Transformation of Carbonyl Compounds to Different Azaheterocycles via Direct Catalytic C-C Bond Cleavage

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触媒的直接炭素−炭素結合切断による、カルボニル化合物から異なる窒素含有複素環化合物への変換反応の開発

Transformation of Carbonyl Compounds to Different Azaheterocycles via Direct Catalytic C–C Bond Cleavage

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環境調和創薬化学分野

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Index

Abstract

Activation and cleavage of carbon-carbon (C–C) bonds in organic molecules are challenging in organic synthesis due to the strength and inertness of the bonds. Recent developments focused on transition metal-catalyzed methods and pre-activated substrates, but these approaches are often limited by high cost, functional group intolerance, and the need for toxic reagents. Consequently, this type of reaction continues to hold significant research value.

1. Transformation of Unactivated 2-Acylimidazoles and Related Azaarenes to Other Heterocycles via C–C Bond Cleavage

In previous research, the C-C bond cleavage of 2-acylimidazole occurs only using nucleophiles alone without any catalysts or additives. Therefore, we thought that it is possible to cut the C-C bond of 2-acylimidazole by using nucleophiles containing two nucleophilic centers such as amino aniline via the benzimidazoline intermediate by an acid catalyst.

As a result of various conditions, we found that by using $Sc(OTf)_3$ as a catalyst, direct conversion reactions to nitrogen-containing heterocyclic compounds via C-C bond cleavage of various 2-acylimidazoles can be achieved. In contrast to our previous study, this reaction progressed without the necessity of a solvent amount of nucleophile. Furthermore, various nucleophilic agents were also applicable, enabling the direct synthesis of a wide range of heterocyclic compounds. Notably, other complex rings such as acylated pyridines, indoles, benzothiazoles, pyrroles, and others, which were previously challenging to apply in our study, can now be utilized in this transformation.

2. Transformation of ketone containing α quaternary carbon to Other Heterocycles via C-C Bond Cleavage

We have successfully developed a direct transformation reaction that generates nitrogen-containing heterocyclic compounds by cleaving C-C bonds in 2-acylimidazoles. However, the heteroatoms on the aromatic ring are always necessary. Aromatic ketones or aliphatic ketones without heteroatoms are challenging to cleave.

Aliphatic ketones containing quaternary carbon are typically only reported undergoing the Norrish reaction using photocatalysis.

In our previous work, we discovered that ketone substrates containing α quaternary carbon can also be applied to the reaction conditions. C-C bond cleavage was achieved in an unconfirmed manner. The process occurs in an inert gas atmosphere without the addition of additional oxidants or lighting conditions. This results in comparable or even higher reaction activity compared to other studies achieved solely using acid catalytic conditions.

Therefore, we hope to study the mechanism of this cleavage reaction to explore the possibility of developing a novel C-C bond cleavage strategy for ketone compounds containing α quaternary carbon. Additionally, we aim to broaden the scope of application of the substrate to enhance its practicality in synthetic work.

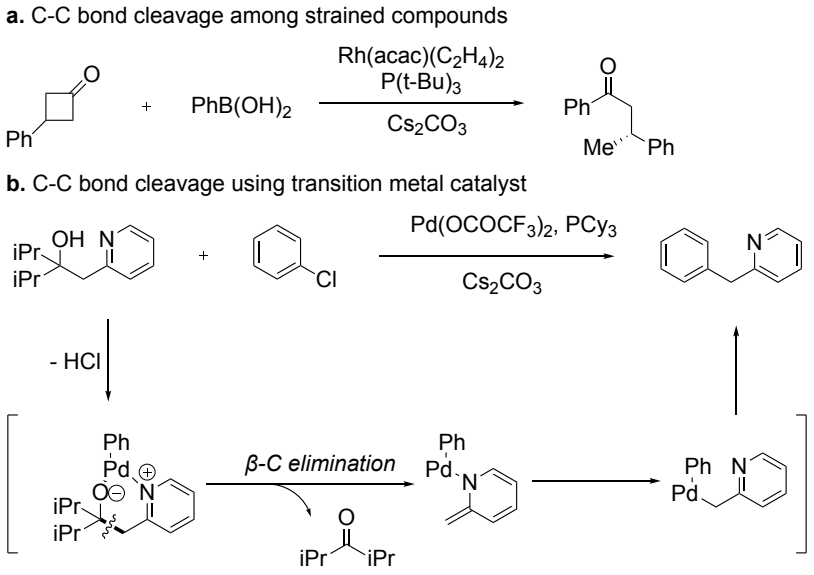
Chapter 1. Introduction

1.1 Strategies of C-C bond cleavage

The carbon-carbon (C-C) bond serves as the structural backbone of organic compounds, making C-C activation a potent strategy for organic synthesis. Despite its significance, its utilization has been relatively limited compared to C-C bond formation, primarily attributed to the higher energy required for C-C bond formation. To address this challenge, researchers have explored various approaches, including increasing the energy state of starting materials using small ring compounds[1–6] and decreasing the energy state of intermediates through the application of chelating agents to facilitate cyclometallation.[7–9]

A catalytic ring-opening of cyclobutanones with arylboronic acids was reported by Murakami's group in 2004 (Scheme 1.1.a) involved the oxidative addition of the Rhodium to α quaternary alcohol C-C bond followed by β-carbon elimination from the resulting rhodium alcoholate[10].

Scheme 1.1 strategies of C-C bond cleavage



When unstrained compounds are utilized as substrates, C-C bond cleavage can also be achieved through catalysis of transition metals. In 2007, Oshima's research group developed a reaction (Scheme 1.1.b) that cleaves α quaternary alcohol C-C bonds using a Pd catalyst and pyridine as a directing group[11]. These two cases illustrate the

feasibility of the C-C cleavage strategies previously mentioned, thereby facilitating the development of subsequent reactions.

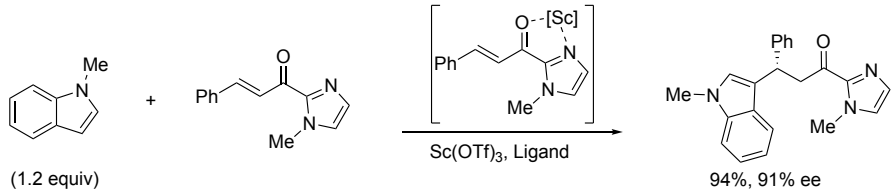
A typical example of C-C bond cleavage reactions is the conversion reaction of 2-acylimidazole, which is utilized in various chemoselective and stereoselective reactions as directing groups. Directing groups are employed to functionalize substrates and confer positive effects on the reaction efficiency, selectivity, and scope. Prior to elucidating the conversion reaction of acyl imidazole, it is imperative to introduce its role in synthetic chemistry.

1.2 Utility of 2-acylimidazoles as a directing group

2-Acylimidazoles have recently become one of the most frequently used directing groups as a post-transformable carboxylic acid equivalent, which has been successfully applied to various chemoselective and enantioselective reactions[12–14]. Chemical compounds with such a directing group are possible to form a chelate with metals via bidentate coordination, leading to a better anchoring of metals and an increased structural transition state organization[15].

The first enantioselective reaction involving α, β-unsaturated 2-acylimidazoles was reported by David A. Evans and his team in 2005[16], This discovery unveiled the distinctive capability of these compounds to facilitate Friedel-Crafts reactions. (Scheme 1.2.1). This team used scandium(III) triflate as a pre-catalyst and chiral bis(oxazolinyl)pyridine (pybox) as a ligand leading to the enantioselectivity. Several electron-rich heterocycles with various substituents were tested as substrates and led the corresponding Friedel-Crafts reaction products in good yield with high enantiomeric excess.

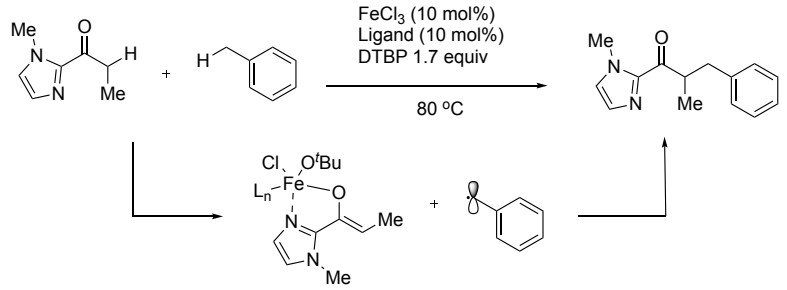
Scheme 1.2.1 Enantioselective reaction using α, β-unsaturated 2-acylimidazoles



In 2018, our group developed a method using acyl methyl imidazole as a directing group to activate the hydrogen atom at the carbonyl alpha position [14] (Scheme 1.2.2),

completed the chemical selective substitution reaction through the free radical mechanism, and successfully introduced the benzyl group at the carbonyl alpha position with a high yield.

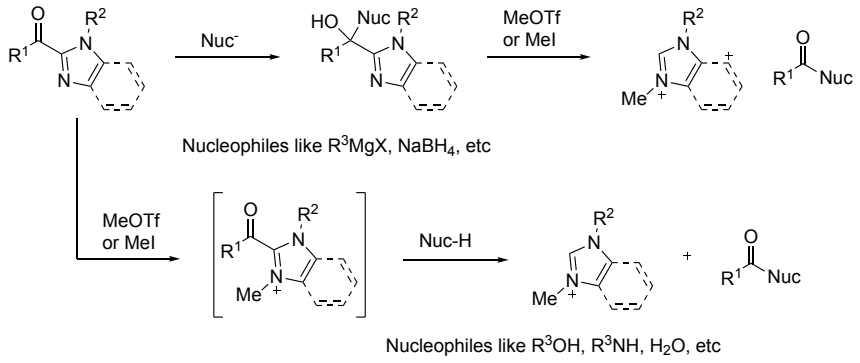
Scheme 1.2.2 Chemoselective reaction using 2-acylimidazoles in our group



1.3 Post-transformation of 2-acylimidazoles

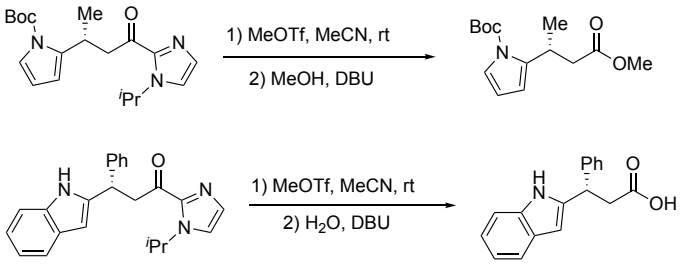
Before our research about C-C bond cleavage of 2-acylimidazoles, a great contribution was made in the last few years on the post-functionalization of 2-acylimidazole substituents. It shows that imidazolium salt produced after *N*-alkylation of the imidazolyl group can be an effective leaving group enabling the post-transformation easily into various carbonyl derivatives[17–19] (Scheme 1.3.1). The initial report reported the C-C bond cleavage reaction of acylimidazole after methylation reagent activation.

Scheme 1.3.1 Post-transformation of 2-acylimidazoles



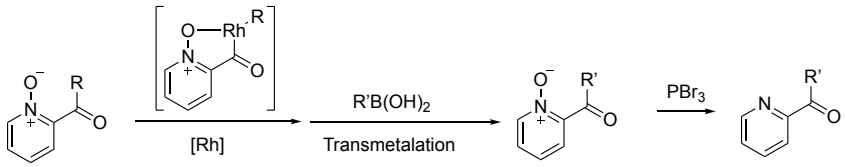
In later studies, the synthesis of corresponding carboxyl derivatives through the above conversion reaction after the selective reaction of acyl imidazole has been reported many times. In 2006, MeOTf was used as a methylation reagent, completing the transformation from acyl imidazole to esters and carboxylic acids(Scheme 1.3.2)[20].

Scheme 1.3.2 Post-transformation of 2-acylimidazoles



1.4 Utility of acylpyridine-N-oxide as a directing group

Scheme 1.4 Utility of acylpyridine-N-oxide as a directing group

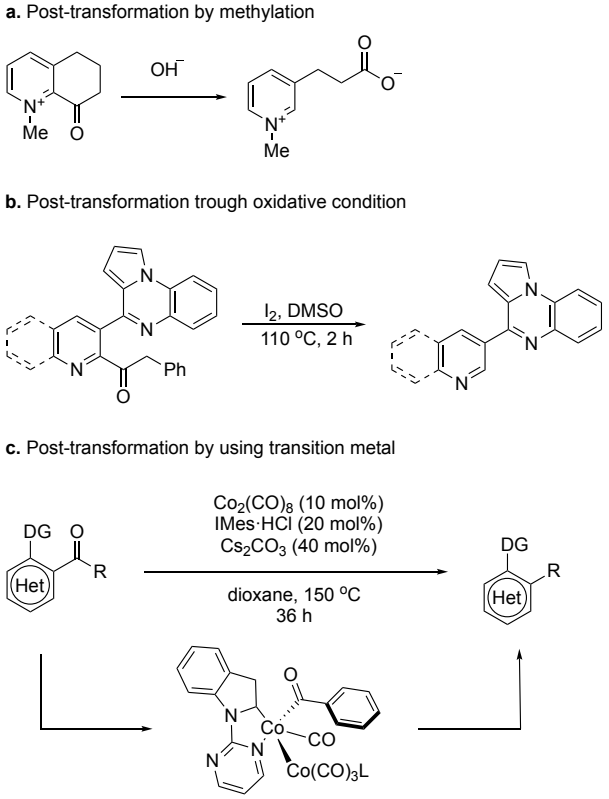


Other acyl azaalenes, such as acylpyridine-N-oxide, catalyzed by transition metals，were used as a directing group to promote C-C bond cleavage (Scheme 1.4)[21]. Because the complex intermediate formed by pyridine oxide and transition metal is much more stable than the intermediate formed by direct complexion with pyridine, the C-C bond that is usually difficult to cleavage can be activated. It is also a relatively common method of selective chemical bond activation, which is widely used in synthesis work. Through simple post-treatment, acylpyridine-N-oxide can be reduced to acylpyridine, and the subsequent conversion reactions of such compounds still need to be developed and studied.

1.5 Post-transformation of 2-acylpyridines

Like acyl imidazole, methylation of pyridine is necessary before the C-C bond cleavage reaction occurs to generate a good leaving group(Scheme 1.5. a) [22–24]. Unactivated acylpyridine is difficult to cleavage directly.

Scheme1.5 Post-transformation of 2-acylpyridines



According to a newer study, such compounds were found to cleavage by oxidation reactions. In 2021, Kapil Mohan Saini's group reported the C-C bond cleavage of acylpyridine (acylbenzopyridine) through oxidation conditions[25] (Scheme 1. 5.b), but no systematic substrate screening, and there was no discussion about the structure determination of the cut-off acyl part. The reaction may go through the oxidative cleavage of the aliphatic carbon on the carbonyl alpha position, and the resulting carboxylpyridine is further decarboxylated to form the target product. Low atomic economy and restrictions on the substrate structure might be the problems that need to be improved.

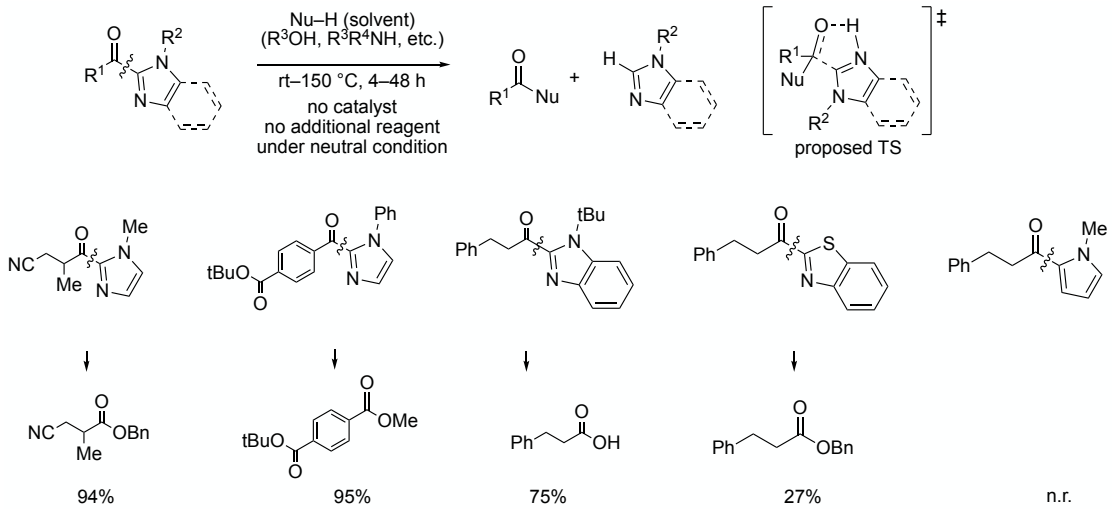
In addition, the cross-coupling reaction catalyzed by transition metals, which is more widely used in the C-C cleavage reaction, can also be applied to such acylpyridine

compounds (Scheme 1. 5.c)[26]. Through directing group activation, the oxidation insertion reaction of the metal to the C-C bond is promoted, and the substitution product is finally obtained. Although the C-C bond cleavage reaction has successfully developed, but the complex reaction conditions, the longer reaction time, and the pyrimidine need to be imported as a directing group to promote the reaction still need to be improved in the future.

1.6 Previous work

In our previous research, we successfully developed a C-C bond cleavage reaction that does not require any catalysts or additives and exhibits a wide range of functional group tolerance [27]. This reaction undergoes a transition state through proton transformation to activate the C-C bond, enabling the generation of carbonyl derivatives that are readily amenable to further transformations. (Scheme 1.6).

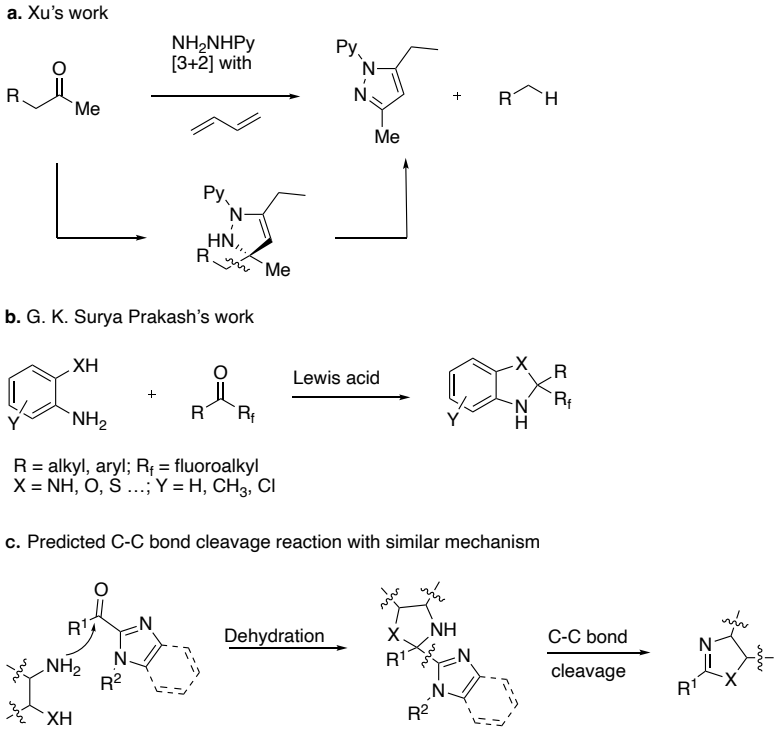
Scheme 1.6 Previous work



However, an excessive amount of nucleophile is necessary, and the reaction cannot be effectively applied to other acyl heterocyclic compounds. For example, 2-acylbenzothiazole only generates 27% of the target product, and we couldn't detect the product when 2-acylpyrrole was applied as substrate.

1.7 Work hypothesis.

Scheme 1.7 Work hypothesis.



In 2019, Xu's group reported a new strategy to promote C-C bond cleavage reaction by constructing heteroatomic aromatic rings as a good leaving group in situ of the carbonyl group (Scheme 1.7.a)[28].it seems that more stable products would be generated when the aromatization occurs after the cleavage reaction, which can promote the progress of the reaction.

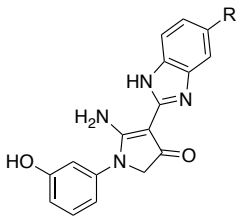
G. K. Surya Prakash's group reported a benzimidazoline generation reaction catalyzed by Lewis acid (Scheme 1.7.b)[29], which inspired us to use such kind of nucleophile with two nucleophilic centers reacting with carbonyl compounds leading to cleavage of C-C bond.

Herein, the first half of our work is aimed at offering a new possibility of the cleavage of the Csp^2-Csp^2 bond from unactivated 2-acylimidazole compounds or other acyl-heterocyclic compounds and a new method to synthesize heterocyclic compounds like 2-substituted benzimidazoles from ketone structures catalyzed at the same time by simple Lewis acid without any other additives(Scheme 1.7.c).

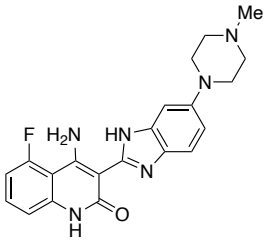
1.8 The utility of compounds with benzimidazole group

N-Heterocycles such as benzimidazoles are used as versatile and key synthetic intermediates for the preparation of several natural products and bioactive compounds. In 2016, A series of derivatives of this chemical scaffold were synthesized and evaluated as FGFR1 inhibitors by A.A. Gryshchenko and his team. It was revealed that the most promising compounds 5-amino-1-(3-hydroxy-phenyl)-4-(6-methyl-1*H*-benzoimidazol-2-yl)-1,2-dihydro-pyrrol-3-one (**a**) and 5-amino-4- (1*H*-benzoimidazol-2-yl)-1-(3-hydroxy-phenyl)-1,2-dihydro-pyrrol-3-one (**b**) inhibit FGFR1 and possess antiproliferative activity against KG1 myeloma cell line[30]. Concurrently, the anticancer drug (**c)**, which has been commercially available, also possesses a benzimidazole skeleton.

Scheme 1.8 Reported bioactive compounds with benzimidazole substituted



a: R=CH_3
b: R=H



c

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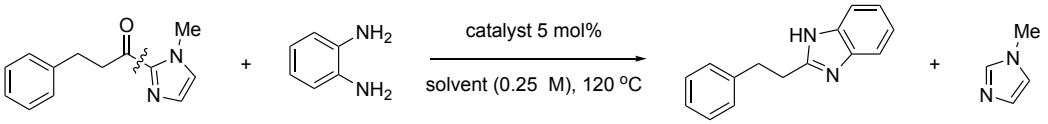
Chapter 2. Transformation of Unactivated 2-Acylimidazoles and Related Azaarenes to Other Heterocycles via C–C Bond Cleavage

2.1 Catalyst screening

In the beginning, 2-acyl-N-methylimidazole was selected as the model substrate. The reaction was designed to be conducted in PhCl at 120 °C stirred for 6 h with the loading of 5 mol % scandium (III) trifluoromethanesulfonate as a catalyst since it shows excellent activation in facilitating the generation of ketamine in the previous work in our group. As we expected, the model substrate was transformed into the desired benzimidazole in 45% yield. Various Lewis catalysts with the same anion group were also tested.

The desired transformation was processed in all entries with different yields. However, trivalent metal catalysts showed higher conversions than divalent metal catalysts. In all the cases of Lewis acid screen, scandium trifluoromethanesulfonate showed high reactivity for facilitating this transformation. In addition, two Brønsted acids were tested in entries 11 and 12, but neither showed better activity than scandium trifluoromethanesulfonate. With the result of the catalyst screen in hand, we determined to use scandium trifluoromethanesulfonate as the catalyst. Although scandium nitrate showed better reactivity in this transformation, we still determined to use scandium trifluoromethane sulfonate as the catalyst due to the lower price.

Table 1. Initial Screening of Catalysts and Solvents



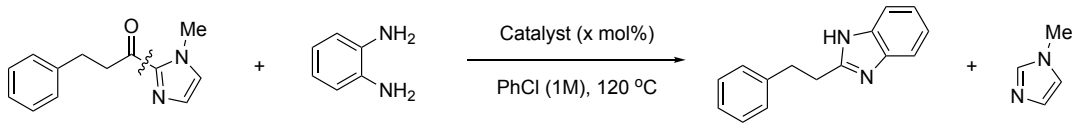
1 **2** (1.5 equiv) **3** **4**

Entry[a]	catalyst	6 h ^{1}H NMR yield of **3**
1	**$Sc(OTf)_3$**	**45%**
2	$Zn(OTf)_2$	18%
3	$Cu(OTf)_2$	20%
4	$Y(OTf)_3$	36%
5	$La(OTf)_3$	33%
6	$Bi(OTf)_3$	38%
7	$In(OTf)_3$	30%
8	$Mg(OTf)_2$	23%
9	**$Sc(NO_3)_3 \cdot 4H_2O$**	**56%**
10	$Sc(OAc)_3$	n.r
11	p-TsOH	9%
12	PPTS	29%

[a] PhCl (0.40 mL, 0.25 M) was used as the solvent.

