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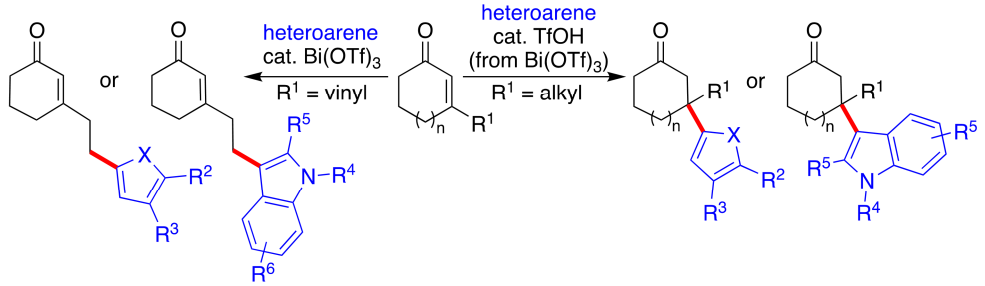
Department of Chemistry, Iowa State University and College of Chemistry, Beijing Normal University



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Synthesis of heteroarylated ketones via bismuth(III) triflate-promoted regioselective 1,4- and 1,6-additions of electron-rich heteroarenes to cyclic enones and dienones

Tanner L. Metz[a], Mingwan Leng[a,b], Joshua Evans[a], and Levi M. Stanley[a] *

[a]*Department of Chemistry, Iowa State University, Ames, Iowa 50011, United States*
[b]*College of Chemistry, Beijing Normal University, Beijing 100875, China*

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ABSTRACT

The development and optimization of bismuth(III) triflate-promoted regioselective 1,4- and 1,6-additions of electron-rich heteroarenes to cyclic, β,β-disubstituted enones and dienones is described. Additions of a range of heteroarenes, including furan, thiophene, pyrrole, and indole nucleophiles, to cyclic, β,β-disubstituted enones occur to form all-carbon quaternary centers in up to 88% yield. In addition, regioselective 1,6-additions of electron-rich heteroarenes to 3-vinyl-2-cyclohexenone occur to produce a variety of δ-heteroarylated, β,β-disubstituted enones in up to 93% yield. The high 1,6-selectivity for these reactions is attributed to the increased steric bulk at the β-position relative to the δ-position, and no competing 1,4-conjugate addition is observed.

* Corresponding author. Tel.: +1-515-294-3609; e-mail: lstanley@iastate.edu

1. Introduction

Bismuth(III) triflate has drawn the interest of synthetic organic chemist as an inexpensive and environmentally friendly Lewis acid catalyst and easily handled source of triflic acid.[1] These attractive properties have led to the emergence of bismuth(III) triflate as a privileged catalyst that has been utilized in a wide range of organic transformations over the past decades.[2] Among such transformations, 1,4-additions of electron-rich heteroarenes to α,β-unsaturated ketones in the presence of bismuth(III) triflate are a valuable set of reactions to generate β-heteroarylated ketones. Until recently, these studies were limited to 1,4-additions of indole nucleophiles to unsubstituted and β-substituted, α,β-unsaturated carbonyl compounds and related Michael acceptors.[3]

Our group has actively pursued a program aimed at developing catalytic additions of aryl and heteroaryl nucleophiles to construct quaternary carbon centers and sterocenters. Early efforts from our laboratory focused on developing palladium-catalyzed 1,4-additions of arylboron nucleophiles to β,β-disubstituted enones.[4] However, these processes do not encompass additions of heteroarylboron nucleophiles due to the relative instability of these reagents.[5] To address this issue, we recently reported direct additions of electron-rich heteroarenes to β,β-disubstituted enones that are catalyzed by triflic acid generated *in situ* from bismuth (III) triflate (Fig 1A).[6] These reactions encompass additions of furan, thiophene, pyrrole, and indole nucleophiles to a variety of β,β-disubstituted enones to construct heteroarylated all-carbon quaternary centers. During the course of these studies, we observed that the addition reactions are sensitive to the identity of β-substitutents present in the β,β-disubstituted enone. For example, additions of 2,3-dimethylfuran to cyclic enones containing relatively small alkyl substituents at the β-position occur to form the β-heteroarylated ketone products in good yields. However, additions to cyclic enones with sterically demanding substituents at the β-position either do not occur to form the β-heteroarylated ketone products or lead to 1,2-addition and elimination sequences that generate heterarylated dienes (Fig 1B).[7] Based on these results, we hypothesized that we could leverage the differences in reactivity and selectivity to develop regioselective 1,6-additions of electron-rich heteroarenes to β-vinylenones in the presence of bismuth(III) triflate to form δ-heteroarylated enones.

