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Palladium-Catalyzed [3,3]-Rearrangement for the Facile Synthesis of Allenamides

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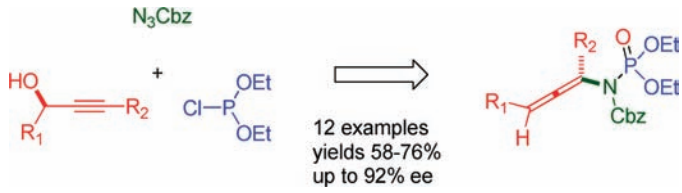
ABSTRACT



A [3,3]-rearrangement that is used for facile construction of chiral allenamides is described. A propargylic alcohol, a chlorophosphite, and Cbz-azide are combined to provide a propargylic phosphorimidate that, in the presence of catalytic palladium(II), rearranges to an allenamide. By varying the substitution pattern on the propargylic alcohol, mono-, di-, and trisubstituted allenamides can be accessed in good yields. Additionally, the use of an enantiomerically enriched propargylic alcohol enables the preparation of stereochemically defined allenamides.

Allenamides have attracted much attention as versatile precursors for the preparation of an array of synthetic targets, including 1,2-aminoalcohols,[1] cyclobutanes,[2] dihydrofurans,[3] pyranyl heterocycles,[4] and 2-amido-dienes.[5] Thus, significant efforts have been devoted toward general methodologies to access allenamides; however, these often require complex precursor syntheses, and the preparation of enantiomerically enriched allenamides is particularly cumbersome.[6]

One of the most commonly used methods for the formation of highly substituted chiral allenamides is the iterative addition of functionality to a monosubstituted stucture.[6a] In this stepwise approach, the synthesis of stereochemically defined allenamides requires a chiral auxiliary.[6a] Another method for forming allenamides is the use of [2,3]-rearrangements of propargylic sulfides. An advantage of this strategy is that it enables predictable transfer of stereochemical information to the allenamide. However, preparation of the starting propargylic sulfide, particularly in enantiomerically enriched form, requires several synthetic manipulations.[6b−d]

On the basis of work that has been previously carried out in our laboratory,[7] we envisioned using a propargylic phosphorimidate as the key intermediate in a palladium-catalyzed [3,3]-rearrangement for the formation of fully protected allenamides. Unlike propargylic sulfides, propargylic phosphorimidates are easily prepared in a single synthetic step from three readily available starting materials: a propargylic alcohol, a chlorophosphite, and an azide. Further, this could be readily applied to the synthesis of stereochemically defined allenamides simply through the use

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of a commercially available or readily synthesized[8] enantioenriched propargylic alcohol.

Although [3,3]-rearrangements have proven useful for the preparation of allenes,[9] the application to allenamides has garnered little attention.[10] The most extensively studied example is the Overman rearrangement of propargylic trichloroacetimidates to form allenamides, which proceeded in low yields (10−20%) and with limited substrate scope.[10a,b] We hypothesized that a propargylic phosphorimidate would be a good candidate for a [3,3]-rearrangement as the resulting allenamide would be fully protected. This would provide a more stable allenyl species, as well as allowing for the possibility of unmasking an amine after carrying out further reactions.[7,11]

In keeping with earlier reports,[7,11] the key phosphorimidate intermidate would be generated by combination of a propargylic alcohol with a chlorophosphite to yield a phosphorus ester that would be oxidized with an azide via a Staudinger reduction. The resulting phosphorimidate could then undergo the desired rearrangement under transition-metal-catalyzed conditions (Figure 1). We expected, on the basis of similar

