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 much attention over the last decades. However, this type of reaction has so far been limited to activated allenes bearing an electron-withdrawing group. On the other hand, cleavage of an amide C−N bond to forge other chemical bonds has been widely reported but restricted to low atom economy due to the waste of the amine moiety of amides. We initiated a project of metal-catalyzed amino-acylation of allenes via cleavage of amide C−N bonds. Surprisingly, an amino-acylation of weakly activated aryl allenes was discovered via Lewis base catalysis, providing 2-methyl-3-aroylindole products, "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. 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.

Mechanism: sequential [1,4]- and [1,6]-proton transfer

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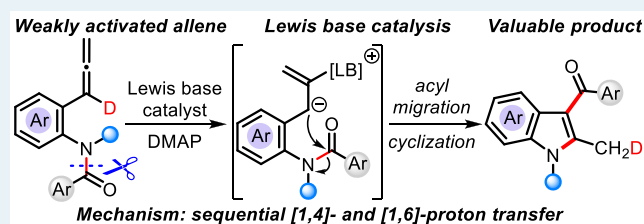
INTRODUCTION

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, or Ru, have been widely used in the conversion of allenes by coordinative activation, mostly via a π-allyl metal

intermediate.[2a,d,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 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 a 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 nonactivated or weakly activated allenes via Lewis base catalysis, such as aryl allenes or alkyl allenes. This may be due to the high activation barrier of nucleophilic addition of the central carbon atom of nonactivated 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

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

Mode A: Metal catalysis

Coordinative activation

Mode B: Lewis Base catalysis (Nucleophilic catalysis)
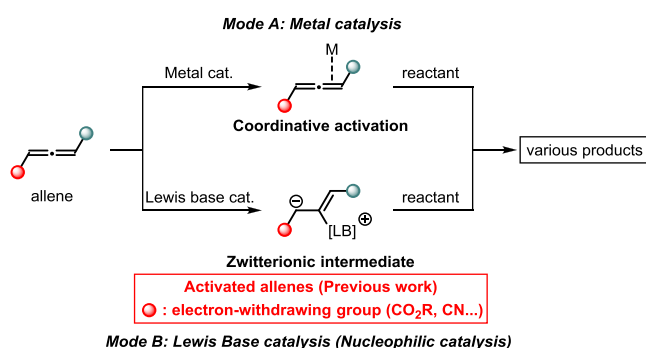
activated phenylallene with tributylphosphine was reported in 1984 furnishing a phosphacyclopropane product.[9]

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 intermediates. 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 antibonding orbital (π^*) of the carbonyl group.[10] The selective breaking of the C−N bond in amides has been recognized a long-standing 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 organometallic reagents[12] or unsaturated chemical compounds.[13] Transition-metal-free transamidation via cleavage of 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 waste of the amine moiety of amides (Scheme 2, type 1).

Scheme 2. Two Reaction Types for the Cleavage of Amide C−N Bonds to Construct New Chemical Bonds
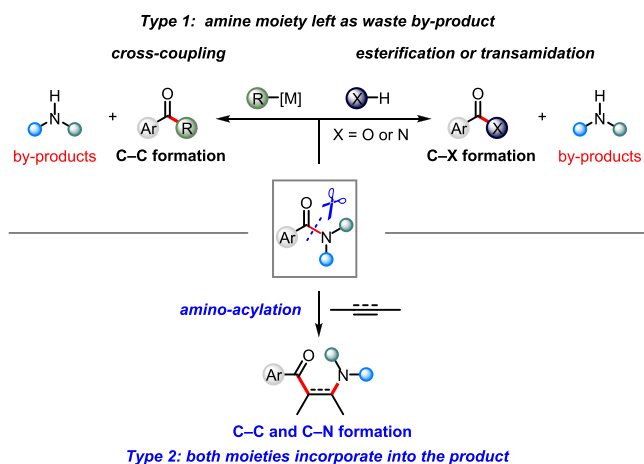
In contrast, the amino-acylation of multiple chemical bonds will be highly desirable, as it incorporates both moieties of the amide into the product (Scheme 2, type 2). These reactions were usually achieved via electrophilic activation of the alkyne, followed by N-addition of the amide to form a zwitterionic intermediate and subsequent [1,3]-acyl migration.[15] Unfortunately, there are only limited reports in this area, even though there has been some other progress 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.

