Synlett C. Li et al. Letter

NHPI- and TBAI-Co-Catalyzed Synthesis of Allylic Esters from Toluene Derivatives and Alkenes

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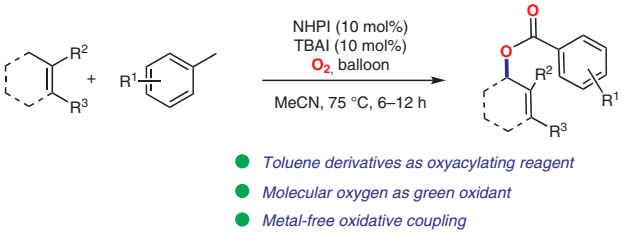


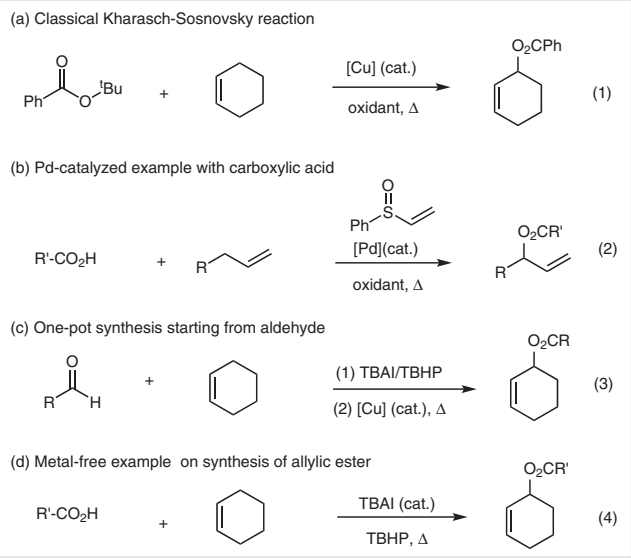
Received: 29.10.2017
Accepted after revision: 06.12.2017
Published online: 15.01.2018
DOI: 10.1055/s-0036-1591748; Art ID: st-2017-w0801-l

Abstract An *N*-hydroxyphthalimide (NHPI) and tetrabutylammonium iodide (TBAI) co-catalyzed oxidative coupling reaction of toluene derivatives and alkenes has been disclosed. This method can serve as a new strategy to access allylic ester using toluene derivatives as oxyacylating reagent. This metal-free protocol also features the readily available starting materials, broad substrate scope, and mild reaction conditions.

Key words oxyacylation, toluene derivatives, oxidative coupling, allylic ester, metal-free

As a direct C–H functionalization method, cross-dehydrogenative coupling (CDC) reaction avoids the prefunctionalization of starting materials and has emerged as a fundamental and highly valuable tool in organic synthesis.[1] It is therefore not surprising that many efforts have been devoted to the development of new bond-forming strategies with different hybrid C–H substrates using CDC reaction in the past decades.[2,3] On the other hand, allylic esters are considered to be significant structural motifs that are frequently found in many natural products and bioactive molecules.[4] Traditionally, these building blocks can be synthesized through acylation of the corresponding allylic alcohols with carboxylic acids or their derivatives in organic synthesis.[5] However, these methods also suffered from the limited substrate scope and harsh reaction conditions. To overcome these drawbacks, the direct α-oxyacylation[6] of sp^3 C–H bonds of alkenes through oxidative cross-coupling has drawn much attention from synthetic community.[7] Among them, the pioneering Kharasch–Sosnovsky reaction (Scheme 1, a) that involves a Cu-catalyzed esterification of an allylic C–H bond is considered as a classical method in this area.[8] After that, studies on the asymmetric version of this reaction catalyzed by chiral copper salts were also well documented.[9] Furthermore, White and co-workers have widely investigated the palladium-catalyzed synthesis of allylic esters from carboxylic acids and monosubstituted olefins via selective C–H bond oxidation (Scheme 1, b),[10] which is believed to be a significant breakthrough. Following these works, Wan and co-workers have also developed a one-pot synthesis of allylic ester using aldehyde as the oxyacylating reagent (Scheme 1, c).[11] This strategy combined the aldehydes C–H oxidation and the Kharasch–Sosnovsky reaction, thus offering a new route to allylic ester directly from simple olefins and aldehydes. Of late, the Wan group has also disclosed another metal-free synthesis of allylic ester from carboxylic acid and alkene (Scheme 1, d).[12] Although much progress has been achieved, there is still a continuing demand to develop novel and environmentally benign methods for the synthesis of allylic esters in an efficient manner.

