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# Regio- and Enantioselective (3+3) Cycloaddition of Nitrones with 2-Indolylmethanols Enabled by Cooperative Organocatalysis

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Dedicated to those who are committed to advocating diversity in chemistry

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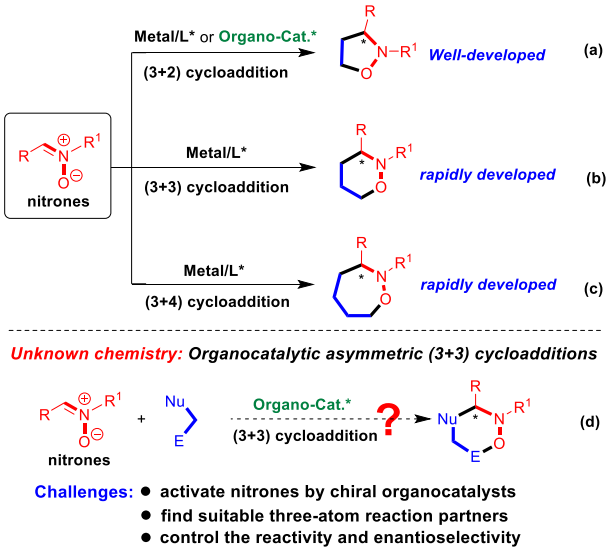
**Abstract:** The regio- and enantioselective (3+3) cycloaddition of nitrones with 2-indolylmethanols was accomplished by the cooperative catalysis of hexafluoroisopropanol (HFIP) and chiral phosphoric acid (CPA). Using this approach, a series of indole-fused six-membered heterocycles were synthesized in high yields (up to 98%), with excellent enantioselectivities (up to 96% ee) and exclusive regiospecificity. This approach enabled not only the first organocatalytic asymmetric (3+3) cycloaddition of nitrones but also the first C3-nucleophilic asymmetric (3+3) cycloaddition of 2-indolylmethanols. More importantly, theoretical calculations elucidated the role of the cocatalyst HFIP in helping CPA control the reactivity and enantioselectivity of the reaction, demonstrating a new mode of cooperative catalysis.

## Introduction

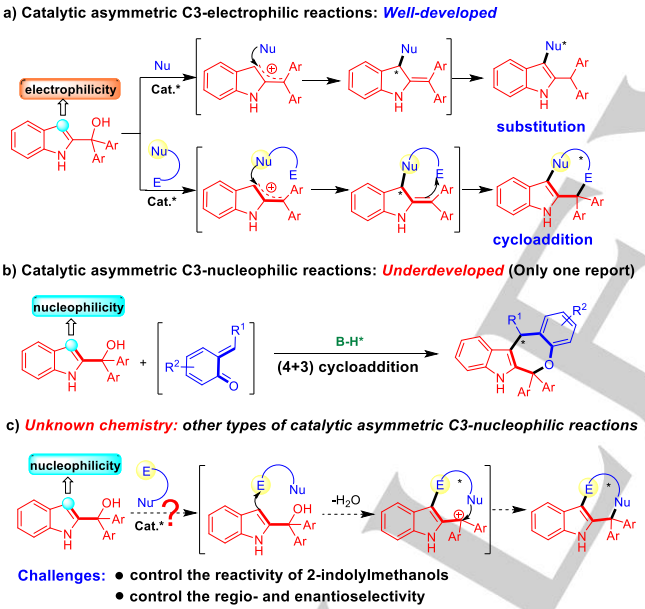
Nitrones are basic materials and important intermediates in organic synthesis that have attracted intense attention from the chemistry community.[1] In particular, nitrones can act as three-atom building blocks in catalytic asymmetric (3+n) cycloadditions, providing a useful tool for the synthesis of enantioenriched heterocyclic compounds (**Scheme 1**).[2-9] Nitrones are suitable 1,3-dipoles for constructing optically pure five-membered isoxazolidine frameworks via catalytic asymmetric (3+2) cycloadditions (**Scheme 1a**).[2-6] Notably, most asymmetric (3+2) cycloadditions of nitrones are catalyzed by metal/chiral ligands (L*),[2-3] and only a small fraction of the transformations are enabled by chiral organocatalysts.[4-6] In addition to well-developed (3+2) cycloadditions, catalytic asymmetric (3+3)[7-8] and (3+4)[9] cycloadditions of nitrones have been rapidly developed, but all of these transformations are enabled by metal catalysts (**Scheme 1b**-**1c**). In particular, the catalytic asymmetric (3+3) cycloaddition of nitrones is a powerful method for the enantioselective construction of six-membered heterocyclic scaffolds, and the reaction partners are mainly cyclopropanes, trimethylenemethanes, vinyldiazoacetate, and alkenyl gold complexes.[1e,8] *However, despite these rapid developments, the organocatalytic asymmetric (3+3) cycloaddition of nitrones has not yet been achieved and remains unexplored* (**Scheme 1d**).[10] There are some challenging issues for this type of transformation. The first issue is that nitrones are difficult to activate with organocatalysts, and there are very few examples of the activation of nitrones by chiral organocatalysts.[5-6] The second issue is the identification of suitable three-atom reaction partners that can be easily activated by chiral organocatalysts to undergo asymmetric (3+3) cycloaddition with nitrones. The final issue is the identification of effective chiral organocatalysts that can control the reactivity and enantioselectivity of the (3+3) cycloaddition. Therefore, the development of organocatalytic asymmetric (3+3) cycloadditions of nitrones is a challenging task.




**Scheme 1.** Profile of catalytic asymmetric cycloadditions of nitrones

In this context, we wondered whether 2-indolylmethanols could serve as suitable three-atom reaction partners to undergo organocatalytic asymmetric (3+3) cycloaddition with nitrones.

