

Divergent Reactivity in Amine- and Phosphine-Catalyzed C–C Bond-Forming Reactions of Allenates with 2,2,2-Trifluoroacetophenones

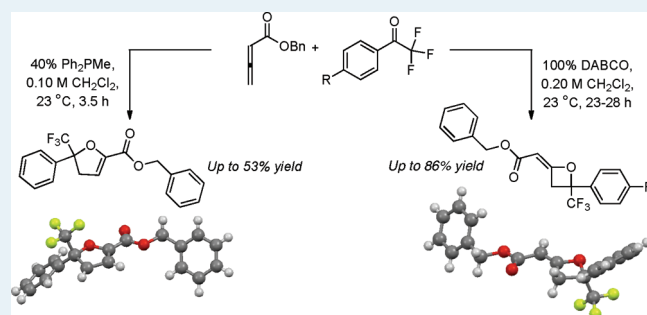
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Supporting Information

ABSTRACT: A divergent reactivity pattern of allenates with 2,2,2-trifluoroacetophenones under Lewis base catalysis is reported. Whereas phosphine catalysis leads to a [3 + 2]-cycloaddition to form dihydrofurans, an alternative pathway was discovered in which 1,4-diazabicyclo-[2.2.2]-octane catalyzes a formal [2 + 2]-cycloaddition to form oxetanes. This unusual mode of reactivity leads to structurally complex products in moderate to excellent yields (32–86%) and adds to the repertoire of Lewis base-catalyzed allenate transformations.

KEYWORDS: allenate, Lewis base catalysis, cycloaddition, oxetane, dihydrofuran



The Lewis base-catalyzed¹ addition of allenic esters (allenates) to electrophiles has been an area of intense research in recent years.^{2–6} The diverse reaction pathways, which depend on the nucleophile, electrophile, and other reaction conditions, can lead to a variety of complex structures and raise intriguing mechanistic possibilities.^{7,8} Moreover, these reactions create possibilities for diversity-oriented synthesis.⁹ In an effort to expand the range of electrophiles with which allenates can react under Lewis base catalysis, we turned our attention to new C–C bond-forming reactions of allenates with 2,2,2-trifluoroacetophenones. We chose to examine the 2,2,2-trifluoromethyl ketones, in part, due to their heightened reactivity in carbonyl additions. However, it is also worth noting that this functional group is often one of interest in the context of the preparation of druglike substances.¹⁰ We found that methyldiphenylphosphine catalyzes a [3 + 2]-cycloaddition of allenate **1a** with 2,2,2-trifluoroacetophenone **2a** to give dihydrofuran **3** in good yield (Scheme 1).¹¹ The structure of **3** was confirmed by X-ray crystallography (Figure 1a). This study is among the first reports of a Lewis base-catalyzed addition of an α -unsubstituted allenate to a ketone.^{12,13}

In the process of screening various Lewis bases for their ability to catalyze this reaction, we found that amines (specifically, 1,4-diazabicyclo-[2.2.2]-octane (DABCO)) catalyze a mechanistically divergent pathway, leading to unique products.¹⁴ Rather than forming **3**, DABCO leads to the formation of a formal [2 + 2]-cycloaddition product **4a**.^{15,16} The structure of oxetane **4a**, including the assignment of the olefin as the *E* isomer, was unambiguously determined by X-ray crystallography (Figure 1b).

The initial DABCO-catalyzed reaction conditions gave 47% yield of **4a** and 12% yield of the *Z*-olefin isomer **5a** (Table 1, entry 1). A solvent screen showed that dichloromethane was ideal,

