Highly Reactive Cyclic Monoaryl Iodoniums Tuned as Carbene Generators Couple with Nucleophiles under Metal-Free Conditions

HIGHLIGHTS
- Highly reactive cyclic monoaryl-vinyl iodoniums were designed and synthesized
- Coupling reactions with various nucleophiles took place in metal-free condition
- A mechanism involving carbene species from cyclic vinyl iodoniums was hypothesized
- Flexible transformations to build up chemical library through DOS strategy

Wang et al., iScience 23, 101307
July 24, 2020 © 2020 The Authors.
https://doi.org/10.1016/j.isci.2020.101307
Highly Reactive Cyclic Monoaryl Iodoniums Tuned as Carbene Generators Couple with Nucleophiles under Metal-Free Conditions

Haiwen Wang,1 Liyun Liang,1 Zhirong Guo,1 Hui Peng,1 Shuang Qiao,1 Nemai Saha,2 Daqian Zhu,1 Wenbin Zeng,3 Yunyun Chen,4 Peng Huang,1,* and Shijun Wen1,5,*

SUMMARY
Cross-coupling reactions between aryl iodide and nucleophiles have been well developed. Iodoniums equipped with a reactive C-I(III) bond accelerate cross-coupling reactions of aryl iodide. Among them, cyclic diaryliodoniums are more atom economical; however, they are often in the trap of metal reliance and encounter regioselectivity issues. Now, we have developed a series of highly reactive cyclic monoaryl-vinyl iodoniums that can be tuned to construct C-N, C-O, and C-C bonds without metal catalysis. Under promotion of triethylamine, coupling reactions with aniline, phenol, aromatic acid, and indole proceed rapidly and regioselectively at room temperature. The carbene species is conceptualized as a key intermediate in our mechanism model. Furthermore, the coupling products enable diversity-oriented synthesis strategy to further build up a chemical library of diverse heterocyclic fragments that are in demand in the drug discovery field. Our current work provides a deep insight into the synthetic application of these highly reactive cyclic iodoniums.

INTRODUCTION
Cross-coupling reactions have become one of the most effective synthetic methods for constructing chemical bonds and linking molecular fragments (Liu et al., 2011). The traditional cross-coupling reactions between aryl iodide and nucleophiles are often transition-metal catalyzed, for example, Heck, Ullmann, and Suzuki-Miyaura cross-couplings (Evano et al., 2008; Ruiz-Castillo and Buchwald, 2016). The bond cleavage of C-I in aryl iodide to make new bonds often requires high-temperature, transition-metal catalysis, and long reaction time (Figure 1A) (Biffis et al., 2018). To overcome such limitations, new reactants and methods are demanded to enable coupling reactions more conveniently (Sun and Shi, 2014). Hypervalent aryl iodine(III), also called aryliodonium(III), has increased the reactivity of C-I bond to make coupling reactions easier (Luukomt and Gaunt, 2017; Merritt and Olofsson, 2009; Teskey et al., 2017; Yoshimura and Zhdankin, 2016). Compared with linear aryliodoniums, cyclic diaryliodoniums (cDAIs) are more atom economical in their coupling reactions. cDAIs are able to react with a broad range of reagents and to construct diverse multi-aromatic fragments that often exist in drugs and natural products (Mathew et al., 2017; Zhu et al., 2018). However, some innate defects of cDAIs particularly including the reliance on catalytic metal (Chatterjee and Goswami, 2017; Hu et al., 2019) and poor regioselectivity (Deprez and Sanford, 2009; Liu et al., 2014), limit their synthetic applications (Figure 1B). Breaking the diaryl framework of cDAIs, cyclic monoaryl-vinyl iodoniums (cMAVIs) could be conceived. In this new framework, the hypervalent iodine is structurally asymmetrical and unbalanced in charge distribution, which may enhance the reaction regioselectivity. Furthermore, compared with cDAIs, the deficient electron density of the hypervalent iodine in cMAVIs is not easy to offset in the monoaryl-vinyl system, rendering them highly electrophilic. However, cMAVIs are almost unexplored until very recently Moran and co-workers reported the synthesis of cMAVIs with limited chemical study (Beringer et al., 1972; Kepski et al., 2019). Herein, we report a special series of cMAVIs that could be finely tuned to react with various nucleophilic reagents regioselectively, enabling the rapid construction of C-N, C-O, and C-C bond under metal-free conditions via a carbene pathway (Figure 1C).

RESULTS AND DISCUSSION
The Design of New cMAVIs and Their Reactivity Study
To commence our study, four types of cMAVIs have been designed (Figure 2A). While a carbonyl group was installed to stabilize the iodine charge, various R groups were taken into consideration to test its impact on
chemical properties, including alkyl (1a), aryl (1b), halogen (1c), and hydrogen (1d). After the preparation of precursors 1° of cMAVIs (see Supplemental Information) (Ho et al., 2007; Puri et al., 2014; Roy et al., 2011), cMAVIs 1a-1d were obtained in good yields using the procedure for the synthesis of cDAIs (Zhu et al., 2013). The crystal X-ray diffraction unambiguously verified the structure of 1a. With these four cMAVIs at hand, we tested their stability under various conditions (Table S1). The cMAVIs were all stable in either powder or solution at room temperature and even under heating. However, in the presence of triethylamine, cMAVIs 1a-1c underwent a reductive ring opening to produce 3a-3c. Meanwhile, 1d had β-hydrogen elimination ring opening, which is consistent with Moran’s report (Figures 2B and S1) (Kepski et al., 2019). The newly obtained results indicated that these cMAVIs were vulnerable to triethylamine. On the other hand, their instability to bases implied that they might be highly reactive even without a transition metal, which is unusual for traditional cDAIs (Li et al., 2019; Wu and Yoshikai, 2015). It would be valuable if their reactivity could be tuned under refined conditions. Meanwhile, the iodine moving to the aryl side in the reductive products 3 implied that an excellent regioselectivity with cMAVIs could be achieved, which is challenging in unsymmetrical cDAIs. Thus, we hypothesized that our synthesized cMAVIs might provide a synthon platform and achieve the complete regioselectivity under transition-metal-free condition, which is highly demanded in the field of synthetic chemistry (Ellwart et al., 2016).

Considering that triethylamine is a strong organic base, p-toluidine with weak basicity was employed to test whether it could undergo amination with cMAVIs. In the presence of p-toluidine only, 1a-1c remained intact, although 1d still led to the β-hydrogen elimination, implying that activation of 1a-1c could be initiated by trimethylamine but not p-toluidine. While both triethylamine and p-toluidine were added into the solution of cMAVIs, a new C-N bond was formed rapidly to provide the amination product 4a at an excellent yield (Figure 2B). The iodine was located to the aryl side, and p-toluidine was linked to the vinyl side.
selectively. Moreover, the internal C-C double bond unexpectedly migrated to the adjacent methyl. Such amination did not happen in cMAVIs 1b and 1c, and only reductive products 3b and 3c remained (Figure S1). After the success of 1a attached with a methyl group, ethyl was also tested. However, the cMAVI with ethyl could not fulfill this amination and it almost converted to 3a-like reductive product, likely due to its spatial effect. Meanwhile, 1a was under thorough investigation to optimize the amination condition. Further screening demonstrated that organic bases including triethylamine and diisopropyl ethylamine were most effective (Figure 2C). Environment-friendly solvent EtOH and THF were as effective as dichloromethane, so they were selected in further study. Variation of temperature did not compromise the amination yields. After success in tuning cMAVI 1a to react with \( p \)-toluidine in complete regioselectivity under metal-free condition, a series of 1a-alike cMAVIs were designed and synthesized (Figure 2D).

**The Exploration of Coupling Reactions with 1a-alike cMAVIs**

As the optimal condition for the coupling amination of cMAVI 1a with \( p \)-toluidine was obtained, the scope of both cMAVIs and amines was investigated (Figure 3A). 1a-alike cMAVIs (1ab-1ag) underwent amination smoothly to provide desired compounds 4aa-4ag at excellent yields. Simultaneously, the vinyl migration to the terminal methyl proceeded. Then, the scope of anilines was also tested to further explore the transformation generality. It turned out that not only simple aniline but also the sterically hindered anilines with an ortho substituent reacted well (4ah-4al). The acetylene group was well tolerated in this reaction (4ak), although terminal acetylenes reportedly react with traditional cDAIs (Xie et al., 2017). The structure of 4ak was further unambiguously verified by X-ray diffraction. It is worth mentioning that amidation of benzene-1,2-diamine with the intramolecular ester of 1a simultaneously proceeded along with conventional amination to make 4al. 

\[ N \]-substituted methyl group was also allowed to provide 4am. Furthermore, benzylamines were suitable substrates for such amination as well while the reactions were done in THF (4an and 4ao). Other alkylamines did not provide the desired products, most likely due to their strong basicity. As azoles could be employed as \( N \)-nucleophiles and important heterocyclic fragments (Sun et al., 2015, 2016).
2020), benzotriazole was used to investigate the transformation. However, the double bond in the coupling product remained internal, likely due to strong electron-withdrawing effect of the triazole motif (data not shown).

After the amination success, we went to test whether coupling reactions with other nucleophiles would be possible under such metal-free condition. Initially, O-nucleophiles were taken into consideration for potential oxygenation of cMAVIs (Figure 3B). Phenol was chosen to react with 1a under the standard condition but with THF as the solvent due to a potential breakup of the newly formed ester bond by ethanol. The oxygenation product 4ba was indeed successfully obtained at a moderate yield. Vinyl migration to the terminal methyl took place simultaneously. Other phenols substituted with various functional groups also gave the desired products at moderate to good yields (4bb–4bf). Benzoic acids, another type of O-nucleophiles (Kitano et al., 2018; Petersen et al., 2011), were suitable substrates to couple with 1a, albeit

Figure 3. Scope of 1a-Alike cMAVIs and Nucleophiles in Transition-Metal-Free Coupling Reaction
(A) Scope of 1a-alike cMAVIs and N-nucleophiles.
(B) Scope of O-nucleophiles coupled with 1a
(C) Scope of C-nucleophile coupled with 1a.
Note: standard condition: 1 (1.0 equiv), 2 (1.5 equiv), Et3N (2.0 equiv), EtOH, r.t., 30 min; isolated yields. *1 gram scale reaction for 1a; †12 h; ‡in THF; §in THF, Et3N (3.5 equiv); unless stated, R1, R2 are H.
at slightly low yields (4bg-4bi). Aromatic α, β-unsaturated acids such as phenylpropiolic acid and cinnamic acid also gave the desired coupling products (4bj-4bk). However, alkyl carboxylic acids failed to undergo such oxygenation. Generally, it seemed that hard nucleophiles gave lower yields in the coupling reactions.

As indole fragment, a mild C-nucleophile (Leitch et al., 2017; Lin et al., 2019), is widely present in natural products and pharmaceuticals (Kochanowska-Karamyan and Hamann, 2010; Wan et al., 2019), its potential C-C bond formation with cMAVIs under the metal-free condition was of our interest. First, simple indole itself was tested under the standard condition and satisfactorily gave the desired product 4ca with C-C formation at 3-position of indole (Figure 3C). Other indole derivatives with methyl substitution on different positions were then investigated to expand the reaction generality. Except 3-methyl indole, the other tested indoles underwent the C-C coupling reaction successfully (4cb-4ce), implying that the C-C coupling reaction proceeded at 3-position of indole under our condition (Modha and Greaney, 2015). The successful reaction with indole demonstrated that cMAVIs were highly reactive at room temperature under catalyst-free conditions, although the yields were not satisfactory.

**Coupling Reactions Utilized to Construct Chemical Libraries**

Under these aforementioned explorations, we successfully tuned these novel highly reactive cMAVIs to rapidly couple with aniline, phenol, aromatic acid, and indole under transition-metal-free conditions with complete regioselectivity. Diversity-oriented synthesis (DOS) is an efficient strategy to quickly offer a large collection of structurally diverse small molecules for drug discovery (Grossmann et al., 2014). It was also our interest to employ DOS strategy to build chemical libraries. Starting from 1a and 1a-alike cMAVIs, our structurally diversified coupling products 4 could be transformed into different series of heterocyclic fragments (Figure 4). 4aa-4ag underwent palladium-catalyzed intracellular C-N formation to accomplish the indole ring construction in series 1 compounds (5a-5g) (Bugaenko et al., 2018; Ignatenko et al., 2010). Meanwhile, the terminal vinyl double bond in 4aa could be used as an acceptor for halogenation (Meimetis et al., 2014; Song et al., 2013). Then, NBS was utilized to assemble 2-substituted 3-quaternary carbon-centered indole 6 that is not easily prepared via conventional methods (series 2) (Golubev and Krasavin, 2017). As mentioned earlier, ortho-substituted functional groups in anilines were well tolerated in the
amination (Figure 3, 4ai-4al). Moreover, these groups were able to participate in further transformation so that more series of heterocyclic fragments could be obtained. The condition used for the construction of series 1 compounds also enabled 4ai to finish the formation of two rings featuring 5 and 7 members (7, series 3). Ortho-bromo-substituted 4ao and alike derivatives could undergo double C-C bond formations to build up 5- and 6-membered rings (8a-8d, series 4) (Gómez-Lor and Echavarren, 2004; Rousseaux et al., 2010). Orthoboronic acid functional group in anilines was also compatible for the amination; however, it was labile during the silica column chromatography. Without further purification, these obtained intermediates 4 were directly subjected to a palladium-mediated condition. Consequently, a specific azepine scaffolding, which is an important structural subunit in many bioactive alkaloids and medicines (Poulie and Bunch, 2013; Singh et al., 2017), was constructed successfully at moderate yields (9a-9d, series 5). Indole-incorporating compound 4ca could undergo a palladium-catalyzed cyclization to provide a specific carbazole fragment (10, series 6). Taken together, six series of chemical fragments are rapidly built from our developed cMAVIs in two steps. These high-quality fragments are demanded in the drug discovery, especially in the fragment-based approaches (Alen et al., 2019; Heightman et al., 2018; Kirsch et al., 2019).

**Coupling Reactions’ Mechanism Study**

Due to the observation of vinyl migration, we hypothesized that carbene pathway might be involved (Dempsey Hyatt et al., 2015; Hyatt and Croatt, 2012; Kepski et al., 2019). A series of experiments were performed to test our hypothesis. Deuterated p-toluidine was employed to react with cMAVI 1a. Indeed α-deuterium is present in product 11-D (Figure 5A), confirming the possible presence of carbene intermediate species. It is worth mentioning that 11-H with α-hydrogen verified by 1HNMR spectra likely resulted from a hydrogen-deuterium exchange with the abstracted protons from 1a’s methyl by triethylamine. In another control experiment in which styrene was added, a cyclopropane product 12 in the reaction mixture was detected by liquid chromatography-mass spectrometry (MS) spectroscopy showing a mass ion peak at 433.1 (Figure 5B), further confirming the appearance of carbene species. On subjection of 1a to EtOH as solvent in the absence of additional nucleophiles, compound 13 was observed and confirmed by NMR (Figure 5C) (Hyatt and Croatt, 2012). Based on these observations, a potential mechanism of the reactions was proposed (Figure 5E). After hydrogen abstraction in methyl from a base, internal double bond of cMAVI 1a would migrate to the terminal to form ylide species A1 (Ivanov et al., 2014). Reversible conversion into carbene species A2 initiated the forthcoming nucleophilic insertion of a nucleophile (Ar-XH) to quickly generate 4. Without competitive nucleophile, A2 would couple with Et3N to produce an ylide salt B, and B tended to rearrange into an ammonium salt C. Finally, C underwent two-electron transfer from the triethylamino motif that underwent β-H elimination to provide 3a. The formation of oxidative species D was confirmed by gas chromatography-MS (Figure S2). However, the exact mechanism remains to be fully elucidated. With other groups instead of methyl, 1b and 1c might undergo a direct nucleophilic attack from triethylamine to form F that is similar to C, and 3b and 3c were then formed (Figure S3).

**Conclusion**

In summary, we have developed a series of novel cyclic monoaryl-vinyl iodoniums that are highly reactive. These unique iodonium species have been well tuned to couple with various nucleophiles including aniline, phenol, aromatic acid, and indole, constructing C-N, C-O, and C-C bonds regioselectively without metal catalysis. Activated by organic bases represented by triethylamine, the reactions are performed in environment-friendly solvents EtOH and THF at ambient temperature. Moreover, the coupling products allow further diversification. Six series of chemical libraries are quickly built via a DOS strategy, providing high-quality drug-like fragments that are desirable in the drug discovery field. In the mechanism study, we propose that these cMAVIs can be employed as a new source to generate carbene species, which would open a venue to accomplish diverse transformations.

