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Iridium-catalyzed enantioselective direct vinylogous allylic alkylation of coumarins

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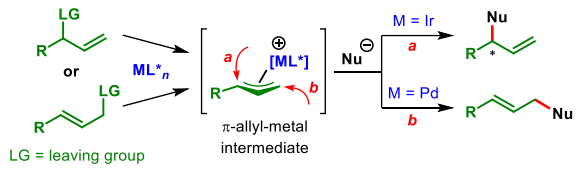
The first iridium-catalyzed enantioselective vinylogous allylic alkylation of coumarins is presented. Using easily accessible linear allylic carbonates as the allylic electrophile, this reaction installs unfunctionalized allyl groups at the γ-position of 4-methylcoumarins in exclusively branched-selective manner generally in high yields with excellent level of enantioselectivity (up to 99:1 er).

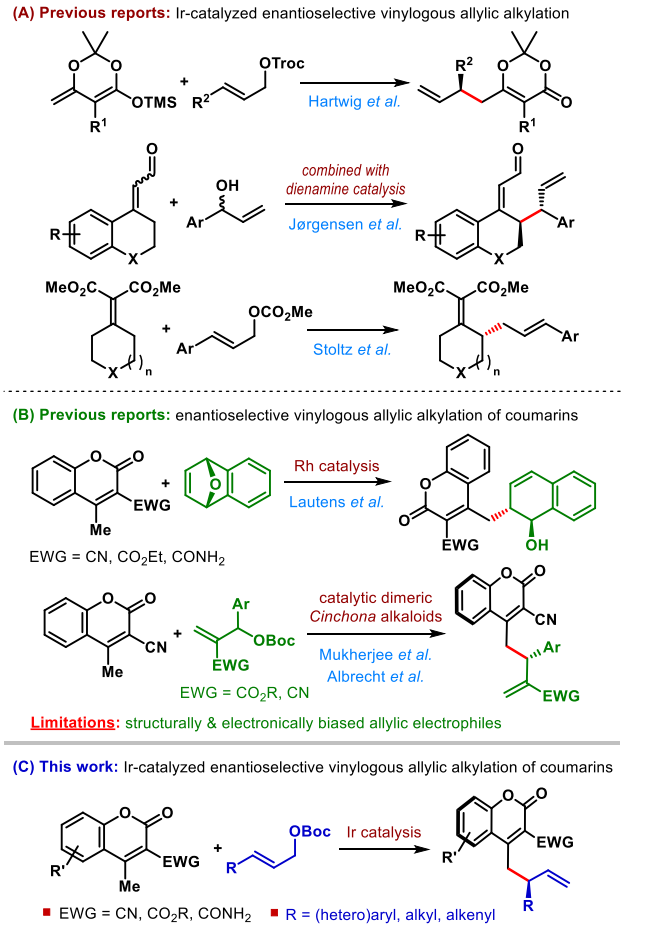
Introduction

Transition-metal-catalyzed asymmetric allylic substitution (AAS) reactions have emerged as an extremely powerful and versatile method for the synthesis of enantioenriched compounds from easily available starting materials through enantioselective construction of carbon-carbon and carbon-heteroatom bonds.[1] In contrast to initially developed and more commonly used palladium catalysts, iridium-catalyzed AAS reactions enable the synthesis of branched products from unsymmetrical allylic electrophiles through preferential attack of nucleophiles at the more substituted terminus of the π-allyl-Ir intermediate (Scheme 1).



Scheme 1 Transition-metal-catalyzed allylic substitution

This characteristic of the Ir-catalyzed AAS overcomes the limitations associated with Pd-catalysis with respect to the scope of reaction partners and allows for the use of even achiral (non-prochiral) carbon and heteroatom nucleophiles in reactions with unsymmetrical allylic electrophiles.[2] Consequently, a wide variety of nucleophiles have been applied[3-5] to highly regioselective (branched-to-linear) and enantioselective allylic alkylation reactions ever since the introduction of Ir-catalysts in 1997.[6] Despite these developments during the past two decades, the use of vinylogous nucleophiles in Ir-catalyzed asymmetric allylic alkylation (AAA) has received much less attention and only a handful of reports exist till date (Scheme 2A).[7-9]



