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NH_2-Directed C−H Alkenylation of 2-Vinylanilines with Vinylbenziodoxolones

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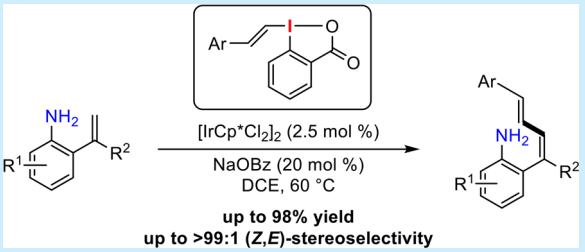
Supporting Information

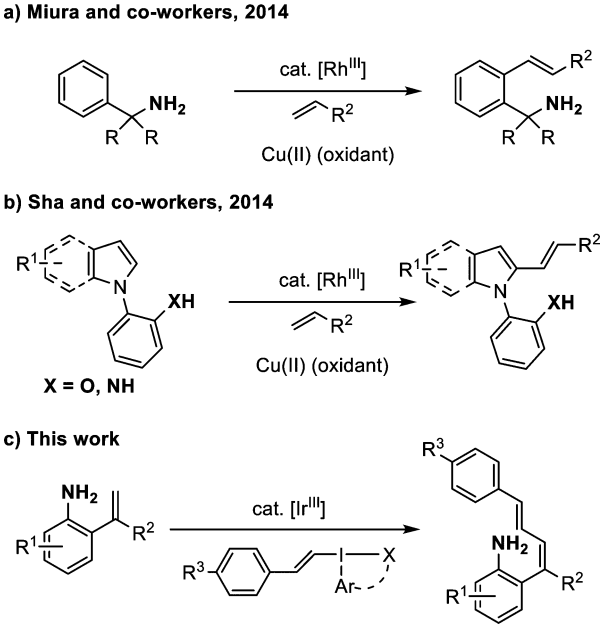
ABSTRACT: The first directing-group-mediated C−H alkenylation with alkenyl-λ^3-iodanes as electrophilic alkene-transfer reagents has been developed. The application of free aromatic amines as challenging but synthetically valuable directing groups in combination with an Ir^{III} catalyst enabled the synthesis of highly desirable 1,3-dienes in excellent yields of up to 98% with high to perfect (*Z*,*E*) stereoselectivity. A broad substrate scope and further synthetic modifications are demonstrated.



Transition-metal-catalyzed C−H activation provides a straightforward approach for the direct functionalization of C−H bonds.[1] In particular, the direct alkenylation of (hetero)aryl and olefinic C−H bonds is an intensely investigated reaction because of the high synthetic versatility of vinylated (hetero)arenes and 1,3-dienes.[2−4] To enable controlled C−H alkenylations, common directing groups such as nitrogen-containing heterocycles, oximes, amides, carbamates, and *N*-oxides have frequently been used.[2] In sharp contrast, free amines, hydrazines, and hydroxyl groups have been described only rarely in such transformations because of undesired side reactions such as catalyst deactivation and subsequent heterocycle formation.[5] This can be bypassed by in situ protection, as demonstrated by Cheng and co-workers.[6] Miura and co-workers described direct *ortho*-alkenylations of benzylamines with alkenes using a Rh(III) catalyst in combination with Cu(II) as a co-oxidant (Scheme 1a).[7] Sha and co-workers reported the efficient alkenylation of indoles at C2 directed by free phenolic hydroxyl groups or aromatic amines under similar oxidative conditions (Scheme 1b).[8] Our group is interested in the directed transformation of C(sp^2)−H bonds in combination with hypervalent-iodine-based group-transfer reagents. Recently, we demonstrated the use of alkynyl-substituted aryl-λ^3-iodanes such as benziodoxolones and alkynyl(aryl)iodonium salts in direct alkynylations of 2-vinylphenols and anilines to give highly substituted 1,3-enynes.[9] Now we want to demonstrate that alkenyl-substituted λ^3-iodanes can be used in similar C−H-activating alkenylations to give 1,3-dienes (Scheme 1c). In contrast to diaryl-[10] and alkynyl-λ^3-iodanes,[9,11] their utilization has not been described to date in C−H-activating reactions of arenes and alkenes.

Initially, we investigated the coupling between 2-(prop-1-en-2-yl)aniline (**1a**) as the free-amine-containing substrate and phenylvinylbenziodoxolone (**3a**, Ph-VBX; Table 1), published recently by Olofsson and co-workers,[12] as the alkene-transfer reagent. Choosing the optimized reaction conditions of our directed C−H alkynylation,[9a] using $[IrCp^*Cl_2]_2$ as the catalyst, KOAc as the base, and pyridine as an additive, we were pleased to isolate **2a** in 79% yield after 73 h (Table 1, entry 1).

