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Investigations into the enantioselective *C*-protonation of prostereogenic enolate(s) derived from *N*,*N*′-diisopropyl-2-phenylpropanamide using suicide *C*-based proton sources

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Abstract—The synthesis of enantiomerically enriched (−)-(*R*)-*N*, *N*′-diisopropyl-2-phenylpropanamide was achieved in up to 69% enantiomeric excess by symmetrisation of the corresponding racemic amide by addition of *sec*-BuLi (to give the corresponding achiral lithium enolate) and subsequent desymmetrisation by the addition of a chiral *C*-based proton source. We discuss potential factors that may be responsible for this observed enantioselectivity and comment on the role of the chiral acid.

1. Introduction

The synthesis of optical active α-substituted carbonyl compounds by enantioselective protonation of enolic species derived from racemic carbonyl derivatives such as ketones,[1] esters,[2] amides,[3] lactones[4] and carboxylic acids[5] is well documented.[6,7] Within this area, there are two main approaches, those that rely on the use of an internal proton source[6,7] (such as enantiomerically pure chiral acids)[6] and those that rely on an external proton source[6,7] (by coupling an achiral acid with a chiral Lewis base) to control facial protonation.[8] The majority of these have used heteroatomic acids, such as *O*-based carboxylic acids,[9] phenols,[10] alcohols[4a,11] and water,[12] *N*-based succinimides,[13] amides,[14] sulfonamides,[15] oxazolidinones,[16] anilines,[17] ammonium salts,[18] and amines,[19] and *S*-based thiols.[20] The success of these types of proton donors is largely due to their mild acidity[21] and efficient proton transfer.[22]

Over the last few years, we have been interested in the use of *C*-based proton donors as potential proton sources for the stereoselective *C*-protonation of enolates.[23] The use of *C*-based proton donors for enantioselective *C*-protonation of prostereogenic enolates has been limited.[24] This may be in part due to their limited availability, weakly acidic nature and intrinsically slower *carbon*-to-*carbon* proton transfer.[22] We now wish to report our study into the use of *C*-based proton donors as potential chelating proton donors for the enantioselective *C*-protonation of prostereogenic enolates. In an attempt to promote stereoselective *C*-protonation, we chose to study an unusual class of stereogenic *C*-based acids **7a**–**l** in which the carbon bearing the *pro* proton was stereogenic. To avoid problems associated with racemisation of the parent proton source, we chose to investigate the use of weakly acidic substituted esters as our potential *C*-based proton sources. To ensure efficient removal of the weakly acidic proton from these esters **7a**–**l**,[21,25] we decided to use a prostereogenic lithium enolate (*Z*)-**2**[3c] [derived from Vedejs' amide (*rac*)-**1**] as our standard substrate as this is sufficiently basic to fully deprotonate the parent acid (Scheme 1). In order to prevent in situ racemisation of the required enantiomerically enriched amide (*R*) or (*S*)-**1** by the intermediate conjugate base (derived from the chiral proton source), we needed to ensure that the conjugate base fragmented to form a less basic species.[25]

The required racemic amide (*rac*)-**1** for our study was efficiently synthesised by refluxing 2-phenylpropanoic acid (*rac*)-**3** in thionyl chloride ($SOCl_2$) to give 2-phenylpropanoyl chloride **4** in 94% yield, subsequent addition of diisopropylamine (2 equivalents) in dichloromethane gave the required amide (*rac*)-**1** in 95% yield (Scheme 2).[3c] Due to the near-identical nature of the starting amide (*rac*)-**1** and the required product, amide (*R*)- or (*S*)-**1**; we focussed on the initial symmetrisation step to

