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Enantio- and Diastereoswitchable C–H Arylation of Methylene Groups in Cycloalkanes

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Abstract

A complementary set of chiral *N,N*-ligands enables the Pd-catalyzed β -C–H arylation of unbiased internal methylene groups in good and with high levels of enantio- and diastereoselection. Both the dia- and enantioselectivity can be reversed, thus allowing to selectively arylate any one of the four β -C–H bonds in cycloalkanecarboxamides of various ring sizes. The method is applicable to a broad range of aryl iodides with electron-withdrawing and -donating substituents in *o*-, *m*-, or *p*-position.

Graphical Abstract

An unprecedentedly selective β -C–H arylation of directing group-substituted cycloalkanes is reported. Known APAQ-ligands give *cis*-products with high yields, enantio- and diastereoselectivities. New ligands reversed the diastereoselectivity in favour of the *trans* products.

Keywords

C–H functionalization; methylene activation; enantioselective; diastereoselective; catalyst-control

The design of catalytic methods that enable the selective activation of specific C–H bonds within complex molecules is among the most important goals of modern method development. This is due to their potential to steeply increase molecular complexity, bypassing prefunctionalization or deconvolution steps. However, it is tremendously

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challenging to achieve the required selectivity levels, since even small molecules usually contain a large number of C–H bonds in comparable steric environments and with near-identical bond strengths.

Although the past decade has witnessed remarkable progress in this field, there are still only few reports of intermolecular enantioselective functionalization of alkane $\text{sp}^3\text{-C-H}$ bonds. Most of these rely on directing groups (DGs) that facilitate metalation of specifically one of the nearby C–H bonds.^[1] Diastereoselectivity in C–H activation is usually based on substrate control, e.g. in directed *cis*-selective functionalization of small cycloalkane rings,^[2,3] five-membered heterocycles,^[4] six-membered heterocycles with certain substitution patterns,^[5,4b] in transannular C–H functionalizations,^[6] and for acyclic amino acids.^[7] However, this approach requires substrates with strong diastereoiduction. Substrates with moderate diastereoiduction usually yield mixtures of *cis/trans*-isomers with inconsistent diastereoselectivities, e.g. in medium-sized cycloalkanes.^[8] Moreover, the use of strategies based on substrate control for enantioselective transformations inherently depends on the availability of enantiopure starting materials (Scheme 1A).^[4a,7]

Asymmetric induction via use of chiral ligands is still in its infancy in $\text{sp}^3\text{-C-H}$ functionalization. Encouraging results have been achieved for sterically accessible methyl groups^[9] and for methylene groups with electronic bias, including strained cycloalkyl systems,^[3,8a,8b] benzylic positions,^[10] and α -heteroatom-substituted methylene C–H bonds.^[11,4c,4d] However, the control of both enantio- and diastereoselectivity in $\beta\text{-C-H}$ functionalizations of simple, unbiased methylene groups is still an unsolved challenge. Especially diastereoiduction by an external catalyst has not been demonstrated in directed C–H activation.

Recently, an enantioselective β -arylation of amides via asymmetric metal insertion into methylene C–H bonds has been achieved using chiral bidentate acetyl-protected aminoethyl quinoline (APAQ) ligands (Scheme 1B).^[12] This prototype system was efficient only for amides with α -unbranched, aliphatic carbon chains. Unfortunately, it gave unsatisfactory results yields and selectivities when we attempted to apply it to amides with α -branched carbon chains (see Supporting Information). This is understandable, because the β -arylation of α -branched substrates with four similarly accessible C–H groups within reach of a directing group adds tremendous challenges to controlling selectivity (Scheme 1C).

For symmetrical substrates, monoarylation can now lead to two diastereomeric pairs of enantiomers. In order to selectively access any of the four C–H monoarylation products, not only the enantioselectivity, but also the diastereoselectivity of the transformation must be fully controlled, ideally by the catalyst-ligand system alone, overriding substrate effects (Scheme 1C).

