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Communication

Enantioselective Organocopper-Catalyzed Hetero Diels–Alder Reaction through *in Situ* Oxidation of Ethers into Enol Ethers

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ABSTRACT: We disclose a catalytic method for the enantio- and diastereoselective union of alkyl ethers and heterodienes. We demonstrate that a chiral Cu–BOX complex catalyzes the efficient oxidation of ethers into enol ethers in the presence of trityl acetate. Then, the organocopper promotes stereoselective hetero Diels–Alder reaction between the *in situ* generated enol ethers and *β,γ*-unsaturated ketoesters, allowing for rapid access to an array of dihydropyran derivatives possessing three vicinal stereogenic centers.

Chiral ethers are essential building blocks of various natural products, pharmaceuticals, and polymers.[1−9] Such moieties can be accessed by stereoselective transformations of alkyl enol ethers (e.g., BOX–Cu-catalyzed hetero Diels–Alder reaction with 2,3-dihydrofuran; Figure 1A).[10−29] However, only a limited number of enol ethers are commercially available, and their synthesis and purification are often cumbersome (e.g., partial hydrogenation of alkynyl ethers, Wittig reaction).[30−32] An enabling strategy to obviate these key limitations would be to perform enantioselective transformations of enol ethers that are generated *in situ* by oxidation of significantly more accessible and otherwise stable alkyl ethers (Figure 1B).[33−40] Such an approach not only would be operationally simple but would generate less waste (vs the processes that demand preformation of enol ethers).[41−70]

In contemplating ways to develop a protocol for the enantioselective union of various alkyl ethers **1** and heterodienes **2**, we envisioned using a combination of a chiral Cu-based complex and a trityl-containing compound (Ph_3C–OR, Figure 1B). It has been reported that $[Ph_3C]^+[BF_4]^-$ serves as a recipient of hydride from acetals and ethers.[71−79] Inspired by these studies, we imagined that Ph_3C^+ (**I**), generated by the reaction of organocopper and Ph_3C–OR, receives a hydride from an ether (**1**), leading to the formation of Ph_3C–H and an oxocarbenium ion (**II**). A Brønsted base would subsequently deprotonate **II** to furnish enol ether **III**. An ensuing enantio- and diastereoselective [4 + 2] cycloaddition between enol ether **III** and a *β,γ*-unsaturated ketoester **2**, activated by the chiral organocopper catalyst, would deliver a dihydro-2*H*-pyran derivative **3**. A key advantage of this strategy is that it allows the enantioselective union of otherwise-difficult-to-access enol ethers (vs methods that are limited to relatively simple and readily available dienophiles, e.g., Figure 1A).[10−12,30−32,80] Thus, a considerable range of dihydro-2*H*-pyrans **3** comprised of stereogenic centers at the C1, C2, and C3 positions may be prepared. However, to achieve highly enantioselective synthesis of **3**, Ph_3C^+ and the chiral Cu-based Lewis acid must be able to perform their independent roles without overlapping

