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# Enantioselective Organocopper-Catalyzed Hetero Diels-Alder Reaction Through in situ Oxidation of Ethers into Enol Ethers

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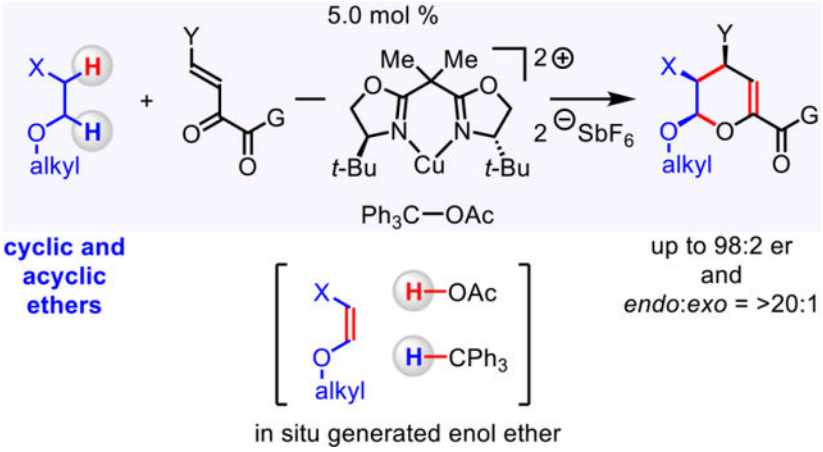
## Abstract

We disclose a catalytic method for the enantio- and diastereo-selective union of alkyl ethers and hetero dienes. 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 $\beta,\gamma$-unsaturated ketoesters, allowing for rapid access to an array of dihydropyran derivatives possessing three vicinal stereogenic centers.

## Graphical Abstract




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

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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.

**Supporting Information Available:** Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge *via* the Internet at http://pubs.acs.org.

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 would not only 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 hetero dienes **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 diastereo-selective [4+2] cycloaddition between enol ether **III** and a $\beta,\gamma$-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 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 which promotes in situ oxidation of acyclic and cyclic ethers into enol ethers, and their enantioselective cycloaddition with hetero dienes.

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.

Based on 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 using 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 6–7). The catalysts possessing $SbF_6$ counterions were substantially more reactive than those complexes with OTf or $ClO_4$ anions (entries 5 vs 8–9). 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 12–13).

An assortment of acyclic and cyclic ethers (**1a**–**1s**) could be merged with different $\beta,\gamma$-unsaturated ketoesters (**2a**, **2b**, **2t**–**2w**) to afford the corresponding hetero Diels-Alder products with high enantio- and/or diastereo-selectivity (**3a**–**3j** and **3l**–**3w**, Tables 2–3). 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 $\beta,\gamma$-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 $^1H$ 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 Supporting Information for details). These results indicate that $Ph_3C^+$-mediated hydride abstraction occurs selectively at the more electronically accessible $OCH_2Bn$ 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 5-membered cyclic ethers (**3h**–**3i**). Oxidation of *rac*-2-phenyl-tetrahydrofuran (***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 (Figures 2C–2D). 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 $Ph_3COAc$, 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 $\beta,\gamma$-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 $CD_2Cl_2$ to stir at 22 °C for 36 hours (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. Based on 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 $CD_2Cl_2$ 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 $\beta,\gamma$-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**), 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 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 $Ph_3COAc$ and a longer reaction time were necessary (see the Supporting Information for details). $\beta,\gamma$-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 diastereo-selective 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 $Ph_3COAc$, it is possible to convert ethers into enol ethers and then promote their enantio- and diastereo-selective reaction with $\beta,\gamma$-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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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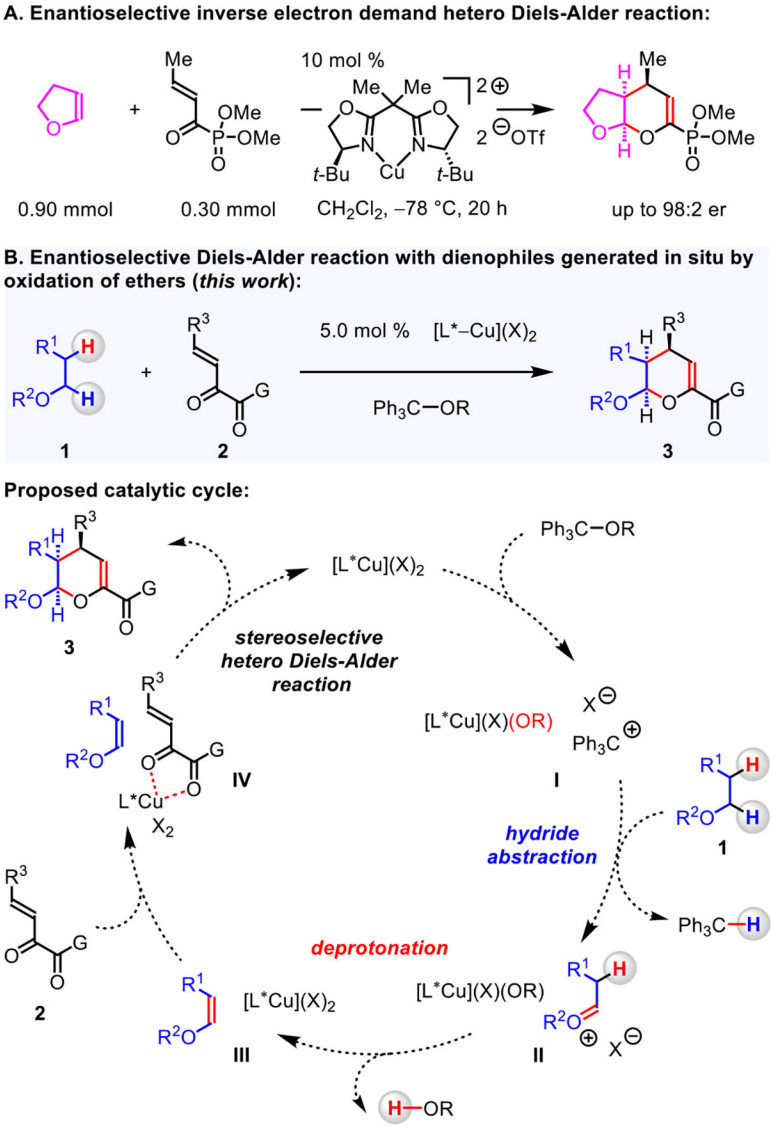



