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Design of a new class of chiral C_2-symmetric dipyridylmethane ligands and their application in asymmetric catalysis

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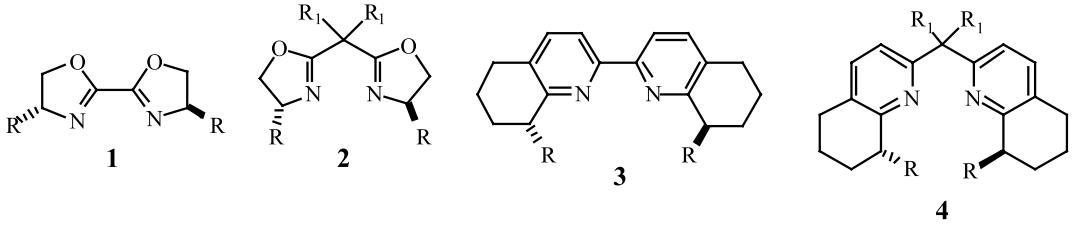
Abstract—A new class of chiral C_2-symmetric dipyridylmethane ligands was prepared from naturally occurring monoterpenes, according to a method based on a double Michael–azaannellation–aromatization sequence. These ligands were assessed in the enantioselective palladium-catalyzed allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethylmalonate and in the copper-catalyzed cyclopropanation of styrene with ethyl diazoacetate. Enantioselectivity up to 88% ee was obtained. © 2002 Published by Elsevier Science Ltd.

It has been recognized that to obtain an effective transfer of the chiral information from the catalyst to a product it is necessary a close interaction between the substrate and the chiral ligand into the intermediate metal complex.[1] That can be obtained by a careful ligand design that would contemplate, among various factors, the change of the chelate ring size of the metal-complex and consequently the ligand bite-angle.[2] As these parameters increase, the substituents on the stereocenters are pushed towards the substrate and thus the chiral recognition is generally enhanced. The importance of this concept in the optimization of a catalytic process is represented by chiral C_2-symmetric bis(oxazoline) ligands.[3] In fact, the bis(oxazoline) ligands **2**, forming a six-membered metal chelate, are generally more efficient ligands than the related bis(oxazoline) ligands **1** which form a five-membered chelate ring because the two heterocycles are directly bonded[3] (Scheme 1).

Since chiral C_2-symmetric 2,2′-bipyridines of type **3**, which can be roughly related to the bis(oxazoline) ligands **1**, have been found useful ligands for metal mediated asymmetric catalysis,[4] we have been evaluating the possibility to extend the chelate ring size of these systems by introducing a proper spacer between the two pyridine rings.[5]

Herein, we describe the preparation of three new chiral dipyridine ligands of type **4**, from naturally occurring monoterpenes, which possess an isopropylidene backbone between two pyridine rings. We also report the preliminary results obtained in two reactions that are frequently investigated to explore the potential utility of these chiral ligands as chiral controllers for enantioselective metal-catalyzed reaction namely, the palladium-catalyzed allylic substitution and copper-catalyzed cyclopropanation reactions.



Scheme 1.

Keywords: dipyridylmethane ligands; allylic alkylation; cyclopropanation; enantioselectivity.
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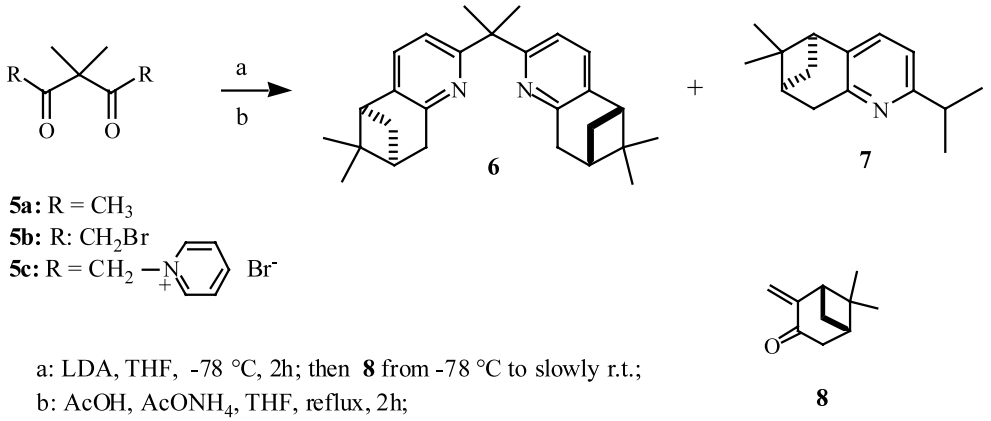
For the synthesis of the dipyridines of type **4** we considered that a convenient approach could involve the Kröhnke methodology for the synthesis of pyridines.[6] This route demands the reaction of an acylpyridinium salt with a α,β-unsaturated carbonyl compound in the presence of an ammonium acetate/acetic acid mixture.

