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Published on Web 10/15/2002

# Development of a Catalytic Enantioselective Conjugate Addition of 1,3-Dicarbonyl Compounds to Nitroalkenes for the Synthesis of Endothelin-A Antagonist ABT-546. Scope, Mechanism, and Further Application to the Synthesis of the Antidepressant Rolipram

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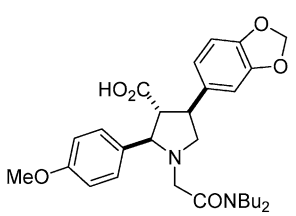
Received May 3, 2002

***Abstract:*** The enantioselective synthesis of endothelin-A antagonist **ABT-546** has been accomplished via the discovery and development of a highly selective catalytic asymmetric conjugate addition of ketoesters to nitroolefins. Employing just 4 mol % bis(oxazoline)-Mg(OTf)$_2$ complex with an amine cocatalyst, we obtained the product nitroketone with 88% selectivity at the aryl-bearing stereocenter and in good yield on scales ranging to 13 mol. The effects of ligand structure, metal salt, and solvent on the reaction are described. Particularly important to the reaction is the water content. While water is necessary during the generation of the catalyst, the water must be then removed to maximize stereoselectivity and reactivity. The reaction has been extended to other dicarbonyl substrates, and a variety of substitution patterns are tolerated on the nitroolefin partner. The reaction has also been employed in the synthesis of the antidepressant rolipram. Investigations relating to the mechanism of the reaction are also described.

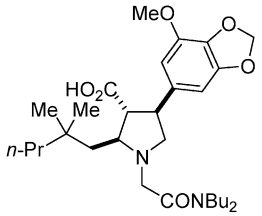
## Introduction

Endothelin-1 (ET) is a potent vasoconstrictive 21 amino acid peptide[1] whose activity is mediated by its interaction with receptors endothelin A ($ET_A$) and endothelin B ($ET_B$).[2] Selective $ET_A$ antagonists are possible targets for the treatment of cancer and congestive heart failure.[3,4] While the $ET_A$ receptor has been implicated in ET's proliferative and vasoconstrictive effects, $ET_B$ is a shunt receptor which consumes ET. Therefore, selectivity between the $ET_A$ and $ET_B$ receptors is important in the design of effective antagonists.[4]

At Abbott Laboratories, a series of stereochemically rich tetrasubstituted pyrrolidines have been found both to bind strongly to the $ET_A$ receptor and to exhibit high selectivity for $ET_A$ over $ET_B$. **ABT-627**,[5,6] with excellent selectivity ($ET_A$/$ET_B$ = 1900) and potency ($K_i$ = 0.034 nM), has been found in clinical trials to delay the progression of end-stage, hormone refractory prostate cancer.[7] **ABT-546**[4,8] was identified as possessing even higher selectivity (28 000), although it has lower potency ($K_i$ = 0.46 nM), and was chosen to be a clinical backup to **ABT-627**. Thus, an efficient synthesis of **ABT-546** was required which would be amenable to multikilo scale production.



**ABT-627**



**ABT-546**

Although a synthetic route was developed to prepare the racemic pyrrolidine core of **ABT-546**, (±)-**4** (Scheme 1), its resolution proved inefficient. Of the numerous chiral acids screened, only D-tartaric acid effectively provided an enantiomeric resolution, but the process required several crystallizations, and the resolved tartrate salt **5** was obtained in only 20% yield (40% of theory). Thus, it was concluded that for the preparation

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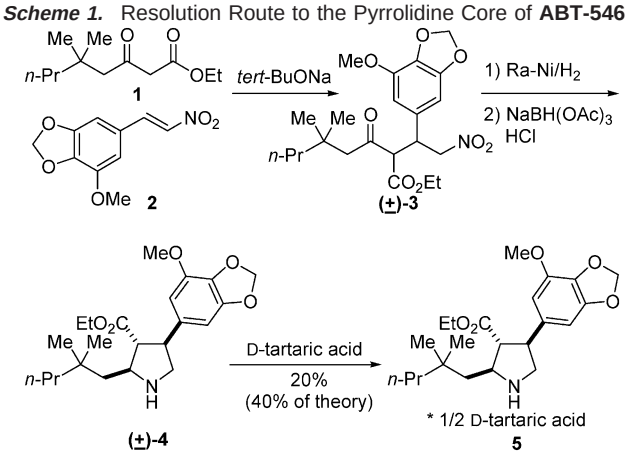
***Scheme 1.*** Resolution Route to the Pyrrolidine Core of **ABT-546**

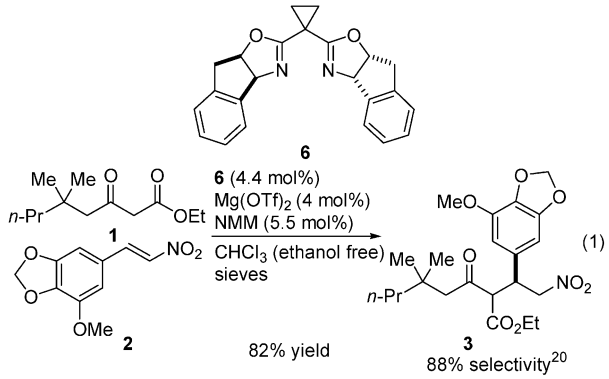



of clinical material, an asymmetric synthesis of the pyrrolidine core of **ABT-546** would have to be developed.

While a number of asymmetric pyrrolidine syntheses could be envisioned,[9] we were attracted to the highly convergent nature of the racemic synthesis. As the initially formed aryl-bearing stereocenter in nitroketone **3** relays stereochemical information to the other centers in subsequent steps, we reasoned that an asymmetric conjugate addition reaction would provide a convergent asymmetric synthesis.[10] The challenge lay in developing an asymmetric reaction in which enolization would merge with addition in a catalytic cycle.

Soft enolization techniques have emerged as powerful methods for activating carbonyl compounds for enolate bond constructions.[11] While catalytic asymmetric enolate bond constructions generally require the initial formation of a stable enolate surrogate,[12] in recent years significant effort has gone into the development of enolization/addition reactions which are both highly enantioselective and catalytic in the metal.[13−16]

Because of their relatively high acidity, 1,3-dicarbonyl compounds would appear to be good candidates for the development of catalyzed soft enolization/addition reactions. While enantioselective versions of such reactions have been reported,[17] highly selective variants are rare.[16b,c] In the present work, we report the discovery and development of a highly selective conjugate addition of ketoester **1** to nitrostyrene **2**, catalyzed by the complex of bis(oxazoline) **6** with $Mg(OTf)_2$ and an amine cocatalyst (eq 1).[18] This reaction has been employed in the multikilogram synthesis of **ABT-546** and has been extended to other 1,3-dicarbonyl compounds, including malonates, with a variety of nitroolefins. To further demonstrate its utility, the methodology was employed in the efficient preparation of the antidepressant rolipram. Kinetics investigations discussed herein support a catalyzed soft enolization/addition mechanism for this highly enantioselective reaction of 1,3-dicarbonyl compounds to nitroolefins.[19]




## Results and Discussion

**Development of the Catalyzed Reaction.** In an initial screening of ligand−metal combinations, the first experiments to show significant selectivity (>20%)[20] employed a complex derived from bis(oxazoline) **6**[21] and $Mg(OTf)_2$,[22] combined with ketoester **1** and nitrostyrene **2** in $CHCl_3$ at 60 °C; the product

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(12) For a review of Lewis acid-catalyzed additions of enolate surrogates to electrophiles, see: (a) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357−389. See also: (b) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095−1120. For a recent example of a highly selective Mukaiyama Michael reaction, see: (c) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335. (d) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994−1995.

