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Atom-economic and stereoselective catalytic synthesis of fully substituted enol esters/carbonates of amides in acyclic systems enabled by boron Lewis acid catalysis†

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Carboacyloxylation of internal alkynes is emerging as a powerful and straightforward strategy for enol ester synthesis. However, the reported examples come with limitations, including the utilization of noble metal catalysts, the control of regio- and *Z*/*E* selectivity, and an application in the synthesis of enol carbonates. Herein, a boron Lewis acid-catalyzed intermolecular carboacyloxylation of ynamides with esters to access fully substituted acyclic enol esters in high yield with generally high *Z*/*E* selectivity (up to >96 : 4) is reported. Most importantly, readily available allylic carbonates are also compatible with this difunctionalization reaction, representing an atom-economic, catalytic and stereoselective protocol for the construction of acyclic β,β-disubstituted enol carbonates of amides for the first time. The application of the carboacyloxylation products to decarboxylative allylations provided a ready access to enantioenriched α-quaternary amides. Moreover, experimental studies and theoretical calculations were performed to illustrate the reaction mechanism and rationalize the stereochemistry.

Introduction

The chemistry of enolates can be considered one of the cornerstone areas in organic chemistry, driven by this compound class's role as carbon nucleophiles.[1] As a crucial subclass of enolates endowed with a delicate balance of reactivity and stability, enol ester/carbonate derivatives have proven to be fascinating building blocks due to their versatility for further synthetic transformations such as aldol-[2] and Mannich-type reactions,[3] cross-coupling reactions,[4] asymmetric hydrogenations,[5] cyclizations,[6] and decarboxylative allylations.[7] The enol ester skeleton is also found in an array of natural products and pharmaceuticals.[8] Due to the importance of enol esters/carbonates, many efforts have been focused on their synthesis. Most of the conventional methods for their preparation rely on α-deprotonation of the corresponding carbonyl compounds and subsequent *O*-acylation of enolates, a route that is typically plagued with regio- or stereoselectivity issues and incompatible with base-sensitive functional groups (Scheme 1A).[9] Recently, several attractive catalytic approaches for the preparation of enol esters have been reported including the hydroacyloxylation of alkynes,[10] rearrangements of propargylic esters,[11] Chan-Lam couplings,[12] organocatalyzed Michael addition-rearrangement of ynals with carboxylic acids,[13] and others.[14] Despite significant progress, construction of fully substituted acyclic enol esters remains limited because of inevitable issues including significant steric hindrance and the difficulty to distribute the various substituents in a stereo- and regioselective way.

Attractive solutions to this problem have been described, and one of the most straightforward catalytic routes to rapidly build these valuable enol esters is the 1,2-difunctionalization of internal alkynes.[15] For example, the Cramer group performed pioneering work on the heteroaryl acyloxylation of alkynes by cooperative rhodium/copper catalysis. However, the substrates were mainly symmetrical dialkyl alkynes, and the reaction

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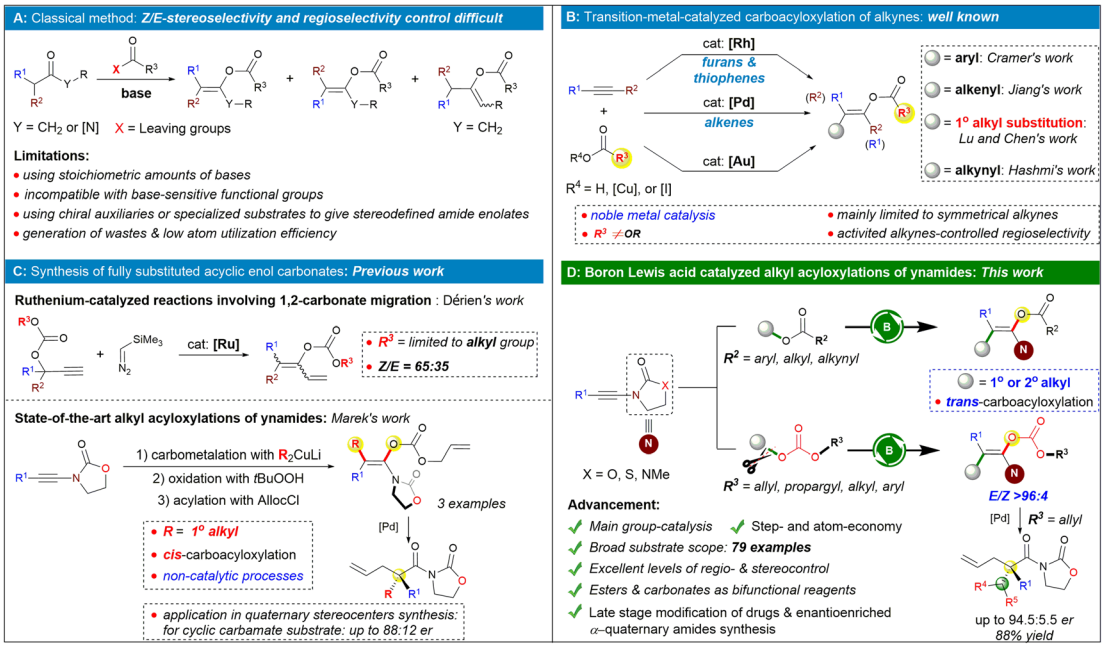


Scheme 1 Our catalytic strategy to access fully substituted acyclic enol ester/carbonates and its scientific context.

afforded the desired products with poor regioselectivities when unsymmetrically substituted alkynes were used (Scheme 1B, top).[16] On the other hand, pioneered by Lu, *trans*-acetoxypalladation of alkynes followed by olefin insertion and depalladation of the C–Pd bond was demonstrated by the groups of Lu,[17a–d] Chen,[17e] and Jiang[17f] as an efficient method for accessing fully substituted acyclic enol esters (Scheme 1B, middle). It has been reported that unsymmetrical internal alkynes activated by an electron-withdrawing group showed improved regioselectivity for the reaction,[17c,e] probably due to the polarization of the triple bonds. However, as for normal unactivated unsymmetrical alkynes, their regioselective carboacyloxylation is still a formidable challenge.

