Pergamon

Tetrahedron Letters 41 (2000) 7723–7726

TETRAHEDRON LETTERS

Electronically controlled asymmetric cyclopropanation catalyzed by a new type of chiral 2,2′-bipyridine

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Received 5 June 2000; accepted 28 July 2000

Abstract

An optically active atropisomeric 2,2′-bipyridine was synthesized and its copper complex was used in the asymmetric cyclopropanation of *para*-substituted styrenes with e.e. values up to 86%; the enantioselectivity exhibited a substrate electronic effect in a linear free energy relationship.

The use of transition metal complexes of chiral atropisomeric biaryls for asymmetric synthesis has generated immense interest. The ligands based on the 1,1′-binaphthalene skeleton have achieved significant successes in asymmetric catalysis[1] especially the use of BINOL[2] and BINAP.[3] Synthesis and application of chiral 2,2′-bipyridine ligands are also well explored.[4] We note that the chirality of these 2,2′-bipyridines comes from the chiral substituents which are far away from the metal centers that play crucial roles in catalysis. Synthesis of atropisomeric pyridines such as 8,8′-disubstituted-bis-1,1′-isoquinolines has appeared but facile racemization still occurs.[5] It is interesting to design a new type of chiral atropisomeric 2,2′-bipyridine.[6] Here we report the synthesis of a chiral atropisomeric bipyridine and its application in asymmetric cyclopropanation.

Our recent success in the synthesis of extremely sterically hindered atropisomeric pyridyl phenol[7] has led us to explore the synthesis and catalytic activities of its dimer. As shown in Scheme 1, a bromo-group was introduced to the *ortho* position of the pyridyl ring of **1** by lithiation with *tert*-butyllithium and quenching with 1,2-dibromoethane. 2-Bromopyridylanisole **2** was then demethylated with 48% HBr/HOAc to give **3** which was subsequently separated into enantiomers by chiral HPLC.[8] Nickel(0) catalyzed homo-coupling of (*S*)-**3** gave (*S*,*S*)-**4** without any racemization. Methylation of the chiral tetradentate ligand (*S*,*S*)-**4** gave the chiral bipyridine (*S*,*S*)-**5**.

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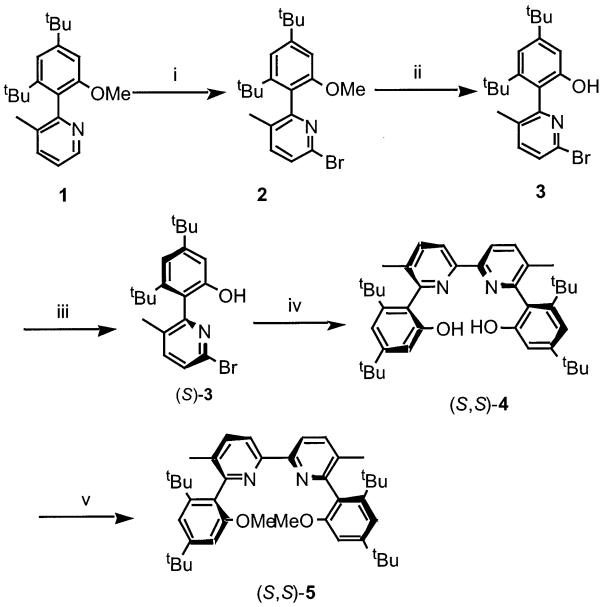
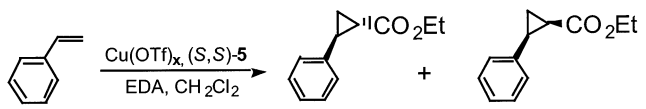
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01306-X



Scheme 1. *Reagents and conditions*: (i) ^{t}BuLi (1.5 equiv.), THF, −78°C, 1 h, $BrCH_2CH_2Br$ (2 equiv.), THF, −78°C–rt, 4 h, 71%; (ii) 48% HBr (10 equiv.), HOAc, 120°C, 8 h, 95%; (iii) Daicel chiral OD column, hexane/2-propanol = 8:1; (iv) $Ni(PPh_3)_2Cl_2$ (1 equiv.), Zn (2 equiv.), Et_4NI (1.5 equiv.), THF, 60°C, 8 h, 89%; (v) NaOH (2 equiv.), MeOH, rt, 1 h, Me_2SO_4 (2 equiv.), 40°C, 2 h, 90%

The copper complex of the chiral atropisomeric bipyridine **5** was applied to the asymmetric cyclopropanation of styrene derivatives with ethyl diazoacetate. In general, good cyclopropane conversion and diastereoselectivities were achieved, the major products, *trans*-cyclopropanes, were obtained with good enantioselectivity (Table 1). The use of copper(I) triflate and copper(II) triflate gave cyclopropanes with similar e.e. values and *trans*/*cis* ratios. When the reaction temperature was lowered from 20 to 0°C, the e.e. of the *trans*-cyclopropane increased from 80 to 86%. When the catalyst loading was increased from 1 to 3% (Entry 4), the enantioselectivity remained unchanged while the diastereoselectivity increased; the reason for this remains unclear.

