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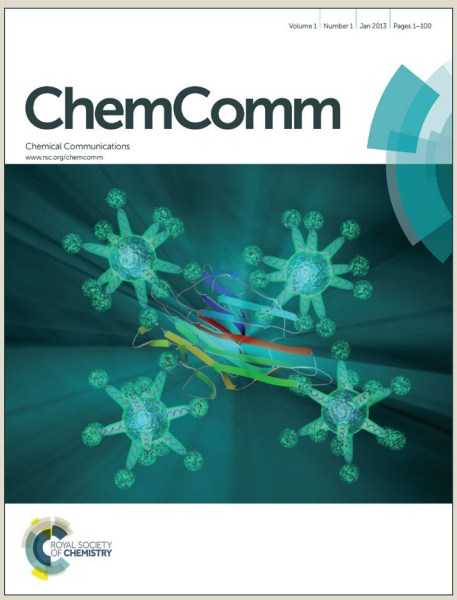

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Phosphine-Catalyzed Dearomatizing [3+2] Annulations of Isoquinolinium Methylides with Allenes

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A phosphine-catalyzed dearomatizing [3+2] annulation of isoquinolinium methylides with allenoates or allenones yields highly functionalized pyrroloisoquinolines with high regioselectivity and in viable yields.

The pyrroloisoquinoline framework is present in a wide array of biologically active natural products and pharmaceutically active compounds.[1] Among these bioactive pyrroloisoquinolines, crispine A exhibits cytotoxic activity against SKOV3, KB, and HeLa human cancer cell lines;[1d] Trolline has appreciable antibacterial activity against respiratory bacteria and moderate antiviral activity against influenza virus A and B; [1f] JNJ-7925476 acts as a novel triple monoamine uptake inhibitor, possessing potent antidepressant-like activity.[1g] Due to their biological relevance, the development of efficient methodologies to rapidly construct the pyrroloisoquinoline scaffold remains highly desirable.[2]

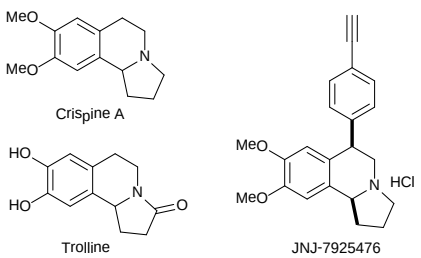
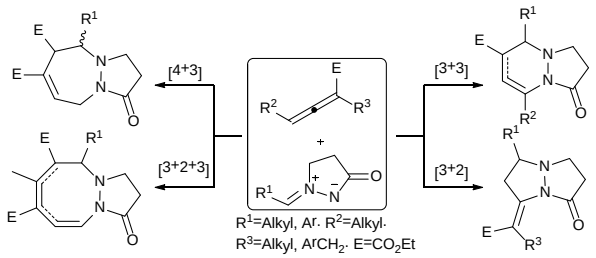


Fig. 1 Representative examples of bioactive pyrroloisoquinolines

Inspired by bioactive natural products, chemical biology research through biology oriented synthesis (BIOS) has been actively pursued in our group.[3] According to the BIOS reasoning, privileged scaffolds present in natural products can be considered as valid starting points for the development of compound collections which provide the foundation for further chemical biology research. Hence, the development of efficient synthetic methods to construct privileged scaffolds inspired by bioactive natural products forms an integral part of BIOS. In continuation of our efforts we developed an efficient and novel methodology to construct a compound collection based on the pyrroloisoquinoline scaffold.

Nucleophilic phosphine catalysis for transformations of allenes with electrophiles has emerged as one of powerful and efficient synthetic strategies for the synthesis of highly functionalized carbocycle or heterocycle motifs.[4] Very recently, Kwon *et al.* demonstrated that allenoates can participate in unprecedented [3+2], [3+3], [4+3] and [3+2+3] annulations with azomethine imines as C3 or/and C2 synthons (Scheme 1), providing novel routes to dinitrogen-fused heterocycles.[5,6] Although azomethine imines have received considerable attention in nucleophilic phosphine catalysis reactions, azomethine ylides[7] which are well documented 1,3-dipoles, remain unexplored. Herein, we disclose the first regioselective phosphine-catalyzed dearomatizing [3+2] annulation of isoquinolinium methylides with both allenoates and allenones for the expedient syntheses of valuable pyrroloisoquinolines.

