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Xiaoping Liu, Jean-Marc Sotiropoulos, Marc Taillefer. A New Route to E -Stilbenes through the Transition-Metal-Free KO t Bu/DMF-Promoted Direct Coupling of Alcohols with Phenyl Acetonitriles. European Journal of Organic Chemistry, 2022, 2022 (26), pp.e202200631. 10.1002/ejoc.202200631 . hal-03871591

HAL Id: hal-03871591

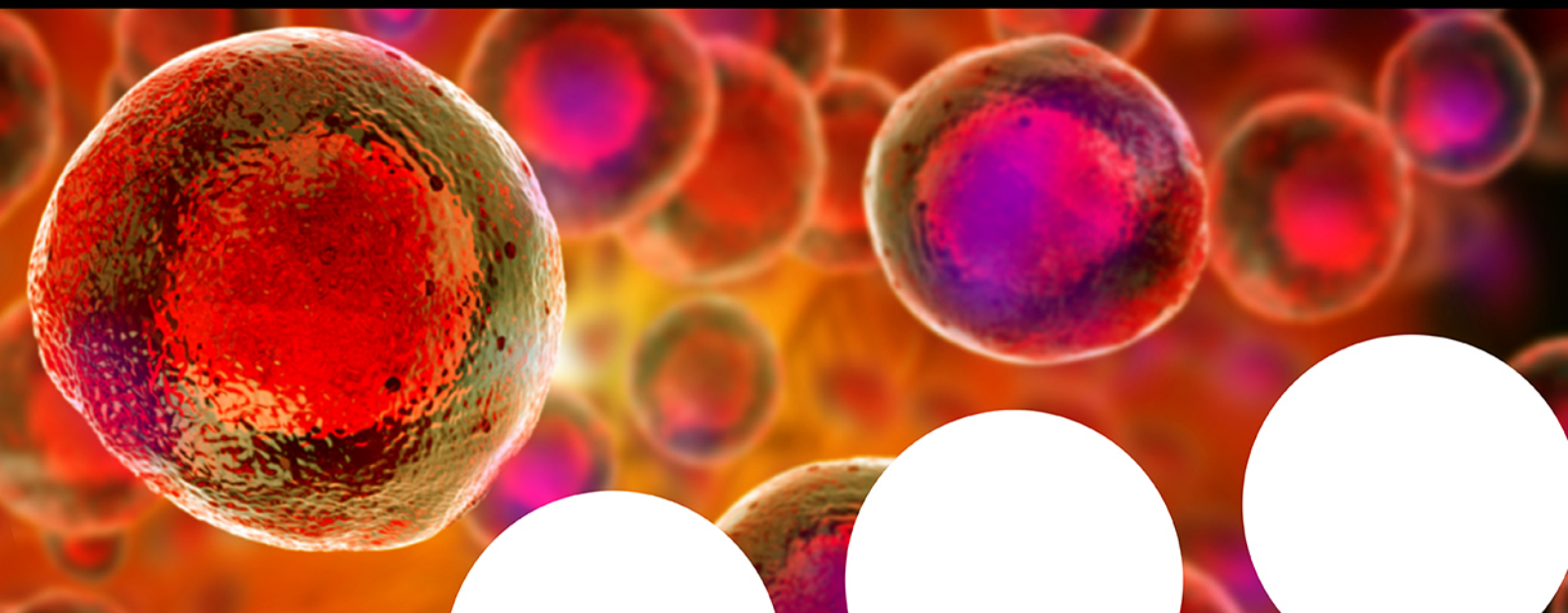
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Submitted on 25 Nov 2022

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A New Route to *E*-Stilbenes through the Transition-Metal-Free KO^tBu/DMF-Promoted Direct Coupling of Alcohols with Phenyl Acetonitriles

