A More Critical Role for Silicon in the Catalytic Staudinger Amidation: Silanes as Non-Innocent Reductants

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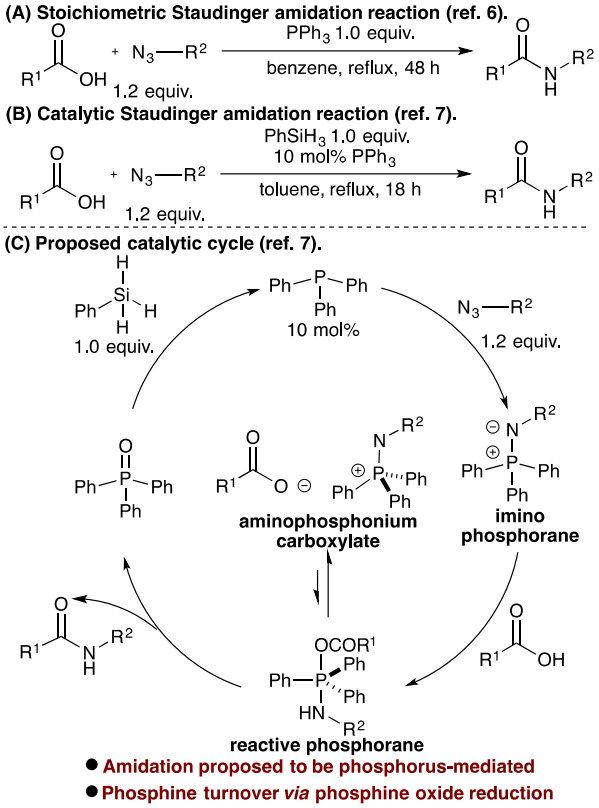
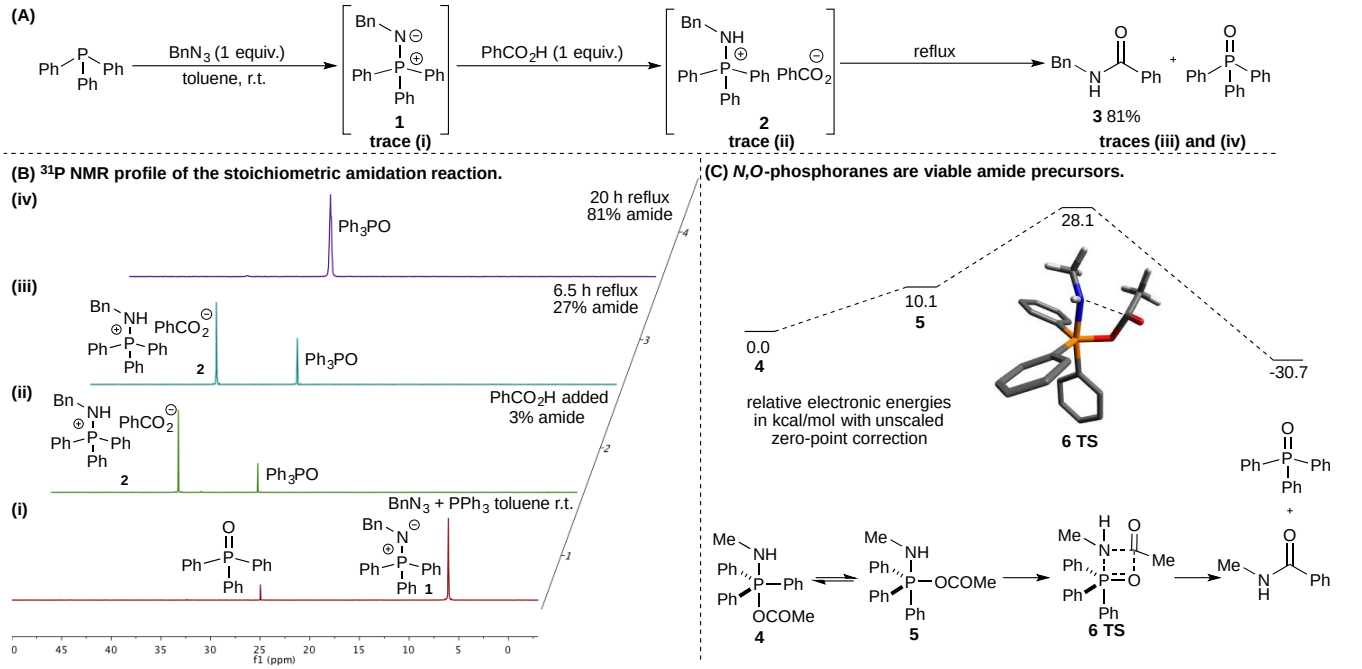
Amides are ubiquitous in organic chemistry and occur in some of the most important natural and non-natural molecules such as peptides, pharmaceuticals and polymers.[1] For this reason, amidation reactions are some of the most frequently carried out procedures in chemical synthesis.[2] Amidation reactions between azides and carboxylic acid derivatives have found widespread application owing to the fact that they can be deployed in varied and complex reaction media.[3,4,5] While many of these methods use carboxylic acid-derived activated esters, the phosphine-mediated amidation reaction between free acids and azides was reported in 1983 by Garcia and co-workers (Scheme 1A).[6] The utility of the process is undermined somewhat by the production of triphenylphosphine oxide as a stoichiometric by-product. However, this problem was overcome in 2012 by Ashfeld and co-workers who reported a catalytic, traceless Staudinger ligation reaction (Scheme 1B).[7] This process represents a combination of Garcia's amidation with the work of O'Brien,[8] who was the first to demonstrate chemoselective phosphine oxide reduction with phenylsilane in the context of a catalytic Wittig reaction.[9–14] Given that the catalytic reaction was constructed on this basis, the authors proposed a catalytic cycle (Scheme 1C) involving two key steps: (a) phosphorus-mediated amidation *via* an aminophosphonium carboxylate and the reactive *N,O*-phosphorane; and (b) chemoselective silane-mediated phosphine oxide reduction to return the phosphine catalyst. While these two steps are established as *discrete processes, their conflation into a catalytic cycle presents an intriguing chemoselectivity issue*, namely the reduction of triphenylphosphine oxide in the presence of reductively labile iminophosphorane, aminophosphonium and *N,O*-phosphorane intermediates.[15]



