Supporting Information for:

Heavier Alkaline Earth Amides as Catalysts for the Tischenko Reaction

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Experimental procedures

General procedures

All manipulations were carried out using standard Schlenk line and glovebox techniques under an inert atmosphere of either nitrogen or argon. All solvents were distilled under dinitrogen and dried with conventional drying agents. Volatile non-enolizable aldehydes were dried over CaH₂, distilled and freeze-thaw degassed prior to use. Enolizable aldehydes were distilled directly before use. The β -diketiminate ligand ArNHC(Me)CHC(Me)NAr (Ar = 2,6-diisopropylphenyl), the heteroleptic amide **1** and the homoleptic heavier alkaline earth amides M{N(SiMe₃)₂}₂(THF)₂ (M = Ca, Sr and Ba) were synthesized by literature procedures.¹⁻²

Heavier alkaline earth catalyzed dimerization of aldehydes

NMR scale experiments: In a glove box, the aldehyde (20 μ L, 0.115 mmol) was added to a solution of the catalyst (1-5 mol %) in C₆D₆ either by micro-pipette or as a solution in the same solvent. The solution was then loaded into a Young's tap NMR and the reaction monitored by ¹H NMR spectroscopy. The NMR yield was measured by integration of the product and starting material peaks, using the -N(SiMe₃)₂ group as an internal standard.

General preparative scale experiment: To a solution of the aldehyde (10 mmol) in dried benzene (5 mL) under an atmosphere of nitrogen at room temperature was added $\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2(\text{THF})_2$ (0.1–0.5 mmol) as a 0.2 M solution in benzene. Typically, upon addition an exothermic reaction was observed. The reaction mixture was then stirred for 24 h at room temperature, quenched with H_2O and extracted with diethyl ether (3 x 20 mL). The combined ether extracts were dried over MgSO_4 and the solvent removed *in vacuo* to yield the crude ester. The latter could be purified by flash column chromatography upon silica gel, recrystallization or bulb-to-bulb distillation.

Synthesis of benzyl benzoate:

The aldehyde (1.6 g, 15.1 mmol) was dimerized using 1 mol% of the catalyst, the product could be purified by distillation to give the ester as a viscous colourless oil (1.19 g, 5.59 mmol, 74 %). ^1H NMR (CDCl_3 , 400 MHz) 5.27 (s, 2H), 7.22–7.37 (m, 7H), 7.45 (t, 1H, $J = 7.4$, 7.4), 8.0 (dd, 2H, $J = 7.9$, 1.0); ^{13}C NMR (CDCl_3 , 100 MHz) 66.5, 128.0, 128.1, 128.2, 128.5, 129.6, 123.0, 132.9, 135.9, 166.2; IR (neat, cm^{-1}) 3065, 3033, 2953, 2889, 1723, 1601, 1585, 1452, 1376, 1314, 1270, 1108, 1026.³

Synthesis of 3-trifluorobenzyl 3-trifluorobenzoate:

The aldehyde (1.70 g, 9.7 mmol) was dimerized using 2 mol% catalyst (99 mg, 0.20 mmol), the product could be purified by flash column chromatography to give the ester as a viscous colourless oil (1.48 g, 4.3 mmol, 87 %). ^1H NMR (CDCl_3 , 400 MHz) 5.45 (s, 2H), 7.51–7.67 (m, 4H), 7.71 (apparent s, 1H), 7.83 (d, 1H, $J = 7.8$), 8.26 (d, 1H, $J = 7.9$), 8.34 (apparent s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) 66.3, 122.4 (q, $J = 31.7$), 125.1 (q, $J = 5.4$), 125.2 (q, $J = 31.5$), 125.3 (q, $J = 3.6$), 126.6 (q, $J = 3.7$), 129.1, 129.2, 129.8 (q, $J = 3.4$), 130.6, 131.0 (q, $J = 5.3$), 131.3 (q, $J = 5.9$), 131.6, 132.9, 136.5, 165.0; ^{19}F NMR (CDCl_3) -62.7, -62.8; m/z (CI, ammonia) 366 ($[\text{M}+\text{NH}_4]^+$, 100 %), 173 ($[\text{M}-\text{C}_8\text{H}_6\text{F}_3\text{O}]^+$,

20 %). Anal. Calc. for $C_{16}H_{10}F_6O_2$; HRMS calc. for $C_{16}H_{14}NO_2F_6$ 366.0929 found 366.0928.

