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Asymmetric Lewis Acid Catalyzed Addition of Isocyanides to Aldehydes – Synthesis of 5-Amino-2-(1-hydroxyalkyl)oxazoles

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Stannous chloride efficiently catalyzes condensations between α-isocyanoacetamides (**1**) and a variety of aldehydes to afford the corresponding 5-amino-2-(1-hydroxyalkyl)-oxazoles (**3**) in good to excellent yields. The [Sn-(*R*)-Ph-PyBox](OTf)$_2$-catalyzed reaction between **1a** and 2-(benzyloxy)acetaldehyde (**2g**) shows an isoinversion effect, with the maximum enantiomeric excess of oxazole **3g** (80%) being obtained at –40 °C.

Introduction

Isocyanide-based multicomponent reactions (IMCRs) such as the classic Passerini (P-3CR)[1] and Ugi[2] (U-4CR) reactions have been widely used for generating molecular complexity and molecular diversity.[3] Furthermore, one chiral center is created in the course of these reactions, consequently providing the potential for the synthesis of chiral nonracemic compounds. Although several efficient diastereoselective P-3CRs[4] and U-4CRs[5] using chiral substrates or chiral auxiliaries have been developed,[6] progress on the development of enantioselective P-3CRs and U-4CRs has been slow in spite of the great efforts dedicated to these important reactions.[7] Denmark et al. reported the first examples of enantioselective Passerini-type reactions by combined use of silicon tetrachloride and a chiral Lewis base [chiral bis(phosphoramide)],[8] Dömling et al. screened a large number of metal/ligand combinations and found that the Ti/Taddol complex was capable of promoting the P-3CR, albeit with low to moderate enantioselectivity,[9] and Schreiber et al. developed a P-3CR catalyzed by an indane (PyBox)-Cu^{II} complex, affording the α-acyloxy-amides with good to excellent *ee* values when chelating aldehydes were used as reaction partners.[10]

We have recently developed a three-component synthesis of 5-aminooxazoles[11] based on the unique reactivity of α-isocyanoacetamides[12] and have subsequently devised a number of multicomponent syntheses of heterocycles[13] and macrocycles[14] by taking advantage of the reactivity of the transient 5-aminooxazoles. In view of the synthetic importance of oxazoles,[15] we were interested in rendering this reaction enantioselective as a prelude to the development of general enantioselective IMCRs. Here we report that reactions between α-isocyanoacetamides and aldehydes can be efficiently catalyzed by stannous chloride and document that the reaction between **1** and α-(benzyloxy)acetaldehyde catalyzed by [Sn-(*R*)-Ph-PyBox](OTf)$_2$ at –78 °C affords the corresponding 5-aminooxazole in high yield with up to 80% *ee*.

Results and Discussion

The condensation between α-benzyl-α-isocyanoacetamide (**1a**) and heptanal (**2a**) in toluene at 0 °C was used as a standard reaction for the screening of a suitable Lewis acid catalyst (0.1 equiv.), and representative results are summarized in Table 1.[16] We had previously shown that lithium bromide (LiBr) is capable of promoting the reaction between **1a** and **2a** at 60 °C to produce 5-amino-2-(1-hydroxyalkyl)oxazole.[17] However, only a trace amount of adduct was produced when the reaction was performed at 0 °C in the presence of a catalytic amount of LiBr (0.1 equiv., Table 1, Entry 1). Copper halides, regardless of their oxidation states, were ineffective (Entries 2–4), while titanium chloride ($TiCl_4$), known to promote the P-3CR[18] and U-4CR,[19] afforded the oxazole **3a** in only 7% yield (Entry 5). The reactions catalyzed by $Cu(OTf)_2$, $CoCl_2$, $CdBr_2$, $PdCl_2$, $CrCl_3$, $BiCl_3$, $AlCl_3$, or $BF_3{\cdot}Et_2O$ furnished the desired oxazole in moderate to good yields (Entries 6–13), while to our delight, excellent yields of **3a** were obtained when $ZnCl_2$ (Entry 14) or tin chloride ($SnCl_2$, $SnCl_4$)

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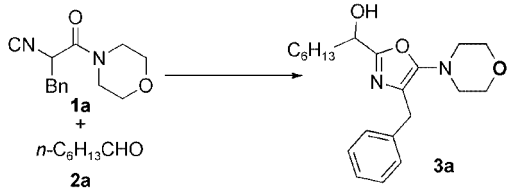
and tin triflate [$Sn(OTf)_2$] were used as catalysts (Entries 15–17). We stress that a significant rate acceleration was observed in the presence of stannous chloride, since the condensation went to completion at 0 °C within 1 h. Note that the reaction did not take place at 0 °C in the absence of Lewis acid catalyst, even upon prolonged reaction time (Entry 18).

