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Asymmetric Heck cyclization route to indolizidine and azaazulene alkaloids: synthesis of (+)-5-epiindolizidine 167B and indolizidine 223AB

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Abstract—Asymmetric intramolecular Heck cyclization of endocyclic enamides occurs at room temperature to give indoloizidine and azaazulene ring systems in up to 86% enantiomeric excess. A synthesis of (+)-epiindolizidine 167B and formal synthesis of 5*E*,9*Z*-indolizidine 223AB is described.

The intramolecular Heck reaction has proven to be a powerful method for the construction of heterocyclic and carbocyclic ring systems.[1] Asymmetric variations of this process are useful for the production of non-racemic compounds as demonstrated by the many applications of this reaction to the total synthesis of natural products.[2] Strategically, the enantioselective Heck reaction provides a method for the introduction of either a chiral tertiary or quaternary carbon center.[3] The former variation of the enantioselective Heck reaction has been applied to syntheses of decalin, hydrindan and indolizidine ring systems.[3,4] As part of a program directed towards the enantioselective production of nitrogen heterocycles, we envisioned Heck cyclization of endocyclic enamides related to substrates studied by Shibasaki[5] and shown in Fig. 1 to afford pyrrolizidine, indolizidine and azaazulene heterocycles as reaction products. These ring systems are frequent structural features of many alkaloids and thus would provide a potentially expedient entry into these complex natural products. Furthermore, we hoped PCP-type[6] catalysts would prove effective and provide an opportunity to develop a new class of catalysts for asymmetric Heck cyclizations.[7] Herein, we describe the results of these investigations that culminated in syntheses of (+)-5-epi-indolizidine 167B and indolizidine 223AB.

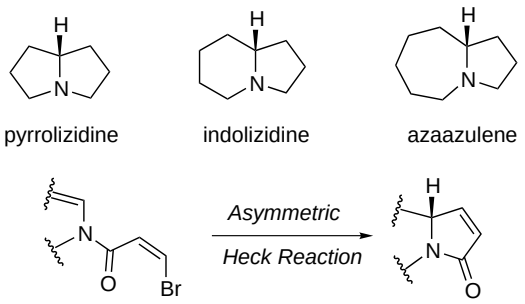

Figure 1.

Endocyclic enamides, such as **2a**–**c**, are typically generated by the in situ acylation of the corresponding cyclic imine. For example 2,3,4,5-tetrahydropyridine ($n=1$) has been produced from *N*-chloropiperidine by base-promoted elimination of hydrochloric acid and acylation to afford the corresponding enamide.[8] However, in our hands this procedure was somewhat capricious and not readily applicable to other cyclic *N*-chloro amines ($n=0$ and $n=2$).[9] In contrast, *N*-formyl enamides (**1a**–**c**) are readily available starting from the corresponding *N*-formyl amine by electrochemical methoxylation followed by thermal elimination of methanol.[10] We reasoned that simple deformylation of, for example, **1b** should provide 2,3,4,5-tetrahydropyridine or its equivalent. To this end, enamide **1b** on treatment with phenylmagnesium bromide (1.2 equiv.) followed by the addition of (*Z*)-3-bromopropenoyl chloride gave cyclic enamide **2b** in 40–54% yield.[11] In a similar fashion enamides **2a** and **2c** were also prepared starting from formyl enamides **1a** and **1c**, respectively (Scheme 1).

Heck cyclization of enamide **2b** using Ag_3PO_4 as a halide scavenger in combination with Pd·(*R*)-BINAP complex in DMF at room temperature provided **3** in

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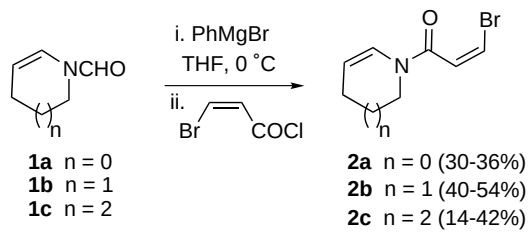


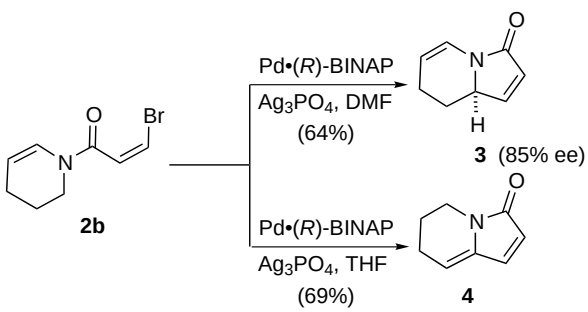
Scheme 1.

