Organic LETTERS

Letter

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Asymmetric Induction in Hydroacylation by Cooperative Iminium Ion−Transition-Metal Catalysis

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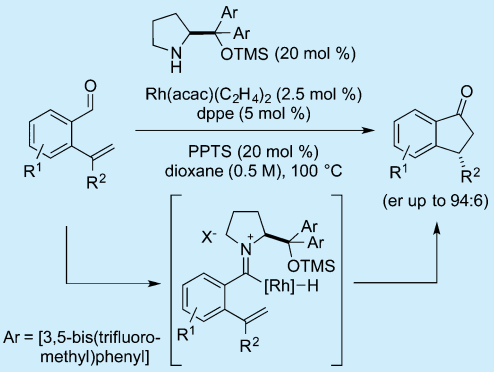
Supporting Information

ABSTRACT: A new strategy for the rhodium-catalyzed enantioselective hydroacylation is described. This has been achieved through the merger of iminium ion catalysis and transition-metal catalysis such that asymmetric induction derives from a readily accessible, inexpensive chiral nonracemic secondary amine catalyst rather than a chiral nonracemic phosphine as is typical of conventional asymmetric hydroacylation methods.

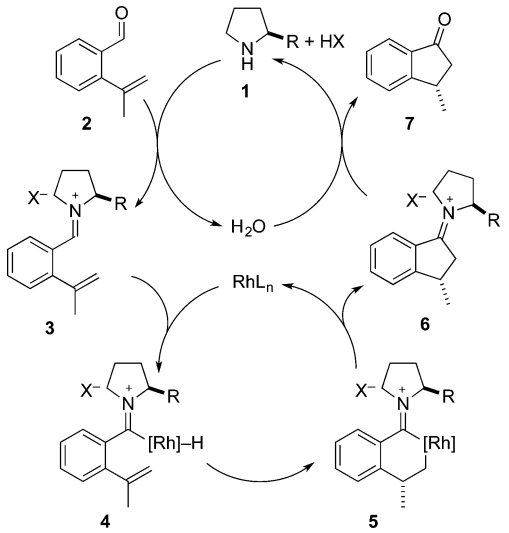


The rhodium-catalyzed enantioselective hydroacylation[1] of alkenes is a highly attractive, atom-economical approach to the synthesis of chiral nonracemic ketones.[2] Such reactions are thought to proceed via the oxidative insertion of Rh(I) into the aldehydic C−H bond, followed by migratory insertion of an alkene into the Rh−H bond, which is followed by reductive elimination to generate the desired ketone. To achieve asymmetric induction in such reactions, Rh species having expensive chiral, nonracemic ligands have been used with considerable success.[3] Unfortunately, in some cases, a competing side reaction in these transformations is decarbonylation of the acyl−metal hydride intermediate. One means of circumventing this side reaction is through the incorporation of chelating functionality in the aldehyde substrate,[4] which serves to stabilize the acyl−metal hydride intermediate, thereby suppressing or altogether preventing its decarbonylation. While effective, such methods are, of course, restrictive with regard to their substrate scope, since only aldehydes capable of such intramolecular chelation are viable substrates. A clever means of mitigating unwanted decarbonylation, while not restricting the substrate scope of the reaction, was put forth by Suggs[5] in 1979 and expanded upon by Jun, starting in 1997.[6] In this approach, an imine is formed from the aldehyde and 2-amino-3-picoline,[7] which enables a stabilizing complexation with Rh that does not require any additional structural contribution from the aldehyde.

It occurred to us that since an imine intermediate is required of such reactions, it might be possible for an iminium to serve in its place. Indeed, such a species should be even more susceptible to oxidative insertion than an imine. If that were the case, then it might be possible to circumvent the use of a Rh species having expensive chiral nonracemic phosphine ligands for asymmetric induction and instead use a readily accessible, inexpensive chiral nonracemic secondary amine as the source of both asymmetric induction and initial C−H activation, thereby merging asymmetric iminium ion catalysis and transition-metal catalysis.[8] In what follows, we outline our preliminary efforts along these lines in which the combination of a catalytic amount of a chiral nonracemic secondary amine and an achiral Rh species are used to effect asymmetric hydroacylation.

