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Phosphines catalyzed nucleophilic addition of azoles to allenes: synthesis of allylazoles and indolizines

David Virieux,* Anne-Françoise Guillouzic and Henri-Jean Cristau

Laboratoire de Chimie Organique, UMR 5076, Ecole Nationale Supérieure de Chimie de Montpellier 8, rue de l'Ecole Normale, 34296 Montpellier cedex 5, France

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Abstract—Triphenylphosphine was used as nucleophilic catalyst for umpolung addition of azoles to electron-deficient allenes. This strategy offers a simple and efficient method for functional allylation of azoles under neutral conditions and affords heterocyclic substituted Michael olefins. Furthermore, this catalytic methodology has been extended to addition–cyclization reactions between electron-deficient allenes or alkynes and pyrrole-2-carboxaldehyde in the presence of catalytic amount of tributylphosphine. In such conditions, substituted indolizine-7-carboxylates are easily obtained.

1. Introduction

The last few years, an impressive development took place in metal free catalytic methods. Exciting results in organocatalyses attracted a deep attention, taking the advantages of often simple, inexpensive and commercially available catalysts.[1] The great potential of organocatalyses was also recently highlighted in reviews as broad and useful methodologies to elaborate complex structures. Among them, nucleophilic organocatalysis was also proved to be efficient for the synthesis of polyfunctionalized structural units and in some recent extensions of the Morita–Baylis–Hillman reaction, high enantioselectivities can be obtained, demonstrating its wide range of synthetic applications.[2]

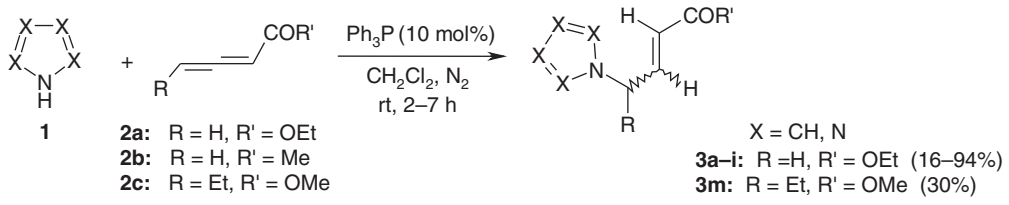
Some years ago, Cristau et al. reported a sequential multistep synthesis using stoichiometric amount of triphenylphosphine for the umpolung γ-addition of various nucleophiles on electron-deficient allenes.[3] Initiated by Trost, the catalytic version of this reaction was expanded till recently to a large set of nucleophiles.[4]

The development of new synthetic methods to functionalize or to construct heterocycles, merely using both tandem reactions and nucleophilic organocatalysis is a question of interest. We report herein the catalytic N-functional allylation of azoles using electron-deficient allenes. In a second time, a catalytic tandem reaction of properly functionalized azoles giving directly indolizines will be presented.

2. Results and discussion

2.1. Functional allylation of azoles

As depicted in Scheme 1, reaction of azoles **1** with activated allenes[5] **2** in the presence of catalytic amount of triphenyl-



1

2a: R = H, R' = OEt
2b: R = H, R' = Me
2c: R = Et, R' = OMe

3a–i: R =H, R' = OEt (16–94%)
3m: R = Et, R' = OMe (30%)

Scheme 1. Allylation of azoles reaction.

Keywords: Phosphines; Nucleophilic catalysis; Allylation; Azoles; Indolizines.
* Corresponding author. Tel.: +33 467144314; fax: +33 467144319; e-mail: virieux@enscm.fr

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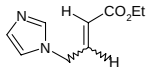
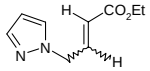
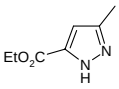
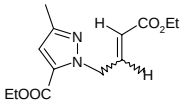
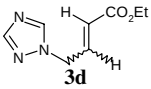
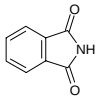
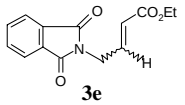
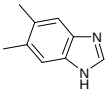
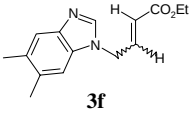
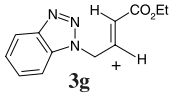
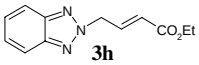
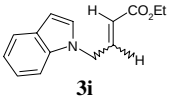
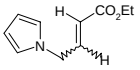
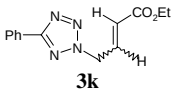
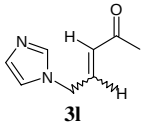
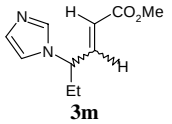
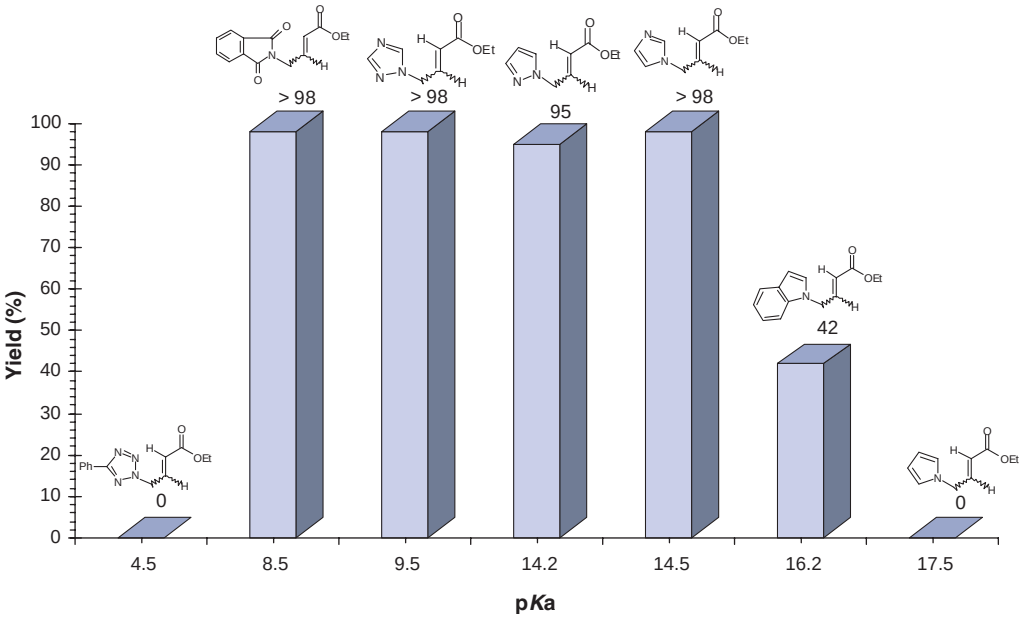
phosphine readily affords the functional 1-allylazoles **3** in excellent to good yields (72–94%) when compounds **1** are imidazole, pyrrazole, triazole, phthalimide and their benzo-analogues (Table 1, entries 1–6).

For the benzotriazole (entry 7), in which a competitive N-allylation either at position 1-N and 2-N is possible, the reaction takes place principally on the position 1 with a ratio 74/26. This experimental result agrees with the ab initio calculations of the charge distribution in the benzotriazolate anion indicating the π-charge is mainly located on the two nitrogen atoms, 1-N and 3-N, adjacent to the benzene ring.[6] The two reaction products **3g** and **3h** are easily identified and assigned by ^{1}H and ^{13}C NMR. Indeed, the resulting addition product **3h** on position 2 presents a plane of symmetry. As a consequence, the ^{1}H and ^{13}C NMR spectra show only two types of signals for the aromatic CH.

Table 1. Triphenylphosphine-catalyzed γ-addition of azoles to electron-deficient allenes

Entry	1	2	3	Yield	Isolated yield (%)	*Z*/*E* ratio[a]
1		**2a**	 **3a**	>98[b]	72	18/82
2		**2a**	 **3b**	95[c]	80	36/64
3		**2a**	 **3c**	92[c]	89	18/82
4		**2a**	 **3d**	>98[b]	79	16/84
5		**2a**	 **3e**	>98[b,c]	94	11/89
6		**2a**	 **3f**	89[c]	72	8/92
7		**2a**	 **3g** +  **3h**	54[c] 20[c]	53 19	0/100 0/100
8		**2a**	 **3i**	42[c]	16	35/65
9		**2a**	 **3j**	—	0	—
10		**2a**	 **3k**	—	0	—
11		**2b**	 **3l**	—	0	—
12		**2c**	 **3m**	>30[b]	30	3/97

[a] *Z*/*E* ratio determined in the reaction mixture by GC/MS or ^{1}H NMR.
[b] Formation yield determined by ^{1}H NMR.
[c] Formation yield determined by GC/MS.



Graph 1. Yield versus pK_a of heterocycles **1** by reaction with ethyl allenoate.

