# Introducing efficient palladium catalyzed cross coupling reaction of tertiary alcohols and aroyl chlorides for the synthesis of highly substituted esters

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# Introducing efficient palladium catalyzed cross coupling reaction of tertiary alcohols and aroyl chlorides for the synthesis of highly substituted esters

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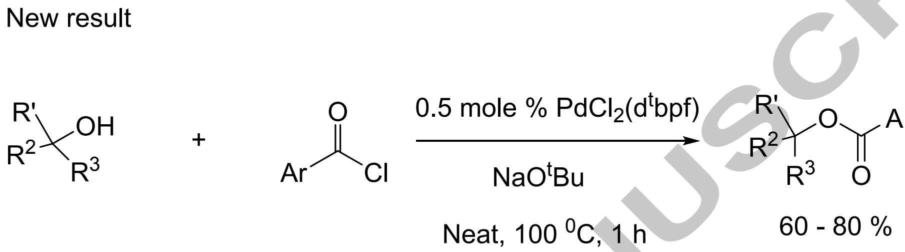
**Abstract:** Esters are chemical compounds with many practical uses. The common type of esterification is called the Fischer esterification. Another one is by the action of acid chlorides on alcohols but not with tertiary alcohols. The stable carbenium ions formed from tertiary alcohols favor elimination and the byproduct, hydrogen chloride prevents ester formation. In this new report, palladium inserted ArCOPdCl species reacts with tertiary alcohols and cross-coupling under microwave heating, minimizes the formation of probable carbenium ion, and promotes successful production of highly substituted esters in good to high yields.

**Keywords** Tertiary alcohols, ArCOPdCl, Solvent free, Microwave

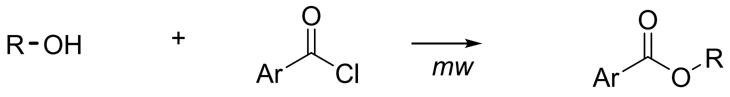
Over the years there have been many studies done on the formation of esters. Many of these studies have shown how readily primary alcohols react to form such esters. However, few reactions have effectively used secondary or tertiary alcohols. The purpose of this research project was to find a more efficient and economical way to synthesize esters that are more complex by using the secondary and tertiary alcohols. Esters have many applications in industries such as medicine.[1,2] Esters are not only a source for the flavor of fruits but also for the smell of everyday products. Industries where esters have an application are in agriculture chemistry,[3,4,5] polymer chemistry,[6] petro chemistry.[7] There are many applications of esters in the real world and there are also many ways to make esters. One commonly used synthetic process for ester synthesis is Fischer esterification.[8] Transition metal catalysis and cross-coupling reactions is believed to be one of the most important advancement in the field of organic chemistry.[9] In our report, we focus on palladium inserted ArCOPdCl[10] species and making functional groups labile aromatic ester via treatment with tertiary alcohols (Scheme 1).

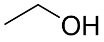
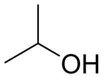
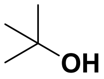
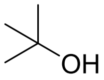
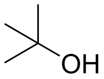
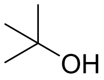
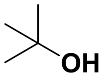


**Scheme 1. Cross-coupling of tertiary alcohols and aroyl chlorides**

This not only makes a more efficient way of synthesizing highly substituted aromatic esters, but also cuts down on the production of unwanted or unsafe by-products. We also have observed that this kind of reaction succeeds under microwave heating without any catalyst or base for primary alcohols and in some cases for secondary alcohols as well. The complication lies with tertiary alcohols (Table 1). Cross coupling reactions of tertiary alcohols and aroyl chlorides are largely unknown.[11,12] Use of an ArCOPdCl species, a new source of ArCO moiety, to react with tertiary alcohols and form bulky esters has yielded interesting findings. Reactions of tertiary alcohols successfully ran with aroyl chlorides containing several varieties of functional groups. These substituents classify as either electron-withdrawing group (EWG) or electron-donating group (EDG) depending on their effectiveness at attracting or giving away an electron. Among several other available palladium complexes, a minimum load of $PdCl_2(d^tbpf)$ proved to offer an effective catalytic effect for esterification. $PdCl_2(d^tbpf)$ complex has been successfully employed as a catalyst in various organic transformations.[13] The higher cone angle of P-Pd-P in $PdCl_2(d^tbpf)$ improves its effectiveness as a catalyst.[14] To extend further application of this Pd-complex in esterification, we scanned it along with many bases and found best results with $NaO^tBu$.

