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Enantioselective synthesis of chiral γ-aryl α-keto ester by copper-catalyzed 1,4-conjugate addition using D_2-symmetric biphenyl phosphoramidite ligand

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ABSTRACT

Cu-catalyzed enantioselective 1,4-conjugate addition of β,γ-unsaturated α-keto ester compound was carried out to afford chiral γ-substituted γ-aryl α-keto ester, which could be conveniently converted to the potential skeleton of new Pril drugs. Up to 81% ee and 99% yield were afforded for the 1,4-conjugate addition using D_2-symmetric biphenyl phosphoramidite ligand.

1. Introduction

Inhibitors of angiotensin converting enzyme (ACE-inhibitors), also known as Pril drugs, were efficient for treating high blood pressure (hypertension), congestive heart failure, and preventing strokes. Lots of Pril drugs have been developed in the past few decades due to their high efficiency versus low kidney damage in people with hypertension.[1,2] Typically, almost all the Pril drugs were made of two parts, a peptide moiety and an (*S*)-homophenyl-alanine moiety, which could be introduced starting from (*R*)-2-hydroxy-4-phenylbutyrate.[2] For the development of new Pril drugs, many efforts have been focused on the modification of their peptide moiety so far, while no example was reported on the modification of (*S*)-homophenyl-alanine moiety.[1,2] In fact, the introduction of new functional group to the later could enhance the drug effect and broaden the scope of ACE-inhibitors.

On the other hand, the copper-catalyzed 1,4-conjugate addition of α,β-unsaturated carbonyl and/or nitro compounds is a powerful way to construct chiral β-substituted carbonyl and/or nitro compounds.[3–6] Amongst the reported catalyst systems in the asymmetric 1,4-conjugate addition, chiral phosphoramidite ligands, such as central chiral ligands **L1** derived from TADDOL backbone[4] and C_2-symmetric chiral ligands **L2** and **L3** with biaryl backbones derived from BINOL[5] and Biphenol,[6] respectively, were tested to be the most efficient ones with good to excellent results (Fig. 1). Recently, our group have developed a new type of D_2-symmetric biphenyl phosphoramidite ligand **L4**, which afforded one of the best asymmetric catalytic results in the asymmetric 1,4-conjugate addition of diethylzinc to α,β-unsaturated ketones and nitroalkene due to their symmetry and easier modification on 3,3′,5,5′-positions of biphenol backbone.[7]

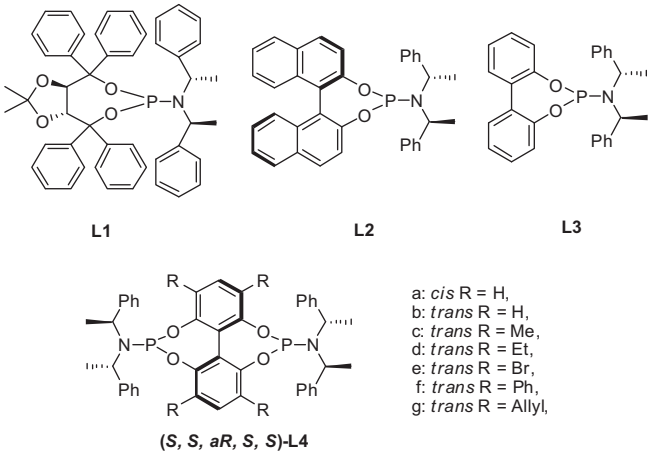

Fig. 1. Some chiral phosphoramidite ligands.

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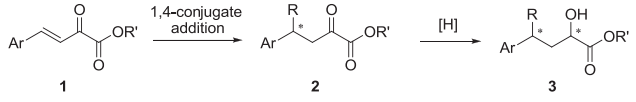
Therefore, we want to carry out the copper-catalyzed enantioselective 1,4-conjugate addition of β,γ-unsaturated α-keto ester compound **1** to afford γ-substituted γ-aryl α-keto ester compound **2**, which could be easily converted to series of chiral 4-substituted 2-hydroxy-4-arylbutyrate **3** (Scheme 1).[2a] Compound **3** may be a potential important intermediate for new Pril drug development as mentioned above. Here, we report our results on the copper-catalyzed asymmetric 1,4-conjugate addition of **1** with a series of chiral phosphoramidite ligands including our D_2-symmetric ones.

