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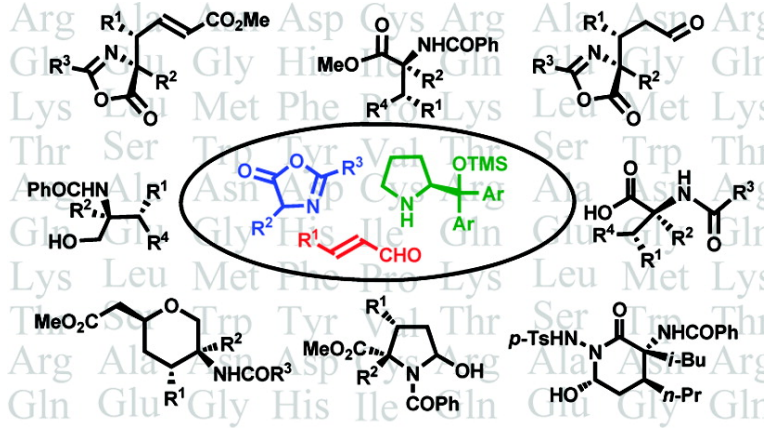
J. Am. Chem. Soc., **2008**, 130 (36), 12031-12037 • DOI: 10.1021/ja804567h • Publication Date (Web): 13 August 2008



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Organocatalytic Asymmetric Synthesis of α,α-Disubstituted α-Amino Acids and Derivatives

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Abstract: It is shown that racemic oxazolones are excellent reagents for the synthesis of chiral quaternary amino acids and its derivatives by the diastereo- and enantioselective nucleophilic addition to α,β-unsaturated aldehydes catalyzed by diarylprolinol silyl ethers. The scope of this new organocatalytic reaction is demonstrated for different oxazolones having aromatic and alkyl groups at the reactive carbon atom and different aromatic and aliphatic substituted α,β-unsaturated aldehydes, for which the stereoselective reaction proceeds with good yield, moderate to good to very high diastereoselectivity, and very high enantioselectivity. The potential of the reaction is shown for the synthesis of optically active α,α-disubstituted α-amino acids, α-quaternary proline derivatives, amino alcohols, lactams, and tetrahydropyranes. Furthermore, we have calculated by DFT-methods the transition-state structures that account for both the diastereo- and enantioselectivity observed for the addition of oxazolones to the α,β-unsaturated aldehydes. For one class of compounds, the stereoselectivity is controlled by a hydrogen-bonding interaction of the enolate-form of the oxazolone with an *ortho*-hydroxy-phenyl substituent of the α,β-unsaturated aldehyde, whereas the benzhydryl-protecting group in the oxazolone determines the diastereo- and enantioselectivity in a more general manner for both aromatic and aliphatic α,β-unsaturated aldehydes.

Introduction

The synthesis of non-natural amino acids and their derivatives, as well as the design of peptides and proteins, is an area of great interest in biological and medicinal chemistry.[1] A particular class of non-natural amino acids, which has received considerable interest, is the α,α-disubstituted (quaternary) α-amino acids.[2] There are several reasons for the importance of these α,α-disubstituted α-amino acids, such as stability toward racemization *in vivo* and restricted conformational flexibility. The latter property is highly important for, for example, the secondary structure of proteins, which can lead to an improvement of the resistance against chemical and enzymatic degradation.[3] Furthermore, α,α-disubstituted α-amino acids are also present in many biologically active compounds and some antibiotics, such as altemicidin.[4]

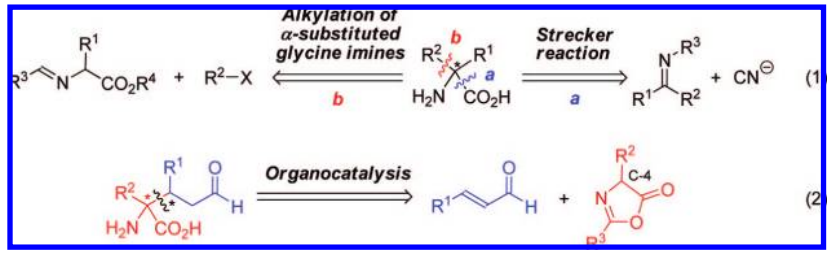
The importance of α,α-disubstituted α-amino acids has caused an increased interest in the development of efficient methodologies for the asymmetric synthesis of these valuable optically active compounds. One of the challenges is to have procedures that provide flexible and simple methods for obtaining optically active α,α-disubstituted α-amino acids and that, furthermore, give diversity in structural and electronic properties.

A classical procedure for the synthesis of α-amino acid derivatives[5] is the Strecker reaction[6] (eq 1, right part, Scheme 1). This reaction is well-established for the asymmetric synthesis of chiral α-substituted amino acids starting from aldimines; however, the synthesis of chiral α,α-disubstituted α-amino acids using ketimines is now in progress and shows some limitations.[7] These limitations are related to the lower reactivity and easy enolization of the ketimines, as well as the difficulties to synthesize the starting compounds. A more recent approach for the preparation of optically active α,α-disubstituted α-amino acids is the alkylation of imines derived from Schiff bases with chiral phase-transfer catalysis (eq 1, left part, Scheme 1).[8]

One of the less explored methods to obtain chiral α,α-disubstituted α-amino acids is the use of oxazolones as a masked

(1) Venkatraman, J.; Shankaramma, S. C.; Balaram, P. *Chem. Rev.* **2001**, *101*, 3131.
(2) For reviews on synthesis of α,α-disubstituted α-amino acids, see, for example:(a) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517. (b) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 3517. (c) Ohfune, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, 5127. (d) Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406.
(3) (a) Khosla, M. C.; Stachowiak, K.; Smeby, R. R.; Bumpus, F. M.; Piriou, F.; Lintner, K.; Fermandjian, S. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 757. (b) O'Connon, S. J.; Liu, Z. *Synlett* **2003**, 2135. (c) Tanaka, M. *Chem. Pharm. Bull.* **2007**, *55*, 349.
(4) (a) Takahashi, A.; Naganawa, H.; Ikeda, D.; Okami, Y. *Tetrahedron* **1991**, *47*, 3621. (b) Kan, T.; Kawamoto, Y.; Asakawa, T.; Furuta, T.; Fukuyama, T. *Org. Lett.* **2008**, *10*, 168.
(5) For a recent review on catalytic asymmetric synthesis of α-amino acids, see:Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584.
(6) (a) Gröger, H. *Chem. Rev.* **2003**, *103*, 2795. (b) Vilaivan, T.; Bhanthumnavin, W.; Sritana-Anant, Y. *Curr. Org. Chem.* **2005**, *9*, 1315.
(7) For a highlight of the Strecker reaction, see:(a) Connon, S. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1176.
(8) For recent reviews of phase-transfer catalysis, see:(a) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222. (b) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656.

