Enantioselective Propargylation

DOI: 10.1002/ange.201200239

Diastereo- and Enantioselective Iridium-Catalyzed Carbonyl Propargylation from the Alcohol or Aldehyde Oxidation Level: 1,3-Enynes as Allenylmetal Equivalents**

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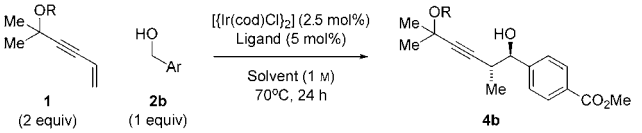
Carbonyl propargylation has been the topic of intensive investigation for over half a century.[1,2] An effective approach to enantioselective carbonyl propargylation involves the addition of chirally modified allenylmetal reagents,[3–7] including axially chiral derivatives.[5] Contributions include allenylboron reagents that are chirally modified at boron, as reported by Yamamoto,[3a] Corey,[3b] and Soderquist,[3c,d] allenylstannanes that are chirally modified at tin, as first reported by Mukaiyama,[4] as well as axially chiral allenylstannanes, allenylsilanes, allenylboron, and allenylzinc reagents that engage aldehydes in enantioselective propargylation, as described by Marshall,[5a,b,e,f] Hayashi,[5d] and Panek,[5c] respectively. Increasingly effective protocols for carbonyl propargylation, which involve stoichiometric chirality transfer, continue to be developed.[6,7] Enantioselective aldehyde propargylation using allenyltin[8] and allenylsilicon[9] reagents may be catalyzed by chiral Lewis acids or chiral Lewis bases, as first reported by Keck[8a] and Denmark,[8f] respectively. Copper catalysts promote enantioselective carbonyl propargylation by employing allenylboron and propargylboron reagents, as reported by Kanai and Shibasaki and Boehringer–Ingelheim Pharmaceuticals Inc.[10] More recently, Schaus, Antilla, and Reddy reported chiral H-bond donor and Brønsted acid catalyzed propargylations using allenylboron reagents.[11] Finally, catalytic enantioselective Nozaki–Hiyama coupling of propargyl halides delivers products of carbonyl propargylation.[12] Withstanding the Nozaki–Hiyama protocol,[12] methods available for enantioselective carbonyl propargylation have relied on stoichiometric allenyl- or propargylmetal reagents. Moreover, while carbonyl propargylations for the construction of non-methylated polyacetate subunits are common, catalytic diastereo- and enantioselective propargylations that convert achiral reactants to polypropionate substructures remain undeveloped. We envisioned an alternative strategy for carbonyl propargylation based on the "transfer hydrogenative coupling"[13] of 1,3-enynes and primary alcohols. Although related Rh- and Ni-catalyzed reductive couplings occur at the acetylenic terminus of the enyne,[14,15] ruthenium catalysts were found to promote enyne–alcohol C–C coupling to form the desired products of propargylation as single regioisomers, but without stereocontrol.[16] Herein, we report that iridium catalysts modified by (*R*)-segphos[17] or (*R*)-DM-segphos promote highly *anti*-diastereo- and enantioselective enyne-mediated carbonyl propargylation from the alcohol or aldehyde oxidation level in the absence of stoichiometric allenyl- or propargylmetal reagents.

Initial studies focused on the C–C coupling of benzylic alcohol **2b** to enynes **1a** and **1b**, which are derived from 2-methyl-3-butyn-2-ol (47 USD/Kg).[18] Whereas enyne **1a** failed to participate in C–C coupling to benzylic alcohol **2b** under the conditions of iridium catalysis (Table 1, Entry 1), the corresponding TBS ether **1b** couples to benzylic alcohol **2b** to form the desired propargylation product **4b**-TBS in 69% yield as a 1:1 mixture of diastereomers upon exposure to the catalyst generated from [{Ir(cod)Cl}$_2$] and dppf (Table 1, Entry 2). At this stage, a series of chiral ligands were assayed

Table 1: Structure–selectivity relationships between enynes **1** and ligands.[a]



