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Transition-Metal-Free Redox-Neutral One-Pot C3-Alkenylation of Indoles Using Aldehydes

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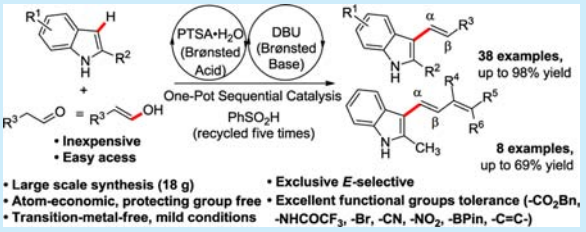
Supporting Information

ABSTRACT: The synthesis of sensitive β-alkyl 3-vinylindoles having diverse functional groups with good selectivity remains a challenging task. Keeping the synthetic utility of 3-alkenylindoles in mind, we explored a unique approach to synthesize them from unprotected indoles in a domino fashion. A transition-metal-free C3-alkenylation of indole is reported by using sequential Brønsted acid/base catalysis. Several β-substituted 3-alkenylindoles and conjugated 1,3-dienes are synthesized by direct coupling of indole and readily available aliphatic aldehydes. Excellent scalability and recycling of benzenesulfinic acid for successive alkenylation reactions up to five times make this method economically viable.



Synthesis of functionalized indoles has gained considerable attention in recent years due to their presence in various bioactive natural products, drugs, and other alkaloids.[1] C3-Alkenylindoles are one of the key building blocks and play a pivotal role in synthesizing these materials. Their diverse synthetic utility has been demonstrated in [4 + 2] cycloaddition reactions,[2] acid-catalyzed dimerization reactions,[3] and 1,4-addition reactions,[4] and they have also been used as vinylogous indole nucleophiles.[5] In addition, 3-alkenylindoles show their bioactivities as various anticancer, antibacterial, and antiviral agents.[6] Natural products having 3-alkenylindole moieties are also well documented in the literature (Figure 1).[7] In addition, they are important precursors for the synthesis of many important, biologically relevant molecules such as indole alkaloids,[8] carbolines,[9] and carbazoles.[10]

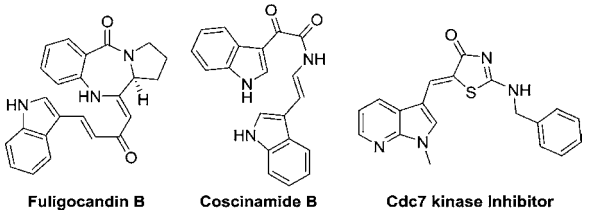
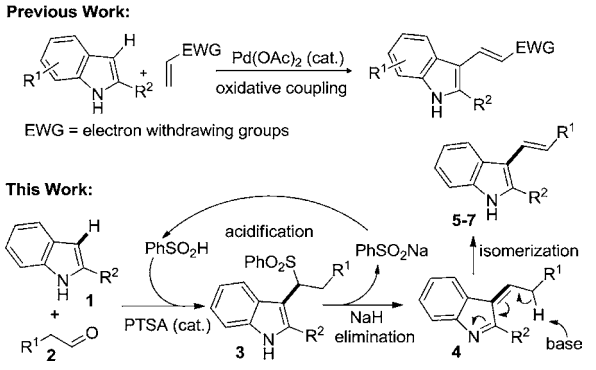


Figure 1. Natural products having a 3-alkenylindole moiety.

Despite the considerable number of methods reported in the literature,[11] syntheses of β-alkyl-substituted C3-alkenylindoles in particular are extremely limited. Wittig olefination is a well-practiced method to avail them.[12] However, this approach requires two to four consecutive steps starting from unprotected indole[2,13] and is often plagued by poor yields, limited scope, and low selectivity between geometrical isomers, resulting in difficulty in purification.[2,12b] Alkenylation protocols based on transition-metal-catalyzed cross-coupling reactions (Scheme 1)[14] and 1,4-addition followed by either oxidation or elimination[15] are largely limited to the activated alkenes.

