

Phosphine-Catalyzed Aza-MBH Reactions of Vinylpyridines: Efficient and Rapid Access to 2,3,5-Triarylsubstituted 3-Pyrrolines

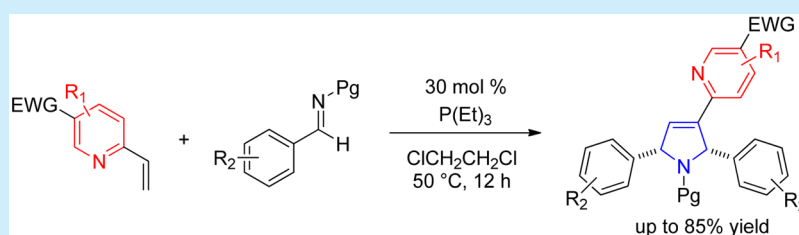
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S Supporting Information



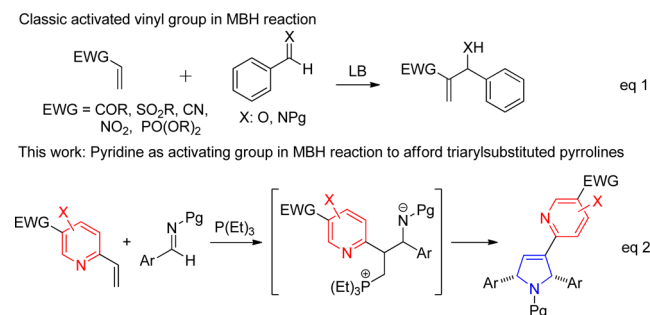
ABSTRACT: Vinylpyridines have been developed in aza-Morita–Baylis–Hillman (MBH) reaction to construct triarylsubstituted 3-pyrrolines. The first electron-deficient aromatic ring is marked as an activating mode for the vinyl group in the MBH reaction. This method provides efficient and rapid access to a range of triarylsyrrolines in good yields and at an excellent level of diastereoselectivity. Moreover, the synthetic potential of this protocol is further enhanced by the straightforward synthesis of unsymmetrical tri- and polyarylsubstituted pyrroles.

The Morita–Baylis–Hillman (MBH) reaction is an efficient metal-free C–C bond formation of the electron-poor system with a carbon nucleophile catalyzed by a Lewis base to provide a wide range of multifunctional molecules.¹ The electron-poor system can be activated alkenes,² allenes,³ and allylic compounds.⁴ Compared with the versatile derived forms and the diversity of coupling partners, the choice of activating group for alkene, allene, and allylic compounds was mainly restricted in carbonyl,⁵ nitrile,⁶ sulfones,⁷ sulfonates,⁸ and phosphonates (Scheme 1, eq 1).⁹ To the best of our knowledge, developing a new electron-poor system with the MBH reaction is still challenging. Vinylpyridine is normally used as a valuable Michael acceptor through C–C, C–N, and C–S bond formation at the β -position.¹⁰ On the

contrary, the α -position activation of vinylpyridine is extremely rare. These transformations rely on the hydrogenation of the β -position of vinylpyridine first, followed by a cascade coupling reaction of the α -position to the electrophiles.¹¹ Our laboratory recently focused on the metal-free activation of pyridine substrates and vinylheteroarenes.¹² We wish to develop vinylpyridine as new electron-poor system in the MBH reaction.

Highly substituted 3-pyrrolines are versatile scaffolds and precursors for the synthesis of pyrroles, an important unit present in a wide range of natural products,¹³ bioactive synthetic substances,¹⁴ and useful building blocks.¹⁵ In this regard, a number of synthetic methods have been developed for the synthesis of these heterocycles. The phosphine-catalyzed annulation reaction of 2-butyne or 2,3-butadiene with *N*-tosylimines was realized for the synthesis of 3-pyrrolines.¹⁶ Lu developed a [3 + 2] annulation reaction of allylic compounds with *N*-tosylimines.¹⁷ Shi reported the unusual MBH reaction between *N*-tosylimine and methyl vinyl ketone to give the mixture of 3-pyrroline and pyrrole products.¹⁸ However, it is difficult to obtain pure 3-pyrrolines with this method. Herein, we wish to report the first example of phosphine-catalyzed aza-MBH reaction using vinylpyridine as a nonclassical α,β -unsaturated system. The process serves as an

