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Asymmetric Synthesis of 1,1-Diarylalkyl Units by a Copper Hydride Catalyzed Reduction: Differentiation Between Two Similar Aryl Substituents

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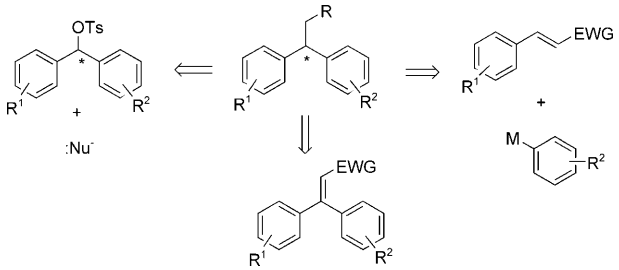
Abstract: An efficient method for the preparation of enantiomerically enriched 1,1-diarylalkyl units has been developed. The use of copper hydride complexed by the (*R*)-1-[(*S*)-2-diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine (Josiphos) ligand effects a highly enantioselective conjugate reduction of β,β-diaryl-substituted α,β-unsaturated nitriles with aryl groups of similar steric demand and no secondary coordination site. A range of substrates with *meta* and *para* substituents on the aryl group were reduced with good to excellent enantioselectivities (up to 97% enantiomeric excess (*ee*)) and this methodology was applied to the formal synthesis of indatraline.

Keywords: asymmetric catalysis · copper · enantioselectivity · silanes · reduction

Introduction

1,1-Diarylalkyl moieties, ArAr′CH–R, are frequently occurring units in a number of physiologically active compounds, which include antidepressants,[1] antihistamines,[2] antihypertensives,[3] hypolipidemics,[4] and others.[5] As such, catalytic asymmetric approaches towards enantioenriched 1,1-diarylalkyl units have become a subject of importance. Reported asymmetric syntheses of the units involve nucleophilic displacement at the benzylic position of enantioenriched 1,1-diarylmethanols,[6] asymmetric conjugate addition of organometallic reagents to β-aryl-substituted unsaturated substrates,[7] and asymmetric reductions of β,β-diaryl-substituted α,β-unsaturated carbonyl compounds (Scheme 1).[8] Notably, the asymmetric reduction approach has rarely been employed except when a large steric difference is generally expected between the two aryl groups, for example, *ortho* substituted aryl versus phenyl groups[8a] or when cyclic precursors are used.[8b] Moreover, asymmetric hydrogenation with rhodium or ruthenium complexes as catalysts was utilized in most of the cases and these catalysts required an additional coordinating functionality to be present in the substrate for reactivity and enantioselectivity.[8]



Scheme 1. Asymmetric approaches towards 1,1-diarylalkyl units. Ts = tosyl and EWG = electron-withdrawing group.

Efficient catalytic asymmetric reductions of 1,1-diaryl-substituted alkenyl substrates are still lacking, and enantiodifferentiation of compounds possessing two sterically similar aromatic groups with no secondary coordinating functional groups remains a substantial challenge. Previously, we have reported our preliminary results on the asymmetric conjugate reduction of α,β-unsaturated nitriles with β-aryl-β-pyridyl substitution, catalyzed by copper hydride complexes.[9] Although the nitrile group is a versatile functional group in organic synthesis, the linear structure provides no opportunity for intramolecular coordination to the metal for reduction of the conjugated double bond. Herein, we report our investigation on the efficient copper hydride catalyzed asymmetric conjugate reduction of β,β-diaryl-substituted α,β-unsaturated nitriles with sterically similar aryl groups, such as phenyl and *meta*- or *para*-substituted aryl groups.

