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Direct Acyl Substitution of Carboxylic Acids: A Chemoselective O- to N-Acyl Migration in the Traceless Staudinger Ligation

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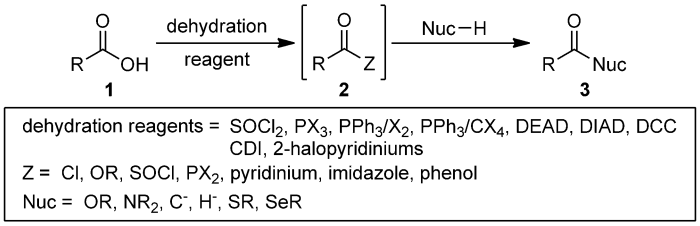
Abstract: A chlorophosphite-modified, Staudinger-like acylation of azides involving a highly chemoselective, direct nucleophilic acyl substitution of carboxylic acids is described. The reaction provides the corresponding amides with analytical purity in 32–97% yield after a simple aqueous workup without the need for a pre-activation step. The use of chlorophosphites as dual carboxylic acid–azide activating agents enables the formation of acyl C–N bonds in the presence of a wide range of nucleophilic and electrophilic functional groups, including amines, alcohols, amides, aldehydes, and ketones. The coupling of carboxylic acids and azides for the formation of alkyl amides, sulfonyl amides, lactams, and dipeptides is described.

Keywords: acyl substitution · amides · azides · carboxylic acids · Staudinger ligation

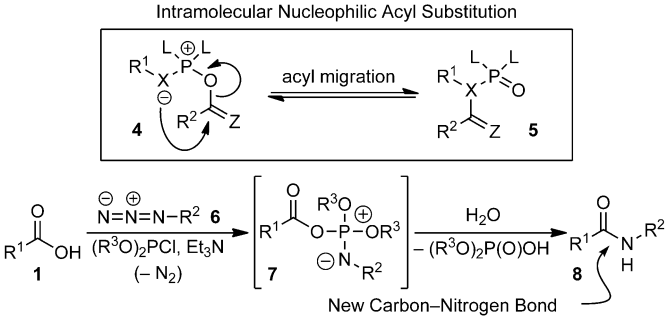
Introduction

The interconversion of carboxylic acid derivatives through nucleophilic acyl substitution constitutes one of the most fundamental transformations in chemical synthesis.[1] Whether in enzymatic reactions,[2] or the construction of biologically active natural products by using macrocyclization and fragment coupling reactions,[3] the functionalization of carboxylic acid derivatives is widespread. Although recent developments in transition-metal-catalyzed acyl substitution reactions[4] have greatly expanded the number of accessible carbonyl functional groups, the dehydration of carboxylic acids **1** to form an activated acyl intermediate **2** en route to derivative **3** is still one of the most widely utilized strategies for carbonyl functionalization (Scheme 1).[5] However, separation of the product from undesired byproducts, in combination with the often harshly acidic conditions associated with many conventional methods, has led to recent efforts to develop alternative protocols.[6] Although the ready availability of carboxylic acids makes them ideal substrates, a direct dehydration protocol that proceeds with high chemoselectivity and requires minimal purification remains elusive. Herein, we report the use of chlorophosphites as dual activating agents for the direct nucleophilic acyl substitution of carboxylic acids in the context of C–N bond formation.

To concurrently address the challenges of selectivity and product isolation, we sought to develop a method for the direct functionalization of carboxylic acids that proceeds in the presence of nucleophilic and electrophilic functional groups (e.g., ROH, RNH_2, and RCHO), while avoiding the formation of undesirable byproducts (e.g., $Ph_3P{=}O$ and ureas). We hypothesized that the desired chemoselectivity could be achieved by designing a Staudinger-type ligation[7] in which the key C–N bond is formed through an acyl migration of a phosphite ylide **4** (X = N, Z = O) to provide the desired amide upon hydrolysis of phosphonyl imide **5** (Scheme 2). Application of this concept in the construction



Scheme 1. Carboxylic acid functionalization. X = halide, DEAD = diethyl azodicarboxylate, DIAD = diisopropyl azodicarboxylate, DCC = *N*,*N*′-dicyclohexylcarbodiimide, CDI = carbonyldiimidazole.



Scheme 2. Dual carboxylic acid–azide activation.

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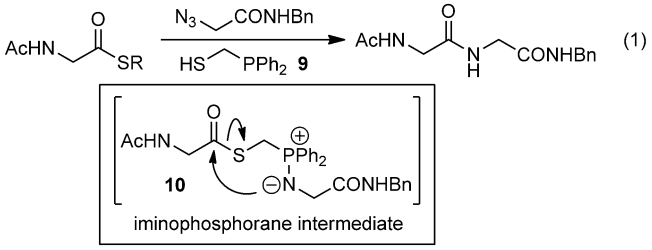
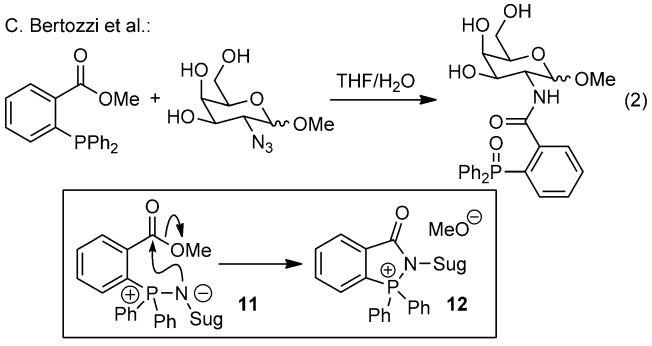
of amides[6f] relies on the concomitant activation of carboxylic acid **1** and azide **6** by using a bifunctional chlorophosphite to generate the intermediate ester azaylide **7**, which would lead to amide **8**. The intramolecularity of the acyl substitution allows for carbonyl functionalization in the presence of more electrophilic and nucleophilic functional groups. Additionally, the phosphate acid and basic byproducts are readily removed through an aqueous workup, thereby greatly simplifying product purification.