For the reaction between acetylallene **2b**[7] and imidazole, only oligomerization of allene was observed.[8]

Finally, using a γ-substituted allenoate, the desired product is obtained with a lower yield (30%, Table 1, entry 12). The isomerization of the allene into the corresponding diene was the main reaction.[9]

The method provides functional 1-allylazoles with a predominant *E*-stereoselectivity, the *E*/*Z* ratio ranging from 64/36 to 100/0. The stereoselectivity can be easily explained by assuming that the elimination step follows an E1cB mechanism where unfavorable steric hindrance between the azole and the electron withdrawing group induces the preferential formation of the *E*-isomer.[10]

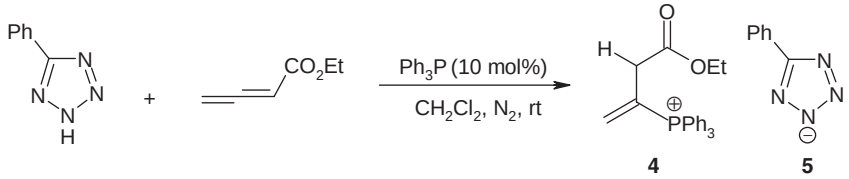
The results described above when ethyl allenoates are used, have been plotted in a histogram representing the yield versus the pK_a of the heterocycle. The higher yields are observed for pK_a ranging from 8 to 14–15 (Graph 1).

Indeed, for phenyltetrazole (pK_a=4.5) (entry 10), only the fast and complete conversion of Ph_3P into a unique product at 25.5 ppm is observed by ^{31}P NMR. It was assigned to the α-substituted vinylphosphonium **4** with tetrazole anion as counter-ion, thanks to the co-addition in the reaction mixture of an authentic sample of the α-substituted vinylphosphonium iodide **4**[11] (Scheme 2). Monitoring the reaction by ^1H NMR and GC/MS shows that the remaining reactants are almost not consumed. Consequently, it can be reasonably proposed that the conjugated base of tetrazole **5** is not nucleophilic enough to add to the vinylphosphonium **4**.

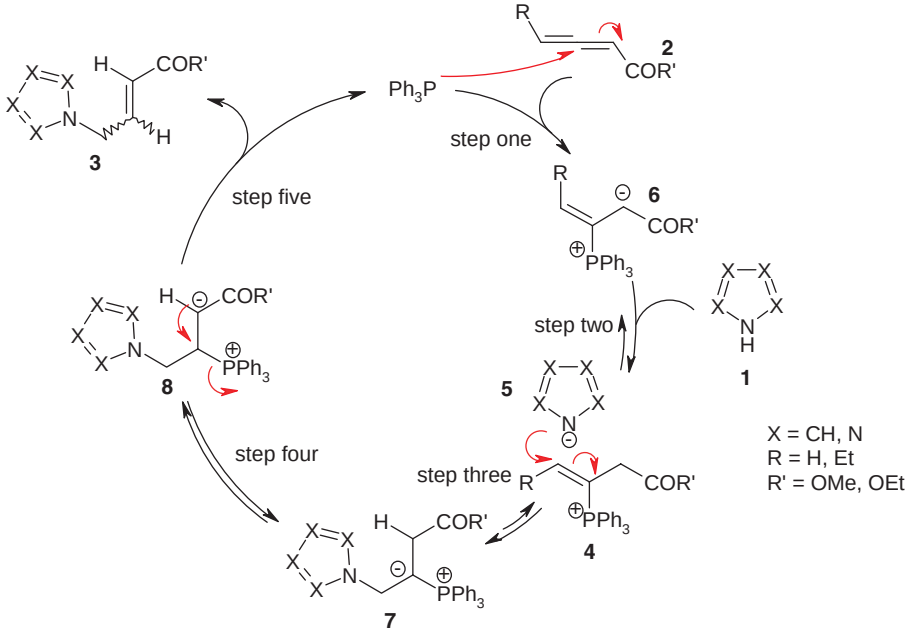
With pyrrole (pK_a 17.5) and indole (pK_a 16.2) (entries 8–9), we mainly observe the formation of a mixture of allene oligomeric products. *N*-allyl indole has been obtained in only 16% yield after chromatography. A possible explanation means the intermediate ylide **6** (see Scheme 3) is not basic enough to deprotonate the azole. As a consequence, the acid–base reaction competes unfavorably with the polymerization of allene.[8] An excess of triphenylphosphine does not improve the yields.

Mechanism

In an attempt to rationalize all these results, the following mechanism can be proposed (Scheme 3). The catalytic cycle might be initiated by a nucleophilic addition of triphenylphosphine to the electron-deficient allene **2**. The enolate **6** then deprotonates the azole **1** generating the nucleophilic species **5** and the vinylphosphonium **4**. Consecutively, nucleophilic addition of **5** to vinylphosphonium **4** leads to the ylide **7**. Finally, enolate **8** is obtained by prototropy and then undergoes a β-elimination affording the final γ-addition allylazole **3** and regenerating the nucleophilic catalyst.



Scheme 2. Formation of the α-substituted vinylphosphonium **4**.



Scheme 3. N-allylation mechanism of azoles.

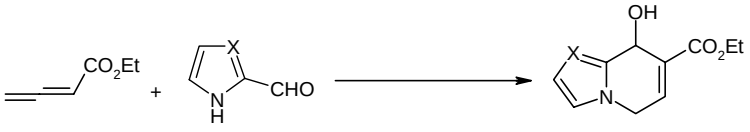
2.2. Addition–cyclization reactions: synthesis of indolizines

In a continuation of our investigations, we took advantage of the intermediate formation of enolate **8** to obtain fused bicyclic compounds. In this regard, another functionality is required on the azoles to react successively as pronucleophile and as electrophile. The commercially available 2-formylazoles **1n–o** could be good candidates for the formation of allylation-Morita–Baylis–Hillman products **9** (see Table 2).

Initial efforts focused on triphenylphosphine-catalyzed addition–cyclization between electron-deficient allenes **2** and 2-formylazoles **1n–o**. In opposition to our expectations, the reaction with imidazole-2-carboxaldehyde **1n** (entry 1) only gave the vinylphosphonium salt **4** resulting from the addition of triphenylphosphine to the electron deficient allene **2**.

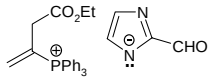
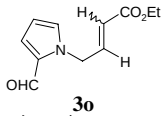
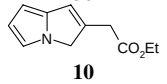
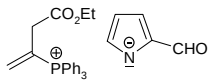
Addition products **3o**-*Z* and **3o**-*E* were obtained in 63% yield by mixing ethyl 2,3-butadienoate with pyrrole-2-carboxaldehyde in the presence of triphenylphosphine

Table 2. Triphenylphosphine-catalyzed reactions of azoles **1n–o** with allene

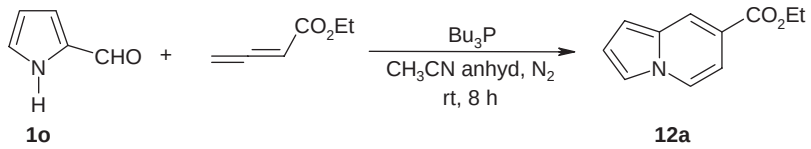


1n (X = N)
1o (X = CH)

9

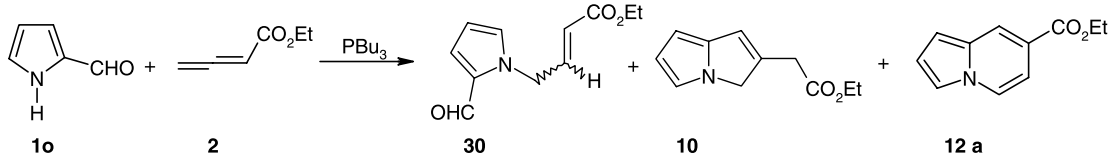
Entry	1	Conditions	Product	Yield (%)	*Z*/*E* ratio[a]
1	**1n**	Ph_3P (10 mol%), DMF, 20 °C, 3 h	 **4**	10[b]	—
2	**1o**	Ph_3P (10 mol%), CH_2Cl_2, 20 °C, 20 h	 **3o**	63[c]	38/62
			 **10**	6[c]	—
3	**1o**	Ph_3P (20 mol%), $BF_3 \cdot Et_2O$ (or $ZnCl_2$) CH_2Cl_2, 20 °C, 16	 **4**	20[c]	—

[a] *Z*/*E* ratio determined in the reaction mixture by GC/MS or ^1H NMR.
[b] One Hundred percentage conversion estimated by ^{31}P NMR.
[c] Isolated yield.



Scheme 4. Synthesis of ethyl indolizine-7-carboxylate **12a**.

Table 3. Optimisation indolizine synthesis **12a**

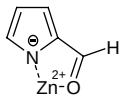


Entry	Ratio **2/1o**	Bu_3P (mol%)	Solvent	T (°C)	t	Conversion (%)[a]		Yield (%)[a]	
						1o	**3o**	**10**	**12a**
1	1	10	CH_2Cl_2	20	20 h	95	77	4	14
2	1	30	CH_2Cl_2	Reflux	3 days	94	44	8	42
3	1.5	30	CH_3CN	20	8 h	93	0	5	88 (54)[b]
4	2.5	30	CH_3CN	20	5 h	100	0	3	97 (57)[b]

[a] Conversion and yield were measured by GC/MS on the reaction mixture.
[b] Yields in brackets correspond to isolated yields.

(10 mol%) (entry 2). From the reaction mixture was also isolated a small fraction (6%) of a bicyclic compound **10**, as the result of a tandem Michael–Wittig reaction.

