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Cu(I)- and Cu(II)-Catalyzed Cyclo- and Michael Addition Reactions of Unsaturated β-Ketoesters

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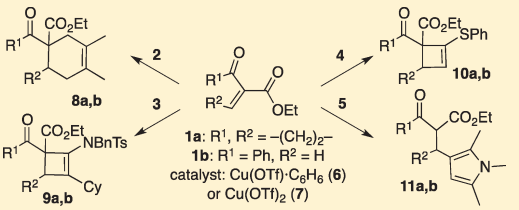
Supporting Information

ABSTRACT: The α-alkylidene β-ketoesters 2-carbethoxycyclopentenone (**1a**) and ethyl 2-benzoylacrylate (**1b**) react with 1,2-dimethylbutadiene (**2**) (Diels–Alder), *N*-benzyl-*N*-(cyclohexylethynyl)-4-methylbenzenesulfonamide (**3**) (Ficini reaction), ethynyl(phenyl)sulfane (**4**) ([2 + 2] cycloaddition), and 1,2,5-trimethyl-1*H*-pyrrole (**5**) (Michael addition) in the presence of copper(I) (**6**) or copper(II) triflate (**7**) (1–2 mol %) in dichloromethane. This convenient protocol converts **1a** and **1b** to the corresponding cycloaddition (**8**–**10**) or Michael addition (**11**) products in good yields after reaction times of 0.5–3 h without requiring purified solvents or inert gas atmosphere.

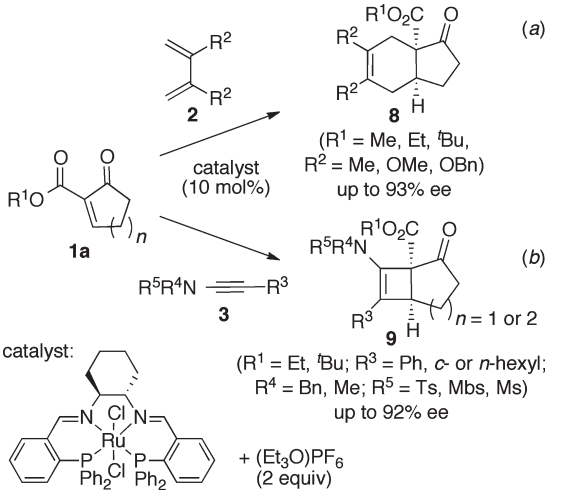


β-Ketoesters are versatile reagents in organic synthesis and find widespread application,[1] particularly in the formation of all-carbon quaternary centers.[2] In the transformations of their unsaturated, α-alkylidene analogues, Diels–Alder and cycloaddition reactions play a major role.[3] However, α-unsaturated β-ketoesters are challenging substrates because of their tendency for polymerization and keto–enol tautomerization.[4] Consequently, they react under harsh conditions and usually give low yields,[5] with the notable exception of alkoxycarbonylquinones, which are more reactive and easier to handle and have been applied in a number of highly efficient catalytic reactions.[6]

We have recently developed dicationic catalysts derived from the chiral complex [$RuCl_2$(PNNP)] for the functionalization of 2-ethoxycarbonyl-2-cyclopenten-1-one (**1a**) and related substrates (PNNP is *N*,*N*′-bis[*o*-(diphenylphosphino)benzylidene]-(1*S*,2*S*)-diaminocyclohexane). This system efficiently catalyzes the Diels–Alder reaction of **1a** with dienes such as 2,3-dimethylbuta-1,3-diene (**2**)[7] to give, among others, alkoxycarbonyltetrahydro-1-indanones **8** in excellent yield (Scheme 1a). High enantioselectivity was achieved with the *tert*-butyl ester analogue of **1a**. With the same catalyst and class of substrates, we also reported the Ficini [2 + 2] cycloaddition reaction[8] with ynamides[9] like *N*-benzyl-*N*-(cyclohexylethynyl)-4-methylbenzenesulfonamide (**3**) to give cyclobuteneamides **9** (Scheme 1b).[10]

