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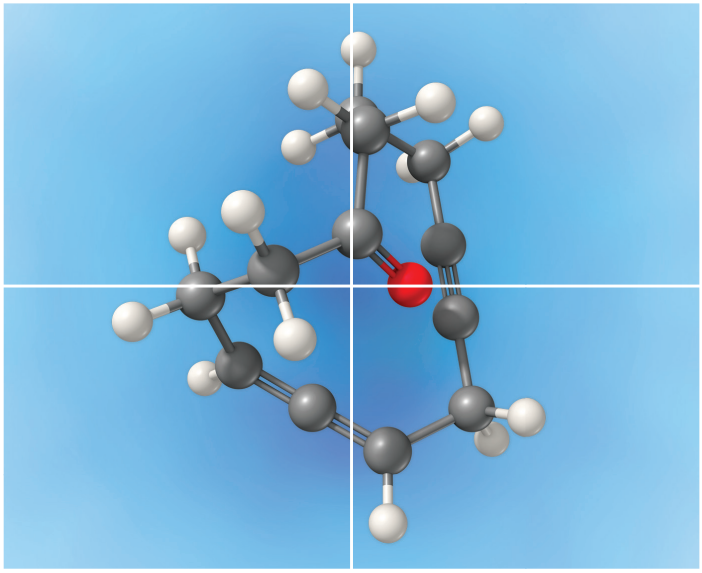

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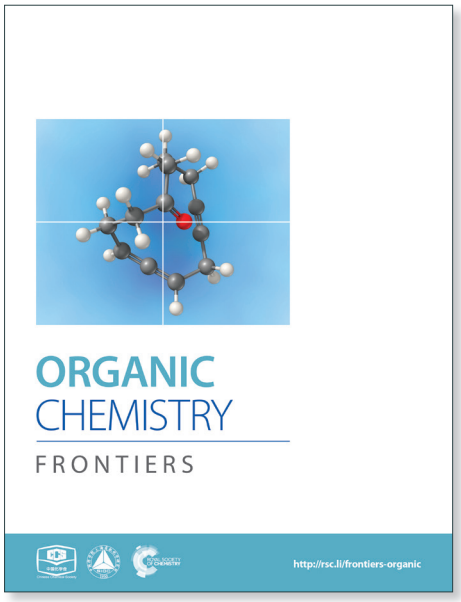

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ARTICLE

Synthesis of 1,4-benzodiazepinones and 1,4-benzoxazepinones via palladium-catalyzed amino and oxyacetoxylation†

A.D. Manick, G. Duret, D.N. Tran, F. Berhal,* and G. Prestat *

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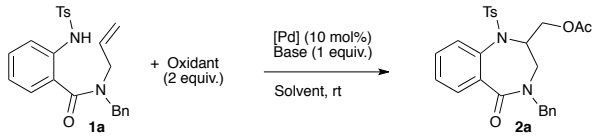
Palladium-catalyzed amino and oxyacetoxylation have been developed to furnish 1,4-benzodiazepinones and 1,4-benzoxazepinones through diheterofunctionalization of alkenes. This study demonstrates the ability of this new methodology to allow 7-*exo* ring-closure.

Metal-catalyzed vicinal dioxygenation[1] and oxyamination[2] of alkenes is a powerful tool in organic synthesis. In 2005, Sorensen reported a palladium-catalyzed aminoacetoxylation of unactivated olefins in the presence of (diacetoxyiodo)benzene as an oxidant.[3] This new synthetic methodology has emerged as an interesting alternative to the classical osmium-based Sharpless dihydroxylation[4] and aminohydroxylation.[5] The reaction proceeds through an initial nucleopalladation[6] followed by oxidation of the organopalladium(II) intermediate thus generated to an organopalladium(IV) complex allowing the formation of the second hetero-carbon bond with concomitant released of the catalyst. The flexibility of such a process allows to achieve oxyamination[3,7] dioxygenation,[8] diamination,[9] as well as aminofluorination[10] of alkenes.[11] Although this strategy appears highly attractive from a synthetic point of view, it has been the subject of a very limited number of reports dealing with the synthesis of biological relevant compounds. Moreover, cyclizing processes were studied for the formation of five- and six-membered rings only.

