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A New, General, and Stereoselective Method for the Synthesis of Trisubstituted Alkenes

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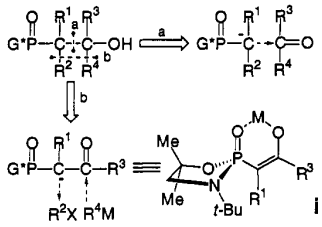
The importance of stereodefined carbon–carbon double bonds in organic chemistry cannot be overemphasized. In recognition of the importance of this central functional group, many ingenious and selective synthetic methods have been devised over the years.[1] Nonetheless, the need for a general and highly selective method for the constructive synthesis of *trisubstituted* alkenes remains.[2] A case in point is the venerable Wittig reaction (the method of choice for creating stereodefined disubstituted alkenes),[3] for which the problems in formation of tri- and especially tetrasubstituted alkenes are well documented.[3d,4,5] The failure of the Wittig construction can be understood by consideration of the stereocontrol features shown in Scheme I. The problems with the classic Wittig synthesis (disconnection a) arise from poor control of the relative configurations of the α- and β-centers due to either modest topological selectivity in or reversibility of the condensation. We sought to control the introduction of the α- and β-centers relative to a stereogenic phosphorus unit, i.e., disconnection b. By adapting the basic structural picture of Horner–Wadsworth–Emmons reagents,[3d,6] we devised the chiral reagent **i**. From the highly dissymmetric environment around phosphorus and the potential for chelation-controlled reactions, we anticipated a high level of relative asymmetric induction in the construction of α- and β-centers.[7] We report below the stereoselective construction of various β-hydroxy phosphonamidates and their stereospecific conversion to trisubstituted olefins.

At the outset it must be stressed that all chiral reagents need only be used in racemic form. The phosphorus heterocycles **2**[8] and **3**[8] can be prepared on a large scale from the readily available amino alcohol **1**[8] by either (1) Arbuzov reaction of the ethyl phosphite or (2) direct condensation with *n*-propylphosphonic dichloride, Scheme II.

Scheme I



Scheme II

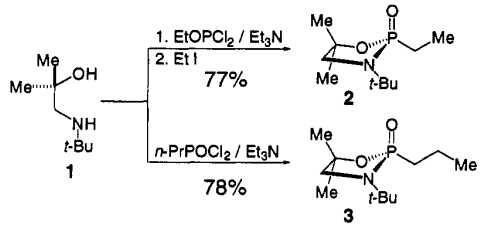
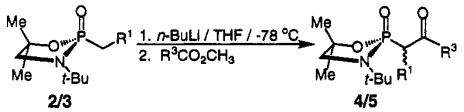


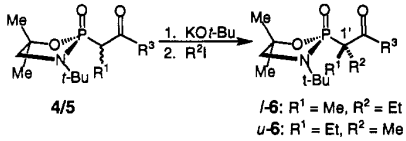
Table I. Preparation of β-Keto Phosphonamidates **4** and **5**



substrate	R^1	R^3	product	yield,[a] %
2	Me	n-$C_{11}H_{23}$	**4a**	63
2	Me	cyclohexyl	**4b**	55
2	Me	1-adamantyl	**4c**	60
2	Me	4-t-BuC_6H_4	**4d**	82
3	Et	n-$C_{11}H_{23}$	**5a**	74
3	Et	cyclohexyl	**5b**	54
3	Et	1-adamantyl	**5c**	64
3	Et	4-t-BuC_6H_4	**5d**	60

[a] Yield of analytically pure material.

