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Asymmetric Friedel–Crafts reaction of unsaturated carbonyl-tethered heteroarenes *via* vinylogous activation of Pd^0-π-Lewis base catalysis†

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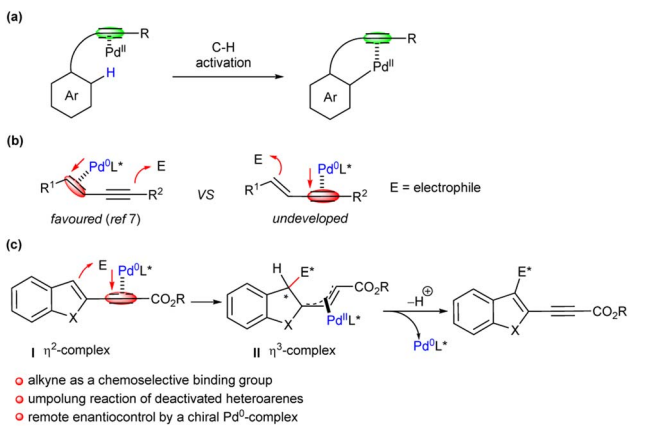
The alkyne group can undergo facile transformations under palladium catalysis, such as hydropalladation, Wacker reaction, *etc.* Here we demonstrate that a chiral Pd^0 complex can chemoselectively dihapto-coordinate to the alkyne moiety of 2-indolyl propiolates, and raise the Highest Occupied Molecular Orbital (HOMO)-energy ofthe deactivated heteroarenes *via* π-Lewis base catalysis. As a result, asymmetric C3-selective Friedel–Crafts addition to activated alkenes occurs, finally affording [3 + 2] or [3 + 4] annulation products with high enantioselectivity and exclusive *E*-selectivity. Moreover, this π-Lewis base vinylogous HOMO-activation strategy can be extended to remote Friedel–Crafts reaction of diverse five-membered heteroarenes tethered to a 2-enone or 2-acrylate motif with imines or 1-azadienes, and excellent enantiocontrol is generally achieved for the multifunctional adducts, which can be effectively converted to diverse frameworks with higher molecular complexity. In addition, NMR and density functional theory calculation studies are conducted to elucidate the catalytic mechanism.

Introduction

As a fundamental functional group, alkyne is readily available and enables abundant transformations in organic chemistry.[1] Possessing π-electrons, alkynes can be activated by complexation with transition metals, and a variety of reactions,[2] such as hydrogenation,[3] Wacker-type addition,[4] carbometallation,[5] *etc.*, have been facilitated accordingly, furnishing fruitful products in high efficiency. As far as palladium catalysis is concerned, apart from the well-established direct activation and reaction patterns, the alkyne moiety has been introduced in some molecules as a directing group for the C–H activation of aromatic rings under Pd^{II} catalysis, affording functionalised aryl substances (Scheme 1a).[6]

Recently, our group and others uncovered that Pd^0 could chemoselectively form η^2-complexes with the alkene moiety of 1,3-enynes.[7] As a result, the alkyne group could be HOMO (the Highest Occupied Molecular Orbital)-raised upon π-Lewis base activation of Pd^0, and undergo vinylogous nucleophilic attack towards electrophiles, even enantioselectively. Density functional theory (DFT) also supported that regioselective dihapto-coordination to the alkene group by Pd^0 was favoured, as outlined in Scheme 1b. Although an array of polyconjugated systems has been successfully utilised *via* Pd^0-π-Lewis base catalysis recently,[8] exclusive coordination of Pd^0 to the alkene moiety was proposed. It would be highly intriguing that the



Scheme 1 Selected activation modes of alkyne-containing substrates *via* palladium catalysis. (a) Alkyne as a directing group for C–H activation *via* Pd^{II} catalysis. (b) Chemoselective activation of 1,3-enynes by forming η^2-Pd^0-alkene complexes. (c) This work: HOMO-activation of alkyne-tethered deactivated heteroarenes *via* Pd^0 catalysis.

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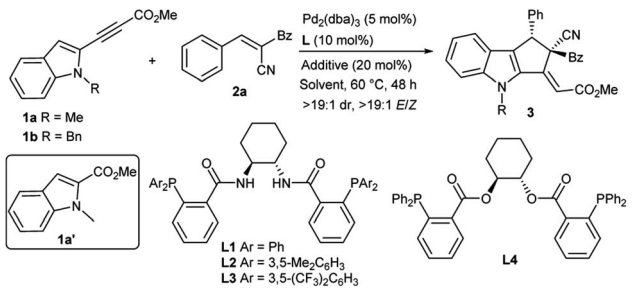
† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data for new compounds, NMR, HRMS spectra, and HPLC chromatograms, and CIF files of products **3i**, *rac*-**4d**, **6c**, **9f**, **11g** and **21**. CCDC 2251805–2251810. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3sc03996j

