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PII: S0040-4020(18)31243-2

DOI: 10.1016/j.tet.2018.10.037

Reference: TET 29870

To appear in: *Tetrahedron*

Received Date: 6 July 2018

Revised Date: 8 October 2018

Accepted Date: 15 October 2018

Please cite this article as: Lu X-Y, Li J-S, Hong M-L, Wang J-Y, Ma W-J, Synthesis of trisubstituted olefins via nickel-catalyzed decarboxylative hydroalkylation of internal alkynes, *Tetrahedron* (2018), doi: https://doi.org/10.1016/j.tet.2018.10.037.

Graphical Abstract

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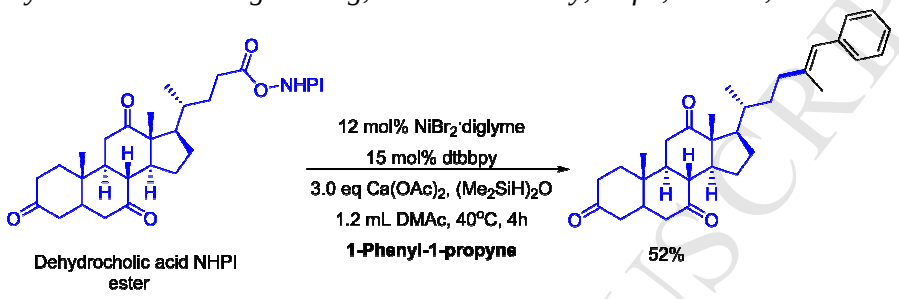

Tetrahedron
journal homepage: www.elsevier.com

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Trisubstituted Olefins
Decarboxylative
Hydroalkylation
Internal Alkynes
Nickel-Catalyzed

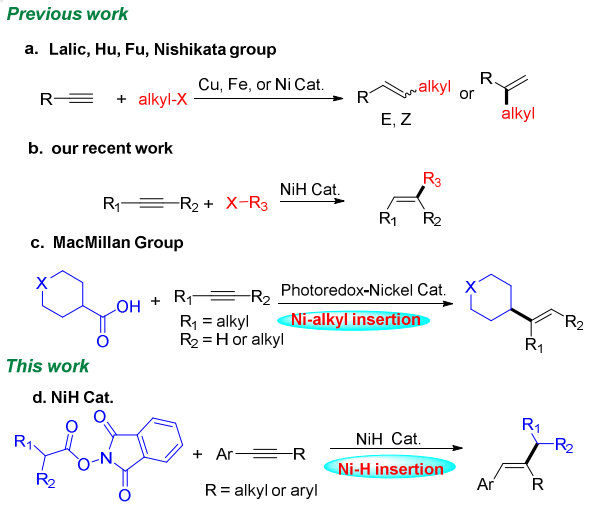
ABSTRACT

A novel NiH-catalyzed decarboxylative hydroalkylation of internal alkynes has been developed. Trisubstituted olefins were obtained in moderate to good yields with good regioselectivities. The reaction involves cis addition of NiH to the internal alkyne. The reaction shows good functional-group tolerance.

1. Introduction

Substituted alkenes are important synthetic intermediates, and are widely present in drug molecules and chemical materials [1-10]. In the past century, various methods for the synthesis of substituted olefins have been reported [11-17]. Alkynes are one of the most important organic synthons [18-23]. Recently, hydroalkylation reactions of alkynes have been identified as a convenient method for obtaining substituted alkenes. The use of different substituted alkynes enables control of the regio- and stereo-selectivity of the hydroalkylation reaction to produce different olefins. Lalic's, Hu's, Fu's, and Nishikata's groups achieved control of the regioselectivity of the hydroalkylation of terminal alkynes (**Scheme 1a**) [24-28]. These methods can be used to synthesize different disubstituted olefins. Trisubstituted alkenes are in great demand in organic chemistry. The efficient synthesis of stereochemically well-defined trisubstituted alkenes is a significant challenge. In this context, we achieved the first example of regio- and stereo-selective hydroalkylation of internal alkynes with alkyl halides (**Scheme 1b**) [29]. This provides a highly efficient method for the synthesis of trisubstituted alkenes.

Carboxylic acids are one of the most important classes of organic compounds, and are found in many drug molecules and natural products. Recently, the decarboxylation of carboxylic acids and their derivatives has emerged as a powerful tool for the construction of C–C bonds. The decarboxylation of carboxylic acids has been extensively explored by MacMillan's group [30-35]. Among carboxylic acid derivatives, redox-active esters synthesized from aliphatic carboxylic acids and N-hydroxyphthalimide (NHPI) are efficient electrophiles in cross-coupling reactions [36-37]. For example, Baran's and Weix's group reported a series of Ni-catalyzed cross-coupling reactions with redox-active esters (NHPI esters) as alkyl electrophiles [38-41]. Inspired by these results, we have explored the decarboxylative hydroalkylation reactions of alkynes. Recently, MacMillan's group reported a photoinduced Ni-catalyzed decarboxylative alkyne hydroalkylation reaction (**Scheme 1c**) [32]. The scope of this work included terminal and alkyl–alkyl internal alkynes. The authors did not report decarboxylative hydroalkylation of aryl–alkyl acetylenes. The authors suggested that the reaction proceeds via Ni–alkyl migratory insertion, therefore the reaction mechanism is different from that in Ni–silane-catalyzed hydroalkylation of alkynes. Based on our



