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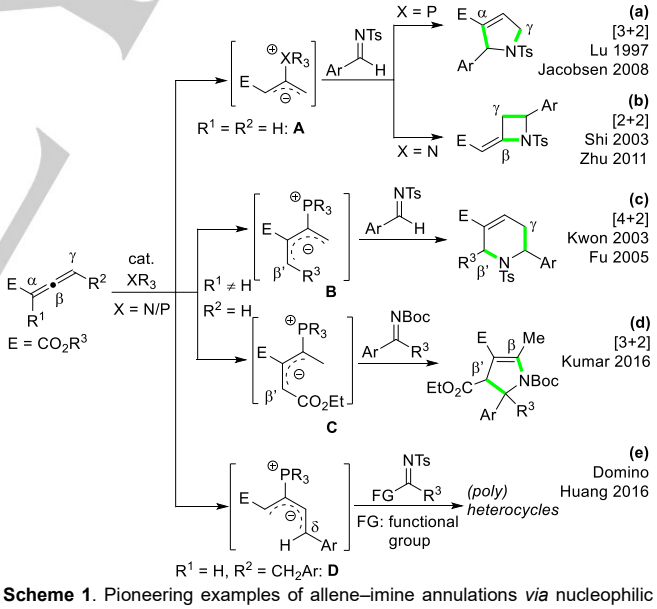
Phosphine-Catalyzed [4+1] Cycloadditions of Allenes with Methyl Ketimines, Enamines, and A Primary Amine

Ze-Hun Cao†[a], Yu-Hao Wang†[a], Subarna Jyoti Kalita[a], Uwe Schneider[b] and Yi-Yong Huang*[a]

Abstract: Unprecedented phosphine-catalyzed [4+1] cycloadditions of allenyl imides have been discovered using various *N*-based substrates including methyl ketimines, enamines, and a primary amine. These transformations provide a one-pot access to cyclopentenoyl enamines and imines, or (chiral) γ-lactams *via* two geminal C–C bond or two C–N bond formations, respectively. Several *P*-based key intermediates including a 1,4-(bis)electrophilic α,β-unsaturated ketenyl phosphonium species have been detected by ^{31}P NMR and HRMS analyses, which shed light on the postulated catalytic cycle. The synthetic utility of this new chemistry has been demonstrated through a gram-scaling up of the catalytic reaction as well as regioselective hydrogenation and double condensation to form cyclopentanoyl enamines and fused pyrazole building blocks, respectively.

Introduction

Nucleophilic catalysis, e.g. the conjugate addition of a phosphine or an amine catalyst across electrophilic allenes to generate reactive zwitterionic intermediates, has emerged as an indispensable method for the synthesis of both carbocycles and heterocyles.[1] Catalytic nucleophile-induced annulation between allenyl esters and imines has drawn great attention since Lu's pioneering work in 1997.[2] To date, five types of allene–imine annulations have been established to build diverse *N*-heterocycles (Scheme 1). (1) Lu's phosphine-catalyzed [3+2] cycloaddition using non-substituted allenyl esters (R^1 = R^2 = H; Scheme 1a): zwitterionic intermediate **A** has been involved to give various racemic[3] and enantiomerically enriched[4] functionalized pyrrolines through α-C–C and γ-C–N bond formations; (2) Shi's [2+2] cycloaddition using the same types of substrates and generating an isomerizable intermediate with DABCO or cinchona alkaloid amide catalysts (Scheme 1b): racemic[5] and enantiomerically enriched azetidines[6] have been formed stereoselectively through γ-C–C and β-C–N bond formations; (3) Kwon's phosphine-catalyzed [4+2] cycloaddition using α-substituted allenyl esters (R^1 = CH_2R^3, R^2 = H; Scheme 1c):[7] 1,4-dipole **B** has been generated as a key intermediate to form tetrahydropyridines through γ-C–C and β'-C–N bond formations. Here, the electron delocalization in **B** is extended to the β'-C atom[8]; (4) Kumar's phosphine-catalyzed [3+2] cycloaddition using α-substituted allenyl esters (R^1 = CH_2CO_2Et, R^2 = H; Scheme 1d):[9] In contrast to Kwon's mode, a zwitterionic 1,3-dipole **C** was engaged in the annulation through β'-C–C and β-C–N bond formations when isatine-derived *N*-Boc-ketimines were used; (5) Huang's sequential domino annulations using γ-benzyl allenyl esters (R^1 = H, R^2 = CH_2Ar; Scheme 1e) to give (poly)heterocycles: here, the electron delocalization in intermediate **D** is extended to the δ-C atom.[10] Based on the putative reaction mechanisms, these allene-derived zwitterionic intermediates all exhibit initial *nucleophilicity* to imines, and play a pivotal role in the above dipolar cycloadditions. From the viewpoint of both mechanism- and diversity-oriented synthesis, the development of fundamentally distinct allene–imine annulation methodologies to generate complex molecules in a simple and efficient manner is still in great demand but remains a significant challenge. Assuming that new reactive intermediates may be discovered in the event, these could be trapped by other reaction partners with the purpose of widening the synthetic versatility.



Scheme 1. Pioneering examples of allene–imine annulations *via* nucleophilic catalysis.