We set out to address this fascinating problem by establishing a method for stereoselective arylation of cycloalkylamides. A stereocontrolled β -arylation of cycloalkanes would be synthetically highly valuable. Alternative asymmetric entries to 1,2-disubstituted cycloalkanes, e.g. conjugate addition across trisubstituted double bonds, *cis*-selective hydrogenation, or *trans*-selective hydroarylation of olefinic substrates, have significant

limitations.^[13] Especially for diversity-oriented synthesis in drug discovery, a unified and rapid enantioselective entry to all possible stereoisomers via β -arylation of cyclohexanecarboxylic acid derivatives would be advantageous.

We chose the model reaction of *p*-iodotoluene **2a** with cyclohexane **1a** bearing our proven perfluorinated tolylamide directing group in order to tackle this long-standing challenge, and search for ligands that control both dia- and enantioselectivity of this C–H arylation. We thus evaluated the APAQ ligands reported in ref. 12 along with several new APAQ ligands bearing different substituents, and systematically investigated the influence of structural parameters on yield, diastereo- and enantioselectivity. Selected results are shown in Table 1.

The achiral parent ligand **L1** promoted the arylation in moderate yield with an encouraging diastereomeric ratio (dr) of 2:1 in favor of the *cis*-compound.^[14] Creating a stereocenter proximal to the ligand's amide group by introduction of a phenyl substituent in **L2** gave a comfortable level of asymmetric induction in the C–H arylation. The aromatic substituent also increased diastereoselectivity in favor of the *cis* product *cis*-**3aa**, with the best results being obtained with the sterically crowded aromatic 3,5-*t*Bu₂Ph group. Both optical induction and diastereoinduction were further enhanced by a second stereocenter in the ligand backbone. Following upfront screening experiments, we focused on *syn*-APAQ ligands in which the two substituents would both point either up- or downwards in the palladacycle.^[12] The relatively small methyl group in **L5** proved to be the optimal residue with respect to yield, enantiomeric ratio (er) and *cis/trans* ratio. In the reaction of these sterically demanding substrates, the key challenge turned out to be achieving high conversions while preserving high levels of steric induction. This was finally achieved by the addition of AgOAc^[15,16] to the reaction mixture. A high yield in combination with a high selectivity for the 1*R*,2*S* configured *cis*-product were, thus, obtained when arylating substrate **1a** in the presence of a catalyst system generated from (PdOAc)₂ and ligand **L5**, using a mixture of Ag₂CO₃ and AgOAc as the base, in HFIP at 80°C for 36 h in a sealed vial under air in the dark.

Intending to increase the steric bulk in the ligand backbone beyond the 3,5-*t*Bu₂Ph group, we designed a new series of APAQ-ligands **L6–L9** with α -tertiary alkyl substituents replacing the planar aryl group. This structural modification was decisive in reverting the diastereoselectivity from *cis*- to *trans*-arylation. Near-quantitative yields and good selectivities in favor of the *trans*-diastereomer were achieved with adamantyl-substituted **L9** (99% yield, dr = 24:76, er = 84:16). Introduction of a second substituent to the backbone of **L9** led to a sharp decline in yield and stereoselectivity (Table S2, Supporting Information), which might point to steric overcrowding. A rationalization of the reversed diastereoselectivity can be found in the mechanistic discussion depicted in Scheme 2.

Next, we turned to exploring the scope of the aryl iodide coupling partners and found that a wide range of derivatives can be converted (Table 2). Electron-rich electrophiles gave consistently higher yields than those bearing electron withdrawing substituents, but in all cases, diastereo- and enantioselectivity remained high. Selected *ortho*-substituted aryl iodides were smoothly converted, which is remarkable considering Pd-catalysts' notorious sensitivity to steric crowding in C–H activation. Unfortunately, the oily products did not

permit an investigation of their absolute stereochemistry by X-ray diffraction. However, combined HPLC and VCD investigation revealed the substitution pattern of the aryl halide to have a strong influence on the stereochemical outcome (Supporting Information).

