Copper(I) mediated cross-coupling of amino acid derived organozinc reagents with acid chlorides

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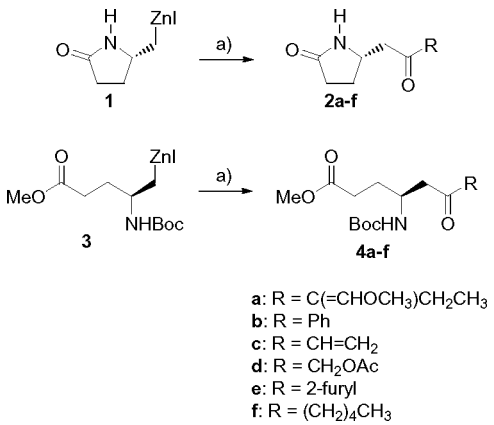
This paper describes the development of a straightforward experimental protocol for copper-mediated cross-coupling of amino acid derived β-amido-alkylzinc iodides **1** and **3** with a range of acid chlorides. The present method uses CuCN·2LiCl as the copper source and for organozinc reagent **1** the methodology appears to be limited to reaction with more stable acid chlorides, providing the desired products in moderate yields. When applied to organozinc reagent **3**, however, the protocol is more general and provides the products in good yields in all but one of the cases tested.

Introduction

In connection with a total synthesis project,[1] we recently became interested in cross-coupling reactions involving acid chlorides and the two amino acid derived β-amido-alkylzinc iodides **1** and **3** to give coupling products **2** and **4**, respectively (Scheme 1).[2] Although our initial interest was focused on the synthesis of **2a** and **4a**, we also tested the generality of our developed methodology on a range of selected acid chlorides and the results are presented in this paper, along with a comparison with alternative cross-coupling techniques.

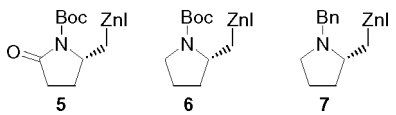


Scheme 1 Cross-coupling reactions of β-amido-alkylzinc iodides **1** and **3** with acid chlorides to give derivatives **2** and **4**, respectively. Key: (a) transmetallation, RCOCl.

L-Pyroglutamic acid derived organozinc reagent **1** has previously been used in Cu(I) mediated reactions with various electrophiles using either CuBr·DMS or the THF-soluble copper salt CuCN·2LiCl[3] as copper source.[4] Thus, reaction of **1** with propargylic tosylates in DMF,[4a] 1-iodo alkynes in THF–DMF,[4b] and bromoallene in DMF,[4c] gave the derived products in moderate yields (49–59%). Although reaction of **1** with an acid chloride has not been documented, reaction of an analogous L-serine derived organozinc reagent with benzoyl chloride in THF after transmetallation with CuCN·2LiCl has been reported to give the coupling product in 71% yield.[5]

More thorough investigations of organozinc reagent **3** have been published,[6] and Pd(0)-catalysed reaction of this L-glutamic acid derivative with a range of acid chlorides has been reported to give coupling products **4b–e** in moderate yields (45–52%) while failing to provide **4f** (Scheme 1).[6c]

Since no method for cross-coupling of organozinc reagent **1** with acid chlorides had been reported previously we decided to use this reagent as the basis for the present study. Furthermore, since relatively little work concerning this type of reagent has been published, we likewise decided to synthesize and test the stability and reactivity of *N*-protected β-amido-alkylzinc iodide **5** and β-amino-alkylzinc iodides **6** and **7** (Scheme 2). To our knowledge, the generation and use of these reagents has not been reported in the literature.



Scheme 2 Other protected pyroglutamic acid-derived (**5**) and proline-derived (**6** and **7**) organozinc reagents of interest.

Results and discussion

Acid chlorides

All but one of the required acid chlorides were commercially available. Synthesis of the last acid chloride, **10**, was achieved in three steps from methyl 2-bromobutyrate in 57% overall yield (Scheme 3).

Ester **8** was obtained in 87% yield by a Reformatsky reaction of methyl 2-bromobutyrate with α,α-dichloromethyl methyl ether in the presence of zinc dust.[7] Although this method makes use of the toxic α,α-dichloromethyl methyl ether, the relative ease and the good yield of this reaction makes it preferable over the other reported pathway to **8** in two steps in 78% overall yield starting

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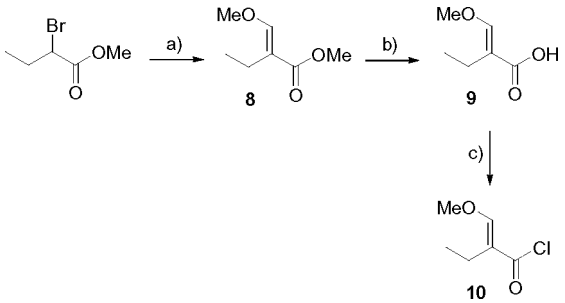
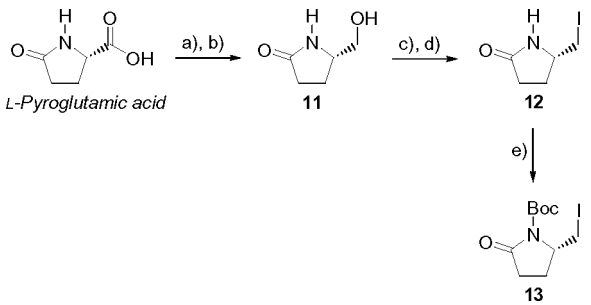


Scheme 3 Synthesis of acid chloride **10** from methyl 2-bromobutyrate. Key: (a) Zn, $MeOCHCl_2$, Et_2O, Δ, 87%; (b) 2 M NaOH, Δ; then HCl, 76%; (c) $(COCl)_2$, DMF (cat.), benzene, rt, 86%.

from commercially available, but expensive, ethyl 2-ethylacrylate.[8] Hydrolysis of **8** to **9** was effected in 76% yield by refluxing with 2 M NaOH,[8] and **10** was then obtained in 86% yield by reaction of **9** with oxalyl chloride.[8]

Synthesis of proline, glutamic acid and pyroglutamic acid derived iodides

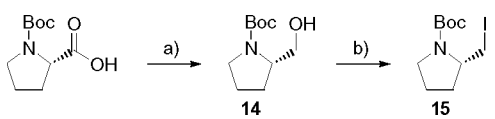
The synthesis of **12** and **13** as precursors to organozinc reagents **1** and **5**, respectively, is shown in Scheme 4.



Scheme 4 Synthesis of iodides **12** and **13**. Key: (a) $SOCl_2$, MeOH, −15 °C to rt; (b) $NaBH_4$, EtOH, 0 °C to rt, two steps, 91%; (c) TsCl, Et_3N, DMAP, CH_2Cl_2, rt; (d) NaI, MeCN, Δ, two steps, 94%; (e) Boc_2O, NaH, THF, −20 °C to rt, 64%.

L-Pyroglutamic was converted into alcohol **11** by reaction with $SOCl_2$ in MeOH followed by reduction of the crude methyl ester with an excess of $NaBH_4$ in EtOH. The overall yield for these two steps was 91% and this route is based on a modified literature procedure.[9] Iodide **12** was then obtained by tosylation of **11** with TsCl in the presence of Et_3N and DMAP,[10] followed by refluxing a mixture of the crude product and NaI in MeCN[11] (94% yield for the two steps and 86% overall yield from L-pyroglutamic acid). Iodide **13** was obtained by reaction of **12** with Boc_2O using NaH as base,[12] in 64% yield.

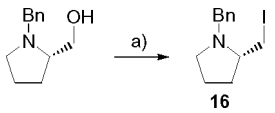
Synthesis of iodide **15** (Scheme 5) as precursor to **6** was achieved in two steps from commercially available *N*-Boc L-proline following literature procedures.



Scheme 5 Synthesis of iodide **15**. Key: (a) BH_3·DMS, THF, rt to reflux, 73%; (b) I_2, imidazole, PPh_3, Et_2O or CH_2Cl_2, rt, 83%.

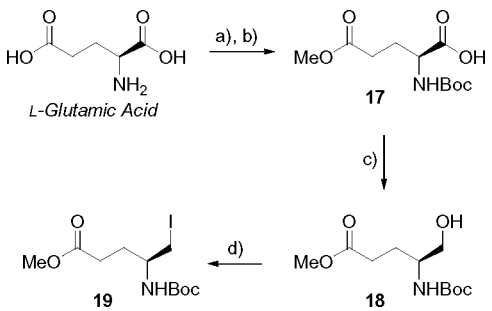
Reduction of the acid functionality in *N*-Boc L-proline with BH_3·DMS in refluxing THF[13] provided alcohol **14** in 73% yield after workup and crystallization. Further conversion into the desired iodo derivative **15** was effected in 83% yield by reaction with I_2, imidazole and PPh_3 in Et_2O or CH_2Cl_2.[14] We found that use of a 2:1 mixture of Et_2O–CH_2Cl_2 as solvent for this reaction proved to be optimal, giving **15** in 61% overall yield.

