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Tetrazolic Acid Functionalized Dihydroindol: Rational Design of a Highly Selective Cyclopropanation Organocatalyst

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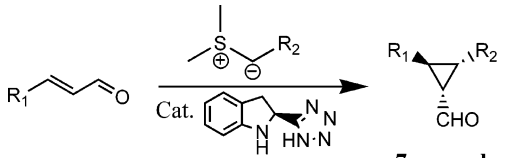

Herein we wish to report our development of an improved catalyst (*S*)-(-)-indoline-2-yl-1H-tetrazole (**1**) for the enantioselective organocatalyzed cyclopropanation of α,*β*-unsaturated aldehydes with sulfur ylides. The new organocatalyst readily facilitates the enantioselective organocatalytic cyclopropanation, providing cyclized product in excellent diastereoselectivities ranging from 96% to 98% along with enantioselectivities exceeding 99% enantiomeric excess for all reacted α,*β*-unsaturated aldehydes. The new catalyst provides the best results so far reported for intermolecular enantioselective organocatalyzed cyclopropanation.

The cyclopropane unit is a frequently encountered structural unit in many naturally occurring compounds. Synthetic methodology enabling the construction of these highly strained systems was thoroughly explored in the middle of the 20th century whereas the enantioselective construction of diversely substituted cyclopropane units has gained widespread interest during the last 20 years.[1]

Early development in stereospecific cyclopropanation utilized a Simmons-Smith type of process, in which iodomethylzinc reagents[2] generated by different methods allowed the enantioselective cyclopropanation of structurally diverse cyclic and acyclic alkene systems to be carried out by utilizing the chiral pool,[3] chiral auxiliaries,[4] and catalytic asymmetric cyclopropanation, using iodomethylzinc with C_2-symmetric disulfonamide ligands[5] and Ti-taddolates.[6]

An increasingly important reaction type features a nucleophile undergoing intermolecular Michael addition forming an enolate followed by intramolecular ring closure accompanied by loss of leaving group either present on the Michael acceptor or at the nucleophile furnishing cyclopropanated product.[7] This reaction type is classified as a Michael initiated ring closure (MIRC) reaction. The most commonly employed nucleophiles in MIRC are α-halocarbanions,[8] sulfur ylides,[9] phosphorus ylides,[10] arsenium ylides,[11] and telleronium ylides[12] allowing a range of structurally divergent substrates to be reacted, thus creating a plethora of cyclopropane architectures.

In an important paper Ley et al. disclosed an intermolecular asymmetric organocatalyzed cyclopropanation catalyzed by quinine alkaloids.[13] The reaction incorporates α-halocarbonyls, α,*β*-unsaturated ketones, or esters coupled with an external base. In another seminal paper, published by MacMillan et al., (*S*)-(−)-indoline-2-carboxylic acid catalyzes the intermolecular enantioselective organocatalytic cyclopropanation utilizing α,*β*-unsaturated aldehydes as Michael acceptors, providing cyclopropated products in enantiomeric excesses up to 95%.[14] The proposed mechanistic postulate is based upon the concept of directed electrostatic activation where the catalyst carboxylate provides enantiofacial discrimination for the incoming nucleophile accompanied by electrostatic association whereas selective formation of a catalyst derived zwitterionic (*Z*)-iminum isomer ensures a high degree of enantiocontrol. In line with our interest in catalyst development for organocatalyzed reactions we envisioned an improved catalyst that catalyzes the cyclopropanation reaction with excellent diastereoselectivity and enantioselectivity. Second-generation catalyst, in which the carboxylic acid of (*S*)-(−)-indoline-2-carboxylic acid is replaced by a

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(1) A thorough review has been published on the topic: Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.