The above results are a breakthrough in the application of alkylidene β-ketoesters in cycloaddition reactions, for which no simple and straightforward protocols were available. As an illustrative example, the screening of a number of Lewis acids in the reaction of 2-methoxycarbonyl-2-cyclohexen-1-one with various dienes gave the best results with $SnCl_4$ (0.5 equiv), which is toxic, inconvenient to handle, and requires anhydrous solvents, and the yields were only moderate.[11] In an alternative approach that compensates for the low reactivity of alkylidene β-ketoesters as dienophiles, 1-methylbuta-1,3-diene has been activated with a stoichiometric amount of a cobalt complex and refluxed in THF during 72 h in the presence of a large excess (4 equiv) of 2-methoxycarbonyl-2-cyclohexen-1-one, followed by the cleavage of the resulting cobalt complex.[12] As for the Ficini reaction of ynamides onto unsaturated β-ketoesters, it is unprecedented with the exception of our report, the closest analogue being Hsung's recently developed reaction of cyclohexenone with ynamides, which was the first example of its class.[13] However, the catalyst system based on a combination of copper(II) chloride (20 mol %) and silver(I) hexafluoroantimonate (60 mol %) uses high catalyst loading and gives moderate yields.

Scheme 1. Asymmetric Diels–Alder and Ficini Reaction of Alkylidene β-Ketoesters



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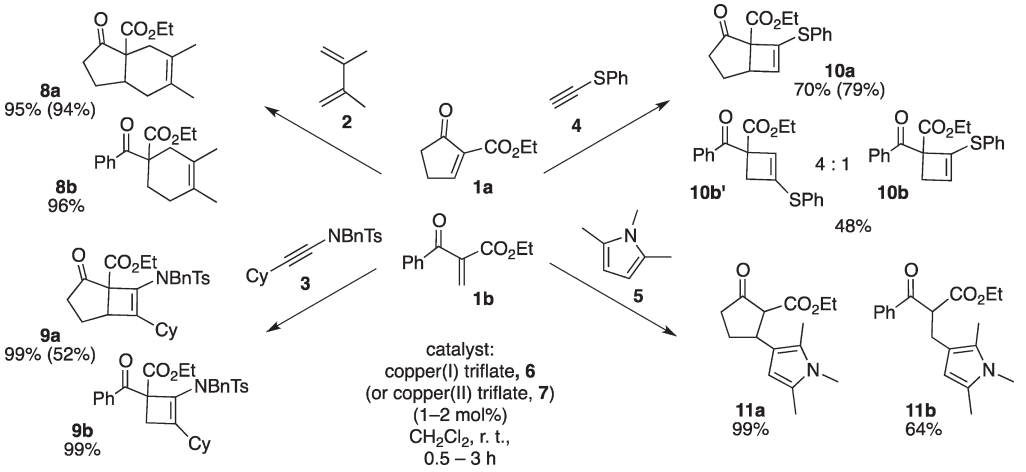
Scheme 2. Synthesis of 8−11 Catalyzed by 6 (Yields with 7 in Parentheses)



In view of the lack of simple and efficient nonenantioselective synthetic methods, we were confronted with the necessity of developing a new method to prepare racemic reference substances such as 1-ethoxycarbonyl-3,4-dimethyl-9-oxobicyclo[4.3.0]oct-3-ene (**8a**) and ethyl-8-[*N*-benzyl-4-methylphenylsulfonamido]-7-cyclohexyl-2-oxobicyclo[4.2.0]oct-7-ene-1-carboxylate (**9a**) for the determination of the enantioselectivity of the [$RuCl_2$(PNNP)] system during our previous studies.[7,10] Thus, we tested the copper(I) triflate benzene complex [$Cu_2(\mu^2\text{-}O_3SCF_3)_2(\mu^2\text{-}\eta^2\text{-}C_6H_6)]_n$ (**6**) as a mild Lewis acid, as copper-based catalysts are commonly used Lewis-acidic catalysts and have found application in related reactions with α-thioacrylates[14] and alkylidene malonates.[15] In fact, complex **6** turned out to catalyze the Diels−Alder and Ficini reactions with a number of cyclic alkylidene β-ketoesters. At this stage, the copper-catalyzed reaction was not optimized, and its products were not isolated but rather used as racemic references for chiral HPLC analysis.[7,10] The present paper describes a protocol developed from these preliminary experiments for which we chose **1a** and **1b** as representative examples of cyclic and acyclic α-alkylidene β-ketoesters (Scheme 2).[16]

We also extended the study to other reactions of alkylidene β-ketoesters. In particular, ethynyl(phenyl)sulfane (**4**), which is known to react with unsaturated β-ketoesters in the presence of a high catalytic loading of copper(II) triflate (**7**) (30 mol %),[17] was chosen as alternative [2 + 2] cycloaddition reagent. Finally, we studied the Michael addition of 1,2,5-trimethyl-1*H*-pyrrole (**5**) (Scheme 2), as there is some precedent with furan derivatives.[18] For the sake of comparison, selected reactions were run with copper(II) triflate (**7**) as catalyst. Both **6** and **7**, as well as the saturated precursors of the ethyl esters **1a** and **1b**, are commercially available.

