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Hydroxy-directed iridium-catalyzed enantioselective formal β -C(sp²)–H allylic alkylation of α,β -unsaturated carbonyls†

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Hydroxy-directed iridium-catalyzed enantioselective formal β -C(sp²)–H allylic alkylation of kojic acid and structurally related α,β -unsaturated carbonyl compounds is developed. This reaction, catalyzed by an Ir(i)/(P,olefin) complex, utilizes the nucleophilic character of α -hydroxy α,β -unsaturated carbonyls, to introduce an allyl group at its β -position in a branched-selective manner in good to excellent yield with uniformly high enantioselectivity (up to >99.9 : 0.1 er). To the best of our knowledge, this report represents the first example of the use of kojic acid in a transition metal catalyzed highly enantioselective transformation.

Introduction

Iridium-catalyzed asymmetric allylic substitution (AAS) reaction has been established as a reliable method for enantioselective construction of carbon–carbon and carbon–heteroatom bonds using various classes of nucleophiles.¹ In the realm of carbon-centered nucleophiles, both stabilized as well as unstabilized nucleophiles were successfully employed and led to several formal C(sp³)–H allylic alkylation (AA) reactions.² Ir-catalyzed enantioselective C(sp²)–H AA reactions, in contrast, are far less developed and confined primarily to electron-rich (hetero) aromatic C(sp²)–H bonds.³

The ability to selectively introduce an allyl group either at the α - or at the β -position of α,β -unsaturated carbonyl compounds while retaining the unsaturation marks a synthetic strategy having the potential to access a relatively less explored chemical space. Such C(sp²)–H allylic alkylation reactions are exceedingly rare.⁴ Although sporadically known since 2003,^{4a} we have recently developed the first enantioselective formal α -C(sp²)–H allylic alkylation under cooperative Lewis base (LB) and Ir-catalysis (Scheme 1A).^{4a} These α -selective allylic alkylation reactions of α,β -unsaturated carbonyl compounds were made possible due to their latent enolate character, which renders their α -position nucleophilic.⁵

The β -position of α,β -unsaturated carbonyls, on the other hand, is intrinsically electrophilic (Scheme 1A). Consequently, β -C(sp²)–H allylic alkylation of α,β -unsaturated carbonyls using

an electrophilic allyl fragment is challenging due to the inherent polarity mismatch and therefore remains elusive.⁶

With the aim of expanding the synthetic toolbox involving β -C(sp²)–H functionalization of α,β -unsaturated carbonyl compounds, we became interested in conceptual development of this intriguing transformation. We surmised that a suitably positioned and easily modifiable electronic directing group (X in Scheme 1B) within the core structure of α,β -unsaturated carbonyl might impart sufficient nucleophilicity at its β -position to allow for the introduction of an electrophilic fragment.

To this end, our initial thoughts revolved around α -hydroxy α,β -unsaturated carbonyls (X = OH, Scheme 1B) since the hydroxyl functionality, after serving its role as the electronic directing group, can be transformed into a leaving group, and engage in various cross-coupling reactions. The overall process would retain the unsaturation and represent a formal β -C(sp²)–H functionalization of α,β -unsaturated carbonyl compounds.

Our search for suitable α -hydroxy α,β -unsaturated carbonyl compounds led us to kojic acid (**1a**) – a naturally occurring chelating agent produced primarily by fungi (Scheme 1C).⁷ Due to its high bioavailability, encouraging toxicity profile as well as high metal binding affinity,⁸ this class of 3-hydroxy-4-pyrones found a wide range of medicinal applications.⁹