Scheme 1. Transition-Metal-Catalyzed C−H Alkenylations Directed by Free Hydroxyl and Amine Groups



The product showed high (*Z*,*E*) isomeric purity with complete *Z* stereoselectivity for the addition of the styryl moiety to the exocyclic double bond. Exchange of pyridine with AgOAc or $AgNTf_2$ led to dramatically prolonged reaction times (Table 1, entries 2 and 3). We therefore performed the reaction without any additives, which resulted in a decreased reaction time (53 h) and an increased yield of 87% (Table 1, entry 4).

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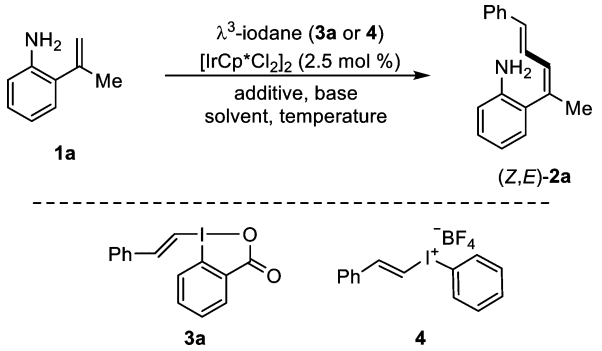
Table 1. Optimization of the Reaction Conditions[a]



entry	additive (mol %)	base (mol %)	temp (°C)	time (h)	yield (%)[b] (Z,E/Z,Z)[c]
1	pyridine (5)	KOAc (80)	rt	73	79 (96:4)
2	AgOAc (15)	KOAc (80)	rt	185	82 (97:3)
3	$AgNTf_2$ (15)	KOAc (80)	rt	216	72 (96:4)
4	–	KOAc (80)	rt	53	87 (96:4)
5[d]	–	KOAc (150)	rt	163	40 (95:5)
6	–	KOAc (80)	60	4.5	85 (97:3)
7	–	KOAc (20)	60	1.5	86 (97:3)
8	–	K_2CO_3 (20)	60	5	82 (97:3)
9	–	NaOBz (20)	60	1	89 (97:3)
10[e]	–	NaOBz (20)	60	4	84 (98:2)
11[f]	–	NaOBz (20)	60	1.5	88 (96:4)

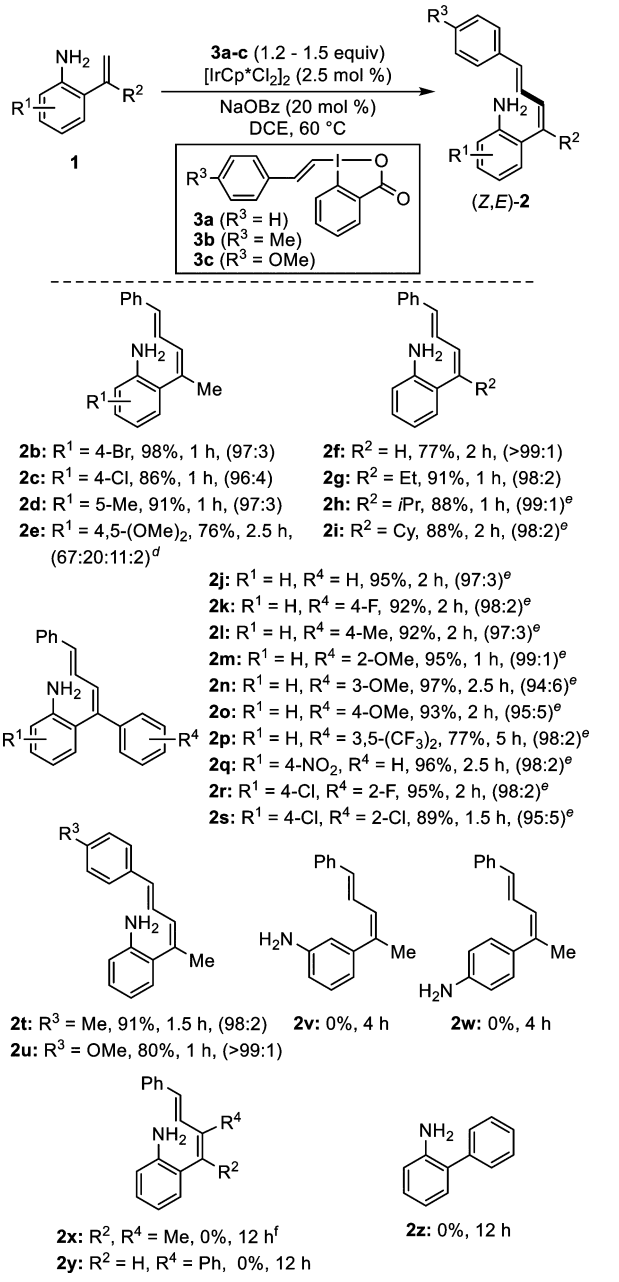
[a]Reaction conditions: **1a** (26.6 mg, 0.2 mmol) and **3a** (84.0 mg, 0.24 mmol) in 1,2-dichloroethane (DCE) (2 mL) without exclusion of air or moisture. [b]Isolated yields after column chromatography. [c]Determined by ^{1}H NMR spectroscopy. [d]**4** was used instead of **3a**. [e]Toluene was used as the solvent. [f]MeCN was used as the solvent.

