A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Asymmetric Hydroesterification of Diarylmethyl Carbinols

Authors: Wenjun Tang, Duanshuai Tian, Ronghua Xu, Jinbin Zhu, Jianxun Huang, Wei Dong, and Jerome Claverie

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202015450

Link to VoR: https://doi.org/10.1002/anie.202015450

WILEY-VCH

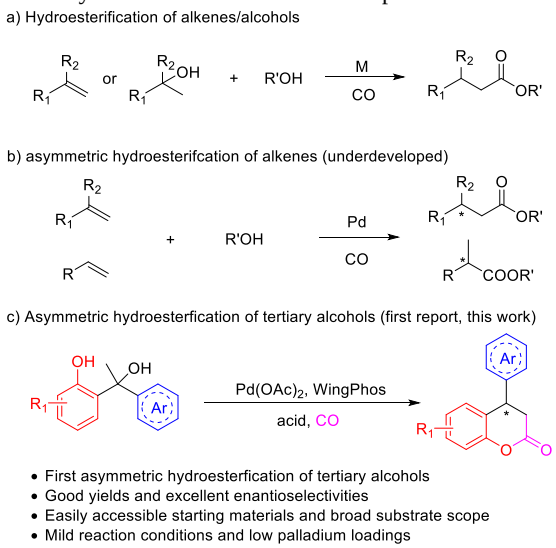
Asymmetric Carbonylation DOI: 10.1002/anie.200((will be filled in by the editorial staff))

Asymmetric Hydroesterification of Diarylmethyl Carbinols

*Duanshuai Tian[a]; Ronghua Xu[a]; Jinbin Zhu[a]; Jianxun Huang[a]; Wei Dong[a]; Jerome Claverie,[*] Wenjun Tang[a]**

***Abstract**: An efficient asymmetric hydroesterfication of diarylmethyl carbinols is developed for the first time with a Pd-WingPhos catalyst, resulting in a series of chiral 4-aryl-3,4-dihydrocoumarins in excellent enantioselectivities and good yields. The method features mild reaction conditions, a broad substrate scope, use of easily accessible starting materials, and low palladium loadings. A plausible stereochemical model is also proposed with the Pd-WingPhos catalyst. This method has enabled a 4-step asymmetric synthesis of (R)-tolterodine from readily available starting materials.*

The hydroesterification of alkenes (Reppe carbonylation) using carbon monoxide as the C1 feedstock is a powerful and essential transformation for producing carboxylic acid derivatives in both academia and industry.[1][2] Recent development on this transformation have extended to various functionalized substrates including alcohols, halides, pseudo halides, and et al.[3] Accordingly, asymmetric hydroesterification of alkenes to produce nonracemic carboxylic acid derivatives have received considerable attention, with the development of a few efficient examples.[4][5][6][7] Nevertheless, asymmetric hydroesterification is an underdeveloped area with limited effective chiral catalysts and substrates. Development of an effective asymmetric hydroesterification with high enantioselectivities, yields, regioselectivities, and low catalyst loadings remains an important goal. Asymmetric hydroesterification of tertiary alcohols, utilizing more convenient starting materials than disubstituted olefins, would provide an even more facile method for chiral carboxylic acid derivatives and such approach has not been studied to our knowledge (Scheme 1). Herein we report the first asymmetric hydroesterification of diarylmethyl carbinols that have provided a wide array of chiral 4-aryl-3,4-dihydrocoumarins in good yields and excellent enantioselectivities. The method enjoyed mild reaction conditions with the palladium loading as low as 0.1 mol %.



Scheme 1. Asymmetric hydroesterfication of diarylmethyl carbinols

Coumarin derivatives are important structural units in numerous biologically active natural products.[8] The chiral 4-aryl-3,4-dihydrocoumarins are also important building blocks for the synthesis of chiral diarylpropanoic acid derivatives, which exist in the structures of numerous bioactive compounds or therapeutic agents including RORγ inhibitor **I**[9], GPR40 agonist **II**[10], and muscarinic antagonist (*R*)-tolterodine (**III**) [11] (Figure 1). Asymmetric synthesis of chiral 4-aryl-3,4-dihydrocoumarins has become an important research subject. Although a few asymmetric synthetic methods toward 4-aryl-3,4-dihydrocoumarins are available,[12-17] the asymmetric hydroesterification of diarylmethyl carbinols, which are readily prepared from nucleophilic addition of 2'-hydroxyacetophenone with aryl Grignard reagent, would offer a convenient and facile synthetic method of such structures. Herein we report a convenient synthesis of (*R*)-tolterodine by asymmetric hydroesterification.

