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Catalyst- and Substituent-Controlled Regio- and Stereoselective Synthesis of Indolyl Acrylates by Lewis-Acid-Catalyzed Direct Functionalization of 3-Formylindoles with Diazo Esters

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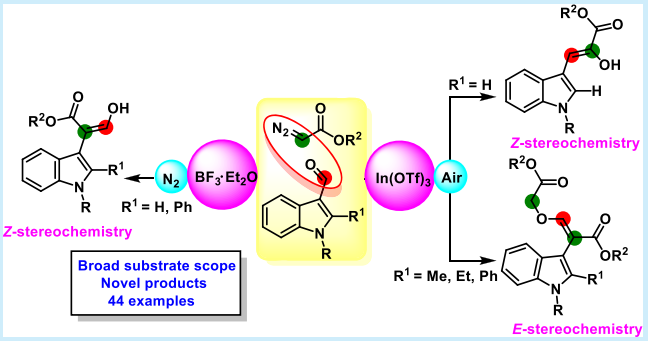
ABSTRACT: A facile and efficient $In(OTf)_3$- and $BF_3{\cdot}OEt_2$-catalyzed direct transformation of 3-formylindoles with diazo esters has been developed for synthesizing diverse and functionalized indolyl acrylates. This one-pot protocol furnishes various (*Z*)-*α*-hydroxy-*β*-indolyl acrylates, (*E*)-*β*-(2-alkoxy-2-oxoethoxy)-*α*-indolyl acrylates, and (*Z*)-3-hydroxy-2-indolyl acrylates by a catalyst- and substituent-controlled, regio- and stereoselective cascade reaction. The protocol has several advantages, including low loading of the catalyst, mild reaction conditions, broad scope, and high functional group tolerance. The synthesized compounds can be further converted into diversely functionalized materials.



Diazo compounds are one of the most valuable starting materials and versatile intermediates in organic synthesis.[1,2] They have been extensively used to synthesize bioactive natural products,[3] pharmaceuticals,[4] and many heterocycles.[5] The transition-metal-catalyzed, thermal, and photoreactions of diazo compounds have been well explored for the synthesis of diverse molecules.[6] In this regard, several synthetic methodologies based on the use of arylaldehydes and diazo acetates have been reported, including transition-metal-catalyzed olefination,[7] racemic or asymmetric aldol-type addition for *β*-hydroxy-*α*-ketoesters,[8,9] Lewis-acid- and metal-catalyzed formation of *β*-ketoesters,[10] and transition-metal-catalyzed epoxidation.[11] Although the capabilities of diazo compounds for olefination, *β*-hydroxy-*α*-ketoester formation, and *β*-ketoester epoxidation are well established, their ability to afford unsaturated *α*-hydroxy esters has not yet been elucidated.

Indoles are the principal scaffolds in several bioactive natural and synthetic products and are also present in many pharmaceuticals.[12] The indole moiety of indolic compounds is currently present in 24 commercialized pharmaceuticals.[13] In particular, the formyl group of indoles is an important synthetic building block in organic synthesis as well in the chemical industry.[14] Among them, 3-formylindoles and their derivatives are key starting materials and intermediates in the preparation of biologically active molecules through organic reaction transformation.[15] A few methods using diazo esters have been reported for the transformation of 3-formylindoles. For example, the Lebel group has demonstrated the copper-catalyzed olefination of 3-formylindole with diazo acetate for the preparation of conjugated esters (Scheme 1A).[16] The $TrBF_4$-catalyzed reaction of 3-formylcarbonyl with *α*-diazo acetates to yield the corresponding *β*-keto esters was also reported by the Lv group (Scheme 1B).[17] However, the Lewis-acid-catalyzed reaction of 3-formylindoles with diazo acetates to afford conjugated esters bearing *α*-hydroxy or *β*-alkoxyester groups is yet to be studied. Thus we envisioned the development of a novel protocol for introducing new moieties at the three-position on the indole nuclei, starting from 3-formyl indoles and diazo esters.

