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Ruthenium(II)-Catalyzed C-H Allenylation-Based Approach to Allenoic Acids

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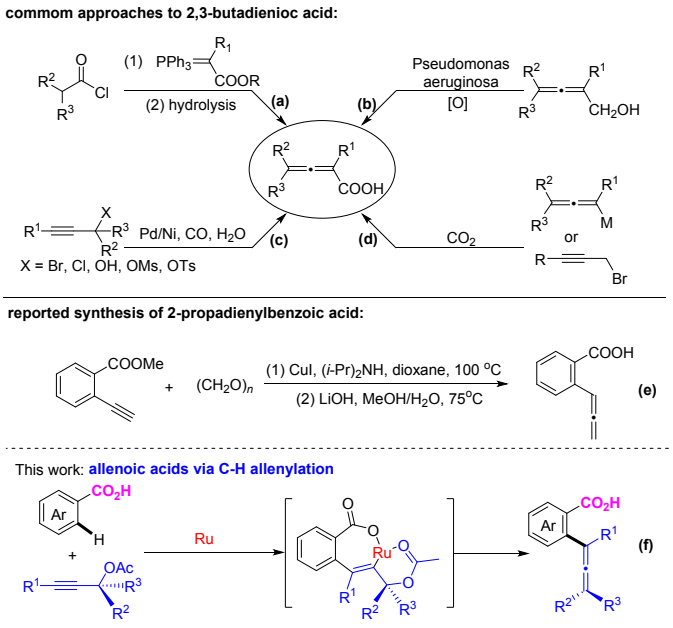
A Ru(II)-catalyzed direct access to various functionalized allenoic acids via C-H allenylation of readily available aryl carboxylic acid with propargylic acetates is reported. Axially chiral allenoic acids could be obtained in high ee by using optically active propargylic acetates through chirality transfer strategy.

Allene moieties are not only present in natural products but also precious building blocks due to their unique structures and multiple reactive sites.[1] Allene chemistry has experienced an explosion during the last decades.[2] Thus, the synthesis of functionalized allenes is of crucial importance. Of particular interest is the synthesis of synthetically versatile allenoic acids.[3] Common approach to 2,3-allenoic acids is the hydrolysis of 2,3-allenoates, which suffers from poor step-economy, and an issue of selectivity forming allenoic acids and 3-alkynoic acids (Scheme 1a).[4] The only example of the oxidation of allenols is realized through microbial transformations (scheme 1b).[5] Pd- or Ni- catalyzed carboxylation of propargylic compounds with CO in the presence of water (Scheme 1c),[6] and the carboxylation of 2-alkynyl bromides or allenylmetallic reagents with CO_2 (scheme 1d)[7] have also been reported. Crabbé homologation of *o*-methoxycarbonylphenylacetylene with paraformaldehyde provides a synthesis of methyl 2-propadienylbenzoate, which would undergo hydrolysis to afford the corresponding allenoic acid. (scheme 1e).[8] The limitations are harsh condition, the use of toxic carbon monoxide or stoichiometric amount of reductants and limited substrates. On the other hand, C-H activation has been proven to be a powerful tool in synthetic chemistry because of the atom- and step-economy.[9] The synthesis of allenes based on C-H activation is undoubtedly an ideal strategy.[10] We reasoned that the most straightforward approach for the allenoic acids would be the use of benzoic acids with the carboxylic acid acting as an inherent directing group.[11] Herein, we wish to report the realization of Ru-catalyzed synthesis of allenoic acids via direct C-H allenylation of benzoic acids (Scheme 1f).



Scheme 1. Approaches to allenoic acids.