Table 1. Survey of Lewis acid catalysts.[a]



Entry	Lewis acid	Time (h)	Yield (%)
1	LiBr	8	trace
2	$CuCl_2$	4	6
3	$CuBr_2$	8	23
4	CuCl	8	trace
5	$TiCl_4$	8	7
6	$Cu(OTf)_2$	2.5	41
7	$CoCl_2$	8	24
8	$CdBr_2{\cdot}4H_2O$	8	43
9	$PdCl_2$	8	29
10	$BiCl_3$	1.5	58
11	$CrCl_3{\cdot}6H_2O$	8	55
12	$AlCl_3$	2	67
13	$BF_3{\cdot}Et_2O$	1	64
14	$ZnCl_2$	8	87
15	$SnCl_2{\cdot}2H_2O$	1	86
16	$SnCl_4$	2	85
17	$Sn(OTf)_2$	2	83
18	–	24	0

[a] General reaction conditions: 0.14 M toluene solution of **1a**, 0.1 equiv. per mol of catalyst, 0 °C.

In light of its easy handling and higher catalytic activity, the generality of the tin chloride catalyzed synthesis of 5-aminooxazoles was examined and the results are shown in Figure 1. In general, aliphatic aldehydes, whether linear or α-branched, gave the corresponding oxazoles in higher than 80% yield (**3a**–**3f**). It is worth noting that the reaction went smoothly even with sterically encumbered 2,2-dimethylpropanal, to afford the corresponding adduct (**3f**) in 87% yield. *N*,*N*-Diethyl-α-isocyano-β-phenylpropionamide (**1b**) reacted with aldehydes as efficiently as the morpholinyl counterpart (**1a**) to afford the desired compounds in good to excellent yields (**3o**–**3q**). The morpholinyl derivative **1c** of the parent α-isocyanoacetamide also participated in this reaction to afford the expected adduct **3r** in 60% yield. The double addition product (2,4-dialkylated oxazole) was not formed under these conditions. Long reaction times (0 °C, 8 h) were generally required for less reactive aromatic aldehydes to furnish the oxazoles in moderate yield, but 4-nitrobenzaldehyde (**3n**, 88%) was an exception, affording the corresponding oxazole in 80% yield, presumably due to its high electrophilicity.

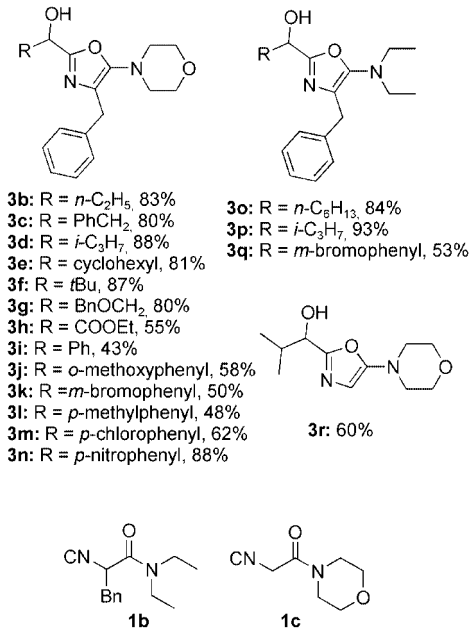


Figure 1. Structures of 5-aminooxazoles **3b**–**3r** and α-isocyanoacetamides **1b** and **1c**.