We have previously developed new methodologies to synthesize biologically interesting heterocycles[18] and diverse organic molecules starting from diazo compounds.[19] Extending the study of diazo-compound-based synthetic new protocols, herein we report a novel and efficient strategy to synthesize biologically important (*Z*)-*α*-hydroxy-*β*-indolyl acrylates via oxygen atom transfer (Scheme 1C), (*E*)-*β*-(2-alkoxy-2-oxoethoxy)-*α*-indolyl acrylates via indolyl migration (Scheme 1D), and (*Z*)-3-hydroxy-2-indolyl acrylates via indolyl migration (Scheme 1E) by $In(OTf)_3$- and $BF_3{\cdot}OEt_2$-catalyzed reactions of 3-formylindoles and diazo esters.

The reaction of 1-methylindole-3-carboxaldehyde (**1a**) with ethyl diazoacetate (**2a**) was investigated using different solvents and catalysts (Table 1). In initial attempts with

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Scheme 1. Synthesis of Three-Functionalized Indoles by the Reaction of 3-Formylindoles with Diazoacetates

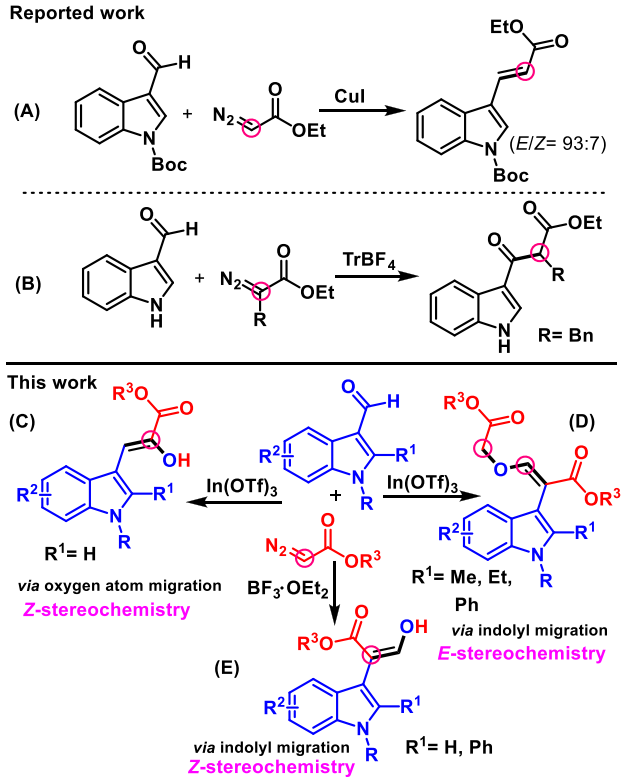
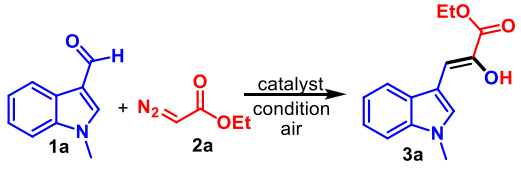


Table 1. Reaction Optimization for the Synthesis of 3a[a]



