OL Organic Letters

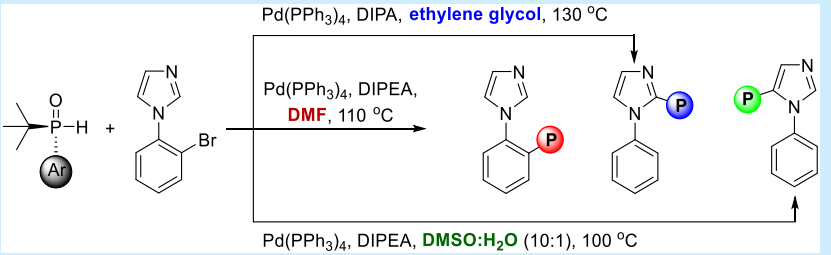
pubs.acs.org/OrgLett Letter

Solvent-Switchable Remote C−H Activation via 1,4-Palladium Migration Enables Site-Selective C−P Bond Formation: A Tool for the Synthesis of *P*-Chiral Phosphinyl Imidazoles

Ifenna I. Mbaezue, Shi-Guang Li, Angula C. S. Reddy, Hatem M. Titi, and Youla S. Tsantrizos*

Cite This: *Org. Lett.* 2024, 26, 4200−4204 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: Solvent-switchable and site-selective phosphorylation of imidazoles at the C2 or C5 position of the imidazole ring was achieved via 1,4-palladium migration. *P*-Chiral *tert*-butyl(aryl)phosphine oxides were cross-coupled to 1-(2-bromophenyl)-1*H*-imidazoles with high enantiospecificity, thereby leading to a novel class of chiral imidazole-based phosphine oxides. As proof of concept, reduction of an analogue yielded the corresponding *P*-chiral 2-phosphinyl imidazole ligand, which was shown to induce high enantioselectivity in the formation of axially chiral molecules synthesized via Pd-catalyzed Suzuki−Miyaura cross-coupling.

In 2001, Grotjahn et al. first reported the 2-phosphinyl imidazole ligands and demonstrated that they can form Ru complexes capable of catalyzing the anti-Markovnikov hydration of terminal alkynes.[1] In addition to their monodentate properties, these hemilabile ligands can engage in bidentate η^2-*P*,*N*-chelation of metals through the formation of four-membered metallacycles.[2] Soon after, Beller et al. reported applications of various 2-phosphinyl imidazoles (Figure 1; **L1a-h**) in complexes with metals and their use in several reactions, including Buchwald−Hartwig amination and Suzuki−Miyaura cross-coupling (Pd-**L1a,b**),[3a] Sonogashira cross-coupling (Pd-**L1c**),[3b] hydroxylation of aryl halides (Pd-**L1c,d**),[3c] carbonylative Heck cross-coupling (Pd-L**1d**),[3d] hydroformylation of olefins (Os-**1f**, Ru-**L1e−h**, Ru-**L2**),[3e−g] and more recently, the methylation of nitroarenes with methanol (Pd-**L3**).[3h] Baudoin et al. has also reported the Pd-catalyzed Barbier−Negishi coupling of secondary alkyl bromides with aryl and alkenyl triflates, as well as nonaflates with limited isomerization of the alkylpalladium complex (Pd-**L1i**).[4]

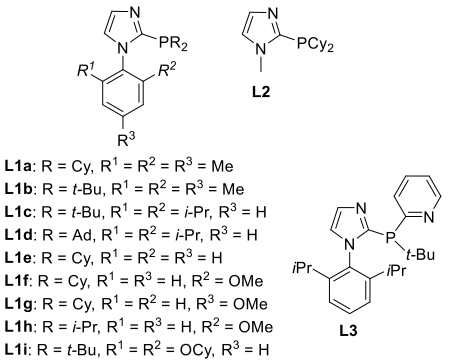


Figure 1. Representative examples of 2-phosphinyl imidazoles in catalysis.

Despite the achievements highlighted above, the synthesis and applications of *P*-chiral phosphinyl imidazolyl ligands have not been reported. Traditionally, 2-phosphinyl imidazoles are synthesized by quenching C2-metalated imidazoles with the requisite chlorophosphines,[1,5] which requires the handling of highly sensitive reagents. Furthermore, the configurational instability of chlorophosphines[6] precludes the synthesis of *P*-chiral analogues via this approach. We reasoned that stereoretentive reduction of chiral imidazole-based phosphine oxides could circumvent these challenges and afford *P*-chiral phosphinyl imidazoles.