In our earlier study, allenyl imides bearing a 2-oxazolidinyl group has been successfully subjected to a Lewis acid-catalyzed [2+2] cycloaddition/isomerization sequence with non-activated aldimines.[11] Further exploiting allenyl imides in phosphine catalysis are based on the following observations and anticipations: (1) we previously found that the 2-oxazolidinyl group of an α,β-alkenyl imide was readily detached when exposed to nucleophiles (Scheme 2a);[12] (2) a common approach to ketenes is base-mediated elimination of HCl from acyl chlorides (Scheme 2b);[13] (3) upon reaction of allenyl imide **1** with a nucleophilic phosphine catalyst, *nucleophilic* zwitterionic intermediate **E** is initially formed via conjugate addition; the

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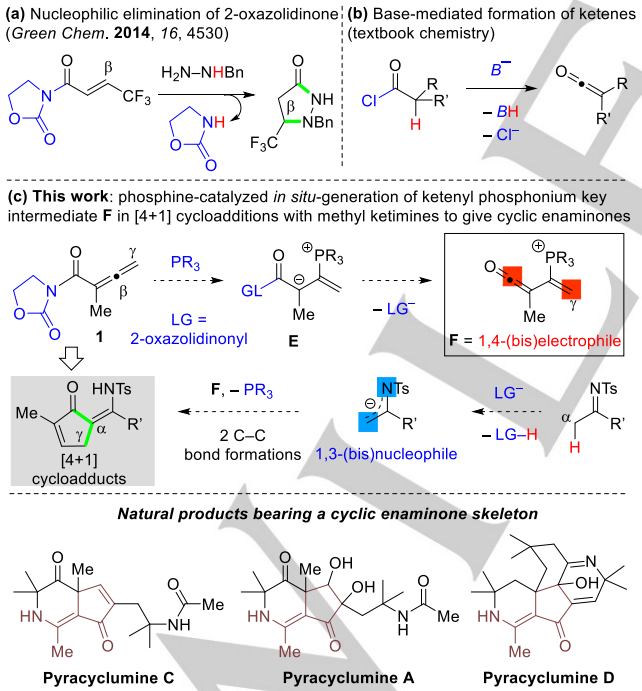
elimination of the 2-oxazolidinyl group may result in the generation of the intriguing α,β-unsaturated ketenyl phosphonium intermediate **F**; the latter may act as a 1,4-(bis)*electrophile* and trigger unprecedented annulations (Scheme 2c). It is noted that the synthetic utility of 1,4-(bis)electrophilic intermediates generated *via* phosphine-induced elimination of an acetate group from β'-acetoxy allenyl esters has been reported by Tong,[14] Fu,[15] and Lu;[16] to the best of our knowledge, however, the use of imines as reaction partners in this context is unprecedented. In order to test the possibility of generating and synthetically exploiting intermediate **F**, methyl *N*-tosyl ketimines have been chosen as reactions partners (Scheme 2c). These imines may serve as both 1*C*,1*C*-(bis)nucleophiles or 1*C*,3*N*-(bis)nucleophiles[17] to capture the putative 1,4-(bis)electrophile **F**, which may result in [4+1] or [4+3] annulations, respectively. If a [4+1] pathway proceeded,[18] the construction of a functionalized cyclopentenone motif[19] under atypical metal-free conditions would be anticipated.[20] In this context, in view of producing synthetically useful cyclopentenonyl enamines and imines, we report herein original results on novel [4+1] annulations of allene **1** with methyl ketimines and enamines (two geminal C–C bond formations through a one-pot method). Indeed, the synthesis of these building blocks and their applications have drawn particular interest;[21] e.g. pyracyclumines C, A, and D –isolated from the roots of *Anacyclus pyrethrum* feature this type of key sub-structure (Scheme 2c).[22] These transformations feature both *P*-based intermediates of opposite polarity and products of distinct connectivity compared with the reported allene–imine annulations (cf. Scheme 1). In addition, ^{31}P NMR and HRMS analyses regarding the reaction mechanism have been carried out, leading to the extension of this methodology to the use of an amine (formation of γ-lactams; two geminal C–N bond formations one-pot).

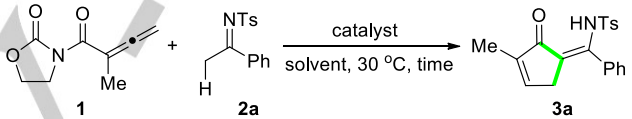


Scheme 2. New reaction design for allene–imine annulations.

Results

Optimization of reaction conditions for the allene–imine annulation. We commenced the study using allenyl imide **1** and ketimine **2a** in the presence of tertiary phosphine catalysts (Table 1). The use of PPh_3 and PCy_3 in DCM at 30 °C for 24 h did not promote the [4+1] cycloaddition in acceptable yields (entries 1 and 2); on the other hand, the use of the more nucleophilic PBu_3 (20 mol%) increased the yield of product **3a** to 54% (entry 3). In **3a**, the α-methyl group of **2a** was found to be connected to the γ- and carbonyl carbon atoms of **1** with an apparent loss of the 2-oxazolidinyl leaving group (two C–C geminal bond formations). The structural assignment of **3a** with a (*Z*)-configured enamine unit was spectroscopically determined and later confirmed by X-ray crystallography of product **3k** (*vide infra*). Significantly, the successful [4+1] reaction outcome validated our hypothesis in Scheme 2c, especially the *in situ* formation of 1,4-(bis)electrophile **E**; a plausible reaction pathway for the formation of **3a** is detailed *vide infra*. Next, a solvent screening was carried out (entries 4–13); the reaction in benzene gave **3a** in 60% yield within 3 h (entry 9). However, further experimentation did not lead to a better result (entries 10–12). Likewise, the use of Brønsted basic additives including Cs_2CO_3 has proved disappointing (see Table S–1). To our delight, product **3a** was obtained in 70% yield when dichloroethane was used as a solvent (entry 13).

