Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

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Cite this: *Chem. Sci.*, 2022, **13**, 12433

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# Formal nucleophilic pyrrolylmethylation *via* palladium-based auto-tandem catalysis: switchable regiodivergent synthesis and remote chirality transfer†

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Received 19th September 2022
Accepted 5th October 2022

DOI: 10.1039/d2sc05210e

rsc.li/chemical-science

Although nucleophilic benzylation-type reaction to introduce various aromatic systems into molecules has been widely explored, the related pyrrolylmethylation version remains to be disclosed. Reported herein is a palladium-catalysed multiple auto-tandem reaction between *N*-Ts propargylamines, allyl carbonates and aldimines in the presence of an acid, proceeding through sequential allylic amination, cycloisomerisation, vinylogous addition and aromatisation steps. A diversity of formal pyrrolylmethylated amine products were finally furnished efficiently. In addition, switchable regiodivergent 3-pyrrolylmethylation and 4-pyrrolylmethylation were realised by tuning catalytic conditions. Moreover, remote chirality transfer with readily available enantioenriched starting materials was well achieved with an achiral ligand, relying on diastereoselective generation of $\eta^2$-Pd(0) complexes between Pd(0) and chiral 1,3-diene intermediates in the key vinylogous addition step. A few control experiments were conducted to elucidate the palladium-involved tandem reaction and regiodivergent synthesis.



## Introduction

Nucleophilic benzylation-type reaction provides an effective approach to introduce an aromatic system into molecules. In comparison with many protocols available for benzylic functionalisation of six-membered aromatic compounds [Scheme 1a(i)],[1] reactions involving five-membered heteroaromatic benzylic nucleophiles or relevant precursors have been significantly underdeveloped. You and Newhouse independently made an important breakthrough relying on the formation of Lewis acid stabilised deprotonated methyl azaarenes in the presence of excess strong Brønsted bases (TMPZnX) [Scheme 1a(ii)].[2] However, electron-rich heterocyclic aromatic compounds, such as methyl-substituted pyrroles and furans, were not applicable, because of the lack of an appropriate activation strategy to overcome the intrinsic weak acidity of benzylic protons. On the other hand, a few methylene-substituted heterocycles could perform as nucleophilic benzylation precursors to couple with electrophiles through an Alder-ene reaction, which provided an alternative access to diverse heteroarylmethylated products [Scheme 1a(iii)].[3] Unfortunately, these preformed electron-rich dienes, especially pyrrole-derived ones, were liable to aromatise, which not only limited their application scope, but also rendered formal pyrrolylmethylation reaction unsuccessful.[3a,4] As a result, a new synthetic strategy remains to be developed to accomplish the efficient construction of pyrrolylmethylated products.

Enynes are readily accessible and versatile synthons, and the transition metal-catalysed cycloisomerisation reaction of 1,6-enynes,[5] pioneered by Trost,[6] provides a powerful access to exocyclic conjugated 1,3-dienes, which can be efficiently trapped by various dienophiles in a tandem Diels–Alder cycloaddition reaction (Scheme 1b).[7] However, other types of derivation reactions of 1,3-dienes initiated from cycloisomerisation of 1,6-enynes have been significantly underdeveloped, probably because such 1,3-dienes are thermally unstable, which should be prepared freshly and used immediately. Recently, our group disclosed a Friedel–Crafts-type coupling reaction of linear 1,3-dienes and imines *via* Pd(0)-based π-Lewis base catalysis (Scheme 1c).[8] We further noticed that the expected 1,3-dienes, though in an exocyclic form, would be readily obtained from simple propargyl amines and allyl carbonates *via* a palladium-catalysed tandem allylic amination and cycloisomerisation process. We envisioned

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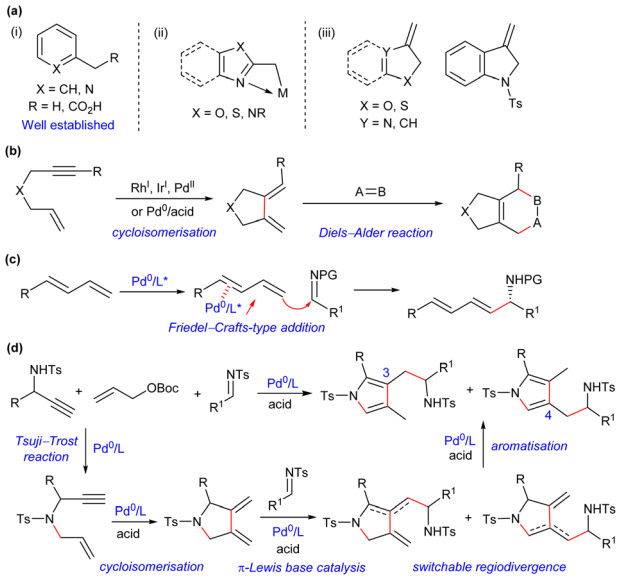
† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data for new compounds, NMR spectra, HRMS spectra, ECD spectra and HPLC chromatograms, CIF file of racemic products **4a** and **7o**. CCDC [2184605 and 2184606]. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d2sc05210e




