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An unusual base-dependent α-alkylation and β-elimination of *tert*-butyl 2-phenyl-2-oxazoline-4-carboxylate: practical synthesis of (±)-α-alkylserines and *tert*-butyl benzamidoacrylate

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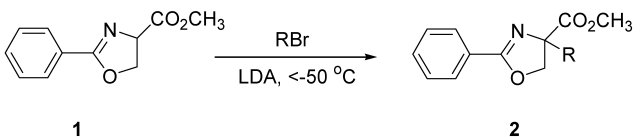
Abstract—Practical synthesis of (±)-α-alkylserines and *tert*-butyl benzamidoacrylate from *tert*-butyl 2-phenyl-2-oxazoline-4-carboxylate (**6**) were developed. The α-alkylation and β-elimination of **6** are dramatically dependent upon base conditions. The phase-transfer catalytic condition bearing solid KOH in toluene gives α-alkylation (up to >99%), and *t*-BuOK in DMF gives β-elimination (98%).

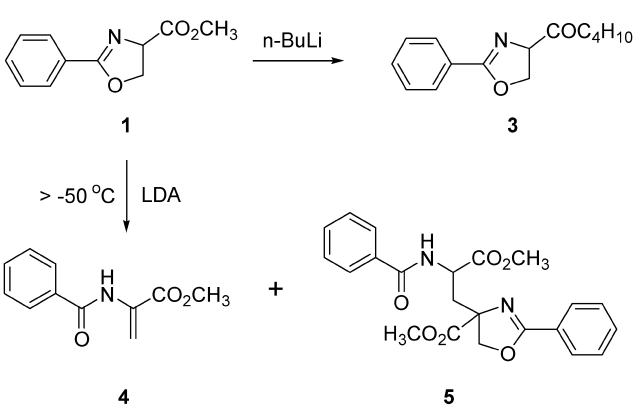
1. Introduction

α-Alkylserines have been extensively studied, due to their important roles in the fields of synthetic and biological chemistry.[1] As their quaternary carbon centers induce preferable conformations in peptide backbones,[2] α-alkylserine moieties have been employed in the design of biologically active peptidomimetics.[3] In addition, α-alkylserines are frequently found in several biologically active natural products, such as mycestericins,[4] (+)-lactacystin,[5] and (+)-conagenin,[6] and α-alkylserines themselves are useful synthetic building blocks via chemical transformations.[1] A number of synthetic methods[7] have been reported for α-alkylserines. Among them, the alkylation of phenyloxazoline derivatives of serine esters is the most practical (Scheme 1).[7l]



Scheme 1.

The oxazoline moiety can not only provides sufficient acidity to the α-hydrogen of the ester group, but also acts as an excellent protecting group for both the amino and hydroxyl groups in the serine ester. The following hydrolysis under acidic conditions can provide α-alkylserines. However, it usually requires a strong base (LDA) and low temperature conditions below −50 °C for alkylation, otherwise β-elimination (**4**) and the following Michael addition (**5**) are predominant.[7l] In the case of *n*-BuLi at −100 °C, only the corresponding *n*-butyl ketone can be prepared by substitution (Scheme 2).[8] Herein, we report the unusual base dependent α-alkylation and β-elimination in the oxazoline ester and the practical reaction conditions for the selective synthesis of (±)-α-alkylserines and *tert*-butyl benzamidoacrylate.



Scheme 2.

