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# Conjugate Addition of Lithium *N*-Phenyl-*N*-(α-methylbenzyl)amide: Application to the Asymmetric Synthesis of (*R*)-(−)-Angustureine

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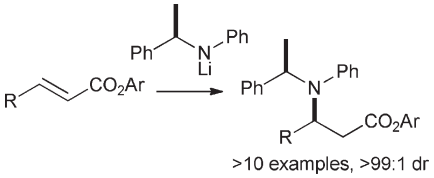
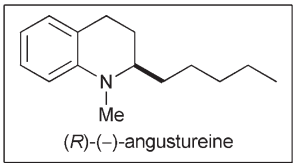
## ABSTRACT




**The conjugate addition of lithium (*R*)-*N*-phenyl-*N*-(α-methylbenzyl)amide to a range of α,β-unsaturated 4-methoxyphenyl esters proceeds with excellent levels of diastereoselectivity to give the corresponding β-amino esters in good yield and as single diastereoisomers (>99:1 dr). The synthetic utility of this methodology has been demonstrated via the short and concise asymmetric synthesis of the tetrahydroquinoline alkaloid (*R*)-(−)-angustureine in six steps and 32% overall yield from commercially available oct-2-enoic acid.**

The conjugate addition reaction was first reported over 125 years ago by Komnenos, who demonstrated the 1,4-addition of diethyl sodiomalonate to diethyl ethylidenemalonate.[1] Today, the conjugate addition reaction is a powerful tool in the organic chemists' synthetic arsenal due to the wide range of nucleophiles and α,β-unsaturated carbonyl compounds which participate in this reaction manifold.[2] We have previously shown that the conjugate addition of a range of secondary lithium amides derived from α-methylbenzylamine to a range of achiral and chiral α,β-unsaturated esters proceeds with very high levels and a predictable sense of diastereoselectivity.[3] This methodology has found numerous synthetic applications, such as use in the total synthesis of natural products[4] and in enantiorecognition phenomena,[5] and was reviewed comprehensively in 2005.[6] In >200 reported examples of this reaction, several adaptations of the substructure of the lithium amide have been successfully deployed for synthesis,[6,7] although to date there are no examples involving the use of a lithium *N*-aryl-*N*-(α-methylbenzyl)amide as a chiral aniline equivalent for conjugate addition. In this manuscript we report a resolution to this limitation: the diastereoselective conjugate addition reaction of lithium

(1) Komnenos, T. *Liebigs Ann. Chem.* **1883**, *218*, 145.
(2) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. Smith, M. B.; March, J. *March's Advanced Organic Chemistry – Reactions, Mechanisms, and Structure*, 5th ed.; John Wiley & Sons Inc.: New York, 2001.

(3) Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *2*, 183. Davies, S. G.; Garrido, N. M.; Kruchinin, D.; Ichihara, O.; Kotchie, L. J.; Price, P. D.; Price Mortimer, A. J.; Russell, A. J.; Smith, A. D. *Tetrahedron: Asymmetry* **2006**, *17*, 1793. Davies, S. G.; Mulvaney, A. W.; Russell, A. J.; Smith, A. D. *Tetrahedron: Asymmetry* **2007**, *18*, 1554. Davies, S. G.; Fletcher, A. M.; Roberts, P. M. *Org. Synth.* **2010**, *87*, 143.

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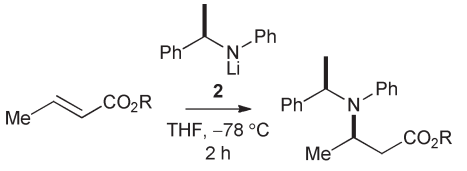
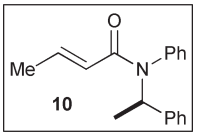
*N*-phenyl-*N*-(α-methylbenzyl)amide to a range of α,β-unsaturated 4-methoxyphenyl esters is described.

