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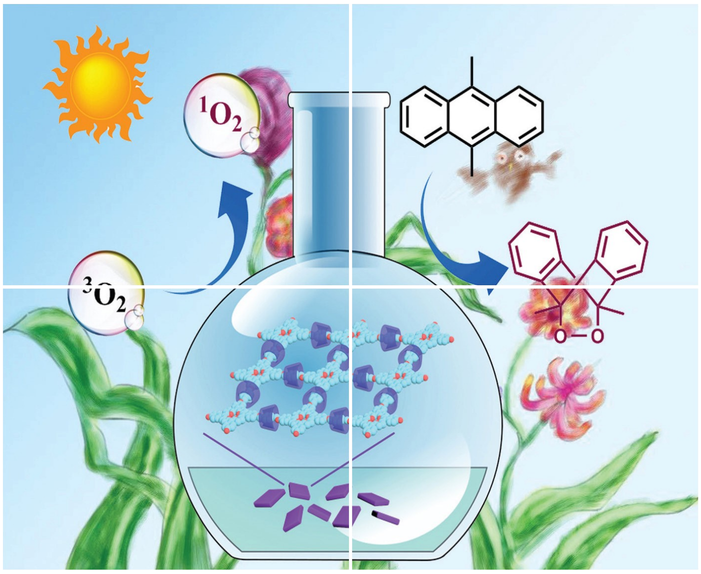

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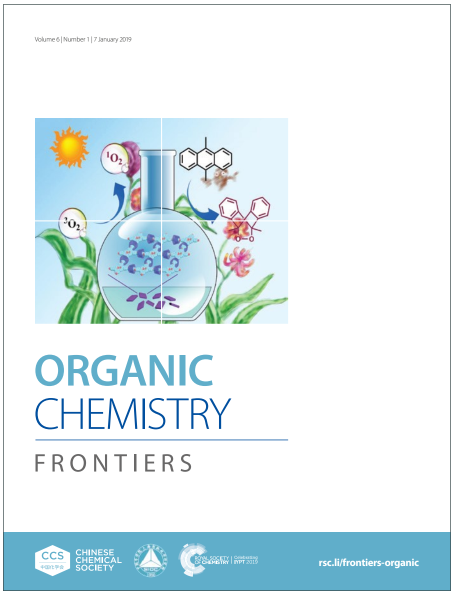

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ARTICLE

Biocompatible Indole C2 Functionalization via Transient *N*-Acyliminium Borate Intermediates

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In this work, we report a metal-free strategy for indole C2 functionalization in aqueous media, enabled by ion-pair catalysis via transient N-Acyliminium intermediates. This approach overcomes the intrinsic instability of iminium species in water, enabling efficient coupling with indoles under mild and environmentally benign conditions. The protocol exhibited broad substrate scope, accommodated late-stage functionalization of drug molecules and tryptophan residues in peptides, and proceeded with excellent chemo- and regioselectivity while preserving stereochemical integrity. This operationally simple method provided a versatile platform for biomolecular modification with potential applications in drug discovery, therapeutic development, and chemical biology.

Introduction

Iminium ions are among the most important electrophilic intermediates in organic synthesis, owing to their distinctive reactivity and broad utility in organic transformations such as Mannich reaction, Prins cyclization, and polyene cyclizations.[1] Since their discovery in the early twentieth century, iminium ion chemistry has evolved into a fundamental strategy for the construction of complex molecular architectures and has demonstrated particular value in natural product synthesis and the preparation of pharmaceutical intermediates.[2] Therefore, the generation and interception of iminium ions have attracted sustained interest from both synthetic and medicinal chemists. Nevertheless, the practical use of iminium ions remains severely limited by their intrinsic instability, especially in aqueous media (Fig. 1A).[3] In the presence of water, iminium ions are prone to hydrolysis, regenerating the corresponding carbonyl compounds and amines, which diminished reaction efficiency. Moreover, the poor solubility of organic compounds in water often limits their reactivity and requires the use surfactants to facilitate the reactions for weak nucleophiles. To break through these limitations, conventional methods typically rely on rigorously anhydrous conditions, excess nucleophiles, or using flammable organic solvents.[4-10] However, there strategies not only increase operational complexity and environmental burden, but also restrict the application of iminium ion chemistry in settings that require mild and water-compatible conditions, particularly biomolecular functionalization. Therefore, the development of a direct and efficient strategy to exploit iminium reactivity in aqueous systems still remains a significant challenge.