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(17) For an early example of a highly selective catalyzed reaction, see: (a) Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625−628. Reactions in which amines catalyze conjugate additions have been reported: (b) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370−4371. (c) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423−2425. (d) Betancourt, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 4441−4444. (e) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975−2978. For reviews of catalyzed conjugate addition reactions, see: (f) Krause, N.; Hoffman-Roder, A. *Synthesis* **2001**, 171−196. (g) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033−8061. (h) Ferigna, B. I.; de Vries, A. H. M. *Advances in Catalytic Processes*; JAI Press: London, 1995; pp 151−192.

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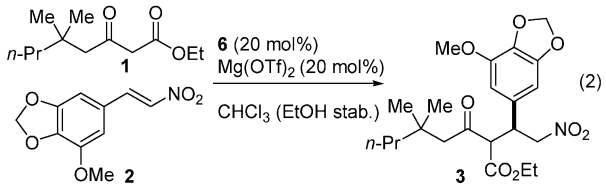
***Table 1.*** Effect of NMM Equivalents in the Conjugate Addition[a]

| entry | NMM amount | NMM/Mg mol ratio | selectivity[20] | conv. (5 h) |
|---|---|---|---|---|
| 1 | none | | nd | 4%[b] |
| 2 | 10 mol % | 0.5 | 78% | 33% |
| 3 | 20 mol % | 1.0 | 73% | 46% |
| 4 | 50 mol % | 2.5 | 73% | 49% |
| 5 | 100 mol % | 5.0 | 69% | 46% |

[a] Conditions: 1.2 equiv of ketoester **1**, 1.0 equiv of nitrostyrene **2**, 20 mol % ligand **6**, 20 mol % $Mg(OTf)_2$, in $CHCl_3$ (EtOH stabilized) at room temperature. [b] Conversion after 24 h at room temperature.

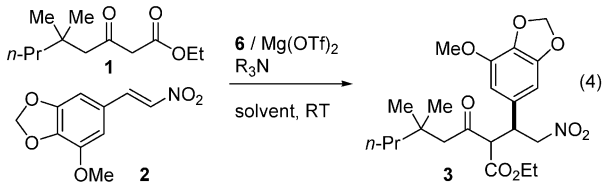
was obtained with moderate, although variable, selectivity (eq 2). On addition of *N*-methylmorpholine (NMM) as a cocatalyst, the reaction proceeded at ambient temperature with a concomitant increase in selectivity.[23] Interestingly, the structure of the base cocatalyst had little effect on the reaction,[24] although stronger bases displayed poorer selectivity, presumably the result of an observed background reaction. Under these conditions, other metal salts again were found to be ineffective in promoting the reaction.




without amine cocatalyst, 60 °C: 40-68% selectivity[20]
with 20 mol% *N*-methylmorpholine (NMM), RT: 70% selectivity[20]

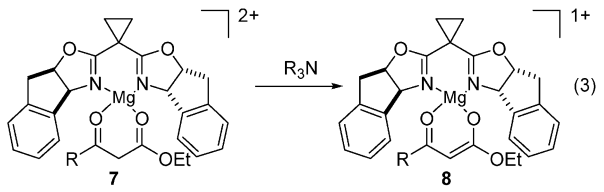
Another series of experiments revealed the quantity of base required for efficient reaction (Table 1). As noted above, in the absence of an amine additive, the reaction is slow, and the reaction rate is maximized at 1 equiv of amine relative to metal complex. Surprisingly, the addition of up to 5 equiv does not inhibit the reaction, indicating that amine binding to the metal center is not competitive with substrate binding. The above results are consistent with a reaction manifold in which catalyst-bound ketoester complex **7** (which is acidified relative to free ketoester) is deprotonated by the amine to generate chiral magnesium enolate **8**, which adds diastereoselectively to the nitrostyrene (eq 3). Because of the low basicity of nitroarenes ($pK_a$ of the conjugate acid of nitrobenzene $\approx -11$),[25] we favored this hypothesis over a mechanism in which the metal complex acts solely as a Lewis acid.

***Table 2.*** Effect of Solvent and Molecular Sieves in the Conjugate Addition




| entry | solvent | sieves[a] | selectivity[20] |
|---|---|---|---|
| 1 | $CHCl_3$ (ethanol stabilized) | no | 80% |
| 2 | toluene | no | 80% (61%)[b] |
| 3 | $CH_2Cl_2$ | no | 65% |
| 4 | EtOAc | no | 60% |
| 5 | $CHCl_3$ (hydrocarbon stabilized) | no | 87% |
| 6 | $CHCl_3$ (hydrocarbon stabilized) | yes | 91% |

[a] 200 mg of activated 4 Å sieves/mmol nitrostyrene. [b] Number in parentheses indicates reaction at 65 °C.




A number of ligands were screened in the reaction. The initial bis(oxazoline) ligand **6** derived from aminoindanol with a cyclopropane bridge proved to be the superior ligand (80% selectivity). Replacing the cyclopropane bridge with a variety of substituents led to a dramatic reduction in both selectivity and reactivity. With the exception of cyclopropane-bridged bis(4,5-diphenyloxazoline) (77% selectivity), other bis(oxazoline) substitution patterns led to poor results, as did bis(imine) ligands, and we continued to focus on ligand **6**.[26]

The choice of counterion is critical to selectivity with more coordinating counterions leading to poorer results (OTf, 80%; I, 65%; Br, 22%). More surprising was the dramatic solvent effect (Table 2, eq 4). The above reactions had been run in ethanol-stabilized $CHCl_3$. Toluene gave similar selectivities at ambient temperature (80%); however, due to the poor solubility of nitrostyrene **2**, the reaction required heating to 65 °C to achieve reasonable reaction rates, and at this temperature the selectivity suffered (61%). When ethanol was eliminated by

(20) Selectivity is defined as selectivity at the position $\beta$ to the product nitro group. The adducts of $\beta$-ketoesters with nitrostyrenes are generally formed as 1:1 mixtures of compounds diastereomeric at the product ketoester α-position due to rapid equilibration under the reaction conditions. By NMR, the enol tautomer is also observed sometimes. See the Supporting Information.

