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Rhodium(III)-Catalyzed Regioselective C7-Allylation of Indazoles

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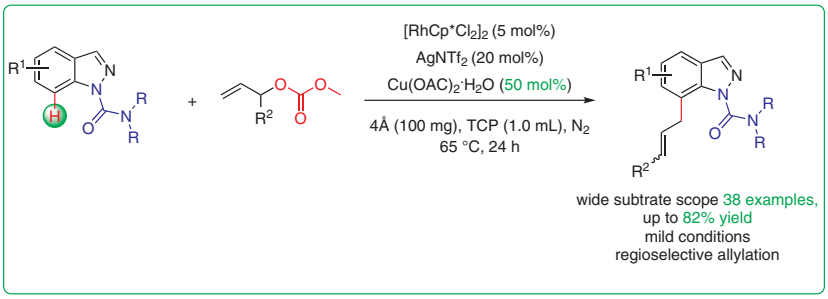

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Abstract An efficient rhodium-catalyzed regioselective C–H allylation of *N*,*N*-diisopropylcarbamoyl indazoles with allylic carbonates as allylating agents has been developed. This methodology provides facile access to C7-allylated indazoles with high regioselectivity, ample substrate scope and broad functional group tolerance.

Key words indazoles, C–H activation, regioselectivity, allylation, rhodium catalysis

Indazole derivatives, which are bioisosteres of indole, have attracted enormous attention due to their wide biological activities and irreplaceable role in pharmaceuticals as anti-inflammatory, antiarrhythmic, antitumor, antifungal, antibacterial, and anti-HIV agents.[2] There is hence a continuing high demand for efficient synthetic methodology enabling the construction of indazole derivatives.[3] Direct functionalization of indazoles, which could significantly simplify synthetic routes to this important class of heteroarene, provides probably one of the most efficient and straightforward approaches to access structurally diverse indazole derivatives.[4]

In the last decade, great progress has been made in transition-metal-catalyzed C–H activation, which has already become a useful tool for late-stage functionalization of complex organic molecules.[5] Owing to its high step-efficiency and atom-economy, direct C–H bond-functionalization processes have clear advantages in structural diversity oriented synthesis and in the modification of bio-organic molecules.[6] On account of the higher electron density of the azole ring, extensive research has been done on the direct C3 functionalization of indazole, such as arylation,[7] alkenylation,[8] phosphonylation,[9] trifluoromethylation,[10] thiocyanation,[11] and oxyalkylation.[12] However, the inherently poor reactivity means that direct regioselective functionalization of indazole at the benzene core (C4-C7 positions), especially when lacking any substituent at the 3-position, remains challenging.[7c] To override this intrinsic selectivity, the introduction of directing groups on the *N*-1 atom of indazole has proven to be an efficient strategy to ensure high regioselectivity of these inactive positions.[13] Very recently, our group has reported the first example of direct C7-olefination of indazoles by using $[Cp^*RhCl_2]_2$ as a catalyst and *N*,*N*-diisopropylcarbamoyl as a directing group.[14] Without any protection or blocking group at the C3-position, this method displayed excellent C7-regioselectivity, which provides a powerful way to introduce a wide variety of side chains at the C7-position of indazole derivatives.

Allylation has been considered as one of the most important and fundamental transformations in organic synthesis because the allyl moieties can be easily handled and they allow access to various and versatile functional groups by classical oxidation, olefin metathesis and coupling reactions.[15] Furthermore, the installation of an allyl group on bioactive heteroarenes may cause a dramatic change in its biological and physical properties.[16] For example, widely distributed in the genera *Penicillium* and *Aspergillus* of ascomycota, C7-allylated indole natural products often carry distinct biological and pharmacological activities compared with their non-allylated precursors. We can envision that the introduction of an allyl group into the C7-position of the indazole would provide a platform not only for the preparation of structurally complex and diverse molecules through manipulation of the allyl groups, but also for the introduction of a variety of indazole molecules with distinct biological and pharmacological activities.[17] Considering the high importance of both allyl groups and indazole moiety, and our continuous efforts in regioselective C–H activation of bioactive heteroarenes, herein, we disclose the first regioselective C–H allylation of indazoles at the C7 position.[14,18]

