VIP Amide Activation | Very Important Paper

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Chemoselective Intermolecular α-Arylation of Amides**

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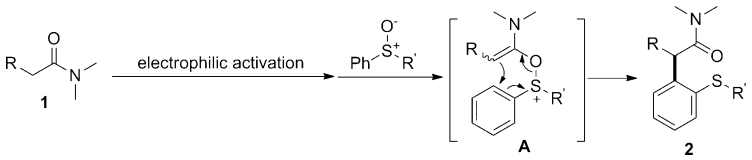
Abstract: *A new approach for the fully chemoselective α-arylation of amides is presented. By means of electrophilic amide activation, aryl groups can be regioselectively introduced α- to amides, even in the presence of esters and alkyl ketones. Mechanistic studies reveal key reaction intermediates and emphasize a remarkably subtle base effect in this transformation.*

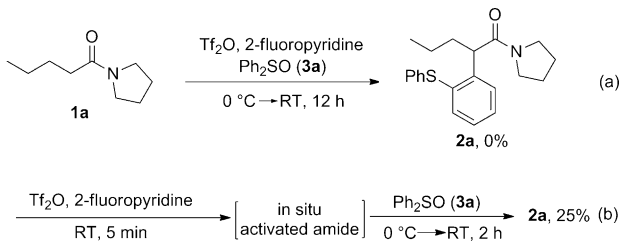


Scheme 1. Electrophilic amide activation used for the α-arylation of amides.

The α-arylation of carbonyl compounds continues to receive considerable attention from the synthetic community.[1] Most advances in this field rely on the transition-metal-catalyzed coupling of enolates (or their equivalents) with aryl halides, pseudohalides, or more reactive reagents.[2] Noble-metal-free processes developed include nucleophilic addition to electron-deficient arenes,[3a,b] nucleophilic substitution of aryl halides,[3c,d] arylation of enolate anions (or equivalents) with the highly reactive electrophilic aromatic species of Bi^{V},[4] Pb^{IV},[5] and I^{III},[6] and benzynes,[7] and organocatalytic transformations.[8] However, arylation at the α-position of simple amides[9] remains a sizeable synthetic challenge.[10] To the best of our knowledge, all existing intermolecular approaches rely on the strong-base-promoted α-arylation of amides via the corresponding enolate.[10a,11–14] Given that α-protons of esters and ketones have a lower pK_A than those of the corresponding amides, the presence of those functional groups limits the use of strong-base-dependant procedures. Though intramolecular α-arylations have been extensively studied, especially in oxindole synthesis,[12a–i] intermolecular approaches are scarce.[12j–q] Herein, a novel mechanism-based approach for the intermolecular α-arylation of amides, as well as a mechanistic study of the reaction, is presented. The mild conditions of this method allow the exclusive α-arylation of amides over esters and ketones.

Our initial design (Scheme 1) hinges on the formation of pivotal intermediate **A**,[15,16] which should undergo a [3,3]-sigmatropic rearrangement forming the C_α–C_{aryl} bond.[17] We hypothesized that the bond reorganization of intermediate **A** en route to the product, involving the cleavage of a weak S–O bond along with the simultaneous formation of the strong amide carbonyl, might counterbalance the transient loss of aromaticity predicated by the rearrangement itself.[16a,e,18]

In first attempts, amide **1a** was treated with Tf_2O, which was used to activate the amide, and Ph_2SO in the presence of the mild base 2-fluoropyridine (Scheme 2a).[16e] Unfortunately, no desired product could be detected. This was ascribed to the competitive activation of amide and Ph_2SO by the strongly electrophilic Tf_2O, highlighting the challenge of this transformation. After further experimentation it was found that pre-activating the amide, followed by addition of Ph_2SO, afforded the desired **2a** in 25% yield (Scheme 2b).



Scheme 2. Initial results indicating a crucial addition protocol.

