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# Superacidic Activation of Maleimide and Phthalimide and Their Reactions with Cyclohexane and Arenes[‡]

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When activated in the $CF_3SO_3H/SbF_5$ acid system maleimide (**1**) and phthalimide (**2**) undergo selective ionic hydrogenation with cyclohexane to give 1,5-dihydropyrrol-2-one (**3**) and phthalimidine (**11**), respectively. When treated with aluminum halides, *N*-phenylmaleimide (**4**) reacts with cyclohexane to give *N*-phenylsuccinimide (**5**), whereas **2** still gives **11**. Imide **1** also condenses with benzene in trifluoromethanesulfonic acid ($CF_3SO_3H$) to give 1,5-dihydro-5,5-diphenylpyrrol-2-one (**7**) as the major product. However, in the presence of aluminum halides **1** reacts with benzene, toluene, and *o*-dichlorobenzene to give 3-arylsuccinimides **8**–**10**, respectively. Imide **2** reacts with benzene under the influence of trifluoromethanesulfonic acid as well as aluminum halides to yield 3,3-diphenylphthalimidine (**12**). The mechanism of these reactions, with potential involvement of superelectrophilic dicationic intermediates, is discussed.


## Introduction

Maleimide (**1**) and phthalimide (**2**) are readily available and useful materials in various synthetic applications, such as peptide preparation, the Gabriel synthesis of primary amines, Diels–Alder cycloadditions, polymerization reactions, etc. However, reactions of **1** and **2** as effective electrophiles are unprecedented, but reasonable when considering electrophilic reactions of maleic and phthalic anhydrides as well as isatin and thioisatin in strong acids, which have been extensively studied.[2] For these compounds, much of the work has been directed towards their reactions with benzene and activated arenes (ArH) to obtain the acylated or alkylated products depending on the reaction conditions (Scheme 1).[2]

On the other hand, it has been shown recently that superacidic activation of α,β-unsaturated amides produces their condensation with aromatic compounds as well as selective ionic hydrogenation with cyclohexane.[3] In a related area, a successful result was also achieved, for example, in superacid-induced reactions of 5-amino-1-naphthol,[4] isomeric quinolinols and isoquinolinols,[5] piperidinones,[6] acetyl-substituted heteroarenes,[7] quinoline- and pyridinecarboxaldehydes,[8] ninhydrin,[9] and 1,2-dicarbonyl compounds[10] with cyclohexane and/or aromatics, and this reactivity has been conveniently applied for the preparation of a number of unique and useful compounds. Remarkably, in all these reactions the key intermediates were recognized to be superelectrophilic[11] *O*,*C*-, *N*,*C*-, *N*,*O*- and *O*,*O*-diprotonated dications of the precursors.[3–10]

In this respect, it is significant that the possibility of activation of **1** and **2** by their *O*,*O*-diprotonation has already been demonstrated (Scheme 2).[12] Herein, in continuation of our studies on superelectrophilic activation in superacids, we report synthetically useful reactions of maleimide (**1**) and phthalimide (**2**) with cyclohexane and arenes.

## Results and Discussion

### Theoretical Study of Possible Diprotonated Forms

Imides **1** and **2** in addition to the experimentally observed[12] dications **1a** and **2a** (Scheme 2) could also produce isomeric *O*,*C*-diprotonated dication **1b** and *O*,*N*-diprotonated dications **1c** and **2b** (Table 1 and Scheme 3) upon protonation. The possibility of formation of **1b** seems reasonable taking into account the analogous *O*,*C*-diprotonation of α,β-unsaturated amides,[3a,3b] acids,[13] and ketones[14] in superacids at low temperature. The formation of ions **1c** and **2b** based on the unfavorable kinetic factor of *O*,*N*-diprotonation is less likely as it requires overcoming significant charge–charge repulsion. Moreover, the protonation of nitrogen would eliminate lone electron pair participation with the conjugated π-system, which is clearly unfavorable based on energy considerations. Anyway, depending on the balance between stability (concentration in the reac-