The Staudinger-type ligation[8] of carboxylic acid derivatives with azides has seen a recent resurgence since its initial discovery in 1968, primarily due to its utility in the installation of bioactive probes for the study of metabolic function and the synthesis of peptide frameworks.[9] The addition of in situ generated azaylides to carboxylic acid derivatives, including acid chlorides, anhydrides, and thioesters, has proven to be an effective strategy for amide bond construction. The Vilarrassa group and others have demonstrated the utility of these nucleophilic nitrogen species in the acyl substitution of carboxylic acid derivatives.[10] In 2000, the groups of Raines[11] and Bertozzi[12] independently reported alternative Staudinger-like ligation reactions for the conversion of thioesters and esters, respectively, into their corresponding amides. Raines and co-workers demonstrated the utility of phosphinothiol **9** in the ligation of thioesters and azides to yield dipeptides through an intramolecular acylation involving iminophosphorane **10** [Eq. (1); Bn = benzyl].[13] In contrast, Bertozzi and co-workers have developed a highly effective, rapid screening ligation protocol for the synthesis of glycoproteins from phosphine-containing esters and glycosidic azides to study glycosyltransferase activity [Eq. (2)].[9b] Mechanistic studies indicate that a five-*exo-trig* cyclization involving azaylide **11** followed by hydrolysis of intermediate **12** occurs to yield the desired amide.[14] Although the Raines' and Bertozzi's methods exhibit broad reactivity profiles, the inherent instability of phosphine **9**,[13b] the inability to use widely available carboxylic acids directly, and the stoichiometric phosphine oxide generated prompted us to pursue an alternative ligation strategy.

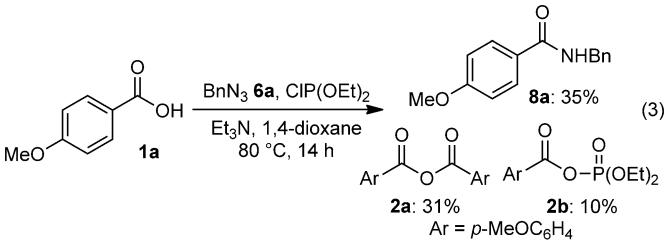
R. Raines et al.:



C. Bertozzi et al.:



Although analogous to these phosphorus-based amidation methods, it was not clear at the outset whether an intermediate ester phosphite would tolerate the presence of nucleophilic functionality, react with a range of azides to generate the putative ester azaylide intermediate, or undergo the desired acyl migration to give the C–N bond. However, we pursued the strategy outlined in Scheme 2 because it would provide a powerful method for the direct, chemoselective functionalization of carboxylic acids without the need for exotic reagents or additional purification other than a simple aqueous workup. To evaluate our hypothesis, we initially focused on the coupling of anisic acid (**1a**) with benzyl azide (**6a**) by using readily available diethyl chlorophosphite [Eq. (3)]. Formation of the phosphite ester by treatment of acid **1a** with Et_3N and $ClP(OEt)_2$ at 0 °C in 1,4-dioxane was followed by addition of azide **6a** and warming to 80 °C for 2 h to facilitate azaylide formation.[7a] Heating the reaction at reflux for an additional 12 h led to the formation of benzyl amide **8a** in 35 % yield. Also formed under these conditions were anhydride **2a** and acyl phosphonate **2b** in 31 and 10 % yield, respectively, indicating efficient phosphite ester formation, but sluggish O-to-N-acyl migration.[15]



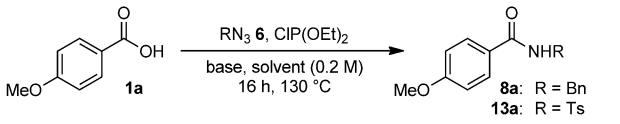
Emboldened by this result, we directed our efforts toward the detailed analysis of this modified Staudinger ligation protocol. Herein, we report our findings on the use of inexpensive and readily available chlorophosphites for the ligation of carboxylic acids with azides to generate amides and lactams, as well as peptide bonds. This work reveals a highly chemoselective method for the direct functionalization of carboxylic acids that will find broad applicability to the assembly of a wide array of amide-containing synthetic targets.

Results and Discussion

Optimization of base and solvent: We began our initial optimization studies by varying the amine base and reaction

conditions for the conversion of acid **1a** into amide **8a** (Table 1). In an effort to access higher reaction temperatures, we initially examined the use of high-boiling-point sol-

Table 1. Identification of the best base and solvent for the reaction.[a]



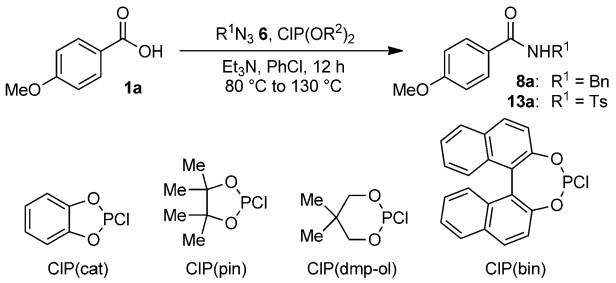
Entry	R	Base	Solvent	Yield [%][b]
1	Bn (**6a**)	Et_3N	PhMe	16 (**8a**)
2	Bn (**6a**)	Et_3N	xylenes	38 (**8a**)
3	Bn (**6a**)	Et_3N	PhCl	40 (**8a**)
4	Ts (**6b**)	Et_3N	PhCl	41 (**13a**)
5	Bn (**6a**)	Et_3N	PhCl (0.5 M)	21 (**8a**)
6	Bn (**6a**)	Et_3N	PhCl (2.0 M)	23 (**8a**)
7	Bn (**6a**)	DBU	PhCl	31 (**8a**)
8	Bn (**6a**)	DABCO	PhCl	<5 (**8a**)
9	Bn (**6a**)	iPr_2NH	PhCl	17 (**8a**)
10	Bn (**6a**)	DMAP	PhCl	10 (**8a**)

[a] Reactions conducted by using azide **6** (0.3 mmol), **1a** (0.39 mmol), $ClP(OEt)_2$ (0.39 mmol), and a base (0.39 mmol) in the solvent indicated (see the Supporting Information for details). DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, DABCO = 1,4-diazabicyclo[2.2.2]octane, DMAP = 4-dimethylaminopyridine, Ts = *para*-toluenesulfonyl. [b] Isolated yield.

