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Diastereo- and Enantioselective Iridium Catalyzed Coupling of Vinyl Aziridines and Alcohols: Site-Selective Modification of Unprotected Diols and Synthesis of Substituted Piperidines

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Abstract

The chiral cyclometalated π -allyliridium *ortho*-*C,O*-benzoate complex (*R*)-Ir-**VIb** derived from [Ir(cod)Cl]₂, allyl acetate, 4-cyano-3-nitrobenzoic acid, and (*R*)-MeO-BIPHEP catalyzes the coupling of *N*-(*p*-nitrophenylsulfonyl) protected vinyl aziridine **3a** with primary alcohols **1a–1l** to furnish branched products of C-C bond formation **4a–4l** with good levels of *anti*-diastereo- and enantioselectivity. In the presence of 2-propanol, but under otherwise identical conditions, vinyl aziridine **3a** and aldehydes **2a–2l** engage in reductive coupling to furnish an equivalent set of adducts **4a–4l** with roughly equivalent levels of *anti*-diastereo- and enantioselectivity. Using the enantiomeric iridium catalysts, vinyl aziridine **3a** reacts with unprotected chiral 1,3-diols **1m–1o** in a site-selective manner to deliver the diastereomeric products of *C*-allylation *syn*-**4m**, **4n**, **4o** and *anti*-**4m**, **4n**, **4o**, respectively, with good isolated yields and excellent levels of catalyst-directed diastereoselectivity. These adducts were directly converted to the diastereomeric 2,4,5-trisubstituted piperidines *syn*-**5m**, **5n**, **5o** and *anti*-**5m**, **5n**, **5o**.

Introduction

Redox-triggered carbonyl addition *via* transfer hydrogenation enables direct primary alcohol C-H functionalization in the absence of premetallated reagents or discrete alcohol to aldehyde redox reactions.¹ Enantioselective variants of these processes are remarkably broad in scope, encompassing alcohol C-H allylation,² crotylation,³ reverse prenylation,⁴ and numerous other allylative^{5–14} and propargylative¹⁵ transformations (Figure 1).^{16,17} An especially important and unique feature of these processes involves the ability to engage unprotected diols and higher polyols in site-selective primary alcohol C-H allylation.^{2f,g,14,18} This capability stems from a high kinetic preference for primary *vs* secondary alcohol dehydrogenation, despite the greater endothermicity of the former.^{19,20}

The prospect of expanding technologies that streamline or eliminate the use of protecting groups^{21a} and redox reactions^{21b} in chemical synthesis compelled us to develop related site-

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ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectroscopic data for all new compounds (¹H NMR, ¹³C NMR, IR, HRMS), including images of NMR spectra. Single crystal x-ray diffraction data for **4b** and *anti*-**5m**. This material is available free of charge *via* the internet at <http://pubs.acs.org>

selective redox-triggered carbonyl additions. Toward this end, we recently found that vinyl epoxides, such as isoprene oxide, will engage unprotected diols in site-selective C-C coupling to form products of *tert*-(hydroxy)prenylation.¹⁴ Inspired by these outcomes and the importance of nitrogen containing functional groups in pharmaceutical ingredients,²² in particular, the ubiquity of substituted piperidines,²³ we commenced exploration of vinyl aziridines as nucleophilic partners in redox-triggered carbonyl addition with primary alcohol proelectrophiles, including unprotected diols. We were further motivated by the fact that *enantioselective umpoled allylations of aldehydes with vinyl aziridines to form products of carbonyl (α -aminomethyl)allylation have not been described.*²⁴

Here, we report that the cyclometalated π -allyliridium *ortho*-C,*O*-benzoate complex (*R*)-Ir-**Vb** catalyzes the C-C coupling of *N*-(*p*-nitrophenylsulfonyl) protected²⁵ vinyl aziridine **3a** with primary alcohols **1a–1l** to furnish branched products of (α -aminomethyl)allylation **4a–4l** with excellent levels of *anti*-diastereo- and enantioselectivity. Further, using enantiomeric iridium catalysts, vinyl aziridine **3a** reacts with unprotected chiral 1,3-diols **1m–1o** in a site-selective manner to form the diastereomeric products of C-allylation *syn*-**4m–4o** and *anti*-**4m–4o**, respectively, in good isolated yields and excellent levels of catalyst-directed diastereoselectivity. Under Mitsunobu reaction conditions, these adducts are directly converted to the diastereomeric 2,4,5-trisubstituted piperidines *syn*-**5m–5o** and *anti*-**5m–5o** (Figure 1).