Ynamides are versatile nitrogen-containing alkyne synthons in organic synthesis. Owing to their unique reactivity and regioselectivity, ynamides have been regarded as versatile building blocks to react with diverse starting materials providing a concise and flexible approach to construct various useful nitrogen-containing molecules.[18,19] Thus, ynamides are accordingly selected as the reaction substrates in the investigation of the 1,2-difunctionalization process.[20] Along these lines, the Hashmi group reported an impressive example of a regio- and stereoselective intermolecular acyloxyalkynylation of ynamides based on an Au(I)/Au(III) catalytic cycle using ethynylbenziodoxolones as bifunctional reagents (Scheme 1B, bottom).[21]

Despite the progress made, the carboacyloxylation of alkynes continues to face several challenges such as (a) the carboacyloxylation strategy could not be extended to benzyl acyloxylations and secondary alkyl acyloxylations of alkynes; (b) in contrast to transition-metal catalysis, the complementary main group-catalyzed carboacyloxylation of alkynes in a sustainable manner is still scarce. A landmark in this field was described by Melen and co-workers, yet this reaction proceeds in an intramolecular fashion.[22] (c) So far, most of the transformations were focused on the carboacyloxylation of alkynes for synthesis of enol esters while less work was reported on the selective delivery of a carbon atom and a carbonate across an alkyne for synthesis of enol carbonates, probably due to the carbonate's ability to undergo decarboxylation.[23] Marek's group developed a state-of-the-art strategy for preparation of stereodefined acyclic α,α-dialkylsubstituted amide enol carbonates through a regio- and stereoselective carbocupration reaction of ynamides followed by a stereoretentive oxidation with an oxenoid and subsequent enolate trapping with allyl chloroformate (AllocCl; Scheme 1C, bottom).[24] Of note, other elegant methods for the generation of stereo-defined amide enolates mentioned above typically require highly specialized substrates, often incorporating chiral auxiliaries to impart selectivity in the enolate formation step (Scheme 1A).[25] Thus, the development of a catalytic protocol for accessing this important structural motif would be highly desirable. As a rare example, Dérien and co-workers reported a ruthenium-catalyzed synthesis of dienyl carbonates from propargylic carbonates and silyl diazo compounds by 1,2-carbonate migration of the propargylic carbonates, affording the desired products with poor to moderate *Z*/*E* ratios (Scheme 1C, top).[26]

An ester is one of the most common functional groups in organic chemistry. Carboxylates, especially carbonate, were always utilized as ideal leaving groups for the electrophile.[27] In contrast to the studies on the difunctionalization reactions by using carboxylic acids, the successful use of esters as the bifunctional reagents[28] in difunctionalization of unsaturated hydrocarbons to build molecular complexity still lags behind and had been limited to the intramolecular reactiosn.[29] In line with our interest in developing atom-economic reactions and

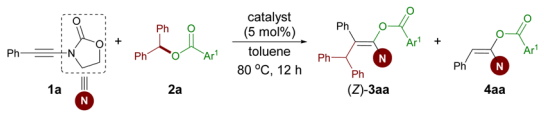
main group catalysis,[30] we report here a complementary and main-group-catalyzed intermolecular 1° and 2° alkyl acyloxylations of ynamides with benzyl carboxylates or carbonates, in which the RCO_2-C(sp^3) bond is formally cleaved and added across ynamides to generate the acyclic β,β-disubstituted enol esters/carbonates of amides. The synthetic utility is illustrated by the late-stage modification of natural products and drug derivatives and the construction of acyclic quaternary carbon centers by palladium-catalyzed decarboxylative allylic alkylation of fully substituted amide enolates.

Results and discussion

Catalytic synthesis of fully substituted enol esters

Given that geminal diaryl skeletons are prevalent in many natural products and pharmaceuticals,[31] benzhydryl carboxylate **2a** was selected as the model substrate, which can be easily prepared and also serves as a suitable cation precursor.[27b,c] Initially, diaryl ester **2a** and ynamide **1a** were treated with commonly used metal-based Lewis acid catalysts such as $Cu(OTf)_2$, $Zn(OTf)_2$, and $ZnCl_2$ in toluene at 80 °C for 12 h. These catalysts led to no conversion (Table 1, entries 1–3). Using $Sc(OTf)_3$ or $BF_3 \cdot Et_2O$ as the catalyst, a mixture of **3aa** with a poor *Z*/*E* ratio and yield and some hydro-oxycarbonylation side product **4aa** was obtained (entries 4 and 5). Brønsted acid catalyst TfOH failed to afford the desired product (entry 6). In light of Komeyama's and Takaki's[29d] as well as Melen's[22] elegant work on intramolecular carbo-oxycarbonylation of alkynyl esters, we tried to perform the current intermolecular 1,2-difunctionalization reaction by means of bismuth and boron Lewis acid catalysis, respectively.[32–34] Gratifyingly, with the use of $B(C_6F_5)_3$, the reaction provided the desired stereodefined fully substituted enol ester (*Z*)-**3aa** in 94% NMR yield (entry 8). The structure and configuration of (*Z*)-**3aa** were confirmed by X-ray diffraction.[35] In contrast, $Bi(OTf)_3$ failed to give the desired product (entry 7 *versus* 8). A decrease in the yield and stereoselectivity was observed when the reaction was conducted at 60 °C (entry 9) or in the presence of a hindered Lewis basic phosphine (entries 10 and 11).

