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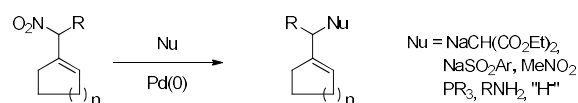
Mansour Dolè Kerim,^a Shuanglong Jia,^a Chrysoula Theodorakidou,^a Sébastien Prévost^{*a} and Laurent El Kaïm^{*a}

Nitro allylic derivatives were converted into dienes through elimination of the nitro group under basic treatment, in the presence of a palladium catalyst. This reaction probably involves the formation of a palladium π -allyl complex followed by a base promoted β -hydride elimination. This reaction, combined with the condensation of ketones with nitromethane and the functionalization of the resulting nitrocycloalkenes, constitutes a very powerful synthetic tool for the formation of dienes. A particular attention has been brought to the application of this methodology to the formation of 1-substituted naphthalenes from 1-tetralone.

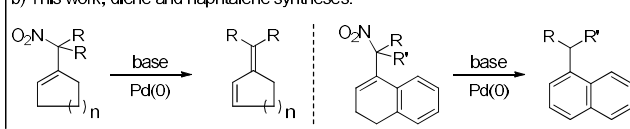
The easy functional modification of the nitro group together with its strong electron withdrawing properties has turned aliphatic nitro derivatives into one of the most fascinating synthetic platform. Indeed, the ability to deprotonate simple aliphatic nitro derivatives under smooth basic treatment has led to very efficient carbon-carbon bond formations,¹ such as observed in the Henry reaction,² the Michael³ or Mannich additions of nitro derivatives.⁴ These transformations coupled with easy reduction to amines, conversion to carbonyl derivatives (Nef reaction)⁵ or nitrile oxides (Mukaiyama reaction)⁶ have been at the center of many simple and efficient syntheses of heterocycles.⁷ In contrast to these important progresses made decades ago, transition metal based transformation of nitro compounds has made little progress being mainly limited to reductive transformation to amine derivatives using various hydrogen donors.⁸ This is particularly true for palladium catalyzed reactions working on aromatic as well as aliphatic nitro compounds. However, in the 80's, the groups of Hegedus and Tamura reported the properties of nitro allylic compounds to form π -allyl complex in presence of a palladium (0) catalyst in order to realize allylic substitution

reactions.⁹ Since these first works, very few examples of palladium catalyzed substitution of nitro allylic derivatives have been reported (Scheme 1.a).¹⁰ Albeit an easy access to highly functionalized starting materials, these reactions have been poorly explored in synthesis. Stimulated by our interest in Tsuji-Trost reactions,¹¹ we envisioned that, in the absence of a potential nucleophilic group, the π -allyl intermediate derived from nitro compounds could afford, under basic conditions, an interesting access to dienes or aromatic derivatives after β -hydride elimination (Scheme 1.b). Due to the synthetic importance of 1,3-dienes in organic transformations ([4+2] cycloadditions, polymerizations or diene functionalizations)¹² and their presence in natural products,¹³ several methods, such as enyne metathesis, Wittig type reactions or alkynes isomerisation, have been developed to have access to this moiety.¹⁴ Herein, we report a new synthesis of 1,3-dienes and aromatic derivatives based on a palladium catalyzed Tsuji-Trost reaction of nitro allylic derivatives. When coupled with prior functionalization of nitro compounds, this elimination process could be the key to valuable synthetic building blocks.

a) Nucleophilic substitution of cyclic nitro allylic derivatives:



b) This work, diene and naphthalene syntheses:



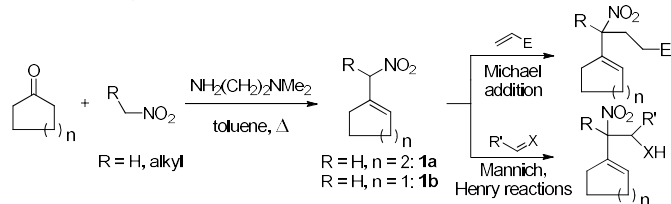
Scheme 1 Palladium catalyzed diene synthesis from nitro allylic derivatives

Cyclic nitro allylic derivatives are particularly useful synthetic intermediates. Easily prepared through ethylenediamine triggered Knoevenagel type reactions between cyclic ketones and nitroalkanes, the resulting nitrocycloalkenes can be further functionalized using standard nitro chemistry (Michael, Henry or Mannich reaction) allowing the formation of highly

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France. sebastien.prevost@ensta-paristech.fr; laurent.elkaim@ensta-paristech.fr Electronic Supplementary Information (ESI) available: details of experimental procedures, ¹H NMR and ¹³C NMR spectra for all unknown compounds, See DOI: 10.1039/x0xx00000x

functionalized nitroderivatives (Scheme 2, see the supporting information).