Scheme 1. Two Classic Different Approaches for the Synthesis of α,α-Amino Acids (eq 1) and the Alternative Organocatalytic Asymmetric Synthesis of α,α-Disubstituted α-Amino Acids (eq 2)



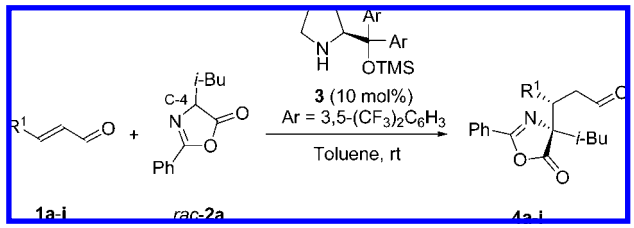
amino acid fragment.[9] These compounds have been applied for, for example, the synthesis of α,α-disubstituted α-amino acids by ring-opening reactions of chiral quaternary oxazolones, generated by the Steglich reaction,[10] as electrophile source, whereas the application of oxazolones as nucleophiles is mainly restricted to alkylation by metal catalysis.[11]

In the past few years, organocatalysis has been intensively studied.[12] During the recent rise in the development of new organocatalytic methodologies, asymmetric 1,4-conjugate/Michael additions have emerged as efficient and environmentally friendly processes for the synthesis of optically active organic compounds.[13] In this field, secondary amines have demonstrated to be one of the most successful type of organocatalysts that allow the sequential functionalization of aldehydes or α,β-unsaturated aldehydes, via enamine-[14] or iminium-ion intermediates,[15] in combination with electrophiles or nucleophiles, respectively. Furthermore, two new concepts—dienamine[16] and SOMO organocatalysis[17]—have emerged.

Here we will demonstrate a new development in organocatalysis, that racemic oxazolones can act as excellent reagents for the synthesis of chiral quaternary amino acids by nucleophilic addition to α,β-unsaturated aldehydes.[18] This new reaction leads to α,α-disubstituted α-amino acid derivatives with two new chiral centers in a one-step synthesis (eq 2, Scheme 1), that is, to both control the stereocenter formed from β-carbon atom in the α,β-unsaturated aldehyde and the C-4 carbon atom in the racemic oxazolone. To the best of our knowledge, this is the first organocatalytic Michael addition of oxazolones. The use of oxazolones for these reactions adds a further potential to organocatalysis, as the oxazolones contain orthogonal reactive sites that make them excellent substrates for their use in diversity oriented synthesis.[19] On the basis of this concept, we will also show that the optically active compounds formed undergo a number of diverse transformations leading to the formation of optically active α,α-disubstituted α-amino acids, α-quaternary proline derivatives, amino alcohols, lactams, and tetrahydropyranes. Furthermore, we will present these by using DFT-calculations transition-state models, which account for the

