Organic LETTERS

Letter

pubs.acs.org/OrgLett

Pyridine–Hydrazones as *N,N′*-Ligands in Asymmetric Catalysis: Pd(II)-Catalyzed Addition of Boronic Acids to Cyclic Sulfonylketimines

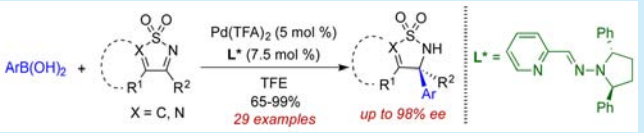
Yolanda Álvarez-Casao,[†] David Monge,*[,†] Eleuterio Álvarez,[‡] Rosario Fernández,*[,†] and José M. Lassaletta*[,‡]

[†]Departamento de Química Orgánica and Centro de Innovación en Química Avanzada (ORFEO–CINQA), University of Seville, C/Prof. García González, 1, 41012 Seville, Spain

[‡]Instituto de Investigaciones Químicas (CSIC-US) and Centro de Innovación en Química Avanzada (ORFEO-CINQA), University of Seville, Avda. Américo Vespucio, 49, 41092 Seville, Spain

Supporting Information

ABSTRACT: The design, synthesis, and coordination features of a novel class of chiral pyridine–hydrazone ligands are described. As a first application, L/Pd(TFA)$_2$ complexes served as catalysts in the 1,2-addition of arylboronic acids to saccharin-derived cyclic ketimines, affording products in high yields and enantioselectivities. The method was also applied to more challenging 3,4-disubstituted 1,2,5-thiadiazole 1,1-dioxides, affording again high yields and enantioselectivities along with high regioselectivities for unsymmetrically substituted derivatives.



The design and synthesis of new chiral ligands is one of the cornerstones for the formidable developments achieved in the field of asymmetric metal catalysis.[1] Nowadays, there is an increasing interest in nitrogen-based ligands,[2] which offer an extraordinary structural variability and are in general stable and easy to handle compounds. In this context, hydrazones appear as an interesting and yet underexplored class of ligands. Our results employing glyoxal bis-hydrazone **L1** in Cu(II)–catalyzed Diels–Alder cycloadditions[3] and Pd(0)–catalyzed Suzuki–Miyaura cross-couplings[4] revealed that insertion of C_2-symmetric 2,5-diphenylpyrrolidine as terminal dialkylamino groups is key to reach high enantioselectivities, and this design was later extended to phosphino hydrazones that were also used as ligands in Suzuki–Miyaura couplings with complementary families of substrates.[5] In these ligand families, steric crowding around the metal center is modulated by the structure of the dialkylamino fragment, which in turn also controls the electronic behavior of C=N group [$n \rightarrow \pi$ (N–N=C) conjugation]. Additionally, the C_2-symmetric chiral scaffold makes N–N bond rotation in catalyst–substrate complexes inconsequential, preventing potential loss of appropriate chiral environments.

Aiming to expand the scope of this strategy, we now present heterofunctional N,N′ ligands with pyridine–hydrazone structures (Figure 1). The chiral hydrazone fragment plays the role of the N(sp^2)-based groups present in the well-established Pyrox and iminopyridine ligands of type **I**,[6] which have shown excellent properties in many reactions of interest. The proposed pyridine–hydrazone ligands possess potentially distinct features compared with **L1**: (i) better stability of their metal complexes, (ii) more versatile coordination ability (heterobidentate and potentially hemilabile[7]), (iii) higher modularity, and (iv) tunability of the steric and electronic properties by introduction of appropriate substituents on the pyridine ring. The above-mentioned

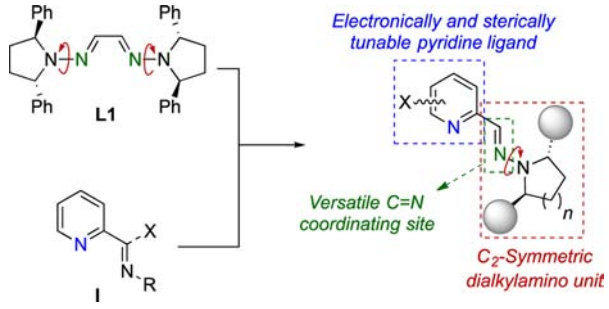


Figure 1. Pyridine–hydrazone ligand design.

