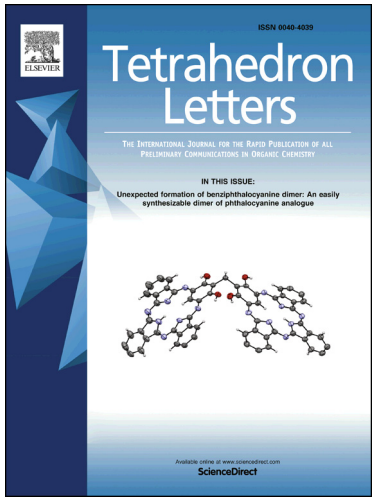

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Palladium(II) acetate catalyzed acylative cleavage of cyclic and acyclic ethers under neat conditions

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Abstract

During the development of a palladium catalyzed C–H activation cross-coupling reaction involving acyl halides, it was noted that palladium(II) acetate catalyzes the acylative cleavage of tetrahydrofuran (used as a solvent) at room temperature to afford the corresponding 4-chlorobutyl ester derivative. After optimization, the reaction was shown to work well with epoxides, oxetane and tetrahydrofuran, but only barely with oxanes at room temperature. Acyclic ethers systematically failed to react under similar conditions, but underwent complete conversion in a microwave reactor at 100 ^{o}C.

***Keywords*:** Palladium(II) acetate, acylative ether cleavage, haloesters, microwave

Introduction

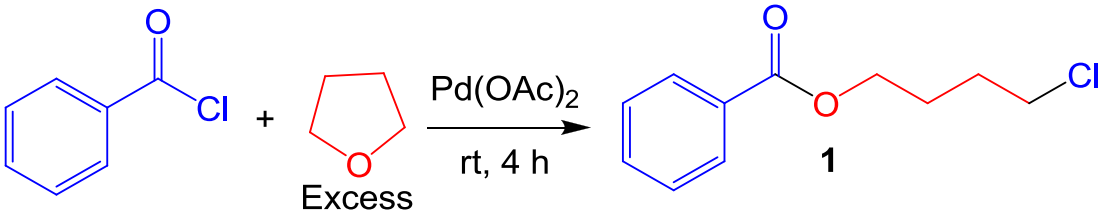
Transition-metal catalysts have evolved as powerful tools in organic synthesis, mainly due to their involvement in coupling and cross-coupling reactions, including direct C–H activation, with palladium-catalyzed reactions being among the most prominent.[1] Ethers are among the most widely used solvents for these transformations, mainly because of their high chemical stability, and the ease with which they are removed from the reaction mixture as a result of their low boiling points. Ethers are also capable of dissolving both polar and nonpolar molecules, and their cleavage is normally possible only under acidic or extremely basic conditions. Nevertheless, the cleavage of ethers as a synthetic strategy, especially in the protection and deprotection of alcohols, is well documented.[2] Furthermore, the synthesis of chloroesters through the deconstruction of cyclic ethers by acyl halides is been known since the early 1900.[3] In recent years, several reports involving the acylative cleavage of cyclic, acyclic, symmetrical and unsymmetrical ethers have appeared in the chemical literature. These transformations often require the presence of Lewis acids,[4] either alone or in combination with a metal catalyst.[5] In a comparative analysis, Guo and co-workers[6] found that $MoCl_5$, WCl_6, $NbCl_5$ and $TaCl_5$ were more efficient for the acylative cleavage of the ether C–O bond than conventional Lewis acid catalysts such as $ZnCl_2$, $AlCl_3$, $SnCl_4$ and $TiCl_4$. It also should be mentioned that a wide range of other metals and/or their salts or complexes, including Mg,[7] Pt,[5d] Pd,[5e] Hg,[5f] Fe,[5a] Zn,[4i, 8] Co,[4b, 4c, 9] Rh,[5b, 5c] In[4e] and Bi[4d, 4g] have been used to catalyze or mediate these types of transformations. With respect to the palladium catalyzed acylative cleavage of ethers, the only report in the chemical literature, to the best of our knowledge, was published by Pri-Bar and Stille in 1982,[5e] utilizing palladium(II) complexes including $PhCH_2PdCl(PPh_3)_2$, $PhCOPdCl(PPh_3)_2$, and $[(\pi\text{-}C_3H_5)_2PdCl]_2$ in combination with triphenylphosphine as catalysts.[5e] However, in order for the reaction to proceed, the addition of triorganotin halides such as *n*-Bu_3SnCl, Me_3SnCl or Me_3SnBr was required.[5e]

With the above in mind, upon unexpectedly discovering that palladium(II) acetate can catalyze the cleavage of tetrahydrofuran in the presence of acyl halides at room temperature without requiring any additive, it seemed appropriate to further explore the reaction as it could be of interest in organic synthesis. Furthermore, in addition to developing a new method for the acylative cleavage of ethers, this study provides some insights into the conditions under which ethers could still be used as a solvent for palladium catalyzed coupling reactions involving acyl halides without a risk of acylative cleavage side-products.