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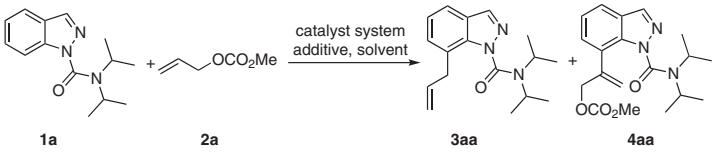
According to our previous study, we initially examined a set of potential *N*-amide direction groups in the reaction of indazole derivatives with allylic carbonate **2a** (Table S-1 in the Supporting Information).[14] It was found that in the presence of $[Cp^*RhCl_2]_2$, $AgNTf_2$, and $Cu(OAc)_2{\cdot}H_2O$ in DCE at 65 °C, *N*,*N*-diisopropylcarbamoyl indazole **1a** gave a better performance, producing the C7-allyation product **3aa** in 64% yield (Table S-1, entry 5). It is noteworthy that the large size of the directing group and the N-disubstituted directing group both play important roles in facilitating this transformation.

Encouraged by the initial result, we selected *N*,*N*-diisopropylcarbamoyl indazole **1a** and allylic carbonate **2a** as model substrates to optimize the reaction conditions (Table 1). An investigation of alternative counterion additives showed that $AgNTf_2$ was most suitable for this reaction; the reaction could not occur when AgOTf or AgOTs were used (entries 1–4).

Replacing $Cu(OAc)_2{\cdot}H_2O$ with $Cu(OAc)_2$ or AgOAc as additives gave slightly lower yields (Table 1, entries 5 and 6), while $Cu(OTf)_2$ was found to be almost entirely ineffective, with only 6% yield being isolated (entry 7). Further screening of a series of representative solvents revealed that this transformation is highly solvent-dependent. Solvents including dichloromethane, dimethyl sulfoxide, methanol, acetonitrile, and tetrahydrofuran gave poor results of the desired product (entries 8–12). To our delight, 1,2,3-trichloropropane showed a great promoting effect on the transformation, affording the **3aa** in 78% yield (entry 13). The best conditions were obtained when 4Å molecular sieves were added while shortening the reaction time to 24 h.[19] We speculated that molecular sieves could remove the generated MeOH from the reaction system, thus improving the

Table 1 Optimization of Reaction Conditions[a]



