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Unusual regioselectivity in Pd(0)-catalyzed coupling of allylic monoacetates and nitroalkanes: one-pot isomerization–alkylation

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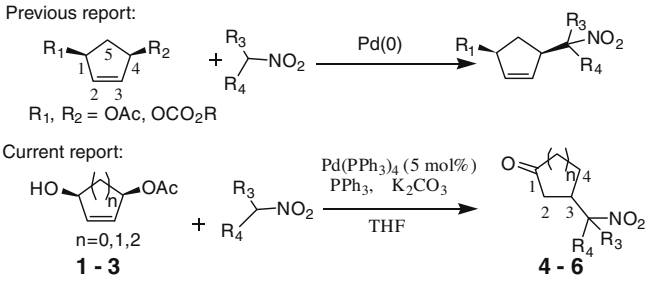
ABSTRACT

A hitherto unknown palladium-catalyzed reaction of nitroalkanes with hydroxy allylic acetates is reported. The reaction led to the formation of γ-nitrocarbonyl compounds instead of the usual unsaturated nitroalcohol expected upon displacement of the allylic acetate group.

Palladium-catalyzed allylic alkylation, also known as Tsuji–Trost reaction, has been extensively used in organic syntheses.[1] A broad range of nucleophiles, which include, active methylene and methine compounds, and various heteroatom (N, O, S) nucleophiles have been employed in this type of reaction. The survey of the literature[1,2] reveals that in Pd-catalyzed alkylation the new carbon–carbon bond is formed at the allylic carbon of the electrophile, that is, unsaturated compounds are formed and the new carbon–carbon bond is formed at the C-2 or C-4 (Scheme 1). Recently, we reported chemoenzymatic synthesis of furan and isoxazoline derivatives via Pd-catalyzed allylic alkylation and cyclizations starting from a *meso*-diol.[3]

In our quest for enzyme-coupled Pd(0)-catalyzed reactions, we have investigated coupling reaction of allylic monoacetate and nitroalkanes. Surprisingly, nitroalkanes have received little attention in Pd-catalyzed allylic alkylations as a nucleophile source even though nitro group can be easily converted to other functional groups.[4] The scarce utilization of nitroalkanes in Pd(0)-catalyzed allylic alkylations can presumably be attributed to their ambident nature (C- vs O-alkylation), low reactivity of bulky nitroalkanes, and formation of side products.[5] In this Letter, we report a hitherto unknown Pd-catalyzed reaction of nitroalkanes with hydroxy allylic acetates **1**–**3** (Scheme 1).

The reactions with 1° and 2° nitroalkanes led to the formation of γ-nitro carbonyl compounds instead of the usual unsaturated nitroalkanes expected upon displacement of the allylic acetate group. This represents the first example of Pd-catalyzed one-pot synthesis of γ-nitro carbonyl compounds. Another interesting feature of this reaction was the unusual regioselectivity of the new C–C bond formation from the expected C-4 to C-3 (Scheme 1) suggesting an isomerization to be involved in the reaction pathway. This reaction adds a new tool to the arsenal of Pd-mediated C–C bond-forming methodologies. Our efforts to evaluate the utility



Scheme 1. Pd-catalyzed alkylations of nitroalkanes.

of this reaction and establish a plausible mechanistic explanation for the 'isomerization–alkylation' are described in this Letter.

To understand the mode of the reaction, various solvents, bases, catalyst, and ligands were evaluated (Table 1). The reaction was highly dependent on the nature of the solvent. No reaction was observed in protic solvents (*t*-BuOH, *t*-BuOH + THF) or in nonpolar solvents (toluene, $CHCl_3$) with full recovery of the starting material. In polar aprotic solvents (DMF, DMSO, THF), however, the reaction resulted in the γ-nitro carbonyl compound **4c** in 10–12 h. Owing to its relative ease of handling, THF was selected as the solvent of choice for subsequent investigations. The rate and outcome of the reaction also depended on the base used. While KO^tBu and DABCO led to the product formation, K_2CO_3 proved to be the most effective base for this reaction. We also found that $Pd(OAc)_2$ and $PdCl_2$ did not catalyze the reaction suggesting that the reaction was only catalyzed by Pd(0) complexes. In order to study the substrate scope of the reaction, cyclic and acyclic allylic acetates as well as primary and secondary nitroalkanes were subjected to the alkylation (Table 2). Allylic cyclic acetates **1** and **2** resulted in the formation of the corresponding γ-nitro ketones **4** and **5**, respectively. The acyclic acetate **3** led to γ-nitro aldehydes **6**. 1° and 2° nitroalkanes reacted with equal ease under these reaction conditions; even bulky nitroalkanes, such as nitrocyclohexane,

