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Catalytic Asymmetric Synthesis of Stable Oxetenes via Lewis Acid-Promoted [2 + 2] Cycloaddition

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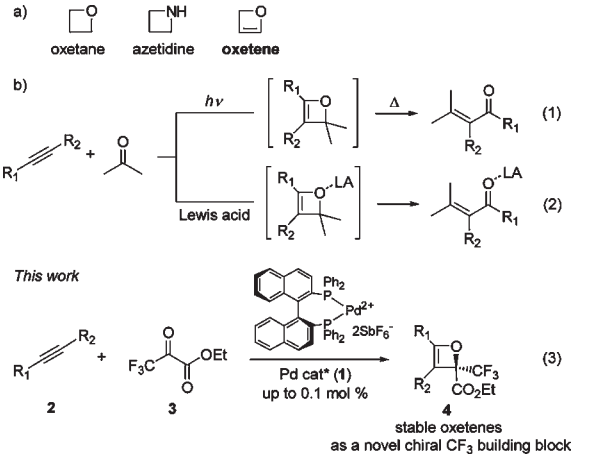
Supporting Information

ABSTRACT: A highly enantioselective and atom-economical [2 + 2] cycloaddition of various alkynes with trifluoropyruvate using a dicationic (*S*)-BINAP−Pd catalyst has been established. This is the first enantioselective synthesis of stable oxetene derivatives, whose structure has been clarified by X-ray analysis. This catalytic process offers a practical synthetic method for oxetene derivatives (catalyst loading: up to 0.1 mol %), which can serve as novel chiral building blocks for pharmaceuticals and agrochemicals and can also be transformed into a variety of enantiomerically enriched CF_3-substituted compounds with high stereoselectivity.

Saturated four-membered heterocyclic compounds bearing one heteroatom in the ring, such as oxetanes and azetidines, have received attention as small-molecule modules of key biophysical and chemical properties of pharmaceutically relevant scaffolds (Scheme 1a).[1] Particularly intriguing are oxetanes, which bear an oxygen atom in the ring and would be expected to serve as widely available building blocks for the synthesis of natural and unnatural compounds with significant biological activities.[1a−c] In sharp contrast, oxetenes are considerably less stable under thermal and acidic conditions because the double bond increases the ring strain. Some oxetene derivatives have been synthesized to date, but their isolation and purification are much more difficult.[2] Furthermore, enantiomerically enriched oxetenes have never been prepared by asymmetric synthetic methods. Oxetenes have been reported as reaction intermediates in photochemical or Lewis acid-promoted [2 + 2] cycloadditions (Scheme 1b). Photoinduced [2 + 2] cycloaddition of $n\pi^*$ excited-state carbonyl compounds with alkynes gives labile oxetene intermediates (eq 1 in Scheme 1b).[2e,h,3] The corresponding α,β-unsaturated carbonyl compounds are obtained through electrocyclic ring opening of the thermodynamically unstable oxetenes. Lewis acid-promoted [2 + 2] cycloaddition also provides the oxetene intermediates, but ring opening to give α,β-unsaturated carbonyl compounds readily takes place because of the Lewis acid, even at low reaction temperatures (eq 2 in Scheme 1b).[4,5]

We have developed a variety of catalytic asymmetric C−C bond-forming reactions using chiral dicationic Pd complexes as efficient Lewis acid catalysts.[6,7] Here we present a highly enantioselective and atom-economical [2 + 2] cycloaddition of various alkynes **2** with ethyl trifluoropyruvate (**3**) catalyzed by the chiral cationic BINAP−Pd complex **1** (eq 3 in Scheme 1b). This is not only the first synthetic method for stable oxetene derivatives stabilized by the CF_3 group but also a new entry to chiral CF_3-containing building blocks for pharmaceuticals and agrochemicals. Currently, the development of useful methods to provide enantiomerically enriched organofluorine compounds bearing the CF_3 group in particular is strongly desired.[8] This catalytic process affords a variety of stable and enantiomerically enriched oxetene derivatives bearing the CF_3 group.

