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Synergistic Lewis base and anion-binding catalysis for the enantioselective vinylogous addition of deconjugated butenolides to allenoates†

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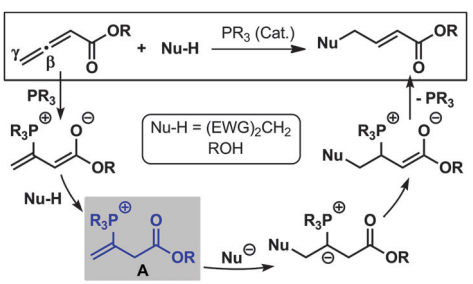
An enantioselective vinylogous umpolung addition of deconjugated butenolides to allenoates has been developed for the first time with the help of synergistic combination of an achiral phosphine and a chiral squaramide, and represents the first example of a catalytic enantioselective Cγ–Cγ bond formation between two different carbonyl partners.

Regioselective functionalization of carbonyl compounds occupies the centre stage in organic synthesis. In 1995, Lu reported a phosphine catalyzed umpolung addition of nucleophiles to the relatively electron rich β,γ-double bond of allenoates (Scheme 1).[1] This reaction along with the related additions to alkynoates, pioneered by Trost,[2] has been recognized among the few general methods available for the installation of substituents at the γ-position of the carbonyl compounds.[3] As a result, much attention has been paid to the development of catalytic asymmetric variants of these reactions. Initial breakthrough by Zhang[4] followed by a series of reports from Fu[5] established chiral phosphines as efficient catalysts for enantioselective γ-addition of an array of carbon, nitrogen and sulphur nucleophiles to various allene derivatives (Scheme 2A).



Scheme 1 Umpolung addition to allenoates and the plausible mechanism.

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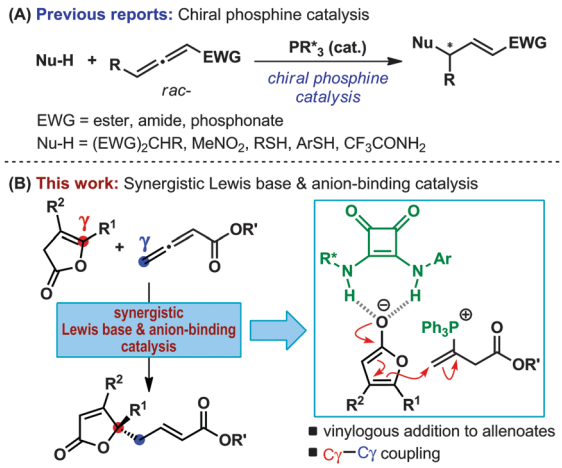
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data for all relevant compounds together with HPLC traces of all the products. See DOI: 10.1039/c3cc46858e



Scheme 2 Asymmetric umpolung addition to allene derivatives.

For the reactions proceeding *via* cationic intermediates, counteranion-directed catalysis and anion-binding catalysis have recently emerged as powerful modes of asymmetric induction.[6] In this context the use of chiral (thio)ureas proved particularly effective due to their anion-binding ability by means of dual hydrogen bonding.[7] Based on this strategy, a wide variety of asymmetric transformations have been accomplished, primarily due to the work by Jacobsen and Seidel.[8]

Considering the cationic nature of the key intermediate (**A** in Scheme 1) in the umpolung addition to allenoates and its potential ion-pairing with the active (anionic) nucleophile, we envisioned an enantioselective version of this reaction with the help of anion-binding catalysis. We reasoned that an achiral phosphine and a chiral hydrogen bond donor could act in a synergistic fashion to induce asymmetry in the transition state (Scheme 2B).[9] Along the line of our interest in vinylogous reactivity,[10] we decided to study vinylogous nucleophilic addition to allenoate under synergistic Lewis base and anion-binding catalysis. To the best of our knowledge, there is no report on the addition of vinylogous nucleophiles to alleonates, let alone an asymmetric version. The choice of deconjugated butenolides as the nucleophiles is inspired by the prevalence of the γ-butenolide moiety in various bioactive targets.[11]

