

# Fragment-Based Reaction Discovery of Non-Ene-Type Carbon–Carbon Bond-Forming Reactions: Catalytic Asymmetric Oxetane Synthesis by Screening Olefinic Reactants without Allylic Hydrogen

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**Abstract:** Through fragment-based reaction discovery, catalytic asymmetric [2+2] cycloaddition was found to produce oxetanes from trifluoropyruvate and olefinic reactants without allylic hydrogen. This non-ene-type carbon–carbon bond-forming reaction smoothly proceeded under the influence of chiral Pd or Cu complexes as Lewis acid catalysts. The [2+2] cycloaddition afforded the oxetane derivatives in high yields and enantioselectivities even under 0.1 mol% catalyst loading and solvent-free conditions.

**Key words:** fragment-based, Lewis acid catalyst, [2+2] cycloaddition, oxetane, trifluoromethyl

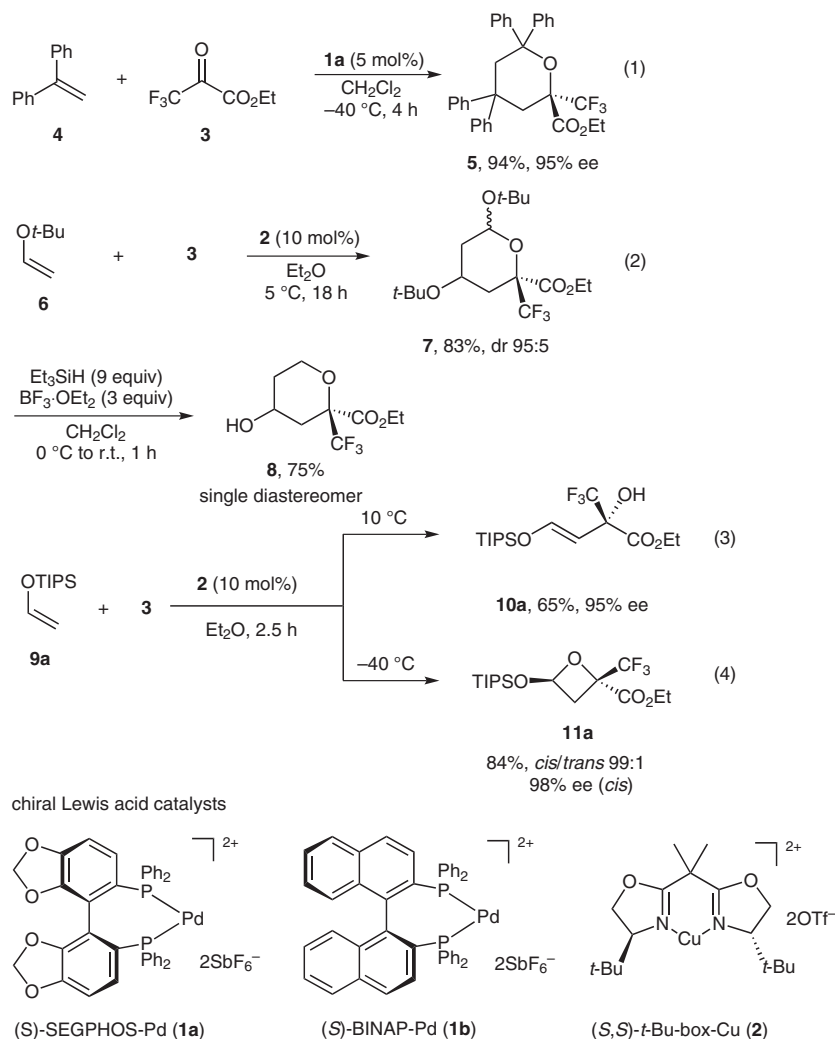
Development of catalytic asymmetric carbon–carbon bond-forming (CCF) reactions for molecular skeletal construction is currently one of the most important subjects in modern organic synthesis.<sup>1</sup> Generally, chiral catalysts are screened in order to establish the best catalysts for a specific CCF reaction, e.g., the carbonyl-ene reaction of olefinic reactants with allylic hydrogen.<sup>2</sup> In sharp contrast, we report here the ‘fragment-based’<sup>3</sup> reaction discovery of a catalytic asymmetric non-ene-type CCF reaction that has previously been unexplored. By changing chiral Lewis acid catalysts, carbonyl substrates, and olefinic reactants without allylic hydrogen in particular, the catalytic asymmetric oxetane formation was found to fit with the complexes of a carbonyl compound and chiral Lewis acid (Pd, Ti or Cu) catalysts.<sup>4–6</sup> The optically active oxetanes are biologically and synthetically promising, as typically shown in oxetanocines<sup>7</sup> or oxetin.<sup>8</sup> Moreover, the oxetane products, as chiral building blocks<sup>9</sup> bearing the quaternary trifluoromethyl carbinol cores,<sup>10</sup> are expected to be of biological and synthetic importance. Catalytic asymmetric oxetane formation can thus be found by the fragment-based reaction discovery approach to non-ene-type catalytic asymmetric CCF, particularly using olefinic reactants without allylic hydrogen.

