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Efficient, enantioselective synthesis of a β,β-disubstituted carboxylic acid by Ru-XylPhanePhos-catalyzed asymmetric hydrogenation

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ABSTRACT

Enantioselective preparation of a key $\alpha_v\beta_3$ integrin antagonist intermediate was accomplished via catalytic asymmetric hydrogenation of the corresponding β,β-disubstituted α,β-unsaturated carboxylic acid bearing a 3-quinolinyl moiety. The successful application of a Ru-(*R*)-XylPhanePhos catalyst to this type of substrate is unprecedented. In situ NMR experiments of pre-catalyst formation/activation by CH_3CO_2H, and reaction parameter modification, revealed that $[Ru(COD)(CF_3CO_2)_2]_2$/(*R*)-XylPhanePhos is a highly active and efficient catalytic system.

Carboxylic acids with a β-aryl group on a stereogenic center are important building blocks in the synthesis of pharmaceuticals and fine chemicals. Various asymmetric synthetic approaches to this class of intermediates have been devised, including the conjugate addition of aryl organocopper reagents to chiral *N*-enoylamides,[1a] rhodium catalyzed 1,4-addition of arylboronic acids to α,β-unsaturated esters,[1b] 1,4-reduction with a enantioselective phosphine-copper catalyst,[1c] and homogeneous hydrogenation of α,β-unsaturated carboxylic acids[2,3] or dehydroamino acid derivatives.[3] Significant progress in chiral hydrogenations of α,β-unsaturated carboxylic acids has been achieved by using chiral ruthenium catalysts.[3] The applicability of this important methodology to the synthesis of pharmaceutical intermediates has been demonstrated on small scale,[3a] with a few examples being advanced to an industrial scale.[4] However, methods that have proven effective for simple β-aryl groups can break down when the aryl group contains a nucleophilic heteroatom, which can interfere with formation of a stable organometallic species or formation of the requisite catalytic complex.[5]

Integrin $\alpha_v\beta_3$ antagonists have attracted attention as potential treatments for cancer, rheumatoid arthritis, osteoporosis, or diabetic retinopathy.[6] The (*S*)-β-heteroaryl carboxylic acid motif is a common structural element in several orally bioavailable $\alpha_v\beta_3$ integrin antagonists.[7] Because of encouraging oral efficacy for compound **4** in models of ocular vasculopathy,[7d] we sought to develop an enantioselective synthesis of quinoline intermediate **2** from β,β-disubstituted unsaturated acid **1**. It was previously shown that **2** can be converted to the β-tetrahydroquinoline-containing $\alpha_v\beta_3$ antagonist **4** via **3** (Fig. 1).[7c]

In this context, the feasibility of catalytic asymmetric hydrogenation of **1** was explored. The use of asymmetric hydrogenation for the reduction of β,β-disubstituted unsaturated acids has not been well studied.[2,3a] Increased steric hindrance at the β-position and subtle differences between β-substituents[3a] make this process somewhat challenging. Also, the presence of a coordinating heteroatom in **1** lends further difficulty to the process. Because of the precedent with β-heteroaryl unsaturated acids,[2c] we initially focused on using biarylphosphine-ruthenium catalysts (e.g., BINAP and P-Phos-types) for the reduction of **1** (*Z* form).[8] However, only disappointing enantioselectivity was obtained with this substrate.[9] A broader catalyst screen, involving Ru- and Rh-based metal precursors in combination with structurally varied chiral bisphosphine ligands,[10] led to an efficient

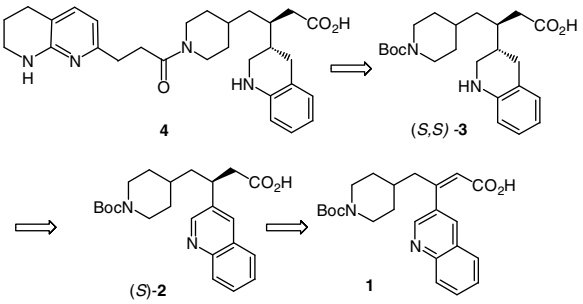

Figure 1. Retrosynthetic analysis of **4**.

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catalytic asymmetric hydrogenation, involving a novel Ru-paracyclophane-based bisphosphine system, which has not been previously applied to enantioselective hydrogenation of α,β-unsaturated carboxylic acids.

