Palladium(0)-Catalyzed Enantioselective Intramolecular Arylation of Enantiotopic Secondary C–H Bonds

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In memory of Kilian Muñoz

Abstract: The enantioselective functionalization of nonactivated enantiotopic secondary C–H bonds is one of the greatest challenges in transition-metal-catalyzed C–H activation proceeding by an inner-sphere mechanism. Such reactions have remained elusive within the realm of Pd⁰ catalysis. Reported here is the unique reactivity profile of the IBiox ligand family in the Pd⁰-catalyzed intramolecular arylation of such nonactivated secondary C–H bonds. Chiral C₂-symmetric IBiox ligands led to high enantioselectivities for a broad range of valuable indane products containing a tertiary stereocenter, as well as the arylation of secondary C–H bonds adjacent to amides. Depending on the amide substituents and upon control of reaction time, indanes containing labile tertiary stereocenters were also obtained with high enantioselectivities. Analysis of the steric maps of the IBiox ligands indicated that the level of enantioselectivity correlates with the difference between the two most occupied and the two less occupied space quadrants, and provided a blueprint for the design of even more efficient ligands.

Introduction

Enantioselective organometallic C–H activation is a current topic of great interest, providing a straightforward access to high value-added scalemic intermediates from easily accessible precursors.^[1] Indeed, the replacement of a hydrogen atom by a carbon or heteroatom on a C(sp³) center is arguably one of the simplest ways to construct stereogenic centers. Of course, this is far from trivial to achieve in practice, due to the lack of reactivity of C(sp³)–H bonds towards cleavage by transition metals.^[2] To tackle this challenge, a variety of directing group and oxidative addition based strategies have been deployed to render the C–H activation step intramolecular and hence kinetically more accessible. In partic-

ular, Pd⁰-catalyzed C(sp³)–H activation induced by C(sp²)–X oxidative addition has proven a general and effective method to construct a variety of cyclic systems.^[3] In the past decade, enantioselective versions have been developed,^[4] which can be classified in two main categories: 1. Type I: the desymmetrization of two enantiotopic alkyl groups, leading to the generation of a stereogenic center remote to the activated C–H bond (Scheme 1a).^[4,5] If the activation site is secondary (R ≠ H), then the two hydrogen atoms at this site are also diastereotopic and two adjacent stereocenters are generated.^[4a-c,5a,b] As an extension, parallel kinetic resolution may occur when the two alkyl groups are different, thereby leading to the formation of two enantioenriched regioisomeric products.^[6] 2. Type II: the desymmetrization of enantiotopic hydrogen atoms on secondary carbons, creating a stereogenic center at the activated site (Scheme 1b).^[7] To date, type I reactions, which are enabled by a variety of chiral ancillary ligands or chiral anions,^[4,5] are by far the most developed. An application in natural product synthesis was recently reported by our group.^[8] The prevalence of type I reactions over type II can be explained by the high density of C–H bonds (4 for

a) type I: desymmetrization of enantiotopic alkyl groups

b) type II: desymmetrization of enantiotopic hydrogen atoms

single precedent:

this work:

Scheme 1. Enantioselective Pd⁰-catalyzed C(sp³)–H activation.

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methylenes and 6 for methyl groups) on substrates bearing two alkyl groups, that strongly favors the C–H activation step. In contrast, despite the conceptual simplicity and the potentially greater applicability of type II reactions, only one example was reported so far, i.e. the synthesis of β -lactams from α -chloroamides by Cramer and co-workers (Scheme 1b), using chiral phosphoramidite ligands.^[7] However, this transformation is so far limited to activated secondary C–H bonds on benzylic positions. Nonetheless, it should be noted that in contrast to Pd⁰ catalysis, the Pd^{II}-catalyzed enantioselective intermolecular functionalization of nonbenzylic enantiotopic secondary C–H bonds (type II reactions) has been recently reported using a directing group strategy.^[9] However, such reactions are less suited to the construction of scalemic carbo- and heterocycles.

