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Heterobimetallic Pd–Sn catalysis: highly selective intermolecular hydroarylation of α-methyl substituted aryl alkenes

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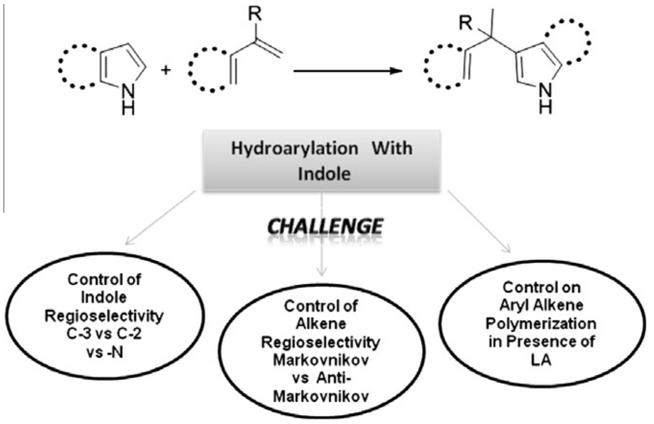
ABSTRACT

The heterobimetallic catalyst [Pd(COD)Cl–$SnCl_3$] efficiently promotes the intermolecular hydroarylation of α-methyl substituted arenes (otherwise known to be dimerized/polymerized in presence of Lewis Acids) with indoles and other O-, S-heteroarenes leading to Markovnikov adducts. The reaction takes place under air and moisture insensitive condition.

Alkylated indoles are important structural motifs frequently encountered in a broad range of biologically active compounds.[1,2] Conventionally, 3-alkylated indoles are synthesized by carbon–carbon bond-forming reactions such as (a) acid- or base-promoted alkylation or (b) transition metal catalyzed alkylation. In general Lewis or Brønsted acid catalyzed activation of electrophiles takes place through Friedel–Crafts like path[2,3] while transition metal-catalyzed alkylations proceed via electrophilic π-metal complex.[2,4] Hydroarylation of an alkene represents an atom economic alternative to Friedel–Crafts like alkylation specially for the construction of a benzylic stereocenter. Although intermolecular hydroarylation of indole was well investigated with electron-deficient Michael acceptor,[2,5] only a few examples are available where an unfunctionalized terminal alkene (like aryl alkene) was used. The challenges associated with intermolecular hydroarylation of aryl alkene with indole are: (i) to direct the regioselectivity at a selective site out of the many probable ones in the indole ring and in the aryl alkene, and (ii) to inhibit the polymerization of aryl alkenes as is the case in the presence of Lewis acids[6] (Scheme 1).

In this respect Widenhoefer and co-workers demonstrated that platinum(II) acts as an efficient catalyst for the intermolecular hydroarylation of unactivated alkenes with indoles; but with higher alkenes the regioselectivity observed was poor.[7] Liu and co-workers reported the use of triflic acid (TfOH) as a catalyst for hydroarylation of alkenes, but the hydroarylation reaction was limited to N-phenylsulfonyl protected indoles.[8,9] Che and co-workers developed the hydroarylation of styrene with indole under thermal or microwave-assisted conditions using a combination of [AuCl(PPh_3)]/AgOTf as catalyst.[10] Recently Hiyama and co-workers reported a nickel-catalyzed hydroheteroarylation of vinylarenes with electron-poor heteroarenes which leads to 1,1-diarylethanes.[11] Pathak and Sigman reported a palladium-catalyzed hydroheteroarylation reaction of alkenes using alkyl chloride as the sacrificial hydride source; unfortunately the reaction is specific to vinyl phenols only.[12] It is noteworthy that in all the above cases,



Scheme 1. Challenge in hydroarylation of aryl alkene with indole.

