Enantioselective Allylations of Azlactones with Unsymmetrical Acyclic Allyl Esters

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Abstract: A catalytic asymmetric synthesis of quaternary amino acids has been developed. The method derives from the asymmetric allylic alkylation (AAA) reaction with chiral palladium catalysts derived from π-allylpalladium chloride dimer and the bis-2-diphenylphosphinobenzamide of *R,R*-1,2-diaminocyclohexane and related ligands. Highly symmetrical allylating agents such as allyl acetate and 2-methallyl acetate give moderate to low ee. On the other hand, 1-monosubstituted and 1,1-disubstituted allyl systems give excellent results with ee's normally ≥90%. A most interesting dichotomy occurs in the facial selectivity with respect to the azlactone as it depends on the allylating agent as well as the ligand. For example, prenylation gives 99% ee derived from attack on the *si* face of the azlactone with a *R,R*-ligand, but cinnamylation gives a 90% ee of the product derived from attack on the *re* face with the *same* ligand. A model based upon the catalyst creating a chiral pocket is presented to explain these results. Using a trimethylsilyl-substituted allylating agent, excellent ee (97%) was obtained. Protodesilylation then provides the simple allylated amino acid with high ee. Oxidative cleavage of these allylated systems provides a practical asymmetric synthesis of α-alkylated aspartic acids where variation of the alkyl group derives from using variously substituted azlactones. The ability to modify the double bond provides further flexibility to generate unusual amino acids.

Quaternary amino acids constitute an important target for asymmetric synthesis because of their value in biological applications. Since the first isolation of α-aminoisobutyric acid in 1872,[1] α-alkylated-α-amino acids have generated an ever growing interest in biology and pharmacology as well as chemistry. Some are naturally occurring or are structural components of natural products which have interesting properties such as antibiotic.[2−5] Unnatural α-methyl-α-amino acids have also shown powerful reversible inhibition of amino acid decarboxylases.[6,7] More recently, their use in peptidomimetics has been a major focus.[8] Introduction of alkyl chains at the α-carbon of amino acids introduces conformational constraints that can probe the molecular structure of receptors or enhance the biological activity by helping to preorganize the optimum conformation for binding.[9,10] Such substitution inhibits metabolic degradation as well as restricting conformational flexibility. The biological consequences of these effects are immense and have led to useful therapeutic agents. Thus, increased access to enantiomerically pure quaternary amino acids increases opportunities for new drug discovery.

Asymmetric creation of any quaternary center constitutes a difficult challenge.[11] The most successful route for catalytic asymmetric synthesis of amino acids, catalytic hydrogenation,[12] does not apply to quaternary amino acids. Virtually all methods involve controlling diastereoselectivity either by use of chiral auxiliaries[13] or by involving what is termed self-reproduction of chirality.[14] The applicability of the recently reported asymmetric alkylation of glycine derivatives to such cases remains to be established.[15] A very recent report of the palladium-catalyzed asymmetric alkylation of α-amido-β-keto esters[16]

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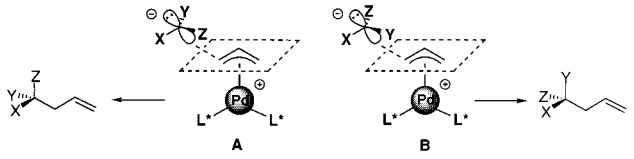
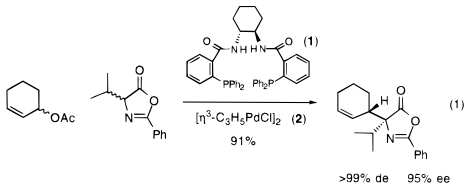


Figure 1. Asymmetric induction at prochiral nucleophile.

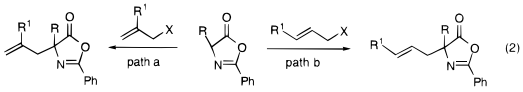
stimulates us to report our results on the asymmetric alkylation of azlactones with achiral allyl esters.[17]

Introduction of asymmetry at a pro-chiral nucleophilic center as shown in Figure 1 by the asymmetric allylic alkylation (AAA) reaction[18] suggests that such induction is a real stretch. Since the nucleophile attacks the π-allyl unit on the face distal to palladium and therefore quite far from the chiral inducing elements,[19] L*, it would appear remote to believe that good enantioselectivity could be achieved in such a case.[20] In our initial work directed toward quaternary amino acids, we employed 1,3-disubstituted allyl systems with great success (see eq 1).[17] In such a case, stereoinduction occurs at **both** the



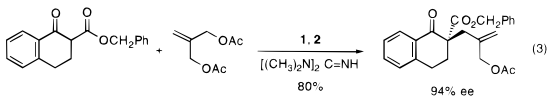
(1)

electrophile and nucleophile. The excellent stereocontrol at the nucleophile may be a secondary effect of stereoinduction at the electrophile. If there is no stereoinduction associated with the allyl group being introduced as illustrated in eq 2, will high ee



(2)

be observed? Our results in the AAA reaction of β-ketoesters[21] encouraged us to consider this situation. For example, the alkylation shown in eq 3 proceeds with excellent enantioselectivity. Nevertheless, the fact that use of a five-membered ring β-ketoester saw a significant decrease in ee did not bode well for our azlactone substrates.



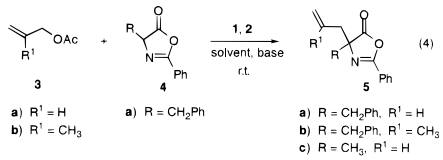
(3)

Because of the symmetry properties of the π-allylmetal intermediates for the two types of allylating agents of eq 2 are quite different, both types must be examined. Allylating agents of eq 2, path a (which we will refer to as type A), form achiral π-allylmetal complexes and do not generate a product wherein a stereogenic center is also being created at the allyl unit. On the other hand, allylating agents of eq 2, path b (which we will refer to as type B), form chiral π-allylmetal complexes even though the products do not possess an allylic stereogenic center. Thus, the transition states for alkylation on the enantiotopic faces of the allyl unit are diastereotopic even with achiral ligands. Our initial effort examined the simplest allylating agent, allyl acetate (eq 4 and Table 1).

Table 1. Alkylations of Type A[a]

entry	R	R^1	solvent	base	time (h)	yield[c] (%)	er[d] (% ee)
1	CH_2Ph	H (**3a**)	CH_3CN	$(C_2H_5)_3N$	2.5	98	70:30 (40)
2	CH_2Ph	H (**3a**)	CH_3CN	PMG[b]	5	70	65:35 (30)
3	CH_2Ph	H (**3a**)	$PhCH_3$	$(C_2H_5)_3N$	2	100	67:33 (34)
4	CH_2Ph	CH_3 (**3b**)	CH_3CN	$(C_2H_5)_3N$	2	79	55:45 (10)

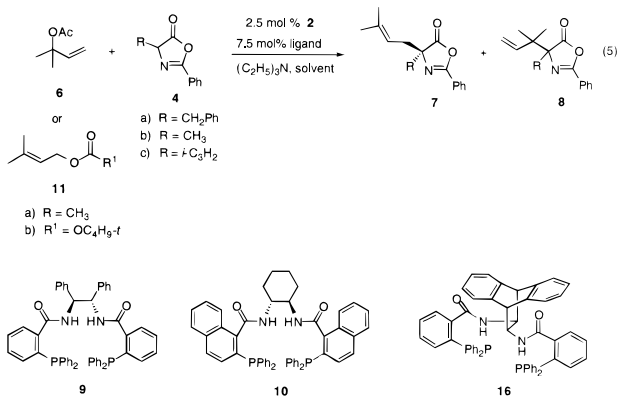
[a] Reactions performed as in eq 4 with 1.0 equiv of allylating agent and 2.25 equiv of azlactone. [b] Pentamethylguanidine. [c] Isolated yields. [d] er = enantiomeric ratio.



(4)

The very first result (Table 1, entry 1) wherein a 40% ee of **5a** was observed appeared promising. However, the enantioselectivity was far from the typical >95% ee observed with cycloalkenylating agents. In the case of β-ketoesters, changing base to tetramethylguanidine and solvent to toluene proved beneficial. Tetramethylguanidine could not be used here since it opened the azlactone. Employing pentamethylguanidine (entry 2) or changing to toluene (entry 3) decreased the enantioselectivity. Introducing a methyl group at the central carbon of the allylating agent to give **5b** also decreased the er (entry 4).

Switching to allylating agents of type B led to dramatically different results. Initially, reactions of allyl acetate **6** with azlactone **4** were examined as summarized in eq 5 and Table 2.



(5)

Comparing entries 1−3 of Table 2 indicates that the reaction is better performed at room temperature compared to those at lower

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Table 2. Prenylation of Azlactones[a]

entry	azlactone	prenylating agent	ligand	solvent	time	isolated yields[b] (%) **7** (**8**)	ee[c] (%) **7** (**8**)
1	**4a**	**6**	1	CH_3CN	rt (2h)	44 (23)	97 (4)
2	**4a**	**6**	1	CH_3CN	−20° (6h)	41 (41)	97 (25)
3	**4a**	**6**	9	CH_3CN	rt (2h)	59 (17)	−97[i] (3)
4	**4a**	**6**	1	$PhCH_3$	rt (3h)	72 (23)	98 (20)
5[d]	**4a**	**6**	1	$PhCH_3$	rt (6h)	15 (3)	95 (20)
6[e]	**4a**	**6**	1	$PhCH_3$	rt (2h)	57 (23)	99 (21)
7	**4a**	**6**	1	$PhCH_3$	70° (18h)	65 (23)	93 (9)
8	**4a**	**6**	10	$PhCH_3$	rt (24h)	32 (47)	96 (12)
9[f]	**4a**	**6**	1	$PhCH_3$	rt (24h)	75 (15)	99 (20)
10	**4a**	**11a**	1	$PhCH_3$	rt (6h)	78 (12)	99 (27)
11	**4a**	**11a**	9	$PhCH_3$	rt (6h)	62 (12)	−99[i] (20)
12[g]	**4a**	**11a**	1	$PhCH_3$	rt (3h)	65 (11)	99 (31)
13	**4a**	**11b**	1	$PhCH_3$	rt (3h)	74 (16)	99 (27)
14	**4a**	**11b**	1	CH_3CN	rt (3h)	56 (16)	98 (17)
15	**4b**	**6**	1	$PhCH_3$	rt (3h)	55 (13)	96 (14)
16[h]	**4b**	**6**	1	$PhCH_3$	rt (2h)	53 (31)	98 (10)
17	**4b**	**11a**	1	$PhCH_3$	rt (4h)	67 (17)	98 (21)
18	**4c**	**6**	1	$PhCH_3$	rt (72h)	57 (−)	97 (−)
19	**4c**	**11a**	1	$PhCH_3$	rt (18h)	47 (−)	91 (−)

[a] All reactions were run as in eq 5 using 1.0 equiv of allyl ester and 2.25 equiv of azlactone at 0.1 M concentration unless stated otherwise. [b] All yields are for isolated pure compounds for each regioisomer. [c] Determined by chiral HPLC; the absolute configuration of the product is as depicted in **7** unless otherwise indicated. [d] Pentamethylguanidine (PMG) used as base. [e] Reaction performed by slow addition of the prenylating agent. [f] Reaction performed with 1.2 equiv of **4a**, 1.0 equiv of **6**, 0.5 mol % **2**, and 1.5 mol % **1** at 1 M concentration. [g] Reaction performed by slow addition of a mixture of azlactone and triethylamine. [h] Reaction performed with 0.1 mol % **2** and 0.3 mol % **1**, 1.05 equiv of **4** and 1.3 equiv of **6** at 1.0 M. [i] In this case, the mirror image of **7** is obtained.

