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Chemoselectivity

Atmosphere-Controlled Chemoselectivity: Rhodium-Catalyzed Alkylation and Olefination of Alkylnitriles with Alcohols

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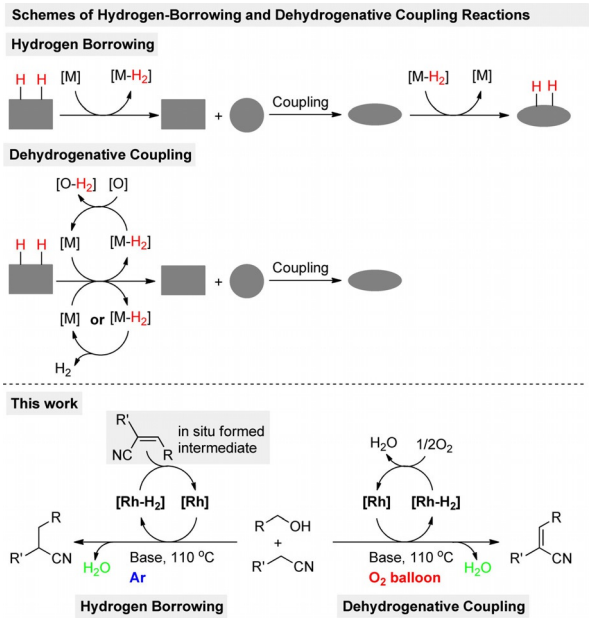
In memory of Takao Ikariya

Abstract: The chemoselective alkylation and olefination of alkylnitriles with alcohols have been developed by simply controlling the reaction atmosphere. A binuclear rhodium complex catalyzes the alkylation reaction under argon through a hydrogen-borrowing pathway and the olefination reaction under oxygen through aerobic dehydrogenation. Broad substrate scope is demonstrated, permitting the synthesis of some important organic building blocks. Mechanistic studies suggest that the alkylation product may be formed through conjugate reduction of an alkene intermediate by a rhodium hydride, whereas the formation of olefin product may be due to the oxidation of the rhodium hydride complex with molecular oxygen.

Dehydrogenation has been used in organic synthesis as a strategy to activate inert molecules.[1] A metal catalyst is generally employed to dehydrogenate a substrate to generate a more reactive intermediate and a metal hydride (Scheme 1, top). The activated intermediate could couple with other molecules to form more complex molecules, the unsaturated bonds of which could then be reduced to furnish a hydrogen-borrowing/-autotransfer process.[1d,2] Alternatively, the metal hydride could be protonated to release hydrogen gas or accepted by an oxidant to accomplish a dehydrogenative coupling process (Scheme 1, middle).[1a–c,e,2e] The selectivity between these two processes has rarely been addressed but appears to be determined by the nature of catalyst used, and different catalysts are required to achieve either hydrogen-borrowing or dehydrogenative coupling. The chemoselective access to both hydrogen-borrowing and dehydrogenative coupling products with a single catalyst is mechanistically interesting and practically useful. However, such catalysts are rare. Kaneda and co-



Scheme 1. Controlling the chemoselectivity between hydrogen-borrowing and dehydrogenative coupling reactions.

workers reported a heterogeneous Ru catalyst for the α-alkylation of nitriles with alcohols through hydrogen borrowing under argon at 180 °C.[3] The Ru catalyst could also catalyze the formation of olefin products under an oxygen atmosphere, but this necessitates a two-step operation.[4] Zhang and Hanson showed that 4 Å molecular sieves could alter the chemoselectivity between imines[5] and amines[6] in a cobalt-pincer-catalyzed coupling of amines and alcohols. Our group recently demonstrated that iridacycle catalysts could also enable both the hydrogen-borrowing reaction and dehydrogenative coupling of amines and alcohols.[7] Here, we present a binuclear Rh complex-catalyzed chemoselective alkylation and olefination of alkylnitriles with alcohols, with the selectivity controlled by simply altering the reaction atmosphere (Scheme 1, bottom). The alkylation reaction performed under Ar is a hydrogen-borrowing reaction, whereas the olefination reaction under O_2 is a dehydrogenative coupling process.

