

Telescoped Synthesis of Stereodefined Pyrrolidines

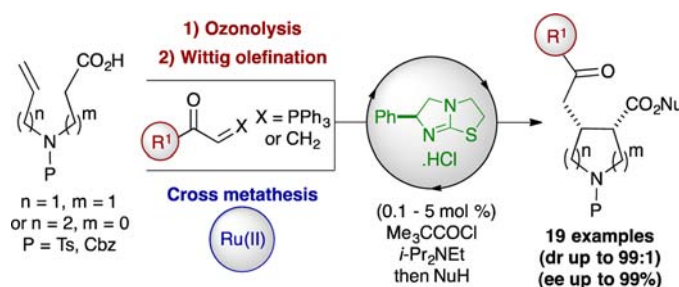
Dorine Belmessieri, David B. Cordes,[†] Alexandra M. Z. Slawin,[†] and Andrew D. Smith*

*EaStCHEM, School of Chemistry, University of St. Andrews, North Haugh,
St. Andrews KY16 9ST, U.K.*

ads10@st-andrews.ac.uk

Received June 4, 2013

ABSTRACT



Telescoped and one-pot olefination/asymmetric functionalization approaches to disubstituted pyrrolidines (dr up to 99:1, up to 99% ee) have been developed using commercially available tetramisole (0.1 to 5 mol %). Using OTMS-quinidine as the Lewis base gives preferential access to an *anti*-configured pyrrolidine in high enantioselectivity.

The pyrrolidine motif is a valuable heterocyclic framework present within a variety of natural products,¹ as well as bioactive and pharmaceutically relevant species.² This remarkably versatile scaffold has also been employed as a chiral auxiliary,³ a chiral ligand,⁴ and an organocatalyst⁵ for a range of asymmetric transformations. The

wide-reaching applications of this five-membered heterocycle have inspired many novel strategies toward its asymmetric synthesis,⁶ with a range of organocatalytic strategies having been developed.⁷ It is widely recognized that a synthetic methodology leading rapidly to structural complexity from readily available starting materials through telescoped or one-pot reaction sequences is highly desirable, with the minimal manual operations involved in these processes saving time, effort, and cost. Isothioureas,⁸ initially used as acylation catalysts by Birman and Okamoto,⁹ have proven useful organocatalysts for a range of asymmetric processes.¹⁰ Recent work by ourselves and Romo has utilized isothioureas to promote the catalytic asymmetric Michael addition– and aldol–lactonization (NCAL) of a number of enone–acids and keto–acids,

[†] These authors contributed crystallographic determination
(1) (a) Lewis, J. R. *Nat. Prod. Rep.* **2001**, *18*, 95–128. (b) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435–446.

(2) (a) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748–8758. (b) Fish, P. V.; Andrews, M. D.; Fray, M. J.; Stobie, A.; Wakenhut, F.; Whitlock, G. A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2829–2834. (c) Lexa, K. W.; Carlson, H. A. *Proteins* **2011**, *79*, 2282–2290.

(3) For examples, see: (a) Whitesell, J. K. *Chem. Rev.* **1989**, 1581–1590. (b) Klatt, M.; Enders, D. *Synthesis* **1996**, 1403–1418. (c) Kim, B. H.; Lee, H. B.; Hwang, J. K.; Kim, Y. G. *Tetrahedron: Asymmetry* **2005**, *16*, 1215–1220.

(4) (a) Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159–2232. (b) Caputo, C. A.; Jones, N. D. *Dalton T.* **2007**, 4627–4640.

(5) For selected reviews, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175. (c) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724.

(6) For relevant reviews, see: (a) Moyano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703–4832. (b) Pellissier, H. *Adv. Synth. Catal.* **2012**, *354*, 237–294. For examples, see: (c) Sakaguchi, H.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2007**, *9*, 1635–1638. (d) Kawabata, T.; Majumdar, S.; Tsubaki, K.; Monguchi, D. *Org. Biomol. Chem.* **2005**, *3*, 1609–1611. (e) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron* **1999**, *55*, 261–270. (f) Hirai, Y.; Terada, T.; Yamazaki, T.; Momose, T. *J. Chem. Soc., Perkin. Trans. 1* **1992**, 509–516.