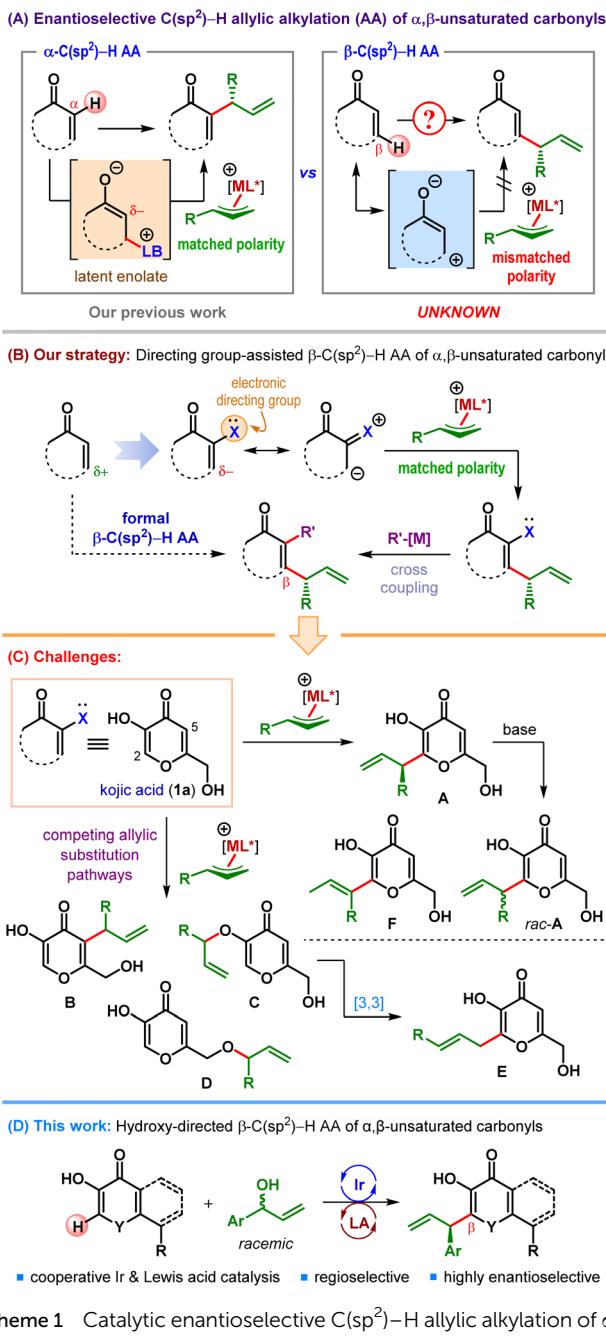
Despite its widespread prevalence and densely functionalized scaffold, catalytic enantioselective reactions involving kojic acid remain surprisingly underdeveloped.¹⁰ In 2010 Bode *et al.* reported an elegant enantioselective Coates–Claisen rearrangement of kojic acid derivatives catalyzed by N-heterocyclic carbenes.¹¹ Later on, Zlotin and Reddy groups independently disclosed kojic acid as a nucleophile in organocatalytic asymmetric Michael reactions with electrophilic partners such as nitroolefins and β,γ -unsaturated α -ketoesters.¹² Nonetheless, compared to these organocatalytic reactions, metal catalyzed

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Scheme 1 Catalytic enantioselective $\text{C}(\text{sp}^2)\text{-H}$ allylic alkylation of α,β -unsaturated carbonyls.

transformations of kojic acid are rare,¹³ let alone their enantioselective variants.¹⁴

A possible reason for this paucity is the presence of several Lewis basic functionalities in kojic acid, which can open up multiple reaction pathways apart from chelating the metal ions. For example, a reaction of unprotected kojic acid (**1a**) with an allylic electrophile can potentially result in two different allylic etherification products¹⁵ (**C** and **D**) and a C5-allylic alkylation product (**B**) apart from the desired C2-allylic alkylation product **A** (Scheme 1C). In fact, multiple allylic alkylation of kojic acid is also possible. The allylic ether **C** can subsequently undergo Claisen rearrangement^{13,14,16} to generate a linear C2-allylic

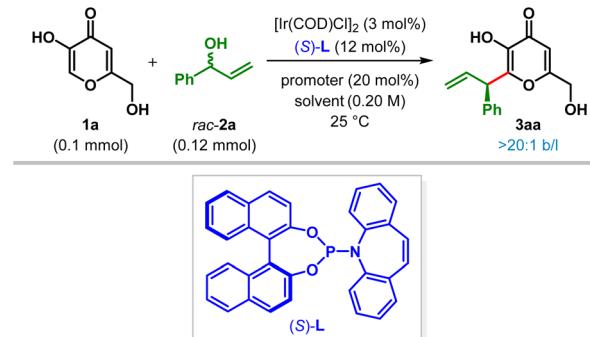
alkylation product **E**. The competing branched *vs.* linear selectivity in the allylic substitution step can further complicate the scenario. In addition, the adjacent α,β -unsaturated carbonyl functionality renders the proton present at the stereocenter in **A** reasonably acidic, which can cause racemization under basic conditions and even stereoablation through olefin isomerization to thermodynamically favored **F**. Therefore, a successful $\beta\text{-C}(\text{sp}^2)\text{-H}$ allylic alkylation of kojic acid necessitates the circumvention of all these competing pathways.