Scheme 1 Reported nucleophilic benzylation-type strategies and our design for formal pyrrolylmethylation. (a) Typical nucleophilic benzylation precursors. (b) Tandem cycloisomerisation/Diels–Alder reaction of 1,6-enynes. (c) Coupling of 1,3-dienes and imines *via* π-Lewis base catalysis of Pd(0). (d) This work: formal pyrrolylmethylation *via* palladium-based auto-tandem catalysis.

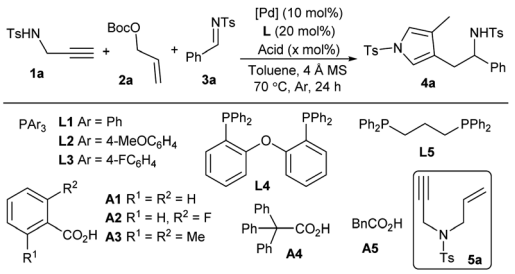
that such 1,3-dienes would be feasibly assembled with imines under auto-tandem Pd(0) catalysis, and the unprecedented formal pyrrolylmethylation products, which are not readily accessible by other means, would be finally furnished after isomerisation, as proposed in Scheme 1d. Moreover, potential regiodivergent vinylogous additions of the unsymmetric 1,3-diene intermediates might be achievable by properly tuning the catalytic conditions,[9] which would enrich the structural diversity of densely substituted pyrrole frameworks. Consequently, such a multicomponent reaction, starting from readily available building blocks and combining palladium-mediated four consecutive transformations, would finely demonstrate the synthetic efficacy and versatility of auto-tandem catalysis (ATC).[10]

## Results and discussion

### Condition optimisation

tWe began our exploration by examining the reaction with *N*-Ts propargyl amine **1a**, allylic carbonate **2a** and *N*-Ts aldimine **3a** in toluene at 70 °C in the presence of catalytic amounts of $Pd(PPh_3)_4$ and benzoic acid **A1**. Pleasingly, the proposed tandem reaction occurred as expected, and the aromatic pyrrole product **4a**, proceeding through an *N*-allylation, cycloisomerisation, vinylogous addition and aromatisation sequence, was obtained in a moderate yield after 24 h (Table 1, entry 1). The combination of $Pd_2dba_3$ with $PPh_3$ **L1** demonstrated to be less efficient (entry 2). Electron-richer ligand **L2** delivered comparable results (entry 3), but electron-deficient ligand **L3**, bisphosphine **L4** and **L5** could not promote the allylic amination to produce **5a** (entries 4–6). An acid additive was found to be crucial for the tandem conversion, as only *N*-allylation intermediate **5a** was isolated quantitatively in

Table 1 Screening conditions for the tandem reaction of propargyl amine **1a**, allylic carbonate **2a** and imine **3a** [a]




| Entry | [Pd] | L | Acid | *x* | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | $Pd(PPh_3)_4$ | — | **A1** | 20 | 58 |
| 2 | $Pd_2dba_3$ | $PPh_3$ | **A1** | 20 | 54 |
| 3 | $Pd_2dba_3$ | **L2** | **A1** | 20 | 53 |
| 4 | $Pd_2dba_3$ | **L3** | **A1** | 20 | NR |
| 5 | $Pd_2dba_3$ | **L4** | **A1** | 20 | NR |
| 6 | $Pd_2dba_3$ | **L5** | **A1** | 20 | NR |
| 7 | $Pd(PPh_3)_4$ | — | **A1** | 0 | **5a**, 95 |
| 8 | $Pd(PPh_3)_4$ | — | **A1** | 10 | 50 |
| 9 | $Pd(PPh_3)_4$ | — | **A1** | 40 | 68 |
| 10 | $Pd(PPh_3)_4$ | — | **A1** | 80 | 68 |
| 11 | $Pd(PPh_3)_4$ | — | **A2** | 40 | 86 |
| 12 | $Pd(PPh_3)_4$ | — | **A3** | 40 | 54 |
| 13 | $Pd(PPh_3)_4$ | — | **A4** | 40 | 65 |
| 14 | $Pd(PPh_3)_4$ | — | **A5** | 40 | 66 |
| 15[c] | $Pd(PPh_3)_4$ | — | **A2** | 40 | 80 |
| 16[d] | $Pd(PPh_3)_4$ | — | **A2** | 40 | 41 |
| 17[e] | $Pd(PPh_3)_4$ | — | **A2** | 40 | 80 |

