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A "Traceless" Staudinger Ligation for the Chemoselective Synthesis of Amide Bonds

Eliana Saxon, Joshua I. Armstrong, and Carolyn R. Bertozzi*

Departments of Chemistry and Molecular and Cell Biology, University of California, Berkeley, California 94720

Bertozzi@cchem.berkeley.edu

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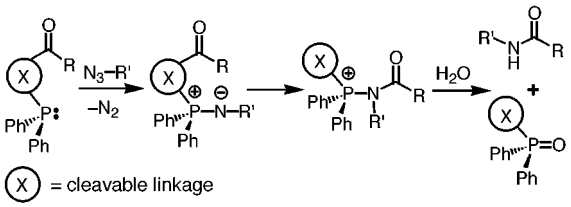
ABSTRACT

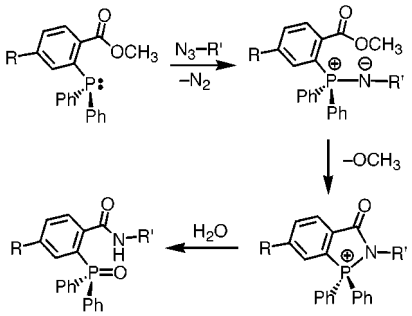


Here we report a novel modification of our previously reported "Staudinger ligation" that generates an amide bond from an azide and a specifically functionalized phosphine. This method for the selective formation of an amide bond, which does not require the orthogonal protection of distal functional groups, should find general utility in synthetic and biological chemistry.

Chemoselective ligation reactions are now established tools for diverse applications in chemistry and biology.[1] The functional groups that participate in these transformations are mutually reactive and tolerant of numerous coexisting functional groups, thus eliminating the need for protecting group strategies. For example, the condensation of aldehydes or ketones with hydrazide or aminooxy groups to form hydrazones and oximes respectively has found widespread utility in the synthesis of highly functionalized biomolecules[2] and libraries of druglike small molecules.[3]

We have recently reported a modification of the Staudinger reaction that allows the chemoselective formation of amide-linked products from azides and triaryl phosphines (Scheme 1).[4] Termed the "Staudinger ligation", this reaction proceeds by the nucleophilic attack of a phosphine on an azide to form an aza-ylide intermediate. A methoxycarbonyl group situated on one of the aryl rings of the phosphine traps the aza-ylide in an intramolecular fashion, resulting in an amide-linked phosphine oxide after hydrolysis. The phosphine and azide react with such high selectivity and the intramolecular acylation step is so fast that the transformation can be executed among complex biomolecules in an aqueous medium on the surfaces of living cells.[4] The broad potential utility of the Staudinger ligation in biological chemistry has prompted us to explore related reactions as tools for organic

Scheme 1. The Staudinger Ligation



(1) Lemieux, G. A.; Bertozzi, C. R. *TIBTECH* **1998**, *16*, 506.
(2) (a) Rose, K. *J. Am. Chem. Soc.* **1994**, *116*, 30. (b) Mahal, L. K.; Yarema, K. J.; Bertozzi, C. R. *Science* **1997**, *276*, 1125. (c) Zhang, L. S.; Torgerson, T. R.; Liu, X. Y.; Timmons, S.; Colosia, A. D.; Hawiger, J.; Tam, J. P. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 9184. (d) Rodriguez, E. C.; Marcaurelle, L. A.; Bertozzi, C. R. *J. Org. Chem.* **1998**, *63*, 7134.
(3) Maly, D. J.; Choong, I. C.; Ellman, J. A. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 2419.
(4) Saxon, E.; Bertozzi, C. R. *Science* **2000**, *287*, 2007.

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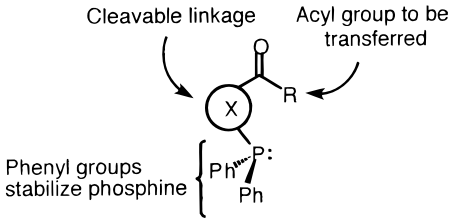
synthesis. Ideally, the reaction would produce an amide bond between two coupling partners without an intervening triarylphosphine oxide group. Here we report the first example of such a "traceless" Staudinger ligation.