Encouraged by this preliminary result, we further optimized the reaction using amide **1a** as a model substrate (Table 1).[19] Notably, the time and temperature of the pre-activation appear to have a strong impact on this transformation (entries 1–5). Furthermore, 2-iodopyridine is a superior base for this intermolecular amide α-arylation (entry 6). The use of either pyridine or 2,4,6-collidine completely shut down the reactivity (entries 8 and 9, vide infra). Changing to 4-iodopyridine afforded the product in only 30% yield.

This sensitivity of the reaction towards specific parameters employed prompted us to study the reaction mechanism in more detail. In particular, we sought to elucidate the nature of the "activated amide" species whose preformation is crucial for the success of this procedure. A combination of IR and in situ NMR[19] analysis made it possible to observe an

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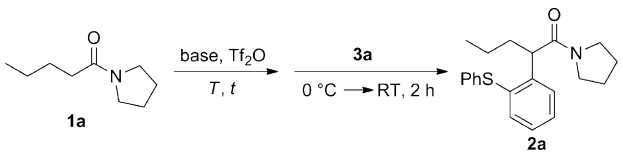
Table 1: Optimization of reaction conditions.[a]



Entry	Base	T [°C]	t [min]	Yield [%][b] of **2a**
1	2-fluoropyridine	RT	5	25
2	2-fluoropyridine	RT	60	0
3	2-fluoropyridine	−78	60	0
4	2-fluoropyridine	0	<1	12
5	2-fluoropyridine	0	15	75
6	**2-iodopyridine**	**0**	**15**	**93**
7	4-iodopyridine	0	15	30
8	pyridine	0	15	0
9	2,4,6-collidine	0	15	0

[a] A mixture of amide (0.1 mmol) and base (3.0 equiv) in CH_2Cl_2 (1 mL) was treated with Tf_2O (1.0 equiv). The mixture was stirred at the indicated temperature for the indicated time, then diphenyl sulfoxide (2.0 equiv) was added at 0 °C. [b] Yield determined by NMR analysis with mesitylene as the internal standard.

enamine-like intermediate characterized as **B1** (characteristic stretch at $\nu = 1673\ cm^{-1}$), formed as soon as Tf_2O was added to a mixture of **1a** and 2-iodopyridine (Figure 1a).[19] An enamine related to **B1** has been previously characterized by NMR spectroscopy and reported by Charette and Grenon when they employed pyridine as base.[15e] We have prepared and characterized (in situ IR and NMR spectroscopy) such an enamine **B2** from amide **1a** by addition of triflic anhydride to a solution of **1a** and pyridine (Figure 1b). Remarkably, this enamine **B2** (with a stretching frequency virtually identical to that of **B1**) does not react upon subsequent addition of diphenylsulfoxide and no further reaction was observed. This highlights the crucial role played by the base in this arylation reaction.

Besides the in situ IR measurements, NMR studies were also conducted. Admixing **1a** and 2-iodopyridine led to no reaction (Figure 2, spectrum A); however, after addition of Tf_2O, an immediate change was observed. The obtained mixture (Figure 2, spectrum B) displays the presence of two intermediates which were characterized as **B1** (major), solely as its *Z*-isomer, and the presumed iminium triflate **C1** (minor) (2D-NMR; Scheme 3).[19] As already confirmed by IR spectroscopy, upon addition of Ph_2SO, **B1** is completely converted into **2a** within 2–3 h (spectrum C). When the same reaction was conducted with pyridine as the base, the presence of **B2** was again confirmed. The more nucleophilic and basic pyridine led, however, to the complete consumption of **C1** and afforded **B2** as the only intermediate, but as a mixture of *Z*- (major) and *E*-isomers. As in the in situ IR experiment, the addition of Ph_2SO to **B2** resulted in no apparent change.[19]

