Double asymmetric hydrogenation of conjugated dienes: a self-breeding chirality route for C_2 symmetric 1,4-diols

Félix León,[a] Javier Francos,[b] Joaquín López-Serrano,[a] Sergio E. García-Garrido,[b] Victorio Cadierno*[b] and Antonio Pizzano*[a]

The synthesis and double asymmetric hydrogenation of (*Z,Z*)-1,3-diene-1,4-diyl diacetates is described. In this reaction C_2/meso ratios up to 80:20 and enantioselectivities up to 97 % ee have been achieved. As the hydrogenation products can be converted in chiral 1,4-diols, key starting materials for the preparation of best catalysts used, this catalytic system conforms a self-breeding chirality process.

Double asymmetric hydrogenation of dienes is a valuable tool for organic synthesis as it can generate two stereogenic centers in a single transformation. Although it has not been much exploited, several applications, featuring good levels of enantio- and diastereoselectivity, convincingly demonstrate the high potential of this approach in the synthesis of chiral compounds.[1-3] For instance, Andersson and coworkers have reported very high enantioselectivities in the hydrogenation of a wide range of prochiral 1,4-cyclohexadiene derivatives with Ir catalysts.[1c] Likewise, Heibl has reported the synthesis of several bis(α-aminoacids) by the Rh catalyzed hydrogenation of bis(enamides).[2b] Regarding dienes, substantial differences are expected between skipped and conjugated ones towards hydrogenation. For the former, two hydrogenation steps should occur independently, displaying a behavior similar to monoenes.[2a,2c] In contrast, conjugation in the latter opens the way to 1,4-additions[4] as well as to η^4-diene coordination modes.[5] Moreover a potential competition between substrate and catalyst for enantiocontrol in the second hydrogenation may be also of importance in the case of conjugated dienes, as shown by Burgess.[6] Therefore, first and second hydrogenation steps for a conjugated diene may have substantial differences, outlining a demanding task for a single catalyst.

Herein, we describe preliminary results on the enantio- and diastereoselective double hydrogenation of 1,3-diene-1,4-diyl acetates of structure **1** with Rh catalysts (Figure 1a). This unprecedented reaction offers a convenient alternative to the classical electrochemical or enzymatic methods[7] for the synthesis of C_2 symmetric 1,4-diols, key building blocks in the preparation of a wide range of 2,5-disubstituted 5-membered heterocycles (Figure 1b).[8]

The 1,3-diene-1,4-diyl diacetates **1b**-**1j** used as substrates were synthesized by homocoupling of the respective (Z)-β-iodoenol esters **2**.[9] Among available methodologies for the homocoupling of alkenyl halides,[10] the Ni(0)-catalyzed one developed by Sasaki and coworkers showed to be the most effective in the present case,[11] allowing the generation of the desired dienes **1** in good yields (71-89%) under mild conditions (Scheme 1). In addition, the homocoupling process proceeded with preservation of the stereochemistry of the C=C bond of the starting iodo-olefins **2**, which results in the exclusive formation of the corresponding *Z,Z* stereoisomers, as confirmed by X-ray crystallography of diene **1f** (see supporting information). As the extension of this methodology to the synthesis of **1a** would require the cumbersome preparation and handling of the relatively volatile 1-iodopropyne, an alternative synthetic route was applied in this case. Thus, **1a** was obtained in 60% yield through the Au(I)-catalyzed double stereospecific hydrocarboxylation of 2,4-hexadiyne with acetic acid (Scheme 1).[12,13]

