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Stereoselective synthesis of 3-substituted phtalides via asymmetric transfer hydrogenation using well-defined ruthenium catalysts under neutral conditions

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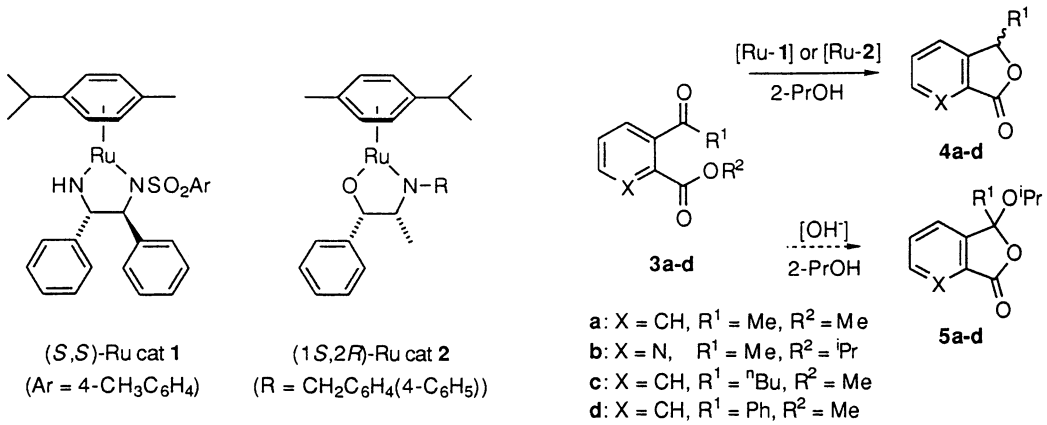
Abstract—The asymmetric transfer hydrogenation of methyl 2-acylbenzoates and 2-propyl 3-acetylpyridine-2-carboxylate in 2-propanol, in the absence of base, with presynthesized Ru-{β-amino alcohol) or Ru-{TsDPEN} true catalysts provides 3-alkylphtalides in high yields and 92–97% ee. The procedure is, however, not as efficient for the preparation of optically active 3-phenylphtalide.

Chiral 1(3*H*)-isobenzofuranones (phtalides), almost all of them having an *S* configured chiral center, feature an impressive list of applications due to their pharmacological effects, e.g. anti-tumor,[1,2] anti-convulsant,[3] anaesthesia prolongation,[4] $PGF_{2\alpha}$ inhibitors,[5]… They are also key intermediates for the synthesis of several alkaloids.[6,7] Accordingly, many approaches have been developed for their asymmetric syntheses. Representative examples involve the use of chiral lithiated oxazolines,[8] reaction of aldehydes with chiral aryllithium reagents,[9,10] alkylation reactions with chiral alkyltitanium reagents[11] or using dialkylzinc compounds in the presence of chiral amino alcohols.[12,13] Asymmetric reduction of alkyl 2-acylbenzoates using microbial agents,[14] Binal-H,[15] borane reagents,[16] and by hydrogenation using a Binap-Ru(II) catalyst[17] has also been applied to prepare optically active 3-alkylphtalides. Catalytic approaches, especially the highly enantioselective one-step hydrogenation of 2-acylbenzoates,[17] are of particular interest because they do not use stoichiometric amounts of chiral auxiliaries.



Scheme 1.

Keywords: asymmetric transfer hydrogenation; chiral phtalides; chiral Ru catalysts.

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Table 1. Ruthenium-catalyzed asymmetric transfer hydrogenation of 2-acylarylcarboxylates **3** in 2-propanol[a]

