C–H Activation

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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(sp^3)–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.

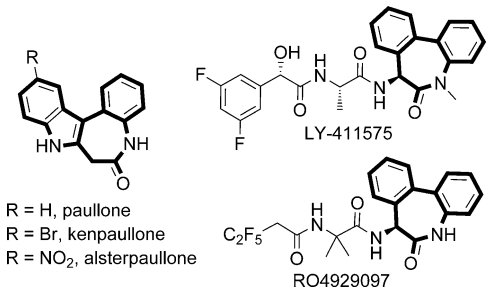

Figure 1. Examples of relevant bioactive compounds featuring the dibenzazepinone scaffold.

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

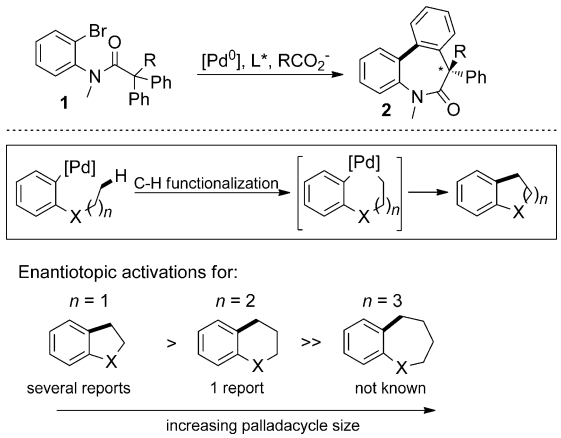

Figure 2. C–H arylation strategy for chiral dibenzazepinones and the influence of the palladacycle size on asymmetric intramolecular C–H arylations.

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 taddol-based 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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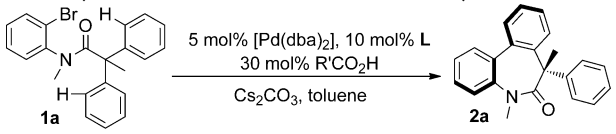
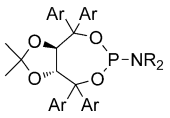
Table 1: Optimization of the enantioselective C–H arylation of **1a**.[a]



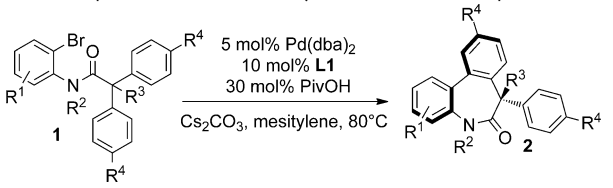


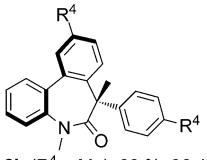
L1 (R = Me, Ar = Ph)
L2 (R = Me, Ar = 3,5-Me-phenyl)
L3 (R = Me, Ar = 3,5-*t*Bu-phenyl)
L4 (R_2 = $(CH_2)_4$, Ar = Ph)
L5 (R = Bu, Ar = Ph)

Entry	L	R′CO_2H	*T* [°C]	Yield [%][b]	e.r.[c]
1	**L1**	PivOH	110	93	94.5:5.5
2	**L2**	PivOH	110	87	91.5:8.5
3	**L3**	PivOH	110	59	76:24
4	**L4**	PivOH	110	97	93.5:6.5
5	**L5**	PivOH	110	47	94:6
6	**L1**	PivOH	80	95	96.5:3.5
7	**L1**	CyCO_2H	80	80	95.5:4.5
8	**L1**	AdCO_2H	80	93	96.5:3.5
9	**L1**	–	80	6	–
10[d]	**L1**	PivOH	80	93	97.5:2.5

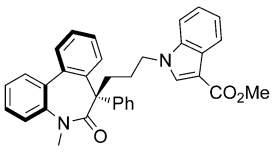
[a] Reaction conditions: 0.05 mmol **1a**, 15.0 μmol of RCO_2H, 2.50 μmol [Pd(dba)$_2$], 5.00 μmol **L**, 1.5 equiv Cs_2CO_3, 0.30 M in toluene at the indicated temperature for 12 h. [b] Yield of isolated product. [c] Determined by HPLC with a chiral stationary phase. [d] Gram-scale reaction: 1.73 g (4.39 mmol) **1a**, 4 mol% [(η^3-cinnamyl)PdCp], 8 mol% **L1**, 0.50 M in toluene. Cp = cyclopentadienyl, Cy = cyclohexyl, Piv = pivaloyl.

Table 2: Scope of enantioselective synthesis of dibenzazepinones **2**.[a]

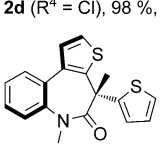




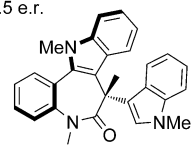
2b (R^4 = Me), 99 %, 96:4 e.r.
2c (R^4 = OMe), 95 %, 96.5:3.5 e.r.
2d (R^4 = Cl), 98 %, 95.5:4.5 e.r.



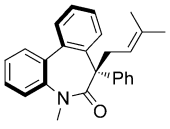
2e,[b] 93 %, 97:3 e.r.