Based upon these results we propose the mechanism depicted in Scheme 3. After initial formation of **C1** through activation of the amide with Tf_2O, it is likely converted to the high-energy intermediates iminium dication **D1** or ketenimininium triflate **D2**, although neither was ever directly observed by Charette and Grenon or by us when tertiary amides bearing α-protons were employed.[15e] A second equivalent of base then leads to **B1**. We believe that both the stability and the reactivity of this intermediate are crucial for the fate of the reaction. With pyridine, the strongest nucleophile in our series, the biased equilibrium between **B2** and ketenimininium **D2** lies completely on the side of **B2**. This not only explains

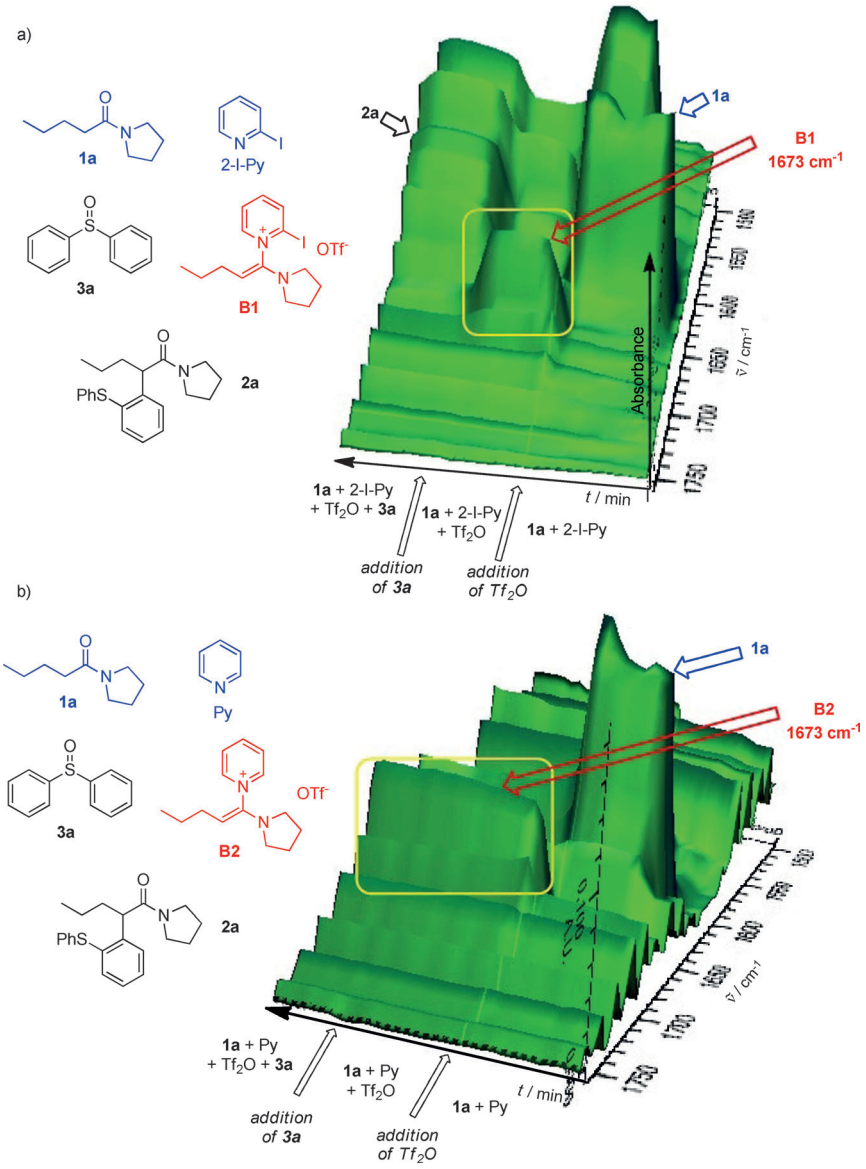


Figure 1. IR studies on the reaction mechanism and the crucial role played by the base.

