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A four-component reaction to access 3,3-disubstituted indolines *via* the palladium–norbornene-catalyzed *ortho* amination/*ipso* conjunctive coupling†

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As an important class of multicomponent reactions, the palladium/norbornene (Pd/NBE) cooperative catalysis has been mainly restricted to the coupling of an aryl halide, an electrophile and a nucleophile. Here, we report the development of a Pd/NBE-catalyzed four-component reaction, which involves *ortho* C–H amination/*ipso* conjunctive coupling using an alkene and an external nucleophile. The use of alkene-tethered nitrogen electrophiles provides a rapid and modular synthesis of 3,3-disubstituted indolines from readily available aryl iodides. The reaction exhibits broad functional group tolerance, and its utility is exemplified in a streamlined formal synthesis of a rhodamine dye. Preliminary results of the asymmetric version of this reaction have also been obtained.
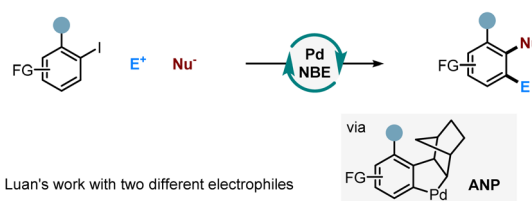
Introduction

Multicomponent reactions—the reactions that assemble multiple reactive moieties in a sequential manner to form a single product—offer a rapid and modular approach to access complex structures from readily available reactants.[1] These reactions have found broad utilities in synthesizing analogues and constructing compound libraries. As a unique class of multicomponent reactions, the palladium/norbornene (Pd/NBE) cooperative catalysis,[2] also known as the Catellani-type reaction, has become an increasingly useful tool for arene functionalization. It allows simultaneous functionalization of the *ortho* C–H bond of aryl halide substrates through reacting with an electrophile and the *ipso* position *via* coupling with a nucleophile (including alkenes) (Scheme 1a). While significant progress has been made in this field, the Pd/NBE catalysis has been primarily restricted to the coupling of three components: aryl (or alkenyl) substrates, electrophiles, and nucleophiles. To the best of our knowledge, the only exception to date is the seminal work by Luan (Scheme 1b).[3] This reaction shows a four-component coupling involving an aryl iodide, two kinds of electrophile (an anhydride and an alkyl halide),[4] and a nucleophile, in which the two *ortho* C–H bonds of the arene substrate are functionalized by the different electrophiles. Then, an intriguing question arose: is it possible to involve two

different kinds of nucleophile in a Catellani-type reaction? Here, we report the development of a unique four-component Pd/NBE catalysis, which employs two kinds of nucleophile,
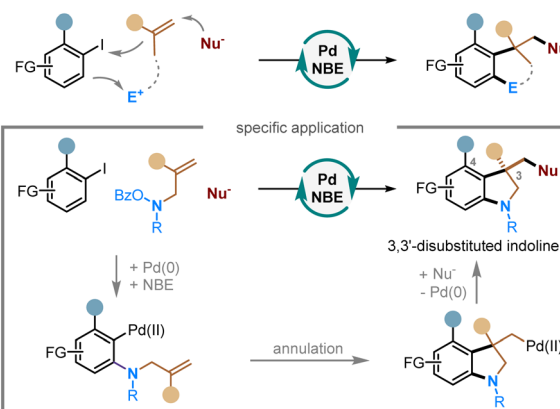

Scheme 1 The Pd/NBE cooperative catalysis.

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i.e., an alkene and an external nucleophile, to functionalize the arene *ipso* position through conjunctive coupling (Scheme 1c).[5] As a specific application, this reaction allows for rapid construction of 3,3-disubstituted indolines,[6] which are key structural motifs found in numerous FDA-approved drugs[7] (*e.g.*, vincristine[8]) and various other bioactive compounds[9] (Fig. 1). We hypothesized that, by tethering an amine electrophile[10] with a 1,1-disubstituted alkene,[11] the normal *ipso* Heck reaction should be interrupted, and the resulting alkyl Pd(ɪɪ) species can be trapped by an external nucleophile to realize the conjunctive coupling and furnish a quaternary carbon centre.[12,13]

Fig. 1 Representative bioactive compounds bearing 3,3'-disubstituted indoline moieties.