Xiaoping Liu,^[a] Jean-Marc Sotiropoulos,^{*[b]} and Marc Taillefer^{*[a]}

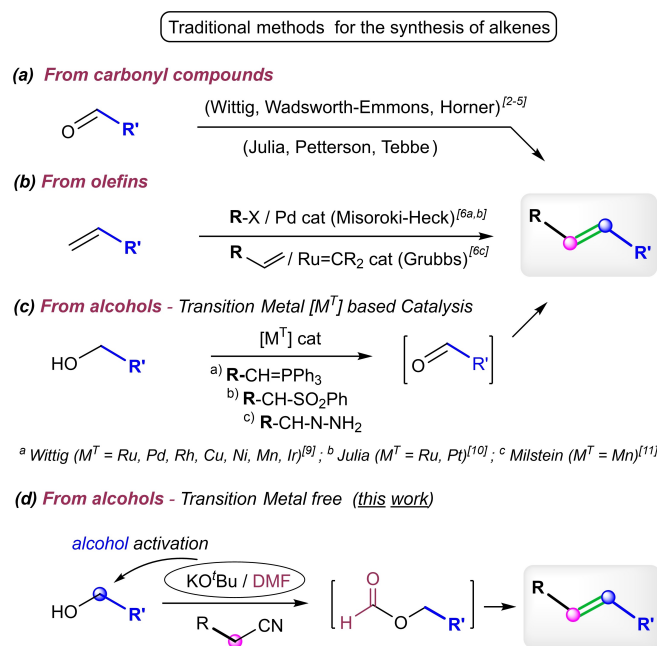
An alternative route to synthesise alkenes, based only on the KO^tBu/DMF promoted activation and direct coupling of alcohols with phenyl acetonitriles, is reported. Various *E*-stilbenes have thus been obtained directly from alcohols that are sustainable sources of carbon, which to our knowledge, is unprecedented

in the absence of transition metal based catalysts. A variation allowing, through a Csp₃–Csp₃ bond formation, the selective synthesis of *N*-Heteroarenes is also described. A mechanism for the olefination pathway proceeding via an original activation of alcohols under alkyl formates is provided.

Introduction

The synthesis of olefins is a process of fundamental importance in organic synthesis, as alkenes are widely present in bioactive natural products and are highly useful key building blocks for the synthesis of a broad range of materials and drugs.^[1] The most common methods for the synthesis of alkenes are mainly based on classical olefination of carbonyl compounds. Among others, widely used approaches are Wittig,^[2a,b] Wadsworth-Emmons^[2a,c] and Horner reactions,^[2a,d] Julia olefination,^[3] Peterson reaction,^[2a,4] and Tebbe olefination (Scheme 1a).^[2a,5] The other classical olefination routes are based on pre-synthesised olefins as starting materials and include palladium catalysed Misoroki-Heck and ruthenium catalysed metathesis reactions (Scheme 1b).^[6]

Alcohols are cheap and environmentally benign substrates which, moreover, can be obtained from biomass and in particular, from lignocellulose. They are therefore a sustainable source of carbon compared to fossil resources and their direct use to access bulk and fine chemicals is therefore of increasing interest.^[7] However, as alcohols are quite unreactive, especially with nucleophiles because of the very poor leaving group capacity of the hydroxy moiety, their direct activation is a very important challenge^[8] which constitutes one of the 10 key



Scheme 1. Traditional methods and the new concept proposed for the synthesis of alkenes directly from alcohols.

green chemistry research areas from a pharmaceutical manufacturers' perspective.^[8d]

In this context, the direct conversion of alcohols to alkenes has been investigated and competitive alternatives to well-established olefination methods have been described. Among the main methods reported, the olefination from alcohols, via their *in situ* conversion in carbonyl compounds, has been reported with the Ru-, Pd-, Rh-, Cu-, Ni-, Mn and Ir-catalysed Wittig-type reaction,^[9] the Ru- or Pt-catalysed Julia-type reaction,^[10] or with Mn-catalysts using hydrazine or hydrazine as coupling partner (Scheme 1c).^[11]

As part of our studies on transition metal free promoted reactions,^[12] we now report a new route to alkenes, based only on the KO^tBu/DMF promoted activation and direct coupling of

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Supporting information for this article is available on the WWW under
<https://doi.org/10.1002/ejoc.202200631>

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alcohols with phenyl acetonitriles. The coupling of nitriles with carbonyl compounds, formed *in situ* from alcohols by a dehydrogenative process, is very well documented but in most cases it is catalysed by transition metal complexes and leads to vinyl^[13] or α -alkylated^[14] nitriles. With our method, the olefination has been performed in transition metal free conditions and a variation allowing the selective synthesis of *N*-Heteroarenes, through a Csp₃–Csp₃ bond formation, is also described. A mechanism, proceeding via the intermediate formation of alkyl formats, is proposed.