The development of enantioselective reactions of type II (Scheme 1b) faces a number of obstacles, including the lower reactivity of secondary C–H bonds compared to primary ones, the low density of C–H bonds as already noted above, and the competitive β -H elimination leading to olefins instead of reductive elimination products.^[10] Herein, we report that IBiox-type chiral NHCs show both an exceptional reactivity towards unbiased secondary C–H bonds and a high enantioselectivity for the formation of enantioenriched indanes (Scheme 1b, bottom).

Results and Discussion

We started to explore the reactivity of aryl bromide **1a** with ligands that were previously employed in both enantioselective and non-enantioselective Pd⁰-catalyzed C(sp³)–H activation reactions (Figure 1A).^[4–7] Compound **1a** was chosen both for its accessibility and because the *gem*-diesters should favor the challenging C–H activation step via the Thorpe–Ingold effect. However, electronically diverse ligands, from the electron-poor phosphonite **L**¹,^[5c] to increasingly σ -donor phosphines PPh₃,^[5d] Binapine **L**²,^[5b] PCy₃,^[11] PAd₂(*n*-Bu),^[5e] and N-heterocyclic carbenes IPr and IAd, furnished only marginal amounts of product **2a** even at a high temperature, while proto-debromination and decarboxylation were observed as main side-reactions.^[12] In addition, the chiral NHC **L**³, which was successfully employed in a range of desymmetrization reactions (Scheme 1a),^[4a,5a,6,8] did not furnish a reactive catalyst in the current case. The first breakthrough was achieved when IBioxMe₄, designed by Glorius and co-workers,^[13] was employed, providing a 30% conversion. Moreover, the spirocyclic analogue IBiox6^[14] furnished an improved conversion of 73%, hence establishing IBiox-type NHCs as uniquely reactive ligands for this transformation. Although the reasons behind this unique reactivity are not clear yet, it was previously argued that these ligands possess “flexible steric bulk” favoring difficult catalytic elementary steps and hemilabile interactions such as agostic bonds,^[15] which might be crucial for the current challenging C–H activation step occurring through the concerted metalation-deprotonation (CMD) mechanism.^[11,16]

Then, we prepared and tested a number of C₂-symmetric chiral IBiox ligands^[17] and analyzed the conversion and

Figure 1. Initial ligand screen. Standard conditions: Pd₂dba₃ (phosphorus ligands) or [Pd(π -cinnamyl)Cl]₂ (NHCs) (5 mol%), ligand (10 mol%), CsOPiv (1.0 equiv), Cs₂CO₃ (1.5 equiv), mesitylene, 160 °C, 18 h. Ar¹ = 3,5-di-CF₃Ph, Ar² = 3,5-di-*t*-Bu-4-OMePh, Fc = ferrocene. Conversions were determined by ¹⁹F NMR.

enantioselectivity (Figure 2). The results are shown with optimized conditions employing 5 mol % [Pd(π -allyl)Cl]₂ as the Pd source, 10 mol % ligand, 30 mol % CsOPiv and 1 equiv Cs₂CO₃ in PhCF₃ at 140 °C.^[12] The most sterically demanding chiral IBiox NHCs provided again the highest conversions, and the best enantioselectivities were achieved with ligands containing tertiary stereogenic centers equipped with bulky alkyl groups. In particular, IBiox_oTu and the new IBioxAd furnished both high conversions (ca. 90%) and enantiomeric ratios (e.r. 98:2). The very bulky menthyl-derived ligand IBioxMenth^[17b] provided a high conversion but a lower enantioselectivity (e.r. 86:14) whereas the aminoindanol-derived IBioxInd provided a poor conversion. Kündig's ligand **L**³ (see Figure 1) was re-tested under these optimized conditions and little conversion was again observed, hence further illustrating the unique behavior of IBiox-type ligands for this challenging transformation. Interestingly, control experiments with stoichiometric cesium pivalate and cesium carbonate alone did not furnish any product, which indicates that the C–H activation step could involve both bases, presumably as a cluster.^[18]

