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Iridium-Catalyzed Direct Asymmetric Vinylogous Allylic Alkylation

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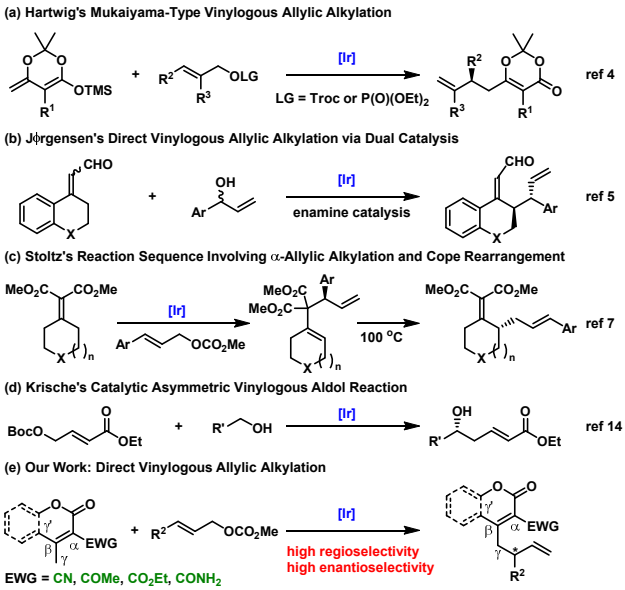
The catalytic asymmetric vinylogous allylic alkylation of α,β-unsaturated lactones (including coumarins) was achieved with excellent regio- and enantioselectivity. Transformations of the product were carried out by means of the versatile terminal olefin and lactone moieties. Synthetic application of the present methodology was showcased by the asymmetric synthesis of an advanced synthetic Merk intermediate toward new drug candidate.

Catalytic asymmetric vinylogous reactions have gained a preeminent position in organic synthesis due to its extensive application in the synthesis of complex natural products and biologically active pharmaceuticals.[1] Although transition metal-catalyzed asymmetric allylic alkylation of carbonyl compounds is identified as one of the most fundamental strategies to construct chiral α-substituted carbonyl compounds,[2] its vinylogous version leading to synthetically valuable chiral γ-substituted α,β-unsaturated carbonyl compounds[3] was not studied extensively. Catalytic asymmetric vinylogous allylic alkylation is challenging due to some concerns, such as regioselectivity (α- vs γ-allylic alkylation, γ- vs γ'-allylic alkylation), chemoselectivity (C- vs O-allylic alkylation) and remote control of enantioselectivity.

In 2014, Hartwig and co-worker disclosed an iridium-catalyzed highly selective asymmetric vinylogous allylic alkylation of silyl dienolates derived from dioxinones (Scheme 1a).[4a] Later, the scope of allylic electrophiles was successfully expanded from disubstituted allylic carbonates to trisubstituted allylic phosphates (Scheme 1a).[4b] In 2015, Jørgensen group reported an asymmetric γ-allylation of α,β-unsaturated aldehydes through combined organocatalysis and transition-metal catalysis (Scheme 1b).[5] The key to perfectly control the regioselectivity was mainly ascribed to the bulkiness of organocatalyst (a prolinol derivative).

An indirect but effective method to achieve asymmetric γ-allylic alkylation is to employ a sequential combination of catalytic asymmetric α-allylic alkylation and Cope rearrangement, which was reported by Tunge group and Cossy group.[6] In 2016, Stoltz and co-workers disclosed an elegant catalytic asymmetric vinylogous allylic alkylation of α,β-unsaturated malonates or ketoesters, involving iridium-catalyzed α-allylation of α,β-unsaturated malonates or ketoesters and following Cope rearrangement at 100 °C (Scheme 1c).[7] In 2018, Peters group reported an similar strategy by using isoxazolinones as the pronucleophiles and finally accomplished asymmetric *N*-allylation through an aza-Cope rearrangement.[8] It is evident from the literature that a direct catalytic asymmetric vinylogous allylic alkylation of α,β-unsaturated compounds is not easy to achieve.