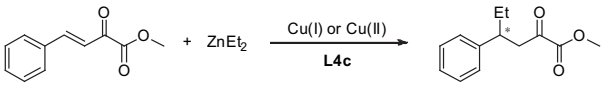


Scheme 1.

2. Results and discussion

Compound **1** could be easily prepared from pyruvic acid and corresponding aromatic aldehyde through aldol reaction.[8] Then we used compound **1** as the substrate in the copper-catalyzed asymmetric 1,4-conjugate addition with Et_2Zn (Table 1, entry 1). Firstly, different temperatures were screened in the asymmetric 1,4-conjugate addition with Cu(II)$(OAc)_2$-**L4c** as catalytic system in toluene (Table 1, entries 1–5). The catalytic system showed high reactivity and the reaction completed in 2 h. The enantioselectivity increased gradually with decreasing the temperature from rt to −20 °C (Table 1, entries 1–3). Further decreased the temperature, however, the enantioselectivity declined (entry 4). It is interesting that the configuration was reversed at −78 °C (entry 5). This phenomenon had also been reported by Sibi and Casey groups.[9]

Table 1
Condition optimization of 1,4-conjugate addition reaction[a]



Entry	Cu salt	Solvent	Temp (°C)	Yield[b](%)	ee(%)[c]
1	Cu(II)$(OAc)_2\cdot H_2O$	Toluene	rt	81	58
2	Cu(II)$(OAc)_2\cdot H_2O$	Toluene	0	85	64
3	Cu(II)$(OAc)_2\cdot H_2O$	Toluene	−20	88	68
4	Cu(II)$(OAc)_2\cdot H_2O$	Toluene	−30	92	66
5	Cu(II)$(OAc)_2\cdot H_2O$	Toluene	−78	16	−19
6	Cu(II)Br_2	Toluene	−20	70	29
7	Cu(II)$ClO_4\cdot 6H_2O$	Toluene	−20	96	66
8	Cu(II)$(OTf)_2$	Toluene	−20	87	63
9	Cu(II)$(acac)_2$	Toluene	−20	96	64
10	Cu(II)$(Me_3CCO_2)_2$	Toluene	−20	99	68
11	Cu(I)TC	Toluene	−20	92	62
12	Cu(I)(C_6H_6)OTf	Toluene	−20	92	66
13	Cu(I)$(MeCN)_4PF_6$	Toluene	−20	79	65
14	Cu(I)$(MeCN)_4BF_4$	Toluene	−20	99	67
15	Cu(I)$(MeCN)_4ClO_4$	Toluene	−20	100	74
16	Cu(I)$(MeCN)_4ClO_4$	Et_2O	−20	90	69
17	Cu(I)$(MeCN)_4ClO_4$	THF	−20	88	67
18	Cu(I)$(MeCN)_4ClO_4$	DCM	−20	71	6
19	Cu(I)$(MeCN)_4ClO_4$	$PhCF_3$	−20	92	25
20	Cu(I)$(MeCN)_4ClO_4$	DMF	−20	20	67

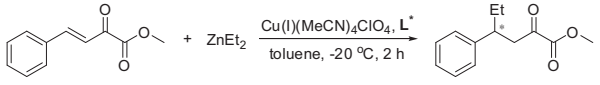
[a] Cu salt (2 mol %), 4 mol % **L4c**, 1.5 equiv $ZnEt_2$, the reaction completed in 2 h.
[b] Determined by ^1H NMR spectroscopy.
[c] Determined by HPLC, Chiralcel OJ-H column: *i*-PrOH/hexane 10/90, 1 mL/min, 210 nm.

Then, the effects of copper salts on the reaction were investigated at −20 °C with toluene as solvent (Table 1, entries 6–15). Among the examined copper salts, Cu(I)$(MeCN)_4ClO_4$ was the best one according to the yield and enantioselectivity (entry 15).

