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A new synthesis of 3-substituted-1*H*-indenes through reaction of *o*-(β-magnesioalkyl)phenylmagnesium dihalides with carboxylate esters

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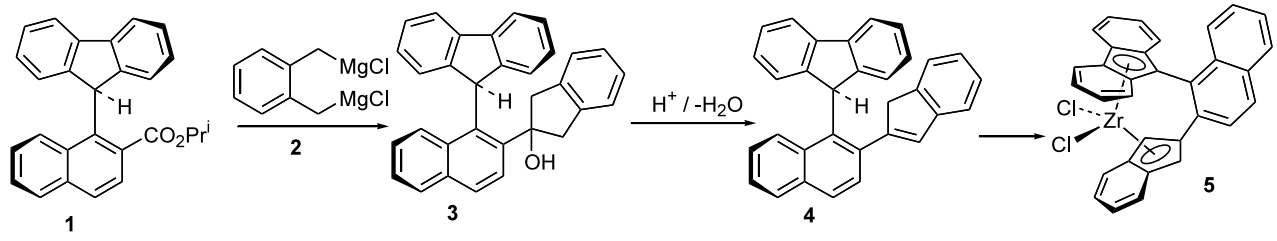
Abstract—A new synthesis of 3-substituted-1*H*-indenes has been developed through the reaction of *o*-(β-magnesioalkyl)phenylmagnesium dihalides with carboxylate esters, followed by dehydration of the intermediate 1-substituted-1-indanols. Di-Grignard reagents allowing the synthesis of 3-substituted-, 2-methyl-3-substituted-, and 4-methyl-3-substituted-1*H*-indenes have been prepared, with overall yields for the two-step sequence ranging from 45 to 95%.

When an indenyl anion is asymmetrically substituted, having differing substituents at either the 1,3-, 4,7-, or 5,6-positions, the faces of the ligand are heterotopic and metalation leads to the formation of a complex with a planar chiral element.[1] Such complexes, in particular those with asymmetric substitution at the 1,3-positions, are of considerable interest as stereoselective catalysts. Group 4 metallocene complexes incorporating asymmetrically substituted indenyl ligands (and their 4,5,6,7-tetrahydro derivatives) have been intensively studied as catalysts for the stereoselective polymerisation of α-olefins,[2] as well as for a range of asymmetric synthetic transformations.[3] More recently there has been growing interest in the use of asymmetrically substituted indenyl ligands for the preparation of planar chiral half-sandwich complexes of late transition metals.[4] The standard methods for preparing indenes substituted at the 1- or 3-positions involve either the alkylation of indenyl anions, or the reaction of 1-indanones with organolithium or Grignard reagents followed by dehydration.[5] In addition to these approaches, Halterman and co-workers have prepared 3-substituted indenes through cross coupling reactions of organozinc complexes with 3-indenyl triflates,[6] or of indenylzinc complexes with aryl halides,[7] and through the alkylation of enolates with 2-bromobenzyl bromide, followed by Cr(II)/Ni(II)-mediated ring closure of the resulting bromoaryl ketones to afford 1-substituted-1-indanols which are subsequently dehydrated to 3-substituted indenes.[8]

We have recently described the preparation of the 1,2-naphthalene bridged *ansa*-zirconocene complex **5** (Scheme 1),[9] with the key step for the formation of the 2-indenyl ligand **4** involving reaction of the ester **1** with the di-Grignard reagent **2**. This method for preparing a 2-substitued indene was first reported by Bosnich and co-workers.[10] Some further examples of the utility of



Scheme 1.

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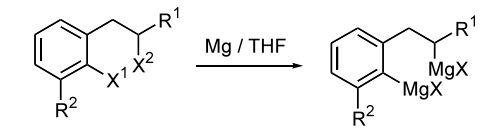
this methodology have recently been reported by Waymouth and co-workers.[11] We were interested in preparing the 1-indenyl analogue of **5** and an attractive approach appeared to be to prepare the *o*-(β-magnesioethyl)phenylmagnesium dihalide analogue of the di-Grignard reagent **2**.