When $Sc(OTf)_3$ was used as a catalyst, TfOH might be generated from a small amount of water, which can also promote the progress of the reaction. So, we tested the activity of TfOH using it as the catalyst. It was found that when using 5 mol% of TfOH, the reaction speed was lower than that of $Sc(OTf)_3$, but when 15mol% was used, the results showed the same reaction activity as $Sc(OTf)_3$. This phenomenon might be related to the fact that 5mol% of $Sc(OTf)_3$ and 15mol% of TfOH possess the same chemical equivalent of TfO^-. Given the potential for direct catalysis by $Sc(OTf)_3$, we subsequently investigated the effects of the two catalysts by comparing their applicability to various substrates. On the other hand, TfOH is a corrosive liquid that presents greater handling difficulties. Consequently, we have ultimately decided to utilize scandium trifluoromethane sulfonate as the catalyst.

Table 2. Comparison with Two Catalysts



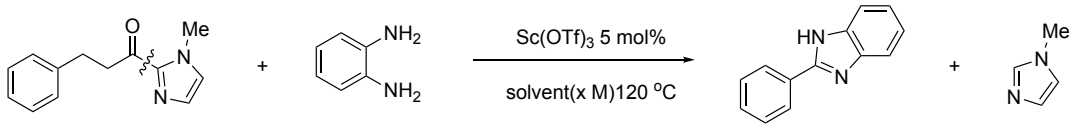
1 **2** (1.5 equiv) **3** **4**

Entry	catalyst	eq. (x mol%)	6 h ^{1}H NMR yield	24 h ^{1}H NMR yield
1	$Sc(OTf)_3$	5 mol%	85%	>99%
2	TfOH	5 mol%	18%	-
3	TfOH	15 mol%	86%	>99%

2.2 Solvent screening

To further optimize the solvent used in this transformation, different kinds of solvent were tested, and the reaction was conducted at 120 °C catalyzed by scandium (III) trifluoromethanesulfonate with the loading of 5 mol%. The transformation proceeded in all the solvents we tested. However, no solvent showed better results than PhCl. Although the reaction was conducted at a concentration of 0.25 M, we later discovered that higher concentration conditions could enhance the reaction rate. However, it is crucial to use a moderate amount of solvent to ensure that the substrates dissolve at the reaction temperature. After careful experimentation, we determined that scandium trifluoromethanesulfonate, with a loading of 5 mol%, was an optimal catalyst. This catalyst was used in 1 M PhCl at 120 °C, resulting in the complete conversion of the substrates to the corresponding acyl benzimidazoles within 24 hours.

Table 3. Condition optimization of solvent



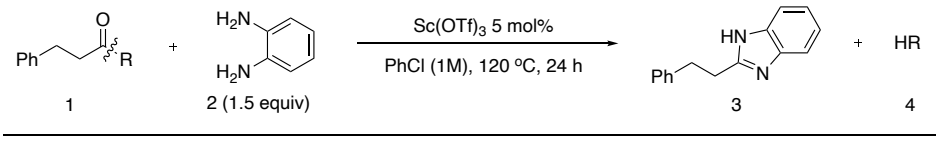
1 2 (1.5 equiv) 3 4

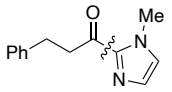
Entry	solvent	concentration (x M)	6 h ^{1}H NMR yield	24 h ^{1}H NMR yield
1	tolune	0.25 M	39%	-
2	1,4-dioxane	0.25 M	31%	-
3	DMF	0.25 M	15%	-
4	DMSO	0.25 M	9%	-
5	t-AmOH	0.25 M	40%	-
6	PhCl	0.25 M	45%	71%
7	PhCl	0.5 M	65%	88%
8	**PhCl**	**1 M**	**85%**	**>99%**
9[a]	**PhCl**	**1 M**	**86%**	**>99%**

[a] 15 mol% TfOH was used.

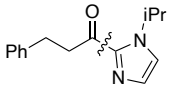
2.3 Substrate scope

Table 4. Substrates scope of 2-acylimidazoles with different N-substituents[a]

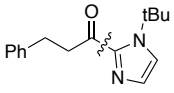




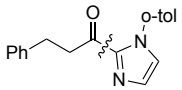
1aa 96%



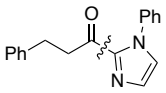
1ab 73%



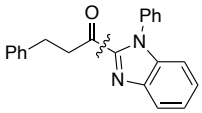
1ac 57%[b, d]



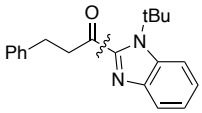
1ae 86%



1ag 97% (94% recovered by 1-phenylimidazole)[e]



1ad 93%[c]



1af 91%[b]

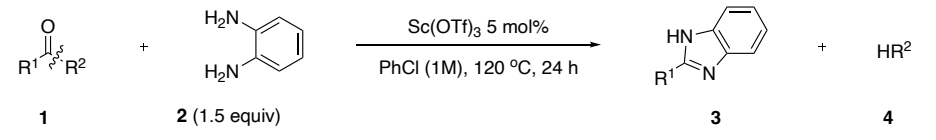
[a]Substrate scope were carried out with a scale of 0.1 mmol. All yields are isolation yields.
[b] At 150 °C. [c]At 80 °C. [d]2.0 equiv of o-phenylenediamine was used. [e]3 mmol scale.

During the initial phase of our substrate scope investigation, several 2-acylimidazoles (**1aa**, **1ab**, **1ac**, **1ae**, **1ag**) and 2-acylbenzimidazoles (**1ad**, **1af**) were synthesized and tested under the optimized conditions previously described. Notably, N-methyl imidazole (**1aa**), N-isopropylimidazole (**1ab**), N-phenylimidazole (**1ag**), and N-phenylbenzimidazole (**1ad**) have been the most extensively utilized compounds in recent years.

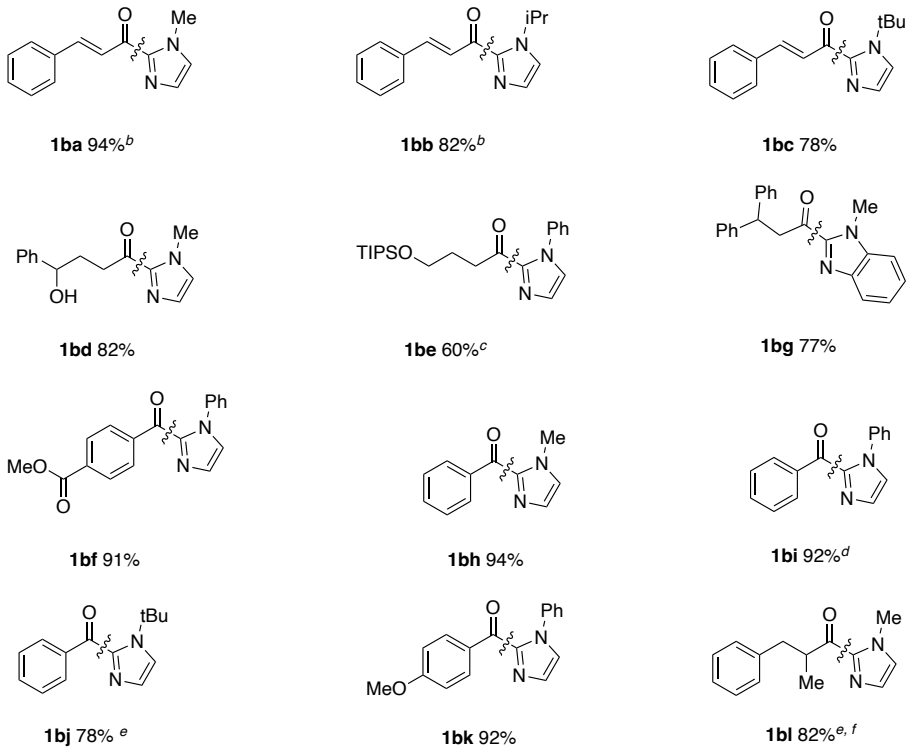
As observed, all the substrates successfully transformed into desired benzimidazoles with moderate to good yields. The effect of the N-substituent on reactivity is found to be related to steric hindrance. The bulkiest *t*-Bu group on imidazole (**1ac**, **1af**) exhibited the lowest reactivity. It appears that the nucleophilic attack from diamine is partially restricted by steric hindrance. Consequently, we presume that the nucleophilic attack is the rate-determining step rather than the cleavage of the C-C bond. Furthermore, a larger-scale synthesis of **1ag** was conducted with perfect efficiency, resulting in 94% coverage of 1-phenylimidazole.

Several unsaturated 2-acylimidazoles with different N-substituents (**1ba**, **1bb**, **1bc**) were soon tested and showed better reactivity than saturated substrates. The unsaturated N-methyl-2-acylimidazole (**1ba**) led to the corresponding unsaturated benzimidazole in 94% yield only in 3 hours under optimized conditions.

Table 5. Substrates scope of 2-acylimidazoles[a]



1 **2** (1.5 equiv) **3** **4**



1ba 94%[b] **1bb** 82%[b] **1bc** 78%

1bd 82% **1be** 60%[c] **1bg** 77%

1bf 91% **1bh** 94% **1bi** 92%[d]

1bj 78% [e] **1bk** 92% **1bl** 82%[e, f]

[a]Substrate scope were carried out with a scale of 0.1 mmol. All yields are isolation yields.
[b] For 3 hours. [c]At 80 °C. [d]At 100 °C. [e]At 150 °C. [f] 2 equiv phenylenediamine was used.

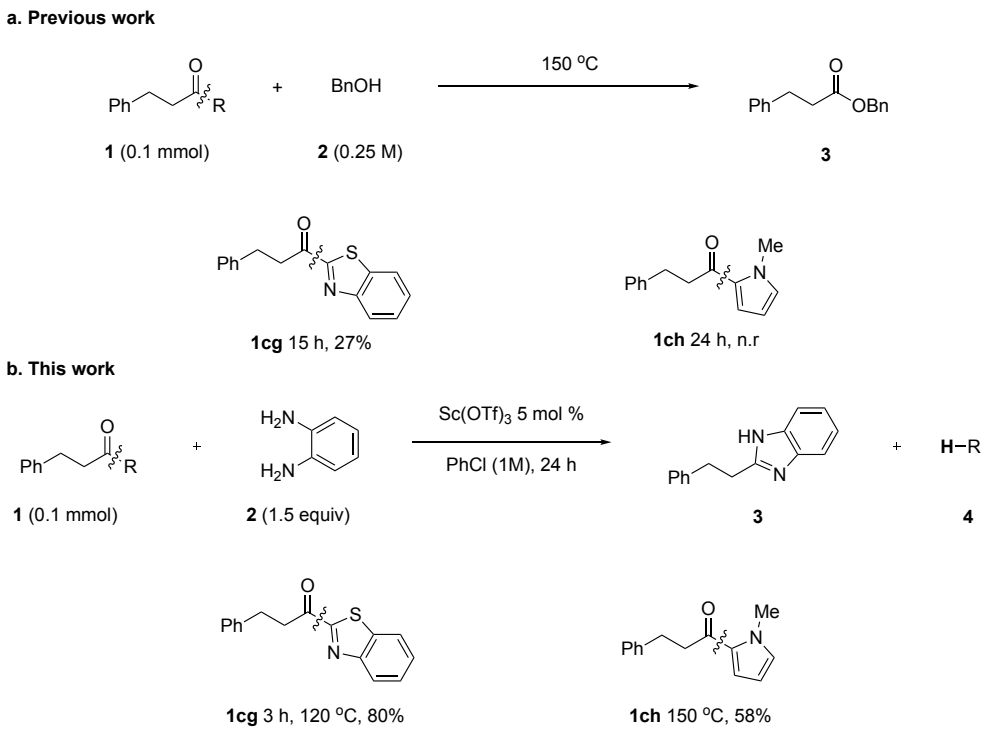
The same trend of the effect caused by steric hindrance was indicated in this case (**1ba**, **1bb**, **1bc**), which might prove our hypothesis. Aromatic 2-acylimidazoles (**1bh**, **1bi**, **1bj**) also showed good reactivity with different N-substituents. In addition, various substrates with functional groups were also applicable in this transformation. The substrate containing the methyl ester group (**1bf**) is successfully transformed into the target benzimidazole without being hydrolyzed. Although a small amount of substrates containing TIPS (**1be**) are hydrolyzed and converted into alcohol, it still showed a

separation yield of up to 60%. Furthermore, substrates with a tertiary carbon at the alpha position (**1bl**) were successfully transformed into the desired product.

2.4 Substrate scope of other heterocyclic compounds

The C-C bond cleavage reaction promoted by the alcohol we previously developed cannot be effectively applied to other acyl heterocyclic compounds. For example, 2-acylbenzothiazole (1cg) only generates 27% of the target product, and we couldn't detect the product when 2-acylpyrrole (1ch) was applied as substrate.

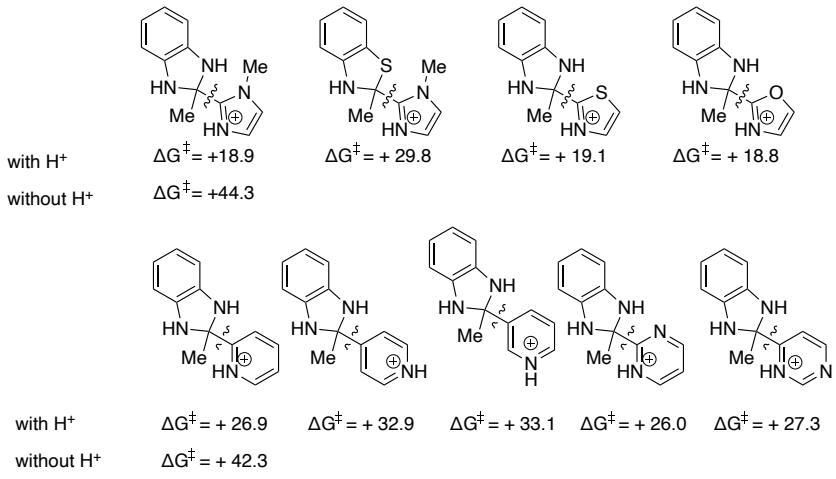
Scheme 2.1 Contrast of substrate scope of other acylated azaarenes



However, both substrates were successfully converted into target products through the utilization of diamine as a nucleophile. I posit that other asylized azaarenes can be employed in this conversion, prompting me to consider the following approach.

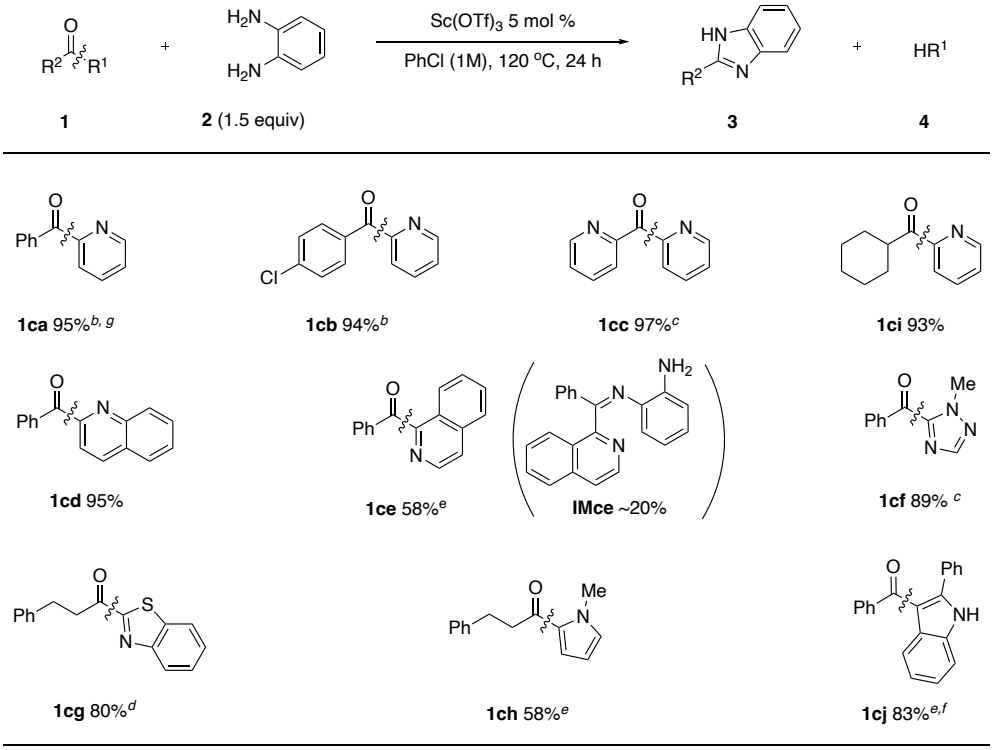
Prior to testing the substrate of other nitrogen-containing aromatic compounds, we initiated a thermodynamic analysis of various acyl heterocyclic compounds that may potentially be applicable in the reaction. We anticipated that the reaction would progress through the benzimidazoline intermediate, so the energy of the transition state of benzimidazoline intermediate of distinct heterocyclic substrates underwent cleavage were calculated. Our findings indicated that methylimidazole successfully completed the cleavage reaction with a remarkably low energy barrier. Under H-catalyzed conditions, ΔG was only 18.9 kcal/mol (Scheme 2.2), whereas the energy required for pyridine substrates was considerably higher.This is different from our experimental results, which proves that the H-catalytic model cannot perfectly replace the Sc model for calculation. When Sc is used as a catalyst, it may have a more obvious effect on the reaction promotion of pyridine substrates.

Scheme 2.2 DFT calculation of the intermediates of various acyl heterocycles



To our surprise, phenyl(pyridin-2-yl)methanone (**1ca**) exhibited exceptional reactivity and could be scaled up to 3 mmol (approximately 0.6 grams of 2-benzoylpyridine) to afford the corresponding benzimidazole in 95% yield only at 100 °C (Table 6). Chloro-substituted 2-acylpyridine (**1cb**) and dipyridine ketone (**1cc**) also demonstrated high reactivity, resulting in the corresponding benzimidazoles in excellent yields within a shorter reaction time of only 6 hours.

Table 6. Substrate scope of other heterocyclic compounds



[a]Substrate scope were carried out with a scale of 0.1 mmol. All yields are isolation yields.
[b]At 100 °C [c]For 6 hours. [d]For 3 hours. [e]At 150 °C.[f]2 equiv phenylenediamine was used. [g] 3 mmol scale.

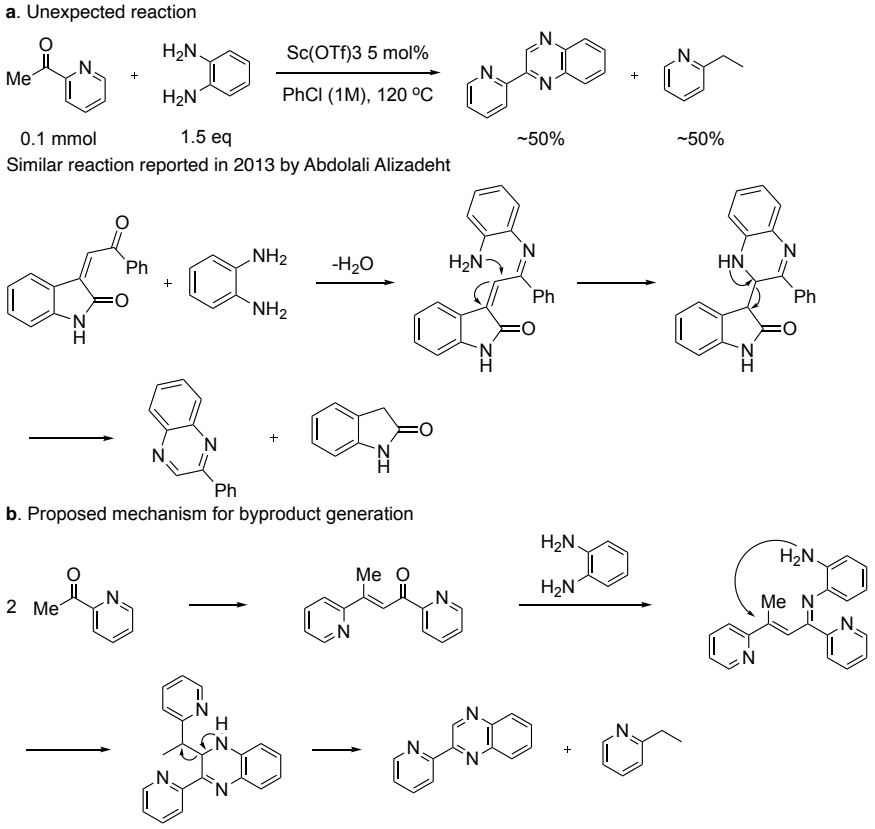
The substrate bearing a quinoline (**1cd**) moiety exhibited high reactivity comparable to the model substrate, affording the desired product with a 95% yield under optimized conditions. Conversely, the substrate with an isoquinoline (**1ce**) moiety gave only 58% yield at 150 °C. Notably, over 20% of the material transformed into an imidazoline intermediate, suggesting that the reaction mechanism is similar to the C–C bond cleavage of 2-acylimidazoles, with the C–C bond cleavage step being significantly more challenging for the substrate with isoquinoline. Furthermore, not only aromatic substituted acyl-pyridine substrates but also alpha-aliphatic substituted 2 acyl-pyridine substrates (**1ci**) also obtained the desired product with excellent yield under optimized conditions.

The substrate with N-methyltriazole (**1cf**) also proved to be suitable for this transformation, exhibiting good reactivity. The substrate with 2-acylbenzothiazole (**1cg**) exhibited exceptional reactivity, yielding the desired product in 83% yield within 3 hours under optimized conditions. Additionally, 2-acylpyrole (**1ch**) exhibited moderate reactivity at 150 °C, whereas such transformations were not observed in our previous

work using alcoho as the nucleophile. Furthermore, the 3-acylindole (**1cj**) derivative was successfully transformed into the desired benzimidazole with moderate reactivity. The substrate with an acyl indole group, commonly found in medicinal structures, also demonstrated good reactivity, albeit with the use of a higher nucleophile concentration.

When alkyl-substituted 2-acylpyridine was utilized as substrate under optimized conditions, an unexpected transformation occurred to yield a reduction product in approximately 50% yield. Benzopyrazine derivative was also isolated by column chromatography, and its yield was determined by ^{1}H NMR analysis in 50%. Scheme 2.3.a illustrates a possible mechanism for the transformation of acylpyridine to alkylpyridine. Initially, two molecules of acylpyridine undergo aldol condensation to form an unsaturated acylimidazole. Subsequently, a nucleophilic attack by diamine leads to the formation of a ketimine intermediate. Subsequently, ring formation occurs, resulting in the cleavage of the C-C bond, leading to the desired benzipyrazine and alkylpyridine. A similar mechanism has been previously reported in 2013 by Alizadeh (Scheme 2.3.b), which may provide support for this proposed mechanism[31].

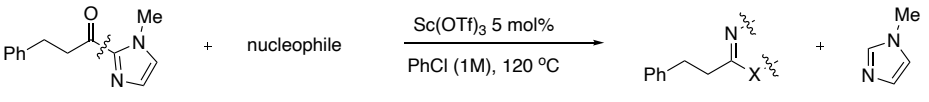
Scheme 2.3. Other findings during substrate scope



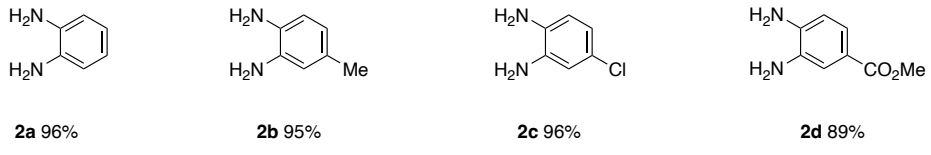
2.4 Nucleophile scope

To enhance the product diversity resulting from this transformation, various diamines and other nucleophiles with two nucleophilic centers were investigated (Table 7). Initially, several substituted ortho-phenylenediamines were utilized in this transformation. Phenylenediamines substituted with electron-donating groups (**2b**, **2c**) exhibited enhanced reactivity, while those substituted with electron-withdrawing groups (**2d**, **2e**) exhibited diminished reactivity. In the case of nitro-substituted phenylenediamines (**2e**), only 79% of the desired nitro-substituted benzimidazole was obtained at 150 °C.