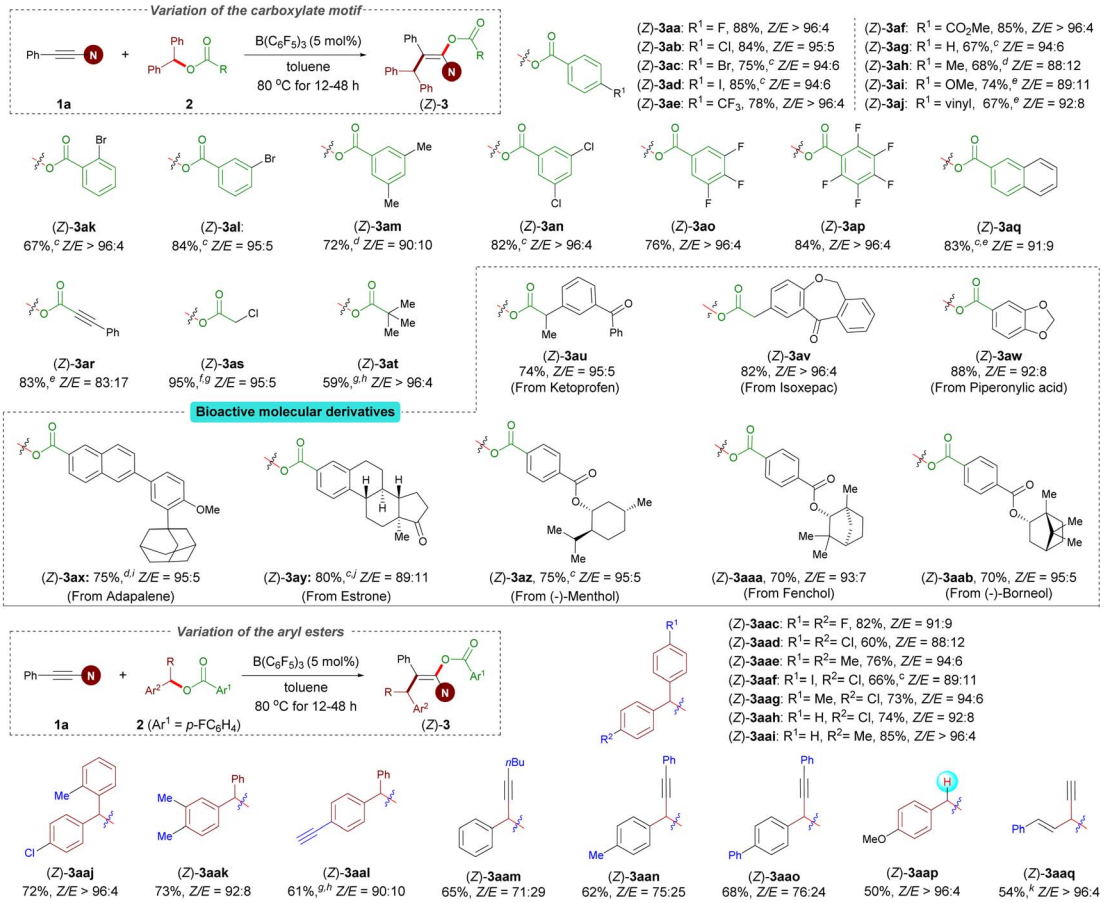
Table 1 Selected examples of the optimization of the alkyl acyloxylations of ynamides[a]



Entry	Catalyst	Conv.[b] [%]	(*Z*)-**3aa**[b,c] [%]	(*Z*)-**3aa** : (*E*)-**3aa**[b]	**4aa**[b,c] [%]
1	$Cu(OTf)_2$	0	—	—	—
2	$Zn(OTf)_2$	0	—	—	—
3	$ZnCl_2$	0	—	—	—
4	$Sc(OTf)_3$	25	<5	75 : 25	10
5	$BF_3 \cdot Et_2O$	20	12	79 : 21	8
6	TfOH	100	0	—	15
7	$Bi(OTf)_3$	13	0	—	9
8	**$B(C_6F_5)_3$**	**100**	**94**	**>96 : 4**	**5**
9[d]	$B(C_6F_5)_3$	13	9	90 : 10	3
10[e]	$B(C_6F_5)_3$	82	64	93 : 7	11
11[f]	$B(C_6F_5)_3$	96	65	78 : 22	4

[a] Unless otherwise noted, the reactions were performed with **1a** (0.24 mmol), **2a** (Ar^1 = 4-FC_6H_4; 0.2 mmol) and catalyst (5.0 mol%) in toluene (2 mL) at 80 °C for 12 h. [b] Determined by ^1H NMR spectroscopy of the crude reaction mixture with CH_2Br_2 as an internal standard. [c] NMR yield. [d] The reaction was run at 60 °C. [e] 5 mol% $B(C_6F_5)_3$ and 5 mol% Mes_3P used. [f] $B(C_6F_5)_3$ (0.2 mmol) and Mes_3P (0.2 mmol) used.

With optimized reaction conditions established, we examined the reactions of benzhydryl esters **2** containing various carboxylates with **1a**. Esters **2a–q** derived from aryl carboxylic acids were subjected to Conditions A described in Scheme 2. This protocol is amenable to a variety of esters bearing different R^1 functional groups, including halogen (**2a–d**), trifluoromethyl (**2e**), carboxyl (**2f**), methoxy (**2i**), and vinyl (**2j**) groups in the *para* position of the aromatic ring, and led to the corresponding enol esters in good to excellent yields and diastereocontrol with *Z*/*E* up to >96 : 4. In general, substrates with an electron-withdrawing group showed higher yield and *Z*/*E* ratio than the other substrates bearing an electron-donating group (**2e** *versus* **2h** and **2f** *versus* **2i**). As expected, functional groups at the *meta*- and *ortho*-positions gave satisfactory results for 10 mol% catalyst loading (**2k** and **2l**). In addition, disubstituted (**2m** and **2n**) and polysubstituted (**2o** and **2p**) substrates were found to function exceptionally well in this reaction. Of note, benzhydryl propiolate **2r** reacted chemoselectively (ynamides over electron-deficient alkynes) in good yield. The present protocol can also be efficiently applied to benzhydryl acetate derivative **2s** and pivalic acid ester **2t** to afford the corresponding products **3as** and **3at** in high yields and with excellent *Z*/*E* ratios. Importantly, our protocol allowed the incorporation of the enol ester fragment into bioactive molecules such as ketoprofen, isoxepac, adapalene, estrone, and borneol (**2u–ab**). Notably, when benzhydryl esters **2z–ab** bearing an additional ester functional group were subjected to the standard reaction conditions, only the benzhydryl ester motif was successfully incorporated into the products, affording corresponding products in good yields and *Z*/*E* ratios. We next investigated the scope of the aryl ester. Symmetrical diaryl esters bearing electron-withdrawing (4-F as in **2ac** and 4-Cl as in **2ad**) and electron-donating (4-Me as in **2ae**) groups all worked well for the reactions when coupled with **1a** generating **3aac–3aae** in good yields; The unsymmetrical diaryl esters containing halogen (**2af–ah** and **2aj**), electron-neutral (H as in **2ai**), alkyl in the *ortho*- (**2aj**) or *meta*-position (**2ak**), and even alkynyl (**2al**) groups on the aryl ring were all tolerated and gave the corresponding products (**3aaf–aal**) in good yields and *Z*/*E* ratios ranging from 89 : 11 to >96 : 4. Rather than diaryl esters, alkynyl(aryl) esters were also competent to afford products **3aam–aao**, albeit with a lower yield and stereoselectivity. It is particularly noteworthy that the reaction of 4-methoxybenzyl 4-fluorobenzoate **2ap** was successful under Conditions A, yielding **3aap** in reasonable yield and with an excellent *Z*/*E* ratio. Besides benzyl ester derivatives, the reaction of alkynyl(alkenyl)