Results and discussion

To explore the proposed synthesis of 3,3-disubstituted indolines *via ortho* amination/*ipso* conjunctive coupling, we started with a model reaction system employing 2-iodoanisole (**1a**) as the arene substrate, *N*-benzoyloxy 2-methylallylamine (**2a**) as the alkene-tethered electrophile, and isopropyl alcohol as the hydride (external nucleophile) source.[14] After systematically evaluating various reaction parameters, the desired indoline product **4a** was obtained with a satisfying 83% yield (Table 1,
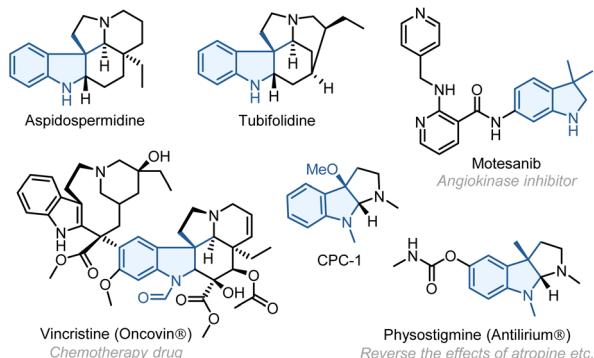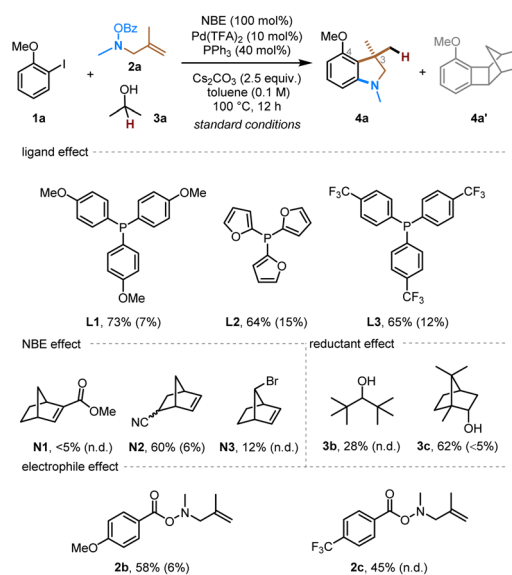
Table 1 Control experiments[a]

Entry	Change from the "standard conditions"	Yield of **4a**[b]	Yield of **4a'**[b]
1	None	83%	10%
2	No PPh₃	n.d.	n.d.
3	PPh₃ (25 mol%)	50%	<5%
4	Other ligands instead of PPh₃	Listed above	
5	No NBE or no Pd(TFA)₂	n.d.	n.d.
6	NBE (50 mol%)	68%	<5%
7	Other NBEs instead of simple NBE	Listed above	
8	Other reductants instead of **3a**	Listed above	
9	Other electrophiles instead of **2a**	Listed above	
10	Pd₂dba₃ instead of Pd(TFA)₂	58%	<5%
11	Pd(OAc)₂ instead of Pd(TFA)₂	71%	10%
12	1,4-Dioxane instead of toluene	39%	18%

[a] Unless otherwise noted, all reactions were carried out with **1a** (0.1 mmol), **2a** (0.2 mmol) and **3a** (0.12 mmol), in 1.0 mL of solvent for 12 h. The number in parentheses refers to the yield of side-product **4a'**. [b] NMR yields were determined using 1,1,2,2-tetrachloroethane as the internal standard.