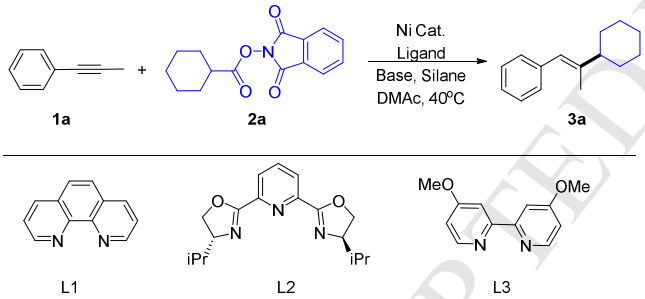
Scheme 1. Hydroalkylation of Alkynes with Alkyl Electrophiles.

previous work, we have developed the first example of Ni–silane-catalyzed regio- and stereo-selective decarboxylative hydroalkylation of phenyl–alkyl acetylenes (**Scheme 1d**). This method does not require sensitive organometallic reagents and both the alkynes and carboxylic acids are readily available substrates. This new decarboxylative hydroalkylation reaction shows good functional-group compatibility and provides a highly efficient method for synthesizing trisubstituted alkenes from carboxylic acids and alkynes.

2. Results and discussion

We chose 1-phenyl-1-propyne (**1a**) and redox-active NHPI ester (**2a**) for the model reaction (Table 1). First, we examined the use of previously reported conditions for Ni-catalyzed hydroalkylation of internal alkynes with alkyl halides in our decarboxylative reaction. However, only 5% yield was obtained (entry 1). Next, we examined the effects of different bases on the decarboxylative reaction (entries 2-7). When LiOAc or $Ca(OAc)_2$ was used as the base, the desired product was obtained in moderate yield (entries 6 and 7). We then used $Ca(OAc)_2$ as a base and examined the effects of different nitrogen ligands, namely phenanthroline (**L1**), pybox (**L2**), and 4,4'-dimethoxy-2,2'-bipyridine (**L3**), on the reaction (entries 8-10). Use of these ligands did not increase the yield. We then screened a series of silanes to optimize the reaction conditions (entries 11-14). Use of $(Me_2SiH)_2O$ as the hydride donor gave the optimal results **(82% GC yield and 75% isolated yield, entry 13, product ratio >50:1)**. When another Ni source, i.e., $Ni(PPh_3)_2Cl_2$, was used instead of $NiBr_2$·diglyme, the yield decreased (entry 15). Finally, no product was detected in the absence of a Ni source (entry 16).

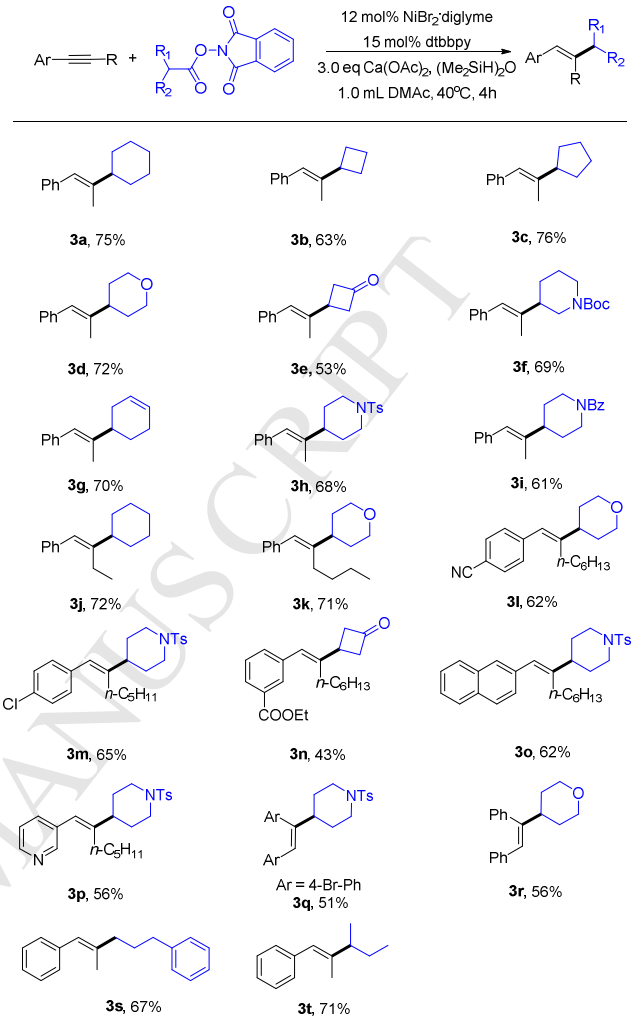
Table 1. Optimization of the reaction conditions.