vents.[16] However, treatment of acid **1a** with azide **6a**, $ClP(OEt)_2$, and Et_3N in PhMe led to a reduced yield of **8a** (Table 1, entry 1), whereas running the reaction in xylenes increased the yield to 38% (Table 1, entry 2). We quickly discovered that performing the reaction in PhCl provided the best yield of benzyl amide **8a** after 16 h at 130 °C (Table 1, entry 3). Employing TsN_3 (**6b**) under the same conditions gave results comparable to those for azide **6a** (Table 1, entry 4). Not surprisingly, the reaction concentration proved crucial, as illustrated by the lower yields of **8a** obtained for reactions at 0.5 M and 2.0 M (Table 1, entries 5 and 6). Substituting Et_3N for DBU, DABCO, iPr_2NH, and DMAP provided inferior results (Table 1, entries 7–10). With these findings in hand, we next sought to determine the optimal chlorophosphite reagent.

Effect of phosphite ligation in the Staudinger-like ligation: To determine what effect varying the alkoxy ligands on the phosphite coupling reagent would have on amide bond formation, we began by examining a series of bidentate ligand scaffolds, including chlorophosphites derived from catechol [ClP(cat)], BINOL [ClP(bin)], 2,2-dimethylpropane-1,3-diol [ClP(dmp-ol)], and pinacol [ClP(pin)] (Table 2).[17] Treatment of acid **1a** and azide **6b** with ClP(cat) in place of $ClP(OEt)_2$ improved the yield of amide **13a** (Table 2, entry 1). Moreover, when ClP(pin) and ClP(dmp-ol) were used, the yield of **13a** dramatically improved to 96 and 89%, respectively (Table 2, entries 2 and 3). Interestingly, by employing the seven-membered-ring phosphite ClP(bin), **13a** was obtained in a mere 20% yield (Table 2, entry 4). A similar

Table 2. Chlorophosphite ligation.[a]



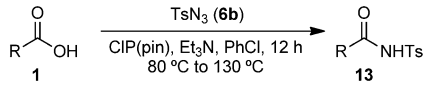
Entry	R^1	$ClP(OR_2)_2$	**1a**/**6** [equiv]	Yield [%][b]
1	Ts (**6b**)	ClP(cat)	1.3:1.0	69 (**13a**)
2	Ts (**6b**)	ClP(pin)	1.3:1.0	96 (**13a**)
3	Ts (**6b**)	ClP(dmp-ol)	1.3:1.0	89 (**13a**)
4	Ts (**6b**)	ClP(bin)	1.3:1.0	20 (**13a**)
5	Bn (**6a**)	ClP(cat)	1.3:1.0	48 (**8a**)
6	Bn (**6a**)	ClP(pin)	1.3:1.0	63 (**8a**)
7	Bn (**6a**)	ClP(pin)	1.0:3.0	59 (**8a**)

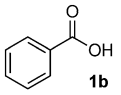
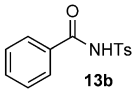
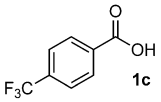
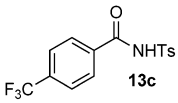
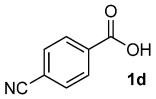
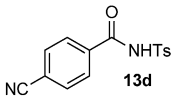
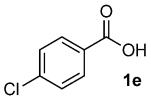
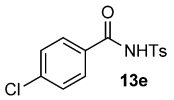
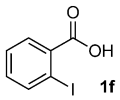
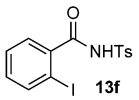
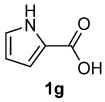
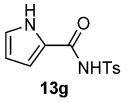
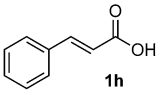
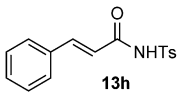
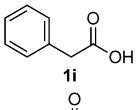
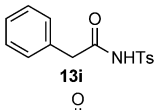
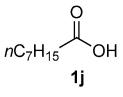
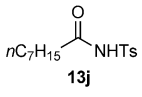
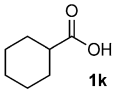
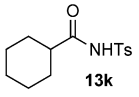
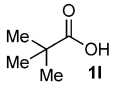
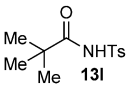
[a] Reactions conducted on a 0.3 mmol scale at 0.2 M by using the stoichiometry of **1a** and **6** indicated, with $ClP(OR)_2$ and Et_3N in equimolar amounts to **1a** (see the Supporting Information for details). [b] Isolated yield.

trend was observed in the formation of amide **8a** from acid **1a** and azide **6a** by using ClP(cat) and ClP(pin) (Table 2, entries 5 and 6). The relative stoichiometry of acid **1a** and azide **6a** proved important to the efficiency of the coupling event. When an excess of azide **6a** relative to acid **1a** was used, the yield of **8a** dropped slightly to 59% (Table 2, entry 7). Based on these findings, we used the optimized conditions of ClP(pin) and Et_3N with a 1.3:1.0 ratio of acid to azide in PhCl to complete our study.

Carboxylic acid and azide substrate scope: Satisfied that we had identified the optimal reaction conditions to promote C–N bond construction while suppressing anhydride formation, we turned our attention to determining the structural variability tolerated within the carboxylic acid component **1** with sulfonyl azide **6b** (Table 3). In general, good to excellent yields were obtained by using an assortment of aromatic and aliphatic carboxylic acids, regardless of stereoelectronic factors. Benzoic acid (**1b**) gave an excellent yield of amide **13b** (Table 3, entry 1). Electron-deficient benzoic acid derivatives underwent smooth conversion to the corresponding amides in 81–96% yield (Table 3, entries 2–5). Nitriles were well tolerated (Table 3, entry 3), and the presence of aryl halides in **1e** and **1f** did not adversely affect the formation of amides **13e** and **13f** (Table 3, entries 4 and 5). Notably, conversion of pyrrole **1g** into amide **13g** occurred in 81% yield, highlighting the viability of unprotected N-heterocyclic substrates (Table 3, entry 6). Treatment of cinnamic acid (**1h**) with **6b** and ClP(pin) provided amide **13h** in excellent yield without formation of the 1,4-adduct that would result from a [3,3]-rearrangement of the intermediate ester azaylide (Table 3, entry 7).[18] Phenyl acetic acid (**1i**) and octanoic acid (**1j**) underwent C–N coupling to