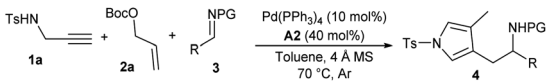
[a] Unless noted otherwise, reactions were performed with **1a** (0.1 mmol), **2a** (0.1 mmol), **3a** (0.05 mmol), [Pd] source (10 mol%), **L** (20 mol%), acid (*x* mol%) and 4 Å MS (20 mg) in degassed dry toluene (0.5 mL) at 70 °C for 24 h under Ar. [b] Yield of isolated product **4a**. [c] At 80 °C. [d] In xylene (0.5 mL). [e] Without 4 Å MS.

the absence of **A1**, indicating the necessity of both palladium and acid for subsequent cycloisomerisation (entry 7). A slight effect was observed for different acid loadings (entries 8–10). More acids were examined (entries 11–14), and stronger *o*-fluorobenzoic acid **A2** improved the yield significantly (entry 11). In addition, temperature and solvents were further evaluated, but no better results were obtained (entries 15 and 16). Moreover, a slightly reduced yield was obtained in the absence of 4 Å MS, probably due to the partial decomposition of imine **3a** (entry 17).[11]

### Substrate scope of three-component ATC reaction

Consequently, the substrate scope and limitations of the multicomponent auto-tandem reaction were investigated under the catalysis of $Pd(PPh_3)_4$ and *o*-fluorobenzoic acid **A2**. As summarised in Table 2, an array of aryl aldimines **3** bearing either electron-donating or -withdrawing groups performed well in the reactions with propargyl amine **1a** and allylic carbonate **2a**, and corresponding products **4b–4g** were isolated in moderate to good yields (Table 2, entries 2–7). Similar results were obtained with naphthyl and heteroaryl derived aldimines (entries 8–10). Nevertheless, alkyl-tethered aldimines proved to

Table 2 Substrate scope and limitations of three-component auto-tandem reactions[a]




| Entry | *R* | PG | *t* (h) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | Ph | Ts | 24 | **4a**, 86 |
| 2 | 2-Me$C_6H_4$ | Ts | 24 | **4b**, 93 |
| 3 | 3-Me$C_6H_4$ | Ts | 36 | **4c**, 70 |
| 4 | 4-Me$C_6H_4$ | Ts | 24 | **4d**, 80 |
| 5 | 4-Ph$C_6H_4$ | Ts | 24 | **4e**, 79 |
| 6 | 4-F$C_6H_4$ | Ts | 24 | **4f**, 68 |
| 7 | 4-Cl$C_6H_4$ | Ts | 24 | **4g**, 74 |
| 8 | 2-Naphthyl | Ts | 24 | **4h**, 66 |
| 9 | 2-Furyl | Ts | 24 | **4i**, 80 |
| 10 | 2-Thienyl | Ts | 36 | **4j**, 72 |
| 11 | $PhCH_2CH_2$ | Ts | 96 | **4k**, 62 |
| 12 | *c*-Hexyl | Ts | 96 | **4l**, 23 |
| 13 | Ph | Ns | 96 | **4m**, 52 |
| 14[c] | Ph | Bz | 24 | **4n**, 70 |
| 15[c] | Ph | $SO_2NMe_2$ | 24 | **4o**, 90 |
| 16[d] | Ph | Ts | 24 | **4a**, 82 |

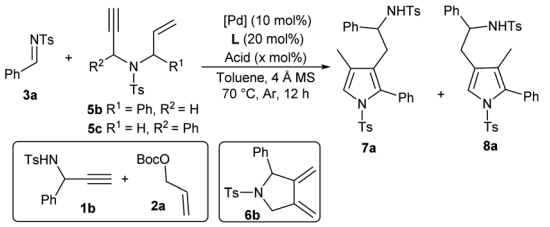
[a] Unless noted otherwise, reactions were performed with **1a** (0.2 mmol), **2a** (0.2 mmol), imine **3** (0.1 mmol), $Pd(PPh_3)_4$ (10 mol%), **A2** (40 mol%) and 4 Å MS (40 mg) in degassed dry toluene (1.0 mL) at 70 °C under Ar. [b] Yield of isolated product. [c] With **5a** (0.2 mmol) instead of **1a** and **2a**. [d] On a 1.0 mmol scale.

be less reactive, and a longer reaction time was required to obtain better results (entries 11 and 12). Besides, aldimines with other *N*-protecting groups were also applicable, affording **4m–4o** with comparable yields (entries 13–15). In addition, the reaction took place efficiently on a 1.0 mmol scale (entry 16).