Scheme 1. Vinylpyridines in the MBH Reaction

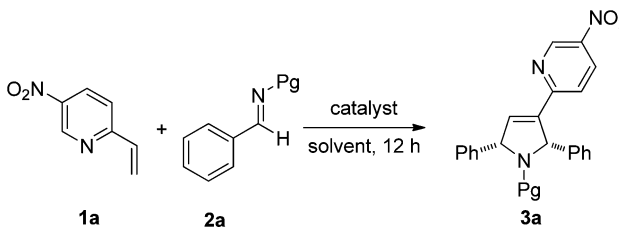


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efficient approach to triarylsubstituted 3-pyrrolines containing a pyridine moiety (Scheme 1, eq 2).

In the initial study of this aza-MBH reaction, the mixture of 5-nitro-2-vinylpyridine (**1a**) and *N*-benzylidenebenzenesulfonamide (**2a**, 2.5 equiv) in tetrahydrofuran (THF) catalyzed by 30 mol % of $P(CH_3)_3$ was stirred for 12 h at rt. The reaction proceeded smoothly to afford the pyridine-containing *cis*-triaryl 3-pyrroline **3a** with excellent diastereoselectivity (Table 1, entry 1).¹⁹ Different protecting groups of

Table 1. Optimization of the Reaction Conditions^a



entry	catalyst	solvent	Pg	yield (%) ^b
1	$P(CH_3)_3$	THF	SO_2Ph	52
2	$P(CH_3)_3$	THF	Ts	58
3	$P(CH_3)_3$	THF	Boc	nd
4	$P(CH_3)_3$	THF	Ph	nd
5	$P(CH_3)_3$	toluene	Ts	23
6	$P(CH_3)_3$	dioxane	Ts	29
7	$P(CH_3)_3$	DCM	Ts	60
8	$P(CH_3)_3$	$ClCH_2CH_2Cl$	Ts	67
9	$P(Et)_3$	$ClCH_2CH_2Cl$	Ts	70
10	$P(n-Bu)_3$	$ClCH_2CH_2Cl$	Ts	41
11 ^c	$P(Et)_3$	$ClCH_2CH_2Cl$	Ts	75
12 ^{c,d}	$P(Et)_3$	$ClCH_2CH_2Cl$	Ts	83
13 ^{c,e}	$P(Et)_3$	$ClCH_2CH_2Cl$	Ts	54

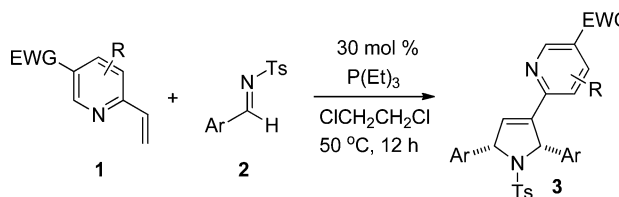
^aUnless specified, all reactions were carried out using 5-nitro-2-vinylpyridine (0.2 mmol), aldimine (0.5 mmol), and catalyst (30 mol %) in the solvent (1 mL) for 12 h at rt. ^bIsolated yields. ^cReaction was run at 50 °C with 3.5 equiv of aldimine. ^dReaction concentration was 0.1 M. ^eReaction concentration was 0.4 M.

imines were tested first, and the results showed that *N*-tosylimines (Ts) were critical for this reaction (entry 2). Boc and phenyl as the protecting group gave a messy mixture without further identification (entries 3 and 4). Then, the solvents were screened. Toluene and dioxane afforded the product with poor reaction yield (entries 5 and 6). CH_2Cl_2 gave a slightly higher yield than THF (entry 7). When 1,2-dichloroethane was used, the reaction yield was improved to 67% (entry 8). PEt_3 was more efficient and provided the product in 70% isolated yield (entry 9). The larger $P(n-Bu)_3$ gave much lower yield (41%, entry 10). However, the more bulky $P(t-Bu)_3$ and $P(Cy)_3$ and other classic Lewis bases used for the MBH reaction did not facilitate any product formation.²⁰ When *N*-tosylimine was increased to 3.5 equiv and the reaction temperature was increased to 50 °C, the reaction yield was increased to 75% (entry 11). The concentration of the reaction was also very important. When the reaction concentration was decreased to 0.1 from 0.2 M, the yield was increased to 83% (entry 12), and higher concentration (0.4 M) gave even lower yield due to its poor solubility (entry 13).

