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# Diastereoselective Synthesis of 6-Trifluoromethyl-5,6-dihydropyrans via Phosphine-Catalyzed [4 + 2] Annulation of α-Benzylallenoates with Ketones

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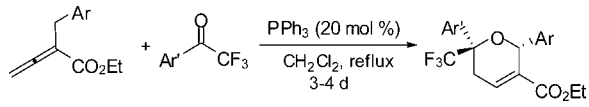
## ABSTRACT




**The highly diastereoselective synthesis of 6-trifluoromethyl-5,6-dihydropyrans was realized by the phosphine-catalyzed [4 + 2] annulation of ethyl α-benzylallenoates and trifluoromethyl ketones.**

Substituted pyrans and dihyropyrans present important structural motifs in a number of biologically active compounds and natural products.[1] Among the many methods developed, the hetero-Diels−Alder (HDA) reaction of a diene or its analogue with carbonyl compound remains one of the most powerful tools for the synthesis of these six-membered heterocycles.[2,3] However, electron-rich dienes are generally required for the HDA reaction, which limit the scope of accessible dihydropyrans. Thus, the construction of dihyropyrans from diene or its analogues with diverse substituents, especially those with electron-withdrawing groups, are still highly desired.

Organophosphorous compounds have been demonstrated successfully as nucleophilic catalysts (Lewis base catalysts) for a wide variety of reactions.[4] In early 1990s, Trost et al. and Lu et al. independently developed a series of reactions of electron deficient alkynes catalyzed by a tertiary phosphine, such as the isomerizations of alkynes to conjugated dienes[5] and the umpolung addition to α- or γ-carbon of allenoates and butynoates.[6]

(1) (a) Elliot, M. C. *J. Chem. Soc. Perkin Trans. 1* **1998**, 4175. (b) Conway, J. C.; Quayle, P.; Regan, A. C.; Urch, C. J. *Tetrahedron* **2005**, *61*, 11910. (c) Liu, R. H.; Zhang, W. D.; Gu, Z. B.; Zhang, C.; Su, J.; Xu, X. K. *Nat. Prod. Res.* **2006**, *20*, 866. (d) Larghi, E. L.; Kaufman, T. S. *Synthesis* **2006**, 187. (e) Shoji, M.; Hayashi, Y. *Eur. J. Org. Chem.* **2007**, 3783. (f) Brioche, J. C. R.; Goodenough, K. M.; Whatrup, D. J.; A. Harrity, J. P. *J. Org. Chem.* **2008**, *73*, 1946.

(2) For reviews, see: (a) Jørgensen, K. A. *Eur. J. Org. Chem.* **2004**, 2093. (b) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558.

(3) For recent examples of the synthesis of pyran derivatives, see: (a) Barroso, S.; Blay, G.; Muñoz, M. C.; Pedro, J. R. *Adv. Synth. Catal.* **2009**, *351*, 107. (b) Zhao, S.-L.; Zheng, C.-W.; Wang, H.-F.; Zhao, G. *Adv. Synth. Catal.* **2009**, *351*, 2811. (c) Avery, T. D.; Caiazza, D.; Culbert, J. A.; Taylor, D. K.; Tiekink, E. R. T. *J. Org. Chem.* **2005**, *70*, 8344. (d) Steinhuebel, D. P.; Fleming, J. J.; Bois, J. D. *Org. Lett.* **2002**, *4*, 293. (e) Usher, L. C.; Estrella-Jimenez, M.; Ghiviriga, I.; Wright, D. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 4560. (f) Sabitha, G.; Reddy, K. B.; Bhikshapathi, M.; Yadav, J. S. *Tetrahedron Lett.* **2006**, *47*, 2807. (g) Franke, P. T.; Richter, B.; Jørgensen, K. A. *Chem.—Eur. J.* **2008**, *14*, 6317. (h) Mao, S.; Probst, D.; Werner, S.; Chen, J.; Xie, X.; Brummond, K. M. *J. Comb. Chem.* **2008**, *10*, 235. (i) Fernández de la Pradilla, R.; Tortosa, M.; Lwoff, N.; del A′guila, M. A.; Viso, A. *J. Org. Chem.* **2008**, *73*, 6716. (j) Sevenard, D. V.; Lork, E. *J. Fluorine Chem.* **2004**, *125*, 125. (k) Gao, X.; Hall, G. D.; Deligny, M.; Favre, A.; Carreaux, F.; Carboni, B. *Chem.—Eur. J.* **2006**, *12*, 3132. (l) Li, P.; Chai, Z.; Zhao, S.-L.; Yang, Y.-Q.; Wang, H.-F.; Zheng, C.-W.; Cai, Y.-P.; Zhao, G.; Zhu, S.-Z. *Chem. Commun.* **2009**, 7369.