Entry	Cat.	Ligand	Base	Silane	Yield %
1	$NiBr_2$·diglyme	dtbbpy	K_2CO_3	DEMS	5
2	$NiBr_2$·diglyme	dtbbpy	Na_2CO_3	DEMS	3
3	$NiBr_2$·diglyme	dtbbpy	Cs_2CO_3	DEMS	trace
4	$NiBr_2$·diglyme	dtbbpy	$Mg(OAc)_2$	DEMS	10
5	$NiBr_2$·diglyme	dtbbpy	KOAc	DEMS	5
6	$NiBr_2$·diglyme	dtbbpy	LiOAc	DEMS	55
7	$NiBr_2$·diglyme	dtbbpy	$Ca(OAc)_2$	DEMS	61
8	$NiBr_2$·diglyme	L1	$Ca(OAc)_2$	DEMS	8
9	$NiBr_2$·diglyme	L2	$Ca(OAc)_2$	DEMS	5
10	$NiBr_2$·diglyme	L3	$Ca(OAc)_2$	DEMS	46
11	$NiBr_2$·diglyme	dtbbpy	$Ca(OAc)_2$	$(EtO)_3SiH$	65
12	$NiBr_2$·diglyme	dtbbpy	$Ca(OAc)_2$	Ph_3SiH	1
13	**$NiBr_2$·diglyme**	**dtbbpy**	**$Ca(OAc)_2$**	**$(Me_2SiH)_2O$**	**82(75[c])**
14	$NiBr_2$·diglyme	dtbbpy	$Ca(OAc)_2$	PMHS	68
15	$Ni(PPh_3)_2Cl_2$	dtbbpy	$Ca(OAc)_2$	$(Me_2SiH)_2O$	46
16	-	dtbbpy	$Ca(OAc)_2$	$(EtO)_3SiH$	trace[b]

[a] The reactions were conducted on a 0.2 mmol scale. Conditions: 2.5 equiv 1a, 1 equiv 2a, 12 mol% $NiBr_2$·diglyme, 15 mol% dtbbpy, 3 equiv base, 180 µL silane, 1 mL DMAc, 40 °C, 4 h. Yields determined by GC analysis use biphenyl as internal standard. [b] Without $NiBr_2$·diglyme. [c] Yield of isolated product. DEMS= diethoxymethylsilane, PMHS= poly-(methylhydrosiloxane).

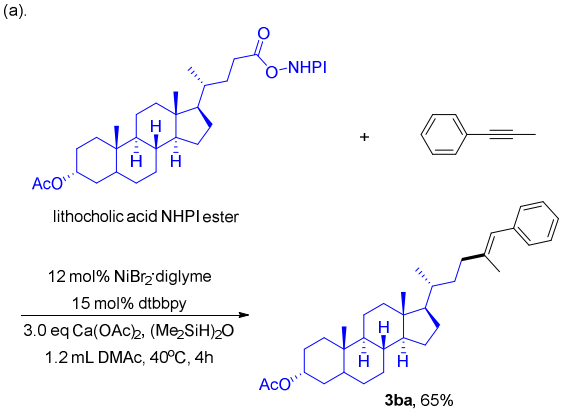
Table 2 Scope of cross-couping.



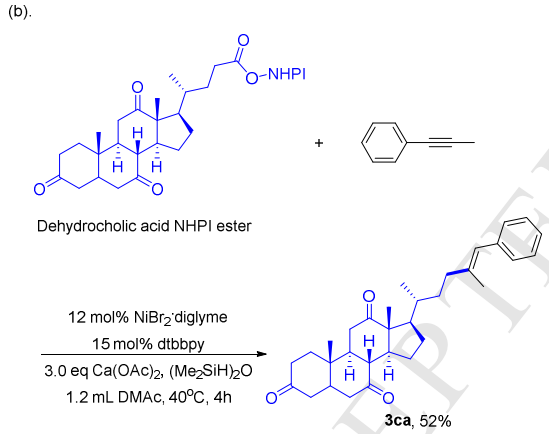
With the optimized conditions in hand, we explored the scope of the decarboxylative hydroalkylation reaction. A variety of aryl–alkyl acetylenes and aliphatic acid NHPI esters were successfully converted to the desired products in modest to excellent yields (Table 2). Coupling partners with different functional groups were satisfactorily converted to the products. The reaction worked well with cyclic aliphatic acid esters, and the ring size had no effect on the reaction conversion (**3a-3f**). Because of the mild reaction conditions, the decarboxylative hydroalkylation of internal alkynes showed good compatibility with many functional groups, e.g., ether (**3d**), carbamate (**3f**), sulfonamide (**3h**), and amide (**3i**). Some sensitive functional groups such as nitrile (**3l**), ketone (**3e** and **3n**), and ester (**3n**) groups were well tolerated. Some heterocyclic compounds such as pyrans (3k and 3l), naphthalene (**3o**), piperidines (**3f**, **3h**, and **3i**), and pyridine (**3p**) also survived in the reaction. The internal alkene group (**3g**) does not affect the decarboxylative hydroalkylation of internal alkynes. Aryl–Cl (**3m**) and aryl–Br (**3q**) bonds did not hinder the reaction. In addition to aryl–alkyl acetylenes, aryl–aryl acetylenes (**3q** and **3r**) were suitable reaction substrates. Acyclic primary aliphatic acid esters, e.g., **3s**, were also converted to the product. Acyclic secondary alkyl NHPI ester is also a suitable substrate (**3t**). The data in Table 2 show that our protocol gave excellent regio- and stereo-selectivity (all product ratios >40:1). More

importantly, the regioselectivity of this NiH-catalyzed alkyl addition to internal alkynes is different from that in Wu's photoinduced Ni-catalyzed hydroalkylation of aryl–alkyl acetylenes [42].