On the other hand, activation by Lewis acids such as boron trifluoride etherate ($BF_3 \cdot Et_2O$, 100 mol%) or zinc chloride ($ZnCl_2$, 50 mol%) fails to give the expected addition–cyclization reaction (entry 3). Only the vinylphosphonium formation is observed, indicating that activation with Lewis acid decreases dramatically the azole nucleophilicity. A possible explanation could be the formation of stable complexation products as the bidentate complex **11** with zinc.



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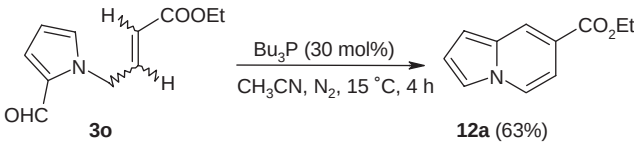
Using tributylphosphine as a more nucleophilic catalyst dramatically changes the behavior of the reaction. Accordingly, addition of a solution of ethyl 2,3-butadienoate to a mixture of pyrrole-2-carboxaldehyde **1o** and tributylphosphine (30 mol%) affords ethyl indolizine-7-carboxylate **12a** isolated in 57% yield after column chromatography (Scheme 4).

To improve the yields, solvent and quantities of reactants were optimized. In dichloromethane with 10 mol% tributylphosphine, addition products **3o** (*Z*/*E*) were obtained as the major products in 77% yield (Table 3, entry 1) together with 4% of Michael–Wittig product **10** and 14% of the expected indolizine **12a** as minor products, while 95% aldehyde was converted. When adding 20 mol% PBu_3 and heating to reflux the latest reaction mixture, cyclization proceeded smoothly and furnished indolizine **12a** in 42% yield (entry 2). In the same way, Wittig product **10** yield also increased to 8%.

In acetonitrile at 20 °C, indolizine **12a** was obtained as the main product in 8 h and in 88% yield, together with small quantities of **10** (5%). Finally, the use of an excess of allene (2.5 equiv) allows the total aldehyde conversion and gives an optimal indolizine yield (97%) after stirring 5 h at 20 °C (entry 4). **12a** was isolated in 57% yield.

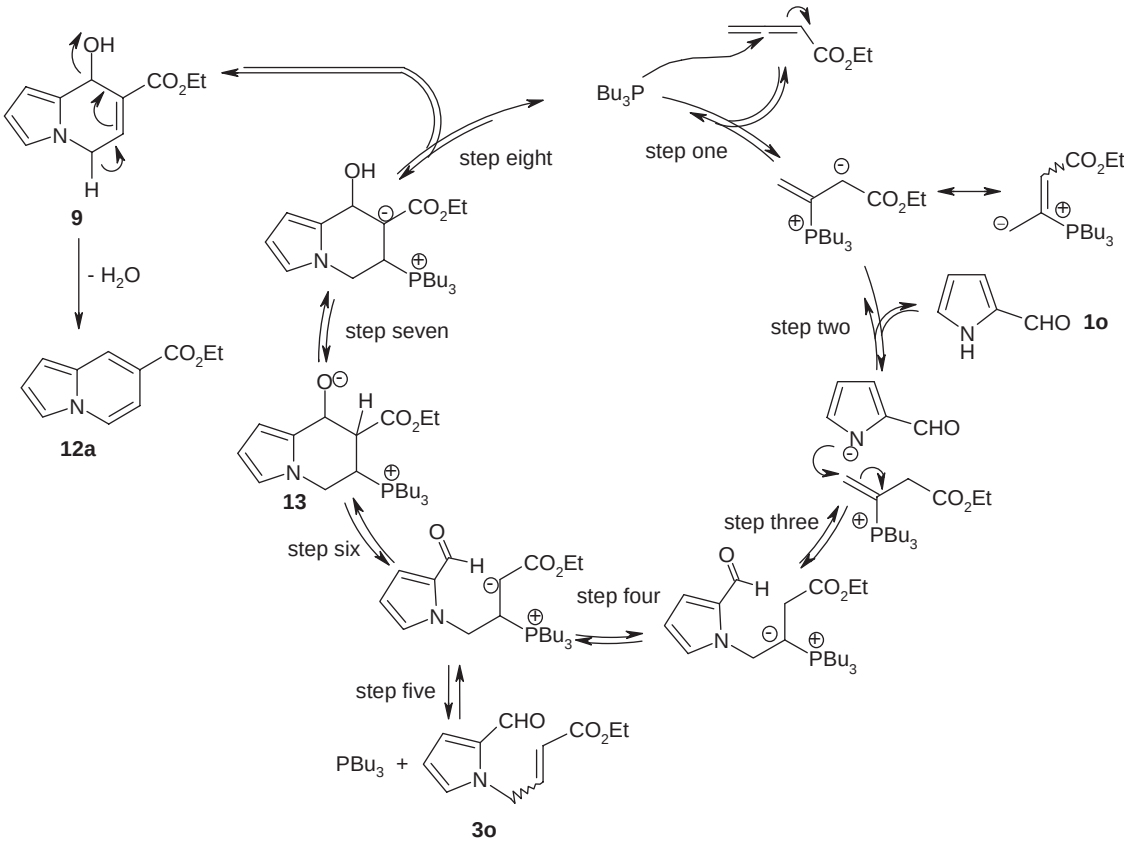
Based on these results, in association with the reactivity observed with triphenylphosphine, the mechanism is most certainly an addition–cyclization sequence. Indeed, in dichloromethane we first observed the formation of allylazole **3o** at room temperature then its cyclization by refluxing the reaction mixture (Table 3, entries 1 and 2).

For confirmation, we ran the following reaction: tributylphosphine was stirred with allylazole **3o** and after 4 h, indolizine **12a** identified by ^1H NMR was formed in 63% yield (Scheme 5).



Scheme 5. Synthesis of indolizine **12a** from **3o**.

In accordance with the previous one (see Scheme 3), the plausible mechanism for this tributylphosphine-catalyzed addition–cyclization reaction is proposed in Scheme 6. The first four steps are similar to those observed previously. When triphenylphosphine is used as catalyst, step five is almost irreversible and allylpyrrole **3o** is preferentially obtained, whereas tributylphosphine is nucleophilic enough to add to the substituted Michael



Scheme 6. Mechanism of formation of indolizine **12a**.

olefin **3o**. Consequently, the aldolization (step six), which is generally considered as the rate limiting step[12] in the Morita–Baylis–Hillman reaction occurs giving the alkoxide **13**.

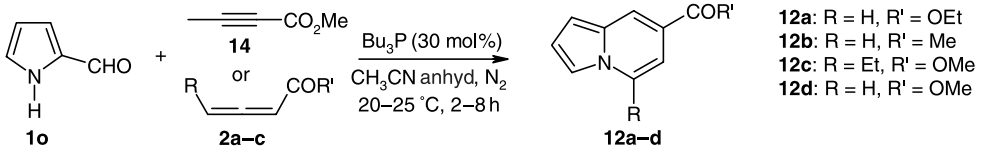
After regeneration of the catalyst (steps seven and eight), the intramolecular Morita–Baylis–Hillman adduct **9** aromatizes spontaneously in the reaction mixture, into indolizine **12a** by elimination of water.

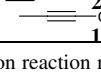
A variety of electron-deficient allenes and also methyl 2-butynoate **14** are then used (see Table 4). Unfortunately, acetylallene **2b** is too reactive and converted essentially into oligomeric products. Indolizine **12b** was formed in poor yield (28%) and isolated in 5% yield.

With methyl 2,3-hexadienoate **2c** (entry 3), the reaction competes with an isomerization into 2,4-dienoate and the indolizine **12c** was obtained in 4% yield.

Finally, more convincing was the reaction with methyl 2-butynoate **14**, which gave the indolizine **12d** in 85% yield (isolated in 50% yield). This new synthetic method to obtain functionalized indolizines seems to fit better with non-isomerizable allenic esters and alkynoates.

Table 4. Synthesis of indolizines **12**



Entry	Reagent	Product	Yield (%)[a]	Isolated yield (%)
1	 **2a**	**12a**	97	57
2	 **2b**	**12b**	28	5
3	 **2c**	**12c**	7	4
4	 **14**	**12d**	85	50

[a] Yield was determined by GC/MS on reaction mixture.

3. Conclusion

In conclusion, nucleophilic phosphinocatalysis offers a simple and efficient method for the functional allylation of azoles under neutral conditions and furnishes attractive heterocyclic substituted Michael olefins. This reaction has been successfully expanded to a variety of azoles. However, there is an optimal range of pK_a in order to avoid the polymerization of allene or the lack of nucleophilicity for the deprotonated azole.

Using the conjunction of pyrrole carboxaldehyde and tributylphosphine with electron deficient allenes or alkynes, we were able to obtain substituted indolizines by a tandem reaction.