With the optimal reaction conditions in hand, we then examined the substrate scope of this aza-MBH reaction, and the

results are shown in Table 2. The procedure serves as a general approach to various triarylsubstituted 3-pyrrolines with

Table 2. Substrate Scope of the Reaction^a



entry	EWG	R	Ar	yield (%) ^b
1	NO_2	H	Ph	83 (3a)
2	NO_2	H	4-MePh	48 (3b)
3	NO_2	H	4-FPh	65 (3c)
4	NO_2	H	4-ClPh	77 (3d)
5	NO_2	H	4- CF_3 Ph	76 (3e)
6	NO_2	H	3-BrPh	71 (3f)
7	NO_2	H	3-MePh	59 (3g)
8	NO_2	H	2-MePh	0
9	NO_2	H	2-naphthyl	53 (3h)
10	NO_2	H	3-F-4-MeOPh	85 (3i)
11	NO_2	6-Me	Ph	66 (3j)
12	CN	H	Ph	58 (3k)
13	CN	6-Cl	Ph	78 (3l)
14	CN	4-Me-6-Cl	Ph	80 (3m)

^aUnless specified, the reactions were carried out using **1** (0.2 mmol), **2** (3.5 equiv), and PEt_3 (30 mol %) in $ClCH_2CH_2Cl$ (2 mL) at 50 °C for 12 h. ^bIsolated yields.

structural variation on the benzene and pyridines in moderate to good yields. The *N*-tosylimines with electron-donating substitutions at the *para*-position of the benzene ring gave low yield (entry 2), while electron-withdrawing groups (EWG) afforded higher yields due to their capacity to elevate the activity of imines (entries 3–5). Similar results were also observed in the imines with EWG and electron-donating groups at the *meta*-position (entries 6 and 7). Reaction of the imine-bearing *ortho*-methyl substitution on the phenyl ring would not happen at all, which reminded us that the steric effect was an important issue in this protocol (entry 8). Furthermore, 2-naphthylaldimine was also a compatible substrate with formation of the product in 53% yield (entry 9). Additionally, the imine with disubstituted groups on benzene performed well under the standard condition to give 3-pyrroline with 85% yield (entry 10). Moreover, 2-vinylpyridine bearing two substituents reacted smoothly to give the desired product with high yield (entry 11). It is recognized that the EWG at the 5-position was the key point for the reactivity of vinylpyridine. When the cyano group at the 5-position of 2-vinylpyridine was tested, the reaction worked well with acceptable yield (entry 12). Di- and trisubstituted groups, including the cyano group on 2-vinylpyridine, also reacted smoothly to afford 3-pyrrolines with high yields (entries 13 and 14). However, when the substituted group was changed to trifluoromethyl or acetyl at the 5-position of 2-vinylpyridine, no reaction occurred.

The configuration of 3-pyrrolines was further confirmed by X-ray diffraction of **3a**, where two phenyl groups were determined to be in *cis* configuration (Figure 1 and see Supporting Information).²¹

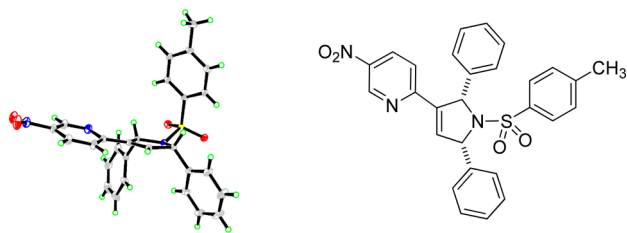
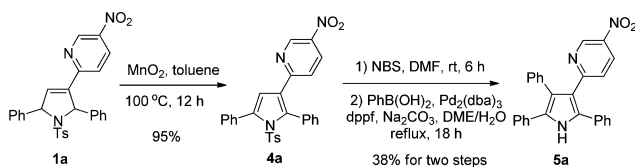


Figure 1. X-ray crystal structure of compound 3a.