**Limitations of the Study**

In our current work, alkyl amines and alkyl carboxylic acids are not suitable substrates to realize the coupling reactions.

**Resource Availability**

**Lead Contact**

Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact, Shijun Wen (wenshj@sysucc.org.cn).
The experiment with deuterated aniline

\[ \text{1a} + \text{D}_5 \rightarrow \text{D}_5 \]

The experiment with 4-methyl styrene

\[ \text{1a} + \text{Et}_3\text{N, EtOH} \rightarrow \text{12} \]

The experiment with EtOH

\[ \text{1a} + \text{EtOH, Et}_3\text{N, r.t., 30 min} \rightarrow \text{13} \]

Proposed reaction mechanism

Figure 5. The Mechanism Studies

(A) The insertion of deuterated aniline.  
(B) The cycloaddition with 4-methyl styrene.  
(C) The insertion of EtOH.  
(D) A proposed mechanism to generate 4 and 3a.

Materials Availability

This study generated new unique reagents, cyclic monoaryl-vinyl iodoniums.

Data and Code Availability

The X-ray crystallographic coordinates for structures reported in this article have been deposited at the Cambridge Crystallographic Data Center (1a: 1893710, 4ak: 1972497). These data could be obtained free of charge.
from The Cambridge Crystallographic Data Center via https://www.ccdc.cam.ac.uk/structures/. Original data in this paper have been deposited to Research Data Deposit (https://www.researchdata.org.cn) with a RDD number of RDD20200000876.

METHODS
All methods can be found in the accompanying Transparent Methods supplemental file.

SUPPLEMENTAL INFORMATION
Supplemental Information can be found online at https://doi.org/10.1016/j.isci.2020.101307.

ACKNOWLEDGMENTS
This work was supported by National Natural Science Foundation of China (81672952, 81872440), Guangdong Science and Technology Program (2017A020215198), and Guangzhou Science and Technology Program (201807010041).

AUTHOR CONTRIBUTIONS
H.W. and S.W. conceived the study; H.W. carried out most of the reaction and analyzed the data. H.W., S.W., L.L., Z.G., H.P., S.Q., N.S., D.Z., W.Z., and P.H. prepared the manuscript and Supplemental Information; Y.C. collected and analyzed the crystallographic data. All authors discussed the results and commented on the manuscript.

DECLARATION OF INTERESTS
The authors declare no competing interests.

Received: February 28, 2020
Revised: May 5, 2020
Accepted: June 18, 2020
Published: July 24, 2020

REFERENCES
Alein, J., Schade, M., Wagener, M., Christian, F., Nordhoff, S., Merla, B., Dunkern, T.R., Bahrenberg, G., and Ratcliffe, P. (2019). Fragment-based discovery of novel potent sepiapterin reductase inhibitors. J. Med. Chem. 62, 6391–6397.

Beringer, F.M., Ganis, P., Avitabile, G., and Jaffe, H. (1972). Synthesis, structure, and reactions of a benzodiazolium cation. J. Org. Chem. 37, 879–886.

Biffis, A., Centomo, P., Del Zotto, A., and Zecca, M. (2018). Pd metal catalysts for cross-couplings and related reactions in the 21st century: a critical review. Chem. Rev. 118, 2249–2295.

Bugaenko, D.I., Dubrovina, A.A., Yurovskaya, M.A., and Karchava, A.V. (2018). Synthesis of indoles via electron-catalyzed intramolecular C-N bond formation. Org. Lett. 20, 7358–7362.

Chatterjee, N., and Goswami, A. (2017). Synthesis and application of cyclic diaryliodonium salts: a platform for bifunctionalization in a single step. Eur. J. Org. Chem. 2017, 3023–3032.

Dempsey Hyatt, I.F., Nasrallah, D.J., Maxwell, M.A., Harriston, A.C.F., Abdalhameed, M.M., and Croatt, M.P. (2015). Formation and in situ reactions of hypervalent iodonium alkyl triflates to form cyanocarbenes. Chem. Commun. 51, 5287–5289.

Deprez, N.R., and Sanford, M.S. (2009). Synthetic and mechanistic studies of Pd-catalyzed C-H arylation with diaryliodonium salts: evidence for a bimetallic high oxidation state Pd intermediate. J. Am. Chem. Soc. 131, 11234–11241.

Ellwart, M., Makarov, I.S., Achrainer, F., Zipse, H., and Knochel, P. (2016). Regioselective transition-metal-free allyl-allyl cross-couplings. Angew. Chem. Int. Ed. 55, 10502–10506.

Evano, G., Blanchard, N., and Tourmi, M. (2008). Copper-mediated coupling reactions and their applications in natural products and designed biomolecules synthesis. Chem. Rev. 108, 3054–3131.

Golubev, P., and Krasavin, M. (2017). Sterically constrained and encumbered: an approach to the naturally occurring peptidomimetic tetrahydropyrazino[1,2-a]indole-1,4-dione core. J. Org. Chem. 82, 1740–1744.

Gómez-Lor, B., and Echavarren, A.M. (2004). Synthesis of a triaza analogue of crushed-fulerene by intramolecular Palladium-catalyzed arylation. Org. Lett. 6, 2993–2996.

Grossmann, A., Bartlett, S., Janecek, M., Hodgkinson, J.T., and Spring, D.R. (2014). Diversity-oriented synthesis of drug-like macrocyclic scaffolds using an orthogonal organo- and metal catalysis strategy. Angew. Chem. Int. Ed. 53, 13093–13097.

Heightman, T.D., Berdini, V., Braithwaite, H., Buck, I.M., Cassidy, M., Castro, J., Courtin, A., Day, J.E.H., East, C., Fazal, L., et al. (2018). Fragment-based discovery of a potent, orally bioavailable inhibitor that modulates the phosphorylation and catalytic activity of ERK1/2. J. Med. Chem. 61, 4978–4992.

Ho, M.L., Flynn, A.B., and Ogilvie, W.W. (2007). Single-isomer iodoniation of alkynes and chlorination of alkenes using tetrabutylammonium iodoide and dichloroethane. J. Org. Chem. 72, 977–983.

Hu, T., Xu, K., Ye, Z., Zhu, K., Wu, Y., and Zhang, F. (2019). Two-in-one strategy for the Pd(II)-catalyzed tandem C-H arylation/carboative annulation involved with cyclic diaryliodonium salts. Org. Lett. 21, 7233–7237.

Hyatt, I.F.D., and Croatt, M.P. (2012). Reactions of hypervalent iodonium alkyl triflates with azides: generation of cyanocarbenes. Angew. Chem. Int. Ed. 51, 7511–7514.

Ignetenko, V.A., Deligonul, N., and Viswanathan, R. (2018). Branch-selective synthesis of oxindole and indene scaffolds: transition metal-controlled intramolecular aryl amidation leading to C3 reverse-prenylated oxindoles. Org. Lett. 12, 3594–3597.

Ivanov, A.S., Popov, I.A., Boldyrev, A.I., and Zhdankin, V.V. (2014). The I=X (X=O,N,C) double
Soc.

Kesch, P., Jakob, V., Oberhausen, K., Stein, S.C., Cucarro, I., Schulz, T.F., and Empting, M. (2019). Fragment-based discovery of a qualified hit targeting the latency-associated nuclear antigen of the oncogenic Kaposi’s sarcoma-associated herpesvirus/human herpesvirus 8. J. Med. Chem. 62, 3924–3939.

Kitano, H., Ito, H., and Itami, K. (2018). Palladium-catalyzed esterification of carboxylic acids with aryl iodides. Org. Lett. 20, 2428–2432.

Kochanowska-Karamyan, A.J., and Hamann, M.T. (2010). Marine indole alkaloids: potential new drug leads for the control of depression and anxiety. Chem. Rev. 110, 4489–4497.

Leitch, J.A., Bhonoah, Y., and Frost, C.G. (2017). Beyond C2 and C3 transition-metal-catalyzed C–H functionalization of indole. ACS Catal. 5, 5618–5627.

Li, Q., Zhang, M., Zhan, S., and Gu, Z. (2019). Copper-catalyzed enantioselective ring-opening of cyclic diaryliodoniums and O-alkylhydroxylamines. Org. Lett. 21, 6374–6377.

Lin, J., Li, T., Liu, J., Jiao, G., Gu, Q., Cheng, J., Guo, Y., Hong, X., and Liu, X. (2019). Cu/Cr(II)-phosphonic acid-catalyzed asymmetric three-component radical-initiated 1,2-dicarboxfunctionalization of alkenes. J. Am. Chem. Soc. 141, 1074–1083.

Liu, C., Zhang, H., Shi, W., and Lei, A. (2011). Bond formations between two nucleophiles: transition metal catalyzed oxidative cross-coupling reactions. Chem. Rev. 111, 1780–1820.

Liu, Z., Zhu, D., Luo, B., Zhang, N., Liu, Q., Hu, Y., Pi, R., Huang, P., and Wen, S. (2014). Mild Cu(I)-catalyzed cascade reaction of cyclic diaryliodoniums, sodium azide, and alkynes: efficient synthesis of triazolephenanthridines. Org. Lett. 16, 5600–5603.

Lukamto, D.H., and Gaunt, M.J. (2017). Enantioselective copper-catalyzed arylation-driven semipinacol rearrangement of tertiary allylic alcohols with diaryliodonium salts. J. Am. Chem. Soc. 139, 9160–9163.

Mathey, B.P., Yang, H.J., Kim, J., Lee, J.B., Kim, Y.T., Lee, S., Lee, C.Y., Choe, W., Myung, K., Park, J.U., et al. (2017). An annulative synthetic strategy for building triphenylenes frameworks by multiple C–H bond activations. Angew. Chem. Int. Ed. 56, 5007–5011.

Meimets, L.G., Carlson, J.C., Giedt, R.J., Kohler, R.H., and Weisleder, R. (2014). Ultrafluorogenic coumarin-tetrazine probes for real-time biological imaging. Angew. Chem. Int. Ed. 53, 7531–7534.

Merritt, E.A., and Olofsson, B. (2009). Diaryliodonium salts: a journey from obscurity to fame. Angew. Chem. Int. Ed. 48, 9052–9070.

Modha, S.G., and Greaney, M.F. (2015). Atom-economic transformation of diaryliodonium salts: tandem C–H and N–H arylation of indoles. J. Am. Chem. Soc. 137, 1416–1419.

Petersen, T.B., Khan, R., and Olofsson, B. (2011). Metal-free synthesis of aryl esters from carboxylic acids and diaryliodoniums. Org. Lett. 13, 3462–3465.

Poulie, C.B., and Bunch, L. (2013). Heterocycles as nonclassical biosoesters of α-amino acids. ChemMedChem 8, 205–215.

Pun, S., Thirupathi, N., and Sridhar Reddy, M. (2014). Iodo Meyer-Schuster rearrangement of 3-alkoxy-2-yn-1-ols for α-mono (exclusively) z-selective/disubstituted α-iodo-z,β-unsaturated esters. Org. Lett. 16, 5246–5249.

Rousseaux, S., Gorelsky, S.I., Chung, B.K.W., and Gorelsky, S.I. (2010). Investigation of the mechanism of C(sp3)–H bond cleavage in Pd(0)-catalyzed intramolecular alkane arylation adjacent to amides and sulfonamides. J. Am. Chem. Soc. 132, 10692–10705.

Roy, S., Anoop, A., Biradha, K., and Basak, A. (2011). Synthesis of angularly fused aromatic compounds from alkanyl enediones by a tandem radical cyclization process. Angew. Chem. Int. Ed. 50, 8316–8319.

Ruiz-Castillo, P., and Buchwald, S.L. (2016). Applications of Palladium-catalyzed C–N cross-coupling reactions. Chem. Rev. 116, 12564–12649.

Singh, A.K., Rai, J., and Saha, S. (2017). Indole-fused azepines and analogues as anticancer lead molecules: privileged findings and future directions. Eur. J. Med. Chem. 142, 244–265.

Song, L., Luo, S., and Cheng, J. (2013). Catalytic intermolecular haloadDITION of single alkynes with N-halophosphamides as both nitrogen and halogen source. Org. Lett. 15, 5702–5705.

Sun, C., and Shi, Z. (2014). Transition-metal-free coupling reactions. Chem. Rev. 114, 9219–9280.

Sun, K., Wang, X., Liu, L., Sun, J., Liu, X., Li, Z., Zhang, Z., and Zhang, G. (2015). Copper-catalyzed cross-dehydrogenative C–N bond formation of azines with azoles: overcoming the limitation of oxidizing N–O activation strategy. ACS Catal. 5, 7194–7198.

Teskey, C.J., Sohel, S.M.A., Bunting, D.L., Modha, S.G., and Greaney, M.F. (2017). Domino N–C–arylation via in situ generation of a directing group: atom-efficient arylation using diaryliodonium salts. Angew. Chem. Int. Ed. 56, 5263–5266.

Wan, Y., Li, Y., Yan, C., Yan, M., and Tang, Z. (2019). Indole: a privileged scaffold for the design of anti-cancer agents. Eur. J. Med. Chem. 183, 111691.

Wu, B., and Yoshikai, N. (2015). Conversion of 2-iodobenzonitriles into 2,2′-diodobenzonitriles via oxidation-iodination sequences: a versatile route to ladder-type heterofluorenes. Angew. Chem. Int. Ed. 54, 8736–8739.

Xie, H., Ding, M., Liu, M., Hu, T., and Zhang, F. (2017). Synthesis of functionalized biaryl and polyheteroaryl containing medium-sized lactones with cyclic diaryliodonium salts. Org. Lett. 19, 2600–2603.

Yoshimura, A., and Zhdkankin, V.V. (2016). Advances in synthetic applications of hypervalent iodine compounds. Chem. Rev. 116, 3328–3435.

Zhu, D., Liu, Q., Luo, B., Chen, M., Pi, R., Huang, P., and Wen, S. (2013). Synthesis of carbazoles via one-pot Copper-catalyzed amine insertion into cyclic diphenyliodoniums as a strategy to generate a drug-like chemical library. Adv. Synth. Catal. 355, 2172–2178.

Zhu, D., Wu, Z., Luo, B., Du, Y., Liu, P., Chen, Y., Hu, Y., Huang, P., and Wen, S. (2018). Heterocyclic iodiniums for the assembly of oxygen-bridged polycyclic heteroarenes with water as the oxygen source. Org. Lett. 20, 4815–4818.
Supplemental Information

Highly Reactive Cyclic Monoaryl Iodoniums
Tuned as Carbene Generators Couple
with Nucleophiles under Metal-Free Conditions

Haiwen Wang, Liyun Liang, Zhirong Guo, Hui Peng, Shuang Qiao, Nemai Saha, Daqian Zhu, Wenbin Zeng, Yunyun Chen, Peng Huang, and Shijun Wen
Supplemental Information
Table of Contents

1. Supplemental tables and figures

2. Transparent methods
   2.1. General information
   2.2. Synthesis and characterization of products 4
   2.3. Coupling Reaction Utilities to Construct Chemical Library
   2.4. Coupling Reaction Mechanism Studies
   2.5. The synthesis of cMAVIs 1
   2.6. The characterization of 3

3. Data S1. The copies of NMR spectra.
1. Supplemental tables and figures:

Table S1. The stabilities of cMAVIs, related to Figure 2.

| Condition | Store-Stability | Heat-Stability | Base-Stability | Nucleophile-stability | Base+Nucleophile-Stability |
|-----------|-----------------|----------------|----------------|-----------------------|---------------------------|
| Compound  | a               | b              | c              | d                     | e                         |
| 1a        | yes             | yes            | No             | yes                   | No                        |
| 1b        | yes             | yes            | No             | yes                   | No                        |
| 1c        | yes             | yes            | No             | yes                   | No                        |
| 1d        | yes             | No             | No             | No                    | No                        |

a cMAVI 1 was checked daily a month in both powder form and solution in dichloromethane for their state and color change. Moreover, NMR was used to determine its stability; b cMAVI 1 (0.10 mmol) was solved in dichloromethane (2.0 mL) and heated to 90 ºC for 30.0 min before it was checked by NMR to determine its purity; c To the solution of cMAVI 1 (0.10 mmol) in dichloromethane (2.0 mL), Et3N (30.0 uL, 0.20 mmol) was added. The mixture was stirred for 30.0 min at room temperature, and then checked by TLC and determined by NMR; d To the solution of cMAVI 1 (0.10 mmol) in dichloromethane (2.0 mL), p-toluidine (23.0 mg, 0.15 mmol) and Et3N (30.0 uL, 0.20 mmol) was added successively. The mixture was stirred for 30.0 min at room temperature, and then checked by TLC and determined by NMR.