Table 7. Nucleophile scope



1 **2** (1.5 equiv) **3** **4**



2a 96% **2b** 95% **2c** 96% **2d** 89%

2e 79%[b] **2f** 94%[b] **2g** 85%[b] **2h** 85%

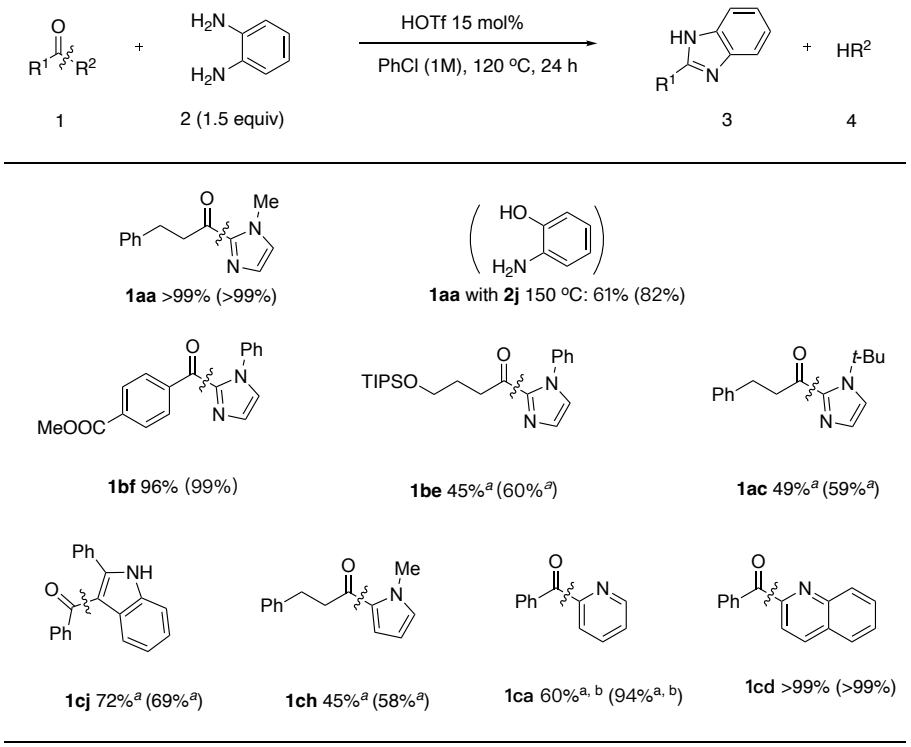
2i 88% **2j** 79%[b, c] **2k** 88%[b] **2l** 91%[d]

[a] Substrate scope was carried out with a scale of 0.1 mmol. All yields are isolation yields.
[b]At 150 °C. [c] 10 mg MS4A was added. [d] for 48 hours.

Furthermore, we also presumed that such transformation could lead to other heterocyclic compounds not only benzimidazoles by using different aromatic or aliphatic amines such as 2-aminobenzenemethanamine (**2h**), 1,8-naphthalenediamine (**2g**), 2-aminophenol (**2j**), and 2-aminobenzenethiol (**2k**). The corresponding products were obtained in moderate to good yields, although a harsher reaction condition was required. In addition, N-substituted benzimidazoles could be obtained by using N-substituted diamine (**2f**, **2i**) as the nucleophile. Surprisingly, 2-aminobenzamide (**2l**) is also applicable in this transformation to yield the desired lactam in good yield, although a longer reaction time was necessary.

2.5 Activity comparison with two catalysts

Table 8. Activity comparison with two catalysts



Yield was determined by 1H NMR analysis of the crude mixture. The results of using $Sc(OTf)_3$ as a catalyst was indicated in parentheses. [a] Isolated yield. [b] 100 °C, 6 hours.

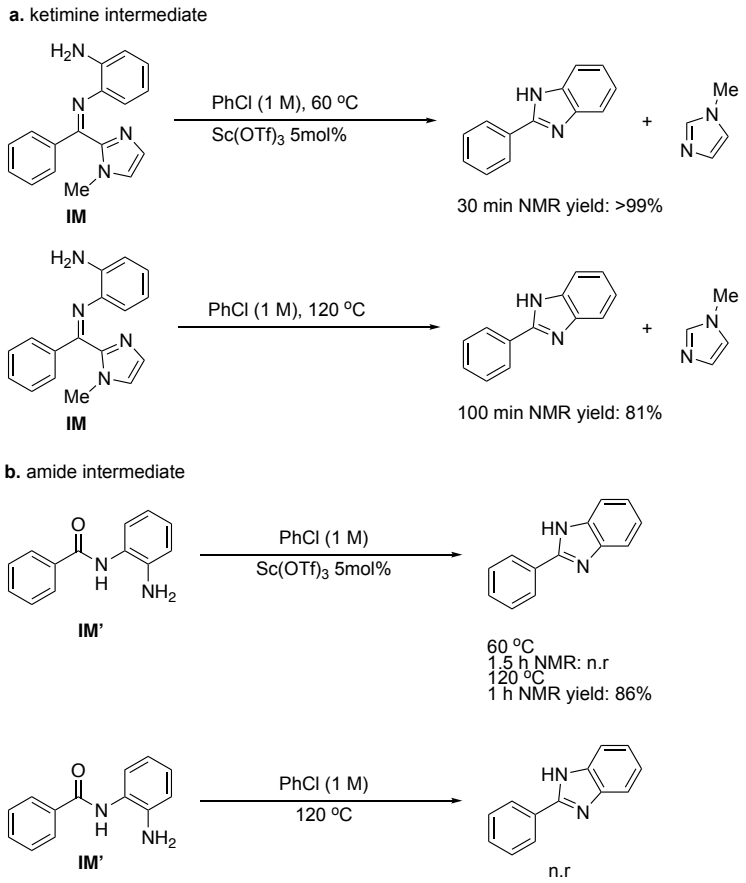
Finally, we compared the activities of two catalysts using several representative substrates. We observed that although the catalytic activity of the two catalysts for the model substrate (**1aa**) was comparable, $Sc(OTf)_3$ exhibited superior reactivity when the nucleophile was substituted with aminophenol (**2j**). Furthermore, we noted that when the substrate bearing a TIPS group (**1be**) was utilized, the yield catalyzed by TfOH (45%) was lower when employing 5 mol% $Sc(OTf)_3$ as the catalyst (60%), resulting in a higher proportion of products being hydrolyzed into alcohols. Additionally, when N-tert-butyl imidazole substrate (**1ac**), 2-acylpyridine (**1ca**) and 2-acylpyrrole (**1ch**), the reaction speed catalyzed by TfOH was diminished. There was minimal variation in the reaction activity of the other substrates.

2.6 Mechanism study

We subsequently proposed two distinct pathways for leading the tertiary alcohol intermediate to the product: one giving rise to a ketimine intermediate (path A) and the other giving rise to an amide intermediate (path B) by desorption of the imidazolide

anion (Scheme 2.4). To differentiate these two potential pathways, we conducted control experiments to gain insight into the reaction pathway.

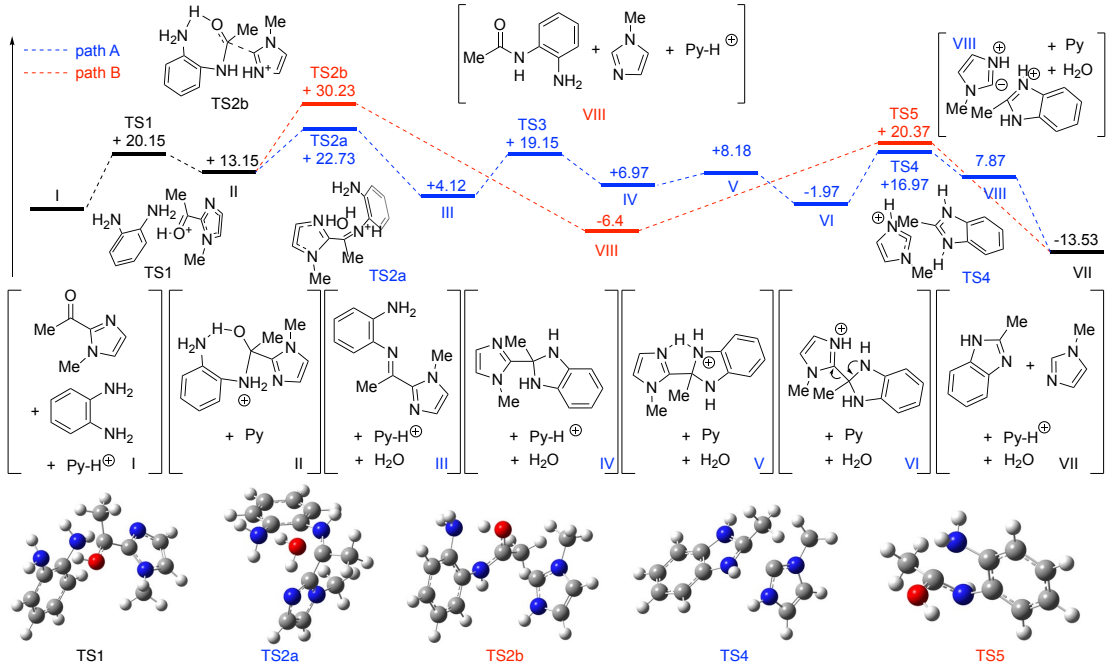
Scheme 2.4 Control experiment



Several control experiments were conducted to validate the mechanism pathway by utilizing the intermediates in both pathways. First, the ketimine intermediate in path a was synthesized and tested under optimized conditions with only temperature changes. As anticipated, the ketimine intermediate transformed into the desired benzimidazole with complete conversion in 30 minutes. When the ketimine intermediate was tested without a catalyst at 120 °C, it also yielded the corresponding product in 81% yield within 100 minutes, as detected by ^{1}H NMR analysis. In contrast, the amide intermediate that emerged in path b exhibited significantly lower reactivity, and no product was observed at 60 °C in 1.5 hours. The transformation only occurred when the temperature was elevated to 120 °C, resulting in benzimidazole in 86% yield. Furthermore, the amide intermediate demonstrated no reactivity without a Lewis acid catalyst even at 120 °C. These findings also suggest that scandium

trifluoromethanesulfonate plays a pivotal role in facilitating the nucleophilic attack process. To further evaluate the validity of these two possible pathways, we performed density functional theory (DFT) calculations at the level of M06-2X/6-311+G(d,p)/PCM(PhCl)//B3LYP/6-31+G(d,p)

Scheme 2.5 DFT calculation of two mechanism pathway



DFT calculations were performed at the level of M06-2X/6-311+G(d,p)/PCM(PhCl)//B3LYP/6-31+G(d,p).

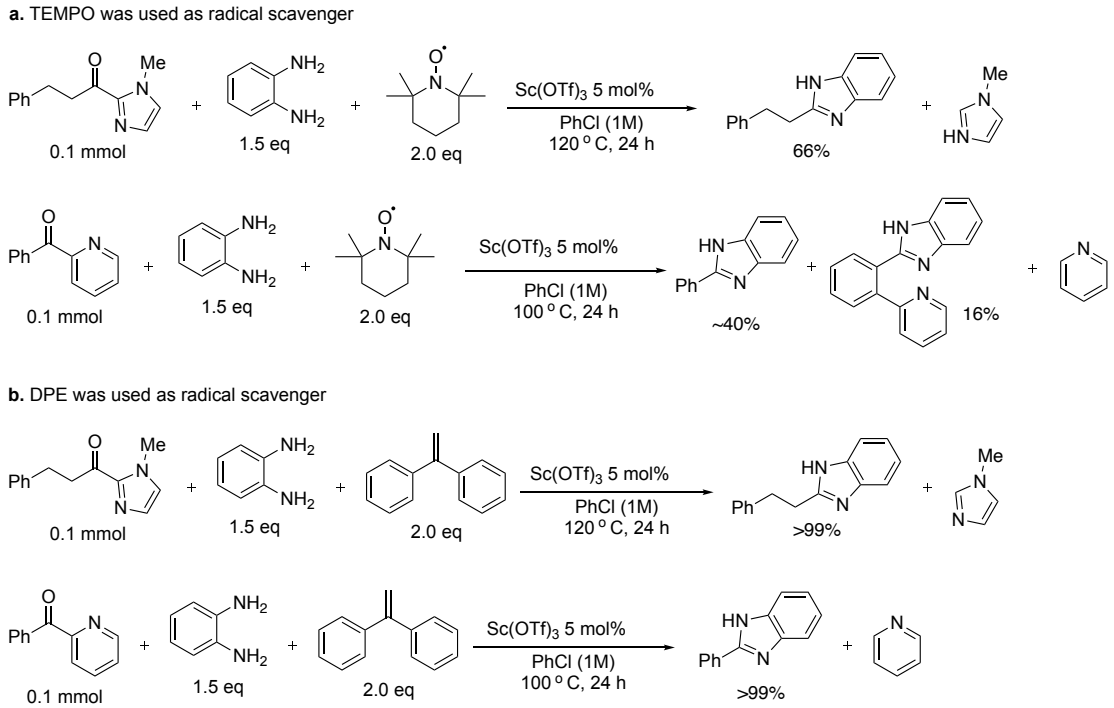
The results of the DFT calculation revealed that the nucleophilic attack initially occurs via TS1, with a barrier of 20.15 kcal/mol. Subsequently, the proposed mechanism splits into two pathways, as depicted in Scheme 2.4. In path A, the tertiary alcohol intermediate undergoes a conversion to a ketimine intermediate via TS2a, resulting in an overall activation energy of 22.73 kcal/mol. In contrast, the overall activation energy of TS2b in path B is 30.23 kcal/mol. These calculations indicated that the C–C bond cleavage process is the rate-determining step in path B, which contradicts the experimental result obtained in the substrate scope presented in Table 4.

Continuing in path A, a ketimine intermediate with an activation energy of 4.12 kcal/mol can readily transform into a benzimidazoline intermediate via TS3, with a barrier of only 15.03 kcal/mol. Subsequently, C–C bond cleavage occurs via TS4, resulting in the corresponding benzimidazole and N-methylimidazole. Furthermore, the experimental results of the mechanism study are corroborated by the calculated results.

The amide intermediate, with the energy of -6.4 kcal/mol, is sufficiently stable under the catalyzed conditions at 60 °C. Additionally, an extra heat input of 20.37 kcal/mol is required to overcome the barrier of TS4 and afford the benzimidazoline intermediate. Consequently, the DFT calculations suggest that the ketimine pathway (path A) is the most viable option.

To confirm whether the cleavage process going through the free radical pathway, experiments were conducted by adding a free radical scavenger under standard reaction conditions.

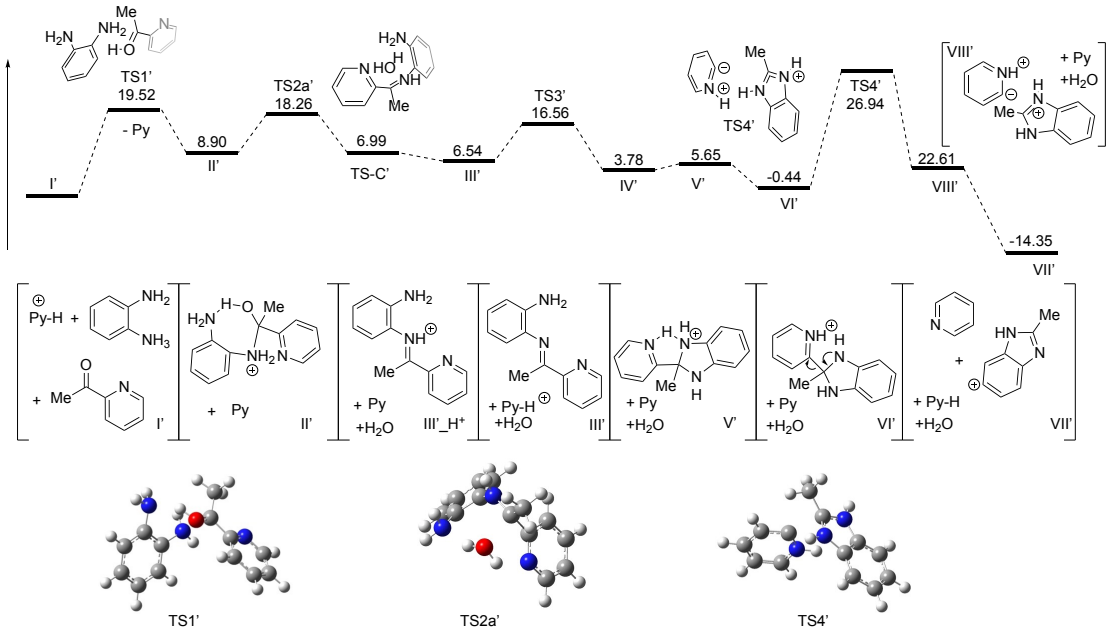
Scheme 2.6 Mechanism study using radical trapper reagents



We observed that while TEMPO was employed as a free radical scavenger (Scheme 2.5.a), the rate of the reaction that generates the target product was reduced, but the corresponding free radical transition state was not captured by TEMPO. The reduction of the reaction rate alone does not imply that the reaction has progressed through the free radical pathway. There is a possibility that TEMPO facilitates a side reaction that transfers the pyridine group to benzene. In contrast, when DPE was utilized (Scheme 2.5.b), no reduction in the rate of generating target products was observed. Furthermore, no signals of the product generated from the corresponding radicals transition state and DPE were detected in DART-MS. Based on these findings, the possibility that this

reaction proceeds via a free radical pathway have been eliminated.

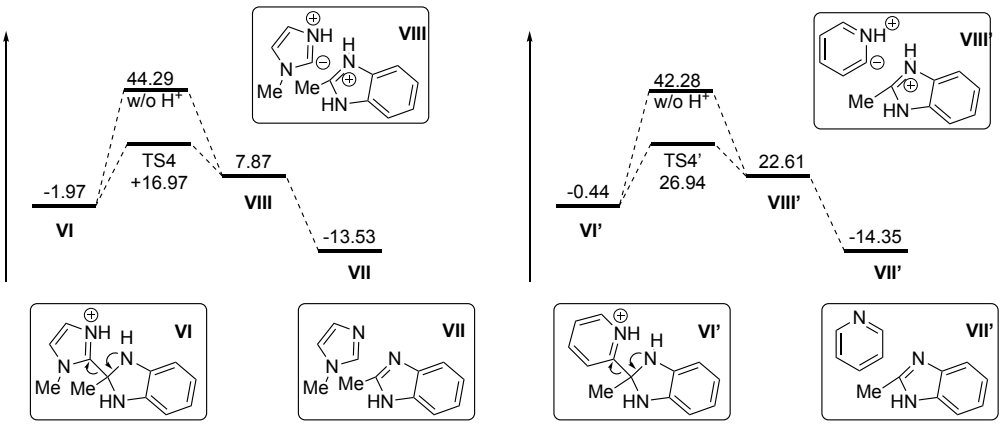
Scheme 2.7 DFT calculation for 2-acylpyridine substrates



DFT calculations were performed at the level of M06-2X/6-311+G(d,p)/PCM(PhCl)//B3LYP/6-31+G(d,p).

We also performed calculations of acylpyridine substrate undergoes a similar reaction pathway. The computational results indicate that, unlike the acylimidazole substrate, the C-C bond cleavage step exhibits a higher energy barrier, which serves as the rate-determining step of the reaction. However, the experimental findings suggest that the pyridine substrate exhibits enhanced reaction activity compared to the imidazole substrate, contradicting the higher energy barrier of the pyridine substrate in the computational analysis. Consequently, we propose that the generated pyridine carbene transition state interacts with the metal catalyst, thereby reducing the energy barrier of the C-C bond cleavage transition state. This reduction in energy facilitates the cleavage of the C(acyl)-C(pyridyl) bond, which is generally considered to be a challenging reaction step.

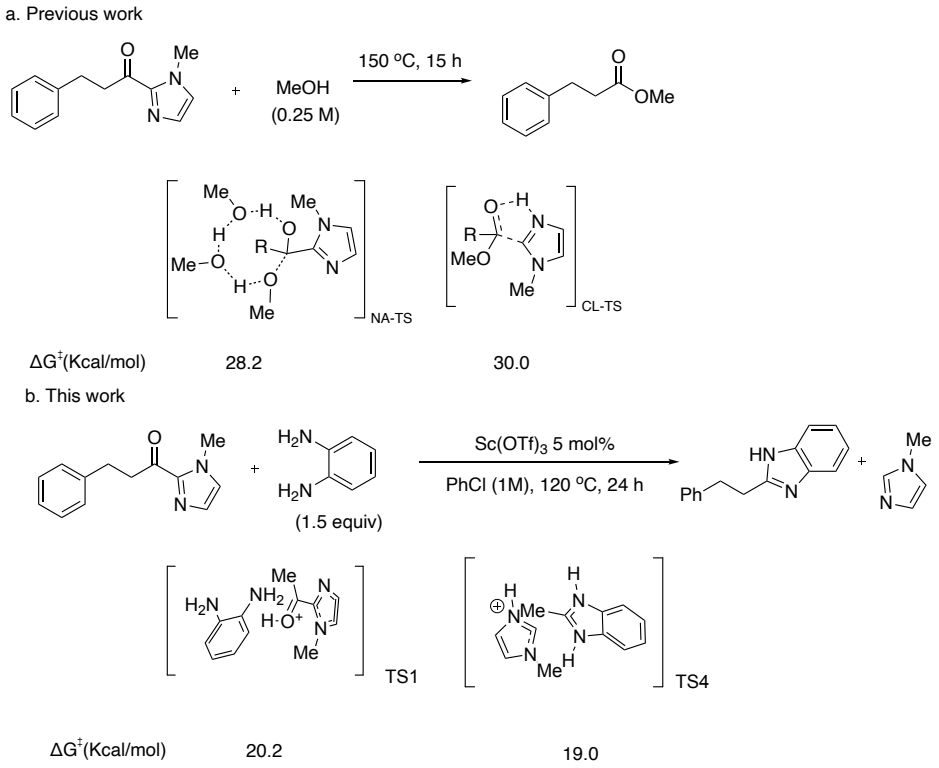
Scheme 2.8 Effect of acid on transition state stability



DFT calculations were performed at the level of M06-2X/6-311+G(d,p)/PCM(PhCl)//B3LYP/6-31+G(d,p).

We can also observe a significant difference in the transition state generated through the C-C bond cleavage process when employing an acid catalyst compared to the absence of an acid catalyst. This implies that an acid catalyst plays a crucial role in stabilizing the transition state (Scheme 2.8).

Scheme 2.9 Discussion of The Necessary of Using Catalyst in This Study



DFT calculations were performed at the level of M06-2X/6-311+G(d,p)/PCM(PhCl)//B3LYP/6-31+G(d,p).

In our previous study, we demonstrated that nucleophilic reagents alone can facilitate the cleavage of acylimidazole without the involvement of catalysts. However, in this study, under the absence of catalysts, the reaction did not proceed as anticipated.

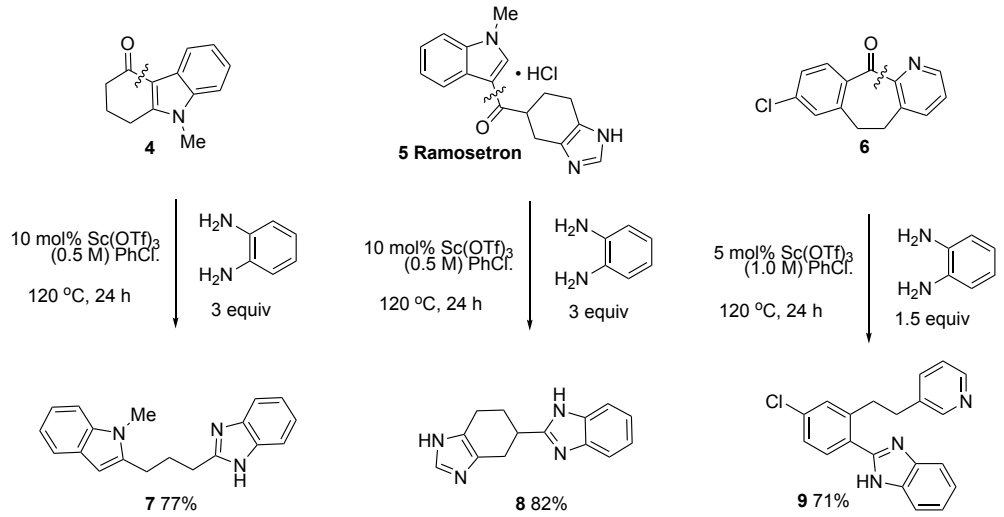
We hypothesize that nucleophilic reagents with solvent content can significantly accelerate the reversible nucleophilic attack process and provide the driving force for dehydration to generate imine intermediates. Alcohol was also serves as a proton source, catalyzing the subsequent cleavage process and completing the reaction. The reduced usage of nucleophilic reagents in this study does not effectively promote the formation of imine intermediates.

