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An Epoxide-Mediated Deprotection Method for Acidic Amide Auxiliary

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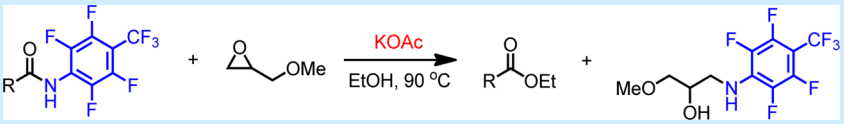
Supporting Information

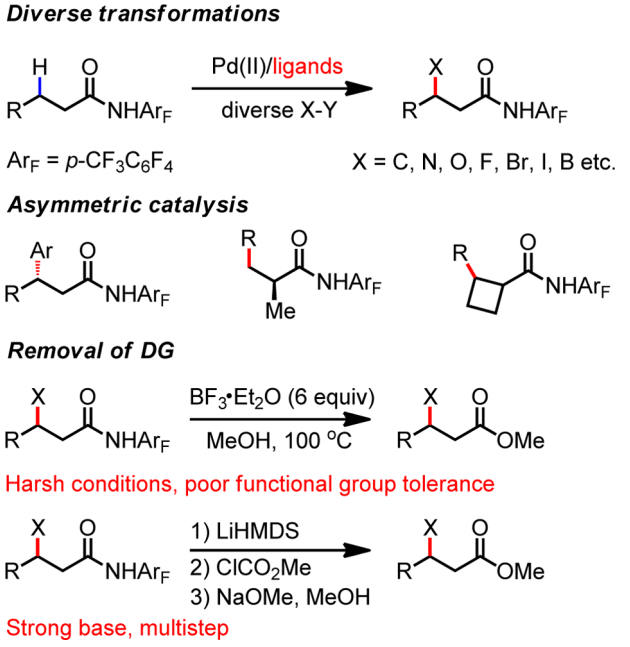


ABSTRACT: A practical method for the removal of a versatile acidic amide auxiliary has been developed. Facile alcoholysis of the amide in the presence of KOAc is enabled by an epoxide, which mechanistically resembles the removal of the Myers' auxiliary. The protocol has been applied to the removal of a variety of amide substrates and their C−H functionalization products with high efficiency and low cost, representing a step forward toward the development of a versatile directing group for C−H activation.

Designing effective auxiliary directing groups has been instrumental in developing a wide range of Pd-catalyzed C−H activation reactions.[1] While many factors are taken into account when evaluating the practicality of a directing group, the ease of its installation and removal is crucial. Guided by our main goal of developing new ligands, especially chiral bidentate ligands for Pd-catalyzed C−H activation, we have largely focused on developing weakly coordinating monodentate directing groups.[2] Among those, the acidic amide group ($CONHAr_F$, Ar_F = p-$CF_3C_6F_4$) has found broad utility, accommodating a wide range of transformations[3] and asymmetric C−H activation reactions.[4] This versatile auxiliary has also been adopted by both academic and industrial efforts.[5] Currently, three main methods are used to remove this directing group: methanolysis promoted by a Lewis acid (BF_3·Et_2O); installing an electron-withdrawing group onto the nitrogen atom of the amide to promote methanolysis; hydrolysis by treating with CF_3SO_3H.[5] However, many substrates are not compatible with these strongly acidic or basic conditions in synthetic applications. We report a convenient protocol for facile alcoholysis of amides using a mild base (KOAc). *N*-Alkylation of the amide with an epoxide and subsequent intramolecular alcoholysis facilitate the removal of the amide auxiliary, in similar fashion to that of the Myers' auxiliary (Scheme 1).[6]

During our reaction development, we observed that the amide auxiliary can be readily *N*-alkylated by an epoxide coupling partner.[7] This observation prompted us to test whether the tethered hydroxyl group can attack the amide to perform intramolecular alcoholysis. Then the product can potentially undergo transesterification with ethanol solvent to give the desired ester, thereby providing a facile deprotection method (Scheme 2). We therefore began to screen various epoxides and reaction conditions in the presence of an alcohol and mild bases. First, we chose the simple epoxide **2a**, the model substrate **1a**, and ethanol as the solvent to test different bases. As shown in Table 1, we started the screening with K_2CO_3 as the base. To our delight, the desired product was detected in 22% yield. Next, we evaluated a range of potassium salts with different anions. Encouragingly, the yield of the product was drastically increased to 74% by using $KHCO_3$.

