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Enantio- and Regioselective Iridium-Catalyzed Allylic Hydroxylation

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Supporting Information

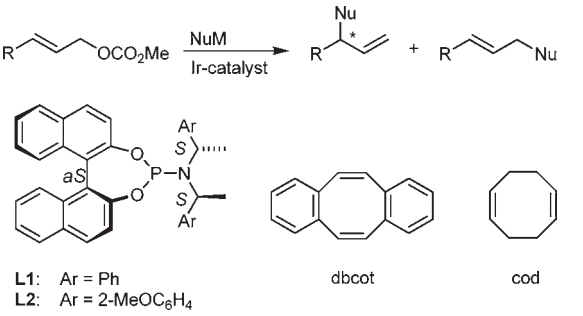
ABSTRACT: The first enantioselective allylic hydroxylation to prepare branched allylic alcohols directly is described. Bicarbonate was used as nucleophile in conjunction with new single component Ir-catalysts, which are stable to air and water. Excellent regio- and enantioselectivities have been achieved with a representative set of substrates.

The transition-metal catalyzed allylic substitution is one of the most studied approaches for the synthesis of chiral allyl compounds. For many years this field was dominated by Pd-catalyzed reactions[1] of symmetrically disubstituted substrates, which are often cumbersome to prepare. More recently, enantioselective reactions with readily available monosubstituted substrates (Scheme 1) have come into focus. With these, particularly good results were obtained for allylic alkylations and aminations upon use of iridium catalysts.[2] Less developed are reactions with O-nucleophiles, because standard reaction conditions working well for C- and N-nucleophiles are usually not suitable. Nevertheless, procedures have been worked out for enantioselective allylic reactions with phenolates and alkoxides as well as carboxylates using Ir-,[3] Pd-,[4] Rh-,[5] or Ru-catalysts.[6]

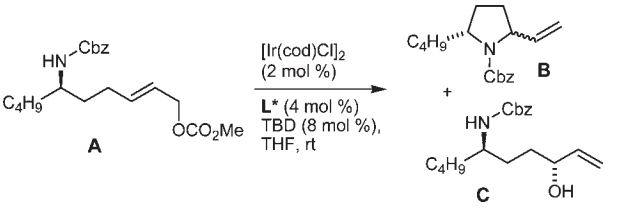
Despite the recent progress, the direct allylic hydroxylation (Nu=OH), yielding synthetically highly valuable allylic alcohols[7] and arguably the most important reaction with O-nucleophiles, has defied all attempts. Carreira et al. have perhaps most intensely pursued this topic.[8] Their catalyst was generated in situ from $[Ir(cod)Cl]_2$ (cod = cyclooctadiene), a chiral phosphoramidite ligand and a base for C−H activation; this in situ catalyst is notoriously sensitive to air and moisture. As substitute for the elusive reaction the Carreira team successfully used a reaction with a silanolate as nucleophile yielding branched allylic silyl ethers.

In view of the prior art, we are pleased to report the first highly enantioselective allylic hydroxylation of linear carbonates to give branched allylic alcohols directly. Our starting point was the cyclization reaction described in Scheme 2, which shows strong substrate control. Upon double asymmetric induction, the matched combination (**L*** = *ent*-**L2**) was fast and gave the pyrrolidine **B** with excellent diastereoselectivity (>98:2) in favor of the *trans*-isomer, while the mismatched combination (**L*** = **L2**) was slow, and the diastereomerically pure alcohol **C** was isolated in up to 16% yield as a side product. This compound could be formed by a direct reaction of an intermediary (π-allyl)Ir complex with H_2O or OH^-. Another possibility is a reaction with HCO_3^- anion (eq 1), resulting from the reaction of water with $H_3COCO_2^-$ formed from the leaving group. Gais et al. have shown that bicarbonate anion is a good nucleophile in Pd-catalyzed dynamic kinetic resolution (DYCAT) of racemic allylic carbonates.[9] Accordingly, a route according to eq 1 appeared most likely.