### Switchable regiodivergent tandem reaction

After establishing the auto-tandem catalysis, we turned to explore substrates with more complicated substitutions. Interestingly, the 1,6-enyne **5b**, which could lead to the formation of unsymmetric exocyclic 1,3-diene intermediate **6b** *via* cycloisomerisation, delivered a pair of separable regioselective isomers **7a** and **8a** efficiently in combination with imine **3a** under the catalysis of $Pd(PPh_3)_4$ and acid **A1** (Table 3, entry 1). While using other acid additives had a marginal effect on the regioselectivity (entries 2 and 3), it was pleasing that increasing the loadings of acid **A1** dramatically improved the formation of 3-pyrrolylmethylated product **7a** (entry 4), and excellent yield and regioselectivity were obtained by employing stoichiometric **A1** (entry 5). In order to switch the regioselectivity, more reaction parameters were investigated. A series of Pd(II) sources were tested. While using $Pd(OAc)_2$ or $[Pd(allyl)Cl]_2$ still favoured the formation of isomer **7a** (entries 6 and 7), the combination of Pd(allyl)Cp and $PPh_3$ could promote the production of 4-pyrrolylmethylated adduct **8a** dominantly (entry 8).[11] A survey of acid additives (entries 9–12) showed that **A3** further improved the yield and regioselectivity (entry 10). Notably, the regioselectivity was significantly eroded by using stoichiometric **A3** (entry 13).

Table 3 Screening conditions for regiodivergent tandem reaction[a]




| Entry | [Pd] | L | Acid | *x* | Yield[b] (%) | rr[c] |
|---|---|---|---|---|---|---|
| 1 | $Pd(PPh_3)_4$ | — | **A1** | 20 | 75 | 52 : 48 |
| 2 | $Pd(PPh_3)_4$ | — | **A2** | 20 | 65 | 63 : 37 |
| 3 | $Pd(PPh_3)_4$ | — | **A3** | 20 | 60 | 54 : 46 |
| 4 | $Pd(PPh_3)_4$ | — | **A1** | 50 | 90 | 75 : 25 |
| 5 | $Pd(PPh_3)_4$ | — | **A1** | 100 | 91 | 94 : 6 |
| 6 | $Pd(OAc)_2$ | $PPh_3$ | **A1** | 20 | 48 | 60 : 40 |
| 7 | $[Pd(allyl)Cl]_2$ | $PPh_3$ | **A1** | 20 | 36 | 67 : 33 |
| 8 | Pd(allyl)Cp | $PPh_3$ | **A1** | 20 | 71 | 13 : 87 |
| 9 | Pd(allyl)Cp | $PPh_3$ | **A2** | 20 | 80 | 40 : 60 |
| 10 | Pd(allyl)Cp | $PPh_3$ | **A3** | 20 | 82 | 8 : 92 |
| 11 | Pd(allyl)Cp | $PPh_3$ | **A4** | 20 | 47 | 24 : 76 |
| 12 | Pd(allyl)Cp | $PPh_3$ | **A5** | 20 | Trace | — |
| 13 | Pd(allyl)Cp | $PPh_3$ | **A3** | 100 | 62 | 44 : 56 |
| 14[d] | $Pd(PPh_3)_4$ | — | **A1** | 100 | 87 | 96 : 4 |
| 15[d] | Pd(allyl)Cp | $PPh_3$ | **A3** | 20 | 73 | 30 : 70 |
| 16[e] | $Pd(PPh_3)_4$ | — | **A2** | 40 | 80 | 95 : 5 |

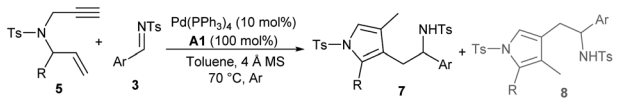
[a] Unless noted otherwise, reactions were performed with 1,6-enyne **5b** (0.1 mmol), imine **3a** (0.05 mmol), [Pd] source (10 mol%), **L** (20 mol%), acid (*x* mol%) and 4 Å MS (20 mg) in degassed dry toluene (0.5 mL) at 70 °C for 12 h under Ar. [b] Isolated yield. [c] rr = **7a** : **8a**, determined by $^1$H-NMR analysis. [d] With **5c** (0.1 mmol) instead of **5b**. [e] With **1b** (0.1 mmol) and **2a** (0.1 mmol) instead of **5b** at 80 °C.

Moreover, employing 1,6-enyne **5c** instead of **5b** still furnished **7a** in a good yield in the presence of $Pd(PPh_3)_4$ and acid **A1** (entry 14), but poor regioselectivity was observed when the optimal conditions for isomer **8a** were utilised (entry 15). Importantly, the catalytic three-component cascade reaction of propargylamine **1b** and allylic carbonate **2a** as precursors of **5c** still proceeded well, giving isomer **7a** in a good yield (entry 16).[11]

Consequently, we first explored the substrate scope for the construction of 3-pyrrolylmethylated adducts **7** using catalytic $Pd(PPh_3)_4$ and stoichiometric benzoic acid **A1**. As summarised in Table 4, a broad variety of aryl- or heteroaryl substituted aldimines **3** were well tolerated in the reactions with 1,6-enyne **5b**. High regioselectivity was generally observed, and the expected regioselective products **7b–7k** were smoothly isolated in moderate to excellent yields (Table 4, entries 2–11). On the other hand, 1,6-enynes **5** with diverse aryl or heteroaryl substituents also reacted well with imine **3a**, giving products **7l–7o** in good yields (entries 12–15). In addition, 2-styryl- or alkyl-substituted 1,6-enynes **5** were also applied to give the desired products **7p–7s** with excellent regioselectivity (entries 16–19).

