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(54) Title: METHOD OF FORMING A MULTI-SUBSTITUTED BENZENE COMPOUND

(57) Abstract: The invention relates to a method of forming a multi-substituted benzene compound. In particular, the method involves benzene construction via organocatalytic formal [3+3] cycloaddition reaction.

METHOD OF FORMING A MULTI-SUBSTITUTED BENZENE COMPOUND

Cross-Reference to Related Application

[001] This application claims the benefit of priority of Singapore Patent Application No. 10201404336U, filed July 23, 2014, the contents of which being hereby incorporated by reference in its entirety for all purposes.

Technical Field

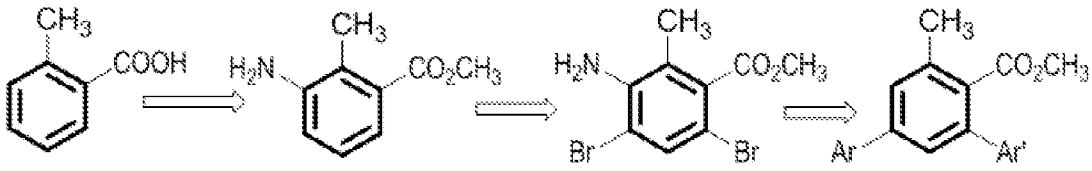
[002] The invention relates to a method of forming a multi-substituted benzene compound. In particular, the method involves benzene construction via organocatalytic formal [3+3] cycloaddition reaction.

Background

[003] The benzene unit, in its substituted forms, is a most common scaffold in natural products, bioactive molecules and polymer materials. Nearly 80% of the 200 best selling small molecule drugs contain at least one benzene moiety. Not surprisingly, the synthesis of substituted benzenes receives constant attentions. At present, the dominated methods use pre-existing benzene framework to install substituents by using conventional functional group manipulations or transition metal-catalyzed carbon-hydrogen bond activations. These otherwise impressive approaches require multiple synthetic steps and are ineffective from both economic and environmental perspectives.

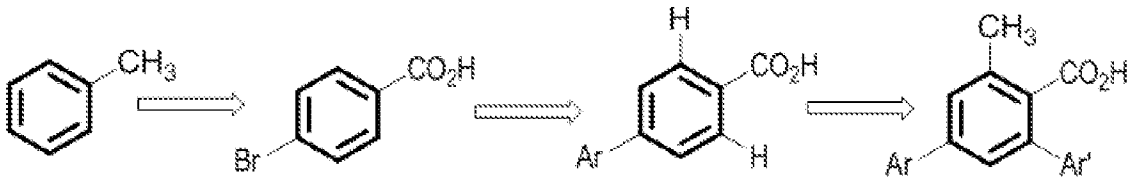
[004] The classic approach relies on stepwise eletrophilic substitution (such as Friedel-Crafts reaction) or eletrophilic halogenation and successive transition metal-catalyzed couplings. However, regio- selectivity and chemo-selectivity can only be achieved through rather tedious functional group (including protecting group) manipulations. For example, the classic synthesis of a 2,4,6-trisubstituted benzoate needs the introduction of a temporary amine group to ensure

selectivities in a key bromination reaction step, and the overall synthesis requires over 8 steps (Scheme 1a).



Scheme 1a. Classical substitution methods (e.g. about 8 steps)

[005] Another approach for access to substituted benzenes is based on transition metal-catalyzed direct C-H activations. While providing impressive shortcuts for benzene substitutions (Scheme 1b), this C-H activation method has its own limitations. For example, the presence of directing groups (for coordination with the metal catalyst) is often necessary and the instruction of multiple substituents is difficult (in part due to steric congestion). In a different direction for substituted benzene synthesis, the benzene core is newly formed. Representative methods include transition metal-catalyzed [2+2+2] or [4+2] reactions such as acetylene trimerisations. In this cycloaddition approach, partial or complete intramolecular reaction is usually indispensable to ensure the regioselectivity.



Scheme 1b. Transition metal-catalyzed C-H activation methods (e.g. about 5 steps)

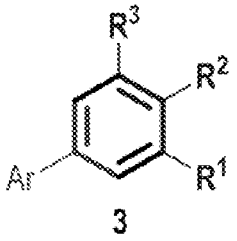
[006] The above methods for the synthesis of multisubstituted benzene mainly rely on the installation of substituents to pre-existing benzene. These methods usually require very long synthetic steps and are ineffective from both economic and environmental perspectives (as shown in Schemes 1a and 1b).

[007] Therefore, there remains a need to provide for an alternative method that overcomes, or at least alleviates, the above drawbacks.

Summary

[008] It is herein described a new strategy for providing highly effective access to multi-substituted benzenes through the construction of the benzene core *via* a formal [3+3] cycloaddition reaction. The reactions make use of readily available enals and unsaturated ketones, thereby allowing a single-step access to tetra-substituted benzenes in high yields.

[009] Accordingly, one aspect of the invention relates to a method of forming a multi-substituted benzene compound of formula (3)



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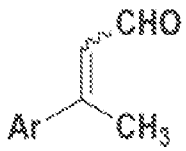
the method comprising:

reacting an enal of formula (1)



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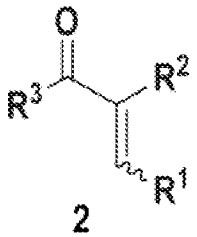
with an enone of formula (2)



2

in the presence of a N-heterocyclic carbene (NHC) pre-catalyst, an oxidant, a base, and an organic solvent ,

wherein:

R^1, R^2, and R^3 are independently selected from the group consisting of a linear or branched, substituted or unsubstituted C_1-C_{20} alkyl; linear or branched, substituted or unsubstituted C_2-C_{20} alkenyl; linear or branched, substituted or unsubstituted C_2-C_{20} alkynyl; linear or branched, substituted or unsubstituted C_1-C_{20} alkoxy; substituted or unsubstituted C_3-C_{20} cycloalkyl; substituted or unsubstituted C_3-C_{20} cycloalkenyl; substituted or unsubstituted C_5-C_{15} aryl; substituted or unsubstituted C_3-C_{15} heteroaryl, -C(O)-R, -NRR', -OR, -SR, -COOR, -CN, -NO_2, -C(O)-NRR', -NR'-C(O)-R, -SO_2-R and –(SO_2)-OR;

R and R' are independently selected from H and linear or branched, substituted or unsubstituted C_1-C_{10} alkyl; and

Ar is a substituted or unsubstituted C_5-C_{15} aryl, or a substituted or unsubstituted C_3-C_{15} heteroaryl.

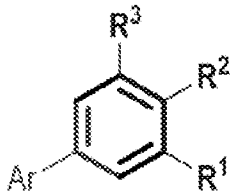
Description

[010] The following detailed description refers to the accompanying drawings that show, by way of illustration, specific details and embodiments in which the invention may be practised. These embodiments are described in sufficient detail to enable those skilled in the art to practise the invention. Other embodiments may be utilized and chemical and structural changes may be made without departing from the scope of the invention. The various embodiments are not necessarily mutually exclusive, as some embodiments can be combined with one or more other embodiments to form new embodiments.

[011] Described herein is an extremely efficient one-step method for the synthesis of substituted benzene molecules. Instead of relying on pre-existing aromatic rings, the benzene core is constructed through a carbene-catalyzed formal [3+3] reaction. Given the unusual simplicity and high efficiency, it can be expected that this strategy would be of wide use especially for large scale preparation of biomedicals and functional materials.

[012] Besides affording a highly effective one-step access, the benzene product bearing four substituents with completely predictable substitution patterns in high regioselectivity can be obtained. This approach will not only simplify many organic synthesis, but also offers previously unavailable insights into the design of concise synthetic strategies for complex molecules.

[013] Thus, in accordance with one aspect of the invention, there is disclosed a method of forming a multi-substituted benzene compound of formula (3)



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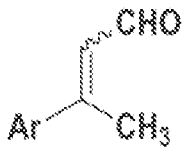
[014] The method comprises:

reacting an enal of formula (1)



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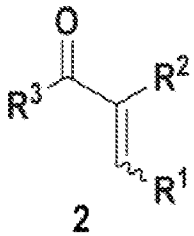
with an enone of formula (2)



2

in the presence of a N-heterocyclic carbene (NHC) pre-catalyst, an oxidant, a base, and an organic solvent ,

wherein:

R^1, R^2, and R^3 are independently selected from the group consisting of a linear or branched, substituted or unsubstituted C_1-C_{20} alkyl; linear or branched, substituted or unsubstituted C_2-C_{20} alkenyl; linear or branched, substituted or unsubstituted C_2-C_{20} alkynyl; linear or branched, substituted or unsubstituted C_1-C_{20} alkoxy; substituted or unsubstituted C_3-C_{20} cycloalkyl; substituted or unsubstituted C_3-C_{20} cycloalkenyl; substituted or unsubstituted C_5-C_{15} aryl; substituted or unsubstituted C_3-C_{15} heteroaryl, -C(O)-R, -NRR', -OR, -SR, -COOR, -CN, -NO_2, -C(O)-NRR', -NR'-C(O)-R, -SO_2-R and –(SO_2)-OR;

R and R' are independently selected from H and linear or branched, substituted or unsubstituted C_1-C_{10} alkyl; and

Ar is a substituted or unsubstituted C_5-C_{15} aryl, or a substituted or unsubstituted C_3-C_{15} heteroaryl.

[015] In present context, the term "aliphatic", alone or in combination, refers to a straight chain (i.e. linear) or branched chain hydrocarbon comprising at least one carbon atom. Aliphatics include alkyls, alkenyls, and alkynyls. In certain embodiments, aliphatics are optionally substituted, i.e. substituted or unsubstituted. The term "optionally substituted" or "substituted or unsubstituted" refers to a group in which none, one, or more than one of the hydrogen atoms have been replaced with one or more groups such as, but are not limited to, alkyl, heteroalkyl, haloalkyl, heteroholoalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, or non-aromatic heterocycle.

[016] Aliphatics include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, ethenyl, propenyl, butenyl, ethynyl, butynyl, propynyl, and the like, each of which may be optionally substituted. As used herein, aliphatic is not intended to include cyclic groups.

