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Phosphite Catalyzed C–H Allylation of Azaarenes via an Enantioselective [2,3]-Aza-Wittig Rearrangement

Abdul Motaleb,[†] Soniya Rani,[†] Tamal Das, Rajesh G. Gonnade and Pradip Maity*

Abstract: A phosphite mediated [2,3]-aza-Wittig rearrangement has been developed for the regio- and enantioselective allylic alkylation of six-membered hetero-aromatic compounds (azaarenes). The nucleophilic phosphite adduct of N-allyl salts undergoes a stereoselective base mediated aza-Wittig rearrangement and dissociation of the chiral phosphite for overall C–H functionalization of azaarenes. This method provides efficient access to tertiary and quaternary chiral centers in isoquinoline, quinoline, and pyridine systems, tolerating a broad variety of substituents on both allyl part and azaarenes. Catalysis with chiral phosphites is also demonstrated with synthetically useful yields and enantioselectivities.

Chiral six-membered azaarenes, such as pyridines, quinolines, and isoquinolines are among the most ubiquitous structural motifs in pharmaceutical drugs, bioactive natural products, and chiral ligands in asymmetric synthesis (Figure 1a).[1] Consequently, great advances have been made in their enantioselective synthesis.[2] For example, methods have been developed that commence from acyclic precursors or pre-functionalized azaarene halides and organometallic reagents.[2,3] Recently, elegant protocols for the direct C–H alkylation from feedstock azaarenes have also been reported.[4-6] Unfortunately, an enantioselective C–H allylation of azaarenes has remained elusive, despite the potential utility of the synthetically versatile chiral allylated azaarene products for further functionalization (Figure 1b).

In this Communication, we report the first enantioselective C–H allylation of azaarenes via a conceptually novel chiral phosphite promoted [2,3]-aza-Wittig rearrangement (Figure 1c). Our interest in enantioselective C–H functionalization of imines embedded in azaarenes prompted us to explore the possibility of umpolung reactivity.[7,8] We hypothesized that the phosphite-azaarene adduct **3** of N-allyl pyridinium **1** would undergo a base-mediated stereoselective aza-Wittig rearrangement, in which the chiral phosphite would dictate the stereochemical outcome of the reaction. Subsequent elimination of the chiral phosphite from rearranged product **5** would reestablish aromaticity in the final product (**6**). We further anticipated that the energy gain in rearomatization might compensate for an otherwise less-favored aza-Wittig rearrangement (Figure 1c).[9]

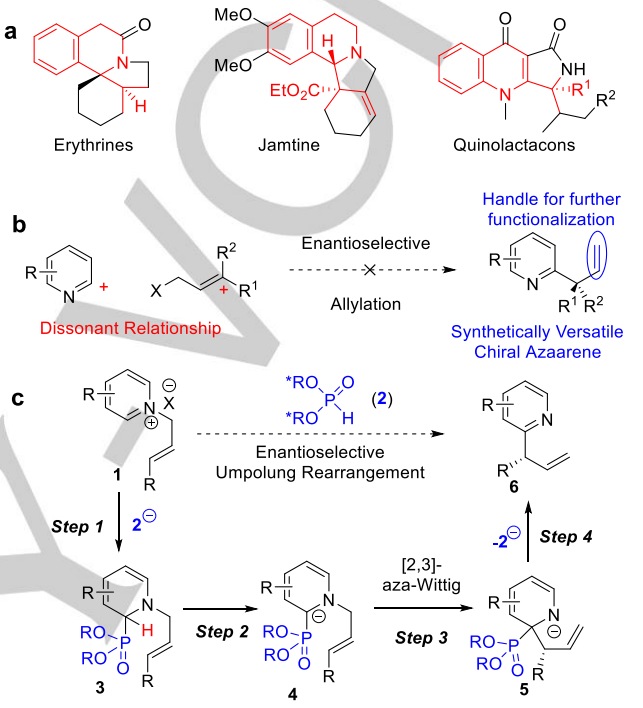

Figure 1. Chiral azaarenes via a novel enantioselective C-H allylation. [a] Chiral azaarene containing natural products. [b] Challenge in direct C-H allylation. [c] Proposed phosphite catalyzed protocol with N-allyl salts.

