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Regioselective synthesis of C6-alkylated indoles utilizing electronic–steric effects enabled by imino exchange and phosphorus ylide addition†

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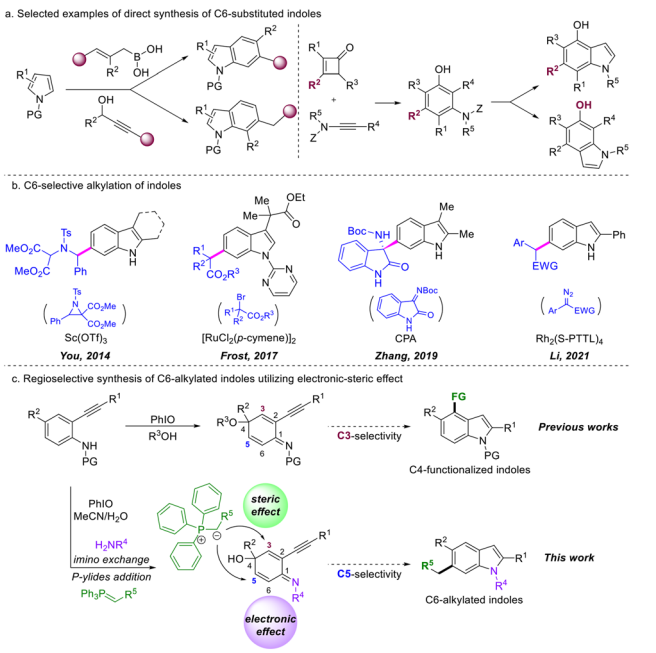
Herein, we report the regioselective synthesis of C6-alkylated indoles utilizing the electronic effect enabled by imino exchange and the steric effect of phosphorus ylide addition. The protocol adopts readily available P-ylides as alkylating reagents and alkylamines, used principally for regulating regioselectivity, from 2-alkynylanilines, to give the desired C6-alkylated indoles (C3–H and N1 with diverse substituents) with excellent regioselectivity.

Introduction

The development of new methods for the synthesis of functionalized indoles has attracted considerable attention due to their privileged scaffolds, which are found in many natural products and bioactive molecules.[1] In particular, building upon the promising bioactivities observed in C6-substituted indole derivatives,[2] selective C6-functionalization of indoles has shown significant and hard-earned progress, considering that electrophilic aromatic substitution reactions occur preferentially at the N1, C2 and C3 positions of the pyrrole core, rather than at the less reactive C4–C7 positions of the benzene core. The C6 site has been regarded as the most difficult position to functionalize amongst these four positions.[3] Existing direct synthesis of C6-substituted indoles typically relies on pre-installed substituents that become incorporated at the C6 position during indole skeleton construction.[4] These approaches often generate poly-substituted indole products with compromised regioselectivity (Scheme 1a). Promisingly, directing group-assisted C–H functionalization enables regiocontrolled installation of diverse substituents specifically at the C6 position. To overcome the limitation of C6 intrinsic reactivity, one strategy, of installing a larger directing group at the N1 site, has succeeded in affording *meta*-selective metal-catalyzed C–H functionalization, outcompeting the *ortho*-selectivity. Selected examples include: Pd-catalyzed C6-alkenylation using a U-shaped template, by Yu *et al.*;[5] Ir-catalyzed C6-borylation using a TIPS group, by Baran *et al.*;[6] and CuO-catalyzed C6-arylation using a TBPO group, by Shi *et al.*[7] More recently, another strategy for C6-alkenylation through Ru-catalyzed *ortho* C–H activation directed by the C7-amide group has been reported by Dawande *et al.*[8] However, selective C6-alkylation of indoles in this way appears to be more complicated due to the limitation of alkylating reagents for chelation-assisted cyclometallation. Other protocols to achieve selective



Scheme 1 (a) Direct synthesis of C6-substituted indoles. (b) C6-selective alkylation of indoles. (c) Strategy of regioselective synthesis of C6-alkylated indoles utilizing electronic–steric effects.

