Cobalt(III)-Catalyzed Diastereoselective Three-Component C–H Bond Addition to Butadiene and Activated Ketones

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Abstract A highly diastereoselective three-component C–H bond addition across butadiene and activated ketones is described. This transformation provides homoallylic tertiary alcohols through the formation of two C–C bonds and with complete selectivity for an E-alkene isomer. The reaction exhibits good scope with respect to activated ketone inputs, including highly strained cyclic and electron-deficient cyclic and acyclic ketones. Additionally, high diastereoselectivities were achieved for alcohols prepared from unsymmetrical ketones.

Key words C–H activation, cobalt, ketones, diastereoselectivity, multicomponent reaction, homogeneous catalysis

Transition-metal-catalyzed C–H bond additions to a large variety of coupling partners provide a robust approach to assemble synthetically useful motifs.1 While reaction of a C–H bond substrate with two different coupling partners potentially represents a powerful approach to access complex structures, relatively few examples have been reported to date. The Catellani reaction initiated by Pd-catalyzed oxidative addition of an aryl halide has proven to be an effective strategy to accomplish three-component additions.2 We and others have recently explored an alternative approach that proceeds by C–H activation followed by sequential coupling with two different coupling partners.3 Relevant to the study described in this article, previous work by our lab3e,h and others3f has demonstrated that Co(III)- and Rh(III)-catalyzed three-component C–H bond additions with butadiene, monosubstituted or 1,2-disubstituted dienes, and aldehydes provide homoallylic alcohols with high diastereoselectivity (Scheme 1, eq. 1, 2).

Ketones are inherently more stable and sterically congested than aldehydes, and consequently, direct C–H bond additions even to activated ketones have only rarely been reported.4 Recently, our lab reported the first examples of Co(III)-catalyzed three-component coupling to internally substituted dienes and activated ketones (eq. 3, 4). However, only those diene and ketone combinations that gave products with a single stereogenic center were investigated. To expand upon these first examples of intermolecular sequential C–H bond additions to dienes and ketones, we sought to evaluate a broader array of ketones, in particular for diastereoselective additions to give products with two stereogenic centers. Herein, we describe a Co(III)-catalyzed three-component C–H bond addition to butadiene and activated ketones to provide homoallylic tertiary alcohols with
the formation of two new C–C σ-bonds (eq. 5). Notably, for the first time, alcohols bearing two stereogenic centers can be obtained with high diastereoselectivity for three-component additions with both cyclic and acyclic unsymmetrical ketones.

We began by exploring the reaction parameters for the coupling of benzamide 1a with butadiene (2) and ethyl benzoylformate (3a), which proved to be one of the more challenging ketone coupling partners (vide infra). Under the optimized reaction conditions that had previously been adopted for the coupling of butadiene and aldehydes (Table 1, entry 1), none of the desired three-component product was observed, and only 13% of a product resulting from two-component C–H bond addition to butadiene was obtained. Considering the greater stability and steric encumbrance of ketones relative to aldehydes, a higher reaction temperature was next investigated. At 70 °C, 20% of three-component product 4a was obtained as a single diastereomer (entry 2). However, at a higher reaction temperature of 90 °C, the yield of 4a dropped to 12% (entry 3). Substrate concentration was next evaluated, with 1.0 M leading to lower conversion than 0.4 M (entry 4), while 0.2 M provided a modest increase in the yield of 4a to 25% (entry 5). Finally, additives that have been employed in other Co(III)-catalyzed C–H addition reactions were examined as well.3k,5 Although replacing AcOH with LiOAc led to no conversion (entry 6), PivOH was a superior additive for this transformation and provided 4a in 50% yield (entry 7).

Having optimized the reaction conditions, we next explored the scope for the ketone coupling partner with benzamide 1a as the C–H bond substrate (Scheme 2). In addition to ethyl benzoylformate (3a), highly strained four-membered cyclic ketones also provided homoallylic tertiary alcohols in good to excellent yields. N-Carboxybenzyl (Cbz)-protected 3-azetidinone and 3-oxetanone furnished products 4b and 4c in 92% and 83% yield, respectively. Additionally, reaction with less activated cyclobutanone gave alcohol 4d in 50% yield. Electron-deficient isatin provided homoallylic alcohol 4e with two contiguous stereogenic centers in high yield and with high diastereoselectivity. Additions with N-methylisatin and N-benzylisatin afforded products 4f and 4g in 66% and 82% yield, respectively, also with high diastereoselectivity. Moreover, more electron-deficient 6-chloroisatin derivatives afforded alcohols 4h and 4i in near quantitative yields and with >20:1 dr.

