Stereoselective Catalysis

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Enantioselective Palladium-Catalyzed Decarboxylative Allylation of Carbazolones and Indolones: Formal Synthesis of (+)-Kopsihainanine A**

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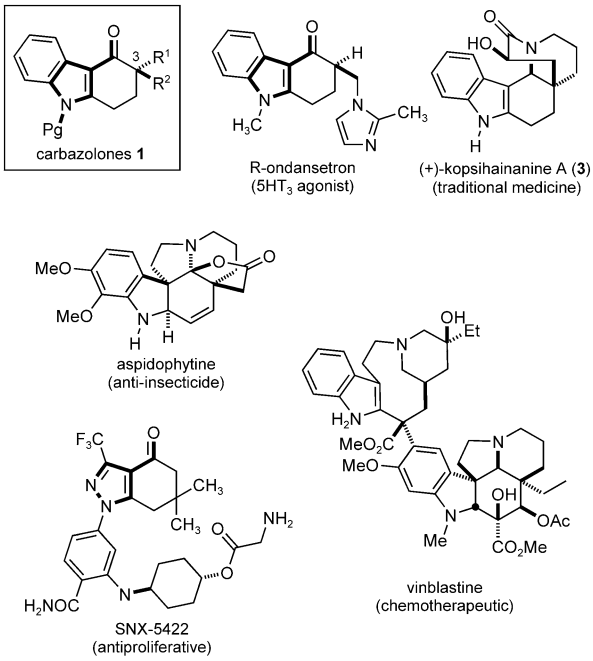
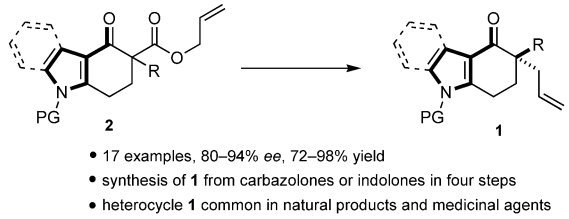
The elaboration of readily available nitrogen heterocycles to complex targets is integral to medicinal and natural products chemistry, as such new strategies to derivatize heterocycles retain relevance. As part of ongoing studies on alkaloid synthesis,[1] we noted a lack of direct enantioselective methods for the assembly of C3-chiral carbazolones (i.e., **1**), motifs common in medicinal[2] and natural products chemistry (Scheme 1).[3] This is a striking observation, as a host of methods for the stereoselective installation of functionality α to the carbonyl functionality of the parent carbazolone should potentially be viable. Furthermore, our examination of the literature reveals only one, ultimately unsuccessful, attempt to demonstrate this strategy.[4]



Scheme 1. C3-chiral carbazolones **1** and representative medicinal and natural products.

Motivated by the notion that direct access to chiral carbazolones, such as **1**, should provide a valuable chiral synthon useful in target directed synthesis,[5] we commenced studies on this topic. Herein, we report the realization of this strategy with a four-step synthesis of a diverse range of enantioenriched carbazolones and indolones (i.e., **1**) by exploiting the enantioselective Pd-catalyzed decarboxylative allylation of **2** (Scheme 2).[6] Preliminary studies on the utility of carbazolones **1** have been undertaken, resulting in the completion of a formal synthesis of (+)-kopsihainanine A (**3**).[7]



Scheme 2. Enantioselective Pd-catalyzed decarboxylative allylation described herein.

Although Pd-catalyzed decarboxylative allylation[8,9] of carbazolones are yet to be reported,[10,11] the transformations of related vinylogous esters and thioesters are known.[12] In these studies, the enhanced enantioselectivity of the thioester relative to the ester is attributed to the modest π-donation of the sulfur atom. We postulated that carbazolones should behave as vinylogous amides,[13,14] thus appropriate indole protection should allow attenuation of the π-donation of the nitrogen atom and induce high enantioselectivity. Supporting the viability of such a strategy is a recent report by Stoltz and co-workers, who demonstrate improved enantioselectivity with the allylation of lactams that bear electron-withdrawing N-protection.[15] Hence, our studies commenced with an investigation of the role of N-protection on enantioselectivity.