Scheme 1 Prior Arts in Ir-Catalyzed Asymmetric Vinylogous Allylic Alkylation and Our Work



Coumarins **1** are selected as pronucleophiles because coumarin structures are not only frequently found in natural

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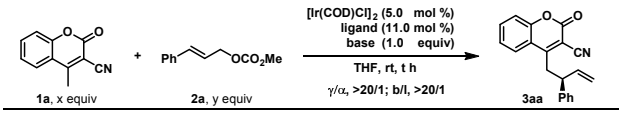
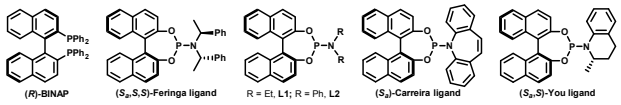
products, but also serve as "privileged" scaffolds of biological and pharmaceutical interests.[9] Coumarins **1** have been successfully applied in catalytic asymmetric vinylogous alkylation,[10] vinylogous allylic alkylation,[11] vinylogous ring-opening,[12] and vinylogous propargylation.[13] Inspired by above mentioned seminar works with iridium catalysts and Krische's extinguished iridium-catalyzed asymmetric vinylogous aldol reaction (Scheme 1d),[14] we achieved a high regio- and enantioselective vinylogous allylic alkylation of cyclic α,β-unsaturated compounds (including coumarins **1** and **4**) with iridium catalyst (Scheme 1e), which followed our research interest in catalytic asymmetric vinylogous reactions.[15]

Table 1 Optimization of the Reaction Conditions with **1a** and **2a**[a]



entry	x	y	ligand	base	t	yield (%)[b]	ee (%)[c]
1	1.0	1.0	(S_a,*S*,*S*)-Feringa ligand	Et_3N	24	22	96
2	1.0	1.0	(S_a,*S*,*S*)-Feringa ligand	Cy_2NMe	24	16	95
3	1.0	1.0	(S_a,*S*,*S*)-Feringa ligand	TMG	24	61	94
4	1.0	1.0	(S_a,*S*,*S*)-Feringa ligand	LiO^{t}Bu	24	40	92
5	1.0	1.0	(S_a,*S*,*S*)-Feringa ligand	NaO^{t}Bu	24	33	93
6	1.0	1.0	(S_a,*S*,*S*)-Feringa ligand	KOMe	24	23	94
7	1.0	2.0	(S_a,*S*,*S*)-Feringa ligand	TMG	24	44	94
8	2.0	1.0	(S_a,*S*,*S*)-Feringa ligand	TMG	24	91	94
9	2.0	1.0	(*R*)-BINAP	TMG	24	trace	-
10	2.0	1.0	L1	TMG	24	trace	-
11	2.0	1.0	L2	TMG	24	trace	-
12	2.0	1.0	(S_a)-Carreira ligand	TMG	24	30	51
13	2.0	1.0	(S_a,*S*)-You ligand	TMG	10	99	-96
14[d]	2.0	1.0	(S_a,*S*)-You ligand	TMG	24	89	-94
15[e]	2.0	1.0	(R_a,*R*)-You ligand	TMG	10	99	95

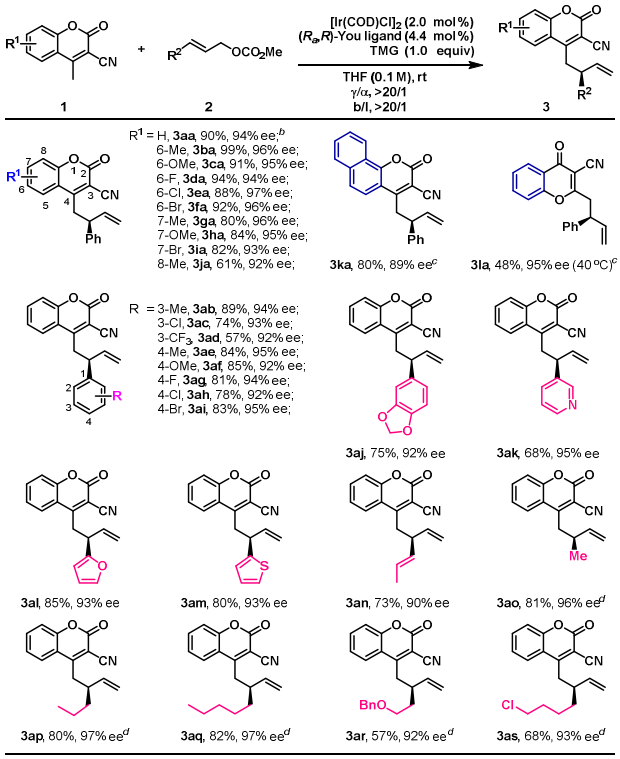
[a]**1a**: 0.10 mmol or **2a**: 0.10 mmol. THF: 1 mL. [b]Determined by ^{1}H NMR analysis of reaction crude mixture using mesitylene as an internal standard. [c]Determined by chiral-stationary-phase HPLC analysis. [d]1.0 mol % $[Ir(COD)Cl]_2$ and 2.2 mol % ligand employed. [e]2.0 mol % $[Ir(COD)Cl]_2$ and 4.4 mol % ligand employed. TMG = tetramethyl guanidine.



