

Chiral Ligands Based on Binaphthyl Scaffolds for Pd-Catalyzed Enantioselective C–H Activation/Cycloaddition Reactions

José Manuel González,[†] Xandro Vidal,[†] Manuel Angel Ortuño, José Luis Mascareñas,^{*} and Moisés Gulías^{*}



Cite This: *J. Am. Chem. Soc.* 2022, 144, 21437–21442



Read Online

ACCESS |



Metrics & More



Article Recommendations



Supporting Information

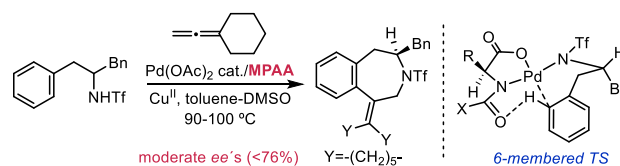
ABSTRACT: We report the first examples of the use of a new class of ligands (NOBINAc) for performing asymmetric C–H activations using palladium catalysts. These ligands combine the axial chirality of binaphthyl scaffolds with the bifunctional and bidentate coordination properties of mono-*N*-protected amino acids (MPAAs), which are well-known to favor Pd-promoted C–H activations via concerted metalation–deprotonation mechanisms. We demonstrate that our new ligands enable substantially higher enantioselectivities than MPAAs in the assembly of 2-benzazepines through formal (5 + 2) cycloadditions between homobenzyltriflamides or *o*-methylbenzyltriflamides and allenes.

Transition-metal-catalyzed C–H functionalization reactions have emerged as one of the more powerful tools in the field of organic synthesis.¹ A major ongoing challenge in the area is the development of enantioselective versions, especially for reactions in which the asymmetry is created in the C–H activation step.² Despite significant progress, the number of such asymmetric reactions is still small, and in many cases the resulting enantioselectivities are far from optimal.³ A major breakthrough in the field was the discovery by Yu and co-workers of mono-*N*-protected amino acids (MPAAs) as efficient chiral ligands to promote a broad variety of Pd-catalyzed enantioselective C–H functionalizations.⁴ Mechanistic studies have established that these ligands bind the metal in a bidentate manner, with the *N*-acyl moiety acting as an internal base to drive the C–H activation step (concerted metalation–deprotonation (CMD) mechanism). The metal chelation leads to a relatively rigid transition state, which allows efficient transfer of asymmetric information from the chiral center of the amino acid to the resulting palladacycle intermediate.⁵

Relying on these chiral ligands, we have recently reported a Pd-catalyzed desymmetrizing cycloaddition between α -diarylmethyltriflamides and allenes to give valuable tetrahydroisoquinolines via enantioselective C–H activation/cycloaddition processes.⁶ The best conditions to perform this transformation involved the use of 2,6-difluorobenzoylleucine as the ligand, which allowed enantioselectivities of up to 95% *ee*.

Unfortunately, homologous α -dibenzylmethyltriflamides, which have an extra methylene carbon between the stereogenic center and the aromatic ring and therefore provide appealing benzazepines in their annulation to allenes, led to very poor enantioselectivities (barely 14% *ee*).⁷ After an intense screening of other MPAAs and reaction conditions, the best results were obtained with Boc-valine, which in the best of the cases gave a yet modest 76% *ee*. This poor asymmetric efficiency might be related to the formation of relatively flexible six-membered palladacycles in the C–H activation step (Scheme 1).

Scheme 1. Preliminary Studies on the Synthesis of Benzazepines through a Formal (5 + 2) Annulation



With this state of the art, we reasoned that ligands featuring axial instead of point chirality might allow for more efficient transmission of chiral information. These ligands with atropisomeric chirality are well-established in the field of asymmetric catalysis, but curiously, they have essentially never been used as bidentate anionic ligands in palladium-mediated C–H functionalization processes.⁸

Herein, we demonstrate that acylated versions of NOBIN (NOBINAc) are excellent ligands for asymmetric Pd-catalyzed C–H activation/annulation processes, clearly outperforming standard MPAAs. Specifically, we report their use to achieve highly enantioselective (5 + 2) annulations between homobenzyltriflamides or *o*-methylbenzyltriflamides and allenes. These reactions allow the construction of a variety of enantioenriched 2-benzazepines using either desymmetrization or kinetic resolution strategies and in reactions that involve activation of either sp² or sp³ C–H bonds.⁹

Atropisomeric bidentate ligands such as BINAP have been widely used as privileged scaffolds in many metal-catalyzed asymmetric reactions.¹⁰ The restricted rotation around the

Received: September 5, 2022

Published: November 15, 2022



aryl–aryl bond generates a rigid asymmetric environment that can be efficiently sensed by substrates when coordinated to the metal center.

