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Enantioselective iridium-catalyzed carbonyl isoprenylation *via* alcohol-mediated hydrogen transfer†

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Highly enantioselective iridium catalyzed carbonyl (2-vinyl)allylation or "isoprenylation" is achieved *via* hydrogen auto-transfer or 2-propanol-mediated reductive coupling from primary alcohol or aldehyde reactants, respectively. Using this method, asymmetric total syntheses of the terpenoid natural products (+)-ipsenol and (+)-ipsdienol were achieved.

Under the conditions of hydrogenation, transfer hydrogenation or hydrogen auto-transfer, diverse metal-catalyzed carbonyl reductive couplings may be conducted with high levels of enantioselectivity and atom-efficiency in the absence of pre-metalated C-nucleophiles or stoichiometric metals.[1] Among reactions of this type, stereo- and site-selective allylative carbonyl additions that directly convert lower alcohols to higher alcohols[1f,3] have proven especially effective for polyketide and terpenoid construction, enabling remarkably concise total syntheses of diverse natural products.[2] In the course of designing a synthetic route to amphidinolide V, it became of interest to develop a catalytic enantioselective carbonyl isoprenylation (Fig. 1).[4,5] Two enantioselective reactions of this type are reported in the literature, which exploit *B*-(5-isoprenyl) and *Sn*-(5-isoprenyl) reagents that are derived *via* potassiation of isoprene under cryogenic conditions using Schloβer's base.[5] Here, using the *tert*-butoxy carbonate of isoprenyl alcohol as pronucleophile, we report a catalytic enantioselective method for alcohol-mediated carbonyl isoprenylation, including asymmetric total syntheses of the terpenoid natural products (+)-ipsenol and (+)-ipsdienol and asymmetric isoprenylations of an unprotected glycol and a chiral α-stereogenic alcohol.

In an initial series of experiments, 4-bromobenzyl alcohol **1a** (100 mol%) was exposed to a series of chromatographically isolated π-allyliridium *C*,*O*-benzoate complexes derived from 4-cyano-3-nitrobenzoic acid, (*S*)-Ir-**I** to (*S*)-Ir-**VI**, in the presence of isoprenyl *tert*-butoxy carbonate **3a** (200 mol%) and K_3PO_4 (100 mol%) in THF (0.5 M) at 80 °C (Table 1, entries 1–6). The desired product of isoprenylation **4a** was formed in each case; however, excellent levels of enantiomeric enrichment were only observed for the catalyst modified by (*S*)-DM-SEGPHOS, which provided a modest 43% isolated yield of **4a** (Table 1, entry 6). In the parent iridium-catalyzed allylation and crotylation reactions,[6] rapid alcohol-aldehyde redox equilibration in advance of carbonyl addition was demonstrated, corroborating turnover-limiting carbonyl addition. More Lewis acidic catalysts with electron-withdrawing groups at the 4-position of the 3-nitro-*C*,*O*-benzoate moiety were shown to improve conversion and enantioselectivity. Accordingly, the π-allyliridium *C*,*O*-benzoate complex derived from 3,4-dinitrobenzoic acid and (*S*)-DM-SEGPHOS was evaluated in the reaction of 4-bromobenzyl alcohol **1a** with isoprenyl *tert*-butoxy carbonate **3a**.

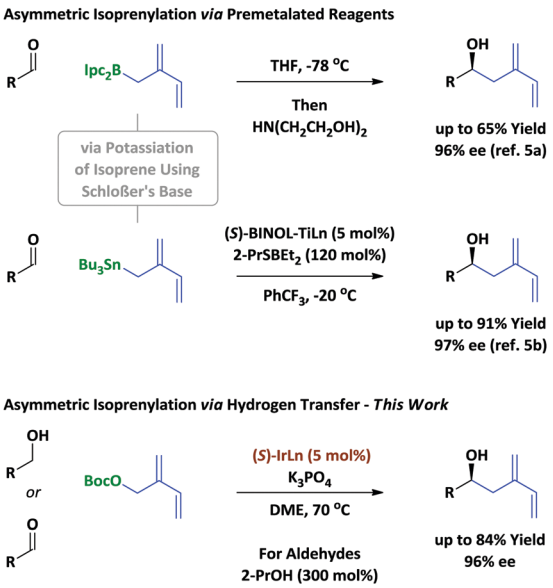

Fig. 1 Enantioselective methods for carbonyl isoprenylation.

