Synthesis of *N*,*N*-Dimethylpropanediamide and its Utility for the Preparation of 2-(Acetamidomethyl)-4-aryloxazoles

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Dedicated to Professor Clayton Heathcock in honor of his stewardship of the College of Chemistry at the University of California, Berkeley, and in recognition of his seminal contributions to organic synthesis, particularly in the areas of biomimetic alkaloid synthesis and acyclic stereocontrol

Abstract: A practical, readily scaleable synthesis of *N*,*N*-dimethylpropanediamide (**1**) is reported. The utility of this bis-amide is demonstrated in the preparation of several 2,4-disubstituted oxazoles from α-bromoketones.

Key words: oxazole, bromo-ketone, annulation, *N*,*N*-dimethylpropanediamide, heterocycle

Oxazoles are an important class of heterocycles, due to their ubiquity as both secondary metabolites and pharmacologically active agents.[1] We recently required a method for preparing 2-(acetamidomethyl)-4-aryl-oxazoles such as **2** (Figure 1). Preparation of 2-alkyl-substituted oxazoles from primary amides and α-bromoketones is known,[2] suggesting that direct access to oxazole **2** could be realized from bis-amide **1** and the appropriate bromoketone. While bis-amides similar to **1** have been reported, we were surprised to find no experimental data describing the synthesis of **1**.[3] Herein we describe a practical synthesis of **1** and demonstrate its utility in the preparation of a variety of 2,4-disubstituted oxazoles **2**.

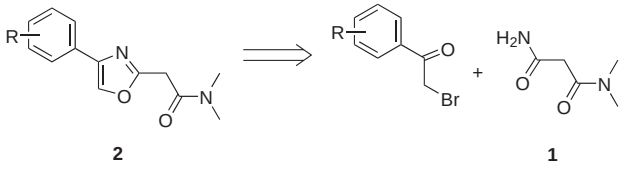
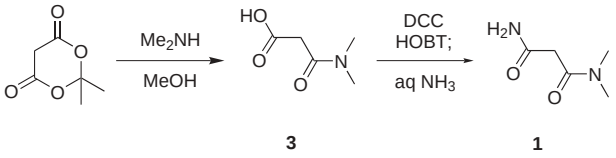


Figure 1

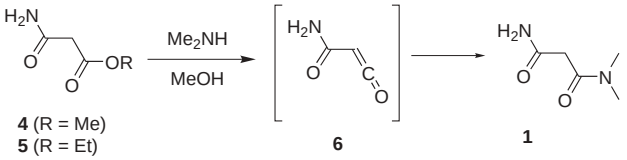
Our first synthesis of bis-amide **1** utilized a strategy described by Gellman to prepare a variety of unsymmetrical malonamides from Meldrum's acid (Scheme 1).[3] Amide-acid **3** was prepared by condensation of dimethylamine with Meldrum's acid, as described by Gellman. Activation with DCC and HOBT, followed by condensation with aqueous ammonia, provided bis-amide **1**, albeit in modest yield and contaminated with residual HOBT-derived impurities.

We next turned to commercially available methyl malonamide **4** (Scheme 2). Reasoning that the increased acidity of the central methylene might render this ester more prone to trans-amination, we treated **4** (or **5**) with 2 M Me_2NH in MeOH. After three days at room temperature, concentration and trituration with isopropanol provided **1** as a white solid, which was isolated by filtration in 87% yield on 50 g scale. We suspect that this remarkably facile ester-amide exchange is due to the intermediacy of ketene **6**.[4,5]



Scheme 1

On larger scale, it was more convenient to use gaseous Me_2NH. A methanol solution of **4** and **5** was treated with three equivalents of gaseous Me_2NH, added portionwise over the course of 3–4 days. The reaction was monitored by concentration of an aliquot and analysis by ^1H NMR. When >90% conversion was reached, the methanol was displaced with isopropanol, and the product collected by filtration. This procedure provided an 86% yield on 1 kg scale.



Scheme 2

With access to bis-amide **1**, we examined its condensation with a range of α-bromoketones (Table 1). It was found to be an effective reagent for formation of 2,4-disubstituted oxazoles by simply combining with the requisite bromoketone and warming to 100 °C in the polar, aprotic solvent *N*-methylpyrrolidinone (NMP). Following an aqueous workup, products were isolated by either trituration with isopropyl ether (IPE) (entries 1, 2), or by flash chromatography (entries 3–9). Most of the products were solids, and could be further purified by recrystallization from ethyl acetate–hexane.

