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Nickel(II)-Catalyzed Direct Olefination of Benzyl Alcohols with Sulfones with the Liberation of H_2†

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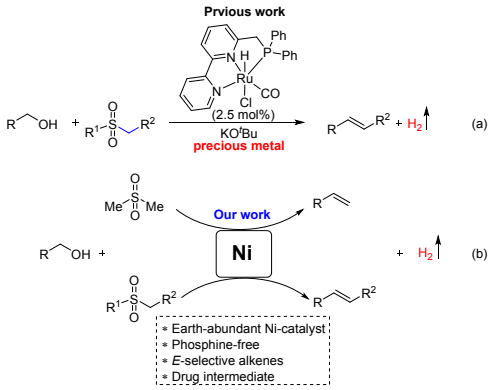
A nickel(II)-catalyzed direct olefination of benzyl alcohols with sulfones to access various terminal and internal olefins with the liberation of hydrogen gas is reported.

Olefins are high-value organic compounds in many research areas because of their extensive usage in cross-coupling reactions, synthesis of natural products, pharmaceuticals, dyes, agro-chemicals, and production of polymers.[1] Over the past decades, considerable efforts have been devoted towards the synthesis of olefins by employing traditional reactions such as Wittig,[2-3] Horner–Wadsworth–Emmons,[4] Peterson olefination,[5] Julia olefination[6] and Tebbe olefination.[7]

Sulfones are commonly utilized in the multi-step classical Julia olefination *via* the formation of β-acyloxy alkyl sulfones from aldehydes followed by the reductive elimination with sodium amalgam to furnish the olefin. However, in some cases, the necessary aldehydes or ketones are not readily available or may undergo undesired side-reactions, e.g., aldol condensation. Therefore, it is not surprising that in spite of the existing methods the development of new versatile, and efficient protocols for their synthesis is of continuing interest. Nevertheless, research progress has been made for the synthesis of olefins *via* oxidation of alcohols under oxygen in the presence of palladium, rhodium, copper, ruthenium, and also catalyst-free conditions by alcohol as a solvent and a copious amount of base.[8] The research group of Alonso reported nickel nanoparticles promoted Wittig-type olefination of alcohols under oxidative conditions; however, it suffers from lack of product selectivity.[8g]

Acceptorless dehydrogenative coupling (ADC)[9-12] has emerged as a powerful strategy for the straightforward synthesis of value-added chemicals. Of late, Milstein and co-workers reported catalytic olefination of alcohols with sulfones catalyzed by a well-defined Ru-PNN pincer complex (Scheme 1).[12a]



Scheme 1. Olefination *via* acceptorless dehydrogenative coupling (ADC).

Henceforth, an alternative to precious metal catalysts and to develop a new catalytic system based on earth-abundant, economical, low-toxic first-row transition metals is highly demanding.[13-14] In recent times, widespread applications of nickel catalysis in chemical manufacturing and the pharmaceutical industry have been carried out as an alternative to noble metal catalysts.[15] To date, the application nickel catalysts for dehydrogenation and related reactions has proven highly demanding and remains elusive.[16,17c] Herein we report a Ni(II)-complex pertaining NNN-type ligand[17] catalyzed direct olefination of alcohols with sulfones to access various terminal and internal olefins with the liberation of hydrogen gas.

The reaction of 3,4-dimethoxyphenyl)methanol (**2o**) with dimethylsulfone (**1**) was chosen as a model system for the acceptorless dehydrogenative coupling to form **3o** (see ESI†, for optimization studies). We began our investigation using dimethyl sulfone (DMS) (**1**) as a model substrate and (3,4-dimethoxyphenyl)methanol (**2o**) as a coupling reagent in the presence of $NiCl_2$ (3 mol %), and KO*t*Bu (1.1 equiv) as a base in refluxing toluene for 12 h to yield the expected product **3o** in

