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

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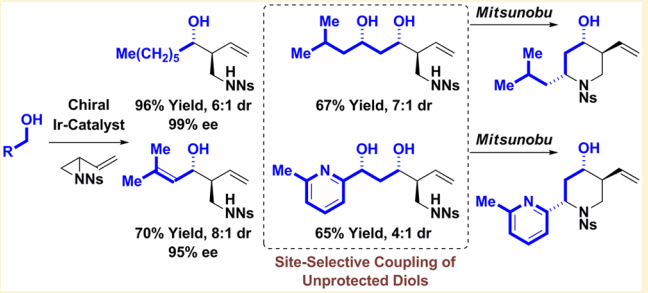
Supporting Information

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-nitro-benzoic 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 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 premetalated 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 propargylative[15] 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.[2,14,18] 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-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-**VIb** catalyzes the C−C coupling of *N*-(*p*-nitrophenylsulfonyl) protected[25] 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 *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,

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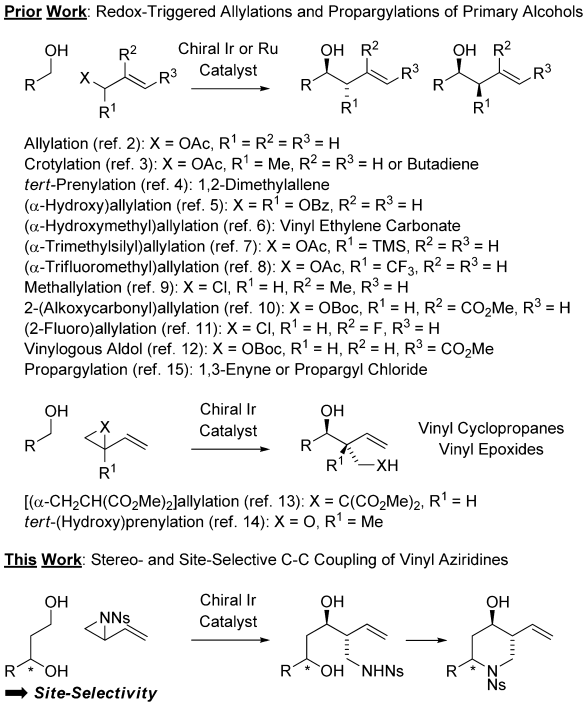
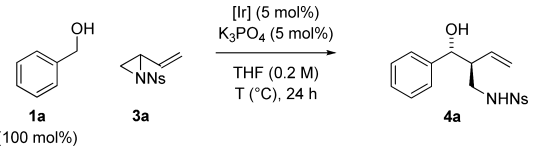


Figure 1. Direct, byproduct-free catalytic enantioselective coupling of vinyl cyclopropanes, vinyl epoxides, and vinyl aziridines with primary alcohols.

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-**IIa** and (*R*)-Ir-**IIb**, which incorporate (*R*)-SEGPHOS, 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-**IIc**, which incorporates (*R*)-DM-SEGPHOS, 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-**IIIa,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.

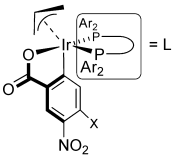
To evaluate the scope of the iridium catalyzed (α-aminomethyl)-allylation, diverse primary alcohols **1a**−**1l** (100 mol %) were exposed to vinyl aziridine **3a** (300 mol %) in the presence of complex (*R*)-Ir-**VIb** (5 mol %) and substoichiometric potassium phosphate (5 mol %)

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]

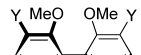


1a (100 mol%) **3a** **4a**

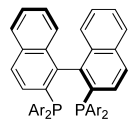
Entry	**3a** (mol%)	[Ir]	T (°C)	**4a** yield (dr, ee%)
1	200	(*R*)-Ir-**Ia**	60	15% (2:1, 90)
2	200	(*R*)-Ir-**Ib**	60	20% (2:1, 91)
3	200	(*R*)-Ir-**Ic**	60	14% (2:1, 94)
4	200	(*R*)-Ir-**Id**	60	14% (2:1, 91)
5	200	(*R*)-Ir-**IIa**	60	26% (8:1, 91)
6	200	(*R*)-Ir-**IIb**	60	69% (6:1, 90)
7	200	(*R*)-Ir-**IIc**	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)**