[017] In present context, the term “alkyl”, alone or in combination, refers to a fully saturated aliphatic hydrocarbon. The alkyl may be linear or branched. In certain embodiments, alkyls are optionally substituted. In certain embodiments, an alkyl comprises 1 to 20 carbon atoms, for example 1 to 10 carbon atoms, wherein (whenever it appears herein in any of the definitions given below) a numerical range, such as "1 to 20" or "C_1-C_{20}", refers to each integer in the given range, e.g. "C_1-C_{20} alkyl" means that an alkyl group comprising only 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, 6 carbon atoms, 7 carbon atoms, 8 carbon atoms, 9 carbon atoms, 10 carbon atoms, 11 carbon atoms, 12 carbon atoms, 13 carbon atoms, 14 carbon atoms, 15 carbon atoms, 16 carbon atoms, 17 carbon atoms, 18 carbon atoms, 19 carbon atoms, or 20 carbon atoms. Examples of alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, tert-amyl, pentyl, hexyl, heptyl, octyl and the like.

[018] In present context, the term “alkoxy”, alone or in combination, refers to an aliphatic hydrocarbon having an alkyl-O- moiety. The alkoxy may be linear or branched. In certain embodiments, alkoxy groups are optionally substituted. In various embodiments, the alkoxy comprises 1 to 20 carbon atoms, i.e. C_1-C_{20} alkoxy. Examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, butoxy and the like.

[019] In present context, the term “alkenyl”, alone or in combination, refers to an aliphatic hydrocarbon having one or more carbon-carbon double-bonds, such as two or three carbon-carbon double-bonds. The alkenyl may be linear or branched. In certain embodiments, alkenyls are optionally substituted, i.e. substituted or unsubstituted. In certain embodiments, an alkenyl comprises 2 to 20 carbon atoms. “C_2-C_{20} alkenyl” means that an alkenyl group comprising only 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, 6 carbon atoms, 7 carbon atoms, 8 carbon atoms, 9 carbon atoms, 10 carbon atoms, 11 carbon atoms, 12 carbon atoms, 13 carbon atoms, 14 carbon atoms, 15 carbon atoms, 16 carbon atoms, 17 carbon atoms, 18

carbon atoms, 19 carbon atoms, or 20 carbon atoms. Examples of alkenyls include, but are not limited to, ethenyl, propenyl, butenyl, 1,4-butadienyl, pentenyl, hexenyl, 4-methylhex-1-enyl, 4-ethyl-2-methylhex-1-enyl and the like.

[020] In present context, the term “alkynyl”, alone or in combination, refers to an aliphatic hydrocarbon having one or more carbon-carbon triple-bonds, such as two or three carbon-carbon triple-bonds. The alkynyl may be linear or branched. In certain embodiments, alkynyls are optionally substituted, i.e. substituted or unsubstituted. In certain embodiments, an alkynyl comprises 2 to 20 carbon atoms. “C_2-C_{20} alkynyl” means that an alkynyl group comprising only 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, 6 carbon atoms, 7 carbon atoms, 8 carbon atoms, 9 carbon atoms, 10 carbon atoms, 11 carbon atoms, 12 carbon atoms, 13 carbon atoms, 14 carbon atoms, 15 carbon atoms, 16 carbon atoms, 17 carbon atoms, 18 carbon atoms, 19 carbon atoms, or 20 carbon atoms. Examples of alkynyls include, but are not limited to, ethynyl, propynyl, butynyl, and the like.

[021] In present context, the term "non-aromatic ring" refers to a group comprising a covalently closed ring that is not aromatic. The term “alicyclic” refers to a group comprising a non-aromatic ring wherein each of the atoms forming the ring is a carbon atom. Alicyclic groups may be formed by three, four, five, six, seven, eight, nine, or more than nine carbon atoms. In certain embodiments, alicyclics are optionally substituted, i.e. substituted or unsubstituted. In certain embodiments, an alicyclic comprises one or more unsaturated bonds, such as one or more carbon-carbon double-bonds. Alicyclics include cycloalkyls and cycloalkenyls. Examples of alicyclics include, but are not limited to, cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclopentadiene, cyclohexane, cyclohexene, 1,3-cyclohexadiene, 1,4-cyclohexadiene, cycloheptane, and cycloheptene.

[022] In present context, the term "aryl" refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. Aryl rings may be formed by five, six, seven, eight, nine, or more than nine carbon atoms. Aryl groups may be optionally substituted.

[023] In present context, the term "heteroaryl" refers to an aromatic heterocycle. Heteroaryl rings may be formed by five, six, seven, eight, nine, or more than nine atoms. Heteroaryls may be optionally substituted. Examples of heteroaryl groups include, but are not limited to, aromatic C_5-C_{15} heterocyclic groups comprising one oxygen or sulfur atom or up to four nitrogen atoms, or a combination of one oxygen or sulfur atom and up to two nitrogen atoms, and their substituted as well as benzo- and pyrido-fused derivatives, for example, connected via one of the ring-forming carbon atoms.

[024] In various embodiments, the NHC pre-catalyst may be

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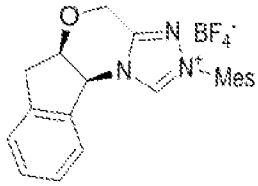

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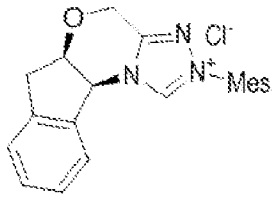


, or a mixture thereof.

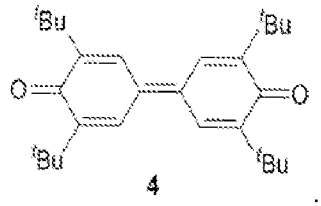
[025] In various embodiments, the organic solvent may be selected from the group consisting of THF, CH_2Cl_2, toluene, CH_3CN, DMF, and a mixture thereof.

[026] Preferably, the organic solvent is THF.

[027] In various embodiments, the base may be selected from the group consisting of Cs_2CO_3, Et_3N, DBU, ^tBuOK, K_2CO_3, DIEA, TBD, and a mixture thereof.

[028] Preferably, the base is Cs_2CO_3.

[029] In various embodiments, the oxidant comprises a compound of formula (4)



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[030] The reaction may be carried out at room temperature.

[031] In various embodiments, the reaction may be carried out for a period of between 1 and 10 hours, say between 5 and 10 hours.

[032] Preferably, the reaction is carried out for 8 hours and at room temperature.

[033] Preferably, the reaction is carried out in an inert atmosphere, such as in a nitrogen atmosphere.

[034] The multi-substituted benzene compound of formula (3) formed by the presently disclosed method may include any one of the following:

1-(5'-methyl-[1,1':3',1''-terphenyl]-4'-yl)ethanone (3a);

(*E*)-1-(3-methyl-5-styryl-[1,1'-biphenyl]-4-yl)ethanone (3b);

(*E*)-1-(4'-methoxy-3-methyl-5-styryl-[1,1'-biphenyl]-4-yl)ethanone (3c);

(*E*)-1-(3,4'-dimethyl-5-styryl-[1,1'-biphenyl]-4-yl)ethanone (3d);

(*E*)-1-(4'-chloro-3-methyl-5-styryl-[1,1'-biphenyl]-4-yl)ethanone (3e);

(*E*)-1-(3'-methoxy-3-methyl-5-styryl-[1,1'-biphenyl]-4-yl)ethanone (3f);

(*E*)-1-(3'-bromo-3-methyl-5-styryl-[1,1'-biphenyl]-4-yl)ethanone (3g);

(*E*)-1-(2-methyl-4-(naphthalen-2-yl)-6-styrylphenyl)ethanone (3h);

(*E*)-1-(4-(furan-2-yl)-2-methyl-6-styrylphenyl)ethanone (3i);

(*E*)-1-(2-methyl-6-styryl-4-(thiophen-2-yl)phenyl)ethanone (3j);

(*E*)-ethyl 3-methyl-5-styryl-[1,1'-biphenyl]-4-carboxylate (3k);

(*E*)-ethyl 3-methyl-5-(prop-1-en-1-yl)-[1,1'-biphenyl]-4-carboxylate (3l);

(*E*)-1-(3-methyl-5-(prop-1-en-1-yl)-[1,1'-biphenyl]-4-yl)ethanone (3m);

methyl 5'-methyl-[1,1':3',1"-terphenyl]-4'-carboxylate (3n);

methyl 4"-fluoro-5'-methyl-[1,1':3',1"-terphenyl]-4'-carboxylate (3o);

methyl 4",5'-dimethyl-[1,1':3',1"-terphenyl]-4'-carboxylate (3p);

methyl 4"-methoxy-5'-methyl-[1,1':3',1"-terphenyl]-4'-carboxylate (3q);

1-(4"-chloro-5'-methyl-[1,1':3',1"-terphenyl]-4'-yl)ethanone (3r);

(*E*)-methyl 3-methyl-5-styryl-[1,1'-biphenyl]-4-carboxylate (3s);

(*E*)-methyl 3-ethyl-5-styryl-[1,1'-biphenyl]-4-carboxylate (3t);

(*E*)-methyl 3-isopropyl-5-styryl-[1,1'-biphenyl]-4-carboxylate (3u);

1-(4"-chloro-4-methoxy-5'-methyl-[1,1':3',1"-terphenyl]-4'-yl)ethanone (3v);

1-(5'-ethyl-[1,1':3',1"-terphenyl]-4'-yl)propan-1-one (3w);

(*E*)-ethyl 4'-methoxy-3-methyl-5-styryl-[1,1'-biphenyl]-4-carboxylate (3x);

4-methoxy-5'-methyl-4'-nitro-1,1':3',1"-terphenyl (3y);

1-(4-methoxy-5'-(trifluoromethyl)-[1,1':3',1"-terphenyl]-4'-yl)ethanone (3z); and

(4-methoxy-5'-(trifluoromethyl)-[1,1':3',1"-terphenyl]-4'-yl)(phenyl)methanone (3z1).

[035] In order that the invention may be readily understood and put into practical effect, particular embodiments will now be described by way of the following non-limiting examples.

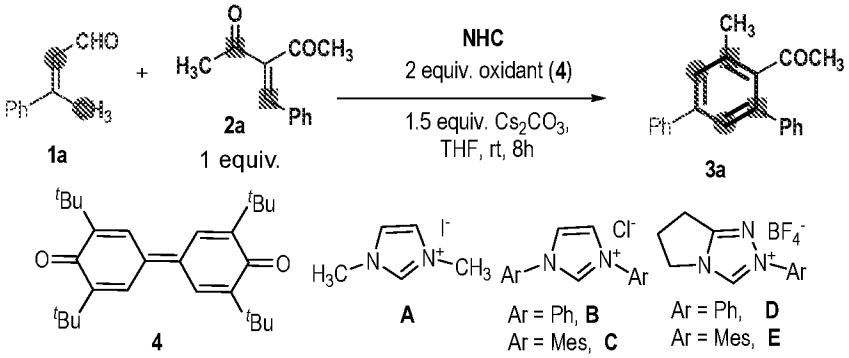
Examples

[036] In this example, the presently disclosed method is studied and optimized as follows.