2. Results and discussion

As part of our program for the conformational studies of the peptidomimetics bearing α-alkylserines, we needed

Keywords: α-Alkylserines; Benzamidoacrylate; Phase-transfer catalytic alkylation.
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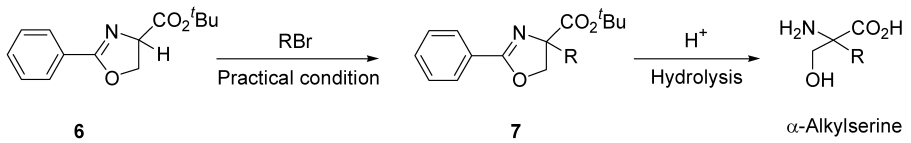


6 7

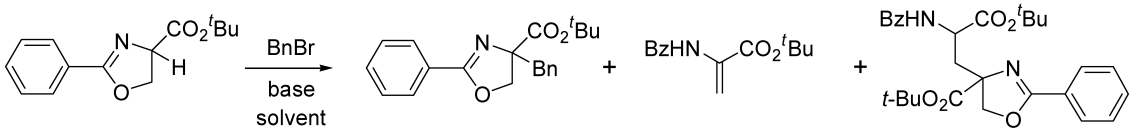
Scheme 3.

practical synthetic methods for the various α-alkylserines. So we adapted the α-alkylation of 2-phenyl-2-oxazoline-4-carboxylic ester and investigated the practical reaction conditions. As shown in Scheme 3, we chose the *tert*-butyl ester **6** as the substrate, which might reduce the ester hydrolysis in the practical base conditions, such as mild alkali bases at 0 °C or room temperature.

Substrate **6** is easily prepared by coupling ethyl benzimidate and serine *tert*-butyl ester in 98% yield.[9] To determine the optimal alkylation conditions, the benzylation was performed using *tert*-butyl 2-phenyl-2-oxazoline-4-carboxylate **6** along with benzyl bromide (5 equiv.), and various bases (5 equiv.) in tetrahydrofuran at 0 °C. K_2CO_3[10] (entry 1) and DBU[11] (entry 2), which have been applied in the α-epimerization of oxazoline esters, unexpectedly gave no α-alkylation and β-elimination product. Interestingly, in the series of *tert*-butoxide bases, the relative ratio of **7f** (α-alkylation) to **8** and **9** (β-elimination) depended on the cation, as shown in Table 1. The α-benzylation increased as follows: $Li^+ > Na^+ > K^+$ (entries 3–5). We assume that the enhanced covalent bond character of the enolate intermediate might contribute to the increase in α-alkylation. In the case of solid alkali hydroxides, although they are weak bases as compared to alkali *tert*-butoxides, they delivered **7f** in modest chemical yields (83%–85%), except for LiOH (entries 6–8). Notably, 40% aq. tetrabutylammonium hydroxide gave only **7f** without any β-elimination products, although the chemical yield was low because of partial hydrolysis (entry 9). These results finally prompted us to employ a phase-transfer catalytic reaction. Surprisingly, solid KOH in the presence of a catalytic amount of tetrabutylammonium bromide (TBAB, 5 mol%) in toluene afforded **7f** in a very high chemical yield (99%), without any β-elimination (entry 10). The high chemical yield could be produced even at room temperature (98%, entry 11). The replacement of solid KOH with 50% aq. KOH reduced the chemical yield, due to low reaction rate (entry 12). The hydrolysis of **7f** with 6 N-HCl, followed by the purification using ion-exchange resin afforded (±)-α-benzylserine in 98% yield.[4m,12] Further investigations of the phase-transfer catalytic alkylation with various alkyl halides, using the above optimal reaction conditions,[13] were performed. As shown in Table 2, all the active alkyl halides (entry c–m) performed α-alkylation in very high yield, but aliphatic halides (entry a and b) provided relatively lower chemical yield, which might be due to the low reactivity. The high chemical yields indicate that phase-transfer catalytic condition is very efficient for the synthesis of (±)-α-alkylserines.