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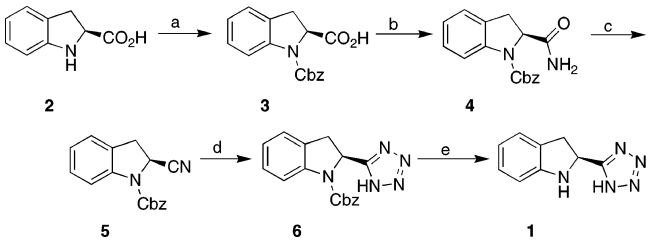
SCHEME 1. Synthesis of (*S*)-(−)-Indoline-2-yl-1*H*-tetrazole (1)[a]



[a] Reagents and conditions: (a) Cbz-Cl, 2 M NaOH, 5 °C, 5 h; (b) Boc_2O, NH_4HCO_3, MeCN, pyridine, 68 h, room temperature; (c) cyanuric chloride, DMF, 24 h, rt; (d) NaN_3, $ZnBr_2$, 2-Propanol, water, reflux; (e) Pd/C, H_2(g), AcOH:H_2O (9:1), 60 °C.

known bio-isostere[15] such as tetrazolic acid, was expected to improve enantioselectivity as a consequence of increased steric bulk while retaining important structural functionality associated with the proposed directed electrostatic activation mechanistical postulate.

Since the introduction of tetrazolic acids in enantioselective organocatalyzed reactions by Ley,[16] Yamamoto,[17] and ourselves[18] the number of applications where catalysts containing tetrazol acid moieties has significantly increased in literature displaying the profound impact of tetrazolic acid based catalysts in asymmetric organocatalyzed reactions.[19] Thus, herein we report our development of an improved catalyst for the organocatalyzed asymmteric cyclopropanantion, initially discovered by MacMillan, containing a tetrazolic acid moiety instead of the carboxylic acid of (*S*)-(−)-indoline-2-carboxylic acid.

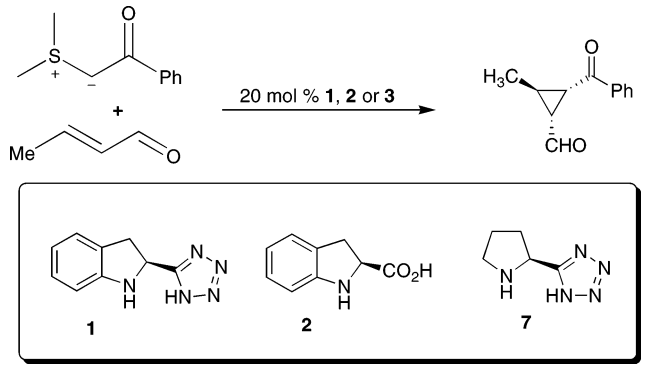
The new organocatalyst **1** was synthesized from commercially available (*S*)-(−)-indoline-2-carboxylic acid, according to Scheme 1. The synthesis commenced from Cbz protection of (*S*)-(−)-indoline-2-carboxylic acid[20] with use of Schotten-Baumann conditions[21] to give the Cbz protected (*S*)-(−)-indoline-2-carboxylic acid (**3**), which was subsequently converted to the corresponding primary amide (**4**)[22] by in situ activation of the carboxylic acid followed by dehydration furnishing the nitrile (**5**).[23]The nitrile was then further converted to the corresponding protected tetrazole (**6**) utilizing the "click chemistry" protocol developed in the Sharpless laboratory.[24] The target compound **1** was obtained after catalytic hydrogenation and purification by a solid-phase catch and release procedure followed by recrystallization to give pure product.[25]

TABLE 1. Solvent and Catalyst Screening for the Reaction Depicted in Scheme 2

entry[a]	solvent	catalyst	yield[b] (%)	de[c] (%)	ee[d] (%)
1	$CHCl_3$	**1**	82	96	99
2	$CHCl_3$	**2**	74	95	89
3	$CHCl_3$	**7**	84	88	43
4	DMF	**1**	34	75	−38
5	DMSO	**1**	32	80	−32
6	THF	**1**	69	93	83

[a] The reaction was conducted at 4 °C. [b] Isolated yield after column chromatography. [c] Determined by ^{1}H NMR analysis of crude reaction mixture. [d] Determined by means of GLC analysis.

