Direct asymmetric N-propargylation of indoles and carbazoles catalyzed by lithium SPINOL phosphate

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Catalytic asymmetric functionalization of the N–H groups of indoles and carbazoles constitutes an important but less developed class of reactions. Herein, we describe a propargylation protocol involving the use of a lithium SPINOL phosphate as the chiral catalyst and our recently developed C-alkynyl N,O-acetals as propargylating reagents. The direct asymmetric N-propargylation of indoles and carbazoles provides hitherto inaccessible N-functionalized products. Notably, the efficiency of the system allows reactions to be run at a very low catalyst loading (as low as 0.1 mol%). Mechanistic information about the titled reaction is also disclosed. This study represents an advance in the direct asymmetric functionalization of the N–H bonds of indoles and carbazoles, and additionally expands on the application of chiral alkaline metal salts of chiral phosphoric acids in asymmetric catalysis.

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https://doi.org/10.1038/s41467-019-13886-9
The synthesis of enantioenriched indoles is of wide interest, owing to their prevalence in natural products and pharmaceuticals, and agrochemicals. Therefore, extensive efforts have been devoted to developing catalytic asymmetric methods for the functionalization of indoles. Great progress has been made in the catalytic asymmetric C-alkylation, especially at the C3 position, due to the innate nucleophilicity of C3 of the indole ring. In contrast, the catalytic asymmetric functionalization of the N–H of indole, particularly in an intermolecular manner, has remained underdeveloped, owing to the mitigated nucleophilicity of this position. To avoid the regioselectivity issue, several indirect strategies have been elegantly designed. To date, efficient strategies for the asymmetric N-functionalization of indoles are still rather limited and most reported intermolecular reactions relied on N-allylation. Very recently, the catalytic asymmetric N-benzylation has been elegantly developed to afford chiral N-benzylic indoles recently, the catalytic asymmetric N-benzylation has been reported intermolecular reactions relied on N-allylation. Very functionalization of indoles are still rather limited and most development of the direct catalytic asymmetric N-propargylation have been limited to the formation of C2,3-dimethyl indole with propargylic acetates using a chiral carbon-based nucleophiles (Fig. 2a). Nevertheless, despite these elegant achievements, there is still no report for the direct catalytic asymmetric functionalization of the N–H of indole through a propargylation strategy.

Catalytic asymmetric propargylation has been recognized as an important class of reactions in organic chemistry, because they create a propargylic chiral center and introduce a synthetically versatile and biologically important alkyn functional group in one step. Although great efforts have been devoted in this area, the potential of catalytic asymmetric propargylations has not been fully exploited and the scope of applicable nucleophiles and electrophiles is still rather limited. The direct catalytic asymmetric N-propargylation of indoles and carbazoles as nucleophiles has not yet been achieved. In addition, there are only limited types of chiral catalyst systems for the asymmetric propargylation to date.

The direct catalytic asymmetric N-propargylations using 1H-indole derivatives as nucleophiles have proven far more challenging than allied reactions such as allylations and have not been successful. Indeed, You and colleagues explored the reaction of 2,3-dimethyl indole with propargylic acetates using a chiral copper–pybox complex as the catalyst, but only obtained the C-propargylated product (Fig. 1). Thus, the challenges in the development of the direct catalytic asymmetric N-propargylation of indoles and carbazoles as the nucleophiles are to find a suitable propargylating reagent and an efficient catalyst system.

