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

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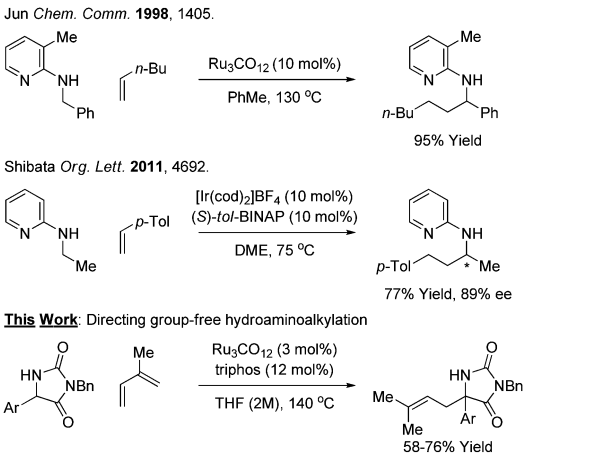
The ruthenium catalyst derived from $Ru_3(CO)_{12}$ and triphos $[Ph_2P(CH_2CH_2PPh_2)_2]$ promotes the direct C–C coupling of isoprene with aryl substituted hydantoins 1a–1f at the diene C4-position to furnish products of *n*-prenylation 2a–2f. A mechanism involving hydantoin dehydrogenation followed by diene-imine oxidative coupling to furnish a transient aza-ruthencyclopentene is proposed.

Metal catalyzed hydroaminoalkylation[1] 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] titanium[4] and niobium[5] 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 ruthenium[6] and iridium[7] 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 Ru_3CO_{12} catalyzed hydroaminoalkylation of olefins employing 3-methyl-2-(*N*-benzylamino)pyridine (Scheme 1, top).[6a] The second is our own report of the Ru_3CO_{12} catalyzed hydrohydroxyalkylation of isoprene and myrcene employing substituted mandelic esters.[8] Taken together,



Scheme 1 Overcoming the requirement of directing groups in late transition metal catalyzed hydroaminoalkylation. Triphos = $[Ph_2P(CH_2CH_2PPh_2)_2]$.

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 phenylglycine esters were exposed to isoprene in the presence of Ru_3CO_{12} and tricyclohexylphosphine, PCy_3, 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 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 Ru_3CO_{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 Ru_3CO_{12} (3 mol%) and triphos $[Ph_2P(CH_2CH_2PPh_2)_2]$ (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

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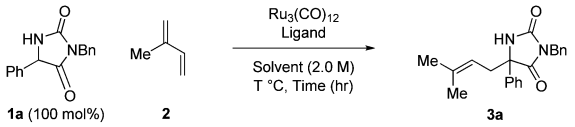
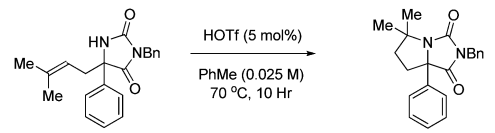
Table 1 Selected optimization experiments in the hydroaminoalkylation of isoprene **2** with hydantoin **1a** to form the prenylated adduct **3a**

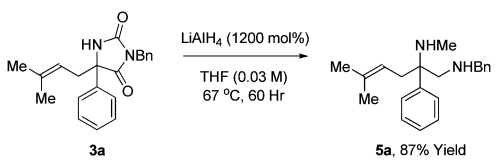


Entry	$Ru_3(CO)_{12}$ (mol%)	Ligand	2 (mol%)	T (°C)	Time (h)	NMR yield (%)
1	2	Pcy_3	400	150	72	9
2	2	$^{i}PrPPh_2$	400	150	72	20
3	2	$Ph_2PCH_2PPh_2$	400	150	72	26
4	2	$Cy_2P(CH_2)_2PCy_2$	400	150	72	26
5	2	$PhP(CH_2CH_2PPh)_2$	400	150	72	37
6	2	$PhP(CH_2CH_2PPh)_2$	400	140	72	72
7	2	$PhP(CH_2CH_2PPh)_2$	600	140	72	81
8	2	$PhP(CH_2CH_2PPh)_2$	600	140	48	70
9	2.5	$PhP(CH_2CH_2PPh)_2$	600	140	48	77
⇨10	3	$PhP(CH_2CH_2PPh)_2$	600	140	48	87

of the prenylated adducts **3a–3f**, the yields determined by ^{1}H 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 prenylatation **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 (*vida 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]



