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Cross coupling reactions of organozinc iodides with solid-supported electrophiles: synthesis of 4-substituted benzoic and 3-substituted (*E*)- and (*Z*)-propenoic acids and amides

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The solid-supported iodobenzoic acid derivatives **8**–**10** were coupled with a range of organozinc reagents **1**–**4** under palladium(0) catalysis. The coupled products released by acidic cleavage with TFA were obtained in high purities after recrystallisation. Analogous coupling of solid-supported (*E*)- and (*Z*)-3-iodoacrylic acids **18a**, **18b**, **19** and **20** gave (*E*)- and (*Z*)-α,β-unsaturated acids and amides **21**–**27** stereospecifically.

Introduction

The advantages of using solid-phase synthesis techniques for the rapid preparation of functionalised targets have been widely recognised. Early solid-phase work was concerned with the preparation of carbon–heteroatom bonds, and it is only relatively recently that methods for the formation of carbon–carbon bonds have been widely explored, and reviewed.[1,2] The power of Pd-catalysed processes in the formation of carbon–carbon bonds has been recognised, and large sections of both reviews have been devoted to examples of the Stille, Heck and Suzuki reactions. It is quite striking that the Negishi reaction has been exploited to a much smaller extent, although the reaction of aryl and benzylic zinc halides with solid-supported aryl halides and triflates has been reported by Arlt[3] and Knochel.[4] The preparation of solid-supported zinc reagents has also been explored: Kondo has reported the preparation of solid-supported aryl zincates,[5] and we have reported a method for the synthesis of solid-supported dialkylzinc reagents.[6] Subsequently, the preparation of solid-supported imidazol-2-yl zinc halides has been described.[7]

We now report the results of a study into the use of aliphatic zinc reagents, including those derived from amino acids, in cross coupling reactions with solid-supported 4-iodobenzoic acid, and also both (*E*)- and (*Z*)-3-iodopropenoic acid. This has resulted in the development of a straightforward solid-phase method for the synthesis of 4-substituted benzoic acids and 3-substituted (*E*)- and (*Z*)-propenoic acids, and the corresponding primary amides, following cleavage from the resin.

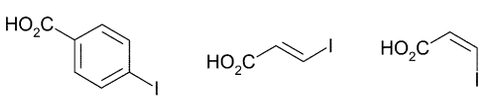
As representative organozinc iodides, we selected the simple pentylzinc iodide **1**, the iodopropionate derivative **2** and the two serine-derived reagents **3** and **4**.

1 **2** **3**, R = Z, R' = ^{t}Bu; **4**, R = Fmoc, R' = Me

In considering a solid support, we selected Wang resin,[8] since it is widely used (including in Knochel's work) and easily prepared. We also chose to use a PEG-grafted polystyrene resin because the PEG graft confers wider solvent compatibility, and affects the solvent environment within the gel. In choosing the NovaSyn® TG HMP support we noted that the cleavage conditions were similar to those required for Wang resin. We also chose the more highly acid labile Rink acid and amide resins, so as to explore the compatibility of this chemistry with these linkers.

Results and discussion

Three acids, 4-iodobenzoic acid **5**, (*E*)-3-iodoacrylic acid **6** and (*Z*)-3-iodoacrylic acid **7** were immobilised on the resins using DCC coupling conditions, with 3 molar equivalents being used relative to the resin. Although loading of the 4-iodobenzoic acid proceeded smoothly, careful control of the conditions was necessary for successful loading of the iodoacrylic acids. Treatment of 3-iodoacrylic acids with carbodiimides gives activated *O*-acyl intermediates which rearrange to the *N*-acyl species. As already noted in solution-phase studies,[9,10] this unproductive process can be avoided by conducting the reaction at −20 °C in dichloromethane. The loading of the solid-supported iodo acids and amides was determined by cleavage of the acid/amide from a portion of resin with TFA, under conditions appropriate for the individual resin.



5 **6** **7**

Coupling of solid-supported iodobenzene derivatives

The resin-bound iodobenzene derivatives **8**–**11** (0.1–0.5 mmol) were treated with three molar equivalents of a representative selection of the organozinc reagents **1**–**4**, under palladium catalysis. The organozinc reagents were prepared from the corresponding iodides using zinc dust in THF at ambient temperature. The organozinc solutions were decanted from excess zinc and added to the solid-supported partners and catalyst. The active catalyst was prepared *in situ* from $Pd_2(dba)_3$ and P(*o*-tolyl)$_3$. Reactions were performed in THF at ambient temperature, overnight. The catalyst and by-products were removed from the solid-supported products by thorough washing, and the coupled products released by treatment with TFA. A 50% solution of TFA was used for Wang and Rink amide resins, and neat TFA was used for the NovaSyn® resin. The products from

