REVIEW

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Recent studies on the regioselective C-protonation of enol derivatives using carbonyl-containing proton donors

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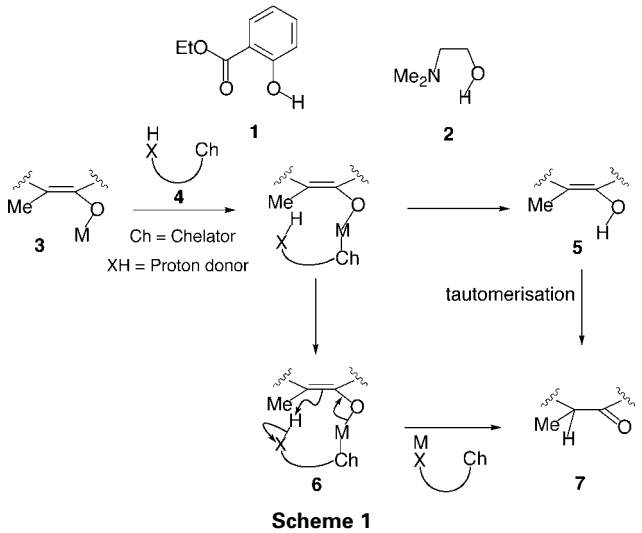
Enolate protonation can occur by two different pathways. With strong acids regioselective protonation generally occurs on the oxygen of the enolate to give an enol and then acid catalysed tautomerisation leads directly to the thermodynamically preferred carbonyl motif. However, with much weaker acids kinetic protonation on carbon can occur to give directly the carbonyl derivative. This review discuss recent developments into the use of chelating acids to promote this stereochemically important *C*-protonation and we comment on factors that appear to promote this selectivity.

Keywords: Regioselective C-protonation, enol derivatives.

Both enantio-[1] and diastereoselective[2] *C*-protonation of achiral and chiral enolates is well known. Many of these reports deal with proton transfer under kinetic control,[3] whereas protonation under thermodynamic control has become more popular when diastereoselective control is required.[4]

There are only a few cases where the stereochemistry-determining protonation step is under reagent control,[5] the most notable examples being the use of *chelating proton donors* (CPDs) such as salicylic esters **1**,[6] and β-amino alcohols **2** (Scheme 1).[7] The salient feature of these chelating acids such as **4** is their ability to chelate to the metal cation of an enolate such as **3** and aid protonation directly onto carbon[8] of the corresponding enolate **6** (to give the carbonyl derivative **7**), rather than in some cases the preferred protonation on oxygen (to give the enol **5**),[9] tautomerisation of which would lead to the thermodynamically preferred carbonyl derivative **7**.[10]



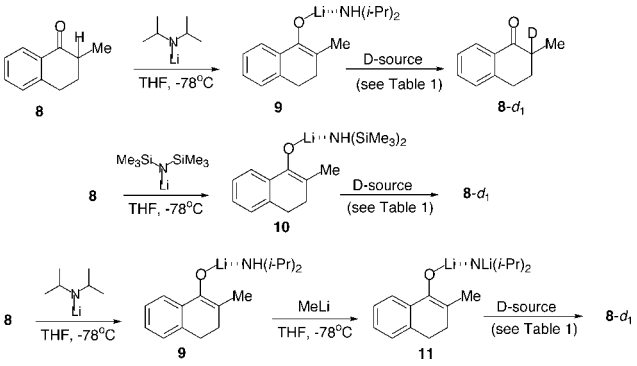
Scheme 1

Regioselective deuteriation of endocyclic enolates

Previous methods have relied on simple deuteriation under kinetic control to measure this inherent regiocontrol.[11] In many cases, the amount of deuterium incorporation was modest, but not complete.[12] We have assumed that regioselective *C*-deuteriation would lead directly to the carbonyl derivative with *D*-incorporation, whereas the alternative *O*-deuteriation would give the *D*-enol. However, by this pathway the *D*-label has the potential to be lost due to tautomerisation under aqueous work-up (H_2O/ether).[13]