After the optimization of the selective α-alkylation, we focused our attention toward optimizing the β-elimination condition for *tert*-butyl benzamidoacrylate **8**, which is one of the versatile synthetic intermediates. There have been a few synthetic methods for benzamidoacrylates, but generally they need several steps or gave relatively low chemical yields.[14] In Table 1 (entry 3), *tert*-BuOK showed the most promising possibility for the selective β-elimination, but there was still some amount of dimeric side product **9** via

Table 1. Optimal conditions for the alkylation of **6**[a]

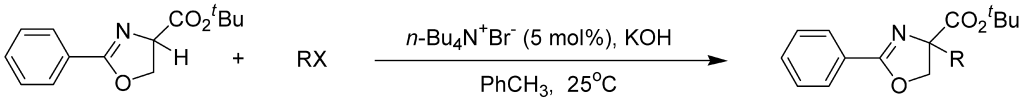


6 7f 8 9

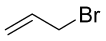
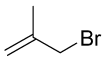
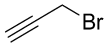
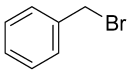
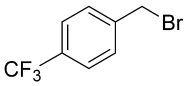
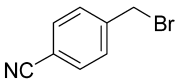
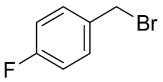
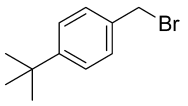
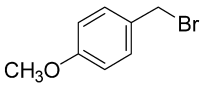
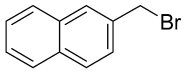
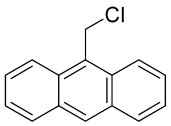
No	Base	Solvent	Temperature (°C)	Time	**7f** Yield[b] (%)	**8** Yield[b] (%)	**9** Yield[b] (%)
1	K_2CO_3[c]	DMF/*t*-BuOH	rt	12 h	0	0	0
2	DBU[c]	CH_2Cl_2	rt	12 h	0	0	0
3	*t*-BuOK	THF	0	2 min	0	83	5
4	*t*-BuONa	THF	0	2 min	18	43	9
5	*t*-BuOL	THF	0	2 min	57	18	10
6	KOH	THF	0	0.75 h	83	0	3
7	NaOH	THF	0	1.25 h	85	0	3
8	LiOH	THF	rt	5 day	25	0	0
9	40% aq. n-Bu_4NOH	THF	0	10 min	38	0	0
10	KOH/TBAB[d]	$PhCH_3$	0	3 h	99	0	0
11	KOH/TBAB[d]	$PhCH_3$	rt	2 h	98	0	0
12	50% aq. KOH/TBAB[d]	$PhCH_3$	0	2 day	32	0	0

[a] The reaction was carried out with 5.0 equiv. of benzyl bromide and 5.0 equiv. of base in tetrahydrofuran or toluene under the given conditions.
[b] Isolated yields.
[c] **6** was recovered.
[d] 5 mol% of tetra-*n*-butylammonium bromide (TBAB) was used.

Table 2. Phase-transfer catalytic alkylation[a]



6 **7**

Entry	RX	Time (h)	Yield[b] (%)
a	CH_3I	2.5	65
b	CH_3CH_2I	1.0	52
c		0.4	>99
d		0.4	>99
e		0.4	>99
f		2.0	98
g		2.5	>99
h		3.5	99
i		3.0	98
j		1.0	92
k		0.2	80
l		1.0	96
m		0.5	95

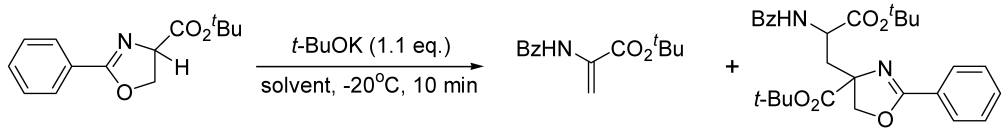
[a] The reaction was carried out with 5.0 equiv. of alkylating agent and 5.0 equiv. of solid KOH in toluene under the given conditions.
[b] Isolated yields.

1,4-addition. To increase the selectivity for β-elimination, various solvents were employed at the lower reaction temperature (−20 °C). As shown in Table 3, generally the more polar aprotic solvent gave the higher selectivity for β-elimination, which might be due to the stabilization of the enolate intermediate by the solvation. Among the solvents, DMF showed the best result in both the selectivity and the chemical yield (98%), but no reaction was detected in case of *t*-BuOH.

