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Palladium(0)/indium iodide-mediated allylations of electrophiles generated from the hydrolysis of Eschenmoser's salt: one-pot preparation of diverse carbocyclic scaffolds

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ABSTRACT

A formyl equivalent was generated in situ from Eschenmoser's salt in aqueous THF and was reacted with an allylindium species. Acylnitroso-derived hetero-Diels–Alder adducts and related allyl acetates were shown to be substrates for Pd(0)/InI-mediated allylations of formaldehyde-related species to provide homoallylic alcohols. Hydroxymethyl groups were installed with regio- and diastereocontrol to provide relevant disubstituted carbocyclic scaffolds. Enantiopure anti-disubstituted cyclopentene products were prepared from a chiral allyl acetate.

Formaldehyde is one of the most reactive carbonyl electrophiles used in organic syntheses. Although gaseous formaldehyde may be generated from paraformaldehyde, self-polymerization has limited its general use.[1] Additionally, commercially available 37% aqueous formaldehyde is an inadequate source of monomeric formaldehyde because formaldehyde hydrate exists in solution.[2] In order to achieve high yielding reactions with formaldehyde, stable formaldehyde–organoaluminum complexes have been generated[3] and water-tolerant Lewis acids have promoted direct hydroxymethylations in aqueous formaldehyde solutions.[4] We envisioned an alternative method to generate formaldehyde or related species (in situ hydrolysis of Eschenmoser's salt) and then using the simple synthon as an allylation acceptor to prepare hydroxymethylated carbocyclic platforms (±)-**1a**, (+)-**1b**, and (+)-**1c** (Fig. 1).

Carbocycles (±)-**1a**, (±)-**1b**, and (±)-**1c** are precursors to carbocyclic nucleosides[5] and related carbasugars.[6] To date, direct access to these diverse substrates from a common precursor has not been achieved. Compound (±)-**1a** and related derivatives[7] have been prepared from an initial Diels–Alder reaction between a sulfonyl isocyanate and cyclopentadiene followed by hydrolysis to afford 2-azabicyclo[2.2.1]hept-5-en-3-one (Vince's lactam); reductive opening of the lactam provides substrate (±)-**1a**.[8]

Conversely, a multi-step synthetic sequence may be employed to prepare carbocyclic scaffolds bearing 4′-hydroxymethyl groups. For example, the C4′–C5′ bond has been installed by Pd(0)-catalyzed allylic alkylations with nitromethane,[9] ethyl nitroacetate,[10] and (phenylsulfonyl)-nitromethane.[11] In each case, the 4′-hydroxymethyl group was then ultimately revealed through an oxidation–reduction sequence. Although scaffolds (±)-**1a**[12] and (±)-**1b**[13] have been reported, the diastereomers are prepared by two unrelated synthetic methods. In order to develop a direct hydroxymethylation reaction and synthesize diverse carbocyclic platforms from a common substrate, Pd(0)/InI-mediated allylations of formaldehyde and formyl equivalents with hetero-Diels–Alder cycloadduct (±)-**2b** and allyl acetate (−)-**8** were investigated to ultimately prepare (hydroxymethyl)cyclopentenyl scaffolds (±)-**1a**, (+)-**1b**, and (+)-**1c** (Fig. 1).

Allylindium reagents are mild nucleophilic species that readily react with aldehydes and ketones to afford homoallylic alcohols.[14] Our group has previously developed Pd(0)/InI-mediated allylations of diverse electrophiles with hetero-Diels–Alder cycloadducts (±)-**2a** and (±)-**2b**.[15]

In an initial attempt to affect hydroxymethylation, phenylacetyl cycloadduct (±)-**2a** was treated with Pd(0) and InI in the presence of 37% aqueous formaldehyde (1.5 equiv) to afford an equal distribution of *syn*-1,4, *anti*-1,4, and *anti*-1,2 allylation products (±)-**3a**, (±)-**3b**, and (±)-**3c**, respectively, in an overall 30% isolated yield (Scheme 1).[15b]