The highly effective chiral Lewis acid catalysts were first scrutinized for the non-ene-type catalytic asymmetric CCF reactions of trifluoropyruvate **3** with olefinic reactants without allylic hydrogen. The progress of a non-ene-type CCF reaction was monitored by TLC and/or NMR analyses until products were at least partly formed and

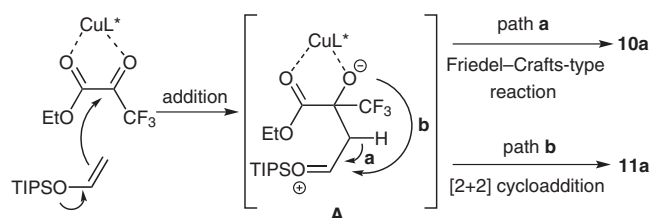
olefinic reactants were virtually all consumed. After extensive screening of chiral Lewis acid catalysts and olefinic reactants without allylic hydrogen, we identified that the reactions shown in Scheme 1 were mediated by Lewis acid catalysts **1a**, **1b**, and **2** in particular. Combination of trifluoropyruvate (**3**) with 1,1-diphenylethylene (**4**) in the presence of (*S*)-SEGPHOS-Pd catalyst (**1a**) gave pyrane **5** via [2+2+2] cycloaddition in high yield and enantioselectivity (94%, 95% ee), along with trace amounts of the Friedel–Crafts alkylation product (Scheme 1, equation 1). The use of other chiral transition metal catalysts such as BINOL-Ti<sup>5</sup> and (*S,S*)-*t*-Bu-Box-Cu (**2**),<sup>6</sup> however, gave no reaction product. On the other hand, in the presence of Pd catalysts **1a** or **1b**, *tert*-butyl vinyl ether **6**, which is more reactive as a nucleophile, gave polymerization products. However, (*S,S*)-*t*-Bu-Box-Cu catalyst **2** provided the [2+2+2]-cycloaddition product **7** in 83% yield with a 95:5 diastereomeric ratio (Scheme 1, equation 2).<sup>11</sup> Reduction of the acetal portion of **7** with triethyl hydrosilane and boron trifluoride diethyl etherate gave the single diastereomer **8**, which indicated that the diastereomers of pyrane **7** are anomers at the anomeric carbon center. By further tuning the olefinic reactants to tri(isopropyl)silyl enol ether (**9a**), oxetane **11a** was obtained as the single product under Cu catalysis in good yield (84%), with excellent enantioselectivity and diastereoselectivity (98% ee; *cis/trans* = 99:1) when the reaction was conducted at –40 °C for 2.5 hours (Scheme 1, equation 4). In contrast, the Friedel–Crafts alkylation product **10a** was obtained in 65% yield with 95% ee at higher temperature (10 °C; Scheme 1, equation 3). The Mukaiyama aldol product was not observed in the reaction of the carbonyl compound **3** even with the silyl enol ether. However, the Pd catalysts **1** gave only polymerization products in this case of tri(isopropyl)silyl enol ether (**9a**), presumably because of the higher Lewis acidity of the dicationic Pd catalysts **1** than the *t*-Bu-Box-Cu catalyst **2**.

As a proposed reaction mechanism, the attack of tri(isopropyl)silyl enol ether (**9a**) on the complexes of trifluoropyruvate **3** and the Cu catalyst **2** would provide the zwitter ionic intermediate **A** (Scheme 2); Path **a**, which proceeds through dissociation of a proton, leads to the Friedel–Crafts-type product **10a** and the ring-closing reaction as shown in path **b** provides the oxetane **11a**.

