A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Gold-Catalysed Atroposelective Synthesis of 1,1'-Binaphthalene-2,3'-diols

Authors: Manuel Alcarazo, Jianwei Zhang, Martin Simon, and Christopher Golz

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201915456
Angew. Chem. 10.1002/ange.201915456

Link to VoR: http://dx.doi.org/10.1002/anie.201915456
http://dx.doi.org/10.1002/ange.201915456

WILEY-VCH

10.1002/anie.201915456

WILEY-VCH

Gold-Catalysed Atroposelective Synthesis of 1,1'-Binaphthalene-2,3'-diols

Jianwei Zhang, Martin Simon, Christopher Golz and Manuel Alcarazo*[a]

Abstract: A highly atroposelective (up to 97% ee) Au-catalyzed synthesis of 1,1'-binaphthalene-2,3'-diols is reported starting from a range of substituted naphthyl alkynones. Essential for the achievement of high enantioselectivity during the key assembly of the naphto-3-ol unit is the use of TADDOL-derived α-cationic phosphonites as ancillary ligands. Our preliminary results demonstrate that the transformation of the obtained binaphthyls into axially chiral monodentate phosphines is possible without degradation of enantiopurity.

The presence of substituents at the *ortho*-positions flanking the aryl-aryl bond in biaryls restricts and may even cancel the rotation around that bond, rendering molecules containing such architectures axially chiral.[1] Far from being just a curiosity, this type of isomerism, specifically called atropoisomerism, is ubiquitous in natural products,[2] pharmaceuticals,[3] organocatalysts[4] and ligands for transition metals[5] (Figure 1a). This has stimulated the development of a number of atroposelective routes targeting the preparation of such motives in highly enantiopure form.[6] Arguably, one of the most commonly found axially chiral architectures is the one derived from 1,1'-naphthyl-2,2'-diol (BINOL), which has been recognized as a "privileged structure" in the area of enantioselective catalysis due to its ability to promote high enantioinduction in mechanistically non-related asymmetric processes.[7] BINOL itself and related C_2-symmetrical 1,1'-biaryl-2,2'-diols are often prepared by oxidative coupling of the corresponding phenols; a process which takes place with very high regioselectivity and can be carried out in large scale.[8] However, the asymmetric synthesis of other isomers of BINOL, in particular those non-C_2-symmetric, is more challenging since in addition to enantio-discrimination, regio-, and/or diasteroselection need to be simultaneously controlled and optimized.[9] For example, the formal displacement of one of the –OH units in the original BINOL scaffold to the adjacent C-position renders 1,1'-naphthyl-2,3'-diol, which is the basic structural motive of Denthyrsinone. Only one enantioselective synthesis, recently reported by Tanaka and coworkers, is available for this scaffold.[10] These authors were able to construct the 3-naphthol unit through a Au-catalyzed atroposelective hydroarylation of an alkynone moiety strategically located in position 1- of the 2-naphthol fragment (Figure 1b). The transformation proceeds with good to excellent yields, but only moderate enantioselectivities (up to 67 % ee) were obtained despite of the exhaustive inspection of a complete series of non-structurally related chiral diphosphine ligands.