entry 1). The major side-product was the benzocyclobutene **4a′** (10% yield), resulted from direct reductive elimination from the ANP intermediate.[2h] Control experiments were conducted to understand the role of each reactant. First, PPh$_3$ was found to be the optimal ligand, and its absence led to no product formation (entry 2). Lowering the ligand loading decreased the yield to some extent (entry 3). In addition, replacement of PPh$_3$ with other monodentate phosphine ligands gave somewhat lower yield (entry 4). Both NBE and palladium are essential to this reaction (entries 5). The use of 50 mol% NBE still afforded a comparable yield with reduced side-product formation (entry 6). For comparison, no obvious advantage was observed using structurally modified NBEs (smNBEs)[2j] such as **N1**,[15] **N2** (ref. 16) and **N3** (ref. 17 and 11c) for this substrate (entry 7). Furthermore, isopropanol was identified as the optimal hydride source, as lower efficiency was observed with bulkier alcohols, such as **3b** or borneol (**3c**) (entry 8). Changing the leaving group on the nitrogen electrophile from simple benzoyl to a more electron-rich *para*-methoxy-substituted one or a more electron-deficient *para*-trifluoromethyl-substituted one gave no improvement of the yield (entry 9). The use of other Pd pre-catalysts, such as Pd$_2$dba$_3$ and Pd(OAc)$_2$, gave comparable results (entries 10 and 11). Toluene proved to be a more suitable solvent; in contrast, the more polar 1,4-dioxane gave much lower yield and more

Table 2 Substrate scope[a]
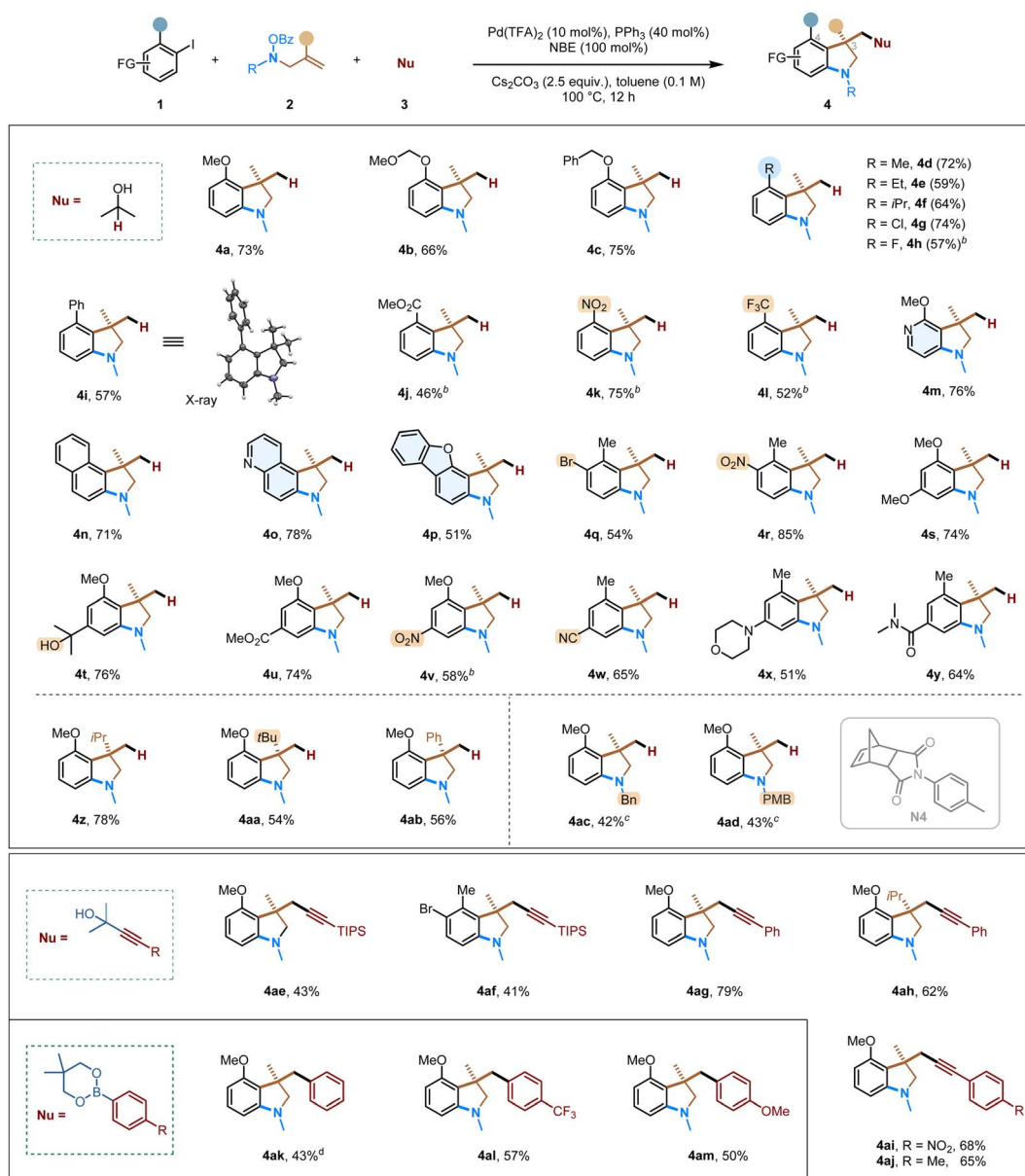
[a] Unless otherwise noted, all reactions were carried out with **1** (0.2 mmol), **2** (0.4 mmol) and **3** (0.24 mmol) in 2.0 mL of toluene for 12 h; all yields are isolated yields. [b] P(4-CF$_3$C$_6$H$_4$)$_3$ (**L3**) as ligand. [c] 120 °C with **N4**. [d] Phenylboronic acid was used as the nucleophile.