A. The reactivity of 1b and 1c under Et3N and p-toluidine

\[
\begin{align*}
\text{1b, 1c, } R= \text{Ph, Cl} & \quad \text{(1.0 equiv)} \\
\text{conditions} & \rightarrow \\
\text{CH}_2\text{Cl}_2, \text{rt, 30 min} & \rightarrow \\
\text{R} & \quad \text{OEt} \\
\end{align*}
\]

| Condition | 3 | 4 |
|-----------|---|---|
| Et3N (2.0 equiv) | 100% | 0% |
| p-Toluidine (2.0 equiv) | 0% | 0% (1b, 1c intact) |
| p-Toluidine (2.0 equiv), Et3N (2.0 equiv) | 100% | 0% |

B. The reactivity of 1d under Et3N and p-toluidine

\[
\begin{align*}
\text{1d, (1.0 equiv)} & \quad \text{conditions} \\
\text{CH}_2\text{Cl}_2, \text{rt, 30 min} & \rightarrow \\
\text{R} & \quad \text{OEt} \\
\end{align*}
\]

| Condition | 3d | 4 |
|-----------|----|---|
| Et3N (2.0 equiv) | 100% | 0% |
| p-Toluidine (2.0 equiv) | 100% | 0% |
| p-Toluidine (2.0 equiv), Et3N (2.0 equiv) | 100% | 0% |

Figure S1. Exploration of new cMAVIs and their reactivity, related to Figure 2.
(A) The reactivity of 1b and 1c under Et3N and p-toluidine.
(B) The reactivity of 1d under Et3N and p-toluidine.
2. Transparent methods:

2.1 General information

Unless stated otherwise, chemicals and reagents were commercially available and used directly. Anhydrous CH$_2$Cl$_2$ was distilled over calcium hydride, and anhydrous THF, and ether distilled over sodium wire under argon. Flash column chromatography was performed on silica gel of 200−400 mesh. Reactions were monitored by thin-layer chromatography (TLC) and occasionally by GC/MS. TLC plates were visualized with UV and in an iodine chamber, or with phosphomolybdic acid (PMA), ninhydrin, and KMnO$_4$ solution. The $^1$H and $^{13}$C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Advance spectrometer at 400/500 and 100/126 MHz respectively. Chemical shifts are given in ppm (δ) referenced to CDCl$_3$ with 7.26 for $^1$H and 77.16 for $^{13}$C; DMSO-d$_6$ with 2.50 for $^1$H and 39.5 for $^{13}$C. The following abbreviations were used to describe splitting patterns of $^1$HNMR: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. All coupling constants are recorded in hertz. HRMS were obtained on Waters Xevo G2 QTOF (ESI) spectrometer.

2.2 The synthesis and characterization of products 4:

General procedure exemplified by the synthesis of 4aa: In a 10 mL one-neck round bottomed flask equipped with a magnetic stirring bar, the solution of Et$_3$N (2.0 equiv), EtOH, r.t., 30 min X = NH or N, O, Cl(3-indole) to give 4aa as yellow liquid (38.0 mg, 90% yield).
Ethyl 3-(2-iodophenyl)-2-(phenylamino)but-3-enoyate (4aa): Yellow liquid. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.88 (dd, J = 8.0, 1.1 Hz, 1H, Ar-CH$_3$), 7.31 (td, J = 7.5, 1.2 Hz, 1H, Ar-CH$_3$), 7.19 (dd, J = 7.6, 1.7 Hz, 1H, Ar-CH$_3$), 7.01 – 6.96 (m, 3H, Ar-CH$_3$), 6.68 – 6.60 (m, 2H, Ar-CH$_3$), 5.72 (d, J = 0.9 Hz, 1H, C=CH$_2$), 5.27 (s, 1H, C=CH$_2$), 4.94 (s, 1H, CH), 4.14 – 4.04 (m, 2H, CH$_2$), 2.24 (s, 3H, CH$_3$), 1.09 (t, J = 7.1 Hz, 3H, CH$_3$) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.4 (C=O), 146.8, 144.8, 144.1, 139.5, 129.9, 129.6, 129.2, 128.0, 127.7, 119.7, 113.9, 98.8, 61.9, 61.8, 20.6, 14.0 ppm. HRMS (ESI) $m/z$: calcd for C$_{19}$H$_{21}$INO$_2$ [M + H]$^+$ 422.0612, found 422.0620.

Ethyl 3-(4-bromo-2-iodophenyl)-2-(p-tolylamino)but-3-enoyate (4ab): Following the general procedure of the synthesis of 4aa, 4ab was obtained from 1ab (54.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (44.0 mg, 88% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.03 (d, J = 2.0 Hz, 1H, Ar-CH$_3$), 7.44 (dd, J = 8.2, 2.0 Hz, 1H, Ar-CH$_3$), 7.05 (d, J = 8.2 Hz, 1H, Ar-CH$_3$), 7.00 (d, J = 8.3 Hz, 2H, Ar-CH$_3$), 6.61 (d, J = 8.4 Hz, 2H, Ar-CH$_3$), 5.73 (d, J = 0.8 Hz, 1H, C=CH$_2$), 5.28 (s, 1H, C=CH$_2$), 4.88 (s, 1H, CH), 4.18 – 4.04 (m, 2H, CH$_2$), 2.24 (s, 3H, CH$_3$), 1.13 (t, J = 7.1 Hz, 3H, CH$_3$) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$) δ 171.1 (C=O), 145.9, 143.9, 143.7, 141.4, 131.1, 130.5, 123.0, 127.9, 121.9, 120.4, 114.0, 99.3, 61.9, 61.9, 20.6, 14.1 ppm. HRMS (ESI) $m/z$: calcd for C$_{19}$H$_{21}$BrNO$_2$ [M + H]$^+$ 499.9717, found 499.9739.

Ethyl 3-(4-fluoro-2-iodophenyl)-2-(p-tolylamino)but-3-enoyate (4ac): Following the general procedure of the synthesis of 4aa, 4ac was obtained from 1ac (48.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (40.0 mg, 92% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.60 (dd, J = 8.2, 2.6 Hz, 1H, Ar-CH$_3$), 7.15 (dd, J = 8.5, 5.9 Hz, 1H, Ar-CH$_3$), 7.05 (dd, J = 8.1, 2.6 Hz, 1H, Ar-CH$_3$), 7.01 (dd, J = 6.6, 5.2 Hz, 2H, Ar-CH$_3$), 6.65 – 6.60 (m, 2H, Ar-CH$_3$), 5.74 (d, J = 1.0 Hz, 1H, C=CH$_2$), 5.27 (s, 1H, C=CH$_2$), 4.89 (s, 1H, CH), 4.17 – 4.06 (m, 2H, CH$_2$), 2.24 (s, 3H, CH$_3$), 1.13 (t, J = 7.1 Hz, 3H, CH$_3$) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.2 (C=O), 162.5 (d, Jc-F = 245.1 Hz, C-F), 145.9, 144.0, 140.9 (d, Jc-F = 7.8 Hz, C-F), 130.2 (d, Jc-F = 7.8 Hz, C-F), 127.9, 126.4 (d, Jc-F = 3.2 Hz, C-F), 120.4, 115.2 (d, Jc-F = 21.0 Hz, C-F), 113.9, 98.2, 62.0, 61.9, 20.6, 14.1 ppm. HRMS (ESI) $m/z$: calcd for C$_{19}$H$_{20}$FINO$_2$ [M + H]$^+$ 440.0517, found 440.0542.

Ethyl 3-(2-iodo-4-isopropylphenyl)-2-(p-tolylamino)but-3-enoyate (4ad): Following the general procedure of the synthesis of 4aa, 4ad was obtained from 1ad (51.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (43.0 mg, 95% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.73 (s, 1H, Ar-CH$_3$), 7.17 (d, J = 7.9 Hz, 1H, Ar-CH$_3$), 7.10 (d, J = 7.8 Hz, 1H, Ar-CH$_3$), 7.00 (d, J = 8.1 Hz, 2H, Ar-CH$_3$), 6.64 (d, J = 8.2 Hz, 2H, Ar-CH$_3$), 5.70 (s, 1H, C=CH$_2$), 5.27 (s, 1H, C=CH$_2$), 4.94 (s, 1H, CH), 4.13 – 4.04 (m, 2H, CH$_2$), 2.86 (dt, J = 13.8, 6.9 Hz, 1H, CH), 2.24 (s, 3H, CH$_3$), 1.24 (d, J = 6.9 Hz, 6H, 2 x CH$_3$), 1.09 (t, J = 7.1 Hz, 3H, CH$_3$) ppm. $^{13}$C
Ethyl 3-(2-iodo-4-methylphenyl)-2-(p-tolylamino)but-3-enolate (4ae): Following the general procedure of the synthesis of 4aa, 4ae was obtained from 1ae (48.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (39.0 mg, 90% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.72 (s, 1H, Ar-CH), 7.14 – 7.09 (m, 1H, Ar-CH), 7.06 (d, $J$ = 7.8 Hz, 1H, Ar-CH), 7.00 (d, $J$ = 8.4 Hz, 2H, Ar-CH), 6.63 (d, $J$ = 8.3 Hz, 2H, Ar-CH), 5.69 (s, 1H, C=CH$_2$), 5.25 (s, 1H, C=CH$_2$), 4.91 (s, 1H, CH), 4.44 (s, 1H, NH), 4.15 – 4.06 (m, 2H, CH$_2$), 2.30 (s, 3H, CH$_3$), 2.24 (s, 3H, CH$_3$), 1.12 (t, $J$ = 7.1 Hz, 3H, CH$_3$) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$) δ 171.4 (C=O), 146.6, 144.2, 141.8, 140.0, 139.3, 129.9, 129.2, 128.8, 127.7, 119.6, 113.9, 98.7, 62.1, 61.7, 20.6, 20.6, 14.0 ppm. HRMS (ESI) $m/z$: calcd for C$_{20}$H$_{23}$INO$_2$ [M + H]$^+$ 436.0768, found 436.0799.

Ethyl 3-(2-iodo-5-methylphenyl)-2-(p-tolylamino)but-3-enolate (4af): Following the general procedure of the synthesis of 4aa, 4af was obtained from 1af (48.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (36.5 mg, 84% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.73 (d, $J$ = 8.1 Hz, 1H, Ar-CH), 7.02-7.00 (m, 3H, Ar-CH), 6.81 (d, $J$ = 8.0 Hz, 1H, Ar-CH), 6.65 (d, $J$ = 7.9 Hz, 2H, Ar-CH), 5.70 (s, 1H, C=CH$_2$), 5.25 (s, 1H, C=CH$_2$), 4.94 (d, $J$ = 7.7 Hz, 1H, CH), 4.46 (d, $J$ = 7.9 Hz, 1H, NH), 4.14 – 4.07 (m, 2H, CH$_2$), 2.29 (s, 3H, CH$_3$), 2.24 (s, 3H, CH$_3$), 1.10 (t, $J$ = 7.2 Hz, 3H, CH$_3$) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$) δ 171.4 (C=O), 146.8, 144.6, 144.1, 139.2, 137.9, 130.5, 130.2, 129.9, 127.7, 119.4, 114.0, 94.6, 61.9, 61.7, 21.0, 20.6, 14.0 ppm. HRMS (ESI) $m/z$: calcd for C$_{20}$H$_{23}$INO$_2$ [M + H]$^+$ 436.0768, found 436.0771.

Ethyl 3-(1-iodonaphthalen-2-yl)-2-(p-tolylamino)but-3-enolate (4ag): Following the general procedure of the synthesis of 4aa, 4ag was obtained from 1ag (51.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (42.0 mg, 90% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.29 (d, $J$ = 8.6 Hz, 1H, Ar-CH), 7.78 (d, $J$ = 8.2 Hz, 2H, Ar-CH), 7.62 – 7.58 (m, 1H, Ar-CH), 7.56 – 7.48 (m, 1H, Ar-CH), 7.30 (d, $J$ = 8.3 Hz, 1H, Ar-CH), 7.01 (d, $J$ = 8.1 Hz, 2H, Ar-CH), 6.69 (d, $J$ = 8.3 Hz, 2H, Ar-CH), 5.85 (d, $J$ = 0.9 Hz, 1H, C=CH$_2$), 5.36 (s, 1H, C=CH$_2$), 5.04 (s, 1H, CH), 4.15 – 4.00 (m, 2H, CH$_2$), 2.25 (s, 3H, CH$_3$), 0.99 (t, $J$ = 7.1 Hz, 3H, CH$_3$) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.3 (C=O), 148.2, 144.3, 144.0, 135.0, 133.6, 133.2, 130.0, 128.6, 128.3, 128.2, 127.0, 126.8, 120.0, 114.2, 104.4, 62.2, 61.8, 20.6, 13.9 ppm. HRMS (ESI) $m/z$: calcd for C$_{20}$H$_{23}$INO$_2$ [M + H]$^+$ 472.0768, found 472.0776.

Ethyl 3-(2-iodophenyl)-2-(phenylamino)but-3-enolate (4ah): Following the general procedure of the synthesis of 4aa, 4ah was obtained from 1a (47.0 mg) and aniline (14.0 mg)
after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (37.0 mg, 90% yield).

1H NMR (500 MHz, CDCl₃) δ 7.88 (dd, J = 8.0, 1.1 Hz, 1H, Ar-CH), 7.31 (td, J = 7.5, 1.2 Hz, 1H, Ar-CH), 7.22 – 7.16 (m, 3H, Ar-CH), 7.01 – 6.96 (m, 1H, Ar-CH), 6.79 – 6.73 (m, 1H, Ar-CH), 6.71 (dd, J = 8.6, 0.9 Hz, 2H, Ar-CH), 5.73 (d, J = 1.1 Hz, 1H, C=CH₂), 5.28 (s, 1H, C=CH₂), 4.97 (s, 1H, CH), 4.14 – 4.05 (m, 2H, CH₂), 1.09 (t, J = 7.1 Hz, 3H, CH₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 171.2 (C=O), 146.6, 146.4, 144.8, 139.6, 129.6, 129.5, 129.2, 128.0, 119.8, 118.5, 113.8, 98.8, 61.8, 61.7, 14.0 ppm. HRMS (ESI) m/z: calcd for C₆H₅H=CHNO₂ [M + H]⁺ 408.0455, found 408.0451.

Ethyl 2-((2-hydroxymethyl)phenyl)amino)-3-(2-iodophenyl)but-3-enoate (4ai): Following the general procedure of the synthesis of 4aa, 4ai was obtained from 1a (47.0 mg) and (2-aminophenyl)methanol (19.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (29.0 mg, 66% yield). 1H NMR (400 MHz, CDCl₃) δ 7.88 (d, J = 7.9 Hz, 1H, Ar-CH), 7.31 (t, J = 7.5 Hz, 1H, Ar-CH), 7.25 – 7.16 (m, 2H, Ar-CH), 7.10 (d, J = 7.3 Hz, 1H, Ar-CH), 7.03 – 6.95 (m, 1H, Ar-CH), 6.75 – 6.67 (m, 2H, Ar-CH), 5.73 (s, 1H, C=CH₂), 5.30 (s, 1H, C=CH₂), 5.03 (s, 1H, CH), 4.75 – 4.68 (m, 2H, CH₂), 4.16 – 4.07 (m, 2H, CH₂), 1.12 (t, J = 7.1 Hz, 3H, CH₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 171.5 (C=O), 146.7, 145.8, 144.9, 139.5, 129.7, 129.6, 129.4, 129.3, 128.0, 125.4, 119.6, 111.8, 98.7, 64.7, 61.8, 61.3, 14.0 ppm. HRMS (ESI) m/z: calcd for C₁₅H₁₉I₂N₂O₂ [M + H]⁺ 438.0561, found 438.0580.

Ethyl 2-((2-hydroxyethyl)phenyl)amino)-3-(2-iodophenyl)but-3-enoate (4aj): Following the general procedure of the synthesis of 4aa, 4aj was obtained from 1a (47.0 mg) and 2-[(aminophenyl)ethan-1-ol (21.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (34.0 mg, 74% yield). 1H NMR (400 MHz, CDCl₃) δ 7.88 (d, J = 7.9 Hz, 1H, Ar-CH), 7.32 (t, J = 7.5 Hz, 1H, Ar-CH), 7.22 (dd, J = 7.6, 1.4 Hz, 1H, Ar-CH), 7.16 – 7.05 (m, 2H, Ar-CH), 6.99 (td, J = 7.8, 1.5 Hz, 1H, Ar-CH), 6.74 (t, J = 7.4 Hz, 1H, Ar-CH), 6.65 (d, J = 8.0 Hz, 1H, Ar-CH), 5.72 (s, 1H, C=CH₂), 5.31 (s, 1H, C=CH₂), 5.00 (s, 1H, CH), 4.17 – 4.08 (m, 2H, CH₂), 3.96 – 3.81 (m, 2H, CH₂), 2.95 – 2.89 (m, 1H, CH₂), 2.83 – 2.76 (m, 1H, CH₂), 1.13 (t, J = 7.1 Hz, 3H, CH₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 172.0 (C=O), 146.8, 145.1, 145.0, 139.6, 130.9, 129.68, 129.3, 128.0, 128.0, 124.8, 119.8, 118.7, 111.8, 98.8, 63.2, 61.8, 61.6, 35.4, 14.1 ppm. HRMS (ESI) m/z: calcd for C₂₀H₂₁I₂N₂O₂ [M + H]⁺ 452.0717, found 452.0749.