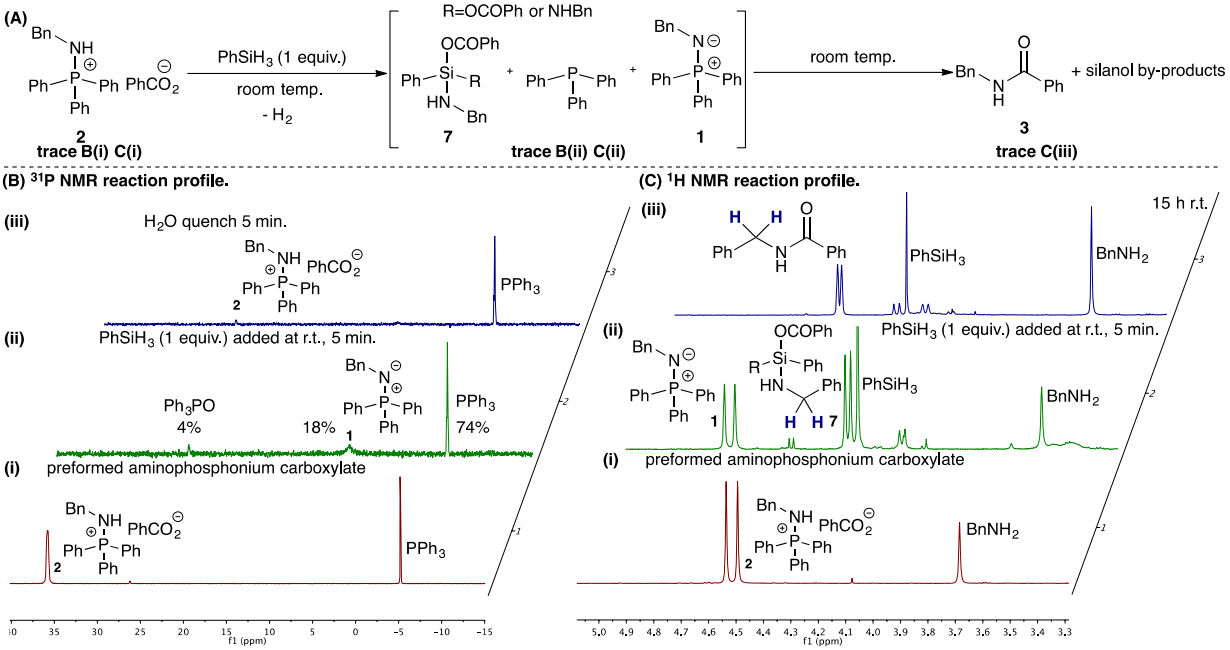
Scheme 1 (A) Stoichiometric Staudinger amidation. (B) and (C) Catalytic, traceless Staudinger ligation.