During preliminary studies to develop regioselective 1,6-additions of electron-rich heteroarenes, we noted that examples of 1,6-additions of heteroarenes to *para*-quinone methides for the synthesis of triarylmethanes are established (Fig 1C).[8] However, regioselective 1,6-additions of heteroarenes to dienones to synthesize δ-heteroarylated, β,β-disubstituted enones are limited to one report on additions of furans to steroidal dienones.[9] The development of 1,6-addition reactions that encompass additional heteroarenes and dienone electrophiles would provide rapid access to additional classes of δ-heteroarylated, β,β-disubstituted enones with a synthetic handle for further functionalization (Fig 1D).

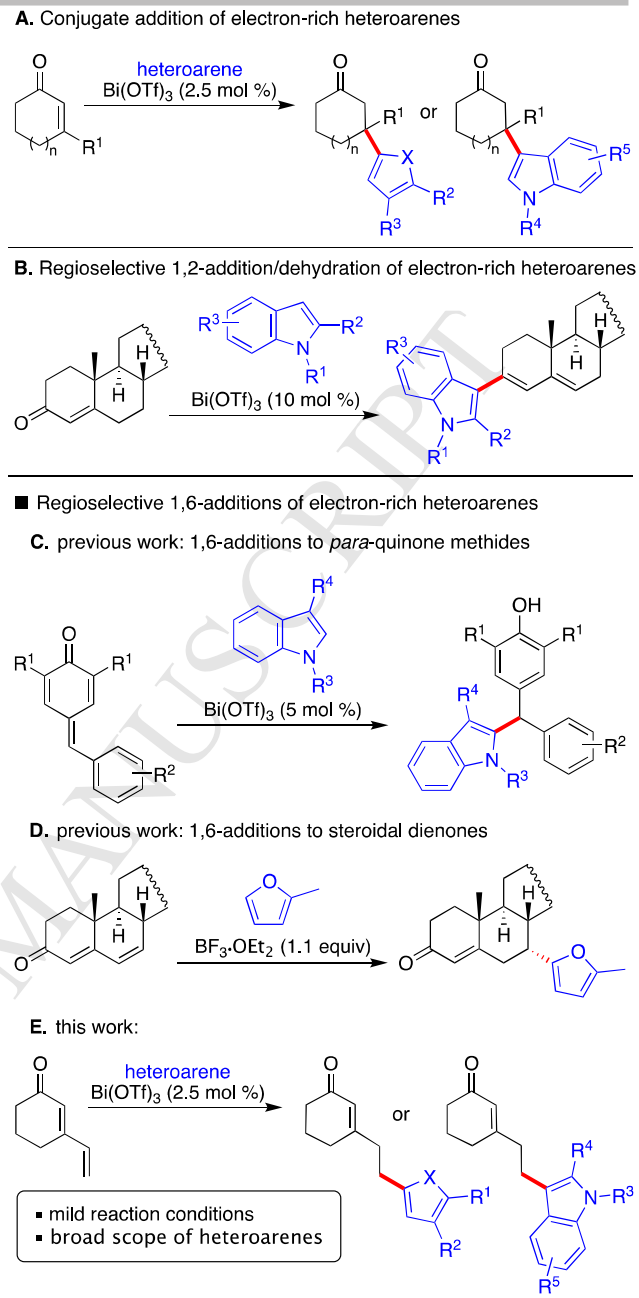


Fig 1. Regioselective 1,4-addition (A), 1,2-addition (B), and 1,6-additions (C-E) of electron-rich heteroarenes enones and dienones.

In this article, we provide a full account of our studies to develop 1,4-additions of heteroarenes to cyclic β,β-disubstituted enones to generate quaternary carbon centers and related regioselective 1,6-additions of heteroarenes to 3-vinyl-2-cyclhexenone to generate δ-heteroarylated enones in the presence of catalytic bismuth(III) triflate.