3. Conclusions

We founded the unusual base dependent α-alkylation and β-elimination of *tert*-butyl 2-phenyl-2-oxazoline-4-carboxylate (**6**). The α-alkylation and β-elimination are dramatically dependent upon base conditions. The phase-transfer catalytic condition in the presence of alkyl halides could selectively give the corresponding α-alkylated products in high yield. In case of *t*-BuOK, *tert*-butyl

Table 3. β-Elimination for benzamidoacrylate[a]



6 **8** **9**

No	Solvent	**8** Yield[b] (%)	**9** Yield[b] (%)
1	THF	91	2
2	*n*-Hexane	50	8
3	DMF	98	0
4	*t*-BuOH[c]	0	0

[a] The reaction was carried out with 1.1 equiv. of base in the corresponding solvent at −20 °C for 10 min.
[b] Isolated yields.
[c] **6** was recovered.

benzamidoacrylate could be obtained in high yield by the selective β-elimination. The easy preparation of substrate **6**, the high chemical yields, and the very mild reaction conditions could make these methods very practical for the synthesis of (±)-α-alkylserines and *tert*-butyl benzamidoacrylate, which are very useful synthetic intermediates.

4. Experimental

4.1. General

Infrared spectra were taken on a Perkin–Elmer 1710 FT-IR spectrometer. Mass spectra were obtained on a VG Trios-2 GC-MS and JEOL JMS-700 instrument. ^{1}H and ^{13}C NMR spectra were measured with a JEOL JNM-LA 300 and a JEOL JNM-GCX 400 spectrometers using TMS as the internal standard. Most reagents were obtained from commercial suppliers and used without further purification unless noted. Tetrahydrofuran was distilled from Na and benzophenone, and methylenechloride from CaH_2.

4.1.1. 2-Phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (6). To a methylenechloride solution (60 mL) of ethyl benzimidate hydrochloride (3.71 g, 20.0 mmol) and L-serine *tert*-butyl ester hydrochloride (3.52 g, 20.0 mmol) in methylenechloride was added triethylamine (5.58 mL, 40.0 mmol). The reaction mixture was refluxed for 2 h and stirred for 10 h at room temperature. The reaction mixture was diluted with methylenechloride (200 mL), washed with sat. aq. $NaHCO_3$ soln. (2×50 mL) and water (2×50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc=9:1) to afford **6** (5.16 g, 98% yield) as a white solid; mp: 42–45 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J=7.1 Hz, 2H), 7.53–7.36 (m, 3H), 4.84 (dd, J=8.0, 10.5 Hz, 1H), 4.62–4.53 (m, 2H), 1.51 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 165.9, 131.6, 128.5, 128.1, 127.0, 82.0, 69.7, 69.3, 27.9 ppm; IR (KBr) 2979, 1734, 1644, 1453, 1364, 1298, 1222, 1156, 1089, 1026, 967, 846, 777, 696 cm^{-1}; MS (FAB) *m*/*z* 248 [M+H]$^+$; HRMS calculated for $C_{14}H_{17}NO_3$: 247.1208. Found: 248.1285 [M+H]$^+$.

4.2. General procedure for the phase-transfer catalytic alkylations (7a-7m)

To a toluene solution (0.80 mL) of 2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester **6** (50.0 mg, 0.200 mmol), tetrabutylammonium bromide (3.2 mg, 0.01 mmol) and KOH (56.1 mg, 1.00 mmol) was added the corresponding alkyl halide (1.00 mmol) at 0 °C. The reaction mixture was stirred at room temperature. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (20 mL), washed with water (2×5 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc=20:1) to afford the compounds **7a**-**7m**.

