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Asymmetric Reductive Coupling of Dienes and Aldehydes Catalyzed by Nickel Complexes of Spiro Phosphoramidites: Highly Enantioselective Synthesis of Chiral Bishomoallylic Alcohols

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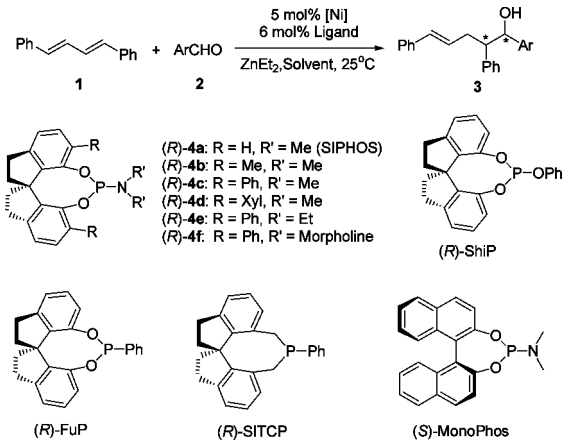
Alkenylation and allylation of aldehydes for preparing allylic and homoallylic alcohols are fundamental processes in organic synthesis, and many efficient methods, including asymmetric versions, have been well developed.[1] However, homoallylation of aldehydes in the preparation of bishomoallylic alcohols, which are important intermediates for preparing heterocyclic compounds and various 1,4- or 1,5-difunctional molecules, has hitherto achieved less progress. In fact, the available methods for the synthesis of bishomoallylic alcohols are very limited. Homoallylation of carbonyl groups with homoallylic metal reagents is one of the few reliable strategies for preparing bishomoallylic alcohols, but the homoallylating reagents are restricted to highly electropositive metals such as Mg and Ti, which are sensitive to atmospheric conditions and moisture.[2] To avoid using homoallylic metal reagents, a nickel-catalyzed reductive coupling reaction of 1,3-dienes and carbonyl groups employing commercially available organometallic compounds or silanes as reducing reagents has been developed for the preparation of bishomoallylic alcohols.[3] In 1994, Mori et al.[4] disclosed that the nickel-catalyzed cyclization of 1,3-dienes with tethered carbonyl groups in the presence of Bu^i_2Al(acac) or silanes afforded a mixture of bishomoallylic alcohols and homoallylic alcohols. Soon after that Tamaru et al.[5] realized both intermolecular and intramolecular reductive coupling reactions of 1,3-dienes and carbonyl compounds by using $ZnEt_2$ or BEt_3 as reducing reagents to produce bishomoallylic alcohols with high regio- and stereoselectivities. Although the nickel-catalyzed reductive coupling of 1,3-dienes and carbonyl compounds has attracted much attention, the asymmetric version of this reaction is limited. Recently, the Mori group[6] reported an intramolecular nickel-catalyzed asymmetric reductive coupling (cyclization) of 1,3-dienes with aldehydes in the presence of silanes employing a 2,5-dimethyl-1-phenylphospholane ligand, giving a mixture of bishomoallylic and homoallylic cyclic alcohols with good enantioselectivities (up to 86% ee). However, an example of intermolecular catalytic asymmetric reductive coupling of 1,3-dienes and carbonyl groups, to the best of our knowledge, has not been documented.[7] Here we report a nickel-catalyzed asymmetric reductive coupling of 1,3-dienes and aldehydes, providing a useful method for preparing chiral bishomoallylic alcohols in excellent diastereoselectivity (*anti/syn*: >99/1) and enantioselectivity (up to 96% ee).

We recently developed various monophosphorus ligands based on the chiral spirobiindane scaffold (Scheme 1). These ligands have been demonstrated to be highly efficient for asymmetric hydrogenation[8] and other asymmetric catalysis.[9] When these chiral spiro monophosphorus ligands were tested in the nickel-catalyzed asymmetric reductive coupling reaction of 1,4-diphenylbuta-1,3-diene (**1**) and benzaldehyde in the presence of Et_2Zn, the chiral bishomoallylic alcohol **3a** was produced in high yields (92−99%) and excellent diastereoselectivities (*anti/syn*: >99/1). However, the enantioselectivities were low, with spiro phosphoramidite SIPHOS

Scheme 1



being the most enantioselective ligand (45% ee) (Table 1). Optimizing the reaction conditions such as solvents, reducing reagents, Ni precursors, and reaction temperatures made no improvement on the enantioselectivity of the reaction. By comparison, the chiral MonoPhos ligand bearing a binaphthyl scaffold was also tested under identical reaction conditions, and its enantioselectivity (38% ee) was found to be not as good as that of its spiro counterpart SIPHOS.

It has been proven that only one ligand coordinates with the central nickel during the catalytic cycle in the reductive coupling of 1,3-dienes with aldehydes, and a bulky phosphine ligand was facilitated to stabilize the active catalyst in the reaction.[10] We therefore envisaged that increasing the bulkiness of the chiral phosphorus ligand might also enhance its enantioselectivity in the asymmetric reductive coupling of 1,3-dienes with aldehydes by restricting the rotation of the P−Ni bond of the catalyst. The ligands were improved by introducing substituents onto 6,6′-positions of the spirobiindane backbone and by changing alkyl groups on the nitrogen atom of the phosphoramidite ligand.[11]