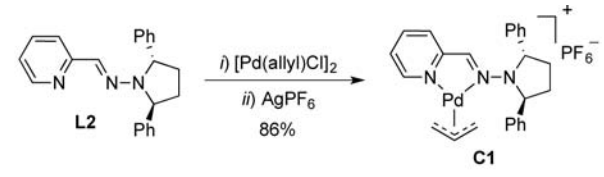
properties make pyridine–hydrazones appealing ligands for asymmetric metal catalysis.

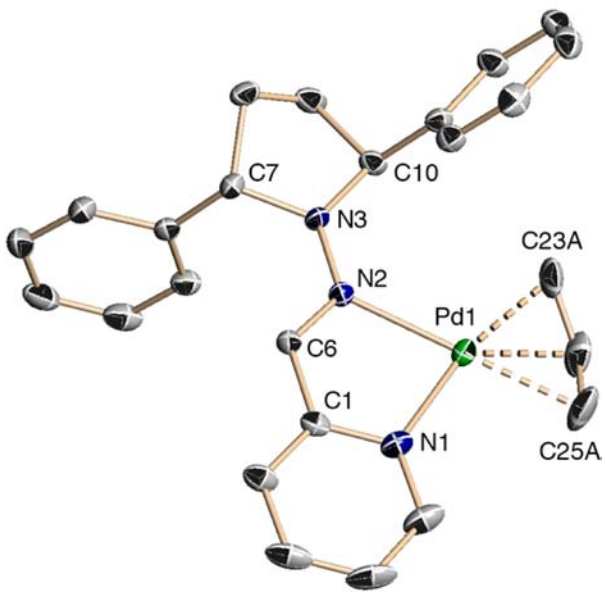
A first set of pyridine–hydrazone ligands **L2**–**L11** (Table 1) was synthesized by simple condensation of C_2-symmetric hydrazines **1**[8] and readily available pyridine- or quinoline-2-carbaldehydes **2** in good yields (see the Supporting Information). To gain further insight in the coordination features of these compounds, a representative π-allyl Pd(II) complex **C1** was synthesized from the simplest ligand **L2** (Scheme 1), and its solid-state structure was determined by single-crystal X-ray diffraction. The analysis of the structure shows the expected square-planar coordination geometry. The Pd(1)–N(1) distance of 2.085(4) Å is significantly shorter than the Pd(1)–N(2) bond [2.169(3) Å]. On the other hand, the Pd–C bond *trans* to the pyridine N [Pd(1)–C(23B) 2.150(5) Å] is significantly longer compared to the Pd–C bond *trans* to the hydrazone C=N [Pd(1)–C(25B) 2.099(5) Å], reflecting the higher *trans*

Received: September 10, 2015
Published: October 1, 2015

DOI: 10.1021/acs.orglett.5b02613
Org. Lett. 2015, 17, 5104–5107

Scheme 1. Synthesis of π-Allyl Pd(II) Complex C1[a]



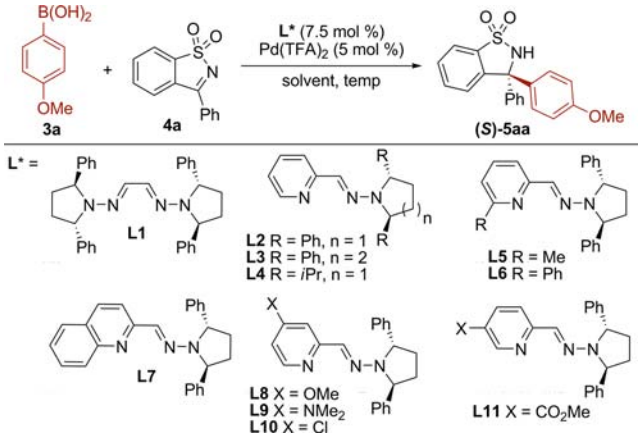


[a]ORTEP drawing of complex **C1**. Thermal ellipsoids are drawn at the 30% probability level. Hydrogen atoms and PF_6^- counteranion are omitted for clarity.

