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Lewis Base-Catalyzed Amino-Acylation of Arylallenes via C–N Bond Cleavage: Reaction Development and Mechanistic Studies

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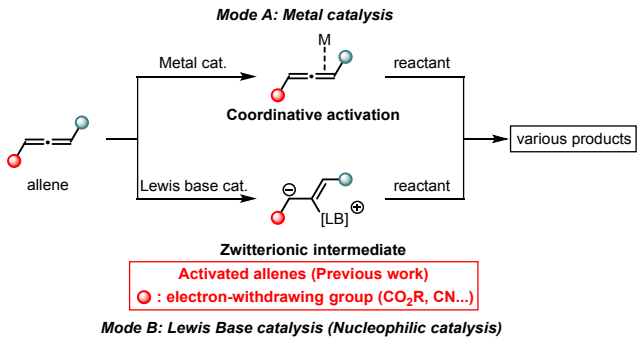
ABSTRACT: Lewis base-catalyzed transformations of allenes have received great attention over the last decades. However, this type of reactions has so far been limited to activated allenes bearing an electron-withdrawing group. On the other hand, cleavage of amide C−N bond to forge other chemical bonds have been widely reported, but restricted to low atom economy due to the wastage of the amine moiety of amides. We initiated a project of metal-catalyzed amino-acylation of allenes via cleavage of amide C−N bond. Surprisingly, an amino-acylation of weakly activated aryl allenes was discovered via Lewis base catalysis, providing 2-methyl-3-aroylindole products, a "privileged structures" in drug discovery. This is a unique example of Lewis base catalysis of weakly activated allenes which was not reported yet. Extensive experimental and computational studies have been conducted to provide insight into the reaction mechanism. The nucleophilic addition of Lewis base catalyst to aryl allene is the rate-limiting step. And a challenging [1,3]-proton transfer is realized by nitrogen anion intermediate assisted sequential [1,4]- and [1,6]-proton transfer in the reaction pathway.

KEYWORDS: Lewis base catalysis, C−N bond cleavage, proton transfer, weakly activated allenes, 3-aroylindoles

Introduction

The allenes are three-carbon functional groups possessing a 1,2-diene moiety and serve as valuable synthetic precursors for the construction of highly complex target molecules of biological and industrial importance.[1] Coordinative activation of the cumulated double bonds with metal catalyst is one of the most popular reaction modes for transformation of allenes, which facilitate the attack of nucleophiles to form a new C−C or C−heteroatom bond in an inter- or intramolecular fashion (Scheme 1, Mode A).[2] Transiton-metal-catalyst, such as Pd, Rh, Ir, Ru, have been widely used in the conversion of allenes by coordinative activation, mostly via π-allyl metal intermediate.[3] Because of their soft and carbophilic character, the gold or platinum catalysts have also been widely used for the selective activation of allenes in the cyclization reactions.[4] Another important mode for allene activation is Lewis base catalysis, also named nucleophilic catalysis (Scheme 1, Mode B).[5] This type of reaction starts from a nucleophilic addition of allene with Lewis base catalyst, such as phosphine, to generate a zwitterionic intermediate.[6,7] Countless catalytic transformations of allenes have been reported affording useful products via Lewis base catalysis. However, all of these reactions are limited to activated allenes bearing an electron-withdrawing group, for example, allenyl esters. To date, there is no example of catalytic transformations of non-activated or weakly activated allenes via Lewis base catalysis, such as aryl allenes or alkyl allenes. This may owe to the high activation barrier of nucleophilic addition of the central carbon atom of non-activated or weakly activated allene with Lewis base catalyst, which kinetically disfavors the formation of a zwitterionic intermediate.[8] To the best of our knowledge, only one stoichiometric addition reaction of weakly activated phenylallene with tributylphosphine was reported in 1984 furnishing a phosphacyclopropane product.[9]

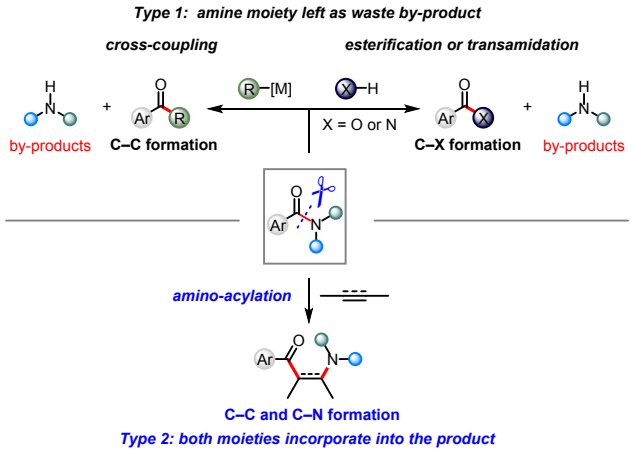
Scheme 1. Two General Activation Modes for the Transformation of Allenes



The amide is a ubiquitous functional group with numerous methods for its synthesis. However, it is noteworthy that the amides feature only limited use as synthetic intermediate. It comes as no surprise that the C−N bonds of amide have high stability and rigidity due to the strong resonance effect between the nitrogen lone pair and the anti-bonding orbital (π*) of the carbonyl group.[10] The selective breaking C−N bond in amides has been recognized a longstanding challenge in synthetic chemistry. Recently,