Inspired by these structures and considering the dianionic nature of MPAA ligands and the key role of the amide moiety as an internal base for the C–H activation (CMD mechanism),^{4b,5} we reasoned that acylated NOBIN derivatives such as **L** (Figure 1a) might be effective ligands in Pd-catalyzed

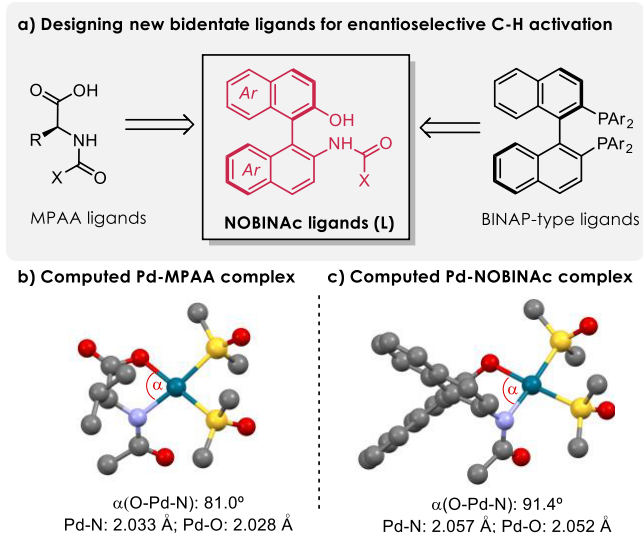


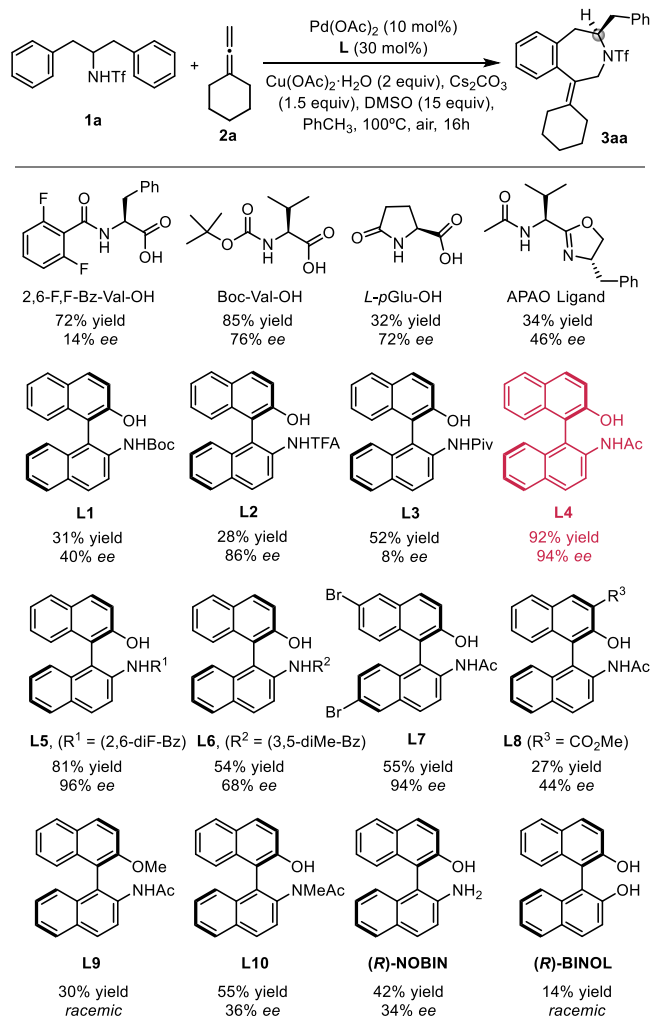
Figure 1. (a) Design of NOBINAc ligands for asymmetric Pd-catalyzed activation. (b, c) DFT-optimized structures for qualitative comparison between $[\text{LPd}(\text{DMSO})_2]$ complexes (L = MPAA and NOBINAc).

asymmetric C–H activations. Preliminary DFT calculations confirmed that this class of ligands can provide unstrained palladacycles like those obtained using MPAA, with similar bond distances between the metal and the O and N atoms. The metal geometry is also rather similar (square-planar), although with a higher bite angle (Figure 1b,c). More importantly, the chiral environment resulting from the complexation of NOBINAc is different, which may have consequences in the asymmetric transfer process.

As indicated above, our study on asymmetric annulations to form benzazepines started with the use of 2,6-difluorobenzoyl-leucine as the ligand. The reaction between triflyl-protected homobenzylamine **1a** and commercially available vinylidene-cyclohexane (**2a**) using conditions similar to those described for benzylamides⁶ gave a good yield (72%), but the product was isolated with only 14% *ee*. After intensive screening with different MPAA, we found that the best conditions involved the use of Boc-valine, which produced the cycloadduct in 85% yield but with a still modest 76% *ee* (Scheme 1; see the Supporting Information for the complete screening). Other ligands sporadically used in asymmetric C–H activation with palladium, such APAO, APAQ or *p*-GluOH, gave lower yields and *ee*'s (Scheme 2).¹¹

Remarkably, the *N*-Boc-protected (*R*)-NOBIN derivative **L1** was a valid ligand for the reaction, but the product was obtained in a low 31% yield with 40% *ee*. While this initial enantioselectivity was poor, the experiment validated the use of this type of ligand with the binaphthyl scaffold and a phenol handle instead of the carboxylic acid of MPAA. Using the trifluoromethylacetyl NOBIN derivative increased the enantio-

Scheme 2. Screening of Ligands^a



^aReaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), Pd(OAc)₂ (10 mol %), Ligand **L** (30 mol %), Cu(OAc)₂·H₂O (2 equiv), Cs₂CO₃ (1.5 equiv), DMSO (15 equiv), PhCH₃ (1.0 mL), air, 100 °C, 16 h. Isolated yields are reported.

