Synthetic Methods

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Palladium-Catalyzed Insertion of α-Diazoesters into Vinyl Halides To Generate α,β-Unsaturated γ-Amino Esters**

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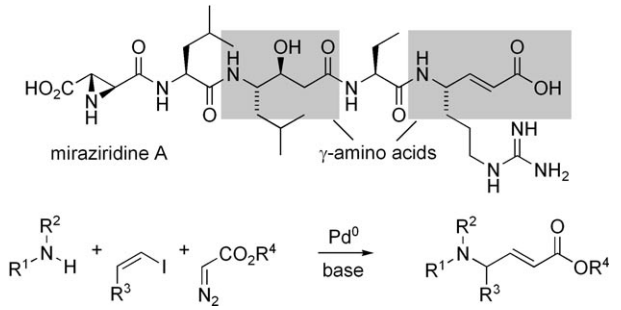
Palladium-catalyzed insertion of trimethylsilylcarbenes, derived from trimethylsilyldiazomethane, into vinyl halides has recently been shown to be a powerful method for the formation of vinylsilanes with allylic amino groups.[1] The analogous process, when carried out with α-diazoesters, would provide direct access to chiral α,β-unsaturated γ-amino acids; such as those found in various bioactive natural products, like miraziridine A (Scheme 1),[2] and in synthetic

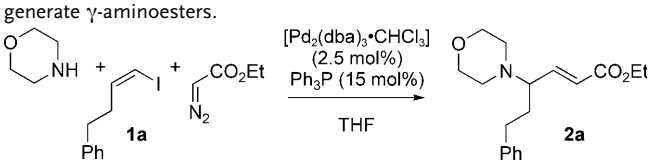


Scheme 1. Three-component coupling of amines, vinyl iodides, and ethyl diazoacetate to generate γ-amino acid derivatives.

inhibitors.[3] Peptides composed solely of γ-amino acids can readily form secondary structures and tend to adopt helical conformations, even in protic solvents.[4] α,β-Unsaturated γ-amino esters are generally made through olefination of the corresponding N-protected α-amino aldehydes;[5] the α-amino aldehydes can be highly sensitive to racemization, so they are generally prepared through reduction of N-protected α-amino acids to give α-amino alcohols, which are then reoxidized to the aldehydes under mild reaction conditions.[5] A modular method for the direct synthesis of γ-amino esters would be highly valuable, particularly if applicable to non-natural amino acid side chains (Scheme 1).

There is growing interest in palladium-catalyzed carbene insertion reactions.[6,7] In previous work involving palladium-catalyzed three-component coupling to generate vinylsilanes, we noted that ethyl diazoacetate (EDA) could be substituted for trimethylsilyldiazomethane; albeit in lower yields. Two potential competing pathways make palladium-catalyzed insertions using α-diazoesters more challenging than the corresponding reactions of trimethylsilyldiazomethane: firstly, cross-coupling of the vinyl halide and the diazo compound can occur,[8] secondly, palladium chloride can catalyze polymerization of ethyl diazoacetate.[9] In the unoptimized reaction, there was a significant amount of unreacted starting material (**1a**; Table 1, entry 1). We

Table 1: Optimization of the three-component coupling reaction to generate γ-aminoesters.



Entry	Equivalents of amine	Equivalents of EtO_2CCHN_2	*t* [h]	*T* [°C]	Yield [%]
1	8	1.5	20	46	≤30
2	3	1.5	24	46	31
3	3	1.5	24	66	34
4	3	3	24	66	41
5	3	10	24	66	65
6	3	10	4/4[a]	66	90
7	3	5	2	66	94

[a] The EtO_2CCHN_2 was added over the first 4 hours, and was followed by an additional 4 hours of stirring. dba = *trans*,*trans*-dibenzylideneacetone, THF = tetrahydrofuran.

hypothesized that the large excess of nucleophilic amine could deactivate the catalyst through direct ligation or formation of chelating by-products. To test this hypothesis we lowered the stoichiometry of the amine from eight to three equivalents, and resulted in a slight improvement in yield (Table 1, entry 2). To improve catalyst turnover the reaction temperature was increased to 66 °C, thus resulting in another slight increase in yield (Table 1, entry 3). To consume more of this starting material, we added an additional 1.5 equivalents of diazoester, which led to a further improvement in conversion of vinyl iodide **1a** into product (Table 1, entry 4). Since additional EDA seemed to exert a beneficial effect on the yield, the reaction was repeated using 10 equivalents of EDA. Although the yield was further improved to 65% (Table 1, entry 5), none of the remaining vinyl iodide was recovered. α-Diazoesters are known to undergo [3+2] cycloadditions with α,β-unsaturated esters.[10] Indeed, when the enoate **2a** was heated with 2 equivalents of ethyl diazoacetate in THF over 24 hours, none of the enoate could