On the basis of these findings, a range of silyl enol ethers **9b–d** were investigated for [2+2] cycloaddition (Table 1).



**Scheme 1** Fragment-based reaction discovery by screening of chiral Lewis acid catalysts and olefinic reactants without allylic hydrogen



**Scheme 2** Plausible reaction mechanisms

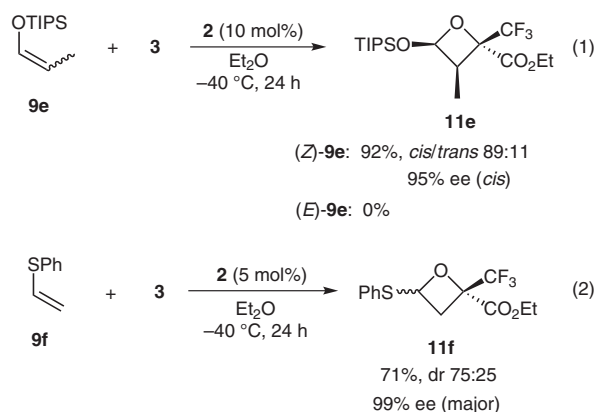
In this catalytic system, solvents dramatically affected not only yield but also the stereoselectivity of the [2+2] cycloaddition; diethyl ether was found to give the best results (Table 1, entries 1–4). At lower reaction temperature (–60 °C), oxetane **11a** was obtained with almost complete stereoselectivity (>99% ee; *cis/trans* = 99:1) in 94% yield (Table 1, entry 5). High yield and enantioselectivity could be maintained even with low catalyst loading of 1 mol% (94% yield, 95% ee, *cis/trans* = 98:2), while lower catalyst loading up to 0.5 mol% decreased the enantioselectivity to 88% ee (Table 1, entries 6 and 7 vs. 1). No desired product was obtained in the reaction using **9b** (with TMS group), because of the decomposition of **9b** under the re-

action conditions (Table 1, entry 8). The use of a TBS group resulted in a decrease in both the yield and enantioselectivity (Table 1, entry 9). Silyl enol ether **9d**, bearing a sterically more demanding TBDPS group, provided a higher yield and enantioselectivity, albeit after a longer reaction time (Table 1, entries 10 vs. 1). In addition, the reaction with the *Z*-isomer of **9e** proceeded to give the oxetane **11e**, in which the anomeric silyloxy group and trifluoromethyl substituent were mainly positioned with *cis*-orientation (*cis/trans* 89:11), in high yield with good stereoselectivity (Scheme 3, equation 1). In sharp contrast, the *E*-isomer of **9e** did not participate in the reaction at all. In the presence of 5 mol% Cu catalyst **2**, the choice of phenyl vinyl sulfide **9f** instead of silyl enol ethers **9a–e** also accomplished excellent enantioselectivity (99% ee; Scheme 3, equation 2).

Silyl enol ether **9g** (*Z/E* = 67:33) was then prepared from 1,3-propanediol and the [2+2] cycloaddition was examined under the optimized conditions (Scheme 4). The reaction proceeded efficiently to give oxetane **11g** with high enantioselectivity (90% ee) and *cis*-selectivity (*cis/trans* = 97:3). An NOE experiment with oxetane **12**, which was

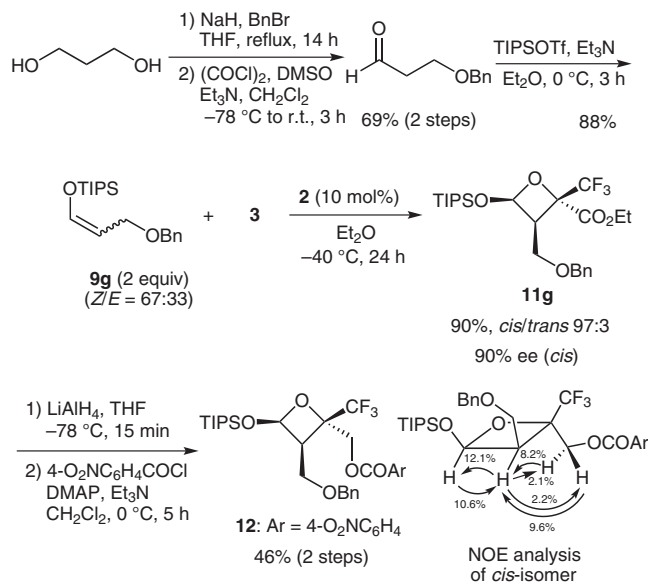
**Table 1** Enantioselective [2+2] Cycloaddition Catalyzed by *t*-Bu-Box-Cu (**2**)<sup>a</sup>

