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Modular chiral thiazolidine catalysts in asymmetric aryl transfer reactions

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Abstract—Modular chiral thiazolidine derivatives were synthesized in a single step from inexpensive and commercially available starting materials. These ligands catalyzed enantioselective arylation of different aldehydes using aryl boronic acids as a source of transferable aryl groups. The products were obtained in excellent yields and good enantioselectivities.

1. Introduction

The addition of organometallic reagents to carbonyl compounds represents an attractive area in current organic synthesis. The catalytic enantioselective version of this reaction provides particularly useful access to chiral alcohols, which are synthetically important chiral building blocks for pharmaceutically active compounds. In recent years, considerable efforts have been made and great progress achieved in the catalytic enantioselective arylation of aldehydes.[1] Diarylmethanols are key intermediates in the synthesis of antihistamic agents such as neobenodine, orphenadrine, carbinoxamine, antimuscarinics, antidepressants, and endothelin antagonists. As a result, the asymmetric synthesis of optically active arylcarbinols has attracted much attention due to their high availability as starting materials.

Among the available methods for the synthesis of chiral diarylmethanols, the asymmetric addition of arylzinc showed the advantages of a wide substituent tolerance, mild reaction conditions, and the use of relatively nontoxic zinc metal.[2] The initial approach was centered upon the use of the expensive diphenylzinc as the aryl source.[3] However, its enantioselective addition to aldehydes is a challenging endeavor, since this reagent is much more reactive than the well known diethylzinc. The uncatalyzed background addition thus competes with the enantioselective pathway, leading to the formation of the racemic product. In order to circumvent this problem, diethylzinc was found to reduce the reactivity of the arylzinc reagent, by forming PhZnEt, which is less reactive than diphenylzinc itself. This strategy improves the overall system performance, since the aryl transfer reaction proceeds slowly when compared to the reaction with Ph_2Zn alone.[4] Additionally, it accounts for a higher selectivity for the phenyl transfer and allows the use of a reduced amount of the expensive diphenylzinc. These two protocols, however, have a serious drawback. The scope of the aryl group to be transferred is limited to the phenyl ring, since only diphenylzinc is a commercially available diarylzinc reagent. Thus, there is a growing interest in the development of methods that allow the asymmetric transfer of a broader range of substituted aryl groups, starting from inexpensive and readily accessible sources. In this context, an interesting protocol was recently introduced by Bolm, which takes advantage of the use of boronic acids as the source of the nucleophilic aryl species, by a boron-to-zinc exchange reaction with diethylzinc.[5] This modified methodology broadened the scope of such an addition reaction and enabled synthetic chemists to elaborate functionalized arylzinc reagents as nucleophiles in salt free conditions.

Unfortunately, only a few elegant and efficient catalysts have been developed for this purpose. The most successful results toward optically active diarylmethanols have been obtained mainly by the use of chiral β-amino alcohols.[6] In this field, our group recently reported the use of amino

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alcohols in the catalytic asymmetric aryl transfer to aldehydes, furnishing the respective carbinols in excellent yields and enantiomeric excesses.[7] Furthermore, the efficient use of ligands bearing organochalcogen moieties has recently been reported for this purpose.[8] In most of the previous reports concerning the preparation of chiral ligands, multistep syntheses are required. Thus, the development of a new, flexible and easily prepared effective catalysts is an important challenge for the practical applications of phenyl transfer reactions.

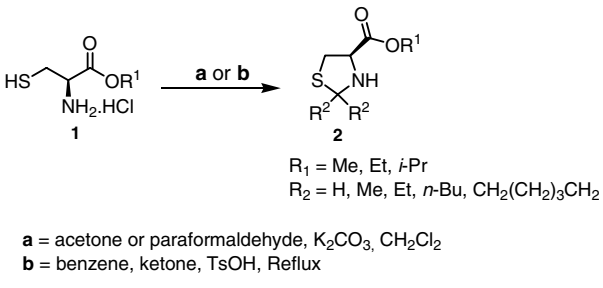
Based on our ongoing interest the asymmetric aryl transfer to aldehydes and the recent reports employing thiazolidines as catalysts, mainly in the asymmetric addition of diethylzinc to aldehydes,[9] we report herein the behavior of these compounds as catalysts in the enantioselective arylation of aldehydes.

