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Palladium-catalyzed stereoselective construction of chiral allenes bearing nonadjacent axial and two central chirality†

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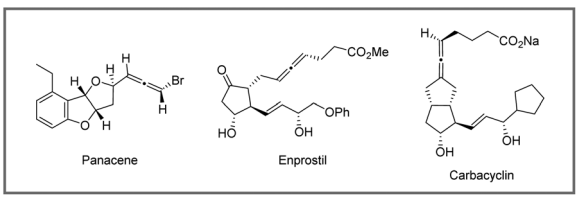
It is challenging to enantioselectively construct molecules bearing multiple nonadjacent stereocenters, in contrast to those bearing a single stereocenter or adjacent stereocenters. Herein, we report an enantio- and diastereoselective synthesis of substituted chiral allenes with nonadjacent axial and two central chiral centers through a combination of retro-oxa-Michael addition and palladium-catalyzed asymmetric allenylic alkylation. This methodology exhibits good functional-group compatibility, and the corresponding allenylic alkylated compounds, including flavonoid frameworks, are obtained with good yields and diastereoselectivities and excellent enantioselectivities (all >95% ee). Furthermore, the scalability of the current synthetic protocol was proven by performing a gram-scale reaction.

Introduction

Bearing a peculiar three-carbon axially chiral skeleton, chiral allenes are featured in many naturally occurring products, pharmaceuticals,[1] materials,[2] and chiral ligands.[3] Additionally, as important building blocks in organic synthesis,[4] allenes have attracted increasing interest. Recently, some novel synthetic methods to access functionalized chiral allenes have been designed and developed, and mainly control either the axial or the central chirality.[5] However, the efficient simultaneous control of the axial and central chirality,[6] especially multiple central chiral centers, remains a challenge, despite their presence in natural products and pharmaceuticals. For instance, panacene is a metabolite of the sea hare *Aplysia brasiliana*, acting as a fish antifeedent.[1,7] (Scheme 1) Besides this, enprostil is a prostaglandin E2 (PGE_2) analogue that strongly inhibits gastric-acid secretion and carbacyclin is a promising antithrombotic agent.[1,8] Thus, the development of efficient methods to prepare allenes bearing multiple chiral elements is highly desirable. A few asymmetric catalytic reactions have been developed to construct chiral allene derivatives bearing multiple adjacent stereocenters.[9] As for the more difficult stereoselective construction of allenes with multiple nonadjacent stereocenters, to the best of our knowledge, limited methodologies have been devised. In 2018, Trost and co-workers synthesized chiral exocyclic allenic compounds bearing nonadjacent axial and two central chiral centers through a palladium-catalyzed asymmetric [3 + 2] cycloaddition reaction.[10] Recently, our group realized the synthesis of enantioenriched substituted allenes with multiple nonadjacent stereocenters through the palladium-catalyzed asymmetric allenylic alkylation of thiochromanone derivatives.[11] Despite these advances in synthesis of chiral allenes, the preparation of diverse chiral allenes bearing multiple nonadjacent stereo-centers is still a conundrum.

The flavonoid structural motif is widely distributed in numerous naturally occurring compounds.[12] Previously, we synthesized substituted flavonoids by utilizing the strategy of retro-oxa-Michael addition, constructing two contiguous stereogenic centers in nucleophilic flavonoids.[13] As a nontrivial extension to this work, we devoted our efforts to exploring the combination of the retro-oxa-Michael addition process and palladium-catalyzed asymmetric allenylic alkylation, which



Scheme 1 Representative examples of axially chiral allenes in natural products and pharmaceuticals.

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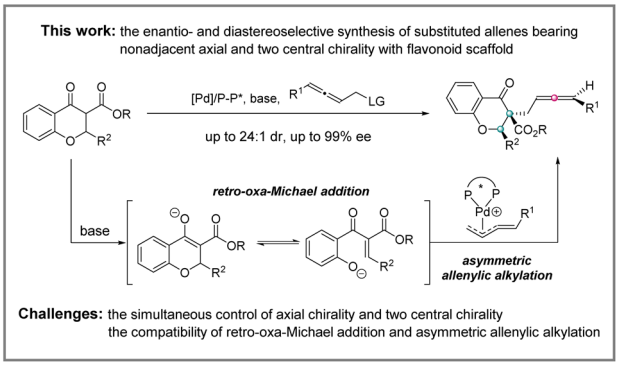
could construct chiral allene products with multiple nonadjacent stereocenters (Scheme 2).

