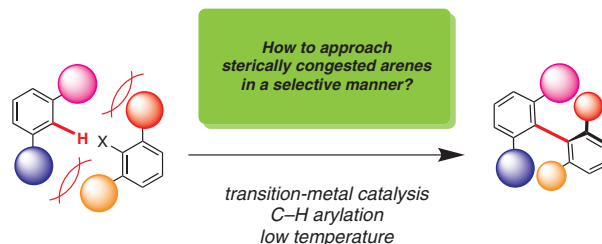


# Challenging Atroposelective C–H Arylation

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**Abstract** Atropisomeric molecules are privileged scaffolds, not only as ligands for asymmetric synthesis, but also as biologically active products and advanced materials. Although very attractive from a sustainability viewpoint, the direct construction of the stereogenic axis through asymmetric C–H arylation is very challenging and consequently only a few examples have been reported. This short review summarizes these very recent results on the atropo-enantio or diastereoselective synthesis of atropisomeric (hetero)biaryl molecules; transformations during which the Ar–Ar atropisomeric axis is formed during the C–H activation process.

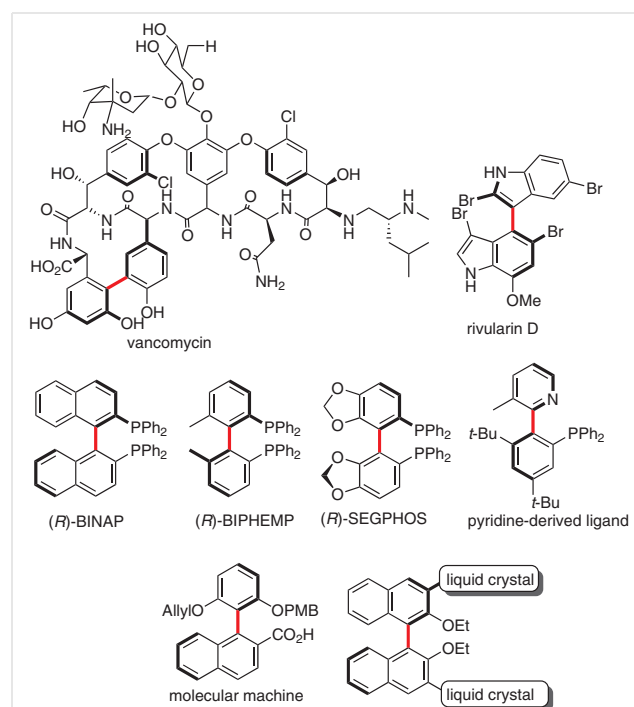
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**Key words** atropisomeric axis, atropisomeric biaryls, C–H arylation

## 1 Introduction

Atropisomerism<sup>1a</sup> is a fundamental feature of many molecular scaffolds with important application in materials, pharmaceuticals, natural products and in organic synthesis

as chiral catalysts. This chiral element, resulting from the hindered rotation around an axis, has been recognized as an important factor governing the biological activities of many natural products.<sup>1b–d</sup> Representative examples are depicted in Figure 1, including not only the well-known vancomycin but also (hetero)biaryl motifs such as rivularin D (Figure 1). Moreover, atropisomerism is the fundamental feature of classes of ligands in asymmetric catalysis. Indeed, BINOL, BIPHEMP or SEGPHOS are undeniably privileged chiral inductors.<sup>2</sup> More recently, atropisomeric pyridine-

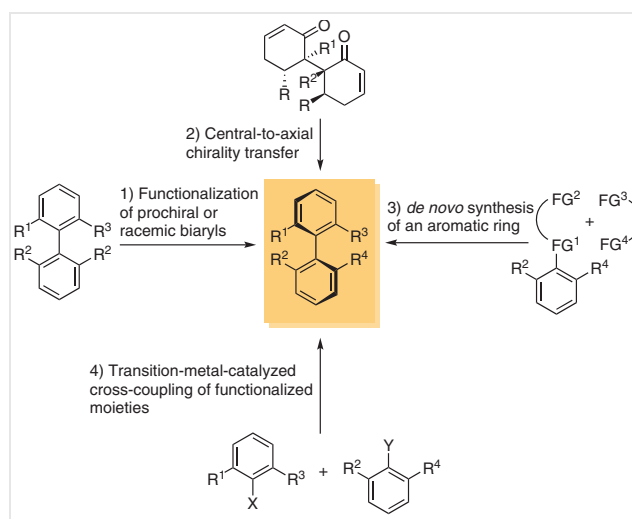


**Figure 1** Representative atropisomeric molecules

derived ligands<sup>3</sup> have also attracted increasing attention. Several modern materials,<sup>4</sup> including liquid crystals and molecular machines, may also contain atropisomeric biaryl elements.

The key importance of atropisomerism is further illustrated by the expanding number of applications of such molecules in pharmaceutical industry.<sup>5</sup> Indeed, an analysis of 1900 small drug molecules from the USD FDA Drug Bank (FDA: Food and Drug Administration) reveals that approximately 15% of FDA-approved scaffolds contain one or more atropisomeric axes and an additional 10% of molecules are 'proatropisomeric', meaning that a simple modification of a molecule in proximity of an axis would render it chiral.<sup>5</sup> Even more marked, the prevalence of atropisomeric compounds has been expanding dramatically since 2011 and, in 2018, almost one out of three FDA-approved small molecules contained an atropisomeric element and an additional 16% were proatropisomeric.<sup>5</sup>

Consequently the past decade has witnessed significant advances in the field of atropisomeric synthesis of biaryls.<sup>6</sup> The most common strategies to access such compounds include (1) stereoselective transformations of prochiral or racemic biaryls;<sup>7,6b</sup> (2) methods relying on a central-to-axial chirality transfer;<sup>8</sup> (3) *de novo* synthesis of an aromatic ring,<sup>9</sup> or (4) asymmetric transition-metal-catalyzed cross-coupling of functionalized moieties (Figure 2).<sup>10</sup>



**Figure 2** Different approaches towards atropisomeric biaryls

In addition, atroposelective metal-catalyzed C–H functionalization has recently become established as a powerful strategy for the atroposelective construction of chiral biaryls.<sup>6g</sup> Applications of the C–H activation protocols for the synthesis of the enantiomerically enriched atropisomeric compounds remain rare and are mainly concerned with the stereoselective C–H functionalization of prochiral or race-

### Biographical Sketches



**Joanna Wencel-Delord** studied chemistry at the Ecole Nationale Supérieure de Chimie de Rennes, France and she received her Ph.D. in 2010 from the University of Rennes 1, France (Dr. C. Crévisy and Dr. M. Mauduit). After postdoctoral studies with Prof. F. Glorius at the Westfälische Wilhelms-Universität Münster (Germany) and a tem-

porary assistant professor position (ATER) at the University of Strasbourg (Prof. P. Compain), she joined CNRS (The French National Centre for Scientific Research) in 2013 as an associate researcher in the group of Prof. F. Colobert (University of Strasbourg, France). Her research focuses on the transition-metal-catalyzed

asymmetric C–H activation and synthesis of axially chiral compounds, including C–N atropisomeric molecules. Her recent awards and distinctions include an Emerging Investigator Prize of Organic Chemistry Division, French Chemical Society (2018), Bronze Medal of CNRS (2020), and ERC SG (2020).



