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Rhodium-Catalyzed Asymmetric Synthesis of β-Branched Esters from Allylic Amines

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Allylic amines are converted to chiral, β-branched esters under rhodium catalysis in the presence of alcohol nucleophiles. Allylic amines with aliphatic and aromatic vinylic substituents are converted to ester products with excellent enantioselectivities in all cases. Several alcohol nucleophiles have been utilized in the reaction including 1° and 2° derivatives.

The installation of esters into complex molecular scaffolds has been the subject of much investigation in recent years.[1] Chiral, β-branched esters are prevalent moieties in pharmaceuticals, fragrances, materials, and agrochemicals (Figure 1), and esters themselves serve as versatile synthetic handles for further functionalization.[2] In an effort to diversify the pool of β-branched esters that are rapidly accessible, we report herein a method that sets the β-stereocenter while also constructing the ester in the same chemical operation through an isomerization/oxidation manifold.

Traditionally, esters are generated through reactive intermediates, such as acyl halides, or carboxylic acids paired with stoichiometric coupling reagents (Steglich esterification) as well as *via* strong acid catalysis (Fischer esterification). Though these approaches generally proceed with high conversion, the conditions required to generate acyl halides or strongly acidic conditions are not amenable to sensitive functionalities. Stoichiometric coupling reagents generate high molecular weight byproducts that can be challenging to separate from the desired product. Early reports of catalytic esterification, such as the Tishchenko reaction, generate simple homocoupled products (Scheme 1a).[3] In recent years, the catalytic esterification of aldehydes *via* transfer hydrogenation has emerged as a meaningful alternative to stoichiometric coupling reactions; however, many of these reactions require solvent quantities of the alcohol nucleophile and are generally sterically limited such that β-branched esters as products are difficult to obtain in synthetically useful yields.[4–6]

Much of the work in generating chiral, β-branched esters has focused on asymmetric conjugate reduction[7] and

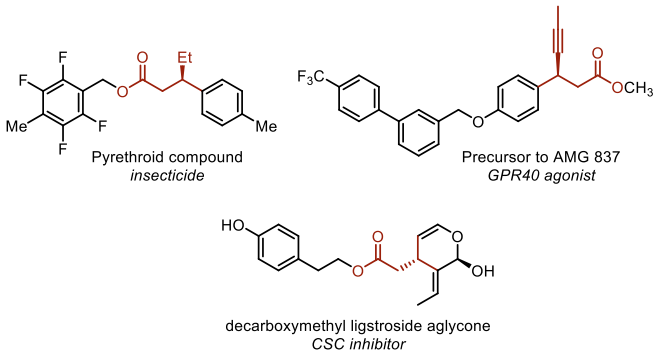
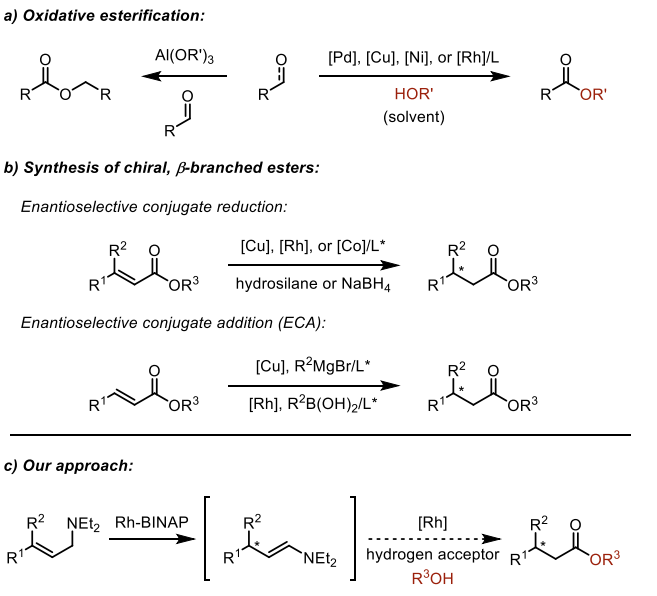


Figure 1 Biologically active β-branched esters.



Scheme 1 Precedent for the catalytic synthesis of chiral, β-branched esters.