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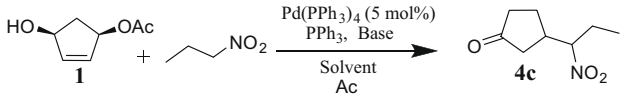
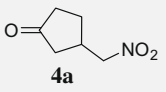
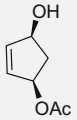
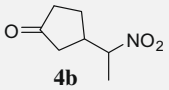
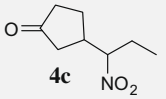
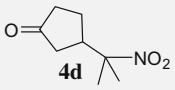
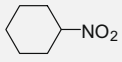
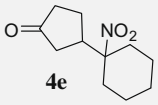
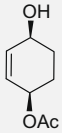
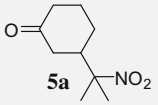
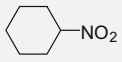
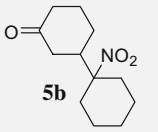
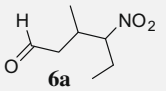
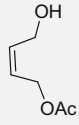
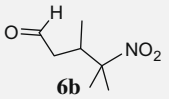
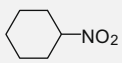
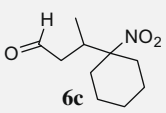
Table 1
Solvent and base effect



Entry	Base	Solvent	Yield[a]	*dr*[d]
1	K_2CO_3	THF	60	1:1
2	K_2CO_3	DMF	54	1:1.1
3	K_2CO_3	DMSO	53	1:1
4	K_2CO_3	$CHCl_3$	—[b]	—
5	K_2CO_3	Toluene	—[b]	—
6	K_2CO_3	*t*-BuOH	—[b]	—
7	K_2CO_3	*t*-BuOH + THF(1:1)	—[b]	—
8	Cs_2CO_3	THF	—[c]	—
9	KO^{t}Bu	THF	40[c]	1.7:1
10	DIPA	THF	—[b]	—
11	DABCO	THF	52	1.1:1

[a] Isolated yields.
[b] Starting material was recovered.
[c] *meso*-Cyclopent-2-en-1,4-diol was also formed (20%).
[d] Diastereomeric ratio (*dr*) based on GC analyses.

Table 2
Pd-catalyzed isomerization–alkylation of allylic acetates

Entry	Acetate	Nitroalkane	Product	Conv.[a] isolated[b]
1		CH_3NO_2	 **4a**	88 (65)
2	 (> 99% ee) **(1)**	$C_2H_5NO_2$	 **4b**	85 (59)
3		$C_3H_7NO_2$	 **4c**	83 (60)
4			 **4d**	88 (58)
5			 **4e**	90 (62)
6	 (±) **(2)**		 **5a**	75[b]
7			 **5b**	85[b]
8		$C_3H_7NO_2$	 **6a**	82 (58)
9	 **(3)**		 **6b**	77 (53)
10			 **6c**	76 (60)

[a] Based on GC analyses of the reaction mixture.
[b] Isolated yield after column chromatography.

reacted successfully with both acyclic and cyclic hydroxyl allylic substrates. The reaction required 5–8 mol % catalyst loading and was completed in 10–12 h. The structures of the γ-nitro carbonyl compounds were established unambiguously from the analysis of the ^{1}H and ^{13}C NMR spectral data and its comparison with the literature data when available.[6] The reaction conversions were determined using gas chromatography and the products were isolated by column chromatography over silica gel.

The stereochemical analyses of the products identified these to be a mixture of diastereomers and enantiomers, for example, starting from the optically pure (1*S*, 4*R*)-4-acetoxylcylcopent-2-en-1-ol (**1**)[7] a racemic mixture of the respective products **4a–e** was obtained. Products **4b** and **4c** were separated into its corresponding diastereomers by column chromatography and were identified to be racemic mixture of enantiomers. The loss of optical purity was somewhat intriguing as the Pd(0)-catalyzed reactions are known to proceed with stereochemical retention via a double inversion.[1b,1c,3,7] Importantly, the reactions performed in the presence of chiral ligands such as (*R*)-BINAP and (*S*)-TolBINAP did not lead to optically pure products; only marginal influence on diastereomeric ratio was observed. It was evident that the mechanistic pathway of the reaction involved loss of stereochemistry possibly through racemization of the reaction intermediates.