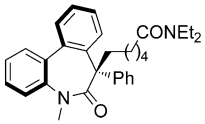
2f,[c,d] 87 %, 95.5:4.5 e.r.



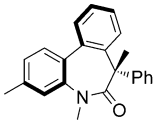
2g,[c] 87 %, 86.5:13.5 e.r.



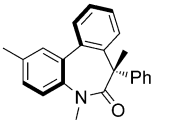
2h,[c,d] 84 %, 93:7 e.r.



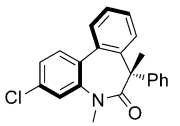
2i,[e] 97 %, 93.5:6.5 e.r.



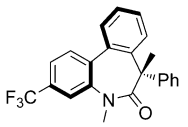
2j, 97 %, 96:4 e.r.



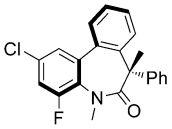
2k, 89 %, 96.5:3.5 e.r.



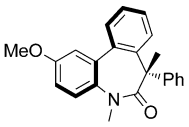
2l,[d] 90 %, 97.5:2.5 e.r.



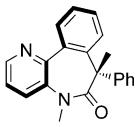
2m,[d] 99 %, 97:3 e.r.



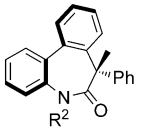
2n,[d] 78%, 96.5:3.5 e.r.



2o, 99 %, 97:3 e.r.



2p,[f] 81 %, 54:46 e.r.



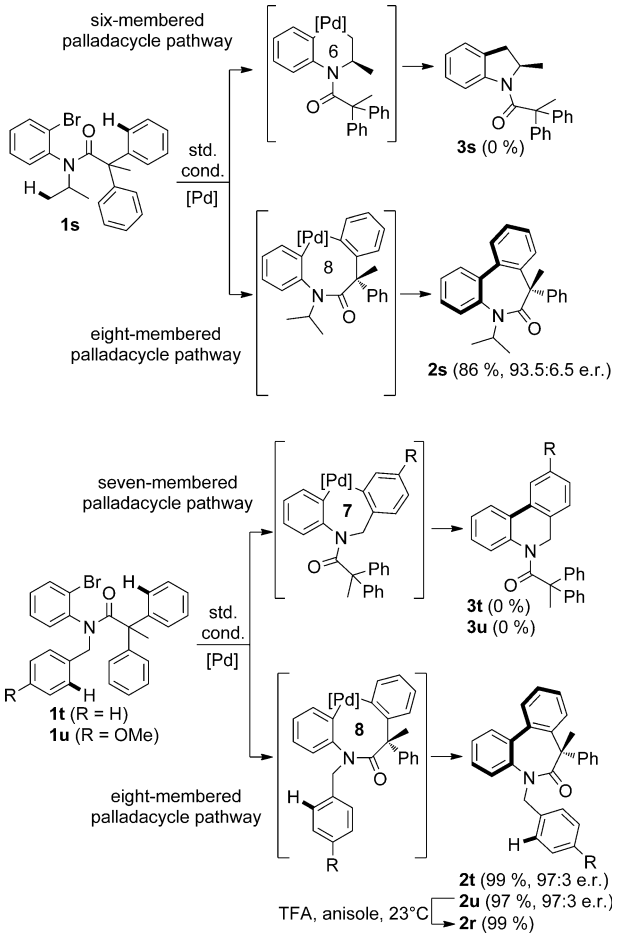
2q (R^2 = Et), 95 %, 97.5:2.5 e.r.
2r (R^2 = H), 0 %

[a] Reaction conditions: 0.05 mmol **1a**, 15.0 μmol of the indicated carboxylic acid, 2.50 μmol [Pd(dba)$_2$], 5.00 μmol **L**, 1.5 equiv Cs_2CO_3, 0.30 M 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)$_2$].

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 groups like amides, esters, substituted indoles, and electron-neutral 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 [(η^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,

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 isopropyl-substituted 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.[8b–e] Despite proceeding by a less preferred palladacycle (eight-membered versus six-membered), complete selectivity for the C(sp^2)–H (**2s**) over the C(sp^3)–H (**3s**) arylation is observed (Scheme 1).[18] Additional 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**.



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

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

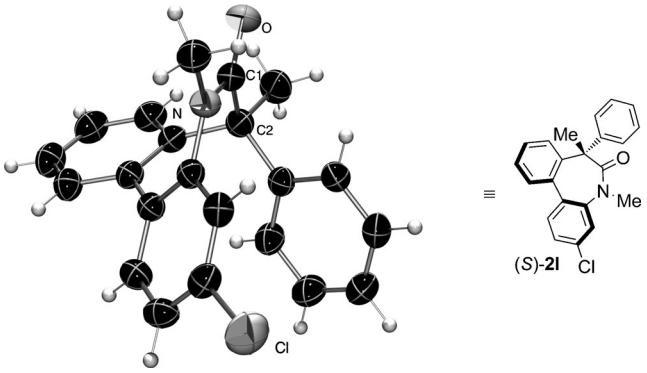


Figure 3. ORTEP representation of (*S*)-**2l** (thermal ellipsoids shown at 50% probability).

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 eight-membered 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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Keywords: asymmetric catalysis · C–H activation · cooperative effects · heterocycle · palladium

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