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Diastereo- and Enantioselective Iridium Catalyzed Carbonyl (α -Cyclopropyl)allylation *via* Transfer Hydrogenation**

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Graphical Abstract

Alcohol Solves Problems: Chiral iridium catalysts modified by (*R*)-SEPHOS catalyze the transfer hydrogenative coupling of racemic α -cyclopropyl allyl acetate with diverse primary alcohols with good *anti*-diastereo- and exceptional enantioselectivity. These processes represent the first diastereo- and enantioselective carbonyl (α -cyclopropyl)allylations.

Keywords

Iridium; Cyclopropane; Transfer Hydrogenation; Enantioselective Catalysis; Green Chemistry

Introduction

Due to its relatively high metabolic stability with respect to oxidation and unique geometrical features, the cyclopropane ring has emerged as an important structural motif in human medicines, agrochemicals and fragrance ingredients (Figure 1).^[1,2] Cyclopropanes are ubiquitous in nature^[3] and owing to the energetic driving force associated with the release of ring strain they also serve as important functional groups in chemical synthesis, including enantioselective processes.^[4] Consequently, efforts toward the development of asymmetric methods that create or introduce the cyclopropane ring are longstanding, and encompass some of the earliest examples of enantioselective catalysis.^[5,6] Despite increasing interest in cyclopropane chemistry^[1–5] and longstanding capabilities *vis-à-vis*

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carbonyl allylation^[7] there are no examples of catalytic enantioselective allylative methods for the delivery of cyclopropanes rings.^[8] Studies in our laboratory on the catalytic redox-triggered C–C coupling of primary alcohols^[9] and allylic carboxylates suggest that α -cyclopropyl allyl acetate might serve as a reagent for diastereo- and enantioselective carbonyl (α -cyclopropyl)allylation,^[9–11] however, the feasibility of such a process was uncertain due to the potential lability of (α -cyclopropyl)allyliridium intermediates with respect to fragmentation of the cyclopropanes ring.^[12,13] Here, we report that chiral cyclometalated iridium *C,O*-benzoate complex modified by (*R*)-SEGPHOS, (*R*)-Ir-**I**, catalyzes the direct, redox triggered C–C coupling of primary alcohols with α -cyclopropyl allyl acetate to form products of carbonyl (α -cyclopropyl)allylation with excellent control of *anti*-diastereo- and enantioselectivity.

Results and Discussion

In an initial set of experiments, the *ortho*-cyclometalated π -allyliridium complexes (*R*)-Ir-**I**, (*R*)-Ir-**II**, and (*R*)-Ir-**III**, which are modified by (*R*)-SEGPHOS, (*R*)-BINAP and (*R*)-Cl,MeO-BIPHEP, respectively, were assayed for their ability to catalyze the coupling of α -cyclopropyl allyl acetate **3** with benzyl alcohol **1a** (Table 1, entries 1–3). Moderate isolated yields of the desired homoallylic alcohol **4a** were obtained and, in the case of the SEGPHOS modified catalyst (*R*)-Ir-**I**, promising levels of enantioselectivity were evident (Table 1, entry 1). Further experiments revealed higher levels of *anti*-diastereoselectivity are achieved at lower concentration (0.5 M THF) (Table 1, entries 4–5). Improvements in both diastereo- and enantioselectivity were observed for reactions conducted at successively lower temperatures (Table 1, entries 6–8). Thus, at 45 °C in THF (0.5 M), α -cyclopropyl allyl acetate **3** reacts with benzyl alcohol **1a** to deliver the homoallylic alcohol **4a** in 75% yield as a 6.3:1 (*anti*:*syn*) mixture of diastereomers with a 99% enantiomeric excess (Table 1, entry 8).

To assess scope, these optimal conditions were applied to primary alcohols **1a–1j** (Table 2). Benzylic alcohols **1a–1e** undergo carbonyl (α -cyclopropyl)allylation to provide the respective homoallylic alcohols **4a–4e** with good levels of *anti*-diastereoselectivity and uniformly high levels of enantioselectivity. As illustrated in the reaction of **1e**, which incorporates a 2-(6-bromo-pyridyl) substituent, *N*-heterocycles bearing activated halides are tolerated. Conversion of the allylic alcohols geraniol (**1f**) and cinnamyl alcohol (**1g**) to adducts **4f** and **4g** occurred in the absence of internal redox isomerization^[14] in a stereoselective fashion. Finally, aliphatic primary alcohols **1h–1j** were transformed to the secondary alcohols **4h–4j** with good control of *anti*-diastereo- and enantioselectivity. The stereochemical assignment of adducts **4a–4j** is supported by single crystal X-ray diffraction analysis of a derivative of compound **4b** (see Supporting Information). In an analogous set of transformations, the reductive coupling of α -cyclopropyl allyl acetate **3** with aldehydes **2a–2j** was performed using 2-propanol (200 mol%) as terminal reductant under conditions otherwise identical to those employed in the coupling of alcohols **1a–1j** (Table 3). An equivalent set of adducts **4a–4j** were obtained, however, the reactions of aldehydes were typically more rapid than those conducted from the alcohol oxidation level (12 h vs. 48 h) and displayed uniformly higher levels of *anti*-diastereoselectivity.

