## **Ruthenium Pincer-Catalyzed Cross-Dehydrogenative Coupling** of Primary Alcohols with Secondary Alcohols under Neutral Conditions

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Received: May 24, 2012; Published online:

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200438.

**Abstract:** Cross-dehydrogenative coupling of primary alcohols with secondary alcohols to obtain mixed esters with the liberation of molecular hydrogen is achieved in high yield and good selectivity under neutral conditions, using a bipyridyl-based PNN ruthenium(II) pincer catalyst.

**Keywords:** cross-esterification; dehydrogenation; homogeneous catalysis; oxidative coupling; ruthenium pincer complexes

Alcohol esterification is one of the most fundamental reactions in synthetic organic chemistry.<sup>[1]</sup> It has various applications in the production of synthetic intermediates, biologically active natural products, fragrances, polymers, polyesters, plasticizers, fatty acids, paints and pharmaceuticals.<sup>[2]</sup> The reaction is usually performed by coupling of a carboxylic acid or its derivative (acid chloride or acid anhydride) with an al-cohol.<sup>[3]</sup> Transesterification is also a very useful reaction.<sup>[4]</sup> In recent years, much attention has been directed at the search for environmentally benign esterification methods.<sup>[5]</sup> Although several catalytic dehydrogenative esterifications of primary alcohols to esters have been reported so far,<sup>[5f,k-r,7b,d]</sup> less attention has been paid to the oxidative cross-esterification reactions. Available oxidative cross-esterification methods are limited to methyl esterification of primary alcohols<sup>[6]</sup> and palladium-catalyzed oxidative crossesterification of primary alcohols using oxygen.<sup>[5c,d]</sup> None of these cross-esterification reactions is based on the generation of molecular hydrogen, or use of a secondary alcohol, which, being more bulky, is expected to be less reactive. The ruthenium-catalyzed  $\beta$ - alkylation of secondary alcohols with primary alcohol is known.  $\ensuremath{^{[7]}}$ 

We have developed several environmentally benign reactions catalyzed by pincer complexes of ruthenium based on pyridine<sup>[8]</sup> and acridine backbones,<sup>[9]</sup> including dehydrogenative coupling of primary alcohols to give esters,<sup>[8b,d,g]</sup> the dehydrogenation of secondary al-cohols to give ketones,<sup>[8a,d]</sup> the hydrogenation of esters to give alcohols,<sup>[8c,g]</sup> efficient synthesis of amides<sup>[8e,g]</sup> and imines<sup>[10]</sup> from alcohols and amines, acylation of alcohols using esters,<sup>[8h]</sup> and amidation of esters.<sup>[8i]</sup> Recently we have prepared the Ru-bipyridine-based pincer complex 1 (Figure 1) and explored its catalytic activity toward the hydrogenation of amides,<sup>[11a]</sup> bio-mass-derived cyclic diesters,<sup>[11b]</sup> and urea derivatives<sup>[12]</sup> as well as organic carbonates, carbamates and formates.<sup>[13]</sup> These reactions are thought to involve a new mode of metal-ligand cooperation based on ligand aromatization-dearomatization which has also led to C-H activation<sup>[14a,b]</sup> and N-H activation<sup>[14c]</sup> reactions, and to consecutive water splitting.<sup>[14d]</sup>

Here we report on the dehydrogenative cross-coupling of primary alcohols with secondary alcohols catalyzed by complex **1** under mild, neutral conditions (Scheme 1).

Complex **1** was prepared as described in our previous report.<sup>[11a]</sup> When a toluene solution containing



Figure 1. Dearomatized Bipy-PNN ruthenium pincer complex.