Table 3. Cinnamylations of Azlactones[a]

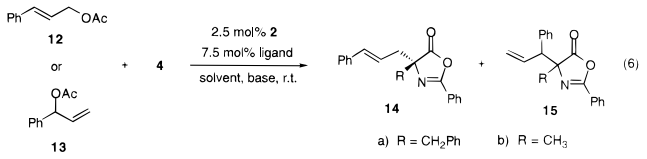
entry	azlactone	cinnamylating agent	ligand	base	solvent	time (h)	isolated yields[b] **14** (**15**)	ee[c] **14**
1	**4a**	6	**1**	$(C_2H_5)_3N$	CH_3CN	2	76 (−)	77
2	**4a**	12	**9**	$(C_2H_5)_3N$	CH_3CN	6	65 (−)	−72[h]
3	**4a**	12	**1**	$(C_2H_5)_3N$	$PhCH_3$	3	91 (−)	90
4	**4a**	12	**1**	$C_2H_5N(i\text{-}C_3H_7)_2$	$PhCH_3$	3	92 (−)	91
5	**4a**	12	**1**	$(C_2H_5)_3NPh$	$PhCH_3$	3	95 (−)	89
6	**4a**	12	**1**	NONE	$PhCH_3$	3	94 (−)	89
7[d]	**4a**	12	**1**	$(C_2H_5)_3N$	$PhCH_3$	3	91 (−)	85
8	**4a**	13	**1**	$(C_2H_5)_3N$	$PhCH_3$	3	45 (47)[g]	90
9	**4b**	12	**1**	$(C_2H_5)_3N$	$PhCH_3$	24	74 (−)	86
10	**4b**	12	**9**	$(C_2H_5)_3N$	$PhCH_3$	3	80 (−)	−69[h]
11	**4b**	12	**16**	$(C_2H_5)_3N$	$PhCH_3$	2	84 (−)	31
12[e]	**4b**	12	**1**	$(C_2H_5)_3N$	$PhCH_3$	2 + 2	72 (−)	69
13[f]	**4b**	12	**1**	$(C_2H_5)_3N$	$PhCH_3$	6	75 (12)[g]	90

[a] Reactions performed as in eq 6 using 1.0 equiv of cinnamylating agent and 2.25 equiv of azlactone at 0.1 M concentration at room temperature unless specified otherwise. [b] Isolated yield of each pure regioisomer. [c] Determined by chiral HPLC; the absolute configuration observed is depicted in **14** unless indicated otherwise. [d] Reaction performed at −40 °C. [e] Reaction performed at −78 °C for 2 h and at −45 °C for 2 h. [f] Reaction performed with 0.1 mol % **2**, 0.3 mol % **1**, and co-equal amounts of **4b** and **12** at 1 M concentration. [g] Yield of mixture of two diastereomers; in entry 8 each diastereomer isolated in 28 and 19%, respectively; in entry 13, each diastereomer isolated in 8 and 4%, respectively. [h] The product is the mirror image of that depicted in **14**

temperatures and that there is a dependence of regioselectivity on the choice of ligand. It is quite surprising that we obtain such significant amounts of alkylation at the tertiary allyl terminus wherein the two quaternary centers are being created adjacent to each other (vide infra). Better yields of the alkylation products are obtained in toluene compared to those in acetonitrile. Such a difference was not observed in our previous studies with cyclic allyl esters. A guanidine base, which was superior in the alkylation of β-keto esters, was unsatisfactory here (entry 5). Slow addition (entry 6) or increasing temperature (entry 7) had little effect. Ligands (entries 8 and 11) other than the "standard" one were also not beneficial. Surprisingly, the ee of the major alkylation product **7a** was excellent and that of the minor alkylation product **8a** was poor regardless of conditions. The simplest conditions proved to give among the best results (entries 4, 9, 10, and 13) wherein the alkylated azlactone **7a** was isolated in 72−78% yields having 98−99% ee. For preparative purposes, minimizing the amount of catalyst is desirable. As shown in entry 9, with only 0.5 mol % of **2** and a 1.2:1 rato of **4a:6**, a 75% yield of **7a** of 99% ee was produced.

A similar result was obtained with the somewhat less hindered azlactone **4b** (entries 15−17). In this case, the best result gave the alkylated product **7b** in 67% yield with an ee of 98%. Decreasing the amount of palladium catalyst to 0.1% and using nearly stoichiometric amounts of the **4b** and **6** gave results similar to those with higher loadings and excess azlactone (entry 16 vs 15). The yield of the alkylation product derived from attack at the tertiary allylic position **8** increased upon reduction of the catalyst loading which may indicate that this regioisomer may come, in part, from a non-palladium-catalyzed event. This suggestion also may account for the low ee always observed for the minor product. On the other hand, increasing the steric demand of the nucleophile, i.e., **4c**, led to one regioisomeric product **7c** having 97% ee (entry 18).

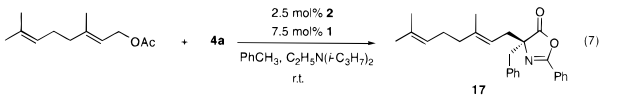
The cinnamyl system was examined as an example of an allylating agent bearing only one substituent. Table 3 and eq 6



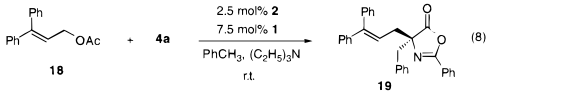
summarize the results. As previously observed in the prenylation reaction, toluene (entries 3−13) proved superior to acetonitrile (entries 1−2) as solvent. Varying the nature of the tertiary amine base (entries 3−5) had no effect. In fact, deleting the base (entry 6) gave fully equivalent results. Lower temperatures than room temperature were slightly detrimental (entry 7). The "standard" ligand was preferred among the limited range explored. A quite noticeable effect occurred upon using the regioisomeric cinnamylating agent **13**. In this case, an almost equal amount of the two regioisomeric products were obtained; whereas, in all the cases employing **12**, only **14a** was observed. By this method, the latter is available in 91−95% yield and 90 ± 1% ee (entries 3−6).

Using the less hindered nucleophile **4b**, the same excellent regioselectivity was observed under our standard conditions (entries 9−12). Clearly, the "standard" ligand **1** gave better results than the other ones examined (entries 9−11). Once again, lower temperatures proved detrimental (entry 12). Decreasing the catalyst loading to 0.1 mol % of **2** (entry 13) and using only a 1:1 ratio of the two substrates **4b** and **12** gave excellent reactivity and enantioselectivity. As previously, these conditions did see formation of some amount of the regioisomer **15b**, an isomer not observed with higher catalyst loads.

Given the successful regio- and enantioselective alkylations with the prenyl and cinnamyl systems, we broadened our survey to other allylating agents. Switching from a prenylation to the sterically more demanding geranylation led to excellent regio- and enantioselectivity as summarized in eq 7. Although the



reaction was sluggish, requiring 24 h to consume the geranylating agent, the alkylated azlactone **17** was isolated in 66% yield with an ee of 87%. Using the sterically even more demanding allylating agent **18**, the reaction was incomplete after 3 days but still gave a quite satisfactory result (eq 8). The desired



alkylated azlactone **19** was isolated in 84% yield (96% brsm), with 13% recovery of allyl acetate **18**, and had an ee of 89%.

Starting with an unsymmetrical 1,1-disubstituted allylating agent has the danger of generating two different geometrical isomeric products. If one starts with the allylating agent possessing the trisubstituted double bond, the product retains that alkene geometry (e.g., eq 7).[20c] On the other hand, if the regioisomeric starting material is employed, there is no necessary predisposition of the allylation proceeding to give either geometrical isomer of the product. To ascertain if the ligand could influence this selectivity, the allyl acetate **20** was subjected to the alkylation (eq 9 and Table 4). Under the three conditions

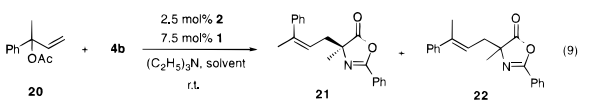


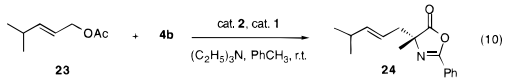
Table 4. Alkylations with 3-Acetoxy-3-phenyl-1-butene[a]

entry	ligand	solvent	time (h)	isolated yields (%) **21** (**22**)	ee (%) **21** (**22**)
1	**1**	CH_3CN	18	45 (35)	97 (46)
2	**1**	$PhCH_3$	3	47 (41)	97 (12)
3	**9**	$PhCH_3$	18	40 (26)	−91 (4)

[a] All reactions were performed as outlined in eq 9 using 1.0 equiv of **20** and 2.5 equiv of **4b**.

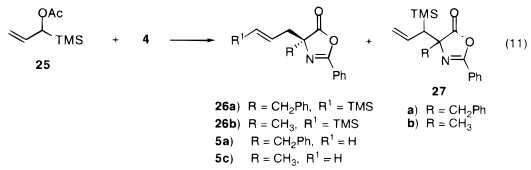
employed, almost no geometrical selectivity was observed as mixtures of both the *E* and *Z* isomers were obtained. The geometry of the two double bonds was established by nOe's between the methyl group and the vinyl hydrogen in **21** and the allylic methylene group in **22**. Curiously, the *Z*-alkene **21** showed high ee in all cases, but the ***E***-alkene did not. The latter showed a significant variability of ee with solvent (entry 1 vs 2) and ligand (entry 2 vs 3).

Several additional monosubstituted alkenes were also examined. Using a simple branched alkyl group as in the case of **23** (eq 10) led to satisfactory results. Using 2.5 mol % **2**, 7.5 mol

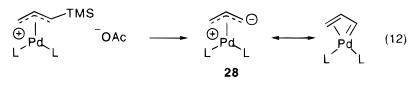


% **1** and a 2.25:1 ratio of **4b:23** at 0.1 M concentration, an 82% yield of alkylated azlactone **24** of 80% ee was obtained. Somewhat better results were achieved by dropping the catalyst to 0.1 mol % **2** and 0.3 mol % **1** with a 1:1 ratio of **4b**:**23** at 1 M concentration. Under these conditions, the azlactone **24** was isolated in 88% yield and had an ee of 83%.

