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Enantioselective Synthesis of α-Allyl-α-aryldihydrocoumarins and 3-Isochromanones via Pd-Catalyzed Decarboxylative Asymmetric Allylic Alkylation

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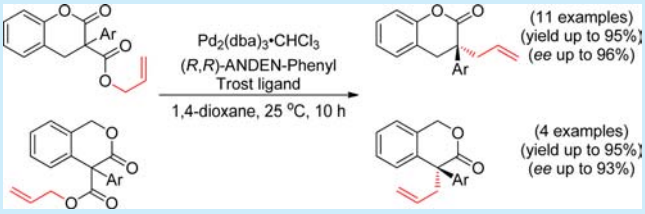
Supporting Information

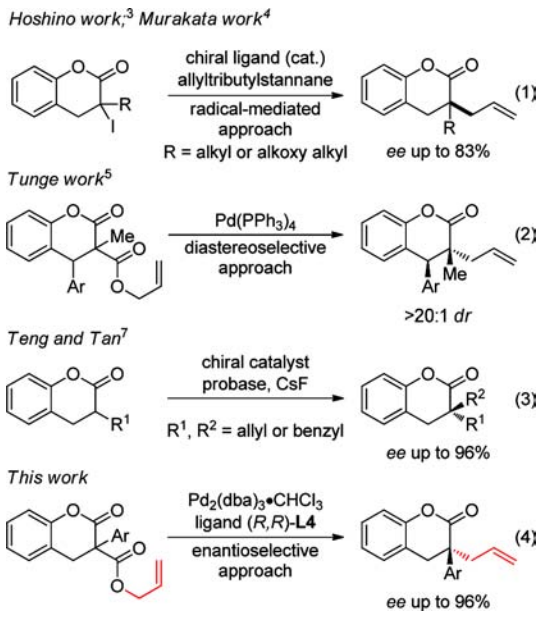
ABSTRACT: An enantioselective Pd-catalyzed DAAA of α-aryl-β-oxo esters has been developed employing the (*R*,*R*)-ANDEN-phenyl Trost ligand to prepare a series of α-aryl-α-allyldihydrocoumarins and 3-isochromanones. A variety of aryl groups were successfully employed to afford the dihydrocoumarin and 3-isochromanone products in high yields up to 95% and ee's up to 96%. Under these conditions, substrates containing di- and mono-*ortho*-substituted aryl groups gave the highest levels of enantioselectivities. This work represents the first example of the enantioselective preparation of all-carbon quaternary α-allyl-α-aryl dihydrocoumarins and 3-isochromanones.



The dihydrocoumarin scaffold is prevalent in natural products and a number of bioactive molecules.[1] In order to determine the potential bioactivity of this class of compounds, it is necessary to develop new ways to derivatize these compounds.[2] The α-carbon is the most accessible point to novel structures which can be further elaborated. Ideally, the enantioselective construction of an all-carbon quaternary center on the scaffold would offer the greatest amount of structural diversity. There have been some notable approaches to access all-carbon α-quaternary dihydrocoumarins (Scheme 1). Hoshino developed an efficient radical-mediated catalytic enantioselective allylation of racemic α-alkyl-α-iodolactones using a binaphthol-derived chiral Lewis acid, enabling the formation of α-quaternary dihydrocoumarins in up to 83% ee.[3] Murakata modified this approach using an organocatalyst, again forming α-alkyl-α-allyldihydrocoumarins, albeit in a significantly lower ee of 30%.[4] Tunge reported a diastereoselective decarboxylative allylation forming both α-tertiary and α-quaternary stereocenters (dr >20:1) with an aryl group in the β-position. The α-quaternary stereocenters prepared in these studies were limited to α-methyl-α-allyl derivatives.[5] During the preparation of this manuscript, Fang, Hou, and co-workers reported a single example of the preparation of an α-methyl-α-allyldihydrocoumarin using a base-mediated asymmetric allylic alkylation in 94% ee,[6] and Teng, Tan, and co-workers described a low-temperature (−40 °C), highly enantioselective phase-transfer alkylation generating a range of α-allyl-α-benzyldihydrocoumarins in up to 96% ee.[7]

