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# Pd(0)/InI-Mediated Allylic Additions to 4-Acetoxy-2-azetidinone: New Route to Highly Functionalized Carbocyclic Scaffolds

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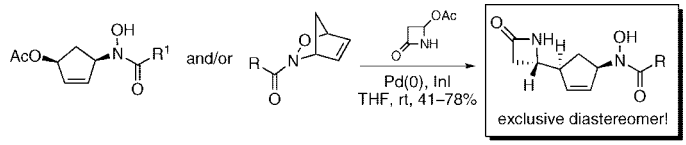
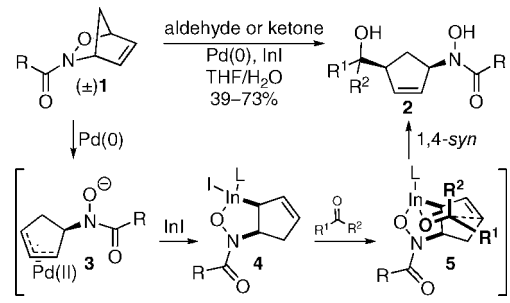
## ABSTRACT




**Acylnitroso-derived hetero-Diels−Alder cycloadducts are susceptible to C−O bond cleavage with Pd(0) and InI to form allylic indium(III) species. The in situ prepared allylindium compounds readily react at room temperature with Eschenmoser's salt. Allylation of 4-acetoxy-2-azetidinone provides derivatized cyclopentenes in high regio- and diastereoselectivity.**

Indium-mediated allylations have gained considerable attention due to their ability to achieve carbon−carbon bond formation under mild conditions with high stereo- and regioselectivities.[1] Although many indium-promoted allylations have been successful with diverse electrophilic substrates (including aldehydes,[2] imines,[3] hydrazones,[4] epoxides,[5] etc.), methodologies have mainly focused on simple allylindium reagents (generated in situ from allyl bromide and indium metal) as the reactive nucleophilic species. Herein, we report the diastereoselective allylation of 4-acetoxy-2-azetidinone from a unique allylindium precursor, acylnitroso-derived hetero-Diels−Alder adduct **1**, to incorporate highly functionalized cyclopentenes at the azetidinone C4 position.

**Scheme 1.** Pd(0)/InI-Mediated Allylation with Cycloadduct (±)**1**




Our group has optimized conditions for Pd(0)/InI-mediated allylations of aldehydes and ketones with several hetero-Diels−Alder cycloadducts (±)**1** (Scheme 1).[6] By investigating aromatic aldehydes, aliphatic aldehydes, and ketones as suitable electrophiles for the metal-mediated allylation reactions, a diverse set of 1,4-*syn* products **2** have been prepared in 39−73% yields (Scheme 1). The stereo- and regioselective

(1) For recent reviews, see: (a) Araki, S.; Hirashita, T. In *Comprehensive Organometallic Chemistry III*; Crabtree, R. H., Mignos, D. M. P., Eds.; Elsevier: Oxford, 2007; Vol. 9, Chapter 9.14. (b) Podlech, J.; Maier, T. C. *Synthesis* **2003**, *5*, 633–655.

(2) Loh, T.-P.; Tan, K.-T.; Yang, J.-Y.; Xiang, C.-L. *Tetrahedron Lett.* **2001**, *42*, 8701–8703.

(3) Loh, T.-P.; Ho, D. S.-C.; Xu, K.-C.; Sim, K.-Y. *Tetrahedron Lett.* **1997**, *38*, 865–868.

(4) Cook, G. R.; Kargbo, R.; Maity, B. *Org. Lett.* **2004**, *6*, 1741–1743.

(5) Yadav, J. S.; Anjaneyulu, S.; Ahmed, M.; Reddy, B. V. *Tetrahedron Lett.* **2001**, *42*, 2557–2559.

(6) Lee, W.; Kim, K. H.; Surman, M. D.; Miller, M. J. *J. Org. Chem.* **2003**, *68*, 139–149.

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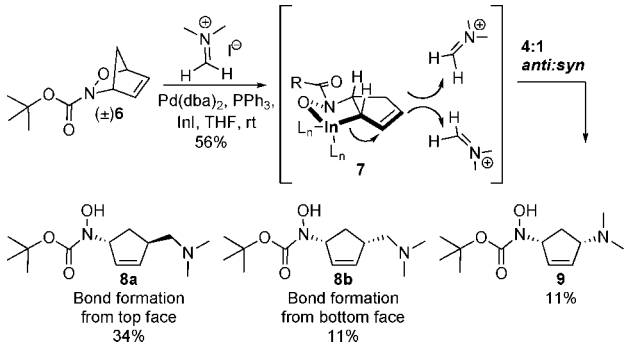
outcome may be rationalized by initial Pd(0)-mediated ring opening of hetero-Diels−Alder-derived cycloadduct **1** to form $\pi$-allylpalladium(II) complex **3**.[7] The resultant $\pi$-allylpalladium(II) **3** may undergo reductive transmetalation with indium(I) iodide[8] to produce allylic indium(III) species **4**. Diastereo- and regioselective allylation may occur through indium−aldehyde chelation in proposed transition state **5** and accounts for stereocontrol at the peripheral carbon to afford allylation product **2**.