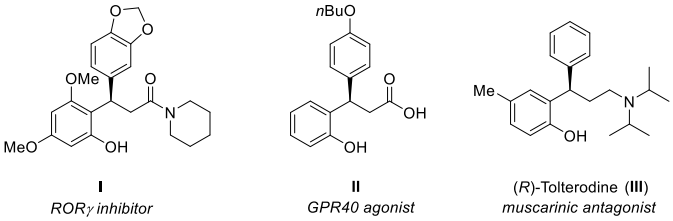


Figure 1. Bioactive compounds or therapeutic agents containing chiral diarylpropanoic acid substructures

To realize an efficient asymmetric hydroesterification of diarylmethyl carbinols, we set out a program to develop an effective asymmetric hydroesterification of 1,1-diaryl olefins. The Pd-catalyzed hydroesterification of 2-(1-phenylvinyl)phenol (**1a**) was thus studied with various chiral phosphorus ligands (Table 1). The reactions were carried out at 90 °C under syngas atmosphere (CO/H_2 5:1, 600 psi) with $Pd(OAc)_2$ (2.5 mol %) as the catalyst precursor, a chiral bisphosphorus ligand (5 mol %), *p*-toluenesulfonic acid (10 mol %) as the additive, and dichloromethane as the solvent (Table 1). Previous work by Shi reported a low yield (30%) and a moderate ee (56%) with DTBM-SEGPHOS as the ligand.[7a] Under the current reaction conditions, a low ee (9%) and a moderate yield (52%) were obtained with DTBM-SEGPHOS (Entry 2). A poor ee was also observed with (*S*)-DM-SEGPHOS, (-)-DIOP or (*S*)-BINAP as the ligand (Entries 1, 3-4). When a BIBOP-type ligand such as (*R,R,R,R*)-*i*PrO-BIBOP(**L1**) or (*R,R,R,R*)-BnO-BIBOP (**L2**) was employed, the enantioselectivity remained low (Entries 5-6). To our

[*] Prof. Dr. W. Tang, D. Tian, State Key Laboratory of Bio-Organic and Natural Products Chemistry
Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Ling Ling Rd, Shanghai 200032
E-mail: tangwenjun@sioc.ac.cn

Prof. Dr. W. Tang
School of Chemistry and Materials Science, Hangzhou Institute for Advanced Study, University of Chinese Academy of Sciences, 1 Sub-lane Xiangshan, Hangzhou 310024, China
Prof. Dr. Jerome Claverie
Department of Chemistry, University of Sherbrooke, 2500 Blvd de l'Université, Sherbrooke, Qc, J1K2R1, Canada
Email: Jerome.Claverie@USherbrooke.ca

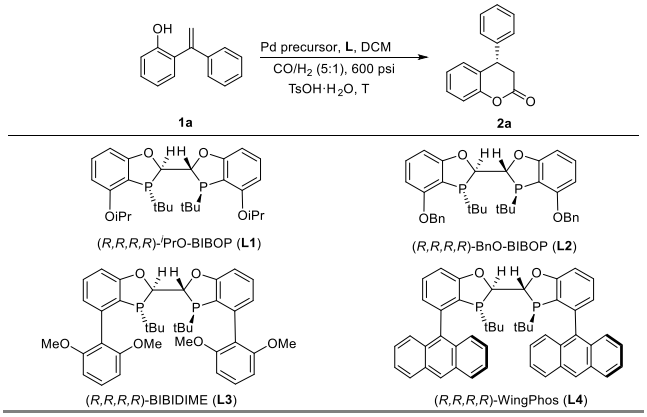
[**] We are grateful to the Strategic Priority Research Program of the Chinese Academy of Sciences XDB20000000, CAS (QYZDY-SSW-SLH029), NSFC (21725205, 21432007, 21572246), and K.C. Wong Education Foundation.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

10.1002/anie.202015450

delight, the enantioselectivity increased to 61% with (*R,R,R,R*)-BIBIDIME (**L3**) as the ligand, (Entry 7). When (*R,R,R,R*)-WingPhos(**L4**)[18] was applied as the ligand, the desired lactone **2a** was obtained in 67% ee and 88% yield (Entry 8). We then investigated the temperature effect of the asymmetric hydroesterification. When the reaction temperature dropped from 90°C to 50°C with **L4** as the ligand, the enantioselectivity increased to 87%, while the yield did not drop (Entry 9). When the reaction temperature was further reduced to 45°C, product **2a** was afforded in 89% yield and 90% ee with a prolonged reaction time (48 h, Entry 10). Further screening of various palladium precursors such as $Pd(O_2CCF_3)_2$ and $Pd(dba)_2$ provided similarly high yields and ee values (Entries 11-12). However, no reaction was observed when $Pd(PPh_3)_2Cl_2$ was employed as the palladium precursor (Entry 13). Finally, the effect of *p*-toluenesulfonic acid as the additive was studied. When the reaction was performed in the absence of *p*-toluenesulfonic acid, no formation of product **2a** was observed, indicating the importance of the acidic environment for the transformation (Entry 14).

Table 1. Asymmetric hydroesterification reaction of **1a** [a][g]