Scheme 1. Literature Survey



Fe(III)-catalyzed direct alkenylation of indole using aldehydes is limited to 2-substituted indoles, and only β-aryl alkenes can be synthesized.[16] Brønsted acid mediated alkenylation of indoles requires relatively harsh reaction conditions and *N*-alkyl-protected indoles, and by this method only β,β-disubstituted alkenes can be synthsized.[17] Keeping the broad synthetic utility of 3-alkenylindoles and the above-mentioned limitations to synthesize them in mind, herein we report a highly efficient, transition metal and protecting group free method to access 3-alkenylated indoles using readily available aliphatic aldehydes as an alkenylating agent via one-pot sequential Brønsted acid/base catalysis.[18,19]

Brønsted acid plays a crucial role to activate aldehydes for achieving several unique transformations.[20] Reaction of indole

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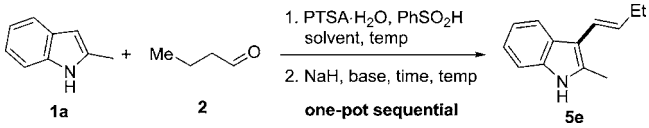
with aldehydes in the presence of a catalytic amount of Brønsted acid gives bis-indolylmethanes as the major product.[21] Therefore, direct C3-alkenylation of unprotected indole with aliphatic aldehydes, in particular, is challenging under the Brønsted acid or Lewis acid catalysis. To circumvent this problem, we envisioned that the presence of a phenylsulfonyl group, which can be installed under acidic conditions and can also be removed under basic conditions, will help us to solve this long-standing problem.[22] We hypothesized that, on treatment with base, **3** generates vinylogous imine intermediate **4** which in the presence of a non-nucleophilic base might facilitate β-proton abstraction from intermediate **4**, leading to the formation of 3-alkenylindole **5**–**7**.

During the optimization study, we were pleased to discover that simple PTSA·H_2O and DBU were suitable catalysts for this transformation.[23] Unlike Wittig olefination, this method provided **5e** in excellent yield having exclusive (*E*)-selectivity. Lowering the PTSA·H_2O loading to 5 mol % did not affect the formation of **3e** or the yield of **5e** (Table 1, entry 4). The

Table 1. Optimization of Reaction Conditions[a]



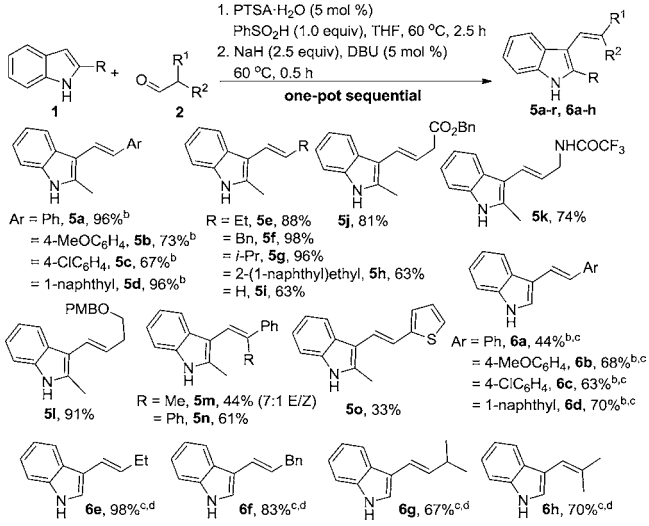
entry	PTSA [mol %]	NaH [equiv]	base/ mol %	solvent	temp [°C]	Time (step 1/2) [h]	yield [%][b]
1[c]	20	3.5	DBU/10	EtOAc	rt	5/5	77
2[c]	20	3.5	DBU/5	EtOAc	rt	5/5	90
3[c]	20	3.5	DABCO/5	EtOAc	rt	5/18	45
4[c]	5	3.5	DBU/5	EtOAc	rt	7/3	90
5[c]	5	2.5	DBU/5	EtOAc	rt	7/3	88
6[d]	5	2.5	DBU/5	EtOAc	rt	7/3	81
7[d]	5	2.5	DBU/5	THF	rt	3.5/0.5	81
8[d]	5	2.5	DBU/5	THF	60	2.5/0.5	88
9[d]	5	1.25	DBU/5	THF	60	2.5/1	63
10[d]	-	2.5	DBU/5	THF	60	19.5/0.5	43[e]
11[d]	5	0	DBU/5	THF	60	2.5/45.5	<5
12[d]	5	2.5	-	THF	60	2.5/21.5	<5

