Organic Syntheses

Discussion Addendum for:

Preparation of (*S*)-*tert*-ButylPHOX and (*S*)-2-Allyl-2-Methylcyclohexanone

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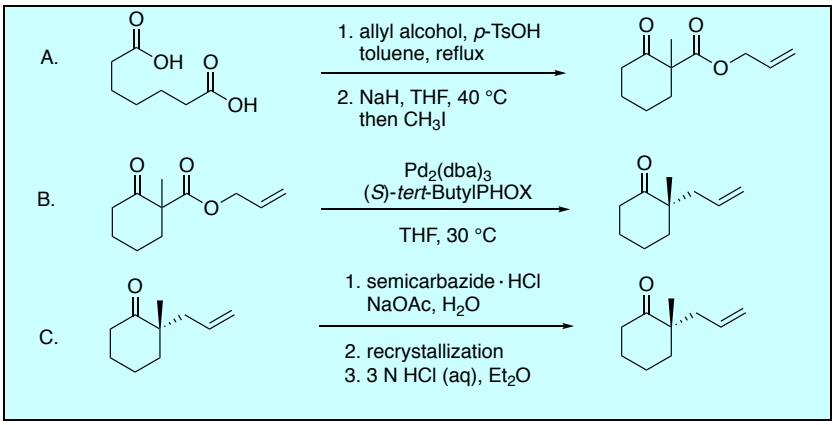
Original Articles: Krout, M. R.; Mohr, J. T.; Stoltz, B. M. Org. Synth. **2009**, *86*, *181–193; Krout, M. R.; Mohr, J. T.; Stoltz, B. M. Org. Synth.* **2009**, *86*, *194–211*.



Phosphinooxazoline (PHOX) ligands, originally developed by Pfaltz, Helmchen, and Williams,[2-4] comprise a privileged class of P,N type ligands with extensive applications in various transition-metal catalyzed processes, including allylic alkylations, Heck-type reactions, and catalytic hydrogenation.[5,6] The PHOX ligand class is highly modular and has grown to encompass numerous structural variations, of which only a few major classes are shown in Figure 1. Every component of the ligand scaffold is modifiable as exemplified by R^1 variations on the oxazoline ring (**1**, **2**), substitution of the aryl rings with perfluoroalkyl groups (**2**) or ferrocenyl

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systems (**3**), and various alkyl and spirocyclic[7] linkers joining the oxazoline ring to the phosphine backbone (**4a-b**).[6]