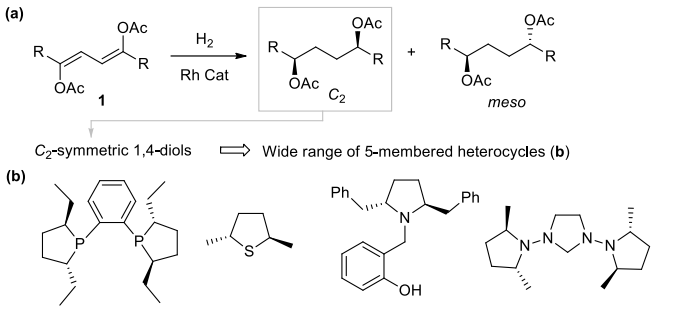
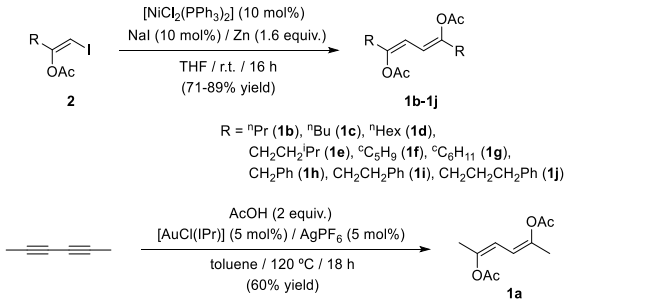


Figure 1. Double hydrogenation of dienes **1** (a). Some examples of five-membered heterocycles prepared from chiral C_2 symmetric 1,4-diols (b).

The hydrogenation of representative diene **1c** with a variety of Rh(I) catalysts bearing phosphine-phosphite (P-OP; Figure 2) or diphosphine ligands (P-P) of formula [Rh(NBD)(P-OP)]BF_4 [P-OP = **L1**-**L3** (**3a**-**3c**)[9a,14]] or [Rh(COD)(P-P)]BF_4 [P-P = **L4**-**L5** (**4a**-**4b**),[15,16] **L6**-**L9** (**5a**-**5d**)[7a,17]] was examined. A first set of reactions in DCM (entries 1-7, Table 1) showed best results with Et-Duphos catalyst (**5b**), providing good diastereoselectivity [dr (C_2:*meso*) = 69:31] and high enantioselectivity (95 % ee, entry 7). Further improvement was obtained using DCE over other solvents (entries 8-11).[14] Moreover, comparable results were also obtained in this solvent using the Ph-BPE catalyst (**5d**, entry 13). In addition, an experiment at a lower catalyst loading using **5b** afforded comparable high conversion (96 %) and good selectivity (dr = 72:28, 95 % ee; entry 14). The relatively high amounts of *meso*-**6c** observed are in sharp contrast with very high C_2:*meso* ratio (ca. 98.5:1.5) reported by Hiebl in the hydrogenation of a bis-dehydroaminoacid derivative featuring the 1,3-butadiene moiety using the same catalyst **5b**,[2b] pointing to the high impact caused by the nature of the α-substituent (alkyl vs ester) in the hydrogenation.

Given the satisfactory results achieved with **1c**, we next examined the hydrogenation of the whole family of dienes **1** (Table 2). Thus, substrates with primary alkyl groups (**1a**-**1e**) gave satisfactory levels of diastereoselectivity (from 72:28 to 85:15) and enantioselectivities (94-97 % ee) with catalysts **5b** and **5d** (entries 1-7). In contrast, hydrogenation of substrates with cycloalkyl substituents (**1f** and **1g**) afforded poorer dr

values (entries 8-13), even favouring the *meso* isomer (entries 8, 9 and 12). For these substrates best enantioselectivities were provided by **5d** in the case of **1f** (60 % ee, entry 10) and **5c** for **1g** (77 % ee, entry 12).



Scheme 1. Synthesis of dienes **1**.

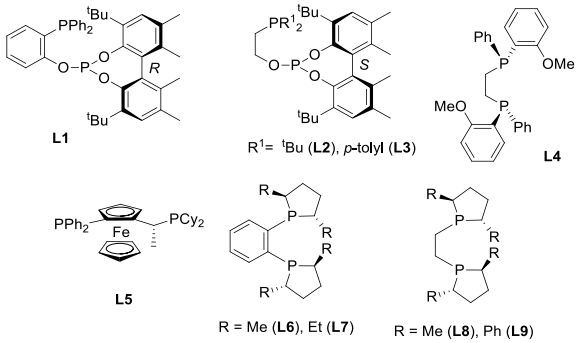
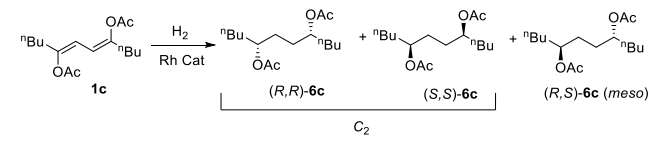


Figure 2. Chiral ligands used in the present study.