In combination with ligand **L5**, aryl iodides bearing substituents in *para*- and in *meta*-position preferentially gave the *cis*-products. In sharp contrast, aryl iodides bearing *ortho*-substituents gave the *trans*-diastereomers. At this stage, we can only speculate on what causes the remarkable reversal in diastereoselectivity between *ortho*- and *meta*-substituted aryl iodides, well-illustrated by α - and β -naphthyl iodides (*cis*-**3a α** and *trans*-**3a β** in Table 2). One might view it to be a consequence of the different steric demands of the two aryl scaffolds. This seems to lead to a different outcome in the competition of the aryl and cycloalkane residues for the least hindered space within the coordination sphere of palladium (see Scheme 2). Moreover, the chiral induction is opposite in *para*- than in *meta*-substituted products.

Application width with regard to the cyclic amides was also probed. Arylation of five- and seven-membered cycloalkanes with **L5** gave the *cis*-configured products **3ba** and **3ca** with high diastereomeric and enantiomeric induction. Flexible, acyclic substrates such as 2,2-diethylacetamide gave only low yields and stereoselectivities (Supporting Information), which can partially be attributed to their higher degree of rotational freedom. Not only does this enlarge the pool of potential transition structures, but it also causes additional steric restraints at the catalyst center, further reducing its activity.

We next probed whether the use of ligand **L9** would consistently reverse the diastereoselectivity for a broad range of substrates (Table 3). Indeed, *trans*-products were obtained for *para*- and *meta*-substituted aryl iodides, while *ortho*-substitution resulted in *cis*-products, which is the opposite of what was observed for **L5**. Therefore, both ligands exhibit completely complementary diastereoinduction.

Other than in 6- and 7-membered cycloalkanes, the required palladacyclic intermediates en route to a *trans*-configured 3- to 5-membered ring product would be much more strained than their *cis*-configured counterpart (Supporting Information). It is thus not surprising that the steric interaction imposed by ligand **L9** was insufficient to enforce a reversal of diastereoselectivity for such substrates (**3ba** in Table 3).

A tentative mechanistic sketch of the transformation is outlined in Scheme 2. Based on preceding work,^[16] it is reasonable to assume that the reaction is initiated by coordination of the amide substrate **1** to the palladium center, followed by C–H metalation. Whereas this step has been proposed to be stereo-determining for unbranched substrates,^[12,16] this can be ruled out here since the substitution pattern of the aryl iodide **2** has a profound influence on the stereochemistry of the products. Thus, the stereo-determining step must be either the oxidative addition of the aryl iodide or the reductive elimination. Oxidative addition can lead to a number of Pd^{IV} isomers, each present in different quantities and with variable reactivities towards reductive elimination. One might speculate that ligands **L5** and **L9** facilitate the reductive elimination from different Pd^{IV} conformers, resulting in the release of

different diastereomers. This would be in agreement with reports on stereodivergent reaction outcomes based on reductive elimination from Pd^{IV} species.^[17,10d]

Irrespective of whether the oxidative addition, reductive elimination, or a combination of both dictate the stereochemical outcome, the differentiation must take place within the Pd^{IV} intermediate, because both substrates and the ligand all affect the outcome. The remarkable reversal in diastereoselectivity between *ortho*- and *meta*-substituted aryl iodides, well-illustrated by α - and β -naphthyl iodides (*cis*-**3aa** and *trans*-**3a β** in Table 2), could be a consequence of different steric demands of the aryl scaffolds. This seems to lead to a different outcome in the competition of the aryl moiety and the cycloalkane residue for the least hindered space within the coordination sphere of palladium.

In conclusion, we have established the first example of a catalyst-controlled enantio- and diastereoselective C–H arylation of two unbiased β -methylene groups. The two enantiomers of the complementary ligands **L5** and **L9** allow to preferentially functionalize each of the four accessible β -C–H bonds of cyclohexyl carboxamides providing straightforward access to their 2-arylated derivatives with unprecedented spatial control over two contiguous stereocenters. Although the ligand influence is not yet sufficiently strong to override all substrate effects, this is an important step towards gaining full stereocontrol over C–H functionalization.