(7) For selected methods, see: (a) Enders, D.; Göddertz, D. P.; Beceno, C.; Raabe, G. *Adv. Synth. Catal.* **2010**, *352*, 2863–2868. (b) Chen, X.-H.; Zhang, W.-Q.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 5652–5653. (c) Lin, S.; Deiana, L.; Zhao, G.-L.; Sun, J.; Córdova, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 7624–7630. (d) Jui, N. T.; Garber, J. A. O.; Finelli, F. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 11400–11403.

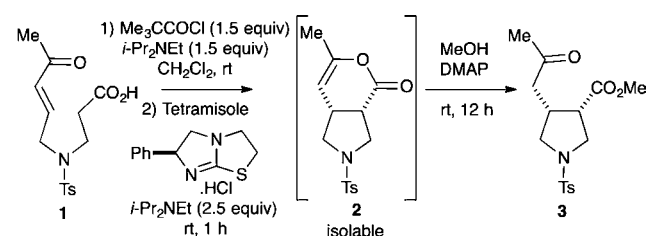
(8) For a comprehensive review of the catalytic uses of guanidines, amidines, and isothioureas, see: Taylor, J. E.; Bull, S. D.; Williams, J. M. J. *Chem. Soc. Rev.* **2012**, *41*, 2109–2121.

(9) (a) Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536–6537. (b) Kobayashi, M.; Okamoto, S. *Tetrahedron Lett.* **2006**, *47*, 4347–4350.

respectively, via an assumed ammonium enolate intermediate.¹¹ Building upon these precedents, this manuscript describes approaches to the catalytic asymmetric syntheses of stereodefined 2,3- and 3,4-disubstituted pyrrolidines directly from readily available α - and β -amino acid derivatives.¹²

Initial model studies upon an isolated model enone β -amino acid **1** using pivaloyl chloride as an in situ activating agent showed that commercially available tetramisole was the optimal catalyst for this transformation.¹³ While lactone **2** could only be isolated in modest yield due to product instability upon chromatography, conversion into methyl ester **3** via in situ methanolysis gave reproducibly higher isolated product yields, giving pyrrolidine **3** with excellent diastereo- and enantiocontrol (dr 99:1, ee = 99%, Table 1).

Table 1. Reaction Optimization



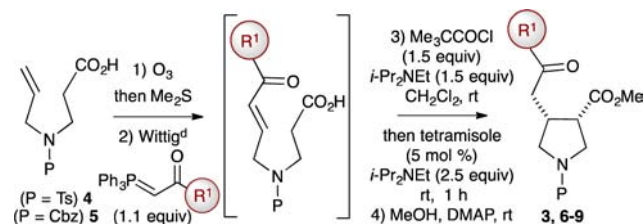
entry	tetramisole (mol %)	dr ^a	lactone 2 yield ^b (%), ee ^c (%)	ester 3 yield ^b (%), ee ^c (%)
1	20	99:1	48, 97	70, 99
2	5	99:1	—	67, 99

^a Determined by ¹H NMR spectroscopic analysis of the unpurified reaction mixture. ^b Isolated yield of product following chromatography. ^c Determined by chiral HPLC analysis.

Following these model studies, the incorporation of this sequence within a telescoped olefination/functionalization

approach to pyrrolidines was investigated. Starting from readily prepared *N*-sulfonyl-protected *N*-allyl β -amino acid **4**, consecutive ozonolysis, Wittig olefination, and asymmetric tetramisole-promoted Michael addition–lactonization, followed by ring-opening with MeOH, gave pyrrolidine **3**. Two solvent changes were required in this sequence, allowing **3** to be isolated as a single diastereoisomer in 52% isolated yield after a single chromatographic purification (Table 2, entry 1).¹⁴ The generality of this approach was next studied through variation of the enone substituent and the *N*-protecting group. Aromatic groups on the enone bearing either electron-donating or electron-withdrawing substituents are readily incorporated (entries 2–4), while *N*-Cbz substitution was also tolerated in this reaction sequence (entry 5).

Table 2. Synthesis of 3,4-*syn*-Pyrrolidines via Telescoped Wittig Olefination/Functionalization Procedure



entry	P	product, R ¹	dr ^a	yield ^b (%)	ee ^c (%)
1	Ts	3 , Me	99:1	52	99
2	Ts	6 , 4-MeC ₆ H ₄	99:1	57	96
3	Ts	7 , 4-CF ₃ C ₆ H ₄	99:1	49	90
4	Ts	8 , 4-MeOC ₆ H ₄	99:1	64	98
5	Cbz	9 , Me	99:1	85	96

^a Determined by ¹H NMR spectroscopic analysis of the unpurified reaction product. ^b Isolated yield of pyrrolidine ester over complete reaction sequence from the β -amino acid. ^c Determined by chiral HPLC analysis. ^d See Supporting Information for full details.

