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Temperature dependent reversal of stereochemistry in enantioselective conjugate amine additions

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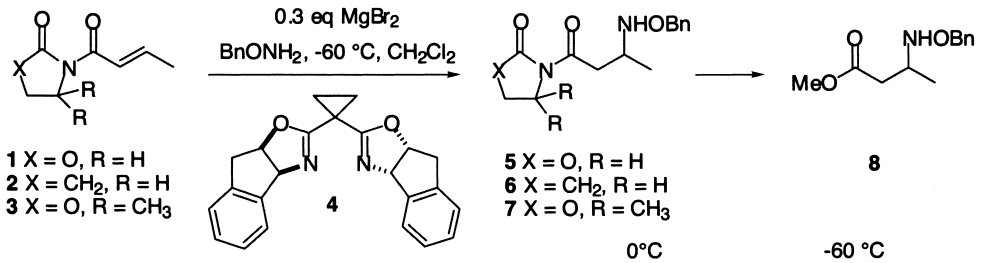
Abstract—Enoates derived from 4,4-disubstituted-2-oxazolidinones undergo enantioselective conjugate amine addition when mediated by a chiral Lewis acid derived from magnesium bromide and a bisoxazoline. The face selectivity in these amine additions is temperature dependent. They show an unusual reversal at two different temperatures.

Asymmetric synthesis using chiral Lewis acid catalysis continues to attract interest from organic chemists.[1] The principal strategy to access both enantiomers of the product has traditionally relied on the use of enantiomeric series of ligands as part of the chiral Lewis acid. This option could prove difficult when the enantiomeric ligands are either not readily available or one isomer is very expensive. Thus strategies involving modifications to the readily available chiral Lewis acid (Lewis acid+the more abundant and/or cheap enantiomer of the ligand) system such that both enantiomers of the product can be synthesized merits consideration. Lewis acid, additives, solvent, templates, and temperature have all been shown to play a key role in reversing selectivity in enantioselective transformations while using a chiral Lewis acid from a single chiral source.[2] In this context, reaction temperature,[3] a parameter that can be altered easily, is an ideal variant for careful consideration to synthesize both enantiomers.[4] We have recently shown β-amino acid derivatives can be readily prepared in high enantiomeric excess by the conjugate addition[5] of hydroxylamines to enoates using substoichiometric amounts of chiral Lewis acids.[6] During a breadth and scope study of this process we made the observation that variation of temperature led to reversal of enantioselectivity. Details of this interesting observation, is the focus of this paper.

We have previously shown that 3,5-dimethylpyrazole derived enoates undergo chiral Lewis acid-mediated conjugate *O*-benzylhydroxylamine addition with good chemical efficiency and high selectivity. The achiral template, 3,5-dimethylpyrazole, played a key role in this reaction.[7] As part of a more comprehensive study, we investigated the utility of oxazolidinone and pyrrolidinone templates in the conjugate additions (Scheme 1).[8] Addition of 1.1 equiv. *O*-benzylhydroxylamine to **1** using a chiral Lewis acid (30 mol%)[9] prepared from magnesium bromide



	0°C		-60 °C	
	%Yield	%ee	%Yield	%ee
5	99	66 (*R*)	99	66 (*R*)
6	96	68 (*R*)	97	71 (*R*)
7	79	50 (*R*)	80	43 (*S*)

Scheme 1.

Keywords: enantiomers; chiral Lewis acid; achiral template.

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Table 1. Reaction of **3** with chiral Lewis acid (30 mol%) derived from ligand **4**

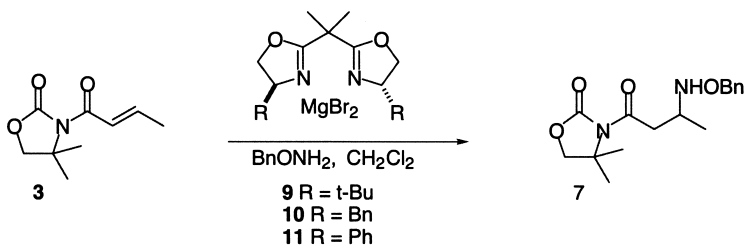
Entry	Lewis acid	Temperature (°C)	Time (h)	Yield[a] (%)	% ee (configuration)[b]
1	$MgBr_2$	rt	2	79	40 (*R*)
2	$MgBr_2$	0	3	85	50 (*R*)
3	$MgBr_2$	−20	8	82	27 (*R*)
4	$MgBr_2$	−40	14	82	23 (*S*)
5	$MgBr_2$	−60	48	80	43 (*S*)
6	$Mg(ClO_4)_2$	rt	4	78	25 (*S*)
7	$Mg(ClO_4)_2$	0	6	90	21 (*S*)
8	$Mg(ClO_4)_2$	−60	72	77	50 (*S*)
9	$Mg(OTf)_2$	rt	5	79	38 (*S*)
10	$Mg(OTf)_2$	0	7	91	35 (*S*)
11	$Mg(OTf)_2$	−60	48	83	*37 (S)*
12	MgI_2	rt	2.5	66	*09 (S)*
13	MgI_2	0	4	76	*31 (S)*
14	MgI_2	−60	60	89	37 (*S*)

