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Synthesis of α-oxazolinylalkanamides

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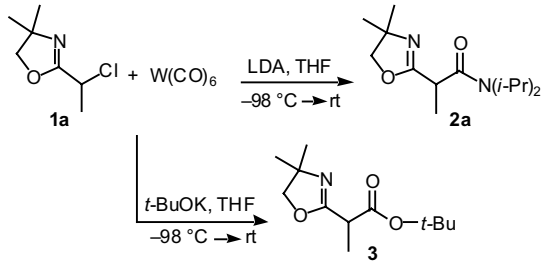
Abstract—The synthesis of α-oxazolinylalkanamides **2**, based on the reaction of α-chloroalkyloxazolines **1** with hexacarbonyltungsten [$W(CO)_6$] and lithium amides, has been developed. A plausible mechanism involving the ketene **5** as the intermediate is also proposed.

Alkanamides bearing a heterocyclic residue on the α position of the amide functionality are of some interest in medicinal chemistry for being biologically active compounds in the field of herbicides,[1] antagonists of the peptidic Y receptors,[2] blood anticoagulants,[3] fungicides,[4] selective noncovalent inhibitors of Cathepsin K, which is a cysteine protease of the papain superfamily highly and selectively expressed in osteoclasts.[5] The synthetic utility of α-heterosubstituted alkanamides has also been investigated: in particular, certain oxazoline-substituted alkanamides have been reported to be useful synthetic equivalents of chiral β-dicarbonyls.[6]

Herein, we report a quite simple route to oxazolinylalkanamides based on the reaction of 2-(1-chloroalkyl)oxazolines, hexacarbonyltungsten [$W(CO)_6$] and lithium amides.

We found that the reaction of 2-(1-chloroethyl)oxazoline **1a** and $W(CO)_6$ with lithium diisopropylamide (LDA) in THF at low temperature resulted in the formation of *N*,*N*-diisopropyl-α-oxazolinylpropanamide **2a**, which was characterized by ^1H and ^{13}C NMR, DEPT, GC–MS, IR and elemental analysis (Scheme 1).[7]



Scheme 1.

A reasonable explanation for the outcome of this reaction is illustrated in Scheme 2 where the key steps are the addition of **1a**–**Li**[8] to $W(CO)_6$ to give the tungsten complex **4**. Elimination of $W(CO)_5Cl$ would furnish the oxazolinyl ketene **5** and addition of diisopropylamine, which is present in the reaction medium, would produce **2a**.

Support to such a mechanistic hypothesis came from the observation that the addition of *t*-BuOK instead of LDA to the mixture of **1a** and $W(CO)_6$ resulted in the formation of the *t*-butyl ester **3** (38 % yield) (Scheme 1).[9]

We later proved that the reaction of **1a** and $W(CO)_6$ was not restricted to LDA but was common to a number of other lithium amides, including secondary and primary, cyclic and open-chain amides, affording oxazolinyl amides **2b**–**i** (Table 1).

Keywords: Oxazolinylalkanamides; α-Chloroalkyloxazolines; Lithium amides; Hexacarbonyltungsten.
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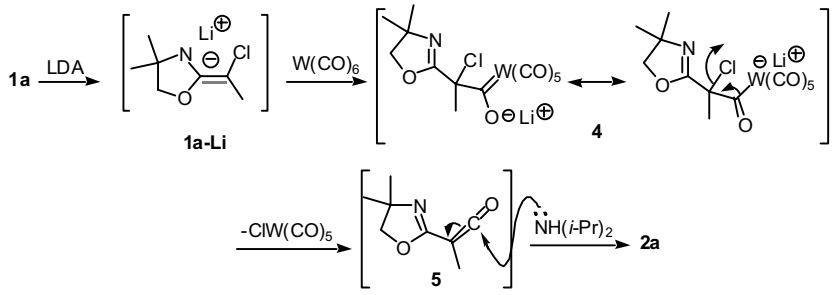
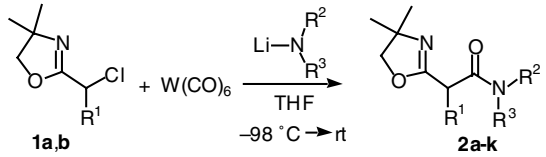


Scheme 2.