Results and Discussion

We started our investigations with benzyl alcohol **2a** and phenyl acetonitrile **1a** as the template substrates and an initial test was performed under argon in the presence of 1 equivalent of KO^tBu, in 2 mL of DMF for 24 h at 140 °C. In absence of reactivity the loading of KO^tBu was increased up to 4 equivalents and the selective formation of the olefination product **3aa** (*E*-stilbene) was obtained in 54% yield (Table 1 entries 1–3). With other bases such as KOH, K₂CO₃, K₃PO₄ or LiNH₂ (Table 1, entries 4–7), the stilbene was not observed and replacing DMF with non-polar or polar solvents, among which 1,4-dioxane, toluene, *N*-methyl-2-pyrrolidone, dimethyl sulfoxide (DMSO) or tetrahydrofuran (THF) were trialed, also failed to furnish **3aa** (Table 1, entry 8). While lowering the **1a**/**2a** ratio was not beneficial, increasing the reaction temperature by only 10 °C afforded **3aa** in 82% yield (Table 1, entries 9, 10). With other alkali alkoxides, such as LiO^tBu no reactivity was observed, whilst with NaO^tBu the olefination product **3aa** was obtained in only 40% yield (Table 1, entries 11, 12). It should be noted that the results reported in Table 1 were obtained using resublimed KO^tBu (purchased from Alfa Aesar – 99.994%), thus ruling out the possibility of a reaction catalysed by undesirable metallic contaminants.

Table 1. Olefination of benzyl alcohol **2a** with phenyl acetonitrile **1a**, in the presence of KO^tBu/DMF: reaction conditions.^[a]

Entry		Base [equiv.]	Yield of 3aa [%] ^[b]	Entry		Base [equiv.]	Yield of 3aa [%] ^[b]
1	KO ^t Bu	1	0	7	LiNH ₂	4	0
2	KO ^t Bu	2	40	8	KO ^t Bu	4	0 ^[c]
3	KO ^t Bu	4	54	9	KO ^t Bu	4	50 ^[d]
4	KOH	4	0	10	KO ^t Bu	4	82 ^[e] (75) ^[f]
5	K ₂ CO ₃	4	0	11	LiO ^t Bu	4	0
6	K ₃ PO ₄	4	0	12	NaO ^t Bu	4	40

[a] Reactions performed under argon with 0.5 mmol of **1a** and 1 mmol of **2a**, with KO^tBu (purchased from Alfa Aesar (99.994%) and resublimed), in 2 mL of DMF (except otherwise noted). [b] Yield of **3aa** determined by ¹H NMR spectroscopy as well as GC-MS with 4-iodoanisole as an internal standard. [c] Solvents tested: 1,4-dioxane, toluene, *N*-methyl-2-pyrrolidone, DMSO or THF. [d] **1a**/**2a**=0.5/1.5. [e] Reaction performed at 150 °C. [f] Isolated yield.