Herein, we present the results of a study which culminated in the first catalytic enantioselective $\beta\text{-C}(\text{sp}^2)\text{-H}$ allylic alkylation of kojic acid, its derivatives and structurally related α -hydroxy α,β -unsaturated carbonyl compounds (Scheme 1D).

Results and discussion

To address the challenges discussed above, we initially focused on finding reaction conditions which would allow for the access of C2-allylic kojic acid selectively. Our preliminary experiments were aimed on probing the effects of different combinations of substrates with ligands, promoters and solvents on the efficiency and selectivity of the reaction.¹⁷ Gratifyingly, in the presence of 3 mol% $[\text{Ir}(\text{COD})\text{Cl}]_2$ and 12 mol% Carreira's (*P*-olefin) ligand (*S*)-**L**^{1c} along with 20 mol% $\text{Zn}(\text{OTf})_2$ as the Lewis acidic promoter in THF at 25 °C, the desired C2-allylic alkylation of kojic acid **1a** took place using branched allylic alcohol *rac*-**2a** as the electrophilic partner (Table 1). Under these

Table 1 Optimization of reaction parameters



Entry	Promoter	Solvent	<i>t</i> [h]	Yield ^a [%]	er ^b
1	$\text{Zn}(\text{OTf})_2$	THF	48	50 ^c	99.8 : 0.2
2 ^d	$\text{Zn}(\text{OTf})_2$	THF	24	54	99.9 : 0.1
3	$\text{Fe}(\text{OTf})_2$	THF	24	81 ^c	99.9 : 0.1
4	$\text{Sc}(\text{OTf})_3$	THF	36	62	99.9 : 0.1
5	$\text{Fe}(\text{OTf})_2$	2-Me THF	24	72 ^c	99.9 : 0.1
6	$\text{Fe}(\text{OTf})_2$	Toluene	24	50 ^c	>99.5 : 0.5
7	$\text{Fe}(\text{OTf})_2$	Acetone	24	75	99.9 : 0.1
8 ^e	$\text{Fe}(\text{OTf})_2$	THF	22	91 ^c	99.9 : 0.1

^a Yields were determined by ^1H -NMR spectroscopy with mesitylene as an internal standard. ^b Enantiomeric ratio (er) of the desired product was determined by HPLC analysis on a chiral stationary phase. ^c Yield corresponds to the isolated product after chromatographic purification. ^d Reaction at 50 °C. ^e Reaction on a 0.2 mmol scale with 1 : 1.5 ratio of **1a** and **2a**.



conditions, β -C(sp²)-H allylic kójic acid **3aa** was isolated in 50% yield after 48 h with 99.8 : 0.2 er (entry 1). We were pleased to find that neither any of the allylic etherification products (**C** and **D**, Scheme 1C) nor the C5-allylic alkylation product **B** could be detected and **3aa** was isolated exclusively as a single regioisomer (>20 : 1 b/l). Despite rate enhancement, no significant improvement in yield was observed when the reaction was carried out at an elevated temperature (entry 2). Switching the promoter to Fe(OTf)₂ led to an increase in reaction rate and yield while retaining the enantioselectivity (entry 3). The use of other Lewis acidic promoters and solvents proved deleterious to the yield of this reaction (entries 4–7). As expected, no reaction took place in the absence of a Lewis acid promoter.¹⁷ Increasing the amount of allylic electrophile **2a** turned out to be beneficial, and a 1 : 1.5 ratio of **1a** and **2a** proved to be the best, furnishing **3aa** essentially as a single enantiomer in 91% yield (entry 8).

