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Selection between Diastereomeric Kinetic vs Thermodynamic Carbonyl Binding Modes Enables Enantioselective Iridium-Catalyzed *anti*-(α -Aryl)allylation of Aqueous Fluoral Hydrate and Difluoroacetaldehyde Ethyl Hemiacetal

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Abstract

Enantioselectivity increases with increasing carbonyl electrophilicity in 2-propanol-mediated reductive couplings of aldehydes with branched aryl-substituted allylic acetates to form products of carbonyl *anti*-(α -aryl)allylation. This unusual phenomenon is caused by aldehyde coordination to diastereomeric kinetic *vs* thermodynamic carbonyl binding sites that deliver enantiomeric products. Exploiting this effect, *anti*-diastereo- and enantioselective (α -aryl)allylations of fluoral hydrate and difluoroacetaldehyde ethyl hemiacetal were developed.

Graphical Abstract

In the course of exploring alcohol-mediated carbonyl reductive couplings, our laboratory has developed a broad suite of catalytic enantioselective allylations and propargylations.¹ Whereas uniformly high levels of diastereo- and enantioselectivity are observed across diverse reactions of this type,^{1,2} for branched *aryl-substituted* allylic acetate pronucleophiles, enantioselectivities were highly variable: while high levels of asymmetric induction were observed in 2-propanol-mediated reductive couplings of paraformaldehyde,³ enantioselectivities in additions to higher aldehydes were found to increase with increasing carbonyl electrophilicity - *spanning a range of 1 to 94% ee*. An investigation into this intriguing effect was undertaken and has led to two major outcomes: (a) a novel mechanism

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds (¹H NMR, ¹³C NMR, IR, HRMS), including images of NMR spectra. HPLC traces of racemic and enantiomerically enriched products. Crystallographic data for compounds **4l** and **5l**. This material is available free of charge *via* the internet at <http://pubs.acs.org>

for enantioinduction was uncovered wherein aldehyde coordination to diastereomeric kinetic *vs* thermodynamic binding sites of the iridium catalyst results in formation of enantiomeric products, and (b) the development of catalytic enantioselective *anti*-(α -aryl)allylations of aqueous fluoral and difluoroacetaldehyde ethyl hemiacetal.

Only isolated examples of enantioselective carbonyl (α -aryl)allylation appear in the literature, which involve stoichiometric chirality transfer from auxiliaries.⁴ Notwithstanding a single report of asymmetric Sakurai-type allylations of glyoxamides,^{5e} no systematic studies of catalytic enantioselective carbonyl (α -aryl)allylation exist and, for the isolated examples that have been described, modest levels of asymmetric induction are typically observed.⁵ Catalytic enantioselective (α -aryl)allylations of fluoral and difluoroacetaldehyde are unknown and, despite the importance of fluorinated substructures in pharmaceutical and agrochemical ingredients,⁶ nearly all related enantioselective metal-catalyzed fluoral additions require anhydrous conditions or conditions involving *in situ* generation of gaseous fluoral.⁶ⁱ Finally, although difluoromethyl groups are unique in their ability to serve as lipophilic hydrogen-bond donors,⁷ there is a surprising paucity of catalytic methods for formation of enantiomerically enriched CHF₂-bearing stereocenters.⁸ Here, we show that commercially available 75 wt% solutions of fluoral hydrate in water or 90 wt% solutions of difluoroacetaldehyde ethyl hemiacetal in ethanol can be exploited in highly *anti*-diastereo- and enantioselective carbonyl (α -aryl)allylations. To illustrate the preparative utility of this method, it was applied to syntheses of di- and trifluoromethylated derivatives of the FDA approved alkaloid *d*-hyoscyamine (*dextro*-atropine).

In an initial set of experiments, *para*-substituted benzaldehydes **1a–1f** were subjected to 2-propanol-mediated reductive couplings with 1-(4-bromophenyl)allyl acetate **2b** using the cyclometallated π -allyliridium *C,O*-benzoate complex modified by (*S*)-Cl,MeO-BIPHEP as catalyst (Table 1). An unusual correlation between the electronic properties of the aldehyde and enantioselectivity emerged. Whereas electron-rich aldehydes such as *p*-(dimethylamino)benzaldehyde **1a** and anisaldehyde **1b** provided products **3a** and **3b** in nearly racemic form, the degree of asymmetric induction gradually improved with increasing aldehyde electrophilicity. Ultimately, using aqueous fluoral hydrate **1i** as the carbonyl electrophile in the presence of 4 Å molecular sieves, the product of carbonyl (α -aryl)allylation **4b** was formed in 88% yield with complete *anti*-diastereoselectivity in 94% enantiomeric excess (Table 1, entry 9). In the absence of molecular sieves, only trace quantities of reductive coupling product **4b** were observed. As our iridium catalyst is tolerant of aqueous organic conditions,¹ the primary role of molecular sieves would appear to involve dehydration of fluoral hydrate.