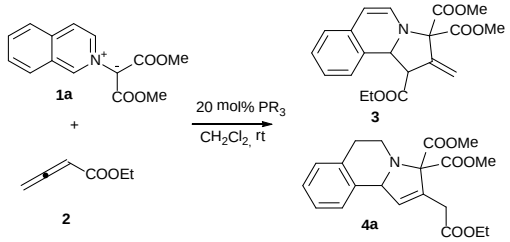


Scheme. 1 Phosphine-catalyzed [3+*N*] cyclization of azomethine imines with allenoates

Our initial attempts to develop phosphine-catalyzed annulations of azomethine ylides commenced with the reaction of isoquinolinium bis(methoxycarbonyl) methylide (**1a**) and ethyl 2,3-butadienoate (**2**). As summarized in Table 1, screening of reaction conditions was carried out for the model reaction. Considering possible background reactions resulting from direct [3+2] cycloaddition of isoquinolinium methylides and allenoates, we initially tested the model reaction in DCM without any phosphine catalyst. As expected, the desired direct [3+2] cycloadduct **3** was formed in 51% yield and with incomplete conversion in 6 h (Table 1, entry 1). Under the same conditions, the addition of 20 mol% of PPh_3 gave one new product together with the direct [3+2] cycloaddition product in 6 h. However, the new product turned out to be unstable, therefore

sequential reduction *in situ* by treatment with excess acetic acid and $NaBH_4$ at 0 ℃ in one pot, furnished a stable product in 57% yield for two steps (Table 1, entry 2).Screening of tertiary phosphines was carried out, since the nature of the tertiary phosphine generally dominates the efficiency of nucleophilic phosphine catalysis. PBu_3 proved to be the best catalyst providing 75% yield of the new product in 10 minutes (Table 1, entry 3).

Table 1 Screening studies of phosphine-catalyzed dearomatizing [3+2] annulation of isoquinolinium methylides and allenoates[a]



Entry	PR_3	Time	Yield[b] (%) 3	4a
1[c]	-	6 h	51	0
2	PPh_3	6 h	8	57
3	PBu_3	10 min	<5	75
4	$MePPh_2$	10 min	<5	62
5	Me_2PPh	10 min	<5	68
6	PCy_3	2 h	<5	62

[a] Unless otherwise noted, reactions were performed with **1a** (0.1 mmol), **2** (0.15 mmol), PR_3 (0.02 mmol) in CH_2Cl_2 (1 mL) at room temperature. After reactions were completed, $NaBH_4$ (0.3 mmol) and acetic acid (1 mmol) were added sequentially at 0 ℃. [b] Isolated yield after column chromatography. [c] Reaction was performed without phosphine catalyst and sequential reduction.

X-ray crystallography of **4a** disclosed the structure of the new product to be a [3+2] cycloaddition product. Notably, there is an unusual alkene translocation followed by [3+2] cycloaddition resulting in the more stable product as shown in **Fig 2**.

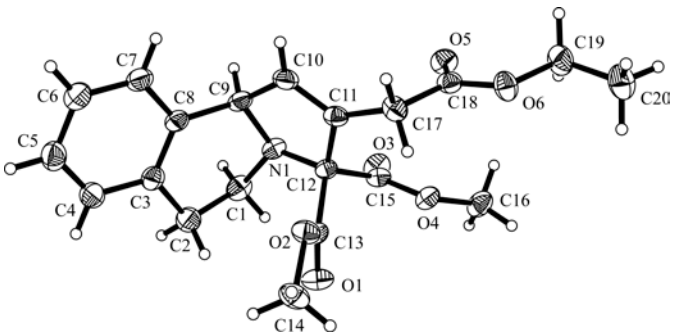
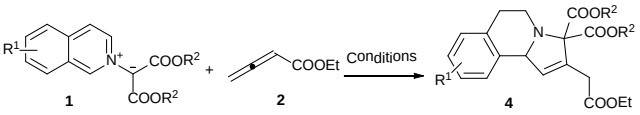
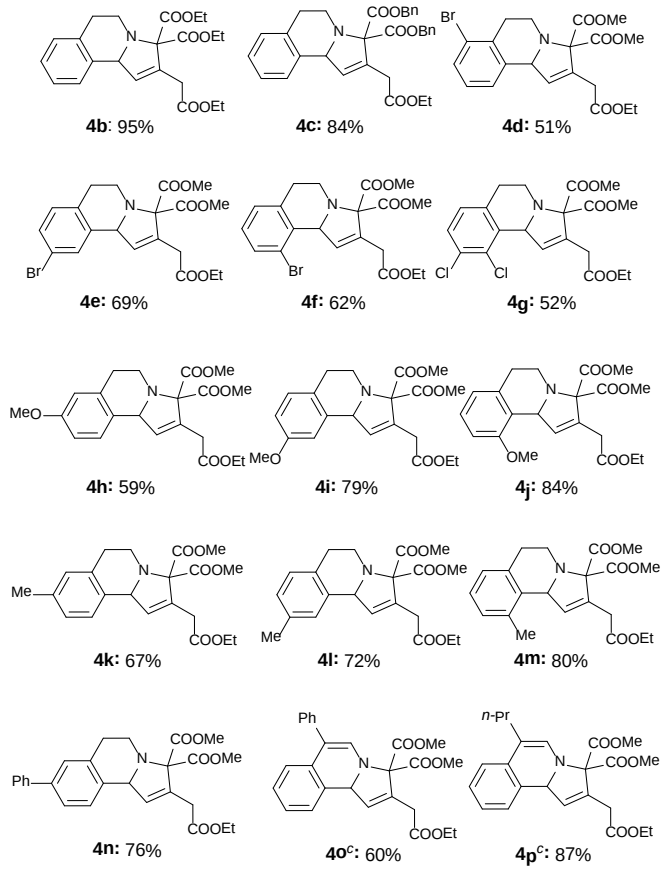


