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Metal-free synthesis of adipic acid via organocatalytic direct oxidation of cyclohexane under ambient temperature and pressure

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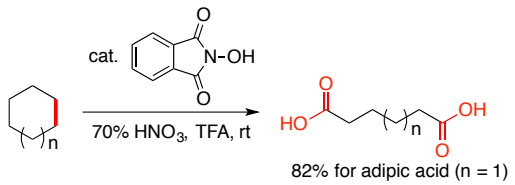


82% for adipic acid (n = 1)

• Metal-free direct oxidation of cycloalkanes
• Ambient temperature and pressure • Simple operating procedure

ABSTRACT: A direct metal-free approach for the production of adipic acid from cyclohexane is reported. The use of an *N*-hydroxyphthalimide (NHPI) catalyst in the presence of HNO_3/TFA enables the direct oxidation of cyclohexane to yield adipic acid under ambient temperature and pressure via a simple procedure. This reaction proceeds through an initial oxidation of cyclohexane to cyclohexanone oxime and cyclohexanone followed by a second oxidation of these intermediates to adipic acid. NHPI plays a crucial role in both oxidation steps to achieve a high yield and selectivity of adipic acid.

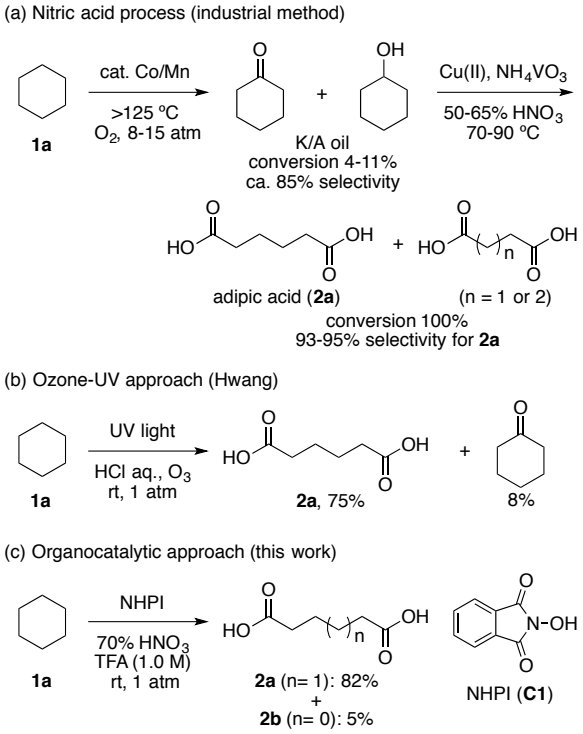
Keywords: adipic acid • metal-free reaction • organocatalysis • radical • oxidation

1. INTRODUCTION

Adipic acid is an important building block in the preparation of nylon-6,6 and other polyesters, and more than 3.5 million tons of adipic acid are employed worldwide each year.[1] Currently, the most widely-used industrial procedure for adipic acid synthesis is the two-step nitric acid oxidation from cyclohexane (Scheme 1a).[2] In the first step of this process, cyclohexane is oxidized under air to yield a mixture of cyclohexanone and cyclohexanol (K/A oil). This transformation requires the presence of metal salts in addition to a high temperature (125–165 °C) and pressure (8–15 atm), and the conversion of cyclohexane must be controlled at only 4–11% to achieve a high selectivity (85%). Subsequently, the metal-catalyzed oxidation of K/A oil using nitric acid as the oxidant proceeds with high efficiency to give adipic acid. While a number of other synthetic strategies for adipic acid have been developed, such as one-step oxidation methods from cyclohexene and multi-step procedures from non-petroleum feedstocks,[3,4] the single-step oxidation of cyclohexane to give adipic acid in the presence of metal catalysts has also received significant attention in the context of cost and efficiency.[5,6]

However, in recent years, focus has shifted to metal-free synthetic processes for environmental reasons.[7] For example, in 2014, Hwang reported a direct oxidation of cyclohexane into adipic acid using ozone under UV irradiation (Scheme 1b).[8] While this oxidation process is highly simple and efficient, issues regarding the performance of the UV reactors in addition to the formation of organic peroxide side products should be considered in the context of industrial scale applications.[9] Furthermore, although organocatalysis has also been studied for a variety of transformations,[10] the organocatalytic oxidation of cyclohexane into adipic acid has received little attention, and remains a challenge in the context of achieving high conversions and selectivities.[11] Thus, we herein report the metal-free direct oxidation of cyclohexane to yield adipic acid in the presence of the radical precursor *N*-hydroxyphthalimide (NHPI) as the sole catalyst (Scheme 1c).

