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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

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

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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 3pyrrolylmethylation 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 η^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.

> benzylic protons. On the other hand, a few methylenesubstituted heterocycles could perform as nucleophilic benzylation precursors to couple with electrophiles through an Alderene 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 1,6enynes,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 1,6enynes 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 car	bonate 2a a	and imin	e 3a ^a			

	$\begin{array}{c} \text{TSHN} & \text{BocO} \\ \hline \textbf{1a} & \textbf{2a} \\ \hline \textbf{PAr_3} & \textbf{L1} \text{ Ar = Ph} \\ \textbf{L2} \text{ Ar = 4-HCOC} \\ \textbf{L3} \text{ Ar = 4-FC_0H_4} \\ \hline \textbf{L3} \text{ Ar = 4-FC_0H_4} \\ \hline \textbf{CO_2H} & \textbf{A3} \text{ R}^1 = F \\ \textbf{R}^1 \end{array}$	H_{4} H_{4	Pd] (10 mol%) L (20 mol%) Acid (x mol%) Ts iluene, 4 Å MS 0 °C, Ar, 24 h PPh ₂ Ph ₂ h h CO_2H BnC h Add AS		PPh2 5a
Entry	[Pd]	L	Acid	x	$\operatorname{Yield}^{b}(\%)$
L	Pd(PPh ₃) ₄	_	A1	20	58
2	Pd ₂ dba ₃	PPh₃	A1	20	54
3	Pd ₂ dba ₂	L2	A1	20	53
1	Pd ₂ dba ₂	L3	A1	20	NR
5	Pd ₂ dba ₃	L4	A1	20	NR
5	Pd ₂ dba ₃	L5	A1	20	NR
7	Pd(PPh ₃) ₄	_	A1	0	5a , 95
3	$Pd(PPh_3)_4$	—	A1	10	50
Ð	$Pd(PPh_3)_4$	—	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 autotandem reactions⁶

	TsHN BocO 1a Pa Pa Pa Pa	NPG Pd(PPh ₃) ₄ (10 mc A2 (40 mol%) Toluene, 4 Å M: 3 70 °C, Ar	I%) → Ts−N	NHPG 4
	_		t	
Entry	R	PG	(h)	Yield ⁵ (%)
1	Ph	Ts	24	4a , 86
2	$2-MeC_6H_4$	Ts	24	4b , 93
3	$3-MeC_6H_4$	Ts	36	4c , 70
4	$4-MeC_6H_4$	Ts	24	4d , 80
5	$4\text{-PhC}_6\text{H}_4$	Ts	24	4e , 79
6	$4 \text{-FC}_6 \text{H}_4$	Ts	24	4f , 68
7	$4-ClC_6H_4$	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	<i>c</i> -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	40 , 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(PPh₃)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-40 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 3pyrrolylmethylated 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 PPh₃ 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	$\operatorname{Yield}^{b}(\%)$	rr ^c
1	Pd(PPh ₂) 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 ¹H-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-envne 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, PPh₃ 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^{α}



Entry	Ar	R	<i>t</i> (h)	$\operatorname{Yield}^{b}(\%)$	rr^{c}
1	ph	ph	10	70.00	05 . 5
_		PII	12	7 a , 90	95:5
2	$2-MeC_6H_4$	Ph	36	7 b , 76	>95:5
3	$3-MeC_6H_4$	Ph	24	7c, 88	>95:5
ł	$4-MeC_6H_4$	Ph	36	7 d , 71	>95:5
5	$4\text{-PhC}_6\text{H}_4$	Ph	24	7e 64	91:9
ō	$2-FC_6H_4$	Ph	12	7 f , 56	81:19
7	$4-FC_6H_4$	Ph	12	7g , 75	93:7
3	$4-ClC_6H_4$	Ph	12	7 h , 82	95:5
)	2-Naphthyl	Ph	36	7i, 82	90:10
0	2-Furyl	Ph	36	7j , 74	>95:5
1	2-Thienyl	Ph	36	7 k , 51	>95:5
2	Ph	$4-MeC_6H_4$	12	7 l , 81	93:7
3	Ph	$4-ClC_6H_4$	12	7m, 76	92:8
4	Ph	2-Furyl	36	7n , 90	>95:5
5	Ph	2-Thienyl	36	7 0 , 80	>95:5
6	Ph	2-Styryl	48	7 p , 36	>95:5
7	Ph	<i>n</i> -Butyl	48	7q , 87	>95:5
8	Ph	<i>i</i> -Propyl	48	7 r, 47	>95:5
9	Ph	<i>c</i> -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(PPh₃)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 ¹H NMR analysis.

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 2substituted 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 Pd₂dba₃ 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

Table 5 Substrate scope for the preparation of 4-pyrrolylmethylated products $\mathbf{8}^a$



			t	·	
Entry	Ar	R	(h)	Yield ^b (%)	rr^{c}
1	Ph	Ph	36	8a 75	7 • 93
2	2-MeC ₆ H ₄	Ph	36	8b. 74	7:93
3	3-MeC ₆ H ₄	Ph	24	8c, 66	10:90
4	4-MeC ₆ H ₄	Ph	96	8d , 67	18:82
5	$4\text{-PhC}_6\text{H}_4$	Ph	24	8e , 72	<5:95
6	$2-FC_6H_4$	Ph	24	8f , 54	<5:95
7	$4-FC_6H_4$	Ph	12	8g , 72	<5:95
8	$4-ClC_6H_4$	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	$2-MeC_6H_4$	36	81, 73	<5:95
13	Ph	$4-MeC_6H_4$	12	8m , 62	18:82
14^e	Ph	$2-ClC_6H_4$	36	8n, 67	<5:95
15	Ph	2-Furyl	36	7n, 76	>95:5
16	Ph	<i>n</i> -Butyl	48	7 q , 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%), PPh₃ (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 ¹H NMR analysis. ^{*d*} Total yield of 7j and 8j, with 20 : 80 rr as inseparable isomers. ^{*e*} With 1 : 1 dr for atropisomers.

the η^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(PPh₃)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.



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, PPh₃ 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 oxygentethered 1,6-envne 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 envnes 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 CCl₄ 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 BF₃-·Et₂O (product 13).¹⁵ On the other hand, 7a could be chemoselectively brominated by NBS in CH3CN, 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-envne 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 η^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 4pyrrolylmethylated 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 PPh₃



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 η^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 1,6enynes or even *N*-Ts propargylamines for both regiodivergent reactions with an achiral ligand, relying on the diastereoselective generation of η^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 palladiumbased 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.

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