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Adv. Synth. Catal. 0000, 000, 0-0

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**Scheme 1.** Cross-esterification between primary and secondary alcohols.

hexanol and cyclohexanol (3 mmol each) and 0.03 mmol of complex **1** was refluxed under an argon atmosphere, cyclohexyl hexanoate was obtained in 79% yield, together with 16% hexyl hexanoate (by the self-esterification of hexanol) and 12% of cyclohexanone (by dehydrogenation of cyclohexanol), as

Table 1. Dehydrogenative	cross-coupling	of primary	and	secondary	alcohols	cata-
lyzed by <b>1</b> . <sup>[a]</sup>						

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Entry	Primary alcohol	Secondary alcohol	Cross ester	Time [h]	Yield [%]
1	ОН	но-	~0	24	93 (79) <sup>[b]</sup>
2	ОН	но-🔿 ~	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	26	63
3	ОН	но-🔿 🔨	0 	26	90
4	ОН	но-{	~~~o	26	93
5	ОН	HO $\prec^{Ph}_{CH_3}$	$\sim 0$ $\sim Ph$ $\sim CH_3$	26	58
6	∽∽∽он	но-	~~~~o~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	25	95
7	₩	но-	~0	24	96
8	∽∽∽он	HO≺ <sup>Ph</sup> CH₃	$\sim 0$ Ph $\sim 0$ $\sim CH_3$	38	46
9	ОН	но-	~O	25	95
10	ОН	но-	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	26	93
11	∽∕он	но-		26	70
12	Ч∽он	но-		25	99
13	↓он	но-		25	95
14	MeO	но-		24	98
15	Ph <sup>^^</sup> OH	но-	O Ph <sup>L</sup> O-	24	91

<sup>[</sup>a] Complex 1 (0.03 mmol), primary alcohol (3 mmol), secondary alcohol (7.5 mmol) and toluene (2 mL) were refluxed (oil bath temperature 135 °C) under argon. Yields of products were determined by GC using *m*-xylene as internal standard.

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<sup>&</sup>lt;sup>[b]</sup> The yield in parenthesis was obtained when equimolar amounts of hexanol and cyclohexanol were employed.

determined by GC and confirmed by GC-MS (Table 1, entry 1). The relatively selective formation of the ester of the secondary alcohol is noteworthy. Although use of equivalent amounts of the secondary and primary alcohols resulted in good yield of the cross-esterification product, a higher yield was obtained when excess of the secondary alcohol was used, as expected. Thus, when a toluene solution containing 3 mmol hexanol, 7.5 mmol of cyclohexanol and 0.03 mmol of complex 1 was refluxed under an argon atmosphere, a 93% yield of cyclohexyl hexanoate (based on hexanol) was obtained (Table 1, entry 1). Cyclohexanone (34%) was also formed. Pure cyclohexyl hexanoate was isolated by evaporation of the solvent followed by silica gel chromatography and analysis by NMR and GC-MS.

Studying the scope of this reaction with regard to cyclic secondary alcohols, the reaction of 1-hexanol with cyclopentanol in the presence of 1 mol% of 1 (entry 2) resulted after 26 h reflux in toluene in the formation of cyclopentyl hexanoate (63% yield), accompanied by hexyl hexanoate as side product (25% yield). Reaction of 1-hexanol with cycloheptanol under the same conditions gave cycloheptyl hexanoate in 90% yield (entry 3) and hexyl hexanoate (8%).

Expanding the scope of the reaction to acyclic secondary alcohols, the optimized reaction conditions were applied to 3-pentanol and 1-phenylethanol. Reaction of 3-pentanol with 1-hexanol gave the crossester in 93% yield (entry 4), while in the case of 1phenylethanol the cross-ester was formed in 58% yield (entry 5) in addition to hexyl hexanoate (25% yield). The lower yield of the cross-esterification product is a result of facile dehydrogenation of 1-phenylethanol to acetophenone (46%).

Next we studied the reaction of 1-pentanol with various secondary alcohols. Reaction of 3 mmol of 1-pentanol with 7.5 mmol cyclohexanol led to a 95% yield of cyclohexyl pentanoate after 25 h (entry 6). Upon refluxing of 1-pentanol with 3-pentanol in toluene, a 96% yield of the cross-ester were formed (entry 7). Only a trace of pentyl pentanoate was detected by GC-MS, while in both cases cyclohexanone was formed in 35% yield. The reaction of 1-pentanol with 1-phenylethanol after 38 h gave the cross-ester (46% yield) (entry 8) and acetophenone (58% yield).