With these results in hand, an enantioselective process was next sought. (Benzyloxy)acetaldehyde (**2g**) was selected as a substrate because of its bidentate nature, and chiral bis(oxazoles) as well as diamines were examined as supporting ligands (Figure 2) for different metal salts. Dichloromethane, instead of toluene, was used in this study. As can be seen, the catalysts formed in situ from tridentate (*R*)-Ph-PyBox (**4a**);[20] and $Cu(OTf)_2$, $AlCl_3$, or $ZnCl_2$ were indeed capable of catalyzing the reaction, but no asymmetric induction was observed (Entries 1–3, Table 2). It is interesting to note that a catalyst formed in situ from a combination of **4a** and $Cu(OTf)_2$ was capable of catalyzing the P-3CR with simple isocyanides to give the α-acyloxyamide with excellent *ee* values.[10] These results illustrated the significant difference between simple isocyanides and α-isocyanoacetamides in the development of chiral catalysts. We reasoned that the presence of the amide function in α-isocyanoacetamides **1** might interfere with the metal coordination sphere, consequently leading to a different chiral environment. Gratifyingly, the [Sn-(*R*)-Ph-PyBox]$(OTf)_2$-catalyzed reaction between **1a** and **2g** at –78 °C (Table 2, Entry 4) afforded the desired oxazole **3g** in 71% *ee*.[21] The reaction outcome turned out to be highly dependent on the reaction temperature and showed an isoinversion effect.[22] The best results were obtained when the same reaction was performed at –40 °C to furnish the oxazole **3g** in 63% yield and 80% *ee* (Entry 7). To investigate the steric effect of ligands, the (*S*)-*i*Pr-Pybox **4b**, the *trans*-diphenyl-substituted PyBoc **4c**, and the conformationally constrained PyBox **4d** derived from (1*S*,2*R*)-re efficient than ligand **4a** (Entries 10–13). Bidentate Box ligands (**4e** and **4f**) were also ineffective

for this transformation (Entries 14, 15).[23] Finally, the $Sn(OTf)_2$-diamine complexes (**4g**, **4h**) failed to catalyze the formation of oxazole (Entries 16, 17).[24]

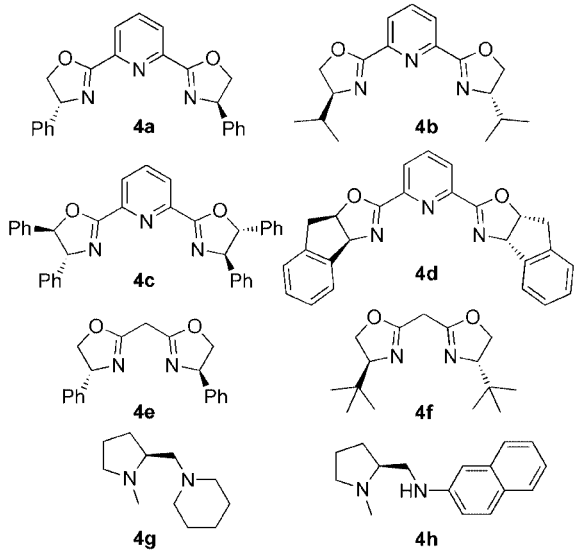
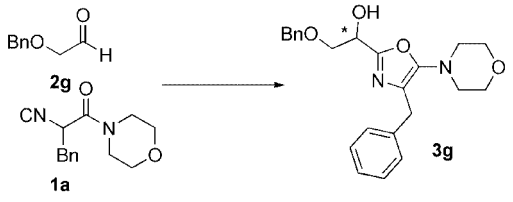


Figure 2. Structures of chiral ligands.

Table 2. Enantioselective synthesis of 5-aminooxazole **3g**.[a]