influence of the more basic pyridine nitrogen. The structure reveals also an efficient $n \rightarrow \pi$ conjugation in the hydrazone moiety as deduced from the very low pyramidalization degree at the N(sp^3) atom [virtual dihedral angle N(2)−N(3)−C(7)−C(10) = 176.4°][9] and the nearly perfect coplanarity in the hydrazone moiety [torsion angles C(6)−N(2)−N(3)−C(7) = −2.3(6)° and C(6)−N(2)−N(3)−C(10) = −178.3(4)°]. As expected, there is also a nearly perfect coplanarity between the ligand [defined by N(1)−C(1)−C(6)−N(2)] and coordination [defined by N(1)−N(2)−Pd(1)−C(25)−C(23)] planes, deviated by only 1.8° from each other. This particular feature is in sharp contrast with related phosphino hydrazone complexes, where the six-membered system forces a strong deviation of both planes, making it necessary to consider the existence of two conformers.[5,10]

The Pd(II)-catalyzed arylation of cyclic *N*-sulfonyl ketimines was chosen as a platform to evaluate the efficiency of the new ligands. Pioneered by Hayashi, different groups have described Rh-catalyzed asymmetric additions of arylboron reagents to several types of ketimines.[11] Alternatively, high enantioselectivities have been obtained employing alkyl-substituted cyclic *N*-sulfonyl ketimines in combination with Pd(II)/Pyrox (*N,N′* ligand)[12] or Pd(II)/Phox (*P,N* ligand)[13] complexes. Although valuable progress has been made in this area, achieving stereocontrol with a broad substrate scope still represents a challenging task. We began by studying the reaction between *p*-anisylboronic acid **3a** and phenyl-substituted cyclic ketimine **4a** as a model reaction. Disappointingly, using **C1** as the catalyst and Cs_2CO_3 as the base afforded only trace of product **5aa** after 48 h in MeOH at 60 °C. A survey of reaction conditions employing

Table 1. Optimization of Reaction Conditions[a]



entry	solvent	L*	temp (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	MeOH	**L2**	60	48	50[d]	96
2	MeOH	**L1**	60	48	nr[d]	
3	MeOH	**L3**	60	48	35[d]	80
4	MeOH	**L4**	60	48	20[d]	70
5	MeOH	**L5**	60	48	trace[d]	
6	MeOH	**L6**	60	48	trace[d]	
7	MeOH	**L7**	60	48	trace[d]	
8	TFE	**L2**	60	20	85	96
9	TFE	**L2**	40	20	98	97
10	TFE	**L8**	40	20	85	95
11	TFE	**L9**	40	20	96	94
12	TFE	**L10**	40	20	56	96
13	TFE	**L11**	40	20	88	94

[a]Reactions were performed under air at a 0.2 mmol scale. [b]Isolated yield after column chromatography. [c]Determined by HPLC on chiral stationary phases. [d]Palladium black was eventually formed.

complexes prepared in situ from **L2** and different Pd(II) sources served to identify **L2**/$Pd(TFA)_2$ as the most efficient catalytic system and MeOH as the best solvent, affording (*S*)-**5aa** in moderate yield (50%) but excellent enantioselectivity (96% ee; Table 1, entry 1).