Research Design and Methods

The feasibility of engaging vinyl aziridines in metal catalyzed C-C couplings with primary alcohols was rendered uncertain by competing electrophilic of *O*-allylation of the resulting π -allyliridium complexes,^{26,27} as well as the propensity of vinyl aziridines to participate in metal catalyzed ring expansion.²⁸ Despite these potential liabilities, our initial experiments revealed promising results. Specifically, a series of chromatographically purified cyclometalated π -allyliridium *ortho*-C,*O*-benzoate complexes derived from [Ir(cod)Cl]₂, allyl acetate, 4-substituted-3-nitro-benzoic acids, and axially chiral chelating phosphine ligands were assayed for their ability to catalyze the C-C coupling of vinyl aziridine **3a** with benzyl alcohol **1a** (Table 1). Complexes (*R*)-Ir-**Ia** - (*R*)-Ir-**Id**, which incorporate BINAP-type ligands provided uniformly low isolated yields of coupling product **4a**, although high levels of enantiomeric excess were observed (Table 1, entries 1–4). Complexes (*R*)-Ir-**Ia** and (*R*)-Ir-**Ib**, which incorporate (*R*)-SEPHOS, enforced higher levels of conversion (Table 1, entries 5 and 6), suggesting ligands that incorporate alkoxy-substituted biaryl backbones might be efficacious. Complex (*R*)-Ir-**Ic**, which incorporates (*R*)-DM-SEPHOS, gave only trace quantities of **4a** (Table 1, entry 7), hence, subsequent experiments focused solely on diphenylphosphino-substituted ligands. As amply demonstrated in prior studies,^{2–15} the 4-substituent of the C,*O*-benzoate moiety can influence both conversion and selectivity. In the case of complexes (*R*)-Ir-**IIa,b**, (*R*)-Ir-**IVa,b**, (*R*)-Ir-**Va,b**, and (*R*)-Ir-**VIa,b** which incorporate (*R*)-SYNPHOS, (*R*)-C3-TUNEPHOS, (*R*)-Cl,MeO-BIPHEP and (*R*)-MeO-BIPHEP ligands, respectively, those modified by 4-cyano-3-nitrobenzoate moieties promote uniformly higher conversion than the corresponding 4-chloro-3-nitrobenzoate complexes (Table 1, entries 8–15). From these

studies, it was found that (*R*)-Ir-**VIb**, which incorporates (*R*)-MeO-BIPHEP (the “Roche ligand”),²⁹ provided the most favorable results, delivering adduct **4a** in 85% yield with a 5:1 *anti*-diastereoselectivity and 96% enantiomeric excess (Table 1, entry 15). At lower temperature, a slight improvement in enantioselectivity was observed, but the isolated yield decreased significantly (Table 1, entry 16). Conversely, at higher temperature, conversion improved but enantioselectivity declined (Table 1, entry 17). Whereas decreased loadings of vinyl aziridine **3a** (100 mol%) diminished the isolated yield of adduct **4a** (Table 1, entry 18), the use of excess vinyl aziridine **3a** (300 mol%) provided adduct **4a** in 96% isolated yield with 5:1 *anti*-diastereoselectivity and 97% enantiomeric excess (Table 1, entry 19). The use of alternate reaction solvents, such as dioxane or toluene, or omission of potassium phosphate led to substantially diminished yields.

To evaluate the scope of the iridium catalyzed (α -aminomethyl)allylation, diverse primary alcohols **1a–1l** (100 mol%) were exposed to vinyl aziridine **3a** (300 mol%) in the presence of complex (*R*)-Ir-**VIb** (5 mol%) and substoichiometric potassium phosphate (5 mol%) in THF (0.2 M) at 60 °C (Table 2). As illustrated in the conversion of **1a–1f** to **4a–4f**, a range of benzylic alcohols participate in C-C coupling, including alcohol **1f**, which incorporates a Lewis basic pyridyl-substituent. Cinnamyl alcohol **1g**, prenyl alcohol **1h** and geraniol **1i** are transformed to adducts **4g–4i**, illustrating use of allylic alcohols as coupling partners. Internal redox isomerization of allylic alcohols **1g–1i** to form aldehydes was not observed.³⁰ Finally, as demonstrated by the conversion of heptanol **1j**, *O*-benzyl 1,3-propane diol **1k** and cyclopropyl methanol **1l** to adducts **4j–4l**, respectively, aliphatic alcohols participate in coupling. In each case examined, good to excellent yields, good *anti*-diastereoselectivities and uniformly high enantioselectivities were observed.

