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ORIGINAL PAPER

Nitrohydroxylation of Olefins with Nitric Acid Using Tridentate NHC–Amidate–Alkoxide Containing Palladium Catalysts

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Abstract
In an attempt to explore the method of nitrohydroxylation which is fairly underdeveloped, our tridentate NHC–amidate–alkoxide containing palladium catalyst was used to nitrohydroxylate a variety of olefins in the presence of nitric acid. These reactions furnished β-nitro alcohols selectively to serve as a direct method for the synthesis of such compounds from various kinds of olefins. Dioxane served as an effective solvent, particularly in conjunction with TFA and $AgNO_3$, which selectively generated the desired products. Vinyl arenes and other olefins produced a wide range of desired products in moderate to good yields.

Keywords Nitrohydroxylation · β-Nitro alcohols · NHC–amidate–alkoxide containing palladium catalyst

1 Introduction

Development of an effectual method for synthesizing polyfunctional small molecules as building blocks is indispensable in a number of applications such as biological studies, new material discovery, and molecular synthesis. One such family of small molecules with great synthetic importance is nitro alcohols and their derivatives. Due to their simplistic derivatization of numerous compounds, nitro alcohols have great significance for organic chemistry research as well as industrial feedstocks. Bordwell devised nitroacetoxylation by adopting acetyl nitrate with styrene to afford a mixture of nitroalkenes, β-nitro nitrates, and β-nitro acetates [1–4]. Even though, Bordwell's methodology offered simultaneous C–O and C–N bond formation, it was still deficient to be a useful method due to unwieldly procedure and conditions. Furthermore, poor chemoselectivity and diastereoselectivity were observed as a problem as well. With extensive literature search, direct nitro-hydroxylation was found to be underdeveloped and underutilized due to low efficiency, poor chemoselectivity and diastereoselectivity, and drastic conditions.

Successful nitrohydroxylation would synthesize β-nitro alcohols (or nitro aldols) [5], which can also be prepared by the Henry reaction [6]. While the Henry reaction utilizes carbonyl and nitroalkane substrates, nitrohydroxylation utilizes alkenes and nitric acid, both of which are readily available. Though, the Henry reaction has exhibited very few successful cases with ketones, generating disubstituted nitro alcohols [7, 8]. The direct regioselective addition of nitric acid across an olefin through nitrohydroxylation could not only provide an efficient and straightforward manner for generating nitro alcohols but also furnish excellent alternative to the Henry reaction with wider scope of reactivity and applicability. Nevertheless, most reports on the use of nitric acid in conjunction with alkenes have focused on the synthesis of nitro olefins [9]. Herein, we report an effective method for synthesizing β-nitro alcohols from olefins and nitric acid using our tridentate NHC–amidate–alkoxide containing palladium catalyst **1** (Fig. 1).

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11244-018-0915-4) contains supplementary material, which is available to authorized users.

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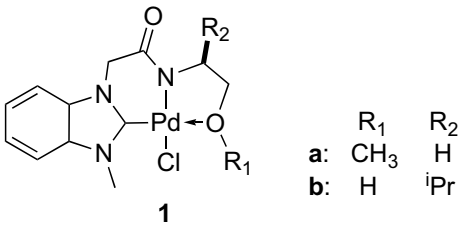


Fig. 1 Palladium catalyst of tridentate NHC–amidate–alkoxide ligands [11]

2 Experimental

2.1 Solvent and Temperature Variation

To an oven dried screw cap vial equipped with a stir bar and the threads covered with Teflon tape, were added catalyst **1** (0.05 mmol), $AgNO_3$ (0.1 mmol), and desired solvent (1.5 mL). After the reaction mixture was stirred for 10 min at room temperature to activate the catalyst, styrene (1.0 mmol) and nitric acid (2.0 mmol) were added. The reaction was then capped and stirred for 24 h at desired temperatures (50–150 °C). The crude reaction mixture was filtered through a pad of Celite and then subjected to flash column chromatography using a polarity gradient system (hexanes to 2:1 hexanes/ethyl acetate) to obtain the desired product.