4. Experimental

4.1. General remarks

All reactions involving air or moisture sensitive reagents or intermediates were carried out under nitrogen in flame-dried glassware. Reagents and solvents were purified before use and stored under nitrogen atmosphere. All reactions were monitored by GC/MS, ^{31}P or ^{1}H NMR. Flash column chromatography was performed using E. Merck silica gel 60 (35–70 μm) or neutral alumina gel (70–230 μm) and compressed air. Melting points were determined with a Electrothermal Digital Melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 1000 Fourier transform spectrometer. For ^{1}H, ^{13}C, and ^{31}P NMR spectra (δ in ppm) a Bruker Avance 400, a Bruker Avance 250 and Bruker AC 200 spectrometers were used. Assignments were made using a combination of 1D and 2D spectra (COSY, HMQC). Mass spectra were run with a Jeol JMS DX-300 spectrometer (positive FAB ionization and exact mass measurements using *p*-nitrobenzyl alcohol matrix). Elemental analyses were performed on a THERMOFINNIGAN Flash EA 1112 apparatus.

4.2. General procedure for functional allylation of azoles

To a mixture of azole (0.3 mol L^{-1}, 1 equiv) and PPh_3 (0.1 equiv) in anhydrous dichloromethane was added dropwise over 2 h at 18 °C a solution of ethyl 2,3-butadienoate (0.3 mol L^{-1}, 1 equiv) in anhydrous dichloromethane. The reaction was monitored by ^{1}H NMR or by GC/MS. After completion of the reaction, the solvent was evaporated under reduced pressure and the product was purified by flash column chromatography of silica gel.

4.2.1. (*E*/*Z*)-Ethyl 4-(imidazol-1′-yl)but-2-enoate (3a). The compound was eluted with dichloromethane–ethanol (99.5/0.5–98/2). Yield: 72% (497 mg), colorless oil; IR (KBr film): ν=3115, 2983, 1722 (C=O), 1499 (C=N) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): *E* isomer δ= 1.26 (t, $^{3}J_{(H,H)}$=7.1 Hz, 3H, CH_3), 4.18 (q, $^{3}J_{(H,H)}$=7.1 Hz, 2H, CH_2), 4.72 (dd, $^{3}J_{(H,H)}$=5.0 Hz, $^{4}J_{(H,H)}$=1.9 Hz, 2H, CH_2), 5.70 (dt, $^{3}J_{(H,H)}$=15.5 Hz, $^{4}J_{(H,H)}$=1.9 Hz, 1H, α-CH), 6.90 (dd, $^{3}J_{(H,H)}$=1.3 Hz, $^{4}J_{(H,H)}$=1.3 Hz, 1H, 4-CH), 6.98 (dt, $^{3}J_{(H,H)}$=15.6, 5.1 Hz, 1H, β-CH), 7.10 (dd, $^{3}J_{(H,H)}$=1.1 Hz, $^{4}J_{(H,H)}$=1.1 Hz, 1H, 5-CH), 7.48 (dd, $^{3}J_{(H,H)}$=1.1 Hz, $^{4}J_{(H,H)}$=1.1 Hz, 1H, 2-CH); *Z* isomer δ= 1.32 (t, $^{3}J_{(H,H)}$=7.1 Hz, 3H, CH_3), 4.22 (q, $^{3}J_{(H,H)}$=7.1 Hz, 2H, CH_2), 5.18 (dd, $^{3}J_{(H,H)}$=6.0 Hz, $^{4}J_{(H,H)}$=2.1 Hz, 2H, CH_2), 5.94 (dt, $^{3}J_{(H,H)}$=11.4 Hz, $^{4}J_{(H,H)}$=2.1 Hz, 1H, α-CH), 6.23 (dt, $^{3}J_{(H,H)}$=6.0, 11.4 Hz, 1H, β-CH), 6.94 (dd, $^{3}J_{(H,H)}$=1.3 Hz, $^{4}J_{(H,H)}$=1.3 Hz, 1H, 4-CH), 7.07 (dd, $^{3}J_{(H,H)}$=1.0 Hz, $^{4}J_{(H,H)}$=1.0 Hz, 1H, 5-CH), 7.51 (dd, $^{3}J_{(H,H)}$=1.1 Hz, $^{4}J_{(H,H)}$=1.0 Hz, 1H, 2-CH); ^{13}C NMR (100 MHz, $CDCl_3$): *E* isomer δ=14.12 (CH_3), 47.31 (CH_2), 60.78 (CH_2), 119.15 (4-CH), 123.60 (α-CH), 130.05 (5-CH), 137.26 (2-CH), 141.55 (β-CH), 165.37 (1-C); *Z* isomer δ=14.16 (CH_3), 45.11 (CH_2), 60.66 (CH_2), 118.81 (4-CH), 122.18 (α-CH), 129.99 (5-CH), 137.08 (2-CH), 143.19 (β-CH), 165.56 (1-C); FAB (+): *m*/*z* (%)= 181 (100) [M$^+$+H], 135 (3) [M$^+$−OEt], 107 (5) [M$^+$− CO_2Et]; HRMS: calcd for $C_9H_{12}N_2O_2$ 181.0977; found 181.0974.

4.2.2. (*E*/*Z*)-Ethyl 4-(pyrazol-1′-yl)but-2-enoate (3b). The two isomers were separated using hexane–ethyl acetate eluent (95/5 and 92/8). Yield: 80% (165 mg (*Z* isomer) and 426 mg (*E* isomer)), colorless oils; IR (KBr film): *E* isomer ν=3118, 2935, 1721 (C=O) cm^{-1}; *Z* isomer ν=3120, 2984, 2939, 1715 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *E* isomer δ=1.27 (t, $^{3}J_{(H,H)}$=7.2 Hz, 3H, CH_3), 4.18 (q, $^{3}J_{(H,H)}$=7.2 Hz, 2H, CH_2), 4.91 (dd, $^{3}J_{(H,H)}$=5.3 Hz, $^{4}J_{(H,H)}$=1.8 Hz, 2H, CH_2), 5.71 (dt, $^{3}J_{(H,H)}$=15.6 Hz, $^{4}J_{(H,H)}$=1.8 Hz, 1H, α-CH), 6.31 (t, $^{3}J_{(H,H)}$=2.1 Hz, 1H, 4-CH), 7.04 (dt, $^{3}J_{(H,H)}$=15.6, 5.3 Hz, 1H, β-CH), 7.41 (d, $^{3}J_{(H,H)}$=2.3 Hz, 1H, 3-CH), 7.55 (d, $^{3}J_{(H,H)}$=2.0 Hz, 1H, 5-CH); *Z* isomer δ=1.31 (t, $^{3}J_{(H,H)}$=7.2 Hz, 3H, CH_3), 4.22 (q, $^{3}J_{(H,H)}$=7.2 Hz, 2H, CH_2), 5.37 (dd, $^{3}J_{(H,H)}$=5.8 Hz, $^{4}J_{(H,H)}$=2.3 Hz, 2H, CH_2), 5.92 (dt, $^{3}J_{(H,H)}$=11.5 Hz, $^{4}J_{(H,H)}$=2.2 Hz, 1H, α-CH), 6.26 (t, $^{3}J_{(H,H)}$=2.2 Hz, 4-CH), 6.42 (dt, $^{3}J_{(H,H)}$=11.5, 5.9 Hz, 1H, β-CH), 7.42 (dd, $^{3}J_{(H,H)}$=2.2 Hz, $^{4}J_{(H,H)}$=0.5 Hz, 1H, 3-CH), 7.53 (dd, $^{3}J_{(H,H)}$=2.0 Hz, $^{4}J_{(H,H)}$=0.6 Hz, 1H, 5-CH); ^{13}C NMR (100 MHz, $CDCl_3$): *E* isomer δ=14.15 (CH_3), 52.42 (CH_2), 60.61 (CH_2), 106.25 (4-CH), 123.42 (α-CH), 129.41 (5-CH), 139.98 (β-CH), 141.96 (3-CH), 165.60 (C); *Z* isomer δ=14.18 (CH_3), 50.39 (CH_2), 60.47 (CH_2), 105.87 (4-CH), 121.25 (α-CH), 129.30 (5-CH), 139.88 (β-CH), 143.95 (3-CH), 165.78 (C); FAB (+): *m*/*z* (%)=181 (100) [M$^+$+H], 135 (18) [M$^+$−OEt], 107 (11) [M$^+$−CO_2Et]; HRMS: calcd for $C_9H_{12}N_2O_2$ 181.0977; found 181.0988 (*E* isomer).