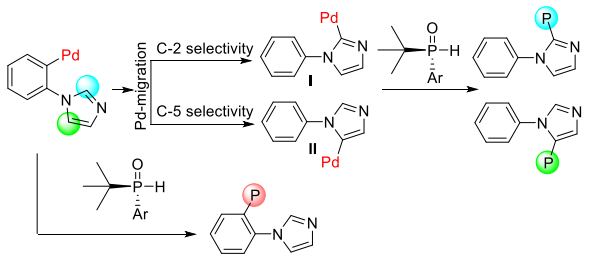
Over the past two decades, 1,4-palladium migration has emerged as a powerful strategy for the construction of C−C,[7]

Received: March 11, 2024
Revised: May 7, 2024
Accepted: May 9, 2024
Published: May 13, 2024

https://doi.org/10.1021/acs.orglett.4c00903
Org. Lett. 2024, 26, 4200−4204

C–N,[7] C–O,[8] C–B,[9] C–Si,[10] and very recently, C–P[11a] bonds. We envisioned that the remote C(sp^2)–H activation of imidazoles via 1,4-palladium migration could furnish palladated intermediates of various substitution patterns (Scheme 1; intermediates **I** and/or **II**). The subsequent coupling of these intermediates with *P*-chiral secondary phosphine oxides (SPOs), could furnish tertiary phosphine oxides (TPOs) that could serve as precursors to *P*-chiral phosphinyl imidazoles. It is noteworthy that in addition to metal-catalyzed 1,4-migration, other strategies, such as dehydrogenative cross-coupling, have been utilized in C–P bond construction.[11b] Herein, we report the first solvent-switchable and site-selective *P*-chiral phosphorylation of imidazoles via 1,4-palladium migration. Additionally, we provide an example of the utility of this methodology toward the synthesis of a novel *P*-chiral phosphinyl imidazole ligand and its subsequent use in an asymmetric catalytic transformation.

Scheme 1. Proposed Strategy toward the Installation of *P*-Chiral SPOs on Imidazoles

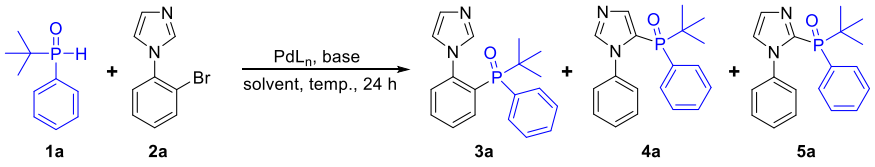


We reasoned that a thorough exploration of reaction conditions could reveal parameters that could favor palladium migration selectively to either the C2 or the C5 position of the imidazole moiety. We began by investigating the effects of various catalysts, solvents, bases, and temperatures on the coupling of the racemic secondary SPO **1a** with imidazole **2a** (Table 1; refer to the Supporting Information for more details). Cross-coupling catalyzed by $Pd(PPh_3)_4$ in the presence of *N*,*N*-diisopropylethylamine (DIPEA) at 110 °C in DMF, led predominantly to the direct cross coupling with the phenyl moiety, which led to a ratio of the products **3a**/**4a**/**5a** of 90:9:1, as estimated by ^{31}P NMR (Table 1; entry 1). However, replacement of DMF with DMSO as the solvent led to a decrease in the formation of **3a** and an increase in the formation of the C5-coupled product **4a**, presumably via 1,4-palladium migration (entry 2). Changing the catalyst to $Pd(OAc)_2/PPh_3$ did not make a significant difference in improving the selectivity for **4a** (entry 3), whereas reactions in a mixture of DMSO/H_2O (in variable ratios) and slightly lower temperatures led to more appreciable selectivity for the formation of **4a** (entries 4–7). Decreasing the content of water in the solvent (from 1:1 to 10:1 DMSO/H_2O) seemed to further favor the formation of **4a** (entries 4 vs 5). Interestingly, simple alcohols reversed the selectivity to the direct cross-coupling at the phenyl moiety (Table S1), whereas replacement of DMSO/H_2O with ethylene glycol/H_2O (10:1) led to preferential coupling of the SPO at the C2 of the imidazole (entry 8).