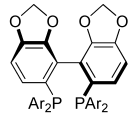
(*R*)-Ir-**Ia**, L = (*R*)-BINAP, X = H
(*R*)-Ir-**Ib**, L = (*R*)-BINAP, X = CN
(*R*)-Ir-**Ic**, L = (*R*)-Tol-BINAP, X = CN
(*R*)-Ir-**Id**, L = (*R*)-Xylyl-BINAP, X = CN
(*R*)-Ir-**IIa**, L = (*R*)-SEGPHOS, X = H
(*R*)-Ir-**IIb**, L = (*R*)-SEGPHOS, X = CN
(*R*)-Ir-**IIc**, L = (*R*)-DM-SEGPHOS, X = CN
(*R*)-Ir-**IIIa**, L = (*R*)-SYNPHOS, X = Cl
(*R*)-Ir-**IIIb**, L = (*R*)-SYNPHOS, X = CN
(*R*)-Ir-**IVa**, L = (*R*)-C3-TUNEPHOS, X = Cl
(*R*)-Ir-**IVb**, L = (*R*)-C3-TUNEPHOS, X = CN
(*R*)-Ir-**Va**, L = (*R*)-Cl,MeO-BIPHEP, X = Cl
(*R*)-Ir-**Vb**, L = (*R*)-Cl,MeO-BIPHEP, X = CN
(*R*)-Ir-**VIa**, L = (*R*)-MeO-BIPHEP, X = Cl
(*R*)-Ir-**VIb**, L = (*R*)-MeO-BIPHEP, X = CN



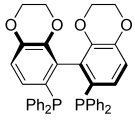
(*R*)-Cl,MeO-BIPHEP
Y = Cl
(*R*)-MeO-BIPHEP
Y = H
The "Roche Ligand"



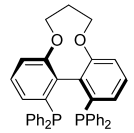
(*R*)-BINAP, Ar = Ph
(*R*)-Tol-BINAP
Ar = 4-MePh
(*R*)-Xylyl-BINAP
Ar = 3,5-Me2Ph



(*R*)-SEGPHOS
Ar = Ph
(*R*)-DM-SEGPHOS
Ar = 3,5-Me2Ph



(*R*)-SYNPHOS



(*R*)-C3-TUNEPHOS

[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for further details.

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

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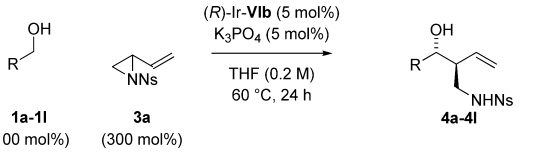
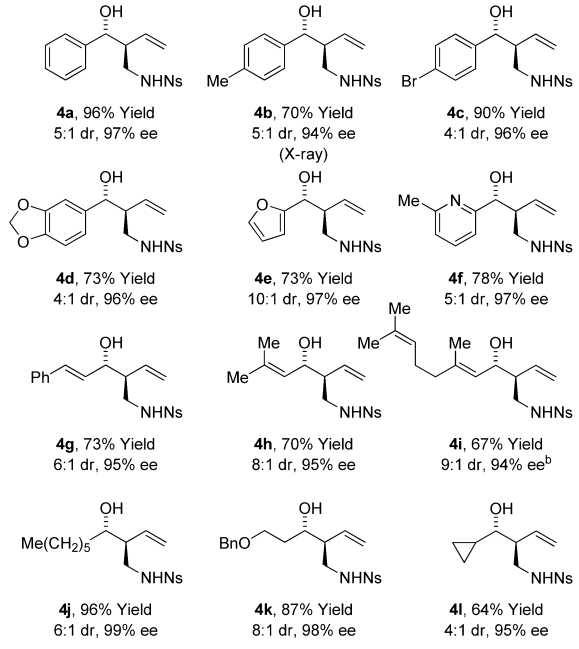
Table 2. Regio-, Diastereo-, and Enantioselective Iridium Catalyzed (α-Aminomethyl)Allylation of Alcohols 1a−1l with Vinyl Aziridine 3a[a]



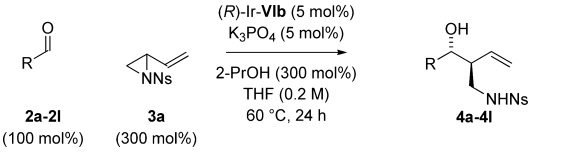
1a, R = Ph; **1b**, R = 4-Me-Ph; **1c**, R = 4-Br-Ph
1d, R = piperonyl; **1e**, R = 2-furyl; **1f**, R = 2-(6-Me-pyridyl)
1g, R = (*E*)-CH=CHPh; **1h**, R = CH=CMe$_2$; **1i**, geraniol
1j, R = (CH$_2$)$_5$Me; **1k**, R = (CH$_2$)$_2$OBn; **1l**, R = *c*-Pr