Fig. 2 Crystal structure of compound **4a**. Thermals ellipsoids are shown with 30% probability (CCDC 1031363).

Table 2 Substrate scope and limitation for the reactions with allenoates[a,b]





[a] Unless otherwise noted, reactions were performed with **1** (0.1 mmol), **2** (0.15 mmol), PBu_3 (0.02 mmol) in CH_2Cl_2 (1 mL) at room temperature for 10 min. After the reactions were completed, $NaBH_4$ (0.3 mmol) and acetic acid (1 mmol) were added sequentially under 0 ℃ for another 10 min. [b] Isolated yield after column chromatography. [c] Reactions were performed without sequential reduction in one pot.

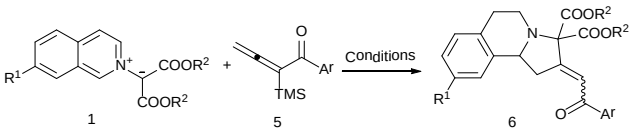
With the optimized conditions in hand, we examined the substrate scope of the dearomatizing [3+2] cycloaddition reaction followed by reduction in one pot with regard to other isoquinolinium methylides. As shown in Table 2, methyl, ethyl, and benzyl esters were tolerated well in the reactions, providing the desired products **4a-4c** in excellent yield up to 95%. With respect to variation of R^1, pyrroloisoquinolines with halide substituents on the aromatic ring **4d-4g** were obtained in moderate yields from the corresponding isoquinolinium methylides. For isoquinolinium methylides with electron donating groups such as methoxyl, methyl and phenyl, the reactions also proceeded smoothly, furnishing the desired cycloadducts **4h-4n** in satisfactory yield. Furthermore, relatively stable cycloadducts **4o-4p** were obtained without sequential reduction *in situ* for isoquinolinium methylides bearing electron donating groups of either aromatic or aliphatic substituents in the 4-position. Some limitations on the substrates were also encountered when exploring the reaction scope (see the SI). For example,

isoquinolinium methylides with an electron withdrawing group at C4 failed to produce the stable cycloadducts for further purification and characterization. Allenoates with substituents on either α or γ position displayed complex reactivity. After exploration of the substrate scope and its limitations, we investigated the possibility of an asymmetric version of this reaction. Unfortunately, screening of either commercially available or synthesized chiral phosphines failed to give cycloadducts with high enantioselectivity (see the SI).

In contrast to allenoates, the application of corresponding allenones in cycloaddition reactions has been less explored due to their higher tendency to dimerize upon treatment with phosphine, especially for aromatic substrates.[8] In 2009, Loh *et. al.* demonstrated α-trimethylsilyl substituted aryl allenones as capable of participating in [3+2] annulations with electron deficient alkenes as C3 synthons, furnishing totally γ-selective cycloadducts.[8b] In this case, the α-trimethylsilyl substituent plays a double role as directing group to γ-selectivity and inhibiting factor for self-dimerization of allenones.

