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Generation of metalloenamines by carbon–carbon bond formation: ring opening reactions of 2-methyleneaziridines with organometallic reagents

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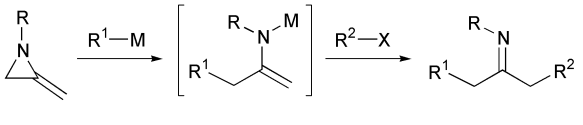
Ring opening of 2-methyleneaziridines with Grignard reagents in the presence of CuI yields metalloenamines in a regiospecific fashion which can be further reacted with electrophiles to produce functionalised ketones *via* a one-pot process.

Following their introduction independently by Stork[1] and by Wittig,[2] metalloenamines (metallated imines) have become established as one of the best methods of forming carbon–carbon bonds at the α-carbon atom of aldehydes and ketones.[3] Metalloenamines are known to be extremely reactive and undergo clean *C*-alkylation reactions with a wide range of electrophiles including primary and secondary alkyl halides, aldehydes, ketones, nitriles, epoxides and oxetanes. Consequently, alkylation reactions of these carbanions are widely used in organic synthesis. Metalloenamines are traditionally made by deprotonation of the corresponding imine using a strong base such as EtMgBr or LDA. One limitation with this method stems from the fact that regiochemical control in the enolisation process is not always possible when imines derived from unsymmetrical ketones are used, resulting in mixtures of alkylated products being formed.[4] Few alternative methods for the generation of metalloenamines have been developed, with the only notable contributions being made by Wender.[5] We imagined that ring opening of 2-methyleneaziridines with organometallic reagents might provide an alternative entry into metalloenamines, as depicted in Scheme 1. We felt that this conceptually new approach to metalloenamines might offer two significant advantages over the traditional route to such species by way of imine enolisation. Firstly, the overall transformation would result in the formation of two new carbon–carbon bonds and thus could be considered as an efficient and potentially highly flexible three-component coupling reaction. Secondly, the ring opening of the aziridine might be expected to provide the metalloenamine as a single regioisomer, circumventing problems associated with regioselectivity in the deprotonation of unsymmetrical imines. Here, we describe our preliminary results regarding the ring opening reactions of 2-methyleneaziridines with organometallic reagents and demonstrate their potential as metalloenamine precursors.

At the outset of this study, no ring opening reactions of methyleneaziridines using carbon based nucleophiles had been reported.[6,7] Initially, we chose to investigate the ring opening reactions of methyleneaziridine (±)-**1** (R = CHMePh) as it is very easy to prepare on a multigram scale.[8] Since Ganem has shown that simple *N*-alkylated aziridines can be ring opened with Gilman-type cuprates in the presence of boron trifluoride ethereate,[9] we anticipated that these conditions might effect ring opening of 2-methyleneaziridines. Gratifyingly, treatment of



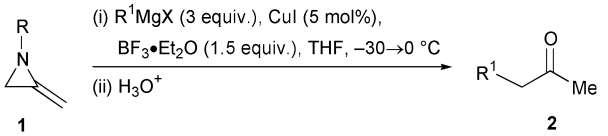
where M = metal, X = leaving group

Scheme 1

methyleneaziridine **1** (R = CHMePh) with Bu_2CuLi (1.5 equiv.) and $BF_3{\cdot}OEt_2$ (1.5 equiv.) in THF (−78 → 0 °C) and subsequent hydrolysis with aqueous acid furnished heptan-2-one in 40% isolated yield after distillation. Further studies determined that this ring opening reaction can be accomplished more conveniently using BuMgCl in the presence of $BF_3{\cdot}OEt_2$ and a catalytic amount of CuI (Table 1, entry 1). The modest isolated yield observed for the formation of heptan-2-one is due to its volatility, as the chemical conversion is excellent as judged by GC analysis using an internal standard. The copper catalysed ring opening of methyleneaziridines with Grignard reagents appears general and we have used it to make a variety of methyl ketones **2** in moderate to good yields (Table 1).† Importantly, in control experiments, we have determined that at low temperatures, both CuI and the Lewis acid are essential for rapid ring opening to occur.

Our initial attempts to alkylate the presumed metalloenamine intermediate produced by ring opening of methyleneaziridine **1** (R = CHMePh) with BuMgCl, CuI and $BF_3{\cdot}OEt_2$ were entirely unsuccessful. Introduction of an electrophile such as BnCl into the vessel prior to aqueous hydrolysis did not result in the formation of any further alkylated products. Control experiments using a metalloenamine made by the traditional method of imine deprotonation using EtMgCl revealed that the presence of $BF_3{\cdot}OEt_2$ in the reaction mixture completely suppresses alkylation reactions of the metalloenamine. To overcome this problem, we sought conditions to effect the ring opening of 2-methyleneaziridines with organometallic reagents in the absence of an added Lewis acid. After further experimentation, we determined that the ring opening could be achieved using Grignard reagents in the presence of CuI (20 mol%) by warming the mixture to room temperature and stirring for an extended period (24 h) prior to introduction of the electrophile. Using these conditions, treatment of methyleneaziridine **1** (R = CHMePh) with BuMgCl then BnCl yielded alkylated ketone **4** in 78% isolated yield after imine hydrolysis and silica gel

Table 1



1 **2**

Entry	R	R^1	Yield[a] (%)
1	CHMePh	$(CH_2)_3CH_3$	56 (90)[b]
2	CHMePh	$(CH_2)_7CH_3$	81
3	CHMePh	Ph	65
4	CHMePh	CH_2Ph	69
5	CHMePh	Cyclohexyl	50
6	CHMePh	C_6H_4OMe	60
7	CHMePh	$(CH_2)_6CH{=}CH_2$	88
8	Cyclohexyl	$(CH_2)_7CH_3$	85

[a] Refers to yield of purified product after work-up and purification by silica gel chromatography. [b] GC yield determined using nonane as internal standard.