*N*-Arylation of (*R*)-α-methylbenzylamine (99% ee)[8] according to a modification of the procedure described by Larock[9] gave (*R*)-*N*-phenyl-*N*-(α-methylbenzyl)amine **1** in 59% yield and >99% ee.[10] Deprotonation of **1** with BuLi in THF at −78 °C gave a pale yellow solution of lithium (*R*)-*N*-phenyl-*N*-(α-methylbenzyl)amide **2**. Addition of *tert*-butyl crotonate **3** (1.0 equiv) to the lithium amide solution (2.0 equiv) gave only returned starting material, while under identical conditions addition of methyl crotonate **4** resulted in incomplete conversion (34%)[11] to β-amino ester **7** as a single diastereoisomer (>99:1 dr). However, when phenyl crotonate was empolyed, complete conversion to a mixture of products containing a 75:25 mixture of β-amino ester **8** and α,β-unsaturated amide **10** (resulting from competing 1,2-addition of the lithium amide)[12] as the major components was observed. Variation of the electronics of the ester group revealed that upon conjugate addition of lithium amide **2** to 4-methoxyphenyl crotonate **6**, the competing 1,2-addition reaction was completely suppressed and β-amino ester **9** was produced as a single product. Further experimentation showed that the optimum procedure involved use of 1.1 equiv of lithium amide **2**, which allowed the isolation of β-amino ester **9** as a single diastereoisomer in 80% yield (Scheme 1).

**Scheme 1**




| | R | conversion | β-amino ester | yield (dr) % |
|---|---|---|---|---|
| **3** | $^t$Bu | 0[a] | n/a | n/a |
| **4** | Me | 34[a] | **7** | 28 (>99:1) |
| **5** | Ph | 100[a] | **8** | 37 (>99:1) |
| **6** | 4-MeOC$_6$H$_4$ | 100[b] | **9** | 80 (>99:1) |




[a] Reactions were performed using 1.0 equiv of α,β-unsaturated ester and 2.0 equiv of lithium amide **2**. [b] Reaction was performed using 1.0 equiv of α,β-unsaturated ester **9** and 1.1 equiv of lithium amide **2**.

The relative configuration within β-amino ester **9** was unambiguously established via single crystal X-ray diffraction analysis,[13] with the absolute (*R*,*R*)-configuration being assigned from the known configuration of the (*R*)-α-methylbenzyl stereocenter (Figure 1). This analysis reveals that the facial bias elicited by lithium (*R*)-*N*-phenyl-*N*-(α-methylbenzyl)amide **2** in its conjugate addition to α,β-unsaturated esters is consistent with that of other members of this class of lithium amide[14] [e.g., lithium *N*-benzyl-*N*-(α-methylbenzyl)amide[6] and lithium *N*-allyl-*N*-(α-methylbenzyl)amide].[15] On this basis, the absolute (*R*,*R*)-configurations within β-amino esters **7** and **8** were confidently assigned. In support of these assumptions, the configurations within β-amino esters **8** and **9** were correlated to that of the known dihydroquinolin-4-one **13**. Attempted treatment of either **8** or **9** with polyphosphoric

(4) For selected examples from this laboratory, see: Davies, S. G.; Kelly, R. J.; Price Mortimer, A. J. *Chem. Commun.* **2003**, 2132. Davies, S. G.; Burke, A. J.; Garner, A. C.; McCarthy, T. D.; Roberts, P. M.; Smith, A. D.; Rodriguez-Solla, H.; Vickers, R. J. *Org. Biomol. Chem.* **2004**, *2*, 1387. Davies, S. G.; Haggitt, J. R.; Ichihara, O.; Kelly, R. J.; Leech, M. A.; Price Mortimer, A. J.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2004**, *2*, 2630. Abraham, E.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Roberts, P. M.; Russell, A. J.; Sánchez-Fernández, E. M.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2007**, *18*, 2510. Abraham, E.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1655. Abraham, E.; Brock, E. A.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Perkins, J. H.; Roberts, P. M.; Russell, A. J.; Sánchez-Fernández, E. M.; Scott, P. M.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 1665. Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Smith, A. D. *Tetrahedron* **2009**, *65*, 10192. Davies, S. G.; Hughes, D. G.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Williams, O. M. H. *Synlett* **2010**, 567. Davies, S. G.; Ichihara, O.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2011**, *67*, 216. Bagal, S. K.; Davies, S. G.; Fletcher, A. M.; Lee, J. A.; Roberts, P. M.; Scott, P. M.; Thomson, J. E. *Tetrahedron Lett.* **2011**, *52*, 2216.