| 9a-d  |           | 3   | 2 (X mol%)                      |           | conditions |                        | 11a-d                     |                     |
|-------|-----------|-----|---------------------------------|-----------|------------|------------------------|---------------------------|---------------------|
| Entry | Si        | X   | Solvent                         | Temp (°C) | Time (h)   | Yield (%) <sup>b</sup> | dr <sup>c</sup> cis/trans | ee (%) <sup>d</sup> |
| 1     | TIPS (a)  | 10  | Et <sub>2</sub> O               | −40       | 2.5        | 84                     | 99:1                      | 98                  |
| 2     | TIPS (a)  | 10  | THF                             | −40       | 24         | 21                     | 92:8                      | 70                  |
| 3     | TIPS (a)  | 10  | CH <sub>2</sub> Cl <sub>2</sub> | −40       | 24         | 16                     | 52:48                     | 0                   |
| 4     | TIPS (a)  | 10  | toluene                         | −40       | 6          | 38                     | 91:9                      | 86                  |
| 5     | TIPS (a)  | 10  | Et <sub>2</sub> O               | −60       | 4          | 94                     | 99:1                      | >99                 |
| 6     | TIPS (a)  | 1   | Et <sub>2</sub> O               | −40       | 24         | 94                     | 98:2                      | 95                  |
| 7     | TIPS (a)  | 0.5 | Et <sub>2</sub> O               | −40       | 48         | 91                     | 95:5                      | 88                  |
| 8     | TMS (b)   | 10  | Et <sub>2</sub> O               | −40       | 24         | 0                      | —                         | —                   |
| 9     | TBS (c)   | 10  | Et <sub>2</sub> O               | −40       | 1.5        | 38                     | 82:18                     | 98                  |
| 10    | TBDPS (d) | 10  | Et <sub>2</sub> O               | −40       | 24         | 95                     | 97:3                      | 99                  |

<sup>a</sup> Ratio of silyl enol ether **9** to trifluoropyruvate **3** = 1:2.<sup>b</sup> Isolated yield.<sup>c</sup> Determined by <sup>19</sup>F NMR analysis (CDCl<sub>3</sub>).<sup>d</sup> Enantiopurity of *cis*-isomer was determined by chiral GC analysis.**Scheme 3**

obtained via reduction of the ester group using LiAlH<sub>4</sub> following by *p*-nitrobenzoyl protection of the resultant alcohol group, indicated a *cis*-configuration between the siloxy (OTIPS), benzyloxymethyl (BnOCH<sub>2</sub>), and trifluoromethyl (CF<sub>3</sub>) substituents.

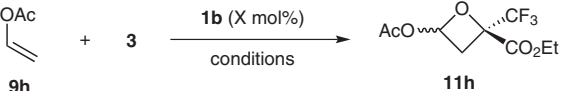
Catalytic asymmetric oxetane formation using chiral Lewis acids is novel and is particularly intriguing in view of the precedent report that Box-Cu-catalyzed oxetane formation is a less likely process as predicted by the excellent study based on DFT (UB3 LYP/6-31G\*) and two-layered ONIOM calculations (UB3 LYP/6-31G\*:PM3).<sup>12</sup> Therefore, oxetane formation was further scrutinized with the BINAP-Pd catalyst **1b**, by tuning the much less expensive and relatively less reactive vinylacetate (**9h**); the re-