Originally we planned an intramolecular amino-acylation of allene using a 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 bonds, followed by migratory insertion and reductive elimination (Scheme 3a). However, we found that an unexpected metal-free amino-
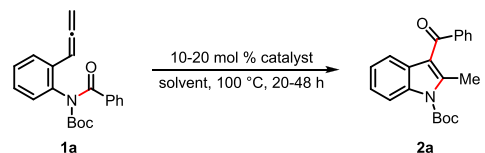
Scheme 3. Amino-acylation of Allenes via Selective Cleavage of Amide C−N Bond
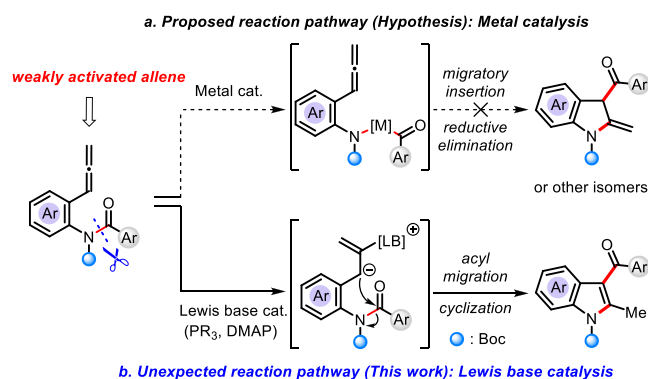
acylation occurred (Scheme 3b). Herein, we report a novel intramolecular amino-acylation of arylallenes via Lewis base catalysis and C−N bond cleavage, affording the 2-methyl-3-aroylindoles that have been recognized as "privileged structures" in the pharmaceutical industry.[18] Lewis base catalysis of weakly activated allenes has been achieved for the first time in this research. The detailed mechanism is elucidated by control experiments and DFT calculations.

■ 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 amide.[19] With **1a** as the substrate, intramolecular amino-acylation of allene was investigated with various transition-metal catalysts. 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 yield of **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 the 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 the 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. A 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). Moderate yields of **2a** were obtained with THF, CH$_3$CN, and toluene, but **2a** was not detected with a 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

Table 1. Reaction Development[a]

entry	catalyst	solvent	t (h)	yield (%)[b]
1[c]	Rh(cod)$_2$OTf/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	d
6	P(n-Bu)$_3$	1,4-dioxane	20	d
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[e]	DMAP	1,4-dioxane	48	37
12[e]	DMAP	THF	48	61
13[f]	**DMAP**	**THF**	**48**	**66 (63)**[g]
14[f,h]	DMAP	THF	48	50
15[f,I]		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]Trace. [e]Solvent (1 mL). [f]THF (2 mL). [g]Isolated yield in the parentheses. [h]With 10 mol % DMAP. [I]Without catalyst.

concentration (0.05 M) (Table 1, entry 13). The yield was decreased to 50% when the catalyst loading was reduced 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 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 groups (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 to be 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-methylindole **2l** was obtained in good yield.

Next, we investigated the scope of the acyl group of **1**. The aroyl moieties bearing electron-donating groups (Me, OMe) and electron-withdrawing groups (CO$_2$Me, 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 the aryl group (**2r−2u**). Moreover, heteroaroyl groups, 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$_2$CO$_3$/MeOH/H$_2$O), and subsequent bromination with N-bromosuccinimide (NBS) afforded 3H-indole **3** in overall 74% yield in 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.

2-Methyl-3-aroylindole is one of the "privileged structures" in drug discovery due to its excellent capability of binding to many receptors with high affinity.[18] For example, pravadoline (WIN 48098), an anti-inflammatory 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, pravadoline was easily obtained in 77% yield in two steps through Boc deprotection and subsequent substitution reaction with the corresponding alkyl bromide (Scheme 4).