(5) For selected examples from this laboratory, see: Davies, S. G.; Hermann, G. J.; Sweet, M. J.; Smith, A. D. *Chem. Commun.* **2004**, 1128. Cailleau, T.; Cooke, J. W. B.; Davies, S. G.; Ling, K. B.; Naylor, A.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2007**, *5*, 3922. 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. Davies, S. G.; Durbin, M. J.; Goddard, E. C.; Kelly, P. M.; Kurosawa, W.; Lee, J. A.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Scott, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2009**, *7*, 761. Davies, S. G.; Fletcher, A. M.; Hermann, G. J.; Poce, G.; Roberts, P. M.; Smith, A. D.; Sweet, M. J.; Thomson, J. E. *Tetrahedron: Asymmetry* **2010**, *21*, 1635.

(6) Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833.

(7) For selected examples, see: Okamoto, S.; Iwakubo, M.; Kobayashi, K.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 6984. Bull, S. D.; Davies, S. G.; Roberts, P. M.; Savory, E. D.; Smith, A. D. *Tetrahedron* **2002**, *58*, 4629. Williams, P. G.; Yoshida, W. Y.; Quon, M. K.; Moore, R. E.; Paul, V. J. *J. Nat. Prod.* **2003**, *66*, 651. Bentley, S. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E.; Toms, S. M. *Tetrahedron* **2010**, *66*, 4604. Brock, E. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2011**, *13*, 1594.

(8) Enantiopure (*R*)-α-methylbenzylamine (99% ee) is commercially available.

(9) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198.

(10) The enantiomeric purity of (*R*)-*N*-phenyl-*N*-(α-methylbenzyl)-amine **1** was determined by chiral HPLC analysis for which the authors would like to thank Darren J. Dixon and Pavol Jakubec.

(11) The reaction conversion was calculated from the ratio of excess (*R*)-*N*-phenyl-*N*-(α-methylbenzyl)amine **1** to β-amino ester **7** due to the volatility of methyl crotonate **4**.

(12) An authentic sample of α,β-unsaturated amide **10** was prepared (in 83% yield) via acylation of (*R*)-*N*-phenyl-*N*-(α-methylbenzyl)amine **1** with crotonoyl chloride.

(13) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 805285.

(14) Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1999.

(15) Davies, S. G.; Fenwick, D. R. *J. Chem. Soc., Chem. Commun.* **1995**, 109. Davies, S. G.; Hedgecock, C. J. R.; McKenna, J. M. *Tetrahedron: Asymmetry* **1995**, *6*, 827. Davies, S. G.; Hedgecock, C. J. R.; McKenna, J. M. *Tetrahedron: Asymmetry* **1995**, *6*, 2507. Davies, S. G.; Fenwick, D. R. *Chem. Commun.* **1997**, 565. Davies, S. G.; Fenwick, D. R.; Ichihara, O. *Tetrahedron: Asymmetry* **1997**, *8*, 3387.

(16) (a) Paradisi, M. P.; Romeo., A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 596. (b) Liu, J.; Wang, Y.; Sun, Y.; Marshall, D.; Miao, S.; Tonn, G.; Anders, P.; Tocker, J.; Tang, H. L.; Medina, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6840.