Having established IBioxAd as the ligand of choice and the optimal reaction conditions, we investigated the scope of

Figure 2. Identification of the optimal chiral ligand. Optimized conditions: $[\text{Pd}(\pi\text{-allyl})\text{Cl}]_2$ (5 mol%), NHC·HOTf (10 mol%), CsOPiv (30 mol%), Cs_2CO_3 (1.0 equiv), PhCF_3 , 5 Å MS, 140 °C, 18 h. Conversions were determined by ^{19}F NMR spectroscopy and *ee* values by HPLC using a chiral stationary phase. The absolute configuration of **2a** was ascribed by analogy to **2c**, **2t** and **2ja**. a) The opposite enantiomer of this ligand was used, hence resulting in the other enantiomer of **2a**.

the reaction (Scheme 2). First, different unfunctionalized alkyl chains underwent selective C–H activation at the proximal methylene group, hence leading to the corresponding indane products in good yields and excellent enantioselectivities (**2b–2e**). Of note, indane **2c** was obtained in good yield and enantioselectivity from both the aryl bromide and aryl chloride precursors, thereby establishing the latter as competent substrates. Other products thereafter were also obtained from chlorides (**2o**, **2p**, **2q**). Moreover, alkyl chains bearing a terminal fluorine atom (**2f**) and a range of functional groups such as an ester (**2g**), protected alcohols (**2h,i**) and a protected amine (**2j**) worked well, which opens the possibility for further synthetic transformations. In some cases, recrystallization allowed further enantioenrichment (**2h**, **2j**). To test the robustness of this method, substrate **1j** was engaged in a gram scale reaction. Although a slight decrease in enantioselectivity (e.r. 95:5) was observed for the crude mixture, product **2j** was isolated in 63% yield as a single observable enantiomer after recrystallization. The *gem*-diester groups adjacent to the activated methylene, which allow an easy access to the reaction substrates by standard alkylation procedures, were also essential for the reaction to proceed, presumably because they induce a strong Thorpe–Ingold effect.^[19] In addition, these esters could

Scheme 2. Reaction scope. a) After recrystallization. b) E.r. of the crude mixture. c) Performed on a gram scale. d) Using the well-defined complex $[\text{Pd}(\text{IBioxAd})(\pi\text{-allyl})\text{Cl}]$ (10 mol%). e) Using 10 mol% $[\text{Pd}(\pi\text{-allyl})\text{Cl}]_2$, 20 mol% IBioxAd·HOTf, 60 mol% CsOPiv and 2 equiv Cs_2CO_3 . Reactions were performed from aryl bromides (X = Br) and on a 0.2 mmol scale unless otherwise stated. E.r. values were determined by HPLC using a chiral stationary phase. Absolute configurations were ascribed by analogy to **2c**, **2t** and **2ja**. PMP = *p*-methoxyphenyl, TBS = *tert*-butyldimethylsilyl, Phth = Phthalimide.

enhance the reactivity of the C–H bonds at the β position through inductive effects. However, exchanging the methyl with ethyl (**2k**) or isopropyl (**2l**) esters did not affect the enantioselectivity, although the latter was isolated with a much reduced yield due to a difficult separation from the protodehalogenated product.

Next, we probed the influence of substituents on the aromatic ring. Electron-withdrawing substituents in *meta* or *para* position to the initial bromine atom were well tolerated (**2a**, **2m–2q**) and gave consistently good results. A more moderate yield but a comparable enantioselectivity was observed with substrate **1r** bearing an electron-donating 1,3-dioxolane motif. It is noteworthy that very similar results were obtained for **2a** with the well-defined complex $[\text{Pd}(\text{IBioxAd})(\pi\text{-allyl})\text{Cl}]$,^[12] thus showing that the *in situ* deprotonation and coordination of the imidazolium NHC precursor to form the active Pd–NHC complex do not have a significant impact

on the reactivity. Finally, the double C–H activation product **2s** was obtained in high enantioselectivity (e.r. > 20:1) upon doubling the catalyst loading. The *meso* diastereoisomer was probably formed in small quantities but could not be isolated.