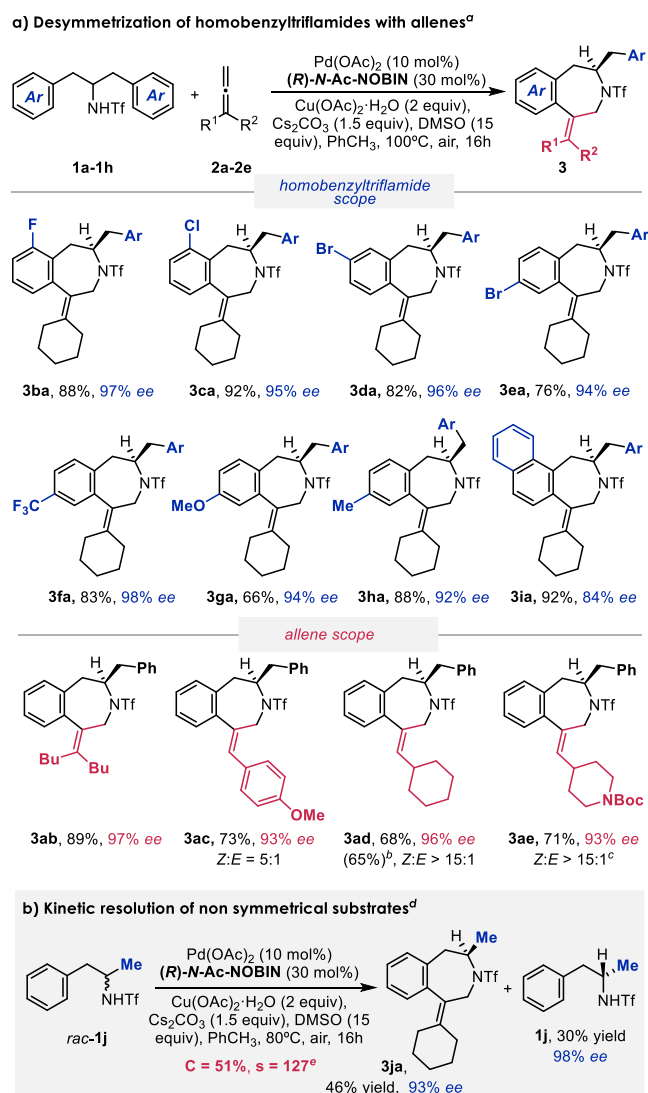
selectivity to a promising 86% *ee*, although the product was obtained in only 28% yield. Gratifyingly, with the *N*-acetyl derivative **L4** [(*R*)-Ac-NOBIN] the reaction took place in an excellent 92% yield with 94% *ee*. We could even increase the enantiomeric excess to 96% *ee* using 2,6-benzoyl analogue **L5**, but at the cost of a slight decrease in the reaction yield to 81%, while 3,5-benzoyl analogue **L6** was clearly less effective. Other *N*-acetyl NOBIN derivatives with substituents on the naphthyl skeleton, such **L7** and **L8**, gave worse results.

Importantly, a control experiment using the methyl ether derivative **L9** led to lower conversion and a racemic product, a result similar to that obtained when the reaction was carried out in the absence of ligands (40% yield after 16 h), while ligand **L10** with the methylated amino group led to a 55% yield with 36% *ee*. When the free amine NOBIN was used as the ligand, the reaction was also low-yielding (34%), although it could induce some enantioselectivity (42% *ee*). Not surprisingly, when binaphthol was used instead of NOBINAc, the reaction was very inefficient (14% yield) and furnished the product in racemic form. All of these results support the requirement of a dianionic palladium ligand with an acetamide

group capable of promoting the CMD process. The cation of the base also plays a role in the reaction, since the yields and enantioselectivities decreased when K_2CO_3 (82% yield, 86% *ee*) or especially Li_2CO_3 (38% yield, 6% *ee*) was used instead of the cesium salt. Interestingly, a comparison of reaction rates between reactions with and without ligand showed that the reaction with ligand is about 2 times faster (see the Supporting Information).

With the optimal conditions in hand, we tested the scope of the annulation. Gratifyingly, benzazepine products **3ba**–**3ea** containing halogens at the *ortho*, *meta*, and *para* positions were assembled in excellent yields (76–92%) with enantioselectivities of up to 97% *ee* (Scheme 3). Other types of substituents

Scheme 3. Scope of the Asymmetric (5 + 2) Annulation



^aConditions: **1** (0.1 mmol), **2** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), ligand (30 mol %), $Cu(OAc)_2 \cdot H_2O$ (2 equiv), Cs_2CO_3 (1.5 equiv), DMSO (15 equiv), $PhCH_3$ (1 mL), air, 100 °C, 16 h. ^bThe reaction was run at a 0.5 mmol scale of **1a**. ^cThe reaction time was 48 h. ^dThe reaction was run at 80 °C with 0.5 mL of $PhCH_3$. ^eThe conversion (*C*) and selectivity (*s*) were calculated as $C = ee^{SM} / (ee^{SM} + ee^{PR})$ and $s = \ln[(1 - C)(1 - ee^{SM})] / \ln[(1 - C)(1 + ee^{SM})]$, respectively, where ee^{SM} is the *ee* of recovered starting material **1** and ee^{PR} is the *ee* of product **3**.

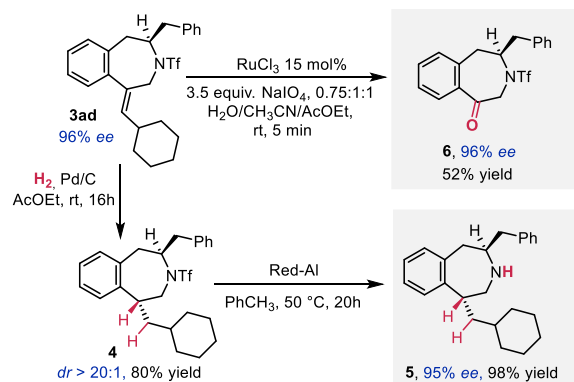
are also tolerated, as illustrated for the trifluoromethyl (**3fa**, 98% *ee*), methoxy (**3ga**, 94% *ee*), and methyl (**3ha**, 92% *ee*) derivatives. A homonaphthylamide precursor was also tested and gave the expected product **3ia** in 92% yield with 84% *ee*.