Scheme 1. Synthetic approaches towards the production of adipic acid

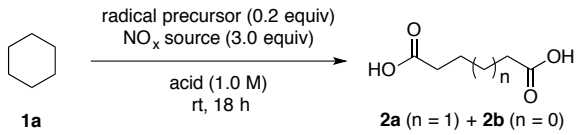


2. RESULTS AND DISCUSSION

Upon the treatment of cyclohexane **1a** with 3.0 equiv of 70% HNO_3 and 0.2 equiv of NHPI (**C1**) in trifluoroacetic acid (TFA) at room temperature for 18 h, the desired adipic acid **2a** was obtained in 82% yield along with a small amount (5%) of glutaric acid **2b** (Table 1, entry 1). Inspired by this result, other radical precursors were evaluated in the oxidation of cyclohexane. However, stoichiometric amount of peroxide reagents, such as 30% hydrogen peroxide and *tert*-butyl hydroperoxide, led to complex mixtures (entries 2 and 3). Thus, we then moved on to evaluate the effect of the NO_x source concentration using **C1** as the radical precursor. Interestingly, when 99% HNO_3 was employed in the reaction, both the yield and the selectivity of **2a** decreased (entry 4), while the use of 60% HNO_3 produced **2a** in a lower yield but with improved selectivity (entry 5). The use of 2 equiv of 70% HNO_3 also resulted in a decreased yield (entry 6). Surprisingly, $NaNO_2$, which gave the optimal result in our previous study into the oxidation of cycloalkanols,[12] failed to yield **2a** under the conditions employed herein (entry 7). The choice of the reaction medium was also important to obtain the desired product in a high yield and selectivity. More specifically, the use of a strong mineral acid (i.e., H_2SO_4 or HNO_3) led to the decomposition of **C1** (entries 8 and 9). Other halogenated and nonhalogenated organic acids were ineffective with the exception of $CF_3CF_2CO_2H$, affording **2a** in decreased yields, likely due to their higher pK_a values and the low solubility of **C1** in these acids (entries 10–15).[13] Although the oxidation proceeded without TFA, the yield of **2a** decreased drastically (entry 16). These results indicated that the properties of TFA (i.e., the appropriate pK_a value and the ability to dissolve **C1**) could play a crucial role to promote this oxidation efficiently. It is noteworthy that the presence of **C1** and HNO_3 was essential to promote the direct oxidation of **1a** to **2a** at ambient temperature and pressure, as the reaction was unsuccessful in the absence of these

components (entries 17–19). Based on these results, we selected a combination of 70% HNO_3 and TFA as the optimal NO_x source and the reaction medium for this transformation.