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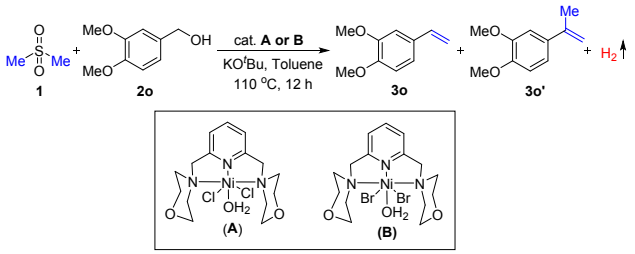
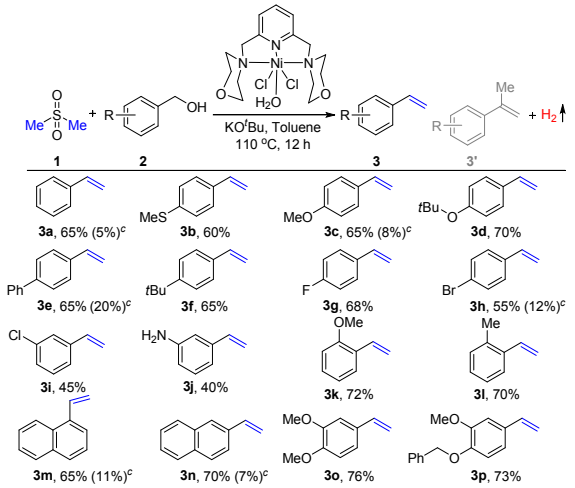
32% isolated yield. Interestingly, by employing NNN-Ni(II) complexes **A** and **B** under optimal conditions, the product **3o** was obtained in 76% and 72% yield, respectively (Scheme 2). Notably, the liberated hydrogen gas was detected on gas chromatography and quantified.



Scheme 2. Ni-catalyzed olefination of alcohols *via* ADC.

After having optimized conditions in hand, the general applicability of the present NNN-Ni(II)-catalyzed olefination of alcohols were investigated (Table 1). Thus, a variety of benzylic alcohols with electron-neutral, electron-deficient, and electron-rich substituents led to the corresponding olefins in good yields with excellent selectivity. The *para*-substituted benzyl alcohols pertaining a range of functional groups, such as ether, aryl, alkyl, fluoro, bromo, and chloro were well tolerated and gave the corresponding styrene derivatives (**3a**-**3i**) in good yields (up to 70% isolated yield). Gratifyingly, the unprotected amine group such as 3-aminobenzyl alcohol (**2j**) underwent the ADC reaction smoothly and gave 3-aminostyrene as a single product in 45% yield. The methenylation of *ortho*-substituted benzyl alcohols, and π–extended benzyl alcohols (1-naphthyl, and 2-naphthyl) proceeded efficiently and yielded the corresponding olefins in very good yields (products **3k** in 72%, **3l** in 70%, **3m** in 65%, and **3n** in 70% isolated yields). Notably, the reaction was found to be compatible with disubstituted alcohols (**2o** and **2p**) and afforded the methenylated products in excellent yields (products **3o** in 76% and **3p** in 73%).

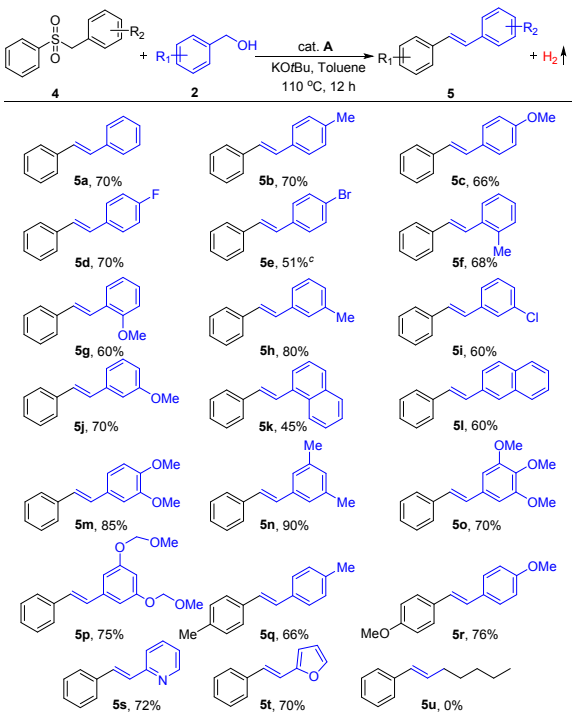
Table 1. Olefination of alcohols: Scope of benzyl alcohols[a,b]



[a]Reaction conditions: **1** (0.5 mmol), alcohol (0.5 mmol), cat. **A** (3 mol%), KO*t*Bu (0.55 mmol), and toluene (1 mL), 110 °C, 12 h. [b]Isolated yields. [c]α-methyl substituted product (**3'**) was observed by GC.