Ethyl 2-((2-ethynylphenyl)amino)-3-(2-iodophenyl)but-3-enoate (4ak): Following the general procedure of the synthesis of 4aa, 4ak was obtained from 1a (47.0 mg) and 2-ethynylaniline (18.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (30.0 mg, 68% yield). 1H NMR (500 MHz, CDCl₃) δ 7.88 (d, J = 7.9 Hz, 1H, Ar-CH), 7.37 (d, J = 7.6 Hz, 1H, Ar-CH), 7.32 (t, J = 7.5 Hz, 1H, Ar-CH), 7.22-7.19 (m, 2H, Ar-CH), 6.99 (t, J = 7.5 Hz, 1H, Ar-CH), 6.70-6.66 (m, 2H, Ar-CH), 5.72 (s, 1H, C=CH₂), 5.62 (d, J = 7.5 Hz, 1H, CH), 5.30 (s, 1H, C=CH₂), 5.02 (d, J = 7.6 Hz, 1H, NH), 4.17 – 4.05 (m, 2H, CH₂), 3.46 (s, 1H, C=CH₂), 1.09 (t, J = 7.1 Hz, 3H, CH₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 170.6 (C=O), 147.8, 146.1, 144.6, 139.6, 132.9, 130.4, 129.6, 129.3, 128.1, 119.9, 117.4, 110.8, 107.5, 98.8, 83.5, 80.4, 61.9, 61.2, 14.0 ppm. HRMS (ESI) m/z: calcd for C₂₀H₁₅I₂N₂O₂ [M + H]⁺ 432.0455, found 432.0451.
3-(1-(2-Iodophenyl)vinyl)-3,4-dihydroquinoxalin-2(1H)-one (4a1): Following the general procedure of the synthesis of 4aa but stirring for 12.0 h, 4a1 was obtained from 1a (47.0 mg) and benzene-1,2-diamine (17.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (27.0 mg, 71% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.26 (s, 1H, NH), 7.81 (dd, $J = 7.9$, 1.0 Hz, 1H, Ar-CH), 7.29 – 7.24 (m, 1H, Ar-CH), 7.14 (dd, $J = 7.6$, 1.7 Hz, 1H, Ar-CH), 7.02 – 6.93 (m, 1H, Ar-CH), 6.87 (td, $J = 7.6$, 1.5 Hz, 1H, Ar-CH), 6.75 – 6.62 (m, 3H, Ar-CH), 5.59 (s, 1H, C=CH$_2$), 5.19 (s, 1H, C=CH$_2$), 4.90 (s, 1H, CH), 4.27 (s, 1H, NH) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 165.9 (C=O), 149.8, 146.5, 144.8, 139.7, 130.1, 129.3, 129.2, 128.1, 119.6, 118.9, 115.4, 114.2, 98.7, 60.9 ppm. HRMS (ESI) $m/z$: calcd for C$_{19}$H$_{14}$NO [M + H]$^+$ 377.0145, found 377.0143.

Ethyl 3-(2-Iodophenyl)-2-(methyl(phenyl)amino)but-3-enolate (4am): Following the general procedure of the synthesis of 4aa, 4am was obtained from 1a (47.0 mg) and $N$-methylaniline (16.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (27.0 mg, 65% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.84 (d, $J = 7.7$ Hz, 1H, Ar-CH), 7.28 – 7.24 (m, 1H, Ar-CH), 7.24 – 7.17 (m, 3H, Ar-CH), 6.94 (t, $J = 7.6$ Hz, 1H, Ar-CH), 6.78 (d, $J = 8.1$ Hz, 2H, Ar-CH), 6.73 (t, $J = 7.2$ Hz, 1H, Ar-CH), 5.61 (s, 1H, C=CH$_2$), 5.53 (s, 1H, C=CH$_2$), 5.39 (s, 1H, CH), 4.15 (q, $J = 7.0$ Hz, 2H, CH$_2$), 3.06 (s, 3H, N-CH$_3$), 1.20 (t, $J = 7.1$ Hz, 3H, CH$_3$) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.6 (C=O), 149.8, 146.5, 144.8, 139.7, 130.1, 129.3, 129.2, 128.1, 120.7, 117.9, 113.7, 97.7, 65.6, 61.0, 34.6, 14.3 ppm. HRMS (ESI) $m/z$: calcd for C$_{19}$H$_{21}$NO$_2$ [M + H]$^+$ 422.0612, found 422.0604.

Ethyl 2-(benzylamino)-3-(2-Iodophenyl)but-3-enolate (4an): Following the general procedure of the synthesis of 4aa but in THF, 4an was obtained from 1a (47.0 mg) and phenylmethanamine (16.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (30.0 mg, 70% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.85 (d, $J = 7.8$ Hz, 1H, Ar-CH), 7.37 – 7.23 (m, 6H, Ar-CH), 7.16 (dd, $J = 7.6$, 1.4 Hz, 1H, Ar-CH), 6.97 (td, $J = 7.8$, 1.5 Hz, 1H, Ar-CH), 5.68 (s, 1H, C=CH$_2$), 5.24 (s, 1H, C=CH$_2$), 4.22 (s, 1H, CH), 4.10 (q, $J = 7.1$ Hz, 2H, CH$_2$), 3.91 (d, $J = 13.2$ Hz, 1H, CH$_2$), 3.81 (d, $J = 13.2$ Hz, 1H, CH$_2$), 1.13 (t, $J = 7.1$ Hz, 3H, CH$_3$) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$) δ 172.4 (C=O), 148.0, 145.3, 139.5, 139.4, 130.0, 129.0, 128.5, 128.4, 127.9, 127.3, 118.61, 98.5, 64.9, 61.2, 51.9, 14.2 ppm. HRMS (ESI) $m/z$: calcd for C$_{19}$H$_{21}$NO$_2$ [M + H]$^+$ 422.0612, found 422.0622.

Ethyl 2-((2-bromo-4-methylbenzyl)amino)-3-(2-Iodophenyl)but-3-enolate (4ao): Following the general procedure of the synthesis of 4aa but in THF, 4ao was obtained from 1a (47.0 mg) and (2-bromo-4-methylphenyl)methanamine (28.0 mg) after flash column chromatography.
Ethyl 3-(2-iodophenyl)-2-phenoxbut-3-enoate (4ba): Following the general procedure of the synthesis of 4aa but in THF, 4ba was obtained from 1a (47.0 mg) and phenol (15.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as colorless liquid (25.0 mg, 60%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.88 (d, J = 7.9 Hz, 1H, Ar-CH), 7.32 (t, J = 7.6 Hz, 1H, Ar-CH), 7.20 – 7.21 (m, 1H, Ar-CH), 5.94 (s, 1H, C=CH$_2$), 5.43 (s, 1H, C=CH$_2$), 5.37 (s, 1H, CH), 4.12 – 4.10 (m, 2H, CH$_2$), 2.28 (s, 3H, CH$_3$), 1.11 (t, J = 7.1 Hz, 3H, CH$_3$) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 169.3 (C=O), 155.6, 145.6, 143.8, 139.5, 131.5, 130.5, 130.1, 129.5, 129.1, 122.1, 120.2, 115.8, 98.4, 78.7, 61.7, 14.1 ppm. HRMS (ESI) $m/z$: calcd for C$_{19}$H$_{18}$IO$_{2}$Na $[M + Na]^+$ 445.0271, found 445.0261.

Ethyl 3-(2-iodophenyl)-2-(p-tolloyloxy)but-3-enoate (4bb): Following the general procedure of the synthesis of 4aa but in THF, 4bb was obtained from 1a (47.0 mg) and p-cresol (17.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as colorless liquid (25.0 mg, 59% yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.59 (d, J = 8.0 Hz, 2H, Ar-CH), 7.4 (d, J = 7.9 Hz, 1H, Ar-CH), 7.03 (d, J = 7.8 Hz, 3H, Ar-CH), 5.91 (s, 1H, C=CH$_2$), 5.52 (s, 1H, C=CH$_2$), 5.42 (s, 1H, CH), 4.14 (q, J = 7.0 Hz, 2H, CH$_2$), 1.13 (t, J = 7.0 Hz, 3H, CH$_3$) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 168.2 (C=O), 160.7, 144.6, 143.2, 139.6, 134.2, 130.5, 129.8, 128.3, 119.9, 116.2, 105.5, 98.3, 78.4, 62.1, 14.0 ppm. HRMS (ESI) $m/z$: calcd for C$_{19}$H$_{19}$NO$_3$Na $[M + Na]^+$ 456.0067, found 456.0056.

Ethyl 2-(4-cyanophenoxy)-3-(2-iodophenyl)but-3-enoate (4bc): Following the general procedure of the synthesis of 4aa but in THF, 4bc was obtained from 1a (47.0 mg) and 4-hydroxybenzonitrile (19.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as colorless liquid (34.0 mg, 77% yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.88 (d, J = 7.9 Hz, 1H, Ar-CH), 7.59 (d, J = 8.0 Hz, 2H, Ar-CH), 7.34 (t, J = 7.4 Hz, 1H, Ar-CH), 7.22 (d, J = 7.5 Hz, 1H, Ar-CH), 7.03 (d, J = 7.8 Hz, 3H, Ar-CH), 5.91 (s, 1H, C=CH$_2$), 5.52 (s, 1H, C=CH$_2$), 5.42 (s, 1H, CH), 4.14 (q, J = 7.0 Hz, 2H, CH$_2$), 1.13 (t, J = 7.0 Hz, 3H, CH$_3$) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 168.2 (C=O), 160.7, 144.6, 143.2, 139.6, 134.2, 130.5, 129.8, 128.3, 119.9, 116.2, 105.5, 98.3, 78.4, 62.1, 14.0 ppm. HRMS (ESI) $m/z$: calcd for C$_{19}$H$_{18}$NO$_3$Na $[M + Na]^+$ 456.0067, found 456.0056.
Ethyl 3-(2-iodophenyl)-2-(4-nitrophenoxy)but-3-enenoate (4bd): Following the general procedure of the synthesis of 4aa but in THF, 4bd was obtained from 1a (47.0 mg) and 4-nitrophenol (22.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as colorless liquid (37.0 mg, 80% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.21 (d, J = 8.2 Hz, 2H, Ar-CH), 7.89 (d, J = 7.9 Hz, 1H, Ar-CH), 7.35 (t, J = 7.4 Hz, 1H, Ar-CH), 7.23 (d, J = 7.5 Hz, 1H, Ar-CH), 7.04 (d, J = 8.0 Hz, 3H, Ar-CH), 5.93 (s, 1H, C=CH$_2$), 5.56 (s, 1H, C=CH$_2$), 5.44 (s, 1H, CH), 4.16 (d, J = 6.7 Hz, 2H, CH$_2$), 1.14 (t, J = 6.8 Hz, 3H, CH$_3$) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$) δ 168.1 (C=O), 162.3, 144.5, 143.2, 142.5, 139.6, 130.5, 129.8, 128.2, 126.1, 120.9, 115.5, 98.3, 78.6, 62.2, 14.1 ppm. HRMS (ESI) m/z: calcld for C$_{18}$H$_{16}$INO$_3$Na [M + Na]$^+$ 475.9965, found 475.9944.

Ethyl 2-(4-fluorophenoxy)-3-(2-iodophenyl)but-3-enenoate (4be): Following the general procedure of the synthesis of 4be but in THF, 4be was obtained from 1a (47.0 mg) and 4-fluorophenol (18.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as colorless liquid (26.5 mg, 60% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.88 (dd, J = 7.9, 0.9 Hz, 1H, Ar-CH), 7.33 (td, J = 7.5, 1.1 Hz, 1H, Ar-CH), 7.29 – 7.20 (m, 1H, Ar-CH), 7.06 – 6.91 (m, 5H, Ar-CH), 5.93 (s, 1H, C=CH$_2$), 5.40 (s, 1H, C=CH$_2$), 5.39 (s, 1H, CH), 4.13 (q, J = 7.1 Hz, 2H, CH$_2$), 1.11 (t, J = 7.1 Hz, 3H, CH$_3$) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 169.05 (C=O), 159.3 (d, J=CF = 245.1 Hz, C-F), 153.7 (d, J=CF = 3.0 Hz, C-F), 145.4, 143.6, 139.5, 130.5, 129.6, 128.1, 120.2, 117.3 (d, J=CF = 7.8 Hz, C-F), 116.2 (d, J=CF = 21.0 Hz, C-F), 98.4, 79.6, 61.8, 14.1 ppm. HRMS (ESI) m/z: calcld for C$_{18}$H$_{16}$INO$_3$Na [M + Na]$^+$ 449.0020, found 449.0020.

Ethyl 2-(3-cyanophenoxy)-3-(2-iodophenyl)but-3-enenoate (4bf): Following the general procedure of the synthesis of 4aa but in THF, 4bf was obtained from 1a (47.0 mg) and 3-hydroxybenzonitrile (18.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as colorless liquid (24.0 mg, 55% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.91 (d, J = 7.9 Hz, 1H, Ar-CH), 7.48 – 7.22 (m, 6H, Ar-CH), 7.06 (td, J = 7.8, 1.6 Hz, 1H, Ar-CH), 5.94 (s, 1H, C=CH$_2$), 5.50 (s, 1H, C=CH$_2$), 5.45 (s, 1H, CH), 4.19 (q, J = 7.1 Hz, 2H, CH$_2$), 1.17 (t, J = 7.1 Hz, 3H, CH$_3$) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$) δ 168.4 (C=O), 157.6, 144.8, 143.3, 139.6, 130.7, 130.5, 129.8, 128.2, 125.9, 120.8, 120.7, 118.9, 118.5, 113.6, 98.3, 78.7, 62.1, 14.1 ppm. HRMS (ESI) m/z: calcld for C$_{18}$H$_{16}$INO$_3$Na [M + Na]$^+$ 456.0067, found 456.0043.

1-Ethoxy-3-(2-iodophenyl)-1-oxobut-3-en-2-yl 4-methylbenzoate (4bg): Following the general procedure of the synthesis of 4aa but in THF and with Et$_3$N (50.0 ul, 3.5 equiv), 4bg was obtained from 1a (47.0 mg) and 4-methylbenzoic acid (21.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as colorless liquid (20.0 mg, 45% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.98 (d, J = 7.6 Hz, 2H, Ar-CH), 7.89 (d, J = 7.9 Hz, 1H, Ar-CH), 7.34 (t, J = 7.4 Hz, 1H, Ar-CH), 7.28 (d, J = 7.6 Hz, 1H, Ar-CH), 7.25 (d, J = 7.9 Hz, 2H, Ar-CH), 7.01 (t, J = 7.6 Hz, 1H, Ar-CH), 5.36 (s, 1H, C=CH$_2$), 5.89 (s, 1H, C=CH$_2$), 5.41 (s, 1H, CH), 4.19 (q, J = 7.1 Hz, 2H, CH$_2$), 2.41 (s, 3H, CH$_3$), 1.18 (t, J = 7.1 Hz, 3H, CH$_3$) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$) δ 168.0 (C=O), 165.8 (C=O), 144.5, 144.4, 143.7, 139.6, 130.2, 130.1, 129.6, 129.3, 128.1, 128.7, 121.1, 98.6, 74.7, 61.9, 21.9, 14.1 ppm. HRMS (ESI) m/z: calcld for C$_{20}$H$_{19}$O$_3$Na [M + Na]$^+$ 473.0220, found 473.0207.
1-Ethoxy-3-(2-iodophenyl)-1-oxobut-3-en-2-yl 4-fluorobenzoate (4bh): Following the general procedure of the synthesis of 4aa but in THF and with Et3N (50.0 µl, 3.5 equiv), 4bh was obtained from 1a (47.0 mg) and 4-fluorobenzoic acid (22.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as colorless liquid (20.0 mg, 43% yield). 1H NMR (500 MHz, CDCl3) δ 8.15 – 8.07 (m, 2H, Ar-CH), 7.90 (dd, J = 8.0, 0.9 Hz, 1H, Ar-CH), 7.35 (td, J = 7.5, 1.1 Hz, 1H, Ar-CH), 7.28 (d, J = 1.7 Hz, 1H, Ar-CH), 7.18 – 7.09 (m, 2H, Ar-CH), 7.02 (td, J = 7.7, 1.7 Hz, 1H, Ar-CH), 5.96 (s, 1H, C=CH2), 5.88 (d, J = 0.9 Hz, 1H, C=CH2), 5.43 (s, 1H, CH), 4.20 (q, J = 7.1 Hz, 2H, CH2), 1.19 (t, J = 7.1 Hz, 3H, CH3) ppm. 13C NMR (126 MHz, CDCl3) δ 167.9 (C=O), 167.3 (d, JC-F = 245.1 Hz, C-F), 164.8 (C=O), 144.3, 143.6, 139.6, 132.7 (d, JC-F = 7.8 Hz, C-F), 130.0, 129.6, 128.1, 125.7 (d, JC-F = 3.2 Hz, C-F), 121.3, 115.9 (d, JC-F = 21.0 Hz, C-F), 98.6, 74.9, 62.0, 14.1 ppm. HRMS (ESI) m/z: calcd for C19H16IO4Na [M + Na]+ 476.9970, found 476.9970.