**Françoise Colobert** received a Ph.D. in organic chemistry in 1985 from the University Pierre et Marie Curie (Paris) working with Prof. Jean-Pierre Genêt in the field of asymmetric catalysis. After a post-doctoral position in the group of Prof. Jules

Hoffman (Nobel Prize, Strasbourg) in molecular biology, she became an assistant professor in the group of Prof. Guy Soladié and was appointed full professor of organic chemistry in 2001 at the University of Strasbourg. Her current re-

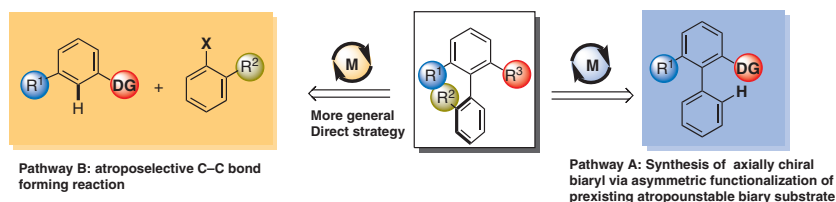
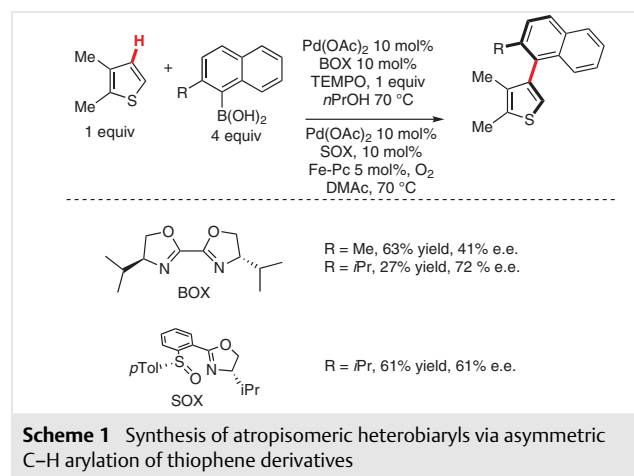
search interests are oriented towards transition-metal-catalyzed asymmetric C–H functionalization, access to axially chiral molecules, the use of chiral hypervalent iodine in copper catalysis, and the synthesis of biologically active molecules.

mic biaryls through the introduction of an additional *ortho*-substituent on a biaryl substrate bearing a directing group (Figure 3, Pathway A).<sup>11</sup> Without doubt, the synthesis of atropisomeric biaryls through C–H functionalization of an atropo-unstable precursor can be considered as one of the most general and efficient strategies. Enantioselective or diastereoselective approaches, together with the elegant use of a transient chiral directing group, have paved the way to a variety of high-value-added biaryls of interest either in the field of natural biologically active products or asymmetric catalysis.<sup>11</sup> In contrast, efficient control of atroposelectivity through direct C–H arylation (Figure 3, Pathway B) of (hetero)arenes certainly appears much more challenging. In fact, the atroposelective coupling of two bulky aryl moieties has been recognized as extremely difficult, even by using standard cross-coupling protocols, such as Suzuki couplings.<sup>10</sup> Indeed the difficulty of these reactions arises from the antagonism between the steric hindrance of both coupling partners (a prerequisite to ensure the configurational stability of the biaryl) translating to the drastic reaction conditions necessary to promote the Ar–Ar bond-forming event and the limited atropostability of the newly generated compounds under the reaction conditions. This antagonism could explain the current scarcity of enantioselective Suzuki–Miyaura biaryl coupling reactions for which different classes of both mono- and bidentate ligands and Pd-catalysts have been designed.<sup>12</sup> It is also important to note that the current substrate scope of atroposelective Suzuki couplings is generally limited to specific substrates, such as trisubstituted binaphthyl, phenyl-naphthyl and, more sporadically, biphenyl compounds and substrates bearing coordinating substituents such as an aldehyde or phosphonate group. However, the synthesis of tetrasubstituted cores or heterobiaryls via Suzuki coupling remains an essentially unmet goal.

Taking account the recent advances achieved in the field of C–H activation, it was evident that chemists would try to synthesize atropisomeric biaryl moieties by direct C–H arylation of (hetero)arenes (Figure 3, Pathway B). To attain this goal, the issue of the antagonism between hindrance necessary to reach atropostability and elevated temperatures required not only to activate the C–H bond, but also to couple two hindered moieties, needs to be tackled. The few elaborated strategies that have been used to achieve this challenge are discussed in detail in this short review.

## 2 Atropo-enantioselective Intermolecular Pd-Catalyzed C–H Arylation of Thiophene Derivatives

The first efforts in this challenging field, unambiguously illustrating the inherent difficulty of atroposelective C–H arylation, were undertaken by Yamaguchi and Itami. In 2012 they reported the Pd-catalyzed coupling reaction between naphthylboronic acids and thiophene derivatives using the chiral ligand, 2,2'-bis(oxazoline) BOX in presence of TEMPO (Scheme 1).<sup>13</sup> To ascertain the configurational stability of the substituted aryl thiophenes, the rotational barrier was evaluated by DFT calculation and was high enough (33 kcal/mole for 3-methyl-4-(2-methylnaphthalene-1-yl)thiophene) to exist as a stable isomer at room temperature. After optimization of the reaction conditions the authors succeeded in affording the enantioenriched heterobiaryl products. The results showed unambiguously a clear antagonism between efficiency and stereoselectivity of this transformation. To achieve a satisfactory enantiomeric excess, a bulky naphthyl boronic acid with an isopropyl group in the *ortho*-position was required, but the product was isolated in a significantly decreased yield. One year later a second-generation catalytic system was proposed by Itami and Yamaguchi.<sup>14</sup> A novel sulfoxide-oxazoline SOX ligand and a catalytic amount of iron-phthalocyanine (FePc) as cooxidant were employed. By using these aerobic conditions the atropisomeric arylated product was obtained in better yield but with a slightly lower chiral induction.



