Asymmetric Catalysis

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Enantioselective Carbonyl Propargylation by Iridium-Catalyzed Transfer Hydrogenative Coupling of Alcohols and Propargyl Chlorides**

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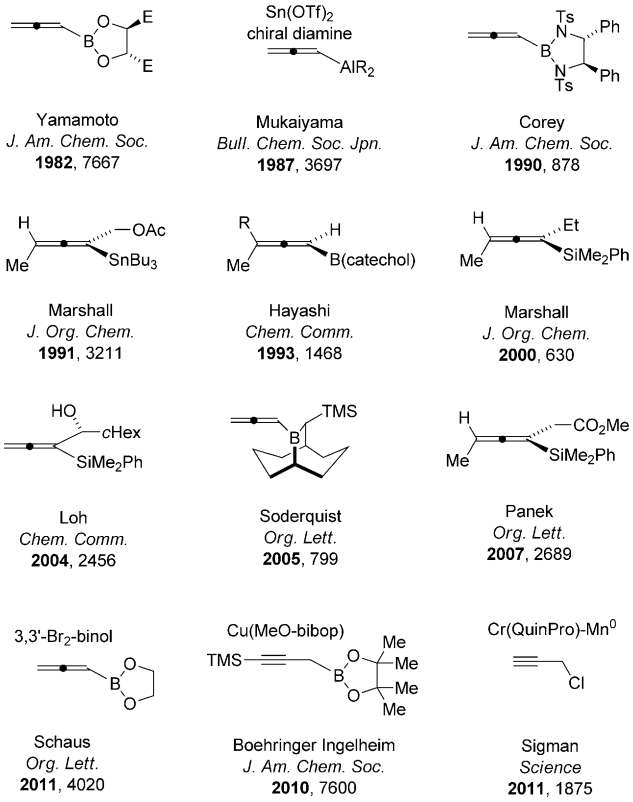
Carbonyl propargylation is typically conducted using preformed allenyl- and propargylmetal reagents.[1,2] Enantioselective variants have been achieved using allenylmetal reagents that incorporate chiral modifiers at the metal center, as in the case of boron[3] and tin[4] reagents. Axially chiral allenylmetal reagents based on tin,[5a] silicon,[5b,c] boron,[5d] and zinc[5e–g] also have proven effective. Methods for enantioselective carbonyl propargylation that involve stoichiometric chirality transfer continue to be developed.[6,7] Chiral catalysts also promote enantioselective carbonyl propargylation. Chiral Lewis acids or chiral Lewis bases have been used in combination with allenyltin[8] and allenylsilicon[9] reagents. Copper catalysts promote enantioselective carbonyl propargylation in combination with allenylboron and propargylboron reagents.[10] More recently, chiral hydrogen-bond donors and Brønsted acids have been used to catalyze propargylations that employ allenylboron reagents.[11] Finally, catalytic enantioselective Nozaki–Hiyama reactions of propargyl halides have been reported (Scheme 1).[12]

Without exception, all aforementioned methods for enantioselective carbonyl propargylation employ aldehyde electrophiles in combination with either stoichiometric allenyl- and propargylmetal reagents, or propargyl halides in combination with stoichiometric metallic reductants. In the course of exploring redox-triggered C–C couplings of alcohols and π-unsaturated reactants through transfer hydrogenation,[13] a protocol for *anti*-diastereoselective and enantioselective formal carbinol C–H propargylation employing 1,3-enynes as propargyl donors was developed by our research group.[14] This protocol bypasses stoichiometric metallic reagents and provides polypropionate building blocks in the form of methyl-substituted homopropargylic alcohols. To access the corresponding polyacetate substructures, a related redox-triggered C–C coupling of alcohols and propargyl chlorides was envisioned. Herein, we report that



Scheme 1. Selected allenyl- and propargylmetal reagents for enantioselective carbonyl propargylation. Ac = acetate, bibop = bi-dihydrobenzoxaphosphole, binol = 1,1'-bi(2-naphthol), Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl, Ts = *p*-toluenesulfonyl.

