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The Chemistry of Amine−Azide Interconversion: Catalytic Diazotransfer and Regioselective Azide Reduction

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Abstract: Azides have proven to be useful precursors to amines in organic syntheses. This report describes an improvement of the diazotransfer reaction and the first example of a regioselective azide reduction of compounds containing multiple azides. The use of a specific ratio of solvents and zinc chloride as a catalyst resulted in a more efficient diazotransfer reaction capable of delivering >90% conversion per amine with shorter reaction times than those previously reported. Azides can be reduced with good regioselectivity in moderate yields by a modification of the Staudinger reaction using trimethylphosphine at low temperatures. Electronic factors determine the selectivity for azide reduction, and the reaction is predictable by NMR analysis of the starting material. Several examples for the diazotransfer and regioselective azide reduction reactions are given, and a mechanistic hypothesis for both is proposed.

Introduction

The quest to overtake the rate of antibiotic resistance development necessitates the search for new molecules that possess antibiotic activity. One strategy to provide new antibiotics is the modification of existing antibiotics to restore or enhance their activity against resistant strains of bacteria. Aminoglycoside antibiotics have found significant clinical use, but the rapid proliferation of resistance to these compounds has limited their applicability. Previously, synthetic chemists have made modifications of known aminoglycoside antibiotics to fight resistant bacteria.[1,2] The presence of multiple amines, whose high reactivity inhibits selective engagement, however, hampers regioselective aminoglycoside modification. Several methods for protecting unhindered amines have been presented,[3−5] but the search for other methods resulted in an interesting discovery.

The development of new aminoglycosides with antibiotic activity has been an interest in our group for some time, and we have had success using azides as amino protecting groups.[6−10] Azides have several advantages as amino protecting groups over carbamates and amides, including less steric hindrance, greater solubility, and no rotamer formation or hydrogen or carbon nuclei to complicate NMR spectra. Azides, which have proven to be useful precursors for amines in chemical syntheses, can be introduced by displacement of a suitable nucleofuge or direct conversion of an existing amine by a diazotransfer reaction. Furthermore, azides are resistant to many reaction conditions and can be easily reduced to amines either generally (hydrogenation, metal hydrides, etc.) or orthogonally (Staudinger reaction).[11] Azides are especially valuable in carbohydrate chemistry, because azides at the 2 position of glycosyl donors are nonparticipatory, allowing greater α selectivity for glycosylation reactions. In an attempt to explore the possibility of selective reductions of azides, a general and predictable methodology, based on the Staudinger reaction,[12,13] for the reduction of one azide regioselectively in molecules containing multiple azides was discovered. This report describes this new methodology, as well as an improvement of the diazotransfer reaction.

Improvements to the Diazotransfer Reaction

The diazotransfer reaction is ideal for protecting amines in such natural products as aminoglycoside antibiotics, because the transformation from an amine to an azide occurs with retention of configuration.[14−17] Recently, we reported that the addition of a catalytic amount of a transition metal salt greatly

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Table 1. Attempts To Optimize Triflyl Azide Formation

solvent	NaN_3 equiv	temp	PTC[a]	time	yield (%)
CH_2Cl_2/H_2O[b]	5	0 °C	no	0.5 h	62
CH_2Cl_2/H_2O	5	0 °C	no	1 h	68
CH_2Cl_2/H_2O	5	0 °C	no	2 h	72
CH_2Cl_2/H_2O	5	0 °C	no	18 h	42
CH_2Cl_2/H_2O	2	0 °C	no	2 h	63
CH_2Cl_3/H_2O[b]	5	0 °C	no	2 h	68
CH_2Cl_2	5	25 °C	no	18 h	<1
CH_2Cl_2	5	25 °C	yes[c]	18 h	<1
CH_2Cl_2	5	25 °C	yes[d]	15 h	81

[a] Phase-transfer catalyst. [b] 1:1 ratio. [c] Tetrabutylammonium hydrogen sulfate, 5 mol %. [d] 18-Crown-6, 5 mol %.

increased the rate and efficiency of this reaction.[6] However, the procedure was still somewhat unreliable, with highly variable reproducibility. Because of this irreproducibility, an optimization of the diazotransfer reaction conditions was undertaken.