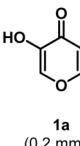
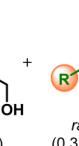
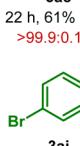
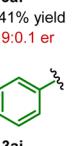
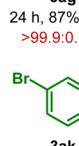
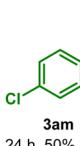
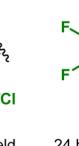
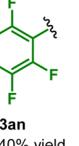
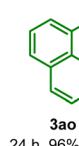
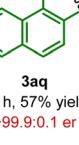
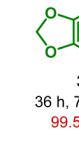
Having optimized the catalyst, promoter and the other reaction parameters (Table 1, entry 8), we assessed the generality of this hydroxy-directed β -C(sp²)-H allylic alkylation of α , β -

unsaturated carbonyl compounds. These conditions were found to be suitable for a variety of branched allylic alcohols **2**. As shown in Table 2, allylic alcohols (**2b**–**2s**) bearing both electron-rich as well as electron-deficient aryl substituents were tolerated and delivered the products (**3ab**–**3as**) in moderate to excellent yield with uniformly high enantioselectivity. Allylic alcohols with electron-rich aryl substituents generally resulted in the products with higher yield compared to those having electron-deficient aryl groups. Highly electron deficient *p*-cyanophenyl and pentafluorophenyl substituted allylic alcohols (**2f** and **2n**, respectively) adversely affected the yield of the reaction. Similarly, *ortho*-substituents on the aryl ring of allylic alcohols resulted in the products (**3al**, **3am**, **3an** and **3aq**) with only diminished yield, even though outstanding enantioselectivity was retained in each of these cases.

Heterocyclic substituents such as dioxolane and thiophene could also be introduced into the product under our standard reaction conditions with moderate to good yield and excellent enantioselectivity (**3ar**–**3as**). In all cases, the products were obtained exclusively as a branched isomer. No competing side reaction (cf. Scheme 1C) was detected in any of these cases. Unfortunately, alkyl substituted allylic alcohols failed to participate in this allylic alkylation reaction and remained as a limitation of our protocol.¹⁷

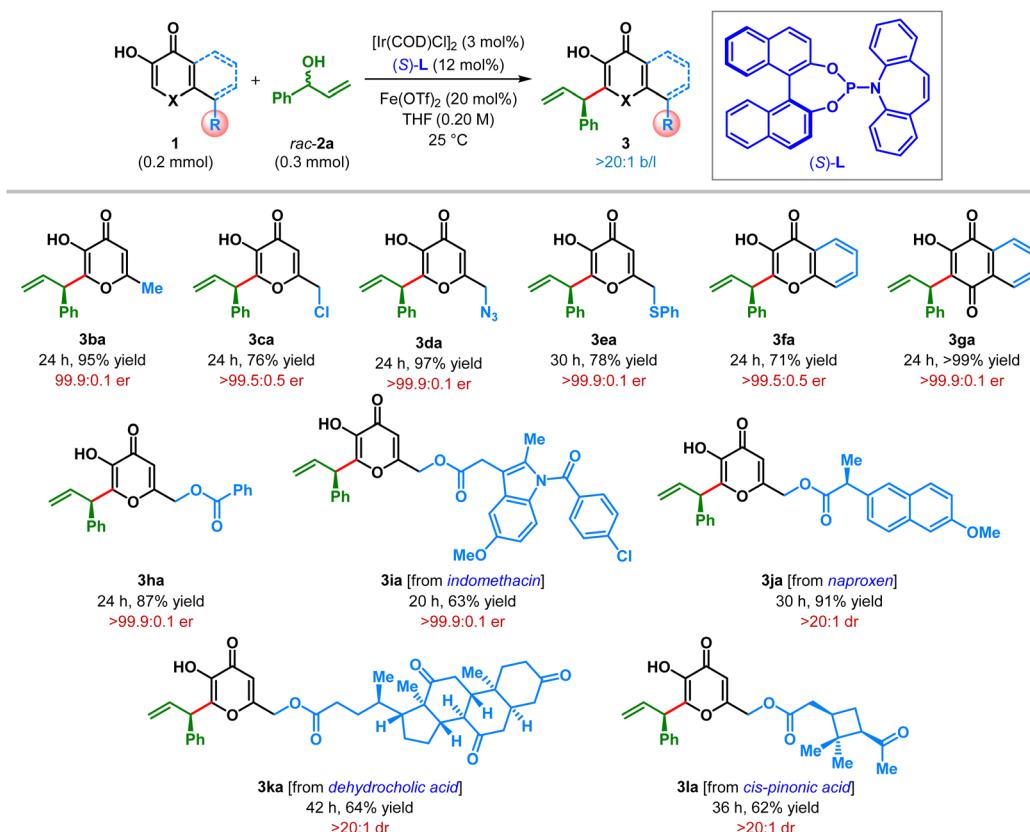
After demonstrating the generality and limitations of allylic electrophile, we set out to explore the scope of nucleophile in this enantioselective AA reaction. Accordingly, a number of kójic acid derivatives and structurally related α -hydroxy α , β -unsaturated carbonyl compounds were tested. We were pleased to find that kójic acid derivatives bearing a variety of substituents at the C6 position underwent facile allylic alkylation under our optimized reaction conditions (Table 3). For example, maltol (**1b**), devoid of a hydroxyl group, furnished the desired product **3ba** in excellent yield with 99.9 : 0.1 er. To showcase the functional group tolerance of this protocol, the hydroxyl unit of the hydroxymethyl group at the C6 position of kójic acid was replaced with other functionalities. These examples include chloro (**1c**), azide (**1d**), thiophenol (**1e**) and benzoyl ester (**1h**), all of which were found to be competent substrates in this reaction and underwent highly enantioselective allylic alkylation. These products (**3da**, **3ea** and **3ha**) contain synthetically relevant functional groups, which can serve as handles for further manipulation (see below). Allylic alkylation of structurally related α -hydroxy α , β -unsaturated carbonyl compounds such as 3-hydroxy chromone (**1f**) and 2-hydroxy naphthoquinone (**1g**) also proceeded without any difficulty, affording the products (**3fa**–**ga**) with excellent enantioselectivities. The success of the benzoyl-protected kójic acid (**1h**) in this reaction opened the possibility of tagging biologically relevant compounds to our products, for testing further functional group tolerance and stereochemical outcome. Consequently, the C6-hydroxymethyl group of kójic acid was acylated with pharmaceuticals such as indomethacin, naproxen, dehydrocholic acid and *cis*-pinonic acid. All these kójic acid derivatives (**1i**–**l**) were found to be suitable substrates in this AA reaction and furnished the corresponding products (**3ia**–**la**) in good to excellent yields with outstanding stereoselectivities, while retaining the existing

