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C-Propargylation Overrides O-Propargylation in Reactions of Propargyl Chloride with Primary Alcohols *via* Rhodium Catalyzed Transfer Hydrogenation**

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Graphical abstract

A Path Less Travelled. The canonical S_N2 behavior displayed by alcohols and activated alkyl halides in basic media (*O*-alkylation) is superseded by a pathway leading to carbinol *C*-alkylation under the conditions of rhodium catalyzed transfer hydrogenation. Racemic and asymmetric propargylations are described.

Keywords

Rhodium; Propargylation; Homopropargyl Alcohols; Transfer Hydrogenation; BINAP

The merger of carbonyl addition and transfer hydrogenation has enabled a new class of metal catalyzed C-C couplings wherein lower alcohols are converted directly to higher alcohols.¹ Three mechanistic pathways are corroborated, in which alcohol dehydrogenation mediates (a) C-C π -bond hydrometalation (Ir^I , Ru^{II}), (b) metalacycle transfer hydrogenolysis (Ru^0 , Os^0) or (c) C-X bond reductive cleavage (Ir^I).^[1] In the latter context, iridium-based catalysts operate exclusively, promoting the coupling of primary alcohols with a diverse array of allylic carboxylates^[2a-d] and related pronucleophiles, such as vinyl epoxides^[2e] and vinyl aziridines.^[2f] The identification of metal catalysts beyond iridium that promote alcohol C-H functionalization *via* C-X bond reductive cleavage pathways should enable further expansion of scope. Rhodium-based catalysts, being isostructural with respect to iridium, were viewed as promising candidates. However, rhodium is used less frequently than iridium in transfer hydrogenation,^[3] with the vast majority of examples involving analogues of the

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classic ruthenium-based system $\text{RuCl}(\text{Tsdpen})(\eta^6\text{-arene})$.^[4,5b-e] Indeed, rhodium analogues of the broadly utilized cyclometalated π -allyliridium *ortho*-*C,O*-benzoate complexes developed in our laboratory have not yet proven effective (Figure 1).

As the pronucleophile serves as oxidant in all transfer hydrogenative couplings, we reasoned that more easily reduced pronucleophiles might be accommodated by rhodium, which is a weaker reductant than iridium.^[6] Accordingly, we turned our attention to the redox-triggered coupling of primary alcohols with propargyl chloride with the goal of developing methods for enantioselective carbonyl propargylation (Figure 2).^[7-15] In earlier work from our laboratory,^[16] an iridium-catalyzed transfer hydrogenative carbonyl propargylation was developed (eq. 1),^[16c] but suffered from two severe limitations in scope: (a) trialkylsilyl substitution was required at the acetylenic terminus of the propargyl chloride, and (b) only benzylic alcohols would participate in C-C coupling. To determine whether rhodium catalysts could overcome these restrictions, a series of experiments were performed (Scheme 1). The rhodium analogue of the optimal iridium catalyst identified for the coupling of the silyl-terminated propargyl chloride **1a** with benzyl alcohols was prepared and evaluated in the coupling of benzylic alcohol **2b** with the unsubstituted propargyl chloride **1b**. The desired product, homopropargyl alcohol **3b**, was obtained in 23% yield (eq. 2). Further improvements in the yield of **3b** were obtained by conducting the reaction at 40 °C in toluene – a remarkably low temperature for alcohol dehydrogenation – using a neutral rhodium-BINAP catalyst and increasing the loading of propargyl chloride **1b** (1000 mol%). Applied in concert, these changes enabled formation of homopropargyl alcohol **3b** in 80% yield (eq. 3). Reactions conducted at lower loading of **1b** (500 mol%) under otherwise identical conditions led to a modest but significant decrease in the yield of **3b** (10-15% lower). A comparable decrease in the yield of **3b** is observed upon omission of 2-propanol. Remarkably, products of *O*-propargylation *via* $\text{S}_{\text{N}}2$ substitution were not observed.^[17]

