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Copper-catalysed *meso*-bislactone ring opening using Grignard and mixed triorganozinc reagents

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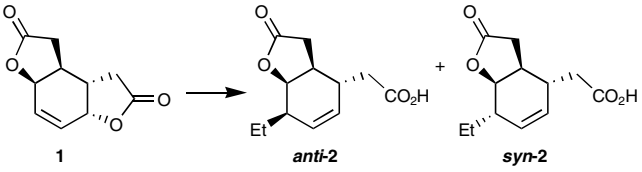
Abstract—An efficient copper-mediated S_N2' ring-opening reaction of a *meso*-bislactone has been developed using Grignard reagents and, for the first time, mixed triorganozinc reagents.

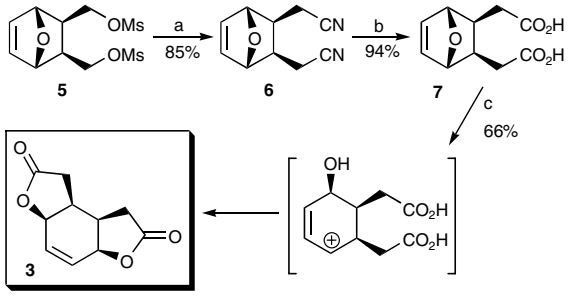
The formation of new carbon–carbon bonds by allylic substitution has been shown to be especially convenient for transferring the chirality of a C–X bond to a C–C bond. To date, a large range of copper-mediated and copper-catalysed stereoselective allylic substitutions have been reported to achieve this.[1]

Recently, we described a rapid stereocontrolled entry to the tetracyclic core of neotuberostemonine,[2] where an *anti*-selective S_N2' ring-opening reaction of a racemic C_2-symmetric bislactone **1** was developed (Scheme 1).

In exploring the scope of this process, we identified the corresponding *meso*-bislactone **3** (Scheme 2) as an alternative desymmetrisation substrate.[3] Compound **3** differs from the C_2-symmetric bislactone **1** in two distinct ways: (a) the cis-relationship between the two lactone groups could potentially lead to a stereoselective addition (*anti* vs *syn*); (b) a catalytically mediated asymmetric desymmetrisation of **3** could provide access to enantioenriched products containing four contiguous stereogenic carbon centres.



Scheme 1. S_N2' ring-opening reaction of C_2-symmetric bislactone **1** using organocopper reagents. Reagents and conditions: EtMgCl (10 equiv), CuBr·Me_2S (10 equiv), THF/Me_2S 2:1, −20 °C, 89%, *anti*/*syn* = 8.5:1.



Scheme 2. Synthesis of *meso*-bislactone **3**. Reagents and conditions: (a) KCN (3 equiv), DMSO 100 °C, 4 h; (b) KOH (8 equiv), H_2O, 100 °C, 3 h; (c) 4 M HCl, 100 °C, 4 h.

The preparation of *meso* compound **3** was achieved, in gram quantities, by modifying the previously described synthetic route for the C_2-symmetric compound **1**.[2] Thus, treatment of the readily available bismesylate **5**[4] with KCN in DMSO allowed access to dinitrile **6**. Hydrolysis under basic conditions led to diacid **7**, which upon heating in 4 M HCl underwent double lactonisation to **3** in 66% yield (Scheme 2). Compared to the C_2-symmetric isomer the success of the ring opening/lactonisation sequence of **7** was surprising, that is, the furan is likely to first undergo protonation and cleavage to a cation thus rendering it susceptible to side reactions such as arene formation.