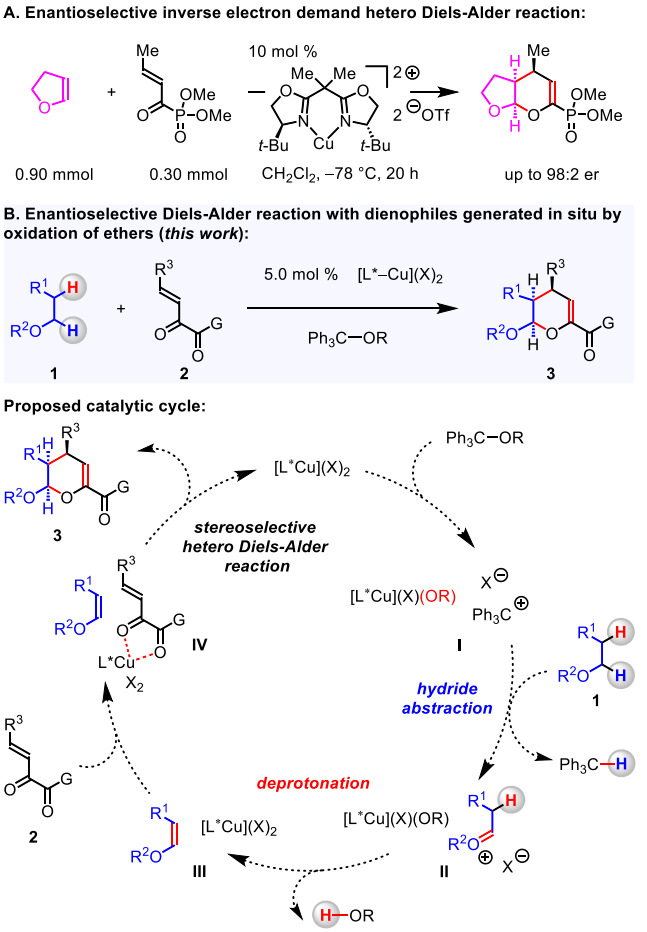

Figure 1. Strategies for enantioselective synthesis of ethers.

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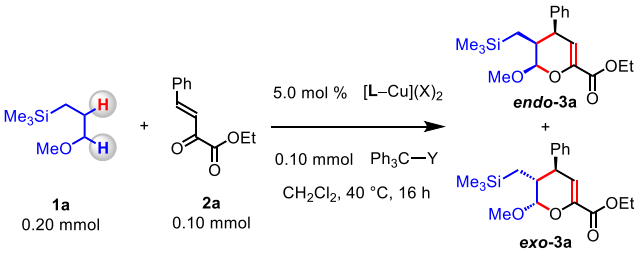
functions; otherwise, Ph_3C^+ could promote racemic cycloaddition by activating **2**, likely resulting in diminished enantioselectivity.[81] Herein, we report an organocopper-based catalyst system that promotes *in situ* oxidation of acyclic and cyclic ethers into enol ethers, and their enantioselective cycloaddition with heterodienes.

We set out to identify a combination of a Cu-based complex and a trityl-containing compound that could promote the enantioselective union of (3-methoxypropyl)trimethylsilane **1a** and ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **2a**, generating **3a** (Table 1). We began by reacting **1a** (0.20 mmol) and **2a** (0.10 mmol) in the presence of 5.0 mol % [*t*-BuBOX(**L1**)−Cu]$(SbF_6)_2$ and 0.10 mmol $[Ph_3C]^+[BF_4]^-$ (CH_2Cl_2, 40 °C, 16 h); this afforded *rac*-**3a** in 75% yield (*endo*:*exo* = 1.4:1; entry 1). The formation of *rac*-**3a** indicates that Ph_3C^+ not only abstracts a hydride from **1a** but also activates **2a** and facilitates its reaction with the **1a**-derived dienophile (vs the desired cycloaddition catalyzed by [**L1**−Cu]$(SbF_6)_2$; **IV** → **3a**, Figure 1B). Indeed, $[Ph_3C]^+[BF_4]^-$ was found to mediate the formation of *rac*-**3a** in the absence of [**L1**−Cu]$(SbF_6)_2$ (39% yield, *endo*:*exo* = 1.3:1; entry 2). These results suggest the need for a catalyst system that is capable of generating a small concentration of Ph_3C^+ *in situ* which rapidly reacts with **1a** to afford Ph_3C−H. This may allow the ensuing hetero Diels−Alder reaction to be solely catalyzed by the chiral organocopper complex, thereby resulting in an enantioselective process.