We shifted our focus to formyl equivalents and related electrophiles as alternative options to install the requisite hydroxymethyl group by using Pd(0)/InI allylation chemistry. Unfortunately, several electrophiles (i.e., *s*-trioxane, trifluoroethyl formate, benzylozymethyl chloride, methyl cyanoformate, CO_2, and DMF acetals) were unreactive toward Pd(0)/InI allylation conditions in the

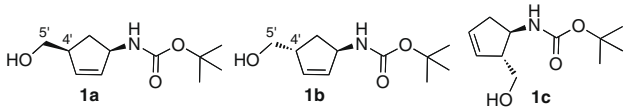

Figure 1. Carbocyclic target molecules.

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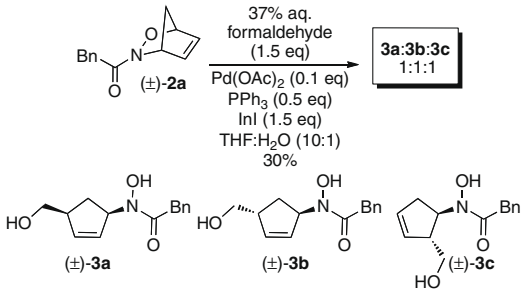


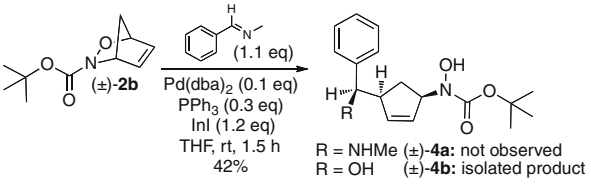
Scheme 1. Pd(0)/InI-mediated allylation of aqueous formaldehyde.

presence of cycloadducts (±)-**2a** and (±)-**2b** even with increased temperatures.[16] When more reactive electrophiles (i.e., Vilsmeier's reagent, Viehe's salt, and 1,3-benzodithiolylium tetrafluoroborate) were used for the Pd(0)/InI allylation chemistry, cycloadducts (±)-**2a** and (±)-**2b** were consumed and complex product mixtures were obtained.

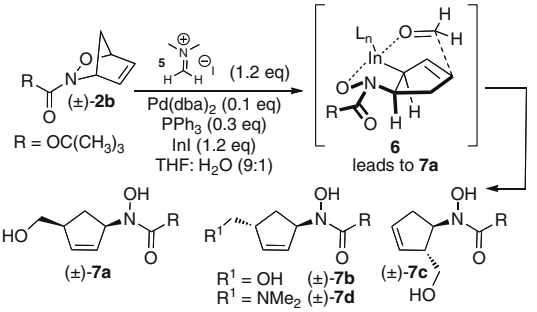
Although we had extensively explored formyl equivalents and related electrophiles as potential substrates for Pd(0)/InI-mediated allylation chemistry with cycloadducts (±)-**2a** and (±)-**2b**, a related indium-allylation reaction led us to discover an appropriate source of a formyl species. During the course of identifying iminium species for Pd(0)/InI-mediated allylation chemistry, we recognized that treatment of Boc cycloadduct (±)-**2b** with Pd(0) and InI in the presence of *N*-benzylidenemethylamine did not produce the anticipated homoallylic amine (±)-**4a** (Scheme 2).[17] We isolated homoallylic alcohol (±)-**4b** in 42% yield. These results are consistent with the in situ hydrolysis of *N*-benzylidenemethylamine to provide benzaldehyde and subsequent allylation to afford (±)-**4b**.