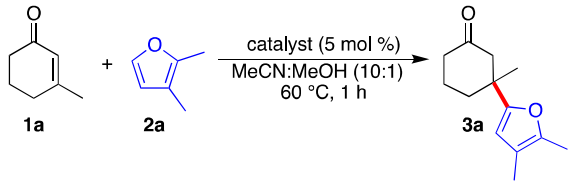
2. Development of 1,4-additions of electron-rich heteroarenes to β,β-disubstituted enones to form quaternary carbon centers

2.1. Identification of reaction conditions

Our studies to identify practical catalysts of 1,4-additions of electron-rich heteroarenes to cyclic β,β-disubstituted enones began by evaluating the reaction of 2,3-dimethylfuran (**2a**) with 3-methyl-2-cyclohexenone (**1a**) in the presence of a selection of Lewis acid catalysts. These results are summarized in Table 1.

We initially evaluated $RuCl_3 \cdot xH_2O$ based on the high activity of this catalyst for the conjugate addition of indole to progesterone; however, the ketone product **3a** was generated in modest yield (60%, entry 1).[10] We were pleased to find that running the model reaction in the presence of scandium(III) and bismuth(III) triflate salts led to the formation of ketone product **3a** in increased yields. (74-76%, entries 2-3). Previous studies have established that triflic acid can be derived from the hydrolysis of bismuth(III) triflate, and the observed catalytic activities may be attributed to either Brønsted and/or Lewis acid activation.[11] We next carried out the model reaction in the presence of triflic acid to determine whether triflic acid derived from hydrolysis of bismuth(III) triflate is an active catalyst (entry 4). When the model conjugate addition reaction is run the presence of 10 mol % triflic acid, the ketone product **3a** is formed in 67% yield (entry 4). This result suggests that bismuth(III) triflate is being hydrolyzed to triflic acid, and that the model reaction proceeds by Brønsted acid catalysis. To verify this mode of activation, we conducted our model reaction in the presence of catalytic amounts of bismuth(III) triflate and 2,6-di-*tert*-butylpyridine. Under these reaction conditions ketone **3a** was not generated, suggesting that triflic acid is serving as the active catalyst (entry 7). We chose to proceed with further studies using bismuth(III) triflate as a convenient source of triflic acid.

Table 1
Catalyst identification[a]



entry	Lewis acid catalyst	additive (mol %)	yield [b] **3a** (%)
1	$RuCl_3 \cdot xH_2O$	-	60
2	$Sc(OTf)_3$	-	74
3	$Bi(OTf)_3$	-	76
4[c]	TfOH	-	67
5	$Bi(OTf)_3$	2,6-di-*tert*-butylpyridine (15)	0

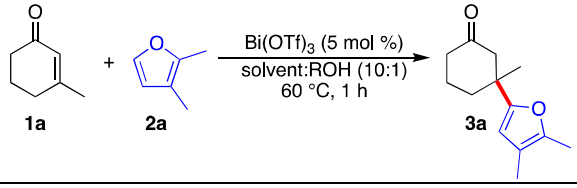
[a] Conditions: Reactions were performed with 3-methyl-2-cyclohexenone **1a** (0.25 mmol), 2,3-dimethylfuran **2a** (0.50 mmol), catalyst (0.013 mmol), acetonitrile/methanol (10:1, 0.5 mL), 60 °C for 1h.

[b] Determined by ^{1}H NMR spectroscopy using dibromomethane as an internal standard.

[c] 10 mol % TfOH.

Identification of triflic acid derived from bismuth(III) triflate as a promising catalyst prompted us to investigate the effects of solvent on the yield of the model reaction. These results are summarized in Table 2. Unfortunately, variation of the identity of the aprotic and protic components of our binary solvent system did not lead to improved yields of ketone **3a**. Conducting the model reaction in the presence less polar solvents afforded the corresponding ketone product **3a** in reduced yields (entries 2-4). Running the model reaction in the absence of a protic co-solvent had a deleterious impact on the reaction and led to the formation of **3a** in only 22% yield. (entry 5). We also evaluated the effect of different protic co-solvents. Running the model reaction in the presence of ethanol or 2-propanol resulted in a slight decrease in yield of the corresponding ketone product **3a** (entries 6-7). However, the use of more acidic protic co-solvents, such as hexafluoro-2-propanol and phenol, afforded ketone **3a** in significantly lower yields (entries 8-9).