A generalized catalytic cycle consistent with our proposed idea is shown in Scheme 1. Condensation of an aldehyde with a

Scheme 1. Proposed Catalytic Cycle



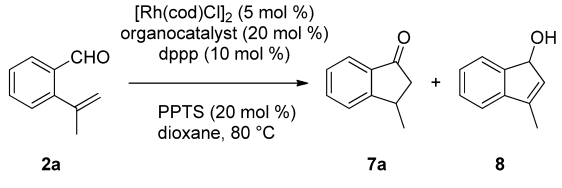
Received: September 20, 2016

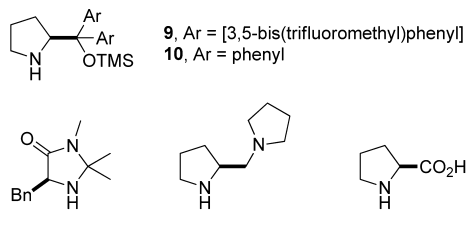
DOI: 10.1021/acs.orglett.6b02825
Org. Lett. XXXX, XXX, XXX−XXX

catalytic amount of a *chiral* nonracemic secondary amine would generate an iminium species that would act as a substrate for oxidative insertion of an *achiral* rhodium species of some sort. While such an oxidative insertion has never before been reported, we felt that it should be even more viable than related known insertions to imine species.[5−7] Diastereoselective olefin addition followed by reductive elimination would then provide an iminium ion that would undergo hydrolysis to liberate the desired cyclic ketone in enantiomerically enriched form, along with both the Rh catalyst and the chiral secondary amine catalyst. The success of the proposed method would require that iminium formation and Rh insertion proceed more rapidly than the background rhodium-catalyzed hydroacylation of the aldehyde. The latter would, of course, result in the formation of the desired product, but in a nonenantioselective manner, and would potentially lead to decarbonylation as well. Nonetheless, we felt that it may well be possible to achieve the proposed catalytic process since iminium formation would be expected to be rapid under acid-catalyzed conditions and since insertion of the Rh catalyst into the iminium C−H bond should be faster than insertion into the corresponding aldehyde bond.

The proposed transformation was tested using aldehyde **2a** as a model substrate. To do so, **2a** was combined with amine **9** (20 mol %), $[Rh(cod)Cl]_2$ (5 mol %), dppp (10 mol %), and PPTS (20 mol %) in dioxane, and the resulting mixture was heated to 80 °C for 16 h (Table 1, entry 1).

Table 1. Screening of Chiral, Nonracemic Secondary Amines





entry	amine	conversion (%)[a]	7a/8	er
1	**9**	30	1:1	80:20
2	**10**	60	3.3:1	54:46
3	**11**	<5	nd[b]	nd
4	**12**	50	1:0	65:35
5	**13**	<5	nd	nd

[a]As judged by ^{1}H NMR. [b]nd = not determined.

We were pleased to find that the desired cyclized product **7a** was indeed obtained from this transformation, with a promising er of 80:20.[9] Unfortunately, **7a** was produced in low yield and was formed along with an approximately equal amount of byproduct **8**, the latter being the result of an acid-catalyzed Prins reaction.[10] In an effort to improve on the reaction outcome, we attempted the same reaction but using different chiral nonracemic secondary amines **10**−**13**. The yield of the reaction was improved significantly in the case of both amine **10** and amine **12** (entries 2 and 4, respectively), but unfortunately, the er was diminished in comparison to the use of amine **9**. Interestingly, the hydroacylation reaction was almost completely suppressed when amines **11** and **13** were used. Since amine **9** had given the best er of those tried, we decided to focus on it and attempt to improve the outcome of the transformation by modifying other reaction parameters.

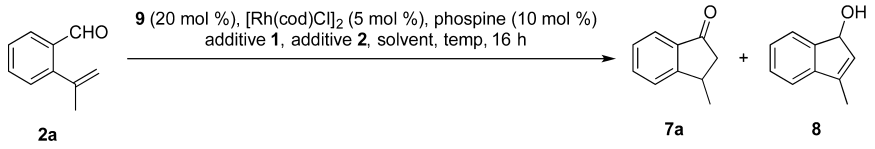
We began this work by examining the phosphine ligand. Shortening the length of the bisphosphine ligand by one methylene unit through the use of dppe in place of dppp led to detectable enantiomeric enrichment (85:15) (Table 2, entry 1). Use of the more structurally rigid bisphosphine ligands BINAP and Dpe-Phos (Table 2, entries 2 and 3, respectively) caused the enantioselectivity to decrease appreciably. In the case of the BINAP ligand, an excellent hydroacylation outcome was observed (>99% conversion), but unfortunately it seemed that the rate of the background aldehyde hydroacylation was relatively very fast in comparison to formation and Rh insertion into the iminium ion, as the desired product (**7a**) was obtained as a racemate. The exchange of PPTS for *p*-TsOH·H_2O promoted the selective production of byproduct **8** (Table 2, entry 4). The use of various solvents other than dioxane diminished the overall reactivity as well as the product ratio (Table 2, entries 5−7). Notably, despite this, the use of THP resulted in excellent asymmetric induction (er = 98:2). The use of the additive $AgSbF_6$, which was expected to generate a cationic Rh(I) species in situ[11] (Table 2, entry 8), apparently accelerated the background reaction, producing the desired product with essentially complete conversion but in racemic form. When the amount of PPTS was increased to 50 mol % and the temperature was raised to 90 °C (Table 2, entry 10), the conversion and enantioselectivity were significantly increased. Using the conditions of entry 10 as a new benchmark, we next focused our attention on the remaining two untested reaction parameters, namely the rhodium source and the reaction concentration.