Related reductive couplings of vinyl aziridine **3a** with aldehydes **2a–2l** also were evaluated (Table 3). Using 2-propanol (300 mol%) as terminal reductant under conditions otherwise identical to those employed in the coupling of alcohols **1a–1l**, aryl aldehydes **1a–1f** were converted to adducts **4a–4f**, respectively. Similarly, the α,β -unsaturated aldehydes cinnamaldehyde **2g**, prenyl aldehyde **2h** and geraniol **2i** were transformed to adducts **4g–4i**, respectively. Finally, the aliphatic aldehydes **2j–2l** provided adducts **2j–2l**, respectively. Good to excellent yields, good *anti*-diastereoselectivities were accompanied by uniformly high enantioselectivities in each case. These data demonstrate that (α -aminomethyl)allylation *via* transfer hydrogenation proceeds with equal facility from the alcohol or aldehyde oxidation levels. The relative and absolute stereochemical assignment of adducts **4a–4l** was made in analogy to the structural assignment of adducts **4b**, which was determined by single crystal X-ray diffraction analysis. Based on the collective data,^{1a} a general catalytic mechanism accounting for the reaction of primary alcohols **1a–1l** with vinyl aziridine **3a** to form adducts **4a–4l** is given (Scheme 1). It should be noted that attempted preparation of *N*-nosyl vinyl aziridines substituted at the allylic position failed due to spontaneous ring opening, and *N*-carbamoyl substituted vinyl aziridines underwent ring expansion upon exposure to coupling conditions.

Having demonstrated the feasibility and scope of the coupling of primary alcohols **1a–1l**, the catalyst-directed diastereo- and site-selective C-C coupling of unprotected diols **1m–1o** with

vinyl aziridine **3a** was investigated (Table 4).^{2f,g,14,18} Conditions used in the coupling of primary alcohols **1a–1l** were not directly transferable. Longer reaction times were required. Additionally, the optimal pairing of diol **1m–1o** and catalyst was case dependent. For example, in the coupling of diol **1m** with vinyl aziridine **3a**, the iridium catalyst (*R*)-Ir-**Vb**, which is modified by (*R*)-Cl,MeO-BIPHEP, gave slightly better results than catalyst (*R*)-Ir-**VIIb**, which is modified by (*R*)-MeO-BIPHEP. In each case, the products of (α -aminomethyl)allylation *syn*-**4m**, *syn*-**4n** and *syn*-**4o** were formed in good yield and with good levels of catalyst-directed diastereoselectivity. In a parallel set of experiments, the unprotected diols **1m–1o** were reacted with the respective enantiomeric iridium catalysts. The diastereomeric adducts *anti*-**4m**, *anti*-**4n** and *anti*-**4o** were formed in good yields with excellent levels catalyst-directed diastereoselectivity. The preparation of *syn*-**4o** and *anti*-**4o**, which incorporate pyridine rings, underscores the high level of functional group compatibility displayed by the iridium catalysts.

To illustrate the utility of this methodology, the diol coupling products *syn*-**4m**, *syn*-**4n** and *syn*-**4o** were exposed Mitsunobu reaction conditions (Table 5).³¹ Cyclization proceeded most efficiently using DIAD (diisopropyl azodicarboxylate), delivering the 2,4,5-trisubstituted piperidines *syn*-**5m**, *syn*-**5n** and *syn*-**5o** as single stereoisomers. Similarly, exposure of the diol coupling products *anti*-**4m**, *anti*-**4n** and *anti*-**4o** to Mitsunobu conditions led to formation of the diastereomeric 2,4,5-trisubstituted piperidines *anti*-**5m**, *anti*-**5n** and *anti*-**5o** (Table 5). In all cases, cyclization proceeded with complete inversion of the carbinol stereocenter in good to excellent yield. Finally, as illustrated in the conversion of piperidine *syn*-**5n** to the free secondary amine *syn*-**6n**, the *N*-(*p*-nitrophenylsulfonyl) protecting group²⁵ may be removed in an efficient, selective manner (eq. 1).