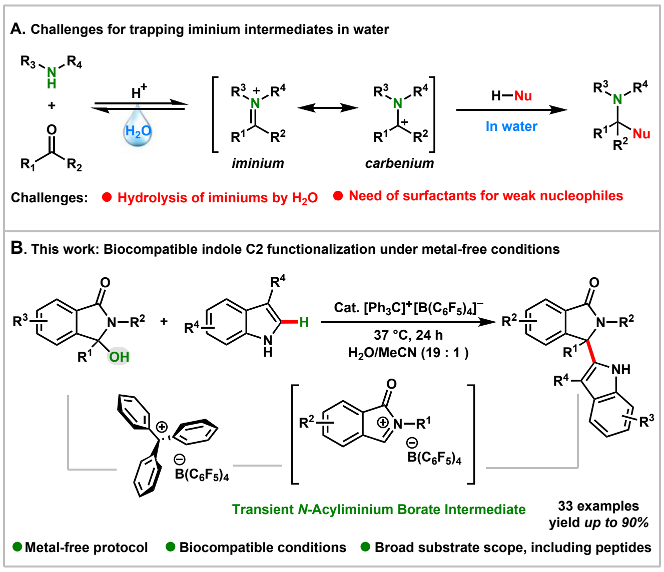

Figure 1. (A) Challenges for trapping iminium intermediates in water. (B) This work: Biocompatible indole C2 functionalization under metal-free conditions.

Weakly coordinating anions (WCAs) have emerged as powerful enabling elements for the generation and stabilization

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Electronic Supplementary Information (ESI) available: ^1H, ^{13}C and ^{19}F NMR (PDF). X-ray crystallographic data for **17** (CCDC: 2513501). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x of kinetically persistent carbocation intermediates, thereby facilitating their characterization and selective conversion into value-added products.[11,12] In particular, recent advances in vinylation chemistry based on persistent vinylium–WCA ion pairs have demonstrated the unique ability of WCAs to unlock highly reactive cationic species for synthetic applications.[12-14] Despite these advances, the use of WCA-based ion-pair catalysis to control carbocation-mediated transformations in aqueous media remains largely unexplored.

Tryptophan, a particularly Indole derivative, is the least abundant of the 20 proteinogenic amino acids, only 1.4% of amino acid residues in proteins, but it is present in nearly 90% of natural proteins and plays critical roles in maintaining structural stability, mediating intermolecular recognition, and regulating biological function.[15] Owing to this low abundance combined with high functional significance, tryptophan has emerged as a privileged target for residue-selective modification in peptide and protein engineering.[16] Conventional strategies for modifying the C2, C4, and N1 positions of the indole ring include sulfonation, organic radical addition, transition-metal-catalysed C–H bond radicalization, photoredox catalysis, and electrochemical coupling *etc.*[17] More recently, efforts have been made to modify the indole framework at diverse sites. For instance, the Shi group reported a photocatalytic method for modification at the tryptophan β-position, with universality for Michael acceptors and simple, endogenous peptides, demonstrating high chemoselectivity between amino acid residues and achieving activation of the tryptophan β-position C–H bond, providing a new strategy for residue-specific peptide modification.[18] In 2025, the Chiang group developed a facile, metal-free photo-electrocatalytic strategy to achieve pyrazolation functionalization at the tryptophan β-position, allowing for high chemoselective modification of tryptophan residues in peptides and proteins.[19] In 2026, the Wang group reported a rhodium-catalyzed, trivalent phosphorus-directed method for the selective arylation of the C7 position of tryptophan residues.[20] Despite the development of numerous methods for tryptophan modification, several limitations still remain. Photoredox and photoelectrochemical strategies often rely on metal-based photocatalysts, whose potential toxicity limited their application in biological systems. Therefore, the development of metal-free catalytic approaches that combine high efficiency with biocompatibility is highly desirable.