Mechanistic Study. To gain insight into the reaction mechanism, several control experiments were performed. In order to explore the possibility of a radical mechanism,[21] a radical inhibiting or trapping experiment was first conducted. When 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was used as an additive under the standard conditions, there was 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 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, 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 that could exchange with

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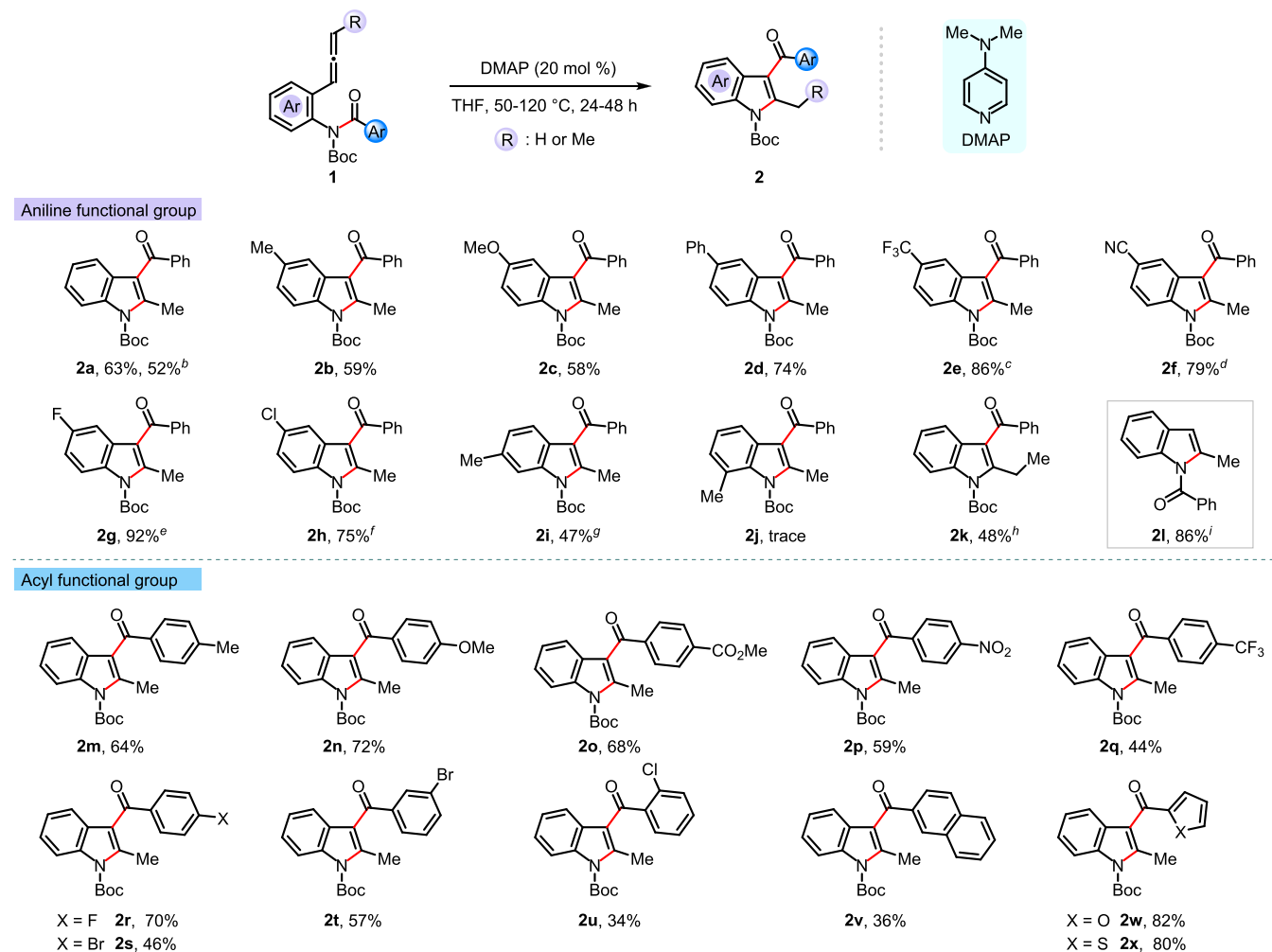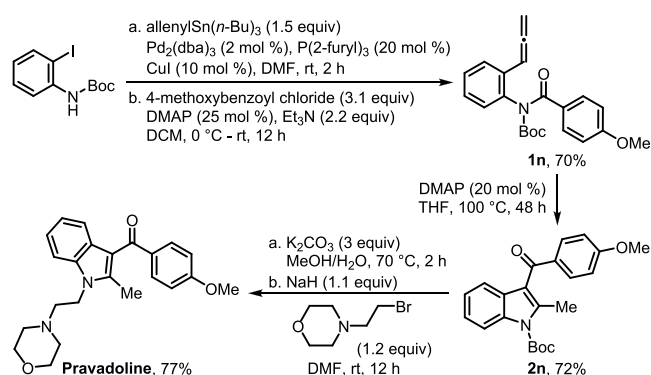

