Cation-controlled chemoselective synthesis of *N*-aroylureas and imides *via* amidation of *N*-Boc arylamides

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In this study, the first highly chemoselective amidation of Boc and amide groups of *N*-R-*N*-Boc arylamides is advanced. This practical and operationally-simple method enables the preparation of either *N*-aroylureas or imides in good to excellent yields without addition of transition metals. The choice of base plays a significant role in controlling the reactivity of the inequivalent carbonyl groups. The amidation of the Boc group was observed with arylamides, $ArCONH_2$, when subjected to KO^tBu while imides were produced with LiOH. DFT studies are employed to explore the divergent mechanisms. It is anticipated that these chemoselective methods will be of interest to the synthetic and medicinal chemistry communities.

N-Acylureas are important functional groups in the fields of agrochemistry[1] and medicinal chemistry (with anticancer,[2] anti-inflammatory,[3] antidiabetic,[4] and anticonvulsant[5] properties). These compounds are also common building blocks in materials chemistry[6] and synthetic organic chemistry.[7] Traditionally, the preparation of *N*-acylureas was largely based on two approaches: (1) acylation of ureas with activated carboxylic acids, such as acid chlorides, anhydrides, and carbodiimides (Scheme 1A)[8] and (2) coupling of isocyanates with amides[9] and acyl isocyanates with amines (Scheme 1B).[7a, 10] Despite the wide utility of these methods, both have shortcomings. The acylation method usually suffers from limited substrate scope due to the high reactivity of the activated carboxylic acid derivatives. The isocyanates and acyl isocyanates used in the latter approach are unstable and frequently made from phosgene, which is dangerous and requires special safety precautions. Recently, palladium-catalyzed carbonylation of acyl azides or ureas were employed in the synthesis of *N*-acylureas.[10e, 11] Other routes such as acylation of alkenyl esters,[12] amidation of acylcarbamates with amines[13] and boronic acid-catalyzed condensation of acids with ureas[14] have been disclosed. However, most of these methods have their drawbacks, such as the use of transition-metal catalysts that can be hard to remove from the final products and multi-step preparation of starting materials. Further development of efficient and greener methods for the synthesis of *N*-acylureas, therefore, remains desirable.

Another group of valuable synthetic targets are imides, which are structural cores of various pharmaceuticals[15] and natural products.[16] The most popular methods to prepare these important compounds include Mumm rearrangement of isoimides[17] and acylation of amides with activated carboxylic acid derivatives.[18] Despite the popular application of these methods in organic synthesis, both have shortcomings. These include poor functional

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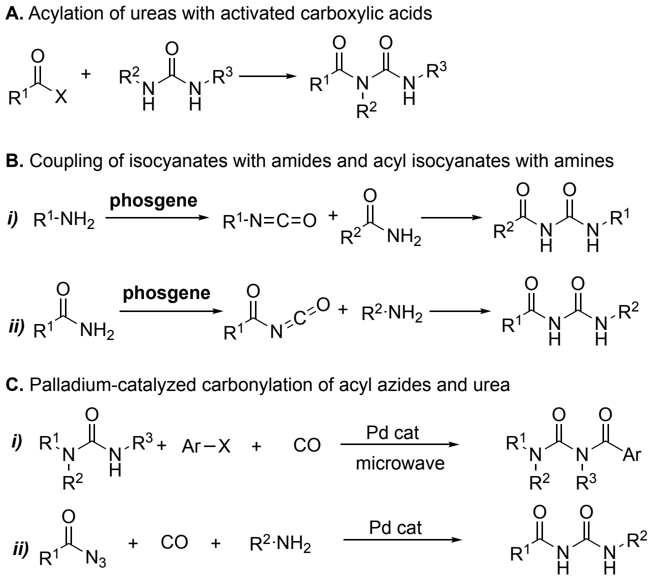
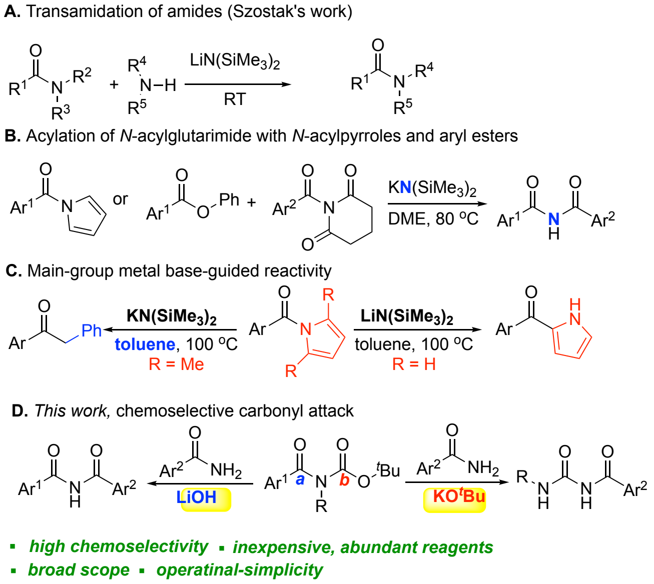
group tolerance and tedious substrate prefunctionalization.