Entry	Catalyst	Temp (°C)	Yield (%)	*ee* (%)
1	$Cu(OTf)_2$ + **4a**	–70	44[a,c]	0
2	$AlCl_3$ + **4a**	–70	31[a,c]	0
3	$ZnCl_2$ + **4a**	–70	46[a,c]	0
4	$Sn(OTf)_2$ + **4a**	–70	28[a,c]	71
5	$Sn(OTf)_2$ + **4a**	–78	40[b]	67
6	$Sn(OTf)_2$ + **4a**	–60	45[b,c]	76
7	$Sn(OTf)_2$ + **4a**	–40	63[b]	80
8	$Sn(OTf)_2$ + **4a**	–20	72[b]	59
9	$Sn(OTf)_2$ + **4a**	0	60[b]	57
10	$Sn(OTf)_2$ + **4b**	–70	22[a,c]	46
11	$Sn(OTf)_2$ + **4b**	0	54	35
12	$Sn(OTf)_2$ + **4c**	0	10[b]	23
13	$Sn(OTf)_2$ + **4d**	–20	68[b]	30
13	$Sn(OTf)_2$ + **4d**	–78	37[b,c]	44
14	$Sn(OTf)_2$ + **4e**	0	40[b]	0
15	$Sn(OTf)_2$ + **4f**	0	37[b]	20
16	$Sn(OTf)_2$ + **4g**	–78	trace	0
17	$Sn(OTf)_2$ + **4h**	–78	trace	0

[a] General conditions: 0.1 M CH_2Cl_2 solution of **1a**, 0.1 equiv. per mol of catalyst; reaction time 6–8 h. [b] Reaction time 48 h. [c] Isocyanoacetamide was not fully consumed.

It is interesting to note that chiral information was transmitted solely from the catalyst. The chirality of α-isocyanoacetamide **1a** in fact exerted no influence on the diastereoselectivity since both the (*S*) and the racemic form of **1a** provided similar enantioselectivity.

Conclusions

We report Lewis acid catalyzed condensations between α-isocyanoacetamides and aldehydes. An enantioselective version using [Sn-(*R*)-Ph-PyBox]$(OTf)_2$ has also been developed for (benzyloxy)acetaldehyde, leading to the corresponding 5-amino-2-(1-hydroxyalkyl)oxazole with *ee* values of up to 80%. Although the *ee* values remained moderate (80%), we emphasize that there is a significant challenge in developing isocyanide-based enantioselective transformations and indeed that until now very few efficient catalytic systems existed. We are working on the development of a more general catalyst that is applicable to nonchelating aldehydes and the results will be reported in due course.

Experimental Section

General Procedure for the Stannous Chloride Catalyzed Three-Component Synthesis of 5-Amino-2-(hydroxyalkyl)oxazoles: Stannous chloride (9.5 mg, 0.05 mmol) was added to a toluene solution (3.5 mL) of the starting aldehyde (**2**, 0.6 mmol) and isocyanide (**1**, 0.5 mmol), cooled to 0 °C. The reaction mixture was stirred at 0 °C until the disappearance of isocyanide by TLC analysis. The mixture was quenched with saturated aqueous $NaHCO_3$ solution and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried with anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel to give the corresponding oxazole **3**.

Compound 3a: Colorless oil, yield 86%. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.87 (m, 3 H), 1.27–1.43 (m, 8 H), 1.78–1.88 (m, 2 H), 2.96 (m, 4 H), 2.98 (br. s, 1 H), 3.72 (m, 4 H), 3.80 (s, 2 H), 4.62 (t, J = 6.5 Hz, 1 H), 7.18–7.29 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.1, 22.5, 25.0, 28.9, 31.7, 31.7, 35.4, 51.1, 66.9, 67.9, 124.8, 126.2, 128.4, 128.5, 139.4, 152.0, 160.5 ppm. IR (KBr): $\tilde{\nu}$ = 3404, 2925, 2856, 1664, 1454, 1375, 1262, 1116 cm^{-1}. MS (ESI): *m/z* = 359 [M + H], 381 [M + Na]. HRMS (ESI): calcd. for $C_{21}H_{30}N_2O_3$ + Na 381.21333; found 381.2132.

Compound 3b: White solid, m.p. 51–52 °C, yield 83%. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.95 (t, J = 7.4 Hz, 3 H), 1.89 (m, 2 H), 2.96 (m, 4 H), 3.31 (br., 1 H), 3.71 (m, 4 H), 3.80 (s, 2 H), 4.56 (t, J = 5.6 Hz, 1 H), 7.15–7.29 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 9.4, 28.5, 31.7, 51.1, 66.9, 69.0, 124.7, 126.2, 128.4, 128.5, 139.4, 152.0, 160.4 ppm. IR (KBr): $\tilde{\nu}$ = 3216, 2963, 2915, 2858, 1667, 1547, 1453, 1374, 1239, 1116 cm^{-1}. MS (ESI): *m/z* = 303 [M + H], 325 [M + Na]. $C_{17}H_{22}N_2O_3$ (302.16): calcd. C 67.53, H 7.33, N 9.26; found C 67.28, H 7.35, N 9.29.