2.2 Catalyst Comparison

Desired catalyst (0.05 mmol) was added to 1.5 mL dioxane in pre-dried screw cap vial equipped with a stir bar. Styrene (1.0 mmol) and nitric acid (2.0 mmol) were added to the resulting solution. The reaction was then capped and stirred for 24 h at 90 °C. The crude reaction mixture was filtered through a pad of Celite and then subjected to flash column chromatography using a polarity gradient system (hexanes to 2:1 hexanes/ethyl acetate) to obtain the desired product.

2.3 General Nitrohydroxylation

Catalyst **1a** or **1b** (0.05 mmol) and $AgNO_3$ (0.1 mmol) were added into pre-dried screw cap vial equipped with 1.5 mL dioxane. The reaction mixture was stirred for 10 min at room temperature to activate the catalyst. To the resulting solution, were added olefin (1.0 mmol) and nitric acid (2.0 mmol). The reaction was then capped and stirred for 24 h at 90 °C. The crude reaction mixture was filtered through a pad of Celite and then subjected to flash column chromatography using a polarity gradient system (hexanes to 2:1 hexanes/ethyl acetate) to obtain the desired product.

3 Results and Discussion

While we were exploring the synthesis of β-nitro alcohols with palladium catalyst **1a**, we found direct nitrohydroxylation on styrene in the presence of nitric acid (Scheme 1). Initially, this reaction was run by using styrene as a substrate and two equivalents of nitric acid in acetonitrile at 50 °C for 20 h. In this reaction we were able to observe nitrohydroxylation to form β-nitro alcohols **2** (28% yield based on styrene) as well as about 3% of dinitro compound **3**.

With this result, we tried to investigate direct nitrohydroxylation on olefin. As the first step, solvent variation was monitored (Table 1, entries 1–5). In DCM, nitro alcohol **2** was obtained in 31% (entry 1). While lower conversion yields (15 and 28%, respectively) were observed in DMF and acetonitrile (entries 2 and 3), *β*-nitro alcohol **2** was produced with higher yields (38 and 41%) repeatedly in ether solvents including THF and dioxane (entries 4 and 5). In addition, since dioxane has a higher boiling point than THF, we were able to raise the reaction temperature to 90 °C and detected a higher yield of 55% (entry 6). However, it produced a lower yield when the reaction temperature was further increased to 150 °C (entry 7). This might be due to the decomposition

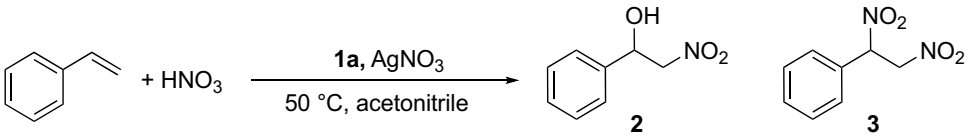
Table 1 Variation of reaction conditions

Entry	Solvent	Temp (°C)	Yield for **2** (%)[a]	Ratio (**2:3**)
1	DCM	50	31	3:1
2	DMF	50	15	3:1
3	Acetonitrile	50	28	10:1
4	THF	50	38	4:1
5	Dioxane	50	41	4:1
6	Dioxane	90	55	4:1
7	Dioxane	150	45	4:1

1a (5 mol%) was mixed with $AgNO_3$ (10 mol%) in 1.5 mL of desired solvent, and styrene (1 mmol) was added. The mixture was placed in a sand bath which was preheated to desired temperatures. Reaction mixture was stirred for 24 h

[a]Yields were based on the isolation of products

Scheme 1 Nitrohydroxylation of styrene by catalyst



of the catalyst. For the selectivity between **2** and **3**, acetonitrile produced **2** with high selectivity (91%), however other solvents showed 75–80% selectivity for **2**.

With the optimal choice of solvent conditions (Table 1, entry 6), various commercially available catalysts were directly compared with catalyst **1a** and the results are presented in Table 2.