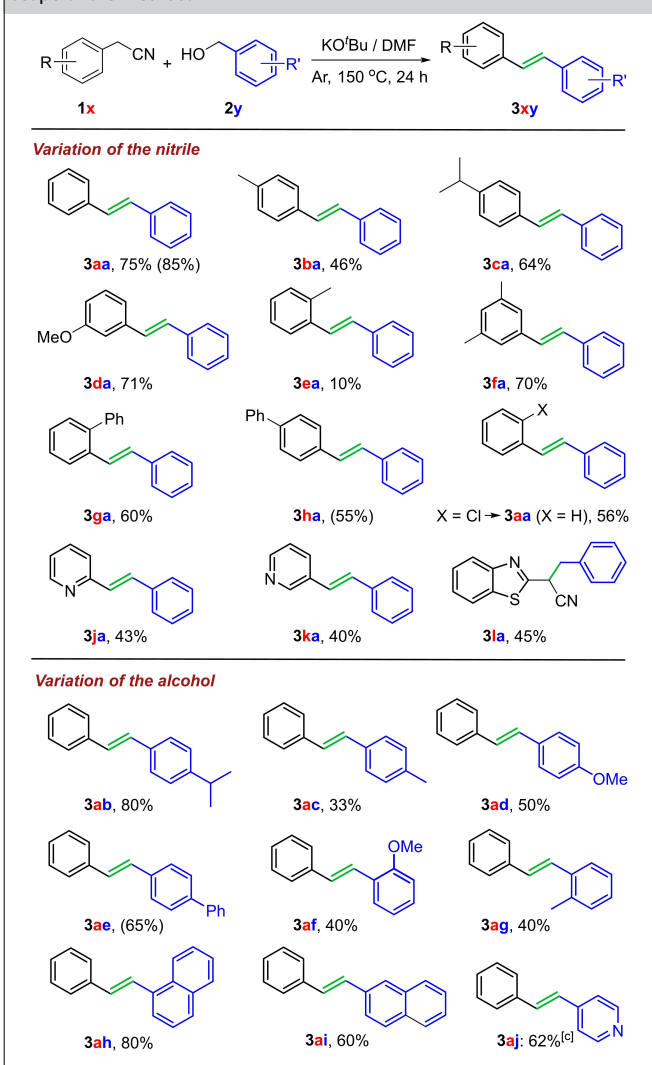
With the optimised conditions in hand (entry 10), we explored the scope of this new route for synthesis of stilbene directly from alcohols in transition metal free conditions.^[15] From the benzyl alcohol **2a** and phenyl acetonitriles substituted by electron donating groups (*para*-methyl, *para*-isopropyl, *meta*-anisyl), the *E* olefination products **3ba**, **3ca** and **3da** were obtained in good, isolated yields. Interestingly, while from *ortho*-tolylacetonitrile a low yield was observed (**3ea**), the system proved to be very efficient in the presence of *m,m'*-dimethyl substituents on the aromatic ring (**3fa**). The procedure was also compatible with 2- and 4- biphenyl acetonitriles (**3ga**, **3ha**), but the reaction performed from the 2-chlorobenzyl cyanide only led to the reduction product (*E*-stilbene **3aa**). From 2- and 3-pyridyl acetonitriles, a fair, isolated yield was observed (**3ja**, **3ka**) and starting from 2-cyanomethyl-1,3-benzothiazole the α -alkylated nitrile **6la**, which may be an intermediate to an olefination compound, was isolated in 45% yield. The procedure, tested from the phenyl acetonitrile **1a** and *p*-isopropyl-, *p*-methyl-, *p*-methoxy- and *p*-phenyl- benzyl alcohols, efficiently led to the expected products (**3ab** to **3ae** – Table 2), the presence of *ortho* substituents (Me, OMe) on the aromatic cycle being also compatible with our system (**3af**, **3ag**). 1- And 2-naphthyl methanol also underwent the reaction with phenyl acetonitrile to give the desired products **3ah** and **3ai** with good yields.

Surprisingly, when we used pyridyl-substituted methanols, the olefination was directed towards the selective formation of a Csp₃–Csp₃ bond. Unexpected decyanation-alkylation products (**4aj**, **4bj**, **4hj**, **4dj**, **4mj**) were obtained from the 4-pyridyl methanol **2j** and substituted phenyl acetonitriles (4-methyl, 4-phenyl, 3-methoxy or 3,5-dimethyl groups), under the standard conditions (Table 3). The procedure, tested with the phenyl acetonitrile **1a** and alcohols, including 2-quinolinyl methanol, (3-methyl-2-pyridyl) methanol and 2-pyridyl methanol, also led to the alkylation products (**4ak** to **4am**). This was also observed with 2- and 3-pyridyl acetonitriles (**1j**, **1k**) and 4-pyridylmethanol (Table 3). *N*-Heteroarenes **4** are prevalent motifs in pharmaceuticals, agrochemicals and in materials.^[16] Their historic synthetic pathway involves the C(sp³)–H alkylation of methyl azaarenes with prefunctionalised electrophiles,^[17] but the recent synthetic pathways often proceed via the transition metal catalysed borrowing hydrogen process, in which alcohols act as alkylating agents towards methyl azaarenes.^[12h,18] These preliminary results therefore constitute an interesting and complementary alternative to the previously reported methods.