unsaturated alkyne group could be chemoselectively employed as the binding motif in the presence of other unsaturated systems. It is expected that a five-membered heteroarene tethered to an electron-withdrawing propiolate motif would be deactivated in a Friedel–Crafts (FC) reaction;[9] nevertheless, the chemoselective coordination of Pd^0 to the alkyne group, rather than the 2,3-double bond of the heteroarene, would be favoured, as illustrated in complex **I** (Scheme 1c). Therefore, an unusual FC addition reaction at 3-position of the heteroarene might be enhanced upon vinylogous activation of Pd^0-π-Lewis base, even enantioselectively through remote control.[10] Next, the resultant η^3-complex **II** would undergo aromatisation *via* a β-H elimination or deprotonation process to give the FC adduct and Pd^0 catalyst. Nevertheless, a few challenging issues, as briefly summarised in Scheme 1c, need to be conquered.

Table 1 Screening conditons for the asymmetric FC and Michael addition cascade of 2-indolyl propiolates **1** and α-cyano chalcone **2a**[a]



Entry	1	L	Additive	Solvent	Yield[b] (%)	ee[c] (%)
1[d]	**1a**	/	/	Toluene	NR	/
2[e]	**1a**	/	/	Toluene	**3a**, 64	/
3[f]	**1a**	/	/	Toluene	NR	/
4[e]	**1a′**	/	/	Toluene	NR	/
5	**1a**	**L1**	/	Toluene	**3a**, 68	89
6	**1a**	**L2**	/	Toluene	**3a**, 68	77
7	**1a**	**L3**	/	Toluene	**3a**, 46	39
8	**1a**	**L4**	/	Toluene	**3a**, 76	41
9	**1a**	**L1**	TBAB	Toluene	**3a**, 86	86
10	**1a**	**L1**	TBAB	1,4-Dioxane	**3a**, 89	84
11	**1b**	**L1**	/	1,4-Dioxane	**3b**, 49	92
12	**1b**	**L1**	TBAB	1,4-Dioxane	**3b**, 70	91
13[g]	**1b**	**L1**	TBAB	1,4-Dioxane	**3b**, 86	92
14[g]	**1b**	**L1**	TBAC	1,4-Dioxane	**3b**, 76	92
15[g]	**1b**	**L1**	TBAI	1,4-Dioxane	**3b**, 81	91
16[g]	**1b**	**L1**	KBr	1,4-Dioxane	**3b**, 52	92
17[g,h]	**1b**	**L1**	TBAB	1,4-Dioxane	**3b**, 83	91
18[g,i]	**1b**	**L1**	TBAB	1,4-Dioxane	**3b**, 50	73

[a] Unless noted otherwise, reactions were carried out with **1** (0.025 mmol), **2a** (0.03 mmol), $Pd_2(dba)_3$ (5 mol%), **L** (10 mol%) and additive (20 mol%) in solvent (0.25 mL) at 60 °C under Ar. [b] Yield of the isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Without catalyst, for 24 h. [e] With $Pd(PPh_3)_4$ (10 mol%). [f] With $Pd(OAc)_2$ (10 mol%). [g] With **1b** (0.1 mmol) and **2a** (0.13 mmol) in 1,4-dioxane (0.5 mL). [h] With $Pd_2(dba)_3$ (2.5 mol%), **L1** (5 mol%) at 60 °C for 96 h. [i] With $Pd_2(dba)_3$ (1.25 mol%), **L1** (2.5 mol%) at 80 °C for 96 h.