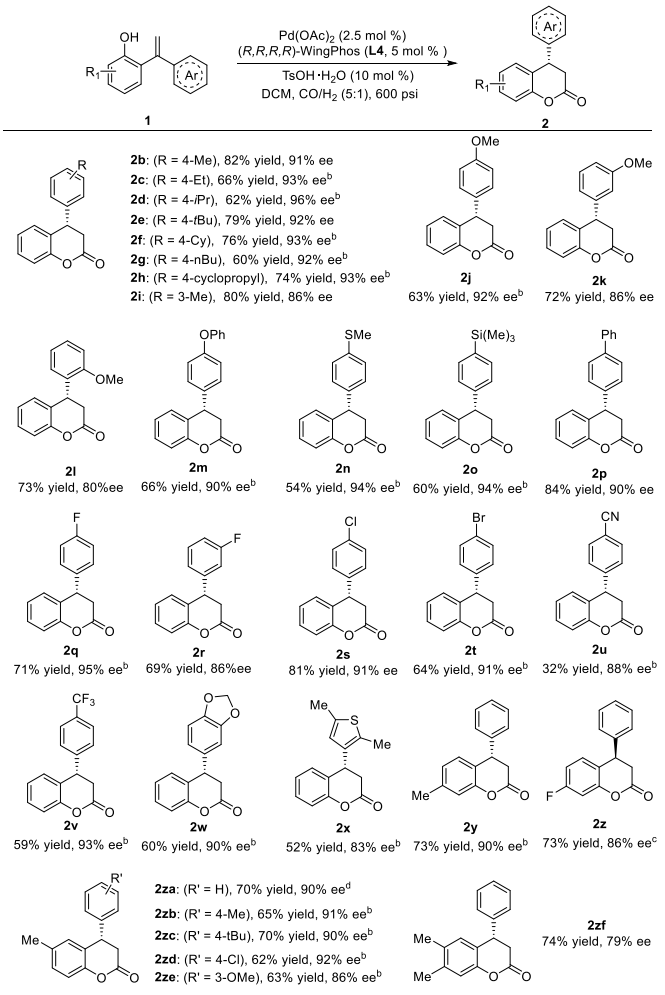


Entries	Pd precursor	L	T/°C	Yield (%)[b]	Ee (%)[c]
1	$Pd(OAc)_2$	(*S*)-DM-SEGPHOS	90	84	22
2	$Pd(OAc)_2$	(*S*)-DTBM-SEGPHOS	90	52	9
3	$Pd(OAc)_2$	(-)-DIOP	90	88	7
4	$Pd(OAc)_2$	(*S*)-BINAP	90	85	23
5	$Pd(OAc)_2$	L1	90	86	15
6	$Pd(OAc)_2$	L2	90	85	25
7[d]	$Pd(OAc)_2$	L3	90	86	61
8	$Pd(OAc)_2$	L4	90	88	67
9	$Pd(OAc)_2$	L4	50	88	87
10[d][f]	$Pd(OAc)_2$	L4	45	89	90
11[d]	$Pd(O_2CCF_3)_2$	L4	45	87	88
12[d]	$Pd(dba)_2$	L4	45	82	90
13[d]	$Pd(PPh_3)_2Cl_2$	L4	45	0	ND
14[d][e]	$Pd(OAc)_2$	L4	45	0	ND

[a] Unless otherwise specified, all reactions were performed in dichloromethane (1.5 mL) for 24 h with **1a** (0.2 mmol), Pd precursor (2.5 mol %), **L** (5 mol %), $TsOH{\cdot}H_2O$ (10 mol %) and syngas (CO/H_2 5:1, 600 psi). The absolute configuration of **2a** was determined by comparing the sign of the optical rotation with reported data[13b]. [b] Isolated yields. [c] Determined by chiral HPLC on a chiralcel OD-H column. [d] t: 48 h. [e] Without $TsOH.H_2O$. [f] Pure CO instead of syngas was also employed with least influence. [g] TsOH: *p*-toluenesulfonic acid; DCM：dichloromethane.

We then looked into the asymmetric hydroesterification of 1,1-diaryl olefins. As depicted in Table 2, a series of chiral 4-aryl-3,4-dihydrocoumarins were obtained in excellent ee's and moderate to good yields with Pd-WingPhos as the catalyst. Substrates containing either electron-donating substituents such as alkyl, alkoxy, and trimethylsilyl groups (**2a-o 2za-zf**), or electron-withdrawing substituents such as phenyl, fluoro, chloro, bromo, and trifluoromethyl groups (**2p-2v**) were all applicable, providing 79-96% ee's. When the substituent on the aryl group was at *ortho* or *meta* position, the enantioselectivity dropped slightly (**2k, 2l, 2r**). Interestingly, the hydroesterification was compatible with heteroaryl group such as thiophene (**2x**). Substituents with strong coordinating ability such as methylthio and cyano groups were all compatible and products **2o** and **2u** were afforded in excellent enantioselectivities and good yields. It was particularly noteworthy that this transformation was tolerant with substrates with halogen substituents (**2s, 2t, 2zd**). Even the bromo-substituted lactone **2t** was isolated in 91% ee and 64% yield without noticeable formation of dehalogenation and other related side-products. Delightfully, asymmetric hydroesterification of 4-methyl-2-(1-phenylvinyl)phenol (**1za**, 2.1 g) was carried out at a gram scale in the presence of $Pd(OAc)_2$ (0.1 mol %) and (*R,R,R,R*)-WingPhos (**L4**, 0.12 mol %), and the desired chiral lactone **2za** (1.6 g) was afforded in 70% yield and 90% ee, demonstrating the high practicality of this asymmetric transformation.

