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Enantioselective Iridium-Catalyzed Carbonyl Isoprenylation via Alcohol-Mediated Hydrogen Transfer

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Abstract

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.

Introduction

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 premetalated *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 (Figure 1).^[4,5] Two enantioselective reactions of this type are reported in the literature, which exploit *B*-(5-isoprenyl) and *S_n*-(5-isoprenyl) reagents that are derived via potassiation of isoprene under cryogenic conditions using Schloßer'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 K₃PO₄ (100 mol%) in THF (0.5M) at 80 °C (Table 1, entries

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Conflict of interest

There are no conflicts to declare.

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-SEGPPOS, 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-SEGPPOS was evaluated in the reaction of 4-bromobenzyl alcohol **1a** with isoprenyl *tert*-butoxy carbonate **3a**. 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).

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,^[7] 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.^[8,9] 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.^[10] Similarly, the cyclometallated π -allyliridium *C,O*-benzoates developed in our laboratory display a high kinetic preference for primary alcohol oxidation, enabling direct asymmetric allylation of unprotected diols.^[11] The ability to conduct protecting group-free isoprenylation of chiral glycols was briefly examined using commercially available (*R*)-butane diol **1p** (eq. 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 (eq. 2).^[12] 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.

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 (eq. 3).^[13] 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** (eq. 4).^[14]

Conclusions

In summary, we report the first examples of catalytic enantioselective carbonyl isoprenylation via hydrogen auto-transfer. 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 premetallated 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Notes and references

- [1]. For recent reviews on alcohol-mediated carbonyl addition, see: a) Hassan A, Krische MJ, Org. Proc. Res. Devel 2011, 15, 1236; b) Ketcham JM, Shin I, Montgomery TP, Krische MJ, Angew. Chem.Int. Ed 2014, 53, 9142; Angew. Chem. 2014, 126, 9294; c) Perez F, Oda S, Geary LM, Krische MJ, Top. Curr. Chem 2016, 374, 365; d) Shin I, Krische MJ, Top. Curr. Chem 2016, 372, 85; [PubMed: 26187028] e) Nguyen KD, Park BY, Luong T, Sato H, Garza VJ, Krische MJ, Science 2016, 354, 300; f) Kim SW, Zhang W, Krische MJ, Acc. Chem. Res 2017, 50, 2371. [PubMed: 28792731]
- [2]. For application of alcohol-mediated carbonyl addition in natural product total synthesis, see: a) Dechert-Schmitt A-MR, Schmitt DC, Gao X, Itoh T, Krische MJ, Nat. Prod. Rep 2014, 31, 504;