The reaction is also quite general with respect to the allene component. A nonadiene, as an example of other 1,1-disubstituted allenes, gave the expected benzazepine adduct **3ab** in 89% yield with 97% *ee*. Monosubstituted allenes also provided good results, as exemplified for the synthesis of products **3ac**, **3ad**, and **3ae**, which were obtained with high enantioselectivities (93–96% *ee*), good *E:Z* diastereoselectivity, and complete regioselectivity. Compound **3ad** was crystallized, which allowed us to assign the absolute configuration of the product as *R*.

Importantly, the annulation can be extended to non-symmetric precursors, providing very efficient kinetic resolutions. When we tested the reaction with α -methylphenethylamide **1j** and allene **2a**, the corresponding benzazepine **3ja** was isolated in 46% yield with 93% *ee*, and the chiral homobenzyltriflamides were recovered in 30% yield with 98% *ee*, which translates to a selectivity factor of 127.

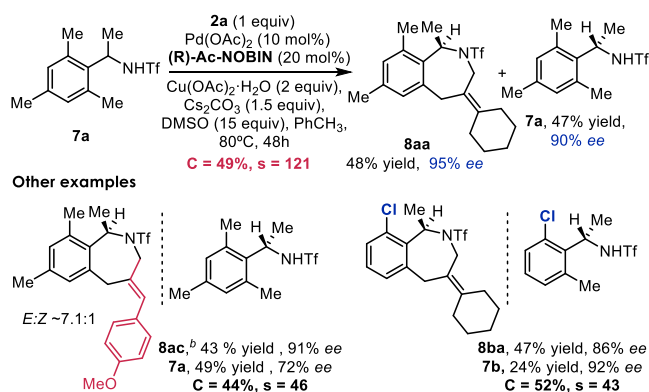
The benzazepine cycloadducts can be easily manipulated thanks to the presence of the exocyclic double bond. For instance, product **3ad** can be easily hydrogenated to give the saturated product **4** with complete *trans* diastereoselectivity in 80% yield (Scheme 4). This product can be deprotected using

Scheme 4. Derivatization of the Benzazepine Products



Red-Al without deterioration of the enantioselectivity. Product **3ad** can also be selectively oxidized in one step to the corresponding ketone using ruthenium trichloride catalyst and periodate, again without affecting the *ee*.

We recently reported that benzazepines can also be assembled by annulation of *o*-methylbenzylamides with allenes in a reaction that involves the activation of $C(sp^3)$ –H bonds.¹² Unfortunately, the asymmetric version using MPAAC-type ligands led to low enantioselectivities (less than 79% *ee* in the best of the cases, with a selectivity factor of 13). Remarkably, under the standard conditions with NOBINAc ligand **L4**, the enantioselectivities rose to 95% *ee* and 90% *ee* for the product **8aa** and the starting material **7a** (Scheme 5), and the selectivity factor increased to 121. The reactions are also effective for other substrates, and again, the obtained products exhibited excellent enantioselectivities (Scheme 5, bottom). Overall, the above results confirm the NOBINAc structures as excellent ligands for the above asymmetric annulations involving a C–H activation and $Pd(II)/Pd(0)$ catalytic cycles.

Scheme 5. Kinetic Resolution of *o*-Methylbenzyltriflamides^a

^aReaction conditions: *rac*-1a (0.1 mmol), 2a (0.1 mmol), Pd(OAc)₂ (10 mol %), Ac-NOBIN (30 mol %), Cu(OAc)₂·H₂O (2 equiv), Cs₂CO₃ (1.5 equiv), DMSO (15 equiv), PhCH₃ (1 mL), air, 80 °C, 48 h. ^b1.5 equiv of 2c.

Why is the NOBINAc scaffold so effective in the asymmetric induction? To shed light on this question, we computed the relative Gibbs energies of the C–H bond activation transition states using DFT, with ligand L4 and homobenzylamide 1a. We used the M06 density functional¹³ as implemented in Gaussian 16.¹⁴ We explored several conformations, but only the most stable ones are reported and discussed herein.^{15,16}

We considered two main topologies for the six-membered transition state structures,^{5a} depending on whether the coplanar *ortho* C–H bond (to be activated) points downward (D) or upward (U) with respect to the Pd coordination plane (see the Supporting Information). Remarkably, the rigid framework of NOBINAc favors structures D, as the alternative forms U exhibit strong distortions of the Pd square-planar geometry (N–O–N–C dihedral angle for TS-US = 24.9°; Figure 2a). This is in clear contrast to the results obtained

using Ac-Val-OH, where lower distortions are found in both types of transition state topologies D and U (dihedral angles = 0–13°; see the Supporting Information). Indeed, with the amino acid ligand the lowest-energy transition states for each isomer are TS-DR and TS-US, and the Gibbs energy difference is 4.8 kcal/mol. However, in the case of NOBINAc, the most stable transition states leading to the R and S enantiomers are TS-DR and TS-DS, respectively (Figure 2b), with TS-DR clearly preferred by 8.2 kcal/mol. While this number suggests that complete enantioselection should be obtained, it is very likely that there could be some ligand-free reaction, and especially some background reaction in which NOBINAc acts as monodentate ligand.^{5b} These processes might contribute to partial erosion of the enantioselectivity. Furthermore, it is important to note that these calculations do not simulate the full experimental scenario, and therefore, the energetic values should be taken carefully, although they are very useful for comparative purposes.