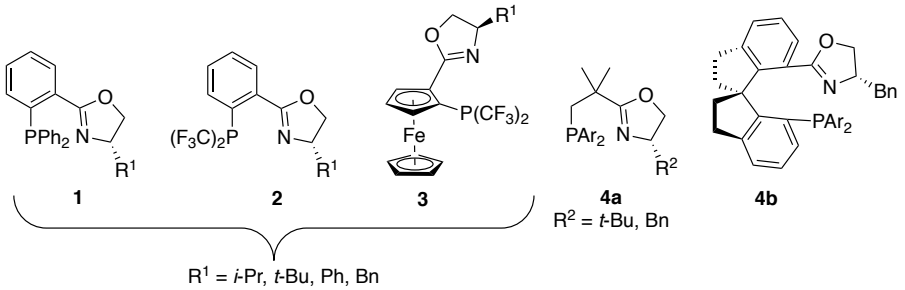


Figure 1. Phosphinooxazoline (PHOX) ligands are highly modular

The substituted tri-aryl PHOX ligands **1** are of particular interest to our laboratory. Since our 2009 *Organic Syntheses* articles, which described an optimized route to the valuable PHOX ligand (*S*)-*t*-BuPHOX **1a** and its use in a Pd-catalyzed decarboxylative allylic alkylation reaction toward the synthesis of (*S*)-2-allyl-2-methylcyclohexanone,[8,9] electronic and steric modifications to the scaffold of **1a** have found increasing traction in the literature.[10-12] In particular, electron-deficient counterparts such as (*S*)-$(CF_3)_3$-*t*-BuPHOX (**5**), (*S*)-$(CF_3)_4$-*t*-BuPHOX (**6**), and (*S*)-$(CF_3)_4$(F)-*t*-BuPHOX (**7**), which contain trifluoromethyl groups at strategic positions on the aryl rings, have been uniquely effective and in many cases superior to **1a** in various highly enantioselective metal-catalyzed reactions.[13,14] These ligands may be synthesized through modified procedures based on our original *Organic Syntheses* article.[8,10,13] This Discussion Addendum highlights recent

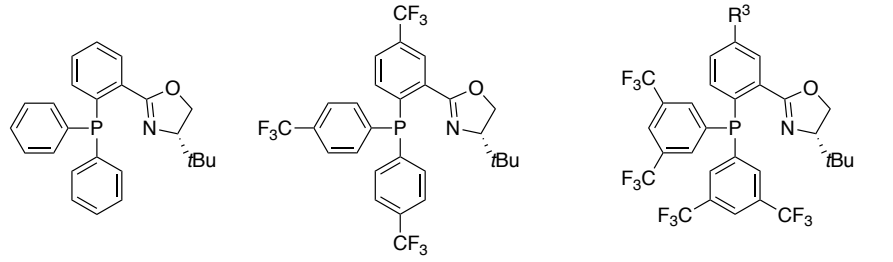
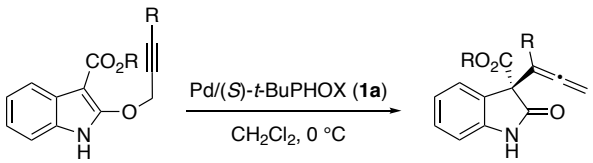


Figure 2. Electron-deficient variants of (*S*)-*t*-BuPHOX PHOX Ligands in Reaction Development

applications of **1a** and its electron-deficient variants **5-7** in total synthesis and reaction development, with an emphasis on decarboxylative asymmetric allylic alkylation reactions.

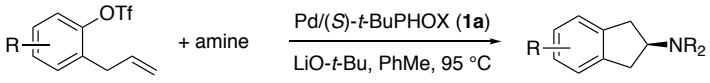
Aside from their common use in various asymmetric allylic allylation-type reactions,[15,16,17] PHOX ligands **1a** and **5-7** have recently been utilized in diverse transformations including sigmatropic rearrangements,[18] hydroarylation reactions,[19] carboaminations,[20] asymmetric alkylations and protonations,[21,22] and cascade reactions.[23] The chemical motifs produced by these PHOX-catalyzed reactions are often found in biologically active small molecules and can also serve as synthetically valuable intermediates. For instance in 2012, Kozlowski presented a rare example of a catalytic enantioselective Saucy-Marbet Claisen rearrangement using **1a** to effect the transformation of propargyl ethers **8** into allenyl oxindoles **9** (Scheme 1).[18] However, **1a** was effective only for a subset of aryl-substituted alkyne substrates.



8 **9**

Scheme 1. Synthesis of quaternary allenyl indoles using an enantioselective Saucy-Marbet Claisen rearrangement

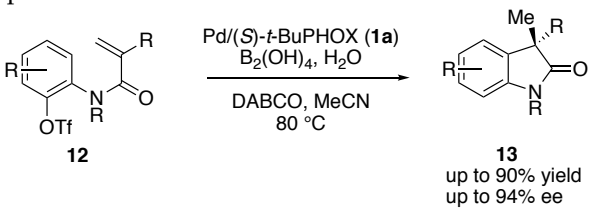
Later in 2015, **1a** was also utilized by Wolfe in a Pd-catalyzed alkene carboamination reaction involving allylphenyltriflates **10** and aliphatic amines to generate chiral aminoindanes **11**, a motif that appears in a variety of pharmacologically active molecules (Scheme 2).[20] Interestingly, the crucial aminopalladation step consists of an intermolecular reaction.