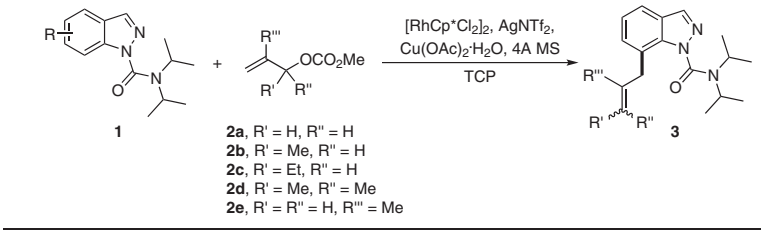
1a 2a 3aa 4aa

Entry	Catalyst System	Additive	Solvent	Yield (%)[b]
1	$[RhCp^*Cl_2]_2/AgNTf_2$	$Cu(OAc)_2{\cdot}H_2O$	DCE	64
2	$[RhCp^*Cl_2]_2/AgSbF_6$	$Cu(OAc)_2{\cdot}H_2O$	DCE	41
3	$[RhCp^*Cl_2]_2$/AgOTs	$Cu(OAc)_2{\cdot}H_2O$	DCE	n.d.
4	$[RhCp^*Cl_2]_2$/AgOTf	$Cu(OAc)_2{\cdot}H_2O$	DCE	n.d.
5	$[RhCp^*Cl_2]_2/AgNTf_2$	$Cu(OAc)_2$	DCE	62
6	$[RhCp^*Cl_2]_2/AgNTf_2$	AgOAc	DCE	50
7	$[RhCp^*Cl_2]_2/AgNTf_2$	$Cu(OTf)_2$	DCE	6
8	$[RhCp^*Cl_2]_2/AgNTf_2$	$Cu(OAc)_2{\cdot}H_2O$	DCM	37
9	$[RhCp^*Cl_2]_2/AgNTf_2$	$Cu(OAc)_2{\cdot}H_2O$	DMSO	n.d.
10	$[RhCp^*Cl_2]_2/AgNTf_2$	$Cu(OAc)_2{\cdot}H_2O$	MeOH	<5
11	$[RhCp^*Cl_2]_2/AgNTf_2$	$Cu(OAc)_2{\cdot}H_2O$	MeCN	n.d.
12	$[RhCp^*Cl_2]_2/AgNTf_2$	$Cu(OAc)_2{\cdot}H_2O$	THF	50
13	$[RhCp^*Cl_2]_2/AgNTf_2$	$Cu(OAc)_2{\cdot}H_2O$	TCP	78
14	$[RhCp^*Cl_2]_2/AgNTf_2$	$Cu(OAc)_2{\cdot}H_2O$	TCP	82[c,d]
15	$[RhCp^*Cl_2]_2/AgNTf_2$	$Cu(OAc)_2{\cdot}H_2O$	TCP	78[e]
16	$[RhCp^*Cl_2]_2/AgNTf_2$	$Cu(OAc)_2{\cdot}H_2O$	TCP	74[f]
17	$[RhCp^*Cl_2]_2$/–	$Cu(OAc)_2{\cdot}H_2O$	TCP	n.d.[c]
18	–/$AgNTf_2$	$Cu(OAc)_2{\cdot}H_2O$	TCP	n.d.[c]
19	$[RhCp^*Cl_2]_2/AgNTf_2$	–	TCP	<5[c]

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (1.0 mmol), catalyst (5 mol%), counterion (20 mol%), additive (50 mol%), solvent (1.0 mL), 65 °C, 48 h. TCP = 1,2,3-trichloropropane, Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl.
[b] Yield of **3aa** (n.d. = not detected).
[c] 4Å MS (100 mg/mL) was added, 65 °C, 24 h.
[d] **4aa** was obtained in 11% yield.
[e] 4Å MS (100 mg/mL) was added, 50 °C, 24 h.
[f] 4Å MS (100 mg/mL) was added, 80 °C, 24 h.

yield (entry 14). Interestingly, under optimized reaction conditions, branched product **4aa**, which was accessed through 1,2-migratory insertion and subsequent β-elimination, was also inevitably isolated in 11% yield. The reaction proceeded most efficiently at 65 °C; either lowering or increasing the temperature resulted in reduced yield (entries 15 and 16). Finally, control reactions established that [Cp^*RhCl_2] as catalyst, $AgNTf_2$ as counterion and $Cu(OAc)_2{\cdot}H_2O$ as additive were all essential to this reaction (entries 17–19). The structure of **3aa** was unambiguously confirmed by single-crystal X-ray diffraction analysis.

With the optimized reaction conditions in hand (Table 1, entry 14), we subsequently investigated the limitations and functional group tolerance of this transformation



3aa: R = H, 82%
3ba: R = Me, 78%
3ca: R = COOMe, 68%
3da: R = COOEt, 60%[a]
3ea: R = COO^{i}Pr, 61%[a]
3fa: R = Cl, 74%
3ga: R = NPhth, 70%

3ha: R = Me, 76%
3ia: R = COOMe, 70%
3ja: R = COO^{i}Pr, 55%[b]
3ka: R = F, 71%
3la: R = Cl, 75%
3ma: R = Br, 77%

3na: R = Me, 75%
3oa: R = OMe, 81%
3pa: R = OEt, 75%[a]
3qa: R = COOMe, 71%
3ra: R = F, 69%
3sa: R = Cl, 77%
3ta: R = Br, 72%
3ua: R = I, 75%
3va: R = NO_2, 30%[c]

3wa: R = F, 80%
3xa: R = Cl, 11%
3ya: R = Br, 0%
3za: R = Me, 0%

3ab: R = H, 55%[b] (E/Z = 6:1)
3bb: R = Me, 50%[b] (E/Z = 7:1)
3cb: R = COOMe, 30%[d] (E/Z = 7:1)

3hb, 41%[b] (E/Z = 7:1)

3nb: R = Me, 35%[b] (*E*/*Z* = 6:1)
3ub: R = I, 30%[b] (*E*/*Z* = 5:1)

3wb: 35%[b] (*E*/*Z* = 5:1)