(9) Fisk, J. S.; Mosey, R. A.; Tepe, J. J. *Chem. Soc. Rev.* **2007**, *36*, 1432. See also ref 2d.
(10) Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532.
(11) (a) Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727. (b) Trost, B. M.; Dogra, K. *J. Am. Chem. Soc.* **2002**, *124*, 7256. (c) Trost, B. M.; Jakel, C.; Plietker, B. *J. Am. Chem. Soc.* **2003**, *125*, 4438.
(12) For recent reviews of organocatalysis, see *e.g.*:(a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (b) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; VCH: Weinheim, Germany, 2004. (c) *Acc. Chem. Res.* **2004**, *37* (8), special issue on organocatalysis. (d) Seayed, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (e) List, B.; Yang, J.-W. *Science* **2006**, *313*, 1584. (f) List, B. *Chem. Comm.* **2006**, 819. (g) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. C. *Drug Discovery Today* **2007**, *2*, 8. (h) Dalko, P. I. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, 2007. (i) *Chem. Rev.* **2007**, *107* (12), special issue on organocatalysis. (j) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560. (k) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638.
(13) For general reviews of organocatalytic conjugate addition, see:(a) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (b) Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. (c) Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2007**, 2065.
(14) For some recent examples of enamine organocatalyzed reactions, see, for example:(a) Yang, J. W.; Stadler, M.; List, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 609. (b) Brauman, T.; Vogt, H.; Bräse, S. *Eur. J. Org. Chem.* **2007**, 266. (c) Alemán, J.; Cabrera, S.; Maerten, E.; Overgaard, J.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5520. (d) Ramasastry, S. S. V.; Albertshofer, K.; Utsumi, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2007**, *46*, 5572. (e) Tiecco, M.; Carlone, A.; Sternativo, S.; Marini, F.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 6882. (f) Palomo, C.; Vera, S.; Velilla, I.; Mielgo, A.; Gómez-Bengoa, E. *Angew. Chem., Int. Ed.* **2007**, *46*, 8054. (g) Rodríguez, B.; Bruckmann, A.; Bolm, C. *Chem.—Eur. J.* **2007**, 4710. (h) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas III, C. F. *J. Am. Chem. Soc.* **2007**, *129*, 288. (i) Sulzer-Mosse, S.; Tissot, M.; Alexakis, A. *Org. Lett.* **2007**, *9*, 3749. (j) Utsumi, N.; Imai, M.; Tanaka, F.; Ramasastry, S. S. V.; Barbas III, C. F. *Org. Lett.* **2007**, *9*, 3445. (k) Hayashi, Y.; Urushima, T.; Arakate, S.; Okano, T.; Obi, K. *Org. Lett.* **2008**, *10*, 21. (l) Zhang, H.; Mitsumori, S.; Utsumi, N.; Imai, M.; Garcia-Delgado, N.; Mifsud, M.; Albertshofer, M.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas III, C. F. *J. Am. Chem. Soc.* **2008**, *130*, 875. (m) Luo, S.; Xu, H.; Zhang, L.; Li, J.; Cheng, J.-P. *Org. Lett.* **2008**, *10*, 653. (n) Pouliquen, M.; Blanchet, J.; Lasne, M.-C.; Rouden, J. *Org. Lett.* **2008**, *10*, 1029. See the following revision in enamine chemistry: (o) Mukherjee, S.; Woon-Yang, J.; Hoffman, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.
(15) For some recent examples of iminium activation, see, for example, :(a) Bertelsen, S.; Dinér, P.; Johansen, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 1536. (b) Dinér, P.; Nielsen, M.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1983. (c) Enders, D.; Bonten, M. H.; Raabe, G. *Synlett* **2007**, *6*, 885. (d) Carlone, A.; Bartoli, G.; Bosco, M.; Sambri, L.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 4504. (e) Ibrahem, I.; Rios, R.; Vesely, J.; Hammar, P.; Erikson, L.; Himo, F.; Córdova, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4507. (f) Maerten, E.; Cabrera, S.; Kjærsgaard, A.; Jørgensen, K. A. *J. Org. Chem.* **2007**, *72*, 8893. (g) Gotoh, H.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 5307. (h) Fustero, S.; Jiménez, D.; Moscardo, J.; Catalán, S.; del Pozo, C. *Org. Lett.* **2007**, *9*, 9905. (i) Lee, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 15438. See also: (j) Woon-Yang, J.; Hechavarria-Fonseca, M. T.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 6660. See the following revision in iminium chemistry: (k) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416.
(16) (a) Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973. (b) Bench, B. J.; Liu, C.; Evett, C. R.; Watanabe, C. M. H. *J. Org. Chem.* **2006**, *71*, 9458. (c) de Figueiredo, R. M.; Fröhlich, R.; Christmann, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1450.
(17) (a) Sibi, M. P.; Hasegawa, M. *J. Am. Chem. Soc.* **2007**, *129*, 4124. (b) Beeson, T. D.; Mastracchio, A.; Hong, J.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582. (c) Jang, H.-Y.; Hong, J.-B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004. (d) Kim, H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 398. For other revisions about radicals in organocatalysis, see: (e) Bertelsen, S.; Nielsen, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7356. (f) Mukherjee, S.; List, B. *Nature* **2007**, *447*, 152.
(18) One example of a TMS-enolate of a tertiary amino lactone adding to an α,β-unsatuarated aldehyde in enantioselective organo-cascade catalysis has been reported:(a) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051.
(19) For a review on diversity oriented synthesis, see:(a) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46.

Table 1. Reaction of α,β-Unsaturated Aldehydes **1** with Racemic Oxazolone *rac*-**2a**[a]



entry	R^1	dr[b]	product	yield (%)[c]	ee (%)[d]
1	Ph (**1a**)	1:1	**4a/4a′**	46	92/90
2	*o*-NO_2−C_6H_4 (**1b**)	3:1	**4b**	72	93
3	*o*-OH−C_6H_4 (**1c**)	>20:1	**4c**	36[e]	86
4	Me (**1d**)	3:1	**4d**	82	91
5	Et (**1e**)	4:1	**4e**	91	94
6	*n*-Pr (**1f**)	7:3	**4f**	88 (56)[f]	83 (84)[f]
7	Hepthyl (**1g**)	3:1	**4g**	87	92
8	(*Z*)-*n*-Hex-3-enyl (**1h**)	2:1	**4h**	76	93
9	$BnOCH_2$ (**1i**)	2:1	**4i**	53[g]	84

[a] All reactions were performed on a 0.2 mmol scale in 0.2 mL of toluene. [b] Diastereoisomeric ratio determined by ^{1}H NMR spectroscopy of the crude mixture. [c] Overall yield of both diastereoisomers after FC. [d] Determined by HPLC of the major diastereoisomer after derivatization (see the Supporting Information). [e] Overall yield of the major diastereoisomer after derivatization into **5**. [f] Reaction performed in a 4 mmol scale. [g] Yield of the major diastereoisomer after FC.

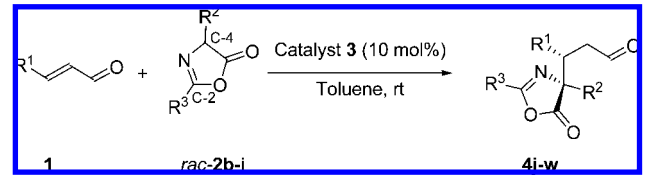
diastereo- and enantioselectivity observed for the different classes of α,β-unsaturated aldehydes and oxazolones applied.

Results and Discussion

Our initial screening showed two main observations: (a) the best results were achieved using 10 mol% of (*S*)-2-[bis(3,5-bis-trifluoromethylphenyl)trimethylsilyloxymethyl]pyrrolidine **3** as the catalyst[20] and toluene as solvent at room temperature (see Table SI-1 of Supporting Information for further details); (b) the new stereocenter created in the α,β-unsaturated aldehyde counterpart could be completely controlled, whereas control of the stereocenter generated in the oxazolone counterpart was more difficult. However, these difficulties were solved by choosing the appropriate protecting group in the oxazolone (see below).