85% enantiomeric excess, while reactions conducted in tetrahydrofuran gave dieneamide **4** as the major product (Scheme 2). Additives such as Tl(I) and Ag(I) salts failed to suppress double bond migration or led to no reaction.[12] In all cases the primary Heck product (with no double bond migration) was not observed. Other palladium complexes (including PCP-type[6] catalysts) proved completely ineffective in promoting cyclization, led to the elimination of HBr to afford the corresponding alkynamide or resulted in incomplete reaction. The absolute stereochemistry of **3** was assigned by hydrogenation to (−)-indolizidone and comparison of optical rotation to a sample of known absolute configuration.[13] The sense of asymmetric induction for the cyclization of **2b** to **3** is in accord with models proposed by Overman for cationic Heck reactions.[3b]

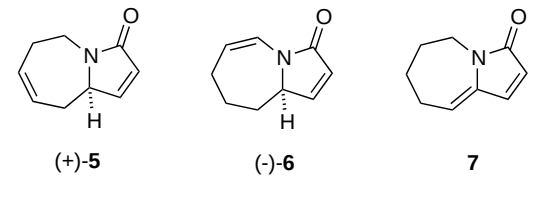
We also examined Heck cyclization of endocyclic enamide **2c**. Using reaction conditions developed in the context of enamide **2b** and THF as a solvent we observed the production of three isomeric products (+)-**5** (42% yield), (−)-**6** (7% yield), and **7** (12% yield) (Scheme 3). The optically active isomers, (+)-**5** and (−)-**6**, were isolated in 73 and 86% ee, respectively. The absolute stereochemistry of (+)-**5** and (−)-**6** were assigned following hydrogenation to identical levorotatory products and based on analogy to the sense of enantioselectivity established in Heck cyclization of **2b** (Scheme 2). Next, reaction of **2c** using the identical palladium catalyst system and now DMF as a solvent-promoted double bond isomerization and provided a mixture of (+)-**5** (9% yield) and enamide (−)-**6** (29% yield) in low enantiomeric excess, 27 and 28% ee, respectively. The sense of asymmetric induction was identical to that observed using THF as a solvent.

The indolizidine ring system is a common structural motif among dendrobatid alkaloids isolated from neotropical dart-poison frogs.[14] Due to their biological activity these alkaloids have been the subject of numerous total synthesis investigations. In a recent publication 5-epiindolizidine 167B (**13**) was produced by reduction of indolizidone **11**.[15] Also, in 1982 Hart and co-workers described the conversion of racemic **11** to 5*E*,9*Z*-indolizidine 223AB (**13**), one of the less abundant diastereomers of indolizidine 223AB.[16] In order to illustrate the synthetic utility of Heck cyclization product indolizidone (+)-**3** we prepared (+)-**11** as outlined in Scheme 4. First, reduction of **3** with L-selectride gave lactam **8**. Introduction of the C5 propyl group was accomplished by treatment of **8** with acidic methanol to give aminal **9** which on allylation afforded **10** as the only detectable diastereomer in accord with a earlier publication by Stevenson and co-workers.[17] Finally, hydrogenation of **10** afforded indolizidone **11** in near quantitative yield. Reduction of **11** with lithium aluminumhydride gave (+)-5-epiindolizine 167B (**12**).

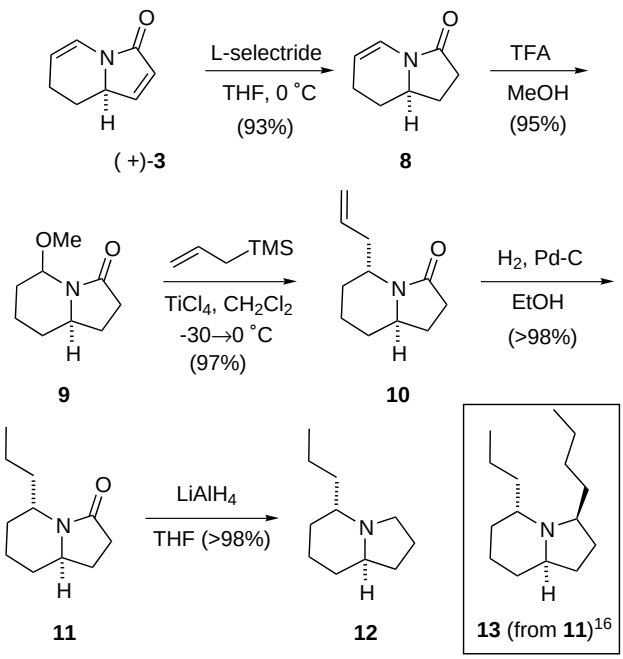
An unusual feature of the enantioselective Heck cyclization of endocyclic enamides **2b** and **2c** is the effect of solvent on the distribution of isomeric cyclization products. For example, Heck cyclization of enamide **2b** using DMF as a solvent afforded enamide **3** as the only product, the result of double bond migration following the initial Heck vinylation reaction. On the other hand