Table II. Alkylation of β-Keto Phosphonamidates **4** and **5**



l-**6**: R^1 = Me, R^2 = Et
u-**6**: R^1 = Et, R^2 = Me

substrate	R^1	R^2	R^3	product[a]	ratio *l*/*u*-**6**[b]	yield,[c] %
4a	Me	Et	n-$C_{11}H_{23}$	*l*-**6a**	28/1	96
4b	Me	Et	cyclohexyl	*l*-**6b**	27/1	96
4c[d]	Me	Et	1-adamantyl	*l*-**6c**	64/1	97
4d[e]	Me	Et	4-t-BuC_6H_4	*l*-**6d**	24/1	83
5a	Et	Me	n-$C_{11}H_{23}$	*u*-**6a**	1/120	97
5b	Et	Me	cyclohexyl	*u*-**6b**	<1/145[f]	98
5c[d]	Et	Me	1-adamantyl	*u*-**6c**	1/97	89
5d[e]	Et	Me	4-t-BuC_6H_4	*u*-**6d**	1/24	77

[a] The *l*,*u* descriptors define the relative configuration between P and C(1′). [b] Determined by ^{31}P NMR. [c] Yield of analytically pure material. [d] NaOt-Bu was used. [e] KH was used. [f] Signal-to-noise minimum.

To survey reaction generality, we examined four classes of olefin substituents (R^3): *n*-, *sec*-, and *tert*-alkyl and aryl. Thus, construction of the key β-keto phosphonamidates **4**/**5**[8] involved acylation of the lithiated heterocycles with various methyl esters,[9,10] Table I.

(1) (a) For reviews, see: Kelly, S. E. In *Comprehensive Organic Synthesis, Additions to C–X π Bonds, Part 1*; Schreiber, S. L., Ed.; Pergamon Press: Oxford, 1991; Vol. 1, Chapter 3. (b) Reucroft, J.; Sammes, P. G. *Q. Rev. Chem. Soc.* **1971**, *25*, 135. (c) Faulkner, D. J. *Synthesis* **1971**, 175. (d) Julia, M. *Pure Appl. Chem.* **1985**, *57*, 763. (e) Arora, A. S.; Ugi, I. K. In *Methoden der Organischen Chemie (Houben-Weyl)*, 4th ed.; Müller, E., Ed.; Georg ThiemeVerlag: Stuttgart, 1972; Vol. 5/1b, p 728.

(2) See ref 1a, pp 797–800.

(3) (a) Gosney, I.; Rowley, A. G. In *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic Press: New York, 1979; Chapter 2. (b) Walker, B. J. In *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic Press: New York, 1979; Chapter 3. (c) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73. (d) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(4) For a discussion of this problem, see: (a) Bottin-Strzalko, T.; Etemad-Moghadam, G.; Seyden-Penne, J.; Pouet, M.-J.; Simonnin, M.-P. *Nouv. J. Chim.* **1983**, *7*, 155. (b) Etemad-Moghadam, G.; Seyden-Penne, J. *Tetrahedron* **1984**, *40*, 5153.

(5) For some solutions, see: (a) Schlosser, M.; Christmann, K.-F. *Synthesis* **1969**, 38. (b) Corey, E. J.; Yamamoto, H. *J. Am. Chem. Soc.* **1970**, *92*, 226. (c) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

(6) (a) Bottin-Strzalko, T.; Seyden-Penne, J.; Breuer, E.; Pouet, M.-J.; Simonnin, M.-P. *J. Chem. Soc., Perkin Trans. II* **1985**, 1801. (b) Seyden-Penne, J. *Bull. Soc. Chim. Fr.* **1988**, 238. (c) Teulade, M.-P.; Savignac, P.; About-Jaudet, E.; Collignon, N. *Phosphorus Sulfur* **1988**, *40*, 105.

(7) Warren has adapted the Wittig–Horner process for the synthesis of di- and trisubstituted alkenes by making use of the α-stereocenter to control the β-hydroxyl configuration by reduction. (a) Buss, A. D.; Warren, S. *Tetrahedron Lett.* **1983**, *24*, 111. (b) Ayrey, P. M.; Warren, S. *Tetrahedron Lett.* **1989**, *30*, 4581 and references cited therein. For a similar approach using β-keto phosphonamides, see: (c) Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1968**, *90*, 6816.

(8) All new compounds have been fully characterized by spectroscopic and analytical methods.