Table 3. Carboxylic acid substrates.[a]



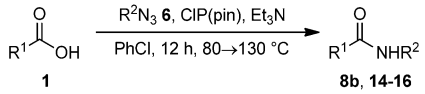
Entry	Carboxylic acid	Product	Yield [%][b]
1	 **1b**	 **13b**	93
2	 **1c**	 **13c**	81
3	 **1d**	 **13d**	96
4	 **1e**	 **13e**	91
5	 **1f**	 **13f**	83
6	 **1g**	 **13g**	81
7	 **1h**	 **13h**	93
8	 **1i**	 **13i**	94
9	 **1j**	 **13j**	91
10[c]	 **1k**	 **13k**	80
11	 **1l**	 **13l**	56[c]

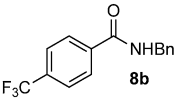
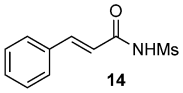
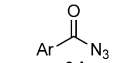
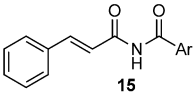
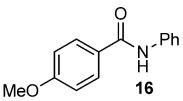
[a] Reactions conducted by using TsN_3 (**6b**; 0.3 mmol), **1** (0.39 mmol), ClP(pin) (0.39 mmol), and Et_3N (0.39 mmol) in PhCl (0.2 M; see the Supporting Information for details). [b] Isolated yield. [c] This reaction employed NaH in place of Et_3N.

give amides **13i** and **13j** in 94 and 91% yield, respectively (Table 3, entries 8 and 9). The amidation reaction also proved tolerant of sterically encumbered α-substituted aliphatic acids. The presence of cyclohexyl and *tert*-butyl substitution in acids **1k** and **1l** did not hinder acyl substitution, providing amides **13k** and **13l** in 80 and 56% yield, respectively (Table 3, entries 10 and 11). Additionally, the efficient conversion of pivalic acid **1l** into amide **13l** indicates that the reaction does not proceed through a ketene intermediate.[19]

With the reaction scope towards substituted carboxylic acids established, we focused our attention on the variability of the azide component (Table 4). Consistent with our earlier observations by using anisic acid **1a**, BnN_3 (**6a**) reacted smoothly with electron-deficient benzoic acid derivative **1c** and ClP(pin) to provide amide **8b** in 85% yield (Table 4, entry 1). The more reactive MsN_3 (**6c**) compared favorably with TsN_3 (**6a**), as demonstrated by the formation of amide **14** in 76% yield upon treatment with cinnamic acid **1h** (Table 4, entry 2). Given the notable instability of acyl azides,[20] we were pleased to discover that treatment of benzoyl azide **6d** with acid **1h** provided imide **15** in 77% yield (Table 4, entry 3). In addition, phenyl azide (**6e**) reacted smoothly with acid **1a** and ClP(pin) to yield acylated aniline **16** in 89% yield (Table 4, entry 4). This result highlights the utility of this approach as a complementary method for the synthesis of protected anilines, which are a prevalent structural motif in biologically active natural products and pharmaceutical targets.[21] The results presented in Tables 3 and 4 highlight the versatility of this carboxylic acid ligation strategy in the context of a diversity-oriented approach to the construction of amide derivatives by using widely available carboxylic acids and functionally diverse azides.

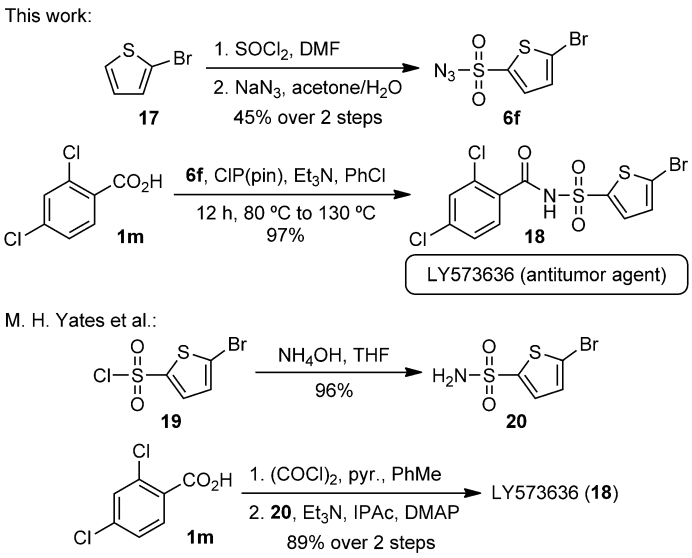
Table 4. Azide substrates.[a]



Entry	Azide	Acid	Product	Yield [%][b]
1	 **6a**	**1c**	 **8b**	85
2	 **6c**	**1h**	 **14**	76
3[c]	 **6d** Ar = *p*-$MeOC_6H_4$	**1h**	 **15** Ar = *p*-$MeOC_6H_4$	77
4	 **6e**	**1a**	 **16**	89

[a] Reactions conducted by using azide **6** (0.3 mmol), **1** (0.39 mmol), ClP(pin) (0.39 mmol), and Et_3N (0.39 mmol) in PhCl (0.2 M; see the Supporting Information for details). Ms = methanesulfonyl. [b] Isolated yield. [c] This reaction employed NaH in place of Et_3N and was run at 80 °C.