Table 1. Influence of reaction parameters



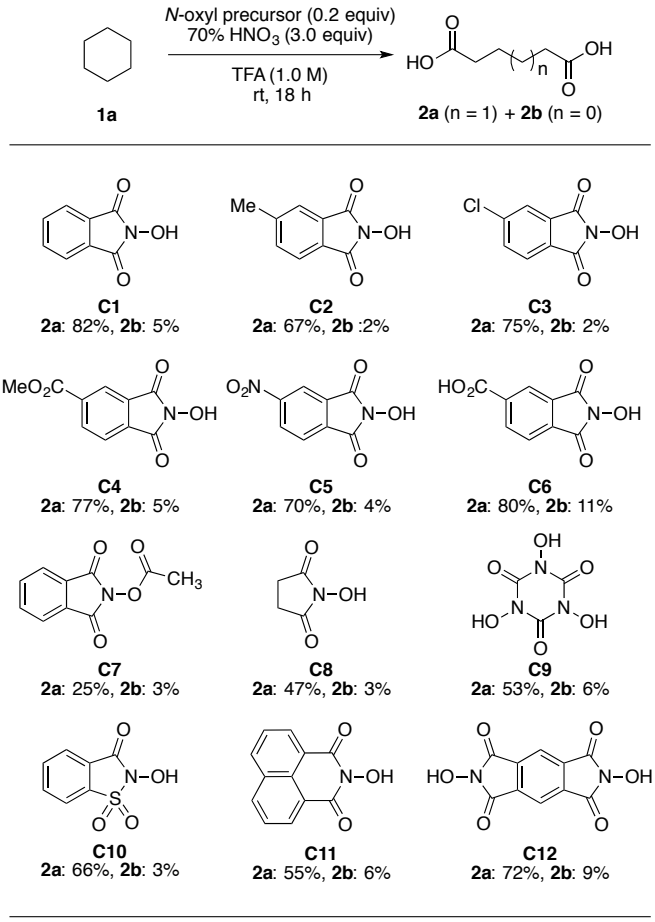
entry	radical precursor	NO_x source	acid	yield (%)[a]	
				2a	**2b**
1	NHPI (**C1**)	70% HNO_3	TFA	82	5
2	30% H_2O_2[b]	70% HNO_3	TFA	c.m.	c.m.
3	TBHP[b]	70% HNO_3	TFA	c.m.	c.m.
4	**C1**	99% HNO_3	TFA	61	5
5	**C1**	60% HNO_3	TFA	79	2
6[c]	**C1**	70% HNO_3	TFA	57	4
7	**C1**	$NaNO_2$	TFA	n.d.	n.d.
8	**C1**	70% HNO_3	H_2SO_4	n.d.	n.d.
9	**C1**	70% HNO_3	70% HNO_3	12	trace
10	**C1**	70% HNO_3	$CF_3CF_2CO_2H$	75	5
11	**C1**	70% HNO_3	CCl_3CO_2H	31	trace
12	**C1**	70% HNO_3	$CHCl_2CO_2H$	33	2
13	**C1**	70% HNO_3	CH_2ClCO_2H	n.d.	n.d.
14	**C1**	70% HNO_3	HCO_2H	trace	trace
15	**C1**	70% HNO_3	CH_3CO_2H	n.d.	n.d.
16[d]	**C1**	70% HNO_3	none	23	6
17	none	70% HNO_3	TFA	trace	trace
18	**C1**	none	TFA	n.d.	n.d.

19[d]	**C1**	none	none	n.d.	n.d.

[a] Yields were determined by ^{1}H NMR spectroscopy using DMF as an internal standard. [b] The radical precursor (1.0 equiv) was employed. [c] 70% HNO_3 (2.0 equiv) was employed. [d] Dichloromethane (1.0 M) was used instead of TFA. c.m. = complex mixture, n.d. = not detected.

The catalytic activities of various NHPI derivatives were then evaluated, as the presence of a substituent on the aryl ring of NHPI is known to affect the NO-H bond dissociation energy (BDE) (Table 2).[14] As indicated, the catalyst bearing an electron-donating methyl group (**C2**) was less effective, affording **2a** in 67% yield. In addition, although the introduction of electron-withdrawing groups on the NHPI aryl ring has been reported to increase the NO-H BDE[14b] to potentially generate a more reactive *N*-oxyl species, the introduction of chloro (**C3**) and ester (**C4**) groups gave **2a** in slightly decreased yields (i.e., 75 and 77%, respectively). Interestingly, a nitro substituted NHPI (**C5**) also afforded **2a** in 70% yield, despite the fact that **C5** and other nitro-substituted substrates were not tolerated in the NHPI/Co^{II}-catalyzed benzylic oxidation.[15] Furthermore, the catalyst bearing a carboxyl group (**C6**) provided **2a** in a high yield (80%), although the selectivity towards **2a** was poor, potentially due to the higher reactivity of the *N*-oxyl species. Moreover, the use of **C7**, which gradually generates **C1** via hydrolysis[16] resulted in a significant decrease in selectivity. We also found that *N*-oxyl precursors derived from succinimide (**C8**), cyanuric acid (**C9**), *o*-sulfobenzimide (**C10**), and naphthalimide skeletons (**C11**) were ineffective, affording **2a** in lower yields. Although the presence of two *N*-hydroxyl groups in the catalyst (**C12**) afforded **2a** in a high yield, the selectivity towards **2a** was poor. Based on these results, we therefore selected **C1** as the preferred organocatalyst for this oxidation system.

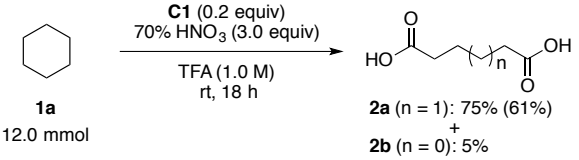
Table 2. Screening of *N*-oxyl precursors[a]



[a] Yields were determined by ^{1}H NMR spectroscopy using DMF as an internal standard.