The planar chiral bisphosphine PhanePhos[12] family of ligands features a unique [2.2]paracyclophane backbone. Originally reported in 1997 by Rossen and Pye,[12a] this chiral phosphine and its derivatives[12b] have been shown to promote outstanding activity and selectivity in a variety of metal-catalyzed asymmetric transformations such as rhodium catalyzed asymmetric hydrogenation of dehydroaminoacids,[12a,b] allylic alcohols,[12c] ruthenium-catalyzed asymmetric hydrogenation of β-ketoesters,[12d] 'Noyori-type' hydrogenation of nonfunctionalized ketones,[12e] or enantioselective hydroboration of cyclopropenes.[12f]

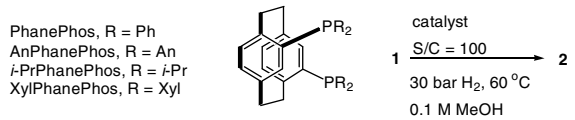
Table 1 summarizes the screening results of [(Phanephos) Rh (L)]X cationic complexes or [(Phanephos) Ru (L) X_2] catalysts. Full conversions and ee's up to 73% using Rh-PhanePhos-based catalysts were obtained (Table 1, entries 1–6), while three Ru-XylPhanePhos systems resulted in full conversions and 82–87% ee, with substrate to catalyst ratios (*S*/*C*) of 100 (Table 1, entries 8–10). Isolation experiments of crude product **2** from the Ru-(*R*)-XylPhanePhos-catalyzed reductions showed that the enantiopurity of (*S*)-**2** could be upgraded from 82–87% ee to higher than 98% ee by extraction of the major *S*-enantiomer in CH_2Cl_2/MeO-*t*-Bu. This prompted us to optimize the efficiency of the Ru-XylPhanePhos-based catalyst.

Initially we focused on varying the reaction parameters of catalyst loading, hydrogen pressure, and reaction temperature[13] in the hydrogenation of **1** with [(*R*)-XylPhanePhos $RuCl_2$ $(DMF)_n$] catalyst (Table 2). This catalyst is an undefined species that is easily prepared by heating the ligand and $[Ru(benzene)Cl_2]_2$ in DMF.[14] Such [bisphosphine RuX_2 (L)] (X = halide, L = arene, DMF) catalysts, where the chiral bisphosphine is usually an atropoisomeric ligand, have been widely used as pre-catalysts in the asymmetric hydrogenation of functionalized ketones[2] and, to a lesser extent, of α,β-unsaturated acid salts.[2c,15]

We have found that the presence of a base is needed to activate the Ru-halide catalyst and to generate the corresponding carboxylate, which in turn coordinates to the metal center and participates in the catalytic cycle.[2c,15b] By using 0.5 equiv of Et_3N relative to the substrate, the reaction with [(*R*)-XylPhanePhos $RuCl_2$ $(DMF)_n$] reached full conversion and afforded 85% ee in the desired (*S*)-**2** within 3 h at a *S*/*C* ratio of 500 (Table 2, entry 4). Lower catalyst loadings led to moderate-low conversions (Table 2, entries 6 and 7). The role of Et_3N was highlighted in experiments at a *S*/*C* ratio of 1000. The activity was dependent on the amount of Et_3N, reaching a maximum of 66% conversion when 0.1 equiv of Et_3N was used (Table 2, entries 8–11). This outcome suggests that Et_3N is necessary to activate the catalyst; however, larger amounts were not required since the quinoline group may serve as an internal base in generating the carboxylate anion.[16] Having reached a plateau in activity in the case of [(*R*)-XylPhanePhos $RuCl_2(DMF)_n$], we switched our attention to different ruthenium complexes (Table 3). To the best of our knowledge, there has been only one example of the [PhanePhos Ru $(CF_3CO_2)_2$] pre-catalyst, and that was used for the asymmetric hydrogenation of functionalized ketones.[12d] On the other hand, atropoisomeric bisphosphine-Ru-dicarboxylate pre-catalysts have been extensively used in the asymmetric hydrogenation of α,β-unsaturated carboxylic acids under a myriad of reaction conditions.[3b] Pre-catalysts generated in situ from $[Ru(COD)(CF_3CO_2)_2]_2$ or Ru(COD)(Me-allyl)$_2$ precursors and (*R*)-XylPhanePhos showed full conversions and ee's higher than 85% with a *S*/*C* ratio of 500 (Table 3, entries 1 and 6). No Et_3N was used since we expected these catalysts to be activated either by protonation of the Ru–C bond or by substitution of the trifluoroacetate by the acid substrate.[17]