We were eager to identify additional electrophiles to react with hetero-Diels−Alder cycloadduct (±)**1** under Pd(0)/InI-mediated allylation conditions. We turned our attention to iminium species which display similar electrophilic character as the successful carbonyl-containing electrophiles. Accordingly, *N*,*N*-dimethylmethyleneammonium iodide (Eschenmoser's salt) was selected as an electrophile to probe the reactivity of allylindium species **7** (Scheme 2). When Boc cycloadduct (±)**6** was exposed to Pd(0) and InI in the presence of Eschenmoser's salt, the reaction was complete within 1.5 h and revealed a mixture of *anti*-1,4- and *syn*-1,4 dimethylaminomethylcyclopentenes **8a** and **8b** (4:1 *anti*/*syn*) as an inseparable mixture of diastereomers in 45% overall yield. In contrast to previously studied reactions with carbonyls,[6] the iminium species does not have electrons available to coordinate to indium in the transition state and *anti*-1,4 products result. Therefore, allylation is directed to the less hindered top face of proposed allylindium species **7** to afford major 1,4-*anti* product **8a**. Interestingly, the reaction of dimethylamine (hydrolysis product of Eschenmoser's salt) with $\pi$-allylpalladium(II) complex **3** is competitive with reductive transmetalation and thus affords undesired byproduct **9** in 11% yield.

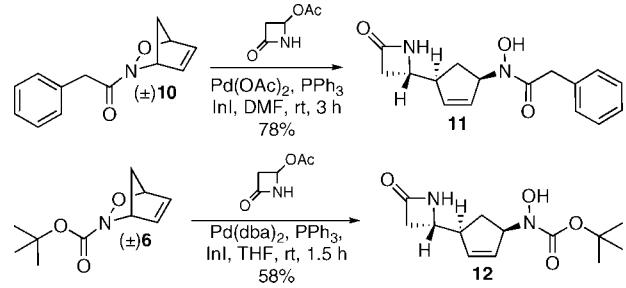
**Scheme 2.** Pd(0)/InI-Mediated Allylation of Eschemoser's Salt




Encouraged by our initial result with Eschenmoser's salt, we investigated acyl imine precursor,[9] 4-acetoxy-2-azetidinone, as a suitable electrophile. The reaction of 4-acetoxy-2-azetidinone with allylindium and crotylindium species has been reported.[10] Additionally, Lee and co-workers have disclosed indium-mediated allenylations of 4-acetoxy-2-azetidinones and subsequent cyclization to carbapenems.[11] Our research group has previously synthesized related carbapenems;[12] allylation products derived from azetidinones and cycloadduct (±)**1** would provide new carbocyclic platforms that would allow us to gain entry to tricyclic $\beta$-lactam antibiotics[13] and related structures.

Phenylacetyl cycloadduct (±)**10** was treated with 4-acetoxy-2-azetidinone in the presence of Pd(0) and InI to afford $\beta$-lactam-derived carbocyclic scaffold **11**[14] in 78% isolated yield as exclusively the *syn*-1,4-substituted diastereomer with additional stereocontrol at the C4 azetidinone center (Scheme 3). $^1$H NMR and LCMS of the crude reaction mixture confirmed the absence of additional allylation products. When Boc cycloadduct (±)**6** was exposed to Pd(0) and indium (I) iodide in the presence of 4-acetoxy-2-azetidinone, derivatized azetidinone **12** was obtained as a single diastereomer in 58% isolated yield; an identical isolated yield was attained when the reaction was performed on large scale (33 mmol).

**Scheme 3.** Pd(0)/InI-Mediated Allylation of 4-Acetoxy-2-azetidinone




In order to identify the newly formed stereocenter at C4 of the azetidinone, we embarked on 2D NMR studies while concurrently growing suitable crystals of **11** for X-ray crystallography. We immediately identified product **11** as the 1,4-*syn* substituted diastereomer from diagnostic *J* values.[15] Unfortunately, several resonances in the $^1$H NMR spectrum were very broad and required manipulation of sinebell and line broadening functions (massaging) to extract *J* values. Even though we identified $J(H_c-H_f) = 6.8$ Hz,

(7) (a) Mulvihill, M. J.; Surman, M. D.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 4874–4875. (b) Surman, M. D.; Mulvihill, M. J.; Miller, M. J. *Org. Lett.* **2002**, *4*, 139–141.

(8) Araki, S.; Kamei, T.; Hirashita, T.; Yamamura, H.; Kawai, M. *Org. Lett.* **2002**, *2*, 847–849.

(9) Ueda, Y.; Maynarda, S. C. *Tetrahedron Lett.* **1985**, *26*, 6309–6312.

(10) Kang, K.-U.; Baik, T.-G.; Jiao, X.-H.; Lee, K.-J.; Lee, C.-H. *Synlett* **1999**, *4*, 447–449.

(11) Lee, P. H.; Kim, H.; Lee, K.; Kim, M.; Noh, K.; Kim, H.; Seomoon, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 1840–1843.