This phase of our study was initiated by changing the rhodium catalyst to $Rh(acac)(C_2H_4)_2$ while otherwise maintaining the conditions from entry 10 of Table 2. Under these conditions (Table 3, entry 1), there was a slight reduction in conversion and asymmetric induction, but the desired product and byproduct ratios remained the same. We next tried increasing the reaction concentration from 0.1 to 0.5 M (Table 3, entry 2), which turned out to have a profound effect on the reaction outcome; the product ratio increased substantially in favor of the desired product (5:1) while the enantioselectivity remained equally high (86:14). We then reduced the Rh catalyst, phosphine ligand, and PPTS loadings to 2.5, 5, and 20 mol % respectively (Table 3, entry 3). These changes resulted in the reaction going to completion (100% conversion) and producing excellent enantioselectivity. However, unfortunately, the ratio of **7a** to **8** decreased to 3:1. Next, we tried increasing the reaction temperature to 100 °C (entry 4), which led to an improvement in the product ratio (4:1) in comparison to that observed for entry 3 in Table 3 while maintaining both high conversion and asymmetric induction.

Satisfied that we had established suitable reaction conditions to effect our new asymmetric hydroacylation reaction, we set out to conduct a preliminary exploration of its scope (Scheme 2). We first investigated varying substituents on the aromatic ring. In the event, a wide array of both electron-donating and -withdrawing groups were tolerated with good to excellent er. Depending on the positioning and electronic nature of the aryl substituent, the asymmetric induction varied. Interestingly, the

DOI: 10.1021/acs.orglett.6b02825
Org. Lett. XXXX, XXX, XXX−XXX

Table 2. Screening of Reaction Conditions[a]

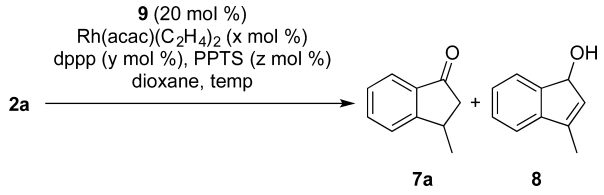


2a 7a 8

entry	phosphine	additive 1	additive 2	solvent	temp (°C)	conv (%)[b]	7a/8	er
1	dppe	PPTS (20 mol %)	none	dioxane	80	49	1:3	85:15
2	BINAP	PPTS (20 mol %)	none	dioxane	80	>99	10:1	55:45
3	Dpe-Phos	PPTS (20 mol %)	none	dioxane	80	88	1:2.3	55:45
4	dppe	*p*-TsOH·H_2O (20 mol %)	none	dioxane	80	93	0:1	nd[c]
5	dppe	PPTS (20 mol %)	none	THP[d]	80	39	1:2.5	98:2
6	dppe	PPTS (20 mol %)	none	DCE[e]	80	24	0:1	nd
7	dppe	PPTS (20 mol %)	none	PhH	80	14	0:1	nd
8	dppe	PPTS (20 mol %)	$AgSbF_6$ (10 mol %)	dioxane	80	100	1:0	50:50
9	dppe	PPTS (50 mol %)	none	dioxane	80	50	1:2	96:4
10	dppe	PPTS (50 mol %)	none	dioxane	90	83	1:1.8	95:5

[a]All reactions were carried out at 0.1 M concentration. [b]determined by ^{1}H NMR. [c]nd = not determined. [d]Tetrahydropyran. [e]DCE = 1,2-dichloroethane.