the iridium catalyst, [Ir(cod){(*R*)-segphos}]OTf, promotes highly enantioselective C–H propargylation of benzylic alcohols; the reaction employs silyl-substituted propargyl chlorides and proceeds through redox-triggered generation of allenyliridium–aldehyde pairs. The same products are generated through a reductive coupling of propargyl chlorides and aldehydes in the presence of isopropanol, which functions as the terminal reductant. Thus, enantioselective propargylation is achieved from the alcohol or aldehyde oxidation level in the absence of premetalated reagents or metallic reductants (Scheme 2).

Initial studies focused on the C–C coupling of benzylic alcohol **2d** and propargyl chlorides **1** to form the homopropargylic alcohol **4d**. When the catalyst was generated in situ from $[Ir(cod)_2]OTf$ and biphep, the coupling reaction involving parent propargyl chloride **1a** did not give **4d** (R = H);

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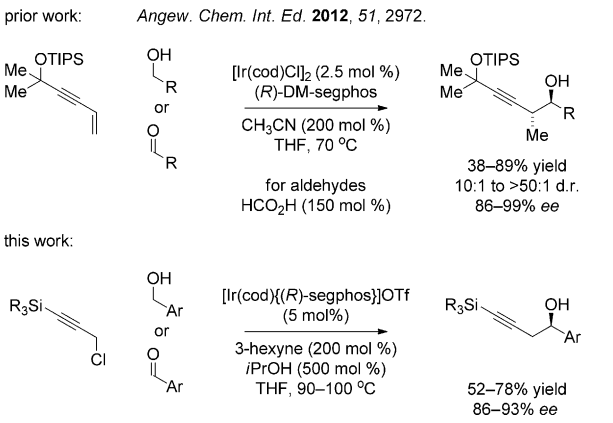


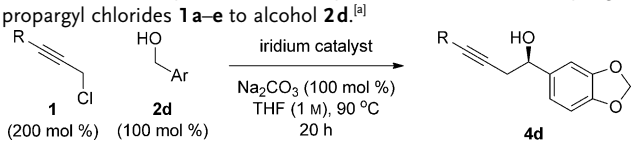
Scheme 2. Carbonyl propargylation through C–C bond forming transfer hydrogenation. cod = 1,5-cyclooctadiene, DM-segphos = 5,5′-bis-[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole, segphos = 5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole, TIPS = triisopropylsilyl.

however, the reaction involving TMS-substituted propargyl chloride **1b** delivered the homopropargylic alcohol **4d** (R=TMS) in 17% yield (Table 1, entries 1 and 2). Based on this result, other silyl-substituted propargyl chlorides were tested. Although, no significant improvement in yield was observed when the TBS-substituted propargyl chloride **1c** was used (Table 1, entry 3), the alcohol **2d** was fully converted into piperonal **3d**. This observation suggested that an exogenous hydride source might increase conversion of the transient aldehyde into the desired product. Indeed, upon addition of isopropanol to the reaction mixture, product **4d** (R = TBS) was obtained in 40% yield upon isolation (Table 1, entry 4). The use of the TIPS-substituted chloride **1d** in the absence of isopropanol gave only trace amounts of **4d** (R = TIPS), suggesting that the steric demand of the silyl group may influence the equilibrium between the allenyliridium and propargyliridium species to favor the latter. This led us to explore the smaller and more electron deficient Me_2PhSi-substituted propargyl chloride **1e**, which performed better than chlorides **1a**–**1d** in the absence of isopropanol (Table 1, entry 6). Furthermore, upon addition of isopropanol, the Me_2PhSi-substituted propargyl chloride **1e** delivered **4d** (R=$PhMe_2Si$) in 62% yield upon isolation (Table 1, entry 7). At this stage, the chiral catalyst modified by (*R*)-segphos[15] was evaluated. Gratifyingly, the homopropargylic alcohol **4d** (R = $PhMe_2Si$) was formed in 65% yield and 91% *ee* upon isolation (Table 1, entry 8). Extending the reaction time led to product decomposition, which included alkyne reduction. It was found that the use of 3-hexyne as an additive improved conversion and enantioselectivity, allowing **4d** (R = $PhMe_2Si$) to be obtained in 72% yield and 93% *ee* upon isolation (Table 1, entry 9). Finally, the use of other chiral ligands, for example (*R*)-binap and (*R*)-Cl,MeO-biphep, did not lead to improved selectivity or enhanced yield (Table 1, entries 10 and 11).