Previous studies have revealed that this approach can be problematic.[14] It can be complicated further by the method chosen to generate the required enolate. Many methods rely on direct deprotonation using a metal amide,[15] or an organolithium reagent,[16] whereas others involve the addition of organo-lithium reagents to an enol derivative, such as a silyl enol ether[17] or enolacetate[18] to give the required enolate. The use of electron transfer reagents, such as SmI_2 has become increasingly popular.[19] The presence of additional competing bases such as di-isopropylamine has been shown to cause contamination *via* internal proton return in the deuteriation step.[13] This has been partially solved by removing the NH proton from the di-isopropylamine by further deprotonation to form an enolate–amide complex,[20] or by ensuring the formation of a less basic amine, such as hexamethyldisilylamide (HMDS).[21]

We originally chose 2-methyltetralone **8** as our model system[22] due to its UV activity, predictable enolate configuration, and ease of analysis as the distinctive 2-CH proton is lost on enolate formation. Under traditional lithium amide conditions, the base-enolate **9** can be readily formed by simple addition of LDA (Scheme 2). Addition of a series of *D*-acids to this enolate at –78°C gave little or no *D*-incorporated tetralone **8**-d_1 (Table 1). For those sources, which were *D*-acidic enough to deuteriate the residual amine (derived from the lithium amide) or the enolate on oxygen (to give the enol), no incorporation occurred.[23] For weakly acidic *D*-sources, such as D_2O, moderate incorporation did occur. Alternatively, by ensuring the amine in the enolate complex **10** was less basic, by using lithium hexamethyldisilylamide (LiHMDS) as the lithium



Scheme 2

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Table 1 Conversion of 2-methyltetralone **8** into 2-methyltetralone **8**-d_1

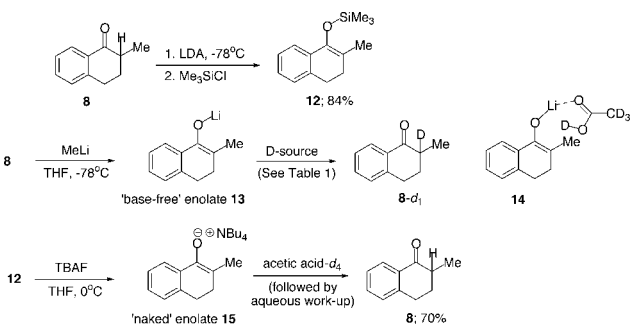
	D-source	D_2O	MeOH-d_4	Diethyl Malonate-d_2	Acetic acid-d_4	$MeNO_2$-d_3	DCl/D_2O
LDA	[D]:[H]	52:48[a] (72%)[b]	55:45 (67%)	<2:98 (88%)	<2:98 (90%)	<2:98 (82%)	72:28 (78%)
Base LiHMDS	[D]:[H]	89:11 (78%)	78:22 (81%)	62:38 (79%)	38:62 (87%)	16:84 (78%)	90:10 (72%)
LDA, MeLi	[D]:[H]	62:38 (62%)	58:42 (66%)	52:48 (58%)	35:65 (70%)	41:59 (69%)	83:17 (63%)
MeLi	[D]:[H]	98:2 (72%)	86:14 (66%)	86:14 (69%)	>95:5 (68%)	38:62 (74%)	84:16 (70%)

[a]isotopic [D]:[H] ratio; [b]chemical yield.

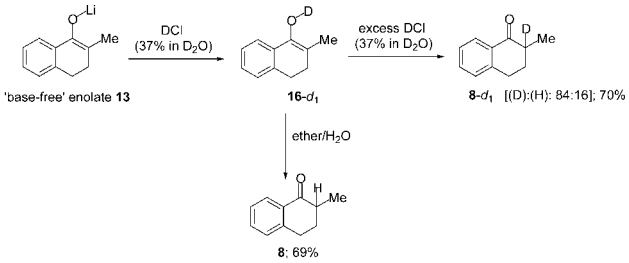
amide base,[21] the level of *D*-incorporation increased (Table 1). This amine effect can be partially removed by using a double deprotonation method[20] (using LDA, followed by the addition of MeLi to remove the proton from di-isopropylamine in **9**) to generate the enolate.amide complex **11**. Addition of a series of *D*-reagents gave only moderate *D*-incorporation (Table 1).

