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An Intramolecular [2 + 2] Cycloaddition of Ketenimines *via* Palladium-Catalyzed Rearrangements of *N*-Allyl-Ynamides

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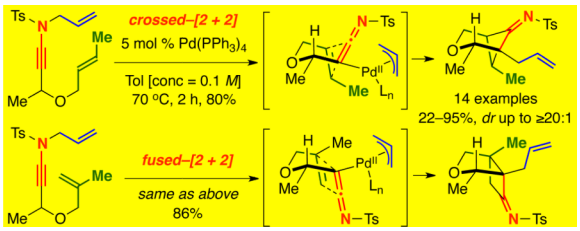
Abstract



A cascade of Pd-catalyzed *N*-to-C allyl transfer–intramolecular ketenimine–[2 + 2] cycloadditions of *N*-allyl ynamides is described. This tandem sequence is highly stereoselective and the [2 + 2] cycloaddition could be rendered in a crossed or fused manner depending on alkene substitutions, leading to bridged and fused bicycloimines.

Throughout our studies on palladium catalyzed *N*-to-*C* allyl transfers[1] of *N*-allyl ynamides[2–4] to ketenimines,[5] we have anticipated the possibility of effecting an intramolecular ketenimine-[2 + 2] cycloaddition with tethered alkenes [Scheme 1]. Seminal work on cycloadditions involving ketenes[6] and keteniminium ions have been studied extensively by Marko,[7] Snider,[8] Brady,[9] and recently by Minehan,[10] giving rise to cyclobutanones through fused–[11] and/or crossed–[2 + 2][12] pathways. For our own designs, we imagined that ketenimino-Pd-**π**-allyl complexes prepared by *N*-to-*C* allyl transfers of *N*-allyl ynamides **1** could also participate in fused, or more rarely, crossed [2 + 2] cycloadditions to afford highly substituted bicycloimines **2** or **3** *via* intermediates **5** or **6**.

During our pursuit of this endeavor, Tu[13] demonstrated beautifully the feasibility of carrying out intramolecular crossed–[2 + 2] cycloadditions using ketenimines generated *in situ* by extrusion of N_2 from *N*-tosyl azides in a retro [3 + 2] manner.[2a,14] In their work, the resulting bicycloimines were immediately hydrolyzed to ketones, and the crossed cycloaddition was the exclusive pathway. Our findings deviate significantly from theirs, and we report herein our successful development of highly diastereoselective crossed and fused ketenimine–[2 + 2] cycloadditions from *N*-allyl ynamides.

We quickly discovered that, in fact, **γ**-branched *N*-allyl ynamide **7** featuring an oxygen tethered styryl moiety cleanly underwent the desired Pd-catalyzed rearrangement–intramolecular [2 + 2] cycloaddition sequence to give bridged bicycloimine **8** in 80% yield

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Supporting Information Available: Experimental procedures as well as NMR spectra, and characterizations are available for all new compounds and free of charge via Internet http://pubs.acs.org.

as a single diastereomer [Scheme 2].[15] It is noteworthy that cycloadduct **9** from a fused–cycloaddition pathway was not observed.

Unlike in Tu's system,[13] the directly resulting imine was isolable by silica gel column chromatography and also crystalline, allowing for unambiguous determination of its structure by single crystal X-ray analysis [Figure 1]. By orienting the alkene to engage the orthogonal imine **π**-system and the bulky *c*-hexyl group into a pseudo-equatorial position, diastereomeric transition states **10** and **10'** can be envisioned. The $A^{1,3}$ strain between the *c*-hex group and imine disfavored **10'**, leading to **8** as the exclusive product with the imine *anti* to the *c*-hexyl.

The substrate scope proved to be exceptional, tolerating an array of propargylic substitutents and tethered olefins [Table 1]. Styryl-tethered ynamide **11** led to bicycle **14** in near quantitative yield [entry 1]. By utilizing crotyl-tethered ynamides **12a–c**, cycloadducts **15a–c** were isolated in good yields, though a competing carbocyclization[1a,16] involving the Pd-**π**-allyl moiety was also observed in 10–20% yield [entries 2–4, see Scheme 4].