Following our efforts towards palladium-catalyzed synthesis of heterocycles,[12] we were intrigued to know if such a methodology would allow the formation of the seven-membered heterocyclic core found in benzodiazepine that is considered as a privileged structure.[13] Palladium-catalyzed access to 1,4-benzodiazepines has been previously reported via alkene aminopalladation,[14] alkene carboamination,[15] and an allene carbopalladation/amination domino sequence.[16] We report in this communication the successful synthesis of 1,4-benzodiazepin-5-ones via a palladium-catalyzed aminoacetoxylation of alkenes. Moreover, we demonstrate that a slight modification of the reaction conditions allows the access to 1,4-benzoxazepin-5-ones through the corresponding oxyacetoxylation.

Compound **1a** was chosen as a model substrate to study the aminoacetoxylation reaction (scheme 1).



Scheme 1 Synthesis of 1,4-benzodiazepinone **2a** via palladium-catalyzed aminoacetoxylation.

In a first set of experiments, the reaction was run in the presence of $Pd(OAc)_2$ (10 mol%) and $PhI(OAc)_2$ (2 equiv.) in DCM at rt and the influence of the base was studied. The use of Bu_4NOAc allowed the formation of the desired product **2a** in 56% yield (entry 1, table 1). Sodium, potassium and silver acetates led to a large decrease of the yield (10, 25 and 15% respectively, entries 2-4, table 1). A poor 7% yield was obtained on the use of both potassium and cesium carbonates (entries 5-6, table 1). Organic bases were next tested. The use of pyridine completely inhibited the reaction while DABCO, DBU and proton sponge were found to be poorly effective (entries 7-10, table 1). Triethylamine allowed a moderate 44% yield (entry 11, table 1) while diisopropylethyl amine (DiPEA) afforded the desired benzodiazepinone **2a** in 71% yield (entry 12, table 1). Palladium source was next tested. Replacing $Pd(OAc)_2$ with $PdCl_2(CH_3CN)_2$ or $PdCl_2(PhCN)_2$ in the presence of DiPEA gave less satisfactory results (54% and 55% respectively, entries 13-14, table 1). In the absence of any palladium source no product formation was observed (entry 15, table 1). Moreover, keeping DiPEA as the base and decreasing the palladium concentration to 5 mol% induced a lowering of the yield to 40% (entry 16, table 1). Finally, raising the amount of oxidant $PhI(OAc)_2$ (2,5 equiv.) in the presence of $Pd(OAc)_2$ (10 mol%) led to a 74% yield (entry 17, table 1).

Table 1 Optimization of the base and palladium source for the aminoacetoxylation of **1a**.[a]

Entry	[Pd]	Base	Yield[b] of **2a** (%)
1	$Pd(OAc)_2$	Bu_4NOAc	56
2	$Pd(OAc)_2$	NaOAc	10
3	$Pd(OAc)_2$	KOAc	25
4	$Pd(OAc)_2$	AgOAc	15
5	$Pd(OAc)_2$	K_2CO_3	7
6	$Pd(OAc)_2$	Cs_2CO_3	7
7	$Pd(OAc)_2$	Pyridine	0
8	$Pd(OAc)_2$	DABCO	5
9	$Pd(OAc)_2$	DBU	21
10	$Pd(OAc)_2$	Proton sponge	13
11	$Pd(OAc)_2$	NEt_3	44
12	$Pd(OAc)_2$	DiPEA	71
13	$PdCl_2(CH_3CN)_2$	DiPEA	54
14	$PdCl_2(PhCN)_2$	DiPEA	55
15	-	DiPEA	0
16	$Pd(OAc)_2$	DiPEA	40[c]
17	$Pd(OAc)_2$	DiPEA	74[d]

[a] Reaction conditions : **1a** (1 equiv.), $PhI(OAc)_2$ (2 equiv.), [Pd] (10 mol%), base (1 equiv.), DCM, rt, 2 h. [b] Yields refer to isolated products. [c] $Pd(OAc)_2$ (5 mol%). [d] $PhI(OAc)_2$ (2.5 equiv.).