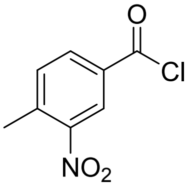
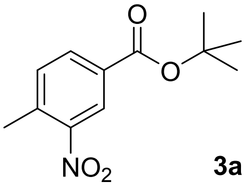
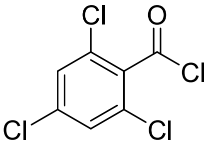
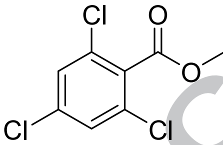
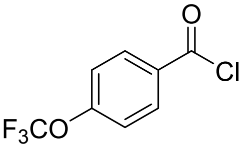
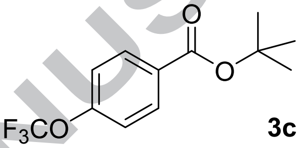
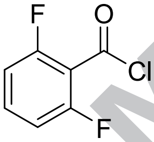
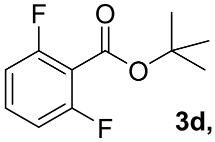
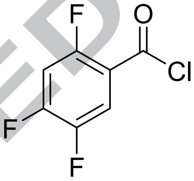
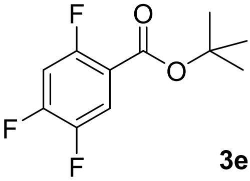
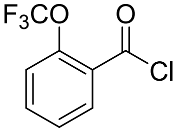
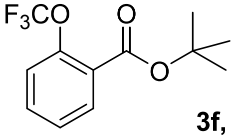
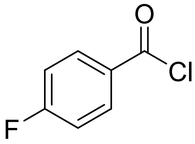
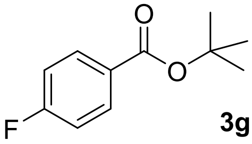
**Table 1. Solvent free ester synthesis from aroyl chlorides and tertiary alcohols**



| **Alcohols** | **$PdCl_2(d^tbpf)$** | **$NaO^tBu$** | **Temp** | **Time** | **Ester** |
|---|---|---|---|---|---|
|  | No catalyst | No base | 100 °C | 30 min | 100 % |
|  | No catalyst | No base | 100 °C | 30 min | 62 % |
|  | **No catalyst** | **No base** | 100 °C | 30 min | **No product** |
|  | $PdCl_2(d^tbpf)$ | **No base** | 100 °C | 30 min | **No product** |
|  | **No catalyst** | $NaO^tBu$ | 100 °C | 30 min | **No product** |
|  | $PdCl_2(d^tbpf)$ | $NaO^tBu$ | 100 °C | 30 min | ester formed |
|  | **$PdCl_2(d^tbpf)$** | **$NaO^tBu$** | 100 °C | **1 h<br>better result** | **ester formed<br>good yields** |

Best results are displayed in Table 2, Table 3, and Table 4. We utilized microwave irradiation to cut down the time and energy necessary for esterification. Another significant point of this process is