(21) (a) Davies, I. W.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett*. **1996**, *37*, 813−814. (b) Davies, I. W.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett*. **1996**, *37*, 1725−1728. (c) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett*. **1996**, *37*, 3815−3818. For a review of the use of $C_2$-symmetric bis(oxazoline) ligands in asymmetric catalysis, see: (d) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1−45.

(22) For examples of the use of bis(oxazoline)-magnesium complexes in catalysis, see: Conjugate additions of *O*-benzylhydroxylamine to unsaturated amides: (a) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc*. **1998**, *120*, 6615−6616. Radical additions to α,$\beta$-unsaturated imides: (b) Sibi, M. P.; Ji, J. *J. Org. Chem*. **1997**, *62*, 3800−3801. (c) Sibi, M. P.; Chen, J. *J. Am. Chem. Soc*. **2001**, *123*, 9472−9473. Additions of 1,3-dicarbonyl-2-radical species: (d) Yang, D.; Gu, S.; Yan, Y.-L.; Zhu, N.-Y.; Cheung, K.-K. *J. Am. Chem. Soc*. **2001**, *123*, 8612−8613. Diels−Alder reaction: (e) Kanemasa, S.; Oderaotoshi, Y.; Sakaguchi, S.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Am. Chem. Soc*. **1998**, *120*, 3074−3088. (f) Carbone, P.; Desimoni, G.; Faita, G.; Filippone, S.; Righetti, P. *Tetrahedron* **1998**, *54*, 6099−6110. (g) Desimoni, G.; Faita, G.; Invernizzi, A. G.; Righetti, P. *Tetrahedron* **1997**, *53*, 7671−7688. (h) Takacs, J. M.; Quincy, D. A.; Shay, W.; Jones, B. E.; Ross, C. R., II. *Tetrahedron: Asymmetry* **1997**, *8*, 3079−3087. (i) Corey, E. J.; Ishihara, K. *Tetrahedron Lett*. **1992**, *33*, 6807−6810. Nitrone 1,3-dipolar cycloadditions: (j) Gothelf, K. V.; Hazell, R. G.; Jorgensen, K. A. *J. Org. Chem*. **1998**, *53*, 5483−5488.

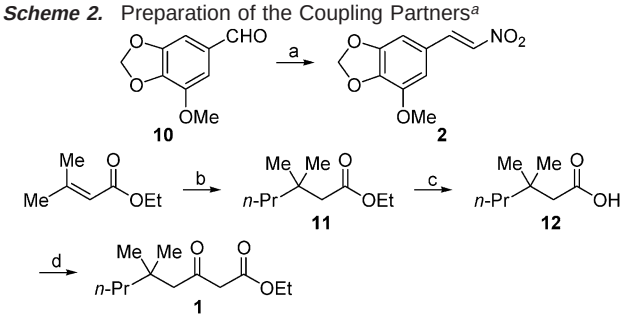
(23) It was later found that initial lots of ketoester **1** contained small amounts of imidazole. When the reaction described in eq 2 was run using imidazole-free ketoester in the absence of any amine additive, almost no reaction occurred.

(24) Selected amines: 2,6-lutidine, 77% selectivity; imidazole, 74%; 5,6-dimethylbenzimidazole, 80%; *N*-ethylpiperidine, 64%; triethylamine, 68%.

(25) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley-Interscience: New York, 1992; p 250.

(26) See the Supporting Information for the results using other ligands. For studies of the effect of the bridge substituents of bis(oxazoline) ligands, see ref 22a,b and: (a) Davies, I. W.; Gerena, L.; Castonguay, L.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Chem. Commun*. **1996**, 1753−1754. (b) Davies, I. W.; Gerena, L.; Cai, D.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett*. **1997**, *38*, 1145−1148. (c) Davies, I. W.; Deeth, R. J.; Larsen, R. D.; Reider, P. J. *Tetrahedron Lett*. **1999**, *40*, 1233−1236. See also ref 21. (d) Denmark, S. E.; Stiff, C. M. *J. Org. Chem*. **2000**, *65*, 5875−5878.

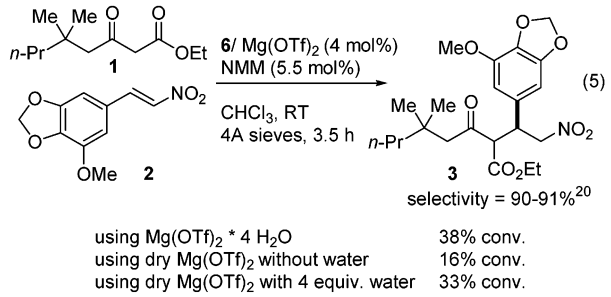
***Scheme 2.*** Preparation of the Coupling Partners[a]



[a] (a) $CH_3NO_2$, $NH_4OAc$, HOAc. (b) *n*-PrMgCl, CuI, TMSCl, THF, −10 °C. (c) NaOH, EtOH, $H_2O$, 65 °C. (d) (i) CDI, THF; (ii) potassium ethyl malonate, $MgCl_2$.

employing hydrocarbon stabilized $CHCl_3$, the result was higher selectivity (87%, entry 5) and a 20% increase in rate. Finally, when the reaction was run in the presence of molecular sieves, not only did the selectivity of the reaction improve (91%, entry 6), but the rate also increased 3-fold. *As a result, the reaction could be run using only 4 mol % catalyst at slightly elevated temperatures (35 °C), to complete the reaction in a reasonable amount of time (~18 h) and with good selectivity (88%).* Control experiments in a related reaction (vide infra) demonstrated that the sieves served only to remove water.[27] This was especially interesting in light of the lack of effect excess amine imparted to the reaction (vide supra).

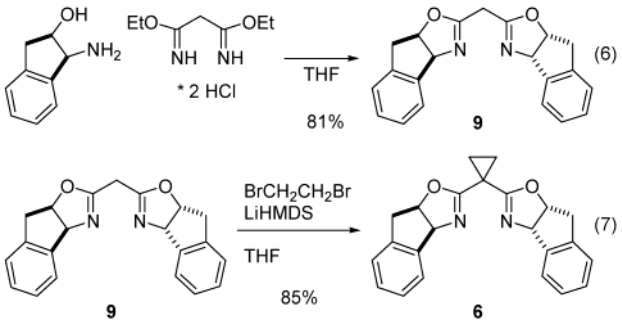
For the previous reactions, the $Mg(OTf)_2$ had been obtained as the tetrahydrate. When a "dry" lot of magnesium salt (containing only 20 mol % water) was employed in the reaction, the rate dropped dramatically, although no effect on the selectivity was observed (eq 5). The activity of the catalyst was restored by adding water to the dry $Mg(OTf)_2$.[28] Thus, while water is an inhibitor of the catalyst, it is nonetheless necessary for water to be present during the complexation step to generate fully active catalyst.




