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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201900705

Link to VoR: http://dx.doi.org/10.1002/adsc.201900705

10.1002/adsc.201900705

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Palladium-Catalyzed Selective Synthesis of Dibenzo[*c*,*e*]azepin-5-ols and Benzo[*c*]pyrido[2,3-*e*]azepin-5-ols

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

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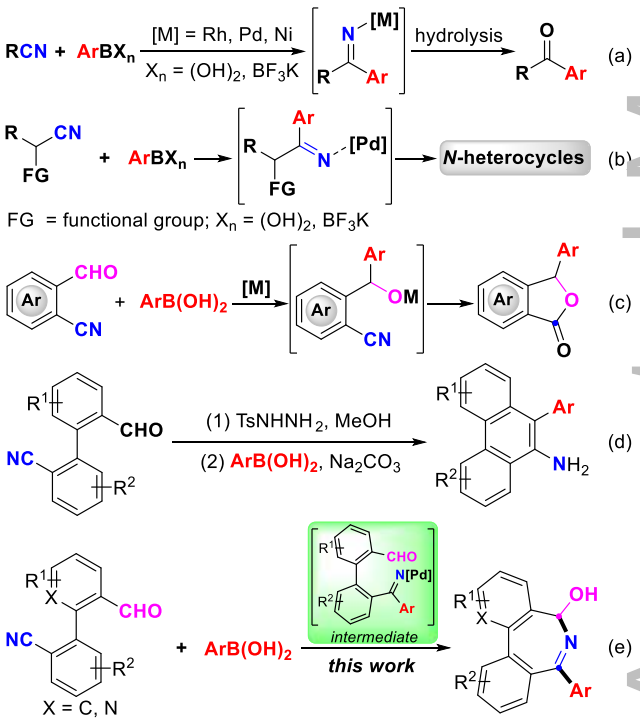
Abstract. An efficient palladium-catalyzed tandem addition/cyclization of 2'-formyl-[1,1'-biaryl]-2-carbonitriles with arylboronic acids is reported. This reaction affords dibenzo[*c*,*e*]azepin-5-ols and benzo[*c*]pyrido[2,3-*e*]azepin-5-ols with excellent selectivity and wide functional group compatibility. The dibenzo[*c*,*e*]azepin-5-ols show good cell growth inhibitory activity against a triple-negative breast cancer cell line. Moreover, the proposed mechanistic rationale for this tandem process is supported by theoretical calculations.

Keywords: palladium-catalyzed; tandem reaction; dibenzo[*c*,*e*]azepin-5-ols; benzo[*c*]pyrido[2,3-*e*]azepin-5-ols; nitriles

Introduction

The development of transition-metal-catalyzed addition of nitriles to organoboron reagents for ketone and derivative synthesis has had remarkable success over the past decade (Scheme 1a).[1] However, the nitrile's nitrogen atom has not been used effectively due to the hydrolysis of the ketamine intermediate to limit the practicality of these types of transformations for the synthesis of *N*-heterocycles. Development of a new strategy for the selective synthesis of *N*-heterocycles is a significant research goal because of their importance in laboratory synthesis and industrial applications. Our laboratory recently demonstrated a palladium-catalyzed tandem reaction of nitriles with organoboron reagents for the synthesis of six-membered *N*-heterocycles with high selectivity (Scheme 1b).[2] In addition, Cheng[3] and Liu[4] independently developed a cascade reaction of formyl-substituted nitriles with arylboronic acids for the synthesis of five-membered phthalides (Scheme 1c) or six-membered 9-amino-10-arylphenanthrenes (Scheme 1d).

