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Diastereoselective Protonation of Chiral Enolates derived from 2,4-Dimethyl-1-tetralone using Carbonyl Chelating Proton Donors

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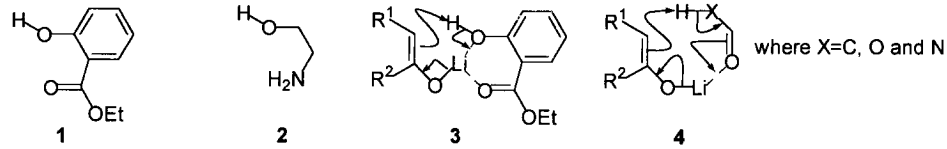
Abstract: The synthesis of *syn*-2,4-dimethyl-1-tetralone **6** *via* a deprotonation-reprotonation strategy using chelating proton sources is discussed. We comment on the differences between direct protonation and deprotonation-reprotonation of chiral enolates in the presence of diisopropylamine and LiBr.

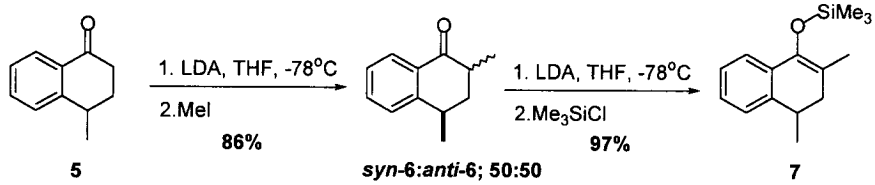
Diastereoselective protonation of chiral enolates is well known.[1] Of these reports, the majority deal with direct protonation of chiral enolates under either kinetic[2] or thermodynamic substrate control.[3] There are few cases where the diastereoselective stereochemical determining protonation step is under reagent control,[4] the most notable examples being the use of *chelating proton donors* (CPD's) such as salicylic esters **1**,[5] and β-amino alcohols **2**.[6] The behaviour of these acids are characterised by their ability to chelate to lithium enolates and kinetically direct protonation, regioselectively on carbon of an enolate, such as **3**, (rather than the preferred kinetic protonation on the oxygen).[1]



1 **2** **3** **4**

We now wish to report our study into the use of carbonyl based chelating proton donors (like **4**) for regioselective and kinetic protonation of enolates at carbon by using a diastereoselective protonation approach. We also comment on factors (acidity of the acid, solvent and salt effects) which affect the outcome of the stereoselective protonation step, all of which help to elucidate to the mechanism of the title reaction.

We chose the tetralone framework as our model system as there is no ambiguity with the formation and configuration of the *endo*-cyclic enolate geometry. The 2,4-dimethyl tetralone **6** required for this study was synthesised by deprotonation of the commercially available 4-methyl tetralone **5** with LDA in THF at –78°C, and subsequent alkylation with methyl iodide; this gave the *syn* and *anti*-2,4-dimethyl tetralone **6** as a partially separable mixture (50:50) of diastereoisomers in excellent yield. Evidently, there was no substrate control upon alkylation of this type of chiral enolate with methyl iodide.



5 ***syn*-6:*anti*-6; 50:50** **7**

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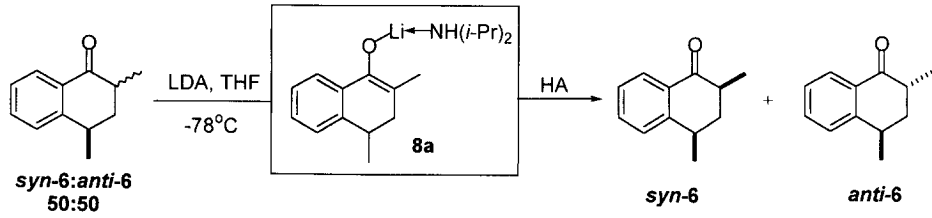
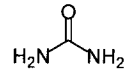
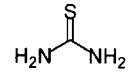
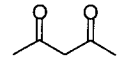
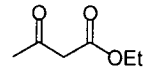
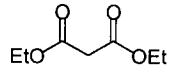
We were interested in diastereoselective protonation of the chiral enolate **8a** in the presence of the diisopropylamine (derived from the LDA), which is known to bind to the enolate causing deaggregation[4] and also act as a potential competitive base.[7] Treatment of the diastereoisomeric mixture of 2,4-dimethyl tetralone **6** with LDA in THF at –78°C and re-protonation with a series of carbonyl based acids gave the diastereoisomeric tetralones *syn*- and *anti*-**6** (see Table 1).

Table 1: Deprotonation and reprotonation of *syn*- and *anti*-2,4-dimethyl tetralone **6**

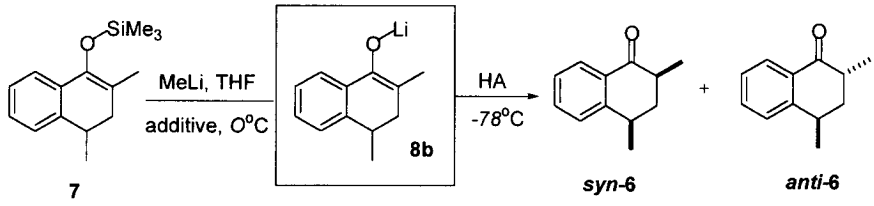


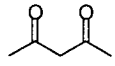
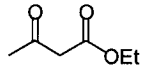
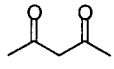
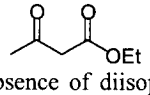
Entry	Acid (HA)	*syn*-6:*anti*-6	Yield (%)
1		60:40	92
2		62:38	96
3		55:45	93
4		85:15	92
5		94:6	97
6		**95:5**	**98**
7		52:48	94