Under these optimized reaction conditions, propargyl chlorides **1e**–**1g** were coupled with benzylic alcohols **2a**–**2k** to form homopropargyl alcohols **4a**–**4k** in good yields with high levels of enantioselectivity (Table 2). Notably, *o*-, *m*-, and *p*-substituted benzyl alcohols are tolerated (Table 2, entries 5–7). Whereas electron-neutral and electron-rich benzylic alcohols couple efficiently with chloride **1e** (Table 2, entries 1–7, 10, and 11), lower yields and enantioselectivities were observed for electron-deficient benzylic alcohols **2h** and **2i**. To address this issue, the Ph_2MeSi-substituted propargyl chloride **1f** was used, which improved the yield and enantiomeric excess of isolated homopropargylic alcohol **4h** (Table 2, entry 8). For alcohol **2i**, which incorporates a *p*-carbomethoxy substituent, the use of *o*-TolMe_2Si-substituted propargyl chloride **1g** was necessary to improve enantioselectivity (62% yield, 87% *ee*, Table 2, entry 9). Finally, in a reaction with chloride **1e**, heteroaryl methanols **2j** and **2k** were converted into homopropargylic alcohols **4j** and **4k**, albeit in modest yield (Table 2, entries 10 and 11). Under identical conditions aryl aldehydes are converted into an identical set of homopropargylic alcohols **4a**–**4k** with similar yields and *ee* values upon isolation (Table 2, entries 1–11).

In the presence of tetrabutylammonium fluoride (TBAF) in THF, propargylation products **4d**, **4g**, and **4h** were converted into the corresponding terminal alkynes **5d**, **5g**, and **5h** (Scheme 3). Homopropargylic compound **5h** is a known compound of established absolute stereochemistry. The absolute stereochemical assignments of adducts **4a**–**4k**

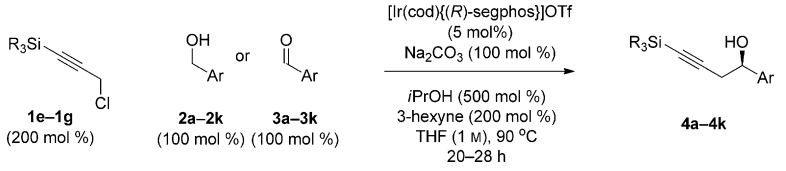
Table 1: Selected experiments in the optimization of the C–C coupling of propargyl chlorides **1a**–**e** to alcohol **2d**.[a]

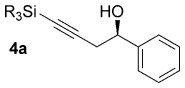
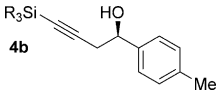
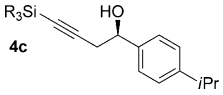
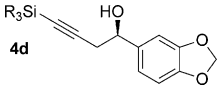
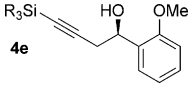
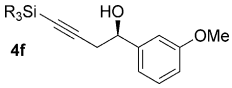
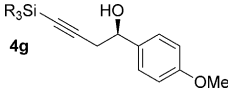
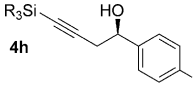
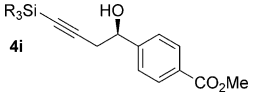
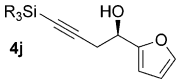
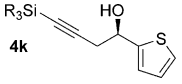