Scheme 1. Versatility of the Acidic Amide in C−H Functionalizations and Conditions for Removal



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Scheme 2. Proposed Strategy for the Alcoholysis of the Acidic Amide

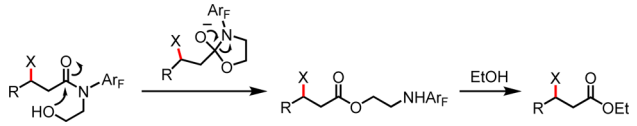
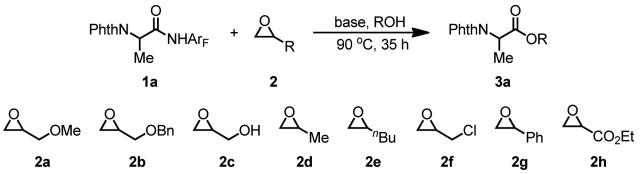


Table 1. Optimization of Reaction Conditions[a]



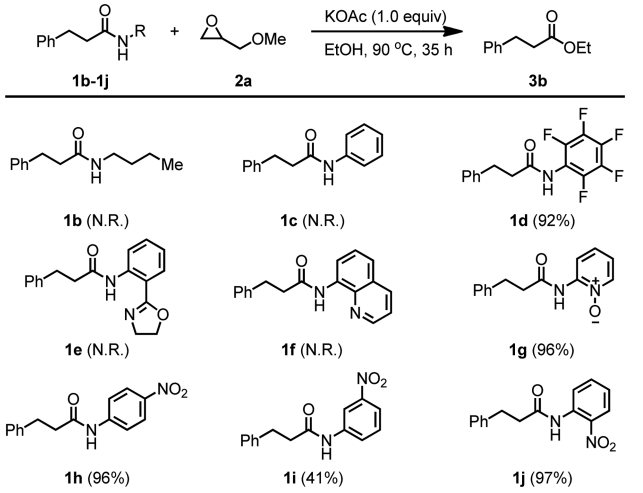
entry	base	epoxide	alcohol	yield (%)[b]
1	K_2CO_3	**2a**	EtOH	22
2	$KHCO_3$	**2a**	EtOH	74
3	K_3PO_4	**2a**	EtOH	33
4	K_2HPO_4	**2a**	EtOH	27
5	KH_2PO_4	**2a**	EtOH	trace
6	KF	**2a**	EtOH	36
7	KCl	**2a**	EtOH	31
8	KOAc	**2a**	EtOH	93
9	KOTFA	**2a**	EtOH	95
10	NaOAc	**2a**	EtOH	87
11	LiOAc	**2a**	EtOH	90
12	NH_4OAc	**2a**	EtOH	0
13	$Cu(OAc)_2$	**2a**	EtOH	trace
14	$Mn(OAc)_2$	**2a**	EtOH	0
15	TEA	**2a**	EtOH	72
16	DIPEA	**2a**	EtOH	9
17	KOAc	**2b**	EtOH	92
18	KOAc	**2c**	EtOH	47
19	KOAc	**2d**	EtOH	69
20	KOAc	**2e**	EtOH	89
21	KOAc	**2f**	EtOH	87
22	KOAc	**2g**	EtOH	21
23	KOAc	**2h**	EtOH	68
24	KOAc	**2a**	MeOH	91
25	KOAc	**2a**	*i*PrOH	95
26	KOAc	**2a**	*i*BuOH	92
27	KOAc	**2a**	*i*AmylOH	87
28	KOAc	N/A	EtOH	trace
29	N/A	**2a**	EtOH	trace

[a]Reaction conditions: **1a** (0.2 mmol), epoxide (0.6 mmol), base (0.2 mmol), EtOH (2.0 mL), N_2, 90 °C, 35 h. [b]Isolated yields.