This consideration is based on our understanding of the chemistry of 2-indolylmethanols (**Scheme 2**).[11-13] In recent years, 2-indolylmethanols have proven to be versatile reactants in organocatalytic asymmetric reactions due to their unique property of C3 electrophilicity,[11] and they have been widely used in catalytic asymmetric C3-electrophilic substitutions[14] and cycloadditions[15] (**Scheme 2a**). *However, in sharp contrast, the C3 nucleophilicity of 2-indolylmethanols has scarcely been reported, and the catalytic asymmetric C3-nucleophilic reactions of 2-indolylmethanols are rather underdeveloped* (**Scheme 2b**). To date, only one report in the literature has described the asymmetric C3-nucleophilic (4+3) cycloaddition of 2-indolylmethanols catalyzed by a chiral Brønsted acid (B*-H).[16] Despite this progress, other types of catalytic asymmetric C3-nucleophilic reactions of 2-indolylmethanols are still unknown (**Scheme 2c**), most likely due to the intrinsic challenges involved in conducting these reactions. For example, how can the reactivity of 2-indolylmethanols be controlled to exhibit C3 nucleophilicity instead of the predominant C3 electrophilicity? Additionally, how can the regioselectivity and enantioselectivity of the reaction caused by the different reactivities of 2-indolylmethanols be controlled? Thus, it is highly valuable to devise innovative strategies toward realizing catalytic asymmetric C3-nucleophilic reactions of 2-indolylmethanols.

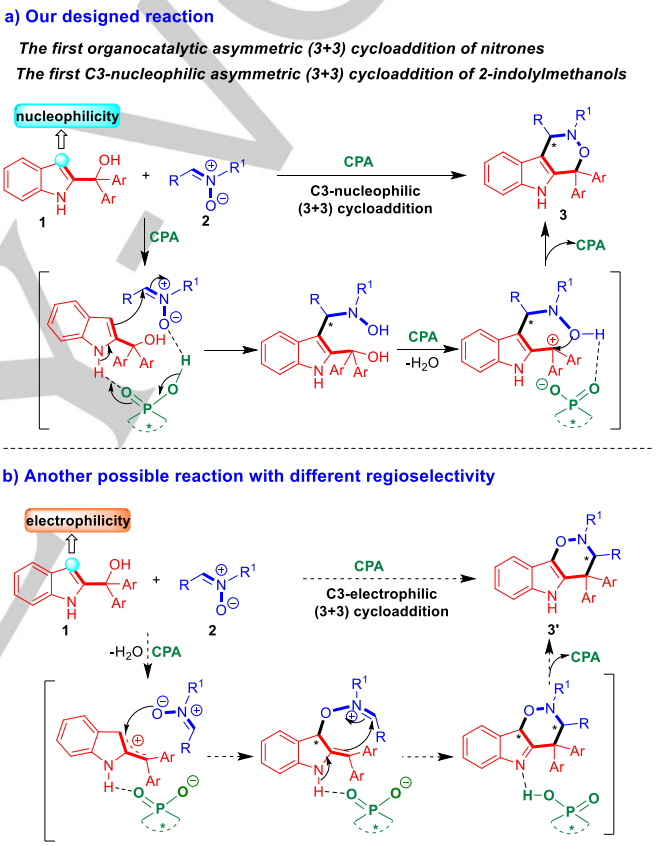



**Scheme 2.** Profile of the catalytic asymmetric reactions of 2-indolylmethanols

To develop organocatalytic asymmetric (3+3) cycloadditions of nitrones and to realize catalytic asymmetric C3-nucleophilic reactions of 2-indolylmethanols, we designed a chiral phosphoric acid[17] (CPA)-catalyzed asymmetric (3+3) cycloaddition of nitrones with 2-indolylmethanols (**Scheme 3a**). The choice of CPA as an organocatalyst was based on the consideration that CPA can simultaneously activate both 2-indolylmethanols **1** and nitrones **2** via hydrogen-bonding interactions, causing the C3 position of 2-indolylmethanols to become nucleophilic and attack the imine group of nitrones, thus accomplishing an enantioselective C3-nucleophilic (3+3) cycloaddition to give chiral products **3**. This design realizes the first organocatalytic asymmetric (3+3) cycloaddition of nitrones and the first C3-nucleophilic asymmetric (3+3) cycloaddition of 2-indolylmethanols.

However, another reaction between 2-indolylmethanols and nitrones with different regioselectivity also appears to be possible (**Scheme 3b**). Namely, in the presence of CPA, 2-indolylmethanols **1** can transform into a delocalized carbocation via dehydration. Due to the well-established C3 electrophilicity of the delocalized carbocation, in principle, the oxygen anion of nitrones **2** can attack the C3 position of the indole ring, thus undergoing asymmetric (3+3) cycloaddition to give products **3'** with different regioselectivity.

Therefore, controlling the reactivity, regioselectivity and enantioselectivity is a key factor for achieving the (3+3) cycloaddition of nitrones with 2-indolylmethanols that we designed. Herein, we report our investigation in detail.



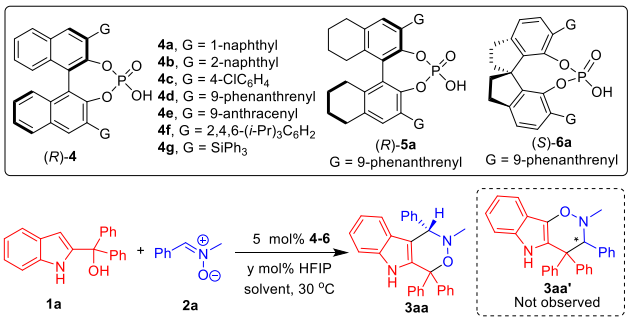

**Scheme 3.** Our designed reaction and another possible reaction with different regioselectivity

## Results and Discussion

Based on the design mentioned above, we attempted to react 2-indolylmethanol **1a** with nitrone **2a** in the presence of the CPA catalyst **4a** in toluene at 30 °C (**Table 1**, entry 1). As expected, **1a** exhibited C3 nucleophilicity, undergoing (3+3) cycloaddition with **2a** to afford the desired product **3aa** with exclusive regioselectivity, and regioisomer **3aa'** was not observed, demonstrating the feasibility of our design. However, the yield and enantioselectivity of **3aa** were extremely low (26% yield, 11% ee), demonstrating the great challenge of controlling the reactivity and enantioselectivity of the designed C3-nucleophilic (3+3) cycloaddition. To tackle this challenge, we considered the

strategy of the cooperative catalysis of CPA with another cocatalyst because cooperative catalysis involving CPAs has proven to be a powerful strategy for achieving unprecedented enantioselective reactions that are inaccessible or disfavored in the presence of a single catalyst.[18-19] Therefore, we tentatively added hexafluoroisopropanol (HFIP) to the reaction system as a cocatalyst due to its special effects on organic reactions.[20]