The true extent of this regioselective *C*-deuteriation could only be seen by studying the reaction in the absence of any other competitive bases. This was achieved using Stork's original procedure[24] for generating 'base-free' enolates, by addition of MeLi to the silyl enol ether **12**, to give the required 'base-free' enolate **13** and tetramethylsilane (Scheme 3). Virtually all *D*-sources tested gave moderate levels of incorporation (Table 1). *C*-Deuteriation was not unexpected for weakly *D*-acidic reagents like D_2O and MeOH-d_4 because competitive *O*-deuteriation was no longer favoured.[23] However, for acetic acid-d_4 which has the potential kinetically to deuteriate both *C*- and *O*-positions of an enolate, it was quite surprising to find high levels of regiocontrol. This is unusual when one considers that the relative rate of analogous proton transfer between highly electronegative atoms such as an *O*-based acid and base is at least 1000 fold faster than that between an analogous *C*-based base.[25] It is evident that the structural nature of the deuterium donor is important, as well as its *D*-acidity, for the outcome of the reaction. We believe this high regiocontrol was due to the carbonyl oxygen directing *C*-deuteriation of the enolate **14** by co-ordination to the lithium cation of the enolate (Scheme 3). This control was dependent on the presence of the Lewis acidic lithium cation. By exchanging it with a non-co-ordinating cation in the form of a tetrabutyl ammonium ion **15** (by the addition of TBAF to the silyl enol ether **12**) no incorporation occurred. This is presumably due to increased *O*-basicity of the enolate resulting in *D*-enol formation, tautomerisation of which under aqueous work-up provides a mechanism for the loss of the deuterium label.

Addition of an excess of DCl (37% in D_2O, 3 equivalents) to this enolate gave good *D*-incorporation (84:16) (Scheme 4). This was presumably due to initial *D*-enol **16**-d_1 formation and subsequent thermodynamic tautomerisation in the presence of DCl to give the tetralone **8**-d_1 in good yield. However, using one equivalent of DCl no incorporation occurs, presumably due to the washing out of the label in **16**-d_1 by tautomerisation during aqueous work-up.

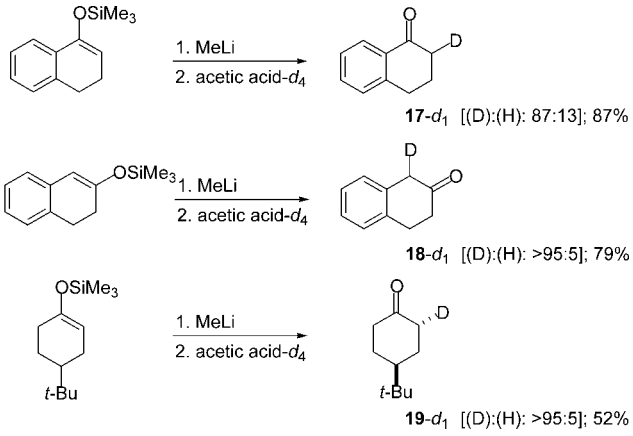


Scheme 3

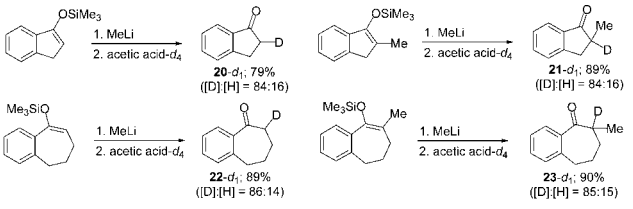


Scheme 4

The use of 'base-free' enolates was particularly effective. A single equivalent of acetic acid-d_4 was required, which alleviates the difficulty associated with product separation due to high incorporation. In cases where over-incorporation could occur, this does not happen, as shown by the synthesis of single isotopically labelled substituted cyclohexanones **17**-d_1, **18**-d_1 and *anti*-**19**-d_1 (Scheme 5). The level of *D*-incorporation was further shown to be dependent on the ring size of the *endo*-cyclic enolate. Better control occurred within a six-membered ring, such as tetralone **8**-d_1 and **17**-d_1, whereas for related substituted cyclopentanones and heptanones **20–23**-d_1, slightly lower regiocontrol occurs (Scheme 6). This apparent selectivity difference is presumably due to an *endo*-cyclic enolate preferring *C*-deuteriation for a six-membered ring since it can proceed *via* the more favourable half-chair transition state.