Commercially available 2-(*o*-chloro- and 2-(*o*-bromophenyl)ethanol were both converted to the corresponding chlorides, **6** and **7** (Scheme 2), respectively, on treatment with PCl_5 in chloroform at reflux (ca. 75% yields). A THF solution of the dichloride **6** was added over 30 min to an excess of magnesium (4 equiv., activated through prior reaction with 1,2-dibromoethane) in THF at room temperature. After stirring overnight, the reaction was quenched with water. GC and ^1H NMR analysis indicated the formation of a ca. 50:50 mixture of ethylbenzene and *o*-chloroethylbenzene, suggesting incomplete formation of the desired di-Grignard reagent **10** (Scheme 2), accompanied by the mono-Grignard reagent 2-(*o*-chlorophenyl)ethylmagnesium chloride. A similar result was obtained when the dichloride **6** was added over 30 min to magnesium in THF at reflux, with heating then continued for a further 4 h. However, when *o*-bromo-(2-chloroethyl)benzene **7** was allowed to react with an excess of magnesium in THF at room temperature, quenching the reaction with water returned only ethylbenzene, suggesting complete formation of the desired di-Grignard reagent **11**.

An excess (2 equiv.) of the di-Grignard reagent **11** was added to methyl benzoate in THF solution at −78°C and the reaction then allowed to warm slowly to room temperature over 20 h. The crude product from this reaction was then treated with a catalytic amount of *p*-toluenesulfonic acid in benzene solution at reflux for 2 h. Following flash chromatography, 3-phenyl-1*H*-indene **14** was isolated in 45% yield based on the ester (entry 1, Table 1). Returning to our original target, reaction of the ester **1** with an excess (3 equiv.) of the di-Grignard reagent **11** afforded the 1-indanol in 85% isolated yield. On treatment with catalytic *p*-toluenesulfonic acid in benzene solution at reflux, the desired 3-indene **15** was isolated in 72% yield (an overall yield of 61% from the ester; entry 2, Table 1).

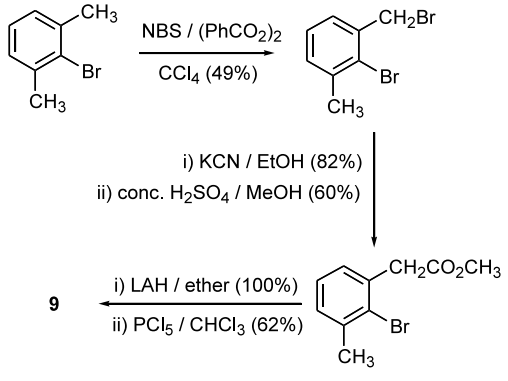
On examining further the scope of this methodology, we were particularly interested in the possibility of introducing additional substituents into the sterically demanding 2- or 4-positions of the indene, potentially leading to systems possessing a stable rotational axis.[12] We had previously attempted the preparation of such systems through the reaction of hindered aryllithium or aryl Grignard reagents with 1-indanones (both with and without $CeCl_3$ additive) and isolated little or none of the desired 1,2-addition products owing to the competing enolisation of the 1-indanone.[6] In order to introduce a 2-methyl group, *o*-bromo-(2-bromopropyl)-benzene **8** was prepared from *o*-bromophenylacetone[13] through reduction ($NaBH_4$/ethanol; 100% yield) and then treatment of the alcohol with CBr_4/Ph_3P (97% yield). The di-Grignard reagent **12** was prepared from **8** through reaction with an excess of magnesium in THF at room temperature, and an excess (2 equiv.) of **12** then reacted with methyl benzoate. Following dehydration of the crude product with catalytic *p*-toluenesulfonic acid in benzene solution at reflux, 2-methyl-3-phenyl-1*H*-indene **16** was isolated in an overall yield of 86% from the ester (entry 3, Table 1). Reaction of an excess of the di-Grignard **12** (2 equiv.) with methyl 2-benzyloxy-1-naphthoate (entry 4, Table 1), followed by dehydration (carried out in this case under basic conditions with $SOCl_2/EtNPr^i_2$), afforded the naphthol **17** and the benzyl-protected naphthol **18** in 10 and 53% yields, respectively (it was established that partial loss of the protecting group occurred during the reaction with the di-Grignard reagent). The benzyl-protecting group was readily removed from **18** on treatment with NaI/BF_3,[14] providing the naphthol **17** in 96% yield. We have prepared **17** previously (by a less convenient route) and shown that the axially chiral enantiomers have a high barrier to atropisomerisation.[12b]

