Tandem Catalytic Allylic Amination and [2,3]-Stevens Rearrangement of Tertiary Amines

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S *Supporting Information*

ABSTRACT: We have developed a catalytic allylic amination involving tertiary aminoesters and allylcarbonates, which is the first example of the use of tertiary amines as intermolecular nucleophiles in metal-catalyzed allylic substitution chemistry. This process is employed in a tandem ammonium ylide generation/[2,3]-rearrangement reaction, which formally represents a palladium-catalyzed Stevens rearrangement. Low catalyst loadings and mild reaction conditions are compatible with an unprecedented substrate scope for the ammonium ylide functionality, and products are generated in high yields and diastereoselectivities. Mechanistic studies suggested the reversible formation of an ammonium intermediate.

The synthetic utility of ammonium ylides is exemplified by their selective sigmatropic rearrangements into complex nitrogen-containing products. For example, allylic ammonium enolates undergo [2,3]-Stevens rearrangements to produce unnatural amino acid derivatives with multiple stereocenters (Scheme 1).[1] Unfortunately, the broad application of these rearrangements has not been fully realized because of the difficulties associated with synthesizing and isolating many ammonium salt precursors.[2,3] The development of a mild and general metal-catalyzed tandem ammonium ylide generation/[2,3]-rearrangement would obviate the need to synthesize and isolate these reactive intermediates. While metal carbenoid-mediated couplings between tertiary allylic amines and diazoesters represent the most successful catalytic strategy for generating ammonium ylides, the challenge of synthesizing diazoesters with diverse functionalities reduces the potential scope of this approach.[4]

To address the need for a more general catalytic method of synthesizing allylic ammonium ylides for [2,3]-rearrangements, we turned our attention to allylic substitution chemistry. Metal-catalyzed allylic amination involving primary or secondary amines and allylic electrophiles has become one of the most versatile methods for synthesizing nitrogen-containing compounds.[5] As an intriguing extension of these protocols, the coupling of tertiary aminoesters with allylic electrophiles would generate synthetically useful ammonium ylides (Scheme 1). Unfortunately, tertiary amines are not generally appreciated as nucleophiles in allylic amination processes. In this communication, we describe the catalytic allylic amination reaction of tertiary aminoesters and allylcarbonates, which constitutes the first example of the use of tertiary amines as intermolecular nucleophiles

in metal-catalyzed allylic substitution chemistry.[6] Our discovery that tertiary amines participate in this mode of reactivity may provide a general strategy for synthesizing complex molecules, as highlighted by the development of a tandem ammonium ylide generation/[2,3]-rearrangement reaction. This transformation formally represents a palladium-catalyzed Stevens rearrangement with an unprecedented substrate scope for the ammonium ylide functionality and high diastereoselectivity for products having two stereocenters.

Initially, we focused on establishing tertiary aminoesters as intermolecular nucleophiles for allylic amination. With $Pd_2dba_3 \cdot CHCl_3$ as a catalyst and Cs_2CO_3 as an external base, we attempted to couple aminoester **1a** with cinnamyl carbonate **2** (Table 1). While we did not observe appreciable amounts of product in the absence of ligand (entry 1) or in the presence of several phosphine ligands (entries 2−5), we obtained the [2,3]-Stevens rearrangement product **4** in 90% yield, albeit as a modest 2:1 mixture of diastereomers, when PPh_3 was used (entry 6).

To increase the diastereoselectivity of this process, we employed *tert*-butyl aminoester **1b** (entry 7). Although the diastereomeric ratio increased to 9:1, the product yield decreased dramatically to 39%. We examined a series of electronically distinct ligands to optimize the efficiency of this reaction with the less reactive *tert*-butyl aminoester **1b** (entries 8−11). Once we realized that electron-deficient ligands led to greater yields of product, we employed the electron-deficient and sterically unencumbered $P(2\text{-furyl})_3$ ligand (entry 11), which generates a π-acidic palladium complex that is more susceptible to nucleophilic attack by *tert*-butyl aminoester **1b**.[7] Interestingly, the electronic characteristics of the ligand had no effect on the diastereoselectivity of the tandem process, and we isolated the desired product **4** in 95% yield with a diastereomeric ratio of 9:1.[8] The rearranged product **4** was formed in diminished yield even in the absence of Cs_2CO_3, which suggests that the ethoxide byproduct from the ethyl carbonate is basic enough to convert the ammonium salt into ammonium ylide **3** (entry 12).