Next, different solvents were screened with the above optimal reaction conditions (Table 1, entries 15–20). The results showed that high yields and enantioselectivities were obtained with solvents, such as toluene, Et_2O, THF (entries 15–17). On the contrary, when the reaction carried out in solvents, such as DCM, $PhCF_3$, DMF, very low yields or very low ee values were given (entries 18–20). Based on the above results, the optimal reaction conditions were that Cu(I)$(MeCN)_4ClO_4$ was used as copper source, toluene was used as solvent and the reaction was conducted at −20 °C.

Finally, a series of phosphoramidite ligands were applied in the catalytic reaction using the above optimized reaction conditions (Table 2). Moderate catalytic activities and low enantioselectivities were provided with (−)-TADDOL-derived central chiral monophosphoramidite ligand **L1**, axial chiral monophosphoramidite ligand **L2** and **L3** (entries 1–3). To our delight, much better results were achieved by using D_2-symmetric axial dibridged phosphoramidite ligand **L4** (entries 4–10). The ligand **L4** with trans configuration has better catalytic effect compared to that with cis configuration (entries 4 and 5). It was found that the substituted group on 3,3′,5,5′-positions had a very important effect not only on enantioselectivity but also on absolute configuration of the products. When the substituted group on 3,3′,5,5′-positions was H, −60% ee value was obtained (entry 5). As increased size of substituted group to methyl, the steric hindrance increased. It was interesting to find that the configuration of product reversed and 74% ee value was obtained (entry 6). When the size of substituted group continuously increased to ethyl, the steric hindrance increased further and a −54% ee value was obtained (entry 7). These results were also consistent with our previous research.[7] If the substituted groups were changed to Br and Ph, 32% and 30% ee values were obtained, respectively (entries 8 and 9). When the substituted group was changed to allyl, a nearly racemic catalytic product was obtained (entry 10). These results suggest that the reversal of the product's configuration could be controlled by adjusting different functional group, which were rarely reported.[7,10]

Table 2
Optimization of ligands used in 1,4-conjugate addition reaction to **1a**[a]



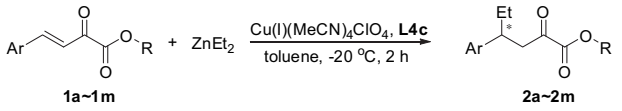
Entry	Ligand	Yield(%)[b]	ee(%)[c]
1	**L1**	45	6
2	**L2**	52	29
3	**L3**	62	48
4	*cis-aR*-**L4a**	48	−39
5	*trans-aR*-**L4b**	90	−60
6	*trans-aR*-**L4c**	100	74
7	*trans-aR*-**L4d**	67	−54
8	*trans-aR*-**L4e**	57	32
9	*trans-aR*-**L4f**	55	30
10	*trans-aR*-**L4g**	18	2

[a] Cu salt (2 mol %), 4 mol % ligand, 1.5 equiv $ZnEt_2$.
[b] Determined by ^1H NMR spectroscopy.
[c] Determined by HPLC, Chiralcel OJ-H column: *i*-PrOH/hexane 10/90, 1 mL/min, 210 nm.

With the optimized reaction conditions in hand, we investigated the scope of substrates using Cu(I)$(MeCN)_4ClO_4$-**L4c** as catalytic system in toluene at −20 °C and the results were shown in Table 3.

With the increase of the size of alkyl groups R at keto ester side, the enantioselectivity decreased (Table 3, entries 1 and 2). When the R group was changed to benzyl, the configuration of the product

Table 3
Substrates scope of enantioselective 1,4-addition reaction[a]



1a~1m 2a~2m

Entry	Substrate	Ar	R	Yield[b](%)	ee(%)[c]
1	**1a**	Ph	Me	100	74
2	**1b**	Ph	Et	50	46
3	**1c**	Ph	Bn	84	−71
4	**1d**	4-MePh	Me	99	59
5	**1e**	3-MePh	Me	99	60
6	**1f**	2-MePh	Me	49	18
7	**1g**	4-OMePh	Me	78	61
8	**1h**	4-ClPh	Me	88	71
9	**1i**	4-BrPh	Me	99	81
10	**1j**	4-FPh	Me	97	71
11	**1k**	4-NO_2Ph	Me	96	ND[d]
12	**1l**	β-Naph	Me	72	57
13	**1m**	Furan	Me	61	6