Scheme 1. (a) Four-Membered Heterocycles; (b) [2 + 2] Cycloadditions of Alkynes with Carbonyl Compounds



We recently reported a catalytic asymmetric alkynylation reaction based on the formation of a stable β-cation intermediate using **3** and alkynylsilane **2a**, which possesses phenyl and trimethylsilyl groups at the terminal positions.[9] The chiral complex **1** catalyzes the reaction to produce the corresponding propargylic alcohol **6** in 85% yield with 99% ee after desilylation by treatment with acid (eq 1 in Scheme 2).[9] During the course of this research project, we found that the use of alkynylsilane **2b** bearing a more electron-rich *p*-methoxyphenyl group facilitated a [2 + 2] cycloaddition to afford oxetene **4b** and hydrolyzed α-hydroxy-γ-ketoester **5b** in a 4.2:1 ratio as determined by ^1H and ^{19}F NMR analyses. Being sensitive to acidic conditions, **4b** was hydrolyzed to **5b** even through a thin pad of silica gel (eq 2 in Scheme 2). Protodesilylation and hydrolysis of the four-membered enol ether structure can provide **5b**, as hydrolysis of oxetenes **4m** and **4n** (see below) also led to **5b**. With basic alumina, however, column chromatography gave only **4b** in 88% yield with 99% ee without hydrolysis or electrocyclic ring opening. To synthesize more stable oxetenes, the more sterically demanding dimethylphenylsilyl group in alkynylsilane **2c** was employed; the combination of **2c** and **3** in the presence of **1** (2 mol %) afforded the stable oxetene **4c** in

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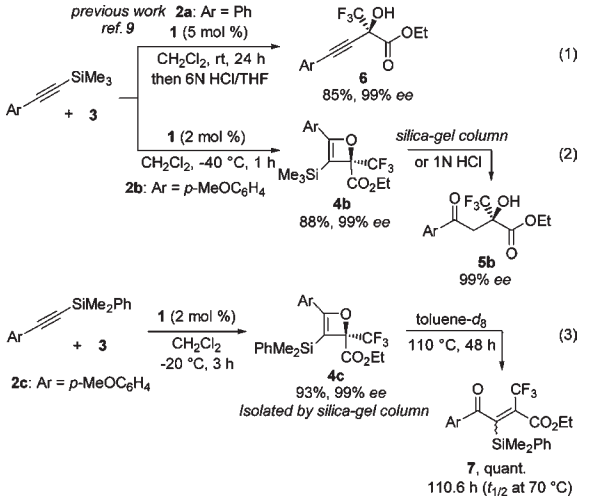
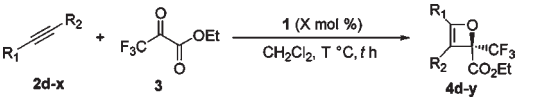
Scheme 2. Catalytic Asymmetric [2 + 2] Cycloaddition versus Alkynylation



excellent yield (93%) and enantioselectivity (99% ee); **4c** could be isolated and purified by silica-gel column chromatography without conversion to **5b** or α,β-unsaturated ketone **7** (eq 3 in Scheme 2). Heat treatment of **4c** in toluene-d_8 resulted in electrocyclic ring opening[2−5] to gave **7** quantitatively.[10] Monitoring of the reaction at 70 °C revealed a long half-life of 110.6 h. The absolute configuration of **4b** was determined to be *R* by derivatization to the known α-hydroxy-γ,δ-unsaturated ester.[11]

It was predicted that electron-rich aryl substituents on the alkyne, which can stabilize the vinyl cation intermediate,[9] would play an important role in facilitating the formation of the oxetene. Thus, a range of internal alkynes without a silyl group could be used in the [2 + 2] cycloaddition with **3** in the presence of complex **1** (Table 1). The reactions of *p*-methoxyphenyl-substituted alkynes **2d**−**n** with various substitution patterns were initially investigated in CH_2Cl_2 (entries 1−12). Alkynes **2d**−**h** with aliphatic and aromatic groups gave the desired products in good-to-excellent yields and enantioselectivities (entries 1−6). In particular, even with a catalyst loading of 0.1 mol %, the good yield (83%) and excellent enantioselectivity (98% ee) were maintained in the reaction with alkyne **2d** (entry 2). Alkynes **2f** and **2g** with electron-donating and -withdrawing aromatic substituents, respectively, gave good yields and asymmetric inductions (entries 4 and 5). The reactions using alkynes **2i**−**k** with electron-withdrawing groups (CO_2Et, CHO, and CF_3) required slightly higher temperatures [room temperature (rt) to 40 °C] to provide the corresponding oxetenes with good-to-excellent enantioselectivities (91−97% ee) (entries 7−9). The [2 + 2] cycloaddition of alkynes bearing iodide (**2l**) and pinacolborane (**2m**) proceeded smoothly at −20 °C within 1 h to give the highly enantioenriched oxetenes (entries 10 and 11). Terminal alkyne **2n** gave the corresponding oxetene **4n** in good yield but with low enantioselectivity (entry 12). In spite of reduced reactivity, alkynes **2o** and **2p** bearing a phenyl group instead of the *p*-methoxyphenyl group could also be used (entries 13 and 14). Especially with the sterically less demanding methyl and phenyl groups in alkyne **2o**, use of the sterically more demanding (*S*)-DTBM-SEGPHOS ligand was essential to enhance the enantioselectivity (entry 13). The reactions of alkynes **2q** and **2r** bearing *p*-tolyl and *m*-methoxyphenyl groups,