**Scheme 4**

sults are summarized in Table 2. In the first instance, we employed 10 mol% **1b** in dichloromethane at −20 °C to provide the desired oxetane **11h** in higher yield and stereoselectivity than those obtained at 0 °C (Table 2, entries 1 vs. 2). Importantly, the reaction with vinylacetate using *t*-Bu-Box-Cu **2** did not proceed at all, probably due to the lower Lewis acidity of **2**. In toluene, the yield was increased, while the diastereoselectivity was slightly decreased (Table 2, entry 3). The use of (*S*)-SEGPHOS instead of (*S*)-BINAP decreased the yield and both the diastereo- and enantioselectivity (Table 2, entries 3 vs. 4). Even with reduced catalyst loadings up to 0.5 and 0.1 mol%, satisfactory yields, high diastereo- and enantioselectivities were obtained with the (*S*)-BINAP-Pd complex **1b** (Table 2, entries 5 and 6). Significantly, the high yield and stereoselectivity were maintained under solvent-free conditions even with 0.1 mol% catalyst loading (Table 2, entry 7).

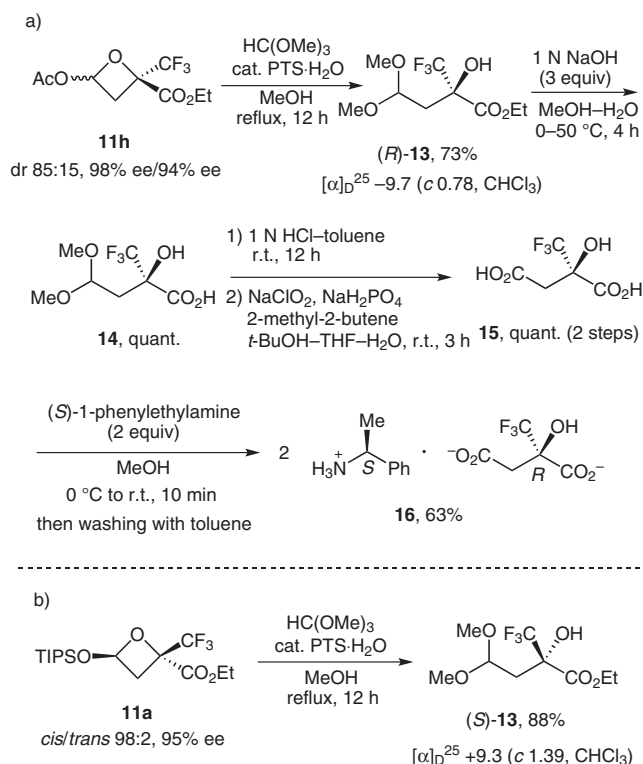
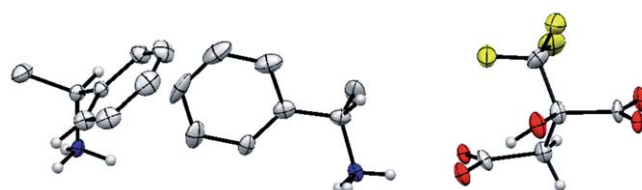
Highly optically active oxetanes obtained through catalytic asymmetric [2+2] cycloaddition are of synthetic significance as chiral building blocks bearing quaternary trifluoromethyl carbinol units.<sup>9,10</sup> Transformation of the oxetanes was thus executed. Ring opening of oxetane **11h** in methanol under acidic conditions provided the acetal product **13** in 73% yield. Hydrolysis of the ester group in **13** by treatment with 1 N NaOH led to the monocarboxylic acid **14** quantitatively. Hydrolysis of the acetal group under acidic conditions and oxidation followed by an addition of two equivalents of (*S*)-1-phenylethylamine provided the corresponding ammonium salt of 2-hydroxy-1,4-dicarboxylic acid **16** in 63% yield in three steps (Scheme 5a). X-ray crystal structure analysis of the ammonium salt **16** was performed and, consequently, the absolute configuration of the quaternary carbon in the oxetane **11h** was determined to be *R* (Figure 1).<sup>13</sup> On the other hand, the absolute configuration of acetal **13**, prepared from **11a**, was determined to be *S* by comparison