In spite of their role as commonly used solvents, toluene and its derivatives have found widely application in organic synthesis as simplest and readily available starting materials in nature.[13,14] From a mechanistic point of view, toluene derivatives can serve as benzyl precursor[15] and acyl source,[16] which makes them widely used in a variety of carbon–carbon and carbon–heteroatom bond-forming reactions. In the past years, we became interested in developing novel transformations using toluene derivatives as versatile building blocks.[17] For instance, we have described a palladium-catalyzed direct synthesis of Δ^2-isoxazolines from toluene derivatives and olefins.[17a] In addition, we have also developed a TBAI-catalyzed direct α-oxyacylation of carbonyl compounds using simple toluene derivatives as efficient



Scheme 1 Representative examples on the synthesis of allylic esters from alkene and other starting materials

oxyacylating reagent.[17b] Most recently, we have just disclosed the coupling reaction of toluene derivatives with isocyanides.[17c] As a continuation of our previous research,[18] herein we wish to disclose a NHPI/TBAI-catalyzed oxidative coupling reaction of alkene and toluene derivatives. To the best of our knowledge, no such example has been reported yet.

We began our reaction optimization using cyclohexene **1a** and toluene**2a** as model substrates. In the presence of catalytic amount of *N*-hydroxyphthalimide (NHPI), heating the mixture in toluene afforded product **3a** in 46% yield (Table 1, entry 1). The screening of solvents was then conducted. The employment of MeCN slightly increased the yield of **3a** to 52% (Table 1, entry 2), whereas using other solvent including DCE and PhCl did not bring any improvement with respect to the yield of **3a** (Table 1, entries 3–5). Also, no desired product was detected when reactions were conducted in other solvents such as DMSO and DMF (Table 1, entries 6–8). To our delight, the yield of **3a** was increased to 61% when a new NHPI/TBAI catalyst system was applied (Table 1, entry 10). In sharp contrast, the direct use of tetrabutylammonium iodide (TBAI) as single catalyst led to negative result (Table 1, entry 13). Several experiments using TBHP as oxidant were also carried out subsequently, which brought no improvement on the reaction performance (Table 1, entries 14–16).

With the optimized conditions in hand, we then focused our attention to the scope and limitation of this oxidative reaction. As shown in Scheme 2, a series of toluene derivatives **2** having electron-donating and electron-deficient groups at the aromatic ring was used to react with cyclohexene **1a**. Substrates **2** containing substituents such as *tert*-butyl, methoxyl, methyl, chloro, bromo, fluoro groups

Table 1 Optimization of the Reaction Conditions[a]