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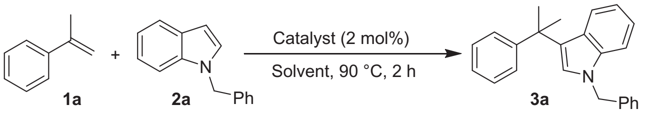
Table 1
Hydroarylation model study: catalyst screening[a]



#	Catalyst	Solvent	Yield of **3a**[b] (%)
1[c]	HCl	DCE	~0
2	pTSA	DCE	~0
3[c]	TfOH	DCE	15
4[c,d]	TfOH	DCM	<5
5	$SnCl_2$	DCE	<10
6	$ZnCl_2$	DCE	<5
7	$FeCl_3$	DCE	17
8	$AlCl_3$	DCE	11
9	$InCl_3$	DCE	~0
10	$SnCl_4$	DCE	<10
11	$Bi(OTf)_3$	DCE	<10
12	$Yb(OTf)_3$	DCE	<10
13	$La(OTf)_3$	DCE	12
14	$Sc(OTf)_3$	DCE	15
15	$Cu(OTf)_2$	DCE	22
16	$Ru(PPh_3)_3Cl_2$	DCE	~0
17	$PtCl_2(MeCN)_2$	DCE	~0
18	**$PdCl(COD)SnCl_3$ (C1)**	**DCE**	**72**
19	$PdCl(PPh_3)_2SnCl_3$ (**C2**)	DCE	<10
20	$PdCl_2(COD)$	DCE	~0
21	$[(PPh_3)AuCl]/AgOTf$	DCE	12
22[e]	$[(PPh_3)AuCl]/AgOTf$	Toluene	18
23	$PdCl(COD)SnCl_3$ (**C1**)	Toluene	<5
24	$PdCl(COD)SnCl_3$ (**C1**)	MeCN	<5

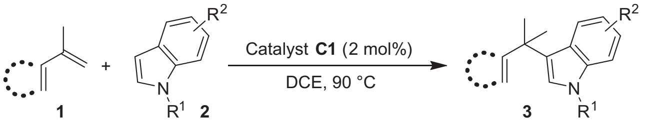
[a] A mixture of **1a** (0.5 mmol), **2a** (0.25 mmol), and catalyst (2 mol %) in 2 mL of solvent was stirred at 90 °C for 2 h.
[b] ^1H NMR yield using triphenyl methane as external standard.
[c] 5 mol % catalyst was used.
[d] Carried out at 25 °C for 16 h with **1a**:**2a** = 1:1 according to the Ref. 8.
[e] Carried out according to the Ref. 10.

the reactions were promising with simple styrene derivatives (FG-Ar-CH═CH$_2$). To our knowledge, an efficient methodology for the regioselective hydroarylation of α-methyl substituted aryl alkenes (FG-Ar-C(Me)═CH$_2$) (well known for their propensity to dimerize/polymerize in presence of LA)[6] with indole derivatives is yet to emerge.

In continuation of our success with bimetallic catalysis for carbon–carbon and carbon–heteroatom bond formation,[13] we developed herein a heterobimetallic 'Pd–Sn' catalyst which promotes the intermolecular hydroarylation of α-methyl substituted aryl alkenes with indoles with high efficiency and regioselectivity. An added bonus is the fact that the reactions proceed under moisture and air insensitive conditions. The intermolecular hydroarylation is also briefly extended to O- and S- heteroarenes.

The insertion reaction of $SnCl_2$ across 'Pd–Cl' was used in the presence of ligand to generate the corresponding 'Pd–Cl' motif $PdCl(COD)–SnCl_3$ **C1** and $PdCl(PPh_3)_2–SnCl_3$ **C2**.[13g] Initially, the performance of different Brønsted acids, monometallic salts, and bimetallic complexes (2 mol %) was tested for the model reaction of α-methyl styrene **1a** (0.5 mmol) and 1-benzyl-1*H*-indole **2a** (0.25 mmol) in 1,2-dichloroethane (DCE) as solvent for 2 h at 90 °C. Gratifyingly, the heterobimetallic $Pd(COD)Cl–SnCl_3$ (**C1**) catalyst showed excellent catalytic efficiency and regioselectivity leading to the Markovnikov product **3a** (Table 1, entry 18). Notably, it is not necessary to exclude air or moisture in this reaction. Individually $[Pd(COD)Cl_2]$ was inactive while $SnCl_2$ and the other bimetallic 'Pd–Sn' catalyst **C2** showed poor reactivity. Catalytic amounts of various Brønsted acids did not show product formation (entries 1 and 2). Even LAs such as $ZnCl_2$, $FeCl_3$, $AlCl_3$, $InCl_3$, and $SnCl_4$ were ineffective or poorly active (entries 6–10). Likewise, among the metal triflates screened, only $Cu(OTf)_2$ and $Sc(OTf)_3$ led to the