Gratifyingly, styryl-tethered ynamide **13** featuring an *N*-Ts linkage could also be used to afford **16** in quantitative yield as a 9:1 mixture of diastereomers [entry 9]. Interestingly, nOe of **16**[15] implied a switch of stereoselectivity. Subsequently, X-ray analysis showed that the once propargylic phenyl was indeed *syn* to the imine in **16** [Figure 2], opposite to the observed stereochemistry in the oxygen-tethered system employing a similarly sized propargylic *c*-hex moiety [see Figure 1].

It is noteworthy that such a selectivity switch was not observed in Tu's study.[13] The switch in diastereoselectivity for the crossed cycloaddition with *N*-Ts tethered ynamides is likely a result of a gauche interaction between the phenyl and the *N*-sulfonyl moiety as shown in **17'** [Figure 2]. Instead, the cycloaddition favored chair-flipped **17** with the phenyl pseudo-axial, explaining the formation of **16** with the imine and phenyl *syn* as the major diastereomer.

In Table 1, we revealed that a competing carbocyclization was operational to give cyclopentenimines in 10–20% yield with several of the **γ**-branched ynamides. Upon attempting to carry out cycloadditions with tethered *cis* alkenes, this reaction dichotomy was exemplified [Scheme 3]. As anticipated, ynamide **18** bearing a tethered *trans*-olefin afforded the desired crossed cycloadduct **20** in ≥95% yield. However, the *cis*-olefin tethered analogue **21** [10:1 *cis*:*trans*] gave cyclopentenimine **24** in 55% yield with only a trace amount of cycloadduct **20** observed, which likely arose from the *trans* impurity in the starting ynamide and not from reaction of the *cis* alkene. Clearly, the *cis* olefin geometry would have disfavored the cycloaddition transition state **22**, and instead the carbocyclization through **23** ensued.

Furthermore, when *t*-Bu-substituted ynamide **24** was subjected to the reaction conditions, the desired cycloadduct **25** was isolated in only 22% yield, however cyclopentenimine **26** was obtained in 57% yield [Scheme 4]. This further illustrates the necessity for the cycloaddition to occur through the highly-organized transition state **28**, as disfavorable steric interactions clearly favor carbocyclization through **29**.

Next, we wished to assess how an unsubstituted allyl group serving as the cycloaddition partner would behave under the reaction conditions, as Pd-catalyzed deallylation was also possible [Scheme 5]. Additionally and notably, Tu found unsubstituted alkenes to be unreactive in their system.[13] Interestingly, when ynamide **30** was heated to 70 °C with 5 mol % $Pd(PPh_3)_4$, a 1:1 mixture of cycloadduct **31** and cyclopentenimine **32** was isolated in 61% yield, arising from competing fused–[2 + 2] cycloaddition and carbocyclization. Fortunately,

fused cycloadduct **31** crystallized cleanly from the mixture, allowing us to confirm its structure by X-ray analysis. The cycloaddition was highly diastereoselective, giving **31** with the imine *syn* to the *c*-hexyl as a single diastereomer through **33** to minimize $A^{1,2}$ strain suffered in **33'**.

Similar to what has been well documented for ketene–[2 + 2] cycloadditions,[6] we found that tethered internally substituted alkenes also favored formation of fused cycloadducts in our system [Table 2]. Ynamides **34a–d** featuring a variety of propargylic substituents gave fused cycloadducts **36a–d** in good yields with excellent diastereoselectivity. Further supporting the switch to a fused cycloaddition pathway, the imine carbon NMR signal for the fused cycloadducts was consistently 3–5 ppm upfield from the imine signal in the related bridged systems [194–195 ppm vs. 198–199 ppm]. The relative stereochemistry of **36a** and **37**, derived from the phosphoryl-substituted ynamide **35**,[17] were assigned by nOe analysis.[15]