Entry	Ketone	Catalyst[b]	Temp. (°C)	Time[c] (h)	Conv.[d] (%)	Sel. **4**[d] (%)	ee[e] (%)
1	**3a**	Ru-**1** in situ	20	18	92	32[f]	97 (*S*)
2[g]	**3a**	Ru-**1** in situ[g]	20	16	61	96[f]	97 (*S*)
3	**3a**	Ru-**1** preformed	20	23	93	99	97 (*S*)
4	**3a**	Ru-**1** preformed	50	3.5	96	>99	94 (*S*)
5	**3a**	Ru-**2** in situ	20	16	65	41[f]	84 (*S*)
6	**3a**	Ru-**2** in situ	50	16	75	47[f]	73 (*S*)
7	**3a**	Ru-**2** preformed	20	3	96	>99	83 (*S*)
8	**3b**	Ru-**1** in situ	50	2[h]	65[h]	96	94 (−)
9	**3b**	Ru-**1** preformed	50	1	100	>99	96 (−)
10	**3b**	Ru-**2** preformed	20	3	99	>99	23 (−)
11	**3c**	Ru-**1** preformed	20	18[i]	80[i]	98	92 (*S*)
12	**3c**	Ru-**1** preformed	50	22	91	98	80 (*S*)
13	**3c**	Ru-**2** preformed	20	18	99	>99	72 (*S*)
14	**3c**	Ru-**2** preformed	50	1.5	97	98	66 (*S*)
15	**3d**	Ru-**1** preformed	50	48	23	>99	15 (*S*)
16	**3d**	Ru-**2** preformed	20	18	99	>99	10 (*S*)

[a] The reaction was carried out using 2.0 mmol of **3** and 0.02 mmol of Ru in a 0.1 M 2-propanol solution.

[b] Unless otherwise noted in situ catalysts were generated as follows: A solution of $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (6.2 mg, 0.01 mmol) and the appropriate chiral ligand (0.04 mmol) in dry freshly distilled 2-propanol (5 mL) was heated under nitrogen at 80°C for 20 min. After cooling down the orange solution to room temperature, a solution of **3** (2.0 mmol) in 2-propanol (14 mL) and 2-PrOK (1.0 mL, 0.12 M in 2-propanol, 0.12 mmol) were added. The resulting solution was stirred at the desired temperature and the reaction was monitored by GLC.

[c] Reaction time was not necessarily optimized.

[d] Conversions of **3** and selectivities for **4**/**5** were determined by quantitative GLC analysis using a BPX5 column and by ^{1}H NMR.

[e] ee's Were determined by chiral GLC analysis using a Chirasil-DEX CB column and H_2 as a carrier gas. Absolute configuration of the major enantiomer was determined from the sign of rotation of the isolated product.[14,16]

[f] Compound **5** accounts for the balance.

[g] 2 equiv. (versus Ru) of base were used.

[h] 65% Conv. and 95% ee after 24 h of reaction.

[i] 94% Conv. and 90% ee after 43 h of reaction.

Ruthenium-catalyzed asymmetric transfer hydrogenation of 2-propanol to ketones has recently emerged as a convenient and viable tool for the synthesis of chiral alcohols.[18,19] This process is achieved using combinations of a chlororuthenium(II)arene complex with a chiral monoaryl-sulfonylated-1,2-diamine, e.g. TsDPEN,[19,20] or simple chiral β-amino alcohol ligands[21] in the presence of a base, usually present in excess. The true catalysts for these systems, e.g. Ru cat **1** and Ru cat **2** (Scheme 1), have been isolated and characterized by Noyori et al.[22] and by us,[23] respectively. Herein we report the application of transfer hydrogenation to the synthesis of chiral 3-substituted phtalides in high yield and enantiomeric excess (ee) and demonstrate the possibility of performing selectively the reaction with the true catalysts under neutral conditions (Scheme 1, Table 1).

Treatment of methyl 2-acetylbenzoate (**3a**) with the in situ catalytic combination $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2/(S,S)$-TsDPEN (1:4) in 2-propanol in the presence of 6 equiv. (versus Ru)[18,20] of 2-PrOK at 20°C for 18 h provided a mixture of 3-methylphtalide (**4a**) and 3-(2-propoxy)-3-methylphtalide (**5a**) in 30 and 62% yields, respectively. The analysis of lactone **4a** by chiral GLC showed an ee of 97% (entry 1). When the same reaction was performed with only 2 equiv. (versus Ru) of base, i.e. the stoichiometric amount, lactone **4a** was recovered selectively in 59% yield with the same ee (entry 2). The reaction carried out using the preformed true catalyst Ru-**1** without any added 2-PrOK gave comparable results; lactone **4** was obtained after 23 h in 93% yield and 97% ee (entry 3). These results show that the presence of a slight excess of the base necessary for the generation of the active catalyst from its precursors favours the formation of side-product **5a**, most likely via lactonization of the hemiacetal of **4a**.[24] The same improvement in the chemoselectivity of the reaction was observed by using preformed catalyst Ru-**2** in pure 2-propanol in place of the equivalent in situ combination in the presence of 6 equiv. (versus Ru) of base (entries 5–7). The β-amino alcohol catalyst Ru-**2** was found to be more active, although significantly less enantioselective, than the TsDPEN catalyst Ru-**1**. With the latter catalyst, increasing the reaction temperature to 50°C allowed us to reduce the completion time with a slight decrease in the enantioselectivity from 97 to 94% ee (entry 4). The results of this study revealed that over the reaction time studied (typically 2–24 h), only limited erosion of the ee ($\leq$2%) was observed.