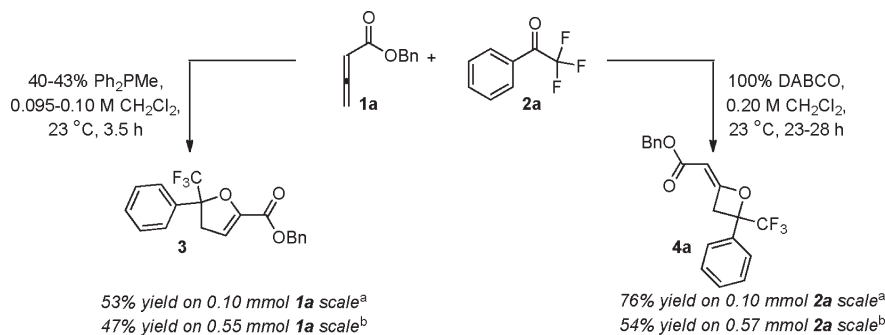
providing 55% conversion to **4a** and only 4% conversion to **5a** (entry 2). More polar solvents led to similar or reduced yields (entries 3–4). Increasing the concentration of the reaction was beneficial, giving 63% conversion to **4a** (entry 5). Although it is clear that the reaction proceeds with catalytic turnover, increasing the amount of DABCO to 100 mol % led to improved results, providing **4a** in 83% conversion and 76% isolated yield without any formation of isomer **5a** (entry 8).

The optimized reaction conditions were applied to a variety of electronically disparate 2,2,2-trifluoroacetophenones to provide products **4** in moderate to high yields (Table 2). In each case, the illustrated olefin geometry is assigned by analogy to compound **4a**. We found the ¹H NMR data to be quite consistent throughout the series.¹⁷ The unsubstituted ketone **2a** produces oxetane **4a** in 76% isolated yield on small scale (entry 1a), and on larger scale, a good yield is still obtained (54% yield, entry 1b).¹⁸ Electron-withdrawing groups on the trifluoroacetophenone aryl ring, including *p*-F and *p*-Br (**2b** and **2c**), afford oxetanes **4b** and **4c** in good to excellent yields (68% and 86% isolated yield, respectively, entry 2a and 3a). High yields are still obtained with these ketones on larger scale (62% and 55% yield, entries 2b and 3b). The reaction tolerates ketones with electron-donating groups on the aryl ring, *p*-OMe and *p*-*t*-Bu (**2d** and **2e**), although the oxetanes (**4d** and **4e**) are delivered in reduced yields as compared with the previous examples (32% and 40% yield, respectively, entries 4a and 5a). These yields are consistent on larger scale reactions (30% and 41% yield, entry 4b and 5b).

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Scheme 1. Divergent Reactivity of Allenic Ester **1a** with 2,2,2-Trifluoroacetophenone **2a** under Amine vs. Phosphine Catalysis

^a Average isolated yield of two runs. See the Supporting Information for more details. ^b Isolated yield of one run.

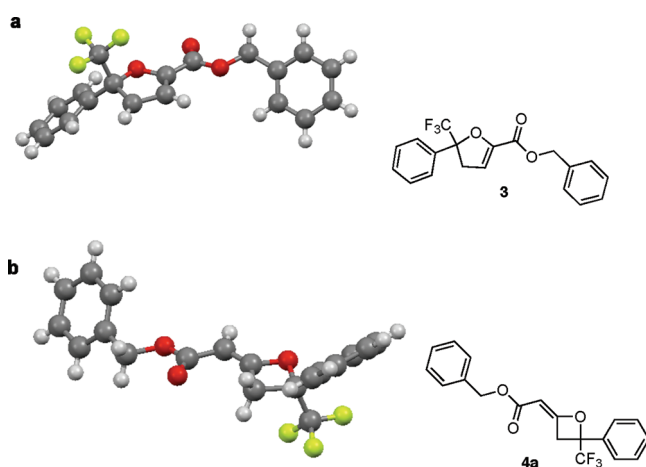
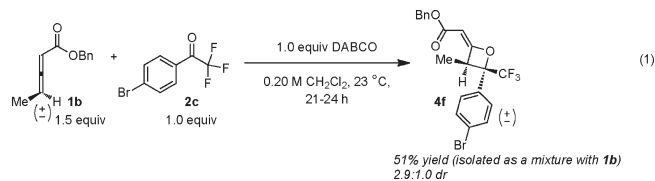


Figure 1. (a) X-ray crystal structure of product **3**. (b) X-ray crystal structure of product **4a**.