Furthermore, the inability to observe imine or imidazoline intermediates in the reaction process despite adjusting the reaction conditions suggests that the Lewis acid catalyst effectively promotes the cleavage process. This rapid cleavage occurs at the moment of imidazoline generation. Consequently, reducing the concentration of imide or imidazoline intermediates within the system facilitates the reversible nucleophilic attack process.

To support these inferences, thermodynamic calculation results from our previous work indicate that the highest reaction barrier of methylimidazole during the cleavage process occurs, while in this study, the highest energy barrier during the initial nucleophilic attack process occurs. This difference in reaction activity between the two reactions is attributed to these factors.

2.7 Applications of this transformation

Scheme 2.10 Applications of C-C Bond Cleavage to Pharmaceutical-Related Compounds



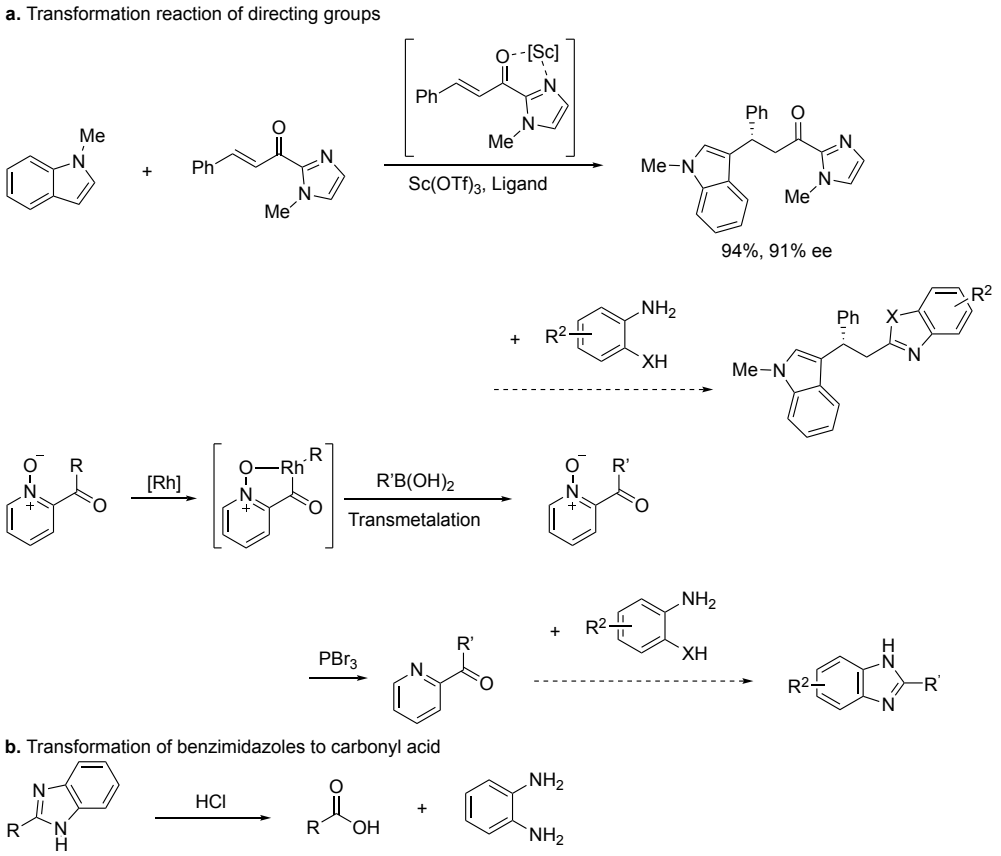
To investigate the application scope of this reaction, we have identified pharmaceutical-related compounds as suitable substrates. By adjusting the reaction conditions, the aforementioned three compounds can be transformed into the desired product with satisfactory yields. Notably, the precursor 9-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one of Ondansetron (**7**) and the precursor 8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one (**8**) with a seven-membered ring structure undergo C–C bond cleavage to give the desired benzimidazole derivative in 71% yield. Furthermore, Ramosetron (**9**), a serotonin 5-HT3 receptor antagonist used for treating nausea and vomiting, exhibited high reactivity. Although the hydrochloride of the compound was directly utilized in the reaction, the desired product was obtained in 90% yield. These findings demonstrate the potential of this reaction to be applied to a wide range of acyl-pyridine and acyl-indole structural compounds found in pharmaceutical compounds or natural products.

2.8 Further possibility for this transformation

Acyl heterocyclic groups are frequently introduced to chemical structures to attain exceptional selectivity, but their removal from the product after the selective reaction is necessary. This process typically entails additional reaction steps and the utilization of toxic methylation reagents, as reported in existing literature. However, our developed

reactions offer a more efficient approach to transforming Acyl heterocyclic compounds into alternative structures (Scheme 2.9.a). In addition, benzimidazole can also generate carboxy acid through simple acid treatment (Scheme 2.9.b), so that it can be modified more flexibly.

Scheme 2.11 The possibility of this transformation in synthetic chemistry

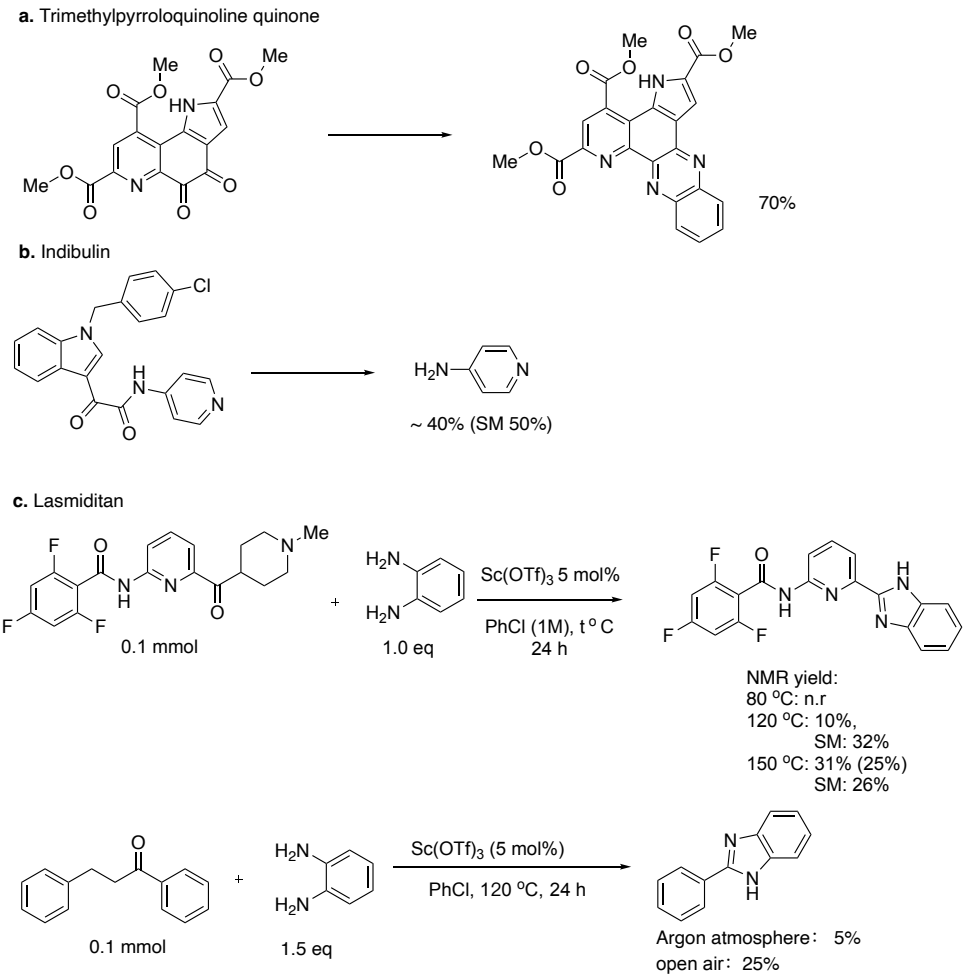


2.9 Medical compounds failed to apply to this transformation.

When **trimethoxyl pyrroloquinoline quinone** (Scheme 2.11.a) is used as a reaction substrate, due to the adjacent dicarbonyl structure, the two amino groups of diamine were dehydrated with the two carbonyl groups leading to the cyclization reaction respectively, and the cleavage reaction could not occur.

When **indibulin** (Scheme 2.11.b) was used as a substrate, we observed that the reaction produced 40% aminopyridine under standard reaction conditions, and more than 50% of the raw materials did not participate in the reaction after 24 hours. It means that the reaction condition gives priority to the cleavage of the amide bond, and the expected C-C bond cleavage reaction cannot occur.

Scheme 2.12 Cases of C(acyl)-C(alkyl) bond cleavage



When using lasmiditan as the substrate (Scheme 2.12.c), the formation of the target compound was not detected. On the contrary, we found that the C-C bond on the aliphatic side was cleavaged so that most of the structure of the substrate in the product was retained. Because the reports of unstrained acyl-aliphatic C-C bond cleavage reactions are mostly concentrated in transition metal catalytic reactions, we think that this reaction strategy may be applied to a wider substrate group.

In previous studies, we have tested the applicability of aliphatic phenyl ketones under optimized conditions. Because the cleavage of C-C bonds between carbonyl phenyls is much more difficult than that of acyl imidazole, so as expected, the target product was not generated, but 25% of the C-C bonds on the other side was cleavaged when the reaction was operated under the air condition, resulting in phenyl-substituted benzimidazole, which brought inspiration to our next topic.

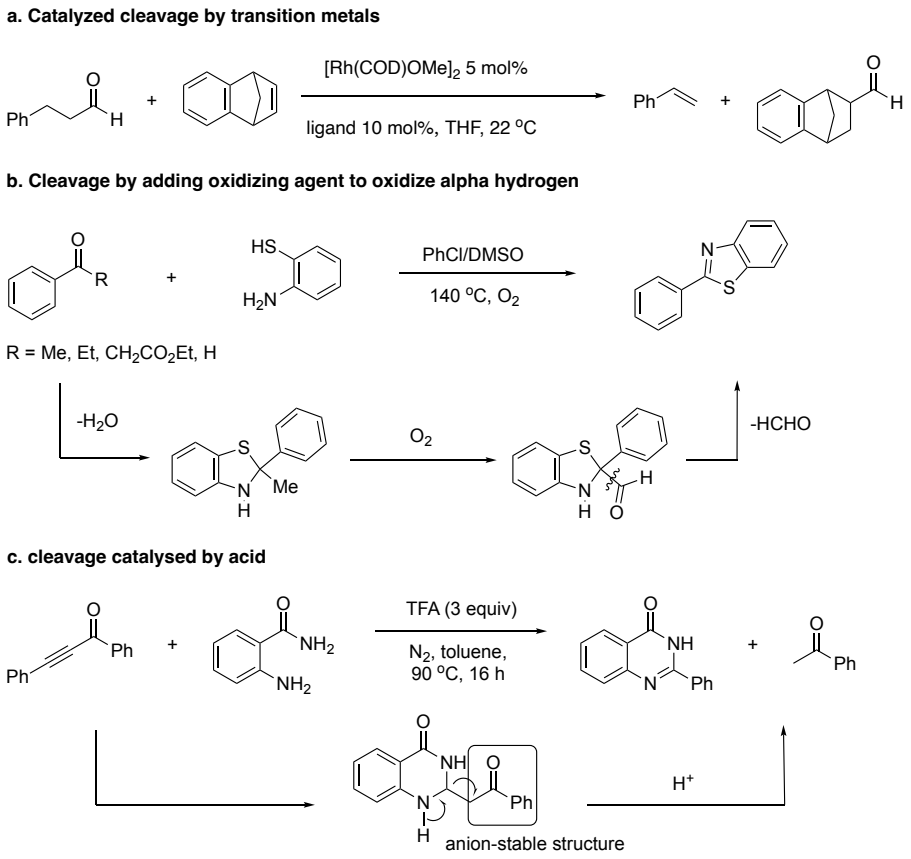
Summary

In conclusion, a novel C-C bond cleavage reaction for building benzimidazole derivatives was developed. The reaction is catalyzed by simple Lewis acid and can be applied to various functionalized 2-acylimidazoles and other acyl-hetero cyclic compounds with a nitrogen atom. In addition, various products could be afforded by utilizing different nucleophiles. Mechanistic studies indicated that the C−C bond cleavage proceeds with the assistance of the imidazolium moiety. We hope that the present findings will promote the future development of C–C bond cleavage which was thought to be difficult without appropriate activating reagents or catalysts and contribute to reactions with 2-acylimidazoles and lead a new way for their post transformations

Chapter 3. Transformation of ketone containing α quaternary carbon to Other Heterocycles via C-C Bond Cleavage

3.1 C-C bond cleavage of aliphatic ketone

Scheme 3.1 Background on C-C bond cleavage of alkyl ketone



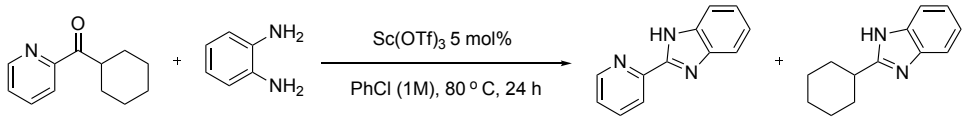
Previously, we discussed the research background and application value of C-C bond cleavage reaction in acyl heterocyclic compounds. Due to the existence of heteroatoms in aromatic rings, C-C bond cleavage is more likely to occur, instead, aromatic ketone or aliphatic ketone without heteroatoms is difficult to cleavage.

The C-C bond cleavage reactions of more extensively reported unstrained aliphatic ketones are generally categorized into three distinct groups: catalyzed cleavage by transition metals such as Rh (Scheme 3.1.a) [32]; cleavage by adding an oxidizing agent to oxidize alpha hydrogen (Scheme 3.1.b)[33]; acid-catalyzed reaction to afford an anion-stable structure as the leaving group (Scheme 3.1.c) [34].

3.2 Our previous work

During our research on the screening of pyridine substrates, we observed that while the alpha position is primary, secondary carbon, aldol condensation is readily accessible, hindering the generation of the anticipated products. Conversely, when the alpha position is tertiary carbon, the substantial steric hindrance impedes the condensation process. In contrast, the oxidation reaction of the alpha position occurs, leading to C-C bond cleavage reaction on C(sp2)-C(sp3) bond.

Scheme 3.2 Chemoselective reaction controled by different atmosphere



0.1 mmol　　1.5 eq

	NMR yield (%)	NMR yield (%)
under Argon	9%	58%
Open air	45%	31%
under Argon (in glove box)	3%	97% (isolated 93%)

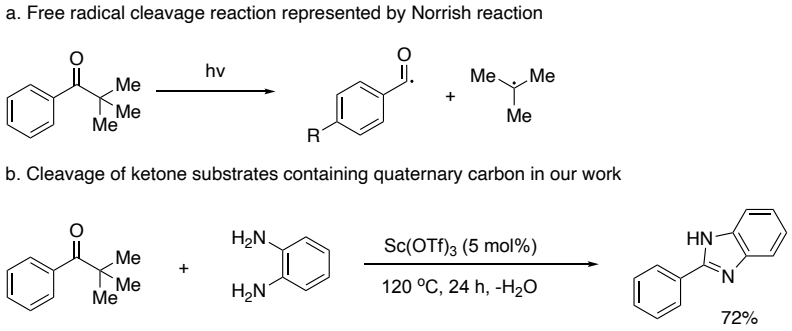
Upon initial testing of the applicability of cyclohexylpyridine, we achieved an high conversion rate exceeding 50%. However, we also observed that approximately 10% of the substrates exhibited C-C bond cleavage on the reverse side, resulting in the replacement of pyridine with acylbenzimidazole group. Notably, when we exposed the reaction system to air, the proportion of generated C(sp2)-C(sp3) bond cleavage product increased significantly, leading to a yield comparable to that of the C(sp2)-C(sp2) product. We posit that the oxygen present in the air likely activates the C-C bond by oxidizing the α hydrogen of the carbonyl group, thereby completing the generated C(sp2)-C(sp3) bond cleavage. Although argon replacement was performed in the initial test, a small amount of air still entered the system, resulting in a minor degree of oxidation reaction. Subsequently, when we conducted the reaction inside a glove box, we successfully increased the yield of this reaction to 90%, thereby validating our hypothesis.

We discovered a selective reaction capable of controlling the cleavage of C-C bonds solely by altering the gas atmosphere. However, we promptly identified a similar oxidation cleavage reaction reported by Deng and his research group in 2012 (Scheme

3.1.b)[33]. This condition has been widely utilized in various oxidation C-C cleavage reactions. Although only a limited number of substrates were tested, and there was no information regarding the participation of branched-chain substrates in the reaction, we temporarily suspended our in-depth investigation of the relevant content.

According to this research and related derivative reports, we found that because the oxidized C-C bond cleavage reaction requires the existence of α hydrogen of the carbonyl group, the intermediate of aldehyde or ketone generated by oxidizing adjacent hydrogen and the cleavage process of C-C bond is finally completed. Therefore, most of these reactions can only be based on alpha-placed or single-substituted compounds. The reaction is usually difficult when the alpha position is tertiary carbon or quaternary carbon. Driven by curiosity, we tried tert-butyl-substituted phenyl ketone as a substrate and were surprised to find that the substrate had the same level of reaction activity as the cleavage reaction of acyl-imidazole substrates. Since the cleavage reaction of quaternary carbon as the substrate is rarely reported, so we began to study the reaction principle and substrate applicability of such reactions.

Scheme 3.3 Background on C-C bond cleavage of ketone containing α quaternary carbon



As we known, the C-C bond cleavage reaction of those kind of substrate is basically only reported going through Norrish reaction using photocatalysis (Scheme 3.3.a) [35,36]. Because there is no alpha hydrogen, it cannot be oxidized by the oxidizer to achieve cleavage, and considering the steric hindrance of the quaternary carbon, it is bound to affect the attack process of the carbonyl group.

Considering the previous strategy for the cleavage of aliphatic ketones, we propose that benzimidazoline intermediates will still be formed under the catalytic conditions of Lewis acid when the more challenging tert-butyl ketone serves as the substrate. If the

C-C bond cleavage can be successfully achieved, tert-butyl carbon radicals are more likely to be stable compared to the possible tert-butyl carbon anions. The reaction will proceed in a manner similar to the Norrish reaction, ultimately leading to the formation of benzimidazole as the target product. Consequently, the primary focus of my research is on the development of a C-C bond cleavage reaction for aliphatic ketones.

Reference

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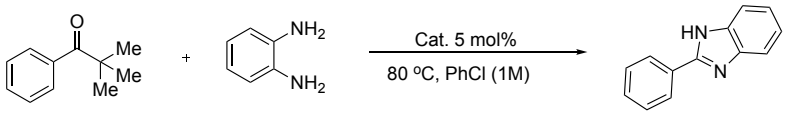
3.3 Catalyst screening

In the initial study, we optimized the reaction conditions of the reaction and tested various Lewis acids and Bronsted acids. We discovered that $Cu(OTf)_2$, a Lewis acid with high catalytic activity, achieved an 88% conversion rate at a reaction temperature of 100 degrees. PPTS, a Bronsted acid, exhibited comparable catalytic activity. However, highly acidic Bronsted acids, such as TfOH, did not demonstrate particularly prominent catalytic activity.

Subsequently, we observed that ammonium salt catalysts exhibited more pronounced catalytic activity. The reaction time of 24 hours at an 80-degree reaction temperature was sufficient to transform the substrate and obtain the desired cleavage reaction product. Consequently, we will utilize NH_4OTf as the optimal catalyst for the subsequent research.

Table 3.1 Catalyst optimization

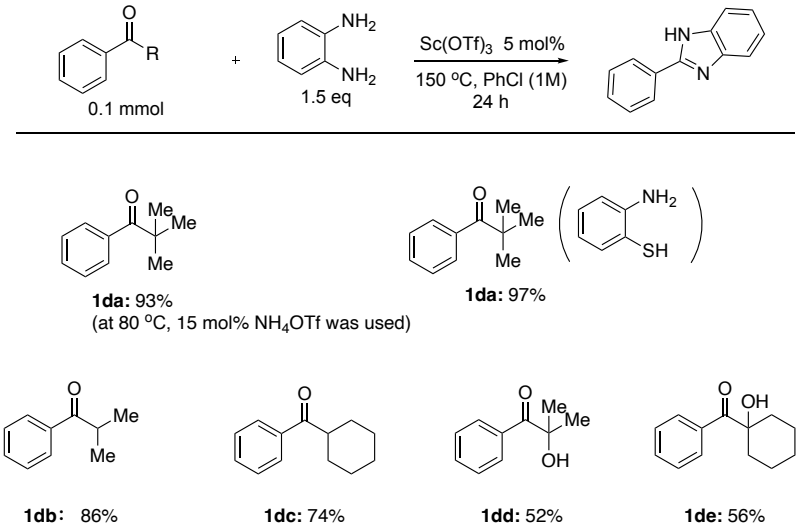


0.1 mmol 1.5 eq

entry	Cat.	temp ºC	TM % (6h)	TM % (24h)
1	$Mg(OTf)_2$	120 ºC	22%	-
2	**$Sc(OTf)_3$**	**120 ºC**	**55%**	**82%**
3	AgOTf	120 ºC	57%	-
4	$Ni(OTf)_2$	120 ºC	11%	-
5	$Zn(OTf)_2$	120 ºC	31%	-
6	$In(OTf)_3$	120 ºC	33%	-
7	**$Cu(OTf)_2$**	**120 ºC**	**70%**	**94%**
8	$Sc(OTf)_3$	80 ºC	-	41%
9	TfOH (15 mol%)	80 ºC	-	40%
10	PPTS (15 mol%)	80 ºC	-	76% (isolated 73%)
11	**NH_4OTf (15 mol%)**	**80 ºC**	**-**	**99%**
12	**CF_3COONH_4 (15 mol%)**	**80 ºC**	**-**	**93% (isolated 82%)**
13	$FeCl_3$	80 ºC	-	15%
14	$Cu(NO_3)_2 \cdot 3H_2O$	80 ºC	-	45%
15	$CuCl_2$	80 ºC	-	5%
16	CuCl	80 ºC	-	5%
17	$Cu(OAc)_2$	80 ºC	-	4%

3.4 Initial substrate scope

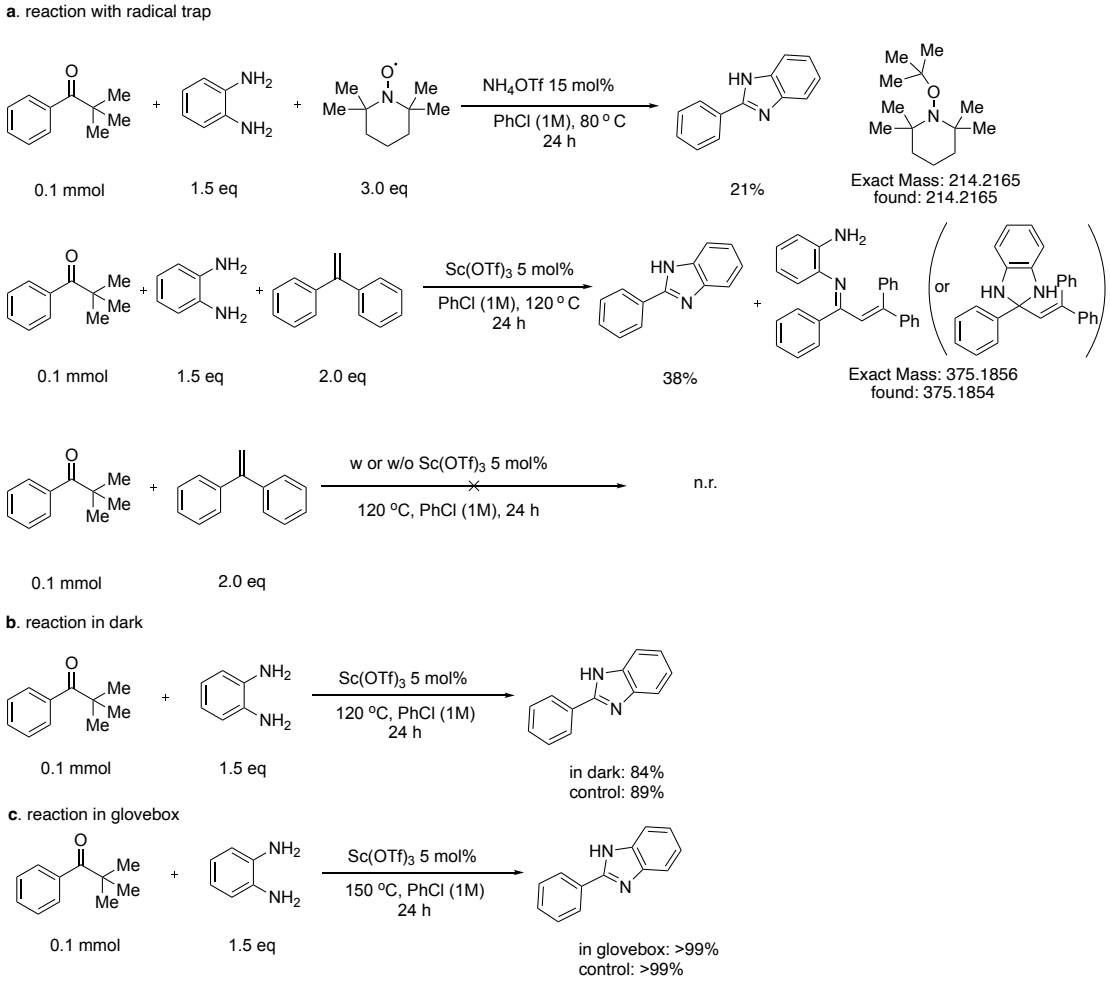
Table 3.2 Substrate scope



As an initial study, we also selected some substrates for screening. We discovered that in addition to quaternary carbon, tertiary carbon can also successfully participate in the reaction and yield the expected cleavage products. However, due to the low molecular weight of the cleavaged quaternary carbon fragment, we were unable to obtain the structural information of the product. Furthermore, we explored the possibility of other nucleophilic reagents being applied to the reaction. Mercaptonoaniline successfully completed the cleavage task, resulting in the benzothiazole product, suggesting that the reaction possesses potential product diversity.