The Pd-catalyzed asymmetric decarboxylative allylic alkylation reaction (DAAA) has become a key transformation in the toolkit of modern catalytic asymmetric reactions.[2,8] The use of β-keto esters as substrates has proven to be most successful due to regiospecific in situ enolate generation, relative ease of preparation, and the stability of quaternary β-keto esters. The application of the DAAA to the synthesis of quaternary α-aryl carbonyls has been limited to a small number of examples.[2f,9] We have previously developed the catalytic asymmetric synthesis of a range of tertiary and quaternary α-aryl ketones

Scheme 1. Approaches To Access All-Carbon α-Quaternary Dihydrocoumarins



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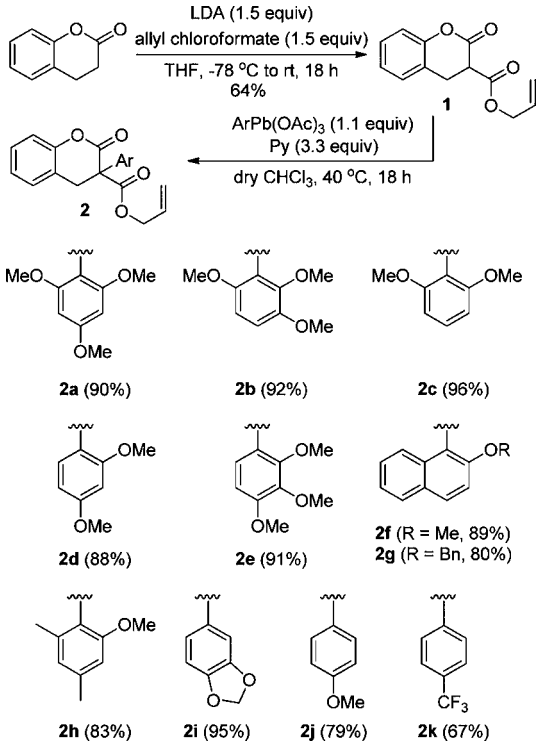
by Pd-catalyzed decarboxylative asymmetric protonations[10] and allylic alkylation.[11] We now report the results of our investigations on the application of DAAA to the enantioselective preparation of α-allyl-α-aryldihydrocoumarins and 3-isochromanones.

The α-aryl-β-oxo allyl ester **2** substrates were prepared in two steps from commercially available dihydrocoumarin (Scheme 2). Base-mediated acylation with allyl chloroformate formed the

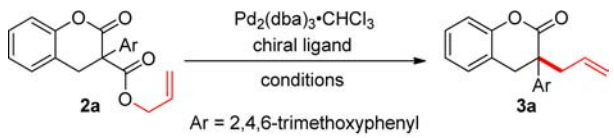
Scheme 2. Synthesis of α-Aryl-β-oxo Allyl Esters

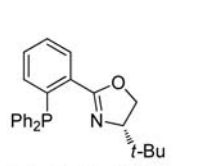


β-oxo allyl ester in 64% yield. This was followed by direct α-arylation of the 1,3-dicarbonyl system **1** using aryllead triacetate ($ArPb(OAc)_3$) reagents under relatively mild conditions of 40 °C in the presence of pyridine. These reagents have a remarkable ability for the α-arylation of β-oxo esters, particularly for their propensity to introduce sterically bulky aryl groups in very high yields and are superior to diaryliodonium salts for the steric and the electronic variety of aryl groups available.[12] A total of 11 sterically hindered $ArPb(OAc)_3$ were prepared either via direct plumbation of arenes or B/Sn–Pb exchange.[10] We chose these electron-rich, substituted aryl groups as we believed this to be important to achieve high levels of enantioinduction, based on our previous investigations.[11] These $ArPb(OAc)_3$ reagents were then successfully applied in the α-arylation of **1**, forming a series of α-aryl-β-oxo allyl ester substrates **2a–k** in very good to excellent yields (67–96%, Scheme 2).