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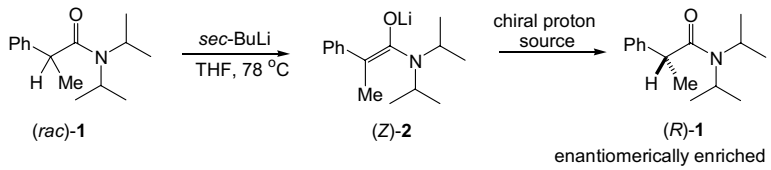
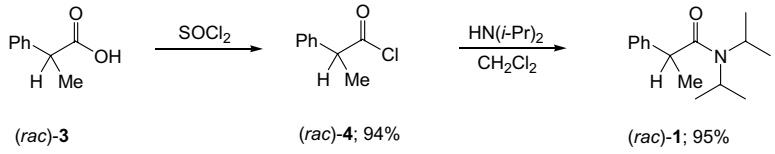


Scheme 1. Proposed synthetic route to enantiomerically enriched amide **1**.

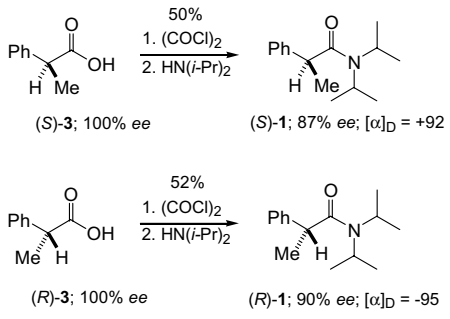


Scheme 2. Synthesis of *N*,*N*-diisopropyl-2-phenylpropanamide (*rac*)-**1**.

ensure full deprotonation of the parent amide and subsequent formation of the intermediate lithium enolate **2** (Scheme 1). Addition of an excess of *sec*-BuLi (2.5 equivalents)[3] to a stirred solution of racemic amide (*rac*)-**1** at −78 °C was required for efficient deprotonation. The resulting enolate **2** was trapped efficiently with D_2O[26] to give the required deuterium labelled amide **1**-d_1 ([D]:[H] = >98:2) in 60% yield (Scheme 3). It is interesting to note that deprotonation of the parent amide (*rac*)-**1** and subsequent formation of the enolate **2** accounts for at least 60% of the starting amide. As for the remainder, it is presumably removed by competitive nucleophilic addition of *sec*-BuLi to the carbonyl group to give the corresponding substituted *sec*-butyl ketone after aqueous work-up. This particular competitive nucleophilic pathway is very well documented.[27]

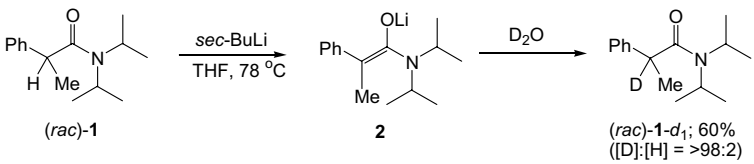
We next studied a variety of structurally related chiral proton sources **7a**–**l** for the enantioselective protonation of lithium enolate **2** to give the required enantiomerically enriched amide **1** (Scheme 1). The enantiomeric excesses were determined by analytical HPLC using a chiralcel OD column eluting with hexane:isopropanol (9:1) with a flow rate of 0.5 ml per minute. The relative configurations were determined by comparison with authentic samples of enantiomerically enriched amides (*R*)- and (*S*)-**1** (Scheme 4). These were synthesised by addition of diisopropylamine to the corresponding enantiomerically pure acid chloride **4** (formed by addition of oxalyl chloride to the parent 2-phenylpropionic acid **3**) in a non-polar solvent,[3c] such as toluene, to prevent in situ racemisation (Scheme 4).[3c]

The required esters **7a**–**l** were synthesised by deprotonation of the parent oxazolidinone **5** (with *n*-BuLi) and addition of the corresponding sulfonyl chloride **6a**–**l**