Compound 3c: White solid, m.p. 107–108 °C, yield 80%. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.87 (m, 4 H), 3.12 (m, 2 H), 3.65 (m, 4 H), 3.69 (s, 2 H), 4.35 (br., 1 H), 4.81 (t, J = 5.90 Hz, 1 H), 7.09–7.24 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 31.6, 41.9, 51.1, 66.9, 69.6, 124.8, 126.2, 126.6, 128.4 (3 C), 128.5, 129.5 (2 C), 136.9, 139.4, 152.0, 160.0 ppm. IR (KBr): $\tilde{\nu}$ = 3179, 2956, 1662, 1495, 1451, 1232, 1118 cm^{-1}. MS (ESI): *m/z* = 365 [M + H], 387 [M + Na]. $C_{22}H_{24}N_2O_3$ (364.18): calcd. C 72.50, H 6.64, N 7.69; found C 72.26, H 6.67, N 7.57.

Compound 3d: White solid, m.p. 101–102 °C, yield 88%. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.91 (d, J = 6.8 Hz, 3 H), 0.95 (d, J = 6.8 Hz, 3 H), 2.12 (m, 1 H), 2.95 (m, 4 H), 3.72 (m, 4 H), 3.81 (s, 2 H), 4.38 (m, 1 H), 7.16–7.29 (m, 2 H) ppm. ^{13}C NMR

($CDCl_3$,75 MHz): δ = 17.4, 18.3, 31.7, 33.5, 51.1, 66.9, 73.0, 124.6, 126.2 (2 C), 128.4 (2 C), 139.4, 152.1 ppm. IR (KBr): $\tilde{\nu}$ = 3203, 2961, 2861, 1726, 1666, 1545, 1453, 1371, 1239, 1114, 1067 cm^{-1}. MS (ESI): *m/z* = 317 [M + H], 339 [M + Na]. HRMS (ESI): calcd. for $C_{18}H_{24}N_2O_3$ + Na 339.1684; found 339.1665.

Compound 3e: Colorless oil, yield 81%. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.08–1.80 (m, 11 H), 2.93 (m, 4 H), 2.96 (br., 1 H), 3.71 (m, 4 H), 3.72 (s, 2 H), 4.36 (d, *J* = 5.99Hz, 1 H), 7.17–7.28 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 25.9, 26.0, 26.3, 28.0, 28.7, 31.7, 43.0, 51.0, 66.8, 72.4, 124.5, 126.2, 128.4 (2 C), 139.4, 152.0, 160.0 ppm. IR (KBr): $\tilde{\nu}$ = 3293, 3028, 2924, 2852, 1662, 1451, 1235, 1116 cm^{-1}. MS (ESI): *m/z* = 357 [M + H]. $C_{21}H_{28}N_2O_3$ (356.21): calcd. C 70.76, H 7.92, N 7.86; found C 70.64, H 7.92, N 7.79.

Compound 3f: Colorless oil, yield 87%. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.96 (s, 9 H), 2.93 (m, 4 H), 2.95 (br., 1 H), 3.71 (m, 4 H), 3.80 (s, 2 H), 4.28 (s, 1 H), 7.17–7.28 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 25.6, 31.7, 36.0, 51.1, 75.9, 124.5, 126.2, 128.4 (2 C), 139.4, 152.0, 159.6 ppm. IR (KBr): $\tilde{\nu}$ = 3399, 2957, 2859, 1722, 1663, 1453, 1236, 1116 cm^{-1}. MS (ESI): *m/z* = 331 [M + H], 353 $[M + Na]^+$, 369 [M + K]. $C_{19}H_{26}N_2O_3$ (330.19): calcd. C 69.06, H 7.93, N 8.48; found C 69.03, H 8.15, N 8.48.

