Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX-XXX

pubs.acs.org/OrgLett

Highly Enantioselective Asymmetric Hydrogenation of Carboxy-Directed α,α-Disubstituted Terminal Olefins via the Ion Pair Noncovalent Interaction

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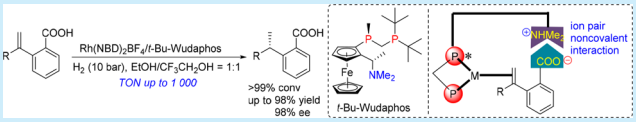
Supporting Information

ABSTRACT: The *t*-Bu-Wudaphos was successfully applied into Rh-catalyzed asymmetric hydrogenation of α,α-disubstituted terminal olefins bearing a carboxy-directed group with excellent reactivities and enantioselectivities via the ion pair noncovalent interaction (up to >99% conversion, 98% yield, 98% ee) under mild reaction conditions without base. In addition, control experiments were conducted, and the results demonstrated that the ion pair noncovalent interaction between ligand and substrate played an important role in achieving an outstanding performance in this asymmetric hydrogenation.



The chiral benzylmethyl center is an important motif in biologically active compounds and natural products,[1] such as H_1-antihistamine,[2] (+)-curcudiol,[1b,3] (+)-curcumene,[4] and (+)-curcuphenol[1b,3] (Figure 1). Owing to its great importance, much more attention has been paid to the development of efficient catalytic methodologies to prepare the chiral benzylmethyl motif in the last decades.[5] The transition-metal-catalyzed asymmetric hydrogenation of prochiral unsaturated compounds is one of the most efficient and powerful methods to access chiral compounds.[6] Recently, Zhou and co-workers successfully developed carboxy-directed asymmetric hydrogenation of 1,1-diarylethenes and 1,1-dialkylethenes catalyzed by chiral iridium catalysts bearing spiro phosphine−oxazoline ligands.[7] Subsequently, they realized Ir-catalyzed asymmetric hydrogenation of other olefins bearing carboxylic acid group.[8] It is well-known that substituents of double bonds with different sizes in asymmetric hydrogenation were favorable in achieving excellent chiral induction.[5b,9] Therefore, it is difficult to realize highly efficient asymmetric hydrogenation of 1,1-disubstituted ethenes bearing a similar substituent group with excellent enantioselectivity. Several groups developed asymmetric hydrogenation of α,α-diarylethenes with the aid of −OH,[10] −OMe,[11] $-NH_2$,[12] and −COOH[7,8a,13] as directing groups.

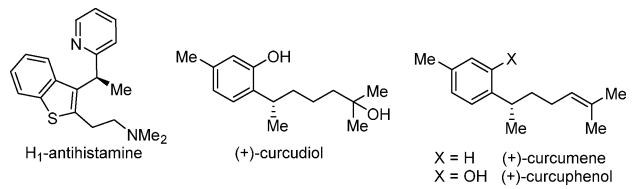


Figure 1. Biologically active compounds and natural products.

Most recently, we were devoted to developing a series of privileged ferrocenyl chiral bisphosphorus ligands Wudaphos,[14a,b] SPO-Wudaphos,[14c−e] and *t*-Bu-Wudaphos.[14f] These ligands performed excellently in Rh-catalyzed asymmetric hydrogenation of various types of unsaturated carboxylic acids through the ion pair noncovalent interaction between the amino group of the ligands and the acid group of the substrates.[14] Since there is great importance of the ion pair noncovalent interaction between the amino group of the ligands and the acid group of the substrates,[14,15] we believe that the asymmetric hydrogenation of α,α-disubstituted terminal olefins bearing a carboxy-directed group should provide excellent results with our ferrocenyl chiral bisphosphorus ligands. Herein, the ion pair noncovalent interaction between the amino group of the ligands and the acid group of the substrates proved to be very efficient in this Rh-catalyzed asymmetric hydrogenation of α,α-disubstituted terminal olefins (Scheme 1, up to 98% ee, >99% conversion, TON up to 1000).