Table 2. Asymmetric hydroesterification of alkenes compound **1** [a]



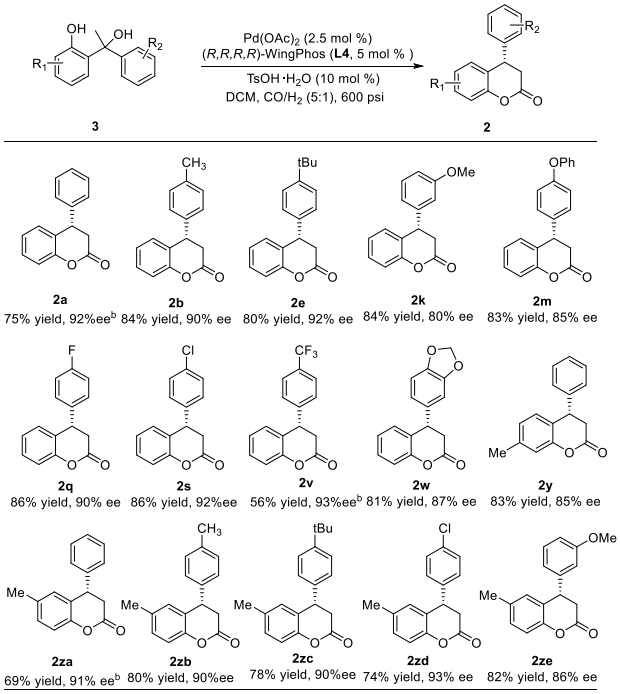
[a] Unless otherwise specified, all reactions were performed in dichloromethane (1.5 mL) and 45 °C for 48 h with **1** (0.2 mmol), $Pd(OAc)_2$ (2.5 mol %), **L** (5 mol %), $TsOH{\cdot}H_2O$ (10 mol %) and syngas (CO/H_2 5:1, 600 psi). [b] T: 35 °C. [c] (*S,S,S,S*)-**L3** (5 mol %) was employed as the ligand. [d] $Pd(OAc)_2$ (0.1 mol %).

The successful development on asymmetric hydroesterification of 1,1-diaryl olefins prompted us to further investigate the asymmetric hydroesterification of diarylmethyl carbinols, which were more advantageous from a point view of process chemistry: 1) the diarylmethyl carbinols can be readily prepared from methyl aryl ketones by nucleophilic addition with aryl Grignard reagent, thus eliminating the additional step for preparation of the corresponding olefins; 2) in contrast to often oily nature of 1,1-diaryl olefins, most diarylmethyl carbinols were solids easy for purity control and storage. Despite with no precedence, we envisioned that the diarylmethyl carbinol will be readily converted to 1,1-diaryl olefin by elimination of water under the reaction conditions. If water can

10.1002/anie.202015450

be tolerated during the course of carbonylation, asymmetric hydroesterification of diarylmethyl carbinols could be accomplished. Indeed, when a series of diarylmethyl carbinols **3** were subjected to hydroesterification with Pd-WingPhos catalyst under similar reaction conditions mentioned above, an array of enantiomerically enriched 4-aryl-3,4-dihydrocoumarin products were successfully obtained without significant deterioration of both enantioselectivities and yields (Table 3). The *in situ* formed water was well tolerated with the Pd-WingPhos catalyst system. Thus, we have developed for the first time an efficient asymmetric hydroesterification of tertiary alcohols.

Table 3. Asymmetric hydroesterification reaction of tertiary alcohols **3** [a]



[a] Unless otherwise specified, all reactions were performed in dichloromethane (1.5 mL) and 45 ºC for 48 h with **3** (0.2 mmol), $Pd(OAc)_2$ (2.5 mol %), **L4** (5 mol %), $TsOH{\cdot}H_2O$ (10 mol %) and syngas (CO/H_2 5:1, 600 psi), isolated yields, ee's were determined by chiral HPLC. [b] T = 40 ºC

A plausible mechanism was proposed in Figure 2. Oxidative addition of the Pd(0)-WingPhos species (**A**) with TsOH forms the cationic Pd(II)-WingPhos hydride species **B**. This is followed by coordination with olefin **1a**, which is formed by elimination of **3a** under acidic conditions, and an ensuring insertion to provide the alkyl Pd(II) species **C**. Next, CO insertion of **C** forms the acyl Pd(II) species **D**, which undergoes reductive elimination to form the lactone product **2a** and regenerate the Pd(0)-WingPhos catalyst. Apparently, the olefin coordination and insertion process from **B** to **C** determines the stereoselectivity of this transformation. Based on the X-ray structure of the Pd-(*R,R,R,R*)-WingPhos complex in our previous report[18], the upper left and lower right parts of the C_2-symmetric Pd hydride species are blocked by two anthracenyl groups. When olefin **1a** approaches the cationic Pd species through a chelating fashion with olefin coordination in the same plane as the phosphorus centers and the hydroxy group in apical position, the phenol moiety would locate preferentially at lower left position of the Pd species as shown in Figure 2c and the resulting migratory insertion and further transformations proceed to provide lactone **2a** with the observed *S* configuration.

