Investigations of a Nucleophilic Alaninol Synthon Derived from Serine

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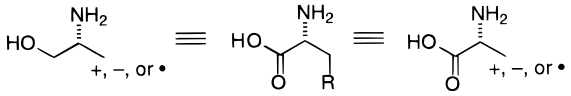
Abstract: A nucleophilic synthon, (*S*)-(+)-4-(2-oxazolidonyl)-methyltriphenylphosphinyl iodide **6**, available from L-serine in five steps (overall yield of 52%), reacts with aldehydes to produce alkenes in good to excellent yields (74−89%) and, in some cases, provides excellent stereocontrol of the new double bond. The geometry of the newly formed double bond is influenced by the nature of the aldehyde and reaction conditions. The trends in olefin configuration are discussed. Application of this methodology allows for easy preparation of molecules containing double bonds allylic to nitrogen, including oxazolidinones and β,γ-unsaturated amino alcohols. Several of the unsaturated oxazolidinones are converted to β,γ-unsaturated amino alcohols in high yields (75 to 90%).

Naturally occurring difunctional amino acids with their rich array of functional groups and inherent chirality are ideal building blocks for the preparation of useful chiral synthons. Serine, an amino acid readily available in both enantiomeric forms, has served as one such starting material. Differentially protected serine and derivatives derived from the parent amino acid are useful synthons in the preparation of natural and unnatural amino acids and amino alcohols. The chemistry of nucleophilic, electrophilic, and radical alanine or alaninol equivalents derived from serine has been explored in several laboratories,[3] most notably by Baldwin,[4] Garner,[5] Jackson,[6] Sasaki,[7] Vederas[8] and Viallefont.[9] Work in our laboratory has also focused on synthons derived from serine.[10] The chemistry of a nucleophilic alaninol synthon is the subject of this paper.[11]



A major emphasis of the utility of nucleophilic alanine (alaninol) synthons has been in the development of new methodologies for the syntheses of nonproteinogenic amino acids. These amino acids are significant because of their wide range of biological activities.[12] In particular, β,γ-unsaturated amino acids have attracted considerable interest because of their

(1) Taken in part from the M. S. thesis of Drew Rutherford (North Dakota State University, 1994) and M. S. thesis of Biqin Li (North Dakota State University, 1992).

(2) Undergraduate research participant 1988−1990, NSF-REU participant 1988.

(3) General: Williams, R. M. *Synthesis of Optically Active* α*-Amino Acids*; Pergamon: New York, 1989; Chapter 2 and references therein. Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539. Nucleophilic synthons: (a) Seebach, D.; Wasmuth, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 971. (b) Wolf, J.-P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 3164. (c) Daddu, R.; Eckhardt, M.; Furlong, M.; Knoess, H. P.; Berger, S.; Knochel, P. *Tetrahedron* **1994**, *50*, 2415. (d) Ye, B.; Otaka, A.; Burke, T. R., Jr. *Synlett* **1996**, 459. (e) Malan, C.; Morin, C. *Synlett* **1996**, 167. (f) Duthaler, R. O. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 705. (g) Blanchard, P.; El Kortbi, M. S.; Fourrey, J.-L.; Robert-Gero, M. *Tetrahedron Lett.* **1992**, *33*, 3319. Electrophilic synthons: (h) Dureault, A.; Tranchepain I.; Depezay, J.-C. *J. Org. Chem.* **1989**, *54*, 5324. (i) Sato, K.; Kozikowski, A. P. *Tetrahedron Lett.* **1989**, *30*, 4073. Radical alaninol synthons: (j) Maria, E. J.; Da Silva, A. D.; Fourrey, J.-L.; Machado, A.; Robert-Gero, M. *Tetrahedron Lett.* **1994**, *35*, 3301.

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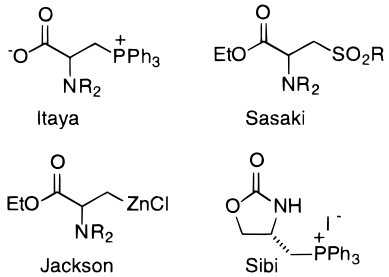
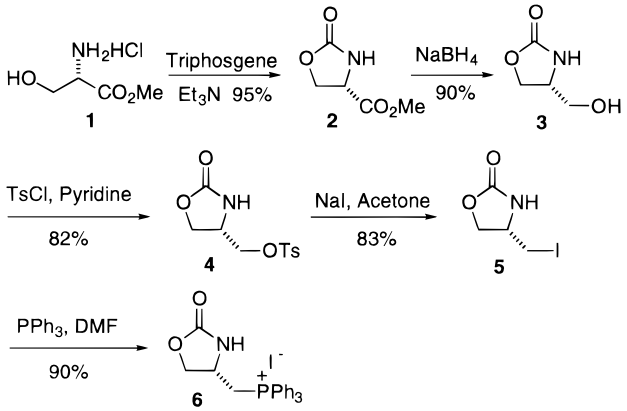
potential as suicide enzyme inhibitors,[13] and several procedures are available for their synthesis.[14] Sasaki et al.[7] have prepared very useful synthons from L- and D-serine and evaluated them as nucleophilic alaninol equivalents. Itaya and co-workers,[15] in their synthesis of wybutine, showed that a Wittig reagent derived from serine undergoes olefination with little racemization, albeit in very low yields (5−13%). A modification of this reagent and Wittig reactions with slightly better efficiency was recently reported by the same group.[16] We were interested in preparing a nucleophilic alaninol synthon from serine which could be used for the generation of either *E* or *Z* β,γ-unsaturated amino alcohols and amino acids, with good stereocontrol, and in high chemical yields.[17] This paper describes the synthesis and reactions of one such synthon and presents a mechanistic explanation for the observed stereoselectivities in the olefination.