[a]1.5 mmol scale; butanal (1.0 equiv). [b]Isolated yield. [c]1.1 equiv of $PhSO_2H$. [d]1.0 equiv of $PhSO_2H$. [e]3,3′-(butane-1,1-diyl)bis(2-methyl-1*H*-indole) was also isolated in 26% yield.

presence of PTSA·H_2O catalyst was essential to convert intermediate bis-indolylmethane to **3** (entry 10). To confirm this, in a control experiment when bis-indolylmethane was subjected with $PhSO_2H$ (1.0 equiv) and PTSA·H_2O (5.0 mol %) in THF, 60% of **3e** was isolated along with 24% of **1a**.[23] Both NaH and DBU were essential for the reaction as no **5e** was formed in their absence (entries 11 and 12). No alkenylated product was detected for **8** under identical reaction conditions.[24]

At first, we explored the scope of this alkenylation reaction with various aliphatic aldehydes. Arylacetaldehydes containing electron-withdrawing and -donating groups did not affect the outcome of the reaction, and **5a**–**d** were isolated in 67–96% yields (Scheme 2). Aldehydes, having normal as well as branched aliphatic chains, reacted smoothly to provide alkenylated products **5e**–**h** in 63–98% yields. Simple acetaldehyde was also found to be a suitable substrate for our reaction (**5i**, 63%).

Scheme 2. Scope of Aldehydes[a]



[a]Reaction conditions: indole **1** (1.0 equiv), aldehyde **2** (1.0 equiv), $PhSO_2H$ (1.0 equiv), PTSA·H_2O (5 mol %), THF, 60 °C; NaH (2.5 equiv), DBU (5 mol %) in THF at 60 °C under N_2; isolated yield. [b]In the case of aryl acetaldehydes **2a**–**d**, minor alkenylated products **5a**–**d** and **6a**–**d** were observed in the first step. [c]EtOAc as solvent. [d]Reaction was conducted after the corresponding **3** was isolated.

Aldehydes bearing ester, amide, and ether functional groups were also well tolerated under these reaction conditions and provided the alkenylated products **5j**–**l** in good to excellent yields (74–91% yields). Despite the basic reaction medium and high temperature, no double-bond-isomerized product was detected for **5j**. Trisubstituted alkenes **5m,n** were also synthesized in moderate yields (44–61%) using 2,2-disubstituted acetaldehydes. Thiophene-2-acetaldehyde also reacted under these optimized conditions (**5o**, 33%), although the yield was lower due to the incomplete conversion of bis-indole to sulfonyl indole. For indoles having no substitution at the 2-position, a similar one-pot strategy was applied. As observed before, different aryl acetaldehydes provided alkenes **6a**–**d** in moderate to good yields (44–70%). However, in the case of aliphatic aldehydes, a stepwise strategy was adopted due to the difficulties in product purification as well as incomplete conversion of bis-indole to sulfonyl indole **3**. Using this stepwise strategy, products **6e**–**h** were isolated in 67–98% yields.

Next, the scope of the reaction was further investigated using various functionalized indoles. Sterically hindered 2-phenylindole and 2-*tert*-butylindole were reactive enough, and products **5ea,eb** were isolated in excellent yields (89–90%, Scheme 3). In general, indoles having electron-withdrawing CO_2Me, CON(OMe)Me, and Br functional groups at the 2-position were also suitable substrates for this transformation (**5ec**–**ef**, 50–80%). Even the presence of a sterically hindered carboxymenthyl group at the 2-position did not deter the reactivity of the indole. Indoles having various electron-withdrawing groups such as Br, NO_2, and CN at the 5-position underwent smooth conversion and gave the corresponding alkenes **5eg**–**ei** in moderate to excellent yields (67–87% yields). An indole having pinacolatoboron substitution, which might not be a suitable substrate for transition-metal-catalyzed alkenylation reactions, also underwent smooth conversion to provide **5aj** in 74% yield. Alkyl-substituted indoles such as 6,7-dimethylindole and 4,7-dimethylindole also gave the desired alkenes **6i,j** in 68% and 57% yields, respectively.