We have showcased here a highly diastereoselective cascade of Pd-catalyzed *N*-to-*C* allyl transfer–intramolecular–[2 + 2] cycloadditions to afford highly substituted bicycloimines from *N*-allyl ynamides. The alkene substitution pattern played an imminent role in favoring either the fused or crossed cycloaddition pathway, leading to fused or bridged cycloadducts. Also uncovered is a competing carbocyclization pathway when hindered alkenes or sterically-demanding propargylic substitutents were employed, giving rise to α,β-unsaturated cyclopentenimines. Applications and a further mechanistic understanding these unique cycloaddition manifolds are currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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13. Li B-S, Yang B-M, Wang S-H, Zhang Y-Q, Cao X-P, Tu Y-Q. Chem. Sci. 2012; 3:1975.
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15. See Supporting Information.
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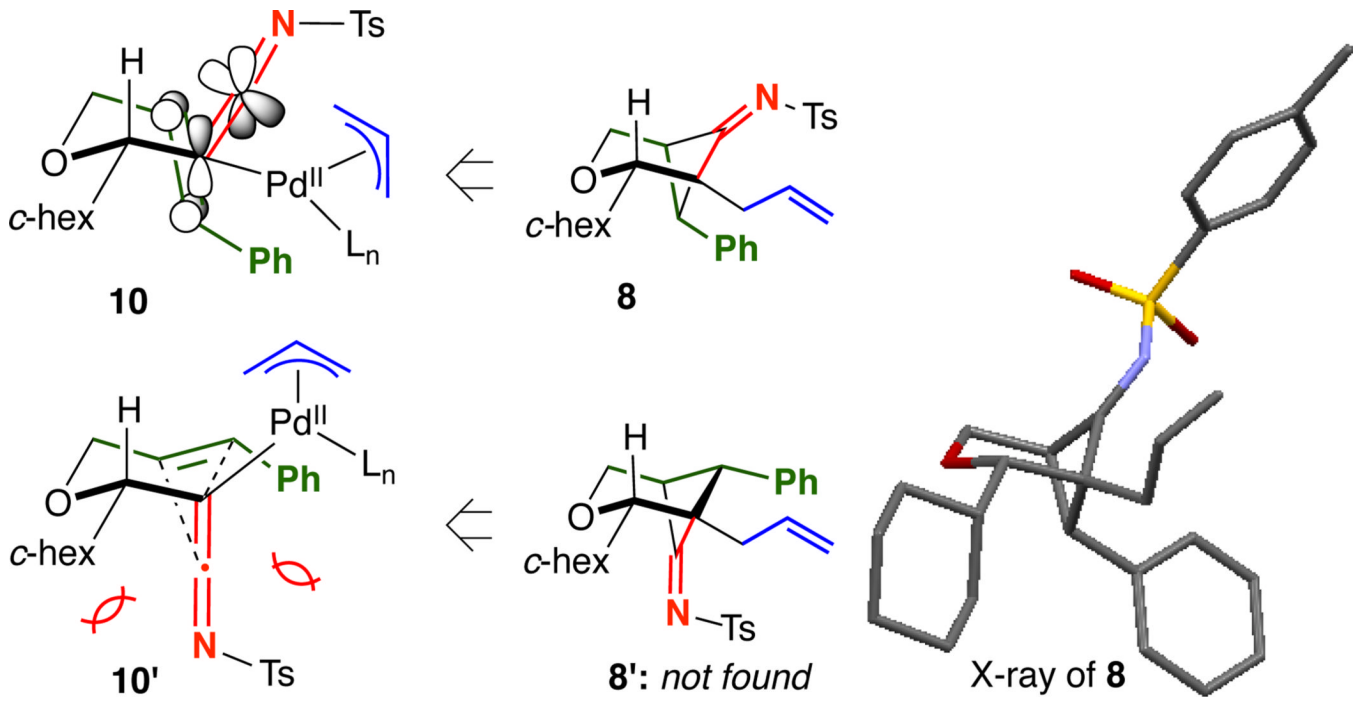