4.2.3. (*E*/*Z*)-Ethyl 4-(5′-ethoxycarbonyl-3′-methyl-pyrazol-1′-yl)-but-2-enoate (3c). Compound **3c** was eluted with dichloromethane–ethanol (100/0–98/2). Yield: 89% (93 mg (mixture of *E*,*Z* isomers) and 92 mg (*E* isomer)), colorless oils; IR (KBr film): *E* isomer ν=3140, 2982, 1720 (C=O), 1716 (C=O) cm^{-1}; *Z* isomer ν=3120, 3053, 2984, 1715 (C=O) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): *E* isomer δ=1.27 (t, $^{3}J_{(H,H)}$=7.1 Hz, 3H, CH_3), 1.40 (t, $^{3}J_{(H,H)}$=7.2 Hz, 3H, CH_3), 2.28 (d, $^{4}J_{(H,H)}$=0.7 Hz, 3H, CH_3), 4.18 (q, $^{3}J_{(H,H)}$=7.1 Hz, 2H, CH_2), 4.40 (q, $^{3}J_{(H,H)}$=7.2 Hz, 2H, CH_2), 4.94 (dd, $^{3}J_{(H,H)}$=4.6 Hz, $^{4}J_{(H,H)}$=2.0 Hz, 2H, CH_2), 5.52 (dt, $^{3}J_{(H,H)}$=15.7 Hz, $^{4}J_{(H,H)}$=1.9 Hz, 1H, α-CH), 6.63 (q, $^{4}J_{(H,H)}$=0.8 Hz, 1H, 4-CH), 7.00 (dt, $^{3}J_{(H,H)}$=15.7 Hz, $^{4}J_{(H,H)}$=4.6 Hz, 1H, β-CH); *Z* isomer δ=1.28 (t, $^{3}J_{(H,H)}$=7.1 Hz, 3H, CH_3), 1.69 (t, $^{3}J_{(H,H)}$=7.2 Hz, 3H, CH_3), 2.30 (s, 3H, CH_3), 4.25 (q,

$^3J_{(H,H)}$=7.2 Hz, 2H, CH_2), 4.41 (q, $^3J_{(H,H)}$=7.1 Hz, 2H, CH_2), 5.44 (dd, $^3J_{(H,H)}$=5.7 Hz, $^4J_{(H,H)}$=2.2 Hz, 2H, CH_2), 5.95 (dt, $^3J_{(H,H)}$=11.4 Hz, $^4J_{(H,H)}$=2.2 Hz, 1H, α-CH), 6.34 (dt, $^3J_{(H,H)}$=11.4 Hz, $^4J_{(H,H)}$=5.7 Hz, 1H, β-CH), 6.58 (q, $^4J_{(H,H)}$=0.7 Hz, 1H, 4-CH); ^{13}C NMR (63 MHz, $CDCl_3$): *E* isomer δ=11.41 (CH_3), 14.56 (CH_3), 14.80 (CH_3), 50.97 (CH_2), 61.15 (CH_2), 61.37 (CH_2), 109.22 (4-CH), 123.51 (α-CH), 140.56 (5-C), 141.52 (β-CH), 143.60 (s, 3-C), 162.77 (C), 165.87 (C); ^{13}C NMR (100 MHz, $CDCl_3$); *Z* isomer δ=11.26 (CH_3), 14.19 (CH_3), 14.34 (CH_3), 48.47 (CH_2), 60.59 (CH_2), 60.88 (CH_2), 108.59 (4-CH), 121.50 (α-CH), 142.98 (5-C), 143.35 (β-CH), 148.04 (s, 3-C), 162.36 (C), 165.79 (C); FAB (+): *m/z* (%)=289 (20) [M+Na], 267 (70) [M^++H], 221 (100) [M^+−OEt], 193 (12) [M^+−CO_2Et], 147 (10) [M^+−COOEt–OEt+H]; HRMS: calcd for $C_{13}H_{11}N_2O_4$ 267.1345; found 267.1338 (*E*+*Z* isomers).

4.2.4. (*E*/*Z*)-Ethyl 4-([1,2,4]-triazol-1′-yl)but-2-enoate (3d). The two isomers were separated with hexane–ethyl acetate eluent (50/50–45/55). Yield: 79% (79 mg (*Z* isomer), 397 mg (*E* isomer) and 52 mg (mixture of *E*,*Z* isomers)), colorless oils; IR (KBr film): *E* isomer ν=3120, 2983, 1719 (C=O) cm^{-1}; *Z* isomer ν=3121, 2984, 2940, 1713 (C=O) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): *E* isomer δ=1.14 (t, $^3J_{(H,H)}$=7.1 Hz, 3H, CH_3), 4.06 (q, $^3J_{(H,H)}$=7.1 Hz, 2H, CH_2), 4.88 (dd, $^3J_{(H,H)}$=5.4 Hz, $^4J_{(H,H)}$=1.8 Hz, 2H, CH_2), 5.68 (dt, $^3J_{(H,H)}$=15.6 Hz, $^4J_{(H,H)}$=1.8 Hz, 1H, α-CH), 6.89 (dt, $^3J_{(H,H)}$=15.8, 5.4 Hz, 1H, β-CH), 7.87 (s, 1H, 5-CH), 8.07 (s, 1H, 3-CH); *Z* isomer δ=1.28 (t, $^3J_{(H,H)}$=7.2 Hz, 3H, CH_3), 4.18 (q, $^3J_{(H,H)}$=7.2 Hz, 2H, CH_2), 5.40 (dd, $^3J_{(H,H)}$=5.9 Hz, $^4J_{(H,H)}$=2.1 Hz, 2H, CH_2), 5.96 (dt, $^3J_{(H,H)}$=11.4 Hz, $^4J_{(H,H)}$=2.2 Hz, 1H, α-CH), 6.36 (dt, $^3J_{(H,H)}$=11.4, 5.9 Hz, 1H, β-CH), 7.93 (s, 1H, 5-CH), 8.12 (s, 1H, 3-CH); ^{13}C NMR (63 MHz, $CDCl_3$): *E* isomer δ=14.43 (CH_3), 50.13 (CH_2), 61.11 (CH_2), 124.67 (α-CH), 140.36 (β-CH), 143.82 (5-CH), 152.64 (3-CH), 165.50 (C); *Z* isomer δ=14.11 (CH_3), 47.66 (CH_2), 60.62 (CH_2), 122.43 (α-CH), 141.59 (β-CH), 143.21 (5-CH), 152.30 (3-CH), 165.52 (C); FAB (+): *E* isomer *m/z* (%)=182 (98) [M^++H], 136 (52) [M^+−CO_2Et], 69 (55) [triazole]$^+$; *Z* isomer *m/z* (%)=82 (27) [M+H]$^+$, 136 (25%) [M−CO_2Et]$^+$: *m/z*=113 (44%) [$C_6H_8O_2$+H]$^+$; HRMS: calcd for $C_{13}H_{11}N_2O_4$ 182.0930; found 182.0922 (*Z* isomer), 182.0933 (*E* isomer).

4.2.5. (*E*/*Z*)-Ethyl 4-(phtalimid-1′-yl)but-2-enoate (3e). The two isomers were separated with hexane–ethyl acetate eluent (90/10). Yield: 94% (70 mg (*Z* isomer), 508 mg (*E* isomer) and 78 mg (mixture of *E*,*Z* isomers)), white solids; mp 102 °C (*E* isomer), 119 °C (*Z* isomer); IR (KBr): *E* isomer ν=3100, 2989, 2941, 1774 (C=O_{ester}), 1712 (C=O_{amide}) cm^{-1}; *Z* isomer ν=3105, 2983, 1762 (C=O_{ester}), 1708 (C=O_{amide}), 1700 (C=O_{amide}) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): *E* isomer δ=1.26 (t, $^3J_{(H,H)}$=7.1 Hz, 3H, CH_3), 4.17 (q, $^3J_{(H,H)}$=7.1 Hz, 2H, CH_2), 4.45 (dd, $^3J_{(H,H)}$=5.1 Hz, $^4J_{(H,H)}$=1.7 Hz, 2H, CH_2), 5.89 (dt, $^3J_{(H,H)}$=15.6 Hz, $^4J_{(H,H)}$=1.7 Hz, 1H, α-CH), 6.93 (dt, $^3J_{(H,H)}$=15.8, 5.2 Hz, 1H, β-CH), 7.90–7.74 (2 m, 4H, $CH_{aromatic}$); *Z* isomer δ=1.34 (t, $^3J_{HH}$=7.1 Hz, 3H, CH_3), 4.24 (q, $^3J_{HH}$=7.1 Hz, 2H, CH_2), 4.95 (dd, $^3J_{HH}$=5.5 Hz, $^4J_{HH}$=2.2 Hz, 2H, CH_2), 5.92 (dt, $^3J_{HH}$=11.4 Hz, $^4J_{HH}$=2.2 Hz, 1H, α-CH), 6.14 (dt, $^3J_{HH}$=11.4, 5.5 Hz, 1H, β-CH), 7.89–7.72 (m, 4H, $CH_{aromatics}$); ^{13}C NMR (50 MHz, $CDCl_3$): *E* isomer δ=14.14 (CH_3), 38.17 (CH_2), 60.55 (CH_2), 123.14 (α-CH), 123.49 (4-CH and 7-CH), 131.90 (3a-C and 7a-C), 134.22 (5-CH and 6-CH), 140.67 (β-CH), 165.54 (C), 167.50 (1-C and 3-C); *Z* isomer δ=14.23 (CH_3), 37.05 (CH_2), 60.43 (CH_2), 121.74 (α-CH), 123.37 (4-CH and 7-CH), 132.05 (3a-C and 7a-C), 134.08 (5-CH and 6-CH), 143.78 (β-CH), 165.70 (C), 167.88 (s, 1-C and 3-C); FAB (+): *E* isomer *m/z* (%)=260 (6) [M^++H], 214 (10) [M^+−OEt], 186 (10) [M^+−CO_2Et]; *Z* isomer *m/z* (%)=260 (20) [M^++H], 214 (23) [M^+−OEt], 186 (31) [M^+−CO_2Et]; elemental analysis calcd (%) for $C_{14}H_{13}NO_4$ (259.26): C 64.86, H 5.05, N 5.40; found: C 64.48, H 5.06, N 5.79 (*E* isomer), C 64.38, H 5.11, N 5.39 (*Z* isomer).