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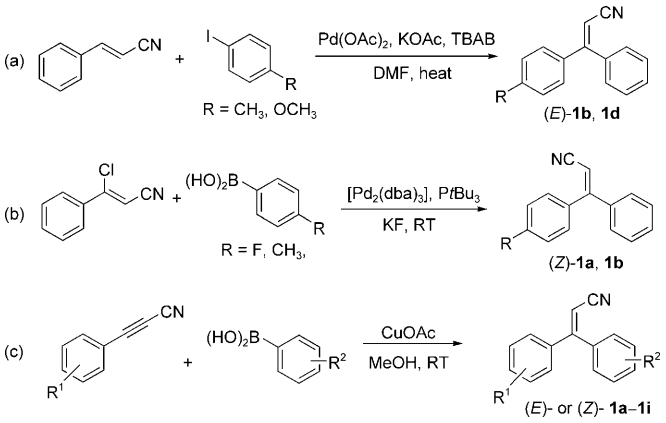
Results and Discussion

For this investigation, the starting unsaturated nitriles, **1**, were prepared as shown in Scheme 2. Our initial attempts to

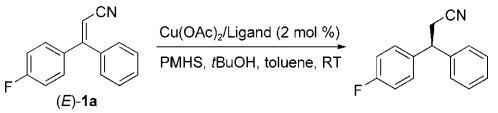


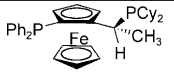
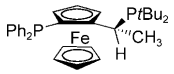
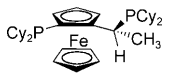
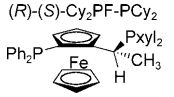
Scheme 2. Preparation of isomerically pure unsaturated nitriles. TBAB = tetrabutylammonium bromide.

isolate *E* and *Z* isomers in a geometrically pure form by chromatography of Horner–Wadsworth–Emmons products were unsuccessful. The desired nitrile substrates were stereoselectively prepared by Heck couplings of an aryl iodide with cinnamonitrile[10] (Scheme 2a), a Suzuki–Miyaura cross-coupling reaction of phenyl-substituted 3-chloroacrylonitrile with arylboronic acids[11] (Scheme 2b), or a copper-catalyzed hydroarylation reaction between alkynyl nitriles and arylboronic acids (Scheme 2c).[12] In general, the hydroarylation approach gives products with complete stereoselectivity regardless of the combination of coupling partners, which is in contrast to the other two methods and was therefore used for the preparation of most of the substrates. The stereochemistry of the products was assigned based on the mechanism of each coupling method and corroborated by comparison of the ^{1}H NMR spectra with known literature data for the unsaturated nitriles **1a**–**1e** or by X-ray crystal structure determination for product (*Z*)-**1b**.

We chose (*E*)-3-(4-fluorophenyl)-3-phenylacrylonitrile (**1a**) as a model substrate because it has the least steric difference between the aryl groups and screened a series of Josiphos-type ligands (Josiphos = (*R*)-1-[(*S*)-2-diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine) on the basis of the successful use of such a ligand skeleton in the reduction of β-aryl-β-pyridyl nitriles. The reduction of (*E*)-**1a** with $Cu(OAc)_2$ (2 mol%) in the presence of excess polymethylhydrosiloxane (PMHS) resulted in full conversion within hours and moderate to high levels of enantioselectivity (Table 1). The Josiphos ligand (**3**) gave the highest enantioselectivity (Table 1, entry 1) compared with other analogues of the Josiphos ligand. These results revealed that nitrile substrates possessing aryl substituents of similar steric demands on the C=C bond are good substrates for the copper-

Table 1. Asymmetric reduction of (*E*)-**1a** with a series of Josiphos ligands.



	Ligand[a]	*t* [h]	Conv. [%]	Yield [%][b]	*ee* [%][c]
1	 (*R*)-(*S*)-PPF-PCy$_2$ (**3**)	2	100	92	91
2	 (*R*)-(*S*)-PPF-P*t*Bu$_2$	6	100	82	81
3	 (*R*)-(*S*)-Cy$_2$PF-PCy$_2$	6	100	80	68
4	 (*R*)-(*S*)-PPF-Pxyl$_2$	6	100	84	77

[a] Cy = cyclohexyl, xyl = xylyl. [b] Yield of the isolated product. [c] Determined by HPLC analysis on a chiral phase.