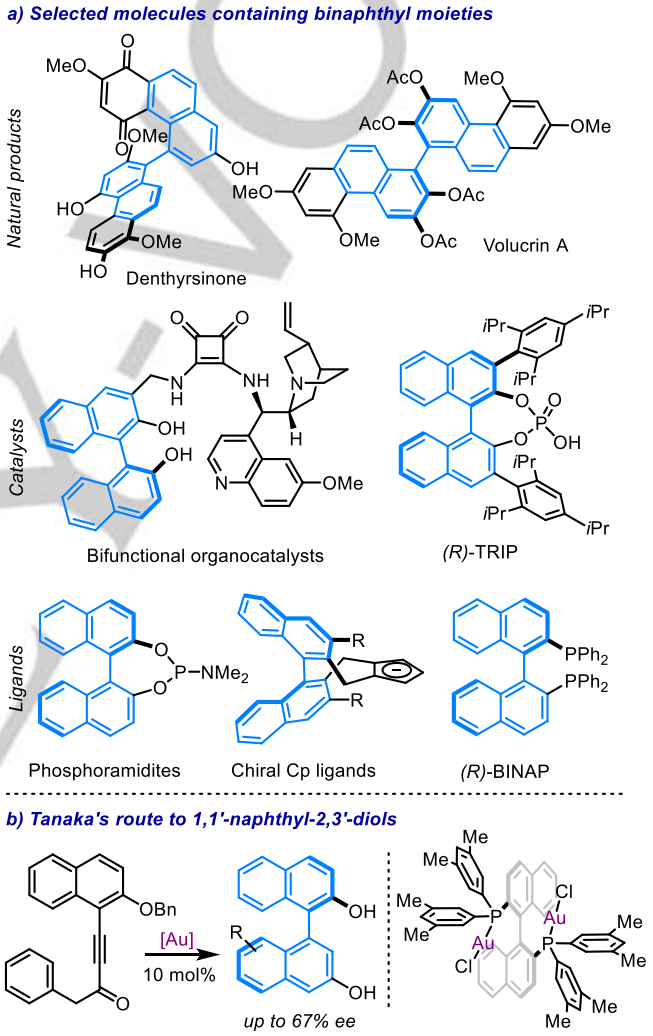


Figure 1. a) Axially chiral natural products, catalysts and ligands; b) Available route for the preparation of 1,1'-naphthyl-2,3'-diols.

Very recently, we reported the synthesis of TADDOL-derived α-cationic phosphonites and their application as ancillary ligands in the Au-catalyzed hydroarylation of dyines into [6]helicenes.[11,12] In these ligands the chiral information is provided by an easily available and well-precedented TADDOL-derived moiety, whose modular synthesis allows an easy modification of their structures upon demand. Moreover, the positively charged heterocylic rest directly attached at the phosphorus center provides enhanced Lewis acidity at the metal center if compared with traditional catalysts. This is translated into higher catalytic activity and the possibility to work at lower

[a] Dr. J. Zhang, M. Simon, Dr. C. Golz and Prof. Dr. M. Alcarazo
Institut für Organische und Biomolekulare Chemie
Georg August Universität Göttingen
Tammannstr 2, 37077 Göttingen, Germany
E-mail: malcara@gwdg.de

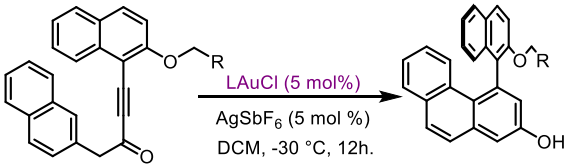
Supporting information for this article is given via a link at the end of the document.

10.1002/anie.201915456

temperatures.[13] Given these precedents, we hypothesized that even if the use of α-cationic ligands for the induction of atroposelectivity has not been studied, these ligands might be beneficial for the enantioselective preparation of 1,1'-naphthyl-2,3'-diols as well. Our advances in this direction are reported herein.

We initially studied the performance of catalysts **5a-c** employing Tanaka's model substrates **1a**. Already from the very early set of experiments, 4-(trifluoromethyl)phenyl groups on the TADDOL moiety were identified to be essential to promote enantiomeric excess (Table 1, Entries 1-3); hence, that substituent was fixed and a subsequent optimization round started focused on the evaluation of the impact of the outer TADDOL backbone. Interestingly, we found that flexible dimethyl ether groups were superior than a cyclic acetonide to achieve enantiodiscrimination (Table 1, Entry 5).[14]

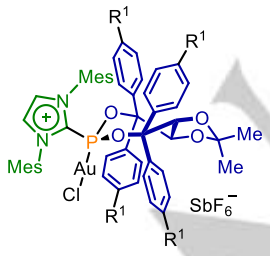
Table 1. Ligand and substrate optimization.