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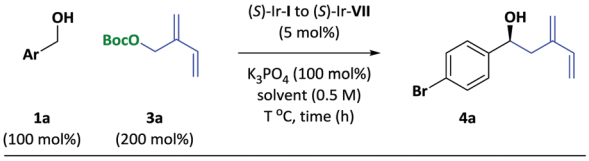
† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic and HPLC data for all new compounds. Crystallographic data for compound **4c**. CCDC 1873061. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8cc09706b

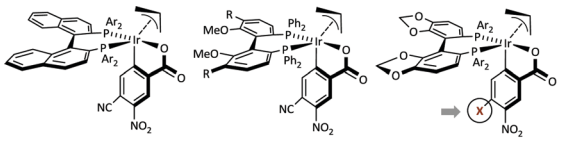
‡ These authors contributed equally to this work.

Table 1 Selected optimization experiments in the enantioselective iridium-catalyzed isoprenylation of 4-bromobenzyl alcohol **1a**[a]



1a (100 mol%) **3a** (200 mol%) **4a**

Entry	[Ir]	solvent	time (h)	T °C	Yield% **3a**	ee%
1	(*S*)-Ir-**I**	THF	48	80	70	56
2	(*S*)-Ir-**II**	THF	48	80	72	63
3	(*S*)-Ir-**III**	THF	48	80	44	60
4	(*S*)-Ir-**IV**	THF	48	80	66	50
5	(*S*)-Ir-**V**	THF	48	80	69	81
6	(*S*)-Ir-**VI**	THF	48	80	43	90
7	(*S*)-Ir-**VII**	THF	48	80	70	94
8	(*S*)-Ir-**VII**	THF	24	70	70	95
➡ 9	(*S*)-Ir-**VII**	DME	24	70	80	95



(*S*)-Ir-**I**, Ar = Ph
(*S*)-Ir-**II**, Ar = *p*-Tol

(*S*)-Ir-**III**, R = H
(*S*)-Ir-**IV**, R = Cl

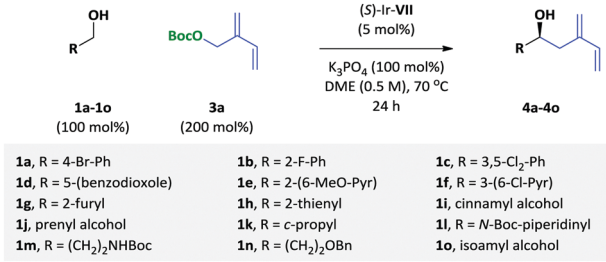
(*S*)-Ir-**V**, Ar = Ph
X = CN
(*S*)-Ir-**VI**, Ar = 3,5-Me_2-Ph
X = CN
(*S*)-Ir-**VII**, Ar = 3,5-Me_2-Ph
X = NO_2

[a] Yields are of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See ESI for further experimental details.

To our delight, both conversion and enantioselectivity improved (Table 1, entry 7). This level of efficiency persisted at lower reaction temperature (70 °C) and lower reaction time (24 h) (Table 1, entry 8). Finally, using DME as solvent, the isoprenylation product **4a** could be obtained in 80% yield and 95% enantiomeric excess (Table 1, entry 9). Carbonate **3a** is prepared *via* base-mediated "ring opening elimination" of isoprene oxide followed by quenching with Boc-anhydride.[7] The corresponding halides, which are less tractable and would require an additional step to prepare, were not evaluated.