To establish the generality of these conditions, in particular, the ability to engage aliphatic alcohols in *C*-propargylation, these conditions were applied to primary alcohols **2a-2o** (Table 1). Benzylic alcohols **2a-2h**, including *ortho*-substituted benzylic alcohol **2f** and heteroaromatic benzylic alcohol **2h** were converted to the corresponding homopropargylic alcohols **3a-3h** in good to excellent yield. Remarkably, allylic alcohols **2i** and **2j** were converted to homopropargyl alcohols **3i** and **3j** without competing internal redox isomerization.¹⁸ Most importantly, aliphatic alcohols **2k-2o** were converted to the homopropargylic alcohols **3k-3o**, respectively, in good yield. Finally, as illustrated in the conversion of *dehydro-2b* to homopropargyl alcohol **3b**, these conditions are applicable to the 2-propanol mediated reductive coupling of propargyl chloride **1b** with aldehydes (eq. 4).

(Eq. 4)

Products **3a-3o** were generated using a racemic rhodium-BINAP catalyst (Table 1). Using enantiomerically pure BINAP, moderate levels of enantioselectivity are observed (40-55%ee). Efforts to improve enantioselectivity while maintaining high levels of conversion have, thus far, been unrequited. Hence, match-mismatch effects in the *C*-propargylation of the enantiomerically enriched α -stereogenic amino alcohol **2p** were explored (eq. 5). First, to establish the intrinsic diastereofacial bias, the rhodium catalyst modified by racemic BINAP was used. The *anti*- and *syn*-diastereomers **3p** and *epi*-**3p** are formed in a 2.3:1 ratio, respectively. This diastereofacial bias suggests intervention of an internal NH-O hydrogen bond in the transient aldehyde *dehydro*-**2p**, which directs carbonyl addition to the sterically less encumbered face of the chelate. When the propargylation is conducted using (*S*)-BINAP, the mismatched case, **3p** and *epi*-**3p** are in formed in a 1:2.6 ratio, respectively. When the reaction is conducted using (*R*)-BINAP (the matched case), **3p** and *epi*-**3p** are formed in a 5:1 ratio, respectively. It was reasoned that reactions conducted in a lower dielectric medium more conducive to hydrogen bonding would display higher diastereoselectivities. Indeed, in toluene, **3p** and *epi*-**3p** are in formed in an 11:1 ratio, respectively, albeit in slightly lower yield.

(Eq. 5)

These conditions were applied to *C*-propargylation of enantiomerically enriched α -amino alcohols **2p-2u** (Table 2). Due to solubility issues, it was necessary to use THF as solvent. Nevertheless, the products of asymmetric *C*-propargylation **3p-3u** were formed in a stereoselective manner, with diastereoselectivities increasing with increasing size of the α -substituent. HPLC Analysis of adduct **3p** prepared through asymmetric propargylation was compared to a mixture of all 4 stereoisomers, revealing that racemization of the transient aldehyde does not occur (see Supporting Information).

Although at this early stage precise details of the catalytic mechanism are unknown, a very simple working model has been proposed as a basis for further refinement (Scheme 2). It is postulated that catalysis is initiated by oxidative addition of propargyl chloride **1b** to rhodium complex **I** to form the η^1 -allenylrhodium(III) complex **III**. Precedent for this step in the catalytic mechanism is found in the oxidative addition of propargyl chloride **1b** to Vaska's complex, which provides well defined η^1 -allenyliridium(III) complexes.¹⁹ Equilibration may occur between η^1 -allenylrhodium(III) complex **III** and propargylrhodium(III) complex **II**, however, the η^1 -allenylmetal isomers are thermodynamically preferred.²⁰ Complex **III** undergoes substitution with benzyl alcohol **2a** to form the rhodium(III) alkoxide complex **IV**, which upon β -hydride elimination generates