[a]All reactions were conducted with **1** (0.1 mmol) and DMAP (20 mol %) in THF (2 mL) at 100 °C for 48 h, and isolated yield was provided unless otherwise noted. [b]With 1 mmol **1a**. [c]At 70 °C, 36 h. [d]At 50 °C, 24 h. [e]At 60 °C, 36 h. [f]At 70 °C, 24 h. [g]At 120 °C, 36 h. [h]30 mol % DMAP, THF (1 mL). [i]With corresponding ArNH(COPh) **1l**
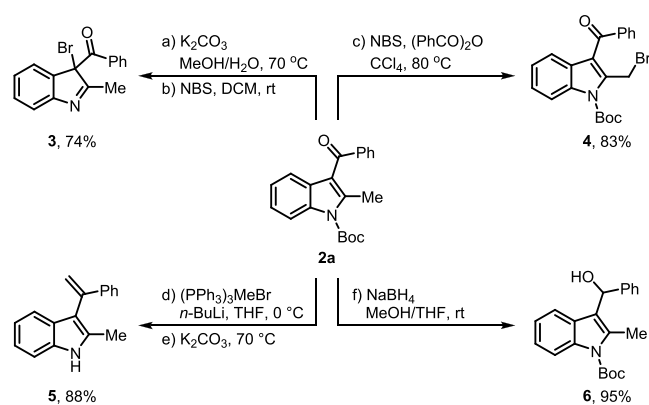
Figure 1. Transformations of 2-methyl-3-aroylindole **2a**.

Scheme 4. Synthesis of Anti-inflammatory and Analgesic Drug Pravadoline

active hydrogen in the proton transfer process, such as the NH intermediate or heteroatom anions.

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 equiv of deuterium oxide (D₂O), which afforded d_3-**2a** as the product incorporating three deuterium atoms (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
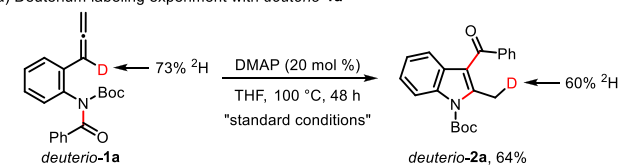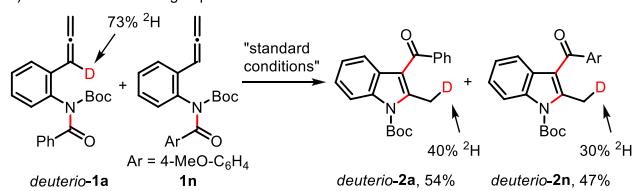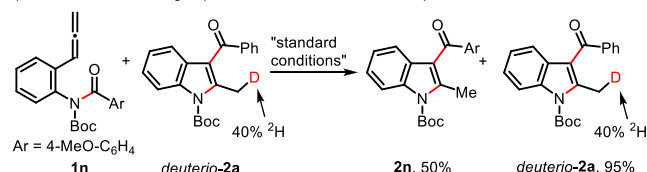
Scheme 5. Control Experiments