Next, additional C–H bond substrates 1 were investigated for several different ketones 3 (Scheme 3). In addition to tertiary benzamide 1a, the secondary N-methylbenzamide is also an effective C–H bond substrate, coupling with 1-Cbz-3-azetidine to give product 4j in 86% yield. The secondary N-methylbenzamide also reacted with the acrylic ketone ethyl benzoylformate to furnish product 4k in 74% yield and with >20:1 dr. An X-ray crystal structure of the major diastereomer of alcohol 4k rigorously established the relative configuration of the methyl and hydroxyl groups for this ketone coupling partner. N-Phenylpyrazole with a methyl substituent at the meta position coupled with N-methylisatin to provide tertiary alcohol 4l in 48% yield and with high diastereoselectivity. The relative stereochemistry for 4l was confirmed by X-ray crystallography, thereby providing the stereochemical relationship for isatin-derived products. Pyrimidine also served as an excellent directing group as demonstrated for three-component addition with ethyl benzoylformate to afford alcohol 4m in 70% yield and with >20:1 dr. However, a blocking group, such as a methyl group at the meta position, is necessary to prevent bis-functionalization. The 2-phenylpyrimidine C–H bond substrate is also effective for coupling with N-Cbz-3-azetidinone

### Table 1 Screening of Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Temp (°C)</th>
<th>Conc (M)</th>
<th>Yield (%) of 4a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcOH</td>
<td>50</td>
<td>0.4</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>AcOH</td>
<td>70</td>
<td>0.4</td>
<td>20</td>
</tr>
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<td>12</td>
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<tr>
<td>4</td>
<td>AcOH</td>
<td>70</td>
<td>1.0</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>AcOH</td>
<td>70</td>
<td>0.2</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>LiOAc</td>
<td>70</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>PivOH</td>
<td>70</td>
<td>0.2</td>
<td>50</td>
</tr>
</tbody>
</table>

*a Reaction conditions: 1a (0.1 mmol), 2 (0.2 mmol), 3a (0.3 mmol).

*b Yields determined by 1H NMR analysis relative to 1,3,5-trimethoxybenzene.
Scheme 2  Three-component coupling of benzamide 1a, butadiene (2), and diverse ketones 3. Reactions were performed at 0.1 mmol scale; isolated yields of products after purification by chromatography.

Scheme 3  Three-component coupling of C–H bond substrates 1 with butadiene (2) and selected ketones 3. Reactions were performed at 0.1 mmol scale; isolated yields of products after purification by chromatography. For the X-ray crystal structures of 4k and 4l, hydrogen atoms are omitted for clarity.
to furnish alcohol \(4n\). Isatin derivatives like 5-nitroisatin and \(N\)-benzyl-6-chloroisatin afforded the corresponding products \(4o\) and \(4p\) in 82% and 65% yield, respectively, with good diastereoselectivity.

To evaluate the scalability of the reaction, the three-component product \(4b\) was prepared at a 15-fold larger scale (Scheme 4). Reaction of benzamide \(1a\) with butadiene (2) and 1-Cbz-3-azetidinone (3b) at 1.5 mmol scale provided product \(4b\) in 95% yield, which is consistent with the yield obtained for the corresponding smaller scale reaction.

A catalytic cycle is depicted in Scheme 5, which is based on prior mechanistic studies for three-component additions to dienes and aldehydes.\(^{3,4}\) The Co(II)-catalyzed C–H bond activation of 1 through concerted metalation–deprotonation forms metallocycle A. Migratory insertion into butadiene subsequently affords Co–allyl species B. To obtain the necessary connectivity observed in the product, \(\beta\)-hydride elimination at C1 then provides Co–diene complex C, which undergoes alkene insertion into the Co–H bond to afford Co–allyl species D. Diastereoselective addition of intermediate D with ketone 3 via a chair-like transition state depicted in E, followed by protonolysis to release the catalyst, would then provide product 4.

In conclusion, we have developed a Co(III)-catalyzed three-component C–H bond addition to butadiene and ketones. Efficient coupling was observed for a number of different activated ketones and C–H bond substrates. Notably, Co(III)-catalyzed diastereoselective additions with unsymmetrical ketones have been demonstrated for the first time. In addition, the relative stereochemistry of the two stereo-ergic centers in the three-component addition products for isatins and ethyl benzoylformate was rigorously established by X-ray crystallography.