the rhodium(III) hydrochloride complex **V** and the aldehyde *dehydro-2a*. At this stage, complex **V** may undergo C-H reductive elimination to form propyne, which may account for the requirement of relatively high loadings of propargyl chloride **1b**. An ion consistent with the molecular weight of propyne (or allene) is observed by GC-MS analysis of aliquots taken from reaction mixtures in the coupling of propargyl chloride **1b** and benzyl alcohol **2a**. This pathway, which effects net catalytic transfer hydrogenolysis of propargyl chloride **1b**, delivers unreacted aldehyde, which is converted back to the alcohol by 2-propanol-mediated reduction, reinitiating the catalytic cycle. Nonconjugated aldehydes derived from alcohols **2k-2u** appear more reactive toward addition. Hence, 2-propanol is not required. Alternatively, complex **V** may eliminate HCl with the assistance of base, as documented in stoichiometric transformations.²¹ The latter pathway delivers the η^1 -allenylrhodium(I) complex **VI**, which coordinates aldehyde to form complex **VII**, which, in turn, triggers carbonyl addition to generate the homoallylic rhodium(I) alkoxide **VIII**. Protonolytic cleavage then releases the homopropargylic alcohol **3a** and regenerates complex **I** to close the catalytic cycle. The stereochemistry of the octahedral complexes **II-V** should be considered tentative.

In summary, new reactivity is the most fundamental basis for innovation in the field of chemical synthesis. Here, using the concepts of C-C bond formation transfer hydrogenation pioneered in our laboratory, the canonical S_N2 behavior displayed by alcohols and activated alkyl halides in basic media (*O*-alkylation) is superseded by an alternate pathway leading to products of carbinol *C*-alkylation. This method enables direct conversion of primary alcohols, including simple aliphatic alcohols, to secondary homopropargyl alcohols using inexpensive, commercial reagents. More broadly, these studies further demonstrate how the native reducing features of alcohol reactants can mediate reductive carbonyl addition, thus bypassing preformed carbanions or stoichiometric metallic reductants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

- [1]. Ketcham JM, Shin I, Montgomery TP, Krische MJ. Angew. Chem. 2014; 126:9294–9302. Angew. Chem. Int. Ed. 2014; 53:9142–9150.
- [2]. a) Kim IS, Ngai M-Y, Krische MJ. J. Am. Chem. Soc. 2008; 130:14891–14899. [PubMed: 18841896] b) Kim IS, Han SB, Krische MJ. J. Am. Chem. Soc. 2009; 131:2514–2520. [PubMed: 19191498] c) Zhang YJ, Yang JH, Kim SH, Krische MJ. J. Am. Chem. Soc. 2010; 132:4562–4563. [PubMed: 20225853] d) Hassan A, Zbieg JR, Krische MJ. Angew. Chem. 2011; 123:3555–3558. Angew. Chem. Int. Ed. 2011; 50:3493–3496. f) Montgomery TP, Hassan A, Park BY, Krische MJ. J. Am. Chem. Soc. 2012; 134:11100–11103. [PubMed: 22734694] e) Feng J, Garza VJ, Krische MJ. J. Am. Chem. Soc. 2014; 136:8911–8914. [PubMed: 24915473] f) Wang G, Franke J, Ngo CQ, Krische MJ. J. Am. Chem. Soc. 2015; 137:7915–7920. [PubMed: 26074091]
- [3]. Suzuki T. Chem. Rev. 2011; 111:1825–1845. [PubMed: 21391567]
- [4]. Hashiguchi S, Fujii A, Takehara J, Ikariya T, Noyori R. J. Am. Chem. Soc. 1995; 117:7562–7563.
- [5]. a) Imai H, Nishiguchi T, Fukuzumi K. J. Org. Chem. 1974; 39:1622–1627. b) Murata K, Ikariya T. J. Org. Chem. 1999; 64:2186–2187. c) Ikariya T, Blacker AJ. Acc. Chem. Res. 2007; 40:1300–1308. [PubMed: 17960897] d) Zaitsev AB, Adolfsson H. Org. Lett. 2006; 8:5129–5132.