Table 2
Evaluation of reaction solvents[a]

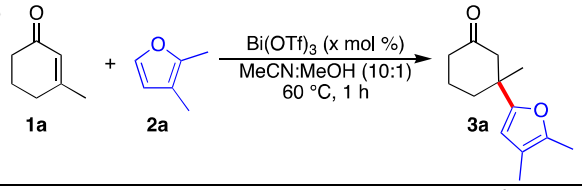


entry	solvent	protic co-solvent	yield [b] **3a** (%)
1	acetonitrile	methanol	76
2	1,4-dioxane	methanol	55
3	dichloroethane	methanol	48
4	toluene	methanol	44
5	acetonitrile	-	22
6	acetonitrile	ethanol	62
7	acetonitrile	2-propanol	64
8	acetonitrile	phenol	21
9	acetonitrile	HFIP	34

[a] Conditions: Reactions were performed with 3-methyl-2-cyclohexenone **1a** (0.25 mmol), 2,3-dimethylfuran **2a** (0.50 mmol), $Bi(OTf)_3$ (0.013 mmol), solvent/cosolvent (10:1, 0.5 mL), 60 °C for 1h.

[b] Determined by ^{1}H NMR spectroscopy using dibromomethane as an internal standard

Table 3
Optimization of substrate concentrations[a]



entry	ratio **1a**:**2a**	$Bi(OTf)_3$ (x mol %)	yield [b] **3a** (%)
1	1:2	5	76
2[c]	1:2	5	76
3	1:1	5	62
4	2:1	5	89
5	3:1	5	98
6	3:1	2.5	98
7	3:1	1	82
8[c]	3:1	1	98

[a] Conditions: Reactions were performed with 3-methyl-2-cyclohexenone **1a** (0.25-0.75 mmol), 2,3-dimethylfuran **2a** (0.50-0.25 mmol), $Bi(OTf)_3$ (0.0025-0.013 mmol) MeCN/MeOH (10:1, 0.5 mL), 60 °C for 1h.

[b] Determined by ^{1}H NMR spectroscopy using dibromomethane as an internal standard.

[c] Reaction ran for 2 hours.

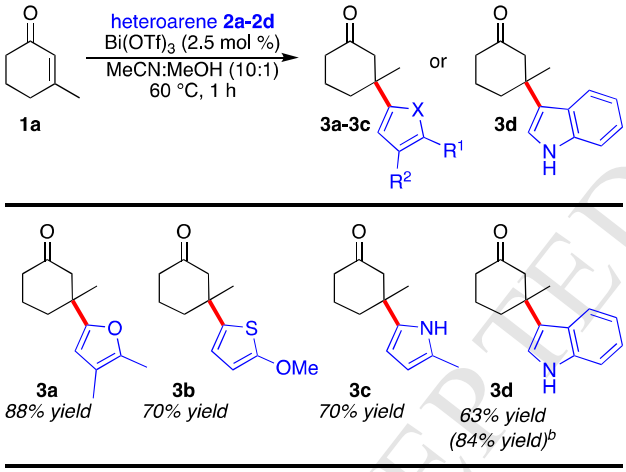
To improve the yield of our model reaction, we investigate the impact of reaction time and substrate concentration. Running the model reaction for longer periods of time failed to deliver the corresponding ketone product **3a** in increased yield (compare Table 3, entries 1 and 2). This observation led us to hypothesize that inhibition of the catalyst by ketone **3a** may be significant as the reaction progresses. With this hypothesis in mind, we examined the impact of increasing the concentration of 3-methyl-

2-cyclohexenone **1a** relative to 2,3-dimethyl furan **2a**. We found that running the reaction in the presence of excess enone enabled the construction of the desired ketone product **3a** in good-to-excellent yields (89-98%, entries 3-5). In the presence of excess enone, the loading of bismuth(III) triflate can be lowered to 2.5 mol % without impacting the yield of **3a** (entry 6). Upon lowering the catalyst loading to 1 mol %, the model reaction generated **3a** in 82% yield; however, if the reaction time is increased, product **3a** is generated in 98% yield (entries 7 and 8).

2.2. Determination of substrate scope

To establish the scope of heteroarene nucleophiles, additions of a variety of electron-rich heteroarenes to 3-methyl-2-cyclohexenone **1a** were conducted under the reaction conditions identified in entry 6 of Table 3. These results are summarized in Table 4. As noted above, the addition of 2,3-dimethyl furan **2a** to **1a** occurs in high yield and **3a** is isolated in 88% yield. The conjugate addition reactions are not limited to furan nucleophiles. The addition of 2-methoxythiophene **2b**, 2-methylpyrrole **2c**, and indole **2d** to 3-methyl-2-cyclohexenone **1a** occur to form ketone products **3b** and **3c** in 70% yield and **3d** in 63% yield. The reduced yield observed for the addition of indole **2d** to **1a** prompted us to reinvestigate reaction parameters to improve the yield of this reaction. We found that the yield of **3d** can be improved to 84% by running the reaction with 5 equiv of enone **1a** for 3 h.