Scheme 1 General routes to *N*-acylureas.

To overcome these issues, substantial efforts have been made to develop new methods for the synthesis of imides.[19] For example, recently Szostak and co-workers demonstrated the direct transamidation of activated and unactivated amides with non-nucleophilic amines could be accomplished under transition metal-free conditions (Scheme 2A).[20] We have also worked to develop new methods for the synthesis of imides (Scheme 2B).[21] In this study, *N*-Bn-*N*-Boc arylamides served as nucleophiles and were selectively acylated by *N*-acylpyrroles and aryl esters. Our team has had a long-standing interest in the impact of main group counterions in altering the course of reactions,[22] which have been attributed to cation-π interactions in some cases. Most recently, in our study of toluene aroylations,[23] we found that N-acyl pyrroles underwent benzylation in the presence of toluene and $KN(SiMe_3)_2$ while the parent N-acyl pyrrole underwent isomerization in the presence of $LiN(SiMe_3)_2$ (Scheme 2C).[24]

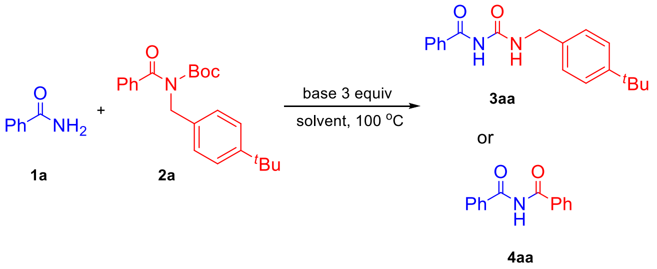
Based on our past work (Scheme 2B) on imide synthesis, and our interest in the impact of main group metals on chemoselectivity, we were curious if arylamides could be employed as nucleophiles in related transformations. Herein we report the surprising results of a study to answer this question. Indeed, we found that imides could be prepared from *N*-Boc protected aroyl amides when LiOH was employed as base. Surprisingly, by simply replacing LiOH with KO^{t}Bu, a change in chemoselectivity was observed enabling the generation of a series of *N*-acylureas with the same electrophiles. In this latter transformation, the carbonyl group of the Boc, instead of the amide group, is attacked by the aromatic amide-derived nucleophile followed by the cleavage of the C−N bond of the amide group, enabling the formation of *N*-acylureas. It is interesting that the Boc group, which is a popular and dependable protecting group, serves as the reactive carbonyl under these conditions. It is also noteworthy that high selectivity was achieved by the choice of bases employed in the reactions.



Scheme 2 (A) Transamidation of amides under transition metal-free conditions. (B) Acylation of *N*-acylgluarimide with *N*-acylpyrroles and aryl esters. (C) Application of different main group bases to change the course of the reaction. (D) Chemoselective reaction controlled by main group metal and base.

Our initial studies focused on the coupling between benzamide **1a** and *N*-*tert*-butylbenzyl-*N*-Boc benzamide **2a**. As shown in Table 1, the choice of base is critical in controlling the chemoselectivity. The weaker bases K_3PO_4 and LiOH yielded the imide product **4aa** in 46% and 74% yield. Surprisingly, KO^{t}Bu and NaO^{t}Bu generated the *N*-acylurea **3aa** exclusively in 72% and 62% yields, respectively (Table 1, entries 1−4). It is known that main group metals can have a dramatic impact on reactivity,[25] including in our past work with *N*-acyl pyrroles (Scheme 2C).[24] In contrast to the results above, LiO^{t}Bu and KOH gave a mixture of imide (65% vs 58%) and *N*-acylurea (23% vs 36%) (entries 5−6). A solvent screen showed that DME was the best solvent for both transformations (entries 7−9 and 10−12). Further screening of the reaction temperature indicated that elevated temperature (120 °C) did not improve the yields (Table 1, entries 13 and 15) of either product, while lower temperature (80 °C) was deleterious due to lower conversions (entries 14 and 16).