(eq. 1)

Conclusions

In summary, we report the first enantioselective umpoled allylations of aldehydes with vinyl aziridines to form products of carbonyl (α -aminomethyl)allylation. These processes may be conducted efficiently from the alcohol or aldehyde oxidation level, delivering products of C–C bond formation in good to excellent yield, good levels of *anti*-diastereoselectivity and uniformly high levels of enantioselectivity. Further, using enantiomeric iridium catalysts, vinyl aziridine **3a** reacts with unprotected chiral 1,3-diols **1m–1o** in a site-selective manner to form the diastereomeric products of *C*-allylation *syn*-**4m**, *syn*-**4n** and *syn*-**4o** and *anti*-**4m**, *anti*-**4n**, *anti*-**4o**, respectively, in good isolated yields and excellent levels of catalyst-directed diastereoselectivity; a capability that enables concise access to 2,4,5-trisubstituted

piperidines. Future work will focus on related methods for the direct site-selective modification of polyols including natural products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Prior Work: Redox-Triggered Allylations and Propargylations of Primary Alcohols

Allylation (ref. 2): X = OAc, R¹ = R² = R³ = H

Crotylation (ref. 3): X = OAc, R¹ = Me, R² = R³ = H or Butadiene

tert-Prenylation (ref. 4): 1,2-Dimethylallene

(α -Hydroxy)allylation (ref. 5): X = R¹ = OBz, R² = R³ = H

(α -Hydroxymethyl)allylation (ref. 6): Vinyl Ethylene Carbonate

(α -Trimethylsilyl)allylation (ref. 7): X = OAc, R¹ = TMS, R² = R³ = H

(α -Trifluoromethyl)allylation (ref. 8): X = OAc, R¹ = CF₃, R² = R³ = H

Methallylation (ref. 9): X = Cl, R¹ = H, R² = Me, R³ = H

2-(Alkoxy carbonyl)allylation (ref. 10): X = OBoc, R¹ = H, R² = CO₂Me, R³ = H

(2-Fluoro)allylation (ref. 11): X = Cl, R¹ = H, R² = F, R³ = H

Vinyllogous Aldol (ref. 12): X = OBoc, R¹ = H, R² = H, R³ = CO₂Me

Propargylation (ref. 15): 1,3-Enyne or Propargyl Chloride

[(α -CH₂CH(CO₂Me)₂]allylation (ref. 13): X = C(CO₂Me)₂, R¹ = H

tert-(Hydroxy)prenylation (ref. 14): X = O, R¹ = Me

This Work: Stereo- and Site-Selective C-C Coupling of Vinyl Aziridines

Figure 1.

Direct, byproduct-free catalytic enantioselective coupling of vinyl cyclopropanes, vinyl epoxides and vinyl aziridines with primary alcohols.

Scheme 1.

General catalytic mechanism for iridium catalyzed (α -aminomethyl)allylation of alcohols **1a–1l** with vinyl aziridine **3a**.

Table 1

Selected optimization experiments in the redox-triggered C-C coupling of aziridine **3a** with benzyl alcohol **1a** to form *p*-nitrophenylsulfonyl protected aminoalcohol **4a**.^a

Entry	3a (mol%)	[Ir]	T(°C)	4a yield (dr, ee%)
1	200	(R)-Ir- Ia	60	15% (2:1, 90)
2	200	(R)-Ir- Ib	60	20% (2:1, 91)
3	200	(R)-Ir- Ic	60	14% (2:1, 94)
4	200	(R)-Ir- Id	60	14% (2:1, 91)
5	200	(R)-Ir- IIa	60	26% (8:1, 91)
6	200	(R)-Ir- IIb	60	69% (6:1, 90)
7	200	(R)-Ir- IIc	60	trace conversion
8	200	(R)-Ir- IIIa	60	28% (4:1, 93)
9	200	(R)-Ir- IIIb	60	86% (4:1, 90)
10	200	(R)-Ir- IVa	60	50% (7:1, 84)
11	200	(R)-Ir- IVb	60	61% (3:1, 95)
12	200	(R)-Ir- Va	60	28% (3:1, 96)
13	200	(R)-Ir- Vb	60	65% (3:1, 94)
14	200	(R)-Ir- VIa	60	51% (5:1, 96)
15	200	(R)-Ir- VIb	60	85% (5:1 96)
16	200	(R)-Ir- VIb	45	70% (5:1 97)
17	200	(R)-Ir- VIb	80	88% (2:1 85)
18	100	(R)-Ir- VIb	60	36% (5:1 95)
⇒ 19	300	(R)-Ir- VIb	60	96% (5:1 97)