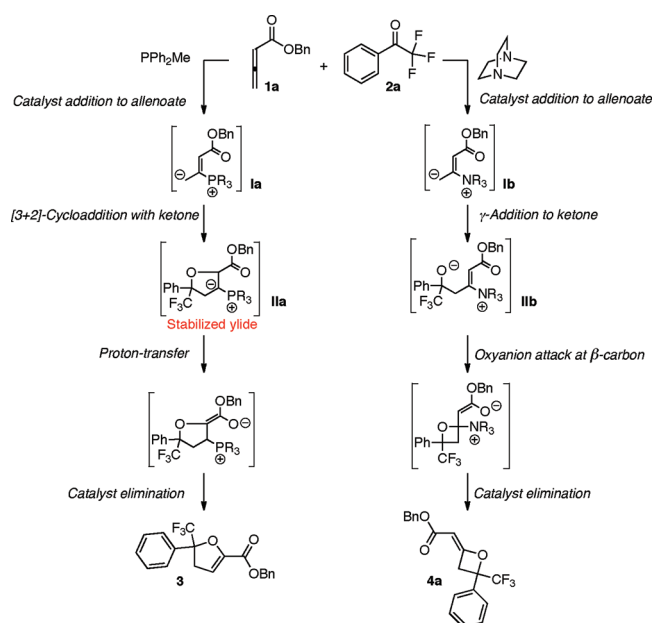
Interestingly, ketones that do not possess a trifluoromethyl group, including benzophenone, 4,4'-dichlorobenzophenone, and 4'-nitroacetophenone, are completely unreactive under analogous reaction conditions (not shown).

To our delight, we found that the same reaction conditions can also be applied to allenic esters that are substituted at the γ -position to lead to highly substituted oxetane products that are previously unreported. Indeed, a racemic mixture of methyl- γ -substituted allenic ester **1b** reacts with 4'-bromo-2,2,2-trifluoroacetophenone **2c** to afford oxetane **4f** in 51% yield with a 2.9:1.0 diastereomeric ratio (dr) (eq 1).¹⁹ Our tentative assignment of the major diastereomer, based on ¹H NMR chemical shifts, has the γ -methyl group *cis* to the trifluoromethyl group.²⁰ In addition, the olefin geometry is assigned analogous to that of **4a** because of the similarities in the ¹H NMR chemical shifts.²¹ The successful production of **4f** suggests that highly substituted oxetane products can be made by this method, and the exploration of these reactions is now a frontier in our laboratory.



The divergent reactivity in the amine- versus the phosphine-catalyzed reactions of allenic esters with 2,2,2-trifluoroacetophenones

Scheme 2. Proposed Mechanisms for the Phosphine- and Amine-Catalyzed Reactions



can be rationalized by analysis of the relevant reaction mechanisms (Scheme 2). Both catalytic cycles involve initial attack of the nucleophilic catalyst on the electrophilic β -carbon of allenic ester **1a** to form zwitterionic intermediate **Ia** or **Ib**. In the phosphine-catalyzed reaction, this is followed by a [3 + 2]-cycloaddition with ketone **2a** to form stabilized ylide intermediate **IIa**, which can subsequently undergo proton transfer and catalyst elimination to give the dihydrofuran product **3**.^{22–25} Conversely, the amine catalyst is less well-suited to stabilize an analogous ylide intermediate.²⁶ Therefore, γ -addition of intermediate **Ib** to ketone **2a** gives intermediate **IIB**, which is followed by oxyanion attack at the allenate β -carbon and catalyst elimination to give oxetane **4a**. Although this mechanistic hypothesis remains to be verified, it accounts for the conditionally dependent reactivity of **1a** and **2a** in the presence of different nucleophilic catalysts.

In conclusion, we have developed two sets of conditions for C–C bond-forming reactions of allenic ester **1a** with 2,2,2-trifluoroacetophenones **2** to afford either dihydrofurans **3** or oxetanes **4**, depending on the nature of the nucleophilic catalyst. The reactions are specific for trifluoromethyl-substituted ketones