When N-methyl-protected carbazolone **4a** was subjected to conditions developed by Stoltz and co-workers,[16] namely the PHOX ligand (**L1**)[17] and $[Pd_2(dba)_3]$ at room temperature, no reaction occurred. However, heating to 80 °C provided allyl carbazolone **1a** in 69% yield and 66% *ee* (Table 1, entry 1). Trost's ligand **L3** was unsuitable for this reaction at any temperature (Table 1, entry 2). Changing from N-methyl to N-benzyl protection was tolerated, although carbazolone **1b** formed with decreased enantioselectivity

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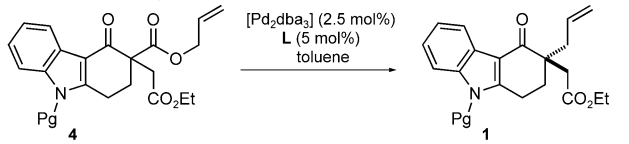
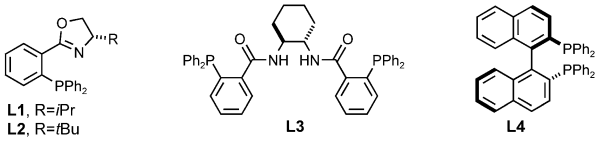
Table 1: Selected optimization.



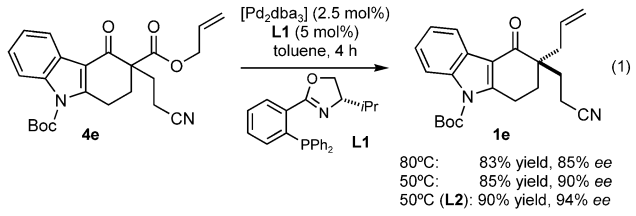
Entry	4	PG	L	T [°C]	t [h]	Yield [%][a]	ee [%][b]
1	**4a**	CH_3	**L1**	80	0.5	69	66
2	**4a**	CH_3	**L3**	80	12	–	–
3	**4b**	Bn	**L1**	80	1	78	37
4	**4c**	Ts	**L1**	80	4	98	83
5	**4d**	Boc	**L1**	80	4	94	81
6	**4d**	Boc	**L1**	50	4	92	78
7	**4d**	Boc	**L4**	80	4	90	16
8	**4d**	**Boc**	**L2**	**80**	**4**	**82**	**87**

[a] Yield of isolated product following flash column chromatography. [b] Enantiomeric excess determined by HPLC analysis on various chiral stationary phases. The entry in bold highlights the optimized reaction conditions.



(Table 1, compare entries 1 and 3). In contrast, electron-withdrawing tosyl protection improved the enantioselectivity, providing allyl carbazolone **1c** in 98% yield and 83% *ee* (Table 1, entry 4), while Boc-protected carbazolone **4d** performed equally well (Table 1, entry 5). Because of the ubiquity of Boc protection, **4d** was used in subsequent optimizations. Lowering the temperature to 50°C had no effect on the outcome, while switching from **L1** to BINAP (**L4**) provided **1d** with decreased enantioselectivity (Table 1, entries 6 and 7). Finally, use of the *tert*-butyl-substituted ligand **L2** provided allyl carbazolone **1d** in an improved 87% *ee* (Table 1, entry 8).

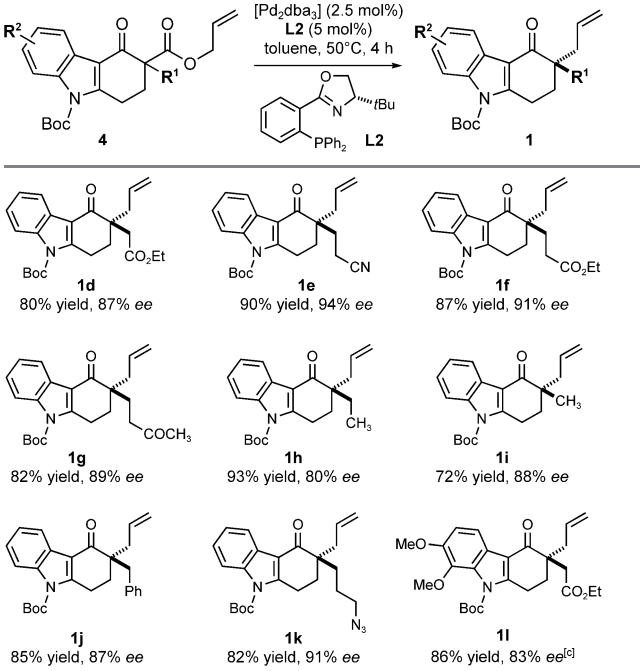
The apparent temperature-insensitive enantioselectivity using carbazolone **4d** (Table 1, compare entries 5 and 6) was re-examined with nitrile-substituted carbazolone **4e** [Eq. (1)].