If the diazotransfer reaction was to be improved, the efficiency of trifluoromethanesulfonyl (triflyl) azide formation needed to be tested. However, its inherent explosiveness when dried has made attempts to quantify its formation difficult.[14] Previous attempts to isolate pure triflyl azide by distillation have been reported,[18] but these practices are too dangerous to repeat. Because triflyl azide in solution has never caused a problem in our hands or been reported to be explosive in the literature, ^{19}F NMR was recommended to study the progress and yield of its formation. After workup, the trifluoromethyl group of triflyl azide at δ 75.9 ppm could be clearly distinguished from 2,2,2-trifluoromethylacetophenone (δ −71.9 ppm), which was used as an internal standard for quantitation. As shown in Table 1, variations in temperature, stoichiometry, solvent, and concentration had very little impact on the yield of the reaction. Moving from a water/dichloromethane biphasic mixture to pure dichloromethane solution also failed to improve the yields. The presence or absence of tetrabutylammonium hydrogen sulfate failed to induce significant conversion to triflyl azide. The only productive catalyst was 18-crown-6, which at 5 mol % was capable of complete conversion after 18 h. However, in all of the cases, the isolated yield was 60−80%, regardless of the conditions. The reactions reported herein used 2 equiv of sodium azide, and a conservative yield of 50% was used to determine the necessary conditions.

The ratio of solvent was found to have a dramatic influence on the rate and reproducibility of the reaction. The diazotransfer reaction reported previously used varying ratios of water, methanol, and dichloromethane.[6,8] These solvents become monophasic at an approximate ratio of 1:2.5:1 H_2O/MeOH/CH_2Cl_2, respectively, but a ratio of 3:10:3 minimized precipitation of salts from the reaction. The total volume was determined by the approximate volume of the triflyl azide solution needed for the reaction. Using a standardized solvent system that maximized the concentration decreased the yield variations and increased rates for all of the catalysts. No further optimization of the solvent ratio was attempted but might prove necessary for substrates that exhibit poor solubility in the reaction conditions.

Another area of improvement for the diazotransfer reaction was the choice of transition metal salt catalyst. Previously, copper sulfate was reported to be the preferred catalyst for the reaction, but other metal salts also demonstrated catalytic activity.[6] Experiments showed that, although some metals were capable of rate enhancement, isolated yields and reaction times were catalyst-dependent (see Table 2). Reactions using zinc chloride as the catalyst would generally proceed no more than 2.5 h, whereas reactions employing copper sulfate would require 18 h to complete the reaction. The one exception found for zinc chloride catalysis was with neomycin sulfate, **1a**, where copper sulfate proved to be the better catalyst. Reactions with **1a** using zinc chloride would become cloudy and were not reproducible or efficient. One explanation could have been the in situ formation of zinc sulfate, which has low solubility in alcohols, but this hypothesis was discounted when the hydrochloride salt of neomycin behaved identically to the sulfate salt. It was concluded that this was probably a zinc-neomycin precipitate, and precipitates of neomycin with divalent metal ions have been documented in the literature.[19] These findings suggest that either copper sulfate or zinc chloride is an effective catalyst for the diazotransfer reaction on various substrates, but optimization for solubility may be necessary in some cases.

Regioselective Azide Reduction

In the literature, there are relatively few examples of a regioselective azide reduction. Knouzi and co-workers reported previously that steric hindrance could potentially allow a selective azide reduction in the Staudinger reaction.[20] They found in competitive experiments that the selectivity for azides when using triphenylphosphine was primary > secondary > tertiary. An attempt to selectively reduce the primary azide of **5** led to the discovery of a new regioselective azide reduction (Scheme 1). Compound **5** was prepared from per-azido-per-benzyl neomycin, **4**, by a copper chloride-catalyzed hydrolysis,[21] which represented an improvement over the previously reported methodology.[8] Subjection of **5** to a variant of the Staudinger reaction using trimethylphosphine at low temperatures was envisioned to reduce the more sterically accessible 6′-azide. Surprisingly, the major product of this reaction was not the anticipated compound, but was in fact **6**, the product of reduction at the more hindered 2′-azide. With **5**, triphenylphosphine did not react under similar conditions, and tri-*N*-butylphosphine failed to go to completion.

