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Synthesis of Isoquinuclidines from Highly Substituted Dihydropyridines via the Diels–Alder Reaction

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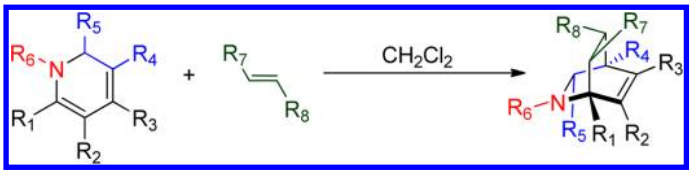
ABSTRACT



A stereo- and regioselective Diels–Alder reaction for the synthesis of highly substituted isoquinuclidines from dihydropyridines and electron-deficient alkenes has been developed. While reactions with activated dienophiles proceed readily under thermal conditions, the use of Lewis acid additives is necessary to facilitate cycloadditions for less reactive alkenes. This procedure affords the target compounds in high yields and diastereoselectivities.

The synthesis of nitrogen heterocycles is an important area of research due to their prevalence in natural products and drugs.[1,2] Recently, we reported Rh(I)-catalyzed β-C–H bond alkenylation of α,β-unsaturated imines followed by in situ electrocylization to give *N*-alkyl and -aryl 1,2-dihydropyridines (Scheme 1A).[3] These highly substituted dihydropyridines would be difficult to prepare by alternative methods and have proven to be versatile intermediates to other classes of heterocycles.[4] For example, aromatization to the corresponding pyridines can be accomplished in an overall one-pot procedure (Scheme 1A).[3a,5] Alternatively, 1,2,3,6-tetrahydropyridines can be obtained with high diastereoselectivities via protonation of the enamine followed by in situ reduction of the resulting iminium.[3b]

In our efforts to further harness the 1,2-dihydropyridine intermediates generated through Rh-catalyzed C–H activation, we became interested in the potential of generating isoquinuclidines utilizing a Diels–Alder reaction (Scheme 1B). Isoquinuclidines have been used as intermediates in the preparation of tetrahydroisoquinoline

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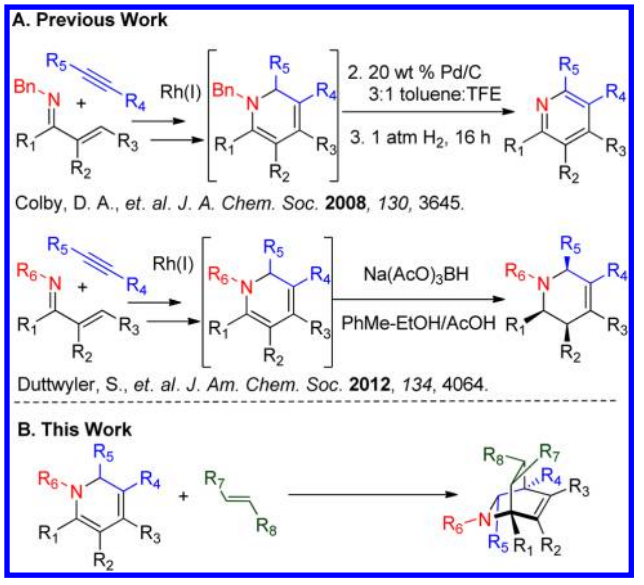
Scheme 1. Rh-Catalyzed C−H Functionalization Provides Versatile 1,2-Dihydropyridine Intermediates



alkaloids,[6] piperidines,[7] Iboga alkaloids,[8] and the related Cantharanthus alkaloids,[9] which have been developed as cancer therapeutics. Isoquinuclidines are most often prepared by a Diels−Alder reaction of 1,2-dihydropyridines generated by *N*-acylation followed by nucleophilic addition to pyridines.[10−13] However, the incorporation of an acyl protecting group attenuates the nucleophilicity of the dihydropyridine substrates.[11] Moreover, reliance on pyridine inputs generally results in dihydropyridine products lacking a high degree of substitution.[4] Herein, we report that isoquinuclidines with unprecedented substitution levels are obtained in good yield and with high regio- and stereoselectivities by Diels−Alder reaction between highly substituted *N*-alkyl and aryl-1,2-dihydropyridines and electron-deficient alkenes.