Table 1. Chemoselective Reaction Development and Optimization[a]

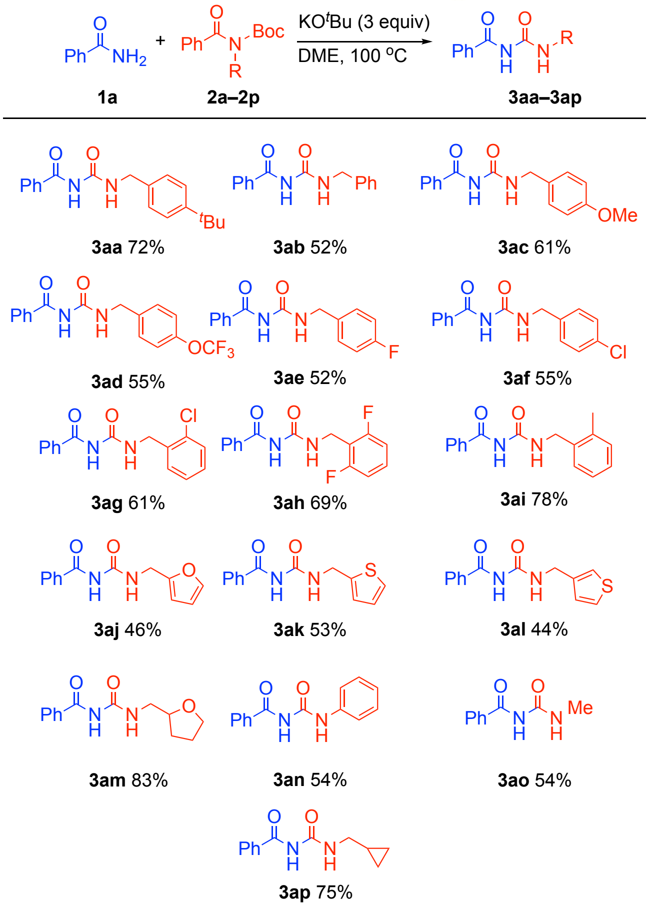


E	Solvent	Base	Temp	3aa[b]	4aa[b]
1	DME	K_3PO_4	100 °C	0	46
2	DME	LiOH	100 °C	0	74
3	DME	KO^{t}Bu	100 °C	74	0
4	DME	NaO^{t}Bu	100 °C	62	0
5	DME	LiO^{t}Bu	100 °C	23	65
6	DME	KOH	100 °C	36	58
7	THF	LiOH	100 °C	6	70
8	toluene	LiOH	100 °C	trace	0
9	dioxane	LiOH	100 °C	12	54
1	THF	KO^{t}Bu	100 °C	69	0
1	toluene	KO^{t}Bu	100 °C	33	0
1	dioxane	KO^{t}Bu	100 °C	63	0
1	DME	KO^{t}Bu	120 °C	65	0
1	DME	KO^{t}Bu	80 °C	45	0
1	DME	LiOH	120 °C	0	72
1	DME	LiOH	80 °C	0	68

[a] Reactions were conducted with benzamide **1a** (0.1 mmol), *N*-*tert*-butylbenzyl-*N*-Boc benzamide **2a** (0.1 mmol), base (0.2 mmol), solvent (1 mL), 12 h. [b] Isolated yields.

With the optimized conditions for the chemoselective reactions established, we focused on the synthesis of *N*-acylureas (standard conditions in entry 4 of Table 1). The substrate scope of *N*-R-*N*-Boc arylamides was explored with benzamide **1a** (Table 2) Various *N*-R-*N*-Boc arylamides bearing different substituents on the nitrogen were found to be excellent substrates, including those with *N*-benzyl groups bearing electron-donating (4-OMe, **3ac**, 61% yield), electron-withdrawing or electronegative groups (4-OCF_3; **3ad**, 4-F; **3ae** and 4-Cl; **3af**, 52–55% yields), and *ortho* substituents (**3ag**, **3ah**, **3ai**, 61–78% yields). In addition, heterocyclic substrates also participated in this reaction, giving the product **3aj**–**3am** in 44–83% yields. Replacing the *N*-benzyl group with an *N*-phenyl group, the *N*-Ph-*N*-Boc arylamide underwent amidation with benzamide and furnished the product **3an** in 54% yield. *N*-Alkyl groups, such as *N*-methyl and *N*-cyclopropylmethyl, were also tested under these conditions and resulted in the formation of the target imides **3ao** and **3ap** in 54% and 75% yields, respectively.