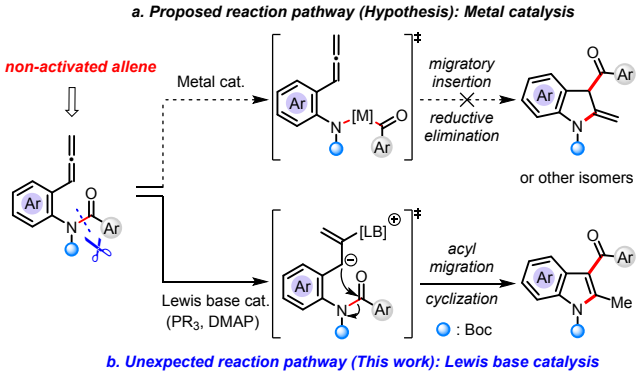
considerable progress has been achieved for transition-metal catalyzed cleavage of amide C−N bonds.[11] In particular, various ketones have been successfully synthesized via catalytic cross-coupling of amides with the organometallic reagents[12] or the unsaturated chemical compounds.[13] And transition-metal-free transamidation via cleavage of the amide C−N bonds has also been developed.[14] This strategy has become a powerful tool to construct C−C or C−heteroatom bonds. Despite these elegant precedents in transformation of amides via cleavage of C−N bonds, all these reactions are inherently restricted to low atom economy due to the wastage of the amine moiety of amides (Scheme 2, type 1). In contrast, the amino-acylation of multiple chemical bonds will be highly desirable, as it incorporates both moieties of the amide into the product (Scheme 2, type 2). These reactions were usually achieved via electrophilic activation of the alkyne, followed by *N*-addition of the amide to form a zwitterionic intermediate and subsequent [1,3]-acyl migration.[15] Unfortunately, there are only limited reports in this area, even though there are some other progresses showing that the amino-acylation of highly active arynes[16] and ynones[17] with amides can be realized. In this regard, development of new catalytic amino-acylation reactions of multiple chemical bonds via cleavage of the amide C−N bond is highly desirable.

Scheme 2. Two Reaction Types for the Cleavage of Amide C−N Bonds to Construct New Chemical Bonds



Originally we planned an intramolecular amino-acylation of allene by using transition metal catalyst (Scheme 3). We proposed that an acylmetal-amido species could be generated by oxidative addition of low-valent metal catalyst into the amide C−N bond.[11] The subsequent amino-acylation would be achieved by coordination of this acylmetal-amido intermediate to multiple chemical bond, followed by migratory insertion and reductive elimination (Scheme 3a). However, we found that an unexpected metal-free amino-acylation occurred (Scheme 3b). Herein, we would like to report a novel intramolecular amino-acylation of arylallenes via Lewis base catalysis and C−N bond cleavage, affording the 2-methyl-3-aroylindoles that have been recognized as "privileged structure" in pharmaceutical industry.[18] Lewis base catalysis of weakly activated allenes has been achieved for the first time in this research. The detailed mechanism is elucidated by control experiments and DFT calculations.

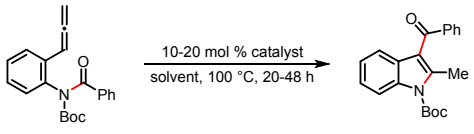
Scheme 3. Amino-acylation of Allenes via Selective Cleavage of Amide C−N Bond

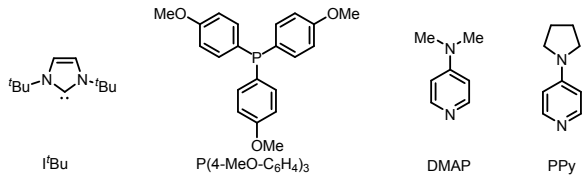


Results and Discussion

We designed and synthesized an arylallene containing amide **1a** as the starting material. Transition-metal-catalyzed alcoholysis or Suzuki coupling reaction have been achieved recently via cleavage of the amide C−N bond in this type of amides.[19] With **1a** as the substrate, intramolecular amino-acylation of allene was investigated with various transition metal catalyst. To our delight, Rh-catalyzed amino-acylation of **1a** afforded the desired product **2a** in 12% yield with *N*-heterocyclic carbene (NHC) I^{t}Bu as ligand at 80 °C (Table 1, entry 1). Screening other metal catalysts did not improve the

Table 1. Reaction Development[a]





entry	catalyst	solvent	t (h)	yield (%)[b]
1[c]	$Rh(cod)_2OTf$/I^{t}Bu	THF	20	12
2[c]	I^{t}Bu	THF	20	31
3[c]	I^{t}Bu	1,4-dioxane	20	33
4	I^{t}Bu	1,4-dioxane	20	35
5	PPh_3	1,4-dioxane	20	trace
6	P(*n*-Bu)$_3$	1,4-dioxane	20	trace
7	PCy_3	1,4-dioxane	20	38
8	P(4-MeO-C$_6$H$_4$)$_3$	1,4-dioxane	20	46
9	DMAP	1,4-dioxane	20	51
10	PPy	1,4-dioxane	20	48
11[d]	DMAP	1,4-dioxane	48	37
12[d]	DMAP	THF	48	61
13[e]	**DMAP**	**THF**	**48**	**66 (63)**[f]
14[e,g]	DMAP	THF	48	50
15[e,h]	-	THF	48	0

[a]Reaction conditions: **1a** (0.1 mmol), catalyst (20 mol %), solvent (0.5 mL), 100 °C. [b]The yield was determined by GC with *n*-dodecane as an internal standard. [c]80 °C. [d]Solvent (1 mL). [e]THF (2 mL) [f]Isolated yield in the parenthesis. [g]With 10 mol % DMAP. [h]Without catalyst.

yield of the **2a** (see Table S1 in Supporting Information). Surprisingly, the control experiment showed that **2a** was obtained in 31% yield with I^{t}Bu as catalyst without transition-metal-catalyst (Table 1, entry 2). The yield of **2a** was increased to 35% when the reaction was performed at 100 °C in 1,4-dioxane (Table 1, entry 4). Because transformations of activated allenes bearing an electron-withdrawing group via Lewis base catalysis have been broadly investigated, we speculated that the I^{t}Bu might play a role of Lewis base catalyst in this reaction due to its good σ-donor property and the conjugated effect of arylallene. Phosphines were subsequently tested because they are the most common Lewis base catalysts in the transformation of activated allenes. The trace amount of **2a** was observed with triphenylphosphine or tributylphosphine (Table 1, entries 5 and 6). However, the electron-rich tricyclohexylphosphine and tri(4-methoxyphenyl)phosphine yielded **2a** in 38% and 46% yield, respectively (Table 1, entries 7 and 8). We then turned to pyridine-based Lewis base catalyst and found that the yield of **2a** was increased to 51% when the readily available and bench-stable 4-dimethylaminopyridine (DMAP) was used (Table 1, entry 9). Different solvents were then examined (see Table S1 in Supporting Information). The moderate yields of **2a** were obtained with THF, CH_3CN, and toluene, but **2a** was not detected with the protonic solvent, such as MeOH. Further evaluation of the reaction concentrations showed that the yield of **2a** could be improved to 66% in THF at lower concentration (0.05 M) (Table 1, entry 13). The yield was decreased to 50% when lowering the catalyst loading to 10 mol % (Table 1, entry 14). Finally, a control experiment revealed the importance of the catalyst, and no reaction occurred in the absence of Lewis base catalyst (Table 1, entry 15).