[037] Enal **1a** and enone **2a** were started as the model substrates, in the presence of two equiv quinone **4** as an oxidant and Cs_2CO_3 as a base. No formation of the proposed benzene **3a** was observed in the absence of an NHC pre-catalyst (Table 1, entry 1). The *N*-methyl imidazolium NHC **A** and *N*-phenyl imidazolium **B** could not initiate the reaction (Table 1, entries 2-3). It was then found that with *N*-Mes imidazolium **C** as the NHC pre-catalyst, the proposed product **3** was formed in 88% isolated yield (Table 1, entry 4). Triazolium-based NHCs behaved similarly as the imidazolium catalysts: triazolium **D** (with a N-phenyl substituent) could not

catalyze the reaction; while the use of triazolium **E** with a N-mesityl substituent could lead the formation of **3** in 47% yield (Table 1, entries 5-6). It was then evaluated the effects of solvents and bases. Although the combination of THF and Cs_2CO_3 was optimal, other common organic solvents (such as CH_2Cl_2, toluene, CH_3CN, DMF) and organic/inorganic bases (such as Et_3N, DBU, ^tBuOK, K_2CO_3) could also be used (see Table 2). Further investigation showed the catalyst loading of **C** could be decreased to 5 mol% with acceptable 76% yield (Table 1, entry 7).

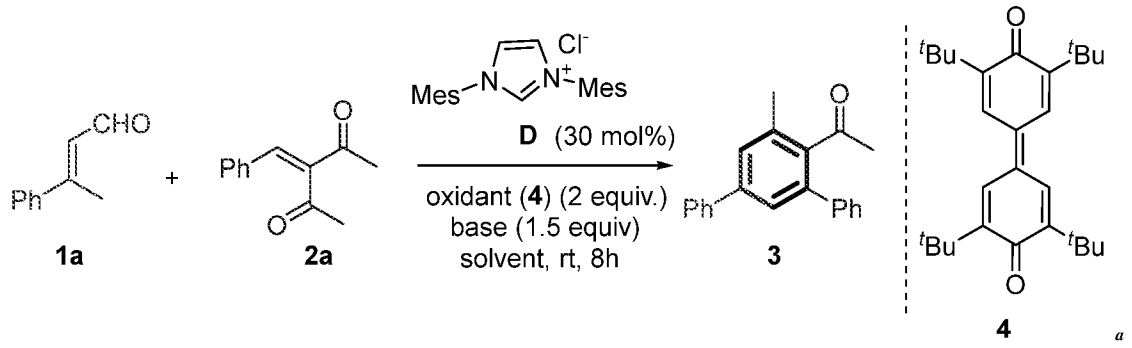
Table 1. condition optimization for NHC catalyzed [3+3] benzene construction.*



Entry	NHC (mol%)	Yield* (%)
1	0	0
2	**A** (30)	trace
3	**B** (30)	trace
4	**C** (30)	88
5	**D** (30)	trace
6	**E** (30)	47
7	**C**(5)	76

* isolated yield.

Table 2. Base and solvent optimization

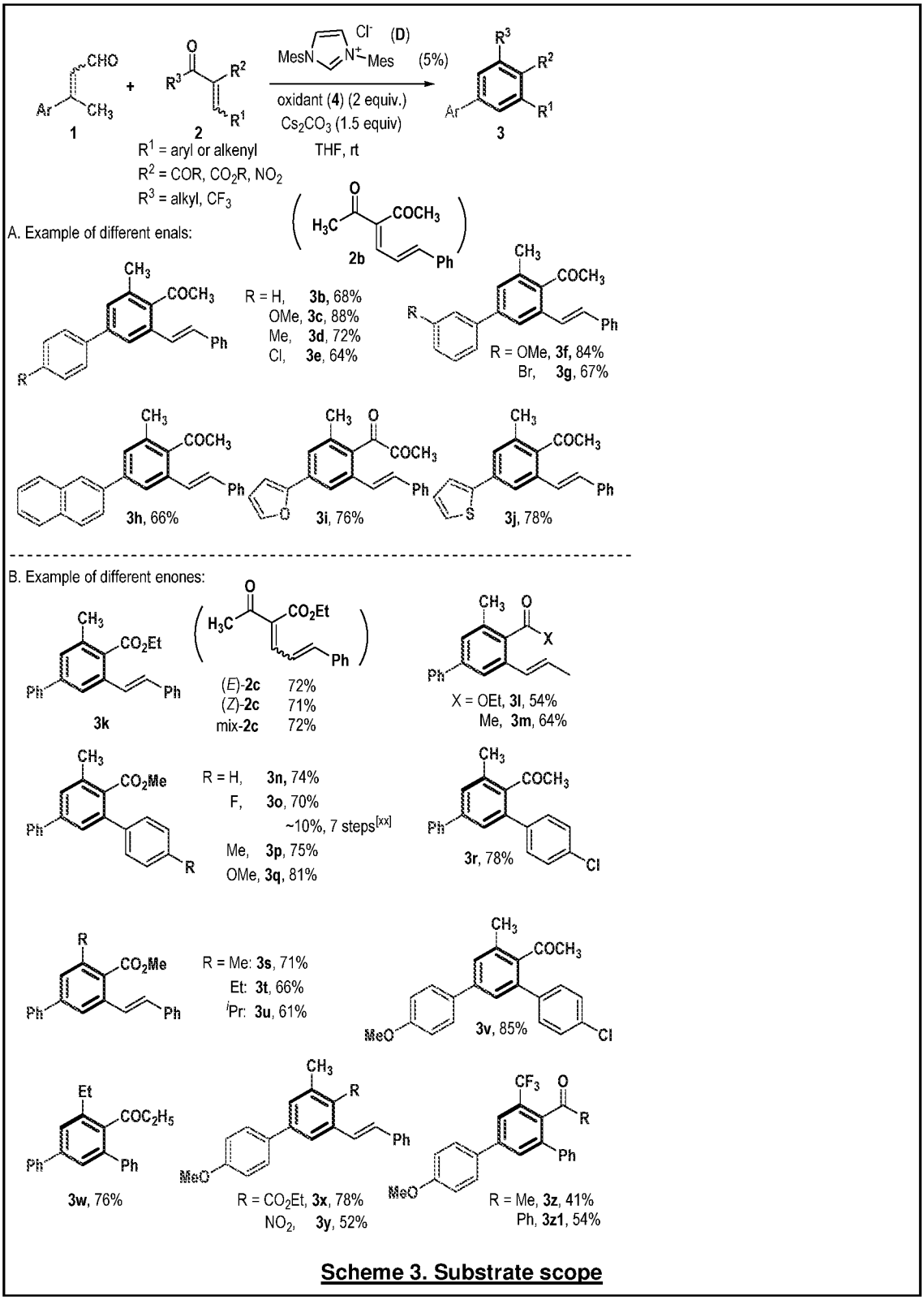


Entry	Base	Solvent	Yield (%)[b]
1	^{t}BuOK	THF	76
2	Cs_2CO_3	THF	88
3	K_2CO_3	THF	71
4	DBU	THF	82
5	Et_3N	THF	68
6	DIEA	THF	64
7	TBD	THF	75
8	Cs_2CO_3	CH_2Cl_2	51
9	Cs_2CO_3	^{t}BuOH	42
10	Cs_2CO_3	CH_3CN	54
11	Cs_2CO_3	Toluene	68
12	Cs_2CO_3	DMF	47
13	Cs_2CO_3	Acetone	74
14	Cs_2CO_3	EtOAc	62
15[e]	Cs_2CO_3	THF	76
16[c]	Cs_2CO_3[d]	THF	62
17[c,e]	Cs_2CO_3	THF	48

[a] unless further mentioned, the reactions were carried out with enal **1a** (0.1 mmol), enone **2a** (0.1 mmol), oxidant **4** (0.2 mmol), catalyst **D** (0.03 mmol), base (0.15 mmol) in solvent (1.0 mL). [b] isolated yield. [c] 0.005 mmol catalyst **D** was used. [d] 0.1 mmol base was used. [e] 0. 1 mmol oxidant **4** was used.

As shown in Table 2, screening of different inorganic and organic bases showed that Cs_2CO_3 was the best base (Table 2, entries 1-7). Employing other solvents all led to decrease of yield (Table 2, entries 8-14). THF remained the best choice. The catalyst loading could be reduced to 5 mol% without obvious yield decline (Table 2, entry 15). Reducing amount of base (Table 2, entry 16) or oxidant (Table 2, entry 17) would decrease the yield. Condition described in entry 15 was selected as the optimized condition.

[038] With an acceptable reaction condition on hand (Table 1, entry 4), the scope of the reaction was evaluated. To demonstrate broader synthetic utility of this method, enone **2b** bearing an alkene group (amenable for further transformation) was chosen as a model enone substrate to study the generality of the enal substrates (Scheme. 3A, product **3b-x**). Both electron-donating (product **3c-d**, **3f**) and electron-withdrawing group (product **3e**, **3g**) at the *para* position (product **3c-e**) or *meta* position (product **3f-g**) of the β-phenyl group were well tolerated. Replacement of the β-phenyl substituent with a naphthyl (product **3h**) or heteroaryl unit (product **3i-j**) had little effect on the reaction outcome. It is worth to note that *E*- or *Z*-isomer of enal **1** gave essentially the same yields, so a mixture *E*-/*Z*-enals can directly used.



