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A Highly Efficient Friedel–Crafts Reaction of Tertiary α-Hydroxyesters or α-Hydroxyketones to α-Quaternary Esters or Ketones

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The acid-catalyzed Friedel–Crafts reaction of alcohols and electron-rich aromatic compounds is a highly atom-efficient method for the preparation of aromatic compounds with diverse applications, and only water is generated as the by-product.[1,2] During the past decade, significant progress has been made in the development of a catalytic version of this transformation, including the construction of hindered all-carbon quaternary centers.[1,3] Generally, carbenium ions are invoked as intermediates in this SN_1-type reaction, and substituents that can stabilize the intermediates could facilitate this reaction (Figure 1).[1,4] Accordingly, most of the known

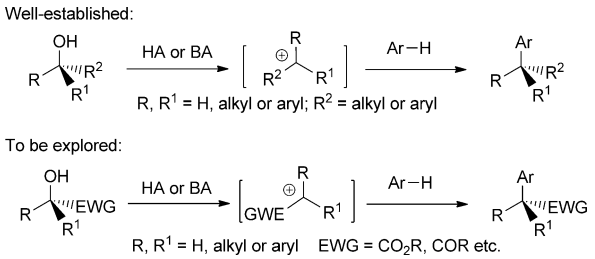

Figure 1. The catalytic Friedel–Crafts arylation of alcohols.

catalytic protocols are based on alcohols with electron-donating groups that could stabilize the intermediate carbocations. The limited catalytic arylation reactions of alcohols with an α-electron-withdrawing substituent have been restricted to alcohols that could form reactive oxonium[3e] or vinylogous iminium[3f–k] intermediates. If the catalytic Friedel–Crafts arylation reaction could be extended to alcohols with an α-electron-withdrawing group such as α-hydroxyesters or α-hydroxyketones, it would provide a facile method for the α-arylation of esters and ketones. However, to the best of our knowledge, the catalytic version of this reaction has not been reported.[5]

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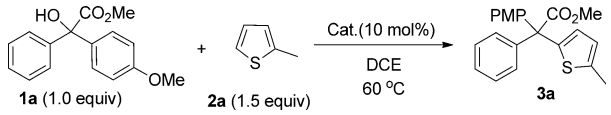
The α-quaternary carbonyl compounds, especially α-diaryl or α-triaryl-substituted carbonyl compounds, have wide applications in organic synthesis, medicinal research, and catalyst design.[6] However, synthetic methods to afford these building blocks are very limited, and they often involve multistep synthesis.[7] For example, triarylacetic acid derivatives were often prepared by the reaction of CO_2 and organolithium compounds derived from triarylmethyl chlorides, which were obtained from the corresponding α-triaryl-substituted tertiary alcohols.[6b] Therefore, the development of efficient methods for the diverse synthesis of these compounds is highly desirable.

As part of a program directed at the catalytic construction of tetrasubstituted carbon centers using easily available starting materials and catalysts,[8] we were interested in the elaboration of tertiary α-functionalized alcohols. In this context, we have recently developed the catalytic Friedel–Crafts[9a] and Ritter reaction[9b] of 3-substituted 3-hydroxyoxindoles, and a tandem reaction towards 3,3-disubstituted benzofuranones.[9c] Based on these results, we further tried catalytic Friedel–Crafts arylation of tertiary α-hydroxyesters or α-hydroxyketones.

The reaction of hydroxyester **1a** and 2-methylthiophene **2a** was carried out to evaluate different acid catalysts; this reaction was carried out in 1,2-dichloroethane (DCE) at 60 °C. We focused on using cheap and easy to handle metal perchlorate hydrates as the Lewis acid catalysts, which have been widely used in a number of reactions.[10] Initial screening studies revealed that Co^{II}-, Mg^{II}-, Ba^{II}-, Zn^{II}-, Mn^{II}-, Ca^{II}-, Cd^{II}-, Pb^{II}-, and Ni^{II}-derived perchlorate hydrates were unable to catalyze the desired reaction. To our delight, several metal perchlorate hydrates catalyzed this reaction well (Table 1, entries 1–8). Among them, $Hg(ClO_4)_2{\cdot}3H_2O$ turned out to be the most efficient one, and afforded the desired product in 99% yield within 2.5 h (Table 1, entry 3). Brønsted acids[11] such as $HClO_4$ and TfOH could also catalyze the reaction (Table 1, entries 9 and 10), and, in particular, $HClO_4$ was as efficient as $Hg(ClO_4)_2{\cdot}3H_2O$. This result was to some extent unexpected, as $Hg(ClO_4)_2{\cdot}3H_2O$ was found to be much more efficient than $HClO_4$ in the Friedel–Crafts arylation of 3-hydroxyoxindoles,[9a] possibly owing to the aromatic mercuration. In light of this, both catalysts were comparatively evaluated in some typical solvents.