**Table 1.** Optimization of the reaction conditions[a]

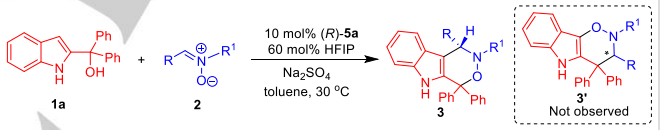



| entry | Cat. | solvent | y | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | **4a** | toluene | 0 | 26 | 11 |
| 2 | **4a** | toluene | 50 | 64 | 45 |
| 3 | **4b** | toluene | 50 | 93 | 41 |
| 4 | **4c** | toluene | 50 | 92 | 27 |
| 5 | **4d** | toluene | 50 | 95 | 68 |
| 6 | **4e** | toluene | 50 | 95 | 53 |
| 7 | **4f** | toluene | 50 | 94 | 67 |
| 8 | **4g** | toluene | 50 | 46 | 13 |
| 9 | **5a** | toluene | 50 | 95 | 73 |
| 10 | **6a** | toluene | 50 | 75 | 13 |
| 11 | **5a** | toluene | 20 | 75 | 72 |
| 12 | **5a** | toluene | 60 | 95 | 75 |
| 13 | **5a** | DCE | 60 | 93 | 48 |
| 14 | **5a** | EtOAc | 60 | N.R. | - |
| 15 | **5a** | $CH_3CN$ | 60 | 91 | <5 |
| 16 | **5a** | THF | 60 | N.R. | - |
| 17 | **5a** | acetone | 60 | N.R. | - |
| 18[d] | **5a** | toluene | 60 | 95 | 91 |
| 19[d,e] | **5a** | toluene | 60 | 73 | 94 |
| 20[d,e,f] | **5a** | toluene | 60 | 95 | 95 |

[a] The reaction was performed on a 0.1 mmol scale in a solvent (1 mL) for 12 h, and the molar ratio of **1a**:**2a** was 1.2:1. [b] Isolated yield of **3aa**. [c] The enantiomeric excess (*ee*) of **3aa** was determined by HPLC. [d] $Na_2SO_4$ (100 mg) was used as an additive. [e] The volume of toluene was 8 mL. [f] Catalyzed by 10 mol% **5a** for 48 h at a **1a**:**2a** molar ratio of 2:1. N.R. = no reaction.

Gratifyingly, the addition of HFIP indeed greatly improved the yield and enantioselectivity (**Table 1**, entry 2 vs entry 1), demonstrating that HFIP was a good cocatalyst for CPA. Then, under the cooperative catalysis of HFIP and CPA, several CPAs **4b**-**4g** were evaluated for this reaction (**Table 1**, entries 3-8), and it was discovered that **4d** bearing 3,3'-di-9-phenanthrenyl groups was superior to the others (**Table 1**, entry 5 vs entries 2-4 and 6-8) in controlling the enantioselectivity. The change in the backbone of **4d** from BINOL to $H_8$-BINOL and SPINOL (**Table 1**, entries 9-10) revealed that $H_8$-BINOL-derived CPA **5a** was the optimal chiral catalyst for this reaction with regard to the enantioselectivity of **3aa** (**Table 1**, entry 9). Then, the effect of the amount of the cocatalyst HFIP on the reaction was investigated (see the SI for details), and it was discovered that as little as 20 mol% of HFIP promoted the reaction, affording a good yield and enantioselectivity (**Table 1**, entry 11), and that 60 mol% of HFIP delivered the best results for the reaction (**Table 1**, entry 12). Considering the low cost of HFIP, 60 mol% of HFIP was used in the subsequent condition optimization (see the SI for details). Briefly, the evaluation of different solvents revealed that toluene controlled the reactivity and enantioselectivity better than any other solvent (**Table 1**, entries 13-17 vs entry 12). The addition of sodium sulfate as an additive improved the enantioselectivity to a good level of 91% ee, with a high yield of 95% (**Table 1**, entry 18). It was discovered that diluting the reaction concentration (from 1 mL toluene to 8 mL toluene) further improved the enantioselectivity from 91% ee (**Table 1**, entry 18) to 94% ee, albeit with a decreased yield of 73% (**Table 1**, entry 19). Finally, a suitable modulation of the reagent ratio with a prolonged reaction time led to a high yield of 95% and an excellent enantioselectivity of 95% ee (**Table 1**, entry 20). Notably, the regioisomer **3aa'** was not observed during the optimization of the conditions, demonstrating the high regioselectivity of the (3+3) cycloaddition. Therefore, the two sets of conditions given in entry 20 (conditions A) and entry 18 (conditions B) were selected as the optimal conditions for the subsequent investigation of the substrate scope of nitrones **2** and 2-indolylmethanols **1**.

**Table 2.** Substrate scope of nitrones **2**[a]




| entry | R/$R^1$ (**2**) | **3** | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | Ph/Me (**2a**) | **3aa** | 95 | 95 |
| 2 | 4-$FC_6H_4$/Me (**2b**) | **3ab** | 96 | 93 |
| 3 | 4-$ClC_6H_4$/Me (**2c**) | **3ac** | 98 | 92 |
| 4 | 4-$BrC_6H_4$/Me (**2d**) | **3ad** | 83 | 91 |
| 5 | 4-$IC_6H_4$/Me (**2e**) | **3ae** | 95 | 94 |
| 6 | 4-$MeC_6H_4$/Me (**2f**) | **3af** | 98 | 90 |
| 7 | 4-$PhC_6H_4$/Me (**2g**) | **3ag** | 64 | 91 |
| 8 | 3-$ClC_6H_4$/Me (**2h**) | **3ah** | 66 | 91 |
| 9 | 3-$BrC_6H_4$/Me (**2i**) | **3ai** | 81 | 89 |
| 10 | 3-$MeOC_6H_4$/Me (**2j**) | **3aj** | 67 | 93 |
| 11[d] | 2-$MeC_6H_4$/Me (**2k**) | **3ak** | 96 | 78 |
| 12 | 2-naphthyl/Me (**2l**) | **3al** | 96 | 95 |
| 13[d] | 2-furyl/Me (**2m**) | **3am** | 83 | 91 |
| 14[d] | Et/Me (**2n**) | **3an** | 52 | 85 |
| 15[d] | Ph/Ph (**2o**) | **3ao** | 26 | 86 |

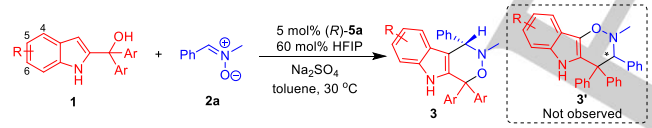
[a] Conditions A: The reaction was performed on a 0.1 mmol scale and catalyzed by 10 mol% (*R*)-**5a** and 60 mol% HFIP in toluene (8 mL) with $Na_2SO_4$ (100 mg) as an additive at 30 °C for 48 h, and the molar ratio of **1a**:**2** was 2:1. The absolute configuration of **3aa** was determined to be (*S*) by single-crystal X-ray analysis.[21] [b] Isolated yield. [c] The *ee* was determined by HPLC. [d] Reaction time of 4 days.

