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Merging Brønsted Acid and Hydrogen-Bonding Catalysis: Metal-Free Dearomatization of Phenols *via ipso*-Friedel-Crafts Alkylation to Produce Functionalized Spirolactams

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Abstract. Intramolecular dearomative cyclization of phenols with α-diazoamide units for synthesizing functionalized spirolactams was developed by merging Brønsted acid and hydrogen-bonding catalysis as an advantageous alternative to transition metal catalysis. This metal carbenoid-free strategy enables high chemoselectivity by suppressing potentially competing C–H insertion reactions and a Büchner reaction. Preliminary mechanistic studies were performed to elucidate the positive effect of the combined use of the catalysts, and extension to an asymmetric reaction was achieved.

Keywords: Brønsted acid; diazo compounds; lactams; carbenoids; dearomatization; spirocycles

Introduction

Spirocyclic molecular frameworks are pivotal scaffolds for synthesizing an extensive range of biologically important compounds. Among the cyclic motifs, 2-azaspiro[4.5]decane derivatives are a highly important class of compounds due to their ubiquity in bioactive natural[1] and unnatural products[2] (Figure 1). The development of an efficient and straightforward methodology for synthesizing azaspirocyclic core structures with diverse functionalities, therefore, continues to be an area of great interest in the synthetic community.[3]

As part of our ongoing work aimed at developing metal carbenoid reactions,[4] we recently reported a highly chemoselective spirocyclization of phenols with α-diazoamides using a silver catalyst to produce azaspirocyclic molecules.[5] Mechanistic analysis revealed that high electrophilicity of the silver carbenoid species was key to the success. Among the various transformations using diazocompounds,[6] Brønsted acid catalysis is a well-established process[7] for the generation of diazonium cations as electrophiles. For example, O–H insertion reactions,[8] esterifications of carboxylic acids,[9] and nucleophilic substitution reactions[10] are representative transformations for the effective use of diazonium cations generated from the diazo functionality and Brønsted acid catalyst.

Catalytic dearomatization of phenol derivatives *via* a *ipso*-Friedel-Crafts-type reaction process has proven to be one of the most straightforward approaches to access the functionalized spirocyclohexadienones as versatile synthetic scaffolds.[11] Intramolecular phenol dearomatization using transition-metal-catalyzed alkylation or arylation reactions has been reported, with leading examples by us,[11a] You,[11b] Buchwald,[11c] and Luan.[11d] Given this background, we hypothesized that spirocyclization of phenols with diazoamides would be realized *via* protonation to generate diazonium cations under Brønsted acid catalysis, followed by *ipso*-Friedel-Crafts-type nucleophilic alkylation. This transition metal and carbenoid-free pathway would contribute to the chemoselectivity to suppress C–H insertion reactions and a Büchner reaction, which are competing processes in reactions using metal carbenoid species.[5,12] Herein we describe the development of an alternative method for spirocyclization using organocatalysis[13] *via* a dearomative *ipso*-Friedel-Crafts (DIFC) reaction to produce functionalized spirolactams.

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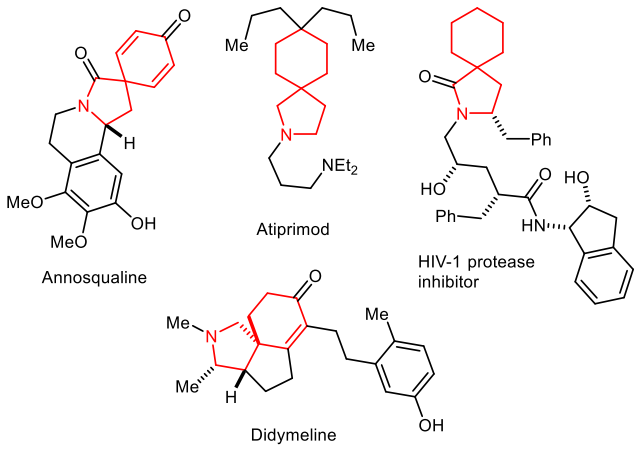
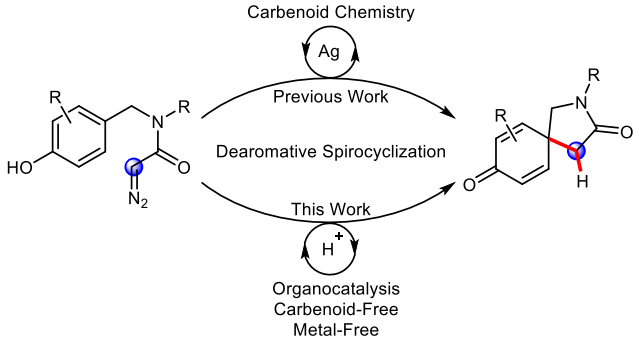


Figure 1 Biologically active molecules possessing a 2-azaspiro[4.5]decane core



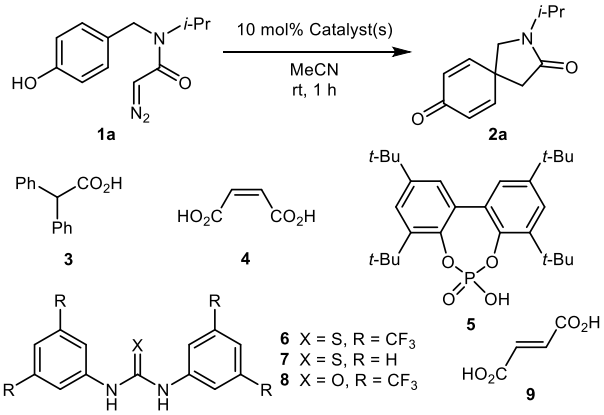
Scheme 1 Comparison of transition metal catalysis and organocatalysis in the DIFC reaction.