4.2.1. 4-Methyl-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7a). A pale yellow oil (34 mg, 65% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J=7.3 Hz, 2H), 7.59–7.38 (m, 3H), 4.46 (d, J=8.8 Hz, 1H), 4.11 (d, J=8.8 Hz, 1H), 2.30 (s, 3H), 1.47 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 164.7, 131.8, 128.7, 128.3, 127.0, 82.0, 76.2, 74.5, 27.9, 24.8 ppm; IR (KBr) 2978, 1729, 1645, 1452, 1287 cm^{-1}; MS (FAB) *m*/*z* 262 [M+H]$^+$; HRMS calculated for $C_{15}H_{19}NO_3$: 261.3163. Found: 262.1443 [M+H]$^+$.

4.2.2. 4-Ethyl-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7b). A pale yellow oil (29 mg, 52% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J=8.3 Hz, 2H), 7.51–7.37 (m, 3H), 4.71 (d, J=8.9 Hz, 1H), 4.21 (d, J=8.9 Hz, 1H), 1.95 (qd, J=1.4, 7.5 Hz, 2H), 1.50 (s, 9H), 0.94 (t, J=7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 164.1, 131.5, 128.5, 128.2, 127.4, 81.7, 78.9, 73.4, 31.0, 27.9, 8.0 ppm; IR (KBr): 2973, 2926, 1726, 1646, 1455, 1364, 1252, 1146, 1067, 1026, 971, 845, 778, 694 cm^{-1}; MS (ESI) *m*/*z* 276 [M+H]$^+$, 298 [M+Na]$^+$; HRMS calculated for $C_{16}H_{21}NO_3$: 275.1521. Found: 276.1600 [M+H]$^+$.

4.2.3. 4-Allyl-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7c). A pale yellow oil (59 mg, >99% yield); ^{1}H NMR (300MHz, $CDCl_3$) δ 7.98 (d, J=6.8 Hz, 2H), 7.52–7.38 (m, 3H), 5.80–5.66 (m, 1H), 5.20–5.13 (m, 2H), 4.70 (d, J=8.8 Hz, 1H), 4.27 (d, J=8.8 Hz, 1H), 2.76–2.60 (m, 2H), 1.50 (s, 9H) ppm; ^{13}C NMR (100 MHz,

$CDCl_3$) δ 171.3, 164.6, 131.9, 131.6, 128.6, 128.3, 127.2, 119.5, 82.0, 77.8, 73.1, 42.1, 27.9 ppm; IR (KBr) 2979, 1728, 1644, 1452, 1365, 1275, 1147, 1089, 1027, 978, 922, 846, 777, 696 cm^{-1}; MS (FAB) *m/z* 288 $[M+H]^+$; HRMS calculated for $C_{17}H_{21}NO_3$: 287.1521. Found: 288.1601 $[M+H]^+$.

4.2.4. 4-(2-Methyl-allyl)-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7d). A yellow oil (61 mg, >99% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J*=7.0 Hz, 2H), 7.45–7.34 (m, 3H), 4.85 (s, 1H), 4.82 (d, *J*=8.8 Hz, 1 H), 4.68 (s, 1H), 4.29 (d, *J*=8.8 Hz, 1 H), 2.83 (d, *J*=14.6 Hz, 1H), 2.53 (d, *J*=14.6 Hz, 1H), 1.74 (s, 3H), 1.45 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 164.2, 140.9, 131.5, 128.5, 128.2, 127.3, 114.3, 81.9, 77.9, 73.3, 45.5, 27.8, 23.9 ppm; IR (KBr) 2976, 2926, 1727, 1644, 1453, 1365, 1286, 1160, 1102, 978, 898, 846, 776, 695 cm^{-1}; MS (ESI) *m/z* 302 $[M+H]^+$, 324 $[M+Na]^+$; HRMS calculated for $C_{18}H_{23}NO_3$: 301.1678. Found: 302.1755 $[M+H]^+$.