All Co(III)-catalyzed reactions were set up in a \(N_2\)-filled glovebox, using glassware that was oven-dried (150 °C) and evacuated while hot prior to use. Solvents were sparged with argon and purified by elution through a column of activated alumina under argon before use and were stored with 3 A molecular sieves in a \(N_2\)-filled glovebox (molecular sieves were dried at 200 °C overnight under vacuum). Unless otherwise noted, all reagents were purchased from commercial sources and used without further purification. Microwave vials and caps were purchased from Biotage (part number 351521 and 352298, respectively). Product purification was performed by preparative TLC with plates from Analtech (1 mm silica gel, 20 × 20 cm). \(^1\)H and \(^13\)C NMR spectra were recorded on a 400, 500, or 600 MHz instrument. Partial IR spectra are reported. High-resolution mass spectra were obtained using electrospray ionization (ESI) on a time-of-flight mass spectrometer.

Low-temperature X-ray diffraction data (\(\omega\)-scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu Kα radiation (\(\lambda = 1.54178\) Å) for the structures of 4k and 4l.\(^{5}\) The diffraction images were processed and scaled using Rigaku Oxford Diffraction software (CrysAlis\(^\text{®}\)). The structures were solved with SHELXT and refined against \(F^2\) on all data by full-matrix least squares with SHELXL.\(^{7}\) For the full numbering scheme of compounds 4k and 4l, see the full details of the X-ray crystal structure determination (CIF) in the Supporting Information, Section III.

**Homoallylic Tertiary Alcohols 4; General Procedure**

In a \(N_2\)-filled glovebox, a 2.0 ml Biotage microwave vial with a triangular stir bar (1 × 0.5 cm) was charged with the indicated C–H bond partner (0.100 mmol, 1.00 equiv) and \([\text{Cp}^*\text{Co}(\text{C}_6\text{H}_5)][\text{B}(\text{C}_6\text{F}_5)_4]_{12}\) (32.6 mg, 0.0200 mmol, 0.200 equiv). Following this, the corresponding ketone (0.300 mmol, 3.00 equiv) was added. A 0.2 M solution of pivalic acid in 1,4-dioxane (100 µl, 0.0200 mmol, 0.200 equiv) and 1,4-dioxane (350 µl) were added successively. At last, a commercially available 4 M stock solution of butadiene in THF (50 µl, 0.2000 mmol, 2.00 equiv) was added. The reaction vial was then sealed and taken outside the glovebox. The reaction mixture was stirred in a preheated oil bath at 70 °C for 20 h. The reaction vial was then cooled to room temperature and uncapped. The reaction was quenched with saturated NaHCO\(_3\) (10 ml), and the resulting mixture was then extracted with EtOAc (5 × 3 ml). The organic layers were combined and dried over \(\text{Na}_2\text{SO}_4\). After filtration of the mixture through a Celite plug using EtOAc as the eluent, the resulting mixture was then concentrated and purified by the indicated chromatographic method to afford the desired product.
Preparation of Homoallyl Tertiary Alcohol 4b on 1.5 mmol Scale

In a N$_2$-filled glovebox, a 30 mL Biotage microwave vial with a foot-ball-shaped stir bar (2 × 0.5 cm) was charged with phenyl[pyrrolidin-1-yl]methanone (1a; 263 mg, 1.50 mmol, 1.00 equiv) and [Cp$^*$Co(C$_5$H$_5$)]B(C$_6$F$_5$I)$_2$ (489 mg, 0.300 mmol, 2.00 equiv). Following this, benzy 3-oxoazetidine-1-carboxylate (923 mg, 4.50 mmol, 3.00 equiv) was added. A yellow solution of pivalic acid (1.07 mmol, 1.00 equiv) and benzyl 3-oxoazetidine-1-carboxylate (61.5 mg, 0.300 mmol, 0.200 equiv) and 1,4-dioxane (5.25 mL) were added successively. At last, a 4 M stock solution of butadiene in THF (300.19 mL, 1.20 mmol, 1.00 equiv) and oxetan-3-one (21.6 mg, 0.300 mmol, 3.00 equiv) was added. A 0.2 M solution of pivalic acid in 1,4-dioxane (5.0 mL, 1.00 mmol, 2.00 equiv) was added successively. The reaction mixture was stirred in a preheated oil bath at 70 °C for 20 h. The reaction was then cooled to room temperature and uncapped. The reaction was quenched with saturated NaHCO$_3$ (50 mL), and the resulting mixture was then extracted with EtOAc (5 × 15 mL). The organic layers were washed with brine, then cooled to room temperature and uncapped. The reaction was then sealed and taken outside the glovebox. The reaction mixture was then extracted with EtOAc (5 × 15 mL). The organic layers were washed with brine, then dried over Na$_2$SO$_4$. After filtration of the mixture through a medium fritted funnel using EtOAc as the eluent, the resulting mixture was then concentrated and purified by silica gel chromatography (50% ETOAc in hexane) to provide 4a (619 mg, 95% yield) as a yellow oil. The 1H NMR and 13C NMR spectra are in perfect agreement with the corresponding spectra of 4a obtained according to the general procedure (see the Supporting Information, Section II).