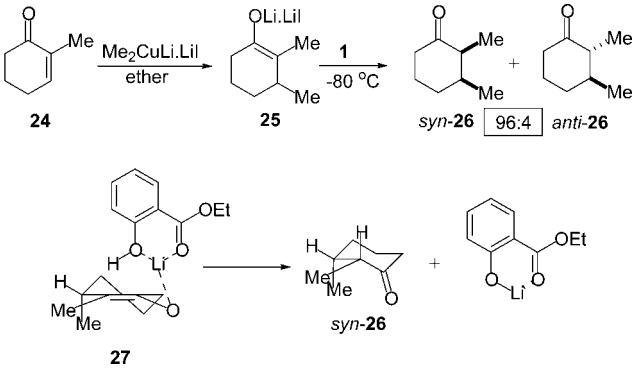
Scheme 5



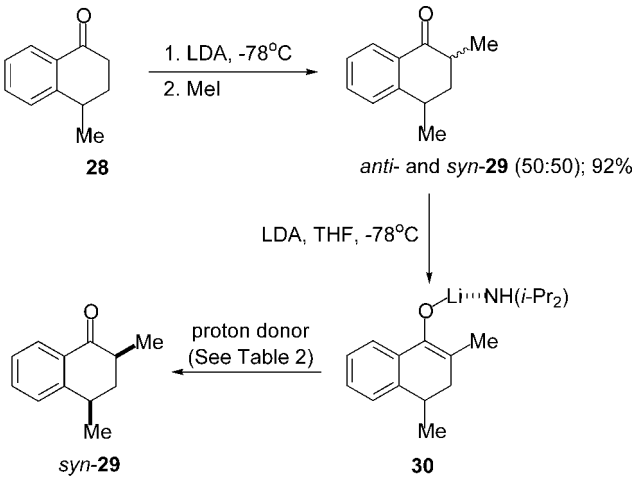
Scheme 6

Diastereoselective protonation of endocyclic enolates

An alternative way of probing the factors that control protonation is through a diastereoselective approach. Previous methods have dealt with protonation of chiral enolates under either kinetic or thermodynamic substrate control. There are a few cases where this stereochemical protonation step is under reagent control, the most notable examples being the use of a chelating phenol **1**[6] and a *β*-amino alcohols **2** (Scheme 1).[7] Krause has elegantly shown the application of a chelating salicyclic ester **1**,[6] in the protonation of chiral enolates like **25** (derived from a Michael addition of $Me_2CuLi.LiI$ to the enone **24**) to give exclusively the *syn*-diastereoisomer **26** in high yield (Scheme 7). This proton transfer occurs *via* an axial protonation involving a chair like transition state **27** rather than *via* a higher energy boat transition state.



Scheme 7



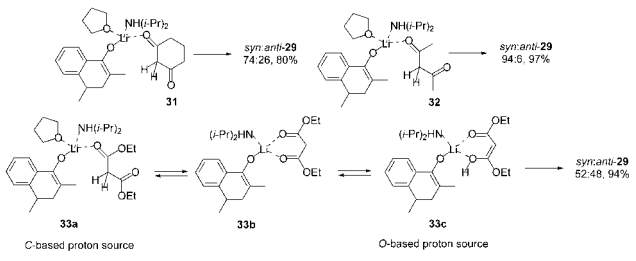
Scheme 8

The use of *anti*- and *syn*-2,4-dimethyltetralone **29** as our model system seemed perfect due to its close resemblance to 2-methyltetralone itself (Scheme 8).[26] The required 2,4-dimethyltetralone was efficiently synthesised by deprotonation of the commercially available 4-methyltetralone **28**[27] with LDA, and subsequent alkylation with MeI. The 2,4-dimethyltetralone **29** was isolated as a partially separable diastereoisomeric mixture (50:50) in 92% yield. This poor selectivity was ideal, since methylation of the intermediate chiral enolate must have occurred equally on both diastereotopic faces and clearly shows that there was no substrate control from the resident stereocentre. Deprotonation of this diastereoisomeric (50:50) mixture with LDA in THF at –78°C and re-protonation with a series of carbonyl based-acids gave the tetralone **29** enriched in the *syn*-diastereoisomer (Table 2). The structural nature and acidity of the proton donor was important to the outcome of the reaction.[28] Conformationally restricted sp^2 nitrogen acids, such as urea gave little stereocontrol giving the *syn*-tetralone **29** as the major isomer (ratio 60:40; 92%), whereas the ratio was vastly improved by using the more acidic and conformationally mobile acetic acid. Greater control came from mildly acidic carbon-based acids, such as pentane-2,4-dione and ethyl acetoacetate, whereas, the related diethyl malonate caused the selectivity to be markedly reduced (major isomer syn-29, ratio 52:48, yield 94%).