First, we investigated the substrate scope of nitrones **2** (**Table 2**). As shown in entries 1-12, a variety of nitrones **2a-2l** bearing different R substituents, such as *para*-, *meta*-, or *ortho*-

substituted phenyl groups (**Table 2**, entries 1-11) and a 2-naphthyl group (**Table 2**, entry 12), smoothly participated in the reaction to give products **3aa**-**3al** in overall high yields with excellent enantioselectivities. More importantly, nitrones **2m-2n** bearing heteroaromatic (2-furyl) and aliphatic (ethyl) R groups successfully underwent enantioselective (3+3) cycloaddition with 2-indolylmethanol **1a** in moderate to good yields with high enantioselectivities (**Table 2**, entries 13-14). In addition, the $R^1$ group of the nitrones could be changed from a methyl to a phenyl group (**Table 2**, entry 15), and although this substrate **2o** exhibited much lower reactivity, it ultimately participated in the reaction to afford product **3ao** with good enantioselectivity. It should be noted that in all cases, regioisomers **3'** were not observed.

Then, the substrate scope of 2-indolylmethanols **1** in the catalytic asymmetric (3+3) cycloaddition was studied by reaction with nitrone **2a** (**Table 3**). As shown in entries 2-7, a series of 2-indolylmethanols **1b-1g** bearing electronically different Ar groups with *para*-, *meta*- or *ortho*-substitutive patterns served as suitable substrates in the reaction, delivering products **3ba**-**3ga** in moderate to high yields with excellent enantioselectivities. Moreover, 2-indolylmethanols **1h-1n** bearing either electron-donating or electron-withdrawing groups at different positions of the indole ring acted as suitable reaction partners, undergoing (3+3) cycloaddition with nitrone **2a** to generate products **3ha**-**3na** in generally high yields with good enantioselectivities. Clearly, C5-substituted 2-indolylmethanols **1i-1m** exhibited higher reactivities and gave higher enantioselectivities than C6- and C4-substituted 2-indolylmethanols (**1h** and **1n**) (**Table 3**, entries 9-13 vs entries 8 and 14). In all cases, regioisomers **3'** were not observed, demonstrating the exclusive regiospecificity of the (3+3) cycloaddition.

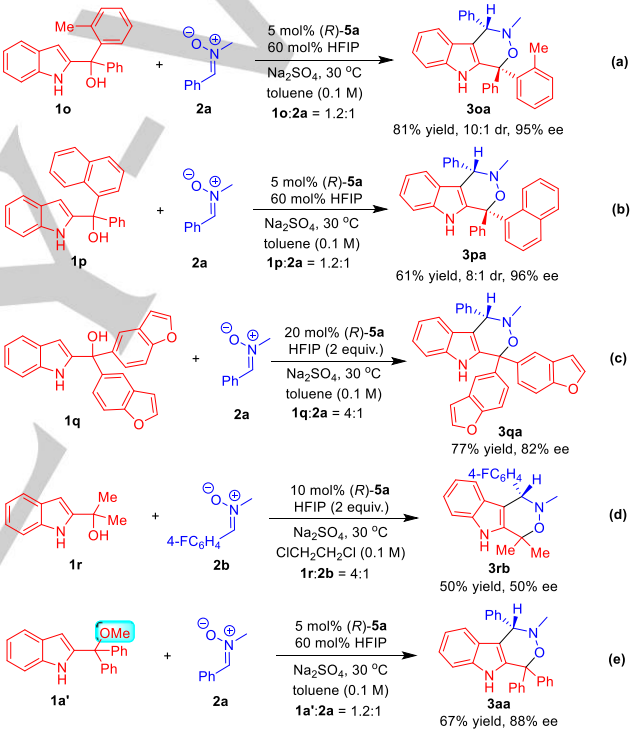
**Table 3.** Substrate scope of 2-indolylmethanols **1**[a]




| entry | R/Ar (**1**) | **3** | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | H/Ph (**1a**) | **3aa** | 95 | 91 |
| 2 | H/*p*-ClC$_6$H$_4$ (**1b**) | **3ba** | 51 | 92 |
| 3 | H/*p*-MeC$_6$H$_4$ (**1c**) | **3ca** | 98 | 90 |
| 4 | H/*m*-FC$_6$H$_4$ (**1d**) | **3da** | 98 | 93 |
| 5 | H/*m*-ClC$_6$H$_4$ (**1e**) | **3ea** | 93 | 89 |
| 6 | H/*m*-MeC$_6$H$_4$ (**1f**) | **3fa** | 98 | 90 |
| 7 | H/*o*-MeC$_6$H$_4$ (**1g**) | **3ga** | 53 | 90 |
| 8[d] | 6-Cl/Ph (**1h**) | **3ha** | 54 | 84 |
| 9 | 5-F/Ph (**1i**) | **3ia** | 98 | 91 |
| 10 | 5-Cl/Ph (**1j**) | **3ja** | 89 | 90 |
| 11 | 5-Br/Ph (**1k**) | **3ka** | 85 | 90 |
| 12 | 5-Me/Ph (**1l**) | **3la** | 98 | 92 |
| 13 | 5-OMe/Ph (**1m**) | **3ma** | 98 | 93 |
| 14[e] | 4-Me/Ph (**1n**) | **3na** | 53 | 75 |