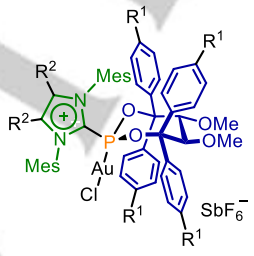
1a, R = Ph; **1b**, R = H
2a, R = 2-naphthyl

3a, R = Ph; **3b**, R = H
4a; R = 2-naphthyl

Entry	Substrate	Catalyst	Yield (%)[a]	ee (%)[b]
1	**1a**	**5a**	90	(+)-2
2	**1a**	**5b**	93	0
3	**1a**	**5c**	91	(+)-30
4	**1a**	**6a**	85	(-)-38
5	**1a**	**6b**	83	(-)-50
6	**1a**	**6c**	90	(-)-95
7	**1a**	**6d**	86	(-)-88
8	**2a**	**6c**	90	(-)-97
9	**2a**	**6d**	87	(-)-95
10	**1b**	**6c**	81	(-)-64



5a; R^1 = H
5b; R^1 = *t*-Bu
5c; R^1 = CF_3



6a; R^1 = H, R^2 = H
6b; R^1 = CF_3, R^2 = H
6c; R^1 = CF_3, R^2 = Me
6d; R^1 = CF_3, R^2 = Cl

All reaction were conducted in a 0.25 mmol scale in DCM (0.05 M). [a] Yields are isolated; [b] ee's were determined by chiral HPLC.

At that stage, the influence of substitution at the backbone of the imidazolium ring was examined. To our surprise, we found that the mere presence of substituents in that region translates into higher levels of enantioinduction, and this is independent of the electronic nature of the group incorporated (Me- or Cl-) as can be seen in Table 1, Entries 6 and 7. Careful scrutiny of the X-ray structures of **5c** and **6c**, an overlay is shown in Figure 2, manifested that the geometries adopted by both frameworks are very similar. It worth mentioning however that the Me- or Cl-groups at the imidazolium unit slightly push the vicinal mesityl rests towards the inner cavity of the ligand narrowing the chiral pocket around the Au atom. One *p*-(CF_3)Ph rest suffers an identical effect on introduction of the Me-groups.[15] The increment of steric pressure is confirmed by comparison of the percent buried volumes (%V_{Bur}; **5c**, 46.1% and **6c**, 47.8%), and the topographic steric maps for both ligands, depicted in Figure 2 as well.[16] Hence, the ultimate reason for such beneficial effect still remains obscure, but we tend to believe that it is the tighter puckering of the ligand around the metal atom what causes the improved enantioinduction.

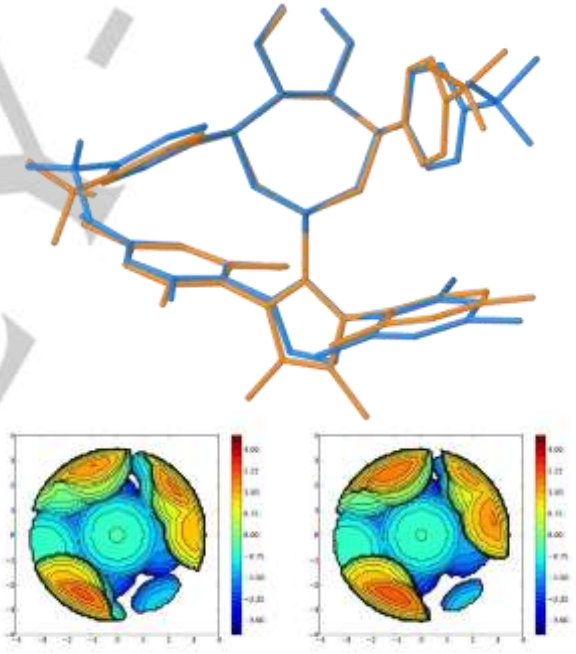


Figure 2. Overlay of the X-ray structures of **5c** (blue) and **6c** (orange) seen from the Cl-Au-P axes; only the inward orientated *p*-(CF_3)Ph groups are shown for clarity. Steric maps for **5c** (left) and **6c** (right); %V_{Bur} ; **5c**, 46.1% and **6c**, 47.8%.