[a] Isolated yields for column purified materials.
[b] The ee values determined by chiral HPLC analysis. The absolute configuration for the product was assigned by converting **8** to a known compound.

and bisoxazoline **4** at 0°C gave the conjugate addition product **5** in high yield and moderate selectivity. The configuration of the newly formed stereocenter in **5** was assigned as (*R*) by converting into the known ester **8**.[6a,8] Decreasing the temperature to −60°C did not lead to improvement in selectivity [66% ee, (*R*)]. Reactions with the pyrrolidinone enoate **2** gave similar results as **1** [high yields and moderate selectivity; 71% ee (*R*)]. In contrast, conjugate amine addition at 0°C to **3**, the crotonate derived from 4,4-dimethyloxazolidinone, gave **7** in good yield also with (*R*) configuration.[10] More interestingly, cooling the temperature to −60°C in amine addition to **3**, led to a reversal of product configuration [(*S*) product] from that observed for reaction at 0°C [(*R*) product]. Thus a simple change in reaction temperature led to products of opposite configuration using the same chiral Lewis acid.

In order to probe this unusual reversal of selectivity with change in reaction temperature, we then undertook a more detailed investigation of the effect of chiral Lewis acid in the conjugate addition using **3** as a substrate (Table 1). Initially the temperature where inversion[11] occurs was investigated by conducting reactions at several intermediate temperatures between room temperature and −60°C (entries 1–5) using magnesium bromide as the Lewis acid. Results from these experiments show that inversion occurs between −20 and −40°C (entries 3 and 4).[12] Varying the counterion of the magnesium Lewis acid also led to interesting outcomes. Conjugate additions with magnesium perchlorate as the Lewis acid were equally effective (entries 6–8), however, there was no inversion of configuration with change in reaction temperature. Similar results were obtained when magnesium triflate (entries 9–11) or magnesium iodide (entries 12–14) was used as the Lewis acid: no reversal of stereochemistry with change in reaction temperature. These results suggest a correlation between the ionicity of the Lewis acid and reversal of selectivity with temperature. The only Lewis acid which shows reversal is magnesium bromide, a reagent in which the counterion is least likely to dissociate from the metal. Reactions with magnesium iodide, perchlorate, or triflate, salts in which the counterion is more loosely held, shows no reversal of selectivity with temperature.[13]

To probe the effect of the chiral ligand in the conjugate amine addition, reactions with three other bisoxazolines (**9**–**11**) were undertaken (Scheme 2). Results from conjugate addition of *O*-benzylhydroxylamine to **3** mediated by a chiral Lewis acid derived from magnesium bromide and **9**–**11** are tabulated in Table 2. In contrast to moderate selectivity with the chiral Lewis acid derived from $MgBr_2$ and **4** (entries 1–3, data shown for comparison), the



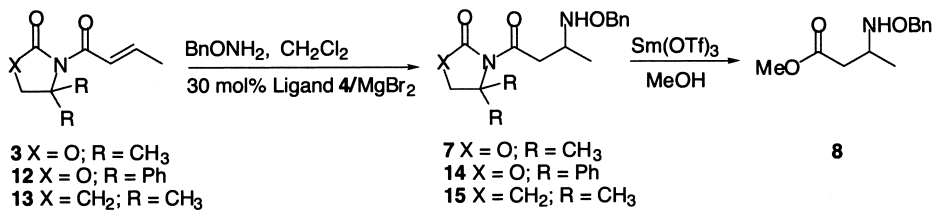
Scheme 2.

conjugate addition using the bulky bisoxazoline **9** as the ligand gave **7** in good yield but essentially as a racemic mixture (entry 4). Changes in the reaction temperature showed no improvement and **7** was obtained in low enantiomeric excess (entries 5 and 6). The reaction at −60°C was very slow. Conjugate additions using bisoxazoline **10** was equally ineffective with respect to selectivity (entries 7–9). However, reactions using bisoxazoline **11** was effective at rt and 0°C with ~40% ee values (entries 10 and 11). Cooling the reaction to −60°C resulted in a slow addition and the ee for the product was lower (15%) than for reactions at rt or 0°C (compare entry 10 or 11 with 12).