Scheme 2 Enantioselective vinylogous allylic alkylation

In 2014, Hartwig et al. reported the first application of vinylogous nucleophile, namely preformed silyl dienolates, in Ir-catalyzed AAA.[7] Jørgensen group combined the concept of dienamine activation with Ir-catalyzed AAA for regio-,

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diastereo- and enantioselective γ-allylic alkylation of α,β-unsaturated aldehydes.[8] More recently, Stoltz group developed a formal enantioselective γ-allylic alkylation of α,β-unsaturated malonates through a sequential Ir-catalyzed AAA/Cope rearrangement.[9]

With our own interest in vinylogous nucleophilic reactivity,[10] we embarked into the development of direct catalytic enantioselective allylic alkylation of other vinylogous nucleophiles.

We became particularly interested in 4-methylcoumarins as the potential vinylogous nucleophile due to wide abundance of coumarin derivatives in over 1000 natural products and bioactive targets as well as their utility in dye industries.[11] Although this class of nucleophiles received considerable attention since the introduction of 3-cyano-4-methylcoumarins by Xie et al. in 2010,[12] enantioselective allylic alkylation of this potentially useful class of vinylogous nucleophile remained underexplored until recently. Lautens' group developed the first enantioselective γ-allylic alkylation of 4-methylcoumarins in 2016 through a Rh-catalyzed desymmetrizing ring-opening reaction of oxabicycles (Scheme 2B).[13] Very recently, our group[14] and subsequently Albrecht et al.[15] independently developed the first organocatalytic enantioselective γ-allylic alkylation of 3-cyano-4-methylcoumarins using Morita-Baylis-Hillman carbonates as the allylic electrophile (Scheme 2B). While excellent level of enantioselectivity has been achieved, the success of these reactions is inherently dependent on the type of allylic electrophiles – both structurally and electronically, thereby limiting their scope.

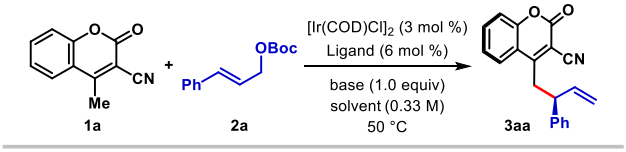
Since Ir-catalyzed allylic alkylation reactions are not constrained by such structural and electronic bias on the allylic electrophile, we believed that Ir-catalysis would provide a general strategy for the synthesis of coumarin derivatives that were previously challenging to access.

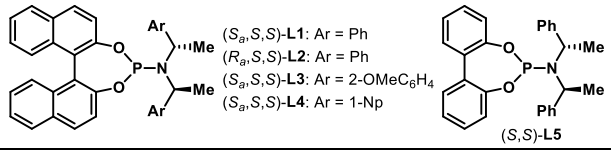
The purpose of this communication is to disclose the first Ir-catalyzed enantioselective vinylogous allylic alkylation of coumarins (Scheme 2C).

Results and discussion

We began our investigation with the optimization of catalyst and reaction conditions[16] for a model reaction between 3-cyano-4-methylcoumarin **1a** and *tert*-butyl cinnamyl carbonate **2a** in dichloroethane (DCE) at 50 °C (Table 1). A combination of $[Ir(COD)Cl]_2$ and Feringa's phosphoramidite ligand **L1**,[17] pioneered by Hartwig and co-workers,[5i] was initially tested. In the absence of any external base to activate **1a**, the desired γ-allylated product **3aa** was formed exclusively as a single regioisomer with a promising enantioselectivity, although in only 22% yield (entry 1). The *tert*-butoxide anion, generated *in situ* from the reaction between Ir-complex and **2a**, was anticipated to be the active base in this reaction.[18] In line with the observation reported previously for Ir-catalyzed AAS reactions,[3-5] choice of external base was found to have profound influence on both the reaction efficacy and enantioselectivity. Extensive exploration of various bases (entries 2–7), including inorganic and organic bases, revealed DABCO to be the optimum,[19] affording the product in high yield and enantioselectivity (entry 7). A number of ligands for iridium were then tested under the influence of DABCO (entries 8–11). Use of ligand **L2**, a diastereomer of **L1**, failed to catalyze the reaction (entry 8). Ligand **L3**, an *ortho*-methoxy-derivative of **L1**, introduced by Alexakis et al.[20] and generally known to act as a superior ligand compared to **L1** in many AAS reactions, furnished **3aa** with improved er but in poor yield (entry 9). No improvement in yield or enantioselectivity was observed with **L4** or **L5** (entries 10-11), and **L1** remained the ligand of choice. A solvent screening (entries 12-14) at this point revealed dichloromethane as the optimum, providing the product in 86% isolated yield and with 98:2 er (entry 14).