The versatility of a silicon substituent led us to employ acetate **25**[22] (eq 11). Initial studies with benzylazlactone **4a** were



encouraging. The major product under standardized conditions, **26a**, was obtained in 69% yield and had an ee of 98%. The desilylated product **5a** was isolated in 27% yield but had an ee of only 13%. None of the regioisomeric allylated product **27a** was isolated. The presence of the desilylated product was in contrast to our previous work that showed that this allylating agent did not have a propensity to desilylate.[23] With 1-trimethylsilyl-3-substituted π-allylpalladium intermediates, desilylation did occur upon alkylation and this behavior was attributed to formation of a carbene complex. The higher stability of the anions of azlactones may slow the alkylation sufficiently that a similar intermediate **28** (eq 12) may now be forming even in

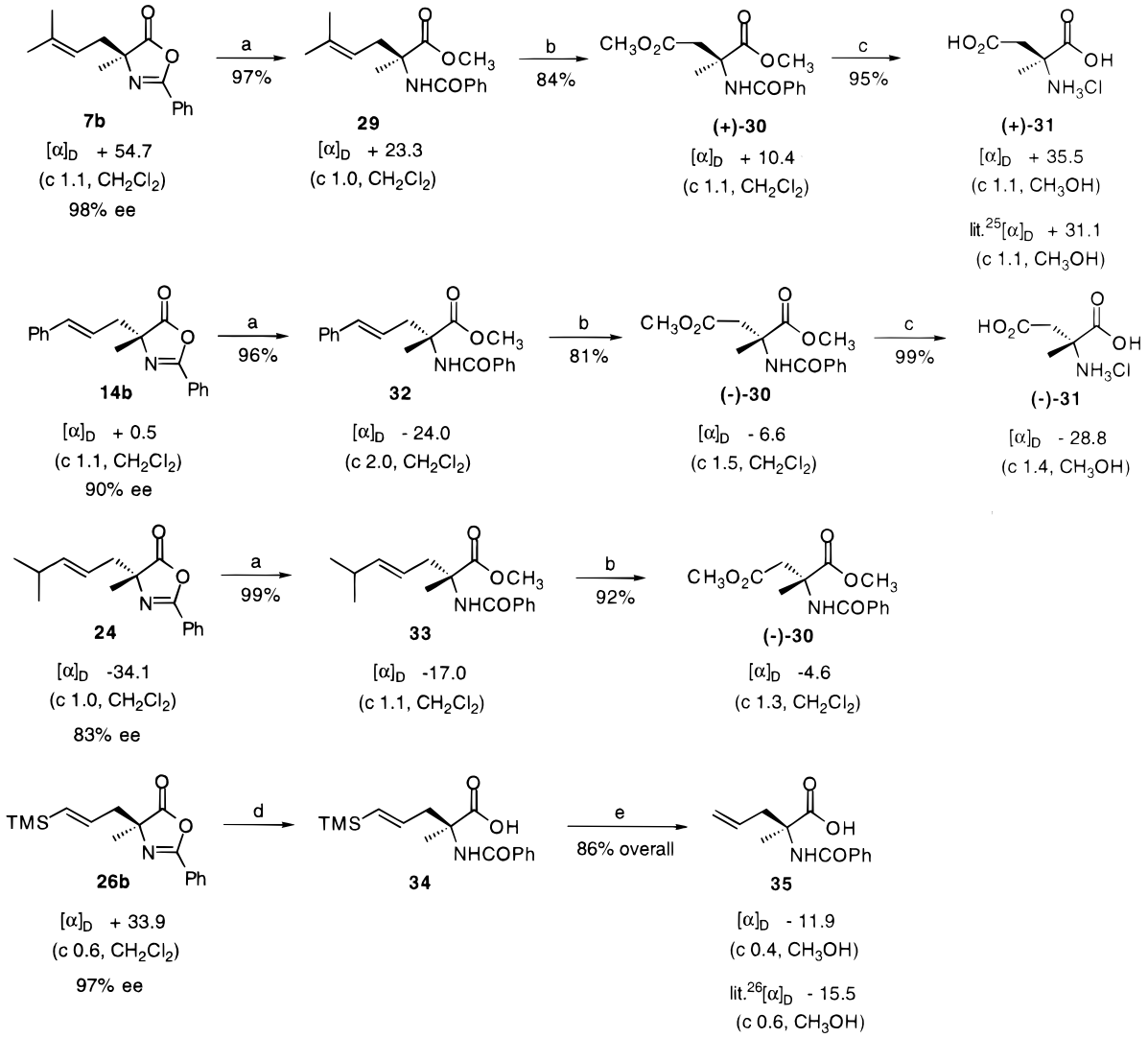


this case. This behavior was attributed to the stability of the 1,3-dipole **28** which may be considered a carbene complex. With the less hindered azlactone **4b**, a more complicated product

(22) a) Danheiser, R. L.; Fink, D. M.; Okano, K.; Tsai, Y.-M.; Szczepanski, S. W. *J. Org. Chem.* **1985**, *50*, 5393. (b) Danheiser, R. L.; Fink, D. M.; Okano, K.; Tsai, Y.-M.; Szczepanski, S. W. *Org. Synth.* **1988**, *66*, 14.

(23) Trost, B. M.; Self, C. R. *J. Am. Chem. Soc.* **1983**, *105*, 5942.

Scheme 1. Determination of Absolute Configuration[a]



[a] (a)TMS-Cl, CH_3OH, room temperature. (b) O_3, NaOH, CH_3OH, CH_2Cl_2, −78°. (c) 6 N HCl, reflux. (d) HCl, CH_3CN, room temperature. (e) HCl, CH_3CN, 70°.

mixture was observed. The direct allylated azlactone **26b** was the major product, isolated in 53% yield and having an ee of 97%. The desilylated product **5c** was isolated in only 8% yield (7% ee). However, two additional products were formed. The regioisomeric allylated azlactone **27b** was obtained in 20% yield with good stereocontrol—93% de and 99% ee (for the major diastereomer). The *Z*-alkene related to **26b** was a minor product, formed in 7% yield (3% ee). Changing the ligand to that derived from stilbenediamine **9** gave reduced amounts of **27b** (9%) but increased amounts of the *Z*-alkene isomer of **26b** (16%). The net result was an unchanged 52% isolated yield of **26b** of 97% ee.

The absolute configurations of four of the allylated products were established by correlation to known compounds (see Scheme). The methanolysis product **29** from the prenylated azlactone **7b** was ozonized[24] to the protected amino ester (+)-**30**. Global deprotection gave the hydrochloride salt of α-methylaspartic acid **31**.[25] Comparison of its rotation to the known amino acid salt indicated it was the *S* isomer (+)-**31**. Repetition of the sequence using the cinnamylated derivative **14b** gave the hydrochloride of α-methylaspartic of opposite configuration, i.e., the *R* isomer (−)-**31**. This result was most surprising since both alkylated azlactones resulted from using the same enantiomer of the ligand.

Performing the same sequence with azlactone **24** produced *R*-aspartic acid derivative (−)-**30**. Thus, nucleophilic attack occurred on the *re* face of the azlactone following the same trend as the cinnamyl case. The silylated azlactone **26b** was correlated with the known α-allylated alanine derivative **35**.[26] Mild exposure to concentrated hydrochloric acid in acetonitrile simply effected hydrolysis to the acid **34**. Raising the temperature of this reaction to 70 °C then effected desilylation to **35**. This stereochemistry derives from alkylation of the *si* face of the azlactone and follows that observed with prenyl.

Discussion

The results demonstrate the feasibility of using the AAA reaction to synthesize quaternary amino acids simply with high yields and enantioselectivities. In contrast to the alkylations of the β-ketoesters, the symmetry properties of the allylating agent

(24) Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1993**, *58*, 3675.

(25) Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A.; Lapeña, Y. *Tetrahedron* **1997**, *53*, 5891 and references therein.

(26) Frauer, A.; Mehlführer, M.; Thirring, K.; Berner, H. *J. Org. Chem.* **1994**, *59*, 4215.

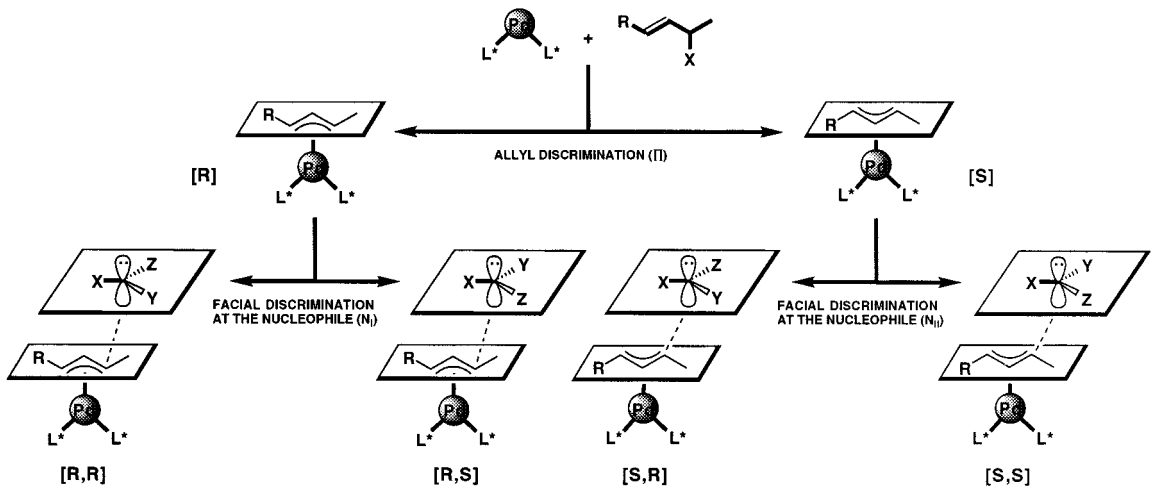


Figure 2. Allyl and nucleophile facial discrimination.