4.2.6. (*E*/*Z*)-Ethyl 4-(5,6-dimethylbenzoimidazol-1′-yl)but-2-enoate (3f). The two isomers were separated with dichloromethane–ethanol eluent (99/1). Yield: 89% (30 mg (*Z* isomer), 310 mg (*E* isomer) and 184 mg (mixture of *E*,*Z* isomers)), colorless oils; IR (NaCl film): *E* isomer ν=3025, 2977, 2939, 1715 (C=O), 1663 (C=N) cm^{-1}; *Z* isomer ν=2990, 2940, 1712 (C=O), 1659 (C=N) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): *E* isomer δ=1.27 (t, $^3J_{(H,H)}$=7.2 Hz, 3H, CH_3), 2.40 (s, 6H, 2 CH_3), 4.18 (q, $^3J_{(H,H)}$=7.2 Hz, 2H, CH_2), 4.92 (dd, $^3J_{(H,H)}$=4.7 Hz, $^4J_{(H,H)}$=1.9 Hz, 2H, CH_2), 5.68 (dt, $^3J_{(H,H)}$=15.7 Hz, $^4J_{(H,H)}$=1.9 Hz, 1H, α-CH), 7.08 (dt, $^3J_{(H,H)}$=15.8, 4.7 Hz, 1H, β-CH), 7.09 (s, 1H, 7-CH), 7.61 (s, 1H, 4-CH), 7.80 (s, 1H, 2-CH); *Z* isomer δ=1.38 (t, $^3J_{(H,H)}$=7.1 Hz, 3H, CH_3), 2.40 (s, 6H, 2 CH_3), 4.30 (q, $^3J_{(H,H)}$=7.1 Hz, 2H, CH_2), 5.40 (dd, $^3J_{(H,H)}$=5.8 Hz, $^4J_{(H,H)}$=2.2 Hz, 2H, CH_2), 6.00 (dt, $^3J_{(H,H)}$=11.4 Hz, $^4J_{(H,H)}$=2.2 Hz, 1H, α-CH), 6.28 (dt, $^3J_{(H,H)}$=11.4, 5.8 Hz, 1H, β-CH), 7.14 (s, 1H, 7-CH), 7.59 (s, 1H, 4-CH), 7.84 (s, 1H, 2-CH); ^{13}C NMR (100 MHz, $CDCl_3$): *E* isomer δ=14.13 (CH_3), 20.26 and 20.61 (2 CH_3), 45.33 (CH_2), 60.79 (CH_2), 109.70 (7-CH), 120.56 (α-CH), 123.39 (4-CH), 131.46 (5-C), 132.10 (s, 7a-C), 132.66 (6-C), 141.17 (β-CH), 142.09 (2-CH), 142.40 (3a-C), 165.47 (C); *Z* isomer δ=13.22 (CH_3), 19.23 and 19.55 (2 CH_3), 42.38 (CH_2), 59.69 (CH_2), 108.72 (7-CH), 119.44 (α-CH), 121.21 (4-CH), 130.23 (5-C), 131.10 (7a-C), 131.32 (6-C), 141.05 (β-CH), 141.56 (3a-C), 142.65 (2-CH), 164.77 (C); FAB (+): *E* isomer *m/z* (%)=259 (100) [M^++H], 229 (4) [M^+−C_2H_5], 185 (11) [M^+−CO_2·C_2H_5], 147 (15) [$C_9H_{11}N_2^+$]; *Z* isomer *m/z* (%)=259 (100) [M^++H], 229 (2) [M^+−C_2H_5], 185 (10) [M^+−CO_2 C_2H_5], 147 (15) [$C_9H_{11}N_2^+$]; HRMS: calcd for $C_{15}H_{19}N_2O_2$ 259.1447; found 259.1447 (*E* isomer), 259.1454 (*Z* isomer).

4.2.7. (*E*)-Ethyl 4-(benzotriazol-1′-yl)but-2-enoate (3g). The two regioisomers **3g** and **3h** were separated with dichloromethane–ethyl ether eluent (98/2). Yield: 72% for both regioisomers (214 mg (isomer **3g**), 72 mg (isomer **3h**) and 296 mg (mixture of isomers **3g** and **3h**)), oils; Yield=53% for **3g**; IR (NaCl film): 2982, 2938, 2905, 1716 (C=O), 1663 (C=N) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): 1.27 (t, $^3J_{(H,H)}$=7.2 Hz, 3H, CH_3), 4.20 (q, $^3J_{(H,H)}$=7.2 Hz, 2H, CH_2), 5.47 (dd, $^3J_{(H,H)}$=5.1 Hz, $^4J_{(H,H)}$=1.8 Hz, 2H, CH_2), 5.75 (dt, $^3J_{(H,H)}$=15.6 Hz, $^4J_{(H,H)}$=1.8 Hz, 1H, α-CH), 7.14 (dt, $^3J_{(H,H)}$=15.6, 5.1 Hz, 1H, β-CH), 7.40 (m, 3H, 5-CH+6-CH+7-CH), 8.11 (m, 1H, 4-CH); ^{13}C

NMR (100 MHz, $CDCl_3$): 14.13 (CH_3), 48.55 (CH_2), 60.88 (CH_2), 109.19 (7-CH), 120.30 (4-CH), 124.23 and 124.26 (2s, α-CH+5-CH), 127.86 (s, 6-CH), 132.84 (7a-C), 139.74 (β-CH), 146.13 (3a-C), 165.21 (C); FAB (+): *m/z* (%)= 232 (100) [M^++H], 120 (10) [$M^+-C_6H_4N_3+H$]; HRMS: calcd for $C_{12}H_{14}N_3O_2$ 232.1086; found 232.1081.

4.2.8. (*E*)-Ethyl 4-(benzotriazol-2′-yl)but-2-enoate (3h). This regioisomer was obtained together with **3g**. Yield= 19% for **3h**, oil; IR (NaCl film): 3068, 2982, 2939, 1722 (C=O), 1664 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$): 1.27 (t, $^3J_{(H,H)}$=7.1 Hz, 3H, CH_3), 4.16 (q, $^3J_{(H,H)}$=7.1 Hz, 2H, CH_2), 5.49 (dd, $^3J_{(H,H)}$=5.8 Hz, $^4J_{(H,H)}$=1.8 Hz, 2H, CH_2), 5.87 (dt, $^3J_{(H,H)}$=15.7 Hz, $^4J_{(H,H)}$=1.8 Hz, 1H, α-CH), 7.18 (dt, $^3J_{(H,H)}$=15.7, 5.8 Hz, 1H, β-CH), 7.39 (ddd, $^3J_{(H,H)}$=8.7, 6.8 Hz, $^4J_{(H,H)}$=1.0 Hz, 2H, 5-CH+6-CH), 7.87 (ddd, $^3J_{(H,H)}$=8.7 Hz, $^4J_{(H,H)}$=1.0 Hz, $^5J_{(H,H)}$= 1.0 Hz, 2H, 4-CH+7-CH); ^{13}C NMR (100 MHz, $CDCl_3$): 14.16 (CH_3), 56.66 (CH_2), 60.78 (CH_2), 118.15 (4-CH +7-CH), 124.79 (α-CH), 126.74 (5-CH +6-CH), 139.42 (β-CH), 144.64 (3a-C+7a-C), 165.24 (C); FAB (+): *m/z* (%)=232 (100) [M^++H], 186 (14) [$M^+-OC_2H_5$], 158 (13) [M^+-CO_2 C_2H_5]; HRMS: calcd for $C_{12}H_{14}N_3O_2$ 232.1086; found 232.1087.