Finally, given the highly aromatic nature of both, substrate and catalyst, and the complementary electronic properties of their substituents, it was rationalized that attractive π-stacking interactions surely play a fundamental role to achieve enantiodiscrimination in this process.[17] Having that in mind, we exchanged the benzyl group in **1a** by a more π-extended 2-naphthalenemethyl in **2a**. Our intention was to reinforce the attractive interaction between ligand and substrate substituents and thus, reduce conformational degrees of freedom in the

10.1002/anie.201915456

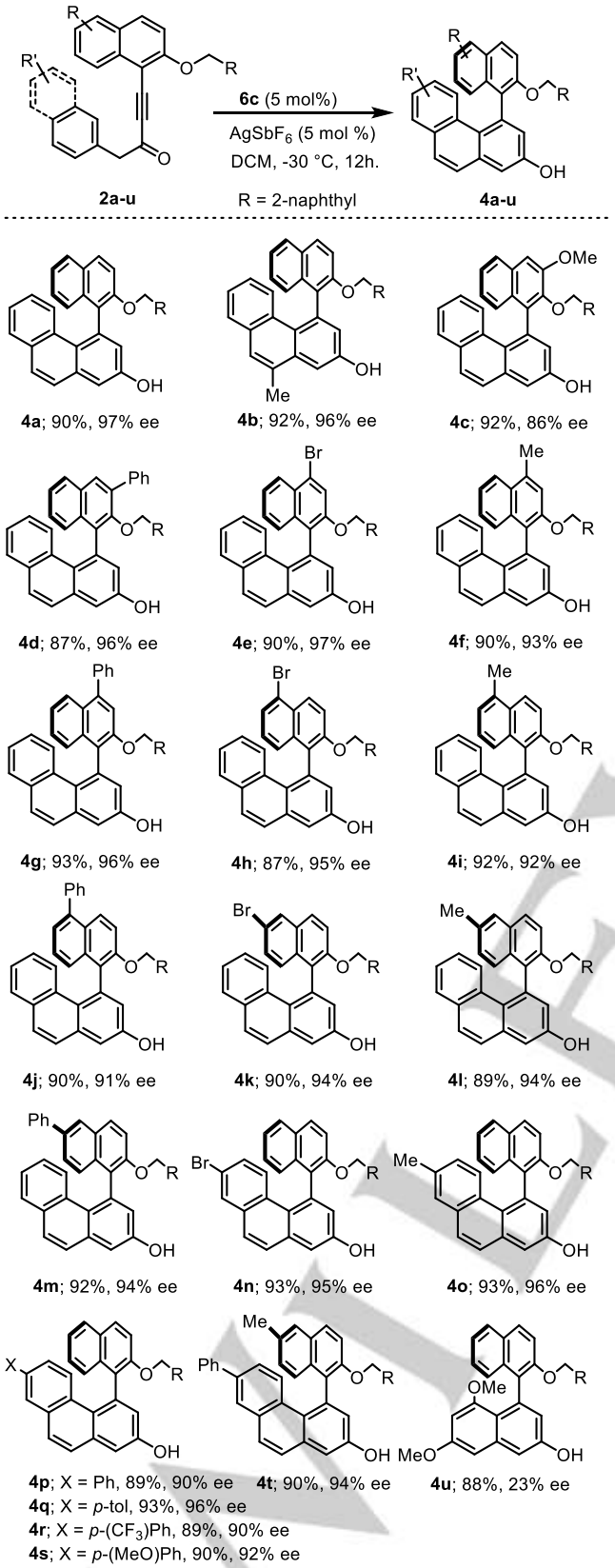
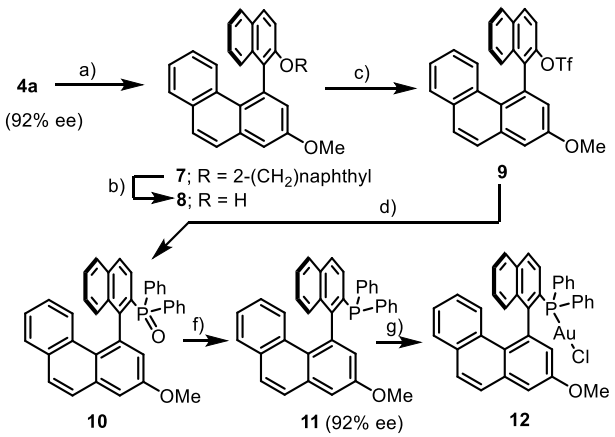