Our initial attempt began with the benzoic acid **1a** and propargylic acetate **2a** in the presence of $[Ru(p\text{-cymene})Cl_2]_2$ and NaOAc at 50 °C using toluene as solvent. To our delight, the monoallenylation product **3aa** was generated in 7% yield together with 67% recovery of **2a** (Table 1, entry 1). We then investigated the solvent effect (Table 1, entries 2-7). The reaction could proceed in dioxane, DCE, CH_3CN, THF, even in water, albeit affording monoallenylation product **3aa** and double allenylation product **4aa** in rather low yields (Table 1, entries 2-6). To our surprise, the yield could be greatly improved when the reaction was conducted in MeOH: 36% yield of monoallenylation product **3aa** and 16% yield of double allenylation product **4aa** were obtained (Table 1, entry 7). We

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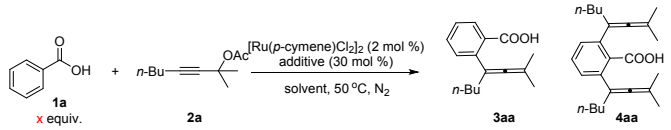
next examined a series of additives as shown in entries 8-13: when K_2CO_3 was employed, the reaction gave 64% combined yield of **3aa** and **4aa** (Table 1, entry 13). The reaction in EtOH under optimal conditions led to increased combined yield but a lower selectivity of **3aa**/**4aa** (Table 1, entries 13-14). When 2.6 equiv of benzoic acid were used, the yield is the highest with a selectivity of 58/14 (Table 1, entries 15-18). When the reaction was conducted in air, the influence is negligible (Table 1, entry 19).

Table 1. Optimization of the *ortho*-allenylation of benzoic acid **1a**.[a]

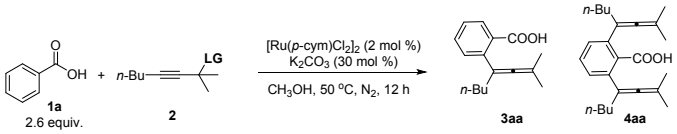


entry	x	solvent	additive	Time (h)	combined yield (**3aa**/**4aa**) (%)[b]	recovery of **2a** (%)[b]
1	1.5	Toluene	NaOAc	46	7 (7/0)	67
2	1.5	Dioxane	NaOAc	46	15 (12/3)	20
3	1.5	DCE	NaOAc	46	14 (14/0)	24
4	1.5	CH_3CN	NaOAc	46	27 (23/4)	26
5	1.5	THF	NaOAc	46	30 (23/7)	6
6	1.5	H_2O	NaOAc	46	19 (12/7)	23
7	1.5	MeOH	NaOAc	46	52 (36/16)	13
8	1.5	MeOH	NaOAc	12	57 (39/18)	29
9	1.5	MeOH	K_3PO_4	12	41 (30/11)	7
10	1.5	MeOH	*t*-BuONa	12	22 (18/4)	21
11	1.5	MeOH	Na_2CO_3	12	57 (40/17)	18
12	1.5	MeOH	Cs_2CO_3	12	60 (42/18)	20
13	1.5	MeOH	K_2CO_3	12	64 (45/19)	27
14	1.5	EtOH	K_2CO_3	12	69 (36/33)	9
15	2.0	MeOH	K_2CO_3	12	66 (48/18)	16
16	2.4	MeOH	K_2CO_3	12	63 (50/13)	16
17	2.6	MeOH	K_2CO_3	12	72 (58/14)	20
18	3.0	MeOH	K_2CO_3	12	61 (52/9)	21
19[c]	2.6	MeOH	K_2CO_3	12	69 (56/11)	18

[a] The reaction was conducted with **1a**, **2a** (0.2 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (0.004 mmol), and additive (0.06 mmol) in solvent (0.5 mL) under 50 °C. [b] Determined by ^1H NMR analysis using CH_2Br_2 as the internal standard. [c] in air.

We further investigated the leaving group (LG) effect by performing the reaction of benzoic acid **1a** with several propargylic alcohol derivatives and found that OAc was still the best leaving group (Table 2).

