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Enantioselective construction of sterically hindered tertiary α-aryl ketones: a catalytic asymmetric synthesis of isoflavanones†

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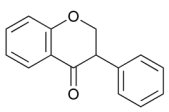
A method for the catalytic asymmetric α-arylation of ketones bearing very sterically hindered aryl rings has been developed. This reaction occurs under mild conditions, in short reaction times and has been applied to the first catalytic asymmetric synthesis of isoflavanones.

Isoflavanones **1**, such as Vestinone **2**, constitute a class of plant secondary metabolites which display a range of useful medicinal properties including anti-cancer[1a] and immunosuppressant activities.[1b]



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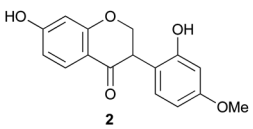

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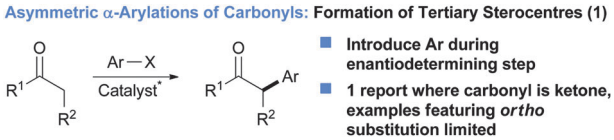
Despite the multitudinous approaches to isoflavanones,[2] to date only one asymmetric synthesis has been realised, which employed the use of chiral auxiliaries.[3] The catalytic asymmetric alkylation of isoflavanones has been reported using chiral phase transfer catalysis to afford the corresponding quaternary stereocentres.[4]

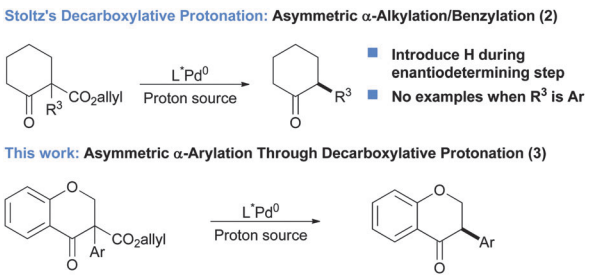
Recently catalytic asymmetric α-arylation of carbonyls has emerged as an important C–C bond forming reaction in organic synthesis, and in the case of the asymmetric synthesis of quaternary α-aryl carbonyl sterocentres has been well investigated.[5] In contrast, the catalytic asymmetric construction of tertiary α-aryl carbonyl compounds remains a prominent challenge due to the ease at which such compounds may be racemised. Recently, noticeable progress was made in this area by Fu when he reported a series of nickel catalysed α-arylations. By using a combination of Ni^{II}, a chiral ligand and an aryl nucleophile a variety of α-halocarbonyls could be arylated in excellent yields and enantioselectivities.[6] Further elegant examples followed with MacMillan combining organocatalysis with Cu^{II} catalysis to enantioselectively α-arylate aldehydes with diaryliodonium salts[7] and the groups of both MacMillan[8a] and Gaunt[8b] α-arylating *N*-acyloxazolidinones with Cu-bisoxazoline complexes and diaryliodonium salts. More recently, Zhou reported an α-arylation of silyl ketene acetals with aryl triflates using a Pd H_8-BINOL catalyst system.[9]



While these examples consisted of a number of carbonyl groups being arylated, reports of chiral tertiary α-aryl ketones being catalytically generated are rare, limited to only one report by Fu.[6c] Furthermore examples of catalytic asymmetric arylations to form tertiary sterocentres on any type of carbonyl with mono-*ortho* substitution are limited and with di-*ortho* substitution almost non-existent.[10]

The prevalence of α-aryl carbonyls in both nature and pharmaceuticals drives the discovery and development of further methods for their efficient asymmetric preparation.

Within the field of Pd-allyl chemistry, asymmetric decarboxylative allylations have recently emerged as a powerful transformation in organic synthesis,[11] chiefly due to the pioneering efforts of the Stoltz,[12] Trost,[13] and Tunge[14] groups, among others.[15] In 2006 Stoltz reported an asymmetric protonation whereby the intermediate enolate in the decarboxylative allylation was intercepted with a proton (eqn (2)).[16] Crucial to the success of this reaction was the use of chiral P,N-ligands. While this transformation was able to generate α-tertiary ketones with a range of alkyl groups in excellent enantioselectivites and yields, there was no report of this methodology being applied to the synthesis of an α-aryl ketone.