N-allyl isoquinoline **1a** was selected as the substrate for the initial development of the stereoselective C–H allylation of azaarenes (Table 1). As a proof of concept, stoichiometric achiral dimethylphosphite (**2a**) was examined to test the feasibility of the proposed reaction manifold. Addition of pre-formed phosphite anion to **1a** in the absence of light and oxygen led to adduct **3**,[10] which yielded 58% of the rearranged product **6a** upon treatment with LiHMDS (entry 1). Next, we performed the reaction with chiral TADDOL based phosphite **2b**.[11] Catalytic amounts (20 mol%) of **2b** led to the formation of the desired product in low yield, although with encouraging enantioselectivity (78% ee, entry 2). The low yield in the range of catalyst loading prompted us to carefully examine each step of the proposed phosphite mediated cycle. Background reaction in the absence of phosphite showed that in addition to deprotonating intermediate **3**, the base can also decompose **1a** (entry 3). Therefore we planned for slow addition of base to maintain its concentration below intermediate **3**. At -40 °C, the rate of formation of **3** was studied with a varying stoichiometry of **1a** (see SI) to determine the base addition rate during the course of its consumption. Under slow base addition via syringe pump, the product **6a** yield increased to 28%, along with 32% N-allyl isoquinolone **7a** (entry 4). We believe the longer reaction time required for the slow first step of the catalytic process (Figure 1c,

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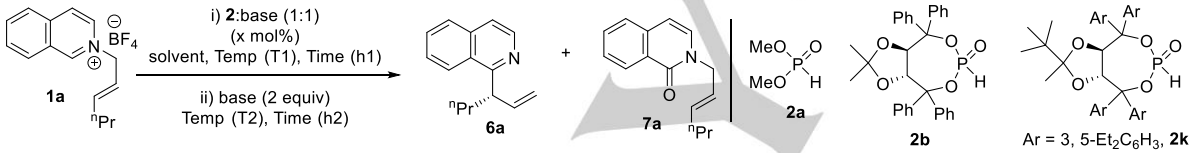
Step 1, **1** to **3**) led to the unavoidable incorporation of aerobic oxygen during base addition. As a result, substantial oxidation of intermediate **4** occurred to form by-product **7a**.[12] Since carbanion **4** is the only oxidation prone intermediate, we tested the base addition portion-wise instead to generate and rearrange **4** in a discrete manner. Simple argon purging for 5 minutes before each portion-wise base addition led to 68% rearrangement product with <5% oxidation (entry 5). Although we could obtain near oxygen free rearrangement conditions, moisture incorporation remained a problem, generating hydroxide base upon reaction with LiHMDS. The hydroxide also decomposes the starting material **1a** slowly under the reaction condition, leading to moderate yields.

The phosphite **2b** was easily recovered during silica column purification of the product. Hence, we tested the use of a stoichiometric amount of **2b** to form **3** at 0 °C, with subsequent cooling and single base addition (<5 min) for the formation of the desired product **6a**. High yield was obtained (entry 6) in shorter reaction time, and importantly, >95% of the chiral phosphite was recovered after column chromatography. The chiral phosphite that was recovered from column chromatography was recycled for another reaction, which led to the formation of the desired product with the same efficiency (entry 7). We opted to use the stoichiometric phosphite method because of its easy operation, shorter reaction time, and practicality. In addition, the chiral phosphite was recovered and recycled.

Guided by previous reports of the counter cation effect on stereoselective anionic [2,3]-Wittig rearrangements,[13] we carried out a systematic screening of counter cations of the base. The use of KHMDS led to a significant drop in yield and enantioselectivity (entry 8). Base strength also impacted the efficiency of the reaction, with stronger bases such as LDA and n-BuLi leading to significant drops in both yields and enantioselection (entries 9-10). After screening several solvents, we identified THF as the optimal reaction medium. Other solvents resulted in diminished yields and/or enantioselectivities. We screened additional chiral phosphites to improve the enantioselectivity of the reaction (see Supporting Information for a complete optimization). Gratifyingly, in the presence of phosphite **2k**, the desired C–H allylation product **6a** was generated in 81% yield and 92% ee (entry 11).