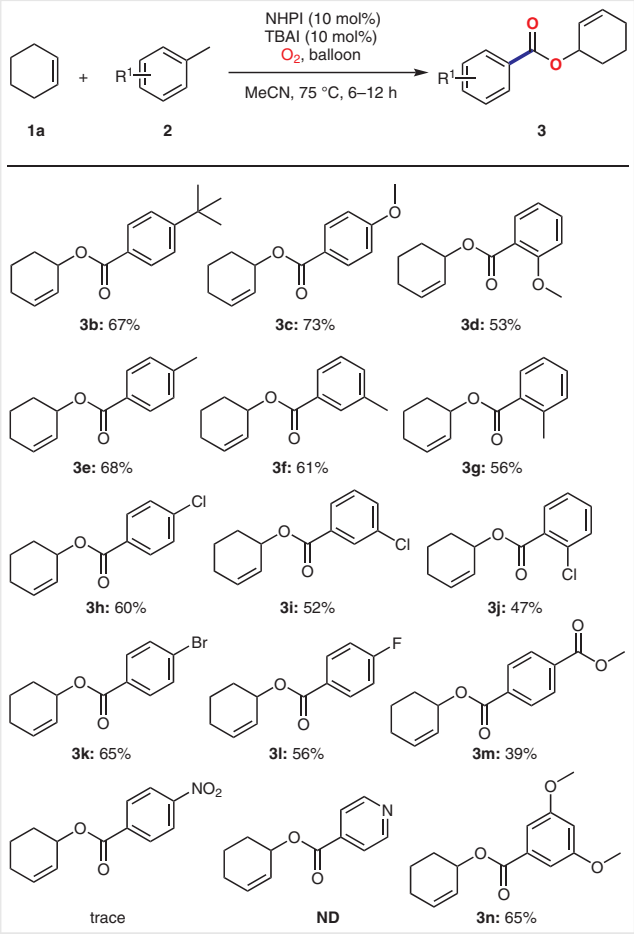
1a 2a 3a

Entry	Catalyst	Oxidant[b]	Solvent	Yield (%)[c]
1	NHPI	O_2	toluene	46
2	NHPI	O_2	MeCN	52
3	NHPI	O_2	DCE	37
4	NHPI	O_2	EtOAc	24
5	NHPI	O_2	PhCl	32
6	NHPI	O_2	DMSO	0
7	NHPI	O_2	DMF	0
8	NHPI	O_2	DMAc	0
9	NHPI	O_2	dioxane	30
10	NHPI/TBAI	O_2	MeCN	61
11[d]	NHPI/TBAB	O_2	MeCN	54
12[e]	NHPI/TEBAC	O_2	MeCN	49
13	TBAI	O_2	MeCN	0
14	NHPI/TBAI	TBHP	MeCN	19
15	NHPI	TBHP	MeCN	0
16	TBAI	TBHP	MeCN	26

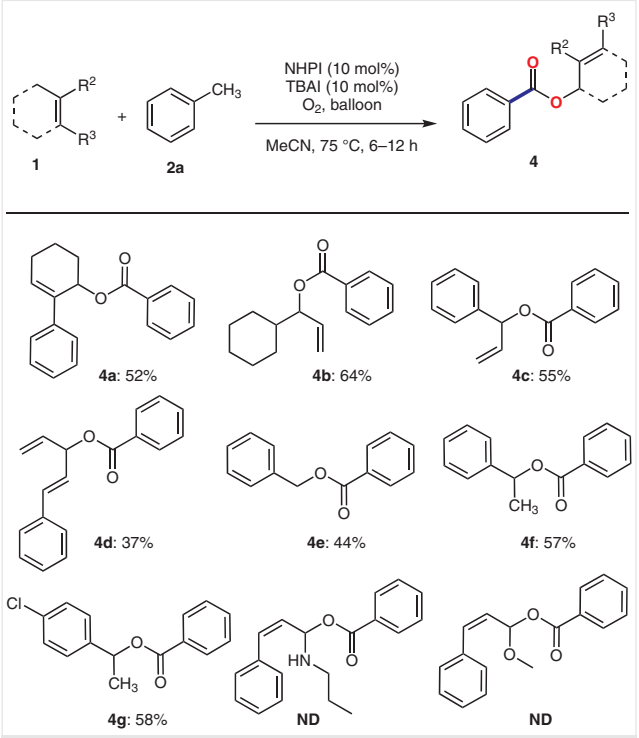
[a]Until otherwise noted, all reactions were carried out with cyclohexene **1a** (1 mmol), toluene **2a** (3 mmol), catalyst (10 mol%), oxygen balloon, solvent (8 mL), 75 °C for 6–12 h.
[b] TBHP (6.0 equiv) was added.
[c]Isolated yields.
[d]TBAB = tetrabutylammonium bromide.
[e]TEBAC = benzyltriethylammonium chloride.

were proven to be effective partners to yield the corresponding products **3b–m**. In sharp contrast, the presence of a strong electron-withdrawing group seemed to be unfavorable to the formation of product **3**. Only trace amount of product **3n** was isolated when the nitro group was present. Furthermore, no desired product was detected when substrate containing a pyridyl group was used.