Iodide **16** was prepared from commercially available *N*-benzyl L-prolinol (Scheme 6). Only 38% yield was obtained; the product was found to be unstable and was thus used as soon as possible after isolation.



Scheme 6 Synthesis of iodide **16**. Key: (a) I_2, imidazole, PPh_3, CH_2Cl_2, rt, 38%.

Iodide **19**, the precursor to organozinc reagent **3**, was synthesised as shown in Scheme 7.



Scheme 7 Synthesis of iodide **19** from L-glutamic acid. Key: (a) $SOCl_2$, MeOH, −15 °C to rt; (b) Boc_2O, Et_3N, dioxane–water, two steps, 89%; (c) *N*-methyl morpholine, $ClCO_2Et$, THF, −10 °C; then $NaBH_4$, MeOH, THF, 0 °C, 64%; (d) I_2, imidazole, PPh_3, Et_2O–CH_2Cl_2, rt, 85%.

Selective monoesterification of L-glutamic acid was achieved by reaction with $SOCl_2$ in MeOH using a modified literature procedure.[9,15] Concentration of the reaction mixture followed by reaction with Boc_2O in dioxane–water in the presence of Et_3N,[16] afforded the desired *N*-protected product **17** in 89% yield for the two steps. Derivative **17** was then transformed into a mixed anhydride by reaction with *N*-methyl morpholine and $ClCO_2Et$ and subsequent reduction with $NaBH_4$ in THF–MeOH gave the desired alcohol **18** in 64% yield using a modified literature procedure.[17] Synthesis of iodo derivative **19** was completed by subjecting **18** to our developed conditions I_2–imidazole–PPh_3 in Et_2O–CH_2Cl_2 (2 : 1) giving **19** in 85% yield. Overall, the synthesis of **19** was realized in 4 steps and 48% overall yield from L-glutamic acid.

With the three β-amido iodides **12**, **13** and **19** and the two β-amino iodides **15** and **16** now available, we proceeded to study the zinc insertion process.

Subjection of proline and pyroglutamic acid derived iodides to zinc insertion

As mentioned above, organozinc reagent **1**, generated by reaction of activated zinc dust with the parent iodide **12** in DMF at

0 °C, has earlier been used in Cu(I) mediated reactions with various electrophiles in DMF or DMF–THF giving the desired products in moderate yields.[4] An important finding was that **1** was unstable in THF at rt giving rise to substantial amounts of β-elimination.[4a] It has previously been reported that dipolar aprotic solvents such as DMF, DMA, NMP and DMSO stabilize β-amido zinc reagents,[6a] and use of DMF as solvent for this zinc insertion accordingly reduced β-elimination to less than 10%. β-Elimination was completely eliminated by rinsing the activated zinc and lowering the temperature to 0 °C.[4a]

We decided to utilize this reported method for zinc insertion as a basis for the study at hand with one important modification: DMF has been reported to react with acid chlorides under similar conditions, a problem which was suppressed by using DMA instead of DMF.[18] Therefore, we decided to make use of these findings and replace DMF with DMA in our study which was initially concentrated on organozinc reagents **1** and **5–7**.

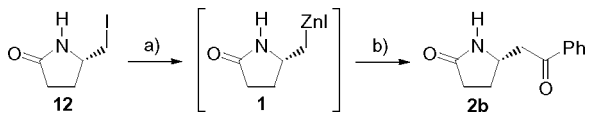
Not surprisingly, it was found that the quality and mode of activation of the zinc dust was of major importance for the insertion reaction. The most reliable results were obtained when using zinc dust (<10 micron), purchased from Aldrich, after activation with 1,2-dibromoethane (0.05 equiv.) at 60 °C, followed by TMSCl[19] (0.04 equiv.) and sonication[20] at rt under N_2 in DMA.[3,4a] Reaction of the activated zinc with iodides **12**, **13**, **15** and **16** (Scheme 8) was then followed by TLC. When no starting material remained the reactions were quenched (with water or 0.1 M HCl) and the crude product compositions were investigated by ^{1}H-NMR spectroscopy. Thus, if zinc insertion had taken place and the resulting zinc reagent was stable, one would expect to isolate the reduced products **20**, **21**, **24** and **25**. If the generated organozinc intermediate was unstable toward β-elimination, one would expect the NMR to show the presence of the unsaturated products **22**, **23**, **26** and **27**.

We started with the known organozinc reagent **1**. Zinc insertion in DMA was complete within 2–3.5 hours at 0 °C and as expected, NMR of the crude product after aqueous quench showed the presence of almost exclusively the reduced product **20**†,[21] and only traces of **22**‡. Unfortunately, none of the three other cyclic organozinc reagents were found to be stable under these conditions: zinc insertion into **13** in DMA was complete within one hour at 0 °C but ^{1}H-NMR of the quenched reaction mixture showed the almost exclusive presence of **23** resulting from β-elimination. This was perhaps not so surprising, since **5** was expected to be less stable than **1** as a result of the better leaving group abilities of the amide moiety and better coordinating ability of the nitrogen protecting group with zinc. The latter effect has been proposed to be a key parameter in β-elimination from β-amido-alkylzinc iodides.[6c,6f,22]

Similarly, in our hands, the proline derived organozinc reagents **6** and **7**, derived from reaction of **15** (in DMA) and **16** (in DMA–THF 1 : 1), respectively, proved very unstable and only the elimination products **26** and **27** were present after zinc insertion and aqueous quench as judged by ^{1}H-NMR. We note that only a few applications of β-amino-alkylzinc iodides have been reported,[23] and these types of reagents, as well as being prone to elimination–degradation, also showed reduced reactivity, possibly due to intra- or inter-molecular complexation between the nitrogen and the metal center.[5,23a]

Reaction of pyroglutamic acid derived organozinc reagent with acid chlorides

We thus concentrated our efforts on organozinc reagent **1** in order to find the optimal conditions for reaction with acid chlorides, using benzoyl chloride as standard (Scheme 9).

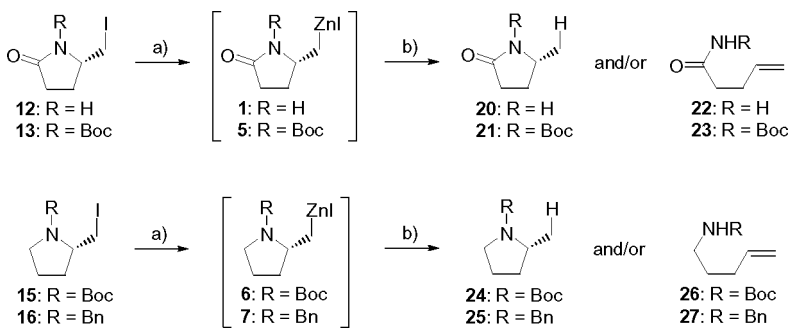


Scheme 9 Desired product **2b** from reaction of **1** with benzoyl chloride after transmetallating with a copper- or a palladium source. Key: (a) Zn*, DMA, 0 °C; (b) BzCl, copper or palladium transmetallation.

Initially, literature procedures for copper-mediated reactions[4] involving **1** were directly adapted to our DMA-based system and the results are listed in Table 1. The DMA solution of the formed organozinc reagent **1** was first added to a solution of CuCN·2LiCl (1.0 equiv.) in THF at −40 °C. The mixture was then stirred for 10 minutes at 0 °C to ensure formation of the organocopper reagent. Cooling to −30 °C followed by addition of benzoyl chloride provided the desired product in a moderate 49% yield after workup (entry 1). Reaction of **1** in DMA at −10 °C with benzoyl chloride in the presence of CuBr·DMS (0.2 equiv.) was likewise attempted (entry 2) but yielded only traces of the

† Characteristic ^{1}H-NMR signals from the formed CH_3-group in **20**: δ 1.19 (3 H, d, J 6.3).

‡ Characteristic ^{1}H-NMR alkene-signals in **22**: δ 4.96 (1 H, m, J 10.2), 5.02 (1 H, m, J 17.2) and 5.77 (1 H, m).