Using (*E*)-styryl(phenyl)iodonium tetrafluoroborate (**4**) instead of Ph-VBX gave **2a** in only 40% yield after 7 days (Table 1, entry 5), thus demonstrating Ph-VBX to be the superior alkene-transfer reagent.

Dramatic acceleration of the reaction was achieved by increasing the temperature to 60 °C. Full conversion of **1a** was observed after just 4.5 h, affording **2a** in 85% yield with high stereoselectivity (Table 1, entry 6). On the basis of these results, we investigated the influence of the base. By decreasing the amount of KOAc to 20 mol %, we were pleased to observe a further reduced reaction time of 1.5 h while maintaining the previous yield (Table 1, entry 7). With K_2CO_3 the reaction was significantly slower and gave a slightly lower yield, whereas sodium benzoate led to full conversion of the starting material after only 1 h with an increased yield of 89% (Table 1, entries 8 and 9). Finally, different solvents were tested. Although toluene and MeCN were suitable, further improvement in the yield and reaction time could not be achieved (Table 1, entries 10 and 11), leaving 1,2-DCE the solvent of choice.

With the optimized reaction conditions in hand, we investigated the substrate scope of this transformation (Scheme 2). Electron-poor 2-(prop-1-en-2-yl)anilines **1b** and **1c** with

Scheme 2. Substrate Scope[a,b,c]



[a]Reaction conditions: **1** (0.20 mmol), **3a–c** (0.24–0.30 mmol), $[IrCp^*Cl_2]_2$ (2.5 mol %), and NaOBz (20 mol %) in DCE (2 mL) at 60 °C. [b]Isolated yields after column chromatography are shown. [c](*Z,E*)/(*Z,Z*) isomeric ratios were determined by ^{1}H NMR spectroscopy. [d](*Z,E*)/(*Z,Z*)/(*E,Z*) or (*E,E*) isomeric ratio. [e]1.5 equiv of **3a** was used. [f]A 1:1 mixture of isomers was used for the reaction.

different halogen substituents (4-Br, 4-Cl) as well as the more electron-rich 5-methyl-substituted derivative **1d** showed high reactivities similar to that of the unsubstituted substrate **1a**, affording the desired dienes **2b–d** in 86–98% yield with high stereoselectivity. In contrast, compound **2e** with strongly electron-donating OMe substituents was isolated in a slightly decreased yield of 76% after a prolonged reaction time (2.5 h) as an inseparable mixture of four isomers (67:20:11:2) in favor of the desired (*Z,E*) configuration.

We then varied the substitution pattern of the exocyclic double bond. 2-Vinylaniline (**1f**, R^2 = H) showed good

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reactivity, yielding the unsubstituted diene **2f** in 77% with perfect selectivity for the (*Z*,*E*) configuration. Substrates with different alkyl side chains (R^2 = Et, *i*Pr, Cy) reacted well, affording the corresponding products **2g**–**i** in 88–91% yield with excellent isomeric ratios of up to 99:1 in 1–2 h. However, in case of the sterically more demanding isopropyl and cyclohexyl derivatives **1h** and **1i**, 1.5 equiv of Ph-VBX was necessary to achieve full substrate conversion.

Next, different α-aryl vinylanilines (R^2 = aryl, **1j**–**s**) were investigated. In most cases, slightly prolonged reaction times were observed, and 1.5 equiv of Ph-VBX was needed, thus indicating a lower reactivity in comparison with the α-alkyl vinylanilines. The isolated yields, however, were excellent. The desired dienes **2j**–**o** were obtained in 92–97% yield with high to excellent stereoselectivities after 1.0–2.5 h regardless of the electronic nature of the substituents. Only the 3,5-$(CF_3)_2$-substituted derivative **2p** was isolated in a slightly decreased yield of 77% after a prolonged reaction time. Very electron-poor derivatives **1q**–**s** with either a nitro group or a halogen functionality on both aromatic rings afforded the desired products **2q**–**s** in excellent yields of 89–96% with high (*Z*,*E*)/(*Z*,*Z*) isomeric ratios.