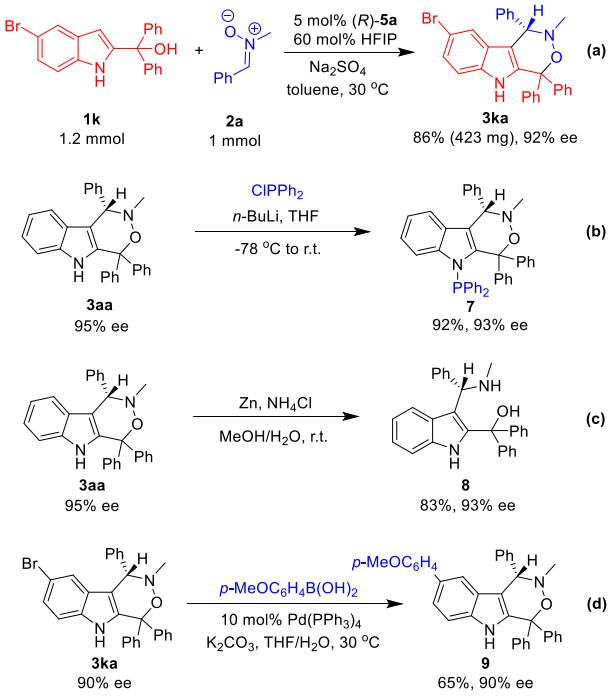
[a] Conditions B: The reaction was performed on a 0.1 mmol scale and catalyzed by 5 mol% (*R*)-**5a** and 60 mol% HFIP in toluene (1 mL) with $Na_2SO_4$ (100 mg) as an additive at 30 °C for 12 h, and the molar ratio of **1**:**2a** was 1.2:1. [b] Isolated yield. [c] The *ee* was determined by HPLC. [d] Catalyzed by 20 mol% (*R*)-**5a** in toluene (8 mL) for 4 days using a **1h**:**2a** molar ratio of 2:1. [e] Reaction time of 48 h.

More importantly, we further extended the substrate scope of this reaction to different types of 2-indolylmethanols **1o-1r** and ether **1a'** substrates (**Scheme 4**). Under standard conditions B, indolylmethanols **1o-1p** bearing two different aryl groups could successfully participate in the (3+3) cycloaddition to give products **3oa**[21] and **3pa** in good yields with high diastereoselectivities and excellent enantioselectivities (**Scheme 4a-4b**). However, when dibenzofuryl-substituted 2-indolylmethanol **1q** and dimethyl-substituted 2-indolylmethanol **1r** were used as the substrates, few products could be obtained because these indolylmethanols easily decomposed into a complex mixture. After modulating the reaction conditions such as by greatly increasing the amount of indolylmethanols **1q**-**1r** and HFIP, these indolylmethanols could smoothly participate in the (3+3) cycloaddition to give products **3qa** and **3rb** in moderate to good results (**Scheme 4c-4d**). Interestingly, ether **1a'** was suitable for (3+3) cycloaddition, affording product **3aa** in a good yield with a high enantioselectivity (**Scheme 4e**). In all cases, regioisomers **3'** were not observed.




**Scheme 4.** Further extension of the substrate scope

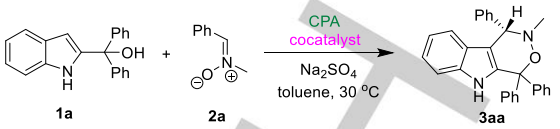
To examine the utility of the catalytic asymmetric (3+3) cycloaddition, we performed a one-mmol-scale reaction and some synthetic transformations of the products (**Scheme 5**). As illustrated in **Scheme 5a**, the one-mmol-scale reaction of 2-indolylmethanol **1k** with nitrone **2a** successfully proceeded to give product **3ka** in a retained high yield of 86% with an excellent enantioselectivity of 92% ee, and these results were comparable to those of the small-scale reaction (**Table 3**, entry 11). In addition, product **3aa** was transformed into chiral phosphane **7** in a high yield with almost maintained enantioselectivity (**Scheme 5b**). Moreover, **3aa** underwent a ring-opening reaction to produce compound **8** with nearly the same enantioselectivity (**Scheme 5c**), and **3ka** smoothly underwent a Suzuki coupling reaction with arylboronic acid to generate compound **9** with no decrease in the enantioselectivity (**Scheme 5d**).




**Scheme 5.** One-mmol-scale reaction and synthetic transformations

To gain some insights into the role of HFIP as a cocatalyst in the catalytic asymmetric (3+3) cycloaddition, some control experiments were carried out (**Table 4**). As listed in entry 1, when cooperatively catalyzed by 5 mol% (*R*)-**5a** and 60 mol% HFIP (standard conditions B), the (3+3) cycloaddition of 2-indolylmethanol **1a** with nitrone **2a** afforded product **3aa** in a high yield of 95%, with an excellent enantioselectivity of 91% ee (see also **Table 3**, entry 1). When the same reaction was performed in the absence of HFIP (**Table 4**, entry 2), the reaction was very sluggish and afforded **3aa** in an extremely low yield of 12%, with a moderate enantioselectivity of 59% ee. This phenomenon indicated that the single chiral catalyst (*R*)-**5a** catalyzed the (3+3) cycloaddition but in a rather inefficient manner, and the cocatalyst HFIP not only greatly improved the yield but also enhanced the enantioselectivity of the reaction (**Table 4**, entry 1 vs 2). When the reaction was performed in the absence of (*R*)-**5a** (**Table 4**, entry 3), no reaction occurred. This result showed that as a single catalyst, HFIP could not catalyze the (3+3) cycloaddition, and it acted as an important cocatalyst for this reaction. In addition, the effect of the cocatalyst loading of HFIP on the reaction was investigated. It was discovered that the addition of only 10 mol% HFIP evidently improved the yield and enantioselectivity (**Table 4**, entry 4 vs entry 2), but the best results for the reaction were obtained with 60 mol% HFIP (**Table 4**, entry 1). Furthermore, some other alcohols were employed as cocatalysts instead of HFIP under the standard conditions (**Table 4**, entries 5-7). It was revealed that the addition of trifluoroethanol (TFE), another fluorinated alcohol, to the reaction system also increased the yield and enantioselectivity to some extent (**Table 4**, entry 5 vs entry 2). This result implied that TFE could also act as a cocatalyst for this reaction, but its catalytic efficacy was lower than that of HFIP (**Table 4**, entry 5 vs entry 1). However, nonfluorinated alcohols such as isopropanol and tertiary butanol failed to act as cocatalysts for this reaction (**Table 4**, entries 6-7). These results demonstrated the superiority of fluorinated alcohols, particularly HFIP, as cocatalysts for this CPA-catalyzed asymmetric (3+3) cycloaddition, which might be due to the effect of the fluorine atoms in these alcohols.