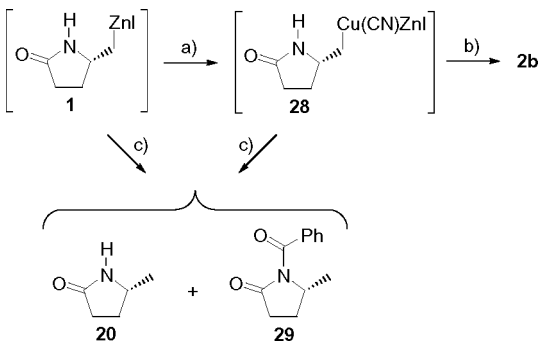
Scheme 8 Generation and possible products from aqueous quenching of organozinc reagents **1** and **5–7** derived from **12**, **13**, **15** and **16**. Key: (a) Zn*, **12**: DMA, 0 °C, 2–3.5 h, **13**: DMA, 0 °C, 1 h, **15**: DMA, −15 °C to 0 °C, 2 h, **16**: DMA–THF 1 : 1, −15 °C to −10 °C, 1 h; (b) water or 0.1 M HCl.

Table 1 Results obtained from reaction of **1** with benzoyl chloride yielding **2b** under different conditions

Entry	Transmet. agent (equiv.)	Solvent	Temperature	Yield (%)
1	CuCN·2LiCl (1.0)	THF–DMA 5 : 1	−40 °C–0 °C–−30 °C	49
2	CuBr·DMS (0.2)	DMA	−10 °C	Trace
3	$Pd(PPh_3)_4$ (0.05)	Toluene–DMA 5 : 1	rt	0

desired product. For comparison, we included an adaptation of a literature procedure[6c] for Pd(0)-catalysed cross-coupling of acid chlorides with acyclic β-amido-alkylzinc iodides; unfortunately, this failed completely in our hands (entry 3).

We thus decided to optimise the conditions for the use of CuCN·2LiCl as transmetallating agent. When reacted with organozinc reagents of the type RZnI, CuCN·2LiCl is reported to give copper reagents tentatively described as RCu(CN)ZnI, but the exact structures of these reagents remain unknown.[2,3] Thus, for the system at hand, **1** would give a copper species formulated as **28** which then provides the desired product **2b** after reaction with benzoyl chloride (Scheme 10). As will be discussed below, a major side product of this reaction was the reduced species **20**, presumably formed as a result of slow deprotonation of the amide functionality by the organozinc reagent **1** and/or copper reagent **28** which yields **20** after aqueous workup. Alternatively, the intermediate deprotonated species could react with benzoyl chloride giving **29**[24] which was also observed in smaller amounts.



Scheme 10 Transmetallation of **1** with CuCN·2LiCl gives a copper reagent tentatively described as **28** which upon reaction with benzoyl chloride gives the desired product **2a**. Byproducts **20** and **29** presumably formed as a result of self-quenching of **1** and/or **28** followed by aqueous quench or reaction with benzoyl chloride. Key: (a) CuCN·2LiCl; (b) BzCl; (c) quench or BzCl followed by quench.

Our original procedure was somewhat tedious due to the temperature changes required during the reaction, in combination with the poor solubility of the reagents during transmetallation. Thus, formation of a sticky precipitate was observed in the THF–DMA solvent mixture, which hindered stirring. We therefore performed some screening experiments, which are summarized in Table 2.

Based on an early observation that the zinc reagent **1** and/or copper reagent **28** were soluble in THF–DMA 5 : 1 when warmed to 0 °C, we initially performed the reaction in this solvent composition, but keeping the temperature at −10 °C throughout the whole reaction (entry 1). Disappointingly, the reagents were not soluble even at this elevated temperature and furthermore the yield decreased from 49% to 39%, perhaps indicating that the reagents were less stable at higher temperatures. Importantly, though, we proved that the reaction could still provide useful yields when kept at a constant temperature. Changing the solvent to pure DMA made a modest improvement in the yield (44%, entry 2) and eliminated the problems with solubility but revealed another drawback: the presence of an increased volume of DMA relative to THF during the reaction resulted in a crude mixture after aqueous workup that contained substantial amounts of DMA. The result was a slightly impure product still containing traces of DMA even after column chromatography. It was eventually found that concentrating the crude mixture after aqueous workup at *ca.* 45 °C/*ca.* 2 mmHg removed most of the DMA and the rest could be removed by adding butyl benzene and concentrating the resulting mixture at *ca.* 45 °C/*ca.* 2 mmHg. Column chromatography then furnished the pure product and this workup procedure remained our preferred method.

Table 2 Results obtained from reaction of **1** with benzoyl chloride yielding **2a** under different conditions after transmetallating with CuCN·2LiCl

Entry	Solvent	Temperature	**2b** (%)[a]	**20** (%)[b]	**29** (%)[b]
1	THF–DMA 5 : 1	−10 °C	39	—[c]	—[c]
2	DMA	−10 °C	44	21	6
3	THF–DMA 1 : 1	0 °C	29	51	13
4	THF–DMA 1 : 1	−10 °C	36	30	5
5	THF–DMA 1 : 1	−15 °C	38	15	4
6	THF–DMA 1 : 1	−25 °C	52	14	3
7	THF–DMA 1 : 1	−30 °C	51	16	5
8	THF–DMA 1 : 1	−40 °C	44	14	3
9	THF–DMA 2 : 1	−25 °C	—[d]	—[d]	—[d]
10	THF–DMA 3 : 1	−25 °C	—[d]	—[d]	—[d]
11	Toluene–DMA 1 : 1	−25 °C	49	15	3
12	THF–DMSO 1 : 1	−10 °C	0	—[c]	—[c]

[a] Isolated yield after column chromatography. [b] Calculated yield from ^{1}H-NMR. [c] Not determined. [d] **1** and **28** not sufficiently soluble under these conditions, so further work was abandoned.

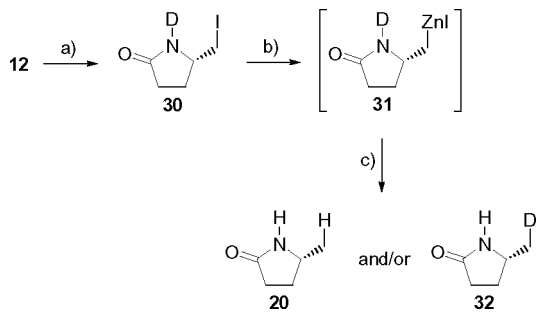
From these two experiments, it seemed that keeping the temperature constant during the reaction and use of an increased volume of DMA relative to THF could improve the reaction at hand. However, it also seemed that elevated temperatures (−10 °C) resulted in lower yields and, since pure DMA freezes at −20 °C, a compromise was needed. THF–DMA 1 : 1 (entries 3–8) proved to be the solvent composition of choice. The reagents were still not completely soluble in this solvent mixture, but the reaction mixture remained an easily stirrable suspension. After having performed the reaction at a range of different temperatures (entries 3–8) we found the optimum temperature to be −25 °C which gave the desired product **2a** in 52% yield (entry 6). Above this temperature (entries 3–5) the decrease in yield is probably a result of the lower thermal stability of zinc reagent **1** and/or copper reagent **28**. This is supported by the substantial increase in the yield of **20** after "self-quenching" from around 15% (entries 5–8) at −15 °C and below to 30% at −10 °C (entry 4) and 51% at 0 °C (entry 3). Furthermore, the yield of **29** also increased from around 4% when performing the reaction at −10 °C or below (entries 3–7) to 13% at 0 °C (entry 2). Interestingly, it was found that less **20** was formed at −10 °C in DMA (21%, entry 1) than in THF–DMA 1 : 1 (30%, entry 3) indicating that the presence of THF may in fact cause a decrease in the stability of organozinc reagent **1** and/or copper reagent **28**. Below −25 °C, the decrease in yield may be explained by the reduced reactivity of **28** and/or that transmetallation is too slow.

Interestingly, toluene could be used instead of THF, with comparable yields (entry 11). Furthermore, organozinc reagent **1** could be formed in DMSO at rt (complete within *ca.* 2 hours),[5] but when further reaction was attempted in THF–DMSO 1 : 1 (entry 12) none of the desired product was obtained.

Overall, the results of these screening experiments did not lead to any real improvement in yield relative to the initial procedure (52%, Table 2, entry 6 *vs.* 49%, Table 1, entry 1) but, importantly, resulted in a more convenient experimental protocol.

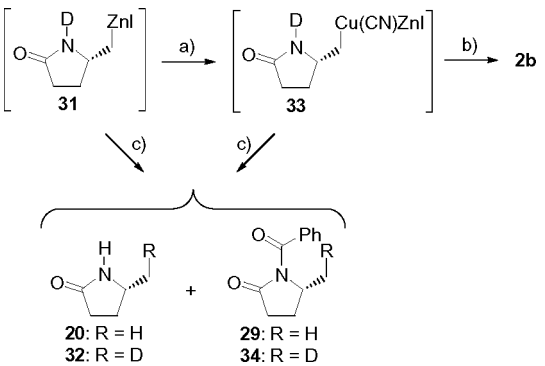
With a convenient experimental procedure at hand, we then tested the generality of the method by reacting copper reagent **28** with a variety of acid chlorides (Scheme 13, Table 3).

