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A concise synthesis of chiral indanes as α_{1A} adrenoceptor partial agonists

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ABSTRACT

The synthesis of a series of chiral indanes with reported α_{1A} partial agonist activity is outlined, applying a rhodium catalysed cyclisation for template construction. This method was extended to the asymmetric synthesis of lead compound PF-03774076 (**1**) which was prepared on >20 g scale in seven steps. Highlights include Rh-mediated cyclocarbonylation and an asymmetric alkene hydrogenation.

Introduction

A series of chiral substituted indanes were previously disclosed as CNS penetrant selective partial α_{1A} adrenoreceptor agonists. This work culminated in the identification of lead candidate compound PF-03774076 (**1**) (Fig. 1).[1–5]

Previous synthetic methods to access similar indane templates had focused on either heating a phenylpropionic acid with polyphosphoric acid (PPA) or Friedel Crafts cyclisation of the corresponding acid chloride under treatment with aluminium trichloride to form the indanone (Scheme 1).[1–3,6]

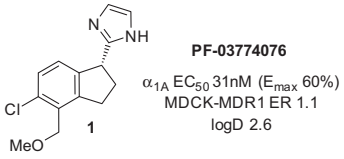
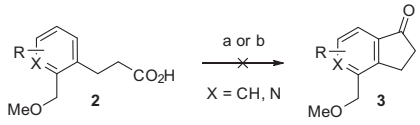


Figure 1. Indane series α_{1A} partial agonist lead.



Scheme 1. Reagents and conditions: (a) PPA, reflux; or (b)(i) $(COCl)_2$, CH_2Cl_2, cat. DMF, 0 °C to rt; (ii) $AlCl_3$, rt.

However these methods did not work well for analogues containing a pendant 4-methoxymethylene substituent **2** as this was unstable under the strongly acidic conditions. As a late stage introduction of the methoxymethyl group would add numerous further synthetic steps, an alternative synthesis of the indane ring **3** was sought.[7]

Results and discussion

Herein, we report a concise and scalable synthesis of these indane compounds based around a rhodium catalysed carbonylative cyclisation with aromatic C–H insertion. This key step

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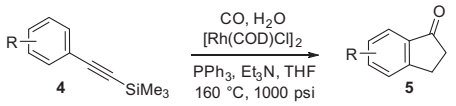
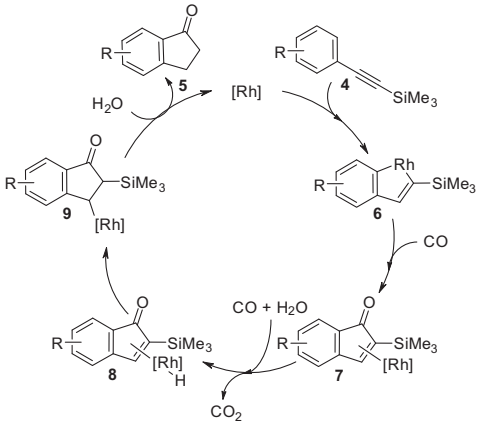
0040-4039/

comprises the reaction of a trimethylsilyl phenylacetylene **4** with rhodium cyclooctadiene as catalyst (1 mol %) and triphenylphosphine (20 mol %) under a 1000 psi CO atmosphere at 160 °C for 4 h to form the corresponding indanone **5**. An amine base promoter (Et_3N) and water co-solvent were both required for successful reaction (Scheme 2).



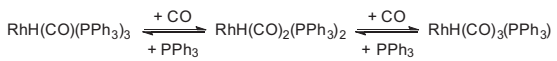
Scheme 2. Rhodium catalysed carbonylative cyclisation.

This rhodium catalysed reaction was first reported by Takeuchi, building on earlier work by Takahashi.[8–14] The mechanism postulated by Takeuchi in which co-ordination of rhodium to the acetylene **4** induces oxidative addition to the neighbouring aromatic C–H bond was also corroborated by experimental observations. This results in the formation of complex **6** after initial intramolecular insertion of the coordinated acetylene into the Rh–H bond followed by isomerisation. Insertion of CO results in the assembly of the indenone skeleton **7**. Association of hydrogen derived from water and CO via the water gas shift reaction gives complex **8** leading in turn to reduction of the indenone to yield **9**. After 1,3-rearrangement of the silyl group, hydrolysis affords the desired indanone **5**, releasing the catalytic Rh (Scheme 3).



