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Palladium-Catalyzed Synthesis of Δ^2-Isoxazoline from Toluene Derivatives Enabled by the Triple Role of Silver Nitrate

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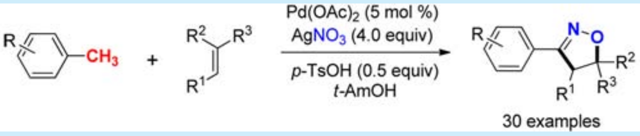
S Supporting Information

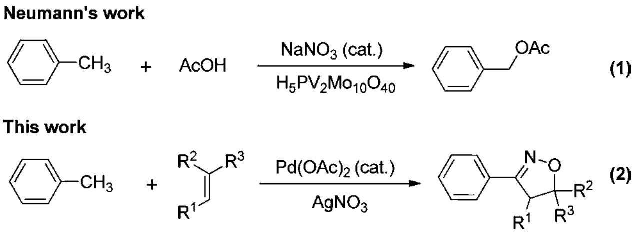
ABSTRACT: A palladium-catalyzed direct synthesis of Δ^2-isoxazoline from toluene derivatives has been established. The present reaction proceeds through nondirected Csp^3–H activation, benzylic nitration, dehydration, and cycloaddition. This protocol also features the unusual triple role of silver nitrate in a one-pot reaction.



Toluene and its derivatives are the simplest and most highly valuable starting materials in nature; hence, developing transformations toward their efficient utilization continues to be a research focus in organic synthesis.[1] On the other hand, transition-metal-catalyzed cross-dehydrogenative coupling (CDC)[2] has been proven to be a powerful tool in various bond-forming reactions.[3] As such, metal-catalyzed benzylic Csp^3–H bond activation[4] of arylmethane has drawn much attention from organic chemists, thus providing a new opportunity to approach diverse organic structures.[5] Of note is the palladium-catalyzed processes, which are quite interesting, as toluene and its derivatives are often used as solvent in many palladium-catalyzed reactions. In 1968, Bryant and co-workers discovered that toluene could undergo acetoxylation with the aid of palladium.[6] Of late, Huang and co-workers reported the oxidative carbonylation of arylmethanes via nondirected activation.[7] In 2013, Sun[8a] and Kwong[8b] reported the directed *ortho* C–H acylation of acetanilides independently. Additionally, palladium-catalyzed efficient acylation of azoarene, 2-arylpyridine, and *N*-nitrosoaniline were also realized using toluene derivatives as an acyl precursor.[9] More recently, the coupling between carbon nucleophile and toluene derivatives has also been disclosed by Kozlowski.[10] Unlike the common radical-mediated process, this protocol underwent palladium-catalyzed C–H activation via a nonradical pathway. Although considerable achievements have been made in the palladium-catalyzed reaction involving benzylic Csp^3–H activation; most examples were limited to the simple coupling of two different C–H bonds or between C–H and X–H bonds.[11] Thus, exploration of the cascade process via a benzylic Csp^3–H activation strategy to construct new heterocyclic compounds remains very attractive.

Δ^2-Isoxazoline derivatives represent an important synthetic skeleton that is frequently found in a wide variety of natural products and biologically active molecules.[12] More importantly, these compounds also serve as important building blocks as well as asymmetric ligands in organic synthesis.[13] It is therefore not surprising that many efforts have been devoted to the construction of the isoxazoline scaffold over the past decades.[14] An extensive literature survey revealed that Δ^2-isoxazolines are usually prepared from oximes or nitro compounds (benzoylnitromethane, nitroacetate).[15,16] To the best of our knowledge, the direct construction of Δ^2-isoxazolines from toluene derivatives via nondirected C–H activation is unknown. In 2006, Neumann and co-workers discovered that alkylmethanes experienced oxidation followed by acetolysis to afford benzylic acetate as the final product.[17] This reaction was believed to proceed via a benzylic nitrite intermediate using nitrate as the catalyst (Scheme 1, eq 1). As a continuation of our interest in synthesizing heterocycles,[18] herein we report a novel palladium-catalyzed cascade reaction to synthesize functionalized Δ^2-isoxazoline from toluene derivatives and alkenes (Scheme 1, eq 2).