The influence of the oxidant was next evaluated using $Pd(OAc)_2$ (10 mol%) and DiPEA (1 equiv.), in DCM (Scheme 1, Table 2). Replacing $PhI(OAc)_2$ with $PhI(OTFA)_2$ or $Cu(OAc)_2$ completely inhibit the formation of any benzodiazepinone (entries 2-3 *vs* 1, table 2). On the other hand, the use 3-NO_2, 4-MeO-(diacetoxyiodo)benzene and (diacetoxyiodo)benzene gave the same result (entries 4-5 and 1, table 2).

Table 2 Optimization of the oxidant for the aminoacetoxylation of **1a**.[a]

Entry	Oxidant	Yield[b] of **2a** (%)
1	$PhI(OAc)_2$	74
2	$PhI(OTFA)_2$	0
3	$Cu(OAc)_2$	0
4	3-NO_2-$C_6H_4I(OAc)_2$	74
5	4-OMe-$C_6H_4I(OAc)_2$	74

[a] Reaction conditions : **1a** (1 equiv.), oxidant (2,5 equiv.), $Pd(OAc)_2$ (10 mol%), DiPEA (1 equiv.), DCM, rt, 2 h. [b] Yields refer to isolated products.

A solvent screening was next undertaken using our optimized conditions (Scheme 1, Table 3). DCM proved to be the solvent of choice for this reaction leading to the highest yield and shortest reaction time. A correlation between the efficiency of the solvent and its physical characteristics (dipole moment, dielectric constant) could not be established (entries 1-9, table 3).

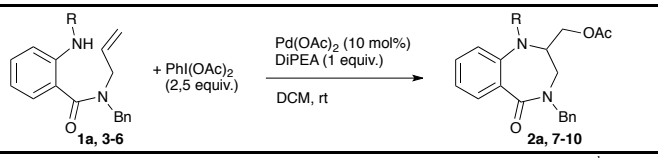
Table 3 Optimization of the solvent for the aminoacetoxylation of **1a**.[a]

Entry	Solvent	Reaction time (h)	Yield[b] of **2a** (%)
1	DCM	2	74
2	Toluene	24	68
3	Cyclohexane	24	44
4	THF	24	24
5	Dioxane	24	46
6	AcOEt	24	47
7	DMF	2	27
8	Acetonitrile	3	59
9	DMSO	2	27

[a] Reaction conditions : **1a** (1 equiv.), $PhI(OAc)_2$ (2,5 equiv.), $Pd(OAc)_2$ (10 mol%), DiPEA (1 equiv.), DCM, rt. [b] Yields refer to isolated products.

Finally the nature of the nitrogen atom protecting group was examined. Replacement of the tosyl with a nosyl group induced a slight decrease in yield (70% vs 74%, entries 1-2, table 4) and a longer reaction time to reach complete conversion. After 24h of reaction, starting material was completely recovered with either Boc or Ac derivatives **4** and **5** (entries 3-4, table 4). On the other hand, decomposition of the starting material was observed with the free aniline derivative **6** (entry 5, table 4).