**Figure 1.**
Strategies for Enantioselective Synthesis of Ethers.

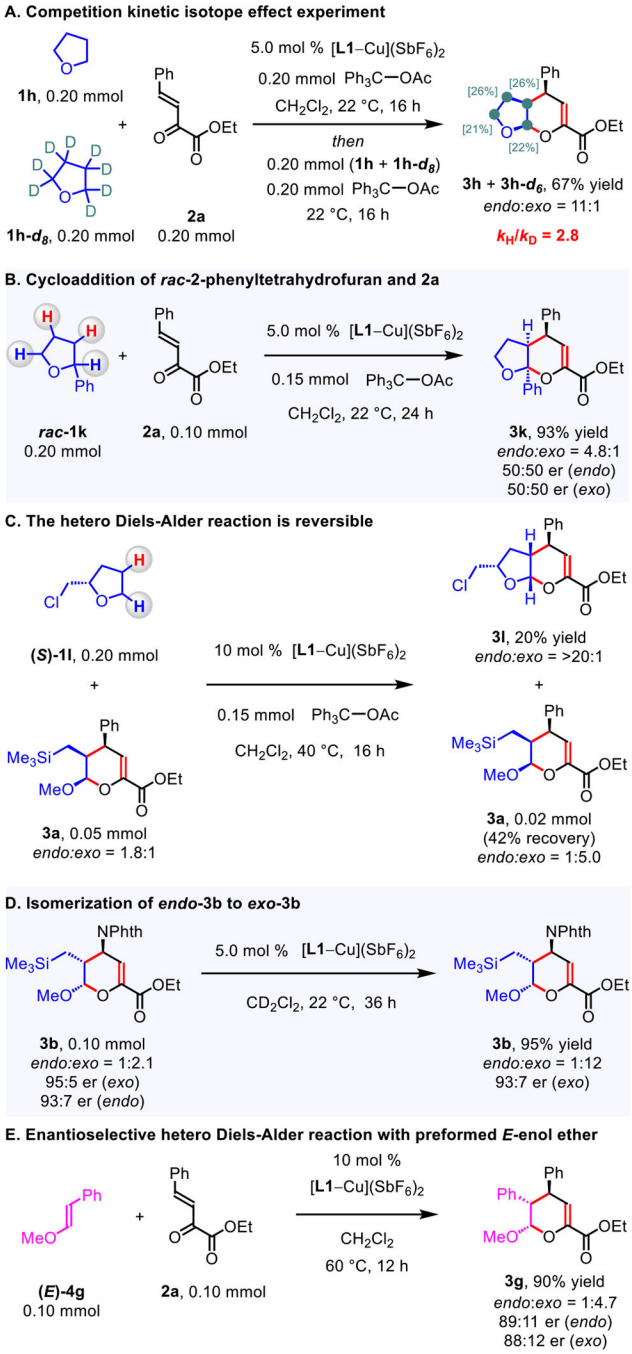
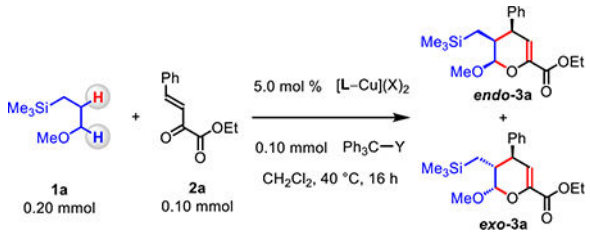