Results and Discussion

Our initial task was to establish optimal reaction conditions for the preparation of the phosphonium salt **6** from readily available L-serine methyl ester hydrochloride[18] such that the intermediates required very little or no chromatographic purification (Scheme 1). In our earlier reported methodology, treatment of serine methyl ester hydrochloride with phosgene (as a 20% toluene solution) in aqueous potassium carbonate (3 h at 0 °C) gave the best conversion to the oxazolidinone **2**. The

Scheme 1



isolation of the product ester required a cumbersome lyophilization due to its high solubility in water. In a modified and optimized procedure, triphosgene can be successfully used as a phosgene equivalent. The yield of this reaction is 95%, and a nonaqueous work up allows for easy isolation of the product oxazolidinone.[19] The next step in the sequence was the reduction of the methyl ester using sodium borohydride which furnished a highly water-soluble alcohol **3** in excellent yields.[20] The alcohol is heat-sensitive and racemizes at high temperatures. The alcohol **3** was then converted to the corresponding iodo compound **5** in a two-step sequence. Tosylation of the primary alcohol using TsCl/pyridine, followed by refluxing with sodium iodide in acetone for 5 h, gave the iodide **5** (68% for two steps). Several alternative one-step processes were evaluated for the conversion of **3** to **5**. These were either inferior to the two-step procedure in overall yields or required chromatographic purification. The phosphonium salt **6** was prepared by stirring the iodo compound with excess triphenylphosphine in DMF at 100 °C for 24 h. The phosphonium salt is stable and can be stored in a desiccator indefinitely. Typically it was dried in an abderhalden apparatus prior to use. The overall yield for the synthesis of the phosphonium salt from serine methyl ester over five steps is 52% and requires no chromatographic purification.

Having established an optimal procedure for the preparation of the phosphonium salt, we were concerned about maintaining the optical integrity of the chiral center during deprotonation and formation of the ylide from **6**. Encouraged by the studies of Meyers and others,[21] we surmised that dideprotonation of **6** should prevent formation of any β-eliminated product and also that the oxazolidinone should reduce the acidity of the methine at the chiral center, rendering it less prone to deprotonation (vide infra). Seebach has also examined the structural features necessary to prevent β-elimination during carbanion formation.[22] Both alkyllithium and metal amide bases were evaluated for the generation of the ylide from **6**. These results are tabulated in Table 1. Treatment of compound **6** with 1.9 equiv of base (*n*-BuLi or LiHMDS) in THF or DME as solvents at −78 °C resulted in an orange to red colored solution which was stirred at that temperature for 1 h and then quenched with benzaldehyde

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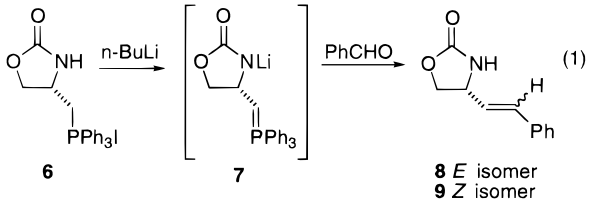
Table 1. Wittig Reactions with Compound **6** and Benzaldehyde

entry	conditions	yield %[a]	*E*:*Z* (**8**/**9**)[b]
1	*n*-BuLi, THF, −78 °C to rt	86	>99:1
2	*n*-BuLi, THF, −78 °C 2.5 h	86	3.6:1
3	*n*-BuLi, DME, −78 °C to rt	87	>99:1
4	*n*-LiHMDS, THF, −78 °C to rt	88	>99:1
5	*n*-LiHMDS, THF, −78 °C 2.5 h	62	3.2:1
6	*n*-BuLi, THF, 20% HMPA, −78 °C to rt	68	1.9:1
7	NaHMDS, THF, −78 °C 2.5 h	57	2.5:1
8	NaHMDS, THF, −78 °C to rt	62	3.2:1

[a] Isolated yield after column chromatography. [b]Ratios determined by ^{1}H NMR.

to produce alkene **8**. The product identity and olefin stereochemistry were established by ^{1}H NMR. The optical purity of the olefin product was established by converting the product to known *N*-BOC-homophenylalanine. No racemization was observed during the olefination process.[23] Addition of HMPA increased the *Z* selectivity of the reaction, providing nearly equal amounts of *E*:*Z* mixture (entry 6). The effect of the base counterion on stereoselectivity was also examined. Use of NaHMDS gave lower chemical yields as well as stereoselectivity (entry 7).[24] A change in temperature did not lead to further improvements (entry 8). For further experiments, *n*-BuLi was used as the base for deprotonation and formation of the ylide.

The next set of reaction conditions was developed to distinguish what factors largely influenced the *E*/*Z* ratios for the Wittig reaction of **6** with aldehydes. Preliminary reactions showed that, besides the identity of the aldehyde, the temperature of the reaction at the time of quenching was the most influential on *E*/*Z* ratios. For the investigation, two standard reaction conditions were selected. In the first method (method A), ylide **7** was generated from **6** using *n*-BuLi (1.95 equiv, −78 °C) as the base and the yellow−orange solution was stirred for 1 h. The aldehyde was added at −78 °C as a solution in THF, the reaction stirred at −78 °C for 2.5 h then quenched with a saturated ammonium chloride solution at −78 °C. The second reaction (method B) was identical to the first, except that the ammonium chloride quench was carried out after warming the reaction to room temperature. The two reactions were conducted side-by-side, and after identical workups, the crude reactions were analyzed to determine the *E*/*Z* olefin ratio of the products **8** and **9**.