Table 2 Comparison of various commercially available catalysts

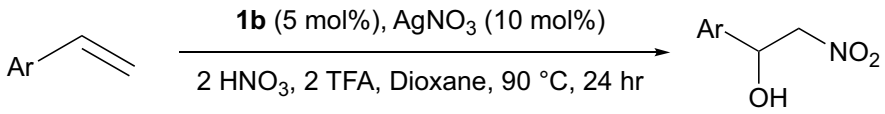
Entry	Catalyst	Yield (%) for **2**[a]
1	No catalyst	0
2	$NiCl_2{\cdot}6H_2O$	19
3	$(Ni(acac)_2)_3$	18
4	$PdCl_2$	22
5	$Pd(PPh_3)_2Cl_2$	22
6	$Pd(CH_3CN)_2Cl_2$	26
7	$Pd(OAc)_2$	26

Styrene (1 mmol) was added into 1.5 mL dioxane solution containing 5 mol% of a catalyst. The mixture was placed in a sand bath preheated to 90 °C. This reaction mixture was stirred for 24 h

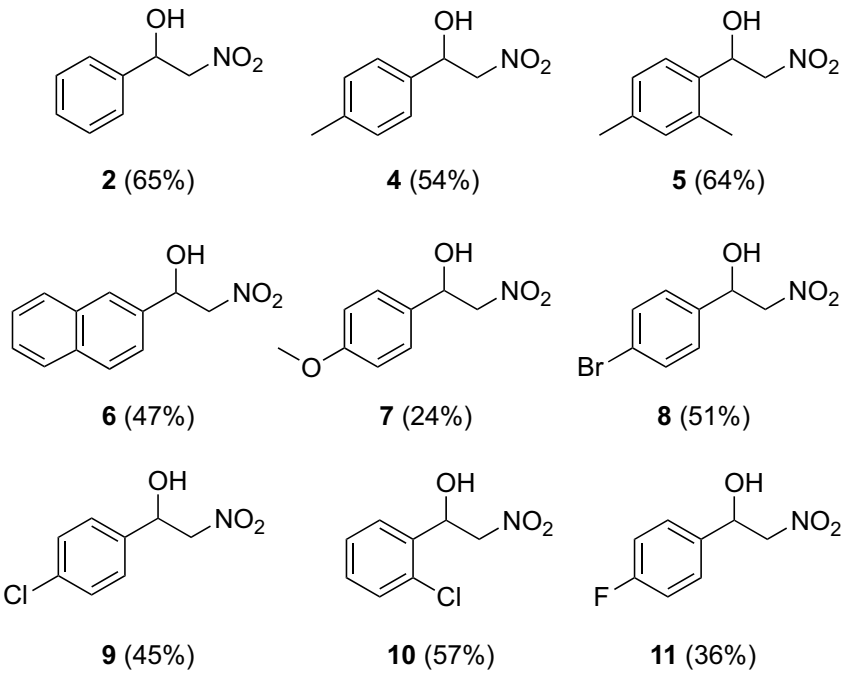
[a]Yields were based on the isolation of products

Without catalyst (entry 1), we didn't detect nitrohydroxylation at all. Both nickel sources (entries 2 and 3) showed relatively low yields (19 and 18%, respectively). Palladium catalysts were relatively efficient. In the case of $PdCl_2$ (entry 4) and $Pd(PPh_3)_2$ (entry 5), nitro alcohol **2** was produced in 22%. $Pd(CH_3CN)_2Cl_2$ and $Pd(OAc)_2$ gave slightly higher yields (26%, entries 6 and 7). These results showed nitrohydroxylation could be performed with various commercially available catalysts but in lower yields than **1a**.

Pursuing optimal conditions, we investigated the use of additives, and found the addition of an acid was beneficial. Trifluoroacetic acid was previously used as a solvent for nitration reactions, and was known to prevent the formation of dinitrogen pentoxide, N_2O_5, which would hamper nitrohydroxylation [10]. As shown in Scheme 2, two equivalents of TFA were added to our conditions, improving the yields of nitro alcohols, i.e., from 55 to 65% for **2**. For the possible enantioselective catalysis due to the stereogenic α position, we employed the chiral palladium catalyst **1b**, which furnished high enantioselectivities for boron Heck-type reaction [11, 12]. This chiral catalyst **1b** showed similar results to