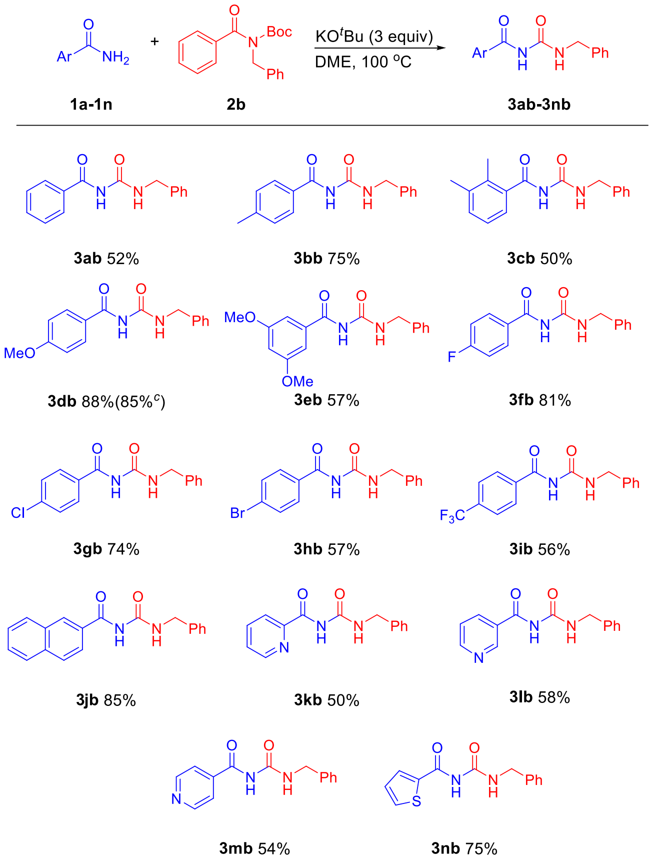
Table 2. Scope of *N*-R-*N*-Boc arylamides in the synthesis of *N*-acylureas [a,b]



[a] Reaction conditions: benzamide **1a** (0.1 mmol), *N*-R-*N*-Boc arylamides **2** (0.1 mmol), KO^{t}Bu (0.3 mmol), DME (0.1 M), 12 h. [b] Isolated yields.

The scope of arylamides was next explored with *N*-Bn-*N*-Boc benzamide **2b**. As shown in Table 3, arylamides possessing electronically-diverse substituents on the phenyl group (4-Me, 2,3-Me_2, 4-OMe, 3,5-$(OMe)_2$, 4-F, 4-Cl, 4-Br, and 4-CF_3) provided the target *N*-acylureas (**3bb**, **3cb**, **3db**, **3eb**, **3fb**, **3gb**, **3hb**, **3ib**) in 50−88% yields. 2-Naphthamide afforded **3ja** in 85% yield. Perhaps most interesting is the capacity of this protocol to facilitate amidation with medicinally relevant heterocyclic motifs,[26] including both electron-deficient heterocycles, such as pyridines (**3kb**, **3lb**, **3mb**), and electron rich heterocycles, such as thiophene (**3nb**). To illustrate the scalability of this amidation reaction, 4 mmol of *N*-Bn-*N*-Boc benzamide was treated with equimolar 4-methoxybenzamide in DME at 100 °C for 12 h under basic conditions (3 equiv of KO^{t}Bu). The target *N*-acylurea **3db** was isolated in 85% yield.

Table 3. Scope of arylamides in the synthesis of *N*-acylureas [a,b]

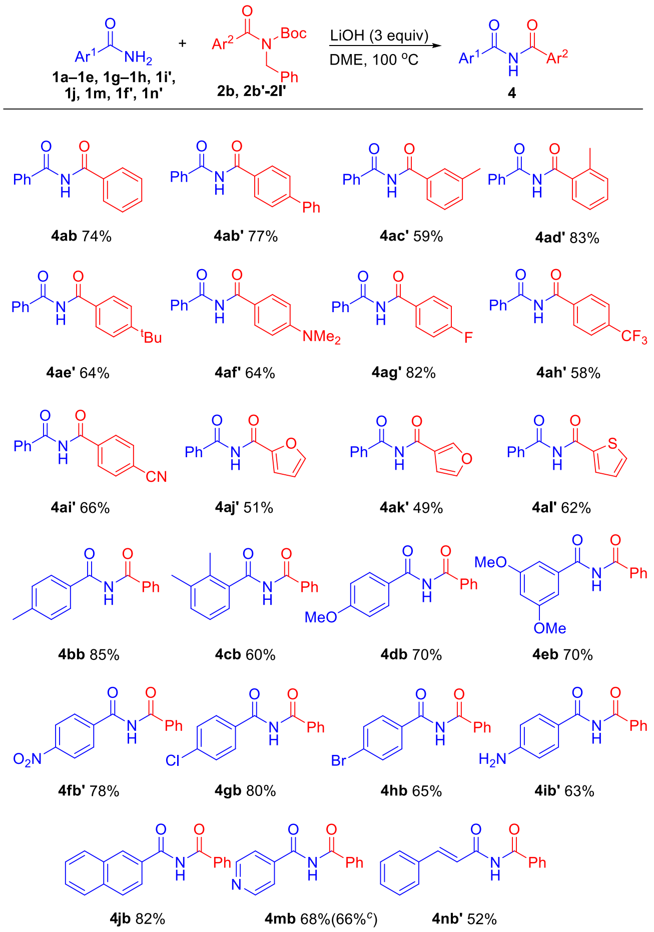


[a] Reaction conditions: arylamides (0.1 mmol), *N*-benzyl-*N*-Boc benzamide **2b** (0.1 mmol), KO^{t}Bu (0.3 mmol), DME (0.1 M), 12 h. [b] Isolated yields. [c] Reaction conducted on 4 mmol scale.