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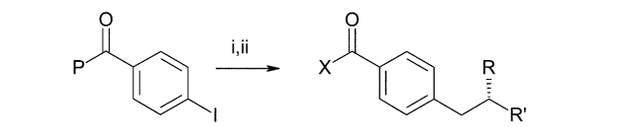
Table 1 Preparation of 4-substituted benzoic acids and 4-substituted benzamides

Aryl iodide	Organozinc	Product	Yield (%)[a]
8	**1**	**12**	78
8	**2**	**13**	99
8	**3**	**14**	83
8	**4**	**15**	49
9	**1**	**12**	87
9	**2**	**13**	95
9	**3**	**14**	93
10	**1**	**16**	55
10	**2**	**17**	49

[a] Isolated yield.

cleavage of the Wang and NovaSyn® TG HMP resin supported electrophiles were the free acids, whilst primary amides resulted from cleavage of the Rink amide-supported resin (Scheme 1, Table 1).



P = Wang-O, **8**
P = NovaSyn® TentaGel-HMP-O, **9**
P = Rink-NH, **10**
P = Rink-O, **11**

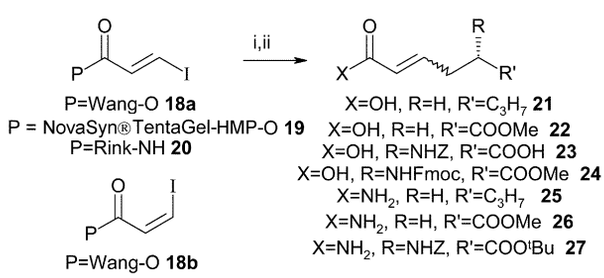
X=OH, R=H, R'=C_3H_7, **12**
X=OH, R=H, R'=COOMe, **13**
X=OH, R=NHCBz, R'=COOH, **14**
X=OH, R=NHFmoc, R'=COOMe, **15**
X=NH_2, R=H, R'=C_3H_7, **16**
X=NH_2, R=H, R'=COOMe, **17**

Scheme 1 *Reagents and conditions*: i, organozincs **1**–**4** in THF (3 equiv.), $Pd_2(dba)_3$ (10 mol%), P(*o*-tolyl)$_3$ (40 mol%), room temp., 16 h; ii, TFA–dichloromethane, 1 h.

Coupling of Rink 4-iodobenzoate **11** with organozinc iodide **2** failed to give either the coupled product **13** or 4-iodobenzoic acid **5**, after treatment with TFA. We reasoned that the acid-labile Rink ester might undergo cleavage under the conditions of the coupling reaction. Treatment of Rink 4-iodobenzoate resin **11** with 3 molar equivalents of zinc iodide in THF, at ambient temperature for 30 min, gave 4-iodobenzoic acid **5** in quantitative yield, supporting this proposal.

Synthesis of α,β-unsaturated acids and amides

Having established the scope and limitations of the process using supported aryl iodides, we now considered the coupling of organozinc reagents to (*E*)- and (*Z*)-iodoacrylic acid derivatives. The organozincs **1**–**4** were coupled with the resin-supported electrophiles **18a**, **18b**, **19** and **20** to give the α,β-unsaturated acids and amides **21**–**27** (Scheme 2, Table 2).



P=Wang-O **18a**
P = NovaSyn®TentaGel-HMP-O **19**
P=Rink-NH **20**

P=Wang-O **18b**

X=OH, R=H, R'=C_3H_7 **21**
X=OH, R=H, R'=COOMe **22**
X=OH, R=NHZ, R'=COOH **23**
X=OH, R=NHFmoc, R'=COOMe **24**
X=NH_2, R=H, R'=C_3H_7 **25**
X=NH_2, R=H, R'=COOMe **26**
X=NH_2, R=NHZ, R'=COO^{t}Bu **27**

Scheme 2 *Reagents and conditions*: i, organozincs **1**–**4** in THF (3 equiv.), $Pd_2(dba)_3$ (10 mol%), P(*o*-tolyl)$_3$ (40 mol%), room temp., 16 h; ii, TFA–dichloromethane, 1 h.

The stereochemistry of the iodoacrylates **18a** and **18b**, and **19** and **20**, was conserved during the coupling reactions. Cleavage of the products from the resin was again effected with TFA (50% for the Wang-supported products, neat for the NovaSyn® TG HMP derivatives and 1% for the Rink amide-supported product). The use of these much milder cleavage conditions for the Rink amide derivative allowed the isolation of the *tert*-butyl ester **27**.