We then turned our attention to the mechanistic study and first attempted the reaction of phenyl acetonitrile **1a** with **2a** and **2j**, in the presence of one equivalent of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) (Scheme 3; reaction (1)).^[19] With this common radical scavenger, we observed the formation, with good yields, of the olefination and alkylation products **3aa** and **4aj** respectively. We then inferred that the reaction did not proceed by a radical pathway.

In a proposed mechanism for the olefination, the deprotonated aryl acetonitrile (**1'a**) could react with the alkyl formate **5y** to give the α -alkylated nitrile **6ay** and potassium formate, the latter probably evolving to water and carbon monoxide

Table 2. Olefination of phenyl acetonitrile derivatives **1x** with alcohols **2y**: scope of the method.^[a,b]

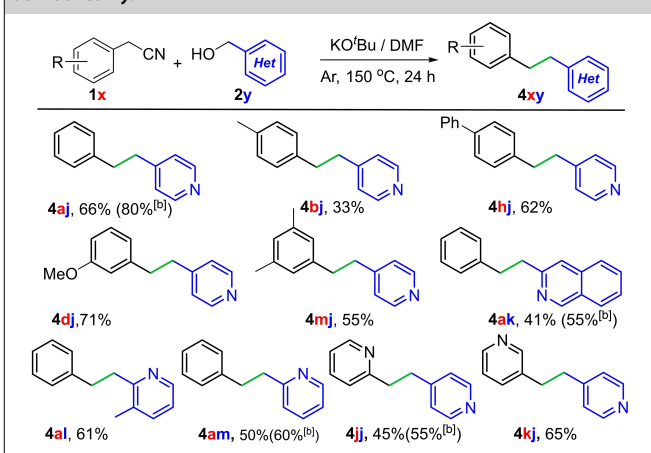


[a] Reaction conditions: phenyl acetonitrile (0.5 mmol), alcohol (1 mmol), KO^tBu (2 mmol), DMF (2 mL). [b] Isolated yield. NMR yields, in brackets, are calculated with 4-iodoanisole as an internal standard. [c] Obtained from **6aj** with two equivalents of KO^tBu.

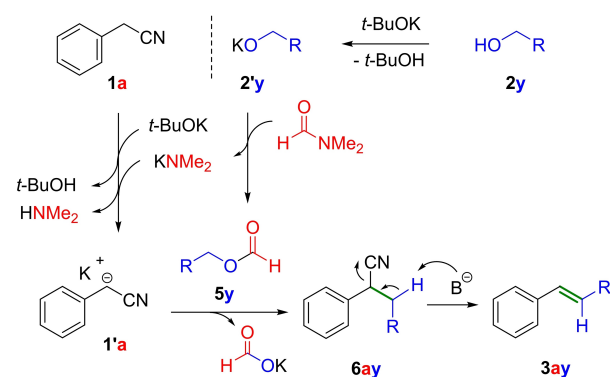
(Scheme 2).^[20] **6ay**, In the presence of base would then lead to the olefination product **3ay**. The alkyl formate **5y** would be obtained from the reaction of the alcoholate **2y** with dimethylformamide, with the phenyl acetonitrile **1'a** being deprotonated by the *in situ* generated potassium dimethyl amide or by KO^tBu. We never observed the formation of the alkyl formate **5y**, but in a control experiment, we verified that **5a** was indeed able of reacting with the phenyl acetonitrile **1a** to give the expected olefination product **3aa** (60%) (Scheme 3, reaction (2)). Interestingly, the proposed α -alkylated nitrile intermediate (**6aa**) was obtained (10%) together with **3aa** during parametric studies performed with a lower loading of base (Scheme 3, reaction (3)). The subsequent *in situ* addition of base shifted the ratio towards the formation of the olefination product (**3aa**).