Dibenz[*c*,*e*]azepine derivatives represent an important class of unique seven-membered bridged biaryl frameworks and have attracted increasing attention because of their importance in synthesis and medicinal chemistry.[5] Although the synthesis of dibenzo[*c*,*e*]azepines has been well-established,[6] only a few examples of the synthesis of dibenzo[*c*,*e*]azepin-5-ols have been reported to date.[7] We envisioned that a palladium-catalyzed addition of



Scheme 1. Design for the construction of dibenzo[*c*,*e*]azepin-5-ols and derivatives.

readily available 2'-formyl-[1,1'-biaryl]-2-carbonitriles or 2-(3-formylpyridin-2-yl)benzonitrile to arylboronic acids would produce the imine intermediate, followed by an intramolecular cyclization with the formyl group to access a new

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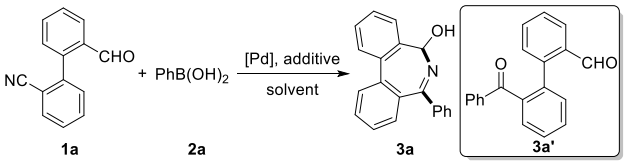
class of dibenzo[*c*,*e*]azepin-5-ols or benzo[*c*]pyrido[2,3-*e*]azepin-5-ols which are often difficult to prepare using existing methods (Scheme 1e). Moreover, the hydroxyl group in the products is a useful handle for further synthetic manipulations, thus broadening the diversity of the products with high value to both synthetic and medicinal chemistry.

Results and Discussion

Initially, the readily available 2'-formyl-[1,1'-biphenyl]-2-carbonitrile (**1a**) and phenylboronic acid (**2a**) were chosen as the model substrates in the presence of $Pd(OAc)_2$ as catalyst, 2,2'-bipyridine as ligand, and trifluoroacetic acid as additive in 2-methyltetrahydrofuran (2-MeTHF) at 90 °C under an air atmosphere for 24 h, to afford the desired 7-phenyl-5*H*-dibenzo[*c*,*e*]azepin-5-ol (**3a**) in 18% yield, along with a small amount of byproduct 2'-benzoyl-[1,1'-biphenyl]-2-carbaldehyde (**3a'**) from hydrolysis of the imine intermediate (Table 1, entry 1). With this promising result, different solvents, catalysts, ligands, and additives were screened sequentially. To our delight, the yield of **3a** could be improved to 58% when THF was used as solvent (Table 1, entries 2−5). It should be noted that the yield of byproduct **3a'** could be improved to 82% using H_2O as a solvent (Table 1, entry 6). An investigation into the effect of catalysts showed that $Pd(TFA)_2$ was more efficient for delivering a high yield of product (Table 1, entries 7−9). Replacement of 2,2'-bipyridine with different nitrogen ligands or phosphine ligands, resulted in lower yields (Table S1 in ESI). Among the different additives examined (Table 1, entries 10−12), CH_3SO_3H was found to be the best one, and the desired product 3a was furnished in 73% yield (Table 1, entry 12). Temperature is also crucial for this reaction, and it becomes sluggish if it is carried out at room temperature (Table S1 in ESI). Further studies revealed that 82% yield could be obtained by using dry THF as solvent at 80 °C (Table 1, entry 13).Finally, we found that the yield of **3a** improved to 86% when the model reaction was performed under an atmosphere of nitrogen. Control experiments indicated that both the catalyst and additive were necessary to afford the desired product **3a** in good yield (Table 1, entries 14−15). Other reaction parameters including the amount of catalyst, additive and ligand were also examined (Table S1 in ESI). The structure of new compound **3a** was determined by its X-ray diffraction.[8a]

Table 1. Optimization of reaction conditions.[a]

