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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Palladium-Catalyzed Enantioselective Domino Heck/Intermolecular C−H Bond Functionalization: Development and Application to the Synthesis of (+)-Esermethole

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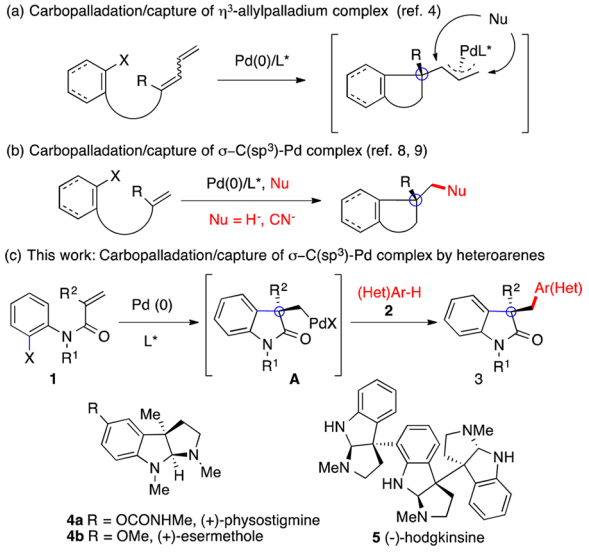
Supporting Information

ABSTRACT: Intramolecular asymmetric carbopalladation of *N*-aryl acrylamides followed by intermolecular trapping of the resulting σ-C(sp^3)−Pd complex by azoles afforded 3,3-disubstituted oxindoles in good yields with excellent enantioselectivities. Two C−C bonds were created with concurrent formation of an all-carbon quaternary stereocenter. Oxadiazole substituted oxindoles were subsequently converted to pyrroloindolines by an unprecedented reductive cyclization protocol. The utility of this chemistry was illustrated by an enantioselective synthesis of (+)-esermethole.

The enantioselective intramolecular Heck reaction, pioneered by Shibasaki[1] and Overman,[2] has been extensively exploited for the synthesis of bioactive natural products having quaternary carbon stereocenters.[3] The development of domino processes involving enantioselective intramolecular carbopalladation of conjugated dienes followed by nucleophilic trapping of the resulting η^3-allylpalladium intermediates have further extended the utility of this powerful reaction (Scheme 1a).[4]

Scheme 1. Domino Reactions Initiated by Enantioselective Carbopalladation Process



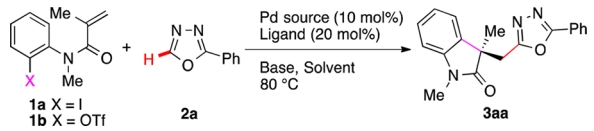
On the other hand, although carbopalladation/nucleophilic capture of σ-alkyl palladium(II) intermediates has been well developed,[5] including the Heck/direct arylation sequence,[6] asymmetric versions of these domino sequences are rather limited.[7] To the best of our knowledge, hydride[8] and cyanide (Scheme 1b)[9] are the only nucleophiles that have been successfully used to terminate the asymmetric Heck process. We report herein the first examples of an enantioselective domino Heck/intermolecular direct arylation process for the synthesis of 3,3-disubstituted oxindoles **3** from *N*-aryl acrylamides **1** and heteroarenes **2** (Scheme 1c).[10,11] We document also rare examples in which intermolecular trapping of σ-alkyl-Pd complex **A** by azoles overtook the alternative intramolecular CH-functionalization process and an unprecedented reductive cyclization of **3** [(Het)Ar = oxadiazole] to pyrroloindoline, a structural motif found in bioactive natural products such as (+)-physostigmine (**4a**)[12] and (−)-hodgkinsine (**5**).[13] Physostigmine is a reversible inhibitor of acetylcholinesterase used for the treatment of glaucoma and Alzheimer's diseases.