As shown in Table 2, while $Hg(ClO_4)_2{\cdot}3H_2O$ could catalyze the desired reaction faster than $HClO_4$ when using DCE, tetrahydrofuran (THF), or ethyl acetate as the solvent

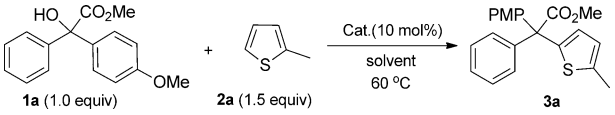
Table 1. Evaluation of catalysts.



Entry[a]	Catalyst	t [h]	Yield [%][b]
1	$Cr(ClO_4)_2 \cdot 6H_2O$	22	99
2	$Al(ClO_4)_3 \cdot 9H_2O$	38	82
3	$Hg(ClO_4)_2 \cdot 3H_2O$	2.5	99
4	$Cu(ClO_4)_2 \cdot 6H_2O$	72	99
5	$AgClO_4 \cdot H_2O$	23	89
6	$In(ClO_4)_2 \cdot 8H_2O$	14	99
7	$Fe(ClO_4)_2 \cdot x H_2O$	11	99
8	$Zr(ClO_4)_2 \cdot 8H_2O$	11	99
9	$HClO_4$	3	99
10	CF_3SO_3H	18	57

[a] On a 0.20 mmol scale; [b] Isolated yield. PMP = *p*-methoxyphenyl.

Table 2. Comparing $Hg(ClO_4)_2 \cdot 3H_2O$ and $HClO_4$.



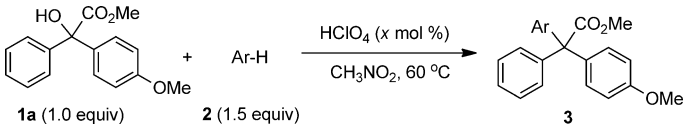
Entry[a]	Solvent	$Hg(ClO_4)_2 \cdot 3H_2O$		$HClO_4$	
		t [h]	Yield[b] [%]	t [h]	Yield[b] [%]
1	DCE	2.5	99	3	99
2	THF	24	63	48	30
3	Ethyl acetate	24	95	26	89
4	Toluene	48	80	8	99
5	CH_3CN	48	trace	10	99
6	CH_3NO_2	3	96	1	99
7	CH_3NO_2	–	–	1	96[c]
8	CH_3NO_2	–	–	3	92[d]

[a] On a 0.20 mmol scale; [b] Isolated yield; [c] 5 mol% of catalyst; [d] 1 mol% of catalyst.

(Table 2, entries 1–3), $HClO_4$ was more efficient than $Hg(ClO_4)_2 \cdot 3H_2O$ in toluene, CH_3CN, and CH_3NO_2 (Table 2, entries 4 and 5). Especially, when using CH_3NO_2 as the solvent, $HClO_4$ could catalyze the reaction to full conversion within one hour (Table 2, entry 6). Furthermore, with only 1 mol% of $HClO_4$, product **3a** could still be obtained in 92% yield within three hours (Table 2, entry 8). Based on these results, the optimal reaction conditions were at 60 °C under air using CH_3NO_2 as the solvent. It should also be noted that $HClO_4$ was used as a 70% aqueous solution, which reduced the danger associated with the use of pure perchloric acid.

Next, the substrate scope with respect to both the electrophile and nucleophile was then investigated, and the catalyst loading of $HClO_4$ was dependent on the reactivity of the substrates. A variety of (hetero)aromatic compounds were first tested. 2-Methylthiophene or furan, anisole, and 1,3-dimethoxybenzene all worked well to afford the corresponding products **3a–d** in high to excellent yield (Table 3). These electron-rich aromatic compounds were very reactive, and only 1 mol% of $HClO_4$ was required. However, *N*-methyl-

Table 3. The substrate scope of different (hetero)arenes.