Meanwhile, the substrate scope for the synthesis of 4-pyrrolylmethylated isomers **8** was investigated under the catalysis of Pd(allyl)Cp, $PPh_3$ and acid **A3**. As summarised in Table 5, moderate to good yields were uniformly attained for an array of

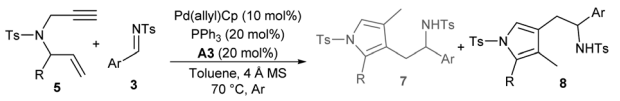
Table 4 Substrate scope for the preparation of 3-pyrrolylmethylated products **7**[a]




| Entry | Ar | *R* | *t* (h) | Yield[b] (%) | rr[c] |
|---|---|---|---|---|---|
| 1 | Ph | Ph | 12 | **7a**, 90 | 95 : 5 |
| 2 | 2-Me$C_6H_4$ | Ph | 36 | **7b**, 76 | >95 : 5 |
| 3 | 3-Me$C_6H_4$ | Ph | 24 | **7c**, 88 | >95 : 5 |
| 4 | 4-Me$C_6H_4$ | Ph | 36 | **7d**, 71 | >95 : 5 |
| 5 | 4-Ph$C_6H_4$ | Ph | 24 | **7e** 64 | 91 : 9 |
| 6 | 2-F$C_6H_4$ | Ph | 12 | **7f**, 56 | 81 : 19 |
| 7 | 4-F$C_6H_4$ | Ph | 12 | **7g**, 75 | 93 : 7 |
| 8 | 4-Cl$C_6H_4$ | Ph | 12 | **7h**, 82 | 95 : 5 |
| 9 | 2-Naphthyl | Ph | 36 | **7i**, 82 | 90 : 10 |
| 10 | 2-Furyl | Ph | 36 | **7j**, 74 | >95 : 5 |
| 11 | 2-Thienyl | Ph | 36 | **7k**, 51 | >95 : 5 |
| 12 | Ph | 4-Me$C_6H_4$ | 12 | **7l**, 81 | 93 : 7 |
| 13 | Ph | 4-Cl$C_6H_4$ | 12 | **7m**, 76 | 92 : 8 |
| 14 | Ph | 2-Furyl | 36 | **7n**, 90 | >95 : 5 |
| 15 | Ph | 2-Thienyl | 36 | **7o**, 80 | >95 : 5 |
| 16 | Ph | 2-Styryl | 48 | **7p**, 36 | >95 : 5 |
| 17 | Ph | *n*-Butyl | 48 | **7q**, 87 | >95 : 5 |
| 18 | Ph | *i*-Propyl | 48 | **7r**, 47 | >95 : 5 |
| 19 | Ph | *c*-Hexyl | 48 | **7s**, 79 | >95 : 5 |

[a] Unless noted otherwise, reactions were performed with 1,6-enyne **5** (0.2 mmol), imine **3** (0.1 mmol), $Pd(PPh_3)_4$ (10 mol%), **A1** (100 mol%) and 4 Å MS (40 mg) in degassed dry toluene (1.0 mL) at 70 °C under Ar. [b] Yield of isolated pure product **7**. [c] rr = **7 : 8**, determined by $^1$H NMR analysis.

Table 5 Substrate scope for the preparation of 4-pyrrolylmethylated products **8**[a]