(9) (a) Reference 7c. (b) Aboujaoude, E. E.; Collignon, N.; Savignac, P. *J. Organomet. Chem.* **1984**, *264*, 9. (c) Torr, R. S.; Warren, S. *J. Chem. Soc. Pak.* **1979**, *1*, 15.

(10) Other acylating agents are likely to be superior. (a) Mathey, F.; Savignac, Ph. *Tetrahedron* **1978**, *34*, 649. (b) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 2374.

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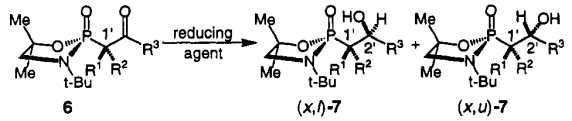
Table III. Reduction of β-Keto Phosphonamidates **6**

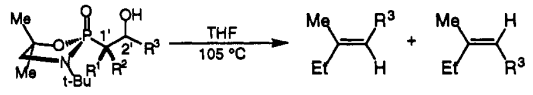


6 (*x,l*)-**7** (*x,u*)-**7**

substrate	R^1	R^2	R^3	reducing agent	product[a]	ratio (*x/l*)-7/(*x/u*)-7[b]	yield,[c] %
l-**6a**	Me	Et	*n*-$C_{11}H_{23}$	$CeCl_3/NaBH_4$	(*l,u*)-**7a**	1/150	93
u-**6a**	Et	Me	*n*-$C_{11}H_{23}$	$LiBHEt_3$	(*u,u*)-**7a**	1/24	99
l-**6b**	Me	Et	cyclohexyl	*i*-Bu_2AlH	(*l,l*)-**7b**	14/1	78
u-**6b**	Et	Me	cyclohexyl	*i*-Bu_2AlH	(*u,l*)-**7b**	65/1	97
l-**6c**	Me	Et	1-adamantyl	*i*-Bu_2AlH	(*l,l*)-**7c**	73/1	99
u-**6c**	Et	Me	1-adamantyl	*i*-Bu_2AlH	(*u,l*)-**7c**	>97/1	89
l-**6d**	Me	Et	4-*t*-BuC_6H_4	$CeCl_3/NaBH_4$	(*l,u*)-**7d**	1/44	83
u-**6d**	Et	Me	4-*t*-BuC_6H_4	$LiBH(s\text{-}Bu)_3$	(*u,u*)-**7d**	1/19	84

[a] The *l,u* descriptors define the relative configuration between P and (C(1'), C(2')). [b] Determined by ^{31}P NMR. [c] Yield of analytically pure material.

Table IV. Formation of Trisubstituted Olefins (*E*)- and (*Z*)-**8**



7 (*E*)-**8** (*Z*)-**8**

substrate[a]	R^1	R^2	R^3	time, h	product	ratio[b] (*E*)/(*Z*)-**8**	yield,[c] %
(*u,u*)-**7a**	Et	Me	*n*-$C_{11}H_{23}$	20	(*E*)-**8a**	102/1	92
(*l,u*)-**7a**	Me	Et	*n*-$C_{11}H_{23}$	22	(*Z*)-**8a**	1/160	86
(*l,l*)-**7b**[d]	Me	Et	cyclohexyl	12	(*E*)-**8b**	21/1	85
(*u,l*)-**7b**	Et	Me	cyclohexyl	18	(*Z*)-**8b**	1/184	96
(*l,l*)-**7c**	Me	Et	1-adamantyl	9	(*E*)-**8c**	104/1[e]	98
(*u,l*)-**7c**	Et	Me	1-adamantyl	10	(*Z*)-**8c**	<1/99[e]	94
(*u,u*)-**7d**	Et	Me	4-*t*-BuC_6H_4	6	(*E*)-**8d**	130/1	94
(*l,u*)-**7d**	Me	Et	4-*t*-BuC_6H_4	10	(*Z*)-**8d**	1/121	98

[a] >100/1 diastereomeric purity by ^{31}P NMR. [b] Determined by capillary GC (50-m HP U-2). [c] Yield of analytically pure material. [d] 21/1 by ^{31}P NMR. [e] Determined by ^1H NMR integration (400 MHz).