Table 3. Screening of Reaction Conditions with $Rh(acac)(C_2H_4)_2$ as Catalyst



7a 8

entry	X	Y	Z	concn (M)	temp (°C)	conv[a] (%)	7a/8	er
1	10	20	50	0.1	90	73	1:1.7	87:13
2	10	20	50	0.5	90	93	5:1	86:14
3	2.5	5	20	0.5	90	100	3:1	94:6
4	2.5	5	20	0.5	100	100	4:1	94:6

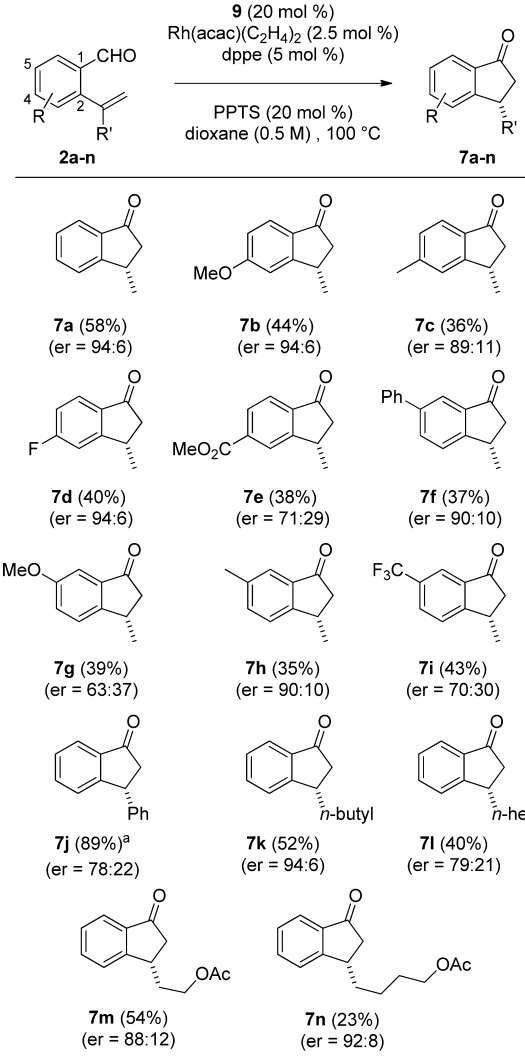
[a]As judged by ^{1}H NMR.

hydroacylation product **7e**, containing a strongly electron-withdrawing group in the 4-position, produced much lower er compared to the other compounds with electron-donating or weakly withdrawing substituents at the 4-position (**7b–d**). Electronically neutral substituents in the 5-position (**7f** and **7h**) were formed with very good enantioselectivity; however, when either electron-donating or -withdrawing groups were incorporated at the 5-position, the er was diminished. We next explored the scope of the hydroacylation reaction with respect to the vinyl group substituent. Addition of a phenyl group to the vinyl moiety (**7j**) provided a moderate er but vastly improved the yield. Alkyl groups of varying length were also examined. Interestingly, incorporation of an *n*-butyl group (**7k**) provided excellent er, but when an *n*-hexyl group was used (**7l**) the er was somewhat diminished. Lastly, acetates **7m** and **7n** were furnished with a very good er.

A crystal structure of compound **7b** was obtained which indicated the configuration of the newly formed stereogenic center is *S* (Figure 1).

In conclusion, we have demonstrated a new approach to effecting asymmetric induction in the venerable hydroacylation reaction. Our approach is based on the merger of asymmetric immium ion catalysis and transition-metal catalysis. Asymmetric induction is achieved through the use of a readily accessible, inexpensive chiral nonracemic secondary amine catalyst rather than through the use of a chiral nonracemic phosphine, as is typical of asymmetric hydroacylation methods. A key feature of

Scheme 2. Preliminary Test of Substrate Scope



[a]Reaction conducted at 80 °C.

DOI: 10.1021/acs.orglett.6b02825
Org. Lett. XXXX, XXX, XXX−XXX

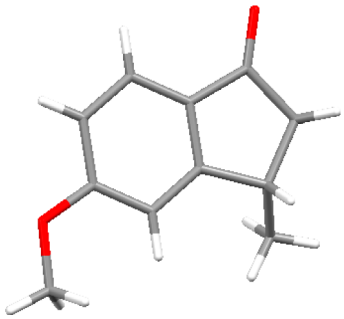


Figure 1. X-ray crystal structure of **7b**.

our method appears to be a novel oxidative insertion of Rh into an iminium C−H bond. Studies are underway to investigate the mechanism of the transformation and to expand its scope. Furthermore, the utility of iminium C−H insertion in the context of other transformations is being explored and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02825.

Experimental procedures and analytical data for all new compounds (PDF)

X-ray crystallographic data for **7b** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to Dr. Daniel Lim (Yeshiva University) for conducting preliminary experiments related to this work and Dr. James Korp (University of Houston) for X-ray crystal structure determination. We thank the NSF (NSF 1300652), the Welch Foundation (E-1806), and the University of Houston for financial support.

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(9) Determined by GC analysis using a chiral, nonracemic stationary phase. See the Supporting Information for details.

(10) It was found that byproduct **8** is formed as a racemate.

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DOI: 10.1021/acs.orglett.6b02825
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