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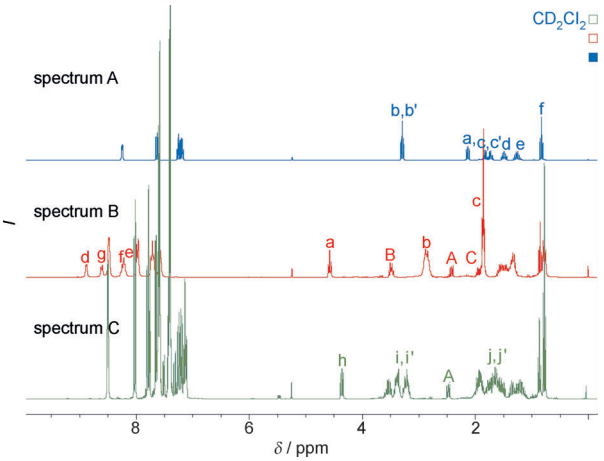
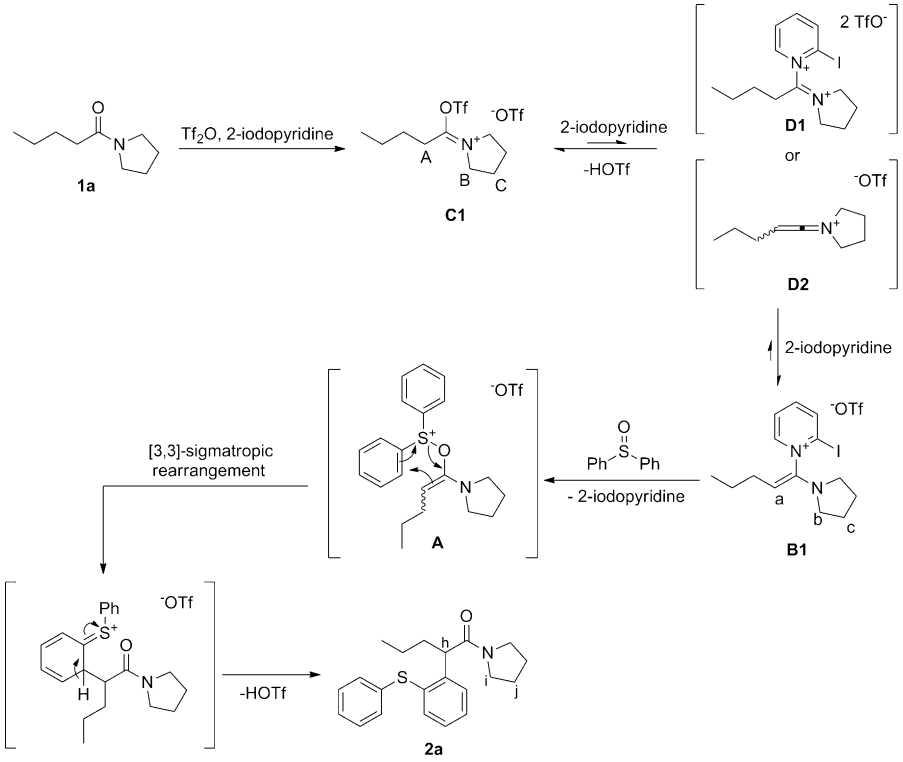


Figure 2. ^{1}H NMR studies on the reaction mechanism.



Scheme 3. Proposed reaction mechanism for the formation of **2a**.

the complete inertia of **B2** towards Ph_2SO, but in addition the observed complete consumption of **C1**. With 2-fluoropyridine, a weaker nucleophile than 2-iodopyridine, **C1** (and thus its corresponding intermediate **B**) was only consumed to a small extent. The optimal base is therefore a species not only nucleophilic and/or basic enough to convert **C1** to enamine **B**, but one which is also a good enough leaving group to be displaced by Ph_2SO and produce enamine **A**.

