

Palladium-Catalyzed Direct Functionalization of Imidazolinone: Synthesis of Dibromophakellstatin

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Supporting Information

General Comments	S1
Mechanistic Studies	S2
Computational Details	S4
Experimental Section	S9
NMR Spectra	S17

General Comments

We have examined the direct arylation of imidazolinone (**1**) with 6 different palladium sources, 15 different phosphine ligands, 12 different bases and 14 different solvent systems. There is no significant difference between using Pd(OAc)₂ and Pd(TFA)₂. This reaction proceeds less efficiently or reproducibly with Pd₂(dba)₃/*o*-biphenylPCy₂, O=PCy₃, O=PPh₃, P(OMe)₃, PCy₃·HBF₄, PCy₃, P^{*n*}Bu₃/DMF, NMP/Na₂CO₃.

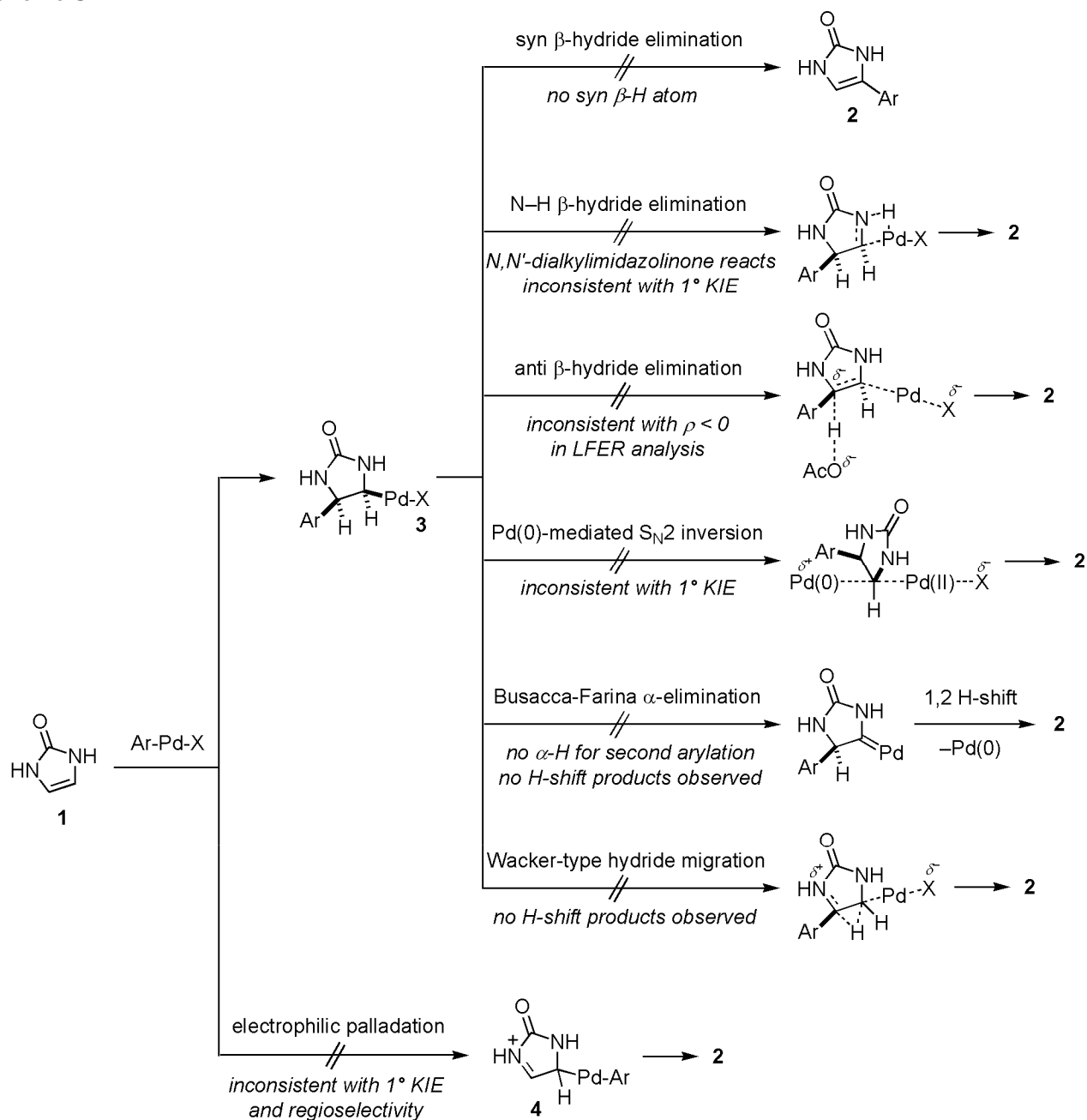
Aryl bromides are less reactive; however, good results can be obtained with electronic-deficient aryl bromides. The electron-rich aryl bromides only react slowly. We suspect that the rate-limiting step shifts to oxidative addition of palladium(0) to aryl bromide in these cases.

For the synthesis of dibromophakellstatin, phthalimide **11** can be prepared in DMSO and used in situ for the subsequent vinylation reaction. However, removal of the potassium bromide salt improves the efficiency of the palladium-catalyzed vinylation reaction. We have found that **12** decomposed upon prolonged heating, and **13** was obtained in only ~25% overall yield using the standard protocol. Therefore, **1** was used in large excess to decrease the reaction time. Unreacted imidazolinone **1** can be recovered from washing the reaction mixture with water directly or through a short pad of reverse-phase silica gel. Partial removal of palladium black with reverse-phase silica gel reduces the adsorption problem and increases the overall yield. After hydrogenation, the remaining palladium black can be easily filtered off. The diminished overall yield of **13** is due to the adsorption of reaction products by palladium. The one-pot hydrogenation/phthalimide deprotection method gave ~30% yield of **13**.

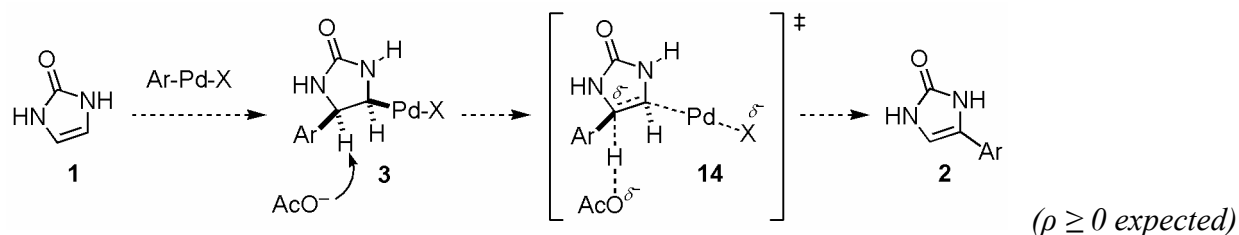
Mechanistic Studies

Scheme S1 summarizes the experimentally excluded mechanisms. Additional evidences against the *anti*- β -H elimination, α -elimination and electrophilic palladation pathway are also presented below.

Scheme S1.

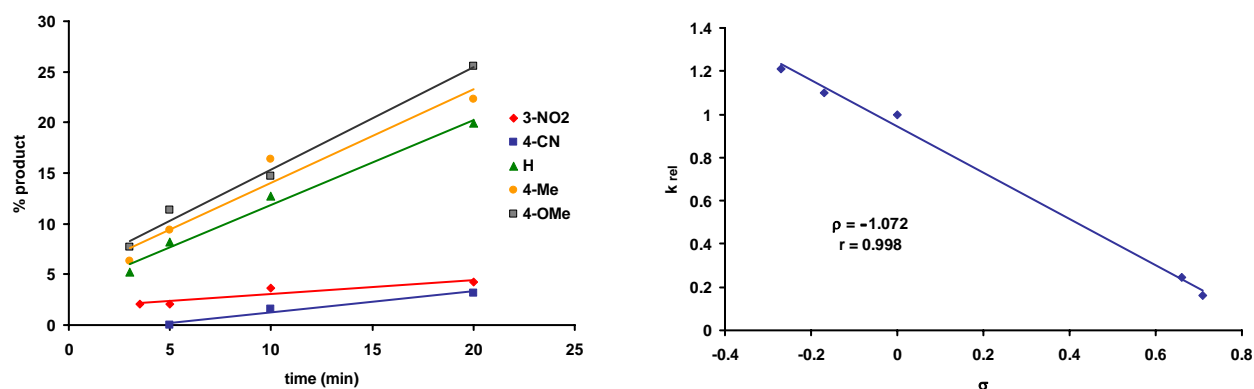


***anti*- β -H Elimination.** The *anti*- β -H elimination is believed to proceed through a base-promoted E2 or E1_{cb} mechanism (Scheme S2). An electron-rich or neutral center adjacent to the aryl group in **14** is therefore expected to form, with $\rho \geq 0$ in the linear free-energy relationship (LFER) analysis. However, the LFER analysis suggests that an electron-deficient center ($\rho = -1.072$) adjacent to the aryl group was developed in the transition state (Table S1, Figure S1). The reaction proceeded cleanly without detectable side-products and intermediates for the aryl iodides used in Table S2.