We postulated that the behavior of **4d** might arise from stabilizing coordination of the C-bound Pd–enolate through the ester carbonyl, hence impeding epimerization that is necessary for enantioselectivity.[18] When the decarboxylative allylation of nitrile **4e** was examined at 80°C, carbazole **1e** formed in 85% *ee* (using ligand **L1**). When the reaction was repeated at 50°C, the enantioselectivity increased to 90% *ee* [Eq. (1)], while using the preferred ligand **L2** at 50°C, provided carbazolone **1e** in 94% *ee*.

Having identified optimal conditions the scope of the reaction was examined (Table 2). The reaction tolerated additional carbonyl functionalities, with ester- and ketone-

Table 2: Decarboxylative allylation of carbazolones **4**.[a,b]

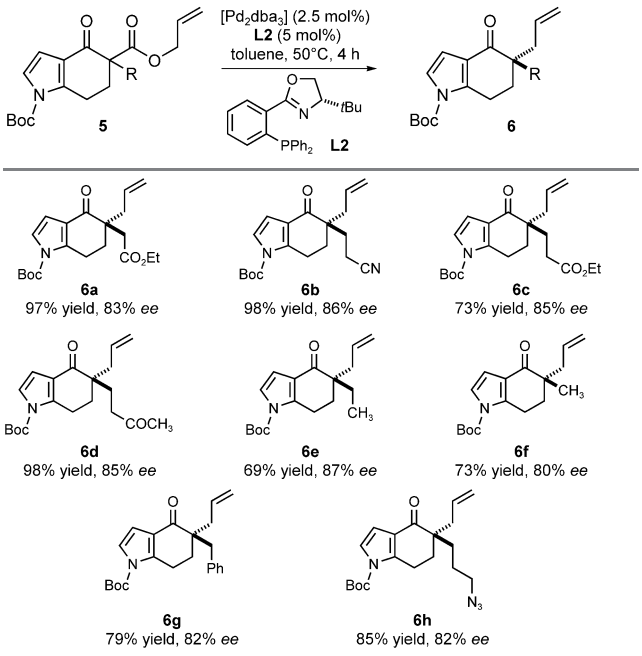


[a] Yields of isolated products following flash column chromatography. [b] Enantiomeric excesses determined by HPLC analysis on chiral stationary phases. [c] Reaction performed using ligand **L1**.

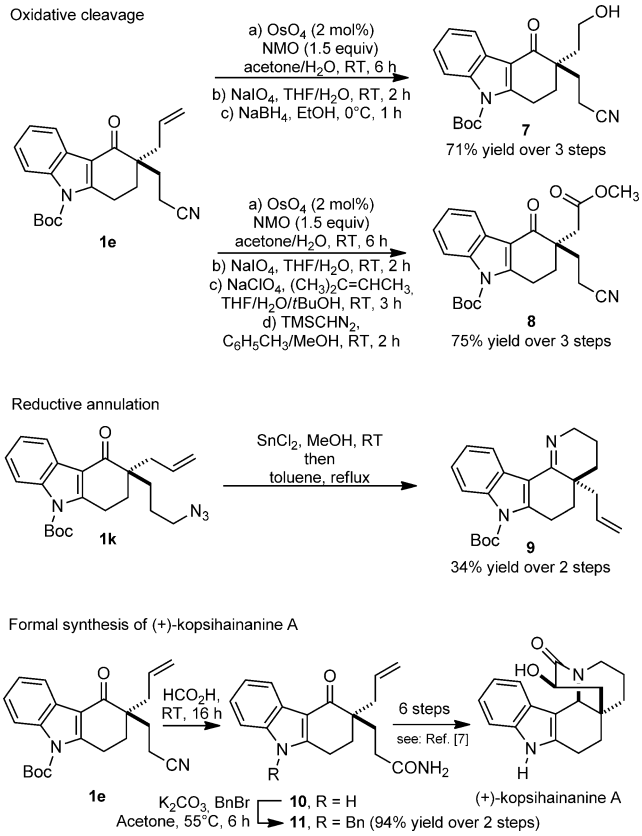
containing carbazolones **1f** and **1g** produced in high yield and enantioselectivity, 91 and 89% *ee*, respectively. Ethyl-containing carbazolone **1h** was prepared in 80% *ee*, while methyl- and benzyl-bearing carbazolones **1i** and **1j** were formed in 88 and 87% *ee*, respectively. Next, azide **4k** was assembled. As with nitrile **4e,** this substrate bears functionality suited for reductive annulation to generate the piperidine ring common to many aspidosperma alkaloids (see below). The decarboxylative allylation of **4k** provided **1k** in 82% yield and 91% *ee*. Finally, introduction of methoxy substituents into the substrate, as observed with alkaloids such as aspidophytine (Scheme 1),[19] was addressed using carbazolone **4l**. While its transformation to **1l** was achieved using the non-optimal ligand **L1**, the reaction proceeded with good enantioinduction.

