

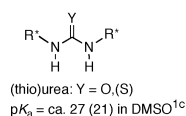
Helical Chiral 2-Aminopyridinium Ions: A New Class of Hydrogen Bond Donor Catalysts

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In recent years, electrophile activation by small-molecule hydrogen bond (H-bond) donors has become an important paradigm for asymmetric catalysis.¹ Chiral (thio)ureas are among the most generally applicable classes of H-bonding catalysts. Their remarkable success can be attributed to the ability to form two H-bonds to a substrate. Such two-point binding is thought to further activate a substrate and constrain it to a well-defined orientation necessary for asymmetric induction. Other types of chiral catalysts that are capable of donating two H-bonds, such as amidinium,² amino-phosphonium,³ guanidinium,⁴ pyridinium⁵ species, quinolinium thio-amides,⁶ squaramides,⁷ and sulfonamides,⁸ have also been reported.⁹



In sharp contrast to (thio)ureas, 2-aminopyridinium ions have been much less explored as H-bonding catalysts.^{2d,5,6} As part of our efforts aimed at developing dual H-bonding catalysts with significantly increased acidity (i.e., reactive),^{10–12} we recently described that 2-aminopyridinium ions efficiently activate nitroalkenes.¹³ An intrinsic challenge to the design of their chiral variants is the difficulty in positioning stereochemical elements (R*) on the bonding side of the catalyst due to the directionality of H-bonds. Our approach is to merge a 2-aminopyridinium core into the framework of helicene^{14,15} to position an *inherently chiral* barrier at the H-bonding site. Herein, we report the development and successful demonstration of a new class of H-bond donor catalysts readily prepared from 1-azahelicene *N*-oxides.^{14,16}

To evaluate the potential of the helical chiral catalysts, we focused on additions of 4,7-dihydroindoles to nitroalkenes,^{17–19} which afford β -nitro-indol-2-yl products (instead of 3-substituted indoles^{6,20}) after subsequent oxidation (Table 1). Notably, these products are versatile intermediates²¹ for the preparation of chiral indol-2-yl derivatives, which are prevalent motifs found in biologically active compounds and natural products.²² To our delight, 10 mol % of **1a** efficiently promoted the reaction affording the product with moderate enantioselectivity (entry 1). The possible erosion of enantioselectivity by adventitious acid was ruled out by conducting the reaction in the presence of 4 Å molecular sieves²³ (entry 2). Single H-bond donor **1b** was found virtually nonselective, indicating that the 2-amino group is required for asymmetric induction (entry 3). Benzo analogue **2a** was equally reactive but more selective than **1a**, the results of which were nearly maintained at -60°C , or with only 2 mol % catalyst loading (entries 4–6). Next, *N*-alkylated catalysts **2b–e** were evaluated (entries 7–10). The enantioselectivity gradually improved as the degree of alkyl substitution increased. We were pleased to find a powerful means for tuning

Table 1. Evaluation of Helical Chiral 2-Aminopyridinium Catalysts^a

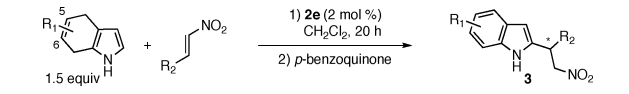
entry	cat (R-)	mol %	temp (°C)	time (h)	yield (%) ^b	er ^b
1	1a (H ₂ N-)	10	-40	20	80	64:36
2 ^c	1a (H ₂ N-)	10	-40	20	75	64:36
3	1b (H)	10	-40	20	65	53:47
4	2a (H ₂ N-)	10	-40	20	85	69:31
5	2a (H ₂ N-)	10	-60	20	87	70:30
6	2a (H ₂ N-)	2	-40	20	71	69:31
7	2b (BnHN-)	2	-40	20	72	69:31
8	2c (2-adHN-) ^d	2	-40	20	73	83:17
9	2d (tBuHN-)	2	-40	20	79	92:8
10	2e (1-adHN-)	2	-40	20	88	93:7
11	2e (1-adHN-)	0.5	-40	20	55	92:8
12	2e (1-adHN-)	0.5	-40	48	80	92:8

^a Only (P)-catalysts are shown for clarity. ^b Determined after oxidation. ^c With 4 Å molecular sieves. ^d ad = adamantyl.

the catalyst selectivity. The improved enantioselectivity was maintained when the catalyst loading was reduced to 0.5 mol % (entries 11 and 12).