In a test performed using toluene as the solvent, we treated **1a** with **2a**, while adding 3 equivalents of DMF. Whilst in

Table 3. Alkylation of phenyl acetonitriles **1x** with pyridyl methanol derivatives **2y**.^[a,b]



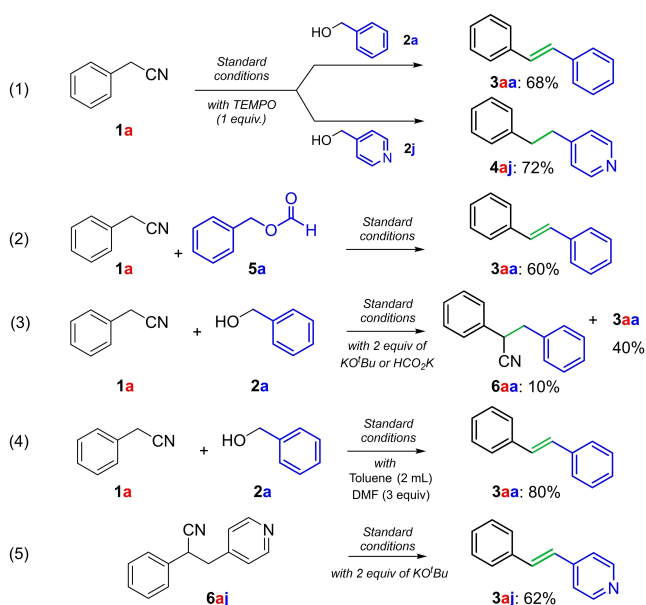
[a] Reaction conditions: phenyl acetonitrile (0.5 mmol), alcohol (1 mmol), KO^tBu (2 mmol), DMF (2 mL). [b] Isolated yield. NMR yields, in brackets, are calculated with 4-iodoanisole as an internal standard.



Scheme 2. Proposed mechanism for the olefination of aryl acetonitriles with alcohols, promoted by the KO^tBu/DMF system.

toluene alone, no reactivity was observed, however in these conditions the formation of the expected product **3aa** was successful, and obtained in 80% yield (Scheme 3, reaction (4)). This result is consistent with the involvement of DMF as a reactant in the overall process and with the proposed formation of the alkyl formate **5y** (Scheme 2). Concerning the alkylation pathway, we do not have evidence clear enough to propose a mechanism. However, the α -alkylated nitrile **6aj** was tested as a starting reagent in standard conditions, and only led to the olefination product, therefore it is unlikely to be a reaction intermediate (Scheme 3, reaction (5)).

To assess the hypothesis of the olefination pathway, we performed DFT calculations at the M06-2X/6-311++G(d,p) level of theory, with the influence of the solvent being taken into account using the polarisable continuum model (PCM) (See SI). It has already been shown with a similar KO^tBu/DMF system for the synthesis of N-heteroarenes,^[12h] that the reaction could go through an intermediate of type **5a**. Considering here also such a hypothesis, we present a thermodynamically very favourable mechanism towards **6aa** via the reaction of **5a** with



Scheme 3. Control experiments for preliminary mechanistic studies.

the deprotonated phenyl acetonitrile 1a ($\Delta G = -94.44 \text{ kcal mol}^{-1}$) (Figure 1). This step, easily occurring (as shown in reaction (2), Scheme 3) with an activation energy of $27.03 \text{ kcal mol}^{-1}$, is moreover facilitated from a kinetic point of view by temperature and reaction duration. The intermediate 6aa can then be deprotonated in the presence of the potassium *tert*-butanolate present in the solution (the deprotonation by the *in situ* generated KNMe_2 is also possible). This low energy reaction ($\text{TS} = +13.72 \text{ kcal mol}^{-1}$) leads to a carbanionic species which very quickly loses the cyanide ($\text{TS} = +8.86 \text{ kcal mol}^{-1}$) to lead to the corresponding alkene 3aa , in a thermodynamically favourable step.

Concerning the alkylation pathway, a modelling approach performed from the analogous *N*-heteroalcohol confirmed, as

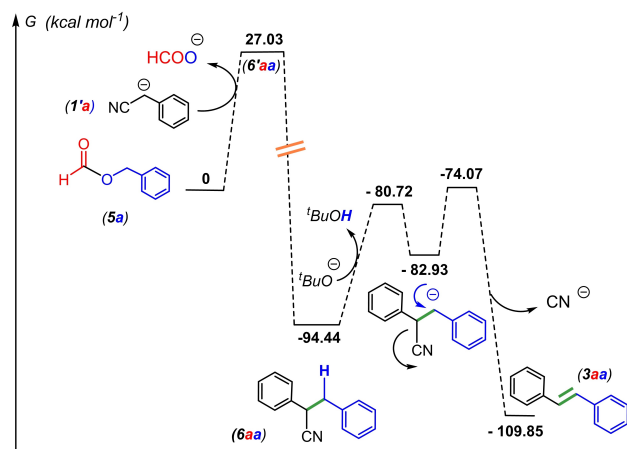


Figure 1. Gibbs energy levels (G, given in Kcal mol^{-1}) for all steps of the olefination reaction starting from the formate 5a . M06-2X/6-311++G(d,p) level of theory, in DMF, is used.