Herein we report our efforts to develop a catalytic asymmetric synthesis of isoflavanones an interest which was prompted by a previously reported racemic synthesis by Donnelly.[2c]

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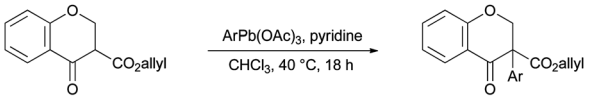
† Electronic supplementary information (ESI) available: Experimental procedures, details of optimisation studies, and spectroscopic data for all new compounds. CCDC 894384 (**7c**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc36452b

Table 1 Arylation of β-ketoester **3** with aryllead triacetates



3 **4a-k**

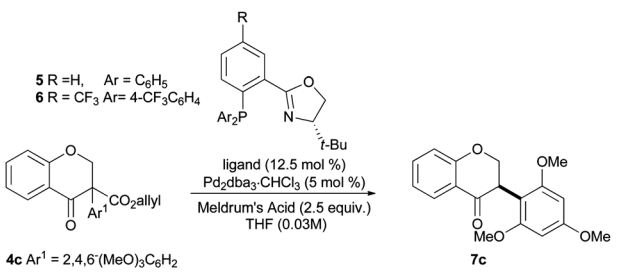
Substrate	Ar	Yield[a] (%)
4a	4-$MeOC_6H_4$	63
4b	2,4-$(MeO)_2C_6H_3$	60
4c	2,4,6-$(MeO)_3C_6H_2$	80
4d	(3,4)-OCH_2O–C_6H_3	78
4e	2,3,4-$(MeO)_3C_6H_2$	80
4f	2,6$(MeO)_2C_6H_3$	86
4g	2,3,6-$(MeO)_3C_6H_2$	84
4h	2-MeO,4,6-$(Me)_2C_6H_2$	75
4i	2,6-$(Me)_2C_6H_3$	70
4j	2-$BnOC_{10}H_6$	80
4k	2-$MeOC_{10}H_6$	89

[a] Refers to isolated yield after column chromatography.

This consisted of a lead mediated arylation of a β-keto ester followed by a Pd-catalysed decarboxylative protonation to give the product isoflavanone (eqn (3)). Thus our synthesis began with the arylation of β-keto ester **3** with a variety of aryllead triacetates to give substrates **4a–k** for catalysis (Table 1).[17] At the commencement of our investigations we chose allyl-3-(4-methoxyphenyl)-4-oxochroman-3-carboxylate **4a** as our model substrate and screened it with several classes of P,N-type ligands.[18] The isoflavanone precursor **4a** proved to be a highly active substrate for the decarboxylative protonation with full consumption of starting material observed within 1 h.

Disappointingly however, the product isoflavanone, **7a**, was obtained in poor enantioselectivities regardless of the P,N ligand class employed. In an effort to probe what effect steric bulk on the aryl ring would have upon the transformation the 2′,4′-dimethoxy substituted substrate **4b** was tested. This led to an increase in selectivity to 19% ee with (*S*)-*t*-Bu PHOX **5**. Encouraged by this we further increased the steric bulk on the aryl ring with the 2′,4′,6′-trimethoxy substituted substrate **4c**.

Table 2 Optimisation of enantioselective decarboxylative protonation



4c Ar^1 = 2,4,6-$(MeO)_3C_6H_2$ **7c**

Entry	Ligand	Substrate	Temp (°C)	Time (h)	Conv.[a]	ee[b]
1	**5**	**4c**	rt	1	100	78 (*R*)[c]
2	**6**	**4c**	0	1	100	89 (*R*)[c]
3	**6**	**4c**	7	0.5	100	92 (*R*)[c]

[a] Determined by HPLC or ^{1}H NMR spectroscopy. [b] Determined by chiral phase HPLC. [c] Determined by X-ray crystallography.

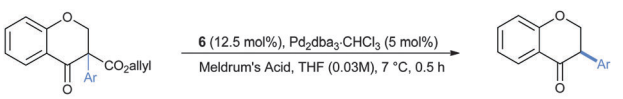
This substrate provided a significant increase in enantioselectivity and gave the product isoflavanone **7c** in 78% ee (Table 2, entry 1). Decreasing the temperature in an attempt to improve selectivity resulted in a sharp decrease in conversion. This temperature limitation was overcome by using the more electronically deficient (*S*)-$(CF_3)_3$-*t*-Bu PHOX **6** which provided 2′,4′,6′-trimethoxyisoflavanone **7c** in 89% ee in 1 h at 0 °C (Table 2, entry 2). Further optimisation showed that a marginal increase in selectivity could be obtained in a shorter reaction time by running the reaction at 7 °C to give **7c** in 92% ee and an isolated yield of 92% (Table 2, entry 3).