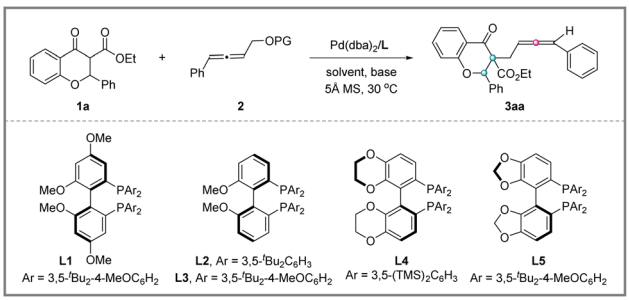
Results and discussion

Our initial investigations focused on condition optimization of the asymmetric allenylic alkylation by selecting a racemic 2,3-disubstituted flavanone (**1a**) as the model substrate, a [Pd]/**L1** complex as the catalyst and Cs_2CO_3 as the base. First, the solvent effect was examined (Table 1, entries 1–3). Fortunately, the desired product **3aa** was obtained in 93% yield with 11 : 1 dr and 97% ee for the major diastereoisomer when tetrahydrofuran was used. After screening a series of commercially available bisphosphine ligands with large steric hindrance (entries 4–7), **L1** was found to be the best choice for the allenylic alkylation. Subsequently, allene partners with various protecting groups were tested (entries 8–11), amongst which the one with an ethoxycarbonyl group performed better in the control of diastereoselectivity (entry 8). Then, the palladium precursor was investigated and it was found that $Pd(dba)_2$ was still optimal (entry 8), while other catalyst precursors, such as $Pd_2(dba)_3$, $[Pd(C_3H_5)Cl]_2$ and $Pd(OAc)_2$, showed lower stereoselectivity (entries 12–14). Both organic and inorganic bases were also screened (entries 15 and 16). Considering the low solubility of cesium carbonate at decreased temperature, 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) was selected as the base for the next investigation. To further improve the diastereoselectivity and enantioselectivity, the reaction temperature was decreased to −20 °C, affording **3aa** in 92% yield with 16 : 1 dr and 99% ee for the major diastereoisomer.



Scheme 2 Palladium-catalyzed asymmetric allenylic alkylation.

Table 1 Optimization of reaction conditions[a]