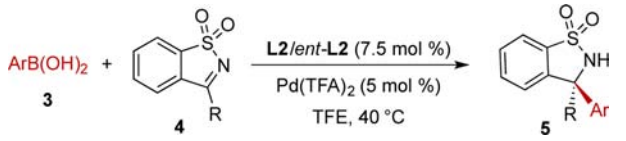
Interestingly, the $Pd(TFA)_2$ complex from glyoxal bis-hydrazone **L1** was totally inactive (Table 1, entry 2), suggesting the need for a more basic pyridine nitrogen in the ligand as in **L2**. Subsequently, the structural variability in different pyridine−hydrazone ligands was explored. Piperidine-derived **L3**, which possesses higher conformational flexibility, and 2,5-diisopropyl-pyrrolidine-derived **L4** provided poorer catalytic activities and less efficient chiral environments than **L2** (Table 1, entries 3 and 4). It was therefore decided to retain the 2,5-diphenylpyrrolidine unit and explore the influence by substituents on the pyridine ring. The presence of alkyl or aryl groups at the C-6 of pyridine (**L5**, **L6**, or quinoline-derived **L7**) had a detrimental effect on reactivity, affording only trace amounts of product **5aa** after 48 h (Table 1, entries 5−7). It has been reported that use of some additives or more polar and protic solvents may improve palladium-catalyzed addition reactions of arylboronic acids.[14] To our delight, performing the reaction in trifluoroethanol (TFE) with **L2**/$Pd(TFA)_2$ increased reactivity and avoided self-coupling of arylboronic acid, affording (*S*)-**5aa** in good yield (85%) and excellent 96% ee (Table 1, entry 8). The beneficial effect of this solvent allowed the reaction to be carried out at 40 °C with a higher 98% yield and 97% ee in only 20 h (Table 1, entry 9). The modulation of the donor ability of the ligand by

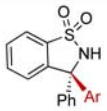
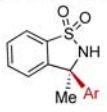
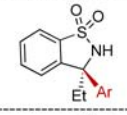
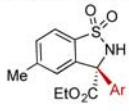
DOI: 10.1021/acs.orglett.5b02613
Org. Lett. 2015, 17, 5104−5107

introduction of electron-donating or -withdrawing functional groups in the pyridine ring was also investigated under these conditions (Table 1, entries 10−13). Intriguingly, results obtained with ligands **L8**, **L9**,[15] and **L11** were comparable to **L2**, while **L10** afforded (*S*)-**5aa** in lower yield.

Successive studies were aimed at analyzing the scope of the reaction (Table 2). Thus, aryl- and alkyl-substituted cyclic

Table 2. Addition to Cyclic Sulfonyl Ketimines 4[a]



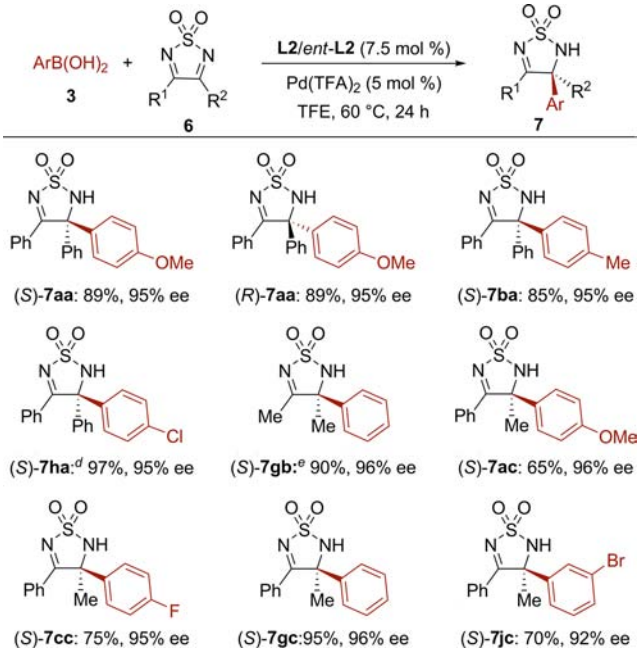
	Ar	t (h)	product		yield (%)[b]	ee (%)[c]
1	4-MeO-C_6H_4	20		(*S*)-**5aa**	98	97
2	4-MeO-C_6H_4	20		(*R*)-**5aa**	98	95
3	4-Me-C_6H_4	24		(*S*)-**5ba**	95	97
4[d,e]	4-F-C_6H_4	48		(*S*)-**5ca**	75	93
5	3,4-(OCH_2O)-C_6H_3	48		(*S*)-**5da**	80	96
6	3,5-$(Me)_2$-C_6H_3	48		(*S*)-**5ea**	70	90
7	3,5-$(Me)_2$-4MeO-C_6H_3	48		(*S*)-**5fa**	99	95
8	4-MeO-C_6H_4	24		(*S*)-**5ab**	96	98
9[e]	4-F-C_6H_4	48		(*S*)-**5cb**	90	98
10	Ph	24		(*S*)-**5gb**	95	97
11	Ph	24		(*R*)-**5gb**	95	98
12	4-MeO-C_6H_4	24		(*S*)-**5ac**	99	92
13	Ph	24		(*S*)-**5gc**	94	97
14	4-MeO-C_6H_4	12		(*S*)-**5ad**	98	86
15	Ph	12		(*S*)-**5gd**	93	92
16	4-Cl-C_6H_4	16		(*S*)-**5hd**	98	93
17	4-Cl-C_6H_4	16		(*R*)-**5hd**	98	93
18	3-Cl-C_6H_4	16		(*S*)-**5id**	85	92
19	3-Br-C_6H_4	16		(*S*)-**5jd**	99	92
20	2-Me-C_6H_4	48		(*S*)-**5kd**	85	92