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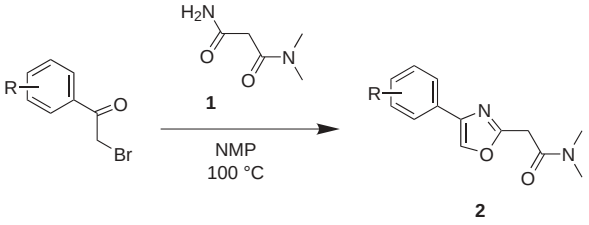


Scheme 3 Condensation of bis-amide **1** with bromoketones to provide oxazole **2** (see data in Table 1)

The majority of examples provided moderate to good yields (57–68%, entries 1–4, 7, 8). In these examples, the desired oxazole was the major product observed by TLC and ^{1}H NMR analysis. Silica gel chromatography retained a fair amount of colored impurities at the baseline, suggesting that the remaining mass balance was accounted for by competing processes that generated significantly more polar materials.

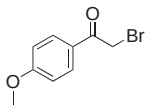
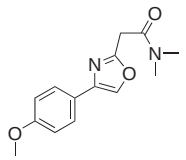
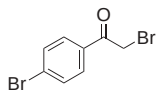
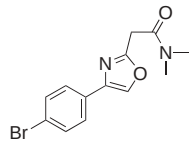
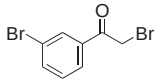
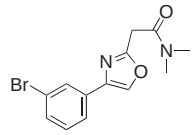
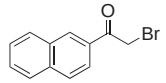
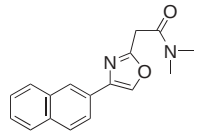
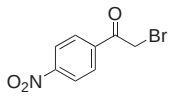
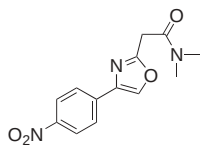
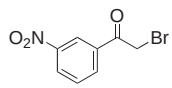
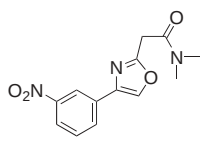
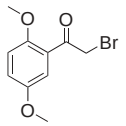
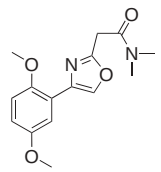
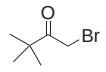
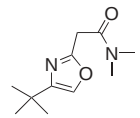
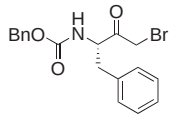
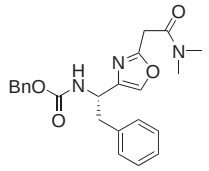
Electron deficient arenes were less efficient (entries 5 and 6), particularly the 4-nitro case (entry 5, 27% yield). One reason for this was competitive formation of the bromoreduction product 4-nitroacetophenone, which was isolated in 11% yield. The remaining mass balance was primarily in highly colored, polar impurities which remained at the baseline on silica gel, and which were not characterized. Interestingly, the *meta*-substituted nitro analogue suffers less severely from this effect (entry 6, 46% yield).

Entry 9 represents the only example in which there is an enolizable position α to the ketone on the other side of the α-bromo substituent. This substrate was also less efficient (39% yield), although apparently not due to enolization away from the α-bromoketone, as the optical purity was retained (as described below).