With the suitable reaction conditions in hand, we explored the scope of different *N*-(*ortho*-allenylaryl)amides (Table 2). The electronic effects of different aniline substituents were first examined. Introduction of the electron donating groups, such as *p*-Me, *p*-OMe, and *p*-Ph, to the aniline moiety of **1** led to the corresponding products **2b**, **2c** and **2d** in moderate to good yields (58-74%). The substitutions of electron-withdrawing group (*p*-CF_3 or *p*-CN) on the aryl ring of the aniline moiety provided **2e** and **2f** in 86% and 79% yield. The halogen atoms were also well tolerated (**2g** and **2h**). Notably, the good functional group tolerance makes this method very useful for the synthesis of highly functionalized 3-aroylindoles. The substrate with *meta*-Me on the aryl ring of aniline gave **2i** in moderate yield. However, a trace amount of product **2j** was obtained with the substrate bearing methyl group at the *ortho*-position of aniline moiety, presumably due to the steric effect. Furthermore, the 2-ethyl-3-aroylindole **2k** was obtained in moderate yield with corresponding **1k** (R = Me) as substrate. Finally, the Boc group was found essential for the successful C−N bond cleavage. When the substrate **1l** without *N*-Boc protection was used as substrate, no C−N bond cleavage was detected and a direct addition product 2-methyl indole **2l** was obtained in good yield.

Next, we investigated the scope of the acyl group of **1**. The aroyl moiety bearing electron-donating groups (Me, OMe) and electron-withdrawing groups (CO_2Me, NO_2, CF_3) are well tolerated affording the corresponding 3-aroylindoles in moderate to good yields (**2m**−**2q**, 44−72%). The reaction tolerated halogen atoms (F, Cl, Br) at the *para*-, *meta*-, and *ortho*- positions of phenyl in aryl group (**2r**−**2u**). Moreover, the hetero-aroyl group, such as furan-2-carbonyl and thiophene-2-carbonyl, could also be tolerated, leading to the corresponding products **2w** and **2x** in 82% and 80% yield.

Synthetic Application. To demonstrate the synthetic utility of this new methodology, 2-methyl-3-aroylindole product **2a** was converted into several useful synthetic intermediates via common manipulations (Figure 1). The Boc protecting group can be easily removed under mild conditions (K_2CO_3/MeOH/H_2O), subsequent bromination with *N*-bromosuccinimide (NBS) afforded 3*H*-indole **3** in overall 74% yield by two steps. Alternatively, a direct bromination of **2a** with NBS gave benzilic bromide **4** in 83% yield. Furthermore, by sequential Wittig reaction and Boc deprotection, 3-alkenyl indole **5** was obtained easily in 88% yield. In addition, routine reduction of **2a** with $NaBH_4$ generated the corresponding alcohol **6** in excellent yield.

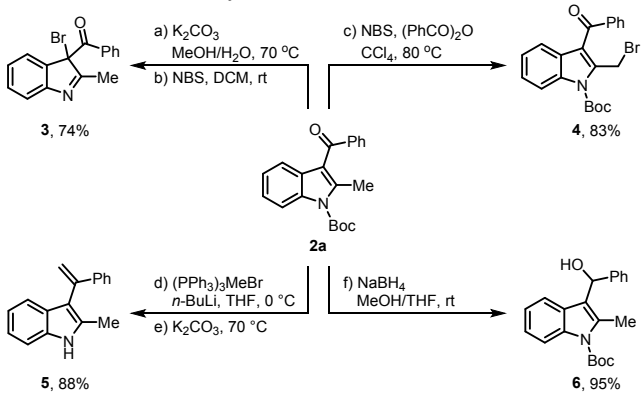


Figure 1. Transformations of 2-methyl-3-aroylindole **2a**

2-Methyl-3-aroylindole is one of the "privileged structures" in drug discovery due to their excellent capability of binding to many receptors with high affinity.[18] For example, Pravadoline (WIN 48098), an antiinflammatory and analgesic drug, contains the core structure of 2-methyl-3-aroylindole.[20] By Pd-catalyzed cross-coupling and the following acylation, **1n** was easily prepared in two steps by one column separation. from commercially available reagents. Then, DMAP-catalyzed amino-acylation of **1n** afforded **2n** in good yield under the standard conditions. With **2n** as the substrate, the pravadoline was easily obtained in 77% yield by two steps through Boc deprotection and sequent substitution reaction with the corresponding alkyl bromide (Scheme 4).