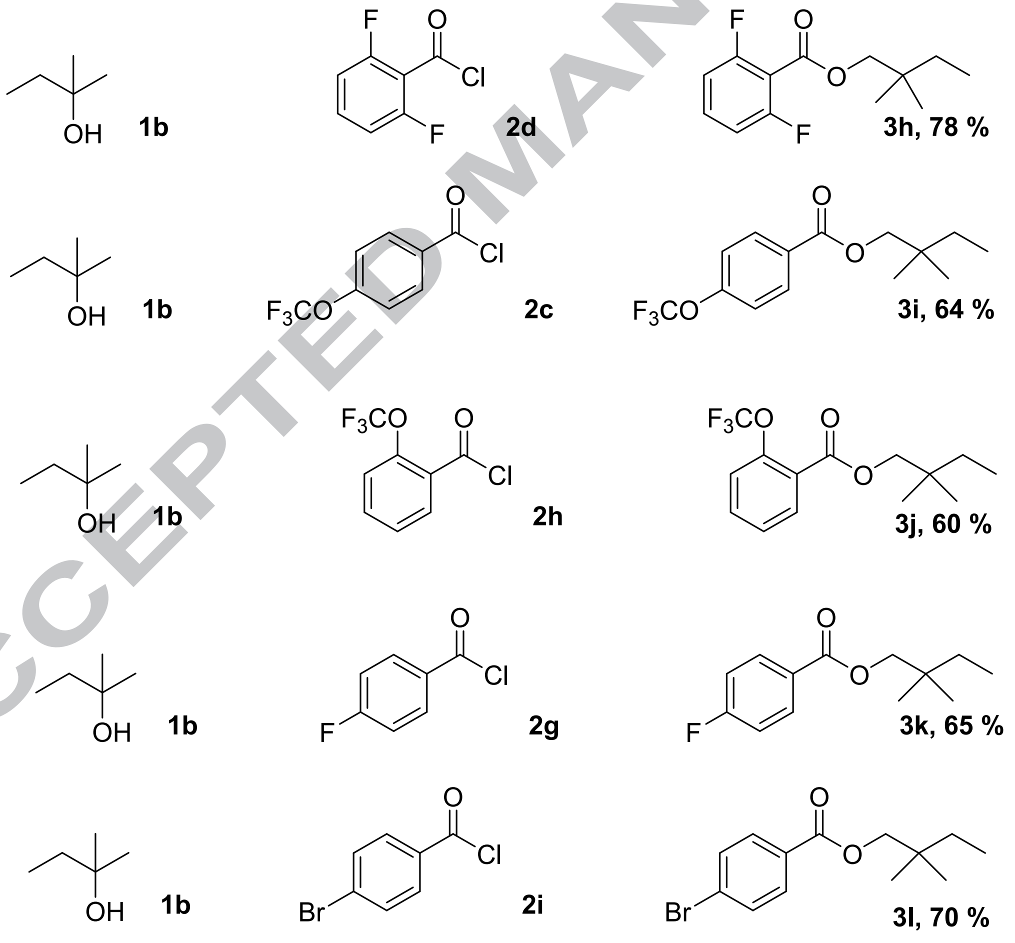
**Table 2. Esters from tertiary butanol and aroyl chlorides[a]**

| | | | | | |
|---|---|---|---|---|---|
|  | **1a** |  | **2a** |  | **3a, 68 %** |
|  | **1a** |  | **2b** |  | **3b, 60 %** |
|  | **1a** |  | **2c** |  | **3c, 66 %** |
|  | **1a** |  | **2d** |  | **3d, 58 %** |
|  | **1a** |  | **2e** |  | **3e, 53 %** |
|  | **1a** |  | **2f** |  | **3f, 55 %** |
|  | **1a** |  | **2g** |  | **3g, 64 %** |