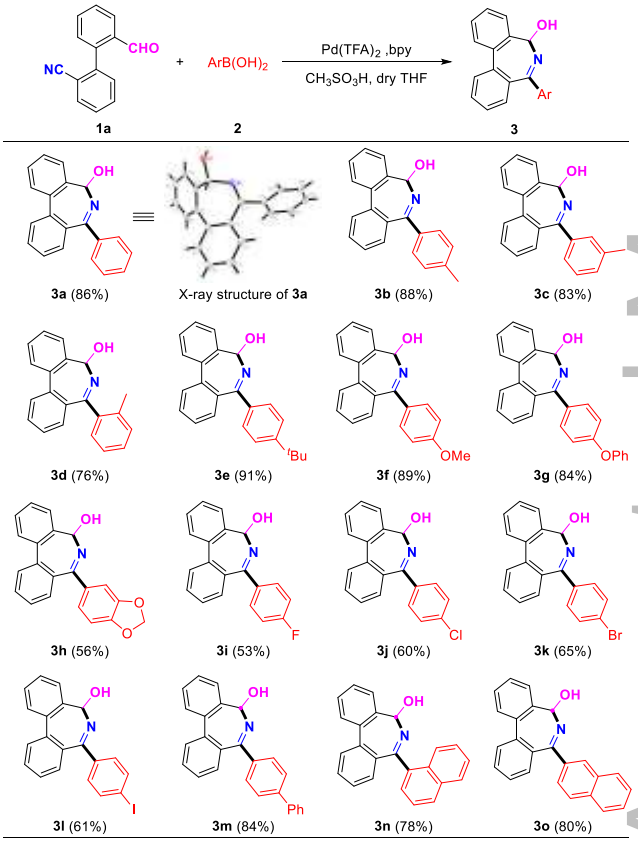


1a 2a 3a 3a'

Entry	[Pd]	Solvent	Additive	Yield (%)[b]	
				3a	**3a'**
1	$Pd(OAc)_2$	2-MeTHF	TFA	18	7
2	$Pd(OAc)_2$	toluene	TFA	27	trace
3	$Pd(OAc)_2$	DMF	TFA	32	8
4	$Pd(OAc)_2$	acetone	TFA	41	6
5	$Pd(OAc)_2$	THF	TFA	58	trace
6	$Pd(OAc)_2$	H_2O	TFA	trace	82
7	$Pd(acac)_2$	THF	TFA	62	10
8	$Pd_2(dba)_3$	THF	TFA	66	13
9	$Pd(TFA)_2$	THF	TFA	70	8
10	$Pd(TFA)_2$	THF	$TsOH·H_2O$	56	15
11	$Pd(TFA)_2$	THF	D-CSA	66	12
12	$Pd(TFA)_2$	THF	CH_3SO_3H	73	6
13[c]	**$Pd(TFA)_2$**	**dry THF**	**CH_3SO_3H**	**82 (86**[d]**)**	trace
14	$Pd(TFA)_2$	dry THF		0	0
15		dry THF	CH_3SO_3H	0	0

[a] Conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), Pd catalyst (6 mol %), bpy (12 mol %), additive (10 equiv), solvent (2 mL), 90 °C, 24 h, air.
[b] Isolated yield.
[c] At 80 °C.
[d] Under N_2 atmosphere.

Table 2. Scope of arylboronic acids.[a]

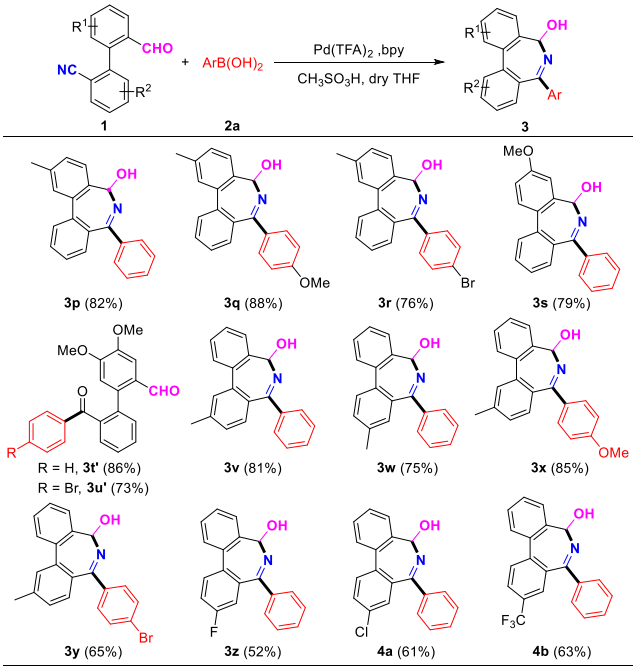


[a] Conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $Pd(TFA)_2$ (6 mol%), bpy (12 mol%), CH_3SO_3H (10 equiv), dry THF (2 mL), 80 °C, 24 h, N_2, isolated yield.