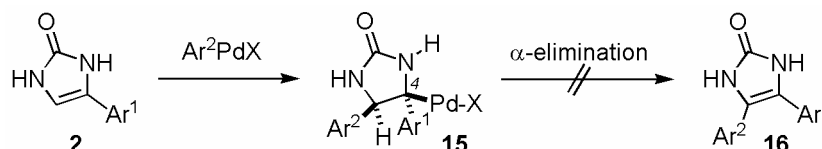
Scheme S2.**Table S1.** The linear free-energy relationship analysis of arylation of **1**.

Ar-I	% product*				slope	r	k_{rel}	σ
	3 min	5 min	10 min	20 min				
3-NO ₂ -C ₆ H ₄ -I	2.1 [†]	2.1	3.7	4.2	0.134	0.921	0.161	0.71 [‡]
4-CN-C ₆ H ₄ -I	–	~0	1.6	3.2	0.206	0.982	0.246	0.66 [‡]
H-C ₆ H ₄ -I	5.2	8.2	12.7	19.2	0.836	0.993	1.000	0
4-Me-C ₆ H ₄ -I	6.3	9.4	16.4	22.3	0.920	0.973	1.100	-0.17 [‡]
4-OMe-C ₆ H ₄ -I	7.7	11.3	14.7	25.6	1.013	0.995	1.212	-0.27 [‡]

* Determined by NMR with 10 s recycle delay. [†] Sample taken at 3.5 min. [‡] Data taken from Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed. HarperCollins: New York, 1987; pp 144.

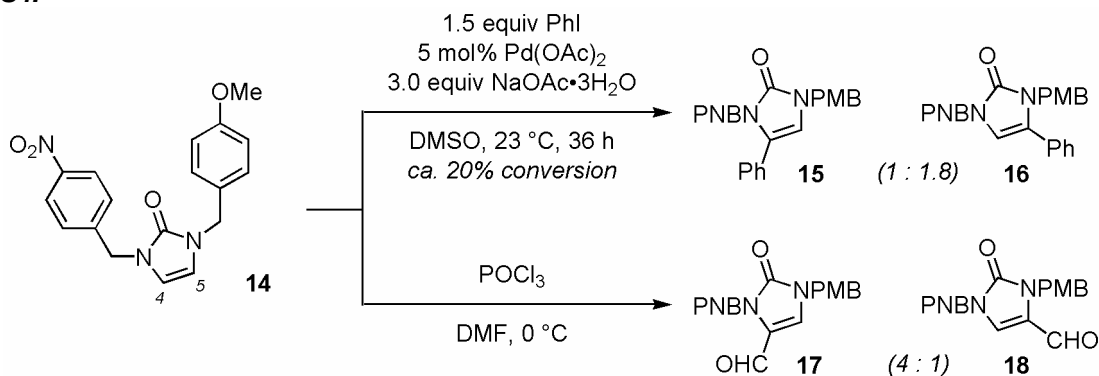
**Figure S1.** The Hammett linear free-energy relationship analysis.

α -Elimination. In addition to the absence of H/D migration products with **8-d₁** (Scheme 4), the α -elimination mechanism can not explain the formation of the bisarylation products. During the second arylation step, there is no α -H available for the elimination in **15** (Scheme S3).

Scheme S3.

Electrophilic Palladation. In addition to the arylation of **8**, arylation of **17** also occurs preferentially at the less electron-rich 5-position (Scheme S4). The regioselectivity is opposite to the electrophilic formylation of **17**.

Scheme S4.



Computational Studies

The activation barriers for the acetate ligand-assisted C–H insertion of the *cis*- and *trans*-PdL₂X₂ complex (Scheme S5, Table S2) were evaluated. All the computations were performed on Jaguar 6.5 suite^{S1} using the B3LYP functional and LACVP**++ basis set.^{S2,3} All stationary points were subjected to frequency analysis and characterized as a minimum (no imaginary frequencies) or as a saddle point (single imaginary frequency) on the potential energy surface. Transition states were verified by imaginary frequency animation with desired vibrational modes. The single-point energy and solvation energy (DMSO, dielectric constant: 47.240, probe radius: 2.41 Å) calculations were then performed on the gas-phase optimized geometries. The solvation was treated with a self-consistent reaction field (SCRf) method, using its own Poisson-Boltzmann solver.^{S4,5} Zero-point-energy (ZPE) and entropy corrections were derived using unscaled frequencies. Thermodynamic properties were calculated assuming ideal gas at 298.15 K. The resulting activation barrier for the *cis*-PdL₂X₂ complex ($\Delta H_{\text{DMSO},298.15\text{K}}^{\ddagger} = 17.9$ kcal/mol) is comparable to the reported activation barriers for the Wacker oxidation ($\Delta H_{\text{H}_2\text{O},0\text{K}}^{\ddagger} = 12.5\text{--}18.8$ kcal/mol) calculated by the same method.^{S3}

Scheme S5.

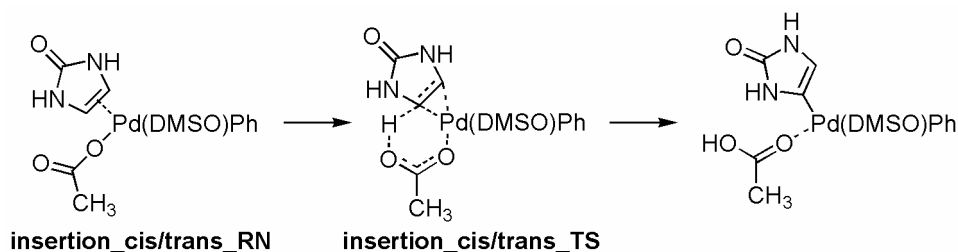
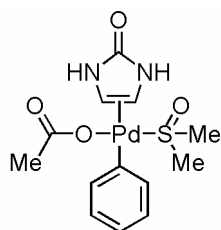


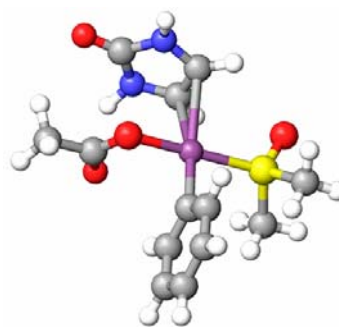
Table S2. The computed energies for the C–H insertion pathway.

	SCFE(gas) (hartree)	ZPE* (kcal/mol)	solvation* (kcal/mol)	H(gas) (hartree)	$\Delta H(\text{soln})^*$ (kcal/mol)	G(gas) (hartree)	$\Delta G(\text{soln})^*$ (kcal/mol)
insertion_cis_RN	-1441.628703	188.34	-29.217	-1441.303087	0	-1441.385285	0
insertion_cis_TS	-1441.599126	185.41	-26.648	-1441.278736	17.85	-1441.360336	18.23
insertion_trans_RN	-1441.630662	188.36	-31.219	-1441.305082	0	-1441.387571	0
insertion_trans_TS	-1441.586045	184.63	-27.597	-1441.266744	27.68	-1441.348879	27.90

* Converting unit: 1 hartree = 627.50947093 kcal/mol.



insertion_cis_RN



Gas-phase SCF energy: -1441.62870306573 hartrees

Solvation energy: -0.04656015308 hartrees

Zero point energy (ZPE): 188.343560 kcal/mol

T = 298.15 K

Total internal energy, Utot (SCFE + ZPE + U): -1441.304032 hartrees

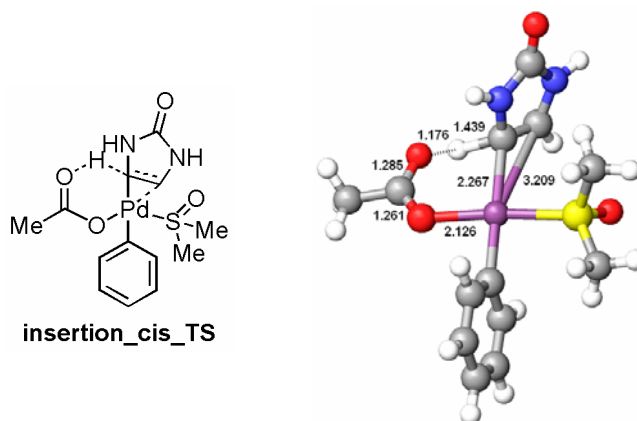
Total enthalpy, Htot (Utot + pV): -1441.303087 hartrees