side-product formation (entry 12), likely because the amine electrophile tends to decompose in more polar solvents.

With the optimized conditions established, we next proceeded to explore the substrate scope for the formation of 3,3-disubstituted indolines (Table 2). Aryl halides with both electron-donating (4a–4f, 4i) and – withdrawing (4g, 4h, 4j–4l) groups proceeded smoothly, and the corresponding indoline products were obtained in good yields. Besides *ortho*-substituted aryl iodides, *ortho*-, *meta*-disubstituted and *ortho*-, *para*-disubstituted substrates (4q–4y) also worked well. A wide range of common functional groups are well tolerated in the reaction, including chloro (4g), fluoro (4h), biphenyl (4i),[18] ester (4j, 4u), nitro (4k, 4r), trifluoromethyl (4l), bromo (4q), tertiary alcohol (4t), nitrile (4w), amine (4x), and amide (4y) groups. The tolerance of aryl bromide allows the products to potentially undergo various downstream transformations. Besides monocyclic aryl iodides, 1-iodonaphthalene (4n) and heteroaromatic ones, such as substituted pyridine (4m), quinoline (4o) and dibenzofuran (4p), are also suitable substrates. Regarding the side products of these reactions, in addition to the norbornylbenzocyclobutene type, the NBE-attached uncyclized products have also been detected.

Other alkene-tethered *O*-benzoyl hydroxylamines were explored next. Bulkier olefin substituents, *i.e.*, those bearing isopropyl (4z), *tert*-butyl (4aa), and phenyl groups (4ab), are tolerated in this reaction. These substrates generate an all-carbon quaternary centre at the C3 position. Besides forming *N*-methyl substituted indolines, the corresponding removable benzyl group (4ac) or *para*-methoxybenzyl group (4ad) can also be introduced. The increased steric with these substrates reduced the reactivity substantially; however, using a smNBE (N4) under an elevated reaction temperature led to decent efficiency.

In addition to hydride-mediated conjunctive couplings, other nucleophilic species, such as masked acetylides (4ae-4aj)

and organoboronates (4ak-4am), can all undergo the desired transformations. These reactions also afforded an all–carbon quaternary centre in the desired indoline products, and the main side products are the direct *ipso* Sonogashira or Suzuki coupling without cyclization. As such, this multi-component strategy can rapidly increase the molecular complexity from simple building blocks with high chemoselectivity.