SCHEME 2. Catalyst and Solvent Screening



Catalyst **1** and tetrazolic acid containing catalyst **7**[18] along with the original catalyst **2** were assessed in the benchmark reaction of crotonaldehyde and sulfur ylide to furnish product in various yields, diastereoselectivities, and enantioselectivities. The results clearly indicate that chloroform was the solvent of choice providing the products in high enantiomeric excesses whereas high dielectric constant solvents render products of low optical purity as concluded in the previous study.[14] More importantly, this initial screening indicated that catalyst **1** offered higher enantioselectivity compared to catalyst **2** (Table 1, entries 1 and 2).

After initial catalyst and solvent screening the substrate scope was investigated (Table 2,, entries 1−7, catalyst **1**; and Table 3, entries 1−7, catalyst **2**).[26]The novel catalyst **1** provides products in slightly higher isolated yields compared to reactions catalyzed by **2** but more importantly renders products of significantly higher optical purity for all investigated α,β-unsaturated aldehydes (Table 2 and 3, entries 1−7). Catalyst **1** facilitates the reactions between straight chain α,β-unsaturated aldehydes and stabilized aromatic sulfur ylides with excellent diastereo- and enantioselectivity, see products **8a**−**10a** (Table 2, entries 1−3) compared to catalyst **2**, which renders products of lower optical purity (Table 3, entries 1−3). Notably, a

(15) For a thorough review of the topic see: Herr, R. J. *Bioorg. Med. Chem.* **2002**, *10*, 3379.
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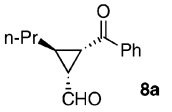
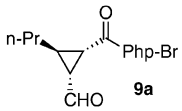
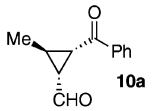
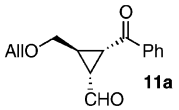
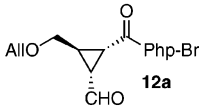
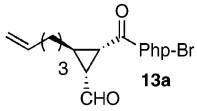
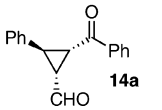
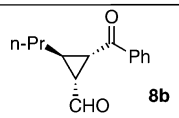
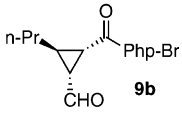
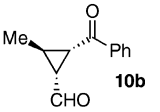
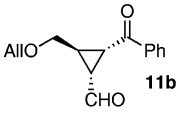
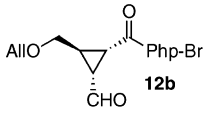
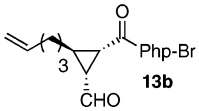
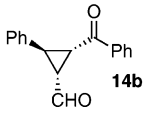
(25) Almquist, G. R.; Chao, W.; White-Jennings, C. *J. Med. Chem.* **1985**, *28*, 1067.
(26) Both catalytic systems were assessed as in the previous report (ref 14), which allowed correlation of the relative and absolute stereochemistry of products generated by catalyst (**1**) from the retention time of products in GC or HPLC generated from catalytic system **2**.

TABLE 2. Scope of Organocatalytic Ylide-Cyclopropanation Depicted in Scheme 3[a,b]

entry	R_1	R_2	product	yield %[c]	(de:ee) %[c]
1	C_3H_7	Ph	 **8a**	82	(97:99)
2	C_3H_7	*p*-Br-Ph	 **9a**	74	(97:99)
3[e]	CH_3	Ph	 **10a**	85	(96:99)
4	$C_3H_5OCH_2$	Ph	 **11a**	91	(98:99)
5	$C_3H_5OCH_2$	*p*-Br-Ph	 **12a**	83	(98:99)
6	C_5H_9	*p*-Br-Ph	 **13a**	86	(97:99)
7	C_6H_5	Ph	 **14a**	74	(97:99)

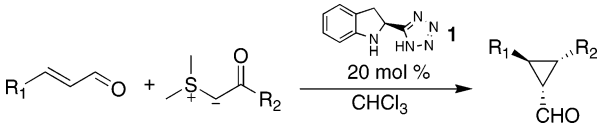
[a] The reactions are performed at −10 °C unless otherwise stated. [b] Relative and absolute configuration was assigned through correlation of obtained products to reference substances generated with catalyst **2**.[14] [c] Isolated yield after column chromatography. [d] de (diastereomeric excess) is determined by ^{1}H NMR or GLC analysis and ee (enantiomeric excess) is determined by GLC or HPLC analysis. [e] The reaction is performed at 4 °C.