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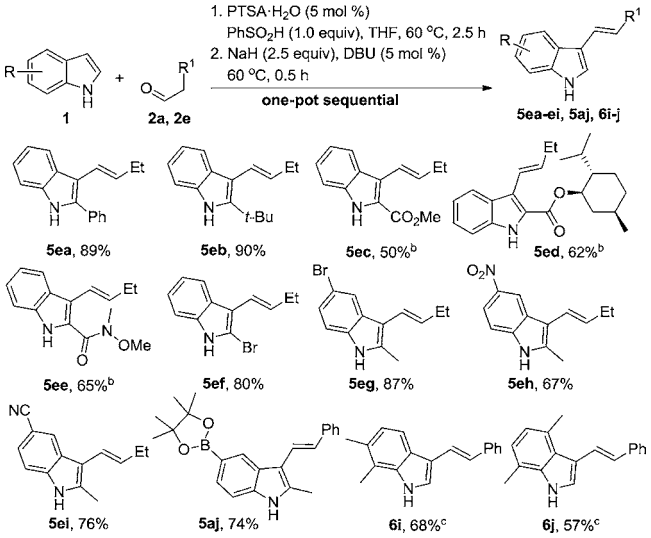
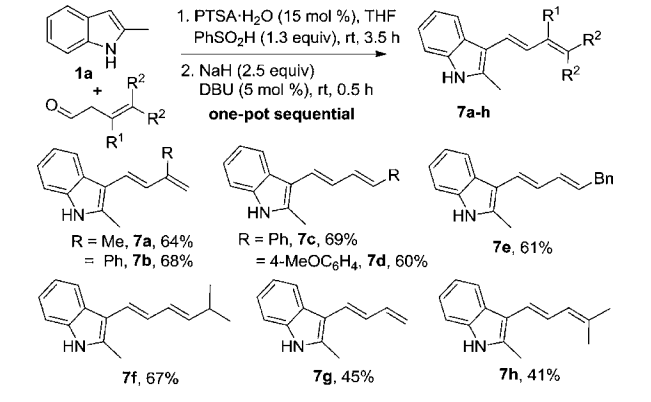
Scheme 3. Scope of Indoles[a]



[a]Reaction conditions: indole **1** (1.0 equiv), aldehyde **2** (1.0 equiv), $PhSO_2H$ (1.0 equiv), PTSA·H_2O (5 mol %), THF, 60 °C; NaH (2.5 equiv), DBU (5 mol %) in THF at 60 °C under N_2; isolated yield. [b]CH_2Cl_2 as solvent. [c]EtOAc as solvent.

1,3-Dienes are considered to be among the most powerful building blocks in organic synthesis and served as valuable precursors for a wide range of reactions.[25] 3-Indolyl-1,3-diene has been used for the synthesis of structurally unique indole alkaloids yuehchukene and murrapanine.[26] Intrigued by our method's mildness and wide functional group tolerability, we next aimed to install a 1,3-diene moiety at the C3-position of indole. Despite the fact that the preparation of functionalized alkenes **5** and **6** is well documented, syntheses of 1,3-dienes **7** are very scarce in the literature.[27] At first, 3-methyl-3-buten-1-al was subjected to the standard conditions, and 1,3-diene **7a** was isolated in 64% yield (Scheme 4). Similarly, 3-phenylbut-3-enal

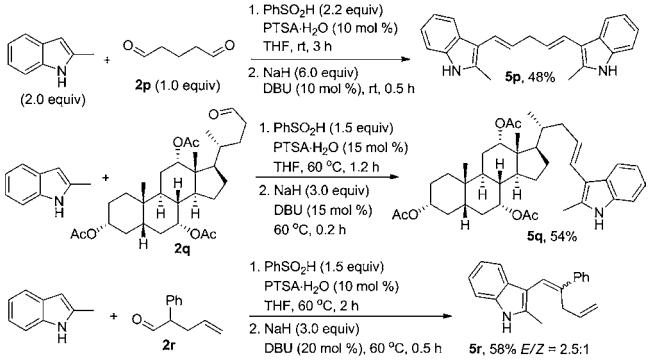
Scheme 4. Scope of 1,3-Dienes



gave the corresponding 1,3-diene **7b** in 68% yield. Aldehydes having aromatic groups such as phenyl and 4-methoxyphenyl at the 4-position of aldehyde underwent smooth conversion, and the corresponding 1,3-dienes **7c,d** were isolated in good yields (60−69%). In a similar fashion, benzyl- and isopropyl-substituted 1,3-dienes **7e,f** were also prepared in 61−67% yields. Simple 3-indolyl-1,3-diene **7g** and terminally dimethyl substituted 1,3-diene **7h** were also synthesized in 45% and 41% yields. We found that the *β*-alkyl-substituted compounds **5**−**7**, in particular, are highly unstable in the presence of trace acid.[12b]

