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The effect of adding Crabtree's catalyst to rhodium black in direct hydrogen isotope exchange reactions

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A new catalytic system based on rhodium black using Crabtree's catalyst as an additive for direct hydrogen isotope exchange in aromatic compounds has been investigated. The level of deuterium incorporation can be improved from for example 16 to 93%. The new catalyst mixture tolerates a variety of solvents.

Keywords: rhodium black; Crabtree's catalyst; deuterium; catalytic direct hydrogen isotope exchange

Introduction

Isotopically labelled compounds are important in the screening of pharmaceutical candidates in drug development programmes. Such compounds facilitate studies of pharmacokinetics and metabolism, as well as other important assays. Owing to an increased attention to speed for drug development and the quality of the drug candidate, isotopically labelled compounds have to be prepared, preferably in a fast and efficient way. The synthesis of labelled compounds can often be laborious and synthetically challenging. The use of catalysts for direct exchange of hydrogen isotopes can ameliorate some of these difficulties associated with the preparation of isotopically labelled compounds because no synthesis of appropriate precursor is required.

Recently, Alexakis *et al.*[1] reported the use of heterogeneous systems in THF as suitable catalysts for promoting hydrogen isotope exchange in pyridines and other nitrogen heteroaromatic compounds. These catalytic systems were based on group VIII metals such as rhodium or ruthenium, used as rhodium black, rhodium on alumina or ruthenium black.

Crabtree's catalyst, $[Ir(COD)(PCy_3)(Py)]PF_6$, is a homogeneous catalyst based on iridium, coordinated to pyridine and tricyclohexyl phosphine (Figure 1). Crabtree's catalyst is a well-established catalyst used for hydrogen isotope exchange reactions.[2–9] It is able to promote deuterium or tritium incorporation into arenes at positions *ortho* to a directing group such as the carbonyl group.[2–4, 6–9]

Here we report improvements that can be obtained by adding Crabtree's catalyst to rhodium black.

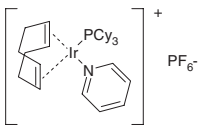

Figure 1. Crabtree's catalyst.

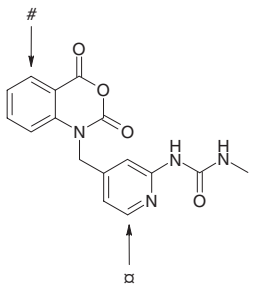

Figure 2. The structure of **1**. Marks indicate sites for anticipated deuteration using Crabtree's catalyst (♯) and Rhodium black (¤).

Results and discussion

As part of a medicinal chemistry programme we were interested in labelling compound **1**[10] with deuterium. Three experiments were set up, one using Crabtree's catalyst that was expected to promote H/D-exchange in the *ortho*-position to the carbonyl group, a second experiment using rhodium black that was anticipated to effect H/D-exchange in the *ortho*-position to the pyridine nitrogen (Figure 2) and finally a third experiment where a mixture of the two catalysts was used to potentially provide the dilabelled form of **1**. To our surprise there was little or no incorporation of deuterium using either Crabtree's catalyst (no incorporation) or rhodium black (16% incorporation *ortho* to pyridine nitrogen). However, using the mixture an incorporation

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level of 93% deuterium was observed in the position *ortho* to the nitrogen in the pyridine ring.

To further investigate this surprising observation a set of experiments were undertaken to test the generality of the catalyst mixture in comparison with the single catalysts. We investigated substrates that were electron rich, electron poor and sterically hindered pyridines (Table 1).

As shown in Table 1 (entries 2, 3, 4, 6, 7, 8 and 15), there is a clear trend towards greater incorporation of deuterium, although not all compounds show increased incorporation of deuterium using the catalyst mixture.