Synthesis of 3-methoxybenzyl 3-methoxybenzoate:

The aldehyde (1.75 g, 12.9 mmol) was dimerized using 5 mol% catalyst (325 mg, 0.64 mmol), the product could be purified by distillation to give a viscous colourless oil (1.26 g, 4.6 mmol, 72 %). 1H NMR ($CDCl_3$, 400 MHz) 3.72 (s, 3H), 3.74 (s, 3H), 5.24 (s, 2H), 6.78 (dd, 1H, $J = 8.2, 2.4$) 6.89 (s, 1H), 6.93 (d, 1H, $J = 7.5$), 7.00 (dd, 1H, $J = 7.9, 2.3$), 7.18-7.24 (m, 2H), 7.50 (s, 1H), 7.58 (d, 1H, $J = 7.7$); ^{13}C NMR ($CDCl_3$, 100 MHz) 55.1, 55.3, 66.5, 113.5, 113.5, 114.1, 119.4, 120.2, 122.0, 129.3, 129.6, 131.3, 137.5, 159.5, 159.7, 166.1; IR (neat, cm^{-1}) 2938, 2836, 1721, 1600, 1488, 1454, 1275, 1225, 1157, 1103, 1042; m/z (CI, ammonia) 290 ($[M+NH_4]^+$, 100 %), 169 ($[M+NH_4 - C_8H_9O]^+$, 70 %), 152 ($[M-C_8H_8O]^+$, 30 %); HRMS calc. for $C_{16}H_{20}NO_4$ 290.1392 found 290.1397.

Synthesis of 4-methoxybenzyl 4-methoxybenzoate:

The aldehyde (1.75 g, 12.9 mmol) was dimerized using 5 mol% catalyst (325 mg, 0.64 mmol), the product could be purified by distillation to give a viscous colourless oil (0.17 g, mmol, 10 %). 1H NMR ($CDCl_3$, 400 MHz) 3.82 (s, 3H), 3.85 (s, 3H), 5.28 (s, 2H), 6.91 (d, 2H, $J = 8.9$), 6.93 (d, 2H, $J = 8.7$), 7.40 (d, 2H, $J = 8.7$), 8.03 (d, 2H, $J = 8.9$); ^{13}C NMR ($CDCl_3$, 100 MHz) 55.1, 55.3, 66.2, 113.5, 113.8, 122.6, 128.3, 129.9, 131.6, 159.4, 163.3, 166.1; IR (neat, cm^{-1}) 3002, 2933, 2838, 1715, 1605, 1513, 1456, 1274, 1167, 110, 1032.⁴

Synthesis of 4-phenylbenzyl 4-phenylbenzoate:

The aldehyde (2.0g, 11.0 mmol) was dimerized using 2.5 mol% catalyst (138 mg, 0.27 mmol), the product was isolated by recrystallization of the crude from diethyl ether/hexane to give a white solid (1.48 g, 4.1 mmol, 74 %). M.p (CHCl₃) 140-142 °C; ¹H NMR (CDCl₃, 400 MHz) 5.46 (s, 2H), 7.36-7.44 (m, 2H), 7.47-7.51 (m, 4H), 7.57 (d, 2H, *J* = 8.2), 7.62-7.68 (m, 6H), 7.69 (d, 2H, *J* = 8.4), 8.19 (d, 2H, *J* = 8.4); ¹³C NMR (CDCl₃, 100 MHz) 66.4, 127.0, 127.1, 127.2, 127.3, 127.4, 128.1, 128.7, 128.8 (2 signals) 128.9, 130.2, 135.1, 139.9, 140.7, 141.2, 145.8, 166.3; IR (nujol mull, cm⁻¹) 3055, 2927, 2853, 1713, 1604, 1453, 1266, 1104, 1041; m/z (CI, ammonia) 382 ([M+NH₄]⁺, 100 %), 184 ([M-C₁₃H₈O]⁺, 90 %); HRMS calc. for C₂₆H₂₄NO₂ 382.1807 found 382.1811.

