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Asymmetric synthesis of 2-alkyl- and 2-aryl-3-aminopropionic acids (β^2-amino acids) from (*S*)-*N*-acryloyl-5,5-dimethyloxazolidin-2-one SuperQuat derivatives

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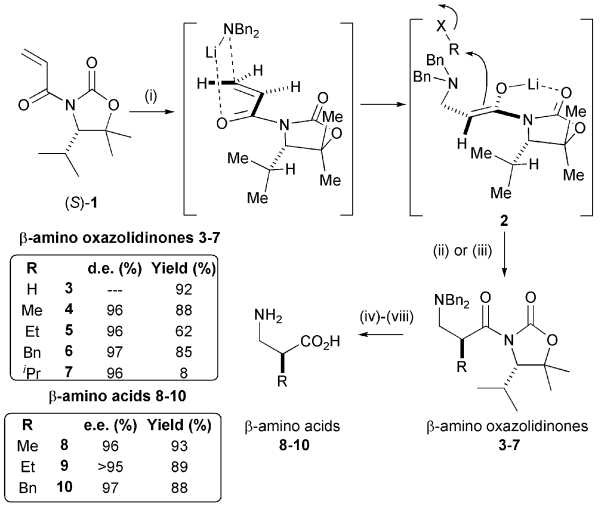
Conjugate addition of lithium amides to (*S*)-*N*-acryloyl- or (*S*)-*N*-2′-alkylacryloyloxazolidinones and alkylation or protonation of the resulting enolates with 2-pyridone respectively provides a highly stereoselective and product complementary route to a range of (*R*)- and (*S*)-2-alkyl-3-aminopropionic acids in good yield and in high ee.

α-Substituted β-amino acids (2-alkyl-3-aminopropionic acids, β^2-amino acids) occur naturally within pseudopeptides,[1] while short chain oligomers containing this motif show well-defined secondary structural characteristics.[2] A variety of asymmetric syntheses have been developed for the preparation of these desirable compounds in enantiomerically enriched form,[3] with the most popular involving the stereoselective alkylation of chiral β-alanine enolate equivalents,[4] asymmetric Mannich reactions,[5] the conjugate addition of nitrogen nucleophiles[6] or the addition of carbon nucleophiles to α-methylene β-alanine derivatives.[7] We report herein our preliminary findings concerning the conjugate addition of lithium amides to *N*-acryloyloxazolidinones, and the utility of this methodology for the asymmetric synthesis of a range of α-substituted-β-amino acid derivatives.

Although amines add in a conjugate fashion to acrylate derivatives,[8] the conjugate addition of metallated amides to acrylates is rare,[9] presumably due to facile polymerisation of the activated olefin. To test the susceptibility of *N*-acryloyloxazolidinones toward conjugate addition, lithium dibenzylamide was added to (*S*)-*N*-acryloyl-5,5-dimethyloxazolidinone **1**, giving β-alanine derivative **3** as the sole reaction product in 92% isolated yield (Scheme 1). The utility of this methodology for the asymmetric synthesis of β^2-amino acid derivatives was next studied, *via* the *in situ* elaboration of the enolate arising from conjugate addition by alkylation with an activated alkyl halide. Conjugate addition of lithium dibenzylamide to (*S*)-**1**, followed by addition of methyl iodide gave (4*S*,2′*S*)-2′-methyl **4** in 96% de and in 88% isolated yield. The generality of this conjugate addition/alkylation protocol was explored further with the use of ethyl iodide and benzyl bromide as alkylating agents, giving the (4*S*,2′*S*)-α-alkyl oxazolidinones **5** and **6** with high diastereoselectivity (>95% de) and in good yield (62–85%). Extension of this protocol to alkylation with isopropyl iodide proceeded to only low conversion (~10%), giving the α-isopropyl oxazolidinone **7** in >95% de but in only 8% isolated yield. The observed diastereoselectivity is consistent with conjugate addition of lithium dibenzylamide to oxazolidinone **1** in the *anti-s-cis* conformation,[10] with alkylation occurring preferentially upon the unhindered face of the resultant chelated *syn*-(*Z*)-enolate **2**. The (4*S*,2′*S*)-configuration within β-amino oxazolidinones **4–6** (>95% de) was confirmed by successive treatment with LiOMe, hydrogenolysis and ester hydrolysis, furnishing the known (*S*)-2-alkyl-3-aminopropanoic acids **8–10** in >95% ee after ion exchange chromatography.