| Entry | Ar | *R* | *t* (h) | Yield[b] (%) | rr[c] |
|---|---|---|---|---|---|
| 1 | Ph | Ph | 36 | **8a**, 75 | 7 : 93 |
| 2 | 2-Me$C_6H_4$ | Ph | 36 | **8b**, 74 | 7 : 93 |
| 3 | 3-Me$C_6H_4$ | Ph | 24 | **8c**, 66 | 10 : 90 |
| 4 | 4-Me$C_6H_4$ | Ph | 96 | **8d**, 67 | 18 : 82 |
| 5 | 4-Ph$C_6H_4$ | Ph | 24 | **8e**, 72 | <5 : 95 |
| 6 | 2-F$C_6H_4$ | Ph | 24 | **8f**, 54 | <5 : 95 |
| 7 | 4-F$C_6H_4$ | Ph | 12 | **8g**, 72 | <5 : 95 |
| 8 | 4-Cl$C_6H_4$ | Ph | 12 | **8h**, 73 | <5 : 95 |
| 9 | 2-Naphthyl | Ph | 36 | **8i**, 69 | 14 : 86 |
| 10[d] | 2-Furyl | Ph | 36 | **7j+8j**, 70 | 20 : 80 |
| 11 | 2-Thienyl | Ph | 36 | **8k**, 60 | 26 : 74 |
| 12[e] | Ph | 2-Me$C_6H_4$ | 36 | **8l**, 73 | <5 : 95 |
| 13 | Ph | 4-Me$C_6H_4$ | 12 | **8m**, 62 | 18 : 82 |
| 14[e] | Ph | 2-Cl$C_6H_4$ | 36 | **8n**, 67 | <5 : 95 |
| 15 | Ph | 2-Furyl | 36 | **7n**, 76 | >95 : 5 |
| 16 | Ph | *n*-Butyl | 48 | **7q**, 45 | >95 : 5 |

[a] Unless noted otherwise, reactions were performed with 1,6-enyne **5** (0.2 mmol), imine **3** (0.1 mmol), Pd(allyl)Cp (10 mol%), $PPh_3$ (20 mol%), **A3** (20 mol%) and 4 Å MS (40 mg) in degassed dry toluene (1.0 mL) at 70 °C under Ar. [b] Yield of isolated pure product **8**. [c] rr = **7 : 8**, determined by $^1$H NMR analysis. [d] Total yield of **7j** and **8j**, with 20 : 80 rr as inseparable isomers. [e] With 1 : 1 dr for atropisomers.

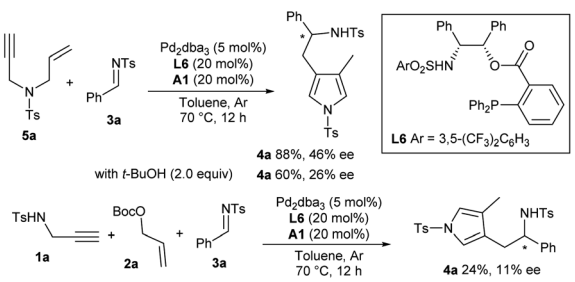
assemblies of 1,6-enynes **5** and aldimines **3** (Table 5, entries 2–14). It should be noted that for products **8l** and **8n** with a 2-substituted phenyl group, apparent diastereoselectivity was observed for the newly generated axial chirality because of the hindered rotation (entries 12 and 14). However, the regioselectivity for heteroaryl or alkyl substituted 1,6-enynes was not switched, whereas 3-pyrrolylmethylated products **7n** and **7q** were produced exclusively (entries 15 and 16).

### Asymmetric catalytic exploration

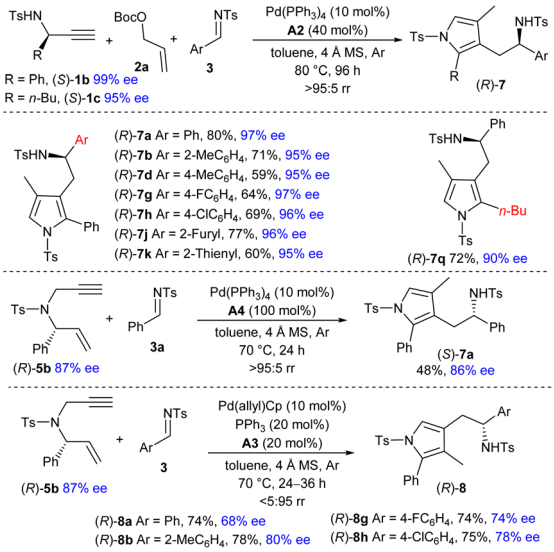
Much effort was dedicated to investigating the asymmetric catalytic version of this new cascade process. A number of commonly used chiral ligands in combination with $Pd_2dba_3$ failed to promote the reaction of imine **3a** and pre-prepared 1,6-enyne **5a** or give poor enantioselectivity.[11] To our delight, a bifunctional phosphine ligand **L6** exhibited good catalytic activity and moderate enantiocontrol.[12] However, poor enantiocontrol was observed for the three component auto-tandem reaction due to the presence of *in situ* formed *t*-BuOH, which has been verified by a control experiment (Scheme 2).

### Enantioselective synthesis through chirality transfer

Although satisfactory results were not obtained for the catalytic asymmetric reaction of *in situ* formed symmetric exocyclic 1,3-diene **6a**, we envisioned that the diastereoselective formation of the $\eta^2$-Pd(0) complex would be expected if an enantioenriched 1,3-diene **6b** was involved. As a result, remote chirality transfer would be potentially applicable in the vinylogous addition step,[13] which could provide an alternative strategy for constructing chiral pyrrole derivatives. As illustrated in Scheme 3, employing the readily available propargyl amine (*S*)-**1b** (99% ee) as the chiral starting material, the asymmetric three-component reaction with carbonate **2a** and imine **3a** took place efficiently under the catalysis of $Pd(PPh_3)_4$ and acid **A2**. Notably, excellent chirality transfer was achieved, and the 3-pyrrolylmethylated product (*R*)-**7a** was furnished with only marginal ee losses. More imines with diverse substitutions also delivered the corresponding chiral adducts with outstanding enantioselectivity.