Figure 3. Substrate scope. All reaction were conducted in a 0.25 mmol scale in DCM (0.05 M). Yields are isolated and ee's were determined by chiral HPLC.

selectivity determining step of the catalytic cycle. We were glad to see that this assumption seems to be correct. In fact, both precatalysts **6c** and **6d**, were able to scratch some additional percentage points of enantiomeric excess after this subtle change (Table 1, Entries 8 and 9). In contrast, substitution of the benzyl group in **1a** by a methyl one in **1b** leads to severe drop in the enantioselectivity (Table 1, Entry 10). This leaded to the identification of **6c** as the optimal catalysts, and the 2-naphthalenemethyl unit as the preferred protecting group for the 2-naphthol moiety.

With the optimal conditions in hand, the scope of the cyclization was evaluated using alkynones **2a-u**, which contain diverse substitution pattern, including additional halogene-, arene-, and alkyl-substituents at diverse positions of the original architecture (See the Supporting Information for the preparation of ynones **2a-u**). Gratifyingly, high chemical yields were obtained for the desired hydroarylation process, and the high enantioinduction imparted by **6c** was consistently maintained all through the series. It worth also noting that, a priori, two positions (1- and 3-) of the naphthalene substituent in **2a-t** might attack the activated alkyne, affording two regioisomeric binaphthols; however, only the shown binaphthols **4a-t** were observed, even if these are the more sterically demanding regioisomers. Low ee was observed for substrate **2u**, containing a benzyl alkynone instead of 2-(methyl)naphthyl alkynone substituent; this result again corroborates the positive influence of expanded π-systems on the enantioselectivity of the cyclisation when using our catalytic system.

Willing to demonstrate the utility of the products obtained, we decided to further elaborate **4a** into an axially chiral monodentate phosphine. Thus, methylation of the free alcohol followed by hydrogenolysis of the 2-(CH_2)naphthyl group afforded alcohol **8** in 82% yield (two steps), which was subsequently transformed into the corresponding triflate **9** by treatment with trifluoromethanesulfonic anhydride. This compound was then submitted to palladium-catalyzed phosphinylation under already reported conditions to render the expected phosphine oxide **10** in 78% yield. [18] Reduction of **10** to the desired phosphine **11** was achieved employing a $HSiCl_3$/Et_3N mixture in boiling toluene. Importantly, analysis by chiral HPLC of compounds **7-11** revealed no erosion of the enantiomeric purity along the complete sequence. Finally, reaction of **11** with (Me_2S)AuCl afforded Au-complex **12** (Scheme 1).



Scheme 1. Transformation of **4a** into a new axially chiral phosphine. Reagents and conditions: a) MeI, K_2CO_3, CH_3CN, 93%; b) Pd/C, H_2, EtOH, reflux, 88%; c)Tf_2O, Et_3N, 60%; d) $Ph_2P(O)H$, $Pd(OAc)_2$ (10 mol%), dppb (12 mol%), DMSO, 110°C, 78%; e) $HSiCl_3/NEt_3$ (5:7 equiv.), 100°C, 18h, 87%; f) $(Me_2S)AuCl$, DCM, 0°C→r.t. (90%).

Monocrystals of **12** were obtained by slow diffusion of diethylether into a saturated dichloromethane solution of the tittle compound, and its structure was determined by X-ray diffraction. This analysis allowed the assignment of the absolute configuration of **12**, and by extension that of **4a-t**, to be *M* (Figure 4).