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

enantioselective conjugate addition (ECA)[8] to α,β-unsaturated esters (Scheme 1b). The major limitation of such strategies is poor substrate scope for individual catalysts. Changes to the substitution pattern of the substrate can require a different metal/ligand scaffold meaning in the context of a synthesis, extensive screening may be required.[9] These methods often rely on significant steric differentiation between the substituents at the β-position or are dependent on olefin geometry to achieve high stereoselectivity.[7a,c,e,f]

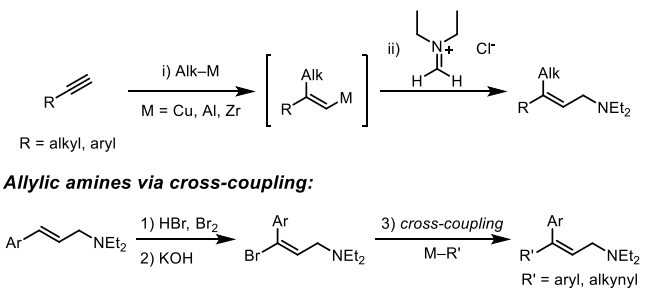
To overcome the limitations of previous reports, we drew inspiration from the asymmetric isomerization of allylic amines to optically pure enamines, developed by Noyori and Otsuka.[10] Because the enantioselectivity of the isomerization of the allylic amine proceeds *via* a suprafacial 1,3-hydride shift and the initial binding of the substrate to the catalyst is facially selective,[10e] steric differentiation between the substituents at the prochiral center is not required to achieve enantiopurity. This isomerization approach could pave the way for a critical advance in the asymmetric synthesis of β-branched esters. We envisioned the resulting enantioenriched enamines undergoing a dehydrogenative coupling with alcohol nucleophiles in the presence of water to produce esters (Scheme 1a, c). Furthermore, allylic amines are compelling substrates as they can be readily accessed in a diastereomerically pure fashion through a variety of methods (Scheme 2).

Our group has published a similar transformation for the formation of amides from allylic amines and amine nucleophiles.[11] During those investigations, we discovered that a Rh-BINAP complex with $NaBAr^F_4$ in ethereal solvents were the ideal conditions for the clean conversion of allylic amines to amides. To modify this method for the synthesis of esters, we believed we could replace amine nucleophiles with alcohols; however, there are some inherent challenges with such an approach. Alcohols are less nucleophilic than amines, disfavoring the formation of the hemiacetal intermediate necessary for the final dehydrogenation.[6] For this reason, we were particularly concerned with identifying conditions for the selective synthesis of esters over other byproducts such as alcohol nucleophile homocoupling, aldol condensation, or deleterious reduction pathways in the presence of a Rh–H species.

When our catalytic amidation conditions were employed with 1-hexanol as a nucleophile instead of an amine, a tertiary amine byproduct **4** was observed along with the desired ester product **3a**, consistent with our earlier hypotheses (Table 1). We found that the identity of the solvent played a key role in improving the chemoselectivity of the reaction. Changing the solvent from THF to DME limited the formation of **4** to trace quantities. Further modification of the reaction conditions identified Na_3PO_4 as an effective base (Table 1, entry 4) with styrene as a sufficient hydrogen acceptor necessary for catalyst turnover (see Supporting Information).

After optimizing the reaction conditions, we investigated the nucleophile scope of the reaction (Table 2). A variety of 1° alcohol nucleophiles including 1-hexanol (**3a**), ethanol (**3b**), and methanol (**3c**) are well-suited for the reaction providing esters in good yields. Nucleophiles containing heterocycles such as a pendant morpholino group (**3e**) are well-tolerated under the reaction conditions despite the ability of 3° amines to strongly coordinate to many transition metal catalysts. Benzyl alcohol and its derivatives demonstrate the effect of electronic variation on the yield of the reaction; electron neutral and slightly electron deficient alcohols are most efficient (**3f-3j**). More hindered nucleophiles give slightly diminished yields, demonstrating some sensitivity to steric hinderance (**3k-3m**). Unfortunately, phenols are not competent nucleophiles under the current reaction conditions. This may be attributed to the competitive binding of the phenol to the cationic Rh(I) species.[12]

We were pleased to discover that the reaction is amenable to a broad range of substitution patterns on the allylic amine (Table 3). Several β,β-dialkyl esters, such as those containing silyl ethers (**3n**)‡ or distal arenes (**3o**, **3p**), can be accessed from the corresponding allylic amines with excellent enantiomeric excess in all cases. Even when the substituents on the starting alkene are sterically similar, the catalyst maintains high enantiocontrol (**3q**). 3,3-diaryl allylic amines show good reactivity and enantioselectivity; however, increased catalyst loading and temperature are necessary to establish good conversion of starting material to product. Electron-rich furyl



Scheme 2 Synthesis of diastereomerically pure allylic amines. See Supporting Information for details of substrate synthesis.