In recent years, our group has focused on the development of biocompatible bioconjugation strategies based on weakly coordinating anion (WCA)-stabilized iminium intermediates. Building on the successful modification cysteine and tyrosine.[21-24] Herein, we described a triarylcarbenium ion pair-catalyzed protocol of the efficient indole C2 functionalization in aqueous media via transient N-Acyliminium intermediates, enabling the modification of tryptophan and its derivatives in peptides (Fig. 1B).

Results and discussion

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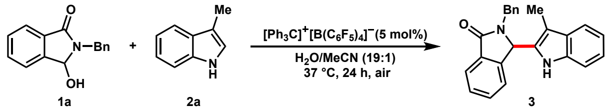
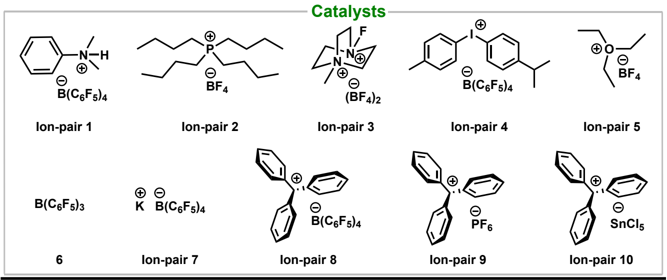
Table 1 Optimization of the reaction conditions[a]





Entry	Catalysts	Catalyst loading	Solvent	Time (h)	Yield (%)[b]
1	-	-	H_2O	12	n.r
2	Ion-pair 1	15 mol%	H_2O	12	trace
3	Ion-pair 2	15 mol%	H_2O	12	n.r
4	Ion-pair 3	15 mol%	H_2O	12	n.r
5	Ion-pair 4	15 mol%	H_2O	12	39
6	Ion-pair 5	15 mol%	H_2O	12	18
7	$B(C_6F_5)_3$	15 mol%	H_2O	12	58
8	Ion-pair 7	15 mol%	H_2O	12	trace
9	Ion-pair 8	15 mol%	H_2O	12	72
10	Ion-pair 9	15 mol%	H_2O	12	10
11	Ion-pair 10	15 mol%	H_2O	12	13
12	Ion-pair 8	15 mol%	various buffer solutions	12	41–72
13	Ion-pair 8	15 mol%	H_2O/MeCN (19:1)	12	78
14	Ion-pair 8	15 mol%	H_2O/MeCN (19:1)	24	96
15	Ion-pair 8	5 mol%	H_2O/MeCN (19:1)	24	90
16	Ion-pair 8	5 mol%	H_2O/MeCN (19:1)	24	89[c]

[a]Reaction conditions: **1a** (0. 2 mmol), **2a** (0.4 mmol) and catalyst (5 mol%) in solvent (2.0 mL) at 37 °C for 24 h under air. [b]Isolated yield. [c]Under an argon atmosphere. n.r = no reaction.

As shown in Table 1, we initiated our study using 3-hydroxy-2-methylisoindolin-1-one **1a** and 3-methylindole **2a** as the substrates, with trityl tetrakis-(pentafluorophenyl)-borate ($[Ph_3C]^+[B(C_6F_5)_4]^-$) as the catalyst to optimize the reaction conditions (see Supporting Information for details).[23a,25] In the absence of a catalyst, no desired reaction was observed in water at 37 °C after 12 h (Table 1, entry 1). We next screened a series of ion-pair catalysts (15 mol%) in water and found that ion-pair **8** delivered the target product **3** in 72% yield (Table 1, entries 2–11). Subsequent examination of the solvent effect showed that various buffer systems did not improve the reaction efficiency (Table 1, entry 12). By contrast, the addition of 5% MeCN as a co-solvent increased the solubility of the substrates and improved the yield to 78% (Table 1, entry 13). Further prolonging the reaction time to 24 h led to a marked increase in yield, affording **3** in 96% yield (Table 1, entry 14). Notably, lowering the catalyst loading from 15 mol% to 5 mol% still gave the desired product in 90% yield, and the transformation proceeded efficiently under an argon atmosphere (Table 1, entries 15 and 16). Finally, the optimal conditions were identified as 5 mol% ion-pair **8** in H_2O/MeCN (19:1) at 37 °C for 24 h under air.