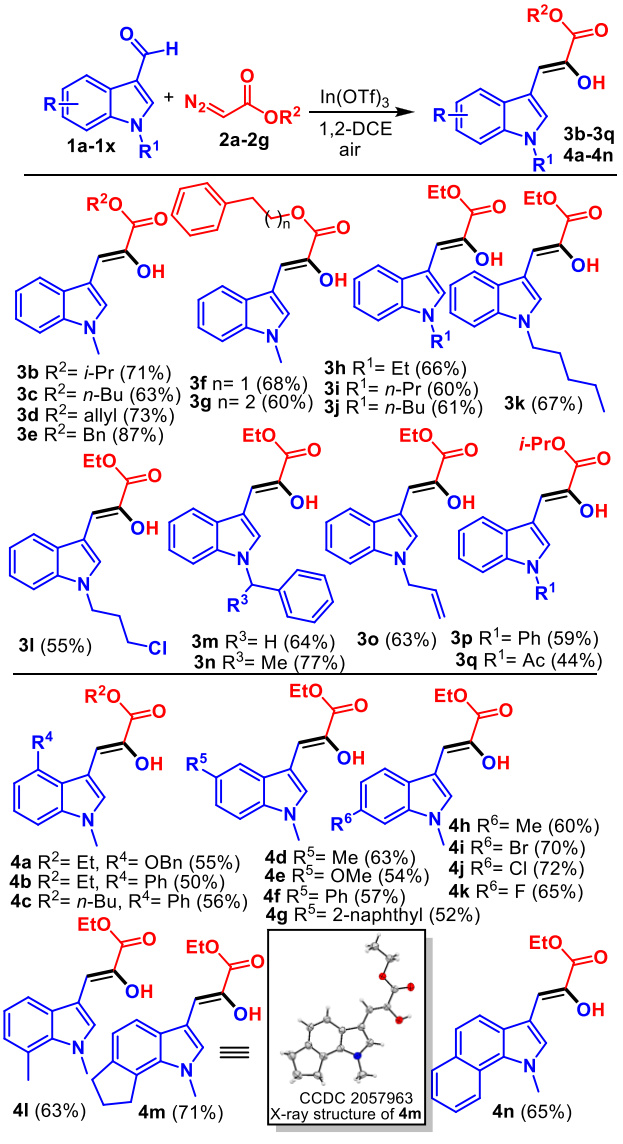
entry	cat. (mol %)	solvent	temp (°C)	time (h)	yield (%)[b]
1	$Rh_2(OAc)_4$ (2)	toluene	80	24	0
2	$Cu(OAc)_2$ (5)	toluene	80	24	0
3	$Cu(OTf)_2$ (5)	toluene	80	12	0
4	$InCl_3$ (5)	toluene	80	12	0
5	$InBr_3$ (5)	toluene	80	12	0
6	$Yb(OTf)_3$ (5)	toluene	80	12	10
7	$Sc(OTf)_3$ (5)	toluene	80	8	54
8	$In(OTf)_3$ (5)	toluene	80	8	68
9	$In(OTf)_3$ (5)	1,2-DCE	reflux	6	76
10[c]	$In(OTf)_3$ (5)	1,2-DCE	reflux	6	63
11	$In(OTf)_3$ (5)	THF	reflux	24	0
12	$In(OTf)_3$ (5)	DMF	80	12	0
13	$In(OTf)_3$ (5)	CH_3CN	reflux	12	0
14	$In(OTf)_3$ (2)	1,2-DCE	reflux	12	44
15	$In(OTf)_3$ (10)	1,2-DCE	reflux	12	57

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.1 mmol), and solvent (3 mL). [b]Isolated yield. [c]Reaction under N_2.

$Rh_2(OAc)_4$, $Cu(OAc)_2$, $Cu(OTf)_2$, $InCl_3$, and $InBr_3$ in toluene at 80 °C for 12−24 h, no product **3a** was formed at all (entries 1−5). Thus other catalysts such as $Yb(OTf)_3$, $Sc(OTf)_3$, and $In(OTf)_3$ were next screened. Interestingly, treating **1a** with **2a** using $Yb(OTf)_3$, $Sc(OTf)_3$, and $In(OTf)_3$ in toluene at 80 °C for 8−12 h led to **3a** in 10, 54, and 68% yields, respectively (entries 6−8). Importantly, the expected olefination and *β*-keto formation products were not isolated at all. A better yield (76%) was obtained with 5 mol % $In(OTf)_3$ on refluxing in 1,2-dichloroethane for 6 h in an open atmosphere (entry 9) as compared with the same reaction in an inert N_2 atmosphere (entry 10). Notably, the reaction in other solvents, including THF, DMF, and CH_3CN, in 5 mol % $In(OTf)_3$ did not afford **3a** (entries 11−13). Decreasing or increasing the quantity of $In(OTf)_3$ to 2 or 10 mol %, respectively, did not improve the yield (entries 14 and 15). The (Z)-stereochemistry of **3a** was confirmed by X-ray crystallography of **4m**.