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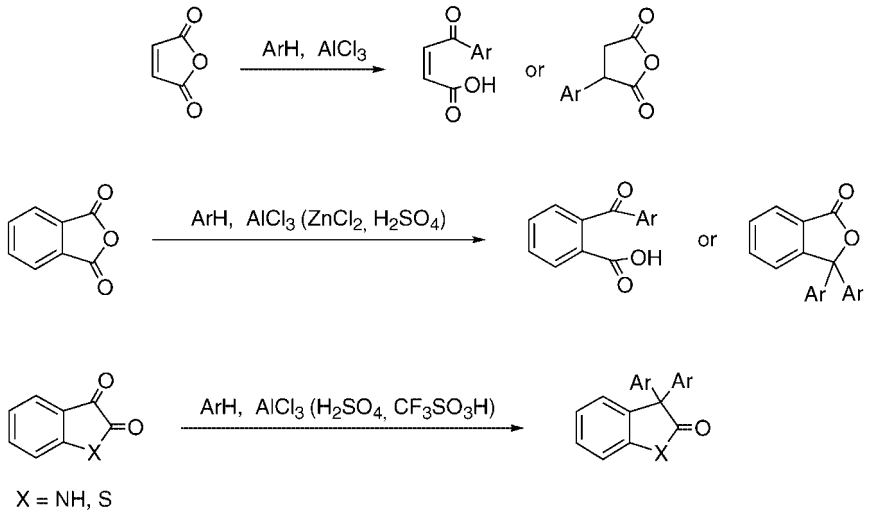
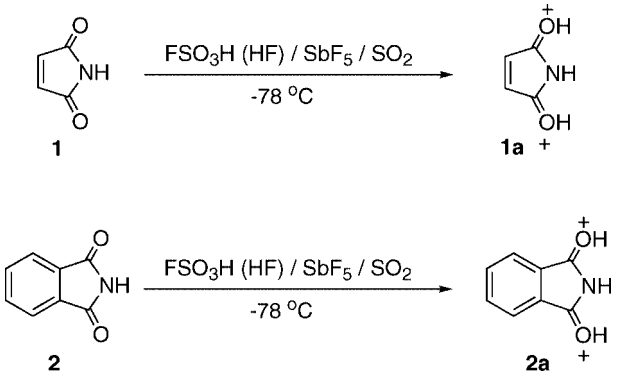
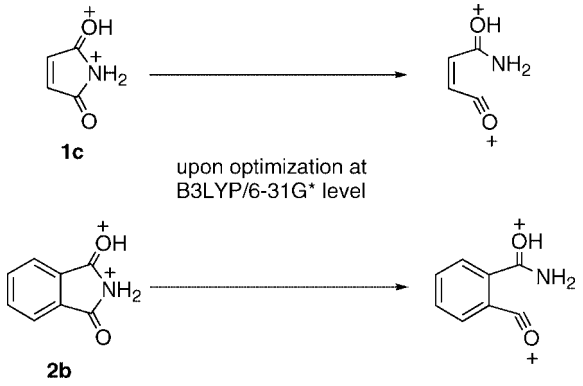



Scheme 1.




Scheme 2.




Scheme 3.

tion media) and reactivity, dications **1a**–**c** and **2a**,**b** could give a variety of corresponding products with the nucleophiles.

Table 1. Energies of the LUMO ($\varepsilon_{LUMO}$), the square of the coefficients on the carbon atoms at the LUMO ($c_i^2$),[a] and the NBO charges on the carbon atoms or CH groups ($q_i$)[a] of dications **1a**,**b** and **2a** calculated by the DFT method.

| Dication | | | |
|---|---|---|---|
| $q_i$ ($c_i^2$) | 0.17 (0.14), 0.79 (0.41) | 0.68 (0.92) | 0.78 (0.38) |
| | **1a** | **1b** | **2a** |
| $\varepsilon_{LUMO}$ [eV] | −14.93 | −16.46 | −13.00 |

[a] These parameters are given for positions with the most significant values of $c^2$ at the LUMO or $q$ (the calculated structures **1a** and **2a** are symmetrical).

In order to estimate the relative stabilities and electrophilicities of dications **1a**–**c** and **2a**,**b** we computed their relative energies, the energies of their lowest unoccupied molecular orbital ($\varepsilon_{LUMO}$), the squares of the coefficients of the carbon atoms at the LUMO ($c_i^2$), and the distribution of atomic charge ($q_i$) localized at the carbon atoms (for carbonyl groups) or carbon atoms and pendent hydrogen atoms. The calculations were carried out with the Gaussian 98 program system.[15] The geometry optimization was performed using the DFT[16] method at the B3LYP[17]/6-31G* level.[18] Vibrational frequency at the B3LYP/6-31G*// B3LYP/6-31G* level was used to characterize each stationary point as a minimum [number of imaginary frequency (NIMAG) = 0]. The values of $q_i$ were obtained using the natural bond orbital analysis[19] (NBO) method.

