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Glyoxal bis-hydrazones: a new family of nitrogen ligands for asymmetric catalysis†

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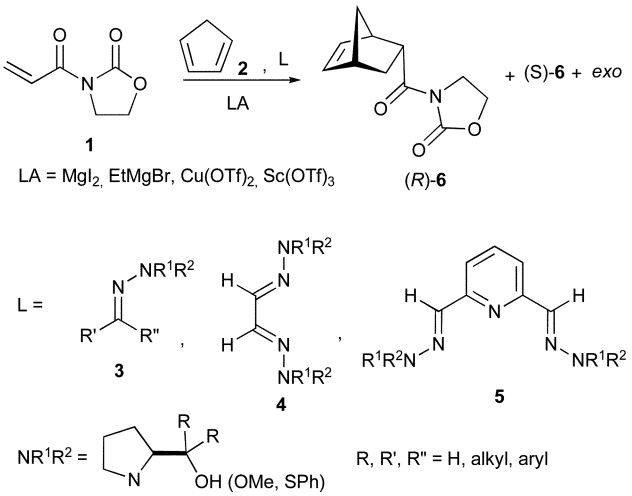
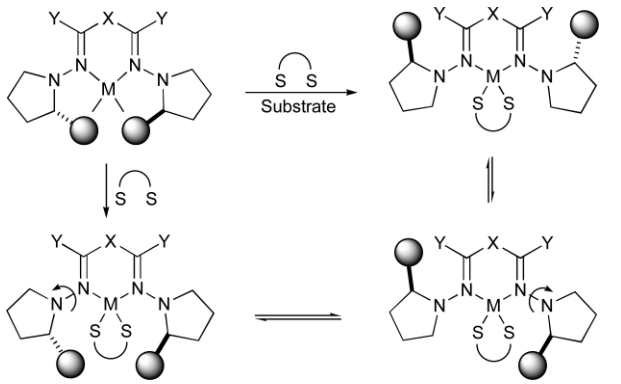
The introduction of C_2-symmetric dialkylamino substructures in chiral non-racemic glyoxal bis-hydrazones such as 9 appears as the key design element for this novel ligand class, as shown in the highly enantioselective copper(II)-catalyzed Diels–Alder reaction.

The design and synthesis of new families of chiral ligands constitutes the starting task for the many particular pieces of research that have contributed to the spectacular growth of asymmetric catalysis during the last 30 years. Currently, there is a growing interest in nitrogen-based ligands, which offer a much higher structural variability and are easier to handle and recycle than the widespread phosphorus-based ligands. In addition, most nitrogen ligands are readily available, either from commercial precursors or from the chiral pool (amines, amino acids, *etc.*). The latest advances in the use of nitrogen-based chiral ligands have been recently reviewed.[1]



Scheme 1 Preliminary screening of new ligands.



Scheme 2 Rotational isomerism in catalyst–substrate complexes.

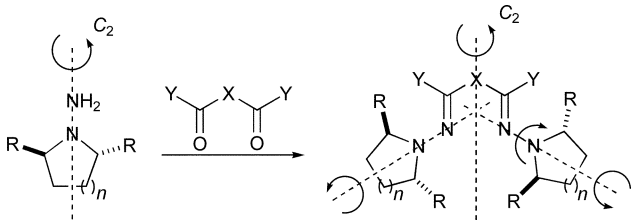
During the last few years we have accumulated some knowledge about the synthesis, reactivity and structural aspects of the chemistry of *N*,*N*-dialkylhydrazones.[2] These compounds, viewed as *N*-dialkylamino imines, exhibit a higher thermal stability than *N*-alkyl(aryl) derivatives as a result of the n → π conjugation. The behavior of the C=N bond is strongly dependent on the structure of the amine moiety,[2] which in turn controls the efficiency of the conjugation and may incorporate structural elements able to modulate the steric crowding around the coordination site. In addition, a wide variety of chiral hydrazines are available from inexpensive starting materials such as proline,[3] carbohydrates,[4] diketones,[2e] and others,[5] while many others can be easily prepared from chiral secondary amines by a nitrosation–reduction protocol.[3] In summary, the electronic characteristics and structural variability of hydrazones make these compounds an interesting class of potentially useful ligands.

Despite these peculiarities, a literature survey revealed very few examples of the use of chiral monohydrazones as ligands in asymmetric catalysis,[6] while, to the best of our knowledge, the use of chiral bis-hydrazones as ligands in this context has no known precedents. In this communication, we wish to report on the first application of C_2-symmetric bis-*N*,*N*-dialkylhydrazones as a new class of efficient ligands in the enantioselective metal-catalyzed Diels–Alder reaction.[7]

The well-known reaction of *N*-acryloyloxazolidinone **1** and cyclopentadiene **2** was used as the model system. In a preliminary survey, several proline-derived monohydrazones **3**, as well as bis-hydrazones **4** and **5**, were used as multidentate ligands in combination with several Lewis acids. Though the cycloaddition reaction proceeded cleanly in all cases to afford the expected *endo* cycloadduct **6**, the observed enantioselectivities (0–18%) were disappointing (Scheme 1).

