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THE *ANTI*-SELECTIVE MICHAEL ADDITION OF TIN(II) ENOLATES OF CYCLIC KETONES TO β-NITROSTYRENE

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The tin(II) enolates of cyclic ketones were found to react with β-nitrostyrene to afford the corresponding 4-nitroketones with unprecedented *anti*-selectivity. In the case of the reaction of the tin(II) enolate of cyclohexanone with β-nitrostyrene, the *anti*-adduct was yielded in >93:7 diastereomeric excess.

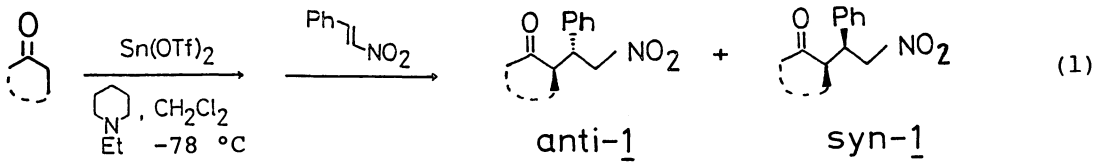
Control of acyclic stereochemistry is currently one of the foremost goals of synthetic organic chemistry.[1] Particularly noteworthy is the staggering amount of progress that has been made in the aldol reaction[2] with often essentially only one diastereomer being obtained. In contrast, examination of the diastereoselection achievable in the Michael addition reaction, with the generation of two new centers of chirality, has received substantially less attention.[3] In this respect, perhaps the pioneering work of Valentin et al.[4] on the stereoselective addition of enamines derived from cyclic ketones to nitroolefins is the most well established with excellent *syn*-selectivity being reported. More recently, Seebach and coworkers[5] have further demonstrated that open-chain (E)-enamines react with nitroolefins in a highly diastereoselective manner (> 90%) to yield the corresponding 4-nitroketones, though the relative stereochemistry at the two new vicinal chiral carbon centers was not unequivocally established. Other investigations on the addition of lithium enolates[6] or silyl enol ethers[7] to nitroolefins have proven to be non-selective in general.

Since Valentin et al.[4] have firmly established the relative configuration of the two respective diastereomers yielded from the reaction of the enamines of cyclic ketones with β-nitrostyrene, we undertook a parallel investigation of the diastereoselectivity achievable in the reaction of tin(II) enolates of cyclic

ketones with β-nitrostyrene. And, in this communication, we wish to disclose our preliminary findings on the unprecedented *anti*-selective Michael addition of tin(II) enolates, derived from cyclic ketones, to β-nitrostyrene.

In the first place, to the tin(II) enolate of cyclohexanone, generated in situ at -78 °C in dichloromethane, was added β-nitrostyrene. The reaction mixture was then immediately warmed to -45 °C and stirred at this temperature for 5 h. Standard work-up of the reaction mixture gave the desired 4-nitroketone 1 in 64% isolated yield. Moreover, examination of the diastereomeric purity of 1 revealed that the *anti*-adduct had been afforded in excess of 93%. That the sense of diastereoselection is completely *opposite* to both the reactions of enamine and lithium enolates[6b] with nitroolefins (*syn*-selective) is unprecedented.

As a test of the generality of the *anti*-selectivity of this reaction, the reaction of the tin(II) enolate of other selected cyclic ketones with β-nitrostyrene was examined. Again, unprecedented *anti*-selectivity was observed, albeit only with moderate diastereomeric bias. Results are summarized in the Table 1.



(1)

Table 1. *Anti*-selective michael addition to β-nitrostyrene

Entry	Ketone	Reaction conditions[a]	Yield /%[b]	Anti : Syn[c]
1		-78 °C, 3 h	64	>93 : 7
2		-45 °C, 5 h	82	70 : 30
3		-45 °C, 13 h	76	62 : 38[d,e]

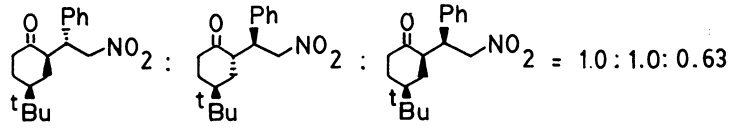
Molar ratio of $Sn(OTf)_2$: N-ethylpiperidine : ketone : β-nitrostyrene = 1.3 : 1.4 : 1.0 : 0.8.

a) Enolization was carried out at -78 °C for 30 min.

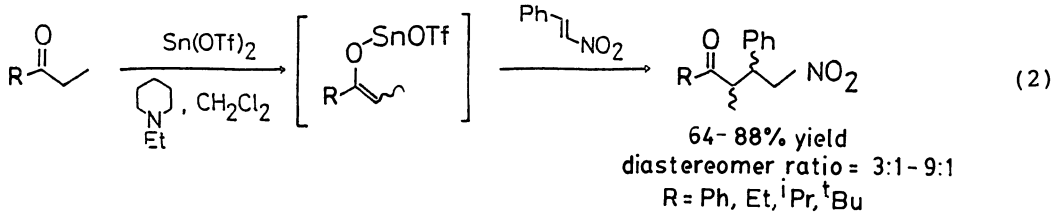
b) Isolated yield. All compounds gave satisfactory spectral data.

c) Determined by 90 MHz ^1H NMR analysis of crude reaction mixture.

d) Determined after separation of isomers on preparative tlc.

e)  = 1.0 : 1.0 : 0.63

Unfortunately, the reason for this unprecedented *anti*-selectivity is not clear at this stage. Much speculation on the mechanism of the reaction of enamines with nitroolefins has been put forth,[8] however, the almost total lack of studies on the stereocontrolled addition of metal enolates to nitroolefins relinquishes any formalization of the present results. Furthermore, studies on the reaction of the kinetic (Z)-enolates of acyclic ketones with nitroolefins is yet to be explored, and hence the correlation of enolate geometry with that of product selectivity remains unclear. Our own investigations[9] in this area have given promising results (see Eq. 2) with moderate to excellent stereoselection being observed, though relative stereochemical assignment has yet to be unambiguously established.



(2)

Thus, it is noted that the tin(II) enolates of cyclic ketones react with β-nitrostyrene to afford the corresponding 4-nitroketones with moderate to excellent *anti*-selectivity. The reaction of the tin(II) enolates of *acyclic* ketones with nitroolefins and extrapolation to the stereochemical outcome of such a reaction will be the subject of further studies in this laboratory.

References

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