Further work extended this process to the preparation of proline derivatives from *N*-butenyl- α -amino acid **10**.¹⁵ In this system, the telescoped ozonolysis, Wittig olefination and asymmetric Michael-addition lactonization/ring-opening process again proved viable. Using 5 mol % of tetramisole, a range of alkyl and aryl substituents within the enone were readily incorporated (Table 3). The corresponding 2,3-*syn*-proline derivatives were isolated after a single chromatographic purification in 61–80% yield as single diastereoisomers and in 91–99% ee (entries 1, 5–10). Notably, this process can be carried out on a reasonable laboratory scale (3.5 mmol) using 1 mol % of commercially available tetramisole without compromising

(14) Isomerization of the *N*-tosyl enone–acid was observed under the Wittig reaction conditions resulting in decreased yield. See the Supporting Information for details.

(15) The relative and absolute configuration within **15** was confirmed by X-ray crystal structure analysis. CCDC 934644 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(10) For select examples, see: (a) Birman, V. B.; Guo, L. *Org. Lett.* **2006**, *8*, 4859–4861. (b) Belmessieri, D.; Joannes, C.; Woods, P. A.; MacGregor, C.; Jones, C.; Campbell, C. D.; Johnston, C. P.; Duguet, N.; Concellón, C.; Bragg, R. A.; Smith, A. D. *Org. Biomol. Chem.* **2011**, *9*, 559–570. (c) Yang, X.; Birman, V. B. *Adv. Synth. Catal.* **2009**, *351*, 2301–2304. (d) Bumbu, V. D.; Birman, V. B. *J. Am. Chem. Soc.* **2011**, *133*, 13902–13905. (e) Yang, X.; Birman, V. B. *Angew. Chem., Int. Ed.* **2011**, *50*, 5533–5555. (f) Dietz, F. R.; Gröeger, H. *Synthesis* **2009**, 4208–4218. (g) Joannes, C.; Johnston, C. P.; Concellón, C.; Simal, C.; Philp, D.; Smith, A. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 8914–8918. (h) Woods, P. A.; Morrill, L. C.; Bragg, R. A.; Smith, A. D. *Chem.—Eur. J.* **2011**, *17*, 11060. (i) Robinson, E. R. T.; Fallan, C.; Simal, C.; Slawin, A. M. Z.; Smith, A. D. *Chem. Sci.* **2013**, *4*, 2193–2200.

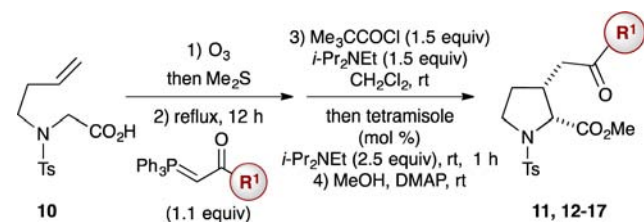
(11) (a) Leverett, C. A.; Purohit, V. C.; Johnson, A. G.; Davis, R. L.; Tantillo, D. J.; Romo, D. *J. Am. Chem. Soc.* **2012**, *134*, 13348–13356. (b) Leverett, C.; Purohit, V.; Romo, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 9479–9483. (c) Belmessieri, D.; Morrill, L. C.; Simal, C.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2011**, *133*, 2714–2720. (d) Simal, C.; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. *Angew. Chem., Int. Ed.* **2012**, *51*, 3653–3657. (e) Morrill, L. C.; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. *Chem. Sci.* **2012**, *3*, 2088–2093.

(12) Starting materials **4**, **5**, and **10** are easily synthesised in three steps and on multigram scale from commercially available materials. See the Supporting Information for full details.

(13) See the Supporting Information for optimization reaction and catalyst screen.

enantioselectivity or yield (entry 3), although further reduction in catalyst loading resulted in reduced isolated yield (entry 4).