Thus, with the optimized conditions in hand we studied the scope of the reaction and in Table 1 are shown the results obtained using different α,β-unsaturated aldehydes and *rac*-**2a** as the nucleophile. The use of cinnamaldehyde **1a** gave a 1:1 mixture of separable diastereoisomers **4a/4a′** with ≥90% ee for both compounds (Table 1, entry 1). The use of different *ortho*-substituents at the aryl group as an electron-withdrawing group (**1b**) or an electron-donating group (**1c**) increased the diastereoselectivity up to >20:1 with an enantioselectivity up to 93% ee (entries 2, 3). Alkyl substituted α,β-unsaturated aldehydes also reacted giving good stereoselectivities (entries 4−7). Thus, short alkyl chains as methyl, ethyl, and propyl or longer chains, such as hepthyl, could be used without losing enantioselective control, giving the corresponding products **4d**-**g** in high yields and enantioselectivities in the range of 83−94% ee (entries 4−7). The reaction could also be scaled up to 4 mmol scale, with only a slight decrease in the yield, but maintaining the enantio- and diastereoselectivity at high levels (entry 6). The catalytic system is also compatible with functionalized alkyl chains containing double bond or benzyl ether functionalities (entries 8, 9), obtaining in both cases good enantioselectivities.

Table 2. Reaction of α,β-Unsaturated Aldehyde **1e** with Racemic Oxazolones **2**[a]



entry	R^1	R^2/R^3	dr[b]	product	yield (%)[c]	ee (%)[d]
1	Et (**1e**)	*i*-Pr/Ph (**2b**)	1.2:1	**4j**	81[e] (73)	96
2	Et (**1e**)	Ph/Tol (**2c**)	7:3	**4k**	85	93
3	Et (**1e**)	Bn/Ph (**2d**)	3:1	**4l**	75	96
4	Et (**1e**)	Me/Ph (**2e**)	5:1	**4m**	65[f]	93
5	Et (**1e**)	Me/$CHPh_2$ (**2f**)	>10:1	**4n**	64[f]	96
6	Et (**1e**)	Ph/*t*-Bu (**2g**)	5:2	**4o**	71[g]	91
7	Et (**1e**)	*i*-Bu/*o*-ClPh (**2h**)	2:1	**4p**	54	88
8	Et (**1e**)	$MeS(CH_2)_2$/Ph (**2i**)	3:1	**4q**	73	94
9	*n*-Pr (**1f**)	Me/$CHPh_2$ (**2f**)	>10:1	**4r**	40	93
10	Ph (**1a**)	Me/$CHPh_2$ (**2f**)	6:1	**4s**	47	94
11	Me (**1d**)	Me/$CHPh_2$ (**2f**)	5:1	**4t**	59	90
12	Hexyl (**1j**)	Me/$CHPh_2$ (**2f**)	>10:1	**4u**	52	94
13	(*E*)-Prop-1-enyl (**1k**)	Me/$CHPh_2$ (**2f**)	>10:1	**4v**	55	92
14	(Z)-Hex-3-enyl (**1h**)	Me/$CHPh_2$ (**2f**)	>10:1	**4w**	38	94

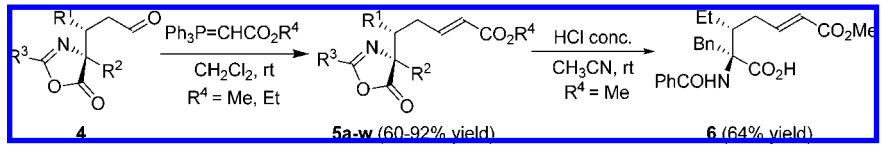
[a] All reactions were performed on a 0.2 mmol scale in 0.2 mL of toluene. [b] Diastereoisomeric ratio determined by ^{1}H NMR spectroscopy of the crude mixture. [c] Overall yield of both diastereoisomes after FC. [d] Determined by HPLC of the major diastereoisomer after derivatization (see the Supporting Information). [e] Conversion yield determined by ^{1}H NMR. [f] Yield of the major diastereoisomer after FC. [g] Overall yield of both diastereoisomers after derivatization into **5**.

Encouraged with these results we studied the addition of different oxazolones to pentenal **1e** (Table 2). The reason for choosing different oxazolones is to show one of the potentials of these reactions as changing the R^2-substituent in the oxazolone to alkyl, benzyl, and aryl will give α,α-disubstituted α-amino acid derivatives having alkyl/alkyl, alkyl/benzyl, and alkyl/aryl groups at the quaternary stereocenter, all of them are very difficult to obtain by only one methodology. Thus, at the C-4 atom in the oxazolone could be placed an alkyl chain (*i*-Pr, **2b**) or an aromatic group (Ph, **2c**), or a benzyl (**2d**) leading in all cases to >90% ee (entries 1−3). In a similar manner, different substituents could also be placed at the C-2 position in the oxazolone, as aromatic groups (**2e**,**h**), benzhydryl (**2f**), or alkyl (**2g**). For these oxazolones, the optically active products were obtained with good enantioselectivities and up to >10:1 dr (entries 4−7). Furthermore, more functionalized oxazolones, such as the methionine derivative **2i**, can also be added to **1e** to obtain the corresponding product **4q** in 94% ee (entry 8). It appears from Table 2, entry 5 that the oxazolone having the benzhydryl group (**2f**) increased the diastereoselectivity significantly and this result prompted us to investigate if we can improve the diastereoselectivity in a more general manner of the reactions giving low diastereoselectivity.

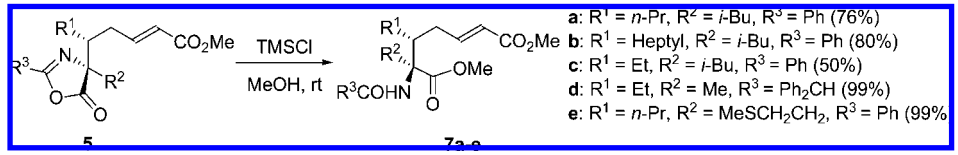
We then carried out the addition of six different α,β-unsaturated aldehydes, aryl (**1a**), three alkyl (**1d**,**f**,**j**), and two containing a double bond in different positions (**1k**,**h**). The

(20) For the first application of diarylprolinol silyl ethers as catalysts, see: (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem. Int. Ed* **2005**, *44*, 794. See also: (b) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703. (c) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (d) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296. (e) Palomo, C.; Mielgo, A. *Chem. Asian J.* **2008**, *3*, 922.