The reaction between coumarin **1a** and allyl methyl carbonate **2a** was studied as a model reaction (Table 1). Phosphoramidites, privileged chiral ligands in asymmetric catalysis,[16] were selected as the ligand in this iridium-catalyzed vinylogous allylic alkylation. Fortunately, in the presence of 5.0 mol % $[Ir(COD)Cl]_2$, 11.0 mol % (S_a,*S*,*S*)-Feringa ligand[16] and 1.0 equiv Et_3N, the reaction proceeded smoothly to afford γ-allyl coumarin **3aa** in excellent regioselectivity (γ/α, >20/1; branched/linear, >20/1) (entry 1). Although the yield was low, the enantioselectivity of **3aa** was satisfactory. Among other common organic bases, TMG outperformed to furnish **3aa** in 61% yield with 94% ee (entry 2-6). Increasing the amount of electrophilic **2a** was not helpful and the yield even decreased, possibly due to the double vinylogous allylic alkylation in the presence of 2 equiv **2a** (entry 7). Changing the ratio of **1a** to **2a** from 1/2 to 2/1 was proved to be effective to enhance the yield as the partial decomposition of **1a** was compensated by the excess amount of **1a** in reaction mixture (entry 8).

The classical bidentate phosphine ligand, (*R*)-BINAP, was proved to be unproductive (entry 9). Ligand **L1** and **L2**, possessing only axial chirality, were found to be not effective either (entry 10-11). Carreira ligand[17] was also investigated, affording the corresponding vinylogous allylic alkylation product **3aa** in 30% yield with 51% ee (entry 12). It was found that You ligand[18] was slightly superior to Feringa ligand in this reaction, leading to **3aa** in excellent yield with -96% ee (entry 13). The loading of $[Ir(COD)Cl]_2$ was successfully decreased to 1 mol % without compromising both yield and enantioselectivity (entry 14). (R_a,*R*)-You ligand resulted in the same yield and enantioselectivity excess for **3aa** as (S_a,*S*)-You ligand did (entry 15).

Table 2 Substrate Scope of Catalytic Asymmetric Vinylogous Allylic Alkylation of **1** and **2**[a]



[a]**1**: 0.40 mmol, **2**: 0.20 mmol. Isolated yield reported. Regioselectivities (γ/α and b/l) determined by ^{1}H NMR analysis of reaction crude mixture. Ee determined by chiral-stationary-phase HPLC analysis. [b]Gram-scale reaction performed. [c]4.0 mol % $[Ir(COD)Cl]_2$ and 8.8 mol % (R_a,*R*)-You ligand employed. [d]5.0 mol % $[Ir(COD)Cl]_2$ and 11.0 mol % (S_a,*S*,*S*)-Feringa ligand employed. TMG = tetramethyl guanidine.

Considering the easy manipulation and commercial availability of (R_a,*R*)-You ligand, 2 mol % $[Ir(COD)Cl]_2$ and 4.4 mol % (R_a,*R*)-You ligand were employed in the following substrate investigation (Table 2). The products (**3aa**-**3ja**) were isolated in good to high yields with uniformly excellent enantioselectivity. Furthermore, product **3ka** containing a naphthyl moiety was generated in good yield and high enantioselectivity. Interestingly, isocoumarin (**1l**) was successfully utilized as a vinylogous pronucleophile in the Ir-catalyzed asymmetric allylic alkylation for the first time, which afforded **3la** in 48% yield with 95% ee. The gram-scale reaction of **3aa** was successfully performed with constant yield and enantioselectivity. As for allyl methyl carbonates (**2b**-**2m**), a number of aryl groups with electron-rich or electron-deficient