[a] Cu salt (2 mol %), 4 mol % **L4c**, 1.5 equiv $ZnEt_2$.
[b] Determined by ^1H NMR spectroscopy.
[c] Determined by HPLC, Chiralcel OJ-H column: *i*-PrOH/hexane 10/90, 1 mL/min, 210 nm.
[d] ND=Not Detected.

even reversed and up to −71% ee was obtained (entry 3). It was worth noting that the steric hindrance on the aryl group had an obvious impact on catalytic reactivity and enantioselectivity (entries 4–6). The *para* and *meta* orientated substrates provided good reactivities and moderate enantioselectivities, respectively (entries 4 and 5), while *ortho* orientated substrate **1f** resulted in 49% yield and 18% ee value (entry 6). Then substrates possessing substituted benzene ring with different electron natures were examined (entries 4–11). The substrate with electron donating group achieved slightly lower enantioselectivity (entries 4, 7). However, substrates with electron withdrawing groups gave an obviously increase on enantioselectivities (entries 8–10). When the *para* position of the benzene ring was substituted by Br, up to 81% ee was achieved (entry 9). For the naphthyl substrate **1l**, only a moderate enantioselectivity was obtained (entry 12). Unfortunately, for the furan substrate **1m**, only low enantioselectivity was provided with a moderate yield (entry 13). Pyridine substrate was also investigated, but the reaction did not occur since its poor solubility.

3. Conclusion

In conclusion, we have developed a new method to prepare series of chiral γ-substituted γ-aryl α-keto ester **2** via copper-catalyzed asymmetric 1,4-conjugate addition with optimized reaction system. Up to 81% ee and 99% yield were obtained by using D_2-symmetric phosphoramidite ligand **L4c**. The chiral product could be easily converted to series of 4-substituted chiral (*S*)-α-hydroxyl-4-phenylbutyrate, a potential skeleton of new Pril drugs.

4. Experimental section

4.1. General

Commercially available reagents were used without further purification other than those detailed below. Substrates **1** were prepared according to modified methods of reported proceedings.[8]

All air- and moisture-sensitive manipulations were carried out with standard Schlenk techniques under nitrogen. Toluene, DMF, THF, Et_2O, dichloromethane, and CF_3Ph were dried according to published procedures. The commercially available reagents were used without further purification. Column chromatography was run on silica gel (100–200 mesh). ^1H NMR (400 MHz) spectra and ^{13}C NMR (100 MHz) spectra were obtained on a Varian MERCURY plus-400 spectrometer. HRMS was performed on a Micromass LCT TM at the Instrumental Analysis Center of Shanghai Jiao Tong University.

4.2. Procedures and analytical data

4.2.1. Preparation of the substrates. All substrates **1** were prepared according to literature.[8]

4.2.2. General procedure for copper-catalyzed conjugate addition by $ZnEt_2$. General procedures for conjugate addition: the flame dried Schlenk tube was charged with $Cu(MeCN)_4ClO_4$ 1.64 mg (0.010 mmol) and 2 equiv of ligand (0.020 mmol) under nitrogen, and the mixture was dissolved in dry toluene (0.5 mL), resulting a colorless solution. The solution was stirred at 25 °C for 2 h and then cooled to −20 °C. The substrate **1** (1.0 mmol dissolved in 1.0 mL dry toluene) was then added dropwise within 3 min. The solution was stirred for 5 min at −20 °C and gradually turned to light yellow. Diethylzinc (1.5 mmol, 3.4 mL of 1 M sol in hexane) was added dropwise within 3 min. The reaction mixture was stirred at −20 °C for 2 h till full conversion monitored by TLC. Then the system was quenched by aqueous satd NH_4Cl and extracted with ethyl acetate (5 mL×2), the organic solution was concentrated and the residue was purified by silica gel column chromotography to afford the product **2**. Enantiomeric excess was determined by chiral HPLC.