The quaternary stereocenter was created by alkylation of the various β-keto phosphonamidates as their potassium (KO*t*-Bu or KH) or sodium (NaO*t*-Bu for **4c**/**5c**) enolates, Table II. Both diasteromeric series of **6**[8] could be prepared in excellent yield with excellent diasteroselectivities by complementary alkylation of series **4** with EtI and series **5** with MeI. The diastereomers of **6** are easily distinguished by ^{31}P NMR and were assigned on the basis of steric approach control and the final configuration of the product olefin.

To access both olefin isomers requires selective installation of the β-stereocenter. This can be accomplished by either of two conceptually distinct protocols: (1) complementary reduction of a single β-keto phosphonamidate or (2) stereoselective reduction of an *l*/*u*-**6** pair in a unidirectional sense (i.e., with the same topicity with respect to phosphorus). At present, the latter protocol has proven more successful, and a complete set of diastereomeric β-hydroxy phosphonamidates **7**[8] has been generated, Table III.[11]

The critical olefination reaction required optimization of reaction conditions. An initial survey of nine bases (Li, Na, K, hydride, *t*-BuO^-, $(Me_3Si)_2N^-$) in THF at room temperature revealed that only NaH and LiH gave stereospecific olefination, albeit sluggishly. Attempts to increase reaction rate with different solvents (DME, Et_2O) and at elevated temperatures (50–105 °C) were not successful. However, control experiments revealed that the *neutral* β-hydroxy phosphonamidates **7** underwent clean thermal cycloelimination in THF at 105 °C.[12] For the purposes of evaluating stereospecificity, the precursors **7** were crystallized or chromatographed to diastereomeric purity where possible (^{31}P NMR, S/N minimum 100/1). The results in Table IV show that the thermal cycloelimination of **7** afforded the olefins **8**[8,13] with excellent yield and stereospecificity independent of configuration and substituent R^3.

The temperatures for the cycloelimination could be reduced by employing the lithium salts of **7**. We have found that freshly precipitated LiH[14] effects the olefination at reduced temperatures. Thus, deprotonation of (*u,u*)-**7a** with activated LiH at 20 °C followed by heating to 50 °C for 8 h afforded (*E*)-**8a** in 56% yield (*E*/*Z*, 97/1). In addition, *n*-BuLi was also effective at lower temperatures (40 °C, 1,2-dimethoxyethane), but the selectivities were highly dependent on the purity of the *n*-BuLi used. Further optimizations on the *n*-BuLi-mediated olefinations are in progress.

In summary, we have developed a general protocol for the highly stereoselective, constructive synthesis of trisubstituted alkenes suitable for various alkenes substitution patterns. Current efforts include the refinement of this methodology and extension to functionalized and tetrasubstituted alkenes.

Acknowledgment. We are grateful to the National Institutes of Health (GM 45532) for generous support of this research. J.S.A. thanks the University of Illinois for a Graduate Fellowship. Mr. L. J. Brice is acknowledged for the optimization and large-scale preparation of **1**.

Supplementary Material Available: Procedures for the preparation and full characterization of compounds **1**, **2**, **3**, **4b**, **5b**, *l*-**6b**, *u*-**6b**, (*l,l*)-**7b**, (*u,l*)-**7b**, (*E*)-**8b**, (*Z*)-**8b** (20 pages). Ordering information is given on any current masthead page.

(11) A case by case analysis of the unusual and unexpected reduction selectivities will be included in a full account of this work.

(12) Corey has demonstrated that stereodefined β-hydroxy phosphonamides undergo *thermal* decomposition to alkenes (refluxing toluene) with 98% stereospecificity.[7c]

(13) The configurations of the olefins **8** were established by combination of NOE experiments and comparison of ^{13}C steric compression shifts. Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*, 3rd ed.; VCH: Weinheim, 1990; pp 115–116, 192–194.

(14) Klusener, P. A. A.; Brandsma, L.; Verkruijsse, H. D.; Schleyer, P. v. R.; Friedl, T.; Pi, R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 465.