The phosphines we designed for this purpose incorporate two key elements (Scheme 2). First, the acyl component

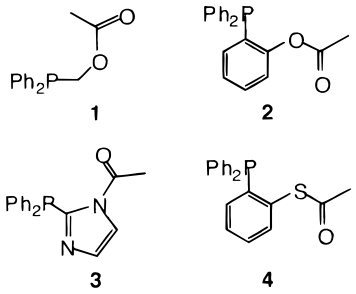
Scheme 2. Design of a Phosphine Reagent for the Selective Formation of Amides from Azides



destined for the amide bond is attached to an aryl ring by a cleavable linkage. The nucleophilic nitrogen atom of the aza-ylide attacks the carbonyl group, displacing the cleavable linkage and attached phosphonium group. Hydrolysis of the rearranged adduct produces an amide bond and liberates a phosphine oxide. Second, at least two aromatic phosphine substituents were included to impart stability toward oxidation under ambient conditions.

Four suitable phosphines (**1**−**4**, Scheme 3) are synthesized to test the traceless Staudinger ligation. Compound **1** was

Scheme 3. Phosphines Designed To Test the Traceless Staudinger Ligation

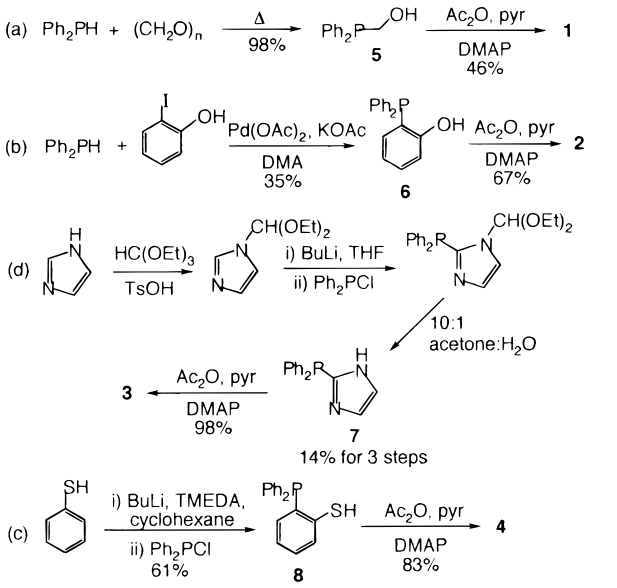


prepared by reaction of diphenylphosphine with paraformaldehyde to give the known compound **5**,[5] followed by acetylation (Scheme 4a). Compound **2** was synthesized by Pd-mediated coupling of diphenylphosphine with 2-iodophenol to afford the known compound **6**,[6] which was then acetylated (Scheme 4b). Imidazole was transformed to imidazole phosphine **7**[7] (Scheme 4c), which was acetylated to yield compound **3**. Finally, ortholithiation of thiophenol followed by reaction with chlorodiphenylphosphine yielded intermediate **8**[8] (Scheme 4d), which was acetylated to provide

(5) Slany, M.; Caminade, A. M.; Majoral, J. P. *Tetrahedron Lett.* **1996**, *37*, 9053.

(6) Herd, O.; Hessler, A.; Hingst, M.; Machnitzki, P.; Tepper, M.; Stelzer, O. *Catal. Today* **1998**, *42*, 413.

Scheme 4. Synthesis of Phosphines



compound **4**. In each case, intramolecular transfer of the acetyl group from the phosphine to an azide-bearing compound would indicate a successful ligation reaction.

Compound **1** (50 mM) was reacted with an azidonucleoside[9] (**9**, 50 mM) in wet THF, and the reaction was monitored by reversed-phase HPLC over a 24-h period (Scheme 5).[10] The azidonucleoside was selected to demonstrate a modicum of functional group compatibility, since the intramolecular cyclization obviates the need for protection of coexisting functional groups.[11] We speculated that the aza-ylide intermediate [**10**] would share key similarities with that generated during the original Staudinger ligation (Scheme 1), i.e., intramolecular reaction via a five-membered ring transition state and an alkoxy anion leaving group. However, the only products observed were those of aza-ylide hydrolysis, compounds **11** and **12**. The traceless Staudinger ligation products **13** and **14** were not observed.[12] We concluded that the flexibility of the methylene bridge in **10** sufficiently reduced the rate of cyclization such that the hydrolysis reaction pathway predominated.

Phosphine **2** introduces conformational rigidity into the aza-ylide intermediate, similar to the phosphine depicted in Scheme 1, although the intramolecular reaction now must proceed via a six-membered ring transition state. When **2** was reacted with azide **9** (both reagents at 50 mM) in wet THF, only the desired Staudinger ligation products were observed (Scheme 6a). There was no evidence by HPLC

(7) Curtis, N. J.; Brown, R. S. *J. Org. Chem.* **1980**, *45*, 4038.

(8) Figuly, G. D.; Loop, C. K.; Martin, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 654.