In this communication, we report the first mechanistic study of the catalytic Staudinger amidation and we disclose an alternative amidation pathway based upon the intervention of previously neglected silyl ester intermediates. We demonstrate that these underappreciated silyl esters exhibit enhanced and augmented reactivity compared to the parent silane and, we propose, that they are the mediators of the catalytic ligation reaction. Our analysis reveals a more critical role for silicon and has mechanistic implications for all silane-terminated catalytic reactions that take place in reaction media that are Lewis basic/Brønsted acidic.



Scheme 2 Stoichiometric amidation is aminophosphonium-mediated. (A) Stoichiometric amidation reaction. (B) ^{31}P NMR profile. (C) B3LYP/6-31G* computed amidation.

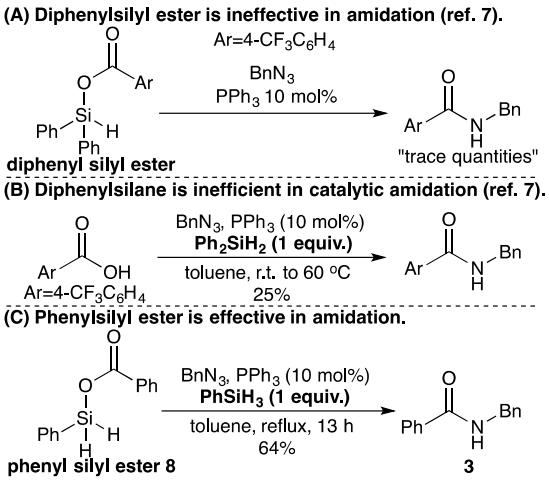
We began by examining the proposed amidation step in isolation *via* ^{31}P NMR spectroscopy. Thus, benzyl azide was treated with triphenylphosphine (Scheme 2A) and the expected iminophosphorane **1** (^{31}P δ=6.2 ppm, Scheme 2B trace (i)) was formed along with triphenylphosphine oxide. Subsequent addition of benzoic acid afforded amino phosphonium carboxylate **2** (^{31}P δ=36.9 ppm, Scheme 2B, trace (ii)), which was observed to be thermally stable with respect to amidation at room temperature. However, upon heating, we observed slow conversion of this species to the corresponding amide **3** and triphenylphosphine (Scheme 2B, traces (iii) and (iv)). Garcia and Ashfeld proposed that the aminophosphonium carboxylate exists in equilibrium with an *N,O*-phosphorane intermediate (Scheme 1C). Given that the reactive phosphorane could not be observed spectroscopically we carried out calculations to establish the viability of unimolecular amidation from this intermediate. To this end intermediate **4** (Scheme 2B) along with the reactive conformer **5** (obtained *via* turnstile pseudo rotation of **4**) were located as minima along with transition structure **6**.[16] These studies corroborate the initial mechanism suggested by Garcia,[6] and we next considered the stability of these intermediates in the context of the catalytic amidation reaction, in which phenylsilane is present as the terminal reductant. Given that the catalytic Staudinger reduction reported by van Delft and co-workers[15] involved phenylsilane reduction of an iminophosphorane to the corresponding phosphine *and that phosphine oxide reduction did not occur under these conditions* we expected both the iminophosphorane and aminophosphonium intermediates to be reductively labile. The aminophosphonium intermediate **2** was again formed (Scheme 3A and Scheme 3B trace (i)) and phenylsilane (1.0 equiv.) was then added at room temperature. After four minutes, ^{31}P NMR (Scheme 3B trace (ii)) indicated near complete reduction of aminophosphonium **2** to triphenylphosphine (^{31}P δ=-5.2 ppm), as well as the regeneration of some iminophosphorane **1** and the evolution of hydrogen gas. Analysis of the ^{1}H NMR (Scheme 3C trace (ii)) showed that no amide product was formed, instead revealing no fewer than two aminosilicon species with general structure **7**, where R is either a second acyloxy group or a second aminobenzyl group. This assignment is corroborated by the absence of silicon hydride signals in the expected range (^{1}H δ=4.8-6.5 ppm) and the observation of *ca*. 35% phenylsilane (^{1}H δ=4.23 ppm) remaining. The benzylaminosilicon species show characteristic CH_2 doublets (^{1}H δ=4.27 ppm, $^{3}J_{HH}$ = 8.0 Hz; 4.07 ppm, $^{3}J_{HH}$ = 8.0 Hz) and two corresponding NH triplets (^{1}H δ=2.29 ppm and 1.79 ppm, both with $^{3}J_{HH}$ = 8.0 Hz) in agreement with discrete literature benzylaminosilanes.[17,18]



