Carbonylative coupling of organozinc reagents in the presence and absence of aryl iodides: synthesis of unsymmetrical and symmetrical ketones

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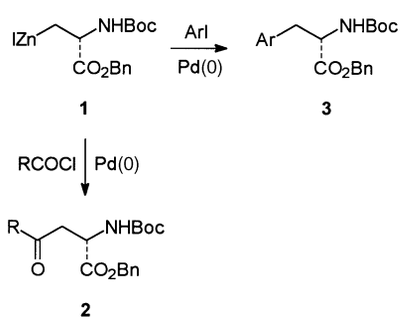
The utility of the palladium(0) catalysed reaction of the iodoalanine-derived organozinc reagent 6a with functionalised aryl iodides, under a carbon monoxide atmosphere, to give protected 4-aryl-4-oxo α-amino acids 8, is illustrated by a short synthesis of L-kynurenine 4. Treatment of functionalised organozinc reagents with catalytic tetrakis(triphenylphosphine)palladium(0) under an atmosphere of carbon monoxide in the absence of any electrophile leads to the formation of symmetrical functionalised ketones 9 in good yields. This reaction is illustrated by a one-step synthesis of protected (2*S*,6*S*)-4-oxo-2,6-diaminopimelic acid 9a from commercially available compounds. It has been established that adventitious molecular oxygen plays a key role in the formation of the symmetrical ketones 9, and that rigorous exclusion of oxygen can result in substantially higher yields of ketones 8 in the cross-coupling with some aromatic iodides.

Over recent years, we have been exploring the applications of iodoalanine-derived organometallic reagents in the synthesis of non-proteinogenic amino acids in enantiomerically pure form. For example, the organozinc reagent **1**, prepared by treatment of appropriately protected iodoalanine with activated zinc in benzene–dimethylacetamide using sonochemical activation, reacts under palladium catalysis with acid chlorides to give 4-oxo α-amino acids **2**, and also with aryl iodides to give 3-aryl α-amino acids **3** (Scheme 1).[1] More recently, we have established

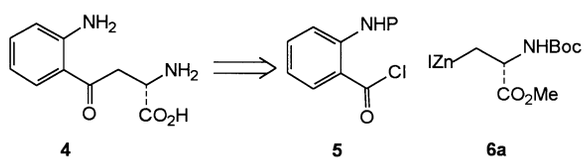


Scheme 1

that iodoalanine-derived zinc reagents may be prepared in THF as solvent,[2] but the reaction of these reagents with acid chlorides in this solvent is compromised by the competitive cleavage of the solvent by the acid chloride promoted by zinc.[3] The only successful coupling reactions that we have carried out in THF between iodoalanine-derived zinc reagents and acid chlorides have involved the use of aromatic acid chlorides.[4]

Synthesis of L-kynurenine

Although we had already used our approach for the synthesis of a range of 4-oxo α-amino acids **2** with additional functionality, the synthesis of L-kynurenine **4**,[5] an intermediate in the metabolism of L-tryptophan to nicotinic acid ribonucleotide *via* the kynurenine pathway,[6] presented us with a challenge. The most direct approach to L-kynurenine **4** would require the coupling of an anthranilic acid chloride **5** with a suitable serine-derived zinc reagent such as **6a**[2] (Scheme 2), prepared from (*R*)-

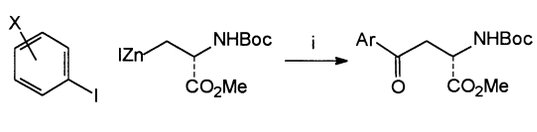


Scheme 2 P = protecting group

methyl 2-(*N*-*tert*-butoxycarbonylamino)-3-iodopropanoate.[7] The most serious problem is the choice of *N*-protecting group for the anthranilic acid chloride **5**. Many nitrogen protecting groups are incompatible with acid chlorides, enhance the acidity of protons on nitrogen or are sufficiently bulky that they severely retard reaction rates. An indirect approach involving attempted coupling of *o*-nitrobenzoyl chloride with zinc reagent **6a** was unsuccessful.

Given these difficulties, our attention then turned to an alternative strategy,[8] involving the palladium-catalysed carbonylative cross-coupling of organozinc reagents with aromatic iodides as a route to unsymmetrical ketones. The viability of this type of process has been well established using a wide variety of organometallic reagents,[9] although the use of zinc reagents has received relatively little attention.[9,10]

In the event, reaction of iodobenzene **7a** with zinc reagent **6a** in THF under an atmosphere of carbon monoxide (1 atm, balloon) in the presence of tetrakis(triphenylphosphine)-palladium(0) [$Pd(Ph_3P)_4$] at room temperature gave the protected 4-phenyl-4-oxo α-amino acid **8a** (60%) (Scheme 3),



Scheme 3 *Reagents and conditions*: i, CO (1 atm, balloon), $Pd(PPh_3)_4$ (5 mol%), THF, room temp., 30 h

identical to material prepared by direct coupling of zinc reagent **6a** with benzoyl chloride according to the general procedure

Table 1 Preparation of protected 4-aryl-4-oxo α-amino acids **8**

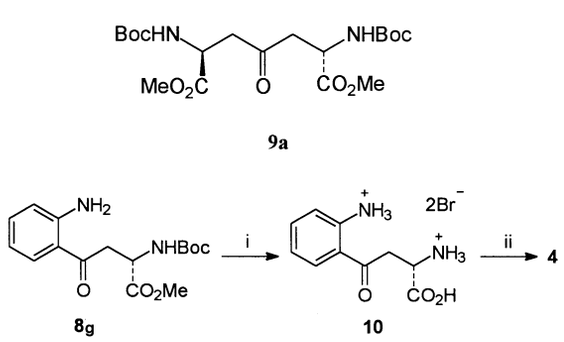
	Aryl iodide	Product	Ar	Yield (%)[a]
7a	Iodobenzene	**8a**	C_6H_5	60
7b	1-Iodonaphthalene	**8b**	1−$C_{10}H_7$	54
7c	4-Iodotoluene	**8c**	4-MeC_6H_4	59
7d	2-Iodoanisole	**8d**	2-$MeOC_6H_4$	50
7e	3-Iodoanisole	**8e**	3-$MeOC_6H_4$	40
7f	4-Iodoanisole	**8f**	4-$MeOC_6H_4$	58
7g	2-Iodoaniline	**8g**	2-$H_2NC_6H_4$	52
7h	3-Iodoaniline	**8h**	3-$H_2NC_6H_4$	17[b] (52)[c]
7i	4-Iodoaniline	**8i**	4-$H_2NC_6H_4$	56
7j	2-Fluoroiodobenzene	**8j**	2-FC_6H_4	29[b]
7k	3-Fluoroiodobenzene	**8k**	3-FC_6H_4	12[b]
7l	4-Fluoroiodobenzene	**8l**	4-FC_6H_4	34[b]
7m	2-Iodonitrobenzene	**8m**	2-$O_2NC_6H_4$	13[b]
7n	3-Iodonitrobenzene	**8n**	3-$O_2NC_6H_4$	27[b]
7o	4-Iodonitrobenzene	**8o**	4-$O_2NC_6H_4$	0[b] (21)[c]