Geometry optimization of *O*,*N*-diprotonated dications **1c** and **2b** resulted in the cleavage of C–N bonds, as shown in Scheme 3. If such a reaction pathway is possible then the corresponding acylated products with the nucleophiles should be realized experimentally.

Dications **1a**,**b** and **2a**, according to their $\varepsilon_{LUMO}$ and $q_i$ values (Table 1), are expected to be strong electrophiles and very reactive towards benzene and cyclohexane.[4,5b–5d] The values of $\varepsilon_{LUMO}$ of dications **1a**, **2a**, and, certainly, **1b** are significantly lower than the computed energy levels of the HOMOs of nucleophiles such as benzene and cyclohexane

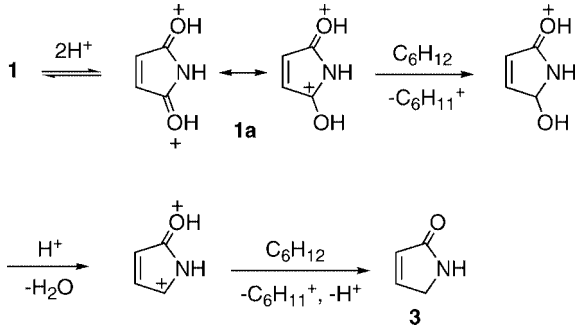
($\varepsilon_{HOMO} \approx -10$ eV).[5b] This, in principle, allows the possibility of one-electron transfer from benzene or cyclohexane to the dications, at least in the idealized gas phase. However, solvation in the condensed phase or in the initial stage of reaction with the nucleophile can considerably elevate the LUMO energetic level of the dications. Consequently, the $\varepsilon_{LUMO}$ values of dications can be considered mainly as a measure of their "thermodynamic" electrophilicity, reflecting the energy contribution of the LUMO–HOMO interaction at the initial stage of the reaction with nucleophiles, whereas the $q_i$ values of the dications, along with the corresponding energetic contribution, can be considered also as a measure of their "kinetic" electrophilicity.[5b–5d]

The dication **1b** can be regarded as the most electrophilic according to the extremely low value of its $\varepsilon_{LUMO}$ (–16.46 eV) and the considerable value of $q$ (0.68) for its CH group. Obviously, this is due to the small size of the dication and the diminished π-system. As expected, *O*,*O*-diprotonated dication **1a** appears to be more stable than dication **1b** (by about 35.2 kcal mol$^{-1}$). This is related to the more effective delocalization of positive charge in **1a**, although there is significant charge localization ($q$ = 0.79) on the carbon atoms of the protonated carbonyl groups. These atoms can be regarded as the electrophilic reaction centers of **1a**. In contrast, the CH groups of this dication are unlikely to be alternative reaction centers according to their negligible values of both $q$ and $c^2$. It is remarkable that the $q$ values of the carbonyl carbon atoms in dications **1a** and **2a** are almost identical. This reflects a similar influence of the double bond and the aromatic ring on the positive-charge delocalization. On the other hand, it also indicates similar electrophilicities of dications **1a** and **2a**. The latter, however, must be a weaker electrophile according to its higher $\varepsilon_{LUMO}$ value.

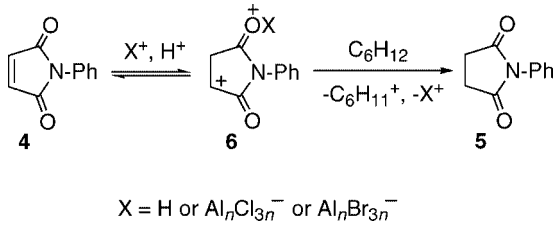
### Reactions of 1 with Cyclohexane and Aromatic Compounds

Imide **1** does not react with cyclohexane in trifluoromethanesulfonic acid ($CF_3SO_3H$, Ho = –14.1). However, **1** reacts readily with cyclohexane in the more acidic $CF_3SO_3H$/$SbF_5$ system (Ho ≈ –18[20]) at room temperature to give, based on $^1$H NMR monitoring, 1,5-dihydropyrrol-2-one (**3**) quantitatively (Scheme 4). The likely mechanism of this reaction includes generation of dication **1a** followed by its selective ionic hydrogenation with cyclohexane. Compound **3**, however, appears to be too labile[21] to be successfully isolated by the usual[5] or special[12] quenching procedures, and a complex mixture of products was obtained.