1 (2 equiv) **2b** (1 equiv) **4b**

Entry	**1**, R	Ligand	Solvent	Yield [%]	d.r.	*ee* [%]
1	**1a**, H	dppf	PhMe	0	–	–
2	**1b**, TBS	dppf	PhMe	69	1:1	–
3	**1b**, TBS	(*R*)-segphos	PhMe	35	1:1	93
4	**1b**, TBS	(*R*)-DM-segphos	PhMe	75	6:1	80
5	**1b**, TBS	(*R*)-DTBM-segphos	PhMe	0	–	–
6	**1c**, TIPS	(*R*)-segphos	PhMe	81	3:1	94
7	**1c**, TIPS	(*R*)-DM-segphos	PhMe	80	8:1	87
8	**1c**, TIPS	(*R*)-DM-segphos	THF	81	12:1	90
9	**1c**, TIPS	(*R*)-DM-segphos	CH_3CN	50	13:1	93
10[b]	**1c, TIPS**	**(*R*)-DM-segphos**	**THF**	**75**	**12:1**	**92**

[a] Yields of isolated materials. Diastero- and enantioselectivities were determined by HPLC or GC analysis on a chiral stationary phase. Entry in bold highlights optimized reaction conditions. See the Supporting Information for details. [b] CH_3CN (2 equiv). cod = cycloocta-1,5-diene, DM = 3,5-dimethyl, dppf = diphenylphospinoferrocene, DTBM = 3,5-di-*tert*-butyl-4-methoxy, (*R*)-segphos = (*R*)-5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole, TBS = *tert*-butyldimethylsilyl, THF = tetrahydrofuran, TIPS = triisopropylsilyl.

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[**] Acknowledgements is made to the Robert A. Welch Foundation (F-0038), the NSF (CHE-1008551), and the Government of Canada's Banting Postdoctoral Fellowship Program (L.M.G.) for financial support. We thank Dr. Taichiro Touge of Takasago for the generous donation of segphos ligands.

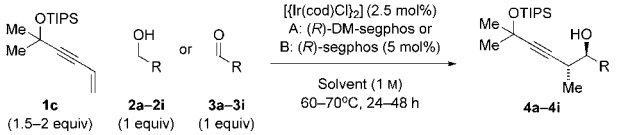
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201200239.

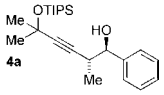
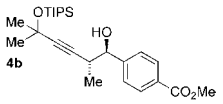
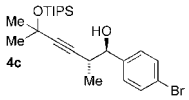
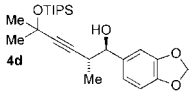
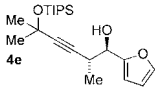
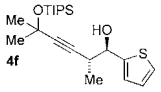
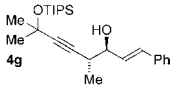
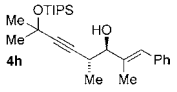
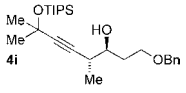
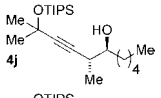
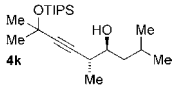
(Table 1, Entries 3–5). Whereas (*R*)-segphos provides homopropargylic alcohol **4b**-TBS in 93% enantiomeric excess, the yield and diastereoselectivity were poor (Table 1, Entry 3). Using (*R*)-DM-segphos, homopropargylic alcohol **4b** was isolated in 75% yield with a promising 6:1 *anti*-diastereoselectivity and 80% enantiomeric excess (Table 1, Entry 4). Increased *anti*-diastereoselectivity upon use of xylyl-substituted ligands also was observed in the binap and p-phos ligand classes, although segphos ligands[17] consistently provided higher diastereo- and enantioselectivity. It was postulated that an even more sterically demanding ligand, (*R*)-DTBM-segphos, might promote higher stereoselectivities, however, this catalytic system did not produce **4b**-TBS (Table 1, Entry 5).