Nitriles are useful building blocks in organic synthesis.[8] With water as the only by-product, the alkylation of alkylnitriles with alcohols through hydrogen borrowing provides a "green" route for the synthesis of new nitrile compounds. Transition-

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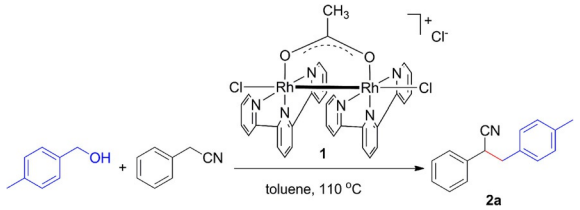
metal catalysts, including Ru,[3,9] Os,[10] Ir,[11] Rh,[12] and Pd,[13] have been employed for this reaction. The olefination of alkylnitriles with alcohols could afford α,β-unsaturated nitriles, which are also valuable intermediates in organic synthesis.[14] However, this transformation is less explored.[4,9b,13,15] Very recently, Milstein and co-workers reported a remarkable example of Mn-catalyzed olefination of nitriles by alcohols under base-free conditions.[15] Despite this progress, a way to control the selectivity between alkylation and olefination of alkylnitriles with alcohols remains to be determined. The protocol described here provides a simple solution to this challenging problem.

Recently, the binuclear Rh catalyst **1** (Table 1) was found to be an effective catalyst for acceptorless dehydrogenative coupling[16] as well as dehydrogenation[17] of alcohols by our group. In continuing our efforts in dehydrogenation-related transformations, the catalytic activity of **1** in the alkylation of alkylnitriles with alcohols was studied. To begin, 4-methylbenzyl alcohol and 2-phenylacetonitrile were chosen as model substrates to test the catalytic activity of **1** (0.5 mol%; Table 1). In the presence of NaOH (0.5 equivalent), the monoalkylated product **2a** was formed in 93% yield in toluene at 110 °C in 12 h (Table 1, entry 1). Other solvents and bases afforded poorer yield (see the Supporting Information for details). Without **1** or NaOH, the coupling reaction did not take place (Table 1, entries 2 and 3). The reaction time could be shortened to 6 h without affecting the yield (Table 1, entry 4). Other Rh complexes showed no or little activity in this reaction (Table 1, entries 5–7).

Table 1. Alkylation of 2-phenylacetonitrile with 4-methylbenzyl alcohol catalyzed by binuclear Rh complex **1**.[a]