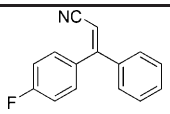
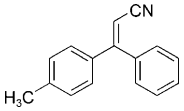
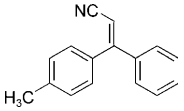
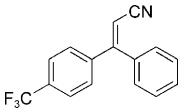
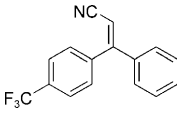
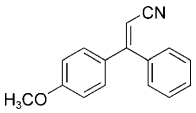
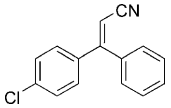
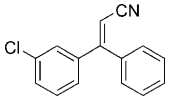
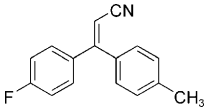
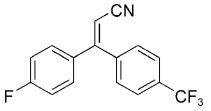
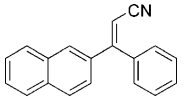
catalyzed asymmetric reduction and that *ortho* substitution is not a requirement for enantioselectivity.

As summarized in Table 2, a wide range of β,β-diaryl-substituted α,β-unsaturated nitriles were examined with $Cu(OAc)_2$ (2 mol%) and (*R*)-(*S*)-**3** to demonstrate the generality of this current method. A variety of substrates possessing a simple phenyl ring and a *meta*- or *para*-substituted aryl group were successfully reduced to the corresponding saturated nitriles at room temperature in high yields and with good to excellent *ee* values. Absolute stereochemical assignments were made by comparison of the optical rotation of products **2** with known data.[13]

Substrates with electron-donating (**1b** and **1d**) or -withdrawing (**1a**, **1c**, and **1e**) substituents on one of the phenyl rings were reduced with similar enantioselectivities, which indicates that electronic factors have little influence on the enantioselectivity. The reduction of *E* and *Z* olefin isomers (**1a**–**1c**) resulted in the formation of opposite enantiomers with the same level of enantioselectivity. Methyl-substituted (*E*)-**1b**, for example, provided (*S*)-**2b** in 93% *ee*, whereas (*Z*)-**1b** gave (*R*)-**2b** in 92% *ee* (Table 2, entries 2 and 3, respectively). Both *para*-chlorophenylnitrile (*E*)-**1e** and *meta*-chlorophenylnitrile (*E*)-**1f** afforded products with similar degrees of enantioselectivity (Table 2, entries 7 and 8, respectively).

High selectivity was also observed for the substrates with substituents on both phenyl rings (**1g** and **1h**), suggesting that electronic dissymmetry is not a requirement for good enantioselectivity (Table 2, entries 9 and 10). Finally, the reduction of the 2-naphthyl-substituted substrate (**1i**) gave the product in 90% *ee* (Table 2, entry 11).

Table 2. Enantioselective conjugate reduction of β,β-diaryl-substituted α,β-unsaturated nitriles.[a]

	Substrate	Product	*t* [h]	Yield [%][b]	*ee* [%][c]
1		(*Z*)-**1a**	(*R*)-**2a**	3	83	89
2		(*E*)-**1b**	(*S*)-**2b**	1	88	93
3		(*Z*)-**1b**	(*R*)-**2b**	3	89	92
4		(*E*)-**1c**	(*S*)-**2c**	6	88	90
5		(*Z*)-**1c**	(*R*)-**2c**	12	82	90
6		(*E*)-**1d**	(*S*)-**2d**	1	87	95
7		(*E*)-**1e**	(*S*)-**2e**	6	91	93
8		(*E*)-**1f**	(*S*)-**2f**	18	78	92
9		(*E*)-**1g**	(*S*)-**2g**	12	90	97
10		(*E*)-**1h**	(*S*)-**2h**	12	88	96
11		(*E*)-**1i**	(*S*)-**2i**	18	78	90

[a] Conditions: $Cu(OAc)_2$ (2 mol%), ligand **3** (2 mol%), PMHS (3 equiv), *t*BuOH (4 equiv), toluene, RT≈22°C. [b] Yield of the isolated product. [c] Determined by HPLC analysis on a chiral phase.