We next turned our attention to the preparation of imides. Employing the optimal conditions in Table 1 (entry 2), we tested the reactivity of a series of *N*-Bn-*N*-Boc benzamides (Table 4). In addition to the parent reaction, *N*-Bn-*N*-Boc 4-biphenylamide furnished **4ab'** in 77% yield. *N*-Bn-*N*-Boc benzamides bearing alkyl (3-Me; **4ac'**, 2-Me; **4ad'**, 4-^{t}Bu; **4ae'**, 59−64% yield), electron-donating (4-NMe$_2$; **4af'**, 64% yields), and electron-withdrawing (4-F; **4ag'**, 4-CF$_3$; **4ah'**, and 4-CN; **4ai'**, 58−82% yields) groups were all tolerated in this protocol. Furthermore, substrates bearing heteroaromatic rings such as furan (**3aj'**, **3ak'**) and thiophene (**3al'**), also participated in this reaction, affording the imide products in 49−62% yields.

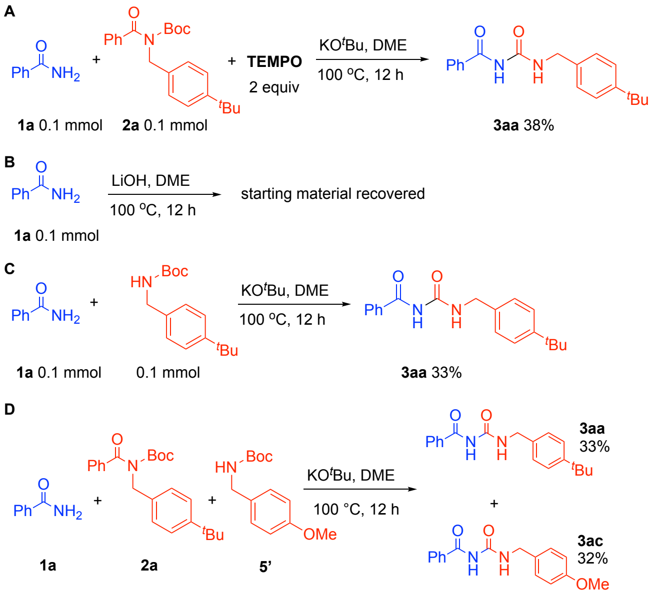
The substrate scope of arylamides in the amidation of *N*-Bn-*N*-Boc benzamide **2b** was subsequently explored (Table 4, lower half). Using benzamide with various substituents on the phenyl group (4-Me, 2,3-Me$_2$, 4-OMe, 3,5-(OMe)$_2$, 4-NO$_2$, 4-Cl, 4-Br, 4-NH$_2$) afforded products (**4bb−4lb**) in 60−85% yields. 2-Naphthamide furnished **4jb** in 82% yield. Additionally, heterocyclic substrates, such as 4-pyridinylamide, furnished the product **4mb** in 68% yield. Interestingly, cinnamamide was also tolerated in this reaction, giving the product **4nb'** in 52% yield under optimal reaction conditions. A scale-up reaction was conducted with 4 mmol of *N*-Bn-*N*-Boc benzamide **2b** and isonicotinamide **1m** in DME at 100 °C for 12 h with LiOH as base. The imide product **4mb** was isolated in 66% yield.

Table 4. Synthesis of imides from *N*-Bn-*N*-Boc benzamides[a,b]



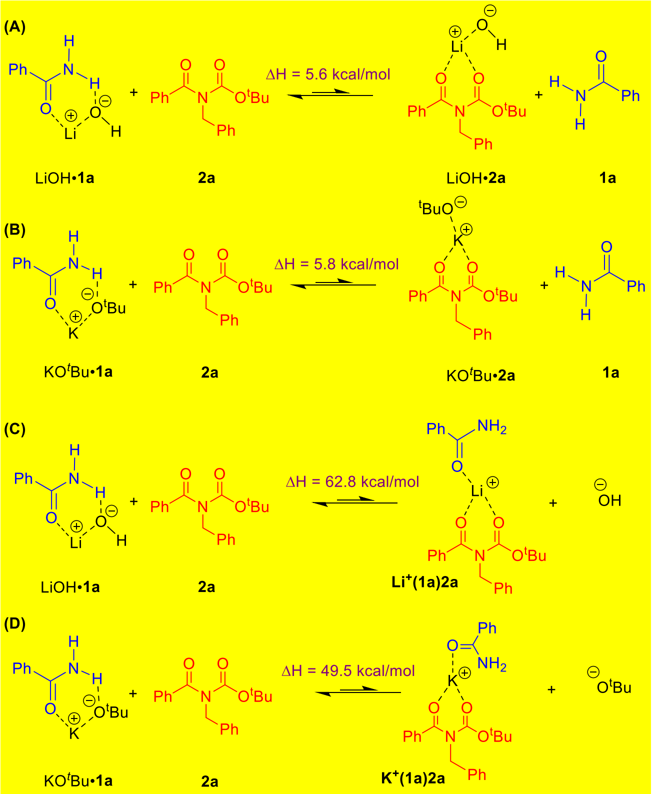
[a] Reaction conditions: arylamides (0.1 mmol), *N*-Bn-*N*-Boc benzamide (0.1 mmol), LiOH (0.3 mmol), DME (0.1 M), 12 h. [b] Isolated yields. [c] Reaction conducted on 4 mmol scale.