3ac: R = H, 21%[b] (*E*/*Z* = 4:1)
3bc: R = Me, 29%[e] (*E*/*Z* = 5:1)

3hc: 30%[e] (*E*/*Z* = 5:1)

3nc: 30%[e] (*E*/*Z* = 5:1)

3ad: 0%

3ae: 0%

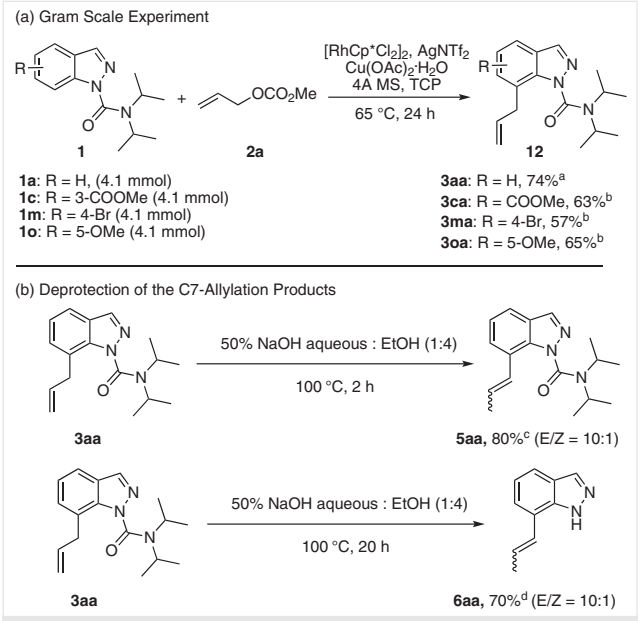
Scheme 1 Substrate scope of regioselective C7-allylation of indazoles. *Reagents and conditions*: [a] **1** (0.2 mmol), **2** (1.0 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgNTf_2$ (20 mol%), $Cu(OAc)_2{\cdot}H_2O$ (50 mol%), TCP (1.0 mL), 4A MS (100 mg), 65 °C, 24 h. [b] 65 °C, 48 h. [c] 65 °C, 72 h. [d] 80 °C, 48 h. [e] $AgNTf_2$ (30 mol%). [f] 65 °C, 96 h.

(Scheme 1). Generally, our methodology was applied to various substituted indazoles with excellent C7-regioselectivity, producing the corresponding C7-allylation products in moderate to good yield in most cases. It was found that indazoles with an electron-donating substituent at the C3, C4 or C5 position afforded the desired products in higher yields relative to those with an electron-withdrawing group (**3ba–ea**, **3ia**, **3ja**, and **3na–qa**). However, the indazole ring bearing a strong electron-withdrawing group such as C5-NO_2 was found to be less reactive; the conversion was moderate even at 80 °C for 48 h and the allylated product **3va** was obtained in only 30% yield. The 3-amino-substituted indazole was not compatible with the catalyst system. We suspect that the ineffective results were presumably due to the competitive chelation of 3-amino to the metal center. When phthalic anhydride protected substrate was used, the reaction proceeded smoothly (**3ga**). To our delight, indazoles with various halogen groups substituted at the C3, C4 and C5 positions were well tolerated, which offers ample opportunity for further derivatization (**3fa**, **3ka–ma** and **3ra–ua**).

Notably, this regioselective C7-allylation reaction is sensitive to steric hindrance. When C6-methyl or C6-bromide substituted indazoles were used, the desired **3ya** and **3za** were not detected. With smaller fluoride groups, higher conversion was observed, delivering **3wa** in 80% yield.

Next, the scope of the C7-allylation reaction was extended to substituted allylic carbonates. When but-3-en-2-yl acetate **2b** was selected as the coupling partner with *N*,*N*-dimethylcarbamoyl-indazole under the standard conditions, no branched product of type **4** was observed and only **3ab** was obtained with low conversion (20%). To improve the conversion rate, we further optimized the reaction temperature and reaction time. It was found that higher temperature such as 80 °C and 100 °C were not beneficial to this process. However, when the reaction time was prolonged to 72 h, **3ab** could be obtained in moderate yield (55%), indicating this transformation is sensitive to steric hindrance again. Under the same conditions, α-methyl and ethyl substituted allylic carbonates (**2b** and **2c**) reacted smoothly with various substituted indazoles **1** to furnish the desired products in acceptable yields in 4:1 to 7:1 *E*/*Z* stereoisomeric rations. Unfortunately, methyl (2-methylbut-3-en-2-yl) carbonate (**2d**) and methyl (2-methylallyl) carbonate (**2e**) were found to be unreactive and the indazole substrate could be completely recovered.