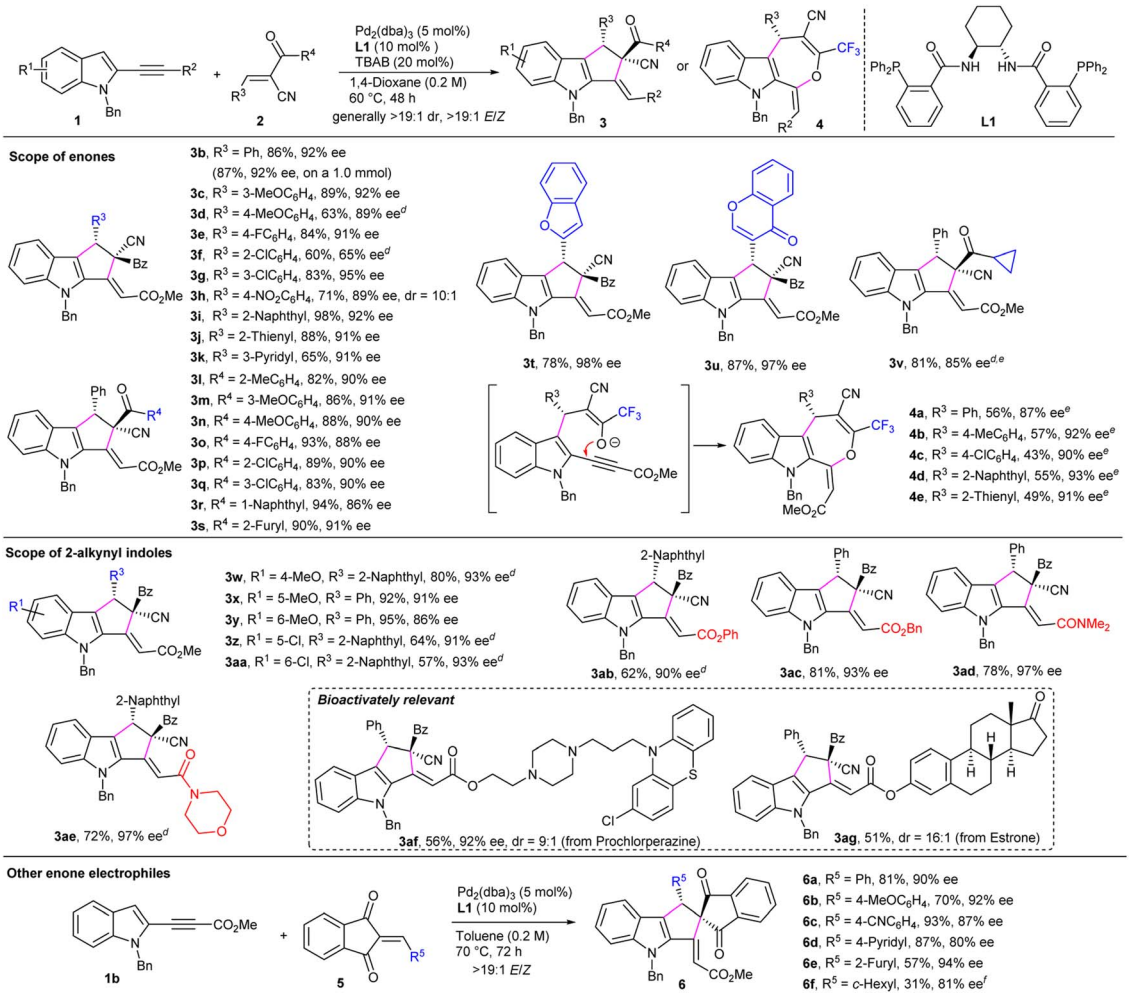
Results and discussion

Investigation of reaction conditions

The initial attempt was between 2-indolyl propiolate **1a** and α-cyano chalcone **2a**. No reaction occurred after heating in toluene at 60 °C for 24 h, indicating the indole moiety was indeed deactivated (Table 1, entry 1).[11] Pleasingly, the conversions were smoothly promoted under the catalysis of $Pd(PPh_3)_4$, and a [3 + 2] annulation product **3a**, *via* cascade FC reaction and intramolecular Michael addition, was isolated in a moderate yield with exclusive diastereoselectivity and *E*/*Z*-selectivity (entry 2). Nevertheless, no product was observed when $Pd(OAc)_2$ was employed, suggesting a Lewis acid catalytic mode might not be involved (entry 3). In addition, no reaction occurred under Pd^0 catalysis by using ester **1a′**, indicating the alkyne moiety was vital forthe vinylogous-type activation (entry 4). Encouraged by the above results, the asymmetric version was investigated by combining $Pd_2(dba)_3$ and various chiral phosphine ligands. Trost's ligand **L1** showed good reactivity as well as enantioselectivity (entry 5), whereas inferior results were obtained with **L2** and **L3** bearing other aryl groups (entries 6 and 7). The one derived from chiral 1,2-cyclohexanediol (**L4**) gave a good yield, but poor enantioselectivity was observed, indicating the N-H group of **L1** might play an important role as a H-bonding donor (entry 8). After more screenings, interestingly, adding catalytic amounts of tetrabutylammonium bromide (TBAB) significantly improved the yield without apparent effect on the enantioselectivity (entry 9). Further screenings of solvents indicated that using 1,4-dioxane was beneficial for the reactivity (entry 10). In addition, employing *N*-benzyl indole **1b** improved the ee value of corresponding adduct **3b** (entry 11), and the yieldalso was significantly improved by adding TBAB (entry 12). A better yield was obtained at a higher concentration (entry 13). Other additives were further tested. Both TBAC and TBAI provided comparable results (entries 14 and 15), but KBr demonstrated to be less effective (entry 16). These results indicated the ammonium cation was important to the reactivity, which was speculated that the ammonium salt might act as a counterion to stablilise intermeidate **II** after the FC addition to acceptor **2a**.[12] Moreover, comparable data were gained with 5 mol% of Pd (entry 17), whereas both yield and enantioselectivity were dramatically decreased by further reducing catalyst loadings (entry 18).

