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Enantioselective Addition of Diethylzinc to Aromatic Aldehydes Using Novel Thiophene-Based Chiral Ligands

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Abstract—Chiral norephedrine-derived β-amino alcohols with a thiophene moiety were synthesized from thiophene carbaldehydes (methyl- or ethyl-substituted) and chiral amino alcohols, such as both enantiomers of norephedrine and 2-aminopropanol. The synthesized ligands were applied to the catalytic asymmetric addition of diethylzinc to aldehydes to obtain optically active alcohols with a high conversion (92%) and excellent enantioselectivities (*ee* up to 99%). The highest enantioselectivity (*ee* 99%) was obtained with *p*-trifluorobenzaldehyde as the substrate containing the strongly electron-acceptor CF_3 group.

Keywords: enantioselective synthesis, chiral amino alcohols, thiolated amino-alcohols, 1,2-addition

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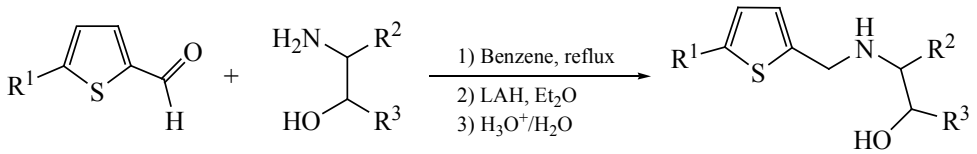
INTRODUCTION

Enantioselective addition of organometallic reagents to aldehydes is an important method for the synthesis of optically active secondary alcohols, which are building blocks for the preparation of natural products, pharmaceuticals, agrochemicals, perfumes, and other compounds. Derivatives of 1-phenylpropan-1-ol are used in cancer therapy as stimulating drugs [1–6]. Since the first report by Oguni and Omi [7, 8], several types of ligands, including amino thiols [9–11], amino alcohols [12–14], amino phenols [6, 15], amides [17, 18], diamines [19–21], diols [22–24], and sulfonamides [25–27], have been used to success as chiral ligands for the enantioselective addition of dialkylzinc to aldehydes.

Chiral amino alcohols are often used as chiral ligands in enantioselective reactions, because they are readily available and provide efficient asymmetric induction. The most successful results were obtained with sterically constrained β-amino alcohols [28–32], such as ephedrine or norephedrine, as well as proline [33–36]. Soai et al. [37–40] were the first to report the highly enantioselective addition of diethylzinc to aldehydes in the presence of enantiomerically pure norephedrine derivatives, specifically *N*,*N*-dialkylnorephedrines. The addition of diethylzinc to aromatic aldehydes catalyzed by these chiral ligands gave 1-arylethan-1-ols in excellent chemical yields and enantioselectivities [41–45].

Among various organometallic compounds, diorganylzinc acts as an ideal alkyl donor in enantioselective alkylation reactions. In ordinary hydrocarbon and ethereal solvents, dialkylzinc compounds do not react with aldehydes in noncatalytic conditions [2, 4, 46–48]. Even though dialkylzinc reagents extremely slowly react with carbonyl compounds, several ligands and transition metal complexes proved to be effective catalysts for these reactions. The high reactivity of organozinc reagents in the presence of chiral ligands, such as amino alcohols, can be explained as follows [49–51]. Monomeric dialkylzinc compounds have a linear geometry around the zinc atom, and, therefore, the zinc–alkyl bond is nonpolar. However, the complexation with a suitable ligand changes the linear structure of R_2Zn compounds to tetrahedral [2, 52] and makes the Zn–C bond longer. Therefore, the energy of the Zn–C bond decreases, and the nucleophilicity of the alkyl group in dialkylzinc increases [53]. In this way, the nucleophilicity of the alkyl group increases, and the addition becomes possible [54]. The amino alcohol acts as a Lewis base which activates the zinc reagent and forms a Lewis acidic zinc species, which activates the aldehyde. Upon treatment of an amino alcohol with an alkylzinc reagent, donor atoms, such as nitrogen and

Scheme 1.