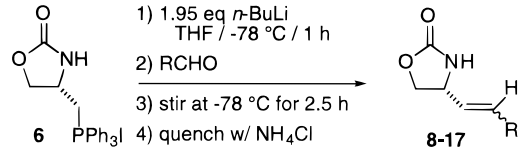
The reactions of **7** with five different aromatic aldehydes using the standard reaction conditions are shown in Table 2. The aldehydes were selected to encompass a range of functionalities on and in the aromatic ring. This included the heteroatomic aromatic aldehydes of thiophene and furan. A general trend is clearly evident from the data. Reactions that were quenched at room temperature gave almost exclusively *E* products (Table 2, entries 1, 3, 5, 7, and 9). In all cases, except the reaction with furyl-2-carboxaldehyde (Table 2, entry 7), no *Z* product was detectable. The *E*/*Z* ratios were established by integration of the olefinic protons in the ^{1}H NMR. In the reactions of **7** with aromatic aldehydes quenched at −78 °C, although the trans product still predominated, the low-temperature quench increased the appearance of the cis isomer (Table 2, entries 2, 4, 6, 8, and 10). It is interesting to note that the identity of the aromatic aldehyde had little effect on the *E*/*Z* outcome of the reactions when comparing the *E*/*Z* ratios of either reactions quenched at room temperature or those quenched at −78 °C.

The reactions of **7** with aliphatic aldehydes are presented in Table 3. The aliphatic aldehydes were chosen to explore steric effects on the reaction: linear vs branched and short- vs long-chain. Examination of the data in Table 3 showed a distinct trend. Reactions of **7** with aliphatic aldehydes gave predominately *Z* products, regardless of the temperature at which the reaction was quenched (except in Table 3, entry 3). This observation is in direct contrast to the reactions of **7** with aromatic aldehydes where the predominant unsaturated product

(23) Several products from the Wittig olefination process have been converted to known compounds. See, for example, refs 10a,b and 17.

(24) The reasons for the variation in stereoselectivity with changes in the base are not apparent.

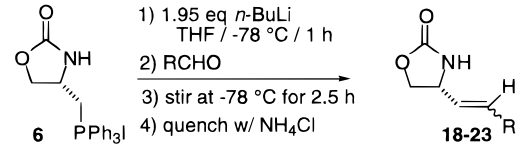
Table 2. *E*:*Z* Ratios of Wittig Reaction Using Aromatic Aldehydes



entry	RCHO	temp. of quench (°C)	yield[a] (%)	product (config.)	*E*:*Z* ratio[b]
1	PhCHO	25	86	**8** (*E*) **9** (*Z*)	100:0
2		−78	86		78:22
3	4-OMe-PhCHO	25	88	**10** (E) **11** (*Z*)	100:0
4		−78	88		79:21
5	4-piperonal	25	81	**12** (E) **13** (*Z*)	100:0
6		−78	73		81:19
7	2-furyl	25	88	**14** (E) **15** (*Z*)	92:8
8		−78	77		81:19
9	2-thienyl	25	88	**16** (E) **17** (*Z*)	100:0
10		−78	86		81:19

[a] Isolated yield after column chromatography. [b] Ratios determined by ^{1}H NMR.

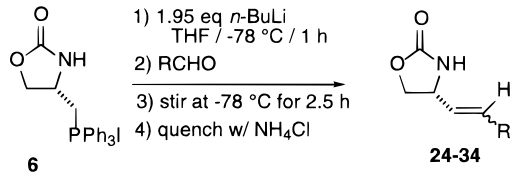
Table 3. *E*:*Z* Ratios of Wittig Reaction Using Aliphatic Aldehydes

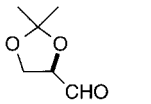
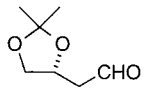


entry	RCHO	temp. of quench (°C)	yield[a] (%)	product (config.)	*E*:*Z* ratio[b]
1	$CH_3(CH_2)_4CHO$	25	89	**18** (*E*) **19** (*Z*)	31:69
2		−78	74		23:77
3	$(H_3C)_2CHCHO$	25	82	**20** (*E*) **21** (*Z*)	50:50
4		−78	59		24:76
5	$CH_3(CH_2)_{13}CHO$	25	86	**22** (*E*) **23** (*Z*)	30:70
6		−78	87		31:69

[a] Isolated yield after column chromatography. [b] Ratios determined by ^{1}H NMR.

Table 4. *E*:*Z* Ratios of Wittig Reaction Using Aldehydes Containing α- and *β*-Heteroatoms



Entry	RCHO	Temp. of Quench	Yield[a] (%)	Product (Config.)	*E*:*Z* Ratio[b]
1	$BnOCH_2CHO$	25 °C	81	**24** (*E*) **25** (*Z*)	33:67
2		-78 °C	76		39:61
3	$BnSCH_2CHO$	25 °C	74	**26** (*E*) **27** (*Z*)	59:41
4		-78 °C	57		61:39
5	$BnO(CH_2)_2CHO$	25 °C	61[c]	**28** (*E*)[d] **29** (*Z*)[e]	19:81
6		-78 °C	77[c]		18:82
7		25 °C	75	**32** (*Z*)	0:100
8		-78 °C	75		0:100
9		25 °C	72[c]	**33** (*E*)[f] **34** (*Z*)[g]	40:60
10		-78 °C	69[c]		40:60

[a] Isolated yield after column chromatography. [b] Ratios determined by ^1H NMR. [c] Isolated yield after Wittig reaction and BOC protection. [d] *E* isomer **28** gave **30** after BOC protection. [e] *Z* isomer **29** gave **31** after BOC protection. [f] *E* isomer **33** gave **35** after BOC protection.[g] *Z* isomer **34** gave **36** after BOC protection.