Table 2 Preparation of α,β-unsaturated acids and amides

Vinyl iodide	Organozinc	Product	Yield (%)[a]
18a	**1**	**21a**	97
18a	**2**	**22a**	100
18a	**3**	**23a**	90
18a	**4**	**24**	46
18b	**1**	**21b** (*Z*)	94
18b	**2**	**22b** (*Z*)	63
18b	**3**	**23b** (*Z*)	37
19	**1**	**21a**	94
19	**2**	**22a**	97
19	**3**	**23a**	78
20	**1**	**25**	81
20	**2**	**26**	99
20	**3**	**27**	98

[a] Isolated yield.

Conclusions

We have shown that aliphatic organozinc halides, including those derived from iodoalanine derivatives, can be effectively cross-coupled with a range of solid-supported 4-iodobenzoic acid derivatives, extending the work of Arlt[3] on aryl zinc reagents and Knochel[4] on aryl and benzylic zinc reagents. A limitation in the use of Rink esters has been uncovered. In addition, we have also demonstrated that solid-supported (*E*)- and (*Z*)-iodoacrylic acid derivatives may also be effectively employed in such reactions, leading to the stereospecific synthesis of 3-substituted (*E*)- and (*Z*)-propenoic acids. The removal of the need for chromatographic purification is a major advantage when compared to the use of solution phase electrophiles.

Experimental

THF was distilled from potassium benzophenone ketyl. ^{1}H NMR spectra were acquired at 500 MHz in $CDCl_3$, referenced to TMS. ^{13}C NMR spectra were acquired at 125 MHz, referenced to TMS. Chemical shifts are given in ppm, coupling constants are given in Hertz. Carboxylic acid protons were generally not observed. Wang resin was prepared from chloromethyl polystyrene (2.0 Meq g^{-1}).[11] All other resins were purchased from NovaBiochem. The following starting materials were prepared by literature methods: iodide **3**,[12] iodide **4**,[13] (*E*)-3-iodoacrylic acid **6**[14] and (*Z*)-3-iodoacrylic acid **7**.[15]

Wang 4-iodobenzoate resin 8

Wang resin (5.03 g, 1.29 Meq g^{-1}), 4-iodobenzoic acid (2.25 g, 11.1 mmol), DCC (2.59 g, 12.5 mmol) and DMAP (149 mg, 1.22 mmol) were combined in DMF (100 cm^3) and stirred gently using a mechanical stirrer at 58–60 °C for 3 h. The solvent was removed by filtration and the resin washed with DMF (3 × 40 cm^3), CH_2Cl_2 (3 × 40 cm^3) and methanol (3 × 30 cm^3). The resin was dried in air and *in vacuo* to constant weight 5.61 g. The loading was determined to be 1.1 Meq g^{-1} by cleavage of a sample using TFA–CH_2Cl_2 (1 : 1).

NovaSyn® TG HMP 4-iodobenzoate resin 9

NovaSyn® TentaGel HMP resin (1.50 g, 0.38 Meq g^{-1}), 4-iodobenzoic acid (282 mg, 1.14 mmol), DCC (255 mg, 1.24 mmol) and DMAP (15 mg, 0.12 mmol) were stirred in DMF

(10 cm^3) for 5 h at 60 °C. The mixture was cooled, and the resin was removed by filtration and washed with DMF (2 × 10 cm^3), THF : water 1 : 1 (3 × 10 cm^3), CH_2Cl_2 (3 × 10 cm^3) and methanol (3 × 10 cm^3). The resin was dried in air and *in vacuo* to constant weight 1.52 g. The loading was determined to be 0.16 Meq g^{-1} by cleavage of a sample using neat TFA.

Rink 4-iodobenzamide resin 10

Fmoc Rink amide resin (0.47 Meq g^{-1}) (995 mg, 0.47 mmol) was treated with piperidine in DMF (20% v/v, 10 cm^3) for 30 min. The resin was washed with DMF (3 × 30 cm^3), CH_2Cl_2 (3 × 10 cm^3) and methanol (3 × 10 cm^3) and dried in air and *in vacuo*. The resin, 4-iodobenzoic acid (352 mg, 1.42 mmol), DCC (309 mg, 1.50 mmol) and DMAP (17 mg, 0.14 mmol) were combined in DMF (10 cm^3) and stirred gently at 58–60 °C for 3.5 h. The solvent was removed by filtration and the resin washed with THF (3 × 10 cm^3), toluene–EtOH 1 : 1 (3 × 10 cm^3), CH_2Cl_2 (3 × 10 cm^3) and methanol (3 × 10 cm^3). The resin was dried in air and *in vacuo* to constant weight 857 mg. The loading was determined to be 0.43 Meq g^{-1} by cleavage of a sample using 1% TFA in CH_2Cl_2.