**[a] All reactions microwaved for 1 h at 100 °C. Isolated and confirmed by NMR.**

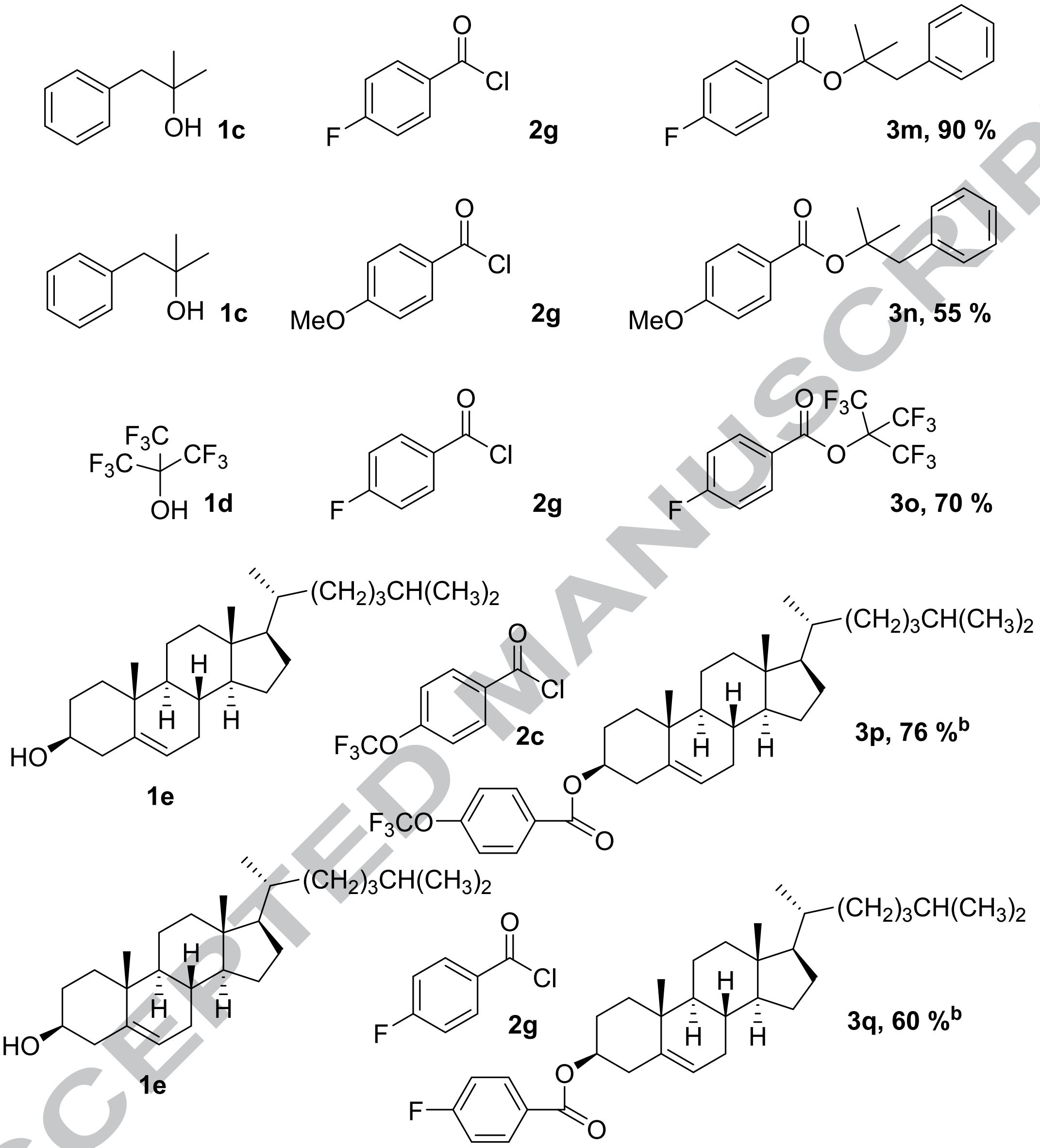
that it is a solvent free reaction. In addition, limitations of this new esterification process were noted when aliphatic acid chlorides instead of aromatic acid chlorides were used. Further studies are underway to overcome this limitation. The probable catalytic cycle of the reaction is displayed in Scheme 2. The ArCOPdCl species is also proposed in Stille's direct cross-coupling reaction of organotin compounds and aroyl chlorides for ketone synthesis.[15] Several others have also reported similar cross-coupling reaction by using arylboronic acids and acid chlorides as starting reagents.[16]

**Table 3. Esters from 2-methyl-2 butanol and aroyl chlorides[a]**



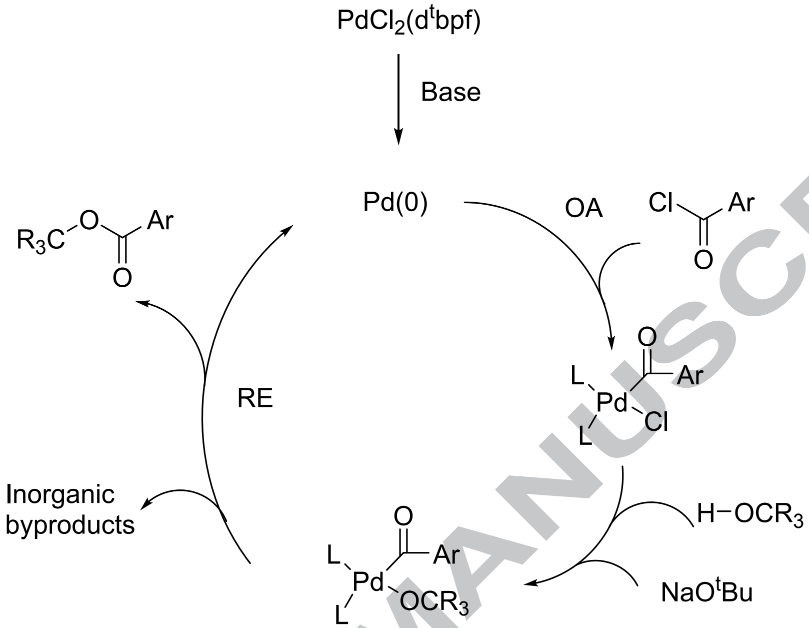
**[a] All reactions microwaved for 1 h at 100 °C. Isolated and confirmed by NMR.**