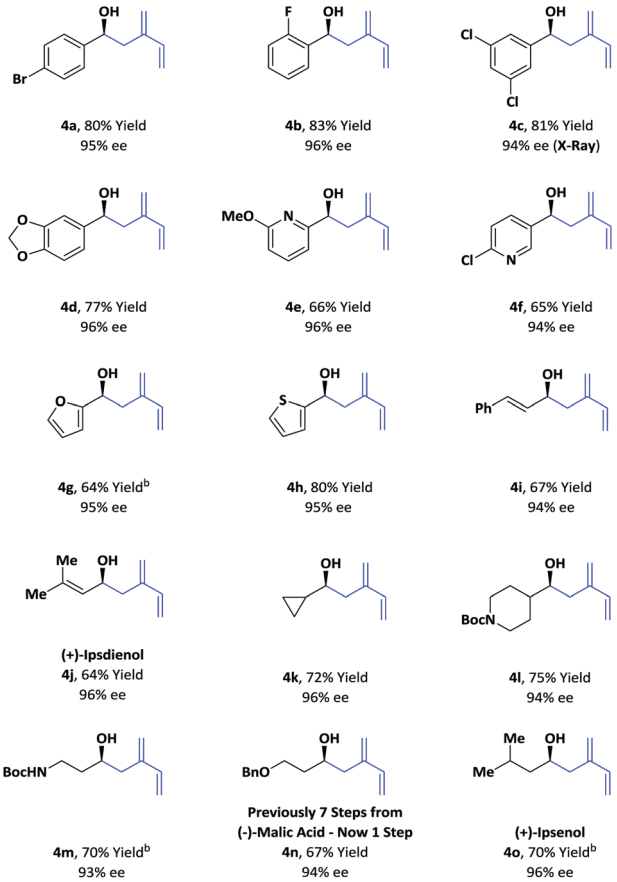
Optimal conditions identified for the formation of isoprenylation product **4a** were applied to a diverse set of benzylic, allylic and aliphatic alcohols (Table 2). In each case, good isolated yields were accompanied by uniformly high levels of enantioselectivity. As illustrated by the formation of **4e**, **4f** and **4h**, these conditions for isoprenylation are compatible with *N*- and *S*-containing heterocycles. Aliphatic alcohols **1m** and **1n** bearing heteroatoms at the β-position are converted to the products of isoprenylation **4m** and **4n**, respectively, without E1cB-elimination at the stage of the transient aldehyde. Notably, the synthesis of compound **4n**, which was previously accomplished in 7 steps from (−)-malic acid,[8] is now accomplished in a single step from commercially available *O*-benzyl propane diol **1n**. The conversion of prenyl alcohol **1j** and isoamyl alcohol **1o** to adducts **4j** and **4o**, respectively, represent enantioselective total syntheses of the terpenoid natural products (+)-ipsenol and (+)-ipsdienol, which are aggregation pheromones of the bark beetle.[9,10]

Table 2 Enantioselective iridium-catalyzed isoprenylation of alcohols **1a–1o**[a]



1a-1o (100 mol%) **3a** (200 mol%) **4a-4o**

1a, R = 4-Br-Ph; **1b**, R = 2-F-Ph; **1c**, R = 3,5-Cl_2-Ph
1d, R = 5-(benzodioxole); **1e**, R = 2-(6-MeO-Pyr); **1f**, R = 3-(6-Cl-Pyr)
1g, R = 2-furyl; **1h**, R = 2-thienyl; **1i**, cinnamyl alcohol
1j, prenyl alcohol; **1k**, R = *c*-propyl; **1l**, R = *N*-Boc-piperidinyl
1m, R = $(CH_2)_2NHBoc$; **1n**, R = $(CH_2)_2OBn$; **1o**, isoamyl alcohol