Total Gibbs free energy, Gtot (Htot - T*S): -1441.385285 hartrees

Geometry Coordinates

atom	angstroms		
	x	y	z
Pd1	0.1134567092	0.0194329846	-0.0428223416
C2	0.0869390083	-0.0130484491	2.4923242386
C3	1.4375253368	-0.0748698712	2.2442450199
H4	2.1221518323	0.7377528254	2.0548409058
N5	1.8526043140	-1.3585117929	2.5634951536
H6	2.7322522031	-1.7802082453	2.3057177336
N7	-0.3056823555	-1.2568159414	2.9779880706
H8	-1.2518250773	-1.6074726142	2.8826173957
C9	0.7617067172	-2.1531977032	2.9361286730
O10	0.7524659286	-3.3509728495	3.1719387466
O11	0.0785928763	-2.0400916121	-0.1046110160
C12	-1.0617479672	-2.5858611883	0.2231914783
O13	-2.0499239689	-1.9554407197	0.6325443754
H14	-0.5320891220	0.8651009891	2.5894273917
C15	-1.0658448109	-4.1019847214	0.1167864231
H16	-0.5734663728	-4.4261512123	-0.8037683746
H17	-2.0904807347	-4.4754973399	0.1560208579
H18	-0.5016421687	-4.5110189451	0.9624491665
C19	-0.4665371925	-0.0361942897	-1.9793992131
C20	-1.3146829351	-0.1923204264	-4.6507152745
C21	0.4755510173	-0.0833436430	-3.0133168167
C22	-1.8333355418	-0.0935663983	-2.2788022675
C23	-2.2532637938	-0.1659482770	-3.6146043157
C24	0.0496468295	-0.1583323199	-4.3474182631
H25	1.5401757784	-0.0867190315	-2.7933604803
H26	-2.5679038715	-0.1226028277	-1.4790413859
H27	-3.3159103122	-0.2175029150	-3.8392774911
H28	0.7873012772	-0.2017041135	-5.1451957233
H29	-1.6434807042	-0.2557700475	-5.6843321342
S30	0.2272873294	2.3491083769	-0.0745432498
O31	0.7090725170	2.9796697533	1.2096394578
C32	-1.3861918170	3.0773508262	-0.4892557438
H33	-1.7152873223	2.6913482139	-1.4559292022
H34	-1.2744277047	4.1642130896	-0.4949993946
H35	-2.0797938862	2.7714720131	0.2956948364
C36	1.2278496965	3.0236390797	-1.4352687420
H37	0.8438220418	2.6502021987	-2.3860173880

H38	2.2501160069	2.6773010477	-1.2750555222
H39	1.1830520449	4.1134270460	-1.3716110978



Imaginary frequency: -815.66 cm⁻¹
 Gas-phase SCF energy: -1441.59912583532 hartrees
 Solvation energy: -0.04246695678 hartrees
 Zero point energy (ZPE): 185.407163 kcal/mol

T = 298.15 K
 Total internal energy, Utot (SCFE + ZPE + U): -1441.279680 hartrees
 Total enthalpy, Htot (Utot + pV): -1441.278736 hartrees
 Total Gibbs free energy, Gtot (Htot - T*S): -1441.360336 hartrees

Geometry Coordinates

atom	angstroms		
	x	y	z
Pd1	-1.6663957445	-0.5430179393	-0.5688994996
C2	-2.4498980561	0.6005035760	1.2243173769
C3	-3.6887129598	0.3387242415	1.7616212674
H4	-4.1853663771	-0.6125210945	1.8826204666
N5	-4.2980541029	1.5215378620	2.1369438913
H6	-5.1894529967	1.6313476658	2.5966806774
N7	-2.3605736915	2.0238123185	1.2905909558
H8	-1.5396230956	2.5681935746	1.0750577004
C9	-3.4619253523	2.6139868986	1.8781573683
O10	-3.6850322051	3.8000605471	2.1101303677
O11	0.2616881107	-0.8866547602	0.2574943248
C12	0.4871208563	-0.8427621410	1.4975322279
O13	-0.3738589216	-0.4788455515	2.3785805104
H14	-1.3389791992	-0.0746185342	1.8420437521
C15	1.8539781350	-1.2343253580	2.0036527102
H16	2.4978522691	-1.5302769561	1.1755854200
H17	1.7511591594	-2.0598827581	2.7146308679
H18	2.2952192706	-0.3914628973	2.5445841401
C19	-0.9585450688	-1.6170230064	-2.1478155935
C20	0.1294429518	-3.1685740701	-4.2276011185
C21	-0.0669430728	-1.0462561043	-3.0637281073
C22	-1.2955415905	-2.9711748693	-2.2724373097
C23	-0.7517620940	-3.7447924727	-3.3078698595
C24	0.4725252967	-1.8188307395	-4.1017057350
H25	0.2285804640	-0.0037438100	-2.9694357605
H26	-1.9768757124	-3.4380740591	-1.5640333777
H27	-1.0167638789	-4.7962844667	-3.3906248652
H28	1.1662597259	-1.3652300753	-4.8057880038
H29	0.5510291867	-3.7674388353	-5.0302352313

S30	-3.7250811180	-0.2581185142	-1.6359328341
O31	-4.9149523996	-0.9510557576	-1.0303707674
C32	-3.7233123652	-0.6589862522	-3.4102574553
H33	-4.7095774065	-0.3940349036	-3.7982015140
H34	-3.5464024463	-1.7304304892	-3.4975660182
H35	-2.9229551695	-0.1112595633	-3.9107527617
C36	-4.0901224859	1.5201670494	-1.7511664213
H37	-3.2822414351	2.0172459116	-2.2932618425
H38	-4.1562381272	1.9079668825	-0.7357831104
H39	-5.0463417144	1.6293351908	-2.2685646740

Summary of the activation energies for cis-PdL₂X₂:

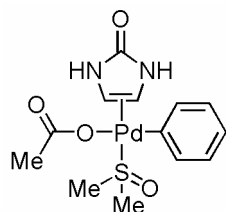
Δ SCFE(gas): 18.56 kcal/mol

Δ ZPE : -2.94 kcal/mol

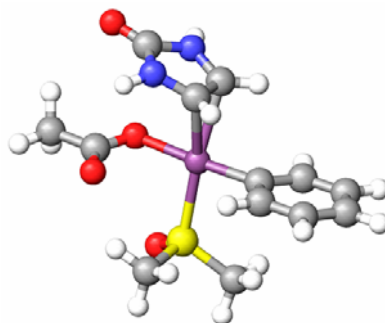
Δ H(gas): 15.28 kcal/mol

Δ G(gas): 15.66 kcal/mol

Solvation correction : 2.57 kcal/mol



insertion_trans_RN



Gas-phase SCF energy: -1441.6306621509 hartrees

Solvation energy: -0.04975049544 hartrees

Zero point energy (ZPE): 188.363 kcal/mol

T = 298.15 K

Total internal energy, Utot (SCFE + ZPE + U): -1441.306026 hartrees

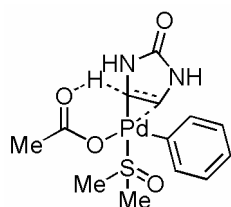
Total enthalpy, Htot (Utot + pV): -1441.305082 hartrees

Total Gibbs free energy, Gtot (Htot - T*S): -1441.387571 hartrees

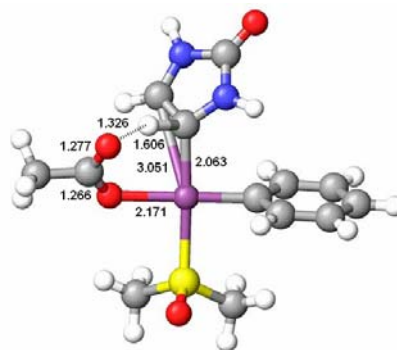
Geometry Coordinates

atom	x	y	z
Pd1	1.6907251180	0.4131613136	-0.1456261863
C2	3.0553979632	-0.1920012618	1.6242202339
C3	3.4944748028	1.0724712461	1.2269473000
H4	4.2361693122	1.3109136451	0.4792801296
N5	3.1587325603	1.9526347508	2.2405298794
H6	3.1024404036	2.9565318134	2.1452396174
N7	2.4661087546	-0.0438891859	2.8701898720
H8	1.8046558795	-0.6999367476	3.2648116456
C9	2.4135696306	1.3057452443	3.2367566618
O10	1.8730963918	1.7990524710	4.2068389561
O11	0.3862858819	1.4516825549	1.1715632501
C12	-0.5110288138	0.7139237999	1.7453906475
O13	-0.5905298225	-0.5232406243	1.5937857807
H14	3.3996443564	-1.1515018060	1.2684641654
C15	-1.4682965064	1.4639446809	2.6561747646
H16	-0.9023014391	1.9356861554	3.4663765477
H17	-2.2112083139	0.7817069919	3.0728399442
H18	-1.9642511163	2.2604775644	2.0928549160