Motivated by the above results, we turned our interest to the intramolecular arylation of secondary C–H bonds adjacent to a carbonyl group. This is a very challenging case since the tertiary stereocenter of the corresponding indane product is both benzylic and adjacent to the carbonyl group and is therefore prone to epimerization. However, we surmised that the current basic conditions, i.e. the combination of Cs₂CO₃ and CsOPiv in an apolar solvent, could be mild enough to escape racemization. The reaction would again proceed through the CMD mechanism, rather than an enolate arylation mechanism.^[20] To test this hypothesis, we prepared various substrates containing the least α -acidic amide group and subjected them to catalysis (Table 1). Gratifyingly, the

Table 1: Enantioselective α -arylation of amides to generate labile tertiary stereocenters.

Entry	Product	R	t [h]	Yield [%] ^[a]	e.r.
1	2t	NMe ₂	18	94	95:5
2	2u	NC ₄ H ₈ O	18	87	68:32
3	2u	NC ₄ H ₈ O	8	95	97:3
4	2v	N(Me)OMe	18	80	70:30
5	2v	N(Me)OMe	4	75	98:2
6	2w	OMe	2	n.d. ^[b]	55:45

[a] Yield of isolated product. [b] Product not isolated. n.d. = not determined. The e.r. values were determined by HPLC using a chiral stationary phase. Absolute configurations were ascribed by analogy to **2c**, **2t**, and **2ja**.

dimethylamide **1t** gave good results under the standard conditions, with a high yield and enantioselectivity (entry 1). However, in the cases of morpholine (**1u**) and Weinreb (**1v**) amides, a significant drop in enantioselectivity was observed (entries 2 and 4). This problem was solved by reducing the reaction time to 8 and 4 h, respectively, indicating that racemization is slower than the reaction and occurs after full conversion (entries 3, 5). The corresponding amide products **2u–v** were obtained in good yields (75–95%) and high enantioselectivities (e.r. 97:3–98:2). In contrast, little enantioselectivity was observed in the reaction of the more acidic methyl ester **1w**, even at short times (entry 6). In this case racemization occurred faster than the reaction. Although currently limited to amides, these results represent, to the best of our knowledge, the first enantioselective Pd-catalyzed α -arylation of carbonyl groups to generate epimerizable tertiary stereocenters without the preformation of a silicon or tin enolate.^[21]

To get an insight on the turnover-limiting step of the reaction, parallel kinetic experiments were conducted from protiated (**1x**) and deuterated (**1y**) isotopomers using the

Figure 3. Formation kinetics of protiated (**2x**, filled circles) and deuterated (**2y**, empty circles) products.

well-defined complex [Pd(IBioxBu)(π -allyl)Cl] (Figure 3).^[12] Despite the presence of an induction period, presumably corresponding to the generation of the active Pd⁰(NHC) complex and preventing the determination of a precise k_H/k_D value, a clear primary kinetic isotope effect was observed, indicating that the C–H activation step is turnover-limiting (see Figure S1 in the Supporting Information for a proposed catalytic cycle).

Furthermore, in an attempt to rationalize the enantioselectivities achieved with the C₂-symmetric chiral IBiox ligands, the steric maps and buried volumes of their DFT-optimized [PdL(π -allyl)Cl] complexes were computed using the SambVca 2.1 application developed by Cavallo and co-workers (Figure 4).^[12,22] As shown with the comparison of IBioxMenth with other ligands, there is no correlation between the buried volumes (% V_{Bur}) and the measured e.r. values. However, the four space quadrants of the steric map of IBioxMenth are occupied, whereas ligands bearing tertiary stereogenic centers display two more occupied and two less occupied quadrants. The mean occupation difference between the two sets of opposite quadrants on such C₂-symmetric ligands can be quantified as % $V_{\text{Bur(OD)}}$, deduced from the % V_{Bur} calculated in each quadrant. These values better correlate to the observed e.r. than the global buried volumes, with higher % $V_{\text{Bur(OD)}}$ values corresponding to higher enantioselectivities (Figures S2 and S3).