A plausible and simplified catalytic cycle is proposed in Scheme 2. The reaction starts with oxidative addition of the aryl halide to form Int I (step A), which then undergoes migratory insertion into NBE to generate Int II (step B), followed by concerted metalation deprotonation (CMD) to give the key ANP intermediate Int III (step C). Afterwards, oxidative addition of the ANP with the nitrogen electrophile (step D) and then reductive elimination (step E) introduce an amino group at the *ortho* position. Subsequent extrusion of NBE *via* β-carbon elimination (step F) sets the stage for the intramolecular migratory insertion with the alkene group (step G). The resulting Pd(ii) intermediate is then trapped by the external nucleophile, which leads to the conjunctive coupling at the *ipso* position and regeneration of the Pd(0) catalyst after the reductive elimination (step H).

The utility of this method was exemplified in the synthesis of compound 7, which is the key intermediate in the preparation of a diaryl rhodamine dye (Scheme 3). This type of dyes are useful fluorescent labels of nucleosides, nucleotides, polynucleotides, and polypeptides, and can be applied in the field of fluorescent nucleic acid analysis, including automated DNA sequencing.[19] Intermediate 7 was previously prepared in eight steps from expensive 1,3-dihydroxynaphthalene (8).[19] We envisioned that our method should allow for a more straightforward and modular access to this intermediate. Indeed, starting from relatively inexpensive 2-methoxynapthalene, the directed lithiation and subsequent iodination afforded the aryl iodide (6),[20] which was then subjected to the Pd/NBE-catalyzed four-component coupling under the modified condition. Note that, compared to other aryl iodide substrates in Table 2, compound 6 is a more challenging substrate due to the meta constraint (the steric hindrance caused by the meta substituent, which hampers the *ortho* C–H activation).[14b] Ultimately, the use of a more stable amine electrophile (2b), together with a more
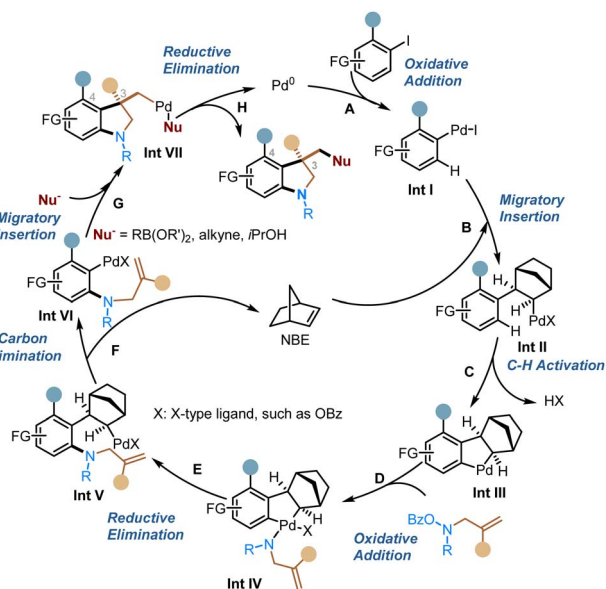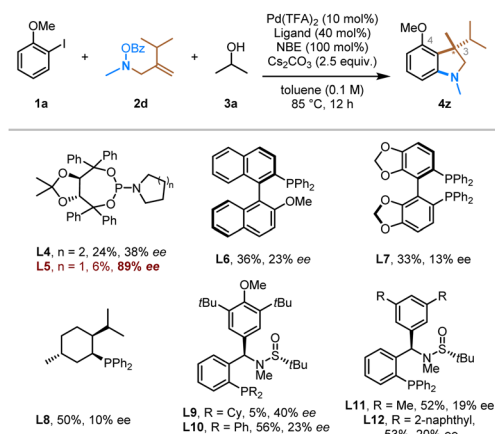