Scheme 2 Nitrocycloalkenyl synthetic platform

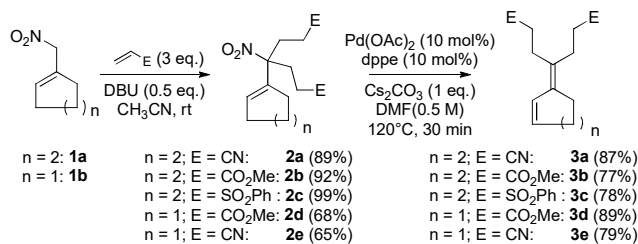
At the outset of these investigations, we focused our attention on the eliminative Tsuji-Trost reaction of quaternary nitro derivatives, as potential trapping of π -allyl intermediates with nitronate derivatives may lead to competing homocoupling reactions. Thus, nitro allylic **2a**, which can be easily synthesized in two steps and very good yields from cyclohexanone (see the supporting information), was selected as model substrate to test the reaction (Table 1). Treating **2a** with 5 mol% of palladium diacetate with triphenylphosphine as ligand and cesium carbonate as base, we were delighted to obtain expected diene **3a** in 62% isolated yield (Table 1, entry 1). Emboldened by this result, different phosphine ligands were screened and dppe (1,2-bis(diphenylphosphino)ethane) showed the best yield (82%, Table 1, entry 1-3). After a screening of the reaction conditions (Table 1, entry 3-7), potassium carbonate in DMF was selected as the best combination of base and solvent. Finally, using 10 mol% of palladium diacetate with 10 mol% of dppe afforded the desired diene **3a** in 87% isolated yield (Table 1, entry 8).

Table 1 Optimisation of Tsuji-Trost diene formation^a

Entry	Phosphine	Base	Solvent	T (°C)	Yield ^b (%)
1	PPh ₃ (15 mol%)	Cs ₂ CO ₃	DMF	120	62
2	P(<i>o</i> -tol) ₃ (15 mol%)	Cs ₂ CO ₃	DMF	120	79
3	dppe (5 mol%)	Cs ₂ CO ₃	DMF	120	83
4	dppe (5 mol%)	K ₂ CO ₃	DMF	120	82
5	dppe (5 mol%)	DIPEA	DMF	120	33
6	dppe (5 mol%)	Cs ₂ CO ₃	Toluene	110	57
7	dppe (5 mol%)	Cs ₂ CO ₃	CH ₃ CN	80	51
8 ^c	dppe (10 mol%)	Cs ₂ CO ₃	DMF	120	87

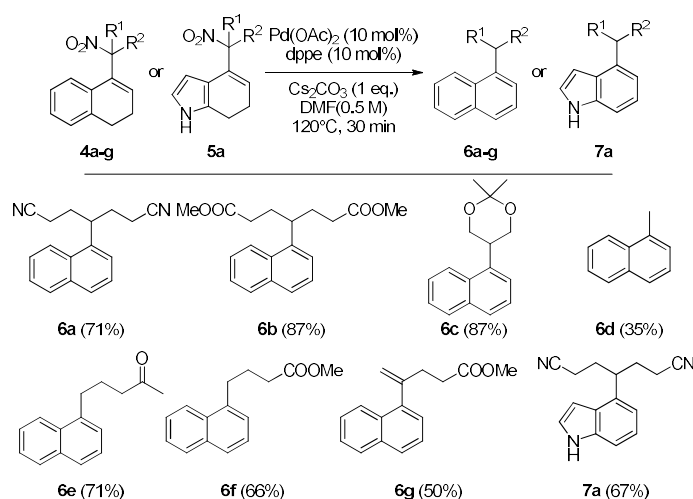
^a Unless otherwise noted, all reactions were performed on 0.5 mmol scale with 5 mol% of Pd(OAc)₂. ^b Isolated yield. ^c 10 mol% of Pd(OAc)₂ was used.