1a, **1b** **2**, **3** **4–7**

1, $R^1 = CH_3$ (**a**), CH_2CH_3 (**b**); **2**, $R^2 = CH_3$, $R^3 = H$; **3**, $R^2 = CH_3$, $R^3 = C_6H_5$; **4**, $R^1 = CH_3$, $R^2 = CH_3$, $R^3 = H$; **5**, $R^1 = CH_2CH_3$, $R^2 = CH_3$, $R^3 = H$; **6**, $R^1 = CH_3$, $R^2 = CH_3$, $R^3 = C_6H_5$; **7**, $R^1 = CH_2CH_3$, $R^2 = CH_3$, $R^3 = C_6H_5$.

Table 1. Preparation of thiophene-based chiral ligands **4–7**

Entry	Thiopene carbaldehyde	Amino alcohol	Ligand	Yield, %
1	**1a**	(*R*)-**2**	(*R*)-**4**	75
2	**1a**	(*S*)-**2**	(S)-**4**	76
3	**1b**	(*R*)-**2**	(*R*)-**5**	72
4	**1b**	(*S*)-**2**	(S)-**5**	74
5	**1a**	(1*R*,2*S*)-**3**	(1*R*,2*S*)-**6**	68
6	**1a**	(1*S*,2*R*)-**3**	(1*S*,2*R*)-**6**	74
7	**1b**	(1*R*,2*S*)-**3**	(1*R*,2*S*)-**7**	70
8	**1b**	(1*S*,2*R*)-**3**	(1*S*,2*R*)-**7**	75

oxygen of the chiral ligands, coordinate to the zinc atom to form chiral complexes which differentiate the enantioface of the aldehyde [2].

We are interested in synthesizing and applying chiral amino alcohol derivatives as ligands for metal complexes in enantioselective catalysis, and we reported that using chiral pyrrole substituted norephedrine-based amino alcohols as ligands allows moderate enantioselectivities and chemical yields in the additions of diethylzinc to benzaldehyde and chalcone. We showed that the absolute configuration of the norephedrine moiety plays an important role in the configuration of the addition products [55, 56].

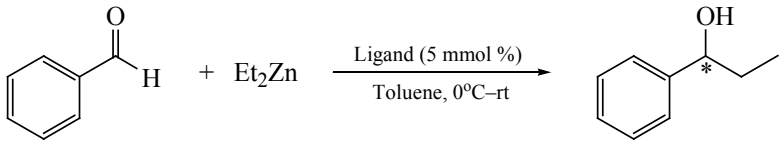
In our previous studies, chiral norephedrine-based β-amino alcohol ligands with a substituted thiophene ring were synthesized from both norephedrine enantiomers **6a–6b**, **7a–7b**. The synthesized chiral ligands were applied as catalysts in the Cu-catalyzed asymmetric Henry reaction. Herein, we report the preparation of substituted chiral 2-amino propanol and norephedrine-based ligands bearing a substituted thiophene ring. These ligands were used as catalysts in the asymmetric addition of diethylzinc to aromatic aldehydes.

RESULTS AND DISCUSSION

Chiral ligands **4** and **5** were easily synthesized from both enantiomers of 2-aminopropanol according to our previously reported procedure (Scheme 1) [55, 56]. The starting chiral amino alcohols are commercially available reagents. The synthesis of compounds **4–7** can be described as follows. (*R*)- and (*S*)-2-Aminopropanol [(*R*)- and (*S*)-**2**] or (1*R*,2*S*)- or (1*S*,2*R*)-norephedrine [(1*R*,2*S*)-**3** or (1*S*,2*R*)-**3**], and 5-substituted thiophene-2-carbaldehyde **1a** or **1b** were mixed in dry benzene and refluxed for 4 h with a Dean–Stark trap to obtain the corresponding Schiff base in a quantitative yield. The resulting Schiff base was reduced in dry diethyl ether with $LiAlH_4$. All possible stereoisomers were isolated after purification of the crude products by column chromatography. The detailed results are presented in Table 1.