Table 1 Ligand screening and reaction optimization[a]





Entry	Ligand	Solvent	Base	*t* [h]	Yield [%][b]	er[c]
1	**L1**	DCE	-	48	(22)	92.5:7.5
2	**L1**	DCE	Cs_2CO_3	48	<5	n.d.
3	**L1**	DCE	DBU	48	<5	n.d.
4	**L1**	DCE	*i*-Pr_2NEt	48	72	96:4
5	**L1**	DCE	Et_3N	48	74	97:3
6	**L1**	DCE	*i*-Pr_2NH	48	76	97:3
7	**L1**	DCE	DABCO	48	84	97.5:2.5
8	**L2**	DCE	DABCO	48	<5	n.d.
9	**L3**	DCE	DABCO	48	11	98:2
10	**L4**	DCE	DABCO	48	<5	n.d.
11	**L5**	DCE	DABCO	48	28	92:8
12	**L1**	THF	DABCO	48	11	96:4
13	**L1**	$CHCl_3$	DABCO	48	67	97:3
14	**L1**	CH_2Cl_2	DABCO	36	88 (86)	98:2

[a] Reaction conditions: 3 mol% $[Ir(COD)Cl]_2$, 6 mol% ligand, 0.24 mmol of **1a**, 0.2 mmol of **2a** and 0.2 mmol of base in 0.6 mL solvent. The catalyst was prepared via *n*-$PrNH_2$ activation. [b] Yields were determined by ^{1}H-NMR spectroscopy with mesitylene as internal standard. Isolated yields are given in the parentheses. [c] Enantiomeric ratio (er) was determined by HPLC analysis on a chiral stationary phase; n.d. = not determined. DCE = 1,2-dichloroethane.

With the optimum ligand and reaction conditions (Table 1, entry 14) in hand, we chose to explore the scope and limitations of this direct vinylogous allylic alkylation protocol. We were pleased to note that the efficacy displayed by the Ir/**L1** combination for the reaction between **1a** and **2a** under the optimum reaction conditions, is indeed a general phenomenon and could be extended to other substrate combinations. As shown in Table 2, 3-cyano-4-methylcoumarin (**1a**) underwent

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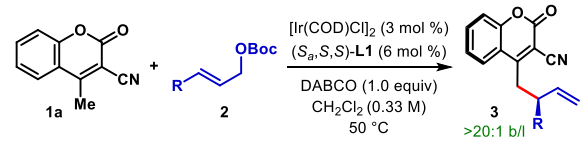
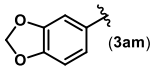
facile allylic alkylation with an assortment of allylic carbonates (**2a**-**u**). Aryl-substituted allylic carbonates with diverse steric and electronic demand on aryl ring (**2a-i**) were well tolerated, providing the products (**3aa-ai**) in high yields with excellent enantioselectivities (Table 2A, entries 1-9). When substituent present in either *meta*- or *para*- position of phenyl ring, products were formed with similar yields and enantioselectivities. In accordance with previously reported AAS reactions with **L1**,[21] *ortho*-substituent on phenyl ring led to slow reaction, giving the product with moderate yield and er (entry 10). This adverse effect of *ortho*-substituent is clearly evident from the comparative outcome of the reactions with dichloro-substituted cinnamyl carbonates **2k** and **2l** (entries 11-12). We were also interested in incorporating pharmaceutically relevant heterocycles into our products, and found that allylic carbonates bearing dioxolane (**2m**), pyridine (**2n**), furan (**2o**) and thiophene (**2p**) delivering the products in good to high yields with excellent er (entries 13-16).