[a] All yields are based on (*R*)-methyl 2-(*N*-*tert*-butoxycarbonylamino)-3-iodopropanoate. [b] The major product in each of these reactions was the symmetrical ketone **9a**. [c] These enhanced yields of the product have been obtained by conducting the reaction with rigorous exclusion of oxygen.

already reported.[4] No protected phenylalanine was isolated from this reaction, implying that direct reaction of iodobenzene and the zinc reagent **6a** did not compete under the reaction conditions. The use of $Pd(Ph_3P)_4$ was crucial for success and other palladium catalysts appeared to be significantly less effective.

Given the effectiveness of this reaction, we have explored the scope and limitations of the process using a wide variety of aryl iodides **7** as substrates. Our results are outlined in Table 1. The reaction is sensitive to the electronic effects of the substituents on the aromatic ring, but does give satisfactory results in all cases except when the substituents are strongly electron-withdrawing or are sited in the *meta* position. Most strikingly, the reaction tolerates the presence of an unprotected amino group in both *ortho* and *para* positions of the aromatic ring. In cases in which low yields of the desired 4-aryl-4-oxo α-amino acids **8** were isolated, significant amounts of protected 4-oxo-2,6-diaminopimelic acid **9a** were isolated. The reasons for the formation of the symmetrical ketone **9a** are discussed later in the paper, together with modifications to the cross-coupling process which can permit improved yields of the desired 4-aryl-4-oxo α-amino acids **8** to be isolated.

The easy access to the adduct **8g** derived from 2-iodoaniline enabled a short synthesis of L-kynurenine **4** to be completed. Removal of the protecting groups from the adduct **8g** was achieved by treatment with 30% HBr–HOAc to give the corresponding bis(hydrobromide) salt **10**, which was then converted to the free amino acid **4** using propylene oxide (90% overall yield from **8g**) (Scheme 4).[11] This completes a very short synthesis of L-kynurenine **4** from commercially available materials, and it is sufficiently flexible that it may be applicable to the preparation of analogues.[12] The low yields of the three nitro-substituted compounds, **8m**–**8o** was rather disappointing, but the fact that the highest yield was obtained for the *meta*-isomer was some consolation, given the report of the high inhibitory activity of (*m*-nitrobenzoyl)alanine against kynurenine-3-hydroxylase.[13]



Scheme 4 *Reagents and conditions:* i, HBr (30% in AcOH), room temp., 20 min; ii, propylene oxide, Pr^{i}OH

Table 2 Preparation of symmetrical ketones **9**

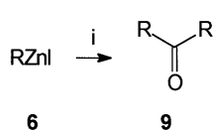
	Organozinc reagent	Product	R	Yield (%)[a]
6b	$MeO_2C(CH_2)_2ZnI$	**9b**	$MeO_2C(CH_2)_2$	84
6c	$PhthN(CH_2)_3ZnI$[b]	**9c**	$PhthN(CH_2)_3$	53
6d	$EtO_2C(CH_2)_3ZnI$	**9d**	$EtO_2C(CH_2)_3$	60
6e	$NC(CH_2)_2ZnI$	**9e**	$NC(CH_2)_2$	43
6f	$C_6H_5CH_2ZnBr$	**9f**	$C_6H_5CH_2$	61

[a] All yields are based on the precursor to the organozinc reagent. [b] PhthN = phthalimido.

Synthesis of symmetrical ketones

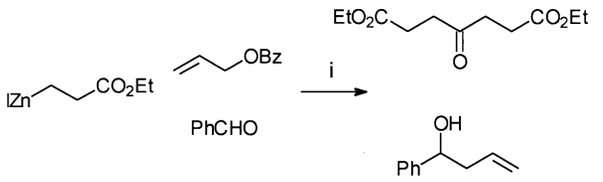
Some time ago, we had established that symmetrical ketones were formed by palladium catalysed reaction of zinc reagents with phenyl chloroformate and that they were also formed in poor yield on treatment of zinc reagents with catalytic amounts of $Pd(Ph_3P)_2Cl_2$ under an atmosphere of CO in the absence of added electrophile.[14] Given the recent report on the preparation of polyfunctional symmetrical ketones by the stoichiometric cobalt-mediated carbonylation of functionalised organozinc reagents,[15] we have decided to attempt to optimise the process for symmetrical ketone formation using $Pd(Ph_3P)_4$.

Our first breakthrough came when we established that an attempted cross-coupling of the zinc reagent **6a** with phenyl trifluoromethanesulfonate using $Pd(Ph_3P)_4$ as the catalyst under carbon monoxide led to the formation of the symmetrical ketone **9a** (60%) as the only coupled material. A subsequent experiment established that the presence of phenyl trifluoromethanesulfonate was completely unnecessary and that the same yield (60%) of coupled product **9a** was obtained in its absence. The generality of this process was established by treatment of a range of organozinc halides under the conditions described above (Scheme 5), which led to the isolation of the corresponding symmetrical ketone **9** in each case (Table 2). In all cases, the reaction was characterised by the development of a deep red colour. It is noteworthy that the reaction proceeded satisfactorily in the case of 2-cyanoethylzinc iodide, in contrast with the cobalt-mediated process.[15] Our process also proceeds satisfactorily in the presence of a static atmosphere of carbon monoxide and it does not require the presence of a co-solvent in addition to THF.