Table 2. Effect of chiral Lewis acid on reversal of selectivity

Entry	Ligand	Temperature (°C)	Yield[a] (%)	% ee (configuration)[b]
1	**4**	rt	79	40 (*R*)
2	**4**	0	85	50 (*R*)
3	**4**	−60	80	43 (*S*)
4	**9**	rt	66	8 (*S*)
5	**9**	0	69	14 (*S*)
6	**9**	−60	35 (38)[c]	8 (*S*)
7	**10**	rt	83	7
8	**10**	0	85	5
9	**10**	−60	19 (45)[c]	3
10	**11**	rt	90	41 (*S*)
11	**11**	0	94	47 (*S*)
12	**11**	−60	36 (40)[c]	15 (*S*)

[a] Isolated yields for column purified materials.
[b] The ee values determined by chiral HPLC analysis. The absolute configuration was determined by converting **7** to **8**.
[c] The number in parenthesis indicates the amount of recovered starting material.



Scheme 3.

Table 3. Effect of the template structure on selectivity

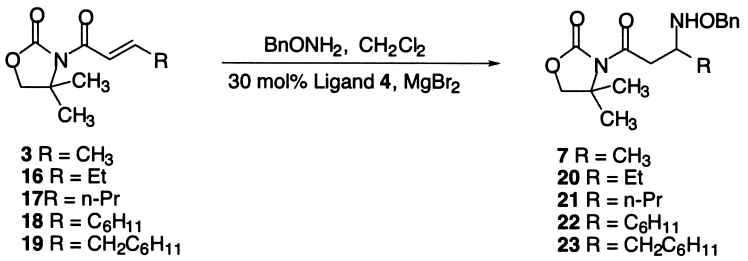
Entry	X	R	Temperature (°C)	Yield[a] (%)	% ee (configuration)[b]
1	O	Me	rt	79	40 (*R*)
2	O	Me	0	85	50 (*R*)
3	O	Me	−60	80	43 (*S*)
4	O	Ph	rt	93	30 (*R*)
5	O	Ph	0	85	37 (*R*)
6	O	Ph	−60	87	44 (*S*)
7	CH_2	Me	rt	48	28 (*R*)
8	CH_2	Me	0	62	30 (*R*)
9	CH_2	Me	−60	49	25 (*S*)

[a] Isolated yields for column purified materials.
[b] The ee values determined by chiral HPLC analysis. Compounds **7**, **14** and **15** were converted to **8** to establish stereochemistry (see Section 2).

These results indicate that reversal could occur with ligand **11** but more likely at a much lower temperature. The ligand study suggest that only **4** and **11** are effective in providing selectivity and of these two, only **4** shows reversal at practical temperatures.

the nature of the template (oxazolidinone or pyrrolidinone) has little impact on stereochemical outcome of the reaction.

The final set of experiments was designed to investigate the effect of the β-substituent of the enoate on reversal of selectivity with temperature (Scheme 4, Table 4). The 4,4-dimethyloxazolidinone template and the chiral Lewis acid derived from magnesium bromide and **4** were used in the study. Results from substrate **3** are included for easy comparison (entries 1–3). Conjugate amine addition to **16**, substrate with a β-ethyl substituent, was facile at the three different temperatures examined (entries 4–6). This substrate also showed reversal of selectivity with change in reaction temperature (compare entry 4 or 5 with 6). Similar reaction outcomes are evident with substrate **17** (entries 7–9) with a β-propyl substituent. The effect of size of the β-substituent on selectivity was also investigated. Reactions with **18** and **19** were efficient and these substrates also gave reversal of selectivity with change in temperature (entries



Scheme 4.

Having established that reactions with magnesium bromide and **4** were the most effective, the effect of alternate achiral templates with 4-substituents was investigated (Scheme 3). The results from these experiments are tabulated in Table 3. As discussed previously, reaction with **3** shows reversal of selectivity with change in temperature (entries 1–3). Conjugate addition to **12**, an oxazolidinone template with a 4-phenyl substituent,[14] was also effective giving product **14** in good yields at three different temperatures (entries 4–6). A reversal of selectivity with temperature was also observed with this template (compare entry 4 or 5 with 6). Reactions with the pyrrolidinone template **13**[15] was slightly less efficient (<60% yield; entries 7–9) at the three different temperatures investigated. This template also gave reversal of selectivity with change in temperature (compare entry 7 or 8 with 9) as was observed with **3** and **12**. The results from this study suggest that one of the requirements for reversal of selectivity with temperature is the presence of a substituent at the 4-position on the template. The size of the 4-substituent (methyl vs phenyl) or

Table 4. Effect of β-substituent on reversal of selectivity

Entry	R	Temperature (°C)	Yield[a] (%)	% ee[b]
1	Me	rt	79	40 (*R*)
2	Me	0	85	50 (*R*)
3	Me	−60	80	43 (*S*)
4	Et	rt	87	35 (−)[c]
5	Et	0	82	28 (−)[c]
6	Et	−60	83	53 (+)[c]
7	Pr	rt	56	40 (−)[c]
8	Pr	0	76	31 (−)[c]
9	Pr	−60	66	81 (+)[c]
10	C_5H_{11}	rt	69	22 (−)[c]
11	C_5H_{11}	0	79	35 (−)[c]
12	C_5H_{11}	−60	87	26 (+)[c]
13	$CH_2C_5H_{11}$	rt	74	25 (−)[c]
14	$CH_2C_5H_{11}$	0	89	29 (−)[c]
15	$CH_2C_5H_{11}$	−60	79	68 (+)[c]

[a] Isolated yields for column purified materials.
[b] The ee values determined by chiral HPLC analysis.
[c] The absolute stereochemistry for the product has not been established. Based on analogy, most likely reactions at higher temperature gives the *R* product. The sign of rotation is indicated.

