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Catalytic oxidative cleavage of catechol by a non-heme iron(III) complex as a green route to dimethyl adipate†

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The catalyst system prepared *in situ* from iron(III) salts, tris(2-pyridylmethyl)amine and a base readily catalyses the intradiol dioxygenation of pyrocatechol in methanol, to primarily afford the half-methyl ester of muconic acid. Dimethyl adipate is obtained by the subsequent, one-step catalytic hydrogenation/esterification, thus providing a green route to this important nylon precursor.

Intradiol catechol dioxygenases are a class of non-heme iron enzymes that selectively cleave the C–C bond between the hydroxyl groups of a catecholic substrate using molecular oxygen and an Fe(III)-containing active site, to afford *cis*,*cis*-muconic acid.[1] Many synthetic non-heme iron(III) complexes have been studied as functional models of these enzymes, providing key insights into various mechanistic aspects of intradiol cleavage.[2] Almost invariably, these studies were concerned with stoichiometric reactions of the activated and readily cleaved substrate 3,5-di-*tert*-butylcatechol. In contrast, the stoichiometric conversion of the unactivated substrate pyrocatechol (**1**)[3] has received little attention and no prior examples of its catalytic cleavage have been reported. Selective catalytic catechol cleavage would nevertheless be advantageous, as hydrogenation[4] of the intradiol cleavage product, muconic acid (**3a**), can provide a greener route to adipic acid or its esters, which are key monomers, *e.g.*, for nylon-6,6.[5] Such a route would make use of non-toxic catalysts and oxidants, be highly atom-efficient and employ a renewable substrate, as catechol may be obtained sustainably from lignin[6] or by fermentation of glucose.[7]

Que *et al.* have reported the most active system for stoichiometric intradiol cleavage of 3,5-di-*tert*-butylcatechol reported to date, using the ligand tris(2-pyridylmethyl)amine (tpa).[8] We have found the catalytic intradiol dioxygenation of catechol to proceed readily with oxygen as the oxidant using 5 mol% of a non-heme iron(III) complex prepared *in situ* from iron(III) perchlorate, tpa and two equivalents of base (with respect to iron) (Scheme 1).

Reactions were performed for 6 h in methanol under controlled air flow, at ambient pressure and at 50 °C. The half-methyl ester of *cis*,*cis*-muconic acid (**3b**) was found to be the major product (Fig. 1), while minor products formed included the free acid (**3a**), half-catechol ester (**3c**) and *cis*,*trans* isomers of the above (**4a–c**), for a typical mole balance of 90%. Notably, all these products derive from the selective intradiol cleavage of catechol and may eventually be converted to dimethyl adipate (**2**) (*vide infra*). Products resulting from the extradiol cleavage of catechol were not observed. Solvolysis of the cyclic muconic anhydride, which is formed as the initial product of the dioxygenation reaction,[2] to obtain **3b** has been previously observed in methanol.[3a,9] Catechol itself is apparently also a competent nucleophile for ring opening of the anhydride. Although catechol esters have not been previously reported as products of intradiol cleavage reactions, the previously reported experiments typically used a stoichiometric amount of the catechol at only 0.5 mM,[8] whereas in the catalytic runs reported here a concentration of 100 mM is used. The *cis*,*trans* isomers are not expected to directly result from the oxidative cleavage cycle, but rather result from a subsequent isomerisation step, which may proceed readily in solution and exclusively affords the isomer where the ester is in the *trans* position.[10] The 10% of original catechol intake that cannot be accounted for is possibly lost to the uncatalysed oxidation of catechol to 1,2-benzoquinone and subsequent condensation with catechol.[11]

UV-Vis-NIR spectra of diluted reaction mixtures show characteristic LMCT bands at 518 nm and 812 nm, confirming that $[Fe(tpa)(catecholato)]^+$ complexes[2b,3c,12] are formed and remain present throughout the reaction. The reaction was found to initially proceed by approximately 0^{th} order kinetics in catechol, consistent with a mechanism where reaction of oxygen with the $[Fe(tpa)(catecholato)]^+$ complex is the rate-limiting step.[13]