**Table 2** Enantioselectivity of the [2+2] Cycloaddition Catalyzed by (S)-BINAP-Pd (**1b**)<sup>a</sup>

|  |     |                                 |           |          |                        |                 |                     |
|---|-----|---------------------------------|-----------|----------|------------------------|-----------------|---------------------|
| Entry   | X   | Solvent                         | Temp (°C) | Time (h) | Yield (%) <sup>c</sup> | dr <sup>d</sup> | ee (%) <sup>e</sup> |
| 1   | 10  | CH <sub>2</sub> Cl <sub>2</sub> | 0         | 5        | 56                     | 63:37           | 90:88               |
| 2   | 10  | CH <sub>2</sub> Cl <sub>2</sub> | –20       | 15       | 52                     | 85:15           | 98:94               |
| 3   | 10  | toluene                         | –20       | 15       | 88                     | 77:23           | 98:91               |
| 4 <sup>b</sup>  | 10  | toluene                         | –20       | 15       | 56                     | 76:24           | 93:83               |
| 5   | 0.5 | toluene                         | –20       | 48       | 93                     | 92:8            | 96:51               |
| 6   | 0.1 | toluene                         | –20       | 48       | 61                     | 91:9            | 96:56               |
| 7   | 0.1 | solvent-free                    | –20       | 48       | 86                     | 92:8            | 96:20               |

<sup>a</sup> Ratio of vinyl acetate **9h** to trifluoropyruvate **3** = 1:2.<sup>b</sup> Catalyst **1a** was used instead of **1b**.<sup>c</sup> Isolated yield.<sup>d</sup> Determined by <sup>19</sup>F NMR analysis (CDCl<sub>3</sub>).<sup>e</sup> Enantiopurity was determined by chiral GC analysis.

with the optical rotation of the acetal (*R*)-**13**, which was prepared from **11h** (Scheme 5b).

**Scheme 5** Oxetanes as chiral building blocks: Determination of the absolute configuration**Figure 1** X-ray crystal structure of **16**

In summary, we have demonstrated a proof of concept for the fragment-based reaction discovery of non-ene-type catalytic asymmetric CCF reactions.<sup>14</sup> The chiral Lewis acid catalyzed oxetane formation of trifluoropyruvate **3** has been discovered by changing olefinic reactants without allylic hydrogen in particular. Optically active oxetanes are biologically and synthetically important, as exemplified by oxetanocines or oxetin. Additionally, the oxetanes are highly promising as chiral building blocks, having the quaternary trifluoromethyl carbinol cores, which are of biological and synthetic importance.