Scheme 1. Representative Transformation of Arylmethane in the Presence of Nitrate



Initially, mesitylene **1a** and *tert*-butyl acrylate **2a** were selected as model substrates for the reaction optimization (see the Supporting Information for full optimization). In the presence of a catalytic amount of Pd(OAc)$_2$, heating the mixture of **1a** and **2a** afforded Δ^2-isoxazoline **3a** in 43% yield

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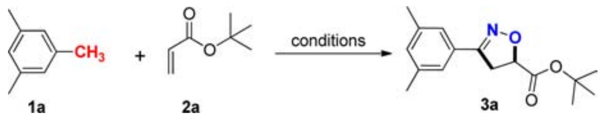
Table 1. Optimization of Reaction Conditions[a]

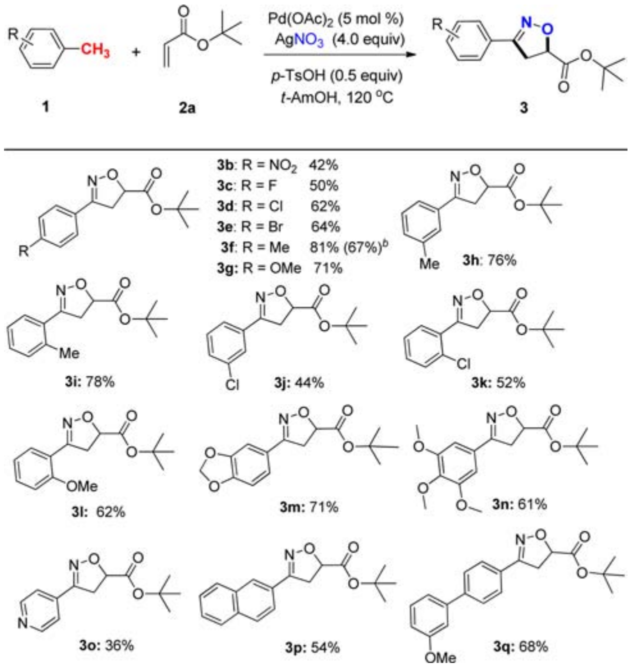


entry	catalyst	solvent	oxidant	yield (%)[b]
1	$Pd(OAc)_2$	mesitylene	$AgNO_3$	43
2[c]	$Pd(OAc)_2$	mesitylene	$AgNO_3$[d]	58
3	$Pd(OAc)_2$	mesitylene	$AgNO_3$[d]	78
4[e]	$Pd(OAc)_2$	mesitylene	AgTFA	51
5[e]	$Pd(OAc)_2$	mesitylene	Ag_2CO_3	0
6[e]	$Pd(OAc)_2$	mesitylene	Ag_2O	<5
7[e]	$Pd(OAc)_2$	mesitylene	$K_2S_2O_8$	0
8[e]	$Pd(OAc)_2$	mesitylene	TBHP	0
9	$Pd(OAc)_2$	C_6H_5Cl	$AgNO_3$[d]	58
10	$Pd(OAc)_2$	DMF	$AgNO_3$[d]	<5
11	$Pd(OAc)_2$	*t*-AmOH	$AgNO_3$[d]	76
12	$Pd(PPh_3)_2Cl_2$	*t*-AmOH	$AgNO_3$[d]	40
13	$Pd(PPh_3)_4$	*t*-AmOH	$AgNO_3$[d]	32
14	$Pd(TFA)_2$	*t*-AmOH	$AgNO_3$[d]	66

[a]Unless otherwise noted, all reactions were carried out with mesitylene **1a** (1 mmol), *tert*-butyl acrylate **2a** (3 mmol), catalyst (5 mol %), oxidant (2.0 equiv), solvent (3 mL), 120 °C in a sealed tube using *p*-TsOH·H_2O (0.5 equiv) as an additive. And 1 mmol **2a** was used when mesitylene was used as the solvent. [b]Yields of product after silica gel chromatography. [c]No additive was added. [d]Another 2.0 equiv $AgNO_3$ were added as an extra nitrogen source. [e]4.0 equiv of $NaNO_3$ were added as an extra nitrogen source.

using $AgNO_3$ as the oxidant (Table 1, entry 1). To our delight, the yield of **3a** was increased to 58% when 4.0 equiv of $AgNO_3$ were used (Table 1, entry 2). Encouraged by these experimental results, the reaction parameters including the additive, the oxidant, the catalyst, and the solvent were subsequently screened to improve the reaction performance. For instance, the employment of *p*-TsOH as additive (see the Supporting Information for details) was found to be particularly effective to increase the yield of **3a** from 58% to 78% (Table 1, entry 3). We then focused our attention on the variation of different oxidants. Of the silver oxidants examined [AgTFA, Ag_2CO_3, Ag_2O], only AgTFA showed discernible catalytic activity (Table 1, entries 4−6). As shown in Table 1, no reaction occurred when oxidants $K_2S_2O_8$ and TBHP were used (Table 1, entries 7−8). In addition, the experimental outcome displayed that solvent also had significant impact on the reaction performance and some representative results were summarized in Table 1. At the beginning, mesitylene was used as reactant as well as solvent. Lower yield was observed when mesitylene was replaced by C_6H_5Cl, whereas the employment of other solvents such as DMF only led to very poor yields (see the Supporting Information for details). Pleasingly, the employment of *t*-AmOH as solvent gave comparable yield with mesitylene (Table 1, entry 11). Subsequent investigation of the catalyst revealed that the yield of **3a** decreased when other catalysts $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$, $Pd(TFA)_2$ were used (Table 1, entries 12−14).

