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New Mixed Metal (Mn/Cu) Catalyzed Stereoselective Cyclizations

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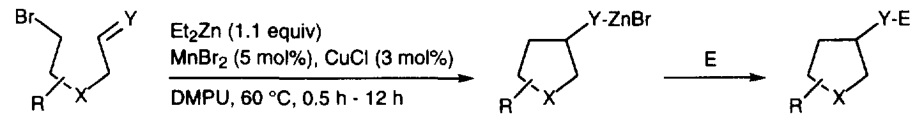
Abstract: Unsaturated alkyl bromides of type **1** undergo a stereoselective ring closure when treated with a $MnBr_2$ (5 mol%) / CuCl (3 mol%) catalytic mixed metal system and diethylzinc at 60 °C in DMPU affording five membered carbo- and heterocycles. An alternative Ni-catalyzed cyclization of bromoalkylketones is also described. Remarkably in this case, the iodine-zinc exchange could be performed with EtZnBr instead of pyrophoric Et_2Zn.

Recently, we have shown that the reaction of various primary alkyl bromides with diethylzinc in the presence of a catalytic mixed metal system consisting of $MnBr_2$ and CuCl led to a smooth bromine-zinc exchange reaction[1] and produced alkylzinc bromides with satisfactory yields. We have suspected a radical mechanism[2,3] for this exchange reaction and have now performed this reaction with unsaturated substrates able to undergo radical cyclization reactions. Herein, we report several new radical cyclizations mediated by this catalytic system. A range of unsaturated alkyl bromides of type **1** (X, Y = CH_2 or O) react with Et_2Zn in the presence of $MnBr_2$ (5 mol%) and CuCl (3 mol%) in DMPU[4] affording the cyclized zincated species **2** which after reaction with an electrophile E under appropriate reaction conditions (a transmetalation reaction to an organo-copper or -palladium intermediate may be necessary). This reaction sequence provides cyclized products of type **3** in good to excellent yields (Scheme 1).

Scheme 1



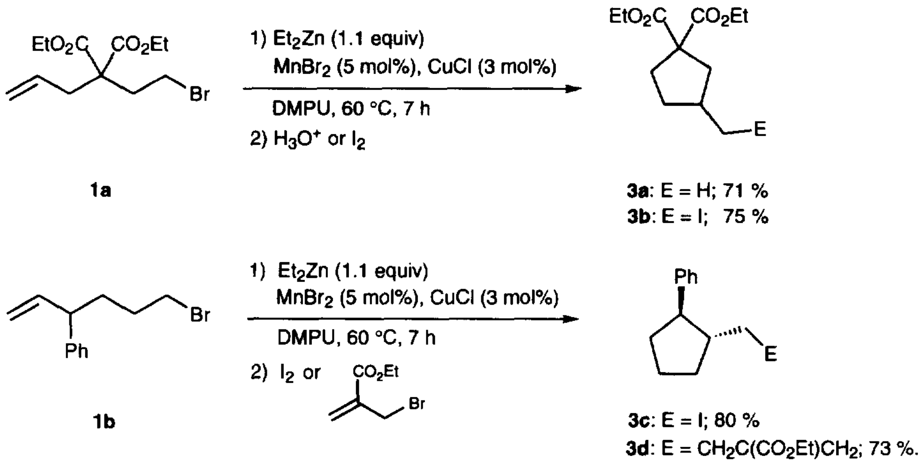
1 : X,Y = CH_2 or O **2** : X,Y = CH_2 or O **3** : X,Y = CH_2 or O

E = I_2, H_2O, allylic bromide, ethyl propiolate, aryl iodide

Thus, the unsaturated alkyl bromides **1a** and **1b** undergo a smooth cyclization with the mixed Mn/Cu catalyst system leading after quenching with an electrophile like H_2O or I_2 to the products **3a-c** in