By comparison, direct protonation with a common proton donor such as MeOH gave a ratio of 60:40 in favour of the *syn*-tetralone **29** (93%). However, under thermodynamic control, treatment of the *syn*-diastereoisomer **29** with *t*-BuOK in THF overnight favoured the equilibrium ratio (50:50). The *syn*-diastereoisomer was shown to be the kinetic product and thus protonation on the less hindered face of the enolate **30** was evidently preferred.

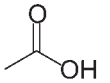
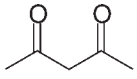
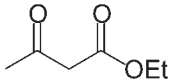
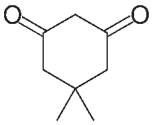
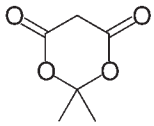
In an attempt to assess whether this control was due to the difference in their co-ordination ability, conformation or acidity, we quenched the enolate **30** with conformationally-restricted carbon-based acids like dimedone (Table 2), and Meldrum's acid (Table 2). The more acidic dimedone gave lower diastereocontrol than the parent acyclic acid pentane-2,4-dione (from 96:4 to 74:26), whereas Meldrum's acid gave an increase (from 52:48 to 79:21). The major conformers of these cyclic acids are clearly different from that of their near relatives. Due to the constraints of the cyclic framework, both carbonyl groups must be in an eclipsed conformation and since both gave similar control, the difference in acidity appears to play a minor role in these cases. Protonation must occur *via* the conformation **31** leading to the *syn*-tetralone **29** as the major diastereoisomer (Scheme 9). For conformationally mobile acyclic 1,3-dicarbonyl-based acids, such as diethyl malonate, the preferred ground state conformer exists where both carbonyl groups are orientated against each other to minimise the molecule's dipole moment.[29] We had originally presumed that a better chelating proton donor would lead to a tighter protonation transition state, and therefore better diastereocontrol. Because the chelating abilities of these proton donors are in the order; diethyl malonate > ethyl acetoacetate > pentane-2,4-dione, it did seem rather surprisingly that the best chelator, diethyl malonate did not obey this trend. There appears to be a fine balance between these acids behaving as chelating donors, *e.g.*, **33a** and co-ordinating acids, *e.g.*, **33b**. When both carbonyl groups were able to chelate to the lithium cation (*e.g.*, **33c**), no stereocontrol occurred, presumably indicating that proton transfer occurred *via* the much more acidic enol acid. The conformers that were responsible for this diastereocontrol are illustrated in Scheme 9.

This effect can be seen further by increasing the co-ordination ability of the lithium cation of the enolate **30** – by removing the di-isopropylamine ligand (Table 2). The stereoselectivity drops significantly for all the screened



Scheme 9

Table 2

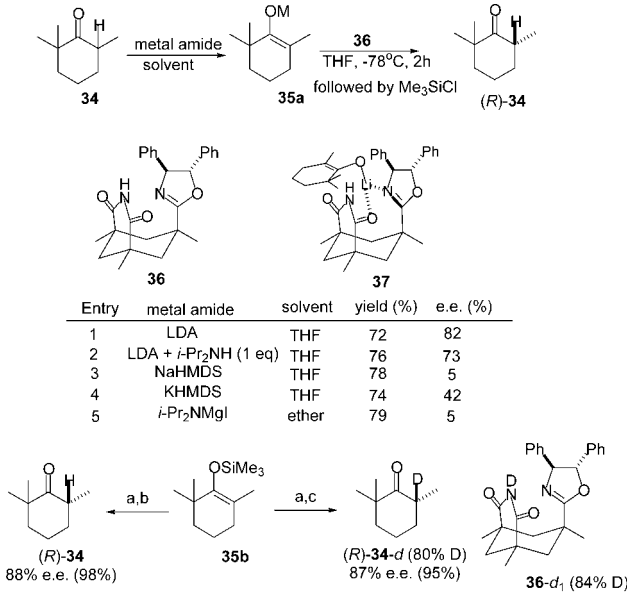
Enolate	proton donor					
30	ratio *syn-*:*anti-***29**	85:15 (92%)	96:4 (97%)	95:5 (98%)	74:26 (80%)	79:21 (80%)
Under 'base-free' conditions	ratio *syn-*:*anti-***29**	95:5 (87%)	80:20 (85%)	70:30 (78%)	90:10 (80%)	74:26 (80%)
Under 'base-free' conditions with a LiBr additive	ratio *syn-*:*anti-***29**	95:5 (88%)	>98:2 (84%)	90:10 (81%)	87:13 (74%)	70:30 (74%)