We recently introduced C-alkynyl N-Boc- and N-Cbz-protected N,O-acetals as a class of coupling partners for asymmetric catalytic transformations; to date, these transformations have been limited to the formation of C–C bonds with the use of carbon-based nucleophiles (Fig. 2a). However, the corresponding asymmetric reaction of C-alkynyl N,O-acetals through carbon–heteroatom bond formation has remained an unmet task. Given the lack of direct methods available for the catalytic asymmetric N-propargylation of indoles and carbazoles, we chose to explore the possibility that 1H-indoles and carbazoles might serve as the first effective heteroatom-based nucleophiles to react with C-alkynyl N,O-acetals (Fig. 2b). Such reaction would provide straightforward access to chiral alkynylated acyclic N,N-aminals of indoles and carbazoles. Recent studies have shown that acyclic N,N-aminal indoles I–III have significant antibiotic properties (Fig. 2c). Thus, there is a need for organocatalytic methods that enable the enantioselective synthesis of acyclic N,N-aminals of indoles or carbazoles, biologically important yet synthetically challenging molecules bearing an acyclic N,N-substituted α-chiral carbon center on the N1-position of indoles or carbazoles. Meanwhile, incorporating alkynes into N,N-aminals is made interesting, owing to the versatile transformations of the alkyne group and the ubiquitous occurrence as a key structural motif in natural products and pharmaceuticals. However, the direct catalytic asymmetric synthesis of N,N-aminals through a propargylation method has not been reported.

On the other hand, chiral alkali and alkaline earth metal-derived salts of chiral phosphoric acids have recently emerged as a class of effective catalysts in various asymmetric transformations. However, this class of chiral catalysts have not been successfully employed in the catalytic asymmetric functionalization of the N–H of indoles or carbazoles. Meanwhile, the direct catalytic asymmetric propargylation reaction catalyzed by chiral alkali or alkaline earth-derived salts of chiral phosphoric acids has remained elusive.

Besides these, there are several other challenges for the catalytic enantioselective C–N bond formation and natural products or pharmaceuticals. Herein, we report the development of highly enantioselective direct catalytic asymmetric N-propargylation of indoles and carbazoles. Mechanistic investigations are also disclosed.\[Fig. 1 Cu-catalyzed asymmetric propargylation of 2,3-dimethyl indole. C-propargylated product was exclusively obtained.\]
must be capable of both catalyzing the EtOH elimination from N, O-acetals to generate challenging N-Cbz-protected C-alkynyl imines and promoting the subsequent N-propargylation reaction, as well as imposing effective stereocontrol. After extensive investigations, we found that chiral alkali and alkaline earth metal-derived salts of chiral phosphoric acids were promising chiral catalysts for the tandem process combining the in situ generation of C-alkynyl N-Cbz imines and N-propargylation. Among them, a lithium SPINOL phosphate, Li[P2], catalyzed the EtOH elimination from N,O-acetal 1a for in situ generation of difficult accessible C-alkynyl N,Cbz imines and the subsequent asymmetric N-propargylic alkylation with 93% enantiomeric excess (ee) (Table 1, entry 3).

Mechanistic investigations. To get an understanding of the N-propargylation, we monitored the reaction of racemic 1a with 2a under the standard conditions by determining ee for both the generated product 3a and the recovered substrate 1a over time (Fig. 3a). It was found that after a reaction time of 6 h, 1a was recovered with 49% ee. With the reaction time further increasing, ee of the recovered 1a began to decrease. Meanwhile, ee of the product 3a was decreased relatively slowly (for details, see Supplementary Table 2).

To investigate whether the enantioriched 1a arising from the reaction of racemic 1a with EtOH under the chiral catalysis of Li[P2], we performed the reaction between racemic 1a and EtOH in the presence of (R)-Li[P2]. The recovered 1a was still racemic and no chiral induction was observed (Fig. 3b), thus excluding such possibility. This result combined with the experiment shown in Fig. 3a implied there might be a kinetic resolution during the process between racemic 1a and 2a in the presence of Li[P2]. To further confirm this issue, we conducted kinetic studies. The (+)-1a (97% ee) and (−)-1a (97% ee) were reacted with 2a in the presence of (R)-Li[P2] as the catalyst, respectively. We found that both enantiomers of 1a delivered the same enantiomer of the product, (R)-3a, regardless of the original configuration of the C-alkynyl N,O-acetal, and the reaction with (+)-1a was faster than that of (−)-1a (Fig. 4. For details, see Supplementary Table 3), thus verifying that there was a moderate degree of kinetic resolution of 1a during the reaction with 2a.