Compound 3g: Yellow oil, yield 80%. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.95 (m, 4 H), 3.40 (br. s, 1 H), 3.72 (m, 4 H), 3.83 (m, 4 H), 4.58 (s, 2 H), 4.85 (m, 1 H), 7.18–7.33 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 31.8, 51.0, 66.9, 67.1, 71.9, 73.4, 124.5, 126.2, 127.7, 127.8, 128.4, 128.5 (2 C), 137.8, 139.4, 152.2, 157.6 ppm. IR (KBr): $\tilde{\nu}$ = 3370, 2957, 2856, 1662, 1562, 1495, 1453, 1236, 1115 cm^{-1}. MS (EI): *m/z* = 394 (90) $[M]^+$, 273 (100), 91 (34). $C_{23}H_{26}N_2O_4$ (394.19): calcd. C 70.03, H 6.64, N 7.10; found C 69.92, H 6.70, N 7.03.

Compound 3h: Yellow solid, m.p. 82–83 °C, yield 55%. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.26 (t, *J* = 7.1 Hz, 3 H), 2.97 (m, 4 H), 3.64 (d, *J* = 6.9 Hz, 1 H), 3.71 (m, 4 H), 3.82 (s, 2 H), 4.31 (t, *J* = 7.1 Hz, 2 H), 5.15 (d, *J* = 6.9 Hz, 1 H), 7.18–7.27 (m, 5 H) ppm. IR (KBr): $\tilde{\nu}$ = 3338, 2964, 2855, 1751, 1662, 1560, 1453, 1371, 1262, 1235, 1115, 1021 cm^{-1}. MS (ESI): *m/z* = 347 [M + H], 369 [M + Na], 385 [M + K]. HRMS (ESI): calcd. for $C_{18}H_{22}N_2O_5$ + Na 369.1426; found 369.1381.

Compound 3i: White solid, m.p. 119–121 °C, yield 43%. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.90 (m, 4 H), 3.67 (m, 4 H), 3.78 (s, 2 H), 3.99 (d, *J* = 5.3 Hz, 1 H), 5.66 (d, *J* = 5.3 Hz, 1 H), 7.18–7.44 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 31.7, 50.9, 66.8, 70.2, 124.7, 126.3, 126.7, 128.3, 128.4, 128.5, 128.6, 139.3, 139.6, 152.5, 159.0 ppm. IR (KBr): $\tilde{\nu}$ = 3255, 2964, 2852, 1672, 1562, 1493, 1456, 1389, 1238, 1113, 1073 cm^{-1}. MS (EI): *m/z* = 350 (100) $[M]^+$, 244 (28). $C_{21}H_{22}N_2O_3$ (350.16): calcd. C 71.98, H 6.33, N 7.99; found C 71.77, H 6.28, N 7.95.

Compound 3j: White solid, m.p. 121–122 °C, yield 58%. ^1H NMR ($CDCl_3$, 75 MHz): δ = 2.88 (m, 4 H), 3.63 (m, 4 H), 3.79 (m, 5 H), 3.87 (br., 1 H), 5.96 (m, 1 H), 6.85–7.32 (m, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 31.8, 51.0, 55.6, 66.6, 66.8, 110.9, 120.9, 124.9, 126.1, 127.9, 128.2, 128.4, 128.5, 129.6, 139.5, 152.0, 157.0, 159.1 ppm. IR (KBr): $\tilde{\nu}$ = 3157, 2956, 2853, 1664, 1550, 1492, 1455, 1249, 1115, 1064 cm^{-1}. MS (ESI): *m/z* = 381 [M + H]. $C_{22}H_{24}N_2O_4$ (380.17): calcd. C 69.46, H 6.36, N 7.36; found C 69.22, H 6.45, N 7.38.