In the 2-substituted pyridines the most significant enhancement was observed using the mixture, except entry 1, where a lower incorporation in the 6-position is observed. In 2-phenyl-pyridine (entry 10) incorporation of deuterium in the 2- and 6- position of the phenyl group was also observed. The same deuteration pattern has earlier been reported using rhodium(III) hydride complexes but with lower level of deuterium incorporation (9%) in the pyridine ring.[11] Ellames *et al.*[12] has investigated the use of iridium based catalysts of the general form $[Ir(PR_3)_2(COD)]^+$ for their capability of promoting H/D isotope exchange. Using PCy_3 as ligand, which is the closest catalyst related to Crabtree's catalyst, they found no incorporation of deuterium into the phenyl group but a level of deuterium incorporation of 50% in the C6-position of the pyridine ring. Surprisingly we found no incorporation of deuterium into the pyridine ring using the iridium based Crabtree's Catalyst. No incorporation was observed in the substituent of 2-isopropyl-pyridine (entry 11), but in this compound attempted exchange with rhodium black alone gave a reaction mixture with no trace of starting material. The catalyst mixture, however, gave 80% deuterium incorporation. Whether deuterium was incorporated before or after degradation of 2-isopropyl-pyridine using rhodium black was not determined.

Using electron rich pyridines (entries 12 and 13) the effect of adding Crabtree's catalyst to rhodium black was less noticeable due to the high level of deuterium incorporation using rhodium black alone.

Concerning the electron poor pyridines, no enhanced effect was observed by adding Crabtree's catalyst to rhodium black. In some cases (entries 2 and 3) high levels of deuterium incorporation were resulting from using rhodium black alone; in other cases (entries 1 and 9) no significant enhancement was observed.

To investigate the scope, two aromatic non-pyridyl compounds, one benzene nucleus and one pyrimidine scaffold were tested. In agreement with the results reported by Ellames *et al.*[2] we found that aniline (entry 15) did not undergo exchange using Crabtree's catalyst. Using rhodium black we found it possible to obtain a level of deuterium incorporation of 51% and using the mixture a level of deuterium incorporation of 72% was obtained. Using Crabtree's catalyst or rhodium black, no incorporation of deuterium in 4-amino-pyrimidine-5-carboxylic acid (entry 14) was obtained. On the other hand using the mixture an incorporation of 60% deuterium was observed.

Sometimes, just an additive effect was observed using the catalyst mixture, but less than an additive effect was also observed (entry 1). The effect of the catalyst mixture cannot be predicted and must be determined by experiments. Most important, however, is the surprisingly positive outcome that sometimes can be found using the catalyst mixture, and substrates not able to undergo direct hydrogen isotope exchange using Crabtree's catalyst or rhodium black alone can be labelled using the catalyst mixture (entry 14).

We conclude that the mechanism of the mixture relates to rhodium black, because the enhanced level of incorporation in all cases are seen in the *ortho*-position to the pyridine nitrogen, the same position involved when rhodium black is used alone. The catalytic effect of rhodium black can be enhanced by adding Crabtree's catalyst, while there is no enhanced catalytic effect of Crabtree's catalyst when rhodium black is added. In two cases, only the mixture was able to promote hydrogen isotope exchange (entries 11 and 14), indicating that a new and more active catalytic system is at hand.

A hypothesis for the enhanced effect may involve a ligand transfer from Crabtree's catalyst to rhodium. To investigate this hypothesis, a set of experiments using **1** as model compound were undertaken, where one or more of the components of Crabtree's catalyst were added to rhodium black (Scheme 1 and Table 2).

It was possible to improve the catalytic effect of rhodium black (Table 2) (from 16% to 42% deuterium incorporation), but not to the same extent as adding Crabtree's catalyst (93% incorporation). The most effective additive was pyridine (entry 15); however, the addition of larger amounts of pyridine did not promote further deuterium incorporation (entries 16 and 17). To investigate whether the enhanced effect of pyridine was an additive effect to rhodium black, pyridine was tested in absence of catalyst, and, as expected, no incorporation could be detected (entries 18 and 19). This indicates that the enhanced catalytic exchange reaction takes place at the rhodium surface.

To test this hypothesis, an experiment was undertaken where Crabtree's catalyst and rhodium black were stirred under D_2-atmosphere for 4 h without **1** added. The heterogeneous catalytic mixture was then centrifuged and divided into solid and solution and each part was then added **1** and stirred under D_2-atmosphere for 4 h. The solid was able to promote an incorporation of 24% deuterium, while no incorporation of deuterium was observed in the solution, supporting that the catalytic exchange takes place exclusively on the rhodium surface and not in solution.