Scheme 4. **Synthesis of Antiinflammatory and Analgesic Drug Pravadoline**

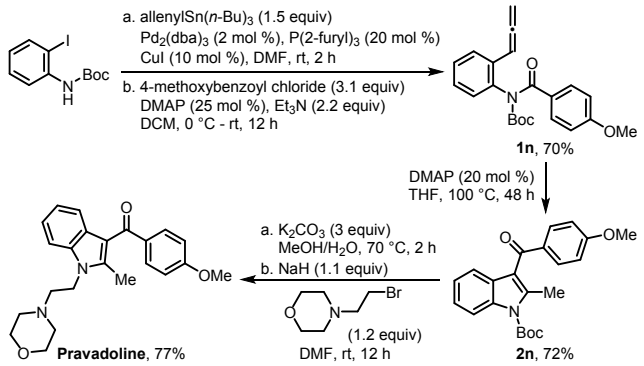
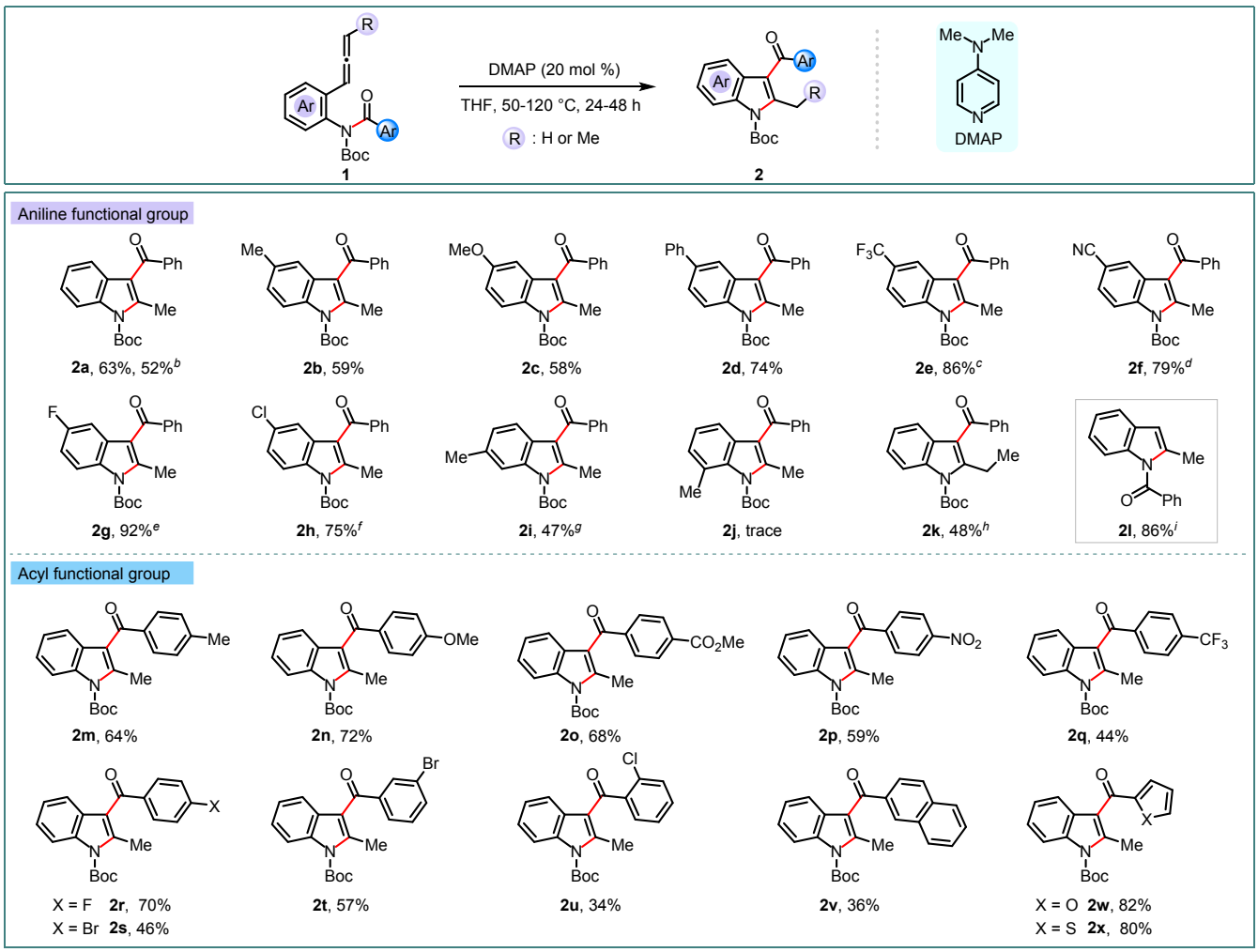


Table 2. Substrate Scope of Intramolecular Amino-acylation of Allenes via C−N Bond Cleavage[a]

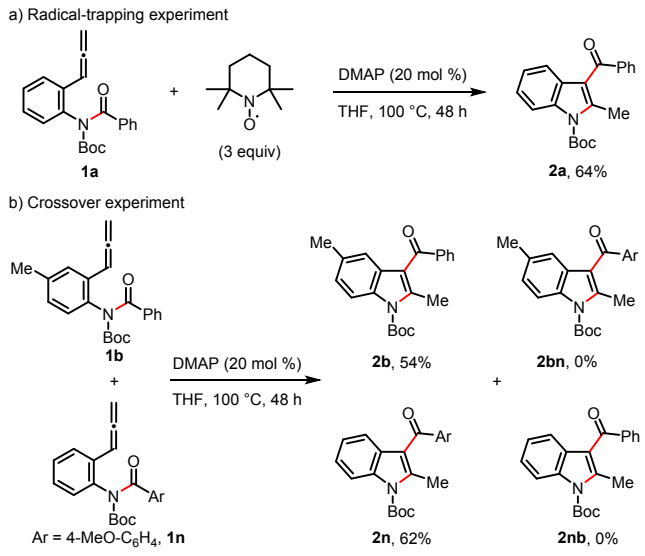


[a]All reactions were conducted with **1** (0.1 mmol), DMAP (20 mol %) in THF (2 mL) at 100 °C for 48 h and isolated yield was provided unless otherwise noted. [b]With 1 mmol **1a**. [c]At 70 °C, 36 h. [d]At 50 °C, 24 h [e]At 60 °C, 36 h. [f]At 70 °C, 24 h. [g]At 120 °C, 36 h. [h]30 mol % DMAP, THF (1 mL). [i]With corresponding ArNH(COPh) **1l**

Mechanistic Study. To gain the insight into the reaction mechanism, several control experiments were performed. In order to explore the possibility of a radical mechanism,[21] the radical inhibiting or trapping experiment was first conducted. When the 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was used as an additive under the standard conditions, there is no effect on the yield of **2a** (Scheme 5a). This result indicates that the reaction does not proceed through a radical pathway. Next, the crossover reaction was carried out with **1b** and **1n** as the substrates. The products **2b** and **2n** were obtained, and no crossover product **2bn** or **2nb** was observed (Scheme 5b). This result demonstrates that the amino-acylation of allene occurs in an intramolecular fashion.