Results and Discussion

The reaction conditions were optimized using phenol derivatives with a diazoacetamide unit (**1a**) as a model substrate for development of the dearomatization process (Table 1). At first, the reaction using 10 mol% 2,2-diphenylacetic acid (**3**) as a manageable solid catalyst was tested in acetonitrile solvent at room temperature for 1 h, but no reaction occurred (entry 1). We continued to examine Brønsted acid catalysts, and revealed that the desired DIFC reaction could be accelerated, depending on the acidity of the catalysts (entries 1-5). All reactions stopped before full conversion, however, even when extremely strong acids such as Tf_2NH or TfOH were used. Schreiner's thiourea (**6**) works as an effective co-catalyst in some reaction systems.[14,15] Thus, we investigated the effect of **6** in the presence of Brønsted acid catalysts. Dramatic positive effects were observed when **6** was used with relatively weak Brønsted acid catalysts (entries 6-7). The use of thiourea **6** only did not promote the spirocyclization reaction at all[16] and fumaric acid (**9**) or (thio)urea **7**, **8** were also ineffectual in this reaction (entries 9-12). Although the reaction in entries 6 and 7 indicated similar results, we decided to combine **6** and **4** as mild Brønsted acid was the best cooperative catalyst system[17] for dearomative spirocyclization from the viewpoint of functional group tolerance, economy, and availability.[18]

With the optimized conditions in hand, we next investigated the scope and limitations of the developed DIFC reaction (Scheme 2). In addition to the model substrate **1a**, other substrates bearing a methyl group at the *ortho*- and *meta*-position of phenols **1b-d** were transformed into the corresponding dearomatized compounds **2b-d** in excellent yields (82%-91%). Methoxy phenol could also be applied, in which case azaspirocyclohexadienones containing an enol ether unit were produced in good yield (**2e-g**, 68%-99%). Electron-deficient phenol, however, was less reactive in this spirocyclization reaction, indicating that phenol dearomatization would proceed *via* the Friedel-Crafts-type reaction (**2h**). α-Diazoacetamide having removable substituent, such as PMB on the amide nitrogen, were applicable (**2i**). In addition, the δ-lactam **2j** possessing an azaspiro[5.5]undecane system was constructed with 30 mol % of **4** and **6** in 60% yield.

Table 1 Optimization of the reaction conditions



entry	catalyst(s)	**2a** [yield]	recovered **1a**
1	**3**	0%	97%
2	**4**	32%	60%
3	**5**	33%	59%
4	Tf_2NH	70%	8%
5	TfOH	73%	10%
6	**4** + **6**	85%	trace
7	**5** + **6**	85%	2%
8	TfOH + **6**	78%	5%
9	**6**	0%	100%
10	**9** + **6**	2%	96%
11	**4** + **7**	41%	50%
12	**4** + **8**	78%	8%

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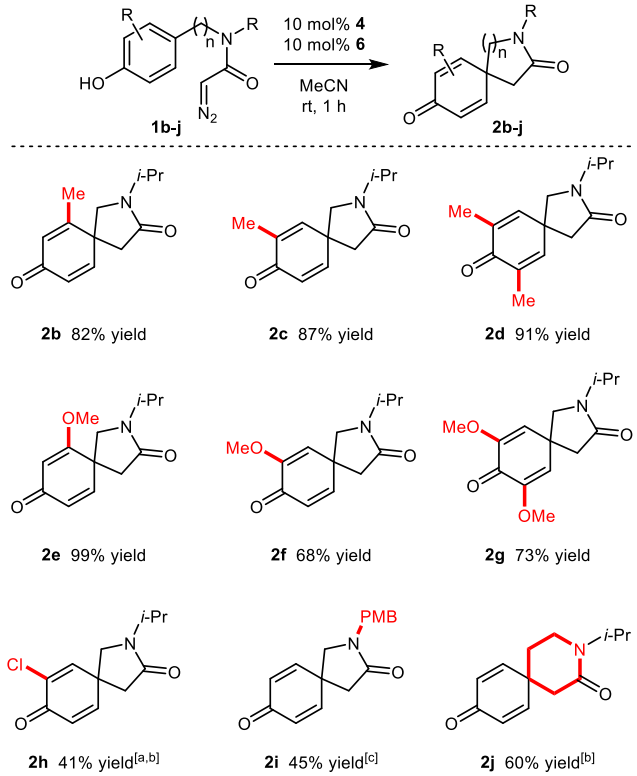
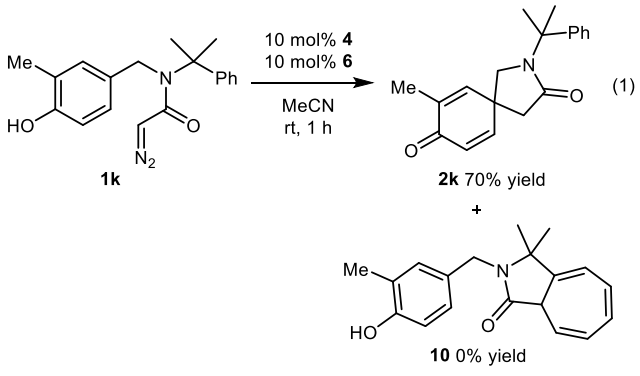
Table 2 Substrate scope

