

## Reduction Reactions

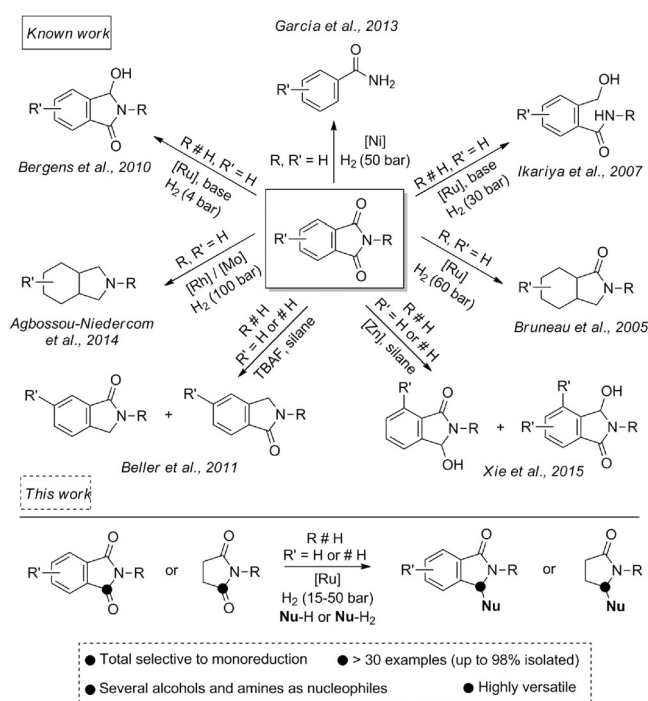
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## Selective Ruthenium-Catalyzed Reductive Alkoxylation and Amination of Cyclic Imides

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**Abstract:** Reported herein, for the first time, is the selective ruthenium-catalyzed reductive alkoxylation and amination of phthalimides/succinimides. Notably, this novel methodology avoids hydrogenation of the aromatic ring and allows methoxylation of substituted imides with good to excellent selectivity for one of the carbonyl groups. The reported method opens the door to the development of new processes for the selective synthesis of various functionalized *N*-heterocyclic compounds. As an example, intramolecular reductive couplings to afford tricyclic compounds are presented for the first time.

Isindolinones and their derivatives constitute attractive building blocks for organic synthesis and represent valuable scaffolds in pharmaceuticals and agrochemicals with diverse biological activities.<sup>[1]</sup> Because of the continuing interest in this class of heterocyclic compounds, in the last years several improved procedures for their synthesis have been developed.<sup>[2]</sup> Among them, the selective monoreduction of easily available phthalimides represents a most convenient and straightforward approach. Unfortunately, in general, stoichiometric amounts of either zinc or tin in the presence of acid, or the use of inorganic metal hydrides have to be employed in these transformations, and thus limits functional-group compatibility and generates significant amounts of waste-products.<sup>[3]</sup> In addition, reductions in the presence of different heterogeneous catalysts have been disclosed under harsher reaction conditions.<sup>[4]</sup> So far only a small number of defined organometallic complexes have been developed for the hydrogenation and hydrosilylation of cyclic imides (Scheme 1). Originally, Patton and Drago reported the hydrogenation of *N*-methylsuccinimide in low yields by using a ruthenium catalyst.<sup>[5]</sup> More recently, Bruneau and co-workers reported an elegant ruthenium-catalyzed hydrogenation of cyclic imides<sup>[6]</sup> with concomitant hydrogenation of the aromatic ring. Later on, Ikariya and co-workers presented the dihydrogenation of cyclic imides to the corresponding ring-opened alcohol-amide products.<sup>[7]</sup> Notably, the group of Bergens reported a ruthenium/base-catalyzed monohydrogenation of phthalimides to give hydroxy lactams, albeit in low yields with limited substrate scope.<sup>[8]</sup> In 2011, our group reported the first selective monoreduction of phthalimides



**Scheme 1.** Different reported examples of homogeneous catalytic reduction of phthalimides using hydrogen or silanes. TBAF = tetra-*n*-butylammonium fluoride.