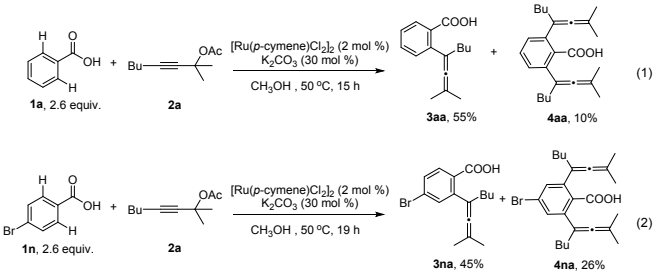
Table 2. Effect of the Leaving Groups



entry	LG	combined yield (**3aa**/**4aa**) (%)[a]	recovery of **2a** (%)[a]
1	OMe (**2a$_1$**)	0 (-/-)	59
2	OCO_2Me (**2a$_2$**)	54 (40/14)	9
3	OCOEt (**2a$_3$**)	57 (47/10)	20
4	OBoc (**2a$_4$**)	61 (47/14)	21
5	OAc (**2a**)	72 (58/14)	20

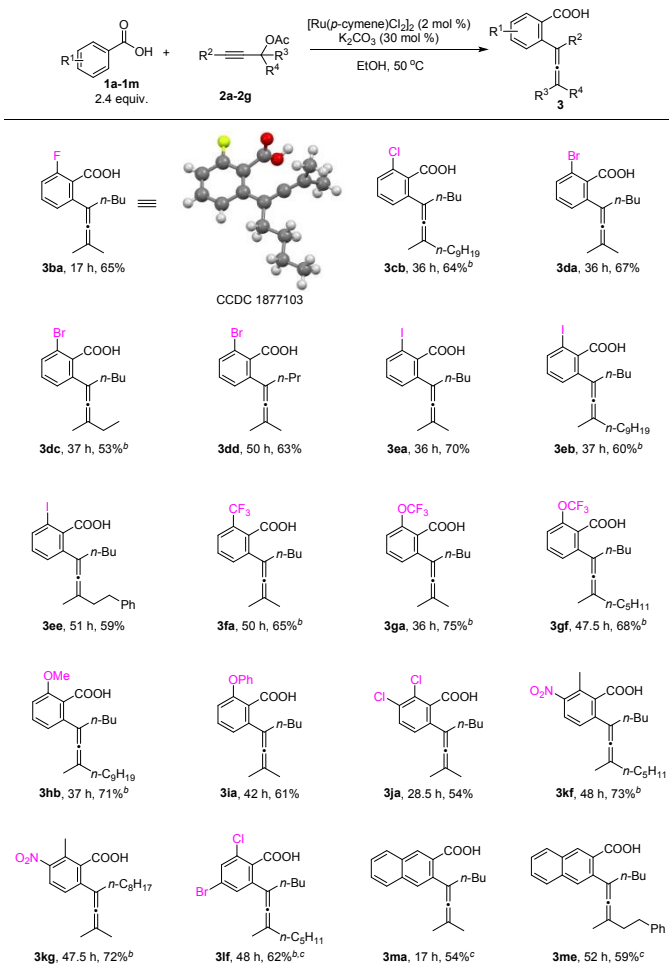
[a] Determined by ^1H NMR analysis using CH_2Br_2 as the internal standard.

With the optimized reaction conditions in hand, the scope of the reaction was investigated on 1.0 mmol scales (eqs 1-2 and Table 3). The parent benzoic acid **1a** afforded the monoallenylation product **3aa** in 55% yield together with diallenylation product **4aa** in 10% yield (eq 1). 4-Bromobenzoic acid **1n** was converted to monoallenylation product **3na** (45% yield) and bisallenylation product **4ma** (26% yield) under the standard conditions (eq 2).



