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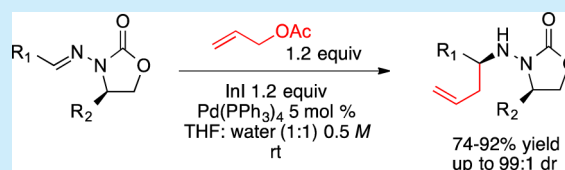
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Highly Diastereoselective Palladium-Catalyzed Indium-Mediated Allylation of Chiral Hydrazones

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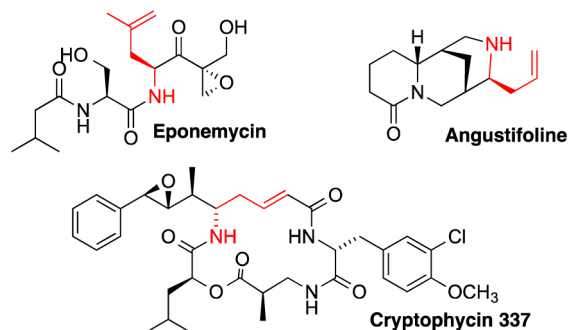
Supporting Information

ABSTRACT: The general and efficient palladium-catalyzed indium-mediated allylation of chiral hydrazones was accomplished with excellent yield (72–92%) and diastereoselectivity (up to 99:1). The development of this reaction and the substrate scope are described. The conversion was found to be proportional to the phosphine concentration, which provided insight into the mechanism and competing pathways of the redox transmetalation process.



Homoallylic amines are valuable synthetic intermediates and are found in various natural products of biological interest (Scheme 1).¹ Additionally, general methods for the

Scheme 1. Homoallylic Amine Moiety in Bioactive Compounds



construction of chiral amines are becoming exceedingly important.² For these reasons, the advancement of stereoselective allylation of imines has been an area of intense effort in our laboratory. Previously we have reported the indium-mediated allylation of *N*-acylhydrazones bearing a chiral auxiliary using allyl halide and indium metal.³ We have also developed this practical method into a highly enantioselective process catalyzed by chiral indium Lewis acids generated in situ by the reaction of allylindium with electron-deficient BINOL derivatives.⁴

Most methods for indium-mediated allylation employ allylic bromides or iodides as the allyl metal precursor. In 2000 Araki and co-workers reported a new method for the preparation of allylindium reagents from allylic acetates and alcohols using a reductive transmetalation protocol catalyzed by Pd(0).⁵ This method is advantageous as it circumvents the use of more sensitive allylic halides and broadens the scope of nucleophiles

that may be employed. Following Araki's work, several reports have appeared using this transmetalation protocol for various nucleophilic allylating reagents. Traditionally, umpolung Pd-catalyzed allylation methods have been applied to aldehyde electrophiles, and their use with imines are rarer.^{7c} In addition to indium, other umpolung methods⁶ have used in situ-generated allylboranes,⁷ borates,⁸ silanes,⁹ and stannanes¹⁰ as the nucleophile.^{11,12}

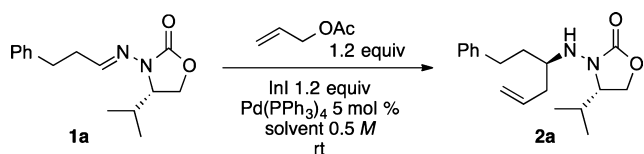
To the best of our knowledge, stereoselective palladium-catalyzed indium-mediated allylation has not been explored thoroughly for imine substrates. From the current standpoint on the importance of chiral amine based molecules, developing allylation protocols for the synthesis of homoallylic amines would be beneficial. Our research group reported the first use of allylindium reagents generated from allylic iodides and indium metal with chiral hydrazine substrates.³ We envisioned that the operational simplicity and ease of handling would be improved for the allylation of chiral hydrazones by using allylic acetates as precursors with the Pd-catalyzed method of Araki rather than allylic iodides.⁵

We first examined the solvent suitable to carry out the desired transformation effectively and selectively. Allyl acetate, indium(I) iodide, and a catalytic amount (5 mol %) of Pd(PPh₃)₄ were reacted with the hydrazone **1a** at room temperature in a variety of solvents. The results are summarized in Table 1. The reaction of hydrazone **1a** to give homoallylic hydrazine **2a** proceeded effectively in a variety of solvents, except for pure water (entry 7) and acetonitrile (entry 8). Optimal results were obtained in methanol or a combination of THF and water (entries 4 and 9–10, respectively). Increasing the amount of water slightly diminished the yield (entry 11). In all cases, the chiral auxiliary was highly effective in controlling diastereoselectivity.