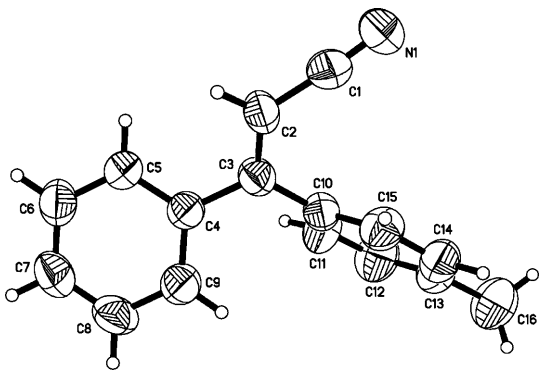
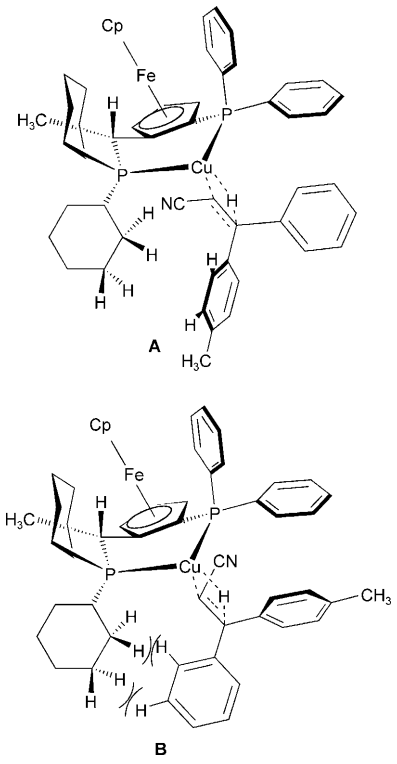


Figure 1. X-ray structure of (*Z*)-**1b**.

tion of the Cu–H bond across the C=C double bond occurs (Scheme 3). The basic skeleton of the catalyst was obtained from an X-ray crystal structure of a mononuclear trigonal



Scheme 3. Transition-state models. Cp = cyclopentadiene.

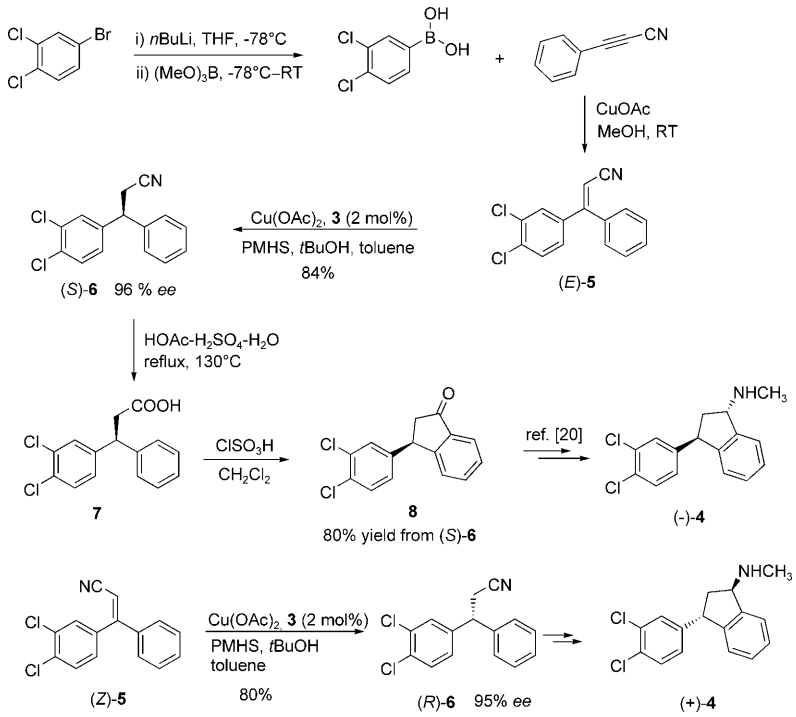
To try to understand the stereochemical outcome and the high selectivity of the reduction for α,β-unsaturated nitriles possessing two sterically similar aryl groups, we obtained an X-ray structure of (*Z*)-**1b** (Figure 1).[14] The *p*-tolyl group *cis* to the CN group is not in conjugation with the C=C bond, since it is tilted approximately 82° from the conjugation plane. It seems that the tilt of one out of the two seemingly similar aromatic groups generates an asymmetric bias, which enables the stereocontrol of the catalyst. Transition-state models for the reaction can be proposed in which the addi-

planar Cu–Josiphos complex.[15,16] In contrast to transition state **B**, the favored transition state **A** is free from steric repulsion between the aryl substituent of (*Z*)-**1b** and the cyclohexyl group of the Josiphos ligand, thus affording (*R*)-**2b** as the major enantiomer (Scheme 3).