10–15). A point of note is the high selectivity in the reaction with **17** at −60°C (entry 9). Results from these studies show that reversal of selectivity is independent of the nature of the substituent on the enoate. The stereochemistry for the products was established by converting the products to compounds of known configuration.[16]

1. Discussion and conclusions

The temperature of the reaction is an important variable in determining the levels of selectivity in both diastereo- and enantioselective transformations.[17] Generally, decreasing reaction temperature leads to an increase in selectivity. This has been attributed to higher activation–enthalpy contribution to the free energy of activation. In certain situations, an increase in reaction temperature also leads to higher selectivity.[18] In these cases, both activation–entropy and activation–enthalpy contribute to the free energy with entropy being the more dominant contributor. There are more examples of these anomalous reactions in the diastereoselective regime. In enantioselective transformations, higher selectivity at higher temperatures is not usually observed.[19] Even more rare are examples of reversal of enantioselectivity with changes in temperature.[20] Otera has previously shown that in chiral Lewis acid catalyzed acylation reactions of enantiotopic hydroxyl groups, face selectivity changes with temperature.[21] In a recent work on enantioselective conjugate thiol addition; Kanemasa has also observed reversal of selectivity with temperature.[22]

We do not have a comprehensive explanation for the temperature-dependent change in reaction enantioselectivity when $MgBr_2$ is used as Lewis acid in conjunction with ligand **4**. However, the most likely explanation is a temperature-dependent change in the coordination complex for magnesium. The coordination number for Mg^{2+} can vary from 4 to 6. While there is only one tetrahedral complex available if both the bidentate ligand and substrate are bound, there are multiple complexes possible if Mg^{2+} is either 5-coordinate (six different complexes possible) or 6-coordinate (five different octahedral complexes possible). All of these scenarios assume a bidentate coordination of the substrate. Thus, our analysis could be more complicated if one takes into consideration single point binding of the substrate. We do not believe that tetrahedral complexes contribute significantly under any of our reaction conditions in this paper. Factors most favorable to a low coordination number would be a weakly-basic/highly-dissociating counterion, high temperature, and steric bulk in either the ligand or the substrate or both. However, under conditions most favorable to a low coordination number (perchlorate or triflate as counterion, with the bulky ligand **4** and the bulky substrate **3** at room temperature), *S* configuration is actually observed (albeit weakly), which is contrary to the *R* configuration predicted by modeling of the tetrahedral complex. Thus we assume that reaction is proceeding from within the maze of available 5- and/or 6-coordinate complexes, and that the equilibrium population is strongly impacted by temperature only in the case of $MgBr_2$ when both the substrate and the ligand are bulky. The relatively low levels of stereoselectivity in the reactions of **3** is consistent with a situation where more than one complex may be present at a given temperature. At present, we believe that the temperature-dependent reversal in selectivity using $MgBr_2$ results from a change from an octahedral complex at low temperature, in which both bromides remain bound, to a 5-coordinate complex at higher temperature, in which one but not both bromides is dissociated. In the case of the less bulky substrates **1** and **2** (Scheme 1), bromide dissociation happens to a lesser degree, not enough to reverse the selectivity but enough to offset the expected improvement in *R* selectivity. That $MgBr_2$ gives different absolute stereochemistry with **1** and **2** than it does with the bulkier substrate **3** suggests that different octahedral complexes are involved. That reversal does not occur with ligands other than **4** (Table 2) may reflect that significant bromide dissociation requires a bulky ligand. When less basic counterions perchlorate, triflate, and iodide are used (Table 1) in conjunction with bulky substrate **3** and bulky ligand **4**, we suspect that counterion dissociation is extensive even at low temperature. A definitive answer for the unusual reversal with temperature needs further experimentation.

2. Experimental

Tetrahydrofuran and dichloromethane were dried by SOLV-TEK alumina column prior to use. Flash chromatography was performed using EM Science silica gel 60 (230–400 mesh). Melting points were determined using the Fisher–Johns melting point apparatus. Reactions with air sensitive materials were carried out by standard syringe techniques.