Inspired by this phenomenon, we investigated the effects of other polar and polyprotic solvents. Cross coupling of **1a** with **2a** under the same overall conditions as in entry 8 (Table 1) with only ethylene glycol as the solvent made a negligible difference to the formation of all products (entries 8 vs 9), whereas glycerol resulted in almost no site selectivity (entry 10). Reverting to ethylene glycol at 130 °C further improved the selectivity for **5a** (entry 11), whereas replacing $PdOAc_2/PPh_3$ with $Pd(PPh_3)_4$ had a negligible effect (entry 11 vs entry 12). Switching the base to diisopropanolamine (DIPA), led to the formation of **5a** as the main product in a ratio of **3a**/**4a**/**5a** of 18:2:80 (entry 13).

Subsequently, we pursued the coupling of the highly enantioenriched SPO (*S*)-**1a** (>99% ee)[12] with imidazoles **2** under the best conditions for each of the potential products: (*S*)-**3a**, (*S*)-**4a**, and (*S*)-**5a** (Figure 2). Under the conditions of entry 1 (Table 1) cross-coupling of (*S*)-**1a** with **2a** gave (*S*)-**3a**

Table 1. Optimization of Reaction Conditions



1a 2a 3a 4a 5a

entry[a]	[Pd]	L_n	base	solvent	temp °C	3a/4a/5a[b]
1	$Pd(PPh_3)_4$		DIPEA	DMF	110	90:9:1
2	$Pd(PPh_3)_4$		DIPEA	DMSO	110	59:37:4
3	$Pd(OAc)_2$	PPh_3	DIPEA	DMSO	110	56:40:4
4	$Pd(OAc)_2$	PPh_3	DIPEA	DMSO/H_2O (1:1)	110	24:47:29
5	$Pd(OAc)_2$	PPh_3	DIPEA	DMSO/H_2O (10:1)	110	31:55:14
6	$Pd(PPh_3)_4$		DIPEA	DMSO/H_2O(10:1)	100	13:74:13
7	$Pd(PPh_3)_4$		DIPA	DMSO/H_2O (10:1)	100	8:64:28
8	$Pd(OAc)_2$	PPh_3	DIPEA	ethylene glycol/H_2O (10:1)	110	26:8:66
9	$Pd(OAc)_2$	PPh_3	DIPEA	ethylene glycol	110	24:8:68
10	$Pd(OAc)_2$	PPh_3	DIPEA	glycerol	110	30:26:44
11	$Pd(OAc)_2$	PPh_3	DIPEA	ethylene glycol	130	17:8:75
12	$Pd(PPh_3)_4$		DIPEA	ethylene glycol	130	24:3:73
13	$Pd(PPh_3)_4$		DIPA	ethylene glycol	130	18:2:80

[a]All reactions were run using racemic **1a** (0.10 mmol) and **2a** (0.15 mmol) for 24 h with either $Pd(OAc)_2$ (10 mol %)/PPh_3 (25 mol %) or $Pd(PPh_3)_4$ (10 mol %) and base (4 equiv) and solvent (1.0 mL). [b]Estimated ratio based on ^{31}P NMR.

https://doi.org/10.1021/acs.orglett.4c00903
Org. Lett. 2024, 26, 4200–4204

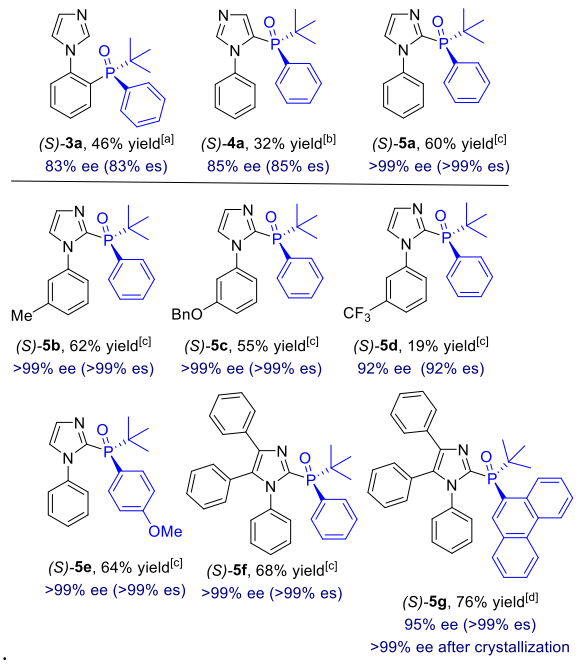


Figure 2. Examples of site-selective coupling products. Reaction conditions: $Pd(PPh_3)_4$ (10 mol %), SPO (0.20 mmol), imidazole (0.30 mmol); [a]SPO > 99% ee, DIPEA (4 equiv), DMF (2 mL), 110 °C, 18 h; [b]DMSO/H_2O (10:1, 2 mL), 100 °C, 48 h; [c]DIPA (4 equiv), ethylene glycol (2 mL), 130 °C, 18 h; [d]SPO (95% ee, 1.08 mmol), imidazole (1.62 mmol), DIPA (4 equiv), ethylene glycol (10.8 mL), 18 h.