Taking these facts into consideration, we envisaged the possibility of using such allenones in cycloaddition reactions with isoquinolinium methylides as C2 synthons to obtain specific γ-selective cycloadducts. As shown in Table 3, four types of aromatic α-trimethylsilyl allenones were synthesized and subjected to the cycloaddition reactions. Both aromatic and heteroaromatic groups are well tolerated, providing the desired γ-selective cycloadducts **6a-6d** (Table 3, entry 1-4), with ratios up to 78:22 of *E*/*Z* isomers for **6c**. Furthermore, the reaction does proceed well for isoquinolinium methylides with either electron withdrawing groups or electron donating groups (Table 3, entry 5-6). Interestingly, there was no alkene translocation for the cycloadducts when allenones were applied as dipoles. In addition, screening of chiral phosphines gave only fair ee values of up to 37% from one bifunctional phosphine catalyst. (see SI)

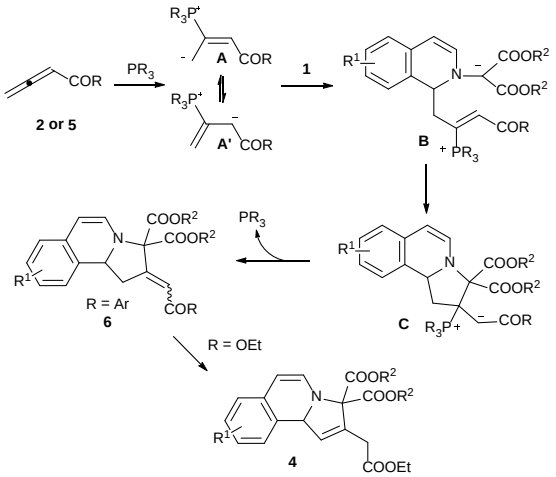
Table 3 Substrate scope and limitation for reactions with allenones[a]



Entry	R^1	R^2	Ar	Prod.	Yield[b] (%)	E/Z
1	H	Et	Ph	**6a**	91	>95:5
2	H	Et	*2*-furyl	**6b**	83	>95:5
3	H	Et	*3*-BrPh	**6c**	83	78:22
4	H	Et	*1*-Nap	**6d**	79	>95:5
5	Br	Me	Ph	**6e**	64	>95:5
6	MeO	Me	Ph	**6f**	78	>95:5

[a] Unless otherwise noted, reactions were performed with **1b** (0.1 mmol), **2** (0.15 mmol), PBu_3 (0.02 mmol) in CH_2Cl_2 (1 mL) at room temperature for 10 min. After reactions completed, $NaBH_4$ (0.3 mmol) and trifluoroacetic acid (1 mmol) were added sequentially under 0 ℃ for another 10 min. [b] Isolated yield.

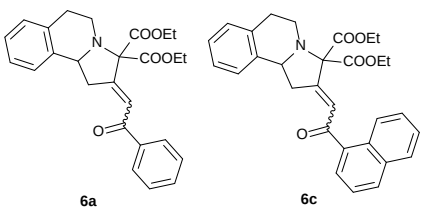
On the basis of the prior mechanistic studies of nucleophilic phosphine catalyzed reactions, a plausible mechanism is proposed as shown in Scheme 2. The active intermediate **A**, generated from the addition of phosphine to allene, exclusively attacks the isoquinolinium methylide **1** at its γ-carbon atom to form **B**, probably due to unfavorable steric interaction of the other intermediate A'. The following intramolecular conjugate addition of **B** and sequential β-elimination of **C** furnishes the [3+2] cyclization, providing the desired cycloadduct **6**, when R is an aromatic group. However, when R is ethoxy, a sequential isomerization occurs to provide the thermally more stable product **4**.



Scheme. 2 A plausible mechanism for isoquinolinium methylides-allenoates annulations

Given the interesting bioactivity of pyrroloisoquinolines, the compound collection was subjected to different cell-based assays, monitoring for instance the hedgehog signaling pathway. For assaying signal transduction through the hedgehog signaling pathway, mouse embryonic mesoderm fibroblast C3H10T1/2 cells were used. These multipotent mesenchymal progenitor cells can differentiate into osteoblasts upon treatment with the smoothened agonist. During differentiation, osteoblast specific genes such as alkaline phosphatase, which play an essential role in bone formation, are highly expressed. Activity of alkaline phosphatase can directly be monitored by following substrate hydrolysis yielding a highly luminescent product.[9] Inhibition of the hedgehog pathway results in reduction of luminescence. Hits showed reduction in the luminescent signal without altering the cell viability. Dose-response analysis for hit compounds was performed, and representative results of the assay are summarized in **Fig 3**. To our delight, several pyrroloisoquinoline-inspired compounds inhibited the hedgehog signaling pathway in the low micromolar range.

Fig 3. Representative results of hedgehog-pathway inhibition.



Conclusions

In conclusion, we have demonstrated for the first time that azomethine ylides such as isoquinolinium methylides can act as efficient dipoles to participate in [3+2] cycloaddition reactions with allenoates and allenones catalysed by phosphines. With this methodology, valuable pyrroloisoquinolines can be accessed regioselectively in good yield.

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Notes and references

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Electronic Supplementary Information (ESI) available. See DOI: 10.1039/c000000x/

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