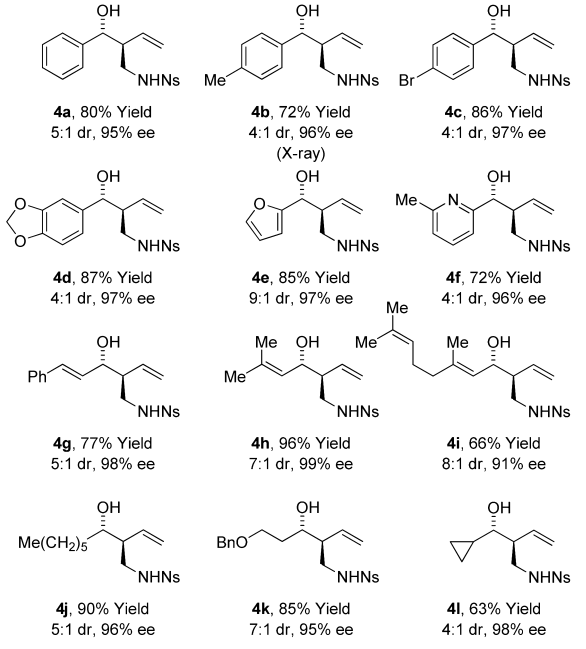
4a, 96% Yield; 5:1 dr, 97% ee
4b, 70% Yield; 5:1 dr, 94% ee (X-ray)
4c, 90% Yield; 4:1 dr, 96% ee
4d, 73% Yield; 4:1 dr, 96% ee
4e, 73% Yield; 10:1 dr, 97% ee
4f, 78% Yield; 5:1 dr, 97% ee
4g, 73% Yield; 6:1 dr, 95% ee
4h, 70% Yield; 8:1 dr, 95% ee
4i, 67% Yield; 9:1 dr, 94% ee[b]
4j, 96% Yield; 6:1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

[a]Yields are of material isolated by silica gel chromatography. [b]48 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 = (*E*)-CH=CHPh; **2h**, R = CH=CMe$_2$; **2i**, geranial
2j, R = (CH$_2$)$_5$Me; **2k**, R = (CH$_2$)$_2$OBn; **2l**, R = *c*-Pr



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

[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for further details.

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 a 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 geranial **2i** were transformed to adducts **4g−4i**, respectively. Finally, the aliphatic aldehydes **2j−2l** provided adducts **4j−4l**, respectively. Good to excellent yields and 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 adduct **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 proposed (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 diastereoselective and site-selective C−C coupling of unprotected diols **1m−1o** with vinyl

Scheme 1. General Catalytic Mechanism for Iridium Catalyzed (α-Aminomethyl)allylation of Alcohols 1a−1l with Vinyl Aziridine 3a