Keywords: Organocopper; Desymmetrisation; Grignard; Organozinc; *meso*-Bislactone.
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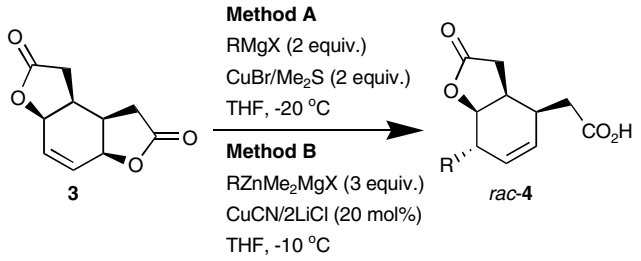
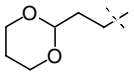
Applying the original desymmetrisation conditions (see Scheme 1) to **3** provided the desired product **4a** in a reasonable isolated yield. After a short optimisation program, it was found that just 2 equiv of ethylcuprate in THF (*c* 0.1 M w.r.t. Cu) at −20 °C provided **4a** in excellent yield (88%, Table 1). It was important to note that the reaction was completely regioselective for S_N2' addition, as well as stereoselective for the *anti*-product **4a**.

With the intention of developing an asymmetric desymmetrisation, it was appropriate to examine the use of catalytic copper in this reaction. Thus, treatment of **3**

Table 1. Copper-catalysed desymmetrisation of **3** using Grignard and mixed triorganozinc reagents

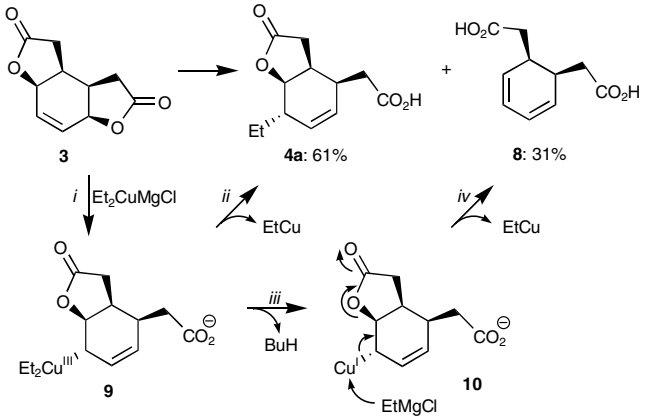


Entry	Product	R(X)	Method	Time (h)	Yield (%)
1	**4a**	Et (Cl)	A	<1	88
			B	<1	84
2	**4b**	*n*-Bu (Cl)	A[a]	1	78
			B	1	78
3	**4c**	Me (Cl)	A[b]	2	83
			B[b]	1	75
4	**4d**	$TMSCH_2$ (Cl)	A[b]	1	73
5	**4e**	$H_2C{=}CH(CH_2)_2$ (Br)	A[c]	<1	62[d]
			B	1	72
6	**4f**	 (Br)	A[a]	<1	58[e]
			B	1	61[e]
7	**4g**	*i*-Pr (Cl)	A[a]	1	88
			B	2	64
8	**4h**	Bn (Cl)	A	<1	58[f]
9	**4i**	Allyl (Br)	A[a,g]	1	41
			B[h]	8	0[i]
10	**4j**	Ph (Cl)	A[a]	5	80[j]
			B	4	60[j]
11	**4k**	4-MeO–C_6H_4 (Br)	A	4	66[k]
			B	1	0[l]
12	**4l**	4-EtO_2C–C_6H_4 (Cl)	B	4	63[m]

[a] 3 equiv of cuprate required.
[b] Carried out at rt.
[c] 2.5 equiv of cuprate used.
[d] Calculated from ^1H NMR as inseparable from diacid **8**.
[e] Calculated from ^1H NMR as the product contains small amounts of homocoupled Grignard reagent.
[f] Diacid **8** isolated in 42% yield.
[g] Me_2S required as a co-solvent.
[h] Warmed to rt after 2 h.
[i] Compound **4c** was isolated in 52% yield.
[j] Isolated in a 2:1 ratio of S_N2':S_N2 addition.
[k] Isolated in a 4:1 ratio of S_N2':S_N2 addition.
[l] Compound **4c** was isolated in 81% yield.
[m] Isolated in a 1:4.5 ratio of S_N2':S_N2 addition.

and CuBr·Me_2S (10 mol %) in THF with EtMgCl (1.8 equiv) resulted in a clean reaction to a mixture of two compounds in a 2:1 ratio. The major component was identified as the addition product **4a**. After further study, the minor product was identified as the double ring-opened diene-diacid **8**, which initially appeared to be an unusual reduction product.