in 83% ee (~83% enatiospecificity (es)) and 46% isolated yield. It is noteworthy that although all of the SPO (*S*)-**1a** was consumed within 18 h, we observed a small amount of the oxidized side product (to the corresponding phosphinic acid) and some debromination of the imidazole **2**, thus compromising the final isolated yield of (*S*)-**3a**.

Following the above studies, we investigated the enantiospecificity of the conditions favoring substitution at the C5 of the imidazole (Table 1, entry 6), and obtained product (*S*)-**4a** with some erosion of chiral integrity (85% ee; 85% es), albeit in low isolated yield (32%). We noted that the oxidation of SPO (*S*)-**1a** to the phosphinic acid was a more significant issue in the presence of water. For this initial study, however, we chose to focus mainly on C2-imidazole phosphorylation using the optimized conditions of entry 13 (Table 1). We were pleased to see that the cross-coupling of (*S*)-**1a** (>99% ee) with **2a** gave (*S*)-**5a** without any erosion in chirality (>99% ee; > 99% es) and in 60% isolated yield. This favorable outcome was also confirmed with a few other electron-rich imidazoles, which led to the formation of products (*S*)-**5b,c,f** in >99% ee (>99% es) and 55−68% isolated yields (Figure 2). Interestingly, the electron-deficient 1-[2-bromo-5-(trifluoromethyl)phenyl]-1*H*-imidazole led to product **5d** in slightly lower enantioretention (92% ee; 92% es) and in only 19% isolated yield, possibly because of the excessive debromination of the imidazole starting material. Subsequently, the cross-coupling of (*S*)-*tert*-butyl(4-methoxyphenyl)phosphine oxide (>99% ee) and (*S*)-*tert*-butyl(phenanthren-9-yl)phosphine oxide (95% ee) were explored under the same reaction conditions, which led to the formation of (*S*)-**5e** (>99% ee; > 99% es) and (*S*)-**5g** (95% ee; >99% es; >99% ee after crystallization), respectively (Figure 2). Both products were formed without any loss of chiral integrity in 64−76% isolated yields. The enantiomeric purity of all products was determined by chiral HPLC. The absolute configuration of key compounds was confirmed by their single-crystal X-ray structure (Figure 3), and that of other compounds was assigned by analogy.

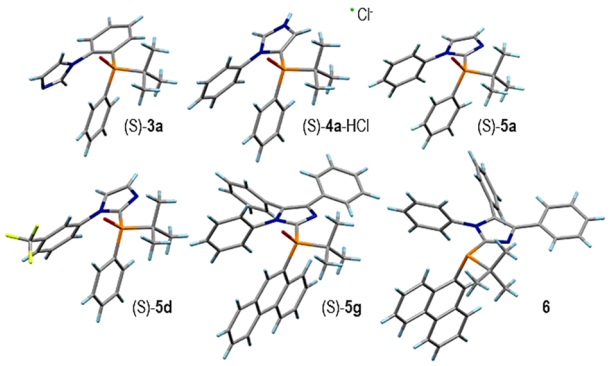


Figure 3. Single-crystal X-ray structure of **3a, 4a, 5a, 5d, 5g**, and *P*-chiral 2-phosphinyl imidazole **6**.