Table 1. Optimization of aza-Wittig rearrangement via umpolung of N-allyl isoquinolinium salt



entry	**2** (mol%)	T1 (°C), h1 (h)	T2 (°C), h2 (h)	solvent	base	**6a** yield (%)	**6a** ee (%)	**7a** yield (%)
1	**2a** (120)	0, 24	0, 1	THF	LiHMDS	58	–	ND
2	**2b** (20)	0, 4	0, 1	THF	LiHMDS	19	78	ND
3[a]	**-**	0, 4	0, 1	THF	LiHMDS	0	ND	ND
4	**2b (20)**	-40, 4	-40, 92	THF	LiHMDS	28	86	32
5[b,c]	**2b (20)**	-40, 4	-40, 92	THF	LiHMDS	68	86	<5
6	**2b** (100)	0, 48	-60, 2	THF	LiHMDS	79	89	ND
7[d]	**2b** (100)	0, 48	-60, 2	THF	LiHMDS	78	89	ND
8	**2b** (100)	0, 48	0, 2	THF	KHMDS	15	15	ND
9	**2b** (100)	0, 48	0, 2	THF	LDA	46	71	ND
10	**2b** (100)	0, 48	0, 2	THF	*n*-BuLi	35	60	ND
11	**2k** (100)	0, 48	-60, 2	THF	LiHMDS	81	92	ND

Reactions were carried out on 0.3 mmol scales. [a]**1a** completely decomposed. [b]portion-wise base addition; [c]with 1.5 mmol **1a**; [d]with recovered phosphite **2b**.

A diverse range of azaarene substrates were examined under stoichiometric phosphite mediated method to determine the scope of chiral phosphite mediated C–H allylation (Table 2). Catalytic variants were tested for each class of azaarene, and the results are presented in parenthesis. For substituted isoquinolines, the reaction was tolerant of 3-bromo substitution (**6b**), but the formation of the 3-phenyl isoquinoline product (**6c**) was sluggish at –60 °C with a lower yield (~10%). An increase in the reaction temperature to –40 °C resulted in the formation of the desired product at a faster rate (4h), resulting in greater yield (67%) and negligible loss in enantioselectivity (90% vs. 91% ee). Isoquinoline substrates with 4-bromo, alkynyl, and phenyl substitution all rearranged at –60 °C with similar efficiencies (**6d-f**). Other functionalized phenyl rings at the isoquinoline C–4 position, including 4-chlorophenyl (**6g**), 4-fluorophenyl (**6h**), 3-trifluoromethylphenyl (**6i**), and 2-bromophenyl (**6j**) were well tolerated. A C–4 cyclopropyl group (**6k**) was also tolerated, as the product was generated in 65% yield and 94% enantioselectivity. 6-Bromo-substitution on the isoquinoline resulted in **6l** with good yield and higher enantioselectivity (96% ee).

