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

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Abstract

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 allenyl 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 ($\pm$)-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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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 allenates 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-alkylsubstituted-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 -aminoalkylallenates. 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, allenyl-*N*-tosyl carbamates **3**.^{12,13} We were pleased to discover that treatment of the allenyl carbamates with a nucleophilic catalyst facilitated the desired rearrangement. The reaction was best facilitated by slowly adding the allenyl carbamate to a solution of one equivalent of DABCO (Table 1).¹³ Interestingly, we isolated the allenate **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 allenate **1b** in 65% yield (entry 2). Extending the chain decreased the efficiency (entries 3 and 4). The reaction also proceeded smoothly when 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 allenates **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 -aminoalkylallenenic esters in hand, we explored their reactivity under nucleophilic catalysis (Table 2). We were pleased to find that addition of 20 mol% of Ph₃P to the allenate **1i** in CH₂Cl₂ 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*-Bu₃P 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 -aminoalkylallenenic 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 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).^{11a,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 allenates **1a** and **1j** underwent cyclizations in higher yields in the absence of any additives (entries 1 and 10). All of the other alkyl-substituted allenates benefited from the combination of catalytic Ph_3P and Brønsted acid/base, cyclizing in moderate to excellent yields. The allenates 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 allenate cyclizing in 69% yield (entry 4). Branched alkyl groups were also tolerated well, with the isopropyl-, cyclopropyl-, cyclopentyl-, and cyclohexyl-substituted allenates 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 allenates 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 allenates, 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 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 allenic esters, through aza-Baylis–Hillman reactions; for alkyl-substituted allenic esters, through novel decarboxylative rearrangements of allenic 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Notes and references

1. Nitrogen-containing heterocycles are present in six of the ten best-selling pharmaceuticals of 2009 (as ranked by worldwide sales): Lipitor® (Pfizer), Zyprexa® (Lilly), Crestor® (AstraZeneca), Seroquel® (AstraZeneca), Nexium® (AstraZeneca), and Plavix® (Bristol–Meyers Squibb). See: Mack DJ, Brichacek M, Plichta A, Njardarson JT. Top 200 Pharmaceutical Products by Worldwide Sales in 2009. <http://cbc.arizona.edu/njardarson/group/top-pharmaceuticals-poster>.
2. (a) Huwe CM, Blechert S. *Tetrahedron Lett.* 1994; 35:7099. (b) Xu Z, Lu X. *J. Org. Chem.* 1998; 63:5031. (c) Green MP, Prodger JC, Hayes CJ. *Tetrahedron Lett.* 2002; 43:6609. (d) Sun W, Ma X, Hong L, Wang R. *J. Org. Chem.* 2011; 76:7826. [PubMed: 21812473]
3. (a) Xu Z, Lu X. *Tetrahedron Lett.* 1997; 38:3461. (b) Xu Z, Lu X. *Tetrahedron Lett.* 1999; 40:549.
4. (a) Zhu X, Henry CE, Kwon O. *Tetrahedron.* 2005; 61:6276. (b) Andrews IP, Kwon O. *Org. Syn.* 2011; 88:138. (c) Zhao G, Shi M. *J. Org. Chem.* 2005; 70:9975. [PubMed: 16292830] (d) Zheng S, Lu X. *Org. Lett.* 2008; 10:4481. [PubMed: 18783233]
5. (a) Castellano S, Fiji HDG, Kinderman SS, Watanabe M, De Leon P, Tamanoi F, Kwon O. *J. Am. Chem. Soc.* 2007; 129:5843. [PubMed: 17439124] (b) Watanabe M, Fiji HDG, Guo L, Chan L, Kinderman SS, Slamon DJ, Kwon O, Tamanoi F. *J. Biol. Chem.* 2008; 283:9571. [PubMed: 18230616] (c) Lu J, Chan L, Fiji HDG, Dahl R, Kwon O, Tamanoi F. *Mol. Cancer Ther.* 2009; 8:1218. [PubMed: 19417142] (d) Wang Z, Castellano S, Kinderman SS, Argueta CE, Beshir AB, Fenteany G, Kwon O. *Chem. Eur. J.* 2011; 17:649. [PubMed: 21207585] (e) Cruz D, Wang Z, Kibbie J, Modlin R, Kwon O. *Proc. Natl. Acad. Sci. U.S. A.* 2011; 108:6769. (f) Du Y, Lu X. *J. Org. Chem.* 2003; 68:6463. [PubMed: 12895091] (g) Pham TQ, Pyne SG, Skelton BW, White AH. *J. Org. Chem.* 2005; 70:6369. [PubMed: 16050699]
6. (a) Jean L, Marinetti A. *Tetrahedron Lett.* 2006; 47:2141. (b) Scherer A, Gladysz JA. *Tetrahedron Lett.* 2006; 47:6335. (c) Bregeot NF, Jean L, Retailleau P, Marinetti A. *Tetrahedron.* 2007; 63:11920. (d) Fang Y, Jacobsen EN. *J. Am. Chem. Soc.* 2008; 130:5660. [PubMed: 18393504] (e) Zheng S, Lu X. *Org. Lett.* 2008; 10:4481. [PubMed: 18783233] (f) Pinto N, Bregeot NF, Marinetti A. *Eur. J. Org. Chem.* 2009; 74:146.
7. Liddell JR. *Nat. Prod. Rep.* 2002; 19:773. [PubMed: 12521269]
8. Sampath M, Lee P-YB, Loh T-P. *Chem. Sci.* 2011; 2:1988.
9. Han X, Zhong F, Wang Y, Lu Y. *Angew. Chem. Int. Ed.* 2012; 51:767.
10. Albeit not in a catalytic form, Cristau demonstrated the first γ -umpolung additions to activated allenes; see: Cristau H-J, Viala J, Christol H. *Tetrahedron Lett.* 1982; 23:1569. For reactions catalytic in tertiary phosphine, see: Trost B, Li C-J. *J. Am. Chem. Soc.* 1994; 116:10819. Lu X, Zhang C. *Synlett.* 1995; 6:645. Chen Z, Zhu G, Jiang Q, Xiao D, Cao P, Zhang X. *J. Org. Chem.* 1998; 63:5631. Alvarez-Iberrera C, Csaky A, Gomez de la Oliva C. *J. Org. Chem.* 2000; 65:3544. [PubMed: 10843645] Lu C, Lu X. *Org. Lett.* 2002; 4:4677. [PubMed: 12489959] Pakulski Z, Demchuk OM, Frelek J, Luboradzki R, Pietrusiewicz KM. *Eur. J. Org. Chem.* 2004; 69:3913. Virieux D, Guillouzic A-F, Cristau H-J. *Tetrahedron.* 2006; 62:3710. Chung YK, Fu GC. *Angew. Chem., Int. Ed.* 2009; 48:2225. Guan X-Y, Wei Y, Shi M. *Org. Lett.* 2010; 12:5024. [PubMed: 20936863] Zhang Q, Yang L, Tong X. *J. Am. Chem. Soc.* 2010; 132:2550. [PubMed: 20131904] Smith SW, Fu GC. *J. Am. Chem. Soc.* 2009; 131:14231. [PubMed: 19772285]
11. (a) Zhu X-F, Lan J, Kwon O. *J. Am. Chem. Soc.* 2003; 125:4716. [PubMed: 12696883] (b) Zhu X-F, Henry CE, Kwon O. *Tetrahedron.* 2005; 61:6276. (c) Zhu X-F, Henry CE, Wang J, Dudding T, Kwon O. *Org. Lett.* 2005; 7:1387. [PubMed: 15787513] (d) Zhu X-F, Schaffner A, Li RC, Kwon O. *Org. Lett.* 2005; 7:2977. [PubMed: 15987184] (e) Tran YS, Kwon O. *Org. Lett.* 2005; 7:4289. [PubMed: 16146409] (f) Dudding T, Kwon O, Mercier E. *Org. Lett.* 2006; 8:3643. [PubMed: 16898781] (g) Mercier E, Fonovic B, Henry C, Kwon O, Dudding T. *Tetrahedron Lett.* 2007; 48:3617. (h) Zhu X-F, Henry CE, Kwon O. *J. Am. Chem. Soc.* 2007; 129:6722. [PubMed: 17488018] (i) Henry CE, Kwon O. *Org. Lett.* 2007; 9:3069. [PubMed: 17629288] (j) Tran YS, Kwon O. *J. Am. Chem. Soc.* 2007; 129:12632. [PubMed: 17914823] (k) Sriramurthy V, Barcan