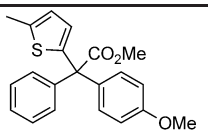
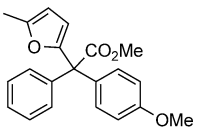
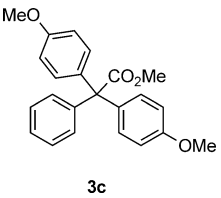
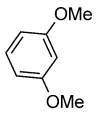
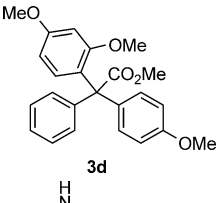
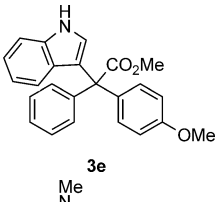
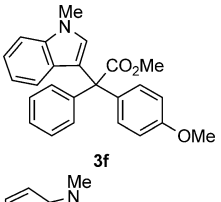
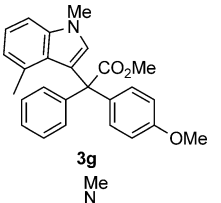
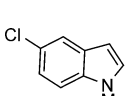
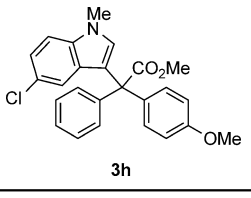
Entry[a]	2	Product 3	x	t [h]	Yield[b] [%]
1	 2a	 3a	1	3	92
2	 2b	 3b	1	2	87
3	 2c	 3c	1	20	87
4	 2d	 3d	1	3	91
5	 2e	 3e	20	96	86
6	 2f	 3f	20	24	91
7	 2g	 3g	5	7	96
8	 2h	 3h	5	2	86

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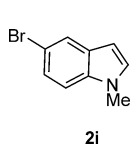
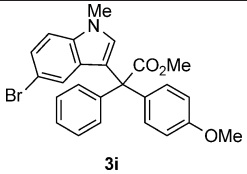
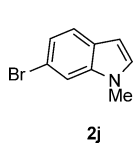
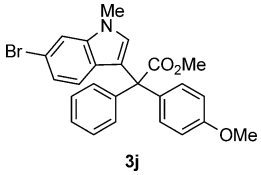
Table 3. (Continued)

Entry[a]	2	Product 3	x	t [h]	Yield[b] [%]
9	 2i	 3i	5	2	86
10	 2j	 3j	5	2	87

[a] On a 0.3 mmol scale; [b] Isolated yield.

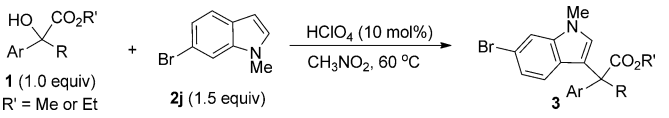
pyrrole was ineffective under these reaction conditions, and the reason is still unkown.

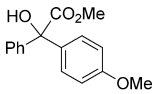
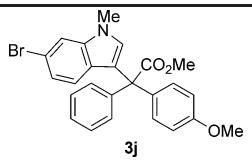
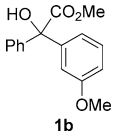
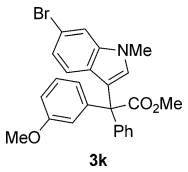
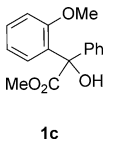
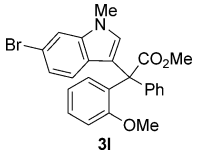
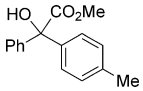
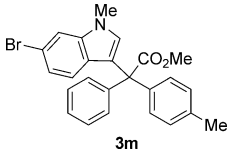
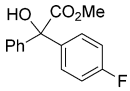
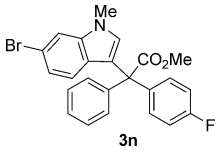
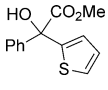
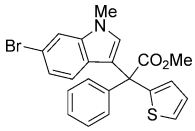
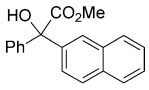
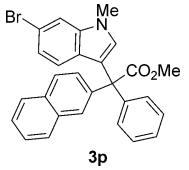
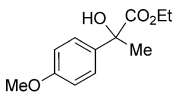
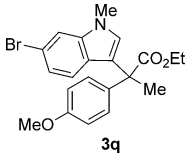
As the indole framework is a "privileged" structure or pharmacophore, significant efforts have been paid to the development of the C3-functionalization reaction of indoles to prepare indole-containing compounds.[12] However, only limited protocols have been reported for the generation of a full-carbon quaternary center adjacent to the C3-position of an indole,[13] and to the best of our knowledge, only one method enabled the synthesis of α-quaternary α-indolyl carboxylic acid in moderate yield, with limited substrate scope.[7a] In light of this, a number of substituted indoles were then examined.

