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Synthetic Methods

Amine-Free Approach toward *N*-Toluenesulfonyl Amidine Construction: A Phosphite-Mediated Beckmann-Like Coupling of Oximes and *p*-Toluenesulfonyl Azide**

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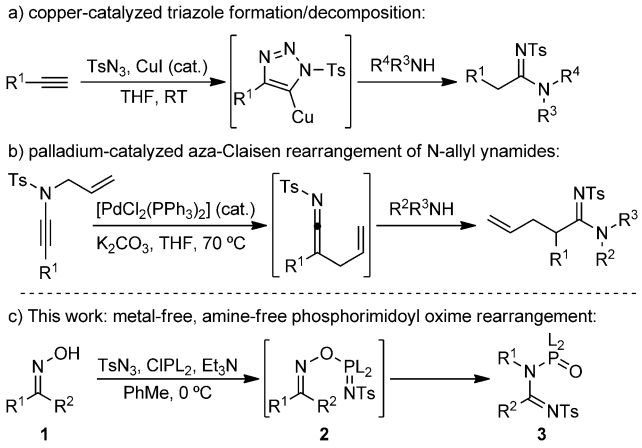
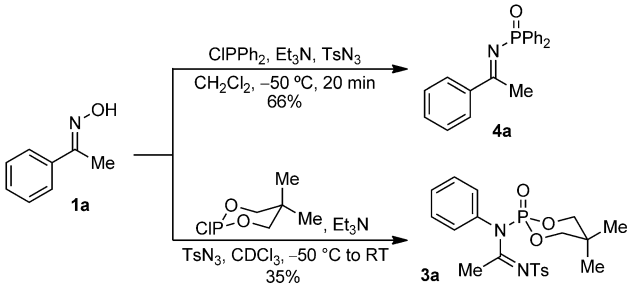
Amidines constitute one of the most prolific and versatile functional groups in organic synthesis. In recent years they have become a common synthetic building block in heterocycle construction[1] and the synthesis of biologically active natural products.[2] They also have emerged as a key functional group in pharmaceutical drug design.[3] Despite their growing biological significance,[4] the use of amidines as bioorthogonal chemical reporters is notably absent.[5] This is likely attributable to the central tenet in reaction design for amidine synthesis as it involves addition of an amine to an activated acyl equivalent.[6] For example, a recent report by Chang and co-workers describes a triazole decomposition strategy resulting in an innovative three-component coupling of an alkyne, sulfonyl azide, and an amine (Scheme 1a).[7] Additionally, Hsung and co-workers employed a remarkable palladium(II)-catalyzed sulfonyl ynamide rearrangement in the presence of an amine to provide *N*-sulfonyl amidines (Scheme 1b).[8] In contrast, we sought to develop a mild and diversifiable route which avoids the direct use of amines and transition-metal catalysts while providing the corresponding *N*-sulfonyl amidines without the need for chromatographic purification.



Scheme 1. Construction of *N*-toluenesulfonyl amidines. THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.

Despite the fact that the Beckmann rearrangement is highly useful for constructing amides,[9] the analogous approach toward amidines by trapping the intermediate nitrilium with a primary amine was found to proceed at best in poor yield.[10] Given our recent work on phosphorus-mediated C–N bond construction,[11] we envisioned a solution to this challenge in amidine construction which involves the coupling of the oxime **1** and TsN_3 to yield the amidine **3** via iminophosphorane **2** (Scheme 1c).[12] The strong driving force of P=O bond formation and preorganization of each component in **2** results in a mild, chemoselective Beckmann-like ligation event.[13] This amine-free approach toward amidine synthesis effectively exploits the bioorthogonal reactivity of azides.[14]

To evaluate our approach toward amidine construction we began with the treatment of oxime **1a** and TsN_3 with $ClPPh_2$ and Et_3N (Scheme 2). However, these reaction conditions



Scheme 2. Phosphinamide versus amidine formation.

failed to provide the desired amidine leading only to the formation of phosphinamide **4a**, presumably resulting from rearrangement of the intermediate phosphinite, in 66% yield even at temperatures as low as –50 °C.[15] Speculating that electron-withdrawing ligands on phosphorus would decrease the rate of O-to-N migration, we chose to examine the use of a chlorophosphite in place of chlorophosphine.[16] Gratifyingly, the addition of 3,3-dimethylpropanediol chlorophos-