Scheme 5 *Reagents and conditions:* i, CO (1 atm, balloon), $Pd(PPh_3)_4$ (5 mol%), THF, room temp., 30 h

The process is, at first sight, very hard to understand. The *stoichiometric* coupling of an alkylzinc halide with carbon monoxide using palladium(II) can be easily rationalised, resulting in the formation of palladium(0) and the symmetrical ketone product. However, in order that the process can be catalytic in palladium(0), the presence of an oxidising agent is necessary to bring about the conversion of palladium(0) into palladium(II). Yasui *et al.* have reported a related preparation of symmetrical ketones by treatment of an organozinc reagent with catalytic palladium(0) under a carbon monoxide atmosphere in the presence of allyl benzoate.[9] This process is efficient only in the presence of benzaldehyde, which serves to trap an



Scheme 6 *Reagents and conditions:* i, CO (1 atm, balloon), $Pd(PPh_3)_4$ (5 mol%), THF, room temp., 20 h

allylzinc species derived from allyl benzoate (Scheme 6). Thus allyl benzoate acts effectively as the re-oxidant. Our results suggest that an alternative pathway for symmetrical ketone formation exists, in which both allyl benzoate and benzaldehyde are unnecessary, but the question of the identity of the oxidising agent in our process remains. Of some relevance is a report that the carbonylative dimerisation of siloxycyclopropanes using bis(triphenylphosphine)palladium dichloride is rendered catalytic in palladium by the use of chloroform as the solvent.[16] However, this clearly cannot be the case in our system.

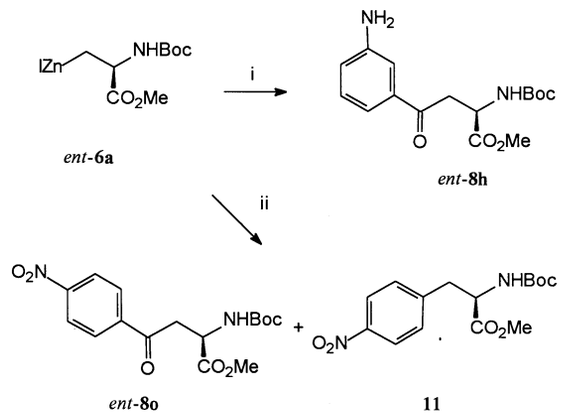
We eventually concluded that the mostly likely oxidant was molecular oxygen, which is certainly capable of diffusing into the carbon monoxide balloon which we had routinely used. In order to investigate this hypothesis, we treated the zinc reagent **6a** with catalytic $Pd(Ph_3P)_4$ under carbon monoxide using our standard conditions, but with two additional precautions. The reaction mixture was carefully degassed by freezing in liquid nitrogen and pumping under vacuum and the atmosphere of carbon monoxide was provided using a glass vessel, avoiding completely the use of a balloon. In this reaction, the deep red colour characteristic of the successful carbonylation reactions did not appear and none of the symmetrical ketone **9a** was isolated (the product was simply protected alanine, derived from protonation of the zinc reagent **6a**).

To establish that palladium catalysed carbonylative couplings with aromatic iodides did proceed under these modified conditions, we carried out a coupling of the D-serine-derived organozinc reagent *ent*-**6a** with 3-iodoaniline and were able to isolate the corresponding 4-aryl-4-oxo α-amino acid *ent*-**8h** in much improved yield (52%, compared with 17% obtained using a balloon). In an analogous manner, coupling of *ent*-**6a** with 4-iodonitrobenzene gave the 4-aryl-4-oxo α-amino acid *ent*-**8o** (21%, compared with 0% using a balloon), together with the product of direct cross-coupling **11** (31%) (Scheme 7).† In neither case was any of the corresponding symmetrical ketone *ent*-**9a** detected. These two results suggest that, for all the examples in Table 1 in which the symmetrical ketone **9a** was formed, substantially improved yields of the cross-coupling products **8** may be obtained provided oxygen is rigorously excluded.

We believe that these results establish that molecular oxygen is the oxidising agent in the symmetrical ketone synthesis.[17] Whatever the detail of the mechanism, the carbonylative dimerisation of organozinc reagents in the presence of catalytic $Pd(Ph_3P)_4$ appears to be a very simple and general method for the synthesis of functionalised symmetrical ketones.

In conclusion, we have established that the palladium(0) catalysed carbonylative coupling of organozinc reagents with aryl iodides is a useful method for the formation of highly functionalised aromatic ketones **8**. We have also shown that symmetrical ketones **9** can be formed in a preparatively useful

† Presumably the presence of the strongly electron-withdrawing nitro group accelerates transmetallation between the zinc reagent and the initial adduct derived from oxidative addition of the aryl iodide to $Pd^{(0)}$ and at the same time reduces the rate of aryl migration to ligated carbon monoxide. These two effects would tend to increase the amount of protected 4-nitrophenylalanine **11** at the expense of the carbonylated product **8o**.



Scheme 7 *Reagents and conditions:* i, 3-iodoaniline, CO (1 atm, glass vessel), $Pd(PPh_3)_4$ (5 mol%), rigorously degassed THF, room temp., 24 h; ii, 4-iodonitrobenzene, CO (1 atm, glass vessel), $Pd(PPh_3)_4$ (5 mol%), rigorously degassed THF, room temp., 24 h

manner under the same conditions in the absence of added electrophile. This process, which can in some cases compete with the carbonylative cross-coupling reaction of organozinc reagents with aryl iodides, is completely suppressed by the rigorous exclusion of oxygen.

Experimental

General experimental procedures and instrumentation are as previously described.[1] *J* values are given in Hz. $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}. *All reactions involving the use of carbon monoxide were carried out in a fume cupboard, with an appropriate detector to warn of any exposure*. Light petroleum refers to that fraction with boiling point 40–60 °C. All organic extracts were dried over anhydrous $MgSO_4$ and solvent was removed using a rotary evaporator.