Our initial investigation was carried out by evaluating the solvent effects in this asymmetric hydrogenation of 2-(1-phenylvinyl)-benzoic acid (**1a**) as the model substrate and with the catalyst generated *in situ* by mixing $Rh(NBD)_2BF_4$ with *t*-Bu-Wudaphos (S/C = 100) at room temperature. As shown in Table 1, except EtOH and CF_3CH_2OH, other solvents, such as MeOH, THF, DCM, $ClCH_2CH_2Cl$, and CH_3CN, showed poor results (Table 1, entries 1−7). EtOH and CF_3CH_2OH can provide full conversions and excellent enantioselectivities (>99% conversion,

Received: September 21, 2017

DOI: 10.1021/acs.orglett.7b02972
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Scheme 1. Asymmetric Hydrogenation of α,α-Disubstituted Terminal Olefins Bearing Carboxy-Directed Group Catalyzed by Rh/*t*-Bu-Wudaphos with Ion Pair Noncovalent Interaction

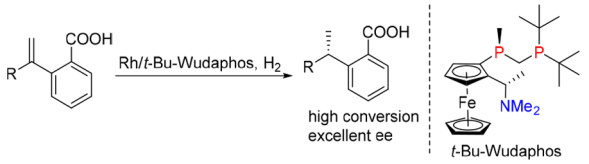
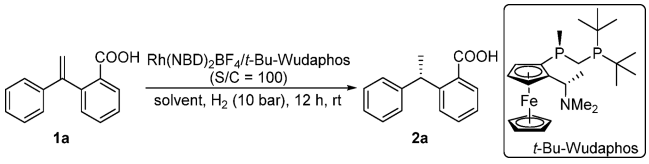


Table 1. Screening Solvents for the Asymmetric Hydrogenation of 2-(1-Phenylvinyl)-benzoic Acid (1a)[a]



entry	solvent	conv (%)[b]	ee (%)[c]
1	MeOH	<5	55
2	EtOH	>99	93
3	CF_3CH_2OH	>99	95
4	THF	<5	25
5	DCM	NR	NA
6	$ClCH_2CH_2Cl$	<5	65
7	CH_3CN	NR	NA
8	EtOH/CF_3CH_2OH = 1:10	>99	94
9	EtOH/CF_3CH_2OH = 1:5	>99	94
10	EtOH/CF_3CH_2OH = 1:1	>99	98
11	EtOH/CF_3CH_2OH = 5:1	>99	95
12	EtOH/CF_3CH_2OH = 10:1	>99	94

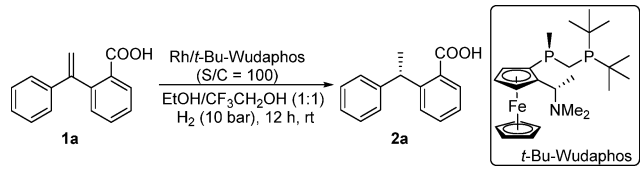
[a]Unless otherwise noted, all reactions were carried out with a [$Rh(NBD)_2BF_4$]/*t*-Bu-Wudaphos/**1a** (0.1 mmol) ratio of 1:1.1:100 in 1.0 mL of solvent at room temperature under hydrogen (10 bar) for 12 h, EtOH/CF_3CH_2OH is volume ratio. [b]Determined by ^1H NMR analysis. [c]Determined by HPLC analysis using a chiral stationary phase. NR = no reaction. NA = not available.

93%−95% ee, Table 1, entries 2−3). In order to improve the enantioselectivity of this transformation, a series of ratios of mixed solvents of EtOH and CF_3CH_2OH were investigated (Table 1, entries 8−12). We found that the mixture solvents of EtOH/CF_3CH_2OH (V/V = 1:1) displayed the best results (>99% conversion, 98% ee, Table 1, entry 10). It is possible that these alcohols were involved in the ion pair noncovalent interaction, which may contribute to high efficiency of the catalytic system.

Subsequently, we examined the catalytic effect of *t*-Bu-Wudaphos with different rhodium sources in the mixture solvents of EtOH/CF_3CH_2OH (V/V = 1:1) (Table 2, entries 1−4). To our delight, all of the rhodium sources can provide full conversions and excellent enantioselectivities (90%−98% ee, Table 2, entries 1−4). $Rh(NBD)_2BF_4$ afforded the best result with >99% conversion and 98% ee (Table 1, entry 1).