In the standard procedure, β-ketoesters **1a** or **1b**, reagents **2**−**5** (1.1 equiv), and the Cu(I) complex **6** (1−2 mol %) were stirred in CH_2Cl_2 until TLC analysis showed that the β-ketoester had been quantitatively converted. Total reaction times were between 30 min and 3 h (Table 1). Copper(I) triflate **6** is only moderately soluble in CH_2Cl_2 and does not dissolve completely under these reaction conditions, which is probably due to its polymeric structure.[19] In the case of diene **2**, 5 equiv was required to drive the reaction to completion because of the low reactivity of 2,3-dimethylbuta-1,3-diene. The above protocol gives the desired products in 48−99% yield without the need for anhydrous solvents or protective gas atmosphere.

Table 1. Reactions of β-Ketoesters 1a and 1b Catalyzed by 6 and 7

entry	β-ketoester/ reagent	catalyst/ loading	time (h)	product	isol yield (%)
1	**1a**/**2**	**6** (2 mol %)	3	**8a**	94
2	**1a**/**2**	**7** (1 mol %)	0.5	**8a**	95
3	**1a**/**3**	**6** (1 mol %)	0.5	**9a**	99
4	**1a**/**3**	**7** (1 mol %)	0.5	**9a**	52
5	**1a**/**4**	**6** (1 mol %)	0.5	**10a**	70
6	**1a**/**4**	**7** (1 mol %)	0.5	**10a**	79
7	**1a**/**5**	**6** (1 mol %)	0.5	**11a**	99
8	**1b**/**2**	**6** (2 mol %)	3	**8b**	96
9	**1b**/**3**	**6** (2 mol %)	3	**9b**	99
10	**1b**/**4**	**6** (2 mol %)	3	**10b′**/**10b**	48[a]
11	**1b**/**5**	**6** (1 mol %)	0.5	**11b**	64

[a] Total yield of **10b′** and **10b** (4:1 ratio).

Cyclic and acyclic β-ketoesters are converted under mild conditions in short reaction times and, apart from flash column chromatography, no workup of the reaction solution is required. The copper(I) catalyst **6** is much more active than the [$RuCl_2$(PNNP)]-based system,[7,10] and the catalyst loading can be reduced to 1 or 2 mol % while maintaining full conversion after 0.5−3 h. This is remarkable in particular for the cycloaddition reactions, which involve the formation of a sterically crowded quaternary all-carbon center.

In the Ficini reaction, both the cyclic (**1a**) and acyclic (**1b**) unsaturated β-ketoesters give the regioisomer expected on the basis of electronic preference (**9a** and **9b**, respectively) as the only product. In contrast, the [2 + 2] cycloaddition of ethynyl(phenyl)sulfane (**4**) onto **1b** gives a 4:1 mixture of the regioisomers **10b** and **10b′**, in which the sterically favored isomer **10b′** is the major component. This is unusual, since sulfanes and ynamides are nucleophilic at the β-position to the heteroatom, which normally efficiently directs the regioselectivity of these formal [2 + 2] cycloadditions notwithstanding the steric situation. The inversed regioselectivity is probably caused by the lower electronic induction of the sulfane as compared to ynamide, in combination with the substantial steric difference between the doubly substituted α- and the unsubstituted β-position of **1b**.

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Table 2. Synthesis of 8a with Different Catalysts[a]

entry	catalyst	isol yield (%)	ee (%)
1	$SnCl_4$ (50 mol %)	55	
2	**6** (2 mol %), in air	95	
3	$[Cu_2(\mu^2\text{-OTf})_2(\mu^2{-}\eta^2\text{-}CH_3C_6H_5)]_n$ (2 mol %), under argon	88	
4	Cu(II)$(OTf)_2$ (**7**) (1 mol %)	94	
5	**6** + Ph-box (20 mol %)	47	23
6	**7** + Ph-box (20 mol %)	66	19

[a] See the Experimental Section for reaction conditions.

This difference is smaller in **1a**, in which the β-position is part of the 5-membered ring, and hence, only the electronically favored regioisomer **10a** is formed. In comparison to the reported protocol,[17] the Cu(I)-catalyzed reaction of **1a** with **4** is run at room temperature (instead of 0 °C), and a much smaller catalyst loading is applied (1% instead of 30 mol %).