At first glance, the observed regioselectivity was thought to involve some kind of hydrogen bonding between the Lewis base trimethylphosphine[22] and the unprotected hydroxyl on the adjacent ring. The hydroxyl of **5** was protected as an acetyl ester and methyl ether, but products of their attempted selective azide reductions were too difficult to purify to determine yields accurately. Nonetheless, phosphines are known to reduce azides by nucleophilic attack on the terminal nitrogen of the azide,[12,13] and it was difficult to envision an intermediate that would place the end of the azide in proximity to the phosphine when coordinated to the hydroxyl group.

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(19) Abu-El-Wafa, S. M.; El-Ries, M. A.; Abou-Attia, F. M.; Issa, R. M. *Anal. Lett.* **1989**, *22*, 2703−2716.
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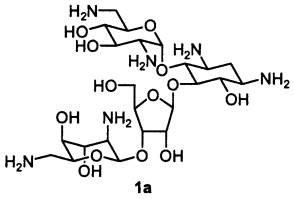
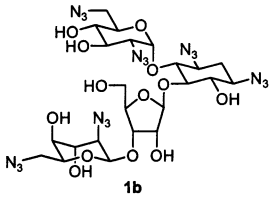
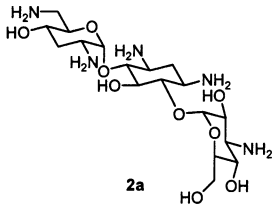
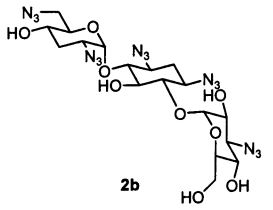
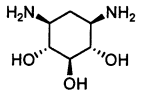
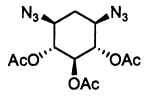
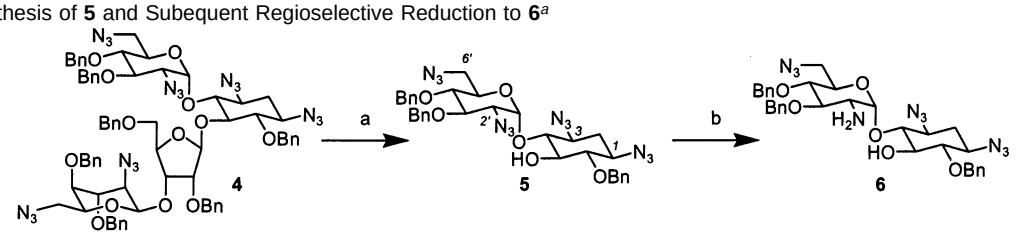
(22) Allman, T.; Goel, R. G. *Can. J. Chem.* **1982**, *60*, 716−722.

Table 2. Diazotransfer Reaction[a]

Substrate	Product	Catalyst	Time	% Yield (per amine)
 **1a**	 **1b**	$CuSO_4$	2.5	64 (93)
			18 h	82 (97)
		$ZnCl_2$	2.5 h	27 (80)[b]
				40 (86)[c]
			18 h	37 (85)
		None	2.5h	14 (72)
			18h	20 (76)
 **2a**	 **2b**	$CuSO_4$	2.5 h	78 (95)
			18 h	95 (99)
		$ZnCl_2$	3 h	95 (99)
			18 h	95 (99)
		None	18h	80 (96)
 **3a**	 **3b**	$CuSO_4$	2.5 h	79 (89)
			18 h	87 (94)
		$ZnCl_2$	3 h	90 (95)
		None	18h	79 (89)

[a] Reagents and conditions: TfN_3 (1.25−1.5 equiv), TEA (3 equiv), H_2O/MeOH/CH_2Cl_2 3:10:3. [b] Reaction was very inconsistent, giving yields from 19 to 74%. [c] Substrate was HCl salt. [d] Product was acetylated: Ac_2O, pyridine, DMAP.