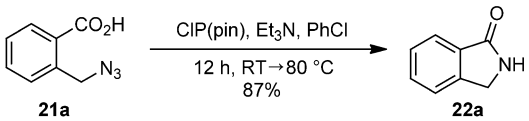
To evaluate the utility of our modified Staudinger ligation in the synthesis of chemotherapeutic agents, we targeted the sulfonamide linkage in the antitumor agent LY573636 (**18**; Scheme 3).[22] Synthesis of azide **6f** was achieved in 45% yield over two steps by sulfonylation of bromothiophene **17**[23] followed by addition of NaN_3. Treatment of carboxylic



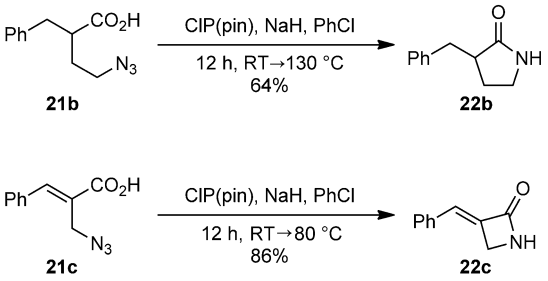
Scheme 3. Synthesis of antitumor agent LY573636. pyr. = pyridine, IPAc = isopropyl acetate.

acid **1m** and azide **6f** with ClP(pin) and Et_3N in PhCl provided LY573636 (**18**) in 97% yield. Our three-step protocol compares favorably to the four-step synthesis of **18** reported by Yates and co-workers in which the crucial amide linkage was constructed by using either CDI or via the acid chloride of **1m**. This efficient and chemoselective route for the synthesis of heterocyclic sulfonamides is ideal for the rapid synthesis and screening of sulfonamide-containing biologically active molecules.[24]

Application to lactam formation: Given the pervasiveness of the lactam motif in chemotherapeutics,[25] and the critical role lactamization reactions play in the construction of biologically active natural products,[26] we chose to assess our method in the context of direct intramolecular coupling of carboxylic acids and azides. Thus, treatment of carboxylic acid **21a**, containing a pendant benzyl azide, with ClP(pin) and Et_3N led to an excellent yield (87%) of lactam **22a** [Eq. (4)]. Likewise, the acyclic azido acid **21b** also underwent intramolecular amidation to give lactam **22b** in 64% yield [Eq. (5)]. The use of NaH in lieu of Et_3N led to a slightly cleaner conversion of acid **21b** into amide **22b** in this instance. Shortening the carbon chain to access β-lactams did not hinder the cyclization, as illustrated by the conversion of **21c** into β-lactam **22c** in 86% yield [Eq. (6)].[27] Again, NaH proved superior to Et_3N for the conversion of azide **21c** into lactam **22c**. Considering the role β-lactams play in the design of new antibiotic treatments, we were



(4)



(5)

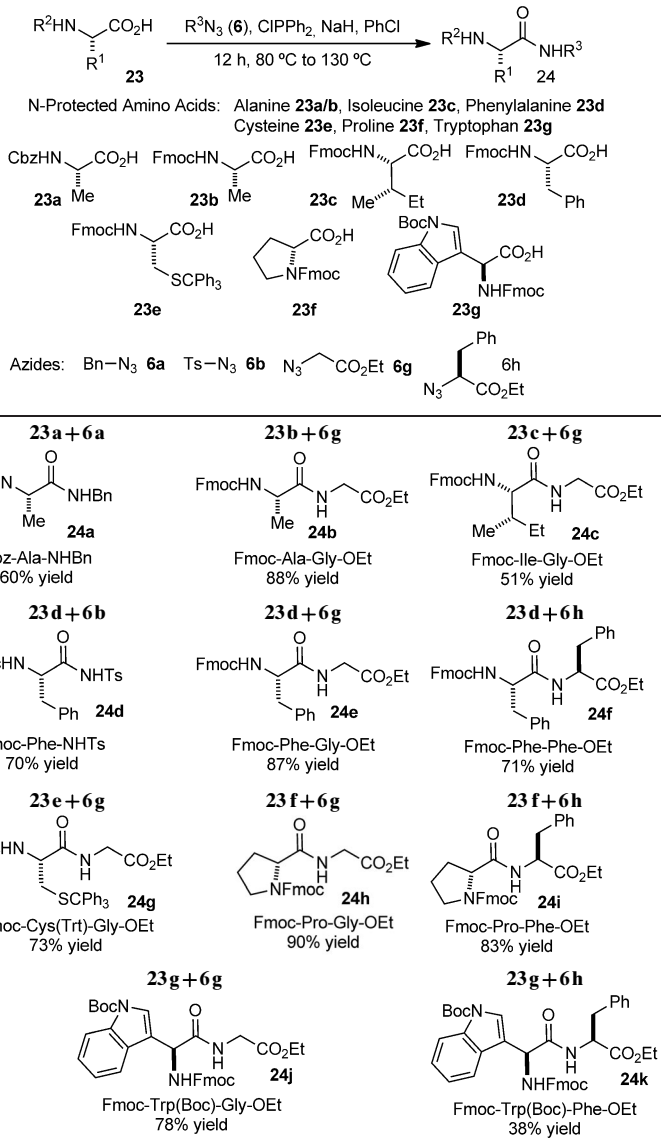
(6)

pleased to see that the formation of such strained heterocycles occurred with ease by employing this method.

Peptide bond formation reactions: Recently, the Staudinger ligation has arisen as a powerful alternative to the "native chemical ligation" approach to peptide fragments[28] that addresses the inherent limitations associated with the need for a cysteine residue at the site of elaboration.[29] To evaluate our method for the derivatization of amino acids and the construction of optically active dipeptides, we assembled a collection of N-protected amino acids **23** and examined their ligation with functionalized azides **6** (Table 5). In general, we discovered that the desired dipeptides were obtained in slightly better yields by employing $ClPPh_2$ than with ClP(pin). It is important to note that the diphenylphosphinic acid generated is easily removed through an aqueous workup. Treatment of Cbz- and Fmoc-protected alanine (**23a** and **23b**) with BnN_3 (**6a**) and the azido ester derivative of glycine **6g** provided amide **24a** and dipeptide **24b** in 60 and 88% yields, respectively. Importantly, C–N bond formation proceeded without loss of optical purity, as determined by comparing the optical rotations of **24a** and **24b** to literature values.[30]