Reaction of **1** with cyclohexane catalyzed by a two- to fivefold molar excess of aluminum halides also resulted in complex reaction mixtures mostly containing 3-halogenosuccinimides as by-products. On the other hand, a derivative of **1**, *N*-phenylmaleimide (**4**), reacts smoothly with cyclohexane in the presence of $AlCl_3$ in $CH_2Cl_2$ at 40 °C as well as $AlBr_3$ in $CH_2Br_2$ at 50 °C to give *N*-phenylsuccinimide (**5**) in 70–80% yield. The probable mechanism of the reaction includes involvement of dicationic species **6** (analogous to dication **1b**) followed by reaction with cyclohexane (Scheme 5). This reaction is similar to the selective ionic hydrogenation of α,β-unsaturated amides and ketones with alkanes in the presence of aluminum halides.[3b,22]




Scheme 4.



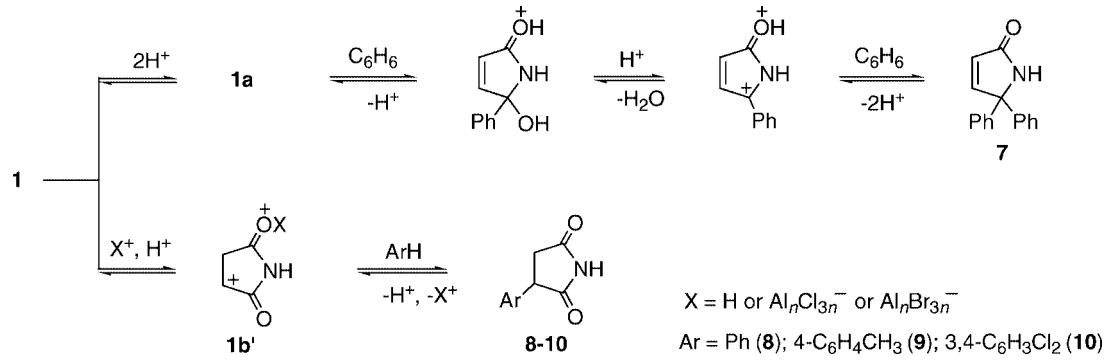

Scheme 5.

Reaction of **1** with aromatic compounds takes place under rather mild conditions at room temperature. The reaction was found to follow two main pathways depending on the nature of the superacid. In trifluoromethanesulfonic acid, **1** reacts with benzene to give 5,5-diphenyl-1,5-dihydropyrrol-2-one (**7**) as the major product in about 70% yield. However, the reaction mixture also contains about 10% of 3-phenylsuccinimide (**8**). Dications **1a** and **1b**, respectively, are considered to be the key electrophilic intermediates in these reactions (Scheme 6).

Compound **8** becomes the major product (80–95%) in the reaction of **1** with benzene in the presence of a two- to threefold molar excess of aluminum halide. Similarly, **1** reacts with toluene and even with an inert aromatic compound such as *o*-dichlorobenzene in the presence of aluminum halides to give 3-(4-methylphenyl)- and 3-(3,4-dichlorophenyl)succinimides **9** and **10**, respectively. In these reactions the dicationic species **1b′** is considered to be the key electrophilic intermediate (Scheme 6). An alternative mechanism could involve the in situ generated traces of 3-halogenosuccinimides undergoing the usual activation with aluminum halide (similar to alkyl halides). However, 3-bromo- as well as 3-chlorosuccinimides, which were isolated as by-products of the reactions of **1** with *o*-dichlorobenzene, appear to be inert towards *o*-dichlorobenzene and even benzene under these reaction conditions.

Imide **1** does not react with *o*-dichlorobenzene in trifluoromethanesulfonic acid (no product was detected after 20 h of reaction at 20 °C), thus indicating the lack of reactivity




Scheme 6.

