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[a016]

Enantioselective Protonation of Prostereogenic Enol Equivalents

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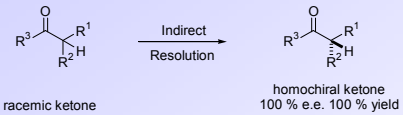
Concept of Enantioselective Protonation

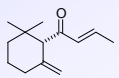


Enantioselective protonation[1] of enol(ate)s allows conversion of a racemic carbonyl compound into one of its single enantiomers in 100% yield, whereas 'traditional resolutions' can only offer a maximum conversion of 50%.

Why is Enantioselective Protonation Important?

Enantioselective protonation of enol(ate)s have the potential to be an industrially applicable method for the synthesis of stereochemically pure α-substituted carbonyl derivatives such as fragrances, pheromones and biologically active anti-inflammatory agents.

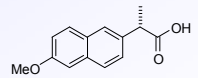
Musk odorant



damascone [2]

"Warm, sensual, animal, natural, long lasting and tenaciuos"
-C.Fehr in Chem.Eur.J. ***2002****, 8, 855*

Profens

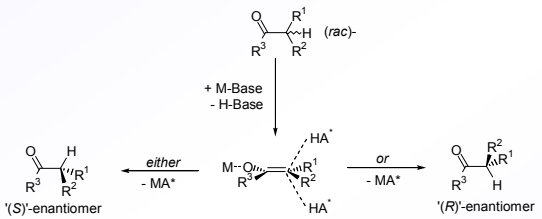


Naproxin[3]

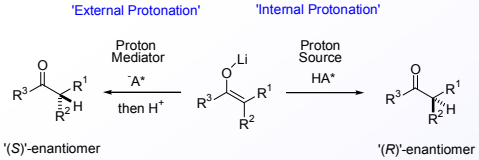
Nonsteroidal antiinflammatory
-A.E.Greene, C.L.Drain and P.Crabbe, J.Am.Chem.Soc., ***1980****, 102, 7583*

Mechanism of Enantioselective Protonation

Deprotonation of a racemic ketone can lead to a stereochemically defined enolate. Re-protonation of this enolate on each face with an enantiomerically pure acid, HA*, leads to either the (*S*)- or (*R*)-enantiomer of the parent ketone. This is an indirect resolution as it involves formation of an intermediate enolate.



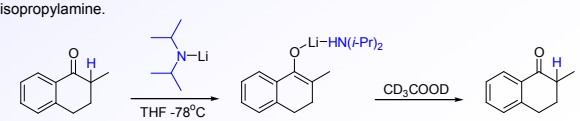
Our Aim:



We aimed to expand this methodology by designing a single proton mediator which will allow individual access to both single enantiomers in 100% yield by use of subtle adjustments to the reaction conditions.

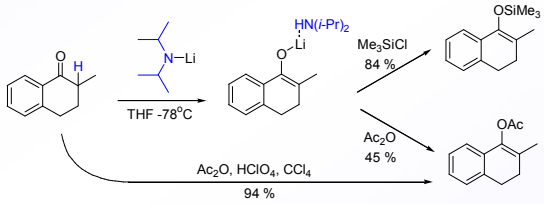
Regioselective Deuteration

We chose to use 2-methyl tetralone as our standard ketone due to its known reliable enolate chemistry, predictable enolate configuration and u.v. activity. For efficient *C*-protonation of the lithium enolate of 2-methyl tetralone this corresponding enolate needs to be 'base-free'. If a competitive base is present, such as diisopropylamine[5] (derived from LDA), proton transfer occurs by an unwanted combination of *C*- and *O*-protonation. This unwanted *O*-protonation mechanism can easily be seen from attempted deuteriation of the lithium enolate-diisopropylamine complex with acetic acid-d_4 which gave no deuterium incorporation. This can presumably be accounted for by use of Seebach's internal proton return,[5] whereby the proton abstracted by LDA is the one returned to the enolate. This concept is particularly important as addition of a 'chiral proton donor' may generate a racemic ketone by internal proton return from the achiral diisopropylamine.