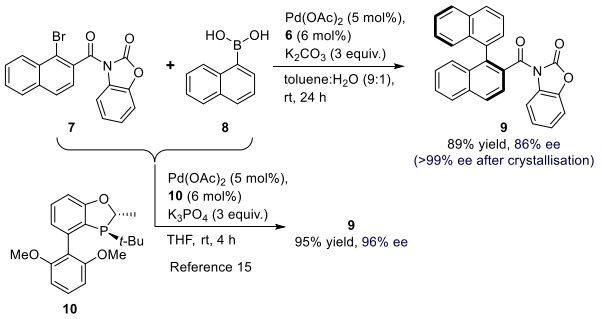
As an initial proof of concept, we also turned our attention to the utility of these chiral ligands and selected the trivalent phosphine analogue of (*S*)-**5g**, as a representative example. Stereoretentive reduction of (*S*)-**5g** using catalytic[13] or stoichiometric amounts of $Ti(O\text{-}i\text{-}Pr)_4$ and a slight excess of tetramethyldisiloxane (TMDS) were unsuccessful. However, with excess amounts of both reagents [40 equiv of TMDS and 20 equiv of $Ti(O\text{-}i\text{-}Pr)_4$], the reduction proceeded within 72 h at 50 °C, to afford **6** in 99% ee and 35% isolated yield after column chromatography and crystallization. In this case, coelution of an unidentified phosphorus-containing byproduct and a silane-polymerized product compromised the isolation of the highly pure phosphine **6** in good yield. Further optimization of this reaction (on a case by case for different phosphine derivatives) is clearly needed and currently in progress. The structure and absolute stereochemistry of **6** was also confirmed by single-crystal X-ray crystallography (Figure 3).

As a proof of concept, we reasoned that the electron-rich nature (^{31}P NMR, CD_2Cl_2, δ = −26.5 ppm) and bulkiness of this ligand could promote the oxidative addition and reductive elimination steps of metal-catalyzed cross-coupling reactions,[3a,14] such as the asymmetric Pd-catalyzed Suzuki−Miyaura reaction. We were pleased to see that the coupling of aryl bromide **7** to naphthalene boronic acid **8** afforded atropisomer **9** in 89% yield and 86% ee (Scheme 2). Interestingly, although crystallization of **9** in Et_2O/DCM at −20 °C led to the formation of crystals with lower enantiomeric purity, the mother liquor was enriched with atropisomer **9** in >99% ee. Tang and co-workers have previously reported the preparation of the same atropisomer[15] in slightly higher yield and enantiomeric purity using the *P*-oxaphosphole ligand **10** (Scheme 2).[15] The absolute configuration of product **9** obtained using our methodology was assigned by comparison of its chiral HPLC data (under the same conditions) with that previously reported.[15]

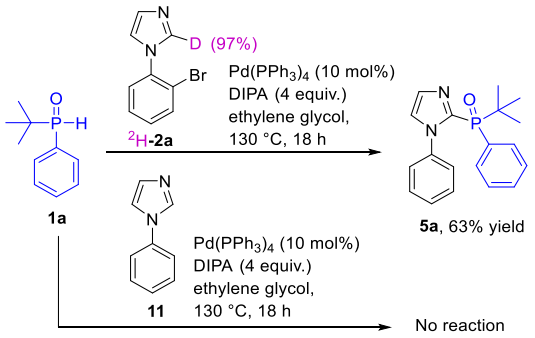
In an effort to gain further insight into the mechanism of the 1,4-palladium migration, SPO **1a** was reacted with C2-deuterated imidazole ^2H-**2a** under conditions favoring cross-coupling to C2 of the imidazole (Scheme 3). However, we did

https://doi.org/10.1021/acs.orglett.4c00903
Org. Lett. 2024, 26, 4200−4204

Scheme 2. Application of Ligand 6 in an Asymmetric Suzuki−Miyaura Cross-Coupling Reaction



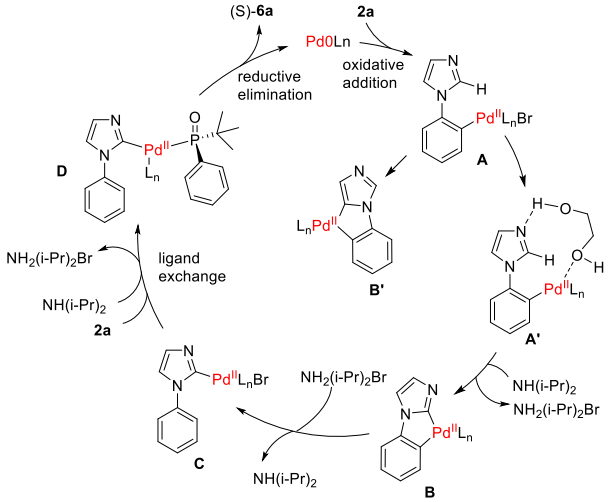
Scheme 3. Mechanistic Investigations



not observe any deuterium incorporation in product **5a**, which suggests that the 1,4-palladium migration is not H-retentive. Additionally, we did not observe the formation of any product when the nonbrominated analogue of **2a** (i.e., compound **11**) was used, which eliminated the possibility of any direct C−H activation or oxidative coupling on the imidazole ring.