(5)

The role of the water is not clearly understood at this time. As the selectivity is unchanged, the reaction behaves empirically as though an inactive complex is generated in the absence of water. In the absence of conclusive data, we postulate that water acts in the initial complexation step to prevent catalyst aggregation to an inactive species. Alternatively, for activity, the magnesium center may require ligation by 1 or 2 equiv of water for which it could compete with the sieves.

**Ligand Preparation.** With a reliable asymmetric coupling reaction in hand, we required a method for the preparation of ligand **6**. We found that the condensation of aminoindanol with diethyl malonimidate proceeded cleanly in THF;[21c] parent ligand **9** was isolated in 81% yield after precipitation from the reaction mixture by the addition of aqueous $NaHCO_3$ (eq 6). A screening of bases for the installation of the cyclopropane bridge with 1,2-dibromoethane[26a] indicated that LiHMDS provided good conversion and purity; the desired ligand **6** was isolated in 85% yield by crystallization from EtOH (eq 7).




**The Synthesis of ABT-546.** The requisite nitrostyrene is prepared by a Henry reaction between aldehyde **10** and nitromethane using $NH_4OAc$ in acetic acid; nitrostyrene **2** conveniently precipitates during the reaction (Scheme 2). The synthesis of ketoester **1** commences with the copper mediated 1,4-addition of *n*-PrMgCl to ethyl dimethylacrylate in the presence of TMSCl at <0 °C. At higher temperatures, or in the absence of TMSCl, byproducts arising from 1,2-addition are formed in significant quantities, and these are difficult to remove from the desired ester **11**. Saponification provides acid **12**, which is homologated to ketoester **1** via activation to the acyl imidazolide with CDI, followed by reaction with the magnesium enolate of potassium ethyl malonate.[29] Residual imidazole in the ketoester is carefully removed by washing the product solution with acid. The unpurified solution of ketoester **1** is then turned over into $CHCl_3$ in preparation for the conjugate addition. This three-step sequence proceeds in 88% yield from ethyl dimethylacrylate without isolations. In the case of both coupling partners, it is imperative to remove residual carboxylic acids (acid **13** or HOAc), which are stoichiometric poisons of the bis(oxazoline)-Mg catalyst.

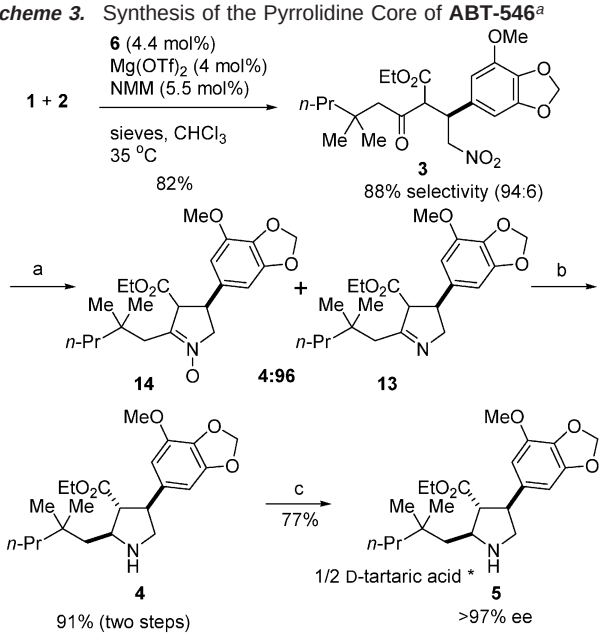
At this point, we were prepared for the critical asymmetric conjugate addition reaction. Dry $Mg(OTf)_2$ (4 mol %) was first hydrated with 4 equiv of water, and then combined with ligand **6** in $CHCl_3$ (Scheme 3). After the mixture was stirred for 1 h, more $CHCl_3$ was added along with the molecular sieves. When the resulting solution was dry (<20 $\mu$g water/mL solution by Karl Fisher coulometry), the remaining reagents were added, and the reaction was heated to 35−40 °C. On lab scale (0.1 mol of nitrostyrene **2**), the product nitroketone **3** was obtained in 73% yield and 88% selectivity. When scaled to 13 mol, the reaction proceeded in 82% yield (average of two runs) and in 88% selectivity. The variability in yields is attributed to a carbon

(27) The effect of water on other reactions catalyzed by bis(oxazoline) magnesium complexes has been described. See ref 22f,g,j.

(28) In a typical experiment, $Mg(OTf)_2 \cdot 4H_2O$ (19.6 mg, 0.05 mmol, 0.05 equiv) and ligand **6** (20.1 mg, 0.055 mmol, 0.055 equiv) are combined in the reaction vessel. One milliliter of $CHCl_3$ is added, and the mixture is stirred for 1 h. Four milliliters of $CHCl_3$ is added, followed by 200 mg of 4 Å molecular sieves, and the resulting mixture is stirred for an additional 90 min. Following this, nitrostyrene (1 mmol, 1 equiv) is added, followed by the 1,3-dicarbonyl coupling partner (1.2 mmol, 1.2 equiv) and *N*-methylmorpholine (6.6 $\mu$L, 0.06 mmol, 0.06 equiv). Conversion and selectivity are determined by HPLC analysis. See the Supporting Information for details.

(29) Clay, R. J.; Collom, T. A.; Karrick, G. L.; Wemple, J. *Synthesis* **1993**, 290−292. The addition of $MgCl_2$ to potassium ethyl malonate in THF is exothermic.

***Scheme 3.*** Synthesis of the Pyrrolidine Core of **ABT-546**[a]




a) Raney nickel, $H_2$, THF. b) $NaBH(OAc)_3$, HCl, MeCN. c) D-tartaric acid, MeCN, MeOH

[a] (a) Raney nickel, $H_2$, THF. (b) $NaBH(OAc)_3$, HCl, MeCN. (c) D-tartaric acid, MeCN, MeOH.

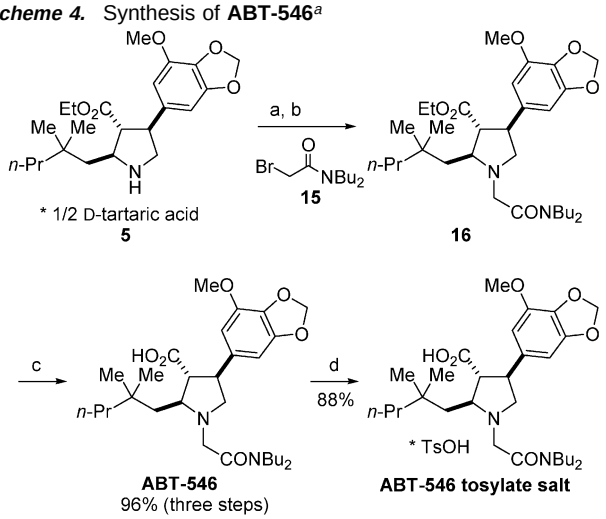
filtration which was incorporated to remove oligomeric impurities from aldehyde **10**.