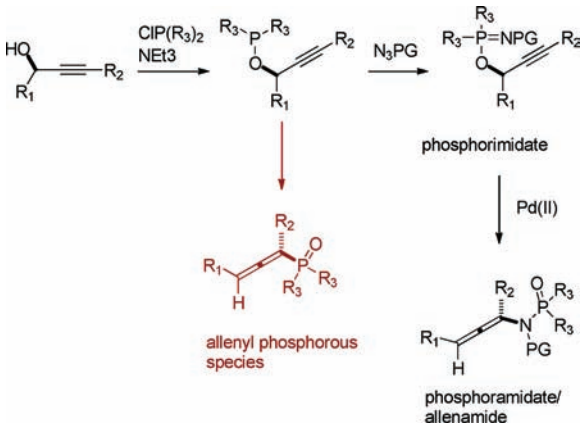
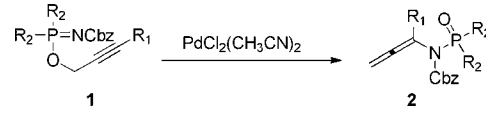


Figure 1. Outline of the rearrangement. In the first step, a propargylic phosphite is formed through combination of a propargylic alcohol with an activated trivalent phosphorus species in the presence of mild base. This can be converted to a phosphorimidate via a Staudinger reduction with an azide. This species can then undergo a transition-metal-catalyzed rearrangement to form a fully protected allenamide. A possible side reaction is formation of an allenyl phosphorus species via rearrangement of the propargylic phosphite.

allylic systems,[7,11,12] that regio- and stereochemistry would be highly conserved in this reaction.

A complicating factor in the development of the phosphorimidate rearrangement is the well-documented spontaneous [2,3]-rearrangement of propargylic phosphites and phosphinates to form allenyl phosphorus species (Figure 1).[13] Indeed, in initial studies conducted with propargyl alcohol as the substrate, trivalent phosphorus esters with either hydrocarbon or amine substituents (Table 1, entries 1 and

Table 1. Optimization of the Rearrangement



1 2

entry[a,b]	R_1	R_2	solvent	temp (°C)	no.	yield
1	H	Ph	---[c]	---		---
2	H	NEt_2	---[c]	---		---
3	H		DCM	25	**2a**	66%[d]
4	Me		DCM	25	**2b**	16%[d]
5	Me		toluene	100	**2b**	13%[e]
6	Me	OEt	DCM	25	**2c**	29%[e]
7	Me	OEt	toluene	25	**2c**	29%[e]
8	Me	OEt	toluene	100	**2c**	60%[d]
9	H	OEt	DCM	25	**2d**	76%[d]

[a] Conditions: (1) propargylic alcohol (1.6 equiv), 1.3 equiv of R_2PCl, and 1.3 equiv of Et_3N in Et_2O, 0 °C, 20 min; (2) Cbz azide (1.0 equiv), rt, 2 h. [b] Phosphorimidate (1.0 equiv), $PdCl_2(CH_3CN)_2$ (3 mol %), solvent to a final concentration of 0.01 M. [c] Phosphorimidate species not formed as a result of rearrangement to allenyl phosphorus species. [d] Isolated yields. [e] NMR yields.

2) rapidly converted to the corresponding allenyl phosphinates. Phosphites, however, could be converted to the desired phosphorimidate through reaction with an electron-deficient azide, such as Cbz-azide, and isolated for use in the rearrangement.

Once conditions for formation of the propargylic phosphorimidates were identified, attention was turned to examination of the rearrangement. Consistent with the related allylic rearrangement,[7] the Cbz-functionalized phosphorimidate did not undergo efficient rearrangement under thermal conditions but required a Pd(II) catalyst. The rearrangement was sensitive to substrate concentration and catalyst load, with higher yields obtained under more dilute reaction conditions. Evidently, bimolecular decomposition pathways are more readily accessible to the propargylic species in comparison with related allylic phosphorimidates.[7] As shown in entry 3 of Table 1, when run at a concentration of 10 mM with 3 mol % Pd(II) catalyst, a 66% yield of allenamide **2a** was isolated.