Synthesis of 4-bromobenzyl 4-bromobenzoate:

The aldehyde (2.0g, 10.8 mmol) was dimerized using 5 mol% catalyst (272 mg, 0.54 mmol), the product was isolated by recrystallization of the crude from hexane at 0 °C to give the product as a white crystalline solid (1.39 g, 3.75 mmol, 70 %) ¹H NMR (CDCl₃, 400 MHz) 5.29 (s, 2H), 7.30 (d, 2H, *J* = 8.3), 7.51 (d, 2H, *J* = 8.3), 7.58 (d, 2H, *J* = 8.6), 7.91 (d, 2H, *J* = 8.6); ¹³C NMR (CDCl₃, 100 MHz) 66.1, 128.3, 128.8, 128.9, 129.9, 131.2, 131.8, 131.9, 134.7, 165.6; IR (DCM film, cm⁻¹) 2924, 2853, 1713, 1589, 1483, 1267, 1117, 1103, 1067.⁵

Synthesis of 2-chloro-4-fluorobenzyl 2-chloro-4-fluorobenzoate:

The aldehyde (2.0g, 12.6 mmol) was dimerized using 5 mol% catalyst (319 mg, 0.63 mmol) over 4 days at room temperature, the product was isolated by recrystallization from a hexane/dichloromethane mixture to give colorless crystals (0.80 g, 2.52 mmol, 40%). M.p (CHCl₃) 87-88 °C; ¹H NMR (CDCl₃, 400 MHz) 5.42 (s, 2H), 6.98-7.05 (m, 2H), 7.16-7.21 (m, 2H), 7.51 (dd, 1H, *J* = 8.5, 6.0), 7.94 (dd, 1H, *J* = 8.2, 6.1); ¹³C NMR (CDCl₃, 100 MHz) 64.1, 114.1 (d, *J* = 5.0), 114.3 (d, *J* = 4.8), 117.2 (d, *J* = 24.8), 118.7 (d, *J* = 24.8), 125.5 (d, *J* = 3.2), 129.2 (d, *J* = 3.4), 131.8 (d, *J* = 7.0), 133.8 (d, *J* = 9.7), 135.0 (d, *J* = 10.5), 136.0 (d, *J* = 11.1), 162.1 (d, *J* = 173.7), 164.2, 164.6 (d, *J* = 179.7); ¹⁹F (CDCl₃) -110.8, -104.8; IR (DCM film, cm⁻¹) 2932, 2855, 1724, 1301, 1582, 1490, 1453, 1254, 1117, 1040; m/z (CI, ammonia) 334 ([M+NH₄]⁺, 100 %); HRMS calc. for C₁₄H₁₂NO₂F₂Cl₂ 334.0213 found 334.0215.

Synthesis of Phthalide:

The dialdehyde (2.00 g, 14.9 mmol) was cyclized using 2 mol% catalyst (151 mg, 0.30 mmol), the product could be purified by recrystallization from DCM : hexane to give the lactone as a white crystalline solid (1.62 g, 12.1 mmol, 81 %). ¹H NMR (CDCl₃, 400 MHz) 5.31 (s, 2H), 7.48-7.54 (m, 2H), 7.68 (ddd, 1H, *J* = 7.6, 7.7, 1.0), 7.90 (d, 1H, *J* = 7.7); ¹³C NMR (CDCl₃, 100 MHz) 69.6, 122.0, 125.4, 128.8, 132.9, 146.4, 171.0; IR (KBr disc, cm⁻¹) 3059, 2945, 2924, 1748, 1465, 1439, 1050, 1000, 739.⁵

Synthesis of cyclohexyl cyclohexanoate:

The aldehyde (0.65 g, 5.8 mmol) was dimerized using 5 mol% catalyst (147 mg, 0.29 mmol) and the product isolated as a colourless oil by bulb-to-bulb distillation (0.53 g, 2.37 mmol, 82 %). ¹H NMR (CDCl₃, 400 MHz) 0.91-0.97 (m, 2H), 1.19-1.30 (m, 6H), 1.38-1.47 (m, 2H), 1.57-1.80 (m, 9H), 1.87-1.92 (m, 2H), 2.28 (1H, dddd, *J* = 3.6, 3.6, 11.3, 11.3), 3.86 (d, 2H, *J* = 6.5); ¹³C NMR (CDCl₃, 100 MHz) 25.4, 25.6, 25.7, 26.3, 29.0, 29.6, 37.1, 43.2, 69.2, 176.1; IR (neat, cm⁻¹) 2929, 2854, 1731, 1449, 1312, 1247, 1171, 1037, 915.³

Synthesis of *tert*-butyl *tert*-butanoate:

The aldehyde (0.95 g, 11.0 mmol) was dimerized using 2 mol% catalyst (112 mg, 0.22 mmol), the pure product was isolated directly from the reaction as a colourless oil (0.91 g, 96 %). ¹H NMR (CDCl₃, 400 MHz) 0.85 (s, 9H), 1.12 (s, 9H), 3.64 (s, 2H); ¹³C NMR (CDCl₃, 100 MHz) 26.4, 27.2, 31.5, 39.0, 73.6, 178.5; IR (neat, cm⁻¹) 2969, 2933, 2873, 1730, 1480, 1366, 1285, 1161, 1039.³

Dimerization of benzaldehyde using 0.1-0.2 mol% of catalyst

Benzaldehyde was dried over CaH₂ under an atmosphere of N₂, distilled under vacuum and stored under nitrogen in a Young's tap schlenk.

