Communications



Enantioselective C–H Arylation Strategy for Functionalized Dibenzazepinones with Quaternary Stereocenters

Tada! Highly functionalized chiral dibenzazepinones are obtained by a mild palladium(0)-catalyzed enantioselective C-H arylation with excellent selectivities

by using simple taddol phosphoramidite ligands. The amide tether allows exclusive regioselectivity through a rare eightmembered palladacycle intermediate.

97%, 97:3 e.r. 20 examples OMe

-NMea

cat. Pd⁰ Regioselective

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C–**H** Activation

Enantioselective C–H Arylation Strategy for Functionalized Dibenzazepinones with Quaternary Stereocenters**

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Transition metal catalyzed C-H functionalization has emerged as a powerful tool to build molecular complexity from widely available starting materials.^[1] While an impressive number of new powerful disconnections have appeared, few enantioselective versions have been reported.^[2] Often, harsh reaction conditions and the lack of suitable chiral ligands hamper the development of asymmetric methods. Introduction of milder reaction conditions coupled with the development of efficient chiral ligand systems requiring a clear mechanistic picture are key to addressing this challenge. For instance, a deeper understanding of the mechanism for palladium(0)-catalyzed direct C-H arylations, proceeding by a concerted metalation deprotonation (CMD) pathway,^[3] resulted in significant progress over the past years.^[1c] Indeed, it allowed the extension of the direct arylation to C(sp³)–H bonds^[4] and to intermolecular processes.^[5] Intramolecular C-H arylations are mostly limited to the synthesis of five- and six-membered rings.^[6] In contrast, few examples of seven-membered ring formations are reported and all require a high catalyst loading (10 mol %) or very high temperatures (>130°C).^[7] This gap is attributed to the difficult formation of intermediate eight-membered palladacycles. Moreover, the direct enantioselective arylation to form seven-membered rings is unknown.^[8-10] We have a longstanding interest in C-H functionalizations to access chiral nitrogen-containing heterocycles which are ubiquitous among natural products and bioactive compounds.[8d,h,9,11] In this respect, dibenzazepinones are a highly important class with interesting biological properties. For instance, the paullone family of compounds are cyclin-dependent kinase inhibitors with antitumoral properties (Figure 1).^[12] RO4929097 and LY-411575 are two examples for potent γ -secretase inhibitors which are being developed for the treatment of melanoma and Alzheimer's disease.^[13] Inhibitors of the γ -secretase enzyme complex inactivate the notch-signaling pathway^[14] and interfere with the processing of the amyloid precursor protein,^[15] thus attracting major efforts.

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Figure 1. Examples of relevant bioactive compounds featuring the dibenzazepinone scaffold.

Herein, we report the syntheses of chiral dibenzazepinones with quaternary stereogenic centers by intramolecular palladium(0)-catalyzed enantioselective C–H arylation (Figure 2). A main challenge is to develop reaction conditions



Figure 2. C–H arylation strategy for chiral dibenzazepinones and the influence of the palladacycle size on asymmetric intramolecular C–H arylations.

enabling the difficult formation of the medium-sized palladacycle intermediate which currently limits extension of this strategic disconnection. Our strategy is based on the cooperative effects between a chiral phosphine ligand and a bulky carboxylate relaying the chirality during the enantiotopical CMD step.

Initial studies were performed with the model substrate **1a** (Table 1). The reaction proceeds smoothly with 5 mol% of a palladium(0) precursor and a range of monodentate phosphine ligands in refluxing toluene. Especially taddolbased phosphoramidites, already successful for related $C(sp^3)$ -H functionalizations of cyclopropanes,^[9] showed promising results for this transformation. The steric bulk of

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[a] Reaction conditions: 0.05 mmol 1 a, 15.0 μ mol of RCO₂H, 2.50 μ mol [Pd(dba)₂], 5.00 μ mol L, 1.5 equiv Cs₂CO₃, 0.30 μ in toluene at the indicated temperature for 12 h. [b] Yield of isolated product. [c] Determined by HPLC with a chiral stationary phase. [d] Gram-scale reaction: 1.73 g (4.39 mmol) 1 a, 4 mol % [(η^3 -cinnamyl)PdCp], 8 mol % L1, 0.50 μ in toluene. Cp = cyclopentadienyl, Cy = cyclohexyl, Piv = pivaloyl.

the aromatic substituents of the taddol backbone has a significant influence on the selectivity of the reaction (Table 1, entries 1-3). A simple phenyl group provides the best selectivity. A brief screen of the amine substituents R revealed that two methyl groups give better results than longer chains or cyclic groups (Table 1, entries 4-5). Thus L1, the simplest and prototypical member of the taddol phosphoramidite family proved to be the best.^[16] Lowering the reaction temperature to 80°C improved the selectivities to 96.5:3.5 e.r. while maintaining an excellent yield (entry 6). This is noteworthy for such reluctant arylation processes.^[7] Several carboxylic acid cocatalysts were tested as well. Adamantyl carboxylic acid gave comparable results compared to pivalic acid (entry 8) while cyclohexyl carboxylic acid was less suitable for this transformation (entry 7). Finally, the absence of a carboxylic acid cocatalyst led to very poor conversion (entry 9). To showcase the scalability and practicality of the reaction, we carried out a gram-scale reaction of 1a (entry 10). The desired product 2a was isolated in comparable excellent yield (93%) and with an slightly higher enantioselectivity of 97.5:2.5 e.r.