Table 2
Pd–Sn catalyzed hydroarylation of aryl alkenes with indoles: substrate scope[a]



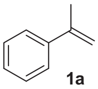
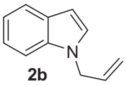
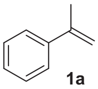
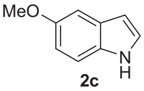
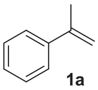
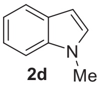
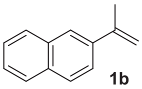
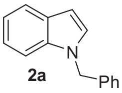
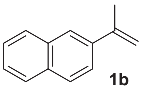
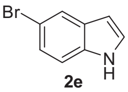
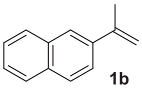
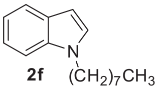
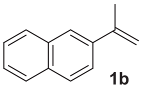
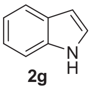
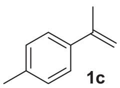
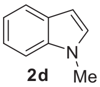
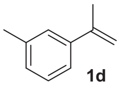
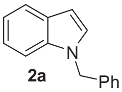
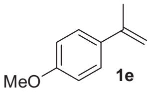
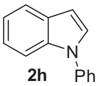
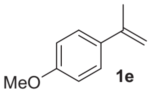
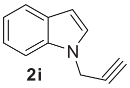
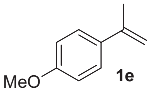
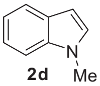
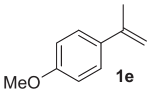
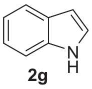
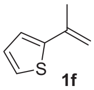
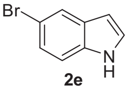
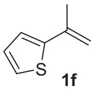
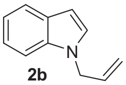
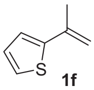
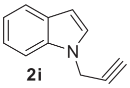
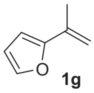
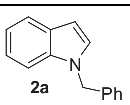
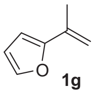
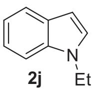
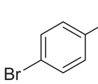
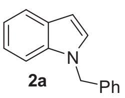
Entry	Alkene	Indole	Time (h)	Yield of **3** (%)
1	 1a	 2b	8	**3b**, 90
2	 1a	 2c	12	**3c**, 50
3[b]	 1a	 2d	10	**3d**, 62
4	 1b	 2a	6	**3e**, 85
5	 1b	 2e	12	**3f**, 60
6	 1b	 2f	10	**3g**, 70
7	 1b	 2g	12	**3h**, 65
8[b]	 1c	 2d	10	**3i**, 68
9	 1d	 2a	8	**3j**, 88
10	 1e	 2h	2	**3k**, 90
11	 1e	 2i	4	**3l**, 65
12	 1e	 2d	4	**3m**, 85
13	 1e	 2g	2	**3n**, 83
14[c]	 1f	 2e	10	**3o**, 76
15[c]	 1f	 2b	6	**3p**, 80
16[c]	 1f	 2i	10	**3q**, 60

Table 2 (*continued*)

Entry	Alkene	Indole	Time (h)	Yield of **3** (%)
17[c]	 **1g**	 **2a**	8	**3r**, 72
18[c]	 **1g**	 **2j**	10	**3s**, 61
19	 **1h**	 **2a**	12	Nil

[a] Unless otherwise mentioned, reaction conditions were as follows: **1** (0.30 mmol), **2** (0.25 mmol), cat. **C1** (2 mol %), solvent DCE (2 mL), 90 °C.

[b] 5 mol % cat. **C1** was used.