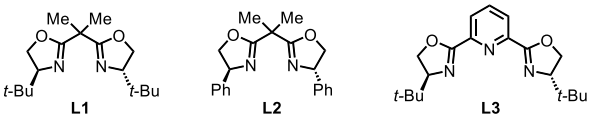
On the basis of these considerations, we evaluated Ph_3C−OH and its derivatives that might react with the Cu-based Lewis acid to furnish Ph_3C^+ in a catalytic quantity. As a result, with Ph_3C−OH, no product formation was observed when the reaction mixture was allowed to stir at 40 °C (entry 3); however, at 60 °C, *endo*-**3a** (90:10 er) and *exo*-**3a** (87:13 er) were produced in 60% overall yield (*endo*:*exo* = 2.7:1; entry 4). By use of the more Lewis acid-sensitive Ph_3C−OAc, the reaction occurred at 40 °C, giving *endo*-**3a** in 35% yield (96:4 er) and *exo*-**3a** in 20% yield (96:4 er; entry 5). To investigate the effect of using different ligands, we tested various Cu-based complexes (see the Supporting Information for details); using [PhBOX(**L2**)−Cu]$(SbF_6)_2$ or [*t*-BuPyBOX(**L3**)−Cu]$(SbF_6)_2$, **3a** was produced in ≤40% yield (50:50 to 76:24 er; entries 6 and 7). The catalysts possessing SbF_6 counterions were substantially more reactive than those complexes with OTf or ClO_4 anions (entries 5 vs 8 and 9). While the use of 0.30 mmol of **1a** resulted in the formation of **3a** in 87% yield (entry 10), with 0.40 mmol of **1a**, **3a** could be obtained in nearly quantitative yield (entry 11). There was no formation of **3a** in the absence of [**L1**−Cu]$(SbF_6)_2$ or Ph_3C−OAc (entries 12 and 13).

An assortment of acyclic and cyclic ethers (**1a**−**1s**) could be merged with different *β*,*γ*-unsaturated ketoesters (**2a**, **2b**, **2t**−**2w**) to afford the corresponding hetero Diels−Alder products with high enantio- and/or diastereoselectivity (**3a**−**3j** and **3l**−**3w**, Tables 2 and 3). The reaction between **1a** and **2a** gave *endo*-**3a** as the major product (*endo*:*exo* = 1.8:1, 96% overall yield). In contrast, with phthalimide-substituted *β*,*γ*-unsaturated ketoester **2b**, *exo*-**3b** (48% yield, 95:5 er) was formed more predominantly than *endo*-**3b** (23% yield, 93:7 er). While the *O*−CH_2CH_2Ph unit of 2-phenethoxyethyl acetate **1c** was efficiently merged with **2a** to give **3c** in 66% yield (*endo*:*exo* = 1:4.0, up to 95:5 er), the *O*−CH_2CH_2OAc group of **1c** remained intact. The union of (2-methoxyethyl)trimethylsilane **1d** and **2a** was found to proceed through the loss of the TMS group to furnish **3d** in 75% yield (*endo*:*exo* = 8.5:1, 95:5 er). Dihydro-2*H*-pyran derivatives possessing benzoate (**3e**, 75% yield, up to 96:4 er) or phthalimide (**3f**, 77% yield, up to 92:8 er) moieties were readily prepared. Next, we synthesized the isotopologues of (2-methoxyethyl)benzene (**1g** and **1g**-d_3) and independently reacted them with **2a**, which resulted in the formation of **3g** (72% yield, *endo*:*exo* = 1:4.0, 95:5 er) and **3g**-d_3 (68% yield, *endo*:*exo* = 1:4.0, 97:3 er), respectively. The ^{1}H NMR analysis of **3g**-d_3 revealed that only 4% of the OCD_3 moiety underwent hydrogen isotope exchange. Furthermore, only a trace amount of Ph_3C−D was detected (see the

Table 1. Evaluation of Reaction Parameters[a,b]