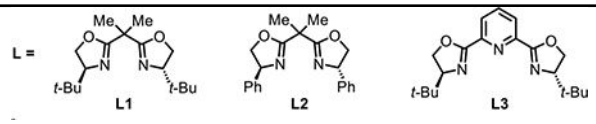

**Figure 2.**
Studies aimed at elucidating the reaction mechanism

**Table 1.**

Evaluation of Reaction Parameters [a,b]




| | | | *endo*-3a + *exo*-3a | | | |
|---|---|---|---|---|---|---|
| **entry** | **[L–Cu](X)$_2$** | **Ph$_3$C—Y** | **yield (%)** | ***endo:exo*** | **er *(endo)*** | **er *(exo)*** |
| 1 | [**L1**–Cu](SbF$_6$)$_2$ | Ph$_3$C$^{\oplus\ominus}$BF$_4$ | 75 | 1.4:1 | 50:50 | 51:49 |
| 2 | none | Ph$_3$C$^{\oplus\ominus}$BF$_4$ | 39 | 1.3:1 | – | – |
| 3 | [**L1**–Cu](SbF$_6$)$_2$ | Ph$_3$C–OH | <5 | ND | ND | ND |
| 4[c] | [**L1**–Cu](SbF$_6$)$_2$ | Ph$_3$C–OH | 60 | 2.7:1 | 90:10 | 87:13 |
| 5 | [**L1**–Cu](SbF$_6$)$_2$ | Ph$_3$C–OAc | 55 | 1.8:1 | 96:4 | 96:4 |
| 6 | [**L2**–Cu](SbF$_6$)$_2$ | Ph$_3$C–OAc | 40 | 7.0:1 | 40:60 | 76:24 |
| 7 | [**L3**–Cu](SbF$_6$)$_2$ | Ph$_3$C–OAc | 21 | 2.0:1 | 49:51 | 50:50 |
| 8 | [**L1**–Cu](OTf)$_2$ | Ph$_3$C–OAc | 0 | ND | ND | ND |
| 9 | [**L1**–Cu](Cl0$_4$)$_2$ | Ph$_3$C–OAc | 13 | 1.6:1 | 86:14 | 88:12 |
| 10[d,f] | [**L1**–Cu](SbF$_6$)$_2$ | Ph$_3$C–OAc | 87 | 1.5:1 | 96:4 | 96:4 |
| 11[e,f] | [**L1**–Cu](SbF$_6$)$_2$ | Ph$_3$C–OAc | >95 | 1.8:1 | 96:4 | 96:4 |
| 12 | none | Ph$_3$C-OAc | 0 | ND | – | – |
| 13 | [**L1**–Cu](SbF$_6$)$_2$ | none | 0 | ND | ND | ND |




[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$_3$C–Y (0.10 mmol), CH$_2$Cl$_2$ (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.

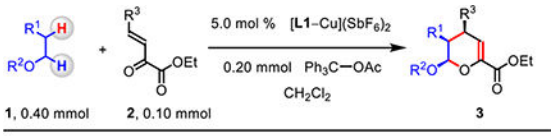
[d]**1a** (0.30 mmol) and Ph$_3$C–OAc (0.20 mmol) were used.

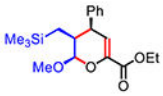
[e]**2a** (0.40 mmol) and Ph$_3$C–OAc (0.20 mmol) were used.

[f]The solution was allowed to stir for 24 h.

