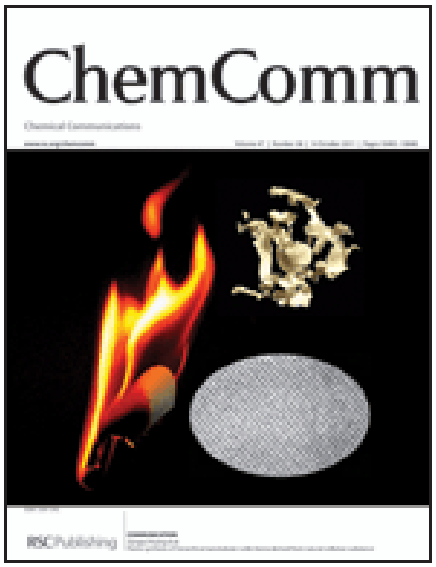

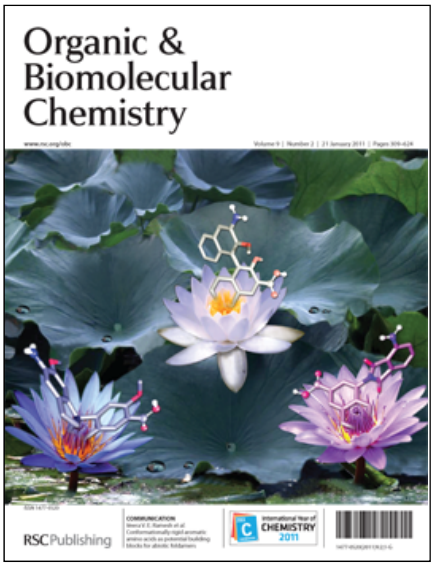

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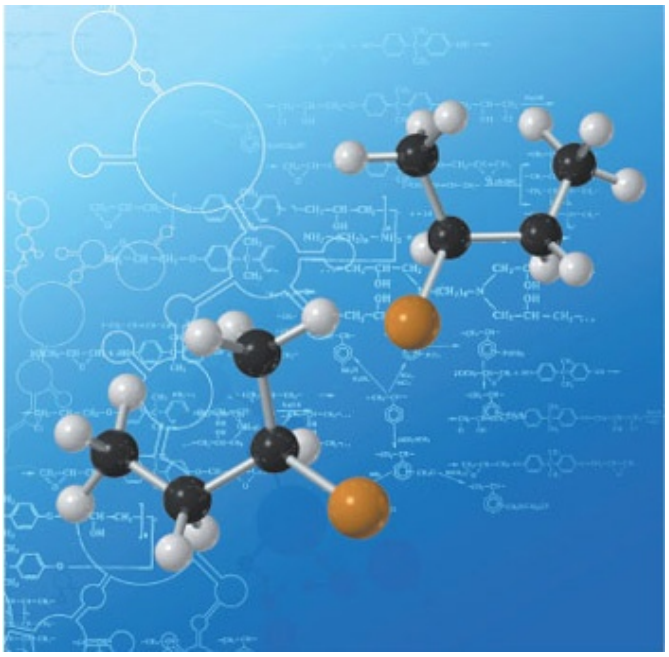

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COMMUNICATION

Phosphine-catalyzed intramolecular γ-umpolung addition of α-aminoalkylallenic esters: facile synthesis of 3-carbethoxy-2-alkyl-3-pyrrolines†‡

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An array of *N*-tosylated α-aminoalkylallenic esters was prepared and their cyclization under the influence of nucleophilic phosphine catalysts was explored. The α-aminoalkylallenic esters were prepared through aza-Baylis–Hillman reactions or novel DABCO-mediated decarboxylative rearrangements of allenylic carbamates. Conversion of these substrates to 3-carbethoxy-2-alkyl-3-pyrrolines was facilitated through Ph_3P-catalyzed intramolecular γ-umpolung addition.