In order to test the hypothesis that the reduced species **20** is formed by slow deprotonation of the amide functionality by the organozinc reagent **1** and/or copper reagent **28** (Scheme 10) we decided to synthesize the deuterated iodide **30** (Scheme 11) and subject this to the zinc insertion procedure to yield **31**. If any self-quenching would occur one would expect to isolate the deutero-species **32** along with, or instead of, **20**.



Scheme 11 Synthesis of deuterated iodide **30** followed by zinc insertion. Key: (a) D_2O, CH_2Cl_2, rt, 95%; (b) Zn*, DMA, 0 °C; (c) quench.

Thus, in parallel experiments, iodides **12** and **30** were subjected to identical conditions during zinc insertion at 0 °C and the reactions were monitored by ^{1}H-NMR. No distinctly measurable differences between the quenched samples from reaction of **12** and **30** were observed within the time needed for completion of zinc insertion. This indicated that the organozinc reagents **1** and **31** were stable with respect to self-quench under the conditions used for zinc insertion. When performing transmetallation of deutero-species **31** with CuCN·2LiCl and further reaction with benzoyl chloride following the optimized method in DMA–THF 1 : 1 at −25 °C (Scheme 12), we subsequently obtained the desired product **2b** in an almost unchanged 48% yield (relative to 52% yield, Table 2, entry 6).



Scheme 12 Transmetallation of organozinc reagent **31** with CuCN·2LiCl to give **33** and further reaction with benzoyl chloride yielding the desired product **2a** along with byproducts **32** and **34** presumably as a result self-quenching of **31** and/or **33**. Key: (a) CuCN·2LiCl, DMA–THF 1 : 1, −25 °C; (b) BzCl, DMA–THF 1 : 1, −25 °C to rt, **2a**: 48%; (c) quench or BzCl followed by quench.

Interestingly, however, a substantial amount of deuterium insertion into the reduced product was observed in ^{1}H-NMR of the crude mixture obtained after aqueous workup. Thus, the reduced products **20** and **32** were formed in an approximately 1 : 1 mixture in 16% overall yield. These products could be easily recognized by the difference in the appearance of characteristic signals in ^{1}H-NMR from the CH_3-group in **20** and the CH_2D-group in **32**§. Thus, under the conditions used for transmetallation and further reaction with benzoyl chloride a slow deprotonation of the amide functionality in **31** and/or **33** yielding **32** is observed. Analogously, the byproducts **29** and **34** were observed in a *ca.* 1 : 1 relationship, again readily apparent from the characteristic signals in their ^{1}H-NMR spectra. Since we do not know whether full transmetallation has taken place under the experimental conditions used, we do not know if these products derive from **31**, **33**, or both.

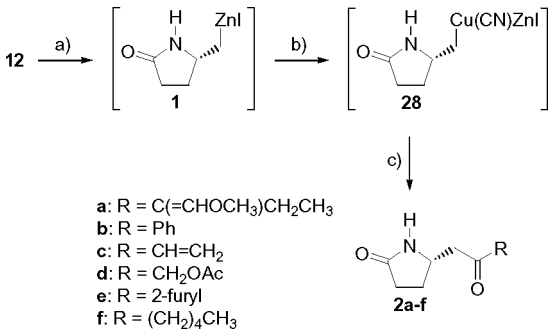
Disappointingly, this cross-coupling technique appears to work only for relatively stable acid chlorides (Table 3, entries 1, 2 and 5), providing the desired products in moderate yields at best. When more reactive acid chlorides were used (entries 3, 4 and 6) none of the desired products were obtained and NMR spectroscopy of the crude mixtures after aqueous workup showed only the presence of reduced product **20** and products resulting from β-elimination.

§ **20**: δ 1.19 (3 H, d, J 6.3); **32**: δ 1.17 (2 H, dt, J 1.9 and 6.3).

Table 3 Results obtained from reaction of copper reagent **28** with a selection of acid chlorides using the developed methodology

Entry	RCOCl	Product	Yield (%)
1	$C(=CHOCH_3)CH_2CH_3$	**2a**	51[a]
2	Ph	**2b**	52
3	$CH=CH_2$	**2c**	0
4	CH_2OAc	**2d**	0
5	2-Furyl	**2e**	44
6	$(CH_2)_4CH_3$	**2f**	0

[a] Calculated from NMR.



Scheme 13 Reaction of copper reagent **28** with a selection of acid chlorides using the developed methodology. Key: (a) Zn*, DMA, 0 °C; (b) CuCN·2LiCl, DMA–THF 1 : 1, −25 °C; (c) RCOCl, DMA–THF 1 : 1, −25 °C to rt. See Table 3 for yields.

Reaction of glutamic acid derived organozinc reagent with acid chlorides

As mentioned above, the acyclic L-glutamic acid derived organozinc reagent **3** has previously been used in Pd(0)-catalyzed reactions with acid chlorides, giving **4b–e** in moderate yields (45–52%) but failing to provide **4f** (Scheme 1).[6c]

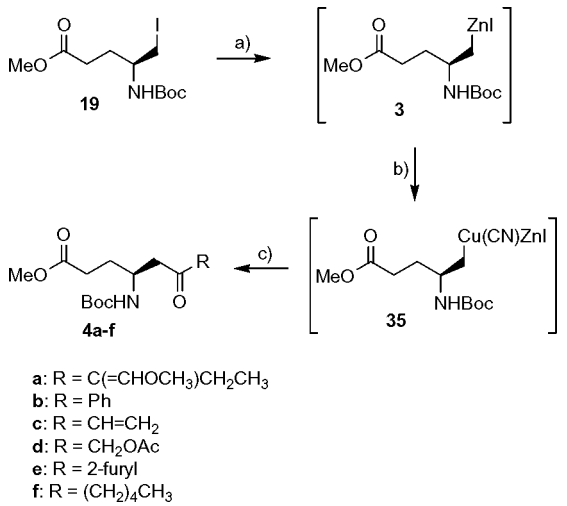
When we applied our optimized method to organozinc reagent **3**, we were satisfied to find that this technique is generally applicable to cross-coupling with a range of acid chlorides (Scheme 14). For this system, organozinc reagent **3** would give a copper species formulated as **35**, and the cross-coupling results are listed in Table 4, where they are compared to the yields reported from use of palladium catalysis.[6c]

As seen in Table 4 the organocopper methodology provided the desired products in good yields (65–78%, entries 1–2 and 4–6) apart from when acryloyl chloride was used; in this case none of the desired product was obtained (entry 3). NMR spectroscopic investigation of the crude reaction mixture after

Table 4 Results obtained from reaction of copper reagent **35** with a selection of acid chlorides using the developed methodology

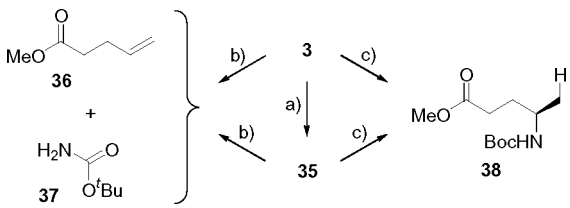
Entry	RCOCl	Product	Yield (%)	Lit. yield (%)[a]
1	$C(=CHOCH_3)CH_2CH_3$	**4a**	68	—
2	Ph	**4b**	75	51
3	$CH=CH_2$	**4c**	0	48
4	CH_2OAc	**4d**	65	52
5	2-furyl	**4e**	78	45
6	$(CH_2)_4CH_3$	**4f**	77	0

[a] Yields reported in the literature utilizing Pd-catalysis.[6c]



Scheme 14 Reaction of copper reagent tentatively described as **35**, derived from organozinc reagent **3**, with a selection of acid chlorides using the developed methodology. Key: (a) Zn*, DMA, 0 °C; (b) CuCN·2LiCl, DMA–THF 1 : 1, −25 °C; (c) RCOCl, DMA–THF 1 : 1, −25 °C to rt. See Table 4 for yields.

aqueous workup showed only the presence of products from elimination degradation, **36** and **37** (Scheme 15), and traces of hydrolyzed organozinc reagent **38**.



Scheme 15 Observed byproducts from elimination degradation (**36** and **37**) and quench (**38**) of **3** and/or **35**. Key: (a) CuCN·2LiCl, DMA–THF 1 : 1, −25 °C; (b) β-elimination then quench; (c) quench.