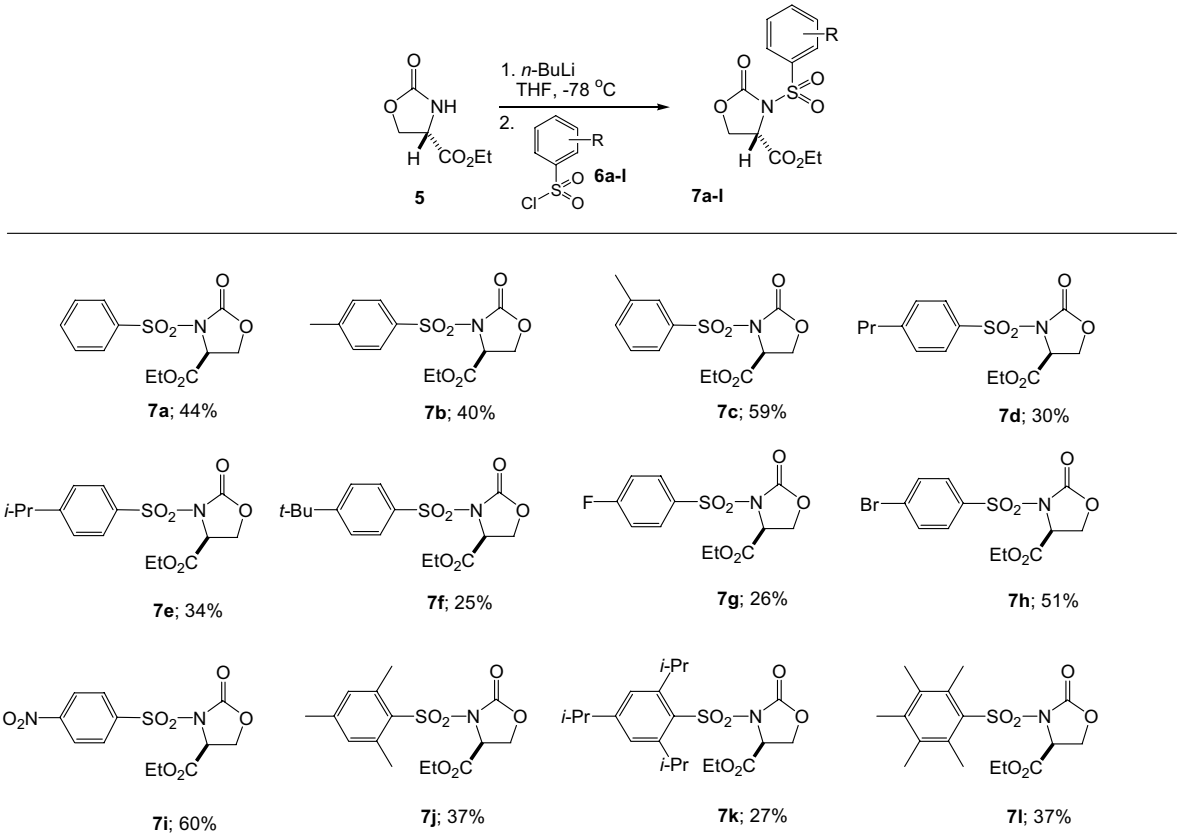


Scheme 4. Synthesis of enantiomerically enriched amide (*S*)-**1** and (*R*)-**1**.

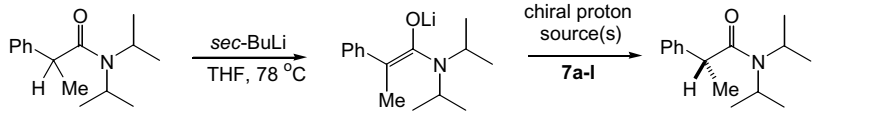
(Scheme 5). The structural and electronic nature of the sulfonamide groupings present within this skeleton **7** were found to be important with regard the stereochemical outcome of enantioselective *C*-protonation of the intermediate enolate **2**. The highest level of enantioselectivity was found to be 69% ee using the 4-isopropyl-substituted sulfonamide **7e** as the chiral proton donor (Scheme 6). For the simplest sulfonamide **7a**, moderate enantioselectivity was observed [(*R*)-45% ee]. Increasing the sterically demanding nature at *C*(4) of the aryl ring of this sulfonamide increased the levels of enantioselectivity from (*R*)-45% ee (for **7a**), to (*R*)-64% ee by addition of a methyl substituent (in **7b**), and to (*R*)-69% ee for a similarly sized isopropyl substituent (in **7e**). Whereas, for a more sterically demanding *tert*-butyl substituent (in the sulfonamide **7f**), the level of enantioselectivity was lowered to (*R*)-36% ee. By comparison, using a fluoro-substituent at *C*(4) (in **7g**) had little effect on the