For comparison, we also tested copper(II) triflate (**7**) in selected instances, such as the Diels–Alder reaction of **1a**, which gives **8a** in excellent yield (Table 1, entry 2). Monitoring of the reaction course by TLC analysis showed that, overall, the reactions with $Cu(OTf)_2$ (**7**) are complete after a shorter reaction time than with the less Lewis-acidic Cu(I) complex **6** (even with a catalytic loading of 1 mol %). Also, **7** gives a slightly higher yield with the less reactive ethynyl(phenyl)sulfane **4** than Cu(I) (70 and 79%, respectively, entries 5 and 6). On the other hand, the mild copper(I) catalyst **6** gives much better yields in combination with acid-sensitive substrates, such as ynamide **3**, whose reaction with **1a** gives **9a** in 99% yield with **6** but only 52% yield with **7**.

A comparison of the copper(I) catalyst **6** with the best literature protocol[11] for the Diels–Alder reaction of unsaturated β-ketoesters with **2** shows that the much stronger Lewis acid $SnCl_4$ (in anhydrous diethylether) gives a significantly lower yield of **8a** (55 vs 95% with **6**), which is probably due to partial polymerization of **1a** under these conditions (Table 2, entries 1 and 2).

To test whether small amounts of a copper(II) species, formed by oxidation or dismutation of **6**, may account for catalytic activity, we repeated the reaction between **1a** and diene **2** with $[Cu_2(\mu^2\text{-}O_3SCF_3)_2(\mu^2\text{-}\eta^2\text{-}CH_3C_6H_5)]_n$, the toluene analogue of **6**. The latter complex is commercially available in 99.9% purity, whereas the batch of **6** used in this study was of technical grade (90%). The reaction was carried out under argon in the dark, and the solution remained colorless throughout the reaction, which indicates that no sizable amounts of Cu(II) are formed. As the yield obtained under these conditions (88%) is similar to that observed with **6** (95%) (Table 2, entries 2 and 3), we conclude that Cu(I) is competent for the catalytic reaction.

Finally, for the sake of comparison with the Ru/PNNP catalyst,[7] we tested (*S*,*S*)-2,2′-isopropylidenebis(4-phenyl-2-oxazoline) (Ph-Box) as chiral ligand in combination with Cu(I) and Cu(II) in the Diels–Alder reaction of **1a** with diene **2**. Copper(I) or copper(II) triflate (20 mol %), ligand Ph-box (1.1 equiv vs metal), and **1a** were dissolved in dichloromethane under argon, and **2** (1.5 equiv) was added thereto. Copper(II) gives full conversion after 1 h at room temperature, whereas the reaction with the copper(I) system **6** reaches completion upon stirring overnight (Table 2, entries 6 and 5). A reasonable explanation is that the ligand further reduces the already modest Lewis acidity of copper(I) and thus deactivates the system considerably. Some asymmetric induction was observed, but the enantioselectivity was low (19–23% ee) and the yields were only moderate (47–66%). Thus, the $[RuCl_2(PNNP)]$-based catalyst[7] remains unchallenged in terms of enantioselective catalysis, although the results with copper may possibly be improved by investigating a larger array of ligands.

In conclusion, we have described a convenient, inexpensive, and fast protocol for Lewis acid-catalyzed reactions of representative examples of alkylidene β-ketoesters. Good yields are obtained in a variety of reactions using commercially available copper(I) or copper(II) triflate, which represents a major advantage to previously reported literature procedures. As for the scope of the reaction, we notice that a number of products with different dienes[7] and ynamides,[10] as well as with a six-membered alylidene β-ketoester,[16] have been prepared in preliminary experiments with the nonoptimized protocol as mentioned above (Scheme 1). Therefore, we are confident that the method may find wide application.