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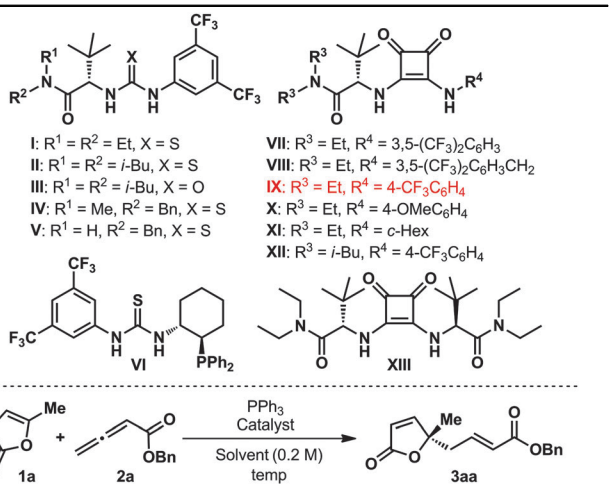
In this communication, we would like to report the first enantioselective vinylogous addition to allenoates. In view of the importance of intermolecular heterocoupling of carbonyl compounds, our protocol represents the first example of a catalytic enantioselective Cγ–Cγ coupling between two different carbonyl partners (Scheme 2B).

At the early stages of our studies, we investigated the dual influence of PPh_3 and various chiral H-bond donors, including some of the well-known (thio)urea derivatives, on the direct vinylogous addition of deconjugated butenolides to allenoates.[12] α-Angelica lactone **1a** and benzyl allenoate **2a** were chosen as the model substrates for the optimization of the catalyst and the reaction conditions (Table 1). As expected, the reaction was found to proceed with only 5 mol% PPh_3 alone and complete consumption of **1a** was observed within 8 h at rt (25 °C), even though the yield of the desired γ-addition product **3aa** remained low at 20% (entry 1). We were delighted to find that addition of 7 mol% of the L-*tert*-leucine derived thiourea **I** led to a significantly cleaner reaction and **3aa** was formed as the sole product (entry 2). Despite a slower reaction rate and low enantioselectivity (65 : 35 er), this experiment clearly validated our hypothesis of a cooperative involvement of both PPh_3 and thiourea. The use of 10 mol% of PPh_3 and 12 mol% of **I** helped to curtail the reaction time and at the same time marginally improved the enantioselectivity (entry 3). Other (thio)urea derivatives with different substituents on the amide nitrogen (**II–V**) failed to improve the enantioselectivity (entries 4–7). A bifunctional phosphino thiourea **VI**, developed by Jacobsen for a [3+2] cycloaddition,[13] was also tested and appeared to be catalytically inactive for our reaction (entry 8). After such disappointing results with (thio)ureas, we turned our attention to squaramide derivatives. Regardless of their overwhelming success as bifunctional catalysts,[14] squaramides found little use as monofunctional catalysts, particularly in asymmetric catalysis. However, for the present study, squaramides proved to be very effective both in terms of their catalytic activity and enantioselectivity. For example, squaramide **VII** catalyzed the complete conversion of **1a** within 1.5 h and the adduct **3aa** was obtained with considerably improved enantioselectivity (entry 9; *cf.* **I**, entry 3). At this stage a quick solvent and temperature optimization revealed the reaction in toluene at 10 °C to be the optimum (entry 13). Various other squaramide derivatives (**VIII–XIII**), including the C_2-symmetric squaramide **XIII**, were tested under these optimized reaction conditions (entries 15–20) and **IX** emerged as the best (entry 16). Better enantioselectivities were obtained by using mesitylene as the solvent (entries 21–24). However, a drastic drop in the reaction rate was encountered when the reaction was conducted at 10 °C (entry 22), primarily due to the oxidation of PPh_3. Phenols are often used as antioxidants for various purposes. Furthermore, a catalytic amount of acid additives is known to play important roles in phosphine catalyzed reactions of allenoates. Consequently, a wide range of protic additives (10 mol%) were tested[12] and in the presence of 2,6-di-*tert*-butylphenol (2,6-DTBP) the reaction rate was substantially enhanced, without compromising the enantioselectivity (entry 23). Enantioselectivity was improved to 91 : 9 er by conducting the reaction at −10 °C, but a second batch of PPh_3 is required for complete conversion of **1a** (entry 24). Attempts to ameliorate the enantioselectivity further by employing other phosphines proved futile.[12]