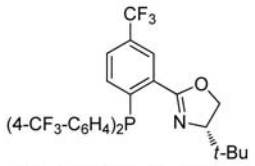
With the substrates in hand we turned our attention to examining conditions for the DAAA (Table 1). We chose the substrate **2a** bearing the 2,4,6-trimethoxyphenyl as the aryl group for reaction optimization and began by screening a series of *P,N* and *P,P*-ligands (6.5 mol %) using $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %) in THF (0.06 M) at 25 °C. PHOX-ligands **L1** and **L2** gave complete conversion with encouraging levels of enantioinduction of 31 and 35% ee, respectively (Table, 1, entries 1 and 2).

Table 1. Optimization of Decarboxylative Asymmetric Allylic Alkylation Using 2a

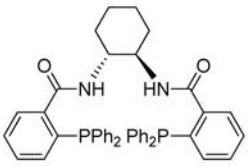




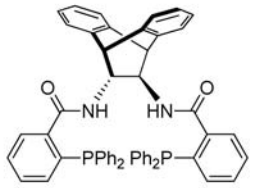
L1: (*S*)-*t*-BuPHOX



L2: (*S*)-$(CF_3)_3$-*t*-BuPHOX



L3: (*R,R*)-DACH-Phenyl Trost



L4: (*R,R*)-ANDEN-Phenyl Trost

entry	L[a]	solvent	temp (°C)	time (h)	conv[g] (%)	yield[h] (%)	ee[i] (%)
1[b,d]	**L1**	THF	25	3	100	90	31
2[b,d]	**L2**	THF	25	3	100	88	35
3[b,d]	**L3**	THF	25	24	68	60	84
4[b,d]	**L4**	THF	25	24	71	61	94
5[b,d]	**L4**	MTBE	25	48	60	48	95
6[b,d]	**L4**	CH_2Cl_2	25	48	25	9	49
7[b,d]	**L4**	toluene	25	48	26	8	91
8[b,d]	**L4**	1,4-dioxane	25	48	76	62	95
9[b,d]	**L4**	1,4-dioxane	40	24	70	65	95
10[c,d]	**L4**	1,4-dioxane	25	10	100	95	96
11[c,e]	**L4**	1,4-dioxane	25	36	100	92	96
12[c,f]	**L4**	1,4-dioxane	25	24	100	93	95

[a]L = ligand. [b]2.5 mol % $Pd_2(dba)_3{\cdot}CHCl_3$ and 6.5 mol % ligand. [c]5.0 mol % $Pd_2dba_3{\cdot}CHCl_3$ and 13.0 mol % ligand. [d]Reactions were carried with 0.06 M. [e]Reaction was carried with 0.03 M. [f]Reaction was carried with 0.09 M. [g]Determined by ^1H NMR of the crude product. [h]Isolated yields after flash column chromatography. [i]Determined by chiral SFC.

We then turned to Trost-type *P,P*-ligands which have previously proven to be very successful in the DAAA reaction.[2a,b,d,f,11] (*R,R*)-DACH-phenyl Trost ligand (**L3**) gave a large improvement in enantioselectivity of 84% ee; however, the conversion was reduced to 68% (Table 1, entry 3). Changing to (*R,R*)-ANDEN-phenyl Trost (**L4**) ligand gave a further increase in enantioinduction up to 94% ee with a similar level of conversion to **L3** (Table 1, entry 4). Although satisfied with this high level of enantioselectivity, we hoped to improve upon the yield by screening a number of solvents using **L4**. Switching to MTBE led to a slightly lower conversion (60%) with the same high level of ee (Table 1, entry 5). Use of dichloromethane led to a sharp reduction in conversion to 25% and 49% ee (Table 1, entry 6). Employing toluene as solvent gave a poor conversion of 26% (Table 1, entry 7), while the reaction in 1,4-dioxane proceeded in a similar manner to THF with a slightly improved conversion (76%), retaining the high

