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Formation of Ketenimines via the Palladium-Catalyzed Decarboxylative π-Allylic Rearrangement of *N*-Alloc Ynamides

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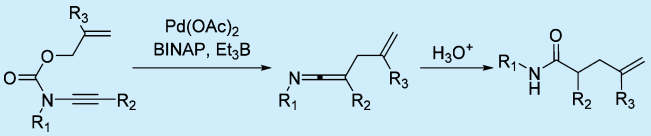
Supporting Information

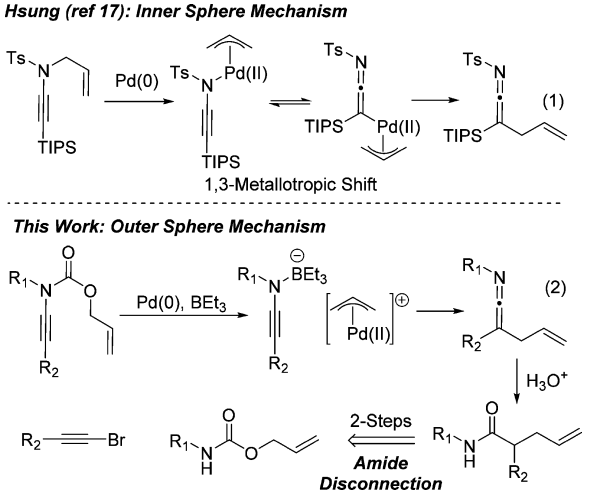
ABSTRACT: A new approach for the formation of ketenimines via a decarboxylative allylic rearrangement pathway that does not require strong stabilizing or protecting groups has been developed. The products can be readily hydrolyzed into their corresponding secondary amides or reacted with sulfur ylides to perform an additional [2,3]-Wittig process. Mechanistic studies suggest an outer-sphere process in which reductive alkylation is rate-limiting.



Ketenimines are versatile compounds that are underutilized in synthesis because of the relatively few general methods for their synthesis. These heteroallenic species contain an electrophilic sp-hydridized central carbon and exhibit reactivity similar to that of ketenes, undergoing nucleophilic and radical additions alongside pericyclic pathways such as cycloadditions, electrocyclizations, and [1,3]-shifts. Ketenimines are generally more stable than ketenes and can be further stabilized by heteroatom substitution (namely sulfur, phosphorus, and silicon) and also via mesomeric groups.[1] Although they can be chiral, there exists a linear nitrilium resonance form that leads to very rapid epimerization. With all carbon-substituted groups, this barrier is just 9−12 kcal/mol.[2] The preparation of functionalized ketenimines can be troublesome because of both their high reactivity and the harsh reaction conditions required for their construction. Common methods include the aza-Wittig reaction with ketenes;[3] Wittig reactions of isocyanates;[4] base-mediated elimination of *S*,*N*-ketene acetals,[5] iminoyl chlorides,[6] iminoyl cyanides,[7] α-halo iminoyl cyanides,[8] and aminoacrylonitriles;[9] dehydration of amides[10] and thioamides;[11] Beckman rearrangements;[12] alkylation of nitriles;[13] and deprotonation of nitriles followed by silylation.[14] These methods are very effective, but they generally require strong acid or base or strongly alkylating conditions. As a result, new reactions to form ketenimines that are functional-group-tolerant, allow a wide range of substituents, and occur under neutral conditions are highly desirable.

Following from our previous report on the decarboxylative rearrangement of *N*-alloc indoles to form indolenines,[15] we envisaged an analogous pathway to ketenimines.[16] The rearrangement of *N*-alloc ynamides would provide ketenimines in a very rapid manner using a functional-group-tolerant Pd catalyst under neutral conditions. Hsung had previously reported the rearrangement of *N*-allyl-*N*-tosyl ynamides, both thermally and Pd-catalyzed, to provide the corresponding ketenimines, which could be trapped by an exogenous nucleophile such as an amine or alcohol (Scheme 1).[17] Although this reaction is very effective, many substrates reported contain a TIPS group at the terminal position of the ynamide. In the absence of this group, N-to-C tosyl migration occurs, forming the corresponding nitrile. These issues could be remedied by performing an aza-Rautenstrauch rearrangement or using the phosphoryl analogue, which suppresses this pathway.[18]