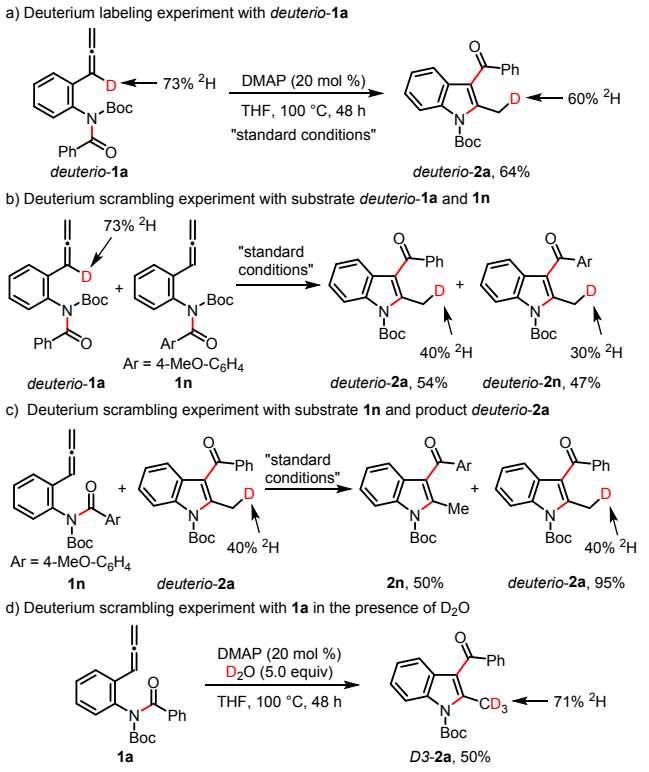
Then, the deuterium labeling experiments were performed to understand the mechanism. The intramolecular amino-acylation of α-deuterium labeled allene *deuterio*-**1a** (73% ^{2}H) afforded *deuterio*-**2a** smoothly under the standard conditions, which incorporates a single deuterium atom (60% ^{2}H) at the 2-methyl group of the product (Scheme 6a). We then performed the crossover deuterium scrambling experiment with *deuterio*-**1a** (73% ^{2}H) and **1n**, leading to the products of *deuterio*-**2a** (40% ^{2}H) and *deuterio*-**2n** (30% ^{2}H) under the standard conditions (Scheme 6b). The result indicates that there may be a reaction intermediate which could exchange with active hydrogen in the proton transfer process, such as the NH intermediate or the heteroatom anions.

Scheme 5. Control Experiments



Furthermore, a deuterium scrambling experiment with substrate **1n** and *deuterio*-**2a** (40% ^{2}H) was performed to rule out the possible deuterium transfer from the relatively active 2-methyl group of 3-aroylindole product (Scheme 6c).[22] As expected, the amino-acylation product **2n** was obtained without deuterium incorporation and the *deuterio*-**2a** (40% ^{2}H) was recovered in 95% yield. Finally, the amino-acylation of **1a** was carried out in the presence of 5 equivalent of deuterium oxide (D_2O), which afforded the *D3*-**2n** as the product incorporated three deuterium atom (71% ^{2}H) at the 2-methyl group of the product (Scheme 6d). This result indicates that a trace amount of water as proton shuttle may assist the proton transfers or an active reaction intermediate that could exchange with active hydrogen exists in the reaction pathway.

Scheme 6. Deuterium Labeling Experiments and Scrambling Experiments



Based on the mechanistic studies, the following reaction pathway was proposed via Lewis base catalysis as depicted in Scheme 7. The reaction starts with nucleophilic addition of DMAP to aryl allene **1a**, affording the pyridinium enamine **INT1**.[23] This zwitterionic intermediate then undergoes nucleophilic addition to the amide's carbonyl to give intermediate **INT2**. Subsequent C−N bond cleavage of the hemiaminal gives the intermediate **INT3**, which can be regarded as a deprotonated amine. We have shown that a direct allylic [1,3]-proton transfer is rather difficult due to the high ring strain in the transition state.[24] Thus, a successive [1,4] and [1,6]-proton transfer generates the α,β-unsaturated ketone **INT5**. The following nucleophilic addition of nitrogen anion to β- position of α,β-unsaturated ketone results in **INT6**.