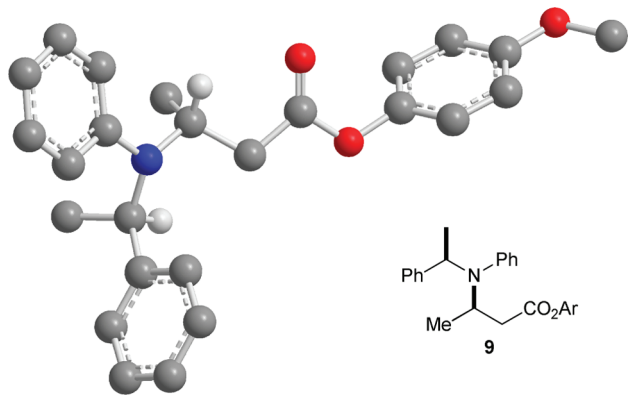
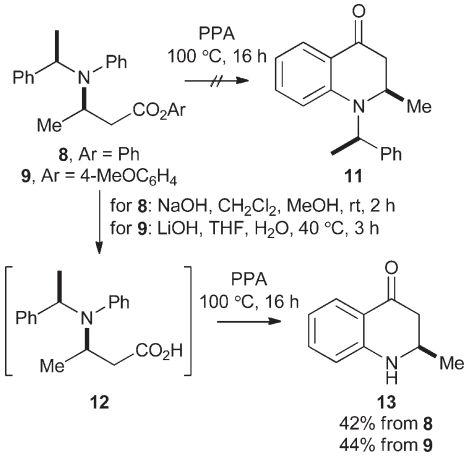



**Figure 1.** Chem 3D representation of the single crystal X-ray diffraction structure of **9** (selected H atoms are omitted for clarity). Ar = 4-MeOC$_6$H$_4$.

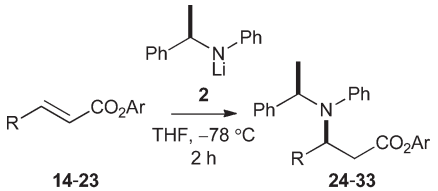
acid (PPA)[16] or a range of Lewis acids resulted only in product decomposition via a retro conjugate addition reaction, with no trace of the desired dihydroquinolin-4-one **11**. However, saponification of **8** and **9** followed by treatment of the resultant $\beta$-amino acid **12** with PPA[16] resulted in cyclization and in situ loss of the α-methylbenzyl group (presumably via an $S_N1$-type pathway) to give dihydroquinolin-4-one **13** in 42 and 44% isolated yield (two steps) from **8** and **9** respectively. Comparison of the values of the specific rotations for these samples of **13** with that previously reported in the literature {$[\alpha]_D^{25}$ +174 (*c* 1.0 in $C_6H_6$) for the sample of **13** derived from **8**; $[\alpha]_D^{25}$ +183 (*c* 1.0 in $C_6H_6$) for the sample of **13** derived from **9**; lit.[16a] $[\alpha]_D^{20}$ +220 (*c* 1.0 in $C_6H_6$)} confirmed the homochirality within **8** and **9** and affirmed their absolute (*R*,*R*)-configurations (Scheme 2).

**Scheme 2**




The generality of this reaction was next established by application to a range of α,$\beta$-unsaturated 4-methoxyphenyl esters bearing diverse substitution at the $\beta$-position. Substituted aryl, heteroaryl, *n*-alkyl, and branched alkyl substituents were all well tolerated within the reaction manifold:[17] conjugate addition of lithium (*R*)-*N*-phenyl-*N*-(α-methylbenzyl)amide **2** to α,$\beta$-unsaturated esters **14**–**23**[18] under our optimal conditions gave, in each case, complete conversion to single diastereoisomers of the corresponding $\beta$-amino esters **24**–**33**, which were isolated in 53–83% yield after chromatographic purification. The absolute configurations of the newly formed C(3)-stereogenic centers within $\beta$-amino esters **24**–**33** were assigned by analogy to those unambiguously established for **8** and **9** (Scheme 3).