entry	[L–Cu](X)$_2$	Ph_3C–Y	*endo*-3a + *exo*-3a yield (%)	*endo*:*exo*	er (*endo*)	er (*exo*)
1	[**L1**–Cu]$(SbF_6)_2$	$Ph_3C^{\oplus}\ominus BF_4$	75	1.4:1	50:50	51:49
2	none	$Ph_3C^{\oplus}\ominus BF_4$	39	1.3:1	–	–
3	[**L1**–Cu]$(SbF_6)_2$	Ph_3C–OH	<5	ND	ND	ND
4[c]	[**L1**–Cu]$(SbF_6)_2$	Ph_3C–OH	60	2.7:1	90:10	87:13
5	[**L1**–Cu]$(SbF_6)_2$	Ph_3C–OAc	55	1.8:1	96:4	96:4
6	[**L2**–Cu]$(SbF_6)_2$	Ph_3C–OAc	40	7.0:1	40:60	76:24
7	[**L3**–Cu]$(SbF_6)_2$	Ph_3C–OAc	21	2.0:1	49:51	50:50
8	[**L1**–Cu]$(OTf)_2$	Ph_3C–OAc	0	ND	ND	ND
9	[**L1**–Cu]$(ClO_4)_2$	Ph_3C–OAc	13	1.6:1	86:14	88:12
10[d,f]	[**L1**–Cu]$(SbF_6)_2$	Ph_3C–OAc	87	1.5:1	96:4	96:4
11[e,f]	[**L1**–Cu]$(SbF_6)_2$	Ph_3C–OAc	>95	1.8:1	96:4	96:4
12	none	Ph_3C–OAc	0	ND	–	–
13	[**L1**–Cu]$(SbF_6)_2$	none	0	ND	ND	ND

L = 

[a]Conditions: Reactions were performed under N_2 atmosphere; (3-methoxypropyl)trimethylsilane (**1a**, 0.20 mmol), ethyl (*E*)-2-oxo-4-phenylbut-3-enoate (**2a**, 0.10 mmol), [L−Cu]$(X)_2$ (5.0 mol %), Ph_3C−Y (0.10 mmol), CH_2Cl_2 (0.6 mL), 40 °C, 16 h. [b]Yield and the ratio of *endo* and *exo* products were determined by ^{1}H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard. ND stands for not determined. [c]The reaction was performed at 60 °C. [d]**1a** (0.30 mmol) and Ph_3C−OAc (0.20 mmol) were used. [e]**1a** (0.40 mmol) and Ph_3C−OAc (0.20 mmol) were used. [f]The solution was allowed to stir for 24 h.

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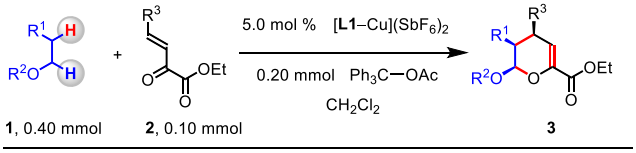
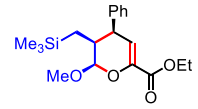
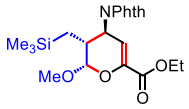
Table 2. Enantioselective Hetero Diels–Alder Reactions[a,b]

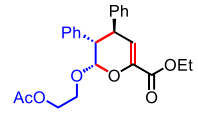




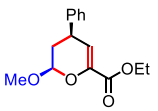
3a, 96% yield
endo:*exo* = 1.8:1
96:4 er (*endo*)
96:4 er (*exo*)



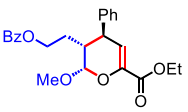
3b, 71% yield
endo:*exo* = 1:2.1
93:7 er (*endo*)
95:5 er (*exo*)



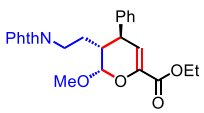
3c, 66% yield[c]
endo:*exo* = 1:4.0
81:19 er (*endo*)
95:5 er (*exo*)



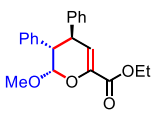
3d, 75% yield[c]
endo:*exo* = 8.5:1
95:5 er (*endo*)



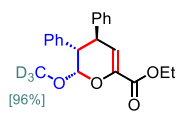
3e, 75% yield[c]
endo:*exo* = 1:1.2
96:4 er (*endo*)
83:17 er (*exo*)



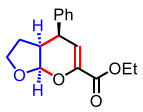
3f, 77% yield[c]
endo:*exo* = 1:1.4
92:8 er (*endo*)
85:15 er (*exo*)



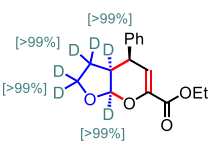
3g, 72% yield[c]
endo:*exo* = 1:4.0
95:5 er (*endo*)
95:5 er (*exo*)