Table 3. Synthesis of 2,3-*syn*-Pyrrolidines via Telescoped Wittig Olefination/Functionalization Procedure



entry	product, R ¹	cat. (mol %)	dr ^a	yield ^b (%)	ee ^c (%)
1	11 , Me	5	99:1	70	93
2 ^d	11 , Me	5	99:1	60	97
3 ^e	11 , Me	1	99:1	65	93
4 ^f	11 , Me	0.1	99:1	30	92
5	12 , <i>t</i> -Bu	5	99:1	61	98
6	13 , Ph	5	99:1	61	93
7	14 , 4-MeC ₆ H ₄	5	99:1	64	91
8	15 , 4-CF ₃ C ₆ H ₄	5	99:1	76	93
9 ^g	16 , 4-ClC ₆ H ₄	5	99:1	78	94
10	17 , 4-MeOC ₆ H ₄	5	99:1	80	99

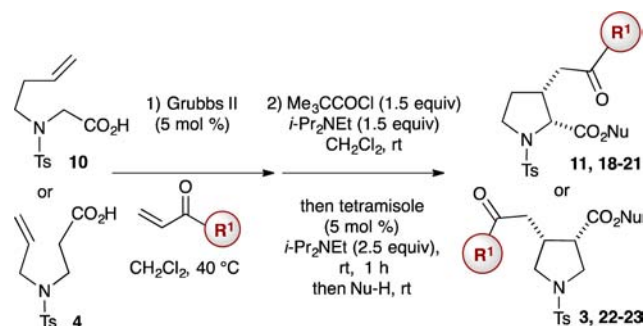
^a Determined by ¹H NMR analysis of the unpurified reaction product. ^b Isolated yield of pyrrolidine ester from **10**. ^c Determined by chiral HPLC analysis. ^d Reaction performed at 0 °C. ^e Reaction performed from 1 g of **10**; see Supporting Information for full details. ^f Reaction time 12 h. ^g The corresponding lactone could also be isolated in 93% ee (45% yield).

Cross-metathesis was next investigated as an alternative to Wittig olefination. Optimization using *N*-butenyl- α -amino acid **10** showed that CH₂Cl₂ could be used as a solvent for both cross-metathesis and asymmetric catalysis, allowing a one-pot process to be developed. Grubbs II promoted cross-metathesis, followed by functionalization using tetramisole (5 mol %), gave pyrrolidines **11** and **18–21** in 68–80% yield and 92–99% ee as a single diastereoisomer in each case (Table 4), confirming the robustness of tetramisole as an organocatalyst in this protocol. Furthermore, the tetramisole loading could be reduced to 0.1 mol % without compromising yield or enantioselectivity (entries 1–3). In addition to methanol, ring-opening was also performed with either isopropylamine or glycine methyl ester (entries 4 and 5) and extended to incorporate other aryl and alkyl enones (entries 6 and 7). This one-pot methodology was also performed in the β -amino acid series, giving pyrrolidines **3** and **22–23** in high yield with excellent diastereo- and enantioselectivity (dr 99:1, ee = 84–97%, entries 8–10).

The ability to *N*-deprotect the pyrrolidine products and access the alternative *anti*-diastereoisomeric series was next investigated. Olefination of readily available *N*-Cbz allyl β -amino acid **5** using both ozonolysis/Wittig and metathesis processes, followed by asymmetric cyclization using tetramisole, afforded *N*-Cbz lactone **24** in good yields and

enantioselectivity (dr 99:1, 71 and 65% yield, ee = 98–99%; Table 5, entries 1 and 2). Derivatization of *N*-Cbz lactone **24** with benzylamine gave **25**, with *N*-deprotection using Pd(OH)₂ giving the parent *syn*-pyrrolidine **26** in 71% yield (dr 99:1 and ee = 99%).^{16,17} Epimerization of *syn*-**25** (dr 99:1, ee = 99%) was also achieved using NaOMe/MeOH, giving *anti*-**28** (dr 1:99, ee = 93%) in 70% yield (Table 5).¹⁸

Table 4. Synthesis of 2,3- and 3,4-*syn*-Disubstituted Pyrrolidines via One-Pot Metathesis Olefination/Functionalization Procedure



entry	amino acid	Nu-H	product, R ¹	dr ^a	yield ^b (%)	ee ^c (%)
1	10	MeOH	11 , Me	99:1	75	97
2 ^d	10	MeOH	11 , Me	99:1	75	97
3 ^e	10	MeOH	11 , Me	99:1	73	98
4	10	<i>i</i> -PrNH ₂	18 , Me	99:1	68	92
5	10	MeO ₂ CCH ₂ NH ₂	19 , Me	99:1	72	97
6	10	MeOH	20 , Et	99:1	80	99
7 ^f	10	MeOH	21 , 2-furyl	99:1	75	96
8	4	MeOH	3 , Me	99:1	71	98
9	4	MeOH	22 , Et	99:1	80	97
10 ^g	4	MeOH	23 , 2-furyl	99:1	63	84

^a Determined by ¹H NMR analysis of the unpurified reaction product. ^b Isolated yield of pyrrolidine ester over complete sequence from **10** or **4**. ^c Determined by chiral HPLC analysis. ^d 1 mol % of tetramisole used. ^e 0.1 mol % of tetramisole used, reaction time 12 h. ^f Using 10 mol % of Grubbs II.