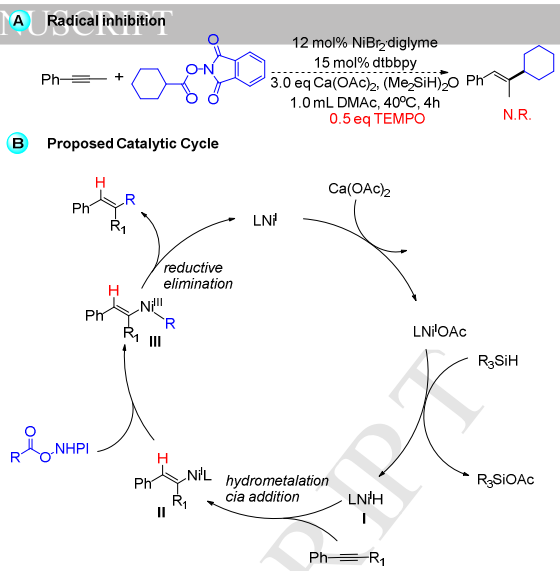
To further demonstrate the synthetic value of the decarboxylative internal alkyne hydroalkylation reaction, we explored its use in the late-stage modification of active molecules (**Scheme 2**). Modification of the NHPI ester of lithocholic acid with 1-phenyl-1-propyne gave **3ba** with high selectivity and in good yield 65% (**Scheme 2a**). Modification of the NHPI ester of dehydrocholic acid, which has three base-sensitive ketone groups, with 1-phenyl-1-propyne gave **3ca** in moderate yield (**Scheme 2b**).



Scheme 2a. Modification of lithocholic acid.



Scheme 2b. Modification of Dehydrocholic acid.



Scheme 3 Reaction Mechanism

We investigated the reaction mechanism by adding 2,2,6,6-tetramethylpiperidineoxy (TEMPO; 0.5 equiv). The reaction was completely inhibited (**Scheme 3A,** we did not observe the TEMPO-trapped alkyl radical, and the starting materials are not detected). Recent reports on decarboxylative reactions of redox-active esters (NHPI esters) [43-46] have suggested that the decarboxylative hydroalkylation reaction proceeds *via* a radical-type process. Furthermore, on the basis of recent work on Ni-silane-catalyzed addition of alkyl radicals to C–C π bonds [27,29,43,47,48], we propose that the reaction proceeds via NiH *cis* addition. Promotion by a base first generates the Ni(I) hydride intermediate (**I**). This intermediate then inserts into the alkyne via cis addition to give (**II**). Finally, oxidative addition and reductive elimination give the product (**Scheme 3B**). Further studies are on-going.

3. Conclusion

Carboxylic acids are among the most important feedstock compounds, and are widely found in drug molecules and natural products. Carboxylic acids have important applications in organic chemistry. In summary, we have developed the first example of NiH-catalyzed decarboxylative hydroalkylation of NHPI esters with aryl–alkyl acetylenes. The reaction shows good functional-group tolerance and provides an efficient method for the synthesis of trisubstituted olefins. This reaction also provides a direct method for the modification of active organic molecules containing carboxylic acid groups.

4. Experimental section

4.1 Preparation of redox active esters

The corresponding carboxylic acids (10 mmol, 1 equiv), N-hydroxyphthalimide (11 mmol, 1.1 equiv), and 4-dimethylaminopyridine (0.1 mmol, 10 mol%) were mixed in a flask with a magnetic stirring bar, 30 mL CH_2Cl_2 was added. Then a solution of N, N´-dicyclohexylcarbodiimide (11 mmol, 1.1 equiv) in CH_2Cl_2 (10 mL) was added slowly at room temperature. The reaction mixture was maintained at room temperature with stirring for 5-10h. The white precipitate was filtered off and the solution was concentrated on a rotary evaporator. The residue was purified by flash

column chromatography to give corresponding redox active esters.

4.2 general procedure

In air, $NiBr_2$.diglyme (12 mol%), $Ca(OAc)_2$ (3 equiv.), dtbbpy (15 mol%) and alkyl NHPI ester (0.2 mmol) were added to a Schlenk tube equipped with a stir bar. The vessel was evacuated and filled with argon (three cycles). 1 mL DMAc was added in turn under argon atmosphere, then alkyne and $(Me_2SiH)_2O$ (180 μL) was added. The reaction was stirred at the 40°C for 4h. Then the reaction was diluted with EtOAc, filtered through silica gel with copious washings. The residue was concentrated, and purified by column chromatography.

*4.3 (E)-(2-cyclohexylprop-1-en-1-yl)benzene(**3a**)*

Pale-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.22 (dd, J = 5.2, 2.9 Hz, 2H), 7.18 – 7.12 (m, 1H), 6.25 (br, 1H), 2.03 – 1.96 (m, 1H), 1.82 (d, J = 1.3 Hz, 3H), 1.79 (dd, J = 6.1, 2.9 Hz, 4H), 1.73 – 1.67 (m, 1H), 1.35 – 1.24 (m, 5H).^{13}C NMR (101 MHz, $CDCl_3$) δ 144.35, 138.97, 129.00, 127.99, 125.72, 123.05, 48.31, 31.96, 26.81, 26.45, 16.21. IR (KBr/cm^{-1}) 3023, 2955, 2926, 2852, 1642,1494, 1448, 1377, 1072, 1029, 745, 698. HRMS (APCI) calcd for C15H21 (M+H+): 201.1638; found: 201.1635.