a) Radical-trapping experiment
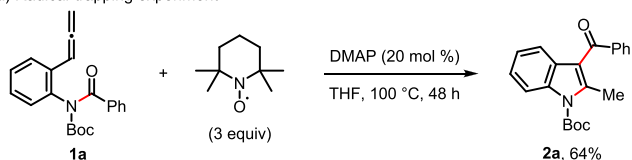

b) Crossover experiment
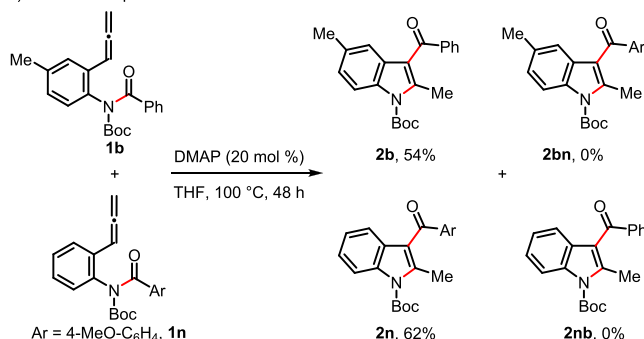
Scheme 6. Deuterium Labeling Experiments and Scrambling Experiments

a) Deuterium labeling experiment with *deuterio*-1a

b) Deuterium scrambling experiment with substrate *deuterio*-1a and 1n

c) Deuterium scrambling experiment with substrate 1n and product *deuterio*-2a

d) Deuterium scrambling experiment with 1a in the presence of D$_2$O
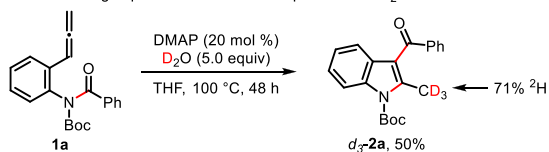
active reaction intermediate that could exchange with active hydrogen may exist in the reaction pathway.

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

Scheme 7. Proposed Mechanism
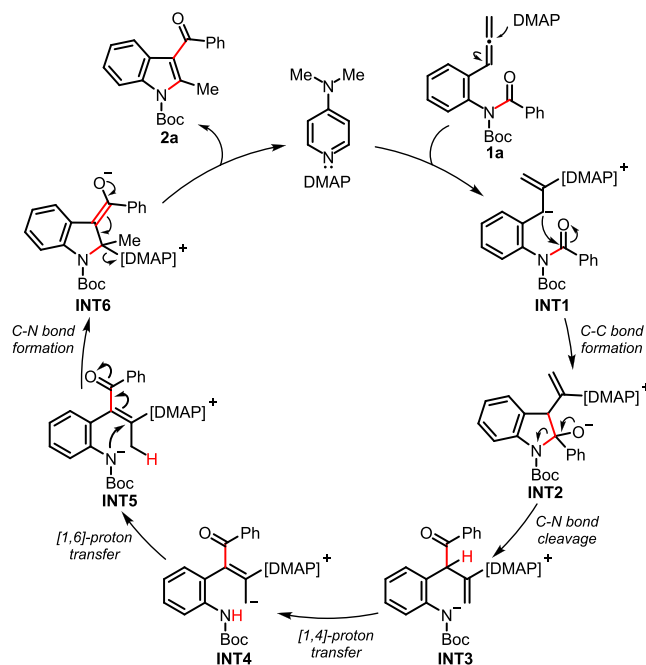
direct allylic [1,3]-proton transfer is rather difficult due to the high ring strain in the transition state.[24] Thus, a successive [1,4]- and [1,6]-proton transfer generates the α,β-unsaturated ketone **INT5**. The following nucleophilic addition of nitrogen anion to the β-position of the α,β-unsaturated ketone results in **INT6**.