Exploring further the scope with regard to the primary alcohol, 1-butanol was reacted with cyclohexanol, resulting in a 95% yield of cyclohexyl butyrate (entry 9) after 25 h. In a similar reaction with 3-pentanol and cycloheptanol 93% and 70% yields of the cross-esterification products, respectively, were formed after 26 h (entries 10 and 11). In the case of cycloheptanol, butyl butyrate (28% yield) was also formed but in the cases of reactions of butanol with cyclohexanol and with 3-pentanol only a trace amount of butyl butyrate was noted by GC-MS.

Excellent yields of the cross-esterification products were obtained also with the primary alcohols 3methyl-1-butanol and 2-methoxyethanol (entries 12, 13, and 14). Reaction of benzyl alcohol with cyclohexanol resulted in a 91% yield of cyclohexyl benzoate (entry 15) together with 34% of cyclohexanone.

Interestingly, the dehydrogenation of the secondary alcohols to the corresponding ketones is slower than the dehydrogenative coupling of the alcohol to ester, generally resulting in the desired cross-esters in excellent yields. In addition, the self-esterification product is observed only as a minor product, if at all.

A possible catalytic cycle for the cross-esterification of primary and secondary alcohols likely involves O– H activation of the primary alcohol followed by  $H_2$ elimination to give an intermediate aldehyde, which forms a hemiacetal with the secondary alcohol. Dehydrogenation of the hemiacetal yields the cross-ester, similar to the proposed mechanism of dehydrogenative self-coupling of primary alcohols to esters.<sup>[8b,g]</sup> The self-esterification product of the primary alcohol, if formed, can be converted to the desired cross-ester by transesterification.<sup>[8h]</sup>

In conclusion, the new cross-esterification reaction of primary alcohols with secondary alcohols is efficiently catalyzed by the dearomatized complex **1** under neutral conditions. In most of the cases the yield of the cross-ester is excellent, although in some cases a small amount of the homocoupling product of the primary alcohol is observed. In most of the cases a ketone side product, generally obtained in low yield by dehydrogenation of the secondary alcohol was observed. This reaction offers an efficient, mild method for the dehydrogenative cross-coupling of primary and secondary alcohols under neutral conditions.

### **Experimental Section**

# General Procedure for the Cross-Esterification Reaction

Complex 1 (0.03 mmol), primary alcohol (3 mmol), secondary alcohol (7.5 mmol) and toluene (2 mL) were added to a Schlenk flask under an atmosphere of nitrogen in a Vacuum Atmospheres glovebox. The flask was equipped with a condenser and the solution was refluxed with stirring in an open system under argon for the specified time (Table 1) at 135 °C oil bath temperature. The reaction products were analyzed by GC-MS. After cooling to room temperature, *m*-xylene (1 mmol) was added as internal standard to the reaction mixture and the products were quantitatively analyzed by GC using a Carboxen 1000 column on an HP 690 series GC system or HP-5 cross linked 5% PH ME Siloxane column (30 m×0.32 mm×0.25 mm film thickness) on an HP 6890 series GC system. Pure esters were obtained by

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silica gel chromatography. Characterization data are available in the Supporting Information.

#### Acknowledgements

This research was supported by the European Research Council under the FP7 framework (ERC No 246837), by the Israel Science Foundation, and by the Helen and Martin Kimmel Center for Molecular Design. D. M. holds the Israel Matz Professorial Chair of Organic Chemistry.

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#### COMMUNICATIONS

Ruthenium Pincer-Catalyzed Cross-Dehydrogenative Coupling of Primary Alcohols with Secondary Alcohols under Neutral Conditions

Adv. Synth. Catal. 2012, 354, 1-5

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