Table 4
Scope of heteroarene nucleophiles[a]

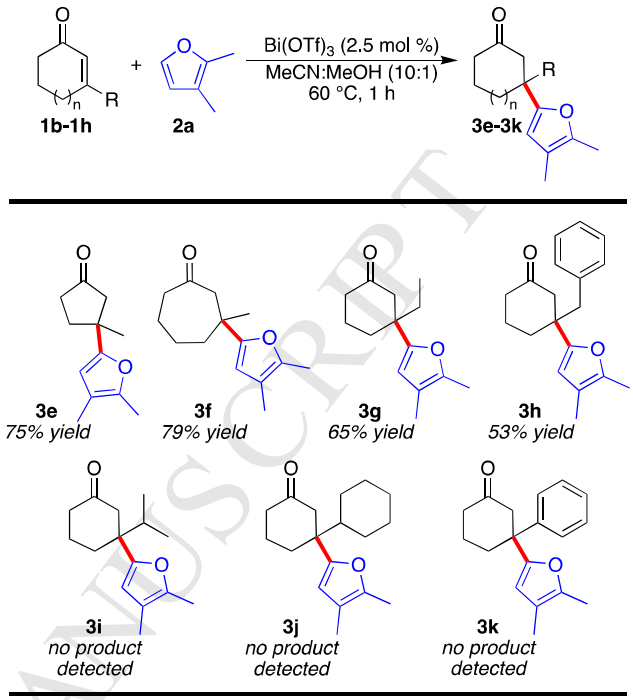


[a] Conditions: Reactions were performed with 3-methyl-2-cyclohexenone **1a** (0.75 mmol), heteroarene **2** (0.25 mmol), $Bi(OTf)_3$ (0.0063 mmol), MeCN/MeOH (10:1, 0.5 mL), 60 °C for 1h.

[b] Reaction was performed with 3-methyl-2-cyclohexenone **1a** (1.25 mmol) for 3h.

Next, we tested a variety of cyclic, β,β-disubstituted enones to establish the scope of the enone electrophiles. These reactions are summarized in Table 5. Additions of 2,3-dimethyl furan to the cyclic five- and seven-membered β,β-disubstituted enones **1b** and **1c** generated ketone products **3e** and **3f** in high yields. Additions to 3-ethyl-2-cyclohexenone **1d** and 3-benzyl-2-cyclohexenones **1e** occurred to form the corresponding ketone products **3g** and **3h** in 65% and 53% yield. However, the conjugate additions of 2,3-dimethylfuran **2a** to cyclic enones containing bulkier β-substituents, such as 3-isopropyl-2-cyclohexenone **1f**, 3-cyclohexyl-2-cyclohexenone **1g**, and 3-phenyl-2-cyclohexenone **1h**, did not occur. The lack of reactivity observed for enones **1f**, **1g**, and **1h** is attributed to the increased steric bulk at the β-position.

Table 5
Scope of enone substrates[a]



[a] Conditions: Reactions were performed with **1** (0.75 mmol), 2,3-dimethylfuran **2a** (0.25 mmol), $Bi(OTf)_3$ (0.0063 mmol), MeCN/MeOH (10:1, 0.5 mL), 60 °C for 1h.

3. Development of regioselective 1,6-additions of electron-rich heteroarenes to 3-vinyl-2-cyclohexenone

3.1. Identification of reaction conditions

The impact that identity of the β-substituent has on 1,4-additions of heteroarenes to cyclic β,β-disubstituted enones led us to hypothesize that regioselective 1,6-additions of electron-rich heteroarenes to 3-vinyl-2-cyclohexenone could occur to generate δ-heteroarylated, β,β-disubstituted enones. To test this hypothesis, we examined the model 1,6-addition of indole **2d** to 3-vinyl-2-cyclohexenone **4**.[12] These results are summarized in Table 6.