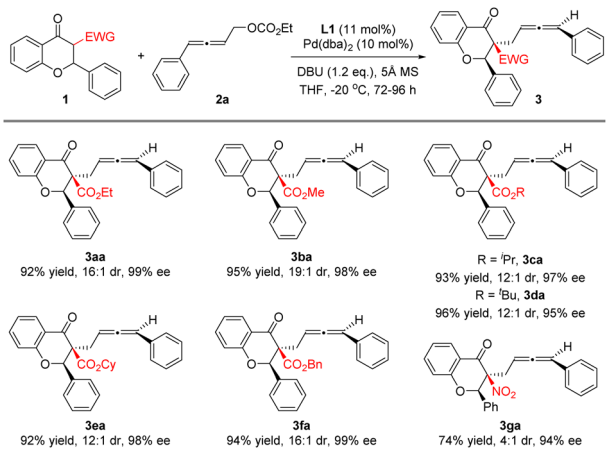


Entry	Solvent	L	PG	[Pd]	Base	Yield[b] (%)	dr[b]	ee[c] (%) Major/minor
1	Toluene	**L1**	CO_2Me	$Pd(dba)_2$	Cs_2CO_3	>95	6 : 1	93/61
2	DMF	**L1**	CO_2Me	$Pd(dba)_2$	Cs_2CO_3	63	10 : 1	98/42
3	THF	**L1**	CO_2Me	$Pd(dba)_2$	Cs_2CO_3	93	11 : 1	97/78
4	THF	**L2**	CO_2Me	$Pd(dba)_2$	Cs_2CO_3	92	9 : 1	96/51
5	THF	**L3**	CO_2Me	$Pd(dba)_2$	Cs_2CO_3	91	9 : 1	89/55
6	THF	**L4**	CO_2Me	$Pd(dba)_2$	Cs_2CO_3	93	6 : 1	39/42
7	THF	**L5**	CO_2Me	$Pd(dba)_2$	Cs_2CO_3	>95	9 : 1	50/10
8	THF	**L1**	CO_2Et	$Pd(dba)_2$	Cs_2CO_3	>95	11 : 1	98/72
9	THF	**L1**	$CO_2{}^iPr$	$Pd(dba)_2$	Cs_2CO_3	>95	10 : 1	97/64
10	THF	**L1**	Ac	$Pd(dba)_2$	Cs_2CO_3	>95	9 : 1	94/41
11	THF	**L1**	$P(O)(OEt)_2$	$Pd(dba)_2$	Cs_2CO_3	93	11 : 1	96/65
12	THF	**L1**	CO_2Et	$Pd_2(dba)_3$	Cs_2CO_3	66	7 : 1	94/08
13	THF	**L1**	CO_2Et	$[Pd(C_3H_5)Cl]_2$	Cs_2CO_3	96	1 : 1	51/27
14	THF	**L1**	CO_2Et	$Pd(OAc)_2$	Cs_2CO_3	94	11 : 1	97/57
15	THF	**L1**	CO_2Et	$Pd(dba)_2$	KO^tBu	71	8 : 1	96/55
16	THF	**L1**	CO_2Et	$Pd(dba)_2$	DBU	87	11 : 1	96/52
17[d]	THF	**L1**	CO_2Et	$Pd(dba)_2$	DBU	92[e]	16 : 1	99/06

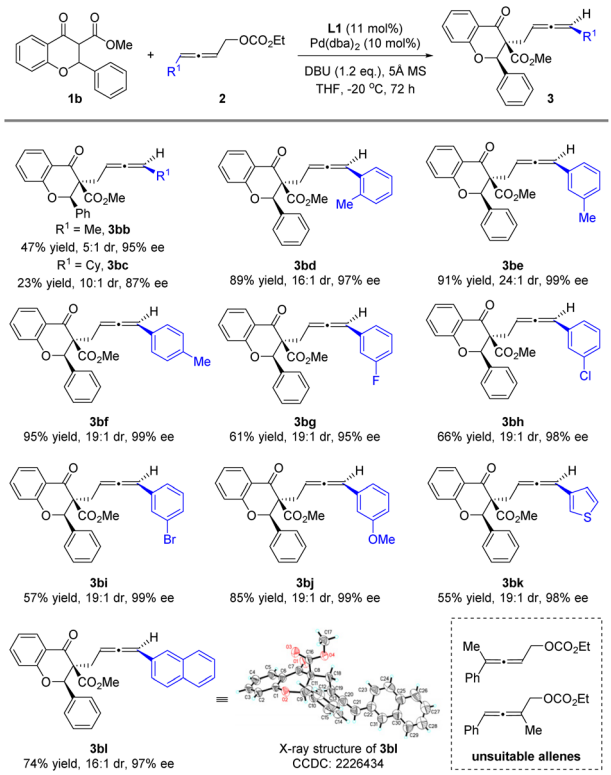
[a] Reactions were carried out with **1a** (0.1 mmol), **2** (1.5 eq.), [Pd] (10 mol%), **L** (11 mol%), base (1.2 eq.), solvent (1.0 mL), 5 Å molecular sieves (MS) (50 mg), 30 °C, 24 h. [b] Yield and diastereomeric ratio were measured by analysis of ^1H NMR spectra using 1,3,5-trimethoxybenzene as the internal standard. [c] Determined by chiral HPLC. [d] −20 °C instead of 30 °C. [e] Isolated yield for the reaction with 0.2 mmol scale after 72 h.