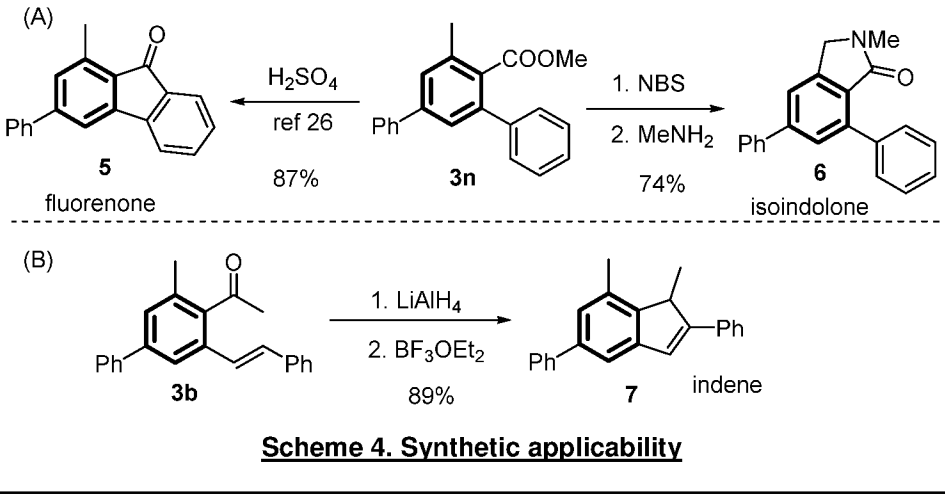
Scheme 3. Substrate scope

[039] With aldehydes **1a** and **1b** (R^1 = 4-OCH_3-C_6H_4) as model nucleophile, the scope of enones was also examined. As shown in Scheme 3B, in nearly all cases, the reaction

proceeded smoothly at room temperature to give polysubstituted benzenes in moderate to good yields. Notably, the *E*-/*Z*-configuration of enone **2** did not affect the reaction outcomes either (e.g., see product **3k**), which greatly simplify substrate preparation process. Both electron-rich (products **3p-q**) or electron-deficient (products **3o** and **3r**) aromatic groups, as well as vinyl groups (product **3k-m**) were all tolerated in β-substituent (R^2) of enone substrates. α-Substituent (R^3) of the enone substrates can be electron-deficient units such as acyl (**3m**, **3r, 3v-3w**), ester (**3k-l**, **3n-q**), or nitro (**3y**) groups. Substituent in carbonyl group of enones **2** (R^4) can be different alkyl group including methyl (**3k-q**, **3r-s**), ethyl (**3t** and **3w**), isopropyl (**3u**) or trifluoromethyl (**3z-z1**) group.

[040] It is important to note that the polysubstituted benzene molecules accessed in a single step with present approach were difficult to prepare previously. For example, previous method for the synthesis of benzoate **3o** required 7 steps with less than 10% overall yields; previous synthesis of **3p** and **3q** needed 3 steps reaction with 35% and 39% overall yield, respectively. Present method also provides extremely effective access to aromatic molecules with trifluoromethyl (CF_3) substituent. In organic synthesis, regioselective C-H trifluoromethylation or methylation of aryl molecules still remains challenging despite the rapid development in recent years.

[041] It is next demonstrated effective transformation of present catalytic reaction products to bicyclic and multicylic aromatic molecules that are found as key scaffold in natural products and functional synthetic molecules. For example, the multi-substituted benzene adduct **3b** could be transformed to indene **7** via reduction followed by Lewis acid-mediated cyclization; 2,4,6-trisubstituted benzoate **3n** can be transformed to fluorenone **5** or isoindolone **6** via straightforward processes (Scheme 4).



Scheme 4. Synthetic applicability

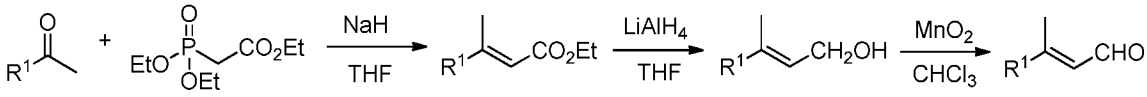
[042] The reactions are expected to construct other type of substitution pattern of benzene and to introduce enantioselective control using chiral *N*-heterocyclic carbene.

[043] Experimental details

[044] Commercially available materials purchased form Alfa Aesar or Aldrich was used as received. THF was distilled from Na and used directly. All anaerobic and moisture-sensitive manipulations were carried out with standard Schlenk techniques under predried nitrogen. Proton nuclear magnetic resonance (^{1}H NMR) spectra and Carbon nuclear magnetic resonance (^{13}C NMR) were recorded on Bruker Avance 400 (400 MHz) spectrometer or Bruker Avance 500 (500 MHz) spectrometer in $CDCl_3$ [using 0.03% tetramethylsilane as internal standard (for ^{1}H NMR, δ = 0.00)]. Fluoride nuclear magnetic resonance (^{19}F NMR) were recorded on Bruker Avance 400 (400 MHz) spectrometer (376 MHz). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Chemical shifts were recorded in parts per million (ppm, δ) relative to chloroform (for ^{1}H NMR, δ = 7.26 ppm, singlet; for ^{13}C NMR, δ = 77.23 ppm, triplet). High resolution mass spectral analysis (HRMS) was performed on Waters Q-TOF Premier mass spectrometer. Analytical thin-

layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness).

[045] General procedure for the preparation of enal substrates



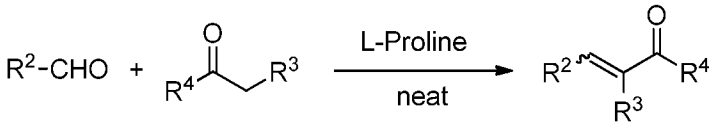
[046] The enal substrates were prepared and characterized according to a known procedure, as briefed below:

[047] Step 1: To a 100 mL round bottom flask containing NaH (20 mmol, 60% mineral dispersion) and anhydrous THF (40 mL) at 0 °C, was added triethyl phosphonoacetate (21.5 mmol) dropwise via an addition funnel. The reaction mixture was naturally warmed to room temperature, followed by a dropwise addition of a acetophenone solution (13 mmol, in 20 mL anhydrous THF). The reaction mixture was stirred for 12 hours, and then poured into a separating funnel containing water. The organic layer was collected, and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was subjected to flash chromatography (hexanes/EtOAc: 95/5) to afford the corresponding α,β-unsaturated ester as a light yellow oil.

[048] Step 2: To a 100 mL round bottom flask containing the unsaturated ester (20 mmol) obtained above and anhydrous THF (40 mL), was carefully added $LiAlH_4$ (25 mmol) in a few portions at 0 °C. The reaction mixture was gradually warmed to room temperature and stirred for overnight. The reaction mixture was then cooled to 0 °C and quenched with 1 M aqueous HCl. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was subjected to flash chromatography (hexanes/EtOAc: 50/50) to afford the corresponding allylic alcohol as a light yellow oil.

[049] Step 3: To a 100 mL round bottom flask containing the allylic alcohol (20 mmol) obtained above, was added activated MnO_2 (100 mmol) and anhydrous $CHCl_3$ (40 mL) at room temperature. The reaction mixture was then stirred at 60 °C. After complete consumption of the starting material (as indicated by TLC analysis), the reaction mixture was filtered through a pad of celite. The resulting filtrate was concentrated under reduced pressure. The crude residue was subjected to flash chromatography (hexanes/EtOAc: 95/5) to afford the corresponding β,β-disubstituted enal as a light yellow oil.

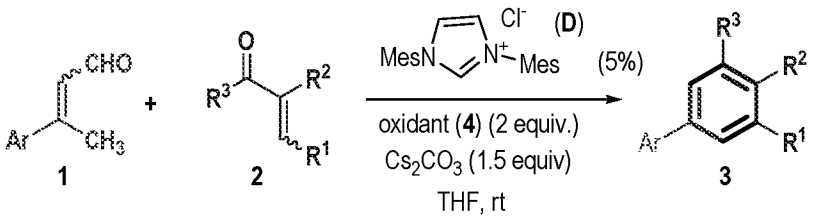
[050] General procedure for the preparation of enone substrates



[051] The enal substrates were prepared and characterized according to a known procedure, as briefed below:

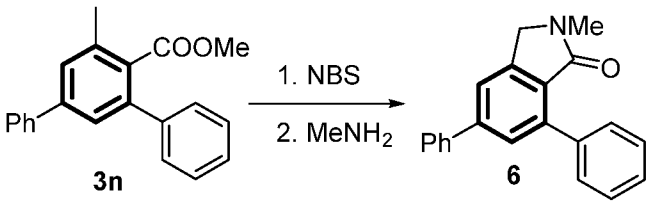
[052] To a 25 mL round bottom flask containing corresponding aldehyde (10 mmol) and ketone (10 mmol) was added L-Proline (115 mg, 1 mmol). If both aldehyde and ketone were solid, 1 mL EtOH was added as solvent. The reaction mixture was stirred at 60 °C. After complete consumption of the starting material (as indicated by TLC analysis), the reaction mixture was concentrated under reduced pressure. The crude residue was recrystallized in EtOH or subject to flash chromatography to afford the corresponding enones.

[053] General procedure for the catalytic [3+3] benzene construction from enal and enone

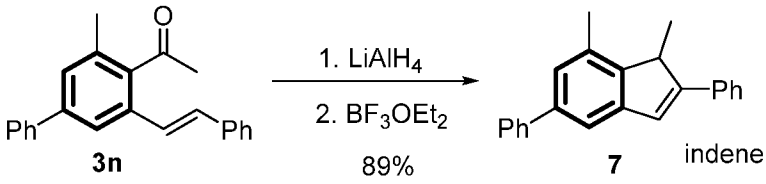


[054] Under N_2 atmosphere, a solution of enal (0.1 mmol), enone (0.1 mmol), oxidant **4** (82 mg, 0.2 mmol), Cs_2CO_3 (48.7 mmg, 0.15 mmol) and imidazolium **D** (1.7 mg, 0.005 mmol) in 1.0 mL THF was stirred at room temperature for 8 hours. The mixture was concentrated under reduced pressure and purified by silica gel column chromatography to afford the corresponding product **3**.

[055] General procedure for the synthetic applicability



[056] Benzoate **6a** (30 mg, 0.1 mmol), NBS (26.7 mg, 0.15 mmol) and AIBN (5 mg, 0.02 mmol) were dissolved in benzene. The mixture was heated to reflux and stirred overnight. The mixture was cooled to room temperature, quenched with $NaHSO_3$ (aq.) and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude bromination product, which was then dissolved in 1 M CH_3NH_2 /MeOH (1 mL), and refluxed for 12h. After complete consumption of the starting material (as indicated by TLC analysis), the mixture was concentrated under reduced pressure and purified by silica gel column chromatography to afford the isoindolone **8** (22 mg, 74% yield).

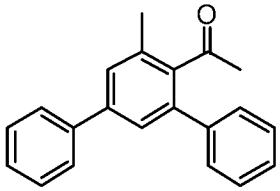


[057] To a solution of acetophenone **5a** in THF at 0 °C was added $LiAlH_4$. The mixture was stirred 0 °C for 15 min. After complete consumption of the starting material (as indicated by TLC analysis), the reaction was quenched with 1M HCl. The mixture was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The

crude residue was dissolved in CH_2Cl_2 and cooled to 0 °C . BF_3OEt_2 was slowly added to the solution. After stirring at 0 °C for further 5 min., the reaction was quenched with drops of $NaHCO_3$ (aq.). The mixture was concentrated under reduced pressure and purified by silica gel column chromatography to afford indene **9** (26 mg, 89% yield).