2. Results and discussion

In order to obtain a quick and easy access to a wide range of ligands, a modular system comprised of simple components is essential. Thus, an economical synthesis of the ligands has to be developed, which allows at any step of the synthesis an easy modification or incorporation of different moieties into the chiral pool. Chiral thiazolidines **2a**–**h** were easily prepared by the condensation of L-cysteine ester **1** with the corresponding aldehyde or ketone in good yields as described in Scheme 1.

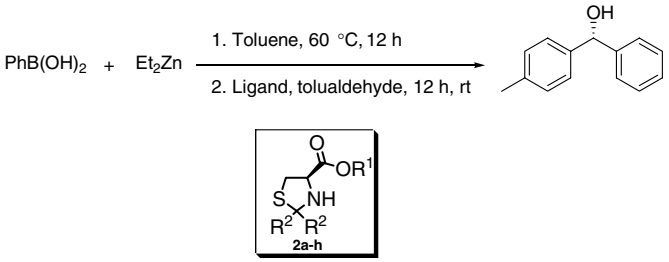
Initially, in order to find out the best ligands and an optimal procedure, we chose the PhZnEt addition to *p*-tolualdehyde as a model reaction in the presence of 20 mol % of ligands **2a**–**h** under different conditions. To the best of our knowledge, this is the first time that ligands containing an ester as a complexing group have been evaluated in this asymmetric reaction. The enantiomeric purity of diarylmethanol was determined by HPLC analysis with a chiral stationary phase column (Daicel Chiralcel OD, hexane/*i*-PrOH).

As seen in Table 1, the first important conclusion was observed when the substituents at the thiazolidine (R_2) moiety were first evaluated, while the R_1 position was kept constant as a methyl group (Table 1, entries 1–5). For example, when chiral ligand **2a** was employed, the addition product was obtained in a 15% ee (Table 1, entry 1). However under the same conditions, the racemic product was obtained



Scheme 1. One-pot synthesis of chiral ligands **2**.

Table 1. Asymmetric phenyl transfer to *p*-tolualdehyde catalyzed by thiazolidines **2a**–**h** (20 mol %)

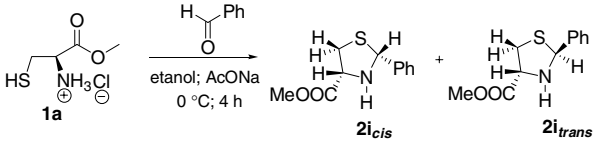


Entry	Ligand	R_1	R_2	Yield (%)[a]	ee (%)[b]
1	**2a**	Me	H	88	15
2	**2b**	Me	Me	93	*Rac.*
3	**2c**	Me	Et	94	56
4	**2d**	Me	$-CH_2(CH_2)_3CH_2-$	91	21
5	**2e**	Et	*n*-Bu	91	65
6	**2f**	*i*-Pr	Et	95	51
7	**2g**	*i*-Pr	Et	93	75
8	**2h**	*i*-Pr	*n*-Bu	97	81

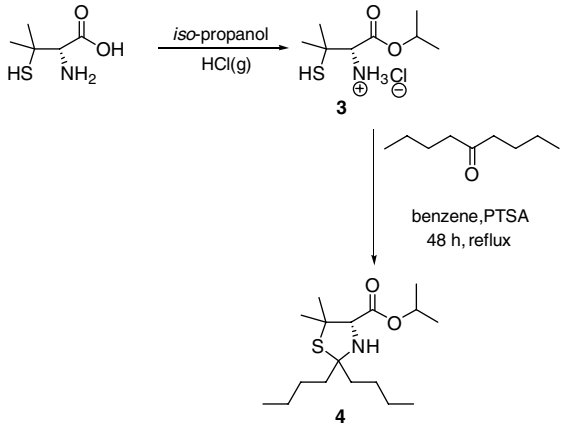
[a] Isolated yield.
[b] Determined by HPLC with a chiralcel OD column.