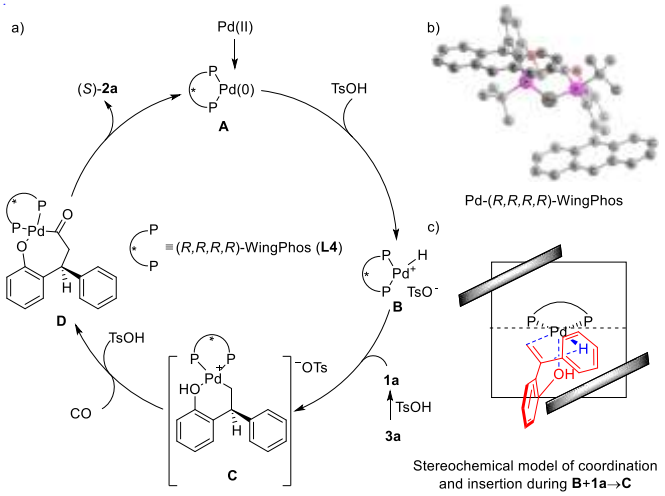
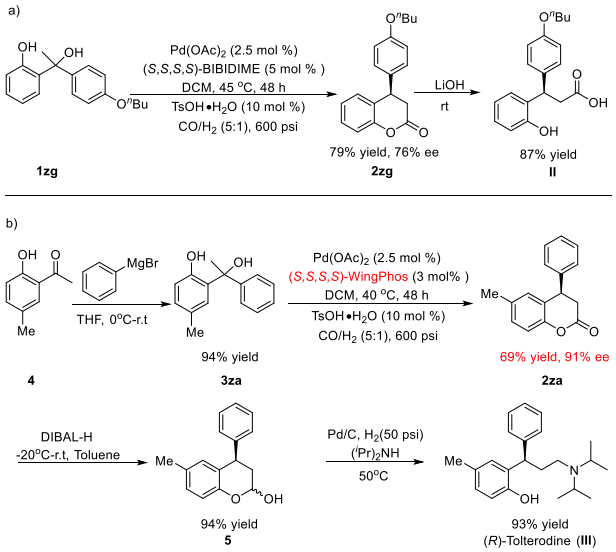


Figure 2. Proposed mechanism

The asymmetric hydroesterification of diarylmethyl carbinols were further applied to the synthesis of biologically intersting compounds or therapeutic agents. Chiral β,β-diaryl carboxylic acid **II** is a potent GPR40 agonist, a potential drug for the treatment of diabetes.[9] Using tertiary alcohol **1zg** as the starting material, we successfully obtained chiral **2zg** in 79% yield and 76% ee with Pd-(*S,S,S,S*)-BIBIDIME as the catalyst by asymmetric hydroesterification. Hydrolysis of **2zg** with LiOH as the base formed II in 87% yield (Scheme 2a). (*R*)-Tolterodine[10] is a therapeutic agent for the treatment of urinary incontinence, frequent urination, and urgency. Its synthesis started with nucleophilic addition of ketone **4** with phenyl Grignard reagent, forming tertiary alcohol **3za** in 94% yield. Asymmetric hydroesterification of **3za** in dichloromethane with $Pd(OAc)_2$ (2.5 mol %) and (*S,S,S,S*)-WingPhos (3 mol %) as the catalyst system at 40 ºC for 48 h led to the formation of **2za** in 91% ee and 69% isolated yield. This was followed by DIBAL-H reduction and reductive amination with diisopropylamine under conditions of Pd/C and H_2, forming (*R*)-tolterodine in four overall steps from ketone **4**. Thus, a convenient synthesis of (*R*)-tolterodine by asymmetric hydroesterification was successfully developed (Scheme 2d).



Scheme 2. Synthetic applications

In conclusion, we have developed for the first time an efficient asymmetric hydroesterification of diarylmethyl carbinols powered by a Pd-WingPhos catalyst, resulting in a series of chiral 4-aryl-3,4-dihydrocoumarins in excellent enantioselectivities and good yields. The method features mild reaction conditions, a broad substrate scope, use of easily accessible starting materials, and low palladium

loadings. A plausible stereochemical model of the asymmetric hydroesterification is proposed with the Pd-WingPhos catalyst. This method has also enabled a 4-step asymmetric synthesis of (*R*)-tolterodine from readily available starting materials.

Received: ((will be filled in by the editorial staff))
Published online on ((will be filled in by the editorial staff))

Keywords: hydroesterification, diarylmethyl carbinols, enantioselectivity, carbon monoxide, tolterodine

[1] For selected reviews, see: (a) Kiss, G. *Chem. Rev.* **2001**,*101*, 3435. (b) Kollár, L.*Modern Carbonylation Methods;*Wiley-VCH: Weinheim, **2008**. (c) Beller, M.; Wu, X.-F. *Transition Metal Catalyzed Carbonylation Reactions;* Springer: Berlin, **2013**. (d) Quintero-Duque, S.; Dyballa, K. M.; Fleischer, I. *Tetrahedron Lett.* **2015**, *56*, 2634. (e) Gehrtz, P. H.; Hirschbeck, V.; Ciszek, B.; Fleischer, I. *Synthesis.* **2016**, *48*, 1573. (f) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Rev.* **2013**,*113*, 1. (g) Fang, W.; Zhu, H.; Deng, Q.; Liu, S.; Liu, X.; Shen, Y.; Tu, T. *Synthesis.* **2014**, *46*, 1689. (h) Barnard, C. F. *J.Organometallics* **2008**, *27*, 5402. (i) Bai, Y.; Davis, D. C.; Dai, M-J.; *J. Org. Chem.* **2017**, *82*, 2319−2328.