EXPERIMENTAL SECTION

General Procedures. Reactions were generally performed in air with synthesis grade solvents. Reactions involving the phenyl-box ligand were carried out under an argon atmosphere using Schlenk techniques in dry CH_2Cl_2 (distilled over CaH_2). 2-Carbethoxycyclopentenone (**1a**) was obtained from its saturated analogue using a selenide oxidation–elimination reaction.[20] Ethyl 2-benzoylacrylate (**1b**) was prepared by a slightly modified literature procedure.[21] Ethyl 3-oxo-3-phenylpropanoate and paraformaldehyde (3 equiv) were heated at reflux under a protective gas atmosphere for 2 h and then for an additional 2 h after addition of 2 equiv of paraformaldehyde. *N*-Benzyl-*N*-(cyclohexylethynyl)-4-methylbenzenesulfonamide (**3**)[10] and ethynyl(phenyl)sulfane (**4**)[22] were prepared as reported. All other reagents, including complex **6** (90%, technical grade), $Cu(OTf)_2$ (**7**) (98%), $[Cu_2(\mu^2\text{-}O_3SCF_3)_2(\mu^2\text{-}\eta^2\text{-}CH_3C_6H_5)]_n$ (99.9%), and Ph-box (≥96%), are commercially available and were used as received. ^1H and ^{13}C positive chemical shifts δ (in ppm) are downfield from tetramethylsilane and are referenced to the residual solvent signal. The enantiomeric excess was determined by GC analysis on a β-DEX column (30 m × 0.25 mm, film 0.25 μm).

General Procedure for Catalytic Reactions. A CH_2Cl_2 solution (1.5 mL) of the unsaturated β-ketoester **1a** or **1b** (0.15 mmol, 1 equiv), the appropriate reagent **2**–**5** (1.1 equiv, 5 equiv for 2,3-dimethylbutadiene **2**), and copper(I) triflate benzene complex (**6**) or copper(II) triflate (**7**) (0.015 or 0.03 mmol, 0.01 or 0.02 equiv) was stirred at room temperature for 0.5–3 h, until TLC analysis showed that the unsaturated β-ketoester was fully converted. The solvent was removed under reduced pressure, and the oily residue was subjected to flash column chromatography on silica.

1-Ethoxycarbonyl-3,4-dimethyl-9-oxobicyclo[4.3.0]oct-3-ene (8a). The reaction of **1a** and 2,3-dimethylbutadiene (**2**) with copper(I) triflate benzene complex (**6**) (0.02 equiv) gave **8a** as a colorless oil after 3 h. Yield (isolated): 33.7 mg, 0.143 mmol, 95%. This material was identical with the known compound based on ^1H NMR spectra data.[7]

Ethyl 8-[*N*-Benzyl-4-methylphenylsulfonamido]-7-cyclohexyl-2-oxobicyclo[4.2.0]oct-7-ene-1-carboxylate (9a). The reaction of **1a** and *N*-benzyl-*N*-(cyclohexylethynyl)-4-methylbenzenesulfonamide (**3**) with catalyst **6** (0.01 equiv) gave **9a** as a colorless oil after 30 min. Yield (isolated): 78.0 mg, 0.15 mmol, >99%. This material was identical with the known compound based on ^1H NMR spectra data.[10]

Ethyl 2-Oxo-7-(phenylthio)bicyclo[3.2.0]hept-6-ene-1-carboxylate (10a). The reaction of **1a** and ethynyl(phenyl)sulfane (**4**) in the presence of **6** (0.01 equiv) gave **10a** as a colorless oil after 30 min. Yield (isolated): 32.0 mg, 0.111 mmol, 74%. ^1H NMR (400 MHz, $CDCl_3$): δ 7.64–7.47 (m, 2H), 7.45–7.30 (m, 3H), 5.88 (s, 1H), 4.23 (q, J = 7.1 Hz,

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2H), 3.68 (d, J = 6.9 Hz, 1H), 3.03 (ddd, J = 18.4, 11.9, 9.2 Hz, 1H), 2.40 (dd, J = 18.3, 8.5 Hz, 1H), 2.26−2.06 (m, 1H), 1.90 (dd, J = 13.4, 9.1 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 208.9, 167.7, 141.0, 134.1, 133.2, 130.3, 129.8, 129.1, 66.7, 61.8, 48.7, 35.3, 22.8, 14.6. IR (liquid film, cm^{-1}): 1719.7 (s, carbonyl C−O), 1736.7 (s, carbonyl C−O). HRMS (ESI): calcd for $C_{16}H_{17}O_3S$ m/z 289.0893, found m/z 289.0889.