With our optimized reaction conditions in hand, we explored the scope of allylcarbonates that can participate in this transformation (Table 2). In addition to using linear allylcarbonates such as **2** (Table 1), we successfully coupled aminoester **1b** with branched carbonates **5**, which are often more synthetically accessible than their linear counterparts. Allylcarbonates with electronically diverse aryl rings were well-behaved in this process (entries 1−7). For example, both halogen-substituted and

Scheme 1
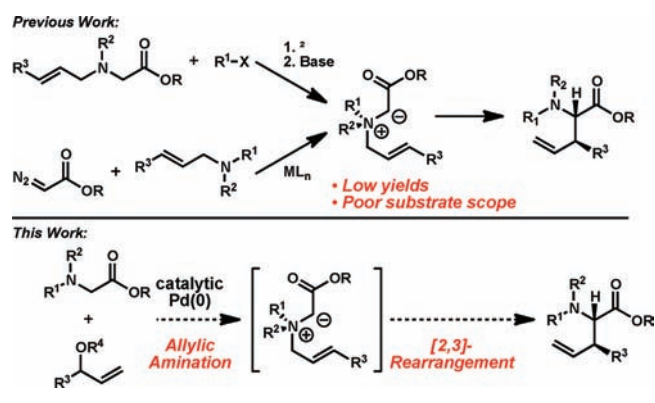
Table 1. Optimization of Reaction Conditions[a]
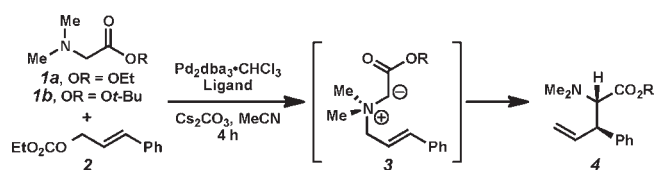
Entry	OR	Ligand	Yield (%)[b]	dr[c]
1	OEt	—	< 5	—
2	OEt	dppp	< 5	—
3	OEt	BINAP	< 5	—
4	OEt	PCy$_3$	< 5	—
5	OEt	P(t-Bu)$_3$	< 5	—
6	OEt	PPh$_3$	90	2:1
7	Ot-Bu	PPh$_3$	39	9:1
8	Ot-Bu	P(p-Tol)$_3$	< 5	—
9	Ot-Bu	P(p-OMe-Ph)$_3$	< 5	—
10	Ot-Bu	P(p-Cl-Ph)$_3$	65	9:1
11	Ot-Bu	P(2-Furyl)$_3$	95	9:1
12[d]	Ot-Bu	P(2-Furyl)$_3$	38	9:1

[a] Reaction conditions: 1.5 equiv of aminoester **1**, 1 equiv of allylcarbonate **2**, 1 mol % Pd$_2$dba$_3$ · CHCl$_3$, 4 mol % ligand, 3 equiv of Cs$_2$CO$_3$, 0.2 M in MeCN. [b] GC yields. [c] Diastereomeric ratios as determined by GC. [d] No Cs$_2$CO$_3$ was used.

methoxy-substituted phenyl derivatives were synthesized in good yields with high diastereomeric ratios. The reaction conditions also tolerated heterocycles with a Lewis basic pyridine functionality (entry 7), which may be especially problematic for protocols mediated by Lewis acids[3] or metal carbenoids.[4] Since aliphatic substituents did not impact the reaction efficiency (entry 8), this method may provide access to a diverse array of unnatural amino acid derivatives. The relative stereochemistry of the major diastereomer of the products was confirmed by X-ray crystallography and is consistent with an exo-selective transition state that is evoked in traditional ammonium ylide [2,3]-rearrangements (see below).[3e]

After demonstrating the wide range of allylcarbonates that can participate in the tandem ammonium ylide generation/ [2,3]-rearrangement, we expanded the utility of the reaction by employing tertiary amine nucleophiles other than *N,N*-dimethylglycine

Table 2. Substrate Scope of Allylcarbonates[a]