[2] For recent representative works, see: (a) Li, H.; Dong, K.; Jiao, H.; Neumann, H.; Jackstell,R.; Beller, M. *Nat. Chem.* **2016**, *8*, 1159−1166. (b) Dong, K.; Fang, X; Franke, R.; Spannenberg, A.; Neumann, H.; Jackstell, R.; Beller, M. *Nat. commun.* **2017**, *8*, 14117. (c) Yang, J.; Liu, J.; Neumann, H.; Franke, R.; Jackstell, R.; Beller, M. *Science.* **2019**, *366*, 1514-1517. (d) Liu, J.; Yang, J.; Baumann, W.; Jackstell, R.; Beller, M. *Angew. Chem.* **2019**, *131*, 10793-10797; *Angew. Chem., Int. Ed.*, **2019**, *58*, 10683–10687. (e) Liu, J.; Dong, K.; Franke, R.; Neumann, H.; Jackstell, R.; Beller, M. *J. Am Chem. Soc.* **2018**, *40*, 10282-10288. (f) Liu, J.; Yang, J.; Schneider, C.; Franke, R.; Jackstell, R.; Beller, M. *Angew. Chem.* **2020**, *132*, 9117-9125; *Angew. Chem., Int. Ed.*, **2020**, *59*, 9032–9040. (g) Sha, F.; Alper, H. *ACS Catal*. **2017**, *7*, 2220- 2229. (h) Chen, J.; Huang, M.; Ren, W.; Chu, J.; Shi, Y. *Eur. J.Org. Chem*. **2020**, 1078-1083.

[3] (a) Ryu, I. *Chem. Soc. Rev.* **2001**, *30*, 16.(b) Dong, K.; Sang, R.; Liu, J.; Razzaq, R.; Franke, R.; Jackstell, R.; Beller, M. *Angew. Chem.* **2017**, *129*, 6299-6303; *Angew. Chem., Int. Ed.*, **2017**, *56*, 6203-6207.

[4] For reviews, see: (a) Godard, C.; Muñoz, B, K.; Ruiz, A.; Claver, C. *Dalton Trans*., **2008**, 853-860. (b) Godard, C.; Perandones, B, F.; Gual, A.; Claver, C. in *Comprehensive Inorganic Chemistry II*, ed. J. Reedijk and K. Poeppelmeier, Elsevier Ltd, 2nd edn, 2013, pp. 383–411.

[5] For leading references on Pd-catalyzed asymmetric intermolecular hydroesterification of olefins with CO gas, see: (a) Consiglio, G. *Helv. Chim. Acta* **1976**, *59*, 124. (b) Hayashi, T.; Tanaka, M.; Ogata, I. *Tetrahedron Lett.* **1978**, *19*, 3925. (c) Cometti, G.; Chiusoli, G. P. *J. Organomet. Chem.* **1982**, *236*, C31. (d) Chelucci, G.; Cabras, M. A.; Botteghi, C.; Marchetti, M. *Tetrahedron: Asymmetry* **1994**, *5*, 299. (e) Zhou, H.; Lu, S.; Hou, J.; Chen, J.; Fu, H.; Wang, H. *Chem. Lett.* **1996**, *25*, 339. (f) Zhou, H.; Hou, J.; Cheng, J.; Lu, S.; Fu, H.; Wang, H. *J. Organomet. Chem.* **1997**, *543*, 227. (g) Oi, S.; Nomura, M.; Aiko, T.; Inoue, Y. *J. Mol. Catal. A: Chem.* **1997**, *115*, 289. (h) Nozaki, K.; Kantam, M. L.; Horiuchi, T.; Takaya, H. *J. Mol. Catal. A: Chem.* **1997**, *118*, 247. (i) Wang, L.; Kwok, W. H.; Chan, A. S. C.; Tu, T.; Hou, X.; Dai, L. *Tetrahedron: Asymmetry* **2003**, *14*, 2291. (j) Kawashima, Y.; Okano, K.; Nozaki, K.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 347. (k) Muñ oz, B.; Marinetti, A.; Ruiz, A.; Castillon, S.; Claver, C. *Inorg. Chem. Commun.* **2005**, *8*, 1113. (l) Guiu, E.; Caporali, M.; Muñ oz, B.; Müller, C.; Lutz, M.; Spek, A. L.; Claver, C.; van Leeuwen, P. W. N. M. *Organometallics* **2006**, *25*, 3102. (m) Godard, C.; Ruiz, A.; Claver, C. *Helv. Chim. Acta* **2006**, *89*, 1610. (n) Muñ oz, B. K.; Godard, C.; Marinetti, A.; Ruiz, A.; BenetBuchholz, J.; Claver, C. *Dalton Trans.* **2007**, 5524. (o) Li, J.; Chang, W.; Ren, C.; Dai, J.; Shi, Y. *Org. Lett.* **2016**, *18*, 5456-5459. (p) Li, J.; Ren, W.; Dai, J.; Shi, Y. *Org. Chem. Front*. **2018**, *5*, 75-79.