[058] Characterization of Products

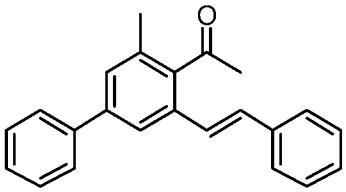
[059] 1-(5'-methyl-[1,1':3',1''-terphenyl]-4'-yl)ethanone (3a)



light yellow oil, 76% yield;

^{1}H NMR (400 MHz, $CDCl_3$) δ1.99 (s, 3H), 2.42 (s, 3H), 7.40-7.66 (m, 10H), 7.68-7.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 32.2, 126.2, 127.2, 127.8, 127.9, 128.4, 128.7, 128.8, 129.0, 134.5, 139.3, 140.24, 140.25, 140.5, 141.8, 207.6 ppm; HRMS (ESI) for $C_{21}H_{19}O$ $[M+H]^+$: calcd 287.1430, found 287.1432;

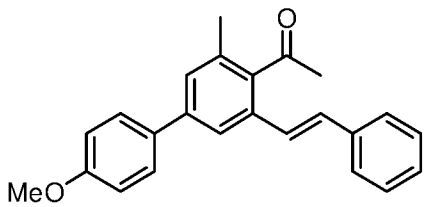
[060] (*E*)-1-(3-methyl-5-styryl-[1,1'-biphenyl]-4-yl)ethanone (3b)



light yellow powder, 68% yield;

ν_{max} (film, cm^{-1}): 1730, 1688, 1595, 1256, 1113, 968; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.53 (s, 3H), 7.08 (s, 2H), 7.32-7.28 (m, 1H), 7.38 (dd, *J* = 14.9, 7.6 Hz, 4H), 7.52-7.43 (m, 4H), 7.62 (d, *J* = 7.2 Hz, 2H), 7.67 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 32.9, 122.5, 125.4, 126.8, 127.2, 127.7, 128.2, 128.5, 128.8, 128.9, 132.3, 133.5, 133.9, 136.9, 140.3, 140.5, 141.9, 208.1 ppm; HRMS (ESI) for $C_{24}H_{23}O_2$ $[M+H]^+$: calcd 313.1587, found 313.1593;

[061] (*E*)-1-(4'-methoxy-3-methyl-5-styryl-[1,1'-biphenyl]-4-yl)ethanone (3c)

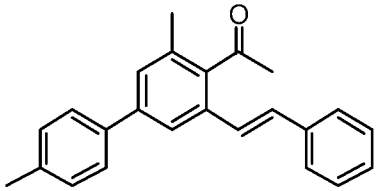


light yellow powder, 88% yield;

ν_{max} (film, cm^{-1}): 1712, 1682, 1595, 1516, 1254, 1180, 952, 827; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.55 (s, 3H), 3.90 (s, 3H), 7.03 (d, *J* = 8.7 Hz, 2H), 7.10 (s, 2H), 7.35-7.29 (m, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.52 (d, *J* = 7.4 Hz, 2H), 7.59 (d, *J* = 8.7 Hz, 2H), 7.66 (s, 1H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 19.4, 33.0, 55.4, 114.3, 122.0, 125.5, 126.8, 128.1, 128.2, 128.8, 132.2, 132.9, 133.5, 133.9, 136.9, 139.8, 141.5, 159.5, 208.2 ppm; HRMS (ESI) for $C_{23}H_{21}O$ $[M+H]^+$: calcd 313.1587, found 313.1593; HRMS (ESI) for $C_{24}H_{23}O_2$ $[M+H]^+$: calcd 343.1693, found 343.1693;

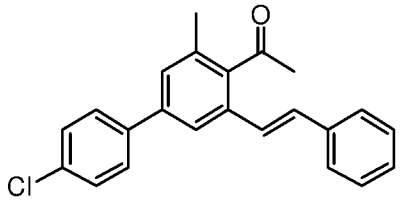
[062] (*E*)-1-(3,4'-dimethyl-5-styryl-[1,1'-biphenyl]-4-yl)ethanone (3d)



light yellow oil, 72% yield;

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.42 (s, 3H), 2.54 (s, 3H), 7.08 (s, 2H), 7.28-7.32 (m, 3H), 7.34 (s, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.49 (d, *J* = 7.2 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.66 (s, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 19.4, 21.1, 32.9, 122.3, 124.1, 125.5, 126.8, 127.0, 128.1, 128.3, 128.8, 129.6, 132.2, 133.5, 133.9, 136.9, 137.6, 140.1, 141.8, 208.1 ppm; HRMS (ESI) for $C_{24}H_{23}O$ $[M+H]^+$: calcd 327.1743, found 327.1747;

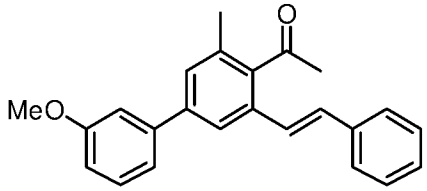
[063] (*E*)-1-(4'-chloro-3-methyl-5-styryl-[1,1'-biphenyl]-4-yl)ethanone (3e)



light yellow oil, 64% yield;

^{1}HNMR (500 MHz, $CDCl_3$) δ 2.38 (s, 3H), 2.55 (s, 3H), 7.09 (s, 2H), 7.33 (s, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 7.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.65 (s, 1H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 19.4, 32.9, 122.3, 125.2, 126.8, 128.3, 128.4, 128.8, 129.0, 132.5, 133.7, 133.9, 134.1, 136.8, 138.9, 140.6, 140.7, 207.9 ppm; HRMS (ESI) for $C_{23}H_{19}ClO$ $[M+H]^+$: calcd 347.1197, found 347.1205;

[064] (*E*)-1-(3'-methoxy-3-methyl-5-styryl-[1,1'-biphenyl]-4-yl)ethanone (3f)

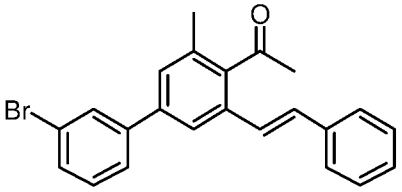


light yellow powder, 84% yield;

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.53 (s, 3H), 3.89 (s, 3H), 6.94 (dd, *J* = 2.0 Hz, 8.0 Hz, 1H), 7.08 (s, 2H), 7.15 (s, 1H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.34 (s, 1H), 7.36-7.41 (m, 3H), 7.49 (d, *J* = 7.5 Hz, 2H), 7.66 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.4, 32.9, 55.4, 113.0,

113.1, 119.7, 122.5, 125.3, 126.8, 128.2, 128.5, 128.8, 129.9, 132.3, 133.5, 133.9, 136.9, 140.4, 141.8, 142.0, 160.0, 208.1 ppm; HRMS (ESI) for $C_{24}H_{23}O_2$ $[M+H]^+$: calcd 343.1693, found 343.1696;

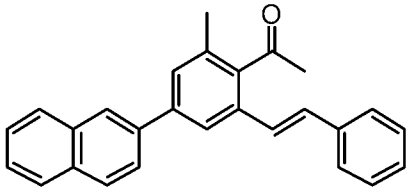
[065] (*E*)-1-(3'-bromo-3-methyl-5-styryl-[1,1'-biphenyl]-4-yl)ethanone (3g)



light yellow powder, 67% yield;

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.53 (s, 3H), 7.08 (dd, *J* = 12.0 Hz, 19.6 Hz, 2H), 7.31 (dd, *J* = 4.0, 3.2 Hz, 2H), 7.33-7.41 (m, 3H), 7.46-7.57 (m, 4H), 7.63 (d, *J* = 0.9 Hz, 1H), 7.76 (t, *J* = 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 32.9, 122.4, 123.0, 125.1, 125.8, 126.8, 128.3, 128.4, 128.8, 130.2, 130.4, 130.7, 132.6, 133.7, 134.1, 136.8, 140.4, 140.8, 142.6, 207.8 ppm; HRMS (ESI) for $C_{23}H_{20}BrO$ $[M+H]^+$: calcd 391.0692, found 391.0699;

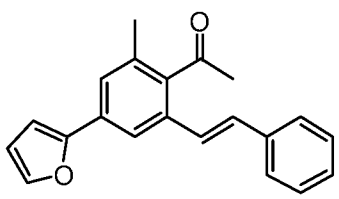
[066] (*E*)-1-(2-methyl-4-(naphthalen-2-yl)-6-styrylphenyl)ethanone (3h)



light yellow oil, 66% yield;

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.40 (s, 3H), 2.56 (s, 3H), 7.12 (dd, *J* = 12.8 Hz, 14.0 Hz), 7.30 (t, *J* = 7.3 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.48 (s, 1H), 7.49-7.57 (m, 4H), 7.78 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.80 (s, 1H), 7.89 (d, *J* = 7.4 Hz, 1H), 7.94 (t, *J* = 7.5 Hz, 2H), 8.08 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.4, 33.0, 122.8, 125.4, 126.0, 126.2, 126.5, 126.8, 127.7, 128.2, 128.3, 128.6, 128.7, 128.8, 132.4, 132.8, 133.7, 134.0, 136.9, 137.8, 140.4, 141.8, 208.1 ppm; HRMS (ESI) for $C_{27}H_{23}O$ $[M+H]^+$: calcd 363.1743, found 363.1747;

[067] (*E*)-1-(4-(furan-2-yl)-2-methyl-6-styrylphenyl)ethanone (3i)

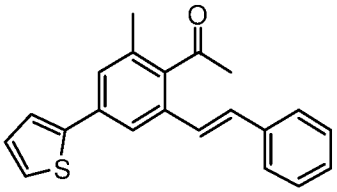


light yellow oil, 67% yield;

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.53 (s, 3H), 6.54 (dd, *J* = 1.6 Hz, 2.8 Hz, 1H), 6.76 (d, *J* = 2.8 Hz, 1H), 7.09 (dd, *J* = 12.8, 23.2 Hz, 2H), 7.32 (t, *J* = 6.0 Hz, 1H), 7.38-7.41 (m, 2H), 7.46 (s, 1H), 7.51-7.54 (m, 3H),