As expected, the 6,6′-disubstituted spirobiindane phosphoramidite ligands displayed higher enantioselectivities in the nickel-catalyzed reductive coupling of a 1,3-diene with aldehydes. For example, the SIPHOS ligand afforded the bishomoallylic alcohol **3a** in 45% ee, but by contrast, ligand **4b** bearing two 6,6′-dimethyl groups on the spirobiindane backbone showed 72% ee in the same reaction. An even higher enantioselectivity (82% ee) was obtained by using ligand **4c**, which has 6,6′-phenyl groups. However, further increasing the steric hindrance of groups at the 6,6′-position of the spirobiindane ring from phenyl to 3,5-dimethylphenyl did not help the enantioselectivity of the reaction. The second stage of ligand improvement was carried out by modifying the amine moiety of the phosphoramidite ligand based on the 6,6′-diphenyl spirobiindane structure. When ethyl groups were substituted for the methyl groups

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Table 1. Ni-Catalyzed Asymmetric Reductive Coupling of 1,4-Diphenylbuta-1,3-diene (**1**) with Benzaldehyde[a]

entry	ligand	yield (%)[b]	ee (%)[c]
1	(*R*)-SIPHOS	99	45
2	(*R*)-ShiP	95	5
3	(*R*)-FuP	92	37
4	(*R*)-SITCP	93	40
5	(*S*)-MonoPhos	95	38
6	(*R*)-**4b**	99	72
7	(*R*)-**4c**	99	82
8	(*R*)-**4d**	96	76
9	(*R*)-**4e**	96	78
10	(*R*)-**4f**	99	96
11[d]	(*R*)-**4f**	95	88
12[e]	(*R*)-**4f**	99	92
13[f]	(*R*)-**4f**	89	90

[a] Reaction conditions: $Ni(acac)_2$/ligand/**1**/**2a**/Et_2Zn = 0.006/0.0072/ 0.12/ 0.24/0.28 (mmol) in toluene (1.2 mL), 25 °C, under argon, 1.0 h. [b] Isolated yield. The *anti/syn* ratio was >99/1 in all cases. [c] Enantioselectivity of the *anti*-isomer was determined on HPLC using a Chiralpak AD-H column.[d] 1 mol % of catalyst was used, 8 h. [e] $Ni(COD)_2$ was used. [f] $NiBr_2$ was used.

Table 2. Ni-Catalyzed Asymmetric Reductive Coupling of 1,4-Diphenylbuta-1,3-diene (**1**) with Different Aldehydes **2**[a]

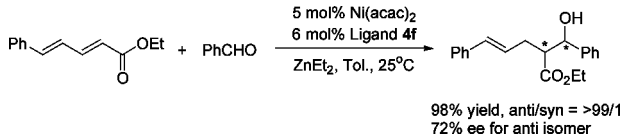
entry	Ar	product	yield (%)	anti/syn	ee (%)
1	Ph	**3a**	99	>99:1	96
2	*o*-MeC_6H_4	**3b**	95	>99:1	93
3	*o*-$MeOC_6H_4$	**3c**	98	>99:1	91
4	*m*-MeC_6H_4	**3d**	94	>99:1	94
5	*m*-$MeOC_6H_4$	**3e**	99	>99:1	92
6	*p*-MeC_6H_4	**3f**	95	>99:1	95
7	*p*-$MeOC_6H_4$	**3g**	94	>99:1	96
8	*p*-$Me_2NC_6H_4$	**3h**	85	99:1	96
9	*p*-ClC_6H_4	**3i**	92	>99:1	90
10	*p*-$CF_3C_6H_4$	**3j**	98	>99:1	85
11	1-naphthyl	**3k**	94	98:2	93
12	2-naphthyl	**3l**	96	>99:1	86
13	2-furyl	**3m**	96	>99:1	92
14	2-thiophyl	**3n**	98	>99:1	91

[a] Reaction conditions were the same as those in Table 1, entry 10. For analysis, see Supporting Information.

on the N atom of ligand **4c**, no enhancement of enantioselectivity was observed in the reductive coupling reaction. However, the enantioselectivity of the nickel-catalyzed reductive coupling reaction of 1,4-diphenylbuta-1,3-diene (**1**) with benzaldehyde was remarkably increased to 96% ee using the phosphoramidite ligand **4f**, which has a morpholine as the amine moiety. With ligand **4f**, other nickel compounds such as $Ni(COD)_2$ and $NiBr_2$ were also shown to be efficient catalyst precursors.

Using ligand **4f**, a variety of aldehydes can be coupled with 1,4-diphenylbuta-1,3-diene (**1**) in excellent diastereoselectivities and enantioselectivities (Table 2). All aromatic aldehyde substrates underwent the reductive coupling reaction in extremely high yields and diastereoselectivities regardless of the nature and the position of the substituents. Generally, an electron-donating substituent such as OMe and NMe_2 at the *para* position slightly enhanced enantioselectivity, while an electron-withdrawing substituent such as Cl and CF_3 at the *para* position diminished the enantioselectivity. In addition to benzaldehyde and its derivatives, naphthaldehyde, furan-2-carbaldehyde, and thiophene-2-carbaldehyde can also be coupled with 1,3-diene **1** to afford the corresponding bishomoallylic alcohols in high enantioselectivities. However, butyraldehyde gave the desired bishomoallylic alcohol in only 72% ee under identical reaction conditions, showing that the aliphatic aldehydes are less

Scheme 2



enantioselective in this reductive coupling reaction. To extend the scope of the reaction, ethyl 5-phenylpenta-2,4-dienoate was investigated. By coupling with benzaldehyde, the corresponding coupling product was obtained in high yield, excellent *anti* selectivity, albeit with moderate enantiomeric excess (Scheme 2).[12]

In conclusion, we have disclosed the first catalytic asymmetric intermolecular reductive coupling of 1,3-dienes and aldehydes. By using nickel complexes with bulky spirobiindane phosphoramidite ligands as catalysts and Et_2Zn as a reducing reagent, chiral bishomoallylic alcohols were produced in high yields with excellent diastereoselectivities and enantioselectivities.

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Supporting Information Available: Experimental procedures, the characterizations of ligands and products, and the analysis of ee values of products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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