Scheme 3 The aminophosphonium carboxylate **2** is reductively labile and amidation is silicon-mediated.

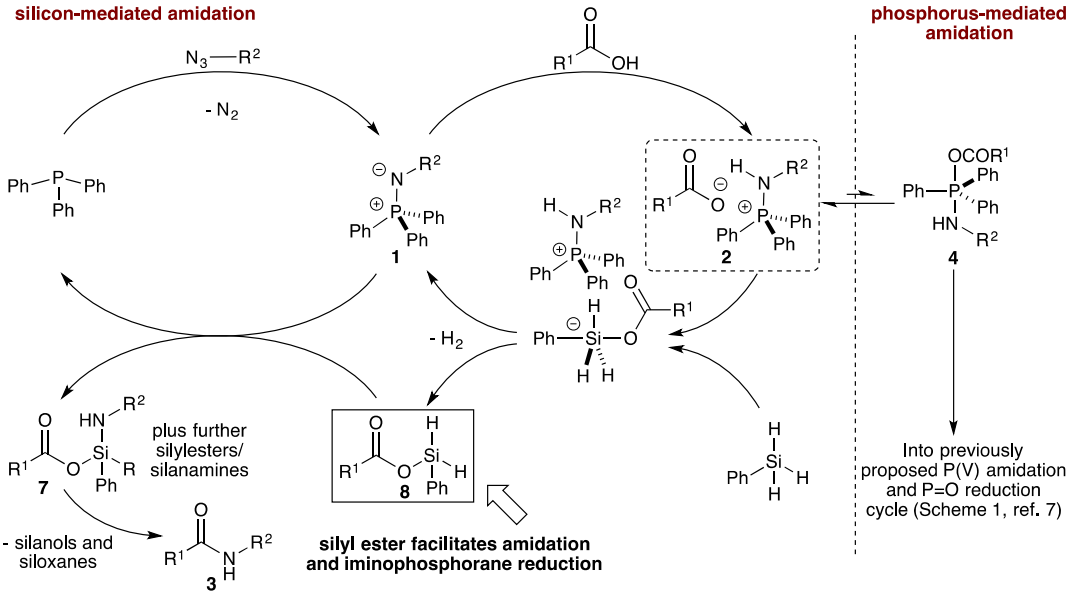
This experiment, which was carried out under ambient conditions with equimolar phenylsilane, demonstrates that the aminophosphonium carboxylate **2** is not a viable intermediate in the catalytic amidation (carried out in refluxing toluene with 10:1 silane:phosphine). It also demonstrates that the phosphine is not formed via reduction of the phosphine oxide, because its formation (in the original cycle, Scheme 1C) is explicitly linked with that of the amide. Finally, after 15 hours at room temperature the amide product was visible (Scheme 3C trace (iii)), and silicon species **7** was significantly depleted suggesting a more critical role for silicon in the amidation process.