On further analysis, it can be suggested that under catalytic Cu conditions diethylcuprate is formed which initially reacts as expected via *anti*-selective S_N2' addition resulting in the Cu(III) intermediate **9**.[5] Instead of transferring an ethyl group to form **4a**, this then undergoes reductive elimination by homocoupling to give Cu(I) intermediate **10** and butane. Nucleophilic attack by EtMgCl on the Cu(I) centre of **10** then induces β-metallolactone fragmentation leading to **8**, whilst returning EtCu(I) to the catalytic cycle (Scheme 3).

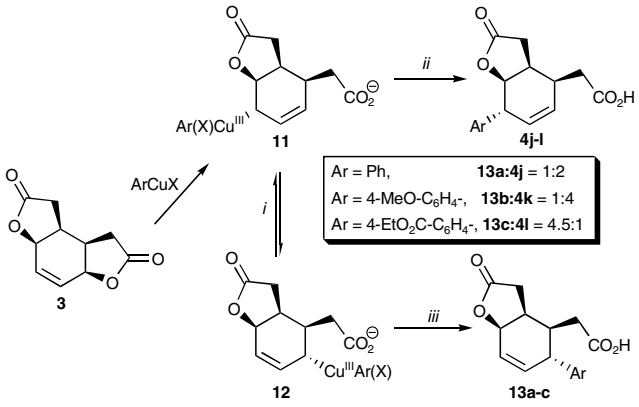


Scheme 3. Formation of diacid **8**. Reagents and conditions: CuBr·Me_2S (10 mol %), EtMgCl (1.8 equiv) THF, −15 °C, 3 h. Pathway: (i) S_N2' ring opening; (ii) 'normal' alkyl transfer; (iii) reductive elimination to **10**; (iv) fragmentation.

As we were unable to halt the formation of diene **8** when using catalytic quantities of copper, attention was focussed on an examination of the range of Grignard nucleophiles, which could be employed in the desymmetrisation (Table 1). In all cases, the organocopper reagents (2 or 3 equiv overall) were pre-formed by stirring a 1:1 mixture of the Grignard reagent and CuBr·Me_2S for 30 min at −20 °C before the addition of **3**.

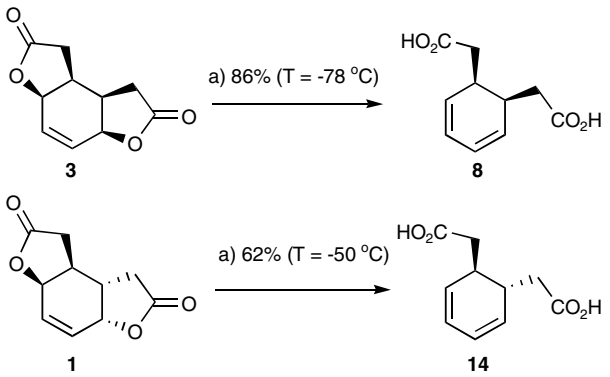
As already mentioned, ethyl addition allowed the formation of **4a** in excellent yield (entry 1, method A). Other alkyl groups were introduced without difficulty, including acetal and alkene functionalised examples (entries 2–6, method A). The introduction of a secondary alkyl group was remarkably successful, furnishing **4g** in 88% yield (entry 7, method A), suggesting that steric factors are of lesser importance in this reaction. Although an extremely fast reaction was observed between the benzyl cuprate reagent and **3**, a mixture of both desired S_N2' ring-opening product **4h** and diacid **8** was formed in this particular case. Careful chromatographic separation allowed **4h** to be isolated in 58% yield, with 42% of **8** (entry 8).