Reduction of nitroketone **3** with $H_2$ over Raney nickel was investigated employing acid catalysts. Use of TFA or $H_2SO_4$ led to complex mixtures of products. HOAc was cleaner, generating a 3:1 mixture of imine **13** and nitrone **14**. Finally, in the presence of $H_3PO_4$, cyclic imine **13** was obtained containing only 4% of nitrone **14**. Next, $NaBH(OAc)_3$ delivered a hydride syn to the 3-carboxylate substituent to provide directly the desired trans,trans pyrrolidine **4** with less than 2% of any other diastereomer (Scheme 3). The basis of the selectivity of this apparently contrasteric reduction is not currently understood. While the resolution of racemic pyrrolidine was problematic (vide supra), the enantiomerically enriched pyrrolidine, prepared as outlined above, was crystallized with D-tartaric acid to yield 77% of salt **5** with >97% ee. In addition to improving the optical purity of the pyrrolidine, the crystallization also served as the first purification in the seven-step sequence from ethyl dimethylacrylate; tartrate salt **5** was isolated with less than 2% of nonsolvent impurities.

The completion of the synthesis was accomplished in a manner similar to that of **ABT-627**.[6] Tartrate salt **5** was broken with aqueous $K_2CO_3$ in THF (Scheme 4). Next, bromoacetamide **15** was added to the THF solution of free base, along with aqueous $NaHCO_3$, and the reaction was heated until alkylation was complete. Finally, to the organic layer was added EtOH and aqueous NaOH to effect the saponification. This three-step, one-pot sequence provided the free base of **ABT-546** in 96% yield. Crystallization of **ABT-546** as its tosylate salt proceeded in 88% yield. Thus, the synthesis of **ABT-546** was accomplished in 39% overall yield in 11 steps from ethyl dimethylacrylate with two isolations.

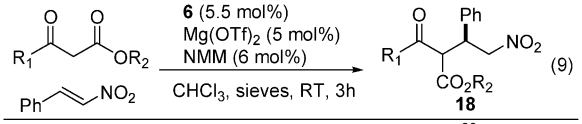
**Scope of the Addition of Ketoesters to Nitrostyrenes.** We next set out to define the scope and mechanism of the asymmetric conjugate addition reaction. Initially, we looked at the

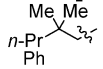
***Scheme 4.*** Synthesis of **ABT-546**[a]



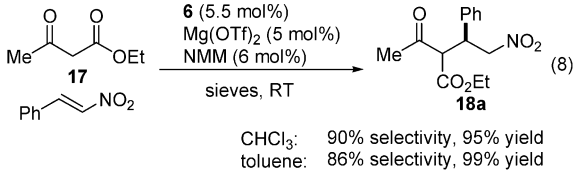

[a] (a) $K_2CO_3$, THF, water. (b) acetamide **15**, $NaHCO_3$, water. (c) NaOH, EtOH, water. (d) TsOH, isopropyl acetate, heptane.

***Table 3.*** Scope of Ketoesters in the Michael Addition



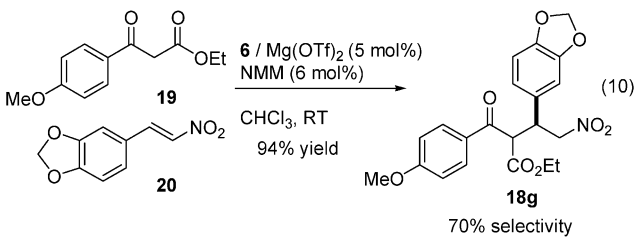

| Entry | $R_1$ | $R_2$ | adduct | selectivity[20] | yield |
|---|---|---|---|---|---|
| 1 | Me | Et | **18a** | 90% | 95% |
| 2 | Me | *i*-Bu | **18b** | 88% | 92% |
| 3 | Me | *tert*-Bu | **18c** | 29% | 94% |
| 4 | $CHMe_2$ | Et | **18d** | 94% | 90% |
| 5 |  | Et | **18e** | 92% | 95% |
| 6 | Ph | Et | **18f** | 87% | 83% |

reaction of ethyl acetoacetate (**17**) with nitrostyrene (eq 8). Using the optimized conditions defined above, we found that this reaction proceeded at room temperature to afford adduct **18a** with 90% selectivity. A number of reaction variables were reinvestigated (solvent, ligand, metal, counterion, and water content), and the same trends were observed as in the case of the reaction of ketoester **1** with nitrostyrene **2** (vide supra). Importantly, due to the improved solubility properties of nitrostyrene, the reaction can be run in toluene at ambient temperature with 86% selectivity.

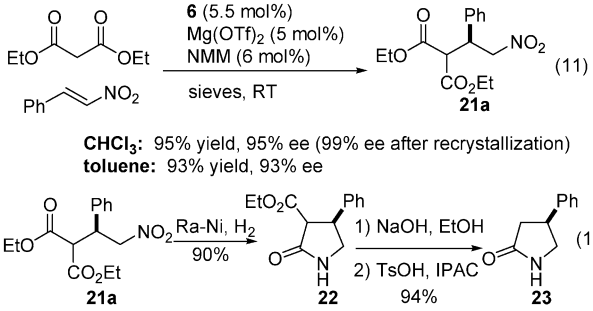



As seen in Table 3, the size of the ester affects the selectivity of the reaction. While *iso*-butyl acetoacetate reacts with 88% selectivity (entry 2), the larger *tert*-butyl acetate is slower, and the product is formed with only 29% selectivity (entry 3). A wide range of substitution patterns are tolerated on the ketone moiety, from ethyl isobutyryl acetate (entry 4, 94%) to the dimethylpentyl derivative (entry 5, 92%) to ethyl benzoyl acetate (entry 6, 87%). Unfortunately, the reaction of ketoester **19** with nitrostyrene **20**, required for the synthesis of **ABT-627**, the clinical predecessor to **ABT-546**, proceeds in only 70% selectivity (eq 10). Because of their increased steric hindrance, 2-sub-

stituted ketoesters (e.g., ethyl 2-methylaceoacetate) are significantly less reactive in the addition reaction with nitrostyrene.[30]




**Malonate Additions to Nitroalkenes.** We also examined the addition of malonates to nitroalkenes and were pleased to find that these substrates are generally as effective, and tolerate a wider range of reaction conditions than ketoesters. For example, the reaction of diethyl malonate with nitrostyrene not only proceeds in 95% ee in $CHCl_3$, but also delivers excellent selectivity in toluene (93% ee, eq 11). To prove the sense of induction of this reaction and to demonstrate the utility of these malonate reactions in the preparation of pyrrolidinones, we converted adduct **21a** to (*S*)-4-phenyl-2-pyrrolidinone (**23**, eq 12).[31] Raney nickel hydrogenation led directly to ethyl 2-pyrrolidinone-3-carboxylate **22** in 90% yield. Saponification of the ester followed by decarboxylation with TsOH yielded (*S*)-4-phenyl-2-pyrrolidinone (**23**, $[\alpha]^{25}_D = +35.2$ (*c* 1.02 MeOH); lit.[32] $[\alpha]^{25}_D = -33.8$ (*c* 0.89 MeOH) for the (*R*)-enantiomer) in 94% yield for the two steps.