Ashfeld and co-workers had considered an alternative amidation involving the *in situ* generation of a silyl ester intermediate.[7] This was necessary since: (a) amidation reactions from pre-formed silyl esters are well documented;[19,20] and (b) phenylsilane is known to mediate *direct* amidation reactions of carboxylic acids and amines,[21] presumably *via* silyl ester intermediates.[22] However, the possible intervention of a silyl ester intermediate in the catalytic Staudinger ligation was dismissed by the authors based upon the experiment depicted in Scheme 4A. *We note that this is equivalent to using diphenylsilane in the catalytic reaction – a very significant difference given that diphenylsilane was proven to be an inferior terminal reductant (Scheme 4B).*[7] Given this key difference we performed a final experiment with a preformed silyl ester derived from chlorophenylsilane; this is equivalent to using phenylsilane, the terminal reductant employed in the catalytic amidation. In this instance, the amide product was obtained in 64% overall yield.



Scheme 4 Amidation from pre-formed silyl esters.

This establishes that the monophenylsilyl ester is capable of mediating amidation in the presence of azide and catalytic phosphine and clearly underscores the necessity to match silane structure between control experiments and catalytic reactions. Based upon the foregoing experiments we propose an alternative, silicon-mediated pathway for the catalytic Staudinger amidation, which is depicted in Scheme 5. Thus, initial phosphorus-mediated azide reduction affords iminophosphorane **1**, which is rapidly protonated to yield aminophosphonium carboxylate **2**. The operative catalytic amidation manifold is now dictated by the reactivity of this key species, specifically the relative rates of reduction versus amidation. Since **2** is relatively kinetically stable with respect to amidation (Scheme 2) it will react rapidly with phenylsilane as demonstrated in Scheme 3.



Scheme 5 Alternative pathway for the catalytic Staudinger amidation involving silyl esters as amidating agents and reductants.

Carboxylate attack of the silane initiates reduction of the aminophosphonium species **2**, generating the key silyl ester intermediate **8** along with the iminophosphorane **1**. A further reaction between these two species then regenerates the phosphine catalyst and produces an aminosilylester species **7** that, ultimately, leads to the amide[23,24] product **3** and silanol/siloxane by-products. We have demonstrated experimentally that such silyl ester/silanamine species are viable amidation precursors (Schemes 3 and 4). Amidation may be mediated intramolecularly from a mixed acyloxysilanamine species, or, in the presence of excess carboxylic acid, Si–N protonolysis may occur, releasing amine and entering a separate (and previously documented) amidation manifold involving silane-mediated coupling of the free acid and amine.[21] *We note that the in situ-generated silyl ester plays two key roles in the revised catalytic cycle. It, first, functions as an activated carboxylic acid and, second, as an enhanced reductant, facilitating phosphine turnover;* studies involving both aspects are currently underway in our laboratory.[25]

In summary, we have provided an alternative pathway for the catalytic Staudinger ligation that is congruous with existing and new experimental results. Furthermore, we have shown that silanes cannot simply be regarded as innocent terminal reductants in reaction media that are Lewis basic/Brønsted acidic and that silyl esters are likely to be involved as enhanced reductants, or even more intimately in key bond forming steps in many other catalytic reactions.[26–29]

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