In most cases, only traces of the hydrolyzed organozinc reagent **38** were observed in the NMR of the crude products, indicating that **3** and **35** were more stable under the reaction conditions than the cyclic analogs **1** and **28** (Scheme 10). When compared to the results obtained when palladium catalysis was employed, our method provided **4f** (entry 6) which the palladium catalysis was unable to, and *vice versa* for **4c** (entry 3). Satisfyingly, the present methodology provided **4b**, **4d** and **4e** in yields superior to those reported for the palladium-catalyzed process (13–33%, entries 2 and 4–5). The results shown in Table 4 thus suggest that our cross-coupling technique, despite using a stoichiometric amount of copper, could provide a useful alternative in cases when the Pd(0)-catalyzed method fails or gives unsatisfactory yields.

Conclusion

We have developed a straightforward experimental protocol for copper-mediated cross-coupling of organozinc iodides **1** and **3** with a range of acid chlorides (Scheme 1). Our method uses CuCN·2LiCl as the copper source and for organozinc reagent **1** the methodology appears to be limited to reaction with more stable acid chlorides, providing the desired products in moderate yields.

When applied to organozinc reagent **3**, however, the protocol is more general and provides the products in good yields in all but one of the cases tested. We consider the latter results to provide a valuable complement to an existing palladium-catalyzed protocol,[6c] delivering amino acid derivatives which are useful building blocks for construction of modified peptides.[6c]

Experimental

General experimental methods

Et_2O, THF and toluene were distilled under N_2 from sodium–benzophenone. CH_2Cl_2 and Et_3N were distilled under N_2 from CaH_2. Benzene, 1,2-dibromoethane, DMA, DMF, DMSO, EtOH, MeCN, MeOH and *N*-methyl morpholine were dried over 4 Å MS. Zn dust (<10 micron) was purchased from Aldrich and was used as received. Ethyl chloroformate was distilled over 4 Å MS and stored over 4 Å MS. All other solvents and chemicals obtained from commercial source were used without further purification unless otherwise stated.

Melting points are uncorrected. Specific rotations were measured on a Perkin Elmer 241 polarimeter using a 10 cm cell and are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on a Perkin Elmer 1600 Series FTIR. NMR spectra were recorded on a Varian Mercury 300 MHz spectrometer. Chemical shifts are referenced to the residual solvent peak and *J* values are given in Hz. Where applicable, assignments were based on DEPT and COSY-experiments. TLC was performed on Merck TLC aluminum sheets, silica gel 60, F_{254}. Reactions were, when applicable, followed by NMR and/or TLC. Visualizing of spots was effected with UV-light and/or ninhydrin in BuOH–AcOH. Flash chromatography was performed with silica gel 60, 0.035–0.070 mm, Amicon 85040. Unless otherwise stated, flash chromatography was performed in the eluent system for which the R_f-values are given.

Elemental analyses were determined at Mikroanalytisches Laboratorium at Institut für Physikalische Chemie, Universität Wien, Austria. HRMS were recorded at the Department of Chemistry, University of Copenhagen, Denmark.

(*E*)-2-Methoxymethylene-butyric acid methyl ester (8). A small amount (5 cm^3) of a mixture of α,α-dichloromethyl methyl ether (5.00 cm^3, 55.3 mmol) and methyl 2-bromobutyrate (13.0 cm^3, 113 mmol) in Et_2O (50 cm^3) was added to a suspension of Zn dust (14.5 g, 222 mmol) in Et_2O (50 cm^3) at rt under N_2. A catalytic amount of 1,2-dibromoethane (0.3 cm^3) was then added to initiate the reaction. The rest of the reagent solution was then added over a period of 1 h while ensuring gentle reflux. After completion of addition, the reaction mixture was refluxed for 20 min. The reaction mixture was allowed to cool to rt, filtered, washed with 3% acetic acid (50 cm^3) and cold water (2 × 50 cm^3), dried over $MgSO_4$, filtered and concentrated. Flash chromatography of the residue yielded **8** (6.96 g, 87%) as a colorless oil: R_f (hexane–EtOAc 12 : 1) = 0.28; bp 62–63 °C/5 mmHg (lit.,[8] 58–65 °C/1 mmHg); NMR spectra were in full accordance with those reported in the literature.[8]

(*E*)-2-Methoxymethylene-butyric acid (9). A mixture of **8** (6.93 g, 48.0 mmol) in 2 M NaOH (36.0 cm^3, 72.0 mmol NaOH) was refluxed for 3 h. After cooling to rt, the reaction mixture was washed with Et_2O (20 cm^3) and acidified to pH 3–4 with 3 M HCl. The resulting suspension was filtered and the solid was washed with a small amount of cold water. Drying the solids *in vacuo* yielded **9** (4.46 g, 71%) as a colorless solid. The filtrate was extracted with Et_2O (3 × 40 cm^3), and the combined organic phases were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo* yielding crude **9** (0.64 g) as a yellowish solid. This crude product was crystallized from water (22 cm^3) to give further pure **9** (0.29 g, 5%) as a colorless solid: mp 89.0–92.0 °C (lit.,[8] 89.6–90.2 °C); NMR spectra were in full accordance with those reported in the literature.[8]

(*E*)-2-Methoxymethylene-butyryl chloride (10). Oxalyl chloride (6.55 cm^3, 75.1 mmol) was added dropwise to a solution of **9** (8.70 g, 62.5 mmol) and DMF (0.02 cm^3, 0.26 mmol) in benzene (45 cm^3) at rt under N_2. The mixture was stirred for 2 h and was then concentrated. Distillation *in vacuo* gave crude **10** (8.34 g) as a colorless oil. Re-distillation *in vacuo* gave pure **10** (7.95 g, 86%) as a colorless oil: bp 58–59 °C/2.0 mmHg and 65–67 °C/3.5 mmHg (lit.,[8] 58 °C/1.2 mmHg); NMR spectra were in full accordance with those reported in the literature.[8]

(*S*)-5-Hydroxymethyl-pyrrolidin-2-one (11). To a solution of L-pyroglutamic acid (14.2 g, 110 mmol) in MeOH (350 cm^3) at −15 °C under N_2 was added $SOCl_2$ (9.60 cm^3, 132 mmol) dropwise. After stirring for 30 min further at −15 °C the reaction mixture was allowed to warm to rt over 1 h and stirring was continued at rt for 1 h. The solvent was then removed and the residue was dried *in vacuo*. The residue was dissolved in EtOH (350 cm^3) under N_2 and the mixture was cooled to 0 °C. To the solution was slowly added $NaBH_4$ (8.32 g, 220 mmol). The reaction mixture was then allowed to heat to rt slowly overnight (stirred for 18 h). Acetic acid (15.0 cm^3, 262 mmol) was added dropwise and the mixture was stirred for 30 min further at rt under N_2. The mixture was then filtered twice, using the same filter and then twice using a glass fiber filter until the filtrate was nearly clear. Silica gel (17.5 g) was added to the filtrate and the resulting mixture was concentrated and dried *in vacuo*. The silica gel mixture was added to the top of a short silica gel column and the product was eluted with EtOAc–MeOH 4 : 1, yielding **11** (11.5 g, 91%) as a colorless solid: R_f (EtOAc–MeOH 4 : 1) = 0.28; mp 71–73 °C (lit.,[25] 72–73 °C); $[a]_D^{20}$ +30.5 (*c* 1.00, EtOH) (lit.,[25] $[a]_D^{20}$ +32.4 (*c* 1.76, EtOH)); NMR spectra were in full accordance with those reported in the literature.[9]

(*S*)-5-Iodomethyl-pyrrolidin-2-one (12). To a solution of **11** (2.00 g, 17.4 mmol) and TsCl (3.97 g, 20.8 mmol) in CH_2Cl_2 (60 cm^3) at rt under N_2 were added Et_3N (4.80 cm^3, 34.4 mmol) and DMAP (212 mg, 1.74 mmol). The mixture was then stirred for 17 h at rt. The reaction mixture was diluted with CH_2Cl_2 (40 cm^3), poured into water (100 cm^3) and acidified with conc. HCl (2.0 cm^3). The organic phase was isolated and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 cm^3). The combined organic phases were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo* to give the crude tosylate (4.97 g) as a pale yellowish solid. The crude product was dissolved in MeCN (100 cm^3) at rt under N_2 and NaI (7.81 g, 52.1 mmol) was added. The solution was then refluxed for 4 h under N_2. After cooling to rt and filtration, the solution was concentrated and dried *in vacuo* (brown solid), acidified with 1 M HCl (30 cm^3) and extracted with $CHCl_3$ (8 × 60 cm^3). The combined organic phases were shaken with 10% aq. $Na_2S_2O_3$ (50 cm^3) until the brownish color disappeared. The

organic phase was isolated and the aqueous phase was extracted with $CHCl_3$ (2 × 100 cm^3). To the combined organic phases was added silica gel (5.00 g) and the suspension was concentrated and dried *in vacuo*. The silica gel mixture was added to the top of a short silica gel column and the product was eluted using EtOAc, yielding **12** (3.66 g, 94%) as a colorless solid: R_f (EtOAc) = 0.33; mp 79.5–81.5 °C (lit.,[11] 81 °C); $[\alpha]_D^{20}$ −63.6 (*c* 1.07, EtOH) (lit.,[11] $[\alpha]_D^{20}$ −63 (*c* 1.24, EtOH)); NMR spectra were in full accordance with those reported in the literature.[11]