Table 1. Hydrogenation of **1c** with catalyst precursors **3**-**5**



Entry[a]	Cat	Solvent	% Conv.	dr (C_2:meso)	% ee (Conf.)
1	**3a**	DCM	50	50:50	n.d.
2	**3b**	DCM	64	50:50	12 (*S,S*)
3	**3c**	DCM	100	53:47	84 (*S,S*)
4	**4a**	DCM	100	52:48	44 (*R,R*)
5	**4b**	DCM	100	50:50	16 (*S,S*)
6	**5a**	DCM	100	69:31	94 (*R,R*)
7	**5b**	DCM	100	69:31	95 (*R,R*)
8	**5b**	DCE	100	74:26	96 (*R,R*)
9	**5b**	TFE	100	54:46	89 (*R,R*)
10	**5b**	IPA	100	70:30	95 (*R,R*)
11	**5b**	THF	93	67:33	98 (*R,R*)
12	**5c**	DCE	100	61:39	70 (*R,R*)
13	**5d**	DCE	100	80:20	95 (*R,R*)
14[b]	**5b**	DCE	96	72:28	95 (*R,R*)

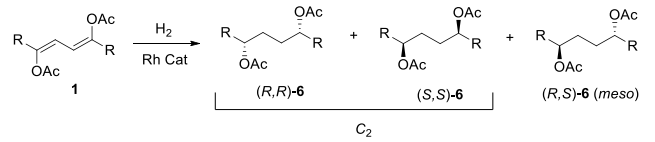
[a]Hydrogenations under 20 bar H_2, [Rh] = 1 × 10^{-3} M, S/C = 100, at 40 °C for 24 h, unless otherwise stated. Conversion determined by ^{1}H NMR; dr and % ee by GC (DCM: dichloromethane, DCE: 1,2-dichloroethane, TFE: 2,2,2-trifluoroethanol, IPA: isopropyl alcohol). See supplementary material for determination of configuration. [b]Reaction performed under 30 bar H_2, [Rh] = 1 × 10^{-3} M and S/C = 500.

On the other hand, for dienes **1h-1j** (entries 14-18), containing phenyl substituted alkyl groups, best results were obtained with **1h** and **1j** and catalyst precursor **5a**, with 96 and 89 % ee, respectively (entries 14 and 18), whereas **1i** gave only 71 % ee (entry 16).

With regard to the mechanism of the double hydrogenation of **1** it may proceed either by two consecutive 1,2-additions (*path a*, Figure 3) or by a 1,4-addition followed by the hydrogenation of the C(2)-C(3) double bond (*path b*). In the latter case, two stereogenic centers are formed simultaneously in the first step and no influence on the diastereomeric product ratio should be expected when the enantiomeric excess of the catalyst is changed.[18] Significant changes in dr were otherwise observed in the hydrogenation of **1c** upon variation of the ee of the catalyst precursor **5b** (Figure 3), from dr = 1.0 with *rac*-**5b** to dr = 3.6 with **5b**. These observations are in accord with a substrate decoordination between the generation of the first and second stereogenic centers, suggesting that *path a* is operating in the present hydrogenation reactions. Further support for this hypothesis was gained through NMR and computational studies. In particular, coordination of diene **1a** was studied upon generation of the corresponding [Rh(**1a**){(*S,S*)-Me-Duphos}]BF_4 species, from the hydrogenation of [Rh(COD){(*S,S*)-Me-Duphos}]BF_4 (**5a**) in MeOH,[19] followed by the addition of **1a** (2 equiv.) and solvent change to CD_2Cl_2 (Scheme 2). A detailed NMR investigation showed the presence of two isomeric species in solution characterized by two inequivalent ^{31}P nuclei in a 3:1 ratio, as well as by coordination of only one of the two olefinic fragments to the metal center (see supporting information for details).