We found that indoles were less reactive than the arenes examined above, and 5–20 mol% of catalyst was required to ensure the high yield of the desired product. For example, in the cases of indole and *N*-methylindole, while the corresponding desired products **3e**,**f** could be obtained in high yield, the reaction time was much longer and 20 mol% of $HClO_4$ was required. In the case of indoles **2h–j**, bearing electron-withdrawing halogen substituents, only 5 mol% of catalyst was required to promote the reaction to completion within a few hours. The reason for these observed unusual electronic effects is still unknown.

The *N*-methyl-6-bromoindole **2j** was chosen to evaluate the scope of hydroxyesters **1a–h** in the presence of 10 mol% of $HClO_4$ (Table 4), as the resulting products, with a bromo substituent, might be further elaborated through transition-metal-catalyzed cross-coupling reactions. The electronic effect was very obvious in this case. For example, α-hydroxyesters **1a** and **1c**, with a methoxy group at the *para* or *ortho* position of the phenyl ring, afforded the products **3j** and **3l**, respectively, in high yield, while hydroxyester **1b**, with a methoxy group at the *meta* position, was much less reactive and almost no reaction took place even at 80 °C with a much longer reaction time (Table 4, entries 1–3). The fluorine atom on the phenyl ring slowed down the rate of the reaction significantly, therefore the reaction of **1e** with **2j** was run at 80 °C, however, product **3n** was obtained in 93% yield. The reactions with α-(2-thiophenyl)- or α-(2-naphthyl)-substituted α-hydroxyesters **1f** or **1g**, respectively, worked well to give the corresponding product **3o** or **3p** in high yield (Table 4, entries 6 and 7). To our delight, this protocol was not limited to the synthesis of triarylacetic acid esters, as α-hydroxy-α-methyl-arylester **1h** was also a viable substrate under these reaction conditions, thereby affording the desired product in reasonable yield. Unfortunately, α-di-

Table 4. Scope of hydroxyesters.



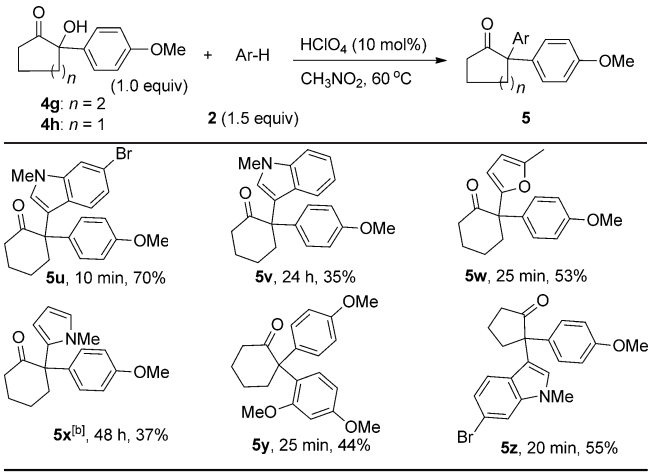
Entry	1	Product 3	t [h]	Yield[b] [%]
1[c]	 1a	 3j	2	87
2[d]	 1b	 3k	23	trace
3	 1c	 3l	3	90
4	 1d	 3m	40	78
5[d]	 1e	 3n	16	93
6	 1f	 3o	5	89
7	 1g	 3p	48	90
8	 1h	 3q	2	96

[a] On a 0.3 mmol scale; [b] Isolated yield; [c] 5 mol% $HClO_4$ was used; [d] 80 °C.

alkyl-substituted α-hydroxyesters such as ethyl 2-hydroxy-2-methylpent-4-enoate were not synthesized under these reaction conditions, possibly owing to the preference of the elimination reaction of the starting materials.