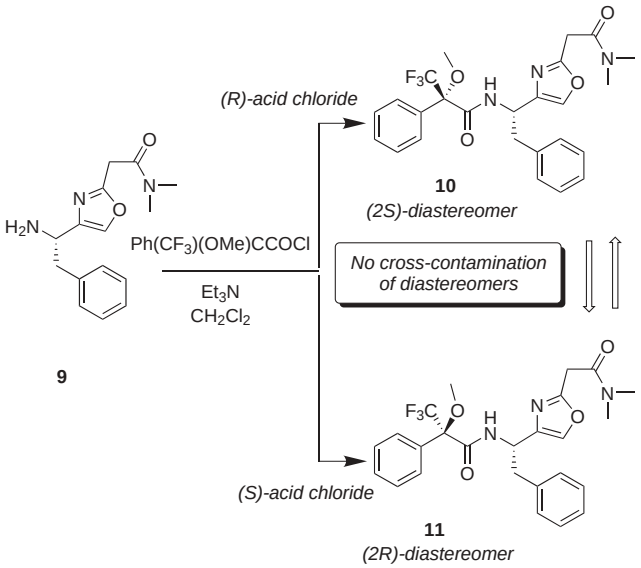
For entry 9, the question arises as to whether racemization of the phenylalanine-derived chiral center occurs under the reaction conditions. This was investigated by cleavage of the CBZ group and acylation of primary amine **9** with each enantiomer of Mosher's acid chloride (Scheme 4); three equivalents of the acid chloride were utilized to minimize potential kinetic resolution of amine enantiomers. The resulting diastereomeric amides (**10** and **11**) were readily separable by HPLC, and each diastereomer was formed as a single isomer within the limits of HPLC detection. Had racemization occurred, a mixture of diastereomers would be observed, in a ratio corresponding to the ratio of enantiomers in amine **9**.[6] Thus, oxazole **8** was formed as a single enantiomer within the limits of detection, retaining the optical purity of the precursor α-bromoketone.

The literature precedent for the indicated oxazole regioisomer is compelling, and is accounted for by the mechanism shown in Scheme 5 (O-alkylation of the bromide followed by cyclization). Because this outcome is not necessarily predictable a priori (e.g. N-alkylation of the bromide would lead to the 2,5-regioisomer), we subjected one of the product oxazoles (**2f**) to single-crystal X-ray

Table 1 Data for the Condensation of Bis-amide **1** with Bromoketones to Provide Oxazole **2**

Entry	Bromoketone	Product	Yield (mp, °C) [a]
1		 **2a**	58% (103.4–107.1)
2		 **2b**	59% (135.1–138.0)
3		 **2c**	57% (110.8–112.0)
4		 **2d**	63% (107.9–108.0)
5		 **2e**	27% (197.1–197.2)[b]
6		 **2f**	46% (147.7–149.2)[c]
7		 **2g**	59% (130.1–131.6)
8		 **7**	68% (62.8–63.9)
9		 **8**	39% (oil)

[a] Average of two or more runs.
[b] 4-Nitroacetophenone was also isolated in 11% yield.
[c] Structure confirmed by single crystal X-ray analysis (see Scheme 5).

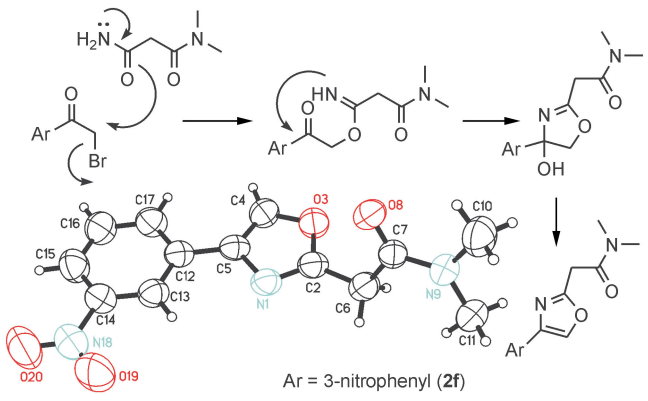


Scheme 4

analysis. This analysis confirmed the indicated regiochemistry about the oxazole ring, as shown in the ORTEP representation in Scheme 5.

In conclusion, a practical synthesis of *N*,*N*-dimethylpropanediamide **1** has been identified starting from esters **4** or **5**, and demonstrated on both laboratory and pilot plant (50–1000 g) scales. This bis-amide is useful for the preparation of a range of aryl- and alkyl-2,4-disubstituted oxazoles from α-bromoketones.

Reagents were purchased from commercial suppliers and used as received unless otherwise noted. *N*-Methylpyrrolidinone (NMP) was purchased in anhydrous form from Aldrich in 'Sure-Seal' glass bottles; all other solvents were reagent grade. Reactions were run under a positive pressure of nitrogen in flame-dried glassware. Reaction progress was monitored by TLC, on precoated sheets of 60 F254 (Merck Art. 5719), and visualized by UV, and/or staining with iodine, phosphomolybdic acid, ceric ammonium molybdate, or *para*-anisaldehyde solutions and heating. Mass spectral data were collected on either a Hewlett-Packard 5890 GC/MS (electron impact ionization), or a Micromass (Fisons) Platform II mas spectrometer (atmospheric pressure chemical ionization). Combustion analyses were performed by Schwarzkopf Microanalytical Laboratory (Woodside, NY) or Quantitative Technologies, Inc. (Whitehouse, NJ). All melting points are uncorrected.