Next, a few structurally unique aldehydes were subjected to standard reaction conditions, and their compatibility with the method were tested. Direct 2-fold alkenylation was also successfully performed on glutaraldehyde **2p** to furnish skipped diene **5p** in 48% yield (Scheme 5). Even highly functionalized

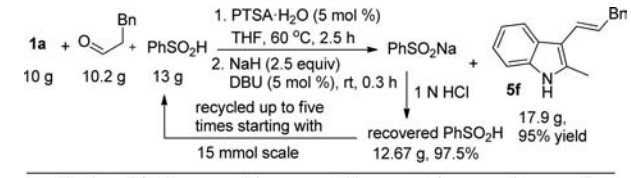
Scheme 5. Scope of Structurally Unique Aldehydes



acetate-protected cholic acid derived aldehyde **2q** was also compatible enough to provide the corresponding alkene **5q** in 54% yield. Last, aldehyde **2r** gave the corresponding skipped diene **5r** in 58% yield as a 2.5:1 mixture of *E*/*Z* isomers.

To demonstrate the scalability of this one-pot protocol, 10 g of 2-methylindole **1a** was reacted with 10.2 g of 3-phenylpropionaldehyde. The corresponding alkene **5f** was isolated in 17.9 g (95% yield, Scheme 6). Keeping in mind that the major

Scheme 6. Gram-Scale Synthesis of 5f and Recycling of Benzenesulfinic Acid



Number of Cycle	1st	2nd	3rd	4th	5th
Recovered $PhSO_2H$ [%]	99	97	81	92	86
5f [%]	94	95	93	96	96

byproduct of this method is sodium benzenesulfinate, which in turn can be acidified easily to isolate benzenesulfinic acid, next we investigated the economical aspect of this method. For this gram-scale reaction, 12.7 g of benzenesulfinic acid was recovered by acidification of the aqueous layer with 1 N HCl. No PTSA·H_2O was detected in the recovered benzenesulfinic acid as confirmed by ^1H NMR analysis.

To check the activity of recovered benzenesulfinic acid for successive alkenylation, a 15 mmol scale reaction was conducted, and **5f** was isolated in 94% yield along with 99% recovery of benzenesulfinic acid (Scheme 6). Successive repetition of the alkenylation−recycling procedure revealed that even after five consecutive cycles the activity of benzenesulfinic acid remained unchanged as the alkenyl indole **5f** was isolated in excellent yields (93−96%). The fact that one can get up to 60 mmol of alkene from 15 mmol of benzenesulfinic acid after five cycles proves the economic advantages of this method.

In summary, C3-alkenylation of unprotected indoles has been developed using readily available aliphatic aldehydes through

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sequential catalysis. Several 3-alkenylindoles were synthesized in one step. Excellent (*E*)-selectivity and tolerance of several functional groups such as ester, amide, nitro, cyano, bromo, and boronic ester demonstrated their further applicability. Importantly, synthesis of challenging 3-indolyl-1,3-dienes was also accomplished. Scalability along with recycling of benzenesulfinic acid render this method attractive and economically viable. Considering its generality on various functionalized aldehydes and indoles, we believe this alkenylation method is more robust and versatile than existing methods. Further studies are currently underway toward the development of similar strategies for other heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03612.

Experimental details, analytical data for all new compounds, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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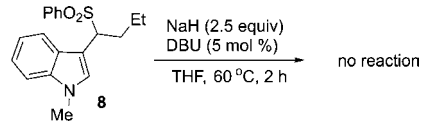
(23) See the Supporting Informations for details.

(24) Reaction with *N*-methyl protected sulfonylindole **8**.



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