Nitrogen-containing heterocycles are ubiquitous structural elements in the realm of natural products and pharmaceutically relevant compounds.[1] Amongst these important scaffolds, 3-pyrrolines occupy a uniquely versatile position in that they can be further transformed into their fully saturated pyrrolidines or more highly oxidized pyrrole and pyrrolidinone counterparts.[2] Of the various approaches toward functionalized 2,5-dihydropyrroles, Lu's phosphine-catalyzed [3 + 2] annulation of allenes and imines has emerged as one of the premiere methodologies.[2b,3] Since its first report, this annulation has undergone many developments, including modifications,[4] applications,[5] and asymmetric renditions.[6] Despite the great utility of this phosphine-catalyzed allene–imine [3 + 2] annulation, it has its limitations—the most evident being the necessity for imines devoid of α-protons. This prerequisite has limited the scope of the reaction to the use of aryl-substituted imines. Overcoming this limitation would expand the potential use of organocatalyzed 3-pyrroline synthesis to applications requiring non-aryl groups substituted onto the heterocycle.[7] The successful implementation of alkyl-substituted *N*-sulfonyl imines was reported only recently: used in conjunction with a Me_3P-catalyzed isomerization of 3-alkynoates or when using diphenylphosphinoyl imines along with a highly nucleophilic peptide-based chiral phosphine.[8,9] The utility of the resultant 3-pyrrolines was demonstrated in the formal syntheses of (±)-allosecurenine and (+)-trachelanthamidine, respectively.[8,9] The development of new methods for forming these types of heterocycles would be a boon to the synthetic community.

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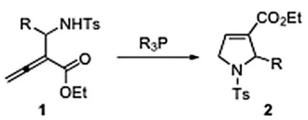
‡ Electronic supplementary information (ESI) available: Experimental details and NMR spectra of new compounds. See DOI: 10.1039/c2cc31347b

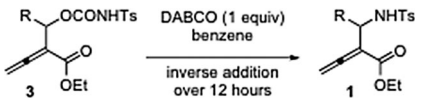
The propensity for 2,3-butadienoates and 2-butynoates to undergo nucleophilic attack at their γ-carbon atom is well documented in the literature; it has been employed in the formation of carbon–carbon, carbon–oxygen, carbon–nitrogen, and carbon–sulfur bonds.[10] Of particular value to our discussion are intramolecular examples of this reactivity; for example, in which a hydroxyl group tethered *via* the γ-carbon atom of an activated alkyne can undergo 5- or 6-*exo* cyclization to yield a number of different oxygen-containing heterocycles (*e.g.*, substituted tetrahydrofurans, dihydrobenzopyrans, and 1,3-oxazines).[10b,i] Stemming from our interest in using nucleophilic phosphine catalysts to activate allenoates and butynoates, in this study we explored the reactivity of electron-deficient allenes bearing a tethered nitrogen-centered nucleophile with the aim of facilitating intramolecular γ-umpolung additions to yield 2-alkyl-substituted-3-pyrrolines (Scheme 1).[11] To the best of our knowledge, there are no previously reported examples of this type of addition occurring *via* 5-*endo* cyclization.

To test the proposed cycloisomerization, we required a method for synthesizing the necessary α-aminoalkylallenoates. For this purpose, we turned to a known tertiary amine-catalyzed rearrangement of allylic *N*-tosyl carbamates and tested it on the similar, but never before utilized, allenylic *N*-tosyl carbamates **3**.[12,13] We were pleased to discover that treatment of the allenylic carbamates with a nucleophilic catalyst facilitated the desired rearrangement. The reaction was best facilitated by slowly adding the allenylic carbamate to a solution of one equivalent of DABCO (Table 1).[13] Interestingly, we isolated the allenoate **1a** in the highest yield (56%) when using dimethyl sulfide as the catalyst in MeCN.[14] Dimethyl sulfide failed to provide any desired rearrangement products from any of our other tested substrates. The DABCO-mediated reaction was tolerant of various alkyl groups, providing the desired products in modest yields. The best result was realized when a methyl substituent was present, providing the desired allenoate **1b** in 65% yield (entry 2). Extending the chain decreased the efficiency (entries 3 and 4). The reaction also proceeded smoothly when



Scheme 1 Phosphine-catalyzed intramolecular γ-umpolung addition.