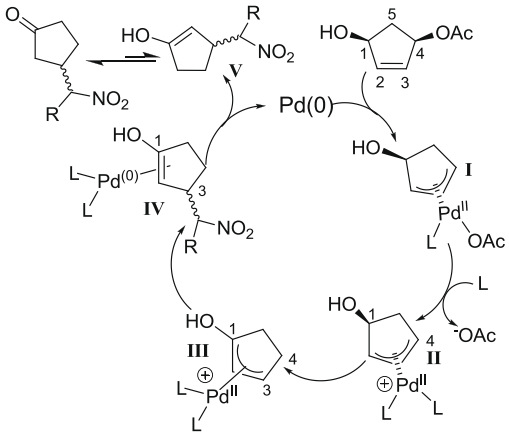
Hegedus *et al*[8] reported the first example of cyclopropanation of ester enolates and has proposed a mechanism involving a palladacyclobutane for direct nucleophilic attack on the central carbon of the π-allyl system. We carefully considered the possibility of a direct nucleophilic attack on the C-3 carbon leading to a palladacyclobutane intermediate, followed by β-H elimination to produce the enol which tautomerizes to give γ-nitro carbonyl compound as the final product (Supplementary data, Scheme S1). However, it has been reported that only σ-donor ligands (e.g., TMEDA, bipy) favor attack on the central carbon, while phosphorus ligands with distinct π-acceptor character (PPh_3, dppf) favor attack on the terminal carbon.[9] In case of π-acceptor ligands, the Pd-complex has more cationic character and the positive charge is located on the terminal carbons of the allyl system.[9] Also, in the cyclopentane and cyclohexane monoacetate substrates, low kinetic stability of such a palladacyclobutane bearing a γ-OH substituent is certainly a cause for concern.[10] Furthermore, this mechanism involving a palladacyclobutane intermediate does not explain the loss of stereochemistry in the final product.

Another possibility involving an initial isomerization of the allylic acetate to α,β-unsaturated ketone followed by a Michael addition using nitroalkane as a nucleophile was also considered. Though formation of α,β-unsaturated carbonyls has been reported but only in aqueous or AcOH containing solvents and not in anhydrous solvents.[11] In the absence of the nitroalkane, 3-cyclopentenone was the only product isolated upon treatment of the monoacetate **1** with PPh_3, $Pd(PPh_3)_4$, and K_2CO_3 at 50 °C, which was in agreement with the previous reports.[12] The reaction was monitored using NMR (see Supplementary data, Fig. S1) for up to 72 h. New resonances were observed within half an hour at 2.89 and 6.1 ppm which corresponded to H-6 and H-7, respectively, of the 3-cyclopentenone. Within 16 h all starting monoacetate was consumed and no significant isomerization was observed even after 72 h of heating, which is important as the 2-cyclopentenone is the more thermodynamically stable enone product. The formation of 3-cyclopentenone, however, can be easily explained from both π-allyl complexes **II** and **III** via a β-hydride elimination and tautomerization (see Supplementary data, Scheme S2).[13] Since the formation of the α,β-unsaturated ketone was not observed and no C-3 alkylation took place with other nucleophiles (active methylene compounds),[1b,1c,3,7] a different mechanism is suggested. Attempts in isolating the intermediate Pd complex were unsuccessful.

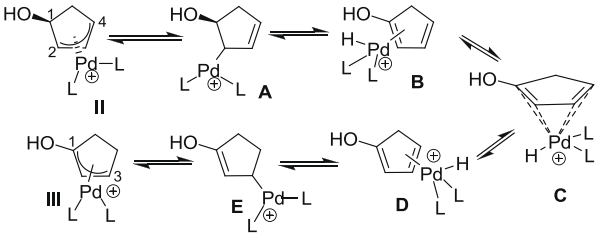
Based on the above-mentioned facts and the following observations; (i) carbonyl group instead of an allylic alcohol is formed, (ii) the new C–C bond formation at C-3 instead of C-4 of the allylic system, and (iii) the loss of stereochemistry, we herein propose a catalytic cycle for the isomerization–alkylation reaction (Scheme 2). The catalytic cycle involves oxidative addition of Pd(0) to the allylic acetate resulting in the formation of the Pd-allyl complex (**I**) which upon ligand exchange generates the complex **II**. Complex **II** is a key intermediate as it can isomerize to a more stabilized complex **III**. Isomerization of π-allyl palladium complexes has been put forward to explain the loss of stereospecificity in some Pd-catalyzed allylic alkylations.[14]