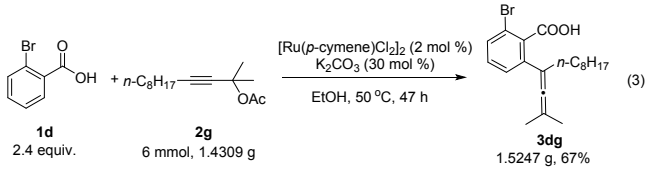
For mono-*o*-substituted benzoic acids, electron withdrawing groups, such as halogen atoms (including fluorine, chlorine, bromine, and iodine), CF_3, and OCF_3 were all well tolerated (Table 3, **3ba**-**3gf**). The structure of **3ba** was confirmed by X-ray diffraction study.[12] Electron-donating groups, such as methoxy, phenoxy-substituted benzoic acids afforded allenylation products **3hb** in 71% yield and **3ia** in 61% yield, respectively. 2,3-Dichloro (**3ja)**, 2-methyl-3-nitrobenzoic acid (**3kf** and **3kg)** and 2-chloro-4-bromobenzoic acid (**3lf)** were also allenylated in moderate to good yields. Notably, when the reaction was conducted with β-naphthoic acid, which has more than one C–H bond, 3-allenylation products **3ma** and **3me** were obtained exclusively. The scope of C-H allenylation with regard to propargylic acetates was also investigated affording **3cb**, **3nb**, **3dc**, **3dd**, **3ee, 3le**, **3kf**, **3gf**, or **3kg** smoothly.

Table 3. Reaction Scope.[a]



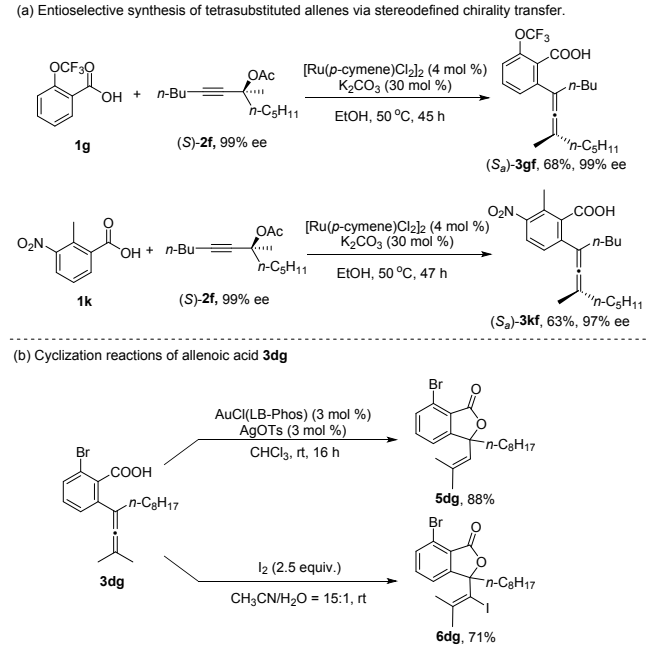
[a] The reaction was conducted with **1** (2.4 mmol), **2** (1.0 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (0.02 mmol), and K_2CO_3 (0.3 mmol) in EtOH (2.5 mL) under 50 °C. [b] 4 mol% [Ru(*p*-cymene)Cl_2]$_2$. [c] 5.0 mL of EtOH as solvent.

A gram scale reaction using 2-bromobenzoic acid **1d** with **2g** afforded allenylation product **3dg** in 67% yield (eq 3).



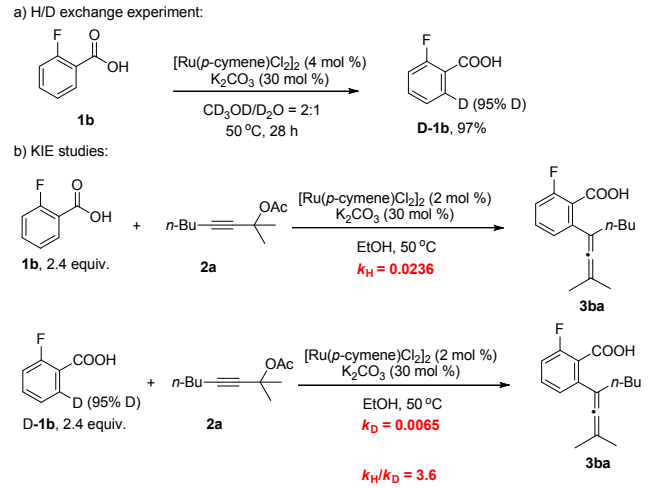
In addition, when optically active acetate (*S*)-**2f** (99% ee) was applied, axially chiral allenoic acid (S_a)-**3gf** (99% ee) and (S_a)-**3kf** (97% ee) could be obtained with a highly efficient chirality transfer (Scheme 2a). This method may open a new avenue for developing practical and synthetically useful methodologies for the synthesis of optically active allenoic acids. Meanwhile, this result indicating that the coordination of acetates and ruthenium species dictated the regioselectivity of alkyne insertion and the stereoselectivity of the β-OAc elimination.