- [PubMed: 24514754] b) Feng J, Kasun ZA, Krische MJ, J. Am. Chem. Soc 2016, 138, 5467. [PubMed: 27113543]
- [3]. For selected reviews on enantioselective carbonyl allylation, see: a) Ramachandran PV, Aldrichim. Acta 2002, 35, 23;b) Denmark SE, Fu J, Chem. Rev 2003, 103, 2763; [PubMed: 12914480] c) Yu C-M, Youn J, Jung H-K, Bull. Korean Chem. Soc 2006, 27, 463;d) Marek I, Sklute G, Chem. Commun 2007, 1683;e) Hall DG, Synlett 2007, 1644;f) Lachance H, Hall DG, Org. React 2008, 73, 1–573;g) Yus M, Gonzalez-Gomez JC, Foubelo F, Chem. Rev 2011, 111, 7774. [PubMed: 21923136]
- [4]. For non-enantioselective methods for carbonyl isoprenylation, see: a) Tokuda M, Mimura N, Yoshioka K, Karasawa T, Fujita H, Suginome H, Synthesis 1993, 1086;b) Masuyama Y, Fuse M, Kurusu Y, Chem. Lett 1993, 1199;c) Kimura M, Fukushima M, Takushima D, J. Am. Chem. Soc 2010, 132, 16346. [PubMed: 21028812]
- [5]. For enantioselective carbonyl isoprenylation, see: a) Brown HC, Randad RS Tetrahedron 1990, 46, 4463;b) Yu C-M, Jeon M, Lee J-Y, Jeon J Eur. J. Org. Chem 2001, 1143.
- [6]. For selected alcohol-mediated enantioselective carbonyl allylations catalyzed by iridium, see: a) Kim IS, Ngai M-Y, Krische MJ, J. Am. Chem. Soc 2008, 130, 14891; [PubMed: 18841896] b) Kim IS, Han SB, Krische MJ, J. Am. Chem. Soc 2009, 131, 2514. [PubMed: 19191498]
- [7]. a) Zhang Z, Xie H, Li H, Gao L, Song Z, Org. Lett 2015, 17, 4706; [PubMed: 26371396] b) Mori K, Ikunaka M, Tetrahedron 1984, 40, 3471.
- [8]. a) Silverstein RM, Rodin JO, Wood DL, Science 1966, 154, 509;b) N., Torbjørn Pure Appl. Chem 1989, 61, 547;c) Zhang Q-H, Birgersson G, Schlyter F, Chen G-F, J. Chem. Ecol 2000, 26, 841.
- [9]. For selected total syntheses of ipsenol and ipsdienol, see refs. 4 and 5, as well as the following literature: a) Franck-Neumann M, Martina D, Heitz MP, Tetrahedron Lett 1989, 30, 6679;b) Mori K, Takikawa H, Tetrahedron 1991, 47, 2163;c) Yamamoto Y, Hara S, Suzuki A, Akira Synth. Comm 1997, 27, 1029;d) Draillard K, Lebreton J, Villiéras J, Tetrahedron: Asymmetry 1999, 10, 4281;e) Kovalenko VN, Matyushenkov EA, Russ. J. Org. Chem 2012, 48, 1168;f) Kovalenko VN, Prokhorevich KN, Russ. J. Org. Chem 2016, 52, 757
- [10]. For an authoritative review on iridium-catalyzed alcohol oxidation, see: Suzuki T, Chem. Rev 2011, 111, 1825. [PubMed: 21391567]
- [11]. a) Dechert-Schmitt A-MR, Schmitt DC, Krische MJ, Angew. Chem. Int. Ed 2013, 52, 3195;b) Shin I, Wang G, Krische MJ, Chem. Eur. J 2014, 20, 13382; [PubMed: 25169904] c) Shin I, Hong S, Krische MJ, J. Am. Chem. Soc 2016, 138, 14246. [PubMed: 27779393]
- [12]. Schmitt DC, Dechert-Schmitt A-MR, Krische MJ, Org. Lett 2012, 14, 6302. [PubMed: 23231774]
- [13]. Funk TF, Efskind J, Grubbs RH, Org. Lett 2005, 7, 187. [PubMed: 15646954]
- [14]. Fiorito D, Mazet C, ACS Catal 2018, 8, 9382.

Asymmetric Isoprenylation *via* Premetalated Reagents

Asymmetric Isoprenylation *via* Hydrogen Transfer - *This Work*

Figure 1.
Enantioselective methods for carbonyl isoprenylation.

Table 1.

Selected optimization experiments in the enantioselective iridium-catalyzed isoprenylation of 4-bromobenzyl alcohol **1a**.^a

1a (100 mol%)	3a (200 mol%)					
Entry	[Ir]	solvent	time (h)	T °C	Yield% 3a	ee%
1	(<i>S</i>)-Ir-I	THF	48	80	70	56
2	(<i>S</i>)-Ir-II	THF	48	80	72	63
3	(<i>S</i>)-Ir-III	THF	48	80	44	60
4	(<i>S</i>)-Ir-IV	THF	48	80	66	50
5	(<i>S</i>)-Ir-V	THF	48	80	69	81
6	(<i>S</i>)-Ir-VI	THF	48	80	43	90
7	(<i>S</i>)-Ir-VII	THF	48	80	70	94
8	(<i>S</i>)-Ir-VII	THF	24	70	70	95
→ 9	(<i>S</i>)-Ir-VII	DME	24	70	80	95