A selection of protic acids was tested for both systems. Carboxylic acids such as CH_3CO_2H and CF_3CO_2H led to full conversions and 85% ee in less than 6 h.[18] We believe these results suggest that the additive plays an important role in catalyst activation and hence affects catalyst activity at lower catalyst load-

Table 1
Hydrogenation of **1** with PhanePhos-based catalysts[11]



Entry	Pre-catalyst[a]	ee (%)
1	[(*R*)-PhanePhos Rh (COD)]BF_4	68 (*S*)
2	[(*R*)-AnPhanePhos Rh (COD)]BF_4	62 (*S*)
3	[(*S*)-*i*-PrPhanePhos Rh (COD)]BF_4	18 (*R*)
4	$[Rh(COD)_2]OTf$/(*R*)-PhanePhos	73 (*S*)
5[b]	$[Rh(COD)_2]OTf$/(*R*)-PhanePhos	40 (*S*)
6	$[Rh(COD)_2]OTf$/(*S*)-XylPhanePhos	67 (*R*)
7[b]	[(*S*)-PhanePhos $RuCl_2$ $(DMF)_n$]	58 (*R*)
8[c]	[(*R*)-XylPhanePhos $RuCl_2$ $(DMF)_n$]	82 (*S*)
9	Ru(COD)(Me-allyl)$_2$/(*R*)-XylPhanePhos	87 (*S*)
10	$[Ru(COD)(CF_3CO_2)_2]_2$/(*R*)-XylPhanePhos	87 (*S*)

[a] COD, 1,5-cyclooctadiene; An, 4-anisyl; Xyl, 3,5-xylyl.
[b] 1 equiv of HBF_4/Et_2O with respect to **1** was used.
[c] 0.5 equiv of Et_3N relative to **1**.

Table 2
Influence of the reaction parameters on the [(*R*)-Xyl-PhanePhos $RuCl_2$ $(DMF)_n$]-catalyzed hydrogenation of **1**[a]

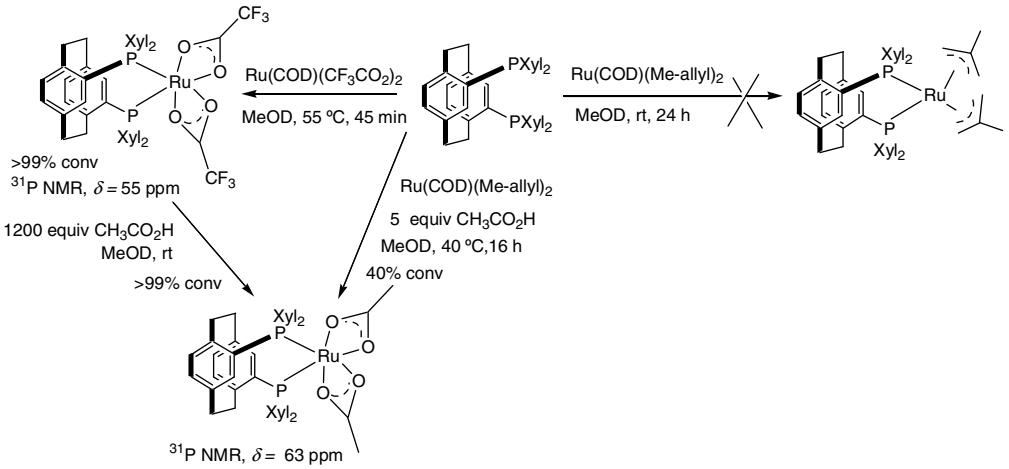
Entry	Et_3N (mol equiv)	*S*/*C*	*P* (bar)	*T* (°C)	Conv (%)	ee[b] (%)
1	0.5	500	30	60	99	84 (*S*)
2	0.5	500	30	40	99	84 (*S*)
3	0.5	500	3	60	94	82 (*S*)
4	0.5	500	10	40	99[c]	85 (*S*)
5	0	500	10	40	99[d]	85 (*S*)
6	0.5	1000	10	60	66	73 (*S*)
7	0.5	2000	10	60	19	64 (*S*)
8	0	1000	10	40	4	ND[e]
9	0.1	1000	10	40	66	82 (*S*)
10	0.5	1000	10	40	47	86 (*S*)
11	1.2	1000	10	40	17	77 (*S*)

[a] Reaction conditions: 0.2 mmol of **1**, catalyst, Et_3N, 2 mL of MeOH.
[b] Absolute configuration for product is given in parentheses.
[c] Reaction reached full conversion in 3 h.
[d] Reaction reached full conversion in 6 h.
[e] ND, not determined.