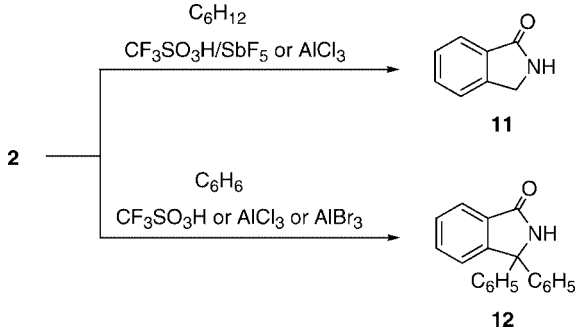
of **1a** under these reaction conditions. This is in agreement with the theoretically estimated lower electrophilicity of dication **1a** in comparison with that of the reactive dication **1b**.

It should be noted here that during the preparation of this paper the transformation **1**→**8** was performed successfully using an H-form of zeolite, which provides an effective excess of acidic sites.[23] The intermediacy of "dicationic" species analogous to **1b** on the solid was invoked.

As seen from our experiments, aluminum halides (and zeolites),[23] in contrast to protic superacids, prompt the involvement of dications **1b** (**1b′**) rather than **1a**. This is probably due to initial *O*-complexation of **1** with a Lewis acid (Lewis acid site in zeolites), which facilitates subsequent *C*-protonation. A similar influence of the nature of the superacid on the regioselectivity of dicationic activation is also known for hydroxy(iso)quinolines.[5c–5d]

### Reactions of 2 with Cyclohexane and Benzene

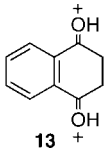
Similar to **1**, imide **2** also does not react with cyclohexane in trifluoromethanesulfonic acid, but reacts in $CF_3SO_3H/SbF_5$ at room temperature as well as in the presence of a four- to fivefold molar excess of $AlCl_3$ at elevated temperature (>100 °C)[24] to give phthalimidine (**11**) in 80% yield (Scheme 7).




Scheme 7.

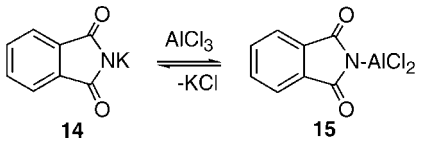
Compound **2** also reacts slowly (time for half conversion is about 150 h at room temperature) with benzene in trifluoromethanesulfonic acid to give 3,3-diphenylphthalimidine (**12**; Scheme 7), although it reacts more readily with benzene in the presence of a fivefold molar excess of $AlBr_3$ on heating under reflux (80 °C) to give **12** in about 70% yield after several hours. To complete the analogous reaction catalyzed by $AlCl_3$ requires 20–40 h at 90–110 °C and gives **12** in 50–60% yield (Scheme 7). The decrease in the yield of **12** is due to parallel formation of 10–20% of 3-phenylphthalimidine, the appearance of which can be explained by a combination of the reaction with benzene and ionic hydrogenation with saturated hydrocarbons. The latter product is also obviously produced as a result of the acid-catalyzed reactions of benzene.[25]

The mechanisms of the reactions of **2** with cyclohexane and benzene can be explained by participation of dications **2a** or analogous complexes with aluminum halides similar to that for dications **1a**. In general, the reactivity of **2** is appreciably lower than that of **1**. Attempts to provoke the reaction of **2** with *o*-dichlorobenzene in trifluoromethanesulfonic acid at room temperature as well as in the presence of $AlCl_3$ at 110 °C were not successful. This is in agreement with the theoretically determined relatively moderate electrophilicity of dications **2a**. However, these dications appear to be a significantly stronger electrophile than the analogous carbocyclic *C*,*C*-diprotonated dications derived by the diprotonation of 1,4-naphthalenediol (**13**). The latter has previously been shown to be inert towards both benzene and cyclohexane, in accordance with its MNDO-computed values of $q_1 = q_4 = 0.39$ and $\varepsilon_{LUMO} = -10.7$ eV.[26]




In addition, it has been found that potassium phthalimide (**14**) also reacts with benzene in the presence of $AlCl_3$ to give **12** in good yield (83%). The reaction appears to be more selective than the similar reaction with **2**. The probable mechanism could involve reaction of **14** or complex **15**[27] with traces of protic acid ($HAlCl_4$ or $HAlCl_3OH$) to give **2**, followed by dicationic activation and reaction with benzene. Under these conditions, protic acid is not accumulated in the reaction mixture in any significant concentration, thus decreasing potential side-reactions.