The reaction generality was further explored using substituted 3-formylindoles **1a−1x** with various diazoacetates **2a−2g** (Scheme 2). The combination of **1a** with diazoacetates **2b−2d** bearing *i*-propyl, *n*-butyl, and allyl groups afforded the products **3b−3d** in 71, 63, and 73% yields, respectively. Other diazo compounds **2e−2g** bearing benzyl, ethylphenyl, and propylphenyl groups resulted in the desired products **3e−3g** in 60−87% yields. When **2a** was treated with *N*-alkyl-substituted indole-3-carboxaldehydes **1b−1f** such as ethyl, *n*-propyl, *n*-

Scheme 2. Substrate Scope of Substituted 3-Formylindoles 1a−1x and Various Diazoacetates 2a−2g



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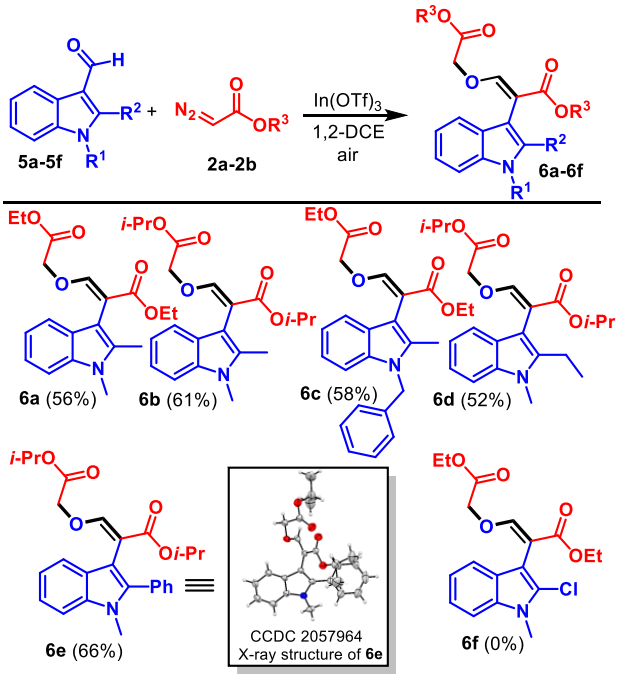
butyl, *n*-pentyl, and 3-chloropropyl, the desired products **3h**−**3l** were obtained in 55−67% yields. Additional reactions of *N*-benzyl-, *N*-allyl-, *N*-phenyl-, and *N*-acyl-substituted indole-3-carboxaldehydes **1g**−**1k** with diazoesters **2a** and **2b** provided **3m**−**3q** in 44−77% yields. Furthermore, the combination of indole-3-carboxaldehydes **1l** and **1m** bearing electron-donating groups at the four-position on the aromatic ring (such as 4-OBn and 4-Ph) with **2a** or **2c** readily generated the corresponding products **4a**−**4c** in 50−56% yields. Similarly, reactions of indole-3-carboxaldehydes **1n**−**1q** bearing substituents at the five-position on the aromatic ring, such as 5-methyl, 5-methoxy, 5-phenyl, and 5-(naphthalene-2-yl), with **2a** provided 52−63% yields of products **4d**−**4g**. Moreover, treatment of indole-3-carboxaldehydes **1r**−**1u** bearing substituents of electron-withdrawing and electron-withdonating groups at the six-position on the aromatic ring, such as 6-Me, 6-Br, 6-Cl, and 6-F, afforded the corresponding products **4h**−**4k** in 60−72% yields. The combination of **1v**, bearing a methyl substituent at the seven-position, with **2a** provided a 63% yield of product **4l**. Notably, the reaction of **2a** with 1-methyl-1,6,7,8-tetrahydrocyclopenta[*g*]indole-3-carbaldehyde (**1w**) and 1-methyl-1*H*-benzo[*g*]indole-3-carbaldehyde (**1x**), having a cyclic or aromatic ring on the indole nuclei, provided the corresponding products **4m** and **4n** in 71 and 65% yields, respectively. However, with indole-3-carboxaldehyde, the desired product was not isolated; instead, 3,4,5-triethoxycarbonyl-2-pyrazoline (**2a′**) was formed (57%) due to trimerization of the diazo compound.[20] (See the Supporting Information.)