Scheme 5

N,N-Dimethylpropanediamide (1):
Method A (50 g scale): Methyl malonamide **4** (50 g, 0.427 mol) was treated with 500 mL of 2 M Me_2NH in MeOH (1 mol) at r.t. Reaction progress was monitored by concentration of an aliquot and analysis by ^1H NMR. After 4 days, the reaction mixture was heated to distill MeOH, with portionwise addition of *i*-PrOH until the reaction volume was ca. 150 mL, and no more MeOH was present in the distillate. Upon cooling, solids formed, and the slurry was stirred overnight. Filtration, rinsing with isopropyl ether, provided 48.3 g of product (87% yield) as a white solid.

Method B (1 kg scale): A mixture of methyl malonamide **4** (450 g, 3.85 mol) and ethyl malonamide **5** (620 g, 4.73 mol) were charged to a 22 L round bottom flask equipped with an overhead mechanical stirrer, gas inlet tube, and a gas scrubber line through a trap charged with 1 N HCl. MeOH (10 L) was then charged, leading to a homogeneous solution.The Me_2NH gas (890 g, 20 mol, 2.3 equiv) was added over the course of 8 h via the gas inlet tube, which was submerged in the solution (the cylinder was weighed continuously during the addition to monitor stoichiometry). Periodic monitoring of the HCl trap indicated that the majority of the Me_2NH was retained in solution. The resulting solution was stirred for another 48 h, at which point NMR analysis indicated 71% conversion. An additional portion of Me_2NH (490 g, 11 mol, 1.3 equiv) was then added over 2 h, and the solution stirred for another 18 h. NMR analysis indicated >90% conversion. The reaction mixture was then placed under partial vacuum and heated on a steam bath to remove methanol through an efficient coiled condenser. When a volume of ca. 3 L was obtained, *i*-PrOH (4 L) was added (solids began to form at this point), and distillation was resumed until a final volume of ca. 5 L was reached. The solution was then cooled to r.t. and stirred overnight. After cooling for 2 h in an ice bath, solids were collected, rinsing with 400 mL cold *i*-PrOH and 1 L of isopropyl ether. The air-dried solids weighed 960 g (86% yield).

Mp 118.7–120.5 °C.

IR (thin film): 3400–3250 (br), 3203, 2949, 1721, 1669, 1616, 1406, 1257, 1216, 1058, 954 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.65–7.75 (br s, 1 H), 5.78–5.85 (br s, 1 H), 3.31 (s, 2 H), 3.05 (s, 3 H), 2.96 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 169.3, 168.3, 40.2, 38.0, 35.9.

MS (EI): *m/z* (%) = 130 (100).

Anal. Calcd for $C_5H_{10}N_2O_2$: C, 46.14; H, 7.74; N, 21.52. Found: C, 45.99; H, 7.62; N, 21.10.

General Procedure for Oxazole Annulation (2a–g, 7, 8):
The α-bromoketone (4–15 mmol) and bis-amide **1** (2.5 equiv) were combined in 2–3 volumes (mL/g of ketone) of NMP. The mixture was placed in a 100 °C oil bath for 4–24 h, until TLC or GC/MS analysis showed complete consumption of the ketone. The mixture was cooled, diluted with EtOAc, and washed with two portions of H_2O and two portions of brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated to provide the crude product, which was purified by chromatography (20–30 g SiO_2 per g of product), granulation in IPE (entries 2a and 2b), and/or crystallization from hexane-EtOAc. The yields in Table 1 represent the average of two or more runs.

2-[4-(4-Methoxy-phenyl)-oxazol-2-yl]-*N*,*N*-dimethylacetamide (2a):
Mp 103.4–107.1 °C.

IR (thin film): 3127, 2939, 1647, 1591, 1578, 1484, 1401, 1105, 1073, 980, 842 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.92 (s, 1 H), 7.53 (d, *J* = 9 Hz, 2 H), 6.80 (d, *J* = 9 Hz, 2 H), 3.82 (s, 2 H), 3.71 (s, 3 H), 2.87 (s, 3 H), 2.72 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 166.8, 159.6, 158.9, 140.8, 133.2, 126.9, 126.7, 123.8, 114.2, 37.9, 35.8, 34.7.