An alternative conjugate addition/protonation strategy was next investigated. As a model substrate, conjugate addition of lithium dibenzylamide to α-methylacrylate oxazolidinone **11** and addition of NH_4Cl(aq) gave a 66 : 34 mixture in favour of (4*S*,2′*R*)-2′-methyloxazolidinone **14**. However, conjugate addition of lithium dibenzylamide to **11** and addition of a solution of 2-pyridone[11,12] in THF gave (4*S*,2′*R*)-**14** in >96% de and 87% isolated yield. Repetition of this protocol for **12** (R = Et) gave (4*S*,2′*R*)-**15** in 79% yield and in 94% de, confirming that this protocol proceeds with the opposite sense of stereoselectivity to the conjugate addition/alkylation strategy. This protocol was also predicted to be suitable for the incorporation of substituents (R = ^{i}Pr, Ph) incompatible with the alternative conjugate addition/alkylation strategy. Conjugate addition of lithium dibenzylamide to 2′-isopropyl-**13** and addition of 2-pyridone gave an inseparable 95 : 5 mixture of diastereoisomers with (4*S*,2′*R*)-**16** predominating (90% de), while the same procedure with 2′-phenyl-**18** gave an inseparable 88 : 12 mixture of diastereoisomers with (4*S*,2′*S*)-**19** predominating (76% de). In order to improve the diastereoselectivity in these latter two cases, the conjugate addition of homochiral lithium amides to the oxazolidinones **13** and **18** and subsequent protonation was investigated. Conjugate addition of lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide to 2′-isopropyl-**13** and addition of 2-pyridone gave a 97 : 3 mixture of diastereoisomers, giving (4*S*,2′*R*)-**17** in 85% yield (94% de). Similarly, conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide to 2′-phenyl-**18** and protonation with 2-pyridone gave a 93 : 7 mixture of diastereoisomers, with purification by chromatography enhancing the diastereoselectivity of the product, giving (4*S*,2′*S*)-**20** as a 98 : 2 mixture of diastereoisomers (96% de) in 73% yield (Scheme 2).

2-Pyridone was chosen for the protonation step in order to facilitate *C*- rather than *O*-protonation through a relay mechanism with concomitant high stereoselectivity. Binding of the pyridone carbonyl (*anti* to the stereodirecting ^{i}Pr group) to the lithium enolate derived from conjugate addition directs the regio- and facial-selectivity of *C*-protonation. The change in the sense of stereoselectivity at C(2′) observed in the aryl (R = Ph) to the alkyl (R = Me, Et, ^{i}Pr) cases presumably arises from preferential



Scheme 1 *Reagents and Conditions:* (i) lithium dibenzylamide, THF, −78 °C; (ii) NH_4Cl (aq), −78 °C to rt; (iii) RX, −78 °C to rt; (iv) LiOMe, 0 °C; (v) Pd/C, H_2 (1 atm), MeOH, rt; (vi) LiOH, THF, H_2O, Δ; (vii) HCl (aq); (viii) Dowex 50W-X8.

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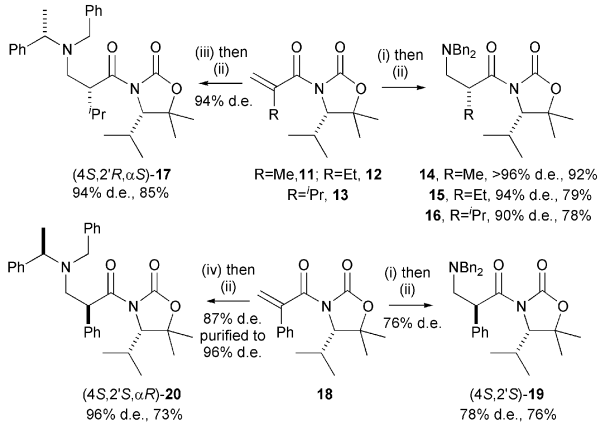

Scheme 2 *Reagents and Conditions*: (i) lithium dibenzylamide, THF, −78 °C; (ii) 2-pyridone, THF, −78 °C to rt; (iii) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide, THF, −78 °C; (iv) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide, THF, −78 °C.