DFT[20] studies examining different coordination modes of **1a** in [Rh(**1a**){(*S,S*)-Me-Duphos}]$^+$ species showed good agreement with the NMR observations. Thus, species **A** (*pro-S*) and **B** (*pro-R*) (Figure 4) featuring a κ^3-*O,C,C* coordination were found to be significantly more stable than those containing the substrate in a η^4-diene coordination mode (**C**-**E**), or those bonded through the distal carbonyl oxygen (**F** and **G**). In addition, in full accord with the calculated relative stabilities of **A** and **B**, NOE experiments (see the supporting information for details) confirmed the nature of the major isomer as the *pro-S* one (**A**). Although the preference for κ^3-*O,C,C* species has been proven only for the Rh(I) part of the catalytic cycle, it may be well maintained during the subsequent steps of the hydrogenation reactions, *i.e.* in the corresponding Rh(III) dihydrides where an stronger oxygen over olefin coordination is expected,[21] thus hindering the access to κ^4-diene structures.

Table 2. Hydrogenation of dienes **1** with precatalysts **5a**-**5d**



Entry[a]	Cat	Diene	% Conv.	dr (C_2:meso)	% ee (Conf.)
1	**5b**	**1a**	100	78:22	97 (*R,R*)
2	**5d**	**1a**	100	85:15	96 (*R,R*)
3	**5b**	**1b**	100	72:28	96 (*R,R*)
4	**5d**	**1b**	100	83:17	94 (*R,R*)
5	**5b**	**1d**	100	74:26	95 (*R,R*)
6	**5b**	**1e**	100	72:28	94 (*R,R*)
7	**5d**	**1e**	100	79:21	95 (*R,R*)
8	**5b**	**1f**	100	45:55	7 (n. d.)
9	**5c**	**1f**	100	26:74	55 (n. d.)
10	**5d**	**1f**	100	59:41	60 (n. d.)
11	**5b**	**1g**	100	52:48	35 (n. d.)
12	**5c**	**1g**	100	36:64	77 (n. d.)
13	**5d**	**1g**	100	60:40	30 (n. d.)
14[b,c]	**5a**	**1h**	99	81:19	96 (*S,S*)
15[c]	**5c**	**1h**	100	67:33	77 (*S,S*)
16	**5a**	**1i**	96	64:36	71 (*R,R*)
17	**5c**	**1i**	100	60:40	70 (*R,R*)
18	**5a**	**1j**	90	71:29	89 (*R,R*)

[a]Hydrogenations under 20 bar H_2, [Rh] = 1 × 10^{-3} M, S/C = 100, at 40 °C in DCE for 24 h, unless otherwise stated. Conversion determined by ^{1}H NMR, dr and % ee by GC or HPLC, with the exception of **6d**, analyzed by ^{19}F{^{1}H} NMR of the corresponding Mosher diester (compound **9** in the supporting information). [b][**1h**] = 0.4 M, [Rh] = 4 × 10^{-3} M. [c]Difference in product configuration results from the change in priority order of substituents of stereogenic carbons.

At the present knowledge of the system it seems uncertain to determine the less enantioselective step responsible of the relatively high levels of *meso* isomer. We however expect a rather demanding second hydrogenation step as it involves the hydrogenation of a α,β-dialkyl substrate. As an indication of such, the hydrogenation of (*Z*)-hex-3-en-3-yl benzoate[14] (a model for the second hydrogenation of dienes **1a-e** bearing

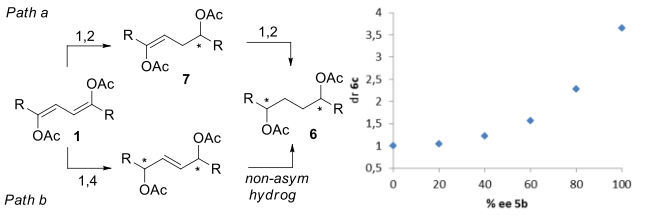
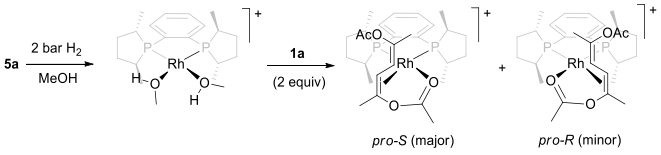


Figure 3. Schematic course of the hydrogenation of dienes **1** (left) and variation of dr with % ee of precatalyst **5b** in hydrogenations of **1c** (right).