Entry	**1**, R	Catalyst, ligand (mol%)	*i*PrOH (mol%)	Yield [%] (*ee* [%])
1	**1a** H	$[Ir(cod)_2]OTf$ (5), biphep (6)	–	0 (rac)
2	**1b** TMS	$[Ir(cod)_2]OTf$ (5), biphep (6)	–	17 (rac)
3	**1c** TBS	$[Ir(cod)_2]OTf$ (5), biphep (6)	–	18 (rac)
4	**1c** TBS	$[Ir(cod)_2]OTf$ (5), biphep (6)	500	40 (rac)
5	**1d** TIPS	$[Ir(cod)_2]OTf$ (5), biphep (6)	–	trace (rac)
6	**1e** Me_2PhSi	$[Ir(cod)_2]OTf$ (5), biphep (6)	–	26 (rac)
7	**1e** Me_2PhSi	$[Ir(cod)_2]OTf$ (5), biphep (6)	500	62 (rac)
8	**1e** Me_2PhSi	[Ir(cod){(*R*)-segphos}]OTf (5)	500	65 (91)
9[b]	**1e** Me_2PhSi	[Ir(cod){(*R*)-segphos}]OTf (5)	500	72 (93)
10	**1e** Me_2PhSi	[Ir(cod){(*R*)-binap}]OTf (5)	500	57 (77)
11	**1e** Me_2PhSi	[Ir(cod){(*R*)-Cl,MeO-biphep}]OTf (5)	500	60 (87)

[a] Yields of isolated material. The *ee* values were determined by chiral stationary phase HPLC analysis. See the Supporting Information for details. [b] 3-Hexyne (200 mol%), 28 h. binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, biphep = 2,2′-bis(diphenylphosphino)-1,1′-biphenyl, rac = racemic, TBS = *tert*-butyldimethylsilyl.

Table 2: Iridium-catalyzed enantioselective carbonyl propargylation from the alcohol or aldehyde oxidation level.[a]



Entry	Product	SiR_3 (**1e–1g**)	Oxidation level	Yield [%] (*ee* [%])
1	 **4a**	$PhMe_2Si$ (**1e**)	alcohol	78 (92)
		$PhMe_2Si$ (**1e**)	aldehyde	75 (91)
2	 **4b**	$PhMe_2Si$ (**1e**)	alcohol	76 (90)
		$PhMe_2Si$ (**1e**)	aldehyde	76 (89)
3	 **4c**	$PhMe_2Si$ (**1e**)	alcohol	61 (91)
		$PhMe_2Si$ (**1e**)	aldehyde	62 (88)[b]
4	 **4d**	$PhMe_2Si$ (**1e**)	alcohol	72 (93)
		$PhMe_2Si$ (**1e**)	aldehyde	67 (93)
5	 **4e**	$PhMe_2Si$ (**1e**)	alcohol	71 (90)
		$PhMe_2Si$ (**1e**)	aldehyde	60 (87)
6	 **4f**	$PhMe_2Si$ (**1e**)	alcohol	63 (90)
		$PhMe_2Si$ (**1e**)	aldehyde	55 (89)[b]
7	 **4g**	$PhMe_2Si$ (**1e**)	alcohol	64 (92)
		$PhMe_2Si$ (**1e**)	aldehyde	59 (92)
8	 **4h**	Ph_2MeSi (**1f**)	alcohol	60 (86)[c]
		Ph_2MeSi (**1f**)	aldehyde	68 (87)[c]
9	 **4i**	(*o*-Tol)Me_2Si (**1g**)	alcohol	62 (87)[c]
		(*o*-Tol)Me_2Si (**1g**)	aldehyde	60 (88)[c]
10	 **4j**	$PhMe_2Si$ (**1e**)	alcohol	54 (91)
		$PhMe_2Si$ (**1e**)	aldehyde	63 (91)[c]
11	 **4k**	$PhMe_2Si$ (**1e**)	alcohol	65 (93)
		$PhMe_2Si$ (**1e**)	aldehyde	52 (93)[c]