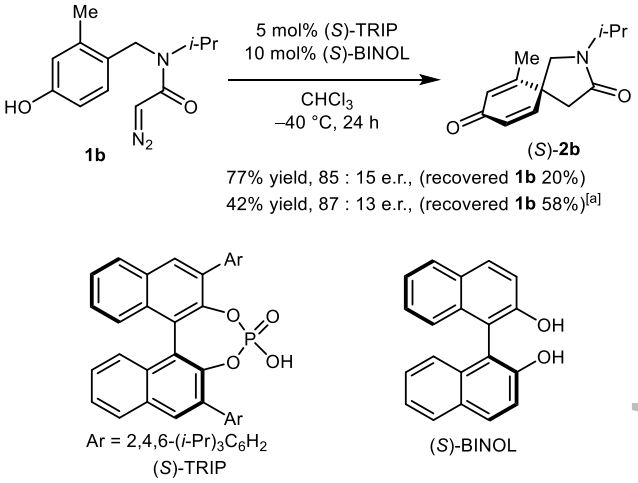


[a] The reaction was performed for 24 h. [b] 30 mol% of **4** and **6** was used. [c] The reaction was performed for 3 h in the presence of 20 mol% of **4** and **6**. PMB is *p*-methoxybenzyl.

The reaction of **1k** possessing a dimethylphenylmethyl group on the amide in the presence of a silver catalyst gives cycloheptatriene **10** formed through a Büchner reaction, which is specific to the carbene reaction (eq 1).[5] To demonstrate the utility of the developed catalyst system, we evaluated the reaction of **1k** using **4** and **6**, which afforded **2k** without the production of **10**.

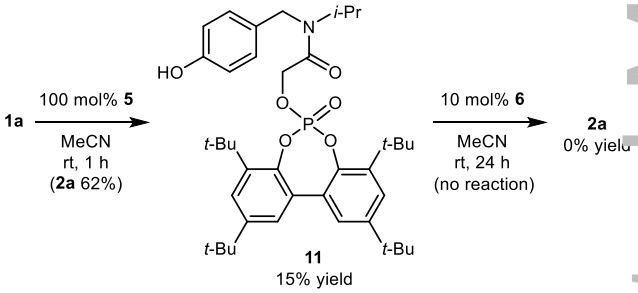


To apply the reaction in asymmetric synthesis, we investigated a chiral Brønsted acid[19] and hydrogen-bonding donor catalyst.[20] The combination of catalysts containing (*S*)-TRIP and (*S*)-BINOL[15b] produced good yield and enantioselectivity, furnishing (*S*)-**2b** with an all-carbon quaternary stereogenic center and enantiomeric ratio of 85:15.



Scheme 2 Enantioselective spirocyclizations. [a] Without (*S*)-BINOL.

The reaction of Scheme 2 ceased before reaching full conversion. To gain mechanistic insight, we scrutinized side products of the DIFC reaction using Brønsted acid and isolated O–H insertion product **11** generated from substrate **1a** and **5**.[21,22] Treatment of **10** with **6** did not afford **2a**, indicating that **10** is not an intermediate for the dearomatization process and therefore a dead-end product.



Scheme 3 Isolation of O–H insertion product

Next, NMR experiments were performed to shed light on the reaction mechanism and the positive effect of merging the Brønsted acid and hydrogen-bonding catalysis (table 3). The chemical shift of vinyl protons of maleic acid **4** had the same value (δ 6.35) as that of **4** in the presence of thiourea **6** in CD_3CN solvent (entries 1,2). The value of a conjugate base of maleic acid, generated from **4** and Hünig's base, with **6** indicated a higher chemical shift than that without **6** (δ 6.12 to δ 6.20, entries 3,4), suggesting an interaction between the conjugate base of **4** and **6** in acetonitrile.