Preparation and coupling of alkylzinc iodides with solid-supported electrophiles. General procedure

Zinc dust (5.5 equiv.) was suspended in dry THF (1 cm^3). 1,2-Dibromoethane (0.25 equiv.) was added and the slurry heated to ~65 °C. After cooling to room temperature TMS-Cl (0.05 equiv.) was added and the slurry stirred for 10 min. The alkyl iodide was then added, and the zinc insertion process monitored by TLC. After insertion was judged to be complete, stirring was stopped and excess zinc was allowed to settle. The solution of alkylzinc iodide (3 equiv.) was transferred to a flask containing the solid-supported aryl or vinyl iodide, $Pd_2(dba)_3$ (0.05 equiv.) and P(*o*-tolyl)$_3$ (0.2 equiv.) suspended in 2 cm^3 solvent. The suspension was stirred gently overnight, then the solid support was washed with THF (4 × 10 cm^3), THF–water (1 : 1, 3 × 10 cm^3), THF (3 × 10 cm^3), and CH_2Cl_2 (3 × 10 cm^3). The coupled products were released by treatment of the resins with 50% TFA in dichloromethane (10 cm^3) for 1 h. The resin was washed with dichloromethane (3 × 10 cm^3) and the combined organic washings evaporated to give the products.

4-*n*-Pentylbenzoic acid 12

Treatment of resin **8** (508 mg, 1.1 Meq g^{-1}) with zinc reagent **1**, according to the general procedure, followed by recrystallisation from EtOH–water, gave **12** (82 mg, 0.43 mmol, 78%). Mp 86–89 °C (lit.,[16] 86–88 °C), liq. cryst.-isotropic transition 124–126 °C (lit.,[16] 126–127 °C).

Treatment of resin **9** (373 mg, 0.16 Meq g^{-1}) with zinc reagent **1**, according to the general procedure, gave **12** (10 mg, 87%).

4-(2′-Methoxycarbonylethyl)benzoic acid 13

Treatment of resin **8** (496 mg, 1.1 Meq g^{-1}) with zinc reagent **2**, according to the general procedure, followed by recrystallisation from CH_2Cl_2–petrol, gave **13** (113 mg, 0.54 mmol, 99%). Mp 155–157 °C; (Found M^+ 208.0739; $C_{11}H_{12}O_4$ requires 208.0736); IR (KBr disc) 3442, 3000, 2954, 2850, 1725, 1687, 1428, and 1346; NMR δ_H 2.67 (2H, t, *J* 7.5), 3.03 (2H, t, *J* 7.5), 3.67 (3H, s), 7.31 (2H, d, *J* 8), and 8.04 (2H, d, *J* 8); δ_C 30.9, 35.1, 51.8, 127.5, 128.5, 130.5, 146.9, 172.0, and 173.0; *m*/*z* (EI) 208 (M^+, 58%), 148 (100), 135 (64), 103 (36), 77 (49), and 69 (82).

Treatment of resin **9** (384 mg, 0.16 Meq g^{-1}) with zinc reagent **2**, according to the general procedure, gave **13** (12 mg, 95%).

4-(2′-Benzyloxycarbonylamino-2′-carboxyethyl)benzoic acid 14

Treatment of resin **8** (502 mg, 1.1 Meq g^{-1}) with zinc reagent **3**, according to the general procedure, followed by recrystallisation from EtOH–water, gave **14** (156 mg, 0.46 mmol, 83%). Mp 200–202 °C (Found $M^+ - ZHNCHCO_2H$ 135.0439; $C_8H_7O_2$ requires 135.0446); IR (KBr disc) 3309, 3031, 2960, 2673, 2551, 1689, 1539, 1425, 1286, and 1268; $[\alpha]_D$ 14.2 (*c* 1.5, EtOH); NMR δ_H 3.12 (1H, dd, *J* 14, 9.5), 3.34 (1H, dd, *J* 14, 5), 4.54–4.59 (1H, m), 5.02 (2H, s), 6.61 (1H, d, *J* 8.5), 7.26–7.35 (5H, m), 7.44 (2H, d, *J* 8.5), and 7.96 (2H, d, *J* 8.5); δ_C (125 MHz, acetone-d_6) 38.1, 55.7, 66.6, 128.5, 128.6, 129.1, 129.8, 130.3, 130.5, 138.1, 143.9, 156.8, 167.5, and 173.0; *m*/*z* (EI) 135 ($CH_2C_6H_4COOH^+$, 100%), 107 (62), 91 (89, $C_7H_7^+$), and 79 (82).

Treatment of resin **9** (370 mg, 0.16 Meq g^{-1}) with zinc reagent **3**, according to the general procedure, gave **14** (19 mg, 93%).