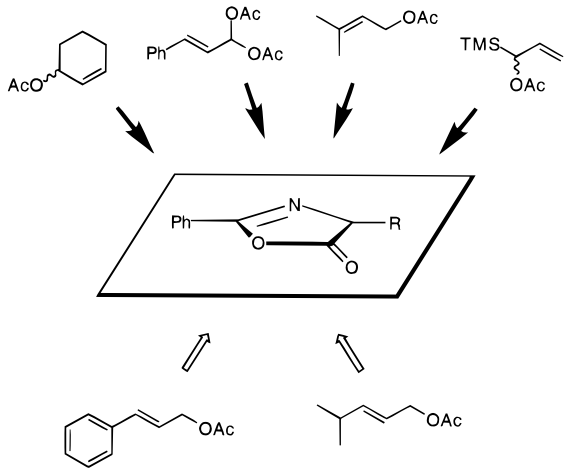
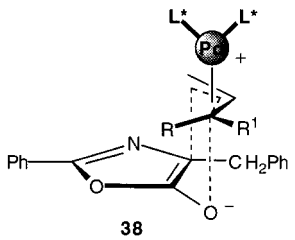


Figure 3. Dependence of azlactone facial discrimination on electrophile.

are important to achieve high ee. The π-allylmetal complex derived from the parent allyl ester is achiral. The transition state for alkylation becomes diastereomeric only in the presence of the chiral ligands as in Figure 1. With the azlactones, this type of enantiodiscrimination led to modest ee's. On the other hand, if the structure of the π-allyl unit creates a diastereotopic transition state in the absence of a chiral ligand, then good ee is seen in these alkylations. The initial studies using 1,3-disubstituted allyl systems such as shown in eq 1 illustrate this point. Discrimination of enantiotopic leaving groups of gem dicarboxylates[27] are another class of reactions that provide excellent enantioselectivity.[17,28] We can now add 1-substituted and 1,1-disubstituted allyl systems to this group that has good chiral recognition. Figure 2 demonstrates that the asymmetric induction derives from three levels of asymmetry—the ligands, the π-allyl, and the nucleophile—regardless of which allyl terminus is attacked. Thus, for azlactones as the nucleophile with this class of ligands, high asymmetric induction requires a synergy between the chirality of the π-allyl moiety and the nucleophile. Figure 3 summarizes the facial discrimination seen with different electrophiles.

The nature of the chiral pocket may amplify the discrimination. Work of the Bosnich group suggested that the energy differences among ground-state π-allyl intermediates would, to some extent, be reflected in the corresponding diastereomeric transition states of nucleophilic attack.[29] Analyzing the equilibrium mixture provided an approximation of the enantioselectivity. This question was explored by ^{31}P NMR spectroscopy for the complex involving ligand **1** and the cinnamyl unit. Two sets of ^{31}P signals were observed, one at δ 22.40 and 22.96 and the other at δ 25.28 and 25.99 in a ratio of 3:1. This pattern suggests that the two diastereomeric complexes are present in this ratio. Molecular mechanics calculations parametrized for palladium (PM-3 and AM-1) gave a 74:26 ratio—in excellent agreement with our observations.[30] Since the ee observed in this case was 90%, it does not appear that this alkylation reflects ground state π-allyl structural stabilities to some extent. For reasons discussed elsewhere, the kinetically most active complex is represented by the cartoons in Figure 4 for the catalyst derived from the *R,R*-ligand **1**.[31] During the alkylation, as the substrate rotates in a clockwise direction because of the change in hapticity from η^3 to η^2, there is increased steric interactions between Z and the ligand in **36** and between Y and the ligand in **37**. The preference to react by attack on the *si* face of the π-allyl with the *R,R*-ligand **1** as depicted in **36** and **37** combined with the preference to attack the *si* face of the nucleophile as in **36** or *re* face as in **37** then accounts for the chiral recognition.

This cartoon representation also helps explain the change in facial selectivity observed between the prenyl and cinnamyl substrates. Figure 5 depicts a preferred transition state to account for this facial selectivity. Considering the positively charged nature of the palladium complex and the negative charge of the nucleophile, a transition state such as **38** is reasonable.



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The depicted orientation in **39** minimizes charge separation as well as steric interactions during rotation accompanying the alkylation. On the other hand, in the case of cinnamylation, the

(27) Trost, B. M.; Lee, C. B.; Weiss, J. M. *J. Am. Chem. Soc.* **1995**, *117*, 7247.

(28) Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **1998**, *120*, 6818.

(29) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033.

(30) Oslob, J. D., unpublished calculations.

(31) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545.

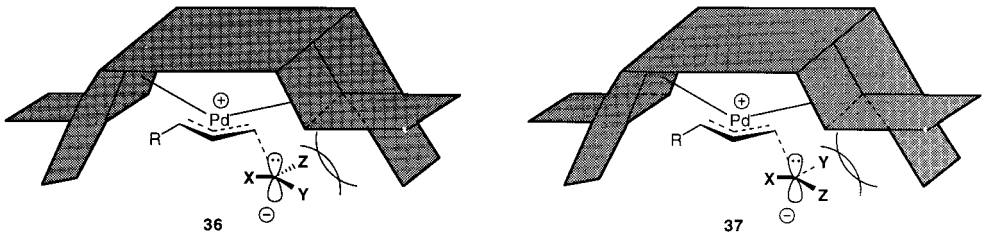

Figure 4. Cartoon representing chiral recognition.

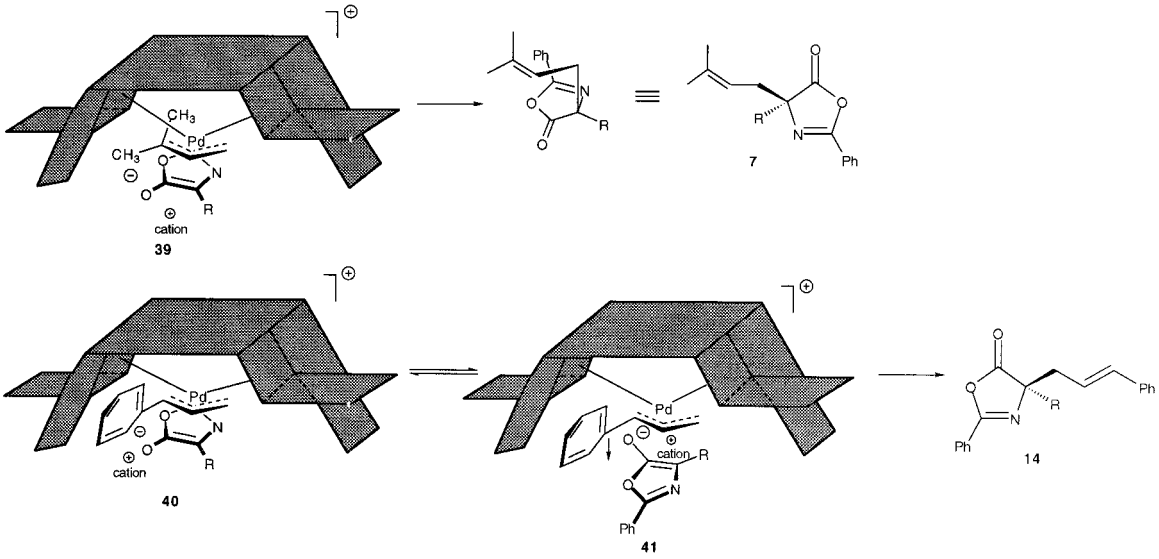

Figure 5. Dependence of facial discrimination upon electrophile.

corresponding transition state **40** becomes destabilized because of steric interactions between the approaching ion pair of the nucleophile and the twisted phenyl ring. Steric interactions with the walls of the chiral pocket forces the phenyl ring to twist such that the plane of this ring is perpendicular to that of the allyl unit.[32] The steric bulk of the phenyl ring then extends in a vertical direction, causing a destabilizing interaction with the nucleophile. Flipping the azlactone ring as depicted in **40** relieves this interaction and provides the observed product. Similar reasoning accounts for the other examples and has been extrapolated to tentatively assign the absolute configuration for the remaining examples.

The regioselectivity is also noteworthy. In the cinnamylation, a pronounced "memory" effect was observed—only primary attack occurred with cinnamyl acetate **12**, but nearly equal amounts of both regioisomers formed from α-phenylallyl acetate **13**. We have previously noted a memory effect with these ligands,[33] and this case demonstrates how strong such an effect may be, considering the steric hindrance created in forming **15**. The memory effect has been attributed to different tight ion pairs depending upon the starting allyl ester. This explanation has been recently questioned.[34] However, the structure of the ion pair is not simply the arrangement of anion and cation and their solvation shell but also includes the conformation of the ligand. An X-ray structure of a related complex clearly shows that the ligand does not possess C_2 symmetry.[35] Such a situation likely exists for this ligand as well. Calculations (AM-1 and PM-3 parametrized for π-allylpalladium) support this conclusion.[36] Thus, accompanying any change in structure of the tight ion pair is a simultaneous change in ligand conformation. Furthermore, there is likely no static "meso-like" π-allyl structure. This symmetry only derives from an averaging of equilibrating structures. At present, this explanation accounts for all the observations. Until detailed structural information is forthcoming in this series, it is not possible to define these structural changes in a more detailed fashion.

On the other hand, prenylation does not show a memory effect. Both regioisomeric starting materials gave significant amounts of attack at the tertiary carbon to form a highly congested product **8**. Recent work established that this family of ligands has a propensity to direct the nucleophile to attack at the more substituted carbon when the diastereomeric complexes are interconverting more rapidly than undergoing nucleophilic attack.[31] In the case of phenols as nucleophiles, excellent regioselectivity for attack at the more substituted allyl terminus was obtained. The formation of **8**, wherein two contiguous quaternary centers are being formed, during the alkylation illustrates how strong this effect might be.

The silyl-substituted allylation becomes a useful functionality for elaboration. Vinylsilanes have great versatility as nucleophiles. This compound also provides a means to overcome the modest ee in the reactions of allyl acetate itself. Protodesilylation of **26a** or **26b** provides the products of simple allylation **5a** and **5c** in high ee. It should be pointed out that the use of the strategy of self-reproduction of chirality for the synthesis of **5c** has been stated to be problematic.[26] The current method offers a reasonable approach.

The present study provides a facile entry to quaternary amino acids using catalytic asymmetric alkylation. The versatility of

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(33) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1996**, *118*, 235.
(34) Lloyd-Jones, G. C.; Stephen, S. C. *Chem. Eur. J.* **1998**, *4*, 2539.
(35) Trost, B. M.; Breit, B.; Peukert, S.; Zambrano, J.; Ziller, J. W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2386.
(36) Hagelin, H.; Åkermark, B.; Trost, B. M.; Norrby, P.-O., to be submitted for publication.