Conditions identified for 2-propanol-mediated reductive *anti*-(α -aryl)allylation of fluoral hydrate **1i** were applied to branched aryl-substituted allylic acetates **2a–2l** (Table 2). The products of carbonyl (α -aryl)allylation **4a–4l** were formed in good to excellent yields as single diastereomers with uniformly high levels of enantioselectivity. The *syn*-diastereomer was not observed upon ¹H NMR analysis of crude reaction mixtures. Beyond products **4b–4e** derived from *para*-substituted α -aryl allyl acetates, adducts **4f**, **4g** and **4h**, which incorporate *ortho*-substituted, 3,5-disubstituted and 3,4-disubstituted aryl moieties, respectively, could be formed in a highly stereoselective fashion. Finally, allyl donors bearing heteroaromatic rings

2i-2l provided the corresponding products of carbonyl (α -aryl)allylation **4i-4l** in good to excellent yields and uniformly high stereoselectivities. The absolute stereochemical assignment of adducts **4a-4k** is made in analogy to that established for compound **4l**, which was determined by single crystal X-ray diffraction analysis.

Encouraged by the preceding results, optimal conditions for carbonyl *anti*-(α -aryl)allylation were applied to difluoroacetaldehyde (Table 3). The feasibility of this process was uncertain, as difluoroacetaldehyde is only available as the ethyl hemiacetal in 90 wt% solutions in ethanol, and ethanol could itself engage in transfer hydrogenative carbonyl addition. In the event, using the same set of branched aryl-substituted allylic acetates **2a-2l**, the CHF₂-bearing β -aryl alcohols **5a-5l** were formed in good to excellent yields with complete *anti*-diastereoselectivity and uniformly high levels of enantioselectivity. The products were accompanied by small amounts of the ethanol coupling side products (3–14% yield), which were easily removed upon chromatographic isolation of the principal reaction products. The absolute stereochemical assignment of adducts **5a-5k** is made in analogy to that established for compound **5l**, which was determined by single crystal X-ray diffraction analysis.

The unusual dependence of enantioselectivity on carbonyl electrophilicity merits discussion, as this phenomenon appears quite unique (Figure 1).⁹ In earlier studies on carbonyl allylation, an inversion in enantioselectivity was observed in response to the steric features of the allyl donor. Specifically, whereas carbonyl allylations^{10a,b} and crotylations^{10c,d} display matching enantiofacial preferences, an inversion in enantiofacial preference is observed in carbonyl *tert*-prenylations¹¹ when using the same enantiomer of the chiral cyclometallated π -allyliridium *C,O*-benzoate catalyst. These data suggest that for small allyl donors, carbonyl addition occurs predominantly through the transition structure indicated on the left-hand side of Figure 1. As steric demand of the allyl donor increases, the allyl fragment prefers to reside in a more open environment, causing addition to occur through the diastereomeric transition structure indicated on the right-hand side of Figure 1. In carbonyl *anti*-(α -aryl)allylations, the steric demand of the (aryl)allyl appears to lie between these extremes. Carbonyl binding to the more accessible coordination site is kinetically preferred (Figure 1, left) and, for sufficiently electrophilic aldehydes, binding triggers carbonyl addition. However, for less electrophilic aldehydes, binding to the kinetically more accessible site (Figure 1, left) less frequently triggers carbonyl addition and the alternate diastereomeric binding mode can be sampled. Consequently, carbonyl addition through the diastereomeric transition structure (Figure 1, left) begins to compete, resulting in an erosion in enantioselectivity. For *anti*-(α -aryl)allylations, the diastereomeric transition structure (Figure 1, left) may be thermodynamically preferred or of comparable thermodynamic stability compared to the kinetically more accessible binding mode.

To illustrate the utility of this method, carbonyl *anti*-(α -aryl)allylation was applied in syntheses of di- and trifluoro-methylated derivatives of the FDA approved alkaloid *d*-hyoscyamine (*dextro*-atropine) (Scheme 1).¹² Specifically, adduct **4a** was converted to the TBS ether and subjected to modified Johnson-Lemieux conditions for alkene oxidative cleavage.¹³ The resulting α,β -stereogenic carboxylic acid **6a** was exposed to tropine under Shiina's esterification conditions¹⁴ to form the TBS-protected ester **7a** in good yield, albeit with some epimerization. Finally, treatment of **7a** with HF-pyridine provided CF₃-

hyoscyamine **8a**. The CHF₂-bearing *anti*-(α -aryl)allylation product **5a** was converted to CHF₂-hyoscyamine **8b** in an analogous manner.

In summary, we report direct methods for 2-propanolmediated *anti*-diastereo- and enantioselective (α -aryl)allylations of fluoral hydrate and difluoroacetaldehyde ethyl hemiacetal using readily accessible branched allylic acetate pronucleophiles. These processes take advantage of a unique mechanism for enantioinduction involving competition between diastereomeric kinetic vs thermodynamic carbonyl binding modes. As illustrated by the formation of di- and trifluoromethylated derivatives of *d*-hyoscyamine (*dextro*-atropine) **8a** and **8b**, these methods broaden access to diverse CF₃- and CHF₂- bearing building blocks, which should assist the small molecule medicinal and agrochemical discovery enterprise.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Stereochemical Model for Iridium-Catalyzed Enantioselective Carbonyl *anti*-(α -Aryl)allylation.