To understand why the recovered 1a and the product 3a decreased gradually with the reaction time further increasing and to gain further insight into the N-propargylation, we made some

Fig. 2 Asymmetric reactions of C-alkynyl N,O-acetals with nucleophiles. a C-based nucleophiles. b 1H-Indoles and carbazoles as N-based nucleophiles (several challenges are shown). c Non-cyclic aminals of indoles and carbazoles as antibiotics. Boc, tert-butyloxy carbonyl, Cbz benzyl oxy carbonyl, PG protecting group.
control experiments. The experiment shown in Fig. 3c (for details, see Supplementary Tables 4 and 5) explained a possible reason for the decrease of enantioselectivity of the recovered 1a over the time. The crossover experiment shown in Fig. 3d (for details, see Supplementary Table 6) indicated that the chiral catalyst was discriminating the two enantiomers of the C-alkynyl N,N-aminal and (R)-3a was converted into the corresponding C-alkynyl N-Cbz imine more faster than (S)-3a in the presence of Li[P2] (there was a kinetic resolution of 3a during this process). These results combined with the control experiments in Fig. 3e (for details, see Supplementary Table 1 Optimization of the reaction conditions).
**Fig. 3 Mechanistic investigations.**

a Enantioselectivity of the product 3a and the recovered substrate 1a over time. b The reaction of racemic 1a with EtOH under the chiral catalysis of Li[P2]. c The reaction of chiral 1a with EtOH under the chiral catalysis of Li[P2]. d Crossover experiment. e The reaction of chiral 3a with 2a under the chiral catalysis of Li[P2]. f The reaction of chiral 3a with EtOH under the chiral catalysis of Li[P2]. g Proposed reaction mechanism.
Supplementary Table 7) and Fig. 3f (for details, see Supplementary Table 8) explained a possible reason for the decrease of ee of the product 3a over the time. The experiment in Fig. 3f also suggested that the alkynylated N,N-amin can react with EtOH to form the corresponding N,O-acetal. Pleasingly, the racemization of the product 3a was found to be effectively suppressed by increasing the amount of the C-alkynyl N,O-acetal substrate 1a to 1.6 eq. (for details, see Supplementary Table 9).

Next, we studied the relationship between the ee of the catalyst Li[P2] and that of the product 3a, and a linear effect was observed (for details, see Supplementary Table 10). On the basis of the above observations, we proposed a possible reaction mechanism shown in Fig. 3g.

**Substrates scope.** With the optimized chiral catalyst and suitable propargylic alkylating reagent in hand, we investigated the scope of the direct catalytic asymmetric N-propargylation of carbazoles. Various C-alkynyl N-Cbz N,O-acetals 1 were reacted with carbazoles 2 to afford the desired N-propargylated products (3a–3h) in high enantioselectivities with good yields (Fig. 5). Moreover, this system was also applicable for the enantioselective N-propargylation of indoles (Fig. 6). The reaction displayed broad substrate scope of both C-alkynyl N,O-acetals and substituted indoles. The corresponding N-propargylic indoles 5a–5z were obtained in good yields with high to excellent enantioselectivities (up to 99% ee) in all the cases examined (26 examples). Notably, in contrast to the work by You and colleagues30, our propargylation reactions occurred at the N1-position exclusively and no competing C3-propargylied product was observed. On the other hand, impressively, the reaction at high temperature (110 °C) can still provide excellent enantioselectivity (5s). Examples with high stereocontrol at such a high temperature are scarce in asymmetric catalysis by chiral alkali and alkaline earth-derived salts of chiral phosphoric acids.

**Product configuration determination and transformations.** The absolute configuration of the N-propargylation products was determined by converting 5k into 6 (Fig. 7a), and the structure of 6 was unambiguously confirmed through X-ray crystal analysis. Reduction of 5a with LiAlH4 afforded 7, which is formally derived from the N-selective and 1,2-selective addition of α,β-unsaturated imine (Fig. 7b). When 5a was reduced with Pd/C under H2 atmosphere, the primary alkyl-substituted product 8 was obtained in quantitative yield.