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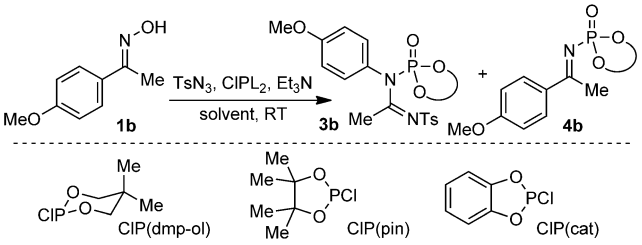
phite [ClP(dmp-ol)] gave the amidine **3a** in 35% yield while concurrently suppressing conversion into the corresponding phosphoramidate **4a**. To the best of our knowledge, this constitutes the first approach toward acyclic amidine C–N bond construction, which avoids the direct use of nucleophilic amines.

Anticipating that an oxime with electron-rich aryl substituents would undergo a more facile rearrangement, we began a systematic evaluation of the reaction conditions in an attempt to optimize the yield of amidine **3b** (Table 1).

Table 1: Optimization of reaction conditions.[a]

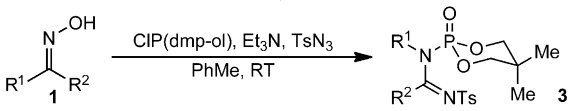


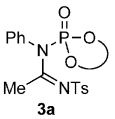
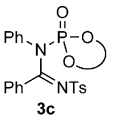
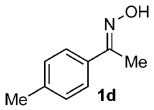
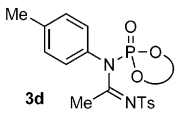
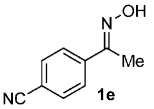
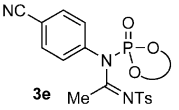
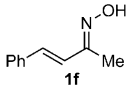
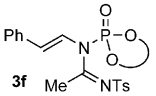
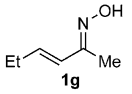
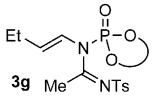
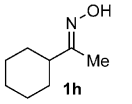
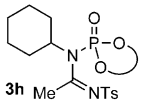
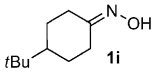
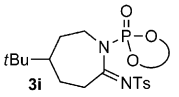
Entry	$ClPL_2$	Solvent	**3b** yield [%][b]	**4b** yield [%][c]
1	ClP(dmp-ol)	PhH	51	0
2	ClP(dmp-ol)	PhMe	98	0
3	ClP(dmp-ol)	PhCl	76	0
4	ClP(dmp-ol)	Et_2O	77	0
5	ClP(dmp-ol)	1,4-dioxane	64	0
6	ClP(dmp-ol)	DMF	0	0
7	ClP(pin)	PhMe	25	55
8	ClP(cat)	PhMe	0	86
9	$ClP(OEt)_2$	PhMe	0	>95

[a] Reaction conditions: 0.3 mmol of **1b**, 0.3 mmol of Et_3N, 0.3 mmol of $ClPL_2$, and 0.3 mmol of TsN_3 at 0.2 M. [b] Yield of isolated product. [c] Quantitative recovery of **1b** observed. DMF = *N*,*N*′-dimethylformamide.

Performing the reaction in PhH provided **3b** in 51% yield, whose structure was verified by single-crystal X-ray diffraction,[17] while PhMe and PhCl gave **3b** in 98% and 76% yield, respectively (entries 1–3). Although ethereal solvents were effective, they proved inferior to PhMe (Table 1, entries 4 and 5). Interestingly, performing the reaction in DMF led only to recovered **1b** (Table 1, entry 6). In addition, the efficiency of the ligation was highly dependent on the chlorophosphite reagent employed. Although ClP(dmp-ol) minimized the rearrangement of **1b** into phosphinite **4b**, in contrast to $ClPPh_2$, pinacol chlorophosphite [ClP(pin)] yielded a 1:2.2 mixture of **3b** and **4b** (Table 1, entry 7). Employing the catechol-derived chlorophosphite [ClP(cat)] or $ClP(OEt)_2$ gave exclusively the undesired **4b** (Table 1, entries 8 and 9). The faster rate of **4b** formation with ClP(pin) and ClP(cat) is likely due to a more facile oxidative rearrangement at phosphorus with the smaller strained ring, and greater lone-pair accessibility, in contrast to ClP(dmp-ol). With our optimized reaction conditions identified, we turned our attention toward evaluating various structural elements of the oxime component.