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- (13) Crystal data for **16**:  $C_{21}H_{27}F_3N_2O_5$ ; orthorhombic; space group  $P2_12_12_1$ ;  $a = 6.3390$  (11) Å,  $b = 17.252$  (3) Å,  $c = 20.143$  (4) Å;  $V = 2202.9$  (7) Å<sup>3</sup>;  $Z = 4$ ;  $D_{\text{calc}} = 1.340$  Mg m<sup>-3</sup>;  $\mu = 0.112$  mm<sup>-1</sup>. All measurements were made with a Bruker APEXII CCD area detector with graphite monochromated Mo-K $\alpha$  radiation at 93 K. Of the 9577 reflections that were collected, 3935 were unique ( $R_{\text{int}} = 0.0329$ ).  $R_1 = 0.0716$ ,  $wR = 0.1805$ , goodness of fit = 1.052; Flack Parameter = 0.1 (13), shift/error = 0.000. CCDC-838360 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif)
- (14) **Enantioselective [2+2] Cycloaddition Catalyzed by (S,S)-*t*-Bu-Box-Cu(2) (Table 2, entry 1); Typical Procedure:** (S,S)-*t*-Bu-Box-Cu(OTf)<sub>2</sub> catalyst was prepared by the addition of Cu(OTf)<sub>2</sub> (3.6 mg, 0.01 mmol) to (S,S)-2,2'-isopropylidenebis(4-*tert*-butyl-2-oxazoline) (3.2 mg, 0.011 mmol) under an argon atmosphere. The mixture was dried under vacuum for 1 h, then Et<sub>2</sub>O (1.0 mL) was added under an argon atmosphere and the resulting suspension was stirred vigorously for 1 h at r.t. To the solution at -40 °C were added ethyl trifluoropyruvate **3** (26.5  $\mu$ L, 0.2 mmol) followed by tri(isopropyl)silyl enol ether (**9a**; 20.0 mg, 0.1 mmol). After stirring at -40 °C for 2.5 h, the reaction mixture was directly loaded onto a short silica gel column (hexane-EtOAc, 1:1) to remove the catalyst. The solution was evaporated under reduced pressure. Purification by silica-gel chromatography (hexane-EtOAc, 20:1) gave the corresponding oxetane **11a** (84% yield) as a clear liquid. The *cis/trans* ratio was determined by <sup>19</sup>F NMR analysis (*cis/trans*, 99:1; the major configuration of the oxetane products was determined to be *cis* from the results of NOE experiments, which are summarized in Scheme 4). **(2S,4R)-Ethyl 2-Trifluoromethyl-4-(triisopropylsiloxy)-oxetane-2-carboxylate (11a)**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 1.06$  (m, 21 H), 1.33 (t,  $J = 7.2$  Hz, 3 H), 2.82 (dd,  $J = 12.6, 4.2$  Hz, 1 H), 3.11 (dd,  $J = 12.6, 5.1$  Hz, 1 H), 4.33 (q,  $J = 7.2$  Hz, 2 H), 5.90 (dd,  $J = 5.1, 4.2$  Hz, 1 H); <sup>13</sup>C NMR (75.5 MHz, CHCl<sub>3</sub>):  $\delta = 11.8, 13.9, 17.5, 37.6$  (q,  $J_{\text{C-F}} = 0.8$  Hz), 62.6, 76.1 (q,  $J_{\text{C-F}} = 33.2$  Hz), 95.7, 122.3 (q,  $J_{\text{C-F}} = 283.1$  Hz), 167.6; <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):  $\delta = -79.0$  (s, 3 F); FTIR (neat): 2947, 2896, 2870, 1751, 1466, 1390, 1286, 1187, 1113, 1039, 919, 883, 685 cm<sup>-1</sup>; HRMS (APCI-TOF):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>16</sub>H<sub>29</sub>F<sub>3</sub>O<sub>4</sub>Si: 371.1865; found: 371.1889;  $[\alpha]_D^{24} -4.48$  (c 1.08, CHCl<sub>3</sub>) for 98% ee (*cis/trans* = 99:1); GC (column, CP-Chirasil-Dex CB, i.d. 0.25 mm  $\times$  25 m, CHROMPACK; carrier gas, nitrogen 75 kPa; column temp. 120 °C; injection and detection temp. 150 °C):  $t_R = 36.2$  (major isomer), 38.3 (minor isomer) min. **(2S,3R,4R)-Ethyl 3-Benzoyloxymethyl-2-trifluoromethyl-4-(triisopropylsiloxy)oxetane-2-carboxylate (11g)**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 1.07$  (m, 21 H), 1.31 (t,  $J = 7.2$  Hz, 3 H), 3.62 (ddd,  $J = 9.6, 5.7, 4.2$  Hz, 1 H), 3.75 (dd,  $J = 9.6, 4.2$  Hz, 1 H), 4.13 (dd,  $J = 9.6, 9.6$  Hz, 2 H), 4.32 (m, 2 H, OCH<sub>2</sub>CH<sub>3</sub>), 4.46 (d,  $J = 18.6$  Hz, 1 H), 4.50 (d,  $J = 18.6$  Hz, 1 H), 5.96 (d,  $J = 5.7$  Hz, 1 H), 7.29 (m, 5 H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>):  $\delta = 11.8, 13.9, 17.5, 47.5, 62.6, 63.1$  (q,  $J_{\text{C-F}} = 2.3$  Hz), 73.4, 80.3 (q,  $J_{\text{C-F}} = 32.5$  Hz), 97.3, 122.2 (q,  $J_{\text{C-F}} = 285.4$  Hz), 127.7, 127.8, 128.3, 137.7, 167.5; <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):  $\delta = -72.8$  (s, 3 F); FTIR (neat): 2947, 2869, 1750, 1656, 1466, 1278, 1200, 1091, 1028, 883, 688 cm<sup>-1</sup>; HRMS (ESI-TOF):  $m/z$  [M + Na]<sup>+</sup> calcd for C<sub>24</sub>H<sub>37</sub>F<sub>3</sub>NaO<sub>5</sub>Si: 513.2260; found: 513.2281;  $[\alpha]_D^{25} +30.68$  (c 1.39, CHCl<sub>3</sub>) for 90% ee (*cis/trans* = 97:3); HPLC (column, CHIRALPAK AS-H, Hexane/2-Propanol = 97/3, flow rate 0.6 mL/min, 20 °C, detection, UV 218 nm):  $t_R = 33.6$  (minor isomer), 41.5 (major isomer) min. **Enantioselective [2+2] Cycloaddition Catalyzed by (S)-BINAP-Pd(1b) (Table 2, entry 3); Typical Procedure:** To a solution of PdCl<sub>2</sub>[(S)-BINAP] (8.0 mg, 0.01 mmol) in toluene (1.0 mL) was added AgSbF<sub>6</sub> (7.6 mg, 0.022 mmol) at r.t. under an argon atmosphere. After stirring for 30 min, ethyl trifluoropyruvate **3** (26.5  $\mu$ L, 0.2 mmol) and freshly distilled vinyl acetate **9h** (9.3  $\mu$ L, 0.1 mmol) were added to the mixture at -20 °C. After stirring at -20 °C for 15 h, Et<sub>3</sub>N (50  $\mu$ L) was added and the mixture was directly loaded onto a short silica gel column (hexane-EtOAc, 1:1) to remove the catalyst. The solution was evaporated under reduced pressure. Purification by silica-gel chromatography (hexane-EtOAc, 4:1) gave the corresponding oxetane product **11h** as a clear liquid (88% yield). The diastereomeric ratio was determined by <sup>19</sup>F NMR analysis (dr = 77:23). **Enantioselective [2+2] Cycloaddition Catalyzed by (S)-BINAP-Pd(1b) under Solvent-Free Conditions (Table 2, entry 7):** To a solution of PdCl<sub>2</sub>[(S)-BINAP] (4.0 mg, 0.005 mmol) in ethyl trifluoropyruvate **3** (1.3 mL, 10 mmol) was added silver hexafluoroantimonate (3.8 mg, 0.011 mmol) at r.t. under an argon atmosphere. After stirring for 30 min, freshly distilled vinyl acetate **9h** (461  $\mu$ L, 5 mmol) was added to the mixture at -20 °C. After stirring at -20 °C for 48 h, Et<sub>3</sub>N (50  $\mu$ L) was added and the mixture was directly loaded onto a short silica gel column (hexane-EtOAc, 1:1) to remove the catalyst. The solution was evaporated under reduced pressure. Purification by silica gel chromatography (hexane-EtOAc, 4:1) gave the corresponding oxetane product **11h** as a clear liquid (86% yield). The diastereomeric ratio was determined by <sup>19</sup>F NMR analysis (dr = 92:8). **(2R)-Ethyl 4-Acetoxy-2-(trifluoromethyl)oxetane-2-carboxylate (11h)**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 1.33$  (t,  $J = 7.2$  Hz, 3 H), 2.12 (s, 3 H), 3.04 (ddq,  $J = 13.2, 4.2$  Hz,