The synthesis of other 3-substituted phtalides was next investigated using preformed catalysts Ru-**1** and Ru-**2**. The reduction of 2-propyl 3-acetylpyridine-2-carboxylate (**3b**) (available from Lancaster Co.) using Ru-**1** in neutral 2-propanol afforded pyridinyl lactone **4b** in

virtually quantitative yield and 96% ee (entry 9).[†] The same reaction was much less enantioselective when Ru-**2** was used as the catalyst (entry 10); this is rather surprising since equivalent Ru-β-amino alcohol in situ combinations have been shown to reduce 2-acetylpyridine in up to 92% ee and their enantioselective performance not to be significantly affected by a variety of alkoxycarbonyl functions.[23,25] The reduction of methyl 2-pentanoylbenzoate (**3c**), readily prepared in 40% overall yield from the reaction of phtalic anhydride with di-*n*-butylcadmium, followed by subsequent esterification of the crude acid with the CH_3I/K_2CO_3 combination, provides the valuable[1–5] (*S*)-3-*n*-butylphtalide (**4c**). Catalyst Ru-**1** afforded **4c** quite sluggishly in 90–92% ee (entries 11–12), while Ru-**2** proved again to be more active but less enantioselective (entries 13–14). The decrease in enantioselectivity observed with both catalysts Ru-**1** and Ru-**2** going from **3a** to **3c** stems from the larger steric crowding of the *n*-butyl group compared to a methyl group. The idea that the enantioselectivity of the reaction is driven by the steric difference between the substituents that flank the ketone is supported by the results obtained in the reduction of methyl 2-benzoylbenzoate (**3d**); in this case, the steric demand between flanking aromatic groups is low and 3-phenylphtalide (**4d**) was recovered with very low ee's (entries 15–16).

In conclusion, we have demonstrated that the ruthenium-catalyzed transfer hydrogenation of 2-acyl arylcarboxylates in 2-propanol under neutral conditions is an excellent method for the synthesis of optically active 3-alkyl-phtalides. Further applications of these well-defined Ru catalysts in which undesirable reactions due to basic conditions can be prevented are currently under investigation.

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[†] In a typical experiment, a solution of 2-propyl 3-acetylpyridine-2-carboxylate (**3b**) (414 mg, 2.0 mmol; previously recrystallized from petroleum ether) in dry freshly distilled 2-propanol (20 mL) was transfered via canula under nitrogen in a Schlenk tube containing complex Ru-**1**[22] (12 mg, 0.02 mmol). The resulting solution was placed in an oil bath at 50°C and stirred with a magnetic bar; the solution initially purple red turned progressively yellow. After 1 h, the reaction mixture was exposed to air and cooled to room temperature. GLC analysis using a BPX5 and a Chirasil-DEX CB capillary column showed complete conversion of **3b** to **4b** with an enantiomeric excess of 96%. After evaporation of volatiles under vacuum the crude product was purified by column chromatography (silica, Et_2O–heptane) to provide 269 mg (90%) of a white powder; $[\alpha]_D^{20}$ −46 (*c* 0.35, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.87 (d, $J=3.7$ Hz, 1H), 7.86 (d, $J=7.8$ Hz, 1H), 7.56 (dd, $J=4.7$ and 7.8 Hz, 1H), 5.61 (q, $J=6.7$ Hz, 1H), 1.66 (d, $J=6.7$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.9, 152.2, 144.8, 143.9, 130.5, 127.2, 75.8, 19.8.

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