C19	3.0133288585	-0.4731290782	-1.4041440927
C20	4.8632485959	-1.6905594812	-3.1642782749
C21	3.1449951607	-1.8710408983	-1.4586758915
C22	3.8276137685	0.3038573453	-2.2451308902
C23	4.7447770608	-0.2981674513	-3.1173837368
C24	4.0605215803	-2.4759565149	-2.3319268001
H25	2.5312200311	-2.5047372870	-0.8206295492
H26	3.7479185370	1.3893684830	-2.2346708050
H27	5.3647460412	0.3229285990	-3.7595737039
H28	4.1456229868	-3.5597050283	-2.3573642489
H29	5.5746373159	-2.1574782369	-3.8395941006
S30	-0.0881033316	0.2587798449	-1.8054875244
O31	-1.1128880883	1.3560480835	-1.8564962394
C32	0.4805077278	-0.0254495899	-3.5130503880
H33	1.1648614188	-0.8742704806	-3.5445655484
H34	0.9929152206	0.8837190333	-3.8306017509
H35	-0.4094039084	-0.1913731550	-4.1247218661
C36	-0.9316505758	-1.3197088832	-1.4826312084
H37	-0.2220337878	-2.1374359777	-1.6306674943
H38	-1.7772719348	-1.3904568789	-2.1714898378
H39	-1.2517144728	-1.2802236557	-0.4388653527



insertion_trans_TS



Imaginary frequency: -1517.95 cm^{-1}
 Gas-phase SCF energy: -1441.58604450836 hartrees
 Solvation energy: -0.04397794937 hartrees
 Zero point energy (ZPE): 183.634 kcal/mol

T = 298.15 K

Total internal energy, U_{tot} (SCFE + ZPE + U): -1441.267688 hartrees
 Total enthalpy, H_{tot} (U_{tot} + pV): -1441.266744 hartrees
 Total Gibbs free energy, G_{tot} (H_{tot} - T*S): -1441.348879 hartrees

Geometry Coordinates

atom	x	y	z
Pd1	0.0947890000	-0.5242480001	0.8105439999
C2	-1.6272030000	0.3484410000	0.0823320000
C3	-2.8722111218	0.1744353405	0.6791067065
H4	-3.1022448721	0.0850773325	1.7308173316
N5	-3.8469093651	0.1336515612	-0.2761533572
H6	-4.8446192919	0.0790758825	-0.1318326254
N7	-1.9509684415	0.4049616455	-1.3056338395
H8	-1.2673646918	0.4366648174	-2.0463045579
C9	-3.2885743335	0.2662243250	-1.5688179499
O10	-3.8950636885	0.2612366544	-2.6320811234
O11	-0.4387060000	0.2414780000	2.7702150000
C12	-0.7677330000	1.4612630000	2.8532190000
O13	-0.8871910000	2.2733330000	1.8748620000

H14	-1.2814370000	1.7878660000	0.7059380000
C15	-0.9950235650	2.0578704271	4.2273647814
H16	-0.8140985600	1.3171213821	5.0070977137
H17	-2.0208649792	2.4337570975	4.2972133727
H18	-0.3281624907	2.9146575458	4.3629453228
C19	0.5725860837	-1.2536253624	-1.0044326593
C20	1.3560272544	-2.3130187725	-3.5027075522
C21	1.6263043217	-0.6739584804	-1.7299052781
C22	-0.0906553260	-2.3636588116	-1.5532888391
C23	0.3014659495	-2.8927451496	-2.7897421957
C24	2.0144720404	-1.2007948782	-2.9708222986
H25	2.1593816807	0.1855401943	-1.3303111127
H26	-0.9255790356	-2.8173290773	-1.0251861539
H27	-0.2261226151	-3.7510368214	-3.1991004675
H28	2.8327957127	-0.7383416034	-3.5175762981
H29	1.6555625250	-2.7189535016	-4.4649643041
S30	2.0528408887	-1.5895960085	1.7858050658
O31	3.3283800270	-0.8006108000	1.9358628642
C32	1.5638753574	-2.1869009010	3.4356031472
H33	2.4403436491	-2.6418715144	3.9032512621
H34	0.7434360499	-2.9015726359	3.3339057111
H35	1.2269483647	-1.3133715823	3.9943499371
C36	2.4726072454	-3.1788998911	1.0062426198
H37	1.5861064197	-3.8160324440	0.9764799154
H38	3.2803435766	-3.6321364170	1.5856035689
H39	2.8023831253	-2.9548243739	-0.0085223217

Summary of the activation energies for trans-PdL₂X₂:

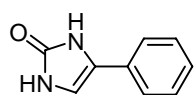
ΔSCFE (gas):	28.00 kcal/mol
ΔZPE :	-3.73 kcal/mol
ΔH (gas):	24.06 kcal/mol
ΔG (gas):	24.28 kcal/mol
Solvation correction:	3.62 kcal/mol

Experimental Section

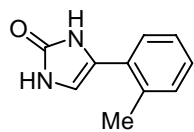
General Experimental Procedures. All reactions were performed in glassware under a positive pressure of argon. Liquids and solvent were transferred via syringe. Organic solutions were concentrated by rotary evaporator at ca. 30 mmHg. Flash column chromatography was performed as described by Still,^{S6} employing EMD RP-18 silica gel 60 (230–400 mesh ASTM) or Fisher Davisil 633 silica gel (200–425 mesh). TLC analyses were performed on EMD 250 μm Silica Gel 60 F₂₅₄ plates and visualized by quenching of UV fluorescence (λ_{\max} = 254 nm), or by staining with phosphomolybdic acid or ceric ammonium molybdate or potassium permanganate. ¹H and ¹³C NMR spectra were recorded on a Varian Inova-400 or Mercury-300 spectrometer. Chemical shifts for ¹H and ¹³C NMR spectra are reported in ppm (δ) relative to residue protium in the solvent (CDCl₃: δ 7.26, 77.23 ppm; DMSO-*d*₆: δ 2.50, 39.51 ppm) and the multiplicities are presented as follows: s = singlet, d = doublet, t = triplet, m = multiplet. Infrared spectra were recorded on a Perkin-Elmer 1000 series FTIR. Mass spectra were acquired on a Shimadzu 2010 LC-MS using the indicated ionization method.

Materials. Commercial solvents and reagents were used as received except that dimethyl sulfoxide was degassed by freeze-pump-thaw cycles, and 2,2,2-trichloroethanol was treated with calcium sulfate and sodium bicarbonate followed by distillation. Imidazolinone (**1**)^{S7} and 2-(3-bromoallyl)isoindoline-1,3-dione (**11**)^{S8,9} are both commercially available and can be easily prepared in large scales.

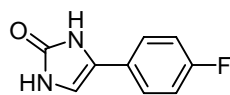
General procedure for the C-arylation of imidazolinone (1). Palladium(II) acetate (6.7 mg, 0.0298 mmol, 0.05 equiv), imidazolinone (1) (50 mg, 0.595 mmol, 1.0 equiv) and sodium acetate trihydrate (242.8 mg, 1.78 mmol, 3.0 equiv) were weighed and added to an argon-filled 16 mL vial. Aryl iodide (0.892 mmol, 1.5 equiv) and degassed dimethyl sulfoxide (2.5 mL) were then added and the vial was purged with argon for 1 min. After stirring in dark at 80 °C with the time indicated in Table 1, the solvent was removed. The crude residue was dissolved in methanol and dry-loaded onto a RP-18 silica gel column for chromatography purification. For arylation using aryl bromides, palladium(II) acetate (13.4 mg, 0.0595 mmol, 0.1 equiv), imidazolinone (1) (50 mg, 0.595 mmol, 1.0 equiv), aryl bromide (0.892 mmol, 1.5 equiv, if solid) and sodium acetate trihydrate (242.8 mg, 1.78 mmol, 3.0 equiv) were added to a 10 mL round-bottom flask and vigorously degassed. Degassed DMSO (2.5 mL) and aryl bromide (0.892 mmol, 1.5 equiv, if liquid) were then added. The reaction was stirred in dark at 80°C with the time indicated in Table 1 and S1.



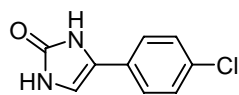
4-Phenyl-1H-imidazol-2(3H)-one. According to the general procedure using iodobenzene and purified with RP-18 silica gel column chromatography (0→80% methanol-water): R_f = 0.30 (10% methanol-methylene chloride); FTIR (neat, cm^{-1}) 1704, 1644, 1616, 1454, 1130, 938, 772, 730; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.50 (s, 1H), 10.04 (s, 1H), 7.49 (d, J = 7.7 Hz, 2H), 7.31 (t, J = 7.6 Hz, 2H), 7.16 (t, J = 7.4 Hz, 1H), 6.88 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 155.1, 130.0, 128.7, 126.2, 122.8, 122.0, 105.8; MS(ES^+) calcd for $\text{C}_9\text{H}_9\text{N}_2\text{O}$ ($\text{M}+\text{H}$) $^+$ 161.07, found 161.00.



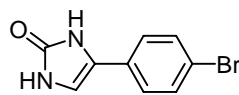
4-(2-Methylphenyl)-1H-imidazol-2(3H)-one. According to the general procedure using 2-iodotoluene and purified with RP-18 silica gel column chromatography (0→80% methanol-water): R_f = 0.34 (10% methanol-methylene chloride); FTIR (neat, cm^{-1}) 1737, 1559, 1496, 1230, 1147, 815, 768, 732; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.28 (s, 1H), 10.07 (s, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.21 (t, J = 7.8 Hz, 2H), 7.14 (d, J = 6.8 Hz, 1H), 6.50 (s, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 154.8, 134.2, 131.0, 129.2, 126.5, 126.4, 126.0, 121.1, 108.3, 21.5; MS(ES^+) calcd for $\text{C}_{10}\text{H}_{11}\text{N}_2\text{O}$ ($\text{M}+\text{H}$) $^+$ 175.09, found 175.02.