The *N*-(2-iodophenyl)-*N*-methyl methacrylamide (**1a**) and 2-phenyl-1,3,4-oxadiazole (**2a**, 1.2 equiv) were chosen as test substrates (see Table S1 in the Supporting Information (SI) for details). Gratefully, we isolated **3aa** in 94% yield by simply heating a THF solution of **1a** and **2a** (80 °C) in the presence of $Pd(OAc)_2$, dppp, and Cs_2CO_3 (entry 1, Table 1). Replacing dppp by BINAP, a highly efficient ligand in asymmetric Heck reaction,[3,10] afforded **3aa** in 60% yield with 20% *ee* (entry 2). Adding Ag_3PO_4 as a halide scavenger inhibited the desired domino process (entry 3). Noteworthy improvement of the enantioselectivity was observed when aryl triflate **1b** was used as a substrate (entry 4, Table 1). Based on these results, conditions were further optimized for the reaction between **1b** and **2a**. Among the chiral ligands screened (entries 4 to 9), *t*BuPHOX (**L6**) proved to be the most effective providing **3aa** in 60% yield with 57% *ee* (entry 9, Table 1).[14] We subsequently found that base played a key role in the reaction outcome (entries 10−14). Using DABCO as a base under otherwise identical conditions **3aa** was formed with 85% *ee*, albeit with a lower yield (entry 14, Table 1). Further screening of the bases (PMP, DIPEA, TMEDA, DMAP, HMTA, proton sponge, and TMG, Figure 1), solvents, and Pd sources (entries 15−21) allowed us to define

Received: November 6, 2015
Published: December 17, 2015

DOI: 10.1021/jacs.5b11625
J. Am. Chem. Soc. 2015, 137, 16028−16031

Table 1. Optimization of the Reaction Conditions[a]



entry	1	PdX_2	base	ligand	yield (%)[i]	ee (%)[j]
1	**1a**	$Pd(OAc)_2$	Cs_2CO_3	dppp	94	–
2	**1a**	$Pd(OAc)_2$	Cs_2CO_3	**L1**	60	20
3[b]	**1a**	$Pd(OAc)_2$	Cs_2CO_3	**L1**	n.d.	–
4	**1b**	$Pd(OAc)_2$	Cs_2CO_3	**L1**	54	36
5	**1b**	$Pd(OAc)_2$	Cs_2CO_3	**L2**	41	23
6	**1b**	$Pd(OAc)_2$	Cs_2CO_3	**L3**	74	45
7	**1b**	$Pd(OAc)_2$	Cs_2CO_3	**L4**	73	51
8	**1b**	$Pd(OAc)_2$	Cs_2CO_3	**L5**	60	3
9	**1b**	$Pd(OAc)_2$	Cs_2CO_3	**L6**	60	57
10	**1b**	$Pd(OAc)_2$	K_2CO_3	**L6**	40	50
11	**1b**	$Pd(OAc)_2$	$NaHCO_3$	**L6**	33	60
12	**1b**	$Pd(OAc)_2$	DBU	**L6**	50	55
13	**1b**	$Pd(OAc)_2$	CsOPiv	**L6**	47	49
14[c]	**1b**	$Pd(OAc)_2$	DABCO	**L6**	40	85
15[c,d]	**1b**	$Pd(OAc)_2$	DABCO	**L6**	39	62
16[c,e]	**1b**	$Pd(OAc)_2$	DABCO	**L6**	44	79
17[c,f]	**1b**	$Pd(OAc)_2$	DABCO	**L6**	40	87
18[c,f]	**1b**	$Pd_2(dba)_3$	DABCO	**L6**	24	86
19[c,f]	**1b**	$PdCl_2(MeCN)_2$	DABCO	**L6**	25	93
20[c,f,g]	**1b**	$PdCl_2(MeCN)_2$	other bases	**L6**	trace	–
21[c,f,h]	1b	**$PdCl_2(MeCN)_2$**	**TMG**	L6	**71**	**94**
22[c,f,h]	**1b**	$PdCl_2(MeCN)_2$	TMG	**L7**	49	67
23[c,f,h]	**1b**	$PdCl_2(MeCN)_2$	TMG	**L8**	52	71
24[c,f,h]	**1a**	$PdCl_2(MeCN)_2$	TMG	**L6**	75	56

[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.12 mmol), Pd-catalyst (10.0 mol %), ligand (20.0 mol %), and base (0.2 mmol) in THF (2.0 mL) in a sealed tube at 80 °C for 14 h. [b]With Ag_3PO_4 (2.0 equiv) [c]Reaction time: 2 days. [d]In toluene. [e]In DMF. [f]In MeCN. [g]Using PMP, DIPEA, TMEDA, DMAP, HMTA, or proton sponge as a base. [h]With 5 equiv of TMG. [i]Isolated yields. [j]Determined by SFC on chiral stationary phase.