- [PubMed: 17048860] e) Ahlford K, Ekström J, Zaitsev AB, Ryberg P, Eriksson L, Adolfsson H. *Chem. Eur. J.* 2009; 15:11197–11209. [PubMed: 19750526]
- [6]. a) Li J, Schreckenbach G, Ziegler T. *J. Am. Chem. Soc.* 1995; 117:486–494. This assertion is consistent with the energy of infrared radiation absorbed by isostructural carbonyl complexes of iridium and rhodium, $(\text{Ph}_3\text{P})_2\text{M}(\text{Cl})(\text{CO})$, $\text{M} = \text{Ir}$, $\nu_{\text{CO}} = 1965 \text{ cm}^{-1}$; $\text{M} = \text{Rh}$, $\nu_{\text{CO}} = 1980 \text{ cm}^{-1}$. b) Vaska L, Peone J. *Chem. Commun.* 1971:418–419. c) Haynes A, McNish J, Pearson JM. *J. Organomet. Chem.* 1998; 551:339–347. d) Grotjahn DB, Collins LSB, Wolpert M, Bikzhanova GA, Lo HC, Combs D, Hubbard JL. *J. Am. Chem. Soc.* 2001; 123:8260–8270. [PubMed: 11516277]
- [7]. a) Ding C-H, Lou X-L. *Chem. Rev.* 2011; 111:1914–1937. [PubMed: 21344874] b) Wisniewska HM, Jarvo ER. *J. Org. Chem.* 2013; 78:11629–11636. [PubMed: 24266761]
- [8]. a) Haruta R, Ishiguro M, Ikeda N, Yamamoto H. *J. Am. Chem. Soc.* 1982; 104:7667–7669. b) Corey EJ, Yu C-M, Lee DH. *J. Am. Chem. Soc.* 1990; 112:878–879. c) Lai C, Soderquist JA. *Org. Lett.* 2005; 7:799–802. [PubMed: 15727444] d) Hernandez E, Burgos CH, Alicea E, Soderquist JA. *Org. Lett.* 2006; 8:4089–4091. [PubMed: 16928081]
- [9]. Minowa N, Mukaiyama T. *Bull. Chem. Soc. Jpn.* 1987; 60:3697–3704.
- [10]. a) Marshall JA, Wang X-J. *J. Org. Chem.* 1991; 56:3211–3213. Allenyltin Reagents: b) Marshall JA, Maxson K. *J. Org. Chem.* 2000; 65:630–633. Allenylsilicon Reagents: [PubMed: 10813988] c) Brawn RA, Panek JS. *Org. Lett.* 2007; 9:2689–2692. [PubMed: 17559219] d) Matsumoto Y, Naito M, Uozumi Y, Hayashi T. *J. Chem. Soc., Chem. Commun.* 1993:1468–1469. Allenylboron Reagents: e) Marshall JA, Adams ND. *J. Org. Chem.* 1998; 63:3812–3813. Allenylzinc Reagents: f) Marshall JA, Adams ND. *J. Org. Chem.* 1999; 64:5201–5204. g) Marino JP, McClure MS, Holub DP, Comasseto JV, Tucci FC. *J. Am. Chem. Soc.* 2002; 124:1664–1668. [PubMed: 11853441]
- [11]. a) Keck GE, Krishnamurthy D, Chen X. *Tetrahedron Lett.* 1994; 35:8323–8324. Metal/Lewis Base Catalyzed Enantioselective Propargylation using Allenyl Tin Reagents: b) Yu C-M, Yoon S-K, Choi H-S, Baek K. *Chem. Commun.* 1997:763–764. c) Yu C-M, Choi H-S, Yoon S-K, Jung W-H. *Synlett.* 1997:889–890. d) Yu C-M, Yoon S-K, Baek K, Lee J-Y. *Angew. Chem.* 1998; 110:2504–2506. *Angew. Chem. Int. Ed.* 1998; 37:2392–2395. e) Konishi S, Hanawa H, Maruoka K. *Tetrahedron: Asymmetry.* 2003; 14:1603–1605. f) Denmark SE, Wynn T. *J. Am. Chem. Soc.* 2001; 123:6199–6200. [PubMed: 11414863]
- [12]. a) Iseki K, Kuroki Y, Kobayashi Y. *Tetrahedron: Asymmetry.* 1998; 9:2889–2894. Metal/Lewis Base Catalyzed Enantioselective Propargylation using Allenyl Silicon Reagents: b) Evans DA, Sweeney ZK, Rovis T, Tedrow JS. *J. Am. Chem. Soc.* 2001; 123:12095–12096. [PubMed: 11724622] (c) Nakajima M, Saito M, Hashimoto S. *Tetrahedron: Asymmetry.* 2002; 13:2449–2452. d) Chen J, Captain B, Takenaka N. *Org. Lett.* 2011; 13:1654–1657. [PubMed: 21366250]
- [13]. a) Shi S-L, Xu L-W, Oisaki K, Kanai M, Shibasaki M. *J. Am. Chem. Soc.* 2010; 132:6638–6639. Copper Catalyzed Enantioselective Propargylation using Allenyl/Propargyl Boron Reagents: [PubMed: 20420398] b) Fandrick DR, Fandrick KR, Reeves JT, Tan Z, Tang W, Capacci AG, Rodriguez S, Song JJ, Lee H, Yee NK, Senanayake CH. *J. Am. Chem. Soc.* 2010; 132:7600–7601. [PubMed: 20481453] c) Fandrick KR, Fandrick DR, Reeves JT, Gao J, Ma S, Li W, Lee H, Grinberg N, Lu B, Senanayake CH. *J. Am. Chem. Soc.* 2011; 133:10332–10335. [PubMed: 21639096] d) Fandrick KR, Ogikubo J, Fandrick DR, Patel ND, Saha J, Lee H, Ma S, Grinberg N, Busacca CA, Senanayake CH. *Org. Lett.* 2013; 15:1214–1217. [PubMed: 23438081] e) Wei X-F, Shimizu Y, Kanai M. *ACS Cent. Sci.* 2016; 2:21–26. [PubMed: 27163022]
- [14]. a) Barnett DS, Schaus SE. *Org. Lett.* 2011; 13:4020–4023. H-Bond Catalyzed Enantioselective Propargylation using Allenyl Boron Reagents: [PubMed: 21732609] b) Jain P, Wang H, Houk KN, Antilla JC. *Angew. Chem.* 2012; 124:1420–1423. *Angew. Chem. Int. Ed.* 2012; 51:1391–1394. c) Reddy LR. *Org. Lett.* 2012; 14:1142–1145. [PubMed: 22273041]
- [15]. a) Bandini M, Cozzi PG, Umani-Ronchi A. *Polyhedron.* 2000; 19:537–539. Catalytic Enantioselective Propargylation *via* Nozaki-Hiyama-Kishi Reaction: b) Bandini M, Cozzi PG, Melchiorre P, Tino R, Umani-Ronchi A. *Tetrahedron: Asymmetry.* 2001; 12:1063–1069. c) Inoue M, Nakada M. *Org. Lett.* 2004; 6:2977–2980. [PubMed: 15330662] d) Naodovic M, Xia G, Yamamoto H. *Org. Lett.* 2008; 10:4053–4055. [PubMed: 18702493] e) Liu S, Kim JT, Dong C-G, Kishi Y. *Org. Lett.* 2009; 11:4520–4523. [PubMed: 19810761] f) Harper KC, Sigman MS. *Science.* 2011; 333:1875–1878. [PubMed: 21960632]