(4) (a) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (b) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035. (c) Lu, X.; Du, Y.; Lu, C. *Pure Appl. Chem.* **2005**, *77*, 1985. (d) Nair, V.; Menon, R. S.; Sreekanth, A. R.; Abhilash, N.; Biju, A. T. *Acc. Chem. Res.* **2006**, *39*, 520. (e) Ye, L.-W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140. (f) Cowen, B. J.; Miller, S. J. *Chem. Soc. Rev.* **2009**, *38*, 3102. (g) Marinetti, A.; Voituriez, A. *Synlett* **2010**, 174.

(5) (a) Trost, B. M.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933. (b) Guo, C.; Lu, X. *Chem. Commun.* **1993**, 394. (c) Guo, C.; Lu, X. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1921. (d) Rychnovsky, S. D.; Kim, J. *J. Org. Chem.* **1994**, *59*, 2659.

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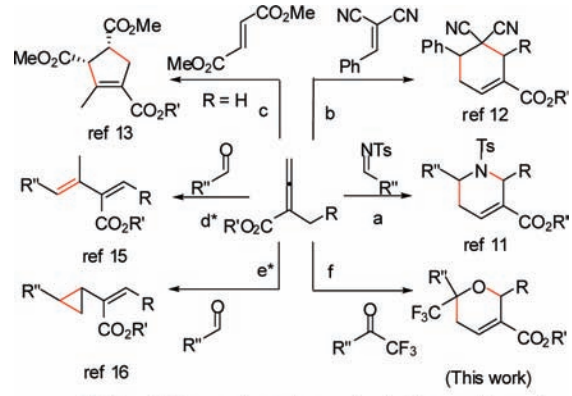
In 1995, Lu et al. published the pioneering triphenylphosphine-catalyzed [3 + 2] annulation of allenoates with electron-deficient olefins for the synthesis of cyclopentenes.[7−9] Soon after, the reaction was successfully expanded to *N*-tosylimines to furnish pyrroline efficiently.[10]

Ten years later, Kwon et al. reported a novel [4 + 2] annulation of α-alkyl allenoates[11] with imines to afford tetrahydropyridines,[12] followed by the reaction of α-alkyl-allenoate with electron-deficient olefins to give cyclohexenes (Scheme 1, reactions a and b).[13] Interestingly, a [3 + 2] annulation was found for the phosphine- and water-cocatalyzed reaction of α-methylallenoates with fumarates by Yu et al. (reaction c).[14] In contrast to imines and olefins, the phosphine-catalyzed reaction of α-alkylallenoate with carbonyl compounds has been hardly reported.[15] During the preparation of this manuscript, Kwon et al. and He et al. independently reported several interesting reaction modes for the phosphine-mediated reaction of α-substituted allenoates with aldehydes to give dienes[16] or cyclopropanes[17] (reactions d and e) instead of [4 + 2] cycloadducts. These reports prompted us to disclose our results of the phosphine-catalyzed [4 + 2] annulation of α-benzyl allenoates with trifluoromethylketones to afford the desired dihydropyrans (reaction f).