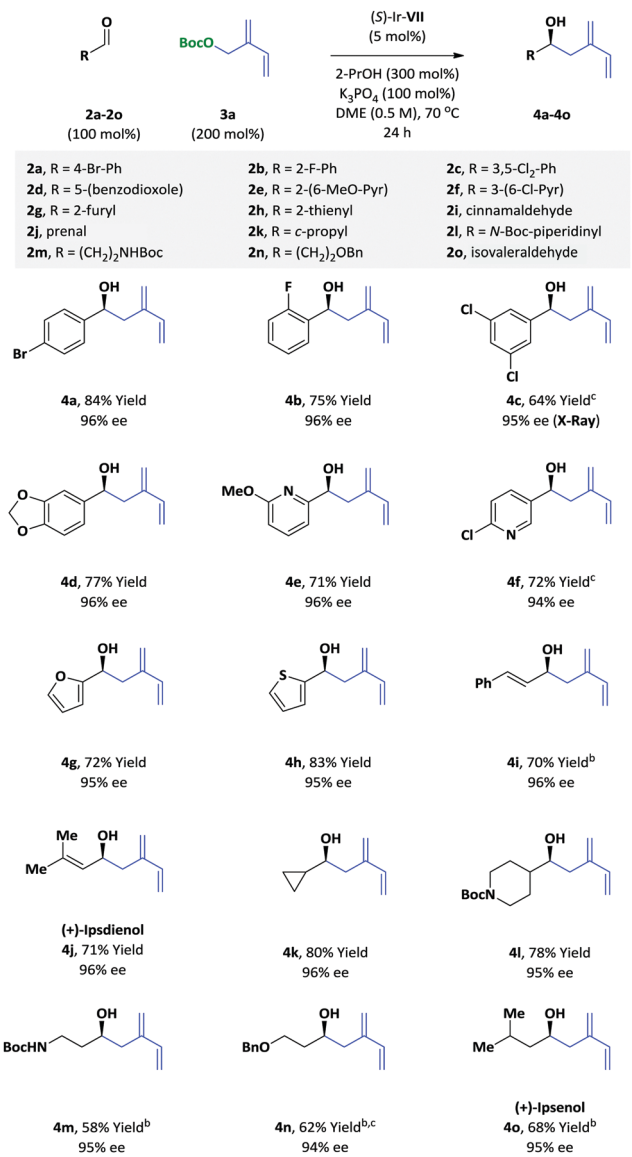


[a] Yields are of material isolated by silica gel chromatography. [b] 48 h.

In these hydrogen auto-transfer processes, the alcohol reactants **1a–1o** serve dually as reductant and aldehyde proelectrophile (Table 2). Carbonyl isoprenylation also can be conducted using the analogous aldehyde reactants **2a–2o** in combination with 2-propanol as reductant under otherwise identical conditions (Table 3). The conversion of aldehydes **2a–2o** to adducts **4a–4o** occurs with similar levels of efficiency and selectivity, although for less stable aldehydes **2m** and **2n**, which incorporate heteroatoms at the β-position, higher isolated yields are obtained *via* isoprenylation of the alcohols **1m** and **1n**.

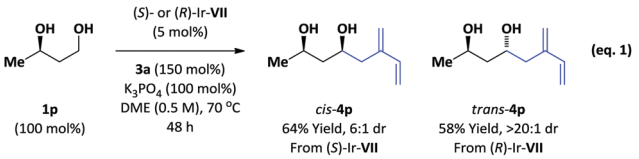
The ability of iridium complexes to catalyze site-selective oxidation of polyols is well documented and typically occurs with a kinetic preference for dehydrogenation of the less-hindered alcohol.[11] Similarly, the cyclometallated π-allyliridium *C*,*O*-benzoates

Table 3 Enantioselective iridium-catalyzed isoprenylation of aldehydes **2a–2o**[a]

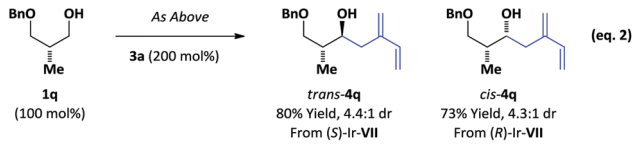


[a] Yields are of material isolated by silica gel chromatography. [b] 48 h. [c] DME (0.2 M). Enantioselectivities were determined by chiral stationary phase HPLC analysis. See ESI for further experimental details.