Results and Discussion

During the development of a palladium catalyzed cross-coupling reaction involving acyl halides, it was noted that palladium(II) acetate can catalyze the cleavage of tetrahydrofuran (used as solvent), in the presence of benzoyl chloride, to produce 4-chlorobutyl benzoate at room temperature after four hours (Scheme 1). A quick optimization of the reaction conditions was performed, using the initial reaction conditions as the starting point (Table 1, entry 1).

The percent conversion increased progressively as the catalyst loading was increased from 0.5 to 2 mol%, with the reaction time set to four hours. However, only at 2 mol% catalyst loading did the reaction proceed to completion within that time frame, producing compound **1** in 98.3% yield as indicated by GC-MS. When the time was reduced to two hours, the reaction did not reach full conversion, and only a 87.9% yield was achieved. On the other hand, the reaction failed to produce any product in the absence of $Pd(OAc)_2$, or when other palladium catalysts such as Pd/C (Entry 7) and $Pd(PPh_3)_2Cl_2$ (Entry 8) were used, even upon extending the reaction time to 24 hours. In these cases, the starting materials were recovered.



Scheme 1: Cleavage of THF by benzoyl chloride in the presence of $Pd(OAc)_2$.

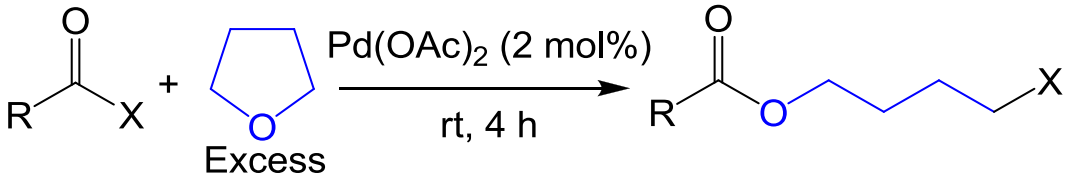
Table 1: Optimization of the reaction conditions

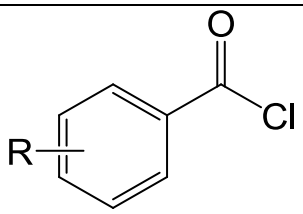
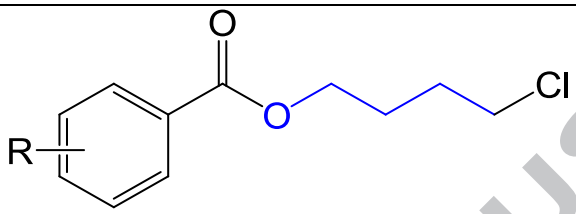
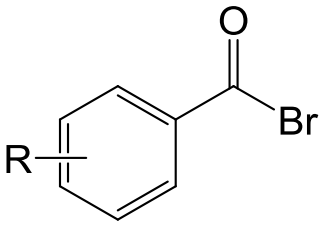
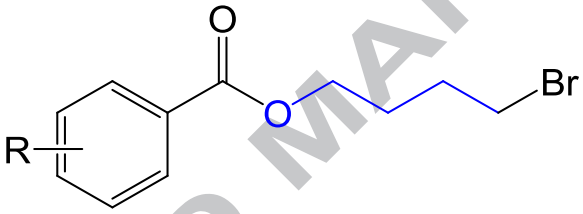
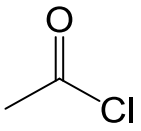
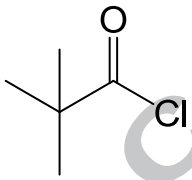
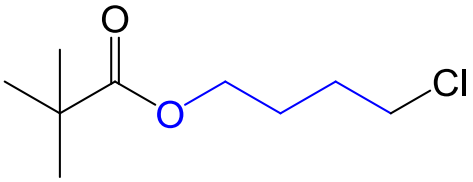
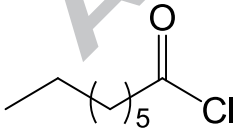
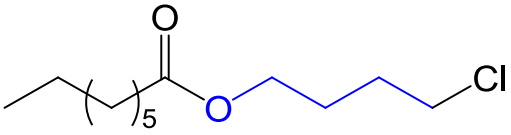
Entry	Catalyst	Loading (mol%)	Time (h)	Yield **1** (%)[a]
1	$Pd(OAc)_2$	1	4	53.7
2	$Pd(OAc)_2$	0.5	4	39.6
3	$Pd(OAc)_2$	1	6	58.0
4	$Pd(OAc)_2$	1.5	4	76.7
5	**$Pd(OAc)_2$**	**2**	**4**	**98.3**
6	$Pd(OAc)_2$	2	2	87.9
7	Activated Pd/C	2	24	N.R
8	$Pd(PPh_3)_2Cl_2$	2	24	N.R