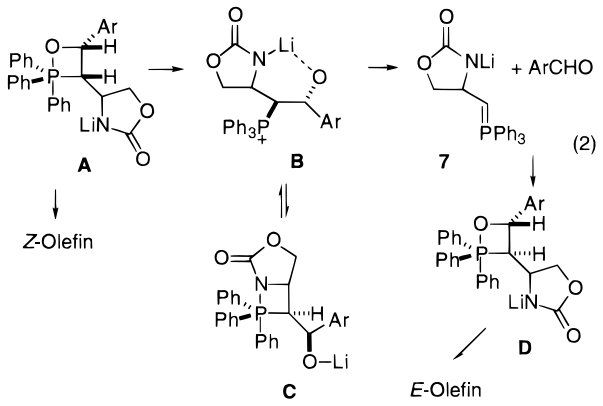
was in the *E* configuration. Reactions that were quenched at −78 °C showed an increase in the amount of the *Z* isomer (Table 3, entries 2 and 4). The identity of the aliphatic aldehyde did affect the *E*/*Z* product distribution to some extent. Reactions of **7** with the more sterically demanding valeraldehyde gave a higher proportion of the *E* product when quenched at room temperature (Table 3, entry 3) as compared to the two linear aldehydes quenched in the same manner (Table 3, entries 1 and 5). Reactions quenched at −78 °C gave predominately *Z* products in similar *E*/*Z* ratios regardless of the aliphatic aldehyde used. *E*/*Z* ratios did not vary outside experimental error for short- vs long-chain linear aliphatic aldehydes (Table 3, entries 1 vs 5 and 2 vs 6).

The third type of aldehyde that was examined in this study was aliphatic aldehydes which contained heteroatoms α and *β* to the carbonyl group. Reactions of **7** with these aldehydes are presented in Table 4. One of the most striking features of these data is that there is no difference between reactions that were quenched at room temperature vs reactions that were quenched at −78 °C. This is in contrast to that observed for reactions with either aromatic or aliphatic aldehydes. Another intriguing feature of these data was the difference in *E*/*Z* values when an oxygen α to the carbonyl was compared to an oxygen that was *β* to the carbonyl (Table 4, entry 1 vs entry 5). The amount of *E* product observed when the oxygen was α was nearly twice that when the same heteroatom was *β*.[25]

When oxygen and sulfur in the α position were compared, a significant change in the *E*/*Z* ratio was observed. With oxygen in the α position, the *E*/*Z* ratio for the reaction with **6** was similar to the *E*/*Z* ratio seen with linear aliphatic aldehydes (Table 4, entry 1 vs Table 3, entry 1 or 5): moderate *Z* selectivity. However, when sulfur was substituted for the oxygen in the α position, the selectivity was reversed: the *E* product predominates.

The highest cis selectivity that was observed with any type of aldehyde was the reaction of D-glyceraldehyde acetonide with the ylide **7** (Table 4, entries 7 and 8). The reaction gave only the *Z* product; no *E* product was observed in the ^1H NMR or isolated by chromatography. Moving the chiral center from the α position to the *β* position had a dramatic effect on the *E*/*Z* ratio. With the chiral center closer to the reaction site, a single product was produced (Table 4, entry 7); when the chiral center was one carbon removed from the reaction site, a 40:60 *Z*/*E* distribution was obtained (Table 4, entry 9).

The ylide **7** investigated in this work exhibits characteristics indicative of both a stabilized and nonstabilized ylide and is best classified as semistabilized.[26] For this system, prediction of *E*:*Z* outcome worked best by examination of the aldehyde rather than the ylide. In systems where the aldehyde was stabilized by resonance interaction with the aromatic ring, predominately *E* configured olefins were produced (Table 2). The comparison of reactions quenched at −78 °C with those quenched at room temperature indicates that equilibration plays a key role in determining product geometry. The low temperature quenches give a kinetic product ratio, whereas room temperature quench results in a thermodynamic outcome. In fact, each of the aromatic aldehydes gave nearly identical *E*:*Z* ratios when the different aldehydes were quenched at −78 °C. The *E* selectivity observed with ylide **7** and aromatic aldehydes at higher temperatures is in most part due to equilibration. Additional enhancements in selectivity may result from nucleophilic participation of the α-amino substituent and subsequent equilibration of the oxaphosphetane intermediates (eq 2), and



(25) The exact reasons for this variation in selectivity with structural modifications of the aldehydes are not apparent at this time. In an analogous series, *N*-protected α-amino aldehydes react with **7** to provide *Z*-olefins only. Sibi, M. P.; Christensen, J. W. *J. Org. Chem.* **1999**, in press.

(26) (a) For comprehensive reviews see: (a) Vedejs, E.; Peterson. M. J. In *Advances in Carbanion Chemistry*; Snieckus, V., Ed.; Jai Press: Greenwich, CT, 1996; Vol. 2, Chapter 1. (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (c) Johnson, A. W. *Ylides and Imines of Phosphorus*; Wiley: New York, 1993. (d) Enholm, E. J.; Satici, H.; Prasad, G. *J. Org. Chem.* **1990**, *55*, 324.

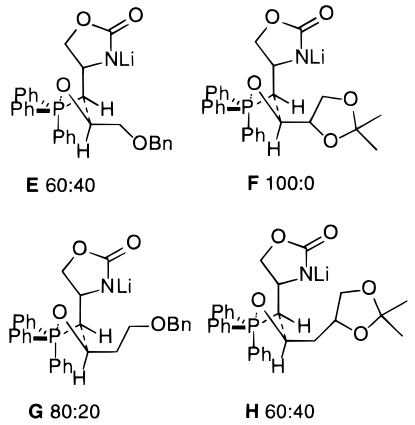


Figure 1.

partly due to salt effects.[27] The observed *E*-selectivity with **7** and aromatic aldehydes agrees well with the results of Meyers,[21] Maryanoff,[28] and Mioskowski[29] for oxido ylides.