Stoichiometric experiments have shown that addition of two equivalents of base relative to iron is required to deprotonate the catechol and form the $[Fe(tpa)(catecholato)]^+$ complex.[14] A systematic screening of bases showed that two equivalents were again found to be the optimum for the catalytic reaction (Table S1, ESI†). If more than two equivalents of base were used, UV-Vis-NIR spectra of these solutions initially showed a strong absorption at 565 nm, which may

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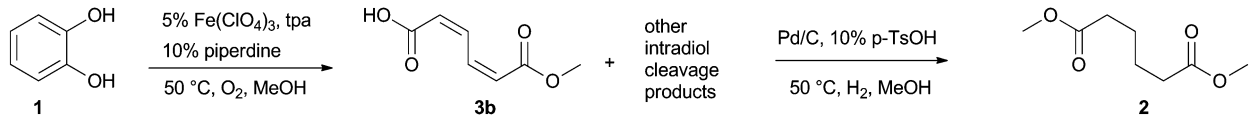

Scheme 1 The intradiol dioxygenation of catechol (**1**) in methanol exclusively affords intradiol cleavage products, which after hydrogenation/transesterification yield dimethyl adipate (**2**).

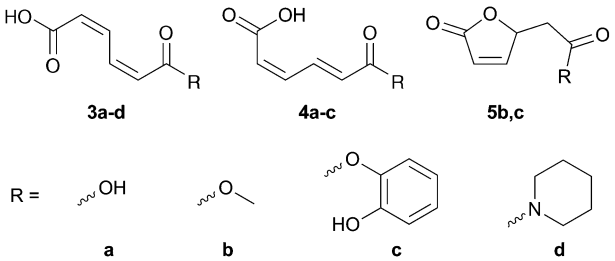

Fig. 1 Products observed in the catalytic dioxygenation of catechol are derivatives of *cis,cis*-muconic acid (**3**), *cis,trans*-muconic acid (**4**) and muconolactone (**5**) and include free acids (a), methyl esters (b), catechol esters (c) and a piperidyl amide (d).

suggest competitive coordination by the base. In addition, a new product, identified as the muconamide of piperidine (**3d**), was formed at higher base loadings.

Even though an acidic product is formed (pK_{a1} 3–4), the $[Fe(tpa)(catecholato)]^+$ complex remained present in the reaction mixture even after multiple turnovers. As muconic acid is certainly a sufficiently strong acid to protonate piperidine (pK_a 11.2), it seems likely that once all base has been protonated, muconate anions become the base that deprotonates the catechol, consistent with the remarkable stability of iron(III)-catecholato complexes.[15] This is further supported by the observation that the reaction still proceeded rapidly even when ammonium acetate is added as a base (Table 1, #2). Indeed, bases of different strengths (Table 1, #1–5) do not seem to significantly affect the activity. However, the use of diisopropylethylamine (DIPEA) or 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) resulted in formation of considerably more *cis*,*trans* isomers as well as two new products, which were identified as lactones of muconic acid (**5b**, **5c**). Both the isomerisation and lactonisation have previously been shown to be base-catalysed.[10c,16]

Lower catalyst loading resulted in higher turnover frequencies, although presumably this is because in those cases the 0th order approximation is more valid. Running the reaction for 24 h at a 1.5% mol Fe loading gives full conversion with a TON of 51. The use of ferric perchlorate or nitrate as the catalyst precursor expectedly gave similar results, as both salts have anions that are non-coordinating. Remarkably, even iron(III) acetylacetonate ($Fe(acac)_3$), despite its strongly bound acac anions, is able to form the catecholato complex and exhibit considerable activity (Table 1, #8), with no additional base needed to be added to this reaction. Several of the stoichiometric intradiol dioxygenation reactions of (substituted) catechols use iron(III) chloride as the iron source,[3a,b,17] but in our case low activity was observed with this precursor (Table 1, #7) with the UV-Vis spectra of this system pointing to rapid catalyst deactivation (Fig. S3, ESI†).