Substrate scope exploration

Consequently, the substrate scope and limitations of the asymmetric cascade FC reaction/Michael addition process was explored under the catalysis of Pd/**L1** and using TBAB as an additive. As summarised in Scheme 2, a spectrum of α-cyano enones **2** were first evaluated in the reactions with 2-indolyl propiolate **1b**. The enones with a variety of β-aryl or -heteroaryl groups were finely compatible, affording corresponding adducts **3b–3k** in moderate to good yields with high enantioselectivity, whereas reduced yield and enantiocontrol were obtained for product **3f** with an *ortho*-substituted phenyl group. Comparable results were also attained on a larger scale (product

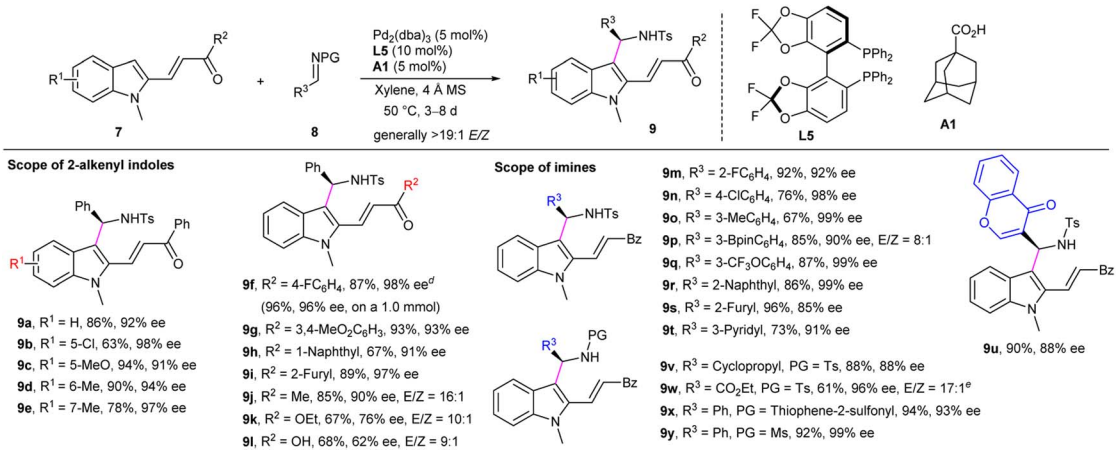


Scheme 2 Substrate scope of the asymmetric [3+2] or [3+4] annulation reaction of 2-alkynyl indoles and enones.[a,b,c a] Unless noted otherwise, reactions were carried out with indole **1** (0.10 mmol), enone **2** (0.13 mmol) or **5** (0.12 mmol), $Pd_2(dba)_3$ (5 mol%), **L1** (10 mol %), and TBAB (20 mol%) in solvent (0.5 mL) under Ar for 48 h. [b] Yield of the isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] With **2** (1.5 equiv) at 80 °C. [e] Without TBAB. [f] At 90 °C for 5 d. The absolute configuration of enantiopure **3i**, **6c** and the structure of *rac*-**4d** was determined by X-ray analysis. The other products were assigned by analogy.

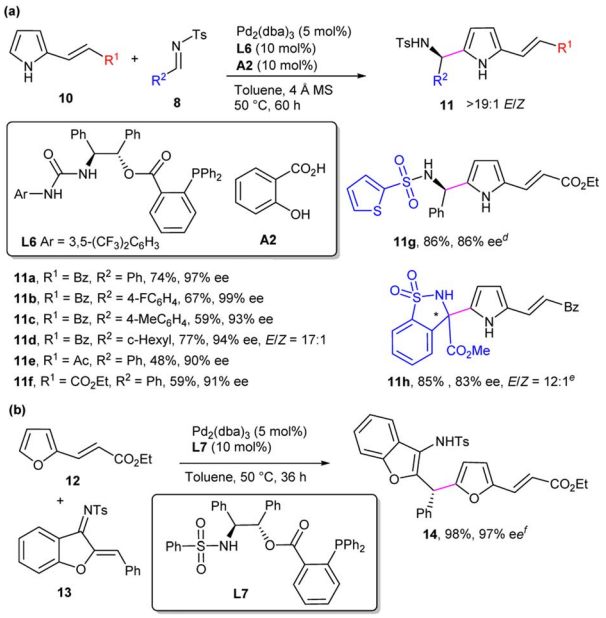
3b). In addition, enones **2** with diverse α′-aryl and -heteroaryl groups were tolerated as well, providing desired products **3l–3u** in high yields and enantioselectivity. In addition, the one with an α′-cyclopropyl-substituent was applicable as well (product **3v**). Interestingly, an intramolecular *O*-Michael reaction instead of C-Michael one took place when some α′-CF_3-substituted enones were utilised, generally affording [3 + 4] cycloadducts **4a–4e** in moderate yields with excellent enantioselectivity and exclusive *E*-selectivity. Moreover, the substitution patterns of 2-alkynyl indoles **1** were evaluated. Electron-donating group-substituted indoles showed good reactivity (products **3w–3y**), and moderate yields were obtained for chloro-substituted products (**3z** and **3aa**), whereas consistently high enantioselectivity was observed. In addition, excellent stereocontrol was achieved for the indoles having various propiolate or propiolamide moieties (products **3ab–3ae**), even for those with complex biologically active scaffolds (products **3af** and **3ag**).