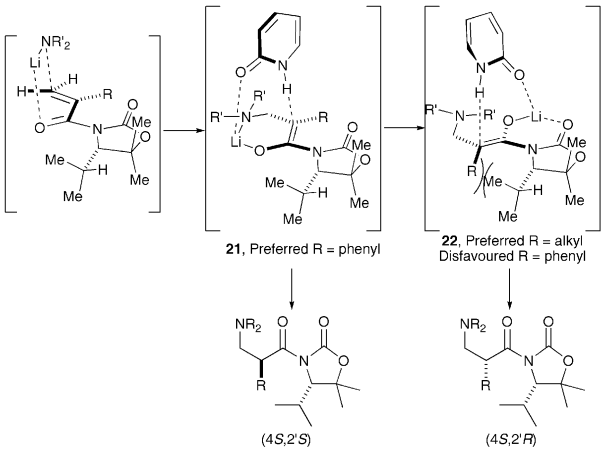

Fig. 1 Model for stereoselective protonation with 2-pyridone.

protonation from either the *anti*-conformer **21** (giving rise to 2′*S*) or the chelated (C=O to OLi) *syn*-conformer **22** (giving rise to 2′*R*). In the alkyl series, the *syn*-conformer **22** is preferred, leading to the (2′*R*)-configuration upon protonation, while with the 2′-phenyloxazolidinone, the *syn*-conformer is precluded due to steric interactions between the oxazolidinone and the C(2′)-aryl ring, and protonation from the *anti*-conformer **21** is preferred (Fig. 1). Furthermore, the configuration of the *N*-α-methylbenzyl stereocentre also has a beneficial effect upon the observed stereoselectivity of the reaction.

With β-amino oxazolidinones **15**, **16** and **20** in hand (94%, 90% and 96% de respectively), their deprotection to the corresponding β-amino acid was investigated. Deprotection was readily achieved *via* standard procedures to give the known (*R*)-2-ethyl- and (*R*)-2-isopropyl-3-aminopropanoic acids **9** and **21** and (*S*)-2-phenyl-3-aminopropanoic acid **22** in high yield and in 94%, 88% and >95% ee respectively after ion exchange chromatography (Scheme 3).

In conclusion, conjugate addition of lithium amides to (*S*)-*N*-acryloyloxazolidinone **1** and alkylation with alkyl halides, or addition to (*S*)-*N*-2-alkylacryloyloxazolidinones **11–13** and stereoselective protonation with 2-pyridone allows the asymmetric synthesis of a range of β[2] amino acids in high ee.

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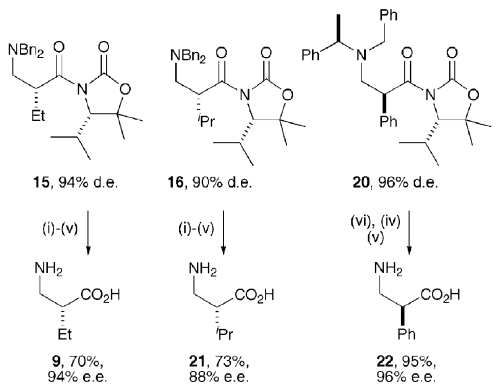

Scheme 3 *Reagents and Conditions*: (i) LiOMe, 0 °C; (ii) H_2 (1 atm), Pd/C, MeOH, AcOH, H_2O, rt, 24 h; (iii) LiOH, THF, H_2O, rt, 15 h; (iv) HCl (aq); (v) Dowex 50W-X8; (vi) LiOH, THF, H_2O, H_2O_2, rt, 24 h.

Notes and references

1 For instance (*R*)-3-amino-2-methylpropanoic acid is a component of the cryptophycins, potent tumour selective cytoxins associated with terrestrial blue algae *Nostoc* sp.: G. Trimurtulu, I. Ohtani, G. M. L. Patterson, R. E. Moore, T. H. Corbett, F. A. Valeriote and L. Demchik, *J. Am. Chem. Soc.*, 1994, **116**, 4729.

2 For reviews see: D. Seebach and J. L. Matthews, *Chem. Commun.*, 1997, 2015; S. H. Gellman, *Acc. Chem. Res.*, 1998, **31**, 173; D. Seebach, M. Overhand, F. N. M. Kühnle, B. Martinoni, L. Oberer, U. Hommel and H. Widmer, *Helv. Chim. Acta*, 1996, **79**, 913; D. Seebach, S. Abele, K. Gademann and B. Jaun, *Angew. Chem., Int. Ed. Engl.*, 1994, **38**, 1595.