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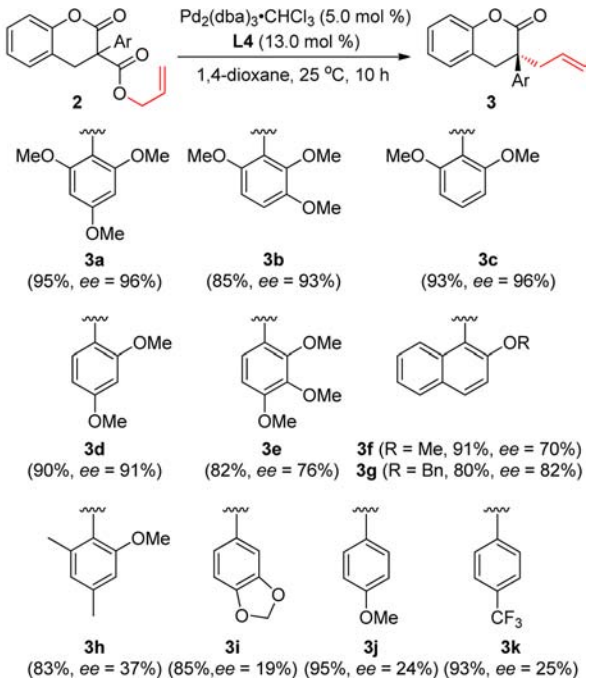
level of enantioselectivity (95% ee) (Table 1, entry 8). Increasing the reaction temperature to 40 °C had no significant effect on conversion or ee (Table 1, entry 9). Complete conversion was achieved by increasing the loading of the catalyst precursors to $Pd_2(dba)_3{\cdot}CHCl_3$ (5.0 mol %) and **L4** (13.0 mol %) and in a reduced reaction time of 10 h leading to a 95% isolated yield with 96% ee (Table 1, entry 10). Diluting the reaction concentration to 0.03 M led to an increase in reaction time to 36 h with no effect on the ee (Table 1, entry 11). Increasing the reaction concentration to 0.09 M had no effect on the reaction (Table 1, entry 12).

We then proceeded to examine the substrate scope of the aryl substituent using the optimized reaction conditions (Table 1, entry 10). All of the substrates tested **2b–k** gave excellent isolated yields (80–95%) and good to excellent ee's in the majority of cases (Scheme 3). The substituent pattern on the *α*-aryl group has a significant impact on the enantioinduction observed. When the di-*o*-methoxy-substituted aryl group **2b** was used as the substrate, a slight reduction in enantioselectivity (93% ee) was observed compared to the 2,4,6-trimethoxyphenyl-substituted **2a** (96% ee). Comparing the 2,4,6-trimethoxyphenyl- **2a** to the 2,3,6-trimethoxyphenyl-substituted substrate **2b** appears to show a slight deleterious effect on the ee when a *m*-methoxy substituent is present (96% ee vs 93% ee). In the absence of a *meta*-substituent, the 2,6-dimethoxyphenyl-substituted substrate **2c**, the ee returns to 96%.

Scheme 3. Scope and Enantioselectivity of *α*-Allyl-*α*-aryldihydrocoumarin Synthesis



Employing the mono-*ortho*-substituted 2,4-dimethoxyphenyl-containing substrate **2d** resulted in a reduction in ee to 91% when compared to the 2,6-dimethoxyphenyl-containing substrate **2c**. The other mono-*ortho*-substituted example, 2,3,4-trimethoxyphenyl (**2e**), gave a significant reduction in enantioselectivity to 76%, which is consistent with the effect of *m*-methoxy substitution observed between **2a** and **2b**. Naphthyl-substituted examples **3f** and **3g** were formed in enantioselectivities of 70 and 82% ee, respectively. A di-*ortho*-substituted aryl group containing an *o*-methyl substituent (**2h**) gave a reduced ee of 37% when compared to the di-*o*-dimethoxy examples. Examples that contain no *ortho*-substitution (**2i–k**) gave poor levels of enantiocontrol, 19–25% ee, highlighting the requirement of at least one *ortho* substituent for high enantioselectivity and an apparent lack of an electronic effect (**2j** vs **2k**).