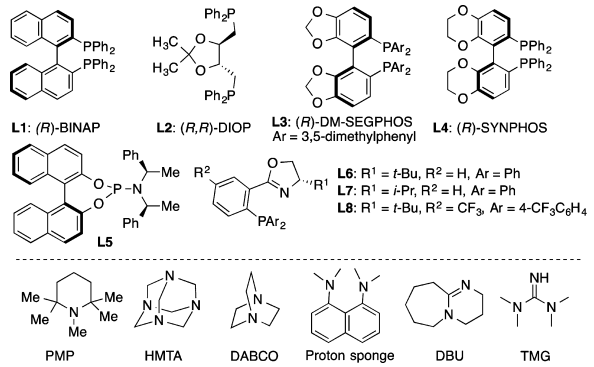
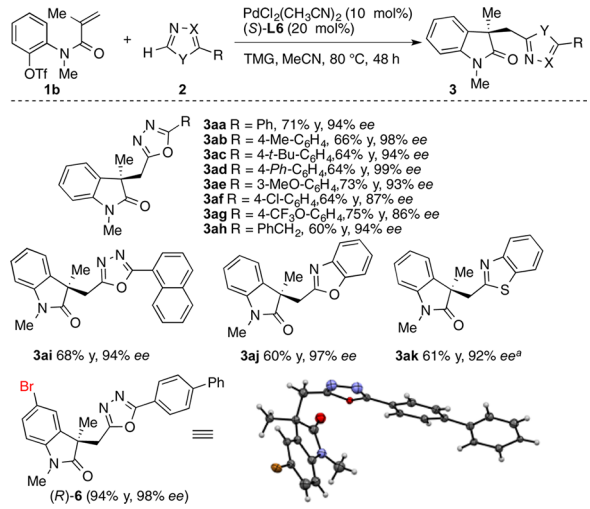


Figure 1. Ligands and bases screened.

the following optimum conditions: $PdCl_2(MeCN)_2$/**L6** as catalyst and *N*,*N*,*N*,*N*-tetramethylguanidine (TMG) as a base in MeCN at 80 °C. Under these conditions, oxindole **3aa** was isolated in 71% yield with 94% *ee* (entry 21). Other PHOX type ligands (**L7**, **L8**) afforded **3aa** with reduced yields and *ee*'s (entries 22, 23). Finally, reaction of aryl iodide **1a** with **2a** under optimized conditions afforded the product **3aa** with much diminished *ee* (entry 24), suggesting that the cationic pathway might be essential for this enantioselective transformation.

With the optimum conditions in hand (Table 1, entry 21), the reaction scope with regard to the structure of azole was first examined (Scheme 2). 2-Aryloxadiazoles having a *p*-methyl, *p*-

Scheme 2. Scope of the Heterocycles[a]



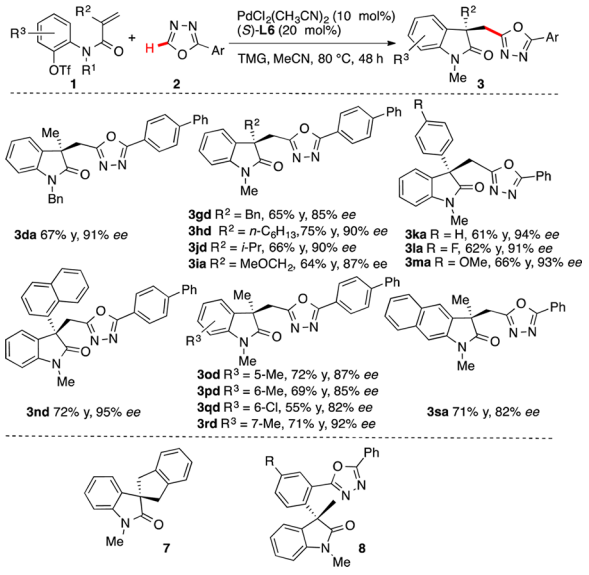
[a](*tert*-Butylimino)tris(pyrrolidino)phosphorane (BTPP) was used as a base.

tert-butyl, *p*-phenyl, and *m*-methoxy group on the phenyl ring reacted efficiently with **1b** to afford products **3ab**–**3ae** in good yields with 93%–99% *ee*. A slightly reduced *ee* was observed for oxadiazoles bearing an electron-withdrawing groups such as chloride and OCF_3.[15] Benzyl and 1-naphthyl substituted oxadiazoles participated in the reaction smoothly to afford the desired product **3ah** and **3ai** with excellent *ee*'s. Benzoxazole and benzothiazole were also accepted as substrates leading to **3aj** and **3ak** in 97% and 92% *ee*'s, respectively.[16] In the latter case, a strong base (BTPP) is needed to ensure the occurrence of the reaction. Finally, regioselective bromination of **3ad** (NBS, MeCN, 0 °C to rt) provided **6** in 94% yield whose absolute configuration (*R*) was determined by X-ray crystal structural analysis.