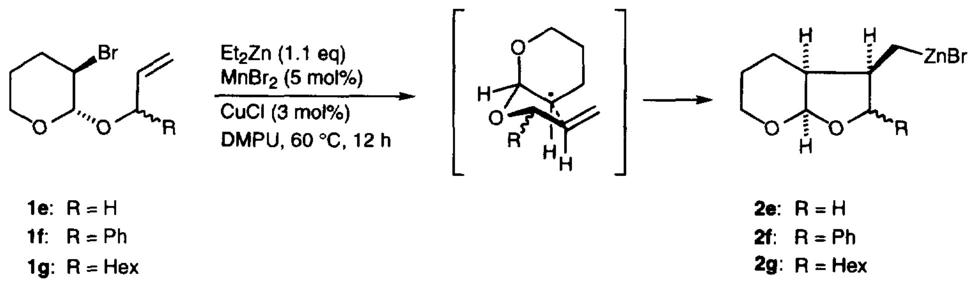
71-80 % yield (Scheme 2). The cyclization of **1b** furnishes after reaction with ethyl (α-bromomethyl)acrylate[5] the allylated product **3d** in 73 % yield. The reaction conditions used were carefully optimized and optimal yields were obtained with stoichiometric amounts of diethylzinc (1.1 equiv) and a reaction temperature of 60 °C. Lower reaction temperatures or the use of less polar solvents such as NMP lead to side products (uncyclized materials).

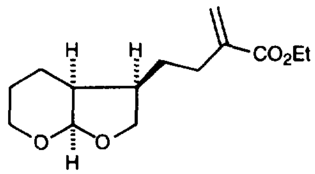
Scheme 2



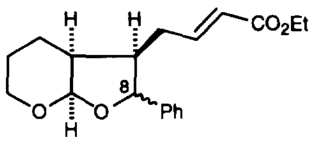
Interestingly, functional groups like esters are well tolerated in these reactions. A stereospecific ring closure is observed in the case of **1b** leading to *trans*-cyclopentane derivatives according to Beckwith radical cyclization rules.[6] The preparation of condensed tetrahydrofuran derivatives can be achieved using the readily available unsaturated bromoacetals **1e-g** as cyclization precursors[3c,d]. Thus, the treatment of the