Table 3
Effect of CH_3CO_2H on the activity of the Ru-(*R*)-XylPhanePhos-catalyzed hydrogenation of **1**[a]

Entry	*S*/*C*	CH_3CO_2H (mol equiv)	Conv (%)	ee (%)
$[Ru(COD)(CF_3CO_2)_2]_2$/(R)-XylPhanePhos				
1[b]	500	0	99	89 (*S*)
2	1000	0	5	
3	1000	0.1	93	86 (*S*)
4	1000	0.5	98	87 (*S*)
5	1000	1.2	99	88 (*S*)
Ru(COD)(Me-allyl)$_2$/(R)-XylPhanePhos				
6[b]	100	0	99	89 (*S*)
7	1000	0	30	87 (*S*)
8	1000	0.1	33	68 (*S*)
9	1000	0.5	86	86 (*S*)
10	1000	1.2	79	82 (*S*)

[a] Reaction conditions: 0.2 mmol of **1**, catalyst, 2 mL of MeOH, additive, 40 °C, 10 bar of H_2, 20 h unoptimized reaction time. In situ catalysts were reacted under N_2 in MeOH for 30 min at rt prior to addition of substrate and additive.
[b] At 25 °C.



Scheme 1.

ings. We opted to study the influence of the amount of CH_3CO_2H additive on the activity of $[Ru(COD)(CF_3CO_2)_2]_2$/(*R*)-XylPhanePhos and Ru(COD)(Me-allyl)$_2$/(*R*)-XylPhanePhos at lower catalyst loading (Table 3). When no additive was employed, only the Ru(COD)(Me-allyl)$_2$/(*R*)-XylPhanePhos pre-catalyst led to moderate-to-low conversion (Table 3, entries 2 and 7). The optimum amount of CH_3CO_2H for the Ru(COD)(Me-allyl)$_2$ precursor was 0.5 equiv (Table 3, entry 9), while 0.1, 0.5, and 1.2 mol equiv of CH_3CO_2H were all productive for the $[Ru(COD)(CF_3CO_2)_2]_2$ precursor (Table 3, entries 3–5).

The results in Table 3 suggest that each catalyst behaves in a different, unique way, influenced by various factors for each reaction system. When the $[Ru(COD)(CF_3CO_2)_2]_2$ precursor was employed, full conversion was obtained in the absence of CH_3CO_2H at a *S*/*C* ratio of 500, but not at a *S*/*C* ratio of 1000. The addition of CH_3CO_2H, in any amount from 0.1 to 1.2 mol equiv led to high conversion and reproducible enantioselectivities. On the other hand, the Ru(COD)(Me-allyl)$_2$ precursor worked to a limited extent without an additive, possibly because substrate **1** activated the Ru–C bond in the Ru(COD)(Me-allyl)$_2$ precursor by protonation. Moreover, in the case of both catalysts, CH_3CO_2H might play a dual role by (i) generation of the true active Ru-diacetate species[2a,3a] and (ii) inhibition of coordination of the quinolinic nitrogen through protonation of the quinoline ring. In our hands, the efficient synthesis and isolation of pure Ru(*R*)-XylPhanePhos$(CH_3CO_2)_2$ or Ru(*R*)-XylPhanePhos$(CF_3CO_2)_2$ catalysts proved elusive. However, this was not surprising because Ru-dicarboxylate complexes are notorious for their reactivity towards traces of moisture.[19]

Catalyst formation for the $[Ru(COD)(CF_3CO_2)_2]_2$/(*R*)-XylPhane-Phos and Ru(COD)(Me-allyl)$_2$/(*R*)-XylPhane-Phos systems was monitored in situ by ^{31}P NMR with MeOD as the solvent (Scheme 1). NMR experiments mimicking the conditions used to generate the catalyst in the hydrogenation reaction (0.002 mmol of catalyst/0.5 mL of MeOD) showed that the Ru(*R*)-XylPhanePhos-$(CF_3CO_2)_2$ complex was fully formed at 55 °C after approximately 45 min (^{31}P NMR, δ 55 ppm). Furthermore, adding 1200 equiv of CH_3CO_2H showed a new peak formation at ~63 ppm, which is characteristic of Ru(bisphosphine)$(CH_3CO_2)_2$ complexes.[19] When the reaction was performed at rt, only 21% of the bisphosphine ligand was coordinated to ruthenium after 30 min (65% after 6 h). Ru(COD)(Me-allyl)$_2$ did not react with (*R*)-XylPhanePhos at rt (24 h), while 40% of the peak at ~65 ppm was observed in the presence of 5 mol equiv CH_3CO_2H at 40 °C overnight. These data correlate with the lower conversions in the asymmetric hydrogenation at lower catalyst loadings in the absence of CH_3CO_2H.