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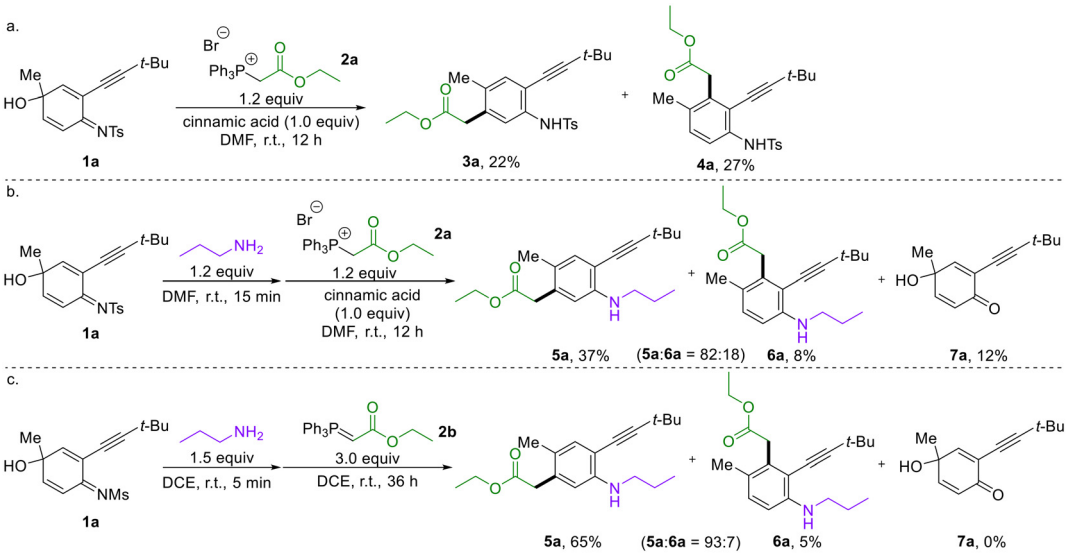
C6-alkylation have also been developed (Scheme 1b). Notably, in 2014, You and co-workers proposed $Sc(OTf)_3$-catalyzed C6-alkylation of 2,3-disubstituted indoles with aziridines involving a reversible [3 + 2] annulation.[9] In 2017, the Frost group used *N*-pyrimidinyl indoles with an ancillary ester directing group at the C3 position, which offered the C6 site as the most reactive vacant C–H site.[10] In 2019, Zhang's group described the first direct chemo-, regio- and enantioselective C6-functionalization of 2,3-disubstituted indoles with isatin-derived *N*-Boc ketimines using chiral phosphonic acid.[11] It can be seen that most of the methods require indoles with blocking groups at the C3 position at least. In 2021, Li and co-workers reported the Rh(II)-catalyzed regioselective coupling of NH and C3–H indoles with diazo compounds.[12] Despite this progress, it is highly desirable to explore more versatile alkylating reagents and/or the use of indole precursors without shielding of other reaction sites to synthesize C6-alkylated indoles.

In recent years substantial progress has been made in utilizing aniline-derived substrates for the synthesis of N-heterocycles.[13] Among these, 2-alkynylanilines have emerged as privileged precursors for constructing indole frameworks. Our group has been devoted to the functionalization of indoles based on the dearomatization strategy of 2-alkynylanilines, such as 3-substituted indoles,[14] 3,4-fused indoles,[15] 4-substituted indoles,[16] 6,7-fused indoles[17] and 7-substituted indoles.[18] Nevertheless, regioselective synthesis of C6-functionalized indoles remains an unmet aim in our research. 2-Alkynylcyclohexadienimines, the dearomatized intermediates, exhibit stronger electrophilicity at the C3 position owing to the C2 electron-withdrawing alkyne group, which leads to nucleophilic addition reactions occurring only rarely at the C5 position (Scheme 1c). In order to regulate the addition selectivity, we first selected commercially available and versatile phosphorus ylides as nucleophiles. Utilizing the effect of their large steric hindrance with the C2 alkyne group as well as its substituent, nucleophilic addition would become difficult at the C3 position. Second, the nitrogen-protecting groups of dearomatized intermediates are generally electron withdrawing and cause the C3 and C5 positions to be more electron deficient. This situation contributes to the selectivity of the nucleophilic addition being dominated by the electronic effect. Hence, we tried to replace the nitrogen substituent *via* an imino exchange reaction in a one-pot reaction. Utilizing the electronic effect of electron-donating nitrogen alkyl substituents to reduce the dominance of the electronic effect, nucleophilic addition would thus be facilitated, occurring at the C5 position under the steric effect. Thus, after cascade intramolecular cyclization, the addition products give rise to C6-alkylated indoles.