TABLE 3. Scope of Organocatalytic Ylide-Cyclopropanation Depicted in Scheme 4[a,b]

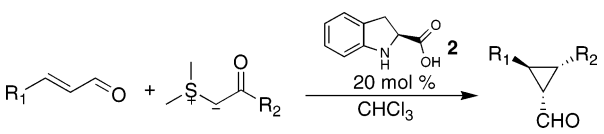
entry	R_1	R_2	product	yield %[d]	(de:ee) %[e]
1	C_3H_7	Ph	 **8b**	74	(97:93)
2	C_3H_7	*p*-Br-Ph	 **9b**	66	(97:93)
3[c]	CH_3	Ph	 **10b**	67	(95:89)
4	$C_3H_5OCH_2$	Ph	 **11b**	77	(96:91)
5	$C_3H_5OCH_2$	*p*-Br-Ph	 **12b**	78	(97:88)
6	C_5H_9	*p*-Br-Ph	 **13b**	71	(96:93)
7	C_6H_5	Ph	 **14b**	93	(97:93)

[a] The reactions are performed at −10 °C unless otherwise stated. [b] These results are reproductions of those experiments performed by MacMillan et al. in their original study,[14] and gave comparable results. The main purpose of these reproductions was to obtain reference material for assigning relative and absolute configuration of product. [c] The reaction is performed at 4 °C. [d] Isolated yield after column chromatography. [e] de (diastereomeric excess) is determined by ^{1}H NMR or GLC analysis and ee (enantiomeric excess) is determined by GLC or HPLC analysis.

SCHEME 3. Scope of Organocatalytic Ylide-Cyclopropanation with Catalyst 1



SCHEME 4. Scope of Organocatalytic Ylide-Cyclopropanation with Catalyst 2



substantial difference is observed for the nonreactive substrate crotonaldehyde (Tables 2 and 3, entry 3). Here the novel catalyst **1** furnishes product **10a** in 85% isolated yield accompanied by 99% enantiomeric excess and 96% diasteromeric excess whereas the existing catalyst gave the product **10b** in 67% isolated yield with 89% ee and 95% de. The α,β-unsaturated terminal allylether aldehyde (Table 2, entries 4 and 5) is converted to the cyclopropanated products **11a** and **12a** by catalyst **1** in enantiomeric excesses exceeding 99% whereas catalyst **2** provide products **11b** and **12b** in enantiomeric excesses ranging from 88% to 91% (Table 3, entries 4 and 5). The terminally unsaturated α,β-unsaturated aldehyde investigated also gave the product **13a** in higher enantiomeric excess with catalyst **1**, as compared with catalyst **2** (Tables 2 and 3, entry 6). An aromatic α,β-unsaturated aldehyde was also reacted successfully yielding product **14a** in >99% enantiomeric excess for catalyst **1**, while catalyst **2** furnished the product **14b** in 93% enantiomeric excess. The new catalyst obviously adapts well to the directed electrostatic activation mechanistic postulate, as indicated by the excellent results for the enantioselective organocatalytic cyclopropanation, where the observed increase in enantioselectivity correlates to the increased steric bulk imposed by the larger tetrazolic acid, as compared to the normal carboxylic acid functionality.

In conclusion, the novel catalyst **1** was synthesized through well-established methodology consisting of a dihydroindol

framework coupled to a tetrazolic acid. The structural features ensure necessary functionality enabling the catalyst to highly selectively catalyze the enantioselective organocatalytic cyclopropanation in excellent enantiomeric excesses, i.e., over 99% ee, for all reacted α,β-unsaturated aldehydes and sulfur ylides attempted. At the same time the catalyst furnishes the products in acceptable to high yields and with comparable diastereoselectivities to the previously reported catalyst. Increased enantioselective induction can be rationalized by the larger steric bulk imposed by the deprotonated tetrazolic acid enhancing enantiofacial discrimination of the incoming nucleophile well in accordance with the directed electrostatic activation mechanistic postulate depicted by MacMillan. The system is robust—no dry solvents are needed in the catalytic reactions—and the catalyst can be stored neat or in chloroform solution without any detectable decomposition. The results convincingly show that carboxylic acid substitution to the corresponding tetrazolic acid indeed has a beneficial effect in terms of asymmetric induction.