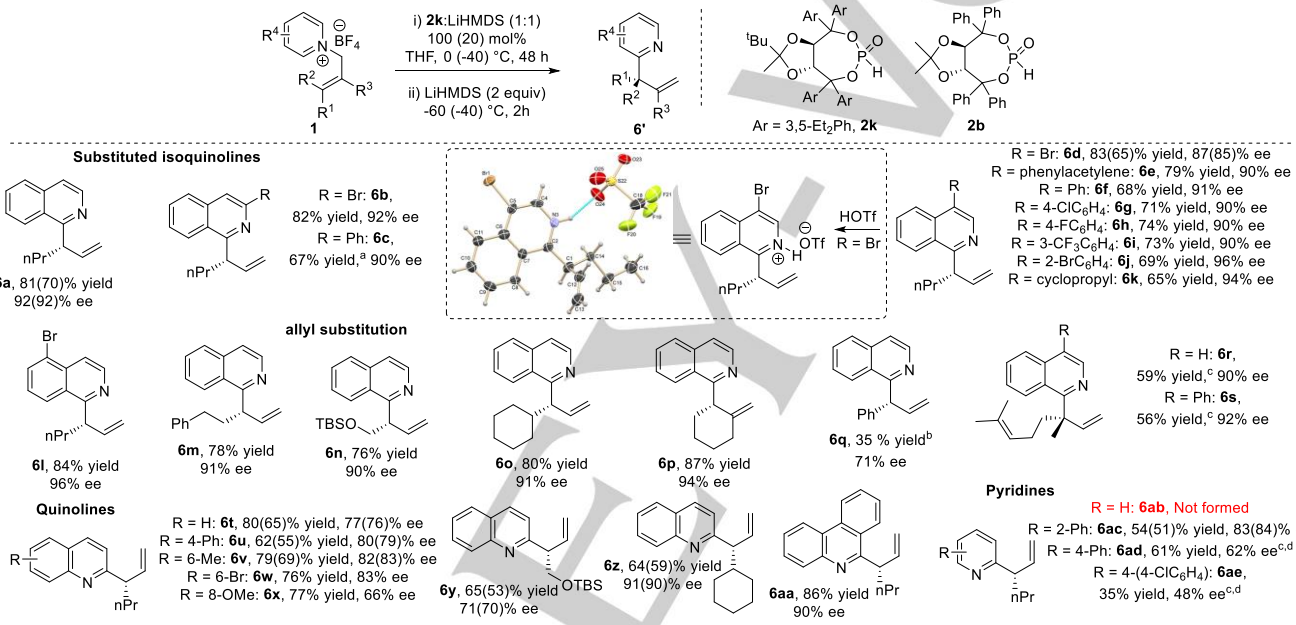
10.1002/anie.201906681

Next, we varied the substitution in the allyl fragment of the substrate. Other primary alkyl groups such as ethylphenyl (**6m**) and TBS-protected hydroxymethyl (**6n**) worked well with no significant effects on yields and enantioselectivities. The substrate with a sterically bulky secondary cyclohexyl substitution also rearranged successfully in good enantioselectivity (**6o**). A six-membered C1–C2 endocyclic allyl ring led to the formation of an exocyclic terminal alkene without any alkene isomerization (**6p**).

The reaction with a cinnamyl moiety led to no product formation. We suspect that the benzylic C–H of the product was rendered more acidic with phenyl substitution, and LiHMDS might deprotonate the product faster than deprotonation of sterically congested intermediate (**3**) of phosphite **2k**. A relatively smaller phosphite **2b** resulted in the product **6q** in 35% yield and 71% ee.

A terminal di-substituted geranyl substrate was examined next to generate an all carbon quaternary stereogenic center. The non-enantioselective version of the rearrangement went uneventful with dimethylphosphite, but it failed to form the product with the chiral phosphite (**2k**).[14] To our delight, a smaller lithium pyrrolidinide base produced the desired product (**6r**) in moderate yield (59%) but with high enantioselectivity (90% ee). N-Geranyl salt of 4-phenyl isoquinoline was also rearranged smoothly to give **6s** in high enantioselectivity.

Table 2. Substrate scope for phosphite mediated (and catalyzed) asymmetric allylation of azaarenes



Conditions: Stoichiometric reaction conditions: THF solution of **1** (0.3 mmol) was added to **2** (0.3 mmol) and LiHMDS (0.3 mmol) in THF (0.1 M) at 0 °C, followed by further addition of LiHMDS (2 equiv, 1 M in THF) at -60 °C for 2 h. Catalytic reaction conditions: **1** (1.5 mmol) and **2k** (0.3 mmol) in THF (12 ml) at –40 °C, followed by portiowise base addition over 90 h. *Results of catalytic reactions are given in parenthesis*. [a]rearrangement step at –40 °C; [b]35% with **2b** and no product with **2k**; [c]lithium pyrrolidinide base instead of LiHMDS; [d]first step for 96 h.

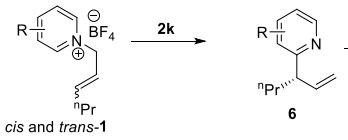
Since most of the asymmetric azaarene functionalization reports are specific to a particular type of azaarene,[3c,6] we eagerly examined our method with other N-heteroaromatic scaffolds. Gratifyingly, N-allyl quinolinium salt rearranged under the same optimized reaction conditions to generate the regioselective 2-allylated product (**6t**) in good yields but with slightly lower enantioselectivity (77% ee) compared to its isoquinoline counterpart (**6a**). 4-Phenyl (**6u**), 6-methyl (**6v**) and 6-bromo (**6w**) substituted quinoline led to slightly better enantioselectivities (80-83% ee), whereas acridine as azaarene (**6aa**) and cyclohexyl substitution on allyl (**6z**) resulted in the enantioselectivity of the product comparable to the isoquinoline level (90, 91% ee). On the other hand, 8-methoxy on quinoline (**6x**) and TBS protected hydroxymethyl substitution on the allyl part (**6y**) had a detrimental effect on enantioselectivity (66, 71% ee).