Results and discussion

As proposed above, we began our study by testing the reaction of *N*-Ts-protected dearomatized substrate **1a** and the P-salt of ethyl ester **2a** with cinnamic acid in DMF at room temperature (Scheme 2). Pleasingly, the C5-selective addition product **3a** was obtained in 22% yield, along with 27% of the C3-selective product **4a**, which suggested that adopting a large hindering nucleophile could partially reverse the addition selectivity (Scheme 2a). When *n*-propylamine was introduced and first reacted with substrate **1a**, the subsequent P-salt addition reaction gave rise to the desired compound **5a** as the major product. The regioselectivity ratio for C5-selectivity and C3-selectivity reached 82 : 18. Clearly, *n*-propylamine played a key role *via* imino exchange in regulating the regioselectivity. However, we also observed the formation of compound **7a** in comparable yield (12%), which resulted from hydrolysis of the imino exchange intermediate under acidic conditions

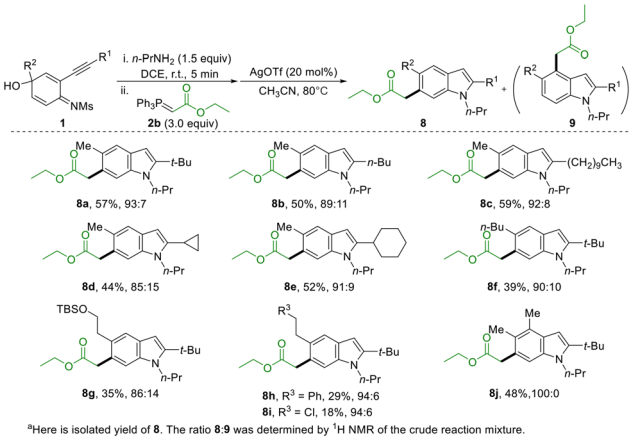


Scheme 2 (a) P-salt addition reaction. (b) Imino exchange and P-salt addition reactions. (c) Result under the optimum reaction conditions.

(Scheme 2b). Therefore, we decided to employ the P-ylide **2b** as a nucleophile without cinnamic acid, and a set of variables, including solvent, temperature and the equivalence of the reagents, was screened (for details see the ESI†). Under the optimum reaction conditions, the yield of **5a** was up to 65%, the ratio of **5a** to **6a** reached 93 : 7 and the hydrolysis by-product **7a** was not observed (Scheme 2c). Selected optimization of P-ylides and alkylamines is shown in Scheme 3. The triphenylphosphine ester or nitrile showed higher selectivity and yield compared with the tributyl phosphorus ylides. Tributyl phosphonium bromide without additives provided 44% combined yield of **5** and **6**, whereas the selectivity was poor. Diethyl (2-oxopropyl)phosphonate merely afforded 10% combined yield. Methyl-substituted and phenyl-substituted triphenylphosphine of esters couldn't give the corresponding addition products. Triphenylphosphine of benzyl ester and cyclopropyl ketone provided 46% and 47% yield, respectively. However, triphenylphosphine of lactone and methanal failed to afford the corresponding addition products. Moreover, in evaluation of alkylamine, *n*-propylamine showed the best reactivity (63% yield and 93 : 7 selectivity) as the nitrogen protecting group was methylsulfonyl (Ms) group.