^{1}H NMR were recorded on a Varian Unity/Inova-500 NB (500 MHz). Chemical shifts are reported in parts per million (ppm) down field from TMS, using residual $CDCl_3$ (7.27 ppm) as an internal standard. ^{13}C NMR were recorded on a Varian Unity/Inova-500 NB (125 MHz) using broad band proton decoupling. Chemical shifts are reported in parts per million (ppm) down field from TMS, using the middle resonance of $CDCl_3$ (77.0 ppm) as an internal standard. HPLC analyses were carried out on a Waters 515 HPLC pump and a 2487 dual λ absorbance detector connected to a PC with millennium^{32} workstation. Rotations were recorded on a JASCO-DIP-370 instrument. High-resolution mass spectra (HRMS) were obtained at the Mass spectrometry Laboratory, Ohio State University, Columbus, OH.

The starting enoates[23] **1**–**3** and ligands[24] **4**, **9**, **10** have been reported in the literature. Ligand **11** was purchased from Aldrich.

2.1. General procedure for the preparation of starting materials. Compounds 12, 13, 16–19

To a stirred solution of the appropriate oxazolidinone (pyrrolidinone) in anhydrous THF (0.3 M) at −78°C was added 1.0 equiv. of *n*-BuLi. After 30 min, 1.1 equiv. of the appropriate acid chloride was added. The mixture was stirred at −78°C for 2–3 h. The reaction was quenched with saturated aqueous ammonium chloride, and the slurry was concentrated under reduced pressure. The residue was redissolved in CH_2Cl_2 and then washed with saturated

aqueous sodium bicarbonate. The combined organic extracts were washed with brine and dried over magnesium sulfate, then filtered, and solvent was removed under reduced pressure. The crude product was purified by flash column chromatography. Average yields of 90%.

2.1.1. Compound 12. Mp 150–152°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92 (d, J=6.8 Hz, 3H), 4.74 (s, 2H), 6.95–7.38 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 71.5, 78.8, 123.2, 127.9, 128.4, 128.7, 139.4, 147.3, 154.2, 165.0; HRMS exact mass calcd for $C_{19}H_{17}NO_3Na^+$ [M+Na$^+$]: 330.1100; found: 330.1127.

2.1.2. Compound 13. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 6H), 1.84–1.92 (m, 4H), 2.51 (t, J=8.0 Hz, 3H), 6.92–7.05 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.6, 26.6, 31.3, 34.8, 63.5, 126.1, 144.4, 167.4, 176.7; HRMS exact mass calcd for $C_{10}H_{15}NO_2Na^+$ [M+Na$^+$]: 204.0994; found: 204.1001.

2.1.3. Compound 16. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (t, J=7.4 Hz, 3H), 1.60 (s, 6H), 2.26–2.32 (m, 2H), 4.02 (s, 2H), 7.02–7.15 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.5, 24.9, 25.9, 60.7, 75.5, 121.6, 151.9, 154.4, 166.5; HRMS exact mass calcd for $C_{10}H_{15}NO_3Na^+$ [M+Na$^+$]: 220.0944; found: 220.0958.

2.1.4. Compound 17. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, J=7.3 Hz, 3H), 1.47–1.56 (m, 2H), 1.59 (s, 6H), 2.20–2.27 (m, 2H), 4.01 (s, 2H), 6.99–7.13 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 21.6, 24.9, 34.8, 60.7, 75.5, 122.5, 150.6, 154.4, 166.4; HRMS exact mass calcd for $C_{11}H_{17}NO_3Na^+$ [M+Na$^+$]: 234.1100; found: 234.1123.

2.1.5. Compound 18. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14–1.31 (m, 5H), 1.59 (s, 6H), 1.65–1.79 (m, 6H), 4.01 (s, 2H), 7.0–7.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 25.6, 25.9, 26.1, 29.0, 31.9, 32.5, 41.1, 60.8, 75.5, 119.3, 120.1, 155.6, 166.7; HRMS exact mass calcd for $C_{14}H_{21}NO_3Na^+$ [M+Na$^+$]: 274.1413; found: 274.1419.

2.1.6. Compound 19. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92–0.97 (m, 2H), 1.12–1.23 (m, 4H), 1.44–1.46 (m, 1H), 1.6 (s, 6H), 1.59–1.73 (m, 6H), 2.15 (t, J=6.7 Hz, 3H), 4.01 (s, 2H), 6.99–7.10 (m, 2H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.9, 26.4, 26.6, 33.4, 37.6, 40.7, 60.7, 75.5, 123.2, 149.7, 154.4, 166.3; HRMS calcd for $C_{15}H_{23}NO_3Na^+$ [M+Na$^+$]: 288.1570; found: 288.1578.

2.2. Representative experimental procedure for chiral Lewis acid catalyzed conjugate addition of *O*-benzylhydroxylamine to enoate (Table 1, entry 1)

Under N_2, a mixture of $MgBr_2$ (0.05 mmol) and bisoxazoline **4** (0.05 mmol) in CH_2Cl_2 (1 mL) was stirred at rt for 30 min. The crotonate (0.167 mmol) (in 1 mL CH_2Cl_2) was added and the mixture was allowed to stir for an additional 30 min at room temperature. The reaction was cooled to 0°C, then *O*-benzylhydroxylamine (0.184 mmol) (in 1 mL CH_2Cl_2) was added. The reaction was monitored by TLC and when judged complete was quenched with H_2O and extracted 2×CH_2Cl_2. The combined organics were dried ($MgSO_4$) and concentrated. The product was purified by silica gel chromatography. The enantiomeric purity was determined by HPLC.