Diels−Alder reactions for a range of dienophiles with differential relative reactivity were first investigated (products **3a**−**d**, Scheme 2). The most reactive dienophile, *N*-phenyl maleimide, underwent efficient cycloaddition to give isoquinuclidine **3a** at room temperature within 16 h with only the endo isomer detected by ^{1}H and ^{13}C NMR analysis of the unpurified reaction mixture. Methyl acrylate and acrylonitrile required more forcing conditions but provided the desired products **3b** and **3c**, respectively, in high yield when run neat with heating to 105 °C. Isoquinuclidines **3b** and **3c** were each produced as a single regioisomer, and for **3b** only the endo product was observed while for **3c** a 93:7 endo/exo ratio was obtained.

Identifying effective conditions for coupling the less reactive crotonaldehyde required significant optimization (Table 1). Performing the reaction at 0.1 or 0.5 M in CH_2Cl_2 with heating to 50 °C provided little if any conversion (entries 1 and 2). Even when the reaction was performed neat with excess crotonaldehyde with heating at 105 °C only a trace amount of product was detected (entry 3). Lewis acid additives have proven to be effective for increasing the rate of Diels−Alder reactions for dienes

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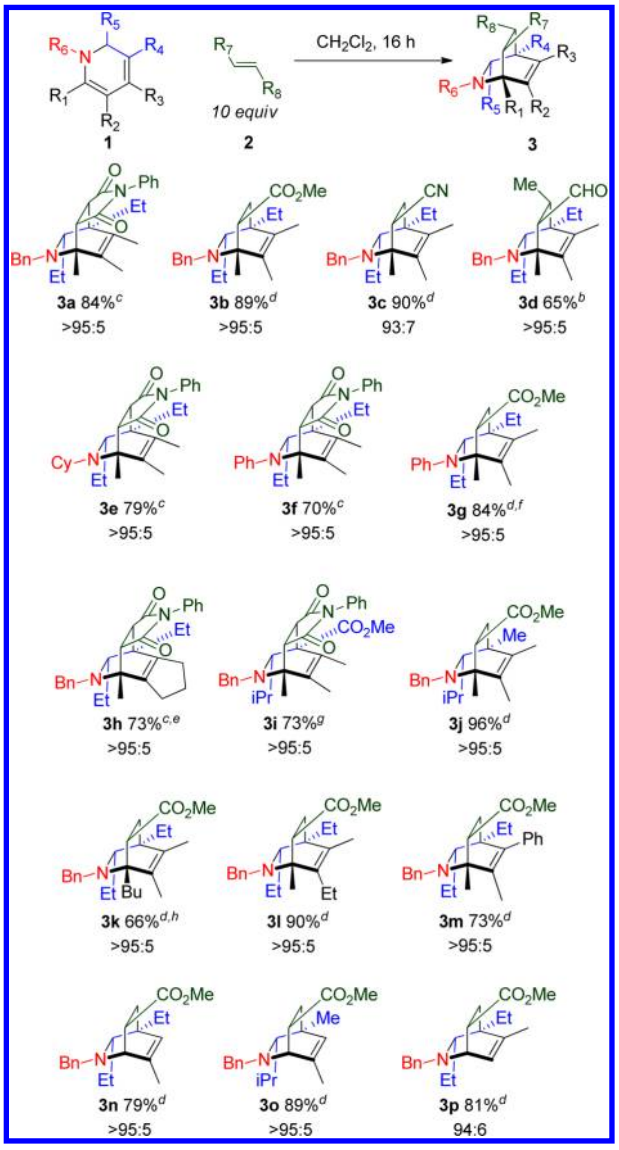
Scheme 2. Substrate Scope of Diels–Alder Reactions[a]