(*S*)-2-Iodomethyl-5-oxo-pyrrolidine-1-carboxylic acid *tert*-butyl ester (13). NaH (60% in oil, 800 mg, 20.0 mmol) was washed with hexane (3 × 5 cm^3) under N_2 and dried *in vacuo*. THF (10.0 cm^3) was added and the suspension was cooled to −20 °C whereupon a solution of **12** (2.25 g, 10.0 mmol) in THF (10.0 cm^3) was added. After gas evolution had ceased, Boc_2O (6.55 g, 30.0 mmol) was added and the reaction mixture was allowed to heat to rt and stirring was continued for 30 min at rt. The reaction mixture was diluted with EtOAc (100 cm^3), poured into water (50 cm^3) and the organic phase was isolated. The aqueous phase was extracted with EtOAc (2 × 100 cm^3) and the combined organic phases were concentrated and dried *in vacuo*. Flash chromatography of the residue yielded **13** (2.07 g, 64%) as a colorless solid: R_f (hexane–EtOAc 4 : 1) = 0.28; mp 80.5–82.5 °C; $[\alpha]_D^{20}$ −70.1 (*c* 1.00, EtOH) (lit.,[26] for enantiomer: $[\alpha]_D^{20}$ +68.4 (*c* 1.14, EtOH)); Found: C, 36.89; H, 4.85; N, 4.27. $C_{10}H_{16}INO_3$ requires C, 36.94; H, 4.96; N, 4.31%; ν_{max}(KBr)/cm^{-1} 2976w, 1773s, 1287m, 1153m; δ_H (300 MHz; $CDCl_3$) 1.54 (9 H, s), 1.96 (1 H, m), 2.20 (1 H, m), 2.45 (1 H, ddd, *J* 3.7, 10.8 and 18.0), 2.69 (1 H, ddd, *J* 9.8, 9.8 and 18.0), 3.39 (1 H, dd, *J* 8.0 and 10.0), 3.50 (1 H, dd, *J* 2.6 and 10.0), 4.22 (1 H, m); δ_C (75.4 MHz; $CDCl_3$) 9.2, 23.1, 28.0 (3 C), 31.1, 57.9, 83.6, 149.6, 173.6.

(*S*)-1-Deutero-5-iodomethyl-pyrrolidin-2-one (30). To a solution of **12** (1.13 g, 5.50 mmol) in CH_2Cl_2 (30 cm^3) at rt under N_2 was added D_2O (3.0 cm^3). The mixture was stirred vigorously for 30 min, whereupon the phases were allowed to separate and the aqueous phase was removed *via* syringe. D_2O (3.0 cm^3) was then added and the mixture was stirred vigorously for another 30 min before the phases were allowed to separate and the aqueous phase was removed *via* syringe. The solution was then concentrated and dried *in vacuo*, yielding **30** (1.08 g, 95%) as a colorless solid: R_f (EtOAc) = 0.33; mp 83–84.5 °C; $[\alpha]_D^{20}$ −63.0 (*c* 0.99, EtOH); Found: C, 26.42; H, 3.46; N, 5.93. C_5H_7DINO requires C, 26.57; H, 3.57; N, 6.20%; ν_{max}(KBr)/cm^{-1} 2976w, 1686s, 1404w, 1340w, 1288w, 1206w; δ_H (300 MHz; $CDCl_3$) 1.74–1.92 (1 H, m), 2.28–2.55 (3 H, m), 3.19 (1 H, dd, *J* 6.5 and 10.1), 3.24 (1 H, dd, *J* 5.7 and 10.1), 3.86 (1 H, m); δ_C (75.4 MHz; $CDCl_3$) 11.1, 27.4, 30.2, 55.0, 177.5.

(*S*)-Hydroxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (14). *N*-Boc L-proline (5.50 g, 25.6 mmol) was dissolved in THF (38 cm^3) at rt under N_2 and BH_3·DMS (95% in DMS, 2.80 cm^3, 28.1 mmol) was added dropwise over 30 min. The reaction mixture was then refluxed for 2 h. After cooling to rt, ice (20 g) was added and the mixture was extracted with CH_2Cl_2 (2 × 100 cm^3). After filtration through Celite, the solvent was removed *in vacuo* giving a crude product (4.99 g) as a colorless solid. Crystallization from Et_2O (6 cm^3) gave pure **14** (3.73, 73%) as a colorless solid: mp 58–61 °C (lit.,[13] 59–60 °C); $[\alpha]_D^{20}$ −53.8 (*c* 1.02, MeOH) (lit.,[13] $[\alpha]_D^{20}$ −50.37 (*c* 1.1, MeOH)); NMR spectra were in full accordance with those reported in the literature.[13]

(*S*)-2-Iodomethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (15). To a suspension of imidazole (1.35 g, 19.8 mmol) and triphenylphosphine (3.92 g, 14.9 mmol) in Et_2O (24 cm^3) at 0 °C under N_2 was added iodine (3.78 g, 14.9 mmol) in three portions over 30 min. A red-brownish solid was formed. After stirring for an additional 10 min at rt, a solution of **14** (2.00 g, 9.94 mmol) in Et_2O (12 cm^3) was added. The red-brownish solid did not dissolve, so CH_2Cl_2 (15 cm^3) was added and the resulting mixture was stirred for 16 h at rt. The reaction mixture was then filtered, concentrated and dried *in vacuo* and flash chromatography of the residue yielded **15** (2.57 g, 83%) as a colorless solid: R_f (hexane–EtOAc 6 : 1) = 0.45; mp 38–41 °C (lit.,[14] 102–104 °C (decomp.)); $[\alpha]_D^{20}$ −33.1 (*c* 0.98, $CHCl_3$) (lit.,[14] $[\alpha]_D^{20}$ −32.8 (*c* 1.46, $CHCl_3$)); NMR spectra were in full accordance with those reported in the literature.[14]

(*S*)-1-Benzyl-2-iodomethyl-pyrrolidine (16). To a suspension of imidazole (717 mg, 10.5 mmol) and triphenylphosphine (2.07 g, 7.90 mmol) in CH_2Cl_2 (13 cm^3) at 0 °C under N_2 was added iodine (2.00 g, 7.90 mmol) in three portions over 30 min. After stirring for an additional 10 min at rt, a solution of *N*-benzyl-L-prolinol (0.96 cm^3, 5.27 mmol) in CH_2Cl_2 (13 cm^3) was added and the resulting mixture was stirred for 2.5 h at rt. The reaction mixture was concentrated and dried *in vacuo* and flash chromatography of the residue yielded **16** (608 mg, 38%) as a yellow oil: R_f (hexane–EtOAc 6 : 1) = 0.45; $[\alpha]_D^{20}$ −22.1 (*c* 1.26, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3026m, 2939s, 2796s, 1453m, 1347m, 1124s, 740s, 698s, 682s; δ_H (300 MHz; $CDCl_3$) 1.57–1.75 (2 H, m), 1.79–1.95 (1 H, m), 2.12–2.30 (2 H, m), 2.52 (1 H, m), 2.78 (1 H, br d, *J* 11.3), 3.05 (1 H, br d, *J* 11.3), 3.49 (1 H, d, *J* 13.3), 3.57 (1 H, d, *J* 13.3), 4.22–4.34 (1 H, m), 7.21–7.36 (5H, m); δ_C (75.4 MHz; $CDCl_3$) 27.1, 27.3, 37.5, 52.9, 62.5, 63.6, 127.1, 128.2 (2 C), 128.9 (2 C), 137.9. The product was unstable, and no satisfactory elemental analysis could be obtained.