[a]Reactions performed under air at a 0.2 mmol scale. [b]Isolated yield after chromatography. [c]Determined by HPLC on chiral stationary phases. [d]Reaction performed at 60 °C. [e]Sequential addition of $ArB(OH)_2$.

ketimines (R = Ph, **4a**; R = Me, **4b**; R = Et, **4c**) reacted with a variety of *para*- and *meta*-substituted arylboronic acids **3**, affording α-triarylamines **5aa**−**fa** (entries 1−7) and α-diaryl alkylamines **5ab**−**gc** (entries 8−13) in good to excellent yields (70−99%) and enantioselectivities (90−98% ee). Arylboronic acids bearing electron-withdrawing groups (R = 4-FC_6H_4, **3c**) and di- or trisubstituted reagents (**3d**−**f**) were well tolerated, although higher temperatures (entry 4) and/or longer reaction times were required (entries 4−7 and 9). As expected, *N*-sulfonyl α-imino ester **4d** reacted faster with arylboronic acids containing electron-donating (OMe) and -withdrawing groups (Cl, Br) to afford α-diaryl amino esters **5ad**−**jd** (entries 14−19) in high yields (85−99%) with high enantioselectivities (86−93% ee). *Ortho*-substituted boronic acids, exemplified by **3k**, also provided benzosultam **5kd** with good results (entry 20).

The method was also successfully extended to the addition of boronic acids **3** to more challenging substrates such as 3,4-disubstituted 1,2,5-thiadiazole 1,1-dioxides **6** for the synthesis of trisubstitued 1,2,5-thiadiazoline 1,1-dioxides **7** (Scheme 2).[16]

Scheme 2. Addition to 1,2,5-Thiadiazole 1,1-Dioxides 6[a−c]



[a]Reactions performed under air at a 0.2 mmol scale. [b]Isolated yield after chromatography. [c]ee's determined by HPLC on chiral stationary phases. [d]*t* = 48 h; sequential addition of $ArB(OH)_2$. [e]*t* = 16 h.

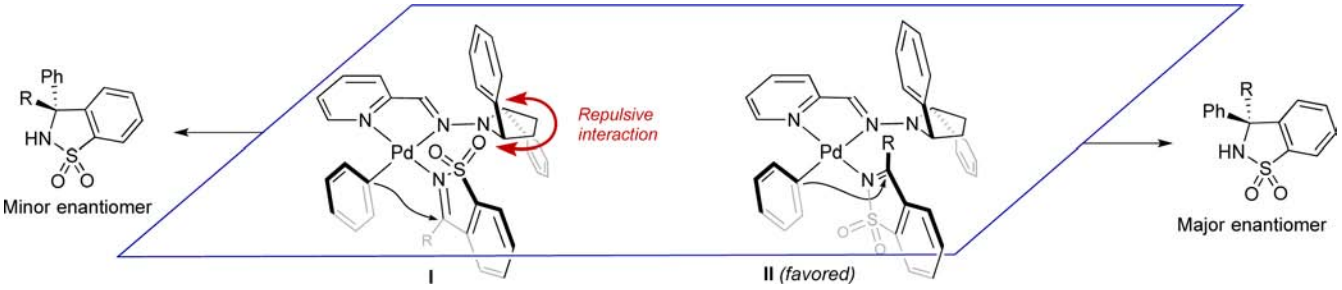
Thus, good yields were achieved in the additions to symmetrically substituted derivatives such as **6a** ($R^1 = R^2$ = Ph) and **6b** ($R^1 = R^2$ = Me), reaching very high enantioselectivities (≥95% ee) in all cases. More importantly, use of unsymmetrically substituted substrate **6c** (R^1 = Ph, R^2 = Me) resulted in highly regio- and enantioselective (ee 92−96%) reactions to afford products **7** resulting from the attack to the methyl-substituted C═N bond C(3).