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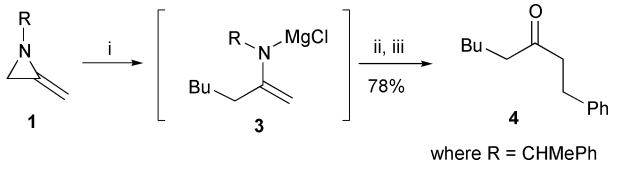
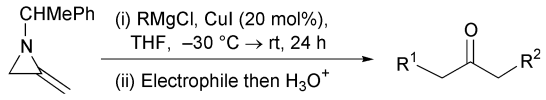


Scheme 2 *Reagents and conditions*: (i) BuMgCl (3.0 equiv.), CuI (20 mol%), THF, −30 °C → rt, 24 h; (ii) BnCl (1.5 equiv.), 40 °C; (iii) 10% HCl, 50 °C, 2 h.

chromatography (Scheme 2).‡ Significantly, the formation of metalloenamine **3** is highly regiospecific, and no trace of 3-benzylheptan-2-one could be detected in the crude reaction mixture.§

We have extended the scope of this method of metalloenamine generation to other Grignard reagents and electrophiles (Table 2).† Moderate to good yields of products are obtained in all cases and the method provides a flexible and efficient approach to functionalised ketones. The only notable limitation with this chemistry is the requirement to use excess Grignard reagent (3 equiv.) to drive the reaction to completion. Currently, we are searching for more active copper catalysts in an effort to address this problem. Future work will also be aimed at extending the scope of this method and to applying it in natural product synthesis.

Table 2



Grignard[a]	Electrophile	R^1	R^2	Yield[b] (%)
BuMgCl	BnCl[c]	Bu	Bn	78
OctylMgCl	$H_2C{=}CHCH_2Br$	Octyl	$H_2C{=}CHCH_2$	80
OctylMgCl	$H_2C{=}CHCH_2CH_2OTs$	Octyl	$H_2C{=}CHCH_2CH_2$	67
BuMgCl	4-$MeC_6H_4CH_2Cl$	Bu	4-$MeC_6H_4CH_2$	75
BnMgCl	4-$MeC_6H_4CH_2Cl$	Bn	4-$MeC_6H_4CH_2$	80
BuMgCl	$TBDMSO(CH_2)_3Br$	Bu	$TBDMSO(CH_2)_3$	58

[a] All reactions performed with 3 equiv. of Grignard reagent and 2 equiv. of electrophile unless otherwise stated. [b] Refers to yield of purified product after work-up and purification by silica gel chromatography. [c] Performed using 1.5 equiv. of electrophile.

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Notes and references

† All new compounds were fully characterised using standard spectroscopic and analytical methods.

‡ *Typical procedure:* CuI (48 mg, 0.252 mmol) in a round-bottomed flask was heated under vacuum then purged with nitrogen (3 cycles performed). Freshly distilled THF (4 ml) was added and the mixture cooled to −30 °C whereupon BuMgCl (2.0 M in THF, 1.89 ml, 3.78 mmol) was added. After stirring for 10 min, *N*-(1-phenylethyl)-2-methyleneaziridine (200 mg, 1.26 mmol) in THF (2 ml) was added. The reaction mixture was allowed to warm up to room temperature and stirred for 24 h. The flask was then cooled to 0 °C and BnCl (218 μl, 1.89 mmol) added dropwise. A reflux condenser was fitted and the reaction mixture heated at 40 °C for 2 h then allowed to cool to room temperature and stirred overnight. Finally, 10% aq. HCl (3 ml) was added, and the mixture heated at 50 °C for 2 h (for all other entries in Table 2, imine hydrolysis was effected using 1 M AcOH–hexane at rt). Upon cooling, solid NaCl was added and the mixture extracted with Et_2O. The combined organic layers were washed with 0.5 M aq. HCl (2 × 15 ml), saturated NH_4Cl (2 × 20 ml), saturated $NaHCO_3$ (2 × 20 ml) and brine (2 × 20 ml). The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo*. Column chromatography on silica gel (2.5% EtOAc in hexane) gave 1-phenyloctan-3-one (201 mg, 78%) as a yellow oil. ν_{max} (thin film) 2947, 2931, 2856, 1713, 1450 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.30–7.17 (5H, m, Ph), 2.89 (2H, m), 2.72 (2H, m), 2.37 (2H, t, *J* 7.6), 1.56 (2H, m), 1.30–1.21 (4H, m), 0.88 (3H, t, *J* 7.2); δ_C (100.9 MHz, $CDCl_3$) 210.5 (s), 141.2 (s), 128.5 (d), 128.3 (d), 126.1 (d), 44.3 (t), 43.0 (t), 31.4 (t), 29.8 (t), 23.5 (t), 22.5 (t), 13.9 (q); Observed 204.1519; $C_{14}H_{20}O$ requires 204.1514.

§ By comparison with an authentic sample of 3-benzylheptan-2-one using gas chromatography and ^1H NMR spectroscopy.

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