The lack of selectivity was interpreted as the loss of a suitable chiral environment around the metallic centre, an undesired process that may take place after formation of the catalyst–substrate complex by rotation around N–N bonds, as shown in Scheme 2 for the bis-hydrazone type of ligand.

In order to check the validity of this working hypothesis and to eventually circumvent the undesired effect of the rotational isomerism, we decided to prepare a second set of C_2-symmetric bis-hydrazones which, carrying in addition C_2-symmetric substructures in the two dialkylamino moieties, would *a priori* be able to provide an adequate chiral environment while making it unnecessary to take care regarding possible rotations around N–N bonds (Scheme 3).



Scheme 3 Ligands with inconsequential rotation around N–N bonds.

† Electronic supplementary information (ESI) available: experimental procedures and spectral and analytical data for new compounds. See http://www.rsc.org/suppdata/cc/b3/b314249c/

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Therefore, novel hydrazines **7** and **8** were synthesized from the corresponding diketones by oxazaborolidine-catalysed reduction,[8] mesylation, and reaction with hydrazine. Their condensation with glyoxal readily afforded the desired ligands **9** and **10** (Scheme 4), and their $Cu(OTf)_2$ 1 : 1 complexes were used as the catalysts in the chosen model reaction.

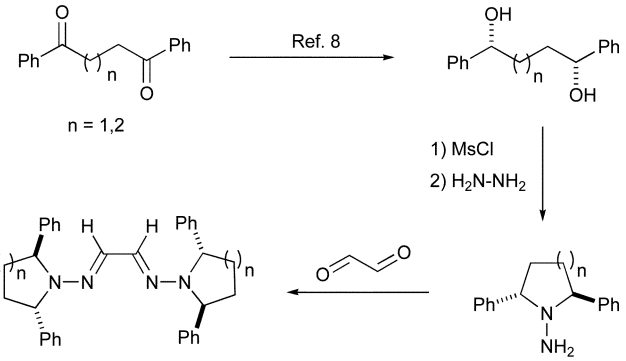
In both cases, cycloadduct **6** was formed with a significant increase of enantioselectivities, thereby validating the suitability of the strategy. As the highest induction was observed for ligand **9**, this result was further optimized to afford cycloadduct **6** in 90% yield as a 98 : 2 *endo* : *exo* mixture and with 95% ee [(*R*,*R*)-*endo*)] (Table 1, entry 1). These conditions were then applied to the cycloaddition of **1** to other conjugated dienes such as cyclohexadiene **11**, isoprene **12**, 2,3-dimethyl-1,3-butadiene **13**, and furan **14**, affording high yields of the corresponding cycloadducts **15–18**, with good enantioselectivities in all cases (entries 2–5). Noteworthy is that adducts **15** and **16** were obtained with complete diastereo- and regioselectivity, respectively (entries 4 and 5). The synthesis of *ent*-**9** and its use in the model cycloaddition afforded *ent*-**6**, thereby highlighting the availability of the desired enantiomer for each cycloadduct.

At this point, it is worth mentioning that, even though the results collected for the cyclic dienes **2** and **11** are similar to those obtained with many other catalysts,[9] the yields and selectivities achieved in the cycloadditions to the more flexible dienes **12** and **13** appear as a more interesting result, matching or exceeding those reported to date.[9b,c,10]

Table 1 Enantioselective Diels–Alder cycloadditions

Entry	Diene	L	*T*/°C	Yield (%)[a]	Product	Conf[b]	de[c]	ee[d]
1	**2**	**9**	−60	90	**6**	*R*,*R*	96	95
2	**11**	**9**	−25	83	**15**	*R*,*R*	> 99	84
3	**12**	**9**	−35	79[d]	**16**	*R*	—	92
4	**13**	**9**	−35	89	**17**	*R*	—	92
5	**14**	**9**	−50	88	**18**	*R*,*R*	74	96
6	**2**	*ent*-**9**	−60	91	*ent*-**6**	*S*,*S*	96	95

[a] Isolated yield. [b] Of major isomer. [c] Determined by HPLC in chiral stationary phases. [d] A single regioisomer was detected by NMR and HPLC.



Scheme 4 Synthesis of ligands **9** and **10**.

In conclusion, the inclusion of C_2-symmetric dialkylamino substructures in glyoxal bis-hydrazones is the key design element resulting in the successful application of these compounds as novel N-ligands for the enantioselective copper(II)-catalyzed Diels–Alder cycloaddition. *Both enantiomers* of the required ligand are easily available on a multigram scale in only three steps from 1,4-diphenylbutanedione. It is hoped that this new class of synthetic nitrogen ligands will find applications in other catalytic organic reactions.

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