(*S*)-2-*tert*-Butoxycarbonylamino-pentanedioic acid 5-methyl ester (17). To a solution of L-glutamic acid (2.21 g, 15.0 mmol) in MeOH (50 cm^3) at −15 °C under N_2 was added $SOCl_2$ (1.30 cm^3, 18.0 mmol) dropwise. After stirring for 30 min further at −15 °C the reaction mixture was allowed to heat to rt over 1 h and stirring was continued for 1 h at rt. The mixture was then concentrated and dried *in vacuo*. The residue was dissolved in dioxane–water 2 : 1 (60 cm^3) at 0 °C and Et_3N (3.5 cm^3, 25.1 mmol followed by 2.0 cm^3, 14.3 mmol after 2 h, in all 39.4 mmol) was added until pH = 9–10. Boc_2O (3.70 g, 17.0 mmol) was added and the reaction mixture was stirred at rt for 3 h. The dioxane was removed *in vacuo* and the reaction mixture was diluted with water (20 cm^3) whereupon Na_2CO_3 (0.30 g, 2.8 mmol) was added in order to keep the solution basic. The mixture was then washed with Et_2O (3 × 10 cm^3) and acidified to pH ~2 with conc. HCl (2.0 cm^3). The product was extracted with Et_2O (4 × 40 cm^3) and the combined organic phases were washed with brine (20 cm^3), dried over $MgSO_4$, filtered, concentrated and dried *in vacuo* yielding **17** (3.47 g, 89%) as a colorless oil: R_f (MeOH) = 0.64; $[\alpha]_D^{20}$ +16.5 (*c* 1.40, $CHCl_3$) (lit.,[16] $[\alpha]_D$ +17.15 (*c* 1.53, $CHCl_3$)); NMR spectra were in full accordance with those reported in the literature.[16]

(*S*)-4-*tert*-Butoxycarbonylamino-5-hydroxy-pentanoic acid methyl ester (18). **17** (3.14 g, 12.0 mmol) was dissolved in THF

(60 cm^3) under N_2 and the solution was cooled to −10 °C. *N*-Methyl morpholine (1.32 cm^3, 12.0 mmol) was added followed by ethyl chloroformate (1.15 cm^3, 12.1 mmol) and the reaction mixture was stirred for 10 min at −10 °C. $NaBH_4$ (1.36 g, 36.0 mmol) was then added followed by slow addition of MeOH (60 cm^3) over a period of 15 min at 0 °C. The solution was stirred for 10 min further and was then neutralized with 1 M HCl (20 cm^3). The organic solvents were removed *in vacuo* and the residue was extracted with EtOAc (3 × 100 cm^3). The combined organic phases were washed with 1 M HCl (50 cm^3), water (50 cm^3), 5% aq. $NaHCO_3$ (50 cm^3), water (2 × 50 cm^3), dried over Na_2SO_4, concentrated and dried *in vacuo.* Flash chromatography of the residue yielded **18** (1.89 g, 64%) as a colorless oil: R_f (hexane–EtOAc 1 : 1) = 0.23; $[\alpha]_D^{20}$ −14.0 (*c* 1.35, $CHCl_3$) (lit.,[16] $[\alpha]_D$ −10.48 (*c* 2.88, $CHCl_3$)); NMR spectra were in full accordance with those reported in the literature.[6b]

(*S*)-4-*tert*-Butoxycarbonylamino-5-iodo-pentanoic acid methyl ester (19). To a suspension of imidazole (908 mg, 13.3 mmol) and triphenylphosphine (2.63 g, 10.0 mmol) in Et_2O–CH_2Cl_2 2 : 1 (20 cm^3) at 0 °C under N_2 was added iodine (2.54 g, 10.0 mmol) in three portions over 30 min; a yellow–gray solid was formed. After stirring for an additional 10 min at rt, a solution of **18** (1.65 g, 6.67 mmol) in Et_2O–CH_2Cl_2 2 : 1 (10.0 cm^3) was added and the resulting mixture was stirred for 22 h at rt. The reaction mixture was filtered, the solids were washed with Et_2O and the filtrate was concentrated and dried *in vacuo.* Flash chromatography of the residue yielded **19** (2.03 g, 85%) as a colorless solid: R_f (hexane–EtOAc 4 : 1) = 0.40; mp 91–92 °C (lit.,[6b] 92–93 °C); $[\alpha]_D^{20}$ −12.2 (*c* 0.98, CH_2Cl_2) (lit.,[6b] $[\alpha]_D$ −15.6 (*c* 1.38, CH_2Cl_2)); NMR spectra were in full accordance with those reported in the literature.[6b]

General procedure for generation and reaction of amino acid derived organozinc reagents with acid chlorides

To a suspension of Zn dust (105 mg, 1.61 mmol) in DMA (0.40 cm^3) at rt under N_2 was added 1,2-dibromoethane (0.014 cm^3, 0.162 mmol), and the resulting mixture was stirred at 60 °C for 10 min. The mixture was cooled to rt and TMSCl (0.016 cm^3, 0.127 mmol) was added whereupon the mixture was sonicated for 30 min at rt. The zinc was allowed to settle and the supernatant was removed *via* syringe. DMA (0.40 cm^3) was added, the solution was cooled to 0 °C and a solution of the iodide (0.80 mmol) in DMA (0.40 cm^3) was added dropwise. The mixture was then stirred at 0 °C (2.5–3.5 h for **12**; 1–2 h for **19**) until no starting material remained as judged by TLC ($CHCl_3$–MeOH 20 : 1 for **12**; hexane–EtOAc 4 : 1 for **19**).

LiCl (68 mg, 1.60 mmol) and CuCN (72 mg, 0.804 mmol) were dried for 5.5 h or overnight at 150 °C *in vacuo* in the flask to be used for reaction. The mixture was dissolved in THF–DMA 3 : 2 (5.0 cm^3) at rt under N_2 and the resulting solution was cooled to −25 °C. The DMA-solution of the previously formed organozinc reagent was then added dropwise, rinsing the residual excess of zinc with DMA (0.20 cm^3), avoiding transferring too much zinc. The reaction mixture was stirred at −25 °C for 10 min whereupon the freshly distilled acid chloride (0.80 mmol) was added dropwise. The reaction mixture was stirred at −25 °C for 3 h and was then allowed to heat to rt overnight. The reaction mixture was diluted with EtOAc (16 cm^3) and poured into satd. aq. NH_4Cl (8 cm^3). The organic phase was isolated and the aqueous phase was extracted with EtOAc (3 × 16 cm^3). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. In order to remove most of the residual DMA, the mixture was concentrated further at *ca.* 45 °C in high vacuum (*ca.* 2 mmHg). For products derived from **12** further (complete) removal of DMA was necessary: The residue was suspended in MeOH (1.0 cm^3), butyl benzene (5 cm^3) was added and the mixture was concentrated at *ca.* 45 °C/*ca.* 2 mmHg. Suspension in MeOH (1.0 cm^3) followed by addition of butyl benzene (5 cm^3) and concentration at *ca.* 45 °C/*ca.* 2 mmHg was repeated twice more. The residue was then suspended in MeOH (10 cm^3) and the mixture was filtered, concentrated and dried *in vacuo.*

(*S*)-5-[(*E*)-3-(Methoxymethylene)-2-oxopentyl]-pyrrolidin-2-one (2a). Reaction of **12** (180 mg, 0.800 mmol) with **10** (119 mg, 0.801 mmol) following the general procedure followed by flash chromatography of the residue yielded **2a** (90 mg, 53%) as a yellowish oil containing 4.0% wt./8.7 mol% hydrolyzed zinc-reagent **20** as judged by NMR. Thus, the effective yield of **2a** was 86 mg, 51%. **2a**: R_f (EtOAc–MeOH 10 : 1) = 0.25; R_f (CH_2Cl_2–MeOH 20 : 1) = 0.26; $[\alpha]_D^{20}$ +27.6 (*c* 0.99, CH_2Cl_2); ν_{max}(neat)/cm^{-1} 3354m, 2968m, 1692s, 1634s, 1462m, 1320m, 1250s, 1147m, 1084m, 1012m, 990m; δ_H (300 MHz; $CDCl_3$) 0.91 (3 H, t, *J* 7.5), 1.60–1.80 (1 H, m), 2.22 (2 H, q, *J* 7.5), 2.25–2.38 (3 H, m), 2.63 (1 H, dd, *J* 9.4 and 16.8), 2.82 (1 H, dd, *J* 3.8 and 16.8), 3.87 (3 H, s), 4.05 (1 H, m), 6.23 (1 H, br s), 7.18 (1 H, s); δ_C (75.4 MHz; $CDCl_3$) 13.2 (CH_3), 16.2 (CH_2), 26.8 (CH_2), 29.6 (CH_2), 43.9 (CH_2), 50.4 (CH), 61.6 (CH_3), 123.6 (C), 160.2 (CH), 177.5 (C), 196.9 (C). This material was not further characterised.