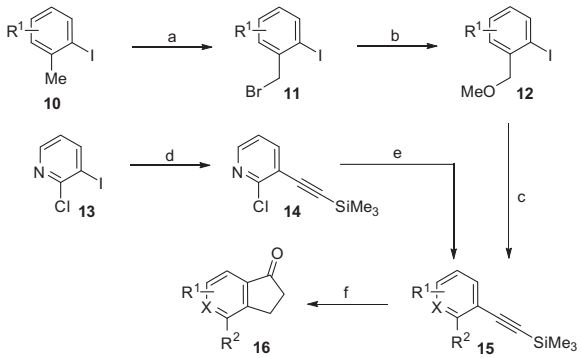
Scheme 3. Proposed catalytic cycle for the Rh-catalysed cyclisation.

A high loading of triphenylphosphine proved essential for successful reaction. It is believed that this likely pushes the catalyst equilibrium to the more reactive rhodium species, which is highly coordinated to triphenylphosphine, as previously demonstrated by Wilkinson's work on hydroformylations (Scheme 4).[15]



Scheme 4. Catalyst equilibrium with triphenylphosphine.

In order to apply this cyclisation to the desired 4-methoxymethylene substituted indanes, the necessary acetylene systems were prepared from commercially available iodotoluenes **10** (Scheme 5).



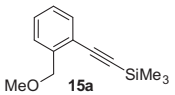
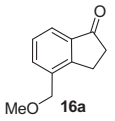
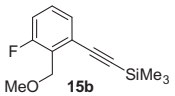
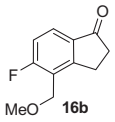
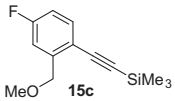
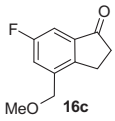
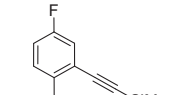
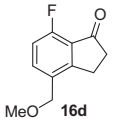
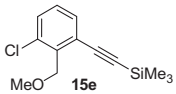
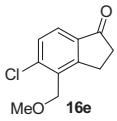
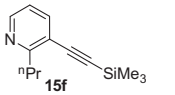
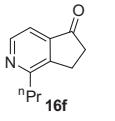
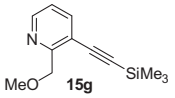
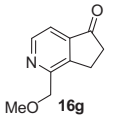
Scheme 5. Reagents and conditions: (a) NBS, CCl_4, $(PhCO_2)_2$, reflux; (b) Na, MeOH, reflux, 30 min; (c) TMS-acetylene, $Pd(PPh_3)_2Cl_2$ (1 mol %), CuI (2.5 mol %), Et_3N, DMF, rt, 16 h; (d) TMS-acetylene, $Pd(PPh_3)_2Cl_2$ (1 mol %), CuI (2.5 mol %), Et_3N, DMF, rt, 16 h; (e) $Fe(acac)_2$ (0.1 equiv), ^nPrMgCl (2.4 equiv), NMP, THF, rt; (f) $[Rh(COD)Cl]_2$ (1 mol %), PPh_3 (20 mol %), Et_3N, water (10 equiv), THF, 160 °C, >1000 psi CO, 12 h. See Table 1 for yields.

Iodotoluenes **10** were converted to the corresponding benzylbromides **11** via reaction with NBS in refluxing carbon tetrachloride. Freshly prepared sodium methoxide was then used to install the requisite methoxymethyl substituent **12**. Sonogashira reaction of the aryl iodide with TMS-acetylene subsequently provided the desired alkyne precursors **15a–e** for cyclisation. Alternatively, an aza analogue could be prepared from iodopyridine **13** via Sonogashira coupling, followed by an iron catalysed coupling of the resulting chloropyridine **14** with *n*-propyl Grignard to provide the corresponding alkyne **15f**.[16] Considering the cyclisation to the indanone, there was concern that the heteroatoms of the methoxy or pyridine groups in the substrates may competitively chelate with the catalyst to either reduce reactivity or direct the regioselectivity of the formylation to an undesired position on the aromatic ring. However, when the acetylenes were reacted under carbonylative conditions, all the desired indanones **16** were formed cleanly in moderate to good yields with some unreacted starting material remaining. Increasing the reaction time and temperature had little effect on the reaction conversion and yield. However, it was noted that if the CO pressure dropped below 1000 psi then the yields dropped considerably. A number of related indanones **16**, including challenging aza-indanone variants (Table 1), were synthesised via this general procedure. Interestingly, comparing yields for fluorinated examples (Table 1, entries 2–4) it was apparent that the lowest yield resulted for the cyclisation of **15d** despite all three substrates being electronically similar. In theory this could be accounted for by the fluorine substituent in **15d** being *ortho* to the C–H bond undergoing insertion, thereby providing an opportunity for fluorine to coordinate to the intermediate rhodacycle, impairing carbonylation. Similarly, the lower yields observed for the pyridine examples (Table 1, entries 6 and 7) could potentially be due to coordination of rhodium to the pyridine nitrogen, thereby impairing reactivity.