4-(4-Fluorophenyl)-1H-imidazol-2(3H)-one. According to the general procedure using 1-fluoro-4-iodobenzene and purified with RP-18 silica gel column chromatography (0→80% methanol-water): R_f = 0.32 (10% methanol-methylene chloride); FTIR (neat, cm^{-1}) 1703, 1650, 1628, 1513, 1235, 1122, 839, 739; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.51 (s, 1H), 10.04 (s, 1H), 7.53 (dd, J = 5.5 Hz, 2H), 7.17 (t, J = 8.8 Hz, 2H), 6.86 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 160.7 (d, J = 242.9 Hz), 155.1, 126.7 (d, J = 30.0 Hz), 124.7 (d, J = 7.6 Hz), 121.2, 115.6 (d, J = 31.8 Hz), 105.7; MS(ES^+) calcd for $\text{C}_9\text{H}_8\text{FN}_2\text{O}$ ($\text{M}+\text{H}$) $^+$ 179.06, found 179.00.

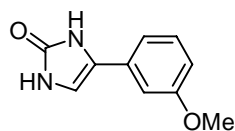


4-(4-Chlorophenyl)-1H-imidazol-2(3H)-one. According to the general procedure using 1-chloro-4-iodobenzene and purified with RP-18 silica gel column chromatography (0→80% methanol-water): R_f = 0.35 (10% methanol-methylene chloride); FTIR (neat, cm^{-1}) 1736, 1654, 1622, 1498, 1420, 1133, 1097, 826, 730; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.55 (s, 1H), 10.12 (s, 1H), 7.51 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 8.6 Hz, 2H), 6.96 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 155.0, 130.3, 129.0, 128.7, 124.4, 106.7; MS(ES^+) calcd for $\text{C}_9\text{H}_8\text{ClN}_2\text{O}$ ($\text{M}+\text{H}$) $^+$ 195.03, found 194.95.

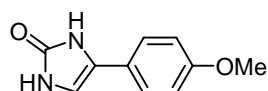


4-(4-Bromophenyl)-1H-imidazol-2(3H)-one. According to the general procedure using 1-bromo-4-iodobenzene and purified with RP-18 silica gel column

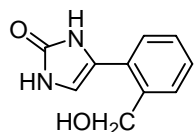
chromatography (0→80% *N,N*-dimethylformamide-water): $R_f = 0.36$ (10% methanol-methylene chloride); FTIR (neat, cm^{-1}) 1759, 1735, 1621, 1490, 1033, 1010, 826, 782, 739; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.55 (s, 1H), 10.13 (s, 1H), 7.51 (d, $J = 8.5$ Hz, 2H), 7.45 (d, $J = 8.5$ Hz, 2H), 6.79 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 155.0, 131.5, 129.3, 124.7, 120.9, 118.7, 106.8; MS(ES^+) calcd for $\text{C}_9\text{H}_8\text{BrN}_2\text{O}$ ($\text{M}+\text{H}$) $^+$ 238.98, found 238.90.



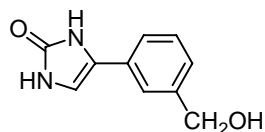
4-(3-Methoxyphenyl)-1H-imidazol-2(3H)-one. According to the general procedure using 3-iodoanisole and purified with RP-18 silica gel column chromatography (0→80% methanol-water): $R_f = 0.34$ (10% methanol-methylene chloride); FTIR (neat, cm^{-1}) 1718, 1618, 1577, 1221, 1046, 864, 781, 744; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.49 (s, 1H), 10.05 (s, 1H), 7.22 (t, $J = 7.6$ Hz, 1H), 7.09 (s, 2H), 6.91 (s, 1H), 6.73 (d, $J = 8.1$ Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 159.7, 155.0, 131.3, 129.7, 121.9, 115.3, 111.9, 108.4, 106.2, 55.1; MS(ES^+) calcd for $\text{C}_{10}\text{H}_{11}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 191.08, found 191.00.



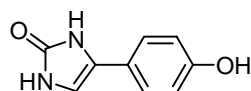
4-(4-Methoxyphenyl)-1H-imidazol-2(3H)-one. According to the general procedure using 4-iodoanisole and purified with RP-18 silica gel column chromatography (0→80% *N,N*-dimethylformamide -water): $R_f = 0.34$ (10% methanol-methylene chloride); FTIR (neat, cm^{-1}) 1700, 1607, 1516, 1252, 1182, 1032, 839, 744, 723; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.40 (s, 1H), 9.90 (s, 1H), 7.43 (d, $J = 8.7$ Hz, 2H), 6.89 (d, $J = 8.7$ Hz, 2H), 6.71 (s, 1H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 157.8, 155.0, 124.2, 122.8, 121.9, 114.2, 104.0, 55.1; MS(ES^+) calcd for $\text{C}_{10}\text{H}_{11}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 191.08, found 191.05.



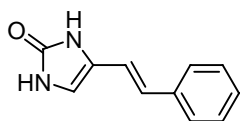
4-(2-(Hydroxymethyl)phenyl)-1H-imidazol-2(3H)-one. According to the general procedure using 2-iodobenzyl alcohol and purified with RP-18 silica gel column chromatography (0→80% methanol-water): $R_f = 0.17$ (10% methanol-methylene chloride); FTIR (neat, cm^{-1}) 1739, 1707, 1618, 1450, 1230, 1042, 810, 768, 735; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.26 (s, 1H), 10.08 (s, 1H), 7.48 (d, $J = 7.0$ Hz, 1H), 7.39 (d, $J = 7.3$ Hz, 1H), 7.29-7.22 (m, 2H), 6.62 (s, 1H), 5.35 (s, 1H), 4.50 (s, 2H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 154.8, 138.0, 128.7, 128.5, 127.2, 126.40, 126.35, 120.1, 108.5, 61.7; MS(ES^+) calcd for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{NaO}_2$ ($\text{M}+\text{Na}$) $^+$ 213.06, found 213.00.



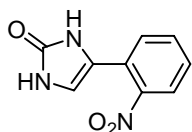
4-(3-(Hydroxymethyl)phenyl)-1H-imidazol-2(3H)-one. According to the general procedure using 3-iodobenzyl alcohol and purified with RP-18 silica gel column chromatography (0→80% methanol-water): $R_f = 0.09$ (10% methanol-methylene chloride); FTIR (neat, cm^{-1}) 1679, 1619, 1227, 1195, 1017, 791, 739; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.50 (s, 1H), 10.04 (s, 1H), 7.45 (s, 1H), 7.36 (d, $J = 7.7$ Hz, 1H), 7.27 (t, $J = 7.5$ Hz, 1H), 7.13 (d, $J = 7.5$ Hz, 1H), 6.85 (s, 1H), 5.19 (s, 1H), 4.46 (s, 2H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 155.0, 142.9, 129.7, 128.5, 124.5, 122.1, 121.2, 121.0, 105.6, 63.0; MS(ES^+) calcd for $\text{C}_{10}\text{H}_{11}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 191.08, found 191.05.



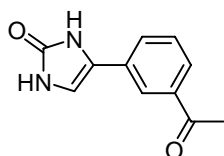
4-(4-Hydroxyphenyl)-1H-imidazol-2(3H)-one. According to the general procedure using 4-iodophenol and purified with RP-18 silica gel column chromatography (0→80% methanol-water): $R_f = 0.10$ (10% methanol-methylene chloride); FTIR (neat, cm^{-1}) 1679, 1602, 1514, 1250, 1179, 1100, 834, 762, 736; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.38 (s, 1H), 9.84 (s, 1H), 9.46 (s, 1H), 7.30 (d, $J = 8.6$ Hz, 2H), 6.71 (d, $J = 8.6$ Hz, 2H), 6.60 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 156.1, 155.1, 124.4, 122.4, 121.1, 115.5, 103.2; MS(ES^+) calcd for $\text{C}_9\text{H}_9\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 177.07, found 177.00.



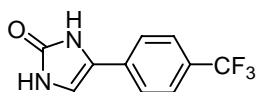
(E)-4-Styryl-1H-imidazol-2(3H)-one. According to the general procedure using β -bromostyrene and purified with RP-18 silica gel column chromatography (0 \rightarrow 80% *N,N*-dimethylformamide-water): R_f = 0.20 (10% methanol-methylene chloride); FTIR (neat, cm^{-1}) 1702, 1641, 1460, 1451, 1113, 949; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.35 (s, 1H), 10.01 (s, 1H), 7.35-7.14 (m, 4H), 6.71 (d, J = 6.3 Hz, 1H), 6.65 (d, J = 6.3 Hz, 1H), 6.47 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 155.5, 137.9, 129.4, 127.5, 126.3, 123.8, 122.6, 117.1, 110.9; MS(ES^+) calcd for $\text{C}_{11}\text{H}_{11}\text{N}_2\text{O}$ ($\text{M}+\text{H}$) $^+$ 187.09, found 187.00.