Table 1. Synthesis of oxazolinylalkanamides **2a–k**

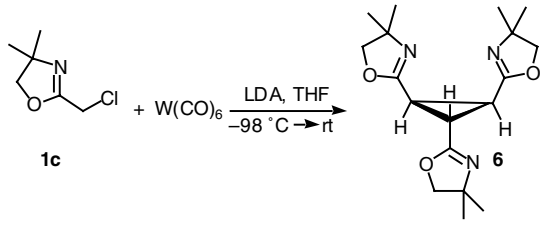


Compound	R^1	R^2	R^3	Amide **2** (yield%)[a]
1a	Me	*i*-Pr	*i*-Pr	**2a** (81)
1a	Me	*n*-Bu	*n*-Bu	**2b** (88)
1a	Me	Et	*i*-Pr	**2c** (80)
1a	Me	Et	Et	**2d** (76)
1a	Me	Cy	Cy	**2e** (70)
1a	Me	*t*-Bu	CH_2Ph	**2f** (75)
1a	Me	*t*-Bu	H	**2g** (72)
1a	Me	$–(CH_2)_4–$		**2h** (80)[b]
1a	Me	$–(CH_3)_2(CH_2)_3(CH_3)_2C–$		**2i** (46)[b]
1b	Ph	*i*-Pr	*i*-Pr	**2j** (46)
1b	Ph	*t*-Bu	CH_2Ph	**2k** (58)

[a] Isolated yields.
[b] Yield calculated by weighing the crude reaction product and ^1H NMR analysis.

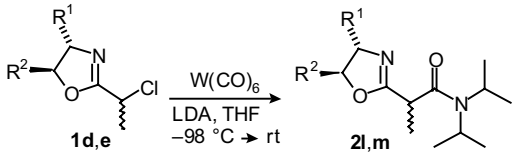
In a similar way, 2-chlorobenzyloxazoline **1b** reacted with LDA and lithium *t*-butylbenzylamide, in the presence of $W(CO)_6$, to generate amides **2j,k** (Table 1), while the reaction of 2-chloromethyloxazoline **1c** with LDA ended up with the formation of 1,2,3-tris(oxazolinyl)-cyclopropane **6** (Scheme 3). Evidently, the already described 'cyclotrimerization' of **1c**,[10] promoted by LDA, proceeds much faster than the reaction with $W(CO)_6$.

The reaction of optically pure 2-(1-chloroethyl)oxazolines **1d** and **1e** was also investigated (Table 2). Both these two oxazolines reacted cleanly with $W(CO)_6$ and LDA to give alkanamides **2l** and **2m** as an inseparable mixture of two diastereomers.



Scheme 3.

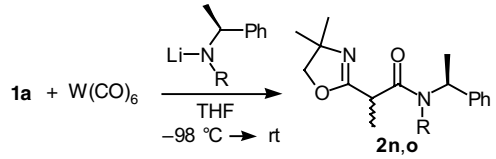
Table 2. Synthesis of oxazolinylalkanamides **2l,m** starting from optically active α-chloroalkyloxazolines **1d,e**



Compound	R^1	R^2	Amide **2** (yield%)[a]	dr[b]
1d	*i*-Pr (4*S*)	H	**2l** (80)	2/1
1e	CH_2OCH_3 (4*S*)	Ph (5*S*)	**2m** (72)	1.2/1

[a] Isolated yields.
[b] Diastereomeric ratio determined by ^1H NMR analysis on the crude reaction mixture.