Scheme 1. Ir-Catalyzed Allylic Substitution

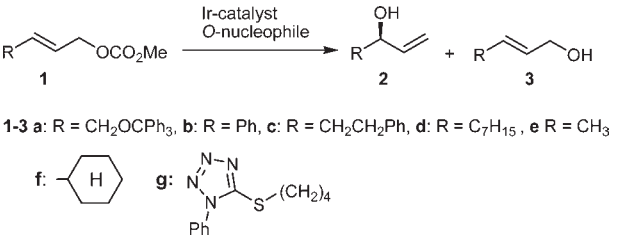


Scheme 2. Allylic Alcohol As Side Product of an Intramolecular Allylic Amination[a]



[a] TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene.

Scheme 3. Iridium-Catalyzed Allylic Hydroxylation



In order to follow the lead provided by Scheme 2, hydroxylation experiments were carried out with the carbonate **1a**, which is

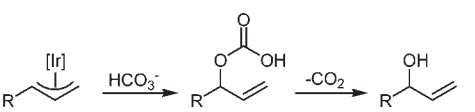


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Table 1. Screening According to Scheme 3 using Carbonate 1a As Substrate[a]

entry	catalyst	pronucleophile	solvent	temp (°C)	time (h)	**2**/**3**[b]	yield (%)[c]	ee (%)[d]	remarks
1	in situ/*ent*-**L2**[e]	H_2O[f]	THF	50	84	n.d.	28	89	many products
2	in situ/**L2**[e]	$KHCO_3$	THF	50	20	n.d.	29[g]	96	many products
3	in situ/**L2**[e]	$KHCO_3$, 18-crown-6	THF	50	19	n.d.	54	97	many products
4	**C1**	H_2O[f]	THF	50	24	-	-	-	no conversion
5	**C1**	$KHCO_3$, 18-crown-6	THF	50	0.5	n.d.	51	93	many products
6	**C3**	H_2O[f]	THF	50	16	n.d.	65[g]	55	clean reaction
7	**C3**	$KHCO_3$, 18-crown-6	THF	50	17	n.d.	38[g]	80	many products
8	**C3**	$KHCO_3$	CH_2Cl_2/H_2O 10:1	rt	96	n.d.	67[g]	89	clean reaction
9	**C3**	$KHCO_3$, 18-crown-6	CH_2Cl_2/H_2O 10:1	rt	2	n.d.	84	87	clean reaction
10	**C3**	$KHCO_3$, NBu_4ClO_4	CH_2Cl_2/H_2O 10:1	42	7.5	n.d.	66	93	clean reaction
11	**C3**	$KHCO_3$	DMF/H_2O 10:1	rt	2	94:6	86	94	clean reaction
12	**C3**	$KHCO_3$	DMF	rt	2	98:2	89	94	clean reaction
13[h]	**C3**	$KHCO_3$	DMF/H_2O 10:1	rt	1	95:5	92	94	clean reaction
14	**C2**	$KHCO_3$	DMF/H_2O 10:1	rt	1	96:4	87	94	clean reaction
15	**C1**	$KHCO_3$	DMF/H_2O 10:1	50	21	78:22	48	76	clean reaction

[a] Conditions: argon atmosphere, carbonate **1a** (1 equiv), pronucleophile (1.7 equiv), catalyst (4 mol %), organic solvent (4 mL/mmol of **1a**), occasionally water (0.4 mL/mmol of **1a**). [b] Determined by ^1H NMR of the crude product; n.d. = not determined. [c] Isolated yield of branched product. [d] Determined by HPLC on a chiral column. [e] In situ preparation: argon atmosphere, $[Ir(cod)Cl]_2$ (2 mol %), **L2** (4 mol %), TBD (8 mol %), THF, rt, 5 min. [f] 2 equiv were used. [g] Incomplete conversion. [h] Reaction under air.

prone to give low degrees of selectivity[10] and therefore is a significant substrate (Scheme 3).

First, a catalyst prepared in situ from ligand **L2** was employed (Table 1, entries 1−3). With water and $KHCO_3$ as pronucleophiles (THF, 50 °C), the yield of the hydroxylation product **2a** was poor, probably because of catalyst deactivation caused by reversibility of the cyclometallation or insolubility of the salt in THF.[11] Considerable improvement with respect to rate was achieved upon addition of 18-crown-6, however, numerous side products were also formed. On the other hand, the enantioselectivity of the reaction with bicarbonate was high.