*4.4 (E)-(2-cyclobutylprop-1-en-1-yl)benzene(**3b**)*

Pale-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.26 – 7.20 (m, 2H), 7.19 – 7.12 (m, 1H), 6.19 (br, 1H), 3.11 – 2.97 (m, 1H), 2.18 – 2.08 (m, 2H), 2.05 – 1.88 (m, 3H), 1.79 (dd, J = 1.4, 0.7 Hz, 3H), 1.78 – 1.70 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.40, 138.79, 128.97, 128.13, 125.87, 122.37, 44.27, 27.48, 17.75, 15.60. IR (KBr/cm^{-1}) 3085, 3052, 3026, 2970, 2950, 2855, 1711, 1682, 1672, 1650, 1500, 1490, 1440, 918,852, 915, 758, 693. HRMS (APCI) calcd for C13H17 (M+H+): 173.1325; found: 173.1326.

*4.5 (E)-(2-cyclopentylprop-1-en-1-yl)benzene(**3c**)*

Pale-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.26 – 7.20 (m, 2H), 7.19 – 7.14 (m, 1H), 6.31 (br, 1H), 2.62 – 2.51 (m, 1H), 1.88 – 1.77 (m, 5H), 1.70 (ddd, J = 8.7, 4.7, 2.8 Hz, 2H), 1.65 – 1.59 (m, 2H), 1.55 – 1.45 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.20, 138.96, 129.07, 128.09, 125.82, 123.30, 49.97, 31.32, 25.54, 16.21. IR (KBr/cm^{-1}) 3085, 3052, 3026, 2970, 2950, 2855, 1711, 1682, 1672, 1650, 1500, 1490, 1440, 918,852, 915, 758, 693. HRMS (APCI) calcd for C14H19 (M+H+): 187.1481; found: 187.1485.

*4.6 (E)-4-(1-phenylprop-1-en-2-yl)tetrahydro-2H-pyran(**3d**)*

Pale-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 2H), 7.21 (ddd, J = 14.5, 11.6, 5.0 Hz, 3H), 6.29 (br, 1H), 4.05 (dt, J = 11.0, 3.1 Hz, 2H), 3.52 – 3.38 (m, 2H), 2.26 (dt, J = 15.4, 7.5 Hz, 1H), 1.85 (d, J = 1.3 Hz, 3H), 1.74 – 1.62 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.12, 138.54, 129.05, 128.13, 126.10, 123.99, 68.42, 45.17, 31.68, 16.14. IR (KBr/cm^{-1}) 3054, 3022, 2954, 2933, 2856, 1644, 1599, 1466, 1443, 1385, 1236, 1131, 1089, 1019, 980, 917, 864, 748, 699,616. HRMS (APCI) calcd for C14H19O (M+H+): 203.1430; found: 203.1431.

4.7 (E)-3-(1-phenylprop-1-en-2-yl)cyclobutan-1-one(**3e**)

Pale-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 2H), 7.28 – 7.17 (m, 3H), 6.42 (br, 1H), 3.29 – 3.08 (m, 5H), 1.93 (d, J = 1.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.70, 138.48, 137.76, 128.99, 128.31, 126.55, 125.05, 51.37, 32.30, 15.86. IR (KBr/cm^{-1}) 2923, 2854, 1783, 1665, 1493, 1447, 1380, 1174, 1105, 1025, 853, 749, 700. HRMS (APCI) calcd for C13H15O (M+H+): 187.1117; found: 187.1117.

*4.8 tert-butyl (E)-3-(1-phenylprop-1-en-2-yl)piperidine-1 carboxylate(**3f**)*

Pale-yellow solid liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 7.25 – 7.12 (m, 3H), 6.30 (br, 1H), 4.11 (br, 2H), 2.79 – 2.48 (m, 2H), 2.21 – 2.04 (m, 1H), 1.99 – 1.89 (m, 1H), 1.86 (d, J = 1.3 Hz, 3H), 1.53 – 1.46 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.04, 140.17, 138.36, 129.05, 128.14, 126.19, 124.97, 79.51, 45.88, 44.71, 29.86, 28.62, 25.56, 24.63, 16.85. IR (KBr/cm^{-1}) 2975, 2932, 2857, 1693, 1599, 1475, 1420, 1391, 1364, 1288, 1255, 1167, 1149, 1073, 1027, 977, 916, 856, 747, 700. HRMS (APCI) calcd for C19H28NO2 (M+H+): 302.2115; found: 302.2119.