4-[2′-(Fluoren-9″-ylmethoxycarbonylamino)-2′-(methoxycarbonyl)ethyl]benzoic acid 15

Treatment of resin **8** (202 mg, 1.1 Meq g^{-1}) with zinc reagent **4**, according to the general procedure, followed by recrystallisation from CH_2Cl_2–petrol, gave **15** (48 mg, 0.11 mmol, 69%). Mp 172–174 °C; IR (KBr disc) 3315, 3065, 3018, 2672, 2554, 1735, 1695, 1533, 1287, and 740; $[\alpha]_D$ 7.8 (*c* 1.0 in EtOH); NMR δ_H 3.15 (1H, dd, *J* 6, 14), 3.22 (1H, dd, *J* 6, 14), 3.74 (3H, s), 4.21 (1H, t, *J* 7), 4.39 (1H, dd, *J* 7, 10.5), 4.48 (1H, dd, *J* 7, 10.5), 4.72 (1H, q, *J* 6), 5.44 (1H, d, *J* 8), 7.18 (2H, d, *J* 8), 7.29–7.34 (2H, m), 7.40 (2H, t, *J* 7.5), 7.58 (2H, t, *J* 6.5), 7.77 (2H, d, *J* 7.5), and 8.03 (2H, d, *J* 8); δ_C 38.3, 47.2, 52.6, 54.6, 67.0, 120.0, 125.0, 127.1, 127.8, 128.3, 129.5, 130.5, 141.4, 142.1, 143.7, 155.6, 171.1, and 171.8; *m*/*z* (EI) 368 (58%), 206 (69), 178 (100), and 88 (61).

4-*n*-Pentylbenzamide 16

Treatment of resin **10** (176 mg, 0.43 Meq g^{-1}) with zinc reagent **1**, according to the general procedure, followed by recrystallisation from petrol–ether, gave **16** (8 mg, 55%). Mp 149–150 °C (lit.,[17] 147–148 °C, aq. EtOH); (Found M^+ 191.1304, $C_{12}H_{17}NO$ requires 191.1310); IR (KBr disc) 3386, 3173, 2927, 2854, 1649, 1617, 1567, 1417, and 1398; NMR δ_H 0.89 (3H, t, *J* 7), 1.25–1.36 (4H, m), 1.59–1.66 (2H, m), 2.65 (2H, t, *J* 7.5), 6.14 (2H, br s), 7.25 (2H, d, *J* 8.5), and 8.00 (2H, d, *J* 8.5); δ_C 14.0, 22.5, 30.8, 31.4, 35.8, 127.5, 128.7, 130.4, 147.8, and 169.9; *m*/*z* (EI) 191 (M^+, 61%), 175 (100), 134 (49) and 91 (39).

4-(2′-Methoxycarbonylethyl)benzamide 17

Treatment of resin **10** (205 mg, 0.43 Meq g^{-1}) with zinc reagent **2**, according to the general procedure, gave **17** (56 mg, 0.27 mmol, 49%); (Found M^+ 207.0887, $C_{11}H_{13}NO_3^+$ requires 207.0895); IR (KBr disc) 3375, 3003, 2998, 2959, 2924, 1725, 1672, 1414, 1402, 1287, 969 and 771; NMR δ_H 2.66 (2H, t, *J* 7.5), 3.01 (2H, t, *J* 7.5), 3.67 (3H, s), 6.40 (1H, br s), 6.55 (1H, br s), 7.30 (2H, d, *J* 8.5), and 7.76 (2H, d, *J* 8.5); δ_C 30.7, 35.2, 51.7, 127.7, 128.6, 130.9, 145.3, 169.4, and 172.9; *m*/*z* (EI) 207 (M^+, 94%), 191 (54), 149 (78), 148 (94), 147 (100), 131 (95), 103 (44), and 91 (44).

Wang (*E*)-3-iodoacrylate resin 18a

Wang resin (2.00 g, 1.29 Meq g^{-1}), (*E*)-3-iodoacrylic acid (1.633 mg, 8.25 mmol) and DMAP (107 mg, 0.88 mmol) were suspended in CH_2Cl_2 (20 cm^3) and cooled to −20 °C. DCC (1.706 mg, 8.27 mmol) was added as a solution in CH_2Cl_2 (1 cm^3) and the suspension stirred gently for 3.5 h at −20 °C. The solvent was removed by filtration and the resin washed with CH_2Cl_2 (3 × 10 cm^3), EtOH–toluene (1 : 1, 4 × 10 cm^3), CH_2Cl_2 (3 × 10 cm^3), and methanol (3 × 5 cm^3). The resin was dried in air and *in vacuo* to constant weight, 2.595 g. The loading was determined to be 1.22 Meq g^{-1} by cleavage of a sample using 1 : 1 (TFA–CH_2Cl_2). Another sample with loading 1.00 Meq g^{-1} was also prepared.