Finally, expulsion of DMAP produces the amino-acylation product **2a** and closes the Lewis base catalytic cycle. The deuterium labeling and scrambling experiments corroborate 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. Furthermore, the Hammett plot of kinetic competition experiments showed a good positive linear effect when the plot was derived from the σ$_m$ values of the *meta*-position of allenes (Figure 2; for details see Figures S1, S2, and S3 in
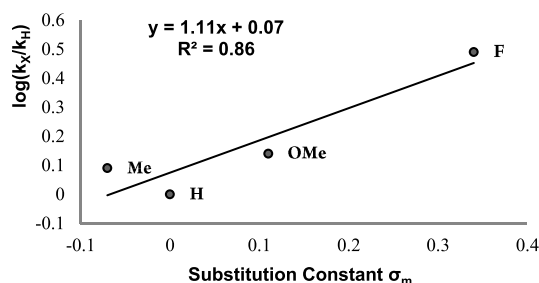
Figure 2. Hammett plot of kinetic competition experiments

Supporting Information). This indicates that the rate-determining 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 density functional theory (DFT) calculations (Figure 3). We chose **1a** as the substrate and DMAP as the catalyst to investigate the reaction mechanism. First, the nucleophilic addition of DMAP to **1a** generates the zwitterionic

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

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 occurs to give **INT2** (via **TS2**) or **INT2′** (via **TS2′**). The Gibbs energy of activat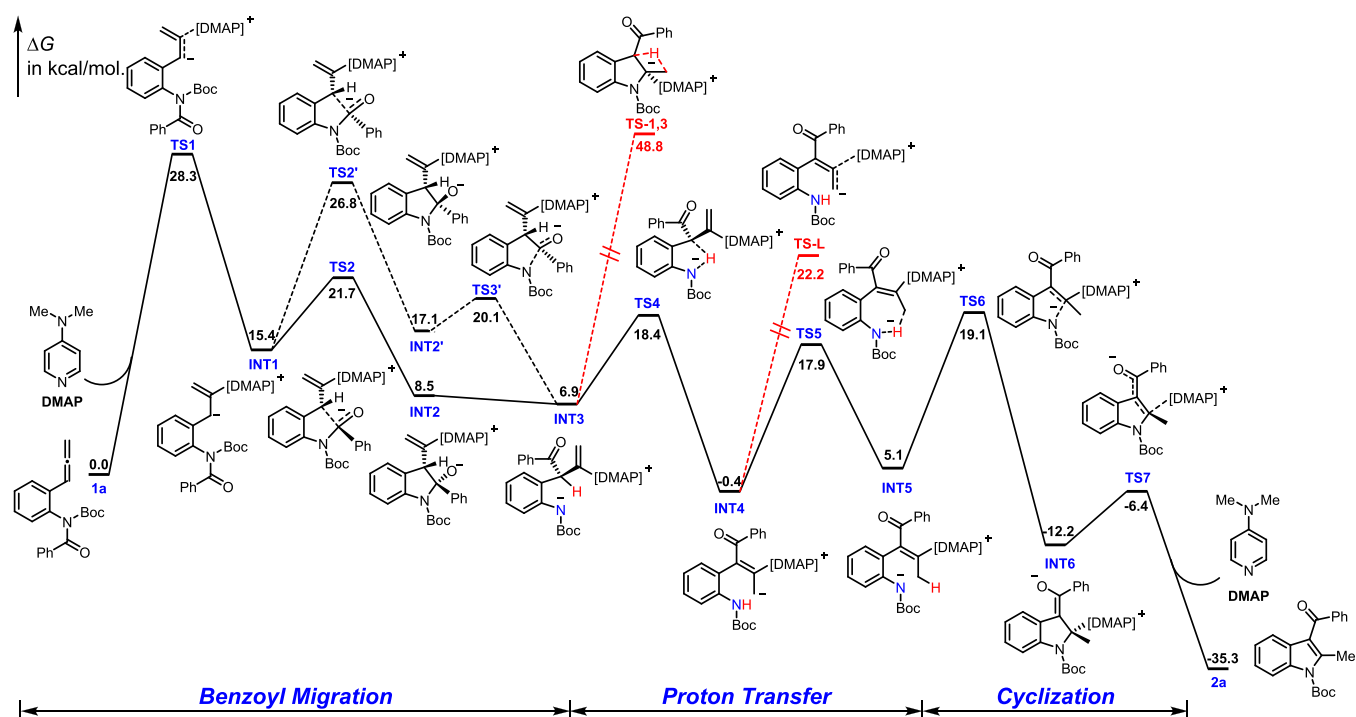ion involving **TS2** is 6.3 kcal/mol, whereas this value for addition reaction involving **TS2′** is 11.4 kcal/mol, indicating that formation of **INT2** is favored. After that, **INT2** undergoes fragmentation, by breaking a C−N bond to give **INT3**, in which an N-Boc anion is generated. This is a barrierless process because scanning the potential energy surface of this C−N 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 an N-Boc 