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Parallel Kinetic Resolution of Acyclic γ-Amino-α,β-unsaturated Esters: Application to the Asymmetric Synthesis of 4-Aminopyrrolidin-2-ones

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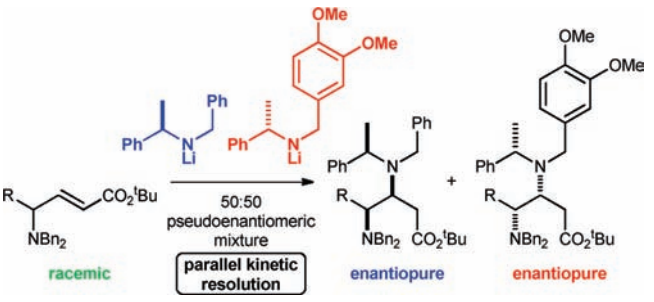
ABSTRACT



Conjugate addition of a 50:50 pseudoenantiomeric mixture of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide and lithium (*S*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide to a range of racemic acyclic γ-amino-α,β-unsaturated esters (derived from the corresponding α-amino acids) effects their efficient parallel kinetic resolution, allowing the preparation of enantiopure β,γ-diamino esters. The β,γ-diamino ester products of these reactions are readily converted into the corresponding substituted 4-aminopyrrolidin-2-ones via *N*-debenzylation and cyclization.

Kinetic resolution is a venerable concept within organic chemistry. It was first observed by Marckwald and McKenzie in 1899, during the esterification of racemic mandelic acid with (−)-menthol.[1] Such is the importance of kinetic resolution that over 100 years later it, together with dynamic kinetic resolution (DKR)[2] and parallel kinetic resolution (PKR),[3] is employed widely in the preparation of enantiomerically pure materials on both laboratory and industrial scales. We have previously developed the PKR of a range of chiral 3- and 5-substituted cyclopent-1-enecarboxylates, and 6-substituted cyclohex-1-enecarboxylates using a 50:50 pseudoenantiomeric mixture of enantiopure lithium amides.[4] This protocol has thus far been limited to these cyclic α,β-unsaturated esters due to the requirement for high levels of substrate control. In this manuscript we report the efficient PKR of racemic acyclic *N*-protected γ-amino-α,β-unsaturated esters (which exhibit very high levels of substrate control) using a 50:50 pseudoenantiomeric mixture of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide and lithium (*S*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide. The enantiopure

(1) Marckwald, W.; McKenzie, A. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 2130.

(2) Pellissier, H. *Tetrahedron* **2003**, *59*, 8291. Pellissier, H. *Tetrahedron* **2008**, *64*, 1563.

(3) Eames, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 885. Dehli, J. R.; Gotor, V. *Chem. Soc. Rev.* **2002**, *31*, 365.

(4) Davies, S. G.; Díez, D.; El Hammouni, M. M.; Garner, A. C.; Garrido, N. M.; Long, M. J. C.; Morrison, R. M.; Smith, A. D.; Sweet, M. J.; Withey, J. M. *Chem. Commun.* **2003**, 2410. Davies, S. G.; Garner, A. C.; Long, M. J. C.; Smith, A. D.; Sweet, M. J.; Withey, J. M. *Org. Biomol. Chem.* **2004**, *2*, 3355. Davies, S. G.; Garner, A. C.; Long, M. J. C.; Morrison, R. M.; Roberts, P. M.; Savory, E. D.; Smith, A. D.; Sweet, M. J.; Withey, J. M. *Org. Biomol. Chem.* **2005**, *3*, 2762. Aye, Y.; Davies, S. G.; Garner, A. C.; Roberts, P. M.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 2195. Abraham, E.; Davies, S. G.; Docherty, A. J.; Ling, K. B.; Roberts, P. M.; Russell, A. J.; Thomson, J. E.; Toms, S. M. *Tetrahedron: Asymmetry* **2008**, *19*, 1356. Davies, S. G.; Durbin, M. J.; Hartman, S. J. S.; Matsuno, A.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Toms, S. M. *Tetrahedron: Asymmetry* **2008**, *19*, 2870.

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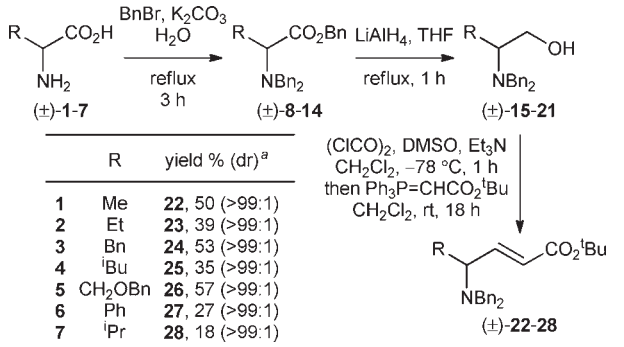
β,γ-diamino ester products of these reactions are valuable building blocks for further elaboration, as demonstrated by their facile conversion to the corresponding substituted 4-aminopyrrolidin-2-ones.