With optimal conditions in hand, we next evaluated the substrate scope of 3-hydroxyisoindolin-1-ones with 3-methylindole (Scheme 1A). A range of *N*-benzyl-substituted substrates were compatible with the reaction conditions. *Para*-substituted electron-donating groups, such as methyl and *tert*-butyl, furnished products **4** and **5** in 89% and 79% yields, respectively, whereas electron-withdrawing substituents, including F and CF_3 groups, gave **6** and **7** in 60% and 73% yields respectively, indicating that electron-rich groups facilitated the desired transformation. Besides *N*-benzyl substitution, an *N*-allyl group was also well tolerated, affording **8** in 72% yield, and an *N*-methyl substituent delivered **9** in 80% yield. In contrast, the *N*-*n*-hexyl substrate showed lower reactivity and required 10 mol% catalyst to provide **10** in 65% yield. Notably, an *N*-furanylmethyl-substituted substrate also reacted with **1a** smoothly to give **11** in 84% yield.

We next investigated the effects of substitution on the isoindolinone framework. Substrates bearing substituents at the C3 position, such as phenyl and methyl groups, underwent efficient coupling to furnish **12** and **13** in 75% and 85% yields, respectively. In addition, C5-substituted indole derivatives bearing *tert*-butyl, halogen atoms (F, Cl and Br), or a phenylethynyl group were all suitable substrates, providing **14**–**18** in 60% to 77% yields. Moreover, single-crystal X-ray diffraction analysis of **17** confirmed that the carbon-carbon bond formation underwent at C2 position of the indole. A bromo-substituted indole at C4 position gave product **19** in 70% yield, while a dichloro-substituted indole derivative afforded **20** in 65% yield with 10 mol% catalyst. Furthermore, 3-hydroxy-2,3,4,5,6,7-hexahydro-isoindolione and 3-hydroxyoctahydro-isoindolinone derivatives were likewise competent coupling partners, delivering the corresponding products **21** and **22** in 86% and 80% yields, respectively. Notably, 5-hydroxy-1-pyrrolidin-2-ones bearing benzyl and methyl substituents reacted with **2a** to afford the corresponding products **23** and **24** in 54% and 72% yields respectively.

Subsequently, we explored the scope of indole partners (Scheme 1B). Indole derivatives, bearing F, Cl and Br substituents at C5 position reacted efficiently with **1a** in the presence of 10 mol% catalyst to furnish **25**–**27** in 83–88% yields. C6-halogenated indoles were also compatible, albeit with slightly lower efficiencies, giving **28**–**30** in 72–81% yields. In contrast, indole bearing an ester substituent at C3 position exhibited significantly lower reactivity and afforded **31** in only 48% yield. When tryptophan derivatives were employed as substrates using $[Ph_3C]^+[B(C_6F_5)_4]^-$ (20 mol%) as the catalyst for 24 hours probably due to their limited solubility in water, the reaction proceeded smoothly to afford the desired products **32** and **33** in 43% and 38% yields.

To demonstrate the synthetic utility of this method, we first conducted the model reaction on gram level. As shown in Scheme 2A, **3** was obtained in 71% isolated yield with 1.25 g. Subsequently, several preliminary mechanistic studies were conducted to elucidate the possible reaction pathway. Notably, the addition of 2,6-di-*tert*-butylpyridine to the model reaction under the standard conditions significantly suppressed the desired reaction, supporting the involvement of proton species (Scheme 2B). Moreover, the result of the competitive experiment between 3-methylindole **2a** and benzylamine **2b** with 3-hydroxy-2-methylisoindolin-1-one **1a** demonstrated the selectivity of this reaction, only affording product **3** in 65% yield (Scheme 2C). Furthermore, in the absence of the ion-pair catalyst, no desired product was