Scheme 1. Outer-Sphere versus Inner-Sphere Mechanism and New Amide Disconnection



Hsung proposed that this transformation proceeds via oxidative addition into the C−N bond to provide an imido−π-allyl complex, which undergoes a 1,3-metallotropic shift followed by reductive elimination. We hypothesized that a more facile method to generate the π-allyl intermediate would be to utilize an *N*-alloc group and perform a decarboxylative rearrangement.[19] This would proceed via an ynamide anion, following decarboxylation, which could be stabilized as a borate complex by the addition of a borane additive, a strategy we utilized with

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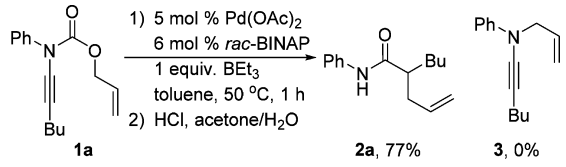
Table 1. Optimization Studies



entry	difference from the optimized conditions	2a:3[a]	yield/%[b]
1	no change	100:0	100 (77)[c]
2	no BEt_3	45:55	100
3	5 mol % Pd_2dba_3·$CHCl_3$, 11% mol % BINAP, 21 h	85:15	100
4	$Pd(PPh_3)_4$	15:85	100
5	$Pd(PPh_3)_4$, CH_2Cl_2, 25 °C, 21 h	0:100	96
6	$[Pd(allyl)Cl]_2$, 19 h	86:14	37
7	$Pd(OTFA)_2$, 19 h	99:1	64
8	$Pd(OTFA)_2$, no BEt_3	100:0	44
9	$Pd(OTFA)_2$, 10 mol % TFA instead of 1 equiv of BEt_3, 21 h	100:0	53
10	$[Pd(allyl)Cl]_2$, 10 mol % TFA instead of 1 equiv of BEt_3, 22 h	100:0	29

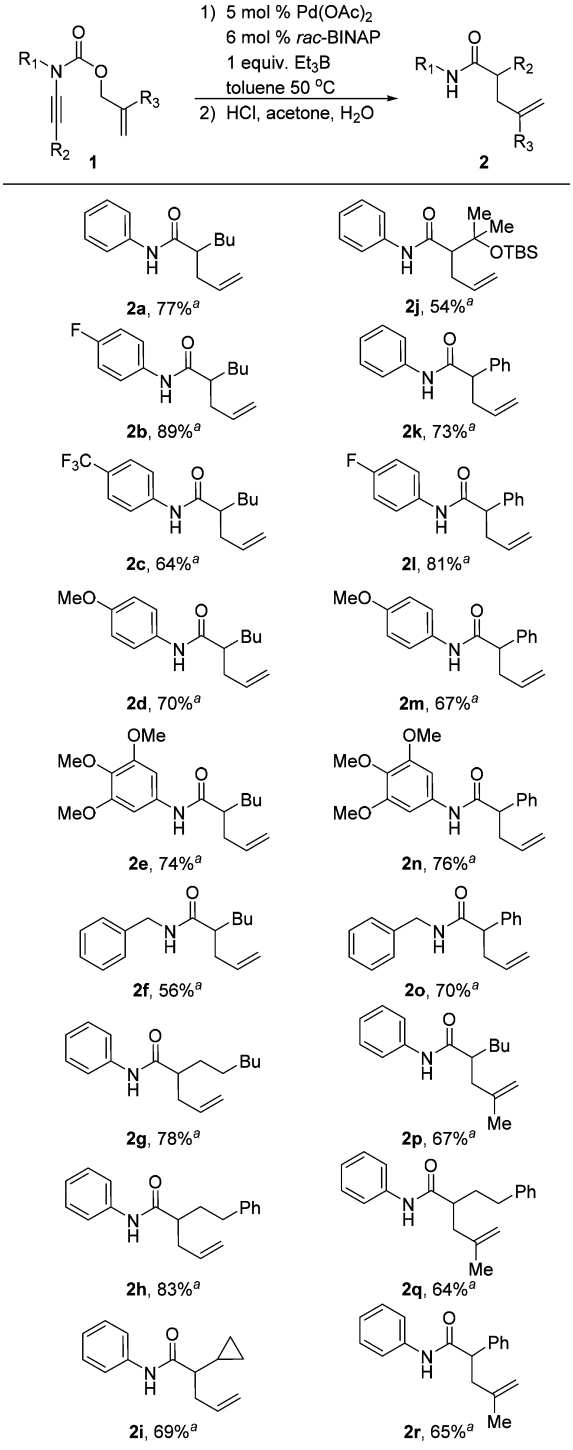
[a]Determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Combined yields of **2a**:**3** determined by ^{1}H NMR analysis against a known amount of DMF as an internal standard that was added to the reaction mixture following workup and immediately prior to preparation of the NMR sample. [c]Isolated yield of **2a**.