7.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 32.9, 105.9, 111.8, 118.9, 1248, 125.2, 126.8, 128.2, 128.8, 131.3, 132.4, 133.6, 134.0, 136.8, 140.2, 142.5, 153.2, 207.9 ppm; HRMS (ESI) for $C_{21}H_{18}O_2$ $[M+H]^+$: calcd 303.1380, found 303.1384;

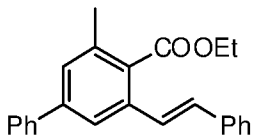
[068] (*E*)-1-(2-methyl-6-styryl-4-(thiophen-2-yl)phenyl)ethanone (3j)



light yellow oil, 78% yield;

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.51 (s, 3H), 7.05 (d, *J* = 2.2 Hz, 2H), 7.11 (dd, *J* = 5.1, 3.6 Hz, 1H), 7.34-7.28 (m, 2H), 7.38 (dt, *J* = 7.8, 5.1 Hz, 4H), 7.50 (d, *J* = 7.2 Hz, 2H), 7.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 32.9, 121.2, 123.7, 125.2, 125.4, 126.8, 127.1, 128.1, 128.2, 128.8, 132.6, 133.8, 134.2, 134.9, 136.8, 140.4, 143.4, 207.7 ppm; HRMS (ESI) for $C_{21}H_{19}OS$ $[M+H]^+$: calcd 319.1151, found 319.1158;

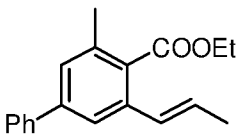
[069] (*E*)-ethyl 3-methyl-5-styryl-[1,1'-biphenyl]-4-carboxylate (3k)



light yellow oil, 72% yield;

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, *J* = 7.1 Hz, 3H), 2.43 (s, 3H), 4.46 (q, *J* = 7.1 Hz, 2H), 7.11 (d, *J* = 16.1 Hz, 1H), 7.23 (d, *J* = 15.0 Hz, 2H), 7.28-7.39 (m, 4H), 7.42 (d, *J* = 10.4 Hz, 1H), 7.45-7.53 (m, 3H), 7.58-7.66 (m, 2H), 7.71 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 19.9, 61.3, 122.0, 125.8, 126.7, 127.2, 127.8, 127.9, 128.3, 128.7, 128.8, 131.6, 131.9, 135.6, 135.8, 137.1, 140.5, 142.5, 169.6 ppm; HRMS (ESI) for $C_{24}H_{23}O_2$ $[M+H]^+$: calcd 343.1693, found 343.1692;

[070] (*E*)-ethyl 3-methyl-5-(prop-1-en-1-yl)-[1,1'-biphenyl]-4-carboxylate (3l)

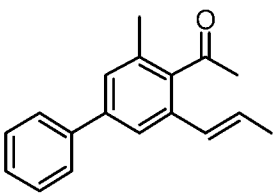


light yellow oil, 54% yield;

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (t, *J* = 7.1 Hz, 3H), 1.89 (d, *J* = 6.6 Hz, 3H), 2.38 (s, 3H), 4.39 (t, *J* = 7.1 Hz, 2H), 6.21-6.31 (m, 1H), 6.49 (d, *J* = 15.6 Hz, 1H), 7.28 (s, 1H), 7.33-7.40 (m, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.53 (s, 1H), 7.57 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 18.8, 19.8, 61.1, 122.0, 127.2, 127.5, 127.6,

128.1, 128.8, 128.9, 131.3, 135.4, 136.0, 140.7, 142.3, 169.9 ppm; HRMS (ESI) for $C_{19}H_{21}O_2$ $[M+H]^+$: calcd 281.1536, found 281.1539;

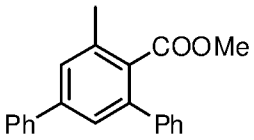
[071] (*E*)-1-(3-methyl-5-(prop-1-en-1-yl)-[1,1'-biphenyl]-4-yl)ethanone (3m)



light yellow oil, 64% yield;

^{1}H NMR (500 MHz, CDCl3) δ 1.89 (dd, *J* = 6.6, 1.6 Hz, 3H), 2.31 (s, 3H), 2.49 (s, 3H), 6.15-6.27 (m, 1H), 6.38 (dd, *J* = 15.6, 1.5 Hz, 1H), 7.28 (s, 1H), 7.33-7.39 (m, 1H), 7.44 (dd, *J* = 10.3, 4.8 Hz, 2H), 7.48 (s, 1H), 7.55-7.62 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.8, 19.3, 32.8, 122.5, 127.2, 127.6, 127.7, 127.9, 128.8, 129.8, 133.2, 134.4, 139.6, 140.6, 141.6, 208.4 ppm; HRMS (ESI) for $C_{18}H_{19}O$ $[M+H]^+$: calcd 251.1430, found 251.1435;

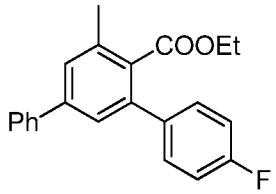
[072] methyl 5'-methyl-[1,1':3',1''-terphenyl]-4'-carboxylate (3n)



light yellow oil, 70% yield;

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (s, 3H), 3.62 (s, 3H), 7.37-7.49 (m, 10H), 7.64 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 51.9, 126.2, 127.3, 127.5, 127.8, 127.9, 128.2, 128.3, 128.8, 131.9, 136.2, 140.3, 140.8, 141.0, 142.4, 170.3 ppm; HRMS (ESI) for $C_{21}H_{19}O_2$ $[M+H]^+$: calcd 303.1380, found 303.1384;

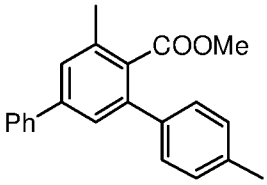
[073] methyl 4''-fluoro-5'-methyl-[1,1':3',1''-terphenyl]-4'-carboxylate (3o)



light yellow oil, 70% yield;

ν_{max} (film, cm^{-1}): 1726, 1607, 1512, 1263, 1088, 839, 760, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (t, *J* = 7.1 Hz, 3H), 2.48 (s, 3H), 4.10 (q, *J* = 7.1 Hz, 2H), 7.09 (t, *J* = 8.7 Hz, 2H), 7.33-7.42 (m, 4H), 7.45 (t, *J* = 7.4 Hz, 3H), 7.57-7.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 19.9, 61.0, 115.1 (d, J_{CF} = 21 Hz), 126.1, 127.2, 127.8, 128.0, 128.9, 130.1 (d, J_{CF} = 0.9 Hz), 132.2, 136.1, 137.0, 139.7, 140.2, 142.3, 162.3 (d, J_{CF} = 245 Hz), 169.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.2 ppm; HRMS (ESI) for $C_{22}H_{20}FO_2$ $[M+H]^+$: calcd 335.1442, found 335.1454;

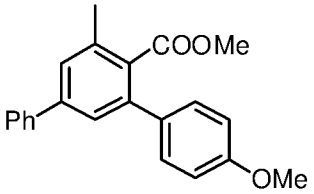
[074] methyl 4'',5'-dimethyl-[1,1':3',1''-terphenyl]-4'-carboxylate (3p)



light yellow oil, 75% yield

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.42 (s, 3H), 2.49 (s, 3H), 3.66 (s, 3H), 7.24 (d, *J* = 7.9 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.45-7.49 (m, 4H), 7.63 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.9, 21.2, 51.9, 126.2, 127.2, 127.7, 127.8, 128.1, 128.8, 129.1, 136.0, 137.2, 138.0, 140.3, 140.7, 142.3, 170.4 ppm; HRMS (ESI) for $C_{22}H_{21}O_2$ $[M+H]^+$: calcd 317.1536, found 317.1544;

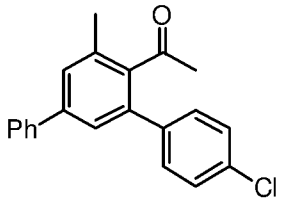
[075] methyl 4''-methoxy-5'-methyl-[1,1':3',1''-terphenyl]-4'-carboxylate (3q)



light yellow powder, 81% yield

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.49 (s, 3H), 3.67 (s, 3H), 3.88 (s, 3H), 6.97 (d, *J* = 8.7 Hz, 2H), 7.37-7.40 (m, 3H), 7.43-7.48 (m, 4H), 7.64 (dd, *J* = 6.0 Hz, 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.9, 51.9, 55.3, 113.8, 126.1, 127.2, 127.5, 127.7, 128.8, 129.4, 132.0, 133.3, 136.0, 136.1, 140.3, 142.3, 159.1, 170.5 ppm; HRMS (ESI) for $C_{22}H_{21}O_3$ $[M+H]^+$: calcd 333.1485, found 333.1486;

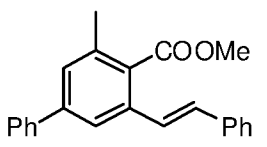
[076] 1-(4''-chloro-5'-methyl-[1,1':3',1''-terphenyl]-4'-yl)ethanone (3r)



light yellow powder, 78% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (s, 3H), 2.39 (s, 3H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.37-7.43 (m, 4H), 7.43-7.49 (m, 3H), 7.58-7.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 32.3, 126.1, 127.2, 127.9, 128.7, 128.9, 30.3, 134.2, 134.6, 137.9, 138.9, 140.1, 140.2, 141.9, 207.3 ppm; HRMS (ESI) for $C_{21}H_{18}ClO$ $[M+H]^+$: calcd 321.1041, found 321.1042;

[077] (*E*)-methyl 3-methyl-5-styryl-[1,1'-biphenyl]-4-carboxylate (3s)

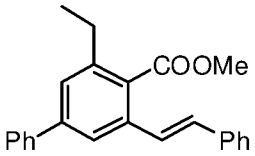


light yellow oil, 71% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 3.97 (s, 3H), 7.12 (d, *J* = 16.0

Hz, 1H), 7.20 (d, *J* = 16.0 Hz, 1H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.35-7.39 (m, 4H), 7.41-7.50 (m, 4H), 7.62 (d, *J* = 7.2 Hz, 2H), 7.72 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 52.2, 122.0, 125.8, 126.8, 127.2, 127.8, 128.0, 128.3, 128.7, 128.8, 131.6, 135.7, 136.0, 137.1, 140.5, 142.6, 170.1 ppm; HRMS (ESI) for $C_{23}H_{21}O_2$ $[M+H]^+$: calcd 329.1536, found 329.1541;