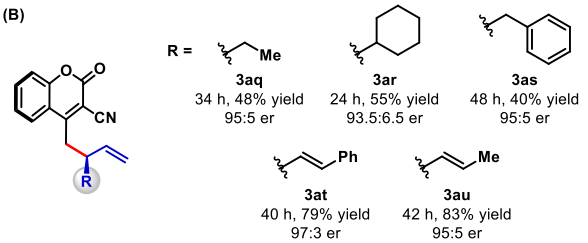
Table 2 Scope of the enantioselective allylic alkylation with regard to allylic carbonates[a]



(A)

Entry	Ar	*t* [h]	Yield [%]	er
1	Ph (**3aa**)	36	86	98:2
2	4-MeC_6H_4 (**3ab**)	36	87	98:2
3	4-(*i*-Pr)C_6H_4 (**3ac**)	36	80	97.5:2.5
4	4-$OMeC_6H_4$ (**3ad**)	22	98	98:2
5	4-$CF_3C_6H_4$ (**3ae**)	36	69	98:2
6	4-$NO_2C_6H_4$ (**3af**)	36	71	96:4
7	4-ClC_6H_4 (**3ag**)	24	79	97:3
8	3-BrC_6H_4 (**3ah**)	20	91	98:2
9	3-FC_6H_4 (**3ai**)	36	78	98:2
10	1-Naphth (**3aj**)	72	62	69:31
11	2,4-$Cl_2C_6H_3$ (**3ak**)	72	51	71:29
12	3,4-$Cl_2C_6H_3$ (**3al**)	48	75	98:2
13	 (**3am**)	30	90	98:2
14	3-Pyr (**3an**)	36	86	97.5:2.5
15	2-Furyl (**3ao**)	38	74	97:3
16	2-Thienyl (**3ap**)	23	86	99:1

(B)

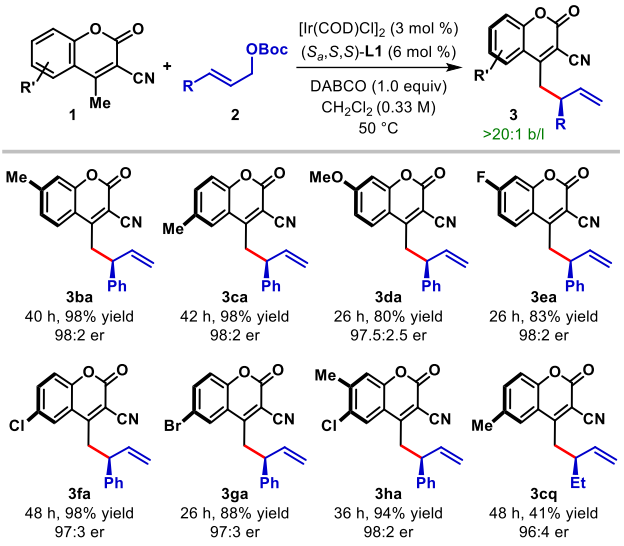


[a] Reaction conditions: 3 mol% $[Ir(COD)Cl]_2$, 6 mol% **L1**, 0.24 mmol of **1a**, 0.2 mmol of **2** and 0.2 mmol of DABCO in 0.6 mL CH_2Cl_2. The catalyst was prepared via *n*-$PrNH_2$ activation. Yields correspond to the isolated product after chromatographic purification. Er was determined by HPLC analysis on a chiral stationary phase.

The scope of our protocol is not limited to (hetero)aromatic allylic carbonates. As illustrated by the examples in Table 2B, allylic carbonates containing a linear (**2q**) and branched alkyl group (**2r**) as well as benzyl (**2s**) returned with good enantioselectivities, albeit with moderate yield. In addition, alkenyl-substituted allylic carbonates (**2t-u**) participated in this reaction and generated the single regioisomeric products (**3at-au**), out of three possible regioisomers, in good yield with good to high er.