To assess the catalytic efficiency of amino alcohols **4–7**, we chose as the model reaction the asymmetric addition of Et_2Zn to benzaldehyde in toluene at 0°C to room temperature in the presence of 10 mol % of catalyst at a 1 : 2 ratio of benzaldehyde and Et_2Zn, leading to a chiral 1-phenylpropan-1-ol. The results are summarized

Table 2. Enantioselective addition of diethyzinc to benzaldehyde catalyzed by chiral ligands



8a **9a**

Entry	Ligand	Yield of **9a**, %[a]	*ee*, %[b]	Configuration[c]
1	(*R*)-**4**	75	66	*R*
2	(*S*)-**4**	76	67	*S*
3	(*R*)-**5**	78	69	*R*
4	(*S*)-**5**	78	70	*S*
5	(1*R*,2*S*)-**6**	82	78	*S*
6	(1*S*,2*R*)-**6**	83	79	*R*
7	(1*R*,2*S*)-**7**	80	81	*S*
8	(1*S*,2*R*)-**7**	79	83	*R*

[a] Yields of ligands after column chromatography.
[b] The *ee* values were determined by HPLC with a Chiralcel OD-H column.
[c] Absolute configurations were assigned by comparison of the HPLC retention times with published data [18].

in Table 2. As seen from Table 2, the product was obtained in yields of 75–83% and *ee* 66–83%.

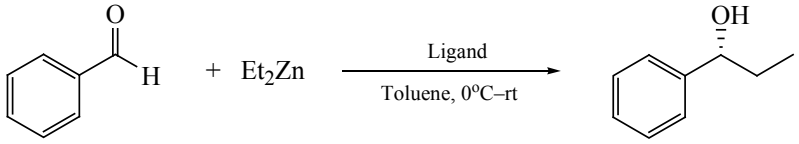
Chiral ligands **4** and **5** were synthesized from (*R*)- and (*S*)-2-aminopropan-1-ol that catalyzed the addition of Et_2Zn to benzaldehyde to form either (*R*)- or (*S*)-1-phenylpropan-1-ol, respectively. In chiral ligands **4** and **5**, the C–OH carbon atom is not a chiral center. With ligands (*R*)-**4** and (*R*)-**5** as chiral catalysts, the corresponding enantiomerically enriched (*R*)-1-phenylpropan-1-ol was obtained in yields of 75 and 78% (*ee* 66 and 69%), respectively (Table 2, entries 1 and 3). The same reaction with (*S*)-**4** and (*S*)-**5** gave an (*S*)-alcohol in yields of 76% and 78% (*ee* 67 and 70%), respectively (Table 2, entries 2 and 4). These observations are in agreement with the observation of Soai et al. [57, 58], who reported that the enantioselectivity was determined by the configuration of the homochiral (*S*)-(+)-diphenyl(*N*-methylpyrrolidin-2-yl)methanol (DPMPM), which has an asymmetric carbon bearing the amino group: (*S*)-DPMPM gave (*S*)-1-phenylpropan-1-ol, whereas (*R*)-DPMPM catalyzed the reaction to afford the (*R*)-alcohol.

It is known that high enantioselectivities are obtained, when the OH-bearing carbon atom of the chiral ligand contains bulky substituents. Chiral ligands (1*R*,2*S*)-**6** and (1*R*,2*S*)-**7** with an (*R*)-configuration of the OH-bearing carbon gave the product with an (*S*)-configuration (Table 2), while chiral ligands (1*S*,2*R*)-**6** and (1*S*,2*R*)-**7** with an (*S*)-configuration of the same stereogenic center gave an (*R*)-product. The reactions with chiral ligands (1*R*,2*S*)-**6** and (1*S*,2*R*)-**6** afford the secondary alcohol in yields of 82% and 83% (*ee* 78 and 79%) for the major (*S*)- and (*R*)-enantiomers, respectively (Table 2, entries 5 and 6).