With the optimized conditions in hand, we examined the reaction of various amides (Scheme 4). Among the (halo)-alkyl- and aryl-substituted substrates **1b–h** tolerated (of which **1h** would likely have undergone cyclization upon treatment with strong base), even simple acetamide **1f** could be used for this transformation. Remarkably, the chemoselectivity of this transformation means that, for the first time, an amide can be directly α-arylated in the presence of an enolizable ester (**2k**,**l**) or even an alkyl ketone with two enolizable α-carbons (**2j**). In addition, the presence of a pyrrolidine moiety is not a necessity, as evidenced by the successful arylations of **1i** and **1l**.

Further, the transformations of substrates **1m** and **1n**, both bearing an allyl ether moiety, are worthy of notice (Scheme 5). These and related compounds have been previously shown by us to readily undergo deallylative lactone formation at low temperatures in the absence of external nucleophiles (Scheme 5a).[16b] However, the intermolecular arylation remarkably overrides the intramolecular reaction, allowing access to the arylated amides **2m** and **2n** (Scheme 5b).

Different aryl sulfoxides (**3b–f**) were then employed as nucleophiles, as shown in Scheme 6. Both electron-rich and electron-poor aryl moieties could be transferred to the α-position of amide **1a**. The products **4ad**, **4ae**, and **4af** further attest to the viability of using monoarylsulfoxides carrying either alkyl or benzyl residues on sulfur.[20]

By performing a competition experiment using equimolar amounts of diarylsulfoxides **3b** and **3c** in the presence of pre-activated amide **1a** (Scheme 7), we observed a remarkable difference in reaction rate for the two sulfoxides. In the event, the reaction exclusively produced the arylated amide **4ab**, resulting from selective reaction with the most electron-rich diarylsulfoxide **3b**. This underscores the crucial role played by electronics in this reaction, as the most nucleophilic sulfoxide completely outperforms its electron-poor counterpart in competition for intermediate **B1.**

In summary, a novel approach for the direct α-arylation of unactivated, simple amides was developed relying on an electrophilic rearrangement strategy. Remarkably, through this approach it is possible for the first time to arylate amides in the presence of enolizable esters and even alkyl ketones. Mechanistic studies revealed the intermediacy of enamine-like intermediates **B1** and **B2**, whose reactivity is dramatically affected by subtle changes of the base used. Further mechanistic study of this α-arylation reaction, exploration of the untapped reactivity of intermediates such as **B**, and broadening of the strategies presented herein are currently in progress and will be reported in due course.

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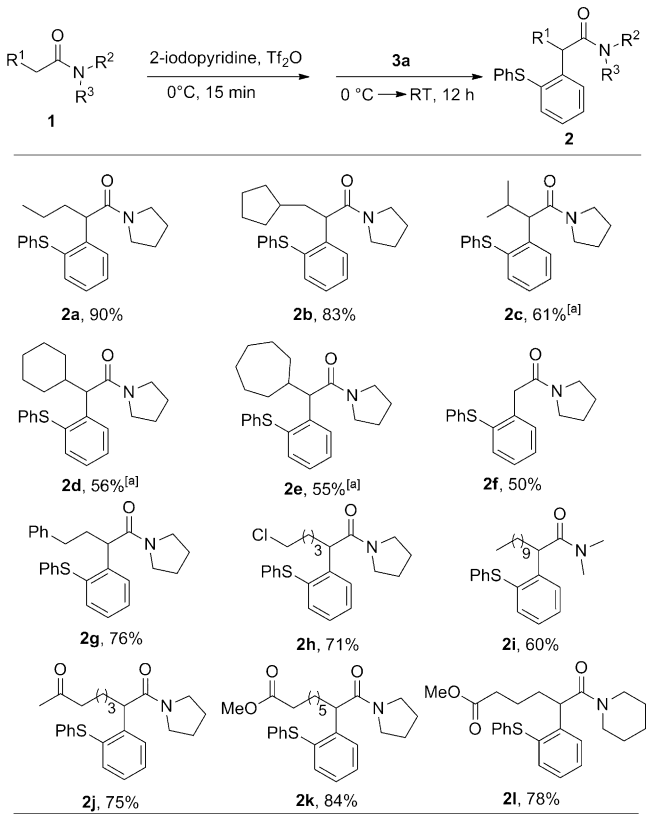
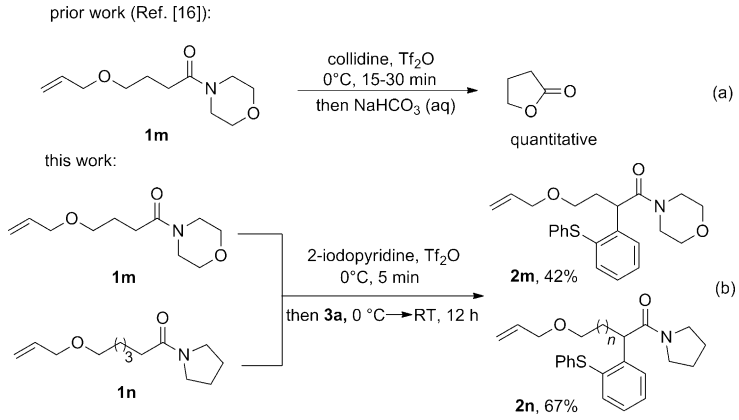


