-Disubstituted aminomethyl)-pyrrolidine. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1687−1690.

(16) Yang, W. K.; Cho, B. T. Facile synthesis of chiral isopropyl carbinols with high enantiomeric excess via catalytic enantiose-lective addition of diisopropylzinc to aldehydes. *Tetrahedron: Asymmetry* **2000**, *11*, 2947−2953.

(17) Prasad, K. R.; Revu, O. 2-Pyridylsulfinamides as effective catalysts in the asymmetric alkylation of aldehydes with diethyl-zinc. *Tetrahedron* **2013**, *69*, 8422−8428.

(18) Shih, Y.-S.; Boobalan, R.; Chen, C.; Lee, G.-H. Novel C2-symmetric chiral O,N,N,O-tetradentate 2,2-bipyridyldiolpropane ligands: synthesis and application in asymmetric diethylzinc addition to aldehydes. *Tetrahedron Asymmetry* **2014**, *25*, 327−333.

(19) Boobalan, R.; Lee, G. H.; Chen, C. Copper Complex of Aminoisoborneol Schiff Base Cu2(SBAIB-d)2: An Efficient Catalyst for Direct Catalytic Asymmetric Nitroaldol (Henry) Reaction. *Adv. Synth. Catal.* **2012**, *354*, 2511−2520.

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