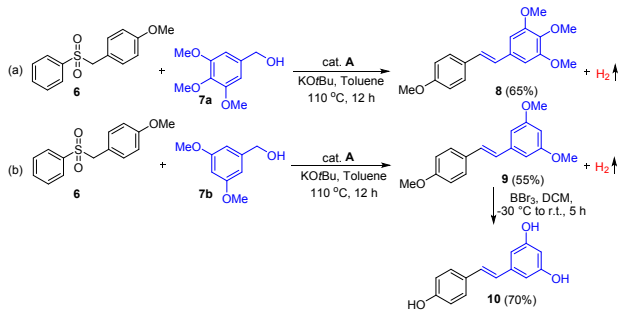
The stereoselective synthesis of olefins is very demanding because of (*E*)-olefinic structures are widely found in many biologically and pharmaceutically active molecules. Delightfully, the Ni-catalyzed selective synthesis of *E*-stilbenes from easily available alcohols using benzyl phenyl sulfone has been successfully addressed (Table 2). Under the optimized reaction conditions, the electron-donating substituents on benzyl alcohols offered higher yield than the electron-withdrawing substituents. Thus, *p*-Me, and *m*-OMe benzyl alcohols gave higher *E*-selective products in good yields (**5b** in 70%, and **5c** in 66% yields). In particular, functionalized alcohols with halide (-F, and -Br) groups were well tolerated (products **5d**-**5e**) under optimal reaction reactions. Various *ortho*-, and *meta*-substituted alcohols were highly tolerated and offered the corresponding olefins with complete *E*-selectivity (products **5f** in 68%, **5g** in 60%, **5h** in 80%, **5i** in 60%, and **5j** in 70% yields). Significantly, the alcohols featuring naphthyl and di/tri-substituted groups were efficiently reacted and gave the corresponding alkenes in good yields with complete *E*-selectivity (products **5k**-**5p**). Importantly, we were able to extend our catalytic system for the synthesis of symmetrical *E*-selective stilbenes in good yields (**5q** in 66%, and **5r** in 76% yield). Furthermore, substrates featuring pyridyl and furyl, which are challenging to undergo olefination due to their coordinating ability to the metal centre, also exhibited good yields with excellent *E*-selectivity under our reaction conditions (products **5s**-**5t**). However, the reaction using unactivated aliphatic alcohol (1-hexanol) didn't yield the expected olefin under our Ni-catalysis. A similar reactivity was observed in the case of Ru(II)-catalyzed olefination reaction.[12a]

Table 2. Olefination of alcohols: Scope of alcohols and sulfone.[a,b]



[a]Reaction conditions: **4** (0.5 mmol), **2** (0.5 mmol), cat. **A** (3 mol%), KO*t*Bu (0.55 mmol), and toluene (1 mL), 110 °C, 12 h. [b]Isolated yields. [c]10% dehalogenated product.

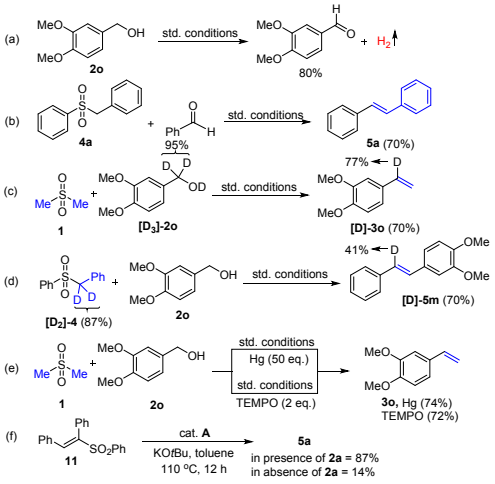
The utility of the present ADC strategy is further demonstrated for the *E*-selective synthesis of pharmaceutically relevant molecules. To our delight, one-step synthesis of DMU-212 (**8**), a drug used for breast cancer treatment has been achieved.[18] Furthermore, we have successfully synthesized a prominent biological activity molecule Resveratrol by two steps protocol. The *E*-selective **9** was accomplished by employing **6** and 3,5-dimethoxybenzyl alcohol (**7b**) under nickel-catalyzed conditions followed by demethylation of **9** to offer the Resveratrol (**10**) in 70% yield (Scheme 3).



Scheme 3. Application in synthesis of DMU-212 (**8**), and Resveratrol (**10**).