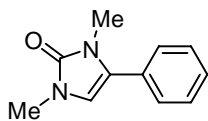
4-(2-Nitrophenyl)-1H-imidazol-2(3H)-one. According to the general procedure using 1-bromo-2-nitrobenzene and purified with RP-18 silica gel (RP-18) column chromatography (0 \rightarrow 80% *N,N*-dimethylformamide-water): R_f = 0.35 (10% methanol-methylene chloride); FTIR (neat, cm^{-1}) 1995, 1705, 1614, 1520, 1354, 1027, 765, 734; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.34 (s, 1H), 10.21 (s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.49-7.45 (m, 1H), 6.50 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 155.3, 147.6, 133.5, 130.5, 128.9, 124.9, 124.2, 117.8, 109.4; MS(ES^+) calcd for $\text{C}_9\text{H}_8\text{N}_3\text{O}_3$ ($\text{M}+\text{H}$) $^+$ 206.06, found 206.00.



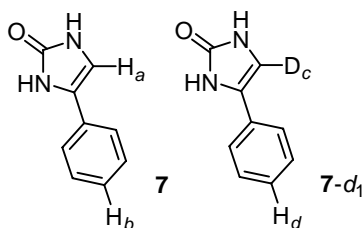
4-(3-Acetylphenyl)-1H-imidazol-2(3H)-one. According to the general procedure using 3-bromoacetophenone and purified with RP-18 silica gel column chromatography (0 \rightarrow 80% *N,N*-dimethylformamide-water): R_f = 0.25 (10% methanol-methylene chloride); FTIR (neat, cm^{-1}) 1995, 1690, 1620, 1462, 1427, 1253, 738; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.64 (s, 1H), 10.13 (s, 1H), 8.05 (s, 1H), 7.73-7.67 (m, 2H), 7.44 (t, d, J = 7.7 Hz, 1H), 7.04 (s, 1H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 203.4, 160.4, 142.7, 135.9, 134.4, 132.5, 130.8, 128.0, 126.5, 32.3; MS(ES^+) calcd for $\text{C}_{11}\text{H}_{11}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 203.08, found 203.00.



4-(4-(Trifluoromethyl)phenyl)-1H-imidazol-2(3H)-one. According to the general procedure using 4-bromobenzotrifluoride and purified with RP-18 silica gel column chromatography (0 \rightarrow 80% *N,N*-dimethylformamide-water): R_f = 0.20 (10% methanol-methylene chloride); FTIR (neat, cm^{-1}) 1758, 1707, 1618, 1450, 1333, 1132, 1063, 844, 747, 723; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.66 (s, 1H), 10.25 (s, 1H), 7.68-7.62 (m, 4H), 7.12 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 154.9, 133.9, 126.0 (q, J = 31.7 Hz), 125.6 (q, J = 3.4 Hz), 124.4 (q, J = 270.1 Hz), 120.7, 118.4, 108.6; MS(ES^+) calcd for $\text{C}_{10}\text{H}_8\text{F}_3\text{N}_2\text{O}$ ($\text{M}+\text{H}$) $^+$ 229.06, found 228.95.

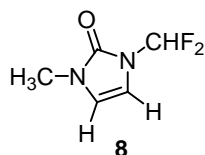


1,3-Dimethyl-4-phenyl-1H-imidazol-2(3H)-one (6). According to the general procedure using **5** and iodobenzene and purified with silica gel (Davisil 633) column chromatography: R_f = 0.11 (100% ethyl acetate); FTIR (neat, cm^{-1}) 2925, 1715, 1681, 1467, 1398, 1291, 1183, 1041, 1016, 855, 787, 766, 728; ^1H NMR (400 MHz, CDCl_3) δ 7.40-7.29 (m, 5H), 6.21 (s, 1H), 3.30 (s, 3H), 3.27 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 154.3, 129.8, 129.0, 128.2, 127.7, 125.0, 109.1, 30.6, 29.5; MS(ES^+) calcd for $\text{C}_{11}\text{H}_{13}\text{N}_2\text{O}$ ($\text{M}+\text{H}$) $^+$ 189.10, found 189.05.

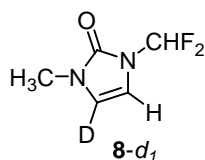


Kinetic isotopic effect experiment. According to the general procedure, **1** (5.0 mg, 0.06 mmol, 1.0 equiv), **1- d_2** (5.0 mg, 0.06 mmol, 1.0 equiv, containing 12% imidazol-2-one- d_1), iodobenzene (0.67 μL , 0.006 mmol, 0.1 equiv), palladium(II) acetate (1.3 mg, 0.006 mmol, 0.2 equiv), and sodium acetate trihydrate (50 mg, 0.36 mmol, 6.0 equiv) was stirred in

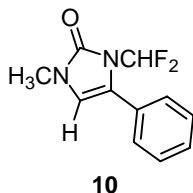
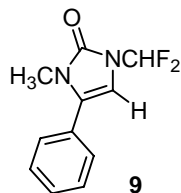
DMSO (0.5 mL) at 80 °C for 12 h. The ratio of **7** and **7-d₁** was determined to be 4:1 by comparing the integration of the vinyl C–H (H_a) and aryl C–H ($H_{b,d}$) in the ¹H NMR spectra. A 10 s recycle delay was used and the integration was calibrated with the pure sample of **7**. A kinetic isotope effect of $k_H/k_D \approx 4.55$ was derived from the following equations: $(H_b + H_d)/H_a = 1.25 : 1 \Rightarrow \mathbf{7} : \mathbf{7-d_1} = 4:1$; $((0.50 \times 2 k_H + 0.06 k_D)/(0.06 k_H + 0.44 \times 2 k_D)) = 4:1 \Rightarrow k_H/k_D = 4.55$.



1-Difluoromethyl-3-methyl-1H-imidazol-2-one (8). A modified procedure was used to form the imidazol-2-one preferentially under aerobic conditions.^{S10} A mixture of *N*-methyl-imidazole (328.5 mg, 4.0 mmol, 1.0 equiv) and sodium fluoride (16.8 mg, 0.4 mmol, 0.1 equiv) in anhydrous 1,2-dimethoxyethane (20 mL) was stirred at 85 °C for 20 minutes before trimethylsilylfluorosulfonyldifluoroacetate (4.00 g, 16.0 mmol, 4.0 equiv) was added dropwise. After stirring the reaction at 85 °C for 16 h, the solvent was removed and the residue was purified by silica gel flash chromatography to give **8** as yellow oil (202.0 mg, 34%); $R_f = 0.22$ (50% ethyl acetate-hexanes); FTIR (neat, cm^{-1}) 1718, 1560, 1443, 1396, 1131; ¹H NMR (400 MHz, CDCl_3) δ 7.04 (t, $J = 59.9$ Hz, 1H), 6.47 (d, $J = 3.2$ Hz, 1H), 6.26 (d, $J = 2.9$ Hz, 1H), 3.24 (s, 3H); ¹³C NMR (75 MHz, CDCl_3) δ 158.8, 114.9, 107.6 (t, $J = 244.0$ Hz), 104.5, 30.2; MS(ES^+) calcd for $\text{C}_5\text{H}_6\text{F}_2\text{N}_2\text{O}$ ($\text{M}+\text{H}$)⁺ 149.04, found 149.00.

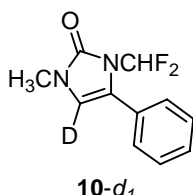
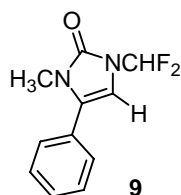


4-Deutero-1-difluoromethyl-3-methyl-1H-imidazol-2(3H)-one (8-d₁). To a solution of 2,5-diiodo-1-methylimidazole^{S11} (1.00 g, 3.0 mmol, 1.0 equiv) in tetrahydrofuran-ether (1:1, 10 mL) at –78 °C was added *tert*-butyllithium (1.7 M in pentane, 7.06 mL, 12.0 mmol, 4.0 equiv) dropwise along the flask wall. After stirring for 5 min, deuterium oxide (1.0 mL) was added. The aqueous phase was removed and the organic phase was concentrated. The residue was re-dissolved in methylene chloride, dried with anhydrous sodium sulfate, filtrated and concentrated to give the 2,5-dideutero-1-methylimidazole as colorless oil, which was converted to **8-d₁** as described above (93% D at C-4 and 9% D at C-5 by NMR).

