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Parallel chemistry investigations of *ortho*-directed hydrogen isotope exchange between substituted aromatics and isotopic water: novel catalysis by cyclooctadienyliridium(I)pentan-1,3-dionates

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Abstract

Novel iridium-based catalysts which promote *ortho*-directed hydrogen isotope exchange between substituted aromatics and isotopic water have been identified via a combination of screening and subsequent ligand optimisation. The catalysts are more active, operate at lower temperature and are applicable to a wider variety of substrates than previously known systems.

Keywords: iridium catalysts; complexes; exchange; deuterium; labelling; metalation; diones.

Compounds labelled with tritium and deuterium are fundamental research tools for the pharmaceutical industry. Consequently a range of methodologies have been developed for labelling organic substrates with these isotopes. Amongst the most powerful of these approaches is *ortho*-directed hydrogen isotope exchange. In this approach, substituted aromatics are induced to undergo isotopic exchange in positions *ortho* to a directing substituent under the influence of a transition metal catalyst. The isotope donor can be either isotopic hydrogen gas[1,2] or isotopic water.[3]

Recently, we initiated a parallel chemistry programme to discover improved catalysts for the latter process. The discovery and optimisation of suitable catalysts by rational solid phase combinatorial techniques[4] still awaits technological developments. Hence we resorted to screening of a wide range of salts and complexes of transition metals for the ability to promote isotopic exchange between deuterium oxide and a selection of model substrates (Fig. 1).

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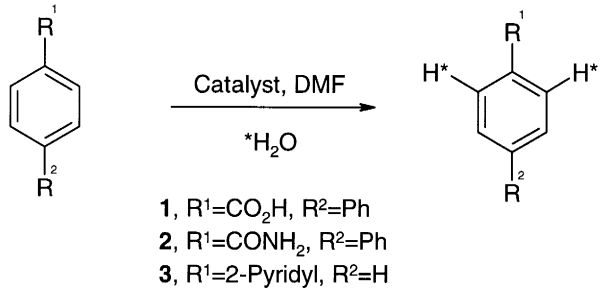

Fig. 1.

The substrates were selected to contain known *ortho*-directing groups, to yield unambiguous HPLC/MS pseudomolecular ions, well-resolved from solvent related peaks, and to possess simple NMR spectra.

The initial screen showed catalytic activity to reside exclusively with the Group VIII metals. Moreover, it was most evident for salts and complexes of Ru, Rh and Ir. Subsequent iterative screening of an increased range of complexes of these latter metals[5] eventually identified CODIrAcac as the compound displaying the best catalytic activity. This compound therefore provided a starting point for further optimisation of activity by variations in the ligand structure.

The dionate ligand was selected as the ligand for optimisation in preference to the more labile cyclooctadiene group. Catalysts were therefore prepared from a range of commercial and freshly synthesised dionates[6–8] via a previously described approach.[9]

The Table 1 shows the result of changing the terminal and central substituents on the dionate ligand. Notable improvements in activity were seen for the fluorinated pentanedionates and for all dionates bearing a 3-substituent.

Table 1
Comparision of active catalysts using the three model substrates

Dionate ligand $R^1.CO.CH(R^3).CO.R^2$			Atom% D Substrate No.					
R^1	R^2	R^3	1		2		3	
Me	Me	H	68	*27*	34	*14*	44	*18*
$C(Me)_3$	$C(Me)_3$	H	65	*32*	23	*11*	26	*12*
CF_3	CF_3	H	66	*34*	41	*21*	93	*47*
CF_3	CF_3	F	57	*30*	29	*15*	91	*48*
CF_3	Me	H	58	*26*	24	*11*	94	*42*
Ph	Ph	H	28	*14*	5	*3*	20	*10*
4-NO_2-Ph	Me	H	12	*7*	3	*2*	5	*3*
Me	Me	Me	95	*39*	90	*37*	84	*35*
Me	Me	Et	94	*40*	89	*38*	71	*30*
Me	Me	1-Pr	93	*41*	89	*39*	76	*34*
Me	Me	2-Pr	95	*42*	92	*41*	56	*25*
Me	Me	1-Bu	93	*42*	89	*41*	70	*32*
Me	Me	CH_2Ph	92	*45*	84	*41*	49	*24*
Me	Me	Ph	91	*43*	70	*33*	76	*36*

Conditions:substrate (5mg) / catalyst (1mg) / DMF (400μl) / D20 (200μl) / 75°C / 1hr.

*Calculated for two exchangeable positions/molecule (values in italics are per μmol of catalyst employed).

The resulting novel catalysts promote deuteriation at rates which allow complete *ortho*-deuteriation in as little as 1 h at 60°C, whilst labelling under even milder conditions is possible at room temperature over several days. In addition *ortho*-deuteriation is now possible for substituents which previously did not function, or functioned only weakly, as directors in the original $RhCl_3$/deuterium oxide system,[10] including primary sulphonamides and indoles.

To demonstrate the simplicity and efficacy of the method a large scale deuteriation of a typical substrate was carried out using a commercially-available catalyst of intermediate activity. Thus, 4-phenylbenzoic acid (**1**, 100 mg) was heated with cyclooctadienyliridium(I)pentan-1,3-dionate (20 mg) in a mixture of DMF (6.6 ml) and deuterium oxide (3.3 ml) at 90°C for 2 h. The resulting solution was cooled, partitioned between ethyl acetate (30 ml) and 5% w/v aqueous sodium hydrogen carbonate solution (10 ml). The aqueous layer was separated, acidified with dilute hydrochloric acid to pH <3, and the precipitated product re-extracted into ethyl acetate (10 ml). After removal of the solvent under reduced pressure, crystallisation of the resulting solid from hot methanol (2.0 ml) yielded 75 mg (74%) of [2,6-$^2H_2$]4-phenylbenzoic acid (m.p. 223–225°C). The ^2H NMR (61.4 MHz in [$^1H_6$]DMSO) showed a single resonance at 8.1 ppm (2,6-positions) with no other resonances detectable. The atom% deuterium by MS was 97%, calculated for the two exchangeable positions.

The high *ortho*-regiospecificity of the isotope incorporation demonstrated above was also observed for the other substrates studied. Such specific *ortho*-directed labelling is expected for a mechanism involving a cyclic *ortho*-metallated intermediate. Many examples of such *ortho*-metallation, mostly involving the formation of five-membered metallocycles, are known for iridium. Moreover, the ease with which late-series transition metals undergo oxidative–addition reactions, together with their tendency to form stable hydrides, even in aqueous systems, could help to explain the catalytic activity observed.

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5. Typical screening procedure.The potential catalysts to be screened (2 mg of each) were dispensed into deep-well reaction boxes each holding 96 polypropylene tubes and then the appropriate substrate (5 mg/tube) dissolved in DMF (400 µl/tube) and deuterium oxide (200 µl/tube) was added. The tubes were then sealed and heated at the appropriate temperature (95°C in the initial screens, 50°C for the more active catalysts prepared later in the programme). After an appropriate time (18 h in the initial screens, 1 h later in the programme) 20 µl aliquots from each the wells were taken, diluted 10-fold with 1:1 DMSO/H_2O and analysed by HPLC/MS (5 micron C_8 silica stationary phase using acetonitrile/aqueous ammonium acetate gradients with positive and negative ion modes) to determine the degree of deuteriation achieved. Later in the programme the *ortho*-regioselectivity of the labelling was confirmed, for the active catalysts, using automated multi-sample NMR techniques.
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