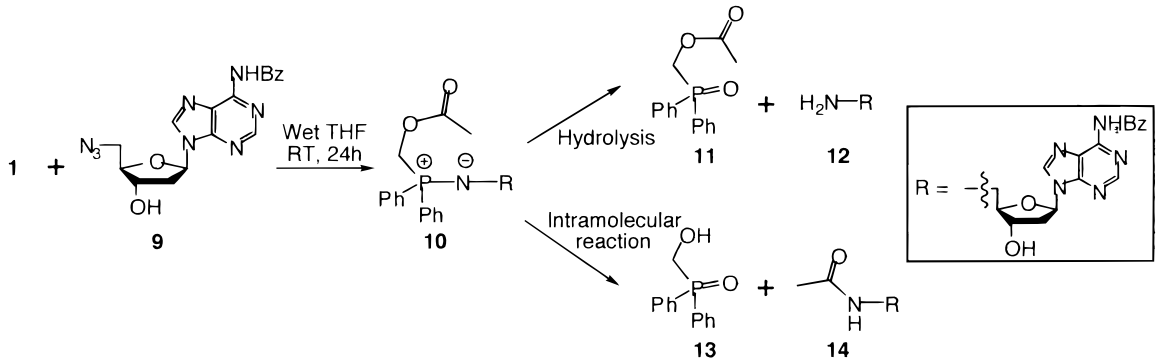
(9) Mag, M.; Engels, J. W. *Nucleosides Nucleotides* **1988**, *7*, 725.

(10) CH_3CN/H_2O gradient (20−70% CH_3CN over 40 min).

(11) (a) Mizuno, M.; Haneda, K.; Iguchi, R.; Muramoto, I.; Kawakami, T.; Aimoto, S.; Yamamoto, K.; Inazu, T. *J. Am. Chem. Soc.* **1999**, *121*, 284. (b) Urpi, F.; Vilarrasa, J. *Tetrahedron Lett.* **1986**, *27*, 4623.

(12) All products were purified by HPLC and analyzed by NMR and mass spectrometry.

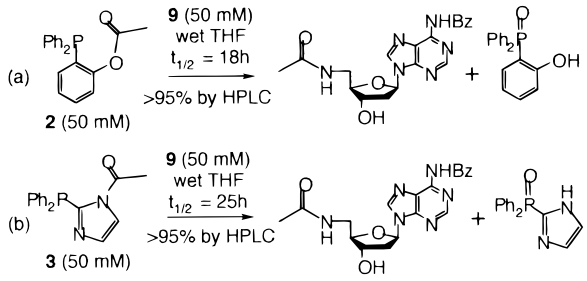
Scheme 5. Reaction of **1** Yields Hydrolysis Products



analysis of aza-ylide hydrolysis products. Thus, a rigid structure linking the phosphine and acyl group appears to be essential for efficient acyl transfer in the presence of water.

In an effort to increase the rate of the reaction, we designed imidazole phosphine **3**, which would form an aza-ylide capable of N-to-N acyl migration through a five-membered ring transition state. The reaction of **3** with azide **9** in wet THF (both reagents at 50 mM) also produced ligation products in high yield (Scheme 6b), with no evidence of aza-ylide hydrolysis. However, the reaction proceeded more slowly than that in Scheme 6a, perhaps the result of phosphine deactivation by the electron-withdrawing imidazole group. In principle, phosphorus lone-pair reactivity could be increased by relieving conjugation with neighboring aryl substituents. Accordingly, we prepared the dicyclohexyl analogue of **3**, but found it prone to air-oxidation and therefore impractical for our intended applications.

Scheme 6. Reactions of **2** and **3** Yield Ligation Products



Finally, we examined thioester phosphine **4** in a traceless Staudinger ligation reaction with **9**. In light of the success with ester phosphine **2**, we hypothesized that the enhanced reactivity of the thioester toward nucleophilic attack would render compound **4** a superior substrate. Furthermore, thioesters are of particular interest by virtue of their utility in the convergent assembly of proteins from unprotected peptide fragments, a technique termed native chemical ligation.[13] Surprisingly, the initial products during the reaction were those of aza-ylide hydrolysis. After several days the ligation products were observed, but these may have arisen from direct acylation of the amine obtained from azide reduction with thioester **4**. Further optimization may be required to render a phosphine thioester amenable to the reaction.

In conclusion, we developed a novel reaction for the formation of amide bonds that capitalizes on the inherent selectivity of the Staudinger reaction between azides and phosphines. The reaction is compatible with diverse functional groups and should prove useful in organic synthesis and biological chemistry. The optimal substrates were phenol ester and *N*-acylimidazole phosphines which are generated readily by acylation of simple precursors. Refinements of these preliminary studies may yield new methods for peptide couplings and for the modification of cellular components.

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