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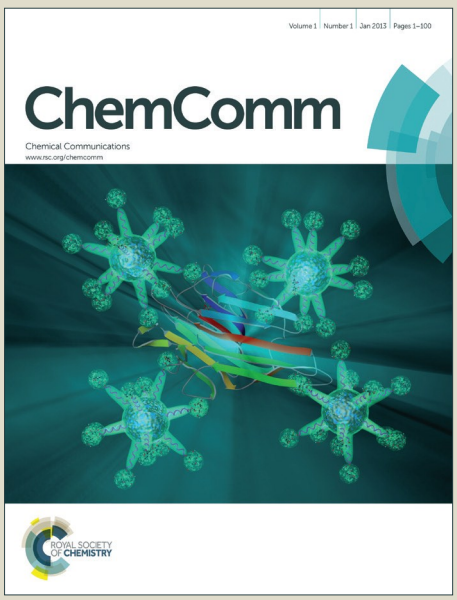

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Hypervalent iodine mediated alkene difunctionalization of vinylphenols: diastereoselective synthesis of substituted indoles and indolizines†

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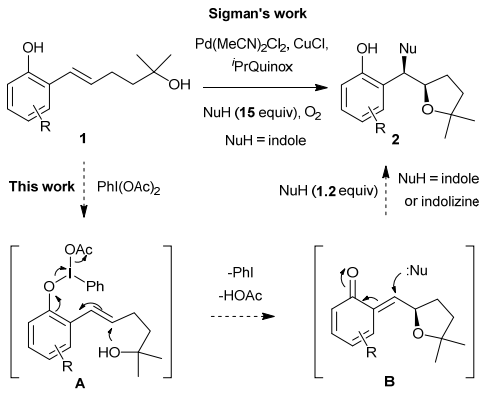
A hypervalent iodine mediated alkene difunctionalization reaction of vinylphenols has been developed. The chemistry is applicable to a wide range of substitution on both the alkene and nucleophile substrates, enabling the rapid synthesis of 3-substituted indoles and 2-substituted indolizines in good yields and high diastereoselectivities under metal-free conditions.

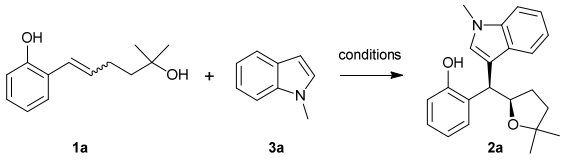
Indoles and indolizines are common architectural backbones in bioactive synthetic and natural products and occupy privileged positions in drug discovery.[1] Therefore, the development of new methods for accessing these unique structures is of great importance for drug lead synthesis. Due to these reasons, employment of indoles and indolizines as nucleophiles in alkene difunctionalization reactions has attracted much attention from synthetic community.[2]



Scheme 1 Quinone methide approaches to alkene difunctionalization.

Recently, Sigman and co-workers reported an elegant Pd-catalyzed alkene difunctionalization reaction of vinylphenol **1** (Scheme 1),[2a] which was proposed to proceed through an intramolecular oxypalladation followed by Michael-type addition of indole to the resulting *ortho*-quinone methide.[3] We envisaged that nucleophilic addition of the pendant hydroxyl group to the alkene moiety of **1** would also occur with the assistance of a hypervalent iodine oxidant, via heterocyclic intermediate **A** in an associative manner.[4] Subsequent formation of the quinone methide intermediate **B** would allow for attack by an exogenous nucleophile, to afford desired product **2**. Herein, we report an iodine(III) mediated alkene difunctionalization reaction of vinylphenols, which resulted in the efficient synthesis of substituted indoles and indolizines with high diastereoselectivities under metal-free conditions.