Application of these conditions to a more substituted propargylic phosphorimidate derived from but-2-yn-1-ol

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(13) Mark, V. *Mechanisms of Molecular Migrations*; Thyagarajan, B. S., Ed.; Wiley Interscience: New York, 1971; Vol. 2, pp 319−437.

produced a low yield (16%) of allenamide with a large amount of phosphorimidate still present (Table 1, entry 4). Attempts to drive the reaction through temperature increase (Table 1, entry 5 for example) were unsuccessful as the phosphorimidate species persisted even under prolonged reaction times. We hypothesized that this could be due to increased steric demand of the more substituted triple bond and thus examined a less constrained phosphite. Consistently, employment of diethyl chlorophosphite to generate the reactive intermediate led to a 2-fold increase in yield when the rearrangement was carried out at room temperature in either dichloromethane (entry 6) or toluene (entry 7). Raising the reaction temperature to 100 °C produced an additional yield enhancement (60%, entry 8) and led to complete depletion of the phosphorimidate. Gratifyingly, it was found that this phosphite also worked well for the less substituted substrate (entry 9) and was thus used in the remaining applications.

Upon identifying conditions that worked for both internal and terminal alkynes, the method was applied to a broader range of propargylic alcohols to better define the scope of the rearrangement. Of particular utility would be substrates that would form di- and trisubstituted allenamides as current methods for accessing these structures require multistep syntheses.[6]

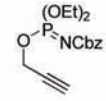
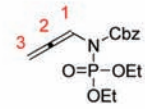
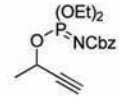
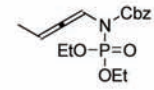
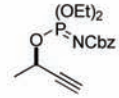
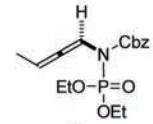
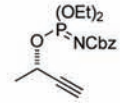
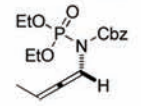
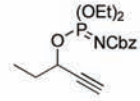
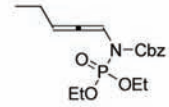
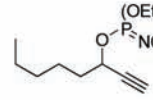
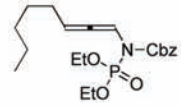
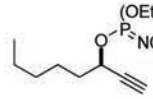
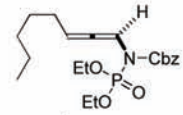
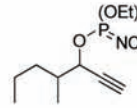
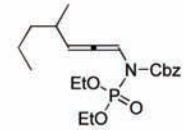
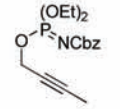
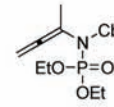
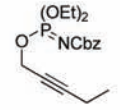
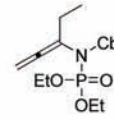
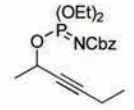
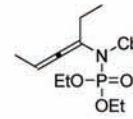
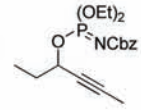
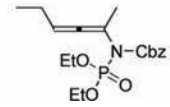
Secondary propargylic alcohols were first examined as they would produce disubstituted allenamides functionalized at the 1 and 3 positions. As shown in Table 2 (entries 2−8), secondary alcohols with both straight chain and branched alkyl subsituents are excellent substrates for the rearrangement. Tertiary propargylic alcohols were not, however, good substrates for the reaction as the intermediate propargylic phosphite underwent rapid conversion to the corresponding allenyl phosphonate.[13]

1,1-Disubstituted allenamides can also be prepared via rearrangement of internal alkynes. As in the earlier examples, alkyl groups are well-tolerated at this position (Table 2, entries 9 and 10). Appending aryl groups at this postion, however, proved to be more challenging; primary alcohols with less electron-rich aryl substituents were able to react under these conditions, albeit with a decrease in yield relative to their alkyl counterparts (41−25% yields, see Supporting Information for details).