Reaction of **3** with allylcuprate failed under the standard conditions, but was found to proceed to product **4i** in a moderate 41% yield with the use of dimethylsulfide as a co-solvent (entry 9). Although stereoselective *anti*-addition was observed in all cases, aromatic cuprates showed a reduction in regioselectivity. Phenyl cuprate, for example, gave an inseparable mixture of the S_N2' product **4j** and S_N2 product **13a**. A 2:1 ratio of **4j**:**13a** was calculated from ^1H NMR, although an excellent overall yield of 80% was obtained (entry 10, method A). The 4-methoxy substituted analogue provided a 4:1 ratio of S_N2':S_N2 products **4k**:**13b** in 66% total yield (entry 11, method A). A possible explanation for this behaviour is that reductive elimination from Cu(III) intermediate **11** is simply slower than the shift of the equilibrium to Cu(III) species **12** (Scheme 4).



Scheme 4. Suggested mechanism for the formation of S_N2 products **13a**–**c**. Pathway: (i) equilibrium via π-allyl-Cu complex; (ii) reductive elimination to give **4j**–**l** (see Table 1); (iii) reductive elimination to give **13a**–**c**.

To continue attempts at creating a catalytic desymmetrisation, we turned our attention to the use of well documented organozinc reagents in place of Grignards. Surprisingly, our initial studies showed that diethylzinc in the presence of catalytic Cu(I) failed to react with **3** even at elevated temperatures. We therefore examined the use of triorganozinc species, a class of reagents known for nearly 150 years[6] but rarely used as a synthetic tool.[7] After optimisation a mixed organozinc species,[7,8] prepared from Et_2Zn (2 equiv) and $TMSCH_2MgCl$ (2 equiv), was found to react with **3** (1 equiv) in the presence of catalytic CuCN·2LiCl (20 mol %). It was extremely encouraging to note that compound **4a** was isolated in 84% yield with no transfer of the less reactive $TMSCH_2$ group and with no formation of diacid **8** observed (cf. entry 4, Table 1). It is important to highlight that without any Cu(I) source no reaction took place. In a more general approach Grignard nucleophiles were first reacted with dimethylzinc to form the mixed triorganozinc species before addition of the catalyst. As methyl groups were found to be less transferable, this method allows selective formation of the organocuprate corresponding to the Grignard species. In general, use of the mixed triorganozinc reagents with catalytic copper (Method B) gave very similar results to Method A (Table 1), yet allowed the use of substoichiometric amounts of copper to be used without problematic formation of the diene-diacid **8**.



Scheme 5. Selective synthesis of *meso* and C_2-symmetric diacids **8** and **14**. (a) MeMgCl (8 equiv), CuBr·Me_2S (4 equiv), THF.

Finally, studies showed that it was possible to optimise the synthesis of diacid **8** using a ratio of 2:1 of Grignard reagent to Cu(I) and lowering the reaction temperature to −78 °C. For example, using MeMgCl **8** could be isolated as the only product in 86% yield (Scheme 5). Applying these conditions to the C_2-symmetric lactone **1**, with a slight increase in temperature to aid dissolution, provided **14** in 62% yield.

In summary, a Cu(I)-mediated S_N2' ring-opening desymmetrisation reaction of *meso*-bislactones has been developed using various Grignard reagents. Significantly, mixed triorganozincates have been shown for the first time to be excellent reagents for Cu(I)-catalysed allylic substitution, particularly in this case where the use of Grignard reagents with catalytic copper led to pronounced side reactions. The desired *anti*-products of type **4** were generally isolated in good to excellent yields. A novel reaction pathway leading to *meso*-diacid **8** was also identified and optimisation of this process was achieved by the variation of the Cu(I) stoichiometry and temperature. The current work is focussed on the use of these methodologies in an asymmetric[9] manner with polycyclic *meso* derivatives of **3**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.146.

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9. So far we have been unable to effect an enantioselective desymmetrisation of **3** using a range of known ligands previously developed for Cu catalysed substitution. For example, the particularly relevant ligands described in Refs. 1f (JOSIPHOS) and 1n (various phosphoramidites) all gave ring opened products with method B but no ee could be detected by chiral HPLC. It is possible that in our case the two enantiotopic alkene carbons on the spherical, convex face of **3** are simply too similar to be differentiated by a ligand/catalyst complex. The current work is concerned with the synthesis of *meso*-bislactones with alkyl substituents on the convex face in order to see if they will prove to be better substrates for enantioselective desymmetrisation with known ligands.