On the basis of all of our observations and literature precedents,[11a,16] we propose the mechanism shown in Scheme 4. Oxidative addition of Pd(0) to **2a** is expected to generate arylpalladium(II) species **A**. The subsequent 1,4-palladium migration can lead to the formation of palladacycles **B** and **B′**, which upon protonation would generate **C** (or the corresponding **C′** intermediate; the latter is not shown). At this time, the solvent effect on the site-selectivity between the

Scheme 4. Proposed Mechanism



C2 and C5 positions of the imidazole remains unclear. However, it is plausible that ethylene glycol can form a monodentate coordination with Pd(II) and simultaneously form a hydrogen bond to the N3 of the imidazole, thus orienting palladation at the C2 position, as indicated in intermediate **A′**. Protonation of intermediate **B** followed by ligand exchange with the SPO is expected to give intermediate **D**, after which reductive elimination can lead to (*S*)-**5a**. Intermediate **B′** can follow a similar catalytic cycle to give (*S*)-**4a**. An analogous mechanism has been proposed by Fu and Feng et al. for the phosphorylation of C(sp^3)−H bonds via a 1,4-palladium migration in the presence of nonchiral H-phosphonates.[11a] In addition to this proposed Pd(0)-to-Pd(II) catalytic cycle, the involvement of other Pd(IV) species in 1,4-palladium migration mechanisms has been proposed by Mota and Dedieu.[16b]

In summary, we have developed an enantiospecific solvent-switchable methodology to access *P*-chiral 2-phosphoryl imidazoles via 1,4-palladium migration. In this initial report, we focused on the reaction conditions that favor the C2-substitution on the imidazole ring, which leads to valuable precursors for the preparation of *P*-chiral 2-phosphinyl imidazole ligands. As a proof of concept, a successful asymmetric Suzuki−Miyaura cross-coupling reaction was achieved. Currently, the synthesis of a structurally diverse library of *P*-chiral compounds of general structures **4** and **5** is in preparation in order to fully explore the potential applications of such ligands in a variety of asymmetric transformations.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c00903.

Data supporting the results of this study, including the experimental procedures; chiral HPLC chromatographs; copies of ^{1}H, ^{13}C, and ^{31}P NMR spectra and crystallographic data; and additional references (PDF)

Accession Codes

CCDC 2153273 and 2339656−2339661 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, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Youla S. Tsantrizos − *Department of Chemistry, McGill University, Montréal, Québec H3A 0B8, Canada;*
orcid.org/0000-0002-6231-7498;
Email: youla.tsantrizos@mcgill.ca

Authors

Ifenna I. Mbaezue − *Department of Chemistry, McGill University, Montréal, Québec H3A 0B8, Canada*

https://doi.org/10.1021/acs.orglett.4c00903
Org. Lett. 2024, 26, 4200−4204

Shi-Guang Li − *Department of Chemistry, McGill University, Montréal, Québec H3A 0B8, Canada;* orcid.org/0009-0002-5558-371X

Angula C. S. Reddy − *Department of Chemistry, McGill University, Montréal, Québec H3A 0B8, Canada*

Hatem M. Titi − *Department of Chemistry, McGill University, Montréal, Québec H3A 0B8, Canada;* orcid.org/0000-0002-0654-1292

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.4c00903

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support through a research grant to Y.S.T. (RGPIN-2020-04049). I.I.M gratefully acknowledges a scholarship in support of his Ph.D. studies provided by Fonds de recherche du Québec. We also wish to thank Boehringer-Ingelheim Pharmaceuticals Inc. (USA) for their generous gift of the chiral auxiliary (*R*)-*N*-[1-(5-chloro-2-hydroxyphenyl)ethyl]-4-methylbenzenesulfonamide.

■ REFERENCES

(1) Grotjahn, D. B.; Incarvito, C. D.; Rheingold, A. L. Combined Effects of Metal and Ligand Capable of Accepting a Proton or Hydrogen Bond Catalyze Anti-Markovnikov Hydration of Terminal Alkynes. *Angew. Chem., Int. Ed.* **2001**, *40*, 3884−3887.