Following up on this model and inspired by work in the bis(oxazoline) and phosphinooxazoline family of ligands,^[23] we synthesized a new IBiox ligand containing *gem*-dimethyl groups on the oxazoline rings, named IBioxBuMe₄ (Scheme 3). These substituents should further restrict the rotation of the *t*-butyl groups and increase their influence on the coordination sphere. The calculated % $V_{\text{Bur(OD)}}$ for this ligand (Figure 4, bottom right) was indeed found to be higher

Figure 4. Steric maps and buried volumes of IBiox ligands (L) in [PdL(π -allyl)Cl] complexes. The quadrant difference buried volume is defined as: $\%V_{\text{Bur(QD)}} = [\%V_{\text{Bur(NE quadrant)}} + \%V_{\text{Bur(SW quadrant)}} - \%V_{\text{Bur(NW quadrant)}} - \%V_{\text{Bur(SE quadrant)}}]/2$.

(23.0) than that of the parent unsubstituted ligand, IBioxTbu (22.2). This higher value correlated with an increased enantioselectivity in the reaction of aryl bromide **1a** (Scheme 3). Indeed, indane **2a** was obtained in 78 % yield with a very high enantioselectivity (e.r. 99.4:0.6). Moreover, nitro-substituted substrate **1n**, which previously gave the lowest e.r. value (94:6) among all substrates with IBioxAd (see Scheme 2), led to indane **2n** with an improved e.r. of 98.5:1.5 with IBioxTbuMe₄ (Scheme 3).

Chiral indanes are widespread structural motifs found in natural products and bioactive molecules,^[24] and hence enantioselective methods to access these systems are of high interest.^[25] To demonstrate the application potential of the current method, we derivatized indane **2j**, which was synthesized in enantiopure form on a gram scale (see Scheme 2). Cleavage of the phthalimide group under standard conditions employing hydrazine was accompanied by lactamization, thus providing the tricyclic product **2ja** in high yield as a single *cis* diastereoisomer (Scheme 4). In addition, the valuable spirocyclic barbiturate^[26] **2jb** was synthesized upon cyclocondensation with urea and methylation.

Of note, it proved challenging to ascribe the absolute configurations of the indane products generated in this study. In particular, despite extensive efforts, it was difficult to

Scheme 4. Post-functionalizations.

obtain crystals of these products or derivatives thereof suitable for X-ray diffraction analysis, and the obtained diffraction data did not show sufficiently precise Flack parameters for an unambiguous assignment. Based on a similar experience with indane products,^[8] we could solve this issue via vibrational circular dichroism (VCD),^[27] by comparing calculated and experimental VCD spectra of three different types of indane products, **2c**, **2t** and **2ja**, which provided similar results (Figures S4–S18). The configurations of other indane products were assigned by analogy.

Conclusion

In conclusion, the enantioselective intramolecular arylation of enantiotopic secondary C–H bonds via Pd⁰ catalysis was developed. The IBiox family of NHC ligands displayed a unique reactivity among all ligand classes tested for the arylation of nonactivated C–H bonds. Chiral C₂-symmetric IBiox ligands possessing the greatest difference between the two most occupied and the two less occupied space quadrants furnished the highest enantioselectivity. The reaction showed high enantioselectivities across a broad range of indanes. Moreover, the arylation of secondary C–H bonds adjacent to amides provided indanes with a sensitive tertiary stereocenter upon careful control of the reaction time. The current method should streamline the access to complex molecules containing a chiral indane motif.

Acknowledgements

This work was financially supported by the Swiss National Science Foundation (grant # 200021_184608) and the University of Basel. We thank Dr. D. Häussinger for NMR experiments, and S. Mittelheisser and Dr. M. Pfeffer for MS analyses.

Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · C–H activation · indanes · N-heterocyclic carbenes · palladium

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