10 **11**
up to 98% ee
up to 98% yield

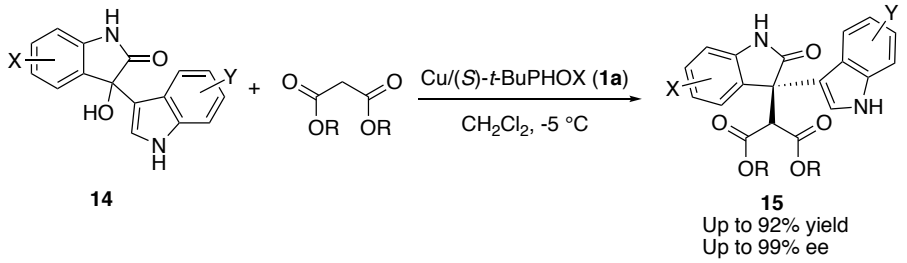
Scheme 2. Synthesis of aminoindanes via alkene carboamination

In 2017, Zhu used **1a** and a stoichiometric amount of tetrahydroxy diboron-water as the hydride donor to effect an asymmetric intramolecular reductive Heck reaction of *N*-aryl acrylamides **12** to give 3,3-disubstituted oxindoles **13** (Scheme 3).[19] Notably, the choice of ligand affected the reaction pathway: whereas PPh_3 led to carboboration products, **1a** gave the desired hydroarylation product **13**.



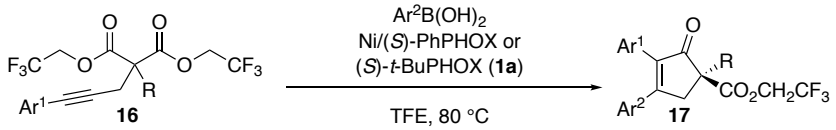
Scheme 3. Synthesis of quaternary oxindoles via asymmetric intramolecular reductive Heck reaction

Recently, in an elegant extension of our work on asymmetric alkylation of 3-halooxindoles,[24] Bisai and co-workers disclosed the use of a Cu-**1a** catalyst to effect malonate addition onto 3-hydroxy 3-indolyl-2-oxindoles **14** (Scheme 4).[21] It is thought that the copper catalyst facilitates a stereoablative elimination of water, followed by asymmetric addition of the malonate.



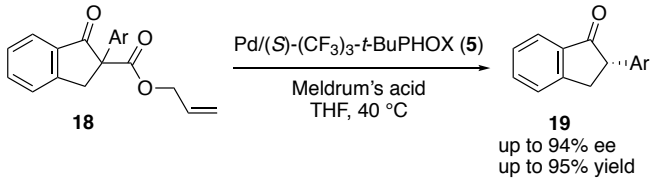
Scheme 4. Synthesis of quaternary dimeric oxindoles by malonate addition onto 3-hydroxy-2-oxindoles

Lam discovered that a Nickel-PHOX catalyst comprised of **1a** or (*S*)-PhPHOX effectively catalyzed the coupling of alkynyl malonate esters **16** with arylboronic esters in a desymmetrizing arylative cyclization (Scheme 5).[23] The resulting cyclopentenone products **17** contain a synthetically challenging fully substituted olefin and a chiral quaternary center.



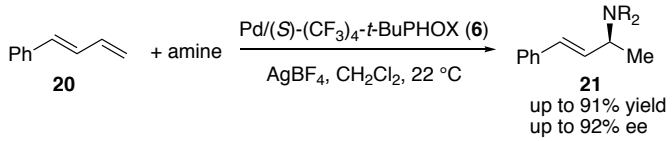
Scheme 5. Synthesis of chiral cyclopentenones via nickel-catalyzed desymmetrization of alkynyl malonate esters with arylboronic acids