**Scheme 1.** Phosphine-Catalyzed/Mediated Reactions of α-Alkylallenoates




* Different $PR_3$ may be used according to the specific reaction

Trifluoromethyl ketones, which are active enough and have wide applications in the synthesis of valuable fluorinated compounds,[18,19] were tested as the potential substrate. To our delight, in the presence of 20 mol % of triphenylphosphine, α-benzyl allenoate (**1a**) and trifluoromethyl(phenyl)ketone (**2a**) could react slowly in refluxing dichloromethane to give the corresponding cycloadduct **3aa** in 72% isolated yield of pure *cis*-isomer with highly diastereoselectivity of the reaction mixture (*cis*/*trans* = 14:1) (Table 1, entry 1).

Solvent screening revealed that dichloromethane is the solvent of choice, while other chlorinated solvents such as chloroform and 1,2-dichloroethane gave decreased yields and diastereoselectivities (entries 1−3). The reaction in toluene or THF went extremely slowly, giving only trace product even after 4 days (entries 4 and 5). Reaction in ethanol or

(6) (a) Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 3167. (b) Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 10819. (c) Trost, B. M.; Dake, G. R. *J. Org. Chem.* **1997**, *62*, 5670. (d) Alvarez-Ibarra, C.; Csákÿ, A. G.; Gómez de la Oliva, C. *Tetrahedron Lett.* **1999**, *40*, 8465. (e) Alvarez-Ibarra, C.; Csákÿ, A. G.; Gómez de la Oliva, C. *J. Org. Chem.* **2000**, *65*, 3544. (f) Zhang, C.; Lu, X. *Synlett* **1995**, 645. (g) Trost, B. M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 7595. (h) Lu, C.; Lu, X. *Org. Lett.* **2002**, *4*, 4677.

(7) (a) Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906. (b) Du, Y.; Lu, X.; Yu, Y. *J. Org. Chem.* **2002**, *67*, 8901. (c) Lu, X.; Lu, Z.; Zhang, X. *Tetrahedron* **2006**, *62*, 457. (d) Lu, Z.; Zheng, S.; Zhang, X.; Lu, X. *Org. Lett.* **2008**, *10*, 3267. (e) Wallace, D. J.; Sidda, R. L.; Reamer, R. A. *J. Org. Chem.* **2007**, *72*, 1051. (f) Sampath, M.; Loh, T.-P. *Chem. Commun.* **2009**, 1568. (g) Henry, C. E.; Kwon, O. *Org. Lett.* **2007**, *9*, 3069. (h) Shu, L.-H.; Sun, W.-Q.; Zhang, D.-W.; Wu, S.-H.; Wu, H.-M.; Xu, J.-F.; Lao, X.-F. *Chem. Commun.* **1997**, 79. (i) O'Donovan, B. F.; Hitchcock, P. B.; Meidine, M. F.; Kroto, H. W.; Taylor, R.; Walton, D. R. M. *Chem. Commun.* **1997**, 81. (j) Dudding, T.; Kwon, O.; Mercier, E. *Org. Lett.* **2006**, *8*, 3643. (k) Xia, Y.; Liang, Y.; Chen, Y.; Wang, M.; Jiao, L.; Huang, F.; Liu, S.; Li, Y.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 3470. (l) Ruano, J. L. G.; Nunez, A., Jr.; Rosario Martin, M.; Fraile, A. *J. Org. Chem.* **2008**, *73*, 9366. (m) Kumar, K.; Kapoor, R.; Kapur, A.; Ishar, M. P. S. *Org. Lett.* **2000**, *2*, 2023. (n) Pham, T. Q.; Pyne, S. G.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **2005**, *70*, 6369.

(8) For the asymmetric Lu reaction, see: (a) Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, X.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836. (b) Wilson, J.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1426. (c) Cowen, B. J.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10988. (d) Voituriez, A.; Panossian, A.; Fleury-Bregeot, N.; Retailleau, P.; Marinetti, A. *J. Am. Chem. Soc.* **2008**, *130*, 14030. (e) Xiao, H.; Chai, Z.; Zheng, C.-W.; Yang, Y.-Q.; Liu, W.; Zhang, J.-K.; Zhao, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 4467.