Ethyl 2-Oxo-5-(1,2,5-trimethyl-1*H*-pyrrol-3-yl)cyclopentanecarboxylate (11a). The reaction of **1a** and 1,2,5-trimethyl-1*H*-pyrrole (**5**) in the presence of **6** (0.01 equiv) gave **11a** as a slightly red oil after 30 min. Yield (isolated): 39.0 mg, 0.148 mmol, 99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.74 (s, 1H), 4.30−4.07 (m, 2H), 3.71 (td, J = 11.6, 6.4 Hz, 1H), 3.38 (s, 3H), 3.21 (d, J = 11.5 Hz, 1H), 2.64−2.36 (m, 2H), 2.35−2.25 (m, 1H), 2.21 (s, 3H), 2.19 (s, 3H), 2.02−1.81 (m, 1H), 1.28 (t, J = 7.1 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 212.5, 169.6, 128.0, 124.9, 118.5, 102.6, 63.7, 61.6, 39.4, 38.8, 30.6, 29.9, 14.6, 12.9, 10.5. IR (liquid film, cm^{-1}): 1720.5 (s, carbonyl C−O), 1750.1 (s, carbonyl C−O). HRMS (ESI): calcd for $C_{15}H_{22}NO_3$ m/z 264.1594, found m/z 264.1588.

Ethyl 1-Benzoyl-3,4-dimethylcyclohex-3-enecarboxylate (8b). The reaction of **1b** and 2,3-dimethylbutadiene (**2**) with **6** (0.02 equiv) as catalyst gave **8b** as a colorless oil after 3 h. Yield (isolated): 41.4 mg, 0.145 mmol, 96%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 7.9 Hz, 2H), 7.53 (t, J = 7.2 Hz, 1H), 7.42 (t, J = 7.6 Hz, 2H), 4.15 (q, J = 7.1 Hz, 2H), 2.53 (s, 2H), 2.38−2.18 (m, 2H), 2.00−1.79 (m, 2H), 1.66 (s, 3H), 1.61 (s, 3H), 1.11 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.5, 174.0, 136.3, 132.9, 128.8, 124.9, 123.2, 61.7, 57.8, 38.0, 29.4, 28.7, 19.2, 14.3, 14.3. IR (liquid film, cm^{-1}): 1681.2 (s, carbonyl C−O), 1731.4 (s, carbonyl C−O). HRMS (ESI): calcd for $C_{18}H_{23}O_3$ m/z 287.1642, found m/z 287.1634.

Ethyl 1 -Benzoyl-2-(*N*-benzyl-4-methylphenylsulfonamido)-3-cyclohexylcyclobut-2-enecarboxylate (9b). The reaction of **1b** and *N*-benzyl-*N*-(cyclohexylethynyl)-4-methylbenzenesulfonamide (**3**) with **6** (0.02 equiv) as catalyst gave **9b** as a colorless oil after 3 h. Yield (isolated): 85.0 mg, 0.149 mmol, 99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 7.6 Hz, 2H), 7.77 (d, J = 8.1 Hz, 2H), 7.54 (t, J = 7.3 Hz, 1H), 7.48−7.37 (m, 4H), 7.31−7.21 (m, 5H), 4.98 (d, J = 14.9 Hz, 1H), 4.81 (d, J = 14.9 Hz, 1H), 4.17−4.05 (m, 1H), 4.04−3.91 (m, 1H), 3.02 (d, J = 12.7 Hz, 1H), 2.43 (s, 3H), 2.48−2.36 (m, 1H), 1.63−1.32 (m, 5H), 0.99 (t, J = 7.1 Hz, 3H), 1.03−0.73 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 195.2, 170.5, 158.3, 143.7, 138.2, 137.9, 136.0, 133.5, 129.8, 128.9, 128.8, 128.7, 128.5, 128.4, 128.3, 127.9, 127.1, 67.7, 62.1, 52.8, 52.8, 37.2, 32.7, 30.1, 29.9, 26.1, 25.9, 21.9, 21.9, 14.0. IR (liquid film, cm^{-1}): 1680.6 (s, carbonyl C−O), 1734.0 (s, carbonyl C−O). HRMS (ESI): calcd for $C_{34}H_{38}NO_5S$ m/z 572.2465, found m/z 572.2472.