Scheme 3. Synthesis of *N*,*N*-diisopropyl-2-phenylpropanamide (*rac*)-**1**-d_1.



Scheme 5. Synthesis of ester-based chiral proton sources **7a**–**l**.



Chiral proton source	Amide **1** Enantiomeric excess	Yield
7a	(*R*)-45% *e.e.*	58%
7b	(*R*)-64% *e.e.*	45%
7c	(*R*)-18% *e.e.*	38%
7d	(*R*)-47% *e.e.*	50%
7e	(*R*)-69% *e.e.*	42%
7f	(*R*)-36% *e.e.*	50%
7g	(*R*)-44% *e.e.*	42%
7h	(*R*)-4% *e.e.*	47%
7i	(*R*)-30% *e.e.*	50%
7j	(*rac*)-0% *e.e.*	31%
7k	(*S*)-20% *e.e.*	50%
7l	(*S*)-10% *e.e.*	50%

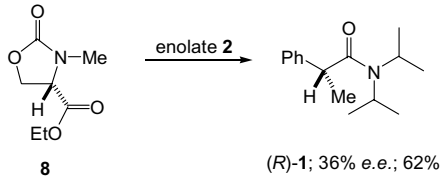
Scheme 6. Enantioselective *C*-protonation of prostereogenic lithium enolate **2**.

level of stereocontrol [(*R*)-44% ee]. In addition, a nitro group (in **7i**) behaved similarly [(*R*)-30% ee], but a slightly larger bromo-substituent (in **7h**) gave little facial control [(*R*)-4% ee]. The position of these substituents was found to be important on the levels of enantioselectivity. Positioning a methyl group at *C*(3) in **7c** only served to lower the level of enantioselectivity [(*R*)-18% ee]. In all these cases, the facial preference of protonation was the same, leading to the (*R*)-enantiomer of the amide **1**.

Whereas, increasing the sterically demanding nature of the sulfonamide group, by altering the substituent(s) at the *C*(2) position of the sulfonamide aryl ring (which are presumably positioned nearer the acidic proton of the ester) in the sulfonamides **7k** and **7l**, not only lowered the overall level of enantioselectivity, but also changed the facial preference in favour of the (*S*)-enantiomer of the amide **1**. The presence of the sulfonamide group in **7** was also found to be important; without it, the levels of enantioselectivity were found to be lower when using a related ester **8** (Scheme 7). This tentatively suggests that the sulfonamide motif in **7** binds to the lithium of the enolate (in **9**) to assist in the discrimination (on protonation) of the faces of the lithium enolate **2** (Scheme 8).

From these studies, it is evident that the subtle changes in the structural nature of the chiral proton source can cause a substantial change in level and facial selectivity of protonation. This may be due to structural subtleties within the lithium enolate aggregate prior to proton transfer. Deprotonation of these chiral proton donors (e.g., **7a**) has been shown to give the corresponding enamide **13** presumably via E1cb fragmentation[25] of the intermediate lithium enolate **10**, decarboxylation of **11** and protonation of **12** during aqueous work-up (Scheme 9).