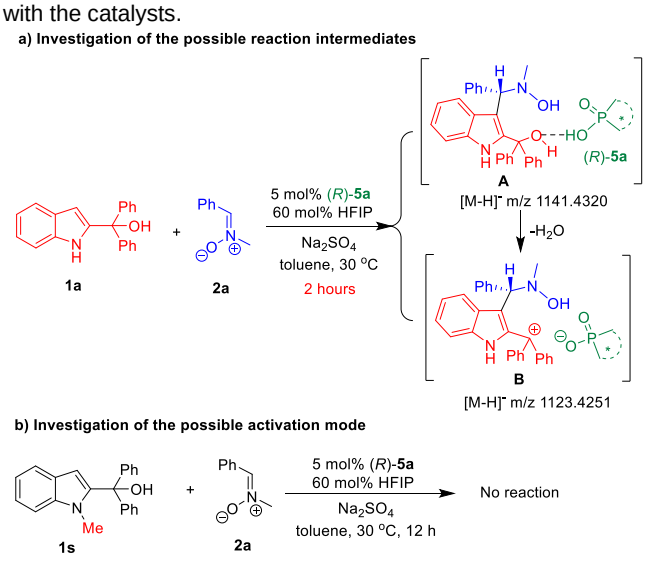
**Table 4.** Control experiments to investigate the role of HFIP[a]




| entry | CPA | cocatalyst | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | 5 mol% (*R*)-**5a** | 60 mol% HFIP | 95 | 91 |
| 2 | 5 mol% (*R*)-**5a** | none | 12 | 59 |
| 3 | none | 10 mol% HFIP | N.R. | - |
| 4 | 5 mol% (*R*)-**5a** | 10 mol% HFIP | 30 | 86 |
| 5 | 5 mol% (*R*)-**5a** | 60 mol% TFE | 48 | 86 |
| 6 | 5 mol% (*R*)-**5a** | 60 mol% *i*-PrOH | trace | - |
| 7 | 5 mol% (*R*)-**5a** | 60 mol% *t*-BuOH | trace | - |

[a] Conditions B: The reaction was carried out at a 0.1 mmol scale and was catalyzed by CPA and a cocatalyst in toluene (1 mL) with $Na_2SO_4$ (100 mg) as an additive at 30 °C for 12 h, and the molar ratio of **1a**:**2a** was 1.2:1. [b] Isolated yield of **3aa**; regioisomer **3aa'** was not observed in all cases. [c] The *ee* was determined by HPLC.

To obtain some insight into the reaction pathway, we monitored the reaction process of 2-indolylmethanol **1a** with nitrone **2a**, but no intermediate products were isolated. Nevertheless, we tried to use HRMS to detect the signals of some possible intermediates. As illustrated in **Scheme 6a**, after performing the reaction for 2 h, a weak signal ([M−H]$^-$ m/z 1141.4320) possibly due to the complex of intermediate **A** with (*R*)-**5a** was detected. In addition, a strong signal ([M−H]$^-$ m/z 1123.4251) that was likely due to the complex of carbocation **B** with the (*R*)-**5a** anion was detected. Thus, the HRMS study supported the generation of possible reaction intermediates and indicated that the (3+3) cycloaddition proceeded via a stepwise process involving the C3-nucleophilic addition of 2-indolylmethanol **1a** to nitrone **2a** and subsequent intramolecular cyclization. Moreover, *N*-Me-protected 2-indolylmethanol **1s** failed to participate in the reaction (**Scheme 6b**), which implied that the NH group of the indole ring formed a hydrogen bond with the catalysts.




**Scheme 6.** Study of the possible reaction intermediates and activation mode

To better understand the role of HFIP and the reaction mechanism, based on the experimental results, we performed theoretical calculations on the possible reaction pathways of the catalytic asymmetric (3+3) cycloaddition of 2-indolylmethanol **1a** with nitrone **2a** (**Scheme 7**). First, the calculation revealed that nitrone **2a** can easily transform into intermediate **C** via protonation in the presence of (*R*)-**5a** (**Scheme 7a**). This interaction between **2a** and (*R*)-**5a** made the reaction pathway for regioisomers **3'** (in **Scheme 3b**) less possible due to the absence of both the oxygen anion of the nitrone and the delocalized carbocation generated from 2-indolylmethanol. Therefore, this finding explained the exclusive formation of regioisomers **3**. In fact, attempts were made to reverse the regioselectivity, but regioisomer **3aa'** was not observed in all cases (see the SI for details).

Second, the reaction pathway involving the cooperative catalysis of (*R*)-**5a** and HFIP was studied. After exploring a series of possible activation modes of the substrates in the cocatalytic system (see the SI for details), we found the most stable structures for related intermediates (INT) and transition states (TS). As illustrated in pathway A (**Scheme 7b**), in **INT-1**, HFIP and the CPA (*R*)-**5a** anion simultaneously activated both 2-indolylmethanol **1a** and intermediate **C** by forming multiple hydrogen bonds, thus facilitating their enantioselective nucleophilic addition via **TS-1** to give chiral **INT-2**. Then, **INT-2** rapidly transformed into **INT-3** via **TS-2**. The subsequent dehydration of **INT-3** via **TS-3** generated carbocation **INT-4**, which underwent intramolecular addition via **TS-4** to give final product (*S*)-**3aa**. Notably, the theoretical calculations revealed that excess HFIP also had some effect on the processes of **TS-2** and **TS-3** after the generation of the chiral center (**TS-1**). In brief, the OH group of HFIP formed a hydrogen bond with the P=O group of CPA, and the combined catalytic system cooperatively activated the substrates via hydrogen-bonding interactions in **TS-2** and **TS-3**. Therefore, the calculation results revealed that HFIP played an important role in the whole reaction pathway.