These results can be understood on the basis of the catalytic mechanism previously proposed for redox-triggered carbonyl crotylation (Scheme 1).^[11a] Due to allylic strain, ionization of α -cyclopropyl allyl acetate **3** occurs with a kinetic preference for formation of the (*E*)- σ -allyliridium haptomer (*E*)-**B**. Capture of the kinetic (*E*)- σ -allyliridium haptomer (*E*)-**B** via turnover limiting carbonyl addition occurs in a stereospecific manner to form the *anti*-diastereomer. This event competes with isomerization to form the (*Z*)- σ -allyliridium haptomer (not shown), which reacts stereospecifically to deliver the *syn*-diastereomer. At the onset of reactions involving aldehydes **2a–2j**, one full equivalent of aldehyde is present, which accelerates capture of the kinetic (*E*)- σ -allyliridium intermediate. In reactions of alcohols **1a–1j**, aldehydes are generated *pairwise* with the kinetic (*E*)- σ -allyliridium intermediate. With less aldehyde present, turn-over limiting carbonyl addition is slower in reactions conducted from the alcohol oxidation level and isomerization to the (*Z*)- σ -allyliridium intermediate can compete more effectively. Thus, diastereoselectivities are higher in reactions of aldehydes **2a–2j** compared to alcohols **1a–1j** as capture of the kinetic (*E*)- σ -allyliridium intermediate is faster.

The utility of this methodology is illustrated by the conversion of adduct **4j**, derived from *N*-Boc-aminopropanol **1j**, to the 4,5-disubstituted piperidine **7**.^[15] The homoallyl alcohol **4j** was subjected to ozonolysis followed by reductive workup with NaBH₄ to provide 1,3-diol **5** in 76% yield. Selective tosylation of the primary hydroxyl moiety of diol **5** furnished the mono-tosylate **6** in 91% yield. Finally, cleavage of *N*-Boc protecting group to deliver the free amine enabled intramolecular S_N2 substitution to form the piperidine ring.^[16] The *N*-Boc moiety was reintroduced to facilitate isolation (Scheme 4)

Conclusion

To summarize, we report the first examples of diastereo- and enantioselective carbonyl α -(cyclopropyl)allylation. Under the conditions of iridium catalyzed transfer hydrogenation using the chiral precatalyst (*R*)-Ir-**I** modified by SEGPHOS, carbonyl α -(cyclopropyl)allylation may be achieved with equal facility from alcohol and aldehyde oxidation levels. This methodology provides a conduit to hitherto inaccessible cyclopropane-containing architectures. The utility of this methodology is highlighted by the conversion of *N*-Boc-aminopropanol **1j** to the 4,5-disubstituted piperidine **7**. Future studies will focus on applying the concept of redox-triggered carbonyl addition to the couplings of alcohols with simple alkyl halides – a true union of the chemistry of Grignard and Sabatier.

Experimental Section

Representative procedure for iridium catalyzed diol C-allylation

Representative procedure for iridium-catalyzed α -(cyclopropyl)allylation of benzyl alcohol (1a**)**—A pressure tube equipped with a magnetic stir bar was charged with K₃PO₄ (42.5 mg, 0.20 mmol, 100 mol%) and (*R*)-Ir-preformed catalyst (*R*)-Ir-**I** (10.3 mg, 0.010 mmol, 5 mol%). The reaction vessel was placed under an atmosphere of argon, and water (18 μ L, 500 mol%), THF (0.40 mL, 0.5 M), benzyl alcohol (**1a**, 21.6 mg, 0.200 mmol, 100 mol%), and α -cyclopropyl allyl acetate (**3**, 56.1 mg, 0.40 mmol, 200 mol%) were added by syringe. The reaction vessel was sealed, and the reaction mixture was stirred at 45 °C for

48 h. The reaction was allowed to cool to ambient temperature, and volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO₂: hexanes:ethyl acetate = 9:1) to furnish (1*R*,2*S*)-2-cyclopropyl-1-phenylbut-3-en-1-ol (**4a**) as a colorless oil in 75% yield with 99% ee for major diastereomer (28.1 mg, 0.149 mmol, *anti:syn* = 6.7:1).