Table 3. Synthesis of oxazolinylalkanamides **2n,o** starting from optically active lithium amides



R	Amide **2** (yield%)[a]	dr[b]
H	**2n** (46)	1/1
CH_2Ph	**2o** (58)	1.2/1

[a] Isolated yields.
[b] Diastereomeric ratio determined by ^1H NMR analysis on the crude reaction mixture.

Equally poorly diastereoselective was the reaction of **1a** and $W(CO)_6$ with lithium amides derived from optically active amines such as (*S*)-1-phenylethylamine and (*S*)-1-phenylethylbenzylamine: amides **2n,o** formed as inseparable diastereomeric mixtures (Table 3).

In conclusion, our work offers the possibility of synthesizing α-oxazolinylalkanamides, which are susceptible of synthetic elaboration at the oxazoline ring,[11] simply by reacting an α-chloroalkyloxazoline with $W(CO)_6$ and a lithium amide.

Acknowledgements

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7. *Typical procedure for the synthesis of N,N-diisopropyl 2-(4,5-dihydro-4,4-dimethyl-oxazol-2-yl)propanamide* **2a**: To a precooled (−98 °C, with a methanol and liquid nitrogen bath) solution of 2-(1-chloroethyl)oxazoline **1a** (1.1 mmol), $W(CO)_6$ (1.0 mmol) and diisopropylamine (DIPA) (0.2 mmol) in dry THF (5 mL), under N_2 and with magnetic stirring, a precooled (−98 °C) solution of LDA [prepared from *n*-BuLi (1.2 mmol) and DIPA (1.2 mmol)] was added dropwise and the resulting mixture stirred at this temperature for 30 min. Then, the mixture was allowed to warm to rt and, after the consumption of $W(CO)_6$, filtered off through a pad of Celite and silica gel. The solvent was removed under reduced pressure and the crude was purified by flash column chromatography (ethyl acetate/hexane 2/3) to give the oxazolinylalkanamide **2a**.
All new compounds gave satisfactory analytical and spectral data. Compound **2a**: yellow solid, mp: 50–51 °C (Et_2O), 81%. ^{1}H NMR (300 MHz): δ 0.90 (s, 3H), 0.92 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H), 1.03 (s, 3H), 1.44 (d, J = 6.9 Hz, 3H), 1.45 (d, J = 6.3 Hz, 3H), 1.50 (d, J = 6.9 Hz, 3H), 2.99 (septet, J = 6.9 Hz, 1H), 3.25 and 3.38 (2 × d, AB system, J = 8.4 Hz, 2H), 3.74 (septet, J = 6.9 Hz, 1H), 4.29 (q, J = 6.3 Hz, 1H); ^{13}C NMR (75.4 MHz, DEPT, $CDCl_3$): δ 15.1 (*C*H$_3$), 20.0 (*C*H$_3$), 20.4 (*C*H$_3$), 20.6 (*C*H$_3$), 20.7 (*C*H$_3$), 27.8 (*C*H$_3$), 28.3 (*C*H$_3$), 42.3 (*C*H), 46.5 (*C*H), 48.9 (*C*H), 71.3 (*C*), 79.0 (*C*H$_2$), 166.0 (*C*=N), 173.1 (*C*=O); GC–MS (70 eV) *m/z* (%) 254 (M^+, 14), 239 (20), 154 (36), 127 (100); FT-IR (film, cm^{-1}): 2933, 1740, (s, C=O), 1622 (s, C=N), 1365, 1109, 940. Anal. Calcd for $C_{14}H_{26}N_2O_2$: C, 66.10; H, 10.30; N, 11.01. Found: C, 66.44; H, 10.62; N, 10.97. Compound **2b**: yellow solid, mp: 47–48 °C (Et_2O), 88%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H), 1.18–1.35 (m, 4H), 1.22 (s, 3H), 1.24 (s, 3H), 1.38–1.54 (m, 4H), 1.44 (d, J = 7.2 Hz, 3H), 3.04–3.41 (m, 4H), 3.56 (q, J = 7.2 Hz, 1H) 3.84 and 3.88 (2 × d, AB system, J = 8.1 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 13.6, 13.8, 15.2, 20.0, 20.1, 28.0, 28.1, 31.3, 31.4, 46.0, 46.6, 47.9, 67.1, 79.2, 164.4 (*C*=N), 169.5 (*C*=O); GC–MS (70 eV) *m/z* (%) 282 (M^+, 2), 239 (100), 223 (33), 144 (49), 115 (34), 105 (18); FT-IR (film, cm^{-1}): 2962, 2874, 1660, 1645, 1462, 1193. Anal. Calcd for $C_{16}H_{30}N_2O_2$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.27; H, 10.74; N, 10.01. Compound **2c**: colourless oil, 80%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (t, J = 7.1 Hz, 3H), 1.20 (d, J = 6.5 Hz, 3H), 1.25 (d, J = 6.5 Hz, 3H), 1.32 (s, 3H), 1.34 (s, 3H), 1.46 (d, J = 7.1 Hz, 3H), 3.15–3.22 (m, 1H), 3.26–3.34 (m, 1H), 3.88 (septet, J = 6.5 Hz, 1H), 4.09 and 4.15 (2 × d, AB system, J = 8.2 Hz, 2H), 4.23 (q, J = 7.1 Hz, 1H), 7.20–7.53 (m, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 14.2, 15.1, 21.2, 21.3, 27.7, 28.2, 36.2, 41.6, 48.6, 71.4, 79.0, 166.8 (*C*=N), 172.9 (*C*=O); GC–MS (70 eV) *m/z* (%) 240 (M^+, 3), 197 (4), 154 (40), 127 (100), 86 (50), 72 (36); FT-IR (film, cm^{-1}): 2965, 1651 (s, C=O), 1644 (s, C=N), 1457, 1384, 1091. Compound **2d**: colourless oil, 76%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (t, J = 7.1 Hz, 3H), 1.10 (t, J = 7.1 Hz, 3H), 1.24 (s, 3H), 1.27 (s, 3H), 1.47 (d, J = 7.2 Hz, 3H), 2.92–3.13 (m, 2H), 3.35–3.51 (m, 2H), 3.60 (q, J = 7.2 Hz, 1H), 3.90 and 3.94 (2 × d, AB system, J = 8.1 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 14.2, 14.5, 15.2, 27.6, 27.9, 41.5, 41.9, 52.7, 66.9, 78.8, 167.5 (*C*=N), 171.6 (*C*=O); GC–MS (70 eV) *m/z* (%) 226 (M^+, 8), 169 (6), 154 (34), 127 (100), 100 (18), 72 (33); FT-IR (film, cm^{-1}): 2978, 2920, 1651, 1630, 1454, 1400, 1385. Compound **2e**: yellow oil, 70%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (s, 3H), 1.27 (s, 3H), 1.25–1.47 (m, 12H), 1.44 (d, J = 7.2 Hz, 3H), 1.50–1.83 (m, 8H), 3.38–3.70 (m, 3H), 3.87 and 3.91 (2 × d, AB system, J = 8.1 Hz, 2H); GC–MS (70 eV) *m/z* (%) 334 (M^+, 6), 251 (28), 180 (100), 154 (19), 127 (67), 55 (23); FT-IR (film, cm^{-1}): 2969, 2932, 1691, 1649, 1454, 1385, 1107. Compound **2f**: white solid, mp: 55–56 °C (Et_2O), 75%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (s, 9H), 1.30 (s, 3H), 1.34 (s, 3H), 1.47 (d, J = 7.2 Hz, 3H), 3.49 (q, J = 7.2 Hz, 1H) 3.85 and 3.88 (2 × d, AB system, J = 8.1 Hz, 2H), 4.53 (d, J = 18.3 Hz, 1H), 4.80 (d, J = 18.3 Hz, 1H), 7.12–7.40 (m, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$) 15.3, 27.7, 28.0, 28.1, 28.3, 46.8, 48.3, 58.1, 66.7, 79.1, 125.4, 128.4, 128.7, 139.3, 165.5 (*C*=N), 171.6 (*C*=O); GC–MS (70 eV) *m/z* (%) 316 (M^+, 8), 259 (100), 187 (27), 154 (53), 127 (33), 91 (77), 57 (42); FT-IR (film, cm^{-1}): 3014, 2970, 2934, 1697, 1651, 1450, 1396, 1191, 753, 699. Anal. Calcd for $C_{19}H_{28}N_2O_2$: C, 72.12; H, 8.92; N, 8.85. Found: C, 72.01; H, 9.07; N, 8.81. Compound **2g**: colourless oil, 72%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (s, 3H), 1.27 (s, 3H), 1.33 (s, 9H), 1.43 (d, J = 7.2 Hz, 3H), 1.46 (br s, exchanges with D_2O, 1H), 3.48 (q, J = 7.2 Hz, 1H), 3.94 (s, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 14.7, 28.0, 28.2, 28.5, 45.2, 49.1, 67.4, 78.7, 166.5 (*C*=N), 172.2 (*C*=O); GC–MS (70 eV) *m/z* (%) 226 (M^+, 3), 154 (12), 127 (100), 112 (15), 57 (11); FT-IR (film, cm^{-1}): 2968, 1670, 1655, 1385, 1191. Compound **2h**: yellow oil, 80%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (s, 3H), 1.27 (s, 3H), 1.42 (d, J = 7.2 Hz, 3H), 1.83–2.08 (m, 4H), 3.36–3.65 (m, 5H), 3.94 (s, 2H); GC–MS (70 eV) *m/z* (%) 224 (M^+, 9), 154 (9), 127 (100), 112 (13), 98 (13), 55 (18); FT-IR (film, cm^{-1}): 2920, 1680, 1645, 1451, 1302, 1109. Compound **2i**: yellow oil, 40%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (s, 3H), 1.23 (s, 3H), 1.20–1.38 (m, 2H), 1.35 (s, 6H), 1.37 (s, 6H), 1.40–1.62 (m, 4H), 1.44 (d, J = 7.2 Hz, 3H), 3.80 (q, J = 7.2 Hz, 1H), 3.98 and 4.05 (2 × d, AB system, J = 8.2 Hz, 2H); GC–MS (70 eV) *m/z* (%) 294 (M^+, 5), 279 (14), 249 (18), 161 (50), 154 (100), 126 (63), 96 (10), 55 (26); FT-IR (film,

