Catalytic Staudinger-Vilarrasa Reaction for the Direct Ligation of Carboxylic Acids and Azides

DOI:
10.1021/jo802825e

JOC Note

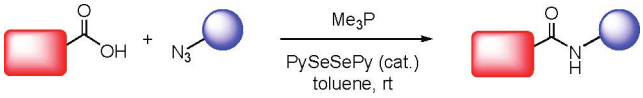
Catalytic Staudinger−Vilarrasa Reaction for the Direct Ligation of Carboxylic Acids and Azides

Jordi Burés, Manuel Martín, Fèlix Urpí, and Jaume Vilarrasa*

Departament de Química Orgànica, Facultat de Química, Universitat de Barcelona, 08028 Barcelona, Catalonia, Spain

jvilarrasa@ub.edu

Received January 1, 2009

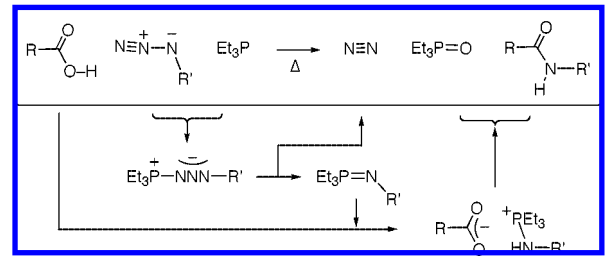


2,2′-Dipyridyl diselenide (PySeSePy) is the catalyst or activator of choice for the direct reaction of carboxylic acids with azides and trimethylphosphine at room temperature. The mechanism of the process, which is not an aza-Wittig reaction, has been elucidated.

In our search for the direct macrolactamization of ω-azido carboxylic acids, we discovered years ago[1] that carboxylic acids, organic azides, and tertiary phosphines reacted slowly in benzene or toluene to give carboxamides, N_2, and phosphine oxide. Triphenylphosphine was soon replaced by Bu_3P and by Et_3P (Scheme 1),[1b] which is even more reactive and practical because the water-soluble $Et_3P{=}O$ is easier to remove.[2] Since organic azides and phosphines give phosphatriazenes,[3] which at room temperature (rt) are converted to phosphazenes (Staudinger phosphazenes)[4] and N_2, the rate-limiting step of our reaction must be the last one, that is, the collapse of the aminophosphonium carboxylates ($RCOO^-$ Et_3P^+NHR') to $RCONHR'$ and $Et_3P{=}O$.[1]

We were aware later that Horner and Gross had carried out a related experiment: among series of reactions to prepare azides, phosphimines, isothiocyanates, and thioureas, they indicated that heating of $Ph_3P{=}NPh$ with benzoic acid in xylene gave PhCONHPh in 30% yield.[5] A few weeks before publication of our first paper,[1a] Moody et al.[6] reported an intramolecular reaction of a $(EtO)_3P$-generated phosphazene with an *o*-COOH group, in the context of aza-Wittig-type cyclization reactions, whereas a few weeks afterward Roberts et al.[7] reported similar results to our own with simple peptides. These authors are independent codiscoverers of the reaction. Later, Vilarrasa et al.[8] examined and optimized the reactions of Staudinger phosphazenes with carboxyl derivatives (cyclic anhydrides, mixed anhydrides, thioesters,[9] among others) and applied their findings to the synthesis of peptides[4k] and macrolactam-like natural products. The reactions with other carboxyl and carbonate derivatives (RCOCl,[10] simple esters intramolecularly,[6,11] $CH_3COOCHO$,[12] Boc_2O,[13] selenoesters,[14] and activated esters[15]) have several "fathers" apart from our own research group. While some researchers[16] name the general process RCO-LG + R_3P + N_3R the Staudinger−Vilarrasa reaction (henceforward, S−V reaction or S−V peptide ligation),[17] other authors refer to these reactions as particular cases of "aza-Wittig" processes.[4c−f]

SCHEME 1. Direct Formation of Amide/Peptide Bonds from Carboxylic Acids, Organic Azides, and Et_3P



We report the first catalytic version of the S−V reaction. It may be related to the classical Mukaiyama reaction of 2-pyridyl

(1) (a) Garcia, J.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1984**, *25*, 4841 (12 simple amides, pyrrolidin-2-one, Z-Ile-Val-NHR, Ac-Sar-Gly-OEt, and Z-Ile-Ile-Gly-OEt were prepared). (b) Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1986**, *27*, 4623 (advantges of Et_3P). (c) Garcia, J. Ph.D. Thesis, Universitat de Barcelona, 1986. (d) Urpí, F. Ph.D. Thesis, Universitat de Barcelona, 1987.