The scope of the reaction with respect to other cyanocoumarin derivatives was next examined (Table 3). A number of substituted cyanocoumarins bearing either electron donating (e.g. Me, OMe) or electron withdrawing (e.g. F, Cl, Br) groups were found to be equally suited under our standard reaction conditions, affording γ-allylated products (**3ba-ga**) with excellent yields and enantioselectivities. Disubstituted cyanocoumarin **1h** also participated in this reaction with equal efficiency.

Table 3 Scope of the enantioselective allylic alkylation with respect to coumarins[a]



[a] Reaction conditions: 3 mol% $[Ir(COD)Cl]_2$, 6 mol% **L1**, 0.24 mmol of **1**, 0.2 mmol of **2** and 0.2 mmol of DABCO in 0.6 mL CH_2Cl_2. The catalyst was prepared via *n*-$PrNH_2$ activation. Yields correspond to the isolated product after chromatographic purification. Er was determined by HPLC analysis on a chiral stationary phase.

After successfully demonstrating the scope of the reaction with cyanocoumarins, we wondered whether the reactivity of the coumarin derivative could be retained by replacing the cyano group with other α-substituents. To our delight, when CN (in **1a**) was replaced with an amide group ($CONH_2$), the vinylogous allylic alkylation reaction indeed took place to furnish the corresponding γ-allylated product **3ia** with similar level of yield and enantioselectivity (Table 4, entry 2). Not only amide but related esters (**1j**-**k**) could also be employed as substrates and afforded the products (**3ja**-**ka**) in high yield and with excellent er (entries 3-4). However, α-carboxylatocoumarin (**1l**) failed to react in the desired fashion and instead resulted in 4-methylcoumarin **1m** in 52% yield through decarboxylation (entry 5). Similarly, unsubstituted 4-methylcoumarin (**1m**) itself remained unreacted under our standard reaction conditions even after 48 h (entry 6).

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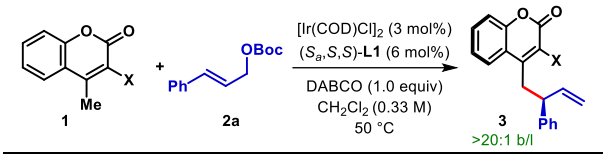
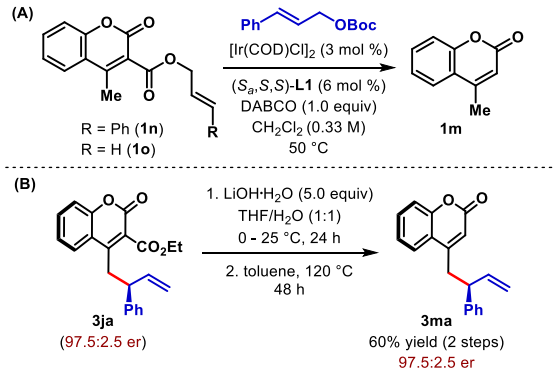
Table 4 Effect of α-substituent on coumarins in enantioselective allylic alkylation[a]



Entry	X	*t* [h]	**3**	Yield [%][b]	er[c]
1	CN (**1a**)	36	**3aa**	86	98:2
2	$CONH_2$ (**1i**)	36	**3ia**	81	98:2
3	CO_2Et (**1j**)	48	**3ja**	80	97.5:2.5
4	CO_2Bn (**1k**)	48	**3ka**	85	98:2
5	CO_2H (**1l**)	42	**3la**	<5[d]	-
6	H (**1m**)	48	**3ma**	<5	-

[a] Reaction conditions: 3 mol% $[Ir(COD)Cl]_2$, 6 mol% **L1**, 0.24 mmol of **1**, 0.2 mmol of **2a** and 0.2 mmol of DABCO in 0.6 mL CH_2Cl_2. The catalyst was prepared via *n*-$PrNH_2$ activation. [b] Yields correspond to the isolated product after chromatographic purification. [c] Er was determined by HPLC analysis on a chiral stationary phase. [d] **1m** was isolated in 52% yield.