4.2.9. (*E*/*Z*)-Ethyl 4-(indol-1′-yl)-but-2-enoate (3i). The two isomers were separated with hexane–ethyl acetate eluent (98/2). Yield: 53% (142 mg (*Z* isomer), 95 mg (*E* isomer)), colorless oils; IR (NaCl film): *E* isomer ν=3102, 2982, 2937, 2881, 1716 (C=O) cm^{-1}; *Z* isomer ν=3055, 2982, 2880, 2820, 1714 (C=O) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): *E* isomer δ=1.27 (t, $^3J_{(H,H)}$=7.1 Hz, 3H, CH_3), 4.18 (q, $^3J_{(H,H)}$=7.1 Hz, 2H, CH_2), 4.91 (dd, $^3J_{(H,H)}$=4.6 Hz, $^4J_{(H,H)}$=1.9 Hz, 2H, CH_2), 5.62 (dt, $^3J_{(H,H)}$- =15.6 Hz, $^4J_{(H,H)}$=1.9 Hz, 1H, α-CH), 6.59 (dd, $^3J_{(H,H)}$= 3.1 Hz, $^5J_{(H,H)}$=0.8 Hz, 1H, 3-CH), 7.10 (dt, $^3J_{(H,H)}$=15.6, 4.6 Hz, 1H, β-CH), 7.05–7.31 (m, 4H, 2-CH+5-CH+6-CH+7-CH), 7.68 (ddd, $^3J_{(H,H)}$=7.6 Hz, $^4J_{(H,H)}$=1.2 Hz, $^5J_{(H,H)}$=0.8 Hz, 1H, 4-CH); *Z* isomer δ=1.39 (t, $^3J_{(H,H)}$= 7.1 Hz, 3H, CH_3), 4.31 (q, $^3J_{(H,H)}$=7.1 Hz, 2H, CH_2), 5.41 (dd, $^3J_{(H,H)}$=5.8 Hz, $^4J_{(H,H)}$=2.1 Hz, 2H, CH_2), 5.95 (dt, $^3J_{(H,H)}$=11.5 Hz, $^4J_{(H,H)}$=2.1 Hz, 1H, α-CH), 6.30 (dt, $^3J_{(H,H)}$=11.5, 5.8 Hz, 1H, β-CH), 6.57 (dd, $^3J_{(H,H)}$=3.2 Hz, $^5J_{(H,H)}$=0.8 Hz, 1H, 3-CH), 7.11–7.37 (m, 4H, 2-CH+ 5-CH+6-CH+7-CH), 7.66–7.70 (m, 1H, 4-CH); ^{13}C NMR (100 MHz, $CDCl_3$): *E* isomer δ=14.16 (CH_3), 46.97 (CH_2), 60.62 (CH_2), 102.24 (3-CH), 109.29 (7-CH), 119.78–121.14–121.98–122.61 (α-CH, 4-CH, 5-CH, 6-CH), 127.82 (2-CH), 128.65 (3a-C), 135.94 (7a-C), 142.86 (β-CH), 165.85 (C); *Z* isomer δ=14.29 (CH_3), 45.06 (CH_2), 60.57 (CH_2), 101.86 (3-CH), 109.42 (7-CH), 119.63–121.06–121.19–121.75 (α-CH, 4-CH, 5-CH, 6-CH), 127.73 (2-CH), 128.80 (3a-C), 135.92 (7a-C), 145.70 (β-CH), 166.04 (C); FAB (+): *E* isomer *m/z* (%)=230 (55) [M^++H], 229 (100) [M]$^+$, 200 (15) [$M^+-C_2H_5$], 156 (40) [$M^+-CO_2C_2H_5$]; *Z* isomer *m/z* (%)=230 (60) [M^++H], 229 (100) [M]$^+$, 156 (30) [$M^+-CO_2C_2H_5$]; HRMS: calcd for $C_{14}H_{15}NO_2$ 229.1103; found 229.1110 (*E* isomer), 229.1102 (*Z* isomer).

4.2.10. (*E*)-Ethyl 4-(imidazol-1′-yl)hexa-2-enoate (3m). The compound was eluted with hexane–ethyl acetate eluent (98/2). Yield: 30% (228 mg (*E* isomer)), oil; IR (KBr film): ν=3115, 2971, 2880, 1726 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.88 (t, $^3J_{(H,H)}$=7.4 Hz, 3H, CH_3), 1.85–2.18 (m, 2H, CH_2), 3.69 (s, CH_3), 4.57–4.62 (m, 1H, CH), 5.68 (dd, $^3J_{(H,H)}$=15.6 Hz, $^4J_{(H,H)}$=1.7 Hz, 1H, α-CH), 6.97 (dd, $^3J_{(H,H)}$=15.6, 5.6 Hz, 1H, β-CH), 6.89 (s, 1H, 4-CH), 7.07 (s, 1H, 5-CH), 7.49 (s, 1H, 2-CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=10.46 (CH_3), 27.75 (CH_2), 51.78 (CH_2), 59.87 (CH_3), 117.06 (4-CH), 122.30 (α-CH), 129.80 (5-CH), 136.29 (2-CH), 145.79 (β-CH), 160.02 (C); FAB (+): *m/z* (%)=195 (100) [M^++H], 179 (3) [M^+-CH_3], 135 (5) [M^+-COMe]; HRMS: calcd for $C_{10}H_{15}N_2O_2$ 195.1086; found 195.1087

4.2.11. (*E*/*Z*)-Ethyl-4-(2′-formylpyrrol-1′-yl)-but-2-enoate (3o). The two isomers were separated with dichloromethane–ethanol eluent (100/0–98/2). Yield: 63% (112 mg (*Z* isomer), 146 mg (*E* isomer), and 118 mg (mixture of *E*,*Z* isomers)), oils; IR (KBr film): *E* isomer ν=3111, 2982, 2938, 2808, 1721 (C=O_{ester}), 1662 (C=$O_{aldehyde}$) cm^{-1}; *Z* isomer ν=3110, 2982, 2806, 1715 (C=O), 1665 (C=$O_{aldehyde}$) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *E* isomer δ=1.28 (t, $^3J_{(H,H)}$=7.1 Hz, 3H, CH_3), 4.18 (q, $^3J_{(H,H)}$=7.1 Hz, 2H, CH_2), 5.16 (dd, $^3J_{(H,H)}$=4.8 Hz, $^4J_{(H,H)}$=2.0 Hz, 2H, CH_2), 5.53 (dt, $^3J_{(H,H)}$=15.5 Hz, $^4J_{(H,H)}$=2.0 Hz, 1H, α-CH), 6.32 (dd, $^3J_{(H,H)}$=3.9, 2.5 Hz, 1H, 4-CH), 6.94 (ddd, $^3J_{(H,H)}$=2.5 Hz, $^4J_{(H,H)}$=1.0, 1.8 Hz, 1H, 3-CH), 7.00 (dd, $^3J_{(H,H)}$=3.9 Hz, $^4J_{(H,H)}$=1.8 Hz, 1H, 5-CH), 7.06 (dt, $^3J_{(H,H)}$=15.5, 4.8 Hz, 1H, β-CH), 9.56 (d, $^4J_{(H,H)}$=1.0 Hz, CH); *Z* isomer δ=1.32 (t, $^3J_{(H,H)}$=7.2 Hz, 3H, CH_3), 4.23 (q, $^3J_{(H,H)}$=7.2 Hz, 2H, CH_2), 5.54 (dd, $^3J_{(H,H)}$=6.1 Hz, $^4J_{(H,H)}$=2.0 Hz, 2H, CH_2), 5.87 (dt, $^3J_{(H,H)}$=11.3 Hz, $^4J_{(H,H)}$=2.0 Hz, 1H, α-CH), 6.25 (dd, $^3J_{(H,H)}$=4.1, 2.5 Hz, 1H, 4-CH), 6.27 (dt, $^3J_{(H,H)}$= 11.4, 6.1 Hz, 1H, β-CH), 6.96 (dd, $^3J_{(H,H)}$=4.1 Hz, $^4J_{(H,H)}$=1.6 Hz, 1H, 5-CH), 7.01 (ddd, $^3J_{(H,H)}$=2.5 Hz, $^4J_{(H,H)}$=1.6, 1.0 Hz, 1H, 3-CH), 9.56 (d, $^4J_{(H,H)}$=1.0 Hz, CH); ^{13}C NMR (100 MHz, $CDCl_3$): *E* isomer δ=14.19 (CH_3), 49.14 (CH_2), 60.59 (CH_2), 110.45 (4-CH), 122.23 (α-CH), 124.86 (5-CH), 131.22 (3-CH), 131.26 (2-C), 143.33 (β-CH), 165.76 (C), 179.45 (CHO); *Z* isomer δ=14.22 (CH_3), 47.21 (CH_2), 60.41 (CH_2), 110.06 (4-CH), 120.92 (α-CH), 124.80 (5-CH), 131.19 (2-C), 131.51 (3-CH), 144.85 (β-CH), 165.87 (C), 179.36 (CHO); FAB (+): *E* isomer *m/z* (%)=208 (40) [M^++H], 134 (100) [$M^+-CO_2C_2H_5$]; *Z* isomer *m/z* (%)=208 (52) [M^++H], 134 (100) [$M^+-CO_2C_2H_5$]; HRMS: calcd for $C_{11}H_{14}NO_3$ 208.0974; found 208.0977 (*E* isomer), 208.0965 (*Z* isomer).

4.2.12. Ethyl (3*H*-pyrrolizin-2-yl)-acetate (10). Yield: 6% (36 mg), oil; IR (NaCl film): ν=3055, 2986, 1731 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.31 (t, $^3J_{(H,H)}$=7.2 Hz, 3H, CH_3), 3.44 (d, $^4J_{(H,H)}$=1.0 Hz, 2H, α-CH_2), 4.19 (q, $^3J_{(H,H)}$=7.2 Hz, 2H, CH_2), 4.51 (ddd, $^4J_{(H,H)}$=1.0, 1.0, 2.0 Hz, 2H, 3-CH_2), 5.88 (dd, $^3J_{(H,H)}$= 3.5 Hz, $^4J_{(H,H)}$=0.8 Hz, 1H, 7-CH), 6.24 (dd, $^3J_{(H,H)}$=2.5, 3.5 Hz, 1H, 6-CH), 6.44 (sextuplet, $^4J_{(H,H)}$=1.0 Hz, 1H, 1-CH), 6.92 (ddd, $^3J_{(H,H)}$=2.5 Hz, $^4J_{(H,H)}$=1.0, 0.8 Hz, 1H, 5-CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.22 (s, CH_3), 35.62 (α-CH_2), 53.58 (3-CH_2), 61.09 (CH_2), 97.05 (7-CH), 111.44 (6-CH), 116.95 (5-CH), 121.50 (1-CH), 134.19 (2-C), 140.87 (8-C), 170.40 (C); FAB (+): *m/z* (%)=192

(100) [M^++H], 118 (92) [$M^+-CO_2C_2H_5$]; HRMS: calcd for $C_{11}H_{14}NO_2$ 192.1025; found 192.1061.