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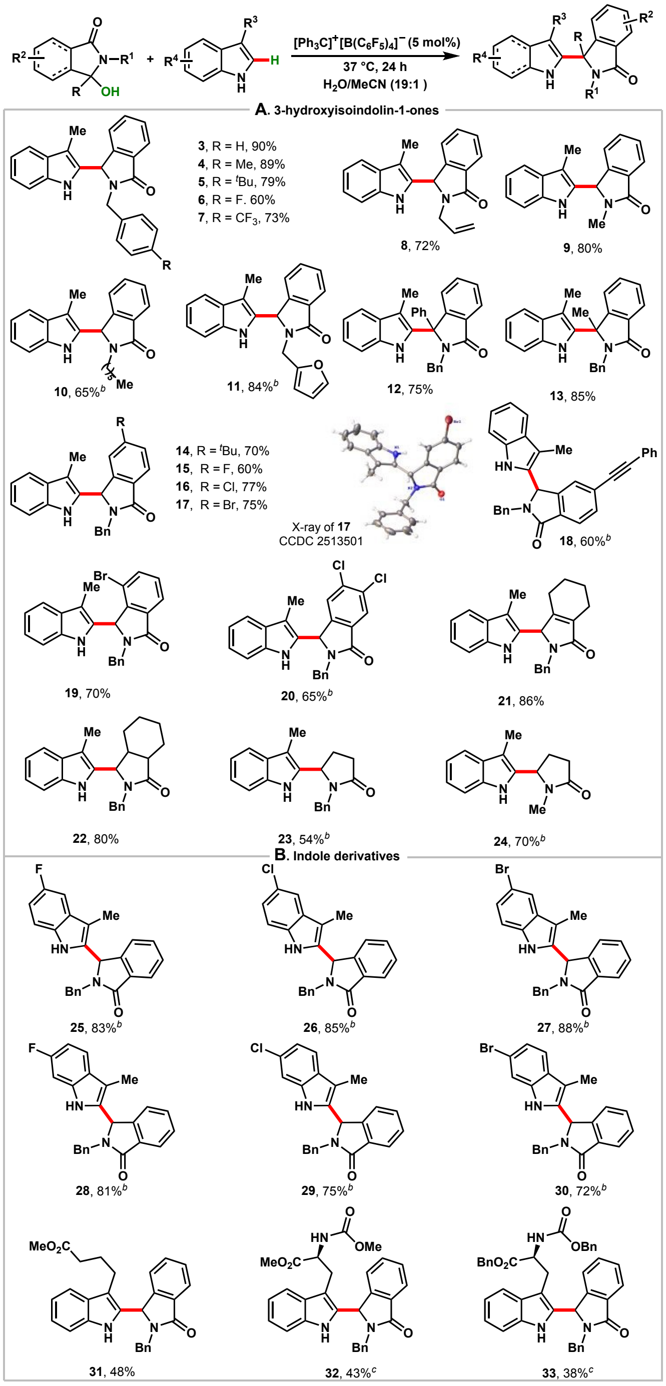

Scheme 1 Scope of substrates.[a] [a]Reaction conditions: 3-hydroxyisoindolin-1-ones (0.2 mmol), indoles (0.4 mmol), $[Ph_3C]^+[B(C_6F_5)_4]^-$ (5 mol%) in H_2O/MeCN (19:1) at 37 °C under air for 24 h. [b]$[Ph_3C]^+[B(C_6F_5)_4]^-$ (10 mol%) as the catalyst. [c]$[Ph_3C]^+[B(C_6F_5)_4]^-$ (20 mol%) as the catalyst. All yields are isolated yields.

