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Reductive cyclization of halo-ketones to form 3-hydroxy-2-oxindoles via palladium catalyzed hydrogenation: a hydrogen-mediated Grignard addition

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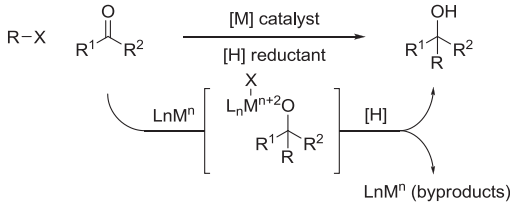
ABSTRACT

The reductive cyclization of *N*-oxoacyl *ortho*-bromoanilides to form 3-hydroxy-2-oxindoles under the conditions of palladium catalyzed hydrogenation is described. This work may be viewed as a prelude to intermolecular hydrogen-mediated Grignard-type reductive couplings of organic halides with carbonyl compounds.

1. Introduction

Carbonyl addition is a cornerstone of chemical synthesis.[1] The Grignard reaction,[2] the magnesium mediated reductive coupling of organic halides and carbonyl compounds, persists as one of the most broadly utilized methods for carbonyl addition. Despite its broad scope, operational simplicity and cost-effective nature, the Grignard reaction requires organomagnesium reagents, which are highly basic and, hence, moisture sensitive, and which generate stoichiometric quantities of metallic byproducts, posing challenges for use on scale.[3–5] Additionally, enantioselective variants of the Grignard addition have proven elusive.[6] These limitations are potentially addressed through the development of metal catalyzed organic halide-carbonyl reductive couplings, especially those employing non-metallic low molecular weight terminal reductants (Scheme 1).[7] The Nozaki-Hiyama-Kishi (NHK) reaction is perhaps the most notable metal catalyzed reaction of this type.[8] While enantioselective variants of the NHK reaction have been developed,[8] this process employs toxic chromium base catalysts and, as elemental manganese is used as terminal reductant, it does not circumvent generation of stoichiometric metallic byproducts.



Scheme 1. Transition metal catalyzed reductive carbonyl addition.

We have developed the first 'C–C bond forming hydrogenations' beyond hydroformylation, the largest volume application of homogeneous catalysis.[9] In these processes, π-unsaturated reactants are hydrogenated in the presence of carbonyl compounds or imines to furnish products of reductive coupling.[10] As catalytic hydrogenation is used routinely for the reduction of organic halides to form the corresponding C–H compounds,[11] we became attracted to the prospect of capturing the intervening organometallic species via carbonyl addition. Such hydrogen-mediated organic halide-carbonyl reductive couplings would bypass the generation of stoichiometric metallic byproducts and potentially provide a conduit to enantiomerically enriched adducts. The feasibility of hydrogen-mediated Grignard-type reactions is supported by reports of related halo-ketone reductive cyclizations under the conditions of transfer hydrogenation, wherein alcohols[12] or tertiary amines[13–15] are utilized as terminal reductants (Scheme 2, Eq. 1–3).[16,17] Here, we demonstrate palladium catalyzed hydrogenation of *N*-oxoacyl

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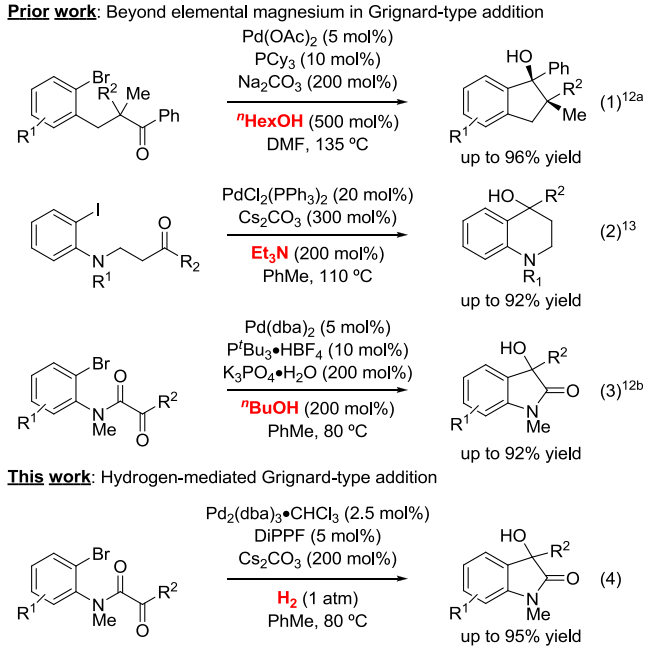
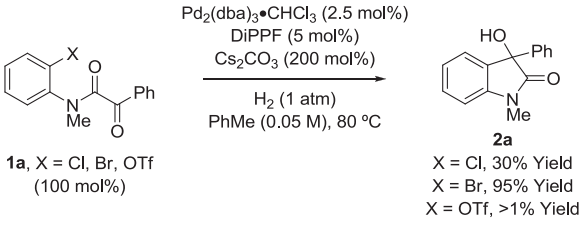
ortho-bromoanilides promotes reductive cyclization to form 3-hydroxy-2-oxindoles in good to excellent yield with complete suppression of conventional aryl halide hydrogenolysis pathways (Scheme 2, Eq. 4).