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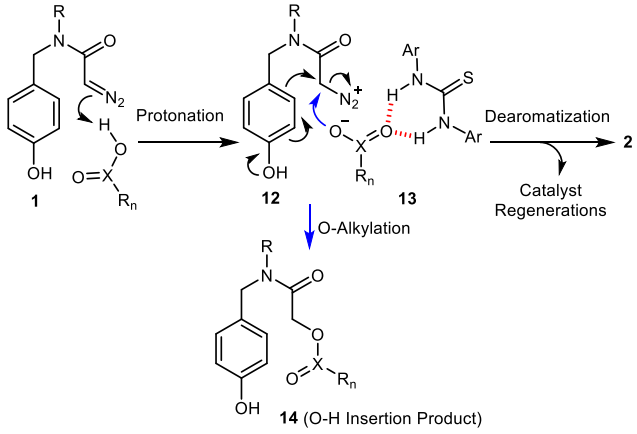
Table 3 ^{1}H NMR analysis of **4** in CD_3CN

entry	sample(s)	vinyl proton of **4** (ppm)
1	**4**	6.35
2	**4** + **6**	6.35
3	**4** + *i*-Pr_2NEt	6.12
4	**4** + **6** +*i*-Pr_2NEt	6.20

Based on the above-described mechanistic information and the results shown in table 1, a possible mechanism is depicted in Scheme 4. At first, diazoamide **1** would be protonated by a Brønsted acid, generating an ion pair of diazonium cation **12** and a conjugate base of the acid catalyst. A nucleophilic substitution reaction by the counteranion could give O–H insertion product **14** as the dead-end product. The interaction of conjugate base and thiourea would work to suppress the undesired pathway and promote the *ipso*-Friedel-Craft-type dearomatization by lowering the electron density of the counteranion to generate a loose ion pair.



Scheme 4 Possible reaction pathways

Conclusions

We developed a dearomative spirocyclization of phenols possessing diazo functionality by merging Brønsted acid and hydrogen-bonding catalysis. This metal- and carbenoid-free methodology will contribute to achieve high chemoselectivity by suppressing C–H insertion reactions and Büchner reactions. The DIFC cyclization was expanded to an asymmetric reaction using chiral catalysts. Mechanistic studies indicated an interaction between the hydrogen-bonding catalyst and conjugate base of the Brønsted acid. Total synthesis of bioactive molecules using the developed dearomative spirocyclization is underway.

Experimental Section

General Methods

IR spectra were recorded on a JASCO FT/IR 230 Fourier transform infrared spectrophotometer, equipped with ATR (Smiths Detection, DuraSample IR II). NMR spectra were recorded on a JEOL ecs 400 spectrometer, operating at 400 MHz for ^{1}H NMR, and 100 MHz for ^{13}C NMR. Chemical shifts in $CDCl_3$ were reported downfield from TMS (=0 ppm) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to the solvent signal [$CHCl_3$ (77.0 ppm)] as an internal reference. The enantiomeric excess (ee) was determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, PU-980; detector, UV-970; mobile phase, n-hexane/i-PrOH. Melting points were measured with a SIBATA NEL-270 melting point apparatus. Column chromatography was performed with silica gel 60 N (spherical, neutral 63-210 mesh). ESI-TOF mass spectra were measured on JEOL AccuTOF LC-plus JMS-T100LP. Reactions were carried out in dry solvent under argon atmosphere. Other reagents were purified by the usual methods.

General Procedure for the Spirocyclization

To a stirred solution of substrate **1c** (61.8 mg, 0.25 mmol) and Schreiner's thiourea **6** (12.5 mg, 0.025 mmol) in MeCN (2.5 mL) was added maleic acid **4** (2.9 mg, 0.025 mmol), and the reaction mixture was stirred for 1 h at room temperature. The reaction was quenched with triethylamine (0.1 mL) and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel to afford spirolactam **2c** (47.6 mg, 87% yield), (hexane / ethyl acetate as an eluent).

^{1}H and ^{13}C NMR, IR, and MS of products **2b**, **2c**, **2e**, **2f, 2h,** and **2k** were identical to those reported.[5] For charts of ^{1}H- and ^{13}C-NMR spectra, see the Supporting Information.

2-Isopropyl-2-azaspiro[4.5]deca-6,9-diene-3,8-dione (2a): 17.4 mg (85% yield); white powder; 103-104 °C; R_f = 0.25 (EtOAc only); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, *J* = 6.8 Hz, 6H), 2.59 (s, 2H), 3.39 (s, 2H), 4.47 (sep, *J* = 7.0 Hz, 1H), 6.35 (d, *J* = 10.0 Hz, 2H), 6.93 (d, *J* = 10.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 41.2, 41.5, 43.0, 49.6, 129.4, 149.8, 170.6, 184.9; IR (ATR) ν 2973, 2341, 1660, 1627, 1486, 1429, 1369, 1277, 1244, 1195, 1092, 862, 762, 711, 636 cm^{-1}; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{12}H_{15}NNaO_2^+$ *m/z* 228.0995, found 228.0997.