Wang (*Z*)-3-iodoacrylate resin 18b

Wang resin (2.00 g, 1.29 Meq g^{-1}), (*Z*)-3-iodoacrylic acid (1.62 g, 8.25 mmol) and DMAP (104 mg, 0.88 mmol) were suspended in CH_2Cl_2 (30 cm^3) and cooled to −20 °C. DCC (1.70 g, 8.27 mmol) was added as a solution in CH_2Cl_2 (2 cm^3) and the suspension stirred gently overnight at −20 °C. The solvent was removed by filtration and the resin washed with CH_2Cl_2 (3 × 50 cm^3), toluene–EtOH 1 : 1 (5 × 50 cm^3), DMF (3 × 30 cm^3), CH_2Cl_2 (3 × 30 cm^3) and methanol (3 × 30 cm^3). The resin was dried in air and *in vacuo* to constant weight, 2.51 g. The loading was determined to be 1.28 Meq g^{-1} by cleavage of a sample using 1 : 1 (TFA–CH_2Cl_2).

NovaSyn® TG HMP (*E*)-3-iodoacrylate resin 19

NovaSyn® TentaGel HMP resin (1.52 g, 0.38 Meq g^{-1}), (*E*)-3-iodoacrylic acid (249 mg, 1.21 mmol) and DMAP (15 mg, 0.12 mmol) were suspended in CH_2Cl_2 (10 cm^3) and cooled to −20 °C. DCC (263 mg, 1.27 mmol) was added as a solution in CH_2Cl_2 (1 cm^3) and the suspension stirred gently for 19 h at −20 °C. The resin was removed by filtration and washed with CH_2Cl_2 (3 × 10 cm^3), toluene–EtOH 1 : 1 (3 × 10 cm^3), CH_2Cl_2 (3 × 10 cm^3) and methanol (3 × 10 cm^3). The resin was dried in air and *in vacuo* to constant weight 1.574 g. The loading was determined to be 0.26 Meq g^{-1} by cleavage of a sample using neat TFA.

Rink (*E*)-3-iodoacrylamide resin 20

Fmoc Rink amide resin (1.00 g, 0.47 Meq g^{-1}) was treated with piperidine in DMF (20% v/v, 10 cm^3) for 30 min. The resin was washed with DMF (3 × 10 cm^3), CH_2Cl_2 (3 × 10 cm^3) and methanol (3 × 10 cm^3) and dried in air and *in vacuo* to give 969 mg of resin. The resin, (*E*)-3-iodoacrylic acid (280 mg, 1.41 mmol) and DMAP (17 mg, 0.14 mmol) were suspended in CH_2Cl_2 (10 cm^3) and cooled to −20 °C. DCC (300 mg, 1.45 mmol) was added as a solution in CH_2Cl_2 (1 cm^3) and the suspension stirred gently for 19 h at −20 °C. The resin was removed by filtration and washed with CH_2Cl_2 (4 × 10 cm^3) and methanol (3 × 5 cm^3). The resin was dried in air and *in vacuo* to constant weight 847 mg. The loading was determined to be 0.47 Meq g^{-1} by cleavage of a sample using 1% TFA in CH_2Cl_2.

(*E*)-Oct-2-enoic acid 21a

Treatment of resin **18a** (476 mg, 1.22 Meq g^{-1}) with zinc reagent **1**, according to the general procedure, gave **21a** (80 mg, 97%), which exhibited identical spectroscopic properties to those in the literature.[18]

Treatment of resin **19** (374 mg, 0.26 Meq g^{-1}) with zinc reagent **1**, according to the general procedure, gave **21a** (13 mg, 94%).

(*Z*)-Oct-2-enoic acid 21b

Treatment of resin **18b** (414 mg, 1.28 Meq g^{-1}) with zinc reagent **1**, according to the general procedure, gave **21b** (70 mg, 94%). NMR δ_H 0.90 (3H, t, *J* 5), 1.27–1.49 (6H, m), 2.68 (2H, dq, *J* 7.5, 1.5), 5.79 (1H, dt, *J* 11.5, 1.5), 6.36 (1H, dt, *J* 11.5, 6); Lit.[1,19]

(*E*)-Hex-2-enedioic acid 6-methyl ester 22a

Treatment of resin **18a** (485 mg, 1.22 Meq g^{-1}) with zinc reagent **2**, according to the general procedure, followed by recrystallisation from CH_2Cl_2–ether, gave **22a** (107 mg, 100%). Mp 56–58 °C (lit.,[20] 58–59 °C, hexane–$CHCl_3$); (Found M^+ 158.0579, $C_7H_{10}O_4$ requires 158.0574); IR (KBr disc) 3001, 2954, 2852, 2687, 2589, 1727, 1701, 1273, and 1158; NMR δ_H 2.46–2.61 (4H, m), 3.69 (3H, s), 5.86 (1H, dt, *J* 15.5, 1.5), and 7.06 (1H, dt, *J* 15.5, 6.5); δ_C 27.3, 32.1, 51.9, 121.4, 149.4, 171.3, and 172.6; *m*/*z* (EI) 158 (M^+, 4%), 140 (45), 127 (39), 108 (100), and 81 (66).