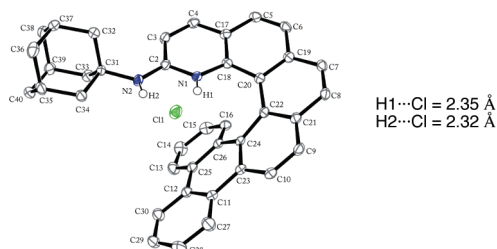
The scope of the reaction is summarized in Table 2. Aromatic nitroalkenes with various steric and electronic properties were tolerated by the optimum catalyst **2e** (entries 1–11). The longer reaction time was required for entries 1, 6, and 8, presumably due to the poor solubility of these nitrostyrenes under the reaction condition. An aliphatic nitroalkene also provided good enantioselectivities (entries 12 and 16). Several substituted 4,7-dihydroindoles and a pyrrole were evaluated next and also found to be good substrates for the present method (entries 13–17). While the first catalyst **1a** was found equally effective for both 4,7-dihydroindole and indole in initial experiments (Table 1, entry 1, and Table 2, entry 18), to our surprise, the catalyst optimized for 4,7-dihydroindoles (**2e**) turned out to be virtually unreactive for an indole nucleophile (entry 19). At the end of these reactions, the corresponding 2-aminopyridines can be recovered (>90%).

We obtained the crystal structure of the HCl salt (X = Cl in **2e**), in which the 2-aminopyridinium cation forms two H-bonds to a chloride anion (Figure 1).^{1a} This result and the high levels of asymmetric induction displayed by **2e** strongly support that the 2-aminopyridinium ion can function as a dual H-bonding catalyst (as opposed to a specific acid catalyst^{1d}) despite its increased acidity. Also evident is that the bottom half of the helicene framework effectively covers the space beneath the two H-bonds.

Table 2. Scope of the Reaction


entry	R ₁	R ₂	temp (°C)	product	yield (%) ^a	er ^d
1 ^b	H	4-Br-Ph	−55	3b	65	97:3
2	H	3-Br-Ph	−65	3c	80	97:3
3	H	2-Br-Ph	−65	3d	74	95:5
4	H	4-Cl-Ph	−55	3e	88	96:4
5	H	4-F-Ph	−50	3f	83	95:5
6 ^c	H	4-MeO-Ph	−50	3g	70	92:8
7	H	3-MeO-Ph	−55	3h	75	96:4
8 ^c	H	2-MeO-Ph	−55	3i	75	98:2
9	H	4-Me-Ph	−50	3j	80	95:5
10	H	1-naphthyl	−50	3k	74	96:4
11	H	3-furyl	−40	3l	50	91:9
12	H	Me	−65	3m	88	91:9
13	5-MeO	Ph	−60	3n	90	96:4
14	5-Me	Ph	−60	3o	90	97:3
15	6-Me	Ph	−60	3p	65	90:10
16 ^d	5-MeO	Me	−65	3q	69	95:5
17	2-Et-pyrrole	Ph	−40	4	55	85:15
18 ^e	1-Me-indole	Ph	0	5	70	60:40
19 ^f	1-Me-indole	Ph	0	5	10	60:40

^a Determined after oxidation. ^b 36 h reaction. ^c 48 h reaction. ^d 1 mmol scale. ^e With **1a** (10 mol %). ^f 72 h reaction.

**Figure 1.** ORTEP of 2-(1-adamantylamino)-1-azahelicene·HCl.

The utility of the method was demonstrated by the asymmetric synthesis of monoamine oxidase (MAO) inhibitor **6**, which was, to our knowledge, previously prepared only in racemic form (eq 1).^{22b} Enantio-enriched **6** was readily synthesized from addition product **3q** (Table 2, entry 16) in two steps with 74% overall yield.



In summary, the results presented above show two things: (1) The 2-aminopyridinium ion functions as a highly efficient catalyst without additional complementary functionalities with which many (thio)urea catalysts are associated.^{1,20b} Therefore, it is a powerful dual H-bonding motif on which to build chiral catalysts. (2) 1-Azahelicenes are effective chiral scaffolds for the construction of catalyst structures that are otherwise difficult to access. These new catalysts are currently being evaluated in a number of other transformations.

Acknowledgment. We thank the Florida Department of Health (07KN-12), the American Cancer Society (IRG-98-277-07), the Sylvester Comprehensive Cancer Center, and the University of Miami for support.

Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA100539C