indoles.[15] The synthesis of *N*-alloc ynamides can be easily achieved through Cu-catalyzed coupling of the carbamate and the corresponding alkynyl bromide.[20] The presence of the carbamate would acidify the N−H group during the coupling step, thus negating the need for an electron-withdrawing group such as tosyl. Hydrolysis of the ketenimine to the corresponding amide would provide a new disconnection for amide bond synthesis from an alloc carbamate and an alkynyl bromide.

Our optimized conditions utilized a $Pd(OAc)_2$/BINAP system with triethylborane as a Lewis acidic additive to stabilize the intermediate anion, in toluene (Table 1, entry 1). The crude reaction mixture was monitored at this stage to determine the product ratios and conversions. As the ketenimines were somewhat unstable, these were immediately hydrolyzed to the corresponding secondary amides prior to isolation, and the optimized conditions led to a 77% isolated yield. When BEt_3 was removed, a loss of selectivity was observed, giving a nearly equal ratio of C- and N-allylated products (entry 2). Modulation of the catalyst resulted in different product ratios. Pd_2dba_3·$CHCl_3$ gave eroded selectivity (entry 3), and the use of $Pd(PPh_3)_4$ favored N-selectivity (entry 4). The reaction could be rendered exclusively N-selective through modulation of the solvent and temperature (entry 5). $[Pd(allyl)Cl]_2$ was much slower to react (entry 6), giving a similar product ratio as Pd_2dba_3·$CHCl_3$. Complete C-selectivity was restored with $Pd(OTFA)_2$, albeit with reduced conversion (entry 7). Interestingly, when the reaction was performed in the absence of BEt_3, the selectivity was retained (entry 8). We attribute this to trace amounts of trifluoroacetic acid in the catalyst. This was confirmed by the addition of 10 mol % TFA to both $Pd(OTFA)_2$ (entry 9) and $[Pd(allyl)Cl]_2$ (entry 10) in the absence of BEt_3, as both reactions were completely selective. As a chiral ligand was used, the enantiopure variant was attempted and led to racemic product, presumably because of the very low barrier to epimerization.[2]

With the optimized conditions in hand, we began examining the substrate scope (Scheme 2). We examined substitution on

Scheme 2. Substrate Scope



[a]Isolated yield following hydrolysis.

the carbamate, alkyne, and allylic groups and found that changes at all of these positions can be tolerated. We discovered that the aryl group can tolerate a range of functional groups and is not overly influenced by the electronic nature of the aryl group (**2a**−**e**). The optimal yields were obtained with more electron-neutral groups, with phenyl (**2a**) and 4-fluorophenyl (**2b**) providing the highest yields (the σ^- values for these substrates are 0 and −0.03, respectively).[21] More electron-rich aromatics (**2d** and **2e**, σ^- = −0.26)[22] and electron-deficient groups (**2c**, σ^- = 0.65) gave lower but still good yields. Alkyl carbamates could also be used,