2-Isopropyl-7,9-dimethyl-2-azaspiro[4.5]deca-6,9-diene-3,8-dione (2d): 21.4 mg (94% yield); pale yellow powder; 99-100 °C; R_f = 0.31 (hexane/EtOAc, 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, *J* = 6.8 Hz, 6H), 1.92 (s, 6H), 2.52 (s, 2H), 3.34 (s, 2H), 4.45 (sep, *J* = 6.8 Hz, 1H), 6.68 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 19.7, 40.7, 41.8, 42.8, 49.8, 135.3, 145.2, 171.2, 186.3; IR (ATR) ν 2972, 2360, 1684, 1633, 1422, 1371, 1272, 1242, 1210, 1127, 1062, 909 cm^{-1}; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{14}H_{19}NNaO_2^+$ *m/z* 256.1308, found 256.1306.

2-Isopropyl-2-azaspiro[4.5]deca-6,9-diene-3,8-dione (2g): 19.4 mg (73% yield); white powder; 175-176 °C; R_f = 0.2 (hexane/EtOAc, 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, *J* = 6.8 Hz, 6H), 2.62 (s, 2H), 3.42 (s, 2H), 3.69 (s, 6H), 4.49 (sep, *J* = 6.8 Hz, 1H), 5.87 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 40.0, 42.7, 43.7, 51.8, 55.3, 117.4, 151.0, 171.2, 175.7; IR (ATR) ν 2971, 2358, 2346, 1669, 1652, 1620, 1424, 1366, 1282, 1238, 1197, 1108, 871 cm^{-1}; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{14}H_{19}NNaO_4^+$ *m/z* 288.1206, found 288.1217.

2-(4-Methoxybenzyl)-2-azaspiro[4.5]deca-6,9-diene-3,8-dione (2i): 5.5 mg (45% yield); yellow oil; R_f = 0.28 (EtOAc only); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61 (s, 2H), 3.28 (s, 2H), 3.80 (s, 3H), 4.45 (s, 2H), 6.27 (d, *J* = 10.4 Hz, 2H), 6.84 (d, *J* = 10.4 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.1, 41.3, 46.3, 53.8, 55.3, 114.5, 127.7, 129.4, 129.7, 149.7, 159.6, 171.2, 184.7; IR (ATR) ν 2932, 2357, 1664, 1628, 1513, 1487, 1419, 1247, 1177, 1091, 1032, 862 cm^{-1}; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{17}H_{17}NNaO_3^+$ *m/z* 306.1101, found 306.1106.

3-Isopropyl-3-azaspiro[5.5]undeca-7,10-diene-2,9-dione (2j): 6.4 mg (60% yield); pale yellow powder; 88-90 °C; R_f = 0.15 (hexane/EtOAc, 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, *J* = 6.8 Hz, 6H), 1.96 (t, *J* = 6.0 Hz, 2H), 2.45 (s, 2H), 3.40 (t, *J* = 6.0 Hz, 2H), 4.98 (sep, *J* = 6.8 Hz, 1H), 6.33 (d, *J* = 10.0 Hz, 2H), 6.85 (d, *J* = 10.0 Hz, 2H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 32.4, 37.4, 39.1, 40.5, 44.2, 129.5, 150.9, 165.7, 185.1 ; IR (ATR) ν 2930, 2359,

1663, 1627, 1495, 1453, 1368, 1323, 1216, 1175, 1096, 922, 858 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{13}H_{17}NNaO_2^+$ *m/z* 242.1151, found 242.1143.

Isolation of O–H insertion product 11

To a stirred solution of substrate **1a** (0.05 mmol, 11.7 mg) in MeCN (0.5 mL, 0.1 M) was added phosphoric acid **5** (23.6 mg, 1 eq), and the reaction mixture was stirred for 1 h at room temperature. The reaction was quenched with triethylamine (0.05 mL) and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (hexane : ethyl acetate = 2:1 to 0:1, then ethyl acetate : methanol = 30 : 1 as eluent) to afford **11** (5.2 mg, 15%) and **2a** (6.4 mg, 62%).

***N*-(4-Hydroxybenzyl)-*N*-isopropyl-2-((2,4,8,10-tetra-*tert*-butyl-6-oxidodibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-yl)oxy)acetamide (11):** white powder; 112-114 °C; R_f = 0.2 (hexane/EtOAc, 2/1); ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (d, *J* = 6.0 Hz, 6H), 1.34 (s, 18H), 1.49 (s, 18H), 4.33 (br s, 2H), 4.65 (br s, 2H), 4.86 (br s, 1H), 5.55 (br s, 1H), 6.70 (d, *J* = 7.2 Hz, 2H), 7.01(br s, 2H), 7.17 (s, 2H), 7.48 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 31.2, 31.5, 34.7, 35.5, 43.8, 47.1, 66.7, 66.7, 115.9, 125.3, 126.6, 127.2, 130.1, 132.2, 140.3, 140.3, 144.4, 144.5, 148.0, 158.5, 166.2.; IR (ATR) 2959, 2360, 1669, 1518, 1458, 1364, 1280, 1172, 1064, 921 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{40}H_{56}NO_6PNa^+$ *m/z* 700.3737, found 700.3734.