Reaction with aromatic iodides and carbon monoxide—general procedure

The zinc reagent **6a** (0.75 mmol) was prepared in THF according to our previously reported method,[2] and allowed to cool to room temperature and the aromatic iodide **7** (1 mmol) and tetrakis(triphenylphosphine)palladium(0) [$Pd(Ph_3P)_4$] (43 mg, 0.038 mmol) were added. The nitrogen atmosphere was then replaced by carbon monoxide (using a balloon). The reaction mixture was then stirred for 30 h at room temperature. The reaction mixture was filtered, partitioned between ethyl acetate (25 cm^3) and water (25 cm^3), washed with brine (25 cm^3), dried, filtered and concentrated to give the crude product. This was purified by flash chromatography using light petroleum–ethyl acetate to give the pure ketone **8**.

(2*S*)-Methyl 2-(*N*-*tert*-butoxycarbonylamino)-4-oxo-4-phenylbutanoate 8a. Using iodobenzene **7a**, the *ketone* **8a** (138 mg, 60%) was isolated as pale brown needles, mp 60–63 °C (Found: C, 62.5; H, 6.85; N, 4.4; M^+, 307.1435. $C_{16}H_{21}O_5N$ requires C, 62.5; H, 6.9; N, 4.6%; *M*, 307.1420); ν_{max}(cap. film)/cm^{-1} 3440m (N–H), 1748s (C=O), 1717s (C=O), 1393m and 1368s [$C(CH_3)_3$], 1169s (C–O–C); δ_H(200 MHz, $CDCl_3$) 1.44 [s, 9 H, $C(CH_3)_3$], 3.5–3.85 [m, 2 H, C(3)H], 3.74 (s, 3 H, OCH_3), 4.71 [m, 1 H, C(2)H], 5.65 (d, 1 H, *J* 8.7, NH), 7.45–8.00 (m, 5 H, Ph); *m*/*z* (EI) 307 (0.3%, M), 248 (30, M − CO_2Me), 192 (50, M − CO_2Me − C_4H_8); $[\alpha]_D^{20}$ +28.2 (*c* 1.2, dichloromethane). The IR spectrum was obtained prior to crystallisation.

(2*S*)-Methyl 2-(*N*-*tert*-butoxycarbonylamino)-4-oxo-4-(1′-naphthyl)butanoate 8b. Using 1-iodonaphthalene **7b**, the *ketone* **8b** (145 mg, 54%) was isolated as a brown oil (Found: M^+, 357.1572. $C_{20}H_{23}NO_5$ requires *M*, 357.1576); ν_{max}(cap. film)/cm^{-1} 3373 (N–H), 1747 (C=O), 1713 (C=O), 1680 (sh, C=O); δ_H(200 MHz, $CDCl_3$) 1.4 [s, 9 H, $C(CH_3)_3$], 3.5–3.9 [m, 2 H, C(3)H], 3.75 (s, 3 H, OCH_3), 4.7 [m, 1 H, C(2)H], 5.65 (d, 1 H, *J* 6,

NH), 7.45–7.65 (m, 3 H, Ar), 7.8–8.1 (m, 3 H, Ar), 8.65–8.75 (m, 1 H, Ar); *m*/*z* (FAB) 358 (10%, MH), 302 (70, M − C_4H_8), 258 (100, M − C_4H_8OCO); $[\alpha]_D^{20}$ +18.0 (*c* 0.3, dichloromethane).

(*S*)-Methyl 2-(*N*-*tert*-butoxycarbonylamino)-4-oxo-4-(4′-methylphenyl)butanoate 8c. Using 4-iodotoluene **7c**, the *ketone* **8c** (77 mg, 39%) was isolated as a brown oil (Found: M^+ − CO_2CH_3, 265.0937. $C_{13}H_{15}NO_5$ requires *M*, 265.0950); ν_{max}(cap. film)/cm^{-1} 3440 (N−H), 1748 (C=O), 1717 (C=O), 1682 (C=O); δ_H(200 MHz, $CDCl_3$) 1.4 [s, 9 H, $C(CH_3)_3$], 2.4 (s, 3 H, CH_3), 3.45–3.75 [m, 2 H, C(3)H], 3.75 (s, 3 H, OCH_3), 4.65 [m, 1 H, C(2)H], 5.6 (d, 1 H, *J* 8, NH), 7.25 (d, 2 H, *J* 7, Ph), 7.8 (d, 2 H, *J* 7, Ph); *m*/*z* (FAB) 322.5 (30%, M), 266.4 (100, M − CO_2CH_3), 222.5 (95, M − C_4H_8OCO); $[\alpha]_D^{20}$ +11.0 (*c* 0.3, dichloromethane).

(2*S*)-Methyl 2-(*N*-*tert*-butoxycarbonylamino)-4-oxo-4-(2′-methoxyphenyl)butanoate 8d. Using 2-iodoanisole **7d**, the *ketone* **8d** (127 mg, 50%) was isolated as a yellow oil (Found: M^+ − $C_5H_8O_2$, 237.1004. $C_{12}H_{15}NO_4$ requires *M*, 237.1001); ν_{max}(cap. film)/cm^{-1} 3440 (N−H), 1748 (C=O), 1717 (C=O), 1680 (C=O); δ_H(200 MHz, $CDCl_3$) 1.4 [s, 9 H, $C(CH_3)_3$], 3.45–3.8 [m, 2 H, C(3)H], 3.75 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 4.6 [m, 1 H, C(2)H], 5.6 (br d, 1 H, NH), 6.95–7.05 (m, 2 H, Ph), 7.45–7.55 (m, 1 H, Ph), 7.75–7.85 (m, 1 H, Ph); *m*/*z* (FAB) 338.5 (80%, MH), 282.4 (100, M − C_4H_8), 238.4 (10, M − C_4H_8OCO); $[\alpha]_D^{20}$ +21.1 (*c* 0.35, dichloromethane).

(2*S*)-Methyl 2-(*N*-*tert*-butoxycarbonylamino)-4-oxo-4-(3′-methoxyphenyl)butanoate 8e. Using 3-iodoanisole **7e**, the *ketone* **8e** (102 mg, 40%) was isolated as a brown oil (Found: MH^+ − C_4H_8, 282.0991. $C_{13}H_{16}NO_6$ requires *M*, 282.0976); ν_{max} (cap. film)/cm^{-1} 3440 (N−H), 1748 (C=O), 1717 (C=O), 1685 (C=O); δ_H(200 MHz, $CDCl_3$) 1.4 [s, 9 H, $C(CH_3)_3$], 3.4–3.8 [m, 2 H, C(3)H], 3.7 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.7 [m, 1 H, C(2)H], 5.65 (br d, 1 H, NH), 7.1–7.6 (m, 4 H, Ph); *m*/*z* (FAB) 338.4 (30%, MH), 282.4 (90, M − C_4H_8), 238.4 (100, M − C_4H_8OCO); $[\alpha]_D^{20}$ +6.7 (*c* 0.15, dichloromethane).