Scheme 7. Proposed Mechanism

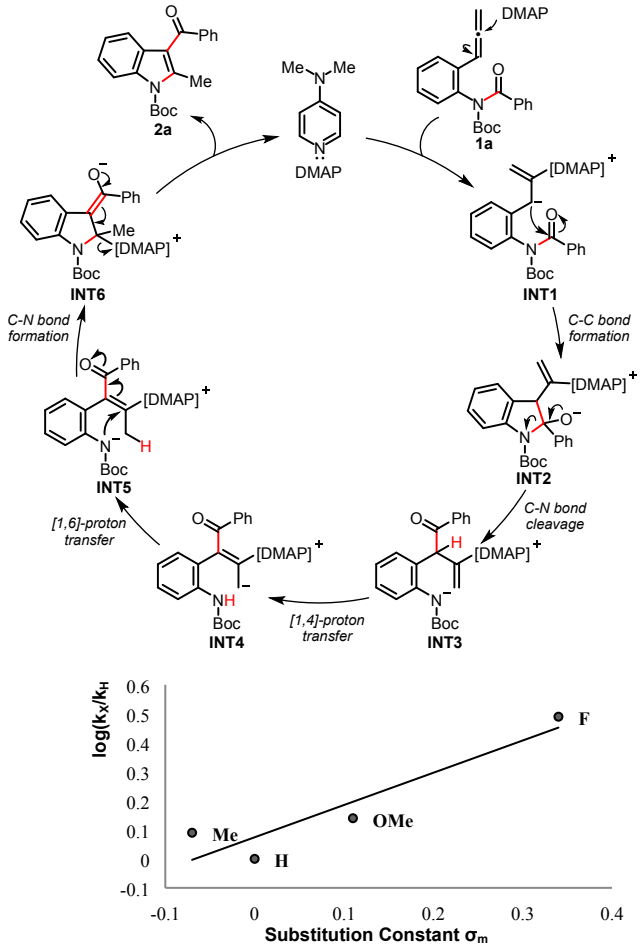


Figure 2. Hammett plot of kinetic competition experiments

Finally, expulsion of DMAP produces the amino-acylation product **2a** and closes the Lewis base catalytic cycle. The deuterium labeling and scrambling experiments corroborates a sequential [1,4] and [1,6]-proton transfer in the proposed catalytic cycle (Scheme 6). However, we are not sure whether a trace amount of water assists the proton transfer process or not. Furthermore, The hammett plot of kinetic competition experiments showed a good positive linear effect when the plot is derived from the *meta*-position of allenes σ_m values (Figure 2. for details see Figure S1, S2, and S3 in Supporting Information). This indicates that the rate-determine step of this amino-acylation reaction may be the nucleophilic addition of DMAP to allene.

DFT Calculations

To further elucidate the reaction mechanism and the proton transfer processes, we performed the density functional theory (DFT) calculations (**Figure 3**). We choose **1a** as the substrate and DMAP as the catalyst to investigate the reaction mechanism. Firstly, the nucleophilic addition of DMAP to **1a** generates the zwitterionic intermediate **INT1** (the Gibbs energy of activation for this step is 28.3 kcal/mol). Subsequently, the intramolecular nucleophilic addition of the zwitterionic species to the carbonyl carbon from different sides occurred to give **INT2** (via **TS2**) and **INT2'**

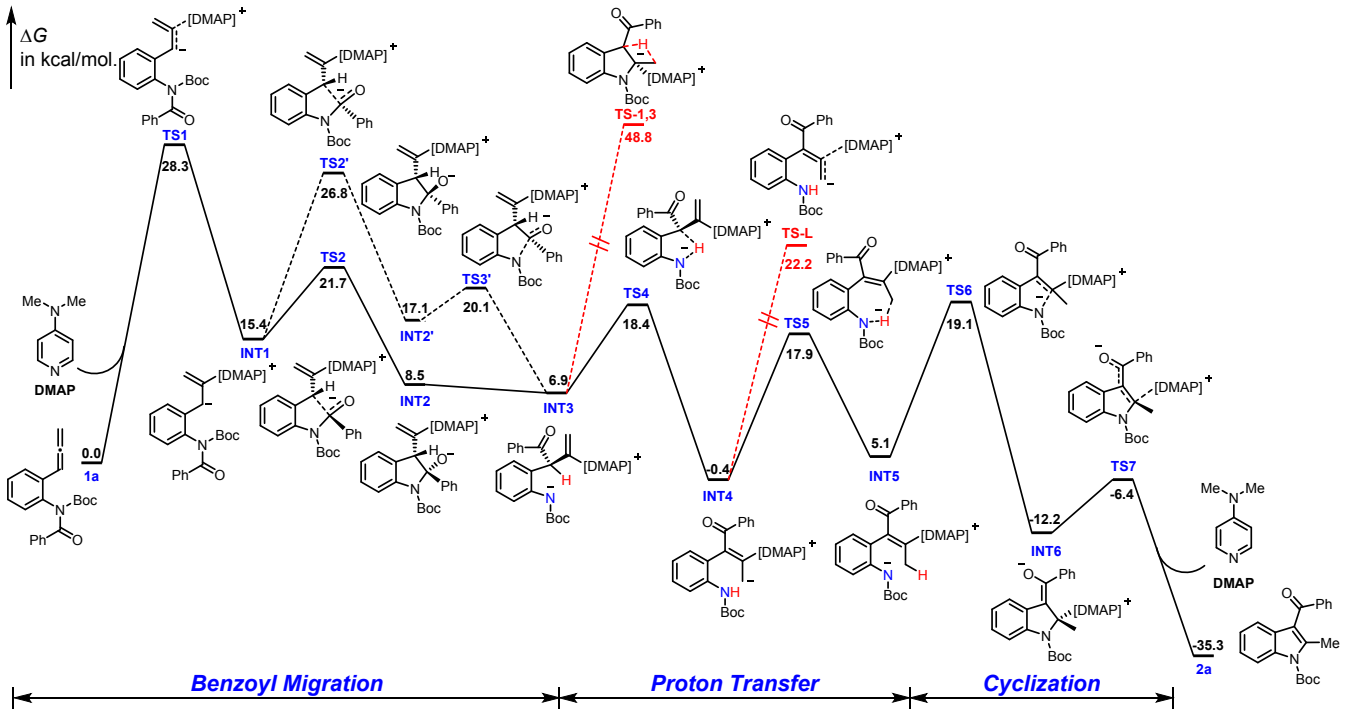


Figure 3 . Gibbs energy profile for the reaction of substrate **1a** under the catalysis of DMAP. Computed at the SMD(THF)/M06-2X/6-311+G(d,p)//M06-2X/6-31+G(d,p) level.