*4.9 (E)-(2-(cyclohex-3-en-1-yl)prop-1-en-1-yl)benzene(**3g**)*

Pale-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.26 – 7.21 (m, 2H), 7.20 – 7.13 (m, 1H), 6.31 (br, 1H), 5.79 – 5.65 (m, 2H), 2.38 – 2.27 (m, 1H), 2.20 – 2.03 (m, 4H), 1.89 – 1.80 (m, 4H), 1.66 – 1.46 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.34, 138.85, 129.08, 128.11, 126.95, 126.84, 125.93, 123.74, 43.95, 30.79, 27.70, 25.97, 16.03. IR (KBr/cm^{-1}) 3055, 3021, 2919, 2856, 2836, 1650, 1599, 1494, 1435, 1265, 1185, 1141, 1702, 1020, 916, 750, 737, 663, 640. HRMS (APCI) calcd for C15H19 (M+H+): 199.1481; found: 199.1480.

4.10 (E)-4-(1-phenylprop-1-en-2-yl)-1-tosylpiperidine(3h)

White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.1 Hz, 2H), 7.40 – 7.08 (m, 7H), 6.24 (br, 1H), 3.90 (d, J = 11.0 Hz, 2H), 2.44 (s, 3H), 2.35 – 2.17 (m, 2H), 1.99 – 1.56 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.55, 141.25, 138.16, 133.29, 129.71, 128.98, 128.14, 127.86, 126.24, 124.59, 46.80, 45.42, 30.25, 21.64, 16.00. HRMS (APCI) calcd for C21H26NO2S (M+H+): 356.1679; found: 356.1681.

*4.11 (E)-phenyl(4-(1-phenylprop-1-en-2-yl)piperidin-1-yl)methanone(**3i**)*

Pale-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.38 (m, 5H), 7.32 (t, J = 7.5 Hz, 2H), 7.20 (dd, J = 16.6, 7.6 Hz, 3H), 6.31 (br, 1H), 4.85 (br, 1H), 3.85 (br, 1H), 3.05 (br, 1H), 2.79 (br, 1H), 2.36 – 2.25 (m, 1H), 1.88 (br, 1H), 1.85 (d, J = 1.1 Hz, 3H), 1.77 – 1.54 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.43, 141.43, 138.25, 136.39, 129.60, 129.00, 128.54, 128.14, 126.97, 126.20, 124.45, 48.36, 46.32, 42.81, 31.57, 30.71, 16.19. HRMS (APCI) calcd for C21H24NO (M+H+): 306.1852; found: 306.1850.

*4.12 (E)-(2-cyclohexylbut-1-en-1-yl)benzene(**3j**)*

Pale-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, J = 7.6 Hz, 2H), 7.23 – 7.14 (m, 3H), 6.22 (br, 1H), 2.25 (q, J = 7.5 Hz, 2H), 2.04 – 1.96 (m, 1H), 1.85 – 1.79 (m, 4H), 1.71 (d, J = 11.5Hz, 1H), 1.36 – 1.18 (m, 5H), 1.06 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.50, 138.96, 128.57, 128.03, 125.70, 122.61, 44.69, 33.00, 27.04, 26.46, 23.60, 13.71. HRMS (APCI) calcd for C16H23 (M+H+): 215.1794; found: 215.1796.

*4.13 (E)-4-(1-phenylhex-1-en-2-yl)tetrahydro-2H-pyran(**3k**)*

Pale-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 2H), 7.19 (ddd, J = 9.9, 6.2, 4.4 Hz, 3H), 6.27 (br, 1H), 4.11 – 4.00 (m, 2H), 3.46 (td, J = 11.4, 2.8 Hz, 2H), 2.30 – 2.16 (m, 3H), 1.76 – 1.59 (m, 4H), 1.49 – 1.38 (m, 2H), 1.36 – 1.23 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 147.10, 138.68, 128.74, 128.20, 126.10, 123.98, 68.66, 41.98, 32.72, 31.23, 30.18, 23.10, 14.04. IR (KBr/cm^{-1}) 3004, 2955,

2927, 2855, 1607, 1509, 1463, 1403, 1300, 1246, 1174, 1037, 838, 821.738. HRMS (APCI) calcd for C17H25O (M+H+): 245.1900; found: 245.1902.

*4.14 (E)-4-(2-(tetrahydro-2H-pyran-4-yl)oct-1-en-1-yl)benzonitrile(**3l**)*

Pale-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.56 (m, 2H), 7.31 – 7.24 (m, 2H), 6.25 (br, 1H), 4.06 (dd, J = 11.2, 2.9 Hz, 2H), 3.46 (td, J = 11.5, 2.5 Hz, 2H), 2.33 – 2.24 (m, 1H), 2.21 (dd, J = 9.4, 6.7 Hz, 2H), 1.67 (d, J = 15.8 Hz, 4H), 1.36 – 1.20 (m, 8H), 0.87 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.65, 143.61, 132.06, 129.37, 122.72, 119.28, 109.60, 68.50, 42.17, 32.55, 31.66, 30.60, 29.60, 28.83, 22.70, 14.17. IR (KBr/cm^{-1}) 2988, 2945, 2928, 2850, 2225, 1602, 1595, 1558, 1493, 1463, 1445, 1353, 1340, 1308, 1247, 1164, 1142, 1093, 1054, 1019, 931, 859, 819, 757, 725, 706, 669, 650, 593. HRMS (APCI) calcd for C20H28NO (M+H+): 298.2165; found: 298.2165.