Table 1. Catalytic Asymmetric Synthesis of Stable Oxetene Derivatives Using 3 and a Variety of Alkynes 2d−y



entry	R_1	R_2		X (mol %)	T (°C)	*t* (h)	yield (%)[d]	*ee* (%)[f]
1		^{n}Bu	(**d**)	2	-40	1	99	98
2[a]				0.1	0	12	83	98
3		Ph	(**e**)	2	0	12	97	97
4		*p*-$MeOC_6H_4$	(**f**)	2	0	12	92	97
5		*p*-$NO_2C_6H_4$	(**g**)	2	0	12	99	92
6		TBDPSOCH$_2$	(**h**)	5	-20	4	95	99
7		CO_2Et	(**i**)	5	rt	12	92	97
8		CHO	(**j**)	5	40	24	89	91
9		CF_3	(**k**)	10	40	24	84	94
10		I	(**l**)	2	-20	1	93	96
11			(**m**)	5	-20	1	88[e]	94
12		H	(**n**)	5	-40	1	79	10
13[b]		Me	(**o**)	5	0	12	84	81
14		I	(**p**)	5	40	12	63	91
15		^{n}Bu	(**q**)	5	-20	5	96	69
16		^{n}Bu	(**r**)	5	rt	12	85	82
17		^{n}Bu	(**s**)	2	0	12	95	98
18			(**t**)	5	rt	24	75	98
19		^{t}Bu	(**u**)	5	-20	12	79	98
20		I	(**v**)	2	-20	3	93	97
21		^{n}Bu	(**w**)	1	-40	5	96	99
22		Ph	(**x**)	2	0	12	86	99
23		^{n}Bu	(**y**)[c]	5	-20	6	88[c]	89[g]

[a] 10/1 toluene/CH_2Cl_2 (1.0 M) was used as the solvent. [b] (*S*)-DTBM-SEGPHOS was used instead of (*S*)-BINAP. [c] *E*/*Z* = 10/1. [d] Isolated yields. [e] ^{19}F NMR yield. [f] Determined by chiral HPLC analyses. [g] Enantiopurity of the *E* isomer.

respectively, gave the products in good yields but with reduced levels of stereoinduction (entries 15 and 16). More bulky 1-naphthyl-substituted alkynes **2s**−**u** afforded excellent enantioselectivities (98% ee) (entries 17−19). Alkynes **2v**−**x** with electron-rich heteroaromatic substituents also gave excellent results (97−99% ee) (entries 20−22). Notably, the aromatic substituent could be replaced with a vinyl group to provide the corresponding oxetene **4y** in good yield (88%) and enantioselectivity (89% ee) (entry 23). The absolute configuration of **4d** was shown to be *R* by X-ray analysis of **17** (see below).[11] The absolute configurations of other oxetene products were tentatively assigned by analogy to **4b** and **4d**.

The structure of oxetene **4z** obtained by the reaction of extremely bulky internal alkyne **2z** bearing *tert*-butyl and 2,4,6-trimethylphenyl (Mes) groups was determined by X-ray analysis of a single crystal (Scheme 3).[11] The four-membered ring consists of two C−O single bonds (1.429 and 1.461 Å), a C−C single bond (1.529 Å), and a C−C double bond (1.341 Å). The C2−C1−O angle is obtuse (97.93°), but the remaining three bond angles of the oxetene are all