Complex **III** is attacked by the nitroalkane carbanion at the sterically favorable C-3 position followed by reductive elimination to yield **IV** which produced the enol **V** and regenerated Pd(0). Enol **V** tautomerizes to give the γ-nitro carbonyl compound. The isomerization of **II** to **III** is manifested in the formation of the new C–C bond at the C-3 and not at the carbon bearing the leaving acetoxy group (C-4). The involvement of **III** is also supported by stereochemical scrambling observed in **1**, an optically pure substrate, resulting in optically inactive γ-nitro carbonyl compounds. Importantly, the hydroxyl-bearing carbon in **III** is sp^2-hybridized which makes the complex racemic and explains the loss of optical purity in the products. The isomerization of complex **II** can be explained as shown in Scheme 3. Initially formed π-allyl complex **II** can undergo π–σ interconversion to **A** which upon syn β-H elimination will yield dienol complex **B**. Complex **B** can be represented as η^4 complex **C** which upon regioselective re-addition (**E**) and σ–π interconversion can yield complex **III**.

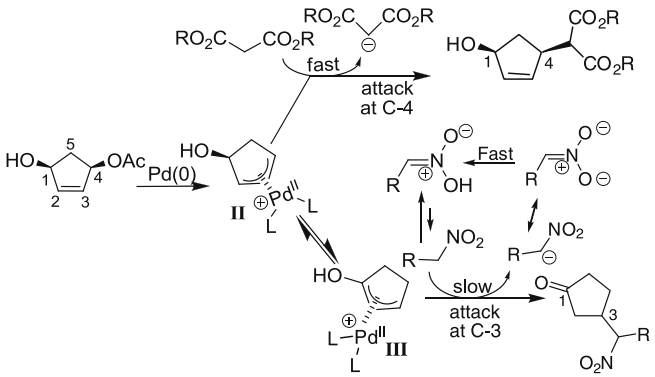
The formation of **III** via an isomerization of **II** is dependent on two very important factors; (1) The availability of the free hydroxyl group to stabilize the resulting carbocation through nonbonding electron pair donation; (2) The slow generation of the carbanion from the nitroalkane. The large degree of charge buildup on the carbon atom during deprotonation of the α-hydrogen in nitroalkanes along with inductive effects of the alkyl groups makes the whole process extremely slow.[15] This unusual property of the nitroalkane combined with the availability of the allylic hydroxyl group results in this unusual isomerization–alkylation reaction to γ-nitro carbonyl compounds.



Scheme 2. The proposed catalytic cycle.



Scheme 3. The 2,4- to 1,3-η^3 allylic isomerization.



Scheme 4. The competing alkylations: C-3 versus C-4.

A schematic of the competing processes in an allylic alkylation of the nucleophiles generated from a diester and nitroalkane is depicted in Scheme 4.[1b,1c,3,7] The coupling with diethyl malonate (fast deprotonation) results in the formation of the allylic alcohols with the new C–C bond formed at the C-4, while in nitroalkanes (slow deprotonation), the new C–C bond is formed at the C-3 resulting in γ-nitro carbonyl compounds.

In conclusion, a hitherto unknown C-3 regioselective Pd-catalyzed coupling of allylic monoacetates and nitroalkanes has been discovered which provides an easy route to synthetically important γ-nitro-ketones and aldehydes. The reaction requires easily obtainable allylic monoacetates and works with a variety of 1°, 2° nitroalkanes. This new Pd(0)-catalyzed alkylation of nitroalkanes can be carried out under mild conditions and the outcome of the reaction is highly dependent on the nature of the solvent.[16] Careful optimization of the reaction conditions proved potassium carbonate and THF to be the best base and solvent, respectively. The resultant γ-nitro carbonyl compounds that can easily be converted to other synthetically important analogs should be valuable as synthons in natural product synthesis.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.025.

References and notes

1. (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442; (b) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*; (c) Tsuji, J. In *Palladium Reagents and Catalysts*; John Wiley and Sons: New York, 2004; (d)*Metal-Catalyzed Cross-Coupling Reactions*; deMeijere, A., Diederich, F., Eds., second ed.; Wiley-VCH: Weinheim, 2004; (e) Hegedus, L. S. In *Transition Metals in the Synthesis of Complex Organic Molecules*, 2nd ed. University Science Books: Sausalito, 1999; (f)*Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley Interscience: New York, 2002; (g)*Cross-Coupling Reactions: A Practical Guide*; Miyaura, N., Ed.; Springer: Berlin, 2002; (h)*Organometallics in Synthesis*;