Unsubstituted pyridine substrate failed to furnish any rearrangement, but 2-phenyl pyridine led to **6ac** in 54% yield and 83% ee. Phenyl and 4-chlorophenyl substitution at C4 of pyridine resulted in the formation of the rearrangement product with dimethylphosphite and LiHMDS base, but chiral phosphite (**2k**) promoted rearrangement failed.[14] Reaction with lithium pyrrolidinide affected the rearrangements to moderate yields and enantioselectivities (Table 2, **6ad** and **6ae**).

The lower enantioselection for most of the quinoline and pyridine substrates prompted us to look into the possible effect of alkene geometry. Unlike [3,3]-rearrangements that proceed through well-ordered 6-membered transition states, the stereoselectivity of [2,3]-rearrangements is often less predictable and influenced by the nature and size of substituents, presumably because of the conformationally more flexible 5-membered transition states.[12a,15,16] Hence, we synthesized *cis*-

10.1002/anie.201906681

allyl salts of quinoline (*cis*-**1t**), isoquinoline (*cis*-**1a**) and pyridine (*cis*-**1ad** and *cis*-**1ae**) substrates. The *cis*-**1a** with catalyst **2k** produced the same enantiomer of **6a**, albeit with slightly reduced enantioselectivity (81 vs. 92% ee). On the other hand, the *cis*-salts of quinoline and pyridine resulted in higher enantioselectivities in the product than the *trans*-salts (Scheme 1). The higher enantioselectivity of *cis*-allyl quinoline and pyridine salts indicates the possibility that other quinoline and pyridine substrates may result in better enantioselectivity with the corresponding *cis*-salts. We propose that the quinoline and pyridine *cis*-substrates may have more pronounced energetic differences in the competing transition states that lead to stereoselective rearrangement products.[17] Interestingly, for all three classes of azaarenes, both *cis*- and *trans*-substrates furnished the same major enantiomer of the allylation product, which suggests that the chiral phosphite dictates the stereochemical outcome of the rearrangement of intermediate **4** to **5**.

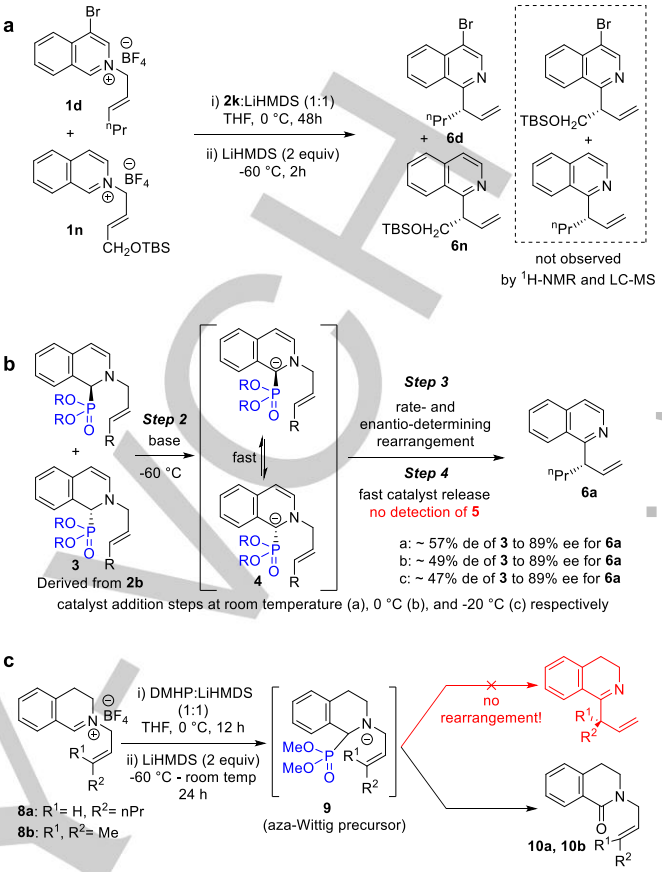


Product	% ee (yield) from *cis*-allyl	*trans*-allyl
6a (isoquinoline)	81(80)	92(81)
6t (quinoline)	87(82)	77(80)
6ad (pyridine)	91(65)	62(61)
6ae (pyridine)	82(57)	48(35)

Scheme 1. Effect of alkene geometry on enantioselectivity of different azaarenes.