^aYields are of material isolated by silica gel chromatography. See Supporting Information for further details.

Table 2

Regio-, diastereo- and enantioselective iridium catalyzed (α -aminomethyl)allylation of alcohols **1a–1l** with vinyl aziridine **3a**.^a

1a–1l (100 mol%)	3a (300 mol%)	4a–4l
1a , R = Ph 1d , R = piperonyl 1g , R = (<i>E</i>)-CH=CHPh 1j , R = (CH ₂) ₅ Me	1b , R = 4-Me-Ph 1e , R = 2-furyl 1h , R = CH=CMe ₂ 1k , R = (CH ₂) ₂ OBn	1c , R = 4-Br-Ph 1f , R = 2-(6-Me-pyridyl) 1i , geraniol 1l , R = <i>c</i> -Pr

4a , 96% Yield 5:1 dr, 97% ee	4b , 70% Yield 5:1 dr, 94% ee (X-ray)	4c , 90% Yield 4:1 dr, 96% ee
4d , 73% Yield 4:1 dr, 96% ee	4e , 73% Yield 10:1 dr, 97% ee	4f , 78% Yield 5:1 dr, 97% ee
4g , 73% Yield 6:1 dr, 95% ee	4h , 70% Yield 8:1 dr, 95% ee	4i , 67% Yield 9:1 dr, 94% ee ^b
4j , 96% Yield 6:1 dr, 99% ee	4k , 87% Yield 8:1 dr, 98% ee	4l , 64% Yield 4:1 dr, 95% ee

^aYields are of material isolated by silica gel chromatography.

^b48 h. See Supporting Information for further details.

Table 3

Regio-, diastereo- and enantioselective iridium catalyzed reductive (α -aminomethyl)allylation of aldehydes **2a–2l** with vinyl aziridine **3a**.^a

2a , R = Ph	2b , R = 4-Me-Ph	2c , R = 4-Br-Ph
2d , R = piperonyl	2e , R = 2-furyl	2f , R = 2-(6-Me-pyridyl)
2g , R = (<i>E</i>)-CH=CHPh	2h , R = CH=CMe ₂	2i , geranial
2j , R = (CH ₂) ₅ Me	2k , R = (CH ₂) ₂ OBn	2l , R = <i>c</i> -Pr
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4a , 80% Yield 5:1 dr, 95% ee	4b , 72% Yield 4:1 dr, 96% ee (X-ray)	4c , 86% Yield 4:1 dr, 97% ee

4d , 87% Yield 4:1 dr, 97% ee	4e , 85% Yield 9:1 dr, 97% ee	4f , 72% Yield 4:1 dr, 96% ee

4g , 77% Yield 5:1 dr, 98% ee	4h , 96% Yield 7:1 dr, 99% ee	4i , 66% Yield 8:1 dr, 91% ee

4j , 90% Yield 5:1 dr, 96% ee	4k , 85% Yield 7:1 dr, 95% ee	4l , 63% Yield 4:1 dr, 98% ee

^aYields are of material isolated by silica gel chromatography. See Supporting Information for further details.

Table 4

Catalyst-directed diastereo- and site-selectivity in the iridium catalyzed (α -aminomethyl)allylation of unprotected 1,3-diols **1m–1o** with vinyl aziridine **3a**.^a

^aYields are of material isolated by silica gel chromatography. See Supporting Information for further details.

Table 5

Conversion of *syn*-**4m**, **4n**, **4o** and *anti*-**4m**, **4n**, **4o** to diastereomeric 2,4,5-trisubstituted piperidines *syn*-**5m**, **5n**, **5o** and *anti*-**5m**, **5n**, **5o**.^a

^aYields are of material isolated by silica gel chromatography. See Supporting Information for further details.