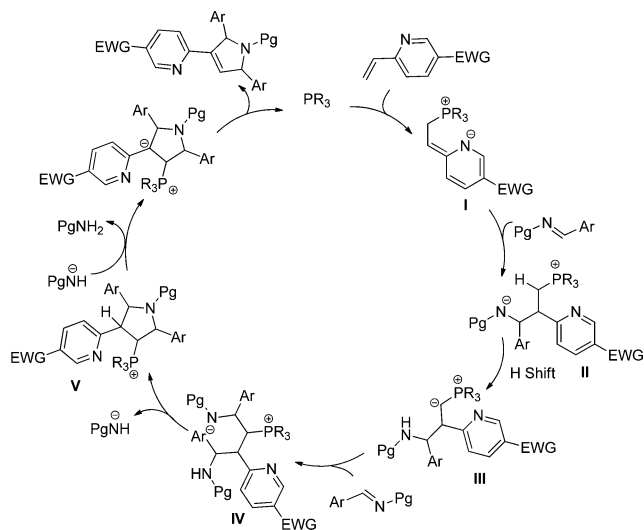
Polyarylsubstituted pyrroles feature special photocharacters and have been used in aggregation-induced emission fluorescence probes²² and biological activity studies.²³ However, the synthesis of unsymmetrical pyridine containing polyarylsubstituted pyrroles is very scarce.²⁴ From 3-pyrroline 3a synthesized in this MBH protocol as an example, we showed that simple oxidation can generate triarylsubstituted pyrrole 4a. Followed by bromination and a cross-coupling reaction, we can synthesize unsymmetrical polyarylsubstituted pyrrole 5a (Scheme 2).

Scheme 2. Synthesis of Polyarylsubstituted Pyrrole



On the basis of this experimental observation, the plausible mechanism of the reaction was proposed (Scheme 3).

Scheme 3. Possible Mechanistic Schemes for Phosphine-Catalyzed Pyrroline Formation



Phosphine initially attacked the β -position of vinylpyridine to generate enamine I, which intercepted *N*-tosylimine to afford intermediate II. The proton shifts from the vicinal carbon of phosphonium to the amide to form ylide III¹⁷ followed by nucleophilic attack to the second *N*-tosylimine to generate new zwitterionic species IV. Subsequent intramolecular nucleophilic attack takes place with concurrent formation of pyrrolidine V. The leaving amino anion captured a proton from the α -position

of pyridine to form the final product and regenerate the catalyst. It is noted that, in Shi's protocol, the mixture of 3-pyrroline and pyrrole products from *N*-tosylimine and methyl vinyl ketone as phosphine catalyst worked as the leaving group during the cyclization process.¹⁸ In our case, the tosylamino anion worked as the leaving group to keep the phosphine that remained in V, which generated more stable 3-pyrroline only. We speculated that the driving force of the reaction that directed the abnormal product but not the normal MBH product was the nitrogen atom stabilizing the phosphonium in the process and facilitated further reaction with the second *N*-tosylimine. It is noteworthy that intramolecular stabilization of phosphonium by nitrogen atoms or other donors with electron lone pairs has precedent in the literature.²⁵

In summary, we have developed 2-vinylpyridines as a new type of electron-poor system in the MBH reaction for the first time. In this reaction, triarylsubstituted 3-pyrrolines are straightforwardly synthesized from 2-vinylpyridines and *N*-tosylimines catalyzed by trialkylphosphine. This cascade reaction afforded triarylsubstituted 3-pyrrolines in good to high yields with excellent diastereoselectivities. Furthermore, we developed a concise pathway to synthesize various highly useful unsymmetrical polyarylsubstituted pyrroles from the 3-pyrroline products. Further efforts directed at the expansion of this novel and valuable activated alkene chemistry to other interesting transformations is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and ¹H and ¹³C NMR and HRMS data for experimental procedures and characterization of the products 3, 4a, 5a, and X-ray information 3a (cif file). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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- (19) The reaction of **1a** (1 equiv) and imine **2a** (1 equiv) under the same reaction condition gave 3-pyrroline **3a** product only. No MBH reaction product was found.
- (20) Lewis base such as DABCO, TEA, P(C₆H₄OCH₃)₃, Ph₂PCH₃, and PPh₃ could not catalyze this reaction.
- (21) CCDC-1054731 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk.
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