In sharp contrast to the aromatic aldehydes, aliphatic aldehydes and aldehydes with α- or *β*-heteroatom showed no evidence of equilibration, as the *E*:*Z* ratios of room-temperature quenches vs quenches at −78 °C were essentially identical. When reactions using aromatic aldehydes were conducted, no precipitation, or very little, of the insoluble triphenylphosphine oxide was observed. However, in reactions of aliphatic or heteroatom containing aldehydes, upon addition of the aldehyde to the ylide, instantaneous formation of triphenylphosphine oxide was observed. The best selectivities were with aldehydes containing a ring system α to the carbonyl (Table 4, entries 7 and 8).[30] A working hypothesis for the observed selectivity with heteroatom containing aldehydes is as follows (Figure 1). The invariance of diastereomeric ratio with temperature indicates that reactions of **7** with aliphatic and heteroatom containing aliphatic aldehydes proceed under kinetic conditions. In these cases, the initial approach of the aldehyde solely dictated the product geometries. Assuming that the stereochemistry is established in the transition state leading to the oxaphosphetanes, the *E:Z* ratio differences within the series of alkoxy aldehydes may be accounted for by considering the transition states shown in Figure 1. The two set of compounds, that is, α- and *β*-alkoxy aldehydes, differ in reactivity, with the former being slightly more reactive than the latter. The highest *Z*-selectivity observed was with glyceraldehyde acetonide (Model **F**, Figure 1). When the structures **E** and **F** are compared, the α-alkoxy group is oriented anti to the carbonyl oxygen to minimize dipole−dipole interactions. In structure **F**, the ether oxygen may provide additional stability by interaction with the lithium cation and thus account for the observed high *Z* selectivity.[31] When **F** and **G** are compared, reactions with the less reactive *β*-alkoxy aldehydes could proceed through a later transition state and account for lower *Z*:*E* selectivity.

(27) For an excellent discussion on stereochemistry and mechanism of Wittig reactions using oxido ylides see: Vedejs, E.; Peterson. M. J. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1994, Vol. 21, Chapter 1.

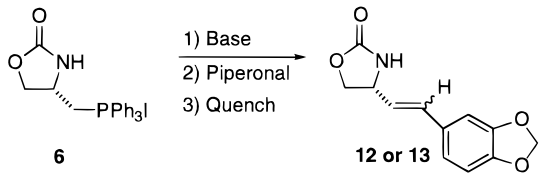
(28) Maryanoff, B. E.; Reitz, A. B.; Duhl-Emswiler, B. A. *J. Am. Chem. Soc.* **1985**, *107*, 217.

(29) Boubia, B.; Mann, A.; Bellamy, F. D.; Mioskowski, C. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1454.

(30) For *Z*-selective olefinations with α-alkoxyaldehydes see: Takanashi, T.; Miyazawa, M.; Ueno, H.; Tsuji, J. *Tetrahedron Lett.* **1986**, *27*, 3881.

(31) The observed high (*Z*)-selectivity for the glyceraldhyde acetonide is mostly due to the reactivity of the aldehyde and the irreversibility of the reaction. Formation of the alternate (*E*)-isomer places the rigid dioxolane ring close to bulky phosphine.

Table 5. Yield *E*/*Z* Ratios of 12:13 as a Function of Base Equivalents



entry	base	equi of base	temp. of quench (°C)	yield (%)	*E*:*Z*[b] (**12**/**13**)
1	*n*-BuLi	1.95	25	62[a]	100:0
2	*n*-BuLi	1.0	25	29	100:0
3	*n*-BuLi	3.0	25	40	100:0
4	*n*-BuLi	3.0	−78	50	91:9
5	LDA	1.95	25	85	100:0
6	LDA	3.0	25	49	100:0

[a] Isolated yield after column chromatography. [b] Ratios determined by ^{1}H NMR.

In the preliminary report for the reactions with the nucleophilic synthon, the double deprotonation of the phosphonium salt was proposed to have prevented the substrate from racemization during ylide formation. To test this theory, we subjected the synthon to several reaction conditions that involved manipulating the number of equivalents of the base. The standard reaction used 1.95 equiv of *n*-BuLi as the base and piperonal as the aldehyde. Yields and *E*/*Z* ratios for this reaction were taken as the reference point.

Two reactions were run side by side; in the first reaction, 1.95 equiv of *n*-BuLi was used, and in the second, only one equivalent was used. Both reactions were quenched at room temperature after a standard reaction sequence was performed (Table 5). The reaction run under standard conditions gave the *E* product exclusively in 62% yield (entry 1). The reaction with one equivalent of base also gave the *E* product exclusively, but in only 29% yield. No racemization was observed in either case. These results show that dideprotonation is necessary for higher yield of the olefin product. This observation is consistent with a competitive deprotonation of the N−H versus the formation of the ylide. The pK_a values for the N−H and the $Ph_3P^+CH_2R$ are similar (∼20.6 for N−H[32] and ∼21−22 for $Ph_3P^+CH_2R$)[33] and will compete for the single equivalent of base. When the nitrogen is deprotonated, it precludes the formation of the ylide and the yield is lowered. A second sequence was carried out with 3 equiv of *n*-BuLi (Table 5, entries 3 and 4). The reactions gave the olefins in reasonable yields and in characteristic *E*/*Z* ratios for the respective quenches. In this case, the yields were lowered because the ylide was in direct competition with the extra equivalent of *n*-BuLi for the aldehyde. The butylated product was formed in 60% (Table 5, entry 3) and 53% (Table 5, entry 4) yield and accounted for the mass balance of the aldehyde. Even in the presence of an extra equivalent of base, the olefins showed no signs of racemization. A third reaction sequence was performed with 3 equiv of nonnucleophilic LDA as the base. The standard reaction with 1.95 equiv was compared to one using 3 equiv (Table 5, entries 5 and 6). The standard reaction (1.95 equiv) gave significantly higher yields than the one with 3.0 equiv. The major byproducts observed in this reaction were piperonyl alcohol (28%) and triphenylphosphine (26%). The piperonyl alcohol presumably arose from the base-catalyzed Cannizarro reaction of the aldehyde, whereas the

(32) (a) Zhang, X.-M.; Bordwell, F. G. *J. Org. Chem.* **1994**, *59*, 6456. (b) Zhang, X.-M.; Bordwell, F. G. *J. Am. Chem. Soc.* **1994,** *116*, 968.

(33) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.