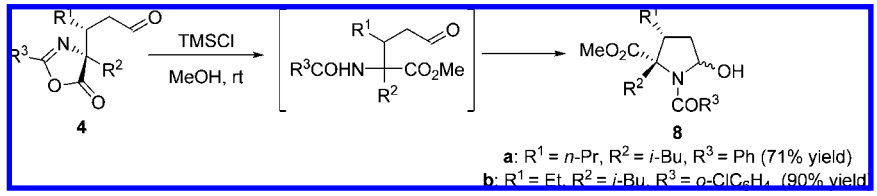
Scheme 2. Transformation to Alkenes **5** from Oxazolones **4** and Formation of Amino Acid Derivative **6**



Scheme 3. Transformation of Oxazolone Alkenes **5** to Amino Acid Esters **7** by Treatment with TMSCl



Scheme 4. Synthesis of Proline-derivatives **8** from Aldehydes **4**



reason for using **1a** was that this substrate gave no diastereoselectivity (Table 1, entry 1), whereas the other α,β-unsaturated aldehydes were used to expand the scope and to show the ability to control the diastereoselectivity of the reaction. We were pleased to find that the use of oxazolone **2f** gave a significant improvement in the diastereoselectivity in all cases (Table 2, entries 9−14); for cinnamaldehyde **1a**, the diastereomeric ratio improved from 1:1 to 6:1 and the major diastereomer was formed with 94% ee (entry 10). For the alkyl derivatives, and those having a double bond in the alkyl chain, **1d**,**f**,**j** and **1k**,**h**, respectively, the obtained diastereoselectivity was improved (up to >10:1) and excellent enantioselectivity was also obtained (entries 9,11−14).

The results in Tables 1 and 2 show that we can control the formation of two new stereocenters, a tertiary and a quaternary, by the proper choice of the C2-protecting group of the oxazolones, demonstrating the synthetic potential of this new asymmetric organocatalytic addition of oxazolones to α,β-unsaturated aldehydes.

Product Elaborations. The optically active products are important starting points for different transformations leading to a diverse number of compounds useful in various fields in life-science. In the following, we will demonstrate some of these transformations.

In most of the cases, the optically active major diastereoisomer products **4** could be isolated with Iatrobeads. For analytical purposes it was most convenient to convert **4** into **5** (Scheme 2), as the latter compounds were much easier to identify for enantiomeric excess determination by HPLC. One of the oxazolones (**5l**) was hydrolyzed to the corresponding protected amino acid **6** using HCl (conc.) in CH_3CN in moderate yield at room temperature.

To obtain the amino acid esters derived from **5**, a series of different products having alkyl chains as R^1-R^3 and also aromatic as R^3 were treated with TMSCl in MeOH to afford the α,α-disubstitued *N*-protected α-amino acid derivatives **7** in good yields (50−99%) without losing enaniopurity compared to the starting material (Scheme 3).

Direct treatment of **4f** and **4p** with TMSCl in MeOH afforded the *N*-protected proline derivatives **8a** and **8b** in 71% and 90% yield, respectively, with 3 stereocenters as only one diastereoisomer.[21] These proline derivatives, have a quaternary stereocenter in position 2, an alkyl group in position 3 and a hydroxy group in position 5, and are synthesized in only two steps following this methodology (Scheme 4). Furthermore, these types of compounds, L-glutamate semialdehydes derivatives, are intermediates in the synthesis of carbapenem antibiotics.[22]

The four reactions in Schemes 2–4 show the scope of this new organocatalytic methodology for the preparation of highly functionalized optically active α,α-disubstituted α-amino acid derivatives in a few steps.

To obtain a suitable crystal for X-ray analysis, we carried out the addition of *p*-tosylhydrazine to the aldehyde **4f** and subsequent recrystallyzation of the resulting solid led to a 1:1 mixture of lactams **9a** and **9b** as aminal and hemiaminal, respectively (Scheme 5). These types of structures, the 3-amino-6-hydroxy-2-piperidone unit, have been found as a constituent in more than 60 cyclic depsipeptides derived from cyanobacteria.[23]

The structures could be obtained by two presumable different pathways. In both cases, the aldehyde and the hydrazine were condesed to form **I** (Scheme 5). In path a, the corresponding aminal is formed first (intermediate **II**), which proceeds by an intramolecular attack to open the oxazolone giving **9a**. In path b, the imine opens the oxazolone to generate **III** by intramolecular attack. The iminium intermediate **III** was then attacked by another hydrazine molecule to give **9a**. Finally, we believe that aminal **9a** is in equilibrium with **9b** via an iminium intermediate.

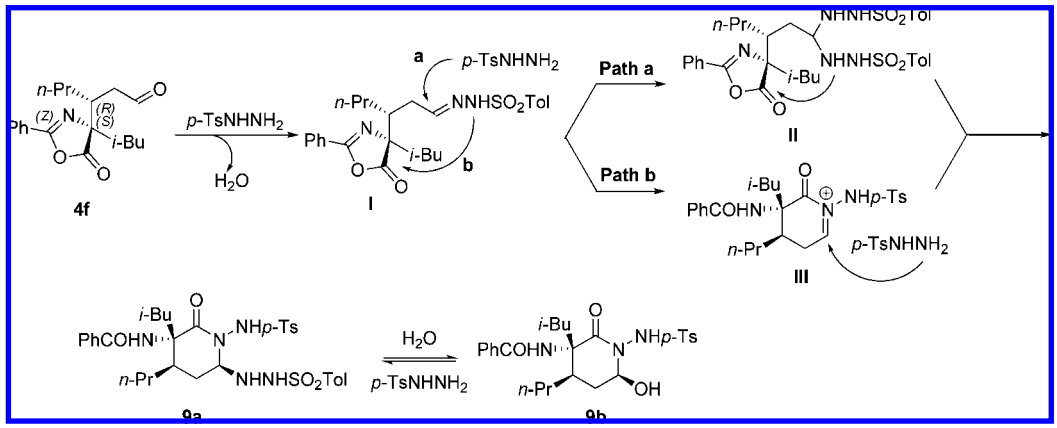
Finally, we determined the absolute configuration by X-ray analysis of compounds **9a** and **9b** which were crystallized as a