*4.2.2.1. Methyl 2-oxo-4-phenylhexanoate (**2a**).* Light yellow oil; 100% yield and 74% ee; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30–7.09 (m, 5H), 3.78 (s, 3H), 3.22 (m, 2H), 3.15–3.09 (m, 1H), 1.70–1.52 (m, 2H), 0.78 (q, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.41, 143.27, 128.69, 128.57, 128.28, 126.78, 53.14, 46.14, 42.50, 29.48, 20.74, 12.13; HRMS (Q-TOF Premier) calcd for $C_{13}H_{16}O_3$ $[M-H]^-$ 219.1021, found: 219.1007. HPLC conditions: Chiralcel OJ-H column, *i*-PrOH/hexane 10/90, flow rate: 1 mL/min, UV detection at 210 nm; Retention time: t_{major}=20.2 min, t_{minor}=32.0 min.

*4.2.2.2. Methyl 2-oxo-4-phenylhexanoates (**2b**).* Light yellow oil; 50% yield and 46% ee; ^1H NMR (400 MHz, $CDCl_3$): δ 7.29–7.26 (m, 2H), 7.21–7.17 (m, 3H), 4.23 (q, *J*=7.06 Hz, 2H), 3.19–3.14 (m, 2H), 3.15–3.09 (m, 1H), 1.71–1.57 (m, 2H), 1.30 (q, 3H), 0.79 (q, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.82, 161.28, 143.70, 128.67, 127.82, 126.75, 62.57, 46.09, 42.59, 29.49, 14.15, 12.12; HRMS (Q-TOF Premier) calcd for $C_{14}H_{18}O_3$ $[M+Na]^+$ 257.1154, found: 257.1158. HPLC conditions: Chiralcel OJ-H column, *i*-PrOH/hexane 10/90, flow rate: 1 mL/min, UV detection at 210 nm; Retention time: t_{major}=13.30 min, t_{minor}=19.83 min.

*4.2.2.3. Benzyl 2-oxo-4-phenylhexanoate (**2c**).* Light yellow oil; 84% yield and −71% ee; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (s, 5H), 7.28–7.25 (m, 2H), 7.2–7.14 (m, 3H), 5.20 (s, 2H), 3.19–3.13 (m, 2H), 3.14–3.04 (m, 1H), 1.72–1.58 (m, 2H), 0.78 (q, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.41, 143.61, 128.97, 128.89, 128.84, 128.69, 127.80, 126.78, 68.08, 46.26, 42.60, 29.49, 12.12; HRMS (Q-TOF Premier) calcd for $C_{19}H_{20}O_3$ $[M-H]^-$ 295.1334, found: 295.1350. HPLC conditions: Chiralcel OJ-H column, *i*-PrOH/hexane 10/90, flow rate: 1 mL/min, UV detection at 210 nm; Retention time: t_{minor}=42.88 min, t_{major}=45.76 min.

*4.2.2.4. Methyl 2-oxo-4-p-tolylhexanoate (**2d**).* Light yellow oil; 99% yield and 59% ee; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26–7.04 (m, 4H), 3.79 (s, 3H), 3.19–3.11 (m, 2H), 3.10–3.04 (m, 1H), 2.30 (s, 3H), 1.70–1.57 (m, 2H), 0.78 (q, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.47, 161.64, 140.55, 136.25, 129.37, 127.65, 53.07, 46.26, 42.13,

29.51, 21.22, 12.13; HRMS (Q-TOF Premier) calcd for $C_{14}H_{18}O_3$ $[M+Na]^+$ 257.1154, found: 257.1158. HPLC conditions: Chiralcel OJ-H column, *i*-PrOH/hexane 10/90, flow rate: 1 mL/min, UV detection at 210 nm; Retention time: t_{major}=12.38 min, t_{minor}=20.48 min.