In conclusion, we have shown that *C*-protonation of an amide-based enolate **2** using enantiomerically pure esters **7a**–**l** can occur enantioselectively to give the corresponding enantiomerically enriched amide **1** with moderate to good levels of enantiomeric excess (up to 69% ee). The structural nature of these proton donors appear to play an important role on the overall level of facial selectivity for the enantioselective protonation of the lithium enolate **2**. This overall strategy amounts to an indirect resolution for carbonyl-based substrates through symmetrisation (by deprotonation with *sec*-BuLi) followed by desymmetrisation (by enantioselective protonation). The nearest analogy to this work has been reported by Vedejs et al.[3c] He has elegantly shown that lithium enolate **2** can be enantioselectively protonated with near perfect facial control using a substituted chiral aniline, giving the required amide (*R*)-**1** with greater than 97% ee.[3c] This approach has now been extended towards the enantioselective protonation of related amide-based enolates using a substoichiometric amount of this chiral aniline in the presence of a stoichiometric amount of achiral proton donor, such as *tert*-butyl phenylacetate to give the corresponding amide with superb levels of enantioselectivity (up to 94% ee).[28] It is interesting to note, that the rate of proton transfer between the enolate and substoichiometric chiral aniline must be significantly faster than that between the corresponding enolate and the stoichiometric *C*-based acid for efficient enantioselective protonation. These results into the use of *C*-based proton donors should be of use for future design of potential chiral *C*-based proton donors and may aid mechanistic interpretation of related reactions, work towards this is currently in progress within our laboratory.

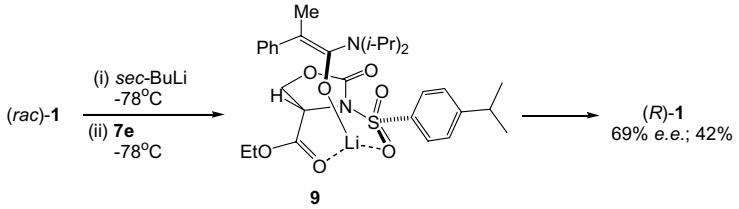


Scheme 7. Enantioselective *C*-protonation of enolate **2**.

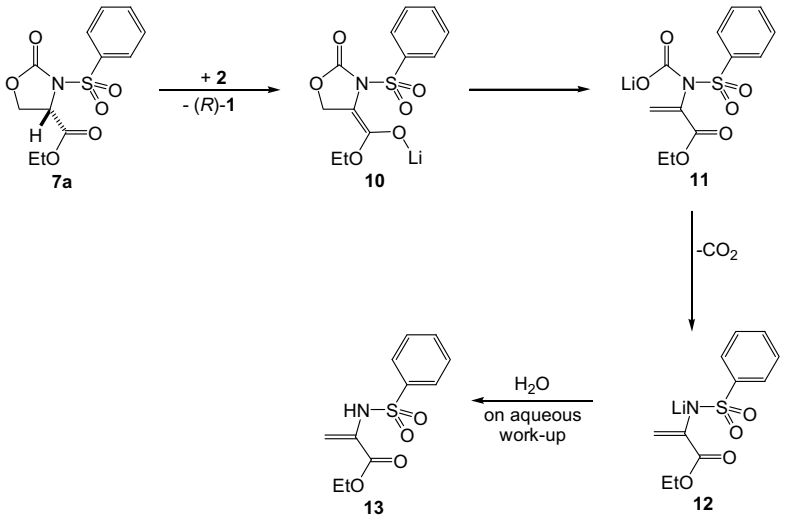
2. Representative experimental procedures

2.1. Synthesis of ethyl 3-(4-isopropylphenylsulfonyl) oxazolidinon-2-on-(4*S*)-4-carboxylate 7e

n-BuLi (2.52 ml, 2.5 M in hexanes, 6.29 mmol) was added to a solution of oxazolidin-2-one **5** (1.00 g, 6.29 mmol) in THF (10 ml) at −78 °C. The solution was stirred for 1 h. A solution of 4-isopropylphenylsulfonyl chloride (1.38 g, 6.32 mmol) in THF (10 ml) was added at −78 °C. The resulting solution was stirred for a further 3 h. Water (20 ml) was added, and the resulting solution was extracted with ether (2 × 50 ml). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with ether to give ethyl 3-(4-isopropylphenylsulfonyl) oxazolidinon-2-on-(4*S*)-4-carboxylate **7e** (0.72 g, 34%) as a white



Scheme 8. Enantioselective protonation of enolate **2** using proton donor **7e**.