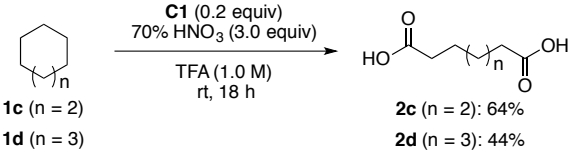
With the optimized condition in hand, we examined the scalability of the present reaction. To our delight, the oxidation of cyclohexane could be performed on a gram-scale, affording adipic acid **2a** in 75% yield (Scheme 2). We also surveyed the effect of the cycloalkane ring size on this reaction. As shown in scheme 3, cycloalkanes larger than cyclohexane gave the desired dicarboxylic acids in moderate to good yields, while those yields were prone to decrease with increasing the cycloalkane ring size.

Scheme 2. Gram-scale experiment for the production of adipic acid[a]



[a] Yields were determined by ^{1}H NMR spectroscopy using DMF as an internal standard. Isolated yield after single recrystallization is shown in parentheses.

Scheme 3. The effect of the ring size on the metal-free direct oxidation of cycloalkanes[a]

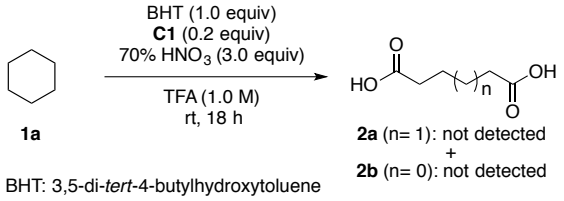


[a] Yields were determined by ^{1}H NMR spectroscopy using DMF as an internal standard.

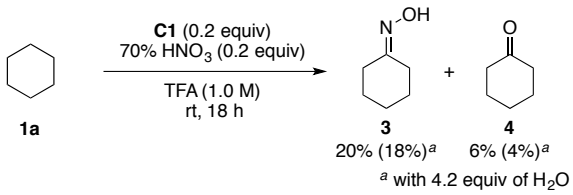
Finally, control experiments were then conducted to gain an improved understanding of the reaction mechanism involved in this transformation. The present oxidation reaction was completely inhibited by 3,5-di-*tert*-4-butylhydroxytoluene (BHT), which is known as a free radical scavenger. The result indicated that this oxidation might proceed via a radical pathway (Scheme 4). When the reaction was performed in the presence of 0.2 equiv of **C1** and 0.2 equiv of 70% HNO_3, cyclohexanone oxime **3** was obtained in 20% yield along with a small amount of cyclohexanone **4** (Scheme 5).[17] Next, compounds **3** and **4** were independently subjected to further control experiments (Scheme 6). Both compounds, in contrast to cyclohexane **1a**, were oxidized to adipic acid **2a** under the HNO_3/TFA system, and a higher yield was obtained by employing oxime **3** as a starting material (entries 1 and 3). When the same reactions were conducted with **C1**, the yield of **2a** from **3** was dropped from 74% to 51%, whereas that from **4** was increased from 33% to 85% (entries 2 and 4). The deteriorated yield from **3** in the presence of **C1** was likely due to the too high reactivity of **3** towards the **C1**/HNO_3/TFA system, because

many unidentified byproducts were observed under the reaction conditions. In fact, the oxidation of **3** proceeded even at 0 °C under the **C1**/HNO_3/TFA system, providing **2a** in a restored yield. On the other hand, cyclohexanone **4** gave trace amount of **2a** under the same reaction conditions (entries 3 and 6). These results indicate that **C1** might play an important role in the nitric acid oxidation of **3** and **4**, and oxime **3** would be more tend to undergo oxidation under this reaction conditions. Moreover, these two intermediates might transform into adipic acid through two distinct oxidation pathways.

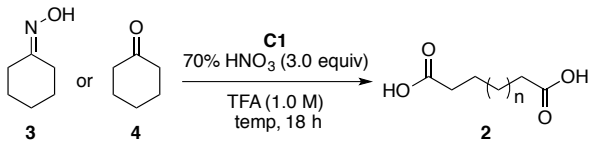
Scheme 4. Effect of a free radical scavenger



Scheme 5. Investigation of intermediates



Scheme 6. Control experiments using oxime **3** or ketone **4** as a starting material



entry	substrate	**C1** (equiv)	temp (ºC)	**2a** (n = 1)	**2b** (n = 0)
1	**3**	0	rt	74%	14%
2	**3**	0.2	rt	51%	7%
3	**3**	0.2	0	78%	trace
4	**4**	0	rt	33%	3%
5	**4**	0.2	rt	85%	5%
6	**4**	0.2	0	trace	n.d.