With the optimized procedure in hand, we explored next the scope of the enantioselective arylation. With no effect on the enantioselectivity, the solvent was switched to mesitylene for a higher operational temperature range. The reaction works for both electron-rich and electron-poor aromatics as well as heteroaromatics (Table 2). Noteworthy, an aryl chloride is well tolerated with this palladium-catalyzed reaction and thus offers orthogonal functionalization options by classical cross-coupling chemistry. The relatively mild reaction conditions allow a range of common functional Table 2: Scope of enantioselective synthesis of dibenzazepinones 2.^[a]



[a] Reaction conditions: 0.05 mmol **1a**, 15.0 μ mol of the indicated carboxylic acid, 2.50 μ mol [Pd(dba)₂], 5.00 μ mol L, 1.5 equiv Cs₂CO₃, 0.30 μ in mesitylene at 80 °C for 12 h. Yield of isolated product. e.r. Determined by HPLC with a chiral stationary phase. [b] At 100 °C. [c] At 90 °C. [d] [(η^3 -cinnamyl)PdCp] instead of [Pd(dba)₂]. [e] At 110 °C. [f] At 140 °C with 10 mol% [Pd(dba)₂].

groups like amides, esters, substituted indoles, and electronneutral olefins. Remarkably, for the olefin-containing substrate **1h** no competitive Heck cyclization product is observed and only **2h** is formed. Moreover, the aniline moiety can be decorated with typical electron-donating and electron-withdrawing groups in *ortho*, *meta*, and *para* positions to the nitrogen atom to provide the dibenzazepinones **2j–o** in high yield and selectivities. For several dibenzazepinone products **2**, dibenzylideneacetone (dba), derived from the palladium precatalyst [Pd(dba)₂], causes purification problems as it could not be removed by chromatographic means. In those cases, a switch to $[(\eta^3-cinnamyl)PdCp]^{[17]}$ as the palladium source is a convenient solution. The aryl bromide **1p**, containing a pyridine nitrogen atom *ortho* to the aryl bromide,

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required not only increased reaction temperature and catalyst loading to give 2p but was as well detrimental to the selectivity. Finally, different substitutions on the amide nitrogen atom proved to be competent for this reaction. However, secondary amides having a restricted amide bond rotation, such as 1r, do not cyclize. We next subjected the isopropylsubstituted amide 1s towards the reaction conditions. Similar substrate were previously used for asymmetric $C(sp^3)$ –H functionalizations, thus leading to indolines like 3s through a six-membered palladacycle (eight-membered versus sixmembered), complete selectivity for the $C(sp^2)$ –H (2s) over the $C(sp^3)$ –H (3s) arylation is observed (Scheme 1).^[18] Addi-



Scheme 1. Regioselective enantioselective C-H arylation and subsequent facile deprotection of compound **2u**.

tional experiments were performed with compounds 1t and 1u, which possess alternative $C(sp^2)$ —H bonds competing for the direct arylation. Again, complete selectivity for the desired dibenzazepinones 2t and 2u is observed. No arylation of the benzyl and PMB groups of 1t and 1u, respectively, by the alternative pathway was detected, even though it would proceed through a principally more favorable seven-membered palladacycle. These results underscore the importance of the tethering groups for a favorable alignment during the activation step. Conveniently, the PMB group of 2u could be

easily cleaved under acidic conditions to give the secondary amide **2r**, which is not accessible by the direct cyclization of **1r**.

The absolute configuration of the dibenzazepinones 2 was established by X-ray crystallography of 21 (Figure 3),^[19] and by analogy the same configuration was attributed to com-



Figure 3. ORTEP representation of (*S*)-21 (thermal ellipsoids shown at 50% probability).

pounds **2a–u**. Notably, the quaternary carbon center induces a chiral biaryl axis and only a single diastereomer is observed. Without the stereocenter at C2, this axis has a rather low inversion barrier.^[20]

In summary, we have reported a new and mild enantioselective palladium(0)-catalyzed direct arylation to access highly functionalized and relevant dibenzazepinones possessing a quaternary stereocenter with excellent selectivities. The enantiodiscriminating CMD step occurs through a rare eightmembered palladacycle, which is unprecedented for an enantioselective process. With these substrates, a complete selectivity over competing C–H activations, which could give five- or six-membered rings, was found. Additional noteworthy features of the process are its good functional-group compatibility and the use of cheap and widely available taddol phosphoramidites as chiral ligands.