Importantly, the calculated TSs allow us to infer the reasons behind the differences in energy between TS-DR and TS-DS, namely, clear steric clashes of the nonreacting Bn substituent with the other benzyl group and with the triflyl group (Figure 2b).

In conclusion, we have discovered a new class of ligands (NOBINAc) for performing palladium-catalyzed enantioselective annulations involving C–H activations. The use of these ligands allows the assembly of a variety of enantioenriched benzazepine products by reaction of very simple starting benzylamide precursors with allenes. The much-better asymmetric induction obtained with this class of ligands over that with classic amino acids originates from the destabilization of U transition state structures due to the introduction of further strain in the Pd square-planar geometries. Our examples represent the first application of metal-catalyzed C–H activation chemistry in the enantioselective construction of seven-membered rings through (5 + 2) annulations. Further developments with this class of activating ligands are currently underway.

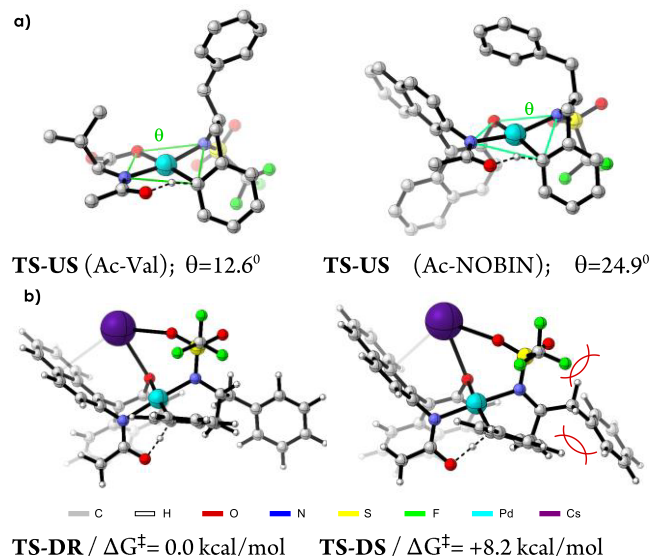


Figure 2. (a) DFT-optimized structures and dihedral angles of TS-US for acetyl-Val and acetyl-NOBIN. Hydrogens and Cs atoms have been omitted for clarity. (b) DFT-optimized structures and relative Gibbs energies of the two more stable conformations of transition states for the key C–H bond activation using NOBINAc ligands.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.2c09479>.

Experimental details, characterization data for all new compounds, and computational details (PDF)

Accession Codes

CCDC 2204297 ((R)-3ad), 2204513 ((R,R)-4), and 2204767 ((R)-8aa) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Authors

Moisés Gulías – Centro Singular de Investigación en Química Biológica e Materiais Moleculares (CIQUS) and Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain; Email: moises.gulias@usc.es

José Luis Mascareñas – Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS) and Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain; Email: joseluis.mascarenas@usc.es

Authors

José Manuel González – Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS) and Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain

Xandro Vidal – Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS) and Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain; orcid.org/0000-0003-0963-1506

Manuel Angel Ortuño – Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS) and Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain

Complete contact information is available at:

<https://pubs.acs.org/10.1021/jacs.2c09479>

Author Contributions

†J.M.G. and X.V. contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work received financial support from the MCIN/AEI/10.13039/501100011033 (Projects PID2019-108624RB-I00, PID2019-110385GB-I00, and PID2020-119116RA-I00 and FPU Fellowship to X.V.), the Consellería de Cultura, Educación e Ordenación Universitaria (ED431C-2021/25, ED431G 2019/03: Centro Singular de Investigación de Galicia accreditation 2019–2022, and fellowship to J.M.G.), and the European Regional Development Fund (ERDF). The orfeocinca network CTQ2016-81797-REDC is also kindly acknowledged. M.A.O. acknowledges the Xunta Distinguished Researcher Program (ED431H 2020/21) for funding and Centro de Supercomputación de Galicia (CESGA) for providing generous computational resources. Figures were created with CYLview20.

REFERENCES

(1) For selected recent reviews of metal-catalyzed C–H functionalizations, see: (a) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. Mild metal-catalyzed C–H activation: examples and concepts. *Chem. Soc. Rev.* **2016**, *45*, 2900–2936. (b) Abrams, D. J.; Provencher, P. A.; Sorensen, E. J. Recent applications of C–H functionalization in complex natural product synthesis. *Chem. Soc. Rev.* **2018**, *47*, 8925–8967. (c) Gulías, M.; Mascareñas, J. L. Metal-catalyzed annulations through activation and cleavage of C–H bonds. *Angew. Chem., Int. Ed.* **2016**, *55*, 11000–11019. (2) For reviews of asymmetric C–H functionalization, see: (a) Saint-Denis, T. G.; Zhu, R.-Y.; Chen, G.; Wu, Q.-F.; Yu, J.-Q. Enantioselective C(sp³)-H bond activation by chiral transition metal catalysts. *Science* **2018**, *359*, eaao4798. (b) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. Transition metal-catalyzed C–H activation reactions: diastereoselectivity and enantioselectivity. *Chem. Soc. Rev.* **2009**, *38*, 3242–3272. (c) Newton, C. G.; Wang, S.-G.; Oliveira, C. C.; Cramer, N. Catalytic Enantioselective Trans-