Scheme 2

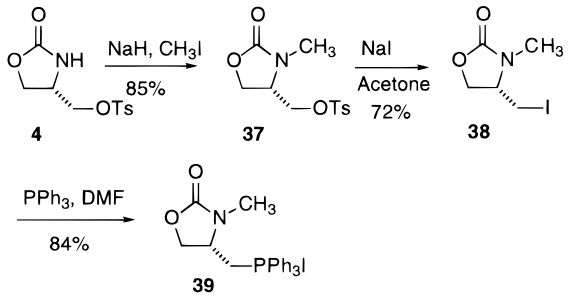
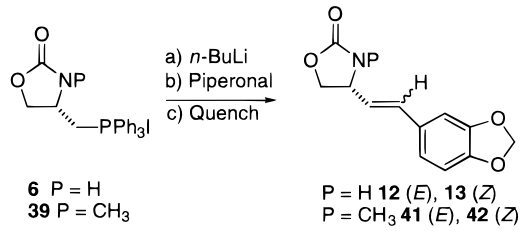


Table 6. Comparison of Ylide 7 and Ylide 40 in Side-by-Side Reactions



entry	P	eq *n*-BuLi	temp of quench (°C)	yield of olefin (%)	*E*:*Z*[a]	ee (%)
1	H	1.95	25	78	100:0	>99
2	CH_3	1.0	25	27	41:59	65[b]
3	H	1.95	−78	67	81:19	>99[c]
4	CH_3	1.0	−78	14	47:53	
5	CH_3	1.0[d]	25	34	48:52	
6	CH_3	2.0	25	14	49:51	

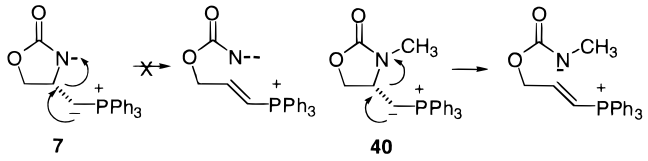
[a] Ratios determined by ^{1}H NMR. [b] Determined by comparison of optical rotation to authentic sample of (*E*) olefin **41** prepared by alkylation of **12**. [c] ee for the major isomer. [d] LDA was used as the base.

triphenylphosphine was a byproduct from decomposition of the ylide. In neither case was any racemization observed. From this study, the highest yields were obtained when 1.95 equiv of the respective base was used. Too little base resulted in significant reduction in yields, whereas excess base increased the number of side reactions.

One of the goals of the present study was to determine what role the anionic nitrogen in ylide **7** played in determining the stereochemical outcome of the olefinic products. To better understand this role, we prepared a phosphonium salt in which the oxazolidinone nitrogen was methylated (Scheme 2). The synthesis of the *N*-methylated phosphonium salt **39** was straightforward. Tosylate **4** was alkylated with methyl iodide in 85% yield, giving *N*-methyl tosylate **37** which was converted to the *N*-methyl iodide **38** by displacement with sodium iodide in refluxing acetone.

The replacement of the acidic hydrogen with a methyl group (**6** vs **39**) significantly altered the reactivity of the phosphonium salt. The methylated Wittig salt **39** was subjected to reaction conditions that normally gave high yields of exclusively *E* olefinic products when using the nonmethylated Wittig salt **6** (aromatic aldehyde and method B). Wittig salts **6** and **39** were converted to their corresponding ylides **7** and **40**, using 1.95 equiv of *n*-BuLi for **6** and 1.0 equiv of *n*-BuLi for **39**. The results are summarized in Table 6. There were two major differences between the two reactions. First, the reaction using **39** provided extremely low yields of the olefinic products; only a 27% yield was observed (Table 6, entry 2). The nonmethylated Wittig salt **6** gave a similar olefin in nearly triple the yield (Table 6, entry 1). Second, the *E*:*Z* ratios were drastically different. The

Scheme 3



dianionic ylide **7** reacted with piperonal to give the *E* product exclusively; however, the methylated ylide **40** gave a mixture of *Z* and *E* products and the *Z* isomer predominated. The substitution of the methyl group for the hydrogen in **39** has nearly reversed the *E*:*Z* trend that was seen for **6**. The results from reactions, which were quenched at −78 °C, are shown in entries 3 and 4 of Table 6. The temperature at which reactions with **39** were quenched made little difference to *E*:*Z* ratios, but chemical yields were lower when the reaction was stopped at lower temperature (Table 6, entries 2 and 4). The low chemical yields observed for reactions with **39** can be explained by considering the electrophilicity of the carbamate carbonyl. When two equivalents of base is added to **6**, the acidic hydrogen is abstracted, leaving a negative charge on the nitrogen which, by resonance, is spread over the amide carbon and oxygen. This drastically reduces the electrophilicity of the carbamate carbonyl, protecting it from nucleophilic attack. Wittig salt **39** and ylide **40**, without the anionic nitrogen, contain reactive carbonyls that are susceptible to nucleophilic attack by *n*-BuLi. Thus a competition between deprotonation to form the ylide and nucleophilic attack may lower the yields of the olefin products (vide infra).[34] Increased chemical yields of olefins from **39** by using a nonnucleophilic base (LDA, Table 6, entry 5) or more equivalents of *n*-BuLi (Table 6, entry 6) were not realized.

The loss of the anionic nitrogen in **7** also opens up another possibility for the decomposition of the ylide. When the ylide was first investigated,[11] it was theorized that the double deprotonation of the phosphonium salt **6** was necessary to reduce the possibility of β-elimination. The negative charge on the nitrogen in **7** significantly decreases the likelihood of the β-elimination pathway (Scheme 3). In order for the elimination to occur, a double negative charge would reside on the nitrogen.