(9) For the application of the [3 + 2] cycloaddition, see: (a) Wang, J.-C.; Ng, S.-S.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 3682. (b) Wang, J.-C.; Krische, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5855. (c) Du, Y.; Lu, X. *J. Org. Chem.* **2003**, *68*, 6463. (d) Jones, R. A.; Krische, M. *J. Org. Lett.* **2009**, *11*, 1849.

(10) (a) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1997**, *38*, 3461. (b) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031. (c) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1999**, *40*, 549. (d) Zhu, X.-F.; Henry, C. E.; Kwon, O. *Tetrahedron* **2005**, *61*, 6276. For asymmetric reactions, see: (e) Jean, L.; Marinetti, A. *Tetrahedron Lett.* **2006**, *47*, 2141. (f) Scherer, A.; Gladysz, J. A. *Tetrahedron Lett.* **2006**, *47*, 6335. (g) Fleury-Bregeot, N.; Jean, L.; Retailleau, P.; Marinetti, A. *Tetrahedron* **2007**, *63*, 11920. (h) Fang, Y.-Q.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 5660. (i) Pinto, N.; Fleury-Brégeot, N.; Marinetti, A. *Eur. J. Org. Chem.* **2009**, 146.

(11) For selected metal-catalyzed reaction of α-alkylallenoates, see: (a) Gu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6002. (b) Park, C.; Lee, P. A. *Org. Lett.* **2008**, *10*, 3359. (c) Gu, Z.; Ma, S. *Chem.—Eur. J.* **2008**, *14*, 2453. (d) Kitagaki, S.; Teramoto, S.; Mukai, C. *Org. Lett.* **2007**, *9*, 2549. (e) Hayashi, Y.; Miyakoshi, N.; Kitagaki, S.; Mukai, C. *Org. Lett.* **2008**, *10*, 2385. (f) Jiang, X.; Ma, S. *J. Am. Chem. Soc.* **2007**, *129*, 11600. (g) Liu, L. P.; Xu, B.; Mashuta, M. S.; Hammond, G. B. *J. Am. Chem. Soc.* **2008**, *130*, 17642. (h) Maity, P.; Lepore, S. D. *J. Am. Chem. Soc.* **2009**, *131*, 4196.

(12) (a) Zhu, X.-F.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716. (b) Zhao, G.-L.; Shi, M. *Org. Biomol. Chem.* **2005**, *3*, 3686. (c) Tran, Y. S.; Kwon, O. *Org. Lett.* **2005**, *7*, 4289. (d) Castellano, S.; Fiji, H. D. G.; Kinderman, S. S.; Watanabe, M.; Pablo de, Leon; Tamanoi, F.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 5843. For a catalytic asymmetric reaction, see: (e) Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234.

(13) Tran, Y. S.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12632.

(14) Liang, Y.; Liu, S.; Yu, Z.-X. *Synlett* **2009**, 905.

(15) The phosphine-catalyzed [3 + 2] annulation of γ-alkyl allenoates with aldehydes was reported: Xu, S.; Zhou, L.; Ma, R.; Song, H.; He, Z. *Chem.—Eur. J.* **2009**, *15*, 8698.

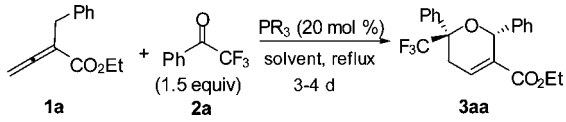
(16) (a) Khong, S. N.; Tran, Y. S.; Kwon, O. *Tetrahedron* **2010**, *66*, 4760. (b) Xu, S.; Zou, W.; Wu, G.; Song, H.; He, Z. *Org. Lett.* **2010**, *12*, 3556.

(17) Xu, S.; Zhou, L.; Ma, R.; Song, H.; He, Z. *Org. Lett.* **2010**, *12*, 544.