<p>(<i>S</i>)-Ir-I, Ar = Ph (<i>S</i>)-Ir-II, Ar = <i>p</i>-Tol</p>	<p>(<i>S</i>)-Ir-III, R = H (<i>S</i>)-Ir-IV, R = Cl</p>	<p>(<i>S</i>)-Ir-V, Ar = Ph X = CN (<i>S</i>)-Ir-VI, Ar = 3,5-Me₂-Ph X = CN (<i>S</i>)-Ir-VII, Ar = 3,5-Me₂-Ph X = NO₂</p>
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^a Yields are of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.

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 1d , R = 5-(benzodioxole) 1g , R = 2-furyl 1j , prenyl alcohol 1m , R = (CH ₂) ₂ NHBoc	1b , R = 2-F-Ph 1e , R = 2-(6-MeO-Pyr) 1h , R = 2-thienyl 1k , R = <i>c</i> -propyl 1n , R = (CH ₂) ₂ OBn	1c , R = 3,5-Cl ₂ -Ph 1f , R = 3-(6-Cl-Pyr) 1i , cinnamyl alcohol 1l , R = <i>N</i> -Boc-piperidiny 1o , isoamyl alcohol
 4a , 80% Yield 95% ee	 4b , 83% Yield 96% ee	 4c , 81% Yield 94% ee (X-Ray)
 4d , 77% Yield 96% ee	 4e , 66% Yield 96% ee	 4f , 65% Yield 94% ee
 4g , 64% Yield ^b 95% ee	 4h , 80% Yield 95% ee	 4i , 67% Yield 94% ee
 4j , 64% Yield 96% ee	 4k , 72% Yield 96% ee	 4l , 75% Yield 94% ee
 4m , 70% Yield ^b 93% ee	 4n , 67% Yield 94% ee Previously 7 Steps from (-)-Malic Acid - Now 1 Step	 4o , 70% Yield ^b 96% ee

^aYields are of material isolated by silica gel chromatography. ^b48 h. ^cDME (0.2 M). Enantioselectivities were determined by chiral stationary phase HPLC analysis. See supporting information for further experimental details.

Table 3.

Enantioselective iridium-catalyzed isoprenylation of aldehydes **2a-2o**.^a

2a , R = 4-Br-Ph 2d , R = 5-(benzodioxole) 2g , R = 2-furyl 2j , prenyl alcohol 2m , R = (CH ₂) ₂ NHBoc	2b , R = 2-F-Ph 2e , R = 2-(6-MeO-Pyr) 2h , R = 2-thienyl 2k , R = <i>c</i> -propyl 2n , R = (CH ₂) ₂ OBn	2c , R = 3,5-Cl ₂ -Ph 2f , R = 3-(6-Cl-Pyr) 2i , cinnamaldehyde 2l , R = <i>N</i> -Boc-piperidinyl 2o , isoamyl alcohol
 4a , 84% Yield 96% ee	 4b , 75% Yield 96% ee	 4c , 64% Yield ^c 95% ee (X-Ray)
 4d , 77% Yield 96% ee	 4e , 71% Yield 96% ee	 4f , 72% Yield ^c 94% ee
 4g , 72% Yield 95% ee	 4h , 83% Yield 95% ee	 4i , 70% Yield ^b 96% ee
 (+)-Ipsdienol 4j , 71% Yield 96% ee	 4k , 80% Yield 96% ee	 4l , 78% Yield 95% ee
 4m , 58% Yield ^b 95% ee	 4n , 62% Yield ^{b,c} 94% ee	 (+)-Ipsenol 4o , 68% Yield ^b 95% ee

^aYields are of material isolated by silica gel chromatography. ^b48 h. ^cDME (0.2 M). Enantioselectivities were determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.