The absolute sense of stereoinduction was confirmed as *R* by obtaining an X-ray crystal structure of product **3e** (Figure 1). This was consistent with the model to predict the facial attack of the enolate onto the [allyl-Pd–ANDEN] complex.[11,13,14]

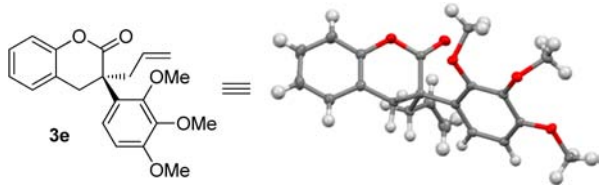
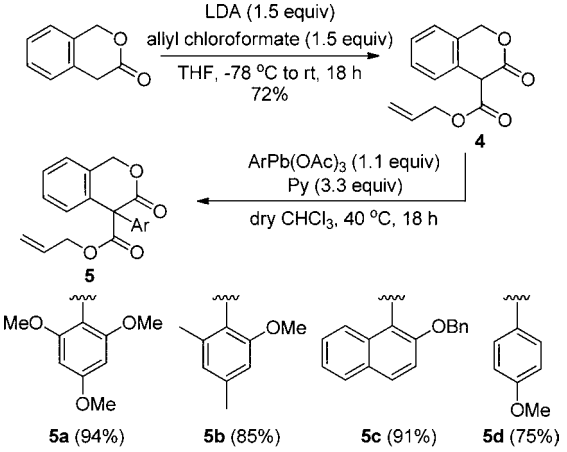


Figure 1. X-ray crystal structure of product **3e**.

3-Isochromanone and its substituted derivatives are very useful synthetic intermediates for agrochemical and pharmaceutical products.[15] Following the successful application of the DAAA to the dihydrocoumarin backbone, we then wanted to test the viability of this transformation on the related 3-isochromanone substrates. The substrates **5a–d** for catalysis were prepared in good to excellent yields using the same two-step acylation/arylation sequence (75–94%, Scheme 4).

Scheme 4. Synthesis of Allyl 4-Aryl-3-oxoisochroman-4-carboxylates



The optimized catalysis conditions (Table 1, entry 10) were then applied to form the products **6a–d** in excellent isolated yields and with enantioselectivities that were broadly in line with those obtained for the dihydrocoumarin examples (Scheme 5).

The 2,4,6-trimethoxyphenyl- and 2-benzyloxynaphthyl-aryl-substituted substrates **5a** and **5c** both provided high ee's of 93%. The 2-methoxy-4,6-dimethylphenyl-containing substrate **5b** gave 64% ee, and the non-*ortho*-substituted, 4-methoxyphenyl-containing substrate **5d** led to an ee of 67%. Using the model of selectivity for the dihydrocoumarin substrate,[14] we propose that the major enantiomer of the products **6a–d** would be, as a result, of the same sense of asymmetric induction. In

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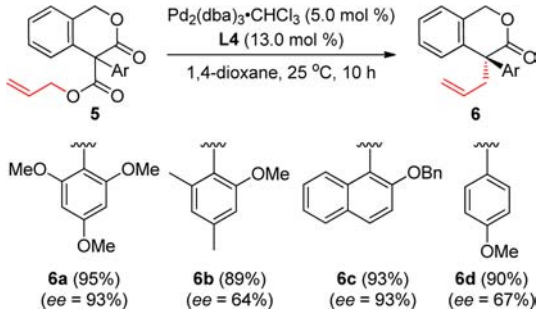
Scheme 5. Synthesis of 4-Allyl-4-arylisochroman-3-ones



addition, the higher ee obtained for products **6b** and **6d** compared to the analogous aryl substitution pattern in the dihydrocoumarin series (**3h** and **3j**) may be rationalized by differences in enolate reactivity and a late versus early transition-state model, respectively.

In conclusion, an enantioselective Pd-catalyzed DAAA of α-aryl-β-oxo esters has been developed employing the (*R*,*R*)-ANDEN-phenyl Trost ligand **L4** enabling the preparation of α-allyl-α-aryldihydrocoumarins and 3-isochromanones in ee's of up to 96%. Under these conditions, substrates containing di-*ortho*-substituted aryl groups gave the highest levels of enantioselectivities. Mono-*ortho*-substituted aryl groups gave up to 93% ee with lower ee values obtained in the absence of an *ortho*-substituent. This work represents the first enantioselective example of the preparation of quaternary α-allyl-α-aryldihydrocoumarins and 3-isochromanones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02584.

Crystallographic data for **3e** (CIF)

Experimental procedures, compound characterization data, and NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(14) For a schematic representation of the model of stereoselectivity observed, see the Supporting Information.

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