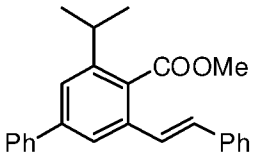
[078] (*E*)-methyl 3-ethyl-5-styryl-[1,1'-biphenyl]-4-carboxylate (3t)



light yellow oil, 66% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.6 Hz, 3H), 2.74 (q, *J* = 7.6 Hz, 2H), 4.00 (s, 3H), 7.14 (d, *J* = 16.0 Hz, 1H), 7.19 (d, *J* = 16.0 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.37-7.43 (m, 4H), 7.48-7.53 (m, 4H), 7.65 (d, *J* = 7.2 Hz, 2H), 7.75 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.7, 27.1, 52.2, 122.1, 125.7, 126.7, 126.8, 127.3, 127.8, 128.0, 128.7, 128.9, 131.3, 131.7, 135.5, 137.1, 140.7, 142.1, 142.8, 170.3 ppm; HRMS (ESI) for $C_{24}H_{23}O_2$ $[M+H]^+$: calcd 343.1693, found 343.1697;

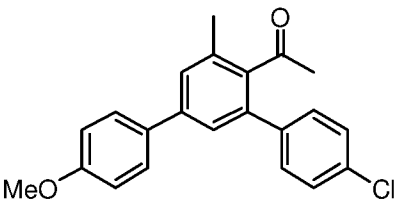
[079] (*E*)-methyl 3-isopropyl-5-styryl-[1,1'-biphenyl]-4-carboxylate (3u)



light yellow oil, 61% yield

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (d, *J* = 6.5 Hz, 6H), 2.98-3.04 (m, 1H), 4.00 (s, 3H), 7.15 (s, 2H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.37-7.44 (m, 3H), 7.48-7.52 (m, 5H), 7.66 (d, *J* = 7.5 Hz, 2H), 7.74 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.0, 31.6, 52.2, 122.1, 123.7, 125.6, 126.8, 127.3, 127.8, 128.0, 128.7, 128.8, 131.3, 131.8, 135.1, 137.1, 140.9, 142.8, 143.4, 170.6 ppm; HRMS (ESI) for $C_{25}H_{25}O_2$ $[M+H]^+$: calcd 357.1849, found 357.1853;

[080] 1-(4''-chloro-4-methoxy-5'-methyl-[1,1':3',1''-terphenyl]-4'-yl)ethanone (3v)

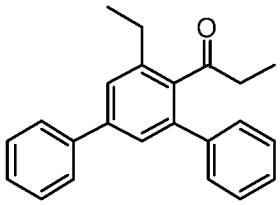


light yellow powder, 85% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (s, 3H), 2.38 (s, 3H), 3.86 (s, 3H), 6.99 (d, *J* = 8.8 Hz, 2H), 7.32-7.36 (m, 3H), 7.39 (s, 2H), 7.42 (d, *J* = 3.2 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

19.8, 32.3, 55.4, 114.3, 125.6, 128.2, 128.3, 128.9, 130.3, 132.5, 134.1, 134.6, 137.9, 139.0, 139.7, 141.5, 159.6, 207.4 ppm; HRMS (ESI) for $C_{22}H_{20}ClO_2$ $[M+H]^+$: calcd 351.1146, found 351.1148;

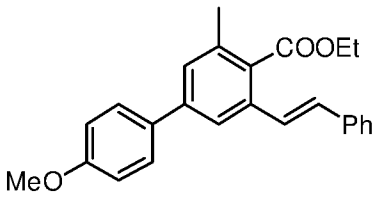
[081] 1-(5'-ethyl-[1,1':3',1''-terphenyl]-4'-yl)propan-1-one (3w)



light yellow oil, 76% yield;

ν_{max} (film, cm^{-1}): 1699, 1595, 1203, 947, 883, 760, 702; ^1H NMR (500 MHz, CDCl3) δ 0.84 (t, *J* = 7.2 Hz, 3H), 1.30 (t, *J* = 7.5 Hz, 3H), 2.19 (q, *J* = 7.2 Hz, 2H), 2.66 (q, *J* = 7.5 Hz, 2H), 7.39 (ddd, *J* = 9.9, 7.9, 3.6 Hz, 6H), 7.43-7.48 (m, 3H), 7.49 (d, *J* = 1.5 Hz, 1H), 7.59-7.67 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.86, 16.1, 26.5, 38.2, 126.2, 126.7, 127.2, 127.7, 128.6, 128.8, 129.1, 139.1, 139.9, 140.5, 140.6, 141.0, 141.8, 210.5 ppm; HRMS (ESI) for $C_{23}H_{23}O$ $[M+H]^+$: calcd 315.1743, found 315.1747;

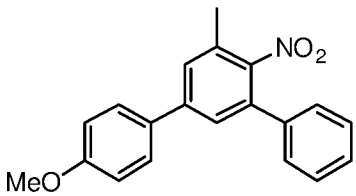
[082] (*E*)-ethyl 4'-methoxy-3-methyl-5-styryl-[1,1'-biphenyl]-4-carboxylate (3x)



light yellow oil, 78% yield

^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, *J* = 7.2 Hz, 3H), 2.42 (s, 3H), 3.87 (s, 3H), 4.46 (t, *J* = 7.2 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 16.0 Hz, 1H), 7.23 (d, *J* = 16.0 Hz, 1H), 7.28-7.32 (m, 1H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.49 (d, *J* = 7.6 Hz, 2H), 7.56 (d, *J* = 7.2 Hz, 2H), 7.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 19.9, 55.4, 61.2, 114.3, 121.6, 125.9, 126.7, 127.90, 127.93, 128.3, 128.7, 131.4, 133.0, 135.6, 135.8, 137.2, 142.1, 159.6, 169.7 ppm; HRMS (ESI) for $C_{25}H_{25}O_3$ $[M+H]^+$: calcd 373.1798, found 373.1799;

[083] 4-methoxy-5'-methyl-4'-nitro-1,1':3',1''-terphenyl (3y)

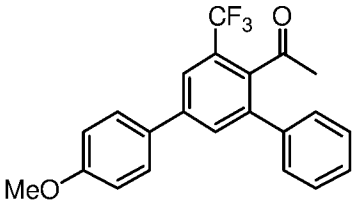


light yellow oil, 52% yield

^1H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 3.89 (s, 3H), 7.02 (d, *J* = 8.4 Hz, 2H), 7.43-7.47 (m, 6H), 7.48 (s, 1H), 7.57 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 55.4, 114.5, 123.5, 126.9, 128.0, 128.3, 128.4,

128.5, 128.8, 130.3, 131.6, 135.0, 137.0, 142.7, 160.0 ppm; HRMS (ESI) for $C_{20}H_{18}NO_3$ $[M+H]^+$: calcd 320.1281, found 320.1285;

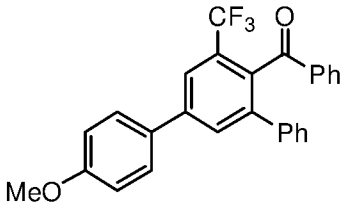
[084] 1-(4-methoxy-5'-(trifluoromethyl)-[1,1':3',1''-terphenyl]-4'-yl)ethanone (3z)



light yellow oil, 41% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (s, 3H), 3.87 (s, 3H), 7.01 (d, J = 8.8 Hz, 2H), 7.36-7.43 (m, 5H), 7.57 (d, J = 8.8 Hz, 2H), 7.71 (s, 1H), 7.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.8, 55.6, 114.8, 122.1 (q, J_{CF} = 268 Hz), 128.5, 128.6, 129.0, 129.4, 129.6, 131.4, 131.7, 139.0, 140.3, 142.0, 160.3, 204.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.91 ppm; HRMS (ESI) for $C_{22}H_{18}F_3O_2$ $[M+H]^+$: calcd 371.1253, found 371.1259;

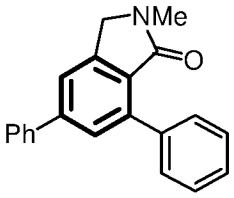
[085] (4-methoxy-5'-(trifluoromethyl)-[1,1':3',1''-terphenyl]-4'-yl)(phenyl)methanone (3z1)



light yellow oil, 54% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 7.03 (d, J = 8.4 Hz, 2H), 7.16-7.24 (m, 7H), 7.39 (t, J = 7.2 Hz, 1H), 7.55 (d, J = 7.6 Hz, 2H), 7.63 (d, J = 8.8 Hz, 2H), 7.75 (s, 1H), 7.96 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 114.6, 123.4 (q, J_{CF} = 274 Hz), 127.8, 128.1, 128.4, 128.5, 128.9, 129.1, 129.4, 131.2, 131.5, 135.2, 137.2, 138.8, 141.9, 142.0, 160.1, 196.4 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.47 ppm; HRMS (ESI) for $C_{27}H_{20}F_3O_2$ $[M+H]^+$: calcd 433.1410, found 433.1418;

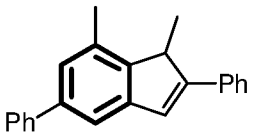
[086] 2-methyl-5,7-diphenylisoindolin-1-one (6)



light yellow oil, 74% yield;

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (s, 3H), 4..47 (s, 2H), 7.42-7.52 (m, 6H), 7.52-7.64 (m, 4H), 7.68 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.5, 51.3, 120.1, 127.4, 127.6, 127.8, 128.1, 128.6, 129.0, 129.8, 137.5, 140.2, 141.2, 143.0, 144.0, 167.8 ppm; HRMS (ESI) for $C_{21}H_{18}NO$ $[M+H]^+$: calcd 300.1383, found 300.1385;

[087] 1,7-dimethyl-2,5-diphenyl-1H-indene (7)



light powder, 89% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (d, *J* = 7.0 Hz, 3H), 2.58 (s, 3H), 4.07 (t, *J* = 7.0 Hz, 1H), 7.15 (s, 1H), 7.27 (s, 1H), 7.35-7.39 (m, 2H), 7.44-7.48 (m, 4H), 7.49 (s, 1H), 7.62 (d, *J* = 7.0 Hz, 2H), 7.66 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8, 18.9, 43.5, 117.8, 125.7, 126.0, 126.9, 127.0, 127.3, 127.4, 128.66, 128.68, 133.1, 135.2, 140.5, 141.8, 144.3, 146.6, 153.2 ppm; HRMS (ESI) for $C_{23}H_{21}$ $[M+H]^+$: calcd 297.1638, found 297.1641.

[088] By "comprising" it is meant including, but not limited to, whatever follows the word "comprising". Thus, use of the term "comprising" indicates that the listed elements are required or mandatory, but that other elements are optional and may or may not be present.