acyclic 1,3-dicarbonyl proton donors indicating an increase in the proportion of acid acting as an enol-acid like **33c**; for example using ethyl acetoacetate as the donor the selectivity changed from 98:2 to 70:30. The best proton donor under these 'base-free' conditions turned out to be the worst chelator, namely pentane-2,4-dione. For conformationally fixed donors like dimedone and Meldrum's acid a slight increase in diastereoselectivity does occur. This Lewis acidic nature of the lithium cation can be lowered – by the addition of a LiBr additive – and the high stereocontrol returns. At best, the proton donor pentane-2,4-dione gave near perfect stereocontrol (ratio >98%:<2% in 84% yield). Other carbonyl-containing chelating donors which do not act as enol-acids, such as acetic acid, gave similar high control under these conditions with or without a LiBr additive. This selectivity was higher than using traditional lithium amide methodology due to the residual di-isopropylamine base assisting in *proton return*[13] *via* an non-co-ordinating ammonium acetate proton donor.

Enantioselective protonation of endocyclic enolates

The concept of efficient regioselective *C*-protonation of enolates is more important in the enantioselective protonation of enol(ate) derivatives because *O*-protonation would lead directly to an achiral enol.[30] Stereorandom tautomerisation of such enol derivatives could potentially erode the overall facial control and lower the optical purity of the carbonyl derivative. There are some reports that suggest chiral base-catalysed tautomerisation can lead to enantiomerically pure carbonyl derivatives.[9,31] However, the majority of these enantioselective protonation studies have focused on the efficient *C*-protonation of enol derivatives using either a chiral chelating acid[32] (involving an internal quench) or a chiral ligand[33] coupled with an external achiral proton source. The use of 'base-free' enolates[18,24] within this methodology is widespread, presumably due to the effect of competing Brönsted and Lewis basic species when using traditional amide methodology.

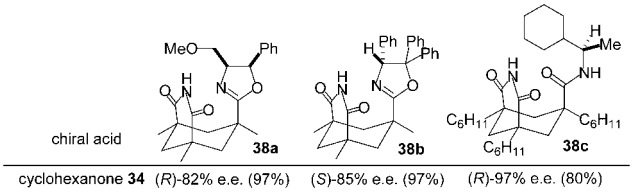
There have been some reports of the enantioselective protonation involving both chiral[34] and achiral carbonyl-containing chelating proton donors.[35] Yamamoto has recently reported an internal carbonyl-based succinimide proton donor **36** using an oxazolidine directing motif.[36] The facial control on protonation of the enol(ate) **35a+b** (derived from the ketone **34**) was slightly better under 'base-free' conditions. It has been postulated that this control was governed by direct chelation to the oxazolidine framework and one of the two diastereotopic carbonyl groups with protonation occurring *via* the intermediate complex **37** (Scheme 10).[37] Slightly lower levels of control were obtained in the presence of one or two equivalents of diisopropylamine, 82 % e.e. (72%) and 73% e.e. (76%) respectively.[38] The metal cation appears to play an important role in determining facial selectivity; sodium and magnesium cations gave no control (<5% e.e.), whereas the larger potassium cation behaved slightly better (42% e.e.; 74%).[38] Repeating



Reagents and conditions: a) MeLi.LiBr, ether; b) **36**, -78°C; c) **36**-d_1, -78°C

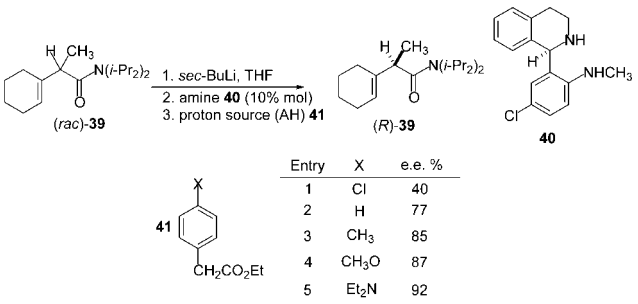
Scheme 10

the reaction with the analogous deuteriated reagent **36**-d_1 (84% D) gave the same level of facial control (87% e.e.) with high *D*-incorporation (80% D) in 95% yield (Scheme 10) indicating that *D*-transfer must occur regioselectively on carbon of the enolate.[38] There is further evidence to suggest that the stereogenicity adjacent to the nitrogen within the oxazolidinone framework (e.g., **38a**) was responsible for the facial control (Scheme 11).