Subsequent mechanistic studies were carried out to gain support for the proposed aza-Wittig-rearomatization sequence and shed light on the enantio-differentiating step (Scheme 2). A crossover experiment with **1d** and **1n** furnished only the respective intramolecular products with no cross products, which indicates the rearrangement (***Step 3***) to be unimolecular (Scheme 2a). The absence of competitive linear [1,2]-allyl product is also suggestive of a concerted mechanism, consistent with pericyclic Wittig rearrangements.[13b,18]

We were also interested in examining the enantio-determining step of the reaction.[13b,16b] To gain insight, we examined the configuration of the phosphite-azaarene adduct **3** and its influence on the enantioselectivity. The ^{1}H-NMR of intermediate **3** with phosphite **2b** showed poor diastereoselectivity for the newly formed carbon stereocenter, which did not correlate with the high enantioselectivity observed for the overall reaction.[19] Formation of intermediate **3** at different temperatures led to different diastereomeric ratios, which had no influence on the product enantioselectivity (Scheme 2b). These results indicate that the initial ratio of diastereomers of carbanion **4** is irrelevant, and that conversion of **4** to **5** involves a dynamic kinetic resolution process whereby one diastereomer of **4** undergoes [2,3]-rearrangement much faster than the other, while the diastereomers of **4** readily interconvert.



Scheme 2. Mechanistic studies. [a] Crossover experiment; [b] Enantio-determining step; [c] Reactivity of non-aromatic substrates.

We also examined our hypothesis that regaining aromaticity to obtain product **6** could be the driving force for this unprecedented aza-Wittig rearrangement.[20] Dihydroisoquinoline salts (**8a, 8b**) failed to rearrange up to room temperature, presumably because of their inability to regain aromatic stabilization. Instead, we observed partial oxidation to the lactam (**10a, 10b**) over a prolonged reaction time (Scheme 2c). The generation of lactam is suggestive of the formation of carbanionic Wittig precursor **9** that reacts with aerobic oxygen, similar to the isoquinoline derived intermediate.[12]

In conclusion, we have developed a new approach for asymmetric allylation of azaarenes via a phosphite promoted tandem aza-Wittig-rearomatization sequence. Careful examination of reaction conditions revealed crucial roles of solvent, counterion, base strength, and alkene geometry on the stereoselectivity. Chiral azaarenes are furnished in good yields and enantioselectivities with a broad range of functional groups. Recovery of the chiral phosphite was almost quantitative and shown to be active for reuse. The method is general for isoquinoline, quinoline, and pyridine; and for the formation of tertiary and all carbon quaternary centers. The evidence for rearomatization as a driving force for the reaction was demonstrated. We are currently exploring this new mode of activation for the development of other stereoselective reactions.

Experimental Section

See Supporting Information (SI) for general procedures and all characterization.

Acknowledgements ((optional))

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Keywords: Azaarene C–H allylation • Asymmetric organocatalysis • Aza-Wittig rearrangement • Rearomatization • TADDOL phosphite

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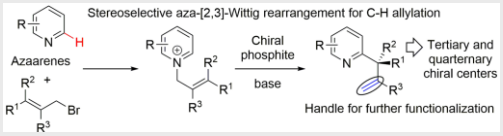

Organocatalyzed enantioselective C–H Allylation of Azaarenes: A nucleophile phosphite catalysis is introduced for overall C–H allylation of azaarenes via an facile aza-[2,3] Wittig rearrangement sequence. TADDOL based phosphites induces high enentioselectivity.

*Abdul Motaleb,[†] Soniya Rani,[†] Tamal Das, Rajesh G. Gonnade and Pradip Maity**

Page No. – Page No.
Phosphite Catalyzed C–H Allylation of Azaarenes via an Enantioselective [?,3]-Aza-Wittig Rearrangement