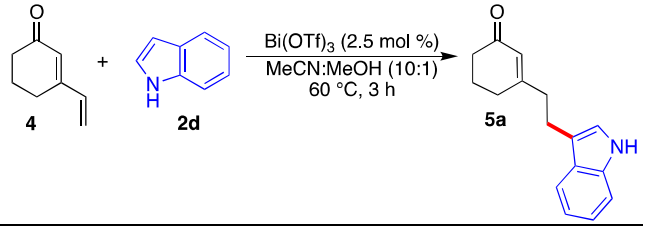
Replicating the reaction conditions described for the 1,4-addition of indole **2d** to 3-methyl-2-cyclohexenone **1a** in Table 4, the addition of **2d** to **4** occurred with complete regioselectivity to generate 3-(2-(1*H*-indol-3-yl)ethyl)cyclohex-2-en-1-one **5a** in 99% yield (entry 1). As shown previously, the 1,4-addition of indole **2d** required high concentrations of the enone substrate **1a** to obtain the corresponding ketone product **3d** in high yields. In contrast, the ratio of dienone to indole in the model 1,6-addition reaction can be lowered to 2:1 without significant impact to the yield of δ-heteroarylated, β,β-disubstituted enone **5a** (entries 2 and 3). The yield of **5a** does decrease significantly when the model 1,6-addition reaction is conducted with a 1:1 ratio of dienone **4**:indole **2d** (entry 4), and extended reaction time did not lead to higher yield of **5a** (entry 5).

We also conducted control experiments to gain insight into the identity of the active catalyst (Table 6, entries 6 and 7). Running the model 1,6-addition reaction in the presence of 10 mol %

triflic acid led to the formation of **5a** in only 50% yield (entry 6). However, the addition of indole **2d** to **4** in the presence of triflic acid is not regioselective. The 1,4- and 1,6-addition products are formed in a nearly 1:1 ratio. We also ran the model reaction in the presence of 2.5 mol % bismuth(III) triflate and 7.5 mol % 2,6-di-*tert*-butylpyridine (entry 7). Under these reaction conditions, δ-heteroarylated, β,β-disubstituted enone **5a** is formed in a modest 70% yield, but the addition occurs with complete regioselectivity for the 1,6-addition product **5a**. Taken together these results suggest that both triflic acid and a Lewis acidic bismuth species are active catalysts of 1,6-addition. However, the complete regioselectivity observed for entry 7 suggests that the 1,6-addition reaction proceeds through a bismuth-catalyzed pathway. Notably, the identification of a bismuth-catalyzed 1,6-addition pathway contrasts the related 1,4-additions of heteroarenes that have been determined to proceed *via* Brønsted acid catalysis.

Table 6

Impact of 3-vinyl-2-cyclohexenone concentration[a]



entry	ratio **4**:**2d**	time (h)	yield [b] **5a** (%)
1	5:1	3	99
2	3:1	3	99
3	2:1	3	97
4	1:1	3	75
5	1:1	24	71
6 [c]	2:1	3	50
7 [d]	2:1	3	70

[a] Conditions: Reactions were performed with 3-methyl-2-cyclohexenone **1a** (0.25-1.25mmol), indole **2d** (0.25 mmol), $Bi(OTf)_3$ (0.0063 mmol) MeCN/MeOH (10:1, 0.5 mL), 60 °C for 3 h.

[b] Determined by ^1H NMR spectroscopy using dibromomethane as an internal standard.

[c] 10 mol % TfOH.