Introduction of a 4-methyl group into the indene was also readily achieved using the di-Grignard reagent **13** prepared from the dihalide **9**, which in turn was prepared in a straightforward fashion from 2-bromo-1,3-dimethylbenzene (Scheme 3). Reaction of an excess (3 equiv.) of the di-Grignard reagent **13** with the menthyl ester **19**[15] (entry 5, Table 1), followed by dehydration of the crude product with catalytic *p*-toluenesulfonic acid in benzene solution at reflux, afforded the 4-methyl-3-substituted-indene **20** in 95% overall yield. Indene **20** exsisted as two diastereoisomers, epimeric about a



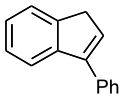
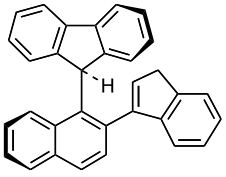
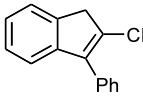
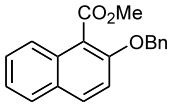
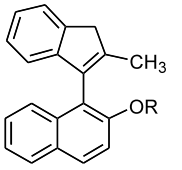
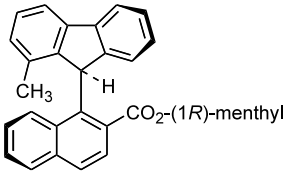
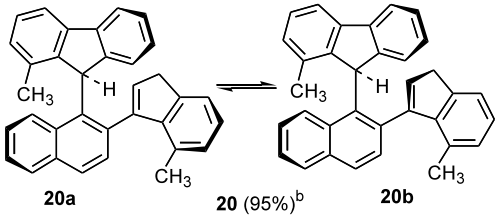
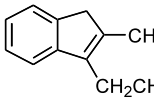
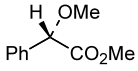
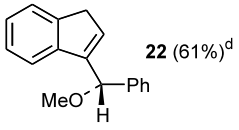
6 X^1= X^2=Cl, R^1=R^2=H
7 X^1=Br, X^2=Cl, R^1=R^2=H
8 X^1=X^2=Br, R^1=Me, R^2=H
9 X^1=Br, X^2=Cl, R^1=H, R^2=Me
10 R^1=R^2=H, X=Cl
11 R^1=R^2=H, X=Br/Cl
12 R^1=Me, R^2=H, X=Br
13 R^1=H, R^2=Me, X=Br/Cl

Scheme 2.



Scheme 3.

Table 1. Preparation of 3-substituted indenes from esters and di-Grignards **11**–**13**

Entry	Ester	di-Grignard[a]	Indene (% yield based on ester)
1	$PhCO_2Me$	**11**	 **14** (45%)[b]
2	**1**	**11**	 **15** (61%)[b]
3	$PhCO_2Me$	**12**	 **16** (86%)[b]
4		**12**	 **17** R=H (10%)[c] **18** R=Bn (53%)[c]
5	 **19**	**13**	 **20a** **20** (95%)[b] **20b**
6	$CH_3CH_2CH_2CO_2Me$	**12**	 **21** (94%)[b]
7		**11**	 **22** (61%)[d]

[a]Excess di-Grignard (2-3 equiv.) in THF added to the ester, -78 °C to r.t. 20 h.

[b]Dehydration of 1-indanol using cat. *p*-toluenesulfonic acid, benzene, reflux 2 h.

[c]Dehydration of 1-indanol using $SOCl_2$ (1.2 equiv.), $EtNPr^i_2$ (2.5 equiv.), CH_2Cl_2, reflux 20 h.