(2) $Me_3P{=}O$ is even more soluble in water, but Me_3P (pyrophoric, low-boiling liquid) was not commercially available at that time.

(3) Phosphatriazenes are also called phosphazides. λ^5-Phosphazenes, or iminophosphoranes, were also called phosphinimines or phosphine imines.

(4) This is one of the reactions discovered by Staudinger: (a) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635 (Ph_3P + N_3Ar to give $Ph_3P{=}NAr$, their hydrolyses, and reaction with CO_2 and CS_2). (b) Staudinger, H.; Hauser, E. *Helv. Chim. Acta* **1921**, *4*, 861 (Ph_3P, $PhEt_2P$, and Et_3P). For recent reviews about the Staudinger reaction and iminophosphorane chemistry, see: (c) Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; Santos, J. M. *Tetrahedron* **2007**, *63*, 523. (d) Eguchi, S. *Arkivoc* **2005**, 98. (e) Köhn, M.; Breinbauer, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 3106. (f) Fresneda, P. M.; Molina, P. *Synlett* **2004**, 1. For ab initio calculations of the phosphatriazene to phosphazene conversion, see: (g) Alajarín, M.; Conesa, C.; Rzepa, H. S. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1811. (h) Widauer, C.; Grutzmacher, H.; Shevchenko, I.; Gramlich, V. *Eur. J. Inorg. Chem.* **1999**, 1659. (i) Tian, W. Q.; Wang, Y. A. *J. Org. Chem.* **2004**, *69*, 4299, and references therein. For the participation of phosphatriazenes in some reactions, see: (j) Inazu, T.; Kobayashi, K. *Synlett* **1993**, *34*, 4671 (glycopeptides). (k) Bosch, I.; Urpí, F.; Vilarrasa, J. *Chem. Commun.* **1995**, 91 (peptides). (l) Velasco, M. D.; Molina, P.; Fresneda, P. M.; Sanz, M. A. *Tetrahedron* **2000**, *56*, 4079 (trapping of a *Z*-phosphazide).

(5) Horner, L.; Gross, A. *Liebigs Ann. Chem.* **1955**, *591*, 117. ("Tertiary phosphines. IV. Use of phosphine imines in causing the introduction of primary amino groups"). Such a reaction cannot be located via SciFinder; even currently, with >190 entries via $Ph_3P{=}NPh$, none is associated with this paper.

(6) Hickey, D. M. B.; MacKenzie, A. R.; Moody, C. J.; Rees, C. W. *Chem. Commun.* **1984**, 776.

(7) Zaloom, J.; Calandra, M.; Roberts, D. C. *J. Org. Chem.* **1985**, *50*, 2601.

(8) Relevant papers: (a) Garcia, J.; Vilarrasa, J.; Bordas, X.; Banaszek, A. *Tetrahedron Lett.* **1986**, *27*, 639 (phthalic anhydride). (b) Bosch, I.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1993**, *34*, 4671 (mixed anhydrides and thioesters, macrolactamization). (c) Reference 4k (peptides). (d) Bosch, I.; Gonzalez, A.; Urpí, F.; Vilarrasa, J. *J. Org. Chem.* **1996**, *61*, 5638 (acyl chlorides and mixed anhydrides, mechanistic studies). (e) Ariza, X.; Urpí, F.; Viladomat, C.; Vilarrasa, J. *Tetrahedron Lett.* **1998**, *39*, 9101 (Boc-ON). (f) Ariza, X.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1999**, *40*, 7515 (ClCOOR). (g) Ariza, X.; Pineda, O.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **2001**, *42*, 4995 (vicinal azido alcohols with Boc_2O or CO_2).

(9) The "traceless ligation" developed by Raines et al. involving $RCOSC_6H_4$-*o*-PR_2 and later $RCOSCH_2PAr_2$ is an exciting application to the peptide field and molecular biology. See: (a) Nilsson, B. L.; Kiessling, L. L.; Raines, R. T. *Org. Lett.* **2000**, *2*, 1939. (b) Soellner, M. B.; Nilsson, B. L.; Raines, R. T. *J. Org. Chem.* **2002**, *67*, 4993. (c) Soellner, M. B.; Nilsson, B. L.; Raines, R. T. *J. Am. Chem. Soc.* **2006**, *128*, 8820, and references therein. Also see: (d) David, O.; Meester, W. J. N.; Bieräugel, H.; Schoemaker, H. E.; Hiemstra, H.; van Maarseveen, J. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4373 (medium-sized lactams). (e) Kleineweischede, R.; Hackenberger, C. P. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 5984 (peptide cyclization).