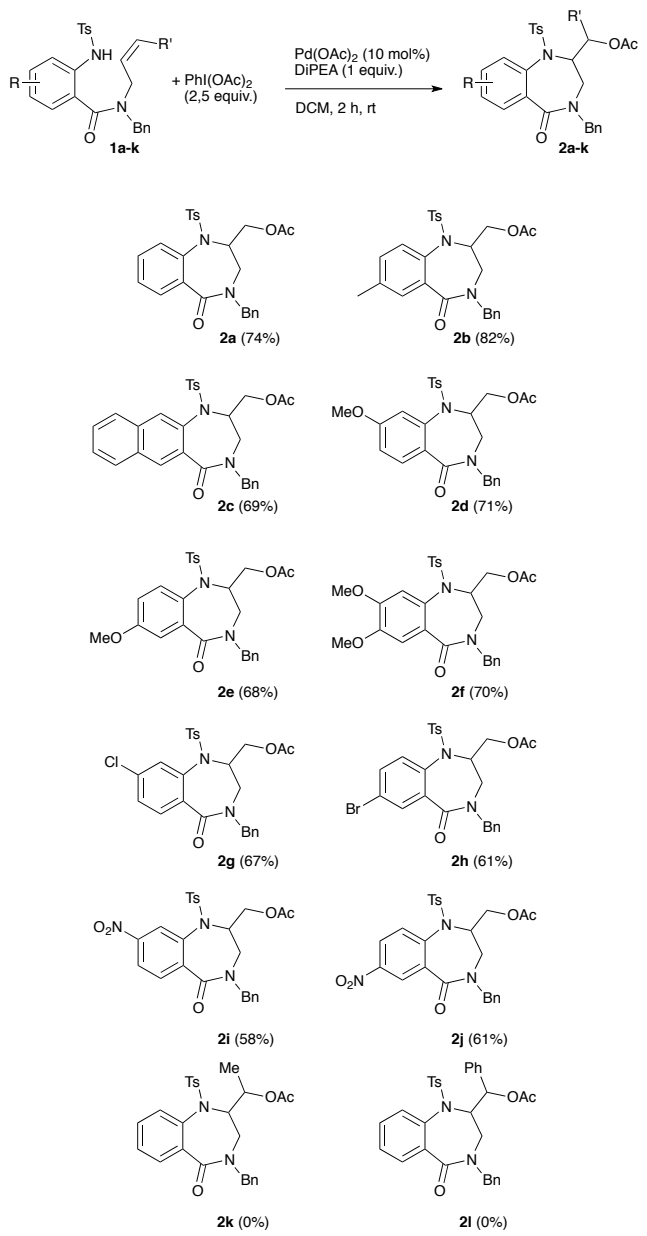
Table 4 Study of the nitrogen protecting group for aminoacetoxylation.[a]



Entry	Substrate	R	Reaction time (h)	Product	Yield[b] (%)
1	**1a**	Ts	2	**2a**	74
2	**3**	Ns	6	**7**	70
3	**4**	Boc	24	**8**	0
4	**5**	Ac	24	**9**	0
5	**6**	H	2	**10**	0

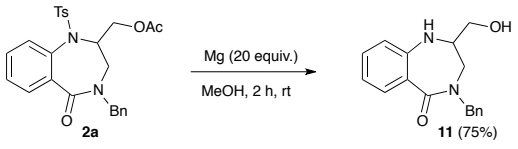
[a] Reaction conditions : substrate (1 equiv.), $PhI(OAc)_2$ (2,5 equiv.), $Pd(OAc)_2$ (10 mol%), DiPEA (1 equiv.), DCM, rt. [b] Yields refer to isolated products.

Having in hand the fully optimized conditions the scope of the reaction was then studied (scheme 2). The reaction proved to easily tolerate electron-donating as well as electron-withdrawing substituents on the aryl ring. The desired amino-acetoxylated compounds were isolated in yields ranging from 58 to 82%. Unsurprisingly, the use of 1,2-disubstituted alkene **1k** completely inhibited the aminoacetoxylation process. This is a known limitation of palladium-catalyzed difunctionalization of alkenes that has been overcome for styrene derivatives only [3, 8a, 9b]. However, using our conditions, a complete lack of reactivity was observed starting with the styryl derivative **1l**.