With the optimal conditions established in entry 17, we further set out to explore the generality of the methodology. First, flavanone moieties bearing various alkyl substituents on the ester group, including ethyl (**1a**), methyl (**1b**), iso-propyl (**1c**), *tert*-butyl (**1d**), cyclohexyl (**1e**) and benzyl (**1f**), were investigated (Scheme 3). The diastereoselectivity of this reaction was slightly sensitive to the steric bulk in flavanones **1**. When *tert*-butoxycarbonyl (**1d**) was introduced, a moderate 12 : 1 dr was obtained. By comparison, a 19 : 1 dr was observed when methoxycarbonyl (**1b**) was introduced. When the nitro group (**1g**) was used as the electron-withdrawing group (EWG), lower diastereoselectivity was observed. Thus, the methoxycarbonyl group was identified as the optimal EWG for the next substrate scope investigation.

The effect of the substituents of allenylic carbonates **2** was further probed, and it was found that they have a strong impact on the reactivity and stereoselectivity in the allenylic alkylation (Scheme 4). It seemed that allenylic carbonates containing aryl groups were better than those with alkyl groups in terms of reactivity and diastereoselectivity. The methyl-substituted allenylic carbonate (**2b**) reacted with **1b** and generated the product **3bb** with 95% ee for the major diastereoisomer, albeit in moderate 47% yield and 5 : 1 dr. When the cyclohexyl group (**2c**) was introduced, the result for the reactivity and diastereoselectivity was even worse. We further tested the effect of the substituent at *ortho* (**2d**), *meta* (**2e**) or *para*-positions (**2f**) of the aryl group, and found that better diastereoselectivity (24 : 1 dr) was obtained with the *meta*-position substituent. Subsequently, when a fluoro, chloro, bromo or methoxy group was introduced at the *meta*-position, the alkylation reaction proceeded smoothly to deliver **3bg**, **3bh**, **3bi** or **3bj** with excellent ee and dr, but moderate yields were observed with the halogen atoms. Furthermore, a thienyl substituent (**2k**) was tolerable, affording **3bk** with 19 : 1 dr and 98% ee for the major diastereoisomer, although a low yield was observed. The allenylic carbonate with a naphthyl substituent (**2l**) was also suitable. Regretfully, trisubstituted allene partners were not suitable for this protocol, giving low reactivity even under more stringent reaction conditions. The absolute configuration of product **3bl** was assigned as (2*R*,3*S*,R_a) by X-ray diffraction analysis (for the details, please see the ESI†), and other products were assigned by analogy.

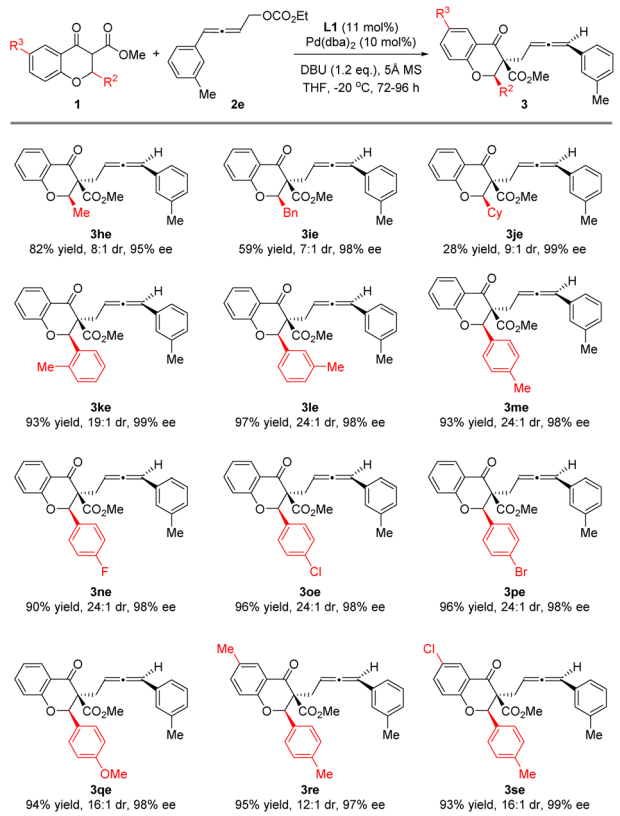


Scheme 3 Substrate scope for the ester group of flavanones **1**.