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For selected reviews on C-H activations, see: a) J. J. Mousseau, A. B. Charrette, Acc. Chem. Res. 2013, 46, 412-424; b) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, Angew. Chem. 2012, 124, 10382-10401; Angew. Chem. Int. Ed. 2012, 51, 10236-10254; c) J. Yamaguchi, A. D. Yamaguchi, K. Itami, Angew. Chem. 2012, 124, 9092-9142; Angew. Chem. Int. Ed. 2012, 51, 8960-9009; d) K. Hirano, M. Miura, Synlett 2011, 294-307; e) J. Wencel-Delord, T. Droge, F. Liu, F. Glorius, Chem. Soc. Rev. 2011, 40, 4740-4761; f) L. Ackermann, Chem. Rev. 2011, 111, 1315-1345; g) D. A. Colby, R. G. Bergman, J. A. Ellman, Chem. Rev. 2010, 110, 624-655; h) T. W. Lyons, M. S. Sanford, Chem. Rev. 2010, 110, 1147-1169; i) C.-L. Sun, B.-J. Li, Z.-J. Shi, Chem. Commun. 2010, 46, 677-685; j) R. Jazzar, J. Hitce, A. Renaudat,

J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654–2672; k) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976–10011; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826; l) X Chen, K. M. Engle, D. H. Wang, J. Q. Yu, *Angew. Chem.* **2009**, *121*, 5196–5217; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115.

- [2] R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, Chem. Soc. Rev. 2009, 38, 3242–3272.
- [3] a) D. García-Cuadrado, P. de Mendoza, A. A. C. Braga, F. Maseras, A. M. Echavarren, J. Am. Chem. Soc. 2007, 129, 6880–6886; b) D. Lapointe, K. Fagnou, Chem. Lett. 2010, 39, 1118–1126.
- [4] a) M. Lafrance, S. I. Gorelsky, K. Fagnou, J. Am. Chem. Soc. 2007, 129, 14570-14571; b) T. Watanabe, S. Oishi, N. Fujii, H. Ohno, Org. Lett. 2008, 10, 1759-1762; c) M. Chaumontet, R. Piccardi, N. Audic, J. Hitce, J.-L. Peglion, E. Clot, O. Baudoin, J. Am. Chem. Soc. 2008, 130, 15157-15166.
- [5] a) M. Lafrance, K. Fagnou, J. Am. Chem. Soc. 2006, 128, 16496–16497; b) M. Livendahl, A. M. Echavarren, Isr. J. Chem. 2010, 50, 630–651.
- [6] a) L.-C. Campeau, K. Fagnou, *Chem. Commun.* 2006, 1253–1264; b) S. Pascual, P. De Mendoza, A. M. Echavarren, *Org. Biomol. Chem.* 2007, *5*, 2727–2734.
- [7] a) M. Burwood, B. Davies, I. Diaz, R. Grigg, P. Molina, V. Sridharan, M. Hughes, *Tetrahedron Lett.* 1995, *36*, 9053–9056;
 b) T. Harayama, H. Akamatsu, K. Okamura, T. Miyagoe, T. Akiyama, H. Abe, Y. Takeuchi, *J. Chem. Soc. Perkin Trans. 1* 2001, 523–528; c) L. C. Campeau, M. Parisien, M. Leblanc, K. Fagnou, *J. Am. Chem. Soc.* 2004, *126*, 9186–9187; d) M. Leblanc, K. Fagnou, *Org. Lett.* 2005, *7*, 2849–2852; e) L. C. Campeau, M. Parisien, A. Jean, K. Fagnou, *J. Am. Chem. Soc.* 2006, *128*, 581–590; f) C. Huang, V. Gevorgyan, *Org. Lett.* 2010, *12*, 2442–2445; g) D. G. Pintori, M. F. Greaney, *J. Am. Chem. Soc.* 2011, *133*, 1209–1211; h) C. B. Bheeter, J. K. Bera, H. Doucet, *Adv. Synth. Catal.* 2012, *354*, 3533–3538.
- [8] For palladium-catalyzed enantioselective C-H functionalization to form five-membered rings, see: a) M. Albicker, N. Cramer, Angew. Chem. 2009, 121, 9303-9306; Angew. Chem. Int. Ed. 2009, 48, 9139-9142; b) M. Nakanishi, D. Katayev, C. Besnard, E. P. Kündig, Angew. Chem. 2011, 123, 7576-7579; Angew. Chem. Int. Ed. 2011, 50, 7438-7441; c) S. Anas, A. Cordi, H. B. Kagan, Chem. Commun. 2011, 47, 11483-11485; d) T. Saget, S. Lemouzy, N. Cramer, Angew. Chem. 2012, 124, 2281-2285; Angew. Chem. Int. Ed. 2012, 51, 2238-2242; e) D. Katayev, M. Nakanishi, T. Bürgi, E. P. Kündig, Chem. Sci. 2012, 3, 1422-1425; f) N. Martin, C. Pierre, M. Davi, R. Jazzar, O. Baudoin, Chem. Eur. J. 2012, 18, 4480-4484; g) R. Shintani, H. Otomo, K. Ota, T. Hayashi, J. Am. Chem. Soc. 2012, 134, 7305-7308;