A range of racemic acyclic *N*-protected γ-amino-α,β-unsaturated esters was prepared from the corresponding racemic α-amino acids (±)-**1**−**7** using a modification of the procedure reported by Reetz and co-workers.[5] Exhaustive benzylation of (±)-**1**−**7** was achieved upon treatment with BnBr in boiling aq K_2CO_3 to give (±)-**8**−**14** and was followed by reduction with $LiAlH_4$ to give the corresponding *N*,*N*-dibenzyl protected α-amino alcohols (±)-**15**−**21**. Swern oxidation of α-amino alcohols (±)-**15**−**21** and olefination of the resultant aldehydes then gave the desired α,β-unsaturated esters (±)-**22**−**28** in 18−57% overall yield (Scheme 1).

Scheme 1



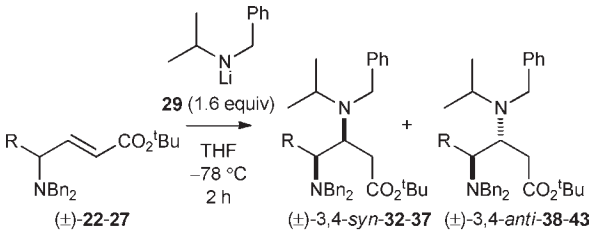
	R	yield % (dr)[a]
1	Me	**22**, 50 (>99:1)
2	Et	**23**, 39 (>99:1)
3	Bn	**24**, 53 (>99:1)
4	^{i}Bu	**25**, 35 (>99:1)
5	CH_2OBn	**26**, 57 (>99:1)
6	Ph	**27**, 27 (>99:1)
7	^{i}Pr	**28**, 18 (>99:1)

[a] Yield over 4 steps.

When investigating PKR,[4] we have promulgated that it is prudent to follow a strategy of first investigating the levels of substrate control offered by the chiral α,β-unsaturated ester upon conjugate addition of an achiral lithium amide, viz. lithium *N*-benzyl-*N*-isopropylamide **29**. The levels of enantiorecognition between the chiral α,β-unsaturated ester (substrate) and lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **30** (chiral reagent) are then evaluated by investigation of their mutual kinetic resolution (MKR), i.e., addition of racemic lithium amide (±)-**30** to racemic α,β-unsaturated ester. This approach eliminates any complicating effects of mass action and allows the maximum levels of enantiodiscrimination (as quantified by the factor, E)[6] to be very simply determined by analysis of the product distribution by ^{1}H NMR spectroscopy. Finally, having identified those substrates that undergo efficient MKR upon addition of racemic lithium amide (±)-**30**, their PKR employing a 50:50 pseudoenantiomeric mixture of enantiopure lithium *N*-benzyl-*N*-(α-methylbenzyl) amide **30** and enantiopure lithium *N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide **31** may be performed. We therefore adopted this approach to investigate the potential of racemic γ-amino-α,β-unsaturated esters (±)-**22**−**28** as substrates for our PKR protocol.

Addition of 1.6 equiv of lithium amide **29** to (±)-**22**−**26** resulted in >95% conversion to the corresponding β,γ-diamino esters (±)-**32**−**36** (≥88:12 dr in all cases), indicating high levels of substrate control. Chromatographic purification allowed isolation of β,γ-diamino esters (±)-**32**−**36** in 60−86% yield and in ≥97:3 dr (Scheme 2). The relative 3,4-*syn*-configuration within (±)-**34** (R = Bn) was unambiguously established by single crystal X-ray diffraction analysis of the corresponding hydrochloride salt (±)-**34**•HCl. The relative 3,4-*syn*-configurations within (±)-**32**, (±)-**33**, (±)-**35**, and (±)-**36** were assigned by analogy.[7] Meanwhile, (±)-**28** proved recalcitrant to addition of lithium amide **29**, even over extended reaction times and when the amount of lithium amide was increased from 1.6 to 10 equiv. Addition to (±)-**27** proceeded with low levels of substrate control to give a 27:73 mixture of 3,4-*syn*-**37**:3,4-*anti*-**43**, which were isolated in 15 and 48% yield as single diastereoisomers (>99:1 dr). The relative 3,4-*anti*-configuration within **43** was unambiguously established by single crystal X-ray diffraction analysis, which therefore allowed the relative 3,4-*syn*-configuration within **37** to be assigned unambiguously (Scheme 2).