**Table 4. Esters from tertiary alcohols 1c, 1d, and cholesterol 1e.[a]**



**[a] All are isolated products. [b] Cholesterol esters formed. Products still contain some impurities.**

The reaction methods used for all the reactions shown in Table 2, Table 3, and Table 4 are the same except for cholesterol, **1e** where 1.0 mL of 1,4-dioxane was added. An oven dry clean microwave vial is loaded with 1.0 mmol of NaO$^t$Bu (100.0 mg), 0.0025 mmol of $PdCl_2(d^tbpf)$ (2.0 mg), capped with air-tight silicon septa and flushed with argon.



**Scheme 2**. Plausible reaction mechanism

Then 0.5 mmol of aroyl chloride was added as limiting reagent via micro syringe, and tertiary alcohol (1.0 mL) was added via dry syringe. The resulting reaction mixture was then microwaved (CEM Explorer 24, 300W) at 100 ˚C for 60 min. Crude reaction product in reaction tube was diluted with dichloromethane and transferred into a separating funnel. Water was then added to the funnel and, after standard extraction, excess alcohol was completely miscible with water. The bottom organic layer was collected in a small Erlenmeyer flask over anhydrous $Na_2SO_4$. The dichloromethane layer was filtered through sintered funnel and filtrate, collected in a round bottom flask, and completely dried by rotary evaporator and under reduced pressure in vacuo. In case of cholesterol **1e**, 0.5 mmol of aroyl chloride, 1.0 mmol of cholesterol, and 1.0 mL of 1,4-dioxane were used. The desired ester product was confirmed by $^1$H NMR, $^{13}$C NMR, and

$^{19}$F NMR. Ester (**Compound 3c**) from tertiary alcohol, **1a**; $^{1}$H NMR ($CDCl_3$, 400 MHz) δ 7.95 (d, J = 8.64, 2H), 7.16 (d, J= 8.36 Hz, 2H), 1.51 (s, 9H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 164.5, 152.3, 130.5, 120.1, 81.5, 28.1. $^{19}$F NMR ($CDCl_3$, 400 MHz) δ -57.7 ($OCF_3$); Ester (**Compound 3k**) from tertiary alcohol, **1b**; $^{1}$H NMR ($CDCl_3$, 400 MHz) δ 8.00 (dd, J = 8.04, 1H), 7.08 (t, J= 8.52 Hz, 1H), 1.92 (q, J = 7.48, 2H), 1.56 (s, 6H), 0.97 (t, J = 7.44 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 166.7, 164.7, 131.8, 128.2, 115.3, 83.6, 33.7, 25.6, 8.3. $^{19}$F NMR ($CDCl_3$, 400 MHz) δ -106.9 (F); Ester (**Compound 3m)** from tertiary alcohol, **1c**; $^{1}$H NMR ($CDCl_3$, 400 MHz) δ 7.24 (dd, J=8.72, 2H), 7.16 (m, 5H), 6.99 (t, J = 8.64 Hz, 2H), 3.1 (s, 2H), 1.51 (s, 6H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 166.8, 165.0, 137.1, 130.6, 128.0, 126.5, 115.4, 83.1, 46.6, 26.14; $^{19}$F NMR ($CDCl_3$, 400 MHz) δ -106.6 (F);

The cross-coupling reaction of tertiary alcohols and aroyl chlorides is significant because it overcomes the limitation of tertiary alcohols in esterification. Since involvement of tertiary alcohols allow for a more complex ester, this process could prove to be very useful in both the chemical and biological fields of study.

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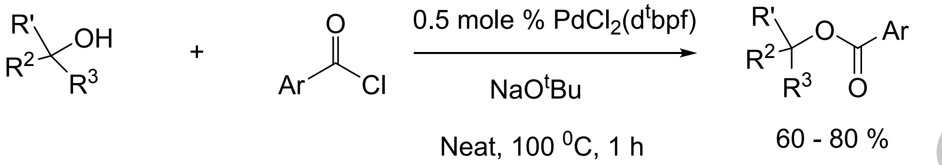

- Tertiary alcohols as cross-coupling partner
- Pd inserted ArCOPdCl species
- Cholesterol ester
- Microwave
- Solvent free reaction

17.