With regard to allylic alkylation-type reactions, **1a** and its electron deficient counterparts **5-7** have found extensive applications: After our initial reports on asymmetric decarboxylative protonation,[25,26] the Guiry group has continued to expand the scope and understanding of this reaction. In one example in 2017, they utilized (*S*)-$(CF_3)_3$-*t*-BuPHOX (**5**) to enable the enantioselective synthesis of tertiary α-arylated indanones **19** (Scheme 6).[27]



Scheme 6. Synthesis of chiral tertiary α-aryl indanones using decarboxylative protonation

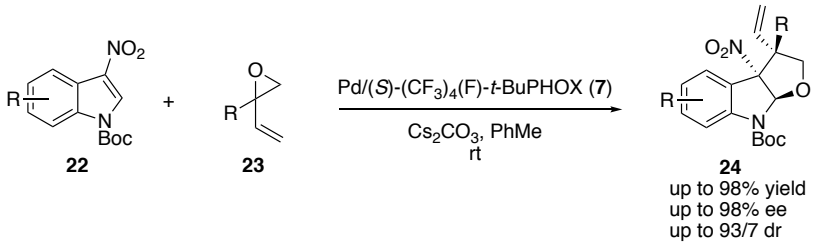
In 2017, Malcolmson introduced a method to synthesize chiral allylic amines **21** through the intermolecular addition of aliphatic amines to acyclic 1,3-dienes **20** (Scheme 7).[15] Here, the electron deficient PHOX ligand **6** was critical in achieving high regioselectivity for the desired 1,2-hydroamination product.



Scheme 7. Synthesis of allylic amines via diene hydroamination

Recently, You employed a Pd-**7** catalyst in a dearomative formal [3+2] cycloaddition of nitroindoles **22** and epoxybutenes **23** to synthesize chiral quaternary tetrahydrofuroindoles **24** (Scheme 8).[14] Notably, the

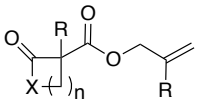
diastereoselectivity of this reaction was affected by the choice of solvent, with toluene and acetonitrile providing differing diastereomers.

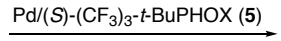


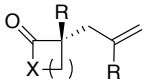
Scheme 8. Synthesis of tetrahydrofuroindoles via dearomative formal [3+2] cycloaddition of nitroindoles and epoxybutenes

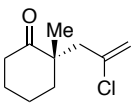
Along with the Trost laboratory and others, our group has pioneered the development of transition metal-catalyzed decarboxylative asymmetric allylic alkylation reactions to generate quaternary stereocenter-containing compounds. Following our initial efforts on cycloalkanone systems using (*S*)-*t*-BuPHOX,[28,29] we have extended the reaction to a wide range of cyclic substrates important in pharmaceuticals and natural product synthesis (Table 1).[30–35] This versatile methodology now enables the synthesis of chiral disubstituted carbocycles of ring size four to eight, "Mannich" adducts, and heterocycles. Especially in the case of lactam systems **29**-**36**, the electron deficient ligand **5** was hypothesized to generate a more reactive palladium catalyst and was required to achieve high levels of asymmetry.

Table 1. Chiral α-disubstituted carbocycles and lactams accessible by decarboxylative allylic alkylation

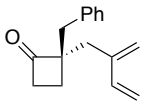




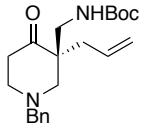




25[a]
reference 26, 27



26
reference 28



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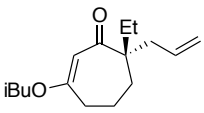
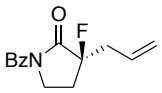
reference 29



28[a]
reference 30



29
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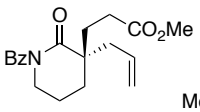

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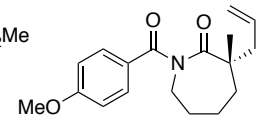

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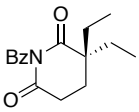
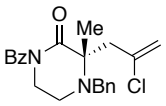