(2*S*)-Methyl 2-(*N*-*tert*-butoxycarbonylamino)-4-oxo-4-(4′-methoxyphenyl)butanoate 8f. Using 4-iodoanisole **7f**, the *ketone* **8f** (147 mg, 58%) was isolated as a yellow oil (Found: C, 60.8; H, 7.2; N, 3.7; M^+ − C_4H_8, 281.0906. $C_{17}H_{23}NO_6$ requires C, 60.5; H, 6.9; N, 4.15%; $C_{13}H_{15}NO_6$ requires *M*, 281.0899); ν_{max}(cap. film)/cm^{-1} 3440 (N−H), 1748 (C=O), 1717 (C=O), 1688 (C=O); δ_H(200 MHz, $CDCl_3$) 1.4 [s, 9 H, $C(CH_3)_3$], 3.4–3.8 [m, 2 H, C(3)H], 3.7 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 4.7 [m, 1 H, C(2)H], 5.6 (br d, 1 H, NH), 7.1–7.6 (m, 4 H, Ph); *m*/*z* (FAB) 338 (49%, MH), 282 (100, M − C_4H_8), 238 (50, M − C_4H_8OCO); $[\alpha]_D^{20}$ +30.1 (*c* 0.35, dichloromethane).

(2*S*)-Methyl 2-(*N*-*tert*-butoxycarbonylamino)-4-oxo-4-(2′-aminophenyl)butanoate 8g. Using 2-iodoaniline **7g**, the *ketone* **8g** (126 mg, 52%) was isolated as a yellow oil (Found: M^+, 322.3595. $C_{16}H_{22}N_2O_5$ requires *M*, 322.3602); ν_{max}(cap. film)/cm^{-1} 3440 (N−H), 1748 (C=O), 1717 (C=O), 1687 (C=O); δ_H(200 MHz, $CDCl_3$) 1.4 [s, 9 H, $C(CH_3)_3$], 3.4–3.6 [m, 2 H, C(3)H], 3.7 (s, 3 H, OCH_3), 4.7 [m, 1 H, C(2)H], 5.6 (d, 1 H, *J* 9, NH), 6.65 (m, 2 H, NH_2), 7.2–7.7 (m, 4 H, Ph); *m*/*z* (FAB) 323 (18%, MH), 267 (100, M − C_4H_8), 223 (70, M − C_4H_8OCO); $[\alpha]_D^{20}$ +14.0 (*c* 0.5, dichloromethane).

(2*S*)-Methyl 2-(*N*-*tert*-butoxycarbonylamino)-4-oxo-4-(3′-aminophenyl)butanoate 8h. Using 3-iodoaniline **7h**, the *ketone* **8h** (42 mg, 17%) was isolated as an amber oil (Found: M^+, 322.1534. $C_{16}H_{22}N_2O_5$ requires *M*, 322.1528); ν_{max}(cap. film)/cm^{-1} 3440 (N−H), 1745 (C=O), 1708 (C=O); δ_H(200 MHz, $CDCl_3$) 1.4 [s, 9 H, $C(CH_3)_3$], 3.4–3.6 [m, 2 H, C(3)H], 3.7 (s, 3 H, OCH_3), 4.7 [m, 1 H, C(2)H], 5.6 (d, 1 H, *J* 9, NH), 6.65 (m, 2 H, NH_2), 7.2–7.7 (m, 4 H, Ph); *m*/*z* (FAB) 323 (18%, MH), 267 (100, M − C_4H_8), 223 (70, M − C_4H_8OCO); $[\alpha]_D^{20}$ +27.9 (*c* 0.2, dichloromethane).

(2*S*)-Methyl 2-(*N*-*tert*-butoxycarbonylamino)-4-oxo-4-(4′-aminophenyl)butanoate 8i. Using 4-iodoaniline **7i**, the *ketone* **8i** (135 mg, 58%) was isolated as a brown oil (Found: M^+ − C_4H_8, 265.0823. $C_{12}H_{13}N_2O_5$ requires *M*, 265.0824); ν_{max}(cap. film)/cm^{-1} 3440 (N−H), 1748 (C=O), 1717 (C=O), 1687 (C=O); δ_H(200 MHz, $CDCl_3$) 1.4 [s, 9 H, $C(CH_3)_3$], 3.3–3.7 [m, 2 H, C(3)H], 3.7 (s, 3 H, OCH_3), 4.6 [m, 1 H, C(2)H], 5.6 (d, 1 H, *J* 8, NH), 6.6 (m, 2 H, NH_2), 7.4–7.8 (m, 4 H, Ph); *m*/*z* (FAB) 323 (40%, MH), 267 (35, M − C_4H_8), 223 (75, M − C_4H_8OCO); $[\alpha]_D^{20}$ +3.0 (*c* 0.15, dichloromethane).

(2*S*)-Methyl 2-(*N*-*tert*-butoxycarbonylamino)-4-oxo-4-(2′-fluorophenyl)butanoate 8j. Using 2-fluoroiodobenzene **7j**, the *ketone* **8j** (71.4 mg, 29%) was isolated as a yellow oil (Found: M^+ − CO_2Me, 266.1184. $C_{14}H_{17}FNO_3$ requires *M*, 266.1192); ν_{max}(cap. film)/cm^{-1} 3440 (N−H), 1748 (C=O), 1717 (C=O), 1682 (C=O); δ_H(200 MHz, $CDCl_3$) 1.4 [s, 9 H, $C(CH_3)_3$], 3.4–3.8 [m, 2 H, C(3)H], 3.7 (s, 3 H, OCH_3), 4.7 [m, 1 H, C(2)H], 5.6 (d, 1 H, *J* 8.5, NH), 7.1–7.3 (m, 2 H, Ph), 7.45–7.6 (m, 1 H, Ph), 7.8–7.95 (m, 1 H, Ph); *m*/*z* (FAB) 326 (40%, MH), 270 (35, M − C_4H_8), 226 (75, M − C_4H_8OCO); $[\alpha]_D^{20}$ +21.2 (*c* 0.5, dichloromethane).