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**. Compared with the intramolecular [1,4]- and [1,6]-proton transfers, assisted by the N-Boc 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 deuterium scrambling experiments could be explained by the generation of **INT4**, which contains an acidic hydrogen that can undergo hydrogen exchange intermolecularly in the reaction process (Scheme 6b,c). The nucleophilic addition of nitrogen anion in **INT5** to the β-position of the 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 do not consider 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, 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 processes, then there could be a competition between direct proton transfer and water-assisted proton transfer. Thus, to verify whether the proton transfers 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 pathway.[25] The reaction barrier of [1,4]-proton transfer is 11.3 kcal/mol (via **TS8**), which is quite similar to that of the intramolecular [1,4]-proton transfer pathway (11.5 kcal/mol, via **TS4** in Figure 3). However, for the [1,6]-proton transfer process assisted by water, the reaction barrier is 25.4 kcal/mol (via **TS9**), which is relatively higher than the intramolecular [1,6]-proton transfer pathway (18.3 kcal/mol, via **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 protonation of **INT4** and **INT5** by water is 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
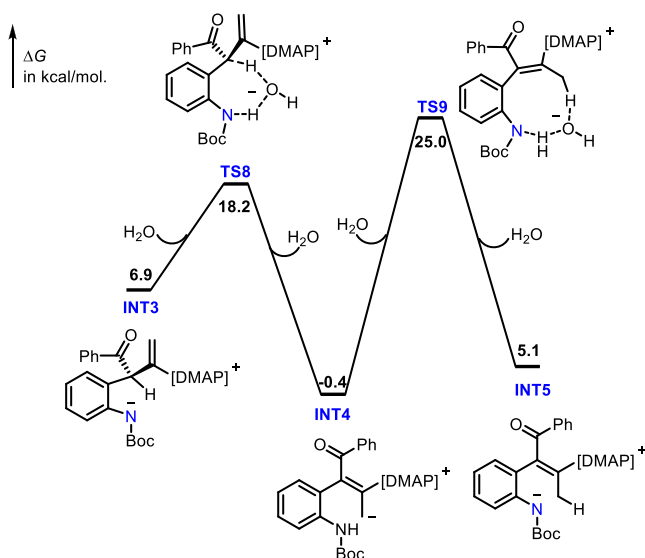
Figure 4. Gibbs energy profile for the proton transfer assisted by water. Computed at the SMD(THF)/M06-2X/6-311+G(d,p)//M06-2X/6-31+G(d,p) level.