- [16]. a) Patman RL, Williams VM, Bower JF, Krische MJ. *Angew. Chem.* 2008; 120:5298–5301. *Angew. Chem. Int. Ed.* 2008; 47:5220–5223. b) Geary LM, Woo SK, Leung JC, Krische MJ. *Angew. Chem.* 2012; 124:3026–3030. *Angew. Chem. Int. Ed.* 2012; 51:2972–2976. c) Woo SK, Geary LM, Krische MJ. *Angew. Chem.* 2012; 124:7950–7954. *Angew. Chem. Int. Ed.* 2012; 51:7830–7834. d) Geary LM, Leung JC, Krische MJ. *Chem. Eur. J.* 2012; 18:16823–16827. [PubMed: 23147989]
- [17]. Banerjee M, Roy S. *Org. Lett.* 2004; 6:2137–2140. Rhodium catalyzed reductive coupling of propargyl chloride 1b with aldehydes mediated by stoichiometric quantities of tin(II) oxide provides mixtures of allenic and homopropargylic alcohols: [PubMed: 15200304]
- [18]. a) Mantilli L, Mazet C. *Chem. Lett.* 2011; 40:341–344. b) Cahard D, Gaillard S, Renaud J-L. *Tetrahedron Lett.* 2015; 56:6159–6169.
- [19]. Collman JP, Cawse JN, Kang JW. *Inorg. Chem.* 1969; 8:2574–2579. J. W.
- [20]. Wojcicki A, Shuchart CE. *Coord. Chem. Rev.* 1990; 105:35–60.
- [21]. Schrock RR, Osborn JA. *J. Am. Chem. Soc.* 1976; 98:2134–2143. Stoichiometric deprotonation of cationic rhodium(III) dihydrides has been documented:

This Work: Rhodium Catalyzed Transfer Hydrogenative Coupling

Figure 1.
Rhodium vs iridium catalysts for redox-triggered carbonyl addition.

Figure 2.
Selected methods for enantioselective carbonyl propargylation.^[17-15]

Scheme 1.

Selected experiments in the development of rhodium catalyzed transfer hydrogenative propargylation.^a

^aYields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.

Scheme 2.

General catalytic mechanism for rhodium catalyzed alcohol C-propargylation..^a

Table 1

Rhodium catalyzed C-C coupling of propargyl chloride **1b** with alcohols **2a-2o** to form homopropargyl alcohols **3a-3o**.^a

 1b (1000 mol%) 2a-2o (100 mol%) 3a-3o		[Rh(cod)Cl] ₂ (2.5 mol%) <i>rac</i> -BINAP (5.5 mol%) Na ₂ CO ₃ (200 mol%) 2-PrOH (500 mol%) PhMe (1.0 M), 40 °C
2a , R = Ph 2d , R = 3-MeO-Ph 2g , R = 4-CF ₃ -Ph 2j , R = HC=CHCH ₂ OBn 2m , R = (CH ₂) ₂ OBn	2b , R = 4-Br-Ph 2e , R = 5-benzodioxole 2h , R = 2-furyl 2k , R = (CH ₂) ₃ Me 2n , (CH ₂) ₅ OTBS	2c , R = 4-Me-Ph 2f , R = 2-Cl-Ph 2i , R = HC=CHPh 2l , R = (CH ₂) ₂ Ph 2o , R = (CH ₂) ₃ Cl
 3a , 75% Yield	 3b , 80% Yield	 3c , 69% Yield
 3d , 75% Yield	 3e , 68% Yield	 3f , 75% Yield
 3g , 89% Yield	 3h , 72% Yield	 3i , 64% Yield
 3j , 62% Yield	 3k , 70% Yield ^b	 3l , 72% Yield ^b
 3m , 64% Yield ^b	 3n , 61% Yield ^b	 3o , 66% Yield ^b

^b2-PrOH was omitted.

^aYields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.

Table 2

Rhodium catalyzed C-C coupling of propargyl chloride **1b** with α -amino alcohols **2p-2u** to form homopropargyl alcohols **3p-3u**.^a

1b (1000 mol%)	2p-2u (100 mol%) Ar = 4-MeO-Ph
2p , R = Me 2s , R = CH ₂ Ph	2q , R = (CH ₂) ₂ SMe 2t , R = CH(CH ₃) ₂
2r , R = CH ₂ CH(Me) ₂ 2u , R = (S)-CH(Me)(Et)
3p , 75% Yield, 5:1 dr 66% Yield, 11:1 dr ^b	3q , 68% Yield, 12:1 dr
3r , 76% Yield, 11:1 dr
3s , 74% Yield, 18:1 dr	3t , 73% Yield, >20:1 dr (X-Ray)
3u , 72% Yield, >20:1 dr	

^bToluene (1.0 M)

^aYields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.