Next, the isolated allyl complex **C1** (Figure 1) derived from **L2**, cod and carbonate **1e** was probed. Complexes of this type have furnished excellent results in allylic substitutions.[12,13a] Their preparation has become very easy with a direct one-step procedure recently developed by us (eq 2).[13b] However, the reaction of **1a** with H_2O as pronucleophile gave no conversion when **C1** was used as catalyst (entry 4). With $KHCO_3$/18-crown-6 as pronucleophile, hydroxylation product **2a** was obtained with high enantiomeric excess though in moderate yield (entry 5).

It appeared likely that the complex **C1** is too sensitive to withstand an aqueous reaction medium.[11] Better stability would be expected for corresponding complexes of dbcot (dbcot = dibenzocyclooctatetraene) (Scheme 1), which displays stronger binding to Ir than cod.[14] Our preparative procedure (eq 2) worked as well with dbcot as with cod as coligand, and the complexes **C2** and **C3** were readily prepared.[15] These compounds indeed were found to be stable toward air and water.

$$[Ir(\text{diene})Cl]_2 + \mathbf{L} + \mathbf{1} + AgOTf \rightarrow \mathbf{C} + AgCl + CO_2 + CH_3OH \quad (2)$$

An initial allylic substitution with water as pronucleophile and **C3** as catalyst gave low enantioselectivity and was slow (entry 6); with $KHCO_3$/18-crown-6 improved selectivity was obtained (entry 7), but there were many unidentified side products. Next we tried the conditions of Gais et al. mentioned above, i.e., $KHCO_3$ as pronucleophile in a biphasic mixture of water and

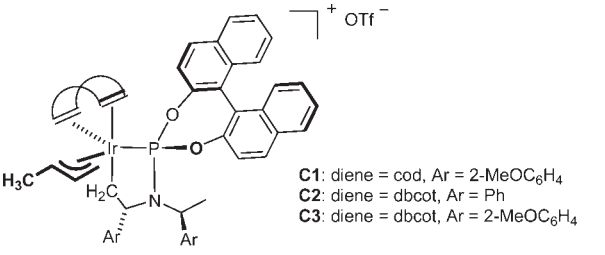

Figure 1. (π-Allyl)Ir-complexes, prepared from **1e** according to eq 2, used in this work.

CH_2Cl_2. The reaction was very slow under these conditions (entry 8). However, phase transfer in the biphasic mixture with 18-crown-6 was beneficial for the rate, the reaction time was 2 h at room temperature (entry 9), but enantioselectivity was low; with NBu_4ClO_4 as additive (entry 10) the situation was reversed.

The results at that stage indicated that the dbcot complexes are very robust catalysts tolerating even water as solvent. As a consequence, it was possible to screen a wide variety of solvents (see Supporting Information). Excellent results were obtained with EtOAc, CH_3CN, and acetone, while Et_2O, toluene, DMSO, and *i*PrOH were not satisfactory. Finally, we found DMF/H_2O 10:1 particularly well suited, because 18-crown-6 was not required as additive (entry 11), although it does accelerate the reaction (see Supporting Information). An excellent regioselectivity of typically 96:4 was found. Control experiments gave further significant results: (a) Water is not a necessary additive in case of DMF as solvent (entry 12); (b) Carbonates other than $KHCO_3$ can be used as pronucleophiles (see Supporting Information); (c) It is possible to carry out reactions without inert gas atmosphere (entry 13); (d) The complex **C2**, derived from the commercially available ligand **L1**, also gave rise to excellent regio- and enantioselectivity (entry 14); and (e) Even under the optimal reaction conditions, the complex **C1** derived from cod failed to give a useful result (entry 15).

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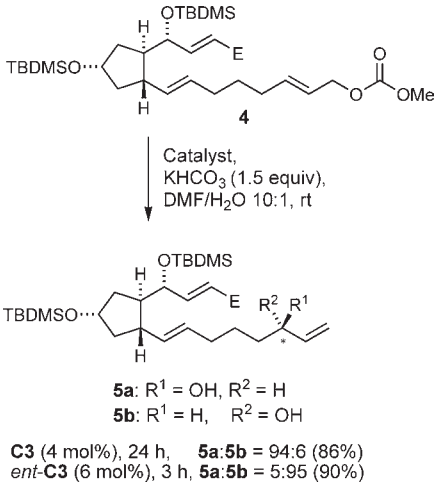
Table 2. Substrate Scope of the Reaction According to Scheme 3[a]