32
reference 31



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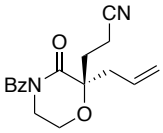
reference 33



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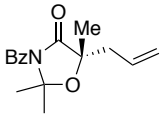
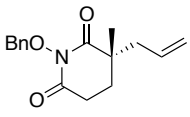
reference 32



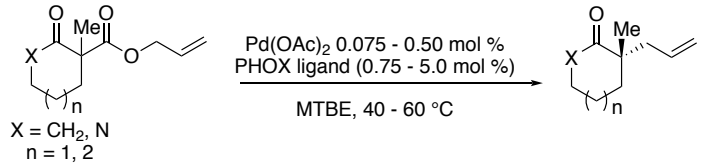
35
reference 32



36
reference 31

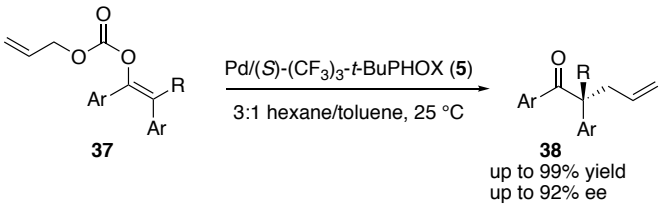
[a](*S*)-*t*-BuPHOX (**1a**) instead of (*S*)-(CF$_3$)$_3$-*t*-BuPHOX (**5**)

Furthermore, in an effort to reduce catalyst loadings to facilitate industrial scale applications, we developed a low-catalyst loading method employing $Pd(OAc)_2$ instead of the usual zero-valent palladium source (Scheme 9).[36] With this protocol, catalyst loadings as low as 0.075 mol %, corresponding with turnover numbers (TON) of up to 1320, could be used while still providing yields and ee's up to 99%.



Scheme 9. Low-palladium loading protocol for decarboxylative allylic alkylation

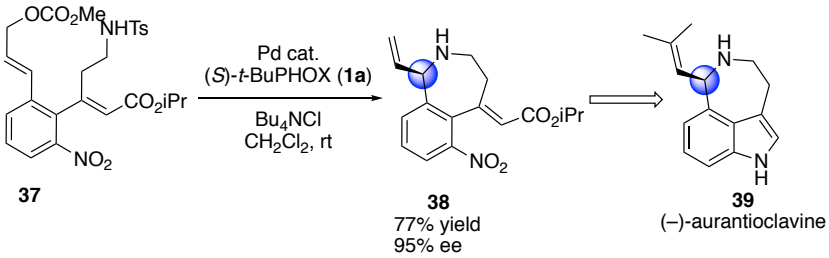
Most recently in 2018, we extended the scope of decarboxylative allylic alkylation toward challenging acyclic substrates by reporting the first asymmetric decarboxylative alkylation of fully substituted acyclic enol carbonates to provide linear α-quaternary ketones **38**, again employing electronic deficient PHOX ligand **5** (Scheme 10).[37,38] Of particular interest, the same enantiomer of product was obtained with comparably high *ee* regardless of the E/Z ratio of the starting material, suggesting a possible dynamic kinetic enolate equilibration during the reaction.



Scheme 10. Synthesis of acyclic α-quaternary ketones using decarboxylative alkylation