Scheme 1.

Enantioselective Syntheses of Di- and Trifluoro-methylated Derivatives of *d*-Hyoscyamine (*dextro*-Atropine) **8a** and **8b**.^a

^aYields of material isolated by silica gel chromatography. See Supporting Information for further experimental details. ^b25 °C. ^c(2-Pr)₂NEt (100 mol%).

Table 1.

Correlation between Aldehyde Electrophilicity and Enantioselectivity in the *anti*-(α -Aryl)allylation of Aromatic Aldehydes and Fluoral Hydrate.^a

Entry	R	σ	1a-1i	3a-3h	Yield%	dr	ee%
1	4-Me ₂ N-Ph	-0.83	1a	3a	16	4:1	1
2	4-MeO-Ph	-0.27	1b	3b	54	9:1	5
3	4-Me-Ph	-0.17	1c	3c	69	4:1	12
4	Ph	0.00	1d	3d	74	4:1	15
5	4-F-Ph	0.06	1e	3e	88	3:1	16
6	4-Br-Ph	0.23	1f	3f	88	4:1	23
7	3-(6-Br-Pyr)	-	19	3g	82	5:1	37
8	2-(6-Br-Pyr)	-	1h	3h	75	4:1	65
9 ^b	CF ₃	-	1i	4b	88	>20:1	94

^aYields of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.

^b4Å molecular sieves 300 wt%). Fluoral hydrate in water (75 wt%).

Table 2.

Enantioselective Iridium-Catalyzed *anti*-(α -Aryl)allylation of Fluoral Hydrate **1i** to Form CF₃-Bearing β -Aryl Alcohols **4a-4l**.^a

1i , 75 wt% in H ₂ O (100 mol%)	2a-2l (200 mol%)	4a-4l
2a , Ar = Ph 2d , Ar = 4-Me-Ph 2g , Ar = 3,5-Cl ₂ -Ph 2j , Ar = 2-Thienyl	2b , Ar = 4-Br-Ph 2e , Ar = 4-MeO-Ph 2h , Ar = 5-Benzodioxolyl 2k , Ar = 5-(2-MeO-Pyr)	2c , Ar = 4-CF ₃ -Ph 2f , Ar = 2-Cl-Ph 2i , Ar = 2-Furyl 2l , Ar = 4-Quinoliny
4a , 85% Yield, >20:1 dr 93% ee	4b , 88% Yield, >20:1 dr 94% ee	4c , 64% Yield, >20:1 dr 93% ee
4d , 77% Yield, >20:1 dr 92% ee	4e , 71% Yield, >20:1 dr 92% ee	4f , 60% Yield, >20:1 dr 89% ee
4g , 91% Yield, >20:1 dr 94% ee	4h , 84% Yield, >20:1 dr 92% ee	4i , 61% Yield, >20:1 dr 94% ee
4j , 82% Yield, >20:1 dr 94% ee	4k , 87% Yield, >20:1 dr 91% ee	4l , 84% Yield, >20:1 dr 93% ee (X-Ray)

^aYields of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.

Table 3.

Enantioselective Iridium-Catalyzed *anti*-(α -Aryl)allylation of Difluoroacetaldehyde Ethyl Hemiacetal **1j** to Form CHF₂-Bearing β -Aryl Alcohols **5a-5l**.^a

1j , 90 wt% in EtOH (100 mol%)	2a-2l (200 mol%)	5a-5l
2a , Ar = Ph 2d , Ar = 4-Me-Ph 2g , Ar = 3,5-Cl ₂ -Ph 2j , Ar = 2-Thienyl	2b , Ar = 4-Br-Ph 2e , Ar = 4-MeO-Ph 2h , Ar = 5-Benzodioxolyl 2k , Ar = 5-(2-MeO-Pyr)	2c , Ar = 4-CF ₃ -Ph 2f , Ar = 2-Cl-Ph 2i , Ar = 2-Furyl 2l , Ar = 4-Quinoliny
5a , 80% Yield, >20:1 dr 94% ee	5b , 84% Yield, >20:1 dr 94% ee	5c , 82% Yield, >20:1 dr 94% ee
5d , 75% Yield, >20:1 dr 95% ee	5e , 82% Yield, >20:1 dr 93% ee	5f , 76% Yield, >20:1 dr 92% ee
5g , 77% Yield, >20:1 dr 95% ee	5h , 89% Yield, >20:1 dr 93% ee	5i , 65% Yield, >20:1 dr 91% ee
5j , 70% Yield, >20:1 dr 88% ee	5k , 75% Yield, >20:1 dr 93% ee	5l , 86% Yield, >20:1 dr 97% ee (X-Ray)

^aYields of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.