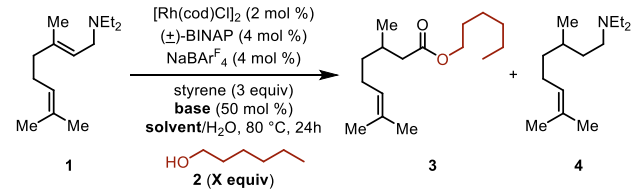


Table 1 Optimization of reaction conditions.

Entry	Base	Solvent	X	**3a** yield (%)[b]	**4** yield (%)[b]
1	Cs_2CO_3	THF	3	52	12
2	Cs_2CO_3	DME	3	56	<5
3	Na_3PO_4	THF	3	79	17
4	**Na_3PO_4**	**DME**	**3**	**91**	**<5**
5	Na_3PO_4	DME	2	82	13
6	Na_3PO_4	DME	1.5	71	10.5
7	Na_3PO_4	DME	1	49	17

[a][Rh(cod)Cl]$_2$ (2 mol %), (±)-BINAP (4 mol %), $NaBAr^F_4$ (4 mol %), **1** (0.12 mmol), **2** (1–3 equiv), styrene (3.0 equiv), base (50 mol %), solvent (0.100 mL), H_2O (1.5 equiv), 80 °C, 24 h. [b]*In situ* yield determined by gas chromatography with comparison to diphenyl methane (10 μL) as an internal standard.

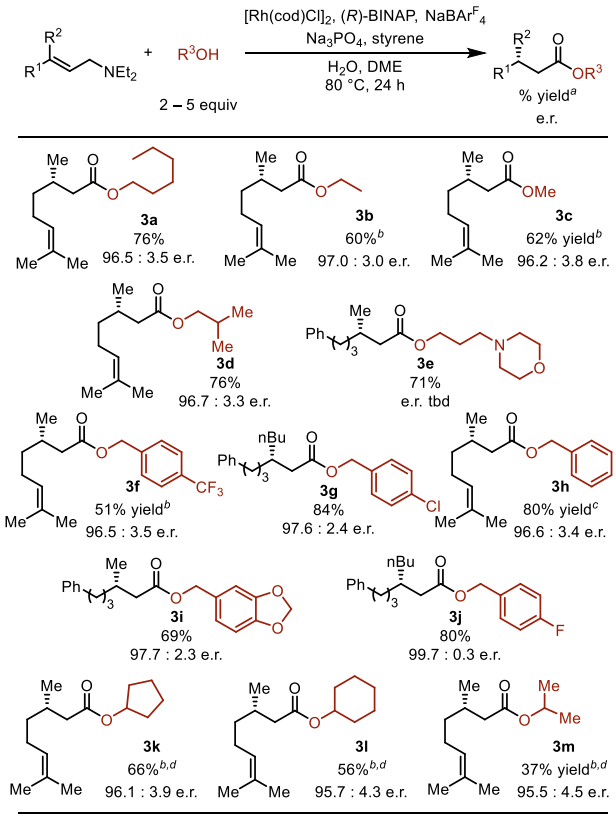


Table 2 Scope of 1° and 2° alcohols for the esterification of allylic amines. [a] $[Rh(cod)Cl]_2$ (2 mol %), (*R*)-BINAP (4 mol %), $NaBAr^F_4$ (4 mol %), Na_3PO_4 (50 mol %), allylic amine (0.12 mmol), alcohol nucleophile (3.0 equiv), styrene (3.0 equiv), H_2O (1.5 equiv), DME (1.2 M), 80 °C, 24 h. [b] with 5.0 equiv nucleophile. [c] with 2.0 equiv nucleophile. [d] at 100 °C.