With these optimized conditions in hand, we investigated the scope of this transformation regarding the synthesis of cyclic dienes (Scheme 3). Different nitro allylic derivatives **2a-e** were synthesized in one step and very good yields from **1a-b** by just changing the Michael acceptor and submitted to our eliminative Tsuji-Trost conditions. Several cyclic dienes bearing different electron withdrawing groups were obtained in excellent yields.



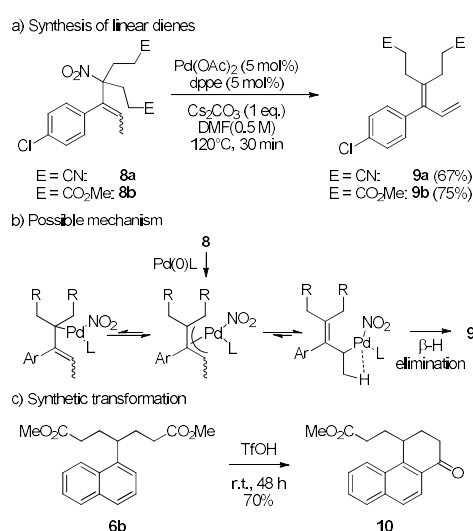
Scheme 3 Substrate scope of the synthesis of cyclic dienes

After having shown the feasibility of this reaction to obtain cyclic dienes, we were keen to use this strategy for the synthesis of aromatic derivatives and especially to obtain naphthalenes and indoles. Indeed, naphthalenes and indoles are important aromatic skeletons in chemistry,^{15,16} and the development of new methods to have access to these scaffolds is very important. For this purpose, we synthesized several 4-(nitromethyl)-1,2-dihydronaphthalenes **4a-g** in two steps from 1-tetralone and tried our optimized conditions (Scheme 4). We were planning that, under these conditions, the naphthalene moiety could be obtained after diene formation and isomerisation due to the aromatic nature of the final product. Indeed, seven naphthalenes were synthesized in moderate to excellent yields. As previously, quaternary nitro derivatives delivered corresponding naphthalenes **6a-c** in very good isolated yields. In addition, the reaction conditions were compatible with secondary and tertiary compounds and 1-methylnaphthalene **6d** was obtained in 35% yield whereas naphthalenes **6e-f** were isolated in good yield. Then, we tried our conditions on **4g** (R¹ = -CH₂OAc; R² = -CH₂CH₂CO₂Me) where the presence of an acetate group could form a second π -allyl complex after the elimination of the nitro group. As expected, naphthalene **6g** bearing an additional double bond was obtained *via* double palladium catalyzed elimination. Finally, very interestingly, this strategy could be applied to the synthesis of indoles. Substrate **5a** reacted smoothly, giving indole **7a** in 67% yield.



Scheme 4 Substrate scope of the aromatic compound synthesis

In order to show the versatility of our system, we applied our conditions to the synthesis of linear dienes (Scheme 5.a). When linear nitro allylic substrates **8a-b** (*E/Z* mixture) were treated with 5 mol% of palladium diacetate in presence of cesium carbonate, dienes **9a-b** were isolated in very good yields. The selective formation of the terminal diene is consistent with an equilibrium between η^3 -allyl and σ -allyl palladium complexes followed by a β -H elimination from the less hindered σ -allyl complex (Scheme 5.b).¹⁷ The same mechanistic considerations may be advanced for the selectivity observed in the conversion of **2a** into **3a**. The high functionalization of nitro starting materials makes our transformation particularly interesting to synthesize polycyclic compounds in few steps. For instance, by treating naphthalene **6b** with triflic acid, tricyclic tetralone derivative **10** was obtained in good yield (Scheme 5.c).



Scheme 5 Application to linear diene synthesis, proposed mechanism and synthetic transformations

To conclude, we have disclosed a new Tsuji-Trost type elimination of nitro allylic derivatives towards dienes. Whereas dienes formation in Tsuji-Trost reaction using allylic acetates is well known,¹⁸ it suffers from low synthetic potential compared to their related substitutions. The situation is quite different for nitro derivatives. Indeed, the high acidity of nitro alkyl compounds together with their high yielding additions to various unsaturated systems make these nitro derivatives a very powerful synthetic platform. After using these properties to control C-C bond formations, the ability to eliminate the nitro group forming dienes offer interesting new strategies in relation with the important literature on the conversion of 1,3-dienes into cyclic systems.¹²

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Conflicts of interest

There are no conflicts to declare.

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