3.5 Mechanism study

Scheme 3.5. Mechanism study



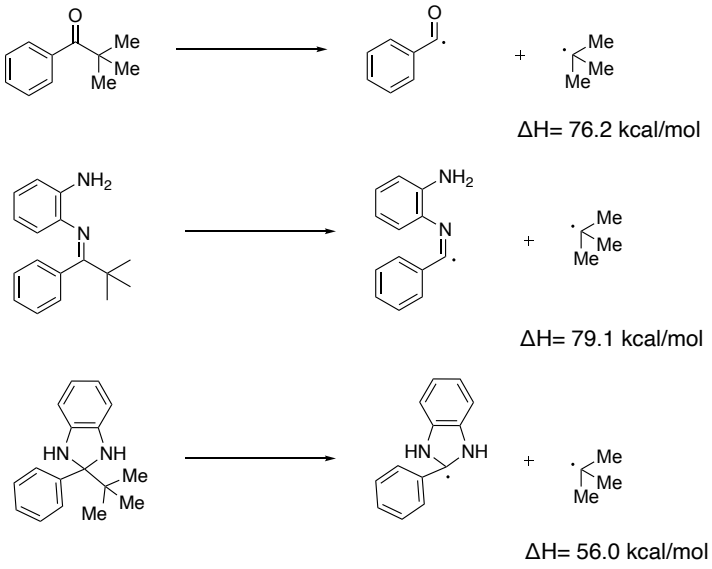
To gain insights into the reaction mechanism, several control experiments were conducted. In the case of using the radical scavenger TEMPO (Scheme 3.5.a), we observed a decline in yield and also detected the products generated by the captured free radicals. Furthermore, when DPE was utilized (Scheme 3.5.b), the product generated by the capture of intermediate free radicals could also be confirmed, and the yield decline was also substantiated. When the reaction is placed in the glove box, it can also exhibit the same reaction activity, demonstrating that the reaction can be completed without the involvement of external oxidants.

Under conditions devoid of nucleophiles and Lewis acids, the reaction did not proceed under these conditions, and the products generated by the capture of free radical transition states were not observed. Based on these findings, we posit that this reaction bears similarities to previous studies. Diamine and the carbonyl group undergo

dehydration, followed by the formation of imine or benzimidazoline. Subsequently, the C-C bond undergoes cleavage via the free radical pathway, culminating in the generation of benzimidazole as the product.

To ascertain whether the reaction conforms to the traditional Norrish mechanism, we additionally tested this reaction in a dark environment. Remarkably, almost identical yields were obtained compared to standard conditions, indicating that this reaction can proceed without light excitation.

Scheme 3.6. calculation of Bond Dissociation Energy



DFT calculations were performed at the level of M06-2X/6-311+G(d,p)/PCM(PhCl)//B3LYP/6-31+G(d,p).

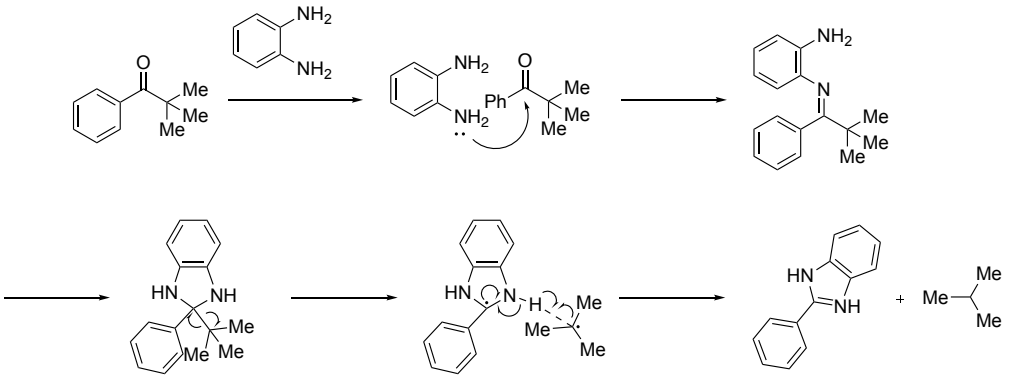
By calculating the carbon-carbon bond dissociation energy of the intermediate, we discovered that while the carbon-carbon bond is directly cleavage from the starting material or the imine intermediate, the generation of free radicals still necessitates high energy. However, when the imidazoline intermediate undergoes a free radical cleavage process, the required carbon-carbon bond dissociation energy diminishes to approximately 56.0 kcal/mol (Scheme 3.6).

3.6 Proposed Mechanism

Based on the aforementioned results, we postulated a potential reaction mechanism (Scheme 3.7). The diamine and the carbonyl group undergo dehydration to form a ketimine intermediate. Subsequently, this intermediate readily transforms into a benzimidazoline intermediate, followed by C–C bond cleavage, generating a

benzimidazoline radical and an isopropyl radical. Finally, these free radicals combine to yield the corresponding benzimidazole.

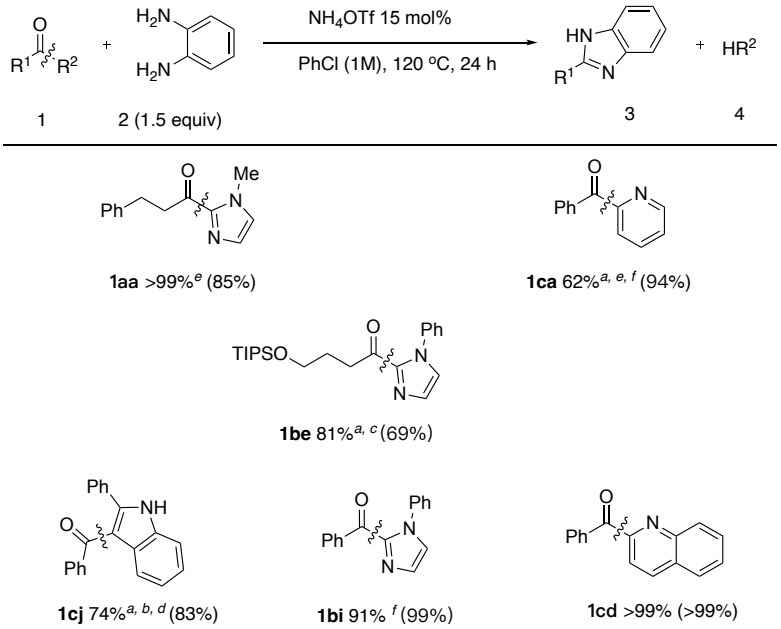
Scheme 3.7 Proposed mechanism



3.7 Activity Comparison with Two Catalysts

According to our previous work, we had already observed the excellent reactivity of NH_4OTf in the cleavage reaction, which we had not tested in Chapter 1. Therefore, we decided to explore the potential of NH_4OTf in catalyzing the cleavage of acyl-hetero aromatic compounds. Our findings revealed that the reaction activity of NH_4OTf was significantly higher compared to the Sc (III) catalyst for the model substrate. However, the improvement in yield was not evident for benzoyl substrates. Notably, the isolation yield for pyridine substrates (**1ca**) experienced a substantial decline, dropping to 62%.

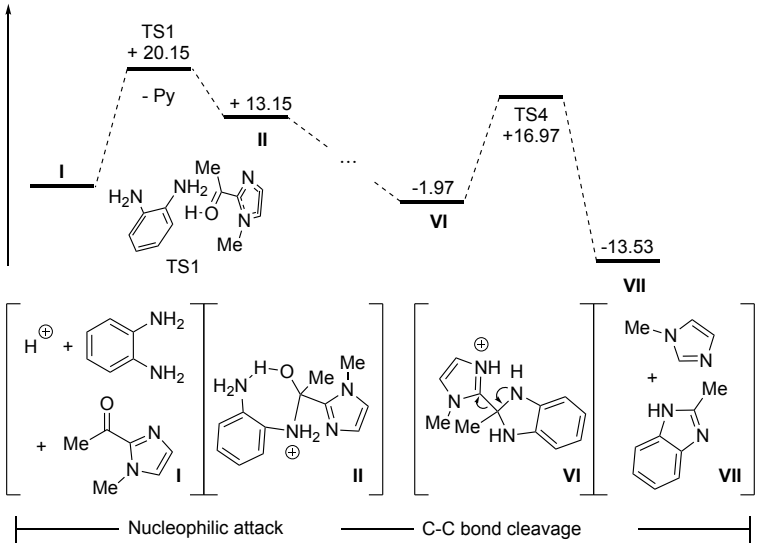
Table 3.3 Activity comparison with two catalysts



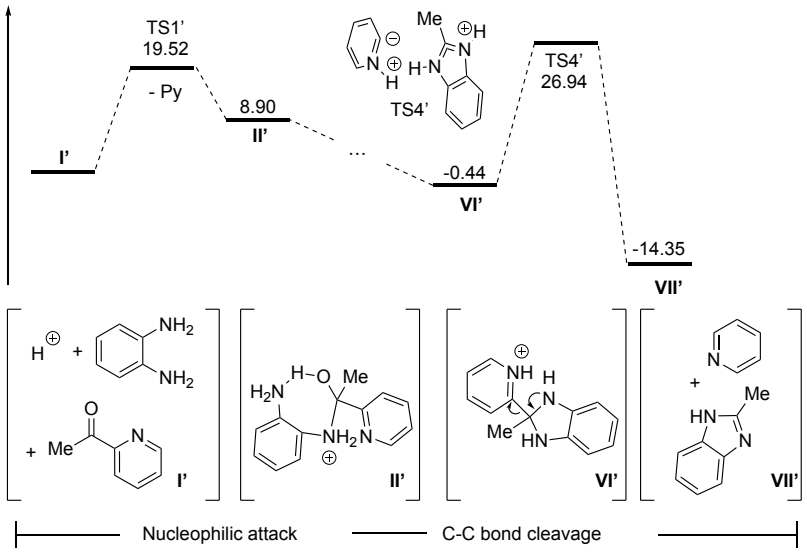
[a] isolation yields. [b] At 150 °C. [c] At 80 °C. [d] 2.0 equiv of o-phenylenediamine was used. [e] 6 hours. [f] At 100 °C .

Scheme 3.8 DFT calculations

a. Acyl imidazole substrates



b. Acyl pyridine substrate

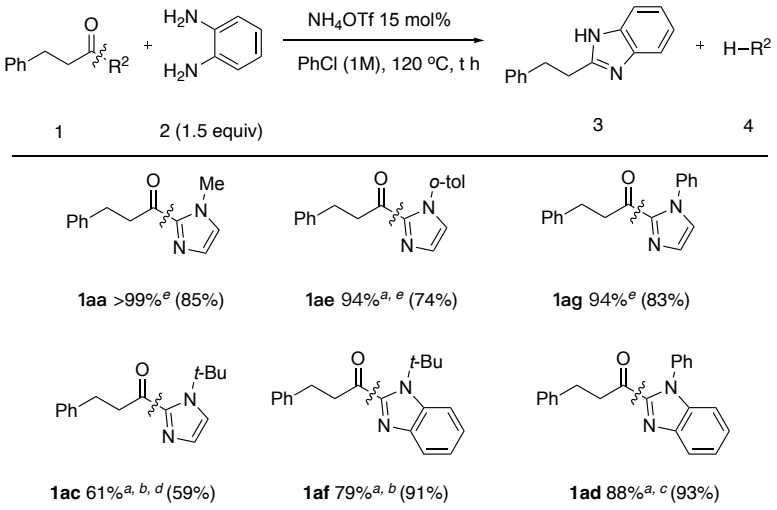


One potential explanation for the observed reactivity differences between the two substrates is the varying activation energy of the C-C bond cleavage step. The ability of Sc_3^+ to stabilize the transition state or the carbene structure generated from this cleavage step of the pyridine substrate may be higher compared to NH_4^+.

Based on the aforementioned results, we re-tested the substrate general under the condition of ammonium salt catalysis. The outcomes were consistent with our expectations, and the yield exhibited a slight increase. However, in the case of N-tert-butyl imidazole or benzimidazole as the substrate, there was no anticipated enhancement in catalytic activity. This observation aligns with the previously discussed

reasons. Although no thermodynamic calculations have been performed, a previous paper provided a calculation suggesting that the cleavage step of the C-C bond in the substrate of tert-butyl substitution is the rate-determining step, which can serve as a reference to support the theoretical framework.

Table 3.4 Reaction activities in alkyl substituted substrates

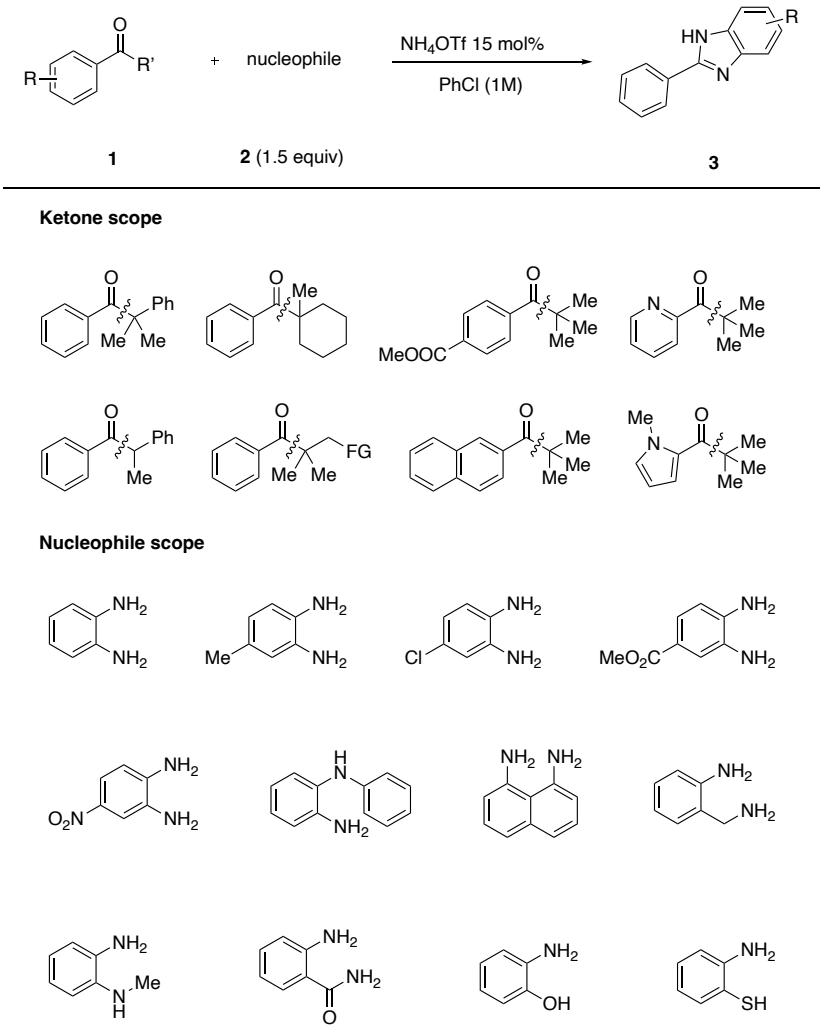


[a] isolation yields. [b] At 150 °C. [c] At 80 °C. [d] 2.0 equiv of o-phenylenediamine was used. [e] 6 hours.

3.8 Further plan for this research

We expect that the substrate of the reaction can be further expanded, and the phenyl part can be replaced with other hydrocarbon aromatic rings such as phenyl and naphthalene. Other heterocyclic substrates are also expected to be applied to the reaction.

Table 3.5 Further plan

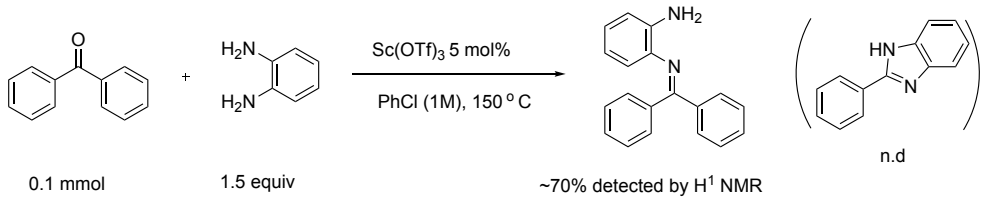


At the same time, the reaction can also enrich the structure of the product by using a variety of nucleophilic reagents, and a variety of nucleophilic reagents are expected to be applied to the reaction.

Unfortunately, the relevant application of this reaction has not been discovered, and we have not yet been able to find the advantages of synthesizing aromatic-substituted heterocyclic compounds through tert-butyl ketone. In the follow-up research work, we hope to find the advantages of this reaction in synthetic applications.

We tried to apply diphenyl ketones to the reaction as well. Unfortunately, we did not get the desired target product. A large amount of condensation intermediates was observed, but there was no sign of the product generated from C-C bond cleavage. The results show that neither proton acid nor Lewis acid can catalyze the C-C bond cleavage process of this kind of substrate. Because the energy required for phenyl radicals or phenyl ions generated by the cleavage step is too high, the energy of the transition state cannot be stabilized by the acid catalyst. It might happen when we add catalysts that promote phenyl radicals or phenyl anions. We hope we can figure out the problem to successfully broaden our C-C bond cleavage reaction to diphenyl ketone substrates.

Scheme 3.9 Failed to applied on benzophenone



Summary

This part proposed a new C-C bond cleavage reaction path of tert-butyl ketone, which is different from the classic Norrish reaction. Although the reaction is likely to pass through the free radical reaction path, it has a more convenient reaction method than the Norrish reaction without light excitation. Under the condition of ammonium salt catalysis, the condensation reaction of diamine compounds with the carbon group is carried out, and the C-C bond cleavage is completed to generate benzimidazole compounds. The specific reaction mechanism of this reaction is valuable for further exploration. In addition, further condition optimization and substrate applicability research are also worth further discussion.

Support information

1. General Experimental Details

All reactions were performed in flame-dried or oven-dried glassware under an argon atmosphere unless otherwise noted. Reagents and catalysts were obtained from commercial sources and used as received unless otherwise stated. Solvents were purchased from commercial sources and dried over molecular sieves before use. Flash silica gel column chromatography was performed with Kanto Chemical silica gel 60N (spherical neutral, particle size 40–50 μm).

Nuclear magnetic resonance (NMR) spectra were acquired on a 500 MHz Bruker Avance III spectrometer. ^{1}H and $^{13}C\{^{1}H\}$ NMR chemical shifts are reported in ppm and referenced to tetramethylsilane or residual solvent peaks as internal standards (for $CDCl_3$, tetramethylsilane 0 ppm for ^{1}H and $CDCl_3$ 77.0 ppm for $^{13}C\{^{1}H\}$). ^{19}F NMR chemical shifts are reported in ppm relative to α,α,α-trifluorotoluene at −62.78 ppm as external reference. Coupling constants are reported in hertz. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Infrared (IR) spectra were recorded with Shimadzu IRAffinity-S1 with Quest ATR diamond accessory. High-resolution mass spectroscopy (HRMS) was obtained with Bruker MicrOTOF II. High performance liquid chromatography (HPLC) was performed with JASCO PU-2089plus pump and UV-2075plus detector. Chiral HPLC analysis was performed with DAICEL CHIRALCEL OD-3 and CHIRALPAK AD-3 column series. Optical rotation was measured with JASCO P2200 polarimeter. Melting points were measured by SANSYO Melting Point Apparatus SMP-500 and are uncorrected.

2. Synthesis of 2-Acylimidazoles and Its Derivatives

All the 2-acylimidazoles and its derivatives were synthesized from the corresponding carboxylic acid derivatives and *N*-substituted (benz)imidazoles **4** according to the reported procedure unless otherwise noted. The starting carboxylic acid derivatives and imidazoles were either obtained from the commercial suppliers or prepared according to the reported procedure.

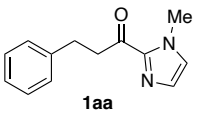
General Procedure for the Synthesis of 2-Acylimidazoles

Method A. To a solution of *N*-substituted (benz)imidazole **4** (1.0 equiv) in dry THF (0.50 M) at −78 °C under argon atmosphere was added dropwise *n*BuLi (2.6 M in *n*-hexane, 1.1 equiv). The cooling bath was removed, and the reaction mixture was stirred at room temperature for 30 min. Then the mixture was again cooled to −78 °C, and the corresponding ester or Weinreb amide (1.1−1.5 equiv) was added. The reaction mixture was stirred at −78 °C for 6−12 h before being quenched with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with EtOAc three times, and the combined organic layers were dried over Na_2SO_4, filtered, and evaporated. The crude mixture was purified by flash silica gel column chromatography to give product.

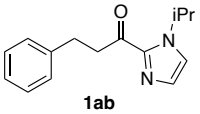
Method B. To a stirred solution of *N*-substituted (benz)imidazole (1.0 equiv) in CH_3CN (0.25 M) at 0 °C was added dropwise acyl chloride (1.5 equiv), followed by the addition of Et_3N (1.5 equiv). The mixture was stirred at room temperature for 12 h, poured into H_2O, and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The crude mixture was purified by flash silica gel column chromatography to give the product.

Detailed Procedure for the Preparation of 2-Acylimidazoles and Its Derivatives

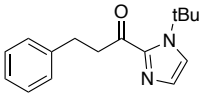
The following 2-acylimidazoles and its derivatives were prepared according to Method A. Note that **1aa**, [14] **1ab**, [27] **1ac**, [27]**1ad**,[27] **1ae**,[37] **1af**,[27] and **1ag**[38] are known compounds.



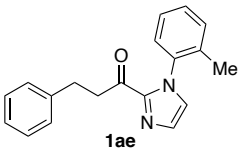
1aa



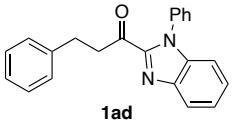
1ab



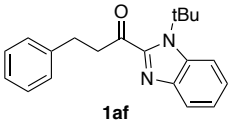
1ac



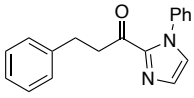
1ae



1ad



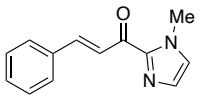
1af



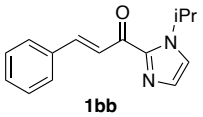
1ag

Detailed Procedure for the Preparation of 2-Acylimidazoles

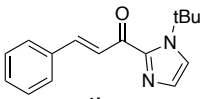
The following 2-acylimidazoles **1** were prepared according to the Method A or B. Note that **1ba**,[27] **1bb**,[27] **1bc**,[27] **1bd**,[14] **1bg**,[27] **1bh**,[39] **1bj**,[39] **1bi**,[39] **1bk**[27] and **1bl**[14] are known compounds.