Ethyl (Z,3S)-2-Hydroxy-3-methyl-2-phenyl-5-[(2-phenyl-1-y carbonyl)phenyl]pent-4-en-4-olate (4a)

The general procedure was followed using phenyl[pyrrolidin-1-yl]methanone (1a; 17.5 mg, 0.100 mmol, 1.00 equiv) and ethyl 2-oxo-2-phenylacetate (53.4 mg, 0.300 mmol, 3.00 equiv). Purification by silica gel chromatography (50% ETOAc in hexane) provided 4b (17.5 mg, 92% yield) as a yellow oil.

IR (neat): 3491, 2975, 2876, 1724, 1615, 1449, 1425 cm$^{-1}$.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{26}$H$_{28}$O$_5$: 435.2278; found: 435.2284.

(E)-2-(3-(3-Hydroxoyxetan-3-yl)but-1-en-1-yl)(pyrrolidin-1-yl) methanone (4c)

The general procedure was followed using 1a (17.5 mg, 0.100 mmol, 1.00 equiv) and oxetan-3-one (21.6 mg, 0.300 mmol, 3.00 equiv). Purification by silica gel chromatography (50% ETOAc in hexane) provided 4d (24.9 mg, 83% yield) as a colorless oil.

IR (neat): 3735, 2962, 2874, 1642, 1430, 1400 cm$^{-1}$.

1H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.45 (d, $J$ = 7.7 Hz, 1 H), 7.37–7.26 (m, 2 H), 6.45 (d, $J$ = 15.9 Hz, 1 H), 6.12 (dd, $J$ = 15.9, 8.2 Hz, 1 H), 4.51 (m, 4 H), 3.63 (t, $J$ = 7.1 Hz, 2 H), 3.10 (t, $J$ = 6.8 Hz, 2 H), 2.77 (m, 1 H), 1.93 (m, 2 H), 1.83 (m, 2 H), 1.11 (d, $J$ = 6.9 Hz, 3 H).

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{29}$H$_{30}$N$_2$O$_4$: 302.1751; found: 302.1756.

(E)-2-(3-{1-Hydroxycyclobutyl}but-1-en-1-yl)(pyrrolidin-1-yl)methanone (4d)

The general procedure was followed using 1a (17.5 mg, 0.100 mmol, 1.00 equiv) and cyclobutanone (21.6 mg, 0.300 mmol, 3.00 equiv). Purification by silica gel chromatography (50% ETOAc in hexane) provided 4d (15.0 mg, 50% yield) as a colorless oil.

IR (neat): 3396, 2971, 2876, 1611, 1452, 1428 cm$^{-1}$.

1H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.48 (d, $J$ = 7.8 Hz, 1 H), 7.30 (m, 1 H), 7.23 (m, 2 H), 6.50 (d, $J$ = 15.9 Hz, 1 H), 6.20 (dd, $J$ = 15.9, 8.2 Hz, 1 H), 3.65 (t, $J$ = 7.0 Hz, 2 H), 3.10 (t, $J$ = 6.8 Hz, 2 H), 2.53–2.44 (m, 1 H), 2.00–1.22 (m, 2 H), 1.98–1.89 (m, 4 H), 1.83 (m, 4 H), 1.09 (d, $J$ = 6.9 Hz, 3 H).

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{30}$H$_{30}$N$_2$O$_4$: 300.1958; found: 300.1974.

(E)-3-Hydroxy-3-[4-(2-pyrrolidin-1-ylcarbonyl)phenyl]but-2-en-2-yl)indol-2-one (4e)

The general procedure was followed using 1a (17.5 mg, 0.100 mmol, 1.00 equiv) and indoline-2,3-dione (44.1 mg, 0.300 mmol, 3.00 equiv). Purification by silica gel chromatography (70% ETOAc in hexane) provided 4e (21.0 mg, 55% yield; >20:1 dr) as a yellow oil.