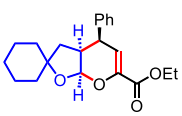
3g-*d*$_3$, 68% yield[c]
endo:*exo* = 1:4.0
97:3 er (*endo*)
97:3 er (*exo*)



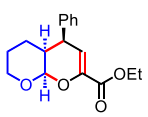
3h, 88% yield[c]
endo:*exo* = 12:1
95:5 er (*endo*)



3h-*d*$_6$, 80% yield[c]
endo:*exo* = 11:1
95:5 er (*endo*)



3i, 72% yield[c]
endo:*exo* = 10:1
98:2 er (*endo*)



3j, 88% yield[c]
endo:*exo* = 2.8:1
94:6 er (*endo*)
79:21 er (*exo*)

[a]Structure of the major stereoisomer is depicted. Conditions: ether (**1**, 0.40 mmol), *β*,*γ*-unsaturated ketoester (**2**, 0.10 mmol), [**L1**–Cu](SbF$_6$)$_2$ (5.0 mol %), Ph$_3$COAc (0.20 mmol), CH$_2$Cl$_2$ (0.6 mL), 40 °C, 24 h under N$_2$ atmosphere. [b]Yield of isolated and purified product. The dr values were determined by the ^{1}H NMR analysis of the unpurified reaction mixture. See the Supporting Information for the determination of the absolute and relative configurations. [c]The reaction mixtures were allowed to stir at different reaction temperatures for the production of **3c** and **3e**–**3g**-*d*$_3$ (60 °C), **3h** and **3h**-*d*$_6$ (22 °C), **3d** (4 °C), and **3i** (−20 °C). The syntheses of **3c** and **3e**–**3g**-*d*$_3$ used 10 mol % of [**L1**–Cu](SbF$_6$)$_2$. **3e** was run in the CHCl$_3$ as the solvent, and for the production of **3f**, 0.30 mmol of Ph$_3$COAc was used. Cyclic ethers (**1h**–**1j**) and Ph$_3$COAc were added in two batches (0.20 mmol **1h**–**1j**/batch and 0.10 mmol Ph$_3$COAc/batch). See the Supporting Information for details.

Supporting Information for details). These results indicate that Ph$_3$C$^+$-mediated hydride abstraction occurs selectively at the more electronically accessible OCH$_2$Bn group of **3g**-*d*$_3$ (as compared to cleavage within less electron-rich OCD$_3$ unit).

The unions of tetrahydrofuran **1h** and its isotopologue (**1h**-*d*$_8$) with **2a** were found to give **3h** (88% yield, *endo*:*exo* = 12:1) and **3h**-*d*$_6$ (80% yield, *endo*:*exo* = 11:1), respectively, with 95:5 er. To determine if the reaction of **1h** and **2a** proceeds more efficiently than the process involving **1h**-*d*$_8$, a competition kinetic isotope effect experiment was performed (Figure 2A). The obtained k_H/k_D value of 2.8 is consistent with the mechanistic scenario that the enol ether formation by sequential hydride abstraction and deprotonation is more facile with **1h**. 1-Oxaspiro[4.4]nonane **1i** was found to be a viable substrate, giving *endo*-**3i** (72% yield, 98:2 er). The reaction of tetrahydropyran **1j** and **2a** was less diastereoselective (**3j**, 88% yield, *endo*:*exo* = 2.8:1, up to 94:6 er) compared to the processes involving five-membered cyclic ethers (**3h**–**3i**). Oxidation of *rac*-2-phenyltetrahydrofuran (*rac*-**1k**) was found to occur regioselectively to provide the more substituted enol ether (Figure 2B); its cycloaddition with **2a** gave *rac*-**3k** in 93% yield (*endo*:*exo* = 4.8:1).