*4.15 (E)-4-(1-(4-chlorophenyl)hept-1-en-2-yl)-1 tosylpiperidine(**3m**)*

Pale-yellow sticky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.1 Hz, 2H), 7.30 – 7.24 (m, 2H), 7.10 (d, J = 8.4 Hz, 2H), 6.17 (br, 1H), 3.92 (d, J = 11.5 Hz, 2H), 2.47 (s, 3H), 2.32 – 2.23 (m, 2H), 2.16 – 2.08 (m, 2H), 1.93 – 1.78 (m, 3H), 1.76 – 1.62 (m, 1H), 1.40 – 1.31 (m, 2H), 1.28 – 1.16 (m, 4H), 0.86 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.13, 143.60, 136.74, 133.20, 131.93, 129.98, 129.75, 128.37, 127.89, 123.30, 77.48, 77.16, 76.84, 47.04, 42.24, 32.12, 31.22, 30.62, 28.63, 22.52, 21.68, 14.14. HRMS (APCI) calcd for C25H33ClNO2S (M+H+): 446.1915; found: 446.1917.

*4.16 ethyl (E)-3-(2-(3-oxocyclobutyl)oct-1-en-1-yl)benzoate(**3n**)*

Pale-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, J = 5.7, 1.8 Hz, 2H), 7.43 – 7.36 (m, 2H), 6.41 (br, 1H), 4.39 (q, J = 7.1 Hz, 2H), 3.28 – 3.07 (m, 5H), 2.34 – 2.23 (m, 2H), 1.40 (t, J = 7.1 Hz, 3H), 1.35 – 1.17 (m, 8H), 0.86 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.39, 166.73, 144.97, 138.06, 133.13, 130.65, 129.83, 128.41, 127.73, 123.50, 61.14, 51.87, 31.70, 30.57, 29.74, 29.51, 28.65, 22.71, 14.48, 14.18. IR (KBr/cm^{-1}) 2955, 2927, 2856, 1787, 1720, 1605, 1464, 1367, 1285, 1199, 1106, 1022, 753. HRMS (APCI) calcd for C21H29O3 (M+H+): 329.2111; found: 329.2109.

*4.17 (E)-4-(1-(naphthalen-2-yl)oct-1-en-2-yl)-1-tosylpiperidine(**3o**)*

Pale-yellow sticky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.73 (m, 3H), 7.68 (d, J = 8.2 Hz, 2H), 7.61 (s, 1H), 7.48 – 7.40 (m, 2H), 7.35 (d, J = 8.1 Hz, 2H), 7.30 (dd, J = 8.5, 1.4 Hz, 1H), 6.36 (s, 1H), 3.93 (d, J = 11.5 Hz, 2H), 2.45 (s, 3H), 2.33 – 2.18 (m, 1H), 1.99 – 1.83 (m, 3H), 1.78 – 1.69 (m, 2H), 1.66 – 1.60 (m, 1H), 1.46 – 1.36 (m, 2H), 1.28 – 1.15 (m, 6H), 0.83 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.86, 143.58, 135.83, 133.48, 133.23, 132.05, 129.74, 127.91, 127.66, 127.42, 127.07, 126.11, 125.62, 124.46, 77.48, 77.16, 76.84, 47.10, 42.39, 31.70, 31.29, 30.78, 29.64, 29.07, 22.72, 21.68, 14.16. HRMS (APCI) calcd for C30H38NO2S (M+H+): 476.2618; found: 476.2615.

*4.18 (E)-3-(2-(1-tosylpiperidin-4-yl)hept-1-en-1-yl)pyridine(**3p**)*

Pale-yellow sticky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 2H), 7.67 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 8.1 Hz, 2H), 7.27 – 7.20 (m, 1H), 6.15 (br, 1H), 3.91 (d, J = 11.5 Hz, 2H), 2.44 (s, 3H), 2.27 (dd, J = 11.7, 10.2 Hz, 2H), 2.18 – 2.09 (m, 2H), 1.92 (d, J = 12.0 Hz, 1H), 1.83 (d, J = 12.8 Hz, 2H), 1.75 – 1.62 (m, 2H), 1.40 – 1.29 (m, 1H), 1.27 – 1.15 (m, 4H), 0.82 (t, J = 6.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.67, 149.06, 147.22, 143.60, 135.85, 133.96, 133.12, 129.72, 127.84, 123.19, 120.73, 77.48, 77.16, 76.84, 46.95, 42.22, 32.03, 31.16, 30.68, 28.67, 22.49, 21.64, 14.08. HRMS (APCI) calcd for C30H38NO2S (M+H+): 476.2618; found: 476.2615.

*4.19 (Z)-4-(1,2-bis(4-bromophenyl)vinyl)-1-tosylpiperidine(**3q**)*

Pale-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 7.20 (d, J = 8.3 Hz, 2H), 6.89 (d, J = 8.2 Hz, 2H), 6.70 (d, J = 8.3 Hz, 2H), 6.29 (br, 1H), 3.86 (d, J = 11.4 Hz, 2H), 2.43 (s, 3H), 2.32 – 2.11 (m, 3H), 1.80 (d, J = 12.5 Hz, 2H), 1.68 – 1.52 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.48, 143.64, 139.01, 135.56, 133.07, 132.05, 131.21, 130.70, 130.51, 129.72, 127.82, 125.10, 121.50, 120.62, 46.72, 44.54, 30.46, 21.65. HRMS (APCI) calcd for C24H33N2O2S (M+Na+): 413.2257; found: 413.2262.