(2*S*)-Methyl 2-(*N*-*tert*-butoxycarbonylamino)-4-oxo-4-(3′-fluorophenyl)butanoate 8k. Using 3-fluoroiodobenzene **7k**, the *ketone* **8k** (30 mg, 12%) was isolated as a yellow oil (Found: C, 59.5; H, 6.3; N, 3.9; M^+ − $C_5H_9O_2$, 224.0714. $C_{16}H_{20}FNO_5$ requires C, 59.1; H, 6.2; N, 4.3%; $C_{11}H_{11}FNO_3$ requires *M*, 224.0723); ν_{max}(cap. film)/cm^{-1} 3440 (N−H), 1748 (C=O), 1717 (C=O), 1683 (C=O); δ_H(200 MHz, $CDCl_3$) 1.4 [s, 9 H, $C(CH_3)_3$], 3.4–3.7 [m, 2 H, C(3)H], 3.7 (s, 3 H, OCH_3), 4.7 [m, 1 H, C(2)H], 5.5 (d, 1 H, *J* 8.7, NH), 7.2–7.8 (m, 4 H, Ph); *m*/*z* (FAB) 326 (10%, MH), 270 (45, M − C_4H_8), 226 (100, M − C_4H_8OCO); $[\alpha]_D^{20}$ +19.0 (*c* 0.05, dichloromethane).

(2*S*)-Methyl 2-(*N*-*tert*-butoxycarbonylamino)-4-oxo-4-(4′-fluorophenyl)butanoate 8l. Using 4-fluoroiodobenzene **7l**, the *ketone* **8l** (83 mg, 34%) was isolated as a yellow oil (Found: M^+, 326.1393. $C_{16}H_{20}FNO_5$ requires *M*, 326.1404); ν_{max}(cap. film)/cm^{-1} 3440 (N−H), 1748 (C=O), 1717 (C=O), 1682 (C=O); δ_H(200 MHz, $CDCl_3$) 1.4 [s, 9 H, $C(CH_3)_3$], 3.4–3.8 [m, 2 H, C(3)H], 3.7 (s, 3 H, OCH_3), 4.7 [m, 1 H, C(2)H], 5.6 (d, 1 H, *J* 8.5, NH), 7.0–7.2 (m, 2 H, Ph), 7.9–8.1 (m, 2 H, Ph); *m*/*z* (FAB) 326 (90%, MH), 270 (60, M − C_4H_8), 226 (50, M − C_4H_8OCO); $[\alpha]_D^{20}$ +40.8 (*c* 0.25, dichloromethane).

(2*S*)-Methyl 2-(*N*-*tert*-butoxycarbonylamino)-4-oxo-4-(2′-nitrophenyl)butanoate 8m. Using 2-iodonitrobenzene **7m**, the *ketone* **8m** (35 mg, 13%) was isolated as a brown oil (Found: C, 54.7; H, 5.9; N, 8.0; M^+, 296.0639. $C_{16}H_{20}N_2O_7$ requires C, 54.5; H, 5.7; N, 7.95%; *M*, 296.0644); ν_{max}(cap. film)/cm^{-1} 3440 (N−H), 1748 (C=O), 1717 (C=O), 1684 (C=O); δ_H(200 MHz, $CDCl_3$) 1.4 [s, 9 H, $C(CH_3)_3$], 3.5–3.8 [m, 2 H, C(3)H], 3.8 (s, 3 H, OCH_3), 4.7 [m, 1 H, C(2)H], 5.6 (d, 1 H, *J* 8, NH), 7.6–7.8 (m, 1 H, Ph), 8.2–8.5 (m, 1 H, Ph), 8.4–8.5 (m, 1 H, Ph), 8.8 (m, 1 H, Ph); *m*/*z* (FAB) 353 (80%, MH), 297 (25, M − C_4H_8), 253 (30, M − C_4H_8OCO).

(2*S*)-Methyl 2-(*N*-*tert*-butoxycarbonylamino)-4-oxo-4-(3′-nitrophenyl)butanoate 8n. Using 3-iodonitrobenzene **7n**, the *ketone* **8n** (71 mg, 27%) was isolated as a brown oil (Found: C, 54.2; H, 5.3; N, 7.9; M^+ − C_4H_8, 296.0636. $C_{16}H_{20}N_2O_7$ requires C, 54.5; H, 5.7; N, 7.95%; $C_{12}H_{12}N_2O_7$ requires *M*, 296.0644); ν_{max}(cap. film)/cm^{-1} 3440 (N−H), 1748 (C=O), 1717 (C=O), 1682 (C=O); δ_H(200 MHz, $CDCl_3$) 1.4 [s, 9 H, $C(CH_3)_3$], 3.5–3.8 [m, 2 H, C(3)H], 3.8 (s, 3 H, OCH_3), 4.7 [m, 1 H, C(2)H], 5.6 (m, 1 H, NH), 7.6–7.8 (m, 1 H, Ph), 8.2–8.5 (m, 1 H, Ph), 8.4–8.5 (m, 1 H, Ph), 8.8 (m, 1 H, Ph); *m*/*z* (FAB) 353 (80%, MH), 297 (25, M − C_4H_8), 253 (30, M − C_4H_8OCO); $[\alpha]_D^{20}$ +13.3 (*c* 0.3, dichloromethane).