Table 2 Scope of allylic alcohols in enantioselective β -C(sp²)-H allylic alkylation of kójic acid^a

		<chem>[Ir(COD)Cl]2 (3 mol%)</chem>	<chem>(S)-L (12 mol%)</chem>	
		<chem>Fe(OTf)2 (20 mol%)</chem>		
		THF (0.20 M)		
				25 °C
1a (0.2 mmol)	rac-2 (0.3 mmol)			
				>20:1 b/l
				
3aa 22 h, 91% yield 99.9:0.1 er	3ab 24 h, 93% yield >99.9:0.1 er	3ac 20 h, 93% yield >99.9:0.1 er	3ad 22 h, 71% yield 99.5:0.5 er	
				
3ae 22 h, 61% yield >99.9:0.1 er	3af 24 h, 41% yield >99.9:0.1 er	3ag 24 h, 87% yield >99.9:0.1 er	3ah 24 h, 87% yield >99.9:0.1 er	
				
3ai 36 h, 87% yield 98.5:1.5 er	3aj 24 h, 92% yield >99.9:0.1 er	3ak 24 h, 80% yield >99.9:0.1 er	3al 24 h, 55% yield >99.9:0.1 er	
				
3am 24 h, 50% yield >99.9:0.1 er	3an 24 h, 40% yield >99.9:0.1 er	3ao 24 h, 96% yield >99.9:0.1 er	3ap 24 h, 94% yield >99.9:0.1 er	
				
3aq 30 h, 57% yield >99.9:0.1 er	3ar 36 h, 76% yield 99.5:0.5 er	3as 24 h, 66% yield 99:1 er		

^a Yields correspond to the isolated product after chromatographic purification. Enantiomeric ratios (er) were determined by HPLC analysis on a chiral stationary phase.