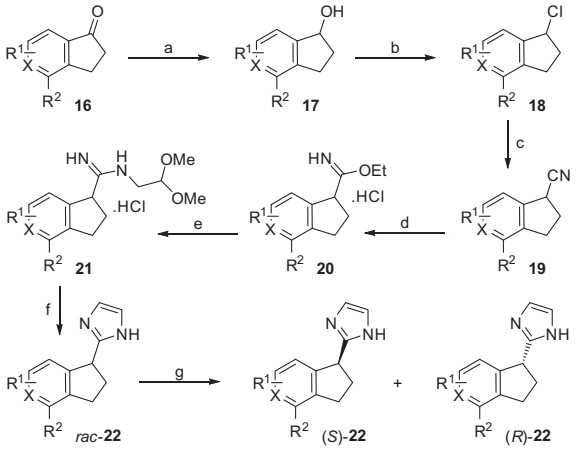
Indanones **16a–f** were subsequently converted into the corresponding chiral imidazole-products **22a–f** in order to enable the structure activity relationship for indane ring substitution to be investigated for α_{1A} agonist potency (Scheme 6).

In order to achieve this, a six-step route was developed whereby the indanones **16** were reduced to racemic alcohols **17** using sodium borohydride, converted to the corresponding chlorides **18** via treatment with thionyl chloride before reacting with sodium cyanide to provide the respective nitriles **19**. Conversion of the nitriles to carbimidates **20** then amidines **21** enabled the requisite imidazole rings to be constructed. The racemic products

Table 1

Entry	Acetylene intermediate	Yield[a] (%)	Indanone product	Yield (%)
1	 **15a**	94	 **16a**	57
2	 **15b**	60	 **16b**	70
3	 **15c**	52	 **16c**	52
4	 **15d**	46	 **16d**	34
5	 **15e**	63	 **16e**	60
6	 **15f**	30[b]	 **16f**	28
7	 **15g**	81[b]	 **16g**	20

[a] Yield over 3-steps.
[b] Yield over 2-steps (see Scheme 5 for details).

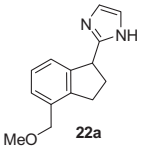
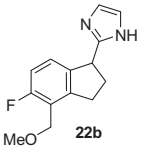
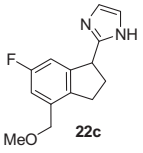
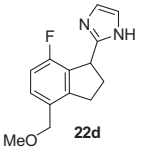
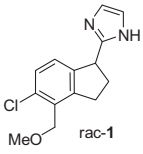
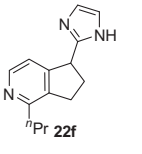


Scheme 6. Reagents and conditions: (a) $NaBH_4$, EtOH, rt, 3 h; (b) $SOCl_2$, CH_2Cl_2, rt, 1 h; (c) NaCN, DMSO, rt, 12 h; (d) HCl, EtOH, 0 °C, 12 h; (e) 2,2-dimethoxyethan-1-amine, MeOH, rt, 2 h; (f) 4 M HCl, dioxane, reflux, 1 h; (g) chiral HPLC.

could then be separated into individual enantiomers by chiral preparative HPLC.

Although this route enabled the delivery of the desired target compounds, this procedure involved many steps and generally resulted in low overall yields of products (Table 2). All final compounds were assessed in vitro for their functional agonist activity

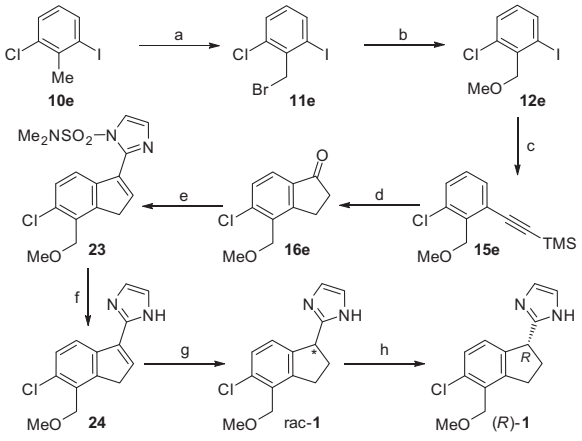
Table 2

Product	Yield[a] (%)	α_{1A} EC_{50} (E_{max})[b]	Product	Yield[a] (%)	α_{1A} EC_{50} (E_{max})[b]
 **22a**	8	37 nM (69%) [n = 15]	 **22b**	17	62 nM (59%) [n = 8]
 **22c**	23	59 nM (87%) [n = 4]	 **22d**	5	658 nM (49%) [n = 7]
 rac-**1**	14	31 nM (60%) [n = 8]	 **22f**	8	2930 nM (43%) [n = 4]