Entry	Carbonate	Product	Yield (%)[b]	dr[c]
1	X = H		87	9:1
2	X = Br		89	7:1
3	X = Cl		87	7:1
4	X = F		87	7:1
5	X = OMe		84	9:1
6			82	12:1
7[d]			76	5:1
8			83	9:1

[a] Reaction conditions: 1.5 equiv of aminoester **1b**, 1 equiv of allylcarbonate **5**, 1 mol % Pd$_2$dba$_3$ · CHCl$_3$, and 4 mol % ligand. [b] Isolated yields. [c] Diastereomeric ratios as determined by NMR analysis. [d] With slow addition of carbonate.

esters (Table 3). In view of the accessibility of the starting materials and the mildness of the reaction conditions, our method provides an efficient alternative to traditional protocols for generating ammonium ylides and metal carbenoid-mediated couplings between tertiary allylic amines and diazoesters. We observed reasonable reactivity with aminoester derivatives containing various nitrogen functionalities (entries 1 and 2). We also extended the metal-catalyzed process to α-amino ketones, which resulted in the stereoselective synthesis of complex cyclic and acyclic products (entries 3–6). For example, a piperidone was coupled with allylcarbonate **5a** to generate a cyclic product with two contiguous stereocenters (entry 3). The diastereoselectivity of the [2,3]-rearrangement of acyclic ketone-derived ammonium ylides was affected by the steric bulk of the ketone substituent (entries 4–6). We were also interested in applying our tandem methodology to the assembly of fully substituted unnatural α-amino acids with multiple stereocenters, which are not easily accessible by known protocols. Gratifyingly, aminoester derivatives with α-substituents furnished the desired [2,3]-Stevens rearrangement products containing fully substituted carbons with good levels of diastereoselectivity (entries 7–8). On the basis of the seminal work by Sweeney and co-workers on chiral auxiliary-based ammonium ylide rearrangements,[2d] we successfully incorporated Oppolzer's camphorsultam into our tertiary amine substrates, highlighting the potential of our metal-catalyzed ammonium ylide generation for use in the stereoselective synthesis of enantioenriched unnatural amino acid derivatives (entries 9–11).

We devised a series of experiments to gain mechanistic insight into our palladium-catalyzed Stevens rearrangement. Although we did not observe the coupled ammonium salts formed by allylic amination of tertiary amines, we designed an internal crossover

Table 3. Substrate Scope of Tertiary Amine Nucleophiles[a]

| Entry	Tertiary Amine	Carbonate	Product	Yield (%)[b]	dr[c]
1[d]		5a		70	3:1
2[d]		5a		76	6:1
3		5a		80	4:1
4		5b		93	2:1
5		5b		93	4:1
6		5a		80	7:1
7[d]		5b		88	6:1
8[d]		5b		90	7:3
9[e]		5c (R=H)		89	20:1
10[d,e]		5d (R=Me)		97	20:2:1:0
11[d,f]		5a (R=Ph)		96	22:2:1:0

[a] Reaction conditions: 1.5 equiv of tertiary amine **7**, 1 equiv of allylcarbonate **5**, 1 mol % Pd$_2$dba$_3$·CHCl$_3$, and 4 mol % ligand. [b] Isolated yields. [c] Diastereomeric ratios as determined by NMR analysis. [d] Reaction time was 16 h. [e] Reaction conditions: 1 equiv of **7**, 2 equiv of **5**, 2 mol % Pd$_2$dba$_3$·CHCl$_3$, and 8 mol % ligand. [f] 1.2 equiv of **7** was used.

substrate **9** that suggested the formation of these fleeting intermediates (Scheme 2a). Subjection of aminoester **9** to the reaction conditions yielded two allylation products, **10** and **11**, which is most easily explained by an allylic amination mechanism in which both the allyl and cinnamyl appendages of ammonium ylide **13** participated in the [2,3]-rearrangement.[9] We attributed the difficulty of observing an ammonium intermediate to the exceedingly high rate of ammonium salt deprotonation to yield an ammonium ylide and subsequent [2,3]-rearrangement (**12** → **13** → **10** + **11**). In addition, we suspected that aminoester **9** formed an unfavorable equilibrium with the initially formed ammonium salt **12**. This hypothesis was confirmed by our observation that morpholine ammonium salt **14** exchanged its cinnamyl substituent with aminoester **1b** under the reaction conditions to yield Stevens rearrangement product **4b**, presumably through