Table 3 Scope of α,β -unsaturated carbonyls in enantioselective β -C(sp²)-H allylic alkylation^a

^a Yields correspond to the isolated product after chromatographic purification. Enantiomeric ratios (er) were determined by HPLC analysis on a chiral stationary phase. Diastereomeric ratios (dr) were determined by ¹H NMR analysis of the crude reaction mixtures.

functionalities and the molecular complexity. The existing stereocenters in these substrates (**1j–l**) did not exert any influence on the stereochemical outcome as these reactions were found to be completely catalyst controlled.

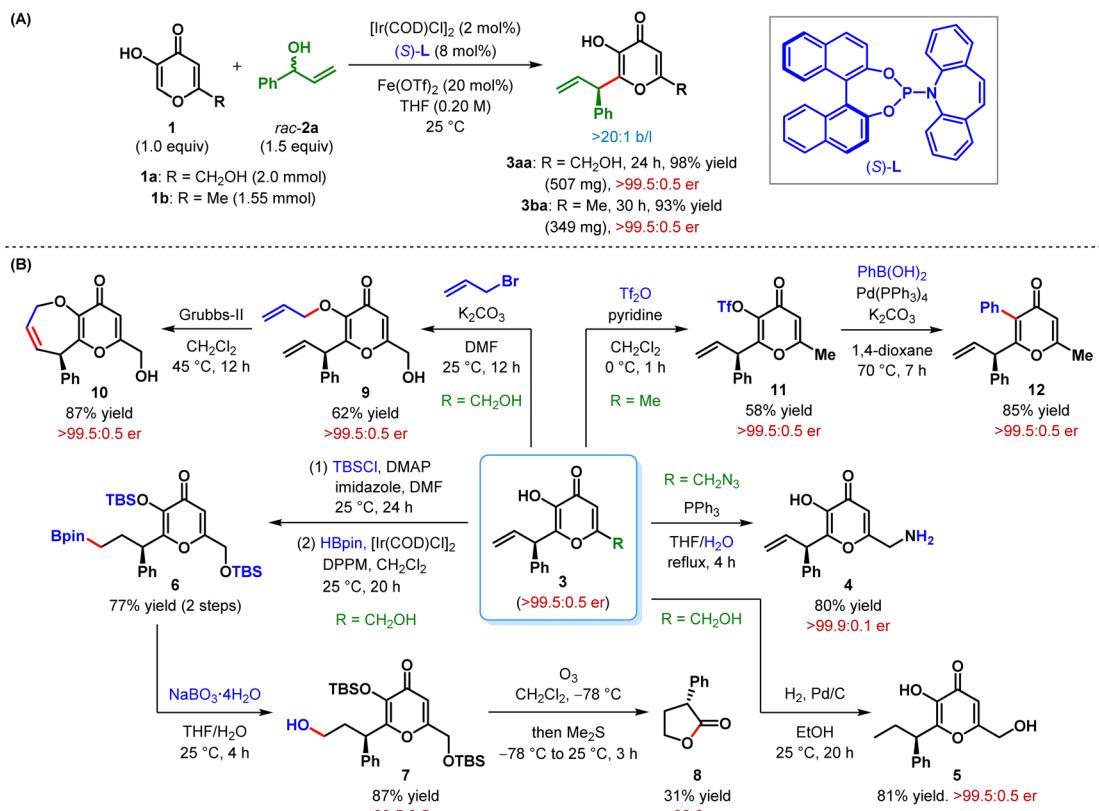
The scalability of our protocol was displayed by larger scale experiments on kojic acid (**1a**) and maltol (**1b**) (Scheme 2A). Using a slightly lower catalyst loading, these reactions, with **2a** as the allylic electrophile, furnished the products (**3aa–ba**) in somewhat improved yield without any erosion in enantioselectivity.