(21) The pyrrolidines **8** were obtained as only one diastereoisomer, determined by ^{1}H NMR spectroscopy of the crude mixture. However during the purification process by flash chromatography the epimerization of the hemi-aminal center was observed (see Supporting Information for more details).

(22) Stapon, A.; Li, R.; Townsend, C. A. *J. Am. Chem. Soc.* **2003**, *125*, 8486.

(23) Yokokawa, F.; Inaizumi, A.; Shioiri, T. *Tetrahedron* **2005**, *61*, 1459.

Scheme 5. Synthesis of δ-Lactams from Aldehydes **4**



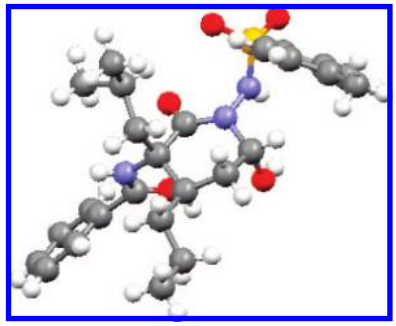
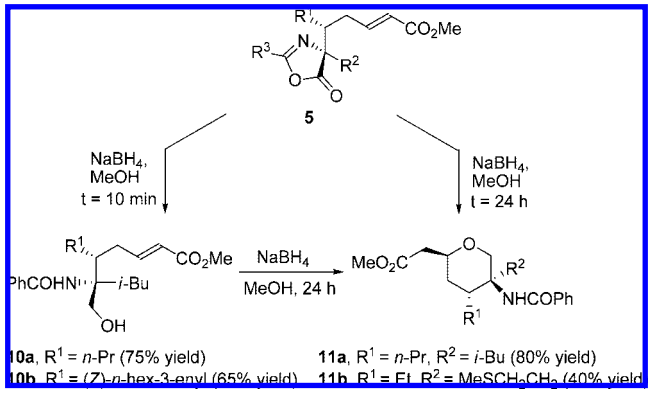


Figure 1. X-ray structure of compound **9b**.

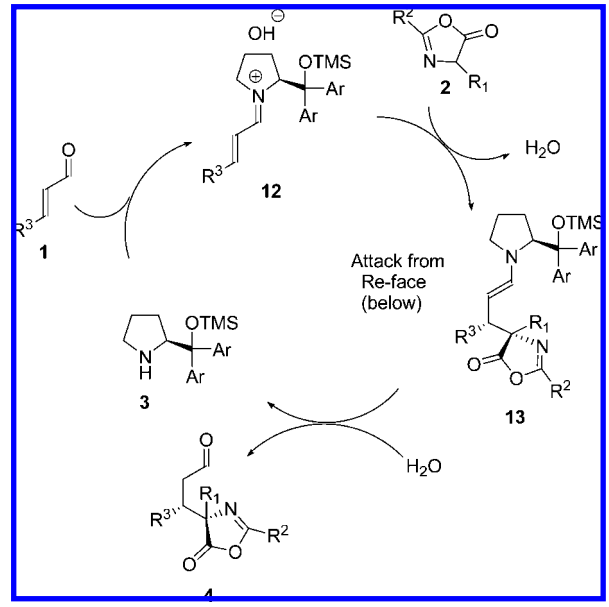
Scheme 6. Synthesis of Amino Alcohol Derivatives **10** and Tetrahydropyranes **11** by Reduction of Alkenes **5**



mixture of 1:1. The three chiral centers in **9b** were determined as 3*S*,4*R*,6*R* (Figure 1).[24]

Further important transformations of the optically active products are the reduction of the Wittig adducts **5f** and **5g** in 10 min by $NaBH_4$, giving the amino alcohol derivatives **10a** and **10b** in good yields (Scheme 6). A large group of important natural products, such as carbohydrates, alkaloids, polyether antibiotics, and pheromones contain polyfunctionalized pyran derivatives as a subunit.[25] Interestingly, it was observed that

Scheme 7. Catalytic Cycle for the Addition of Oxazolones **2** to Aldehydes **1**



when the reduction was maintained for 24 h at room temperature, the alcohol derivatives **10** undergo an intramolecular Michael reaction to the tetrahydropyranes **11**. This reaction proceeds smoothly in good yield and the products were obtained as only one diastereoisomer with three chiral centers without losing enantiopurity (Scheme 6). We have shown that **10** is an intermediate for the formation of **11**, because the treatment of **10a** with $NaBH_4$ in MeOH leads to **11a** in 72% yield.

Mechanistic Considerations. The proposed mechanism for the reaction course of this transformation is summarized in Scheme 7. The Michael addition follows the common path previously reported in the literature.[15] The α,β-unsaturated aldehyde **1** is

(24) CCDC 677671 contains the supplementary crystallographic data. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336−033. E-mail:].