Scheme 2. Generation of the [Rh(**1a**){(*S,S*)-Me-Duphos}]BF_4 species (BF_4^- anions omitted for clarity).

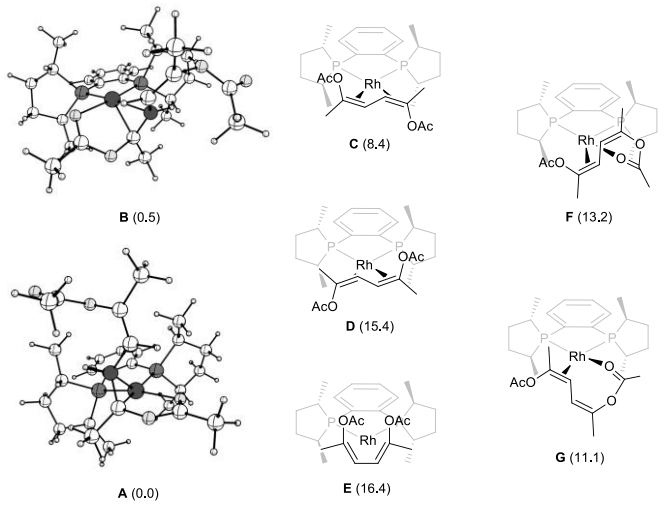
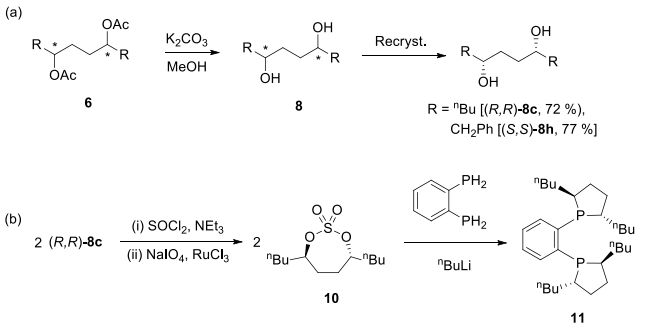


Figure 4. Relative energies (in brackets, kcal·mol^{-1}) for DFT-optimized coordination modes of **1a** in [Rh(**1a**){(*S,S*)-Me-Duphos}]$^+$.

acyclic alkyl substituents, *i.e.* **7** in Figure 3) provided the *R* enantiomer with 40 and 62 % ee using **5a** and **5b**, respectively.

Conversion of diesters **6** to the corresponding diols **8** can be easily performed in good yield by treatment with K_2CO_3 in MeOH (Scheme 3a). Moreover, as these diols are obtained as solids, removal of the undesired *meso* isomer becomes possible by simple crystallization. Indeed, using this procedure (*R,R*)-**8c** and (*S,S*)-**8h** were obtained with satisfactory yields (72-77 %). Finally, a remarkable connection arises from the facts that complexes **5** produce highly effective catalysts in the hydrogenation of **1** and that diols **8** are the key building blocks for the synthesis of Duphos- and BPE-type ligands. Thus, the present system is capable of breeding its own chirality.[22] To further illustrate this feature, we have prepared the ^{n}Bu member of the Duphos family (**11**, Scheme 3b) with *S,S* configuration as well as its corresponding Rh catalyst precursor [Rh(COD)(**11**)]BF_4 (**12**) starting from (*R,R*)-**6c** (via the corresponding diol (*R,R*)-**8c**; details are given in the supporting information). Worth of noting, this catalyst regenerated (*R,R*)-**6c** in the hydrogenation of **1c** with a 92 % ee (dr = 72:28).