1-Ethoxy-3-(2-iodophenyl)-1-oxobut-3-en-2-yl 3-methoxybenzoate (4bi): Following the general procedure of the synthesis of 4aa but in THF and with Et3N (50.0 µl, 3.5 equiv), 4bi was obtained from 1a (47.0 mg) and 3-methoxybenzoic acid (24.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as colorless liquid (24.0 mg, 50% yield). 1H NMR (500 MHz, CDCl3) δ 7.96 (d, J = 7.7 Hz, 1H, Ar-CH), 7.89 (d, J = 7.9 Hz, 1H, Ar-CH), 7.51 (t, J = 7.9 Hz, 1H, Ar-CH), 7.37 – 7.28 (m, 2H, Ar-CH), 7.02-6.98 (m, 3H, Ar-CH), 5.95 (s, 1H, C=CH2), 5.91 (s, 1H, C=CH2), 5.40 (s, 1H, CH), 4.17 (q, J = 7.1 Hz, 2H, CH2), 3.91 (s, 3H, CH3), 1.16 (t, J = 7.1 Hz, 3H, CH3) ppm. 13C NMR (126 MHz, CDCl3) δ 168.1 (C=O), 164.8 (C=O), 160.1, 144.3, 143.7, 139.6, 134.4, 132.6, 130.1, 129.5, 128.0, 121.1, 120.3, 118.7, 112.2, 98.7, 74.7, 61.8, 56.1, 14.1 ppm. HRMS (ESI) m/z: calcd for C20H18IO4Na [M + Na]+ 489.0169, found 489.0154.

Ethyl 3-(2-iodophenyl)-2-((3-phenylpropioloyloxy)but-3-enoate (4bj): Following the general procedure of the synthesis of 4aa but in THF and with Et3N (50.0 µl, 3.5 equiv), 4bj was obtained from 1a (47.0 mg) and 3-phenylpropionic acid (23.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as colorless liquid (21.0 mg, 44% yield). 1H NMR (500 MHz, CDCl3) δ 7.88 (d, J = 7.9 Hz, 1H, Ar-CH), 7.62 (d, J = 7.5 Hz, 2H, Ar-CH), 7.46 (t, J = 7.4 Hz, 1H, Ar-CH), 7.38 (t, J = 7.4 Hz, 2H, Ar-CH), 7.34 (t, J = 7.4 Hz, 1H, Ar-CH), 7.26 – 7.23 (m, 1H, Ar-CH), 7.01 (t, J = 7.6 Hz, 1H, Ar-CH), 5.87 (s, 2H, C=CH2), 5.41 (s, 1H, CH), 4.17 (q, J = 6.9 Hz, 2H, CH2), 1.17 (t, J = 7.1 Hz, 3H, CH3) ppm. 13C NMR (126 MHz, CDCl3) δ 167.3 (C=O), 153.0 (C=O), 143.5, 143.3, 139.6, 133.3, 131.0, 130.3, 129.7, 128.7, 128.2, 121.8, 119.6, 98.5, 88.3, 80.2, 75.3, 62.1, 14.1 ppm. HRMS (ESI) m/z: calcd for C21H17IO4Na [M + Na]+ 483.0064, found 483.0047.
Ethyl 2-(cinnamoyloxy)-3-(2-iodophenyl)but-3-enolate (4bk): Following the general procedure of the synthesis of 4aa but in THF and with Et$_3$N (50.0 ul, 3.5 equiv), 4bk was obtained from 1a (47.0 mg) and 3-(4-chlorophenyl)propionic acid (23.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as colorless liquid (18.0 mg, 38% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.86 (dd, $J = 8.0$ Hz, 2H, Ar-CH), 7.38 (d, $J = 8.1$ Hz, 1H, Ar-CH), 7.33 (d, $J = 2.4$ Hz, 1H, Ar-CH), 7.25 – 7.17 (m, 3H, Ar-CH), 7.13 (t, $J = 7.2$ Hz, 1H, Ar-CH), 6.95 (td, $J = 7.7$, 1.8 Hz, 1H, Ar-CH), 5.37 (s, 1H, C=CH$_2$), 5.20 (s, 1H, C=CH$_2$), 5.14 (s, 1H, CH), 4.14 – 4.02 (m, 2H, CH$_2$), 1.12 (dd, $J = 8.8$, 5.4 Hz, 3H, CH$_3$) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$) δ 172.1 (C=O), 148.6, 146.4, 139.4, 136.4, 130.4, 129.0, 127.9, 127.1, 124.1, 122.4, 121.0, 119.9, 119.3, 111.3, 111.1, 98.2, 61.1, 49.5, 14.2 ppm. HRMS (ESI) $m/z$: calcd for C$_{22}$H$_{19}$IO$_4$Na [M + Na]$^+$ 485.0220, found 485.0203.

Ethyl 2-(1H-indol-3-yl)-3-(2-iodophenyl)but-3-enolate (4ca): Following the general procedure of the synthesis of 4aa, 4ca was obtained from 1a (47.0 mg) and indole (18.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (18.0 mg, 41% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.18 (s, 1H Ar), 7.92 (d, $J = 7.7$, 1.8 Hz, 1H, Ar-CH), 7.26 – 7.21 (m, 4H, Ar-CH), 7.12 (t, $J = 7.2$ Hz, 1H, Ar-CH), 6.95 (t, $J = 7.3$ Hz, 1H, Ar-CH), 5.36 (s, 1H, C=CH$_2$), 5.18 (s, 1H, C=CH$_2$), 5.12 (s, 1H, CH), 4.08 – 4.03 (m, 2H, CH$_2$), 3.79 (s, 3H, N-CH$_3$), 1.11 (t, $J = 7.0$ Hz, 3H, CH$_3$) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$) δ 172.2 (C=O), 148.8, 146.5, 139.4, 137.2, 130.4, 128.9, 128.8, 127.9, 127.6, 121.9, 120.2, 119.3, 119.3, 109.4, 109.3, 98.2, 61.0, 49.4, 33.0, 14.2 ppm. HRMS (ESI) $m/z$: calcd for C$_{26}$H$_{21}$NO$_5$Na [M + Na]$^+$ 468.0431, found 468.0420.

Ethyl 3-(2-iodophenyl)-2-(1-methyl-1H-indol-3-yl)but-3-enolate (4cb): Following the general procedure of the synthesis of 4aa, 4cb was obtained from 1a (47.0 mg) and 1-methyl-1H-indole (19.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (7.0 mg, 15% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.86 (d, $J = 8.0$ Hz, 1H, Ar-CH), 7.81 (d, $J = 8.0$ Hz, 1H, Ar-CH), 7.31 (d, $J = 8.2$ Hz, 1H, Ar-CH), 7.26 – 7.21 (m, 4H, Ar-CH), 7.12 (t, $J = 7.2$ Hz, 1H, Ar-CH), 6.95 (t, $J = 7.3$ Hz, 1H, Ar-CH), 5.36 (s, 1H, C=CH$_2$), 5.18 (s, 1H, C=CH$_2$), 5.12 (s, 1H, CH), 4.08 – 4.03 (m, 2H, CH$_2$), 3.79 (s, 3H, N-CH$_3$), 1.11 (t, $J = 7.0$ Hz, 3H, CH$_3$) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$) δ 172.2 (C=O), 148.8, 146.5, 139.4, 137.2, 130.4, 128.9, 128.8, 127.9, 127.6, 121.9, 120.2, 119.3, 119.3, 109.4, 109.3, 98.2, 61.0, 49.4, 33.0, 14.2 ppm. HRMS (ESI) $m/z$: calcd for C$_{26}$H$_{21}$NO$_5$Na [M + Na]$^+$ 468.0431, found 468.0420.

Ethyl 3-(2-iodophenyl)-2-(2-methyl-1H-indol-3-yl)but-3-enolate (4cc): Following the general procedure of the synthesis of 4aa, 4cc was obtained from 1a (47.0 mg) and 2-methyl-1H-indole (19.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (18.0 mg, 40% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.85 (dd, $J = 12.3$, 6.6 Hz, 2H, Ar-CH), 7.28 – 7.06 (m, 5H,
Ethyl 3-(2-iodophenyl)-2-(4-methyl-1H-indol-3-yl)but-3-enoate (4cd): Following the general procedure of the synthesis of 4aa, 4cd was obtained from 1a (47.0 mg) and 4-methyl-1H-indole (19.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (15.0 mg, 35% yield). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.07 (s, 1H, NH), 7.87 (d, \(J = 7.9\) Hz, 1H, Ar-CH), 7.61 (s, 1H, Ar-CH), 7.31 – 7.24 (m, 3H, Ar-CH), 7.24 – 7.17 (m, 1H, Ar-CH), 7.03 (d, \(J = 8.3\) Hz, 1H, Ar-CH), 6.94 (td, \(J = 7.8, 1.9\) Hz, 1H, Ar-CH), 5.39 (s, 1H, C=CH\(_2\)), 5.20 (s, 1H, C=CH\(_2\)), 5.10 (s, 1H, CH), 4.13 – 4.02 (m, 2H, CH\(_2\)), 2.45 (s, 3H, CH\(_3\)). \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 172.1 (C=O), 148.6, 146.5, 139.4, 134.7, 130.4, 129.1, 128.9, 127.9, 127.4, 124.2, 124.0, 119.7, 119.4, 110.9, 110.6, 98.3, 61.0, 49.5, 21.8, 14.2 ppm. HRMS (ESI) \(m/z\): calcd for C\(_{21}\)H\(_{20}\)INO\(_2\)Na \([M+Na]^+\) 468.0431, found 468.0416.

Ethyl 3-(2-iodophenyl)-2-(5-methyl-1H-indol-3-yl)but-3-enoate (4ce): Following the general procedure of the synthesis of 4aa, 4ce was obtained from 1a (47.0 mg) and 5-methyl-1H-indole (19.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (16.0 mg, 35% yield). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.07 (s, 1H, NH), 7.87 (d, \(J = 7.9\) Hz, 1H, Ar-CH), 7.61 (s, 1H, Ar-CH), 7.31 – 7.24 (m, 3H, Ar-CH), 7.24 – 7.17 (m, 1H, Ar-CH), 7.03 (d, \(J = 8.3\) Hz, 1H, Ar-CH), 6.94 (td, \(J = 7.8, 1.9\) Hz, 1H, Ar-CH), 5.39 (s, 1H, C=CH\(_2\)), 5.20 (s, 1H, C=CH\(_2\)), 5.10 (s, 1H, CH), 4.13 – 4.02 (m, 2H, CH\(_2\)), 2.45 (s, 3H, CH\(_3\)). \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 172.1 (C=O), 148.6, 146.5, 139.4, 134.7, 130.4, 129.1, 128.9, 127.9, 127.4, 124.2, 124.0, 119.7, 119.4, 110.9, 110.6, 98.3, 61.0, 49.5, 21.8, 14.2 ppm. HRMS (ESI) \(m/z\): calcd for C\(_{21}\)H\(_{20}\)INO\(_2\)Na \([M+Na]^+\) 468.0416, found 468.0419.

2.3 Coupling Reaction Utilities to Construct Chemical Library:

2.3.1 The synthesis of series 1 compound 5:

![Chemical structure](image)

General procedure exemplified by the synthesis of 5a: In a 10 mL one-neck round bottom flask equipped with a magnetic stirring bar, K\(_2\)CO\(_3\) (42.0 mg, 0.30 mmol) was added into solution of 4aa (42.0 mg, 0.10 mmol) and Pd(OAc)\(_2\) (2.3 mg, 10 %) in DMF (2.0 mL). The reaction mixture was stirred for 12 h under Ar at 90°C. The reaction solution was diluted by EIOA (20.0 mL) and washed by water (2.0 mL \times 4). The organic phase was washed by saturated brine, dried over Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/PE; 1:10) to afford 5a as yellow liquid (23.0 mg, 80%).
Ethyl 3-methyl-1-(p-tolyl)-1H-indole-2-carboxylate (5a): Yellow liquid. 1H NMR (500 MHz, CDCl₃) δ 7.73 (d, J = 8.0 Hz, 1H, Ar-CH), 7.32 – 7.26 (m, 3H, Ar-CH), 7.19 (d, J = 7.8 Hz, 3H, Ar-CH), 7.08 (d, J = 8.3 Hz, 1H, Ar-CH), 4.21 (q, J = 7.1 Hz, 2H, CH₂), 2.68 (s, 3H, CH₃), 2.46 (s, 3H, CH₃), 1.17 (t, J = 7.1 Hz, 3H, CH₃) ppm. 13C NMR (101 MHz, CDCl₃) δ 160.2 (C=O), 139.8, 137.5, 137.0, 129.7, 127.7, 127.6, 126.2, 125.7, 122.0, 120.7, 120.5, 111.5, 60.4, 21.4, 14.1, 10.7 ppm. HRMS (ESI) m/z: calcld for C₁₉H₂₈NO₂ [M + H]+ 294.1489, found 294.1481.

Ethyl 6-bromo-3-methyl-1-(p-tolyl)-1H-indole-2-carboxylate (5b): Following the general procedure of the synthesis of 5a, 5b was obtained from 4ab (50.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (26.0 mg, 70% yield). 1H NMR (400 MHz, CDCl₃) δ 7.56 (d, J = 8.5 Hz, 1H, Ar-CH), 7.32 – 7.24 (m, 3H, Ar-CH), 7.17 (dd, J = 19.5, 4.8 Hz, 3H, Ar-CH), 4.18 (q, J = 7.1 Hz, 2H, CH₂), 2.63 (s, 3H, CH₃), 2.45 (s, 3H, CH₃), 1.14 (t, J = 7.1 Hz, 3H, CH₃) ppm. 13C NMR (126 MHz, CDCl₃) δ 162.1 (C=O), 140.3, 138.0, 136.4, 129.9, 127.7, 127.6, 126.5, 124.0, 122.0, 121.9, 119.6, 114.3, 60.6, 21.4, 14.1, 10.6 ppm. HRMS (ESI) m/z: calcld for C₁₉H₁₉BrNO₂ [M + H]+ 372.0594, found 372.0594.

Ethyl 6-fluoro-3-methyl-1-(p-tolyl)-1H-indole-2-carboxylate (5c): Following the general procedure of the synthesis of 5a, 5c was obtained from 4ac (44.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (22.5 mg, 72% yield). 1H NMR (400 MHz, CDCl₃) δ 7.63 (dd, J = 8.8, 5.3 Hz, 1H, Ar-CH), 7.29 (d, J = 8.2 Hz, 2H, Ar-CH), 7.15 (d, J = 8.1 Hz, 2H, Ar-CH), 6.93 (td, J = 9.0, 2.2 Hz, 1H, Ar-CH), 6.72 (dd, J = 9.9, 2.2 Hz, 1H, Ar-CH), 4.18 (q, J = 7.1 Hz, 2H, CH₂), 2.68 (s, 3H, CH₃), 2.44 (s, 3H, CH₃), 1.15 (t, J = 7.1 Hz, 3H, CH₃) ppm. 13C NMR (101 MHz, CDCl₃) δ 163.5 (C=O), 162.1, 161.1, 140.0 (d, Jc-F = 7.0 Hz, C-F), 137.8, 136.6, 129.8, 127.5, 124.3, 122.2, 121.9 (d, Jc-F = 3.0 Hz, C-F), 110.0 (d, Jc-F = 21.0 Hz, C-F), 97.6 (d, Jc-F = 21.0 Hz, C-F), 60.4, 21.4, 14.1, 10.7 ppm. HRMS (ESI) m/z: calcld for C₁₉H₁₉FNO₂ [M + H]+ 312.1404, found 312.1404.