The choice of proton donor used for this diastereoselective protonation did give rather markedly different results. Conformationally restricted sp^2 nitrogen based amides, such as urea (Table 1, entry 1), thiourea (entry 2) and the 2-oxazolidinone (entry 3) gave poor diastereoisomeric control, slightly in favour of the *syn*-diastereoisomer. The ratio was substantially improved by the use of the more acidic (glacial) acetic acid (entry 4). But greater diastereoselective control came from mildly acidic carbon based acids like pentane-2,4-dione and ethyl acetoacetate (entry 5 and 6), whereas diethyl malonate (entry 7) gave very poor selectivity. By comparison, direct protonation with MeOH gave a ratio of 60:40 in favour of the *syn*-tetralone **6** (93%). However, under thermodynamic control by treatment of the *syn*-diastereoisomer **6** with *t*-BuOK in THF overnight favoured the equilibrium ratio (50:50). Clearly, the *syn*-diastereoisomer **6** is the kinetic product (relative stereochemistry determined by a 600 MHz NOSEY) and thus protonation on the less hindered face of the enolate **8a** is preferred.

We next considered whether the presence of the residual diisopropylamine in **8a** had any effect on the stereochemistry determining protonation step. We chose to generate the enolate under 'base free' conditions using Koga's silyl enol ether procedure.[8] Treatment of the 2,4-dimethyl tetralone **6** with LDA at –78°C and quenching with Me_3SiCl gave the required silyl enol ether **7** in near quantitative yield, and the addition of MeLi at 0°C generated the 'base free' chiral enolate **8b**. By direct protonation of this lithium enolate at –78°C with acetic acid, 1,3-diketopentane and ethyl acetoacetate gave a series of diastereoisomeric tetralones **6** as presented in Table 2.

Table 2: Direct protonation of the chiral enolate **8b**

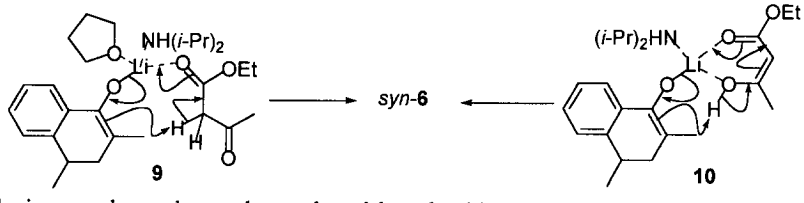


Entry	Acid (HA)	Additive	*syn*-6:*anti*-6	yield (%)
1		none	**95:5**	**87**
2		none	80:20	85
3		none	70:30	78
4		LiBr	95:5	88
5		LiBr	**>98:<2**	**84**
6		LiBr	90:10	81

By comparison, in the absence of diisopropylamine, the diastereoselectivity of protonation was substantially reduced for the carbon based acids, but a slight increase for acetic acid was observed; in all cases the *syn*-diastereoisomer was favoured (Table 2: entry 1-3). In the case of glacial acetic acid it appears that diisopropylammonium acetate (by *insitu*-reaction of acetic acid with diisopropylamine) acts as an additional acid[7] because the presence of the diisopropylamine (Table 1: entry 4) did have a detrimental effect on the diastereoselectivity. To determine whether the potential diisopropylammonium salt could act as an additional acid, we quenched the enolates **8a** (derived from **6**) and **8b** with diisopropylammonium chloride. A much lower diastereoselectivity was observed giving the *syn*- and *anti*-tetralone **6** in a ratio of 75:25 (85%) and 70:30 (80%). Evidently, in this case the diastereoselectivity is being compromised by competitive protonation from the ammonium salt.

However, in the case of the carbon based acids, such as pentane-2,4-dione and acetoacetate, full deprotonation by diisopropylamine is not favoured and proton transfer is known to be much slower, by at least four orders of magnitude.[9] Even more surprising, the presence of this amine in the enolate **8a** and not **8b**, clearly makes the enolates different; since the diastereoselectivity of protonation with a better chelator, such as ethyl acetoacetate falls substantially from 95:5 to 70:30 in the absence of amine. The enolate **8b** can be converted into **8a** (by the simple addition of diisopropylamine) and quenching with ethyl acetoacetate gives identical diastereoselectivity (95:5) in 83% yield. An attempt to increase the diastereoselectivity by protonation in a non polar solvent like toluene, to promote chelation, only lowered the diastereoselectivity (62:38; 82%) in favour of *syn*-**6**.

By the simple addition of LiBr to the enolate (by treatment of **7** with a MeLi.LiBr complex) the diastereoselectivity of protonation improved even further (Table 2: entry 4-6), giving exclusively the *syn*-tetralone **6** (>98:2 by ^{1}H NMR) by using ethyl acetoacetate as the proton source. The effect of diisopropylamine and LiBr on the behaviour of the lithium enolate is dramatic. This is presumably due to a fine balance between the electronic properties of the lithium enolate and the ability for direct coordination which, under these conditions, is surprisingly advantageous for these weakly coordinating 1,3-dicarbonyl acids. Currently, we are investigating whether these 1,3-dicarbonyl acids such as ethyl acetoacetate are behaving as genuine carbon based acids like **9** or as the kinetically preferred oxygen based enol acids such as **10**.



In conclusion, we have shown that carbonyl based acids (like acetic acid, pentane-2,4-dione and acetoactetate) can act as potential *chelating proton donors* for kinetic protonation. Subtle changes in the enolate substructure, change in the solvent, presence of amine and LiBr does have a dramatic effect on the observed diastereoselectivity of protonation of these chiral enolates. High diastereoselectivity (up to >98:2) is generally observed in the presence of diisopropylamine and LiBr when using 1,3-dicarbonyl acids under reagent control.

Acknowledgements

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References and Notes

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