when ligand **2b** was used (entry 2). However, ligands **2c** ($R_1 = Me$, $R_2 = Et$) and **2e** ($R_1 = Me$, $R_2 = n$-Bu) were found to be more efficient in this reaction in terms of reactivity and enantioselectivity (entries 3 and 5). Ligand **2d** also gave a poor ee (entry 4). Additionally, the different substituents attached to the thiazolidine rings also affected the enantioselectivity on the products. It is quite evident that catalyst **2h** (entry 8) showed a higher enantioselectivity than the others. We believe that the butyl group has a greater rotational freedom of movement than other substituents at the thiazolidine ring. Therefore, ligand **2h** could present a larger steric bulk than other ligands near the nitrogen. We believe that the thiazolidine derivatives tend to show higher enantioselectivities when they have a larger steric bulk in the thiazolidine rings. The enantioselectivity of the catalysts was also affected by their amounts present in the catalytic reactions. When we used 10 and 5 mol % of catalyst **2h**, the ee decreased to 63% and 41%, respectively.

In order to examine the influence of a new stereogenic center in this class of compounds, we easily reproduced ligand **2i** (Scheme 2). This chiral thiazolidine was prepared by condensation with benzaldehyde, and then obtained as an inseparable diastereoisomeric mixture in a ratio of 61:39 in favor of the *cis* diastereoisomer.[10] (2*R*,4*R*)-*cis*-Thiazolidine was assigned to be the major diastereomer based on comparison of ^1H NMR data with previous studies reported in the literature.[11] Although the diastereoisomeric mixture furnished 1-phenyl-propanol in an 80% ee and



Scheme 2. Synthesis of ligand **2i** as a diastereoisomeric mixture.



Scheme 3. Synthesis of ligand **4** with 57% yield.

an 84% yield,[9b] unfortunately, the respective aryl transfer afforded the diarylcarbinol in an excellent yield (98%), but essentially in a racemic form.

We also tried to evaluate the influence of steric hindrance near to the sulfur atom in the thiazolidine ring. Based on this, ligand **4** was synthesized starting from D-penicylamine using the same synthetic methodology, as described in Scheme 3.

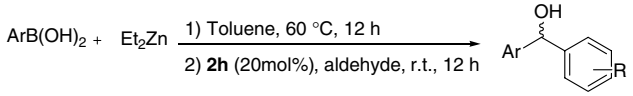
When the efficiency of thiazolidine **4** was examined in the present reaction we could see that the steric bulkiness at the thiazolidine ring strongly affected the enantioselectivity. The size of the group close to the sulfur atom is also important for the outcome of the reaction and a large decrease in the ee and yield was observed. *p*-Tolualdehyde was converted into the corresponding (*R*)-alcohol with a 52% ee and a 79% yield.

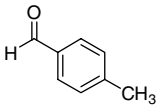
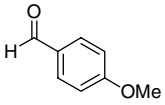
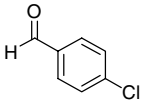
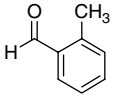
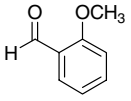
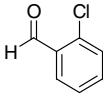
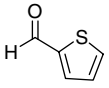
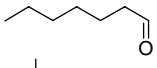
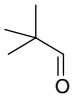
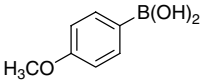
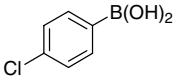
Reaction temperature does not seem to have a significant impact on the enantiomeric excess since reactions conduced at 0 °C afforded the same level of enantioselectivity when compared to reactions conducted at room temperature, using ligand **2h**. Literature concerning the influence of the solvent in the present reaction, meant that its performance was not examined in our catalytic system.[4a,5] Surprisingly, a lower enantioselection and yields were achieved, 71% and 83%, respectively, with the addition of DiMPEG to this reaction. This fact may be due to the strong interactions of DiMPEG and PhZnEt, leading to the delivery of the phenyl group with a low enantioselectivity.