The hydrolysis conditions were reproduced by treating Boc cycloadduct (±)-**2b** with Pd(0) and InI in the presence of Eschenmoser's salt **5** in THF/H_2O (Scheme 3). After 90 min at rt, ^{1}H NMR integration of the crude reaction mixture revealed a mixture of *syn*-1,4, *anti*-1,4, *anti*-1,2, and *anti*-1,4 allylation products (±)-**7a**, (±)-**7b**, (±)-**7c**, and (±)-**7d**, respectively (Scheme 3, entry 1).[18] The preference for *syn*-1,4 product (±)-**7a** was rationalized with transition state **6**. If formaldehyde was the reactive species, indium may coordinate to the *N*-hydroxy carbamate oxygen and the carbonyl oxygen of formaldehyde as shown in complex **6**. Encouraged by this result, we investigated conditions to improve the ratio of *syn*-1,4 product (±)-**7a**. Accordingly, production of (±)-**7d** was suppressed by stirring Eschenmoser's salt in THF/H_2O for 10 min prior to allylation (entries 2 and 6).[19]

An increase of *syn*-1,4 product (±)-**7a** was observed when cycloadduct (±)-**2b** was stirred with Pd(0) and InI for 90 min followed by treatment with a THF/H_2O solution of Eschenmoser's salt (Scheme 3, entry 2). ^{1}H NMR integrations confirmed *syn*-1,4 product (±)-**7a** as the major component of the reaction mixture. After column chromatography, *syn*-1,4 product (±)-**7a** was isolated in 38% yield (>97% de). Despite the low isolated yield, these reaction



Scheme 2. Pd(0)/InI-mediated allylation of benzaldehyde (generated in situ from *N*-benzylidenemethylamine).



entry	order of reagent addition	product distribution (%)				total yield
		7a	**7b**	**7c**	**7d**	
1	Stir **2b**, Pd(0), InI for 90 min; add **5**[a]	67	8	14	11	N/A
2	Stir **2b**, Pd(0), InI for 90 min; add **5**[b]	84	14	2	0	38%[f]
3	Stir **2b**, Pd(0), InI for 0 min; add **5**[b,c]	38	22	34	5	N/A
4	Stir **2b**, **5**, InI for 0 min; add Pd(0)[d]	42	18	34	6	57%[g]
5	Stir **2b**, **5**, InI for 0 min;[e] add Pd(0)[d]	66	15	11	8	N/A
6	Stir **2b**, **5**, InI for 10 min; add Pd(0)[d]	67	19	14	0	78%[g]

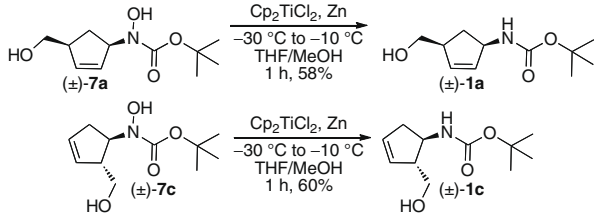
Scheme 3. Pd(0)/InI-mediated allylations of formaldehyde (generated in situ from Eschenmoser's salt). Reagents and conditions: (a) a THF/H_2O solution of Eschenmoser's salt **5** was prepared and added immediately; (b) a THF/H_2O solution of Eschenmoser's salt **5** was stirred for 10 min prior to addition; (c) a THF/H_2O solution of Eschenmoser's salt **5** was added dropwise over 30 min; (d) a THF solution of Pd(0) was stirred for 10 min prior to addition; (e) the reaction was cooled to 0 °C; (f) isolated yield for (±)-**7a**; (g) isolated yields for combined products (±)-**7a**, (±)-**7b**, and (±)-**7c**.

conditions provided highly enriched amounts of the *syn*-1,4 product (±)-**7a**.