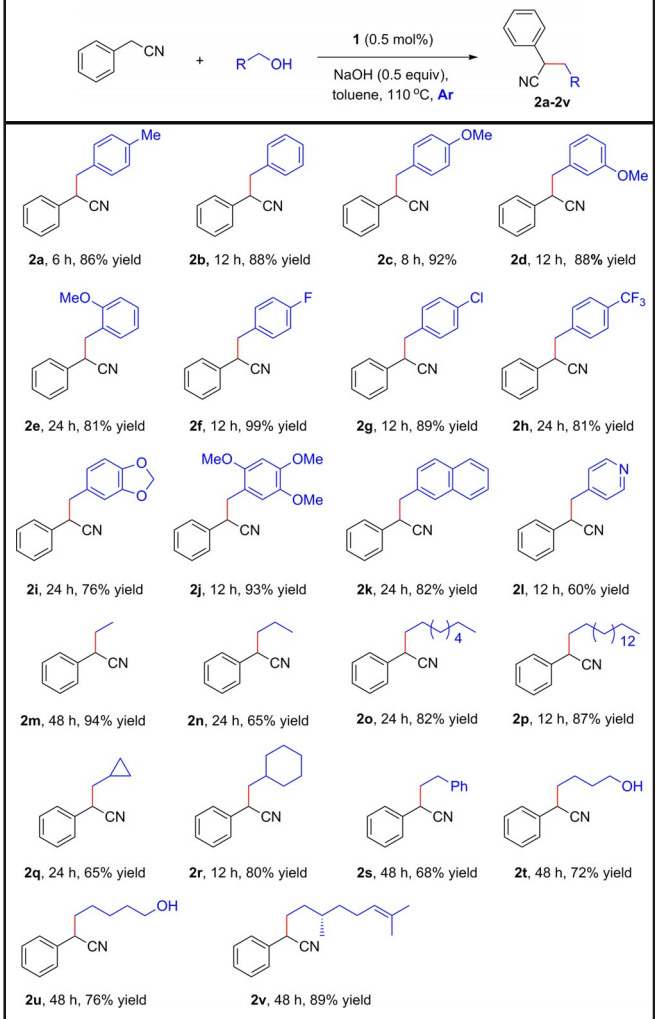


Entry	Catalyst	Base	*t* [h]	Yield [%][b]
1	**1**	NaOH	12	93
2	–	NaOH	12	0
3	**1**	-	12	0
4	**1**	**NaOH**	**6**	**91**
5	$Rh_2(OAc)_2$	NaOH	6	0
6	$[Cp^*RhCl_2]_2$	NaOH	6	6
7	$[Rh(COD)Cl]_2$	NaOH	6	5

[a] Reaction conditions: 4-methylbenzyl alcohol (0.5 mmol), 2-phenylacetonitrile (0.5 mmol), base (0.25 mmol), catalyst (0.5 mol%), toluene (2 mL), 110 °C, under Ar in a sealed tube. Ac = acetyl, Cp* = pentamethylcyclopentadiene, COD = 1,5-cyclooctadiene. [b] Determined by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard. See the Supporting Information for more optimization data.

The substrate scope of this catalytic protocol was then explored. Both benzylic and aliphatic alcohols can react with 2-phenylacetonitrile generally in the presence of 0.5 mol% of **1** and 0.5 equivalent of NaOH in toluene at 110 °C under Ar (Table 2). Benzylic alcohols bearing substituents with varying electronic and steric properties on the phenyl ring are all viable substrates (**2a**–**l**). An alcohol containing a heterocycle gave low yield even with increased catalyst loading (**2l**). Aliphatic alcohols showed better activity with longer chain lengths (**2m**–**p**). Notably, ethanol could be used as substrate, affording α-ethylated nitrile in excellent yield without the formation of dialkylated products (**2m**). Cyclopropyl and cyclohexyl rings could be tolerated (**2q**, **r**). 2-Phenylethan-1-ol afforded moderate yield of **2s**, which can serve as an intermediate for the synthesis of drug molecules (vide infra). One hydroxyl group of diols can react selectively to form molecules containing both a hydroxy and a cyano group, when the diols are added in excess (see the Supporting Information for details). These molecules have not been reported previously and

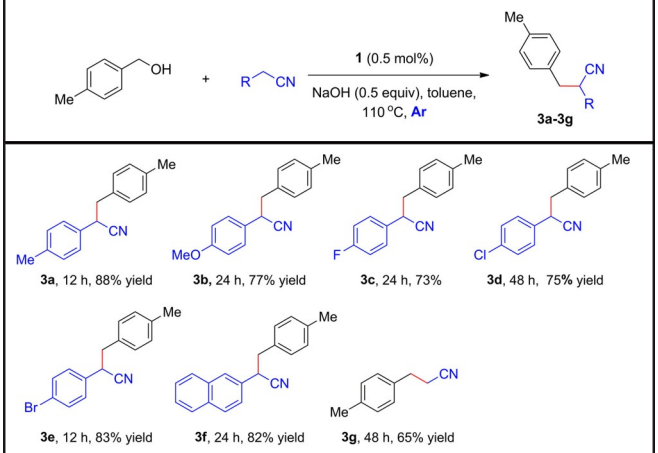
Table 2. Alkylation of 2-phenylacetonitrile with alcohols catalyzed by **1**.[a]



[a] General reaction conditions: alcohol (0.5 mmol), 2-phenylacetonitrile (0.5 mmol), NaOH (0.25 mmol), **1** (0.5 mol%) toluene (2 mL), 110 °C under Ar in a sealed tube, isolated yield. See the Supporting Information for more details.

could be used for the synthesis of more complex compounds (vide infra). The C=C double bond and the chiral center remain intact, when (*S*)-(−)-β-citronellol was used as a substrate, although the newly formed chiral center is essentially racemic (**2v**). The preservation of the isolated C=C double bond showed that the catalyst reduces polarized C=C double bonds selectively, indicative of a conjugated reduction pathway for the reduction of the nitrile–olefin intermediate (vide infra). Different nitriles were then examined (Table 3). Moderate to good yields were obtained for various 2-arylacetonitriles (**3a–f**). Acetonitrile could also react, albeit with a lower activity (**3g**).