10.1021/jo802825e CCC: $40.75 © 2009 American Chemical Society
Published on Web 02/09/2009

thiol esters (RCOSPy) with aliphatic amines,[18] which is a standard in the peptide field and has been used in macrolactonization reactions;[19] C-terminal thioesters are key in many approaches to the synthesis of proteins and glyco-conjugates,[20] so we shall not discuss this type of carboxyl activation. The advantages of operating with the N_3 group (as an amino protecting group) are clear[4k,8,9,11,16] and will not be discussed either.

Our purpose was to identify appropriate catalysts and solvents for reactions such as those depicted in Tables 1 and 2. Me_3P (1 equiv; commercially available in toluene or THF solutions) was added to convert the N_3 group to a $Me_3P{=}N$ group, while an additional 0.3−1.4 equiv of Me_3P and an additive were required to activate the carboxyl group. With hindered carboxylic acids we used 2.4 equiv of Me_3P overall.

The rate of the direct reaction of Boc-Phe-OH, Me_3P, and N_3CH_2COOEt (entry 1 of Table 1) increased significantly when 0.2 equiv of 2,2′-dipyridyl disulfide (PySSPy, entry 5) or 2,2′-dipyridyl diselenide (PySeSePy, entry 6) was added. PySeSePy appeared to be the catalyst or activator of choice also with isobutyric acid instead of Boc-Phe-OH or when ethyl azidoacetate was replaced by benzyl azide (results not included for the sake of simplification). Among the solvents (Table 2), we confirmed[1] that toluene (entry 6) was the best solvent. The 1:1 DMF−toluene mixture (entry 5) was as efficient as toluene for substrates such as those of Table 2, but for more hindered cases toluene alone was better.

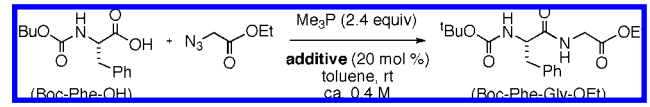
When linear carboxylic acids were used instead of the α-branched examples of Tables 1 and 2, the reactions were always much more rapid but the final yields of the desired amides dropped significantly with PhSSPh or PhSeSePh and moderately when the additive was PySSPy; this was due to the appearance of byproducts (see below). Again, the highest amide yields were obtained with PySeSePy.

On the basis of these results, we carried out the reactions of Table 3, with 240 mol % of Me_3P and 20 mol % of PySeSePy. The simplest amides (entries 1−5) were obtained in 90−100% yields within 2 h; indeed, in these cases the amide yields were practically quantitative even with only 130−150 mol % of Me_3P and 20 mol % of PySeSePy, in 3−4 h at rt.

When one of the reaction partners contained α-branched chains (entries 6−9 of Table 3, substrates of Tables 1 and 2), longer reaction times were required to complete the conversion. As usual, reaction times could be shortened by (i) increasing the amount of PySeSePy (footnote b of Table 3) or (ii) raising the temperature (footnote d). No racemization took place with the lactic acid derivative (entry 8 of Table 3) or in the reaction of Boc-Phe-OH with methyl 2-azidoacetate (entry 6 of Table 1), as checked by chiral HPLC. No racemization occurred in the preparation of Boc-Gly-Ala-OEt (entry 9 of Table 3), but this was expected as enantiopure phosphazenes of general formula $R_3P{=}NCHRCOOR$ do not racemize.[4k]

However, no method is perfect. The reaction of N-protected amino acids (such as Boc-Phe-OH) with sterically hindered

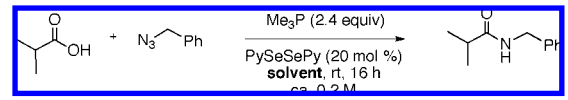
TABLE 1. Catalyst Screening: Yields of Boc-Phe-Gly-OEt



entry	additive (catalyst or activator)	yield, 24 h (%)	yield, 48 h (%)
1	none	35	44
2	PhSSPh	37	46
3	PhSeSePh	39	51
4	4,4′-PySSPy	42	55
5	PySSPy (2,2′-PySSPy)	74	87
6	PySeSePy (2,2′-PySeSePy)	91	100

[a] Boc-Phe-OH (1.0 mmol), ethyl 2-azidoacetate (1.0 mmol), and various additives (0.2 mmol) were mixed with 2.4 mL of 1 M toluene solution of Me_3P at 0 °C under N_2. A few minutes later, the solutions were stirred at rt for 24 or 48 h, quenched, and analyzed by ^1H NMR.