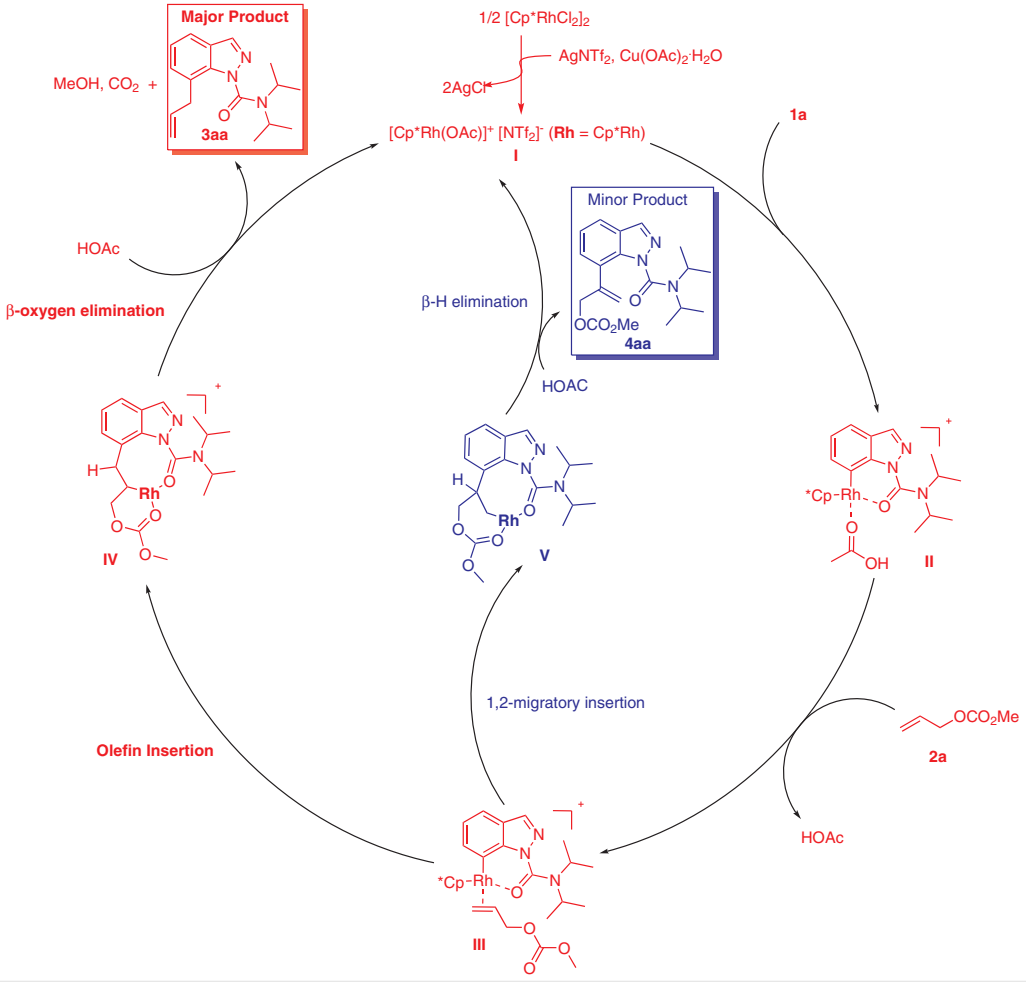
To further demonstrate the synthetic utility of this protocol, we first evaluated the scalability of the current process (Scheme 2a). The reaction of **1a** with **2a** was conducted on 4.1 mmol scale. We were pleased to find that the catalyst loading could be reduced to 2 mol% and the desired product **3aa** could still be obtained in 74% yield. Under the same conditions, other substrates, including C3-CO_2Me (**1c**), C4-Br (**1m**) and C5-OMe (**1o**) were also successfully applied on a gram scale, albeit with slightly diminished yield. Meanwhile, under our previous deprotection method, we observed the olefin migrated product **5aa** and subsequent deprotected C7-alkenylated indazole **6aa** in 80% and 70% yield, respectively, which highlights the synthetic potential of this transformation (Scheme 2b).