Chiral ligand (1*S*,2*R*)-**7** gave the highest enantioselectivity in the asymmetric addition of diethyzinc to benzaldehyde (Table 2, entry 8), and, therefore, it was selected for further optimization of the reaction conditions, specifically solvent, temperature, and amount of the ligand.

The results are summarized Table 3. The solvent was found to have a remarkable effect on enantioselectivity and conversion. In noncoordinating solvents, such as toluene and hexane, higher enantioselectivities were obtained compared to coordinating solvents, such as THF and Et_2O. Toluene gave the best results: yield 79% and *ee* 83% (Table 3, entry 1). In hexane, the enantioselectivity was lower but the conversion was higher increased (Table 3, entry 2). In THF and Et_2O, the enantioselectivity decreased dramatically (Table 3,

Table 3. Asymmetric addition of diethyzinc to benzaldehyde in the presence of chiral ligand (1*S*,2*R*)-**7**



8a (*R*)-**9a**

Entry	Ligand, mmol %	Solvent	Yield, %[a]	*ee*, %[b]
1	5	Toluene	79	83
2	5	Hexane	75	78
3	5	THF	70	62
4	5	Et_2O	65	60
5	5	CH_2Cl_2	70	62
6[c]	5	Toluene	70	52
7[d]	5	Toluene	80	57
8[e]	5	Toluene	72	95
9	10	Toluene	84	79
10	15	Toluene	85	70
11	2.5	Toluene	80	75

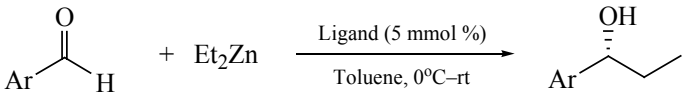
[a] Yields of ligands after column chromatography.
[b] The *ee* values were determined by HPLC on a Chiralcel OD-H column.
[c] The reaction was performed at room temperature.
[d] The reaction was performed at –20°C.
[e] The reaction was performed with 2 mmol Ti(O*i*Pr)$_4$.

entries 3 and 4). The presence of dichloromethane decreased the *ee* of the resulting alcohol (Table 3, entry 5). Consequently, toluene was considered an optimal solvent for the catalytic reaction.

The effect of the reaction temperature was also investigated. Initially, the experiment was performed by slowly adding Et_2Zn to a solution of compound (1*S*,2*R*)-**7** at 0°C. After 1 h, benzaldehyde was added at the same temperature, and then the reaction was kept at room temperature. When the reaction was performed at room temperature, the enantioselectivity decreased to 52% (Table 3, entry 6). Conversely, decreasing the reaction temperature to –20°C led to a lower *ee* of 57% (Table 3, entry 7).

Ligands are essential for controlling the reactivity and selectivity of metal-catalyzed reactions. Alkylzinc reagents can be used in combination with titanium alkoxides to promote the addition reaction of carbon nucleophiles to carbonyl compounds. Evidence showing that additives like titanium tetraisopropoxide Ti(O*i*Pr)$_4$, which can act as Lewis acids, affect the enantioselectivity and yield of similar reactions has been reported [59–61]. The enantioselective addition of diethylzinc to benzaldehyde in the presence of Ti(O*i*Pr)$_4$ increases both yield and *ee* [62–64]. Using catalytic amounts of chiral Lewis acids as catalysts in such reactions provides an efficient way to enantioselective creation of new carbon–carbon bonds. In all cases, the complexation of Lewis acids with the carbonyl group activates the system. In most cases, chiral transition metal complexes, often prepared in situ, are used as catalysts. Recent studies on the mechanism of dialkylzinc addition to aldehydes in the presence of Ti(O*i*Pr)$_4$ seem to indicate that the alkyl moiety is transferred from zinc to titanium by transmetallation and then transferred from the latter to the aldehyde [65]. Considering these published data, the enantioselective reaction was performed with Ti(O*i*Pr)$_4$ as an additive in the presence of chiral catalyst (1*S*,2*R*)-**7**. The resulting