4.2.5. 4-Prop-2-ynyl-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7e). A pale yellow caramel (58 mg, >99% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J*=6.8 Hz, 2H), 7.51–7.36 (m, 3H), 4.85 (d, *J*=8.8 Hz, 1H), 4.47 (d, *J*=8.8 Hz, 1H) 2.95 (dd, *J*=2.7, 16.7 Hz, 1H), 2.69 (dd, *J*=2.7, 16.7 Hz, 1H), 1.95 (t, *J*=2.7 Hz, 1H), 1.49 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 165.5, 131.8, 128.6, 128.2, 126.9, 82.5, 78.7, 77.4, 73.5, 71.0, 27.9, 27.8 ppm; IR (KBr): 2979, 1731, 1641, 1453, 1366, 1279, 1161, 1101, 978, 845, 695 cm^{-1}; MS (FAB) *m/z* 286 $[M+H]^+$; HRMS calculated for $C_{17}H_{19}NO_3$: 285.1365. Found: 286.1442 $[M+H]^+$.

4.2.6. 4-Benzyl-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7f). A pale yellow caramel (67 mg, 98% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J*=7.1 Hz, 2H), 7.50–7.15 (m, 8H), 4.66 (d, *J*=8.8 Hz, 1H), 4.31 (d, *J*=8.8 Hz, 1H), 3.25 (dd, *J*=13.8, 46.7 Hz, 2H), 1.46 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 164.6, 135.6, 131.5, 130.3, 128.5, 128.1, 128.0, 127.2, 126.8, 82.1, 78.7, 72.8, 43.1, 27.8 ppm; IR (KBr) 2978, 1726, 1644, 1453, 1366, 1280, 1160, 1095, 978, 847, 697 cm^{-1}; MS (FAB) *m/z* 338 $[M+H]^+$; HRMS calculated for $C_{21}H_{23}NO_3$: 337.1678. Found: 338.1750 $[M+H]^+$.

4.2.7. 4-(4-Trifluoromethylbenzyl)-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7g). A white solid (82 mg, >99% yield); mp: 61–63 °C: ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J*=7.1 Hz, 2H), 7.51–7.38 (m, 7H), 4.66 (d, *J*=8.9 Hz, 1H), 4.26 (d, *J*=8.9 Hz, 1H), 3.29 (dd, *J*=13.8, 25.1 Hz, 2H), 1.46 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 165.0, 140.0, 131.8, 130.7, 129.3, 128.9, 128.5, 128.3, 127.0, 125.0, 82.5, 78.5, 73.2, 42.9, 27.8 ppm; IR (KBr) 2979, 1728, 1645, 1452, 1366, 1327, 1281, 1163, 1121, 1066, 1023, 980, 849, 695 cm^{-1}; MS (FAB) *m/z* 406 $[M+H]^+$; HRMS calculated for $C_{22}H_{22}F_3NO_3$: 405.1552. Found: 406.1634 $[M+H]^+$.

4.2.8. 4-(4-Cyano-benzyl)-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7h). A pale yellow needle (73 mg, 99% yield); mp: 66–68 °C: ^1H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J*=8.5 Hz, 2H), 7.58–7.37 (m, 7H), 4.63 (d, *J*=9.1 Hz, 1H), 4.23 (d, *J*=9.1 Hz, 1H), 3.35 (d, *J*=13.8 Hz, 1H), 3.18 (d, *J*=13.8 Hz, 1H), 1.43 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 165.0, 141.4, 131.8, 131.7, 131.1, 128.4, 128.2, 126.8, 118.7, 110.7, 82.5, 78.2, 73.3, 43.2, 27.8 ppm; IR (KBr) 2978, 2228, 1728, 1644, 1452, 1366, 1281, 1159, 1092, 979, 847, 759, 697 cm^{-1}; MS (FAB) *m/z* 363 $[M+H]^+$; HRMS calculated for $C_{22}H_{22}N_2O_3$: 362.1630. Found: 363.1696 $[M+H]^+$.