Table 3 shows the effect of adding increasing amounts of Crabtree's catalyst to rhodium black. Even a low amount (0.05 eq.) of Crabtree's catalyst was able to enhance the catalytic effect of rhodium black noticeable, enhancing the incorporation level from 16 to 32% (entry 3).

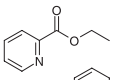
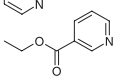
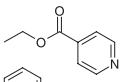
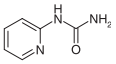
Table 4 shows the effect of varying reaction times, and a high level of deuterium incorporation can be seen after only 1.5 h, and after 3 h an incorporation level of 90% was observed, indicating a highly active catalytic system.

Table 5 shows the catalytic effect of different rhodium sources. All the tested sources of rhodium were able to promote catalytic hydrogen isotope exchange except non-amorphous rhodium, which was unable to promote exchange.

A batch variation of the different rhodium black sources was observed, noticeable when Crabtree's catalyst was added. Rhodium on different supports was quite active even without activation with Crabtree's catalyst. An explanation for the high catalytic activity could be that rhodium on support has a larger surface area than non-amorphous rhodium or even rhodium black.

To test the robustness of the catalytic mixture, experiments in different solvents were performed (Table 6). The catalytic system is more or less independent of the solvent, and acceptable to high incorporation levels were observed in all solvents except diethyl ether, which could be due to low solubility of **1**.

Table 1. Deuteration of substituted pyridines, pyrimidine and benzene using Crabtree's catalyst, rhodium black or the mixture

Entry	Substrate	Crabtree's catalyst[a]					Rhodium black[b]					Mixture[c]				
		2	3	4	5	6	2	3	4	5	6	2	3	4	5	6
% incorporation of deuterium in the given position																
1		—	0	0	0	0	—	28	9	0	55	—	25	16	0	28
2		0	—	0	0	0	23	—	0	0	96	41	—	0	0	96
3		0	0	—	0	0	98	12	—	12	98	98	24	—	24	98
4		—	0	0	0	24	—	0	0	0	67	—	0	0	0	87
5		0	—	0	0	0	93	—	0	0	95	94	—	0	0	93
6		—	23	—	0	31	—	0	—	0	73	—	11	—	0	95
7		—	0	—	0	13	—	0	—	0	69	—	0	—	0	95
8		—	25	—	18	87	—	0	—	0	64	—	25	—	25	96
9		0	0	—	0	0	28	0	—	0	28	29	0	—	0	29
10[d]		—	0	0	0	0	—	0	0	0	71	—	0	0	0	67
11		—	0	0	0	0	—	#[e]	#[e]	#[e]	#[e]	—	0	0	0	80
12		—	0	0	0	0	—	0	44	0	81	—	0	21	0	85
13		0	—	0	0	0	97	—	0	0	97	97	—	0	0	97
14		0	—	—	—	0	0	—	—	—	0	60[f]	—	—	—	0
15		0	0	0	0	0	25	0	0	0	25	36	0	0	0	36

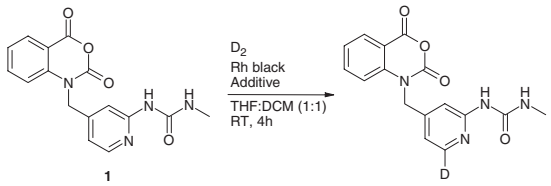
[a]Experimental conditions: Substrate (0.016 mmol), Crabtree's catalyst (0.008 mmol), dry DCM (3 mL), D_2 (1342–1590 mbar), RT, 4 h.
[b]Experimental conditions: Substrate (0.016 mmol), Rh black (0.010 mmol), dry THF (3 mL), D_2 (1342–1590 mbar), RT, 4 h.
[c]Experimental conditions: Substrate (0.016 mmol), Crabtree's catalyst (0.008 mmol), Rh black (0.010 mmol), dry DCM:THF (1:1)(3 mL), D_2 (1342–1590 mbar), RT, 4 h.
[d]Incorporation of D in the Ph-ring in the 2- and 6-position (Crabtree's catalyst: 88%; Rhodium black: 32%; Mixture: 75%)
[e]No trace of starting material. Experiment repeated twice with the same outcome.
[f]Experiment repeated three times.

Consequently, the high solvent tolerance expands the scope and usefulness for the catalyst mixture, allowing a variety of compounds to be labelled.