Table 1 Optimization of the reaction parameters[a]



Entry	Iodine(III) Reagent	Solvent	Temp. (°C)	Yield[b] (%)	dr[c]
1	$PhI(OAc)_2$	CH_2Cl_2	0	72	12:1
2	$PhI(OCCF_3)_2$	CH_2Cl_2	0	54	12:1
3	PhIO	CH_2Cl_2	0	n.d.[d]	-
4	PhI(OH)(OTs)	CH_2Cl_2	0	n.d.	-
5	$PhI(OAc)_2$	DCE	0	67	8:1
6	$PhI(OAc)_2$	$CHCl_3$	0	65	9:1
7	$PhI(OAc)_2$	Toluene	0	13	6:1
8	$PhI(OAc)_2$	CH_3CN	0	9	6:1
9	$PhI(OAc)_2$	HFIP	0	<5	-
10	$PhI(OAc)_2$	CH_2Cl_2	−78	<5	-
11	$PhI(OAc)_2$	CH_2Cl_2	−50	38	>20:1
12	**$PhI(OAc)_2$**	**CH_2Cl_2**	**−20**	**84**	**>20:1**
13	$PhI(OAc)_2$	CH_2Cl_2	rt	66	10:1

[a] Reaction conditions: **1a** (0.20 mmol), **3a** (0.24 mmol), iodine(III) reagent (0.24 mmol) in solvent (10 mL) at indicated temperature. [b] Isolated yields. [c] Determined by crude ^1H NMR analysis. [d] Not detected. DCE = 1,2-dichloroethane, HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.

To test our hypothesis, vinylphenol **1a**[5] and *N*-methylindole (**3a**) were selected as model substrates. The reaction was successful over 1 h by using 1.2 equiv of $PhI(OAc)_2$[6] at 0 °C in CH_2Cl_2, affording indole derivative **2a** in 72% yield and 12:1 dr (Table 1, entry 1). Replacement of $PhI(OAc)_2$ with other iodine(III) reagent

($PhI(OCCF_3)_2$, PhIO, or PhI(OH)(OTs)) gave a decreased yield of **2a** (entries 2–4). Solvents such as DCE and $CHCl_3$ delivered the desired product in acceptable yields and modest diastereoselectivities (entries 5 and 6), whereas toluene, CH_3CN or HFIP led to a much lower yield and dr (entries 7–9). Further investigation on the reaction temperature revealed that –20 °C was most suitable, at which **2a** was obtained in 84% yield and >20:1 dr (entry 12). In contrast, only trace amount of **2a** was formed when the reaction was carried out at –78 °C (entry 10), which could be isolated in 38% yield at –50 °C (entry 11). On the other hand, a slight drop in both yield and dr was observed at room temperature (entry 13 *cf.* entries 1 and 12). It should also be noted that in this reaction both individual *E*- and *Z*-alkene isomers of vinylphenol **1a** gave the same diastereomer **2a**, and only 1.2 equiv of indole **3a** was required for the consumption of **1a**.[7]

With the optimized conditions in hand, the generality and scope of the alkene difunctionalization reaction was explored (Scheme 2a). Vinylphenols bearing electron-neutral, electron-deficient, and electron-rich phenyl rings were converted to the corresponding products in good yields and excellent diastereoselectivities (71–86% yield, >20:1 dr; **2b–e**), which indicated the electronic properties of the phenyl subunit had little influence on the efficiency of this reaction. The reaction demonstrated wide substrate scope in terms of the *N*-alkyl-protected indole structure. Various indoles with different steric and electronic parameters, including 1-substituted, 2-substituted, 4-substituted, and 5-substituted were found to be compatible, again resulting in good to excellent yields and drs (63–81% yield, 13–>20:1 dr; **2f–r**). In addition, both tetrahydrofuran and tetrahydropyran ring systems were formed smoothly (**2s** and **2t**). It should be mentioned that *N*-protection of indole is required, and electron-deficient substituents such as Ts or Boc on the indole nitrogen were also employed, which turned out to substantially decrease the yield due to its weak nucleophilicity. 3-Substituted indoles (e.g. 3-Me, 3-Ph, 3-CO_2Me) as reaction partners were investigated as well, unfortunately, none of the desired 2-substituted products was observed under the standard conditions.[8]