cm^{-1}): 2964, 2878, 1702, 1651, 1385, 1191. Compound **2j**: yellow oil, 46%. ^1H NMR (300 MHz, $CDCl_3$): δ 1.10 (d, $J = 6.5$ Hz, 3H), 1.14 (d, $J = 6.5$ Hz, 3H), 1.20 (d, $J = 6.5$ Hz, 3H), 1.25 (d, $J = 6.5$ Hz, 3H), 1.28 (s, 3H), 1.32 (s, 3H), 3.45 (septet, $J = 6.5$ Hz, 1H), 3.91 (septet, $J = 6.5$ Hz, 1H), 3.89 and 3.95 (2 × d, AB system, $J = 8.4$ Hz, 2H), 4.73 (s, 1H), 7.20–7.53 (m, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$) 20.4, 20.7, 21.2, 21.3, 27.7, 28.0, 42.2, 45.6, 50.6, 67.9, 79.1, 166.2 (*C*═N), 172.4 (*C*═O); GC–MS (70 eV) *m/z* (%) 316 (M^+, 6), 216 (100), 188 (29), 86 (40), 77 (37); FT-IR (film, cm^{-1}): 3034, 2968, 1661, 1650, 1461, 1069. Compound **2k**: yellow oil, 58%. ^1H NMR (300 MHz, $CDCl_3$): δ 1.27 (s, 9H), 1.26 (s, 3H), 1.28 (s, 3H), 3.91 and 3.98 (2 × d, AB system, $J = 8.1$ Hz, 2H), 4.23 (s, 1H) 4.50 (d, $J = 18.3$ Hz, 1H), 4.82 (d, $J = 18.3$ Hz, 1H), 7.12–7.61 (m, 10H); GC–MS (70 eV) *m/z* (%) 378 (M^+, 8), 321 (100), 216 (48), 91 (70), 77 (41), 57 (42); FT-IR (film, cm^{-1}): 3034, 2972, 1697, 1651, 1450, 1191, 753, 699. Compound **2l**: colourless oil, inseparable mixture of two diastereoisomers, 80% overall yield (dr: 1/2). ^1H NMR (300 MHz, $CDCl_3$): δ 0.75 (d, $J = 6.8$ Hz, 3H, major), 0.83 (d, $J = 6.9$ Hz, 3H, minor), 0.89 (d, $J = 6.8$ Hz, 3H, major), 0.91 (d, $J = 6.9$ Hz, 3H, minor), 0.99 (d, $J = 6.8$ Hz, 3H, major), 1.01 (d, $J = 6.9$ Hz, 3H, minor), 1.22 (d, $J = 6.8$ Hz, 3H, major), 1.24 (d, $J = 6.9$ Hz, 3H, minor), 1.29 (d, $J = 6.8$ Hz, 3H, major), 1.31 (d, $J = 6.8$ Hz, 3H, minor), 1.41 (d, $J = 6.8$ Hz, 3H, minor), 1.44 (d, $J = 6.8$ Hz, 3H, major), 1.48 (d, $J = 7.1$ Hz, 3H, major), 1.52 (d, $J = 7.0$ Hz, 3H, minor), 2.54–2.63 (m, 1H, major + 1H, minor), 3.43 (septet, $J = 6.8$ Hz, 1H, major), 3.45 (septet, $J = 6.9$ Hz, 1H, minor), 3.83 (septet, $J = 6.8$ Hz, 1H, major), 3.90 (septet, $J = 6.9$ Hz, 1H, minor), 4.04-4.44 (m, 4H, major + 4H, minor); ^{13}C NMR (75.4 MHz, DEPT, $CDC1_3$): δ 14.0 (CH_3, major + minor), 15.6 (CH_3, major), 15.8 (CH_3, minor), 18.7 (CH_3, major), 18.9 (CH_3, minor), 20.1 (CH_3, minor), 20.4 (CH_3, major), 20.5 (CH_3, major), 