A few experiments were performed to probe the reaction mechanism (Scheme 3). With addition of 2 equiv. of radical scavenger TEMPO, the model reaction afforded the *N*-acylurea product in 64% yield (Scheme 3A). We take this result to indicate that the reaction proceeds by a 2-electron pathway. When benzamide was mixed with 3 equiv. of LiOH for 12 h at 100 °C, only starting material was recovered (Scheme 3B). This result excludes the self-coupling pathway in the synthesis of imides. We found that *N*-Boc-4-^{t}Bu benzylamine **5** reacted with benzamide to give aroylation product **3aa** in 33% yield (Scheme 3C). This observation supports the Boc group being employed as carbonyl source. A cross-over experiment with benzamide **1a**, Boc protected **2a**, and a Boc protected benzyl amine bearing a 4-OMe group **5'** furnished equal amounts of products **3aa** and **3ac** (in a combined yield of 65%), again indicating that the Boc protected benzyl amine is an intermediate in this reaction (Scheme 3D).



Scheme 3 Control experiments.

The roles of LiOH and KO^{t}Bu as base and nucleophile in the divergent reaction mechanisms were examined by DFT calculations (see SI for computational details). According to the experimental reaction conditions, especially entries 2 and 3 in Table 1, LiOH and KO^{t}Bu can act as bases or nucleophiles to attack benzamide (**1a**) and *N-tert*-butyl benzyl-*N*-Boc benzamide (**2a**), respectively.



Scheme 4. Calculated ΔH for isodesmic binding processes.

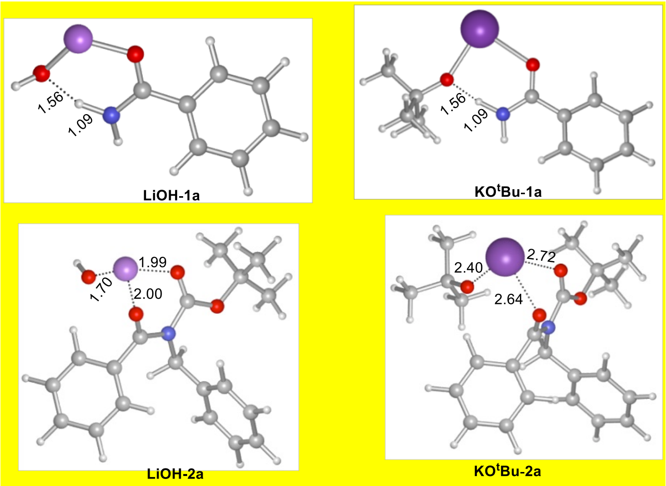
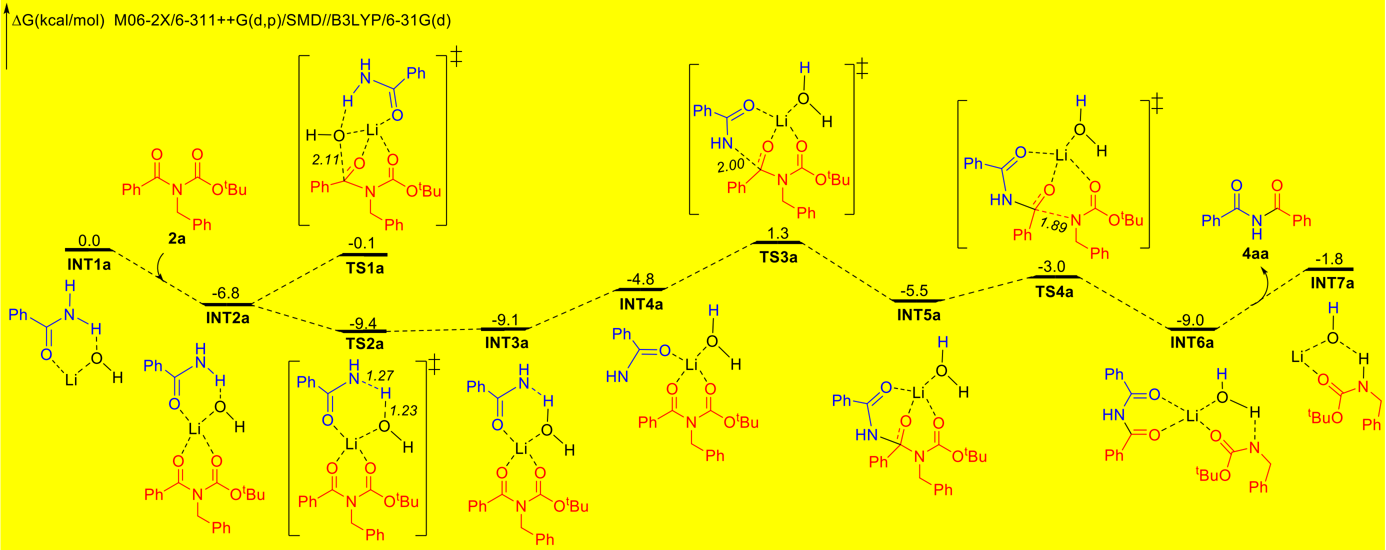