We then investigated the scope of this tandem reaction under the optimized reaction conditions. Firstly, we examined the tandem reaction of 2'-formyl-[1,1'-biphenyl]-2-carbonitrile (**1a**) with a range of arylboronic acids. As shown in Table 2, reaction of a variety of arylboronic acids with substituents at the *ortho*-, *meta*- and *para*-positions

proceeded smoothly to give the desired 7-aryl-5*H*-dibenzo[*c*,*e*]azepin-5-ols in moderate to high yields (**3b**–**3d**). However, the presence of a substituent at the *ortho*-position on the arene ring reduced the efficiency of the reaction, presumably due to the enhanced steric hindrance (**3d**). This reaction tolerates arylboronic acids with electron-donating groups (e.g., ^{t}Bu, OMe, OPh) to provide the corresponding products in good yields (**3e**–**3g**), however, reaction with a highly electron-rich substrate afforded a low yield of the desired product (**3h**). Moreover, halogen-substituted (e.g. F, Cl, Br, I) substrates also reacted with **1a** to produce the desired products with high selectivity (**3i**–**3l**). Of note, polycyclic boronic acids, such as biphenyl-4-ylboronic acid, naphthalen-1-ylboronic acid, and naphthalen-2-ylboronic acid were well tolerated in this protocol, affording the corresponding products in 78–84% yields (**3m**–**3o**).

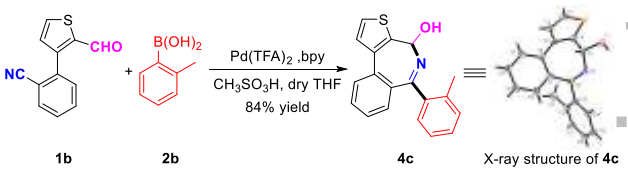
Table 3. Scope of formyl-[1,1'-biaryl]-2-carbonitriles.[a]



[a] Conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Pd(TFA)_2$ (6 mol%), bpy (12 mol%), CH_3SO_3H (10 equiv), dry THF (2 mL), 80 °C, 24 h, N_2, isolated yield.

Next, the scope of formyl-[1,1'-biaryl]-2-carbonitriles was evaluated as outlined in Table 3. Firstly, we examined formyl-[1,1'-biaryl]-2-carbonitriles bearing substituents (R^1) on the aryl formaldehyde moiety. We found that treatment of 2'-formyl-5'-methyl-[1,1'-biphenyl]-2-carbonitrile with arylboronic acids delivered the desired products in 76–88% yields (**3p**–**3r**). The substrate bearing a methoxy group was treated with phenylboronic acid to afford 79% yield of **3s**. However, highly electron-rich substrates such as 2'-formyl-4',5'-dimethoxy-[1,1'-biphenyl]-2-carbonitrile failed to provide the desired products, only affording the addition/hydrolysis byproducts (**3t'**–**3u'**). In addition, the reaction was found to be affected by the substituents (R^2) on the aryl nitrile moiety. Both electron-donating groups such as methyl and electron-withdrawing groups such as fluoro, chloro, and trifluoromethyl, were tolerated, providing the desired products in moderate to high yields (**3v**–**4b**).