We investigated the reversibility of the hetero Diels–Alder reaction (Figure 2C,D). When a dihydro-2*H*-pyran derivative **3a** was reacted with (*S*)-2-(chloromethyl)tetrahydrofuran **1l** in the presence of [**L1**–Cu](SbF$_6$)$_2$ and Ph$_3$COAc, we observed the formation of **3l** in 20% yield (*endo*:*exo* ≥ 20:1). This result implies that an enol ether generated *in situ* by oxidation of **1l** reacts with a transient unsaturated *β*,*γ*-unsaturated ketoester resulting from a reversible reaction of **3a** under the reaction conditions (Figure 2C, see the Supporting Information for details). Then, we reacted the 2.1:1 mixture of *exo*-**3b** and *endo*-**3b** with 5.0 mol % [**L1**–Cu](SbF$_6$)$_2$ and allowed the solution in CD$_2$Cl$_2$ to stir at 22 °C for 36 h (Figure 2D). This resulted in the formation of *exo*-**3b** (93:7 er) as the major product (*endo*:*exo* = 1:12), further supporting the notion that the cycloaddition of **1a**-derived enol ether and **2b** is reversible. On the basis of the stereochemistry of the products (**3a**–**3g**) resulting from acyclic ethers (R^1 group is *cis* to OR^2), only *Z*-configured enol ethers appear to participate in the hetero Diels–Alder reactions. We performed a control experiment using a preformed *E*-enol ether ((*E*)-**4g**, Figure 2E) and **2a** to find that **3g** is formed in 90% yield (*endo*:*exo* = 1:4.7). In addition, 1.0 mol % of [**L1**–Cu](SbF$_6$)$_2$ was found to catalyze the isomerization of (*E*)-**4g** into (*Z*)-**4g** (in CD$_2$Cl$_2$ at 60 °C; see the Supporting Information for details). These results suggest that the acyclic ethers may be oxidized into a mixture of *E*- and *Z*-configured enol ethers that can then equilibrate under the reaction conditions.

The *endo*-selective Diels–Alder reactions between dienophiles generated *in situ* by oxidation of enantiopure ethers and a range of *β*,*γ*-unsaturated ketoesters were carried out in the presence of [(*S*,*S*)-**L1**–Cu](SbF$_6$)$_2$ (Table 3). Dihydrofurans possessing chloro (**1l**), bromo (**1m**), acetoxy (**1n**),

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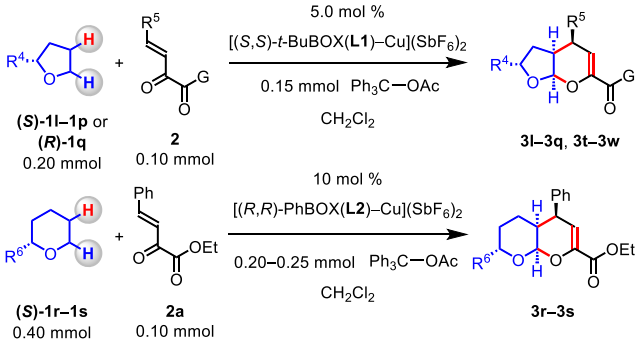
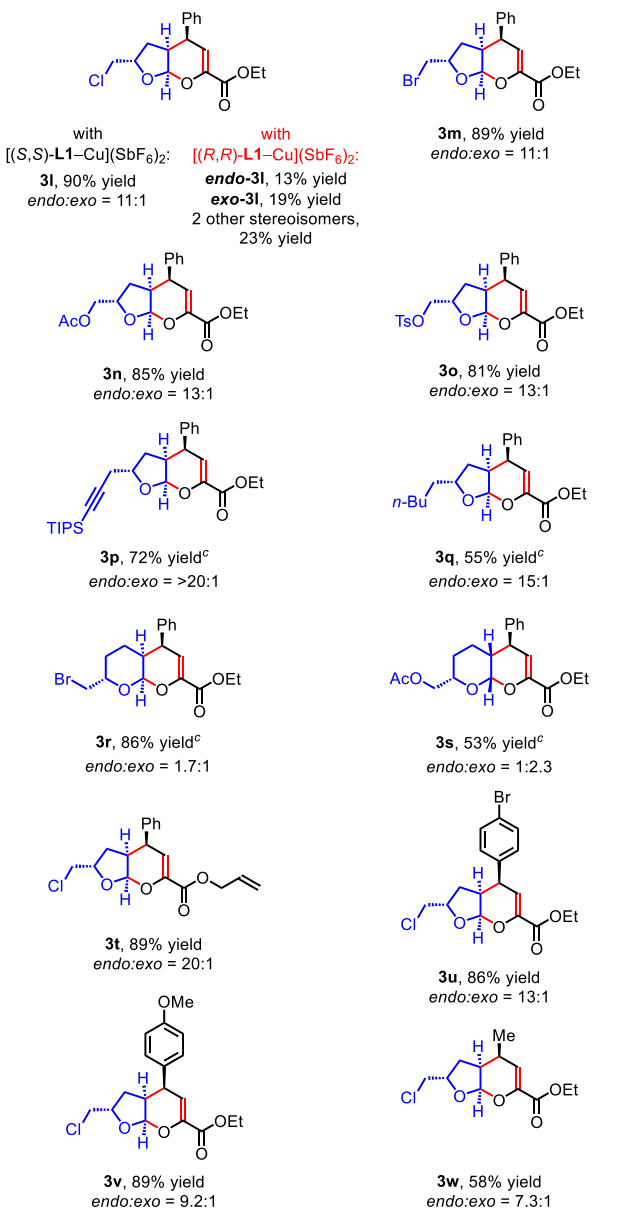
Table 3. Hetero Diels–Alder Reactions with Enantiopure Ethers[a,b]