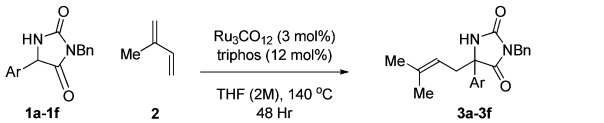
(1)



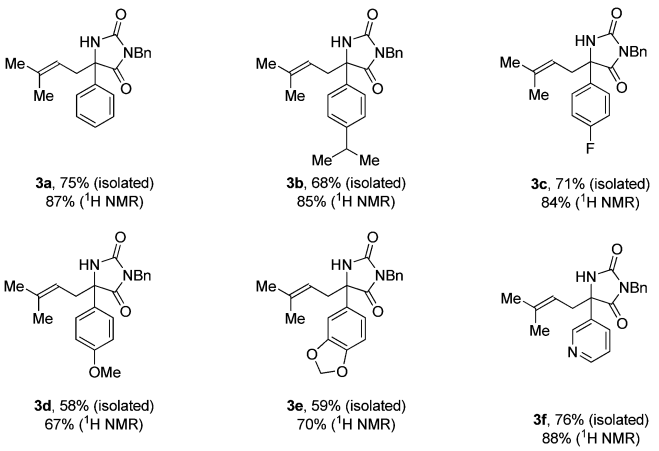
(2)

With regard to the catalytic mechanism, exposure of $Ru_3(CO)_{12}$ 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**.

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



1a, Ar = Ph **1b**, Ar = 4-i-Pr-Ph **1c**, Ar = 4-F-Ph
1d, Ar = 4-MeO-Ph **1e**, Ar = piperonyl **1f**, Ar = 3-pyridyl



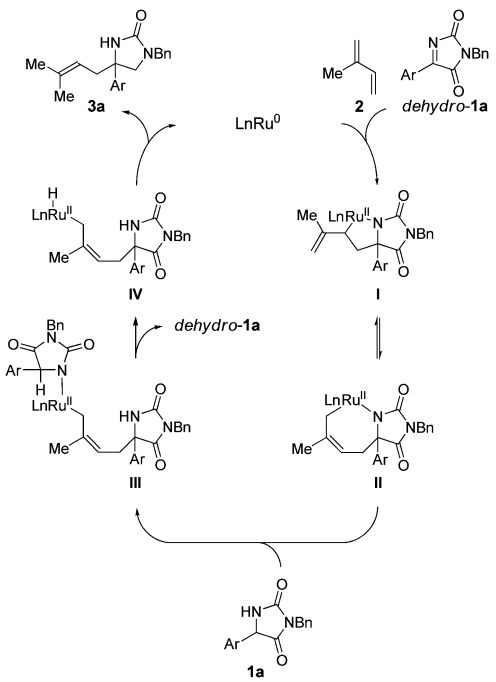
3a, 75% (isolated) 87% (^{1}H NMR) **3b**, 68% (isolated) 85% (^{1}H NMR) **3c**, 71% (isolated) 84% (^{1}H NMR)

3d, 58% (isolated) 67% (^{1}H NMR) **3e**, 59% (isolated) 70% (^{1}H NMR) **3f**, 76% (isolated) 88% (^{1}H NMR)

[a] Yields determined by ^{1}H NMR analysis employed 1,3,5-trimethoxybenzene as an internal standard. See ESI for further details.

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



Scheme 2 Proposed mechanism for ruthenium(0) catalyzed hydroaminoalkylation *via* transfer hydrogenation.

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.

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