TABLE 2. Solvent Screening[a]



entry	solvent	amide yield (%)
1	CH_3CN−toluene (1:1)	17
2	pyridine−toluene (1:1)	35
3	CH_2Cl_2−toluene (1:1)	43
4	THF	47
5	DMF−toluene (1:1)	97
6	toluene	100

[a] To 1.0 mmol of isobutyric acid, 1.0 mmol of benzyl azide, and 0.2 mmol of PySeSePy in 2.4 mL of the "first" solvent were added 2.4 mL of 1 M toluene (THF in entry 4) solutions of Me_3P under N_2.

(10) The reaction of phosphazenes with acid chlorides had precedents: (a) Masriera, M. *An. Soc. Esp. Fís. Quím.* **1923**, *21*, 418 ($Ph_3P{=}NPh$ + AcCl, AcBr, or PhCOCl). (b) Zbiral, E.; Stroh, J. *Liebigs Ann. Chem.* **1969**, 29 (imidoyl chlorides, to obtain tetrazoles). (c) Bachi, M. D.; Vaya, J. *J. Org. Chem.* **1979**, *44*, 4393 (reaction of $PhOCH_2COCl$ with a monobactam triphenylphosphazene). (d) Barluenga, J.; Ferrero, M.; Palacios, F. *J. Chem. Soc. Perkin Trans. 1* **1990**, 2193 (N-acylated vinylphosphazenes). (e) Molina, P.; Alajarín, M.; López-Leonardo, C. *Tetrahedron Lett.* **1991**, *32*, 4041 (rearrangement to *C*-phosphonium salts, see below).

(11) Named by Bertozzi et al. "the Staudinger ligation" in 2000: (a) Saxon, E.; Bertozzi, C. R. *Science* **2000**, *287*, 2007 More than 20 papers since then have been dedicated by this group to applications of this methodology to the biology field. For other leading references, see: (b) Lin, F. L.; Hoyt, H. M.; van Halbeek, H.; Bergman, R. G.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2005**, *127*, 2686. (c) Baskin, J. M.; Bertozzi, C. R. *QSAR Comb. Sci.* **2007**, *26*, 1211.

(12) Hiebl, J.; Zbiral, E. *Liebigs Ann. Chem.* **1988**, 765.

(13) Afonso, C. *Tetrahedron Lett.* **1995**, *36*, 8857.

(14) The reaction of RCOOH, N_3R', PhSeSePh, and Bu_3P was reported under conditions—nearly equimolar amounts of substrates and reagents—in which PhSeH was assumed to reduce the azide to amine (phosphazenes were not involved). See: (a) Ghosh, S. K.; Singh, U.; Mamdapur, V. R. *Tetrahedron Lett.* **1992**, *33*, 805. (b) Ghosh, S. K.; Verma, R.; Ghosh, U.; Mamdapur, V. R. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1705.

(15) (a) Kurosawa, W.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 8112 (pentafluorophenyl esters). (b) Malkinson, J. P.; Falconer, R. A.; Toth, I. *J. Org. Chem.* **2000**, *65*, 5249 (activation with DIC or DCC and 1-hydroxybenzotriazole, HOBt). (c) Chapuis, H.; Strazewski, P. *Tetrahedron* **2006**, *62*, 12108 (DIC, HOBt).

(16) (a) Charafeddine, A.; Chapuis, H.; Strazewski, P. *Chem.—Eur. J.* **2007**, *13*, 5566. (b) Charafeddine, A.; Chapuis, H.; Strazewski, P. *Org. Lett.* **2007**, *9*, 2787. (c) Chapuis, H.; Bui, L.; Bestel, I.; Barthélémy, P. *Tetrahedron Lett.* **2008**, *49*, 6838. (d) Saneyoshi, H.; Michel, B. Y.; Choi, Y.; Strazewski, P.; Marquez, V. E. *J. Org. Chem.* **2008**, *73*, 9435.