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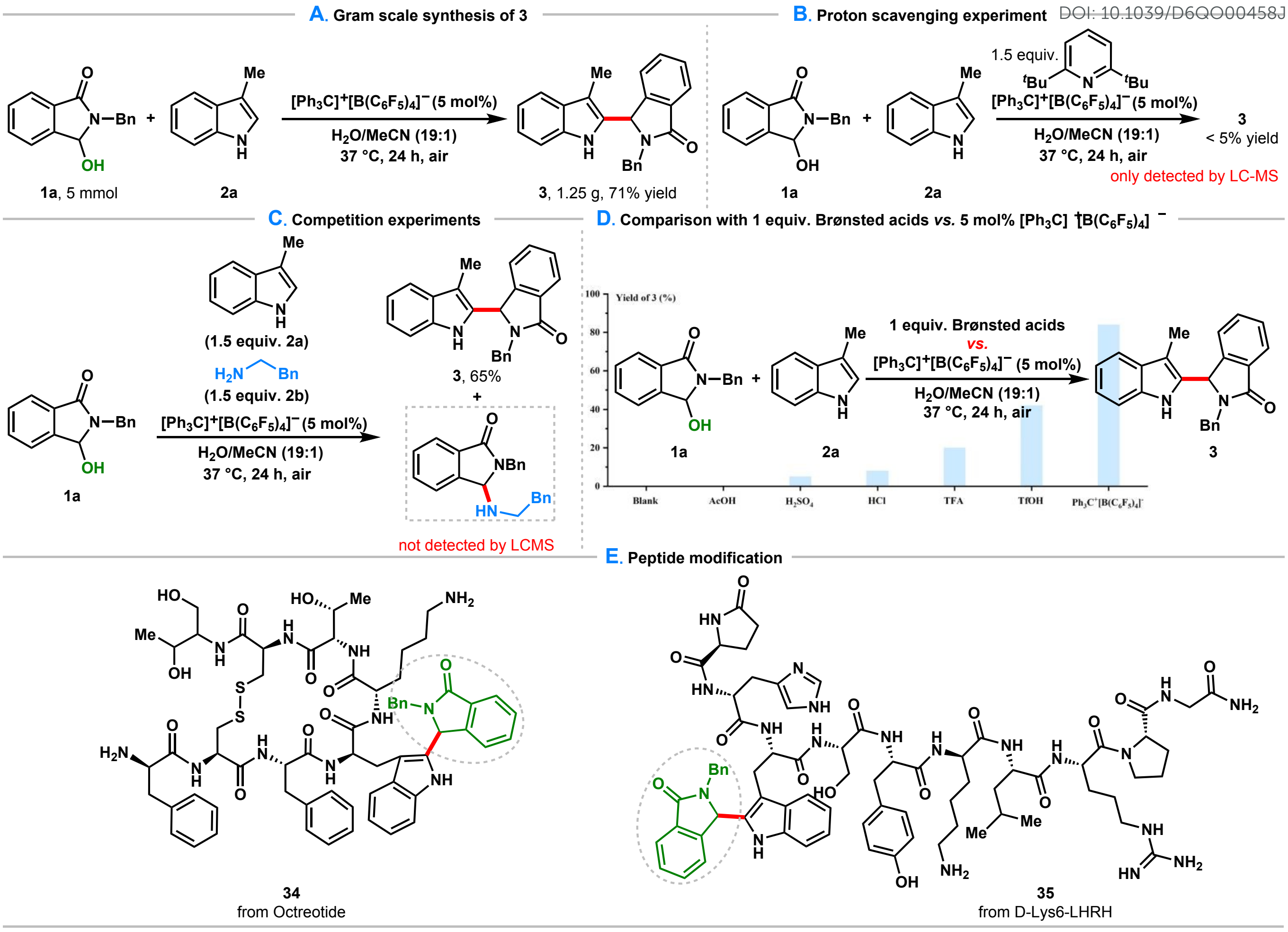
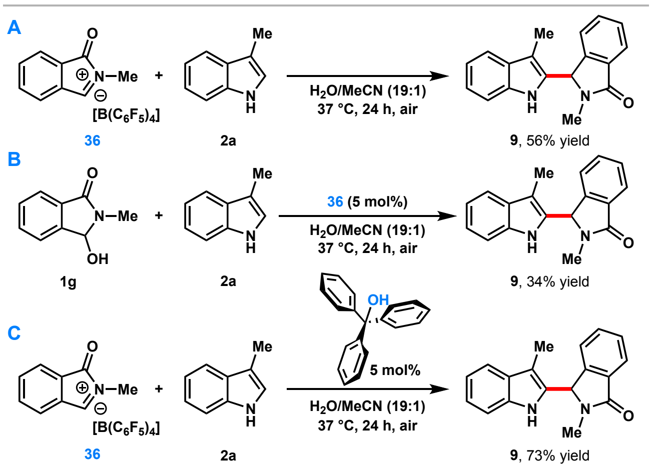


Scheme 2 (A) Gram scale synthesis of **3**. (B) Proton scavenging experiment. (C) Competition experiments. (D) Comparison with 1 equiv. Brønsted acids *vs*. 5 mol% $[Ph_3C]^+[B(C_6F_5)_4]^-$. (E) Peptide modification.