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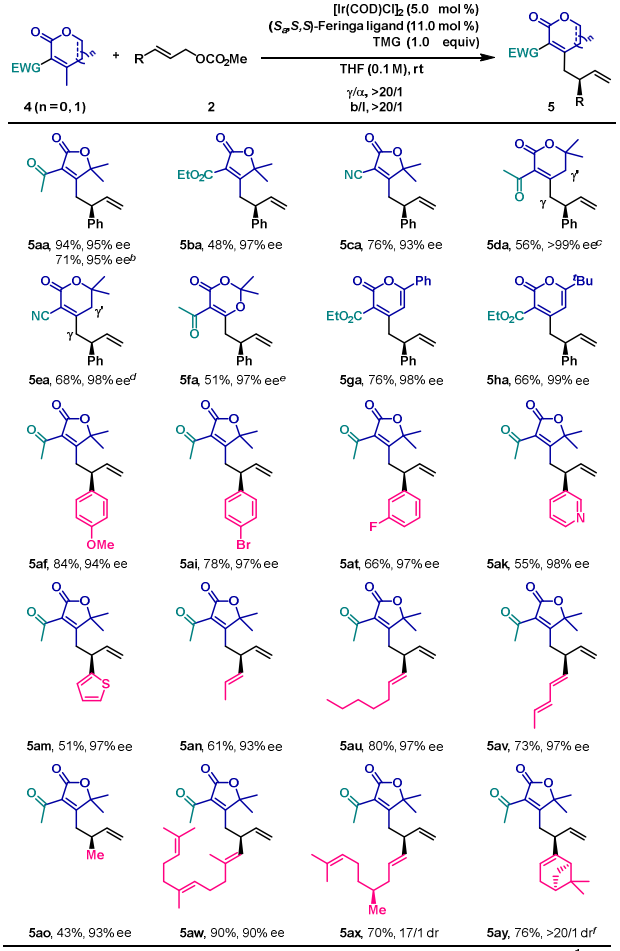
substituents, as well as heteroaromatic groups (3-pyridinyl, 2-furanyl and 2-thienyl), was accepted. The R^2 group was successfully extended to 2-methyl vinyl and alkyl substituents (including alkyls with functional groups, such as benzyloxy or chloride) (**3an**-**3as**). The absolute configuration of **3aa** was determined to be *S* by comparison of its optical rotation value with reported data (for details, see SI).[13] For other products, the absolute configurations were tentatively assigned by analogy.

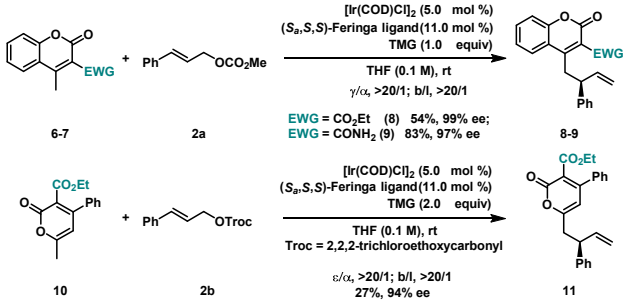
Table 3 Substrate Scope of Catalytic Asymmetric Vinylogous Allylic Alkylation of **4** and **2**[a]



[a]**4**: 1.0 mmol, **2**: 0.20 mmol. Isolated yield reported. Regioselectivities (γ/α and b/l) determined by ^{1}H NMR analysis of reaction crude mixture. Ee determined by chiral-stationary-phase HPLC analysis. [b](R_a,*R*)-You ligand employed. b/l = 12/1. [c]γ/α = 12/1. [d]γ/α = 11/1, b/l = >8/1. [e]35 ºC. **2** (0.05 M). [f]50 ºC. TMG = tetramethyl guanidine.

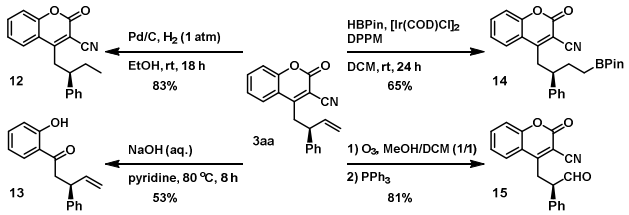
Due to Feringa ligand's superior performance, it was used for evaluation of the substrates without a fused benzene ring instead of You ligand (Table 3, **5aa**). α,β-Unsaturated 1,3-dicarbonyl compounds with a five-member ring and an exocyclic methyl group (**4a**-**4c**) were suitable substrates to undergo the vinylogous allylic alkylation in excellent regio- and enantioselectivity. α,β-Unsaturated 1,3-dicarbonyl compounds with a six-member ring and an exocyclic methyl group (**4d**-**4f**) were relatively less efficient as the products (**5da**-**5fa**) were isolated in moderate yields together with lower regioselectivity in the cases of **4d** and **4e**. Fortunately, no γ'-allylic alkylation was detected in the reactions of **4d** and **4e**. α,β,γ,δ-Unsaturated 1,3-dicarbonyl compounds (**4g** and **4h**) were also tolerated under the present reaction conditions. By using **4a** as the vinylogous pronucleophile, the substrate scope of allyl methyl carbonates was studied. As for R group, aryls (with electron-donating group or electron-withdrawing groups), heteroaryls, substituted vinyls, 1,3-dienyl and alkyl are acceptable substituents (**5af**, **5ai**, **5ak**, **5am**-**5ao** and **5at**-**5av**). More interestingly, complex allyl methyl carbonates generated from natural products (**2w** is derived from farnesal; **2x** is derived from (-)-citronellal; **2y** is derived from (-)-myrtenal; for details, see SI) were applicable in the present reaction protocol.