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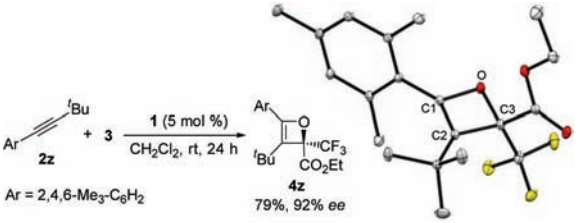
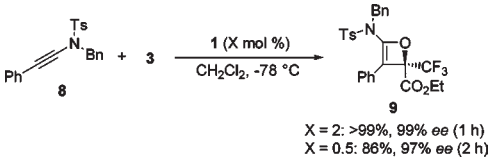
Scheme 3. X-ray Structure of Oxetene 4z[a]



[a] Selected bond lengths (Å) and angles (deg): C1−C2, 1.341; C1−O, 1.429; C2−C3, 1.529; C3−O, 1.461; C1−C2−C3, 86.96; C2−C3−O, 88.73; C1−O−C3, 86.38; C2−C1−O, 97.93.

Scheme 4. Synthesis of 9 Using Ynamide 8 as the Nucleophile



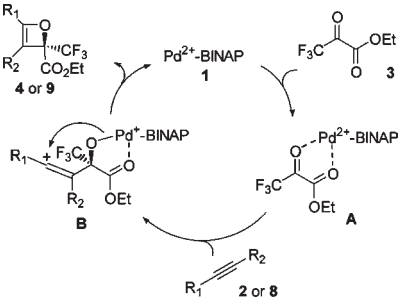
acute (86.96, 88.73, and 86.38°). To the best of our knowledge, this is the first structural confirmation of an oxetene by X-ray analysis.

The reaction of ynamide **8** as an internal alkyne was next executed in the presence of complex **1** (Scheme 4), as there have been only a few reports of catalytic asymmetric transformations involving ynamides.[12] Fortunately, the reaction proceeded smoothly at −78 °C to give the corresponding stable oxetene **9**, which was isolated by silica-gel column chromatography in excellent yield (>99%) and enantioselectivity (99% ee). Even in the case of a catalyst loading of 0.5 mol %, high enantioselectivity (97% ee) was preserved along with a good yield (86%).

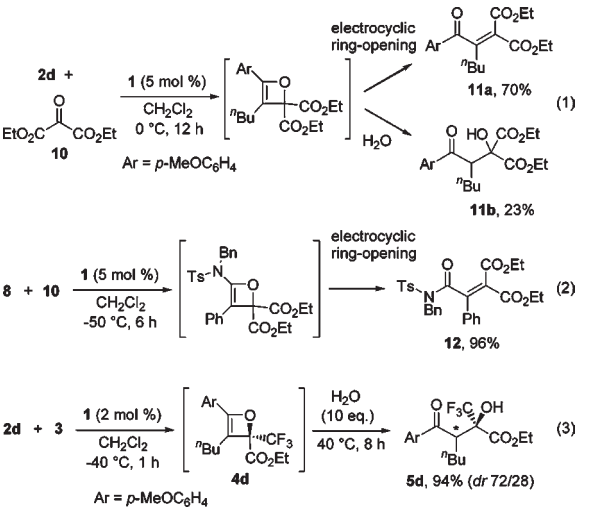
In our proposed reaction mechanism (Scheme 5),[13] bidentate coordination of trifluoropyruvate **3** to dicationic Pd complex **1** would initially form the reactive structure **A**, constructing the efficient asymmetric environment.[6,7,9] Attack on trifluoropyruvate **3** by alkene **2** or **8** as the nucleophile would generate intermediate **B**, which can be stabilized by the strong electron-withdrawing nature of the CF_3 substituent.[8] A subsequent ring-closing reaction would provide the corresponding oxetene **4** or **9**.

With these reaction parameters defined, other carbonyl compounds were examined in the present [2 + 2] cycloaddition. The reactions with ethyl glyoxylate or benzaldehyde instead of **3** did not proceed at all, and trifluoroacetophenone gave complex products even at low temperature. However, the reaction of diethyl ketomalonate (**10**) and alkyne **2d** was promoted to provide α,β-unsaturated ketone **11a** (70% yield) and α-hydroxy-γ-ketomalonate **11b** (23% yield) via the electrocyclic ring-opening reaction and hydrolysis of the labile oxetene, respectively (eq 1 in Scheme 6). In this reaction, no oxetene could be detected. The use of ynamide **8** with **10** produced only the α,β-unsaturated ketone **12** in 96% yield (eq 2 in Scheme 6). On the other hand, after the stable oxetene **4d** was prepared in situ by the reaction of **2d** and **3** in the presence of complex **1**, the addition of H_2O (10 equiv) to the reaction mixture followed by an increase in the reaction temperature solely provided α-hydroxy-γ-ketoester **5d** as the hydrolyzed product of **4d** (eq 3 in Scheme 6). These results indicate that the unprecedented stability of oxetenes obtained by our catalytic system using **3** stems from the unique character of the not only electron-withdrawing but also bulky CF_3 substituent.[14,15]