**Figure 3** Atroposelective formation of biaryls via C–H activation

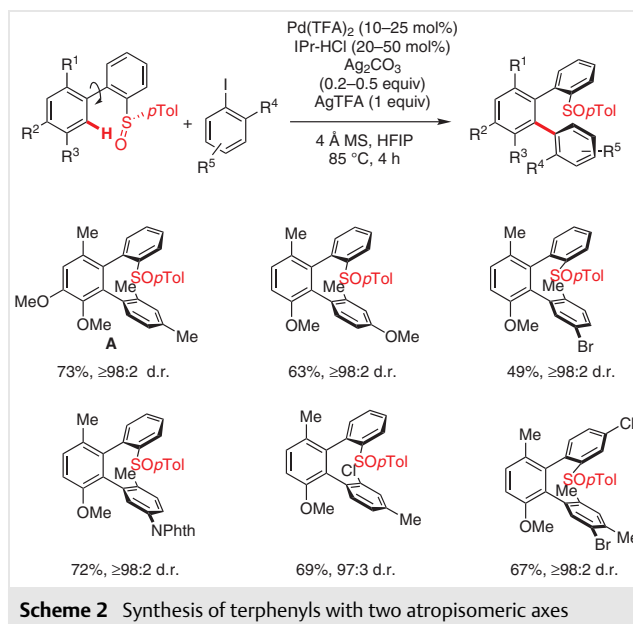
Following these seminal works, which clearly showed the extremely challenging nature of atroposelective C–H arylation, this field remained uncharted for several years and, only very recently, have major breakthroughs been achieved, using first diastereoselective, and later on, enantioselective protocols.

### 3 Atropodiastereoselective Intermolecular Pd-Catalyzed C–H Arylation towards Terphenyl Scaffolds Bearing Two Atropisomeric Axes

Targeting elaboration of unprecedented chiral scaffolds, Colobert and Wencel-Delord in 2018 were interested in the conception of optically pure molecules containing two contiguous atropisomeric axes.<sup>15</sup> They envisaged that such molecules might be obtained by combining diastereoselective C–H functionalization<sup>16</sup> of biaryls and stereoselective C–H arylation. Such triaryl scaffolds should exhibit a unique tridimensional structure, thus becoming an appealing platform to construct unprecedented chiral ligands.

The authors had already reported the Pd-catalyzed atropodiastereoselective C–H acetoxylation and halogenation of biarylsulfoxide substrates<sup>11b,h,i</sup> On the basis of this work, they hypothesized that the C–H arylation should be possible. Moreover, two contiguous atropisomeric axes might be expected in the coupling between biarylsulfoxides bearing an additional substituent in the *meta*-position and an *ortho*-substituted aryl iodide (Scheme 2). Regarding the high steric hindrance of both coupling partners, a significant optimization study was necessary; rewardingly, by using Pd(TFA)<sub>2</sub> with an *N*-heterocyclic carbene ligand, Ag<sub>2</sub>CO<sub>3</sub> and AgTFA, the expected *ortho*-orientated terphenyls were obtained in good yields and with excellent control of both atropisomeric axes in a single transformation (Scheme 2).<sup>17</sup> Use of 1,1,1,3,3,3-hexafluoroisopropanol as solvent and addition of molecular sieves were crucial in this reaction. This catalytic system is compatible with a variety of aryl-iodine coupling partners, including not only Cl- and Br-substituents, but also coordinating motifs such as NPhth or OMe. Moreover, with a Cl- or MeO- group in the *ortho*-position of the aryl iodide, the corresponding terphenyls were afforded in good yields and with excellent stereoselectivities.

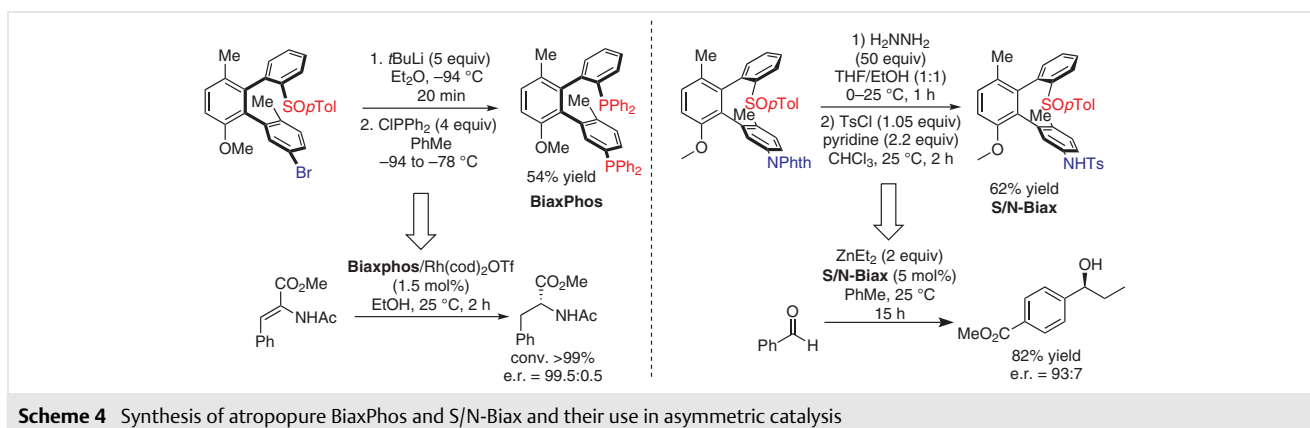
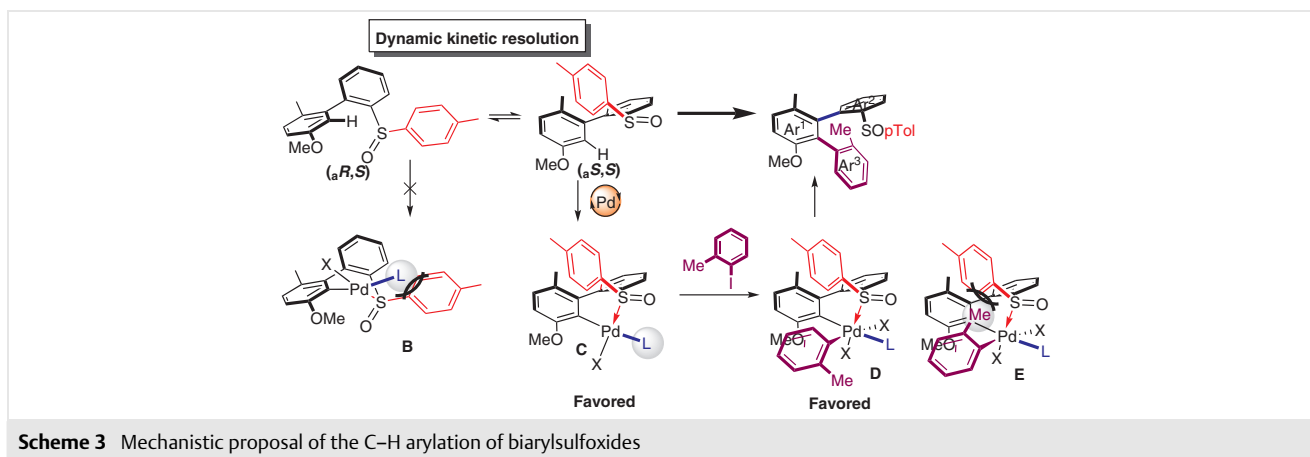
From a mechanistic viewpoint, the stereoselectivity of the Ar<sup>1</sup>–Ar<sup>2</sup> axis is induced during the C–H activation step, which favors palladacycle **C** over **B**. In intermediate **C** the steric interactions between the *para*-Tol group and the NHC ligand (L) are minimized (Scheme 3). A rapid racemization of the substrate indicates dynamic kinetic resolution. Regarding the chirality of the Ar<sup>1</sup>–Ar<sup>3</sup> linkage, the oxidative addition of the aryl iodide coupling partner would occur to minimize the steric interaction between the *SOP*-Tol moiety and the *ortho*-substituent of the aryl iodide, thus con-