Scheme 2 Scope of the palladium-catalyzed aminoacetoxylation.

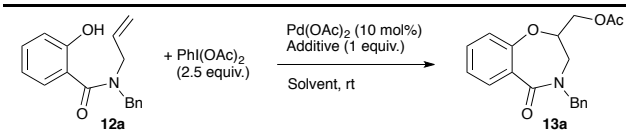
In order to validate our synthetic strategy towards 1,4-benzodiazepin-5-ones, removal of the tosyl group was undertaken using **2a** as a model substrate. Treatment of **2a** by magnesium turnings in methanol led to the removal of both tosyl and acetyl group. The 1,4-benzodiazepinone **11** was isolated in 75% yield (scheme 3).



Scheme 3 Removal of the tosyl group from **2a**.

We next envisioned extending the scope of the reaction by replacement of the nucleophilic nitrogen atom by an oxygen atom. Turning from aminoacetoxylation to oxyacetoxylation and starting with phenol derivative **12a**, the reaction should open a new route to 1,4-benzoxazepin-5-one such as **13a**. Using our optimized conditions for aniline substrates, the desired benzoxazepinone **13a** was isolated in a limited 30% yield (entry 1, table 5). A short optimization of the reaction conditions was thus undertaken. In DCM as solvent, the use of *t*-BuOK or AcOK led to an almost complete inhibition of the reaction (3 and 0% respectively, entries 2-3, table 5). When AcOK was used in the presence of 18-C-6 (1 equiv.) the desired benzoxazepinone **13a** was isolated in 27% yield (entry 4, table 5). Conversely, Bu_4NOAc allowed an increase in yield up to an encouraging 52% while Bu_4NBr completely failed to promote the cylization (entries 5-6, table 5). Keeping Bu_4NOAc as the base, solvent effects were next studied. When the reaction was run in toluene or DMSO, a slight decrease in yield was observed (48 and 46% yield respectively, entries 7-8, table 5). Finally, a satisfying 71% yield was reached upon running the reaction in DMF (entry 9, table 5). In the absence of a palladium source no cyclization product was observed (entry 10, table 5).

Table 5 Optimization for the oxyacetoxylation of **12a**.[a]



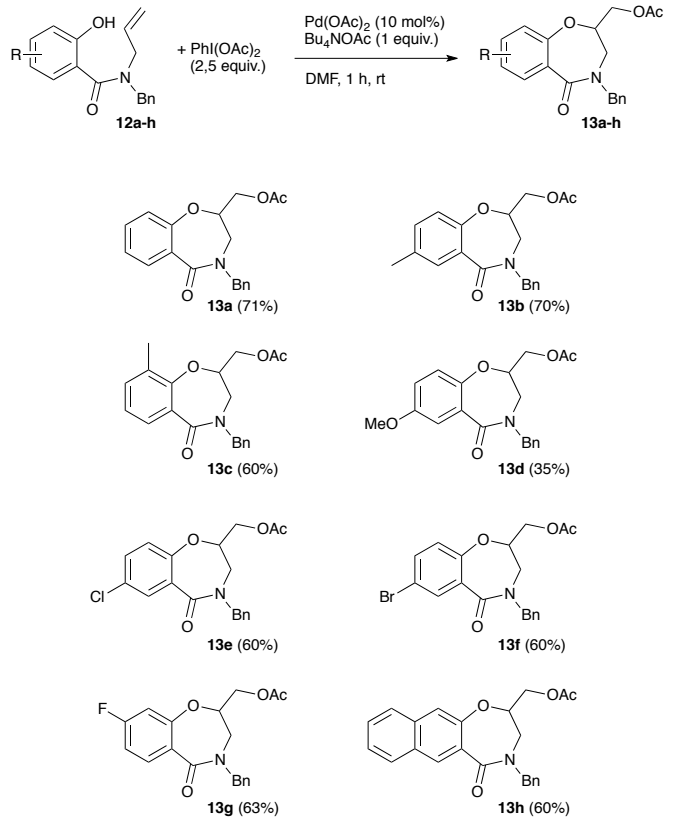
Entry	Additive	Solvent	Reaction time (h)	Yield of **13a** (%)[b]
1	DiPEA	DCM	2	30
2	*t*-BuOK	DCM	2	3
3	AcOK	DCM	2	0
4[c]	AcOK/18-C-6	DCM	2	27
5	Bu_4NOAc	DCM	1	52
6	Bu_4NBr	DCM	2	9
7	Bu_4NOAc	Toluene	1	48
8	Bu_4NOAc	DMSO	1	46
9	Bu_4NOAc	DMF	1	71
10[d]	Bu_4NOAc	DMF	1	0