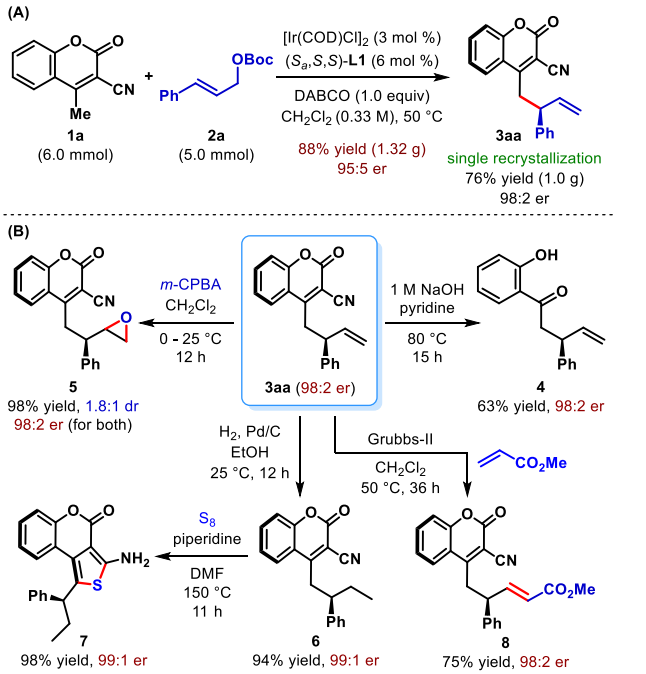
These studies clearly indicate that the presence of an electron withdrawing group at the α-position of 4-methylcoumarin is necessary to exert its vinylogous reactivity. This prerequisite is certainly a limitation of our protocol and prevents the direct vinylogous allylic alkylation of α-unsubstituted 4-methylcoumarin. Our attempts to access this motif (**3ma**) through a one-pot sequential Ir-catalyzed γ-allylic alkylation/deallylative decarboxylation of allyl esters (**1n**-**o**) proved futile and led only to the formation of **1m** (Scheme 3A). Similarly, an attempted intramolecular decarboxylative migratory allyl transfer[22] of **1n** under Ir-catalysis also resulted in deallylative decarboxylation to generate **1m**. Finally, a two-step sequence consisting of ester hydrolysis followed by decarboxylation delivered the desired α-unsubstituted γ-allylcoumarin **3ma** in overall 60% yield from **3ja** without any erosion of enantiopurity (Scheme 3B).



Scheme 3 Attempted and successful synthesis of α-unsubstituted γ-allylcoumarin

The practicality of our enantioselective direct vinylogous allylic alkylation protocol is established by carrying out a gram-scale synthesis of **3aa**, which gave the product in 88% yield but with somewhat diminished enantioselectivity (Scheme 4A). However, a single recrystallization restored the enantiopurity of **3aa** to 98:2 er.

We realized that the ability to transform the existing functionalities present in the products may further increase their synthetic potential. Accordingly, a base-mediate retro-Knoevenagel condensation/hydrolysis of **3aa** was carried out to furnish α-allylated *o*-hydroxyacetophenone **4** with 63% yield (Scheme 4B). Treatment of **3aa** with *m*-CPBA provided the corresponding epoxide **5** in excellent yield but with poor diastereoselectivity (1.8:1 dr). Selective hydrogenation of the terminal double bond of **3aa** was possible under Pd/C and resulted in **6** in 94% yield. A base-catalyzed cyclization of **6** with sulfur furnished tricyclic aminothiophenocoumarin **7**. This structural motif is known for its presence in antifungal agents.[23] The absolute stereochemistry of **3aa**, **6** and **7** has previously been confirmed by Waldmann et al.[24] and in turn established the absolute configuration of our allylated products. Finally, an olefin cross-metathesis of **3aa** with methyl acrylate in the presence of Grubbs 2nd generation catalyst occurred smoothly to give terminally functionalized olefin **8** in 75% yield. In all these cases, the reactions proceeded with complete conservation of stereochemical integrity.