[6] For leading references on Pd-catalyzed asymmetric intermolecular hydroxycarbonylation of olefins with CO gas, see: (a) Botteghi, C.; Consiglio, G.; Pino, P. *Chimia.* **1973**, *27*, 477. (b) Consiglio, G. *J. Organomet. Chem*. **1977**, *132*, C26. (c) Becker, Y.; Eisenstadt, A.; Stille, J. K. *J. Org. Chem*. **1980**, *45*, 2145. (d) Alper, H.; Hamel, N. *J. Am. Chem. Soc.* **1990**, *112*, 2803. (e) Miquel-Serrano, M. D.; Aghmiz, A.; Dieguez, M.; Masdeu-Bulto, A. M.; Claver, C.; Sinou, D. *Tetrahedron: Asymmetry.* **1999**, *10*, 4463. (f) Konrad, T. M.; Fuentes, J. A.; Slawin, A. M. Z.; Clarke, M. L. *Angew. Chem.* **2010**, *122*, 9383-9386; *Angew. Chem., Int. Ed*. **2010**, *49*, 9197. (g) Konrad, T. M.; Durrani, J. T.; Cobley, C. J.; Clarke, M. L. *Chem. Commun.* **2013**, *49*, 3306.

[7] For leading references on Pd-catalyzed intramolecular hydroesterification of olefins with CO gas, see: (a) Li, J.; Chang, W.; Ren, W.; Liu, W.; Wang, H.; Shi, Y. *Org. Biomol. Chem.* **2015**, *13*, 10341-10347.(b) Dong, C.; Alper, H. *J. Org. Chem.* **2004**, *69*, 5011–5014. (c) Yu, W.; Bensimon, C.; Alper, H. *Chem. - Eur. J.* **1997**, *3*, 417−423. (d) El Ali, B.; Okuro, K.; Vasapollo, G.; Alper, H. *J. Am. Chem. Soc.* **1996**, *118*, 4264−4270.

[8] (a) Hoult, J. R. S.; Paya, M. *Gen. Pharmacol.* **1996**, *27*, 713−722. (b) Yu, D.; Suzuki, M.; Xie, L.; Morris-Natschke, S. L.; Lee, K. H. *Med. Res. Rev.* **2003**, *23*, 322−345. (c) Thuong, P. T.; Hung, T. M.; Ngoc, T. M.; Ha, D. T.; Min, B. S.; Kwack, S. J.; Bae, K. *Phytother. Res.* **2010**, *24*, 101−106. (d) Gliszczyńska, A.; Brodelius, P. E. *Phytochem. Rev*. **2012**, *11*, 77−96. (e) Sun, X.; Sneden, A. T. *Planta Med.* **1999**, *65*, 671−673. (f) Ngadjui, B. T.; Kapche, G. W. F.; Tamboue, H.; Abegaz, B. M.; Connolly, J. D. *Phytochemistry* **1999**, *51*, 119−123. (g) Iinuma, M.;Tanaka, T.; Takenaka, M.; Mizuno, M.; Asai, F. *Phytochemistry* **1992**, *31*, 2487−2490. (h) Li, X. M.; Lin, M.; Wang, Y. H.; Liu, X. *Planta Med.* **2004**, *70*, 160−165. (i) Xu, S.; Shang, M. Y.; Liu, G. X.; Xu, F.; Wang, X.; Shou, C.C.; Cai, S. Q. *Molecules* **2013**, *18*, 5265−5287. (j) Tabanca, N.; Pawar, R. S.; Ferreira, D.; Marais, J. P.; Khan, S. I.; Joshi, V.; Khan, I. A. *Planta Med.* **2007**, *73*, 1107−1111. (k) Takechi, M.; Tanaka, Y.; Takehara, M.; Nonaka, G. I.; Nishioka, I. *Phytochemistry* **1985**, *24*, 2245−2250. (l) Sashidhara, K. V.; Singh, S. P.; Singh, S. V.; Srivastava, R. K.; Srivastava, K.; Saxena, J. K.; Puri, S. K. *Eur. J. Med. Chem.* **2013**, *60*, 497−502. (m) Xiong, Q.; Fan, W.; Tezuka, Y.; Adnyana, I. K.; Stampoulis, P.; Hattori, M.; Namba, T.; Kadota, S. *Planta Med.* **2000**, *66*, 127−133.

[9] Huh, J. R.; Englund, E. E.; Wang, H.; Huang, R.; Huang, P.; Rastinejad, F.; Littman, D. R. *ACS Med. Chem. Lett.* **2013**, *4*, 79−84.

[10] Song, F.; Lu, S.; Gunnet, J.; Xu, J. Z.; Wines, P.; Proost, J.; Liang,Y.; Baumann, C.; Lenhard, J.; Murray, W. V.; Demarest, K. T.; Kuo, G. *J. Med. Chem.* **2007**, *50*, 2807.

[11] (a) GageJ. R.; CabajJ. E. U.S. Patent 1,996,003,396, 1998. (b) Mathad, V. T.; Venkataraman, S.; Kumari, R. L.; Arunagiri, M.; Reddy, C. R.; Ramakrishna, M.; Reddy, K. S.; Srinivasan, N.; Srinivas, K. *Org. Process Res. Dev.* **2005**, *9*, 314. (c) Rhee, H.; Park, S.; Park, D.; Ko, J.; Castro, K. D. *Org. Process Res. Dev.* **2007**, *11*, 918.