With the other iron precursors the LMCT bands of the $[Fe(tpa)(catecholato)]^+$ complex were present throughout the reaction, but their intensity did decrease as the reaction progressed. As catechol is still available in the reaction mixture, this points to a gradual deactivation of the catalyst. Remarkably, addition of fresh catechol again led to an increase in intensity of the LMCT bands. This shows that while some decomposition of the active complex does seem to take place during the reaction, it appears to be largely reversible. As differric μ-oxo, μ-carboxylato complexes have been isolated as the products of the reaction in stoichiometric experiments with 3,5-di-*tert*-butylcatechol,[8] a similar complex was considered as the deactivation product here. Indeed, stoichiometric cleavage of catechol with iron(III) perchlorate, tpa and piperidine resulted in the precipitation of a

Table 1 Results of the catalytic dioxygenation of catechol, using a catalyst system prepared *in situ* from tpa and the listed iron precursors and bases[a]

				Yield (%)							
	Precursor	Base	Conv.[b] (%)	**3a**	**3b**	**4a** + **4b**	**3c** + **4c**	**5b** + **5c**	MB[c] (%)	TON[d]	TOF[e] (h^{-1})
1	5% $Fe(ClO_4)_3$	Piperidine	92	5	48	2	13	—	88	16	2.7
2	5% $Fe(ClO_4)_3$	NH_4OAc	94	6	48	4	11	—	87	15	2.5
3	5% $Fe(ClO_4)_3$	2,6-Lutidine	90	6	49	4	10	—	88	16	2.7
4	5% $Fe(ClO_4)_3$	DIPEA[f]	86	4	35	8	9	3	81	14	2.4
5	5% $Fe(ClO_4)_3$	TBD[g]	88	4	40	7	12	2	90	16	2.6
6	5% $Fe(NO3)_3$	Piperidine	88	6	49	2	11	—	91	14	2.3
7	5% $FeCl_3$	Piperidine	30	2	12	—	2	—	92	4	0.7
8	5% $Fe(acac)_3$	—	73	4	21	15	5	8	84	11	1.8
9	2% $Fe(ClO_4)_3$	Piperidine	50	3	27	0	7	—	93	20	3.4
10	1.5% $Fe(ClO_4)_3$[h]	Piperidine	100	2	64	6	8	—	88	51	2.1
11	1% **12**[i]	Piperidine	56	4	31	1	7	—	93	19	3.2
12	1% μ-oxo[j]	Piperidine	51	4	30	1	5	—	94	18	2.9

[a] Conditions: 9.1 mmol catechol, 100 mL MeOH; iron precursor, tpa (1 eq.) and base (2 eq.); 6 h, 50 °C, air flow at 1 atm. [b] Conversion of catechol. [c] Mole balance as moles of C_6 units found divided by the starting amount of catechol. [d] Turnover number. [e] Turnover frequency. [f] Diisopropylethylamine. [g] 1,5,7-Triazabicyclo[4.4.0]dec-5-ene. [h] 24 h reaction. [i] Compound isolated from a stoichiometric reaction using $Fe(ClO_4)_3$, tpa (1 eq.) and base (2 eq.). [j] $[Fe_2(tpa)_2(\mu\text{-}O)(\mu\text{-}OAc)](ClO_4)_3{\cdot}2H_2O$.

Scheme 2 Reversible formation of the active [Fe(tpa)catecholato]$^+$ complex from a μ-oxo, μ-acetato dibridged ferric complex.