*4.20 (Z)-4-(1,2-diphenylvinyl)tetrahydro-2H-pyran(**3r**)*

Pale-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 3H), 7.13 – 7.08 (m, 2H), 7.08 – 7.01 (m, 3H), 6.91 – 6.83 (m, 2H), 6.39 (br, 1H), 4.06 – 3.97 (m, 2H), 3.43 (td, J = 11.6, 2.4 Hz, 2H), 2.62 – 2.48 (m, 1H), 1.76 – 1.56 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.87, 140.94, 137.34, 129.21, 129.00, 128.69, 127.96, 127.10, 126.41, 125.22, 68.45, 44.60, 32.10. HRMS (APCI) calcd for C19H21O (M+H+): 265.1587; found: 265.1588.

*4.21 (E)-(2-methylpent-1-ene-1,5-diyl)dibenzene(**3s**)*

Pale-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 4H), 7.25 – 7.11 (m, 6H), 6.28 (br, 1H), 2.70 – 2.61 (m, 2H), 2.26 – 2.16 (m, 2H), 1.92 – 1.78 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.62, 138.87, 138.72, 128.95, 128.60, 128.44, 128.15, 125.97, 125.85, 125.31, 40.38, 35.64, 29.84, 17.87. IR (KBr/cm^{-1}) 3058, 3024, 2934, 2856, 1716, 1649, 1599, 1495, 1452, 1265, 1179, 1074, 1029, 916, 742, 698. HRMS (APCI) calcd for C18H21 (M+H+): 237.1638; found: 237.1641.

*4.22 (E)-(2,3-dimethylpent-1-en-1-yl)benzene(**3t**)*

Pale-yellow liquid. ^{1}H NMR (400 MHz, CDCl3) δ 7.30 (t, J = 7.5 Hz, 2H), 7.287 – 7.20 (m, 2H), 7.18 (t, J = 7.2 Hz, 1H), 6.26 (br, 1H), 2.17 (dd, J = 14.2, 7.0 Hz, 1H), 1.77 (d, J = 1.2 Hz, 2H), 1.53 – 1.33 (m, 3H), 1.09 (d, J = 6.9 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 143.22, 138.90, 129.09, 128.10, 125.86, 124.56, 45.53, 27.99, 19.55, 14.19, 12.32. HRMS (APCI) calcd for C13H19 (M+H+): 175.1481; found: 175.1487.

*4.23 (3R,8R,9S,10S,13R,14S,17R)-10,13-dimethyl-17-((R,E)-5-methyl-6-phenylhex-5-en-2-yl)hexadecahydro-1H cyclopenta[a]phenanthren-3-yl acetate(**3ba**)*

Pale-yellow sticky liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H), 7.25 – 7.14 (m, 3H), 6.26 (br, 1H), 4.78 – 4.66 (m, 1H), 2.12 – 1.96 (m, 5H), 1.92 – 1.78 (m, 6H), 1.73 – 0.91 (m, 31H), 0.65 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.77, 139.98, 138.87, 128.90, 128.10, 125.83, 124.66, 74.55, 56.67, 56.34, 42.88, 42.04, 40.57, 40.33, 37.54, 35.94, 35.70, 35.18, 34.72, 34.51, 32.39, 28.49, 27.17, 26.77, 26.48, 24.35, 23.47, 21.60, 20.98, 18.78, 18.03, 12.19. IR (KBr/cm^{-1}) 3054, 3022, 2954, 2933, 2843, 2754, 1713, 1644, 1599, 1493, 1443, 1385, 1352, 1236, 1131, 1089, 1019, 980, 917, 863, 748, 699, 617. HRMS (APCI) calcd for C34H51O2 (M+H+): 491.3884; found: 491.3887.

*4.24 (8R,9S,10S,13R,14S,17R)-10,13-dimethyl-17-((R,E)-5-methyl-6-4.21 phenylhex-5-en-2-yl)dodecahydro-3H-cyclopenta[a]phenanthrene-3,7,12(2H,4H)-trione**(3ca)***

White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.08 (m, 5H), 6.26 (br, 1H), 3.02 – 2.79 (m, 3H), 2.49 – 1.93 (m, 15H), 1.85 (s, 3H), 1.76 – 1.53 (m, 2H), 1.40 (s, 3H), 1.36 – 1.21 (m, 4H), 1.08 (s, 3H), 0.97 – 0.80 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.22, 209.26, 208.93, 139.68, 134.38, 128.89, 128.10, 125.86, 124.71, 57.06, 51.94, 49.14, 46.96, 45.91, 45.68, 45.10, 42.90, 38.77, 37.92, 36.59, 36.12, 35.93, 35.38, 33.94, 28.00, 25.31, 22.01, 19.06, 17.97, 11.97. IR (KBr/cm^{-1}) 3200, 3054, 2942, 2868, 1773, 1751, 1707, 1599, 1491, 1467, 1438, 1385, 1307, 1274, 1247, 1181, 1116, 1090, 1052, 1029, 1006, 742, 712, 699, 647, 549, 524. HRMS (APCI) calcd for C32H43O3 (M+H+): 475.3207; found: 475.3202.

Acknowledgement

This work was supported by 2017qd11 and Anhui Province Major Special Projects (16030801108).

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