Experimental Section

Typical procedure, medium scale: Amide **1a** (137.3 mg, 400 μ mol), ligand **L5** (20.0 mg, 48 μ mol), Ag₂CO₃ (193 mg, 700 μ mol), Pd(OAc)₂ (9.0 mg, 40 μ mol), iodo-4-methylbenzene (218 mg, 1.00 mmol) and AgOAc (20 mg, 120 μ mol) were weighed in air and placed in a screw cap vial with a magnetic stirring bar. Hexafluoroisopropanol (4.0 mL) was added, the vial sealed and the mixture was stirred at room temperature for 10 minutes before heating at 80°C in the dark for 36 h. The mixture was allowed to cool to room temperature, filtered through Celite with CH₂Cl₂ and concentrated *in vacuo*. NMR-analysis implied 85% analytical yield (dr 95:5). Column chromatography (SiO₂, PhMe) gave 140 mg *cis*-**3aa** (322 μ mol, 81%), as yellow oil and a mixture of *trans*-**3aa** and starting material **1a** (2:1, .31 mg).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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A: diastereoselective sp^3 -CH activation, substrate-controlled

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B: enantioselective sp^3 -CH activation, ligand-controlled

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C: this work - simultaneous enantio- and diastereocontrol **Scheme 1.**

Stereodivergent directed methylene C–H functionalization.

Scheme 2.
Schematic mechanism, including two representative Pd^{IV} isomers.

Table 1.

Structural optimization of APAQ ligands in cyclohexane arylations.

<p> $\text{Cyclohexyl-CONHAr}_F \xrightarrow{\text{Ligand } p\text{-Tol-I } 2a} \text{R,S-cis-3aa} + \text{S,S-trans-3aa}$ $\text{Ar}_F = p\text{-C}_6\text{F}_4\text{-CF}_3$ </p>					
<p>L1</p>	<p>L2, R = Ph</p>	<p>L3, R = 3,5-(t-Bu)₂Ph</p>	<p>L6</p>	<p>L7, R = Me</p>	<p>L8, R = Ph</p>
<p>L4, R = Et</p>	<p>L5, R = Me</p>		<p>L9</p>		
Ligand	L1	L2	L3	L4	L5
Yield	64%	76%	64%	63%	74% 85% ^a
dr: <i>cis</i> to <i>trans</i>	67:33	80:20	89:11	8:92	96:4 ^a
er: <i>1R,2S</i> to <i>1S,2R</i>	50:50	78:22	89:11	97:3	97:3 ^a
Ligand	L6	L7	L8	L9	
Yield	84%	85%	57%	99%	
dr: <i>cis</i> to <i>trans</i>	34:66	31:69	37:63	24:76	
er: <i>1S,2S</i> to <i>1R,2R</i>	89:11	88:12	87:13	84:16	

Conditions: 100 μmol **1a**, 10 μmol $\text{Pd}(\text{OAc})_2$, 12 μmol **L1-L9**, 175 μmol Ag_2CO_3 , 250 μmol aryl iodide, 1 mL HFIP, 80°C, air, 36 h, a) additional 30 μmol AgOAc .

^{a)} additional 30 μmol AgOAc .

Substrate scope with *cis*-favoring ligand **L5**.

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Table 3.

Scope of aryl iodide coupling partners with *trans*-favoring ligand **L9**.

<p>1a-1c $n = 0-2$</p> <p>L9 Arl</p> <p><i>S,S'</i>-<i>trans</i> (3aa - 3av, 3ba, 3ca) + <i>R,R</i>-enantiomer</p> <p><i>R,S'</i>-<i>cis</i> (3aa - 3av, 3ba, 3ca) + <i>S,R</i>-enantiomer</p>				
<p>3ao</p> <p>98% yield, dr 21:79, <i>cis:trans</i>, er 79:21, <i>trans'</i> <i>S'S':R'R</i></p>				
<p>3av</p> <p>11% yield, dr 64:36, <i>cis:trans</i>, er n.d.</p>				
<p>3ba</p> <p>37% yield, dr 100:0, <i>cis:trans'</i> er n.d.</p>				
<p>3ca</p> <p>59% yield, dr 27:73, <i>cis:trans</i>, er 89:11, <i>trans</i>, <i>S'S':R'R</i></p>				

Conditions: 100 μmol **1**, 10 μmol $\text{Pd}(\text{OAc})_2$, 12 μmol **L9**, 175 μmol Ag_2CO_3 , 250 μmol aryl iodide, 1 mL HFIP, 80°C, air, 36 h