Additional substitution on the amino acid side chain did not adversely affect the amidation reaction, as illustrated by the coupling of Fmoc-protected isoleucine **23c** with azido glycine **6g** to yield dipeptide **24c** in 51% yield. N-Protected phenylalanine **23d** underwent coupling with azides **6b** and **6g** to provide amides **24d** and **24e** in excellent yields. Treatment of **23d** with azido phenylalanine ethyl ester **6h** provided dipeptide **24f** in 71% yield as a single diastereomer and without loss of optical purity. Interestingly, the trityl sulfide in Fmoc-cysteine **23e** did not hinder the formation of dipeptide **24g**, which proceeded in 73% yield.[31] Furthermore, coupling of Fmoc-protected proline **23f** with azido glycine **6g** and phenylalanine **6h** proceeded in excellent yields to give dipeptides **24h** and **24i** in 90 and 83% yield, respectively. As in the formation of dipeptide **24f**, **24i** was obtained as a single, optically active diastereomer. Treatment of the N,N-diprotected tryptophan with azido glycine **6g** provided dipeptide **24j** in 78% yield. Employing the azido ester derivative of phenylalanine (**6h**) led to a modest decrease in yield of the fully protected Trp-Phe dipeptide **24k**, which was formed as a single diastereomer. In each case, C–N bond formation gave the optically active amide, providing

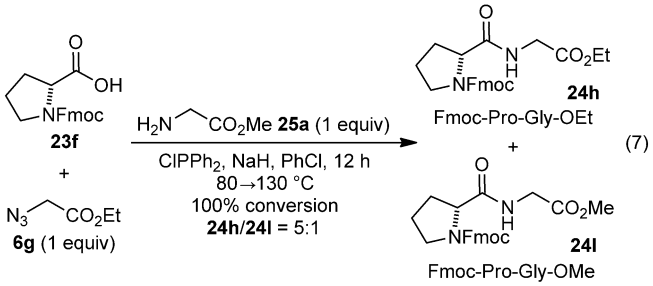
Table 5. Synthesis of peptide bonds.[a]

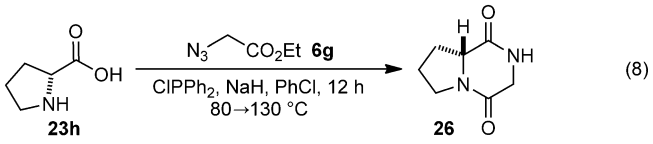


[a] Reactions conducted by using azide **6** (0.3 mmol), **23** (0.39 mmol), $ClPPh_2$ (0.39 mmol), and NaH (0.39 mmol) in PhCl (0.2 M; see the Supporting Information for details). Cbz = carbobenzyloxy, Fmoc = 9-fluoromethyloxycarbonyl.

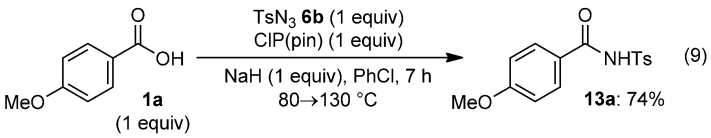
additional evidence that the reaction does not proceed through a ketene intermediate.[19]

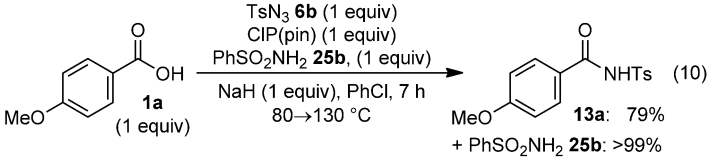
Chemoselectivity for azides: The chemoselectivity in nucleophilic acyl substitution reactions is an important consideration in the synthesis of complex targets.[13a,32] The acyl migration from a putative ester azaylide intermediate outlined herein was designed to tolerate the presence of unprotected electrophilic and nucleophilic functionality, while chemoselectively unmasking the latent nucleophilicity of the azide and electrophilicity of the carboxylic acid. To evaluate azide chemoselectivity, we treated Fmoc-Pro **23f** with azido glycine **6g**, NaH, $ClPPh_2$, and 1 equivalent of methyl glycine **25a** [Eq. (7)]. Amide **24h**, resulting from intramolecular ligation involving azide **6g**, was obtained in a 5:1 ratio with amide **24l**, arising from an acyl substitution of the phosphite ester with amine **25a**. The preference for azide ligation is comparable to that observed by Raines in the competitive ligation of thioeseters (azide/amine = 3:1).[13d] Based on the chemoselectivity for azide **6g** over amine **25a** in the ligation of acid **23f**, we speculated that this phosphite-mediated acyl substitution strategy would enable the peptide coupling of N-unprotected amino acids. Thus, treatment of proline (**23h**) with NaH, $ClPPh_2$, and azido glycine ester **6g** led to formation of the crucial peptide bond en route to the observed cyclic dipeptide **26**, which was formed in 62% yield [Eq. (8)]. The opportunity to avoid additional protection and deprotection steps in peptide synthesis, which is standard in conventional amino acid coupling strategies,[33] constitutes a significant advance in amide construction.



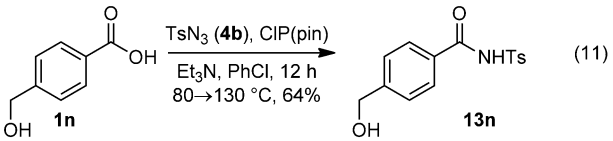


Azide chemoselectivity for sulfonyl azides was evaluated in a head-to-head competition experiment involving a sulfonamide additive. Treatment of 1 equivalent of acid **1a** with 1 equivalent each of TsN_3, ClP(pin), and NaH provided tosyl amide **13a** in 74% yield [Eq. (9)]. When the reaction was performed in the presence of benzene sulfonamide **25b** (1 equiv), amide **13a** was produced in 79% yield, while **25b** was recovered quantitatively [Eq. (10)].