$J_{\text{H-F}} = 0.6$  Hz, 1 H), 3.27 (dd,  $J = 13.2, 5.4$  Hz, 1 H), 4.36 (q,  $J = 7.2$  Hz, 2 H), 6.48 (dd,  $J = 5.4, 4.2$  Hz, 1 H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ ):  $\delta = 13.6, 20.5, 33.4, 62.8, 78.1$  (q,  $J_{\text{C-F}} = 34.0$  Hz), 93.4, 122.7 (q,  $J_{\text{C-F}} = 283.1$  Hz), 165.4, 168.8;  $^{19}\text{F}$  NMR (282.4 MHz,  $\text{CDCl}_3$ ):  $\delta = -79.4$  (s, 3 F, major isomer),  $-79.3$  (s, 3 F, minor isomer); FTIR (neat): 2990, 1764, 1447, 1371, 1308, 1219, 1096, 1037, 961,

679  $\text{cm}^{-1}$ ; HRMS (APCI-TOF):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_9\text{H}_{11}\text{F}_3\text{O}_5$ : 257.0637; found: 257.0680;  $[\alpha]_{\text{D}}^{25} +42.97$  (c 1.21,  $\text{CHCl}_3$ ) for 98% ee/94% ee (dr = 85:15); GC (column, CP-Chirasil-Dex CB, i.d. 0.25 mm  $\times$  25 m, CHROMPACK; carrier gas, nitrogen 75 kPa; column temp 85  $^{\circ}\text{C}$ ; injection and detection temp, 115  $^{\circ}\text{C}$ ):  $t_{\text{R}} = 20.0$  (major isomer), 22.0 (minor isomer) min.

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