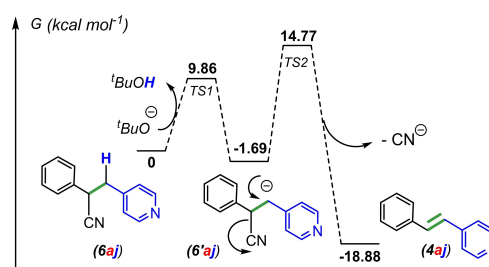


Figure 2. Gibbs energy levels (G, given in Kcal mol^{-1}) for the evolution of α -alkylated nitrile 6aj .

shown above (Scheme 3, reaction 5), that the α -alkylated nitrile (6aj), is probably not a reaction intermediate. Indeed, the relatively acidic benzyl hydrogen atom of 6aj can be deprotonated by KO^tBu (TS1 : $+9.86 \text{ kcal mol}^{-1}$) to form a carbanion intermediate 6'aj ($\Delta G = -1.69 \text{ kcal mol}^{-1}$). The latter could very quickly lose the cyanide (TS2 : $+16.46 \text{ kcal mol}^{-1}$) to lead to the corresponding, thermodynamically favoured alkene, 4aj ($\Delta G = -17.19 \text{ kcal mol}^{-1}$ compared to 6'aj), (Figure 2). We could not highlight a concerted pathway to the alkylation product from the α -alkylated nitrile 6aj and a postulated two-step pathway via a carbocation after cyanide anion departure proved thermodynamically unfavourable ($62.98 \text{ kcal mol}^{-1}$; see Supporting Information).

Work is in progress to elucidate the mechanism of this alkylation pathway, for which we do not yet have clear evidence.

Conclusions

In conclusion, we have discovered a new alternative and competitive route to synthesise alkenes, which are molecules of fundamental importance in chemistry. This new procedure is based only on the KO^tBu /DMF promoted activation and direct coupling of alcohols, which are sustainable sources of carbon compared to fossil resources, with phenyl acetonitriles. Various *E*-stilbenes have thus been obtained directly from alcohols, which is to our knowledge, unprecedented in the absence of transition metal based catalysts. This method avoids drawbacks linked the common activation ways of alcohols by protonation or prefunctionalization into potentially genotoxic sulfonates or halides, or by using costly transition metal catalytic systems required in dehydrogenative processes. This point is a curial advantage for synthesis of pharmaceuticals, as it avoids the leaching of toxic transition metal impurities. A variation allowing, through a $\text{Csp}_3\text{-Csp}_3$ bond formation the selective synthesis of *N*-Heteroarenes which are prevalent motifs in pharmaceuticals, and materials, is also described. Rationalised by experimental and computational studies, a mechanism for the olefination pathway proceeding via an original activation of alcohols under alkyl formate intermediates, was proposed. From an overall perspective, this new method offers a welcome alternative in the field of both olefin synthesis and alcohol

activation. Efforts to expand its utility are in progress and will be reported in due course.

Acknowledgements

We thank the Institut de France, Académie des Sciences for Financial support, the China Scholarship Council for a grant to Mr. Xiaoping LIU, the CNRS, the ENSCM, and the "Direction du Numérique" of the Université de Pau et des Pays de l'Adour. Mésocentre de Calcul Intensif Aquitain & CINES under allocation A005080045 made by Grand Equipement National de Calcul Intensif (GENCI) are acknowledged for computational facilities. We also thank Angus Shepard from James Cook University (Townsville, Australia) for the English corrections.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Alkene synthesis · Alcohol activation · Transition metal free · Mechanistic study · Synthetic methods

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- Manuscript received: May 31, 2022
Revised manuscript received: June 13, 2022
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