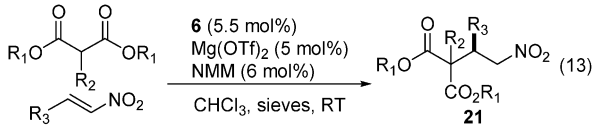



This reaction has been extended to a variety of malonate and nitroalkene substrates (Table 4, eq 13). As in the case of ketoesters, variation in the ester group is tolerated to a point (entries 1−4); di-(*tert*-butyl) malonate reacts in only 33% ee (entry 5). The added reactivity of malonate anions relative to ketoesters encouraged us to employ 2-substituted derivatives. Although the reactions were generally sluggish, several derivatives were screened. While dimethyl methoxymalonate reacted with excellent selectivity (89%, entry 7), methyl (entry 6) or amido (entries 8 and 9) substituents led to low ee's.

The reaction is highly tolerant of different nitroalkene substituents. Electron-rich (entries 10−12) and electron-poor (entry 13) nitrostyrenes react with high selectivity, as does a 2-furyl derivative (entry 14) and aliphatic nitroalkenes (entries 15 and 16).

Because of the increased nucleophilicity of the malonate anion, we have attempted to employ the catalyst system in the addition of malonate to other activated olefins. However, no adduct was formed in reactions with ethyl cinnamate or dimethyl fumarate (10% catalyst, room temperature, $CHCl_3$). Likewise, when ethyl coumarin-3-carboxylate was employed as the electrophile, the desired product was only detected in small amounts by LC-MS.

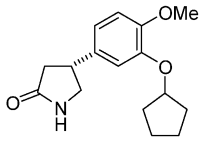
***Table 4.*** Scope of the Malonate Michael Addition




| entry | $R_1$ | $R_2$ | $R_3$ | adduct | ee | yield |
|---|---|---|---|---|---|---|
| 1 | Et | H | Ph | **21a** | 95% | 92% |
| 2 | Me | H | Ph | **21b** | 93% | 96% |
| 3 | $CHMe_2$ | H | Ph | **21c** | 94% | 92% |
| 4 | $CH_2Ph$ | H | Ph | **21d** | 89% | 93% |
| 5 | *tert*-Bu | H | Ph | **21e** | 33% | 88% |
| 6[b] | Et | Me | Ph | **21f** | 46% | 71% |
| 7[b] | Me | OMe | Ph | **21g** | 89% | 83% |
| 8[b] | Et | NHAc | Ph | **21h** | 41% | 50% |
| 9[b] | Et | NHBOC | Ph | **21i** | 56% | 84% |
| 10 | Et | H | 3-MeO-4,5-$OCH_2O$-Ph | **21j** | 92% | 90% |
| 11 | Et | H | 3,4-$OCH_2O$-Ph | **21k** | 93% | 98% |
| 12 | Et | H | 2,6-(MeO)-Ph | **21l** | 97%[a] | 93%[a] |
| 13 | Et | H | 4-F-Ph | **21m** | 90% | 93% |
| 14 | Et | H | 2-furyl | **21n** | 89% | 92% |
| 15 | Et | H | *n*-$C_5H_{11}$ | **21o** | 89% | 93% |
| 16 | Et | H | $Me_2CHCH_2$ | **21p** | 90% | 88% |

[a] Reaction in toluene proceeded in 97% ee and 95% yield. [b] Reaction run with morpholine as base.

**Synthesis of Rolipram.** Because of the high enantioselectivity and yield of malonates addition to nitrostyrenes, we sought to employ this reaction in the syntheses of (*R*)-rolipram (**24**)[33,34] and its (*S*)-enantiomer. Rolipram, (±)-**24**, is an inhibitor of (PDE)-IV, a cyclic adenosine monophosphate (cAMP)-specific phosphodiesterase, and is employed in the treatment of depression.[35] To pursue an efficient asymmetric synthesis of each enantiomer, we surmised that the aryl-bearing stereocenter of rolipram could be established by the chiral Lewis acid catalyzed Michael addition of diethyl malonate to the fully elaborated nitrostyrene **26** (Scheme 5).




(*R*)-rolipram (**24**)

Nitrostyrene **26** was prepared in two steps from isovanillin **25** in 87% yield. Under the optimized conditions described above for the Michael reaction, nitroester (*R*)-**27** was prepared on multigram scale by employing ligand *ent*-**3** in 95% yield (96% ee). Alternatively, the enantiomer (*S*)-**27** was obtained in

(30) Ethyl 2-methylacetoacetate required >24 h to go to 90% conversion (HPLC). The still more hindered diethyl acetylsuccinate was only 50% converted after 126 h. The products were not isolated from these reactions.
(31) Petzoldt, K.; Schmiechen, R.; Hamp, K.; Gottwald, M. U.S. Patent 553911, 1996. Mulzer, J. *J. Prakt. Chem.* **1994**, *336*, 287.
(32) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1993**, *58*, 36−42.
(33) Schmiechen, R.; Horowski, R.; Palenschat, D.; Paschelke, G.; Wachtel, H.; Kehr, W. U.S. Patent 4 193 926, 1980.
(34) (a) For a review of the syntheses of rolipram, see: Mulzer, J. *J. Prakt. Chem.* **1994**, *336*, 287−291. (b) For a conceptually similar synthesis of Rolipram, employing a chiral enolate addition to a nitrostyrene, see: Mulzer, J.; Zuhse, R.; Schmiechen, R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 870−872.
(35) (a) Baures, P. W.; Egglestone, D. S.; Erhard, K. F.; Cieslinski, L. B.; Torphy, T. J.; Christensen, S. B. *J. Med. Chem.* **1993**, *36*, 3274−3277. (b) Sommer, N.; Loeschmann, P. A.; Northoff, G. H.; Weller, M.; Steinbrecher, A.; Steinbach, J. P.; Richtenfiels, R.; Meyermann, R.; Reithmueller, A.; Fontana, A.; Dichgans, J.; Martin, R. *Nat. Med.* **1995**, *1*, 244. (c) Seika, M. *Drugs Future* **1998**, *23*, 108−109 and references therein.