Figure 1.
X-ray of **8** and Diastereoselectivity Rationale

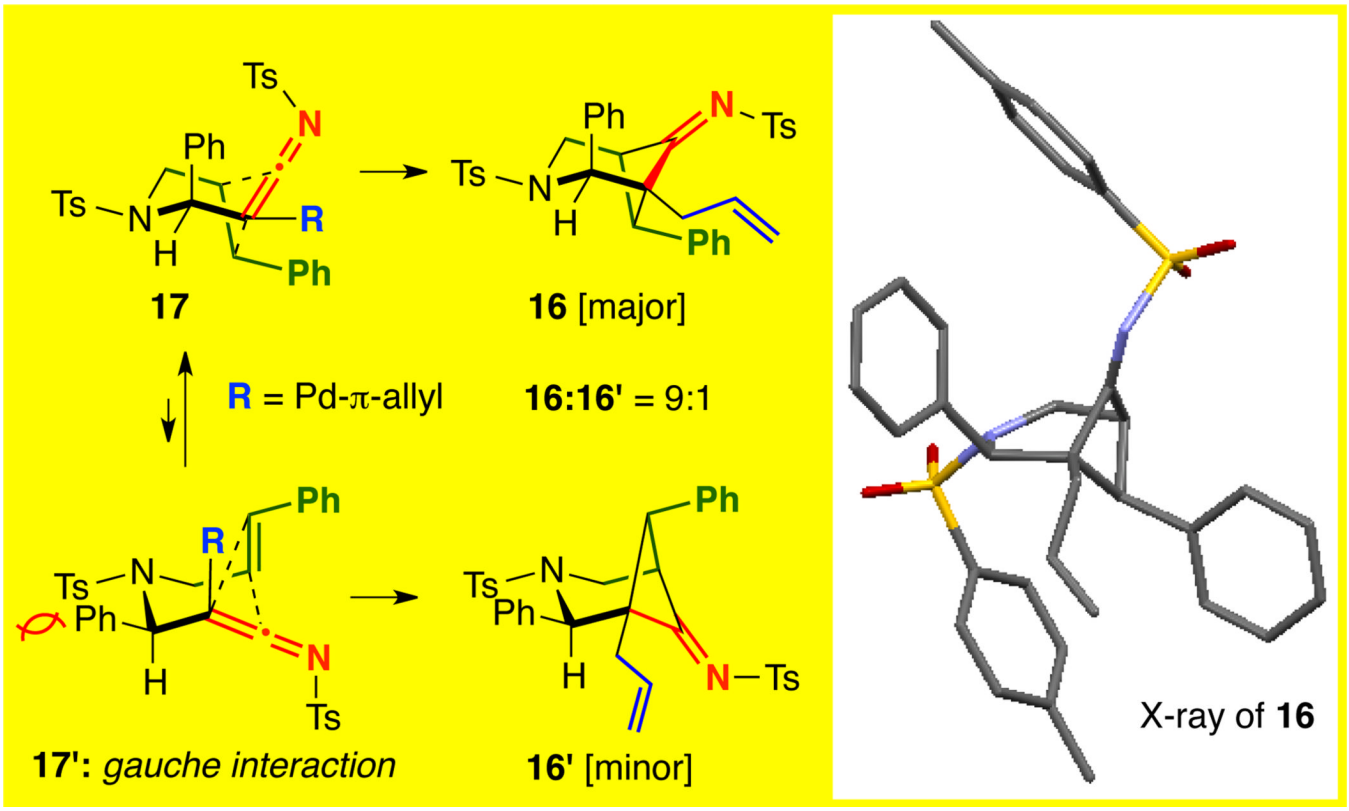
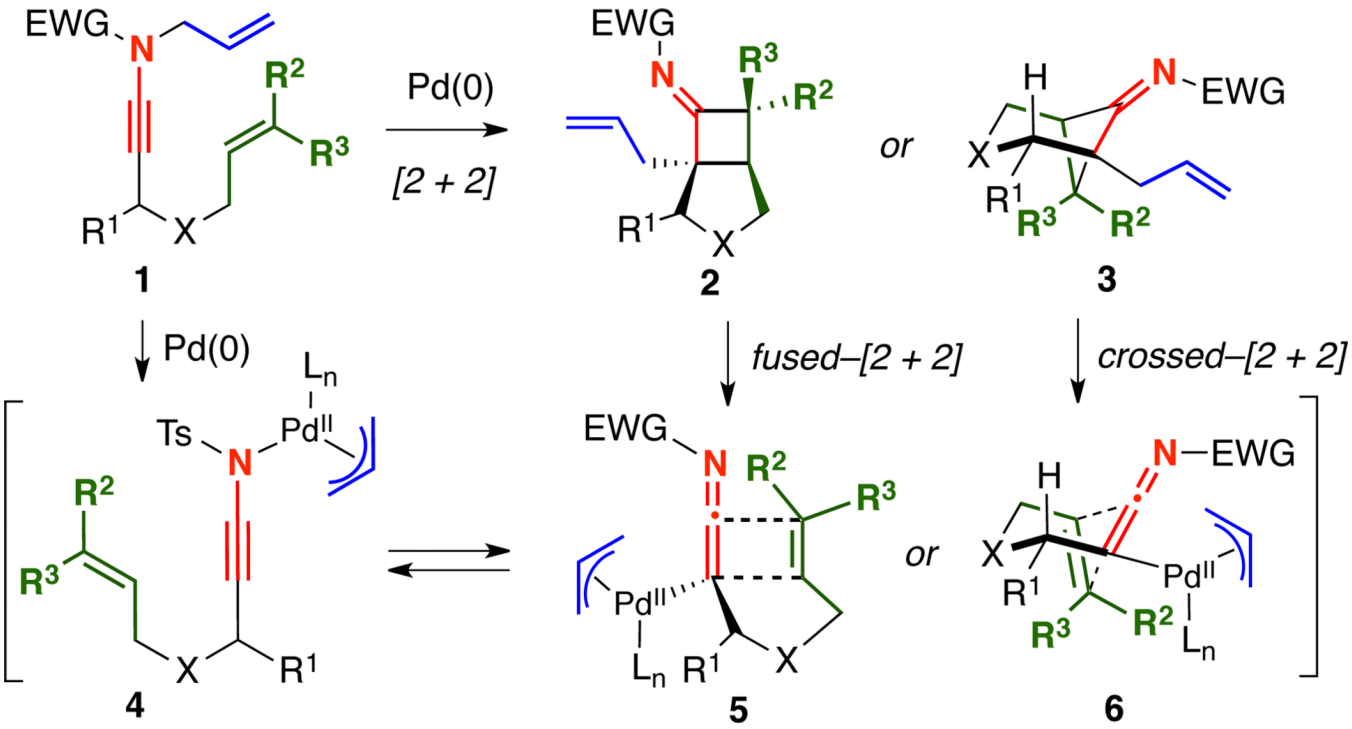
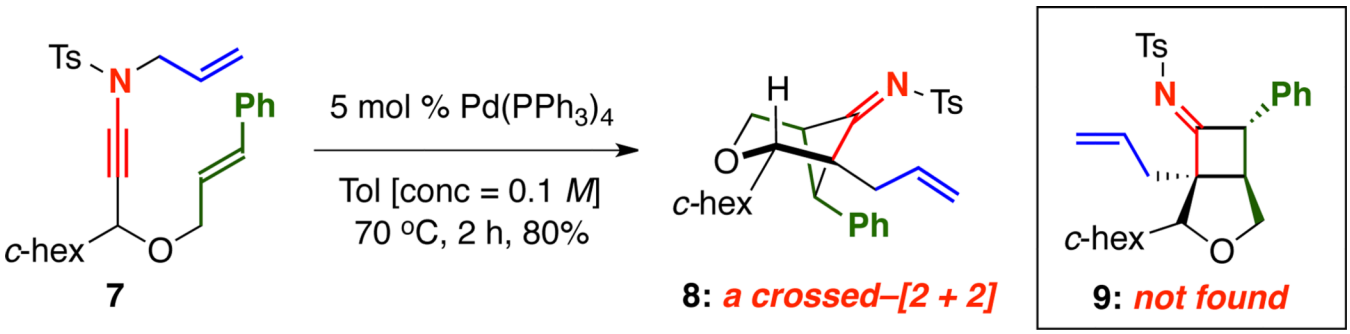


