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Catalytic Enantioselective Synthesis of Tetrahydrofurans: A Dynamic Kinetic Asymmetric [3 + 2] Cycloaddition of Racemic Cyclopropanes and Aldehydes

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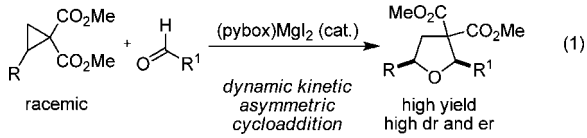
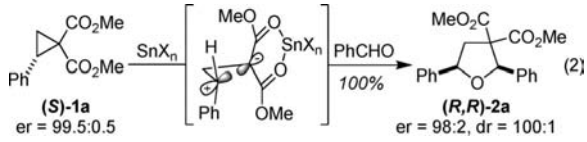
Herein we report an efficient preparation of enantioenriched tetrahydrofuran (THF) derivatives through a dynamic kinetic asymmetric transformation (DyKAT)[1] of racemic malonate-derived donor−acceptor (D−A) cyclopropanes via asymmetric [3 + 2] cycloaddition with aldehydes (eq 1).



(1)

D−A cyclopropanes have gained attention in the past decade because of their synthetic utility and ease of preparation.[2] Recent literature has demonstrated that they provide access to carbocycles[3] and heterocycles[4,5] via rearrangement or [3 + 2], [3 + 3], and [3 + 4] cycloadditions with appropriate dipolarophiles, typically under Lewis acid catalysis. To date, generation of enantioenriched cycloadducts has typically required the use of nonracemic cyclopropane starting materials in reactions proceeding via stereospecific pathways.[4,5k,n,6,7]

Aldehydes undergo stereospecific Lewis acid-catalyzed cycloaddition with D−A cyclopropanes via a configurationally stable intimate ion pair to afford enantioenriched THF derivatives in high yields (eq 2).[4,8] The background racemization of **(*S*)-1a** is

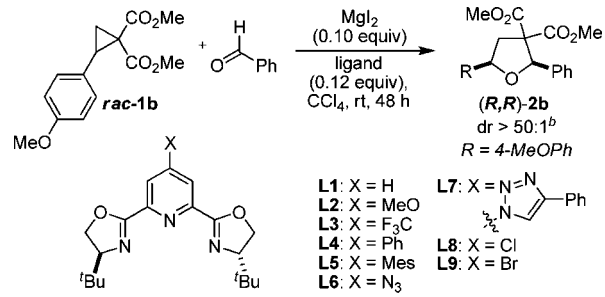


(2)

comparatively slow under these conditions.[4,5k] The identification of a kinetically competent racemization pathway was presumed to be a minimal precondition for the development of the more desirable transformation: a DyKAT of racemic D−A cyclopropanes through a chiral Lewis acid-catalyzed cycloaddition with aldehydes (eq 1). To this end, we sought to discover a Lewis acid that (1) selectively catalyzes the cycloaddition of the aldehyde with one enantiomer of cyclopropane and (2) promotes interconversion of the cyclopropane enantiomers.

p-Methoxyphenylcyclopropane **1b** is known to undergo rapid ring opening and was selected as the test substrate.[4b] The occurrence of a number of 2,5-diaryl-THF natural products bearing electron-rich aromatic moieties further recommended **1b** as an appropriate point of departure for this study.[9] (^{t}Bu-pybox)MgI_2 was identified as an effective catalyst for the cycloaddition of **1b** and benzaldehyde, providing promising yield and enantiocontrol in the production of tetrahydrofuran **2b** as a single diastereomer (Table 1, entry 1).[10] Examination of other pybox ligands revealed that the *tert*-butyl group was necessary for sufficient selectivity and yield, and thus, we explored perturbations of ^{t}Bu-pybox ligands at the

Table 1. Examination of 4-Substituted ^{t}Bu-pybox Ligands[a]



entry	ligand	conversion (%)[c]	yield (%)[c]	er[d]
1	**L1**	93	62	95.5:4.5
2	**L2**	26	5	nd
3	**L3**	100	57	96.5:3.5
4	**L4**	100	73	95.5:4.5
5	**L5**	95	59	94:6
6	**L6**	100	67	96:4
7	**L7**	100	55	93.5:6.5
8	**L8**	100	74[e]	96:4
9[f]	**L8**	100	16	82.5:17.5
10[g]	**L8**	100	40	96:4
11	**L9**	100	75	95:5

[a] Conditions: **1b** (1.0 equiv), benzaldehyde (2.0 equiv), MgI_2 (0.10 equiv), **L** (0.12 equiv), $[\mathbf{1b}]_0$ = 0.05 M in CCl_4, room temperature, 48 h. [b] Determined by ^{1}H NMR spectroscopy of the unpurified product. [c] Determined by ^{1}H NMR spectroscopy using a mesitylene internal standard. [d] Determined by chiral SFC analysis. [e] Average isolated yield of two trials. [f] With CH_2Cl_2 as the solvent. [g] With C_7H_8 as the solvent.

4-position of the pyridine. Altering the substituent X of the 4-X-^{t}Bu-pybox ligands (**L2**−**L9**) had a negligible effect on enantioselectivity but induced a significant variation in yield. Ligands **L8** (X = Cl) and **L9** (X = Br) provided the highest yields and levels of enantiocontrol (Table 1, entries 8 and 11).

L8·MgI_2 catalyzed the enantioselective cycloaddition of various aldehydes with ***rac*-1b** (Table 2). This reaction worked well for electron-rich aryl, cinnamyl, and linear and branched aliphatic aldehydes. Electron-poor aldehydes typically gave lower yields, presumably because of their poor nucleophilicity.[4] This methodology was also extended to activated cyclopropanes bearing 2-thienyl (**1c**) and (*E*)-CH=CHPh (**1d**) donor groups. The remaining mass balance was attributed to cyclopropane decomposition, affording a complex mixture of byproducts.