Scheme 2 Proposed catalytic cycle.
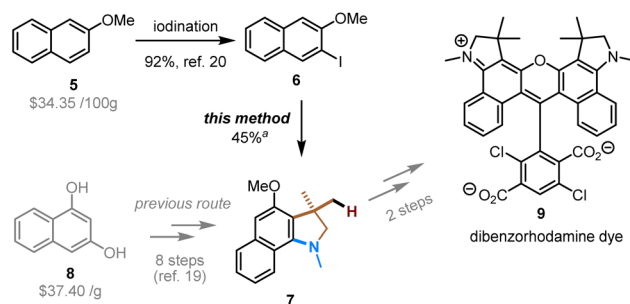
Scheme 3 Synthetic application. [a]The reaction was carried out with 6 (0.1 mmol), 2b (0.2 mmol), 3b (0.12 mmol), Pd(TFA)$_2$ (15 mol%), L2 (35 mol%), N1 (100 mol%), Cs$_2$CO$_3$ (0.25 mmol) in 1.0 mL of toluene at 100 °C for 12 h.

Table 3 Preliminary evaluation of chiral ligands for the enantiose-lective reaction[a,b]

[a] Unless otherwise noted, all reactions were carried out with **1a** (0.1 mmol), **2d** (0.2 mmol) and **3a** (1.2 mmol), Pd(TFA)$_2$ (10 mol%), ligand (40 mol%), NBE (100 mol%), Cs$_2$CO$_3$ (0.25 mmol) in 1.0 mL of toluene at 85 °C for 12 h. [b] NMR yields were determined using 1,1,2,2-tetrachloroethane as the internal standard. The absolute stereochemistry of the major enantiomer is unknown yet.

electron-deficient tri(2-furyl)phosphine ligand (**L2**) and a smNBE (**N1**), delivered the target compound (**7**) in a satisfactory yield (for details, see ESI†).

Finally, we conducted the preliminary exploration of the asymmetric version of this transformation (Table 3). Gu and coworkers reported the first enantioselective Pd/NBE catalysis *via* asymmetric *ipso* Heck coupling using a carefully optimized chiral phosphoramidite ligand;[21] however, other asymmetric *ipso* termination reactions remain challenging.[22] At this stage, a range of different classes of readily available chiral ligands were evaluated in this conjunctive *ipso* coupling reaction, including phosphoramidites (**L4**, **L5**), monodentate phosphines (**L6**, **L8**), bidentate phosphines (segphos, **L7**), and Zhang's sulfinamide-containing phosphine (Sadphos, **L9**–**L12**) ligands.[23] It is encouraging to observe that the chiral monodentate phosphoramidite ligand, *i.e.*, **L5**, can afford the desired product (**4z**) in 89% e.e. While the yield remains low at this stage, this result indicates the feasibility to control the enantioselectivity in the conjunctive *ipso* coupling.

Conclusions

In summary, we have developed a Pd/NBE-catalyzed four-component reaction to incorporate conjunctive coupling of an alkene and a nucleophile at the arene *ipso* position. The use of an alkene-tethered amine-electrophile in this reaction allows for a rapid, chemoselective, and modular synthesis of 3,3-disubstituted indolines, which is distinct from other approaches. The unique reaction mode discovered here could inspire the development of diverse synthetic tactics based on the Pd/NBE catalysis for broader applications. Efforts towards optimizing the enantioselective version using carefully engineered chiral ligands are in progress and will be reported in due course.

Data availability

The data underlying this study are available in the published article and its ESI.† Crystallographic data for compound **4i** has been deposited at the CCDC under CCDC ID 2310334. See DOI: https://doi.org/10.1039/D3SC06409C.

Author contributions

A. R., X. L. and G. D. conceived and designed the experiments. A. R. and R. Y. performed the experiments. A. R., R. Y., X. L. and G. D. wrote the manuscript. X. L. and G. D. directed the research.

Conflicts of interest

There are no conflicts to declare.

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