Table 2: Oxime structural variability.[a]



Entry	Oxime **1**	Amidine **3**	Yield [%][b]
1	 **1a**	 **3a**	95
2	 **1c**	 **3c**	99
3	 **1d**	 **3d**	98
4[c]	 **1e**	 **3e**	26
5	 **1f**	 **3f**	99
6[d]	 **1g**	 **3g**	71
7	 **1h**	 **3h**	64
8	 **1i**	 **3i**	72

[a] Reaction conditions: 0.3 mmol of **1**, 0.3 mmol of ClP(dmp-ol), 0.3 mmol of Et_3N, and 0.3 mmol of TsN_3 in PhMe (0.2 M). [b] Yield of isolated product. [c] Reaction performed at 100 °C in 1,4-dioxane for 2 h. [d] Reaction performed using iPr_2NEt in PhCl at 60 °C for 30 min.

In general, good to excellent yields of the amidine **3** were obtained upon ligation of oxime **1** and TsN_3 with ClP(dmp-ol) and Et_3N in PhMe at 0 °C (Table 2). The conversion of the aryl oximes **1a**, **1c**, and **1d** proceeded smoothly to give the corresponding amidines in 95–99% yield (Table 2, entries 1–3). The electron-deficient aryl oxime **1e** gave **3e** in lower yield than its electron-rich counterparts (Table 2, entry 4). The diminished yield for this substrate is likely a consequence of undesired side-product formation due to the elevated temperatures required for full oxime conversion. The α,β-unsaturated oximes **1f** and **1g** gave enamines **3f** and **3g**, respectively, which resulted from vinyl migration, in excellent yields (Table 2, entries 5 and 6). Secondary alkyl groups also underwent facile ligation to afford *N*-sulfonyl amidines, as illustrated by the conversion of **1h** into amidine **3h** in 64% yield (Table 2, entry 7). Additionally, the cyclic oxime **1i** underwent ring expansion to give the phosphazepanylidene **3i** in 72% yield (Table 2, entry 8). While more reactive electron-

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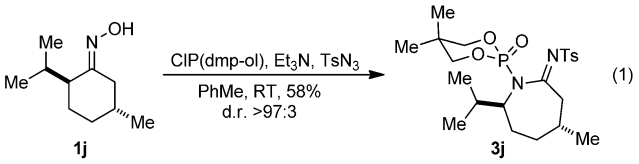
deficient azides (e.g., MsN_3, $CbzN_3$) were also effective at providing the corresponding amidines, yields were generally lower (ca. 20%) than that observed with TsN_3. Not surprisingly, non-stabilized azides (e.g., BnN_3) led to exclusive isolation of rearranged phosphinite as a result of the higher temperatures required for phosphazene generation. The formation of the amidines **3** depicted in Table 2 is consistent with a Beckmann-like ligation in which the *anti*-periplanar oxime substituent migrates preferentially.

To gain insight into the stereochemical outcome of the migration event, we chose to evaluate our phosphite-mediated ligation approach using the α-chiral menthone-derived oxime **1j** [Eq. (1)]. Exposure of **1j** and TsN_3 to ClP(dmp-ol)

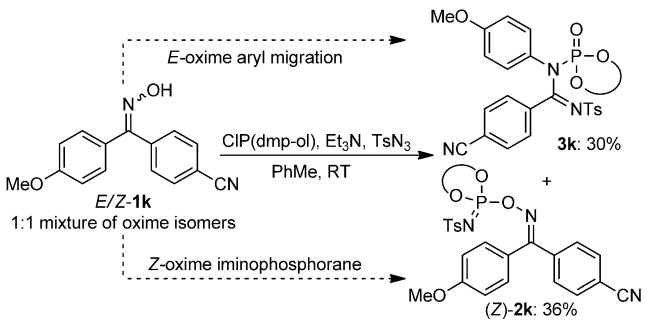


(1)

and Et_3N in PhMe at 0 °C yielded the *N*-sulfonyl phosphoramidine **3j** in 58% yield as a single regio- and stereoisomer.[18] It is important to note that under the reaction conditions, α epimerization of the chiral oxime is not observed, and the retention of absolute configuration at the site of migration is consistent with a concerted [1,2] shift.