Synthesis of L-kynurenine 4[11]

Compound **8g** (36.2 mg, 0.11 mmol) was stirred in 30% HBr in acetic acid (1 cm^3) for 20 min at room temperature. Diethyl ether (12 cm^3) was then added to precipitate the bis(hydrobromide salt) as a colourless solid. The diethyl ether layer was decanted and the procedure repeated several times to remove as much HBr as possible. The last traces of diethyl ether were removed *in vacuo*, and the colourless solid was thoroughly dried. This material was dissolved in propan-2-ol (5 cm^3) and treated with propylene oxide (46.5 μl, 0.7 mmol). L-Kynurenine **4** (21

mg, 0.1 mmol, 90%) precipitated as a light yellow powder, mp 162–163 °C (lit.,[5] 155–160 °C) (Found: C, 57.6; H, 6.2; N, 13.0; M^+ 208.0850. $C_{12}H_{12}N_2O_3$ requires C, 57.7; H, 5.8; N, 13.5%; *M*, 208.0848); ν_{max}(KBr disc)/cm^{-1} 3471 (C–H), 3049 (N–H_3^+), 2994 (C–H), 2704 (N–H_3^+), 1661 (C=O), 1614 (C=O), 1578 (C=O); δ_H(200 MHz, CD_3OD) 3.63–3.77 [dd, 1 H, *J* 9.1 and 18.5, C(3)H], 3.86–3.97 [dd, 1 H, *J* 2.9 and 18.5, C(3)H], 4.16–4.22 [dd, 1 H, *J* 2.9 and 9.1, C(2)H], 6.74–6.83 (dt, 1 H, *J* 1.0 and 8.0, Ph), 6.91–6.96 (dd, 1 H, *J* 1.0 and 8.0, Ph), 7.41–7.49 (dt, 1 H, *J* 1.5 and 8.0, Ph), 7.91–7.96 (dd, 1 H, *J* 1.5 and 8.0, Ph); *m*/*z* (FAB) 209 (64%, MH), 192.6 (70, MH − NH_3); $[\alpha]_D^{20}$ −106.6 (*c* 0.5, methanol).

Preparation of aliphatic zinc reagents

Zinc dust (325 mesh, 300 mg, 4.5 mmol) was added to a nitrogen purged flask. THF (0.34 cm^3) and 1,2-dibromoethane (19.4 cm^3, 0.225 mmol) were added and the flask was heated at 60 °C for 15 min using a hot water bath. The reaction mixture was allowed to cool to room temperature and trimethylsilyl chloride (6.0 µl, 0.046 mmol) was added. The resultant mixture was stirred vigorously for 30 min under nitrogen. The iodide (0.75 mmol) in THF (0.34 cm^3) was added to the flask which was heated at 35 °C until no starting material remained (as judged by TLC, 10 : 1, toluene–ethyl acetate).

Synthesis of symmetrical ketones—general procedure

The zinc reagent was allowed to cool to room temperature and $Pd(Ph_3P)_4$ (43 mg, 0.038 mmol) was added. The nitrogen atmosphere was then replaced with carbon monoxide (a balloon). The reaction mixture was then stirred for 30 h at room temperature. The reaction mixture was filtered, partitioned between ethyl acetate (25 cm^3) and water (25 cm^3), washed with brine (25 cm^3), dried, filtered and concentrated to give the crude product. This was purified by flash chromatography using light petroleum–ethyl acetate to give the pure ketone.

(2*S*,6*S*)-Dimethyl 4-oxo-2,6-bis(*N*-*tert*-butoxycarbonylamino)heptanedioate 9a. Using the zinc reagent **6a**, the *ketone* **9a** (66 mg, 60%) was isolated as a pale yellow powder, mp 89–92 °C (Found: C, 52.3; H, 7.4; N, 6.1; M^+ − NH-$CO_2C_4H_8$, 317.1453. $C_{19}H_{32}N_2O_9$ requires C, 52.7; H, 7.45; N, 6.5%; $C_{14}H_{23}NO_5$ requires *M*, 317.1475); ν_{max}(KBr disc)/cm^{-1} 3440 (N–H), 1748 (C=O), 1717 (C=O); δ_H(200 MHz, $CDCl_3$) 1.4 [s, 18 H, C(CH_3)$_3$], 2.8–3.2 [m, 4 H, C(3)H], 3.8 (s, 6 H, OCH_3), 4.5 [m, 2 H, C(2)H], 5.6 (d, 2 H, *J* 8, NH); *m*/*z* (FAB) 317 (5%, M − $NHCO_2C_4H_8$); $[\alpha]_D^{17}$ +34.3 (*c* 0.7, dichloromethane).

Dimethyl 4-oxoheptanedioate 9b. Using the zinc reagent **6b**, the ketone **9b** (64 mg, 84%) was isolated as a white solid, mp 52–54 °C (lit.,[18] 55 °C) (Found: M^+, 171.0668. $C_9H_{14}O_5$ requires *M*, 171.0667); ν_{max}(KBr disc)/cm^{-1} 3011m (C–H), 2914m (C–H), 1744s (C=O), 1716s (C=O), 1706s (C=O); δ_H(200 MHz, $CDCl_3$) 2.58–2.65 [t, 4 H, *J* 5.9, C(2)H and C(6)H], 2.65–2.79 [t, 4 H, *J* 5.9, C(3)H and C(5)H], 3.68 (s, 6 H, OMe); *m*/*z* (EI) 202 (5.2%, M), 171 (9.5, M − OMe), 143 (25, M − CO_2Me).

1,7-Diphthalimidoheptan-4-one 9c. Using the zinc reagent **6c**, the *ketone* **9c** (47 mg, 53%) was isolated as a white solid, mp 142–146 °C (Found: M^+, 404.1376. $C_{23}H_{20}O_5N_2$ requires *M*, 404.1372); ν_{max}(KBr disc)/cm^{-1} 1721s (C=O), 1707s (C=O); δ_H(200 MHz, $CDCl_3$) 1.83–2.18 [m, 4 H, C(2)H and C(6)H], 2.47 [t, 4 H, *J* 7.1, C(3)H and C(5)H], 3.69 [t, 4 H, *J* 6.7, C(1)H and C(7)H], 7.67–7.89 (m, 8 H, Ph); *m*/*z* (EI) 405 (0.4%, MH), 257 [4.0, M − NH$(CO)_2$Ph].

Diethyl 5-oxononanedioate 9d.[9] Using the zinc reagent **6d**, the *ketone* **9d** (58.4 mg, 60%) was isolated as a clear oil (Found: C, 60.5; H, 8.6; M^+, 258.1462. $C_{13}H_{22}O_5$ requires C, 60.4; H, 8.5%; *M*, 258.1467); ν_{max}(cap. film)/cm^{-1} 1734s (C=O), 1716s (C=O); δ_H(200 MHz, $CDCl_3$) 1.26 (t, 6 H, *J* 7.0, Me), 1.88 [quintet, 4 H, *J* 7.0, C(3)H and C(7)H], 2.35 [t, 4 H, *J* 7, C(4)H and C(6)H], 2.48 [t, 4 H, *J* 7, C(2)H and C(8)H], 4.14 (q, 4 H, *J* 7.0, CO_2CH_2); *m*/*z* (EI) 258 (2%, M), 213 (10, M − OEt), 185 (49, M − CO_2Et).