trolling the chirality of the second atropisomeric axis. Finally, reductive elimination from less congested Pd<sup>IV</sup> intermediate **D** delivers the atropo-enantioenriched product. An epimerization half-life of ca. 73 days at 85 °C, consistent with the computed  $\Delta G^\ddagger$  of 33 kcal mol<sup>-1</sup> was observed for compound **A** (Scheme 2) supporting of the configurational stability of the product during the reaction.

This original tridimensional skeleton with two atropisomeric axes can be viewed as a perfect structure for the synthesis of new chiral ligands. Indeed an X-ray crystal structure showed a spatial proximity of Ar<sup>1</sup> and Ar<sup>3</sup> and an unusual ‘open clam shell’ architecture (Scheme 2), that seems highly appealing for stereogenic ligand design. Therefore, some functional group modifications were investigated and the diphosphine BiaxPhos was prepared through double lithium exchange of the sulfinyl group and bromine atom followed by quenching with chlorodiphenylphosphine. BiaxPhos was found to exhibit excellent reactivity and enantioselectivity in Rh-catalyzed hydrogenation of the trisubstituted methyl (*Z*)- $\alpha$ -acetamidocinnamate. An *S/N*-Biax ligand bearing the sulfinyl and *N*-tosyl groups was also synthesized. Its efficiency in 1,2-addition of Et<sub>2</sub>Zn to benzaldehyde was tested and the corresponding stereogenic carbinol was obtained in high yield and with excellent e.r. of 93:7 (Scheme 4).

This work was the first example of a highly atroposelective Ar–Ar bond formation through a C–H activation process and it also illustrates the potential of such methods to access complex molecules with applications in asymmetric catalysis.

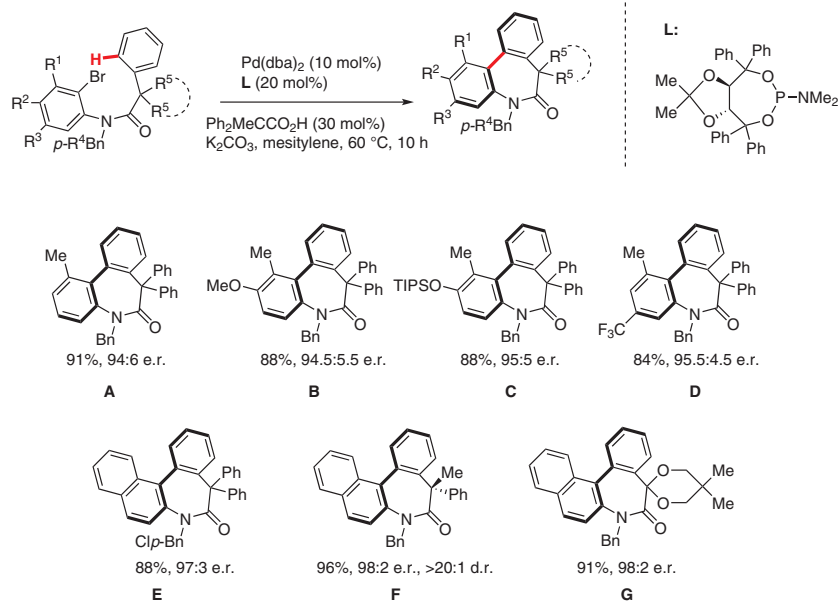


#### 4 Atropo-enantioselective Intramolecular Pd-Catalyzed C–H Arylation towards Atropisomeric Dibenzazepinones

A few months later, an efficient protocol for intramolecular enantioselective C–H arylation was reported by Cramer and co-workers,<sup>18</sup> targeting the synthesis of original atropisomeric benzazepinones (Scheme 5). Benzazepinones are an interesting class of natural products.<sup>19</sup> Notably, point chiral and achiral dibenzazepinones or dibenzodiazepines are present in some drugs, but atropisomeric dibenzazepinones have never been reported. The authors thus surmised that such original atropisomeric products could be readily obtained from bromo-aromatic amides, via Pd-catalyzed intramolecular C–H arylation, with a concomitant introduction of chiral information. The key to success was based on the use of Taddol-derived phosphorus(III) ligands. Such phosphoramidite ligands are known to facilitate Pd<sup>0</sup>/Pd<sup>II</sup>-catalyzed C–H functionalization under mild reaction conditions; the essential prerequisite for the atropostability of the newly generated axially chiral product. A careful optimization of the reaction conditions allowed preparation of dif-