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Table 1. Pd/In Allylation Solvent Screening

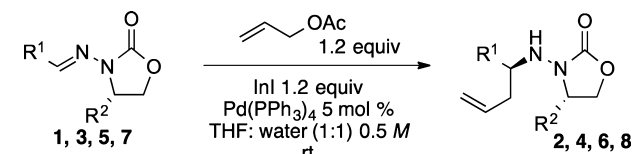


entry	solvent	yield (%) ^a	dr ^b
1	CHCl ₃	65	97:3
2	Et ₂ O	78	98:2
3	THF	79	96:4
4	MeOH	84	98:2
5	DMF	60	98:2
6	toluene	60	98:2
7	H ₂ O	0	—
8	CH ₃ CN	0	—
9	THF/H ₂ O (1:1)	81	99:1
10	THF/H ₂ O (3:1)	81	98:2
11	THF/H ₂ O (1:3)	76	97:3

^aIsolated yields. ^bDetermined by ¹H NMR spectroscopy.

The reaction scope was explored by examining a variety of substrates, and the results are summarized in Table 2. Chiral

Table 2. Pd/In Allylation Substrate Scope



entry	imine	R ¹	R ²	yield (%) ^a	dr ^b
1	1b	Et	<i>i</i> -Pr	92 (2b)	99:1
2	1c	<i>n</i> -Pr	<i>i</i> -Pr	91 (2c)	99:1
3	1d	<i>i</i> -Pr	<i>i</i> -Pr	81 (2d)	99:1
4	1e	<i>i</i> -Bu	<i>i</i> -Pr	74 (2e)	99:1
5	1f	EtOCO	<i>i</i> -Pr	80 (2f)	80:20
6	3a	<i>c</i> -C ₅ H ₉	<i>i</i> -Pr	92 (4a)	99:1
7	3b	<i>c</i> -C ₆ H ₁₁	<i>i</i> -Pr	83 (4b)	99:1
8	3c	PhCH ₂	<i>i</i> -Pr	77 (4c)	99:1
9	5a	Et	PhCH ₂	70 (6a)	99:1
10	5b	<i>i</i> -Bu	PhCH ₂	79 (6b)	97:3
11	5c	Ph(CH ₂) ₂	PhCH ₂	91 (6c)	99:1
12	7a	<i>i</i> -Bu	Ph	69 (8a)	86:14

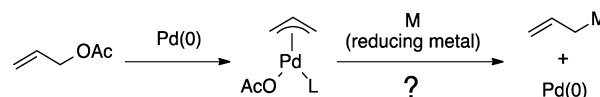
^aIsolated yields. ^bDetermined by ¹H NMR spectroscopy.

hydrazones containing isopropyl-, benzyl-, and phenyl-substituted oxazolidinones were investigated. The isopropyl auxiliary performed extremely well and produced the homoallylic hydrazine product with complete control of the diastereoselectivity as determined by ¹H NMR spectroscopy (entries 1–4 and 6–8). The substrate containing an ester functional group adjacent to the imine (1f; entry 5) was the exception and generated 2f as an 80:20 mixture. The lower selectivity could be due to the presence of another coordinating group for In(III) to bind and chelate the imine, allowing the oxazolidinone auxiliary freedom to rotate from an *s*-*cis* to an *s*-*trans* conformation. Alternatively, the lower selectivity could result from greater reactivity of the substrate. The benzyl-derived auxiliary afforded slightly lower diastereoselectivity compared with the isopropyl auxiliary (entries 9–11). The phenyl auxiliary, on the other hand, afforded the lowest

diastereoselectivity (entry 12). This is likely due to the planar nature of the phenyl ring, which can rotate perpendicular to the plane of the imine, thus affording inefficient shielding of the imine face. In summary, the isopropyl- and benzyl-derived oxazolidinones were the most effective auxiliaries for asymmetric induction. High selectivity was obtained with a variety of hydrazones, with the exception of α -ester derivatives.

While excellent selectivity has been achieved in the Pd/In-mediated allylation of chiral hydrazones, during the course of our studies we often encountered variability in the conversion of starting material to product in these reactions. In some instances the palladium catalyst would precipitate out of solution (black out) and the reactions stall. To understand this phenomenon, we undertook a more detailed investigation of the catalyst parameters in the reaction. While umpolung-type reactions utilizing palladium catalysts and various metals for reductive transmetalation have been known for some time,⁶ very little is understood about the mechanism of the key redox step involving the transfer of the allyl ligand from the Pd(II) intermediate to the reducing metal (Scheme 2).^{6b} As the first

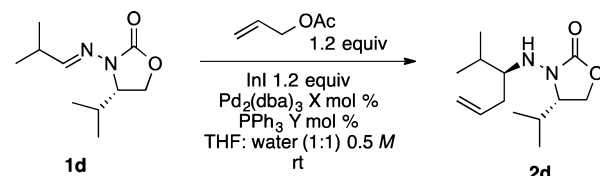
Scheme 2. Pd-Catalyzed Allylmetal Formation



step in this process, the oxidative addition of Pd(0) to allyl acetate to form the Pd(II)–allyl complex, is well-known and well-characterized, we hypothesized that the difficulties encountered in the studies were likely due to inefficient reductive transmetalation.