under mild reaction conditions using hydrosilanes as reducing agents.<sup>[9]</sup> García et al. reported the nickel-catalyzed reduction of phthalimide to benzamide and the carbonyl monohydrogenation of phthalimide without reduction of the aromatic ring but no general substrate scope was presented.<sup>[10]</sup>

Most recently, Agbossou-Niedetcom et al. reported the rhodium/molybdenum-catalyzed full reduction of cyclic imides (Scheme 1).<sup>[11]</sup> Finally, this year Xie et al. reported the zinc-catalyzed reduction of cyclic imides with hydrosilanes.<sup>[12]</sup> In any case, selective reduction of one of the carbonyl groups was not achieved for aryl ring-substituted phthalimides.

In recent years, the so-called ruthenium/Triphos catalyst system [Triphos = 1,1,1-tris(diphenylphosphinomethyl)-ethane] showed unique activity for methylation of amines with carbon dioxide<sup>[13]</sup> and hydrogenation of carboxylic acid derivatives.<sup>[4b,14]</sup> Inspired by this work, the hydrogenation of *N*-methylphthalimide (**1a**) in the presence of [Ru(acac)<sub>3</sub>], Triphos, and an organic acid [methanesulfonic acid (MSA)] as co-catalyst was selected as a starting point of the present investigation.<sup>[15]</sup> Firstly, the hydrogenation of this benchmark substrate was conducted at 50 bar of H<sub>2</sub>, 130 °C, and using

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methanol as a solvent. To our surprise, an unprecedented reductive methoxylation of one of the carbonyl groups occurred, thus affording 3-methoxy-2-methylisoindolin-1-one (**2a**) in 91% yield (see entry 1 in Table SI1 in the Supporting Information). When the reaction was carried out with simple  $[\text{Ru}(\text{acac})_3]$ , the aryl ring-hydrogenated product 2-methyloctahydro-1*H*-isoindole-1,3(2*H*)-dione (**4a**) was afforded in good yield (76%), and traces of 2-methyloctahydro-1*H*-isoindol-1-one (**3a**) were formed by the concomitant ring and carbonyl reduction (see Table SI1, entry 2). Most likely, ruthenium nanoparticles are formed here. Under otherwise identical reaction conditions, the use of the  $[\text{Ru}(\text{acac})_3]/\text{Triphos}$  system in the absence of any cocatalyst generated **3a** in only 22% yield and the lactone isobenzofuran-1(3*H*)-one (**5a**) as the major product (see Table SI1, entry 3). A plausible route for the formation of **5a** involves C–N bond cleavage of the cyclic imide, followed by the reduction of the aldehyde to the alcohol and cyclization after release of methylamine. By using a combination of  $[\text{Ru}(\text{acac})_3]/\text{MSA}$  in the absence of Triphos, only **3a** and **4a** were observed (see Table SI1, entry 4).

Next, the influence of the amount of acid cocatalyst was investigated in more detail (see Table SI1, entries 5–7). Applying 4 mol% of MSA afforded a quantitative yield of **2a**. Gratifyingly, the reaction also proceeded well when using much lower amounts of the catalyst (see Table SI1, entries 9–13). In addition, the influence of hydrogen pressure and temperature were studied as critical parameters. To our delight, **2a** was obtained from **1a** in excellent yield (>99%) at 15 bar of hydrogen (see Table SI1, entry 16). However, when the reaction was conducted at 100°C, **2a** was obtained in lower yield (49%); see Table SI1, entry 18). By comparing different ruthenium pre-catalysts and phosphine ligands (see Tables SI2 and SI3 in the Supporting Information) it was observed that the initially used  $[\text{Ru}(\text{acac})_3]/\text{Triphos}$  system<sup>[14b,d,g,15,16]</sup> was the best, but similar results were also obtained with  $[\text{Ru}(\text{cod})(2\text{-methylallyl})_2]$  (cod = 1,5-cyclooctadiene).