Ethyl 6-isopropyl-3-methyl-1-(p-tolyl)-1H-indole-2-carboxylate (5d): Following the general procedure of the synthesis of 5a, 5d was obtained from 4ad (46.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (27.0 mg, 80% yield). 1H NMR (400 MHz, CDCl₃) δ 7.63 (d, J = 8.3 Hz, 1H, Ar-CH), 7.29 (d, J = 8.1 Hz, 2H, Ar-CH), 7.18 (d, J = 8.1 Hz, 2H, Ar-CH), 7.09 (d, J = 7.5 Hz, 1H, Ar-CH), 6.88 (s, 1H, Ar-CH), 4.18 (q, J = 7.1 Hz, 2H, CH₂), 2.93 (dt, J = 13.8, 6.9 Hz, 1H, CH), 2.64 (s, 3H, CH₃), 2.45 (s, 3H, CH₃), 1.23 (d, J = 6.9 Hz, 6H, 2 x CH₃), 1.15 (d, J = 7.1 Hz, 3H, CH₃) ppm. 13C NMR (126 MHz, CDCl₃) δ 162.5 (C=O), 147.3, 140.1, 137.4, 137.1, 129.7, 127.8, 126.0, 125.8, 122.2, 120.5, 119.8, 108.5, 60.3, 34.8, 24.4, 21.4, 14.2, 10.8 ppm. HRMS (ESI) m/z: calcld for C₂₂H₂₆NO₂ [M + H]+ 336.1958, found 336.1941.
Ethyl 3,6-dimethyl-1-(p-tolyl)-1H-indole-2-carboxylate (5e): Following the general procedure of the synthesis of 5a, 5e was obtained from 4ae (44.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (25.5 mg, 82% yield). 1H NMR (400 MHz, CDCl3) δ 7.58 (d, J = 8.2 Hz, 1H, Ar-CH), 7.28 (d, J = 8.0 Hz, 2H, Ar-CH), 7.20 – 7.14 (m, 2H, Ar-CH), 7.00 (dd, J = 8.2, 1.0 Hz, 1H, Ar-CH), 6.84 (s, 1H, Ar-CH), 4.18 (q, J = 7.1 Hz, 2H, CH2), 2.64 (s, 3H, CH3), 2.45 (s, 3H, CH3), 2.39 (s, 3H, CH3), 1.15 (t, J = 7.1 Hz, 3H, CH3) ppm. 13C NMR (126 MHz, CDCl3) δ 162.5 (C=O), 140.2, 137.4, 137.1, 136.0, 129.7, 127.8, 125.6, 122.5, 122.2, 120.4, 111.0, 60.3, 22.1, 21.4, 14.2, 10.8 ppm. HRMS (ESI) m/z: calcd for C20H22NO2 [M + H]+ 308.1645, found 308.1630.

Ethyl 3,5-dimethyl-1-(p-tolyl)-1H-indole-2-carboxylate (5f): Following the general procedure of the synthesis of 5a, 5f was obtained from 4af (44.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (24.5 mg, 79% yield). 1H NMR (400 MHz, CDCl3) δ 7.48 (d, J = 0.7 Hz, 1H, Ar-CH), 7.28 (s, 1H, Ar-CH), 7.21 – 7.14 (m, 3H, Ar-CH), 7.09 (dd, J = 8.5, 1.4 Hz, 1H, Ar-CH), 6.96 (d, J = 8.5 Hz, 1H, Ar-CH), 4.18 (q, J = 7.1 Hz, 2H, CH2), 2.64 (s, 3H, CH3), 2.47 (s, 3H, CH3), 2.44 (s, 3H, CH3), 1.15 (t, J = 7.1 Hz, 3H, CH3) ppm. 13C NMR (126 MHz, CDCl3) δ 162.5 (C=O), 138.3, 137.4, 137.2, 129.8, 129.6, 127.8, 127.7, 127.6, 126.2, 121.6, 120.0, 111.2, 60.3, 21.6, 21.4, 14.2, 10.7 ppm. HRMS (ESI) m/z: calcd for C20H22NO2 [M + H]+ 308.1645, found 308.1629.

Ethyl 3-methyl-1-(p-tolyl)-1H-benzo[g]indole-2-carboxylate (5g): Following the general procedure of the synthesis of 5a, 5g was obtained from 4ag (47.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (25.5 mg, 75% yield). 1H NMR (500 MHz, CDCl3) δ 7.87 (d, J = 8.1 Hz, 1H, Ar-CH), 7.74 (d, J = 8.7 Hz, 1H, Ar-CH), 7.55 (d, J = 8.8 Hz, 1H, Ar-CH), 7.38 – 7.32 (m, 3H, Ar-CH), 7.30 (d, J = 8.2 Hz, 2H, Ar-CH), 7.13 (t, J = 7.7 Hz, 1H, Ar-CH), 7.06 (d, J = 8.5 Hz, 1H, Ar-CH), 4.18 (q, J = 7.1 Hz, 2H, CH2), 2.72 (s, 3H, CH3), 2.53 (s, 3H, CH3), 1.18 (t, J = 7.1 Hz, 3H, CH3) ppm. 13C NMR (101 MHz, CDCl3) δ 162.2 (C=O), 139.3, 138.8, 133.9, 133.5, 130.0, 129.2, 129.0, 126.0, 125.4, 125.0, 124.5, 122.9, 122.6, 122.0, 119.3, 60.2, 21.6, 14.2, 11.0 ppm. HRMS (ESI) m/z: calcd for C20H22NO2 [M + H]+ 344.1645, found 344.1629.

2.3.2 The synthesis of series 2 compound 6:
General procedure: In a 10 mL one-neck round bottom flask equipped with a magnetic stirring bar, N-Bromosuccinimide (NBS, 36.0 mg, 0.20 mmol) was added into solution of 4aa (42.0 mg, 0.10 mmol) and Et3N (30.0 µL, 2.0 mmol) in EtOH (2.0 mL). The reaction was stirred for 12.0 h at room temperature. The reaction solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/PE; 1:10) to afford 6 as yellow liquid (23.5 mg, 80%).

Ethyl 3-(bromomethyl)-3-(2-iodophenyl)-5-methylindoline-2-carboxylate (6): Yellow liquid. 

1H NMR (400 MHz, CDCl3) δ 7.88 (dd, J = 7.9, 1.0 Hz, 1H, Ar-CH), 7.3-7.29 (m, 2H, Ar-CH), 7.18 (dd, J = 7.6, 1.6 Hz, 1H, Ar-CH), 7.02–6.95 (m, 2H, Ar-CH), 6.63 (d, J = 8.3 Hz, 1H, Ar-CH), 5.71 (d, J = 1.3 Hz, 1H, CH2), 5.30 (s, 1H, CH2), 5.15 (d, J = 7.6 Hz, 1H, CH), 4.97 (d, J = 7.4 Hz, 1H, NH), 4.16–4.06 (m, 2H, CH2), 2.22 (s, 3H, CH3), 1.10 (t, J = 7.1 Hz, 3H, CH3) ppm.

13C NMR (126 MHz, CDCl3) δ 170.6 (C=O), 146.2, 144.5, 141.1, 139.6, 133.1, 129.6, 129.3, 128.5, 128.1, 119.9, 112.4, 110.3, 98.7, 61.9, 61.7, 20.2, 14.0 ppm. HRMS (ESI) m/z: calcd for C19H20BrINO2 [M + H]+ 499.9717, found 499.9715.

2.3.3 The synthesis of series 3 compound 7:

General procedure: In a 10 mL one-neck round bottom flask equipped with a magnetic stirring bar, K2CO3 (42.0 mg, 0.30 mmol) was added into solution of 4ai (44.0 mg, 0.10 mmol) and Pd(OAc)2 (2.3 mg, 10 %) in DMF (2.0 mL). The reaction mixture was stirred for 12.0 h under Ar at 90°C. The reaction mixture was diluted by EtOA (20.0 mL) and washed by water (2.0 mL×4). The organic phase was washed by saturated brine, dried over Na2SO4, filtered and concentrated under reduced pressure to give the crude liquid. The residue was purified by flash column chromatography (EtOAc/PE; 1:10) to afford 7 as yellow liquid (15.0 mg, 59%).

8-Methyl-5H,7-benzo[5,6][1,4]oxazepino[4,3-a]indol-7-one (7): Yellow liquid. 1H NMR (500 MHz, CDCl3) δ 7.78 (d, J = 8.0 Hz, 1H, Ar-CH), 7.73 (t, J = 6.9 Hz, 2H, Ar-CH), 7.56 (t, J = 7.1 Hz, 2H, Ar-CH), 7.43 (t, J = 7.7 Hz, 1H, Ar-CH), 7.36 (t, J = 7.4 Hz, 1H, Ar-CH), 7.30 (t, J = 7.5 Hz, 1H, Ar-CH), 5.27 (d, J = 12.5 Hz, 1H CH2), 4.96 (d, J = 12.0 Hz, 1H CH2), 2.66 (s, 3H, CH3) ppm. 13C NMR (126 MHz, CDCl3) δ 163.0 (C=O), 138.5, 136.3, 130.60, 130.5, 130.2, 128.7, 126.6, 126.5, 126.4, 124.8, 123.5, 121.9, 121.3, 112.0, 67.5, 10.5 ppm. HRMS (ESI) m/z: calcd for C17H14NO2 [M + H]+ 264.1019, found 264.0988.

2.3.4 The synthesis of series 4 compound 8:
General procedure exemplified by the synthesis of 8c: In a 10 mL one-neck round bottom flask equipped with a magnetic stirring bar, K₂CO₃ (42.0 mg, 0.30 mmol) was added into solution of 4aa (51.0 mg, 0.10 mmol) and Pd(OAc)₂ (2.3 mg, 10 %) in DMF (2.0 mL). The reaction mixture was stirred for 12.0 h under Ar at 90°C. The reaction solution was diluted by EtOA (20.0 mL) and washed by water (2.0 mL x 4). The organic phase was washed by saturated brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the crude liquid. The residue was purified by flash column chromatography (EtOAc/PE; 1:10) to afford 8c as yellow liquid (13.0 mg, 42%).

**Ethyl 4,10-dimethyl-7H-pyrrolo[3,2,1-de]phenanthidine-5-carboxylate (8c):** Yellow liquid. ¹H NMR (500 MHz, CDCl₃) δ 7.70 (s, 1H, Ar-CH), 7.58 (d, J = 7.1 Hz, 1H, Ar-CH), 7.49 (d, J = 8.1 Hz, 1H, Ar-CH), 7.17 - 7.08 (m, 3H, Ar-CH), 5.80 (s, 2H, CH₂), 4.44 (q, J = 7.2 Hz, 3H, CH₃), 2.61 (s, 3H, CH₃), 2.41 (s, 3H, CH₃), 1.46 (t, J = 7.0 Hz, 3H, CH₃) ppm. ¹³C NMR (126 MHz, CDCl₃) δ 163.2 (C=O), 137.4, 135.2, 129.1, 128.9, 128.6, 127.4, 125.9, 124.4, 123.0, 121.7, 120.7, 120.1, 119.7, 116.3, 60.5, 49.0, 21.4, 14.6, 11.2 ppm. HRMS (ESI) m/z: calcd for C₂₀H₁₈NO₄ [M + H]⁺ 306.1489, found 306.1435.

**Ethyl 4-methyl-7H-pyrrolo[3,2,1-de]phenanthidine-5-carboxylate (8a):** Following the general procedure of synthesis of 8c, 8a was obtained from the amination product 4 with (2-bromophenyl)methanamine (50.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (13.0 mg, 46% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.89 (d, J = 7.3 Hz, 1H, Ar-CH), 7.58 (d, J = 7.2 Hz, 1H, Ar-CH), 7.49 (d, J = 8.1 Hz, 1H, Ar-CH), 7.33 (dd, J = 10.9, 3.9 Hz, 1H, Ar-CH), 7.28 (td, J = 7.5, 1.3 Hz, 1H, Ar-CH), 7.23 (d, J = 7.5 Hz, 1H, Ar-CH), 7.12 - 7.08 (m, 1H, Ar-CH), 5.83 (s, 2H, CH₂), 4.44 (q, J = 7.1 Hz, 2H, CH₂), 2.61 (s, 3H, CH₃), 1.46 (t, J = 7.1 Hz, 3H, CH₃) ppm. ¹³C NMR (126 MHz, CDCl₃) δ 163.2 (C=O), 135.1, 131.5, 129.2, 128.2, 127.8, 127.6, 126.0, 124.4, 122.5, 121.7, 120.8, 120.3, 119.5, 116.5, 60.5, 49.1, 14.6, 11.2 ppm. HRMS (ESI) m/z: calcd for C₁₉H₁₃NO₂ [M + H]⁺ 292.1332, found 292.1305.

**Ethyl 9-methoxy-4-methyl-7H-pyrrolo[3,2,1-de]phenanthidine-5-carboxylate (8b):** Following the general procedure of synthesis of 8c, 8b was obtained from the amination product 4 with (2-bromo-5-methoxyphenyl)methanamine (53.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (17.0 mg, 52% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.82 (d, J = 8.7 Hz, 1H, Ar-CH), 7.47 (dd, J = 18.0, 7.6 Hz, 2H, Ar-CH), 7.09 (dd, J = 8.1, 7.2 Hz, 1H, Ar-CH), 6.90 (dd, J = 8.6, 2.7 Hz, 1H, Ar-CH), 6.77 (d, J = 2.6 Hz, 1H, Ar-CH), 5.81 (s, 2H, CH₂), 4.44 (q, J = 7.1 Hz, 2H, CH₂), 3.85 (s, 3H, O-CH₃), 2.61 (s, 3H, CH₃), 1.46 (t, J = 7.1 Hz, 3H,
Ethyl 10-fluoro-4-methyl-7H-pyrrolo[3,2,1-de]phenanthridine-5-carboxylate (8d): Following the general procedure of synthesis of 8c, 8d was obtained from the amination product 4 with (2-bromo-4-fluorophenyl)methanamine (52.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (15.0 mg, 50% yield). ^1H NMR (400 MHz, CDCl₃) δ 7.55-7.49 (m, 3H, Ar-CH), 7.19 (dd, J = 8.4, 5.6 Hz, 1H, Ar-CH), 7.10 (t, J = 7.7 Hz, 1H, Ar-CH), 6.98 (td, J = 8.3, 2.5 Hz, 1H, Ar-CH), 5.78 (s, 2H, CH₂), 4.43 (q, J = 7.1 Hz, 2H, CH₂), 2.60 (s, 3H, CH₃), 1.46 (t, J = 7.1 Hz, 3H, CH₃) ppm. ^13C NMR (101 MHz, CDCl₃) δ 163.8 (C=O), 163.2, 134.9, 131.4 (d, Jc-F = 7.8 Hz, C-F), 129.1 (d, Jc-F = 7.8 Hz, C-F), 127.1 (d, Jc-F = 3.2 Hz, C-F), 126.0, 124.5, 121.8, 121.0, 120.8, 118.6 (d, Jc-F = 3.2 Hz, C-F), 116.9, 115.2 (d, Jc-F = 21.0 Hz, C-F), 109.2 (d, Jc-F = 21.0 Hz, C-F), 60.6, 48.7, 14.6, 11.2 ppm. HRMS (ESI) m/z: calcd for C_{19}H_{17}FNO_{3} [M + H]^+ 310.1238, found 310.1254.

2.3.5 The synthesis of series 5 compound 9:

General procedure exemplified by the synthesis of 9a: In a 10 mL one-neck round bottom flask equipped with a magnetic stirring bar, Et$_3$N (30.0 µL, 0.30 mmol) was added into solution of 1a (47.0 mg, 0.10 mmol) and (2-aminophenyl)boronic acid (21.0 mg, 0.15 mmol) in DCE (2.0 mL). The reaction runt for 30.0 min under room temperature. And then Pd(PPh₃)$_4$ (11.0 mg, 0.1 equiv) and K$_2$CO$_3$ (30.0 equiv) was added. The reaction mixture was stirred for 12.0 h under Ar at 110°C. The reaction solution was diluted by water (5.0 mL) and extracted by CH₂Cl₂ (10.0 mL × 3). The organic phase was washed by saturated brine, dried over Na$_2$SO₄, filtered and concentrated under reduced pressure to give the crude liquid. The residue was purified by flash column chromatography (EtOAc/PE = 1:10) to afford 9a as yellow liquid (8.0 mg, 70%).