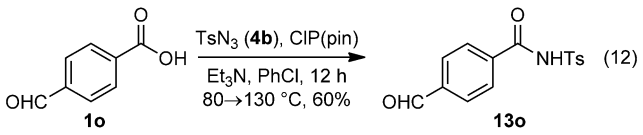




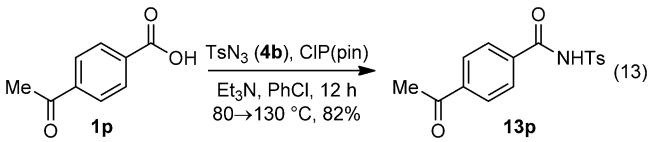
Chemoselectivity for carboxylic acids: The presence of other electrophilic carbonyl derivatives and nucleophilic heteroatoms presents additional challenges to Staudinger ligations involving an activated carboxylic acid and nucleophilic azide. However, the unprotected hydroxyl group in benzoic acid **1n** did not hinder formation of amide **13n**, which proceeded in 64% yield without competitive intermolecular esterification or anhydride formation from the intermediate ester phosphite [Eq. (11)].[5b] More electrophilic carbonyl derivatives also survived the C–N coupling event, as illustrated by the conversion of *para*-formyl benzoic acid **1o** into amide **13o** in 60% yield and acetophenone-substituted acid **1p** into amide **13p** in 82% yield [Eqs. (12) and (13)]. Interestingly, neither the Schmidt rearrangement products, resulting from addition of azide to the electrophilic ketone and aldehyde,[34] nor imines, due to competitive aza-Wittig reactions involving the intermediate azaylide, were observed.[35] In contrast, the addition of BnN_3 (**6a**) and chlorophosphite to benzoic acid derivative **1q**, containing a benzophenone at the *ortho*-position, proved problematic, leading to a low yield of the corresponding amide **8d** [Eq. (14)]. The ligation of **1q** resulted in a mixture of unidentifiable side products, likely resulting from side reactions involving attack of the neighboring carbonyl on the intermediate ester phosphite.



(11)



(12)



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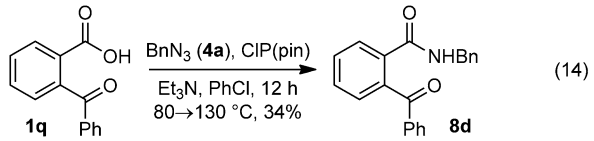
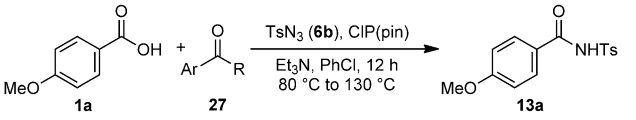
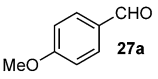
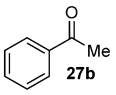
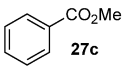


(14)

Intermolecular carboxylic acid chemoselectivity in the phosphite-mediated ligation was examined by using a series of competition experiments between carboxylic acid **1a** and a carbonyl additive (Table 6). Treatment of **1a** and **6b** with ClP(pin) and Et_3N in the presence of aldehyde **27a** led to the formation of amide **13a** in 93% yield and 94% of aldehyde **27a** was recovered (Table 6, entry 1). Although a Schmidt rearrangement of aldehyde **27a** with azide **6b** involving hydrogen migration to bolster the yield of **13a** cannot be ruled out, this appears unlikely in light of the findings by Aubé and co-workers, which indicate a migratory preference of carbon over hydrogen in the absence of a Lewis acid, and the efficient amidation of acid **1n** [Eq. (11)].[36] The addition of acetophenone (**27b**) or methyl benzoate (**27c**) to the reaction of acid **1a** with azide **6b** did not adversely affect the yield of amide **13a**, which was obtained in 93 and 92% yield, respectively, with excellent recovery of **27b** and **27c** (Table 6, entries 2 and 3).

Table 6. Carboxylic acid chemoselectivity.[a]

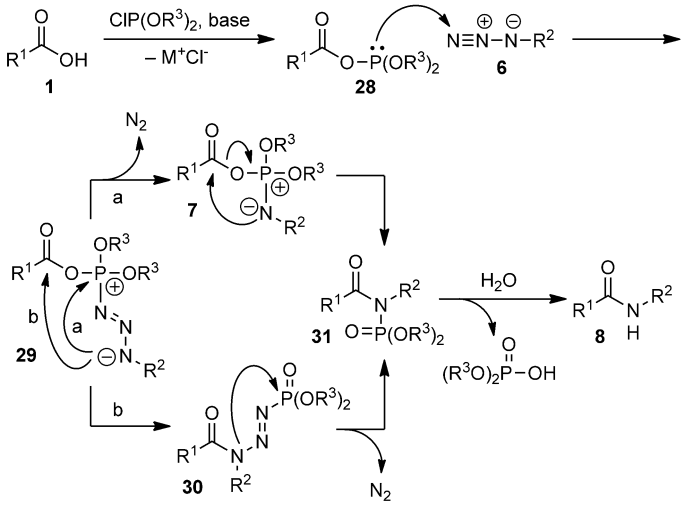


Entry	**18**	Yield of **13a** [%][b]	Recovered **23** [%][b]
1	 **27a**	93	94
2	 **27b**	93	>99
3	 **27c**	92	93

[a] Reactions conducted by using azide **4b** (0.3 mmol), **1a** (0.30 mmol), **27** (0.30 mmol), ClP(pin) (0.30 mmol), and Et_3N (0.30 mmol) in PhCl (0.2 M; see the Supporting Information for details). [b] Isolated yield.

Mechanism of the chlorophosphite and chlorophosphine-mediated Staudinger ligation: A distinct advantage of the amidation protocol described herein is the ability to conduct the acyl substitution of carboxylic acids directly without the product-isolation complications common to conventional dehydration methods. Specifically, the chloride anion (e.g., $Et_3N{\cdot}HCl$ or NaCl) and phosphoric acid byproducts, as well as any unreacted carboxylic acid, are readily removed from the crude reaction mixture through a simple aqueous workup.[30] Unlike other Staudinger ligation methods involving phosphines, the pre-ligation of carboxylic acids directly to phosphorus results in some intriguing mechanistic questions, as well as enhancing the utility of this versatile C–N bond-forming strategy. Although a more complete mechanistic study of the chlorophosphite-facilitated Staudinger ligation is the focus of our current research efforts, our findings thus far allow us to draw some preliminary mechanistic conclusions.