4.3. General procedure for indolizines (12) synthesis

To a mixture of pyrrole-2-carboxaldehyde **1o** (0.2 mol L^{-1}, 1 equiv) and tributylphosphine (0.3 equiv) in anhydrous acetonitrile was added dropwise over 2 h at 18 °C a solution of electron-deficient allene or alkyne (0.2 mol L^{-1}, 2 at 2.5 equiv) in anhydrous acetonitrile. The reaction was monitored by ^{1}H NMR or by GC/MS. After completion of the reaction, the solvent was evaporated under reduced pressure and the product was purified by flash column chromatography on silica or alumina gel.

4.3.1. Ethyl indolizine-7-carboxylate (12a). Reactants: pyrrole-2-carboxaldehyde (1 equiv, 113 mg)/Bu_3P (0.3 equiv, 115 mg)/ethyl buta-2,5-dienoate of ethyl (2.5 equiv, 334 mg).

The product was eluted with hexane–ethyl acetate (99/1) on neutral alumina gel. Yield: 30% (128 mg), yellow solid; mp 38 °C; IR (KBr): ν=3125, 3061, 2981, 1705 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.42 (t, $^3J_{(H,H)}$=7.1 Hz, 3H, CH_3), 4.38 (q, $^3J_{(H,H)}$=7.1 Hz, 2H, CH_2), 6.74 (dddd, $^3J_{(H,H)}$=4.0 Hz, $^4J_{(H,H)}$=1.3, 0.4 Hz, $^5J_{(H,H)}$=1.0 Hz, 1H, 1-CH), 6.89 (dd, $^3J_{(H,H)}$=4.0, 2.6 Hz, 1H, 2-CH), 7.08 (dd, $^3J_{(H,H)}$=7.3 Hz, $^4J_{(H,H)}$=1.8 Hz, 1H, 6-CH), 7.44 (ddd, $^3J_{(H,H)}$=2.6 Hz, $^4J_{(H,H)}$=1.3 Hz, $^5J_{(H,H)}$=0.6 Hz, 1H, 3-CH), 7.91 (dt, $^3J_{(H,H)}$=7.3 Hz, $^4J_{(H,H)}$=1.0 Hz, 1H, 5-CH), 8.23 (dddd, $^4J_{(H,H)}$=1.8, 0.4 Hz, $^5J_{(H,H)}$=1.0, 0.6 Hz, 1H, 8-CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.41 (CH_3), 60.83 (CH_2), 104.42 (1-CH), 109.38 (6-CH), 115.09 (3-CH), 115.31 (2-CH), 118.66 (7-C), 123.13 (8-CH), 124.28 (5-CH), 131.47 (9-C), 166.13 (C); FAB (+): *m/z* (%)=190 (55) [M^++H], 189 (100) [M]$^+$, 161 (30) [$M^+-C_2H_5$+H], 154 (20) [M^+−OEt], 117 (20) [M^+-CO_2Et]; elemental analysis calcd (%) for $C_{11}H_{11}NO_2$ (189.22): C 69.83, H 5.86, N 7.40; found: C 69.50, H 5.83, N 7.53.

4.3.2. 7-Acetylindolizine (12b). Reactants: pyrrole-2-carboxaldehyde (1 equiv, 643 mg)/Bu_3P (0.3 equiv, 410 mg)/acetylallene (2 equiv, 1.11 g).

The product was eluted with hexane–ethyl acetate (99/1–98/2) on silica gel. Yield: 5% (50 mg), yellow solid; mp 49 °C; IR (KBr): ν=3102, 3055, 2964, 1666 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.58 (s, 3H, CH_3), 6.78 (ddd, $^3J_{(H,H)}$=4.1 Hz, $^4J_{(H,H)}$=0.9 Hz, $^5J_{(H,H)}$=1.0 Hz, 1H, 1-CH), 6.90 (dd, $^3J_{(H,H)}$=4.1, 2.4 Hz, 1H, 2-CH), 7.10 (dd, $^3J_{(H,H)}$=7.2 Hz, $^4J_{(H,H)}$=1.8 Hz, 1H, 6-CH), 7.45 (m, 1H, 3-CH), 7.90 (ddd, $^3J_{(H,H)}$=7.2 Hz, $^4J_{(H,H)}$=0.7 Hz, $^5J_{(H,H)}$=1.0 Hz, 1H, 5-CH), 8.07 (m, 1H, 8-CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=25.68 (CH_3), 105.61 (1-CH), 107.99 (6-CH), 115.59 (2-CH), 115.63 (3-CH), 122.97 (8-CH), 124.59 (5-CH), 126.22 (7-C), 131.02 (9-C), 195.89 (C); FAB (+): *m/z* (%)=160 (80) [M^++H], 159 (100) [M^+], 144 (70) [M^+-CH_3]; HRMS: calcd for $C_{10}H_{19}NO$ 159.0686; found 159.0684.

4.3.3. Methyl 5-ethyl-indolizine-7-carboxylate (12c). Reactants: pyrrole-2-carboxaldehyde (1 equiv, 182 mg)/Bu_3P (0.3 equiv, 116 mg)/methyl hexa-2,3-dienoate (2 equiv, 483 mg).

The product was eluted with hexane–ethyl acetate (98/2) on silica gel. Yield: 4% (17 mg), yellow solid; mp 60 °C; IR (KBr): ν=3154, 3113, 3095, 2970, 2944, 1701 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.48 (t, $^3J_{(H,H)}$=7.4 Hz, 3H, CH_3), 2.88 and 2.89 (2qd, $^3J_{(H,H)}$=7.4 Hz, $^4J_{(H,H)}$=1.1 Hz, 2H, CH_2), 3.94 (s, 3H, CH_3), 6.81 (dddd, $^3J_{(H,H)}$=4.0 Hz, $^4J_{(H,H)}$=1.3, 0.5 Hz, 1H, 1-CH), 6.96 (dd, $^3J_{(H,H)}$=4.0, 2.7 Hz, 1H, 2-CH), 7.00 (m, 1H, 6-CH), 7.41 (ddd, $^3J_{(H,H)}$=2.7 Hz, $^4J_{(H,H)}$=1.3 Hz, $^5J_{(H,H)}$=0.7 Hz, 1H, 3-CH), 8.19 (m, 1H, 8-CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=10.21 (CH_3), 24.87 (CH_2), 51.98 (CH_3), 104.97 (1-CH), 105.93 (2-CH), 112.05 (3-CH), 115.25 (8-CH), 118.47 (5-C), 120.87 (6-CH), 132.27 (7-C), 137.34 (9-C), 167.07 (C); FAB (+): *m/z* (%)=204 (55) [M^++H], 203 (100) [M]$^+$, 172 (12) [M^+-OCH_3], 144 (10) [$M^+-CO_2CH_3$]; HRMS: calcd for $C_{12}H_{13}NO_2$ 203.0946; found 203.0936.

4.3.4. Methyl indolizine-7-carboxylate (12d). Reactants: pyrrole-2-carboxaldehyde (1 equiv, 143 mg)/Bu_3P (0.3 equiv, 91 mg)/methyl but-2-ynoate (1.5 equiv, 220 mg).

The product was eluted with hexane–ethyl acetate (99/1) on neutral alumina gel. Yield: 50% (131 mg), yellow solid; mp 102 °C; IR (KBr): ν=3105, 2945, 2850, 1702 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.92 (s, 3H, CH_3), 6.74 (dl, $^3J_{(H,H)}$=3.8 Hz, 1H, 1-CH), 6.90 (dl, $^3J_{(H,H)}$=3.7 Hz, 1H, 2-CH), 7.06 (dd, $^3J_{(H,H)}$=7.3 Hz, $^4J_{(H,H)}$=1.7 Hz, 1H, 6-CH), 7.44 (sl, 1H, 3-CH), 7.91 (d, $^3J_{(H,H)}$=7.3 Hz, 1H, 5-CH), 8.22 (dd, $^4J_{(H,H)}$=1.7 Hz, $^5J_{(H,H)}$=0.9 Hz, 1H, 8-CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=52.02 (CH_3), 104.56 (1-CH), 109.33 (6-CH), 115.17 (3-CH), 115.36 (2-CH), 118.29 (7-C), 123.28 (8-CH), 124.32 (5-CH), 131.43 (9-C), 166.59 (C); FAB (+): *m/z* (%)=176 (60) [M^++H], 175 (100) [M^+], 144 (15) [M^+-OCH_3], 116 (10) [$M^+-CO_2CH_3$]; HRMS: calcd for $C_{10}H_{19}O_2$ 175.0633; found 175.0630.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.01.055.

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