*4.2.2.5. Methyl 2-oxo-4-m-tolylhexanoate (**2e**).* Light yellow oil; 99% yield and 60% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19–7.15 (t, J=7.6 Hz, 1H), 7.01–6.96 (m, 4H), 3.79 (s, 3H), 3.19–3.12 (m, 2H), 3.10–3.02 (m, 1H), 2.32 (s, 3H), 1.71–1.57 (m, 2H), 0.79 (q, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.42, 161.64, 143.61, 138.19, 128.61, 128.55, 127.52, 124.76, 53.07, 46.18, 42.44, 29.46, 21.68, 12.17; HRMS (Q-TOF Premier) calcd for $C_{14}H_{18}O_3$ $[M+Na]^+$ 257.1154, found: 257.1154. HPLC conditions: Chiralcel OJ-H column, *i*-PrOH/hexane 10/90, flow rate: 1 mL/min, UV detection at 210 nm; Retention time: t_{major}=10.05 min, t_{minor}=12.28 min.

*4.2.2.6. Methyl 2-oxo-4-o-tolylhexanoate (**2f**).* Light yellow oil; 49% yield and 18% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17–7.08 (m, 4H), 3.79 (s, 3H), 3.44 (m, 1H), 3.24–3.06 (m, 2H), 2.37 (s, 3H), 1.71–1.58 (m, 2H), 0.79 (q, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.51, 161.59, 142.02, 136.53, 130.59, 126.45, 126.33, 125.78, 53.09, 45.92, 36.82, 29.52, 20.02, 11.93; HRMS (Q-TOF Premier) calcd for $C_{14}H_{18}O_3$ $[M+Na]^+$ 257.1154, found: 257.1149. HPLC conditions: Chiralcel OJ-H column, *i*-PrOH/hexane 10/90, flow rate: 1 mL/min, UV detection at 210 nm; Retention time: t_{major}=13.42 min, t_{minor}=28.40 min.

*4.2.2.7. Methyl 4-(4-methoxyphenyl)-2-oxohexanoate (**2g**).* Light yellow oil; 78% yield and 61% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10–7.06 (m, 2H), 6.84–6.8 (m, 2H), 3.78 (s, 3H), 3.77 (s, 3H), 3.16–3.07 (m, 2H), 3.08–3.02 (m, 1H), 1.69–1.54 (m, 2H), 0.78 (q, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.51, 161.64, 158.39, 135.61, 128.71, 128.68, 114.04, 55.41, 53.08, 53.07, 46.37, 41.79, 29.64, 12.13; HRMS (Q-TOF Premier) calcd for $C_{14}H_{18}O_4$ $[M-H]^-$ 249.1127, found: 249.1124. HPLC conditions: Chiralcel OJ-H column, *i*-PrOH/hexane 10/90, flow rate: 1 mL/min, UV detection at 210 nm; Retention time: t_{major}=25.61 min, t_{minor}=31.12 min.

*4.2.2.8. Methyl 4-(4-chlorophenyl)-2-oxohexanoate (**2h**).* Light yellow oil; 88% yield and 71% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (s, 2H), 7.11–7.06 (m, 2H), 3.78 (s, 3H), 3.17–3.10 (m, 2H), 3.10–3.03 (m, 1H), 1.78–1.58 (m, 2H), 0.77 (q, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.97, 161.48, 142.14, 132.42, 129.18, 128.84, 128.81, 53.19, 45.98, 41.86, 29.44, 12.06; HRMS (Q-TOF Premier) calcd for $C_{13}H_{15}ClO_3$ $[M-H]^-$ 253.0653, found: 253.0648. HPLC conditions: Chiralcel OJ-H column, *i*-PrOH/hexane 10/90, flow rate: 1 mL/min, UV detection at 210 nm; Retention time: t_{major}=12.13 min, t_{minor}=14.47 min.