[089] By "consisting of" is meant including, and limited to, whatever follows the phrase "consisting of". Thus, the phrase "consisting of" indicates that the listed elements are required or mandatory, and that no other elements may be present.

[090] The inventions illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms "comprising", "including", "containing", etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the inventions embodied therein herein disclosed may be resorted to by those

skilled in the art, and that such modifications and variations are considered to be within the scope of this invention.

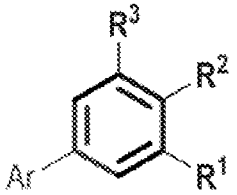
[091] By "about" in relation to a given numerical value, such as for temperature and period of time, it is meant to include numerical values within 10% of the specified value.

[092] The invention has been described broadly and generically herein. Each of the narrower species and sub-generic groupings falling within the generic disclosure also form part of the invention. This includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

[093] Other embodiments are within the following claims and non- limiting examples. In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group.

Claims

1. A method of forming a multi-substituted benzene compound of formula (3)



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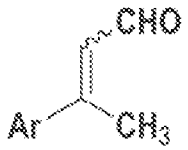
,

the method comprising:

reacting an enal of formula (1)



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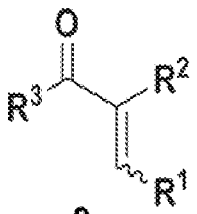
with an enone of formula (2)



2

in the presence of a N-heterocyclic carbene (NHC) pre-catalyst, an oxidant, a base, and an organic solvent ,

wherein:

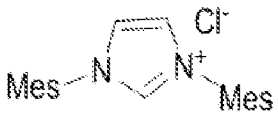
R^1, R^2, and R^3 are independently selected from the group consisting of a linear or branched, substituted or unsubstituted C_1-C_{20} alkyl; linear or branched, substituted or unsubstituted C_2-C_{20} alkenyl; linear or branched, substituted or unsubstituted C_2-C_{20} alkynyl; linear or branched, substituted or unsubstituted C_1-C_{20} alkoxy; substituted or unsubstituted C_3-C_{20} cycloalkyl; substituted or unsubstituted C_3-C_{20} cycloalkenyl;

substituted or unsubstituted C_5-C_{15} aryl; substituted or unsubstituted C_3-C_{15} heteroaryl, -C(O)-R, -NRR', -OR, -SR, -COOR, -CN, $-NO_2$, -C(O)-NRR', -NR'-C(O)-R, $-SO_2$-R and $-(SO_2)$-OR;

R and R' are independently selected from H and linear or branched, substituted or unsubstituted C_1-C_{10} alkyl; and

Ar is a substituted or unsubstituted C_5-C_{15} aryl, or a substituted or unsubstituted C_3-C_{15} heteroaryl.

2. The method of claim 1, wherein the NHC pre-catalyst is selected from the group consisting of:



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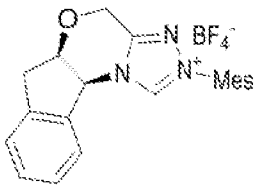
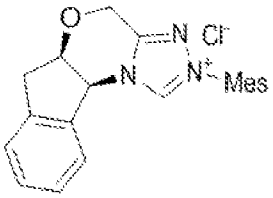


, and


, and a mixture thereof.

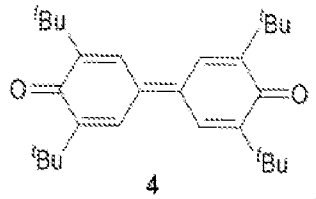
3. The method of claim 1 or 2, wherein the organic solvent is selected from the group consisting of THF, CH_2Cl_2, toluene, CH_3CN, DMF, and a mixture thereof.

4. The method of claim 3, wherein the organic solvent is THF.

5. The method of any one of claims 1-4, wherein the base is selected from the group consisting of Cs_2CO_3, Et_3N, DBU, ^tBuOK, K_2CO_3, DIEA, TBD, and a mixture thereof.

6. The method of claim 5, wherein the base is Cs_2CO_3.

7. The method of any one of claims 1-6, wherein the oxidant comprises a compound of formula (4)



4

8. The method of any one of claims 1-7, wherein the reaction is carried out at room temperature.

9. The method of any one of claims 1-8, wherein the reaction is carried out for a period of between 1 and 10 hours.

10. The method of claim 9, wherein the reaction is carried out for a period of between 5 and 10 hours.

11. The method of claim 10, wherein the reaction is carried out for 8 hours.

12. The method of any one of claims 1-11, wherein the reaction is carried out in an inert atmosphere.

13. The method of any one of claims 1-12, wherein the multi-substituted benzene compound of formula (3) is selected from the group consisting of:

1-(5'-methyl-[1,1':3',1''-terphenyl]-4'-yl)ethanone (3a);

(*E*)-1-(3-methyl-5-styryl-[1,1'-biphenyl]-4-yl)ethanone (3b);

(*E*)-1-(4'-methoxy-3-methyl-5-styryl-[1,1'-biphenyl]-4-yl)ethanone (3c);

(*E*)-1-(3,4'-dimethyl-5-styryl-[1,1'-biphenyl]-4-yl)ethanone (3d);

(*E*)-1-(4'-chloro-3-methyl-5-styryl-[1,1'-biphenyl]-4-yl)ethanone (3e);

(*E*)-1-(3'-methoxy-3-methyl-5-styryl-[1,1'-biphenyl]-4-yl)ethanone (3f);

(*E*)-1-(3'-bromo-3-methyl-5-styryl-[1,1'-biphenyl]-4-yl)ethanone (3g);

(*E*)-1-(2-methyl-4-(naphthalen-2-yl)-6-styrylphenyl)ethanone (3h);

(*E*)-1-(4-(furan-2-yl)-2-methyl-6-styrylphenyl)ethanone (3i);

(*E*)-1-(2-methyl-6-styryl-4-(thiophen-2-yl)phenyl)ethanone (3j);

(*E*)-ethyl 3-methyl-5-styryl-[1,1'-biphenyl]-4-carboxylate (3k);

(*E*)-ethyl 3-methyl-5-(prop-1-en-1-yl)-[1,1'-biphenyl]-4-carboxylate (3l);

(*E*)-1-(3-methyl-5-(prop-1-en-1-yl)-[1,1'-biphenyl]-4-yl)ethanone (3m);

methyl 5'-methyl-[1,1':3',1"-terphenyl]-4'-carboxylate (3n);

methyl 4"-fluoro-5'-methyl-[1,1':3',1"-terphenyl]-4'-carboxylate (3o);

methyl 4",5'-dimethyl-[1,1':3',1"-terphenyl]-4'-carboxylate (3p);

methyl 4"-methoxy-5'-methyl-[1,1':3',1"-terphenyl]-4'-carboxylate (3q);

1-(4"-chloro-5'-methyl-[1,1':3',1"-terphenyl]-4'-yl)ethanone (3r);

(*E*)-methyl 3-methyl-5-styryl-[1,1'-biphenyl]-4-carboxylate (3s);

(*E*)-methyl 3-ethyl-5-styryl-[1,1'-biphenyl]-4-carboxylate (3t);

(*E*)-methyl 3-isopropyl-5-styryl-[1,1'-biphenyl]-4-carboxylate (3u);

1-(4"-chloro-4-methoxy-5'-methyl-[1,1':3',1"-terphenyl]-4'-yl)ethanone (3v);

1-(5'-ethyl-[1,1':3',1"-terphenyl]-4'-yl)propan-1-one (3w);

(*E*)-ethyl 4'-methoxy-3-methyl-5-styryl-[1,1'-biphenyl]-4-carboxylate (3x);

4-methoxy-5'-methyl-4'-nitro-1,1':3',1"-terphenyl (3y);

1-(4-methoxy-5'-(trifluoromethyl)-[1,1':3',1"-terphenyl]-4'-yl)ethanone (3z); and

(4-methoxy-5'-(trifluoromethyl)-[1,1':3',1"-terphenyl]-4'-yl)(phenyl)methanone (3z1).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2015/050223

A. CLASSIFICATION OF SUBJECT MATTER

C07C 2/52 (2006.01) ***C07C 69/78 (2006.01)*** ***C07C 49/784 (2006.01)*** ***C07C 49/796 (2006.01)*** ***C07C 49/84 (2006.01)*** ***C07C 49/813 (2006.01)*** ***C07D 307/46 (2006.01)*** ***C07D 333/22 (2006.01)*** ***C07C 205/35 (2006.01)*** ***C07D 209/46 (2006.01)*** ***C07C 13/465 (2006.01)***

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Espacenet. Applicant and inventor search. "NANYANG" and "Chi" or "Zhu" or "Zhu, Tingshun" or ("Zhu" and C07C) or ("Zhu" and "carbene") or ("Zhu" and "cycloaddition").

STN (CASREACT). Reaction search including reactant/reagents based on the structures of enal of formula 1 and enone of formula 2 of claim 1 and including a product based on the compound of formula 3 of claim 1.

STN (Registry) Structure search based on enal of formula 1 of claim 1 as a reactant and keyword search based upon cycloaddition and carbene.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 September 2015	07 September 2015
Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	Maree Staples AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. 0262223634

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/SG2015/050223**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chiang, P., and Bode, J., "N-mesityl substituted chiral triazolium salts: opening a new world of N-heterocyclic carbene catalysis", TCI Mail, 2012, No. 149, pages 2–17. Page 4, Scheme 3; page 7, Scheme 8; page 5, Scheme 5; and page 11, Scheme 16; and page 10, Scheme 15.	1-13
A	Rong, Z., Jia, M., and You, S., "Enantioselective N-heterocyclic carbene-catalyzed Michael addition to α,β-unsaturated aldehydes by redox oxidation", Organic Letters, 2011, Vol. 13, No. 15, pages 4080–4083. Abstract; page 4081, paragraph bridging columns 1 and 2; page 4082, Table 1; and page 4081, Figure 1.	1-13
A	Nair, V., Vellalath, S., Poonoth, M. and Suresh, E., "N-heterocyclic carbene-catalyzed reaction of chalcones and enals via homoenolate: an efficient synthesis of 1,3,4-trisubstituted cyclopentenes", J. Am. Chem. Soc., 2006, Vol. 128, pages 8736–8737. Page 8736, Table 1 and paragraph 2.	1-13
P,X	Zhu, T., et al, "Benzene construction via organocatalytic formal [3+3] cycloaddition reaction", Nature Communications, 2014, No. 5, Article 5027, pages 1-6. Whole document.	1-13

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/SG2015/050223**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.