**Scheme 3**




| | R | β-amino ester | yield (dr) % |
|---|---|---|---|
| **14** | Ph | **24** | 83 (>99:1) |
| **15** | Ar | **25** | 72 (>99:1) |
| **16** | 4-$NO_2C_6H_4$ | **26** | 83 (>99:1) |
| **17** | 3-$FC_6H_4$ | **27** | 81 (>99:1) |
| **18** | 2-$BrC_6H_4$ | **28** | 53 (>99:1) |
| **19** | 3-pyridyl | **29** | 59 (>99:1) |
| **20** | 3-furyl | **30** | 67 (>99:1) |
| **21** | *n*-$C_5H_{11}$ | **31** | 78 (>99:1) |
| **22** | *i*-Bu | **32** | 75 (>99:1) |
| **23** | $PhCH_2CH_2$ | **33** | 76 (>99:1) |

Ar = 4-methoxyphenyl.

The synthetic utility of this methodology was next demonstrated by application to an asymmetric synthesis

(17) Attempted conjugate addition of lithium (*R*)-*N*-phenyl-*N*-(α-methylbenzyl)amide **2** to 4-methoxyphenyl sorbate [4′-methoxyphenyl (*E*,*E*)-hexa-2,4-dieonate] and 4′-methoxyphenyl (*E*)-4-methylpent-2-enoate under our optimal conditions returned only starting material.

(18) α,$\beta$-Unsaturated 4-methoxyphenyl esters **14**–**23** were prepared either by esterification of the corresponding (commercially available) α,$\beta$-unsaturated carboxylic acid, or through Wadsworth–Emmons olefination of the corresponding aldehyde using 4-methoxyphenyl diethylphosphonoacetate; see the Supporting Information for full details.

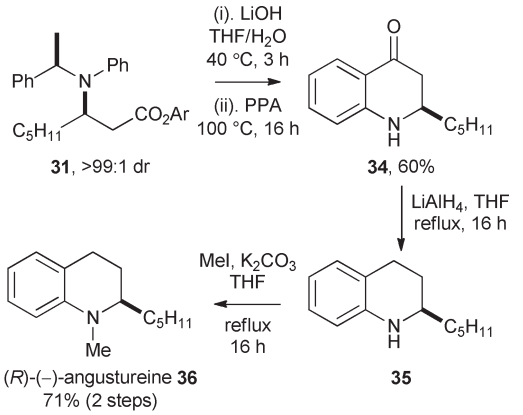
(19) Jacquemond-Collet, I.; Hannedouche, S.; Fabre, N.; Fourasté, I.; Moulis, C. *Phytochemistry* **1999**, *51*, 1167.

(20) For previous syntheses of (±)-angustureine, see: (a) Avemaria, F.; Vanderheiden, S.; Braese, S. *Tetrahedron* **2003**, *59*, 6785. (b) Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 6577. (c) O'Byrne, A.; Evans, P. *Tetrahedron* **2008**, *64*, 8067. (d) Shahane, S.; Louafi, F.; Moreau, J.; Hurvois, J.-P.; Renaud, J.-L.; van de Weghe, P.; Roisnel, T. *Eur. J. Org. Chem.* **2008**, 4622. (e) Kothandaraman, P.; Foo, S. J.; Chan, P. W. H. *J. Org. Chem.* **2009**, *74*, 5947. For previous syntheses of (*S*)-(+)-angustureine, see: (f) Lin, X.-F.; Li, Y.; Ma, D.-W. *Chin. J. Chem.* **2004**, *22*, 932. (g) Theeraladanon, C.; Arisawa, M.; Nakagawa, M.; Nishida, A. *Tetrahedron: Asymmetry* **2005**, *16*, 827. (h) Ryu, J.-S. *Bull. Korean Chem. Soc.* **2006**, *27*, 631. (i) Arisawa, M. *Chem. Pharm. Bull.* **2007**, *55*, 1099. (j) Fustero, S.; Moscardo, J.; Jimenez, D.; Peerez-Carrion, M. D.; Sanchez-Roseslo, M.; del Pozo, C. *Chem.—Eur. J.* **2008**, *14*, 9868. (k) Chen, B.-L.; Wang, B.; Lin, G.-Q. *J. Org. Chem.* **2010**, *75*, 941. For previous syntheses of (*R*)-(−)-angustureine, see: (l) Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2003**, *125*, 10536. (m) Lu, S.-M.; Wang, Y.-Q.; Han, X.-W.; Zhou, Y.-G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2260. (n) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683. (o) Wang, Z.-J.; Zhou, H.-F.; Wang, T.-L.; He, Y.-M.; Fan, Q.-H. *Green Chem.* **2009**, *11*, 767.