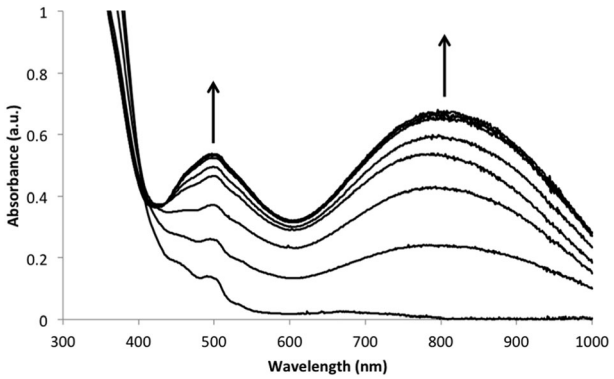

Fig. 2 Spectrophotometric titration of a 0.2 mM solution of **12** in the presence of 0.2 mM piperidine in CH_3CN with addition of 0.5 eq. of catechol in between spectra. The LMCT bands at 518 nm and 812 nm correspond to the formation of the [Fe(tpa)(catecholato)]$^+$ complex.

brown microcrystalline material from solution, which was identified as a differric μ-oxo, μ-carboxylato complex based on its UV-Vis-NIR, NMR and ATR-IR data.[18] The bridging carboxylato group is presumably provided by one of the muconate products formed. In order to investigate the formation of the active catecholato catalyst from μ-oxo, μ-carboxylato species (Scheme 2), which has previously been hypothesised,[19] $[Fe_2(tpa)_2(\mu\text{-}O)(\mu\text{-}OAc)](ClO_4)_3{\cdot}2H_2O$ (**12**) was prepared.

Spectrophotometric titration of **12** in acetonitrile with catechol (Fig. 2) clearly shows the appearance of the catecholato LMCT bands at the expense of the μ-carboxylato absorptions. Indeed, use of the differric μ-oxo, μ-carboxylato complexes as catalyst precursors resulted in a catechol dioxygenation reaction of similar activity and selectivity as with the *in situ* prepared catalysts (Table 1, #9, 11, 12). To our knowledge, this is the first time that the formation of a μ-oxo, μ-carboxylato complex is shown to be reversible under reaction conditions in iron oxidation catalysis.

The product mixture of esters, acids and geometrical isomers obtained after the catechol dioxygenation at first sight looks rather complex, but this complexity can be readily resolved without any required product separation steps by a simple hydrogenation/transesterification reaction. Indeed, the product mixture could be convergently converted to the single end product dimethyl adipate, also a monomer for nylon-6,6, by performing a transesterification of the product mixture simultaneously with hydrogenation. The isolated product mixture was hydrogenated over a Pd/C catalyst (1 atm H_2, 50 °C) in the presence of 10 mol% *p*-toluenesulfonic acid in methanol. Although the equilibrium position of adipic acid and its diester prohibits complete transesterification, dimethyl adipate was still isolated in 55% yield (based on original catechol intake). Most interestingly, isolation of the product mixture prior to hydrogenation/transesterification is not necessary, as the crude reaction mixture, *still containing the iron catalyst*, could be likewise converted to give dimethyl adipate in an isolated yield of 48%. These results show the excellent potential for the two-step synthesis of dimethyl adipate from catechol, a route that does not require any intermediate purification steps.

In conclusion, we have demonstrated the selective catalytic intradiol dioxygenation of catechol under mild conditions, using a catalyst prepared *in situ* from ferric perchlorate, tris(2-pyridylmethyl)-amine and base. The formation of μ-oxo, μ-carboxylato iron complexes was shown to be reversible under reaction conditions. Subsequent hydrogenation and esterification of the dioxygenation products using a Pd/C catalyst afforded pure dimethyl adipate in 55% isolated yield. Thus, we have demonstrated a potentially sustainable, new route towards synthesis of monomers for nylon-6,6. Further studies will be concerned with further improving the catalytic dioxygenation activity.

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