formations Involving C–H Bond Cleavage by Transition-Metal Complexes. *Chem. Rev.* **2017**, *117*, 8908–8976. (d) Yang, K.; Song, M.; Liu, H.; Ge, H. Palladium-catalyzed direct asymmetric C–H bond functionalization enabled by the directing group strategy. *Chem. Sci.* **2020**, *11*, 12616–12632. (e) Achar, T. K.; Maiti, S.; Jana, S.; Maiti, D. Transition Metal Catalyzed Enantioselective C(sp²)-H Bond Functionalization. *ACS Catal.* **2020**, *10*, 13748–13793. (f) Liu, C.-X.; Zhang, W.-W.; Yin, S.-Y.; Gu, Q.; You, S.-L. Synthesis of Atropisomers by Transition-Metal-Catalyzed Asymmetric C–H Functionalization Reaction. *J. Am. Chem. Soc.* **2021**, *143*, 14025–14040. (g) Zhan, B.-B.; Jin, L.; Shi, B.-F. Palladium-catalyzed enantioselective C–H functionalization via C–H palladation. *Trends Chem.* **2022**, *4*, 220–235.

(3) Vidal, X.; Font, M.; Gulías, M.; Mascareñas, J. L. Transition Metal-Catalyzed Desymmetrizations Based on C–H Activation Processes. In *Handbook of CH-Functionalization*; Maiti, D., Ed.; Wiley-VCH, 2022.

(4) (a) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. Pd^{II}-Catalyzed Enantioselective Activation of C(sp²)-H and C(sp³)-H Bonds Using Monoprotected Amino Acids as Chiral Ligands. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882–4886. (b) Shao, Q.; Wu, K.; Zhuang, Z.; Qian, S.; Yu, J.-Q. From Pd(OAc)₂ to Chiral Catalysts: The Discovery and Development of Bifunctional Mono-N-Protected Amino Acid Ligands for Diverse C–H Functionalization Reactions. *Acc. Chem. Res.* **2020**, *53*, 833–851. For examples, see: (c) Shi, B.-F.; Zhang, Y.-H.; Lam, J. K.; Wang, D.-H.; Yu, J.-Q. Pd(II)-catalyzed enantioselective C–H olefination of diphenylacetic acids. *J. Am. Chem. Soc.* **2010**, *132*, 460–461. (d) Du, Z.-J.; Guan, J.; Wu, G.-J.; Xu, P.; Gao, L.-X.; Han, F.-S. Pd(II)-catalyzed enantioselective synthesis of P-stereogenic phosphinamides via desymmetric C–H arylation. *J. Am. Chem. Soc.* **2015**, *137*, 632–635. (e) Hu, L.; Shen, P.-X.; Shao, Q.; Hong, K.; Qiao, J. X.; Yu, J.-Q. Pd^{II}-Catalyzed Enantioselective C(sp³)-H Activation/Cross-Coupling Reactions of Free Carboxylic Acids. *Angew. Chem., Int. Ed.* **2019**, *58*, 2134–2138. (f) Gao, D.-W.; Gu, Q.; You, S.-L. An Enantioselective Oxidative C–H/C–H Cross-Coupling Reaction: Highly Efficient Method To Prepare Planar Chiral Ferrocenes. *J. Am. Chem. Soc.* **2016**, *138*, 2544–2547. (g) Gao, D.-W.; Gu, Q.; You, S.-L. Pd(II)-Catalyzed Intermolecular Direct C–H Bond Iodination: An Efficient Approach toward the Synthesis of Axially Chiral Compounds via Kinetic Resolution. *ACS Catal.* **2014**, *4*, 2741–2745. For a related work with allylamides, see: (h) González, J. M.; Cendón, B.; Mascareñas, J. L.; Gulías, M. Kinetic Resolution of Allyltriflamides through a Pd-Catalyzed C–H Functionalization with Allenes: Asymmetric Assembly of Tetrahydropyridines. *J. Am. Chem. Soc.* **2021**, *143*, 3747–3752.

(5) (a) Cheng, G.-J.; Chen, P.; Sun, T.-Y.; Zhang, X.; Yu, J.-Q.; Wu, Y.-D. A Combined IM-MS/DFT Study on [Pd(MPAA)]-Catalyzed Enantioselective C–H Activation: Relay of Chirality through a Rigid Framework. *Chem. - Eur. J.* **2015**, *21*, 11180–11188. (b) Haines, B. E.; Yu, J.-Q.; Musaev, D. G. Enantioselectivity Model for Pd-Catalyzed C–H Functionalization Mediated by the Mono-N-protected Amino Acid (MPAA) Family of Ligands. *ACS Catal.* **2017**, *7*, 4344–4354.

(6) Vidal, X.; Mascareñas, J. L.; Gulías, M. Palladium-Catalyzed, Enantioselective Formal Cycloaddition between Benzyltriflamides and Allenes: Straightforward Access to Enantioenriched Isoquinolines. *J. Am. Chem. Soc.* **2019**, *141*, 1862–1866.