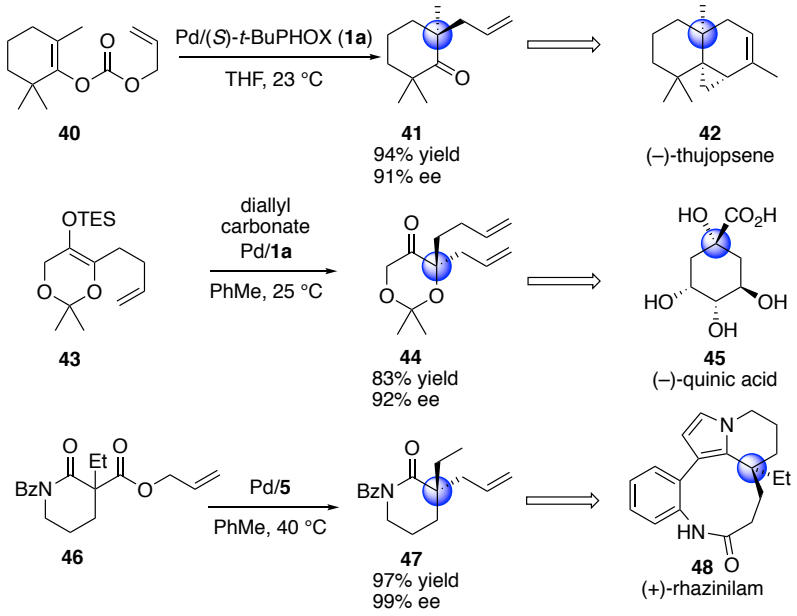
PHOX ligands in Natural Product Synthesis

As a testament to the versatility of allylic alkylation-type reactions, recent total syntheses that utilize PHOX ligands do so heavily in the context of transition-metal catalyzed allylic alkylations and protonations. For instance, in Takemoto's 2014 synthesis of the tricyclic alkaloid (–)-aurantioclavine (**39**), **1a** was used in an intramolecular allylic amination of allyl carbonate **37** to generate an unusual seven-membered azepane **38** (Scheme 11).[39]



Scheme 11. Total synthesis of (–)-aurantioclavine via allylic amination

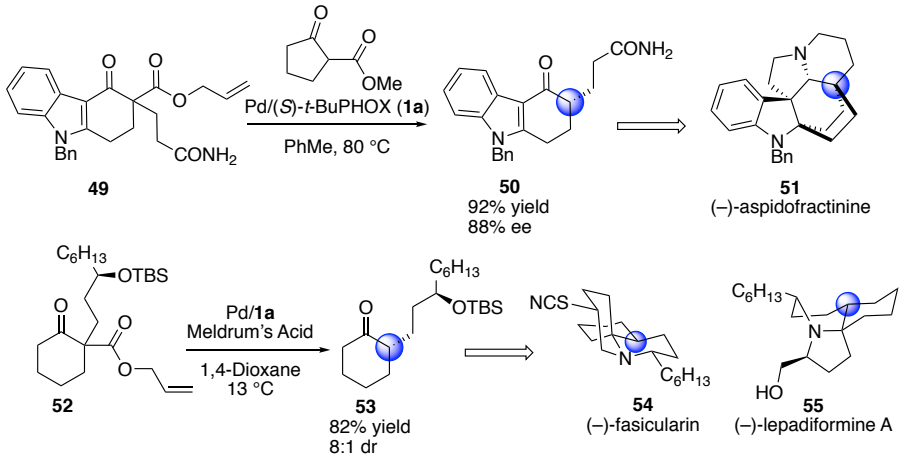
Similarly, in 2012 and 2014, we used a series of powerful allylic alkylations to intercept chiral *gem*-disubstituted cyclic intermediates **41**, **44**, and **47** en route to the formal syntheses of seven natural products including (–)-thujopsene (**42**), (–)-quinic acid (**45**), and (+)-rhazinilam (**48**) (Scheme 12).[33,40]