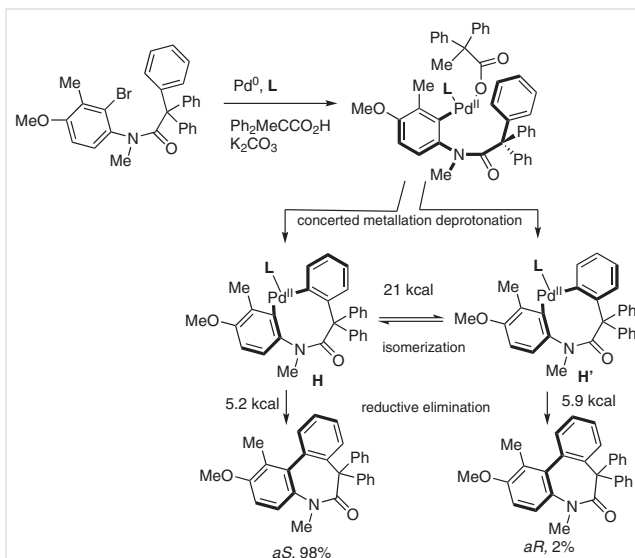
ferently substituted dibenzazepinones starting from achiral amides with different electron-donating (**A**, **B**, **C**) and electron-withdrawing (**D**) substituents on the aniline moiety, as well as a range of *para*-substituted benzyl groups on the 2-naphthylamine moiety (**E**, **F**, **G**). Notably, a gram-scale synthesis of dibenzazepinones bearing a *para*-chlorobenzyl on nitrogen atom **E** was achieved in excellent yield and enantioselectivity, even under reduced catalyst, ligand, and acid additive loadings. The potential of this methodology was further highlighted by its application to the synthesis of product **F**, bearing a stereocenter close to the biphenyl moiety in high diastereo- and enantioselectivities, and a ketal derivative **G**.

The rotational barrier of the newly accessed compounds was measured experimentally and predicted based on DFT calculations. The half life of **A** was determined to be 46 hours at 80 °C and 15 years at 25 °C; a guarantee of the configurational stability of the product during the reaction. In addition, DFT computational analysis suggests that the C–H insertion step, which occurs via a CMD mechanism, is enantiodetermining. Indeed, the two enantiomeric palladacycles **H** and **H'** are isoenergetic and both have a low barrier for reductive elimination (5.2 and 5.9 kcal mol<sup>-1</sup>; Scheme



**Scheme 5** Scope of the intramolecular atropoenantioselective C–H arylation

6). Moreover, a calculated isomerization barrier of 21 kcal mol<sup>-1</sup> appears to disfavor the equilibrium between **H** and **H'**. Accordingly, it can be surmised that the chiral Pd-complex discriminates between the two enantotopic faces of the activated phenyl group, thus setting the atropisomeric axis.

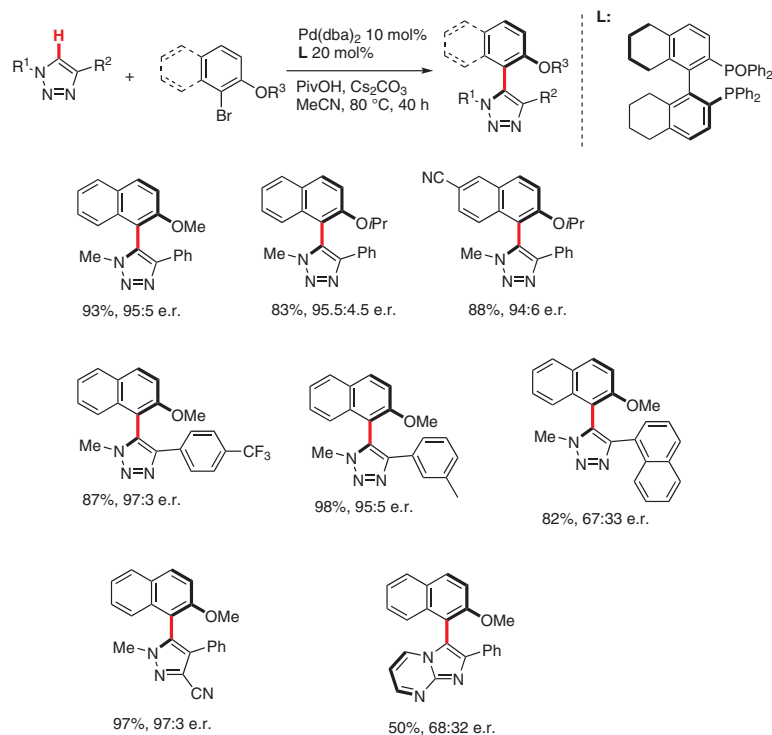


**Scheme 6** Proposed stereomodel for the intramolecular atropoenantioselective arylation

This Pd-catalyzed C–H arylation process illustrates the power of the Taddol-derived ligand in an enantioselective transformation leading to a high level of enantiocontrol as well as excellent yields.

## 5 Atropo-enantioselective Intermolecular Pd-Catalyzed C–H Arylation of Heteroarenes

Following the intramolecular C–H arylation described above, Cramer and Baudoin reported in 2020 the more challenging intermolecular atropoenantioselective C–H arylation of electron-deficient heteroarenes.<sup>20</sup> In their initial study, they focused on the synthesis of Ar-HetAr scaffolds via C–H arylation of 1,2,3-triazole derivatives, which are biologically relevant units recognized as bioisosters and pharmacophores. To achieve a configurational stability of the heterobiaryl axis at 80–100 °C over prolonged reaction times, the coupling between 1-methyl-4-phenyl-1*H*-1,2,3-triazole and 1-bromo-2-methoxy naphthalene, furnishing a product with four *ortho*-substituents around the heterobiaryl axis, was selected (Scheme 7). The racemization barrier of such compounds of approximately 32.4 kcal mol<sup>-1</sup> and a half-life of 1076 years at 25 °C exclude the racemization risk under the reaction conditions. The optimization study revealed that a larger dihedral angle of the ligand induces a higher enantioselectivity and that the use of H<sub>8</sub>-BINAPO with Pd(dba)<sub>2</sub> in the presence of PivOH and Cs<sub>2</sub>CO<sub>3</sub> in acetonitrile was crucial to afford the highly sterically hindered heterobiaryl derivative in excellent yield and atroposelectivity (93% yield, 95:5 e.r.) in 40 hours. Such an optimized catalytic system features excellent reactivity and enantioselectivity with respect to several different bromonaphthalenes with variation of the alkoxy group *ortho* to the stereogenic axis and various substituents at C6 of the naphthalene. Regarding the modification of the aryl substituent of the 1,2,3-triazole, thienyl and 2-naphthyl groups are well tolerated, giving excellent yields and stereoselectiv-