The relative stereochemistry of the products was unambiguously determined by X-ray crystallographic analysis of **2p** (Fig. 1a).[9] The origin of the diastereoselectivity could be possibly explained based on Yamamoto's model[10] for chiral Michael acceptors. A "π-complex" mechanism was hypothesized (Fig. 1b), through which the *syn* isomer was formed predominantly regardless of the double-bond geometry in transition state B (Scheme 1).

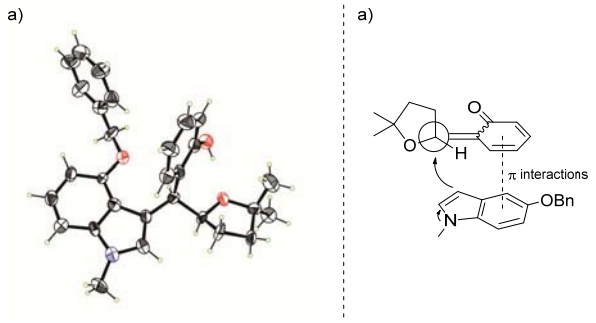
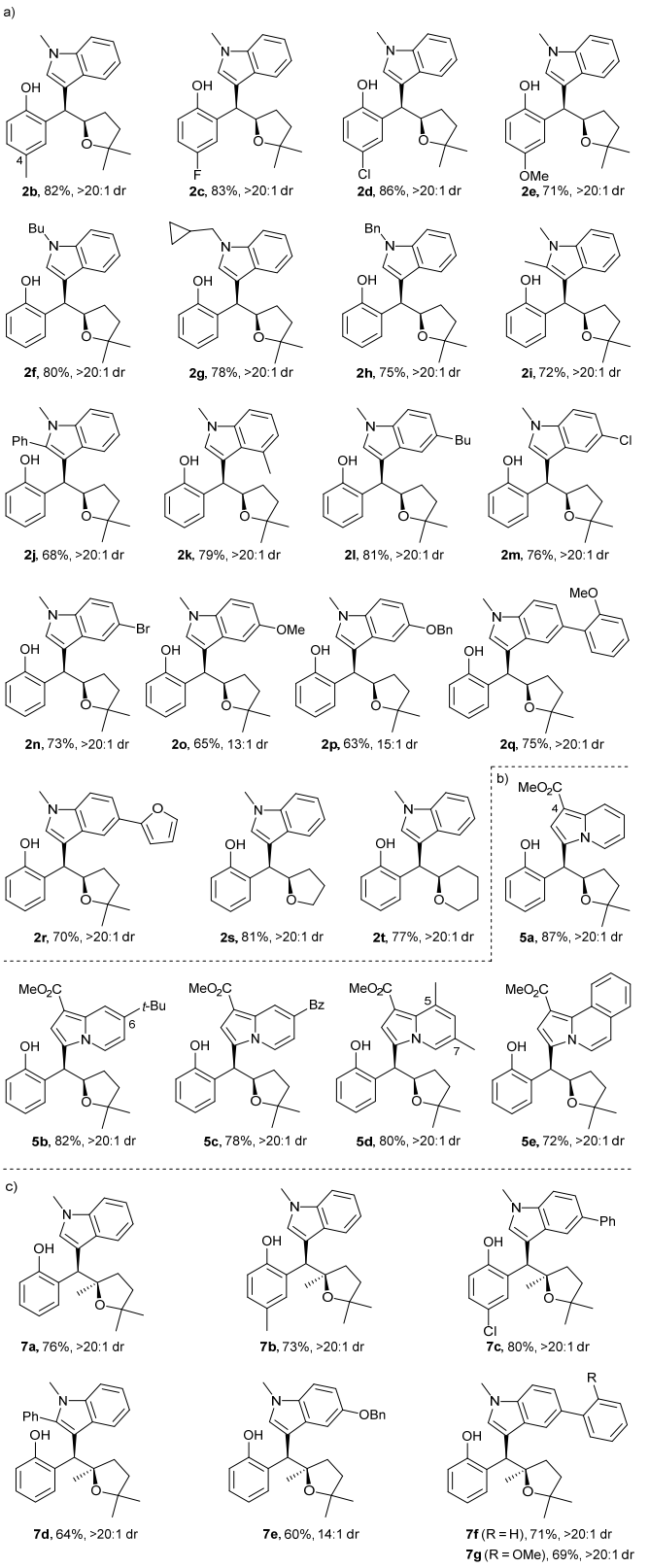