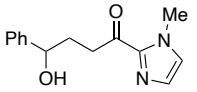
1ba



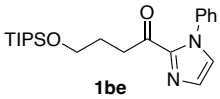
1bb



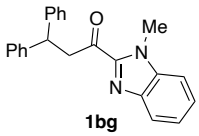
1bc



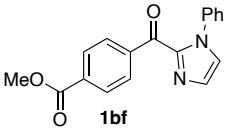
1bd



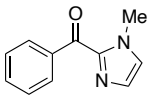
1be



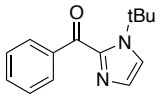
1bg



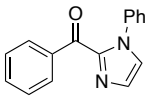
1bf



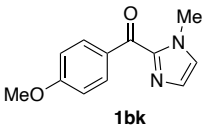
1bh



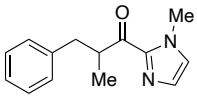
1bj



1bi

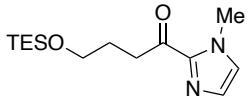


1bk



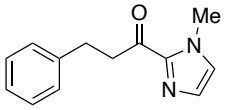
1bl

Detailed Procedure for the Preparation of 2-Acylimidazoles



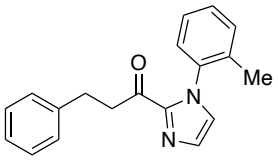
1-(1-methyl-1*H*-imidazol-2-yl)-4-((triethylsilyl)oxy)butan-1-one (1a)[40]: To a solution of 1-methylimidazole (5.0 mmol, 1.0 equiv) in dry THF (0.70 M) at −78 °C under an argon atmosphere was slowly added n-BuLi solution in n-hexane (2.6 M, 5.5 mmol, 1.1 equiv), and the reaction mixture was stirred at room temperature for 0.5 h. The mixture was cooled to −78 °C before adding γ-butyrolactone (6.5 mmol, 1.3 equiv). The reaction mixture was stirred at −78 °C for 5 h and quenched with 1 M aqueous NH_4Cl and saturated aqueous $NaHCO_3$ solutions. The resulting mixture was extracted with CH_2Cl_2, and the organic layer was dried over Na_2SO_4. After removal of the solvent under reduced pressure, to the crude mixture at 0 °C under argon atmosphere were added $NaHSO_4$ (2.2 mg, 0.15 mmol, 0.03 equiv), dry MeCN (0.20 M), triethylamine (5.0 mmol, 1.0 equiv) and TESCl (5.0 mmol, 1.0 equiv). The cooling bath was removed and the reaction mixture was stirred for 3 h at room temperature. After removal of the solvent under reduced pressure, water was added and the resulting mixture was extracted with ethyl acetate. The residue was purified by flash silica gel column chromatography using hexane/ EtOAc = 2/1 as eluent to give 1ua as colorless liquid (506.4 mg, 67% yield in 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12 (s, 1H), 7.00 (s, 1H), 4.00 (s, 3H), 3.69 (t, J = 6.5 Hz, 2H), 3.19 (t, J = 7.0 Hz, 2H), 1.98−1.92 (m, 2H), 0.94 (t, J = 8.0 Hz, 9H), 0.58 (q, J = 8.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.0, 143.1, 128.9, 126.7, 62.2, 36.2, 35.6, 27.4, 6.8, 4.4.



1-(1-methyl-1*H*-imidazol-2-yl)-3-phenylpropan-1-one (1aa)： The reaction was performed according to Method A using ethyl 3-phenylpropanoate (5.0 mmol, 1.0 equiv) and N- methylimidazole (5.5 mmol, 1.1 equiv) for 6 h, and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give 1aa as colorless oil (852 mg, 80% yield).

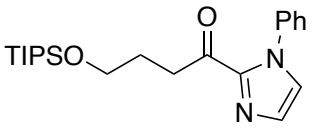
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.26 (m, 4H), δ 7.18-7.16 (m, 1H), δ 7.11 (s, 1H), δ 6.99 (s, 1H), δ 3.97 (s, 3H), δ 3.47 (t, *J* = 7.5 Hz, 2H), δ 3.04 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.0, 142.9, 141.1, 129.0, 128.5, 128.4, 126.9, 126.0, 40.4, 36.1, 30.0.



3-phenyl-1-(1-(*o*-tolyl)-1*H*-imidazol-2-yl)propan-1-one (1ae)[41]**:** To a solution of N-(o-tolyl)-imidazole (2 mmol, 1.0 equiv) in anhydrous THF (0.4 M) at -78 ^{o}C was added n-BuLi (1.1 equiv, 2.5 M in hexane) dropwise. The reaction mixture was stirred at -78 ^{o}C for 30 min, and then stirred at room temperature for another 30 min. The corresponding ester (1.2 equiv in THF) was added dropwise to the flask after the reaction was cooled back down to -78 ^{o}C. The reaction was allowed to warm to room temperature slowly and stirred overnight. The reaction was quenched with AcOH (6.0 equiv), diluted with EtOAc. The organic phase was washed with aqueous saturated $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give 1ae as colorless oil (418 mg 72%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (t, *J* = 7.4 Hz, 1H), 7.32 – 7.20 (m, 7H), 7.16 (t, *J* = 7.0 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 1H), 7.06 (s, 1H), 3.54–3.41 (m, 2H), 2.97 (t, *J* = 7.8 Hz, 2H), 1.94 (s,6H). ^{13}CNMR (125 MHz, $CDCl_3$) δ 190.4, 143.3, 141.0, 137.9, 134.5, 130.7, 129.8, 129.1, 128.45, 128.36, 126.6, 126.4, 126.3, 126.0, 40.4, 30.0, 17.1.

1-(1-Phenyl-1*H*-imidazol-2-yl)-4-((triisopropylsilyl)oxy)butan-1-one (1be)

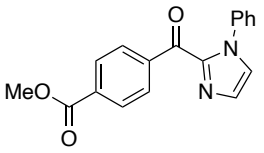


To a solution of 1-phenylimidazole (0.63 mL, 5.0 mmol, 1.0 equiv) in dry THF (0.70 M) at −78 °C under an argon atmosphere was slowly added *n*-BuLi solution in *n*-hexane (2.1 mL, 2.6 M, 5.5 mmol, 1.1 equiv), and the reaction mixture was stirred at room

temperature for 0.5 h. The mixture was cooled to −78 °C before adding γ-butyrolactone (0.5 mL, 6.5 mmol, 1.3 equiv). The reaction mixture was stirred at −78 °C for 5 h and quenched with 1 M aqueous NH_4Cl and saturated aqueous $NaHCO_3$ solutions. The resulting mixture was extracted with CH_2Cl_2, and the organic layer was dried over Na_2SO_4. After removal of the solvent under reduced pressure, to the crude mixture at 0 °C under argon atmosphere were added dry MeCN (0.20 M), triethylamine (0.7 mL, 5.0 mmol, 1.0 equiv), and TIPSCl (1.6 mL, 7.5 mmol, 1.5 equiv). The cooling bath was removed, and the reaction mixture was stirred for 3 h at room temperature. After removal of the solvent under reduced pressure, water was added and the resulting mixture was extracted with ethyl acetate. The residue was purified by flash silica gel column chromatography using hexane/ EtOAc = 2/1 as eluent to give **1be** as white solid (1198.1 mg, 62% yield in 2 steps).

mp. 38–39 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 2.0, 4.0 Hz, 3H), 7.28–7.26 (m, 3H), 7.16 (s, 1H), 3.74 (t, *J* = 6.5 Hz, 2H), 3.25 (t, *J* = 7.5 Hz, 2H), 1.89 (t, *J* = 7.0 Hz, 2H), 1.16–1.01 (m, 21H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 191.4, 143.1, 138.5, 129.4, 128.9, 128.7, 126.9, 125.9, 62.6, 35.7, 27.2, 18.0, 12.0. IR (neat) 2941, 2864, 2359, 2340, 1685, 1406, 1101, 881, 760, 688 cm^{-1}. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{22}H_{35}N_2O_2Si^+$ $[M + H]^+$ 387.2462, found 387.2462.

Methyl 4-(1-phenyl-1*H*-imidazole-2-carbonyl)benzoate (1bf)

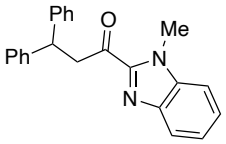


The reaction was performed according to Method B using methyl 4-(chlorocarbonyl)benzoate (1489.5 mg, 7.5 mmol, 1.5 equiv) and *N*-phenylimidazole (0.63 mL, 5.0 mmol, 1.0 equiv), and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 3/1 as eluent to give 1bf as a white solid (842.4 mg, 55% yield).

mp. 105–106 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 2.0, 4.5 Hz, 2H), 8.14 (dd, *J* = 2.0, 6.0 Hz, 2H), 7.49 (dd, *J* = 2.0, 5.0 Hz, 3H), 7.38–7.26 (m, 4H), 3.95 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 182.1, 166.4, 142.9, 140.3, 138.4, 133.6, 130.8, 130.0, 129.3, 129.2, 128.8, 127.0, 125.7, 52.4. IR (neat) 2357, 2341, 1718, 16553,

1501, 1410, 1277, 1107, 930, 899, 826, 762, 744, 692 cm^{-1}. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{18}H_{15}O_3N_2^+$ $[M + H]^+$ 307.1077, found 307.1077.

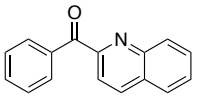
1-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)-3,3-diphenylpropan-1-one (1bg):



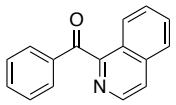
The reaction was performed according to Method A using Weinreb amide (2.2 mmol, 1.1 equiv) and N- methylbenzimidazole (2.0 mmol, 1.0 equiv) for 12 h, and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 10/1 as eluent to give 1bg as a white solid (308 mg, 45% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.45−7.35 (m, 7H), 7.34−7.24 (m, 4H), 7.17−7.14 (m, 2H), 4.85 (t, *J* = 7.8 Hz, 1H), 4.13 (d, *J* = 8.0 Hz, 2H), 4.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.7, 146.2, 144.0, 141.7, 137.0, 128.7, 128.0, 126.5, 126.1, 123.9, 122.0, 110.7, 46.1, 45.7, 32.3.

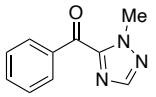
Detailed Procedure for the Preparation of 2-Acylheterocyclic compounds



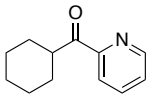
1cd



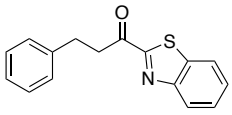
1ce



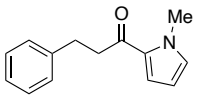
1cf



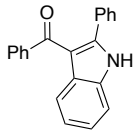
1ci



1cg



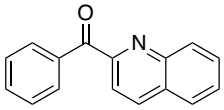
1ch



1cj

The following 2-acylheterocyclic compounds 1ca, 1cb, 1cc are commercially available, **1cd**,[42] **1ce**,[43] **1cf**,[44] **1ci**,[45] **1cg**,[46] **1ch**[47] and **1cj**[48] are known compounds.

phenyl(quinolin-2-yl)methanone (1cd)[49]:

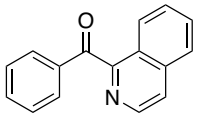


Phenylmagnesium bromide (1 mmol, 2.0 equiv) was added to a solution of the appropriate carbonitrile (1 mmol, 1.0 equiv) in Et_2O (0.4 M) at 0 °C. When TLC showed no more starting material, the reaction was quenched by addition of a solution of NH_4Cl. The organic layer was separated and extracted twice with CH_2Cl_2. After evaporation, the organic layer was redissolved in Et_2O and 1 M HCl was added. After 20 min, the organic layer was separated; the

aqueous layer basified with saturated $NaHCO_3$ and then extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography using hexane/EtOAc = 6/1 to give 1cd as light yellow solid (173 mg, 74%)

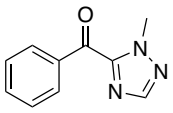
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.5 Hz, 1H), 8.24 (d, *J* = 7.5 Hz, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 8.5 Hz, 1H), 7.79 (t, *J* = 8.5 Hz, 1H), 7.68–7.61 (m, 2H), 7.52 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.8, 154.7, 146.8, 137.1, 136.2, 133.1, 131.5, 130.6, 130.1, 128.9, 128.4, 128.2, 127.6, 120.8.

isoquinolin-1-yl(phenyl)methanone (1ce)[50]:



In a dried schlenk tube, isoquinoline (1.0 mmol, 1 equiv), aldehydes (5.0 mmol, 5 equiv), TBHP in decane (2.0 mmol, 2 equiv) and TFA (1.5 mmol, 1.5 equiv) were stirred in 2.0 mL ethyl acetate for 24 hours at room temperature under an nitrogen atmosphere irradiated by blue LEDs, and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 5/1 as eluent to give 1ce as yellow solid (194 mg, 83% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.60 (d, *J* = 5.5 Hz, 1H), 8.22 (d, *J* = 1.0 Hz, 1H), 8.21-7.91 (m, 3H), 7.81 (d, *J* = 5.5 Hz, 1H), 7.76-7.72 (m, 1H), 7.64-7.60 (m, 2H), 7.47 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.8, 156.5, 141.2, 136.7, 136.6, 133.7, 130.76, 130.75, 128.5, 128.3, 127.3, 127.1, 126.4, 126.2, 122.6.

(1- methyl-1*H*-1,2,4-triazol-5-yl)(phenyl)methanone (1cf)[51]:



(2- A solution of n-butyllithium in hexane (6.0 mmol, 1.2 equiv) was added under argon atmosphere at 0 °C to a solution of 1-methyl-1H-1,2,4-triazole (5.0 mmol, 1.0 equiv) in THF(0.25 M). The mixture was stirred for 15 min, then *N*-methoxy-*N*-methylbenzamide (6.0 mmol, 1.2 equiv) was added and the whole was stirred for 30 min. The product was extracted by addition of water and CH_2Cl_2 to the reaction mixture and the organic layer was evaporated to give an oily residue, and it was purified by flash silica gel column chromatography using hexane/EtOAc = 3/2 as eluent to give 1cf as yellow solid (739 mg, 79% yield). **1**H NMR

(500 MHz, $CDCl_3$): δ 8.36-8.34 (m, 2H), 8.02 (s, 1H), 7.67-7.63 (m, 1H), 7.54-7.51 (m, 2H), 4.27 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 183.3, 149.9, 149.2, 135.8, 134.1, 130.9, 128.5, 38.8.

3. Initial Screening of the Reaction Conditions

General Procedure for Initial Screening of the Catalysts

To a 4 mL vial equipped with a Teflon-lined screw cap and a magnetic stir bar were added 2-acylimidazole **1** (21.4 mg, 0.10 mmol), catalyst (0.005 mmol, 5 mol %), 2-aminoaniline (16.2 mg, 0.15 mmol) and solvent (0.40 mL, 0.25 M) under an argon atmosphere. After the cap was tightly closed, the mixture was stirred at 120 °C for 6 h on a hot plate magnetic stirrer using an aluminum block. After cooling to room temperature, the yield of **3** was determined by ^1H NMR analysis of the crude mixture.

4. Direct C–C Bond Cleavage of Various Unactivated 2-Acylimidazoles and related azaarenes

General procedure for transformation of unactivated 2-acylimidazoles and related azaarenes to other heterocycles via C–C Bond Cleavage.

To a 4 mL vial equipped with a magnetic stirrer bar was added scandium(III) trifluoromethanesulfonate (2.46 mg, 0.0050 mmol, 5 mol %). and the vial was dried under vacuum using a heat gun. After cooling to room temperature, to the vial were added 2-acylimidazoles or other related azaarenes (0.10 mmol), diamine (0.15 mmol, 1.5 equiv) and PhCl (0.10 mL, 1.0 M) under an argon atmosphere. After the cap was tightly sealed, the mixture was stirred at the indicated temperature for indicated time on a hot plate magnetic stirrer. After cooling to room temperature, the solvent was removed, and the crude mixture was directly purified by flash silica gel column chromatography to give the desired product.

Reaction with **1aa (PBO048)**: The reaction was performed according to general procedure using **1aa** (21.4 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) and the crude mixture was purified by flash silica gel column

chromatography using hexane/EtOAc = 1/1 as eluent to give **3aa** as white solid (21.3 mg, 96% yield).

Reaction with **1ab(PBO125)**: The reaction was performed according to general procedure using **1ab** (24.2 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3aa** as white solid (16.2 mg, 73% yield).

Reaction with **1ac(PBO-E-01-0014)**: The reaction was performed according to general procedure using **1ac** (25.6 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) at 150 °C and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3aa** as white solid (12.7 mg, 57% yield).

Reaction with **1ad(PBO176)**: The reaction was performed according to general procedure using **1ad** (32.6 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) at 80 °C and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3aa** as white solid (20.7 mg, 93% yield).

Reaction with **1ae(cjs032)**: The reaction was performed according to general procedure using **1ae** (29.0 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1as eluent to give **3aa** as white solid (19.1 mg, 86% yield).

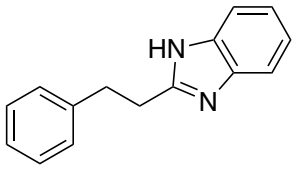
Reaction with **1af(cjs115)**: The reaction was performed according to general procedure using **1af** (30.6 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) at 150 °C and the crude mixture was purified by flash silica

gel column chromatography using hexane/EtOAc = 2/1as eluent to give **3aa** as white solid (20.3 mg, 91% yield).

Reaction with **1cg(PBO170):** The reaction was performed according to general procedure using **1cg** (26.7 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) for 3 hours and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3aa** as white solid (17.6 mg, 80% yield).

Reaction with **1ch(PBO115)**: The reaction was performed according to general procedure using **1ch** (21.3 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) at 150 °C and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 1/1 as eluent to give **3aa** as white solid (12.8 mg, 58% yield).

2-Phenethyl-1*H*-benzo[*d*]imidazole (3aa)[52]



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (s, 2H), 7.30 (t, J = 7.5 Hz, 2H), 7.23 (m, 5H), 3.25 (m, 2H), 3.20 (m, 2H) (Note: one proton signal from secondary amine was broadened and could not be observed). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 153.8, 140.4, 138.1, 128.7, 128.4, 126.6, 122.4, 114.7, 34.2, 31.2.

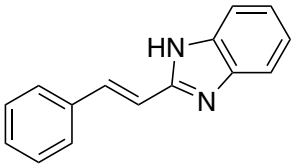
Reaction with **1ba(PBO157)**: The reaction was performed according to general procedure using **1ba** (21.2 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) for 3 hours and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 1/1 as eluent to give **3ba** as white solid (20.7 mg, 94% yield).

Reaction with **1bb(PBO160)**: The reaction was performed according to general procedure using **1bb** (24.0 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) for 3 hours and the crude mixture was purified by flash silica

gel column chromatography using hexane/EtOAc = 1/1 as eluent to give **3ba** as white solid (18.1 mg, 82% yield).

Reaction with **1bc(PBO-E-01-0011)**: The reaction was performed using **1bc** (25.4 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (0.15 mmol, 1.5 equiv) and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 1/1 as eluent to give **3ba** as white solid (17.2 mg, 78% yield).

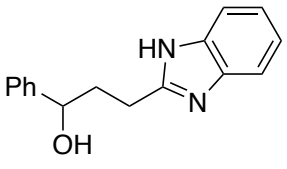
(*E*)-2-Styryl-1*H*-benzo[*d*]imidazole (3ba)



mp: 196–197 °C. 1H NMR (500 MHz, DMSO-d_6) δ 12.64 (s, 1H), 7.68 (s, 1H), 7.67 (s, 1H), 7.65 (s, 1H), 7.54 (br, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.37 (t, J = 7.2 Hz, 2H), 7.22 (d, J = 16.5 Hz, 1H), 7.20-7.17 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 151.4, 144.4, 136.2, 134.7, 129.4, 129.3, 127.5, 126.9, 123.0, 127.5, 126.9, 123.0, 122.1, 119.1, 118.2, 111.5. IR (neat) 3745, 2364, 2191, 2037, 1975, 1539, 1506, 752, 739, 534, 501, 424, 407 cm^{-1}. HRMS (ESI-TOF) m/z: calcd for $C_{15}H_{13}N_2^+$ $[M + H]^+$ 221.1073, found 221.1074.

Reaction with **1bd(PBO270)**: The reaction was performed according to the general procedure Method D using **1bd** (24.4 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3da** as a white solid (20.6 mg, 82% yield).

3-(1*H*-benzo[*d*]imidazol-2-yl)-1-phenylpropan-1-ol (3da)

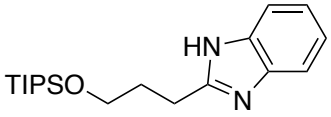


mp. 122–123 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.17 (br, 1H), 7.51 (d, J = 5, 1H), 7.39–7.33 (m, 5H), 7.24 (t, J = 7.2 Hz, 1H), 7.11 (d, J = 5.2 Hz, 2H), 5.46 (br, 1H), 4.66 (br, 1H), 2.92–2.81 (m, 2H), 2.14–2.09 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6)

δ155.5, 146.4, 143.7, 134.8, 128.5, 127.2, 126.3, 121.8, 121.2, 118.5, 111.1, 72.0, 37.7, 25.6. IR (neat) 3053, 3026, 2361, 2342, 1452, 1437, 1273, 742, 700, 669 cm^{-1}. HRMS (ESI-TOF) m/z: calcd for $C_{16}H_{17}N_2O^+$ $[M + H]^+$ 253.1335, found 253.1334.

Reaction with **1be(PBO262)**: The reaction was performed according to the general procedure general procedure using **1be** (38.7 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) at 80 °C and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3ea** as a white solid (20.0 mg, 60% yield).

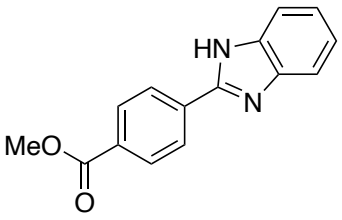
2-(3-((Triisopropylsilyl)oxy)propyl)-1*H*-benzo[*d*]imidazole (3ea)



mp: 89–90 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.16 (br, 1H), 7.50 (d, J = 6.9 Hz, 1H), 7.39 (d, J = 6.9 Hz, 1H), 7.11-7.09 (m, 2H), 3.77 (t, J = 6.3, 2 H), 1.21–1.16 (m, 3H), 1.11 (d, J = 6.5 Hz, 18H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 155.0, 122.1, 63.5, 30.1, 26.9, 18.0, 11.9. IR (neat): 2941, 2864, 2359, 1545, 1458, 1437, 1420, 1273, 1107, 881, 741, 681, 669. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{19}H_{33}ON_2Si^+$ $[M + H]^+$ 333.2357, found 333.2357.

Reaction with **1bf(PBO231)**: The reaction was performed according to the general procedure using **1bf** (30.6 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3fa** as white solid (23.0 mg, 91% yield).

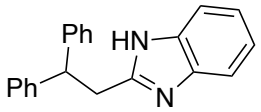
Methyl 4-(1*H*-benzo[*d*]imidazol-2-yl)benzoate (3fa)[53]



^{1}H NMR (500 MHz, DMSO-d_6) δ 13.12 (br, 1H), 8.32 (d, J = 8.6 Hz, 2H), 8.14 (d, J = 8.6, 2H), 7.64 (br, 2H), 7.25 (q, J = 3.1, 6 Hz, 2H), 3.91 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 166.3, 150.4, 134.8, 130.8, 130.3, 127.1, 123.0, 119.7, 112.0, 52.8.

Reaction with **1bg(PBO165)**: The reaction was performed according to the general procedure general procedure using **1bg** (34.0 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 3/1 as eluent to give **3ga** as a white solid (23.0 mg, 77% yield).

2-(2,2-Diphenylethyl)-1*H*-benzo[*d*]imidazole (3ga)



mp: 189–190 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.22 (br, 1H), 7.47 (d, J = 7.2 Hz, 1H), 7.36 (d, J = 7.2 Hz, 5H), 7.26 (t, J = 7.6 Hz, 4H), 7.14 (t, J = 7.4 Hz, 2H), 7.07 (q, J = 5.8, 8.6 Hz, 2H), 4.61 (t, J = 8.1 Hz, 1H), 3.67 (d, J = 8.2 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 153.7, 144.6, 143.7, 134.5, 128.9, 128.0, 126.7, 121.8, 121.2, 118.6, 111.2, 49.4, 35.0. IR (neat) 2357, 2338, 2154, 2046, 1965, 1541, 1456, 1425, 1273, 742, 698, 669, 469, 457 cm^{-1}. HRMS (ESI-TOF) m/z: calcd for $C_{21}H_{19}N_2^+$ $[M + H]^+$ 299.1543, found 299.1543.NEW

Reaction with **1bh (CJS133)**: The reaction was performed according to general procedure using **1bh** (18.6 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 3/2 as eluent to give **3ha** as white solid (18.2 mg, 94% yield).

Reaction with **1bi (CJS117)**: The reaction was performed according to general procedure using **1bi** (24.8 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3ha** as white solid (17.1 mg, 88% yield).

Reaction with **1ca (PBO204)**: The reaction was performed according to general procedure using **1ca** (18.3 mg, 0.10 mmol, 1.0 equiv) at 100 °C and benzene-1,2-

diamine (16.2 mg, 0.15 mmol, 1.5 equiv) and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 1/1 as eluent to give **3ha** as white solid (18.1 mg, 94% yield).

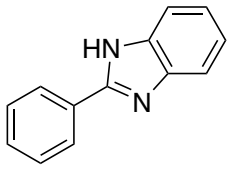
Reaction with **1cd (PBO224)**: The reaction was performed according to general procedure using **1cd** (23.3 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 3/2 as eluent to give **3ha** as white solid (18.5 mg, 95% yield).