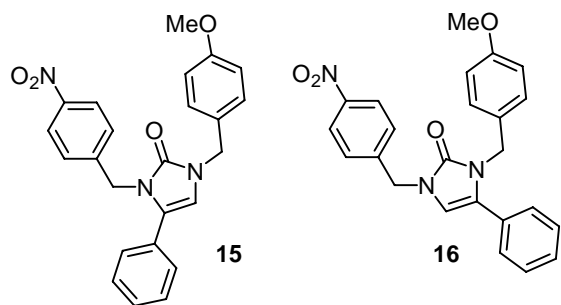


1-Difluoromethyl-3-methyl-4-phenyl-1H-imidazol-2(3H)-one (9) and 1-difluoromethyl-3-methyl-5-phenyl-1H-imidazol-2(3H)-one (10). According to the general procedure, imidazolone **8** was reacted with iodobenzene at 23 °C for 48 h to give **9** and **10** (6:1) as determined by NMR with 10 s recycle delay. Imidazolone **9** and **10** can be separated by PTLC (250 μm Silica Gel 60 F₂₅₄). **9**: $R_f = 0.44$

(50% ethyl acetate-hexanes); FT-IR (neat, cm^{-1}) 1726, 1710, 1459, 1396, 1238, 1180, 1172, 1112, 1022, 921, 893, 770; ¹H NMR (400 MHz, CDCl_3) δ 7.49-7.35 (m, 5H), 7.15 (t, $J = 60.0$ Hz), 6.49 (s, 1H), 3.25 (s, 3H); ¹³C NMR (100 MHz, CDCl_3) δ 152.3, 129.3, 129.2, 128.5, 128.4, 128.1, 107.7 (t, $J = 244.1$ Hz), 101.6, 29.0; MS(ES^+) calcd for $\text{C}_{11}\text{H}_{10}\text{F}_2\text{N}_2\text{O}$ ($\text{M}+\text{H}$)⁺ 225.08, found 224.95. **10**: $R_f = 0.26$ (50% ethyl acetate-hexanes); FTIR (neat, cm^{-1}) 1709, 1437, 1453, 1401, 1355, 1262, 1121, 1047, 1006, 891, 804, 762; ¹H NMR (400 MHz, CDCl_3) δ 7.48-7.37 (m, 5H), 7.20 (t, $J = 59.2$ Hz, 1H), 6.24 (s, 1H), 3.31 (s, 3H); ¹³C NMR (100 MHz, CDCl_3) δ 152.6, 128.8, 128.7, 128.6, 122.1, 112.5, 109.4 (t, $J = 245.8$ Hz), 30.4; MS(ES^+) calcd for $\text{C}_{11}\text{H}_{10}\text{F}_2\text{N}_2\text{O}$ ($\text{M}+\text{H}$)⁺ 225.08, found 224.95.



1-Difluoromethyl-3-methyl-4-phenyl-1H-imidazol-2(3H)-one (9) and 4-Deutero-1-difluoromethyl-3-methyl-5-phenyl-1H-imidazol-2(3H)-one (10-d₁). According to the procedure described above, **8-d₁** and iodobenzene were reacted at 28 °C for 33 h to give **9** (10% D) and **10-d₁** (87% D) after purified by PTLC (250 μm Silica Gel 60 F₂₅₄).

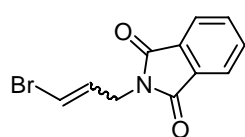
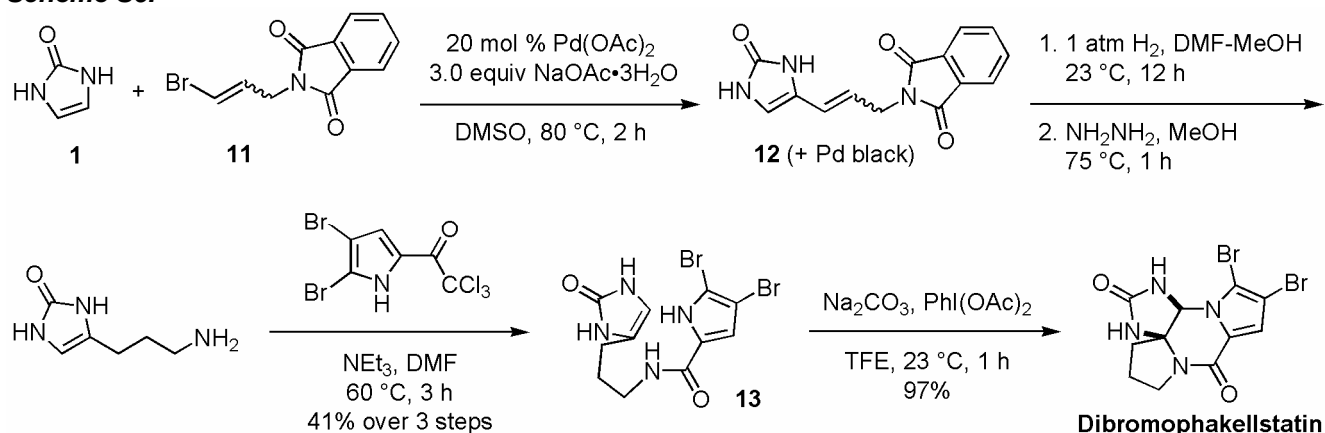


1-(4-Methoxybenzyl)-3-(4-nitrobenzyl)-4-phenyl-1H-imidazol-2(3H)-one (15) and 1-(4-methoxybenzyl)-3-(4-nitrobenzyl)-5-phenyl-1H-imidazol-2(3H)-one (16).

According to the general procedure using imidazolone **13** and iodobenzene, **14** and **15** were obtained as yellow oil from PTLC (250 μm Silica Gel 60 F₂₅₄) in 1.8:1 ratio (ca. 20% conversion by ¹H NMR). **14**: R_f = 0.35 (50% ethyl acetate-hexanes); FT-IR (neat, cm^{-1}) 1682, 1608, 1514, 1453, 1409, 1344, 1247, 1176, 1110, 1032, 819,

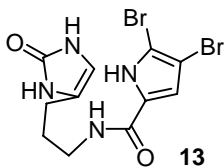
764, 734; ¹H NMR (400 MHz, CDCl_3) δ 8.11 (d, J = 8.8 Hz, 2H), 7.30-7.25 (m, 7H), 7.12-7.09 (m, 2H), 6.89 (d, J = 8.8 Hz, 2H); ¹³C NMR (75 MHz, CDCl_3) δ 159.6, 147.5, 145.4, 129.8, 129.3, 129.1, 129.0, 128.8, 128.7, 128.6, 128.3, 128.1, 127.8, 124.1, 114.5, 108.7, 55.6, 47.2, 45.2; MS(ES^+) calcd for $\text{C}_{24}\text{H}_{22}\text{N}_3\text{O}_4$ ($\text{M}+\text{H}$)⁺ 416.16, found 416.10. **15**: R_f = 0.33 (50% ethyl acetate-hexanes); FTIR (neat, cm^{-1}) 1682, 1609, 1514, 1453, 1410, 1284, 1176, 1108, 1032, 846, 801, 767, 733; ¹H NMR (400 MHz, CDCl_3) δ 8.21 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.8 Hz, 2H), 7.34-7.32 (m, 3H), 7.21-7.19 (m, 2H), 7.00 (d, J = 8.8 Hz, 2H), 6.76 (d, J = 8.6 Hz, 2H), 6.17 (s, 1H), 4.98 (s, 2H), 4.87 (s, 2H), 3.76 (s, 3H); ¹³C NMR (75 MHz, CDCl_3) δ 159.1, 154.2, 147.8, 144.6, 129.9, 129.4, 128.9, 128.8, 128.7, 128.6, 126.0, 124.3, 114.1, 107.9, 55.5, 46.9, 45.3; MS(ES^+) calcd for $\text{C}_{24}\text{H}_{22}\text{N}_3\text{O}_4$ ($\text{M}+\text{H}$)⁺ 416.16, found 416.10.

Scheme S6.



(*E,Z*)-2-(3-bromoallyl)isoindoline-1,3-dione (11).^{S8} 1,3-Dibromo-1-propene (5.149 g, 25.76 mmol, 1.0 equiv) was added dropwise to a suspension of phthalimide potassium salt (4.77 g, 25.76 mmol, 1.0 equiv) and tetrabutylammonium bromide (415.2 mg, 1.29 mmol, 0.05 equiv) in anhydrous

N,N-dimethylformamide (70 mL) at 23 °C.^{S9} After stirring for 16 h, the solvent was removed and the residue was dissolved in methylene chloride (300 mL), washed with water (200 mL \times 3), dried with anhydrous sodium sulfate, concentrated and recrystallized from ethyl acetate-hexanes to give **11** as white crystalline solid (6.256 g, 91% *trans:cis* = 2:3); R_f = 0.29 (20% ethyl acetate-hexane); FTIR (neat, cm^{-1}) 1771, 1712, 1467, 1426, 1391, 1350, 1290, 1188, 1110, 946; ¹H NMR (400 MHz, CDCl_3) δ 7.88-7.86 (m, 2H), 7.74-7.72 (m, 2H), 6.47 (dt, J = 13.7, 1.0 Hz, 1H *trans*), 6.39 (dt, J = 7.2, 1.7 Hz, 1H *cis*), 6.29 (dt, J = 13.6, 6.8 Hz, 1H *trans*), 6.24 (dt, J = 7.2, 6.2 Hz, 1H *cis*), 4.47 (dd, J = 6.1, 1.7 Hz, 2H *cis*), 4.25 (dd, J = 6.8, 1.1 Hz, 2H *trans*); ¹³C NMR (75 MHz, CDCl_3) δ 167.9, 167.7, 134.3 (2), 132.2, 132.1, 130.9, 129.1, 123.6 (2), 111.0 (2), 39.1, 37.6; MS(ES^+) calcd for $\text{C}_{11}\text{H}_8\text{BrNO}_2$ ($\text{M}+\text{H}$)⁺ 265.97, found 265.80.