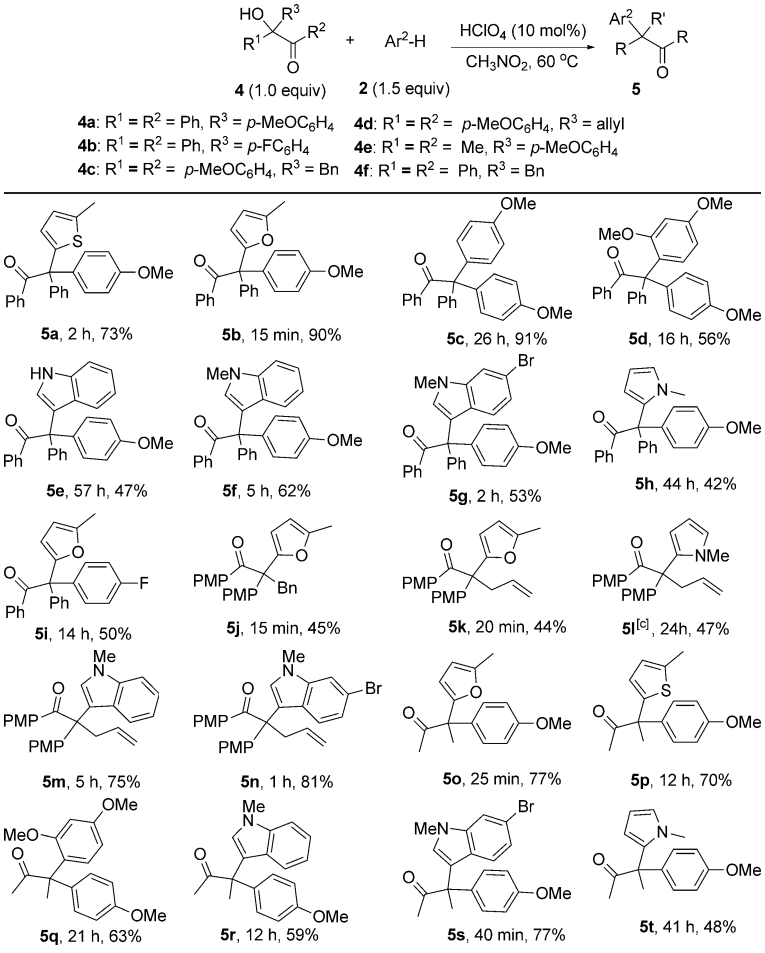
We further examined if our method could be extended to the Friedel–Crafts reaction of α-hydroxyketones **4**. In principle, the ketone moiety of **4** should be more electron-withdrawing than the ester group of α-hydroxyesters **1**, which resulted in the stronger destabilizing effect on the intermediate carbenium ions. It was found that a variety of α,α-diaryl hydroxyketones **4a**,**b**, even with a *p*-fluorophenyl group, worked well with electron-rich arenes such as indoles, pyrroles, thiophenes, furan derivatives, and anisole to give the corresponding α-quaternary ketones **5a–t** in moderate to excellent yield under the standard reaction conditions (Table 5). However, the strong stabilization effect from the *p*-methoxy phenyl group was very important for the α-arylation of α-alkyl α-aryl hydroxyketones **4**. Without the electron-donating methoxy group, the reaction using 2-hydroxy-1,2,3-triphenylpropan-1-one **4f** as the electrophile was unsuccessful. To our delight, α-hydroxy-α-(*p*-methoxyphenyl)-cyclohexanone **4g** could readily react with a variety of electron-rich aromatic compounds to afford the corresponding α,α-diaryl cyclohexanones **5u–y** in moderate to good yield (Table 6). α-Hydroxy-α-(*p*-methoxyphenyl)cyclo-pentanone **4h** could also react with *N*-methyl 6-bromoindole **2j** to give the desired product **5z** in 55% yield.

Table 6. Scope of cyclic α-hydroxyketones.[a]



[a] On a 0.3 mmol scale; [b] 20 mol% of $HClO_4$ was used.

Table 5. Friedel–Crafts reaction of α-hydroxyketones and arenes.



