

FINE CHEMICALS FROM A BIOMASS-DERIVED DICARBOXYLIC ACID: CHIRAL BISOXAZOLINES AND THEIR APPLICATION IN ENANTIOSELECTIVE DIELS-ALDER REACTIONS

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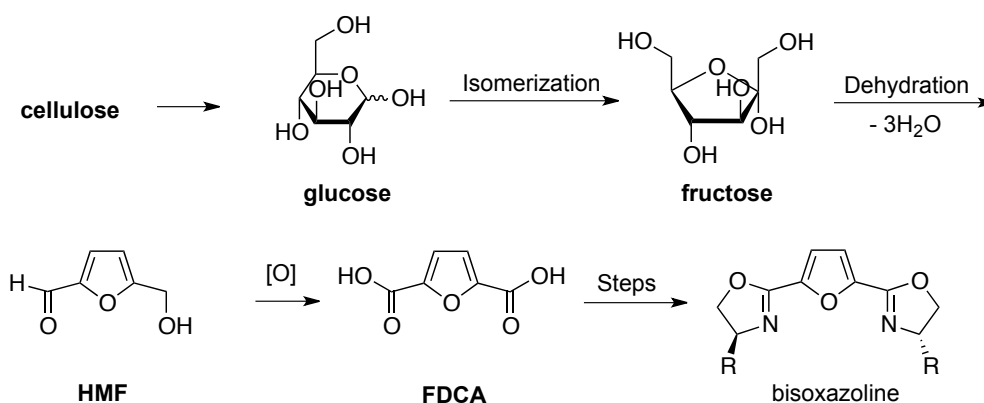
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Abstract – 2,5-Furandicarboxylic acid (FDCA) is a feedstock chemical readily available from cellulosic biomass. Six chiral bisoxazolines varying in the steric size of the blocking group have been synthesized from FDCA in modest to good overall yields. The effectiveness of the new chiral bisoxazolines has been evaluated in enantioselective Diels-Alder reactions.

In the past two decades, there has been a big explosion in the use of feedstocks derived from biomass in a variety of applications.¹ All the three major types of biomass—lignin, cellulose, and tryglycerides from oilseeds; are used in the chemical and associated industries.² In particular, two feedstock chemicals derived from cellulose, 5-hydroxymethylfurfural (HMF) and 2,5-furandicarboxylic acid (FDCA), have received special attention from the synthetic organic community.³ They are both available commercially and have been investigated extensively for monomer synthesis as alternatives to those available from fossil fuels since they are renewable and possess unique structures.⁴ In contrast, HMF and FDCA have found limited utility in the synthesis of fine chemicals.⁵ In this work we describe the synthesis of a privileged class of chiral ligands, the bisoxazolines, from FDCA and demonstrate their utility in enantioselective Diels-Alder reactions.⁶

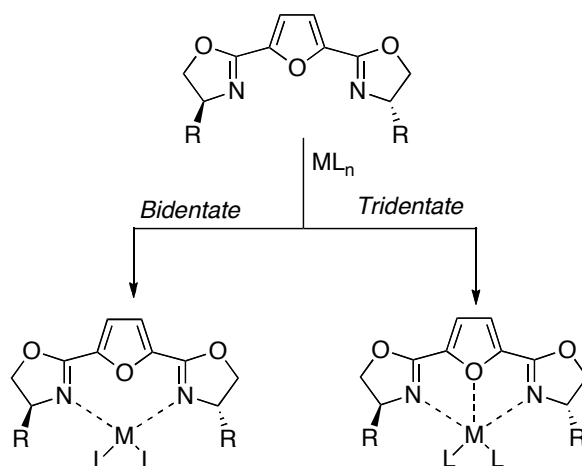
Asymmetric synthesis is one of the important subdisciplines of synthetic organic chemistry. Catalyzed enantioselective transformations, a well-established method for controlling the stereochemistry of a reaction, are integral to asymmetric synthesis. Ligands are essential constituents of chiral Lewis acids. There are a few privileged classes of ligands that have found extensive use in enantioselective reactions, and bisoxazolines is one such class.⁷ Bisoxazolines are readily accessed from chiral amino alcohols and dicarboxylic acids. The number of dicarboxylic acids that have been utilized for chiral bisoxazoline synthesis is rather small, and we surmised that a biomass-derived dicarboxylic acid would make a

positive contribution in this area.