Scheme 2



	R	3,4-*syn*:3,4-*anti* ratio	(±)-3,4-*syn* yield % (dr)	(±)-3,4-*anti* yield % (dr)
22	Me	**32**:**38** >99:1	**32**, 86 (>99:1)	-
23	Et	**33**:**39** 94:6	**33**, 67 (>99:1)	-
24	Bn	**34**:**40** 97:3	**34**, 78 (97:3)	-
25	^{i}Bu	**35**:**41** 98:2	**35**, 72 (98:2)	-
26	CH_2OBn	**36**:**42** 88:12	**36**, 60 (>99:1)	**42**, 5 (>99:1)[a]
27	Ph	**37**:**43** 27:73	**37**, 15 (>99:1)	**43**, 48 (>99:1)
28	^{i}Pr	<5% conversion	-	-

[a] 17% of a 68:32 mixture of **36**:**42** was also isolated.

Previous investigations concerning conjugate addition of a range of nucleophiles to α,β-unsaturated carbonyl compounds with a stereocenter at the γ-position often invoke a modified Felkin−Anh model to rationalize the

(5) Reetz, M. T.; Röhrig, D. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1706.

(6) Horeau, A. *Tetrahedron* **1975**, *31*, 1307.

(7) Comparison with the substrate control elicited in the MKR of (±)-**22**−**26** with lithium amide (±)-**30**, as well as in the PKR of (±)-**22**−**26** with lithium amides (*R*)-**30** and (*S*)-**31**, allows these configurational assignments to be made confidently. In addition, the relative configurations within β,γ-diamino esters (±)-**36** and (±)-**42** [and (3*S*,4*R*,α*R*)-**48**] were subsequently unambiguously established by single crystal X-ray diffraction analysis of a cyclic derivative; see the Supporting Information for full experimental details.

(8) Yamamoto, Y.; Chounan, Y.; Nishii, S.; Ibuka, T.; Kitahara, H. *J. Am. Chem. Soc.* **1992**, *114*, 7652. Kireev, A. S.; Manpadi, M.; Kornienko, A. *J. Org. Chem.* **2006**, *71*, 2630.

observed diastereoselectivity.[8] However, one other simplistic model (not dissimilar to a Felkin–Anh model) which is able to rationalize successfully the experimental data in this case uses insight obtained from single crystal X-ray diffraction analysis of α,β-unsaturated ester (±)-**22**. This revealed a solid state conformation in which the C(4)-hydrogen atom lies almost perpendicular to the plane of the α,β-unsaturated system, with the bulky C(4)-*N*,*N*-dibenzylamino substituent occupying the less hindered "outside" position and the C(4)-methyl group in the more hindered "inside" position (Figure 1). Conjugate addition of lithium amide **29** to (±)-**22** in this conformation would be predicted to occur on the least hindered face past the "small" hydrogen substituent to give (±)-3,4-*syn*-**32**, as observed experimentally. A similar analysis applied to α,β-unsaturated esters (±)-**23**–**26** (R = Et, Bn, ^{i}Bu, CH_2OBn) would also successfully rationalize the observed substrate diastereofacial control, leading to (±)-3,4-*syn*-**33**–**36**. However, increased steric bulk of the C(4)-substituents in α,β-unsaturated esters (±)-**27** and (±)-**28** would serve to disfavor analogous conformations, thereby providing a rationale for their differing behavior. Presumably, the very large steric congestion around C(4) in the case of (±)-**28** (R = ^{i}Pr) precludes addition of the sterically demanding lithium amide to C(3) completely.

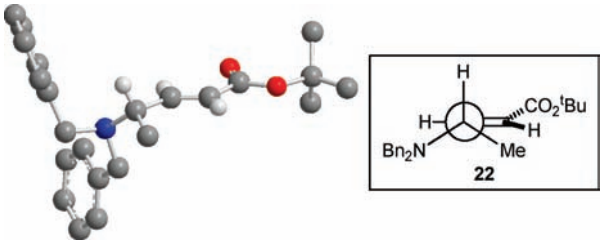
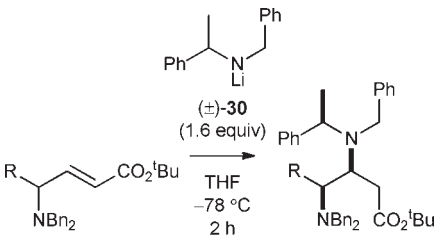


Figure 1. Chem 3D representation of the single crystal X-ray diffraction structure of (±)-**22** [(*S*)-enantiomer depicted; selected H atoms are omitted for clarity], and Newman projection along the C(3)–C(4) bond.