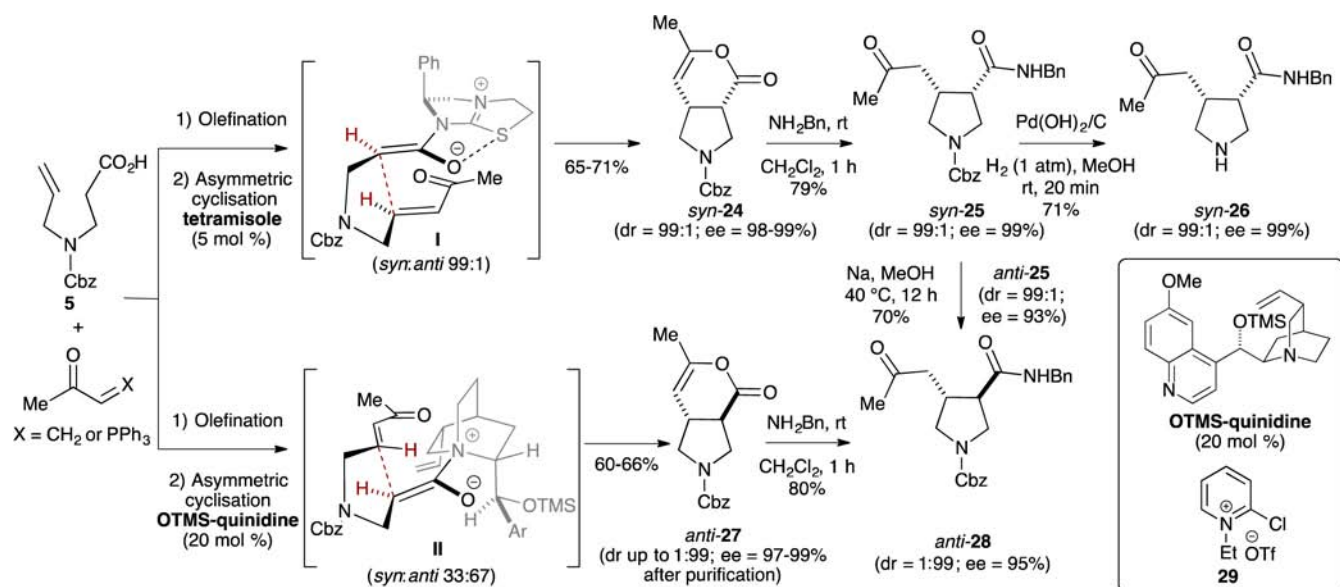
We next investigated a complementary and catalyst selective route into the *anti*-diastereoisomeric pyrrolidines. Following Romo's use of cinchona alkaloid catalysts in NCAL processes,¹⁹ the use of OTMS-quinidine was evaluated. Olefination of β -amino acid **5** via ozonolysis and Wittig reaction, followed by asymmetric functionalization using OTMS-quinidine, gave preferential access to *anti*-lactone **25** (dr *syn:anti* 33:67). Separation of the diastereoisomers via chromatography gave *anti*-**27** in 60%

(16) ee of *syn*-**26** determined by HPLC analysis of Cbz derivative.

(17) *syn*-**26** was synthesised via ozonolysis/Wittig/functionalization/ring-opening/deprotection sequence from **5** in 40% overall yield.

(18) Erosion of ee is presumably due to a competitive retro Michael/Michael process.

(19) (a) Cortez, G. S.; Tennyson, R. L.; Romo, D. *J. Am. Chem. Soc.* **2001**, *123*, 7945–7946. (b) Oh, S. H.; Cortez, G. S.; Romo, D. *J. Org. Chem.* **2005**, *70*, 2835–2838. (c) Morris, K. A.; Arendt, K. M.; Oh, S. H.; Romo, D. *Org. Lett.* **2010**, *12*, 3764–3767.