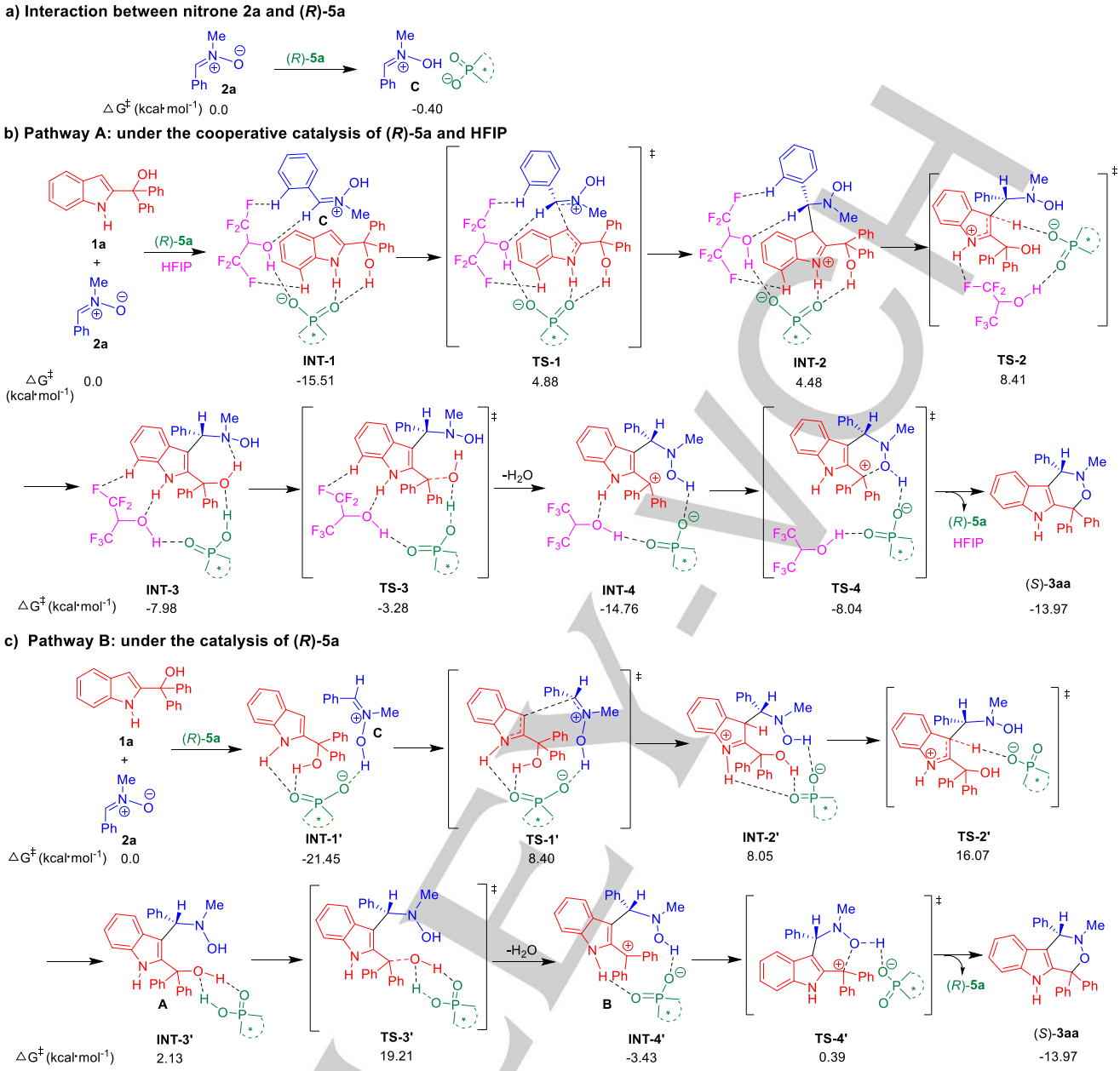
In addition, pathway B was investigated in the presence of the single catalyst CPA (*R*)-**5a** (**Scheme 7c**). In all the calculated structures (**INT-1'** to **INT-4'**, **TS-1'** to **TS-4'**), the substrates were only activated by CPA via a single mode. For example, in **INT-1'**, only the (*R*)-**5a** anion activated 2-indolylmethanol **1a** and intermediate **C** via **TS-1'** to give chiral **INT-2'**. The subsequent transformation of **INT-2'** through **TS-2'** to **TS-4'** gave rise to product (*S*)-**3aa**.

To explain the role of HFIP in the reaction, the calculated free energy profiles of pathways A and B are summarized and compared in **Scheme 7d**. Obviously, the energy barriers of all the transition states of pathway A (**TS-1** to **TS-4**) and pathway B (**TS-1'** to **TS-4'**) were remarkably different. In most of the steps, the energy barrier of pathway A was much lower than that of pathway B. Specifically, it is clear that the energy barrier of **TS-1** in pathway A (20.39 kcal·mol$^{-1}$) was much lower than that of **TS-1'** in pathway B (29.85 kcal·mol$^{-1}$). Because this step was the key step for initiating the C3-nucleophilic (3+3) cycloaddition and generating the chiral center, the large difference in the energy barriers (9.46 kcal·mol$^{-1}$) of this step supported the conclusion that pathway A occurs more readily than pathway B. In addition, the energy barrier of **TS-2** (3.93 kcal·mol$^{-1}$) was 4.09 kcal·mol$^{-1}$ lower than that of **TS-2'** (8.02 kcal·mol$^{-1}$), and the energy barrier of **TS-3** (4.70 kcal·mol$^{-1}$) was 12.38 kcal·mol$^{-1}$ lower than that of **TS-3'** (17.08 kcal·mol$^{-1}$). Moreover, the overall energy barrier of pathway A was 8.41 kcal·mol$^{-1}$ (from the starting point to **TS-2**), which was much lower than the overall energy barrier of pathway B (19.21 kcal·mol$^{-1}$, from the starting point to **TS-3'**). All these results demonstrated that the addition of HFIP to the reaction as a cocatalyst lowered the energy barriers of the key transition states as well as the overall energy barrier.