Treatment of resin **19** (353 mg, 0.26 Meq g^{-1}) with zinc reagent **2**, according to the general procedure, gave **22a** (14 mg, 97%).

(*Z*)-Hex-2-enedioic acid 6-methyl ester 22b

Treatment of resin **18b** (400 mg, 1.28 Meq g^{-1}) with zinc reagent **2**, according to the general procedure, gave **22b** (50 mg, 63%). (Found M^+ 158.0577, $C_7H_{10}O_4$ requires 158.0574); IR (KBr disc) 3001, 2954, 2852, 2687, 2589, 1727, 1701, 1273, and 1158; NMR δ_H 2.49 (2H, t, *J* 7), 2.47–2.51 (2H, m), 3.69 (3H, s), 5.86 (1H, d, *J* 11), and 6.35 (1H, dt, *J* 11, 7.5); δ_C (125 MHz, $CDCl_3$) 24.5, 33.1, 51.8, 121.0, 149.8, 171.9, and 173.4; *m*/*z* (EI) 158 (M^+, 6%), 140 (53), 127 (46), 108 (100), and 81 (61).

(*E*)-(2*S*)-5-(Benzyloxycarbonylamino)hex-2-enedioic acid 23a

Treatment of resin **18a** (469 mg, 1.22 Meq g^{-1}) with zinc reagent **3**, according to the general procedure, followed by recrystallisation from EtOH–water, gave **23a** (175 mg, 90%). Mp 153–156 °C (Found $M^+ - C_7H_7 - CO_2$, 293.0894, $C_{14}H_{15}NO_6$ requires 293.0899); IR (KBr disc) 3337, 3035, 2671, 2581, 2487, 1695, 1534, 1421, and 1283; $[\alpha]_D$ +20 (*c* 1.9 in EtOH); NMR δ_H 2.68–2.75 (1H, m), 2.81–2.87 (1H, m), 4.41–4.46 (1H, m), 5.09 (2H, s), 5.96 (1H, dt, *J* 15.5, 1.5), 6.72 (1H, d, *J* 8), 6.92–6.99 (1H, m), and 7.27–7.42 (5H, m); δ_C 34.8, 66.7, 96.6, 125.1, 128.5, 128.6, 129.2, 138.1, 144.7, 156.9, 166.8, and 172.7; *m*/*z* (EI) 293 ($M^+ - C_7H_7 - CO_2$, 89%), 267 (36), 202 (50, $M^+ - C_7H_7$), 163 (68), 151 (75), 108 (79), 91 (100, $C_7H_7^+$), and 79 (49).

Treatment of resin **19** (374 mg, 0.26 Meq g^{-1}) with zinc reagent **3**, according to the general procedure, gave **23a** (22 mg, 78%).

(*Z*)-(2*S*)-5-(Benzyloxycarbonylamino)hex-2-enedioic acid 23b

Treatment of resin **18b** (414 mg, 1.28 Meq g^{-1}) with zinc reagent **3**, according to the general procedure, followed by recrystallisation from CH_2Cl_2–petrol, gave **23b** (72 mg, 37%). Mp 130–133 °C (Found $M^+ - C_7H_7 - CO_2$, 293.0903; $C_{14}H_{15}NO_6$ requires 293.0899); IR (KBr disc) 3323, 3036, 2621, 2592, 1701, 1689, 1537, 1271, and 1241; $[\alpha]_D$ +27 (*c* 0.92, EtOH); NMR δ_H 3.08–3.26 (2H, m), 4.33–4.44 (1H, m), 5.09 (2H, s), 5.97 (1H, dt, *J* 11.5, 1.5), 6.39 (1H, d, *J* 11.5, 7), 6.72 (1H, d, *J* 7.5), 7.30–7.44 (5H, m); δ_C 32.6, 67.6, 96.6, 124.8, 128.5, 128.6, 129.2, 138.0, 144.4, 156.8, 166.8, and 172.7; *m*/*z* (EI) 293 ($M^+ - C_7H_7 - CO_2$, 29%), 220 (35), 158 (37), 138 (52), 108 (38), 91 (100, $C_7H_7^+$), and 79 (16, $C_6H_5^+$).