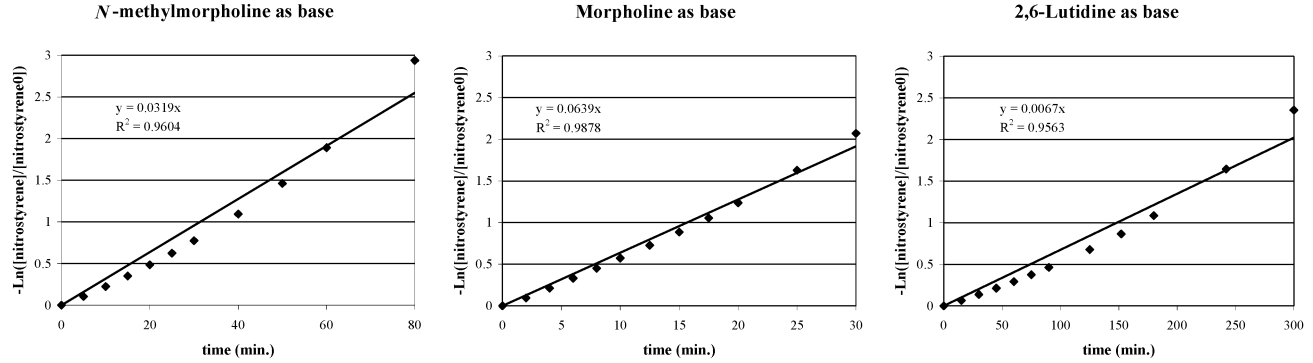
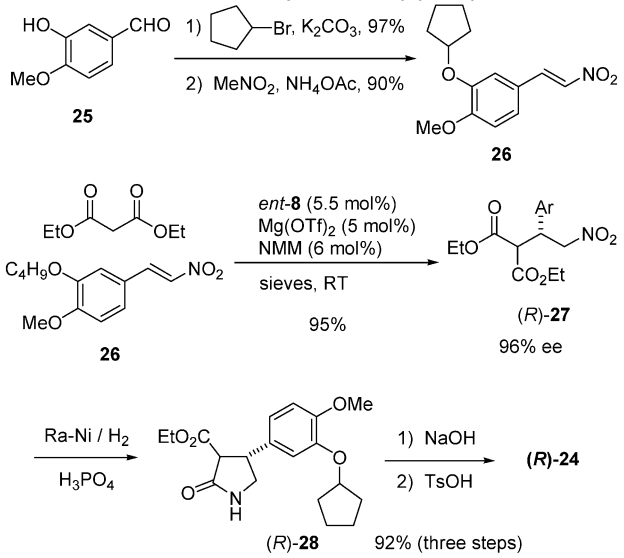



***Figure 2.*** Pseudo-first-order kinetics for malonate addition employing NMM, morpholine, and lutidine as bases. Kinetics of consumption employing amine bases. Reactions were run under pseudo-first-order conditions in malonate. The lines were generated by best-fit to the data points.

***Scheme 5.*** Enantioselective Synthesis of (*R*)-Rolipram




94% yield (97% ee) using ligand **3**. Hydrogenation of (*R*)-**27** with 1 equiv of Raney-Ni in the presence of 10 mol % $H_3PO_4$ in THF at 50−60 °C under $H_2$ (40 psi) gave lactam (*R*)-**28**. The reaction rate was slowed if more $H_3PO_4$ was employed (>20 mol %) due to the competitive reaction between the acid and Raney-Ni. Similarly, slower reaction rates were obtained, and additional byproducts were formed when run with HCl or $CF_3CO_2H$. Without purification, lactam (*R*)-**28** was saponified with NaOH in EtOH/THF (1/1), then decarboxylated using TsOH in refluxing *i*-PrOAc. (*R*)-Rolipram ($[\alpha]^{25}_D = -30.8°$ (*c* 1.02, MeOH) [lit.[36a] (*R*)-rolipram: $[\alpha]^{25}_D = -31.0°$ (*c* 0.5, MeOH)]) was obtained in 92% yield from (*R*)-**27**. The identical process of hydrogenation, saponification, and decarboxylation furnished (*S*)-rolipram ($[\alpha]^{25}_D = 30.1°$ (*c* 1.02, MeOH)) in 90% yield from lactam (*S*)-**27**.

Thus, we achieved a concise and efficient synthesis of both enantiomers of rolipram. The process was accomplished in six steps without chromatography from commercially available isovanillin and proceeds in an overall yield of 76%.

**Mechanistic Studies on the Catalyzed Conjugate Addition Reaction.** A number of mechanistic studies were carried out on the catalyzed reaction of ethyl acetoacetate with nitrostyrene. The reaction was found to be ligand-accelerated, with no reaction in the absence of ligand, and to possess full activity in

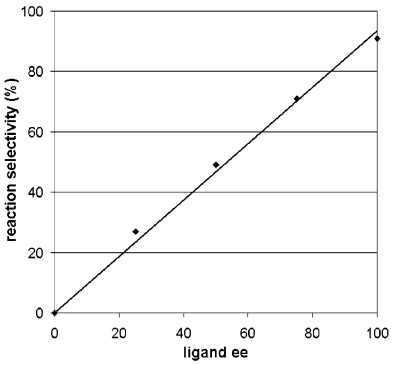



***Figure 1.*** Ligand ee versus reaction selectivity.

the presence of 1 equiv of ligand relative to $Mg(OTf)_2$ (eq 14). The reaction also shows little evidence of nonlinear effects (Figure 1), suggesting that the active catalyst is a monomeric species.[36]


| equiv. ligand (relative to metal) | conversion (1 h) | selectivity |
|---|---|---|
| 0 | 1% | --- |
| 0.55 | 52% | 90% |
| 1.1 | 73% | 91% |
| 1.65 | 74% | 91% |
| 2.2 | 75% | 91% |

A previous report described a dramatic effect of water on the magnesium-bis(oxazoline) catalyzed addition of nitrones to α,β-unsaturated imides.[22j] To explain a reversal in the sense of enantioselectivity, the authors suggested that the catalyst bound to the surface of the sieves, changing the coordination geometry of the magnesium complex. To investigate this possibility in the present study, an experiment was run in which the sieves were removed just prior to the addition of ethyl acetoacetate and nitrostyrene. The reaction proceeded to 76% conv. in 1 h (90% selectivity), as compared with 74% conv. (90% selectivity) in the control reaction. Thus, there is no evidence that the molecular sieves interact with the catalyst other than to remove water from the reaction medium.

Kinetics studies show that the reaction is first-order in nitrostyrene and first-order in catalyst. In the range of ketoester concentration typically employed in this reaction, the order in

(36) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *37*, 2923−2959.