Scheme 9. Fragmentation of chiral proton source **7a**.

solid; R_F (ether) 0.56; $[\alpha]_D^{22}$ − 35.2 (c = 4.2, chloroform); mp 99–101 °C; ν_{max} (film) 3057–2874 cm^{-1} (CH), 1793 cm^{-1} (C═O) and 1751 cm^{-1} (C═O); δ_H (250 MHz, $CDCl_3$) 8.03 (2H, d, J 8.5, 2 × CH; 2,6-CH; Ar), 7.41 (2H, d, J 8.5, 2 × CH; 3,5-CH; Ar), 5.03–5.00 (1H, dd, J 9.4 and 4.3, NCH), 4.59 (1H, t, J 9.4, OCH_AH_B), 4.33–4.22 (3H, m, OCH_AH_B and CH_3CH_2), 3.09–2.92 (1H, septet, J 6.9, $CH(CH_3)_2$), 1.28 (3H, t, J 7.1, CH_3) and 1.27 (6H, d, J 6.9, 2 × CH_3; *i*-Pr); δ_C (62.5 MHz, $CDCl_3$) 160.7, 148.9, 143.6, 126.9, 121.7, 119.4, 57.7, 55.2, 49.5, 26.7, 15.9 and 6.3, found MNH_4^+, 359.1273. $C_{15}H_{23}N_2O_6S$ requires 359.1271.

2.2. Desymmetrisation of amide (rac)-1 via symmetrisation with *sec*-BuLi and enantioselective *C*-protonation with ester 7e

A solution of *sec*-butyllithium (0.54 ml, 1.4 M in cyclohexanes, 0.75 mmol) was added to (*rac*)-amide **1** (0.10 g, 0.43 mmol) in THF (3 ml) at −78 °C under nitrogen. The solution was stirred for 1 h. A solution of ethyl 3-(4-isopropylphenylsulfonyl) oxazolidinon-2-on-(4*S*)-4-carboxylate **7e** (0.29 g, 0.86 mmol) in THF (2 ml) was added and the resulting solution was stirred for a further 30 min. The mixture was quenched with chlorotrimethylsilane (Me_3SiCl) (86 mg, 0.10 ml, 0.79 mmol) and stirred for 1 h. Water (10 ml) was added, and the resulting solution was extracted with ether (2 × 50 ml). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with light petroleum:ether (7:3) to give the enantiomerically enriched amide (*R*)-**1** (42 mg, 42%); 69% ee [enantiomeric excess determined using analytical hplc (CHIRALCEL OD, 25 cm × 0.46 cm I.D.), eluting with hexane/isopropanol (9:1), 0.5 ml/min]; R_F [light petroleum:ether (7:3)] 0.36; mp 39–40 °C; ν_{max} (KBr) 3057–2872 cm^{-1} (aromatic, C–H) and 1638 cm^{-1} (C═O); δ_H (250 MHz, $CDCl_3$) 7.34–7.18 (5H, m, 5 × CH; Ph), 4.10–3.95 (1H, m, NCH), 3.83–3.75 (1H, q, J 6.8, C(2)H), 3.32–3.25 (1H, m, NCH), 1.45 (3H, d, J 6.8, $C(2)HCH_3$), 1.41 (3H, d, J 6.8, CH_3), 1.38 (3H, d, J 6.7, CH_3), 1.13 (3H, d, J 6.7, CH_3) and 0.58 (3H, d, J 6.6, CH_3); δ_C (62.5 MHz, $CDCl_3$) 172.2, 143.1, 128.2, 127.2, 126.6, 48.4, 45.8, 44.9, 21.1, 20.1 and 19.2, found MH^+, 234.1861. $C_{15}H_{24}NO$ requires 233.1782.

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17. For representative examples see Refs. 3b,c,d.
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