Preparation of Enantiomerically Pure Protected Unsaturated α-Amino Acids from a New Serine Derived Zinc–Copper Reagent

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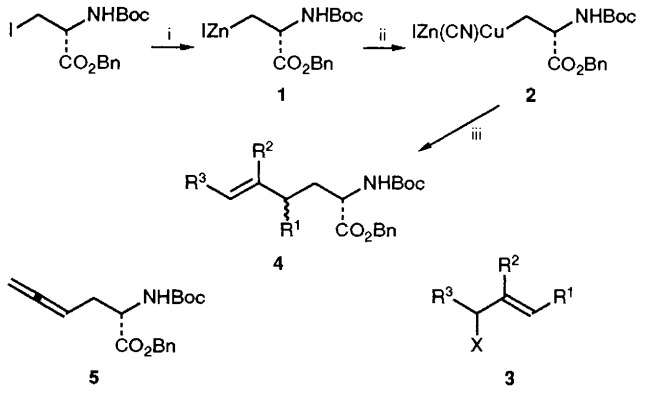
Treatment of the iodoalanine derived zinc reagent **1** with Knochel's soluble copper salt (CuCN·2LiCl) allows the preparation of a reactive copper reagent **2** which couples in moderate to good yield with allyl halides to give protected unsaturated α-amino acids in a single step from easily available precursors.

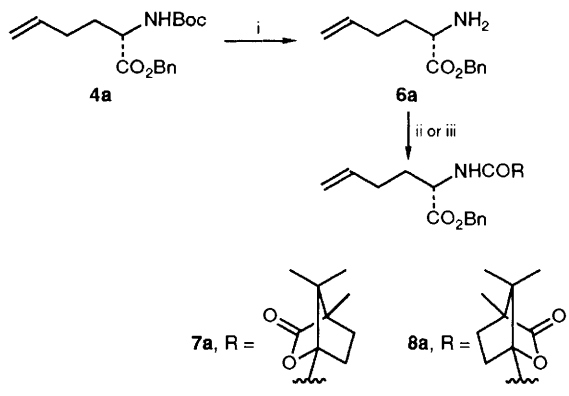
We have recently described a new method for the preparation of enantiomerically pure α-amino acid derivatives involving the use of the serine derived organozinc reagent **1**,[1–4] prepared from protected iodoalanine using ultrasonic activation.† This reagent reacts efficiently with acid chlorides under palladium catalysis, and also with aryl iodides although the yields are generally moderate. The extensive recent development of zinc–copper chemistry, either employing stoichiometric reagents,[5,6] or under catalytic conditions,[7,8] suggested that a more reactive α-amino acid derived nucleophile would be available by transmetallation.[9] We now report that treatment of the organozinc reagent **1** with the tetrahydrofuran (THF)-soluble copper salt CuCN·2LiCl, extensively developed by Knochel,[5] gives a zinc–copper reagent **2** which reacts with allylic halides in an S_N2' manner to give easy access to a range of enantiomerically pure unsaturated α-amino acids (Scheme 1).

Previous direct approaches to enantiomerically pure α-amino acids with remote alkene functionality have generally relied on radical methodology, involving reactions of propynylic[10] and allylic[11] stannanes with protected iodoalanine. The use of ionic chemistry appears to be restricted to a single example of reaction of 4-iodobut-1-ene with a glycine anion equivalent.[12]

† We have recently established that the Pulsatron 95 ultrasonic cleaning bath, available from Kerry Ultrasonics, is extremely effective for this purpose.