Scheme 2 Nitrohydroxylation of vinyl arenes with nitric acid. All the products were isolated and the yields were based on isolation



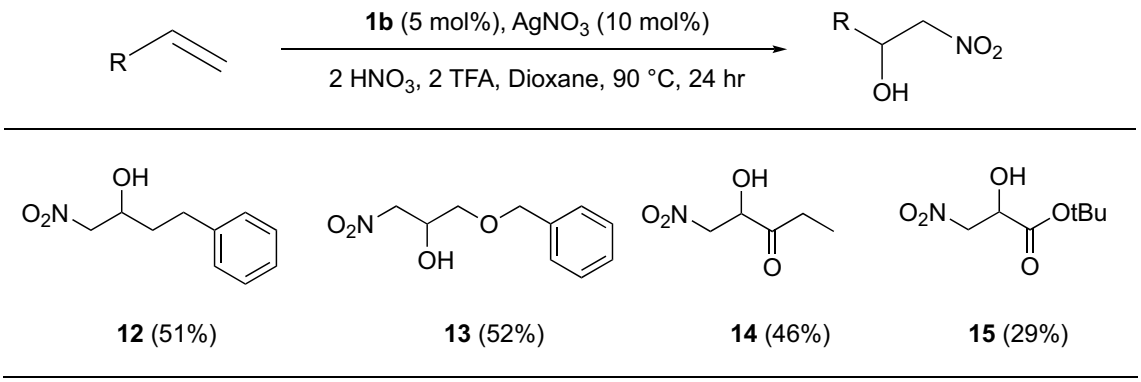
achiral catalyst **1a** in terms of yield for **2** but it produced a racemic mixture. With these conditions in hand, we examined the substrate scope of the reaction with **1b** (*vide infra*) while hoping for possible asymmetric catalysis, which didn't occur.

First, attention was focused on the conversion of vinyl arenes (Scheme 2). Alkyl substituted vinyl arenes furnished the desired nitro alcohols **4** and **5** in good yields of 54 and 64%, respectively. Vinyl naphthalene gave the desired product **6** in a modest 47% yield. The addition of a strong electron donating group to the arene drastically decreased the yield, as demonstrated by the use of 4-methoxy styrene to give the product **7** in a low yield of 24%. This might be due to the polymerization of 4-methoxy styrene under acidic conditions, which was observed in our previous work, hydroalkenylation of arenes [13]. Halogen substituted vinyl arenes produced the desired nitro alcohols **8, 9, 10**, and **11** in moderate to low yields. However, it is noteworthy that these halogen substituted vinyl arenes were compatible with desired chemoselectivity and no Heck or homo coupling products were observed. This feature should lend these reactions to use in tandem or one-pot multi-component dual reaction sequences.

In addition to vinyl arenes, several other alkenes were found to be viable substrates for nitrohydroxylation using this methodology (Scheme 3). The relatively unactivated olefin 4-phenyl-1-butene was converted to the desired product **12** in a 51% yield and allyl benzyl ether gave the desired nitro alcohol **13** at 52%. In the case of α,β-unsaturated carbonyl compounds, ethyl vinyl ketone reacted modestly to give **14** in a 46% yield, while *tert*-butyl acrylate which has an electron donating group reacted poorly to give **15** in only 29% yield.

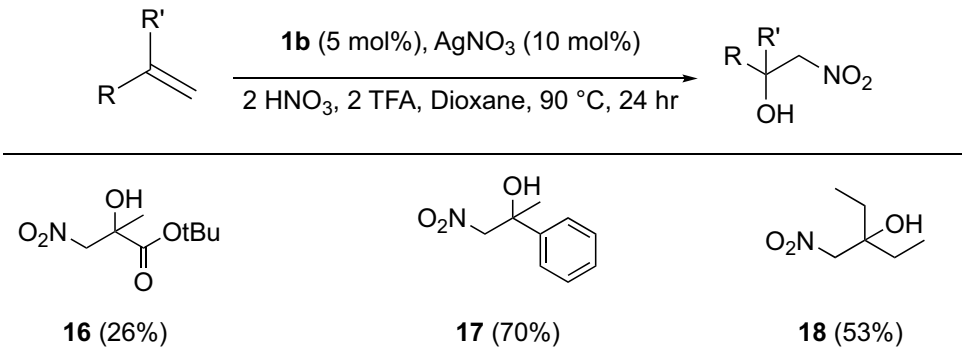
Impressively, it was found that this reaction was compatible to geminal disubstituted olefins, yielding nitro-alcohols possessing a tertiary alcohol (Scheme 4). The nitro alcohol **16** was generated in poor yield, though cleanly, from *tert*-butyl methacrylate. α-Methyl styrene was converted to the desired compound **17** in a good yield of 70%. The yields of **16** and **17** from disubstituted olefins showed similar yields to those of **2** and **15** from mono-substituted olefins, respectively. The alkyl disubstituted olefins such as 2-ethylbutene gave the corresponding desired product **18** in 53% yield.