1,5-Dicyanopentan-3-one 9e. Using the zinc reagent **6e**, the ketone **9e** (38 mg, 43%) was isolated as a clear oil (lit.,[18] mp 37 °C) (Found: C, 61.8; H, 5.9; N, 20.6; M^+, 136.0630. $C_7H_8N_2O$ requires C, 61.75; H, 5.9; N, 20.6%; *M*, 136.0637); ν_{max}(KBr disc)/cm^{-1} 2250 (CN), 1716s (C=O) (lit.,[18] 2250, 1710); δ_H(200 MHz, $CDCl_3$) 2.61–2.68 [t, 4 H, *J* 6.5, C(2)H and C(6)H], 2.84–2.91 [t, 4 H, *J* 6.5, C(3)H and C(5)H]; *m*/*z* (EI) 136 (20.6%, M), 80 [44, M − $(CH_2)_2$CN].

1,3-Diphenylpropan-2-one 9f. Using the zinc reagent **6f**, the *ketone* **9f** (48 mg, 61%) was isolated as a clear oil (Found: M^+, 210.1035. $C_{15}H_{14}O$ requires *M* 210.1045); ν_{max}(cap. film)/cm^{-1} 3062 (C–H), 2918 (C–H), 1716s (C=O); δ_H(200 MHz, $CDCl_3$) 3.71 (s, 4 H, CH_2), 7.01–7.67 (m, 10 H, Ph); *m*/*z* (EI) 210 (7%, M).

Reaction with aromatic iodides and carbon monoxide—improved procedure

The zinc reagent *ent*-**6a** (0.75 mmol) was prepared in the usual manner, allowed to cool to room temperature and the aromatic iodide (1 mmol) and $Pd(Ph_3P)_4$ (43 mg, 0.038 mmol) were added. The reaction was frozen using liquid nitrogen and then put under vacuum for 5 min after which the flask was filled with nitrogen and the reaction mixture allowed to thaw. This process was repeated six times. After the final freezing, carbon monoxide was used to fill the flask whilst the mixture was thawing. The reaction mixture was then stirred for 30 h at room temperature. The reaction mixture was filtered, partitioned between ethyl acetate (25 cm^3) and water (25 cm^3), washed with brine (25 cm^3), dried, filtered and concentrated to give the crude product. This was purified by flash chromatography using light petroleum–ethyl acetate to give the product(s).

(2*S*)-Methyl 2-(*N*-*tert*-butoxycarbonylamino)-4-oxo-4-(3′-aminophenyl)butanoate *ent*-8h. Using 3-iodoaniline as the substrate, the product *ent*-**8h** (126 mg, 52%) was isolated as a brown oil. Data identical with **8h**, apart from $[\alpha]_D^{20}$ −28.5 (*c* 0.3, dichloromethane).

Reaction with 4-iodonitrobenzene. The first eluted product was (2*S*)-methyl 2-(*N*-*tert*-butoxycarbonylamino)-3-(4′-nitrophenyl)propanoate **11** (75 mg, 31%) isolated as brown needles, mp 94–95 °C (lit.,[19] 92–94 °C) (Found: M^+ − CO_2Me, 265.1194; $C_{13}H_{17}O_4N_2$ requires *M*, 265.1188); ν_{max}(cap. film)/cm^{-1} 3393m (N–H), 1730s (C=O), 1393m and 1368s [C(CH_3)$_3$], 1346s (C–NO_2), 1169s (C–O–C); δ_H(200 MHz, $CDCl_3$) 1.42 [s, 9 H, C(CH_3)$_3$], 3.18 [dd, 1 H, *J* 6.2 and 13.7, C(3)H], 3.22 [dd, 1 H, *J* 5.7 and 13.7, C(3)H], 3.74 (s, 3 H, OCH_3), 4.64 [m, 1 H, C(2)H], 5.04 (d, 1 H, *J* 7.5, NH), 7.29–7.34 [d, 2 H, *J* 7.3, C(2′)H and C(6′)H], 8.14–8.19 [d, 2 H, *J* 7.3, C(5′)H and C(3′)H]; *m*/*z* (EI) 265 (0.6%, M − CO_2Me), 223 (5, M − $CO_2C_4H_8$), 137 (80, M − $C_7H_6NO_2$); $[\alpha]_D^{20}$ +53.4 (*c* 1.055, dichloromethane). The second eluted product was (2S)-*methyl* 2-(N-tert-*butoxycarbonylamino*)-4-*oxo*-4-(4′-*nitrophenyl*)*butanoate* (*ent*-**8o**) (55 mg, 21%) isolated as a brown oil (Found: C, 54.7; H, 5.9; N, 8.0; M^+ − $C_2H_3O_2$, 293.1140. $C_{16}H_{20}N_2O_7$ requires C, 54.5; H, 5.7; N, 7.95%. $C_{14}H_{17}O_5N_2$ requires *M*, 293.1137); ν_{max}(cap. film)/cm^{-1} 3385 (N–H), 1747 (C=O), 1684 (C=O); δ_H(200 MHz, $CDCl_3$) 1.41 [s, 9 H, C(CH_3)$_3$], 3.5–3.8 [m, 2 H, C(3)H], 3.73 (s, 3 H, OCH_3), 4.7 [m, 1 H, C(2)H], 5.6 (d, 1 H, *J* 8, NH), 8.0–8.1 (d, 2 H, *J* 9, Ph), 8.2–8.3 (d, 2 H, *J* 9, Ph); *m*/*z* (EI) 296 (19, M − C_4H_8), 252 (20, M − C_4H_8OCO); $[\alpha]_D^{20}$ +26.3 (*c* 0.15, dichloromethane).

Acknowledgements

We thank the EPSRC for a CASE award (D. T.), Sarah Fillingham for experimental assistance and Zeneca Pharmaceuticals for support. R. F. W. J. also thanks the Nuffield Foundation for a One Year Science Research Fellowship.

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Paper 6/06394B
Received 17*th September* 1996
Accepted 30*th October* 1996