The generality of the decarboxylative allylation was examined with other N-containing heterocycles. Indolones were selected because of their use as precursors to natural products and their popularity as scaffold in medicinal chemistry.[20] Pd-catalyzed decarboxylative allylation of Boc-protected indolones **5** proceeded using the conditions previously described to provide allylated materials (Table 3). In most cases, slightly decreased enantioselectivity relative to the carbazolone series was observed (compare Tables 2 and

Table 3: Decarboxylative allylation of indolones **5**.[a,b]



[a] Yields of isolated products following flash column chromatography. [b] Enantiomeric excesses determined by HPLC analysis on chiral stationary phases.



Scheme 3. Derivatization.

3). For example, nitrile- (**5b**), ester- (**5c**), and ketone-bearing substrates (**5d**) afforded allylated indolones **6b–d** in 86, 85, and 85% *ee* in comparison to 94, 91, and 89% *ee* for the analogous carbazolones. Ethyl-bearing indolone **6e** formed in 87% *ee*, while the methyl- (**6f**) and benzyl-bearing (**6g**) substrates formed in 80 and 82% *ee*. Finally, azide **6h** formed in 82% *ee* and excellent yield.

With access to a range of carbazolones, their conversions to intermediates that are potentially valuable in complex-target synthesis where undertaken (Scheme 3). Of interest was the oxidative cleavage of the allyl group, and the annulation to form the piperidine ring common in aspidosperma alkaloids. Oxidative cleavage of the allyl group using ozonolysis provided complex mixtures, however, OsO_4-catalyzed dihydroxylation followed by periodate cleavage and reduction provided the somewhat unstable alcohol **7**. Pinnick oxidation of the aldehyde intermediate and esterification provided the methyl ester **8**. The former compound is well suited for the synthesis of fendleridine,[21] the latter has functionality represented in aspidophytine.[19] Reductive annulation with nitrile **1e** could not be realized without concomitant reduction of the allyl group.[22] In contrast, cyclization of azide **1k** using $SnCl_2$ provided imine **9** and the uncyclized amine, which, after heating in toluene, gave a serviceable yield of imine **9**. During the course of these studies, Xie and She reported the use of carbazolones containing quaternary carbon atoms (i.e., (*rac*)-**11**) in the synthesis of racemic kopsihainanine A.[7] This aspidosperma alkaloid was isolated from *Kopsia hainanensis* in 2011 by Gao,[23] and has been used as a traditional folk medicine in the Hainan Province for a range of ailments. Starting with nitrile **1e**, hydrolysis with formic acid with concomitant Boc group removal gave amide **10**. Benzyl protection then provided **11**, intercepting an intermediate in the synthesis of the racemic product and completing the formal total synthesis of (+)-kopsihainanine, the natural stereoisomer of this material.

The direct enantioselective synthesis of carbazolone and indolone heterocycles has been achieved using Pd-catalyzed decarboxylative allylation. Central to achieving good levels of enantioinduction was the use of electron-withdrawing N-protection of the heterocycle. Using these conditions, a broad range of enantioenriched carbazolones and indolones containing a quaternary carbon center can be assembled in four steps. Preliminary studies on the derivatization of these materials have led to procedures for oxidative cleavage of the allyl group and annulations. In addition, a formal synthesis of (+)-kopsihainanine has been achieved. Future studies will focus on the application of chiral carbazolones in the synthesis of aspidosperma and kopsia natural products, and as scaffolds for medicinal chemistry.

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