The substrate scope with respect to acrylamides was investigated next (Scheme 3). The domino reaction between *N*-benzyl acetanilide **1d** and oxadiazole **2a** proceeded efficiently to provide **3da** in 67% yield with 91% *ee*. As the *N*-benzyl is readily removed, it constitutes a route to *N*-unsubstituted oxindoles. The influence of the Cα substituents (R^2) of the acrylamide double bond on the reaction outcome was also examined. *n*-Hexyl, isopropyl, and methoxymethyl substituents are all well tolerated leading to the corresponding oxindoles in good yields with excellent *ee*'s. Notably, reaction of benzyl substituted acetanilide **1g** with oxadiazole **2d** afforded **3gd** in 65% yield with 86% *ee*. The alternative competing process involving Heck/intramolecular CH-functionalization leading to **7** was not observed.[17,18] We stress herein that only a slight excess of oxadiazole **2** (1,2 equiv) was used in our reaction. The phenyl with different electronic properties and a 2-naphthyl group at the Cα position of the double bond were well tolerated affording the corresponding oxindoles in good yields with excellent *ee*'s. Once again, side product **8** resulting from the possible competitive 1,4-Pd migration/arylation from the σ-C(sp^3)–Pd intermediate **A** (*cf.* Scheme 1) was not isolated.[19] These results provided rare examples wherein the intermolecular C–H functionalization of

DOI: 10.1021/jacs.5b11625
J. Am. Chem. Soc. 2015, 137, 16028–16031

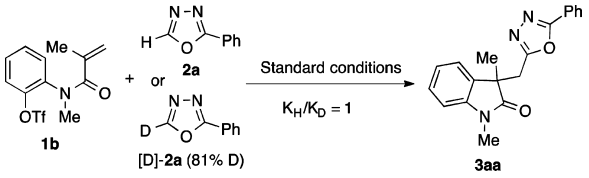
Scheme 3. Scope of Acetanilides



azoles were kinetically much faster than the alternative intramolecular process. Finally, the influence of the substitution pattern in the aniline part was evaluated. Substituted anilides (*para*-, *meta*-, or *ortho*-) and *N*-(naphthalen-2-yl)amide all underwent the domino process without event (**3od**−**3rd**, **3sa**).

A side-by-side kinetic experiments using **2a** and [D]-**2a** as a reaction partner of **1a** provided an intermolecular KIE (k_H/k_D) value of 1.0 (Scheme 4). In addition, rapid H/D scrambling

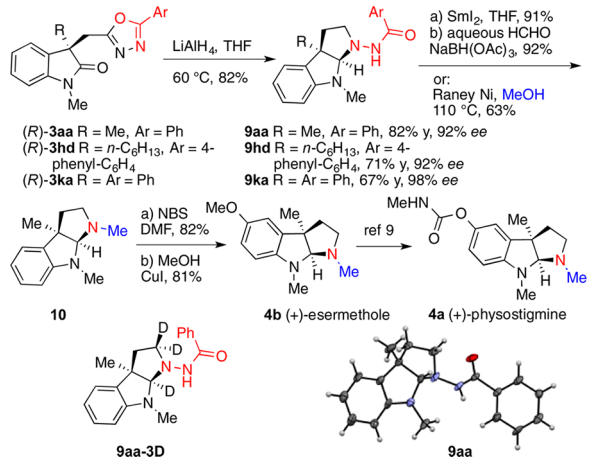
Scheme 4. KIE Experiment



(40%) was observed upon exposure of [D]-**2a** under the standard conditions for 1 h.[20] These results indicated that the C−H activation step might not be a turnover-limiting step in our domino process.