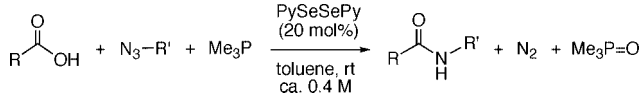
(17) It avoids confusion with the reaction of azides and phosphines (and the reaction of phosphazenes with H_2O, with CO_2, with CS_2, with RNCO, and with $R_2C{=}C{=}O$, the classical Staudinger reactions) and the [2 + 2]-cycloaddition of ketenes and imines (another Staudinger reaction).

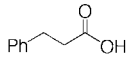
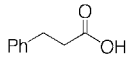
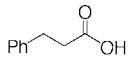
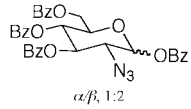
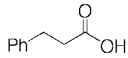
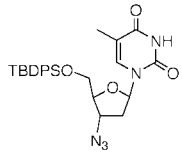
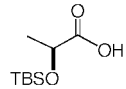
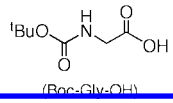
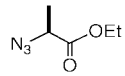
(18) (a) Mukaiyama, T.; Matsueda, R.; Marayama, H. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1271. (b) Mukaiyama, T.; Matsueda, R.; Suzuki, M. *Tetrahedron Lett.* **1970**, 1901. Also see: (c) Lloyd, K.; Young, G. T. *Chem. Commun.* **1968**, 1400.

(19) (a) Corey, E. J.; Nicolaou, K. *J. Am. Chem. Soc.* **1974**, *96*, 5614. For a recent review, see: (b) Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911.

(20) Reviews on the chemical synthesis of proteins: (a) Nilsson, B. L.; Soellner, M. B.; Raines, R. T. *Annu. Rev. Biophys. Biomol. Struct.* **2005**, *34*, 91. (b) Dawson, P. *Chem. Biol.* **2007**, *2*, 567. (c) Hackenberger, C. P. R.; Schwarzer, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 10030. For recent papers on chemical ligation, cf. (d) Haase, C.; Rohde, H.; Seitz, O. *Angew. Chem., Int. Ed.* **2008**, *47*, 6807. (e) Blanco-Canosa, J. B.; Dawson, P. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 6851. Activation via 4-nitrophenyl ester: (f) Wan, Q.; Chen, J.; Yuan, Y.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 15814.

TABLE 3. Direct Ligation of Carboxylic Acids and Organic Azides, Mediated by Me_3P and Catalyzed or Promoted by PySeSePy[a]



entry	acid	azide	time (h)	amide yield (%)
1			2	99
2			2	96
3			2	94
4			2	99
5			2	98
6			48 4	90[b,c] 94[c,d]
		α/β, 1:2		
7			48 2	94[b] 90[d]
8			48	93
9			2 40	90[b] 99
	(Boc-Gly-OH)			

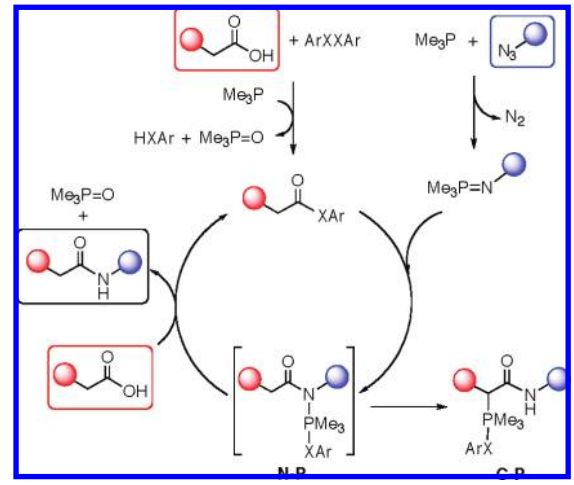
[a] Standard conditions: carboxylic acid (1.0 mmol), azide (1.0 mmol), PySeSePy (0.2 mmol), 2.4 mL of 1 M Me_3P in toluene, 0 °C, under N_2, stirring at rt for 2−48 h depending on the case. [b] This reaction was carried out using 100 mol % of PySeSePy. [c] The β anomer predominated (α/β, 1/10); we think that the re-equilibration of anomers occurs at the *N*-phosphonium intermediate stage (see below). [d] At 100 °C in a MW reactor.