(12) (a) Williams, M. A.; Miller, M. J. *Tetrahedron Lett.* **1990**, *31*, 1807–1810. (b) Williams, M. A.; Hsiao, C. H.; Miller, M. J. *J. Org. Chem.* **1991**, *56*, 2688–2694.

(13) (a) Di Modugno, E.; Erbetti, I.; Ferrari, L.; Galassi, G. L.; Hammond, S. M.; Xerri, L. *Antimicrob. Agents Chemother.* **1994**, *38*, 2362–2368. (b) Rossi, T.; Biondi, S.; Contini, S.; Thomas, R. J.; Marchioro, C. *J. Am. Chem. Soc.* **1995**, *117*, 9604–9605. (c) Martel, S. R.; Wisedale, R.; Gallagher, T.; Hall, L. D.; Mahon, M. F.; Bradbury, R. H.; Hales, N. J. *J. Am. Chem. Soc.* **1997**, *119*, 2309–2310.

(14) Hydroxamic acid **11** was purified on iron-free silica gel; refer to the Supporting Information for preparation of iron-free silica gel.

(15) See: Surman, M. D.; Mulvihill, M. J.; Miller, M. J. *J. Org. Chem.* **2002**, *67*, 4115–4121, ref 14.

the relative stereochemistry could not be elucidated without additional structural information (Figure 1).

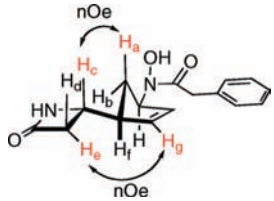



**Figure 1.** Selected NOEs in ROESY spectrum of **11**.

A series of 2D NMR experiments were performed (COSY, TOCSY, HMQC and HMBC) to unambigously assign all proton and carbon resonances.[16] Finally, the 3D structure of **11** was determined by ROESY. The relative stereochemistry at the C4 center of azetidinone **11** was elucidated from NOEs between $H_a$ and $H_c$ and $H_e$ and $H_g$, respectively (Figure 1). Crystals of **11** were obtained by recrystallization from acetonitrile, and the proposed structure was confirmed by X-ray crystallography (Figure 2).

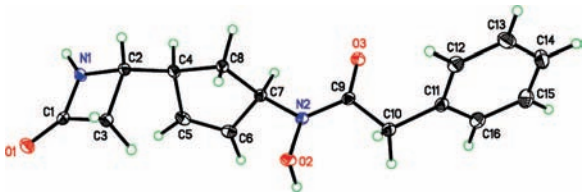
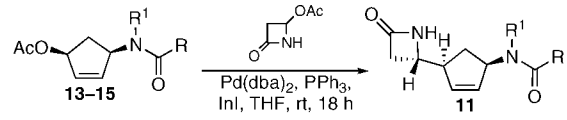



**Figure 2.** X-ray structure of **11** with thermal ellipsoids drawn at 50% probability.

The exclusive diastereoselectivity suggests that coordination to indium in the transition state is relevant. In order to test this hypothesis, phenylacetyl hydroxamic acid **13** was subjected to Pd(0)/InI in the presence of 4-acetoxy-2-azetidinone (Scheme 4). Identical product **11** was isolated as the exclusive allylation product in decreased yield (41%). However, nonhydroxamate-containing starting materials, phenylacetyl amide **14** and Boc carbamate **15**, did not provide allylation products when exposed to Pd(0)/InI conditions in the presence of 4-acetoxy-2-azetidinone. Although complicated mixtures resulted, consumption of acetate starting materials **14** and **15** suggests that an allylindium species formed but did not react with 4-acetoxy-2-azetidinone.[17]

**Scheme 4.** Pd(0)/InI-Mediated Allylation with **13**−**15**




| entry | substrate | R | $R^1$ | product | isolated yield (%) |
|---|---|---|---|---|---|
| 1 | **13** | $CH_2Ph$ | OH | **11** | 41 |
| 2 | **14** | $CH_2Ph$ | H | - | 0 |
| 3 | **15** | $OC(CH_3)_3$ | H | - | 0 |

Although the exact origin of diastereoselectivity at the azetidinone center is unknown, an organized transition state involving coordination of the acyl imine electrophile may be appropriate. Additionally, acetic acid is produced during Lewis acid mediated acyl imine formation and may play a role in the observed diastereoselectivity.

In summary, we have reported a new diastereoselective allylation of 4-acetoxy-2-azetidinone with an allylic indium(III) species generated from cycloadduct (±)**1**. The lack of C−C bond formation in the case of starting materials **14** and **15** indicates that hydroxamate is a crucial component in these Pd(0)/InI-mediated allylations.

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**Supporting Information Available:** General methods, preparation of iron-free silica gel, experimental details, and $^1H$ and $^{13}C$ NMR spectra for **8a**, **8b**, **9**, **11** and **12**. Complete proton and carbon assignments for **11**. X-ray crystallography data for **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Refer to the Supporting Information for complete carbon and proton assignments for **11**.

(17) Phenylacetyl amide **14** reacts with aldehydes in the presence of Pd(0) and InI to afford 1,4-*anti* products, ref 6.