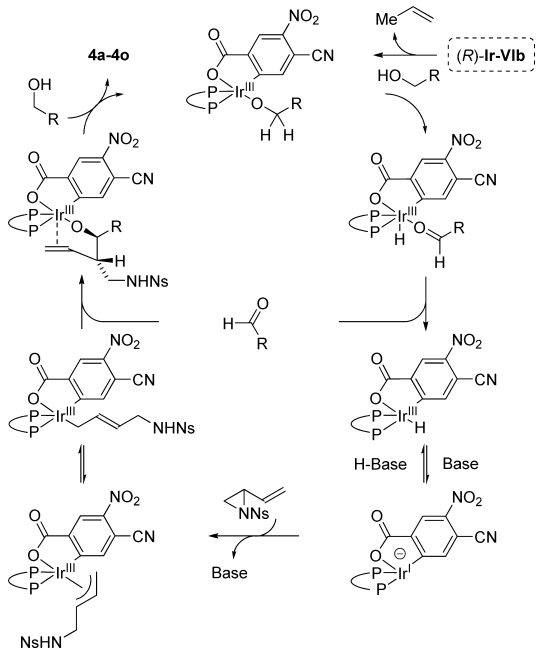


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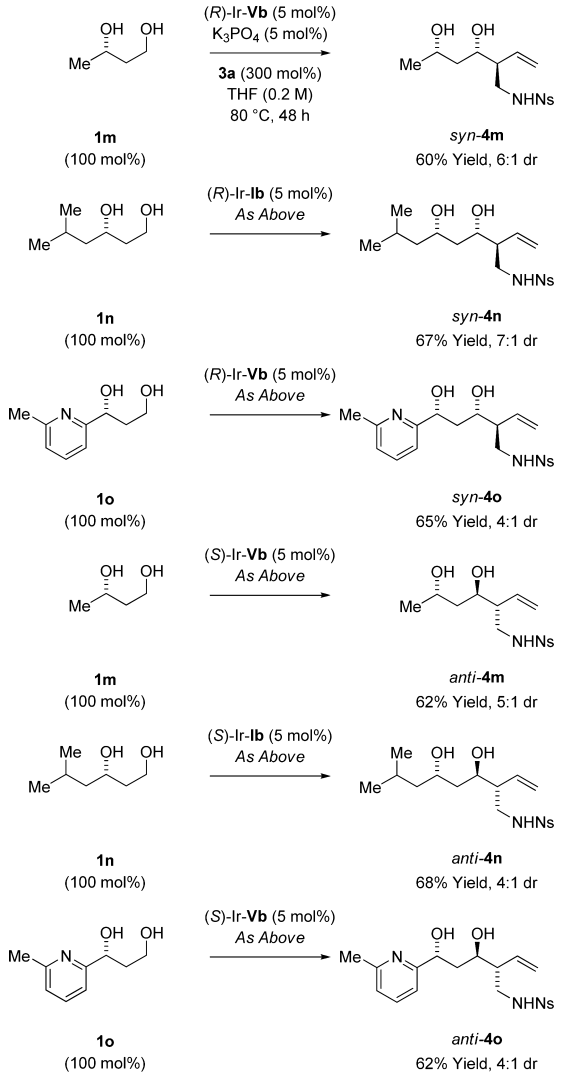
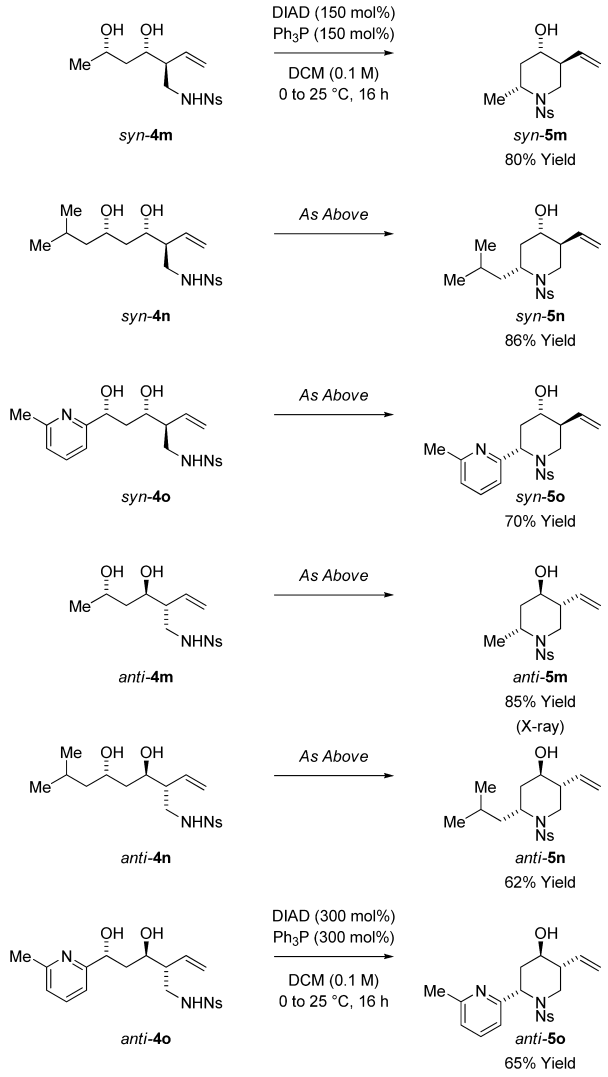
Table 4. Catalyst-Directed Diastereoselectivity and Site Selectivity in the Iridium Catalyzed (α-Aminomethyl)allylation of Unprotected 1,3-Diols 1m−1o with Vinyl Aziridine 3a[a]



[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for further details.

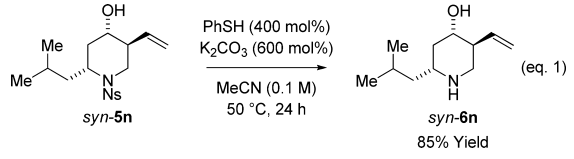
Table 5. Conversion of *syn*-4m, -4n, -4o and *anti*-4m, -4n, -4o to Diastereomeric 2,4,5-Trisubstituted Piperidines *syn*-5m, -5n, -5o and *anti*-5m, -5n, -5o[a]



[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for further details.

aziridine **3a** was investigated (Table 4).[2,14,18] 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-**VIb**, 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 of 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 to Mitsunobu reaction conditions (Table 5).[31] Cyclization proceeded most efficiently using DIAD (disisopropyl 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 group[25] may be removed in an efficient, selective manner (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

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excellent yield, with 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**, *syn*-**4o** and *anti*-**4m**, *anti*-**4n**, *anti*-**4o**, respectively, in good isolated yields and with 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.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS), including images of NMR spectra. Single crystal X-ray diffraction data for **4b** and *anti*-**5m**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04404.

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Notes

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