Enantioselective Radical Cross-Coupling Reactions of Silyl Enol Ethers Using Chiral Oxovanadium

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Asymmetric induction was observed in radical cross-coupling reactions of silyl enol ethers using chiral oxovanadium generated in situ from 8-phenylmenthol and vanadium oxytrichloride in the presence of MS4A (molecular sieves-4A).

Asymmetric induction in radical-mediated reactions is presently of considerable interest in synthetic organic chemistry,[1] and enantioselective radical reactions using organotin reagents and chiral Lewis acids appear in the literature.[2]

Generally, most radical-mediated reactions are conducted through the reductive generation of a radical species, but oxidative radical generation using metal oxidants is now being considered for this purpose.[3] Diastereoselective oxidative radical coupling reactions using chiral auxiliaries have been reported.[4]

Oxidative radical cross-coupling reactions of silyl enol ethers using $VO(OEt)Cl_2$ as a one-electron oxidant to give 1,4-diketones as reported by Hirao and co-workers are unique radical-mediated C–C bond forming reactions[5] (Figure 1). In these reactions, when radical intermediates are subjected to a chiral environment, asymmetric induction may be considered to occur.

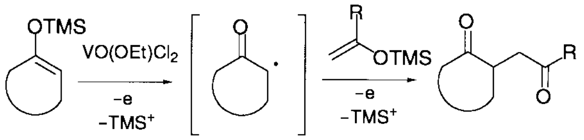


Figure 1.

This paper presents for the first time an enantioselective oxidative radical cross-coupling reaction of silyl enol ethers using the chiral oxovanadium reagents generated in situ from $VOCl_3$ and chiral alcohols in the presence of MS4A (Figure 2).

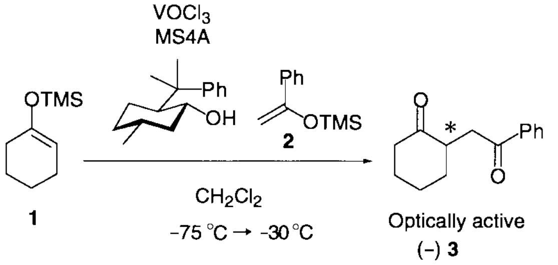


Figure 2.

Bases such as K_2CO_3, NEt_3 and collidine were initially used with $VOCl_3$ and EtOH to form $VO(OEt)Cl_2$ in situ, but no coupling reactions took place, however, the reaction proceeded on using MS4A, and the results are summarized in Table 1. MS4A was found particularly effective for inducing the formation of oxovanadium reagents in situ and coupling reactions.

Table 1. Oxidative radical cross-coupling reactions using oxovanadium reagents generated in situ from $VOCl_3$ and EtOH

$$\mathbf{1} \xrightarrow[CH_2Cl_2,\ -78\ ^\circ C]{\mathbf{2},\ VOCl_3,\ EtOH,\ additive} \mathbf{3}$$

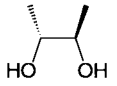
Run	Reagent	Additive	Yield /%[a] of **3**
1	$VO(OEt)Cl_2$		65 (67)[b]
2	$VOCl_3$		0
3	$VOCl_3$+EtOH	K_2CO_3	0
4	$VOCl_3$+EtOH	NEt_3	trace
5	$VOCl_3$+EtOH	collidine	trace
6	$VOCl_3$+EtOH	MS4A	63

[a] Isolated yield. [b] Hirao et al.[4] obtained in 67%.

Table 2. Enantioselective radical-mediated cross-coupling of **1** and **2** with chiral oxovanadium

Run	Reagents	Yield /%[a] of **3**	ee /%[b] of **3**
1	$VOCl_3$+**4**+MS4A	11	0
2	$VOCl_3$+**5**+MS4A	55	31
3	$VOCl_3$+**6**+MS4A	58	85

[a] Isolated yield. [b] Determined by HPLC using a chiral column (DAICEL CHIRALCEL OB Φ 4.6 mm × 250 mm)[hexane : 2-propanol = 20 : 1, flow rate 2.5 mL/min; t_R(min) 9.0 (major enantiomer) and 15.4 (minor enantiomer)]. Absolute configuration was not determined.



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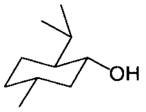

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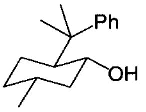

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Asymmetric induction was observed when using menthol and 8-phenylmenthol, (runs 2 and 3 in Table 2) and was best with 8-phenylmenthol as the chiral alcohol (run 3.).

A typical experimental procedure (run 3 in Table 2) is as follows. To a solution of $VOCl_3$ (1.29 mmol) in CH_2Cl_2 (5 mL) were added 8-phenylmenthol (1.29 mmol) in CH_2Cl_2 (1 mL) and powdered MS4A (1 g). The mixture was stirred at r.t. for 1 h and cooled to –75 °C under Ar. With the temperature maintained at –75 °C, 1-phenyl-1-(trimethylsilyloxy)ethylene **2** (0.65 mmol) was added to the reaction mixture, and then 1-trimethylsilyloxycyclohexene **1** (0.43 mmol) dropwise over a period of 20 min. This was followed by additional stirring at –75 °C for 3 h and –30 °C for 4 h. At –30 °C, 5% aqueous $Na_2S_2O_3$ (0.5 mL) and ether (10 mL) were added to the reaction mixture followed by extracting with ether and the addition of concd HCl and extraction again with ether. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried and concentrated. The residue was purified by silicagel column chromatography (hexane:diethyl ether = 10:1) to give 1,4-diketone **3**, $[\alpha]_D^{25}$ –9.8 °(*c* 0.66, $CHCl_3$) in 85% ee. The value of ee was determined by HPLC analysis using a DAICEL CHIRALCEL OB column.

In treating $VOCl_3$ with EtOH in the presence of MS4A in $CDCl_3$, $VO(OEt)Cl_2$ formation was confirmed by the observation of Et peaks of $VO(OEt)Cl_2$ by NMR measurement. When collidine was used instead of MS4A, there was no generation of $VO(OEt)Cl_2$ at all. MS4A would thus appear effective for inducing formation of chiral oxovanadium reagents. In the case of a mixture of 8-phenylmenthol and $VOCl_3$ in the presence of MS4A, it was observed that the formation of chiral oxovanadium reagent caused the downfield shift of the H_A peak (Figure 3.).

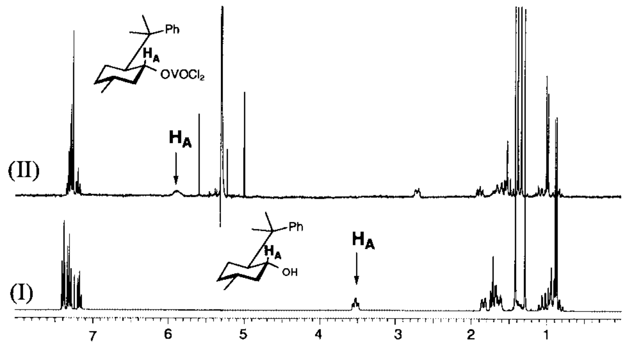

Figure 3. (I) 300 MHz ^{1}H NMR spectra of 8-phenylmenthol. (II) ^{1}H NMR spectra of a mixture of $VOCl_3$, 8-phenylmenthol, and MS4A.

The present reactions represent a new class of enantioselective radical-mediated reactions and the mechanism of the asymmetric induction is currently being studied.

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References and Notes

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