0.1 mol% Catalyst: Ca{N(SiMe₃)₂}₂(THF)₂ (252 mg, 0.5 mmol, 0.1 mol%) was weighed into a schlenk and the benzaldehyde (53 g, 0.5 mol) was added by cannula, an initial exothermic reaction was observed. The reaction was stirred at room temperature and monitored by removing aliquots and analyzing by ¹H NMR spectroscopy. The

reaction was 67 % complete after 88 h at room temperature. Benzaldehyde was removed by distillation at reduced pressure (30 °C at 1.0 mbar) and the residue was taken up in DCM (100 mL), washed with water, dried over MgSO_4 and the solvent removed to give benzyl benzoate (33.18 g, 156 mmol, 62.5 %).

0.2 mol% Catalyst: In a glove box, benzaldehyde (45 g, 0.424 mol) was weighed into a schlenk and $\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2(\text{THF})_2$ (450 mg, 0.89 mmol, 0.21 mol%) was added as a solid. The schlenk was sealed, removed from the glovebox and attached to a vacuum line. The reaction was stirred at room temperature and monitored by removing aliquots and analyzing by ^1H NMR spectroscopy. The reaction was 75 % complete after 48 h at room temperature. Benzaldehyde was removed by distillation at reduced pressure (30 °C at 1.0 mbar) and the residue was taken up in DCM (100 mL), washed with water, dried over MgSO_4 and the solvent removed to give benzyl benzoate (33.45 g, 158 mmol, 74.4 %)

Heavier alkaline earth catalyzed polymerization of terephthalaldehyde (1,4-(CHO) $_2$ C $_6$ H $_4$)

To a stirred solution of terephthalaldehyde (1,4-(CHO) $_2$ C $_6$ H $_4$) (2.0g, 14.9 mmol) in C_6H_6 (20 mL) was added a 0.2 M solution of $\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2(\text{THF})_2$ or $\text{LCa}\{\text{N}(\text{SiMe}_3)_2\}(\text{THF})$ (0.15 mmol) in the same solvent. The reaction was stirred and became viscous within 30 min at room temperature. Stirring overnight resulted in solidification of the reaction mixture. The reaction was quenched with H_2O (20 mL) and extracted with dichloromethane (3 x 50 mL). The combined organics were dried over magnesium sulfate, the solvent removed *in vacuo* and the resultant solid collected by filtration. ^1H NMR analysis showed a complex spectrum with multiple CHO end-groups.

Figure 1. GPC trace of polymer isolated from the reaction of (1,4-(CHO)₂C₆H₄) with **1**

Analysis of reaction by-products

To a stirred solution of benzaldehyde (500 mg, 4.7 mmol) in benzene was added a 0.2 M solution of $\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2(\text{THF})_2$ (238 mg, 0.47 mmol). After 5 min at room temperature, the reaction was quenched by exposure to the atmosphere, filtered and analyzed by GC-MS.

Figure 2. GC-MS trace of the products from the reaction of PhCHO with 10 mol% **2a** quenched after 5 min at room temperature

References

- (1) Carey, D. T.; Cope-Eatough, E. K.; Vilaplana-Mafé, E.; Mair, F. S.; Pritchard, R. G.; Warren, J. E.; Woods, R. J. *Dalton Trans.* **2003**, 1083-1093.
- (2) (a) M. H. Chisholm, J. Gallucci and K. Phomphari, *Chem. Commun.* **2003**, 48; (b) M. H. Chisholm, J. Gallucci and K. Phomphari, *Inorg. Chem.* **2004**, *43*, 6717.
- (3) Morita, K.-I.; Nishiyama, Y.; Ishii, Y., *Organometallics* **1993**, *12*, 3748.
- (4) Onozawa, S.-Y.; Sakakura, T.; Tanaka, N.; Shino, M., *Tetrahedron* **1996**, *52*, 4291.
- (5) Burgstein, M. R.; Berberich, H.; Roesky, P. W., *Chem. Eur. J.*, **2001**, *7*, 3078.

NMR Characterisation Data

5.270
7.236
7.242
7.253
7.269
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7.300
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