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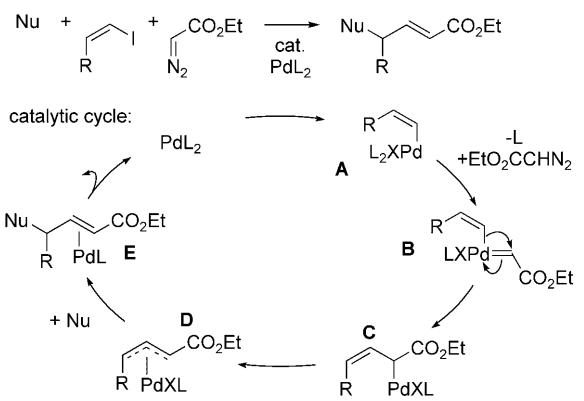
be recovered, thus confirming that the enoate product is sensitive to ethyl diazoacetate.

These results seem to suggest that extended exposure of the product to EDA under these reaction conditions leads to destruction of the product. To test this hypothesis, 10 equivalents of EDA were added over 4 hours; as GC-MS analysis showed the presence of unreacted vinyl iodide, the reaction was allowed to continue for an additional 4 hours. The result was a satisfying 90% yield of the desired allylamine (Table 1, entry 6). Slow addition of the EDA was essential; when all 10 equivalents of EDA were added immediately and the reaction was allowed to stir for 7 hours, the yield of the product was only 24% and the remaining starting material was recovered. Therefore, the palladium catalyst and/or the ethyl diazoacetate is depleted by bolus addition of the diazo compound. To optimize the yield of the allylamine it was best to stop the reaction as soon as the vinyl iodide was consumed. Typically this point was reached after five to seven equivalents of the diazo compound had been added over about 2.5 hours. Under these reaction conditions, the desired allylamine **2a** was generated in 94% yield (Table 1, entry 7).

We hypothesize that the reaction (Scheme 2) starts with oxidative addition of palladium to the vinyl halide to generate vinylpalladium complex **A**, and subsequent formation of a

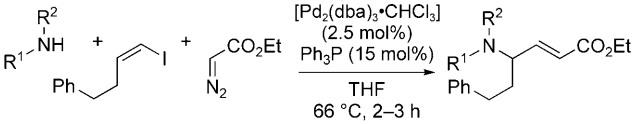


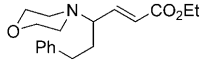
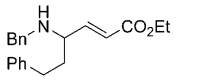
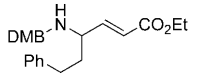
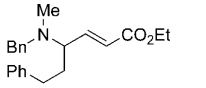
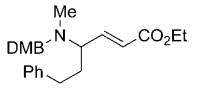
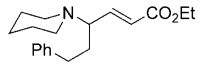
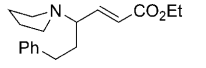
Scheme 2. Proposed mechanism for the palladium-catalyzed reaction. L = ligand, Nu = nucleophile, X = halide.

palladium carbene **B**.[11] Migration of the vinyl ligand to the empty p orbital of the carbene ligand generates the η^1-allylpalladium complex **C**. Migratory insertion is well precedented for CO ligands, but has only recently been demonstrated for palladium carbenes.[12] This step sets the absolute configuration in the reaction. Presumably, the η^1-allylpalladium complex generates an η^3-allylpalladium intermediate **D** that is then attacked by the amine nucleophile at the position distal from the ester group.[13]

With the reaction conditions now optimized for use of morpholine (Conditions A; Table 2, entry 1) as both nucleophile and base, we set out to explore the generality of the amine nucleophiles. Benzylamine and 2,4-dimethoxybenzylamine gave modest yields of the desired coupling product under the general reaction conditions (Table 2, entries 3 and 6), but *N*-methylbenzylamine proved to be more effective (Table 2, entry 9). We note that 2,4-dimethoxybenzyl (DMB)

Table 2: Variation of the amine nucleophile.



Entry	Conditions[a]		Product	Yield [%]
1	A	**2a**		94
2	B	**2a**		62
3	A	**2b**		40
4	B	**2b**		34
5[b]	A	**2b**		68
6	A	**2c**		51
7	B	**2c**		28
8[b]	A	**2c**		71
9	A	**2d**		75
10	B	**2d**		61
11[b]	A	**2e**		91
12	A	**2f**		55
13	B	**2f**		71
14[b]	B	**2f**		80
15	A	**2g**		42
16	B	**2g**		62

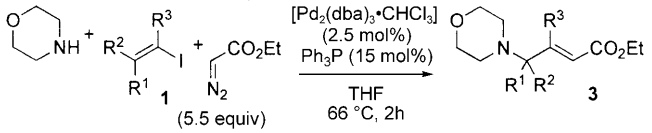
[a] Conditions A: R_1R_2NH (3 equiv); Conditions B: R_1R_2NH (1 equiv), Et_3N (2 equiv). [b] $[Pd_2(dba)_3{\cdot}CHCl_3]$ (5 mol%) was used. Bn = benzyl.

groups can be readily removed from amides under acidic conditions. The cyclic secondary amines piperidine and pyrrolidine are slightly less effective than morpholine (Table 2, entries 12 and 15).