Table 4. Enantioselective addition of diethylzinc to various aromatic aldehydes catalyzed by (1*S*,2*R*)-**6** and (1*S*,2*R*)-**7**[a]



8a–8p (*R*)-**9a–9p**

Entry	Aldehyde	Product	Ligand (1*S*,2*R*)-**6**		Ligand (1*S*,2*R*)-**7**	
			Yield, %[b]	*ee*,%[c]	Yield, %[b]	*ee*, %[c]
1	Benzaldehyde (**8a**)	**9a**	80	83	72	95
2	*p*-Methoxybenzaldehyde (**8b**)	**9b**	75	80	83	83
3	*m*-Methoxybenzaldehyde (**8c**)	**9c**	75	75	80	80
4	*o*-Methoxybenzaldehyde (**8d**)	**9d**	64	72	95	75
5	*p*-Methylbenzaldehyde (**8e**)	**9e**	68	78	82	80
6	*m*-Methylbenzaldehyde (**8f**)	**9f**	79	74	82	76
7	*o*-Methylbenzaldehyde (**8g**)	**9g**	68	72	85	73
8	*p*-Chlorobenzaldehyde (**8h**)	**9h**	89	88	89	90
9	*m*-Chlorobenzaldehyde (**8i**)	**9i**	89	85	92	88
10	*o*-Chlorobenzaldehyde (**8j**)	**9j**	90	83	92	85
11	*p*-Bromobenzaldehyde (**8k**)	**9k**	87	85	85	87
12	*m*-Bromobenzaldehyde (**8l**)	**9l**	91	84	93	83
13	*p*-(Trifluoromethyl)benzaldehyde (**8m**)	**9m**	92	99	94	98
14	Naphthalene-1-carbaldehyde (**8n**)	**9n**	80	72	78	75
15	Naphthalene-2-carbaldehyde (**8o**)	**9o**	81	76	80	78
16	Thiophene-2-carbaldehyde (**8p**)	**9p**	60	58	62	61

[a] The reaction was performed with 2 mmol $Ti(OiPr)_4$.
[b] Yields of ligands after column chromatography.
[c] The *ee* values were determined by HPLC on a Chiralcel OD-H column.

data showed that the use of $Ti(OiPr)_4$ ensures high enantioselectivity (*ee* 95%; Table 3, entry 8).

The loading of the chiral ligand was a crucial factor affecting the catalytic activity in this reaction. When the amount of ligand (1*S*,2*R*)-**7** was increased to 10 and 15 mol %, the *ee* values decreased to 79 and 70% (Table 3, entries 9 and 10), respectively. However, the lowest loading of the chiral ligand (2.5 mol %) led to a lower enantioselectivity (yield 80% and *ee* 74%; Table 3, entry 11).

To demonstrate the influence of the electronic and steric effects of the substrate on this asymmetric addition, a series of different aromatic aldehydes was then examined in toluene at 0°C in the presence (1*S*,2*R*)-**6** or (1*S*,2*R*)-**7** as chiral catalysts. The results are summarized in Table 4. The additions to aromatic aldehydes all gave the corresponding *R*-alcohols as the major isomers with excellent enantiomeric excesses and high yields. Table 4 shows that electron-acceptor substituents increase the electrophilicity of the carbonyl carbon in aryl aldehydes, whereas electron-donor groups decrease it. These results suggest that substrates with electron-acceptor substituents reacted faster, providing higher yields of the products with higher enantiomeric excesses.

Substrates with an electron-acceptor group in aromatic aldehydes afforded than that of benzaldeyde, but higher than those with electron-donating groups.