2.2.1. Compound 5. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18 (dd, J=6.6, 0.7 Hz, 3H), 2.91 (dd, J=16.4, 4.4 Hz, 1H), 3.24 (dd, J=16.4, 8.0 Hz, 1H), 3.62–3.65 (m, 1H), 3.77–3.88 (m, 2H), 4.67 (s, 2H), 5.85 (bs, 1H), 7.27–7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.4, 39.8, 42.6, 53.3, 62.2, 76.7, 128.1, 128.6, 128.7, 137.8, 153.9, 172.4; HRMS exact mass calcd for $C_{14}H_{19}N_2O_4$ [M+H]$^+$: 279.1339; found: 279.1355; HPLC [(Column: Chiralcel AD (0.46 cm×25 cm) (from Daicel Chemical Ind., Ltd)] [254 nm; solvent: hexane/*i*-PrOH=85:15, flow rate=1 mL/min. t_R 17.0 min (*S*-isomer); t_R 19.2 min (*R*-isomer)].

2.2.2. Compound 6. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18 (d, J=6.5 Hz, 3H), 1.94–2.04 (m, 2H), 2.53 (t, J=8.2 Hz, 2H), 2.94 (dd, J=16.9, 4.8 Hz, 1H), 3.18 (dd, J=16.8, 7.7 Hz, 1H), 3.57–3.59 (m, 1H), 3.69–3.73 (m, 2H), 4.20–4.28 (m. 2H), 4.67 (s, 2H), 5.82 (bs, 1H), 7.26–7.33 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.3, 18.6, 33.9, 41.2, 45.6, 53.0, 76.8, 127.9, 128.5, 128.6, 138.1, 173.1, 175.7; HRMS exact mass calcd for $C_{15}H_{20}N_2O_3Na^+$ [M+Na]$^+$: 299.1366; found: 299.1373. HPLC [(Column: Chiralcel OJ (0.46 cm×25 cm) (from Daicel Chemical Ind., Ltd)] [254 nm; solvent: hexane/*i*-PrOH=85:15, flow rate=1 mL/min. t_R 20.8 min (*R*-isomer); t_R 27.4 min (*S*-isomer)].

2.2.3. Compound 7. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (d, J=6.5 Hz, 3H), 1.51 (s, 3H), 1.53 (s, 3H), 2.92 (dd, J=16.6, 5.0 Hz, 1H), 3.16 (dd, J=16.6, 7.6 Hz, 1H), 3.55–3.58 (m, 1H), 3.96 (s, 2H), 4.68 (s, 2H), 5.77 (bs, 1H), 7.26–7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.6, 24.9, 25.0, 41.4, 53.2, 60.6, 75.4, 76.8, 128.0, 128.6, 128.6, 138.1, 154.3, 173.1; HRMS exact mass calcd for $C_{16}H_{23}N_2O_4$ [M+H]$^+$: 307.1652; found: 307.1655. HPLC [Column: Chiralcel AD (0.46 cm×25 cm) (from Diacel Chemical Ind., Ltd)] [254 nm; solvent: hexane/*i*-PrOH=98:2, flow rate=1 mL/min. t_R 39 min; t_R 47 min].

2.2.4. Compound 14. Mp 40–42°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (d, J=6.4 Hz, 3H), 2.97 (dd, J=5.2, 16.8 Hz, 1H), 3.3 (dd, J=7.5, 16.9 Hz, 1H), 3.46–3.52 (m, 1H), 4.65 (s, 2H), 4.7 (dd, J=9.1, 20.7 Hz, 2H), 5.73 (bs, 1H), 7.26–7.36 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.7, 41.0, 52.9, 71.4, 76.8, 78.5, 127.8, 127.9, 127.9, 128.4, 128.5, 128.6, 128.7, 138.2, 139.4, 139.5, 154.2, 171.8; HRMS exact mass calcd for $C_{16}H_{22}N_2O_4Na^+$ [M+Na]$^+$: 453.1784; found: 453.1803. HPLC [Column: Chiralcel AD (0.46 cm×25 cm) (from Diacel Chemical Ind., Ltd)] [254 nm; solvent: hexane/*i*-PrOH=98:2, flow rate=1 mL/min. t_R 37 min; t_R 42 min].