detected (Scheme 2D, Blank). We then compared the efficiency of the model reaction using 5 mol% $[PhC_3]^+[B(C_6F_5)_4]^-$ with stoichiometric conventional Brønsted acids (1.0 equiv.) as promoters, including AcOH, HCl, H_2SO_4, TFA, and TfOH. We found that these acids led to only trace formation of the target product **3**, further highlighting the distinctive catalytic performance of this ion-pair (Scheme 2D). To further demonstrate the applicability of this protocol in modification of peptides, octreotide and [D-Lys^6]-LHRH were respectively examined under standard H_2O/MeCN (19:1) conditions using 20 mol% catalyst. HRMS analysis confirmed that the expected coupling of **1a** to the tryptophan residues of both peptides occurred successfully (Scheme 2E).

To gain further mechanistic insights, we then prepared the intermediate **36** for control experiments. As illustrated in Scheme 3A, **36** reacted with **2a** to afford product **9** in 56% yield under aqueous conditions, indicating **36** as a probable intermediate. Moreover, the use of a catalytic amount of **34** (5 mol%) promoted the desired coupling of **1g** with **2a** to give **9** in 34% yield, suggesting a reversible equilibrium between **36** and the active catalytic species (Scheme 3B). In the presence of 5 mol% triphenylmethanol, the reaction of **36** with **2a** delivered product **9** in 73% yield, which was comparable to that obtained



Scheme 3 Control experiments.

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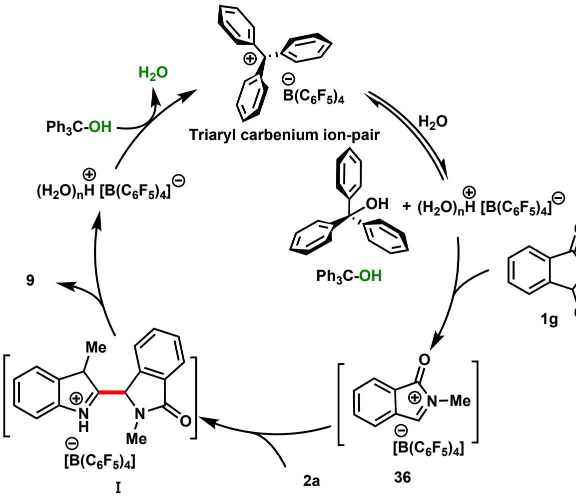
under the standard conditions and further showcased the crucial role of the trityl cation during the catalytic process (Scheme 3C). Based on these results and precedent literatures,[23a,23c] we proposed a plausible mechanism depicted in Scheme 4. Initially, the hydrolysis of the trityl ion pair in water underwent to give the hydrated proton species, $(H_2O)_nH^+[B(C_6F_5)_4]^-$, along with the generation of triphenylmethanol. In the presence of substrate **1g**, rapid dehydration occurred to generate transient *N*-acyliminium borate **36**. Following the electrophilic substitution of **36** with **2a**, the intermediate **I** was afforded**.** After the subsequent deprotonation, the product **9** was obtained, while regenerating the catalyst through protonlysis of triphenylmethanol.



Scheme 4 Proposed mechanism.

Conclusion

In summary, we report a metal-free strategy for indole C2 functionalization in aqueous media. Enabled by $[PhC_3]^+[B(C_6F_5)_4]^-$ as the catalyst, 3-hydroxyisoindolin-1-ones were activated to generate the transient *N*-acyliminium intermediates under mild conditions. This method exhibited broad scope across indoles, peptides, and tryptophan-containing biomolecules. Mechanistic studies indicated the transient *N*-acyliminium formation was crucial for the subsequent carbon-carbon bond construction in water. This work established ion-pair-mediated organic transformation as a practical platform for biomolecular modification and sustainable synthesis.

Author contributions

T.-P. L, Z. J. and P. C. designed and directed the project; H. L, Y. L, L. W. and L. L. conducted the experiments, analysed the results, prepared the supplementary information. P. C. and H. L. wrote the manuscript with input from all other authors.

Conflicts of interest

The authors declare no competing financial interest.

Data availability

The data supporting this article have been included as part of the Supplementary Information.

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