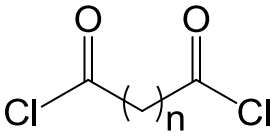
Reagents and conditions: benzoyl chloride (100 mg, 0.71 mmol), THF (3 mL, 37.0 mmol), catalyst, room temperature. [a]Yield determined by GC–MS through a calibrated curve using tridecane as an internal standard. [b]N.R. = No reaction, starting material was recovered.

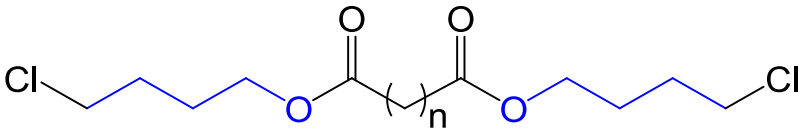
As a result, the conditions in entry 5 (2 mol% $Pd(OAc)_2$, 4 h) were selected for further exploration of the reaction scope, and a wide diversity of acyl halides were reacted with THF at room temperature for four hours (Table 2).

Table 2: Cleavage of THF by a series of acyl halides



Acyl halide	Product	Yield (%)[a]
		**1a:** R = H, 87.4 **1b:** R = 4-OMe, 67.1 **1c:** R = 4-Cl, 78.7 **1d:** R = 3-NO_2, 39.5 **1e:** R = 2-Me, 87.1
		**2a:** R = H, 86.3 **2b:** R = 4-CH_2Br, 80.9
		**3:** 79.7
		**4:** 78.8
		**5:** 81.9





6a: n = 4, 87.7

6b: n = 8, 89.4

Reagents and conditions: acyl halide (1 g) in THF (1M), $Pd(OAc)_2$ (2 mol%), 4 h, room temperature. [a]Isolated yield.

For each of the above reactions, a 1M solution of the acyl halide in THF was used for consistency; however, the reaction works equally well when 1.2 equivalent of THF is used. The reaction proceeds with both aliphatic and aromatic acyl chlorides, including diacyl chlorides (adipoyl chloride and sebacoyl chloride), producing the corresponding product in high yields. Only 3-nitrobenzoyl chloride resulted in a poor yield (**1d**, 39.5%), and most of the starting material was recovered at the end of the reaction. This low yield might be the result of the poor solubility of 3-nitrobenzoyl chloride in the amount of THF used, as no significant impact of the electronic effects of the aromatic ring substituents on the reaction was observed. In fact, benzoyl chloride (**1a**, 87.4%), 2-methylbenzoyl chloride (**1e**, 87.1%) and 4-chlorobenzoyl chloride (**1c**, 78.7%) gave very similar isolated yields. The low yield obtained for 4-methoxybenzoyl chloride (**1b**, 67.1%) is due to the fact that the reaction proceeded beyond the deconstruction of only one THF ring, and a side-product corresponding to the addition of two successive THF rings to the starting material (**1ba**, 20.8%) was also obtained. This successive deconstruction reaction was also observed with other starting materials, but at a significantly reduced rate, making it difficult to isolate these side-products from any of these latter reactions.