## Conclusions

We have found that imides **1** and **2**, when activated by superacids, undergo selective ionic hydrogenation with cyclohexane and condense with aromatic compounds. The experimental data as well as the results of theoretical calculations suggest the involvement of diprotonated dications of **1** and **2** or analogous complexes with aluminum halides. Ionic hydrogenation with cyclohexane can be used in the selective reduction of imides.[28] The reactions with arenes provide a new and effective one-step procedure for the preparation of aryl-substituted derivatives of pyrrolidine, some of which are important intermediates in medicinal chemistry.[29]

## Experimental Section

**General Remarks:** The $^1H$ and $^{13}C$ NMR spectra were recorded with a 300 MHz superconducting NMR spectrometer. High-resolution mass spectra were measured at the Southern California Mass Spectrometry Facility at the University of California at Riverside. Trifluoromethanesulfonic acid, aluminum halides, and compounds **1**, **2**, **4**, and **14** were purchased from suppliers and used as received. Antimony pentafluoride was distilled under argon. Reactions at elevated temperature (>80 °C) were carried out in 15-mL pyrex glass pressure tubes.

**1,5-Dihydropyrrol-2-one (3):** Cyclohexane (0.3 mL) was added to a solution of **1** (0.04 g, 0.4 mmol) in $CF_3SO_3H$ (1.2 g, 8 mmol). Subsequently, $SbF_5$ (0.7 g, 3 mmol) was introduced and the reaction mixture was stirred at 25 °C for 10 min. A solution containing compound **3** (quantitative formation) was obtained. $^1H$ NMR: $\delta$ = 4.24 (s, 2 H), 6.2 (d, $J$ = 7.5 Hz, 1 H), 7.46 (d, $J$ = 7.5 Hz, 1 H), 8.18 ppm (br. s, 1 H). Chemical shifts are given with respect to $(CD_3)_2CO$ as external standard ($\delta$ = 2.04 ppm). The data are comparable to those reported previously.[21]

***N*-Phenylsuccinimide (5). Method a:** Compound **4** (2 g, 12 mmol) and cyclohexane (5 mL) were added to a stirred suspension of $AlCl_3$ (6.5 g, 49 mmol) in $CH_2Cl_2$ (25 mL). The mixture was stirred for 48 h under reflux and, after cooling, poured over several grams of ice and extracted with $CH_2Cl_2$. The organic phase was dried with anhydrous $MgSO_4$. Concentration in vacuo provided a residue that was recrystallized from ethanol to obtain **5** (1.6 g, 79%). M.p. 153–154 °C (sublimation), ref.[30] 153–154 °C.

**Method b:** Compound **4** (1 g, 5.8 mmol) and cyclohexane (2 mL) were added to a solution of $AlBr_3$ (5.4 g, 20 mmol) in $CH_2Br_2$ (10 mL). The resulting mixture was stirred at 50 °C for 2 h to give **5** (0.72 g, 71%) after workup as described above.

**5,5-Diphenyl-1,5-dihydropyrrol-2-one (7):** Benzene (0.3 mL) was added to a solution of **1** (0.06 g, 0.6 mmol) in $CF_3SO_3H$ (2 g, 13 mmol). The resulting mixture was stirred at 20 °C for 36 h and was then quenched with several grams of ice and extracted with $CHCl_3$. The organic phase was washed with aqueous $NaHCO_3$, then dried with anhydrous $MgSO_4$. Concentration in vacuo provided a residue [0.135 g, mixture of **7/8** (9:1), according to $^1H$ NMR spectroscopic data] that was recrystallized from $CHCl_3$/cyclohexane to obtain **7** (0.1 g, 69%). M.p. 202–203 °C. HRMS calcd. for $C_{16}H_{13}NO$: 235.0997; found 235.0998.

**3-Phenylsuccinimide (8). Method a:** Compound **1** (0.2 g, 2 mmol) was added to a stirred suspension of $AlCl_3$ (0.9 g, 6.7 mmol) in benzene (4 mL). The resulting mixture was stirred at 20 °C for 40 h and was then poured over several grams of ice and extracted with $CH_2Cl_2$. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography with $CHCl_3$ to give **8** (0.29 g, 83%). M.p. 89–90 °C, ref.[29b] 90–91 °C.