Scheme 2 Variation of the esters.[a,b] [a] Conditions A: **1a** (0.24 mmol), **2** (0.20 mmol), $B(C_6F_5)_3$ (5.0 mol%), toluene (2.0 mL), at 80 °C for 12–48 h. [b] Isolated yield of (*Z*)-**3**. [c] 10 mol% $B(C_6F_5)_3$ used. [d] Run at 100 °C. [e] Combined isolated yield of *Z*/*E* mixtures which cannot be separated by chromatography. [f] Unstable compound. [g] The yield was estimated by ^{1}H NMR spectroscopy. [h] The desired product containing a trace amount of the hydroacyloxylation side product. [i] 20 mol% $B(C_6F_5)_3$ used. [j] 0.4 mmol **1a** used. [k] Combined isolated yield of the regioisomers which cannot be separated by chromatography.

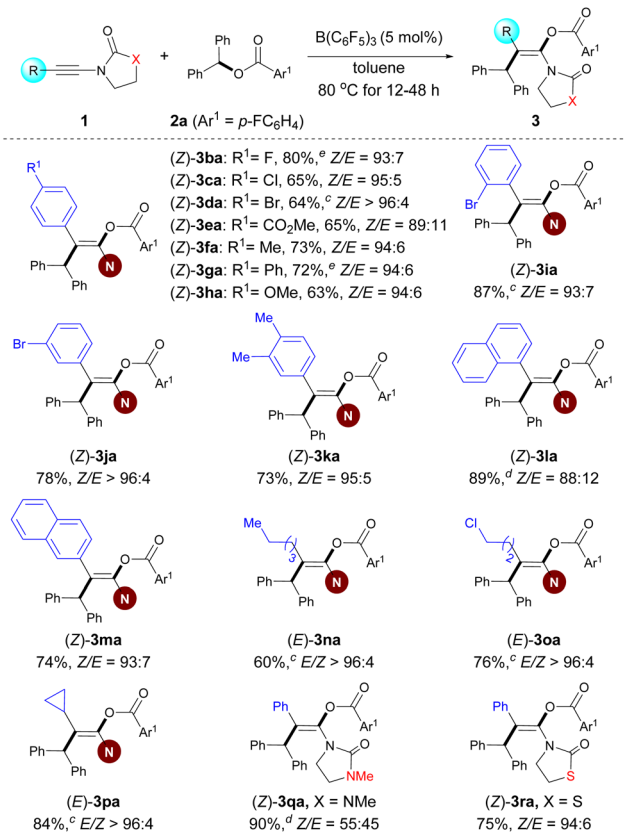
ester **2aq** with **1a** at 80 °C for 12 h resulted in in a mixture of regioisomers in 54% total yield (see the ESI† for details).

After the investigation of the ester scope, we studied the scope with respect to the ynamides (Scheme 3). Several 2-aryl ynamides **1b–k** were tested with the ester **2a**. Different substitution patterns of the aromatic substituent were tolerated independent of their electronic nature, providing products **3ba–ka** in yields between 63% and 87% and with *Z*/*E* ratios ranging from 89 : 11 to >96 : 4. The naphthyl-containing ynamides **1l** and **1m** also afforded the corresponding products in good yields. Moreover, ynamides bearing different primary or secondary alkyl groups afforded the desired products with exclusive *trans* selectivity with a higher catalyst loading (**1n–p**). The amide moiety was not limited to oxazolidin-2-one; ynamides featuring a urea functionality and a thiazolidine-2-one were also competent in this reaction, resulting in the desired products (**3qa–ra**) in excellent yields, albeit with a low stereoselectivity for product **3qa**. Meanwhile, it should be noted that an ynamide containing a sulfonamide group instead of the oxazolidinone group afforded a complex reaction mixture, and attempts to isolate any pure compound failed. It is probably due to the ynamide containing a sulfonamide group, which readily undergoes hydrocarbation as reported by Mayr and co-workers.[36]

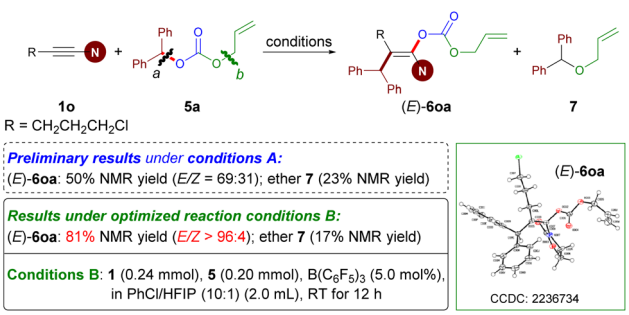
Catalytic synthesis of fully substituted enol carbonates

Enol carbonate derivatives have served as versatile synthons in organic transformations.[7] After the implementation of the carboacyloxylation of ynamides for the synthesis of enol esters, we wondered whether we could expand this catalytic methodology to build enol carbonates. To examine this hypothesis, readily available allyl benzhydryl carbonate **5a** and ynamide **1o** were selected as the model substrates (Scheme 4). In contrast to esters **2**, the employment of carbonates **5** as bifunctional reagents in the current reaction poses formidable challenges. On the one hand, the main challenge is the issue of site selectivity because of the presence of two C–O reactive sites (*e.g.* bond *a versus b*). On the other hand, a competitive side reaction encountered in this case is the formation of ethers *via* decarboxylative etherification.