Scheme 2.



Scheme 3.



Scheme 4.

the same substrate afforded dienamide **4** when THF was used a solvent. As shown in Scheme 5, we suggest Pd-species **II** as a likely branch point for the two reaction pathways leading to **3** and **4**. The conversion of **II** to **3** involves a well-established series of reinsertion–elimination steps leading to overall double bond migration to enamide **3**. On the other hand, dienamide **4** is most likely derived from intermediate **II** or the corresponding palladium-free unsaturated compound by simple base-catalyzed isomerization. An alternative pathway involves direct anti beta-elimination of Pd-H from intermediate **I** leading directly to **4**.[18]

In order to verify the enantiomeric discriminating step leading to **3** (Scheme 6) is the migratory insertion step leading to Pd-species **I** we conducted Heck cyclization of deuterium labeled enamide d-**2**. Heck cyclization of d-**2** employing DMF as a solvent afforded d-**3** without any detected loss of deuterium in the overall process. This supports an asymmetric migratory insertion as the key enantioselective-determining step in the cyclization of endocyclic enamides **2b** and **2c** rather than asymmetric addition of palladium hydride to dienamide **4** (cf. Scheme 5).[19]

In conclusion, endocyclic enamides **2b** and **2c** undergo enantioselective intramolecular Heck cyclizations to give products in up to 86% enantiomeric excess.[20] Heck product indolizidone **3** was converted to **11**, a common intermediate in syntheses of alkaloids 5-epiindolizidine 167B and 5*E*,9*Z*-indolizidine 223AB.

Acknowledgements

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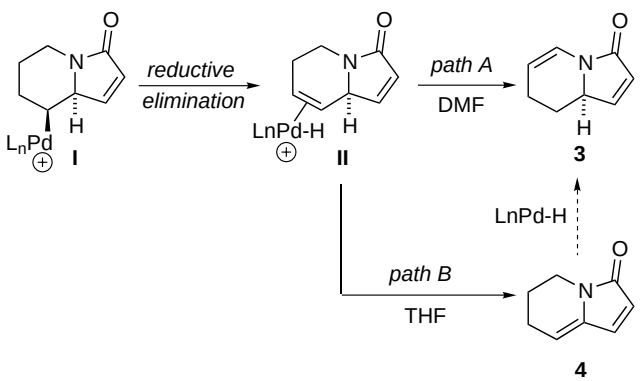
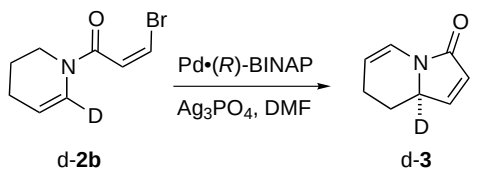


Scheme 5.



Scheme 6.

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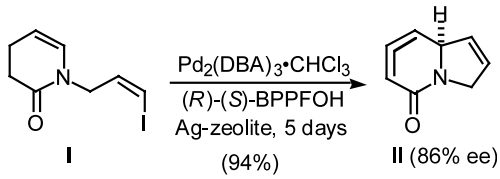
5. Shibasakai and co-workers have prepared indolizidine alkaloids using a closely related intramolecular Heck cyclization (**I→II**) (cf. Ref. 4). Our initial goal was to examine enamides **2a–c** in the context of *chiral PCP-type* catalysts (vide infra).



6. PCP-type catalysts are complexes incorporating the phosphorous–carbon–phosphorous tridentate ligand system such as those derived from the cyclometallation of 2,6-bis(dialkylphosphinomethyl)benzene.
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20. Attempts to effect Heck cyclization on enamide **2a** led to decomposition and/or recovered starting material.