Given these trends, it was postulated that increased steric demand of the enyne might enhance *anti*-diastereoselectivity. Indeed, use of the enyne **1c**, which incorporates a TIPS ether, and the (*R*)-segphos modified catalyst provided homopropargylic alcohol **4b**-TIPS in 81% yield, 3:1 *anti*-diastereoselectivity, and 94% enantiomeric excess (Table 1, Entry 6). Furthermore, by using the TIPS ether enyne **1c** in combination with (*R*)-DM-segphos, homopropargylic alcohol **4b**-TIPS was obtained in 80% yield, 8:1 *anti*-diastereoselectivity, and 87% enantiomeric excess (Table 1, Entry 7). Upon use of THF as solvent, 12:1 *anti*-diastereoselectivity and 90% enantiomeric excess were observed (Table 1, Entry 8). Use of acetonitrile as solvent enhanced stereoselectivity (93% *ee*, 13:1 d.r.), but diminished the yield of isolated product (Table 1, Entry 9). Use of acetonitrile as an additive in THF proved optimal, allowing the homopropargylic alcohol **4b**-TIPS to be generated in 75% yield, 12:1 *anti*-diastereoselectivity, and 92% enantiomeric excess (Table 1, Entry 10). The effect of solvent on stereoselectivity is more pronounced when the reaction is performed from the aldehyde oxidation level.[19] The observed correlation between increased ability of the solvent to coordinate to the metal with selectivity may be consistent with a slowing of the overall reaction rate (see below).

With these optimized conditions in hand, enyne **1c** was coupled to a diverse range of alcohols **2a**–**2k** (Table 2). The homopropargylic alcohols **4a**–**4k** were formed with uniformly high levels of *anti*-diastereo- and enantioselectivity, whether the reaction was performed in pressure tubes or round-bottomed flasks.[20] While reactions of benzylic and allylic alcohols **2a**–**2h** require (*R*)-DM-segphos to enforce stereoselectivity, reactions of aliphatic alcohols **2i**–**k** were highly stereoselective by using (*R*)-segphos as ligand. Reactions with alcohols **2g**–**k** were higher yielding in the presence of either isopropanol or formic acid, although the reason for this observation remains unclear. Aliphatic alcohols branched at the α position are converted to homopropargylic alcohols with exceptional levels of stereoselectivity, however, diminished yields of

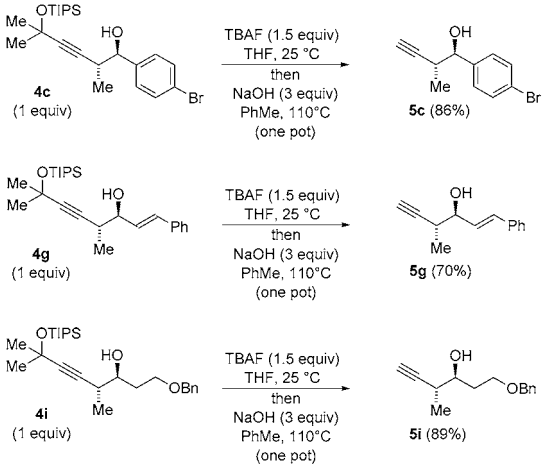
Table 2: *anti*-Diastereo- and enantioselective carbonyl propargylation from the alcohol or aldehyde oxidation level.[a]



Entry	Oxidation level	Lig.	Solv.	Product	Yield [%]	d.r.	*ee* [%]
1	alcohol	A	THF		85	19:1	91[b]
	aldehyde	A	THF		79	12:1	86[b]
2	alcohol	A	THF		75	12:1	92[b]
	aldehyde	A	THF		86	10:1	90[b]
3	alcohol	A	THF		87	12:1	89[b]
	aldehyde	A	THF		89	11:1	87[b]
4	alcohol	A	THF		77	18:1	92[b]
	aldehyde	A	THF		82	20:1	89[b]
5	alcohol	A	THF		82	22:1	94[b]
	aldehyde	A	THF		89	12:1	90[b]
6	alcohol	A	THF		81	29:1	95[b]
	aldehyde	A	THF		78	12:1	95[b]
7	alcohol	A	PhMe		38	≥40:1	99[c]
	aldehyde	A	THF		67	22:1	94
8	alcohol	A	$PhCF_3$		62	32:1	90[d]
	aldehyde	A	THF		82	24:1	89[f]
9	alcohol	B	$PhCF_3$		53	40:1	99[d,e]
	aldehyde	B	THF		89	17:1	99[f]
10	alcohol	B	$PhCF_3$		54	≥50:1	99[d,e]
	aldehyde	B	THF		68	≥50:1	99[f]
11	alcohol	B	$PhCF_3$		48	≥50:1	96[d,e]
	aldehyde	B	THF		68	≥50:1	96[f]