[c] 10 equiv. of **1** was used.

desired product in <25% yield. Transition metal complexes like $Ru(PPh_3)_3Cl_2$ and $PtCl_2(MeCN)_2$ did not show catalytic activity. Notably the activity of **C1** was lost in toluene and acetonitrile as solvents (entries 23 and 24). Finally, the model reaction has been tested with reported TfOH (5 mol %)[8] and $AuCl_3$/AgOTf (2 mol %),[10] however in both cases **3a** was obtained in poor yield (entries 3, 4, 21 and 22).

Having established the optimum condition, we tested the scope and limitation of the hydroarylation reaction using various α-methyl styrenes **1** and N-substituted (alkyl, benzyl, allyl, propargyl, and phenyl) or ring substituted indoles **2** (Table 2). Gratifyingly, in most cases the corresponding alkylated indoles **3** were obtained in moderate to good yields using 1.2 equiv of **1a-1e** (entries 1–13). One may note that in all the cases where we have used free indole, the reactions were completely C3-selective and no *N*-alkyl product was formed. The **C1** catalyzed hydroarylation reaction showed marked dependency on methyl substitution at the α-position of styrene. The reaction of **2a** with simple styrene, α-ethyl styrene, and α-phenyl styrene failed to yield the desired alkylated indole derivatives under the same reaction condition. It was also observed that alkylation of indole proceeded smoothly with electron-rich α-methyl aryl alkenes like **1f**–**1g** (entries 14–18), whereas electron-poor 4-bromo α-methyl styrene **1h** was inactive (entry 19). Under the light of the above substitution effect, we tentatively suggest that an electrophilic mechanism[13d] may be operating in the present case. In a preliminary experiment when ^1H and ^{13}C NMR spectra of **1a** were examined in $CDCl_3$ in the presence of catalyst **C1** at room temperature, marginal shift was obtained. The detailed mechanistic description must await further studies.

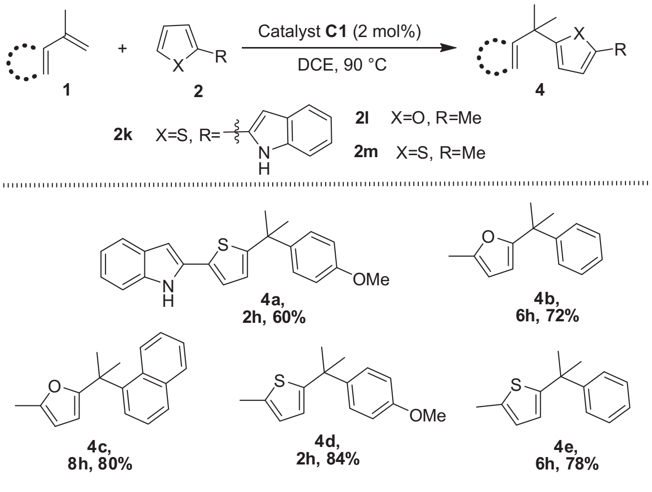


Figure 1. Hydroarylation with O, S-heteroarenes.

An interesting observation was found with 2-(thiophen-2-yl)-1*H*-indole (**2k**), in which instead of C-3 alkylation in the indole ring, solely 5-alkylated thiophene **4a** (Fig. 1) was obtained. This result suggested that besides indoles, other heteroarenes can also be alkylated in the presence of **C1**. Therefore to enrich the scope of the reaction further, we briefly tested different heteroarenes under a similar reaction condition. The progress of the hydroarylation reaction with O-, S-heteroarenes was satisfactory and the corresponding alkylated O-, S-heteroarenes (**4a**–**4e**) were obtained in good yields (Fig. 1). Notably the addition reaction was highly regioselective and in all cases only Markovnikov products were obtained.

In summary, the heterobimetallic 'Pd–Sn' complex **C1** has been found to be an effective catalyst for highly atom-economical and regioselective intermolecular hydroarylation of electron-rich α-methyl substituted aryl alkenes with indoles and other heteroarenes. Extensive catalyst screening clearly established the importance of the bimetallic core in the catalyst; mechanistic studies are underway to understand the initial bond activation stages so that the catalyst can be tuned further. One may also note that ease of handling of the catalyst (insensitive toward air and moisture) makes the reaction more attractive, simple, and practical.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.038.

References and notes

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