The absolute *S* configurations of several products **5** and **7** were assigned after comparison of its optical rotation and/or HPLC retention times with literature values.[17] Assuming a uniform reaction pathway, the absolute configurations of all other products were assigned by analogy. The structure of Pd(II) complex **C1** helped to predict the geometry of the intermediates presumably involved in the enantioselectivity-determining step, also allowing drawing of a tentative stereochemical model. Thus, the aryl group from the boronic acid should be placed *trans* to the less basic hydrazone fragment, leaving the *cis* position for the coordination of the cyclic sulfonylimine (Scheme 3).[18] One the two possible orientations (**I**) of the latter results in a destabilizing steric (and possibly electrostatic) interaction between one of the sulfonyl oxygen atoms and the proximal phenyl group at position C(2′) of the ligand. The alternative orientation **II**, however, does not suffer from such interactions, leading to the products with the observed absolute configuration.

In summary, readily available heterofunctional pyridine−hydrazones constitute a useful nitrogen ligand family with interesting features. As a first application, **L2**/$Pd(TFA)_2$ precatalyst has shown excellent activities and enantioselectivities in 1,2-additions of arylboronic acids to saccharin-derived cyclic

DOI: 10.1021/acs.orglett.5b02613
Org. Lett. 2015, 17, 5104−5107

Scheme 3. Proposed Intermediates and Stereochemical Model



ketimines bearing aryl, alkyl and ethoxycarbonyl groups at C(2). Remarkably, bis-hydrazone ligand **L1** was inefficient in this reaction. Finally, high enantioselectivities were also achieved in the arylation of 3,4-disubstituted 1,2,5-thiadiazole dioxides, which proceed also with high regioselectivities for unsymmetrically substitutes derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02613.

Experimental procedures, characterization data, NMR spectra for new compounds, and HPLC traces (PDF)
X-ray data for compound **C1** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: dmonge@us.es.
*E-mail: ffernan@us.es.
*E-mail: jmlassa@iiq.csic.es.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Ministerio de Economía y Competitividad of Spain (CTQ2013-48164-C2-1-P, CTQ2013-48164-C2-2-P, and predoctoral fellowship to Y.Á.-C.), European FEDER funds, and the Junta de Andalucía. D.M. acknowledges Universidad de Sevilla for a postdoctoral contract.

■ REFERENCES

(1) (a) Ojima, I. *Catalytic Asymmetric Synthesis*, 3rd ed; John Wiley & Sons: Hoboken, 2010. (b) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis, Supplement 1*; Springer: Berlin, 2010. (c) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis, Supplement 2*; Springer: Berlin, 2010.

(2) General reviews on *N*-based ligands: (a) Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159. (b) Caputo, C. A.; Jones, N. D. *Dalton Trans.* **2007**, 4627. Reviews on bispyridines: (c) Chelucci, G.; Thummel, R. P. *Chem. Rev.* **2002**, *102*, 3129. Bisimines (salen): (d) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421. Bisoxazolines: (e) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1. (f) Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561. Pyridine-bisoxazolines: (g) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2003**, *103*, 3119. Bis(imino)pyridines: (h) Gibson, V. C.; Redshaw, C.; Solan, G. A. *Chem. Rev.* **2007**, *107*, 1745.

(3) Lassaletta, J. M.; Alcarazo, M.; Fernández, R. *Chem. Commun.* **2004**, 298.

(4) Bermejo, A.; Ros, A.; Fernández, R.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 15798. See also: Denmark, S. E.; Chang, W.-T. T.; Houk, K. N.; Liu, P. *J. Org. Chem.* **2015**, *80*, 313.