Table 1. Optimization of conditions for the reaction between **1** and **2a**.[a]



1 **2a** **3a**

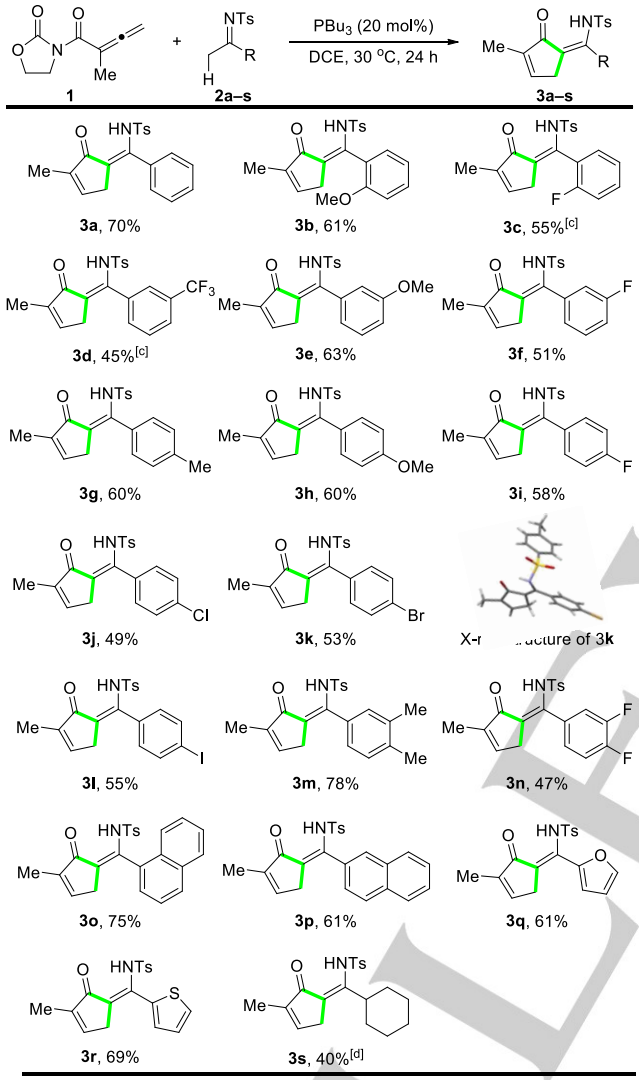
entry	catalyst	solvent	time/h	yield/%[b]
1	PPh_3	DCM	24	11
2	PCy_3	DCM	24	10
3	PBu_3	DCM	24	54
4	PBu_3	ethyl acetate	24	48
5	PBu_3	chloroform	24	50
6	PBu_3	THF	24	39
7	PBu_3	1,4-dioxane	3	27
8	PBu_3	Et_2O	24	32
9	PBu_3	benzene	3	60
10[c]	PBu_3	benzene	6	55
11[d]	PBu_3	benzene	3	43
12[e]	PBu_3	benzene	24	58
13	PBu_3	DCE	24	70

[a] Reaction conditions: **1** (0.10 mmol), **2a** (0.12 mmol, 1.2 equiv), catalyst (20 mol%), solvent (1.0 mL). [b] Isolated yield. [c] 0.5 mL of benzene. [d] Run at 60 °C. [e] 10 mol% of catalyst.

Scope for the use of methyl ketimines. With the optimized conditions in hand, we focused on the methyl ketimine scope (Scheme 3). Pleasingly, a range of highly functionalized cyclopentenonyl enamines **3** were constructed in 40–78% yield. When MeO or F groups were introduced at the *ortho* (**2b–c**), *meta* (**2e–f**), and *para* (**2h–i**) positions of aromatic ketimines, the corresponding cycloadducts **3** were isolated in comparable yields. The use of substrate **2d** with an electron-withdrawing group (CF_3) at the *meta* position gave product **3d** in 45% yield. The use of substrates bearing methyl and halide substituents (Cl, Br, and I) at the *para* position gave the corresponding products **3** in 49–60% yield; the structure of compound **3k** was further confirmed by X-ray crystallographic analysis.[23] The use of *meta*,*para*-disubstituted ketimines was found to be compatible with the reaction conditions; here, it is noted that methyl groups (**3m**, 78%)

proved to be more suitable than fluoro groups (**3n**, 47%). Both 1-naphthyl and 2-naphthyl substitution was tolerated to give products **3o** and **3p** in 75% and 61% yield, respectively. Likewise, heterocylic ketimines including 2-furyl and 2-thienyl groups underwent the [4+1] cycloaddition leading to products **3q** and **3r** in 61% and 69% yield, respectively. Notably, the transformation using the very challenging (bis)aliphatic ketimine **2s** proceeded at 60 °C, providing product **3s** in a respectable 40% yield.

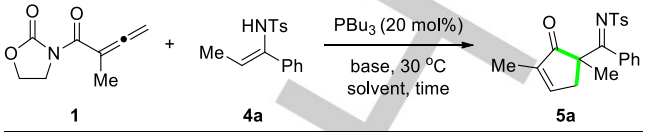
Scheme 3. Scope for the use of methyl ketimines **2**.[a,b]



[a] Reaction conditions: **1** (0.10 mmol), **2** (0.12 mmol, 1.2 equiv), PBu_3 (20 mol%), DCE (1.0 mL), 24 h. [b] Isolated yield. [c] Run for 48 h. [d] Run at 60 °C.

Optimization of reaction conditions for the allene–enamine annulation. In view of a potential imine/enamine tautomerism under the employed basic conditions, the possibility of directly using enamines instead of methyl ketimines was examined. We were pleased to find that this transformation was indeed successful with enamine **4a** giving rise to the corresponding [4+1] cycloadduct **5a**, in which an all-carbon quaternary stereocenter was constructed (Table 2). While other solvents have proved less suitable (entries 1–3), the intended reaction proceeded in DCE at 30 °C for 24 h to give **5a** in 44% yield (entry 4). The use of a variety of inorganic Brønsted base additives seemed to accelerate the transformation (entries 5–11); the best result was obtained in the presence of 20 mol% of cesium carbonate (3 h, 47% yield; entry 7).