*4.2.2.9. Methyl 4-(4-bromophenyl)-2-oxohexanoate (**2i**).* Light yellow oil; 99% yield and 81% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, J=8.8 Hz, 2H), 7.06–7.04 (d, J=8.4 Hz, 2H), 3.79 (s, 3H), 3.17–3.10 (m, 2H), 3.11–3.05 (m, 1H), 1.68–1.58 (m, 2H), 0.77 (q, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.93, 161.47, 142.68, 131.79, 131.76, 129.58, 120.49, 53.18, 45.92, 41.91, 29.37, 12.05; HRMS (Q-TOF Premier) calcd for $C_{13}H_{15}BrO_3$ $[M-H]^-$ 297.0126, found: 297.0123. HPLC conditions: Chiralcel OJ-H column, *i*-PrOH/hexane 10/90, flow rate: 1 mL/min, UV detection at 210 nm; Retention time: t_{major}=11.51 min, t_{minor}=12.99 min.

*4.2.2.10. Methyl 4-(4-fluorophenyl)-2-oxohexanoate (**2j**).* Light yellow oil; 97% yield and 71% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, J=8.8 Hz, 2H), 6.97–6.93 (d, J=8.4 Hz, 2H), 3.77 (s, 3H), 3.16–3.09 (m, 2H), 3.10–3.05 (m, 1H), 1.68–1.57 (m, 2H), 0.76 (q, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.14, 161.53, 139.27, 129.24, 129.27, 115.59, 115.37, 53.16, 46.20, 41.78, 29.60, 12.07; HRMS (Q-TOF Premier) calcd for $C_{13}H_{15}FO_3$ $[M+Na]^+$ 261.0903, found: 261.0905. HPLC conditions: Chiralcel OJ-H column, *i*-PrOH/hexane 10/90, flow rate: 1 mL/min, UV detection at 210 nm; Retention time: t_{major}=13.83 min, t_{minor}=18.25 min.

*4.2.2.11. Methyl 4-(4-nitrophenyl)-2-oxohexanoate (**2k**).* Light yellow oil; 96% yield, the ee has not been detected; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15–8.13 (d, J=8.4 Hz, 2H), 7.36–7.34 (d, J=8.4 Hz, 2H), 3.81 (s, 3H), 3.25–3.20 (m, 2H), 3.20–3.10 (m, 1H), 1.79–1.70 (m, 2H), 0.79 (q, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.33, 161.27, 151.62, 134.87, 128.73, 128.30, 127.47, 124.17, 124.00, 53.31, 45.54, 42.12, 29.29, 12.01; HRMS (Q-TOF Premier) calcd for $C_{13}H_{15}NO_5$ $[M-H]^-$ 264.0872, found: 264.0880.

*4.2.2.12. Methyl 4-(naphthalen-2-yl)-2-oxohexanoate (**2l**).* Light yellow oil; 72% yield and 57% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81–7.78 (m, 3H), 7.63 (s, 1H), 7.48–7.41 (m, 2H), 7.35–7.33 (dd, J_1=1.2 Hz, J_2=2 Hz, 1H), 3.75 (s, 3H), 3.35–3.26 (m, 2H), 3.25–3.16 (m, 1H), 1.82–1.72 (m, 2H), 0.82 (q, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.29, 141.04, 133.65, 132.62, 128.46, 127.86, 127.81, 126.61, 126.24, 125.91, 125.70, 53.10, 46.14, 42.64, 29.38, 12.21; HRMS (Q-TOF Premier) calcd for $C_{17}H_{18}O_3$ $[M-H]^-$ 269.1178, found: 269.1158. HPLC conditions: Chiralcel OJ-H column, *i*-PrOH/hexane 10/90, flow rate: 1 mL/min, UV detection at 210 nm; Retention time: t_{major}=27.27 min, t_{minor}=31.89 min.

*4.2.2.13. Methyl 4-(furan-2-yl)-2-oxohexanoate (**2m**).* Light yellow oil; Obtained 61% yield and 6% ee; ^{1}H NMR (400 MHz, DMSO): δ 7.60–7.57 (d, J=12 Hz, 1H), 6.53–6.42 (m, 1H), 6.19–6.15 (d, J=16 Hz, 1H), 3.78 (s, 3H), 3.32–3.30 (m, 1H), 1.71–1.65 (m, 2H), 0.80 (s, 3H); ^{13}C NMR (400 MHz, DMSO): δ 174.89, 152.37, 143.30, 130.45, 118.28, 112.30, 109.39, 77.74, 52.77, 32.91, 8.49; HRMS (EI) calcd for $C_{11}H_{14}O_4$ $[M-H]^+$ 209.0814, found: 209.0753. HPLC conditions: Chiralcel OJ-H column, *i*-PrOH/hexane 10/90, flow rate: 1 mL/min, UV detection at 210 nm; Retention time: t_{major}=11.14 min, t_{minor}=12.59 min.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.06.059.