The cycloaddition of ***rac*-1a** with *p*-anisaldehyde catalyzed by **L8**·MgI_2 yielded **2p** with an er of 95.5:4.5; the product was determined to be the (*R*,*R*) enantiomer by comparison to previously reported SFC retention times and optical rotation.[4] The recovered cyclopropane was found to be enriched in the (*R*) enantiomer (er = 86:14; Table 3, line 1), and therefore, ***rac*-1a** is a substrate for a simple kinetic resolution rather than a DyKAT.[7] This result suggests that the aldehyde selectively reacts with the (*S*) enantiomer

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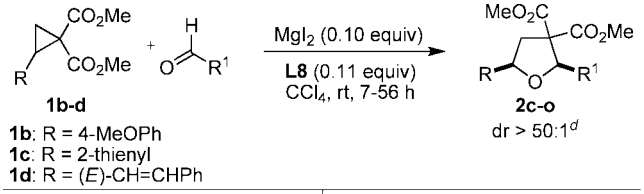
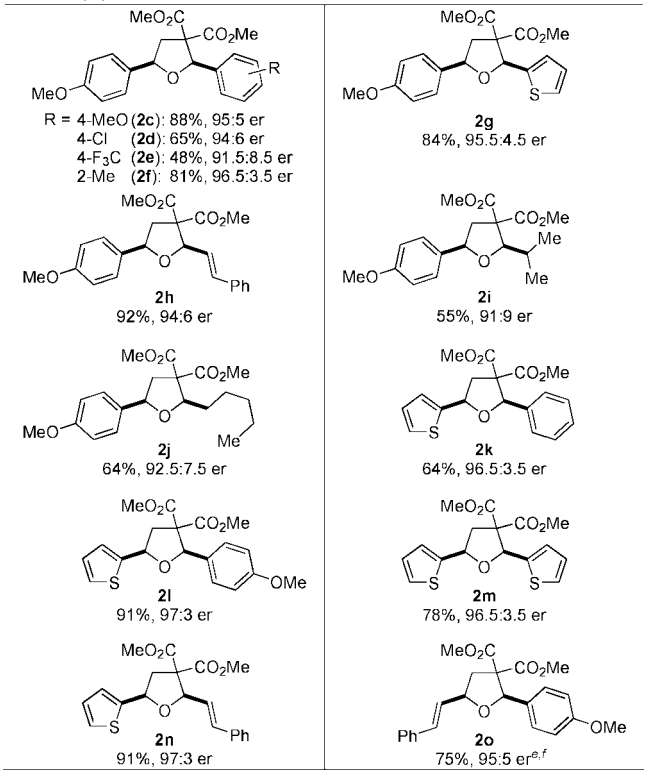
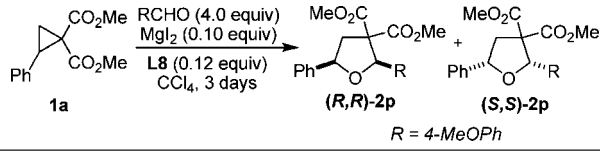
Table 2. Substrate Scope[a–c]





[a] Conditions: **1** (1.0 equiv), aldehyde (2.0−4.0 equiv), MgI_2 (0.10 equiv), **L8** (0.11 equiv), $[\mathbf{1}]_0$ = 0.05 M in CCl_4, room temperature, 7−56 h. See the Supporting Information for additional experimental details. [b] Yield refers to the average isolated yield of at least two trials. [c] er was determined by chiral SFC analysis. [d] Determined by ^{1}H NMR spectroscopy of the unpurified product. [e] dr > 25:1. [f] er was determined for the major (cis) diastereomer.

Table 3. Stereochemical Analysis[a]



substrate	conversion (%)[b]	yield (%)[c]	(*R*,*R*)-**2p**/ (*S*,*S*)-**2p**[d,e]	(*R*)-**1a**/ (*S*)-**1a**[f]
***rac*-1a**	54	38	95.5:4.5	86:14
(*R*)-1a	22	3	21:79	98:2
(*S*)-1a	96	92	99.5:0.5	25:75

[a] Conditions: see Table 2, footnote *a*. [b] The difference in yield and conversion is attributed to cyclopropane decomposition. [c] The yield of **2p** was determined by ^{1}H NMR spectroscopy using a mesitylene internal standard and is the average of two trials. [d] dr > 99:1. [e] er was determined by chiral SFC analysis. [f] er of recovered **1a** as determined by chiral GC analysis.

of the cyclopropane through a stereospecific nucleophilic attack.[4,5l] This interpretation is corroborated by the sluggish reaction of enantiopure **(*R*)-1a**, which gives product **2p** with er = 79:21 in the (*S*,*S*) configuration. Conversely, use of **(*S*)-1a** affords optically pure **(*R*,*R*)-2p** in excellent yield with near complete conversion of the cyclopropane (Table 3).

In summary, a simple protocol for the preparation of enantioenriched THF derivatives through a dynamic kinetic asymmetric [3 + 2] cycloaddition of racemic malonate-derived D−A cyclopropanes and aldehydes has been developed. A variety of cyclopropanes bearing electron-rich donor groups undergo cycloaddition with aryl, cinnamyl, and aliphatic aldehydes to afford products in good yields and enantioselectivity. Current efforts seek to elucidate the mechanism of this new transformation, understand the unique reactivity of the (pybox)MgI_2 catalysts, and extend this methodology to other asymmetric reactions with D−A cyclopropanes.

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Supporting Information Available: Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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