On the basis of the literature reports[12a,18] and the results of our control experiments, a plausible reaction mechanism for the direct oxidation of cyclohexane to adipic acid is proposed, as shown in Figure 1. In this mechanism, initial reaction of **C1** with HNO_3 affords the phthalimide *N*-oxyl radical (PINO) and NO_2. Subsequently, PINO abstracts a hydrogen atom from cyclohexane **1a** to yield cyclohexyl radical **I**. Although Ishii reported the nitration of cyclohexane with in-situ generated NO_2 in trifluorotoluene at 60 ºC using NHPI/HNO_3 system,[18b] trace amount of nitrocyclohexane was observed by ^{1}H NMR spectroscopy. Under our conditions, in-situ generated NO_2 would undergo rapid equilibration between NO_2 and N_2O_4,[19] and hydrolysis of N_2O_4 followed by disproportionation of HNO_2 provide reactive NO radical. Then, radical coupling reaction of cyclohexyl radical **I** with NO radical afford nitrosocyclohexane **II**, which tautomerize to cyclohexanone oxime **3**. Radical **I** might also react with molecular oxygen to generate peroxy radical **III**, which leads to the formation of cyclohexanone **4**. Hydrolysis of **3** might be a conceivable route for the cyclohexanone formation. These two intermediates would be individually oxidized to adipic acid **2a** in the presence of **C1** and HNO_3.[20]

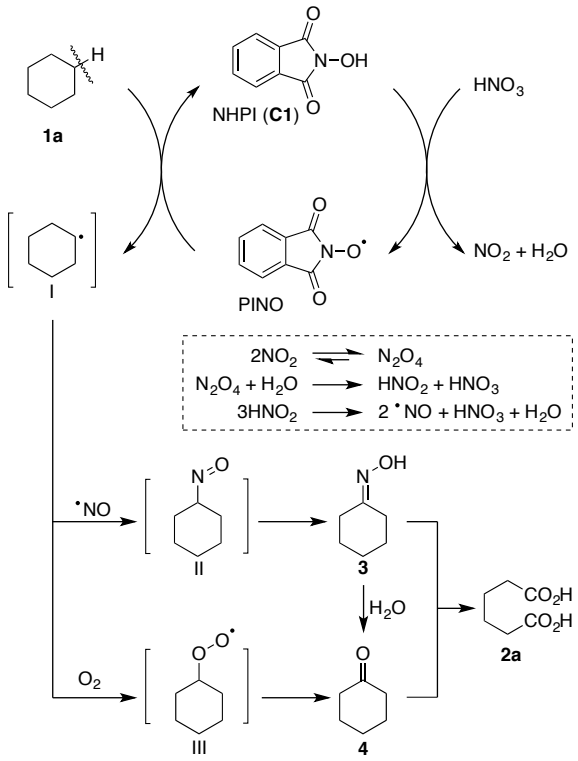


Figure 1. Plausible reaction mechanism for the direct oxidation of cyclohexane to adipic acid.

3. CONCLUSION

We successfully developed a metal-free direct oxidation method for the production of adipic acid from cyclohexane in an excellent yield and selectivity. The NHPI/HNO_3/TFA system described herein was applied to the oxidation of other cycloalkanes affording corresponding dicarboxylic acids. This reaction could be operated under ambient temperature and pressure without any special techniques or experimental manipulations. We therefore believe this reaction could be considered an alternative process for the synthesis of adipic acid. Further studies aimed at improving the yields and selectivities in addition to expanding the substrate scope are currently underway in our laboratory and the results will be presented in due course.

4. EXPERIMENTAL SECTION

General Methods and Materials. Unless otherwise noted, all reactions were performed in a heavy-wall glass tube (Ace Glass, Inc. approximate total capacity: 35 mL) equipped with a magnetic stir bar at room temperature under air. Catalysts **C2-3**[21], **C6**[21], **C7**[22], **C9**[23], **C10**[24], and **C12**[25] were synthesized according to reported methods. All other chemicals were used as received without further purifications.