Experimental

General

All reactions were performed in a stainless steel manifold purchased from RC Tritec, Teufen, Switzerland. D_2 (99.8 at% D) was purchased from Isotec. Anhydrous solvents were dried over molecular sieves (4 Å). All other solvents and reagents were used as received, purchased from Sigma-Aldrich, ABCR, Fluka, Alfa Aesar and Acros. ^1H and ^{13}C NMR spectra were obtained on a Bruker AV600 spectrometer with a 5 mm TCI-Cryoprobe or a Bruker DRX500 spectrometer with a 5 mm PAPPI-probe. The deuterium content was measured on the basis of integration. Chemical shifts are reported in ppm with tetramethylsilane (TMS, $\delta = 0.00$) as internal reference.



Scheme 1. Setup to investigate a possible ligand transfer.

Table 2. Deuteration of **1** using different catalyst components

Entry	Ir	Ir(COD)Cl	Rh(COD)Cl	PCy_3	Py	%D
1	0.5					16
2	0.5			0.5		35
3	0.5				0.5	26
4	0.5			0.5	0.5	27
5		0.5				0
6		0.5		0.5		20
7		0.5		0.5	0.5	16[a]
8		0.5			0.5	13
9			0.6			11
10			0.6	0.5		17
11			0.6		0.5	34
12			0.6	0.5	0.5	26
13				0.5	0.5	27[b]
14				0.5		23[b]
15					0.5	42
16					1	35[b]
17					10	25[c]
18[d]					0.5	0
19[d]					1	0

[a]No deuteration is also observed if 0.5 eq. NH_4PF_6 is added.
[b]Same incorporation level observed if 0.5 eq. COD is added.
[c]Unknown impurity formed.
[d]No rhodium black added. Experimental conditions: **1** (0.016 mmol), Rh black (0.010 mmol), catalyst component/components, dry THF:DCM (1:1)(3 mL), D_2 (1457–1639 mbar), RT, 4 h. Numbers in table are numbers of equivalents added.

General procedure for deuterium exchange reaction

Catalyst was weighed into an 8 mL round bottom reaction flask containing a new teflon coated stir bar (3 × 10 mm), substrate (0.016 mmol) was dissolved in dry solvent (3 mL) and added. The reaction mixture was frozen in liquid N_2 and evacuated (below 3.5×10^{-3} mbar), thawed and then stirred under D_2-atmosphere (1340–1666 mbar) for 4 h at RT. The reaction mixture was filtered through a syringe-filter (Whatman, 0.45 μm) and concentrated *in vacuo*.

NMR-data for non-deuterated compounds

Entry numbers refer to Table 1.

Compound **1**

^{1}H NMR (500 MHz, DMSO-d_6)δ 8.12 (d, J = 5.3 Hz, 1H, Py-C6-H), 8.07 (dd, J = 1.5 and 7.8 Hz, 1H, Ph-C3-H), 7.85–7.68 (m, 1H, Ph-C5-H), 7.35 (t, J = 7.5 Hz, 1H, Ph-C4-H), 7.26 (s, 1H, Py-C3-H), 7.20 (d, J = 8.4 Hz, 1H, Ph-C6-H), 6.96 (dd, J = 1.3 and 5.3 Hz, 1H, Py-C5-H), 5.28 (s, 2H, CH_2), 2.71 (d, J = 4.6 Hz, 3H, urea-CH_3).

Table 3. Incorporation of deuterium using different amounts of Crabtree's catalyst

Entry	Rhodium black	Crabtree's catalyst	%D
1	0.6	0	16
2	0.6	0.02	16
3	0.6	0.05	32
4	0.6	0.1	46
5	0.6	0.5	93

Experimental conditions: **1** (0.016 mmol), Rh black (0.010 mmol), Crabtree's catalyst, dry THF:DCM (1:1)(3 mL), D_2 (1463–1575 mbar), RT, 4 h. Numbers in table are numbers of equivalents added.

Table 4. Incorporation of deuterium observed as a function of time

Entry	Crabtree's catalyst	Reaction time	%D
1	0	2 h	4
2	0.5	1.5 h	69
3	0.5	2 h	84
4	0.5	3 h	90

Conditions: **1** (0.016 mmol), Rh black (0.010 mmol), Crabtree's catalyst, dry THF:DCM (1:1)(3 mL), D_2 (1340–1410 mbar) for the given time at RT. Numbers in table are numbers of equivalents added.