(5) Ros, A.; Estepa, B.; Bermejo, A.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. *J. Org. Chem.* **2012**, *77*, 4740.

(6) (a) Chelucci, G. *Coord. Chem. Rev.* **2013**, *257*, 1887. (b) Kwong, H.-L.; Yeung, H.-L.; Yeung, C.-T.; Lee, W.-S.; Lee, C.-S.; Wong, W.-L. *Coord. Chem. Rev.* **2007**, *251*, 2188.

(7) Achiral pyridine hydrazones are effective in Ir-catalyzed nitrogen-directed borylation of arenes: (a) Ros, A.; Estepa, B.; López-Rodríguez, R.; Alvarez, E.; Fernández, R.; Lassaletta, J. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11724. (b) Ros, A.; López-Rodríguez, R.; Estepa, B.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 4573.

(8) 1-Amino-2,5-diphenylpyrrolidine (**1a**), (2*R*,5*R*)-1-amino-2,5-diphenylpyrrolidine (***ent*-1a**), and (2*S*,6*S*)-1-amino-2,6-diphenylpiperidine (**1b**) were prepared on a multigram scale from known diols after mesylation and reaction with hydrazine hydrate as described previously (ref 3). Crude (2*S*,5*S*)-1-amino-2,5-diisopropylpyrrolidine (**1c**) was obtained following a similar procedure (ref 5).

(9) The virtual angle reaches a limit value of ±180° for a planar atom and ±120° for a tetrahedral atom: Rankin, K. N.; Boyd, R. J. *J. Phys. Chem. A* **2002**, *106*, 11168.

(10) Ros, A.; Estepa, B.; Ramírez-López, P.; Alvarez, E.; Fernández, R.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2013**, *135*, 15730.

(11) (a) Shintani, R.; Takeda, M.; Tsuji, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 13168. (b) Nishimura, T.; Noishiki, A.; Tsui, G. C.; Hayashi, T. *J. Am. Chem. Soc.* **2012**, *134*, 5056. (c) Wang, H.; Jiang, T.; Xu, M.-H. *J. Am. Chem. Soc.* **2013**, *135*, 971. (d) Wang, H.; Li, Y.; Xu, M.-H. *Org. Lett.* **2014**, *16*, 3962. (e) Jiang, T.; Wang, Z.; Xu, M.-H. *Org. Lett.* **2015**, *17*, 528.

(12) (a) Yang, G.; Zhang, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 7540. (b) Quan, M.; Yang, G.; Xie, F.; Gridnev, I. D.; Zhang, W. *Org. Chem. Front.* **2015**, *2*, 398.

(13) Jiang, C.-H.; Lu, Y.-X.; Hayashi, T. *Angew. Chem., Int. Ed.* **2014**, *53*, 9936.

(14) Sun, Y.-W.; Zhu, P.-L.; Xu, Q.; Shi, M. *RSC Adv.* **2013**, *3*, 3153.

(15) **L9** is the best ligand in decarboxylative allylic etherification reactions of allyl aryl carbonates catalyzed by Ru(II) complexes: Egger, L.; Tortoreto, C.; Achard, T.; Monge, D.; Ros, A.; Fernández, R.; Lassaletta, J. M.; Lacour, J. *Adv. Synth. Catal.* **2015**, DOI: 10.1002/adsc.201500534.

(16) This reaction has recently been performed using rhodium catalysts, but no regioselectivity was observed in additions to unsymmetrically substituted derivatives (ref 11d). Poorer results were previously observed for a single example using Pd−Pyrox catalysts (see ref 12a).

(17) **5aa**, **5ba**, **5ca**, and **5da**: ref 11b. **5ab** and **5ac**: ref 11e. **7ha**: ref 11d. **5gb**, **5gc**, and **7gb**: ref 12a. **5id**: Wang, H.; Jiang, T.; Xu, M.-H. *J. Am. Chem. Soc.* **2013**, *135*, 971.

(18) According to a recent computational study (ref 12b), coordination of the substrate to the palladium intermediate is proposed to take place though the N lone pair.

DOI: 10.1021/acs.orglett.5b02613
Org. Lett. 2015, 17, 5104−5107