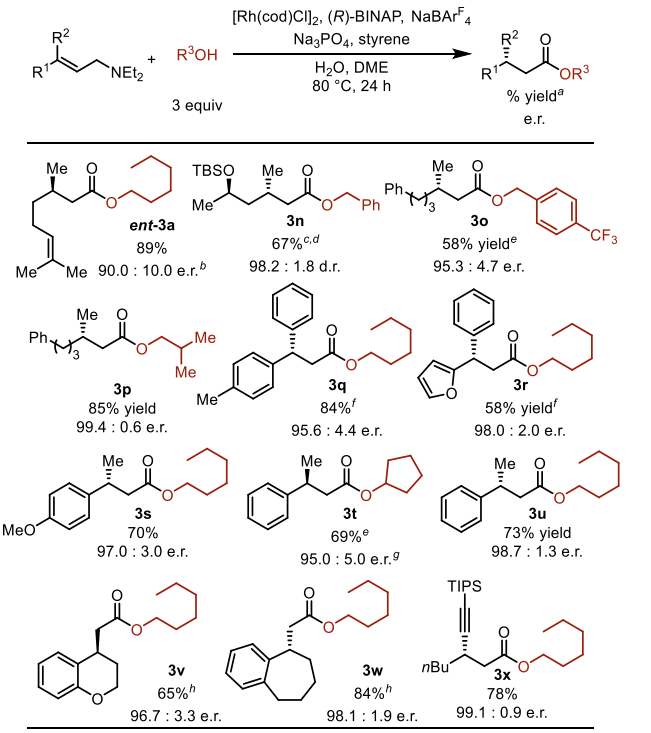
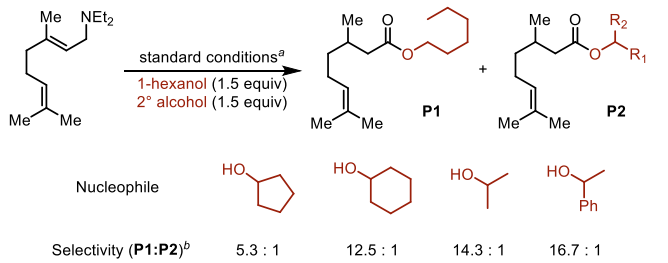


Table 3 Scope of allylic amines for asymmetric oxidative esterification. [a] $[Rh(cod)Cl]_2$ (2 mol %), (*R*)-BINAP (4 mol %), $NaBAr^F_4$ (4 mol %), Na_3PO_4 (50 mol %), allylic amine (0.12 mmol), alcohol nucleophile (3 equiv), styrene (3.0 equiv), H_2O (1.5 equiv), DME (1.2 M), 80 °C, 24 h. [b] from the *Z* isomer of **1** (91.7 : 8.3 *Z*/*E*) [c] with 2.0 equiv nucleophile. [d] 68% and 5.5 : 94.5 d.r. with *S*-BINAP [e] with 5.0 equiv nucleophile. [f] at 100 °C. [g] with (*S*)-BINAP. [h] at 100 °C for 48 h with 8 mol % catalyst.

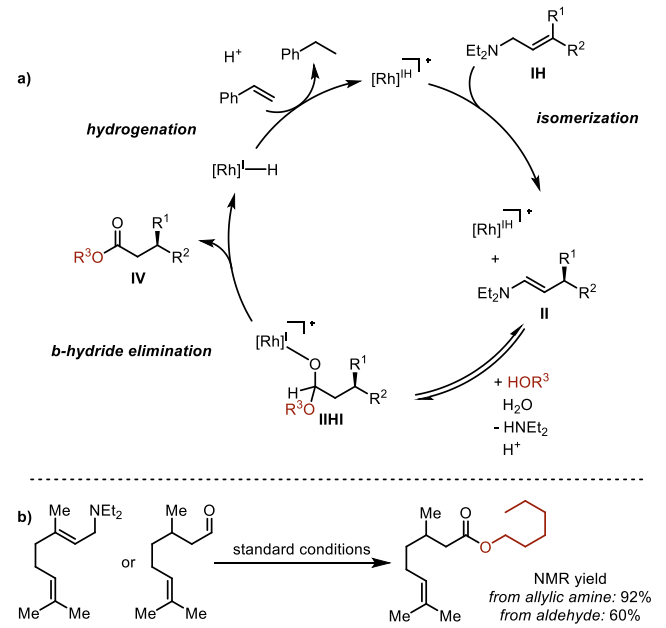
rings are well-tolerated under the reaction conditions (**3r**). Excitingly, we have found that substrates containing exocyclic alkenes, a substrate class rarely demonstrated for asymmetric synthesis of β-substituted carbonyl compounds,[7g] are reactive leading to good yields and enantioselectivities (**3v-3w**). Allylic amines with π-functionality are not only limited to aryl substituents. When a substrate containing an enyne is subjected to the reaction conditions, no hydrogenation of the alkyne is observed (**3x**). Finally, the absolute stereochemistry has previously been unambiguously determined by X-ray crystallography.[11a]