entry	R (substrate)	catalyst (mol %)	time (h)	yield (%)[b]	2/3[c]	ee (%)[d]
1	CH_2OCPh_3 (**1a**)	**C2** (1)	3.5	92	96:4	95
2[e]	Ph (**1b**)	**C2** (1)	7.5	90	99:1	88
3	Ph (**1b**)	**C3** (1)	19.5	86	98:2	95
4[f]	Ph (**1b**)	**C3** (4)	0.7	72	98:2	96
5[e]	CH_2CH_2Ph (**1c**)	**C2** (1)	6.5	82	97:3	87
6	CH_2CH_2Ph (**1c**)	**C3** (1)	19	90	97:3	93
7[f]	CH_2CH_2Ph (**1c**)	**C3** (4)	0.5	81	99:1	89
8	C_7H_{15} (**1d**)	**C2** (1)	5.5	84	96:4	85
9	C_7H_{15} (**1d**)	**C3** (1)	18.5	74	98:2	89
10[f]	C_7H_{15} (**1d**)	**C3** (4)	1.5	77	99:1	86
11	*c*-C_6H_{11} (**1f**)	**C3** (1)	3.5	77	99:1	95
12	$C_{11}H_{13}N_4S$ (**1g**)	**C3** (4)	16	95	99:1	90

[a] Solvent: DMF/H_2O 10:1, rt. [b] Isolated yield of branched product. [c] Determined by ^1H NMR or GC. [d] Determined by HPLC or GC on a chiral column. The absolute configurations were determined by comparison of the optical rotations with those of known compounds. [e] The reaction was carried out at 50 °C. [f] The reaction was carried out in CH_2Cl_2/H_2O 10:1 with additional 18-crown-6 at 40 °C.

Scheme 4. Application of the Iridium-Catalyzed Allylic Hydroxylation in Natural Products Synthesis (E = CO_2CH_3)



The scope with respect to allylic substrates was explored using catalysts **C2** and **C3**, usually at a load of 1 mol %, which was found to suffice in the case of substrate **1a** (Scheme 3, Table 2, entry 1). For the carbonate **1b** (entries 2−4) superior results were obtained with **C3**. In this case the enantioselectivity was even better in CH_2Cl_2/H_2O than in DMF as solvent (entry 4). This once more demonstrates the remarkable robustness of the catalyst. Generally, **C3** was the catalyst of choice with respect to enantioselectivity for substrates with sp^3-bound substituents (entries 5−12). Absolute configurations of the products were as anticipated according to a general rule, which is valid for all Ir-catalyzed allylic substitutions probed so far.[2a]

As an application in natural products synthesis, we have used the new procedure for the preparation of an analog of the antibiotic brefeldin A, 15-desmethyl-15-vinylbrefeldin A, which appears of interest in conjunction with biological effects on the Golgi apparatus.[16] The tetrazole **2g** (Scheme 3) is a precursor for the corresponding side chain of our route[16] to these analogs. This example demonstrates absence of interference by the potentially coordinating tetrazole moiety (Table 2, entry 12).

In another approach to the same target (Scheme 4), the carbonate **4** was prepared from natural brefeldin A and subjected to the hydroxylation reaction (Scheme 4). In this case, the products are diastereomers rather than enantiomers. Substrate control of stereoselectivity was anticipated to be low. Indeed, enantiomeric catalysts **C3** and *ent*-**C3** effected formation of either of the diastereomers **5a** and **5b**, respectively, with the same degree of selectivity, 95:5, as found for the side chain precursor **2g**.

In summary, we have developed the first direct enantioselective allylic hydroxylation to give synthetically valuable branched allylic alcohols directly. Essential for success was the use of a new, air, and moisture stable single component Ir-catalyst and carbonate anion as nucleophile. The system tolerates a wide variety of solvents and reaction conditions as well as air. Excellent regioselectivities and enantioselectivities have been achieved with a representative set of substrates.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, results of catalyst screening experiments, characterization of compounds, determination of regio- and enantioselectivities. This material is available free of charge via the Internet at http://pubs.acs.org.

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