Table 5. Experimental Details for Table 2, Entries 1−14

			product **7**			product **8**		
entry		ligand (mg)	mg	yield (%)	$[\alpha]_D$ (*c*, CH_2Cl_2)	mg	yield (%)	$[\alpha]_D$ (*c*, CH_2Cl_2)
1	**6**	**1** (10.4)	28.0	44	−63.4 (2.67)	14.8	23	−0.8 (1.36)
2	**6**	**1** (10.4)	26.2	41	−63.2 (2.62)	26.2	41	+21.9 (2.62)
3	**6**	**9** (11.8)	37.8	59	+64.3 (3.78)	10.8	17	−12.2 (1.08)
4	**6**	**1** (10.4)	45.9	72	−63.8 (0.78)	14.5	23	+19.5 (1.45)
5	**6**	**1** (10.4)	9.5	15	−57.3 (0.95)	1.9	3	+15.4 (0.19)
6	**6**	**1** (10.4)	36.3	57	−61.3 (0.67)	15.0	23	+18.5 (0.44)
7	**6**	**1** (10.4)	41.7	65	−57.8 (1.11)	14.4	23	−0.9 (0.27)
8	**6**	**10** (11.9)	20.2	32	−62.1 (0.50)	29.8	47	+0.3 (0.51)
9	see text							
10	**11a**	**1** (10.4)	49.8	78	−61.7 (0.97)	7.4	12	+22.1 (0.74)
11	**11a**	**9** (11.8)	39.5	62	+63.9 (0.92)	7.6	12	−42.2 (0.76)
12	**11a**	**1** (10.4)	41.4	65	−62.0 (0.80)	7.2	11	+15.6 (0.72)
13	**11b**	**1** (10.4)	47.1	74	−62.0 (1.16)	10.5	16	+16.3 (1.05)
14	**11b**	**1** (10.4)	35.6	56	−52.4 (0.37)	10.4	16	+15.2 (0.95)

the double bond for further elaborations make asymmetric allylations particularly useful. For example, hydrogenation provides the saturated analogues. Oxidative cleavage provides an entry to α-alkylated aspartic acids. Scheme 1 illustrates access to either enantiomer of α-methylaspartic acid simply by changing the allylating agent—not the chirality of the ligand. Naturally, changing the chirality of the ligand accomplishes the same end result. This compound has generated interest because of its biological activity as a competitive inhibitor of aspartate amino transferase and its possible use as an excitatory amino acid.[25] All of the known asymmetric synthesis routes control relative stereochemistry either via chiral auxiliaries or self-reproduction of chirality.[25,37,38] The route reported herein is the first catalytic asymmetric route and can provide many different α-substituted aspartic acids simply by varying the azlactone.[38]

Experimental Section

Prenylation of 4-Benzyl-2-phenyl-2-oxazolin-5-one (4a). General Procedure. Method A. Allylic substrate (**6** or **11**, 200 μmol), was added to a solution (1 mL) of triethylamine or PMG (400 μmol) and 4-benzyl-2-phenyl-2-oxazolin-5-one (**4a**, 113.1 mg, 450 μmol). Then, a preformed solution (1 mL) of bis(η^3-allyl)di-μ-chlorodipalladium (II) (**2**, 1.8 mg, 4.9 μmol) and chiral ligand (15.1 μmol) was added via cannula. The reaction mixture was quenched with aqueous phosphate buffer (pH 7, 40 mL) and extracted with CH_2Cl_2(3 × 30 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with petroleum ether−AcOEt (97:3) to give first a fraction containing 4-benzyl-4-(2-methyl-3-buten-2-yl)-2-phenyl-2-oxazolin-5-one (**8a**) as an oil and then a second fraction containing 4-benzyl-4-(3-methyl-2-butenyl)-2-phenyl-2-oxazolin-5-one (**7a**) also as an oil. Enantiomeric excess was determined by chiral HPLC (Chiralcel OD column, heptane−2-propanol, 99.9:0.1), t_R(**8a**, −) = 15.3, t_R(**8a**, +) = 16.3; t_R(**7a**, −) = 17.3, t_R(**7a**, +) = 20.7. Tables 2 and 5 summarize the experimental details for each run.

Method B (1% cat). 3-Acetoxy-3-methyl-1-butene (**11a**, 384.5 mg, 3.0 mmol) was added to a solution of triethylamine (420 μL, 3.0 mmol) and 4-benzyl-2-phenyl-2-oxazolin-5-one (**4a**, 829.2 mg, 3.3 mmol) in toluene (27 mL). Then, a preformed solution (2 mL) of bis(η^3-allyl)-di-μ-chlorodipalladium (**2**, 5.5 mg, 15 μmol) and chiral ligand **1** (31.1 mg, 45 μmol) was added via cannula. After 24 h the reaction mixture was quenched with aqueous phosphate buffer (pH 7) and extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with petroleum ether−AcOEt (97:3) to give first a fraction containing 4-benzyl-4-(2-methyl-3-buten-2-yl)-2-phenyl-2-oxazolin-5-one (**8a**): 144.6 mg (15%, 20% ee), $[\alpha]_D$ = +10.1 (*c* = 1.26, CH_2Cl_2) as an oil, and then a second fraction containing 4-benzyl-4-(3-methyl-2-butenyl)-2-phenyl-2-oxazolin-5-one (**7a**): 718.0 mg (75%, 99% ee), $[\alpha]_D$ = −63.4 (*c* = 1.67, CH_2Cl_2) also as an oil.

4-Benzyl-4-(3-methyl-2-butenyl)-2-phenyl-2-oxazolin-5-one (7a): IR (neat film from $CDCl_3$) 1817, 1655, 1602, 1581, 1496, 1451, 1321 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.85−7.82 (m, 2H), 7.51 (m, 1H), 7.44−7.39 (m, 2H), 7.20−7.12 (m, 5H), 5.05 (m, 1H), 3.25 (d, *J* = 13.5 Hz, 1H), 3.17 (d, *J* = 13.5 Hz, 1H), 2.74 (dd, *J* = 14.1, 8.1 Hz, 1H), 2.65 (dd, *J* = 14.1, 7.1 Hz, 1H), 1.65 (s, 3H), 1.64 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 179.7, 159.8, 137.6, 134.7, 132.5, 130.2, 128.7, 128.2, 127.8, 127.1, 125.9, 116.2, 75.2, 43.0, 36.0, 25.8, 18.0. Anal. Calcd for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63, N, 4.39. Found: C, 79.00, H, 6.65, N, 4.37.

4-Benzyl-4-(2-methyl-3-buten-2-yl)-2-phenyl-2-oxazolin-5-one (8a): IR (neat film from $CDCl_3$) 1813, 1658, 1603, 1582, 1496, 1452 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.81−7.78 (m, 2H), 7.49 (m, 1H), 7.42−7.37 (m, 2H), 7.09−7.07 (m, 5H), 6.22 (dd, *J* = 17.8, 10.5 Hz, 1H), 5.23−5.17 (m, 2H), 3.20 (s, 2H), 1.29 (s, 3H), 1.27 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.9, 159.5, 142.6, 134.8, 132.4, 130.5, 128.6, 128.0, 127.8, 127.0, 125.9, 114.6, 79.6, 43.0, 38.6, 22.0, 21.8. Anal. Calcd for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63, N, 4.39. Found: C, 78.84, H, 6.69, N, 4.32.

Prenylation of 4-Methyl-2-phenyl-2-oxazolin-5-one (4b). 3-Acetoxy-3-methyl-1-butene (**6**) or 3-methyl-2-propen-1-yl acetate (**11a**) was added to a solution of triethylamine and 4-methyl-2-phenyl-2-oxazolin-5-one (**4b**) in toluene (1.5 mL). Then a preformed solution of bis(η^3-allyl)di-μ-chlorodipalladium (**2**) and chiral ligand **1** in toluene (0.5 mL) was added via cannula. The reaction mixture was quenched with aqueous phosphate buffer (pH 7, 40 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with petroleum ether−AcOEt (96:4) to give first a fraction containing 4-methyl-4-(2-methyl-3-buten-2-yl)-2-phenyl-2-oxazolin-5-one (**8b**) as an oil and then a second fraction containing 4-methyl-4-(3-methyl-2-butenyl)-2-phenyl-2-oxazolin-5-one (**7b**) also as an oil. Tables 2 and 6 summarize the experimental details for each run.

4-Methyl-4-(3-methyl-2-butenyl)-2-phenyl-2-oxazolin-5-one (7b): Oil. Enantiomeric excess was determined by chiral HPLC (Chiralcel OD column, heptane−2-propanol, 99.5:0.5), t_R(−) = 5.3, t_R(+) = 9.1. IR (neat film from CH_2Cl_2) 1819, 1655, 1602, 1581, 1494, 1451, 1377, 1321 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.00−7.92 (m, 2H), 7.57

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Table 6. Experimental Details for Table 2, Entries 15−19

entry	**1** mg (μmol)	**2** mg (μmol)	$(C_2H_5)_3N$ μL (μmol)	**4b** or **4c** mg (μmol)	**6** or **11a** mg (μmol)	**7b** or **7c** mg (% yield) $[\alpha]_D$ (*c*, CH_2Cl_2)	**8b** mg (% yield) $[\alpha]_D$ (*c*, CH_2Cl_2)
15	10.4 (15.1)	1.8 (4.9)	56 (400)	**4b**, 78.8 (450)	**6**, 25.6 (200)	**7b** 26.7 (55) +48.0 (1.06)	6.4 (13) −4.9 (0.64)
16	4.0 (5.8)	0.7 (1.9)	293 (2100)	**4b**, 385.4 (2200)	**6**, 352.4 (2750)	**7b** 284.4 (53) +54.7 (1.11)	168.2 (31) −4.8 (1.91)
17	10.4 (15.1)	1.8 (4.9)	56 (400)	**4b**, 78.8 (450)	**11a**, 25.6 (200)	**7b** 32.6 (67) +52.8 (1.14)	8.5 (17) −7.2 (0.85)
18	10.4 (15.1)	1.8 (4.9)	56 (400)	**4c**, 91.5 (450)	**6**, 25.6 (200)	**7c** 31.0 (57) +66.4 (0.89)	
19	10.4 (15.1)	1.8 (4.9)	56 (400)	**4c**, 91.5 (450)	**11a**, 25.6 (200)	**7c** 25.7 (47) +66.5 (0.57)	

(m, 1H), 7.51−7.46 (m, 2H), 5.03 (t, J = 7.5 Hz, 1H), 2.64−2.50 (m, 2H), 1.64 (s, 6H), 1.53 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.9, 159.8, 137.6, 132.6, 128.8, 128.0, 126.2, 116.4, 70.2, 36.8, 25.8, 23.0, 18.0. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05, H, 7.04, N, 5.76. Found: C, 73.89, H, 6.89, N. 5.57.

4-Methyl-4-(2-methyl-3-buten-2-yl)-2-phenyl-2-oxazolin-5-one (8b): Oil. Enantiomeric excess was determined by chiral HPLC (Chiralcel OD column, heptane−2-propanol, 99.9:0.1), $t_R(-)$ = 7.1, $t_R(+)$ = 8.3. IR (neat film from CH_2Cl_2) 1819, 1657, 1582, 1494, 1451, 1415, 1371, 1320 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02−7.99 (m, 2H), 7.57 (m, 1H), 7.51−7.45 (m, 2H), 6.06 (dd, J = 17.7, 10.5 Hz, 1H), 5.16−5.10 (m, 2H), 1.45 (s, 3H), 1.20 (s, 3H), 1.17 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.2, 159.7, 142.3, 132.6, 128.8, 128.0, 126.1, 114.6, 74.2, 42.6, 21.5, 21.4, 19.5. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05, H, 7.04, N, 5.76. Found: C, 74.24, H, 6.89, N. 5.63.

Prenylation of 4-Isopropyl-2-phenyl-2-oxazolin-5-one (4c). The reactions were performed as in the case of **4b**. Enantiomeric excess was determined by chiral HPLC (Chiralcel OD column, heptane−2-propanol, 99.9:0.1), $t_R(-)$ = 5.1, $t_R(+)$ = 7.3. The experimental details are summarized in Tables 2 and 6.