The extent of enantiorecognition between α,β-unsaturated esters (±)-**22**–**26** (which offered high levels of substrate control) and lithium amide (±)-**30** was next investigated, with high levels of enantiorecognition being expected. Indeed, addition of 1.6 equiv of lithium amide (±)-**30** to (±)-**22**–**26** gave, in each case, essentially a single diastereoisomeric product **44**–**48** in ≥95:5 dr, indicating very high levels of enantiorecognition between substrate and reagent, and consistent with $E \geq 19$[6] in each case. Purification facilitated isolation of diastereoisomerically pure (>99:1 dr) samples of (±)-**44**–**48**. The relative (3*RS*,4*RS*,α*SR*)-configurations within (±)-**45** and (±)-**47** were unambiguously established by single crystal X-ray diffraction analyses, and therefore the relative configurations within (±)-**44**, (±)-**46**, and (±)-**48** were assigned by analogy. It is notable that the relative configurations of the C(3)- and C(α)-stereogenic centers within both (±)-**45** and

Scheme 3



	R	product ratio	E	yield % (dr)
22	Me	>99:1	>99	**44**, 83 (>99:1)
23	Et	95:5	19	**45**, 70 (>99:1)
24	Bn	96:4	24	**46**, 13 (>99:1)[a]
25	^{i}Bu	99:1	99	**47**, 77 (>99:1)
26	CH_2OBn	>99:1	>99	**48**, 75 (>99:1)

[a] 70% of a sample of **46** in 95:5 dr was also isolated.

(±)-**47** [and, hence, (±)-**44**, (±)-**46**, and (±)-**48**] are in accordance with that predicted by the transition state mnemonic developed by us to rationalize the exceptional facial bias of this class of lithium amide.[9] This reagent control, when combined with that of the α,β-unsaturated ester (substrate control: production of the 3,4-*syn*-diastereoisomer favored), results in very highly selective reactions. These results suggest that α,β-unsaturated esters (±)-**22**–**26** are viable substrates for our PKR protocol[4] (Scheme 3).

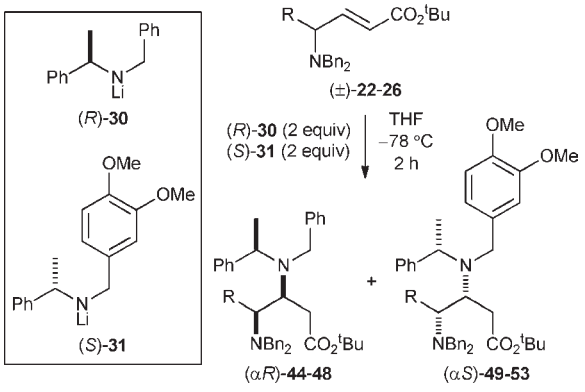
The PKR of α,β-unsaturated esters (±)-**22**–**26** using a 50:50 pseudoenantiomeric mixture of lithium amides (*R*)-**30** (2 equiv) and (*S*)-**31** (2 equiv) was next investigated. These reactions produced, in each case, a 50:50 mixture of the corresponding (α*R*)-adducts **44**–**48** in ≥95:5 dr and the (α*S*)-adducts **49**–**53** in ≥95:5 dr. Facile separation and purification via flash column chromatography allowed isolation of (α*R*)-**44**–**48** in >99:1 dr and 31–42% yield and (α*S*)-**49**–**53** in >99:1 dr and 40–43% yield. In each case, the product of addition of lithium amide (*R*)-**30** was spectroscopically identical to the major diastereoisomer formed in the corresponding MKR reaction. Additionally, the relative configuration within β,γ-diamino ester **49** was unambiguously established via single crystal X-ray diffraction analysis, with the absolute (3*R*,4*R*,α*S*)-configuration being assigned from the known (*S*)-configuration of the α-methylbenzyl stereocenter. Given the pseudoenantiomeric nature of lithium amides (*R*)-**30** and (*S*)-**31**, this analysis

(9) Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1999. For a review, see: Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833.

(10) Hoang, C. T.; Bouillère, F.; Johannesen, S.; Zulauf, A.; Panel, C.; Pouilhès, A.; Gori, D.; Alezra, V.; Kouklovsky, C. *J. Org. Chem.* **2009**, *74*, 4177.