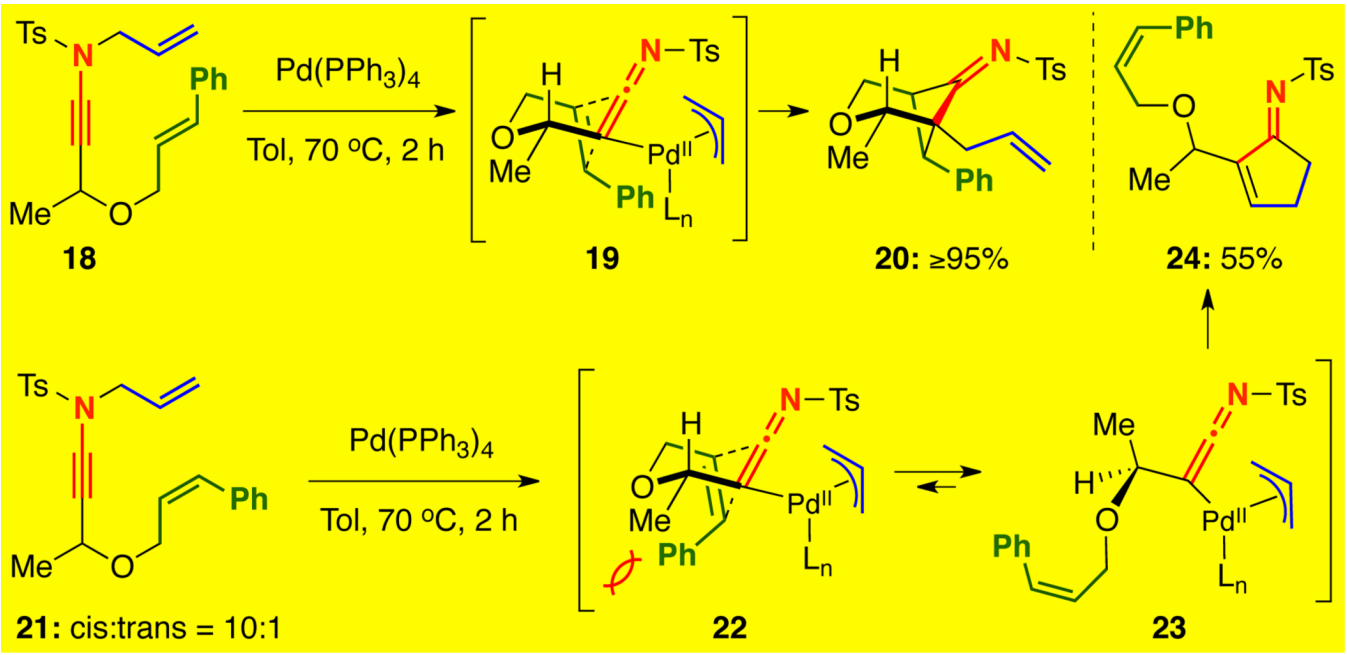
Figure 2.
Switch in Diastereoselectivity with *N*-Ts Tether