Ethyl 7-methyl-5H-dibenzo[b,d]azepine-6-carboxylate (9a): Yellow liquid. ^1H NMR (400 MHz, CDCl₃) δ 7.48–7.33 (m, 5H, Ar-CH), 7.25–7.20 (m, 1H, Ar-CH), 7.13 (td, J = 7.5, 1.1 Hz, 1H, Ar-CH), 6.91 (dd, J = 7.8, 1.0 Hz, 1H, Ar-CH), 5.64 (s, 1H, NH), 4.33 (q, J = 7.1 Hz, 2H, CH₂), 2.46 (s, 3H, CH₃), 1.40 (t, J = 7.1 Hz, 3H, CH₃) ppm. ^13C NMR (126 MHz, CDCl₃) δ 164.9 (C=O), 153.3, 142.8, 139.7, 136.4, 134.1, 133.3, 129.7, 129.5, 128.4, 128.2, 128.0, 127.2, 124.2, 120.2, 61.8, 20.7, 14.5 ppm. HRMS (ESI), m/z: calcd for C_{26}H_{21}NO_{3} [M + H]^+ 380.1332, found 280.1333.

Ethyl 10-fluoro-7-methyl-5H-dibenzo[b,d]azepine-6-carboxylate (9b): Following the general procedure of the synthesis of 9a, 9b was obtained from 1ac (48.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (7.0 mg, 68% yield). ^1H NMR (400 MHz, CDCl₃) δ 7.83–7.62 (m, 2H, Ar-CH), 7.57 (d, J = 7.7 Hz, 1H, Ar-CH), 7.51 (d, J = 1.1 Hz, 1H, Ar-CH), 7.16 (t, J = 7.7 Hz, 1H, Ar-CH), 6.97 (td, J = 8.3, 1.1 Hz, 1H, Ar-CH), 6.89 (s, 2H, CH₂), 4.34 (q, J = 7.1 Hz, 2H, CH₂), 2.43 (s, 3H, CH₃), 1.38 (t, J = 7.1 Hz, 3H, CH₃) ppm. ^13C NMR (126 MHz, CDCl₃) δ 164.9 (C=O), 153.3, 142.8, 139.7, 136.4, 134.1, 133.3, 129.7, 129.5, 128.4, 128.2, 128.0, 127.2, 124.2, 120.2, 61.8, 20.7, 14.5 ppm. HRMS (ESI), m/z: calcd for C_{26}H_{22}FNO_{3} [M + H]^+ 402.1399, found 282.1438.
Ethyl 7,10-dimethyl-5H-dibenzo[b,d]azepine-6-carboxylate (9c): Following the general procedure of the synthesis of 9a, 9c was obtained from 1ae (48.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (7.0 mg, 66% yield). 1H NMR (400 MHz, CDCl₃) δ 7.44 (d, J = 7.4 Hz, 1H, Ar-CH), 7.32 (d, J = 8.0 Hz, 1H, Ar-CH), 7.25 – 7.16 (m, 3H, Ar-CH), 7.12 (t, J = 7.5 Hz, 1H, Ar-CH), 6.89 (d, J = 7.8 Hz, 1H, Ar-CH), 6.51 (s, 1H, NH), 4.32 (q, J = 7.1 Hz, 2H, CH₂), 2.44 (s, 3H, CH₃), 2.40 (s, 3H, CH₃), 1.39 (t, J = 7.1 Hz, 3H, CH₃) ppm. 13C NMR (101 MHz, CDCl₃) δ 165.0 (C=O), 153.2, 140.0, 139.6, 138.1, 135.7, 134.5, 133.4, 130.3, 129.4, 128.3, 128.1, 128.0, 124.1, 120.1, 61.7, 21.4, 20.6, 14.5 ppm. HRMS (ESI) m/z: calcd for C₁₉H₂₀FNO₂ [M + H⁺] 294.1489, found 294.1474.

6-Ethyl 3-methyl 7-methyl-5H-dibenzo[b,d]azepine-3,6-dicarboxylate (9d): Following the general procedure of the synthesis of 9a, 9d was obtained from 1a (47.0 mg) and (2-amino-4- (methoxy carbonyl)phenyl) boronic acid (40.0 mg) after flash column chromatography (EtOAc/PE = 1/10) as yellow liquid (8.0 mg, 63% yield). 1H NMR (400 MHz, CDCl₃) δ 7.79 (dd, J = 8.0, 1.6 Hz, 1H, Ar-CH), 7.56 (d, J = 1.5 Hz, 1H, Ar-CH), 7.48 (d, J = 8.0 Hz, 1H, Ar-CH), 7.44 – 7.37 (m, 4H, Ar-CH), 4.35 (q, J = 7.1 Hz, 2H, CH₂), 3.92 (s, 3H, CH₃), 2.45 (s, 3H, CH₃), 1.41 (t, J = 7.1 Hz, 3H, CH₃) ppm. 13C NMR (126 MHz, CDCl₃) δ 167.0 (C=O), 164.7, 153.1, 143.0, 138.7, 138.0, 136.1, 134.1, 130.0, 129.9, 129.5, 128.4, 128.2, 128.0, 125.4, 121.0, 61.9, 52.4, 20.6, 14.5 ppm. HRMS (ESI) m/z: calcd for C₂₀H₂₀NO₄ [M + H⁺] 338.1387, found 338.1367.

2.3.6 The synthesis of series 6 compound 10:

General procedure: In a 10 mL one-neck round bottom flask equipped with a magnetic stirring bar, K₂CO₃ (41.0 mg, 0.30 mmol) was added into solution of 4ca (43.0 mg, 0.10 mmol) and Pd(PPh₃)₄ (11.5 mg, 0.1 equiv) in DCE (2.0 mL). The reaction mixture was stirred for 12.0 h under Ar at 110°C. The reaction solution was diluted by water (5.0 mL) and extracted by CH₂Cl₂ (10.0 mL × 3). The organic phase was washed by saturated brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the crude liquid. The residue was purified by flash column chromatography (EtOAc/PE; 1:10) to afford 10 as yellow liquid (17.0 mg, 56%).
Ethyl 5-methyl-11H-benzo[a]carbazole-6-carboxylate (10): Yellow liquid. 

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.73 (d, $J = 8.0$ Hz, 2H, Ar-CH), 7.59 (d, $J = 7.6$ Hz, 1H, Ar-CH), 7.39 (dt, $J = 15.3$, 7.6 Hz, 2H, Ar-CH), 7.24 (d, $J = 7.5$ Hz, 1H, Ar-CH), 7.14 (t, $J = 7.4$ Hz, 1H, Ar-CH), 6.84 (d, $J = 7.4$ Hz, 1H, Ar-CH), 6.72 (d, $J = 7.5$ Hz, 1H, Ar-CH), 4.00 – 3.93 (m, 1H, CH$_2$), 3.89 – 3.83 (m, 1H, CH$_2$), 2.72 (s, 3H, CH$_3$), 0.85 (t, $J = 7.1$ Hz, 3H, CH$_3$) ppm.

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 171.9 (C=O), 163.9, 157.6, 156.6, 145.5, 140.7, 137.67, 129.4, 128.5, 128.4, 127.7, 126.7, 122.7, 122.0, 121.6, 121.2, 60.1, 13.6, 13.1 ppm. HRMS (ESI) m/z: calcd for C$_{20}$H$_{18}$NO$_2$ [M + H]$^+$ 304.1332, found 304.1318.

2.4 Coupling Reaction Mechanism Studies:

2.4.1 The experiment with deuterated aniline:

General procedure: In a 10 mL one-neck round bottomed flask equipped with a magnetic stirring bar, anhydrous Et$_3$N (30.0 uL, 0.20 mmol) was added into solution of monoaryl-vinyl iodonium 1a (47.0 mg, 0.10 mmol) and deuterated aniline (15.0 mg, 0.15 mmol) in anhydrous CH$_2$Cl$_2$ (2.0 mL). The reaction mixture was stirred for 30.0 min at room temperature. The reaction solution was concentrated under reduced pressure, and the residue was purified by flash column chromatography (EtOAc/PE; 1:10) to give 11-D containing 11-H, which were determined by NMR. 

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.88 (d, $J = 7.9$ Hz, 1H, Ar-CH), 7.31 (t, $J = 7.5$ Hz, 1H, Ar-CH), 7.20 (d, $J = 7.6$ Hz, 1H, Ar-CH), 6.99 (t, $J = 7.6$ Hz, 1H, Ar-CH), 5.74 (s, 1H, C=CH$_2$), 5.29 (s, 1H, C=CH$_2$), 4.97 (d, $J = 7.8$ Hz, 0.48H for 11-H), 4.59 (d, $J = 12.2$ Hz, 1H, NH), 4.15-4.06 (m, 2H, CH$_2$), 1.09 (t, $J = 7.1$ Hz, 3H, CH$_3$) ppm. 

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.2 (C=O), 146.6, 146.3, 144.8, 139.6, 129.6, 129.2, 128.0, 119.8, 98.8, 61.9, 61.6, 14.0. HRMS (ESI) m/z: calcd for C$_{18}$H$_{13}$D$_6$NO$_2$ [M + H]$^+$ 414.0832, found 414.0817.

2.4.2 The experiment with 4-methyl styrene:

General procedure: In a 10 mL one-neck round bottomed flask equipped with a magnetic stirring bar, anhydrous Et$_3$N (30.0 uL, 0.20 mmol) was added into solution of monoaryl-vinyl iodonium 1a (47.0 mg, 0.10 mmol) and 4-methyl styrene (18.0 mg, 0.15 mmol) in anhydrous CH$_2$Cl$_2$ (2.0 mL). The reaction mixture was stirred for 30.0 min at room temperature. The reaction solution was concentrated under reduced pressure, and the residue was purified by flash column chromatography (EtOAc/PE; 1:10) to give 12 containing 11-H, which were determined by NMR. 

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.88 (d, $J = 7.9$ Hz, 1H, Ar-CH), 7.31 (t, $J = 7.5$ Hz, 1H, Ar-CH), 7.20 (d, $J = 7.6$ Hz, 1H, Ar-CH), 6.99 (t, $J = 7.6$ Hz, 1H, Ar-CH), 5.74 (s, 1H, C=CH$_2$), 5.29 (s, 1H, C=CH$_2$), 4.97 (d, $J = 7.8$ Hz, 0.48H for 11-H), 4.59 (d, $J = 12.2$ Hz, 1H, NH), 4.15-4.06 (m, 2H, CH$_2$), 1.09 (t, $J = 7.1$ Hz, 3H, CH$_3$) ppm. 

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.2 (C=O), 146.6, 146.3, 144.8, 139.6, 129.6, 129.2, 128.0, 119.8, 98.8, 61.9, 61.6, 14.0. HRMS (ESI) m/z: calcd for C$_{18}$H$_{13}$D$_6$NO$_2$ [M + H]$^+$ 414.0832, found 414.0817.
General procedure: In a 10 mL one-neck round bottomed flask equipped with a magnetic stirring bar, Et$_3$N (30.0 uL, 0.20 mmol) was added into solution of monoaryl-vinyl iodonium 1a (47.0 mg, 0.10 mmol) and 4-methylstyrene (17.0 mg, 0.15 mmol) in EtOH (2.0 mL). The reaction mixture was stirred for 30.0 min at room temperature. The reaction mixture was collected as sample to detect by LC-MS directly to confirm the formation of 12. LC-MS m/z: calcd for C$_{21}$H$_{22}$IO$_2$ [M + H]$^+$ 433.06, found 433.1.

2.4.3 The experiment with EtOH:

![Diagram of reaction]

General procedure: In a 10 mL one-neck round bottomed flask equipped with a magnetic stirring bar, Et$_3$N (30.0 uL, 0.20 mmol) was added into solution of monoaryl-vinyl iodonium 1a (47.0 mg, 0.10 mmol) in EtOH (2.0 mL). The reaction mixture was stirred for 30.0 min at room temperature. The reaction solution was concentrated under reduced pressure, and the residue was purified by flash column chromatography (EtOAc/PE; 1:10) to give 13 (4.0 mg, 10% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.85 (d, $J$ = 7.9 Hz, 1H, Ar-H), 7.29 (t, $J$ = 7.5 Hz, 1H, Ar-H), 7.17 (d, $J$ = 7.6 Hz, 1H, Ar-H), 6.98 (t, $J$ = 7.6 Hz, 1H, Ar-H), 5.77 (s, 1H, C=CH$_2$), 5.27 (s, 1H, C=CH$_2$), 4.71 (s, 1H, CH$_3$), 4.10 (q, $J$ = 7.1 Hz, 2H, CH$_2$), 3.76 – 3.63 (m, 2H, CH$_2$), 1.30 (t, $J$ = 7.0 Hz, 3H, CH$_3$), 1.12 (t, $J$ = 7.1 Hz, 3H, CH$_3$) ppm.

2.5 The synthesis of cMAVIs 1:
General procedure for the synthesis of 1'-a: In a 50 mL one-neck round bottom flask equipped with a magnetic stirring bar, n-BuLi (2.4 M, 5.9 mL) was dropwise added into the solution of ethoxy acetylene (45%, 2.0 g, 12.84 mmol) in anhydrous THF (10.0 mL) at -78°C. The mixture was stirred for 2.0 h at -78°C before acetophenone (1.5 g, 1.5 mL, 12.84 mmol) was added at -78°C. The reaction mixture was warmed up to room temperature for 12.0 h. Finally, the deep brown mixture was added half-saturated NH₄Cl aqueous solution (5.0 mL) and then extracted by EtOAc (15.0 mL × 3). The organic phase was washed by saturated brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude liquid residue was purified by flash column chromatography (EtOAc/PE; 1:10) to afford 1'-S as yellow liquid (1.2 g, 51% yield). To the solution of 1'-S (1.2 g, 6.52 mmol) in CH₂Cl₂ (15.0 mL), N-iodosuccinimide (NIS, 2.2 g, 9.78 mmol) was added. The reaction mixture was stirred for 12.0 h at room temperature. The reaction mixture was washed by sodium thiosulfate aqueous solution. The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. The crude liquid residue was purified by flash column chromatography (EtOAc/PE; 1:50) to afford 1'-a as yellow liquid (0.8 g, 37% yield).

General procedure to synthesize 1'-c: In a 50 mL one-neck round bottom flask equipped with a magnetic stirring bar, ICl (1.4 g, 8.41 mmol) was added into the solution of ethyl phenylpropiolate (1.0 g, 5.74 mmol) in CH₂Cl₂ (10.0 mL). The reaction mixture was stirred for 12.0 h at room temperature before it was successively washed by Na₂S₂O₃ aqueous solution and saturated brine. The organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (EtOAc/PE; 1:20) to give 1'-d (1.8 g, 95% yield) as yellow liquid.

General procedure to synthesize 1'-d: In a 50 mL one-neck round bottom flask equipped with a magnetic stirring bar, NIS (2.5 g, 11.31 mmol) was added to the solution of ethyl (triphenylphosphoranylidene)acetate (3.3 g, 9.42 mmol) in CH₂Cl₂ (20.0 mL) at -20°C. After 30.0 min, K₂CO₃ (2.6 g, 18.85 mmol) was added, followed by benzaldehyde (1.0 g, 9.42 mmol). The reaction mixture was stirred for 24.0 h at room temperature. Water (10.0 mL) was added and then the mixture was extracted with CH₂Cl₂ (10.0 mL × 3). The organic phases were washed by saturated brine (10.0 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (EtOAc/PE; 1:20) to give 1'-c (2.5 g, 87% yield) as yellow liquid.

General procedure to synthesize of cMAVIs exemplified by 1a: In a 25 mL one-neck round bottom flask equipped with a magnetic stirring bar, mCPBA (86.0 mg, 0.50 mmol) was added into the solution of 1'-a (100.0 mg, 0.33 mmol) in CH₂Cl₂ (2.0 mL), followed by TfOH (89.0 μL, 1.00 mmol). The reaction mixture was stirred for 2.0 h at room temperature. The reaction mixture was evaporated and then recrystallized by diethyl ether to give 1a as white powder (105.0 mg, 72% yield).
Ethyl-2-iodo-3-phenylbut-2-enolate (1'-a): Yellow liquid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.42 – 7.36 (m, 1H, Ar-Ch), 7.31 (m, 2H, Ar-Ch), 7.21 – 7.15 (m, 2H, Ar-Ch), 4.32 (q, J = 7.1 Hz, 0.88H, CH\(_3\)), 3.92 (q, J = 7.1 Hz, 1.01H, CH\(_2\)), 2.38 (s, 1.42H, CH\(_3\)), 2.35 (s, 1.17H, CH\(_3\)), 1.37 (t, J = 7.1 Hz, 1.34H, CH\(_3\)), 0.89 (t, J = 7.1 Hz, 1.57H, CH\(_3\)) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) δ 166.7 (166.2) (C=O), 153.6 (151.7), 145.8 (141.0), 128.5 (128.3), 128.1 (128.0), 126.8 (126.8), 87.7 (85.2), 62.2 (61.8), 30.6 (23.9), 14.1 (13.5) ppm. HRMS (ESI) m/z: calcd for C\(_{12}\)H\(_{14}\)IO\(_2\) [M + H]^+ 317.0033, found 317.0105.