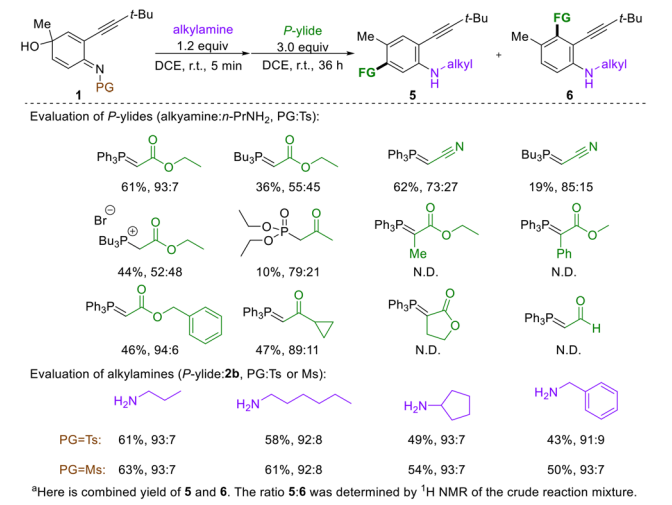
With the optimum conditions of imino exchange and P-ylide addition in hand, we examined the scope of reactants to synthesize C6-alkylated indoles by intramolecular cyclization using AgOTf as catalyst. Various *N*-Ms-protected dearomatized substrates **1** and *n*-propylamine with P-ylide of ethyl ester **2b** were subjected to the optimized conditions (Scheme 4). In most cases, the desired C6-alkylated indoles **8** could be generated smoothly in moderate yields with high regioselectivity. Alkyne groups with different substituents, including linear, branched or cyclic alkyl groups, were well tolerated and could be introduced into the C2 position of the indoles. For example, the templated substrate bearing a *t*-butyl group provided the corresponding product **8a** with 57% yield and 93 : 7 regioselectivity. The reactions of linear *n*-butyl and *n*-decyl groups worked well, to afford products **8b** and **8c** with 50% and 59% yield, respectively. Cyclopropyl and cyclohexyl groups did not have an obvious impact on reaction yields and regioselectivity. As shown for **8f–8i**, linear substituents for R^2 led to decreased yield, probably due to steric hindrance for P-ylide addition, but the regioselectivity remained largely constant. When double methyl groups were at the C3 and C4 positions of substrate **1**, no C4-alkylated product, **9j**, was generated.

Next, various alkylamines and P-ylides with substrates **1** containing diverse functional groups were tested (Scheme 5). The reactions of alkylamines with different alkyl substituents or benzyl groups proceeded smoothly, to afford the corresponding compounds **8k–8n**, with up to 54% yield and 93 : 7 regioselective ratios for **8 : 9**. Cyclic alkylamines, from cyclopropylamine to cyclooctylamine, all provided the desired



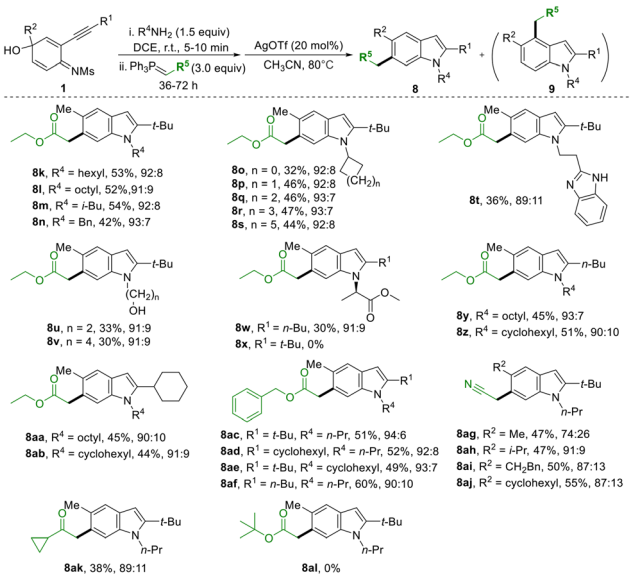
[a]Here is isolated yield of **8**. The ratio **8**:**9** was determined by ^{1}H NMR of the crude reaction mixture.