**Method b:** A mixture of $AlBr_3$ (1.25 g, 4.7 mmol) and **1** (0.15 g, 1.5 mmol) in benzene (4 mL) was stirred at 20 °C for 4 h to give **8** (0.25 g, 95%) after workup as described above.

**3-(4-Methylphenyl)succinimide (9):** Compound **1** (0.4 g, 4.1 mmol) was added to a stirred suspension of $AlCl_3$ (1.33 g, 10 mmol) in toluene (3 mL). The resulting mixture was stirred at 75 °C for 1 h, then cooled, poured over several grams of ice, and extracted with $CH_2Cl_2$. The organic phase was washed with water, then dried ($MgSO_4$) and concentrated. The residue [mixture of **9** and isomeric 3-(2-methylphenyl)succinimide (ca. 5:1) according to $^1H$ NMR spectroscopic data] was recrystallized from benzene/hexane to give **9** (0.52 g, 66%). M.p. 106–108 °C. HRMS calcd. for $C_{11}H_{11}NO_2$: 189.0790; found 189.0788.

**3-(3,4-Dichlorophenyl)succinimide (10):** A mixture of $AlBr_3$ (2.67 g, 10 mmol) and **1** (0.3 g, 3 mmol) in *o*-dichlorobenzene (3 mL) was stirred at 25 °C for 300 h (to complete similar reaction at 130–140 °C requires 2 h). Workup as described above gave a residue containing a mixture of **10**, isomeric 3-(2,3-dichlorophenyl)succinimide, and 3-bromosuccinimide in a molar ratio of about 4:1:1 (according to $^1H$ NMR spectroscopic data), which was recrystallized from $CHCl_3$ to give **10** (0.26 g, 34%). M.p. 151–152 °C. HRMS calcd. for $C_{10}H_7Cl_2NO_2$: 242.9854; found 242.9862.

**Phthalimidine (11). Method a:** Compound **2** (0.4 g, 2.7 mmol) was added to a suspension of $AlCl_3$ (1.8 g, 13.5 mmol) in cyclohexane (5 mL). The resulting mixture was stirred at 110 °C for 5 h, then cooled, poured over several grams of ice, and extracted with $CHCl_3$. The organic phase was dried ($MgSO_4$) and concentrated. The residue was recrystallized from cyclohexane to give **11** (0.33 g, 81%). M.p. 148–150 °C, ref.[31] 149–151 °C.

**Method b:** $SbF_5$ (0.5 g, 2.3 mmol) was added to a solution of **2** (0.03 g, 0.2 mmol) in $CF_3SO_3H$ (1 g, 6.7 mmol) at room temperature. Subsequently, cyclohexane (0.3 mL) was introduced, and the reaction mixture was stirred at 25 °C for 1 h. It was then quenched with several grams of ice. The resulting mixture was neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The organic phase was dried ($MgSO_4$) and concentrated. The residue was washed with hexane to provide **11** (0.024 g, 80%).

**3,3-Diphenylphthalimidine (12). Method a:** A mixture of $AlBr_3$ (10 g, 37 mmol) and **2** (1 g, 7 mmol) in benzene (15 mL) was stirred for 3 h whilst heating under reflux. After cooling it was poured over several grams of ice. Hexane (15 mL) was added to the quenched mixture followed by stirring for 10 min. The crude reaction product was filtered and washed with water and hexane to afford 1-hydroxy-3,3-diphenylisoindolenine hydrobromide (2.1 g). M.p. 182–183 °C (recrystallized from 1,4-dioxane/$CHCl_3$). HRMS calcd. for $C_{20}H_{15}NO$ $[M - HBr]^+$: 285.1154; found 285.1159.

The obtained solid product was stirred with aqueous $Na_2CO_3$ and filtered to give **12** (1.4 g, 72%). M.p. 210–211 °C (benzene), ref. 219–219.5 °C (ethanol),[32a] 200 °C (benzene),[32b] 200 °C ($CH_3COOH$).[32c]

**Method b:** A mixture of $AlCl_3$ (2.7 g, 20 mmol) and **14** (0.7 g, 3.8 mmol) in benzene (6 mL) was stirred at 90 °C for 30 h, followed by treatment as described above to give compound **12** (0.9 g, 83%).

**Supporting Information** (see also the footnote on the first page of this article): $^1H$ and $^{13}C$ NMR spectroscopic data of known as well as newly obtained compounds **5** and **7**–**12**.

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