phosphazenes (such as that arising from the azido derivative of Val-OEt) was very slow under our standard conditions. In such cases (when both partners were α-branched), we also observed the racemization of the stereocenter α to the carboxylic acid moiety. Likely, the reaction was so slow that it allowed the corresponding phosphazene to act as a base. The racemization of Boc-Phe-SePy may occur via standard enolization, by oxazolone formation, or through a ketene intermediate.[21] Therefore, a catalytic protocol cannot be applied to these cases. For the formation of peptide bonds without epimerization from two crowded substrates, we recommend our stoichiometric procedure (Boc-NHCHRCO-LG + $N_3CHR'COOEt$, toluene, 0−5 °C, addition of Me_3P or Bu_3P)[4k] or those of refs 15 and 16.

To gain insight into the key mechanistic steps, we followed by ^1H NMR spectroscopy, in toluene/C_6D_6 at rt, the reactions

(21) Under the standard conditions of Table 3, the reaction of (*S*)-PhCH(OTBS)COOH and $Me_3P{=}NCH_2Ph$ also stopped quickly, and the yield of the corresponding amide was poor. With stoichiometric amounts of PySeSePy, a 52% yield of the amide was isolated after 2 h, but 15% of racemization had already taken place. The acidity of the CH proton (now α to COXAr and Ph) and the phosphazene basicity make easy this racemization.

SCHEME 2. Plausible Mechanism of the Reaction of RCH_2COOH with Azides, Me_3P, and ArXXAr[a]



[a] ArXXAr = PhSSPh, PhSeSePh, PySSPy, or PySeSePy.

of $Me_3P{=}NCH_2Ph$ with PhCOSePh, PhCH(OTBS)COSPh,[22] $PhCH_2CH_2COSePy$, and $CH_3(CH_2)_{16}COSePy$.[23] All reactants were prepared separately and mixed in NMR tubes under N_2, and the spectra were registered at rt every 10 min. The signals of the initial intermediates, corresponding to the expected "N-phosphonium species" (see N−P in Scheme 2 as an example), were maintained. We did not detect other intermediates. In other words, $C(XAr){=}NCH_2Ph$ moieties coming from aza-Wittig reactions between the COXAr groups and $Me_3P{=}NCH_2Ph$ were not observed; the direct loss of $Me_3P{=}O$ if moisture and acid were avoided was not observed either. In the last two experiments ($RCH_2COSePy$ cases), only a very slow appearance of other phosphonium species was detected, characterized by ^1H and ^{31}P NMR as "C-phosphonium species" (C−P, see the Supporting Information).

The formation of C-phosphonium salts $PhCH(PPh_3{}^+Cl^-)$−$CONHCH_2R$ in reactions of $PhCH_2COCl$ with $Ph_3P{=}NCH_2R$ was first reported by Molina, Alajarín, et al.[10e] These anomalous reactions, which are sometimes very rapid and give relatively stable C−P derivatives that are not cleaved readily to the desired amides, were re-examined by us[8d] with $PhCH_2COCl$ or $PhCH_2COOCOAr$ vs $Bu_3P{=}NCH_2Ph$, confirming the results of our colleagues.[10e,24]

When the reaction of $Me_3P{=}NCH_2Ph$ and $CH_3(CH_2)_{16}$-COSePy was repeated with other thio- and selenoesters of stearic acid, the rearrangements from the N−P to C−P intermediates took place more quickly. Spectra at different reaction times are given as Supporting Information. The conversion of $RCH_2CON(PMe_3XAr)CH_2Ph$ to $RCH(PMe_3XAr)CONHCH_2Ph$ followed an increasing order for XAr equal to

$$SePy \ll SPy < SePh \ll SPh$$

In other words, $RCH_2COSePy$ gave rise to lower amounts of C−P byproducts than RCH_2COSPy, $RCH_2COSePh$, and

(22) The reaction of PhCH(OTBS)COSPh with $Me_3P{=}NCH_2Ph$, both prepared separately, gave rise to PhCH(OTBS)CON(PMe_3SPh)CH_2Ph (structure confirmed by ^1H and ^{13}C NMR, as well as by a ^{31}P-decoupled ^1H NMR experiment), which was kinetically stable at rt.

(23) We choose the stearic (octadecanoic) acid derivative because of the hydrophobicity and higher solubility in toluene of the corresponding intermediates (from its reaction with phosphazenes).