Scheme 3. Synthesis of diols **8** (a) and ligand **11** (b).

In conclusion, we have described the stereoselective synthesis and double asymmetric hydrogenation of 1,3-diene-1,4-diyl diacetates **1**. The diastereo- and enantioselectivity levels are highly dependent on the type of substrate, giving

those dienes with acyclic alkyl substituents outstanding enantioselectivities. Since the hydrogenation products can be converted in the diol precursors of 2,5-dialkylphospholane ligands, the present catalytic system conforms a self-breeding chirality process. Investigations regarding the synthetic potential and the mechanism of this process are currently in progress.

This work was supported by MINECO (projects CTQ2016-75193-P; AEI/FEDER, UE, CTQ2016-75986-P and CTQ2016-81797-REDC). Dr. Khiar is acknowledged for valuable comments and Dr. García-Fernández for access to GC facilities. Mass Spectrometry Service of Universidad de Sevilla (CITIUS) is acknowledged for technical assistance. The use of the Supercomputing center of Galicia (CESGA) is also gratefully acknowledged.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 For Ir catalyzed reactions, see: (a) X. Cui, J. W. Ogle and K. Burgess, *Chem. Commun.*, 2005, 672; (b) S. Bell, B. Wuestenberg, S. Kaiser, F. Menges, T. Netscher and A. Pfaltz, *Science*, 2006, **311**, 642; (c) B. K. Peters, J. Liu, C. Margarita, W. Rabten, S. Kerdphon, A. Orebom, T. Morsch and P. G. Andersson, *J. Am. Chem. Soc.*, 2016, **138**, 11930.

2 For examples of reactions catalyzed by Rh, see: (a) J.-C. Poulin and H. B. Kagan, *J. Chem. Soc. Chem. Commun.*, 1982, 1261; (b) J. Hiebl, H. Kollmann, F. Rovenszky and K. Winkler, *J. Org. Chem.*, 1999, **64**, 1947; (c) E. Spahn, A. Albright, M. Shevlin, L. Pauli, A. Pfaltz and R. E. Gawley, *J. Org. Chem.*, 2013, **78**, 2731.

3 For Ru catalyzed reactions, see: (a) H. Muramatsu, H. Kawano, Y. Ishii, M. Saburi and Y. Uchida, *Chem. Commun.*, 1989, 769; (b) V. Beghetto, U. Matteoli and A. Scrivanti, *Chem. Commun.*, 2000, 155; (c) D. P. Steinhuebel, S. W. Krska, A. Alorati, J. M. Baxter, K. Belyk, B. Bishop, M. Palucki, Y. Sun and I. W. Davies, *Org. Lett.*, 2010, **12**, 4201.

4 (a) R. R. Schrock and J. A. Osborn, *J. Am. Chem. Soc.*, 1976, **98**, 4450; (b) X. H. Yang and V. M. Dong, *J. Am. Chem. Soc.*, 2017, **139**, 1774.

5 R. S. Sherbo, G. S. Bindra and P. H. M. Budzelaar, *Organometallics*, 2016, **35**, 2039.

6 (a) X. Cui and K. Burgess, *J. Am. Chem. Soc.*, 2003, **125**, 14212; (b) X. Cui, Y. Fan, M. B. Hall and K. Burgess, *Chem. Eur. J.*, 2005, **11**, 6859.

7 (a) M. J. Burk, J. E. Feaster and R. L. Harlow, *Organometallics*, 1990, **9**, 2653; (b) L. Borén, K. Leijondahl and J.-E. Bäckvall, *Tetrahedron Lett.*, 2009, **50**, 3237.

8 (a) R. P. Short, R. M. Kennedy and S. Masamune, *J. Org. Chem.*, 1989, **54**, 1755; (b) M. J. Burk, J. E. Feaster, W. A. Nugent and R. L. Harlow, *J. Am. Chem. Soc.*, 1993, **115**, 10125; (c) K. T. Sprott and E. J. Corey, *Org. Lett.*, 2003, **5**, 2465; (d) M. Alcarazo, S. J. Roseblade, E. Alonso, R. Fernández, E. Alvarez, F. J. Lahoz and J. M. Lassaletta, *J. Am. Chem. Soc.*, 2004, **126**, 13242; (e) S. A. Snyder, D. S. Treitler and A. P. Brucks, *J. Am. Chem. Soc.*, 2010, **132**, 14303.