[a]Structure of the major stereoisomer is depicted. Conditions: Reactions were performed under N_2 atmosphere; ether (**1**, 0.20 mmol), *β*,*γ*-unsaturated ketoester (**2**, 0.10 mmol), [**L1**–Cu]$(SbF_6)_2$ (5.0 mol %), Ph_3C–OAc (0.15 mmol), CH_2Cl_2 (0.6 mL), 60 °C, 24 h. [b]Yield of isolated and purified product. The dr values were determined by the ^1H NMR analysis of the unpurified reaction mixtures. See the Supporting Information for determination of the absolute and relative configurations. [c]The solutions were allowed to stir at 40 °C for the synthesis of **3p** and at 22 °C for **3q**. For preparation of **3p**, 10 mol % of [**L1**–Cu]$(SbF_6)_2$ was used and **1p** and Ph_3COAc were added in two batches (0.20 mmol **1o**/batch and 0.10 mmol Ph_3COAc/batch). To prepare **3r** and **3s**, 0.40 mmol of **1r** or **1s** and 10 mol % of [(*R*,*R*)-**L2**–Cu]$(SbF_6)_2$ were used; TrOAc was added batchwise. See the Supporting Information for details.

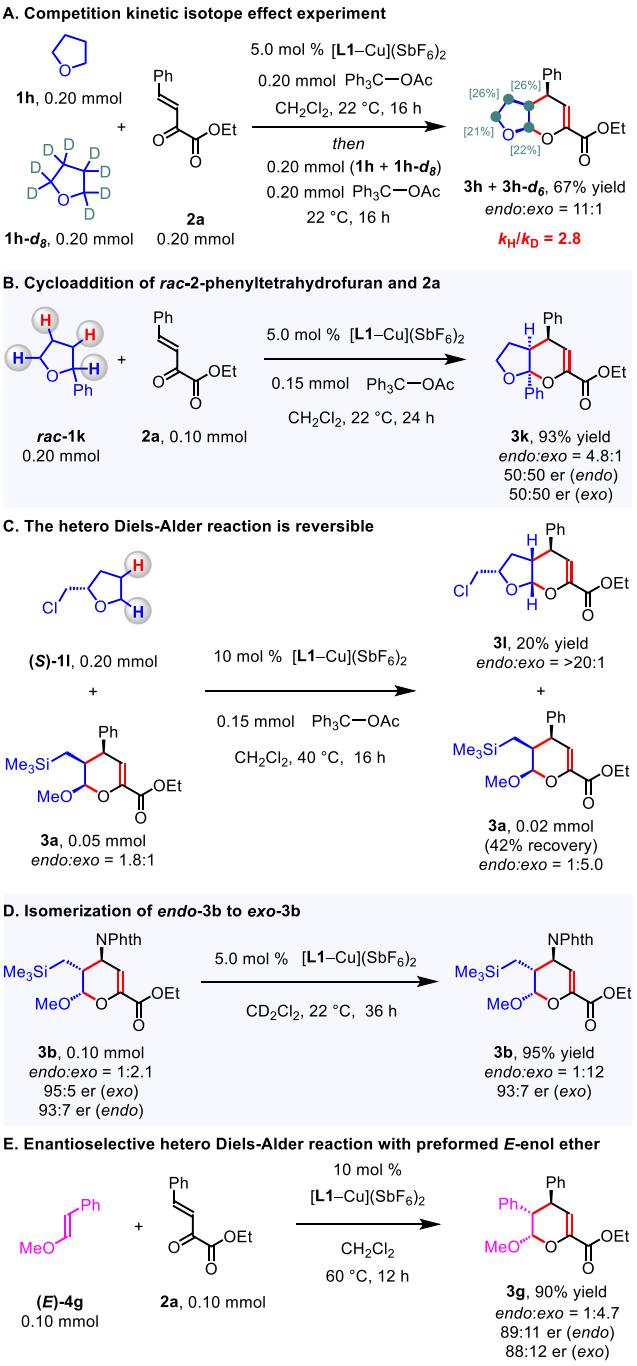


Figure 2. Studies aimed at elucidating the reaction mechanism.

tosyloxy (**1o**), alkynyl (**1p**), and alkyl (**1q**) moieties could be coupled with **2a** to furnish **3l**–**3q** in 55–90% yield (*endo*:*exo* ≥ 20:1–11:1). For the production of **3l** (90% yield, *endo*:*exo* = 11:1), the use of [(*S*,*S*)-**L1**–Cu]$(SbF_6)_2$ was found to be

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crucial; [(*R*,*R*)-**L1**−Cu](SbF$_6$)$_2$ was found to be a mismatched enantiomer of the catalyst as **3l** was obtained as a complex mixture of stereoisomers in 55% overall yield (see the Supporting Information for details). The cycloadditions of tetrahydropyran derivatives (**1r**, **1s**) with **2a** were found to occur less efficiently; **3r** (*endo*:*exo* = 1.7:1) and **3s** (*endo*:*exo* = 1:2.3) were obtained in 86% and 