Table 2. Optimization of conditions for the reaction between **1** and **4a**.[a]

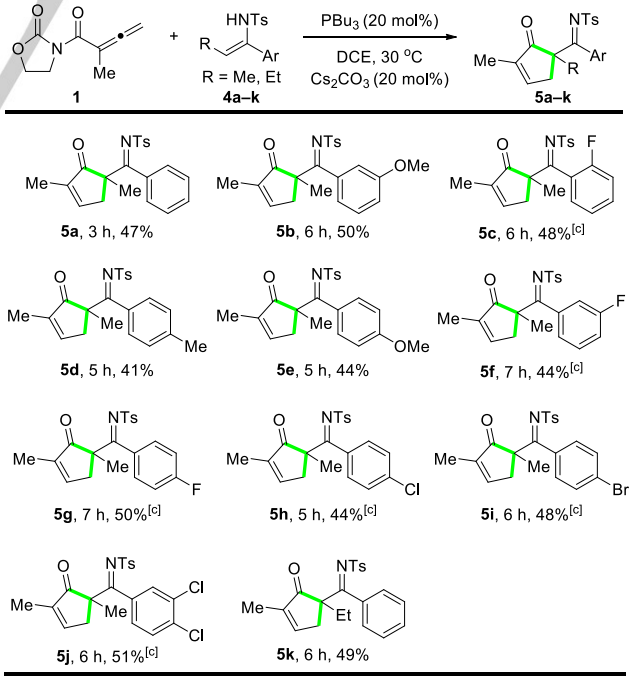


entry	Brønsted base	solvent	time/h	yield/%[b]
1	—	toluene	6	17
2	—	ethyl acetate	6	21
3	—	benzene	6	19
4	—	DCE	24	44
5	Cs_2CO_3 (100 mol%)	DCE	3	25
6	Cs_2CO_3 (50 mol%)	DCE	4	43
7	Cs_2CO_3 (20 mol%)	DCE	3	47
8	Cs_2CO_3 (10 mol%)	DCE	4	33
9	Na_2CO_3 (20 mol%)	DCE	3	29
10	K_2CO_3 (20 mol%)	DCE	3	27
11	NaOH (20 mol%)	DCE	3	30

[a] Reaction conditions: **1** (0.10 mmol), **4a** (0.12 mmol, 1.2 equiv), solvent (1.0 mL), Brønsted base. [b] Isolated yield.

Scope for the use of enamines. Next, we firstly examined the scope of methyl enamines (R = Me; Scheme 4). The use of enamines bearing electron-rich substituents at the aromatic core displayed higher reactivity than electron-neutral substrates, although there was only a marginal impact on the corresponding yields (**5b–j**, 41–51%). It is noted that the conversion of halide-substituted substrates was uniformly performed at 60 °C. Finally, a more challenging ethyl-substituted enamine (R = Et, **4k**) was tested to give product **5k** in a respectable 49% yield.

Scheme 4. Scope for the use of enamines **4**.[a,b]



[a] Reaction conditions: **1** (0.10 mmol), **4** (0.12 mmol, 1.2 equiv), PBu_3 (20 mol%), DCE (1.0 mL), Cs_2CO_3 (20 mol%), 30 °C. [b] Isolated yield. [c] Run at 60 °C.

Control experiments and mechanistic study. In order to shed light on the reaction pathway of this complex transformation, a couple of control experiments were carried out (Scheme 5). Firstly, allene **1** and a benzaldehyde-derived aldimine were reacted in the presence of a catalytic amount of PBu_3 or PPh_3 in DCM; however, the reaction did not occur (Scheme 5a). This result stands in sharp contrast to the studies by Lu[2] and Kwon,[7] and suggests that the use of an allenyl imide –instead of the corresponding ester– involves a novel reactive key intermediate clearly distinct from the reported intermediates **A** and **B** (cf. Scheme 1). Secondly, in order to confirm the effect of water in the assumed proton transfer of this phosphine catalysis,[24] D_2O was used as a stoichiometric additive (Scheme 5b). The use of 1.0 equiv of D_2O had no influence on both rate and yield of **3a** (65%); here, the corresponding product **3a**–*d* was not even detected. On the other hand, the use of 3.0 equiv of D_2O promoted the incorporation of deuterium in the product (33%), while the yield of **3a** decreased to 27%. These results may suggest that water does not play a key role in the catalytic cycle.

Scheme 5. Control experiments using an aldimine or ketimine **2a** in the presence of D_2O.

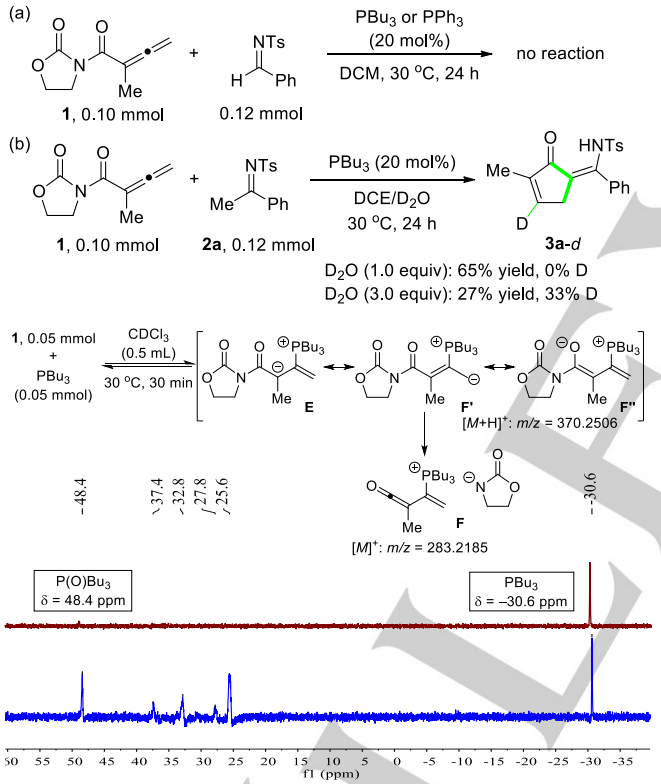


Figure 1. ^{31}P NMR monitoring experiments.