MS (EI): *m/z* (%) = 260 (100).

Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.49; H, 5.89; N, 10.73.

2-[4-(4-Bromo-phenyl)-oxazol-2-yl]-*N*,*N*-dimethylacetamide (2b):
Off-white solid, mp 135.1–138.0 °C.

IR (thin film): 3126, 2993, 2937, 2840, 1643, 1618, 1587, 1505, 1399, 1304, 1176, 1103, 1070, 1034, 846 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.88 (s, 1 H), 7.56 (d, *J* = 8 Hz, 2 H), 7.49 (d, *J* = 8 Hz, 2 H), 3.93 (s, 2 H), 3.10 (s, 3 H), 2.98 (s, 3 H).

MS (APCI): *m/z* = 309, 311 [M + H] (for ^{79}Br and ^{81}Br, 100%).

Anal. Calcd for $C_{13}H_{13}N_2O_2Br$: C, 50.50; H, 4.24; N, 9.06. Found: C, 50.45; H, 3.88; N, 8.23.

2-[4-(3-Bromo-phenyl)-oxazol-2-yl]-*N*,*N*-dimethylacetamide (2c):
Off-white solid, mp 110.8–112.0 °C.

IR (thin film): 3123, 2929, 1645, 1609, 1592, 1497, 1471, 1418, 1137, 1108, 1082, 727 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.88 (s, 1 H), 7.87 (t, *J* = 2 Hz, 1 H), 7.60 (dt, *J* = 1, 7 Hz, 1 H), 7.40 (ddd, *J* = 1, 2, 8 Hz, 1 H), 7.23 (t, *J* = 7 Hz, 1 H), 3.93 (s, 2 H), 3.10 (s, 3 H), 2.98 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 166.6, 159.4, 139.9, 134.9, 133.2, 131.2, 130.5, 128.7, 124.3, 123.1, 38.0, 36.0, 34.8.

MS (EI): *m/z* = 308, 310 [M] (for ^{79}Br and ^{81}Br, 100%).

Anal. Calcd for $C_{13}H_{13}N_2O_2Br$: C, 50.50; H, 4.24; N, 9.06. Found: C, 50.58; H, 4.16; N, 8.98.

***N*,*N*-Dimethyl-2-(4-naphthalen-2-yl-oxazol-2-yl)-acetamide (2d):**
Off-white solid, mp 107.9–108.0 °C.

IR (thin film): 3128, 3111, 3061, 2926, 1659, 1641, 1581, 1491, 1416, 1397, 1141, 1104, 1063, 821 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.25 (br s, 1 H), 7.98 (s, 1 H), 7.86–7.79 (m, 3 H), 7.72 (dd, *J* = 2, 8 Hz, 1 H), 7.48–7.42 (m, 2 H), 3.97 (s, 2 H), 3.10 (s, 3 H), 2.98 (s, 3 H).

^{13}C NMR ($CDCl_3$) one of the 14 sp^2 carbons not resolved: δ = 166.7, 159.3, 141.3, 134.8, 133.8, 133.3, 128.6, 128.4, 127.9, 126.6, 126.3, 124.6, 123.7, 38.0, 36.0, 34.9.

MS (APCI): *m/z* (%) = 281 (100) [M + H].

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.78; H, 5.65; N, 10.0.

2-[4-(4-Nitro-phenyl)-oxazol-2-yl]-*N*,*N*-dimethylacetamide (2e):
White solid, mp 197.1–197.2 °C.

IR (thin film): 3126, 2935, 1645, 1608, 1512, 1398, 1317, 1107, 1072 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.23 (d, *J* = 9 Hz, 2 H), 8.04 (s, 1 H), 7.86 (d, *J* = 9 Hz, 2 H), 3.96 (s, 2 H), 3.12 (s, 3 H), 2.99 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 166.5, 160.0, 147.4, 139.4, 137.5, 136.5, 126.2, 124.4, 37.9, 36.0, 34.6.

MS (APCI): *m/z* (%) = 276 (100) [M + H].

Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.54; H, 4.61; N, 15.09.