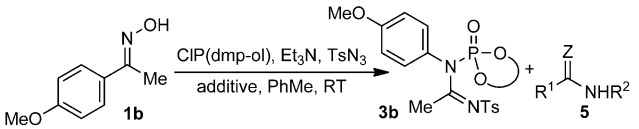
While our results point to a distinct steric influence on the migratory preference of oxime substituents, the relative reactivity of electron-rich and electron-deficient aryl oximes suggest that electronic factors may also impact the rate of rearrangement. Speculating that we could exploit this disparate reactivity to kinetically resolve a mixture of oxime isomers bearing electronically dissimilar, yet sterically congruent substituents, we examined the oxime **1k** as a 1:1 *E*/*Z* mixture of isomers in our azide ligation approach toward amidines. Exposure to our optimized reaction conditions led exclusively to migration of the more electron-rich *anti*-periplanar aryl ring to give the amidine **3k** in 30% yield (Scheme 3). The corresponding *Z*-oxime isomer proceeded no further than azide reduction to give the iminophosphorane (*Z*)-**2k** in 36% yield.[19]

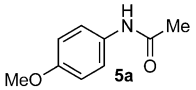
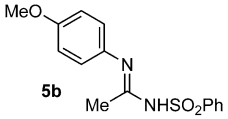
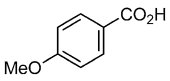
In an effort to evaluate azide chemoselectivity we examined the ligation event in the presence of an added



Scheme 3. Kinetic resolution of oxime isomers.

Table 3: Oxime and azide chemoselectivity.[a]



Entry	Additive	5	3b yield [%][b]	3b/5[c]
1	H_2O		49	4:1[c]
2	$PhSO_2NH_2$		85	>99:1[d]
3		**5a**	40	3:1[c]

[a] Reaction conditions: 0.3 mmol of **1b**, 0.3 mmol of ClP(dmp-ol), 0.3 mmol of Et_3N, 0.3 mmol of TsN_3, and 0.3 mmol of additive in PhMe (0.2 M). [b] Yield of isolated product. [c] Ratio determined by ^1H NMR (600 MHz) spectroscopy. [d] Ratio determined by HPLC.

nucleophile (Table 3). Treatment of **1b** and TsN_3 with ClP(dmp-ol), Et_3N, and H_2O (1 equiv) led to the formation of **3b** and **5** in a ratio of 4:1 (Table 3, entry 1). It is unlikely that **5** is generated by in situ amidine hydrolysis as independent treatment of **3b** under the reaction conditions led solely to recovered amidine. The presence of H_2O also resulted in a less efficient ligation, thus giving **3b** in only 49% yield. However, the addition of $PhSO_2NH_2$ yielded exclusively the azide ligation product **3b** in 85% yield (Table 3, entry 2). Performing the reaction in the presence of *p*-methoxybenzoic acid did not lead to sulfonyl imide formation consistent with our recently reported chlorophosphite-mediated Staudinger-like ligation (Table 3, entry 3).[11b] However, **3b** and **5a**, likely arising from carboxylic acid addition to a nitrilium cation intermediate and subsequent hydrolysis, were obtained in a 3:1 ratio. Our observation that the addition of a radical inhibitor did not hinder the formation of **3b** would indicate a non-radical mechanism.[17] While these results demonstrate a distinct preference for azide ligation indicative of an intermediate iminophosphorane (**2**), C–N bond formation likely occurs through a polar intermolecular process.[20]

To verify the intermediacy of **2** we again exploited the tempered reactivity of the electron-deficient aryl oxime **1l** in the isolation of phosphazene **2l** (Scheme 4). Treatment of **1l** with ClP(dmp-ol), Et_3N, and TsN_3 at room temperature for 30 minutes gave **2l** in 85% yield as a free-flowing solid whose structure was unequivocally ascertained by single-crystal X-ray diffraction.[17] Monitoring of the reaction over time showed the appearance and subsequent disappearance of **2l** en route to **3l** in 40% overall yield. This observation provides compelling evidence that **2l** is a chemically and kinetically viable intermediate under the reaction conditions.[17]