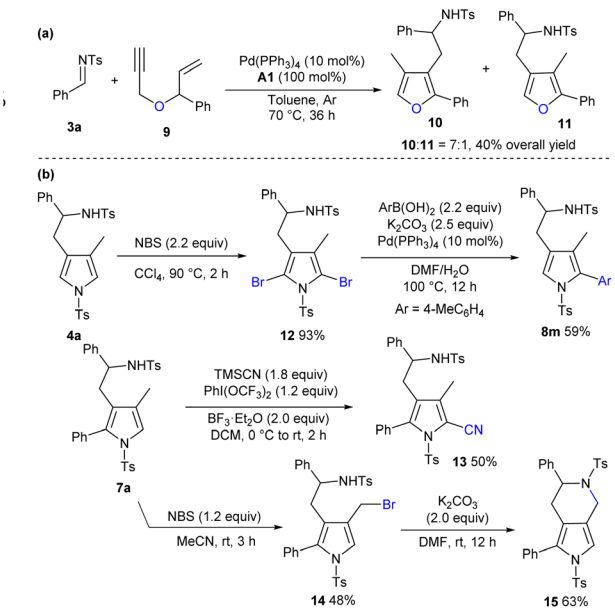

Scheme 2 Asymmetric catalytic cascade reaction.




Scheme 3 Asymmetric synthesis through remote chirality transfer.

Alkyl substituted propargyl amine (*S*)-**1c** (95% ee) could be used to produce chiral (*R*)-**7q** in a good yield. In addition, complete chirality transfer was obtained by using 1,6-enyne (*R*)-**5b** (88% ee), albeit in a significantly reduced yield.

We further investigated the preparation of chiral 4-pyrrolylmethylated adducts (*R*)-**8** by using (*R*)-**5b** as the starting reagent under the catalysis of Pd(allyl)Cp, $PPh_3$ and acid **A3**. Although the addition site is quite far away from the chiral centre, significant chirality was still retained *via* Pd-mediated π-Lewis base catalysis, and a series of enantioenriched isomers (*R*)-**8** were yielded effectively.[14]




Scheme 4 More substrate exploration and synthetic transformations. (a) Construction of trisubstituted furans. (b) Synthetic transformations.

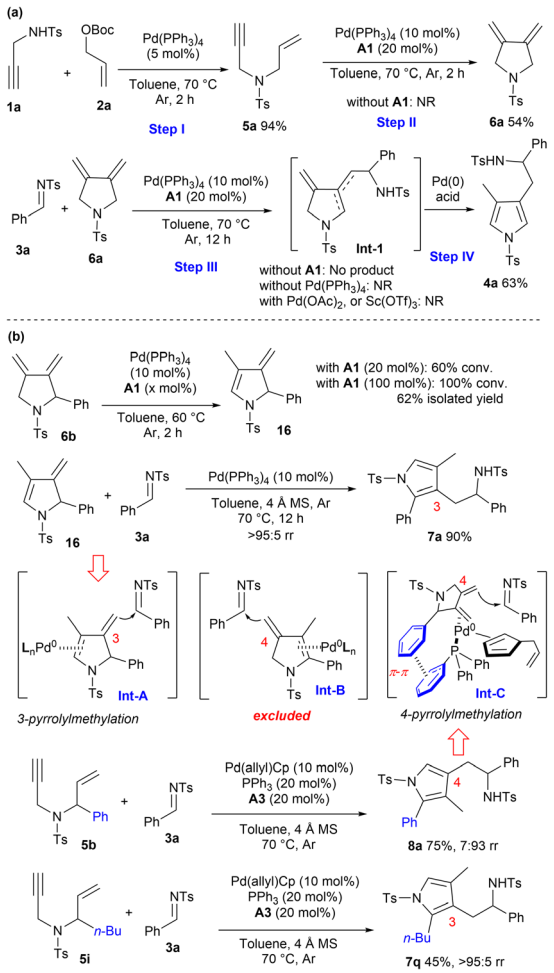
## More substrate exploration and synthetic transformations