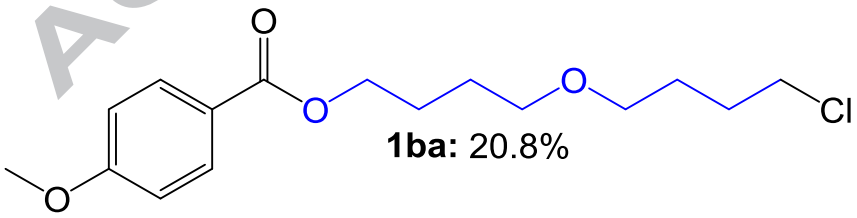
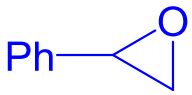
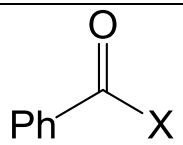
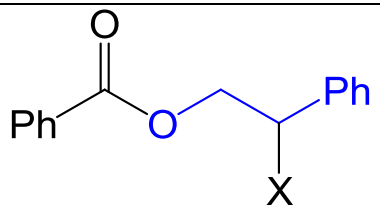
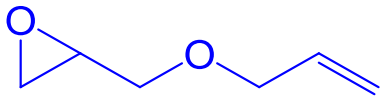
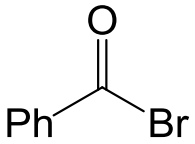
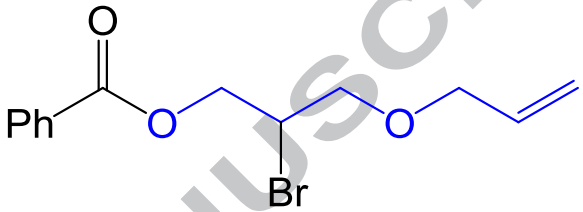
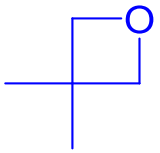
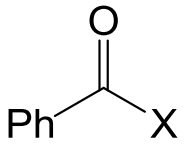
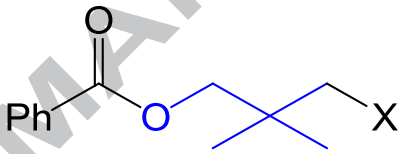
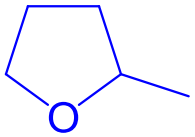
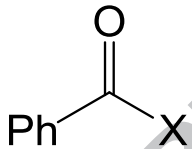
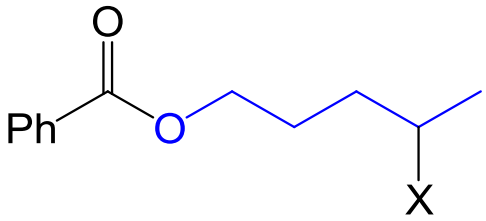


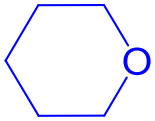
Figure 1: Side-product obtained from the addition of two successive THF rings to 4-methoxybenzoyl chloride

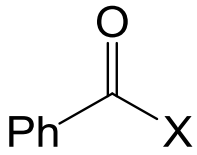
Furthermore, acyl bromides (benzoyl bromide and 4-bromomethylbenzoyl bromide) also produced very good yields (**2a:** R = H, 86.3%, **2b:** R = 4-CH_2Br, 80.9 %). The reaction failed when benzoyl cyanide or methyl benzoate were used as substitutes for the acyl halides.

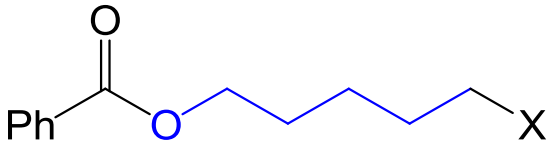
The acylative cleavage of other cyclic ethers including epoxides, 3,3-dimethyloxetane, 2-methyltetrahydrofuran and tetrahydropyran were also investigated (Table 3).

Table 3: Cleavage of other cyclic ethers by acyl halides

Cyclic ether	Acyl halide	Product	Yield (%)[a]
			**7a:** X = Cl, 72.7 **7b:** X = Br, 98.3
			**8:** 76.5
			**9a:** X = Cl, 94.4 **9b:** X = Br, 81.0
			**10a:** X = Cl, 24.5[b] **10b:** X = Br, 18.6[b]







11a: X = Cl, 22.7[b]