To probe the effect of the ligand on the reaction, the role of the phosphine concentration in the conversion of 1d to 2d was examined. A Pd(0) source lacking phosphine ligands, Pd₂dba₃, was employed, and the concentration of the Ph₃P ligand was systematically varied. The results are summarized in Table 3. When 5 mol % Pd catalyst was used with no added phosphine, the reaction did not proceed (entry 1). This was likely due to the lack of formation of the initial Pd–allyl complex. Addition

Table 3. Effect of the Phosphine Concentration



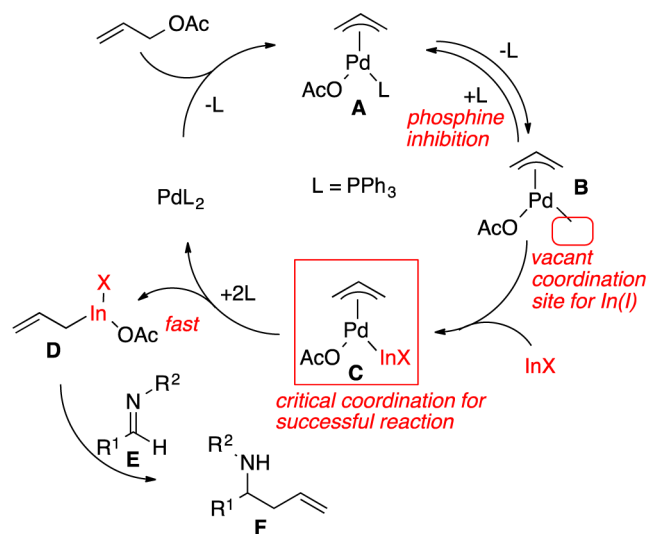
entry	X (mol %)	Y (mol %)	P/Pd ratio	yield (%) ^a
1	5	0	0	0
2	5	2.5	0.25	78
3	5	5	0.5	75
4	5	10	1.0	65
5	5	20	2.0	54
6	5	30	3.0	37
7	2.5	2.5	0.5	86
8	2.5	5	1.0	81
9	2.5	10	2.0	72
10	2.5	15	3.0	61
11	2.5	20	4.0	40

^aIsolated yields.

of a small amount of phosphine (P/Pd ratio = 0.25) resulted in efficient formation of **2d** in an acceptable 78% yield (entry 2). Increasing the P/Pd ratio incrementally from 0.5 to 3.0 had a detrimental effect on the conversion (entries 3–6). The yield dropped from 75% to 37%, with increasing amounts of starting **1d** remaining. Thus, the yield reflects the conversion in the reaction. Lowering the catalyst loading did not result in decreased yield (entries 7–11). The same correlation of P/Pd ratio and conversion was observed, but compared with the higher catalyst loading, the yields were slightly higher. This may reflect the fact that the overall concentration of phosphine in solution was lower.

The most plausible catalytic cycle for the umpolung-type allylation proposed by Araki and co-workers was described in 2000. In this cycle, a π -allylpalladium intermediate is formed, followed by an undescribed redox transmetalation to produce the In(III) allyl reagent and regenerate Pd(0).⁵ To rationalize the inhibitory effect of the phosphine ligand, we hypothesize that a Pd(II)–In(I) coordinative bond must be formed for successful redox and allyl ligand transfer (Scheme 3).¹³ In order

Scheme 3. Mechanistic Hypothesis for the Role of the Phosphine in the Inhibition of Allylation



to form the bimetallic complex **C**, π -allylpalladium complex **A** must undergo ligand dissociation to open up a coordination site (**B**). Only when the Pd complex is coordinatively unsaturated could InI bind. The concentration of phosphine in solution would have a direct influence on the equilibrium of **A** and **B**. Increased concentration would favor the saturated complex **A** and inhibit the subsequent formation of **C** and the redox reaction to form **D**. This would allow degradation pathways resulting in Pd black to compete with successful transmetalation. While no examples of Pd(II)–In(I) complexes have been reported, examples of more stable Pd(0)–In(I) coordination complexes have been described, and crystal structures demonstrating that In(I) can form bonds to Pd have been reported.¹⁴ A Pd(II)–In(I) complex would likely undergo redox rapidly to form Pd(0) and In(III).

In conclusion, we have developed a highly diastereoselective allylation of chiral hydrazones utilizing indium and a palladium catalyst. This method employs an allylindium reagent generated through a reductive transmetalation process and allows the use of allylic acetates as precursors for allylindium reagents.

Evidence of inhibition of the reaction with increased phosphine concentration suggested that an intermediate involving a Pd–In bond is important for generation of the nucleophilic allylindium species. Better understanding of the mechanism of umpolung-type redox transmetalations will allow greater control of reactions and has implications beyond just In-mediated allylation. Toward this goal, we are actively pursuing the mechanistic implications of the phosphine inhibition and its role in other umpolung processes.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental information, procedures, and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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