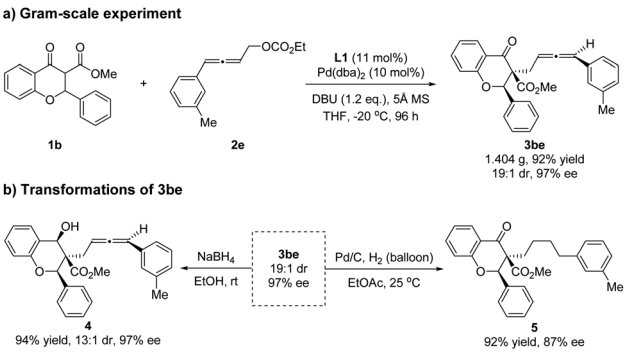


Scheme 4 Substrate scope for allenylic carbonates **2**.

Subsequently, the substrate scope was further investigated with a series of 2,3-disubstituted flavanones or chromanones by using ethyl(4-(*m*-tolyl)buta-2,3-dien-1-yl) carbonate (**2e**) as the allenylic carbonate partner (Scheme 5). As expected, a variety of aryl-substituted flavanones were smoothly converted into the corresponding products in high isolated yields, with excellent dr and ee values (**3ke–3se**), while moderate diastereoselectivity and lower reactivity were observed with the alkyl-substituted chromanones (**1h–1j**). Additionally, the position of the substituents on the phenyl group was probed, showing that a flavanone bearing an *ortho*-position substituent (**1k**) reacted with a slightly lower dr than that bearing a *meta*- (**1l**) or *para*-position (**1m**) substituent. To our delight, when R^2 was a 4-fluoro-, 4-chloro- or 4-bromo-phenyl group (**1n–1p**), those substrates were all compatible with this reaction and led to the corresponding products (**3ne–3pe**) in excellent yields, with high dr and ee values. By contrast, when a methoxy group was introduced at the *para*-position, the alkylation reaction proceeded smoothly but delivered **3qe** with slightly lower diastereoselectivity. Finally, substituents on the carbocyclic ring of the flavanones **1**, such as methyl (**1r**) and chloro (**1s**), had negligible effect on the reactivity and enantioselectivity but a small negative influence on the diastereoselectivity.



Scheme 5 Substrate scope for the flavanones/chromanones **1**.



Scheme 6 Gram-scale experiment and product transformations.

To further showcase the synthetic utility of the current strategy, a gram-scale reaction was carried out under the standard conditions, delivering the product **3be** and maintaining the yield, with slightly diminished stereoselectivity (Scheme 6a). In addition, the transformations of **3be** were concentrated on the reduction. The carbonyl group of **3be** was selectively reduced with sodium borohydride at room temperature, affording reduction product **4** in 94% yield with 13 : 1 dr (the relative configuration of the hydroxyl and phenyl groups in compound **4** was assigned as *cis*-**4** by analogy[11]). Besides this, the single reduction isomer **5** was obtained in 92% yield and 87% ee by hydrogenating the allene moiety of **3be** with 10% Pd/C catalyst, showing that the diastereoisomers of **3be** are ascribed to the axial chirality.

Conclusions

In summary, we have successfully developed an enantio- and diastereoselective construction of substituted chiral allenes bearing nonadjacent axial and two central chiral centers, through a combination of retro-oxa-Michael addition and palladium-catalyzed asymmetric allenylic alkylation under basic conditions. This protocol features high yields, good diastereoselectivities, excellent enantioselectivities and broad substrate scope, achieving straightforward and efficient access to functionalized chiral allenes.

Conflicts of interest

The authors declare no competing financial interests.

Acknowledgements

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