(25) (a) Rahman, A.; Nasreen, A.; Akhtar, F.; Shekhani, M. S.; Clardy, J.; Parvez, M.; Choudhary, M. I. *J. Nat. Prod.* **1997**, *60*, 472. (b) Brimble, M. A.; Prabaharan, H. *Tetrahedron* **1998**, *54*, 2113. (c) Conway, J. C.; Quayle, P.; Regan, A. C.; Urch, C. J. *Tetrahedron* **2005**, *61*, 11910. (d) Liu, R. H.; Zhang, W. D.; Gu, Z. B.; Zhang, C.; Su, J.; Xu, X. K. *Nat. Prod. Res.* **2006**, *20*, 866. (e) Larghi, E. L.; Kaufman, T. S. *Synthesis* **2006**, *2*, 187. (f) Tang, Y.; Oppenheimer, J.; Song, Z.; You, L.; Zhang, X.; Hsung, R. P. *Tetrahedron* **2006**, *62*, 10785. (g) Shoji, M.; Hayashi, Y. *Eur. J. Org. Chem.* **2007**, 3783. (h) Goddard-Boger, E. D.; Ghisalberti, E. L.; Stick, R. V. *Eur. J. Org. Chem.* **2007**, 3925. (i) Brioche, J. C. R.; Goodenough, K. M.; Whatrup, D. J.; Harrity, J. P. A. *J. Org. Chem.* **2008**, *73*, 1946. (j) Kumar, S.; Malachowski, W. P.; DuHadaway, J. B.; LaLonde, J. M.; Carroll, P. J.; Jaller, D.; Metz, R.; Prendergast, G. C.; Muller, A. J. *J. Med. Chem.* **2008**, *51*, 1706.

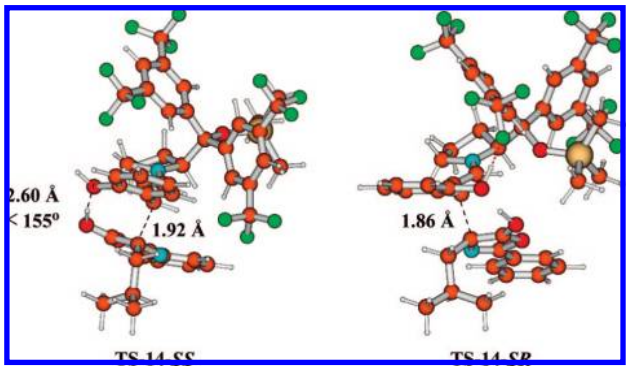


Figure 2. Two transition states leading to the two diastereoisomers in Table 1 **TS-14-*SS*** shows the hydrogen-bonding which leads to the major diastereomer (Table 1, entry 3).

transformed by catalyst **3** and nucleophile **2** into the Michael adduct **13**. The stereocenter formed in the aldehyde is controlled by a *Re*-face attack of the nucleophile on the planar iminium ion **12**. The *Re*-face of the β-carbon atom in the iminium-ion intermediate is favored for approach of the nucleophile owing to the bulk of the C2-substituent in the pyrrolidine ring of the catalyst which shields the *Si*-face, as previously reported for the use of TMS-protected prolinols as organocatalysts.[15] After the formation of the stereocenter, the catalyst is released from the intermediate, which form the functionalized oxazolones **4**. The absolute configuration of the initially formed stereogenic center in the α,β-unsaturated aldehyde indicates that the addition of the nucleophile approaches from the *Re*-face by control of the catalyst, supported by the X-ray structure in Figure 1.

To understand the diastereo- and enantioselectivity observed for addition of the oxazolones to the α,β-unsaturated aldehydes a computational investigation was performed using density functional theory (DFT) calculations.[26] Geometry optimizations were performed using the B3LYP-DFT procedure with the 6−31G(d) basis set[27] and the relative energies of the different transition-state structures were used to predict product ratios.

We started out by investigating the reaction of *rac*-**2a** with the *ortho*-hydroxy-phenyl substituted α,β-unsaturated aldehyde (**1c**) which proceeds with very high diastereoselectivity (>20:1) (Table 1, entry 2). The computational study was carried out with the assumption that it is the enolate-form of the oxazolone which reacts with the iminium-ion (**12**, Scheme 7) of the catalyst (**3**) and the α,β-unsaturated aldehyde (**1**). Our hypothesis is that the diastereoselectivity might be controlled by hydrogen-bonding interaction of the enolate-form of the oxazolone and the *ortho*-hydroxy substituent in **1c**. The two transition states leading to the two different diastereoisomers have been located and computational studies revealed that the transition state with *S*-configuration at the carbon atom in oxazolone, **TS-14-*SS***, was lower in energy than the transition state **TS-14-*SR***, leading to the diastereoisomer with *R*-configuration, (Figure 2, Table 3, entries 1, 2). As it appears from the results in entry 1, Table 3, the formation of the (*S*,*S*)-enantiomer is favored by 3.8 kcal/mol, relative to the (*S*,*R*)-enantiomer. Assuming a Boltzmann distribution of the transition states at room temperature, the calculated diastereomeric ratio is >20:1, which is in very good agreement with the experimental result (Table 1, entry 3). The reason for the nucleophilic approach of *rac*-**2a** to the *Re*-face of **1c** is due to hydrogen-bonding between the nucleophile and the electrophile, in which the *ortho*-hydroxy substituent in **1c** is the hydrogen-bond acceptor and the enolized oxazolone is the hydrogen donor as shown in Figure 2 to the left.

Table 3. Electronic and Free Energies of the Transition States for the Nucleophilic Addition of Oxazolones to α,β-Unsaturated Aldehydes Catalysed by **3** at B3LYP/6-31G(d) Level of Theory

entry	transition state	E_{elec} (Hartree)[a]	ΔE_{elec} (kcal/mol)	G (Hartree)[a]	ΔG kcal/mol
1	**TS-14-SS**	−3677.838468	0[b]	−3677.103654	0[b]
2	**TS-14-SR**	−3677.832459	3.8[b]	−3677.096536	4.5[b]
3	**TS-15-SS**	−3755.026955	0[c]	−3754.275416	0[c]
4	**TS-15-SR**	−3755.255542	0.9[c]	−3754.272994	1.5[c]

[a] Absolute and free energies for calculated transition states. [b] Energy are relative to **TS-14-SS**. [c] Energy are relative to **TS-15-SS**.