Aimed at exploiting the synthetic potential of the bisheterocycles **3**, we serendipitously found that reduction of oxindoles **3aa** with $LiAlH_4$ provided pyrroloindoline **9aa** in 82% yield without erosion of the enantiomeric purity (Scheme 5). When $LiAlD_4$ was used, compound **9aa**-**3D** was isolated in a similar yield.[21] The structure of **9aa** was confirmed by X-ray diffraction analysis (*cf.* SI). Compounds **3hd** and **3ka** were similarly converted to **9hd** (R = *n*-C_6H_{13}) and **9ka** (R = Ph), respectively, indicating the generality of this unprecedented reductive cyclization process. Conversion of pyrroloindoline **9aa** to (+)-esermethole (**4b**) is straightforward. Reductive cleavage of the *N*-*N* bond of hydrazine (SmI_2, THF, rt) followed by *N*-methylation [HCHO, $NaBH(OAc)_3$] afforded **10** in 83% overall yield. Alternatively, we found that treatment of **9aa** with activated Raney Nickel in MeOH directly afforded the *N*-methylated product **10** in 63% yield. While Ni-promoted reductive amination of aniline with alcohol is known, methanol was known to be unsuitable for this purpose due to the rapid disproportionation of the *in situ* generated formaldehyde under

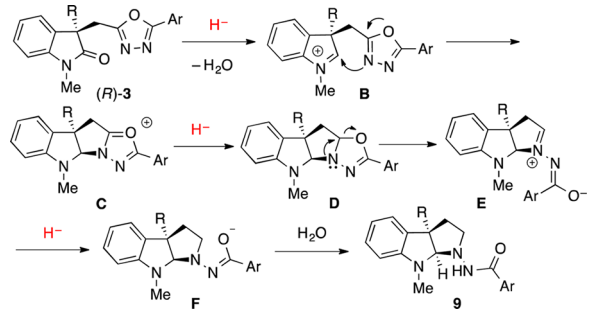
Scheme 5. Reductive Cyclization of Oxindole to Pyrroloindoline: Synthesis of (+)-Esermethole and (+)-Physostigmine



the reaction conditions.[22] The present one-pot procedure involving Ni-promoted N−N bond cleavage[23] followed by *N*-methylation of the resulting secondary amine has, to the best of our knowledge, never been reported. The transformation of **10** to (+)-esermethole (**4b**) was accomplished by a sequence of regioselective bromination followed by CuI-catalyzed methoxylation of the resulting aryl bromide.[24] Esermethole (**4b**) has previously been converted to (+)-physostigmine (**4a**) in two steps in our laboratory.[9a]

A possible reaction pathway accounting for the reductive cyclization of **3** to **9** is proposed in Scheme 6. Reduction of amide

Scheme 6. Reductive Cyclization of Oxindole to Pyrroloindoline: A Possible Reaction Pathway



to hemiaminal followed by dehydration would lead to a highly reactive iminium intermediate **B**, which was trapped by the nitrogen of the tethered oxadiazole to form a tetracyclic intermediate **C**. Reduction of the oxonium followed by ring opening of the resulting fused dihydrooxadiazole **D** would afford iminium **E** that was further reduced to pyrroloindoline **F**. Protonation of the latter would then afford **9**.

In summary, we have developed the first asymmetric domino Heck/intermolecular direct arylation sequence for the construction of oxindole-azole bis-heterocycles bearing a quaternary stereocenter. We note that both oxindole and oxadiazole are important pharmacophores that can be found in marketed drugs.[25] An unprecedented reductive cyclization of oxadiazole substituted oxindoles to pyrroloindolines was discovered serendipitously that allowed us to develop a concise enantioselective synthesis of (+)-esermethole.

DOI: 10.1021/jacs.5b11625
J. Am. Chem. Soc. 2015, 137, 16028−16031

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11625.

Crystallographic data for (*R*)-**6** (CIF)
Crystallographic data for (*R*)-**9aa** (CIF)
Experimental procedures, spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank EPFL, the Swiss National Science Foundation (SNSF), and the Swiss National Centres of Competence in Research (NCCR-Chemical Biology) for financial support. We are grateful to Dr. Rosario Scopelliti for performing X-ray structural analysis.

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(16) Pentafluorobenzene can be used to trap the transient C_{sp^3}–Pd intermediate under racemic conditions. We thank one of the referees for suggesting this experiment. Other heterocycles such as 2-chlorothiophene and oxazoles are also suitable substrates. However, further optimization is needed for the enantioselective version. Pyrimidine, benzoimidazole, and indole failed to participate in this domino process.

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DOI: 10.1021/jacs.5b11625
J. Am. Chem. Soc. 2015, 137, 16028–16031