Studies on Regioselective Addition of Alkyl(phosphine)copper Complexes to Epoxides

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An alkyl(phosphine)copper complex performed alkylative ring opening of a monosubstituted epoxide, but not that of a 1,2-disubstituted or trisubstituted epoxide, and, upon reaction with this complex, a diepoxy compound comprising terminal and internal epoxy functionalities in a single molecule formed a product based on preferential attack at the terminal functionality.

Organocopper reagents, such as homocuprates (R$_2$CuLi),[6] mixed cuprates (RCuCNLi)[7] and higher order mixed cuprates (R$_2$CuCNLi$_2$),[8] accomplish addition reactions with various types of epoxides. As with the organocopper–phosphine complex, however, we have previously found that the methylcopper(I)–phosphine complex promotes chemoselective reduction of oxiranes.[9]

We report herein our results which reveal that alkylcopper(I)–phosphine complexes other than the methyl derivative perform an alkylative ring-opening reaction only with monosubstituted epoxides. Thus, our reaction system can bring about the regioselective alkylation of monosubstituted moieties of diepoxides. Regioselective reaction of a diepoxide with an organocuprate has been only found in a report by Acker[7] using mixed cyanoalkylcuprates, which reveal preferential attack on the less substituted pendant epoxide moiety in diepoxides formed from 4-vinylcyclohexenes.

When 1,2-epoxyoctane (**1a**) (1 equiv.) was treated at 0 °C for 2 h with Bu^{n}MgBr (4 equiv.) in Et$_2$O and CuBr(PPh$_3$)$_2$ (4 equiv.) in THF, an addition product, dodecan-6-ol (**2a**), was afforded in 75% yield. Omission of CuBr(PPh$_3$)$_2$ from this reaction system effected formation of bromohydrin instead of **2a**. The effect of copper(I) halides upon the yields of **2a** was next investigated to reveal that these decreased in the order CuCl, CuBr, CuI (87, 75, 52% yield, respectively) (Scheme 1).

PX$_3$	Yield (%)
PPh$_3$	75
PBu$_3$	77
P(OPh)$_3$	0
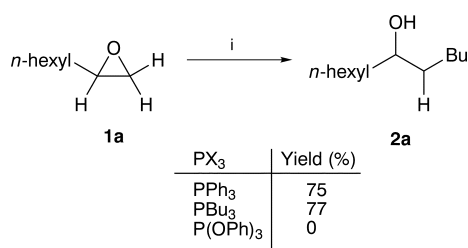
Scheme 1   *Reagents*: i, BuMgBr (4 equiv.), CuBr (4 equiv.), PX$_3$ (8 equiv.)

Next, various types of epoxides were subjected to the reaction in a system composed of BuMgBr and CuBr(PPh$_3$)$_2$. Monosubstituted epoxides such as allyl or methyl glycidyl ethers afforded the butyl addition products in comparable yields (83 and 82%, respectively) with that from **1a**. A 1,1-disubstituted epoxide (*i.e.*, 1,2-epoxy-2-methylpropane) also gave the addition product albeit in a low yield (19%). 1,2-Disubstituted epoxides such as 1,2-epoxycyclohexane and 2,3-epoxyoctane furnished no butyl adduct.

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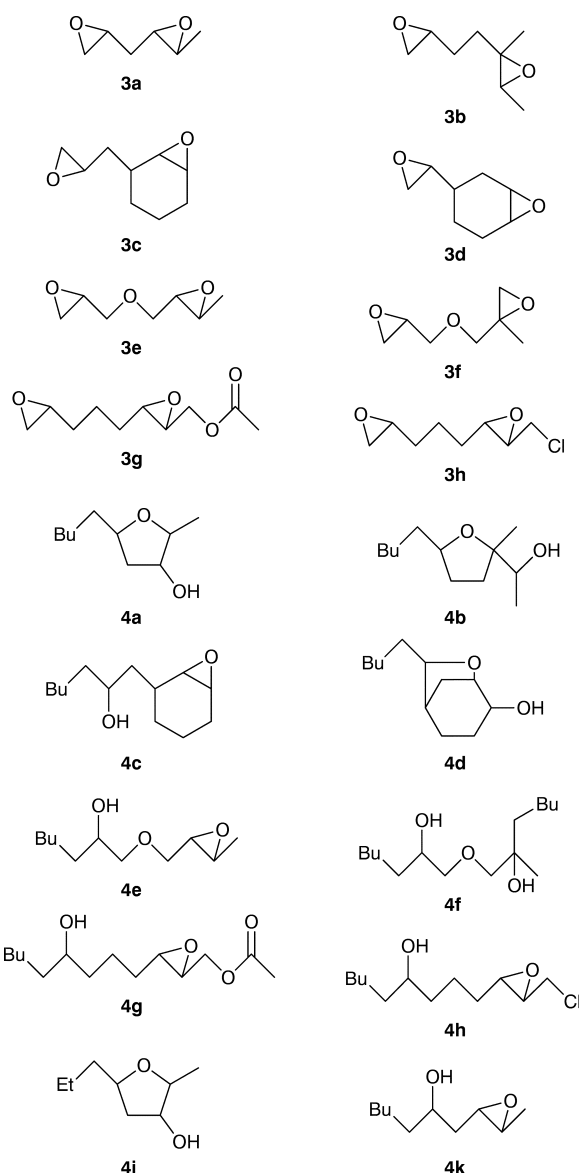
The result that our reaction system brought about this substrate-selective butyl transfer reaction onto a monosubstituted epoxide prompted us to examine the reaction with a diepoxide containing both mono- and multi-substituted epoxy functionalities in a single molecule. 1,2,4,5-Diepoxyhexane (**3a**) afforded the tetrahydrofuranol derivative **4a**, which is derived from addition of a butyl group to the terminal carbon of the monosubstituted epoxy moiety followed by *exo*-intramolecular attack of the resulting alkoxide to the remaining internal epoxy moiety. 1,2,5,6-Diepoxy-5-methylheptane (**3b**) furnished the tetrahydrofuranol derivative **4b**, which stems from an *endo*-type