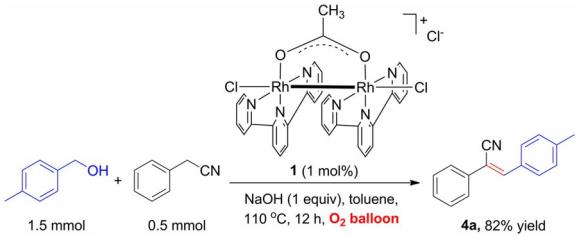
Table 3. Alkylation of various alkylnitriles with 4-methylbenzyl alcohol catalyzed by **1**.[a]



[a] The reaction conditions are the same as those of Table 2. See the Supporting Information for details.

The alkylation reactions above were carried out in an inert atmosphere of argon. Our previous study showed that **1** could catalyze the oxidation of alcohols under either Ar or air, but through different mechanisms.[17] Under air, the rhodium hydride intermediate is probably consumed by reacting with oxygen, affording water and thus becoming unavailable for hydrogenation. We then envisioned that switching the atmosphere of the alkylation reaction from Ar to O_2 could change the reaction pathway from hydrogen-borrowing to dehydrogenative coupling because the rhodium–hydride intermediate would be intercepted by oxygen. Indeed, upon changing the reaction vessel from a sealed tube to a Radleys Carousel tube equipped with a O_2 balloon, the reaction of 2-phenyl acetonitrile and 4-methylbenzyl alcohol produced the olefin product **4a** as the major product in the presence of 1 mol% of **1** and 1 equivalent of NaOH (Scheme 2, see the Supporting Information for more optimization data). Differing from the alkylation protocol, an excess amount of alcohol was used in the olefination reaction to ensure the full consumption of nitrile substrate because part of the alcohol was oxidized to the corresponding carboxylic acid under the reaction conditions.

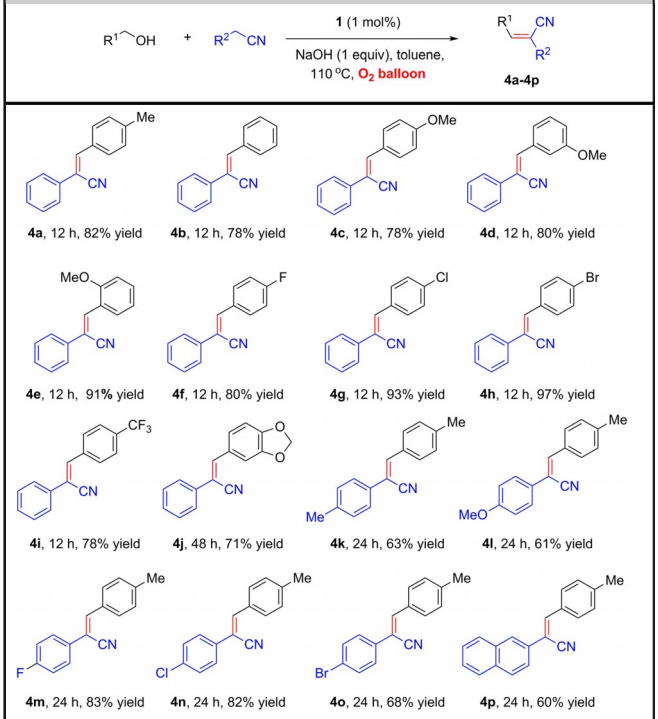
The substrate scope of the dehydrogenative coupling protocol was also examined (Table 4). A rang of benzylic alcohols



Scheme 2. Olefination of 2-phenylacetonitrile with 4-methylbenzyl alcohol catalyzed by **1**.