Scheme 11

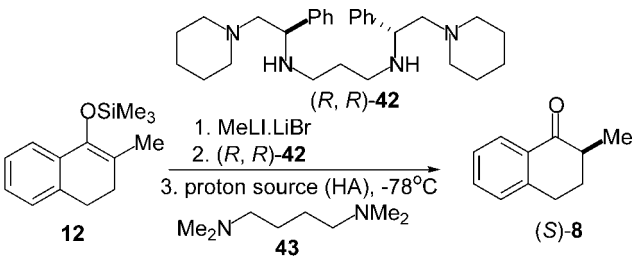
Of the numerous reports into the use of achiral carbon based acids,[35] most have been concerned with the use of stoichiometric acids within a catalytic protonation cycle.[39] Vedejs has shown that substituted ethyl phenylacetates **41** were good proton sources for very basic amide enolates (derived from (*rac*)-**39**) involving the chiral aniline **40** as the catalytic proton transfer reagent (Scheme 12). Other examples have included the use of acetic acid as the carbonyl directing proton source involving amine-based ligands.[40,41] Koga has elegantly shown



Entry	X	e.e. %
1	Cl	40
2	H	77
3	CH_3	85
4	CH_3O	87
5	Et_2N	92

Scheme 12

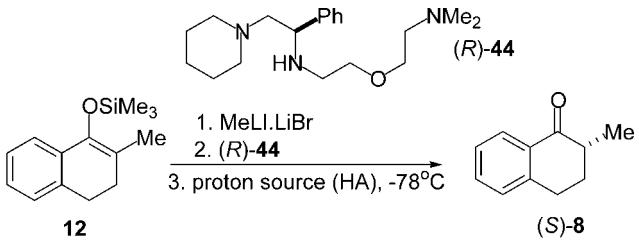
that addition of the C_2 symmetric tetra-amine ligand (*R*,*R*)-**42** to the 'base-free' enolate of 2-methyltetralone **12**, followed by the external addition of citric acid (10% solution in H_2O) gave the (*S*)-2-methyltetralone **8** in 93% e.e. in quantitative yield (Scheme 13).[40] The amount of chiral tetra-amine (*R*,*R*)-**42** could be lowered to 10 mol% (Scheme 13: entry 3–6) without a dramatic change occurring in the facial preference (76% e.e.). The control can be increased further to 89% e.e. by using an additional achiral 'chaperone' ligand **43**. The role of the 'chaperone' ligand is not entirely obvious, but it must evidently assist in the stereochemistry-determining proton transfer step. This increase in selectivity may occur due to an increase in ligand exchange, thus fitting better within the catalytic cycle, or by simply acting as an internal proton transfer reagent. Using this approach, the amount of tetramine (*R*,*R*)-**42** can be reduced further to 2.5 mol%.



Entry	(*R*, *R*)-**42**; eq.	proton source (HA)	additive	e.e. %
1	1.0	10% citric acid/H_2O	none	91
2	0.2	10% citric acid/H_2O	none	85
3	0.1	10% citric acid/H_2O	none	76
4	0.1	10% citric acid/H_2O	**43**	89
5	0.1	H_2O	**43**	86
6	0.1	acetic acid	**43**	56
7	0.05	10% citric acid/H_2O	**43**	91
8	0.025	10% citric acid/H_2O	**43**	88

Scheme 13

The use of acetic acid[41] as the achiral proton donor has previously caused problems within similar catalytic cycles due to competitive stereorandom protonation of the achiral enolate, which lowers the overall optical purity. This has partially been solved by ensuring slow addition of the achiral proton source. For example, using the amine ligand (*R*)-**44** (10 mol%) and succinimide as the proton donor (1.2 eq.) gave 2-methyltetralone (*S*)-**8** in 69% e.e. compared to 28% e.e. when using acetic acid under similar conditions.[41] Using a stoichiometric amount of ligand (*R*)-**44** with a rapid acetic acid quench appears to be better method giving (*S*)-**8** in 91% e.e. in near perfect yield (Scheme 14). The precise mechanism of proton