(*E*)-(2*S*)-5-(Fluoren-9′-ylmethoxycarbonylamino)hex-2-enedioic acid 6-methyl ester 24

Treatment of resin **18a** (156 mg, 1.00 Meq g^{-1}) with zinc reagent **4**, according to the general procedure, followed by recrystallisation from ether–petrol, gave **24** (27 mg, 46%). Mp 152–153 °C (Found MH^+ 396.1427, $C_{22}H_{22}NO_6$ requires 396.1447); IR (KBr disc) 3321, 3065, 2952, 1741, 1700, 1538, 1278, and 739; $[\alpha]_D$ + 19 (*c* 2.7, EtOH); NMR δ_H 2.65–2.76 (1H, m), 2.77–2.86 (1H, m), 3.78 (3H, s), 4.22 (1H, t, *J* 7), 4.38–4.47 (2H, m), 4.53–4.69 (1H, m), 5.33 (1H, d, *J* 7), 5.91 (1H, d, *J* 15), 6.88–6.97 (1H, m), 7.25–7.34 (2H, m), 7.40 (2H, t, *J* 7.5), 7.59 (2H, t, *J* 7.5), and 7.76 (2H, d, *J* 7.5); δ_C (125 MHz, $CDCl_3$) 35.1, 47.1, 52.8, 67.2, 120.0, 124.4, 125.0, 127.1, 127.8, 143.6, 143.7, 144.5, 144.6, 155.7, 170.1, and 171.5; *m*/*z* (EI) 396 (MH^+, 5%), 395 (24), 304 (54), 289 (84), 178 (100, $C_{14}H_{10}^+$), and 165 (31).

(*E*)-Oct-2-enoic amide 25

Treatment of resin **20** (204 mg, 0.47 Meq g^{-1}) with zinc reagent **1**, according to the general procedure, gave **25** (11 mg, 81%).

Mp 125–129 °C (lit.,[21] 129 °C); NMR δ_H 0.89 (3H, t, *J* 6.5), 1.23–1.53 (6H, m), 2.14–2.25 (2H, m), 5.70 (2H, s), 5.84 (1H, dt, *J* 15.5, 1.5), 6.88 (1H, dt, *J* 15.5, 7.0).

(*E*)-5-Carbamoylpent-4-enoic acid methyl ester 26

Treatment of resin **20** (178 mg, 0.47 Meq g^{-1}) with zinc reagent **2**, according to the general procedure, gave **26** (13 mg, 99%). Mp 129–131 °C (Found $M^+ - NH_3$ 140.0473, $C_7H_8O_3$ requires 140.0473); IR (KBr disc) 3328, 3159, 1733, 1676, 1611, 1439, and 1166; NMR δ_H 2.43–2.60 (4H, m), 3.69 (3H, s), 5.79 (2H, s), 5.90 (1H, d, *J* 15.5), and 6.78–6.93 (1H, m); δ_C 25.4, 34.2, 51.9, 126.4, 129.3, 167.3, and 172.6; *m*/*z* (EI) 140 ($M^+ - NH_3$, 100%), 125 (47), 108 (91), 98 (88), 91 (77), and 81 (75).

(*E*)-(2*S*)-2-(Benzyloxycarbonylamino)-5-carbamoylpent-4-enoic acid *tert*-butyl ester 27

Treatment of resin **20** (175 mg, 0.47 Meq g^{-1}) with zinc reagent **3**, according to the general procedure, using 1% TFA in CH_2Cl_2, gave **27** (28 mg, 98%). Mp 111–116 °C (Found $M^+ - C_4H_8$ 292.1066, $C_{14}H_{16}N_2O_5$ requires 292.1059); IR (KBr disc) 3404, 3340, 2853, 1726, 1676, 1647, and 1534; $[a]_D$ +6.0 (*c* 1.7, EtOH); NMR δ_H 1.46 (9H, s), 2.61–2.65 (1H, m), 2.72–2.76 (1H, m), 4.38–4.40 (1H, m), 5.10 (2H, s), 5.46 (1H, s), 5.73 (2H, s), 5.89 (1H, d, *J* 15.5), 6.69–6.76 (1H, m), and 7.29–7.38 (5H, m); δ_C 28.0, 35.4, 53.4, 67.0, 82.9, 125.9, 128.2, 128.2, 128.6, 132.3, 139.8, 155.6, 167.4, and 170.1; *m*/*z* (EI) 292 ($M^+ - C_4H_8$, 4%), 264 (1.5), 203 (46), 164 (45), and 91 (100, $C_7H_7^+$).

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