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Palladium catalyzed arylation reactions of *meta* photocycloadducts

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We describe the first application of a Heck arylation reaction being performed on a *meta* photocycloadduct. The resulting arylation/fragmentation process leads to the formation of a bridged bicyclic ketone and constitutes a dramatic increase in molecular complexity after just two synthetic operations.

The *meta* photocycloaddition reaction[1] involves the 1,3-addition of an olefin across the excited state of a benzene ring (Fig. 1). During this light induced transformation three new bonds, three new rings and up to six new stereocenters are generated in one operation. Different substituents on the aromatic ring control the regioselectivity of addition between the benzene and the alkene portions, with electron-donating groups favouring the *b1* position and electron-withdrawing groups favouring the *b2* and *b4* positions in the photoadduct.[1c]

The *meta* photocycloadduct structure is inherently strained and its synthetic potential for forming bridged [3.2.1] bicycles is realized when the cyclopropane ring is fragmented. Various methods have been used to achieve this and most have involved an oxy-substituted *meta* photocycloadduct reacting with an electrophile such as a proton,[2] bromine[3] or *m*CPBA[4] (Scheme 1).

Of the methods used to initiate *meta* photocycloadduct fragmentation, none so far have involved the formation of new carbon–carbon bonds and the purpose of this communication is to report our preliminary discoveries in this area.

The two key reactive elements of a *meta* photocycloadduct are its alkene and cyclopropane portions, both of which are known to react with palladium compounds.[5–7] We conceived that a Heck-like reaction carried out on an anisole derived *meta* photocycloadduct would lead to a similar cyclopropyl fragmentation process and result in the formation of a new arylated adduct. We began our arylation investigations using **1**,[2] the *meta* photocycloadduct derived from anisole **2** and cyclopentene.

The aryl ketone **3** was prepared in 27% yield by heating a solution of **1**[2] in dimethylformamide with 1-iodo-2-nitrobenzene, palladium acetate (5 mol%), tri-*ortho*-tolylphosphine (15 mol%) and triethylamine at 120 °C for 12 h. The structure of **3** was deduced from NMR studies and later confirmed by X-ray crystallography† (Scheme 2).

A catalytic cycle can be proposed to explain the arylation fragmentation sequence (Scheme 3). It involved oxidative addition of a palladium[0] species with an aryl iodide, followed by carbopalladation with the *meta* photocycloadduct, cyclopropyl fragmentation and then reductive de-iodomethylation to regenerate the palladium[0] species.

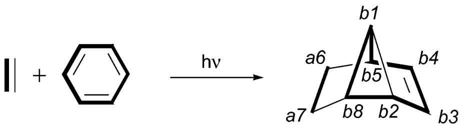
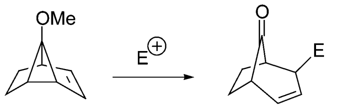


Fig. 1 The *meta* photocycloaddition reaction between benzene and ethene.



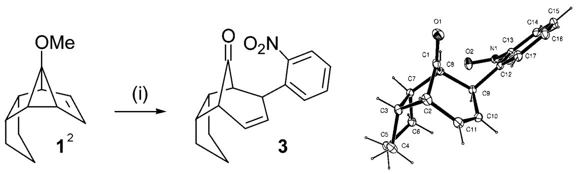
Scheme 1 The reaction of an anisole derived *meta* photocycloadduct with an electrophile E$^+$.

To further probe the reaction mechanism using an unsymmetrical alkene, whilst maintaining our interest in assembling the core skeleton of the alkaloid gelsemine[4,8] (Fig. 2), the *meta* photocycloadduct derived from anisole and allyl alcohol was prepared.

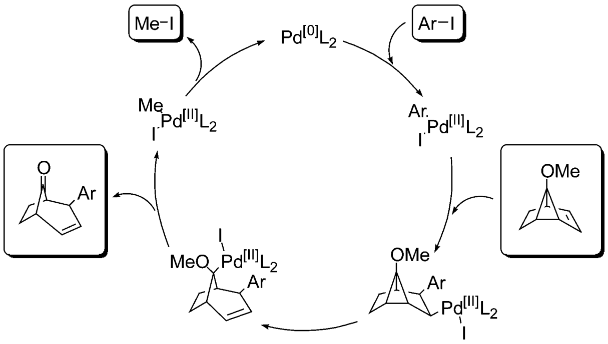
A solution of anisole **2** (2 M) and allyl alcohol **4** (3 M) in cyclohexane was irradiated with 254 nm light in a quartz immersion-well photoreactor using a 16 W mercury vapour lamp for 120 h. The electron donating methoxy group of anisole directed *meta* addition of the allyl alcohol across the 2,6-positions of the aromatic ring during the photo reaction and four *meta* photocycloadduct isomers were obtained, with the desired 7-*endo* isomer **5** being easily separable from the other three (Scheme 4).

Although the conversion of reactants to products was disappointingly low, the simplicity of the starting materials, combined with their volatility, meant that multigram quantities of **5** could be readily obtained. When compound **5** was subjected to the same arylation conditions as before, the two aryl ketones **9** and **10** were obtained in 52% yield as a 4 : 1 ratio (Scheme 5).

The structures of **9** and **10** were deduced from NMR studies, and compound **9** was also confirmed by X-ray crystallography.‡ In both cases the aryl group had been introduced onto the *exo* face of the



Scheme 2 *Reagents and conditions*: (i) 1-iodo-2-nitrobenzene, Pd(OAc)$_2$, P(*o*-Tol)$_3$, NEt$_3$, DMF, 120 °C, 12 h, 27%.



Scheme 3 Proposed catalytic cycle for the cyclopropyl fragmentation and arylation of an anisole derived *meta* photocycloadduct.