To demonstrate the usefulness of this protocol, we went ahead to investigate the generality of this reaction. The optimized reaction conditions (Table 1, entry 24) appeared to be appropriate for various deconjugated butenolide derivatives as well as allenoates (Table 2). Butenolides containing a wide range of γ-substituents including long chain alkyl (entries 4–6), branched alkyl (entry 7), benzyl (entry 8), homobenzyl (entry 9) and bishomobenzyl (entry 10) could be used as the pronucleophiles and the products were obtained in high yield with good to high enantioselectivity. γ-Phenyl substituted butenolide (**1k**) was found to be less reactive and a product was obtained with considerably lower er (entry 11). Different ester substituents on allenoates were tolerated and the products were obtained with a similar level of enantioselectivity (entries 12–15).

Table 1 Catalyst and reaction conditions optimization for the enantioselective direct vinylogous addition of α-Angelica lactone **1a** to benzyl allenoate **2a**[a]



Entry	Catalyst (mol%)	PPh_3 (mol%)	Solvent	T/°C (t/h)	Conv.[b] (%)	er[c]
1	—	5	Toluene	25 (8)	>90	—
2	**I** (7)	5	Toluene	25 (40)	>95	65 : 35
3	**I** (12)	10	Toluene	25 (10)	>95	67.5 : 32.5
4	**II** (12)	10	Toluene	25 (7)	>95	64 : 36
5	**III** (12)	10	Toluene	25 (7)	>95	59 : 41
6	**IV** (12)	10	Toluene	25 (12)	>95	62 : 38
7	**V** (12)	10	Toluene	25 (72)	>95	50 : 50
8	**VI** (7)	—	Toluene	25 (48)	<5	—
9	**VII** (12)	10	Toluene	25 (1.5)	>95	78.5 : 21.5
10	**VII** (12)	10	$PhCF_3$	25 (12)	>95	71 : 29
11	**VII** (12)	10	PhCl	25 (12)	>95	73 : 27
12	**VII** (12)	10	C_6H_6	25 (12)	>95	76.5 : 23.5
13	**VII** (12)	10	Toluene	10 (12)	>95	80 : 20
14	**VII** (12)	10	Toluene	0 (16)	>95	76.5 : 23.5
15	**VIII** (12)	10	Toluene	10 (16)	>95	80.5 : 19.5
16	**IX** (12)	10	Toluene	10 (9)	>95	84 : 16
17	**X** (12)	10	Toluene	10 (34)	50	84 : 16
18	**XI** (12)	10	Toluene	10 (10)	>95	73.5 : 26.5
19	**XII** (12)	10	Toluene	10 (34)	50	80.5 : 19.5
20	**XIII** (12)	10	Toluene	10 (5)	>95	72.5 : 27.5
21	**IX** (12)	10	Mesitylene	25 (6)	>95	85.5 : 14.5
22	**IX** (12)	10	Mesitylene	10 (48)	50	88.5 : 11.5
23[d]	**IX** (12)	10	Mesitylene	10 (10)	>95	88.5 : 11.5
24[d]	**IX** (12)	20[e]	Mesitylene	−10 (72)	>95	91 : 9

[a] Reaction conditions: 1.0 equiv. of **1a** and 1.5 equiv. of **2a**. [b] Conversion of **1a** determined by ^{1}H-NMR analysis of the crude reaction mixture. [c] Determined by HPLC analysis (see ESI). [d] Reaction in the presence of 10 mol% of 2,6-di-*tert*-butylphenol. [e] A second batch (10 mol%) of PPh_3 was added after 24 h.

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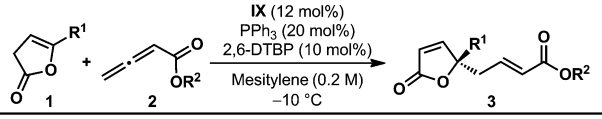
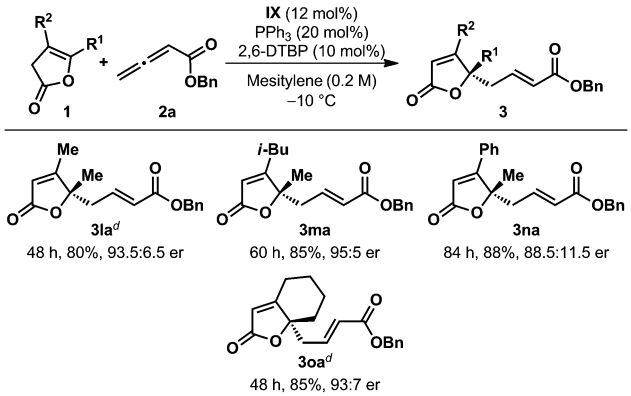
Table 2 Substrate scope for the catalytic enantioselective direct vinylogous addition of butenolides to allenoates[a]