2.2.5. Compound 15. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (d, J=6.4 Hz, 3H), 1.47 (s, 6H), 1.83 (t, J=8.5 Hz, 2H), 2.48 (t, J=8.0 Hz, 2H), 2.91 (dd, J=5.2, 17.3 Hz, 1H), 3.11 (dd, J=7.6, 16.9 Hz, 1H), 3.51–3.54 (m, 1H), 4.68 (s, 2H), 5.87 (bs, 1H,), 7.26–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.7, 26.6, 31.2, 34.6, 42.9, 53.1, 63.6, 127.9, 128.6, 138.2, 174.0, 176.5; HRMS exact mass calcd for $C_{17}H_{24}N_2O_3Na^+$ [M+Na]$^+$: 327.1679; found: 327.1670. HPLC [Column: Chiralcel OJ (0.46 cm×25 cm) (from Diacel Chemical Ind.,

Ltd.)] [254 nm; solvent: hexane/*i*-PrOH=98:2, flow rate=1 mL/min. t_R 25 min; t_R 40 min].

2.2.6. Compound 20. Mp 43–46°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, *J*=7.6 Hz, 3H), 1.49 (s, 3H), 1.52 (s, 3H), 1.58–1.66 (m, 2H), 2.96 (dd, *J*=4.4, 16.6 Hz, 1H), 3.13 (dd, *J*=8.4, 16.6 Hz, 1H), 3.30–3.35 (m, 1H), 3.95 (s, 2H), 4.66 (s, 2H), 5.87 (bs, 1H), 7.25–7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.8, 24.9, 25.0, 25.4, 39.5, 59.1, 60.6, 75.3, 76.6, 127.9, 128.5, 128.6, 138.2, 154.38, 173.5; HRMS exact mass calcd for $C_{17}H_{24}N_2O_4Na^+$ $[M+Na]^+$: 343.1628; found: 343.1643. HPLC [Column: Chiralcel OD (0.46 cm×25 cm) (from Diacel Chemical Ind., Ltd)] [254 nm; solvent: hexane/*i*-PrOH=49:1, flow rate=0.5 mL/min. t_R 43 min; t_R 52 min].

2.2.7. Compound 21. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.9 (t, *J*=7.3 Hz, 3H), 1.31–1.42 (m, 4H), 1.49 (s, 3H), 1.52 (s, 3H), 2.94 (dd, *J*=4.4, 16.5 Hz, 1H), 3.15 (dd, *J*=8.5, 16.5 Hz, 1H), 3.36–3.39 (m, 1H), 3.95 (s, 2H), 4.66 (s, 2H), 5.81 (bs, 1H), 7.26–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 19.6, 24.9, 25.0, 34.7, 39.9, 57.5, 60.7, 75.3, 76.6, 127.9, 128.5, 128.6, 138.2, 154.4, 173.5; HRMS exact mass calcd for $C_{18}H_{26}N_2O_4Na^+$ $[M+Na]^+$: 357.1784; found: 357.1808. HPLC [Column: Chiralcel OD (0.46 cm×25 cm) (from Diacel Chemical Ind., Ltd)] [254 nm; solvent: hexane/*i*-PrOH=49:1, flow rate=0.5 mL/min. t_R 32 min; t_R 40 min].

2.2.8. Compound 22. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96–1.27 (m, 5H), 1.46 (s, 3H), 1.51 (s, 3H), 1.55–1.81 (m, 6H), 2.97 (dd, *J*=3.6, 16.1 Hz, 1H), 3.08 (dd, *J*=9.3, 16.3 Hz, 1H), 3.25–3.29 (m, 1H), 3.93 (s, 2H), 4.63 (s, 2H), 5.86 (bs, 1H), 7.25–7.32 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.8, 24.9, 26.6, 26.7, 29.1, 29.9, 37.3, 39.7, 60.6, 62.4, 75.3, 76.3, 127.9, 128.5, 128.7, 138.3, 154.4, 173.9; HRMS exact mass calcd for $C_{21}H_{30}N_2O_4Na^+$ $[M+Na]^+$: 397.2097; found: 397.2106. HPLC [Column: Chiralcel OD (0.46 cm×25 cm) (from Diacel Chemical Ind., Ltd)] [254 nm; solvent: hexane/*i*-PrOH=49:1, flow rate=0.5 mL/min. t_R 24 min; t_R 29 min].

2.2.9. Compound 23. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86–0.93 (m, 2H), 1.63–1.35 (m, 6H), 1.49 (s, 3H), 1.52 (s, 3H), 1.65–1.68 (m, 5H), 2.88 (dd, *J*=4.4, 16.5 Hz, 1H), 3.18 (dd, *J*=8.1, 16.5 Hz, 1H), 3.46–3.54 (m, 1H), 3.95 (s, 2H), 4.65 (s, 2H), 5.8 (bs, 1H), 7.27–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 25.0, 26.4, 26.5, 26.8, 33.5, 33.8, 34.5, 40.3, 40.4, 55.2, 60.6, 75.3, 76.6, 127.9, 128.5, 128.7, 138.3, 154.4, 173.5; HRMS exact mass calcd for $C_{22}H_{32}N_2O_4Na^+$ $[M+Na]^+$: 411.2254; found: 411.2235. HPLC [Column: Chiralcel OD (0.46 cm×25 cm) (from Diacel Chemical Ind., Ltd)] [254 nm; solvent: hexane/*i*-PrOH=49:1, flow rate=0.5 mL/min. t_R 33 min; t_R 43 min].