Since CN coordination to copper was postulated to be a possible inhibitory factor in some other CuH reduction systems,[17] an experiment was conducted by adding one equivalent of acetonitrile to the identical reduction conditions of (*E*)-**1a** in Table 1 to assess the effect of complexation of the

CN functionality to copper as a coordinating ligand. The reaction proceeded to give the desired product with a negligible change in *ee* value (90% *ee*).[18] Although we cannot completely exclude such coordination during the course of our reaction, judging from the reactivity and enantiodifferentiation exhibited by the catalyst, the contribution is negligible.

This current method was applied to the enantioselective preparation of the indatraline precursor **8** (Scheme 4). Indatraline (**4**) is a potent psychoactive compound with high inhibitory activity for monoamine reuptake.[19] Although several racemic syntheses of **4** have been reported, so far only one catalytic enantioselective synthesis of (+)-**4** has been reported, which employed a rhodium-catalyzed carbenoid C–H insertion reaction.[20] Our synthesis started with the preparation and subsequent addition of dichloroarylboronic acid to phenyl alkynyl nitrile to give the unsaturated nitrile (*E*)-**5** in 62% yield from the bromobenzene derivative. The nitrile was reduced at room temperature under the optimized conditions to give the key intermediate (*S*)-**6**, which is the common intermediate in the synthesis of indatraline by Davies and Gregg, in 96% *ee* and 84% yield. Our asymmetric approach can provide either enantiomer of **6** in good *ee* simply by changing to the antipode of the ligand or by using the other stereoisomer of **5** in the asymmetric reduction. Hydrolysis of (*S*)-**6** with aqueous HCl/AcOH and cyclization by employing chlorosulfonic acid gave indanone **8** in 80% yield. The indanone is a versatile precursor for the construction of optically active **4**.[20]



Scheme 4. Enantioselective formal synthesis of indatraline.

Conclusion

We have developed a conjugate reduction protocol that allows for the catalytic enantioselective preparation of 1,1-diarylalkyl units possessing two sterically similar aryl groups. A series of β,β-diaryl-substituted α,β-unsaturated nitriles that have a *meta* or *para* substituent on the aryl ring have been successfully reduced with good to excellent enantioselectivities by using a copper–Josiphos catalyst in the presence of hydrosilane. The advantages of this catalyst system are the high enantioselectivities for both the *E* and *Z* isomers, mild reaction conditions, and the use of an economically appealing transition metal and hydrosilane. This methodology offers an attractive alternative to conjugate addition reactions of aryl-based organometallic reagents to α,β-unsaturated carbonyl compounds. Finally, we have applied this method to a catalytic enantioselective formal synthesis of indatraline.

Experimental Section

General procedure for the enantioselective reduction of β,β-diaryl-substituted α,β-unsaturated nitriles: $Cu(OAc)_2$ (1.82 mg, 0.010 mmol) and the ligand (*R*)-(*S*)-**3** (6.41 mg, 0.010 mmol, ethanol adduct) were placed in an oven-dried Schlenk tube and toluene (0.5 mL) was added under a nitrogen atmosphere. The reaction mixture was stirred for 10 min at room temperature and PMHS (90 μL, 1.5 mmol) was added. The reaction was stirred for 5 min to activate the catalyst. The unsaturated nitrile (0.5 mmol) in toluene (0.5 mL) was added, followed by *t*BuOH (191 μL, 2.0 mmol). The reaction was sealed and stirred until the starting material was completely consumed, as monitored by TLC. The reaction mixture was quenched with water and transferred to a round-bottomed flask with the aid of EtOAc (10 mL) and aqueous NaOH (2.5 M, 1.2 mL) was added. The biphasic mixture was stirred vigorously for 0.5 h. The layers were separated and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The product was purified by chromatography on silica gel.

Acknowledgements

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