Scheme 2
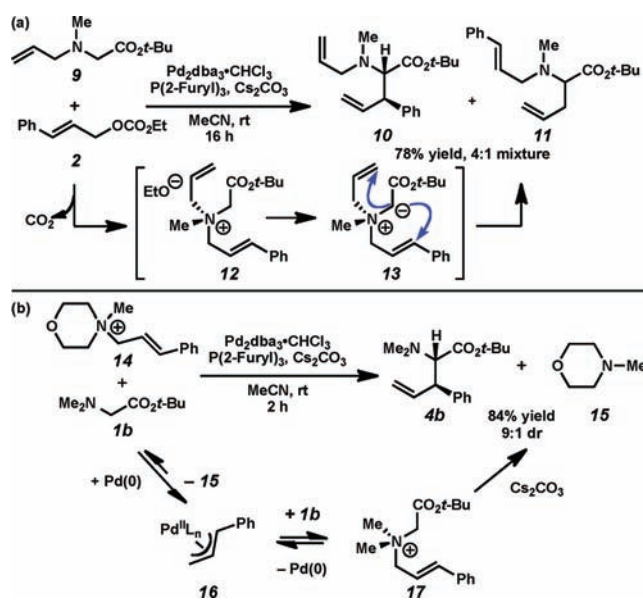
Scheme 3
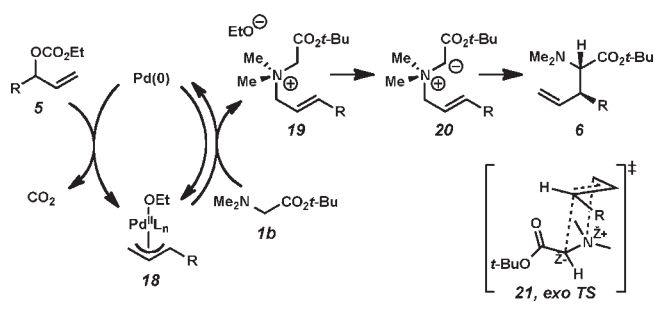
a Pd(II)−π-allyl complex such as **16** (Scheme 2b).[10] An unfavorable equilibrium for the palladium-catalyzed ammonium salt formation, in conjunction with the facile conversion of ammonium salts into the [2,3]-rearrangement products, could account for the difficulty of observing any ammonium intermediates. *We believe that these studies also explain why catalytic intermolecular allylic amination with tertiary amines has not been reported previously.*

On the basis of these experiments, we propose a mechanism wherein aminoester **1b** and Pd(II)−π-allyl complex **18** establish an unfavorable equilibrium with Pd(0) and ammonium salt **19** (Scheme 3). As soon as this unstable ammonium intermediate is formed, it undergoes rapid deprotonation to generate ammonium ylide **20**, which is transformed into the observed [2,3]-rearrangement product **6** through exo transition state **21**.

In conclusion, we have developed a palladium-catalyzed allylic amination involving tertiary amines and allylcarbonates that generates ammonium ylides, which rearrange under the reaction conditions to give unnatural amino acid derivatives and complex α-amino ketones with unprecedented levels of stereocontrol. The mild reaction conditions enable the use of a wide range of tertiary amine nucleophiles and allylcarbonates. Mechanistic studies support the formation of a fleeting ammonium salt intermediate that is formed by allylic amination with a tertiary amine substrate. We also believe that the palladium-catalyzed

allyl exchange of ammonium salts may have broader synthetic utility as a new strategy for allyl transfer. We are currently exploring a catalytic enantioselective version of this process and its application to the synthesis of stereochemically complex natural produdcts.

■ ASSOCIATED CONTENT

ⓢ Supporting Information. Complete experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

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(8) When we resubjected the major diastereomer of the rearranged product to the reaction conditions, we did not observe any epimerization, indicating that the dr in this tandem process reflects the high diastereoselectivity of the [2,3]-rearrangement via a well-ordered transition state.

(9) Direct allylic alkylation of the aminoester was ruled out as a mechanistic possibility for several reasons, including the ligand-independent regioselecitivity and diastereoselectivity of product formation (Table 1) as well as the inability of Cs_2CO_3 to deprotonate an aminoester directly (on the basis of pK_a values).

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