Table 5. Stereodivergent Approach to 3,4-Disubstituted Pyrrolidines^a

entry	olefination	cat.	dr ^b <i>syn:anti</i>	product	yield ^c (%) <i>syn</i>	ee ^d (%) <i>syn</i>	product	yield ^c (%) <i>anti</i>	ee ^d (%) <i>anti</i>
1	O ₃ , Wittig	tetramisole	99:1	<i>syn</i> - 24	71	99			
2	Metathesis	tetramisole	99:1	<i>syn</i> - 24	65	98			
3	O ₃ , Wittig	OTMS-quinidine	33:67	<i>syn</i> - 24	33	(<i>ent</i>) 50	<i>anti</i> - 27	60	97
4	Metathesis	OTMS-quinidine	33:67	<i>syn</i> - 24	30	(<i>ent</i>) 37	<i>anti</i> - 27	66	99

^a Reaction conditions: (1) see Supporting Information for full details; (2) with tetramisole: Me₃CCOCl (1.5 equiv), *i*-Pr₂NEt (1.5 equiv), CH₂Cl₂, rt, then, tetramisole (5 mol %), *i*-Pr₂NEt (2.5 equiv), 1 h; with OTMS-quinidine: **29** (1.5 equiv), *i*-Pr₂NEt (2.5 equiv), OTMS-quinidine (20 mol %), CH₂Cl₂, rt, 2 h. ^b Determined by ¹H NMR spectroscopic analysis of the unpurified reaction mixture. ^c Isolated yield of lactone *syn*-**24** pyrrolidine ester over complete sequence from **5**. ^d Determined by chiral HPLC analysis. ^e Isolated yield of lactone *anti*-**27** over complete sequence from **5**.

yield (dr 1:99, ee = 97%, entry 3) and *syn*-**24** in 33% yield (ee = 50%). Similarly, olefination via metathesis, followed by OTMS-quinidine mediated cyclization, gave access to the *anti*-lactone **27** (dr 1:99) in 66% yield and 99% ee (Table 5, entry 4).²⁰ In the tetramisole-promoted sequence, the *syn*-preference can be explained by invoking pretransition state assembly **I**, in which the enolate oxygen preferentially lies *syn* to the S atom, allowing either an n_O to σ*_{C-S} interaction²¹ or favorable electrostatic stabilization. Preferential Michael addition *anti*- to the stereodirecting Ph unit on the enolate *Re*-face generates the *syn*-product. When OTMS-quinidine is used, the Michael addition proceeds preferentially upon the enolate *Si*-face (through **II**), minimizing steric interactions with the ethylene bridge within the quinidine skeleton and giving the *anti*-diastereoisomer as the major product in high ee.

In conclusion, both telescoped and one-pot olefination/asymmetric functionalization approaches to 2,3- or 3,4-*syn*-disubstituted pyrrolidines from readily available

N-allyl β-amino acids and *N*-butenyl α-amino acid derivatives have been developed. This method provides the corresponding pyrrolidine derivatives with high diastereo- and enantiocontrol (dr up to 99:1, up to 99% ee) using commercially available tetramisole. OTMS-quinidine has been identified as an alternative Lewis base catalyst to preferentially give a 3,4-*anti*-pyrrolidine in high enantioselectivity. The generality of these approaches to hetero- and carbocycle synthesis, as well as the development of alternative reaction processes using chiral Lewis bases in asymmetric catalysis, are underway within our laboratory.

Acknowledgment. We thank the Royal Society for a University Research Fellowship (A.D.S.) and the EPSRC National Mass Spectrometry Service Centre (Swansea). The research leading to these results has received funding from the European Research Council under the European Union's Seventh Framework Programme (FP7/2007-2013)/ERC grant agreement no. 279850

Supporting Information Available. Experimental procedures plus spectroscopic data for all products are available. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.

(20) No epimerization was observed upon treatment of *syn*-lactone **24** under the OTMS-quinidine asymmetric cyclization reaction conditions; see the Supporting Information for full details.

(21) (a) Minkin, V. I.; Minyaev, R. M. *Chem. Rev.* **2001**, *101*, 1247–1266. (b) Brameld, K. A.; Kuhn, B.; Reuter, D. C.; Stahl, M. J. *J. Chem. Inf. Model* **2008**, *48*, 1–24. (c) Nagao, Y.; Hirata, T.; Goto, S.; Sano, S.; Kakehi, A. *J. Am. Chem. Soc.* **1998**, *120*, 3104–3110. (d) Liu, P.; Yang, X.; Birman, V. B.; Houk, K. N. *Org. Lett.* **2012**, *14*, 3288–3291.