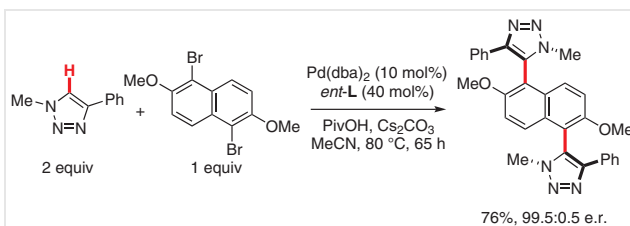


**Scheme 7** Scope of the intermolecular atropoenantioselective C–H arylation of heteroarenes

ities. However, substrates such as sterically hindered *ortho*-tolyl and 1-naphthyl motifs result in lower enantioselectivities. Moreover, aliphatic- and *N*-benzyl substituted triazoles are compatible substrates. Similar results were obtained when changing the triazole ring to related azoles such as pyrazoles bearing an electron-withdrawing group at C3. In contrast, C–H arylation of imidazopyrimidines performed poorly in this catalytic system even at 100 °C in dioxane, indicating that further ligand optimization will be necessary for this reaction.

Recently, compounds with contiguous chiral elements have been recognized as important scaffolds with various topologies and application as chiral ligand, catalysts and optical resolution agents.<sup>15</sup> Following this goal, a double intermolecular C–H arylation of 1,5-dibromo-2,6-dimethoxynaphthalene with 1-methyl-4-phenyl-1*H*-1,2,3-triazole was achieved, affording the triaryl product bearing two stereogenic axes (Scheme 8). Interestingly no *meso*-isomer was observed.

To obtain insight into this novel C–H arylation transformation, mechanistic studies have been performed. First, an intermolecular kinetic isotope effect of 1.8 was measured, and the results suggested that the C–H bond cleavage is the rate-limiting step. The metallation is believed to proceed through a concerted metalation-deprotonation (CMD) mechanism, as supported by the crucial importance of the carboxylic acid co-catalyst on the rate of the reaction but not on the enantioselectivity. Moreover, the reductive elim-



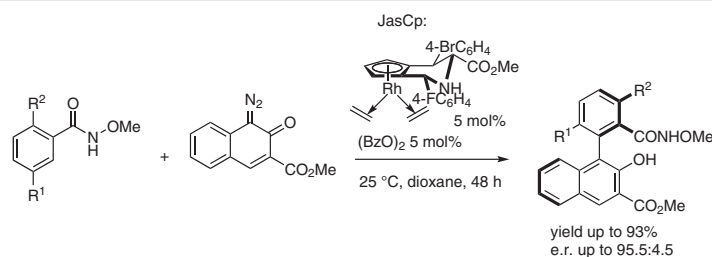
**Scheme 8** Double intermolecular atropoenantioselective C–H arylation of heteroarenes

ination is expected to be the enantiodetermining event because of the strong influence of the dihedral angle of the ligand on the obtained enantioselectivity.

This Pd-catalyzed C–H arylation shows unambiguously the potential of the straightforward approach to obtaining medically relevant aryl-heteroarenes in excellent yields with excellent control of the chiral axis formed in the presence of H<sub>8</sub>-BINAPO.

## 6 Rh-Catalyzed Atropoenantioselective C–H Arylation of Diazonaphthoquinones

An alternative approach towards biaryl synthesis via stereoselective coupling was reported in 2017 by Antonchick and Waldmann.<sup>21</sup> In this specific case a new chiral JasCp-Rh complex allowed direct coupling between *meta*-substituted benzamides and highly reactive diazonaphthoquinones.



**Scheme 9** Atropisomeric tetrasubstituted biaryls by C–H functionalization with diazonaphthoquinones

After the rearomatization step, the biaryl scaffold features two *ortho*-substituents adjacent to the newly generated aryl–aryl linkage, ensuring the configurational stability of the atropisomeric structure (Scheme 9). Such rare tetrasubstituted biaryl scaffolds can be obtained in high yields and enantiomeric ratios, rendering this strategy truly useful. Moreover, further postfunctionalizations can be envisaged because halide substituents are well tolerated.

More recently, a closely related Rh<sup>III</sup>-catalyzed coupling between *N*-phenyl nitron and quinone diazide was disclosed by Li.<sup>22</sup> In this case, however, the atropisomeric biaryls are metastable and undergo intramolecular dearomatic trapping under oxidative conditions, delivering spirocyclic products in high yields and optical purities.

## 7 Conclusion

Over the past decade, the scientific community has witnessed extraordinary advances in asymmetric C–H activation that has enabled the development of efficient strategies to control point chirality, while significantly less attention has been paid to the synthesis of atropisomeric scaffolds. However, over recent years, significant advances have also been achieved in this field, focusing first on the synthesis of atropisomeric molecules via C–H functionalization of biaryls. This short review highlights the breakthroughs in alternative and synthetically more challenging atroposelective C–H arylations. The paucity of reports of this methodology shows unambiguously the difficulties encountered in the stereoselective formation of the atropisomeric axis of chirality during the C–H activation process combining two bulky moieties. Regarding enantioselective methodologies, catalytic systems based on Taddol or H8-BINAPO ligands combined with Pd established themselves as efficient methodologies for such C–H arylation. Nevertheless, atroposelective C–H arylation methodology is still in its infancy and consequently the design of truly versatile, atroposelective syntheses are still required; we hope that this short review article will inspire further progress in this field.