4-Isopropyl-4-(3-methyl-2-butenyl)-2-phenyl-2-oxazolin-5-one (7c): IR (neat film from $CDCl_3$) 1816, 1655, 1581, 1495, 1415, 1387, 1320 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01−7.98 (m, 2H), 7.57 (m, 1H), 7.51−7.46 (m, 2H), 4.97 (m, 1H), 2.62−2.59 (m, 2H), 2.20 (hp, J = 6.8 Hz, 1H), 1.62 (s, 3H), 1.60 (s, 3H), 1.07 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 6.7 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.5, 159.9, 137.3, 132.5, 128.8, 128.0, 126.2, 116.3, 77.3, 34.4, 33.6, 25.8, 18.0, 17.1, 16.8. Anal. Calcd for $C_{17}H_{21}NO_2$ C, 75.25, H, 7.80, N. 5.16. Found: C, 75.12, H, 7.87, N, 5.19.

Cinnamylation of 4-Benzyl- and 4-Methyl-2-phenyl-2-oxazolin-5-one. Following the general procedure, cinnamyl acetate (**12**) or 3-acetoxy-3-phenyl-1-propene (**13**) (35.2 mg, 200 μmol), amine (400 μmol), azlactone (**4a**, 113 mg; **4b**, 78.8 mg; 450 μmol), bis(η^3-allyl)-di-μ-chlorodipalladium (**2**, 1.8 mg, 4.9 μmol), and ligand (15.1 μmol) in 2 mL of toluene or acetonitrile gave the alkylated product **14** after flash chromatography (94:6 petroleum ether−ethyl acetate). In the alkylation of **4a** with **13**, flash chromatography (93:7 petroleum ether−ethyl acetate) gave successively first one diastereomer of **15a**, next a second diastereomer of **15a** and finally **14a**. Tables 3 and 7 summarize the experimental details for each of the runs. Enantiomeric purity was determined by chiral HPLC (Chiralcel OD column, 99:1 heptane−2-propanol $t_R(+)$ = 11.1, $t_R(-)$ = 13.7 for **14a**; $t_R(+)$ = 8.3, $t_R(-)$ = 11.0 for **14b**.

Preparative Run (Table 7, entry 13). Cinnamyl acetate (**12**, 388.4 mg, 2.2 mmol) was added to a solution of triethylamine (305 μL, 2.2 mmol) and 4-methyl-2-phenyl-2-oxazolin-5-one (**4b**, 385.4 mg, 2.2 mmol) in toluene (1.5 mL). Then, a preformed solution of bis(η^3-allyl)-di-μ-chlorodipalladium(II) (**2**, 0.7 mg, 1.9 μmol) and chiral ligand **1** (4.0 mg, 5.8 μmol) was added via cannula in toluene (0.5 mL). The reaction mixture was stirred at room temperature for 6 h, quenched with aqueous phosphate buffer (pH 7, 40 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with petroleum ether−AcOEt (94:6) to give a first fraction of one diasteroisomer of 4-methyl-2-phenyl-4-(1-phenyl-2-propenyl)-2-oxazolin-5-one (**15b**, 48.4 mg, 8%), followed by the other diastereoisomer (**15**, 23.1 mg, 4%) and finally (*E*)-4-methyl-2-phenyl-4-(3-phenyl-2-propen-1-yl)-2-oxazolin-5-one (**14b**) as an oil: 479.1 mg (75%, 90% ee).

Table 7. Experimental Details for Table 3

entry	azlactone/ allyl ester/ solvent	ligand (mg)	base (μL)	product **14** mg (% yield) $[\alpha]_D$ (*c*, CH_2Cl_2)
1	**4a**/**12**/CH_3CN	**1** (10.4)1	$(C_2H_5)_3N$ (56)	55.9 (76) +65.5 (0.50)
2	**4a**/**12**/CH_3CN	**9** (11.8)	$(C_2H_5)_3N$ (56)	47.8 (65) −62.0 (1.05)
3	**4a**/**12**/$PhCH_3$	**1** (10.4)	$(C_2H_5)_3N$ (56)	66.5 (91) +77.0 (0.75)
4	**4a**/**12**/$PhCH_3$	**1** (10.4)	$C_2H_5N(i\text{-}C_3H_7)$ (70)	67.6 (92) +79.6 (1.08)
5	**4a**/**12**/$PhCH_3$	**1** (10.4)	$(C_2H_5)_2NPh$ (64)	69.7 (95) +73.4 (1.24)
6	**4a**/**12**/$PhCH_3$	**1** (10.4)	none	69.2 (94) +77.9 (0.97)
7	**4a**/**12**/$PhCH_3$	**1** (10.4)	$(C_2H_5)_3N$ (56)	66.9 (91) +74.2 (1.28)
8	**4a**/**13**/$PhCH_3$	**1** (10.4)	$(C_2H_5)_3N$ (56)	33.4 (45) +87.3 (0.65)[a]
9	**4b**/**12**/$PhCH_3$	**1** (10.4)	$(C_2H_5)_3N$ (56)	43.2 (74)
10	**4b**/**12**/$PhCH_3$	**9** (11.8)	$(C_2H_5)_3N$ (56)	46.3 (80)
11	**4b**/**12**/$PhCH_3$	**16** (12.2)	$(C_2H_5)_3N$ (56)	49.1 (84)
12	**4b**/**12**/$PhCH_3$	**1** (10.4)	$(C_2H_5)_3N$ (56)	42.2 (72)
13	see text			

[a] First eluting diastereomer of **15a**, 20.4 mg (28% yield); second eluting isomer of **15a**, 14.2 mg (19% yield).

(*E*)-4-Benzyl-2-phenyl-4-(3-phenyl-2-propenyl)-2-oxazolin-5-one (14a): IR (neat film from $CDCl_3$) 1815, 1654, 1601, 1580, 1495, 1451, 1320 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85−7.82 (m, 2H), 7.51 (m, 1H), 7.43−7.38 (m, 2H), 7.30−7.14 (m, 10H), 6.55 (d, J = 15.8 Hz, 1H), 6.08 (dt, J = 15.8, 7.5 Hz, 1H), 3.24 (d, J = 13.4 Hz, 1H), 3.20 (d, J = 13.4 Hz, 1H), 2.94−2.83 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 179.3, 160.2, 135.4, 134.4, 132.6, 130.2, 128.7, 128.5, 128.2, 127.9, 127.6, 127.3, 126.4, 125.7, 122.0, 74.9, 43.2, 40.7. Anal. Calcd for $C_{25}H_{21}NO_2$: C, 81.72, H, 5.76, N, 3.81. Found: C, 81.96, H, 6.00, N, 3.69.

(*E*)-4-Methyl-2-phenyl-4-(3-phenyl-2-propenyl)-2-oxazolin-5-one (14b): IR (neat film from $CDCl_3$) 1819, 1654, 1580, 1495, 1450, 1321 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00−7.98 (m, 2H), 7.57 (m, 1H), 7.50−7.45 (m, 2H), 7.30−7.18 (m, 5H), 6.53 (d, J = 15.8 Hz, 1H), 6.07 (dt, J = 15.8, 7.5 Hz, 1H), 2.84−2.70 (m, 2H), 1.57 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.5, 160.1, 136.9, 135.4, 132.8, 128.9, 128.5, 128.0, 127.6, 126.4, 125.9, 122.2, 69.9, 41.6, 23.2. Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33, H, 5.88, N, 4.81. Found: C, 78.22, H, 5.99, N, 4.78.

Geranylation of 4-Benzyl-2-phenyl-2-oxazolin-5-one. Following the general procedure, geranyl acetate (42.9 μL, 200 μmol), *N*,*N*-diisopropylethylamine (70 μmol, 400 μmol) **4a** (113.1 mg, 450 μmol),

2 (1.8 mg, 4.9 μmol), and **1** (10.4 mg, 15.1 μmol) in 2 mL of toluene after stirring at room temperature for 24 h and flash chromatographic purification (93:7 pet ether−ethyl acetate) gave azlactone **17** (51.0 mg, 66% yield), $[\alpha]_D = -41.2$ ($c = 1.04$, CH_2Cl_2). Enantiomeric excess was determined by chiral HPLC (Chiralcel OD column, heptane−2-propanol, 99.9:0.1), $t_R(-) = 11.2$, $t_R(+) = 12.5$.

4-Benzyl-4-geranyl-2-phenyl-2-oxazolin-5-one (17). IR (neat film from $CDCl_3$) 1817, 1656, 1603, 1581, 1496, 1452, 1376, 1321 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.85−7.82 (m, 2H), 7.51 (m, 1H), 7.43−7.38 (m, 2H), 7.20−7.12 (m, 5H), 5.06 (t, $J = 7.6$ Hz, 1H), 4.96 (m, 1H), 3.25 (d, $J = 13.4$ Hz, 1H), 3.17 (d, $J = 13.4$ Hz, 1H), 2.75 (dd, $J = 14.0$, 8.2 Hz, 1H), 2.67 (dd, $J = 14.0$, 7.1 Hz, 1H), 1.96−1.88 (m, 4H), 1.65 (s, 3H), 1.58 (s, 3H), 1.47 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 179.7, 159.8, 141.3, 134.7, 132.4, 131.6, 130.2, 128.7, 128.2, 127.8, 127.1, 125.9, 123.9, 116.1, 75.3, 43.0, 39.7, 35.9, 26.5, 25.5, 17.4, 16.4. Anal. Calcd for $C_{26}H_{29}NO_2$: C, 80.59, H, 7.54, N, 3.61. Found: C, 80.71, H, 7.38, N, 3.61.

Alkylation of 4-Benzyl-2-phenyl-2-oxazolin-5-one with 3-Acetoxy-1,1-diphenylpropene (18). Following the general procedure, 3-acetoxy-1,1-diphenylpropene (**18**, 50.5 mg, 200 μmol), triethylamine (56 μL, 400 μmol), **4a** (113.1 mg, 450 μmol), **2** (1.8 mg, 4.9 μmol), and **1** (10.4 mg, 15.1 μmol) in 2 mL of toluene gave after 3 days at room temperature and flash chromatographic purification (95:5 pet ether: ethyl acetate), (6.7 mg, 13% recovery) recovered starting material **18**, and azlactone **19** (73.9 mg, 84% yield, 96% yield brsm), $[\alpha]_D = -70.7$ ($c = 0.93$, CH_2Cl_2). Enantiomeric excess was determined by chiral HPLC (Chiralpak AD column, heptane 2-propanol 99:1), $t_R(-) = 9.5$, $t_R(+) = 11.6$.

4-Benzyl-4-(3,3-diphenyl-2-propenyl)-2-phenyl-2-oxazolin-5-one (19): IR (neat film from $CDCl_3$) 1816, 1655, 1601, 1580, 1495, 1452, 1321 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.88−7.85 (m, 2H), 7.54−7.49 (m, 1H), 7.44−7.34 (m, 5H), 7.23−7.11 (m, 12H), 6.03 (t, $J = 7.4$ Hz, 1H), 3.19 (d, $J = 13.4$ Hz, 1H), 3.10 (d, $J = 13.4$ Hz, 1H), 2.85−2.83 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 179.3, 160.0, 146.2, 142.2, 139.4, 134.4, 132.6, 130.2, 130.0, 128.7, 128.4, 128.2, 127.9, 127.5, 127.4, 127.2, 125.7, 120.9, 74.6, 42.9, 37.4. Anal. Calcd for $C_{31}H_{25}NO_2$: C, 83.95, H, 5.68, N, 3.16. Found: C, 84.09, H, 5.49, N, 3.16.