2-[4-(3-Nitro-phenyl)-oxazol-2-yl]-*N*,*N*-dimethylacetamide (2f):
Off-white solid, mp 147.7–149.2 °C.

IR (thin film): 3125, 3097, 2957, 1646, 1591, 1525, 1496, 1417, 1400, 1345, 1145, 1098, 731 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.53–8.52 (m, 1 H), 8.13–8.10 (m, 1 H), 8.01 (s, 1 H), 8.02–8.00 (m, 1 H), 7.53 (t, *J* = 8 Hz, 1 H), 3.95 (s, 2 H), 3.12 (s, 3 H), 2.99 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 166.6, 159.8, 148.8, 139.3, 135.6, 133.0, 131.5, 129.9, 122.8, 120.6, 38.0, 36.0, 34.6.

MS (APCI): *m/z* (%) = 276 (100) [M + H].

Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.74; H, 4.59; N, 15.24.

2-[4-(2,5-Dimethoxy-phenyl)-oxazol-2-yl-*N*,*N*-dimethylacetamide (2g):
Off-white solid, mp 130.1–131.6 °C.

IR (thin film): 3156, 2951, 2936, 2835, 1642, 1467, 1278, 1255, 1179, 1158, 1089, 1057, 1041, 855 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.13 (s, 1 H), 7.67 (d, *J* = 3 Hz, 1 H), 6.87 (d, *J* = 9 Hz, 1 H), 6.81 (dd, *J* = 3, 9 Hz, 1 H), 3.96 (s, 2 H), 3.89 (s, 3 H), 3.83 (s, 3 H), 3.11 (s, 3 H), 2.99 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 166.9, 157.6, 154.0, 151.0, 138.3, 136.3, 120.8, 114.3, 112.9, 111.9, 56.1, 56.0, 38.0, 36.0, 34.9.

MS (EI): *m/z* (%) = 290 (100) [M].

Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65. Found: C, 61.94; H, 5.92; N, 9.61.

2-[4-*tert*-Butyl-oxazol-2-yl]-*N*,*N*-dimethyl-acetamide (7):
Off-white solid, mp 62.8–63.9 °C.

IR (thin film): 3104, 2965, 2903, 2868, 1643, 1585, 1408, 1359, 1146, 1082, 843 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.26 (s, 1 H), 3.85 (s, 2 H), 3.04 (s, 3 H), 2.95 (s, 3 H), 1.22 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 167.1, 158.2, 150.8, 132.6, 37.8, 35.9, 35.0, 31.0, 29.4.

MS (EI): *m/z* (%) = 210 (80), 139 (60), 72 (100).

Anal. Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 63.01; H, 8.59; N, 13.29.

(*S*)-[1-(2-Dimethylcarbamoylmethyl-oxazol-4-yl)-2-phenyl-ethyl]-carbamic acid benzyl ester (8):
Pale yellow oil.

IR (thin film): 3296, 2933, 1720, 1650, 1454, 1402, 1256, 1140, 1046, 741, 700 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.33–7.16 (m, 9 H), 7.07–7.05 (m, 2 H), 5.48 (br d, *J* = 8 Hz, 1 H), 5.05 (d, *J* = 12 Hz, 1 H), 5.01 (d, *J* = 12 Hz, 1 H), 4.96–4.92 (m, 1 H), 3.83 (s, 2 H), 3.16–3.04 (m, 2 H), 3.01 (s, 3 H), 2.95 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 166.7, 159.1, 155.8, 140.4, 137.3, 136.7, 135.7, 129.l6, 128.7, 128.6, 128.3, 128.2, 126.8, 66.9, 49.4, 40.9, 37.9, 35.9, 34.8.

MS (APCI): *m/z* (%) = 408 (100) [M + H].

(1′*S*,2*S*)-*N*-[1′-(2-Dimethylcarbamoylmethyl-oxazol-4-yl)-2′-phenyl-ethyl]-3,3,3-trifluoro-2-methoxy-2-phenyl-propionamide (10):

CBZ-oxazole **8** (556 mg, 1.37 mmol) was dissolved in 15 mL EtOAc, and added to a pressure bottle containing a slurry of 10% Pd/C (50% H_2O wet, 203 mg) in 5 mL EtOH. The mixture was subjected to 45 psi hydrogen on a Parr shaker for 16 h. After purging with N_2, the slurry was filtered through celite, rinsing with EtOAc. Concentration provided the desired amine as a pale yellow oil (652 mg) contaminated with some unconsumed starting material (ca. 5%) and residual NMP. This material was dissolved in 30 mL of 0.1 N HCl, and extracted with three 5 mL portions of EtOAc. The aqueous phase was made basic with 15% NaOH, and extracted with four 10 mL portions of CH_2Cl_2. The organic extracts were dried over K_2CO_3, filtered, and concentrated to provide the desired amine **9** as a pale yellow oil (223 mg, 60% yield). This material was used without further purification in the next two reactions.