Substrate Synthesis

The substrates **1b**, **1c**, **1e**, **1f**, **1h** and **1k** were prepared according to the reported procedure.[5] ^1H and ^{13}C NMR, IR, and MS of products were identical to those reported.[5]

General Procedure for the synthesis of 1a, d, g, i, j: To a stirred solution of 4-hydroxybenzaldehyde derivative in MeOH (0.5 M) was added primary amine (1 eq), and the reaction mixture was stirred for 24 h at room temperature. Then $NaBH_4$ (1.2 eq) was added to the mixture at 0 °C, and stirring was continued for additional 3 h at 0 °C. The reaction was quenched with water, concentrated under reduced pressure to remove most of the MeOH, extracted with EtOAc. The organic layer was acidified with 1 N aqueous HCl, and the water layer was washed with EtOAc. The aqueous solution was basified with 1 N aqueous NaOH, extracted with EtOAc×3, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The obtained crude secondary amine was used for the next step without further purification.

To a stirred solution of crude secondary amine in THF (0.5 M) were added Et_3N (2 eq) and 2,5-dioxopyrrolidin-1-yl 2-diazoacetate[23] at room temperature, and the reaction mixture was stirred for 24 h at room temperature. The reaction was quenched with *N*,*N*-dimethyl-1,3-propanediamine (2 eq), filtered through celite, concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel to afford diazocarbonyl compound **1**.

2-Diazo-*N*-(4-hydroxybenzyl)-*N*-isopropylacetamide (1a): 421.8 mg (60% yield); yellow powder; 110-111 °C; R_f = 0.38 (hexane/EtOAc, 1/2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, *J* = 7.4 Hz, 6H), 4.30 (br d, 2H), 4.85 (br d, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 45.1, 47.1, 47.6, 115.8, 127.6, 130.0, 155.4, 166.9; IR (ATR) ν 2978, 2459, 2104, 1575, 1515, 1427, 1354, 1234, 1203, 1169, 1070, 827, 729 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{12}H_{15}N_3NaO_2^+$ *m/z* 256.1056, found 256.1059.

2-Diazo-*N*-(4-hydroxy-3,5-dimethylbenzyl)-*N*-isopropylacetamide (1d): 400 mg (86% yield); yellow powder; 88-89 °C; R_f = 0.69 (hexane/EtOAc, 1/2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, *J* = 6.8 Hz, 6H), 2.23 (s, 6H), 4.23 (br d, 2H), 4.60 (s, 1H), 4.80 (br d, 1H), 6.83 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9, 20.6, 45.1, 46.8, 47.5, 123.8, 126.3, 129.6, 151.5, 166.7; IR (ATR) ν 2975, 2101, 1578, 1488, 1418, 1371, 1344, 1198, 1146, 1072, 1011, 731, 626 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{14}H_{19}N_3NaO_2^+$ *m/z* 284.1369, found 284.1360.

2-Diazo-*N*-(4-hydroxy-3,5-dimethoxybenzyl)-*N*-isopropylacetamide (1g): 310 mg (53% yield); yellow powder; 105-106 °C; R_f = 0.37 (hexane/EtOAc, 1/2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, *J* = 7.2 Hz, 6H), 3.88 (s, 6H), 4.30 (br d, 2H), 4.84 (br d, 1H), 5.54 (br d, 1H), 6.46 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 45.7, 46.9, 47.3, 56.5, 103.4, 129.7, 134.1, 147.5, 166.6; IR (ATR) ν 2970, 2359, 2101, 1586, 1516, 1419, 1370, 1326, 1201, 1113, 803, 734, 626 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{14}H_{19}N_3NaO_4^+$ *m/z* 316.1268, found 316.1263.

2-Diazo-*N*-(4-hydroxybenzyl)-*N*-(4-methoxybenzyl)acetamide (1i): 2.0 g (46% yield); yellow powder; 114-116 °C; R_f = 0.74 (hexane/EtOAc, 1/2); ^1H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 4.40 (br d, 4H), 5.02 (s, 1H), 6.81 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 7.05 (br d, 2H), 7.14(br d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.2, 49.0, 49.1, 55.3, 55.4, 114.4, 115.9, 128.0, 128.8, 156.1, 159.3, 166.9; IR (ATR) ν 3260, 2108, 1579, 1512, 1437, 1354, 1246, 1173, 1032, 825, 723, 612 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{17}H_{17}N_3NaO_3^+$ *m/z* 334.1162, found 334.1151.

2-Diazo-*N*-(4-hydroxyphenethyl)-*N*-isopropylacetamide (1j): 165.7 mg (34% yield); yellow powder; 108-110 °C; R_f = 0.63 (hexane/EtOAc,1/2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (d, *J* = 6.8 Hz, 6H), 2.78 (t, *J* = 10.0 Hz, 2H), 3.27 (br d, 2H), 4.95 (br d, 1H), 5.03 (br d, 1H), 6.81 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 36.0, 44.6, 47.1, 47.5, 115.7, 129.7, 130.5, 155.1, 165.8; IR (ATR) ν 2978, 2360, 2341, 2105, 1576, 1516, 1431, 1358, 1231, 1164, 827, 645 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{13}H_{17}N_3NaO_2^+$ *m/z* 270.1213, found 270.1211.