The feasibility of using this methodology on vicinal disubstituted olefins was also tested. While substrates tested thus far were terminal and gave no possibility for *syn* and *anti* isomers, we knew that this problem could arise for using vicinally disubstituted olefins. The use of both β-methyl styrene and indene unfortunately resulted in the formation of both the *syn* and *anti* addition products. In the case of

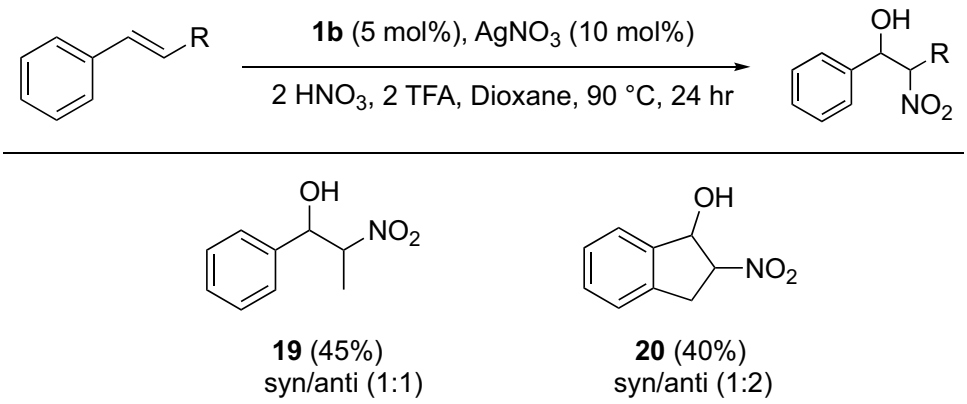


Scheme 3 Nitrohydroxylation of unconjugated olefins with nitric acid. All the products were isolated and the yields were based on isolation

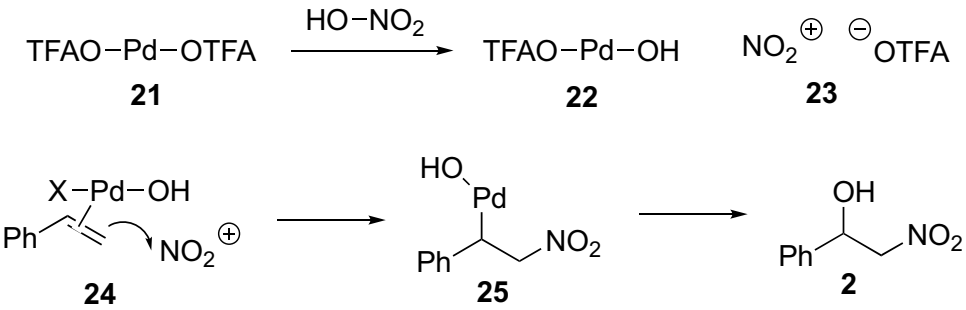
Scheme 4 Nitrohydroxylation of geminal disubstituted olefins with nitric acid. All of product was isolated to calculate yield



Scheme 5 Nitrohydroxylation vicinal disubstituted olefins with nitric acid. All the products were isolated and the yields were based on isolation



Scheme 6 Proposed mechanism and reaction pathway



β-methyl styrene, a 1 to 1 mixture of both isomers **19** was observed while indene showed a preference for the *anti* isomer **20** in a 2 to 1 ratio (Scheme 5).