2.3. Establishment of stereochemistry for the conjugate addition products

2.3.1. Compound 8. To a solution of **7** (120 mg, 0.39 mmol) (40% ee) dissolved in 5 mL of methanol was added $Sm(OTf)_3$ (70 mg, 0.12 mmol) and refluxed for 1 h. Solvent was removed under reduced pressure and the product was purified by silica gel chromatography to yield 80 mg (92%) of the desired product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (d, *J*=6.4 Hz, 3H), 2.36 (dd, *J*=5.6, 15.7 Hz, 1H), 2.59 (dd, *J*=6.9, 15.7 Hz, 1H), 3.46–3.52 (m, 1H), 3.65 (s, 3H), 4.69 (s, 2H), 7.25–7.35 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 38.9, 51.8, 53.2, 76.8, 128.1, 128.6, 137.9. $[\alpha]_D^{25}=-4.66$ (*c* 0.75, $CHCl_3$). HPLC [Column: Chiralcel OD (0.46 cm×25 cm) (from Diacel Chemical Ind., Ltd)] [254 nm; solvent: hexane/*i*-PrOH=49:1, flow rate=0.5 mL/min. t_R 23 min; t_R 28 min].

2.3.2. Compound 24. To a solution of methyl ester **8** (33% ee) (80 mg, 0.36 mmol) in 5 mL of THF and pyridine (0.11 mL, 1.11 mmol) was added benzoylchloride (0.13 mL, 1.43 mmol) dropwise and stirred for 45 min. The reaction was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The product was purified by SiO_2 chromatography to yield 108 mg (92%) of the desired product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (d, *J*=5.6 Hz, 3H), 2.52 (dd, *J*=5.6, 15.3 Hz, 1H), 2.86 (dd, *J*=8.0, 14.1 Hz, 1H), 3.67 (s, 3H), 4.69–4.78 (m, 3H), 7.18–7.65 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.7, 38.4, 52.1, 53.3, 78.5, 128.2, 128.5, 128.7, 129.0, 129.8, 130.9, 134.8, 135.2, 171.6. $[\alpha]_D^{25}=-9.0$ (*c* 0.82, $CHCl_3$). HPLC [Column: Chiralcel OD (0.46 cm×25 cm) (from Diacel Chemical Ind., Ltd)] [254 nm; solvent: hexane/*i*-PrOH=46:4, flow rate=0.5 mL/min. t_R 25 min; t_R 30 min].

2.3.3. Compound 25. To a solution of methyl ester **24** (38% ee) (50 mg, 0.15 mmol) in 5 mL THF was added 0.1 M THF solution of SmI_2 (7.3 mL, 0.73 mmol) until a blue color persisted. After 5 min, the reaction was diluted with CH_2Cl_2 and the combined organics washed with 1 M HCl, brine, and dried ($MgSO_4$). The product was purified by SiO_2 chromatography to yield 23 mg (70%) of the desired product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (d, *J*=6.7 Hz, 3H), 2.61 (dd, *J*=4.6, 15.9 Hz, 1H), 2.70 (dd, *J*=5.2, 16.1 Hz, 1H), 3.72 (s, 3H), 4.56–4.58 (m, 1H), 6.94 (brs, 1H), 7.42–7.51 (m, 3H), 7.77–7.79 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.2, 29.9, 39.7, 42.5, 51.9, 127.1, 128.7, 131.6, 134.8, 166.7, 172.8. HPLC [Column: Chiralcel OD (0.46 cm×25 cm) (from Diacel Chemical Ind., Ltd)] [254 nm; solvent: hexane/*i*-PrOH=45:5, flow rate=0.5 mL/min. t_R 43 min; t_R 47 min]. $[\alpha]_D^{25}=+15.0$ (*c* 0.57, $CHCl_3$); lit. $[\alpha]_D^{25}=-40.8$ (*c* 1.0, $CHCl_3$) (*S*) enantiomer (Amoroso, R.; Cardillo, G.; Sabatino, P.; Tomasini. C.; Trere, A. *J. Org. Chem.* **1993**, *58*, 5615); lit. $[\alpha]_D^{25}=-42$ (*c* 0.77, $CHCl_3$) (*S*) enantiomer (Esterman, H.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1824); lit. $[\alpha]_D^{25}=+35.7$ (*c* 1.04, $CHCl_3$) (*R*) enantiomer (Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615); The sign of the rotation for the final compound indicates that it has *R* configuration. The ee calculates to 39%, consistent with 40% ee for **7**.

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