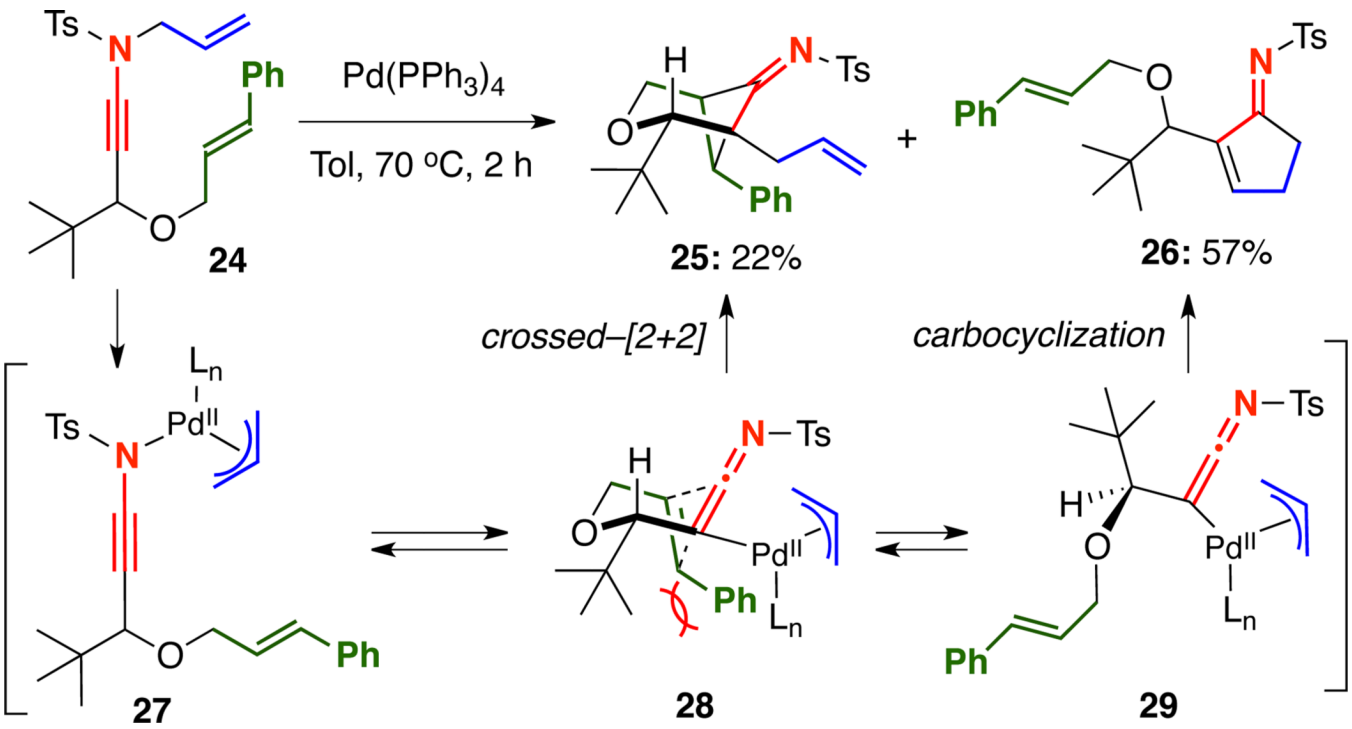
Scheme 1.
Intramolecular Ketenimine–[2 + 2] Cycloadditions



