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Ruthenium catalyzed hydroaminoalkylation of isoprene *via* transfer hydrogenation: byproduct-free prenylation of hydantoins[†]

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Abstract

The ruthenium catalyst derived from Ru₃(CO)₁₂ and triphos [Ph₂P(CH₂CH₂PPh₂)₂] promotes the direct C–C coupling of isoprene with aryl substituted hydantoins 1a–1f at the diene C4-position to furnish products of *n*-prenylation 2a–2f. A mechanism involving hydantoin dehydrogenation followed by diene-imine oxidative coupling to furnish a transient aza-ruthenacyclopentene is proposed.

Metal catalyzed hydroaminoalkylation¹ was discovered by Maspero^{2a} and Nugent^{2b} in the early 1980's. These processes were inefficient and it was not until 2007 that the first high-yielding hydroaminoalkylations were reported by Hartwig, who employed a tantalum-based catalyst.³ Subsequently, other efficient early transition metal catalysts based on tantalum,³ titanium⁴ and niobium⁵ were developed. These early transition metal catalyzed hydroaminoalkylations largely focused on olefin partners, and withstanding one recent report of titanium catalyzed diene hydroaminoalkylation,^{4h} hydroaminoalkylations of other π -unsaturated reactants are unknown. For early transition metal catalysts, functional group compatibility and sensitivity to adventitious moisture pose serious limitations. Hence, it would be desirable to develop less sensitive late transition metal catalysts for hydroaminoalkylation. However, existing ruthenium⁶ and iridium⁷ based catalysts for hydroaminoalkylation require pyridyl directing groups and only have been applied to olefins. In this account, a ruthenium catalyst for diene hydroaminoalkylation is reported that does not require directing groups and employs hydantoins as aminoalkyl donors (Scheme 1).

Our initial experiments were inspired by two separate accounts in the literature. The first is Jun's report of the Ru₃CO₁₂ catalyzed hydroaminoalkylation of olefins employing 3-methyl-2-(*N*-benzyl-amino)pyridine (Scheme 1, top).^{6a} The second is our own report of the Ru₃CO₁₂ catalyzed hydrohydroxyalkylation of isoprene and myrcene employing substituted mandelic esters.⁸ Taken together, these data suggested the feasibility of isoprene mediated prenylations of α -amino acid derivatives catalyzed by zero-valent ruthenium complexes. Toward this end, a diverse set of *N*-protected phenyl-glycine esters were exposed to isoprene in the presence of Ru₃CO₁₂ and tricyclohexylphosphine, PCy₃, in toluene solvent at 130 °C. However, the anticipated products of prenylation were not observed. It was reasoned that the steric demand posed by formation of a fully substituted carbon center

[†]Electronic supplementary information (ESI) available: Characterization data for all new compounds (¹H NMR, ¹³C NMR, IR, LRMS). See DOI: 10.1039/c3cc43463j

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rendered the rate of C–C coupling prohibitively slow. Such steric effects are potentially mitigated for the *N*-benzyl hydantoin **1a** derived from phenylglycine. As hydantoin **1a** is sparingly soluble in toluene, THF solutions of hydantoin **1a** and isoprene were exposed to substoichiometric amounts of $\text{Ru}_3\text{CO}_{12}$ in the presence of various phosphine ligands. Ultimately, it was found that exposure of hydantoin **1a** (100 mol%) to isoprene (300 mol%) in the presence of the ruthenium(0) catalyst derived from $\text{Ru}_3\text{CO}_{12}$ (3 mol%) and triphos $[\text{Ph}_2\text{P}(\text{CH}_2\text{CH}_2\text{PPh}_2)_2]$ (12 mol%) at 140 °C in THF solvent (2 M) provides the prenylated adduct **3a** in 87% yield as determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard (Table 1).

These conditions were applied to C–C coupling of isoprene with aryl substituted hydantoins **1a–1f**. Due to the poor solubility of the prenylated adducts **3a–3f**, the yields determined by ^1H NMR analysis were significantly higher than the corresponding isolated yields due to loss of material in the course of purification by flash silica gel chromatography. Nevertheless, the products of prenylation **3a–3f** could be obtained in 58–76% yield. Both electron deficient and electron rich aryl substituents are tolerated. The reactions did prove to be somewhat sensitive to moisture, perhaps due to hydration of the transient dehydro-hydantoins (*vide supra*), which necessitated drying THF solvent *via* distillation from sodium-benzophenone ketyl and the drying of isoprene over molecular sieves. Under this initial set of conditions, alkyl substituted hydantoins are recovered unchanged from the reaction mixtures (Table 2). The products of hydroaminoalkylation offer several possibilities for further elaboration. For example, upon exposure of adduct **3a** to substoichiometric quantities of triflic acid, the product of hydroamination **4a** is formed in good yield (eqn (1)).⁹ Exposure of adduct **3a** to lithium aluminum hydride provides the vicinal diamine **5a** (eqn (2)).¹⁰