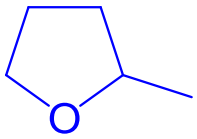
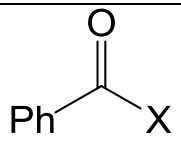
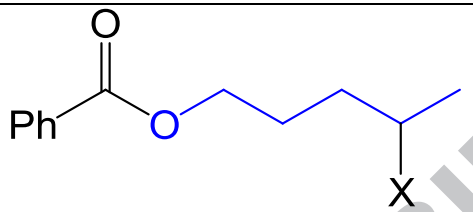
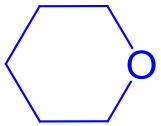
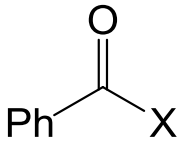
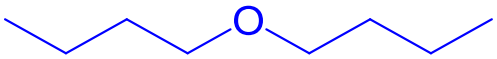
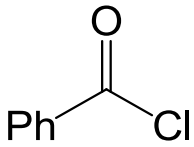
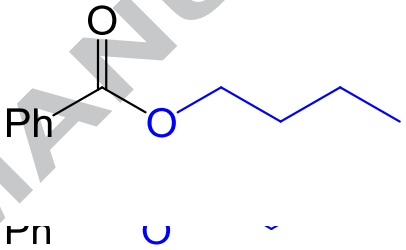
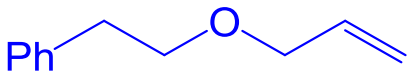
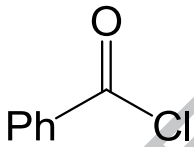
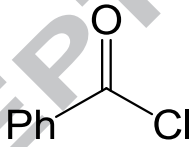
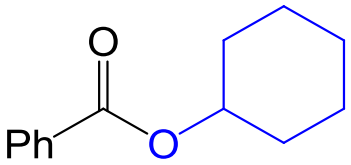
11b: X = Br, 20.9[b]

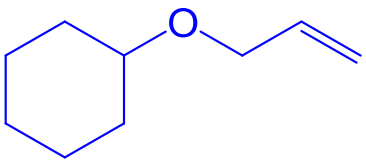
Reagents and conditions: acyl halide (1 g), cyclic ether (1 M, unless otherwise indicated in the ESI), $Pd(OAc)_2$ (2 mol%), 4 h, room temperature. [a]Isolated yield.
[b]Reaction was stirred for 24 h.

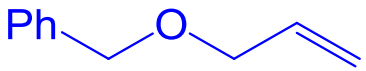
For non-symmetrical cyclic ethers such as 2-phenyloxirane (**7a** and **7b**), allyl glycidyl ether (**8**) and methyltetrahydrofuran (**10a** and **10b**), the ether ring appeared to open from the most substituted side of the C–O bond, resulting in a product in which the ether oxygen attaches to the carbonyl of the acyl halide through its less substituted carbon, while the most substituted carbon becomes halogenated. Although epoxides and 3,3-dimethyloxetane produced very good yields with both benzoyl chloride and benzoyl bromide, it should be noted that 2-methyltetrahydrofuran and tetrahydropyran could not be cleaved within 4 hours, and produced only traces of the expected product as indicated by GC-MS. In fact, even after 24 hours at room temperature, these two cyclic ethers produced only limited amounts of the expected products (**10a** 24.5%, **10b** 18.6%, **11a** 22.7%, **11b** 20.9%, Table 3), while acyclic ethers (diethyl ether, dibutyl ether and 2-chloroethyl ether) failed to produce any product at room temperature, even after 24 hours.

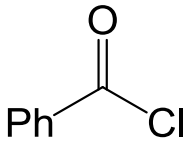
To further explore the limits of this reaction, 2-methyltetrahydrofuran, tetrahydropyran and selected acyclic ethers were heated at 100 ^{o}C under microwave irradiation for two hours in the presence of $Pd(OAc)_2$ (2 mol%) and an acyl halide (Table 4). Under these conditions, both 2-methyltetrahydrofuran (**10a**, 85.1% and **10b**, 81.9%, Table 4) and tetrahydropyran (**11a**, 92.6% and **11b**, 83.2%, Table 4) produced the expected products in high yield with both benzoyl chloride and benzoyl bromide. More importantly, dibutyl ether (**12**, 92.6%) also produced the expected product in excellent yield, while diethyl ether and 2-chloroethyl ether failed to produce any product. This failure might be due to the low boiling point of these two ethers since further studies showed that, when the reaction temperature was lowered to 60 ^{o}C, in the microwave for two hours, even 2-methyltetrahydrofuran and tetrahydropyran, which gave very good yields at 100 ^{o}C, produced only traces of the desired products.