3 H. M. L. Davies and C. Venkataramani, *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 2197; P. Micuh and D. Seebach, *Helv. Chim. Acta*, 2002, **85**, 1567; A. Duursma, A. J. Minnaard and B. L. Feringa, *J. Am. Chem. Soc.*, 2003, **125**, 3700; G. M. Sammis and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2003, **125**, 4442; J. Hübner, J. Liebscher and M. Pätzel, *Tetrahedron*, 2002, **58**, 10485; J. F. Bower, R. Jumnah, A. C. Williams and J. M. J. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1411; A. Kubo, H. Kubota, M. Takahashi and K. Nunami, *J. Org. Chem.*, 1997, **62**, 5830.

4 M. Sibi and P. K. Deshpande, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1461; D. Seebach, A. Boog and W. Bernd Schweizer, *Eur. J. Org. Chem.*, 1999, 335; R. Ponsinet, G. Chassaing, J. Vaissermann and S. Lavielle, *Eur. J. Org. Chem.*, 2000, 83; G. Nagula, V. J. Huber, C. Lum and B. A. Goodman, *Org. Lett.*, 2000, **2**, 3527; O. Muñoz-Muñiz and E. Juristi, *Tetrahedron*, 2003, **59**, 4223; V. M. Gutiérrez-García, H. López-Ruiz, G. Reyes-Rangel and E. Juaristi, *Tetrahedron*, 2001, **57**, 6487; C. Agami, S. Cheramy and L. Duchoux, *Synlett.*, 1999, **11**, 1838.

5 D. A. Evans, F. Urpi, T. C. Somers, J. S. Clark and M. T. Bilodeau, *J. Am. Chem. Soc.*, 1990, **112**, 8215; E. Arvanitis, H. Ernst, A. A. Ludwig, A. J. Robinson and P. B. Wyatt, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1461; T. Hintermann and D. Seebach, *Helv. Chim. Acta*, 1998, **81**, 2093; D. Seebach, L. Schaeffer, F. Gessier, P. Bindschädler, C. Jäger, D. Josien, S. Kopp, G. Lelais, Y. R. Mahajan, P. Micuch, R. Sebasta and B. W. Schweizer, *Helv. Chim. Acta*, 2003, **86**, 1852.

6 H.-S. Lee, J.-S. Park, B. M. Kim and S. H. Gellman, *J. Org. Chem.*, 2003, **68**, 1575.

7 I. T. Barnish, M. Corless, P. J. Dunn, D. Ellis, P. W. Finn, J. D. Hardstone and K. James, *Tetrahedon Lett.*, 1993, **34**, 1323.

8 For examples see: S. Berlin and L. Engman, *Tetrahedron Lett.*, 2000, **41**, 3701; G. Cardillo, L. Gentilucci, I. R. Bastardas and A. Tolomelli, *Tetrahedron*, 1998, **54**, 8217; L. Wessjohn, G. McGaffin and A. de Meijere, *Synthesis*, 1989, 359; S. Kwiatkowski, A. Jeganathan, T. Tobin and D. S. Watt, *Synthesis*, 1989, 946.

9 For literature examples see (*a*) using a lithium amide: S. G. Davies, I. M. Dordor-Hedgecock, K. H. Sutton and J. C. Walker, *Tetrahedron Lett.*, 1986, **27**, 3787; (*b*) using a titanium amide: A. Hosomi, T. Yanagi and M. Hojo, *Tetrahedron Lett.*, 1991, **32**, 2371.

10 Lithium *N*-benzyl-*N*-α-methylbenzylamide adds to α,β-unsaturated *N*-acyloxazolidinones in the *anti-s-cis* conformation: S. G. Davies, G. Hermann, A. D. Smith and M. J. Sweet, *Chem. Commun.*, 2004, 1128.

11 Kuzuya *et al.* have shown that 2-pyridone effects a rate enhancement upon mutarotation of glucose, thought to be due to its ability to act as both a base and an acid simultaneously: M. Kuzuya, A. Noguchi and T. Okuda, *Bull. Chem. Soc. Jpn*, 1984, **57**, 3461.

12 Amide and carbamate proton sources have been used widely in the literature; for selected examples see: K. Tomioka and H. Fujihara, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2377; D. R. Carbery and T. J. Donohoe, *Chem. Commun.*, 2004, 722.