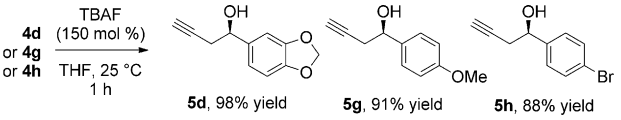
[a] As given in Table 1, entry 9. [b] 100 °C. [c] $[Ir(cod)_2]OTf$ (10 mol %), (*R*)-segphos (12 mol %). Tol = tolyl.

are made in analogy to compound **5h** (see the Supporting Information).

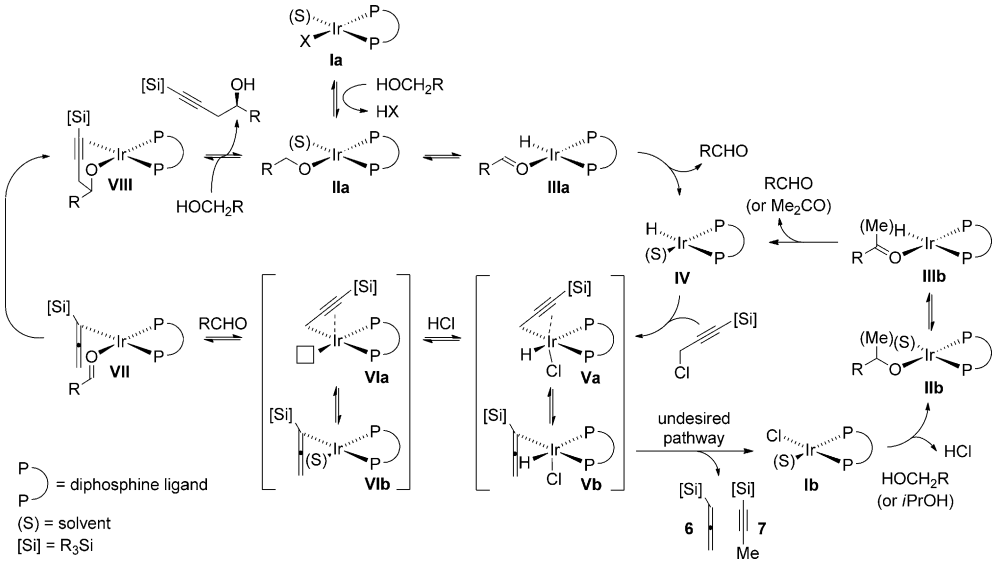
A plausible mechanism begins with the conversion of the iridium(I) halide (or triflate) **Ia** into the iridium(I) alkoxide **IIa** (Scheme 4). β-Hydride elimination delivers the aldehyde complex of iridium(I) hydride **IIIa**. Subsequent dissociation of the aldehyde provides the iridium(I) hydride **IV**. Oxidative addition of **IV** to the propargyl halide provides the propargyliridium(III) complex **Va**, which is presumed to exist in equilibrium with the allenyliridium(III) haptomer **Vb**. At this stage, undesired C–H reductive elimination can occur to form alkyne **6** and allene **7**, which were observed upon ^1H NMR analysis of the crude reaction mixtures, together with the iridium(I) halide (or triflate) **Ib**, which is transformed back into the iridium(I) hydride **IV** via **IIB** and **IIIB**. This undesired pathway prevents the carbonyl-addition reaction of the aldehyde and the allenyliridium species. Because the alcohol is the limiting reagent and promotes reductive generation of the allenyliridium nucleophile from the propargyl chloride, exogenous reductant in the form of isopropanol benefits the reaction by compensating for the loss of primary alcohol reductant. Alternatively, the propargyl- and allenyliridium(III) species **Va** and **Vb** can release HCl, which is consumed by Na_2CO_3, to form the corresponding propargyl- and allenyliridium(I) species **VIa** and **VIb**. Association of the aldehyde to the allenyliridium(I) species is followed by carbonyl addition. Ligand exchange of the resulting homoallylic iridium(I) alkoxide **VIII** with a primary alcohol reactant closes the catalytic cycle.