[a] Yield over 6-steps to racemic product.
[b] EC_{50} and E_{max} determined in vitro by measuring calcium mobilisation in a FLIPR assay configuration; data shown for most potent enantiomer following chiral HPLC separation.[1,17]

at human α_{1A} receptors (Table 2).[1] On balance of the in vitro EC_{50} functional potency and partial E_{max}, compound **1** was selected as the optimal lead.[4]

Once it had been established that compound **1** had a suitable profile for further project studies, it was deemed necessary to synthesise multi-gram quantities of this compound.[4] However, despite the route outlined (Scheme 6) being suitable for small scale analogue synthesis, this route was less attractive for larger scale compound provision. Overall this route to synthesise compound **1** was low yielding (10-steps, 5% yield) and required preparative chromatography after each step. As a result, a shorter improved sequence was developed to support larger scale provision of lead compound **1** by introduction of the imidazole via a Negishi cross-coupling as opposed to ring construction (Scheme 7).



Scheme 7. Reagents and conditions: (a) NBS, 1,1′-azobiscyclohexanecarbonitrile (VAZO-88), MeCN, 80 °C, 16 h, 79%; (b) Na, MeOH, 65 °C, 30 min, 100%; (c) TMS-acetylene, $Pd(PPh_3)_2Cl_2$ (1 mol %), CuI (2.5 mol %), Et_3N, DMF, rt, 16 h, 100%; (d) $[Rh(cod)Cl]_2$ (1 mol %), PPh_3 (40 mol %), Et_3N, water (10 equiv), THF, 160 °C, >1000 psi CO, 12 h, 42%; (e) (i) Tf_2O, 2,6-di-*t*-butyl-4-methylpyridine, CH_2Cl_2, 0 °C, 30 min, (ii) sulfamoyl protected imidazole, *n*BuLi, $ZnCl_2$ (3 equiv), THF, −40 °C to rt, 2 h, (iii) Pd $(PPh_3)_4$ (8 mol %), 60 °C, 2 h, 77%; (f) HCl (2 equiv), EtOH, 55 °C, 1 h, 81%; (g) Pd/C, 100 psi H_2, rt, 18 h; (h) HPLC separation, Chiracel OD-H, heptane/EtOH/Et_2NH, 90:10:0.1.

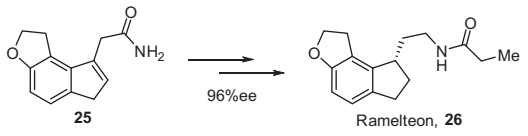
Commercially available 1-chloro-6-iodotoluene **10e** was brominated with NBS in acetonitrile using 1,1′-azobiscyclohexanecarbonitrile (VAZO®-88) as a radical initiator to afford benzyl bromide **11e**. The yield was found to be critically dependent on the purity of toluene **10e**, the use of recrystallised NBS and a reaction concentration of 20 mL/g.[18] The product could be isolated in good purity simply by precipitation of the product upon the addition of water followed by filtration. The crude material was further purified by slurry trituration with methanol followed by filtration to give product **11e** in high purity and 79% yield without the requirement for chromatography.

Subsequent displacement of benzyl bromide **11e** to provide methyl ether **12e** was achieved in quantitative yield and also without the need for chromatography using freshly prepared sodium methoxide. Aryl iodide **12e** was then coupled via a Sonogashira reaction in degassed solvent to give alkyne **15e** in an excellent quantitative yield after chromatography. Interestingly, the corresponding aromatic bromide gave almost no reaction under identical conditions. With bulk quantities of silyl protected alkyne **15e** available, the critical cyclocarbonylation to form indanone **16e** was explored. Due to the sensitive nature of this reaction, initial attempts to scale the reaction led to diminished yields. However, further optimisation highlighted that strict control of initial CO pressure to >1000 psi, an internal temperature of at least 160 °C, and a reaction time of 12 h were required. Concentration was also found to be important with 50 mL/g providing consistent results. Careful maintenance of these parameters ensured the reaction could be scaled to provide indanone **16e** in a moderate 42% yield on a 40 g scale after chromatographic purification. The moderate yield was the result of incomplete conversion of starting material **15e** which could be recovered and recycled.