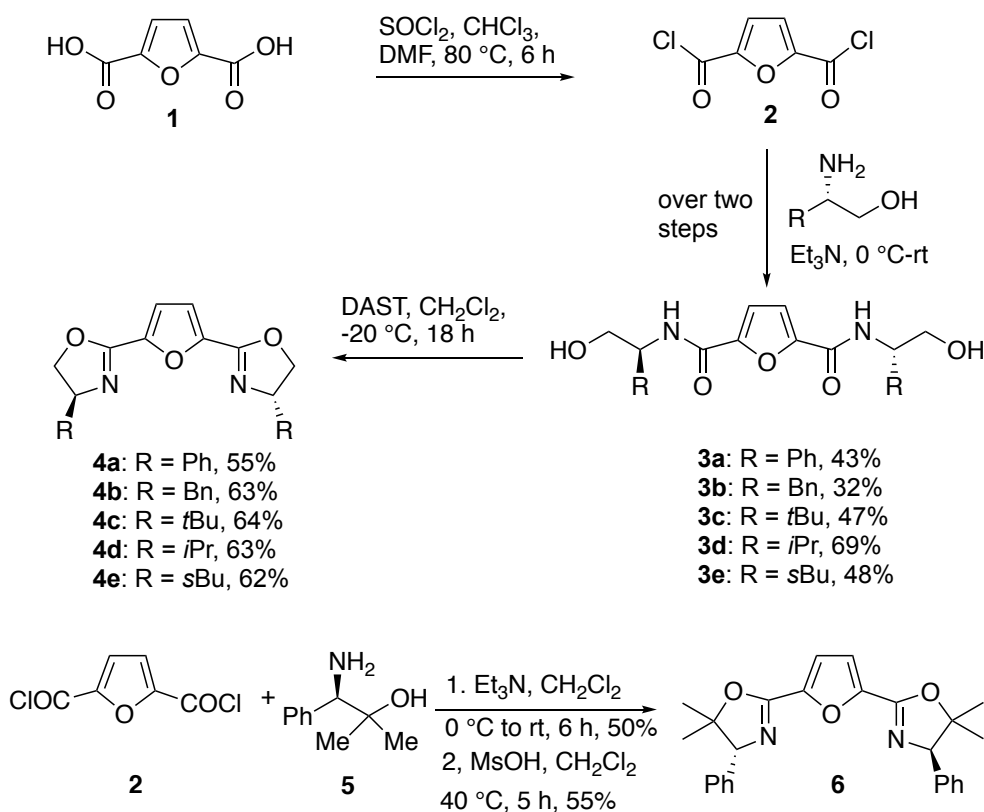
Scheme 1. Fine chemical derived from biomass in ligand synthesis

FDCA is an excellent starting material for the synthesis of chiral bisoxazolines. FDCA has a flat 5-membered ring and has the potential for providing additional coordination to the Lewis acid through its furan oxygen. We were interested in probing the geometry of the chiral Lewis acid complex of FDCA-derived bisoxazolines and its impact on selectivity in asymmetric transformations. The potential coordination modes of FDCA-derived bisoxazolines with Lewis acids are shown in Scheme 2. In general, chiral bisoxazolines form cis-chelated complexes with Lewis acids.⁸ However, trans-chelating ligands, although uncommon, offer some potential advantages. An example of a useful trans-chelating ligand is the dibenzofuran-based bisoxazoline (DBFOX-Ph) popularized by Kanemasa and co-workers.⁹ In this work we have probed the coordination geometry of FDCA-derived bisoxazolines and Lewis acids. We have chosen the Diels-Alder cycloaddition as the reaction of choice for evaluation of the effectiveness of FDCA-derived bisoxazolines in asymmetric transformations.