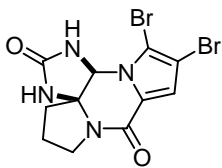
4,5-Dibromo-*N*-(3-(2,3-dihydro-2-oxo-1*H*-imidazol-4-yl)propyl)-1*H*-pyrrole-2-carboxamide (13). Imidazol-2-one (**1**) (840.8 mg, 10 mmol, 10 equiv), vinyl bromide **11** (266.1 mg, 1.0 mmol, 1.0 equiv) and sodium acetate trihydrate (480.2 mg, 3.0 mmol, 3 equiv) were vacuum-dried and filled with argon for 3 times before degassed dimethyl sulfoxide (9 mL) was introduced. After stirring at 80 °C in dark

for 10 min, a solution of palladium acetate (44.9 mg, 0.2 mmol, 0.2 equiv) in degassed dimethyl sulfoxide (1.0 mL) was quickly added. The reaction was stirred at 80 °C in dark for 2 h and quenched by pouring into water (100 mL). The mixture was filtered through a short pad of RP-C18 silica gel and washed with 10% methanol-H₂O (100 mL) followed by *N,N*-dimethylformamide (100–120 mL). The *N,N*-dimethylformamide wash portion was collected and used directly for the next step.

The *N,N*-dimethylformamide portion from the above step was dilute with methanol (120 mL) and was hydrogenated under hydrogen (1 atm) at room temperature for 12 h. The solution was filtered and the filtrate was concentrated to dryness. The solid was washed with methylene chloride (3 mL×3), and concentrated to give 2-(3-(2,3-dihydro-2-oxo-1*H*-imidazol-5-yl)propyl)isoindoline-1,3-dione: *R_f* = 0.43 (10% methanol-methylene chloride); FTIR (neat, cm⁻¹) 3401, 3307, 1996, 1766, 1710, 1631, 1552, 1402,; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.70 (s, 1H), 9.38 (s, 1H), 7.88-7.82 (m, 4H), 5.95 (s, 1H), 3.57 (t, *J* = 6.8 Hz), 2.24 (t, *J* = 7.5 Hz), 1.82-1.74 (m, 2H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 168.0, 154.9, 134.4, 131.6, 123.0, 121.0, 103.9, 37.0, 26.5, 22.7; MS(ES⁺) calcd for C₁₄H₁₃N₃O₃ (M+H)⁺ 272.10, found 272.00.

The 2-(3-(2,3-dihydro-2-oxo-1*H*-imidazol-5-yl)propyl)isoindoline-1,3-dione obtained above was suspended in methanol (200 mL) and heated at 75 °C for 30 min. The remaining palladium was filtered off to afford a clear orange solution. Anhydrous hydrazine (1.28 mL, 40 mmol, → 0.2 M in methanol) was then added dropwise to this solution at 75 °C. After heating at 75 °C for 1 h, the yellow solution was concentrated, azeotroped with ethanol (20 mL×2) and dried under vacuum for 2 h. The resulting solid was then dissolved in deionized water (25 mL), and stirred with activated Dianion WA30 resin (10 mL) until the aqueous phase became clear and colorless. The mixture was filtered and the resin was washed with deionized water (5 mL×2). The aqueous solution was concentrated, azeotroped with toluene (5 mL×3) and dried under vacuum for 6 h to give 5-(3-aminopropyl)-1*H*-imidazol-2(3*H*)-one as a yellow oil, which was used directly for the next step.

The 5-(3-aminopropyl)-1*H*-imidazol-2(3*H*)-one obtained above (64.0 mg, 0.453 mmol, 1.0 equiv), 4,5-dibromo-2-(trichloroacetyl)pyrrole^{S12} (247.8 mg, 0.669 mmol, 1.5 equiv) was dissolved in anhydrous *N,N*-dimethylformamide (8 mL). Triethylamine (0.19 mL, 1.34 mmol, 3.0 equiv) was added and the solution was stirred at 60 °C under argon in dark for 3 h. The solvent was then removed and the residue was triturated with ether (3 mL×4). The solid was washed with HCl (0.1 N, 10 mL), water and dried under vacuum in the presence of phosphorus pentoxide to give **13** as off-white solid (159.8 mg, 41% over 4 steps): *R_f* = 0.15 (10% methanol-methylene chloride); FTIR (neat, cm⁻¹) 3401, 3307, 1996, 1681, 1643, 1531, 1416; ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.67 (s, 1H), 9.75 (s, 1H), 9.42 (s, 1H), 8.12 (t, *J* = 5.6 Hz, 1H), 6.91 (d, *J* = 2.7 Hz, 1H), 5.97 (s, 1H), 3.20 (dt, *J* = 6.8, 6.4 Hz, 2H), 2.24 (t, *J* = 7.3 Hz, 2H), 1.67 (tt, *J* = 7.3, 6.8 Hz, 2H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 158.9, 154.9, 128.2, 121.4, 112.4, 104.4, 103.7, 97.8, 38.0, 27.7, 22.6; MS(ES⁺) calcd for C₁₁H₁₂Br₂N₄O₂ (M+H)⁺ 390.93, found 391.20.



(±)-Dibromophakellstatin. Imidazolinone **13** (50 mg, 0.128 mmol, 1.0 equiv) was suspended in 2,2,2-trifluoroethanol (5 mL) (sonicate the mixture to give fine suspension if necessary) and anhydrous sodium carbonate (136.4 mg, 1.28 mmol, 10 equiv), iodobenzene diacetate (41.1 mg, 0.128 mmol, 1.0 equiv) was added at 23 °C. The reaction mixture became clear after several min. After stirring for 1 h, sodium carbonate was filtered off and the filtrate was concentrated to nearly dryness. With stirring, HCl (0.1 N, 5 mL) was added dropwise to the resulting residue. After stirring for 10 min, the

precipitate was collected by filtration, washed with water, and dried under vacuum in the presence of phosphorus pentoxide to give dibromophakellstatin as off-white solid (48.3 mg, 97%): $R_f = 0.50$ (10% methanol-methylene chloride); FTIR (neat, cm^{-1}) 3401, 3306, 1996, 1722, 1641, 1452; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.27 (s, 1H), 7.98 (s, 1H), 6.91 (s, 1H), 5.99 (s, 1H), 3.58-3.53 (m, 1H), 3.46-3.39 (m, 1H), 2.32-2.26 (m, 1H), 2.18-2.04 (m, 2H), 2.00-1.94 (m, 1H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 157.9, 154.1, 125.4, 113.8, 105.6, 101.2, 79.0, 68.6, 44.2, 40.4, 18.9; MS(ES^+) calcd for $\text{C}_{11}\text{H}_{10}\text{Br}_2\text{N}_4\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 388.92, found 388.70.

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- ^{S1} Jaguar, version 6.5, Schrödinger, LLC, New York, NY, 2006.
- ^{S2} Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299.
- ^{S3} Keith, J. A.; Oxgaard, J.; Goddard, III, W. A. *J. Am. Chem. Soc.* **2006**, *128*, 3132–3133.
- ^{S4} Tannor, D. J.; Marten, B.; Murphy, R.; Friesner, R. A.; Sitkoff, D.; Nicholls, A.; Ringnalda, M.; Goddard, W. A., III; Honig, B. *J. Am. Chem. Soc.* **1994**, *116*, 11875–11872.
- ^{S5} Marten, B.; Kim, K.; Cortis, C.; Friesner, R. A.; Murphy, R. B.; Ringnalda, M. N.; Sitkoff, D.; Honig, B. *J. Phys. Chem.* **1996**, *100*, 11775–11788.
- ^{S6} Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
- ^{S7} Pratt, R. F., Kraus, K. K. *Tetrahedron Lett.* **1981**, *22*, 2431–2434.
- ^{S8} Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031–6034.
- ^{S9} Köhling, P.; Schmidt, A. M.; Eilbracht, P. *Org. Lett.* **2003**, *5*, 3213–3216.
- ^{S10} Xu, W.; Abboud, K. A.; Ghiviriga, I.; Dolbier, Jr., W. R.; Rapp, M.; Wnuk, S. *Org. Lett.* **2006**, *8*, 5549–5551.
- ^{S11} Holden, K. G.; Mattson, M. N.; Cha, K. H.; Rapoport, H. *J. Org. Chem.* **2002**, *67*, 5913–5918.
- ^{S12} Lington, R. G.; Williams, D. E.; Tahir, A.; van Soest, R.; Andersen, R. J. *Org. Lett.* **2003**, *5*, 2735–2738.