With these findings in hand, we decided to study the reductive methoxylation of a wide range of *N*-substituted phthalimides (Table 1). In the case of *N*-alkyl-substituted phthalimides (**1a–d**), the reaction afforded the compounds **2a–d** in up to 92% yield upon isolation (entries 1–4). For phthalimides with alkyl substituents containing a C≡C bond (**1e–f**), methoxylated products (**2e–f**) with a reduced triple bond were obtained in good to excellent yields (entries 5 and 6). Other alkyl-substituted phthalimides containing heteroatoms (**1g–i**) also gave 2-methoxylated products (**2g–i**) in very good yields (entries 7–9). It is noteworthy that for **1h** the ketone group was reduced but not methoxylated, whereas for **1i** the dimethoxylated compound **2i** was obtained. In addition, *N*-substituted phthalimides with aryl or benzyl groups (**1j–l**) afforded the corresponding products **2j–l** in high yields (entries 10–12). Interestingly, the reaction also performed well for the tetrafluoro-substituted derivative **1m** to give the compound **2m** in good yield (entry 13).

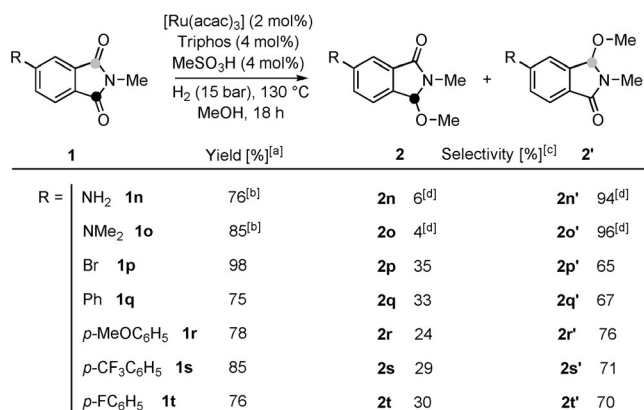
Next, we studied the reduction of more challenging aryl-ring-substituted *N*-methylphthalimides (Scheme 2). To the best of our knowledge regioselective hydrogenations have not

**Table 1:** Ruthenium-catalyzed reductive methoxylation of different substituted phthalimides.

Entry <sup>[a]</sup>	Phthalimide <b>1</b>	Product <b>2</b>	Yield [%] <sup>[b]</sup>
1		<b>2a</b> (R' = Me)	94
2	<b>1b</b>	<b>2b</b> (R' = Et)	85
3	<b>1c</b>	<b>2c</b> (R' = <i>i</i> -Pr)	92
4	<b>1d</b>	<b>2d</b> (R' = <i>n</i> -Bu)	88
5			65
6 <sup>[c]</sup>			86
7 <sup>[d]</sup>			88
8			75
9			96
10			83
11 <sup>[d]</sup>			75
12 <sup>[e]</sup>			83
13 <sup>[c,f]</sup>			76

[a] Standard reaction conditions: Phthalimide (0.5 mmol),  $[\text{Ru}(\text{acac})_3]$  (1 mol%), Triphos (1.2 mol%),  $\text{MeSO}_3\text{H}$  (2 mol%),  $\text{H}_2$  (15 bar), MeOH (2 mL), 130°C, and 18 h. [b] Yield of isolated product. [c] Run with  $[\text{Ru}(\text{acac})_3]$  (4 mol%), Triphos (5 mol%), and  $\text{MeSO}_3\text{H}$  (8 mol%). [d] Run for 6 h. [e] Run for 3 h. [f] Run at 50 bar of  $\text{H}_2$ . acac = acetylacetonate.

been achieved yet. Substrates containing electron-donor groups, such as 4- $\text{NH}_2$  (**1n**) and 4- $\text{NMe}_2$  (**1o**), on the aromatic ring gave excellent selectivities (>94%) in the methoxylation

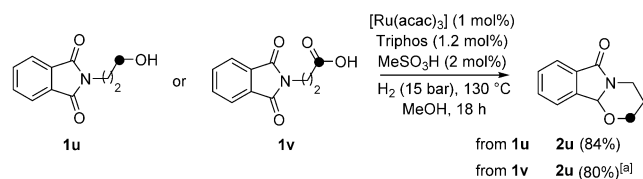


**Scheme 2.** Ruthenium-catalyzed selective reductive methoxylation of different partially aryl-ring-substituted N-methylphthalimides. [a] Combined yield of the two isolated regioisomers. [b] Yield of the isolated major regioisomer. [c] Selectivity was determined by  $^1\text{H}$  NMR analysis (see the Supporting Information). [d] Selectivity was calculated by GC-MS.