With the optimized reaction conditions established ($Rh(NBD)_2BF_4$/*t*-Bu-Wudaphos/10 bar H_2, S/C = 100/room temperature), an array of various α,α-disubstituted terminal olefins **1** bearing an *ortho*-carboxy group were employed as substrates to inspect the generality of this asymmetric hydrogenation. These results are summarized in Scheme 2. A series of α,α-diaryl terminal olefins were hydrogenated smoothly to provide various chiral 2-substituted benzoic acids with full conversions, 97−98% yields and 92−98% ee. The 2-(1-

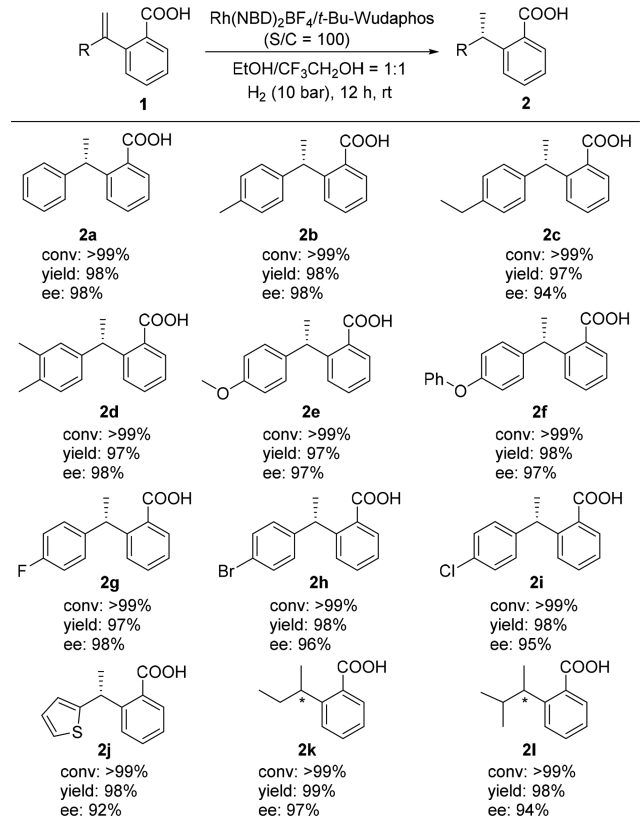
Table 2. Screening Metal Precursor for the Asymmetric Hydrogenation of 2-(1-Phenylvinyl)-benzoic Acid (1a)[a]



entry	[Rh]	conv (%)[b]	ee (%)[c]
1	$Rh(NBD)_2BF_4$	>99	98
2	$Rh(COD)_2BF_4$	>99	97
3	$Rh(COD)_2SO_3CF_3$	>99	97
4	$[Rh(COD)Cl]_2$	>99	90

[a]Unless otherwise noted, all reactions were carried out with a [Rh]/*t*-Bu-Wudaphos/**1a** (0.1 mmol) ratio of 1:1.1:100 in 1.0 mL of EtOH/CF_3CH_2OH (V/V = 1:1) at room temperature under hydrogen (10 bar) for 12 h. [b]Determined by ^1H NMR analysis. [c]Determined by HPLC analysis using a chiral stationary phase. NBD = norbornadiene. COD = 1, 5-cyclooctadiene.

Scheme 2. Substrate Scope of the Carboxy-Directed Asymmetric Hydrogenation of α,α-Disubstituted Terminal Olefins 2[a]



[a]The reaction was conducted in 0.1 mmol scale in 1.0 mL of EtOH/CF_3CH_2OH (V/V = 1:1) at room temperature, $[Rh(NBD)_2]BF_4$ was used as metal precursor, *t*-Bu-Wudaphos as the ligand, H_2 pressure = 10 bar, S/C = 100, and reaction time = 12 h.

aryllvinyl)-benzoic acid substrates bearing electron-donating groups (**1b**−**1f**) and electron-withdrawing groups (**1g**−**1i**) on the phenyl ring performed well with excellent results (>99% conversion, 94−98% ee). It is worth noting that the hydrogenation of heterocyclic aromatic 2-(1-thienylvinyl)-benzoic acid (**1j**) can achieve 92% ee and >99% conversion. To our delight,