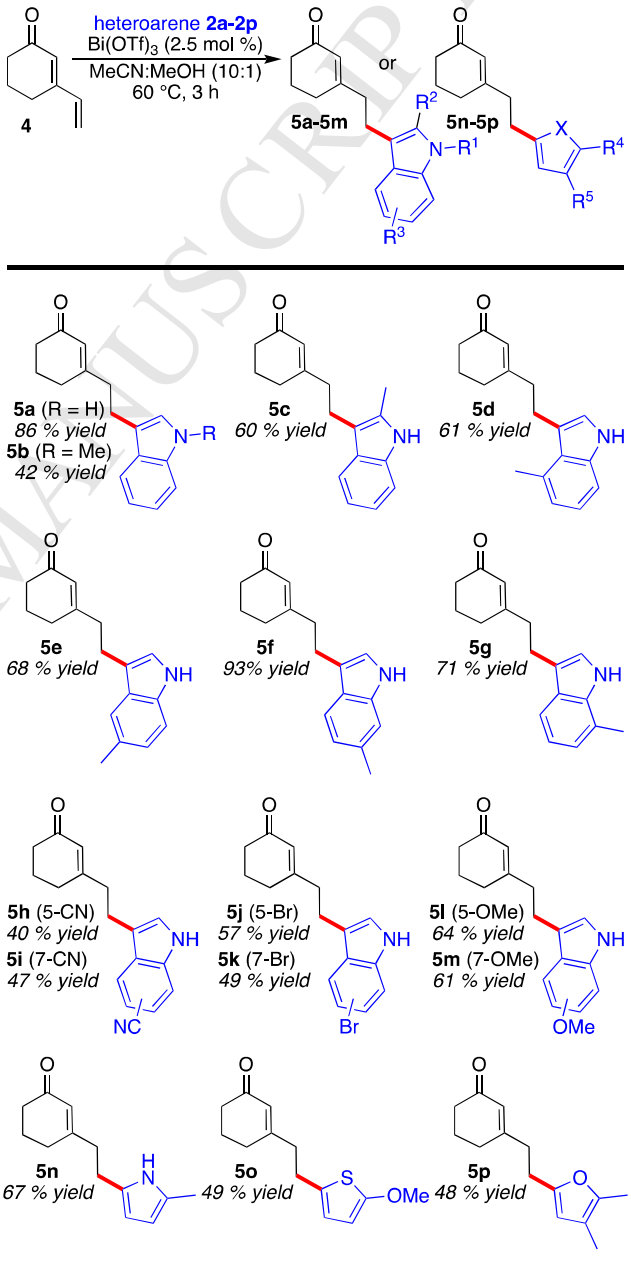
[d] Reaction was run in the presence of 7.5 mol % 2,6-di-*tert*-butylpyridine.

3.2. Scope of heteroarene nucleophiles

After identifying practical reaction conditions for the regioselective 1,6-addition of indole **2d** to 3-vinyl-2-cyclohexenone **4** (Table 6, entry 3), we proceeded to evaluate 1,6-additions of a variety of electron-rich heteroarene nucleophiles. These results are summarized in Table 7. As shown above, the addition of indole **2d** to **4** occurs in in high yield and product **5a** is isolated in 86% yield. Additions of methylated indoles occur to form the corresponding enone products **5b**-**5g**. Additions of *N*-methyl-, 2-methyl-, 4-methyl-, 5-methyl-, 6-methyl-, and 7-methylindole to **4** generated enones **5b**-**5g** in 42-93% yield. The reactivity of 2-methylindole **2f** and 4-methylindole **2g** in 1,6-addition reactions contrasts their reactivity in 1,4-additions to 3-methyl-2-cyclohexenone **1a,** which did not occur to form the corresponding β-heteroarylated ketones. Additions of indoles containing electron-withdrawing substituents at the 5- and 7-positions with **4** occurred to form enone products **5h**-**5k** in moderate yields (40-57%). The addition of 5-methoxyindole **2o** and 7-methoxyindole **2p** to 3-vinyl-2-cyclohexenone **4** occurred to form the corresponding enones **5l** and **5m** in 61% and 64% yield. These 1,6-addition reactions were not limited to the addition of indole nucleophiles, and the additions of 2-methylpyrrole **2c**, 2-methoxythiophene **2b**, and 2,3-dimethylfuran **2a** to **4** occurred to generate the corresponding δ-heteroarylated, β,β-disubstituted enones **5n**-**5p** in 48-67% yield.

Table 7

Scope of heteroarene nucleophiles[a]



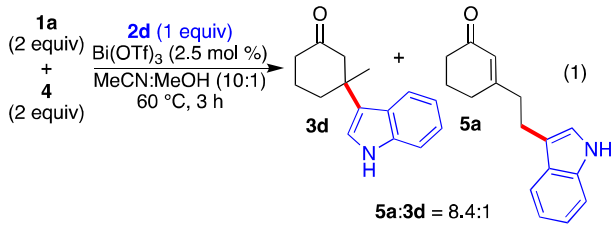
[a] Conditions: Reactions were performed with **4** (0.80 mmol), heteroarene **2** (0.40 mmol), $Bi(OTf)_3$ (0.010 mmol), MeCN/MeOH (10:1, 0.8 mL), 60 °C for 3 h.