[a] Reaction conditions : **12a** (1 equiv.), $PhI(OAc)_2$ (2,5 equiv.), $Pd(OAc)_2$ (10 mol%), Additive (1 equiv.), solvent, rt. [b] Yields refer to isolated products. [c] Reaction was run with AcOK (1 equiv.), 18-C-6 (1 equiv.). [d] Without $Pd(OAc)_2$.

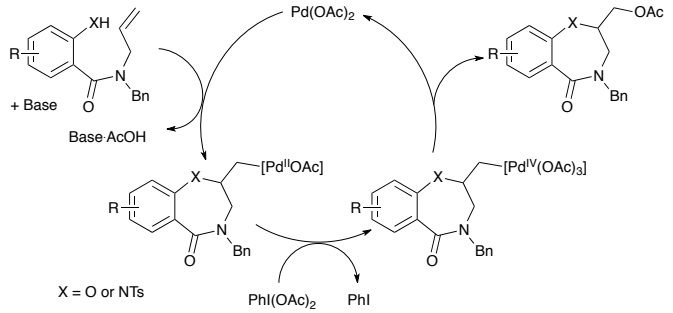
The scope of the oxyacetoxylation leading to benzoxazepinone was next examined (scheme 4). Yields were typically ranging between 60 and 71% using substrates bearing various substituents on the phenyl ring. The methoxy-substituted benzoxazepinone was obtained in a limited 35% yield.

The mechanism of palladium-catalyzed alkenes difunctionalization in the presence of hypervalent iodine have been previously studied by Stahl,[7a,d] Sanford,[7b] and Liu and Muñiz.[7d] Aminopalladation of the alkene is followed by a Pd(II) to Pd(IV) oxidation mediated by $PhI(OAc)_2$. The organopalladium(IV) complex evolves via reductive elimination to form the C-OAc bond and regenerates the Pd(II) catalyst (scheme 5). *Cis*- or *trans*-aminopalladation has been proposed, while reductive elimination might occur with retention or inversion of configuration. Stereoselectivity of

these elementary steps seemed highly substrate and conditions dependent and are still under debate.[7d]



Scheme 4 Scope of the palladium-catalyzed oxyacetoxylation.



Scheme 5 Putative mechanism.

In summary, we have developed a new route to 1,4-benzodiazepin-5-ones based on a palladium-catalyzed aminoacetoxylation process. Slight modifications of the reaction conditions opened the access to 1,4-benzoxazepinones via the corresponding oxyacetoxylation. This study describes for the first time a seven-membered ring-closure diheterofunctionalization of alkenes.

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Notes and references

Address: Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, UMR CNRS 8601, Université Paris Descartes, 45 rue des Saints Pères, 75006 Paris France.
E.mail: farouk.berhal@parisdescartes.fr, guillaume.prestat@parisdescartes.fr.

† Dedicated to Professor Max Malacria on the occasion of his 65th birthday.

Electronic Supplementary Information (ESI) available: Experimental details, compound characterization and NMR spectra. See DOI: 10.1039/b000000x/

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