IR (neat): 3271, 2974, 2324, 1712, 1594, 1462, 1433 cm$^{-1}$.

1H NMR (400 MHz, CDCl$_3$): $\delta$ = 9.28 (s, 1 H), 7.48 (d, $J$ = 7.7 Hz, 1 H), 7.31 (t, $J$ = 7.5 Hz, 1 H), 7.27–7.24 (m, 1 H), 7.23–7.19 (m, 1 H), 7.13 (m, 2 H), 6.92 (t, $J$ = 7.5 Hz, 1 H), 6.70 (d, $J$ = 7.7 Hz, 1 H), 6.60 (d, $J$ = 15.8 Hz, 1 H), 6.27 (dd, $J$ = 15.8, 8.1 Hz, 1 H), 4.99 (s, 1 H), 3.58 (m, 2 H), 3.16 (m, 1 H), 3.11–3.01 (m, 1 H), 2.91 (m, 1 H), 1.79 (m, 4 H), 0.75 (d, $J$ = 6.7 Hz, 3 H).

1C NMR (101 MHz, CDCl$_3$): $\delta$ = 169.9, 156.6, 136.4, 135.7, 133.7, 132.7, 129.3, 128.9, 128.5, 128.1, 127.9, 127.5, 126.5, 126.1, 72.6, 66.9, 60.8, 60.5, 48.6, 45.7, 44.5, 25.9, 14.3, 13.5.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{26}$H$_{28}$N$_2$O$_4$: 435.2278; found: 435.2284.

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(E)-3-Hydroxy-1-methyl-3-(4-(2-pyrrolidin-1-ylcarbonyl)-phenyl)but-3-en-2-yl)indolin-2-one (4f)

The general procedure was followed using 1a (17.5 mg, 0.100 mmol, 1.00 equiv) and 1-methylindoline-2,3-dione (48.3 mg, 0.300 mmol, 3.00 equiv). Purification by silica gel chromatography (50% EtOAc in hexane) provided 4f (25.7 mg, 66% yield; >20:1 dr) as a yellow powder.

HRMS (ESI): m/z [M + H]+ calc for C_{24}H_{27}N_2O_3; 411.1470; found: 411.1476.

(E)-6-Chloro-3-hydroxy-1-methyl-3-(4-(2-pyrrolidin-1-ylcarbonyl)-phenyl)but-3-en-2-yl)indolin-2-one (4i)

The general procedure was followed using 1a (17.5 mg, 0.100 mmol, 1.00 equiv) and 6-chloro-1-methylindoline-2,3-dione (58.7 mg, 0.300 mmol, 3.00 equiv). Purification by silica gel chromatography (50% EtOAc in hexane) provided 4i (38.2 mg, 90% yield; >20:1 dr) as a yellow powder.

IR (neat): 3364, 2968, 2877, 2362, 2339, 1733, 1609, 1456 cm⁻¹.

HRMS (ESI): m/z [M + H]+ calc for C_{34}H_{36}ClNO_4; 425.1626; found: 425.1632.

Benzyl (E)-3-Hydroxy-3-(4-(2-(methylcarbamoyl)phenyl)but-3-en-2-yl)azetidine-1-carboxylate (4j)

The general procedure was followed using N-methylbenzamide (13.5 mg, 0.100 mmol, 1.00 equiv) and benzyl 3-oxoazetidine-1-carboxylate (61.5 mg, 0.300 mmol, 3.00 equiv). Purification by silica gel chromatography (40% EtOAc in CH₂Cl₂) provided 4j (33.9 mg, 86% yield) as a colorless oil.

IR (neat): 3317, 2965, 2881, 1689, 1631, 1412, 1357, 1355 cm⁻¹.

HRMS (ESI): m/z [M + H]+ calc for C_{24}H_{29}N_2O_3; 395.1965; found: 395.1971.

Ethyl 2(R*,3S*,E)-2-Hydroxy-3-methyl-5-(2-(methylcarbamoyl)phenyl)-2-phenylpent-4-enoate (4k)

The general procedure was followed using N-methylbenzamide (13.5 mg, 0.100 mmol, 1.00 equiv) and ethyl 2-oxo-2-phenylacetate (53.4 mg, 0.300 mmol, 3.00 equiv). Purification by silica gel chromatography (40% EtOAc in hexane) provided 4k (27.2 mg, 74% yield; 92:8 dr) as a white solid; mp 133–135 °C.