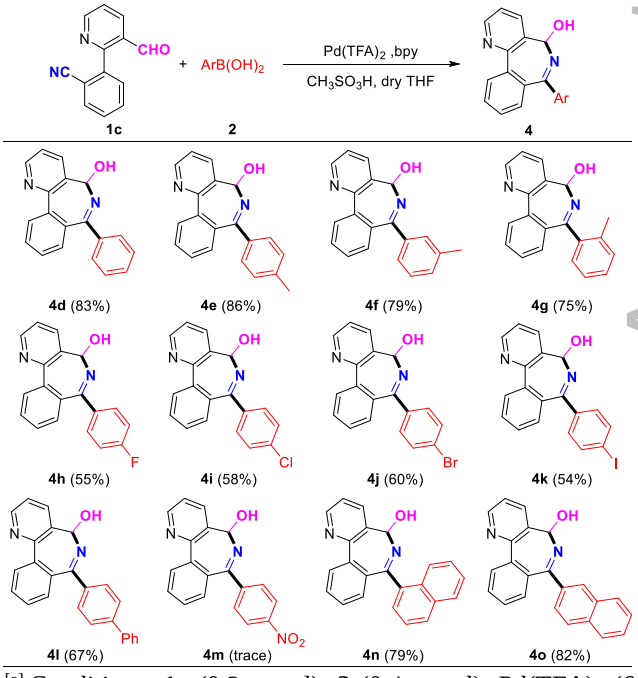
Notably, treatment of 2-(2-formylthiophen-3-yl)benzonitrile (**1b**) with *o*-tolylboronic acid (**2b**) as a representative example is shown in Scheme 2, providing **4c** in 84% yield. The structure of **4c** was identified by X-ray diffraction.[8b]



Scheme 2. Reaction of **1b** with *o*-tolylboronic acid.

Moreover, the scope of an *N*-heterocyclic substrate was examined (Table 4). Pleasingly, the desired product **4d** was isolated in 83% yield from the reaction of 2-(3-formylpyridin-2-yl)benzonitrile (**1c**) with phenylboronic acid. The compatibility of this tandem reaction was confirmed by the tolerance to methyl, fluoro, bromo, chloro, iodo, and phenyl substituents (**4e**–**4l**). However, substrate bearing a strongly electron-withdrawing group (e.g., NO_2) failed to provide the desired product. Of note, naphthyl-substituted substrates were also tolerated well and afforded the desired products in 79–82% yields (**4n**–**4o**).

Table 4. Synthesis of benzo[*c*]pyrido[2,3-*e*]azepin-5-ols.[a]



[a] Conditions: **1c** (0.2 mmol), **2** (0.4 mmol), $Pd(TFA)_2$ (6

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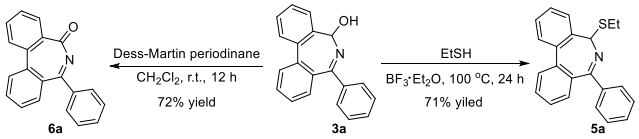
mol%), bpy (12 mol%), CH_3SO_3H (10 equiv), dry THF (2 mL), 80 °C, 24 h, N_2, isolated yield.

Further synthetic transformations of the as-synthesized products were then explored, as outlined in Scheme 3. For example, **3a** could be easily converted into the corresponding 5-(ethylthio)-7-phenyl-5*H*-dibenzo[*c*,*e*]azepine (**5a**) and 7-phenyl-5*H*-dibenzo[*c*,*e*]azepin-5-one (**6a**) in 71% and 72% yield, via a substitution or oxidation reaction, respectively. Thus, the hydroxyl group can be readily transformed into useful carbonyl or ethylthio groups.



Scheme 3. Synthetic applications.