Table 1 Decarboxylative rearrangements of allenylic *N*-tosyl carbamates



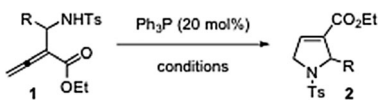
Entry	*R*	Product	Yield[a] (%)
1	H	**1a**	56[b]
2	methyl	**1b**	65
3	ethyl	**1c**	56
4	n-pentyl	**1d**	27
5	i-propyl	**1e**	52
6	cyclopropyl	**1f**	45
7	cyclopentyl	**1g**	45
8	cyclohexyl	**1h**	51
9	phenyl	**1i**	0

[a] Isolated yield after column chromatography. [b] Dimethyl sulfide was used as the catalyst with MeCN as the solvent.

bulkier substituents, namely isopropyl and cycloalkyl groups, were present, albeit in slightly lower yields (entries 5–8). Notably, when an aryl substituent was present, the reaction yielded none of the desired product (entry 9); we could, however, synthesize those allenoates **1** featuring an aryl group as the R unit through aza-Baylis–Hillman reactions between ethyl 2,3-butadienoate and aryl imines.[13,15]

With the requisite α-aminoalkylallenic esters in hand, we explored their reactivity under nucleophilic catalysis (Table 2). We were pleased to find that addition of 20 mol% of Ph_3P to the allenoate **1i** in CH_2Cl_2 at room temperature provided the dihydropyrrole **2i** in 62% yield (entry 1). Screening of various solvents (entries 1–5) revealed that benzene was the most efficient reaction medium in terms of the product yield and reaction time, providing the dihydropyrrole in 93% isolated yield after 18 h (entry 5). Use of the more-nucleophilic *n*-Bu_3P markedly decreased the reaction time, but led to a dramatic loss in product yield (entry 6). Next, we extended the reaction to β′-alkyl–substituted α-aminoalkylallenic esters in an attempt to access 2-alkyl–substituted dihydropyrroles. In a very gratifying initial trial, we transformed the ethyl-substituted allenic ester into the desired 2,5-dihydropyrrole in 92% yield (entry 7). In salient contrast to the reaction of the phenyl-substituted derivative **1i**, the β′-ethyl–substituted allenic ester **1c** required a significantly

Table 2 Optimization of the phosphine-catalyzed cycloisomerization



Entry	*R*	Solvent	Additives	Time	Product	Yield[a] (%)
1	Ph	CH_2Cl_2	none	40 h	**2i**	62
2	Ph	PhMe	none	40 h	**2i**	89
3	Ph	THF	none	40 h	**2i**	0[b]
4	Ph	MeCN	none	40 h	**2i**	0
5	Ph	PhH	none	18 h	**2i**	93
6[c]	Ph	PhH	none	1 h	**2i**	29
7	Et	PhH	none	52 h	**2c**	92
8	Cyp	PhH	none	10 days	**1g**	44
9	Et	PhH	AcOH/NaOAc	32 h	**2c**	97
10	Cyp	PhH	AcOH/NaOAc	4 days	**1g**	85

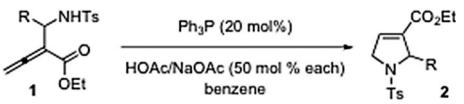
[a] Isolated yield after silica gel chromatography. [b] Recovered starting material. [c] Bu_3P was used.

prolonged reaction time (52 h, *cf.* 18 h). Increasing the steric bulk of the alkyl group generally decreased the yield and increased the reaction time. The substrate bearing a cyclopentyl group required a reaction for 10 days at 40 °C to reach completion, resulting in an isolated yield of only 44% for the desired pyrroline (entry 8). We made several efforts to minimize the reaction time and improve the yields of the alkyl-substituted substrates. Based on reports of added Brønsted acid/base pairs increasing reaction efficiencies for various phosphine-catalyzed reactions, we screened several additives for their effects. To our delight, the addition of sodium acetate and acetic acid (0.5 equivalents each) shortened the reaction times and generally improved the yields (entries 9 and 10).[11o,16]