Reaction with **1ce (PBO228)**: The reaction was performed according to general procedure using **1ce** (23.3 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) at 150 °C and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3ha** as white solid (11.4 mg, 58% yield).

Reaction with **1cf (PBO226)**: The reaction was performed according to general procedure using **1cf** (18.7 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) for 6 hours and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3ha** as white solid (17.2 mg, 89% yield).

Reaction with **1cj**: The reaction was performed according to general procedure using **1cj** (29.7 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3ha** as white solid (16.2 mg, 83% yield).

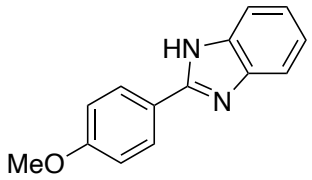
2-Phenyl-1*H*-benzo[*d*]imidazole (3ha)[54]



^{1}H NMR (500 MHz, DMSO-d_6) δ 12.90 (br, 1H), 8.07–8.05 (m, 2H), 7.65 (s, 2H), 7.51–7.46 (m, 3H), 7.28 (q, J = 3.0, 6.0 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 151.5, 130.3, 129.8, 129.1, 126.6, 123.0.

Reaction with **1bk** :The reaction was performed according to general procedure using **1bk** (27.8 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) for 24 hours and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3ka** as a white solid (20.7 mg, 92% yield).

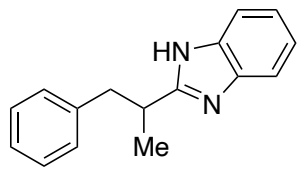
2-(4-methoxyphenyl)-1H-benzo[d]imidazole (3ka)



mp. 171–172 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.44(br, 1H), 7.99(d, J = 9.0 Hz, 2H), 7.78(br, 1H), 7.46 (s, 1H), 7.28-7.23 (m, 2H), 7.02 (d, J = 8.9 Hz, 2H), 3.88(s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ161.1, 151.8, 128.5, 123.2, 122.4, 114.8, 103.6, 91.8, 55.8. IR(neat): cm^{-1}. HRMS(ESI-TOF) m/z: calcd for $C_{14}H_{13}N_2O^+$ $[M+ Na]^+$ 225.1022, found 225.1034.

Reaction with **1bl** :The reaction was performed according to general procedure using **1bl** (22.8 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (21.6 mg, 0.20 mmol, 1.5 equiv) for 24 hours and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3la** as an white solid (19.2 mg, 81% yield).

2-(1-Methyl-2-phenylethyl)-1H-benzimidazole (3la)

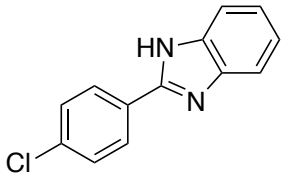


mp: 172–173 °C. ^{1}H NMR (500 MHz, DMSO): δ 12.18(bs, 1H), 7.52(s, 1H), 7.41(s, 1H), 7.24 (t, J = 7.5 Hz, 2H), 7.16 (t, J = 7.5 Hz, 3H), 7.11 (d, J = 4.5 Hz, 2H), 3.33-3.27(m, 1H), 3.22(dd, J = 13.5, 7.0 Hz, 1H), 2.88(dd, J = 13.5, 8.0 Hz, 1H), 1.29(d, J = 7.0

Hz, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO): δ159.3, 143.5, 140.4, 134.6, 129.3, 128.6, 126.5, 121.9, 121.2, 118.7, 111.2, 41.8, 36.1, 19.6. IR(neat): 2704, 2361, 2181, 2035, 2004, 1977, 1958, 1539, 1456, 1418, 1275, 991, 743, 725, 694, 446, 424, 417, 401 cm^{-1}. HRMS(ESI-TOF) m/z: calcd for $C_{16}H_{17}N_2^+$ $[M+ Na]^+$ 237.1386, found 237.1385.

Reaction with **1cb(PBO-E-01-0019)**: The reaction was performed according to general procedure using **1cb** (21.8 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) for 6 hours and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3jb** as an orange solid (22.7 mg, 99% yield).

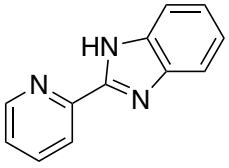
2-(4-Chlorophenyl)-1*H*-benzo[*d*]imidazole (3jb)[55]



^{1}H NMR (500 MHz, DMSO-d_6) δ 12.98 (br, 1H), 8.19 (d, J = 6.5 Hz, 2H), 7.64 (m, 4H), 7.22 (s, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6) δ 150.6, 134.9, 129.5, 128.6, 123.1, 122.3, 119.4, 111.9.

Reaction with **1cc(PBO-E-01-0018)**: The reaction was performed according to general procedure using **1cc** (18.4 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) for 6 hours and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3kb** as white solid (18.9 mg, 97% yield).

2-(Pyridin-2-yl)-1*H*-benzo[*d*]imidazole (3kb)



mp. 103–104 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.84 (d, J = 5.0 Hz, 1H), 8.57 (d, J = 8.0 Hz, 1H), 8.22-8.17 (m, 2H), 8.10-8.07 (m, 1H), 7.96-7.91 (m, 2H), 7.63-7.60 (m, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 154.0, 150.2, 150.1, 144.1, 142.4, 138.3, 131.3, 131.1, 129.8, 129.5, 125.8, 122.2. IR(neat): 3051, 2027, 1591, 1492, 1130, 1059, 962, 806, 787, 741 cm^{-1}. HRMS(ESI-TOF) m/z: calcd for $C_{12}H_{10}N_3^+$ $[M+ Na]^+$ 196.0869,

found 196.0865.

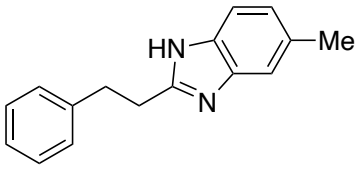
5. Scope of Various Aniline as Nucleophiles

General Procedure for the C–C Bond Cleavage of 2-Acylimidazoles by Using Various Anilines.

To a 4 mL vial equipped with a magnetic stirrer bar was added scandium(III) trifluoromethanesulfonate (2.46 mg, 0.0050 mmol, 5 mol %). and the vial was dried under vacuum using a heat gun. After cooling to room temperature, to the vial were added 2-acylimidazoles (**1aa** 0.10 mmol), aniline (0.15 mmol, 1.5 equiv) and PhCl (0.10 mL, 1.0 M) under an argon atmosphere. After the cap was tightly sealed, the mixture was stirred at indicated temperature for indicated time on a hot plate magnetic stirrer. After cooling to room temperature, solvent was removed, and the crude mixture was directly purified by flash silica gel column chromatography to give the desired product.

Reaction with **1aa** and **2b(PBO186)**: The reaction was performed according to general procedure using **1aa** (21.4 mg, 0.10 mmol, 1.0 equiv) and **2b** (18.3 mg, 0.15 mmol, 1.5 equiv) and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 3/2 as eluent to give **3ab** as an orange solid (22.4 mg, 95% yield).

6-Methyl-2-phenethyl-1*H*-benzo[*d*]imidazole (3ab)

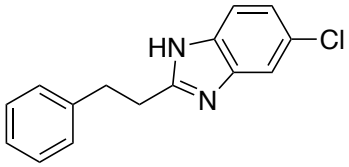


mp. 122–123 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.08 (br, 1H), 7.38 (br, 1H), 7.31–7.22 (m, 5H) 7.18 (t, J = 6.7 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 3.10–3.08 (m, 4H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 154.3, 141.5, 135.0, 132.8, 131.0, 128.8, 128.7, 126.5, 122.7, 118.2, 111.0, 33.8, 30.9, 21.7. IR (neat): 3024, 1541, 1452, 1420, 1279, 804, 650, 698 cm$^{-1.}$ HRMS (ESI-TOF) m/z: calcd for $C_{16}H_{17}N_2^+$ [M + H]$^+$ 237.1386, found 237.1387.

Reaction with **1aa** and **2c(PBO184)**: The reaction was performed according to general

procedure using **1aa** (21.4 mg, 0.10 mmol, 1.0 equiv) and **2c** (21.4 mg, 0.15 mmol, 1.5 equiv) and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 3/2 as eluent to give **3ac** as a white solid (24.7 mg, 96% yield).

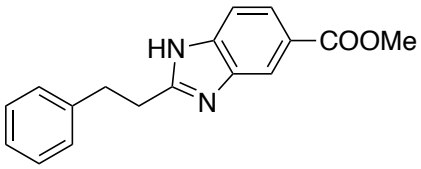
6-Chloro-2-phenethyl-1*H*-benzo[*d*]imidazole (3ac)



mp: 119–120 °C ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.42 (s, 1H), 7.54 (d, J = 1.6 Hz, 1H), 7.48 (d, J = 8.5 Hz, 1H), 7.29–7.24 (m, 4H), 7.18 (t, J = 6.8 Hz, 1H), 7.14 (q, J = 8.5, 2.0 Hz, 1H), 3.12 (s, 4H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 156.4, 141.3, 128.8, 128.7, 126.5, 126.0, 121.8, 120.6, 115.5, 113.1, 111.3. IR (neat) 3734, 2357, 2341, 2334, 1975, 1541, 1448, 1420, 1277, 698, 669, 484, 434, 418 cm^{-1}. HRMS (ESI-TOF) m/z: calcd for $C_{15}H_{14}ClN_2^+$ [M + H]$^+$ 257.0840, found 257.0838.

Reaction with **1aa** and **2d(PBO216)**: The reaction was performed according to general procedure using **1aa** (21.4 mg, 0.10 mmol, 1.0 equiv) and **2d** (24.9 mg, 0.15 mmol, 1.5 equiv) and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 1/1 as eluent to give **3ad** as a yellow solid (24.8 mg, 89% yield).

Methyl 2-phenethyl-1*H*-benzo[*d*]imidazole-6-carboxylate (3ad)

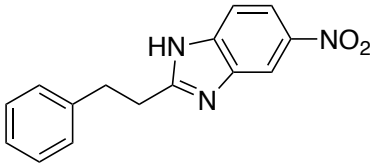


mp: 136–137 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.62 (br, 1H), 8.11 (br, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.57 (br, 1H), 7.30–7.26 (m, 4H), 7.20–7.17 (m, 1H), 3.86 (s, 3H), 3.19-3.11 (m, 4H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 167.3, 157.6, 147.3, 143.4, 141.3, 128.8, 128.7, 126.6, 123.1, 120.2, 113.0, 111.4, 52.4, 33.6, 30.9. IR (neat) 3026, 2953, 1715, 1624, 1433, 1086, 775, 748, 696, 461, 446, 438, 407 cm^{-1}. HRMS (ESI-TOF) m/z: calcd for $C_{17}H_{17}N_2O_2^+$ [M + H]$^+$ 281.1285, found 281.1288.

Reaction with **1aa** and **2e(PBO200)**: The reaction was performed according to general

procedure using **1aa** (21.4 mg, 0.10 mmol, 1.0 equiv) and **2e** (23.0 mg, 0.15 mmol, 1.5 equiv) at 150 °C and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3ae** as a yellow solid (21.1 mg, 79% yield).

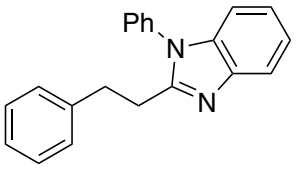
6-Nitro-2-phenethyl-1*H*-benzo[*d*]imidazole (3ae)



mp. 70–71 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.95 (br, 1H), 8.42 (br, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.63 (br, 1H), 7.29–7.25 (m, 4H), 7.20–7.17 (m, 1H), 3.21-3.13 (m, 4H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 159.5, 142.7, 141.1, 139.6, 128.8, 128.7, 126.6, 117.9, 114.6, 111.6, 108.0, 33.4, 30.9. IR (neat) 3097, 3028, 1626, 1597, 1512, 1472, 1452, 1420, 1337, 1284, 1068, 885, 824, 737, 698, 548, 500, 430 cm^{-1}. HRMS (ESI-TOF) m/z: calcd for $C_{15}H_{14}N_3O_2^+$ [M + H]$^+$ 268.1081, found 268.1080.

Reaction with **1aa** and **2f(PBO189)**: The reaction was performed according to general procedure using **1aa** (21.4 mg, 0.10 mmol, 1.0 equiv) and **2f** (27.6 mg, 0.15 mmol, 1.5 equiv) and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 3/2 as eluent to give **3af** as a purple solid (28.9 mg, 94% yield).

2-Phenethyl-1-phenyl-1*H*-benzo[*d*]imidazole (3af)

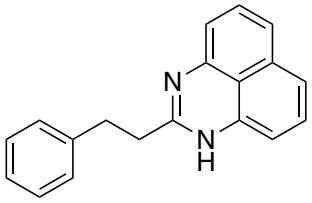


mp: 71–72 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 8.0 Hz, 1H), 7.51 (m, 3H), 7.30 (d, J = 7.0 Hz, 1H) 7.27–7.15 (m, 6H), 7.09–7.06 (m, 3H), 3.17-3.13 (m, 2H), 3.08-3.05 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 154.3, 142.5, 140.8, 136.5, 135.8, 129.9, 128.9, 128.5, 128.4, 127.4, 126.2, 122.7, 122.4, 119.1, 110.1, 34.2, 29.8. IR (neat) 3057, 3026, 1597, 1514, 1499, 1454, 1398, 1327, 1260, 1014, 744, 698, 498, 424 cm^{-1}. HRMS (ESI-TOF) m/z: calcd for $C_{21}H_{19}N_2^+$ [M + H]$^+$ 299.1543, found 299.1544.

Reaction with **1aa** and **2g(PBO188)**: The reaction was performed according to general procedure using **1aa** (21.4 mg, 0.10 mmol, 1.0 equiv) and **2g** (23.7 mg, 0.15 mmol, 1.5

equiv) at 150 °C and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 3/2 as eluent to give **3ag** as a brown solid (23.0 mg, 85% yield).

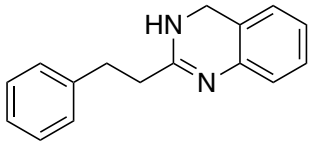
2-Phenethyl-1*H*-perimidine (3ag)



mp. 178–179 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.47 (s, 1H), δ 7.30 (d, J = 4.8 Hz, 4H), 7.21–7.18 (m, 1H), 7.10 (br, 2H), 6.98 (d, J = 6.6 Hz, 2H), 6.55 (s, 1H), 6.27 (s, 1H), 2.98 (t, J = 7.9 Hz, 2H), 2.55 (t, J = 8.1 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ157.0, 141.5, 135.6, 128.8, 128.8, 126.5, 121.9, 119.0, 117.8, 113.5, 102.0, 36.8, 32.6. IR (neat): 3049, 2361, 1603, 1477, 1371, 824, 768, 696 cm^{-1} HRMS (ESI-TOF) m/z: calcd for $C_{19}H_{17}N_2^+$ [M + H]$^+$ 273.1386, found 273.1393.

Reaction with **1aa** and **2h(PBO213)**: The reaction was performed according to general procedure using **1aa** (21.4 mg, 0.10 mmol, 1.0 equiv) and **2h** (18.3 mg, 0.15 mmol, 1.5 equiv) and the crude mixture was purified by flash silica gel column chromatography using EtOAc with 1% Et_3N as eluent to give **3ah** as a white solid (18.7 mg, 90% yield).

2-Phenethyl-1,4-dihydroquinazoline (3ah)

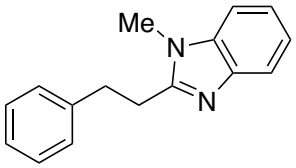


mp. 53–54 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.19 (m, 5H), 7.12 (t, J = 7.0 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 6.87–6.83 (m, 2H), 4.54 (s, 2H), 2.99 (t, J = 8.0 Hz, 2H), 2.52 (t, J = 8.0 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 157.7, 140.9, 128.6, 128.5, 127.9, 126.3, 125.6, 124.0, 119.8, 118.0, 114.9, 46.6, 38.2, 33.5. IR (neat): 3028, 2932, 2363, 1651, 1574, 1481, 1454, 1333, 1265, 935, 750, 696 cm$^{-1.}$ HRMS (ESI-TOF) m/z: calcd for $C_{16}H_{17}N_2^+$ [M + H]$^+$ 237.1386, found 237.1387.

Reaction with **1aa** and **2i(PBO214)**: The reaction was performed according to general procedure using **1aa** (21.4 mg, 0.10 mmol, 1.0 equiv) and **2i** (18.3 mg, 0.15 mmol, 1.5 equiv) and the crude mixture was purified by flash silica gel column chromatography

using hexane/EtOAc = 1/1 as eluent to give **3ai** as a white solid (20.9 mg, 88% yield).

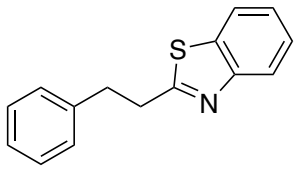
1-Methyl-2-phenethyl-1*H*-benzo[*d*]imidazole (3ai)



mp: 45–46 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76–7.74 (m, 1H), 7.30–7.20 (m, 8H), 3.53 (s, 3H), 3.23–3.21 (m, 2H), 3.18–3.16 (m, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 154.4, 142.5, 140.8, 135.6, 128.6, 128.4, 126.4, 122.1, 121.9, 119.2, 109.0, 34.2, 29.7, 29.5. IR (neat) 3057, 3024, 1510, 1497, 1470, 1452, 1443, 1400, 1329, 1284, 1236, 1007, 766, 742, 700, 571, 484 cm^{-1}. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{16}H_{17}N_2^+$ $[M + H]^+$ 237.1386, found 237.1387.

Reaction with **(2k)**: The reaction was performed according to general procedure using **1aa** (21.4 mg, 0.10 mmol, 1.0 equiv) and 2-aminobenzenethiol **2k** (25.0 mg, 0.2 mmol, 2.0 equiv) and the crude mixture was purified by flash silica gel column chromatography using EtOAc/Hex = 1/1 as eluent to give **3ak** as white solid (21.2 mg, 88% yield).

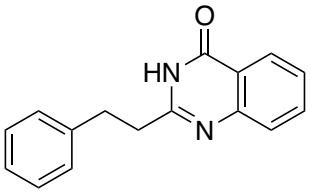
2-phenethylbenzo[d]thiazole (3ak)[56]



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 10.0 Hz, 1H), 7.83 (d, *J* = 10.0 Hz, 1H), 7.48-7.44 (m, 1H), 7.37-7.34 (m, 1H), 7.32-7.29 (m, 2H), 7.27-7.21 (m, 3H), 3.45-3.42 (m, 2H), 3.23-3.20 (m, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 170.9, 153.2, 140.2, 135.1, 128.6, 128.4, 126.4, 126.0, 124.8, 122.6, 121.5, 36.0, 35.6.

Reaction with **(2l)**: The reaction was performed according to general procedure using **1aa** (21.4 mg, 0.10 mmol, 1.0 equiv) and 2-aminobenzamide (20.4 mg, 0.15 mmol, 1.5 equiv) for 48 hours and the crude mixture was purified by flash silica gel column chromatography using EtOAc/Hex = 1/1 as eluent to give **3al** as white solid (22.7 mg, 91% yield).

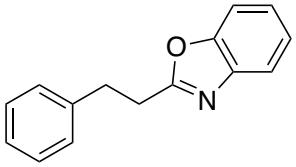
2-phenethylquinazolin-4(3H)-one (3al)[57]



^{1}H NMR (500 MHz, $CDCl_3$) δ 10.7-10.45 (br, 1H), 8.28 (d, *J* = 7.9 Hz, 1H), 7.80-7.77 (m, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 4.8 Hz, 4H), 7.26-7.21 (m, 2H), 3.20 (t, *J* = 7.9 Hz, 2H), 3.07-3.03 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 155.4, 149.3, 140.0, 134.8, 132.9, 128.7, 128.5, 127.3, 126.6, 126.4, 120.7, 37.9, 33.5.

Reaction with **1aa** and **2j(PBO-E-01-0063)**: The reaction was performed according to general procedure using **1aa** (21.4 mg, 0.10 mmol, 1.0 equiv) and **2j** (16.4 mg, 0.15 mmol, 1.5 equiv) at 150 °C and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3aj** as white solid (17.6 mg, 79% yield).

2-Phenethylbenzo[*d*]oxazole (3aj)[58]



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69–7.67 (m, 1H), 7.49–7.47 (m, 1H), 7.32–7.29 (m, 4H), 7.27–7.20 (m, 3H), 3.25–3.23 (m, 4H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 166.3, 150.8, 141.3, 140.1, 128.6, 128.3, 126.5, 124.6, 124.2, 119.6, 110.3, 32.8, 30.5.

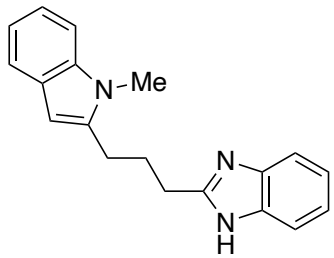
4. Direct C–C Bond Cleavage of medical compound containing acyl-heterocycles

General procedure for transformation of medical compound containing acyl-heterocycles.

To a 4 mL vial equipped with a magnetic stirrer bar was added scandium(III) trifluoromethanesulfonate. and the vial was dried under vacuum using a heat gun. After cooling to room temperature, to the vial were added acyl-heterocycle, diamine and PhCl under an argon atmosphere. After the cap was tightly sealed, the mixture was stirred at indicated temperature for indicated time on a hot plate magnetic stirrer. After cooling to room temperature, solvent was removed, and the crude mixture was directly purified by flash silica gel column chromatography to give the desired product.

Reaction with **4**: The reaction was performed according general procedure using **4** (19.9 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (32.4 mg, 0.3 mmol, 3.0 equiv) and scandium(III) trifluoromethanesulfonate (4.92 mg, 0.010 mmol, 10 mol %) in PhCl (0.20 mL, 0.5 M), and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 1/2 as eluent to give **7** as brown solid (20.5 mg, 71% yield).

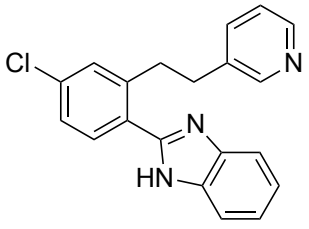
2-(3-(1-methyl-1*H*-indol-2-yl)propyl)-1*H*-benzo[*d*]imidazole (7)



mp: 172–173 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.22 (s, 1H), δ 7.54 (d, J = 7.5 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.42 (d, J = 6.8 Hz, 1H), 7.38 (d, J = 8.2 Hz, 1H), 7.13–7.10 (m, 2H), 7.07 (t, J = 7.6 Hz, 1H), 6.98 (t, J = 7.4 Hz, 1H), 6.28 (s, 1H), 3.67 (s, 3H), 2.95(t, J = 7.5, 2H), 2.87(t, J = 7.5, 2H), 2.22-2.17(m, 2H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 155.2, 143.8, 141.1, 137.5, 134.8, 127.9, 121.9, 121.2, 120.6, 119.7, 119.3, 118.6, 111.2, 109.7, 98.9, 29.7, 28.5, 26.8, 26.0. IR (neat): 3059, 2934, 2361, 1541, 1468, 1454, 1339, 1314, 1271, 1232, 1011, 770, 744, 428. HRMS (ESI-TOF) *m*/*z* calcd for $C_{19}H_{20}N_3^+$ $[M + H]^+$ 290.1652, found 290.1650.

Reaction with **6(PBO219)**: The reaction was performed according general procedure using **6** (24.3 mg, 0.10 mmol, 1.0 equiv) and3 benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **9** as white solid (25.6 mg, 77% yield).

2-(4-Chloro-2-(2-(pyridin-3-yl)ethyl)phenyl)-1*H*-benzo[*d*]imidazole (9)

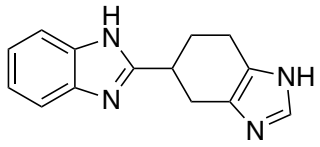


mp: 192–193 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, J = 8.0 Hz, 1H), 8.12 (d, J = 2.0 Hz, 1H), 7.57 (s, 2H), 7.40 (d, J = 8.5 Hz, 1H), 7.36–7.34 (m, 1H), 7.30–7.21 (m, 4H), 6.95 (q, J = 5.0, 7.5 Hz, 1H), 3.36 (t, J = 7.5, 2H), 2.82(t, J = 7.5, 2H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 151.0, 150.0, 147.7, 143.7, 141.9, 137.4,

136.3, 134.4, 131.7, 131.1, 128.9, 126.9, 123.8, 122.7, 105.4, 34.8, 34.6. IR (neat): 3063, 2924, 1595, 1448, 1422, 1275, 1107, 906, 826, 800, 735, 714. HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{17}ClN_3^+$ $[M + H]^+$ 334.1106, found 334.1110.