Ethyl 1-Benzoyl-3-(phenylthio)cyclobut-2-enecarboxylate (10b′) and Ethyl 1-Benzoyl-2-(phenylthio)cyclobut-2-enecarboxylate (10b). The reaction of **1b** and ethynyl(phenyl)sulfane (**4**) in the presence of **6** (0.02 equiv) as catalyst gave a mixture of the two regioisomers **10b′**:**10b** (4:1) as a slightly yellow oil after 3 h. Yield (isolated): 24.4 mg, 0.072 mmol, 48%. ^{1}H NMR (700 MHz, $CDCl_3$): δ 8.10−8.05 (m, 2H, **10b**), 7.93−7.87 (m, 2H. **10b′**), 7.65−7.61 (m, 1H, **10b**), 7.60−7.55 (m, 3H, **10b′**), 7.54−7.50 (m, 2H, **10b**), 7.49−7.45 (m, 2H, **10b′**), 7.38−7.29 (m, 7H, 3H from **10b′** and 4H from **10b**), 7.23−7.19 (m, 1H, **10b**), 6.03 (t, J = 1.0 Hz, 1H, **10b′**), 4.68 (t, J = 7.4 Hz, 1H, **10b**), 4.23−4.17 (m, 2H, **10b**), 4.16−4.07 (m, 2H, **10b′**), 3.41 (dd, J = 12.8, 1.1 Hz, 1H, **10b′**), 3.23 (dd, J = 17.2, 7.6 Hz, 1H, **10b**), 3.15 (dd, J = 17.2, 7.2 Hz, 1H, **10b**), 2.95 (dd, J = 12.8, 1.1 Hz, 1H, **10b′**), 1.20 (t, J = 7.1 Hz, 3H, **10b**), 1.08 (t, J = 7.1 Hz, 3H, **10b′**). ^{13}C NMR (126 MHz, CD_2Cl_2): δ 193.9, 193.7, 170.0, 168.7, 140.1, 136.3, 135.5, 134.2, 133.7, 133.1, 133.1, 131.8, 129.6, 129.5, 129.3, 129.2, 129.1, 128.9, 128.5, 126.7, 126.4, 96.1, 68.2, 66.7, 62.3, 53.8, 37.2, 30.1, 20.7, 14.4, 14.3. IR (liquid film, cm^{-1}): 1680.8 (s, carbonyl C−O), 1731.7 (s, carbonyl C−O). HRMS (ESI): Calcd. for $C_{20}H_{19}O_3S$ m/z 339.1049, found m/z 339.1050.

Ethyl 3-Oxo-3-phenyl-2-((1,2,5-trimethyl-1*H*-pyrrol-3-yl)-methyl)propanoate (11b). The reaction of **1b** and 1,2,5-trimethyl-1*H*-pyrrole (**5**) with **6** (0.01 equiv) as catalyst gave **11b** as a slightly yellow oil after 30 min. Yield (isolated): 30.0 mg, 0.096 mmol, 64%. ^{1}H NMR (700 MHz, CD_2Cl_2): δ 8.07−7.92 (m, 2H), 7.63−7.54 (m, 1H), 7.48 (t, J = 7.8 Hz, 2H), 5.71 (s, 1H), 4.54 (t, J = 7.1 Hz, 1H), 4.28−4.04 (m, 2H), 3.32 (s, 3H), 3.15 (dd, J = 14.6, 7.6 Hz, 1H), 3.10 (dd, J = 14.6, 6.7 Hz, 1H), 2.16 (s, 3H), 2.13 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 195.5, 169.9, 136.5, 133.2, 128.7, 128.5, 127.0, 124.6, 114.4, 105.4, 61.2, 56.4, 30.1, 25.8, 14.0, 12.3, 10.0. IR (liquid film, cm^{-1}): 1682.2 (s, carbonyl C−O), 1731.8 (s, carbonyl C−O). HRMS (ESI): calcd for $C_{19}H_{24}NO_3$ m/z 314.1751, found m/z 314.1746.

Cu(I) and Cu(II) Ph-Box Catalysts. The reactions were performed in close analogy to a procedure published by Aggarwal.[14] The catalyst was prepared by stirring copper(I) triflate benzene complex (**6**) or copper(II) triflate (**7**) (0.03 mmol, 0.2 equiv) and Ph-Box (11.5 mg, 0.033 mmol, 0.22 equiv, Ph-Box is (4*S*,4′*S*)-2,2′-(propane-2,2-diyl)bis(4-phenyl-4,5-dihydrooxazole)) in freshly distilled CH_2Cl_2 (0.5 mL) for 3 h. After the solution was cooled to −78 °C, substrate **1a** (23.1 mg, 0.15 mmol, 1 equiv) in CH_2Cl_2 (1 mL) was added thereto. After 5 min, 2,3-dimethylbutadiene (**2**) (25.5 μL, 0.225 mmol, 1.5 equiv) was slowly added to the reaction solution, and stirring was continued for 2 h at −78 °C, after which neither catalyst gave detectable conversion (by TLC analysis). Cu(II) triflate (**7**) gave about 20% conversion after 1 h at 0 °C, and the conversion was quantitative after 1 h at room temperature. With Cu(I) triflate (**6**), no conversion was observed after 1 h at 0 °C, and the reaction required 24 h at room temperature to achieve completion. In both reactions, the solvent was removed under reduced pressure and the oily residue was subjected to flash column chromatography on silica. Compound **8a** was obtained in 47% yield with **6** and in 65% yield with copper(II) triflate (**7**). Chiral GC: β-DEX column, 120 °C isotherm, retention times t_R (major) = 164.1 min, t_R (minor) = 167.3 min; 19% ee for copper(I) triflate (**6**) and 23% ee for copper(II) triflate (**7**).