Scheme 1. Synthesis of **5** and Subequent Regioselective Reduction to **6**[a]

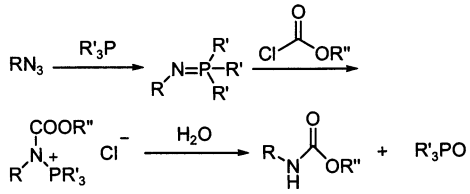


[a] Reagents and conditions: (a) $CuCl_2 \cdot 2H_2O$, CH_3CN, 80 °C, 86%. (b) PMe_3 [1.3 equiv], THF, aqueous NaOH, 0 °C, 46%.

Further searching of the literature suggested that the observed regioselectivity may have very little to do with steric hindrance. Knowles and co-workers reported that azides reduced by propane-1,3-dithiol exhibited different rates of reduction, controlled not only by steric but also by electronic factors, with electron-deficient azides being reduced more rapidly and efficiently than electron-rich azides.[23] The use of an electronic argument to explain the observed regioselectivity in **5** seemed valid, because the 2′-azide is adjacent to the anomeric center. This would suggest that the 2′-azide would be more electron deficient than any of the other azides, making it the most electrophilic azide and, presumably, the most susceptible to phosphine reduction.

The direct conversion of the azide to carbamate, developed by Ariza and co-workers,[24,25] was predicted to be useful in this reaction (Scheme 2). Ariza's reaction never proceeds through

Scheme 2. One-Pot Azide Conversion to Carbamates[24,25]

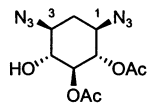
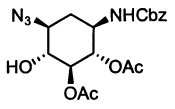
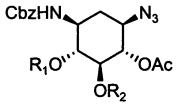
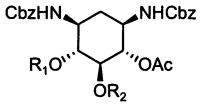
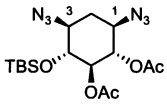
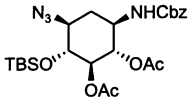
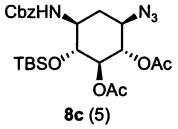
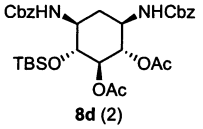
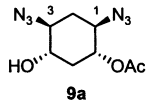
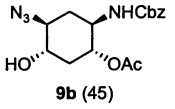
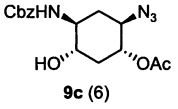
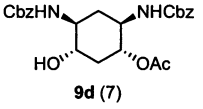
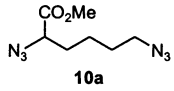
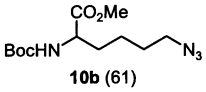
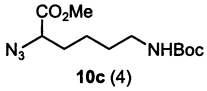
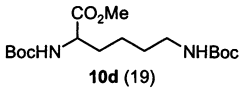
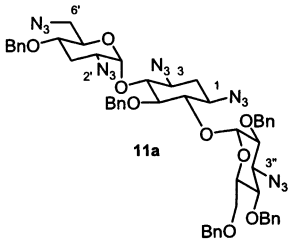
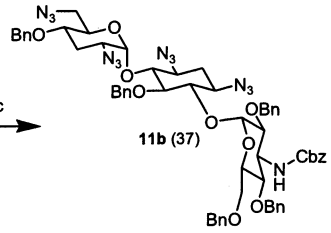


a free amine, easing purification and making the use of acyl protecting groups in this reaction feasible. In all of the following reactions, the reported products were the only isolated compounds that were identifiable.

Several diazides were examined to probe the scope of the observed selectivity (see Table 3). In **7a**,[8] the minor difference between the 4-OH and 6-OAc was sufficient to endow good selectivity for **7b** over **7c**/**d** in modest yields. Identification of products was rendered more difficult due to the formation of **7d**, which presumably arises from a general-base-catalyzed acyl migration of the 5-OAc of **7c** to the adjacent 4-OH by the iminophosphorane intermediate prior to benzyloxycarbonyl (Cbz) capture. Protection of the 4-OH as a *tert*-butyldimethylsilyl (TBS) ether (**8a**) increased the selectivity to 47%/5% **8b**:

(23) Bayley, H.; Standring, D. N.; Knowles, J. R. *Tetrahedron Lett.* **1978**, 3633−3634.
(24) Ariza, X.; Urpí, F.; Viladomat, C.; Vilarrasa, J. *Tetrahedron Lett.* **1998**, *39*, 9101−9102.
(25) Ariza, X.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1999**, *40*, 7515−7517.