[12] (a) Nair, V. *Synth. Commun.* **1987**, *17*, 723−727. (b) Lee, J. M.; Tseng, T. H.; Lee, Y. J. *Synthesis* **2001**, *2001*, 2247−2254. (c) Roelens, F.; Huvaere, K.; Dhooge, W.; Van Cleemput, M.; Comhaire, F.; DeKeukeleire, D. *Eur. J. Med. Chem. 2005*, *40*, 1042−1051. (d) Li, K.; Foresee, L. N.; Tunge, J. A. *J. Org. Chem.* **2005**, *70*, 2881−2883. (e) Fillion, E.; Dumas, A. M.; Kuropatwa, B. A.; Malhotra, N. R.; Sitler, T. C. *J. Org. Chem.* **2006**, *71*, 409−412. (f) Rodrigues-Santos, C. E.; Echevarria, A. *Tetrahedron Lett*. **2007**, *48*, 4505−4508. (g) Sun, J.; Ding, W.

10.1002/anie.202015450

X.; Hong, X. P.; Zhang, K. Y.; Zou, Y. *Chem. Nat. Compd.* **2012**, *48*, 16−22. (h) Niharika, P.; Ramulu, B. V.; Satyanarayana, G. *Org. Biomol. Chem*. **2014**, *12*, 4347−4360.

[13] (a) Kim, H.; Yun, J. *Adv. Synth. Catal.* **2010**, *352*, 1881−1885. (b) Ulgheri, F, Marchetti, M; Piccolo, O. *J. Org. Chem.* **2007**, *72*, 6056-6059.

[14] Rh-catalyzed asymmetric 1,4-addition: (a) Defieber, C.; Paquin, J. F.; Serna, S.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 3873−3876. (b) Chen, G.; Tokunaga, N.; Hayashi, T. *Org. Lett.* **2005**, *7*, 2285−2288. (c) Korenaga, T.; Maenishi, R.; Osaki, K.; Sakai, T. *Heterocycles* **2010**, *80*, 157−162. (d) Luo, Y.; Carnell, A. J. *Angew. Chem.* **2010**, *122*, 2810-2814; *Angew. Chem., Int. Ed.* **2010**, *49*, 2750−2754. (e) Allen, J. C.; Kociok-Köhn, G.; Frost, C. G. *Org. Biomol. Chem.* **2012**, *10*, 32−35. (f) Mino, T.; Miura, K.; Taguchi, H.; Watanabe, K.; Sakamoto, M. *Tetrahedron: Asymmetry* **2015**, *26*, 1065−1068.

[15] Li, X.-H.; Fang, P.; Chen, D.; Hou, X.-L. *Org. Chem. Front.* **2014**, *1*, 969−973.

[16] Caruana, L.; Mondatori, M.; Corti, V.; Morales, S.; Mazzanti, A.; Fochi, M.; Bernardi, L. *Chem. - Eur. J.* **2015**, *21*, 6037−6041.

[17] (a) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Adv. Synth. Catal.* **2007**, *349*, 1759−1764. (b) Yue, G.; Lei, K.; Hirao, H.; Zhou, J. S. *Angew. Chem.* **2015**, *127*, 6631-6635; *Angew. Chem., Int. Ed.* **2015**, *54*, 6531−6635. (c) Ibrahem, I.; Ma, G.; Afewerki, S.; Córdova, A. *Angew. Chem.* **2013**, *125*, 912-916; *Angew. Chem. Int. Ed.* **2013**, *52*, 878−882. (d) Li, G.; Li, Z.; Gu, Q.; You, S.; *Org. Lett*. **2017**, *19*, 1318−1321.

[18] (a) Qian, C.; Tang, W.; *Org, Lett.* **2020**, *22*, 4483-4488 (b) Liu, G.; Liu, X.; Cai, Z.; Jiao, G.; Xu, G.; Tang, W. *Angew. Chem.* **2013**, *125*, 4329-4332; *Angew. Chem., Int. Ed*. **2013**, *52*, 4235-4238. (c) K. Li, M. Nie, W. Tang *Green Synth. Catal.* **2020**, *1*, 173-177. (d) Xu, G.; Senanayake, C. H.; Tang, W. *Acc. Chem. Res.* **2019**, *52*, 1101−1112.

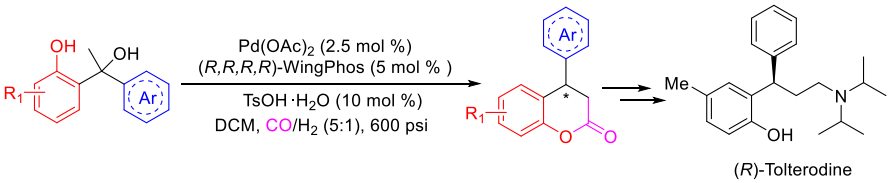
10.1002/anie.202015450

Asymmetric Catalysis

Duanshuai Tian; Ronghua Xu; Jinbin Zhu; Jianxun Huang; Wei Dong; Jerome Claverie;* Wenjun Tang*

Page

Asymmetric Hydroesterification of Diarylmethyl Carbinols



An efficient asymmetric hydroesterfication of diarylmethyl carbinols is developed for the first time with a Pd-WingPhos catalyst, resulting in a series of chiral 4-aryl-3,4-dihydrocoumarins in excellent enantioselectivities and good yields. The method features mild reaction conditions, a broad substrate scope, use of easily accessible starting materials, and low palladium loadings. A plausible stereochemical model is proposed with the Pd-WingPhos catalyst. This method has also enabled a 4-step asymmetric synthesis of (*R*)-tolterodine from readily available starting materials.