Apart from α-cyano enones, 1,3-indanedione-derived electrophiles **5** were compatible. As outlined in Scheme 2, enones **5** with an array of β-aryl and -heteroaryl groups were well tolerated in the reactions with indole **1b** in toluene under the catalysis of Pd/**L1**, delivering corresponding products **6a–6e** in moderate to good yields with satisfactory enantioselectivity, whereas inferior data were obtained for the one with a *c*-hexyl group (product **6f**).

Furthermore, such a vinylogous HOMO-activation strategy was successfully extended to the indoles with electron-poor 2-alkenyl substitutions. As apparent background [3 + 2] annulation was observed in the assembly of indole **7a** (Scheme 3, R^1 = H, R^2 = Ph) and enone **2a**, we turned our attention to less reactive electrophiles, and *N*-Ts imine **8a** was proved to be suitable.[13] After screenings, FC adduct **9a** was obtained in high yield and excellent enantioselectivity under the catalysis of Pd/bisphosphine **L5** and acid **A1**, which might activate the imine as a Brønsted acid. As summarised in Scheme 3, a few indoles bearing electron-withdrawing or -donating groups were well-tolerated, affording corresponding products **9b–9e** in good results. In addition, a variety of aryl and heteroaryl groups could

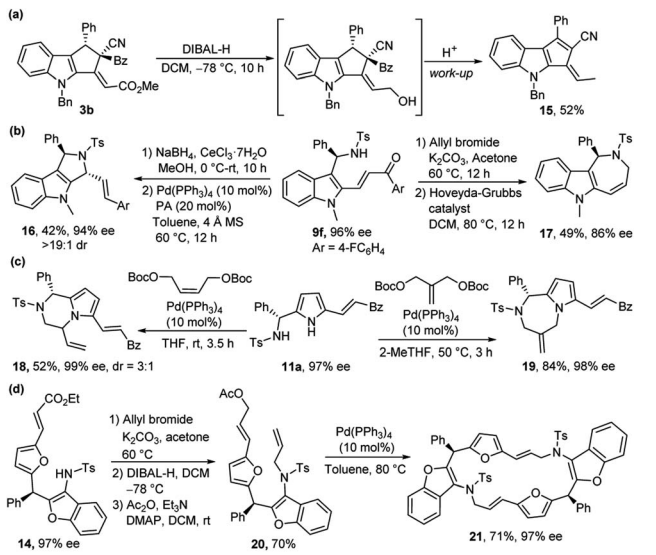


Scheme 3 Substrate scope of the asymmetric FC reaction of 2-alkenyl indoles and imines.[a,b,c a] Unless noted otherwise, reactions were carried out with indole **7** (0.10 mmol), imine **8** (0.20 mmol), $Pd_2(dba)_3$ (5 mol%), **L5** (10 mol%), 4 Å MS (40.0 mg) and **A1** (5 mol%) in xylene (1.0 mL) under Ar for 3–8 d. [b] Yield of the isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The absolute configuration of enantiopure **9f** was determined by X-ray analysis. The other products were assigned by analogy. [e] At 60 °C.



Scheme 4 Asymmetric remote FC reaction of functionalised pyrroles and furans.[a,b,c] (a) Remote FC reaction of pyrrole derivatives. (b) Remote FC reaction of a furan derivative. [a] Unless noted otherwise, reactions were carried out with **10** (0.12 mmol, 1.2 equiv) or furan **12** (0.2 mmol, 2.0 equiv), **8** (0.1 mmol, 1.0 equiv) or 1-azadiene **13** (0.1 mmol, 1.0 equiv), $Pd_2(dba)_3$ (5 mol%), **L** (10 mol%), 4 Å MS (40.0 mg) and **A2** (10 mol%) in toluene (1.0 mL) under Ar. [b] Yield of the isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The absolute configuration of enantiopure **11g** was determined by X-ray analysis. The other products were assigned by analogy. [e] Using **A1** (10 mol%). [f] The absolute configuration of product **14** was determined by converting to derivative **21**.

be smoothly introduced into the α′-site of enone moiety of the indole substrates (products **9f–9i**), even on a larger scale (for product **9f**). Small amounts of *Z*-isomer were generated for a methyl ketone substrate (product **9j**), and apparently reduced yield and stereoselectivity were observed for product **9k** with an acrylate motif. Interestingly, an indole with a free acrylic acid moiety still showed good reactivity,[8e] albeit with moderate enantioselectivity (product **9l**). In addition, a spectrum of aryl- and heteroaryl-substituted imine partners were well applied in the reactions with indole **7a**, and corresponding products **9m–9t** were generally obtained in good yields with excellent enantioselectivity. The imine derived from a chromone aldehyde also performed well (product **9u**). Notably, cyclopropanecarbaldehyde- and ethyl glyoxylate-derived imines underwent the FC reaction smoothly, delivering products **9v** and **9w**, respectively, in good results. Moreover, satisfactory data were obtained for other *N*-sulfonylimines (products **9x** and **9y**).