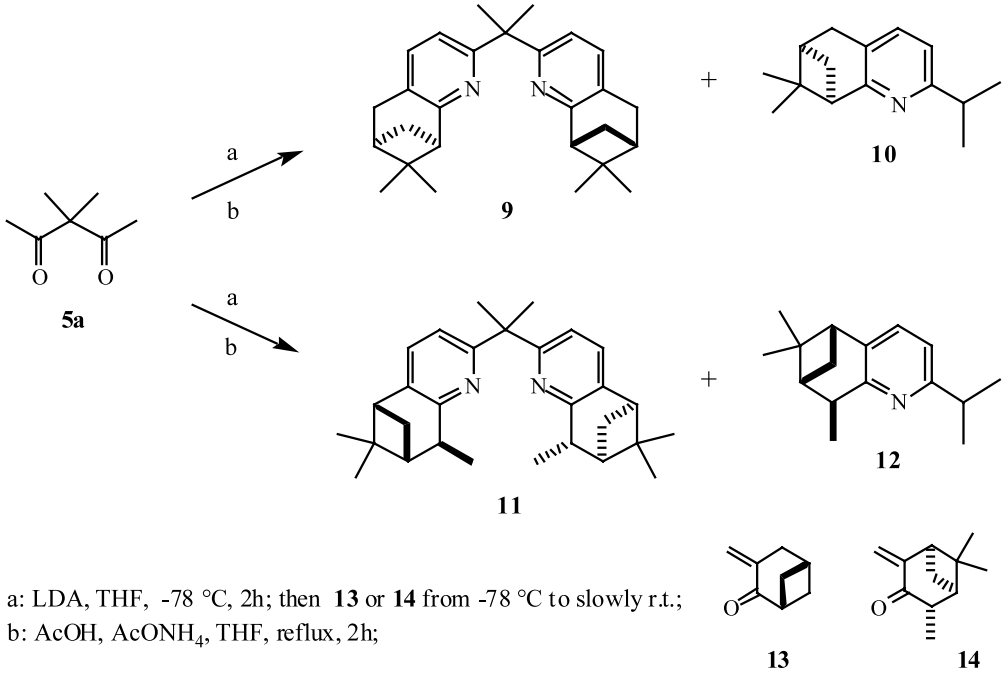
Thus, to test the feasibility of this idea, the diacylpyridinium bromide **5c** was prepared by reaction of the dibromide **5b**[7] with pyridine (Scheme 2) and then treated with (−)-pinocarvone (**8**)[8] that was selected as model α,β-unsaturated ketone. This reaction gave **6**[9] but in very low yield because of the formation of a large amount of 5,6,7,8-tetrahydro-6,6-dimethyl-2-methylethyl-5,7-methanoquinoline (**7**) (Scheme 2). A more successful route consisted of the conjugate addition of the lithium enolate of the diketone **5a** (generated by treatment with lithium diisopropylamine (LDA) at −78°C for 2 h) with **8** (from −78°C to room temperature) followed by azaanellation of unisolated 1,5-dicarbonyl intermediate with the ammonium acetate/acetic acid system. Also in this case a relevant amount of the pyridine **7** was obtained.

With the desired dipyridylmethane **6** in hand, this protocol was extended to other more sterically hindered α-methylene ketones (Scheme 3). Thus, the ketones **13** and **14**, obtained from (−)-β-pinene[10] and (−)-isopinocampheol[11] yielded the dipyridylmethane **9**[9] and **11**,[9] respectively.

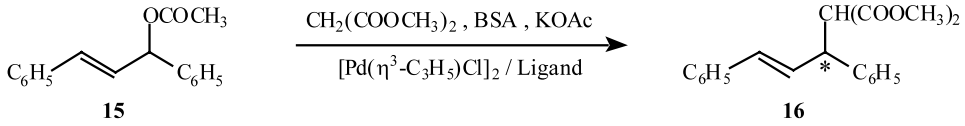
As a model study of palladium-catalyzed allylic substitutions[12] we examined the alkylation of 1,3-



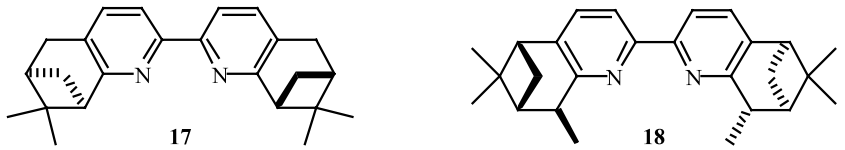
Scheme 2. *Reagents and conditions*: (a) LDA, THF, −78°C, 2 h; then **8** from −78°C slowly to rt; (b) AcOH, $AcONH_4$, THF, reflux, 2 h.