Based on these composite results, our working mechanistic hypothesis involves initial phosphinylation of the oxime **1** and subsequent Staudinger-like reduction of TsN_3 to give iminophosphorane **2** (Scheme 5). A stereo- and regioselective

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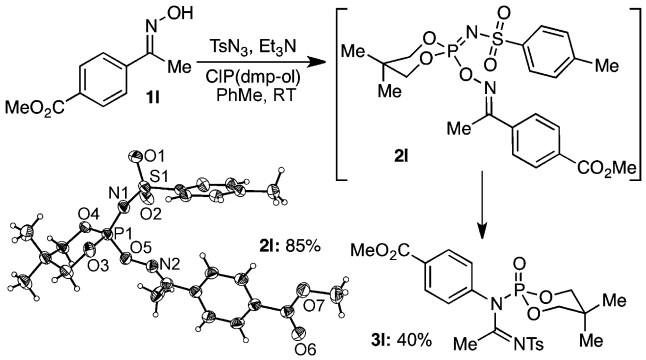
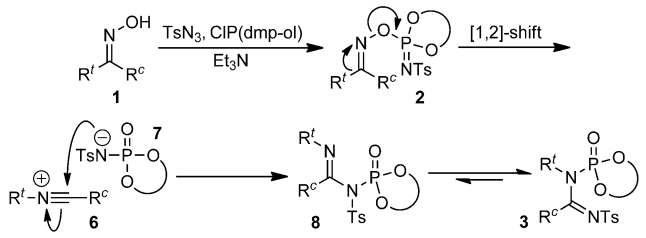


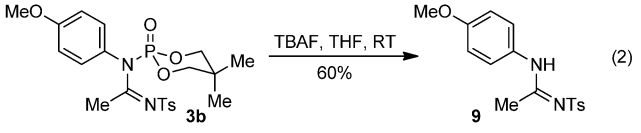
Scheme 4. Evidence for the iminophosphorane **2**. Thermal ellipsoids shown at 50% probability.



Scheme 5. Working mechanistic hypothesis.

[1,2] migration of the *trans* oxime substituent leads to the formation of an ion pair consisting of the nitrilium ion **6** and anionic phosphoramide **7**. Formation of the strong P=O bond in **7** likely serves as a driving force responsible for the mild reaction conditions. Finally, quenching of **6** yields amidine **8**, which after undergoing a 1,3-phosphoryl shift provides the observed amidine **3**. This mechanism is commensurate with a Beckmann-like ligation event involving a stereospecific [1,2] shift and nitrilium cation capture.

While there are a number of methods for phosphoramidine cleavage, dephosphorylation without amidine hydrolysis represents a significant synthetic challenge. A survey of the literature revealed few methods amenable to phosphoramidine P–N bond cleavage without concomitant hydrolysis of the resulting amidine. Not surprisingly, treatment of **3b** by an assortment of conventional hydrolysis conditions led to complex mixtures with no discernible product formation. Employing Brønsted acids (e.g., HCl)[21] and metal alkoxides (e.g., NaOMe, LiOH)[22] led to amide formation, whereas sodium ethanethiolate[23] provided recovered starting material. However, we discovered that treatment of **3b** with TBAF at room temperature for 3.5 hours afforded the *N*-tosyl amidine **9** in 60% yield [Eq. (2); TBAF = tetra-*n*-butyammonium fluoride].[24] This sequence establishes an effective two-step protocol for the conversion of unsymmetrical oximes into the corresponding dephosphorylated amidines.



(2)

In summary, we have developed a phosphite-mediated Beckmann-like approach toward *N*-toluenesulfonyl amidine construction and that avoids the direct use of amines, harsh reaction conditions, and the need for a metal catalyst. The ligation is mechanistically related to the Beckmann rearrangement in that oxime geometry dictates migratory aptitude and proceeds with retention of absolute configuration. This procedure constitutes a new approach toward amidine construction, and is applicable to the assembly of biologically active natural products and pharmaceutical drug targets. Further mechanistic studies and use of this reaction in total synthesis is underway, and will be reported in due course.

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Keywords: amidines · azides · Beckmann rearrangement · rearrangement · oximes

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