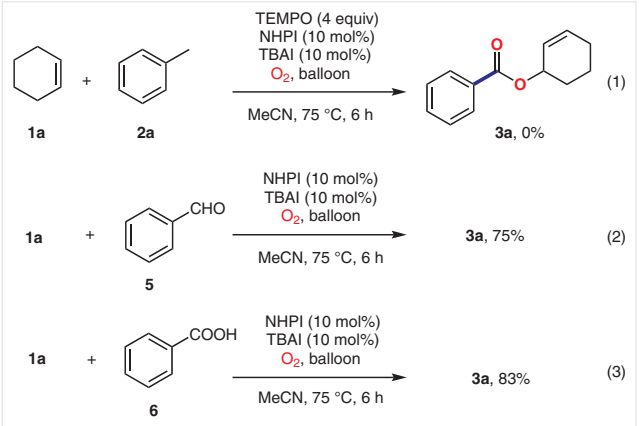
After a broad arylmethane substrate scope has been established, the possibility of substituted alkenes having an α-H were next examined. As shown in Scheme 3, a substituted cyclohexene **1b** bearing a phenyl group was firstly used to react with toluene **1a** to produce **4a**. Next, the allylic hexane **1c** and allylic benzene **1d** were proven to be compatible reaction partners to afford **4b** and**4c**. It was also worthy to note that another interesting reaction took place when no external alkene was added. In such case, products **4e–g** were obtained in which toluene and its derivatives behaved as benzyl and oxo-acylating reagent in one reaction. In contrast, no desired product was detected when a heteroatom, such as oxygen or nitrogen, was present at the allylic position of alkene.



Scheme 2 Scope of the reaction with respect to the arylmethane substrate. *Reagents and conditions*: cyclohexene **1a** (1 mmol), arylmethane **2** (3 mmol), TBAI (10 mol%), NHPI (10 mol%), O_2 balloon, 75 °C in MeCN (8 mL). Isolated yields after silica gel chromatography.



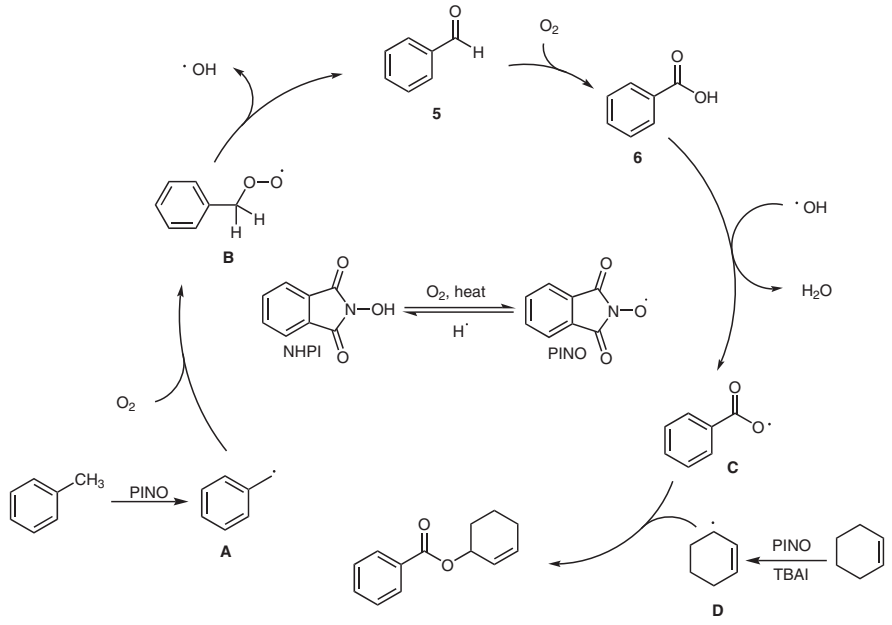
Scheme 3 *Reagents and conditions*: alkene **1** (1 mmol), toluene **2a** (3 mmol), TBAI (10 mol%), NHPI (10 mol%), O_2 balloon, 75 °C in MeCN (8 mL). Isolated yields after silica gel chromatography.