Scheme 12. Formal syntheses of diverse natural products via allylic alkylation

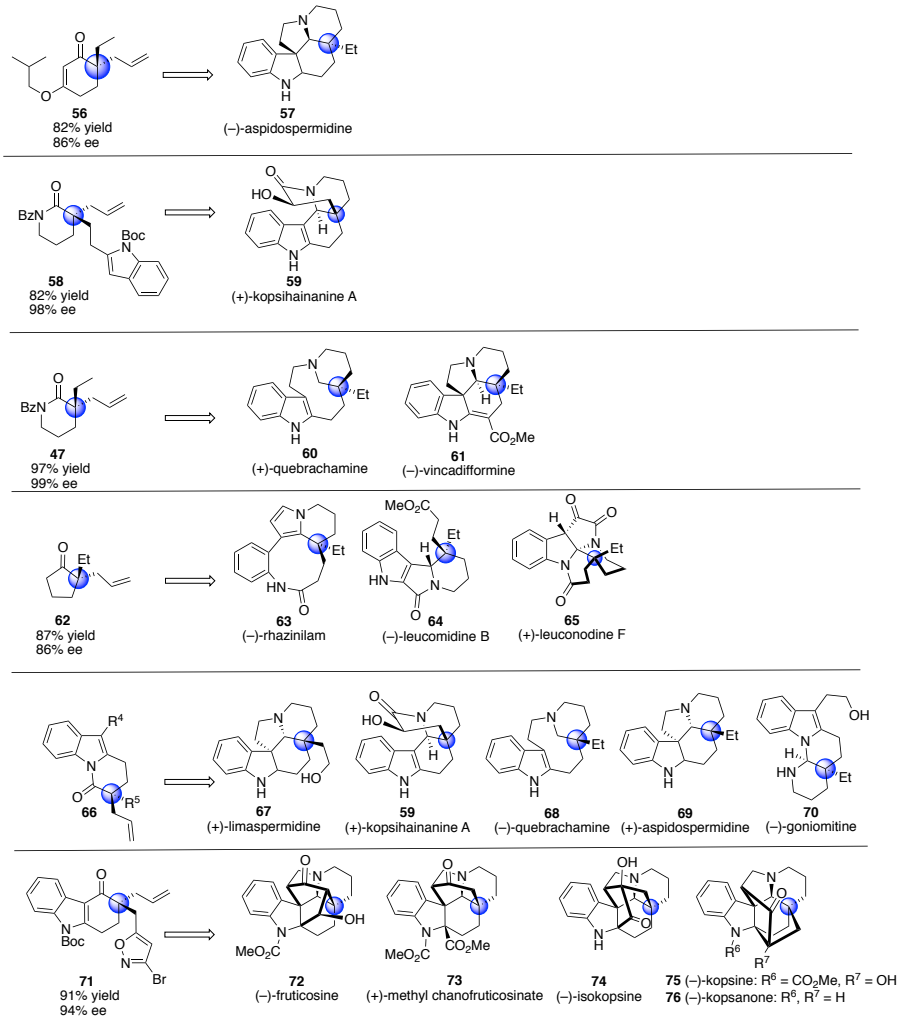
Decarboxylative protonation has also found utility in natural product synthesis. In route to a 2014 catalytic enantioselective formal synthesis of

the hexacyclic caged indole alkaloid (–)-aspidofractinine (**51**), Shao used **1a** in an enantioselective decarboxylative protonation reaction to forge C3-monosubstitutions on medicinally important carbazolone heterocycles **50** (Scheme 13).[41] Later in 2017, Robinson and co-workers also used **1a** in a decarboxylative protonation protocol to make α-substituted ketone **53**, which was then divergently advanced toward the spirocyclic marine alkaloids (–)-fasicularin (**54**) and (–)-lepadiformine (**55**).[42]



Scheme 13. Total syntheses of (–)-aspidofractinine, (–)-lepadiformine, and (–)-fasicularin using decarboxylative protonation

Most of the remaining recent examples of PHOX ligands **1a** and **5**-**7** in total synthesis have been found in the context of decarboxylative allylic alkylation toward the synthesis of indole alkaloid natural products (Scheme 14).[43] For example, vinylogous ether **56**, prepared from a (*S*)-*t*-BuPHOX (**1a**)-catalyzed allylic alkylation, can be advanced to (–)-aspidospermidine (**57**) in a formal total synthesis.[40] Similarly, the familiar *gem*-disubstituted lactam **47** serves as an intermediate in the formal syntheses of (+)-quebrachamine (**60**) and (–)-vincadifformine (**61**).[40] In 2014, Mukai synthesized the pentacyclic indole (+)-kopsihainanine A (**59**) utilizing (*S*)-$(CF_3)_3$-*t*-BuPHOX (**5**) in a decarboxylative alkylation to generate lactam intermediate **58**.[44] Notably, (+)-kopsihainanine A was previously independently synthesized by both Shao and Lupton in 2013, who also also utilized decarboxylative alkylation to synthesize a structurally distinct carbazolone intermediate.[45,46] In 2016,