Compound 3k: Yellow solid, m.p. 124–125 °C, yield 50%. ^1H NMR ($CDCl_3$, 75 MHz): δ = 2.92 (m, 4 H), 3.68 (m, 4 H), 3.78 (s, 2 H), 4.33 (br. s, 1 H), 5.60 (s, 1 H), 7.18–7.29 (m, 6 H), 7.33 (d, *J* = 7.8 Hz, 1 H), 7.43 (d, *J* = 7.8 Hz, 1 H), 7.59 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 31.7, 50.9, 66.8, 69.2, 122.6, 124.6, 125.3, 126.3, 128.5 (2 C), 129.7, 130.1, 131.3, 139.1, 141.7, 152.6, 159.5 ppm. IR (KBr): $\tilde{\nu}$ = 3140, 2959, 2847, 1661, 1549, 1456, 1112, 1052 cm^{-1}. MS (ESI): *m/z* = 429, 431 [M + H], 451, 453 [M + Na], 467, 469 [M + K]. HRMS (ESI): calcd. for $C_{21}H_{21}N_2O_3Br$ + Na 451.0633 and 453.0613; found 451.0662 and 453.0630.

Compound 3l: White solid, m.p. 110–112 °C, yield 48%. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.32 (s, 3 H), 2.88 (m, 4 H), 3.65 (m, 4 H), 3.76 (s, 2 H), 4.24 (br. s, 1 H), 5.62 (s, 1 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 7.16–7.26 (m, 5 H), 7.28 (d, *J* = 8.1 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.2, 31.7, 66.8, 69.9, 124.6, 126.2, 126.7, 128.4, 128.5, 129.3, 136.8, 138.0, 139.3, 152.3, 159.3 ppm. IR (KBr): $\tilde{\nu}$ = 3221, 2967, 2855, 1660, 1513, 1446, 1322, 1263, 1243, 1112, 1049 cm^{-1}. MS (ESI): *m/z* = 365 [M + H]. $C_{22}H_{24}N_2O_3$ (364.18): calcd. C 72.50, H 6.64, N 7.69; found C 72.42, H 6.64, N 7.77.

Compound 3m: White solid, m.p. 117–119 °C, yield 62%. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.90 (m, 4 H), 3.68 (m, 4 H), 3.77 (s, 2 H), 4.23 (br., 1 H), 5.62 (s, 1 H), 7.16–7.37 (m, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 31.7, 50.9, 66.8, 69.4, 124.6, 126.3, 128.0, 128.5, 128.5, 128.7, 134.1, 138.0, 139.1, 152.6, 158.7 ppm. IR (KBr): $\tilde{\nu}$ = 3212, 2966, 1662, 1550, 1491, 1242, 1114 cm^{-1}. MS (ESI): *m/z* = 385 [M + H], 407 [M + Na]. $C_{21}H_{21}ClN_2O_3$ (384.12): calcd. C 65.54, H 5.50, N 7.28; found C 65.14, H 5.49, N 7.23.

Compound 3n: Yellow solid, m.p. 158–159 °C, yield 88%. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.92 (m, 4 H), 3.71 (m, 4 H), 3.79 (s, 2 H), 4.18 (d, *J* = 4.8 Hz, 1 H), 5.73 (d, *J* = 4.8 Hz, 1 H), 7.15–7.27 (m, 5 H), 7.61 (d, *J* = 8.7 Hz, 2 H), 8.21 (d, *J* = 8.7 Hz, 2 H) ppm. IR (KBr): $\tilde{\nu}$ = 3207, 2959, 2840, 1668, 1520, 1393, 1350, 1231, 1112, 1090 cm^{-1}. MS (ESI): *m/z* = 396 [M + H], 418 [M + Na]. HRMS (ESI): calcd. for $C_{21}H_{21}N_3O_5$ + Na 418.1379; found 418.1398.

Compound 3o: Oil, yield 84%. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.86 (m, 3 H), 0.97 (t, *J* = 7.2 Hz, 6 H), 1.28 (m, 8 H), 1.81 (m, 2 H), 2.94 (q, *J* = 7.1 Hz, 4 H), 2.99 (br. s, 1 H), 3.76 (s, 2 H), 4.59 (m, 1 H), 7.14–7.27 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 13.3, 14.0, 22.5, 24.9, 29.0, 31.4, 31.7, 35.5, 48.0, 67.9, 126.0, 128.2, 128.4, 128.6, 139.5, 150.7, 161.3 ppm. IR (KBr) $\tilde{\nu}$ 3276, 2930, 2857, 1714, 1634, 1559, 1455, 1378, 1249, 1180, 1088 cm^{-1}. MS (ESI): *m/z* = 367 [M + Na], 383 [M + K].