Entry	R^1	R^2	t/h	3	Yield[b] (%)	er[c]
1	Me (**1a**)	Bn (**2a**)	72	**3aa**	68	91 : 9
2	Et (**1b**)	Bn (**2a**)	84	**3ba**	77	90 : 10
3	*n*-Pr (**1c**)	Bn (**2a**)	84	**3ca**	75	90 : 10
4	*n*-Pent (**1d**)	Bn (**2a**)	84	**3da**	75	89 : 11
5	*n*-C_8H_{17} (**1e**)	Bn (**2a**)	84	**3ea**	67	92 : 8
6	*n*-$C_{12}H_{25}$ (**1f**)	Bn (**2a**)	64	**3fa**	95	91.5 : 8.5
7	i-Bu (**1g**)	Bn (**2a**)	98	**3ga**	81	90 : 10
8	Bn (**1h**)	Bn (**2a**)	60	**3ha**	84	82 : 18
9	CH_2Bn (**1i**)	Bn (**2a**)	84	**3ia**	70	86.5 : 13.5
10	CH_2CH_2Bn (**1j**)	Bn (**2a**)	48	**3ja**	93	90 : 10
11[d]	Ph (**1k**)	Bn (**2a**)	48	**3ka**	45	61 : 39
12	*n*-C_8H_{17} (**1e**)	Me (**2b**)	60	**3eb**	72	91 : 9
13	*n*-C_8H_{17} (**1e**)	Et (**2c**)	84	**3ec**	69	91 : 9
14	Me (**1a**)	Et (**2c**)	84	**3ac**	62	91 : 9
15[e]	*n*-C_8H_{17} (**1e**)	i-Bu (**2d**)	108	**3ed**	61	93 : 7

[a] Reaction conditions: 1.0 equiv. of **1**, 1.5 equiv. of **2**, 10 mol% PPh_3 and 12 mol% **IX**. A second portion of PPh_3 (10 mol%) was added after consumption of the first batch, typically after 24 h. [b] Isolated yield after column chromatography. [c] Determined by HPLC analysis (see ESI). [d] Reaction at 10 °C. [e] The reaction was conducted with an additional batch (10 mol%) of PPh_3.

Table 3 Substrate scope with respect to β,γ-disubstituted butenolides[a,b,c]



[a] Reaction conditions: 1.0 equiv. of **1**, 1.5 equiv. of **2**, 10 mol% PPh_3 and 12 mol% **IX**. A second portion of PPh_3 (10 mol%) was added after consumption of the first batch, typically after 24 h. [b] Isolated yield after column chromatography. [c] Determined by HPLC analysis (see ESI). [d] The second portion of PPh_3 was not required.

The current protocol is equally applicable for β,γ-disubstituted butenolides as shown in Table 3. In some of these cases, products were obtained with a somewhat higher level of enantioselectivity in uniformly high yield. The absolute configuration of **3ac** was determined to be (*S*) by its one-step conversion to the known natural product (*S*)-(+)-4-methylmuconolactone (see ESI†). The absolute configurations of the other adducts were assigned as the same by analogy. It must be emphasized that for all the examples shown in Tables 2 and 3, the reactions are completely *E*-selective and no trace *Z*-product was detected in any of the reaction.

In summary, we have developed a catalytic enantioselective vinylogous umpolung addition of deconjugated butenolides to allenoates. This work, for the first time, demonstrates that an achiral phosphine and a chiral squaramide can be combined in a synergistic fashion to catalyze an enantioselective transformation. Our protocol also represents the first example of a catalytic enantioselective Cγ–Cγ bond formation between two different carbonyl partners. The search for better catalysts with the objective of improving enantioselectivity is currently underway in our laboratory and will be reported in due course.

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