9 (a) P. J. González-Liste, F. León, I. Arribas, M. Rubio, S. E. García-Garrido, V. Cadierno and A. Pizzano, *ACS Catal.*, 2016, **6**, 3056; (b) P. J. González-Liste, J. Francos, S. E. García-Garrido and V. Cadierno, *J. Org. Chem.*, 2017, **82**, 1507.

10 For a review on homocoupling reactions of alkenes, see: H. A. Stefani, A. S. Guarezemini and R. Cella, *Tetrahedron*, 2010, **66**, 7871.

11 (a) K. Sasaki, K. Nakao, Y. Kobayashi, M. Sakai, N. Uchino, Y. Sakakibara and K. Takagi, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 2446; (b) J. G. Rodríguez and C. Díaz-Oliva, *Tetrahedron*, 2009, **65**, 2512.

12 To the best of our knowledge, no previous examples involving 1,3-diynes have been reported in the literature. For selected reviews on this topic, see: (a) F. Alonso, I. P. Beletskaya and M. Yus, *Chem. Rev.*, 2004, **104**, 3079; (b) L. Hintermann, *Top. Organomet. Chem.*, 2010, **31**, 123; (c) C. Bruneau, *Top. Organomet. Chem.*, 2013, **43**, 203; (d) P. J. González-Liste, J. Francos, S. E. García-Garrido and V. Cadierno, *Arkivoc*, 2018, **ii**, 17.

13 The *Z* configuration of the C=C bonds of **1a** is the result of the expected *anti* addition of the O-H bond of the acid to the corresponding π-alkyne-gold intermediates. See, for example reference 9 and: (a) S. Dupuy, D. Gasperini and S. P. Nolan, *ACS Catal.*, 2015, **5**, 6918; (b) P. J. González-Liste, S. E. García-Garrido and V. Cadierno, *Org. Biomol. Chem.*, 2017, **15**, 1670.

14 F. León, P. J. González-Liste, S. E. García-Garrido, I. Arribas, M. Rubio, V. Cadierno and A. Pizzano, *J. Org. Chem.*, 2017, **82**, 5852.

15 B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman and D. J. Weinkauff, *J. Am. Chem. Soc.*, 1977, **99**, 5946.

16 A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert and A. Tijani, *J. Am. Chem. Soc.*, 1994, **116**, 4062.

17 C. J. Pilkington and A. Zanotti-Gerosa, *Org. Lett.*, 2003, **5**, 1273.

18 B. J. Anderson, S. C. Reynolds, M. A. Guino-o, Z. Xu and D. S. Glueck, *ACS Catal.*, 2016, **6**, 8106.

19 A. Börner and D. Heller, *Tetrahedron Lett.*, 2001, **42**, 223.

20 Calculations at the DFT, B3PWW91 + D3 / 6-31g(d,p) + SDD level in 1,2-dichloroethane using the G09 software: Gaussian 09, Revision D.01, Gaussian, Inc., Wallingford CT, 2013. See the SI for the full Gaussian reference and further details.

21 (a) I. D. Gridnev and T. Imamoto, *ACS Catal.*, 2015, **5**, 2911; (b) I. D. Gridnev and T. Imamoto, *Russ. Chem. Bull.*, 2016, **65**, 1514.

22 (a) M. D. Fryzuk and B. Bosnich, *J. Am. Chem. Soc.*, 1978, **100**, 5491; (b) N. F. Blank, K. C. McBroom, D. S. Glueck, W. S. Kassel and A. L. Rheingold, *Organometallics*, 2006, **25**, 1742; (c) X. Y. Yang, W. S. Tay, Y. Li, S. A. Pullarkat and P. H. Leung, *Chem. Commun.*, 2016, **52**, 4211.