20.6 (CH_3, minor), 22.6 (CH_3, major), 22.7 (CH_3, minor), 29.0 (CH_3, minor), 29.8 (CH_3, major), 31.6 (*C*H, major + minor), 40.6 (*C*H, minor), 40.8 (*C*H, major), 46.3 (*C*H, minor), 46.5 (*C*H, major), 49.2 (*C*H, major + minor), 67.8 (*C*H, major), 68.2 (*C*H, minor), 77.6 (CH_2, major + minor), 166.1 (*C*═N, minor), 166.2 (*C*═N, major), 174.0 (*C*═O, minor), 174.2 (*C*═O, major); GC–MS (70 eV) *m/z* (%) major: 268 (M^+, 4), 253 (21), 168 (23), 127 (100), 100 (5); minor: 268 (M^+, 2), 253 (14), 168 (24), 127(100), 72 (6); FT-IR (film, cm^{-1}) (major + minor): 2963, 2924, 1740 (s, C═O), 1646 (s, C═N), 1454, 1371, 815. Compound **2m**: colourless oil, inseparable mixture of two diastereoisomers, 72% overall yield (dr: 1/1.2). ^1H NMR (300 MHz, $CDCl_3$): δ 0.85 (d, $J = 6.7$ Hz, 3H, major), 0.96 (d, $J = 6.8$ Hz, 3H, minor), 1.05 (d, $J = 6.8$ Hz, 3H, minor), 1.08 (d, $J = 6.7$ Hz, 3H, major), 1.39 (d, $J = 7.1$ Hz, 3H, major), 1.41 (d, $J = 6.7$ Hz, 3H, major), 1.47 (d, $J = 6.7$ Hz, 3H, major), 1.51 (d, $J = 6.8$ Hz, 3H, minor), 1.53 (d, $J = 6.8$ Hz, 3H, minor), 1.62 (d, $J = 7.0$ Hz, 3H, minor), 2.96–3.16 (m, 2H, major + 2H, minor), 3.02 (s, 3H, major), 3.09 (s, 3H, minor), 3.71–4.08 (m, 4H, major + 4H, minor), 4.32 (q, $J = 7.0$ Hz, 1H, minor), 4.38 (q, $J = 7.1$ Hz, 1H, major), 5.30 (d, $J = 5.7$ Hz, 1H, minor), 5.37 (d, $J = 5.9$ Hz, 1H, major), 6.96–7.21 (m, 3H, major + 3H, minor), 7.35–7.53 (m, 2H, major + 2H, minor); ^{13}C NMR (75.4 MHz, DEPT, $CDCl_3$): δ 15.7 (CH_3 major), 15.8 (CH_3, minor), 20.5 (CH_3 major + minor), 20.6 (CH_3, major), 20.7 (CH_3, minor), 20.8 (CH_3, minor), 20.9 (CH_3, major), 21.0 (CH_3, major + minor) 41.7 (*C*H, minor), 42.6 (*C*H, major), 46.6 (CH_3, minor), 46.7 (*C*H, major), 49.0 (*C*H, major + minor), 58.6 (CH_3, major + minor), 72.3 (CH_2, major + minor), 80.3 (*C*H, minor), 80.7 (*C*H, major), 83.8 (*C*H, minor), 84.0 (*C*H, major), 125.9 (*C*H, minor), 126.8 (*C*H, major), 127.9 (2 × *C*H, major), 128.0 (2 × *C*H, minor), 129.3 (2 × *C*H, minor), 129.5 (2 × *C*H, major), 133.0 (*C*, major + minor), 164.8 (*C*═N, minor), 165.1 (*C*═N, major), 175.3 (*C*═O, major), 