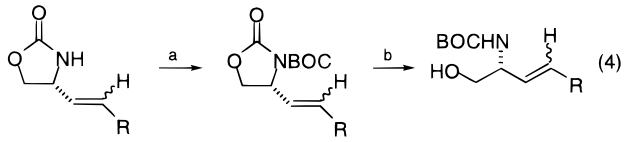
However, with the loss of the anionic nitrogen, as in **39**, the possibility of the β-elimination pathway is increased. In this case, the β-elimination would leave a single negative charge on a highly stabilized amide. This stabilization of the β-elimination pathway would lead to a much more unstable ylide and would reduce the yields significantly. Evidence for this β-elimination pathway was observed by the partial racemization of the olefin in Table 6, entry 2. The elimination mechanism destroyed the stereocenter in **39**, and when **39** was regenerated by reclosure of the ring, a racemized Wittig reagent was formed. Aldehyde condensation with the racemized Wittig reagent produced racemic olefins.

Conversion of Oxazolidinones to β,γ-unsaturated Amino Alcohols. Amino acids and amino alcohols containing unsaturation of defined geometry at the β-position have attracted considerable attention. The conversion of oxazolidin-2-ones into the corresponding amino alcohols has been investigated. The best method available for this transformation, developed by Kunieda,[35] involved a two-step process. The first step was the protection of the oxazolidinone nitrogen as the *tert*-butyloxy-

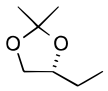
(34) We believe that the major decomposition pathway is through ring opening of the ylide and nucleophilic attack at the carbamate carbonyl is minor. For an example of ring opening of an oxazolidinone by BuLi see: Mirzaei, Y. R.; Balasubramaniam, T. N.; Lefler, B. J.; Natale, N. R. *J. Heterocycl. Chem.* **1990**, *27*, 2000.

(35) Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1987**, *28*, 4185.

Table 7. *E*:*Z* Ratios of Wittig Reaction Using Aldehydes Containing α and *β*-Heteroatoms



Key: a) BOC_2O, NEt_3, DMAP, CH_2Cl_2; b) Cs_2CO_3, MeOH

Entry	R	Oxazolidinone (config.)	Yield (%) Step a	Step b
1	-Ph	(**8**) (*E*)	(**43**) 92	(**45**) 93
2	$-C_{14}H_{29}$	(**16**) (*E*)	(**44**) 88	(**46**) 86
3	$-(CH_2)_2OBn$	(**31**) (*Z*)	(**28**) 77[a]	(**47**) 92
4		(**34**) (*Z*)	(**36**) 72[a]	(**48**) 92

[a] Isolated yield after column chromatography. [b] Ratios determined by ^1H NMR.

carbonyl carbamate using BOC anhydride. The second step was the catalytic hydrolysis of the cyclic carbamate by cesium carbonate (eq 4). This methodology was applied to a sample of olefins available from the Wittig reaction, with the results shown in Table 7. The methodology allowed for smooth conversion of oxazolidinone with either *E* or *Z* configurations, with applicability to simple (Table 7, entry 1) or complex (Table 7, entry 4) side chains in excellent yields. No isomerization of the olefin was noticed with either reaction. To verify that there was no racemization during the Wittig reaction and subsequent transformations, we converted the primary alcohols to their corresponding Mosher esters and established their optical purity to be >97% by ^1H and ^{19}F NMR.[36] The allylic amino alcohols serve as precursors for the synthesis of *β*,*γ*-unsaturated amino acids, compounds with interesting biological profiles. Several methods have been reported for the above transformation.[37]

Conclusions

In summary, we have shown that a new nucleophilic alaninol synthon is easily prepared from serine and that it undergoes condensations with aldehydes smoothly and with high stereoselectivity. The resulting olefins can be easily converted to allylic amino alcohols without any racemization of the chiral center. Additionally, the requirement for a dianionic species to prevent *β*-elimination was also established. An application of the synthon in the enantiospecific synthesis of indolizidine alkaloid slaframine and its analogues is described in a recent paper.[25]

Experimental

All reagents were used as received from the supplier. Compounds **2**−**4** have been previously described (see Supporting Information).[10c] Tetrahydrofuran, ether, and 1,2-dimethoxyethane were distilled from sodium benzophenone/ketyl prior to use. Chloroform, hexane, and CH_2Cl_2 were distilled from calcium hydride. Standard benchtop techniques were employed for handling air-sensitive reagents, and all reactions were carried out under nitrogen. Flash column chromatography was performed using Merck 60 silica gel, 230−400 mesh. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 270 (400) and 65 MHz, respectively. Gas chromatography was performed on a DB-5 capillary column with FID detector. Chiral HPLC analyses were performed using a Chiralcel OD column (Chiral Technologies, Inc.). The minor (cis) isomers from the Wittig condensation of aromatic aldehydes with ylide **7** were obtained by column chromatography of reactions quenched at low temperature (−78 °C).

(*S*)-(−)-4-Iodomethyl-2-oxazolidinone (5). A mixture of 6.50 g (24.0 mmol) of tosylate **4** and 18.2 g (112 mmol) of sodium iodide in 100 mL of freshly distilled dry acetone was refluxed under dry nitrogen until the reaction was judged to be complete by reverse-phase TLC [R_f(tosylate) = 0.71, R_f(iodide)= 0.64 in 50:50 EtOAc/hexanes] and/or ^1H NMR (5 h). The reaction was cooled to room temperature, the excess sodium iodide was filtered off, and the solids were washed with ethyl acetate. The combined filtrate was concentrated on a rotary evaporator. The crude yellow solid was dissolved in EtOAc and washed with a saturated sodium sulfite solution until the layers became colorless. The aqueous layer was extracted with EtOAc (5 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give 5.72 g of a tan solid. Column chromatography using 75:25 EtOAc/hexanes yielded 5.14 g of white solid (95%). The solids may be recrystallized from an EtOAc/hexanes solution: mp 68−71 °C; R_f 0.53 (100% EtOAc); ^1H NMR (400 MHz, $CDCl_3$) *δ* 3.24 (m, 2H), 4.12 (m, 2H), 4.53 (app. t, *J* = 7, 8 Hz, 1H), 6.43 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 8.4, 53.0, 70.4, 159.5; IR ($CHCl_3$) 3448, 3255, 1767 cm^{-1}; MS (GC-MS) *m*/*e* 227 (M^+, 4), 100 (80), 86 (100); $[\alpha]_D^{25}$ −30.2 (*c* 1.6, CH_2Cl_2). Anal. calcd for $C_4H_6INO_2$: C, 21.16; H, 2.66; N, 6.17. Found: C, 21.25; H, 2.63; N, 5.95.