developed in our laboratory display a high kinetic preference for primary alcohol oxidation, enabling direct asymmetric allylation of unprotected diols.[12] The ability to conduct protecting group-free isoprenylation of chiral glycols was briefly examined using commercially available (*R*)-butane diol **1p** (eqn (1)). Using the enantiomeric iridium complexes (*S*)- and (*R*)-Ir-**VII**, the diastereomeric adducts *cis*-**4p** and *trans*-**4p** were isolated in good yield with good to complete levels of catalyst-directed diastereoselectivity, respectively. The isoprenylation of the chiral α-stereogenic alcohol **1q** also was explored (eqn (2)).[13] Absolute π-facial stereoselectivity in the carbonyl addition event was high; however, due to partial racemization of the transient aldehyde, the adducts *trans*-**4q** and *cis*-**4q** were each obtained with modest levels of catalyst-directed diastereoselectivity.

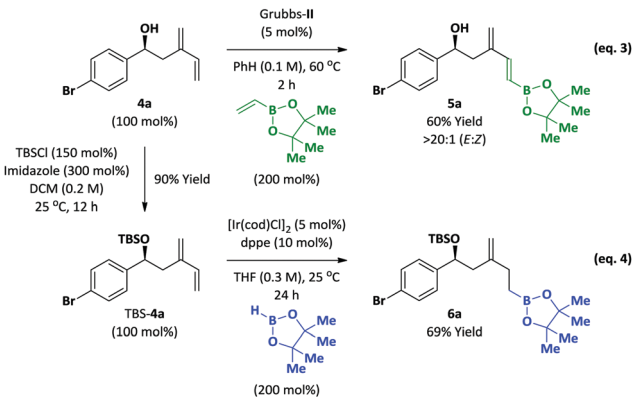


Yields refer to pure material (>20:1 dr) isolated by SiO_2 chromatography. Diastereoselectivity was determined by ^1H NMR analysis of crude reaction mixtures.



Diastereomers were inseparable by SiO_2 chromatography. Yields refer to material isolated by SiO_2 chromatography. Diastereoselectivity was determined by HPLC analysis.

Vinyl and homoallylic boronates are appealing building blocks for synthesis, due to the potential for orthogonal functionalization of both the olefin and the boronate. To illustrate one of many possibilities *vis-à-vis* elaboration of the reaction products, the diene-containing adduct **4a** was exposed to the indicated vinylboronate in the presence of the second-generation Grubbs catalyst to furnish the product of cross-metathesis as a single regio- and stereoisomer (eqn (3)).[14] Additionally, the chemo- and regioselective anti-Markovnikov product of iridium-catalyzed hydroboration, homoallylic boronate **6a**, was achieved in good yield from the 1,3-diene TBS-**4a** (eqn (4)).[15]



In summary, we report the first examples of catalytic enantioselective carbonyl isoprenylation *via* hydrogen autotransfer. This process converts aliphatic, allylic and benzylic alcohols **1a–1o** to the diene-containing adducts **4a–4o** with uniformly high levels of efficiency and enantioselectivity. Using this method, enantioselective total syntheses of the terpenoid natural products (+)-ipsenol and (+)-ipsdienol are achieved in the absence of cryogenic conditions or premetalated reagents. Furthermore, we demonstrate that aldehydes **2a–2o** are converted to an equivalent set of adducts **4a–4o** using 2-propanol as reductant under otherwise identical conditions. Finally, as illustrated by the formation of the diastereomeric adducts *cis*- and *trans*-**4p** and *cis*- and *trans*-**4q**, this method can be applied

to the stereoselective modification of unprotected diols and chiral α-stereogenic alcohols. Studies toward amphidinolide V *via* asymmetric alcohol-mediated carbonyl isoprenylation are presently underway.

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Conflicts of interest

There are no conflicts to declare.

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