Amine **9** (61 mg, 0.23 mmol) was dissolved in 1 mL CH_2Cl_2 and treated with Et_3N (0.16 mL, 1.15 mmol, 5 equiv) and (*R*)-(–)-Mosher's acid chloride (0.13 mL, 0.69 mmol, 3 equiv). After stirring at r.t. for 16 h, 20% aq Na_2CO_3 (2 mL) was added, and the mixture stirred vigorously for 30 min. Extraction with two 5 mL portions of CH_2Cl_2, drying over $MgSO_4$, filtration, and concentration provided a clear, orange oil. This material was purified on 6 g silica gel, eluting with 1:2 to 1:4 hexane–EtOAc. Product-containing fractions were combined and concentrated to provide amide **10** as a pale yellow oil (79 mg, 71% yield).

^{1}H NMR ($CDCl_3$): δ = 7.34–7.07 (m, 11 H), 5.31 (dd, *J* = 8, 15 Hz, 1 H), 3.87 (s, 2 H), 3.23 (s, 3 H), 3.11 (ddd, *J* = 8, 15, 22 Hz, 2 H), 3.02 (s, 3 H), 2.96 (s, 3 H).

HPLC retention time: 9.89 min (reverse phase column, 60:40 aq phosphate buffer/MeCN).

(1′*S*,2*R*)-*N*-[1′-(2-Dimethylcarbamoylmethyl-oxazol-4-yl)-2′-phenyl-ethyl]-3,3,3-trifluoro-2-methoxy-2-phenyl-propionamide (11):

The same procedure described for amide **10** was repeated, using (*S*)-(+)-Mosher's acid chloride, to provide amide **11** as a waxy, colorless solid (95 mg, 78% yield). Comparison of the crude NMR spectra and HPLC traces of **10** and **11** prior to chromatography showed no detectable cross-contamination.

^{1}H NMR ($CDCl_3$): δ = 7.41–7.09 (m, 11 H), 5.24 (dd, *J* = 8, 16 Hz, 1 H), 3.82 (s, 2 H), 3.19 (s, 3 H), 3.14 (apparent d, *J* = 8 Hz, 2 H), 2.99 (s, 3 H), 2.94 (s, 3 H).

HPLC retention time: 10.87 min.

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(3) (a) Gellman, S. H.; Dado, G. P.; Liang, G.-B.; Adams, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 1164. (b) Interestingly, both Beilstein and Sci-Finder searches for bis-amide **1** gave the preceding reference for its synthesis. We suspect that this was a typographical error upon entry in these databases, as there is no description of compound **1** in the Gellman paper. The Beilstein reference gives a reaction time of 63 h and 81% yield, values which are identical to the first experimental procedure in the paper, in which the mono-*N*,*N*-dimethylamide of malonic acid (**3**) is prepared en route to *N*,*N*,*N*′-trimethylpropanediamide.

(4) This effect has recently been noted in the esterification of carboxylic acids activated at the α-carbon with phosphonates, esters, sulfones, and nitriles. A mechanism proceeding through an acyl ketene was supported by trapping of the ketene with DCC in a [4+2] cycloaddition: Shelkov, R.; Nahmanh, M.; Melman, A. *J. Org. Chem.* **2002**, *67*, 8975.

(5) Intermediacy of a ketene is also supported by the following experiment: exposure of ethyl benzoate to the same reaction conditions (2 N Me_2NH in MeOH) for several days showed no detectable formation of *N*,*N*-dimethylbenzamide by ^{1}H NMR or GC/MS.

(6) Actually, the opposite enantiomer of the other diastereomer would be formed. For example, in the condensation of the *R*-acid chloride with racemic amine, the products are amide **10** and (*ent*)-**11**. This has no impact on the achiral HPLC and NMR analyses, however.