Treatment of **1o** and **5a** with $B(C_6F_5)_3$ under Conditions A did afford the desired product **6oa**. However, a lower yield (50%)



Scheme 3 Variation of the ynamides.[a–c] For footnotes *a*–*c*, see Scheme 2. [d] Combined isolated yield of *Z*/*E* mixtures which cannot be separated by chromatography. [e] The desired product containing a trace amount of the hydroacyloxylation side product.

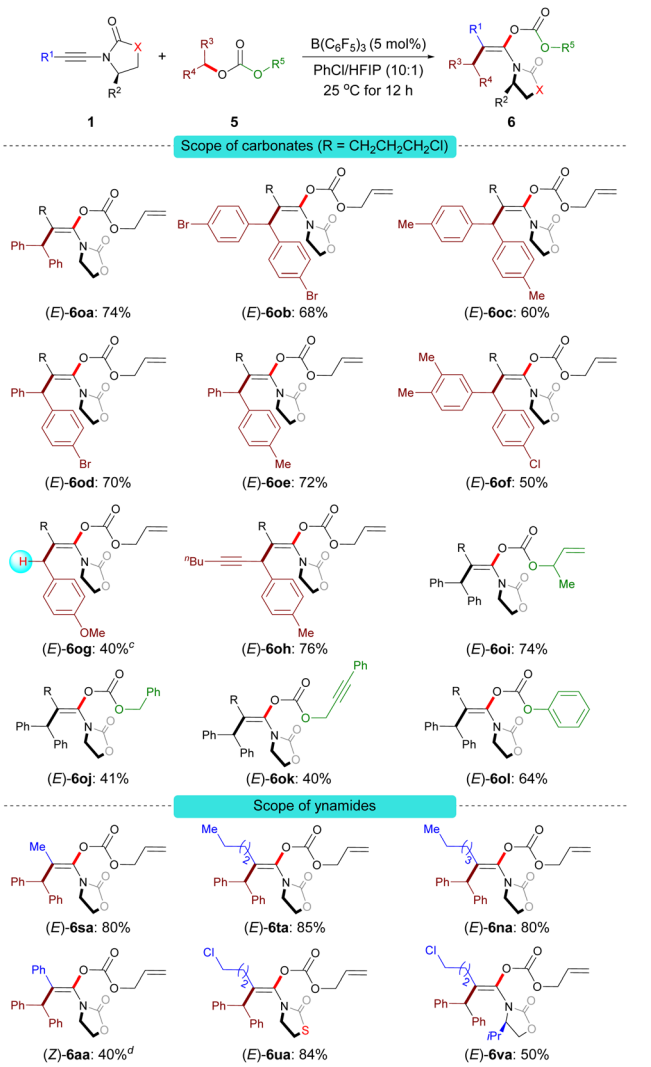


Scheme 4 Preliminary trials and conditions B for the synthesis of stereodefined enol carbonates.

and *E*/*Z* ratio (69 : 31) of **6oa** together with side product ether **7** were obtained. After further investigations leading to the reoptimized reaction conditions B, the carboacyloxylation reaction provided the desired (*E*)-**6oa** in 81% NMR yield with *E*/*Z* > 96 : 4 at room temperature.[35] Of note, the solvent (PhCl/HFIP) and the reaction temperature played an important role in controlling the stereoselectivity and the inhibition of side reactions (see Table S2 in the ESI†).

Under the optimal reaction conditions B, a series of carbonate derivatives **5** were prepared and examined. As shown in Scheme 5, allyl benzhydryl carbonate derivatives **5a–f** bearing either electron-withdrawing or electron-donating groups on the aromatic ring were effectively converted into the stereodefined enol carbonates **6oa–of** in moderate to good yields. The reaction was not limited to allyl benzhydryl carbonates; carbonates **5g** derived from a primary benzylic alcohol and **5h** derived from the alkynyl(aryl) alcohol were also tolerated. Furthermore, the substituent R^5 can be 2-methylallyl (**5i**), alkyl (**5j**), propargyl (**5k**) or phenyl (**5l**). The reactions proceeded smoothly to give the desired stereodefined enol carbonates in reasonable yields.

Having demonstrated the scope of the carbonates, our attention moved towards exploring the versatility of the ynamides. Various alkyl-substituted ynamides were screened and the desired enol carbonates (**6sa–ta** and **6na**) were obtained in excellent yields. Aryl-substituted ynamide **1a** was also compatible, albeit in lower yield. Also, thiazolidine-2-one-



Scheme 5 Scope of the carboacyloxylation of ynamides with carbonate derivatives.[a,b a] Conditions B. [b] Isolated yield of **6**, *E*/*Z* > 96 : 4. [c] The product was obtained along with a trace amount of unidentified mixtures; the yield was estimated by ^{1}H NMR spectroscopy. [d] *Z*/*E* > 96 : 4.

derived ynamide **1u** and chiral ynamide **1v** reacted smoothly to afford the corresponding stereodefined enol carbonates in good yields.