To better understand the reaction, DFT calculations were carried out to model the detailed transformation of **1a** and **2a** to **3a** (Figure 1). According to the postulated mechanism, arylpalladium complex **IN1** coordinates with **1a** to form **IN2**, from which the nitrile insertion occurs via **TS1** with a barrier of 23.3 kcal/mol and forms arylated intermediate **IN3** endergonically. In the next step, intramolecular insertion of the formyl group into the Pd-N bond occurs via **TS2**, which is slightly higher in energy than **TS1**, and preferentially leads to alkoxide **IN4**. The CH_3SO_3H is involved in the last step, forming product complex **IN5** by protonation via **TS3**. Dissociation of **IN5** generates product **3a** and $LPdSO_3CH_3$. The latter complex then regenerates **IN1** by reaction with **2a**. A possible mechanism for the formation of dibenzo[*c*,*e*]azepin-5-ols is proposed (Scheme S1 in ESI).

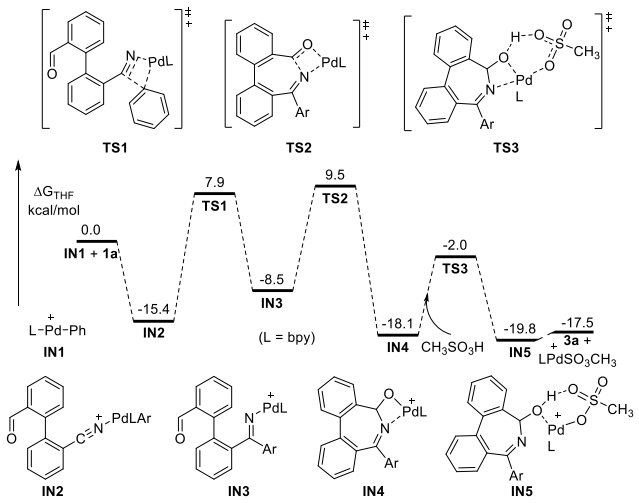


Figure 1. DFT results.

We used the triple-negative breast cancer cell line MDA-MB-468 to evaluate the cell growth inhibitory activity of products using the Cell Counting Kit-8 (CCK-8) protocol, with BS-181 and LDC-3140 as positive controls (Table S2 in ESI). The tested compounds (**3a**, **3d**, **3n**, **3v**) displayed good inhibitory activity, with IC_{50} values ranging from 8.52 to 45.12 μM for the MDA-MB-468 cell line, comparable to that of BS-181 and LDC-3140.[9] These results indicate that dibenzo[*c*,*e*]azepin-5-ols show good cell growth inhibitory activity towards a triple-negative breast cancer cell line and should be investigated as potential inhibitors for other cancer cell lines.

Conclusion

In summary, we have developed a novel transformation to access dibenzo[*c*,*e*]azepin-5-ols and benzo[*c*]pyrido[2,3-*e*]azepin-5-ols in moderate to excellent yields through a Pd-catalyzed tandem addition/cyclization of 2'-formyl-[1,1'-biaryl]-2-carbonitriles with arylboronic acids. Control experiments showed that this tandem process involves sequential carbopalladation of the cyano group generating an imine intermediate, followed by an intramolecular cyclization with the formyl group. DFT calculations were conducted to explain the experimentally observed transformation.

Experimental Section

General Information. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured on a 400 MHz or 500 MHz spectrometer using DMSO-d_6 or $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given n δ relative to TMS, and the coupling constants *J* are given in hertz. High-resolution mass spectra were recorded on an ESI-Q-TOF mass spectrometer. 2'-Formyl-[1,1'-biaryl]-2-carbonitriles (**1**),[4,10] was synthesized according to the method described in the literature. Column chromatography was performed using EM silica gel 60 (300−400 mesh). X-ray crystallographic analysis was performed at the X-ray crystallography facility, Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences (CAS).