Under the optimized conditions, we converted a number of β′-alkyl– and β′-aryl–substituted α-aminoalkylallenic esters **1** to their corresponding dihydropyrroles **2** (Table 3). The yields for these cycloisomerizations were generally very high. The allenoates **1a** and **1j** underwent cyclizations in higher yields in the absence of any additives (entries 1 and 10). All of the other alkyl-substituted allenoates benefited from the combination of catalytic Ph_3P and Brønsted acid/base, cyclizing in moderate to excellent yields. The allenoates bearing short straight-chain alkyl units, namely methyl and ethyl groups, cyclized in 99 and 97% yields, respectively (entries 2 and 3). The presence of a longer n-pentyl group resulted in lower reaction efficiency, with the allenoate cyclizing in 69% yield (entry 4). Branched alkyl groups were also tolerated well, with the isopropyl-, cyclopropyl-, cyclopentyl-, and cyclohexyl-substituted allenoates cyclizing in 97, 95, 85, and 93% yields, respectively (entries 5–8). Aryl-substituted α-aminoalkylallenic esters also cyclized in high yields (entries 9–12), with the more-electronegative 4-chlorophenyl– and 4-cyanophenyl–substituted allenoates resulting in slightly diminished product yields of 88 and 85%, respectively (entries 10 and 12) relative to the more-electron-rich phenyl- and 4-methoxyphenyl–substituted allenoates, which both cyclized in 99% yields (entries 9 and 11).

Fig. 1 displays our proposed mechanism for the cycloisomerization. Addition of Ph_3P to the α-aminoalkylallenic ester **1** leads to the formation of the phosphonium dienolate **4**. Conversion to

Table 3 Phosphine-catalyzed intramolecular γ-umpolung additions



Entry	*R*	Time (h)	Product	Yield (%)
1	H	18	**2a**	87[a]
2	Me	19	**2b**	99
3	Et	32	**2c**	97
4	*n*-Pent	48	**2d**	69
5	*i*-Pr	77	**2e**	97
6	cyclopropyl	72	**2f**	95
7	cyclopentyl	96	**2g**	85
8	cyclohexyl	96	**2h**	93[b]
9	phenyl	12	**2i**	99
10	4-chlorophenyl	4.5	**2j**	88[a]
11	4-methoxyphenyl	22	**2k**	99
12	4-cyanophenyl	2	**2l**	85

[a] Yield in the absence of any additives. [b] Based on recovered starting material (69% isolated yield).

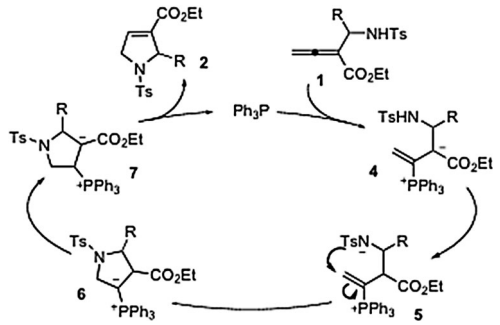


Fig. 1 Mechanism for the intramolecular γ-umpolung addition.

the sulfonamide anion **5** *via* proton transfer, followed by 5-*endo* cyclization, yields the phosphorous ylide **6**. The well-established equilibration between **6** and **7**, followed by *β*-elimination of the phosphine catalyst, furnishes the final product **2**.

In conclusion, we have developed a method for the high-yield formation of 3-carbethoxy-2-alkyl-3-pyrrolines by way of phosphine-catalyzed cycloisomerizations of α-aminoalkylallenic esters. The necessary substrates can be prepared in moderate yields: for aryl-substituted allenoic esters, through aza-Baylis–Hillman reactions; for alkyl-substituted allenoic esters, through novel decarboxylative rearrangements of allenylic carbamates catalyzed by a tertiary amine. This paper illustrates the first example of a 5-*endo* cyclization occurring *via* intramolecular γ-umpolung addition to an activated allene.

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