(via **TS2'**), respectively. The Gibbs energy of activation involving **TS2** is 6.3 kcal/mol, whereas this value for addition reaction involving **TS2'** is 11.4 kcal/mol, indicating that formation of **INT2** is favored. After that, **INT2** undergoes fragmentation, by breaking a C−C bond to give **INT3**, in which a NBoc anion is generated. This is a barrierless process because scanning the potential energy surface of this C−C bond breaking is a downhill process without involving a transition state. It is easy for **INT3** to undergo the intramolecular [1,4]-proton transfer forming **INT4** (the Gibbs energy of activation for this step is 11.5 kcal/mol). Then, an intramolecular [1,6]-proton transfer could form **INT5** with a NBoc anion (the Gibbs energy of activation for this step is 18.3 kcal/mol). **INT4** might also expel DMAP catalyst to generate the allene intermediate. However, the Gibbs energy of activation for this step is 22.6 kcal/mol (via **TS-L**), which is higher than that of the intramolecular [1,6]-proton transfer of forming **INT5**. Comparing with the intramolecular [1,4]- and [1,6]-proton transfers, assisted with NBoc anion, the direct [1,3]-proton transfer is quite difficult (the Gibbs energy of activation for this step is 41.9 kcal/mol, via **TS-1,3**). The crossover deuterium labeling experiments could be explained by the generation of **INT4** that contains an acidic hydrogen which can undergo hydrogen exchange intermolecularly in the reaction process (Scheme 6b and 6c). The nucleophilic addition of nitrogen anion in **INT5** to *β*-position of *α,β*-unsaturated ketone gives **INT6** (the Gibbs energy of activation for this step is 14.0 kcal/mol). Finally, elimination of the DMAP via **TS7** affords product **2a** (the Gibbs energy of activation for this step is 5.8 kcal/mol). The computations suggest that the nucleophilic addition of DMAP to allene is the rate-limiting step, which is consistent with the kinetic competition experiments (Figure 2).

In the above discussion, we don't consider the water catalysis in the proton transfer processes. Previously, we have shown that if the proton transfers (for example, [1,2]- and [1,3]-proton transfers) are very difficult, and water or other proton sources are needed to catalyze these processes.[24] If these proton transfer processes are faster than diffusion controlled process, there is no water assisted proton transfer. However, if the proton transfer processes are slower than diffusion controlled process, then there could be a competition between direct proton transfer and water-assisted proton transfer. Thus, to verify whether the proton shifts can also be assisted by a trace amount of water, we considered the water-assisted pathway (Figure 4). Both [1,4] and [1,6]-proton transfer processes can be assisted by water in a concerted

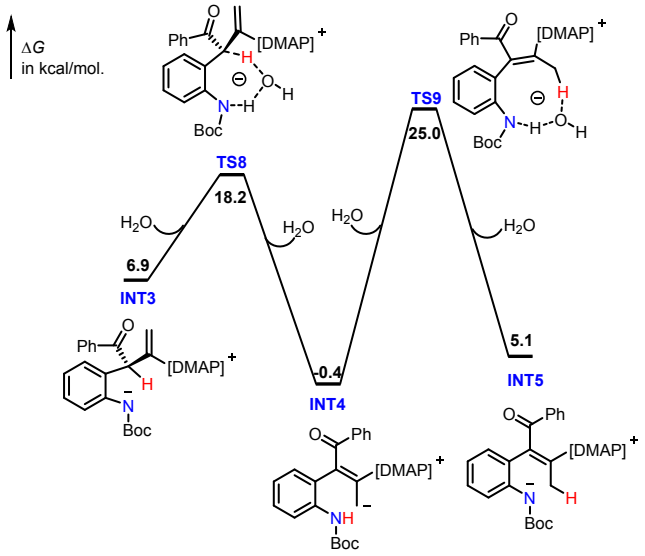


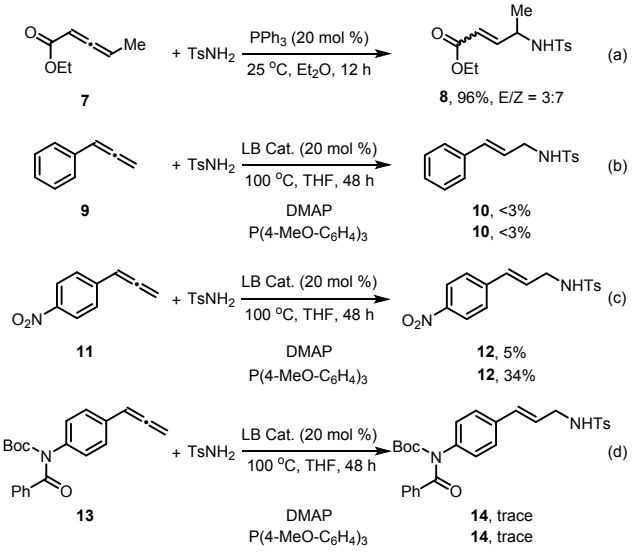
Figure 4 Gibbs energy profile for the proton transfer assisted by water. Computed at the SMD(THF)/M06-2X/6-311+G(d,p)//M06-2X/6-31+G(d,p) level.

pathway.[25] The reaction barrier of [1,4]-proton transfer is 11.3 kcal/mol (**TS8**), which is quite similar to that of the intramolecular [1,4]-proton transfer pathway (11.5 kcal/mol, **TS4** in Figure 3). However, for the [1,6]-proton transfer process assisted by water, the reaction barrier is 25.4 kcal/mol (**TS9**), which is relatively higher than the intramolecular [1,6]-proton transfer pathway (18.3 kcal/mol, **TS5** in Figure 3). These calculations indicate that the [1,4]-proton transfer might be assisted by a trace amount of water in solvent, which can explain the deuterium labeling experiments in Scheme 6 that deuterium and hydrogen can exchange intermolecularly. Also, we have to mention that direct protonations of **INT4** and **INT5** by water are energetically disfavored compared to the water-assisted proton transfers in Figure 4 and these can be ruled out (see Supporting Information).