With ligand **2h** identified as the most effective, we next examined the scope of our system in reactions with several aldehydes with diverse electronic and steric properties. The results of this study are depicted in Table 2.

Based on these results, we were able to observe that the position of the substituent in the aldehyde plays an important role in terms of determining enantioselection. *para*-Substituted aldehydes underwent aryl addition in a high enantiomeric excess and nearly quantitative yields (Table 2, entries 1–3). However, *ortho*-substituted benzaldehydes

Table 2. Catalytic arylation of aldehydes with boronic acids



Entry	Boronic acid	Aldehyde	Yield (%)[a]	ee (%)[b,c]
1	$PhB(OH)_2$		97	81 (*S*)
2	$PhB(OH)_2$		91	75 (*S*)
3	$PhB(OH)_2$		98	79 (*S*)
4	$PhB(OH)_2$		97	73 (*S*)
5	$PhB(OH)_2$		93	56 (*S*)
6	$PhB(OH)_2$		97	42 (*S*)
7	$PhB(OH)_2$		89	33 (*S*)
8	$PhB(OH)_2$		63	06 (*S*)
9	$PhB(OH)_2$		59	20 (*S*)
10		Benzaldehyde	90	80 (*R*)
11		Benzaldehyde	99	57 (*R*)

[a] Isolated yield of the corresponding product.
[b] Enantiomeric excesses were determined by chiral HPLC.
[c] Configuration determined by comparison with literature data.[4]

afforded diarylmethanols in low yields and enantiomeric excess (Table 2, entries 4–6). These results could be explained by the higher steric hindrance that the carbonyl groups present in *ortho*-substituted benzaldehydes, which may hinder the formation of a rigid transition state.

With regards to the electronic effects, we noted that all *para*-substituted aldehydes afforded the same level of enantioselectivity, showing that the electronic nature of the substituent in the aldehyde has a small influence on this reaction. However, when *ortho*-substituted aldehydes were employed, electron-withdrawing and electron-donating groups were screened in the catalytic system, lower ees were

achieved to the respective products, showing that electronic effects play an important role in the enantioselective reaction.

Next, we investigated the possibility of varying the structure of the boronic acid (Table 2, entries 10 and 11). Electron-donating groups achieved the same result as phenyl boronic acid, while electron-withdrawing groups cause a dramatic decrease in the enantiomeric excess, probably due to the decrease in the nucleophilicity of the aryl group to be delivered.

In all cases, no ethyl transfer product was formed, which was consistent with other results[4,5] and related theoretical studies.[12] The boronic acid methodology is one of the most interesting feature employed herein, since both enantiomers of a given product can be easily prepared in excellent yields and good enantiomeric excesses with the same catalyst, just by the appropriate choice of both reaction partners, aryl boronic acid and aldehyde.

3. Conclusion

In conclusion, we have described the asymmetric arylation of aldehydes in the presence of a catalytic amount of a chiral thiazolidine affording the corresponding diarylmethanols in good yields and enantiomeric excess. The one-step synthesis of these ligands from L-cysteine ester, combined with the mild reaction conditions and good enantioselectivity obtained make this chiral catalyst practically useful for general synthesis. The importance of a flexible synthetic methodology, which allows access to a diversity of ligands making possible a structural tuning of the ligands in order to obtain a good catalytic performance is also evident.

The importance of this work lies in the fact that this is the first study involving ester groups in asymmetric catalytic aryl transfer to aldehydes with $PhB(OH)_2/Et_2Zn$ systems. This study opens a new frontier for the development of other catalysts with different complexating groups.

4. Experimental

4.1. General procedure for the synthesis of compounds 2a,b

In a two neck round-bottomed flask, under argon and equipped with magnetic stirrer a solution of L-cyteine methyl ester (1.715 g; 10 mmol) in dry dichloromethane (10 mL) was added. K_2CO_3 (4.2 g; 30 mmol) and parafolmaldehyde (0.45 g; 30 mmol) were then added. The mixture was stirred for 24 h at room temperature. The crude mixture was then filtered and washed with water (30 mL) and extracted with dichloromethane (3×20 mL). The organic layer was dried with $MgSO_4$ and the solvent removed under a reduced pressure yielding the desired product.