Scheme 5. Proposed Reaction Mechanism



Scheme 6. Reactions of Alkynes and Diethyl Ketomalonate



With these successes for a wide scope of alkynes, we could use the oxetene derivatives as chiral building blocks for the enantioselective syntheses of CF_3-substituted compounds (Scheme 7). While treatment of **4d** with Pd/C under H_2 in ethanol gave the ring-opened product **14** quantitatively (eq 2 in Scheme 7), the use of **4d** and **4k** in ethyl acetate as a solvent stereoselectively afforded oxetanes **13d** and **13k** in good yields (eq 1 in Scheme 7). Reduction of the ester group in **4d** using $NaBH_4$ followed by TBS protection of the alcohol provided **15** without decomposition of the oxetene skeleton (eq 3 in Scheme 7). Interestingly, oxidation of **4d** with *m*CPBA gave monobenzoate-protected vicinal diol **16** bearing contiguous quaternary carbon centers as a single diastereomer in 87% yield (eq 4 in Scheme 7). Subsequent reduction of the carbonyl group and migration of the chlorobenzoyl group produced monoprotected triol **17** in 42% yield. X-ray analysis unambiguously disclosed the absolute and relative configurations of **17** with three contiguous chiral centers. In addition, **4l** was converted into **4e** in 61% yield in the presence of palladium catalyst, $PhB(OH)_2$, and KF in THF (eq 5 in Scheme 7).

In conclusion, we have developed a highly enantioselective and atom-economical [2 + 2] cycloaddition of a diverse array of alkynes with trifluoropyruvate using a chiral dicationic BINAP−Pd catalyst to provide unprecedentedly stable oxetene derivatives. The reaction takes place with good-to-excellent yields and various substituents on the internal alkynes. This catalytic process offers not only the first synthetic method of stable oxetene derivatives but also a new entry to oxetenes as novel chiral trifluoromethyl building blocks for pharmaceuticals and agrochemicals.

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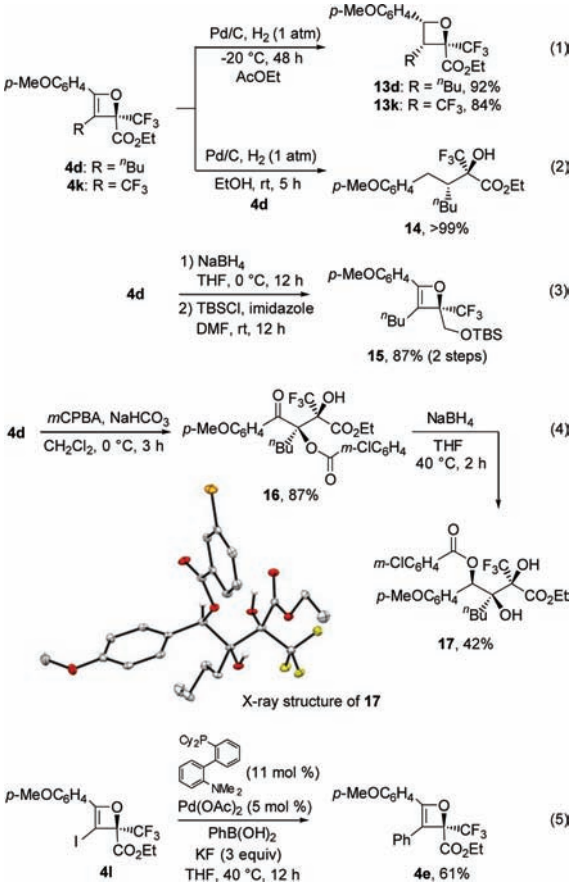
Scheme 7. Transformations of Oxetenes



Detailed studies of the mechanism and generality of the electrocyclic ring-opening transformation are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, compound characterization data, and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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