To further explore the synthetic utility of this method, several synthetic applications were performed (scheme 2b). Allenoic acid **3dg** was easily transformed into the lactone **5dg** by treatment with AuCl(LB-Phos) and AgOTs.[13] This allenoic acid may also undergo a iodolactonization reaction with iodine to afford **6dg** in 71% yield.



Scheme 2. Synthetic Applications.

To gain insight into the mechanism of this methodology, several control experiments were carried out. Firstly, when 2-fluorobenzoic acid **1b** was performed in the mixture of CD_3OD and D_2O (2:1), the corresponding benzoic acid **D-1b** with a 95% deuterium incorporation was obtained (scheme 3a), indicating that the C–H activation step was reversible in the catalytic system. Subsequently, the parallel reactions of **1b** and **D-1b** with **2a** were conducted, we measured the reaction rate (k) of both **1b** and D-**1b** by monitoring the concentration of the product **3ba** by NMR from 2.5 h to 8 h (Scheme 3b, Figure 1). Then, the primary kinetic isotope effect of 3.6 was observed. These results suggest that C-H bond cleavage is the rate-determining step.[14]



Scheme 3. Mechanistic studies.

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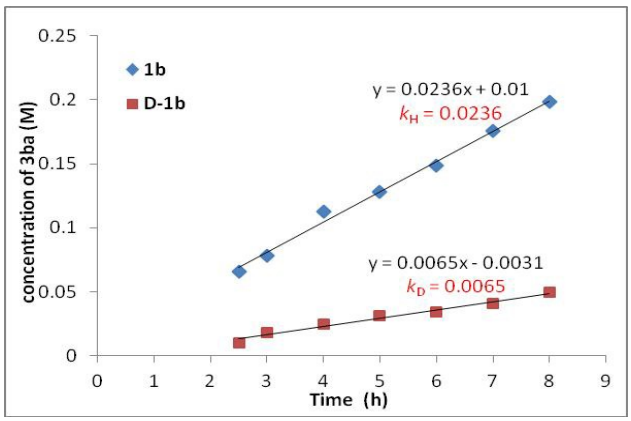


Figure 1. Plot of the concentrations of **3ba** vs. time.

In addition, a first-order dependence of the initial rate on the amount of Ru catalyst was established (Figure 2a, see supporting information for details). The reaction orders of each reactant were also measured by using 2-flurobenzoic acid **1b** and propargylic acetate **2a**. Both **1b** and **2a** follow the first-order reaction rate law, according to the linear relationship with ln([**1b**]) *vs*. reaction time: ln([**1b**]) = $-k_1t$ + ln[**1b**$_0$] (Figure 2b) and ln([**2a**]) = $-k_2t$ + ln[**2a**$_0$] (Figure 2c). Based on these data, we may give the rate equation as d[**3ba**]/dt = k·[Ru]·[**1b**]·[**2a**].