Scheme 5 Synthetic transformations of diverse products. (a) Transformation of [3 + 2] cycloadduct **3b**. (b) Transformation of FC adduct **9f**. (c) Double allylation of FC adduct **11a**. (d) Construction of a 20-membered ring system from adduct **14**.

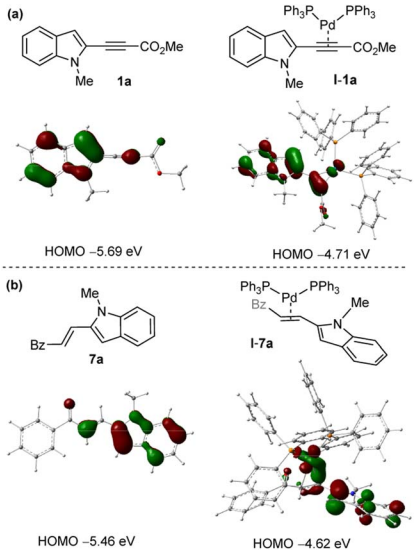


Fig. 1 Frontier molecular orbital (FMO) analysis for Pd^0-alkyne complex (a) and Pd^0-alkene complex (b). The calculations were performed at the B3LYP/6-31G(d)(SDD for Pd) (298.15 K) level of theory.

We further explored the challenging remote asymmetric FC reaction with the five-membered heteroarenes functionalised with a 2-enone or 2-acrylate motif. As illustrated in Scheme 4a, the C5-regioselective reaction between diverse pyrroles **10**with *N*-sulfonylimines **8** proceeded effectively in toluene at 50 °C under Pd^0 catalysis, and high levels of enantioselectivity were generally obtained by employing a bifunctional phosphine ligand[14] **L6** and salicylic acid **A2** as an Brønsted acid additive (products **11a–11g**). Moreover, an activated ketimine was compatible, and product **11h** was obtained in good yield and enantioselectivity. In addition, excellent yield and enantiocontrol were achieved in the remote FC reaction of furan **12** with 1-azadiene **13** under the catalysis of Pd/bifunctional ligand **L7** (product **14**, Scheme 4b).

Synthetic transformations and application

The diversely functionalised products enables versatile transformations. As illustrated in Scheme 5, an indole fused fulvene product **15** was obtained in a moderate yield after reduction of cycloadduct **3b** with DIBAL-H and the subsequent treatment with dilute HCl.[15] After chemoselective reduction of carbonyl of