## References

- (a) Siegel, J. S. *Synlett* **2018**, 29, 2120. (b) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. *Chem. Rev.* **2011**, 111, 563. (c) LaPlante, S. R.; Fader, D. L.; Fandrick, K. R.; Fandrick, D. R.; Hucke, O.; Kemper, R.; Miller, S. P. F.; Edwards, P. J. *J. Med. Chem.* **2011**, 54, 7005. (d) Smyth, J. E.; Butler, N. M.; Keller, P. A. *Nat. Prod. Rep.* **2015**, 32, 1562.
- (a) Li, Y.; Kwong, F.; Yu, W.; Chan, A. *Coord. Chem. Rev.* **2007**, 251, 2119. (b) Ohkuma, T.; Kurono, N. In *Privileged Chiral Ligands and Catalysts*; Zhou, Q.-L., Ed.; Wiley-VCH: Weinheim, **2011**, 1–53.
- Rokade, B. V.; Guiry, P. J. *ACS Catal.* **2018**, 8, 624; and references cited therein.
- Wu, Y.-L.; Ferroni, F.; Pieraccini, S.; Schweizer, W. B.; Frank, B. B.; Spada, G. P.; Diederich, F. *Org. Biomol. Chem.* **2012**, 10, 8016.
- (a) Glunz, P. W. *Bioorg. Med. Chem. Lett.* **2018**, 28, 53. (b) Toenjes, S. T.; Gustafson, J. L. *Future Med. Chem.* **2018**, 10, 409.
- For recent reviews on the synthesis of atropisomeric biaryls, see: (a) Kozłowski, M. C.; Morgan, B. J.; Linton, E. C. *Chem. Soc. Rev.* **2009**, 38, 3193. (b) Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem. Int. Ed.* **2005**, 44, 5384. (c) Baudoin, O. *Eur. J. Org. Chem.* **2005**, 4223. (d) Wencel-Delord, J.; Panossian, A.; Leroux, F. R.; Colobert, F. *Chem. Soc. Rev.* **2015**, 44, 3418. (e) Loxq, P.; Manoury, E.; Poli, R.; Deydier, E.; Labande, A. *Coord. Chem. Rev.* **2016**, 308, 131. (f) Zilate, B.; Castrogiovanni, A.; Sparr, C. *ACS Catal.* **2018**, 8, 2981. (g) Wang, Y.-B.; Tan, B. *Acc. Chem. Res.* **2018**, 51, 534. (h) Liao, G.; Zhou, T.; Yao, Q.-J.; Shi, B.-F. *Chem. Commun.* **2019**, 55, 8514.
- (a) Staniland, S.; Yuan, B.; Giménez-Agulló, N.; Marcelli, T.; Willies, S. C.; Grainger, D. M.; Turner, N. J.; Clayden, J. *Chem. Eur. J.* **2014**, 20, 13084; For the pioneering work see the references cited herein. (b) Armstrong, R. J.; Smith, M. D. *Angew. Chem. Int. Ed.* **2014**, 53, 12822. (c) Osako, T.; Uozumi, Y. *Org. Lett.* **2014**, 16, 5866; for other examples of transition metal-catalyzed desymmetrization of C<sub>3</sub>-symmetric achiral biaryls see the references cited herein. (d) Perron, Q.; Alexakis, A. *Adv. Synth. Catal.* **2010**, 352, 2611. (e) For an application towards the synthesis of natural products see: Graff, J.; Debande, T.; Praz, J.; Guénee, L.; Alexakis, A. *Org. Lett.* **2013**, 15, 4270. (f) Mori, K.; Ichikawa, Y.; Kobayashi, M.; Shibata, Y.; Yamanaka, M.; Akiyama, T. *J. Am. Chem. Soc.* **2013**, 135, 3964. (g) Leroux, F. R.; Berthelot, A.; Bonnafoux, L.; Panossian, A.; Colobert, F. *Chem. Eur. J.* **2012**, 18, 14232. (h) Ashizawa, T.; Tanaka, S.; Yamada, T. *Org. Lett.* **2008**, 10, 2521. (i) Aoyagi, N.; Ogawa, N.; Izumi, T. *Tetrahedron Lett.* **2006**, 47, 4797; for the pioneering work, see the references cited therein. (j) Aoyama, H.; Tokunaga, M.; Kiyosu, J.; Iwasawa,