Scheme 3

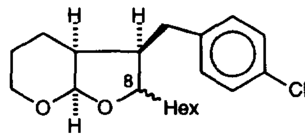




3e: 71 %



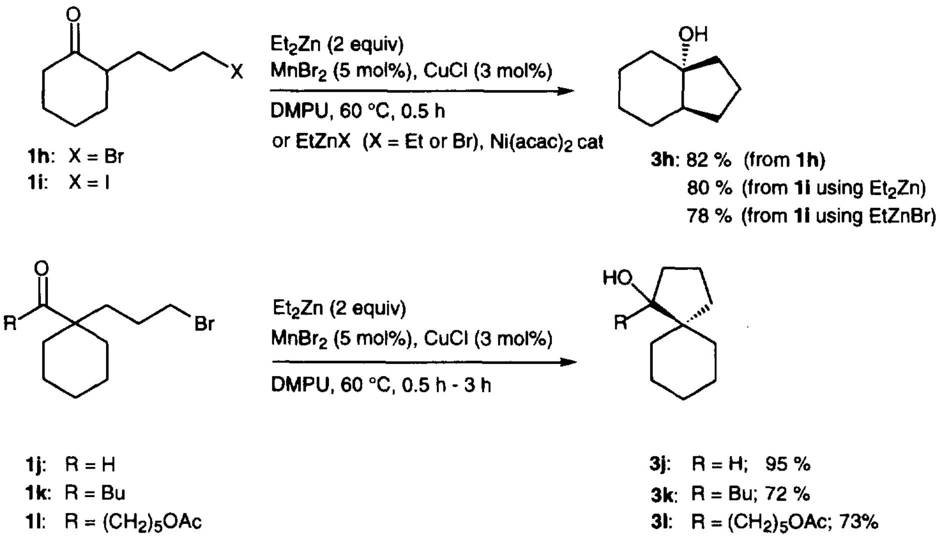
3f: 63 %



3g: 61 %

acetals **1e-g** with Et_2Zn in the presence of the mixed Mn/Cu catalytic system (DMPU, 60 °C, 12 h) furnishes the zinc reagent **2e-g** in which the stereochemistry of three adjacent centers has been controlled. The zinc reagents **2e** and **2f** were transmetalated with CuCN•2LiCl[7] and treated respectively with ethyl (α-bromomethyl)acrylate and ethyl propiolate affording respectively **3e** and **3f** in 71 % and 63 % yield. The reaction of the zinc organometallic **2g** with *p*-chloroiodobenzene in the presence of $PdCl_2$(dppf)[8] (5 mol%) at 60 °C for 4 h gives the phenylated product **3g** in 61 % yield (above). The products **3f** and **3g** were obtained as readily separable 1:1 mixtures of epimers at the position 8. Barbier type cyclizations of 5-bromo substituted aldehydes and ketones **1hj-l** proceed very rapidly using Et_2Zn (2 equiv) in DMPU (60 °C, 0.1-3 h) with a mixed Mn/Cu catalyst system. Thus the bromoketone **1h** is converted to the *cis*-bicyclic tertiary alcohol **3h** in 82 % isolated yield.

Scheme 4



Similarly, a range of spiro-alcohols **3j-l** were obtained in 72-95 % yield by the cyclization of the bromoaldehyde **1j** and the bromoketones **1k-l** (Scheme 4). Interestingly, we have also observed that the Mn/Cu catalytic mixed metal system can be replaced by catalytic amounts of $Ni(acac)_2$ *if the corresponding alkyl iodide* is used instead of the alkyl bromide for the cyclization. Thus, the reaction of 2-(3-iodopropyl)cyclohexanone **1i** with Et_2Zn (2 equiv) in the presence of $Ni(acac)_2$ (10 mol%) produces exclusively the *cis*-bicyclic alcohol **3i** in 80 % yield. In contrast, the corresponding cyclization with SmI_2

gives **3h** as a 1.3:1 *cis:trans* mixture.[9c] Remarkably, it was also found that EtZnBr generated by the reaction of Et_2Zn with $ZnBr_2$ in the presence of $Ni(acac)_2$ (7.5 mol%, rt, 6h) is also able to promote the iodine-zinc exchange reaction with the ketone **1i** leading to the cyclized alcohol **3h** in 78 % yield. This procedure has considerable synthetic potential since a non-pyrophoric zinc reagent (EtZnBr) is used for performing the iodine-zinc exchange instead of Et_2Zn.

In summary, we have developed new transition metal catalyzed cyclization reactions mediated by Et_2Zn and catalyzed by the $MnBr_2/CuCl$ system or in the case of **1i** with $Ni(acac)_2$. We are currently investigating the exact nature of the Mn/Cu system as well as extensions of this reaction[10] to intramolecular cyclizations of imines.

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10. **Typical procedure**. Preparation of (E)-*endo*-7-(3-carbethoxy-3-butenyl)-8-phenyl-2,9-dioxabicyclo-[4.3.0]nonane (**3f**). A 50 mL three-necked flask was charged with $MnBr_2$ (53 mg, 0.25 mmol) and CuCl (15 mg, 0.15 mmol) and DMPU (5 mL). Et_2Zn (0.55 mL, 5.5 mmol) was added at rt and the reaction mixture was stirred for 10 min. The alkyl bromide **1f** (1.48 g, 5 mmol) was added and the reaction mixture was warmed to 60 °C for 12 h. After cooling to -20 °C, a solution of CuCN (0.44 g, 5 mmol) and LiCl (0.42 g, 10 mmol) in THF (10 mL) was added. After warming to 0 °C, the reaction mixture was cooled to -30 °C and ethyl propiolate (0.48 g, 5 mmol) was added. The reaction mixture was stirred for 12 h at -10 °C and worked up as usually. After purification by flash chromatography (hexanes:Et_2O 9:1), the *E-endo*-ester (**3f**) was obtained as a colorless oil (0.99 g, 63 % yield).
Preparation of *cis*-bicyclo[4.3.0]nonan-1-ol (**3h**). A 20 mL three-necked flask was charged with $MnBr_2$ (53 mg, 0.25 mmol), CuCl (15 mg, 0.15 mmol) and DMPU (4.5 mL). Diethylzinc (1.0 mL, 10 mmol) was added at rt resulting in the formation of a black solution. The bromoketone **1h** (1.1 g, 5. mmol) was added and the reaction mixture was heated to 60 °C for 0.5 h. The reaction mixture is cooled back to rt and worked up as usually affording after purification by flash chromatography (hexanes:AcOEt 9:1) the desired product (**3h**) as a clear oil (575 mg, 4.1 mmol, 82 % yield).

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