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References

[1] a) Y.-L. Yang, F.-R. Chang, Y.-C. Wu, *Helv. Chim. Acta* **2004**, *87*, 1392; b) V. Sánchez, A. Ahond, J. Guilhem, C. Poupat, P. Potier, *Bull. Soc. Chim. Fr.* **1987**, 877.

[2] a) W. M. Kazmierski, E. Furfine, A. Spaltenstein, L. L. Wright, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3431; b) A. M. Badger, D. A. Schwartz, D. H. Picker, J. W. Dorman, F. C. Bradley, E. N. Cheeseman, M. J. DiMartino, N. Hanna, C. K. Mirabelli, *J. Med. Chem.* **1990**, *33*, 2963; c) M. Amit-Vazina, S. Shishodia, D. Harris, Q. Van, M. Wang, D. Weber, R. Alexanian, M. Talpaz, B. B. Aggarwal, Z. Estrov, *Br. J. Cancer* **2005**, *93*, 70.

[3] a) B. Hu, Y. Li, W. Dong, K. Ren, X. Xie, J. Wan, Z. Zhang, *Chem. Commun.* **2016**, *52*, 3709; b) C. Ovens, N. G. Martin, D. J. Procter, *Org. Lett.* **2008**, *10*, 1441; c) T. R. Ibarra-Rivera, R. Gámez-Montaño, L. D. Miranda, *Chem. Commun.* **2007**, 3485.

[4] a) S. Harada, R. Kato, T. Nemoto, *Adv. Synth. Catal.* **2016**, *358*, 3123; b) M. Kono, S. Harada, Y. Hamada, T. Nemoto, *Tetrahedron* **2016**, *72*, 1395; c) S. Harada, M. Kono, T. Nozaki, Y. Menjo, T. Nemoto, Y. Hamada, *J. Org. Chem.* **2015**, *80*, 10317.

[5] H. Nakayama, S. Harada, M. Kono, T. Nemoto, *J. Am. Chem. Soc.* **2017**, *139*, 10188.

[6] For reviews on diazo chemistry, see: a) H. M. L. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, *40*, 1857; b) C. N. Slattery, A. Ford, A. R. Maguire, *Tetrahedron* **2010**, *66*, 6681; c) C. J. Moody, *Angew.*

Chem. **2007**, *119*, 9308; *Angew. Chem. Int. Ed.* **2007**, 46, 9148.

[7] a) J. N. Johnston, H. Muchalski, T. L. Troyer, *Angew. Chem. Int. Ed.* **2010**, *49*, 2290; b) A. B. Smith III, R. K. Dieter, *Tetrahedron* **1981**, *37*, 2407.

[8] D. J. Miller, C. J. Moody, *Tetrahedron* **1995**, *51*, 10811.

[9] L. I. Smith, *Chem. Rev.* **1938**, *23*, 193.

[10] a) S. S. So, A. E. Mattson, *Asian J. Org. Chem.* **2014**, *3*, 425; b) C. Zhai, D. Xing, C. Jing, J. Zhou, C. Wang, D. Wang, W. Hu, *Org. Lett.* **2014**, *16*, 2934.

[11] a) T. Nemoto, Y. Ishige, M. Yoshida, Y. Kohno, M. Kanematsu, Y. Hamada, *Org. Lett.* **2010**, *12*, 5020; b) Q.-F. Wu, W.-B. Liu, C.-X. Zhuo, Z.-Q. Rong, K.-Y. Ye, S.-L. You, *Angew. Chem.* **2011**, *123*, 4547; *Angew. Chem. Int. Ed.* **2011**, *50*, 4455; c) S. Rousseaux, J. García-Fortanet, M. A. Del Aguila Sanchez, S. L. Buchwald, *J. Am. Chem. Soc.* **2011**, *133*, 9282. d) L. Yang, H. Zheng, L. Luo, J. Nan, J. Liu, Y. Wang, X. Luan, *J. Am. Chem. Soc.* **2015**, *137*, 4876; e) T. Nemoto, Y. Hamada, *Synlett* **2016**, *27*, 2301; f) Q. Cheng, Y. Wang, S.-L. You, *Angew. Chem.* **2016**, *128*, 3557; *Angew. Chem. Int. Ed.* **2016**, *55*, 3496; g) L. Luo, H. Zheng, J. Liu, H. Wang, Y. Wang, X. Luan, *Org. Lett.* **2016**, *18*, 2082; h) D. Shen, Q. Chen, P. Yan, X. Zeng, G. Zhong, *Angew. Chem.* **2017**, *129*, 3290; *Angew. Chem. Int. Ed.* **2017**, *56*, 3242. i) A. K. Clarke, J. T. R. Liddon, J. D. Cuthbertson, R. J. K. Taylor, W. P. Unsworth, *Org. Biomol. Chem.* **2017**, *15*, 233.