4.2.9. 4-(4-Fluoro-benzyl)-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7i). A yellow caramel (71 mg, 98% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J*=7.1 Hz, 2H), 7.51–7.37 (m, 3H), 7.26–7.21 (m, 2H), 6.96–6.88 (m, 2H), 4.63 (d, *J*=8.8 Hz, 1H), 4.27 (d, *J*=8.8 Hz, 1H) 3.20 (dd, *J*=13.9, 21.2 Hz, 2H), 1.47 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 164.7, 164.1 160.7, 131.9, 131.8, 131.6, 131.3, 128.5, 128.2, 127.1, 115.0, 114.8, 82.2, 78.6, 72.9, 42.3, 27.9 ppm; IR (KBr) 2978, 1726, 1644, 1510, 1366, 1279, 1224, 1160, 1101, 979, 846, 695 cm^{-1}; MS (FAB) *m/z* 356 $[M+H]^+$; HRMS calculated for $C_{21}H_{22}FNO_3$: 355.1584. Found: 356.1666 $[M+H]^+$.

4.2.10. 4-(4-*tert*-Butyl-benzyl)-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7j). A pale yellow caramel (73 mg, 92% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, *J*=7.1 Hz, 2H), 7.51–7.36 (m, 3H), 7.26–7.16 (m, 4H), 4.67 (d, *J*=8.9 Hz, 1H), 4.31 (d, *J*=8.9 Hz, 1H), 3.22 (dd, *J*=13.8, 38.6 Hz, 2H), 1.46 (s, 9H), 1.26 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 164.5, 149.5, 132.5, 131.5, 129.9, 128.5, 128.1, 127.3, 125.0, 82.0, 78.9, 73.0, 42.8, 34.3, 31.2, 27.9 ppm; IR (KBr) 2964, 1723, 1644, 1454, 1365, 1278, 1161, 1091, 1025, 978, 847, 695 cm^{-1}; MS (FAB) *m/z* 394 $[M+H]^+$; HRMS calculated for $C_{25}H_{31}NO_3$: 393.2304. Found: 394.2381 $[M+H]^+$.

4.2.11. 4-(4-Methoxy-benzyl)-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7k). A yellow oil (60 mg, 80% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J*=7.3 Hz, 2H), 7.50–7.36 (m, 3H), 7.17 (d, *J*=8.5 Hz, 2H), 6.75 (d, *J*=8.5 Hz, 2H), 4.65 (d, *J*=8.8 Hz, 1H), 4.30 (d, *J*=8.8 Hz, 1H), 3.72 (s, 3H), 3.19 (dd, *J*=13.9, 17.8 Hz, 2H), 1.47 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 164.5, 158.4, 131.5, 131.3, 128.6, 128.5, 128.2, 127.5, 113.5, 82.1, 78.9, 72.7, 55.1, 42.2, 27.9 ppm; IR (KBr) 2929, 1726, 1643, 1513, 1455, 1365, 1252, 1160, 1091, 1033, 978, 846, 695 cm^{-1}; MS (FAB) *m/z* 368 $[M+H]^+$; HRMS calculated for $C_{22}H_{25}NO_4$: 367.1784. Found: 368.1856 $[M+H]^+$.

4.2.12. 4-(Naphthalene-2-ylmethyl)-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7l). A pale yellow solid (75 mg, 96% yield); mp: 82–84 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J*=7.3 Hz, 2H), 7.76–7.67 (m, 4H), 7.50–7.35 (m, 6H), 4.70 (d, *J*=8.9 Hz, 1H), 4.38 (d, *J*=8.9 Hz, 1H), 3.43 (s, 2H), 1.48 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 164.7, 133.3, 133.2, 132.3, 131.5, 129.0, 128.6, 128.5, 128.2, 127.6, 127.5, 127.4, 127.2, 125.8, 125.5, 82.2, 78.9, 72.8, 43.2, 27.9 ppm; IR (KBr) 2977, 1726, 1643, 1452, 1365, 1280, 1159, 1092, 978, 846, 752, 696 cm^{-1}; MS (FAB) *m/z* 388 $[M+H]^+$; HRMS calculated for $C_{25}H_{25}NO_3$: 387.1834. Found: 388.1910 $[M+H]^+$.