- T.; Obora, Y.; Tsuji, Y. *J. Am. Chem. Soc.* **2005**, *127*, 10474. (k) Ma, G.; Deng, J.; Sibi, M. P. *Angew. Chem. Int. Ed.* **2014**, *53*, 11818. (l) Lu, S.; Poh, S. B.; Zhao, Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 11041. (m) Shirakawa, S.; Wu, X.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 14200. (n) Cheng, D.-J.; Yan, L.; Tian, S.-K.; Wu, M.-Y.; Wang, L.-X.; Fan, Z.-L.; Zheng, S.-C.; Liu, X.-Y.; Tan, B. *Angew. Chem. Int. Ed.* **2014**, *53*, 3684. (o) Latorre, A.; Urbano, A.; Carreño, M. C. *Chem. Commun.* **2009**, 6652. (p) Gustafson, J. L.; Lim, D.; Miller, S. J. *Science* **2010**, *328*, 1251. (q) Ros, A.; Estepa, B.; Rom rez-L pez, P.;  lvarez, E.; Fern ndez, R.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2013**, *135*, 15730. (r) Bhat, V.; Wang, S.; Stoltz, B. M.; Virgil, S. C. *J. Am. Chem. Soc.* **2013**, *135*, 16829. (s) Clayden, J.; Fletcher, S. P.; McDouall, J. W.; Rowbottom, S. J. M. *J. Am. Chem. Soc.* **2009**, *131*, 5331. (t) Li, B.; Chao, Z.; Li, C.; Gu, Z. *J. Am. Chem. Soc.* **2018**, *140*, 9400. (u) Duan, L.; Zhao, Z.; Wang, F.-L.; Zhang, Z.; Gu, Z. *ACS Catal.* **2019**, *9*, 98532. (v) Zhao, K.; Li, N.; Yu, J.; Gong, L.-Z.; Gu, Z. *Angew. Chem. Int. Ed.* **2020**, *59*, 19899; and references cited therein.
- (8) (a) Guo, F.; Konkol, L. C.; Thomson, R. J. *J. Am. Chem. Soc.* **2011**, *133*, 18. (b) Quinonero, O.; Jean, M.; Vanthuyne, N.; Roussel, C.; Bonne, D.; Constancieux, T.; Bressy, C.; Bugault, X.; Rodriguez, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 1401. (c) Link, A.; Sparr, C. *Angew. Chem. Int. Ed.* **2018**, *57*, 7136. (d) Nguyen, T. T. *Org. Biomol. Chem.* **2019**, *17*, 6952.
- (9) For selected examples see: (a) Shibata, T.; Fujimoto, T.; Yokota, K.; Takagi, K. *J. Am. Chem. Soc.* **2004**, *126*, 8382. (b) Gutnov, A.; Heller, B.; Fisher, C.; Drexler, H.-J.; Spannenberg, A.; Sundermann, B.; Sundermann, C. *Angew. Chem. Int. Ed.* **2004**, *43*, 3795. (c) Nishida, G.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 3951. (d) Link, A.; Sparr, C. *Angew. Chem. Int. Ed.* **2014**, *53*, 5458.
- (10) Zhang, D.; Wang, Q. *Coord. Chem. Rev.* **2015**, *286*, 1.
- (11) For selected examples see: (a) Kakiuchi, F.; Le Gendre, P.; Yamada, A.; Ohtaki, H.; Murai, S. *Tetrahedron: Asymmetry* **2000**, *11*, 2647. (b) Hazra, C. K.; Dherbassy, Q.; Wencel-Delord, J.; Colobert, F. *Angew. Chem. Int. Ed.* **2014**, *53*, 13871. For early work, see: (c) Wesch, T.; Leroux, F.; Colobert, F. *Adv. Synth. Catal.* **2013**, *355*, 2139. (d) Zheng, J.; You, S.-L. *Angew. Chem. Int. Ed.* **2014**, *53*, 13244. (e) Ma, Y.-N.; Zhang, H.-Y.; Yang, S.-D. *Org. Lett.* **2015**, *17*, 2034. (f) Zheng, J.; Cui, W.-J.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2016**, *138*, 5242. (g) Gao, D.-W.; Gu, Q.; You, S.-L. *ACS Catal.* **2014**, *4*, 2741. (h) Dherbassy, Q.; Schwertz, G.; Chess , M.; Hazra, C. K.; Wencel-Delord, J.; Colobert, F. *Chem. Eur. J.* **2016**, *22*, 1735. (i) Dherbassy, Q.; Wencel-Delord, J.; Colobert, F. *Tetrahedron* **2016**, *72*, 5238. (j) Li, S.-X.; Ma, Y.-N.; Yang, S.-D. *Org. Lett.* **2017**, *19*, 1842. (k) Yao, Q.-J.; Zhang, S.; Zhan, B.-B.; Shi, B.-F. *Angew. Chem. Int. Ed.* **2017**, *56*, 6617. (l) Liao, G.; Yao, Q.-J.; Zhang, Z.-Z.; Wu, Y.-J.; Huang, D.-Y.; Shi, B.-F. *Angew. Chem. Int. Ed.* **2018**, *57*, 3661. (m) Liao, G.; Zhou, T.; Yao, Q.-J.; Shi, B.-F. *Chem. Commun.* **2019**, 55, 8514. (n) Wang, Q.; Cai, Z.-J.; Liu, C.-X.; Gu, Q.; You, S.-L. *J. Am. Chem. Soc.* **2019**, *141*, 9504.
- (12) (a) For selected examples see: Cammidge, A. N.; Cr py, K. V. L. *Chem. Commun.* **2000**, 1723. (b) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051. (c) Wang, S.; Li, J.; Miao, T.; Wu, W.; Li, Q.; Zhuang, Y.; Zhou, Z.; Qiu, L.-Q. *Org. Lett.* **2012**, *14*, 1966. (d) Zhou, Y.; Wang, S.; Wu, W.; Li, Q.; He, Y.; Zhuang, Y.; Li, L.; Pang, J.; Zhou, Z.; Qiu, L.-Q. *Org. Lett.* **2013**, *15*, 5508. (e) Tang, W.; Patel, N. D.; Xu, G.; Xu, X.; Savoie, J.; Ma, S.; Hao, M.-H.; Keshipeddy, S.; Capacci, A. G.; Wei, X.; Zhang, Y.; Gao, J. J.; Li, W.; Rodriguez, S.; Lu, B. Z.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2012**, *14*, 2258. (f) Shen, X.; Jones, G. O.; Watson, D. A.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 11278. (g) Bermejo, A.; Ros, A.; Fern ndez, R.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 15798. (h) Zhang, S.-S.; Wang, Z.-Q.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2010**, *12*, 5546. (i) Genov, M.; Almor n, A.; Espinet, P. *Chem. Eur. J.* **2006**, *12*, 9346. (j) Yamamoto, T.; Akai, Y.; Nagata, Y.; Suginome, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 8844. (k) Uozumi, Y.; Matsuura, Y.; Arakawa, T.; Yamada, Y. M. A. *Angew. Chem. Int. Ed.* **2009**, *48*, 2708. (l) Xu, G.; Fu, W.; Liu, G.; Senanayake, C. H.; Tang, W. *J. Am. Chem. Soc.* **2014**, *136*, 570. (m) Zhou, Y.; Zhang, X.; Liang, H.; Cao, Z.; Zhao, X.; He, Y.; Wang, S.; Pang, J.; Zhou, Z.; Ke, Z.; Qiu, L.-Q. *ACS Catal.* **2014**, *4*, 1390. (n) Patel, N. D.; Sieber, J. D.; Tcyrulnikov, S.; Simmons, B. J.; Rivalti, D.; Duvvuri, K.; Zhang, Y.; Gao, D. A.; Fandrick, K. R.; Haddad, N.; Lao, K. S.; Mangunuru, H. P. R.; Biswas, S.; Qu, B.; Grinberg, N.; Pennino, S.; Lee, H.; Song, J. J.; Gupton, B. F.; Garg, N. K.; Kozlowski, M. C.; Senanayake, C. H. *ACS Catal.* **2018**, *8*, 10190. (o) Shen, D.; Xu, Y.; Shi, S. *J. Am. Chem. Soc.* **2019**, *141*, 14938.
- (13) Yamaguchi, K.; Yamaguchi, J.; Studer, A.; Itami, K. *Chem. Sci.* **2012**, *3*, 2165.
- (14) Yamaguchi, K.; Kondo, H.; Yamaguchi, J.; Itami, K. *Chem. Sci.* **2013**, *4*, 3753.
- (15) Bao, X.; Rodriguez, J.; Bonne, D. *Angew. Chem. Int. Ed.* **2020**, *59*, 12623.
- (16) Wencel-Delord, J.; Colobert, F. *Synlett* **2015**, 26, 2644.
- (17) Dherbassy, Q.; Djukic, J.-P.; Wencel-Delord, J.; Colobert, F. *Angew. Chem. Int. Ed.* **2018**, *57*, 4668.
- (18) Newton, C. G.; Braconi, E.; Kuziola, J.; Wodrich, M. D.; Cramer, N. *Angew. Chem. Int. Ed.* **2018**, *57*, 11040.
- (19) Junior, F. J. B.; Scotti, L.; Ishiki, H.; Botelho, S. P. S.; Da Silva, M. S.; Scotti, M. T. *Mini-Rev. Med. Chem.* **2015**, *15*, 630.
- (20) Nguyen, Q.-H.; Guo, S.-M.; Royal, T.; Baudoin, O.; Cramer, N. *J. Am. Chem. Soc.* **2020**, *142*, 2161.
- (21) Jia, Z.-J.; Merten, C.; Gontla, R.; Daniliuc, C. G.; Antonchick, A. P.; Waldmann, H. *Angew. Chem. Int. Ed.* **2017**, *56*, 2429.
- (22) Kong, L.; Han, X.; Liu, S.; Zou, Y.; Lan, Y.; Li, X. *Angew. Chem. Int. Ed.* **2020**, *59*, 7188.