General Experimental Procedure for the Palladium-Catalyzed Tandem Reaction

2'-Formyl-[1,1'-biphenyl]-2-carbonitrile or 2-(3-formylpyridin-2-yl)benzonitrile (0.2 mmol), arylboronic acid (0.4 mmol), $Pd(TFA)_2$ (6 mol%), bpy (12 mol%), dry THF (2 mL) and CH_3SO_3H (2 mmol) were successively added to a full of nitrogen Schlenk reaction tube. The reaction mixture was stirred vigorously at 80 °C for 24 hours. After the reaction mixture was cooled to room temperature, washed with saturated $NaHCO_3$, and extracted with ethylacetate (3 × 10 ml). The combined

organic layers were dried over anhydrous Na_2SO_4 and evaporated under a vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (15:1) to afford the desired products 7-aryl-5*H*-dibenzo[*c*,*e*]azepin-5-ol and 7-aryl-5*H*-benzo[*c*]pyrido[2,3-*e*]azepin-5-ols.

Acknowledgements

We acknowledge financial support from the NSFC (No. 21572162), and the Natural Science Foundation of Zhejiang Province (Nos. LY16B020012 and LQ18B020006).

References

[1] a) R. C. Larock, Q. Tian, A. A. Pletnv, *J. Am. Chem. Soc.* **1999**, *121*, 3238-3239; b) C. Zhou, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 2302-2303; c) C. Zhou, R. C. Larock, *J. Org. Chem.* **2006**, *71*, 3551-3558; d) B. W. Zhao, X. Y. Lu, *Org. Lett.* **2006**, *8*, 5987-5990; e) Y.-C. Wong, K. Parthasarathy, C.-H. Cheng, *Org. Lett.* **2010**, *12*, 1736-1739; f) X. Wang, M. Liu, L. Xu, Q. Wang, J. Chen, J. Ding, H. Wu, *J. Org. Chem.* **2013**, *78*, 5273-5281; g) J. Chen, L. P. Ye, W. Su, *Org. Biomol. Chem.* **2014**, 12, 8204-8211; h) S. Yu, L. Qi, K. Hu, J. Gong, T. Cheng, Q. Wang, J. Chen, H. Wu, *J. Org. Chem.* **2017**, *82*, 3631-3638; i) C. A. Malapit, D. R. Caldwell, I. K. Luvaga, J. T. Reeves, I. Volchkov, N. C. Gonnella, Z. S. Han, C. A. Busacca, A. R. Howell, C. H. Senanayake, *Angew. Chem., Int. Ed.* **2017**, *56*, 6999-7002.

[2] a) Y. Zhang, Y. Shao, J. Gong, K. Hu, T. Cheng, J. Chen, *Adv. Synth. Catal.* **2018**, *360*, 3260-3265; b) K. Hu, Q. Zhen, J. Gong, T. Cheng, L. Qi, Y. Shao, J. Chen, *Org. Lett.* **2018**, *20*, 3083-3087; c) J. Zhu, Y. Shao, K. Hu, L. Qi, T. Cheng, J. Chen, *Org. Biomol. Chem.* **2018**, *16*, 8596-8603; d) L. Qi, K. Hu, S. Yu, J. Zhu, T. Cheng, X. Wang, J. Chen, H. Wu, *Org. Lett.* **2017**, *19*, 218-221; e) K. Hu, L. Qi, S. Yu, T. Cheng, X. Wang, Z. Li, Y. Xia, J. Chen, H. Wu, *Green Chem.* **2017**, *19*, 1740-1750.

[3] G. Lv, G. Huang, G. Zhang, C. Pan, F. Chen, J. Cheng, *Tetrahedron* **2011**, *67*, 4879-4886.

[4] Y. Liu, L. Chen, Z. Wang, P. Liu, Y. Liu, B. Dai, *J. Org. Chem.* **2019**, *84*, 204-215.