- GA, Kwon O. J. Am. Chem. Soc. 2007; 129:12928. [PubMed: 17924625] (l) Creech GS, Kwon O. Org. Lett. 2008; 10:429. [PubMed: 18173275] (m) Creech GS, Zhu X, Fonovic B, Travis D, Kwon O. Tetrahedron. 2008; 64:6935. [PubMed: 19606204] (n) Guo H, Xu Q, Kwon O. J. Am. Chem. Soc. 2009; 131:6318. [PubMed: 19374356] (o) Vardhineedi S, Kwon O. Org. Lett. 2010; 12:1084. [PubMed: 20143856] (p) Khong SN, Tran YS, Kwon O. Tetrahedron. 2010; 66:4760. [PubMed: 21359169] (q) Martin TJ, Tran YS, Vakhshori V, Kwon O. Org. Lett. 2011; 13:2586. [PubMed: 21491870] (r) Szeto J, Sriramurthy V, Kwon O. Org. Lett. 2011; 13:5420. [PubMed: 21932819] (s) Fan, YC.; Kwon, O. Phosphine Catalysis, in Science of Synthesis. List, B., editor. Vol. 1. New York: Asymmetric Organocatalysis, Lewis Base and Acid Catalysis, Georg Thieme Verlag KG, Stuttgart; 2012. p. 713-782.
12. (a) Ciclosi M, Fava C, Galeazzi R, Orena M, Sepulveda- Arques J. Tetrahedron Lett. 2002; 43:2199.(b) Kobbelgaard S, Brandes S, Jørgensen KA. Chem. Eur. J. 2008; 14:1464. [PubMed: 18098235]
13. See the Supporting Information† for details regarding reaction optimization. Cursory attempts at employing commercially available cinchona alkaloids for the asymmetric variant of the rearrangement failed to produce the desired products in appreciable yields.
14. Ye L-W, Sun X-L, Wang Q-G, Tang Y. Angew. Chem. Int. Ed. 2007; 46:5951.
15. Cowen BJ, Saunders LB, Miller S. J. Am. Chem. Soc. 2009; 131:6105. [PubMed: 19354290]
16. Trost BM, Dake GR. J. Am. Chem. Soc. 1997; 119:7595.

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

Scheme 1. Phosphine-catalyzed intramolecular γ -umpolung addition.

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

Entry	<i>R</i>	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.

Table 2

Optimization of the phosphine-catalyzed cycloisomerization

Entry	R	Solvent	Additives	Time	Product	Yield ^a (%)
1	Ph	CH ₂ Cl 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 Bu₃P was used

Table 3Phosphine-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	<i>n</i> -Pent	48	2d	69
5	<i>i</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

^aYield in the absence of any additives.^bBased on recovered starting material (69% isolated yield).