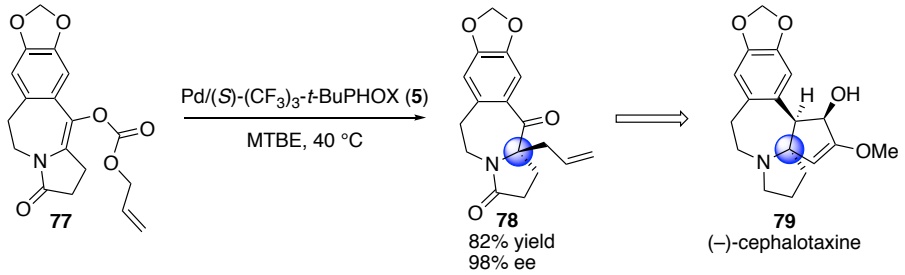


Scheme 14. Decarboxylative allylic alkylation in the total synthesis of indole alkaloid natural products

Zhu accomplished the syntheses of indole alkaloids (–)-rhazinilam (**63**), (–)-leucomidine B (**64**), and (+)-leuconodine F (**65**) via a divergent route from quaternary cyclopentanone **62**, which was synthesized via allylic alkylation using ligand **1a**.[47] Ligand **5** was again utilized to obtain the dihydropyrido[1,2-a]indolone (DHPI) scaffold **66**, which was crucial in our 2016 and 2017 total and formal syntheses of five indole alkaloids, (+)-

limaspermidine (**67**), (+)-kopsihainanine (**59**), (–)-quebrachamine (**68**), (+)-aspidospermidine (**69**), and (-)-goniomitine (**70**).[48,49] Most recently, Qin in 2017 leveraged ligand **1a** to synthesize the quaternary indole **71**, paving the way to a divergent synthesis of five *Kopsia* indole alkaloids: (–)-fruticosine (**72**), (+)-methyl chanofruticosinate (**73**), (–)-isokopsine (**74**), (–)-kopsine (**75**), and (–)-kopsanone (**76**).[50]

Finally, in 2018 Li and co-workers reported an asymmetric synthesis of the pentacyclic anti-tumor alkaloid (–)-cephalotaxine (**79**) using decarboxylative alkylation on allyl enol carbonate precursor **77**.[51] Here, they utilized ligand **5** to attain **78** with high enantioselectivity; in contrast, (*S*)-*t*-BuPHOX (**1a**) provided the desired product in only 80% ee.



Scheme 15. Total synthesis of (–)-cephalotaxine

These aforementioned natural product syntheses highlight the impressive synthetic versatility of enantioselective allylic alkylation reactions facilitated by PHOX ligands. Especially in the cases of indole alkaloid syntheses, decarboxylative alkylation was used to synthesize a range of structurally diverse quaternary stereocenter-bearing intermediates, which were advanced toward the desired natural products. Additionally, electron-deficient variants of (*S*)-*t*-BuPHOX (**1a**) such as (*S*)-(CF$_3$)$_3$-*t*-BuPHOX (**5**) have demonstrated superior efficacy in many instances, and are likely to find even wider use in the future, especially toward the synthesis of novel all-carbon quaternary stereocenter-bearing scaffolds using decarboxylative asymmetric allylic alkylation methodologies. The PHOX ligand class has shown extensive versatility in various transition-metal catalyzed asymmetric transformations, thus enabling access to novel and biologically important chemical space. Their modular nature ensures the continual development of new electronically and sterically modified versions with even greater catalytic potential.

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