(24) Molina, P.; Alajarín, M.; López-Leonardo, C.; Alcántara, J. *Tetrahedron* **1993**, *49*, 5153.

RCH_2COSPh. This explains why the final yields were excellent in the $RCH_2COSePy$ cases (that is, with PySeSePy as the activator), but often poor (with SPh and SePh derivatives) or moderate to good (with SPy derivatives) even at longer reaction times.

Thus, these N−P to C−P rearrangements appear to be more general than we had previously believed.[8d] The PR_3^+ or PR_3XAr groups migrate from the N atoms to the RCH_2CO methylene carbon atoms—the more acidic these methylene protons, the faster the rearrangement—depending on the temperature, medium polarity, and mainly presence of bases (for example, of a relative excess of phosphazene). On the other hand, there was no migration of PR_3XAr from the N atom to the more crowded RR′CHCO methine carbon atoms in the cases we examined. Such a migration is impossible in the PhCOOH derivatives.

Under our catalytic conditions, the carboxylic acids (relatively in excess save at the end) can cleave the initial $N-PMe_3SePy$ species as soon as they are formed. We noted that in the model reaction, followed by NMR, of $CH_3(CH_2)_{16}COSePy$ and $Me_3P{=}NCH_2Ph$, addition of the starting carboxylic acid had a positive effect (much more significant than the addition of 2-selenopyridone), as the amide appeared immediately. Taking into account the data currently available, a plausible mechanism for the reaction of azides, Me_3P, and ArXXAr with RCH_2COOH—the "simplest" acids but the "most complex" since, as indicated, N−P to C−P rearrangements may take place—is summarized in Scheme 2. ArXXAr behave as activators rather than true catalysts.

In conclusion, a catalytic variant of the coupling reaction of Staudinger phosphazenes with carboxyl groups is described here for the first time. It is based on mild in situ activation of COOH as COSePy groups (which overcome COSPy, COSePh, and COSPh). Mechanistically, it is not an aza-Wittig process, a term that should be confined to the reactions of phosphazenes with aldehydes and ketones unless otherwise is demonstrated. The Masriera reaction,[10a] for historical reasons, or the S−V reaction[16,17] are more appropriate names for the ligation of azides and carboxylic acid derivatives. The quick reaction of the intermediate $N-PMe_3SePy$ species with the remaining carboxylic acid, which generates the amide and more selenoester, is key for the success of this catalytic version. For RCH_2COOH, the use of PySeSePy has the additional advantage that a side reaction, the rearrangement of the *N*-phosphonium species [$RCH_2CON(PMe_3XAr)R'$, prone to turnover] to the relatively more stable C-phosphonium species [$RCH(PMe_3X)CONHR'$, not prone to turnover] hardly takes place, in contrast with the other additives. The background for improved ligation procedures has been established.

Experimental Section

Typical Procedure. A commercially available solution of Me_3P (1.0 M in toluene, 2.40 mL, 2.4 mmol) was added to a mixture of carboxylic acid (1.0 mmol), azide (1.0 mmol), and 2,2′-dipyridyl diselenide (PySeSePy, 63 mg, 0.20 mmol) at 0 °C under nitrogen. A few minutes later, when no more nitrogen bubbles were observed, the ice bath was removed and the reaction was stirred at room temperature for 2 h. Then, water (1 mL) was added and the mixture was stirred for 10 min. The mixture was diluted with an excess of CH_2Cl_2 and rinsed with aqueous $NaHCO_3$, cold 1 M HCl (to remove yellow 2-selenopyridone and 2,2′-dipyridyl diselenide), and finally water. The organic phase was dried ($MgSO_4$), filtered, and concentrated to dryness. The crude amide or peptide was purified by flash chromatography on silica gel; the elution conditions are indicated in each case (Supporting Information). With hindered substrates it was necessary to increase the reaction times, the catalyst loading, or the temperature, as indicated in the main text.

Acknowledgment. The Ministerio de Educación y Ciencia contributed through Grant Nos. SAF2002-02728 and CTQ-2006-15393 and a studentship to J.B. and the Generalitat de Catalunya through Grant No. 2001SGR065. We acknowledge the work of authors who, over the last 15 years, have used the methods mentioned in the introduction, and we apologize for not citing them (cf. refs 4c−f). This study is dedicated to Prof. Teruaki Mukaiyama.

Supporting Information Available: General procedures and experimental details for the preparation of the carboxamides. NMR monitoring of different reactions. Copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802825E