(18) For selected synthesis of heterocycles containing a trifluoromethyl group, see: (a) Abid, M.; Torok, B. *Adv. Synth. Catal.* **2005**, *347*, 1797. (b) Zhu, J.; Cheng, Z.; Xie, H.; Li, S.; Wu, Y. *Org. Lett.* **2010**, *12*, 2434. (c) Matoba, K.; Kawai, H.; Furukawa, T.; Kusuda, A.; Tokunaga, E.; Nakaura, S.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 5762.

(19) We recently reported a N-heterocyclic carbene-catalyzed reaction of ketenes with trifluoromethylketones: Wang, X.-N.; Shao, P.-L.; Lv, H.; Ye, S. *Org. Lett.* **2009**, *11*, 544.

**Table 1.** Optimization of Conditions




| entry | $PR_3$ | solvent | additive (20 mol %) | dr[a] | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | $Ph_3P$ | $CH_2Cl_2$ | | 14:1 | 72 |
| 2 | $Ph_3P$ | $CHCl_3$ | | 9:1 | 41 |
| 3 | $Ph_3P$ | DCE | | 7:1 | 45 |
| 4 | $Ph_3P$ | toluene | | ND | trace |
| 5 | $Ph_3P$ | THF | | ND | trace |
| 6 | $Ph_3P$ | EtOH | | 7:1 | 16 |
| 7 | $Ph_3P$ | EtOAc | | 6:1 | 20 |
| 8 | $Ph_3P$ | $CH_2Cl_2$ | $H_2O$ | 11:1 | 58 |
| 9 | $Ph_3P$ | $CH_2Cl_2$ | MeOH | 13:1 | 63 |
| 10 | $Ph_3P$ | $CH_2Cl_2$ | $C_6H_5COOH$ | 17:1 | 59 |
| 11 | $n$-$Bu_3P$ | $CH_2Cl_2$ | | 6:1 | 61 |
| 12 | (*R*)-BINAP | $CH_2Cl_2$ | | ND | trace |
| 13 | (+)-DIOP | $CH_2Cl_2$ | | ND | trace |
| 14[c] | $Ph_3P$ | $CH_2Cl_2$ | | 14:1 | 76 |

[a] Determined by $^1$H NMR (300 MHz) of the reaction mixture. [b] Isolated yield of pure *cis*-isomer. [c] 2.0 equiv of **2a** was utilized. BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene; DIOP = 1,4-bis(diphenylphosphino)-2,3-*O*-isopropylidene-2,3-butanediol. ND = not determined.

ethyl acetate offered cycloadduct in low yield (entries 6 and 7). In view of the possible acceleration effect of trace water in the phosphine-catalyzed reactions,[20] 20 mol % of water, methanol, or benzoic acid was added to the reaction. However, no notable acceleration was observed for these reactions with protonic additives (entris 8−10).

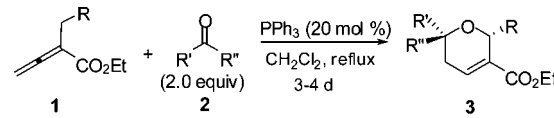
Except for triphenylphosphine, tributylphosphine also worked well for catalyzing the reaction albeit in somewhat low yield (entry 11). Unfortunately, reactions catalyzed by two chiral organophosphines (*R*)- BINAP and (+)-DIOP went extremely slowly and gave only trace cycloadduct after 3 days (entries 12 and 13).

With the optimized reaction conditions in hand, a variety of α-alkyl allenoates and ketones were then examined for the phosphine-catalyzed [4 + 2] annulation (Table 2). It was found that α-benzyl allenoates both with an electron-donating and with an electron-withdrawing substituent (**1b**−**d**, R = 4-$MeC_6H_4$, 4-$MeOC_6H_4$, 4-$BrC_6H_4$) worked well to furnish the corresponding dihydropyrans in good yields with high diastereoselectivities (entries 2−4). α-Benzyl allenoates with a *meta*- or *ortho*-substituent (**1e**−**g**, R = 3-$BrC_6H_4$, 2-$BrC_6H_4$, 2-$MeC_6H_4$) showed comparable results as with a *para*-substituent (entries 5−7). Unfortunately, α-methyl or α-ethoxylcarbonyl allenoate (**1h,i**, R = H, $CO_2Et$) gave no or only trace corresponding [4 + 2] annulation product (entries 8 and 9).