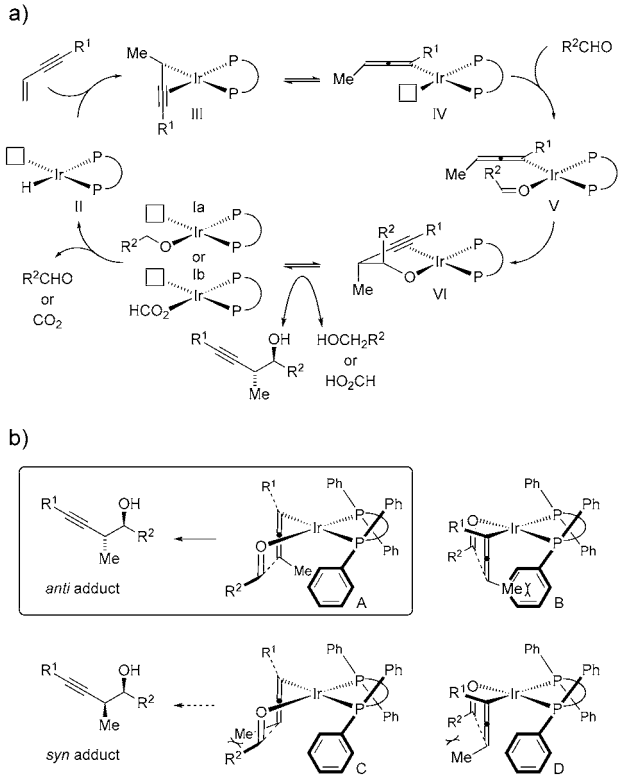
[a] Reaction conditions as described in Table 1. HCO_2H (1.5 equiv) added to reactions with aldehydes. [b] MeCN (2 equiv). [c] *iso*-Propanol (1 equiv). [d] HCO_2H (0.5 equiv). [e] [{Ir(cod)Cl}$_2$] (5 mol%), (*R*)-segphos (10 mol%). [f] Na_2SO_4 (1 equiv).

isolated products were observed for this substrate class. Using formic acid as terminal reductant, enyne **1c** participates in reductive couplings to aldehydes **3a**–**3i** to furnish an equivalent set of homoallylic alcohols **4a**–**4i** in good to excellent yield with outstanding levels of *anti*-diastereo- and enantioselectivity (Table 2). As observed in the coupling of benzylic and allylic alcohols, (*R*)-DM-segphos was required to enforce stereoselectivity in the propargylation of (hetero)aryl and α,β-unsaturated aldehydes **3a**–**3h**, whereas aliphatic aldehydes **3i**–**3k** undergo stereoselective propargylation using (*R*)-segphos as ligand. For aldehydes **3i**–**3k**, higher yields were obtained upon use of Na_2SO_4 (1 equiv) as additive.[21] Propargylation products **4c**, **4g**, and **4i** are directly converted to the corresponding terminal alkynes **5c**, **5g**, and **5i** upon exposure to TBAF and NaOH in refluxing toluene (Scheme 1). As terminal alkynes **5c** and *ent*-**5i** are known compounds of established relative and absolute stereochemistry, their preparation served to confirm the stereochemical assignment of adducts **4a**–**4k**.



Scheme 1. Deprotection of homopropargyl alcohols **4c**, **4g**, and **4i** to generate terminal alkynes **5c**, **5g**, and **5i**. Yields of isolated materials are given. See the Supporting Information for details. TBAF = tetra-*n*-butylammonium fluoride.

A plausible catalytic mechanism is as follows. The combination of $[\{Ir(cod)Cl\}_2]$, ligand, and reactant alcohol provides the iridium(I) alkoxide **I**, which dehydrogenates to form an aldehyde and generate iridium(I) hydride **II**. For reactions conducted from the aldehyde oxidation level, the formate complex **Ib** is converted to iridium(I) hydride **II**. Enyne hydrometallation provides the σ-propargyl- and allenyliridium species **III** and **IV**, respectively. Coordination of the aldehyde by the latter provides **V**, which engages in carbonyl addition through a closed transition structure to furnish the homopropargylic iridium(I) alkoxide **VI**. Alkoxide exchange with a reactant alcohol delivers the product and regenerates the iridium(I) alkoxide **I** (Scheme 2). Although undescribed for iridium, the stoichiometric reaction of 1,3-enynes and $[RuHCl(CO)(PPh_3)_3]$ to form σ-allenyl complexes that have been characterized by single crystal X-ray diffraction is known.[22a] Additionally, the allenyliridium-

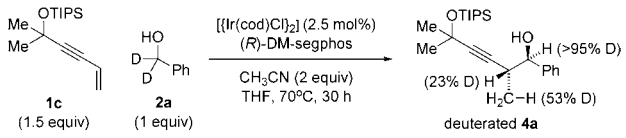


Scheme 2. General catalytic mechanism and stereochemical model accounting for the observed *anti*-diastereo- and enantioselectivity.