The yield of the desired γ-amino ester seemed to be inversely correlated with the basicity (and nucleophilicity) of the secondary amine: morpholine ($pK_a = 7.41$) < BnNHMe ($pK_a = 9.34$) < piperidine ($pK_a = 11.22$) < pyrrolidine ($pK_a = 11.27$). To reduce the nucleophilicity of the reaction medium, we explored an alternative set of reaction conditions that employed one equivalent of the amine nucleophile along with two equivalents of triethylamine ($pK_a = 10.65$) to help neutralize the HI generated in the reaction. These alternative reaction conditions proved to be better for amines that are more basic than triethylamine (Conditions B; Table 2, entries 13 and 16), but not for amines that are less basic than triethylamine (Table 2, entries 2, 4, 7, and 10). The vinyl iodide was not consumed, regardless of how much EDA was added; therefore we attributed catalyst deactivation as the cause of the low yields. However, the yield was improved by increasing the catalyst loading (Table 2, entries 5, 8, 11, and 14). To ensure efficiency, all of the subsequent reactions were carried out using 2.5 mol% of palladium catalyst, unless otherwise noted.

We next set out to evaluate the effect of substituents on the vinyl iodide component. Not surprisingly, silyl-protected ethers perform well in the palladium-catalyzed coupling reaction (Table 3). The trans substrate (*E*)-**1b** fared poorly relative to the cis substrate (*Z*)-**1b**; as observed in previous studies of palladium-catalyzed carbene insertion reactions.[1]

Table 3: Variation of the vinyl iodide.



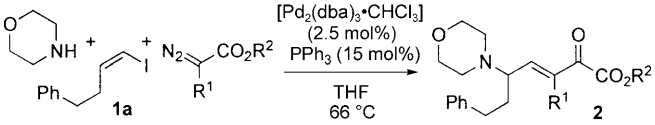
Entry	Vinyl iodide	Product	Yield [%]
1	(*Z*)-**1b**	**3b**	90
2[a]	(*E*)-**1b**	**3b**	18
3	**1c**	**3c**	33
4[b]	**1c**	**3c**	67
5	**1d**	**3d**	91

[a] EtO_2CCHN_2 (10 equiv) was added over 4 hours. [b] $[Pd_2(dba)_3{\cdot}CHCl_3]$ (5 mol%) was used. TBS = *tert*-butyldimethylsilyl.

The internal iodoalkene **1c** gave the corresponding γ-amino ester **3c** as the *Z* stereoisomer in only 33% yield. This pattern of stereoselection has previously been observed in palladium-catalyzed allylic alkylations.[14] Nitrile substituents appear to be well-tolerated in the reaction and led to a high yield of γ-amino ester **3d**. As triphenylphosphine was used as the ligand in these reactions, all of the products (except **3c**) were generated as racemic mixtures. However, the wide range of available chiral phosphine ligands offers the promise of straightforward development of an enantioselective variant of this reaction.

Next we compared the reaction of related α-diazo esters (Table 4). The extra methyl group of ethyl α-diazopropionate[15] clearly lowered the efficiency of the reaction, and afforded the product as a 2:1 mixture of *E* and *Z* isomers (Table 4, entries 1 and 2). *tert*-Butyl diazoacetate was also effective in the reaction when a larger excess of the diazo compound was added over a longer period of time (Table 4, entry 3). *tert*-Butyl esters are readily deprotected under mild acidic conditions.

Table 4: Variation of the diazo compound.



Entry	Diazo substrate R^1	R^2	[equiv]	*t* [h]	Product	Yield [%]
1	H	Et	≈5	2		94
2	Me	Et	3	1.5		53[a]
3	H	*t*Bu	10	6		83

[a] 2:1 mixture of *E* and *Z* isomers.

To demonstrate the utility of the γ-amino acids, which can be generated by this new three-component coupling reaction, we demonstrated that the DMB-protected amine **2c** could be coupled with FmocGlyOH and the DMB group removed to afford an Fmoc-protected dipeptide (Scheme 3).

Scheme 3. Formation of peptide bonds with DMB-protected amino acids. Fmoc = 9-fluorenylmethyloxycarbonyl, HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, NEM = *N*-ethylmorpholine, TFA = trifluoroacetic acid.

In conclusion, we have developed a powerful new method for the synthesis of α,β-unsaturated γ-amino esters through a palladium-catalyzed three-component coupling reaction. The key step in the catalytic cycle is believed to involve migratory insertion of a carbene unit into a vinyl-palladium bond to generate an η^3-allylpalladium intermediate. This unique transformation is important because it complements the multistep synthesis of α,β-unsaturated γ-amino esters from α-amino acids and it can be used to synthesize variants with both natural and non-natural side chains.

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