The prospective potential of this β -C(sp²)-H AA reaction was further illustrated by successful elaboration of some of these intricately functionalized β -allyl 3-hydroxypyranone derivatives (Scheme 2B). For example, Staudinger reduction of **3da** delivered the corresponding kojic amine derivative **4** in 80% yield. Notably, kojic amine is known as a novel γ -aminobutyric acid analogue and exhibits skeletal muscle relaxant as well as anti-nociceptive activities.¹⁸ Selective hydrogenation of the terminal olefin in **3aa** with palladium on carbon afforded **5**, featuring an aliphatic side chain, in 81% yield. Although the Ir-catalyzed hydroboration¹⁹ of the terminal olefin could not be performed directly on **3aa**, the reaction proceeded smoothly on the double-TBS-protected **3aa** to furnish the alkyl boronate **6** in 77% yield over two steps. Oxidation of **6** under sodium perborate resulted

in an overall anti-Markovnikov hydration product **7** in 87% yield. The alcohol **7**, when exposed to ozonolytic conditions, furnished 3-phenyldihydrofuranone **8** via oxidative cleavage of the pyranone ring and cyclization. Notwithstanding the poor yield of butanolide **8** and slight erosion of its enantiopurity during the ozonolysis step, its formation helped us to determine the absolute configuration of the allylic alkylation product **3aa** in retrospect, as the enantioselective synthesis of **8** was previously reported by MacMillan *et al.*²⁰ The absolute stereochemistry of the other products (**3**), shown in Tables 2 and 3, were inferred as the same by analogy.

The enolic hydroxy group of **3aa** could be selectively alkylated with allyl bromide to produce the *O*-allyl kojic acid derivative **9** in 62% yield. Ring-closing metathesis of this diallyl derivative under Grubbs-II furnished chiral dihydropyrano-oxepinone derivative **10** in high yield without any loss of its stereochemical integrity. Upon treatment with triflic anhydride, **3ba** was converted to enol triflate **11** in moderate yield. This triflate derivative **11** was then successfully subjected to Pd-catalyzed Suzuki cross-coupling with phenyl boronic acid to obtain α -phenyl β -allyl pyranone derivative **12** in high yield while maintaining the er. The overall process represents a formal β -C(sp²)-H allylic alkylation of a pyranone derivative, which is inherently electrophilic at its β -position. Introduction of other (herero)aryl,





Scheme 2 (A) Scale-up experiments and (B) synthetic elaborations of β -allyl 3-hydroxypyranone derivatives.



Scheme 3 Control experiment with α -methoxy kojic acid.

alkenyl, alkynyl and even alkyl substituents at the α -position by cross-coupling of triflate such as **11** is in principle possible.²¹

We have conducted a control experiment to ascertain the role of the α -hydroxy group in this regioselective allylic alkylation reaction. Thus, α -methoxy kojic acid **13**, when subjected to our standard reaction conditions, failed to deliver the desired C2-allylic alkylation product, even at 50 °C (Scheme 3). No allylic etherification product, arising out of the reaction of C6-hydroxymethyl group with electrophilic π -allyl-Ir complex, could be detected either under these conditions.

The outcome of this experiment clearly highlights the importance of α -hydroxyl in α,β -unsaturated carbonyl compounds as the electronic directing group in driving this enantioselective allylic alkylation reaction.

Conclusions

In conclusion, we have developed the first asymmetric allylic alkylation of kojic acid and structurally related α -hydroxy α,β -

unsaturated carbonyl compounds. This hydroxy-directed AA reaction is catalyzed by an *in situ* generated Ir(I)/(P,olefin) complex and employs Fe(OTf)₂ as the Lewis acid co-catalyst to activate easily accessible racemic branched allylic alcohols, which are used as the allylic electrophile. The resulting β -allyl 3-hydroxypyranone derivatives, even adorned with pharmaceutically important structural motifs, are generally obtained in good to excellent yield with outstanding enantioselectivity. These enantioenriched kojic acid derivatives, as demonstrated with various transformations, can serve as useful building blocks in organic synthesis. The α -hydroxy group in the AA product is transformed into a phenyl group and the overall process represents the first formal β -C(sp²)-H allylic alkylation of α,β -unsaturated carbonyl compounds. To the best of our knowledge, this report represents the first example of the use of kojic acid in a transition metal catalyzed highly enantioselective transformation. Considering the ubiquity of kojic acid in pharmaceuticals, we believe our protocol will find useful applications.

Data availability

The experimental details, characterization data, NMR spectra, and HPLC chromatograms associated with this article are provided in the ESI.†

Author contributions

S. M. conceived the project and R. S. initiated the optimization studies. S. M. conducted the experiments. A. C. helped with the optimization studies and a part of the substrate scope. S. M. and S. M. wrote the manuscript together with the inputs from A. C. and R. S. All authors have given the approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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