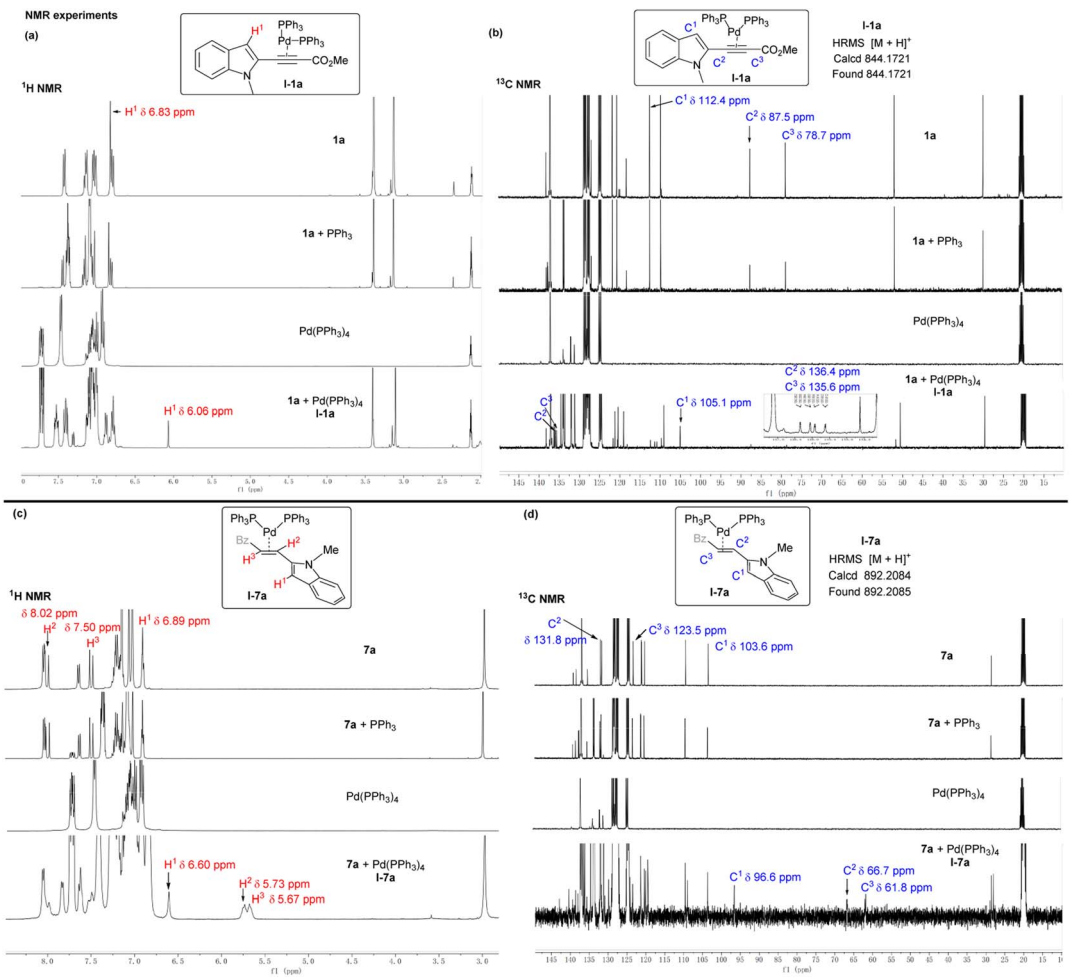


Fig. 2 NMR analysis of the unsaturated indoles and corresponding η^2-Pd^0-complexes. (a) ^{1}H NMR analysis of indole **1a** and complex **I-1a**. (b) ^{13}C NMR analysis of indole **1a** and complex **I-1a**. (c) ^{1}H NMR analysis of indole **7a** and complex **I-7a**. (d) ^{13}C NMR analysis of indole **7a** and complex **I-7a**.

product **9f**, an intramolecular *N*-allylation reaction could be conducted with the resultant allyl alcohol under the catalysis of $Pd(PPh_3)_4$ and phosphoric acid (PA), furnishing product **16** in a fair yield with excellent diastereoselectivity.[16] In addition, after *N*-allylation of **9f** (some ee losses were observed under basic conditions), anazepino[3,4-*b*]indole **17** was constructed in a moderate yield *via* a Metathesis reaction.[17] Moreover, piperazine product **18** (ref. [18]) and diazepane **19**,[19] respectively, were obtained efficiently through palladium-catalysed double *N*-allylations. Besides, an unexpected 20-membered ring system **21** was obtained in a moderate yield with a retained ee value *via* a Pd-catalysed *N*-deallylation and *N*-allylation cascade process of derivative **20**.

Mechanistic studies

To get more insight into the catalytic mechanism, we first conducted frontier molecular orbital (FMO) analysis on the Pd^0 complexes of unsaturated indoles. As illustrated in Fig. 1, in comparison with the parent substrate alkyne **1a** (−5.69 eV) or alkene **7a** (−5.46 eV), the HOMO energy of corresponding η^2-Pd^0-complex **I-1a** (−4.71 eV) or **I-7a** (−4.62 eV) is apparently raised, respectively, supporting the π-Lewis back donation of Pd^0 as a Lewis base. Actually, it has been demonstrated that Pd^0 could form a stable complex by coordinating to a triple or double bond.[20] In our case, the proposed intermediate **I-1a** or **I-7a** indeed has been successfully detected by high-resolution mass spectrometry (HRMS) analysis by mixing alkyne **1a** or alkene **7a** with $Pd(PPh_3)_4$, respectively (Fig. 2). Moreover, we carried out NMR studies on the *in situ* generated complexes. As outlined in Fig. 2a, the ^{1}H NMR analysis showed that 3-H (H^1) of alkyne **1a** experienced apparent high-field shifts when $Pd(PPh_3)_4$ was added (6.06 *vs.* 6.83 ppm). The possible nucleophilic attack of PPh_3 to electron-deficient **1a** was not observed by mixing **1a** and PPh_3. In addition, the ^{13}C NMR analysisexhibited that the signals of the triple bond of **1a** disappeared (around 70−80 ppm) after adding $Pd(PPh_3)_4$ (Fig. 2b), whereas new peaks were observedat the sp^2-carbon region (C^2 and C^3, around 136 ppm); in contrast, C^1 of **1a** experienced significant high-field shifts (105.1 *vs.* 112.4 ppm). Similarly, the signals of H^1, H^2, H^3, C^1, C^2 and C^3 of **7a** were all high-field shifted in the presence of $Pd(PPh_3)_4$, according to the NMR experiments (Fig. 2c and d). These results well supported that the proposed complexes **I-1a** and **I-7a** would be formed, and verified the π-Lewis base activation of Pd^0 through strong coordination to the unsaturated group.[20]

We also investigated the origins of enantioselectivity in the reaction of alkyne **1a** and enone **2a**. Based on the DFT calculation results, the FC addition step in which the first C−C bond was constructed, is the rate- and stereo-determining step.[21] As shown in Fig. 3, four related transition states were considered. Transition states (*R*,*S*)-**TS** and (*S*,*S*)-**TS** would lead to product (*S*,*R*)-**3a** *via* (*R*,*S*)-**II** and (*S*,*S*)-**II**, respectively, and the stereogenic centre at 3-C of indole would disappear through deprotonation/aromatization. On the other hand, (*R*,*R*)-**TS** and (*S*,*R*)-**TS** would lead to enantiomer (*R*,*S*)-**3a** *via* similar transformations. Notably, H-bonding interaction between the NH group of **L1** and the