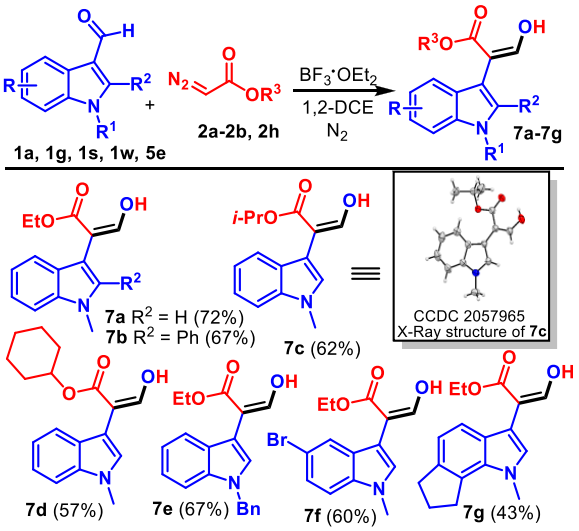
We depict the exploration of the substrate scope of our protocol and the investigation of other reactions of C-2-substituted 3-formylindoles **5a**−**5f** in Scheme 3. Surprisingly, the reactions of 3-formylindoles **5a**−**5e**, having electronic-donating groups such as methyl, ethyl, and phenyl at the two-position on the indole ring, furnished different products of (*E*)-*β*-(2-alkoxy-2-oxoethoxy)-*α*-indolyl acrylates as compared with the previous reactions, shown in Scheme 2. For example, the combination of 1,2-dimethyl 1*H*-indole-3-carboxyaldehyde (**5a**) or 1-benzyl-2-methyl 1*H*-indole-3-carboxyaldehyde (**5b**) with 2.2 equiv of **2a** or **2b** provided the unexpected products **6a**−**6c** in 56, 61, and 58% yields, respectively. In these reactions, any other product containing one unit of diazo compound was not formed, despite the use of 1 equiv of diazoester. Similarly, reactions of **2b** with **5c** or **5d** bearing 2-ethyl and 2-phenyl groups led to products **6d** and **6e** in 52 and 66% yields, respectively. However, with **5f** bearing the electron-withdrawing group (2-Cl), no products were isolated. The (E)-stereochemistry was determined by the X-ray crystallography of **6e**.

Next, the efficacy of the protocol was explored using BF_3·OEt_2 as a metal-free and stronger Lewis acid (Scheme 4).

Scheme 3. Substrate Scope of 3-Formylindoles 5a−5f Bearing C-2 Substituents and Diazoesters 2a and 2b



Scheme 4. BF_3·OEt_2-Catalyzed Reactions of 3-Formylindoles 1a, 1g, 1s, 1w, and 5e with Diazoesters 2a, 2b, and 2h



Interestingly, the reaction of **1a** with **2a** (2.2 equiv) using BF_3·OEt_2 generated the product **7a** in a 72% yield (Scheme 4). Surprisingly, the reaction of the C-2 substituted 3-formylindole **5e** with **2a** yielded 67% of the desired product **7b**. Combinations of **1a**, **1g**, **1s**, and **1w** with **2a**, **2b**, or **2h** provided a 43−67% yield of products **7c**−**7g**. X-ray crystallographic analysis confirmed the (Z)-stereochemistry of compound **7c**. Importantly, in these cases, the products that were formed using the $In(OTf)_3$ catalyst were not isolated.