h) P. A. Donets, T. Saget, N. Cramer, *Organometallics* **2012**, *31*, 8040–8046; i) X.-F. Cheng, Y. Li, Y.-M. Su, F. Yin, J.-Y. Wang, J. Sheng, H. U. Vora, X.-S. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 1236–1239.

- [9] For palladium-catalyzed enantioselective C-H functionalization to form six-membered rings, see: T. Saget, N. Cramer, Angew. Chem. 2012, 124, 13014-13017; Angew. Chem. Int. Ed. 2012, 51, 12842-12845.
- [10] For complementary enantioselective palladium(II)-catalyzed C-H functionalizations, see: a) B.-F. Shi, N. Maugel, Y.-H. Zhang, J.-Q. Yu, Angew. Chem. 2008, 120, 4960-4964; Angew. Chem. Int. Ed. 2008, 47, 4882-4886; b) B.-F. Shi, Y.-H. Zhang, J. K. Lam, D.-H. Wang, J.-Q. Yu, J. Am. Chem. Soc. 2010, 132, 460-461; c) M. Wasa, K. M. Engle, D. W. Lin, E. J. Yoo, J.-Q. Yu, J. Am. Chem. Soc. 2011, 133, 19598-19601; d) D.-W. Gao, Y.-C. Shi, Q. Gu, Z.-L. Zhao, S.-L. You, J. Am. Chem. Soc. 2013, 135, 86-89; e) C. Pi, Y. Li, X. Cui, H. Zhang, Y. Han, Y. Wu, Chem. Sci. 2013, 4, 2675-2679.
- [11] a) M. Waibel, N. Cramer, Angew. Chem. 2010, 122, 4557-4560;
 Angew. Chem. Int. Ed. 2010, 49, 4455-4458; b) M. Pham, B. Ye,
 N. Cramer, Angew. Chem. 2012, 124, 10762-10766; Angew.
 Chem. Int. Ed. 2012, 51, 10610-10614; c) B. Ye, N. Cramer,
 Science 2012, 338, 504-506; d) T. Saget, D. Perez, N. Cramer,
 Org. Lett. 2013, 15, 1354-1357.
- [12] M. Leost, C. Schultz, A. Link, Y.-Z. Wu, J. Biernat, E.-M. Mandelkow, J. A. Bibb, G. L. Snyder, P. Greengard, D. W. Zaharevitz, R. Gussio, A. M. Senderowicz, E. A. Sausville, C. Kunick, L. Meijer, *Eur. J. Biochem.* **2000**, *267*, 5983–5994.
- [13] a) J. S. Nair, T. Sheikh, A. L. Ho, G. K. Schwartz, *Anticancer Res.* 2013, *33*, 1307–1316; b) G. T. Wong, D. Manfra, F. M. Poulet, Q. Zhang, H. Josien, T. Bara, L. Engstrom, M. Pinzon-Ortiz, J. S. Fine, H.-J. J. Lee, L. Zhang, G. A. Higgins, E. M. Parker, *J. Biol. Chem.* 2004, *279*, 12876–12882.
- [14] I.-M. Shih, T.-L. Wang, Cancer Res. 2007, 67, 1879-1882.
- [15] J. L. Jankowsky, D. J. Fadale, J. Anderson, G. M. Xu, V. Gonzales, N. A. Jenkins, N. G. Copeland, M. K. Lee, L. H. Younkin, S. L. Wagner, S. G. Younkin, D. R. Borchelt, *Hum. Mol. Genet.* 2004, *13*, 159–170.
- [16] H. W. Lam, Synthesis 2011, 2011–2043.
- [17] D. M. Norton, E. A. Mitchell, N. R. Botros, P. G. Jessop, M. C. Baird, J. Org. Chem. 2009, 74, 6674–6680.
- [18] An opposite selectivity was observed in Ref. [4a].
- [19] Crystallographic data for 2r: CCDC 936820 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [20] H. Tabata, H. Suzuki, K. Akiba, H. Takahashi, H. Natsugari, J. Org. Chem. 2010, 75, 5984–5993.