Scheme 4 Preliminary mechanistic studies

Several mechanistic experiments were next carried out to have more insight into the present oxidative coupling reaction. As shown in Scheme 4, the coupling reaction was completely inhibited when excessive radical scavenger 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) was added to the mixture of **1a** and **2a** under optimized conditions (Scheme 4, eq. 1), therefore suggesting a free radical process. Furthermore, the reaction of benzaldehyde **5** and cyclohexene **1a** worked well to yield **3a** in 75% yield (Scheme 4, eq. 2). This result also indicated that aldehyde was possible reaction intermediate. Finally, benzoic acid **6** was also used to experience the optimized conditions. In such case, product **3a** was also isolated in good performance (Scheme 4, eq. 3).

On the basis of the aforementioned mechanistic observation, a plausible mechanism is depicted in Scheme 5 to explain this oxidative coupling reaction. The beginning of this reaction involves the homolysis of NHPI to the PINO radical.[19] Then the benzyl radical **A** is generated in the presence of PINO radical. Next, The *in situ* formed benzyl radical **A** is trapped by O_2 to afford the peroxide radical **B**, which then eliminates a hydroxyl radical to produce benzaldehyde intermediate. In the presence of O_2, benzaldehyde is further oxidized to benzoic acid,[20] which then reacts with the hydroxyl radical to yield acyloxy radical **C**. Finally, the coupling of **C** and **D** essentially yields the final product.[21]



Scheme 5 Proposed mechanism

In conclusion, a NHPI/TBAI co-catalyzed oxidative coupling of alkene and toluene derivatives has been disclosed.[22] This protocol allows for the synthesis of allylic ester in an efficient manner. The present strategy still have several distinguished features: (i) metal-free oxidation conditions; (ii) the employment of toluene and its derivatives as readily available oxo-acylating precursors; (iii) the use of molecular oxygen as green oxidant, which meets the requirement of green chemistry; and (iv) milder reaction conditions. In this light, this method has potential to be further applied.

Funding Information

We thank the National Natural Science Foundation of China (Nos: 21472121, 21272148) for financial support.

Acknowledgement

We thank Dr. H. Deng (Laboratory for Microstructures, Shanghai University) for NMR spectroscopy.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591748.

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(20) During our investigation, a little amount of benzoic acid can be detected in most runs under the optimized conditions. And a large amount of benzoic acid can be obtained in the absence of alkene.

(21) Another mechanism involving the addition of acyloxy radical to alkenes followed by H-elimilation is also possible. See: Li, X.; Xu, X.; Zhou, C. *Chem. Commun.* **2012**, *48*, 12240.

(22) **Experimental Procedure and Characterization Data**

A 50 mL three-necked round-bottom flask equipped with a magnetic stir bar was charged with toluene derivatives **2** (3.0 mmol), olefin **1** (1.0 mmol), NHPI (16.3 mg, 10 mol%), and Bu_4NI (36.9 mg, 10 mol%) in MeCN (8 mL) at room temperature. O_2 was bubbled into the mixture at 75 °C for 6–12 h. After the reaction was completed, it was monitored by TLC. The resulting solution was poured into NaCl (15 mL), extracted with DCM (twice). The combined organic layers were dried over anhydrous Na_2SO_4 and solvents were removed in vacuo. The residue was purified by PLC Silica gel plate (eluent: petroleum ether/ethyl acetate = 30:1) to give the desired product.

Compound **3a**: 123 mg, 61% yield; colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.07–8.05 (m, 2 H), 7.56–7.52 (m, 1 H), 7.44–7.41 (m, 2 H), 6.02–5.98 (m, 1 H), 5.86–5.82 (m, 1 H), 5.52–5.51 (m, 1 H), 2.17–2.10 (m, 1 H), 2.08–2.02 (m, 2 H), 1.94–1.92 (m, 2 H),1.74–1.61 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 132.8, 132.7, 130.8, 129.6, 128.3, 125.7, 68.6, 28.4, 24.9, 18.9 ppm.