To elucidate the reaction mechanism, control experiments were carried out as shown in Scheme 5. Treatment of the deuterated compound **1aD** with **2a** under standard conditions provided the product **3aD** with a 50:50 percentage of hydrogen and deuterium at the *β*-position on the acrylate moiety. This result suggested the possibility of keto/enol tautomerization for the formation of **3aD** (Scheme 5a). Treatment of **1aD** with **2a** in the presence of BF_3·OEt_2 provided deuterated product **7aD** in 70% yield (Scheme 5b). However, the reaction of **7a** and **2a** in the presence of $In(OTf)_3$ in ambient air did not provide compound **8**, possibly due to strong intramolecular hydrogen bonding (Scheme 5c). In addition, Lewis-acid-catalyzed reactions of benzaldehyde (**5g**) with **2a** were already reported to afford products **A** and

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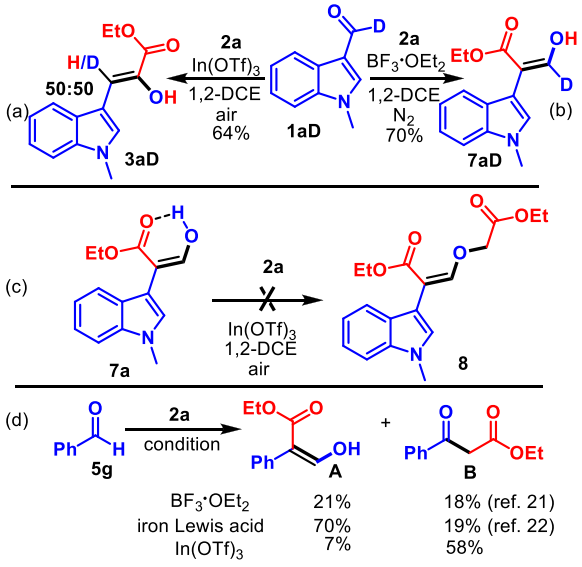
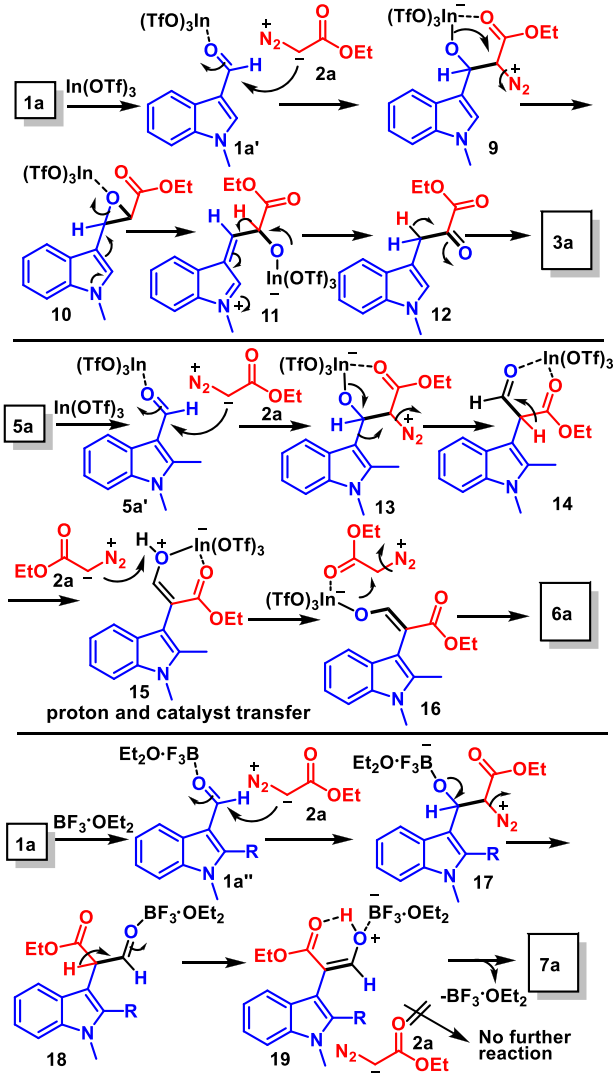
Scheme 5. Control Experiments



B.[21,22] In the presence of $BF_3{\cdot}OEt_2$, products **A** (21%) and **B** (18%) were produced,[21] and under an iron Lewis acid catalyst, product **A** (70%) was obtained as a major component.[22] When we tried this reaction in the presence of 5 mol % of $In(OTf)_3$, major product **B** (58%) was produced with 7% of product **A** (Scheme 5d).