In light of these NMR experiments, the catalyst activation procedure was studied in the hydrogenation of **1** in conjunction with substrate concentration, pressure and temperature (Table 4). When the ruthenium precursor and the ligand were stirred for 2 h at 55 °C in MeOH, full conversions were obtained at 0.1 M, 40 °C (Table 4, entry 1) or 1 M, 50 °C (Table 4, entries 4 and 5). With a 1 M substrate concentration at 40 °C, 86% conversion was obtained, indicating that under such reaction conditions the activity was substrate concentration dependent (Table 4, entry 2 vs entry 1). Full conversion was observed at 40 °C when the solution of the catalyst was pre-activated with CH_3CO_2H (CH_3CO_2H/catalyst ratio = 1200), suggesting that pre-activation and therefore full formation of the Ru$(CH_3CO_2)_2$-(*R*)-XylPhanePhos species prior to catalysis does influence positively the activity (Table 4, cf. entries 3 and 2).

The best conditions, providing the highest conversions and ee's for each system, identified from small-scale reactions in the Biotage Endeavor 8-well hydrogenator, were nicely reproduced in scale-up experiments in a stand-alone Parr autoclave. The catalytic step worked reproducibly on 1.5- and 3-g scale reactions both at 10 and 3 bar of H_2, and the product (*S*)-**2** was isolated in 80% yield and higher than 97% ee by extraction from CH_2Cl_2/hexane/MeO-*t*-Bu mixtures or toluene.

In conclusion, we have identified a ruthenium-based (*R*)-XylPhanePhos catalyst that is effective in the enantioselective hydrogenation of a β,β-disubstituted unsaturated carboxylic acid, namely **1**. This system has been optimized in terms of catalyst formation and activation, and may have wider utility in the hydrogenation of other heterocycle-based intermediates. The optimized procedure involves mild conditions, good volume-efficiency, and

Table 4
Effect of CH_3CO_2H on catalyst performance at CH_3CO_2H/**1**/C = 1200/1000/1[a]

Entry	[*S*] (M)	*P* (bar)	*T* (°C)	Conv (%)	ee (%)
1	0.1	10	40	99	88 (*S*)
2	1	10	40	86	87 (*S*)
3[b]	1	10	40	99.5	92 (*S*)
4	1	10	50	99.7	85 (*S*)
5	1	3	50	99	89 (*S*)

[a] Reaction conditions: substrate **1**, catalyst, 2 mL of MeOH, CH_3CO_2H/**1**/C = 1200/1000/1, 40 °C, 10 bar of H_2, 20 h unoptimized reaction time. In situ catalysts were reacted under N_2 in MeOH at 55 °C for 2 h.

[b] In situ catalyst was reacted under N_2 in MeOH at 55 °C for 2 h, followed by reaction with 1200 equiv of CH_3CO_2H at rt for 10 min.

acceptable catalyst loadings. When combined with the ee upgrade procedure, it offers a practical procedure for preparing key chiral intermediate (*S*)-**2**.

Acknowledgments

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Supplementary data

Experimental procedures, chiral HPLC analysis, and preliminary catalyst screening. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.06.068.

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8. Synthesis of substrate **1** will be reported elsewhere.
9. Atropoisomeric bisphosphine-based catalysts such as [(P-Phos) $RuCl_2$ $(DMF)_n$], [BINAP $RuCl_2$ $(DMF)_n$] led to full conversions and less than 25% ee's.
10. See Supplementary data for bisphosphine ligands employed in the initial catalyst testing.
11. Conversions and ee's throughout this study were determined by HPLC analysis using Chiracel AD-H column, hexane/*i*-PrOH = 80:20, after conversion to methyl ester.
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16. When CH_3CO_2H was employed as an additive, no conversion was observed with the [(*R*)-XylPhanePhos $RuCl_2$ $(DMF)_n$] catalyst.
17. With Et_3N as an additive, no conversion was observed in this system.
18. Experiments were performed with 1 equiv of acid relative to substrate, at *S*/*C* 500, 10 bar, and 40 °C. Use of HCl (1 N in Et_2O) or $HBF_4{\cdot}Et_2O$ in such systems led to low conversions and partial deprotection of the Boc group (3–15%).
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