Schlosser, M., Ed.; John Wiley and Sons: New York, 1994; pp 383–461. Chapter 5; (i) Kobayashi, Y. *Curr. Org. Chem.* **2003**, *7*, 133.
2. (a) Wade, P. A.; Morrow, S. D.; Hardinger, S. A. *J. Org. Chem.* **1982**, *47*, 365; (b) Trost, B. M.; Surivet, J.-P. *J. Am. Chem. Soc.* **2000**, *122*, 6291; (c) Tsuji, J.; Yamakawa, T.; Mandai, T. *Tetrahedron Lett.* **1978**, *19*, 565; (d) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* **1985**, *50*, 1523; (e) Deardorff, D. R.; Savin, K. A.; Justman, C. J.; Karanjawala, Z. E.; Sheppeck, J. E.; Harger, D. C.; Aydin, N. *J. Org. Chem.* **1996**, *61*, 3616; (f) Maki, K.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2007**, *63*, 4250.
3. Khan, P. M.; Wu, R.; Bisht, K. S. *Tetrahedron* **2007**, *63*, 1116.
4. (a) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001; (b) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915; (c) Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017; (d) Barrett, A. G. M.; Grabowski, G. G. *Chem. Rev.* **1986**, *86*, 751; (e) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877; (f) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Helv. Chim. Acta* **1985**, *68*, 1592; (g) Brown, B. R. *The Organic Chemistry of Aliphatic Nitrogen Compounds*; Oxford University: Oxford, 1994; (h) Patai, S., Ed.The Chemistry of Amino, Nitro and Related Groups; John Wiley & Sons: Chichester, 1996.
5. (a) Aleksandrowicz, P.; Piotrowska, H.; Sas, W. *Tetrahedron* **1982**, *38*, 1321; (b) Aleksandrowicz, P.; Piotrowska, H.; Sas, W. *Monatsh. Chem.* **1982**, *113*, 1221; (c) Genet, J. P.; Grisoni, S. *Tetrahedron Lett.* **1988**, *29*, 4543; (d) Rieck, H.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2687.
6. (a) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975; (b) Hanessian, S.; Shao, Z.; Warrier, J. S. *Org. Lett.* **2006**, *8*, 4787.
7. (a) Deardorff, D. R.; Matthews, A. J.; McMeekin, D. S.; Craney, C. L. *Tetrahedron Lett.* **1986**, *27*, 1255; (b) Siddiqi, S. M.; Chen, X.; Schneller, S. W. *Nucleosides and Nucleotides* **1993**, *12*, 267.
8. (a) Hegedus, L. S.; Darlington, W. H.; Russell, C. E. *J. Org. Chem.* **1980**, *45*, 5193; (b) Hoffmann, H. M. R.; Otte, A. R.; Wilde, A.; Menzer, S.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 100.
9. (a) Castanõ, A. M.; Aranyos, A.; Szabó, K. J.; Bäckvall, J. E. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2551; (b) Aranyos, A.; Szabó, K. J.; Castanõ, A. M.; Bäckvall, J. E. *Organometallics* **1997**, *16*, 1058.
10. Szabó, K. J. *THEOCHEM* **1998**, *455*, 205.
11. Minami, T.; Hanaoka, M. *Tetrahedron Lett.* **1994**, *35*, 9425.
12. Suzuki, M.; Oda, Y.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 1623.
13. (a) Buckley, S. L. J.; Harwood, L. M.; Macias-Sanchez, A. J. *ARKIVOC* **2002**, *8*, 46; (b) Tsuda, T.; Tokai, M.; Ishida, T.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 5216.
14. (a) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730; (b) Granberg, K. L.; Bäckvall, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6858; (c) Brunel, J. M.; Maffei, M.; Muchow, G.; Buono, G. *Eur. J. Org. Chem.* **2000**, 1799; (d) Brunel, J. M.; Maffei, M.; Muchow, G.; Buono, G. *Eur. J. Org. Chem.* **2001**, 1009.
15. Green, D.; Johnson, T. *Innovations Pharm. Technol.* **2000**, *79*.
16. *General procedure for Pd-catalyzed alkylation of nitroalkane:* To a solution of allylic acetate **1** (100 mg, 0.704 mmol) in dry THF (10 mL) at room temperature were added $Pd(PPh_3)_4$ (40 mg, 0.035 mmol) and PPh_3 (184 mg, 0.704 mmol) under a nitrogen atmosphere. The reaction mixture was allowed to stir for 5 minutes and then nitropropane (63 mg, 0.704 mmol) and K_2CO_3 (97 mg, 0.704 mmol) were added. The reaction mixture was refluxed for 12 h and then vacuum filtered through celite with subsequent concentration of the filtrate. The product was purified by column chromatography using ethyl acetate/hexane (1:2) to afford **4c** (72 mg, yield = 60%) as a viscous liquid.