175.7 (*C*═O, minor); GC–MS (70 eV) *m/z* (%) major: 346 (M^+, 10), 303 (61), 246 (20), 219 (74), 164 (22), 128 (30), 100 (100), 86 (71); minor: 346 (M^+, 12), 303 (61), 246 (17), 219 (82), 164 (22), 128 (33), 100 (100), 86 (69); FT-IR (film, cm^{-1}) (major + minor): 3012, 2971, 1743, 1614, 1449, 1373, 978, 825, 702. Compound **2n**: colourless oil, inseparable mixture of two diastereoisomers, 46% overall yield (dr: 1/1). ^1H NMR (300 MHz, $CDCl_3$): δ 0.94 (s, 3H), 0.98 (s, 3H), 1.25 (s,6H), 1.44 (d, $J = 7.0$ Hz, 3H), 1.48 (d, $J = 7.0$ Hz, 3H), 1.53 (d, $J = 7.2$ Hz, 3H), 1.57 (d, $J = 7.2$ Hz, 3H), 3.66 and 3.72 (2 × d, AB system, $J = 8.0$ Hz, 2H), 3.76 and 3.83 (2 × d, AB system, $J = 8.0$ Hz, 2H), 4.40 (q, $J = 7.0$ Hz, 1H), 4.48 (q, $J = 7.0$ Hz, 1H), 4.88 (q, $J = 7.2$ Hz, 1H), 5.01 (q, $J = 7.2$ Hz, 1H), 7.06–7.44 (m, 10H), 7.87–7.99 (m, exchanges with D_2O, 2H); GC–MS (70 eV) *m/z* (%) diastereoisomer with the lower t_r 274 (M^+, 1), 231 (11), 159 (20), 132 (26), 127 (100), 105 (35), 77 (8); diastereoisomer with the major t_r: 274 (M^+, 2), 231 (9), 159 (16), 132 (25), 127 (100), 105 (38), 77 (8); FT-IR (film, cm^{-1}): 3018, 2974, 1703, 1641, 1449, 1396, 753, 699. Compound **2o**: colourless oil, inseparable mixture of two diastereoisomers, 58% overall yield (dr: 1/2). ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (s, 3H, minor), 0.92 (s, 3H, major), 1.23 (s, 3H, major), 1.27 (s, 3H, minor), 1.46 (d, $J = 7.1$ Hz, 3H, major), 1.49 (d, $J = 7.0$ Hz, 3H, minor), 1.56 (d, $J = 7.1$ Hz, 3H, major), 1.60 (d, $J = 7.1$ Hz, 3H, minor), 3.49 and 3. 53 (2 × d, AB system, $J = 8.0$ Hz, 2H, minor), 3.58 and 3.65 (2 × d, AB system, $J = 8.0$ Hz, 2H, major), 4.35–4.56 (m, 3H, major + 3H, minor), 4.94 (q, $J = 7.1$ Hz, 1H, major), 5.00 (q, $J = 7.1$ Hz, 1H, minor), 7.09–7.59 (m, 10H, major + 10H, minor); GC–MS (70 eV) *m/z* (%) minor: 364 (M^+, 3), 273 (62), 259 (100), 187 (17), 154 (35), 126 (15), 105 (39), 91 (26), 77 (8); major: 364 (M^+, 5), 273 (66), 259 (100), 187 (17), 154 (37), 126 (15), 105 (38), 91 (26), 77 (8); FT-IR (film, cm^{-1}) (major + minor): 3010, 2972, 1693, 1639, 1394, 1191, 749, 702.