Alkylation of 4-Methyl-2-phenyl-2-oxazolin-5-one with 3-Acetoxy-3-phenyl-1-butene (20). Following the general procedure, 3-acetoxy-3-phenyl-1-butene (**20**, 38 μL, 200 μmol), triethylamine (56 μL, 400 μmol), **4b** (78.8 mg, 450 μmol), **2** (1.8 mg, 4.9 μmol), and **1** (10.4 mg, 15.1 μmol) in 2 mL of toluene gave, after 3 h at room temperature and flash chromatography (96:4 pet ether:ethyl acetate), azlactone **21** (28.5 mg, 47% yield) $[\alpha]_D = -5.0$ ($c = 0.53$, CH_2Cl_2) followed by azlactone **22** (25.3 mg, 41% yield), $[\alpha]_D = +3.7$ ($c = 2.13$, CH_2Cl_2). Enantiomeric excess was determined by chiral HPLC (Chiralcel OD column heptane:2-propanol 99.1:0.1), $t_R(+) = 11.3$, $t_R(-) = 19.5$ for **21**; $t_R(-) = 23.6$, $t_R(+) = 31.1$ for **22**.

(*Z*)-4-Methyl-4-(3-phenyl-2-butenyl)-2-phenyl-2-oxazolin-5-one (21): IR(neat film from CH_2Cl_2) 1820, 1654, 1601, 1580, 1493, 1451, 1374, 1321 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.03−8.00 (m, 2H), 7.57 (m, 1H), 7.52−7.46 (m, 2H), 7.37−7.32 (m, 2H), 7.26 (m, 1H), 7.19−7.16 (m, 2H), 5.37 (tq, $J = 7.3$, 1.3 Hz, 1H), 2.54 (d, $J = 7.3$ Hz, 2H), 1.98 (d, $J = 1.3$ Hz, 3H), 1.44 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.9, 159.8, 141.9, 141.4, 132.7, 128.8, 128.3, 128.0, 127.9, 126.9, 126.1, 118.9, 69.5, 37.5, 25.9, 23.0. Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66, H, 6.27, N, 4.59. Found: C, 78.65, H, 6.22, N, 4.54.

(*E*)-4-Methyl-4-(3-phenyl-2-butenyl)-2-phenyl-2-oxazolin-5-one (22): IR (neat film from CH_2Cl_2) 1820, 1655, 1601, 1581, 1494, 1451, 1381, 1321 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.00−7.97 (m, 2H), 7.56 (m, 1H), 7.50−7.44 (m, 2H), 7.25−7.18 (m, 5H), 5.63 (tq, $J = 7.7$, 1.4 Hz, 1H), 2.79 (d, $J = 7.7$ Hz, 2H), 2.06 (d, $J = 1.4$ Hz, 3H), 1.60 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.7, 160.0, 143.6, 140.4, 132.7, 128.9, 128.2, 128.0 (2), 127.1, 125.9, 119.9, 70.1, 37.3, 23.2, 16.3. Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66, H, 6.27, N, 4.59. Found: C, 78.70, H, 6.43, N, 4.47.

Alkylation of 4-Methyl-2-phenyl-2-oxazolin-5-one with (*E*)-1-Acetoxy-4-methyl-2-pentene (23). Following the general procedure, (*E*)-1-acetoxy-4-methyl-2-pentene (**23**, 284.4 mg, 2.0 mmol), triethylamine (280 μL, 2.0 mmol), **4b** (350.2 mg, 2.0 mmol), **2** (0.7 mg, 1.9 μmol), and **1** (4.0 mg, 5.8 μmol) in 1.5 mL of toluene gave, after 3 h at room temperature and flash chromatography (95:5 petroleum ether−ethyl acetate), azlactone **24** (452.4 mg, 88% yield), $[\alpha]_D = -34.1$ ($c = 1.01$, CH_2Cl_2). Enantiomeric excess was determined by chiral HPLC (Chiralcel OD column, heptane−2-propanol, 99.5:0.5) $t_R(-) = 5.4$, $t_R(+) = 7.8$.

(*E*)-4-Methyl-4-(4-methyl-2-pentenyl)-2-phenyl-2-oxazolin-5-one (24): IR(neat film from CH_2Cl_2) 1823, 1655, 1602, 1581, 1494, 1451, 1321 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.00−7.97 (m, 2H), 7.57 (m, 1H), 7.51−7.45 (m, 2H), 5.54 (dd, $J = 15.4$, 6.8 Hz, 1H), 5.21 (dt, $J = 15.4$, 7.4 Hz, 1H), 2.59−2.46 (AB system, 2H), 2.16 (m, 1H), 1.52 (s, 3H), 0.85 (d, $J = 6.6$ Hz, 3H), 0.84 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.6, 159.7, 144.3, 132.7, 128.8, 127.9, 126.1, 119.0, 70.2, 41.1, 30.9, 22.9, 22.3, 22.1. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68, H, 7.44, N, 5.44. Found: C, 74.68, H, 7.20, N, 5.20.

Alkylations with 3-Acetoxy-3-trimethylsilylpropene (25). 4-Benzyl-2-phenyl-2-oxazolin-5-one: Following the general procedure, 3-acetoxy-3-trimethylsilylpropene (**25**, 34.5 mg, 200 μmol), triethylamine (56 μL, 400 μmol), **4a** (113.1 mg, 450 μmol), **2** (1.8 mg, 4.9 μmol), and **1** (10.4 mg, 15.1 μmol) in 2 mL of toluene gave, after 24 h at room temperature and flash chromatography (95:5 pet ether−ethyl acetate), the silylated azlactone **26a** (50.3 mg, 69%), $[\alpha]_D = -53.7$ ($c = 1.05$, CH_2Cl_2), and desilylated azlactone **5a** (16.8 mg, 27% including catalyst). Enantiomeric excess was determined by chiral HPLC (Chiralcel OD column, heptane−2-propanol, 99.9:0.1), $t_R(-) = 13.4$, $t_R(+) = 18.9$.

(*E*)-4-Benzyl-2-phenyl-4-(3-trimethylsilyl-2-propenyl)-2-oxazolin-5-one (26a): IR (neat film from $CDCl_3$) 1818, 1655, 1605, 1581, 1496, 1452, 1321 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.89−7.86 (m, 2H), 7.54 (m, 1H), 7.46−7.41 (m, 2H), 7.22−7.16 (m, 5H), 6.19 (dt, $J = 14.2$, 7.4 Hz, 1H), 5.70 (d, $J = 14.2$ Hz, 1H), 3.26 (d, $J = 13.3$ Hz, 1H), 3.17 (d, $J = 13.3$ Hz, 1H), 2.82 (dd, $J = 7.4$, 1.2 Hz, 2H), 0.16 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 179.3, 159.9, 139.3, 135.3, 134.4, 132.6, 130.3, 128.7, 128.2, 127.9, 127.3, 125.8, 74.2, 43.2, 40.3, 0.0. Anal. Calcd for $C_{22}H_{25}NO_2Si$: C, 72.69, H, 6.93, N, 3.85. Found: C, 72.77, H, 7.02, N, 3.90.

4-Methyl-2-phenyl-2-oxazolin-5-one. Following the general procedure, 3-acetoxy-3-trimethylsilylpropene (**25**, 172.5 mg, 1.0 mmol), triethylamine (280 μL, 2.0 mmol), **4b** (394.0 mg, 2.25 mmol), **2** (9.0 mg, 24.5 μmol), and **1** (51.8 mg, 75.5 μmol) in 10 mL of toluene gave, after 22 h at room temperature and flash chromatography (97:3 pet ether−ethyl acetate), in order of elution **27b** (56.9 mg, 20% yield), **26b** (151.4 mg, 53% yield), *Z*-isomer of **26b** (19.2 mg, 3% yield), and **5c** (27.0 mg, 7% yield).

(*E*)-4-Methyl-2-phenyl-4-(3-trimethylsilyl-2-propenyl)-2-oxazolin-5-one (26b): Oil. Enantiomeric excess was determined by chiral HPLC (Chiralcel OD column, heptane−2-propanol, 99.9: 0.1), $t_R(-) = 10.4$, $t_R(+) = 13.0$. IR(neat film from CH_2Cl_2) 1821, 1655, 1610, 1581, 1452, 1321 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.01−7.98 (m, 2H), 7.57 (m, 1H), 7.51−7.46 (m, 2H), 6.14 (dt, $J = 14.2$, 7.3 Hz, 1H), 5.68 (d, $J = 14.2$ Hz, 1H), 2.69 (d, $J = 7.3$ Hz, 2H), 1.54 (s, 3H), 0.14 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.4, 159.9, 139.5, 135.2, 132.7, 128.8, 128.0, 126.0, 69.2, 41.2, 23.2, 0.0. Anal. Calcd for $C_{16}H_{21}NO_2Si$: C, 66.86, H, 7.36, N, 4.87. Found: C, 66.71, H, 7.12, N, 4.85.

(*Z*)-4-Methyl-2-phenyl-4-(3-trimethylsilyl-2-propenyl)-2-oxazolin-5-one (*Z*-isomer of 26b): Oil. Enantiomeric excess was determined by chiral HPLC (Chiralcel OD column, heptane−2-propanol, 99.5: 0.5), $t_R(-) = 5.9$, $t_R(+) = 7.0$. IR (neat film from $CDCl_3$) 1821, 1655, 1617, 1581, 1494, 1452, 1321 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.98−7.95 (m, 2H), 7.56 (m, 1H), 7.50−7.44 (m, 2H), 5.84−5.82 (m, 2H), 2.64−2.62 (AB system, 2H), 1.52 (s, 3H), −0.09 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.5, 159.8, 138.3, 137.8, 132.7, 128.8, 127.9, 126.0, 69.8, 45.0, 22.9, −1.7. Anal. Calcd for $C_{16}H_{21}NO_2Si$: C, 66.86, H, 7.36, N, 4.87. Found: C, 67.01, H, 7.30, N, 4.80.

4-Allyl-4-methyl-2-phenyl-2-oxazolin-5-one (5c): Oil. Enantiomeric excess was determined by chiral HPLC (Chiralcel OD column, heptane−2-propanol, 99.9: 0.1), $t_R(-) = 11.7$, $t_R(+) = 22.8$. IR (neat film from $CDCl_3$) 1819, 1655, 1581, 1493, 1451, 1321 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.00−7.97 (m, 2H), 7.57 (m, 1H), 7.51−7.45 (m, 2H), 5.68 (m, 1H), 5.20−5.10 (m, 2H), 2.68−2.54 (AB system,

2H), 1.53 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.4, 160.0, 132.7, 130.9, 128.8, 128.0, 126.0, 120.5, 69.7, 42.2, 23.1. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54, H, 6.09, N, 6.51. Found: C, 72.54, H, 6.15, N, 6.37.