Representative procedure for iridium-catalyzed α -(cyclopropyl)allylation of benzaldehyde (2a**)**—A pressure tube equipped with a magnetic stir bar was charged with K₃PO₄ (42.5 mg, 0.20 mmol, 100 mol%) and (*R*)-Ir-preformed catalyst (*R*)-Ir-**I** (10.3 mg, 0.010 mmol, 5 mol%). The reaction vessel was placed under an atmosphere of argon, and water (18 μ L, 500 mol%), THF (0.40 mL, 0.5 M), benzaldehyde (**2a**, 21.2 mg, 0.20 mmol, 100 mol%), α -cyclopropyl allyl acetate (**3**, 56.1 mg, 0.40 mmol, 200 mol%), and 2-PrOH (31 μ L, 200 mol%) were added by syringe. The reaction vessel was sealed, and the reaction mixture was stirred at 45 °C for 12 h. The reaction was allowed to cool to ambient temperature, and volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO₂: hexanes:ethyl acetate = 9:1) to furnish (1*R*,2*S*)-2-cyclopropyl-1-phenylbut-3-en-1-ol (**4a**) in 85% yield with 99% ee for major diastereomer (32.0 mg, 0.170 mmol, *anti:syn* = 17:1).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Cyclopropanes in human medicine, agrochemistry and the fragrance industry.

Scheme 1.
General catalytic mechanism for redox-triggered α -(cyclopropyl)allylation.

Scheme 2.

Synthesis of 4,5-disubstituted piperidine 7.^a

^aCited yields are of material isolated by silica gel chromatography. See supporting information for further experimental details.

Table 1
Selected optimization experiments in the iridium catalyzed (α -cyclopropyl)allylation of benzyl alcohol **1a**.^a

Entry	[Ir]	T (°C)	[THF]	Yield 4a	dr	ee ^b %
1	(<i>R</i>)-Ir-I	90	1 M	63%	2.6:1	87
2	(<i>R</i>)-Ir-II	90	1 M	34%	1.5:1	76
3	(<i>R</i>)-Ir-III	90	1 M	55%	1.2:1	77
4	(<i>R</i>)-Ir-I	90	2 M	64%	2.3:1	85
5	(<i>R</i>)-Ir-I	90	0.5 M	61%	3.4:1	84
6	(<i>R</i>)-Ir-I	70	0.5 M	77%	3.8:1	93
7	(<i>R</i>)-Ir-I	50	0.5 M	73%	5.3:1	97
$\Rightarrow$ 8	(<i>R</i>)-Ir-I	45	0.5 M	75%	6.3:1	99

(<i>R</i>)-Ir-I	(<i>R</i>)-Ir-II	(<i>R</i>)-Ir-III

^a Cited yields are of material isolated by silica gel chromatography. Diastereomeric ratios were determined by ¹H NMR analysis of crude reaction mixtures, and enantioselectivities were determined by chiral stationary phase HPLC analysis. See supporting information for further experimental details.

Table 2Diastereo- and enantioselective iridium catalyzed (α -cyclopropyl)allylation of alcohols **1a–1j**.^a

Entry	Product	Yield, ee, d.r.
1	4a	75%, 99%, 6.3:1
2	4b	87%, 98%, 7.4:1
3 ^b	4c	83%, 97%, 6.7:1
4	4d	71%, 99%, 10:1
5 ^b	4e	58%, 96%, 7.7:1
6 ^c	4f	72%, 96%, 7.7:1
7	4g	73%, 97%, 6.7:1
8 ^c	4h	71%, 98%, 6.1:1

Entry	Product	Yield, ee, d.r.
9 ^b		87%, 99%, 4.8:1
10 ^b		62%, 98%, 6.7:1

^a Cited yields are of material isolated by silica gel chromatography. Diastereomeric ratios were determined by ¹H NMR analysis of crude reaction mixtures. Enantioselectivities were determined by chiral stationary phase HPLC analysis.

^b 60 °C.

^c 72 h.

See supporting information for further experimental details.

Table 3Diastereo- and enantioselective iridium catalyzed (α -cyclopropyl)allylation of aldehydes **2a–2j**.^a

Entry	Product	Yield, ee, d.r.
1	4a	76%, 99%, 17:1
2	4b	86%, 99%, >20:1
3 ^b	4c	61%, 99%, 18:1
4	4d	78%, 99%, >20:1
5 ^b	4e	73%, 98%, >20:1
6	4f	79%, 96%, 10:1
7	4g	73%, 99%, 12:1
8	4h	57%, 99%, 9.1:1

Entry	Product	Yield, ee, d.r.
9		59%, 99%, 12:1
10		41%, 99%, 17:1

^a Cited yields are of material isolated by silica gel chromatography. Diastereomeric ratios were determined by ¹H NMR analysis of crude reaction mixtures. Enantioselectivities were determined by chiral stationary phase HPLC analysis.

^b 60 °C.

See supporting information for further experimental details.