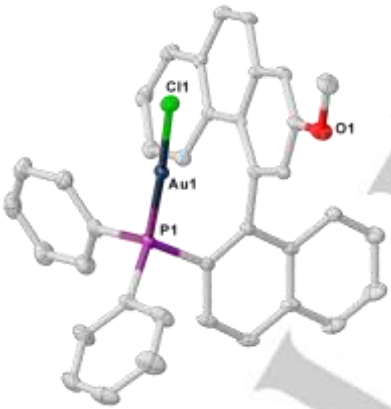


Figure 4. Molecular structure of compound **12** in the solid state. Anisotropic displacement shown at 50% probability level and hydrogen atoms omitted for clarity. [19]

In conclusion, a highly atroposelective synthesis of 1,1'-binaphthalene-2,3'-diols is reported via Au-catalyzed intramolecular hydroarylation of appropriately designed alkynones. The use of 3,4-disubstituted imidazolium units directly attached to the phosphorus atom of the ancillary ligand, and 2-naphthalenemethyl moieties as protecting group at the naphthol substrates **2a-t** revealed to be essential to achieve high enantioselectivities. The possibility to transform the 1'-binaphthalene-2,3'-diols herein described into new chiral phosphines might inspire the development of new asymmetric Au-catalyzed transformations. Explorative studies in this direction are currently in progress in our laboratory.

Acknowledgements

Financial support from the Deutsche Forschungsgemeinschaft (AL 1348/8-1 and INST 186/1237-1) is gratefully acknowledged.

Keywords: Au-catalysis • biaryl synthesis • enantioselective hydroarylation • cationic ligands • chiral phosphines

[1] M. Oki, *Recent Advances in Atropisomerism*. In *Topics in Stereochemistry*; Ed: N. L. Allinger, N. L. Eliel, , S. H., Wilen, John Wiley & Sons, New York, **1983**; Vol. 14, pp 1-81.

[2] J. E. Smyth, N. M. Butler, P. A. Keller, *Nat. Prod. Rep.* **2015**, *32*, 1562-1583.

[3] S. R. LaPlante, L. D. Fader, K. R. Fandrick, D. R. Fandrick, O. Hucke, R. Kemper, S. P. F. Miller, P. J. Edwards, *J. Med. Chem.* **2011**, *54*, 7005-7022.

[4] a) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744-5758; b) S. Brandes, B. Niess, M. Bella, A. Prieto, J. Overgaard, K. A. Jørgensen, *Chem. Eur: J.* **2006,** *12*, 6039-6052.

[5] a) B. Ye and N. Cramer, *Acc. Chem. Res.*, **2015**, *48*, 1308–1318; b) J. F. Teichert, B. L. Feringa, *Angew. Chem. Int. Ed.* **2010**, *49*, 2486,-2528; c) A. Alexakis, D. Polet, S. Rosset, S. March, *J. Org. Chem.* **2004**, *69*, 5660-5667; d) Z. Hua, V. C. Vassar, H. Choi, I. Ojima, Proc. Nat. Acad. Sci. **2004,** *111*, 5411-5416; e) B. L. Feringa, *Acc. Chem. Res.* **2000**, *33*, 346-353.

[6] a) J. Wencel-Delord, A. Panossian, F. R. Leroux, F. Colobert, *Chem. Soc. Rev.* **2015**, *44*, 3418-3430; b) G. Bencivenni, *Synlett* **2015**, *26*, 1915-1922; c) G. Bringmann, A. J. Price-Moritmer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem. Int. Ed.* **2005,** *44*, 5384-5427.

[7] a) Q. -L. Zhou, *Privileged Ligands and Catalysts,* Wiley-VCH, Weinheim, **2011**; c) J. M. Brunel, *Chem. Rev.* **2005**, *105*, 857-898; b) T. P. Yoon, E. N. Jacobsen, *Science* **2003**, *299*, 1691-1693.

[8] a) D. L. Hughes, *Org. Synth*. **2014**, *91*, 1-11; b) H. U. Blaser, H. J. Federsel, Asymmetric Catalysis on Industrial Scale: Chellenges, Approaches, and Solutions, 2nd Ed., Wiley-VCH, Weinheim, **2010**; c) M. C. Kozlowski, B. J. Morgan, E. C. Linton, *Chem. Soc. Rev.* **2009**, *38*, 3193-3207.