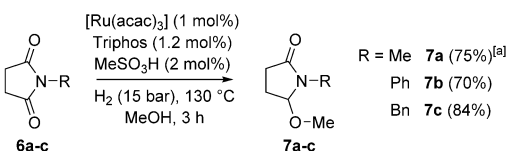
of one of the carbonyl groups, thus affording **2n'** (94 %) and **2o'** (96 %), respectively. When the phthalimide aromatic ring contains an electron-withdrawing group, such as Br, or an aryl substituent (**1p–t**),<sup>[17]</sup> good to excellent yields of the corresponding products were achieved (76–98 %) with good regioselectivities (65–76 %).

Interestingly, the reaction can also be carried out in intramolecular fashion (Scheme 3). Using phthalimide derivatives **1u** and **1v**, the tricyclic compound **2u** was obtained in excellent yield in both cases. Remarkably, this protocol can also be applied for the selective methoxylation of N-substituted succinimides (**6a–c**), thus affording the corresponding 2-methoxysuccinimides **7a–c** in up to 84 % yield (Scheme 4).

The generality of this reductive alkoxylation protocol was further investigated by reaction of **1a** with different alcohols



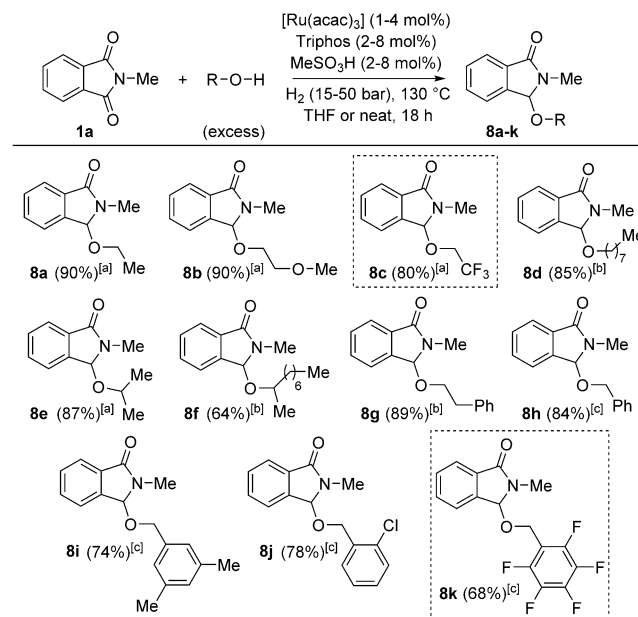
**Scheme 3.** One-pot ruthenium-catalyzed intramolecular reductive cyclization of **1u** and **1v** to give the compound **2u**. Yields of the isolated product are given. [a] Run with  $[\text{Ru}(\text{acac})_3]$  (4 mol%), Triphos (8 mol%),  $\text{MeSO}_3\text{H}$  (8 mol%).