Building on the results above, trisubstituted allenamides can also be prepared through the reaction of more substituted propargylic alcohols (Table 2, entries 11 and 12). Trisubstituted allenamides such as these would be of particular use as substrates in further synthetic transformations, such as the formation of highly substituted 1,2-aminoalcohols.[1]

As noted earlier, the synthesis of enantiomerically enriched allenamides is often synthetically challenging.[6] We thus examined whether this rearrangement could be extended to such molecules, using enantiomerically enriched propargylic alcohols as the starting materials. Either enantiomer of the allenamide derived from 3-butyn-2-ol can be readily prepared (Table 2, entries 3 and 4), both in 92% ee. Additionally, an

Table 2. Scope of the Rearrangement

entry[a]	phosporimidate		allenamide		yield[b]
1		**1d**		**2d**	76%
2		**3**		**4**	68%
3		**5**[c]		**6**	70% 92% ee[d]
4		**7**[c]		**8**	67% 92% ee[d]
5		**9**		**10**	68%
6		**11**		**12**	70%
7		**13**[c]		**14**	70% 80% ee[d]
8		**15**		**16**	65%
9		**1c**		**2c**	58%
10		**17**		**18**	58%
11		**19**		**20**	60%
12		**21**		**22**	58%

[a] Conditions as described in Table 1. See Supporting Information for additional details. [b] Isolated yields. [c] ee of commercially available starting alcohol found to be <95% in each case. [d] ee determined by chiral HPLC. See Suppporting Information for additional details.

enantiomerically enriched allenamide derived from (*R*)-(+)-1-octyn-3-ol was also prepared in 80% ee.[14]

Despite their utility in a variety of reactions, the lability of nitrogen-substituted allenes is a recurring concern.[6a,d] The fully protected allenamides produced in the phosphorimidate rearrangement exhibit considerable stability and can be stored neat at 0 °C for over 2 months with little decomposition. Allenamide **2d** readily undergoes a Diels−Alder reaction to produce enamide **23**. Using conditions similar to those reported for use on allenes,[15] allenamide **2d** can also be converted to the densely functionalized allyl boronate **24**, which is poised for further transformations.[16] To our knowledge, this is the first reported example of this reaction using an allenamide (Figure 2).

In summary, we have demonstrated a straightforward application of a [3,3]-rearrangement to form highly functionalized allenamides. A key feature of the rearrangement is its synthetic simplicity as it requires only a propargylic alcohol, an organic azide and a chlorophosphite, all of which are easily accessible. As enantiomerically enriched propargylic alcohols are easily accessed from either commercial sources or through straighforward synthetic manipulations,[8] this strategy represents a facile entry into stereochemically defined allenamides. This methodology therefore serves as a valuable addition to the current strategies for forming these interesting molecules.

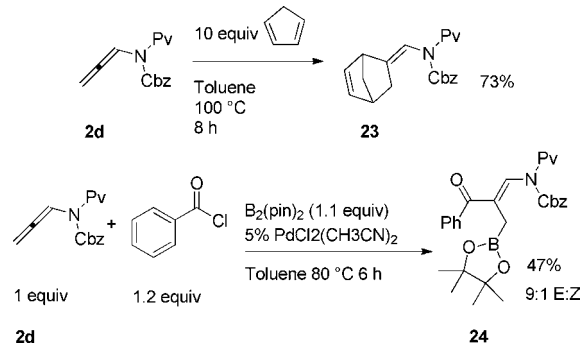


Figure 2. Applications of fully protected allenamides. P^v = diethylphosphate. (Top) Diels−Alder reaction. (Bottom) Formation of boron-substituted enamide. See Supporting Information for additional details.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The indicated stereochemistry is predicted on the basis of the mechanism of closely related allylic rearrangements.[6b,7,11,12] The attenuated % ee is due to a Pd-catalyzed epimerization step that the allenamides undergo. The mechanism of this side reaction is currently under examination. However, one can obtain allenamides of higher stereochemical purity simply by running the reaction for a shorter time period, albeit in lower yields.

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