of the tetrahydroquinoline alkaloid (*R*)-(−)-angustureine **36**, originally isolated in 1999 by Jacquemond-Collet and co-workers from the bark of *Galipea officinalis* Hancock, a shrub indigenous to the mountains of Venezuela.[19,20] Thus, saponification of *β*-amino ester **31** upon treatment with aqueous LiOH gave the corresponding *β*-amino acid which, upon exposure to PPA,[16] underwent cyclization with concomitant loss of an α-methylbenzyl group to give 2-pentyl-2,3-dihydroquinolin-4(1*H*)-one **34** in 60% isolated yield. Reduction of **34** with $LiAlH_4$[16a] gave tetrahydroquinoline **35** (norangustureine) which was *N*-methylated upon reflux in THF in the presence of MeI and $K_2CO_3$[20d,e,g,h] to give (*R*)-(−)-angustureine **36** in 71% yield over the two steps and in >99% ee,[21] consistent with the enantiomeric purity of the (*R*)-*N*-phenyl-*N*-(α-methylbenzyl)amide **2** used in the conjugate addition reaction. The spectroscopic data of our sample of (*R*)-(−)-**36** were in excellent agreement with those previously reported for the sample isolated from the natural source by Jacquemond-Collet[19] and other synthetic samples[20l−o] {$[\alpha]_D^{25}$ −7.0 (*c* 1.0 in $CHCl_3$) for >99% ee;[21] lit.[19] for sample isolated from natural source $[\alpha]_D$ −7.2;[22] lit.[20l] $[\alpha]_D^{15}$ −6.7 (*c* 1.0 in $CHCl_3$) for 94% ee; lit.[20m] $[\alpha]_D^{8}$ −5.5 (*c* 1.1 in $CHCl_3$) for 89% ee; lit.[20n] $[\alpha]_D^{25}$ −6.9 (*c* 1.0 in $CHCl_3$) for 90% ee; lit.[20o] $[\alpha]_D^{20}$ −7.3 (*c* 1.0 in $CHCl_3$) for 94% ee} (Scheme 4).

In conclusion, the conjugate addition of lithium (*R*)-*N*-phenyl-*N*-(α-methylbenzyl)amide to a range of α,*β*-unsaturated 4-methoxyphenyl esters proceeds with excellent levels of diastereoselectivity to give the corresponding *β*-amino esters in good yield and as single diastereoisomers (>99:1 dr). The synthetic utility of this methodology has been demonstrated via its application as the key step in a short and concise asymmetric synthesis of the tetrahydroquinoline alkaloid (*R*)-(−)-angustureine in six steps and 32% overall yield from commercially available oct-2-enoic acid. Further applications of this conjugate addition reaction to facilitate the preparation of other tetrahydroquinoline derived natural products and their derivatives are currently under investigation in our laboratory.

**Scheme 4**




Ar = 4-methoxyphenyl.

**Supporting Information Available.** Experimental procedures, characterization data, copies of $^1H$ and $^{13}C$ NMR spectra, and crystallographic information file (for structure CCDC 805285). This material is available free of charge via the Internet at http://pubs.acs.org.

(21) The enantiomeric purity of (*R*)-(−)-angustureine **36** was determined by chiral HPLC analysis for which the authors would like to thank Darren J. Dixon and Pavol Jakubec.

(22) The conditions under which the specific rotation value was recorded (temperature, solvent, concentration) were not reported by Jacquemond-Collet and co-workers in their manuscript describing the isolation of the natural product (see ref 19).