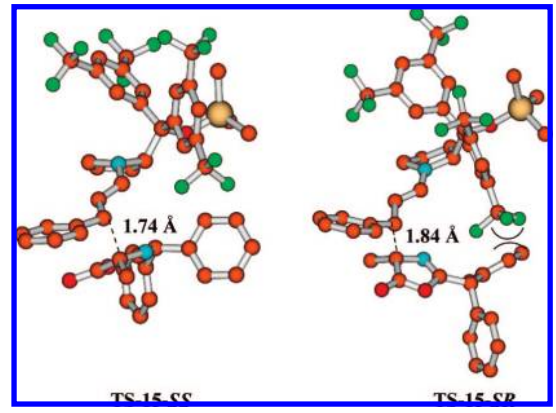


Figure 3. Structures of the two transition states lowest in energy accounting for the high diastereoselectivity with oxazolone having a benzhydryl-protecting group (hydrogen atoms deleted for clearity). The transition state to the left is the one with the lowest energy and the one to the right shows the steric repulsion accounting for the less-favored approach.

The role of the benzhydryl-protecting group in the oxazolone (**2f**) for controlling the high diastereoselectivity in Table 2 was unclear based on the experimental results. However, DFT-calculations provided valuable insight to rationalize the observed diastereoselectivity. The transition-state structures were determined using B3LYP DFT-6-31G(d) basis set and all transition-state structures were characterized by frequency analysis. The calculated results for the reaction between **1a** and **2f** via the iminium-ion intermediate, nicely explain the experimentally observed stereoselectivity and the role of the benzhydryl-protecting group (Figure 3, Table 3, entries 3, 4). The relative energy of the **TS-15-*SS*** and **TS-15-*SR*** transition states shows an energy gap between the diastereoisomers of 0.9 kcal/mol, in favor of **TS-15-*SS***, which is also the major diastereoisomer found experimentally. The diastereoisomeric ratio was calculated to be 4.5:1, using a Boltzmann distribution, on the basis of this difference in relative energy of **TS-15-*SS*** and **TS-15-*SR***, which is in agreement with the experimentally observed ratio of 6:1 (Table 2, entry 2). The diastereoselectivity originates from steric effects, primarily due to the benzhydryl-protecting group in the oxazolone. The bulkiness of this substituent determines the orientation of the nucleophile, and the approach giving the *S*-configuration at the carbon atom in oxazolone is favored. The C−C distance between **1a** and **2f** in the transition state is 0.10 Å shorter in **TS-15-*SS*** than in **TS-15-*SR***. If we, for the latter reaction leading to the transition state **TS-15-*SR***, force the oxazolone to approach even further, steric repulsion of the benzhydryl group and the bis(3,5-bis-trifluoromethylphenyl)trimethylsilyloxymethyl group in the catalyst is observed (Figure 3, right). We propose that this steric repulsion is the reason for being able to control the diastereoselectivity of the reaction.

The diastereo- and enantioselectivity uncovered originates from the deformation of the basic transition structure owing to

the presence of certain groups in either the electrophile or nucleophile, and the interactions giving preferentially the (*S*,*S*)-diastereoisomer are essentially different for the two situations. (i) The electrophile can control the selectivity by a hydrogen-bond acceptor in the *ortho*-position of aromatic α,*β*-unsaturated aldehydes, thus capable of directing the nucleophile via a hydrogen-bonding to the enolate-form of oxazolone. (ii) The nucleophile with a bulky substituent in the C-2 position of the oxazolone, such as benzhydryl, can via steric demands orient the nucleophile in favor of the (*S*,*S*)-enantiomer, to avoid steric repulsion between the catalyst and nucleophile. The steric and electrostatic effect of the substrates plays a prominent role in controlling the proportion of the diastereomeric products. Proper consideration of these properties of bulkiness and activation of substituents has led to design a nucleophilic addition of oxazolones to α,*β*-unsaturated aldehydes catalyzed by **3** that will produce the (*S*,*S*)-diastereomer with high selectivity.

Conclusion

In conclusion, we have shown that racemic oxazolones are excellent reagents for the synthesis of chiral quaternary amino acids by nucleophilic addition to α,*β*-unsaturated aldehydes catalyzed by diarylprolinol silyl ethers. This new organocatalytic reaction proceeds with good diastereoselectivity and excellent enantioselectivity for a broad range of aldehydes and oxazolones. We have demonstrated that the optically active compounds formed undergo a number of diverse transformations leading to the formation of optically active α,α-disubstituted α-amino acids, α-quaternary proline derivatives, amino alcohols, lactams, and tetrahydropyranes. Furthermore, we have shown by DFT calculations of transition states that the stereoselectivity for one class of compounds is due to hydrogen-bonding interactions between an acceptor in the *ortho*-position of the aromatic α,*β*-unsaturated aldehyde interacting with the enolate-form of oxazolone, and in a more general manner, the selectivity can be controlled by a benzhydryl-protecting group in the oxazolone.

Acknowledgment. This work was made possible by a grant from Danish National Research Foundation and OChemSchool. S.C. and J.A. thank the Ministerio de Educación y Ciencia of Spain and E.R. thanks the "Eusko Jaurlaritza-Gobierno Vasco" for postdoctoral fellowships. Thanks are expressed to Dr. Jacob Overgaard for performing X-ray analysis.

Supporting Information Available: Complete experimental procedures and characterization and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

JA804567H

(26) (a) Frisch, M. J. *Gaussian 98*, revision A.7; Gaussian, Inc.: Pittsburgh PA, 1998. (b) Frisch, M. J.; *Gaussian 03*, revision B.05; Gaussian, Inc.: Pittsburgh PA, 2003.

(27) (a) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213. (b) Francl, M. M.; Petro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; DeFrees, D. J.; Pople, J. A. *J. Chem. Phys.* **1982**, *77*, 3654. (c) Becke, A. D. *Phys. Rev.* **1988**, *38*, 5648. (d) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (e) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372. (f) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.