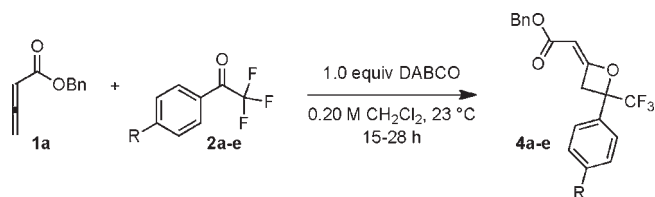
Table 1. Optimization of Reaction Conditions for the Formation of Oxetane 4a



entry	equiv 1a	equiv 2a	mol % DABCO	solvent (conc)	yield (y) or conversion (c) to 4a (%) ^a	yield (y) or conversion (c) to 5a (%) ^a
1	1.5	1.0	20	toluene (0.10 M)	47 (y)	12 (y)
2	1.5	1.0	20	CH ₂ Cl ₂ (0.10 M)	55 (c)	4 (c)
3	1.5	1.0	20	THF (0.10 M)	50 (y)	11 (y)
4	1.5	1.0	20	CH ₃ CN (0.10 M)	13 (c)	0
5	1.5	1.0	20	CH ₂ Cl ₂ (0.20 M)	63 (c)	3 (c)
6	1.0	1.3	20	CH ₂ Cl ₂ (0.20 M)	33 (c)	trace
7	1.5	1.0	50	CH ₂ Cl ₂ (0.20 M)	76 (c)	0
8	1.5	1.0	100	CH ₂ Cl ₂ (0.20 M)	83 (c), 76 (y)	0

^a Isolated yield obtained by flash column chromatography. Conversion measured by ¹H NMR integration as compared with 2,3-dimethylnaphthalene as an internal standard.

Table 2. Substrate Scope for DABCO-Catalyzed Coupling of Benzyl Allenolate 1a to 2,2,2-Trifluoroacetophenones 2



entry ^a	R	ketone	product	yield (%) ^b
1a	H	2a	4a	76
b				54 ^c
2a	F	2b	4b	68
b				62
3a	Br	2c	4c	86
b				55 ^d
4a	OMe	2d	4d	32
b				30
5a	<i>t</i> -Bu	2e	4e	40 ^c
b				41 ^c

^a All reactions were run with 1.5 equiv of allenic ester 1a and 1.0 equiv of ketone 2 unless otherwise indicated. ^b Isolated yield obtained by flash column chromatography. Yield of entry a is on 0.10 mmol scale in ketone 2 and is the average of two runs. Yield of entry b is on 100 mg scale of ketone 2 and is the yield of one run. ^c 1.25 equiv of allenic ester 1a used. ^d Isolated as a mixture of 4c/1a; see the Supporting Information section for more details.

but are tolerant of various substitution on the aryl ring, although yields are highest with electron-neutral or electron-poor substituents. In addition, the reaction was extended to include γ -substituted allenates, which produce highly substituted oxetane core structures.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, analytical and spectral characterization data, crystallographic

information files. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (12) During the preparation of this manuscript, an analogous reaction with PPh₃ as the catalyst was reported; see: Wang, T.; Ye, S. *Org. Biomol. Chem.* **2011**, *9*, 5260–5265.
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(17) Please see the Supporting Information for more details.

(18) The larger-scale yields may be somewhat lower than the small-scale yields for a variety of reasons, including insufficient mixing of the heterogeneous reaction and partial product decomposition due to the necessity of an aqueous workup prior to flash column chromatography.

(19) Because the **4f** diastereomers proved difficult to separate from each other and from compounds derived from the allenic starting material **1b** by conventional methods, we analyzed the reaction outcome from the mixture. Yield and dr calculations were based on relative ¹H NMR integrations. See the Supporting Information for more details.

(20) The assignment of the major diastereomer was rationalized by the fact that the ¹H NMR chemical shift of the methyl group protons was significantly more downfield in the major diastereomer than in the minor diastereomer. We propose that the downfield shift in the major diastereomer results from deshielding from the trifluoromethyl group, whereas the upfield shift in the minor diastereomer results from shielding from the phenyl ring. ¹H NMR nOe experiments did not rule out either diastereomer as the major one, and therefore, the assignment was based on chemical shift data. See the Supporting Information for more information.

(21) The olefin geometry was rationalized by the fact that the ¹H NMR chemical shifts, particularly that of the vinyl proton, were analogous to those of product **4a**. See the Supporting Information for more information.

(22) This mechanism was also suggested in: Wang, T.; Ye, S. *Org. Biomol. Chem.* **2011**, *9*, 5260–5265.

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