Based on the findings by the groups of Bertozzi and Bergman,[14] and independently by the Raines group,[13d] involving esters and thioesters, respectively, our working hypothesis involves initial addition of carboxylic acid **1** to the chlorophosphite (Scheme 4). The formation of ester phosphite **28** is key to the observed reactivity and high levels of chemose-



Scheme 4. Possible mechanistic pathways.

lectivity in the direct nucleophilic acyl substitution of acid **1**, and is consistent with the observed precipitation of either $Et_3N{\cdot}HCl$ or NaCl in the presence of Et_3N or NaH, respectively. Additionally, it is important to note that the omission of chlorophosphite led to quantitative recovery of carboxylic acid **1a** and azide **6a**. Upon addition of the electron-deficient phosphite to azide **6**, the generation of phosphazide **29** concomitantly activates both the carboxylic acid and the azide motifs for the incipient acyl substitution event. One possible acyl substitution pathway involves N_2 evolution to provide ester azaylide **7**, which then undergoes [1,3]-acyl migration to the basic ylide nitrogen (path a).[37] The elevated temperatures required for C–N bond formation would indicate a high-energy transition state consistent with the 4-*exo-trig* cyclization for the formation of phosphorimide **31**, in spite of being driven by formation of a strong P=O bond.[38] Alternatively, one can envisage a reaction pathway in which azaylide formation is slow relative to cyclization (path b); thus a six-membered transition state would provide the acyl phosphoryl triazene **30** without N_2 evolution, leading to **31**.[39] Dephosphorylation under the reaction conditions yields the observed amide **8**. Although it is unclear at present whether acyl substitution is occurring via the ester azaylide **7** or directly from phosphazide **29**, it is conceivable that both pathways operate under the reaction conditions, and this is the subject of current investigations.

Although a mechanism involving intermolecular azaylide addition to ester phosphite **27** or a ketene cannot be ruled out completely, this pathway appears unlikely based on the lack of crossover carbonyl byproducts observed from the reactions of substrates containing nucleophilic functional groups. The exceptional chemoselectivity for carboxylic acid and azide functional groups observed in our study is likely a direct result of the initial O–P bond formation in ester phosphite **28** that precedes acyl migration, resulting in an overall dual activation of the targeted functional groups by phosphorus.

Effect of solvent and phosphite ligation: Drawing comparisons to the aforementioned mechanistic studies on the Staudinger ligation by the groups of Bertozzi/Bergman,[14] and Raines,[13d] a number of empirical observations that support our mechanistic hypothesis are worth noting. During our initial optimization of the phosphite-mediated Staudinger ligation, we speculated that the yield of amide **8a** would improve if intermediates **29** and **7** were stabilized by the use of more polar solvents. Our finding that PhCl (40% yield) proved superior to PhMe (16% yield) in the formation of amide **8a** supports the involvement of a polar intermediate, and is consistent with Bertozzi's and Raines' findings (Table 1). However, the boiling point of the solvent also proved crucial, with more polar solvents, such as THF, MeCN, DMF, DMSO, and 1,4-dioxane, failing to provide amide **8a** in greater than 26% yield.[13d] This is likely due to the inability of these solvents to reach the elevated temperatures necessary to effect a [1,3]-acyl migration.[38]

A previously under-explored aspect of the Staudinger ligation pertains to the geometry around phosphorus, as influenced by the monodentate or bidentate ligand scaffolds.[17–18] Employing a series of different phosphites in the ligation of acid **1a** and azide **6b** reveals an intriguing correlation between the bite angle at phosphorus and the yield of amide **13a** (Table 2). Superior yields were obtained with chlorophosphites containing diol ligands that form five- and six-membered-ring chelates. The improved reaction efficiency in going from $ClP(OEt)_2$ and ClP(bin) to ClP(pin) indicates that the decreased bite angle at phosphorus promotes azaylide formation through improved lone-pair accessibility.[40]

Conclusion

The present method allows for ready access to a diverse assortment of amides through the direct functionalization of carboxylic acids and azides by using a chlorophosphite as a dual activating agent. This procedure complements current amide-bond-forming technology by virtue of the highly chemoselective intramolecular acyl-migration event, and simplified product isolation due to the aqueous solubility of the byproducts generated. The bimodal reactivity of phosphite to unmask the latent electrophilicity of carboxylic acids and nucleophilicity of azides in a controlled fashion is directly applicable to the assembly of biologically active natural products and synthetic targets containing amides, lactams, and peptide linkages. The use of this reaction in total synthesis is currently being pursued, and will be reported in due course.

Experimental Section

Representative procedure for the phosphite-mediated Staudinger-like ligation: Et_3N (0.39 mmol, 1.3 equiv) was added to a solution of carboxylic acid **1** (0.39 mmol, 1.3 equiv) in chlorobenzene (1 mL) at room temperature. This mixture was then cooled to 0 °C and ClP(pin) (0.39 mmol,

1.3 equiv) was added in one portion with rapid stirring. The resulting slurry was allowed to warm slowly to room temperature. This was followed by addition of a solution of the azide (0.30 mmol, 1 equiv) in chlorobenzene (0.3 mL). The mixture was stirred for 1 h, heated to 80 °C and stirred for an additional 2 h, heated to 130 °C and stirred until complete consumption of the starting materials was observed by TLC (ca. 10 h). The solution was diluted with EtOAc (5 mL) and saturated aqueous $NaHCO_3$ (10 mL), extracted with EtOAc (3×10 mL), dried ($MgSO_4$), and concentrated under reduced pressure to provide the corresponding amide in $>90\%$ purity.

Acknowledgements

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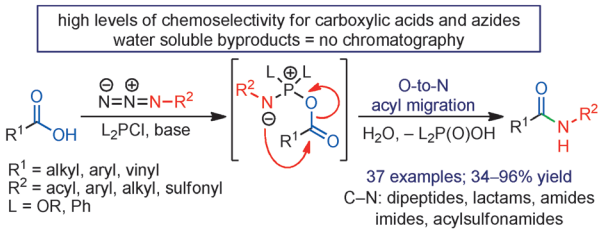

Turning the peptide with azides: A modified Staudinger-like acylation of azides involving a highly chemoselective, direct acyl substitution of carboxylic acids is described. Structurally diverse amides are obtained after a simple aqueous workup (see scheme). The use of chlorophosphites as dual carboxylic acid–azide activating agents enables the formation of acyl C–N bonds in the presence of a wide range of nucleophilic and electrophilic functional groups.

Acyl Substitution

*A. D. Kosal, E. E. Wilson, B. L. Ashfeld** ..... ▮▮▮▮–▮▮▮▮

Direct Acyl Substitution of Carboxylic Acids: A Chemoselective O- to N-Acyl Migration in the Traceless Staudinger Ligation