Table 3. Regioselective Azide Reductions[a]

Substrate	Products (% Yield)		
 **7a**	 **7b** (51)	 **7c/d**[b] (20)	 **7e/f**[b] (7)
 **8a**	 **8b** (47)	 **8c** (5)	 **8d** (2)
 **9a**	 **9b** (45)	 **9c** (6)	 **9d** (7)
 **10a**	 **10b** (61)	 **10c** (4)	 **10d** (19)
 **11a**	 **11b** (37)		

[a] Reagents and Conditions: (a) (i) PMe_3 [1.1 equiv] THF, −78 °C → room temperature, 2 h; (ii) Cbz-Cl, −78 °C → room temperature, 30 min. (b) Boc-ON, PMe_3 [1.1 equiv], THF, −78 °C → room temperature, 18 h. (c) (i) PMe_3 [1.3 equiv], THF, −78 °C → room temperature, 2 h; (ii) Cbz-Cl, −78 °C → room temperature, 30 min. [b] **c**/**e** R_1 = H, R_2 = Ac, 38:62; **d**/**f** R_1 = Ac, R_2 = H ratio undetermined.

8c, or approximately 9:1. This result could be argued on the basis that the increased steric hindrance about the 3-azide caused the increase in selectivity and overshadowed the electronic effects. On the basis of the selectivity observed in the reaction of **5**, it seems that sterics play only a minor role in determining the outcome of the reaction under these conditions. To simplify the analysis, **9a** was synthesized, which has its 4-OH uninhibited for hydrogen bonding. This also exhibited regioselectivity that was consistent with the electronic control hypothesis. The regioselective azide reduction was not limited to aminoglycosides, as the methyl ester of diazidolysine, **10a**, was also converted to the *tert*-butyl carbamate (BOC) with excellent selectivity in modest yields.

On the basis of the examples of **7a**−**10a**, the electron density of the azide appeared to be the critical factor in determining regioselectivity, but a qualitative model that would help predict the outcome of a regioselective azide reduction for molecules containing multiple azides would be useful. Examination of the ^{15}N NMR resonances for **3b**, **7a**, and **8a** by $^{1}H-^{15}N$ HMBC 2D correlation revealed that the difference between the various N_α and N_β easily predicts the azide which will be reduced selectively (Table 4). However, the low abundance and sensitivity of ^{15}N renders this prediction method too cumbersome for routine use. It was suggested that the degree of shielding of the adjacent carbon or proton as determined by their respective NMR chemical shifts might correlate to the relative electron density for individual azides and allow qualitative prediction for the regioselectivity. ^{13}C NMR was helpful but not always accurate, because it predicted the wrong regioisomer in some cases. ^{1}H NMR proved to be very insightful for predicting this reaction (see Table 5). In every example, the azide whose *ipso*-proton resonance was the furthest downfield was the one preferentially reduced, as shown in Chart 1, and the greater the $\Delta\delta$, the higher the selectivity. The accuracy of this qualitative model should not be overestimated, because there were a limited

Table 4. ^{15}N $\Delta\delta$ for Azides

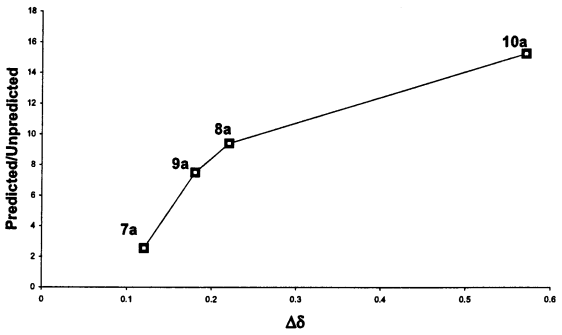
	$R-N_\alpha-N_\beta-N_\gamma$		
compound	$N_{1\alpha}$	$N_{3\alpha}$	$\Delta\delta N_\alpha$
3b	−300.0	−300.0	0.0
7a	−299.7	−299.4	0.3
8a	−299.4	−298.2	1.2