The sense of stereoinduction was ascertained by referring to the optical rotation of naturally occurring isoflavanones[19] and we obtained an X-ray crystal structure which gave unambiguous evidence for the (*R*)-enantiomer.[20]

With optimised conditions in hand further substrates were then synthesised to further understand the effect substitution on the aryl ring would have upon this transformation and to broaden the substrate scope. From the results obtained it was possible to deduce a relationship between the substitution on the aryl ring and the enantioselectivity observed in the product isoflavanone (Table 3). Under the new optimized conditions isoflavanone **7b** was obtained in an improved ee of 35%. An additional methoxy group on the aryl ring in the 3′-position gave **7e** in 51% ee. These results suggest that increasing the electron richness of the aryl ring can have a positive influence on enantioselectivity.

Isoflavanone **7d**, which lacks substitution in the *ortho*-positions of the aryl ring, gave a 23% ee. Conversely, **4f** bearing two methoxy groups in the 2′- and 6′-positions provided **7f** in an ee of 85% underlining the importance of sterics upon the selectivity of the reaction. An additional methoxy group in the 3′-position provided **7g** with an identical level of enantioinduction. The importance of an *ortho*-ethereal substituent was probed by sequential replacement by methyl groups. Products **7h** and **7i** were obtained in lower enantioselectivities of 73 and 71%, respectively. Substituting the aryl ring for a naphthyl ring was shown to still give excellent enantioselectivities with the 2′-benzyloxy substituted **7j** being obtained in 87% ee and the 2′-methoxy substituted **7k** being afforded in an ee of 89%. In all of the above cases regardless of the steric bulk around the aryl ring, the isoflavanones were obtained in good to excellent yields (72–93%).

Table 3 Scope of the decarboxylative protonation reaction in the synthesis of isoflavanones



4d-k **7d-k**

Isoflavanone	Ar	Yield[a] %	ee[b] %
7a	4-$MeOC_6H_4$	98	7
7b	2,4-$(MeO)_2C_6H_3$	87	35
7d	(3,4)-OCH_2O–C_6H_3	72	23
7e	2,3,4,$(MeO)_3C_6H_2$	87	51
7f	2,6$(MeO)_2C_6H_3$	83	85
7g	2,3,6-$(MeO)_3C_6H_2$	90	85
7h	2-MeO,4,6-$(Me)_2C_2H_2$	93	73
7i	2,6-$(Me)_2C_6H_3$	86	71
7j	2-$BnOC_{10}H_6$	81	87
7k	2-$MeOC_{10}H_6$	89	89

[a] Refers to isolated yield after column chromatography. [b] Determined by chiral phase HPLC.

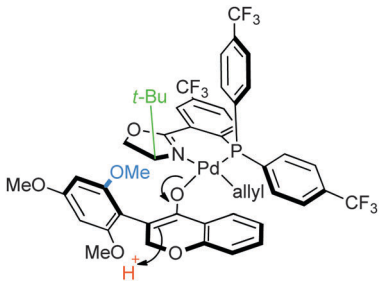


Fig. 1 Proposed transition state in asymmetric protonation.

When we attempted to apply substrate **4c** in an asymmetric decarboxylative allylation we obtained an essentially racemic product.[21] This result is consistent with earlier reports by Stoltz where an α-phenyl substrate provided low levels of enantioselectivity in the decarboxylative asymmetric allylation.[12b]

We propose that the key intermediate in this reaction is likely to consist of a prochiral palladium enolate. One of the *ortho*-methoxy groups and the *t*-Bu group of the ligand combine to block the *Re*-face of the enolate and ensure protonation occurs at the *Si*-face (Fig. 1).

In summary we have reported the first catalytic asymmetric synthesis of 8 novel and 3 previously known isoflavanones. We have shown that this process is influenced by both the sterics and the electronics on the α-aryl ring of the isoflavanone. Enantioselectivities of up to 92% have been achieved for very sterically hindered α-aryl ketones using this methodology.

We believe this method of constructing tertiary α-aryl carbonyl centres is likely to complement existing methods where sterically hindered substrates can lead to reduced yields and enantioselectivites. Whereas previous methods focused on installing the aryl ring in the enantiodetermining step, the methodology in this report has a bulky aryl group already present on the substrate, leading to higher levels of enantiodiscrimination in the protonation step.

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