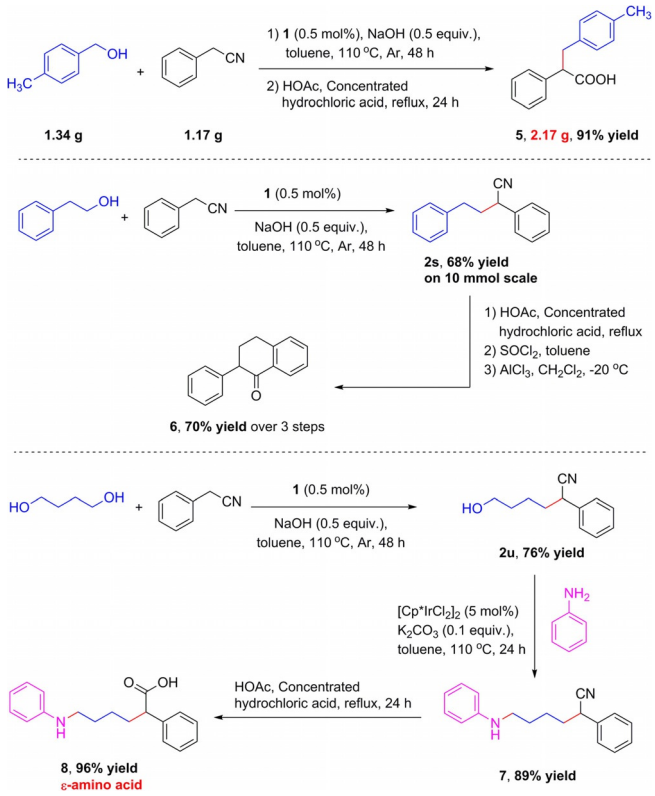
and 2-arylacetonitriles could be used, producing *Z*-nitrile–olefins in moderate to excellent yields (**4a–p**).[18] These nitrile olefin products could be employed as key intermediates for the synthesis of natural products[19] or as substrates for asymmetric hydrogenation.[20]

Table 4. Olefination of nitriles with alcohols catalyzed by **1**.[a]



[a] General reaction conditions: alcohol (0.75 mmol), nitrile (0.25 mmol), NaOH (0.25 mmol), catalyst (1 mol%), toluene (2 mL), 110 °C under O_2 balloon in a Radleys Carousel tube, isolated yields shown. See the Supporting Information for more details.

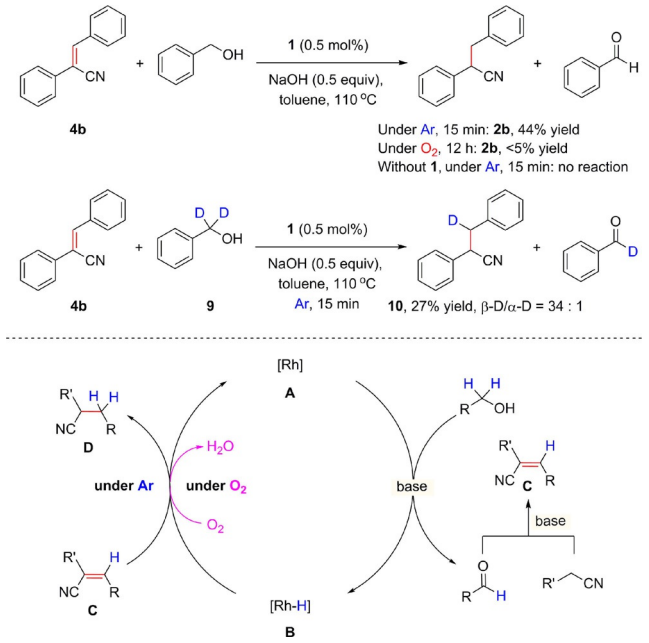
The utility of the alkylation reaction has been further demonstrated by large scale reactions and transformation of the alkylated products into useful organic molecules (Scheme 3). The reaction of 4-methylbenzyl alcohol and 2-phenylacetonitrile was performed at a gram scale, and the corresponding alkylated product was hydrolyzed in situ to a carboxylic acid product **5** in excellent yield (Scheme 3, top). This type of carboxylic acid may serve as an intermediate for the preparation of bio-



Scheme 3. Gram-scale α-alkylation of 2-phenylacetonitrile and application of products.