Entry 1

^{1}H NMR (500 MHz, $CDCl_3$)δ 8.79–8.74 (m, 1H, C6-H), 8.14 (d, J = 7.8 Hz, 1H, C3-H), 7.85 (td, J = 1.7 and 7.7 Hz, 1H, C4-H), 7.48 (ddd, J = 1.0, 4.7 and 7.6 Hz, 1H, C5-H), 4.49 (q, J = 7.2 Hz, 2H, O$\underline{CH_2}CH_3$), 1.45 (t, J = 7.1 Hz, 3H, OCH$_2\underline{CH_3}$).

Entry 2

^{1}H NMR (500 MHz, DMSO-d_6)δ 9.14–9.07 (dd, J = 0.6 and 2.0 Hz, 1H, C2-H), 8.83 (dd, J = 1.7 and 4.8 Hz, 1H, C6-H), 8.30 (dt, J = 2.0 and 8.0 Hz, 1HC4-H), 7.58 (ddd, J = 0.6, 4.8 and 8.0 Hz, 1H, C3-H), 4.37 (q, J = 7.1 Hz, 2H, O$\underline{CH_2}CH_3$), 1.35 (t, J = 7.1 Hz, 3H, OCH$_2\underline{CH_3}$).

Entry 3

^{1}H NMR (600 MHz, DMSO-d_6)δ 8.89–8.78 (m, 2H, C2,6-H), 7.90–7.80 (m, 2H, C3,5-H), 4.45–4.34 (m, 2H, O$\underline{CH_2}CH_3$), 1.37 (dd, J = 5.1 and 12.7 Hz, 3H, OCH$_2\underline{CH_3}$).

Entry 4

^{1}H NMR (500 MHz, DMSO-d_6)δ 8.49–8.41 (m, 1H, C6-H), 7.89 (td, J = 2.0 and 7.7 Hz, 1H, C4-H), 7.53 (dd, J = 0.7 and 8.1 Hz, 1H, C3-H), 7.44 (ddd, J = 0.9, 4.9 and 7.2 Hz, 1H, C5-H).

Entry 5

^{1}H NMR (500 MHz, DMSO-d_6)δ 8.64 (d, J = 2.6 Hz, 1H, C2-H), 8.56 (dd, J = 1.2 and 4.7 Hz, 1H, C6-H), 7.94 (ddd, J = 1.5, 2.5 and 8.2 Hz, 1H, C4-H), 7.47 (dd, J = 4.8 and 8.3 Hz, 1H, C5-H).

Entry 6

^{1}H NMR (500 MHz, DMSO-d_6)δ 8.43 (d, J = 5.5 Hz, 1H, C1-H), 7.86–7.74 (m, 1H, C5-H), 7.67–7.56 (m, 1H, C4-H).

Entry 7

^{1}H NMR (500 MHz, DMSO-d_6)δ 8.27 (d, J = 5.1 Hz, 1H, C6-H), 7.37–7.35 (m, 1H, C3-H), 7.27–7.23 (m, 1H, C5-H), 2.34 (s, 3H, CH_3).

Table 5. Incorporation of deuterium observed using different rhodium sources

Entry	Rhodium source	%D	+0.5 eq. Crabtree's catalyst, %D
1	Rh black (Alfa Aesar)	19	93
2	Rh black (ABCR)	16	50–57
3	Rh black (Aldrich)	16	91
4	Rh (Acros)	0	0
5	Rh (Fluka)	0	0
6	5wt% Rh/act. alumina[a]	75–92	90
7	5wt% Rh/alumina[a]	71	93
8	5wt% Rh/carbon[a]	88	85

[a]Added amount correlates to 0.6 eq. rhodium. Experimental conditions: **1** (0.016 mmol), catalyst/catalysts, dry THF:DCM (1:1)(3 mL), D_2 (1550–1665 mbar), RT, 4 h.