Figure 1. Optimized 3D structures of complexes of base LiOH/KO^{t}Bu with substrate **1a**/**2a**, respectively. Bond lengths are shown in Å.

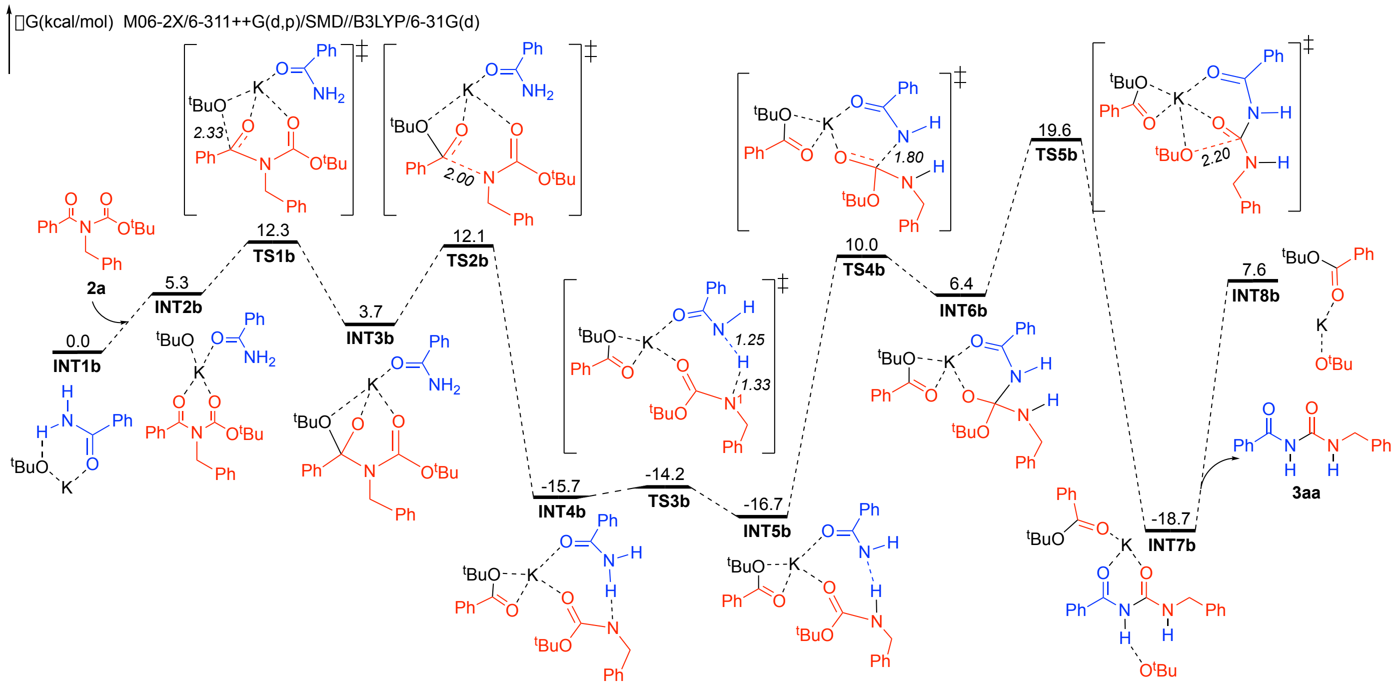
First, the binding energies of **1a**/**2a** with LiOH/KO^{t}Bu were evaluated (Scheme 4A–D). The calculated ΔH for the isodesmic binding processes in Scheme 4A and 4B are endothermic by 5.6 and 5.8 kcal/mol, respectively, suggesting that the binding of substrate **1a** with LiOH/KO^{t}Bu is more favorable than that of **2a**. In addition to the expected Lewis base-Lewis acid interaction between the carbonyl group of **1a** and Li^+/K^+ cations, a favorable H–bonding interaction between the N–H of **1a** and the $^-$OH and $^-$O^{t}Bu also contributes to the preferential binding of **1a** (Figure 1). No significant difference in binding preference of **1a** between LiOH and KO^{t}Bu was observed in the calculated results.