Table 5. Chemical Shifts of *ipso*-Protons of Azides in Substrates

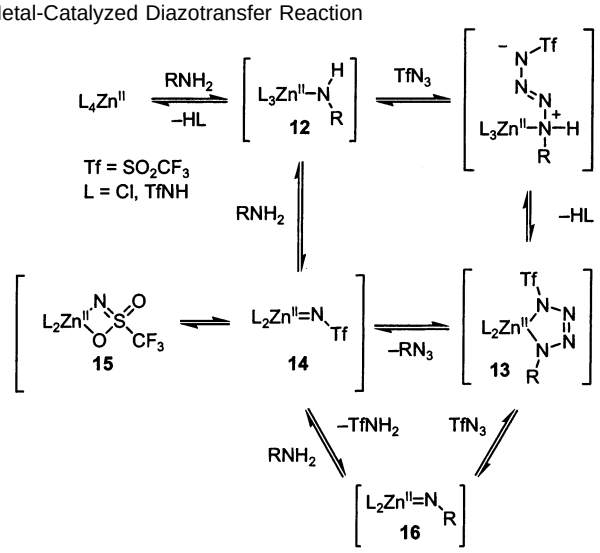
	δCHN_3, given in ppm (azide)
5	3.51 (2′) 3.38 (3) 3.49, 3.35 (6′), 3.18 (1)
7a	3.6[a] (1) 3.48 (3)
8a	3.58 (1) 3.36 (3)
9a	3.51 (1) 3.33 (3)
10a	3.87 (2) 3.30 (6)
11a	3.78 (3″) 3.6[a] (1) 3.27, 3.10 (6′) 3.4[a] (3) 3.00 (2′)

[a] Values are approximated.

Chart 1 ^{1}H $\Delta\delta$ versus Regioselectivity



Scheme 3. Possible Mechanism for the Transition Metal-Catalyzed Diazotransfer Reaction



number of available examples, and ^{1}H chemical shifts are dependent upon many factors.

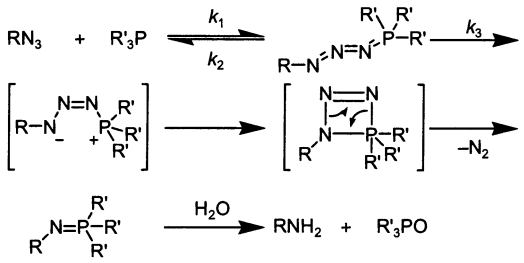
Per-azido per-benzyl tobramycin, **11a**, was synthesized to validate the model. Compound **11a** is similar in structure to **5**, but it had one more azide and was deoxy at the 3′ position. The proton NMR spectrum of **11a** suggested that the 3″-azide was the azide predicted by the model to be selectively reduced, unlike **5**, which predicted the reduction of the 2′-azide. The reduction produced many side products, but the only identifiable product isolated from the reaction was **11b**. This example not only validated proton NMR as a qualitative model for predicting selectivity, but also confirmed that electronics are the dominant factor producing the observed products.

Mechanistic Hypothesis To Explain Observed Products

The mechanism of the diazotransfer reaction is currently unknown. Fischer and Anselme proposed a dianionic tetrazene intermediate stabilized by two sodium ions.[15,26] Extending this proposed mechanism to incorporate a divalent metal ion suggests a mechanism as shown in Scheme 3. Amine complexation to the zinc catalyst, under basic conditions, may provide **12**. Owing to the extreme electrophilicity of triflyl azide, nucleophilic attack by the amine of **12** on the highly electrophilic triflyl azide, followed by deprotonation, might form the zinc-stabilized mixed tetrazene, **13**. The breakdown of **13**, possibly via a reverse [3 + 2] dipolar cycloaddition, would produce the product azide

(26) Anselme, J.-P.; Fischer, W. *Tetrahedron* **1969**, *25*, 855−859.