To probe the chemoselectivity of the transformation, we subjected allylic amine **1a** to the reaction conditions with a 1:1 ratio of 1° alcohol 1-hexanol to a variety of 2° alcohols (Scheme 3). Primary alcohols were preferentially incorporated, with selectivities ranging from 5.3:1 for the least sterically hindered cyclopentanol to 16.7:1 for the most sterically hindered α-hydroxyethylbenzene. In an intramolecular competition study between a 1° and 3° alcohol, the 1° alcohol was exclusively incorporated (see Supporting Information).

Our current mechanistic hypothesis draws inspiration from the work of Noyori, Otsuka, and Tani (Scheme 4a).[10] Cationic Rh(I)-BINAP complexes are known to facilitate an isomerization of allylic amines to form optically pure enamines. The initial β-hydride elimination to form **II** is the enantiodetermining step.[10c,e] Under our reaction conditions, the intermediate enamine **II** can participate in several equilibrium-controlled processes with *in situ* H_2O and nucleophile to form a Rh-alkoxide species **III**.[13] This intermediate can then undergo a β-hydride elimination to form the final ester product **IV** and a Rh–H species. Styrene acts as a hydrogen acceptor to regenerate the active catalyst. Though we believe this process to be redox neutral, a Rh(I)/(III) cycle for the oxidation of intermediate **III** cannot be ruled out. Furthermore, when citronellal was employed as the substrate under standard reaction conditions, the yield of the reaction diminished (Scheme 4b). While no definitive mechanistic conclusion can be drawn by this data alone, it suggests that the reaction does not proceed through build-up of large quantities of a discrete aldehyde intermediate. In fact, crude NMR reveals evidence of aldehyde decomposition under standard conditions (see Supporting Information). Instead, the catalytically formed aldehyde may immediately react with the alcohol to yield the final product, or the



Scheme 3 [a]General reaction conditions: see Table 2. [b]Chemoselectivity determined by ^1H NMR of the crude reaction mixture.



Scheme 4 a) Proposed mechanism. b) Comparison of aldehydes and allylic amines as substrates for the reaction.

alcohol may attack the iminium intermediate directly without proceeding through the aldehyde.

Conclusions

In conclusion, we have disclosed a method by which chiral, β-branched esters can be synthesized in one pot with a broad scope of nucleophiles and substrates. Utilizing an isomerization strategy has enabled enantioinduction that is not limited by the steric differentiation of the substituents at the prochiral center. This method has been demonstrated for the asymmetric synthesis of β,β-dialkyl-, β,β-diaryl-, and β-alkyl-β-aryl-substituted esters, a breadth of substrate scope not commonly observed in methods for the synthesis of similar compounds. Primary and secondary alcohols are competent reaction partners without need for solvent quantities of nucleophile. This method performs similarly under a variety of steric environments, giving good to excellent yields with excellent enantioselectivities in all cases.

Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ When the desilylated analogue of **6** was subjected to the reaction, only the volatile 4,6-dimethyltetrahydro-2H-pyran-2-one was observed by GC/MS of the crude reaction mixture.

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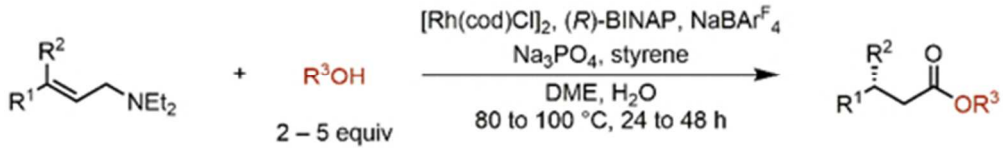
β-Substituted chiral esters are synthesized in excellent yields and enantioselectivities from allylic amines using [(BINAP)Rh]BAr^F_4 as the chiral catalyst.


R2
R1
NEt2
+
R3OH
2 – 5 equiv
[Rh(cod)Cl]2, (R)-BINAP, NaBArF4
Na3PO4, styrene
DME, H2O
80 to 100 °C, 24 to 48 h
R2
O
R1
OR3