4.1.1. (*R*)-Methyl thiazolidine-4-carboxylate 2a. Yield: 75%; ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 4.38$ (dd, $J^1 = 7.4$ Hz, $J^2 = 3.5$ Hz, 1H); 4.23 (s, 2H); 3.72 (s, 3H); 3.26–3.07 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 170.98$; 72.61; 66.49; 56.78; 32.13.

4.1.2. (*R*)-Methyl 2,2-dimethylthiazolidine-4-carboxylate 2b. Yield: 96%; ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 6.73$ (s, 1H); 4.44–4.37 (m, 1H); 3.82 (s, 3H); 3.5 (dd, $J^1 = 11.04$ Hz, $J^2 = 7.0$ Hz, 1H); 3.20 (dd, $J^1 = 11.06$ Hz, $J^2 = 8.2$ Hz, 1H); 1.80 (s, 3H); 1.69 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 173.48$; 75.38; 64.03; 53.19; 43.27; 39.82; 30.07.

4.2. General procedure for the synthesis of compounds 2c–h

In a two neck round-bottomed flask, equipped with magnetic stirrer and Dean–Stark apparatus and reflux condenser, were added L-cysteine methyl ester (0.556 g; 3 mmol), 3-pentanone (0.335 g; 4 mmol), *para*-toluenosulfonic acid (catalytic amount), and benzene (30 mL). The reaction was refluxed for 48 h and then cooled to room temperature. The solvent was removed under vacuum and the reminiscent solid was diluted with an aqueous solution of K_2CO_3 20% (15 mL) and extracted with dichloromethane (3×20 mL). The organic layer was dried with $MgSO_4$ and the solvent removed under reduced pressure yielding the desired product. No further purification were needed.

4.2.1. (*R*)-Methyl 2,2-diethylthiazolidine-4-carboxylate 2c. Yield: 71%; ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 4.05$–3.98 (m, 1H); 3.37 (s, 3H); 3.28 (dd, $J^1 = 10.16$ Hz, $J^2 = 6.6$ Hz, 1H); 2.87–2.77 (m, 1H); 2.33 (s, 1H); 2.01–1.61 (m, 4H); 1.02 (t, $J = 7.3$ Hz, 3H); 0.91 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 173.24$; 84.14; 63.66; 43.07; 38.08; 33.62; 31.06; 9.25; 8.99.

4.2.2. (*R*)-3-Methoxycarbonyl-1-thio-4-azospire[4.5]decane 2d. Yield: 63%; ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 4.06$ (dd, $J^1 = 9.34$ Hz, $J^2 = 6.6$ Hz, 1H); 3.78 (s, 3H); 3.29 (dd, $J^1 = 10.32$ Hz, $J^2 = 6.6$ Hz, 1H); 2.92–2.82 (m, 1H); 2.39 (s, 1H); 1.90–1.25 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 172.10$; 81.64; 63.45; 52.30; 40.80; 39.98; 38.05; 25.47; 25.21; 23.63.

4.2.3. (*R*)-Ethyl 2,2-diethylthiazolidine-4-carboxylate 2e. Yield: 73%; ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 4.22$ (q, $J = 7.2$ Hz, 2H); 3.99 (dd, $J^1 = 9.16$ Hz, $J^2 = 6.7$ Hz, 1H); 3.29 (dd, $J^1 = 10.24$ Hz, $J^2 = 6.6$ Hz 1H); 2.86–2.76 (m, 1H); 2.37 (s, 1H); 2.04–1.61 (m, 4H); 1.29 (t, $J = 7.1$ Hz, 3H); 1.02 (t, $J = 7.3$ Hz, 3H); 0.91 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 172.27$; 84.54; 64.13; 61.13; 43.48; 38.53; 34.03; 31.39; 9.54; 9.31.