Next, the dissociation of the $^-$OH/$^-$O^{t}Bu anion was considered via isodesmic reactions in Scheme 4C and D. Interestingly, the calculated ΔH values for the isodesmic reactions in Scheme 4C and D are endothermic by 62.8 and 49.5 kcal/mol, respectively, implying that the dissociation of the $^-$OH anion is more endothermic than $^-$O^{t}Bu. Consequently, for LiOH promoted reaction, a complex was constructed in which the N–H···OH hydrogen-bonding interaction between **1a** and LiOH is present (**INT1a**, Scheme 5). Next, two possible reaction pathways were considered 1) where $^-$OH acts as a nucleophile and 2) in which the $^-$OH behaves as a base. When the $^-$OH acts as a nucleophile by attacking the carbonyl carbon of **2a**, the corresponding transition state was located as **TS1a**. The predicted activation barrier is 6.7 kcal/mol for this step. When the $^-$OH anion acts as a base, a transition state of proton transfer from the amide group of **1a** to $^-$OH was located as **TS2a**. The computational results suggest that the proton transfer step is nearly barrierless and this is the preferred pathway. Subsequently, the formed PhCONH$^-$ moiety can undergo nucleophilic attack on the carbonyl carbon of **2a** via **TS3a** with a barrier of 6.1 kcal/mol to afford **INT5a**. The adduct **INT5a** can undergo cleavage of the C–N bond via **TS4a** with a barrier of 2.5 kcal/mol to afford the product **4aa**.

Starting from the adduct between amide **1a** to KO^{t}Bu, coordination of **2a** gives **INT2b**, which is up hill by 5.3 kcal/mol (Scheme 6). When the $^{-}$O^{t}Bu acts as a nucleophile to attack the carbonyl carbon of **2a**, the corresponding transition state was located as **TS1b** (7 kcal/mol). Next, the tetrahedral intermediate **INT3b** can undergo C–N bond breakage via **TS2b** (8.4 kcal/mol) to form **INT4b** with a κ^{2}-*tert*-butyl benzoate. Proton transfer from the amide group of **1a** to the deprotonated carbamate via **TS3b** (1.5 kcal) is calculated to give **INT5b**. Subsequently, nucleophilic attack of the deprotonated benzamide (PhCONH^{-}) on the carbonyl carbon of the potassium-coordinated BocNHBn via **TS4b** (26.7 kcal/mol) to generate a new tetrahedral intermediate, **INT6b**. Finally, breakdown of the tetrahedral intermediate **INT6b** by C–O bond cleavage via **TS5b** (13.2 kcal/mol) liberates the alkoxide $^{-}$O^{t}Bu and produces the final product **3aa**. Computational results suggest that the rate-limiting step for the formation of **3aa** is the nucleophilic attack of the bound PhCONH^{-} moiety on the BocNHBn group and subsequent dissociation of the $^{-}$O^{t}Bu anion.



Scheme 5 Energy profile (in kcal/mol) for the LiOH promoted reaction leading to **4aa**. Bond lengths are shown in Å.



Scheme 6 Energy profile (in kcal/mol) for the KO^{t}Bu promoted reaction leading to **3aa**. Bond lengths are shown in Å .

In conclusion, we have introduced a chemoselective method for the synthesis of either *N*-acylureas or imides, both of which are important motifs in medicinal chemistry. The key to achieving high selectivity is the choice of base (KO^{t}Bu vs LiOH), while the other reaction parameters of both processes are nearly identical. DFT calculations help to elucidate the reaction mechanisms of these divergent pathways. These new protocols are complementary to classical routes for *N*-acylurea synthesis, such as acylation of ureas with activated carboxylic acids and isocyanates. Compared to these syntheses, our method stands out for its exceptional chemoselectivity, broad scope, environmentally friendly properties, and avoidance of toxic phosgene or strongly acidic conditions. Further, the utility of the Boc group was broadened in this study in which it was employed as the carbonyl source.[27] In the case of the imide synthesis, traditional methods involve acylation of amides with activated carboxylic acid derivatives and Mumm rearrangement. The amidation process outlined herein is distinguished by its conciseness, convergent character, and avoidance of added transition metals.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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