Both the trifluoromethyl(aryl)ketones **2b,c** with an electron-donating substitutent (R′ = 4-$MeC_6H_4$, 4-$MeOC_6H_4$) and

(20) (a) Xia, Y.; Liang, Y.; Chen, Y.; Wang, M.; Jiao, L.; Huang, F.; Liu, S.; Li, Y.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 3470. (b) Liang, Y.; Liu, S.; Xia, Y.; Li, Y.; Yu, Z.-X. *Chem.—Eur. J.* **2008**, *14*, 4316. (c) Mercier, E.; Fonovic, B.; Henry, C.; Kwon, O.; Dudding, T. *Tetrahedron Lett.* **2007**, *48*, 3617.

**Table 2.** Synthesis of Dihydropyrans through $PPh_3$-Catalyzed Annulation of Allenoates and Ketones

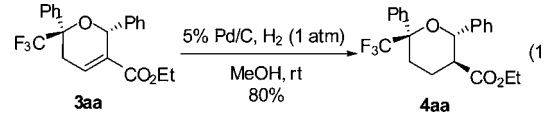



| no. | **1** (R) | **2** (R′, R″) | **3** | dr[a] | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **1a** (Ph) | **2a** (Ph, $CF_3$) | **3aa** | 14:1 | 76 |
| 2 | **1b** (4-$MeC_6H_4$) | **2a** (Ph, $CF_3$) | **3ba** | 15:1 | 75 |
| 3 | **1c** (4-$MeOC_6H_4$) | **2a** (Ph, $CF_3$) | **3ca** | 14:1 | 67 |
| 4 | **1d** (4-$BrC_6H_4$) | **2a** (Ph, $CF_3$) | **3da** | 18:1 | 69 |
| 5 | **1e** (3-$BrC_6H_4$) | **2a** (Ph, $CF_3$) | **3ea** | 13:1 | 65 |
| 6 | **1f** (2-$BrC_6H_4$) | **2a** (Ph, $CF_3$) | **3fa** | 14:1 | 85 |
| 7 | **1g** (2-$MeC_6H_4$) | **2a** (Ph, $CF_3$) | **3ga** | 12:1 | 68 |
| 8 | **1h** (H) | **2a** (Ph, $CF_3$) | **3ha** | | NR |
| 9 | **1i** ($CO_2Et$) | **2a** (Ph, $CF_3$) | **3ia** | | trace |
| 10 | **1a** (Ph) | **2b** (4-$MeC_6H_4$, $CF_3$) | **3ab** | 11:1 | 66 |
| 11 | **1a** (Ph) | **2c** (4-$MeOC_6H_4$, $CF_3$) | **3ac** | 10:1 | 53 |
| 12 | **1a** (Ph) | **2d** (4-$ClC_6H_4$, $CF_3$) | **3ad** | >25:1 | 85 |
| 13 | **1a** (Ph) | **2e** (2-thienyl, $CF_3$) | **3ae** | 13:1 | 58 |
| 14 | **1a** (Ph) | **2f** (Ph, $C_2F_5$) | **3af** | 8:1 | 44 |
| 15 | **1a** (Ph) | **2g** (Ph, $CO_2Me$) | **3ag** | | NR |
| 16 | **1a** (Ph) | **2h** (Ph, CN) | **3ah** | | NR |
| 17 | **1a** | **2i** *N*-methylisatin | **3ai** | | NR |

[a] Determined by $^1$H NMR (300 MHz) of the reaction mixture. [b] Isolated yield of pure *cis*-isomer. NR = No reaction.

ketone **2d** with an electron-withdrawing group (R′ = 4-$ClC_6H_4$) reacted smoothly with allenoate **1a** to furnish the desired dihydropyrans in good yields with high diastereoselectivities (entries 10−12). The ketone **2e** with a heteroaryl group (R′ = 2-thienyl) also worked well (entry 13). Pentafluoroethyl(phenyl)ketone **2f** afforded the corresponding dihydropyran in somewhat low yield with good diastereoselectivity (entry 14). However, no cycloadduct was found for the reaction of methyl 2-oxo-2-phenylacetate (**2 g**), benzoyl cyanide (**2h**), and *N*-methylisatin (**2i**) under current reaction conditions (entries 15−17).