Table 1

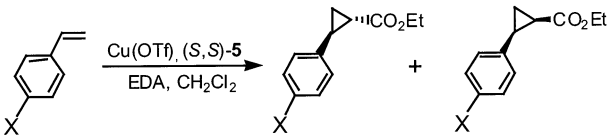


Asymmetric cyclopropanation of styrene with EDA catalyzed by the copper complex of (*S*,*S*)-**5**

Entry	X	Mol (%)	Time (h)	Temp (°C)	Yield (%)	*Trans*/*cis*[a]	e.e. (*trans*)[b,c]
1	1	3	4	20	72	92/8	79.4
2	1	1	5	20	89	86/14	80.1
3	2	1	8	20	88	85/15	80.2
4	2	1	24	0	95	86/14	86.0

[a] Determined by GC–MS.
[b] Determined by HPLC using chiral OD-H column.
[c] Absolute configuration was (1*R*,2*R*) by comparison of optical rotations with literature values (Ref. 13).

Table 2



Asymmetric cyclopropanation of *p*-substituted styrene with EDA catalyzed by the copper-(*S*,*S*)-**5**

Entry	X	Time (h)	*Trans*/*cis*[a]	Yield (%)	e.e. (*trans*)[b,c]
1	OMe	6	86/14	81	73.5
2	Me	6	85/15	86	75.6
3	H	8	85/15	80	80.2
4	Cl	18	86/14	78	84.0

[a] Determined by GC–MS.
[b] Determined by HPLC using chiral OD-H column.
[c] Absolute configuration was (1*R*,2*R*) by comparison of optical rotations with literature values (Ref. 13).

Recently, much work has been done in order to study the electronic influence of the catalyst[9–11]and the substrate[12] in transition metal catalyzed reactions. When *para*-substituted styrenes were subjected to cyclopropanation (Table 2), the most electron-poor olefin gave the highest enantioselectivity. Furthermore, the enantioselectivity depended on the electronic nature of the *para*-substituents and followed a linear free energy relationship (Fig. 1).

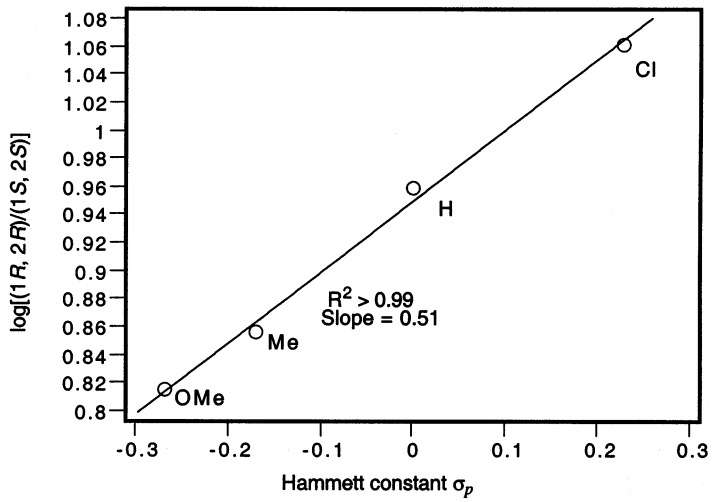


Figure 1. Plot of enantioselectivity versus Hammett constant σ_p

In summary, we have successfully demonstrated a linear Hammett plot for the substrate electronic effect on catalytic asymmetric cyclopropanation using a new type of chiral atropisomeric 2,2′-bipyridine.

Acknowledgements

We thank the Research Grants Council of Hong Kong (CUHK 2160102) for financial support.

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8. The absolute configuration of **3**, **4** and **5** was determined by relating to the absolute configuration of the known compound (*S*)-2-(3-methyl-2-pyridyl)-3,5-di-*tert*-butylphenol.[7] The first fraction of (+)-**3** eluted from the chiral OD-H HPLC column was reacted with ^{n}BuLi (2 equiv.) and quenched with water to give 2-(3-methyl-2-pyridyl)-3,5-di-*tert*-butylphenol with the absolute configuration of (*S*)-(+) determined by chiral HPLC analysis: (Daicel OD column, hexane/2-propanol = 9:1, 0.5 mL/min), $T_R = 9.1$ min. The retention time was identical with that of (*S*)-(+)-2-(3-methyl-2-pyridyl)-3,5-di-*tert*-butylphenol. Since no racemization occurs during the homo-coupling of **4**, the absolute configurations of **3**, **4** and **5** were determined to be (*S*)-(+), (*S*)-(+) and (*S*,*S*)-(+), respectively. All three compounds eluted as the first enantiomer from the OD column.
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