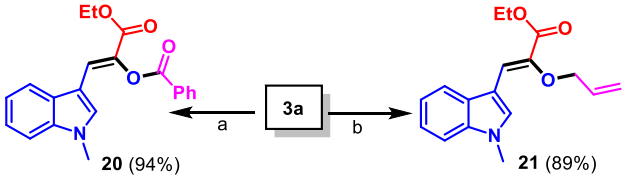
On the basis of the observed results, we propose plausible mechanisms for **3a**, **6a**, and **7a** in Scheme 6. In the presence of $In(OTf)_3$, 3-formyl indole (**1a**) produces complex **1a′**, which reacts with **2a** to afford intermediate **9** via nucleophilic addition. The intramolecular SN_2-type reaction of **9** gives epoxide intermediate **10** that undergoes a ring opening by electron movement from the nitrogen atom to furnish intermediate **11**. The 1,2-hydrogen shift by the movement of the anion on the oxygen atom followed by double-bond migration leads to intermediate **12**, which undergoes tautomerization to provide product **3a**. The possibility of keto−enol tautomerization was already proved in the control experiment using deuterated compound **1aD**. In the case of the C-2-substituted indole-3-carboxaldehydes, complex **5a′** reacts with **2a** to afford intermediate **13**. Subsequently, the indole moiety whose electron density is increased by electron-donating groups such as Me, Et, and Ph at the C-2 position undergoes 1,2-indolyl migration through the movement of electrons on the oxygen atom followed by the liberation of N_2 to yield intermediate **14**. This increase in electron density is expected to provide a product different from that of **3a**. Intermediate **14** gives intermediate **15** by enol formation, which undergoes proton and catalyst transfer to afford intermediate **16**. An SN_2-type reaction proceeds to give the final product **6a**. In the presence of a $BF_3{\cdot}OEt_2$ catalyst, complex **1a″** reacts with **2a** to form a complex intermediate **17**. In this case, the intramolecular SN_2-type reaction does not proceed; instead, the indolyl moiety rearranges to generate the intermediate **18**, which gives intermediate **19** by enol formation. Regeneration of the catalyst affords the final product **7a**. The position of deuterium in **7aD** confirmed the mechanism of this reaction. Intermediate **19** does not react further with **2a** to form any *O*-alkylated products due to strong intramolecular hydrogen bonding, as shown in Scheme 5c.

Scheme 6. Plausible Mechanisms for the Formation of 3a, 6a, and 7a



Furthermore, as an application of this protocol, synthesized compound **3a** was converted into different functionalized products (Scheme 7). The treatment of **3a** with benzoyl

Scheme 7. Further Transformations of 3a[a]



[a]Reaction conditions: (a) BzCl, K_2CO_3, toluene, rt, 12 h. (b) Allyl bromide, K_2CO_3, toluene, rt, 12 h.

chloride and allyl bromide using a mild base K_2CO_3 at room temperature in toluene for 12 h provided products **20** and **21** in 94 and 89% yields, respectively.

In conclusion, an efficient and facile methodology has been developed to construct diverse indolyl acrylates, starting from the readily available 3-formyl indoles and diazo esters via $In(OTf)_3$- and $BF_3{\cdot}OEt_2$-catalyzed cascade reactions. This

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protocol leads to the direct conversion of 3-formylindoles into biologically important (*Z*)-α-hydroxy-β-indolyl acrylates, (*E*)-β-(2-alkoxy-2-oxoethoxy)-α-indolyl acrylates, and (*Z*)-3-hydroxy-2-indolyl acrylates by the catalyst- and substituent-controlled regio- and stereoselective method. Various functional groups are tolerated, and the synthetic compound is further transformed into functionalized materials.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00277.

Detailed experimental procedures, characterization, and ^{1}H NMR and ^{13}C NMR spectra of the final products (PDF)

FAIR data, including the primary NMR FID files, for compounds **1h**, **1q**, **2a′**, **3aD**, **3a-3q**, **4a−4n**, **5c**, **6a−6e**, **7a−7g**, **7aD**, **A**, **B**, **20**, and **21** (ZIP)

Accession Codes

CCDC 2057963−2057965 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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