[d]Dehydration of 1-indanol using cat. *p*-toluenesulfonic acid, CH_2Cl_2, r.t. 4 h.

chiral axis between the 2-naphthyl and 3-indenyl moieties (**20a** and **20b**). These diastereoisomers were partially separable by chromatography at ambient temperatures and the rate of return back to equilibrium (ca. 2:1—the relative configuration of the major and minor diastereoisomers has not yet been determined) was monitored by HPLC at 15°C, allowing determination of the barrier to atropisomerisation as $\Delta G^{\ddagger}_{288} =$ 23.3 kcal mol^{-1} (minor to major).

The use of this methodology is not restricted to arenecarboxylate esters. For example, reaction of methyl butyrate with an excess (3 equiv.) of di-Grignard **12**, followed by dehydration of the crude product with catalytic *p*-toluenesulfonic acid in benzene solution at reflux, afforded 2-methyl-3-propyl-1*H*-indene **21** (entry 6, Table 1) in 94% overall yield. Reaction of the di-Grignard reagent **11** with methyl (*S*)-α- methoxyphenylacetate, followed by dehydration of the crude product with catalytic *p*-toluenesulfonic acid in CH_2Cl_2 solution at room temperature, afforded (*S*)-3-(α-methoxybenzyl)-1*H*-indene **22** (entry 7, Table 1) in 61% overall yield.[16] Significantly, there was no evidence for racemisation of the chiral centre by ^1H NMR analysis in the presence of $Eu(hfc)_3$.

This new methodology should allow the preparation of a wide range of novel 3-substituted indenes, not readily accessible through other approaches, for use as ligands in organometallic complexes.

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16. *Typical procedure: preparation of (S)-3-(α-methoxybenzyl)-1H-indene* ***22***. 1,2-Dibromoethane (0.3 ml, 3.5 mmol) was added dropwise to a stirred suspension of Mg granules [20 mesh (Aldrich), 1.44 g, 59 mmol] in dry THF (10 ml) under an argon atmosphere. Upon cessation of effervescence a solution of *o*-bromo-(2-chloroethyl)benzene **7** (3.0 g, 13.7 mmol) in dry THF (40 ml) was added dropwise at room temperature over 30 min. After stirring overnight, the di-Grignard solution was added dropwise via cannula to a solution of methyl (*S*)-α-methoxyphenylacetate (700 mg, 3.9 mmol) in dry THF (10 ml) at −78°C over 1 h, and the mixture then allowed to warm slowly to room temperature over 20 h. The reaction was then quenched by addition of aqueous NH_4Cl (10%), diluted with CH_2Cl_2, the organic phase separated and washed with water, dried (Na_2SO_4), and the solvent removed under reduced pressure. The crude product was dissolved in CH_2Cl_2 (50 ml) with *p*-toluenesulfonic acid monohydrate (50 mg, 0.3 mmol) and the mixture stirred for 4 h at room temperature under an argon atmosphere. The mixture was then diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and the solvent removed under reduced pressure. Flash chromatography eluting with 3% EtOAc/hexane afforded (*S*)-3-(α-methoxybenzyl)-1*H*-indene **22** (560 mg, 61%) as a colourless oil, $[\alpha]_D = +6.9$ (*c* 2.9, toluene). The ee of the product was shown to be >98% by ^1H NMR analysis in the presence of $Eu(hfc)_3$ (ca. 0.7 equiv., ca. 60 mM); δ_H (400 MHz, C_6D_6) 6.40 and 6.47 (each br s) for the indenyl 2-**H** of the (*R*)- and (*S*)-enantiomers, respectively. Found: M^+, 236.120156. $^{12}C_{17}{}^1H_{16}{}^{16}O$ requires M^+, 236.120115. δ_H (400 MHz, $CDCl_3$) 3.44 [2H, br s, (1-**H**)$_2$], 3.48 (3H, s, OC**H**$_3$), 5.36 (1H, br s, C**H**-OMe), 6.44 (1H, br s, 2-**H**), 7.20–7.53 (9H, m, Ar-**H**). δ_C (100 MHz, $CDCl_3$) 144.7, 144.6, 143.2 and 140.0 (each C), 130.9 (CH), 128.3 (2×CH), 127.7 (CH), 127.3 (2×CH), 126.0, 124.7, 123.7, 120.5 and 81.1 (each CH), 56.9 (CH_3) and 37.7 (CH_2).