Lack of possible enantioselectivity and poor diastereoselectivity led us to considering the stepwise addition of the nitro group and hydroxyl to an alkene as proposed in Scheme 6. Under our conditions, we believe nitronium ion (**23**) would form slowly by the aid of a Pd(II) catalyst, so the potential side reactions such as aromatic nitration, dinitration, nitroso nitrate formation would be minimized. Then, the Pd–π complex **24** would undergo nitration with the external nitronium ion, in which both syn and anti products can be generated [14]. The resulting nitration intermediate **25** would lead to the nitrohydroxylation product such as **2** by reductive elimination. In a cyclic system such as indene, the nitro group would approach in the anti position to the Pd moiety to afford the anti isomer as the major in **20** while the acyclic system would give both syn and anti in the same amounts (**19**). Underway are our efforts to make the addition of NO_2 and OH groups in a concerted manner to offer higher selectivities.

Due to numerous uses of nitro alcohols and their derivatives, palladium catalyzed nitrohydroxylation of olefins is undoubtedly a field of research which needs to be explored in greater detail. Previously reported methods were often limited to narrow substrate scope under harsh and long reaction conditions with the use of large excess nitrate sources. In contrast, the conversion of various olefins to corresponding β-nitro alcohols with nitric acid was accomplished via the use of novel tridentate NHC–amidate–alkoxide containing catalysts. Our reaction turned out to be an efficient way of utilizing many different vinyl arenes under mild conditions with short reaction time in moderate to good yields. Moreover, these reactions occurred with superior regio- and chemo-selectivities. It should provide a straightforward and practical method for generating such nitro alcohols which can be employed in synthetic organic, bioorganic, and material chemistry. Our finding demonstrates that nitrohydroxylation has a potential to serve as an efficient alternative for amino alcohol synthesis. However, this direct synthesis of β-amino alcohols by nitrohydroxylation has not generated enantioselectivity. Therefore, further research is being directed to produce high enantioselectivity through the modification of chiral catalysts **1b** or the application of known chiral catalysts.

Compliance with Ethical Standards

Conflict of interest We do not have any potential conflicts of interest.

Research Involving Human Participants and/or Animals This work doesn't involve any human participants or animals.

Informed Consent We do not have any informed consent.

References

1. Bordwell FG, Garbisch EW (1960) J Chem Soc 82(14):3588–3598
2. Bordwell FG, Garbisch EW (1963) J Org Chem 28(7):1765–1769
3. Bordwell FG, Garbisch EW (1962) J Org Chem 27(9):3049–3055
4. Bordwell FG, Biranowski JB (1967) J Org Chem 32(3):629–634
5. Ono N (2001) The nitro group in organic synthesis. Chapter 3. Wiley-VCH, Weinheim
6. Bodkin JA, Mcleod MD (2002) J Chem Soc 1:2733–2746
7. Palomo C, Oiarbide M, Laso A (2007) Eur J Org Chem 2007(16):2561–2574
8. Luzzio FA (2001) Tetrahedron 57(6):915–945
9. Thimmaiah G, Narayanaswamy N (March 2, 2017) Compounds as Stimuli-responsive Probes, Methods and Applications thereof. WO 2017033163
10. Shen G, Zhao L, Liu W, Huang X, Song H, Zhang T (2017) Synth Commun 47(1):10–14
11. Sakaguchi S, Yoo KS, O'Neill J, Jung KW (2008) Angew Chem Int Ed 47:9326–9329
12. Yoo KS, O'Neill J, Sakaguchi S, Giles R, Lee JH, Jung KW (2009) J Org Chem 75:95–101
13. Zargari N, Gilles R, Kim Y, Kaneshiro K, Runburg R, Park J, LaCroix K, Narain R, Lee BD, Lee JH, Jung KW (2016) Tetrahedron Lett 57:815–818
14. Esteves PM, Carneiro JWM, Cardoso SP, Barbosa AGH, Laali KK, Rasul G, Prakash GKS, Olah GA (2003) J Am Chem Soc 125(16):4836–4849