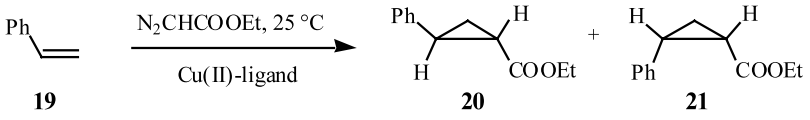


Scheme 3. *Reagents and conditions*: (a) LDA, THF, −78°C, 2 h; then **13** or **14** from −78°C slowly to rt; (b) AcOH, $AcONH_4$, THF, reflux, 2 h.



Scheme 4.





Scheme 5.

diphenylprop-2-enyl acetate (**15**) with dimethyl malonate following a standard protocol,[13] which entails $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as procatalyst and the generation of the nucleophile by in situ treatment of dimethyl malonate, *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate in a methylene chloride solution at room temperature[14] (Scheme 4).

The dipyridine **6** gave a moderately reactive Pd-catalyst that required 60 h at room temperature to convert the starting material **15** to the dimethyl 1,3-diphenylprop-2-enylmalonate (*S*)-**16** in 88% yield and 53% enantiomeric excess. A dramatic reduction of the catalytic activity was, however, observed when dipyridines, bearing a substituent on the 8-position of the tetrahydroquinoline ring, were employed. Thus, with the ligand **9**, differing from **6** by the position of the dimethylmethylene bridge, which in the former ligand is in close proximity to the nitrogen donor center, no reaction occurred after 168 h. The same outcome was obtained with the more sterically encumbered methyl analogue **11**.

These findings clearly demonstrate that the Pd-complexes of this kind of C_2-symmetric ligands turn out to be catalytically unreactive when the substituent close to the tetrahydroquinoline nitrogen is too bulky. Moreover, these results indicate that the behavior of these Pd-complexes is comparable with that of the related C_2-symmetric 2,2′-bipyridines, whose Pd-complexes exhibit low reactivity. Thus, for instance, the 2,2′-bipyridine **17**, analogue to **9**, gave (*S*)-**16** in low yield (28%) and with only 20% ee.[15]

To evaluate the efficiency of these ligands in the copper-catalyzed asymmetric cyclopropanation,[16] we examined the cyclopropanation of styrene using Cu(II) complexes prepared in situ from Cu(II)-triflate and the ligand. The reaction was carried out at room temperature by slow addition (2 h) of ethyl diazoacetate to a solution of styrene in CH_2Cl_2 containing the Cu(II) ligand adduct, which was previously activated by stirring with a few equivalents of the diazoacetic ester[17] (Scheme 5).

The Cu(II) complexes containing ligands **6**, **9** and **11** exhibited high efficiency and afforded the *trans*- and *cis*-cyclopropanes **20** and **21** with good yields (73–85%) but with low *trans*/*cis* diastereoselectivities.[18] Whereas ligands **6** and **9** did not show significant enantiomeric excesses (1 and 9% for the *trans*-isomers, respectively; 1 and 6% for the *cis*-isomers, respectively), ligand **11** exhibited a good enantioselectivity (88% ee for the *trans*-isomer and 74% ee for the *cis*-isomer). It should be noted that the stereochemical result obtained with this ligand is better than that obtained with the related 2,2′-bipyridine **18** (79% ee for the *trans*-isomer and 78% ee for the *cis*-isomer).[19]

In conclusion, we have synthesized a new kind of chiral C_2-symmetric dipyridylmethane ligands from the inexpensive chiral pool, in a two-step sequence. The preliminary results obtained using these dipyiridines in two asymmetric catalytic processes, indicate that their Pd complexes are poorly suitable catalysts for allylic alkylation reactions. On the contrary, the Cu-catalyzed cyclopropanation reaction appears to be a promising application (88% ee) and is worthy of attention for further investigations. Since chiral bipyridine complexes catalyze a vast array of asymmetric reactions, it can be expected that this new class of dipyridine ligands will find a broad application in asymmetric catalysis.

Acknowledgements

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