Experimental Section

General Procedure for Catalytic Asymmetric Cyclopropanation. To a 30 mL flask equipped with a magnetic stirring bar was added the aldehyde (0.508 mmol) and chloroform (21 mL). The mixture was cooled to the desired temperature and stirred for an additional 20 min. To the chilled mixture was then added either (*S*)-(−)-indoline-2-carboxylic acid (**2)** (4.2 mg; 0.026 mmol) or (*S*)-(−)-indoline-2-yl-1*H*-tetrazole (**1)** (4.8 mg; 0.026 mmol) followed by either 2-(dimethyl-λ^4-sulfanylidene)-1-phenylethanone (23 mg; 0.127 mmol) or 2-(dimethyl-λ^4-sulfanylidene)-1-(4′-bromophenyl)-ethanone (33 mg; 0.127mmol). The homogeneous solution was stirred between 24 and 48 h after which the cold solution was filtered through a pad of silica eluting with diethyl ether. The filtrate was concentrated under reduced pressure to give crude products as yellow oils, which were further purified by means of column chromatography.

(1*R*,2*R*,3*S*)-2-Allyloxymethyl-3-(4′-bromobenzoyl)cyclopropanecarbaldehyde (12a; Table 2, entry 5). 5 was prepared according to general procedure from (*2E*)-4-(allyloxy)but-2-enal (64 mg; 0.508 mmol), 2-(dimethyl-λ^4-sulfanylidene)-1-(4′-bromophenyl)-ethanone, and (*S*)-(−)-indoline-2-yl-1*H*-tetrazole (**1**) to give the pure product as a colorless oil (34.1 mg; 83% yield; 99% ee; 23:1 dr) after column chromatography (silica gel, 10% Et_2O in *n*-pentane), R_f 0.06. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.38 (d, J = 6.34 Hz, 1H), 7.9−7.86 (m, 2H), 7.64−7.61 (m, 1H), 5.88 (ddt, J = 17.2, 10.4, 5.6 Hz, 1H), 5.27 (dq, J = 17.2, 1.57 Hz, 1H), 5.21 (ddq, J = 10.4, 1.59, 1.21 Hz, 1H), 4.03−4.00 (m, 2H), 3.74 (dd, J = 10.4, 4.59 Hz, 1H), 3.55 (dd, J = 10.4, 5.5 Hz, 1H), 3.19 (dd, J = 8.81, 6.11 Hz, 1H), 2.78−2.72 (m, 1H), 2.34 (dt, 8.82, 6.21). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.9, 30.3, 31.8, 36.5, 68.4, 71.9, 117.5, 130.0 (2C), 132.0 (2C), 134.1, 135.5, 194.7, 198.5. $[\alpha]_D$ −16.9 (*c* 1.0, $CHCl_3$). The enantiomeric excess and diastereomeric excess were determined by GLC, using column coated with chiral stationary phase (30 m × 0.25 mm), column (200 °C isotherm for 130 min), ramp to (220 °C by 10 °C), hold 0.5 min. Major diastereomer: major enantiomer t_r = 32.6 min and minor enantiomer t_r = 33.3 min Minor diastereomer: major enantiomer t_r = 18.5 min and minor enantiomer t_r = 17.3 min. MS (EI) *m*/*z* (rel intensity) 323 ($[M + 1]^+$, 7), 325 (7), 283 (5), 281 (8), 280 (1), 253 (97), 252 (16), 251 (100), 250 (4), 185(53), 184(8), 183(55), 182(2), 157(22), 156(4), 155(21), 154(1).

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Supporting Information Available: Experimental procedures, ^{1}H NMR and ^{13}C NMR spectra of all synthesized compounds, and HPLC and GLC-MS traces for enantioselectivity determination. This material is available free of charge via the Internet at http://pubs.acs.org.

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