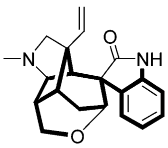


Fig. 2 Gelsemine.

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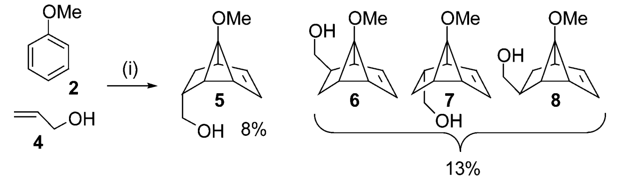
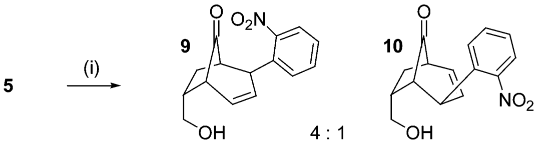


Scheme 4 *Reagents and conditions*: (i) *hν*, 254 nm, cyclohexane, 120 h.



Scheme 5 *Reagents and conditions*: (i) 1-iodo-2-nitrobenzene, Pd(OAc)$_2$ (5 mol%), P(*o*-Tol)$_3$ (10 mol%), NEt$_3$, DMF, 120 °C, 12 h, 52%.

bridged bicyclic ring system. The major isomer **9** was arylated in a manner appropriate for a potential gelsemine synthesis and similar to that described by our proposed catalytic cycle (Scheme 3). The presence of the minor isomer **10** indicated that a π-allyl palladium species **11** (Fig. 3) may also be involved in the reaction pathway. Although not isolated here, compounds similar to **11** have been observed when vinylcyclopropanes undergo halopalladation.[7]

We also found that this arylation/fragmentation reaction could be applied to simple alkyl benzene derived *meta* photocycloadducts. A solution of toluene (1 M) and allyl alcohol (2 M) in cyclohexane was irradiated for 120 h using 254 nm light. The electron donating methyl group again directed *meta* addition of the allyl alcohol across the 2,6-positions of the aromatic ring during the photo reaction, but this time only the 6- and 7-*endo* photoadduct isomers **13** and **14** were isolated (Scheme 6).

The 7-*endo* isomer **14** was reacted under similar Heck conditions with a range of aryl halides and resulted in the formation of the arylation adducts **15** and **16**, which contained an olefin at the bridgehead instead of a ketone (Table 1).

The reaction was not restricted to electron-deficient aryl iodides, as we found that electron-rich aryl bromides would also form **15** and **16**, although chlorobenzene failed to react under the conditions used. Like compound **9**, the major isomer **15** was arylated at what was previously the *b4* position of the former photoadduct (see Fig. 1), whilst the minor isomer **16** was arylated at the *b2* position. This again indicated that a π-allyl palladium species analogous to **11** was probably involved as an intermediate in the arylation process.

In conclusion, we have shown the first examples of a Heck-like arylation reaction performed on *meta* photocycloadducts. In just two synthetic operations a significant portion of the gelsemine skeleton can be assembled in a highly atom efficient manner starting from anisole and allyl alcohol.

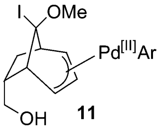
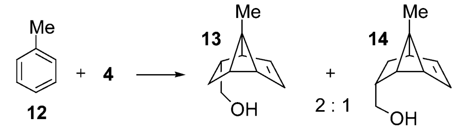
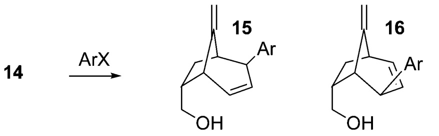


Fig. 3 The proposed π-allyl palladium species **11**, which may be involved as an intermediate during the formation of **10**.



Scheme 6 *Reagents and conditions*: *hν*, 254 nm, cyclohexane, 120 h, 6%.

Table 1 Palladium catalysed arylation reactions of the toluene derived 7-*endo* photoadduct **14**[a]



Entry	Ar	X	Yield of **15**	Yield of **16**
1	2-Nitrophenyl	I	29%	13%
2	2-Nitrophenyl	Br	30%	10%
3	3-Methylphenyl	Br	30%	< 10%
4	4-Methylphenyl	Br	29%	< 10%
5	Phenyl	I	35%	< 10%
6	Phenyl	Cl	no reaction	

[a] ArX, Pd(OAc)$_2$ (5 mol%), P(*o*-Tol)$_3$ (10 mol%), NEt$_3$, DMF, 120 °C, 12 h.

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Notes and references

† Crystal data for **3**: $C_{17}H_{17}NO_3$, M = 283.3, monoclinic, $P2_1/n$ (No. 14), a = 7.9469(3), b = 16.7131(5), c = 10.3861(4) Å, β = 93.298(1)°, U = 1377.2 Å^3, Z = 4, D_{calc} = 1.37 Mg m^{-3}, μ(Mo-Kα) = 0.09 mm^{-1}. R_1 = 0.038 for 1959 reflections with $I > 2\sigma(I)$, wR_2 = 0.101 for all 2301 unique reflections. CCDC 241883. See http://www.rsc.org/suppdata/cc/b4/b404816d/ for crystallographic data in .cif or other electronic format.

‡ Crystal data for **9**: $C_{15}H_{15}NO_4$, M = 273.28, monoclinic, Cc, a = 25.7419(4), b = 7.9982(2), c = 14.0165(3) Å, β = 110.646(1)°, U = 2700.5 Å^3, Z = 8, μ(Mo-Kα) = 0.10 cm^{-1}, R_1 = 0.038 for 4806 reflection with $I > 2\sigma(I)$, wR_2 = 0.084 for all 5411 reflections. CCDC 230790. See http://www.rsc.org/suppdata/cc/b4/b404816d/ for crystallographic data in .cif or other electronic format.

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