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9. *Procedure for the synthesis of 2-(4,5-dihydro-4,4-dimethyl-oxazol-2-yl)propionic acid tert-butyl ester* **5**: To a precooled (−98 °C, with a methanol and liquid nitrogen bath) solution of 2-(1-chloroethyl)oxazoline **1a** (1.1 mmol) and $W(CO)_6$ (1.0 mmol) in dry THF (5 mL), under N_2 and with magnetic stirring, a precooled (−98 °C) suspension of *t*-BuOK (1.2 mmol in 2 mL THF) was added dropwise and the resulting mixture stirred at this temperature for 30 min. Then, the mixture was allowed to warm to rt and, after the consumption of $W(CO)_6$, filtered off on a pad of Celite and silica gel. The solvent was removed under reduced pressure and the crude was purified by flash column chromatography (ethyl acetate/hexane 1/4) to give the ester **3**: colourless oil, 38%. ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (s, 3H), 1.29 (s, 3H), 1.36 (s, 9H), 1.66 (d, $J = 7.2$ Hz, 3H), 4.08 (s, 2H), 4.16 (q, $J = 7.2$ Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 16.1, 27.8, 28.0, 28.7, 43.2, 67.1, 69.3, 78.8, 163.2, 174.0; GC–MS (70 eV) *m/z* (%) 227 (M^+, 2), 212 (11), 156 (16), 154 (30), 141 (24), 126 (19), 57 (100); FT-IR (film, cm^{-1}): 2962, 1715, 1655, 1362, 1193.
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11. Meyers, A. I. *J. Heterocycl. Chem.* **1998**, *35*, 991.