Scheme 4. Mechanism of Staudinger Reduction of Azides to Amines



and zinc-triflyl imido complex **14**. This complex could be in equilibrium with **16**, which is supported by computational work on similar structures by Brandt et al.[27] From here, two possible pathways could be operative. Amine complexation, followed by the transfer of a proton, would provide **14**, with one of the ligands being triflamide. The other plausible mechanism is the transimination of **15** to yield the transient zinc-imido complex **16**. This explanation is similar to the azide metathesis reaction reported by Bergman et al. with zirconium complexes.[28] The imido-metal complex could be engaged with triflyl azide in a [3 + 2] dipolar cycloaddition to alternatively provide **13**. Investigation into the exact mechanism is ongoing in our laboratory and will be the focus of later publications.

The results of an electronically controlled regioselective azide reduction could be rationalized by an examination of the mechanism of the Staudinger reaction, generally accepted to be that shown in Scheme 4. However, the formation of the phosphazide in step 1 is not nearly as well researched as the formation of the phosphinimine in the second step of the reaction.[12,13] The kinetics of the first step of the reaction (k_1) are completely dependent upon the donating properties of the phosphine substituents and the electron deficiency of the azide; steric hindrance about the phosphine or the azide plays no role in determining the selectivity of the first step. The second step is more complicated, because k_3 is dependent upon both steric and electronic factors. The kinetics of azide reduction with trimethylphosphine have not been reported, but the importance of steric screening in the second step (k_3) would presumably be lower for trimethylphosphine than for bulkier phosphines such as triphenylphosphine.

The regioselective azide reductions were conducted at different temperatures to probe the mechanism, but no detectable dependence on temperature for regioselectivity was observed.[29] One possible explanation is that the first step of the reaction is reversible, allowing equilibrium to be established and one to determine the regioselectivity on the basis of the electronic differences between azides. The rate-determining step would presumably be the *E*-to-*Z* isomerization of the phosphazide, which is consistent with previous work studying the Staudinger reaction.[12,13] Prior to this step, regioselectivity is established, but lower temperatures in the hope of further improving selectivity should not affect the outcome of the reaction, because k_3 would proceed too slowly at low temperatures.

(27) Brandt, P.; Söergren, M. J.; Andersson, P. G.; Norrby, P.-O. *J. Am. Chem. Soc.* **2000**, *122*, 8013−8020.
(28) Meyer, K. E.; Walsh, P. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1995**, *117*, 974−985.
(29) Reactions conducted at higher temperatures had a similar distribution of products with more side products as determined by TLC.

Conclusion

This report describes an improvement of the diazotransfer reaction and the first regioselective azide reduction for compounds containing multiple azides. The improvements to the diazotransfer reaction represent a careful optimization of the previously reported methodology.[6] The use of specific ratios of solvents resulted in a general methodology that is capable of reliably delivering >90% conversion per amine on a variety of substrates. Zinc chloride was found to be as equally effective as copper sulfate for catalyzing the conversion of amines to azides, but catalyzed the transformation in significantly less time. Azides can be reduced regioselectively with good selectivity in moderate yields by a modification of the Staudinger reaction using trimethylphosphine at low temperatures. Application of Ariza's one-pot methodology for the conversion of azides to carbamates was useful for expanding the range of substrates amenable to this reaction.[24,25] Electronic factors determine which azide will be selectively reduced, and proton NMR analysis of the starting material predicts the regioselectivity. Electronic discrimination in the Staudinger reaction is attributed to the trimethylphosphine's smaller size relative to triphenylphosphine. Taken together, the improvement of the diazotransfer reaction and the possibility for the regioselective unmasking of protected amines provide the opportunity for new synthetic strategies that were not previously accessible. Applications centered on this work are currently in progress.

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Supporting Information Available: Experimental details and copies of spectral data for compounds **1b**, **2b**, **3b**, **4**, **5**, **6**, **7a**−**f**, **8a**−**d**, **9a**−**d**, **10a**−**d**, **11a**, and **11b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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