Table 6. Incorporation of deuterium observed in different solvents

		% incorporation of deuterium	
Entry	Solvent	No additive	+0.5 e.q Crabtree's catalyst
1	Et_2O		0[a]
2	EtOAc		84
3	DCM		60
4	THF		89
5	THF:DCM (1:1)	16[b]	90–93[c]

[a]**1** is slightly soluble in Et_2O.
[b]Experiment performed in THF-d_8:DCM-d_2 show a similar incorporation level (12%).
[c]Experiment performed in THF-d_8:DCM-d_2 show a slightly decreased incorporation level (68%). Experimental conditions: **1** (0.016 mmol), catalyst/catalysts, dry THF:DCM (1:1)(3 mL), D_2 (1418–1666 mbar), RT, 4 h.

Entry 8
^{1}H NMR (500 MHz, DMSO-d_6)δ 8.64 (d, J = 5.0 Hz, 1H, C6-H), 7.88 (d, J = 1.0 Hz, 1H, C2-H), 7.85 (dd, J = 1.2 and 3.5 Hz, 1H, C5-H), 3.91 (s, 3H, OCH_3).

Entry 9
^{1}H NMR (500 MHz, DMSO-d_6)δ 8.85 (dd, J = 1.6 and 4.4 Hz, 2H, C2,6-H), 7.87 (dd, J = 1.7 and 4.4 Hz, 2H, C3,5-H).

Entry 10
^{1}H NMR (600 MHz, DMSO-d_6)δ 8.69 (ddd, J = 1.0, 1.8 and 4.8 Hz, 1H, C6-H), 8.10 (dt, J = 1.8 and 3.2 Hz, 2H, Ph-C2,6-H), 7.97 (dt, J = 1.0 and 8.0 Hz, 1H, C4-H), 7.89 (td, J = 1.8 and 7.8 Hz, 1H, C3-H), 7.54–7.48 (m, 2H, Ph-C3,5-H), 7.47–7.42 (m, 1H, Ph-C4-H), 7.36 (ddd, J = 1.1, 4.8 and 7.4 Hz, 1H, C5-H).

Entry 11
^{1}H NMR (500 MHz, DMSO-d_6)δ 8.49 (dd, J = 0.8 and 4.8 Hz, 1H, C6-H), 7.69 (td, J = 1.9 and 7.7 Hz, 1H, C4-H), 7.25 (t, J = 7.8 Hz, 1H, C5-H), 7.18 (ddd, J = 1.1, 4.8 and 7.4 Hz, 1H, C3-H), 3.01 (hept, J = 6.9 Hz, 1H, *i*-Pr-CH), 1.23 (d, J = 6.9 Hz, 6H, *i*-Pr-CH_3).

Entry 12
^{1}H NMR (500 MHz, MeOD)δ 8.19 (s, 1H, C6-H), 7.66 (d, J = 7.2 Hz, 1H, C4-H), 7.10 (d, J = 8.4 Hz, 1H, C3-H), 6.99–6.92 (m, 1H, C5-H).

Entry 13
^{1}H NMR (500 MHz, DMSO-d_6)δ 8.31 (d, J = 2.9 Hz, 1H, C3-H), 8.18 (dd, J = 1.3 and 4.5 Hz, 1H, C6-H), 7.38 (ddd, J = 1.2, 2.2 and 4.0 Hz, 1H, C5-H), 7.34 (dd, J = 4.6 and 8.5 Hz, 1H, C4-H), 3.83 (s, 3H, OCH_3).

Entry 14
^{1}H NMR (600 MHz, DMSO-d_6)δ 8.70 (s, 1H, C2-H), 8.51 (s, 1H, C4-H).

Entry 15
^{1}H NMR (600 MHz, DMSO-d_6)δ 7.04–6.94 (m, 2H, C3,5-H), 6.55 (dd, J = 5.5 and 13.1 Hz, 2H, C2,6-H), 6.48 (t, J = 7.3 Hz, 1H, C4-H), 4.98 (s, 2H, NH_2).

Conclusion

A new catalytic system based on rhodium black with Crabtree's catalyst as an additive has been investigated. In general, the mixture has an improved activity, compared with rhodium black alone. In two cases neither Crabtree's catalyst nor rhodium black was able to promote exchange, but using the mixture an incorporation of deuterium was observed. The new catalytic system is active in a variety of solvents, extending the usefulness. This protocol will, of course, also be useful when tritiated compounds are needed. The scope of this new catalytic system is currently being investigated further in our laboratories.

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