(*S*)-(+)-4-(2-Oxazolidonyl)-methyltriphenylphosphonyl Iodide (6). A solution of the iodide **5** (15.00 g, 66.08 mmol) and triphenylphosphine (175.04 g, 668.1 mmol) in 30 mL of dry DMF was stirred at 100 °C for 61 h. The DMF was removed under vacuum, and the resulting residue was triturated with dry THF to remove excess triphenylphosphine, followed by repeated washings with ether to afford a yellow solid. This solid was crystallized from MeOH/EtOAc and dried in an Abderhalden, giving 27.52 g (85%) of a white solid: mp 214−218 °C (decomp); ^1H NMR (400 MHz, D_2O) *δ* 3.79 (m, 1H), 3.96 (m, 1H), 4.04 (app. dd, *J* = 9, 5 Hz, 1H), 4.38 (app. dt, *J* = 9, 2 Hz, 1H), 4.54 (m, 1H), 7.85 (m, 15H); ^{13}C NMR (65 MHz, D_2O) *δ* 28.3 (d), 47.6, 69.2, 116.9 (d), 130.6 (d), 133.7 (d), 135.4, 157.8; IR ($CHCl_3$) 3228, 3174, 1771 cm^{-1}; $[\alpha]_D^{25}$ +34.9 (*c* 2.28, MeOH). Anal. calcd for $C_{22}H_{21}INO_2P$: C, 54.00; H, 4.32; N, 2.86. Found: C, 53.84; H, 4.41; N, 2.65.

Wittig Reaction: General Procedure. (*E*)-(*R*)-(+)-4-(2′-Phenyl-1′-ethylenyl)-2-oxazolidinone (8). Phosphonium salt **6** (0.489 g, 1.00 mmol) was placed in a flame-dried, 50 mL, three-necked, round-bottom flask, and the flask was evacuated and filled with an atmosphere of dry nitrogen (3×). Freshly distilled dry THF (10 mL) was added and the suspension cooled to −78 °C; *n*-BuLi (0.79 mL, 1.9 mmol) was added over a 10 min period to give an orange-colored solution. This solution was stirred at −78 °C for 1 h, and benzaldehyde (0.093 mL, 0.91 mmol) was added slowly over 5 min. The solution was stirred for an additional 2.5 h, the dry ice/2-propanol bath was removed, and the reaction was allowed to warm to room temperature. The reaction was quenched with a saturated NH_4Cl solution (∼10 mL) and stirred for 10 min. THF was removed by rotary evaporation and the aqueous layer extracted with EtOAc (3 × 15 mL), and the combined organic layers were dried with anhydrous $MgSO_4$. The drying agent was filtered off and the organic solvent removed under reduced pressure to leave a thick yellow oil. Column chromatography using 60:40 EtOAc/hexanes yielded 0.1480 g of a white solid (86%) as a single isomer (*E*): mp 140−145 °C; R_f 0.47 (50:50 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) *δ* 4.11−4.15 (m, 1H), 4.52−4.60 (m, 2H), 6.09−6.15 (m, 2H), 6.60 (d, *J* = 16 Hz, 1H), 7.26−7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 55.1, 70.1, 126.4, 126.6, 128.4, 128.7, 133.7, 135.4, 159.6;

(36) Esterification of the primary alcohol with Mosher acid see: Svatos, A.; Valterova, I.; Saman, D.; Vrkoc, J. *Collect. Czech. Chem. Commun.* **1990**, *55*, 485.

(37) For selected methods for the conversion of amino alcohols to amino acids: (a) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559. (b) Pasto, M.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron: Asymmetry* **1995**, *6*, 2329. (c) Burgess, K.; Liu, L. T.; Pal, B. *J. Org. Chem.* **1993**, *58*, 4758. (d) Beaulieu, P. L.; Duceppe, J.-S.; Johnson, C. *J. Org. Chem.* **1991**, *56*, 4196. (e) See refs 7 and 17b.

IR ($CHCl_3$) 3459, 1755, 1658, 1602 cm^{-1}; MS (DIP/EI) *m*/*e* 189 (M^+, 36), 144 (25), 130 (100); $[\alpha]_D^{25}$ +19.3 (*c* 1.945, CH_2Cl_2). Anal. calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.63; H, 5.84; N, 7.32.

General Procedure for Hydrolysis of *N*-(*tert*-Butoxycarbonyl)-2-oxazolidinones to *N*-(*tert*-Butoxycarbonyl)-amino Alcohols. A 1.0 mmol quantity of the *N*-BOC-2-oxazolidinone was dissolved in 10 mL of distilled methanol and stirred at room temperature. A catalytic amount of cesium carbonate (0.3 mmol) was added, and the reaction was stirred until TLC indicated that the reaction was complete (typically 3−6 h). The methanol was removed by rotary evaporation and the crude residue dissolved in 10 mL of CH_2Cl_2. The organic solution was placed in a separatory funnel and washed with 15 mL of a 10% citric acid solution. The aqueous layer was back extracted with CH_2Cl_2 (2 × 10 mL), the combined organics were dried over $MgSO_4$ and filtered, and the organic solvent was removed by rotary evaporation. This residue was column chromatographed to give the *N*-BOC-amino alcohol.

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Supporting Information Available: Characterization data for compounds **9**−**27** and **37**−**39** and data for compounds pertaining to reactions reported in Tables 5 and 6. This material is available free of charge via the Internet at http://pubs.acs.org.

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