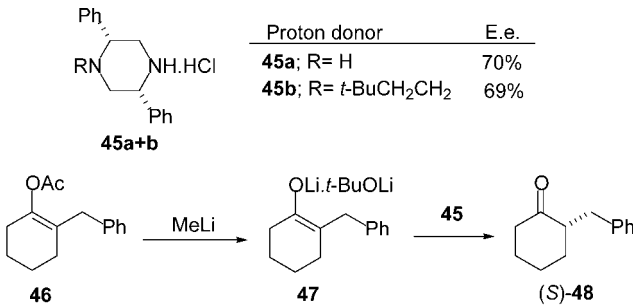
Entry	(*R*)-**44**; eq.	proton source (HA)	e.e. %
1	1.03	AcOH (1.02 eq.)	91
2	0.1	AcOH (1.2 eq.)	28
3	0.1	$Me_2NEt.HCl$	67
4	0.1	succinimide (1.2)	69
5	0.1	succinimide (10)	73
6	0.2	succinimide (10)	83
7	0.011	succinimide (2.3)	54

Scheme 14

transfer in the stereochemistry-determining step is unknown but the achiral acid may be involved directly in *C*-protonation or simply act as a proton source for the chiral ligand for internal proton return. Koga has probed this effect by treating the similar enolates with either acetic acid or MeI.[35b,42] Both reactions occur with opposite facial control and this has led to the idea that the rate-determining protonation step occurs *via* a proton transfer mechanism involving the chiral ligand. This would suggest that the selectivity was less sensitive to the nature of the acid, if rapid proton transfer from the achiral acid to the ligand occurred. This may be the case,[41,43] but is somewhat complicated by the same facial preference being observed when using acids (such as H_2O) in which kinetic ligand protonation is disfavoured.[44]

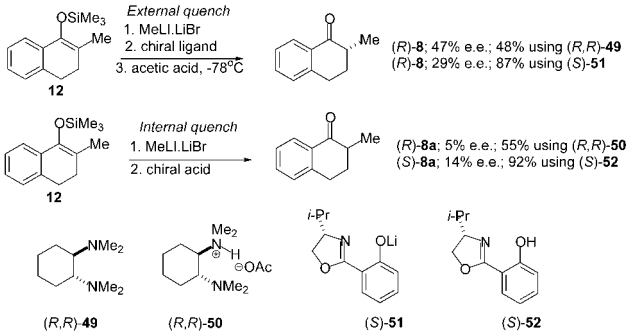
There has been a limited number of reports into the use of ammonium salts as proton donors. One notable case involves the use of a piperazium chloride **45a+b** (Scheme 15).[45] Treatment of the enolacetate **46** with an excess of MeLi gave the *t*-BuOLi.enolate complex **47**, addition of the ammonium salt donor **45a+b** gave the benzylcyclohexanone (*S*)-**48** with moderate enantiomeric excess in good yield. It was difficult to predict the active species due to the complex nature of the ammonium salt and the presence of the competitive base, *t*-BuOLi.

We have recently attempted to probe this competition between an internal and an external protonation using acetic acid as the proton source. We used the diamine (*R*,*R*)-**49**[46] and phenolate (*S*)-**51**[47] scaffold to study the protonation of 2-methyltetralone involving an external quench. The selectivities were modest; 47% e.e. using the diamine (*R*,*R*)-**49** and 29% e.e. using the phenolate (*S*)-**51**. Our attempts to probe whether protonation of the ligand and internal transfer was



Scheme 15

responsible for facial preference centred on quenching the corresponding 'base-free' enolate **13** with the internal acid derivative; the ammonium salt (*R,R*)-**50** and phenol (*S*)-**52**. In the case of the ammonium salt (*R,R*)-**50** little control was observed (5% e.e.), whereas, for the phenol (*S*)-**52** there was an apparent change in facial selectivity in favour of tetralone (*S*)-**8**; 14% e.e. (92%). From this comparison, it is evident that the protonation pathway was significantly different when using an external versus an internal protonation quench, and was clearly dependent on the ligand (Scheme 16).



Scheme 16

Concluding remarks

We have concluded that efficient *C*-protonation of an enolate is dependent on many factors including the kinetic and thermodynamic acidity, structure, solvent, additives, method of generation and the rate of proton transfer. There have been many applications involving enolate protonation as an indirect resolution strategy giving a variety of anti-inflammatory agents,[48] pheromones[49] and fragrances.[50] The gathering of more mechanistic information into the role of additives and the dynamic structure of enolates including their temperature dependence will allow the development of more general reagents and catalysts for both regio-, diastereo- and enantioselective *C*-protonation of enolates.

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