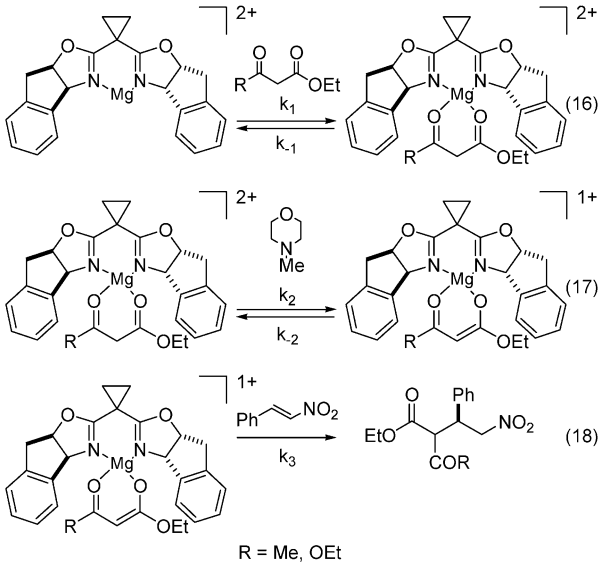
ketoester is zero, although at higher concentrations the reaction rate does decrease. It is not known whether this rate decrease is indicative of competitive ligation of the metal center, or simply a medium effect.

The rate equation is then

$$\text{rate} = k[\text{nitrostyrene}]^1[\text{catalyst}]^1[\text{ketoester}]^0 \quad (15)$$

$k = 0.848\ \text{M}^{-1}\ \text{s}^{-1}$ ([nitrostyrene]$_0$ = 0.1 M, [catalyst] = 0.005 M, [ketoester]$_0$ = 1 M), where catalyst = ligand + $Mg(OTf)_2$ + amine.

This supports the mechanism shown in eqs 16−18 (R = Me) where deprotonation of the catalyst-bound ketoester by the amine to form a chiral magnesium enolate (eq 17) is rapid. The order in ketoester is zero because the concentration of this enolate is solely dependent on the catalyst concentration. This chiral enolate then adds diastereoselectively to the nitrostyrene in the rate-determining step (eq 18). Catalyst turnover could be accomplished by proton transfer from the ammonium species to the catalyst-bound product or from another molecule of ketoester.




When the kinetics of the reaction of diethyl malonate with nitrostyrene were examined under pseudo-first-order conditions in malonate, the result was a slightly curved line (Figure 2). When the initial rate was measured with varying nitrostyrene concentrations, the reaction was found to be 0.6 order in nitrostyrene. In addition, the reaction was found to be 0.45 order in malonate, and first order in catalyst.

The difference between rate equations for ketoester and malonate substrates can be explained as the result of the slower deprotonation of the catalyst-bound malonate (eq 17, R = OEt). This leads to a more complicated kinetic analysis in which all of the species appear in the rate equation. If this were the case, one would expect that changing the strength of the base should alter both the rate of the reaction, and the degree of curvature under pseudo-first-order conditions. Indeed, when the reaction was run with morpholine (relative rate = 2.3) and 2,6-lutidine (relative rate = 0.22), these trends were borne out (Figure 2).

Although there is little data to indicate the structure of the transition state of this reaction, we favor an octahedral or square pyramidal geometry with the ligand and enolate in the plane,

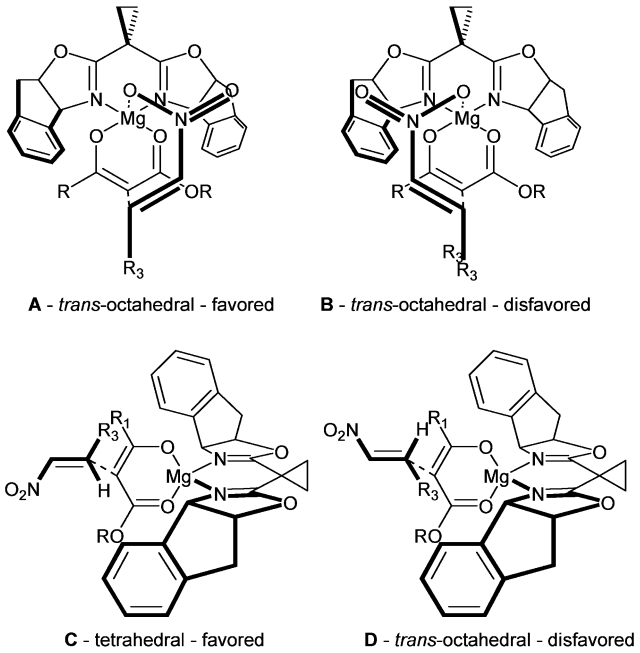


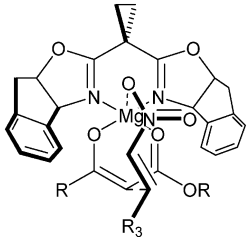

***Figure 3.*** Possible transition structures.

and a triflate counterion or a water molecule in the apical position (Figure 3).[37] In this construct, the incipient nitronate anion is stabilized by an interaction with the open apical position on the metal. As shown in the structures, in the disfavored approach (**B**), the nitro group experiences steric interactions with the ligand. On the other hand, in the favored approach (**A**), that space is occupied by a hydrogen atom.[38] While this argument predicts the correct sense of induction, it is difficult to rule out tetrahedral or *cis*-octahedral structures[39] on the basis of an analysis of these reactions. For instance, the tetrahedral transition structures shown (**C** and **D**) also correctly predict the observed sense of induction.

In conclusion, we have described a novel catalytic enantioselective addition of 1,3-dicarbonyl compounds to nitroolefins. This soft enolization/addition reaction has been shown to proceed with excellent selectivity at the center $\beta$ to the nitro group in a number of cases. Mechanistic studies support a monomeric catalyst which activates the dicarbonyl compound to enolization by the added amine. The resulting chiral enolate adds diastereoselectively to the nitroolefin. The utility of this

(37) Octahedral (ref 22f) and square planar (ref 22d) structures have been proposed for the coordination of 1,3-dicarbonyl compounds to bis-(oxazoline)-magnesium species.

(38) The structures in the text show an "S-cis" addition of the nitroolefin to the enolate. An "S-trans" addition, which would predict the opposite sense of induction, is felt to be disfavored due to the added length of the extended $\pi$-system. In addition, there may be a coulombic interaction between one of the carbonyl oxygens and the nitro oxygen.




(39) Tetrahedral (ref 22b,i) and *cis*-octahedral (ref 22c) structures have been proposed for the coordination of 1,3-dicarbonyl compounds to bis-(oxazoline)-magnesium species.

reaction is demonstrated in the syntheses of the selective endothelin-A antagonist **ABT-546** and the active enantiomer of the antidepressant rolipram.

**Acknowledgment.** The authors thank Dr. Tony Haight for helpful discussions.

**Supporting Information Available:** Experimental procedures, characterization and kinetics data, and ligands screened (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA026788Y