IR (neat): 3529, 3337, 3060, 2939, 2879, 1727, 1630, 1538 cm⁻¹.

HRMS (ESI): m/z [M + H]+ calc for C_{21}H_{24}O_4N; 326.1806; found: 326.1806.

(E)-3-Hydroxy-1-methyl-3-(4-(2-pyrrolidin-1-ylcarbonyl)-phenyl)but-3-en-2-yl)indolin-2-one (4f)

The general procedure was followed using 1a (17.5 mg, 0.100 mmol, 1.00 equiv) and 1-methylindoline-2,3-dione (48.3 mg, 0.300 mmol, 3.00 equiv). Purification by silica gel chromatography (50% EtOAc in hexane) provided 4f (25.7 mg, 66% yield; >20:1 dr) as a yellow powder.

IR (neat): 3351, 2972, 2361, 1706, 1612, 1512, 1461 cm⁻¹.

HRMS (ESI): m/z [M + H]+ calc for C_{24}H_{27}N_2O_3; 377.1860; found: 377.1865.
IR (neat): 3995, 2974, 2928, 1725, 1568, 1555, 1420 cm\(^{-1}\).

(E)-3-Hydroxy-1-methyl-3-(4-(4-methyl-2-(1H-pyrazol-1-yl)-phenyl)but-3-en-2-yl)indolin-2-one (E4)

The general procedure was followed using 1-(m-toly)-1H-pyrazole (15.7 mg, 0.100 mmol, 1.00 equiv) and 1-methylindoline-2,3-dione (48.3 mg, 0.300 mmol, 3.00 equiv). Purification by silica gel chromatography (50% EtOAc in hexane) provided E4 (18.0 mg, 48% yield; >20:1 dr) as a colorless oil.

HRMS (ESI): m/z [M + H\(^{+}\)] calcd for C\(_{36}\)H\(_{39}\)NO\(_{3}\): 368.1862; found: 368.1843.

IR (neat): 3341, 2962, 2324, 1699, 1612, 1460, 1373 cm\(^{-1}\).

(E)-3-Hydroxy-3-(4-(4-methyl-2-(pyrimidin-2-yl)phenyl)but-3-en-2-yl)-5-nitroindolin-2-one (E4o)

The general procedure was followed using 2-(m-toly)pyrimidine (17.0 mg, 0.100 mmol, 1.00 equiv) and 5-nitroindole-2,3-dione (57.6 mg, 0.300 mmol, 3.00 equiv). Purification by silica gel chromatography (50% EtOAc in CH\(_2\)Cl\(_2\)) provided 4o (34.2 mg, 82% yield; 85:15 dr) as a yellow powder.

HRMS (ESI): m/z [M + H\(^{+}\)] calcd for C\(_{26}\)H\(_{28}\)N\(_3\)O\(_3\): 430.2125; found: 430.2131.

\(1^H\) NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.66, 7.56 (m, 1 H), 7.47 (d, J = 7.8 Hz, 1H), 7.30 (t, J = 7.8 Hz, 1H), 7.22–7.17 (m, 3H), 7.02 (t, J = 7.5 Hz, 1H), 1.68 (d, J = 7.8 Hz, 1H), 6.60–6.37 (m, 2H), 6.18 (dd, J = 15.9, 7.9 Hz, 1H), 1.37 (s, 3H), 2.62–2.60 (m, 1H), 2.38 (s, 3H), 0.76 (d, J = 6.7 Hz, 3H).

IR (neat): 3392, 2961, 2361, 1730, 1600, 1568, 1555, 1487, 1436, 1320, 1274, 1263, 1207, 1187, 1099, 79.6, 45.0, 21.2, 14.0; only peaks for the major isomer are listed.

HRMS (ESI): m/z [M + H\(^{+}\)] calcd for C\(_{23}\)H\(_{24}\)N\(_3\)O\(_{2}\): 368.1843.

IR (neat): 3226, 3033, 2925, 1730, 1572, 1465, 1436, 1318, 1378, 1353, 1343, 1340, 1335, 1310, 1280, 1274, 1263, 1207, 1187, 1099, 79.6, 45.0, 21.2, 14.0; only peaks for the major isomer are listed.

HRMS (ESI): m/z [M + H\(^{+}\)] calcd for C\(_{23}\)H\(_{24}\)N\(_{4}\)O\(_{4}\): 417.1563; found: 417.1557.
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**Supporting Information**

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690741.

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(6) CCDC 1956911 (4k) and CCDC 1957083 (4l) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.