To better understand how HFIP worked with (*R*)-**5a** to control the reactivity and enantioselectivity, we compared the structures of the key TSs in pathways A and B (see the SI for details). A comparison of **TS-1** and **TS-1'** in the two pathways is shown in **Figure 1**. In **TS-1**, HFIP formed four hydrogen bonds with the other reagents. In detail, the OH group of HFIP not only formed a hydrogen bond (1.559 Å) with the anion of (*R*)-**5a** but also interacted with the prochiral CH of the protonated nitrone via hydrogen bonding (2.154 Å). More importantly, two fluorine atoms of HFIP formed C-H···F hydrogen-bonding interactions[22] (2.420 Å and 2.462 Å, in red ellipses) with the phenyl C-H groups of the protonated nitrone and 2-indolylmethanol, respectively. In addition, the P=O group of the (*R*)-**5a** anion formed two hydrogen bonds (1.692 Å and 1.698 Å) with the NH and OH groups of 2-indolylmethanol. Therefore, in the cocatalytic system, HFIP and the (*R*)-**5a** anion formed multiple hydrogen bonds with the two substrates, similar to a crab's pincers tightly binding the substrates, thus fixing the steric orientation of the substrates during the nucleophilic addition and controlling the enantioselectivity of this key step. Moreover, the multiple hydrogen-bonding interactions resulted in the stability of **TS-1**. By contrast, in **TS-1'**, the anion of (*R*)-**5a** only generated three hydrogen bonds with the substrates, and the nonbonding interactions between the catalyst and substrates were much weaker than those in **TS-1**, leading to the large difference in the energy barriers (9.46 kcal·mol$^{-1}$) of **TS-1** and **TS-1'**.

Similar observations were also made when comparing **TS-2** with **TS-2'** and **TS-3** with **TS-3'** (see the SI for details). Namely, in **TS-2** and **TS-3**, not only did the OH group of HFIP form a hydrogen bond with the P=O group of (*R*)-**5a** but also one fluorine atom of HFIP formed N-H···F or C-H···F hydrogen-bonding interactions with the substrates. In **TS-2'** and **TS-3'**, these nonbonding interactions were not generated in the absence of HFIP, resulting in much weaker interactions between the catalyst and substrates and the observed higher energy barriers.

Therefore, the theoretical calculations elucidated the role of the cocatalyst HFIP in helping CPA stabilize the key transition states and create a chiral environment to control the reactivity and enantioselectivity of the (3+3) cycloaddition between 2-indolylmethanols and nitrones.




**Scheme 7.** Calculated reaction pathways and free energy profiles for understanding the role of HFIP and the reaction mechanism

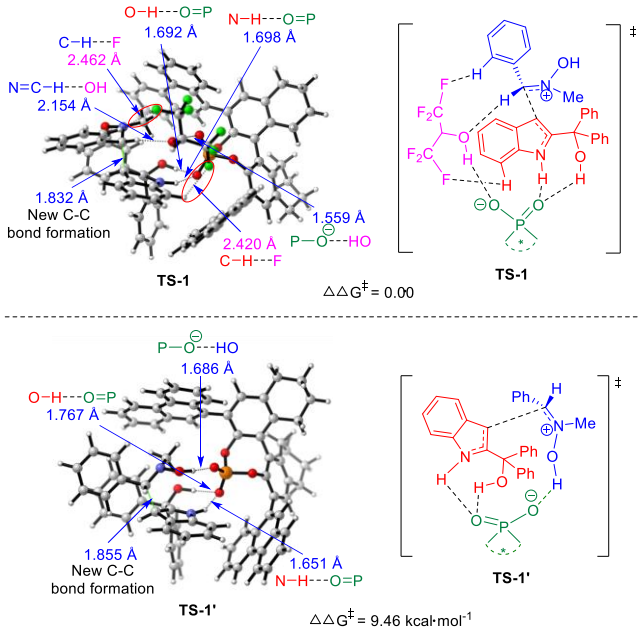



**Figure 1.** Comparison between **TS-1** and **TS-1'** of the two pathways

Finally, considering the importance of the constructed oxacarboline scaffold in chemical biology,[23] we investigated the possible bioactivity of the oxacarboline products **3**. The in vitro cytotoxicities of some selected products **3** against the human prostatic carcinoma PC-3 cell line were evaluated. The tested products **3** exhibited moderate to strong cytotoxicity against the PC-3 cell line, and the $IC_{50}$ values ranged from 40.08 to 222.65 μg/mL (see the SI for details). Therefore, these results of the cytotoxic evaluation demonstrated the importance of this class of oxacarboline products **3**, which exhibited moderate to strong anticancer activity against the PC-3 cell line and are promising compounds for discovering more applications in medicinal chemistry.

## Conclusion

In summary, we have established the regio- and enantioselective (3+3) cycloaddition of nitrones with 2-indolylmethanols enabled by the cooperative organocatalysis of HFIP and CPA. Using this approach, a series of indole-fused six-membered heterocycles were synthesized in high yields with excellent enantioselectivities and exclusive regiospecificity. This design realized not only the first organocatalytic asymmetric (3+3) cycloaddition of nitrones but also the first C3-nucleophilic asymmetric (3+3) cycloaddition of 2-indolylmethanols. More importantly, theoretical calculations elucidated the role of the cocatalyst HFIP in helping CPA stabilize the key transition state and create a chiral environment, thus controlling the reactivity and enantioselectivity. This study not only enriches the chemistry of nitrones and 2-indolylmethanols but also advances the research field of cooperative asymmetric catalysis.

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**Keywords:** nitrone • indolylmethanol • cooperative catalysis • organocatalysis • enantioselectivity • cycloaddition

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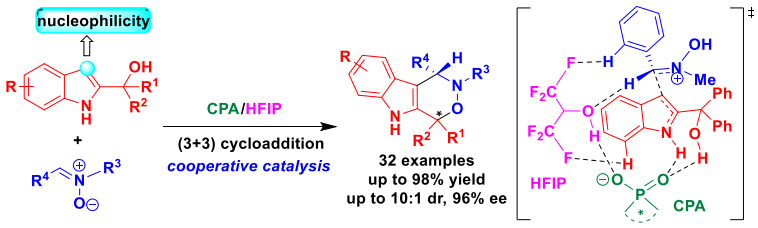


The regio- and enantioselective (3+3) cycloaddition of nitrones with 2-indolylmethanols has been established under the cooperative catalysis of hexafluoroisopropanol (HFIP) and chiral phosphoric acid (CPA). This approach not only realized the first organocatalytic asymmetric (3+3) cycloaddition of nitrones and the first C3-nucleophilic asymmetric (3+3) cycloaddition of 2-indolylmethanols but also revealed a new mode of cooperative catalysis.