catalysis, we performed experiments to compare the reactivity of different allenes though γ-addition reaction with sulfonamide (TsNH₂). 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

Scheme 8. Lewis Base Catalyzed γ-Additions of Sulfonamide to Allenes
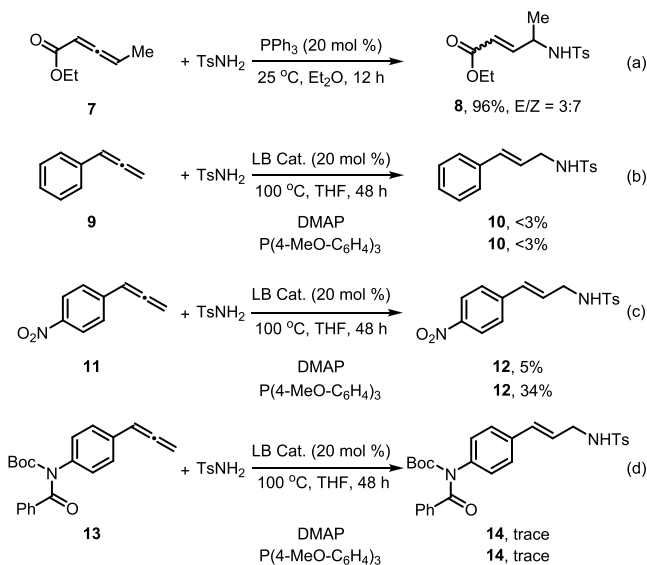
very low reactivity in this Lewis base-catalyzed γ-addition reaction. Addition of phenylallene **9** with TsNH₂ afforded **10** in less than 3% yield at 100 °C, leaving untouched starting material in the reaction (Scheme 8b). When the arylallene **11** bearing an electron-withdrawing nitro group at the *para*-position of phenyl was used to test γ-addition of arylallene, a moderate yield of **12** was obtained at 100 °C (Scheme 8c). However, a trace amount of product **14** was observed for γ-addition of the allene **13** with TsNH₂ 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.

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 density functional theory (DFT) calculations. When the *N*-(*ortho*-allenylphenyl)amide **1a** is used as the substrate, the activation barrier for nucleophilic addition of DMAP to the allene is as high as 28.3 kcal/mol, which is almost the same as phenyl allene **9** (Figure 5a,b). In comparison with the parent allene **15**, the
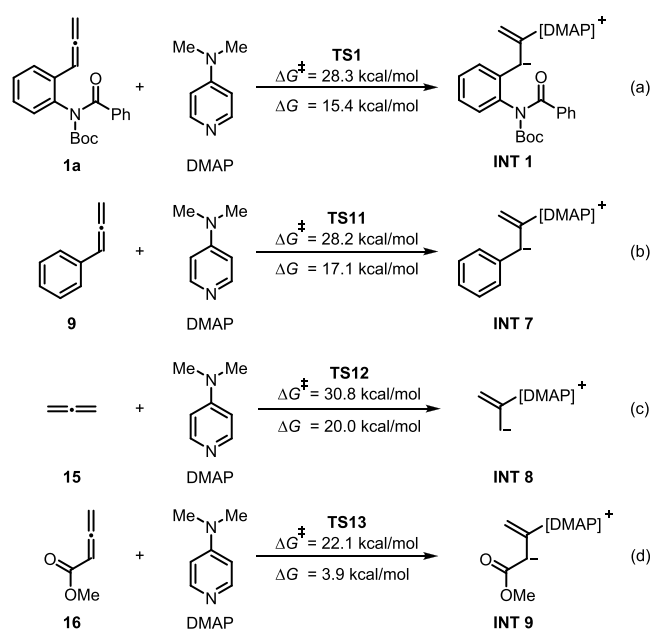

Figure 5. Computed at the SMD(THF)/M06-2X/6-311+G(d,p)//M06-2X/6-31+G(d,p) level.

activation barrier of **1a** is 2.5 kcal/mol less, which indicates that phenyl group has 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 a decreased activation barrier for nucleophilic addition (about 22.1 kcal/mol), which demonstrates that 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.

■ 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 the pharmaceutical industry. Both acyl and amine moieties are incorporated into the products via selective cleavage of amide C–N bonds, overcoming traditional amine moieties as waste 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 successive [1,4]- and [1,6]-proton transfers, which are facile. Like proton shuttles, a nitrogen anion intermediate assists the proton transfer processes via the protonation/deprotonation mechanism. (2) Although a direct [1,3]-proton transfer process could be assisted by a trace amount of water, the process is less favorable than the intramolecular successive [1,4]- and [1,6]-proton transfers (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 the Lewis base catalyst to allene, nucleophilic catalysis of weakly activated allenes is challenging. However, this hurdle may be overcome though generating thermodynamically stable intermediates or products. This may provide a good strategy for the transformation of nonactivated or weakly activated allenes via Lewis base catalysis in the future.

ASSOCIATED CONTENT

SI   **Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c01000.

> Experimental procedures, DFT calculations, and characterization data (PDF)

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Notes

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