Synthetic transformations

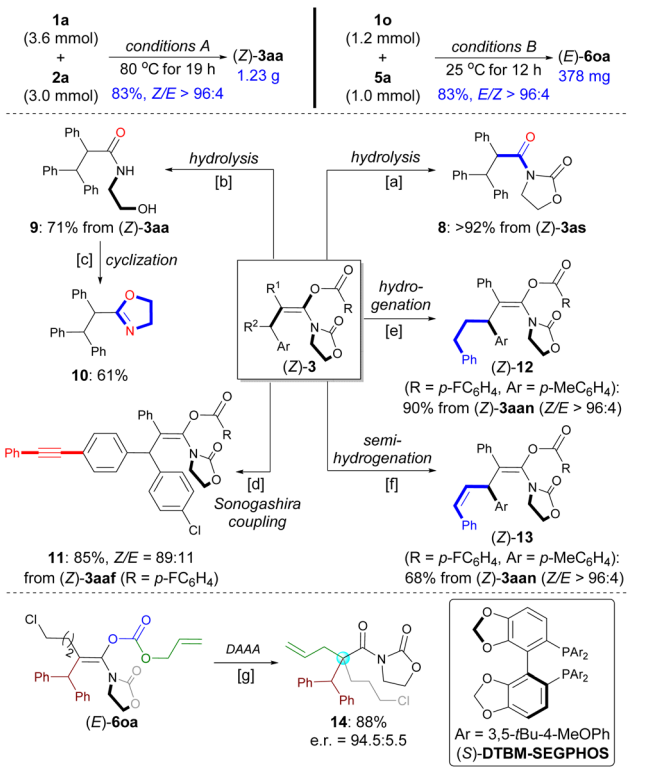
The practicality of this method was demonstrated by performing a gram-scale synthesis of (*Z*)-**3aa** (1.23 g) and a scale-up synthesis of (*E*)-**6oa** (1.0 mmol) with maintaining selectivity and yield (Scheme 6, top). **3as** was found to be unstable and was expected to hydrolyze on silica gel during purification by flash column chromatography. Thus, amide **8** was isolated in 92% yield after subjecting crude **3as** to the silica gel and Et_3N (Scheme 6a). By contrast, both the enol ester group and oxazolidinone were hydrolyzed to give *N*-acyl ethanolamine **9** in 71% yield in the presence of LiOH, which can be readily converted into oxazole **10** (Schemes 6b and c). The functionalized enol ester **11** can be prepared from **3aaf** by chemoselective Sonogashira coupling (Scheme 6d).

The C–C triple bond in (*Z*)-**3aan** was hydrogenated over Pd/C to produce **12** in 90% yield (Scheme 6e). Selective semi-reduction of the alkyne for obtaining *Z*-alkene in 13 was achieved by using Prabhu's protocol (Scheme 6f).[37] These two transformations as alternative strategies have, to a certain extent, served the purposes of the synthesis of corresponding enol esters from alkyl aryl esters or alkenyl aryl esters with ynamides.

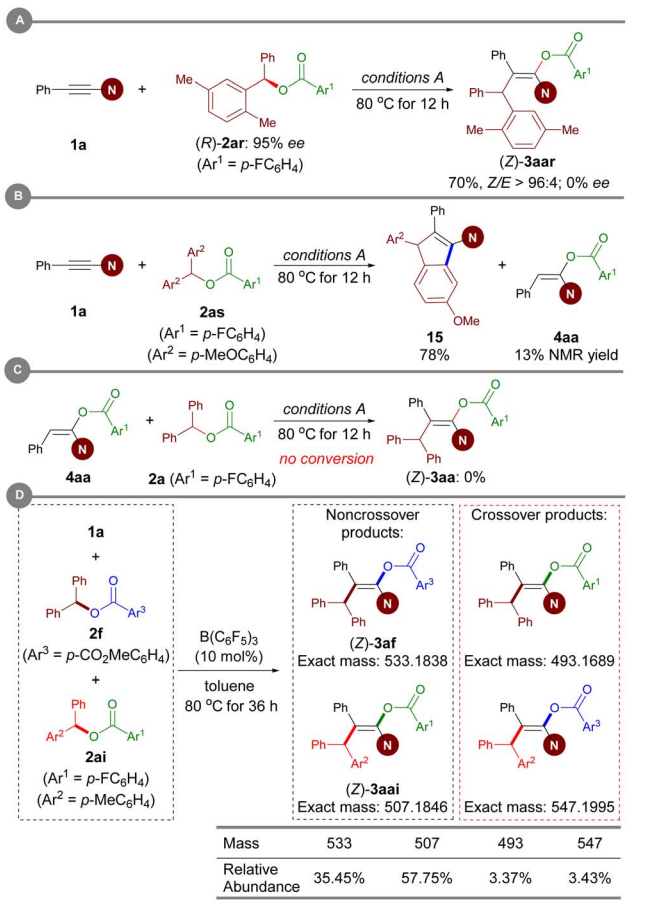
Palladium-catalyzed decarboxylative asymmetric allylic alkylation (DAAA) of fully substituted enol carbonates represents a practical strategy to set a quaternary carbon stereocenter in an acyclic system.[7] In 2017, utilizing chemistry developed by the Marek group for the synthesis of acyclic enolates,[24a] the Stoltz group disclosed the elegant DAAA reactions of acyclic amide enolates utilizing Trost's ligand (Scheme 1C).[24f] The use of acyclic carbamate substrates proved to be crucial to afford products in high enantioselectivities. In contrast, the DAAA of oxazolidinone-based allyl enol carbonates only gave the desired product with up to e.r. = 88 : 12. With a library of stereodefined oxazolidinone-based allyl enol carbonates **6** in hand, we decided to evaluate the palladium-catalyzed DAAA of (*E*)-**6oa** to afford α-quaternary amide **14** that is not reported for Stoltz's system. Gratifyingly, with the use of $Pd_2(dba)_3$/(*S*)-DTBM-SEGPHOS as the catalyst, the reaction provided the desired product **14** in 88% yield with e.r. = 94.5 : 5.5 e.r. (Scheme 6g; see also Table S3 in the ESI†).

Mechanistic studies

To gain insight into the reaction mechanism, several control experiments were conducted. When an enantiomerically pure



Scheme 6 Scope of Gram-scale synthesis and synthetic transformations. [a] SiO_2, Et_3N (2.0 equiv.), toluene, RT. [b] LiOH (1.0 equiv.), MeOH/H_2O (3 : 1), 80 °C. [c] TsCl (1.0 equiv.), CH_2Cl_2/Et_3N (1 : 1), 80 °C. [d] $Pd(PPh_3)_2Cl_2$ (5 mol%), CuI (5 mol%), Et_3N, THF, RT. [e] Pd/C (10%), H_2 (1 atm), MeOH, 50 °C. [f] $Pd(OAc)_2$ (5 mol%), P(*o*-Tol)$_3$ (10 mol%), $B_2(Pin)_2$ (1.2 equiv.), H_2O (5 equiv.), toluene, 80 °C. [g] $Pd_2(dba)_3$ (4 mol%), (*S*)-DTBM-SEGPHOS (16 mol%), THF, −20 °C.