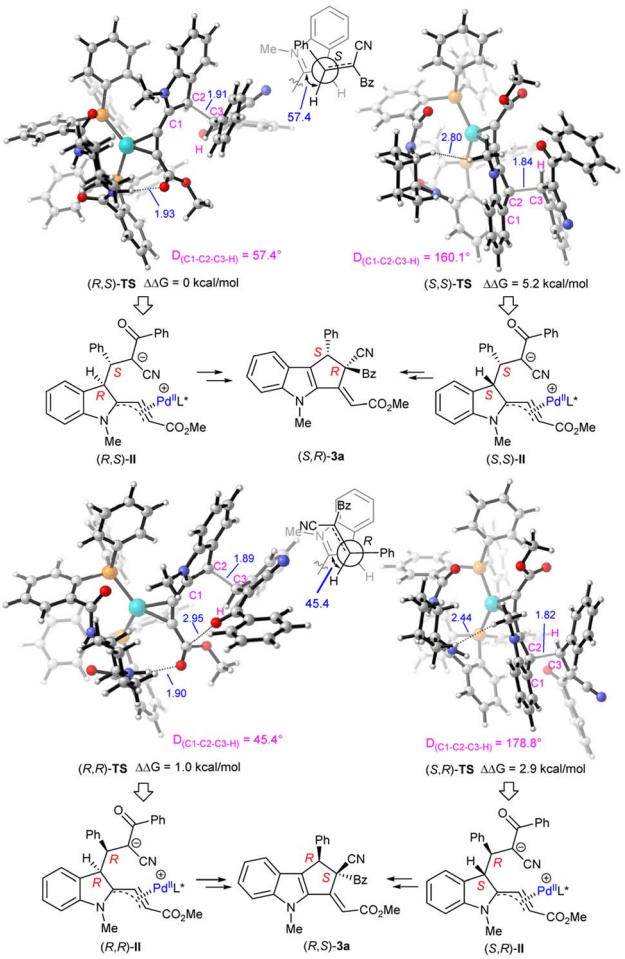


Fig. 3 Origins of enantioselectivity for the FC reaction of **1a** and **2a**. The calculations were performed at the M06/6-311++G(d,p)(SDD for Pd)/SMD//B3LYP/6-31G(d)(SDD for Pd) (298.15 K) level of theory.

carbonyl group of **1a** is observed in (*R*,*S*)-**TS** and (*R*,*R*)-**TS**, while the other two transition states without H-bonding interaction exhibit higher energies [5.2 kcal/mol^{-1} for (*S*,*S*)-**TS**; 2.9 kcal/mol^{-1} for (*S*,*R*)-**TS**]. The results indicate that the H-bonding is beneficial for the reaction, which is consistent with the experimental results (Table 1, entry 5 *vs.* entry 8). Geometric structure analyses show that the forming C−C bond in (*R*,*R*)-**TS** presents a pseudogauche conformation to avoid the steric repulsion between the ester group of **1a** and the carbonyl of **2a**. As a result, the dihedral angle $D_{C^1\text{–}C^2\text{–}C^3\text{–}H}$ is 45.4 with apparent torsional strain. In contrast, (*R*,*S*)-**TS** possesses smaller torsional strain (referring to the corresponding $D_{C^1\text{–}C^2\text{–}C^3\text{–}H} = 57.4$), thus leading to lower energy [0 kcal/mol^{-1} for (*R*,*S*)-**TS** *vs.* 1.0 kcal/mol^{-1} for (*R*,*R*)-**TS**]. Therefore, the most favourable transition state (*R*,*S*)-**TS** would afford (*S*,*R*)-**3a** as the major product after annulation, which is consistent with the experimental observation.[21]

Conclusion

In summary, we demonstrated that Pd^0 could chemoselectively coordinate to the alkyne motif of 2-propiolate-tethered indole

substrates, which would raise the HOMO-energy ofthe deactivated heteroarenes to undergo Friedel–Crafts reaction with enone acceptors upon π-Lewis base catalysis, finally furnishing [3 + 2] or [3 + 4] annulation products with exclusive *E*-selectivity after an intramolecular Michael addition process. Excellent diastereoselectivity and enantioselectivity were generally achieved for substantial substrate assemblies by employing a chiral Trost's bisphosphine ligand. Moreover, this vinylogous activation strategy *via* π-Lewis base catalysis was successfully expanded to deactivated indoles tethered to a 2-enone or acrylate motif, and even very remote C5-selective Friedel–Crafts reactions of similarly deactivated pyrroles and furans could be realised with remarkable enantioselectivity by using a chiral bifunctional phosphine ligand, further enriching the structural diversity and skeletal versatility of relevant products. In addition, NMR analysis and DFT calculations were conducted to rationalise the activation and stereocontrol pathways. We believe that this Pd^0-π-Lewis base catalysis would find more application in asymmetric synthesis.

Data availability

The data that support the findings of this study are available in the ESI† or on request from the corresponding author.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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