All melting points were determined using Yanako micro melting point apparatus without correction. Infrared (IR) spectra were recorded on a Shimadzu IRAffinity-1 spectrophotometer. Data were expressed as frequency of absorption (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-AL400 spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). Chemical shift values are expressed in ppm relative to internal TMS (δ 0.00 ppm) or DMSO-d_6 (δ 2.50 ppm) for ^{1}H NMR and DMSO-d_6 (δ 39.5 ppm) for ^{13}C NMR. Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. High-resolution mass spectra (HRMS) were recorded using electron impact ionization (EI) mass spectrometry or fast atom bombardment (FAB) mass spectrometry.

General Procedure for the Metal-free Oxidation of Cycloalkanes. To a pressure tube vessel (Ace glass, Inc. approximate total capacity: 35 mL) equipped with magnetic stirring bar was added cycloalkane **1** (2.0 mmol), NHPI (**C1**) (65.2 mg, 0.4 mmol, 20 mol%), and trifluoroacetic acid (2.0 mL). To the resultant mixture was added 70% HNO_3 (540 mg, 6.0 mmol), and the vessel was tightly closed with a PTFE plug. After stirring for 18 h, the solvent was removed under reduced pressure (approximately 30 mmHg). The residual solid was treated with 5% $NaHCO_3$ solution and washed with CH_2Cl_2. The aqueous layer was acidified with 10% HCl solution, and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, and

concentrated under reduced pressure to give a mixture of dicarboxylic acid **2** and **C1** as a yellow solid. The yield was determined by ^{1}H NMR spectroscopy using DMF as an internal standard. Recrystallization from hot ethyl acetate afforded the desired product.

Adipic acid (2a). The reaction was performed according to the general procedure using cyclohexane **1a** (168 mg, 2.0 mmol). Recrystallization from ethyl acetate afforded pure **2a** (193 mg, 66%) as a white solid of mp 152 °C. Compound **2a** was isolated in 63% yield by a simplified procedure avoiding an extraction step. For detail, see the *simplified procedure for the Metal-free Oxidation of Cyclohexane* described below. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.46-1.54 (m, 4H), 2.15-2.23 (m, 4H), 12.03 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.93, 33.28, 174.22. IR (ATR): 1683, 2951 cm^{-1}. HRMS (FAB) *m*/*z*: calcd for $C_6H_9O_4$ ([M–H]$^-$) 145.0501, found 145.0502.

Simplified Procedure for the Metal-free Oxidation of Cyclohexane. To a pressure tube vessel (Ace glass, Inc. approximate total capacity: 35 mL) equipped with magnetic stirring bar was added cyclohexane **1a** (168 mg, 2.0 mmol), NHPI (**C1**) (65.2 mg, 0.4 mmol, 20 mol%), and trifluoroacetic acid (2.0 mL). To the resultant mixture was added 70% HNO_3 (540 mg, 6.0 mmol), and the vessel was tightly closed with a PTFE plug. After stirring for 18 h, the solvent was removed under reduced pressure, and the residual solid was dried in vacuo. Recrystallization from hot ethyl acetate afforded the desired product **2a** as a colorless solid (184 mg, 63%).

Gram-scale experiment. To a glass lined stainless autoclave (approximate total capacity: 120 mL) equipped with magnetic stirring bar was added cycloalkane **1** (1.01 g, 12.0 mmol), NHPI (**C1**) (391 mg, 2.4 mmol, 20 mol%), and trifluoroacetic acid (12.0 mL). To the resultant mixture was added 70% HNO_3 (3.24 g, 36.0 mmol), and the reaction vessel was tightly closed with stainless reactor lid. After stirring for 18 h, the solvent was removed under reduced pressure

(approximately 30 mmHg). The residual solid was treated with 5% $NaHCO_3$ solution and washed with CH_2Cl_2. The aqueous layer was acidified with 10% HCl solution, and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, and concentrated under reduced pressure to give a mixture of dicarboxylic acid **2** and **C1** as a yellow solid. The yield of 75% for **2a** and 5% for **2b** was determined by ^1H NMR spectroscopy using DMF as an internal standard. Recrystallization from hot ethyl acetate afforded pure **2a** in 61% as a white solid (1.07 g).

ASSOCIATED CONTENT

Supporting Information.

The following files are available free of charge.

Experimental details and ^1H and ^{13}C NMR spectrum of the products (PDF)

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Notes

The authors declare no conflict of interest.

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