Apart from the construction of pyrrole derivatives, the oxygen-tethered 1,6-enyne **9** was applicable to deliver corresponding aromatic furan products **10** and **11** in moderate regioselectivity and fair yield (Scheme 4a). In addition, more types of electrophiles and enynes were investigated, whereas complex reaction profiles or no obvious conversions were generally observed.[11] As outlined in Scheme 4b, treating product **4a** with *N*-bromosuccinimide (NBS) in $CCl_4$ afforded dibromo product **12** in an excellent yield, and regioselective Suzuki coupling and debromination were conducted to deliver product **8m** in a moderate yield. In addition, a cyano group could be introduced by treating **7a** with TMSCN, phenyliodinebis(trifluoroacetate) and $BF_3$-$\cdot Et_2O$ (product **13**).[15] On the other hand, **7a** could be chemoselectively brominated by NBS in $CH_3CN$, and an intramolecular $S_N2$ reaction of resultant **14** afforded bicyclic framework **15** in a moderate yield. It should be noted that these polysubstituted pyrrole frameworks are widely witnessed in natural products and pharmaceuticals.[16]

## Reaction pathway and regiodivergence proposal

To gain some insight into the reaction process, several control experiments were conducted. As illustrated in Scheme 5a, the reaction of propargyl amine **1a** and allylic carbonate **2a** efficiently delivered 1,6-enyne **5a** in 2 h under Pd(0) catalysis. 1,3-Diene **6a** could be isolated in a moderate yield *via 5-exo-dig* cycloisomerisation of **5a** under the same catalytic conditions, and acid was proved to be crucial for this Pd(0)-mediated reaction.[17] The subsequent vinylogous addition and aromatic isomerisation process between **3a** and **6a** also proceeded smoothly, furnishing the desired adduct **4a** in a moderate yield. The possible diene intermediate **Int-1** was not obtained, and control experiments and Xia's study demonstrated that both palladium and acid were indispensable for the vinylogous addition and aromatisation steps.[18] Moreover, Pd(II) or $Sc(OTf)_3$ could not promote the transformations, indicating that an Alder-ene type process would not be involved.

Meanwhile, more control experiments were carried out to rationalise the origin of regiodivergent pyrrolylmethylation. It was found that exocyclic 1,3-diene intermediate **6b** could gradually isomerise to endocyclic diene **16** in the presence of Pd(0) and benzoic acid **A1**, and complete conversions were observed within 2 h by using stoichiometric **A1**. Moreover, the coupling reaction of diene **16** and imine **3a** proceeded very efficiently under Pd(0) catalysis, exclusively giving 3-pyrrolylmethylated product **7a** in an excellent yield, which well supported that the $\eta^2$-complex **Int-A** would be the key intermediate in the vinylogous addition step (Scheme 5b). In contrast, a similar isomerisation process of 1,3-diene **6b** to deliver the 4-pyrrolylmethylated product **8a** *via* **Int-B** would be excluded, because chirality transfer could not be available even when chiral **6b** was applied. As demonstrated in Scheme 5b, a phenyl group on 1,6-enyne **5b** was crucial for the formation of regioisomer **8a**; in sharp contrast, the *n*-butyl substituted enyne **5i** gave 3-pyrrolylmethylated product **7q** exclusively. Accordingly, a π–π stacking between intermediate **6b** and ligand $PPh_3$




Scheme 5 Control experiments for mechanism and regiodivergence elucidation. (a) Elucidation of auto-tandem catalytic reaction. (b) Proposal of regiodivergent pyrrolylmethylation.

might help stabilise the $\eta^2$-Pd(0) complex **Int-C**,[19] which might be responsible for the observed regioselective 4-pyrrolylmethylation reaction. In addition, the *in situ* formed allyl cyclopentadiene might contribute partially as a potential ligand, as proposed in **Int-C**.[20]

## Conclusions

We have investigated a palladium-catalysed assembly of *N*-Ts propargylamines, allyl carbonates and *N*-Ts aldimines in the presence of an acid additive, chemoselectively proceeding through an auto-tandem allylic amination, 1,6-enyne-cycloisomerisation, vinylogous addition and aromatic isomerisation sequence. A wide spectrum of formal pyrrolylmethylation products with dense substitutions was finally furnished straightforwardly. Importantly, regiodivergent construction of 3-pyrrolylmethylated or 4-pyrrolylmethylated derivatives could be accomplished by tuning catalytic conditions, and a substrate-ligand π–π stacking interaction might play a key role. Although only moderate enantiocontrol was achieved from prochiral precursors *via* asymmetric catalysis, fine remote chirality transfer could be achieved from enantioenriched 1,6-enynes or even *N*-Ts propargylamines for both regiodivergent reactions with an achiral ligand, relying on the diastereoselective generation of $\eta^2$-Pd(0) complexes between Pd(0) and *in situ* formed chiral 1,3-diene intermediates in the key vinylogous addition step. More results with regard to palladium-based auto-tandem catalysis will be reported in due course.

## 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.

## Acknowledgements

We are grateful for the financial support from the NSFC (21901169, 21931006 and 21921002) and 111 project (B18035).

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