Scheme 7 Mechanistic experiments.

sample of ester (*R*)-**2ar** was subjected to Conditions A, the resulting enol ester was obtained in racemic form, thus revealing that carboacyloxylation proceeds through a carbocation intermediate (Scheme 7A). Subsequently, electrophilic addition of the *in situ*-generated carbocation to ynamide 1 could give a keteniminium ion as an intermediate. To verify this proposal, ester **2as** bearing electron-rich aromatic moieties was prepared, and then treated with **1a** under Conditions A. Interestingly, the reaction afforded 1-amidoindene 15 in 78% NMR yield along with 13% NMR yield of **4aa** (Scheme 7B).[19m] Given that **4aa** was observed in current carboacyloxylations, we subjected **4aa** and ester **2a** to Conditions A to test whether the carboacyloxylation product arose from downstream benzylation of the hydroacyloxylation product, but **3aa** was not formed (Scheme 7C). Furthermore, we performed crossover experiments with a mixture of equimolar amounts of ynamide **1a**, and esters **2f** and **2ai** under conditions A (Scheme 7D). Analysis of the products by liquid chromatography-mass spectrometry revealed the presence of all four possible product masses, indicating that the addition of the carboxylate and the benzyl group to the ynamide is proceeding in a stepwise manner, and the resonance-stabilized anion may facilitate crossover by dissociation from the carbocation center.

To further elucidate the mechanistic details of this reaction and to explain the observed stereoselectivity, DFT calculations on a model reaction of ynamide **1a** with diaryl ester **2a** using the $B(C_6F_5)_3$ catalyst were conducted at the M06-2X/cc-pVTZ//M06-2X/6-31G(d,p) level[38] using the Gaussian 16 program.[39] The solvent effect for toluene was taken into consideration using the polarizable continuum model.[40] 3D structures were generated with CYLview.[41] According to our calculations and the aforementioned control experiments (see Table 1, entries 10 and 11), the reaction proceeds through an ionic mechanism rather than a radical pathway due to the high energies required for the related single electron transfer (SET) process[27a,d] (see Fig. S1 in the ESI†). Therefore, the following discussion will be focused on the possible two-electron processes involved in this reaction.