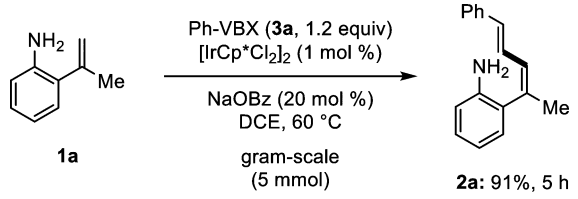
Finally, we investigated different VBX derivatives as alkene transfer reagents. When *p*-toloylvinylbenziodoxolone (**3b**, *p*-Tol-VBX) was used, high reactivity similar to that with Ph-VBX was observed, and the desired product **2t** was isolated in 91% yield after 1.5 h. The reaction with *p*-methoxyphenylvinylbenziodoxolone (**3c**, PMP-VBX) afforded **2u** in 80% yield with a perfect (*Z*,*E*) configuration ratio after 1 h.

When the reaction was performed with *meta*- and *para*-substituted anilines **1v** and **1w**, no conversion of the starting materials was observed after 4 h in both cases, thus demonstrating the importance of the free amino group at the *ortho* position to the exocyclic double bond as the directing group.

Furthermore, the use of the highly substituted alkenylanilines **1x** and **1y** as well as 2-phenylaniline (**1z**) did not lead to any conversion of the substrates after 12 h, which limits the scope of reaction to the use of unsubstituted vinylidenes.

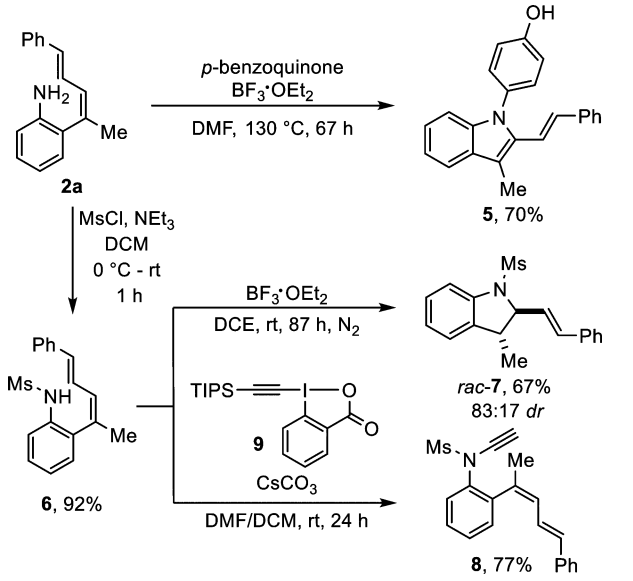
We performed a gram-scale alkenylation of **1a** with a decreased catalyst loading of 1 mol % (Scheme 3) to prove the economic viability of our method. Despite the lower catalyst loading, the reaction still showed high reactivity, affording diene **2a** in an excellent yield of 91% after 5 h.

Scheme 3. Gram-Scale Synthesis of 1,3-Diene 2a



1,3-Dienes are versatile substrates and building blocks for the synthesis of a variety of carbo- and heterocycles as well as natural products[13−16] and also starting materials for polymerizations.[17] Therefore, we investigated a variety of chemical transformations with the obtained 1,3-dienes to demonstrate their synthetic value (Scheme 4). Compound **2a** was used as the model substrate. In a BF_3-mediated condensation–cyclization cascade, diene **2a** was converted to *N*-arylindole **5** with *p*-benzoquinone in 70% yield. Mesylation of compound **2a** gave sulfonamide **6** in 92% yield, which was further cyclized with BF_3 under mild conditions to obtain indoline *rac*-**7** in 67% yield with good *trans* diastereoselectivity.[18] Mild and selective *N*-alkynylation of mesylamide **6** was achieved using TIPS-EBX (**9**) as the alkyne-transfer reagent. In situ cleavage of the TIPS moiety under the basic reaction conditions gave the free ynamide **8** in 77% yield.

Scheme 4. Further Derivatizations of Model Compound 2a



In summary, we have developed a unique and highly effective NH_2-directed C–H alkenylation of 2-vinylanilines using vinylbenziodoxolones as electrophilic alkene-transfer reagents. This method provides direct access to the corresponding 1,3-dienes in excellent yields of up to 98% with high to perfect (*Z*,*E*) stereoselectivity. Moreover, no formation of undesired second alkenylation products was observed. Finally, the synthetic value of the obtained 1,3-dienes was successfully demonstrated in a variety of transformations. Further studies regarding selective isomerization reactions and deeper mechanistic investigations are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02630.

Complete optimization table, detailed experimental procedures, characterization data, and ^1H and ^{13}C spectra for all new compounds (**2a**–**u** and **5**–**8**) (PDF)

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Notes

The authors declare no competing financial interest.

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