Then we found that basic potassium phosphates (K_3PO_4 and K_2HPO_4) gave much lower yields. The reaction was shut down when weakly acidic KH_2PO_4 was used. Potassium halides, such as KF and KCl, provided modest yields. Fortunately, KOAc and KOTFA were found effective and gave excellent yields. Considering the cost, KOAc was selected as the better choice. With acetate as the optimal anion, we also compared different cations and the results indicated that potassium ion was the best cation. Interestingly, organic base like triethylamine (TEA) could deliver the product in 72% yield. However, bulkier diisopropylethylamine (DIPEA) led to much worse reactivity. Having the best base in hand, we set out to probe different structures of epoxides. Changing the protecting group from methyl to benzyl resulted in an almost unnoticeable decrease in the yield. However, the yield nearly halved with a nonprotected hydroxyl group of the epoxide, suggesting that the protection of the hydroxyl is needed for the reaction to proceed well. Replacing the methoxy group with hydrogen, chlorine, and a propyl group caused only a small decrease in the yield. In contrast, the reaction was suppressed significantly with a phenyl group at position 1 of the epoxide. Having an ester group instead at the same position led to a 68% yield. A few other aliphatic and branched alcohols were tested and all gave comparable alcoholysis yields. However, the epoxide-mediated hydrolysis of amide **1a** in water failed to give the desired acid product, instead, the ring opening of epoxide by water was observed as the major side product. Unfortunately, the racemization of **3a** was observed under current alcoholysis conditions.

Having optimized the condition, we proceeded to test it on other amide substrates. As shown in Scheme 3, it is clear that

Scheme 3. Scope of Different Amides



only acidic amides bearing electron-withdrawing groups can be cleaved to give ethyl esters. Nonacidic amides remained intact throughout the reaction, presumably due to (A) their reduced electrophilicity; (B) bad leaving groups; and (C) the *N*-alkylation not happening, as the substrates failed to be deprotonated by KOAc.

In order to test the generality of this method, we also examined structurally different substrates bearing the acidic amide auxiliary prior to C−H activation. α-Hydrogen containing substrates, including α-amino acid, cyclic, and acyclic acids, reacted smoothly, giving the corresponding ethyl esters in excellent yields (**3a**, **3b**, **3f**, **3g**). In addition, the method was similarly successful for bulkier α-quaternary substrates and α, β-unsaturated substrate (**3c**, **3d**, **3e**, **3h**). However, the alcoholysis was less efficient for benzamide derivative, where only a moderate yield was obtained (Scheme 4). Next, we started to investigate the scope of C−H functionalized compounds. First, the method was applied to arylated products of acyclic aliphatic acid substrates. The corresponding esters were obtained in excellent yields (**3j**−**3o**). For cyclic acid substrates, the C(sp^3)−H arylation products underwent facile alcoholysis in good-to-excellent yields (**3p**−**3w**). Notably, the heteroarylated product was also compatible with this method (**3l**). Similarly, other C−H functionalized