Scheme 2 Synthetic utility of C7-allylated indazoles. [a] *Reagents and conditions*: **1** (4.1 mmol), **2a** (20.5 mmol), [RhCp*Cl_2]$_2$ (2 mol%), $AgNTf_2$ (8 mol%), Cu(OAc)$_2$·H_2O (50 mol%), 4A MS (1 g), TCP (5.0 mL), 65 °C, 24 h. [b] 48 h. [c] **3aa** (0.4 mmol), solvent: 50% NaOH aq/EtOH (1:4), 100 °C, 2 h. [d] **3aa** (0.4 mmol), solvent: 50% NaOH aq/EtOH (1:4), 100 °C, 20 h.

Based on previous reports, a plausible catalytic cycle for the present rhodium-catalyzed C–H allylation reaction mechanism is proposed (Scheme 3). First, a catalytically active rhodium species **I** is formed from the dimeric precursor [RhCp*Cl_2]$_2$ with $AgSbF_6$ and Cu(OAc)$_2$·H_2O. Coordination of Rh^{III} species **I** to the *N*-amide group of **1a** and subsequent C–H activation affords a six-membered rhodium metallacycle **II**. Coordination of allylic carbonate **2a** then gives the complex **III**, which may undergo olefin insertion to afford an eight-membered metallacycle **IV** followed by β-oxygen elimination to give the major allylated product **3aa**. The Rh^{III} intermediate **III** may also undergo a 1,2-migratory insertion and further furnish the minor alkenylation product **4aa** by β-H elimination.

In summary, we have developed the first example of rhodium-catalyzed *N*,*N*-diisopropylcarbamoyl directed regioselective C7-allylation reaction with indazoles. The reaction tolerates a wide range of indazoles with electron-donating and electron-withdrawing substituents and gives the product in moderate to good yields. Considering the simple operation, large-scale preparation and high value of C7-allylated indazole scaffolds, this synthetic strategy should have potential synthetic utility for the construction of structurally diverse indazole derivatives.



Scheme 3 Proposed mechanism

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1691488.

Primary Data

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(19) **Preparation of 3aa; Typical Procedure**: To a 10 mL dry Schlenk tube with a stirring bar, indazole substrate **1a** (0.2 mmol), $[RhCp^*Cl_2]_2$ (6.2 mg, 5 mol%), $Cu(OAc)_2{\cdot}H_2O$ (20 mg, 50 mol%), $AgNTf_2$ (15.5 mg, 20 mol%), and 4Å MS (100 mg) were added. The tube was evacuated and backfilled with nitrogen before allyl methyl carbonate **2a** (116 µL, 1.0 mmol) and 1,2,3-trichloropropane (1.0 mL) were added. The reaction mixture was stirred at 65 °C for 24 h. After cooling to room temperature, the reaction mixture was purified by chromatography on silica with a gradient eluent of petroleum ether and ethyl acetate to give the corresponding product.

7-Allyl-*N*,*N*-diisopropyl-1*H*-indazole-1-carboxamide (**3aa**): Yield: 82% (46.7 mg); white solid. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.07 (s, 1 H), 7.61 (d, *J* = 7.9 Hz, 1 H), 7.27 (d, *J* = 7.1 Hz, 1 H), 7.19 (t, *J* = 7.5 Hz, 1 H), 6.06–6.00 (m, 1 H), 5.07 (d, *J* = 10.1 Hz, 1 H), 4.96 (d, *J* = 17.2 Hz, 1 H), 4.12 (brs, 1 H), 3.77 (d, *J* = 4.7 Hz, 2 H), 3.61 (brs, 1 H), 1.56 (brs, 6 H), 1.26 (brs, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.62, 139.15, 136.55, 136.18, 128.91, 125.84, 124.68, 122.73, 119.02, 116.28, 51.36, 46.29, 36.71, 20.59, 20.08. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{24}N_3O^+$: 286.19139; found: 286.19119.