**Low catalyst-loading experiments.** Promoted by the unusual stereocontrol of Li[P2], we examined the N-propargylation reaction with low catalyst loading (Table 2). We found that when the catalyst loading was decreased from 5 to 0.5 mol%, the yield and enantioselectivity were not affected (Table 2, entry 1 and 2). Further decreasing the catalyst loading to 0.2 mol% has only a slight impact on the enantioselectivity (Table 2, entry 4). Even 0.1 mol% catalyst loading can still provide high enantioselectivity and yield (Table 2, entry 5). This is the lowest catalyst loading that has been achieved so far for the asymmetric catalysis by chiral alkali and alkaline earth-derived salts of chiral phosphoric acids.

**N-benzylation of indoles.** Finally, we explored the direct catalytic asymmetric N-benzylation of indoles with C-aryl N-Boc N,O-acetals in the presence of (R)-Li[P2]. Interestingly, the reaction did not occur. These results indicate the reactivity difference between C-alkynyl N-Boc N,O-acetals and C-aryl N-Boc N,O-acetals. Considering that C-aryl N-Boc imines can be prepared,
Fig. 6 Scope of N-propargylation of indoles. Reaction conditions: 1' (0.05 mmol), 4 (0.08 mmol), (R)-Li[P2] (5 mol%), toluene (1 mL). a Run with (S)-Li[P2]. b Run with (R)-Li[P1].
we turned our attention to the use of C-aryl N-Boc imines pre-formed. By utilizing a complementary catalytic mode, hydrogen bonding enantiocontrol, we developed an enantioselective N-benzylation of indoles using a chiral phosphoric acid PA1 as the catalyst (Fig. 8).

Discussion

In summary, we have developed an organocatalytic strategy for the direct asymmetric N-functionalization of indoles and carbazoles through a propargylation. Specifically, we have successfully realized the direct catalytic asymmetric intermolecular N-propargylation of indoles and carbazoles, providing hitherto inaccessible acyclic N,N-aminals of indoles and carbazoles in good yields with high enantiocontrol, despite many potential challenges of this reaction. This C–N formation process is enabled by the use of our newly developed C-alkynyl N,O-acetals as the alkylating reagent and a lithium SPINOL phosphate as the chiral catalyst. The product racemization has been suppressed effectively. A chiral lithium SPINOL phosphate catalyst promotes the activation of N,O-acetals for the in situ formation of challenging accessible C-alkynyl N-Boc or N-Cbz imines, although this class of catalysts were previously employed for the addition of alcohols to imines to form N,O-acetals. Notably, the efficiency of the system allows reactions to be run at a very low catalyst loading of 0.1 mol%. The present protocol represents a significant advance in the asymmetric functionalization of the N–H of indoles and carbazoles, and in the catalytic asymmetric propargylation, as well as opens an application of chiral alkali and alkaline earth-derived salts of chiral phosphoric acids in the asymmetric catalysis and synthesis.

Methods

General procedure for the N-propargylation of carbazoles 2. To a solution of 1 (0.08 mmol) and 2a (0.06 mmol), [(R)-PA1 (5 mol%), c-hexane (1.0 mL), rt.

Table 2 Reaction with low catalyst loading.

| Entry | X | Yield [%] | ee [%] |
|-------|---|-----------|--------|
| 1     | 5 | 78        | 99     |
| 2     | 1 | 78        | 99     |
| 3     | 0.5 | 76 | 99 |
| 4     | 0.2 | 76 | 97     |
| 5     | 0.1 | 72 | 92     |

Fig. 7 Product configuration determination and transformations. a Product configuration determination by X-ray diffraction analysis. b Reduction of the alkyln group into the alkenyl and alkyl groups.

Fig. 8 N-Benzylaion of indoles. Reaction conditions: 9 (0.05 mmol), 2a (0.06 mmol), [(R)-PA1 (5 mol%), c-hexane (1.0 mL), rt.

ARTICLE NATURE COMMUNICATIONS | https://doi.org/10.1038/s41467-019-13886-9
NATURE COMMUNICATIONS | https://doi.org/10.1038/s41467-019-13886-9
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