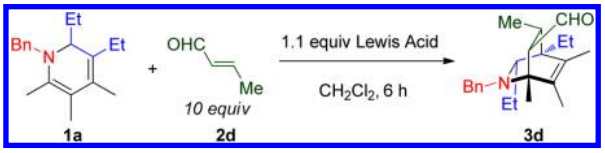


[a] Yields correspond to the yields of isolated products. The diastereoselectivities were determined by ^{1}H NMR analysis of unpurified material. [b] $ZnCl_2$ (1.1 equiv), 0.5 M CH_2Cl_2, 0 °C, 6 h. [c] *N*-Phenyl maleimide (1.05 equiv), 0.1 M CH_2Cl_2, rt. [d] Neat, 105 °C. [e] 24 h. [f] 72 h. [g] *N*-Phenyl maleimide (1.05 equiv), 0.5 M CH_2Cl_2, 50 °C. [h] 48 h.

incorporated within nitrogen heterocycles.[6a,e,12,14] We therefore examined their effect upon our substrate combination (entries 4–6). The aluminum-based Lewis acids $AlEtCl_2$ and $AlCl_3$ led to modest yields of the isoquinuclidine **3d** (entries 4 and 5). Employing $ZnCl_2$ as a Lewis acid additive at 0 °C provided better results, with **3d** obtained as a single diastereomer in 59% yield (entry 6). $BF_3 \cdot OEt_2$ was also investigated but did not yield the desired isoquinuclidine **3d**.

As illustrated in Scheme 2, a range of differently substituted 1,2-dihydropyridines underwent Diels–Alder reactions in high yields. A variety of nitrogen substituents were well-tolerated, including *N*-benzyl (**3a–d**, **h–p**), branched *N*-alkyl (**3e**), and *N*-phenyl (**3f–g**) groups.

Table 1. Optimization of Diels–Alder Reaction with Crotonaldehyde[a]



entry	Lewis acid	concn (M)	temp (°C)	yield[b] (%)
1	–	0.1	50	trace
2	–	0.5	50	trace
3	–	–	105	trace
4	$AlEtCl_2$	0.5	0	10[c]
5	$AlCl_3$	0.5	0	43
6	$ZnCl_2$	0.5	0	59

[a] All reactions were performed using 0.05 mmol of dihydropyridine **1a** and 0.5 mmol of crotonaldehyde. [b] Yields were determined by NMR relative to 1,3,5-trimethoxybenzene. [c] Reaction was performed in 1:1 CH_2Cl_2/hexanes.

Different substitution patterns at other sites within the dihydropyridine ring were also acceptable. The tetracyclic isoquinuclidine **3h** was prepared as a single diastereomer in high yield. Dihydropyridines substituted with the branched isopropyl group were also effective coupling partners (**3i**, **j**, and **o**). Even a dihydropyridine bearing the electronically deactivating methyl ester group reacted with *N*-phenyl maleimide to provide **3i** in good yield and as a single isomer. A 4-phenyl substituted dihydropyridine also underwent a Diels–Alder reaction to provide isoquinuclidine **3m** as a single isomer. Additionally, as should be expected, isoquinuclidines can be prepared in high yields and excellent selectivities from 1,2-dihydropyridines with modestly lower substitution levels (**3n–p**).

The relative configuration of isoquinuclidine **3g** was established by X-ray crystallography of the corresponding ammonium salt (Figure 1). By analogy, we assigned the endo configuration to the other dihydropyridine products.

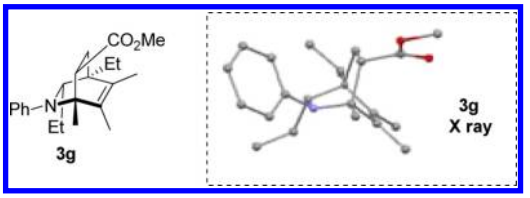


Figure 1. Relative configuration and ball-and-stick representation of **3g**.

In conclusion, the 1,2-dihydropyridines that result from the rhodium-catalyzed C–H alkenylation of α,β-unsaturated imines and subsequent electrocyclization are versatile intermediates for the preparation of highly functionalized nitrogen heterocycles. The Diels–Alder reaction with a variety of dienophiles provides access to isoquinuclidines

with unprecedented substitution levels in high yields and with excellent regio- and stereoselectivities.

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Supporting Information Available. Full experimental procedures, characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.