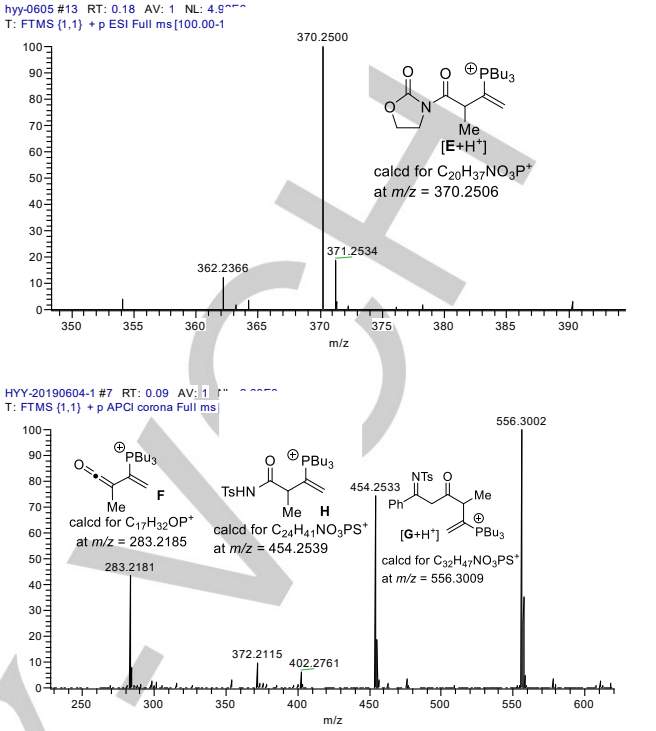


Figure 2. HRMS analysis of the reaction system.

In addition, the reaction system has been examined by ^{31}P NMR spectroscopy and high-resolution mass spectrometry (HRMS; Figures 1 and 2). Initially, allenyl imide **1** and PBu_3 were reacted at an equimolar ratio in $CDCl_3$ (1.0 M) at 30 °C for 30 min (0.05 mmol scale); this reaction was monitored by ^{31}P NMR spectroscopy (Figure 1). This experiment revealed the detection of four new signals (δ = 25.6, 27.8, 32.8, 37.4 ppm) with the major resonance being at 25.6 ppm [in addition to PBu_3 (δ = –30.6 ppm) and $P(O)Bu_3$ (δ = 48.4 ppm)]. These novel peaks have been ascribed to zwitterionic and α,β-unsaturated ketenyl phosphonium intermediates **E** and **F**, respectively (Figure 1) – as confirmed by HRMS; the presence of several signals may be explained by rotational isomers of **E** and/or **F** in a slow equilibrium (relative to the ^{31}P NMR time scale). Next, an aliquot taken from the reaction mixture of allenyl imide **1** and ketimine **2a** in the presence of PBu_3 under standard conditions (6 h) was analyzed by HRMS using both electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI) methods. Here, four major peaks were detected, and these could be ascribed to four key intermediates (Figure 2). For instance, the cation signal at *m*/*z* = 370.2500 (ESI) would correspond to the protonated form of zwitterionic species **E**. Likewise, the ion signals at *m*/*z* = 283.2181 and 556.3002 (APCI) would correspond to α,β-unsaturated ketenyl phosphonium species **F** and the protonated form of zwitterionic C–C bond adduct **G**, respectively. In addition, the ion peak at *m*/*z* = 454.2533 may be attributed to the cationic C–N bond adduct **H** derived from the reaction between **F** and *in situ*-generated $TsNH_2$ (formed by hydrolysis of ketimine **2a**). This unexpected result has inspired us to design a novel [4+1] annulation between allenyl imides and $TsNH_2$ (two geminal C–N bond formations one-pot; *vide infra*).

Plausible reaction mechanism. Based on the collected data above, a plausible reaction mechanism has been proposed for the formation of products **3** or **5** from starting materials **1** and **2** or **4**, respectively (Figure 3). Initially, conjugate nucleophilic addition of PBu_3 to allenyl imide **1** would result in the generation of

zwitterionic intermediate **E**, which would form α,β-unsaturated ketenyl phosphonium species **F**, a 1,4-(bis)electrophile, through loss of the 2-oxazolidinyl anion. This Brønsted base would deprotonate the N–H of enamine substrate **4** to form aza-enolate **I**; **4** may be generated *via* tautomerization if methyl ketimine substrate **2** is used. Nucleophile **I** would add preferentially to the electrophilic C(sp) center of species **F** (first C–C bond formation). The resulting zwitterionic allyl intermediate **F** (cf. Figure 2) may tautomerize to the more stable species **J** (1,3-proton transfer), in which an intramolecular nucleophilic addition would readily occur between the carbanion center and the electrophilic alkene moiety to generate ylide intermediate **K** (second C–C bond formation; 5-*endo*-trig). **K** may isomerize to the more stable species **L** (1,2-proton transfer), from which imine product **5** would be formed by elimination of PBu_3 (catalyst turnover). If R = H, **5** would tautomerize to the corresponding enamine product **3** (1,3-proton transfer).