Treatment of indanone **16e** with triflic anhydride and 2,6-di-*t*-butyl-4-methylpyridine gave the corresponding enol triflate. Commercially available dimethylsulfamoyl imidazole was lithiated at the 2-position then transmetallated to the zincate. Negishi coupling with the enol triflate using catalytic $Pd(PPh_3)_4$ yielded imidazole-indene **23**, applying an excess of zinc chloride to inhibit aggregation of the zincate.[19] The product **23** was isolated in 77% yield with the application of disodium EDTA during reaction work up proving critical to break down residual metal complexes.

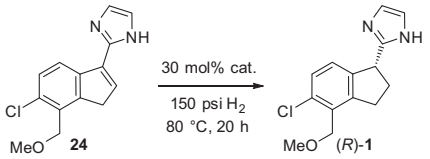
Cleavage of the dimethylsulfamoyl group was carried out in ethanol using 2 M HCl. The resulting salt was collected, purified via ethanol trituration, and converted to the free base with aqueous sodium bicarbonate. The addition of base gave rise to a precipitate that was filtered and dried to afford indene **24** as a white solid in 81% yield and high purity.

Initial routes had relied on achiral hydrogenation to provide racemic final compound material **1** that was subsequently separated into single enantiomers via chiral HPLC. However, in order to maximise the yield of the desired (*R*)-enantiomer, as had been determined by an X-ray structure, an asymmetric synthesis was sought. Catalytic enantioselective alkene reduction remains a field of great interest and is the subject of several recent reviews.[20,21] The reductions of trisubstituted cyclic alkenes are particularly challenging and not commonly exemplified in the published literature. However, some precedent exists for their asymmetric reaction. Notably, chemists at Takeda were able to reduce alkene **25** with $Ru(OAc)_2$[(*R*)-BINAP] in 86% yield and 96% ee en route to the drug molecule Ramelteon **26** (Scheme 8).[22]



Scheme 8. Asymmetric hydrogenation of trisubstituted cyclic alkene **25**.

Table 3
Asymmetric hydrogenation of alkene **24**



Catalyst	% conv.	% ee
$RuCl_2$[(*S*)-BINAP]	100	47
$RhCl_2$[(*S*)-BINAP]	100	37
$IrCl_2$[(*S*)-BINAP]	100	23
$RuCl_2$[(*S*)-tolBINAP][23]	100	29
$RuCl_2$[(*S*)-segPhos][24]	100	24
$RuCl_2$[(*S*)-dmsegPhos][24]	100	23
$RuCl_2$[(*S*)-dtbmsegPhos][24]	100	44
$RuCl_2$[(*S*)-PPhos][25]	100	27
$RuCl_2$[(*S*)-Cl, OMe-BIPHEP][26]	100	0
$RuCl_2$[(*S*)-TunePhos][27]	100	19
$RhBF_4$[SL-J011-1 JosiPhos][28]	92	20
$RhBF_4$[W-009 WalPhos][29]	100	29

Based on this precedent, the selection of chiral metal–ligand catalysts was investigated for the asymmetric hydrogenation of alkene **24**. All reactions were carried out using 30 mol % catalyst, 40 mL methanol per g of substrate, 80 °C, 150 psi H_2, 20 h. All reactions proceeded to good conversion but the enantioselectivities were only moderate (Table 3).

Interestingly, $RuCl_2$[(*S*)-BINAP] as catalyst proved optimal for this substrate, providing the product in 85% yield, 47% ee (3:1 er).[30] It can be post-rationalised that this lower enantioselectivity relative to that achieved for reduction of the Ramelteon example **26** may be due to lack of suitably positioned coordinating groups leading to a less constrained transition state.

This reaction was not optimised further but did translate well on scale up and could be used to process multi-gram quantities of material in 85% yield using 5 mol % of catalyst. The stereochemical mixture obtained was further enriched using preparative HPLC resulting in chemically and stereochemically pure compound **1**.

Conclusion

In conclusion, a concise route to synthesise a series of indane core α_{1A} partial agonists has been described. The route was further modified for the large scale preparation of lead compound PF-03774076 (**1**).[4] The optimised route provided >20 g of material in 7 steps with 18% overall yield and with only four chromatographic purifications required. Significant features of the work were the harnessing of Rh-mediated cyclocarbonylation to construct the indane core of the molecule, a Negishi coupling to introduce a pendant imidazole and the asymmetric hydrogenation of a challenging electron poor tri-substituted alkene. Notably all new C–C bonds were formed via metal-catalysed processes. Compound **1** (PF-03774076, Catalogue No. PZ0263) is now available from Sigma Aldrich.

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Supplementary data

Supplementary data (full experimental details, compound characterisation and selected spectra for key compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.10.004.

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