Scheme 2 Vinylogous Allylic Alkylation with **6** and **7** and Bisvinylogous Allylic Alkylation with **10**



Coumarins **6** and **7**, less efficient[12] or even unreactive[13] in reported asymmetric vinylogous reaction, reacted smoothly with allyl methyl carbonate **2a** to afford the products **8** and **9** in good yields with excellent stereoselectivity (Scheme 2). Moreover, a bisvinylogous allylic alkylation with allyl 2,2,2-trichloroethoxy carbonate (**2b**) was carried out in the present catalytic system (Scheme 2). To our joy, the corresponding product was obtained in 27 % yield with 94 % ee and excellent regioselectivity.

Scheme 3 Transformation of Vinylogous Allylic Alkylation Product **3aa**



The product **3aa** easily underwent transformations to generate functionalized molecules (Scheme 3). In the presence of catalytic Pd/C, a selective hydrogenation occurred to give **12** in 83% yield without touching the unsaturated carbon-carbon double bond. The basic hydrolysis of **3aa** provided chiral ketone **13** in 53% yield. The functionalization of terminal olefin with HBPin in the presence of catalytic iridium complex afforded chiral alkyl borate **14** in 65% yield. Ozonolysis of **3aa** proceeded smoothly to furnish chiral aldehyde **15** in 81% yield.

The present methodology was applied in the asymmetric synthesis of compound **17**, which was identified as an advanced key synthetic intermediate at Merck & Co. (Scheme 4).[19] Catalytic asymmetric vinylogous allylic alkylation of **4f** and **2t** proceeded nicely to afford **5ft** in 50% yield with 91% ee. The

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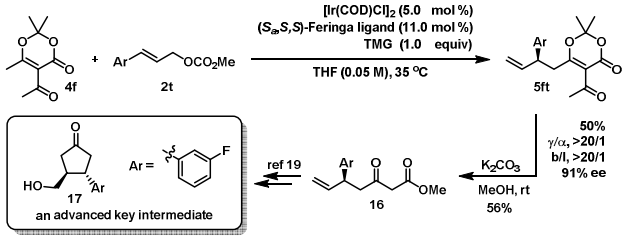
following one-step alcoholysis of **5ft** direct resulted in **16** in 56% yield. Then, by following the reported procedure,[19] the key intermediate **17** could be accessed.

Scheme 4 Application of the Present Methodology in Organic Synthesis



Conclusions

In summary, a highly regio- and enantioselective catalytic asymmetric vinylogous allylic alkylation was achieved by using α,β-unsaturated lactones bearing an electron-withdrawing group at α-position and an exocyclic methyl group at β-position (including coumarins). The present methodology was successfully applied in the asymmetric synthesis of an advanced synthetic intermediate, which was employed in the synthesis of an investigational new drug candidate. The further expansion of pronucleophile types in vinylogous reaction and application of the present methodology to complex natural product synthesis are underway.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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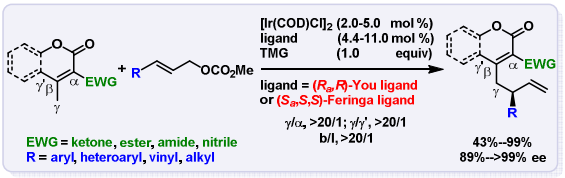

A catalytic asymmetric vinylogous allylic alkylation of α,β-unsaturated lactones with iridium catalyst was achieved with excellent regio- and enantioselectivity.