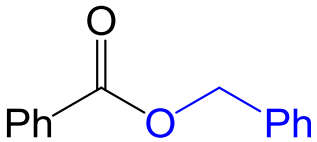
Table 4: Acylative cleavage of tetrahydropyran, 2-(chloromethyl)tetrahydropyran and acyclic ethers

Ethers	Acyl halides	Products	Yields (%)[a]
			**10a:** X = Cl, 85.1 **10b:** X = Br, 81.9
			**11a:** X = Cl, 92.6 **11b:** X = Br, 83.2
			**12:** 96.1
			**13:** 79.5
			**14:** 95.9









15: 38.7

Reagents and conditions: acyl halide (1 g), ether (1 M, unless otherwise indicated in the ESI), $Pd(OAc)_2$ (2 mol%), 2 h, microwave irradiation, 100 ^{o}C. ^{a}Isolated yield.

To explore the reaction selectivity, a series of unsymmetrical acyclic ethers including 2-(allyloxy)ethyl)benzene, (allyloxymethyl)benzene, allyloxycyclohexane, allyloxybenzene, (2-propoxyethyl)benzene, (2-butoxyethyl)benzene and (2-(pentyloxy)ethyl)benzene were investigated.

2-(Allyloxy)ethyl)benzene and allyloxycyclohexane, possessing an allyloxy group at one end of the ether and a phenethyl or cyclohexyl group at the other end, respectively, produced phenethyl benzoate (**13**, 79.5%) and cyclohexyl benzoate (**14**, 95.9%), respectively, in high yields. It is important to note that in these products, the ethers selectively attached the moiety other than the allyl group to the carbonyl of the acyl halide. This selectivity is also observed with (allyloxymethyl)benzene (**15**, 38.7%), and allyloxybenzene for which the purification of the product was impractical due to co-elution with the starting material, even when 1.2 equivalent of the ether was used. It is possible that the allyl group, due to its proximity to the ether oxygen, allows a π-type coordination in the transition state with the palladium catalyst, thus resulting in the observed selectivity. In fact, (2-propoxyethyl)benzene, (2-butoxyethyl)benzene or (2-(pentyloxy)ethyl)benzene, possessing a phenethyl group at one end of the ether and *n*-propyl, *n*-butyl or *n*-pentyl at the other end, respectively, failed to display any selectivity, producing inseparable mixtures of products. Furthermore, while the proximity of the cyclohexyl ring to the ether oxygen seems to have no effect, the reaction yield appeared to diminish drastically as the aromatic ring moves closer to the ether oxygen as illustrated with compound **15**. In this case, the proximity of the aromatic ring might also create the same π-type coordination in the transition state as the allyl group, resulting in the observed reduced yield. This hypothesis still needs to be further investigated.

Conclusion

A palladium(II) acetate catalyzed acylative cleavage of cyclic and acyclic ethers under neat conditions has been developed. The reaction proceeds well with epoxides, 3,3-dimethyloxetane and tetrahydrofuran at room temperature using a diversity of acyl halides, while with 2-methyltetrahydrofuran, tetrahydropyran and open-chain ethers, the reaction mixtures had to be heated at 100 ^{o}C under microwave irradiation for two hours. Furthermore, for asymmetric cyclic ethers, the ring appeared to open from the most substituted side of the C–O bond in such a way that the ether oxygen is attached to the carbonyl of the acyl halide through the less substituted side. For unsymmetrical open-chain ethers possessing an allyloxy group at one end of the ether, the reaction selectively attaches the side of the ether other than that of the allyloxy group to the carbonyl of the acyl halide. However, this selectivity appeared to be limited to the allyloxy group, as ethers with different groups did not display any selectivity. It is expected that this reaction, in addition to becoming a useful synthetic tool for the preparation of different type of esters, can also help in the selection of better ethers solvents to be used for any type of palladium(II) acetate catalyzed reaction involving acyl halides.

Acknowledgements

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Highlights

- $Pd(OAc)_2$ catalyzed cleavage of cyclic, acyclic, symmetrical and unsymmetrical ethers
- The reaction takes place mostly at room temperature, under neat conditions
- Ethers that could not be cleaved at room temperature were heated at 100 ^{o}C in a microwave reactor
- Some unsymmetrical ethers were cleave in a regioselective manner, but this regioselectivity is very limited

Graphical Abstract

Palladium(II) acetate catalyzed acylative cleavage of cyclic and acyclic ethers under neat conditions

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Jean Fotie,[a]* Brandy R. Adolph,[a] Shreya V. Bhatt[a] and Casey C. Grimm[b]