Compound 3p: Colorless oil, yield 93%. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.84–1.02 (m, 12 H), 2.08 (m, 1 H), 2.93 (q, *J* = 7.17Hz, 4 H), 3.18 (br., 1 H), 3.77 (s, 2 H), 4.37 (m, 1 H), 7.16–7.28 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 13.2, 17.3, 18.2, 31.4, 33.5, 48.1, 73.0, 126.0, 128.2, 128.4, 128.6, 139.5, 150.1, 160.1 ppm. IR (KBr): $\tilde{\nu}$ = 3276, 3028, 2970, 2871, 1664, 1560, 1495, 1454 cm^{-1}. MS (ESI): *m/z* = 303 [M + H], 325 [M + Na], 341 [M + K]. $C_{18}H_{26}N_2O_2$ (302.20): calcd. C 65.54, H 5.50, N 7.28; found C 65.14, H 5.49, N 7.23.

Compound 3q: Oil, yield 53%. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.94 (t, *J* = 7.2 Hz, 3 H), 2.91 (q, *J* = 7.2 Hz, 4 H), 3.76 (s, 2 H), 5.62 (s, 1 H), 7.18–7.27 (m, 6 H), 7.32 (d, *J* = 7.7 Hz, 1 H), 7.42 (dd, *J* = 1.6, 7.7 Hz, 1 H), 7.58 (d, *J* = 1.6 Hz, 1 H) ppm. IR (KBr): $\tilde{\nu}$ = 3214, 2973, 1661, 1570, 1454, 1379, 1249, 1184, 1070 cm^{-1}. MS (IE): *m/z* = 414, 416 $[M]^+$. HRMS (ESI): calcd. for $C_{21}H_{23}BrN_2O_2$ + Na 437.0841 and 439.0820; found 437.0864 and 439.0850.

Compound 3r: White solid, m.p. 67–68 °C, yield 60%. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.92 (d, *J* = 6.8 Hz, 3 H), 0.98 (d, *J* = 6.8 Hz, 3 H), 2.12 (m, 1 H), 2.79 (d, *J* = 5.4 Hz, 1 H), 3.08 (m, 4 H), 3.82 (m, 4 H), 4.40 (dd, *J* = 1.2, 5.5 Hz, 1 H), 6.01 (d, *J* = 1.1 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.7, 18.4, 33.3, 48.4, 65.9, 72.8, 102.4, 157.2, 158.0 ppm. IR (KBr): $\tilde{\nu}$ = 3275,

2965, 2852, 1616, 1452, 1382, 1243, 1119, 1047 cm^{-1}. MS (ESI): *m/z* = 227 [M + H], 249 [M + Na]. $C_{11}H_{18}N_2O_3$ (226.13): calcd. C 58.39, H 8.02, N 12.38; found C 58.39, H 7.92, N 12.38.

Enantioselective Passerini Reaction. Synthesis of 3g: A solution of $Sn(OTf)_2$ (20.8 mg, 0.05 mmol) and phenyl-Pybox ligand (**4a**, 20.3 mg, 0.055 mmol) in dichloromethane (5.0 mL) was stirred until the complete dissolution of all components. (Benzyloxy)acetaldehyde (**2g**, 100 mg, 0.67 mmol) was then introduced and the resulting mixture was stirred at room temperature for 30 min. The mixture was cooled to –40 °C, and a solution of α-isocyanoacetamide **1a** (122 mg, 0.5 mmol) in dichloromethane (3 mL) was added slowly by syringe pump (addition time 1 h). After being stirred at –40 °C for 48 h, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution and the mixture extracted with EtOAc. The combined organic phases were washed with brine, dried with anhydrous sodium sulfate, filtered and concentrated. The crude product was then purified by flash chromatography on silica gel (petroleum ether/EtOAc, 1:1) to give the corresponding oxazole **3g** (125.0 mg, 63%, *ee* = 80%).

Supporting Information (see footnote on the first page of this article): Copies of ^1H NMR spectra of **3a**–**3r** and chiral HPLC analysis of **3g**.

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