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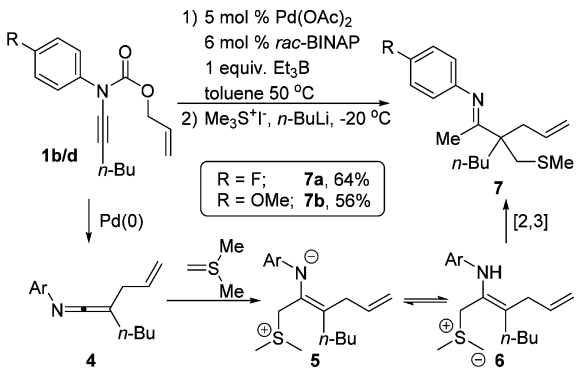
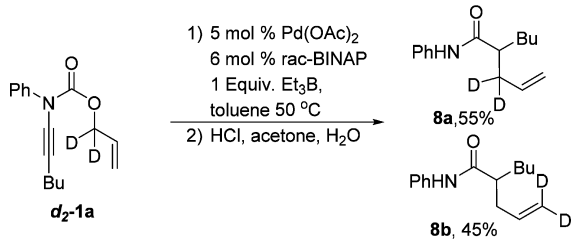
Scheme 3. Reaction of Ketenimine with Sulfur Ylide and Proposed Mechanism



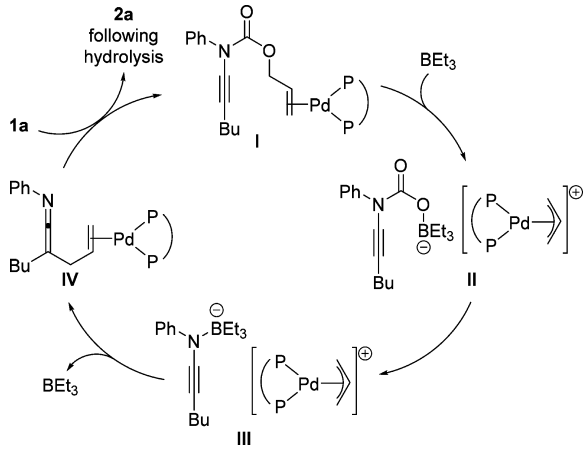
Scheme 4. Deuterium Positioning and KIE Experiment



producing benzyl amide **2f**, albeit in reduced yield. Extended alkyl chains at the R_2 position (**2g** and **2h**) were well-tolerated, as were branched alkyl groups with cyclopropyl (**2i**) and a silyl tertiary ether (**2j**) being formed. Aryl groups could also be incorporated at the α-position (**2k**), and substitution on the *N*-aryl ring (**2k**–**n**) provided the same trends as for the parent substrate. Finally, substitution on the allylic group (R_3) was examined through the use of the methallyl analogue. In these cases (**2p**–**r**), the products were formed in good yields, albeit slower than the unsubstituted cases.

The ketenimine products can also undergo alternative reactions, other than hydrolysis, without isolation. While other heteroatom nucleophiles have been utilized to form amidine and imidate products,[16] the use of carbon nucleophiles is much less common. When ketenimine **4** is treated with a sulfur ylide directly following the reaction, a rearrangement occurs to provide imine **7** with a fully substituted α-carbon (Scheme 3).[23] This rearrangement is proposed to occur via initial nucleophilic addition to the central carbon of the ketenimine followed by C-to-N proton transfer to provide **6**. This can undergo a [2,3]-Wittig rearrangement, and subsequent tautomerization provides **7** in 56–64% yield from the *N*-alloc ynamide precursor. The reaction appears to be insensitive to the electronics on the aryl