Except for its potential biological activity, the resulted highly functionalized dihydropyrans also provide an opportunity for useful chemical transformations. For example, reduction of the dihydropyran **3aa** with hydrogen to give corresponding tetrahydropyran **4aa** in high yield with exclusive diastereoselectivity (eq 1).[21]




The structure and relative configuration of dihydropyran **3ea** was unambiguously established by the X-ray analysis of its crystal (Figure 1).

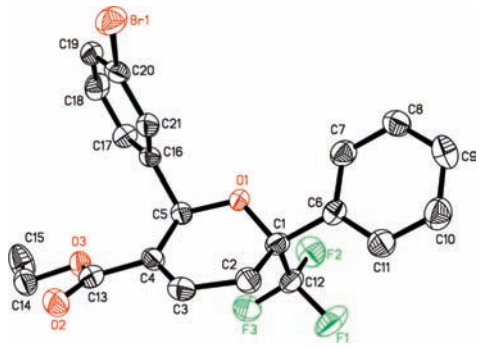



**Figure 1.** X-ray structure of dihydropyran **3ea**.

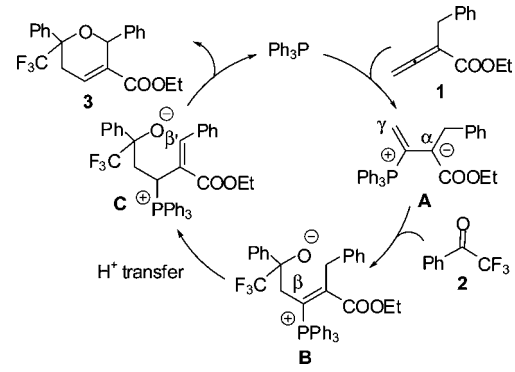



**Figure 2.** Possible catalytic cycle.

This phosphine-catalyzed [4 + 2] annulation of α-benzylallenoates and ketones is expected to go with a similar catalytic cycle as proposed by Kwon et al. (Figure 2).[12a,13] The nucleophilic addition of triphenylphosphine to allene **1** gives an allylic zwitterion **A**. The sterically favored γ-addition of the zwitterion A to ketone **2** leads to α,β-unsaturated ester B, which may equilibrate with α,β′-unsaturated ester C by several proton transfer processes. The intramolecular $S_N'$ substitution in a 6-*endo* cyclization mode furnishs dihydropyran **3** and regenerates the catalyst.

It is worth noting that no olefination or cyclopropanation product is observed in our reaction,[16,17] which is possible due to the thermodynamical and kinetical disfavor of the olefination or cyclopropanation reactions with more sterically demanded ketones instead of aldehydes.

In conclusion, a series of 3-ethoxylcarbonyl-2,6-diaryl-6-trifluoromethyl-5,6-dihydropyrans were synthesized with highly diastereoselectivities through the phosphine-catalyzed [4 + 2] annulation of ethyl α-benzylallenoates and trifluoromethyl ketones. Thus, it demonstrated that, in contrast to the reported olefination and cyclopropanation reactions of α-alkylallenoate with aldehydes, [4 + 2] annulation is also possible for the phosphine-catalyzed reaction of α-alkylallenoates with electron-deficient ketones.

The highly functionalized fluorinated dihydropyrans may find applications in medicinal and synthetic chemistry. The asymmetric [4 + 2] annuations of α-alkylallenoates with ketones and other related reactions are underway in our laboratory.

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**Supporting Information Available:** Experimental procedures, compound characteriations, and crystal structure data of dihydropyran **3ea** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) The relative stereochemistry of **4aa** was assigned by the coupling constants and NOE ananlysis of its NMR spectra.