A lower enantioselectivity was observed for *ortho*-substituted aromatic aldehydes (Table 4, entries 4, 7, and 10) compared to their *meta*- and *para*-substituted analogs (Table 4, entries 3, 6, 9 and 2, 5, 8, respectively). With both (1*S*,2*R*)-**6** and (1*S*,2*R*)-**7**, lower enantiomeric excesses were observed with aromatic aldehydes bearing *ortho*-substituents, probably due to the *ortho*-effect. With less crowded substrates, such as *m*-methoxybenzaldehyde, a higher enantioselectivity (*ee* 75%) was obtained (Table 4, entry 3). The highest enantioselectivity was observed with *p*-(trifluoromethyl)benzaldehyde as the substrate with the strongly electron-acceptor group–CF_3 substituent (*ee* 99%). The sterically less hindered naphthalene-2-carbaldehyde gave a higher enantioselectivity than the sterically more crowded naphthalene-1-carbaldehyde (Table 4, entries 14 and 15). In the case of thiophene-2-carbaldehyde, the reaction provided the corresponding products with moderate enantioselectivities: *ee* 58% with (1*S*,2*R*)-**6** and 61% with (1*S*,2*R*)-**7** (Table 4, entries 19 and 16).

EXPERIMENTAL

Reagents and solvents were purchased from Aldrich, Merck, and Fluka. All solvents were dried before use by standard procedures. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 MHz spectrometer at room temperature, internal reference TMS. Thin layer chromatography was performed using Merck Kieselgel 60 F_{254} plates. Crude compounds were purified by column chromatography on silica gel (60–200 mesh, unless otherwise indicated). The IR spectra were run on a 2000 Perkin–Elmer spectrometer. The optical rotations were measured on an Autopol IV polarimeter. The melting points were determined using an Electrothermal melting point apparatus. The elemental analyses were obtained on a LECO CHNS-932 series analyzer. The enantiomeric excesses were determined by HPLC analysis using Chiracel OD-H and OB and Chiralpak AD-H chiral columns on Shimadzu LC-20AD or Thermo Finnigan Surveyor HPLC instruments. The absolute configurations of the major enantiomers were determined by comparison of the retention times and the signs of specific rotation of the synthesized compounds with published data [55].

Synthesis of chiral ligands. Thiophene-2-carbaldehydes **1a** and **1b**, synthesized by the Vilsmeier–Haack method [66], were treated with both enantiomers of 2-aminopropanol (**2**) and norephedrine (3) to obtain chiral ligands **4–7** by the procedures in [55, 56]. (See Supplementary data for the ^{1}H and ^{13}C NMR of compounds **4–7**). New compounds are described below.

(*R*)-2-[(5-Methylthiophene-2-yl)methylamino]-propanol [(*R*)-4] was prepared from (*R*)-2-amino propanol (5 mmol) and 5-methylthiophene-2-carbaldehyde (5 mmol). Yield 75%, R_f 0.30 (EtOAc–hexane, 1 : 1); $[\alpha]_D^{25}$ –0.80 (*c* 0.35, $CHCl_3$). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 0.77 d (3H, $CHCH_3$, *J* 6.4 Hz), 2.40 s (3H, CH_3), 2.89–2.99 m (1H, $CHCH_3$), 3.88 d (1H, $NHCH_2$, *J* 14.4 Hz), 3.99 d (1H, $NHCH_2$, *J* 14.4 Hz), 3.92 m (1H, CH_2OH), 6.49 d (1H, C^{4}H, thiophene ring, *J* 3.2 Hz), 6.62 d (1H, C^{3}H, thiophene ring, *J* 3.2 Hz). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 13.58 (CH_3), 14.11 ($CHCH_3$), 43.54 (CH_2NH), 65.42 ($CHCH_3$), 70.45 (CH_2OH), 105.94 (C^4, thiophene ring), 108.08 (C^3, thiophene ring), 137.6 (C^5, thiophene ring), 139.4 (C^2, thiophene ring). Found, %: C 58.30; H 8.14; N 7.58; S 17.32. $C_9H_{15}NOS$. Calculated, %: C 58.34; H 8.16; N, 7.56; O 8.63; S 17.31.