(*S*)-5-(2-Oxo-2-phenyl-ethyl)-pyrrolidine-2-one (2b). Reaction of **12** (180 mg, 0.800 mmol) with benzoyl chloride (113 mg, 0.804 mmol) following the general procedure followed by flash chromatography of the residue yielded **2b** (84 mg, 52%) as a yellowish solid: R_f (EtOAc–MeOH 20 : 1) = 0.43; mp 134–136 °C; $[\alpha]_D^{20}$ +72.3 (*c* 0.93, CH_2Cl_2); Found: C, 70.70; H, 6.51; N, 6.81. $C_{12}H_{13}NO_2$ requires C, 70.92; H, 6.45; N, 6.89%; ν_{max}(KBr)/cm^{-1} 3187m, 2897w, 1708s, 1684s, 1654m, 1349m, 1334m, 1206m, 758m, 687m; δ_H (300 MHz; $CDCl_3$) 1.78–1.94 (1 H, m), 2.28–2.52 (3 H, m), 3.11 (1 H, dd, *J* 9.4 and 17.9), 3.33 (1 H, dd, *J* 3.5 and 17.9), 4.14–4.26 (1 H, m), 6.08–6.38 (1 H, br s), 7.44–7.52 (2 H, m), 7.57–7.74 (1 H, m), 7.91–7.97 (2 H, m); δ_C (75.4 MHz; $CDCl_3$) 26.8 (CH_2), 29.7 (CH_2), 45.3 (CH_2), 50.0 (CH), 127.9 (2 C, CH_2), 128.7 (2 C, CH_2), 133.6 (CH), 136.1 (C), 177.6 (C), 198.3 (C).

(*S*)-5-(2-Furan-2-yl-2-oxo-ethyl)-pyrrolidine-2-one (2e). Reaction of **12** (180 mg, 0.800 mmol) with 2-furoyl chloride (105 mg, 0.805 mmol) following the general procedure followed by flash chromatography of the residue yielded **2e** (68 mg, 44%) as a yellowish solid: R_f (EtOAc–MeOH 20 : 1) = 0.26; mp 143–145 °C; $[\alpha]_D^{20}$ +63.2 (*c* 0.76, CH_2Cl_2); Found: C, 61.91; H, 5.77; N, 7.16. $C_{10}H_{11}NO_3$ requires C, 62.17; H, 5.74; N, 7.25%; ν_{max}(KBr)/cm^{-1} 3246m, 3110w, 1664s, 1637m, 1472m, 1401m, 1288w, 1249w, 1004w; δ_H (300 MHz; $CDCl_3$) 1.74–1.92 (1 H, m), 2.28–2.48 (3 H, m), 2.97 (1 H, dd, *J* 9.5 and 17.5), 3.20 (1 H, dd, *J* 3.7 and 17.5), 4.10–4.21 (1 H, m), 6.04–6.26 (1 H, br s), 6.57 (1 H, dd, *J* 1.7 and 3.6), 7.23 (1 H, dd, *J* 0.7 and 3.6), 7.60 (1 H, dd, *J* 0.7 and 1.7); δ_C (75.4 MHz; $CDCl_3$) 26.8 (CH_2), 29.9 (CH_2), 44.8 (CH_2), 49.8 (CH), 112.5 (CH), 117.6 (CH), 146.7 (CH), 152.1 (C), 177.5 (C), 187.2 (C).

(*S*)-4-*tert*-Butoxycarbonylamino-(*E*)-7-methoxymethylene-6-oxo-nonanoic acid methyl ester (4a). Reaction of **19** (286 mg, 0.801 mmol) with **10** (119 mg, 0.801 mmol) following the general procedure followed by flash chromatography of the residue yielded **4a** (188 mg, 68%) as a colorless oil: R_f (heptane–EtOAc 3 : 2) = 0.33; $[\alpha]_D^{20}$ −9.0 (*c* 0.99, CH_2Cl_2); *m/z* HRMS (FAB$^+$) Found $[M + H]^+$ 344.2087. $C_{17}H_{30}NO_6$ requires 344.2073; ν_{max}(neat)/cm^{-1} 3359s, 2976s, 1739s, 1700s, 1633s, 1520s, 1453m, 1366m, 1249s, 1169s; δ_H (300 MHz; $CDCl_3$) 0.91 (3 H, t, *J* 7.5), 1.41 (9 H, s), 1.74–1.96 (2 H, m), 2.23 (2 H, q, *J* 7.5), 2.38 (2 H, t, *J* 7.4), 2.62 (1 H, dd, *J* 6.1 and 15.6), 2.87 (1 H, dd, *J* 4.7 and 15.6), 3.66 (3 H, s), 3.88 (3 H, s), 3.80–3.90 (1 H, m), 5.16 (1 H, br d, *J* 8.2), 7.28 (1 H, s); δ_C (75.4 MHz; $CDCl_3$) 13.2 (CH_3), 16.2 (CH_2), 28.3 (3 C, CH_3), 29.4 (CH_2), 31.1 (CH_2), 41.6 (CH_2), 48.4 (CH), 51.6 (CH_3), 61.6 (CH_3), 79.1 (C), 124.1 (C), 155.5 (C), 160.8 (CH), 173.9 (C), 197.6 (C).

(*S*)-4-*tert*-Butoxycarbonylamino-6-oxo-6-phenyl-hexanoic acid methyl ester (4b). Reaction of **19** (286 mg, 0.801 mmol) with benzoyl chloride (113 mg, 0.804 mmol) following the general procedure followed by flash chromatography of the residue yielded **4b** (200 mg, 75%) as a colorless solid: R_f (heptane–EtOAc 3 : 2) = 0.43; mp 66–68 °C (lit.,[6c] 67–68 °C); $[\alpha]_D^{20}$ −20.3 (*c* 1.09, CH_2Cl_2) (lit.,[6c] $[\alpha]_D^{26}$ −18.0 (*c* 0.850, CH_2Cl_2)); NMR spectra were in full accordance with those reported in the literature.[6c]

7-Acetoxy-4-(*S*)-*tert*-butoxycarbonylamino-6-oxo-heptanoic acid methyl ester (4d). Reaction of **19** (286 mg, 0.801 mmol) with acetoxyacetyl chloride (110 mg, 0.806 mmol) following the general procedure followed by flash chromatography of the residue yielded **4d** (173 mg, 65%) as a colorless solid: R_f (heptane–EtOAc 1 : 1) = 0.35; mp 81–83 °C (lit.,[6c] 83–84 °C); $[\alpha]_D^{20}$ −16.8 (*c* 0.98, CH_2Cl_2) (lit.,[6c] $[\alpha]_D^{26}$ −12.9 (*c* 0.820, CH_2Cl_2)); NMR spectra were in full accordance with those reported in the literature.[6c]

(*S*)-4-*tert*-Butoxycarbonylamino-6-furan-2-yl-6-oxo-hexanoic acid methyl ester (4e). Reaction of **19** (286 mg, 0.801 mmol) with 2-furoyl chloride (105 mg, 0.805 mmol) following the general procedure followed by flash chromatography of the residue yielded **4e** (204 mg, 78%) as a pale yellowish solid: R_f (heptane–EtOAc 1 : 1) = 0.39; mp 59–62 °C; $[\alpha]_D^{20}$ −11.3 (*c* 0.99, CH_2Cl_2) (lit.,[6c] $[\alpha]_D^{25}$ −12.3 (*c* 0.600, CH_2Cl_2)); NMR spectra were in full accordance with those reported in the literature.[6c]

(*S*)-4-*tert*-Butoxycarbonylamino-6-oxo-undecanoic acid methyl ester (4f). Reaction of **19** (286 mg, 0.801 mmol) with hexanoyl chloride (108 mg, 0.802 mmol) following the general procedure followed by flash chromatography of the residue yielded **4f** (202 mg, 77%) as a pale yellowish oil: R_f (heptane–EtOAc 2 : 1) = 0.44; $[\alpha]_D^{20}$ −15.7 (*c* 1.11, CH_2Cl_2); Found: C, 61.77; H, 9.27; N, 4.36. $C_{17}H_{31}NO_5$ requires C, 61.98; H, 9.48; N, 4.25%; ν_{max}(neat)/cm^{-1} 3358m, 2956s, 2872m, 1735s, 1717s, 1522m, 1438m, 1366m, 1249m, 1172s, 1049m; δ_H (300 MHz; $CDCl_3$) 0.88 (3 H, t, *J* 7.0), 1.18–1.35 (4 H, m), 1.41 (9 H, s), 1.54 (2 H, m), 1.75–1.88 (2 H, m), 2.33–2.43 (4 H, m), 2.55–2.72 (2 H, m), 3.66 (3 H, s), 3.81–3.95 (1 H, m), 4.98 (1 H, br s); δ_C (75.4 MHz; $CDCl_3$) 13.8 (CH_3), 22.4 (CH_2), 23.2 (CH_2), 28.3 (3 C, CH_3), 28.3 (CH_2), 29.6 (CH_2), 30.9 (CH_2), 31.2 (CH_2), 43.2 (CH_2), 47.0 (CH), 51.6 (CH_3), 79.2 (C), 155.4 (C), 173.7 (C), 210.0 (C).

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