[12] a) B. Ma, Z. Chu, B. Huang, Z. Liu, L. Liu, J. Zhang, *Angew. Chem.* **2017**, *129*, 2793; *Angew. Chem. Int. Ed.* **2017**, *56*, 2749; b) A. Conde, G. Sabenya, M. Rodríguez, V. Postils, J. M. Luis, M. M. Díaz-Requejo, M. Costas, P. J. Pérez, *Angew. Chem.* **2016**, *128*, 6640; *Angew. Chem. Int. Ed.* **2016**, *55*, 6530; c) M. R. Fructos, T. R. Belderrain, P. de Frémont, N. M. Scott, S. P. Nolan, M. M. Díaz-Requejo, P. J. Pérez, *Angew. Chem.* **2005**, *117*, 5418; *Angew. Chem. Int. Ed.* **2005**, *44*, 5284.

[13] Use of hypervalent iodine catalyst: a) T. Dohi, A. Maruyama, M. Yoshimura, K. Morimoto, H. Tohma, Y. Kita, *Angew. Chem.* **2005**, *117*, 6349; *Angew. Chem. Int. Ed.* **2005**, *44*, 6193; b) M. Uyanik, T. Yasui, K. Ishihara, *Angew. Chem.* **2010**, *122*, 2221; *Angew. Chem. Int. Ed.* **2010**, *49*, 2175; c) T. Dohi, N. Takenaga, T. Nakae, Y. Toyoda, M. Yamasaki, M. Shiro, H. Fujioka, A. Maruyama, Y. Kita, *J. Am. Chem. Soc.* **2013**, *135*, 4558.

[14] a) C. Palo-Nieto, A. Sau, R. Williams, M. C. Galan, *J. Org. Chem.* **2017**, *82*, 407; b) Y. Hayashi, S. Ogasawara, *Org. Lett.* **2016**, *18*, 3426; c) G.-J. Yang, W. Du, Y.-C. Chen, *J. Org. Chem.* **2016**, *81*, 10056; d) Z. Zhang, Z. Bao, H. Xing, *Org. Biomol. Chem.* **2014**, *12*, 3151; e) T. Weil, M. Kotke, C. M. Kleiner, P. R. Schreiner, *Org. Lett.* **2008**, *10*, 1513.

[15] Reviews: a) Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187; b) L. Hong, W. Sun, D. Yang, G. Li, R. Wang, *Chem. Rev.* **2016**, *116*, 4006.

[16] a) S. S. So, A. E. Mattson, *J. Am. Chem. Soc.* **2012**, *134*, 8798; b) B. Bernardim, E. D. Couch, A. M. Hardman-Baldwin, A. C. B. Burtoloso, A. E. Mattson, *Synthesis* **2016**, *48*, 677.

[17] a) S. Matsunaga, M. Shibasaki, *Chem. Commun.*, **2014**, *50*, 1044; b) H. Xu, S. J. Zuend, M. G. Woll, Y. Tao, E. N. Jacobsen, *Science* **2010**, *327*, 986; c) M. Shibasaki, M. Kanai, S. Matsunaga, N. Kumagai, *Acc. Chem. Res.* **2009**, *42*, 1117.

[18] Recently, a similar work was reported by Bower, in which a Brønsted acid was used to generate a potent electrophilic amination reagent for the dearomatization of phenol derivatives, see; J. J. Farndon, X. Ma, J. F. Bower, *J. Am. Chem. Soc.* **2017**, *139*, 14005.

[19] a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew Chem.* **2004**, *116*, 1592; *Angew. Chem. Int. Ed*. **2004**, *43*, 1566. b) D. Uraguchi, M. Terada, *J. Am. Chem Soc*. **2004**, *126*, 5356.

[20] B. Xu, M.-L. Li, X.-D. Zuo, S.-F. Zhu, Q.-L. Zhou, *J. Am. Chem. Soc.* **2015**, *137*, 8700.

[21] Unfortunately, we could not isolate O–H insertion products derived from **1a** and **4**, due to its unstability.

[22] E. T. Satumov, J. J. Medvedev, D. I. Nilov, M. A. Sandzhieva, I. A. Boyarskaya, V. A. Nikolaev, A. V. Vasilyev, *Tetrahedron*, **2016**, *72*, 4835.

[23] W. Zhou, P.-H. Hsieh, Y. Xu, T. R. O'Leary, X. Huang, J. Liu, *Chem. Commun.* **2015**, *51*, 11019.

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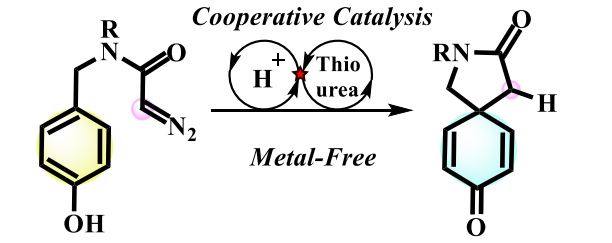
UPDATE

Merging Brønsted Acid and Hydrogen-Bonding Catalysis: Metal-Free Dearomatization of Phenols *via ipso*-Friedel-Crafts Alkylation to Produce Functionalized Spirolactams

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Shingo Harada,[a,*] Irene Mei-Yi Kwok,[a] Hiroki Nakayama,[a] Ayaka Kanda,[a] and Tetsuhiro Nemoto[a,b,*]



A Dearomative ipso-Friedel-Crafts (DIFC) Reaction