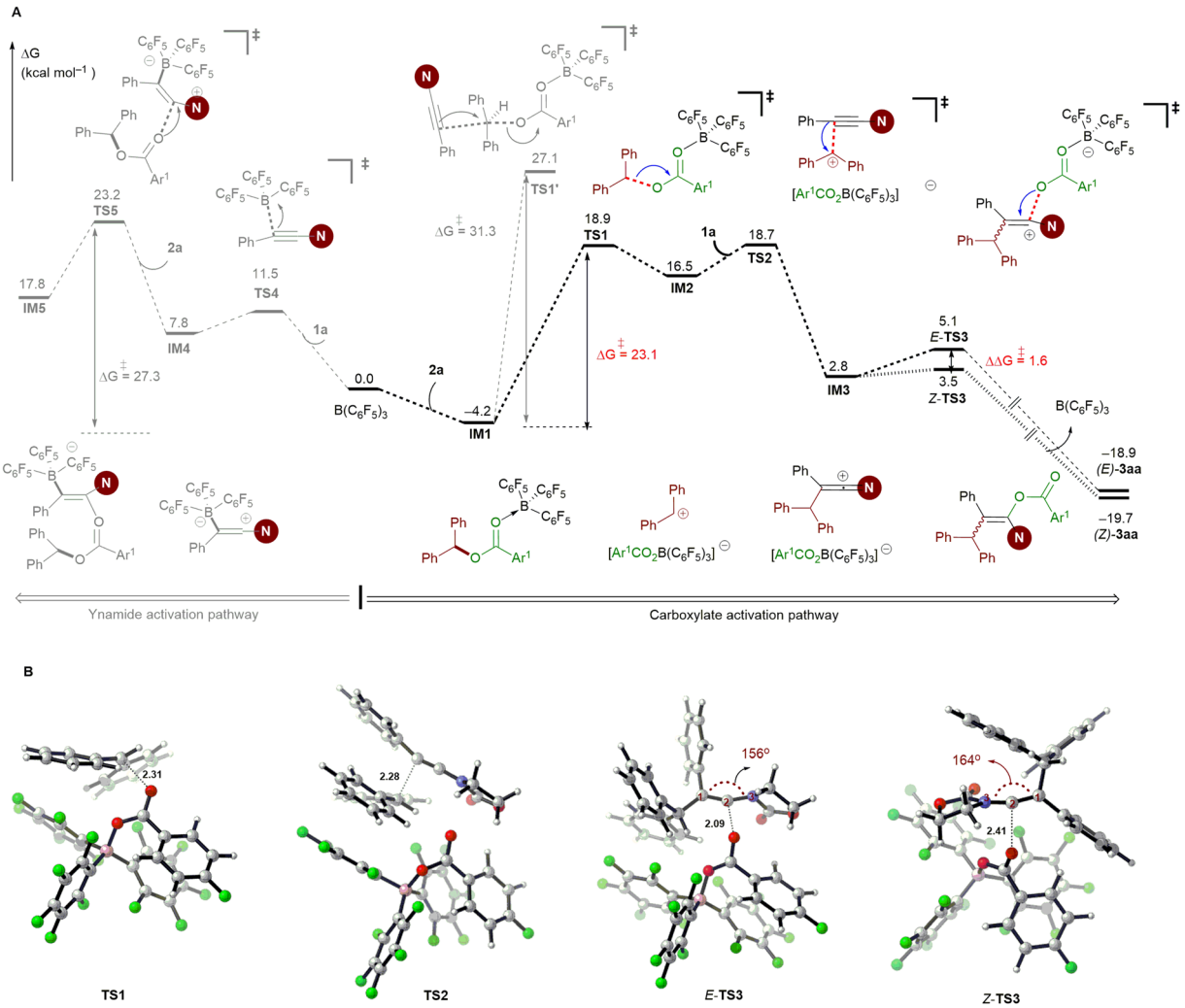


Fig. 1 DFT calculations for the reaction mechanism. A: Reaction coordinate for the $B(C_6F_5)_3$-catalyzed carboacyloxylation of ynamide **1a** with diaryl ester **2a**. Computed at the PCM (toluene)/M062X/cc-PVTZ//PCM (toluene)/M062X/6-31G(d,p) level (Gibbs free energies are in kcal mol^{-1}, $Ar^1 = p\text{-}FC_6H_4$). B: Optimized transition state structures involved in the carboxylate activation pathway (distances are shown in Å). Color code: H, white; B, pink; C, gray; N, blue; O, red; N, blue.

As shown in Fig. 1A, the carboacyloxylation reaction starts with the complexation of **2a** with $B(C_6F_5)_3$ to give the Lewis adduct **IM1**. The formation of **IM1** is exergonic by 4.2 kcal mol^{-1}. Although it is thermodynamically less favorable compared to **1a**·$B(C_6F_5)_3$ carbonyl adduct **IM1′** ($\Delta G = -6.4$ kcal mol^{-1}), our computational results show that the ynamide activation pathway through the complexation of $B(C_6F_5)_3$ with the oxygen atom of **1a** (**IM1′**) can be excluded (see Fig. S2, Table S1† and related discussions for details). **IM1** undergoes C–O cleavage to form ion pair **IM2** with a barrier of 23.1 kcal mol^{-1} (*via* **TS1**). **IM2** consists of an electrophilic carbenium ion and a borate anion $[Ar^1CO_2B(C_6F_5)_3]^-$ as the counteranion, which readily undergo an electrophilic addition reaction with ynamide **1a** to afford the new ion pair **IM3** (*via* **TS2**). This step has a barrier of 22.9 kcal mol^{-1}, and the formation of **IM3** is endergonic by 2.8 kcal mol^{-1} relative to **2a** and $B(C_6F_5)_3$. The borate anion $[Ar^1CO_2B(C_6F_5)_3]^-$ of **IM3** can attack at the carbocationic center of **IM3** from the same and opposite side of the 1,1-diarylmethyl group to give the *syn*- (*via* *E*-**TS3**) and *anti*-addition (*via* *Z*-**TS3**) products, respectively (Fig. 1B). The formation of *E*-**3aa** requires a higher barrier than that of *Z*-**3aa** (3.5 *versus* 5.1 kcal mol^{-1}), and *Z*-**3aa** is thermodynamically more favorable than the *syn*-addition product by 0.8 kcal mol^{-1}. In *E*-**TS3**, the ketene iminium fragment is in a more distorted conformation than it is in the favored transition state *Z*-**TS3** (C1–C2–N3 bond angle: 156° *versus* 164°). This might be attributed to the steric hindrance imparted by the 1,1-diarylmethyl moiety. The calculated free energy difference $\Delta\Delta G^{\ddagger} = 1.6$ kcal mol^{-1} is in good agreement with the experimentally observed stereoselectivity [(*Z*)-**3aa**/(*E*)-**3aa** > 96 : 4].

Alternatively, **IM1** could also react with ynamide *via* a concerted S_N2 transition state to afford the ion pair **IM3** (*via* **TS1′**). Our computations exclude this pathway due to the involvement of a high-energy transition state. This result is supported by the control experiment shown in Scheme 7A. Besides, a pathway proceeding through borane activation of the alkyne for the intramolecular carboacyloxylation of alkynyl carboxylic esters was proposed by Melen and co-workers.[22] Although the addition of $B(C_6F_5)_3$ to ynamide is kinetically feasible ($\Delta G^{\ddagger} = 15.7$ kcal mol^{-1}), the subsequent nucleophilic attack of diaryl ester **2a** to the **1a**·$B(C_6F_5)_3$ adduct **IM4** is kinetically less favored than the above pathway by 4.3 kcal mol^{-1}. Therefore, a pathway involving the activation of the carboxylate of the diaryl ester by $B(C_6F_5)_3$ by an S_N1-type mechanism is likely responsible for this carboacyloxylation process.

Conclusion

In summary, by taking advantage of esters as bifunctional reagents in the metal-free carboacyloxylation reaction of ynamides, an atom-economic and highly selective method for the synthesis of fully substituted acyclic enol esters was developed. To the best of our knowledge, this is the first $B(C_6F_5)_3$-catalyzed intermolecular 1,2-difunctionalization reaction of internal alkynes for the synthesis of acyclic tetrasubstituted alkenes. The salient features of this transformation include readily available starting materials, broad substrate scope, and scalability. The applicability was further illustrated in the late-stage modification of natural products and drug-like molecules. Notably, the protocol is also amenable to the synthesis of stereodefined acyclic β,β-disubstituted enol carbonates of amides, especially amide enol allyl carbonates, in one step. They are difficult to synthesize using transition-metal-catalyzed methods and can only be prepared by non-catalytic processes.[24a,f] Furthermore, we applied a palladium-catalyzed decarboxylative asymmetric allylic alkylation to the amide enol allyl carbonate to generate an α-quaternary amide in high yield and enantioselectivity (up to 88% yield and e.r. = 94.5 : 5.5). Control experiments combined with DFT studies support an S_N1 pathway and rule out a concerted S_N2 mechanism as well as a pathway involving the activation of the alkyne by $B(C_6F_5)_3$.

Data availability

The datasets supporting this article have been uploaded as part of the ESI.†

Author contributions

Y. X., L. T., T.-T. X., and J.-Y.-H. S. performed the experiments and conducted the analytical characterization. Z. Z. and L. Y. conducted the crossover experiments described in Scheme 7D. G. W. executed the theoretical calculations. G. W., M. O. and J.-J. F. wrote the manuscript. J.-J. F. conceived the catalytic system.

Conflicts of interest

There are no conflicts to declare.

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