(1)

(2)

With regard to the catalytic mechanism, exposure of $\text{Ru}_3(\text{CO})_{12}$ to chelating phosphine ligands is known to provide discrete, monometallic complexes.¹¹ Oxidative coupling of isoprene **2** and *dehydro-1a* to form metallacycle **I** finds precedent in the work of Chatani and Murai on Pauson–Khand type reactions of 1,2-diones,¹² and studies from our laboratory.^{8,13,14} Isomerization of metallacycle **I** to metallacycle **II**, the presumably more stable primary σ -allyl haptomer, followed by protonolysis of metallacycle **II** by hydantoin **1a** provides complex **III**. β -Hydride elimination releases *dehydro-1a* and delivers the

alkylruthenium hydride **IV**,¹⁵ which upon C–H reductive elimination generates the product of hydroaminoalkylation and returns ruthenium to its zero-valent form (Scheme 2).

In summary, we report a ruthenium catalyst for diene hydroaminoalkylation that does not require directing groups and employs hydantoins as aminoalkyl donors. This process may be viewed as a formal imine addition from the amine oxidation level, representing a novel addition to the growing family of C–C bond forming transfer hydrogenations.¹⁶ Future studies will focus on the development of related hydroaminoalkylations catalyzed by late transition metals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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This Work: Directing group-free hydroaminoalkylation

Scheme 1.

Overcoming the requirement of directing groups in late transition metal catalyzed hydroaminoalkylation. Triphos = $[\text{Ph}_2\text{P}(\text{CH}_2\text{CH}_2\text{PPh}_2)_2]$.

Scheme 2.

Proposed mechanism for ruthenium(0) catalyzed hydroaminoalkylation *via* transfer hydrogenation.

Table 1

Selected optimization experiments in the hydroaminoalkylation of isoprene **2** with hydantoin **1a** to form the prenylated adduct **3a**

1a (100 mol%)		2		3a	
Entry	Ru ₃ (CO) ₁₂ (mol %)	Ligand	2 (mol %)	T (°C)	Time (h)	NMR yield (%)	
1	2	Pcy ₃	400	150	72	9	
2	2	iPrPPh ₂	400	150	72	20	
3	2	Ph ₂ PCH ₂ PPh ₂	400	150	72	26	
4	2	Cy ₂ P(CH ₂) ₂ PCy ₂	400	150	72	26	
5	2	PhP(CH ₂ CH ₂ PPh) ₂	400	150	72	37	
6	2	PhP(CH ₂ CH ₂ PPh) ₂	400	140	72	72	
7	2	PhP(CH ₂ CH ₂ PPh) ₂	600	140	72	81	
8	2	PhP(CH ₂ CH ₂ PPh) ₂	600	140	48	70	
9	2.5	PhP(CH ₂ CH ₂ PPh) ₂	600	140	48	77	
⇒10	3	PhP(CH ₂ CH ₂ PPh) ₂	600	140	48	87	

Table 2

Ruthenium catalyzed hydroaminoalkylation of isoprene **2** with hydantoin **1a–1f** to form prenylated adducts **3a–3f**^a

<p> 1a–1f (100 mol%) + 2 (600 mol%) $\xrightarrow[\text{THF (2M), 140 °C, 48 Hr}]{\text{Ru}_3\text{CO}_{12} \text{ (3 mol\%)}, \text{triphos (12 mol\%)}}$ 3a–3f </p>		
1a , Ar = Ph 1d , Ar = 4-MeO-Ph	1b , Ar = 4-i-Pr-Ph 1e , Ar = piperonyl	1c , Ar = 4-F-Ph 1f , Ar = 3-pyridyl
<p>3a, 75% (isolated) 87% (¹H NMR)</p>	<p>3b, 68% (isolated) 85% (¹H NMR)</p>	<p>3c, 71% (isolated) 84% (¹H NMR)</p>
<p>3d, 58% (isolated) 67% (¹H NMR)</p>	<p>3e, 59% (isolated) 70% (¹H NMR)</p>	<p>3f, 76% (isolated) 88% (¹H NMR)</p>

^aYields determined by ¹H NMR analysis employed 1,3,5-trimethoxybenzene as an internal standard. See ESI for further details.