References and notes

1. For selected reviews, see: (a) Ondetti, M. A.; Cushman, D. W.; Rubin, B. In *Chronicles of Drug Discovery*; Bindra, J. S., Lednicer, D., Eds.; John: New York, NY, 1983; Vol 2, p 1; (b) Garrison, J. C.; Peach, M. J. In *The Pharmacological Basis of Therapeutics*, 8th ed.; Gilman, A. B., Goodman, L. S., Rall, T. W., Murad, F., Eds.; McGraw-Hill Book: Singapore, 1992; Vol 1, p 749; (c) Hendrik, S.; Dirk, H.; Mathias, R.; Roland, P.; Ralf, H.; Axel, S.; Justin, C.; Kuno, H.; Ursula, U. W.; Karl, W.; Michael, B. *Int. J. Cardiol.* **2010**, *140*, 296–303.
2. For selected papers, see: (a) Herold, P.; Indolese, A. F.; Studer, M.; Jalett, H. P.; Siegrist, U.; Blaser, H. U. *Tetrahedron* **2000**, *56*, 6497–6499; (b) Hornig, B.; Landmesser, U.; Kohler, C.; Ahlersmann, D.; Spiekermann, S.; Christoph, A.; Tatge, H.; Drexler, H. *Circulation* **2001**, *103*, 799–805; (c) Schieffer, B.; Bünte, C.; Witte, J.; Hoeper, K.; Boger, R.; Schwedhelm, E.; Drexler, H. *J. Am. Coll. Cardiol.* **2004**, *44*, 362–368.
3. (a) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771–808; (b) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033–8061; (c) Fleming, F. F.; Wang, Q. Z. *Chem. Rev.* **2003**, *103*, 2035–2078; (d) Syuzanna, R. H.; Tim, D. H.; Koen, G.; Adriaan, J. M.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824–2852.
4. Keller, E.; Maurer, J.; Naasz, R.; Schader, T.; Meetsma, A.; Feringa, B. L. *Tetrahedron: Asymmetry* **1998**, *9*, 2409–2413.

5. (a) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; De Vries, A. H. *Angew. Chem., Int. Ed.* **1997**, *36*, 2620–2623; (b) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346–353.
6. (a) Alexakis, A.; Rosset, B. S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262–5263; (b) Alexakis, A.; Polet, D.; Rosset, S.; March, S. *J. Org. Chem.* **2004**, *69*, 5660–5667.
7. (a) Zhang, H.; Fang, F.; Xie, F.; Yu, H.; Yang, G.; Zhang, W. *Tetrahedron Lett.* **2010**, *51*, 3119–3122; (b) Fang, F.; Zhang, H.; Xie, F.; Yang, G.; Zhang, W. *Tetrahedron* **2010**, *66*, 3593–3598.
8. (a) Stecher, E. D.; Ryder, H. F. *J. Am. Chem. Soc.* **1952**, *74*, 4392–4395; (b) Audrain, H.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2000**, *65*, 4487–4497; (c) Wu, Y. C.; Liu, L.; Li, H. J.; Wang, D.; Chen, Y. J. *J. Org. Chem.* **2006**, *71*, 6592–6595.
9. (a) Sibi, M. P.; Gorikunti, U. M.; Liu, M. *Tetrahedron* **2002**, *58*, 8357–8363; (b) Casey, C. P.; Martins, S. C.; Fagan, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 5585–5592.
10. Xie, F.; Liu, D.; Zhang, W. *Tetrahedron Lett.* **2008**, *49*, 1012–1015.