(2) (a) Grotjahn, D. B.; Gong, Y.; Zakharov, L.; Golen, J. A.; Rheingold, A. L. Changes in Coordination of Sterically Demanding Hybrid Imidazolylphosphine Ligands on Pd(0) and Pd(II). *J. Am. Chem. Soc.* **2006**, *128*, 438−453. (b) Díez, V.; Espino, G.; Jalón, F. A.; Manzano, B. R.; Pérez-Manrique, M. Synthesis and Structure of New Palladium Complexes with the Ligand 2-(Diphenylphosphino)-1-Methylimidazole: Evidence of Hemilability. *J. Organomet. Chem.* **2007**, *692*, 1482−1495.

(3) (a) Harkal, S.; Rataboul, F.; Zapf, A.; Fuhrmann, C.; Riermeier, T.; Monsees, A.; Beller, M. Dialkylphosphinoimidazoles as New Ligands for Palladium-Catalyzed Coupling Reactions of Aryl Chlorides. *Adv. Synth. Catal.* **2004**, *346*, 1742−1748. (b) Torborg, C.; Huang, J.; Schulz, T.; Schäffner, B.; Zapf, A.; Spannenberg, A.; Börner, A.; Beller, M. Improved Palladium-Catalyzed Sonogashira Coupling Reactions of Aryl Chlorides. *Chem.—Eur. J.* **2009**, *15*, 1329−1336. (c) Schulz, T.; Torborg, C.; Schäffner, B.; Huang, J.; Zapf, A.; Kadyrov, R.; Börner, A.; Beller, M. Practical Imidazole-Based Phosphine Ligands for Selective Palladium-Catalyzed Hydroxylation of Aryl Halides. *Angew. Chem., Int. Ed.* **2009**, *48*, 918−921. (d) Wu, X.-F.; Neumann, H.; Spannenberg, A.; Schulz, T.; Jiao, H.; Beller, M. Development of a General Palladium-Catalyzed Carbonylative Heck Reaction of Aryl Halides. *J. Am. Chem. Soc.* **2010**, *132*, 14596−14602. (e) Fleischer, I.; Dyballa, K. M.; Jennerjahn, R.; Jackstell, R.; Franke, R.; Spannenberg, A.; Beller, M. From Olefins to Alcohols: Efficient and Regioselective Ruthenium-Catalyzed Domino Hydroformylation/Reduction Sequence. *Angew. Chem., Int. Ed.* **2013**, *52*, 2949−2953. (f) Fleischer, I.; Wu, L.; Profir, I.; Jackstell, R.; Franke, R.; Beller, M. Towards the Development of a Selective Ruthenium-Catalyzed Hydroformylation of Olefins. *Chem.—Eur. J.* **2013**, *19*, 10589−10594. (g) Wu, L.; Liu, Q.; Spannenberg, A.; Jackstell, R.; Beller, M. Highly Regioselective Osmium-Catalyzed Hydroformylation. *Chem. Commun.* **2015**, *51*, 3080−3082. (h) Wang, L.; Neumann, H.; Beller, M. Palladium-Catalyzed Methylation of Nitroarenes with Methanol. *Angew. Chem., Int. Ed.* **2019**, *58*, 5417−5421.

(4) Zhang, K.-F.; Christoffel, F.; Baudoin, O. Barbier−Negishi Coupling of Secondary Alkyl Bromides with Aryl and Alkenyl Triflates and Nonaflates. *Angew. Chem., Int. Ed.* **2018**, *57*, 1982−1986.

(5) Curtis, N. J.; Brown, R. S. An Easily Introduced and Removed Protecting Group for Imidazole Nitrogen: A Convenient Route to 2-Substituted Imidazoles. *J. Org. Chem.* **1980**, *45*, 4038−4040.

(6) (a) Omelańczuk, J. The First Stereoselective Synthesis of Chiral Halogenophosphines: Optically Active Tert-butyl(phenyl)-chlorophosphine. *J. Chem. Soc. Chem. Commun.* **1992**, 1718−1719. (b) Pabel, M.; Willis, A. C.; Wild, S. B. Attempted Resolution of Free (±)-Chlorophenylisopropylphosphine. *Tetrahedron: Asymmetry* **1995**, *6*, 2369−2374. (c) Humbel, S.; Bertrand, C.; Darcel, C.; Bauduin, C.; Jugé, S. Configurational Stability of Chlorophosphines. *Inorg. Chem.* **2003**, *42*, 420−427.