(III) complex $[IrCl(PPh_3)_2(NHSO_2Ph)(CO)(\eta^1\text{-}CH{=}C{=}CH_2)]$ has been isolated, and characterized by single crystal X-ray diffraction.[22b] The stereochemical outcome of the transformation is predicted on the basis of the indicated model, which involves carbonyl addition through the closed six-centered transition state **A** (Scheme 2). Regarding the conformation of such square-planar allenyliridium species **A**–**D**, it is shown in a related η^1-allenylplatinum(II) complex, *trans*-$[Pt(PPh_3)_2(Br)(\eta^1\text{-}CH{=}C{=}CH_2)]$, that the allenyl moiety lies roughly perpendicular to the square coordination plane.[22c]

As the allenyliridium substructures of transition states **A** and **B** exhibit enantiomeric axial chirality, enantioselective enyne-mediated propargylation requires high kinetic stereoselectivity in the enyne hydrometalation event to form a single diastereomeric allenyliridium intermediate, or reversible enyne hydrometalation to correct for incomplete stereoselectivity, should the less stable allenyliridium species be formed. To probe this issue, the coupling of enyne **1c** and $[D_2]$-benzyl alcohol **2a** was performed under standard conditions (Scheme 3). The distribution of deuterium in deuterated **4a** suggests that the enyne hydrometalation is reversible and that the carbonyl addition occurs by way of a single diastereomeric allenyliridium intermediate, even if the kinetic stereoselectivity of the hydrometalation is incomplete.

In summary, we report highly *anti*-diastereo- and enantioselective iridium-catalyzed enyne-mediated carbonyl propargylations from the alcohol or aldehyde oxidation level. This methodology provides an alternative to stoichiometric (organo)metallic reagents in enantioselective carbonyl propar-



Scheme 3. Deuterium labeling studies suggest reversible enyne hydrometallation in advance of C–C coupling. See the Supporting Information for ^{1}H NMR spectra.

gylation. Additionally, reactions performed directly from the alcohol oxidation level bypass redox manipulations otherwise required for discrete aldehyde generation. Future studies will focus on the development of related C–C bond forming transfer hydrogenations, including the catalytic C–C coupling of propargyl chlorides and alcohols.

Received: January 10, 2012
Published online: February 15, 2012

Keywords: enantioselectivity · homogeneous catalysis · iridium · propargylation · transfer hydrogenation

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[18] 2-Methyl-3-butyn-2-ol may be purchased from City Chemical for $47.17 per kg (October 20, **2011**).

[19] The analogous reactions between enyne **1c** and aldehyde **4b** also gave adduct **4b** in 76% yield, 4:1 *anti*-diastereoselectivity, and 76% enantiomeric excess in toluene as solvent. When the reaction was conducted in THF, a 6:1 *anti*-diastereoselectivity and 86% enantiomeric excess were observed. When the reaction was conducted in THF using CH_3CN (2 equiv) as an additive, **4b** was obtained in 86% yield with 10:1 *anti*-diastereoselectivity and 90% enantiomeric excess.

[20] Experiments reported in Tables 1 and 2 were made in pressure tubes. However, the reaction of enyne **1c** and alcohol **2c** conducted in a round-bottomed flask fitted with a reflux condenser gave **4c** in similar yields and selectivities. See the Supporting Information for details.

[21] The propargylation of aldehyde **3h** gave adduct **4h** in 58% yield in the absence of Na_2SO_4 and 77% yield in the presence of Na_2SO_4 (1 equiv) under otherwise identical conditions. It is possible that Na_2SO_4 is acting as a desiccant, as the deliberate introduction of water (2 equiv) to the reaction mixture dramatically reduces the reaction rate.

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