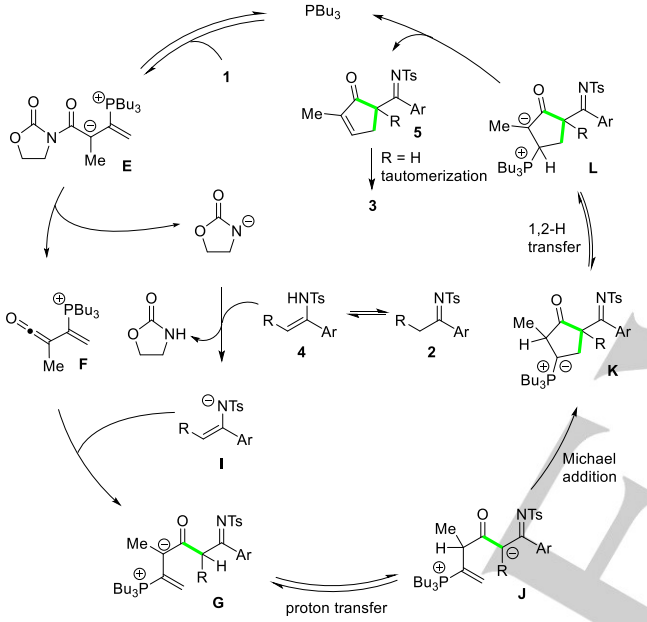
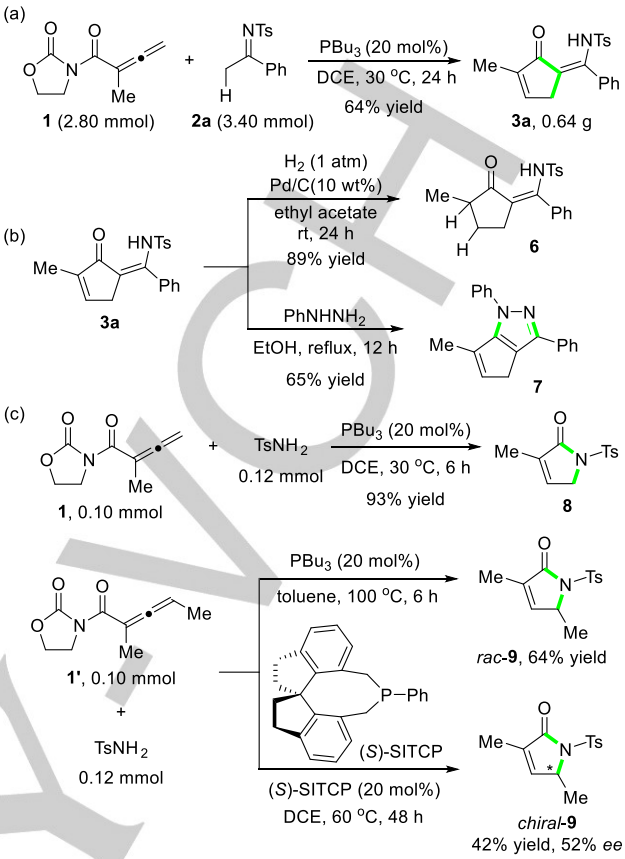


Figure 3. Plausible reaction mechanism.

Synthetic utility. Finally, the synthetic utility of this new chemistry was examined (Scheme 6). The catalytic [4+1] cycloaddition using **1** and **2a** has proved amenable to a gram-scale experiment to give product **3a** in 64% yield (Scheme 6a). Next, a couple of chemical transformations using **3a** were tested. Firstly, Pd/C-catalyzed regioselective hydrogenation of the more electron-poor C=C double bond in **3a** was carried out to form the corresponding cyclopentanonyl enamine building block **6** in 89% yield (Scheme 6b). Secondly, the enaminone fragment in **3a** was converted to the pyrazole sub-structure in **7** through double condensation with phenyl hydrazine (65% yield; Scheme 6b). Finally, based on the unexpected detection of intermediate **H** by HRMS analysis (cf. Figure 2), it was found that this new catalytic method was applicable to using $TsNH_2$ as a 1*N*,1*N*-(bis)nucleophile to give a novel entry to *N*-heterocycles,[25] i.e., γ-lactams such as 1,2-dihydropyrrol-5-one **8** (from allene **1**) and **9** (from α,γ-disubstituted allene **1'**) (two geminal C–N bond formations one-pot).[26] Significantly, when chiral phosphine catalyst (*S*)-SITCP was used, chiral compound **9** was formed in 42% yield with 52% *ee* (Scheme 6c).



Scheme 6. Synthetic utility of the developed chemistry.

Conclusion

In summary, we have developed an unprecedented phosphine-catalyzed [4+1] cycloaddition between an allenyl imide and various methyl ketimines. This catalytic method has proved also valid for the use of enamines under Cs_2CO_3 co-catalysis. These transformations are clearly distinct from and thus complementary to the existing allene−imine annulations. The 2-oxazolidinyl group of the allenyl imide was shown to play a pivotal role in triggering smooth generation of a α,β-unsaturated ketenyl phosphonium key intermediate; as supported by control experiments or NMR and HRMS analyses. These step-economical procedures open up a new avenue to install densely functionalized cyclopentenoyl enamines and imines bearing an all-carbon quaternary stereogenic center. The synthetic utility including gram-scaling up and straightforward access to fused pyrazole and (chiral) dihydropyrrolone building blocks has been demonstrated as well. The use of other types of (bis)nucleophiles and the design of related asymmetric phosphine catalysis is on-going in our lab.

Experimental Section

General Procedure of the [4+1] annulations of allene and ketimine. PBu_3 (0.02 mmol, 20 mol%) was added to a solution of **1** (0.10 mmol) and **2** (0.12 mmol, 1.2 equiv) in DCE (1.0 mL) under an inert atmosphere. The mixture was magnetically stirred at 30 °C for the time indicated (see manuscript), before purification by PTLC to give the corresponding products **3**.

General Procedure of the [4+1] annulations of allene and enamine. PBu_3 (0.02 mmol, 20 mol%) was added to a mixture of **1** (0.10 mmol), **4** (0.12 mmol, 1.2 equiv), and Cs_2CO_3 (20 mol%) in DCE (1.0 mL) under an inert atmosphere. The mixture was magnetically stirred at 30 °C or 60 °C for the time indicated (see manuscript), before purification by PTLC to give the corresponding products **5**.

Acknowledgements

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Keywords: [4+1] Cycloaddition • Allene • Nucleophilic catalysis • Enaminone • Ketene

[1] For reviews, see: a) G. C. Fu, *Acc. Chem. Res.* **2000**, *33*, 412-420; b) Y. Wei, M. Shi, *Acc. Chem. Res.* **2010**, *43*, 1005-1018; c) L.-W. Ye, J. Zhou, Y. Tang, *Chem. Soc. Rev.* **2008**, *37*, 1140-1152; d) H.-C. Guo, Y.-C. Fan, Z.-H. Sun, Y. Wu, O. Kwon, *Chem. Rev*. **2018**, *118*, 10049-10293; e) H.-Z. Ni, W.-L. Chan, Y.-X. Lu, *Chem. Rev.* **2018**, *118*, 9344-9411; For recent representative examples, see: f) K. Z. Li, T. P. Gonçalves, K.-W. Huang, Y. X. Lu, *Angew. Chem. Int. Ed.* **2019**, *58*, 5427-5431; *Angew. Chem.* **2019**, *131*, 5481-5485; g) H.-M. Wang, J.-Y. Zhang, Y.-S. Tu, J.-L. Zhang, *Angew. Chem. Int. Ed.* **2019**, *58*, 5422-5426; *Angew. Chem.* **2019**, *131*, 5476-5480.