(7) For examples of transformations with benzyl and homobenzylamides, see: (a) Chu, L.; Wang, X.-C.; Moore, C. E.; Rheingold, A. L.; Yu, J.-Q. Pd-Catalyzed Enantioselective C–H Iodination: Asymmetric Synthesis of Chiral Diarylmethylamines. *J. Am. Chem. Soc.* **2013**, *135*, 16344–16347. (b) Chu, L.; Xiao, K.-J.; Yu, J.-Q. Room-temperature enantioselective C–H iodination via kinetic resolution. *Science* **2014**, *346*, 451–455. (c) Xiao, K.-J.; Chu, L.; Chen, G.; Yu, J.-Q. Kinetic Resolution of Benzylamines via Palladium(II)-Catalyzed C–H Cross-Coupling. *J. Am. Chem. Soc.* **2016**, *138* (24), 7796–7800. (d) Laforteza, B. N.; Chan, K. S. L.; Yu, J.-Q. Enantioselective *ortho*-C–H Cross-Coupling of Diarylmethylamines with Organoborons. *Angew. Chem., Int. Ed.* **2015**, *54*, 11143–

11146. (e) Zhang, Z.; Wang, J.; Li, J.; Yang, F.; Liu, G.; Tang, W.; He, W.; Fu, J.-J.; Shen, Y.-H.; Li, A.; Zhang, W.-D. Total Synthesis and Stereochemical Assignment of Delavatine A: Rh-Catalyzed Asymmetric Hydrogenation of Indene-Type Tetrasubstituted Olefins and Kinetic Resolution through Pd-Catalyzed Triflamide-Directed C–H Olefination. *J. Am. Chem. Soc.* **2017**, *139*, 5558–5567. (f) Shi, H.; Herron, A. N.; Shao, Y.; Shao, Q.; Yu, J.-Q. Enantioselective remote *meta*-C–H arylation and alkylation via a chiral transient mediator. *Nature* **2018**, *558*, 581–585. (g) Bai, X.-F.; Mu, Q.-C.; Xu, Z.; Yang, K.-F.; Li, L.; Zheng, Z.-J.; Xia, C.-G.; Xu, L.-W. Catalytic Asymmetric Carbonylation of Prochiral Sulfonamides via C–H Desymmetrization. *ACS Catal.* **2019**, *9*, 1431–1436. (h) Han, H.; Zhang, T.; Yang, S.-D.; Lan, Y.; Xia, J.-B. Palladium-Catalyzed Enantioselective C–H Aminocarbonylation: Synthesis of Chiral Isoquinolinones. *Org. Lett.* **2019**, *21*, 1749–1754.

(8) (a) Yue, Q.; Liu, B.; Liao, G.; Shi, B.-F. Binaphthyl Scaffold: A Class of Versatile Structure in Asymmetric C–H Functionalization. *ACS Catal.* **2022**, *12*, 9359–9396. For examples of the use of binaphthyl-based monodentate ligands with different metals, see: (b) Lin, L.; Fukagawa, S.; Sekine, D.; Tomita, E.; Yoshino, T.; Matsunaga, S. Chiral Carboxylic Acid Enabled Achiral Rhodium(III)-Catalyzed Enantioselective C–H Functionalization. *Angew. Chem., Int. Ed.* **2018**, *57*, 12048–12052. (c) Zhou, T.; Qian, P.-F.; Li, J.-Y.; Zhou, Y.-B.; Li, H.-C.; Chen, H.-Y.; Shi, B.-F. Efficient Synthesis of Sulfur-Stereogenic Sulfoximines via Ru(II)-Catalyzed Enantioselective C–H Functionalization Enabled by Chiral Carboxylic Acid. *J. Am. Chem. Soc.* **2021**, *143*, 6810–6816. (d) Hirata, Y.; Sekine, D.; Kato, Y.; Lin, L.; Kojima, M.; Yoshino, T.; Matsunaga, S. Cobalt(III)/Chiral Carboxylic Acid-Catalyzed Enantioselective Synthesis of Benzothiadiazine-1-oxides via C–H Activation. *Angew. Chem., Int. Ed.* **2022**, *61*, e202205341. (e) Yoshino, T.; Matsunaga, S. Chiral Carboxylic Acid Assisted Enantioselective C–H Activation with Achiral Cp^xM^{III} (M = Co, Rh, Ir) Catalysts. *ACS Catal.* **2021**, *11*, 6455–6466. (f) Smalley, A. P.; Cuthbertson, J. D.; Gaunt, M. J. Palladium-Catalyzed Enantioselective C–H Activation of Aliphatic Amines Using Chiral Anionic BINOL-Phosphoric Acid Ligands. *J. Am. Chem. Soc.* **2017**, *139*, 1412–1415.