Reaction with **(5)**: The reaction was performed according to general procedure using **5** (31.6 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (32.4 mg, 0.3 mmol, 3.0 equiv). Saturated sodium carbonate solution was added and the resulting mixture was extracted with ethyl acetate. After removal of the solvent under reduced pressure the crude mixture was purified by flash silica gel column chromatography using EtOAc/MeOH = 2/1 as eluent to give **8** as pink solid (19.5 mg, 82% yield).

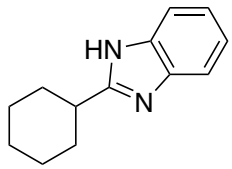
4',5',6',7'-tetrahydro-1H,1'H-2,5'-bibenzo[d]imidazole (8)



mp: 197-198 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.49 (br, 2H), 7.14-7.12 (m, 2H), 3.34-3.28 (m, 1H), 2.97-2.95 (m, 2H), 2.66-2.65 (m, 2H), 2.32-2.28 (m, 1H), 2.09-1.99 (m, 1H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 158.3, 134.0, 129.0, 121.5, 129.0, 121.5, 118.6, 111.2, 35.6, 28.9, 28.1, 22.2. IR (neat): 3279, 2359, 2342, 2044, 1977, 1636, 667, 436, 418. HRMS (ESI-TOF) *m/z* calcd for $C_{14}H_{15}N_4^+$ $[M + H]^+$ 239.1291, found 239.1291

Reaction with **(1ci)**: The reaction was performed according to general procedure using **1ci** (18.9 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) and the crude mixture was purified by flash silica gel column chromatography using EtOAc/Hexane = 2/1 as eluent to give **3ib** as white solid (18.7 mg, 93% yield).

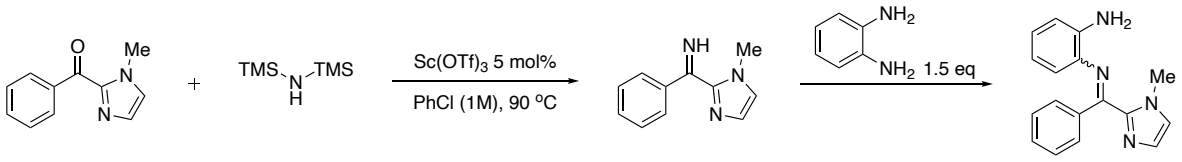
2-cyclohexyl-1H-benzo[d]imidazole (3ib)[59]



mp: 172-173 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.09 (br, 1H), 7.45 (br, 2H), 7.10 (q, J = 3.0 Hz, 2H), 2.87-2.81 (m, 1H), 2.03-2.00 (m, 2H), 2.66-2.65 (tt, J = 3.5, 13 Hz, 2H), 1.72-1.68 (m, 1H), 1.65-1.57 (m, 2H), 1.44-1.35 (m, 2H), 1.31-1.23 (m, 1H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 159.3, 143.7, 134.9, 121.6, 121.4, 118.7, 111.3, 38.2, 31.7, 26.0, 25.9.

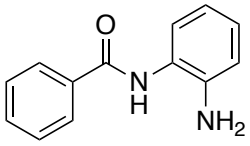
9. Direct C–C Bond Cleavage from Imine and Amide Intermediates

General Procedure for the Synthesis of Imine Intermediate[60]



To a 4 mL vial equipped with a magnetic stirrer bar was added scandium(III) trifluoromethanesulfonate (12.3 mg, 0.025 mmol, 5 mol%). and the vial was dried under vacuum using a heat gun. After cooling to room temperature, to the vial were added (1-methyl-1H-imidazol-2-yl)(phenyl)methanone (93.1 mg, 0.5 mmol), bis(trimethylsilyl)amine (88.8 mg, 0.55 mmol, 1.1 eq) and PhCl (0.5 mL, 1M) under an argon atmosphere. After the cap was tightly sealed, the mixture was stirred at 90 °C for 17 hours on a hot plate magnetic stirrer. Then 2-aminoaniline (81.1 mg, 0.75 mmol, 1.5 eq) was added under an argon atmosphere. After the cap was tightly sealed, the mixture was stirred at 40 °C for another 9 hours on a hot plate magnetic stirrer. After cooling to room temperature, solvent was removed and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 1/2 as eluent to give In-A as orange solid (38.5 mg, 28% yield).

General Procedure for the Synthesis of Imine Intermediate

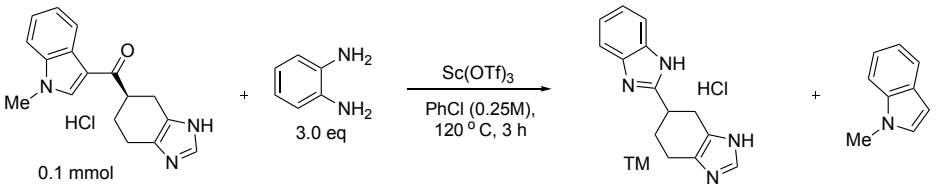


Imine intermediate was prepared according to the reported procedure[61].

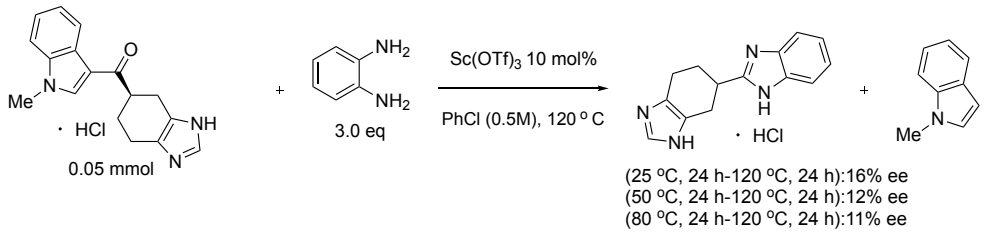
O-Phenylenediamine (8.97 g; 83.1 mmol) was dissolved in dry dichloromethane (350

mL). Triethyl-amine (3.0 mL; 21.6 mmol) was added, and the solution was heated to reflux with stirring. Benzoyl chloride (2.16 g; 20.7 mmol) dissolved in dry dichloromethane (200 mL) was added dropwise to the solution. The solution was allowed to reflux for 2 h. The product was separated by column chromatography using a silica column and an ethyl acetate−hexane (1:1) mixture as the eluent. Recrystallization from ethyl acetate−hexane afforded the product as a white solid (yield, 3.57 g, 81%)

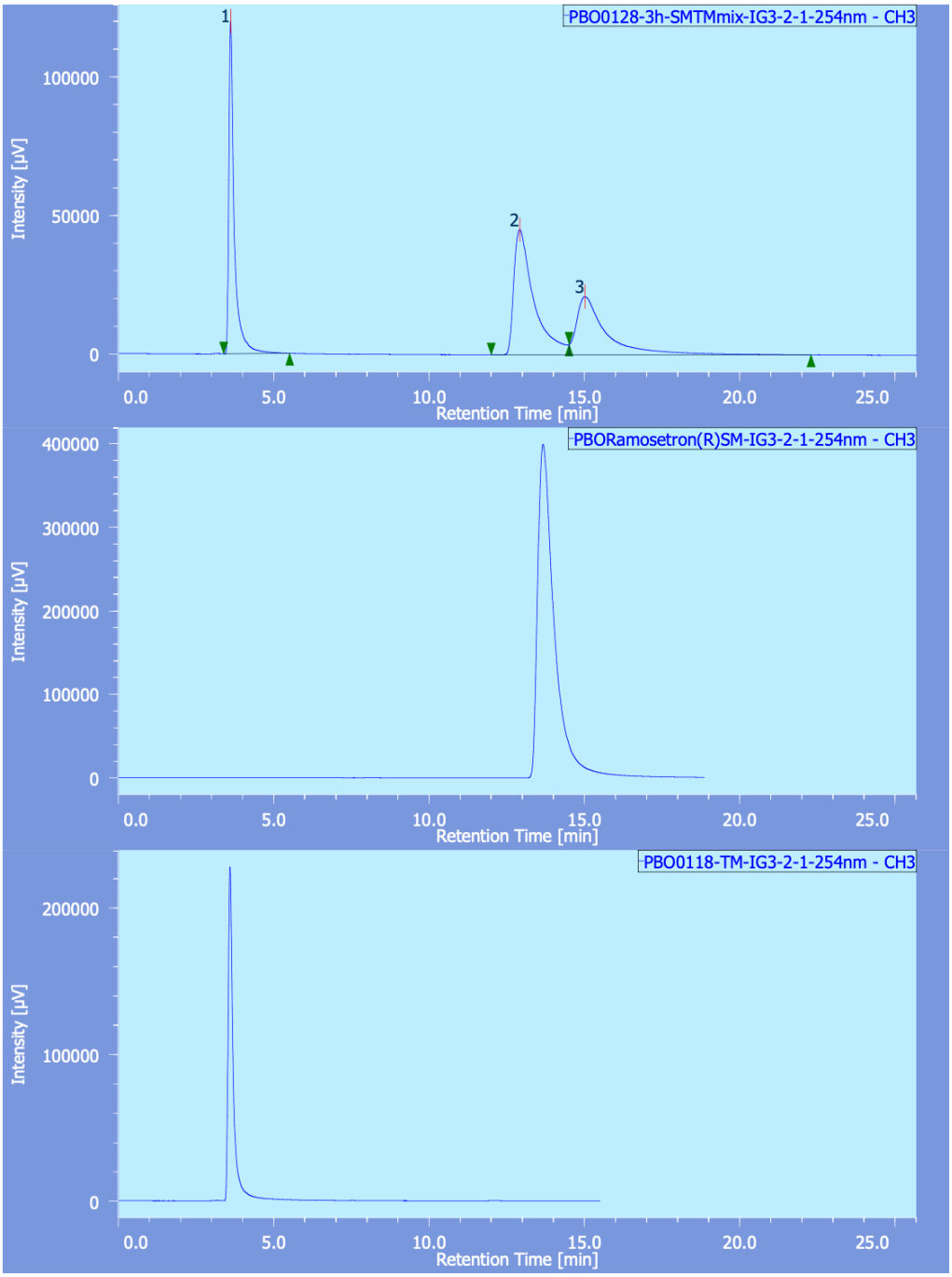
Scheme S3. Racemization of α-Branched Substrate



Procedure for the C−C Bond Cleavage of α-Branched substrate Ramosetron (PBO0118) (>99%ee) To a 4 mL vial equipped with a Teflon-lined screw cap and a magnetic stir bar were added PBO0118 (0.10 mmol) and benzene-1,2-diamine (32.4 mg, 0.3 mmol, 3.0 equiv) and PhCl (0.5 M) under an argon atmosphere. After the cap was tightly sealed, the mixture was stirred at 150 °C for 3 h on a hot plate magnetic stirrer using an aluminum block. The crude mixture was purified by flash silica gel column chromatography using MeOH/EtOAc = 1/1 as eluent to give a mixture of Ramosetron and the product. And the loss of ee% is evident from the results of HPLC.



When we used a lower reaction temperature to activate the reaction and then raised the temperature to 120 degrees, only a small difference was detected indicating that this method can weaken the racemization but the effect is very limited.



Channel & Peak Information Table

Chromatogram Name PBO0128-3h-SMTMmix-IG3-2-1-254nm-CH3

Sample Name

Channel Name UV

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	3.617	1475546	119826	30.118	64.432	N/A	2949	14.423	2.218	
2	Unknown	3	12.917	2009950	45108	41.025	24.256	N/A	2533	1.758	N/A	
3	Unknown	3	15.017	1413795	21037	28.857	11.312	N/A	1926	N/A	N/A	

Chromatogram Name PBORamosetron(R)SM-IG3-2-1-254nm-CH3

Sample Name

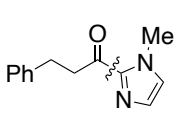
Channel Name UV

Chromatogram Name PBO0118-TM-IG3-2-1-254nm-CH3

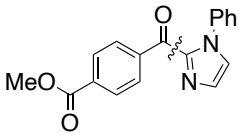
Sample Name

Channel Name UV

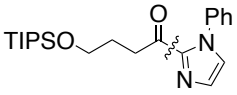
General procedure for transformation of unactivated 2-acylimidazoles and related azaarenes to other heterocycles via C–C Bond Cleavage catalyzed by TfOH.



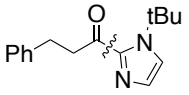
1aa



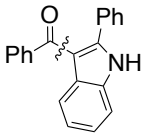
1bf



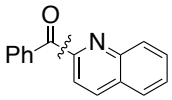
1be



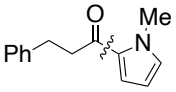
1ac



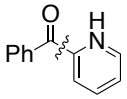
1cj



1cd



1ch



1ca

preparation of 0.15 mmol/ml TfOH solution: To a 20 mL vial equipped with a Teflon-lined screw cap dried by a heat gun under argon atmosphere 0.13 mL TfOH and 10mL PhCl were added under argon atmosphere to afford 1.5 mmol/ml TfOH solution.

To a 4 mL vial equipped with a Teflon-lined screw cap and a magnetic stir bar were added 2-acylimidazole **1** (21.4 mg, 0.10 mmol), 2-aminoaniline (16.2 mg, 0.15 mmol) and TfOH solution (0.10 mL, 0.25 M) under an argon atmosphere. After the cap was tightly closed, the mixture was stirred at 80 °C,100 °C, 120 °C or 150 °C for 24 h on a hot plate magnetic stirrer using an aluminum block. After cooling to room temperature, the yield of **3** was determined by ^{1}H NMR analysis of the crude mixture.

Reaction with **1aa(PBO-E-01-0165)**: The reaction was performed according to general procedure using **1aa** (21.4 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) at 120 °C and the yield of **3** was determined by ^{1}H NMR analysis of the crude mixture. (>99% yield).

Reaction with **1bf(PBO-E-01-0162)**: The reaction was performed according to general procedure using **1bf** (30.6 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) at 120 °C and the yield of **3** was determined by ^{1}H NMR analysis of the crude mixture. (96% yield).

Reaction with **1aa** and **2j(PBO-E-01-0168)**: The reaction was performed according to general procedure using **1aa** (21.4 mg, 0.10 mmol, 1.0 equiv) and **2j** (16.4 mg, 0.15 mmol, 1.5 equiv) at 150 °C and the yield of **3** was determined by ^{1}H NMR analysis of the crude mixture. (61% yield).

Reaction with **1be(PBO-E-01-0173)**: The reaction was performed according to the general procedure general procedure using **1be** (38.7 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) at 80 °C and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3ea** as a white solid (14.3 mg, 45% yield).

Reaction with **1ac(PBO-E-01-0014)**: The reaction was performed according to general procedure using **1ac** (25.6 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) at 150 °C and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3aa** as white solid (?mg, 49% yield)

Reaction with **1cj (PBO-E-01-0179)**: The reaction was performed according to general procedure using **1cj** (29.7 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3ha** as white solid (?mg, 72% yield).

Reaction with **1cd (PBO-E-01-0170)**: The reaction was performed according to general procedure using **1cd** (23.3 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) and the yield of **3** was determined by ^{1}H NMR analysis of the crude mixture. (>99% yield).

Reaction with **1ch (PBO-E-01-0178)**: The reaction was performed according to general procedure using **1ch** (21.3 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2

mg, 0.15 mmol, 1.5 equiv) at 150 °C and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 1/1 as eluent to give **3aa** as white solid (10.1 mg, 45% yield).

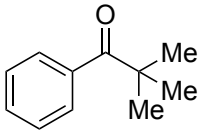
Reaction with **1ca (PBO-E-01-0177)**: The reaction was performed according to general procedure using **1ca** (18.3 mg, 0.10 mmol, 1.0 equiv) at 100 °C and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) and the yield of **3** was determined by ^{1}H NMR analysis of the crude mixture. (>99% yield).

Transformation of ketone containing α quaternary carbon to Other Heterocycles via C-C Bond Cleavage

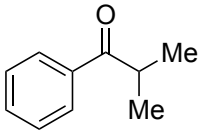
General Procedure for Initial Screening of the Catalysts

To a 4 mL vial equipped with a Teflon-lined screw cap and a magnetic stir bar were added 2,2-dimethyl-1-phenylpropan-1-one **1** (mg, 0.10 mmol), catalyst (0.005 mmol, 5 mol %) or (0.015 mmol, 15 mol %), 2-aminoaniline (16.2 mg, 0.15 mmol) and solvent (0.10 mL, 1 M) under an argon atmosphere. After the cap was tightly closed, the mixture was stirred at 120 °C for 6 h on a hot plate magnetic stirrer using an aluminum block. After cooling to room temperature, the yield of **3** was determined by ^{1}H NMR analysis of the crude mixture.

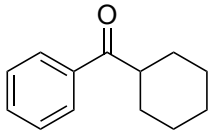
General procedure for transformation of ketone containing α quaternary carbon to Other Heterocycles via C-C Bond Cleavage.



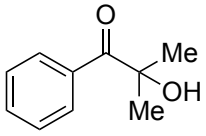
1da



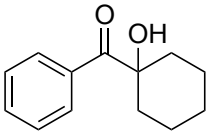
1db



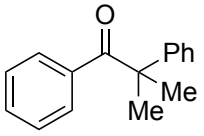
1dc



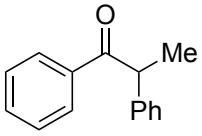
1dd



1de



1df



1dg

Method A

To a 4 mL vial equipped with a magnetic stirrer bar was added catalyst (0.0050 mmol, 5 mol %). and the vial was dried under vacuum using a heat gun. After cooling to room temperature, to the vial were added ketone (0.10 mmol), diamine (0.15 mmol, 1.5 equiv) and PhCl (0.10 mL, 1.0 M) under an argon atmosphere. After the cap was tightly sealed, the mixture was stirred at the indicated temperature for indicated time on a hot plate magnetic stirrer. After cooling to room temperature, the solvent was removed, and the crude mixture was directly purified by flash silica gel column chromatography to give the desired product.

Method B

A 4 mL vial equipped with a magnetic stirrer bar was dried under vacuum using a heat gun. After cooling to room temperature, to the vial were added NH_4OTf (0.0150 mmol, 15 mol %), ketone (0.10 mmol), diamine (0.15 mmol, 1.5 equiv) and PhCl (0.10 mL, 1.0 M) under an argon atmosphere. After the cap was tightly sealed, the mixture was stirred at the indicated temperature for the indicated time on a hot plate magnetic stirrer. After cooling to room temperature, the solvent was removed, and the crude mixture was directly purified by flash silica gel column chromatography to give the desired product.

Reaction with **1da (PBO-E-02-0091)**: The reaction was performed according to the general procedure method B using **1da** (16.2 mg, 17 μL, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) at 80 °C and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3ha** as white solid (18.1 mg, 93% yield).

Reaction with **1da (PBO-E-02-0053)**: The reaction was performed according to the general procedure method A with $Sc(OTf)_3$ (2.46 mg, 0.005 mmol, 5 mol%) as catalyst using **1da** (16.2 mg, 17 μL, 0.10 mmol, 1.0 equiv) and 2-aminobenzenethiol (18.8 mg,

16 μL, 0.15 mmol, 1.5 equiv) at 150 °C and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **?** as white solid (20.4 mg, 97% yield).

Reaction with **1db (PBO-E-02-0071)**: The reaction was performed according to the general procedure method A with $Sc(OTf)_3$ (2.46 mg, 0.005 mmol, 5 mol%) as catalyst using **1db** (14.8 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2mg, 0.15 mmol, 1.5 equiv) at 150 °C and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3ha** as white solid (16.8 mg, 86% yield).

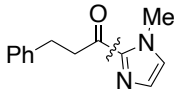
Reaction with **1dc (PBO-E-02-0065)**: The reaction was performed according to the general procedure method A with $Sc(OTf)_3$ (2.46 mg, 0.005 mmol, 5 mol%) as catalyst using **1dc** (18.8 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2mg, 0.15 mmol, 1.5 equiv) at 150 °C and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3ha** as white solid (14.4 mg, 74% yield).

Reaction with **1dd (PBO-E-02-0089)**: The reaction was performed according to the general procedure method A with $Cu(OTf)_2$ (1.81mg, 0.005 mmol, 5 mol%) as catalyst using **1dd** (20.43 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2mg, 0.15 mmol, 1.5 equiv) at 120 °C and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3ha** as white solid (10.2 mg, 52% yield).

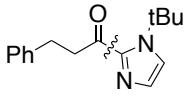
Reaction with **1de (PBO-E-02-0088)**: The reaction was performed according to the general procedure method A with $Cu(OTf)_2$ (1.81mg, 0.005 mmol, 5 mol%) as catalyst

using **1de** (16.4 mg, 15.2 μL, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2mg, 0.15 mmol, 1.5 equiv) at 120 °C and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3ha** as white solid (10.9 mg, 56% yield).

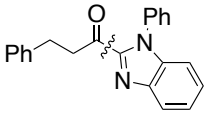
General procedure for transformation of unactivated 2-acylimidazoles and related azaarenes to other heterocycles via C–C Bond Cleavage catalyzed by NH_4OTf.



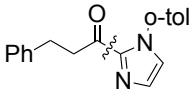
1aa



1ac



1ad



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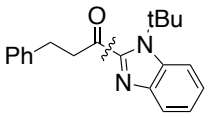

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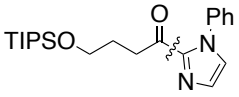
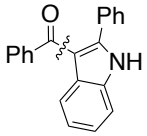
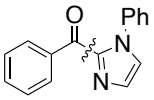


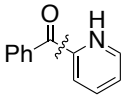
1be



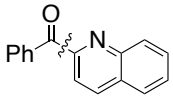
1cj



1bi



1ca



1cd

A 4 mL vial equipped with a magnetic stirrer bar was dried under vacuum using a heat gun. After cooling to room temperature, to the vial were added NH_4OTf (0.0150 mmol, 15 mol %), ketone (0.10 mmol), diamine (0.15 mmol, 1.5 equiv), and PhCl (0.10 mL, 1.0 M) under an argon atmosphere. After the cap was tightly sealed, the mixture was stirred at the indicated temperature for the indicated time on a hot plate magnetic stirrer. After cooling to room temperature, the solvent was removed, and the crude mixture was directly purified by flash silica gel column chromatography to give the desired product.

Reaction with **1aa (PBO-E-01-0186)**: The reaction was performed according to general procedure using **1aa** (21.4 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine

(16.2 mg, 0.15 mmol, 1.5 equiv) at 120 °C for 6 hours, and the yield of **3** was determined by ^{1}H NMR analysis of the crude mixture. (>99% yield).

Reaction with **1ac(PBO-E-01-0190)**: The reaction was performed according to general procedure using **1ac** (25.6 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) at 150 °C and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3aa** as white solid (13.6 mg, 61% yield).

Reaction with **1ad(PBO-E-01-0193)**: The reaction was performed according to general procedure using **1ad** (32.6 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) at 80 °C and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3aa** as white solid (19.5 mg, 88% yield).

Reaction with **1ae(PBO-E-01-0191)**: The reaction was performed according to general procedure using **1ae** (29.0 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) at 120 °C for 6 hours and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1as eluent to give **3aa** as white solid (20.9 mg, 94% yield).

Reaction with **1af(PBO-E-01-0192)**: The reaction was performed according to general procedure using **1af** (30.6 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) at 150 °C for 24 hours and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1as eluent to give **3aa** as white solid (17.6 mg, 79% yield).

Reaction with **1be(PBO-E-01-196)**: The reaction was performed according to the general procedure general procedure using **1be** (38.7 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) at 80 °C for 24 hours and the

crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3ea** as a white solid (25.8 mg, 81% yield).

Reaction with **1cj(PBO-E-01-0194)**: The reaction was performed according to general procedure using **1cj** (29.7 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (21.6 mg, 0.20 mmol, 2.0 equiv) at 150 °C for 24 hours and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3ha** as white solid (14.4 mg, 74% yield).

Reaction with **1bi (PBO-E-01-0197)**: The reaction was performed according to general procedure using **1bi** (24.8 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) at 100 °C for 24 hours, and the yield of **3** was determined by ^{1}H NMR analysis of the crude mixture. (>99% yield).

Reaction with **1ca (PBO-E-01-0187)**: The reaction was performed according to general procedure using **1ca** (18.3 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) and the crude mixture was purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give **3ha** as white solid (12.1 mg, 62% yield).

Reaction with **1cd (PBO-E-01-0195)**: The reaction was performed according to general procedure using **1cd** (23.3 mg, 0.10 mmol, 1.0 equiv) and benzene-1,2-diamine (16.2 mg, 0.15 mmol, 1.5 equiv) at 120 °C for 24 hours, and the yield of **3** was determined by ^{1}H NMR analysis of the crude mixture. (>99% yield).

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