The stereochemical course of the propargylation may be predicted on the basis of the indicated model, which involves carbonyl addition through the closed six-centered transition state **A** (Scheme 5). In the competing transition state **B**, there is a nonbonding interaction between the allene terminus and a diphenylphosphino moiety of the ligand. In transition state **A**, this destabilizing interaction is absent. The roughly perpendicular conformation of the allenyliridium moiety with respect to the square plane of species **A** and **B** finds precedent in the related η^1-allenylplatinum(II) complex, *trans*-$[Pt(PPh_3)_2(Br)(\eta^1\text{-}CH{=}C{=}CH_2)]$.[16,17]

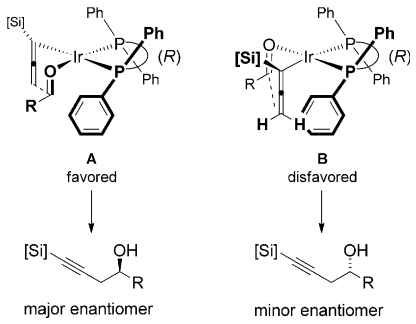
In summary, we report that iridium-catalyzed hydrogen transfer between benzylic alcohols **2a–2k** and silyl-substituted propargylic chlorides **1e–1g** triggers generation of



Scheme 3. Deprotection of homopropargyl alcohols **4d**, **4g**, and **4h** to generate terminal alkynes **5d**, **5g**, and **5h**. Yields given are those obtained upon isolation of material. See the Supporting Information for further details. TBAF = tetra-*n*-butylammonium fluoride.



Scheme 4. Proposed catalytic-cycle mechanism, which accounts for the beneficial effect of isopropanol.



Scheme 5. Proposed stereochemical model based on an (*R*)-segphos modified iridium catalyst.

allenyliridium—aldehyde pairs, which combine to form formal products of carbonyl propargylation **4a**–**4k**. Under identical conditions, wherein isopropanol exclusively serves as the reductant, aryl aldehydes **3a**–**3k** are converted into the same set of homopropargylic alcohols **4a**–**4k** with comparable yields and *ee* values upon isolation. Thus, enantioselective iridium catalyzed propargylation is achieved with equal facility from the alcohol or aldehyde oxidation level. This protocol, when applied to primary alcohol reactants, enhances "redox-economy"[18] by circumventing discrete alcohol oxidation for aldehyde generation. Analogous reactions applicable to aliphatic and allylic alcohols, and that utilize unsubstituted propargyl chloride ($HC{\equiv}CCH_2Cl$), are currently under investigation.

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Communications

Asymmetric Catalysis

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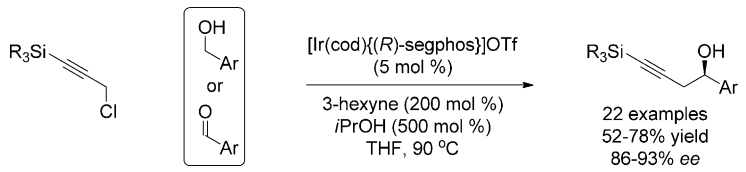
Enantioselective Carbonyl Propargylation by Iridium-Catalyzed Transfer Hydrogenative Coupling of Alcohols and Propargyl Chlorides



It takes alkynes! Exposure of propargyl chlorides to primary benzylic alcohols in the presence of [Ir(cod){(*R*)-segphos}]OTf (cod = 1,5-cyclooctadiene, segphos = 5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole, Tf = trifluoromethanesulfonyl) results in hydrogen exchange to give allenyliridium–aldehyde pairs that combine to form products of propargylation with high *ee* value (see scheme). The reaction can also be conducted using aldehydes.