Scheme 4 Gram-scale synthesis and synthetic elaboration of γ-allylcoumarin **3aa**

A tentative catalytic cycle based on the literature precedence[25] is depicted in Scheme 5 and involve the intermediacy of the iridacycle intermediate **A**. Ligand dissociation from the coordinatively saturated species **A** is likely to generate a species **B** having 16 valence electrons at Ir. Coordination of allylic carbonate (**2**) to **B** followed by oxidative addition-decarboxylation gives the π-allyl-Ir intermediate **C**. An enantiodetermining nucleophilic addition of dienolate **D** to **C** then produces complex **E**, product dissociation from which completes the catalytic cycle. The sense of stereoinduction was found to be the same as predicted by the Hartwig model.[25b]

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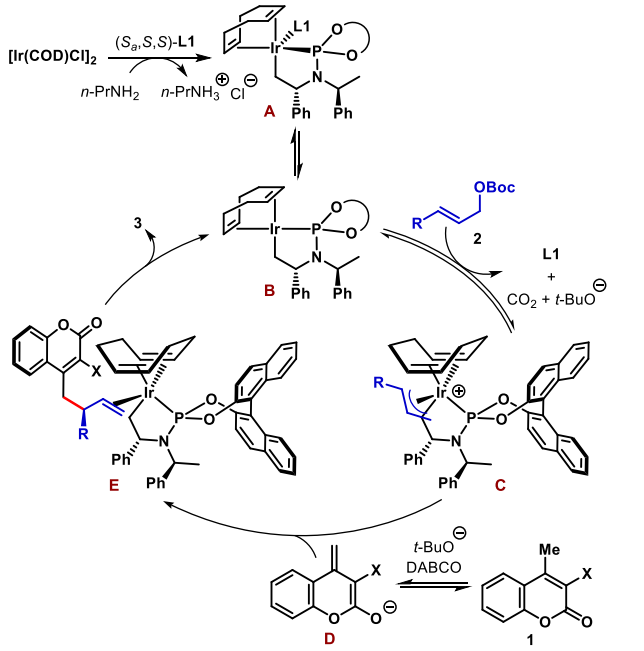

Scheme 5 Tentative catalytic cycle for the Ir-catalyzed enantioselective allylic alkylation of coumarins

Conclusions

In conclusion, we have developed the first Ir-catalyzed enantioselective vinylogous allylic alkylation of coumarins. Our protocol does not require preactivation of 4-methylcoumarins and installs unfunctionalized allyl group using easily accessible linear allylic carbonates as the allylic electrophile. The resulting Ir/phosphoramidite-catalyzed direct vinylogous allylic alkylation reaction produces *γ*-allylcoumarins in exclusively branched-selective manner generally in high yields with excellent level of enantioselectivity. An enantioselective synthesis of α-unsubstituted *γ*-allylcoumarin as well as synthetic elaboration of *γ*-allylcyanocoumarin to a diverse range of products have also been demonstrated. Future efforts in this direction from our laboratory would focus on the studies of other classes of vinylogous nucleophiles.

Acknowledgements

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Iridium-catalyzed enantioselective direct vinylogous allylic alkylation of coumarins

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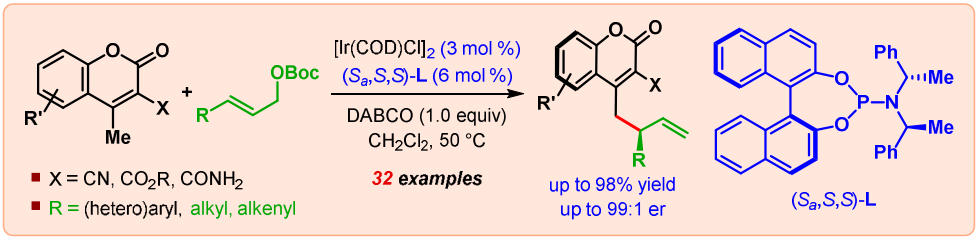

The first iridium-catalyzed enantioselective vinylogous allylic alkylation of coumarins is presented. Using easily accessible linear allylic carbonates as the allylic electrophile, this reaction installs unfunctionalized allyl groups at the γ-position of 4-methylcoumarins in exclusively branched-selective manner generally in high yields with excellent level of enantioselectivity (up to 99:1 er).