(7) For recent reviews, see: (a) Rahim, A.; Feng, J.; Gu, Z. 1,4-Migration of Transition Metals in Organic Synthesis. *Chin. J. Chem.* **2019**, *37*, 929−945. (b) Dong, X.; Wang, H.; Liu, H.; Wang, F. Recent Advances in Transition Metal Migration involving Reactions. *Org. Chem. Front.* **2020**, *7*, 3530−3556. (c) Li, M.-Y.; Wei, D.; Feng, C.-G.; Lin, G.-Q. Tandem Reactions involving 1,4-Palladium Migrations. *Chem.—Asian J.* **2022**, *17*, No. e202200456.

(8) Kesharwani, T.; Larock, R. C. Benzylic C−H Activation and C−O Bond Formation via Aryl to Benzylic 1,4-Palladium Migrations. *Tetrahedron* **2008**, *64*, 6090−6102.

(9) (a) Hu, T.-J.; Zhang, G.; Chen, Y.-H.; Feng, C.-G.; Lin, G.-Q. Borylation of Olefin C−H Bond via Aryl to Vinyl Palladium 1,4-Migration. *J. Am. Chem. Soc.* **2016**, *138*, 2897−2900. (b) Zhang, G.; Li, M.-Y.; Ye, W.-B.; He, Z.-T.; Feng, C.-G.; Lin, G.-Q. Borylation of Unactivated C(sp^3)−H Bonds with Bromide as a Traceless Directing Group. *Org. Lett.* **2021**, *23*, 2948−2953.

(10) Cheng, C.; Zhu, Q.; Zhang, Y. Intermolecular C−H Silylation through Cascade Carbopalladation and Vinylic to Aryl 1,4-Palladium Migration. *Chem. Commun.* **2021**, *57*, 9700−9703.

(11) (a) Ji, X.-M.; Chen, Y.-Z.; Fu, J.-G.; Zhang, S.-S.; Feng, C.-G. Phosphorylation of C(sp3)−H Bonds via 1,4-Palladium Migration. *Org. Lett.* **2022**, *24*, 3781−3785. For a review, see: (b) Hore, S.; Singh, R. P. Phosphorylation of Arenes, Heteroarenes, Alkenes, Carbonyls and Imines by Dehydrogenative Cross-Coupling of P(O)−H and P(R)−H. *Org. Biomol. Chem.* **2022**, *20*, 498−537.

(12) Li, S.-G.; Yuan, M.; Topic, F.; Han, Z. S.; Senanayake, C. H.; Tsantrizos, Y. S. Asymmetric Library Synthesis of P-Chiral t-Butyl-Substituted Secondary and Tertiary Phosphine Oxides. *J. Org. Chem.* **2019**, *84*, 7291−7302.

(13) Petit, C.; Poli, E.; Favre-Réguillon, A.; Khrouz, L.; Denis-Quanquin, S.; Bonneviot, L.; Mignani, G.; Lemaire, M. Unraveling the Catalytic Cycle of Tertiary Phosphine Oxides Reduction with Hydrosiloxane and Ti($OiPr$)$_4$ through EPR and ^{29}Si NMR Spectroscopy. *ACS Catal.* **2013**, *3*, 1431−1438.

(14) Martin, R.; Buchwald, S. L. Palladium-Catalyzed Suzuki−Miyaura Cross-Coupling Reactions Employing Dialkylbiaryl Phosphine Ligands. *Acc. Chem. Res.* **2008**, *41*, 1461−1473.

(15) 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. Efficient Chiral Monophosphorus Ligands for Asymmetric Suzuki−Miyaura Coupling Reactions. *Org. Lett.* **2012**, *14*, 2258−2261.

(16) (a) Campo, M. A.; Zhang, H.; Yao, T.; Ibdah, A.; McCulla, R. D.; Huang, Q.; Zhao, J.; Jenks, W. S.; Larock, R. C. Aryl to Aryl Palladium Migration in the Heck and Suzuki Coupling of o-Halobiaryls. *J. Am. Chem. Soc.* **2007**, *129*, 6298−6307. (b) Mota, A. J.; Dedieu, A. Intramolecular 1,*n*-Palladium Migrations in Polycyclic Aromatic Hydrocarbons. Palladium(II) versus Palladium(IV) Mechanisms: A Theoretical Study. *Organometallics* **2006**, *25*, 3130−3142.