Scheme 2. Scope of the Reaction with Respect to the Arylmethane Substrate 1[a]



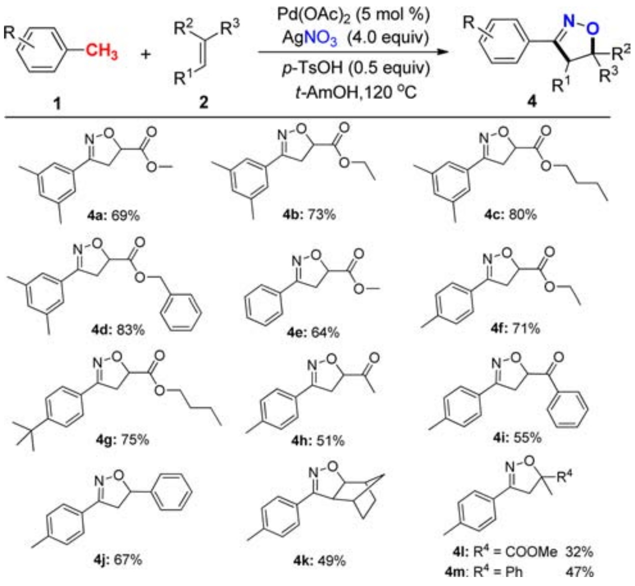
[a]Reaction conditions: arylmethane **1** (1 mmol), *tert*-butyl acrylate **2a** (3.0 mmol), $Pd(OAc)_2$ (5 mol %), $AgNO_3$ (4.0 equiv), *p*-TsOH·H_2O (0.5 equiv), *t*-AmOH (3 mL), 120 °C in a sealed tube, 24 h. [b]Isolated yield on a 10 mmol scale is given in parentheses.

With the optimized conditions in hand, we attempted to establish the scope and limitation of the present reaction. Reactions of various toluene derivatives **1** and *tert*-butyl acrylate **2a** under optimal conditions were subsequently examined, and the representative results were shown in Scheme 2. Pleasingly, all reactions proceeded smoothly to give the desired products **3**. Reactions with substrates **1** bearing a substituent at the *para*-position were first conducted (**3b−3g**). Other toluene derivatives **1** having a substituent at the *meta*- and *ortho*-position were next subjected to the optimal conditions to produce the desired compounds **3h−3l**. The experimental results showed that electron-withdrawing groups on the aromatic ring decreased the reaction reactivity slightly, whereas electron-donating groups seemed to favor the formation of product **3**. Furthermore, di- and trisubstituted arylmethanes **1** were also used to yield the corresponding adducts **3m** and **3n** in satisfactory yields. Remarkably, the present reaction was not limited to simple benzene-based substrates; pyridyl-, naphthyl-, and biphenyl-substituted substrates were also found to be compatible in the present transformation (**3o−3q**).

To further explore the versatility of the above-mentioned cascade reaction strategy, we turned our attention to the possibility of substituted alkenes **3**. As shown in Scheme 3, various alkyl acrylates **2** containing Me, Et, *n*-Bu, and Bn groups were used to react with mesitylene and its derivatives to produce the desired products **4a−4g**. For instance, reactions of methyl vinylketone (MVK) and its analogs furnished **4h** and **4i** in 51% and 55% yields, respectively. The expected cycloaddition adducts **4j** and **4k** were successively obtained when styrene and norbornylene reacted with xylene under the optimized conditions. It was also worthy to note that excellent regioselectivity was exemplified by the employment of 1,1-disubstituted olefins to yield **4l** and **4m**.

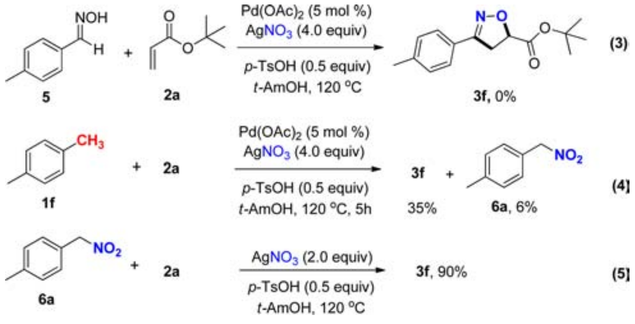
To gain further insight into the reaction mechanism, several mechanistic experiments were subsequently performed (Scheme 4). Since oximes commonly reacted with alkenes to prepare Δ^2-isoxazolines, we initially thought that oxime might

Scheme 3. Scope of the Reaction with Respect to the Alkene Substrate 2[a]



[a]Reaction conditions: arylmethane **1** (1 mmol), alkene **2** (3.0 mmol), Pd(OAc)$_2$ (5 mol %), AgNO$_3$ (4.0 equiv), *p*-TsOH·H$_2$O (0.5 equiv), *t*-AmOH (3 mL), 120 °C in sealed tube, 24 h.