Scheme 2. Different modes of coordination for FDCA-derived bisoxazolines

Our initial goal was to develop an efficient method for the synthesis of bisoxazolines from FDCA. Towards this end, FDCA was converted to its acid chloride, and condensation with various chiral amino alcohols provided the corresponding amides in high yields. The amides were cyclized to form the bisoxazolines using previously established protocols. Five different bisoxazolines were synthesized in good to excellent overall yields (Scheme 3). A sixth bisoxazoline with additional substituents on the heterocycle displaying a more sterically crowded environment, was also synthesized in good yield.¹⁰

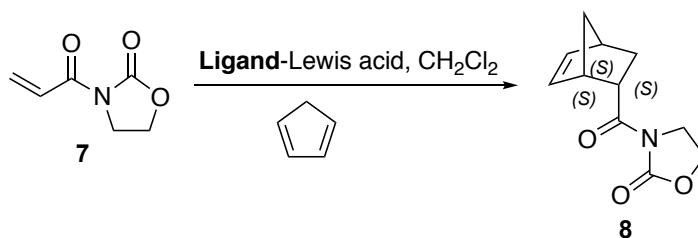


Scheme 3. Synthesis of Chiral Bisoxazolines

We began our investigation by carrying out Diels-Alder reactions of oxazolidinone acrylate with cyclopentadiene to arrive at the optimal chiral Lewis acid derived from FDCA-based bisoxazoline **4a**.¹¹ A variety of 2⁺ and 3⁺ Lewis acids were screened, and these results are tabulated in Table 1. Reaction using 10 mol% of copper triflate as a Lewis acid and ligand **4a** at room temperature gave the Diels-Alder adduct in near quantitative yield and modest *endo/exo* selectivity. The ee for the major *endo* adduct was low (Table 1, entry 1). Reaction with zinc triflate as a Lewis acid showed a modest improvement in ee (Table 1, entry 2). The use of magnesium triflimide as a Lewis acid gave nearly a racemic product (Table 1, entry 3). Although similar in size to zinc cation, the lack of selectivity with magnesium remains unexplained. Reaction with scandium triflate, a 3⁺ Lewis acid, was not effective and gave the racemic adduct (Table 1, entry 4). Nickel perchlorate in combination with the *trans*-chelating DBFOX-Ph ligand

(tridentate coordination) has proven to be highly effective in a variety of asymmetric transformations.¹² In contrast, a combination of **4a** and nickel perchlorate gave a racemic adduct (Table 1, entry 5). Temperature and counterion play an important role in the outcome of DA reaction using **4a**. Lowering the reaction temperature to 0 °C and using zinc triflate (30 mol%) as a Lewis acid gave a small improvement in enantioselectivity of the *endo* adduct (Table, compare entry 6 with 2). Reaction with zinc triflimide (30 mol%) as Lewis acid at -20 °C was also effective and gave the *endo* adduct in 61% ee (Table, entry 7). Further lowering of reaction temperature led to improvement in *endo/exo* selectivity (99:1) as well the enantioselectivity (81% ee) at -78 °C (Table, entries 8-10).

Table. Enantioselective Diels-Alder Reactions with Different Bisoxazolines



Entry	Lewis acid (mol%)	Ligand (mol%)	Temp. (°C)	Time (h)	Yield (%) ^a	Endo:Exo ^b	ee (%) ^c
1	Cu(OTf) ₂ (10)	4a (11)	rt	2	>99	80:20	23
2	Zn(OTf) ₂ (10)	4a (11)	rt	2	>99	89:11	46
3	Mg(NTf ₂) ₂ (10)	4a (11)	rt	2	>99	83:17	02
4	Sc(OTf) ₃ (10)	4a (11)	rt	2	>99	82:18	00
5	Ni(ClO ₄) ₂ ·6H ₂ O (10)	4a (11)	rt	2	>99	85:15	01
6	Zn(OTf) ₂ (30)	4a (33)	0	12	90	93:07	59
7	Zn(NTf ₂) ₂ (30)	4a (33)	-20	2	>99	95:05	61
8	Zn(NTf ₂) ₂ (30)	4a (33)	-40	12	>99	96:04	68
9	Zn(NTf ₂) ₂ (30)	4a (33)	-60	12	>99	99:01	78
10	Zn(NTf ₂) ₂ (30)	4a (33)	-78	12	>99	99:01	81
11	Zn(NTf ₂) ₂ (30)	4b (33)	-78	12	99	91:09	14
12	Zn(NTf ₂) ₂ (30)	4c (33)	-78	12	>99	88:12	-48
13	Zn(NTf ₂) ₂ (30)	4d (33)	-78	12	>99	89:11	08
14	Zn(NTf ₂) ₂ (30)	4e (33)	-78	12	>99	94:06	-12
15	Zn(NTf ₂) ₂ (30)	6 (33)	-78	12	>99	93:07	39

^a Isolated yield. ^b Determined by ¹H NMR spectroscopy. ^c Determined by chiral HPLC.