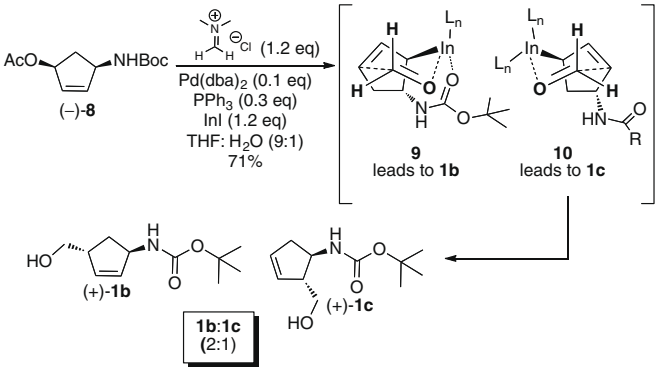
Alternatively, *syn*-1,4 product (±)-**7a** was produced by stirring cycloadduct (±)-**2b** with InI and Eschenmoser's salt in THF/H_2O for 10 min followed by addition of a THF solution of Pd(0) (Scheme 3, entry 6). Although these reaction conditions afforded the highest isolated yield of all allylation products, *syn*-1,4 product (±)-**7a** could not be exclusively isolated by this method because separation by column chromatography was complicated by increased amounts of (±)-**7b** and (±)-**7c**. When cycloadduct (±)-**2b** was stirred with InI, formaldehyde, and dimethylamine in THF/H_2O for 10 min followed by the addition of a THF solution of Pd(0), starting material was consumed and compounds (±)-**7a**, (±)-**7b**, (±)-**7c**, or (±)-**7d** were not observed.

N-Hydroxy carbamates (±)-**7a** and (±)-**7c** were reduced to carbamates (±)-**1a** and (±)-**1c**, respectively, with Cp_2TiCl[20] (Scheme 4). Compound (±)-**1a** represents a key carbocyclic scaffold for the syntheses of carbocyclic nucleoside target molecules and related analogs.

A complementary route was developed to provide *anti*-(hydroxymethyl)cyclopentenyl derivatives as the exclusive products. Allyl acetate (−)-**8** was selected as an appropriate substrate



Scheme 4. Cp_2TiCl-mediated N–O bond reductions.



Scheme 5. Pd(0)/InI-mediated allylations of formaldehyde (generated in situ from Eschenmoser's salt).

because it is easily prepared from Boc cycloadduct (±)-**2b** in three steps and provides enantioenriched allylation products.[21] Additionally, substrate (−)-**8** lacks a coordinating hydroxamate oxygen and, in this case, allylation was anticipated to proceed *anti* to the carbamate substituent. Indeed, Pd(0)/InI-mediated allylation of (−)-**8** provided *anti*-1,4 and *anti*-1,2 scaffolds (+)-**1b** and (+)-**1c**, respectively, in a 2:1 ratio and in overall 71% isolated yield (Scheme 5). If formaldehyde was the reactive species, the preference for *anti*-1,4 product (+)-**1b** may be consistent with transition state **9** in which indium coordinates to the carbamate oxygen and formaldehyde. In transition state **10**, indium may be unable to coordinate to the carbamate as an unfavorable bridged species would result. In-mediated allylation provides *anti*-1,2 carbocycle (+)-**1c** as the minor product. This method was a dramatic improvement to previously reported conditions. Pd(0)/InI-mediated allylation of 37% aqueous formaldehyde with allyl acetate (±)-**8** provided *anti*-1,4 product (±)-**1b** in 10% isolated yield.[15b]

Diverse cyclopentene scaffolds (±)-**1a**, (+)-**1b**, and (+)-**1c** have been prepared from cycloadduct (±)-**2b** and/or allyl acetate (−)-**8**. Two key synthetic transformations, Pd(0)/InI allylations of a formyl species generated in situ from Eschenmoser's salt and Ti(III)-mediated N–O bond reductions, were used to prepare the isomeric products. Syntheses of targeted carbocyclic nucleosides from substrates (±)-**1a** and (+)-**1b** are reported in the subsequent Letter.[22]

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Supplementary data

Supplementary data (General methods, experimental details and characterization for compounds (±)-**1a**, (+)-**1b**, (+)-**1c**, (±)-**4b** and (±)-**7a**–**c**.) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.007.

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