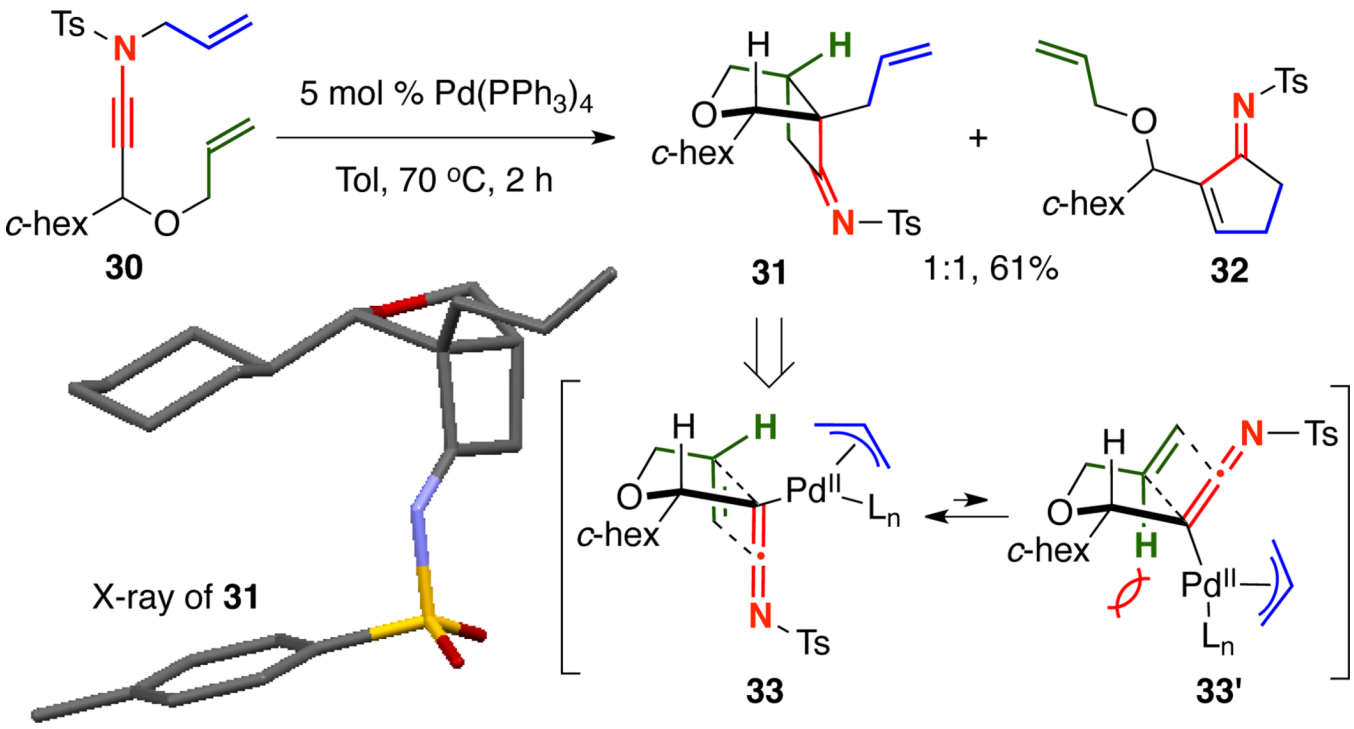
Scheme 2.
Discovery of a Crossed Ketenimine–[2 + 2]