Next, we investigated the effect of the oxazoline substituent on selectivity using the optimal conditions shown in entry 10. Ligand **4b** containing a benzyl group gave poor selectivity (Table, entry 11). Interestingly, ligand **4c** with a bulky *tert*-butyl group the opposite enantiomer in modest ee (Table, entry 12). Several groups have noted this type of selectivity reversal when one replaces a phenyl (or isopropyl) group with a *tert*-butyl group.¹³ Other ligands, **4d**, **4e** and **6**, gave very low selectivity (Table, entries 13-15). From these results, ligand **4a** in combination with zinc triflimide gave the best results.

In an effort to understand the reason for the modest selectivity observed with FDCA-derived ligands, we have obtained crystal structures for **4a** and **4c**.¹⁴ The crystal structure of **4a** is shown in Figure 1. For comparison, the structure of DBFOX-Ph-Ni(ClO₄)₂ is also shown. The distance between the two nitrogen atoms for **4a** in a planar arrangement is 5.30 Å. This is in contrast to the much shorter distance (4.16 Å) observed between the nitrogen-atoms of DBFOX-Ph. Placing a dummy zinc atom in **4a** at 2.12 Å from the furan oxygen (an average bond length from analysis of crystal structures in Cambridge database) shows that the chiral pocket is not compact and the blocking phenyl groups are away from the substrate-bound zinc leading to modest selectivity. On the other hand, nickel-coordinated DBFOX-Ph has a well-defined and compact chiral pocket leading to high selectivity in many asymmetric transformations.

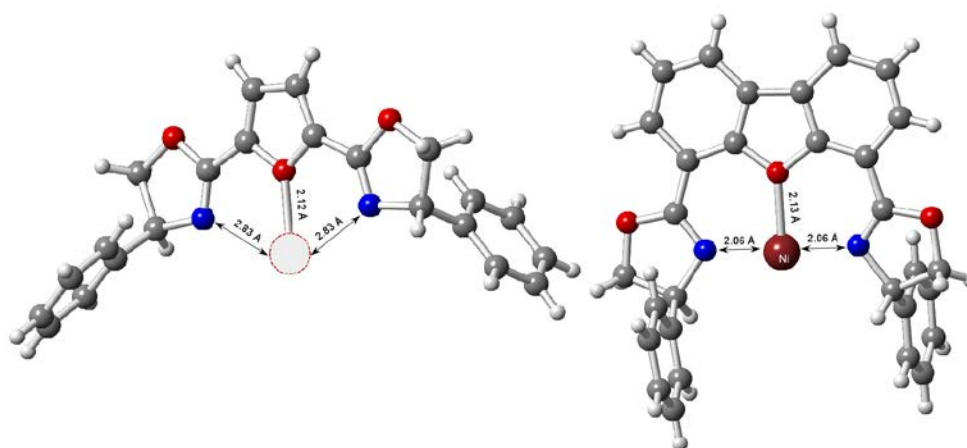


Figure 1. Crystal structure of **4a** with a dummy Zn(II) cation and Ni(ClO₄)₂ coordinated DBFOX-Ph

In conclusion, this work highlights the utility of biomass-derived feedstock for the synthesis of fine chemicals. Six new bisoxazolines have been synthesized from FDCA and evaluated for their effectiveness in asymmetric Diels-Alder reactions. The results suggest that the new ligands provide very good enantioselectivity for the Diels-Alder adduct. Crystal structure analysis suggests that FDCA-derived ligands do not have a very compact chiral pocket. Evaluation of the FDCA-derived ligands in other asymmetric transformations is underway.

ACKNOWLEDGEMENTS

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