Scheme 6. Proposed Mechanistic Cycle

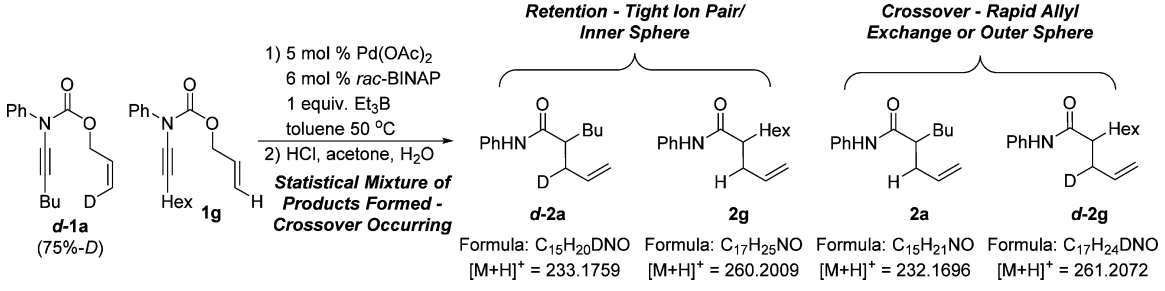


ring, with electron-rich and -deficient groups providing similar yields, suggesting that the proton transfer is fast.

An isotopically labeled alloc group was also synthesized and utilized in the reaction (Scheme 4). This substrate demonstrated the intermediacy of a π-allyl species by providing a 55:45 mixture of regioisomers **8a** and **8b**. The product ratio can also provide us with a kinetic isotope effect. The k_H/k_D value (0.82) is consistent with an inverse secondary isotope effect, suggesting that exogenous nucleophilic attack of the ynamide intermediate is rate-limiting.[24] In combination with the reactivity profile observed with substituted phenyl groups, this indicates that the buildup of charge in the transition state is remote from the nitrogen, possibly on the reacting alkynyl carbon.

We also conducted a crossover experiment (Scheme 5) in which a 1:1 mixture of the deuterated butyl substrate ***d*-1a**[25] and the nondeuterated hexyl analogue **1g** was subjected to the reaction conditions and the reaction mixture was analyzed by mass spectrometry. The very similar butyl and hexyl substrates provide almost identical yields of **2a** and **2g** (Scheme 2). The resulting spectrum clearly indicates the presence of significant amounts of all four possible compounds in ratios consistent with a statistical mixture. The compositions of these ions were confirmed using accurate mass analysis.[26] These crossover products can be formed only via a dissociative solvent-separated ion pair, which was not present in Hsung's system. The presence of a bidentate ligand on the Pd alongside the allylic intermediate would not allow an inner-sphere mechanism to occur because of the lack of coordination sites available. Indeed, during this mass spectrometry experiment we also detected the presence of the cationic $[(BINAP)Pd(Allyl)]^+$ complex. This could also indicate that this is the resting state of the catalyst prior to the rate-limiting nucleophilic attack. We could not identify which anionic

Scheme 5. Crossover Studies



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borate complex was present (**II** or **III**), but the [(BINAP)Pd-(Allyl)]$^+$ complex was the only Pd species observable by mass spectrometry at the end of the reaction (Scheme 6). The preference for electron-neutral substituents and the observation that TFA was a very selective additive could suggest that the reaction proceeds directly from **II** to **IV**. Such a scenario would locate the anion very remote from the aromatic group and form a labile carbamic acid derivative when TFA is used.

In conclusion, we have developed a mild and functional-group-tolerant approach to ketenimines that circumvents many of the issues encountered in other methods. The ketenimines can be hydrolyzed to the corresponding secondary amides, providing a new route that is especially efficient for non-nucleophilic, electron-poor anilines. We have also demonstrated other derivatizations of the ketenimine intermediates, reacting them with sulfur ylides and imines. Mechanistic studies provided evidence of a dissociative outer-sphere mechanism. These studies also suggested that reductive alkylation is rate-limiting. Extensions of this reaction are currently being explored.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02780.

Procedures, characterization, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(25) The deuterium incorporation of ***d*-1a** was 75%.

(26) For full details and a fully annotated mass spectrum from this reaction, see the Supporting Information.

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