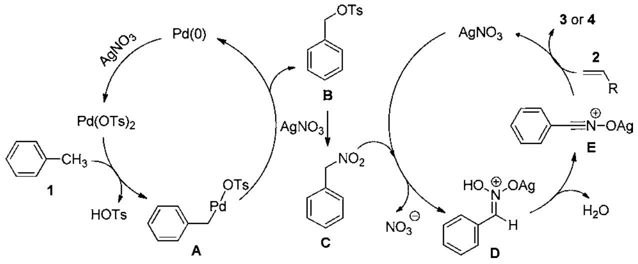
Scheme 4. Preliminary Mechanistic Study



be generated as an intermediate from the present transformation. However, the reaction of oxime **5** and *tert*-butyl acrylate **2a** failed to give the desired product **3f** (Scheme 4, eq 3). Thus, the possibility of oxime as an intermediate could be ruled out. To find out the real reaction intermediate, we heated the solution of xylene **1f** and *tert*-butyl acrylate **2a** for 5 h under optimal conditions and then stopped the reaction. From the resultant reaction mixture we isolated 35% **3f** and 6% side product **6a**, which indicated that (nitromethyl)benzene **6** was a possible reaction intermediate (Scheme 4, eq 4). To verify this hypothesis, we conducted the experiments with *tert*-butyl acrylate **2a** and (nitromethyl)benzene **6a**. Pleasingly, **3f** was isolated in 90% yield in the absence of palladium (Scheme 4, eq 5), which suggested that the present reaction might proceed through intermediate **6**. We also found that when TEMPO (4.0 equiv) was added as a radical scavenger, the reaction of **1f** and **2a** was completely surpressed.

On the basis of the above-mentioned experimental results and mechanistic findings, a possible mechanism is proposed in Scheme 5 to explain the formation of products **3** and **4**. The importance of *p*-TsOH as an additive has been well established during the conditions optimization. According to our analysis, the beginning of the reaction may involve the anion exchange.

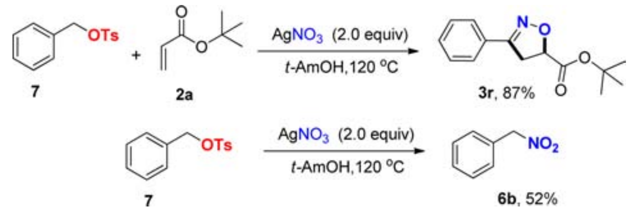
Scheme 5. Proposed Mechanism



In the presence of TsOH, the OTs anion is possible to be attached to Pd(II) in the form of Pd(OTs)$_2$, thus enchancing its reactivity in the following C−H activation step.[19] Then toluene undergoes C−H activation to afford benzyl Pd(II) intermediate **A**.[10] The reductive elimination step essentially leads to the formation of intermediate **B**, which is then transformed to intermediate **C** in the presence of silver nitrate.[20] The second catalytic circle presumably starts from the interaction between silver nitrate and intermediate **C** to generate **D**, which is converted to silver salt **E** after dehydration process.[16a] In the last step, the cycloaddition of intermediate **E** with olefin **2** takes place to yield the final product **3** or **4**, which also delivers the silver nitrate to finish the second catalytic circle.

To verify some processes in the above-mentioned mechanism, two controlled experiments were next carried out. As shown in Scheme 6, in the absence of palladium, heating the mixture of **7** and **2a** essentially afforded **3r** in 87% yields, which indicate that **7** was another possible reaction intermediate. Furthermore, the transformation from **7** to **6** also proceeded well under the same conditions, thus lending more support to our proposed mechanism.

Scheme 6. Controlled Experiments



In conclusion, we have described a palladium-catalyzed direct synthesis of Δ^2-isoxazolines from toluene derivatives and olefins. Experimental results indicated that the present cascade reaction might proceed through nondirected Csp^3−H activation, benzylic nitration, and dehydration followed by cycloaddition. The versatility of silver nitrate to serve as an oxidant for the generation of palladium(II), the nitrogen source, and the dehydration reagent is believed to be the key to the present transformation. Despite its popularity in palladium-catalyzed transformation as an oxidant, the present unprecedented triple role of silver nitrate has never been exploited in previous one-pot reactions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03059.

Experimental procedures and full characterization of all compounds, spectral data, and ^{1}H and ^{13}C NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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