53% yield, respectively. However, a batchwise addition of Ph$_3$COAc and a longer reaction time were necessary (see the Supporting Information for details). *β*,*γ*-Unsaturated ketoesters possessing an allyl acetate moiety (**2t**), *p*-bromophenyl (**2u**), *p*-methoxyphenyl (**2v**), or methyl (**2w**) substituents could be merged with **1l**, affording **3t**−**3w** with *endo* to *exo* ratios of 20:1−7.3:1 (58−89% yield).

In summary, we have developed an enantio- and diastereoselective method for the transformations of vicinal C−H bonds within various acyclic and cyclic ethers to generate dihydro-2*H*-pyran derivatives. We found that by using a blend of [*t*-BuBOX(**L1**)−Cu](SbF$_6$)$_2$ and Ph$_3$COAc, it is possible to convert ethers into enol ethers and then promote their enantio- and diastereoselective reaction with *β*,*γ*-unsaturated ketoesters. The catalyst system is tolerant of a variety of Lewis acid-sensitive functional units and allows for rapid access to valuable chiral ether products containing stereogenic centers at the C1, C2, and C3 positions. The principles outlined above demonstrate that the proper combination of a chiral Lewis acid and an *in situ* generated hydride acceptor may be used for chemo- and enantioselective functionalization of otherwise stable ether-based molecules. This outcome provides a rational basis for the future development of methods for the stereoselective synthesis of biologically relevant ether-based molecules, as well as their late-stage functionalization. Studies aimed at further pursuing these objectives are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c01656.

Experimental procedures and spectral data for all new compounds (PDF)

Accession Codes

CCDC 2151548 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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