Scheme 2. Reductive cyclization of aromatic halo-ketones in the absence of stoichiometric metals.

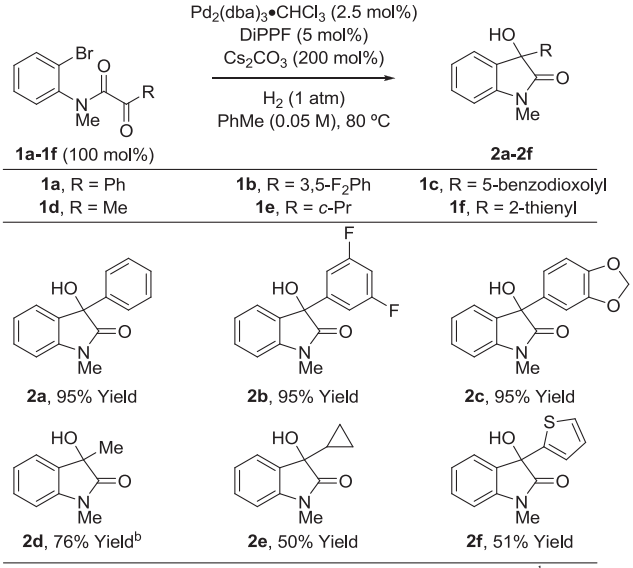
2. Results and discussion

Initial experiments focused on the reductive cyclization of α-ketoamides **1a** (X=Br) under hydrogenation conditions using $Pd_2(dba)_3$•$CHCl_3$ as precatalyst in combination with various phosphine ligands (Eq. 5). Gaseous hydrogen was introduced simply using balloons. Several phosphine ligands were tested for this transformation, for example, 1,1′-bis(di-*tert*-butylphosphino)ferrocene (DtBPF, 55% yield), XPhos (64% yield), and 1,2-bis(dicyclohexylphosphino)ethane (DCyPE, 68% yield). The palladium catalyst modified by the chelating phosphine ligand 1,1′-bis(di-*iso*-propylphosphino)ferrocene (DiPPF) provided the best results, enabling formation of 3-hydroxy-2-oxindole **2a** in 95% yield after isolation by silica gel flash column chromatography. The use of Cs_2CO_3 as base is important, as substantially diminished isolated yields were observed in reactions using Na_2CO_3 (trace conversion), K_2CO_3 (47% yield) or K_3PO_4 (20% yield) under otherwise identical conditions, which may, in part, be due to solubility. Under the indicated conditions (Eq. 5), the corresponding *ortho*-chloro ketoamide **1a** (X=Cl) provided **2a** in 30% yield due to a combination of incomplete conversion and hydrogenolysis of the chloride. The triflyl derivative of ketoamide **1a** (X=OTf) did not convert to oxindoles **2a** under these conditions due to hydrolysis to form the phenol.[14]



Using the following conditions, $Pd_2(dba)_3$•$CHCl_3$ (2.5 mol %), DiPPF (5 mol %), Cs_2CO_3 (200 mol %) in toluene (0.05 M) at 80 °C in the presence of H_2 (1 atm) the reductive cyclization of α-ketoamides **1a**–**1f** was explored (Table 1). The hydroxy oxindoles **2a**–**2f** were obtained in moderate to excellent yields. Aryl **2a**–**2c**, alkyl **2d**–**2e**, and heteroaryl **2f** groups at the C3 position of the resulting oxindoles **2a**–**2f** were tolerated. Reactants **1a**–**1c** that incorporate aryl substituents gave uniformly better results compared to reactants incorporating alkyl groups (**1d**–**1e**) or heteroaryl groups (**2f**).[18]

Table 1
Reductive cyclization of α-ketoamides **1a**–**1f** under the conditions of palladium catalyzed hydrogenation[a]



[a]Yields are of material isolated by silica gel chromatography. [b]K_2CO_3 (200 mol%).[18]

To further probe the scope of this process, compounds **1g** and **1h**, derived from 2-amino-3-bromopyridine and 4-amino-3-bromopyridine, respectively, were subjected to standard conditions for reductive cyclization (Eq. 6,7). Compound **1g** was transformed to 6-aza-3-hydroxy-2-oxindole **2g** in good yield (Eq. 6). For compound **1h**, only trace quantities of the 4-aza-3-hydroxy-2-oxindole **2h** were observed under standard conditions. Elevated temperatures (130 °C) were required to enforce conversion to the 4-aza-3-hydroxy-2-oxindole **2h**, which was isolated in 30% yield along with dehalogenated material (Eq. 7).[18] The diminished reactivity of **1h** may be due to coordination of the less hindered pyridyl nitrogen to the palladium catalyst.