(*R*)-2-[(5-Ethylthiophene-2-yl)methylamino]-propanol [(*R*)-5] was prepared from (*R*)-2-amino-propanol (5 mmol) and 5-ethylthiophene-2-carbaldehyde (5 mmol). Yield 72%, brown oil, R_f 0.32 (EtOAc–hexane, 1 : 1); $[\alpha]_D^{25}$ –0.74 (*c* 0.57, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 0.78 d (3H, $CHCH_3$, *J* 6.8 Hz), 1.25 t (2H, CH_2CH_3, *J* 7.2 Hz), 2.75 q (2H, CH_2CH_3, *J* 7.2 Hz), 2.95–2.97 m (1H, $CHCH_3$), 3.55–3.62 m (2H, CH_2OH), 3.88 d (1H, $NHCH_2$, *J* 14.0 Hz), 3.96 d (1H, $NHCH_2$, *J* 14.4 Hz), 6.55 br.s (1H, C^{4}H, thiophene ring), 6.65 d (1H, C^{3}H, thiophene ring, *J* 3.2 Hz). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 13.67 (CH_2CH_3), 17.81 ($CHCH_3$), 26.67 (CH_2CH_3), 43.55 ($NHCH_2$), 65.21 (CH_3CH), 72.94 (CH_2OH), 105.97 (C^4, thiophene ring), 108.06 (C^3, thiophene ring), 136.75 (C^5, thiophene ring), 139.56 (C^2, thiophene ring). Found, %: C 60.28; H 8.58; N 7.03; S 16.10. $C_{10}H_{17}NOS$. Calculated, %: C 60.26; H 8.60; N 7.03; S 16.09.

Addition of Et_2Zn to aldehydes (*general procedure*). A solution of diethylzinc (2 mL of 1 M hexane solution, 2 mmol) was added dropwise to a solution of chiral ligand **4–7** (0.05 mmol, 5 mol %) in dry toluene (2 mL) under an argon atmosphere, and the mixture was stirred at 0°C for 1 h. A solution of benzaldehyde (1 mmol) in dry toluene (1 mL) was added with a syringe. After stirring for 16 h, the reaction was quenched with saturated

aqueous NH_4Cl (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography to give the corresponding product. Secondary alcohols **9a–9p** are known compounds; they were characterized by comparing their ^1H and ^{13}C NMR spectra with those reported in [49, 58, 60]. The enantiomeric excesses were determined by HPLC on chiral columns. The absolute configurations of the major enantiomers were determined by comparison of the retention times and the signs of specific rotation of known compounds with published data [58, 59]. Compounds **9a–9p** are known compounds; they were characterized by comparing their ^1H, ^{13}C NMR spectra with those published in the literature [47].

1-Phenylpropan-1-ol (9a) was prepared from benzaldehyde (1.00 mmol), yield 79%, *ee* 86% (determined on a Chiralcel OD-H column, 10% 2-propanol–hexane, 0.5 mL/min, λ 254 nm, t_R 15.2 and 20.2 min for the (*R*)- and (*S*)-enantiomers, respectively]. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 0.94 t (3H, CH_3, *J* 7.6 Hz), 1.71–1.85 m (2H, CH_2CH_3), 2.12 s (1H, OH), 4.56 t (1H, CH, *J* 6.80 Hz), 7.23–7.24 m ($5H_{arom}$). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 10.53 (CH_3), 32.29 (CH_2), 76.43 (CH), 126.37 (CH), 127.89 (CH), 128.91 (CH), 145.01. Found, %: C 79.41; H 8.90. $C_9H_{12}O$. Calculated, %: C 79.37; H 8.88.

CONCLUSIONS

In conclusion, thiophene-substituted chiral amino alcohols derived from easily accessible enantiomerically pure norephedrine were prepared and used as chiral catalysts in the asymmetric addition of diethylzinc to aldehydes. The use of these chiral amino alcohols has several advantages, such as high reaction rates and excellent yields, no side reactions, ease of preparation, and a simple experimental procedure.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIALS

Supplementary materials are available for this article at https://doi.org/10.1134/S1070428020050255 and are accessible for authorized users.

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