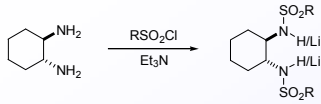


Synthesis of Enolate Precursors

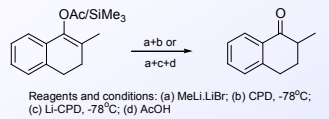
To prevent this internal proton return, we chose to use enol equivalents, such as silyl enol ethers and enol acetates. These have previously been shown in the 1960's to liberate the required 'base-free' lithium enolate by simple addition of MeLi.[6]



Synthesis and use of Chiral Sulfonamides as Chiral proton Sources/Mediators



Synthesis of chiral proton sources/mediators



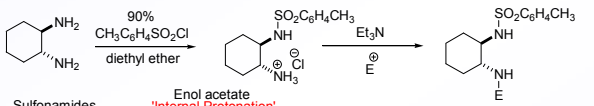
Reagents and conditions: (a) MeLi.LiBr; (b) CPD, -78°C; (c) Li-CPD, -78°C; (d) AcOH

Entry	R=	Yield %	Enol acetate 'Internal Protonation' (a+b) Yield %	e.e. %	Enol acetate 'External Protonation' (a+c+d) Yield %	e.e. %
1	C_6H_5	71	36	(*S*)-12	63	(*S*)-4
2	$C_6H_4CH_3$	79	69	(*S*)-22	50	(*R*)-63
3	1-naphthyl	72	49	(*rac*)-0	47	(*R*)-12
4	2-naphthyl	84	57	(*R*)-64	54	(*S*)-45
5	$C_6H_2(C_3H_7)_3$	94	51	(*R*)-24	53	(*rac*)-0

We chose the cyclohexyl-1,2-diamine as our chiral scaffold for our proton sources due to its rigid conformation. The acidity of the NH's were increased by formation of the corresponding sulfonamides.

Using our standard reaction conditions, we have elegantly shown that substituted sulfonamides can be used to gain access to both enantiomers of 2-methyl tetralone by use of our complementary internal and external proton strategy.

Synthesis and use of Unsymmetrical Sulfonamides



Sulfonamides — Enol acetate 'Internal Protonation'

Entry	Electrophile	Yield %	Yield %	e.e. %	
1	2-naphthyl	88	9%	(*S*)-43	
2	4-nitrobenzyl	57	43%	(*R*)-17	
3	*n*-butyl	43	53%	(*R*)-21	
4	4-*t*-butylbenzyl	88	40%	(*R*)-17	
5	4-toluyl	79	69%	(*S*)-22	

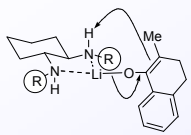
Amides — Enol acetate 'Internal Protonation'

Entry	Electrophile	Yield %	Yield %	e.e. %	
6	acyl	11	15%	(*S*)-60	
7	propyl	18	31%	(*S*)-12	
8	*i*-butyryl	23	26%	(*S*)-22	
9	pivoyl	68	41%	(*S*)-48	

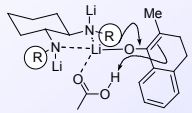
We have extended this strategy by synthesising related unsymmetrical sulfonamides and amides by addition of the corresponding substituted sulfonyl chloride/acid chloride to the tosyl ammonium salt. These proton sources/mediators were screened against our standard lithium enolate derived from the corresponding enol acetate and MeLi (2 equivalents).

Enantioselective *C*-Protonation of the Lithium Enolate of 2-Methyl Tetralone

We propose these enantioselective *C*-protonations occur *via* two complementary routes.



'*via* Internal Protonation'



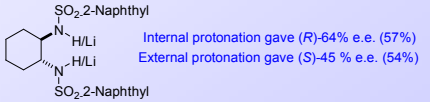
'*via* External Protonation'

For internal protonation, the symmetrical sulfonamide acts as a chiral proton donor delivering the proton to one face of the lithium enolate to give (predominantly) one enantiomer.

Whereas, for external protonation the dilithiated sulfonamide now acts as a chiral scaffold. This presumably assists proton delivery on the LESS hindered face of the lithium enolate to give other the complementary enantiomer.

Conclusion

We have successfully shown the use of two complementary protonation strategies (internal versus external protonation) as a synthetic method for the synthesis of both (enriched) enantiomers of 2-methyl tetralone using a SINGLE chiral scaffold.



References and notes:
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[2] C.Fehr and J.Galindo, *J. Org.Chem.*, **1988**, *53*, 1828-31.
[3] K.Ishihara, D.Nakashima, Y.Hiraiwa and H.Yamamoto, *J.Am.Chem.Soc.*, **2003**, *125*, 24-25.
[4] J.Eames, G.S.Coumbarides and N.Weerasooriya, *Eur.J.Org.Chem.*, **2002**, 181-187; G.S.Coumbarides, J.Eames and M.J.Suggate, *J.Label.Compd.Radiopharm.*, **2004**, *47*, 359-371.
[5] T.Laube, J.D.Dunitz and D.Seebach, *Helv.Chim.Acta.*, **1985**, *68*, 1373-1375.
[6] G.Stork and P.Hudrlik, *J.Am.Chem.Soc.*, **1968**, *90*, 4462-4464; J.Eames, G.S.Coumbarides, M.J.Suggate and N.Weerasooriya, *Eur.J.Org.Chem.*, **2003**, 634-641.