4-Methyl-2-phenyl-4-(1-trimethylsilyl-2-propenyl)-2-oxazolin-5-one (27b): Oil. Enantiomeric and diasteromeric excess were determined by chiral HPLC (Chiralcel OD column, heptane−2-propanol, 99.9:0.1): major isomer: $t_R(-) = 6.3$, $t_R(+) = 6.9$; minor isomer: $t_R = 7.9$, $t_R = 8.5$ (only one observed). IR (neat film from $CDCl_3$) 1823, 1652, 1581, 1494, 1451, 1321 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02−7.99 (m, 2H), 7.58 (m, 1H), 7.52−7.46 (m, 2H), 5.93 (ddd, J = 17.0, 11.0, 10.2 Hz, 1H), 5.16 (dd, J = 10.2, 1.7 Hz, 1H), 5.05 (dd, J = 17.0, 1.7 Hz, 1H), 2.09 (d, J = 11.0 Hz, 1H), 1.46 (s, 3H), −0.03 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.8, 159.5, 134.4, 132.7, 128.9, 127.9, 126.2, 116.9, 70.1, 43.0, 24.9, −2.1. Anal. Calcd for $C_{16}H_{21}NO_2Si$: C, 66.86, H, 7.36, N, 4.87. Found: C, 67.00, H, 7.24, N, 4.86.

(*S*)-Methylaspartic Acid ((+)-31). Methyl (*S*)-2-Benzamido-2,5-dimethyl-4-hexeneate (29). Trimethylsilyl chloride (TMS-Cl) (50 μL, 0.4 mmol) was added to a solution of 4-methyl-4-(3-methyl-2-butenyl)-2-phenyl-2-oxazolin-5-one (**7b**, 251.9 mg, 1.04 mmol, 31, 98% ee) in methanol (5 mL). The solution was stirred for 30 min and concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with petroleum ether−AcOEt (85:15) to afford methyl 2-benzamido-2,5-dimethyl-4-hexeneate (**29**, 276.8 mg, 97%) as a colorless solid, mp: 83−4 °C, $[\alpha]_D = +23.3$ (c = 1.01, CH_2Cl_2). IR (neat film from CH_2Cl_2) 3322, 1741, 1639, 1602, 1580, 1534, 1489, 1451, 1376, 1326 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77−7.74 (m, 2H), 7.50−7.39 (m, 3H), 6.92 (s, 1H), 5.02 (tq, J = 7.7, 1.4 Hz, 1H), 3.78 (s, 3H), 3.00 (dd, J = 14.3, 7.7 Hz, 1H), 2.63 (dd, J = 14.3, 7.7 Hz, 1H), 1.72 (s, 3H), 1.69 (s, 3H), 1.61 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.0, 166.6, 136.5, 135.0, 131.5, 128.6, 126.9, 117.7, 60.4, 52.6, 35.2, 25.9, 22.6, 17.8. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79, H, 7.69, N, 5.09. Found: C, 70.00, H, 7.57, N, 5.14.

Dimethyl (*S*)-2-Benzamido-2-methylsuccinate ((+)-30). A methanolic solution of NaOH (1.74 mL, 4.3 mmol, 2.5 M) was added to a solution of methyl (*S*)-2-benzamido-2,5-dimethyl-4-hexenoate (**29**, 239.3 mg, 0.87 mmol) in CH_2Cl_2 (6.8 mL) at −78 °C. Ozone (ozone: 1.0 mL/min, sample: 0.8 mL/min, 75 V, 7 psi) was bubbled for 30 min. A yellow precipitate appeared, and the solution turned to a light blue after 25 min of bubbling. Water (5 mL) and diethyl ether (5 mL) were added, and the mixture was warmed to room temperature. The aqueous layer was extracted with ether. The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with petroleum ether−AcOEt (4:1) to afford dimethyl (*S*)-2-benzamido-2-methylsuccinate (**(+)-30**), 203.5 mg, 84%) as an oil. $[\alpha]_D = +10.4$ (c = 1.15, CH_2Cl_2). IR(neat film from $CDCl_3$) 3385, 1740, 1654, 1603, 1580, 1528, 1488, 1438, 1319 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80−7.77 (m, 2H), 7.51−7.41 (m, 4H), 3.83 (s, 3H), 3.64 (d, J = 16.5 Hz, 1H), 3.64 (s, 3H), 3.06 (d, J = 16.5 Hz, 1H), 1.76 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.2, 171.4, 166.6, 134.5, 131.7, 128.6, 127.0, 57.9, 53.1, 51.7, 39.9, 23.1. Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21, H, 6.13, N, 5.02. Found: C, 60.41, H, 6.17, N, 5.00.

(*S*)-Methylaspartic Acid Hydrochloride ((+)-31). Concentrated hydrochloric acid (3 mL) was added dropwise to dimethyl (*S*)-2-benzamido-2-methyl-succinate (146.3 mg, 524 μmol) in water (3 mL). The mixture was heated to reflux for 48 h. Then, it was diluted with water (10 mL) and extracted wtih diethyl ether (4 × 5 mL). The aqueous layer was evaporated to dryness to afford (*S*)-methylaspartic acid hydrochloride (**(+)-31**), 91.4 mg, 95%) as a solid, $[\alpha]_D = +35.5$ (c = 1.07, MeOH). IR(KBr) 3500−2100 (broad), 1756, 1691, 1601, 1570, 1508, 1452, 1414, 1388, 1339 cm^{-1}. ^{1}H NMR (300 MHz, D_2O) δ 2.99 (d, J = 18.2 Hz, 1H), 2.70 (d, J = 18.2 Hz, 1H), 1.35 (s, 3H). ^{13}C NMR (75.5 MHz, D_2O) δ 181.6, 181.3, 65.2, 47.8, 30.0.

(*R*)-Methyl Aspartic Acid ((−)-31). From 14b. As above, TMS-Cl (50 μml, 0.4 mmol) and **14b** (291.4 mg, 1.0 mmol, 90% ee) in 5 mL of methanol for 1 h gave, after flash chromatography (85:15 pet ether−ethyl acetate) the ester **32** as a foam (310.8 mg, 96%).

Methyl (*R*,*E*)-2-benzamido-2-methyl-5-phenyl-4-pentenoate (32): $[\alpha]_D = -24.0$ (c = 2.03, CH_2Cl_2). IR(neat film from $CDCl_3$) 3327, 1739, 1644, 1602, 1580, 1532, 1488, 1450, 1376, 1327 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78−7.75 (m, 2H), 7.48 (m, 1H), 7.46−7.37 (m, 2H), 7.30−7.18 (m. 5H), 7.01 (s, 1H), 6.47 (d, J = 15.7 Hz, 1H), 6.06 (dt, J = 15.7, 7.6 Hz, 1H), 3.81 (s, 3H), 3.27 (dd, J = 14.0, 7.6 Hz, 1H), 2.85 (dd, J = 14.0, 7.6 Hz, 1H), 1.76 (s, 3H). 13C NMR (75.5 MHz, CDCl3) δ 174.7, 166.7, 137.0, 134.7, 134.5, 131.6, 128.6, 128.5, 127.5, 126.9, 126.2, 123.8, 60.5, 52.8, 39.6, 22.9. Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28, H, 6.55, N, 4.33. Found: C, 74.08, H, 6.64, N, 4.25.

The ozonolysis was performed as above using a methanolic solution of sodium hydroxide (1.61 mL, 4.0 mmol, 2.5 M) and **32** (260.2 mg, 0.81 mmol) in 6.4 mL of methylene chloride for 30 min to give, after flash chromatography as before, some starting material **32** (8.7 mg, 3% recovery) and **(−)-30** (183 mg, 81% yield, 84% yield brsm). The spectral data are the same as before, and the rotation is opposite.

Global deprotection as above of **(−)-30** (90.8 mg, 325 μmol) with 3 mL of concentrated hydrochloric acid in 3 mL of water for 48 h gave the hydrochloride salt **(−)-31** (58.9 mg, 99%), $[\alpha]_D = -28.8$ (c = 14.4, CH_3OH).

From 24. As above, TMS-Cl (50 μL, 0.4 mmol) and **24** (262.8 mg, 1.02 mmol, 83% ee) in 5 mL of methanol for 30 min gave, after flash chromatography (85:15 pet ether−ethyl acetate) the ester **33** (290.9 mg, 99%).

Methyl (*R*,*E*)-2-benzamido-2,6-dimethyl-4-heptenoate (33): $[\alpha]_D = -17.0$ (c = 1.06, CH_2Cl_2). IR(neat film from $CDCl_3$) 3321, 2956, 2869, 1742, 1642, 1603, 1580, 1532, 1489, 1451, 1375, 1327 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78−7.76 (m, 2H), 7.50−7.40 (m, 3H), 6.93 (s, 1H), 5.50 (dd, J = 15.4, 6.9 Hz, 1H), 5.26 (ddd, J = 15.4, 7.4, 7.1 Hz, 1H), 3.78 (s, 3H), 2.97 (dd, J = 13.6, 7.1 Hz, 1H), 2.55 (dd, J = 13.6, 7.4 Hz, 1H), 2.24 (m, 1H), 1.72 (s, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.5 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.8, 166.5, 143.4, 134.9, 131.5, 128.6, 126.9, 120.4, 60.3, 52.6, 39.8, 31.1, 22.5, 22.4. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56, H, 8.01, N, 4.84. Found: C, 70.54, H, 8.06, N, 4.84.

The ozonolysis was performed as above using a methanolic solution of sodium hydroxide (1.58 mL, 4.0 mmol, 2.5 M) and **33** (228.9 mg, 0.79 mmol) in 6.3 mL of methylene chloride for 35 min to give, after flash chromatograph as before, **(−)-30** (202.4 mg, 92%), $[\alpha]_D = -4.6$ (c = 1.32, CH_2Cl_2).

(*S*)-2-Benzamido-2-methyl-4-pentenoic Acid (35). Concentrated hydrochloric acid (25 μL) was added dropwise to **26b** (30.0 mg, 104 μmol, 97% ee) in acetonitrile (2 mL). The mixture was stirred for 30 min and quenched with HCl (1 N) and extracted with methylene chloride. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. On the basis of ^{1}H NMR, the residue was mainly (*E*)-2-benzamido-2-methyl-5-trimethylsilyl-4-pentenoic acid (**34**). It was dissolved again in acetonitrile (2 mL) with concentrated hydrochloric acid (25 μL) for 30 min at 70 °C. The same type of workup afforded a residue which was purified by flash chromatography on silica gel eluting with AcOEt to afford (*S*)-2-benzamido-2-methyl-4-pentenoic acid (**35**, 19.3 mg, 86%): $[\alpha]_D = -11.9$ (c = 0.39, MeOH).

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