Further Study

To gain insight into the inherent distinction between weakly activated allenes and activated allenes bearing an electron-withdrawing group in Lewis base catalysis, we performed experiments to compare the reactivity of different allenes though γ-addition reaction with sulfonamide ($TsNH_2$). Phosphine-catalyzed γ-addition of activated allene **7** bearing an electron-withdrawing ester group afforded the desired product **8** in excellent yield at room temperature (Scheme 8a).[26] As expected, weakly activated allenes showed very low reactivity in this Lewis base-catalyzed γ-addition reaction. Addition of phenylallene **9** with $TsNH_2$ afforded **10** in less than 3% yield at 100 °C, leaving untouched starting material in the reaction (Scheme 8b). When the arylallene **11** bearing an electron-withdrawing nitro group at the *para*-position of phenyl was used to test γ-addition of arylallene, the moderate yield of **12** was obtained at 100 °C (Scheme 8c). However, a trace amount of product **14** was observed when γ-addition of the allene **13** with $TsNH_2$ in the presence of Lewis base catalyst under the standard amino-acylation conditions (Scheme 8d). These results demonstrate that the reactivity of aryl allenes is much lower than activated allenes and the Boc-*N*-COPh group on the arene is not an electron-withdrawing group for the activation of allenes.

Scheme 8. Lewis Base Catalyzed γ-Additions of Sulfonamide to Allenes



To further understand the difference of weakly activated allenes, parent allene, and activated allenes bearing an electron-withdrawing group, we compared the reactivity of different allenes with DMAP in the zwitterionic pyridinium enamine intermediate formation step by the density functional theory (DFT) calculations. When the *N*-(*ortho*-allenylphenyl)amide **1a** is used as the substrate, the activation barrier for nucleophilic additon of DMAP to the allene is as high as 28.3 kcal/mol, which is almost the same as phenyl allene **9** (Figure 5a and b). In comparision with the parent allene **15**, the activation barrier of **1a** is 2.5 kcal/mol less, which indicates phenyl group have limited capacity to activate the allene (Figure 5c). However, when an ester group is introduced into the parent allene, the corresponding allenyl ester **16** has decressed activation barrier of nucleophilic addition (about 22.1 kcal/mol), which demonstrates an electron-withdrawing group on the allene kinetically favors the formation of a zwitterionic intermediate (Figure 5d). These theoretical results are consistent with the observed reactivities of allenes in Scheme 8. These results suggest that only increasing the reaction temperature is not responsible for stepping over the inherent obstacle of nucleophilic catalysis of the weakly activated allenes.

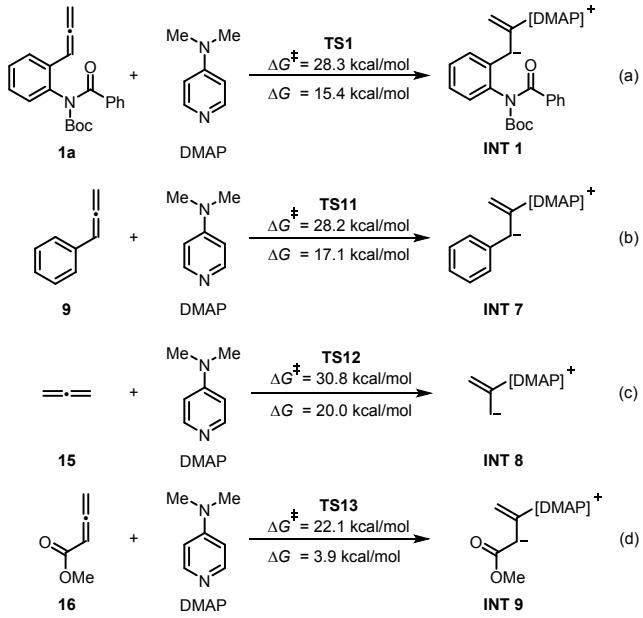


Figure 5 Computed at the SMD(THF)/M06-2X/6-311+G(d,p)//M06-2X/6-31+G(d,p) level.

Conclusion

In summary, we have developed a novel Lewis base-catalyzed amino-acylation of weakly activated allenes to produce 2-methyl-3-aroylindoles, one of the "privileged structures" in pharmaceutical industry. Both acyl and amine moieties are incorporated into the products via selective cleavage of amide C−N bond, overcoming traditional amine moiety as wastage after C(O)−N bond cleavage. The Lewis base catalysis of weakly activated allenes is achieved for the first time. The readily available simple DMAP was used as a nucleophilic catalyst. This protocol provides a simple and efficient strategy for the synthesis of biologically important 2-methyl-3-aroylindoles with a range of substrates. Based on experimental and computational studies, we have proposed a reasonable mechanism for this amino-acylation reaction.

Several conclusions can be drawn from this study. (1) The direct [1,3]-proton transfer is quite difficult. However, this process could be facilitated by a successive [1,4]- and [1,6]-proton transfer which are facile. Likes proton shuttles, nitrogen anion intermediate assists the proton transfer processes via the protonation/deprotonation mechanism. (2) Although direct [1,3]-proton transfer process could be assisted by a trace amount of water, the process is less favorable than intramolecular successive [1,4]- and [1,6]-proton transfer (For details, see Figures S4 and S5 in Supporting Information). (3) The nucleophilic addition of Lewis base catalyst to weakly activated allenes is the rate-limiting step. Due to the high activation barrier of addition of Lewis base catalyst to allene, nucleophilic catalysis of weakly activated allenes is challenging. However, this hurdle may be got over though generating thermodynamically stable intermediates or products. This may provide a good strategy for the transformation of non-activated or weakly activated allenes via Lewis base catalysis in the future.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, DFT calculations, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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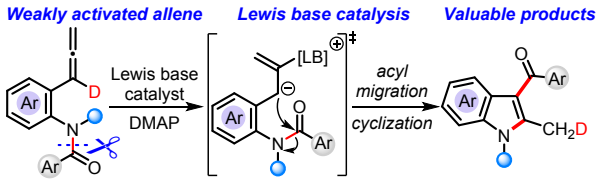
Weakly activated allene
Lewis base catalysis
Valuable products
Lewis base catalyst
DMAP
[LB]
acyl migration
cyclization
Ar
D
N
O
CH2D
Mechanism: sequential [1,4]- and [1,6]-proton transfer