[2] Z. Xu, X. Lu, *Tetrahedron Lett.* **1997**, *38*, 3461-3464.

[3] a) Z. Xu, X. Lu, *J. Org. Chem.* **1998**, *63*, 5031-5041; b) X. Tang, B. Zhang, Z. He, R. Gao, Z. He, *Adv. Synth. Catal*. **2007**, *349*, 2007-2017; c) X.-Y. Chen, R.-C. Lin, S. Ye, *Chem. Commun*. **2012**, *48*, 1317-1319; d) R. Na, C. Jing, Q. Xu, H. Jiang, X. Wu, J. Shi, J. Zhong, M. Wang, D. Benitez, E. Tkatchouk, W. A. Goddard, H. Guo, O. Kwon, *J. Am. Chem. Soc*. **2011**, *133*, 13337-13348.

[4] a) L. Jean, A. Marinetti, *Tetrahedron Lett.* **2006**, *47*, 2141-2145; b) Y.-Q. Fang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 5660-5661; c) C. E. Henry, Q. Xu, Y. C. Fan, T. J. Martin, L. Belding, T. Dudding, O. Kwon, *J. Am. Chem. Soc.* **2014**, *136*, 11890-11893; d) X. Han, W.-L. Chan, W. Yao, Y. Wang, Y. Lu, *Angew. Chem. Int. Ed.* **2016**, *55*, 6492-6496; *Angew. Chem.* **2016**, *128*, 6602-6605; e) M. Sampath, P.-Y. B. Lee, T.-P. Loh, *Chem. Sci*. **2011**, *2*, 1988-1991.

[5] G.-L. Zhao, J.-W. Huang, M. Shi, *Org. Lett.* **2003**, *5*, 4737-4739.

[6] J.-B. Denis, G. Masson, P. Retailleau, J. Zhu, *Angew. Chem. Int. Ed*. **2011**, *50*, 5356-5360; *Angew. Chem*. **2011**, *123*, 5468-5472.

[7] X.-F. Zhu, J. Lan, O. Kwon, *J. Am. Chem. Soc.* **2003**, *125*, 4716-4717.

[8] a) R. P. Wurz, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 12234-12235; b) H. Xiao, Z. Chai, H.-F. Wang, X.-W. Wang, D.-D. Cao, W. Liu, Y.-P. Lu, Y.-Q. Yang, G. Zhao, *Chem. - Eur. J.* **2011**, *17*, 10562-10565; c) S. Takizawa, F. A. Arteaga, Y. Yoshida, M. Suzuki, H. Sasai, *Asian J. Org. Chem*. **2014**, *3*, 412-415; d) X.-Y. Chen, S. Ye, *Eur. J. Org. Chem*. **2012**, *2012*, 5723-5728; e) H. Yu, L. Zhang, Z. Li, H. Liu, B. Wang, Y. Xiao, H. Guo, *Tetrahedron* **2014**, *70*, 340-348; f) Ni, X. Tang, W. Zheng, W. Yao, N. Ullah, Y. Lu, *Angew. Chem. Int. Ed.* **2017**, *56*, 14222-14226; *Angew. Chem*. **2017**, *129*, 14410-14414.

[9] M. G. Sankar, M. Garcia-Castro, C. Golz, C. Strohmann, K. Kumar, *Angew. Chem. Int. Ed*. **2016**, *55*, 9709-9713; *Angew. Chem*. **2016**, *128*, 9861-9865.

[10] a) E.-Q. Li, H.-X. Jin, P.-H. Jia, X.-L. Dong, Y. Huang, *Angew. Chem. Int. Ed.* **2016**, *55*, 11591-11594; *Angew. Chem.* **2016**, *128*, 11763-11766; b) E.-Q. Li, P.-H. Jia, L. Liang, Y. Huang, *ACS Catal*. **2014**, *4*, 600-603.

[11] S. Pang, X. Yang, Z.-H. Cao, Y.-L. Zhang, Y. Zhao, Y.-Y. Huang, *ACS Catal.* **2018**, *8*, 5193-5199.

[12] X. Yang, Z. Chen, Y. Cai, Y.-Y. Huang, N. Shibata, *Green Chem.* **2014**, *16*, 4530-4534.

[13] a) D. H. Paull, A. Weatherwax, T. Lectka, *Tetrahedron* **2009**, *65*, 6771-6803; b) A. D. Allen, T. T. Tidwell, *Chem. Rev.* **2013**, *113*, 7287-7342.

[14] a) Q.-M. Zhang, L. Yang, X.-F. Tong, *J. Am. Chem. Soc.* **2010**, *132*, 2550-2551; b) Y.-T. Gu, P.-F. Hu, C.-J. Ni, X.-F. Tong, *J. Am. Chem. Soc.* **2015**, *137*, 6400-6406; c) X. Chen, D.-D. Gao, D. Wang, T. Xu, W. Liu, P. Tian, X.-F. Tong, *Angew. Chem. Int. Ed*. **2019**, *58*, 15334-15338; *Angew. Chem*. **2019**, *131*, 15478-15482.

[15] a) S. Kramer, G. C. Fu, *J. Am. Chem. Soc.* **2015**, *137*, 3803-3806; b) D. T. Ziegler, L. Riesgo, T. Ikeda, Y. Fujiwara, G. C. Fu, *Angew. Chem. Int. Ed.* **2014**, *53*, 13183-13187; *Angew. Chem*. **2014**, *126*, 13399-13403.

[16] X.-Y. Han, W.-J. Yao, T.-L. Wang, Y.-R. Tan, Z.-Y. Yan, J. Kwiatkowski, Y. Lu, *Angew. Chem. Int. Ed.* **2014**, *53*, 5643-5647; *Angew. Chem.* **2014**, *126*, 5749-5753.