Fig. 1 a) ORETP of compound **2p**; b) proposed origin of the diastereoselectivity.

The reaction was not limited to only indole nucleophiles, as demonstrated in Scheme 2b by the successful employment of indolizines, which led to new pharmacophores in the products.[11] By simply mixing **1a**, **4a–e**, and $PhI(OAc)_2$ together at 0 °C, comparable results (72–87% yield, >20:1 dr) were obtained for the formation of **5a–e** in 2-substituted fashion.

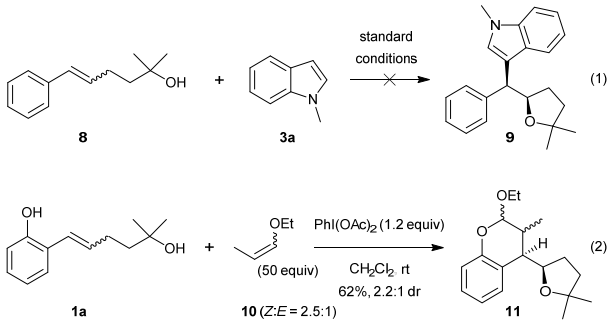


Scheme 2 Substituted indoles and indolizines formed by $PhI(OAc)_2$-mediated diastereoselective alkene difunctionalization.

Encouraged by these results, we next focused on investigating the difunctionalization reaction of vinylphenols **6**, which contain more

complicated trisubstituted alkene moieties (Scheme 2c). The reactions proceeded well under standard conditions, regardless of the electronic variations on both the phenol and indole rings, affording products **7a–g** in only a bit lower yields than that for the corresponding disubstituted alkenes. Worthy of note, the concomitant diastereoselective construction of the quaternary carbon presents a formidable synthetic tool for the construction of highly substituted tetrahydrofuran structures.

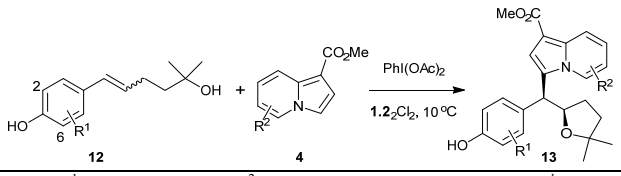
To validate our hypothesis on the mechanism, additional experiments were conducted (Scheme 3). As envisioned, reaction of alkene **8** and **3a** under standard conditions led only to slow decomposition of the starting materials without any detection of **9** (eqn (1)). On the other hand, upon treatment of **1a** with excess amount of enol ether **10** in the presence of $PhI(OAc)_2$, the inverse-electron demand Diels–Alder product **11** could be isolated in moderate yield and diastereoselectivity (eqn (2)).[12] Both outcomes strongly support the quinone methide mechanistic pathway.



Scheme 3 Experimental evidence of the mechanism.