[a] On a 0.3 mmol scale; [b] Isolated yield; [c] 20 mol% of $HClO_4$ was used.

The resulting arylation products **3** and **5** were valuable synthons for the synthesis of a variety of α-quaternary compounds. For example, ester **3a** could be hydrolyzed into the corresponding α-triaryl acid **6** in 86% yield (Scheme 1). $LiAlH_4$ could readily reduce ester **3a** into the corresponding alcohol **7** in 95% yield, which was further converted to α-triaryl aldehyde **8** in 68% yield. The reductive amination of aldehyde **8** using *p*-methoxyphenyl amine afforded the β-quaternary amine **9** in 57% yield. The oxidation of cyclohexanone **5w** with *m*-chloroperoxybenzoic acid (*m*CPBA) gave triketone **10** in 70% yield, while the reduction of **5w** with $NaBH_4$ provided the corresponding cyclohexanol derivative **11** in 70% yield and 3:1 diastereoselectivity. The facile transformation of arylation products into α-quaternary compounds **6–11** further demonstrates the usefulness of our newly developed protocol.

In summary, we have developed the first example of a catalytic Friedel–Crafts arylation of α-hydroxyesters or α-hydroxyketones with electron-rich aromatic compounds to furnish α-quaternary esters or ketones, which could be further transformed into a variety of compounds with a hindered all-carbon quaternary center.[14] The use of cheap and easy to handle catalyst $HClO_4$ (70%, aq) makes this method potentially useful. The development of new efficient acid catalysts to expand the substrate scope is now in progress in our laboratory.

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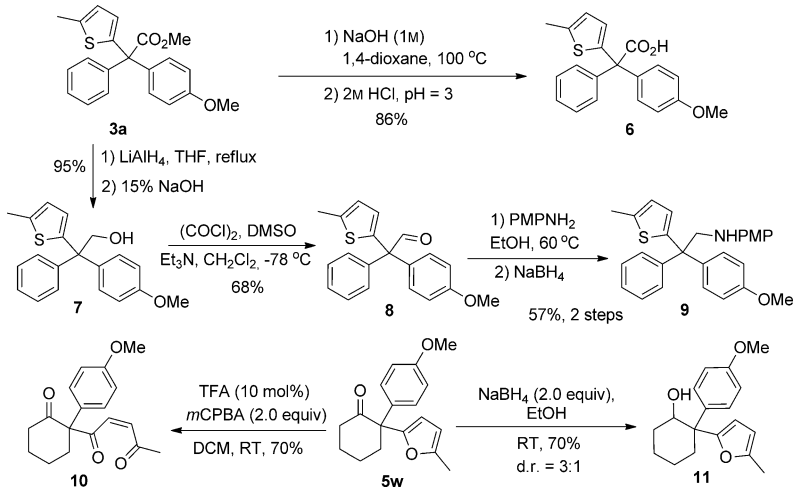

Scheme 1. Product elaboration.

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Keywords: alcohols · Friedel–Crafts reaction · heterocycles · homogeneous catalysis · ketones

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[14] As suggested by one of the reviewers, we tried using (1*R*)-(−)-10-camphorsulfonic acid and (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate as the catalyst for the reaction of **1c** and **2j** to examine if the enantioenriched product **3l** could be generated. However, no reaction took place even at 60 °C in both cases.

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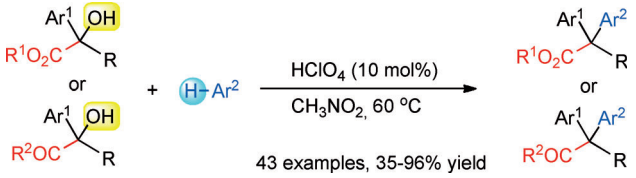

A catalytic Friedel–Crafts arylation of α-hydroxyesters or α-hydroxyketones with electron-rich aromatic compounds to furnish α-quaternary esters/ketones has been developed. The cheap and easy to handle catalyst $HClO_4$ (70%, aq) was identified as a powerful catalyst for this arylation reaction.

Friedel–Crafts Arylation

*Long Chen, Jian Zhou** ____ ▮▮▮▮–▮▮▮▮

A Highly Efficient Friedel–Crafts Reaction of Tertiary α-Hydroxyesters or α-Hydroxyketones to α-Quaternary Esters or Ketones