Scheme 4 Investigation of the scope of the *N*-Ms-protected dearomatized substrates.



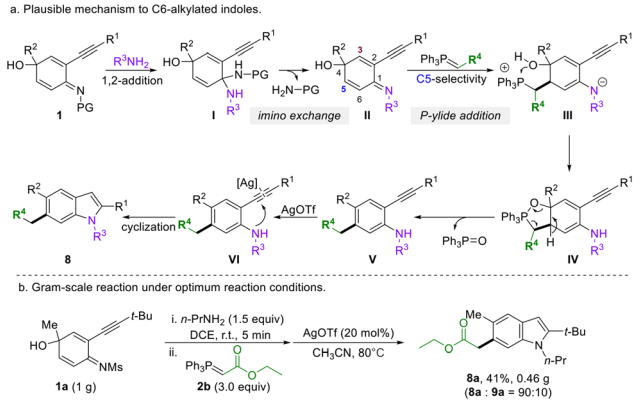
[a]Here is combined yield of **5** and **6**. The ratio **5**:**6** was determined by ^{1}H NMR of the crude reaction mixture.

Scheme 3 Selected optimization of P-ylides and alkylamines.



[a]Here is isolated yield of **8**. The ratio **8**:**9** was determined by ^{1}H NMR of the crude reaction mixture.

Scheme 5 Investigation of the scope of alkylamines and P-ylides.



Scheme 6 Plausible mechanism and gram-scale reaction.

indoles **8o–8s** with moderate yields and excellent regioselectivity (>92 : 8). 1*H*-Benzimidazole-2-ethanamine was used for imino exchange, with product **8t** obtained in 36% yield with a regioselective ratio of 89 : 11. Notably, when ethanolamine and 4-amino-1-butanol were used, the hydroxy groups tended to diminish the yield of products **8u** and **8v**. In addition, the natural amino acid of the ester methyl D-alaninate could also be introduced into the N1 position of C6-alkylated indoles **8w**. However, when the R^1 group was *t*-butyl, the intramolecular cyclization step failed to afford the corresponding product **8x**. Cross-exchange of the alkylamine and R^1 groups could also lead to the formation of the desired C6-alkylated products **8y–8ab**. The reactions of P-ylides of benzyl esters or nitriles worked well to afford the desired C6-alkylated indoles **8ac–8aj** with up to 60% yield and regioselective ratio of 94 : 6. The acyl group, instead of the ester group, could also be introduced to the C6 position to give the product **8ak** in 38% yield and 89 : 11 ratio. However, for P-ylide of the *tert*-butyl ester the addition reaction could occur but not intramolecular cyclization to afford **8al**.

On the basis of these results from experimental investigations, a plausible mechanism is proposed for the regioselective synthesis of C6-alkylated indoles (Scheme 6a). The dearomatization substrates **1** undergo 1,2-addition of alkylamines to **I** and subsequent elimination leads to formation of the imino exchange intermediate **II** (confirmed by LC-MS; Scheme S2 in the ESI†). After regioselective addition of P-ylides at the C5 position *via* five-membered oxaphospholes (**IV**), aromatization affords the alkyl-substituted aniline compounds **V**. The cascade Ag(I)-catalyzed intramolecular cyclization provides C6-alkylated indoles as the final products, **8**. In addition, gram-scale reaction was performed under optimum conditions and gave the C6-alkylated product **8a** with a yield of 41% and regioselectivity ratio of 90 : 10 (Scheme 6b).

Conclusions

We have realized the regioselective synthesis of C6-alkylated indoles. The excellent regioselectivity is achieved by the electronic effect *via* imino exchange and the steric effect of phosphonium ylide addition. Unlike prevailing C6-alkylation reactions, this approach adopts readily available P-ylides as alkylating reagents and alkylamines, used principally for regulating regioselectivity, from 2-alkynylanilines to give the desired C6-alkylated indoles (C3–H and N1 with diverse substituents). This protocol provides a reliable strategy for the less explored regioselective functionalization of indoles.

Conflicts of interest

There are no conflicts to declare.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article and its ESI.†

Acknowledgements

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