[9] a) J. D. Jolliffe, R. J. Armstrong, M. D. Smith, *Nat. Chem.* **2017**, *9*, 558-562; b) K Mori, Y. Ichikawa, M. Kobayashi, Y. Shibata, M. Yamanaka, T. Akiyama, *J. Am. Chem. Soc.* **2013**, *135*, 3964-3970.

[10] M. Satoh, Y. Shibata, Y. Kimura, K. Tanaka, *Eur. J. Org. Chem.* **2016**, 4465-4469.

[11] a) L.D.M. Nicholls, M. Marx, T. Hartung, E. González-Fernández, C. Golz, M. Alcarazo, *ACS Catal.* **2018**, *8*, 6079-6085; b) E. González-Fernández, L.D.M. Nicholls, L.D. Schaaf, C. Farès, C.W. Lehmann, M. Alcarazo. *J. Am. Chem. Soc.* **2017**, *139*, 1428-1431.

[12] For recent reviews on enantioselective Au-catalysis see: (a) Y. Li, W. Li, J. Zhang, *Chem. - Eur. J.* **2017,** 23, 467−512; (b) W. Zi, F. D. Toste, *Chem. Soc. Rev.* **2016**,*45*, 4567−4589; (c) Y.-M. Wang, A. D. Lackner, F. D. Toste, *Acc. Chem. Res.* **2014**, *47*, 889-901.

[13] a) L. D. M. Nicholls, M. Alcarazo, *Chem. Lett.* **2019**, *48*, 1-13; b) H. Tinnermann, L. D. M. Nicholls, T. Johannsen, C. Wille, C. Golz, R. Goddard, M. Alcarazo, *ACS Catal.* **2018**, *8*, 10457-10463; c) M. Alcarazo, *Acc. Chem. Res.* **2016**, *49*, 1797-1805; d) M. Alcarazo, *Chem.–Eur. J.* **2014**, *20*, 7868-7877.

[14] For the use of TADDOL-derived phosphoramidites in asymmetric catalysis see: (a) H. Teller, M. Corbet, L. Mantilli, G. Gopakumar, R. Goddard, W. Thiel, A. Fürstner, *J. Am. Chem. Soc.* **2012**, *134*, 15331-15432; (b) H. W. Lam, *Synthesis* **2011**, 2011-2043; (c) H. Teller, S. Flügge, R. Goddard, A. Fürstner, *Angew. Chem. Int. Ed.* **2010**, *49*, 1949-1953.

[15] For the X-ray structures of complexes **5c** and **6c** see references 11b and 11a, respectively.

[16] L. Falivene, R. Credendino, A. Poater, A. Petta, L. Serra, R. Oliva, V. Scarano, V. Cavallo, *Organometallics* **2016**, *35*, 2286-2293.

[17] a) S, E, Wheeler, T. J. Seguin, Y. Guan, A. C. Doney, *Acc. Chem. Res.* **2016**, *49*, 1061-1069; b) A. Milo, A. J. Neel, F. D. Toste, M. S. Sigman, *Science* **2015**, *347*, 737-743.

[18] a) Y. Uozumi, A. Tanahashi S. Y. Lee, T. Hayashi, *J. Org. Chem.* **1993**, *58*, 1945-1948; b) S. Y. Cho, M. Shibasaki, *Tet. Lett.* **1998**, *39*, 1773-1776.

[19] CCDC 1969546 and 1969748 contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre

10.1002/anie.201915456

WILEY-VCH

COMMUNICATION

*J. Zhang, M. Simon, C. Golz and M. Alcarazo**

Page No. – Page No.

Gold-Catalysed Atroposelective Synthesis of 1,1'-Binaphthanene-2,3'-diol

Remote control: Two methyl groups strategically located at the backbone of the imidazolium rest make the difference. While the catalyst derived from non-substituted imidazolium unit show mediocre performance (50% ee), the 3,4-dimethyl derivative is able to deliver the desired binaphthols in up to 97% ee.