Scheme 4. Substrate scope for the direct amide α-arylation.[a] [a] A mixture of amide (0.2 mmol) and 2-iodopyridine (3.0 equiv) in CH_2Cl_2 (2 mL) was treated with Tf_2O (1.0 equiv). The mixture was stirred at 0 °C for 15 min unless indicated otherwise, then diphenyl sulfoxide (2.0 equiv) was added at 0 °C. [b] 2-Fluoropyridine was used. See Ref. [19].



Scheme 5. Intermolecular arylation can outcompete lactonization.

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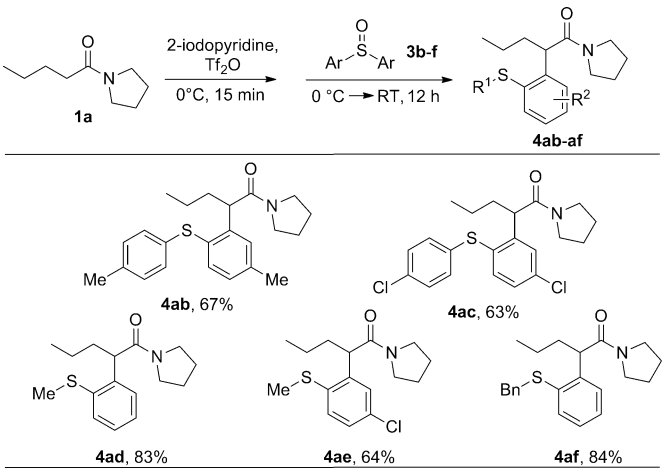
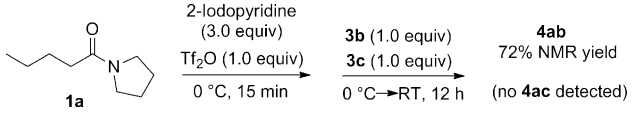


Scheme 6. Scope of sulfoxides for the α-arylation of amide **1a**.[19]



Scheme 7. Competition experiment for the arylation of amide **1a**.

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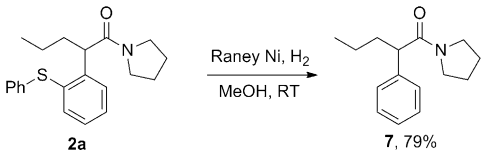
[19] See the Supporting Information for further details.

[20] Hydrogenation can be employed to remove the sulfur appendage, as demonstrated below for compound **2a**. For the cross-coupling of related compounds, see Ref. [18i].



2a **7**, 79%

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