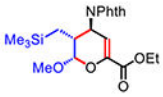
**Table 2.**

Enantioselective Hetero Diels-Alder Reactions [a,b]

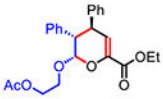


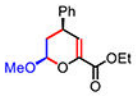
**3a**, 96% yield
*endo*:*exo* = 1.8:1
96:4 er (*endo*)
96:4 er (*exo*)



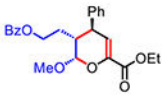
**3b**, 71% yield
*endo*:*exo* = 1:2.1
93:7 er (*endo*)
95:5 er (*exo*)



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

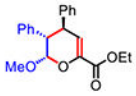


**3d**, 75% yield[c]
*endo*:*exo* = 8.5:1
95:5 er (*endo*)

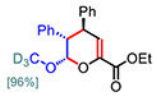


**3e**, 75% yield[c]
*endo*:*exo* = 1:1.2
96:4 er (*endo*)
83:17 er (*exo*)

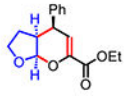
**3f**, 77% yield[c]
*endo*:*exo* = 1:1.4
92:8 er (*endo*)
85:15 er (*exo*)



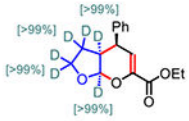
**3g**, 72% yield[c]
*endo*:*exo* = 1:4.0
95:5 er (*endo*)
95:5 er (*exo*)



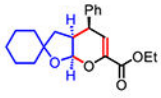
**3g-*d*$_3$**, 68% yield[c]
*endo*:*exo* = 1:4.0
97:3 er (*endo*)
97:3 er (*exo*)



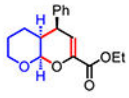
**3h**, 88% yield[c]
*endo*:*exo* = 12:1
95:5 er (*endo*)



**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*)

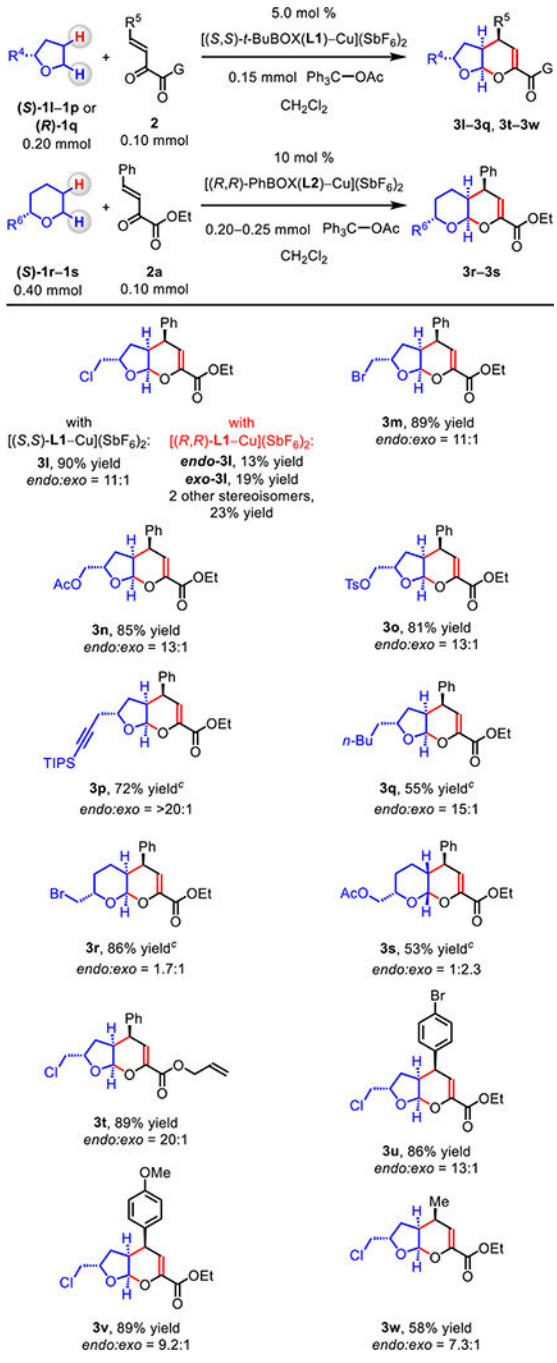
[a]Structure of the major stereoisomer is depicted. Conditions: ether (**1**, 0.40 mmol), $\beta,\gamma$-unsaturated ketoester (**2**, 0.10 mmol), [**L1**–Cu](SbF$_6$)$_2$ (5.0 mol %), Ph$_3$COAc (0.20 mmol), CH$_2$Cl$_2$ (0.6 mL), 40 °C, 24 h under N$_2$ atmosphere.

[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**-***d3*** (60 °C), **3h** and **3h**-***d6*** (22 °C), **3d** (4 °C), and **3i** (–20 °C). The syntheses of **3c** and **3e**–**3g**-***d3*** 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.

**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 $^1$H 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; **1p** and Ph$_3$COAc were added in 2 batches (0.20 mmol **1o**/batch and 0.10 mmol Ph$_3$COAc/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.