Table 4 Reaction of di-epoxides **3** with the RMgBr–CuBr(PPh$_3$)$_2$ system

Run	Reactant	RMgBr/R	Product	Yield (%)^a
1	**3a**	Bu	**4a**	69
2	**3b**	Bu	**4b**	62
3	**3c**	Bu	**4c**	66(50)^b
4	**3d**	Bu	**4d**	79(69)^b
5	**3e**	Bu	**4e**	87(50)^b
6	**3f**	Bu	**4f**	42(33)^b
7	**3g**	Bu	**4g**	(46)^b
8	**3h**	Bu	**4h**	74(60)^b
9	**3a**	Et	**4i**	93
10	**3a**	CH$_2$=CHCH$_2$	**4k**	86(84)^b
11	**3a**	Ph	**4k**	(27)^b

^{a}Conversions (all 100%) and yields determined by VPC analysis.
^{b}Isolated yield.

internal epoxy attack, unlike the *exo* attack in the case of **3a**, of the alkoxide generated from the initial addition of butyl to the terminal epoxy group. The diepoxide **3c** from 3-(prop-2-enyl)cyclohexene formed the product **4c** which is derived from attack of butyl onto the terminal epoxy carbon, with the epoxy cyclohexane unit remaining intact. 4-Vinylcyclohexene dioxide (**3d**) yielded adduct **4d**, assumed to be derived from intramolecular attack at the fused epoxy moiety following the addition of butyl to the pendant epoxy group. The reaction of the diepoxy substrates containing a functionality other than epoxy (*i.e.*, ether, ester or chloro group) in the molecule was then investigated. Diepoxide **3e** from allyl crotyl ether gave product **4e** which underwent only ring opening of the monosubstituted epoxy unit, the 1,2-disubstituted epoxy unit remaining intact. On the other hand, diepoxide **3f** from allyl methallyl ether, which bears both mono- and *gem*-substituted epoxy units in a single molecule, furnished product **4f** derived from attack of butyl at both sites. Diepoxide **3g** from octa-2,7-dienyl acetate afforded product **4g** derived from attack of butyl at the terminal epoxy unit with the internal epoxy group remaining intact. 8-Chloro-1,2,6,7-diepoxyoctane **3h** afforded product **4h** arising from attack of butyl at the terminal epoxide, whilst the internal epoxy and chlorine functionalities remained intact. The regioselectivity of the CuBr(PPh$_3$)$_2$-mediated reaction of some Grignard reagents with **3a** were explored. Ethylmagnesium bromide furnished the tetrahydrofuranol derivative **4i** derived from attack of ethyl at the terminal epoxy unit in better yield (93%) than that (69%) from the use of the butyl Grignard reagent. Allyl- and phenyl-magnesium bromides yielded the bromo-hydrin derivative **4k** derived from the attack of bromide at the terminal epoxy functionality with the internal epoxy group remaining intact. The results obtained with these diepoxy substrates are collected in Table 4.

A mechanism whereby an alkyl(phosphine)copper(I) complex generated by reaction of the Grignard reagent with the copper(I) halide–phosphine complex would operate as a reactive intermediate in our reaction appears reasonable. If so, the increase in the yield of the adduct **2a** in the order X = Cl > Br > I in the reaction system composed of **1a**, BuMgBr and CuX(PPh$_3$)$_2$ might be rationalized in terms of the Lewis acidity of MgBrX along with the BuCu—PPh$_3$ complex generated from the Grignard reagent and
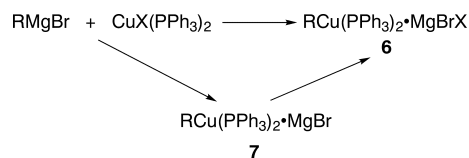
Scheme 2

CuX(PPh$_3$). With this hypothesis in mind, we anticipated that addition of MgCl$_2$ to the reaction system would bring about an increase in the yield of alkylation product on account of enhanced activation of the epoxy group by its high Lewis acidity compared with MgBrX. However, the reaction of **1a** with BuMgBr and CuI(PPh$_3$)$_2$ in the presence of MgCl$_2$ did not lead to the butylation product **2a**, but instead the halohydrins (30 and 50% yields of bromo- and iodo-hydrins, respectively). Therefore, our reaction might not proceed only *via* a pathway containing the alkylcopper complex **6** as the sole intermediate, but may also include the halocuprate complex **7** as an intermediate (Scheme 2). In fact, Backvall *et al.*[10] and Lipshutz and Hackman[11] have both suggested the generation of the halocuprate 'RCuXMBr' from the combination of a Grignard reagent with copper(I) chloride and bromide, respectively, as the working intermediate. Thus, the scenario that the halocuprate **7**, at least in the case of using CuCl, would participate as a valid intermediate with enhanced reactivity compared with the neutral complex **6**, as anticipated in the case of CuI, cannot be ignored.

Techniques used: ^{1}H and ^{13}C NMR, IR, MS, VPC, column chromatography

References: 12

Schemes: 2

Table 1: Reaction of 1,2-epoxybutane (**1a**) with the BuMgBr–CuX(PPh$_3$)$_2$ system

Table 2: Influence of the molar ratio of PPh$_3$ to CuBr upon the yield of **2a**

Table 3: Reaction of mono-epoxides **1** with the BuMgBr–CuBr(PPh$_3$)$_2$ system

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