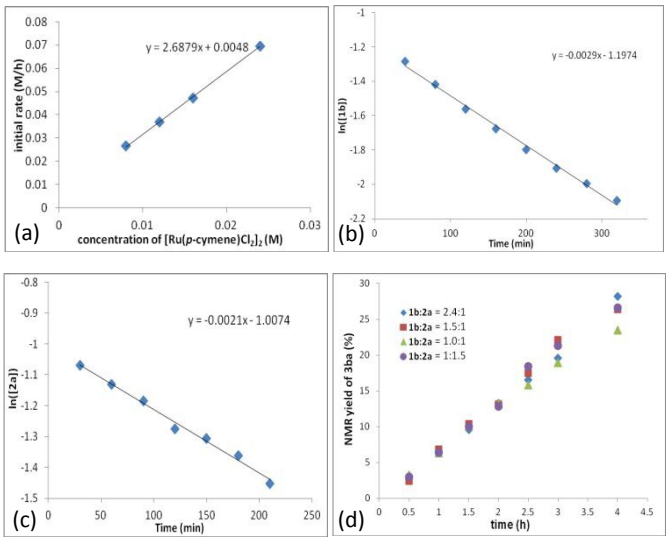
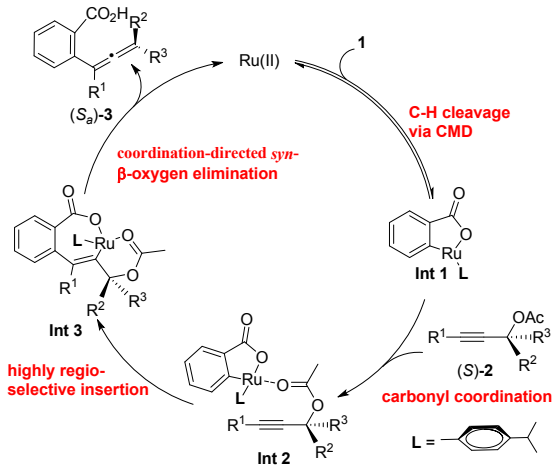


Figure 2. The dependence of initial reaction rate on [Ru(*p*-cymene)Cl$_2$]$_2$ (a), 2-flurobenzoic acid **1b** (b), propargylic acetate **2a** (c). NMR yield of **3ba** vs. time with different molar ratio of **1b** and **2a** (d).

To further understand the role of benzoic acid on the reaction, four experiments were conducted by using different molar ratio of benzoic acid **1b** vs. propargylic acetate **2a** (Figure 2d). The yields vs. time profile is almost the same in the initial four hours, indicates that the loading of benzoic acid has very limited effect on the formation of the final product-the excess benzoic acid did not accelerate the formation of the product greatly.[15] However, due to the catalytic nature, the role of benzoic acid worked as a Brønsted acid to promote the insertion process from **Int 2** to **Int 3** cannot be excluded.[16]

Based on these investigations above, the proposed catalytic cycle is illustrated in Scheme 4. Firstly, the C-H activation step leading to the formation of cyclic intermediate **Int 1** via a CMD process. Subsequently, **Int 2** is generated by the coordination of the carbonyl unit in acetate with the Ru in the cycloruthenated species, which subsequently undergoes the *syn*-insertion of C-C triple bond to afford **Int 3**. After a *syn*-β-OAc elimination step, the allenylation product was generated, and ruthenium species was released to restart the cycle. It should be noted that the acetate plays an important role in the *syn*-insertion as well as the *syn*-β-OAc elimination step.



Scheme 4. A possible mechanism.

Conclusions

In conclusion, we have established a new strategy to access allenoic acids, which based on a ruthenium catalysed carboxylic acid-directed C–H allenylation of benzoic acids with propargylic acetates. The reaction is compatible with air and synthetically useful functional groups such as Cl, Br, I, OCF$_3$ are all tolerated. Optically active allenoic acids could also be prepared through a highly efficient chirality transfer. The formed allenoic acids could be transformed to lactones efficiently under mild conditions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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16 We thank the referee for the suggestion of this possibility.

Graphic abstract

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An efficient Ru-catalyzed approach to tetrasubstituted allenes from benzoic acids and propargylic acetates has been developed.