$SnCl_4$-Catalyzed Diels−Alder Reactions. Following the procedure published by Browne,[11] the reaction of **1a** (23.1 mg, 0.15 mmol, 1 equiv) and 2,3-dimethylbutadiene (**2**) (85 μL, 0.750 mmol, 5 equiv) with $SnCl_4$ (9 μL, 0.075 mmol, 0.5 equiv) gave ethoxycarbonyl-3,4-dimethyl-9-oxo-bicyclo[4.3.0]oct-3-ene (**8a**) as a colorless oil. Yield (isolated): 19.4 mg, 0.082 mmol, 55%.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra for all new compounds and ^{1}H NMR spectra of **8a** and **9a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Benetti, S.; Romagnoli, R.; De Risi, C.; Spalluto, G.; Zanirato, V. *Chem. Rev.* **1995**, *95*, 1065.
(2) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369.
(3) Kobayashi, S.; Jorgensen, K. A. *Cycloaddition Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2001.
(4) Bernardi, A.; Colombo, G.; Scolastico, C. *Tetrahedron Lett.* **1996**, *37*, 8921.
(5) Marx, J. N.; Cox, J. H.; Norman, L. R. *J. Org. Chem.* **1972**, *37*, 4489.

(6) Selected papers: (a) Evans, D. A.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10162. (b) Mikami, K.; Motoyama, Y.; Terada, M. *J. Chem. Am. Soc.* **1994**, *116*, 2812.
(7) (a) Schotes, C.; Mezzetti, A. *J. Am. Chem. Soc.* **2010**, *132*, 3652. (b) Schotes, C.; Mezzetti, A. *Chimia* **2011**, *65*, 231.
(8) Ficini, J. *Tetrahedron* **1976**, *32*, 1449.
(9) Recent review articles on ynamides: (a) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840. (b) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064.
(10) Schotes, C.; Mezzetti, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 3072.
(11) Liu, H.-J.; Ngooi, T. K.; Browne, E. N. C. *Can. J. Chem.* **1988**, *66*, 3143.
(12) Richardson, B. M.; Welker, M. E. *J. Org. Chem.* **1997**, *62*, 1299.
(13) Li, H.; Hsung, R. P.; DeKorver, K. A.; Wei, Y. *Org. Lett.* **2010**, *12*, 3780.
(14) Aggarwal, V. K.; Jones, D. E.; Martin-Castro, A. M. *Eur. J. Org. Chem.* **2000**, 2939.
(15) (a) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994. (b) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134.
(16) In addition to **1a** and **1b**, we have previously shown that the six-membered substrate 2-ethoxycarbonyl-2-cyclohexen-1-one undergoes Ficini reaction with ynamide **3** (nonoptimized protocol with 10 mol % of catalyst; see ref 10).
(17) Ito, H.; Kobayashi, T.; Hasegawa, M.; Kazuo, I. *Tetrahedron Lett.* **2003**, *44*, 1259.
(18) Liu, H.-J.; Ulibarri, G.; Browne, E. N. C. *Can. J. Chem.* **1992**, *70*, 1545.
(19) Hubig, S. S.; Lindeman, S. V.; Kochi, J. K. *Coord. Chem. Rev.* **2000**, *200 − 202*, 831 and reference 33 therein..
(20) Baker, R.; Selwood, D. L.; Swain, C. J.; Webster, N. M. H. *J. Chem. Soc., Perkin Trans. 1* **1988**, *3*, 471.
(21) Bugarin, A.; Jones, K. D.; Connell, B. T. *Chem. Commun.* **2010**, *46*, 1715.
(22) Miura, K.; Saito, H.; Fujisawa, N.; Wang, D.; Nishikori, H.; Hosomi, A. *Org. Lett.* **2001**, *3*, 4055.