(9) For examples of racemic (5 + 2) annulation based on C–H activation, see: (a) Seoane, A.; Casanova, N.; Quiñones, N.; Mascareñas, J. L.; Gulías, M. Straightforward Assembly of Benzoxepines by Means of a Rhodium(III)-Catalyzed C–H Functionalization of *o*-Vinylphenols. *J. Am. Chem. Soc.* **2014**, *136*, 834–837. (b) Casanova, N.; Del Rio, K. P.; García-Fandiño, R.; Mascareñas, J. L.; Gulías, M. Palladium(II)-catalyzed annulation between *ortho*-alkenylphenols and allenes. Key role of the metal geometry in determining the reaction outcome. *ACS Catal.* **2016**, *6*, 3349–3353. (c) Cendón, B.; Casanova, N.; Comanescu, C.; García-Fandiño, R.; Seoane, A.; Gulías, M.; Mascareñas, J. L. Palladium-catalyzed formal (5 + 2) annulation between *ortho*-alkenylanilides and allenes. *Org. Lett.* **2017**, *19*, 1674–1677. (d) Rodríguez, A.; Albert, J.; Ariza, X.; García, J.; Granell, J.; Farràs, J.; La Mela, A.; Nicolás, E. J. Catalytic C–H activation of phenylethylamines or benzylamines and their annulation with allenes. *J. Org. Chem.* **2014**, *79*, 9578–9585. (e) Velasco-Rubio, Á.; Varela, J. A.; Saá, C. Palladium-Catalyzed [5 + 2] Heteroannulation of Phenethylamides with 1,3-Dienes to Dopaminergic 3-Benzazepines. *Org. Lett.* **2020**, *22*, 3591–3595. (f) Bai, D.; Xu, T.; Ma, C.; Zheng, X.; Liu, B.; Xie, F.; Li, X. Rh(III)-Catalyzed Mild Coupling of Nitrones and Azomethine Imines with Alkylidenecyclopropanes via C–H Activation: Facile Access to Bridged Cycles. *ACS Catal.* **2018**, *8*, 4194–4200. (g) Zuo, Z.; Liu, J.; Nan, J.; Fan, L.; Sun, W.; Wang, Y.; Luan, X. Highly Stereoselective Synthesis of Imine-Containing Dibenzo[*b,d*]azepines by a Palladium(II)-Catalyzed [5 + 2] Oxidative Annulation of *o*-Arylanilines with Alkynes. *Angew. Chem., Int. Ed.* **2015**, *54*, 15385–15389.

(10) For examples of the use of BINAP in asymmetric catalysis, see: (a) Akutagawa, S. Asymmetric synthesis by metal BINAP catalysts. *Appl. Catal. A: Gen.* **1995**, *128* (2), 171–207. (b) Deng, R. X.; Huang, Y. Z.; Ma, X. N.; Li, G. C.; Zhu, R.; Wang, B.; Kang, Y. B.; Gu, Z. H. Palladium-catalyzed intramolecular asymmetric C–H functionaliza-

tion/cyclization reaction of metallocenes: An efficient approach toward the synthesis of planar chiral metallocene compounds. *J. Am. Chem. Soc.* **2014**, *136*, 4472–4475. (c) Kuninobu, Y.; Yamauchi, K.; Tamura, N.; Seiki, T.; Takai, K. Rhodium-catalyzed asymmetric synthesis of spiro[3.3]heptane derivatives. *Angew. Chem., Int. Ed.* **2013**, *52*, 1520–1522. (d) Tanaka, K.; Hagiwara, Y.; Hirano, M. Rh-catalyzed [4 + 2] annulation of 4-alkynals with isocyanates and its application to the parallel kinetic resolution of unfunctionalized 4-alkynals. *Angew. Chem., Int. Ed.* **2006**, *45*, 2734–2737. (e) Da Concepción, E.; Fernández, I.; Mascareñas, J. L.; López, F. Highly Enantioselective Cobalt-Catalyzed (3 + 2) Cycloadditions of Alkynylidenecyclopropanes. *Angew. Chem., Int. Ed.* **2021**, *60*, 8182–8188. (f) Fernández, D. F.; Gulías, M.; Mascareñas, J. L.; López, F. Iridium(I)-Catalyzed Intramolecular Hydrocarbonation of Alkenes: Efficient Access to Cyclic Systems Bearing Quaternary Stereocenters. *Angew. Chem., Int. Ed.* **2017**, *56*, 9541–9545.

(11) For examples of the use of these ligands, see: (a) Chen, G.; Gong, W.; Zhuang, Z.; Andrà, M. S.; Chen, Y.-Q.; Hong, X.; Yang, Y.-F.; Liu, T.; Houk, K. N.; Yu, J.-Q. Ligand-Accelerated Enantioselective Methylene C(sp³)-H Bond Activation. *Science* **2016**, *353*, 1023–1027. (b) He, J.; Shao, Q.; Wu, Q.; Yu, J.-Q. Pd(II)-Catalyzed Enantioselective C(sp³)-H Borylation. *J. Am. Chem. Soc.* **2017**, *139*, 3344–3347. (c) Jin, L.; Yao, Q.-J.; Xie, P.-P.; Li, Y.; Zhan, B.-B.; Han, Y.-Q.; Hong, X.; Shi, B.-F. Atroposelective Synthesis of Axially Chiral Styrenes via an Asymmetric C–H Functionalization Strategy. *Chem* **2020**, *6*, 497–511.

(12) Vidal, X.; Mascareñas, J. L.; Gulías, M. Assembly of Tetrahydroquinolines and 2-Benzazepines by Pd-Catalyzed Cycloadditions Involving the Activation of C(sp³)-H Bonds. *Org. Lett.* **2021**, *23*, 5323–5328.

(13) Zhao, Y.; Truhlar, D. G. The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, non-covalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theor. Chem. Acc.* **2008**, *120*, 215–241.

(14) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. *Gaussian 16*, rev. C.01; Gaussian, Inc.: Wallingford, CT, 2016.

(15) Álvarez-Moreno, M.; De Graaf, C.; López, N.; Maseras, F.; Poblet, J. M.; Bo, C. Managing the Computational Chemistry Big Data Problem: The ioChem-BD Platform. *J. Chem. Inf. Model.* **2015**, *55*, 95–103.

(16) All structures are freely available in the open-access platform ioChem-BD via the following database: <http://dx.doi.org/10.19061/iochem-bd-6-155>.