[17] a) J.-J. Cheng, Z.-J. Huang, Y. R. Chi, *Angew. Chem. Int. Ed.* **2013**, *52*, 8592-8596; *Angew. Chem.* **2013**, *125*, 8754-8758; b) A. G. Kravina, J. Mahatthananchai, J. W. Bode, *Angew. Chem. Int. Ed.* **2012**, *51*, 9433-9436; *Angew. Chem.* **2012**, *124*, 9568-9572; c) K.-Q. Chen, Z.-H. Gao, S. Ye, *Angew. Chem. Int. Ed.* **2019**, *58*, 1183-1187; *Angew. Chem.* **2019**, *131*, 1195-1199.

[18] a) J.-R. Chen, X.-Q. Hu, L.-Q. Lu, W.-J. Xiao, *Chem. Rev.* **2015**, *115*, 5301-5365; b) C.-Y. Zhu, Y. Ding, L.-W. Ye, *Org. Biomol. Chem.* **2015**, *13*, 2530-2536.

[19] a) S. P. Simeonov, J. P. M. Nunes, K. Guerra, V. B. Kurteva, C. A. M. Afonso, *Chem. Rev.* **2016**, *116*, 5744-5893; b) D. J. Aitken, H. Eijsberg, A. Frongia, J. Ollivier, P. P. Piras, *Synthesis* **2014**, *46*, 1-24.

[20] a) J. L. Loebach, D. M. Bennett, R. L. Danheiser, *J. Am. Chem. Soc*. **1998**, *120*, 9690-9691; b) C. P. Davie, R. L. Danheiser, *Angew. Chem. Int. Ed.* **2005**, *44*, 5867-5870; *Angew. Chem.* **2005**, *117*, 6017-6020; c) J. H. Rigby, Z. Wang, *Org. Lett.* **2003**, *5*, 263-264; d) K. X. Rodriguez, T. C. Pilato, B. L. Ashfeld, *Chem. Sci.* **2018**, *9*, 3221-3226.

[21] a) B. Stanovnik, J. Svete, *Chem. Rev.* **2004**, *104*, 2433-2480; b) L.-Q. Fu, J.-P. Wan, *Asian J. Org. Chem.* **2019**, *8*, 767-776; c) T. Miura, Y. Funakoshi, M. Morimoto, T. Biyajima, M. Murakami, *J. Am. Chem. Soc.* **2012**, *134*, 17440-17443; d) X.-K. Chen, X.-Q. Fang, Y. R. Chi, *Chem. Sci.* **2013**, *4*, 2613-2618; e) L. Wang, S. Li, M. Blgmel, R. Puttreddy, A. Peuronen, K. Rissanen, D. Enders, *Angew. Chem. Int. Ed.* **2017**, *56*, 8516-8521; *Angew. Chem.* **2017**, *129*, 8636-8641; f) Z.-T. Wang, Y. Zhao, Z.-Y. Wang, Y. Cheng, *J. Org. Chem.* **2015**, *80*, 1727-1734; g) N. P. Burlow, S. Y. Howard, C. M. Saunders, J. C. Fettinger, D. J. Tantillo, J. T. Shaw, *Org. Lett.* **2019**, *21*, 1046-1049.

[22] Q. B. Chen, J. Gao, G. A. Zou, X. L. Xin, H. K. Aisa, *J. Nat. Prod.* **2018**, *81*, 1474-1482.

[23] CCDC 1916891 (**3k**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[24] Y. Xia, Y. Liang, Y. Chen, M. Wang, L. Jiao, F. Huang, S. Liu, Y. Li, Z.-X. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3470-3471.

[25] a) R. J. Lundgren, A. Wilsily, N. Marion, C. Ma, Y. K. Chung, G. C. Fu, *Angew. Chem. Int. Ed*. **2013**, *52*, 2525-2528; *Angew. Chem*. **2013**, *125*, 2585-25288; b) Y.-Q. Fang, P. M. Tadross, E. N. Jacobsen, *J. Am. Chem. Soc.* **2014**, *136*, 17966-17968; c) H.-Y. Wang, C. Guo, *Angew. Chem. Int. Ed.* **2019**, *58*, 2854-2858; *Angew. Chem*. **2019**, *131*, 2880-2884.

[26] a) B. Almohaywi, T. T. Yu, G. Iskander, D. S. H. Chan, K. K. K. Ho, S. Rice, S. D. Black, R. Griffith, N. Kumar, *Med. Chem. Lett.* **2019**, *29*, 1054-1059; b) L. Zhang, Y. Tan, N.-X. Wang, Q.-Y. Wu, Z. Xi, G.-F. Yang, *Bioorg. Med. Chem.* **2010**, *18*, 7948-7956.

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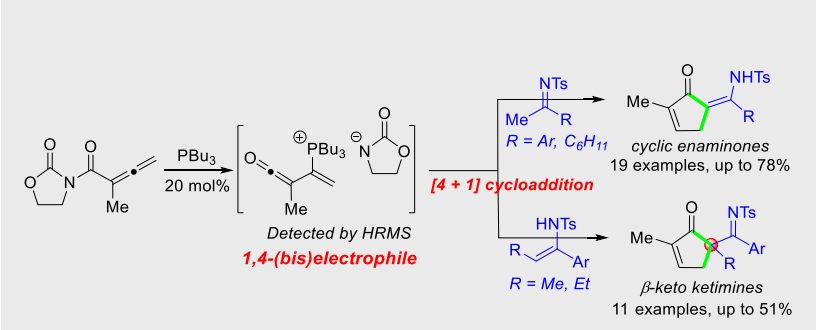

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Phosphine-Catalyzed [4+1] Cycloadditions of Allenes with Methyl Ketimines, Enamines, and A Primary Amine

Phosphine-catalyzed [4+1] cycloadditions of an allene with methyl ketimines and enamines via 1,4-(bis)electrophilic α,β-unsaturated ketenyl phosphonium intermediate have been demonstrated to give cyclopentenoyl enamines and imines, respectively.