Apart from the *ortho*-quinone methide route, the scope of the alkene difunctionalization can also be extended to the *p*-vinylphenols **12**. As shown in Table 2, no matter the substituent group on the phenyl ring is electron-neutral (entries 1–5), electron-deficient (entries 6–8), or electron-rich (entries 9 and 10), the reactions with indolizines occurred uneventfully to afford the corresponding adducts **13a–j** in moderate to good yields and excellent drs. To the best of our knowledge, this 1,6-conjugate addition-involved alkene difunctionalization via a *para*-quinone methide approach has not been described.

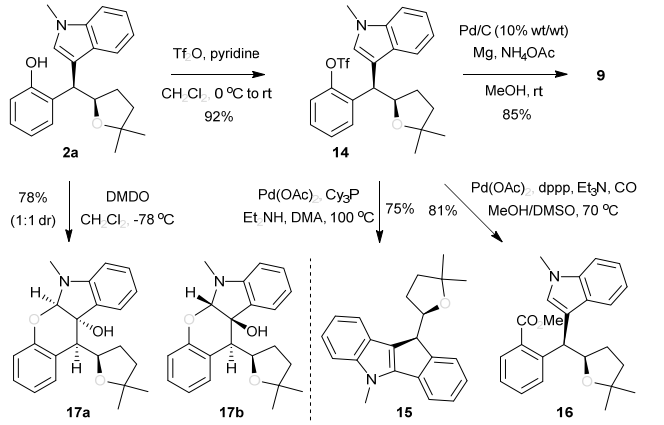
Table 2 $PhI(OAc)_2$-mediated alkene difunctionalization of *p*-vinylphenols[a]



Entry	R^1	R^2	Product	Yield[b] (%)	dr[c]
1	H (**12a**)	H (**4a**)	**13a**	83	>20:1
2	H (**12a**)	6-*t*-Bu (**4b**)	**13b**	80	>20:1
3	H (**12a**)	5,7-diMe (**4d**)	**13c**	77	>20:1
4	H (**12a**)	5,6-benzo (**4e**)	**13d**	70	>20:1
5	2,6-diMe (**12b**)	6-*t*-Bu (**4b**)	**13e**	76	>20:1
6	2-Br (**12c**)	H (**4a**)	**13f**	78	>20:1
7	2-Br (**12c**)	6-*t*-Bu (**4b**)	**13g**	75	>20:1
8	2-Br (**12c**)	5,6-benzo (**4e**)	**13h**	67	>20:1
9	2-OEt (**12d**)	H (**4a**)	**13i**	63	>20:1
10	2-OEt (1**2d**)	5,6-benzo(**4e**)	**13j**	55	>20:1

[a] Reaction conditions: **12** (0.20 mmol), **4** (0.24 mmol), $PhI(OAc)_2$ (0.24 mmol) in CH_2Cl_2 (10 mL) at 10 °C. [b] Isolated yields. [c] Determined by crude ^1H NMR analysis.

The incorporation of phenol subunit in products can be used as a synthetic handle for further transformations (Scheme 4). As one example to demonstrate the utility of this method to rapidly access relatively complex skeletons, intramolecular Heck reaction[13] of triflate **14** resulted in the formation of tetracycle **15** in 75% yield. Additionally, exposure of **2a** to DMDO[2a,14] delivered tetracycles **17a** and **17b** as a 1:1 mixture of diastereomers in 78% yield. Thus, both of these two compounds bearing four contiguous stereogenic centers were obtained in only four steps from salicylaldehyde.[15]



Scheme 4 Synthetic application of **2a**.

In conclusion, we have developed the first hypervalent iodine mediated alkene difunctionalization of vinylphenols, which rendered the facile synthesis of 3-substituted indoles and 2-substituted indolizines with good yields and high diastereoselectivities. This novel method is metal free and has a broad scope of alkene and indole/indolizine substrates. Moreover, the resulting products can be readily transformed to diverse complex structures for further chemical and biological investigations. These studies are currently underway in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedure, characterization data, ^1H and ^{13}C NMR spectra. See DOI: 10.1039/c000000x/

‡ These authors contributed equally.

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