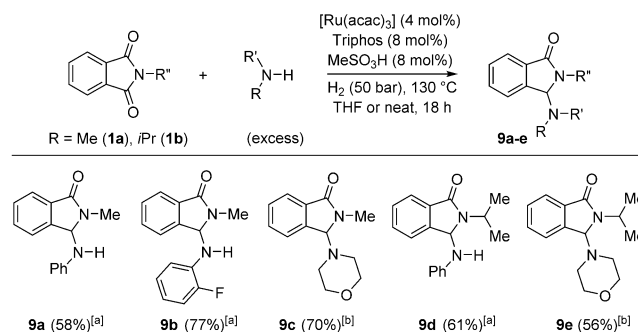
**Scheme 4.** Ruthenium-catalyzed selective reductive methoxylation of N-substituted succinimides. Yields of the isolated product are given. [a] Run for 18 h.

either under neat conditions or in the presence of an excess of alcohol using THF as the solvent (Scheme 5; see Table SI4 in the Supporting Information). To our delight, primary and secondary aliphatic alcohols, as well as phenethyl and benzylic ones gave the corresponding 2-alkoxylated isoindolinones with good to excellent yields (**8a–k**). It should be noted that this methodology allows to obtain fluorinated isoindolinone derivatives in a straightforward manner (**8c** and **8k**).

Finally, instead of alcohols we envisioned the possibility of using amines for a selective reductive amination of phthalimides. As shown in Scheme 6, **1a** and **1b** can be directly



**Scheme 5.** Ruthenium-catalyzed selective reductive alkoxylation of **1a** with alcohols. Yields of the isolated product are given. [a] Reaction conditions: **1a** (0.5 mmol),  $[\text{Ru}(\text{acac})_3]$  (1 mol%), Triphos (1.2 mol%),  $\text{MeSO}_3\text{H}$  (2 mol%),  $\text{H}_2$  (15 bar), alcohol (2 mL),  $130^\circ\text{C}$  and 18 h. [b] Run with  $[\text{Ru}(\text{acac})_3]$  (4 mol%), Triphos (8 mol%),  $\text{MeSO}_3\text{H}$  (8 mol%), alcohol (7.5 mmol, 15 equiv),  $\text{H}_2$  (50 bar), THF (1 mL), and  $150^\circ\text{C}$ . [c] Run with  $[\text{Ru}(\text{acac})_3]$  (2 mol%), Triphos (4 mol%),  $\text{MeSO}_3\text{H}$  (4 mol%), alcohol (7.5 mmol, 15 equiv),  $\text{H}_2$  (50 bar), and THF (1 mL). THF = tetrahydrofuran.



**Scheme 6.** Ruthenium-catalyzed selective reductive amination of **1a** and **1b** with amines. Yields of the isolated product are given. [a] Run with amine (7.5 mmol, 15 equiv) and THF (1 mL). [b] Run with amine (2 mL) as solvent.



aminated, thus affording the corresponding 2-aminated isoindolinones (**9a–e**) in moderate yields. Other types of amines could be used for this transformation.

In conclusion, we demonstrate the first reductive alkoxylation and amination of substituted phthalimides using hydrogen as a reducing agent. By using a [Ru/Tripfos]-based catalyst system in combination with an organic acid, N-substituted phthalimides react with a wide range of alcohols and amines, thus affording the corresponding 2-substituted isoindolinones in good to excellent yields. For aryl-ring-substituted phthalimides an excellent selectivity for the reduction of one of the carbonyl groups has been also achieved for the first time. In addition, the reaction also proceeds successfully in an intramolecular fashion to give tricyclic compounds in high yields. It is shown that N-substituted succinimides can also undergo this transformation successfully.

### Experimental Section

General procedure for the reductive alkoxylation or amination of cyclic imides: A 4 mL glass vial containing a stirring bar was sequentially charged with cyclic imide (0.5 mmol), [Ru(acac)<sub>3</sub>], Tripfos, alcohol or amine (15 equiv), and a freshly prepared 0.2 M MeOH or THF solution of the cocatalyst MeSO<sub>3</sub>H. Afterwards, the reaction vial was capped with a septum equipped with a syringe and set in the alloy plate, which was then placed into a 300 mL autoclave. Once sealed, the autoclave was purged three times with 30 bar of hydrogen, then pressurized to 15–50 bar and placed into an aluminum block, which was preheated at 130–150 °C. After 3–18 h, the autoclave was cooled in an ice bath, and the remaining gas was carefully released. Finally, reaction mixture was purified by silica gel column chromatography (*n*-heptane/ethyl acetate mixtures).

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