Ethyl-3-chloro-2-iodo-3-phenylacrylate (1'-c): Yellow liquid. \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 7.50 – 7.45 (m, 2H, Ar-Ch), 7.45 – 7.39 (m, 2H, Ar-Ch), 7.39 – 7.33 (m, 1H, Ar-Ch), 4.38 (q, J = 7.1 Hz, 1.67H, CH\(_2\)), 3.99 (q, J = 7.1 Hz, 0.33H, CH\(_2\)), 1.39 (t, J = 7.1 Hz, 2.5H, CH\(_3\)), 0.94 (t, J = 7.1 Hz, 0.5H, CH\(_3\)) ppm. \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) δ 165.8 (165.4) (C=O), 138.8 (137.3), 134.8 (134.3), 130.2 (130.0), 128.9 (128.5), 128.4 (128.1), 89.2 (81.3), 62.8 (62.6), 14.0 (13.5) ppm. HRMS (ESI) m/z: calcd for C\(_{11}\)H\(_{10}\)ClO\(_2\)Na [M + Na]^+ 358.9306, found 358.9287.

Ethyl-2-iodo-3-phenylacrylate (1'-d): Yellow liquid. \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 8.26 (s, 1H, Ar-Ch), 7.77 (dd, J = 6.7, 2.8 Hz, 2H, Ar-Ch), 7.48 – 7.39 (m, 3H, Ar-Ch), 4.35 (q, J = 7.1 Hz, 2H, CH\(_2\)), 1.38 (t, J = 7.1 Hz, 3H, CH\(_3\)) ppm. \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) δ 163.9 (C=O), 148.1, 135.7, 130.2, 129.6, 128.4, 91.3, 63.2, 14.4 ppm. HRMS (ESI) m/z: calcd for C\(_{11}\)H\(_{10}\)IO\(_2\)Na [M + Na]^+ 324.9696, found 324.9684.

2-(Ethoxycarbonyl)-3-methylbenzo[b]jiodol-1-ium (1a): White solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 8.52 (d, J = 8.4 Hz, 1H, Ar-Ch), 7.95 (d, J = 7.8 Hz, 1H, Ar-Ch), 7.87 (t, J = 7.6 Hz, 1H, Ar-Ch), 7.79 (dd, J = 11.5, 4.1 Hz, 1H, Ar-Ch), 4.49 (q, J = 7.1 Hz, 2H, CH\(_2\)), 2.82 (s, 3H, CH\(_3\)), 1.45 (t, J = 7.1 Hz, 3H, CH\(_3\)) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) δ 161.5 (C=O), 157.3, 147.0, 134.1, 132.3, 131.5, 131.5, 121.9, 119.0, 65.1, 17.1, 14.4 ppm. HRMS (ESI) m/z: calcd for C\(_{13}\)H\(_{12}\)O\(_2\) [M-OTf]^+ 314.9877, found 314.9867.

2-(Ethoxycarbonyl)-3-phenylbenzo[b]jiodol-1-ium (1b): Following the general procedure, 1b was obtained from corresponding substrate (100.0 mg, 0.26 mmol) according to the general procedure of 1'-a after recrystallization by diethyl ether as white solid (113.0 mg, 81 % yield). \(^1\)H NMR (400 MHz, DMSO) δ 8.40 (d, J = 7.7 Hz, 1H, Ar-Ch), 7.88 – 7.79 (m, 2H, Ar-Ch), 7.59 (m, J = 4.9 Hz, 3H, Ar-Ch), 7.45 – 7.38 (m, 2H, Ar-Ch), 7.34 (d, J = 7.5 Hz, 1H, Ar-Ch), 4.15 (q, J = 6.9 Hz, 2H, CH\(_2\)), 1.01 (t, J = 7.0 Hz, 3H, CH\(_3\)) ppm. \(^{13}\)C NMR (101 MHz, DMSO) δ 161.6 (C=O), 156.6, 146.1, 133.8, 132.7, 131.2, 130.9, 129.5, 128.7, 128.6, 123.6, 123.0, 63.2, 13.4 ppm. HRMS (ESI) m/z: calcd for C\(_{17}\)H\(_{14}\)IO\(_2\) [M-OTf]^+ 392.8982, found 392.8980.
3-Chloro-2-(ethoxycarbonyl)benzo[b]iodol-1-ium (1c): Following the general procedure, 1c was obtained from 1'-c (100.0 mg, 0.30 mmol) after recrystallization by diethyl ether as white solid (103.0 mg, 72% yield). 1H NMR (400 MHz, DMSO) δ 8.42 – 8.36 (m, 1H, Ar-CH), 8.20 (dd, J = 7.9, 1.4 Hz, 1H, Ar-CH), 8.04 – 7.97 (m, 1H, Ar-CH), 7.96 – 7.89 (m, 1H, Ar-CH), 4.44 (q, J = 7.1 Hz, 2H, CH₂), 1.39 (t, J = 7.1 Hz, 3H, CH₃). HRMS (ESI) m/z: calcd for C₁₃H₁₆ClIO₂ [M+OTf]⁺ 334.9330, found 334.9324.

2-(Ethoxycarbonyl)benzo[b]iodol-1-ium (1d): Following the general procedure, 1d was obtained from 1'-d (100.0 mg, 0.33 mmol) after recrystallization by diethyl ether as white solid (115.0 mg, 77% yield). 1H NMR (400 MHz, CDCl₃) δ 8.98 (s, 1H, Ar-CH), 8.56 (d, J = 8.6 Hz, 1H, Ar-CH), 8.09 (dd, J = 7.7, 1.4 Hz, 1H, Ar-CH), 7.86 (t, J = 7.5 Hz, 1H, Ar-CH), 7.76 – 7.65 (m, 1H, Ar-CH), 4.50 (q, J = 7.1 Hz, 2H, CH₂), 1.45 (t, J = 7.1 Hz, 3H, CH₃). HRMS (ESI) m/z: calcd for C₁₂H₁₇ClIO₂ [M+OTf]⁺ 300.9720, found 300.9724.

6-Bromo-2-(ethoxycarbonyl)-3-methylbenzo[b]iodol-1-ium (1ab): Following the general procedure, 1ab was obtained from corresponding substrate (100.0 mg, 0.25 mmol) according to the general procedure of 1'-a after recrystallization by diethyl ether as white solid (101.0 mg, 73% yield). 1H NMR (500 MHz, DMSO) δ 8.46 (d, J = 1.8 Hz, 1H, Ar-CH), 8.14 (dd, J = 8.5, 1.8 Hz, 1H, Ar-CH), 8.06 (d, J = 8.5 Hz, 1H, Ar-CH), 4.41 (q, J = 7.1 Hz, 2H, CH₂), 2.71 (s, 3H, CH₃). HRMS (ESI) m/z: calcd for C₁₂H₁₃BrO₂ [M+OTf]⁺ 392.8982, found 392.8980.

2-(Ethoxycarbonyl)-6-fluoro-3-methylbenzo[b]iodol-1-ium (1ac): Following the general procedure, 1ac was obtained from corresponding substrate (100.0 mg, 0.30 mmol) according to the general procedure of 1'-a after recrystallization by diethyl ether as white solid (91.0 mg, 63% yield). 1H NMR (500 MHz, CDCl₃) δ 8.34 (s, 1H, Ar-CH), 7.91 (dd, J = 8.5, 4.6 Hz, 1H, Ar-CH), 7.59 (t, J = 7.9 Hz, 1H, Ar-CH), 4.49 (q, J = 7.0 Hz, 2H, CH₂), 2.81 (s, 3H, CH₃). 13C NMR (126 MHz, CDCl₃) δ 165.5 (C=O), 154.7, 145.8, 134.1, 133.2, 132.7, 125.4, 123.3, 121.7, 63.8, 16.8, 14.0 ppm. HRMS (ESI) m/z: calcd for C₁₂H₁₁FIO₂ [M+OTf]⁺ 332.9782, found 332.9775.

2-(Ethoxycarbonyl)-6-isopropyl-3-methylbenzo[b]iodol-1-ium (1ad): Following the general procedure, 1ad was obtained from corresponding substrate (100.0 mg, 0.28 mmol) according to the general procedure of 1'-a after recrystallization by diethyl ether as white solid (116.0 mg, 72% yield). 1H NMR (400 MHz, CDCl₃) δ 8.42 (s, 1H, Ar-CH), 7.84 (d, J = 8.2 Hz, 1H, Ar-CH), 7.68 (d, J = 8.2 Hz, 1H, Ar-CH), 4.46 (q, J = 7.1 Hz, 2H, CH₂), 3.09 (dt, J = 13.6, 6.8 Hz, 1H,
2-(Etoxycarbonyl)-3,6-dimethylbenzo[b]iodol-1-ium (1ae): Following the general procedure, 1ae was obtained from corresponding substrate (100.0 mg, 0.30 mmol) according to the general procedure of 1*-a after recrystallization by diethyl ether as white solid (116.0 mg, 80% yield). 1H NMR (400 MHz, DMSO) δ 8.12 (s, 1H, Ar-CH), 8.04 (d, J = 8.1 Hz, 1H, Ar-CH), 7.75 (d, J = 7.5 Hz, 1H, Ar-CH), 4.41 (q, J = 7.1 Hz, 2H, CH₂), 2.71 (s, 3H, CH₃), 2.51 (s, 3H, CH₃). HRMS (ESI) m/z: calcd for C₁₅H₁₄IO₂ [M+OTf]⁺ 357.0346, found 357.0305.

2-(Etoxycarbonyl)-3,5-dimethylbenzo[b]iodol-1-ium (1af). Following the general procedure, 1af was obtained from corresponding substrate (100.0 mg, 0.30 mmol) according to the general procedure of 1*-a after recrystallization by diethyl ether as white solid (118.0 mg, 83% yield). 1H NMR (400 MHz, CDCl₃) δ 8.37 (d, J = 7.1 Hz, 1H, Ar-CH), 7.72 (s, 1H, Ar-CH), 7.57 (d, J = 8.2 Hz, 1H, Ar-CH), 4.47 (q, J = 7.1 Hz, 2H, CH₂), 2.79 (s, 3H, CH₃), 2.56 (s, 3H, CH₃). HRMS (ESI) m/z: calcd for C₁₅H₁₄IO₂ [M+OTf]⁺ 329.0033, found 329.0030.

2-(Etoxycarbonyl)-3-methylnaphtho[1,2-b]iodol-1-ium (1ag): Following the general procedure, 1ag was obtained from corresponding substrate (100.0 mg, 0.27 mmol) according to the general procedure of 1*-a after recrystallization by diethyl ether as brown solid (98.0 mg, 70% yield). 1H NMR (500 MHz, DMSO) δ 8.46 (d, J = 8.6 Hz, 2H, Ar-CH), 8.28 – 8.21 (m, 1H, Ar-CH), 8.11 (d, J = 8.7 Hz, 1H, Ar-CH), 7.88 (tt, J = 7.3, 5.6 Hz, 2H, Ar-CH), 4.44 (q, J = 7.1 Hz, 2H, CH₂), 2.80 (s, 3H, CH₃), 1.40 (t, J = 7.1 Hz, 3H, CH₃) ppm. 13C NMR (101 MHz, DMSO) δ 161.3 (C=O), 156.1, 146.3, 134.4, 131.8, 130.9, 130.1, 129.7, 129.1, 128.2, 127.8, 127.0, 121.1, 64.3, 17.6, 13.9 ppm. HRMS (ESI) m/z: calcd for C₁₅H₁₄IO₂ [M+OTf]⁺ 365.0018, found 365.0018.

2.6 The characterization of 3:

Ethyl (E)-3-(2-iodophenyl) but-2-enoate (3a): Yellow liquid. 1H NMR (400 MHz, CDCl₃) δ 7.85 (d, J = 8.0 Hz, 1H, Ar-CH), 7.33 (t, J = 8.0 Hz, 1H, Ar-CH), 7.13 (d, J = 8.0 Hz, 1H, Ar-CH), 6.99 (t, J = 8.0 Hz, 1H, Ar-CH), 5.75 (s, 1H, C=CH), 4.23 (q, J = 7.1 Hz, 2H, CH₂), 2.45 (s, 3H, CH₃), 1.32 (t, J = 7.1 Hz, 3H, CH₃) ppm. 13C NMR (101 MHz, CDCl₃) δ 166.3 (C=O), 159.5, 148.8, 139.6, 129.2, 128.3, 128.0, 120.8, 95.4, 60.2, 20.9, 14.5 ppm. HRMS (ESI) m/z: calcd for C₁₅H₁₄IO₂ [M+H]⁺ 317.0033, found 317.0022.
Ethyl-3-(2-iodophenyl)-3-phenylacrylate (3b): Yellow liquid as a mixture of cis/trans isomers. 

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.81-7.87 (m, 1H, Ar-CH), 7.11 – 7.30 (m, 7H, Ar-CH), 7.03 (m, 1H, Ar-CH), 6.49 (s, 0.4H, C=CH), 5.97 (s, 0.6H, C=CH), 4.09 (q, $J = 7.1$ Hz, 1.2H, CH$_2$), 4.00 (q, $J = 7.1$ Hz, 0.80H, CH$_2$), 1.13 (t, $J = 7.1$ Hz, 1.80H, CH$_3$), 1.05 (t, $J = 7.1$ Hz, 1.2H, CH$_3$) ppm. 

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 166.1 (165.4) (C=O), 157.3 (157.2), 146.7 (144.3), 140.1 (139.2), 138.3 (137.6), 130.4 (129.9), 129.8 (129.7), 129.3 (129.2), 128.8, 128.1 (128.0), 127.9 (127.7), 121.8 (118.6), 98.0 (97.7), 60.5 (60.3), 14.1 (14.1) ppm. HRMS (ESI) $m/z$: calcd for C$_{17}$H$_{18}$IO$_2$ [M + H]$^+$ 379.0190, found 379.0189.

Ethyl (Z)-3-chloro-3-(2-iodophenyl)acrylate (3c): Yellow liquid with a major isomer. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.89 (d, $J = 8.0$ Hz, 1H, Ar-CH), 7.41 – 7.30 (m, 2H, Ar-CH), 7.07 (td, $J = 7.6, 2.0$ Hz, 1H, Ar-CH), 6.42 (s, 0.12H, C=CH), 6.20 (s, 0.78H, C=CH), 4.29 (q, $J = 7.1$ Hz, 1.70H, CH$_2$), 4.01 (q, $J = 7.1$ Hz, 0.30H, CH$_2$), 1.34 (t, $J = 7.1$ Hz, 2.56H, CH$_3$), 1.05 (t, $J = 7.1$ Hz, 0.44H, CH$_3$) ppm. 

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 163.7 (163.1) (C=O), 147.1 (151.0), 143.7 (142.9), 140.0 (139.3), 130.8 (130.4), 129.4 (128.5), 128.4 (128.3), 121.6 (122.7), 96.0 (95.9), 61.0 (60.8), 14.3 (13.9) ppm. HRMS (ESI) $m/z$: calcd for C$_{11}$H$_{11}$ClO$_2$ [M + H]$^+$ 336.9487, found 336.9495.

Ethyl 3-(2-iodophenyl)propionate (3d): Yellow liquid. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.88 (d, $J = 8.0$ Hz, 1H, Ar-CH), 7.57 (d, $J = 8.0$ Hz, 1H, Ar-CH), 7.36 (t, $J = 8.0$ Hz, 1H, Ar-CH), 7.12 (t, $J = 8.0$ Hz, 1H, Ar-CH), 4.32 (q, $J = 7.1$ Hz, 2H, CH$_2$), 1.37 (t, $J = 7.1$ Hz, 3H, CH$_3$) ppm. 

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 154.0 (C=O), 139.2, 134.5, 131.65, 128.1, 126.8, 101.2, 87.1, 83.6, 62.4, 14.2 ppm. HRMS (ESI) $m/z$: calcd for C$_{11}$H$_{15}$O$_2$Na [M + Na]$^+$ 322.9539, found 322.9542.
3. Data S1. The copies of NMR spectra. Related to Figure 2, Figure 3, Figure 4, and Figure 5.