DOI: 10.1021/acs.orglett.7b02972
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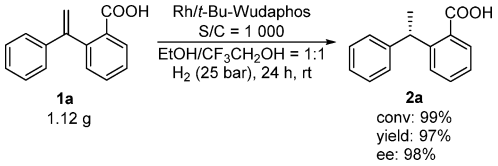
the aliphatic substrates 2-(but-1-en-2-yl)benzoic acid (**1k**) and 2-(3-methylbut-1-en-2-yl)benzoic acid (**1l**) also performed efficiently (>99% conversion, 94−97% ee).

Encouraged by these excellent results, gram-scale reaction with low catalyst loading was conducted to demonstrate the practical application of this Rh/*t*-Bu-Wudaphos-catalyzed hydrogenation. As shown in Scheme 3, when the catalyst loading was reduced to

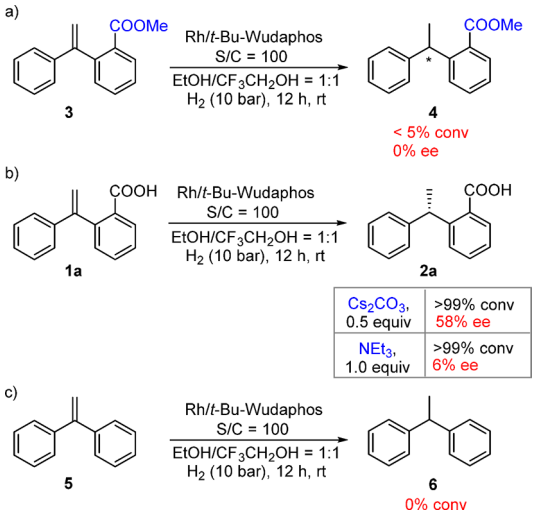
Scheme 3. Gram-Scale Reaction with Lower Catalyst Loading



0.1 mol % (S/C = 1 000), the asymmetric hydrogenation of 2-(1-phenylvinyl)-benzoic acid (**1a**) with 1.12 g proceeded smoothly with full conversion, 97% yield, and 98% ee at room temperature.

In order to reveal the critical role of the ion pair interaction between the ligand and the substrate, primary control experiments were conducted under the standard reaction conditions. The asymmetric hydrogenation of methyl 2-(1-phenylvinyl)-benzoate ester **3** was investigated and poor results were observed (<5% conversion, 0% ee, Scheme 4a). In addition, the base was

Scheme 4. Control Experiments for the Investigation of the Ion Pair Noncovalent Interaction Effect



added into our catalytic system to illustrate the noncovalent ion pair interaction. The enantioselectivity of the asymmetric hydrogenation of 2-(1-phenylvinyl)-benzoic acid (**1a**) dropped after adding 0.5 equiv of Cs_2CO_3 or 1.0 equiv of NEt_3 (Scheme 4b). Finally, the substrate without carboxylic acid group ethene-1,1-diyldibenzene **5** was hydrogenated and did not occur at all (Scheme 4c). These results suggested that the ion pair noncovalent interaction between ligand and acid substrate is extremely important to achieve excellent performance in this asymmetric hydrogenation.

In summary, the *t*-Bu-Wudaphos was successfully applied to the Rh-catalyzed asymmetric hydrogenation of α,α-disubstituted terminal olefins bearing a carboxy-directed group with excellent reactivities and enantioselectivities via the ion pair noncovalent interaction (up to >99% conversion, 98% yield, 98% ee) and under mild reaction conditions without base. Moreover, our control experiment results demonstrated that the noncovalent ion pair interaction between ligand and acid substrate was critical in affording excellent results in this asymmetric hydrogenation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02972.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the financial support of the Important Sci-Tech Innovative Project of Hubei Province (2015ACA058), the National Natural Science Foundation of China (Grant No. 21372179, 21432007, 21502145), Natural Science Foundation of Hubei Province (Grant No. 2016CFB449), and Wuhan Morning Light Plan of Youth Science and Technology (Grant No. 2017050304010307). The Program of Introducing Talents of Discipline to Universities of China (111 Project) is also appreciated.

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