4.2.13. 4-(Anthracenyl-9-ylmethyl)-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (7m). A yellow solid (84 mg, 95% yield); mp: 102–104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51–8.37 (m, 3H), 7.94–7.92 (m, 4H), 7.54–7.33 (m, 7H), 4.63–4.08 (m, 4H), 1.60 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 164.1, 131.5, 131.3, 131.2, 128.8, 128.3, 128.0, 127.8, 127.4, 127.0, 126.2, 125.5, 124.7, 82.3, 79.69, 72.0, 33.4, 27.9 ppm; IR (KBr) 2977, 1723, 1645, 1451, 1230 cm^{-1}; MS (FAB) *m/z* 438 $[M+H]^+$; HRMS calculated for $C_{29}H_{27}NO_3$: 437.1991. Found: 438.2070 $[M+H]^+$.

4.3. Dimeric Michael adduct: 4-(2-benzoylamino-2-*tert*-butoxycarbonyl-ethyl)-2-phenyl-4,5-dihydro-oxazole-4-carboxylic acid *tert*-butyl ester (9)

A yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99–7.26 (m, 10H), 4.73 (d, J=9.2 Hz, 1H), 4.61–4.54 (m, 1H), 4.27 (d, J=9.2 Hz, 1H), 2.62–2.25 (m, 2H), 1.42 (s, 9H), 1.35 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.6, 167.2, 165.3, 134.2, 133.7, 132.1, 131.4, 128.6, 128.2, 127.4, 126.9, 82.8, 81.6, 76.0, 74.4, 52.1, 39.1, 27.9, 27.8 ppm; IR (KBr) 2978, 1732, 1647, 1529, 1487, 1367, 1289, 1154 cm^{-1}; MS (FAB) *m/z* 495 $[M+H]^+$; HRMS calculated for $C_{28}H_{34}N_2O_6$: 494.2417. Found: 495.2498 $[M+H]^+$.

4.4. (±)-α-Benzylserine

To an ethanol solution (1.5 mL) of 4-benzyl-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester **7f** (500 mg, 1.48 mmol) was added 6 N-HCl (1.5 mL) and the reaction mixture was refluxed for 24 h. After the solvent was removed in vacuo, the residue was purified by column chromatography (5% aq. NH_4OH) using ion-exchange resin (Dowex® 50WX8-100) to give (±)-α-benzylserine as a white solid (365 mg, 98%). Physical and spectral properties were consistent with the literature values.[4m,12]

4.5. *tert*-Butyl benzamidoacrylate (8)

To a dimethylformamide solution (1.5 mL) of 2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester **6** (50.0 mg, 0.200 mmol) was added a dimethylformamide solution (0.5 mL) of *tert*-BuOK (25 mg, 0.22 mmol) by dropwise at −20 °C. The reaction mixture was stirred at −20 °C for 10 min. After completion of the reaction, the excess *tert*-BuOK was quenched with a few drops of sat. aq. NH_4Cl. After removal of the solvent in vacuo, the residue was diluted with ethyl acetate (50 mL), washed with water (3×5 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc=5:1) to afford **8** (49 mg, 98% yield) as a yellow needle; mp: 66–68 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (br, 1H), 7.83–7.80 (m, 2H), 7.53–7.40 (m, 3H), 6.69 (s, 1H), 5.88 (s, 1H), 1.53 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 163.3, 134.4, 131.9, 128.7, 126.9, 107.8, 83.1, 60.4, 27.7 ppm; IR (KBr) 3418, 2976, 1677, 1519, 1370, 1338, 1159 cm^{-1}; MS (FAB) *m/z* 248 $[M+H]^+$; HRMS calculated for $C_{14}H_{17}NO_3$: 247.1208. Found: 248.1290 $[M+H]^+$.

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