(11) In the case of β,γ-diamino ester **48**, the yield of the corresponding 4-aminopyrrolidin-2-one **68** (60% isolated yield) was somewhat compromised by the formation of methyl (3*S*,4*R*)-3,4-diacetamido-5-hydroxypentanoate **69** (25% isolated yield). This presumably arises from competing lactone formation (rather than lactam formation) from **58** under the reaction conditions, followed by methanolysis upon workup of the acetylation procedure.

Scheme 4

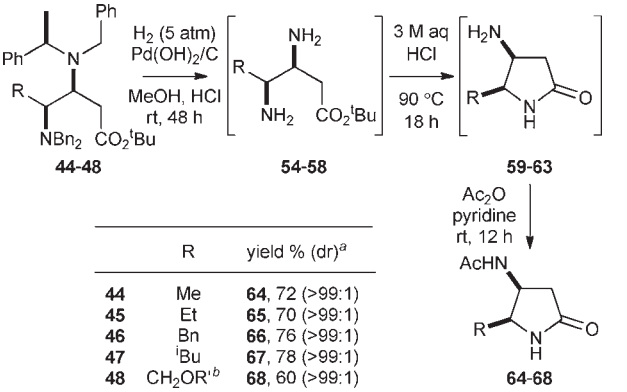


	R	(αR) product ratio	(αS) product ratio	(αR) product yield % (dr)	(αS) product yield % (dr)
22	Me	**44**, >99:1	**49**, >99:1	**44**, 40 (>99:1)	**49**, 43 (>99:1)
23	Et	**45**, 95:5	**50**, 95:5	**45**, 31 (>99:1)	**50**, 40 (>99:1)
24	Bn	**46**, 96:4	**51**, 96:4	**46**, 42 (>99:1)	**51**, 43 (>99:1)
25	^{i}Bu	**47**, 98:2	**52**, >99:1	**47**, 39 (>99:1)	**52**, 43 (>99:1)
26	CH_2OBn	**48**, >99:1	**53**, >99:1	**48**, 37 (>99:1)	**53**, 40 (>99:1)

also allows the assigned relative (3*RS*,4*RS*,α*SR*)-configuration within racemic **44** to be unambiguously confirmed, with the absolute (3*S*,4*S*,α*R*)-configuration within enantiopure **44** following from the known (*R*)-configuration of the α-methylbenzyl stereocenter. By similar reasoning, given the known relative configurations within racemic **45** and **47**, the absolute (3*S*,4*S*,α*R*)-configurations within enantiopure **45** and **47** may be assigned from the known (*R*)-configuration of the α-methylbenzyl stereocenter. Hence, the absolute (3*R*,4*R*,α*S*)-configurations within **50** and **52** can be unambiguously assigned. The absolute (3*R*,4*R*,α*S*)-configurations within **51** and **53** were assigned by analogy (Scheme 4).

With a range of enantiopure *β*,*γ*-diamino esters in hand, their synthetic utility was demonstrated by elaboration of **44**–**48** to the corresponding 5-substituted 4-aminopyrrolidin-2-ones. Hydrogenolytic *N*-debenzylation of **44**–**48** was followed by acid-promoted cyclization[10] to the corresponding 4-aminopyrrolidin-2-ones **59**–**63**, which were isolated as their acetate derivatives **64**–**68** in 60–78% yield over three steps.[11] The absolute configurations within **64**–**68** were assigned from the known absolute

Scheme 5



	R	yield % (dr)[a]
44	Me	**64**, 72 (>99:1)
45	Et	**65**, 70 (>99:1)
46	Bn	**66**, 76 (>99:1)
47	^{i}Bu	**67**, 78 (>99:1)
48	CH_2OR'[b]	**68**, 60 (>99:1)

[a] Yield over 3 steps. [b] For **48**, R′ = Bn; for **58** and **63**, R′ = H; for **68**, R′ = Ac.

configurations of the precursor *β*,*γ*-diamino esters **44**–**48**; ^{1}H NMR NOE analyses of **64**–**68** were also supportive of a relative 4,5-*syn*-configuration (Scheme 5).

In conclusion, conjugate addition of a 50:50 pseudoenantiomeric mixture of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide and lithium (*S*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide to a range of racemic acyclic *γ*-amino-α,*β*-unsaturated esters (derived from the corresponding α-amino acids) effects their efficient parallel kinetic resolution, allowing the preparation of enantiopure *β*,*γ*-diamino esters. The *β*,*γ*-diamino ester products of these reactions are readily converted into the corresponding substituted 4-aminopyrrolidin-2-ones via *N*-debenzylation and cyclization. Further applications of this methodology are currently under investigation within our laboratory.

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Supporting Information Available. Experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra, and crystallographic information files (for structures CCDC 852571–852577). This material is available free of charge via the Internet at http://pubs.acs.org.