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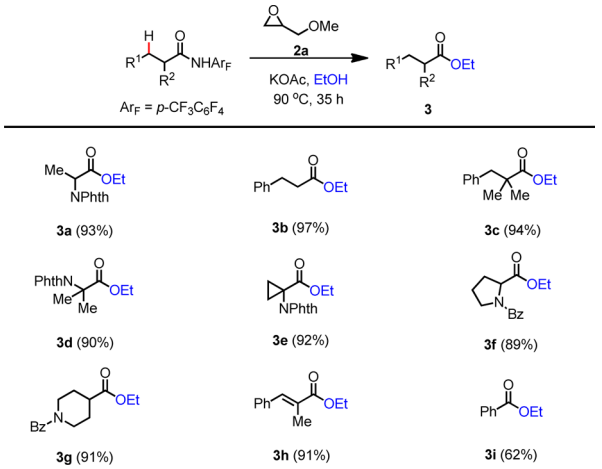
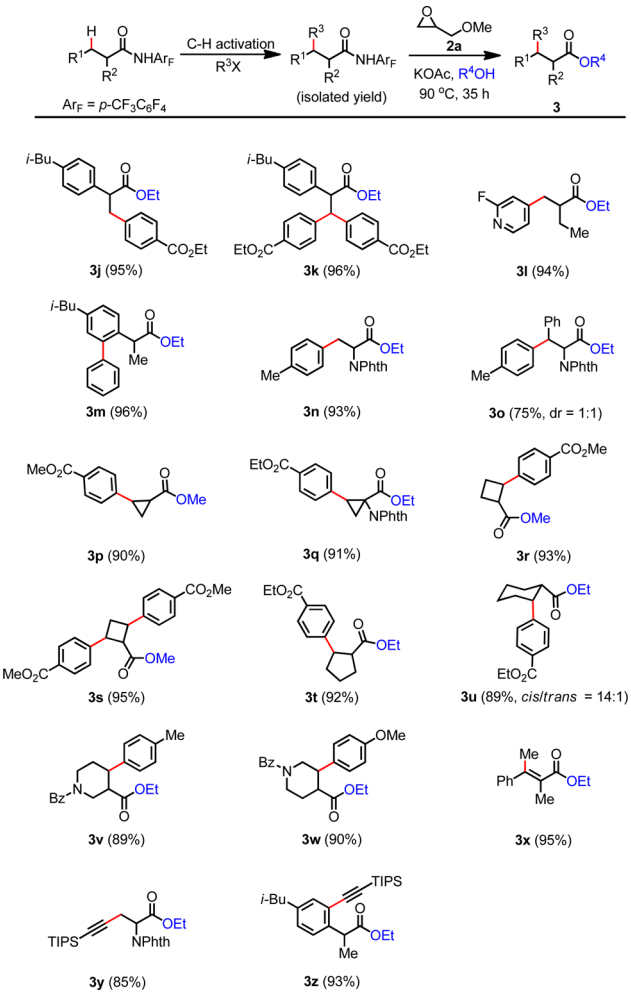
Scheme 4. Alcoholysis of the Simple Acidic Amides



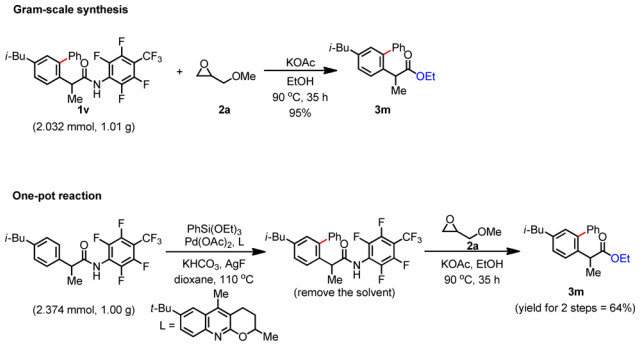
products, such as alkylated and alkynylated products, could be converted to esters effectively (**3x**–**3z**) (Scheme 5).

To further showcase the robustness of this protocol, a scale up reaction was conducted to give the ester product in 95% yield. Moreover, this method can be employed without purification of the C–H functionalization product (Scheme 6).

Scheme 5. Alcoholysis of the C–H Functionalized Acidic Amides



Scheme 6. Gram-Scale and One-Pot Synthesis



In summary, we have developed a practical method for the removal of the versatile acidic amide directing group. A variety of acidic amide substrates and their C–H functionalized products can be converted to esters using mildly basic KOAc. The N-alkylation of the amide with an epoxide and subsequent intramolecular alcoholysis is responsible for this reactivity. The ready availability of this method is likely to facilitate the applications of C–H functionalization reactions directed by this amide auxiliary.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02841.

Experimental procedure and characterization of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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