[5] a) B. K. Albrecht, V. S. Gehling, M. C. Hewitt, R. G. Vaswani, A. Côté, Y. Leblanc, C. G. Nasveschuk, S. Bellon, L. Bergeron, R. Campbell, N. Cantone, M. R. Cooper, R. T. Cummings, H. Jayaram, S. Joshi, J. A. Mertz, A. Neiss, E. Normant, M. O'Meara, E. Pardo, F. Poy, P. Sandy, J. Supko, R. J. Sims III, J.-C. Harmange, A. M. Taylor, J. E. Audia, *J. Med. Chem.* **2016**, *59*, 1330-1339; b) X. Gu, Z. Ren, X. Tang, H. Peng, Q. Zhao, Y. Lai, S. Peng, Y. Zhang, *Eur. J. Med. Chem.* **2012**, *51*, 137-144; c) S. A. Bright, A. Brinkø, M. T. Larsen, S. Sinning, D. C. Williams, H. H. Jensen, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1220-1224; d) T. Kano, H. Sugimoto, K. Maruoka, *J. Am. Chem. Soc.* **2011**, *133*, 18130-18133; e) T. Kano, S. Song, Y. Kubota, K. Maruoka, *Angew. Chem., Int. Ed.* **2012**, *51*, 1191-1194; f) P. C. B. Page, J. C. Bartlett, Y. Chan, D. Day, P. Parker, B. R. Buckley, G. A. Rassias, A. M. Z. Slawin, S. M. Allin, J. Lacour, A. Pinto, *J. Org. Chem.* **2012**, *77*, 6128-6138.

[6] a) S. P. France, G. A. Aleku, M. Sharma, J. Mangas-Sanchez, R. M. Howard, J. Steflik, R. Kumar, R. W. Adams, I. Slabu, R. Crook, G. Grogan, T. W. Wallace, N. J. Turner, *Angew. Chem., Int. Ed.* **2017**, *56*, 15589-15593; b) T. Yang, X. Guo, Q. Yin, X. Zhang, *Chem. Sci.* **2019**, *10*, 2473-2477; c) V. Narbonne, P. Retailleau, G. Maestri, M. Malacria, *Org. Lett.* **2014**, *16*, 628-631. d) P. W. Groundwater, C. Struthers-Semple, J. T. Sharp, *J. Chem. Soc., Chem. Commun.* **1987**, 1367-1368; e) J. J. Fitt, H. W. Gschwend, A. Hamdan, S. K. Boyer, H. M. Haider, *J. Org. Chem.* **1982**, *47*, 3658-3660.

[7] a) J. O. Hawthorne, E. L. Mhielic, M. S. Morgan, M. H. Wilt, *J. Org. Chem.* **1963**, *28*, 2831-2835; b) M. Weitzberg, E. Abu-Shakra, A. Azeb, Z. Aizenshtat, J. Blum, *J. Org. Chem.* **1987**, *52*, 529-536.

[8] a) CCDC 1888666 (**3a**); b) CCDC 1915880 (**4c**) contain the supplementary crystallographic data. These data can be obtained from The Cambridge Crystallographic Data Centre.

[9] a) S. Ali, D. A. Heathcote, S. H. B. Kroll, A. S. Jogalekar, B. Scheiper, H. Patel, J. Brackow, A. Siwicka, M. J. Fuchter, M. Periyasamy, R. S. Tolhurst, S. K. Kanneganti, J. P. Snyder, D. C. Liotta, E. O. Aboagye, A. G. M. Barrett, R. Charles Coombes, *Cancer Res.* **2009**, *69*, 6208-6215; b) T. K. Albert, C. Rigault, J. Eickhoff, K. Baumgart, C. Antrecht, B. Klebl, G. Mittler, M. Meisterernst, Br. *J. Pharmacol.* **2014**, *171*, 55-68.

[10] a) Y. Chen, Y. Wu, Y. Jhan, J. Hsieh, *Org. Chem. Front.* **2014**, *1*, 253-257; b) A. Mondal, R. Hazra, J. Grover, M. Raghu, S. S. V. Ramasastry, *ACS Catal.* **2018**, *8*, 2748-2753.

10.1002/adsc.201900705

FULL PAPER

Palladium-Catalyzed Selective Synthesis of Dibenzo[*c*,*e*]azepin-5-ols and Benzo[*c*]pyrido[2,3-*e*]azepin-5-ols

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