4.2.4. (*R*)-Isopropyl 2,2-diethylthiazolidine-4-carboxylate 2f. Yield: 79%; ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 5.08$ (sept, $J = 6.2$ Hz, 1H); 3.97 (dd, $J^1 = 9.28$ Hz, $J^2 = 6.6$ Hz, 1H); 3.29 (dd, $J^1 = 10.34$ Hz, $J^2 = 6.6$ Hz, 1H); 2.81 (dd, $J^1 = 10.24$ Hz, $J^2 = 9.4$ Hz, 1H); 2.27 (s, 1H); 2.05–1.69 (m, 4H); 1.29 (d, $J = 3.6$ Hz, 3H); 1.26 (d, $J = 3.6$ Hz, 3H); 1.03 (t, $J = 7.3$ Hz, 3H); 0.92 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 171.13$; 84.80; 68.83; 64.19; 38.85; 34.22; 31.22; 21.59; 21.56; 9.68; 9.47.

4.2.5. (*R*)-Methyl 2,2-dibutylthiazolidine-4-carboxylate 2g. Yield: 87%; ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 4.02$ (m, 1H); 3.77 (s, 3H); 3.30 (dd, $J^1 = 10.2$ Hz, $J^2 = 6.6$ Hz, 1H); 2.88–2.79 (m, 1H); 2.40 (s, 1H); 1.91–1.70 (m, 4H); 1.51–1.31 (m, 8H); 0.96–0.89 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 171.74$; 83.42; 63.89; 51.91; 41.58; 39.20; 38.41; 27.51; 27.10; 22.67; 22.63; 13.66; 13.59.

4.2.6. (*R*)-Isopropyl 2,2-dibutylthiazolidine-4-carboxylate 2h. Yield: 71%; ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 5.09$ (sept, $J = 6.2$ Hz, 1H); 3.98 (dd, $J^1 = 7.36$ Hz, $J^2 = 6.7$ Hz, 1H); 3.30 (dd, $J^1 = 10.3$ Hz, $J^2 = 6.7$ Hz, 1H); 2.86–2.76 (m, 2H); 1.91–1.67 (m, 4H); 1.51–1.25 (m, 14H); 0.96–0.90 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 171.13$; 83.84; 68.90; 64.36; 41.85; 39.36; 38.73; 27.69; 27.29; 22.86; 22.83; 21.56; 21.52; 13.86; 13.79.

4.3. General procedure for the synthesis of compounds 2i

The same procedure was used for the synthesis of compounds **2c**–**h**. Yield: 96%; ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.42$–7.20 (m, 10H); 5.76 (s, $1H_{cis}$); 5.51 (s, $1H_{trans}$); 4.19–4.12 (m, $1H_{cis}$); 3.97–3.89 (m, $1H_{trans}$); 3.70 (2s, 6H, OCH_3 *cis* and *trans*); 3.43–3.01 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.54; 170.95; 140.70; 137.74; 128.05; 127.79; 127.24; 126.88; 126.41; 71.89; 70.31; 64.86; 63.78; 51.89; 51.80; 38.49; 37.51.

4.4. General procedure for the synthesis of compounds 4

The same procedure was used for the synthesis of compounds **2c**–**h**. Yield: 57%; ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 5.10$ (sept, $J = 6.2$ Hz, 1H); 3.80 (s, 1H); 3.03 (s, 1H); 1.85–1.74 (m, 4H); 1.60 (s, 3H); 1.31–1.26 (m, 14H); 1.21 (s, 3H); 0.95–0.90 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 169.36$; 80.48; 72.55; 68.89; 58.87; 42.67; 40.82; 28.86; 27.90; 27.86; 27.34; 23.04; 23.00; 21.91; 21.86; 14.03; 13.96.

4.5. General procedure for asymmetric aryl transfer reactions

Diethylzinc (3.6 mmol, toluene solution) was added dropwise to a solution of boronic acid (1.2 mmol) in toluene (2 mL) under an argon atmosphere. After stirring for 12 h at 60 °C, a toluene solution of chiral thiazolidine **2i** (20 mol %) was introduced. The reaction was stirred for an additional 15 min and the aldehyde (0.5 mmol) was subsequently added. After stirring overnight, the reaction was quenched with water and the aqueous layer was extracted with dichloromethane.

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