Scheme 1 *Reagents and conditions*: i, Zn–Cu couple (1.7 equiv.), benzene–dimethylacetamide (15:1), sonication, 30 min; ii, −10 °C, CuCN·2LiCl (1 equiv.) in THF, then 0 °C, 10 min; iii, −25 °C, **3** (1.3 equiv.), then 0 °C, 3 h



Scheme 2 *Reagents and conditions*: i, trifluoroacetic acid, CH_2Cl_2, 20 °C, 1 h; ii, (1*S*)-(−)-camphanic acid chloride (1 equiv.), 4-dimethylaminopyridine (1.1 equiv.), CH_2Cl_2, 20 °C, 16 h; iii, (1*R*)-(+)-camphanic acid chloride (1.1 equiv.), 4-dimethylaminopyridine (1 equiv.), CH_2Cl_2, 20 °C, 16 h

Table 1 Reaction of zinc–copper reagent **2** with allylic substrates **3**

	Allylic substrate **3**					
	R^1	R^2	R^3	X	Product	Yield (%)
3a	H	H	H	Cl	**4a**	65
3b	CH_2Br	H	H	Br	**4b**	48
3c	Ph	H	H	Cl	**4c**	48
3d	H	H	CH_2Cl	Cl	**4d**	55
3e	H	Me	H	OTs/Cl[a]	**4e**	56
3f	H	CO_2Me	H	Br	**4f**	51
3g	CO_2Me	H	H	Br	**4g**	49
3h	H	H	H	Br	**4a**	32
3i	Ph	H	H	Br	**4c**	40

[a] It is known that allylic toluene-*p*-sulfonates generated by reaction of tosyl chloride with lithium alkoxides are contaminated with the corresponding allylic chloride.[7] Ts = *p*-$MeC_6H_4SO_2$.

We have found that treatment of a solution of the zinc reagent **1** in benzene–dimethylacetamide with a THF solution of CuCN·2LiCl at 0 °C for 10 min gives a homogeneous reagent. Addition of a range of allylic halides **3**, followed by stirring at 0 °C for 3 h, resulted in moderate yields of the products of S_N2' substitution. Our results are outlined in Table 1. It is noteworthy that allylic chlorides appear to function significantly better as substrates. For example, reaction of reagent **2** with allyl chloride **3a** gave protected butenylglycine **4a** in significantly better yield than the corresponding reaction with allyl bromide **3h**. Interestingly, 3,4-dichlorobut-1-ene **3d** reacted at 0 °C with both one and two equivalents of the zinc–copper reagent **2** to give only the mono-substitution product **4d**. It appears that allylic halides with a terminal alkene are more reactive than those with an internal alkene. It is also possible to use allylic toluene-*p*-sulfonates as substrates, generated from the corresponding lithium alkoxides and tosyl chloride.[7] For example, use of the toluene-*p*-sulfonate **3e** derived from 2-methylprop-2-en-1-ol allows the preparation of the protected α-amino acid **4e**.

In order to establish the compatibility of the zinc–copper reagent **2** with more functionalised systems, reactions with methyl (2-bromomethyl)acrylate **3f** and methyl 4-bromocrotonate **3g** were investigated. In the former case the differentially protected methylene homoglutamic acid derivative **4f** was isolated and, in the latter case, the 4-vinyl glutamic acid derivative **4g** was produced as a mixture of diastereoisomers. Efforts to convert this compound into ethylidene glutamic acid derivatives are underway. Finally, reaction of the zinc–copper reagent **2** with propyn-2-yl bromide gave protected naturally occurring (*S*)-2-aminohexa-4,5-dienoic acid[10,13] **5** (55%), with no trace of the isomeric terminal alkyne.

Although we have established that products derived from coupling reactions of the organozinc reagent **1** proceed without racemisation, we considered it necessary to establish the stereochemical integrity of one of the products derived from the zinc–copper reagent **2**. Deprotection of the butenylglycine derivative **4a** with trifluoroacetic acid gave the free amine **6a**, and subsequent reaction of this amine with (−)- and (+)-camphanic acid chloride gave the corresponding derivatives **7a** and **8a**, respectively. ^1H NMR analysis of these derivatives indicated no detectable diastereoisomeric contamination.

In conclusion, we have shown that it is possible to prepare a nucleophilic alanine equivalent, with standard amino acid protecting groups, which will react directly with allylic electrophiles with minimal interference from the acidic N–H group. We are currently exploring the scope of the zinc–copper reagent **2** for the preparation of other classes of α-amino acid.

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