logically active compounds, for example, inhibitors of transient receptor potential canonical (TRPC) channel activity.[21] Product **2s**, derived from 2-phenylethan-1-ol and 2-phenylacetonitril, can be conveniently converted to 2-phenyl tetralone **6** (Scheme 3, middle), which could be used for the synthesis of hexahydrobenzo[c]phenanthridine alkaloids.[22] The hydroxyl nitrile compound **2u**, derived from a diol and 2-phenylacetonitile, was transformed into an amino nitrile compound **7** through an iridium-catalyzed hydrogen-borrowing reaction.[23] Hydrolysis of **7** afforded an ε-amino acid **8** in high yield (Scheme 3, bottom), showcasing the usefulness of the method in the synthesis of some unique amino acids, which may find important biological applications.[24]

Preliminary mechanistic studies were carried out to shed light on the reaction pathways. The olefin product **4b** could be reduced to **2b** using benzyl alcohol as hydrogen source under the catalysis of **1** (Scheme 4, top). However, the yield of **2b** varies with the atmosphere applied. Thus, 44% yield of **2b** was obtained with 0.5 mol% of **1** and 0.5 equivalent of NaOH in 15 minutes under Ar (Scheme 4, top), whereas less than 5% yield of **2b** was detected even after a prolonged time of 12 h when the reaction atmosphere was switched from Ar to O_2 (Scheme 4, top). Without **1**, **4b** could not be reduced by benzyl alcohol under the conditions employed (Scheme 4, top). These results suggest that the olefin products are intermediates for the alkylated products under Ar and the presence of O_2 stops the reduction of olefin products. Upon replacing benzyl alcohol with deuterium-labelled benzyl alcohol **9**, **4b**



Scheme 4. Mechanistic studies and proposed mechanism.

was reduced to product **10** in 27% yield in 15 minutes. The deuterium atom goes almost exclusively to the β-position of the cyano group in **10**, suggesting that the formation of **10** goes through a conjugated reduction process by the rhodium-deuteride intermediate generated from dehydrogenation of **9**.

Based on the above mechanistic studies, reaction pathways for both the alkylation and olefination reactions are proposed (Scheme 4, bottom). The active rhodium catalyst **A** dehydrogenates an alcohol to produce a rhodium hydride intermediate **B** and an aldehyde with the aid of a base. The aldehyde intermediate could be detected by ^{1}H NMR and thin layer chromatography (TLC) during the courses of both alkylation and olefination reactions. Moreover, in the absence of the nitrile substrate, aldehyde products could also be detected by ^{1}H NMR. For example, 4-methoxybenzyl alcohol was oxidized to the corresponding aldehyde with an NMR yield of 14% under Ar and 54% under O_2 in the presence of 0.3 equivalent of NaOH with 0.3 mol% of **1** in refluxed toluene for 12 h. The carboxylic acid product could also be observed in small amounts, which differs from our previous system in water.[17] The aldehyde then condenses with the alkyl nitrile to give the olefin product **C** through nucleophilic addition and dehydration promoted by a base. Indeed, the olefin product could be observed by NMR, when reacting benzaldehyde with 2-phenylacetonitrile under the alkylation conditions in the absence of **1**. Under an Ar atmosphere, **C** is reduced by **B** to afford the alkylated product **D** and regenerate the active catalyst **A**. In contrast, under an O_2 atmosphere, the rhodium hydride intermediate **B** reacts preferentially with O_2 to complete the catalytic cycle, thereby giving **C** as the reaction product.

In conclusion, by harnessing the unique catalytic activity of a binuclear rhodium complex, we have achieved the chemoselective alkylation and olefination of alkylnitriles with alcohols by simply controlling the reaction atmosphere. The alkylation

reaction has broad substrate scope and could be applied to the synthesis of some important organic molecules. Mechanistic studies suggest that the conjugate reduction of an alkene intermediate by a rhodium hydride is responsible for the formation of the alkylation product, whereas the interception of the rhodium hydride by molecular oxygen results in the formation of the olefin product. The notion of being able to switch the reaction mode of hydrogen-borrowing versus dehydrogenative coupling by simply changing the reaction atmosphere provides one of the easiest means to access two different classes of products and would be expected to find broader applications.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alcohol · cross coupling · dehydrogenation · nitrile · rhodium

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