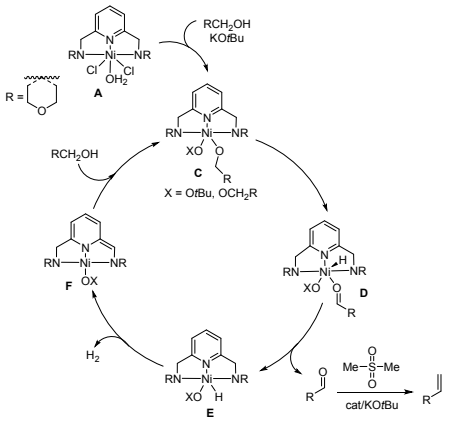
To gain insight into the reaction mechanism, several control experiments were performed (Scheme 4). Under optimal reaction conditions, in the absence of **1** the formation of aldehyde product and H_2 gas were observed (by gas chromatography analysis). Performing the reaction using aldehyde, the reaction proceeded excellently and provided **5a** in 70% yield. Next, the reaction using [**D_3**]-**2o** under optimal conditions showed the deuterium incorporation at the α-position of the styrene (**3o**). Similarly, the reaction of deuterated sulfone [**D_2**]-**4** with **2o** proceeded smoothly and the deuterium incorporation at the α-position of stilbene was observed. These results described that the reaction proceeds *via* aldehyde intermediate. It was proposed that the Ni-H species is originated from the benzylic proton of the alcohol during the dehydrogenation reaction to benzaldehyde.[19a] There are also reports on the generation of nickel hydride species in presence of hydride donors such as sodium borohydride.[19b] In this regard, performing the dehydrogenation reaction of alcohol under NNN-Ni(II) catalysis in the presence of a catalytic amount of $NaBH_4$ as a hydride donor showed the formation of aldehyde (by GC-MS). Next, an attempt to prepare the Ni-H species of Cat. **A** in combination with alcohol (**2o**) was invoked. However, the experimental results evidence that the generation of Ni-H species of Cat. **A** or Cat. **B** is extremely unstable to detect even at low temperature (the formation of aldehyde was only observed). To get further insights, we had chosen an electron-rich tricyclohexyl phosphine derived complex $NiBr_2(PCy_3)_2$ and the Ni-hydride species $(PCy_3)_2NiBrH$ for our studies.[16c,16e] Interestingly, both the complexes yielded the desired olefin in 46% and 37% yields, respectively. Gratifyingly, performing the catalytic dehydrogenation of alcohol (**2o**) using $(PCy_3)_2NiBrH$ gave the corresponding aldehyde in 23% yield. These experimental findings are in agreement with the participation of Ni-H species during the initial dehydrogenation step. Importantly, treatment of (*E*)-(1-(phenylsulfonyl)ethene-1,2-diyl)dibenzene (**11**) in the absence of **2a** led to **5a** in 14% yield. However, the same reaction in the presence of **2a** the product **5a** was observed in 87% yield. These experiments showed that the present NNN-Ni(II) catalyst has a crucial role in the final olefination step also. Based on experimental results, we propose that the present Ni-catalysed strategy consists of a multi-step process, and the initial step is the dehydrogenation of benzyl alcohol **2o** to the corresponding aldehyde with the liberation of H_2, where a transient Ni-H species is generated. Subsequently, Julia-type olefination of intermediate aldehyde with sulfone (**4a**) led to the expected olefin **5a**.

Finally, to confirm the homogenous nature of present nickel-catalysis, the benchmark reaction was carried out in the presence of excess mercury (50 equiv.) and the expected product (**3o**) was observed in 74% yield. Performing the reaction in presence of radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO; 2 equiv.) didn't affect the yield of the product. This result indicates that the radical reaction pathway could be ruled out. The progress of the reaction studied with the kinetic analyses and revealed that the olefination reaction is first order with respect to sulfone and catalyst, and fractional order in alcohol and the base concentration (see ESI).



Scheme 4. Mechanistic investigations.

Based on preliminary experimental results, a plausible mechanism for the NNN-Ni(II) catalyzed direct olefination of alcohol is shown in scheme 5. In the presence of alkoxide, the precatalyst **A** undergoes displacement reaction to give the complex **C**. The complex **C** undergoes β-hydride elimination (of alkoxide) to lead to the corresponding aldehyde and with the formation of Ni-H species **D**. Subsequently, Julia-type olefination of intermediate aldehyde with sulfone to yield the expected olefin. The complex **F** generated from complex **E** with the liberation of H_2. Finally, the complex **F** reacts with alcohol to regenerate the catalyst **A**. The isolation of proposed intermediates is under progress in our laboratory and will be communicated in due course.



Scheme 5. A plausible mechanism.

In summary, an efficient nickel-catalyzed direct olefination of benzyl alcohols with sulfones to access various terminal and internal olefin *via* ADC is reported. The present protocol has been successfully employed for the synthesis of pharmaceutically important compounds.

Conflicts of interest

"There are no conflicts to declare".

Acknowledgements

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