Scheme 3.
A Dichotomy Based on Olefin Geometry



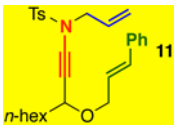
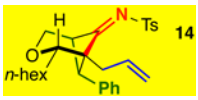
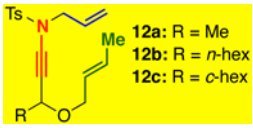
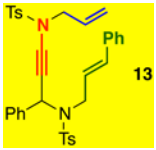
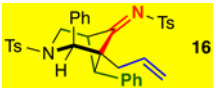
Scheme 4.
Crossed–[2 + 2] versus Carbocyclization



Scheme 5.
Discovery of a Fused–[2 + 2] Cycloaddition

Table 1

Crossed Ketenimine–[2 + 2] Cycloadditions[a]

entry	ynamide	crossed–[2+2] cycloadduct	yield [%][b,c]
1	 11	 14	≥95
2	 12a: R = Me 12b: R = *n*-hex 12c: R = *c*-hex	 15a: R = Me 15b: R = *n*-hex 15c: R = *c*-hex	72[d]
3			74[d]
4			67[d]
5	 13	 16	95[e]

[a]Reaction conditions: 5 mol % $Pd(PPh_3)_4$, Tol [*conc* = 0.1 *M*], 70 °C, 2 h.

[b]Isolated yields.

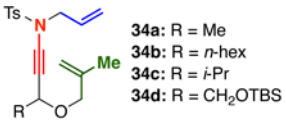
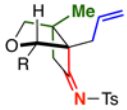
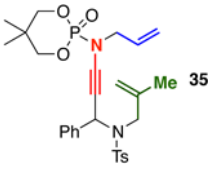
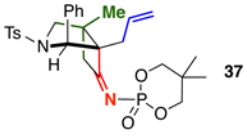
[c]≥20:1 *dr* by ^1H NMR unless otherwise noted.

[d]10–20% cyclopentenimine.

[e]9:1 *dr* as measured by ^1H NMR.

Table 2

Fused Ketenimine–[2 + 2] Cycloadditions

entry	ynamide	fused–[2+2] cycloadduct	yield [%][b,c]
1	 **34a:** R = Me **34b:** R = *n*-hex **34c:** R = *i*-Pr **34d:** R = CH_2OTBS	 **36a:** R = Me **36b:** R = *n*-hex **36c:** R = *i*-Pr **36d:** R = CH_2OTBS	86
2			71[d]
3			85
4			72
5	 **35**	 **37**	85[e]

[a] Reaction conditions: 5 mol % $Pd(PPh_3)_4$, Tol [*conc* = 0.1 *M*], 70 °C, 2 h.

[b] Isolated yields.

[c] ≥20:1 *dr* by ^1H NMR unless otherwise noted.

[d] 10–20% cyclopentenimine.

[e] 9:1 *dr* as measured by ^1H NMR.