Despite the many electron-rich heteroarenes that undergo 1,6-additions to construct heteroarylated δ-heteroarylated β,β-disbustituted enones, there a number of substrates that did not undergo the desired 1,6-addition reaction under our reaction

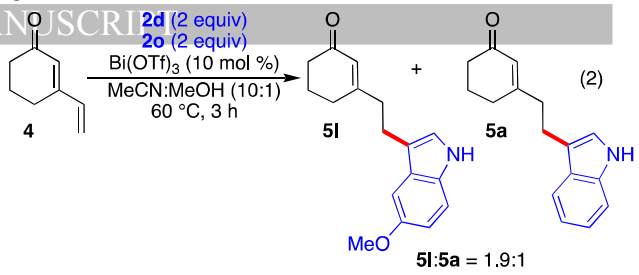
conditions. Additions of less nucleophilic heteroarenes, including 2-bromofuran, and 2-methylthiophene, benzothiophene, and benzofuran, to 3-vinyl-2-cyclohexenone **4** did not occur.

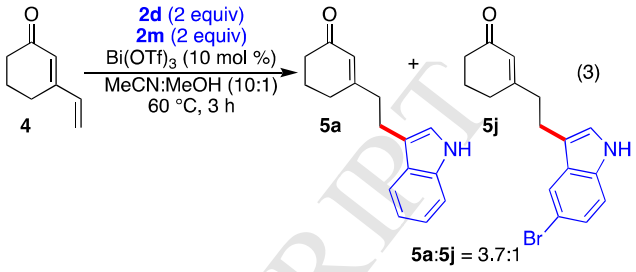
3.3. Competition experiments

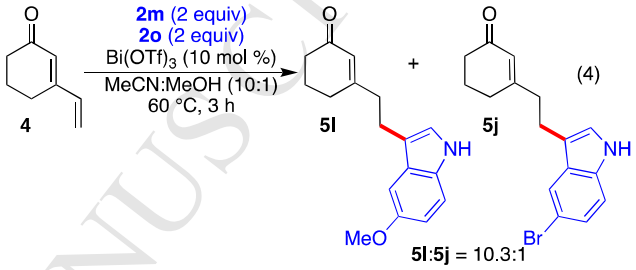
To gain insight into the relative rates of 1,4-addition and 1,6-addition reactions in our studies, we carried out a competition experiment between 3-methyl-2-cyclohexenone **1a** and 3-vinyl-2-cyclohexenone **4** (eq 1). The addition of indole to an equimolar mixture of **1a** and **4** in the presence of 2.5 mol % bismuth(III) triflate occurs to form an 8.4:1 ratio of 1,6-addition:1:4-addition products (**5a**:**3d**). This result clearly indicates that the rate of 1,6-addition to 3-vinyl-2-cyclohexenone **4** is significantly higher than the rate of 1,4-addition to 3-methyl-2-cyclohexenone **1a** in reactions promoted by bismuth(III) triflate and provides further insight into the high preference for 1,6- versus 1,4-selectivity in additions of heteroarenes to 3-vinyl-2-cyclohexenone **4**.



We also performed competition experiments between a selection of electronically distinct indole nucleophiles to gain additional insight into the reactivity of these heteroarenes in 1,6-addition reactions. We conducted a series of competition experiments between indole **2d**, 5-bromoindole **2m**, and 5-methoxyindole **2o** with 3-vinyl-2-cyclohexenone **4** (eq 2-4). The competition experiment between indole **2d** and 5-methoxyindole **2o** formed enones **5l** and **5a** in a 1.9:1 ratio favoring the addition of 5-methoxyindole (eq 2). The observed relative rates of addition of 5-methoxyindole and indole are consistent with nucleophilicity parameters determined for these heterocycles.[13] Similar trends are observed for the competition experiment between indole **2a** and 5-bromoindole **2m** (eq 3) and the competition experiment between 5-bromoindole **2m** and 5-methoxyindole **2o** (eq 4). In each of these experiments the observed relative rates are consistent with the nucleophilicity parameters for these heterocycles and favor addition of the more electron-rich heteroarene.

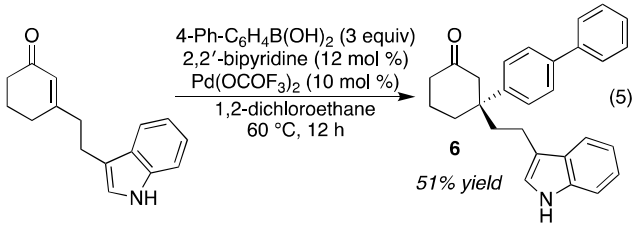






*3.4. Synthetic transformation of enone **5a***

Prior to the current study, 1,6-additions of electron-rich heteroarenes to dienones have been limited to a select few examples. The most common approach involves heteroarene addition to *para*-quinone methides that do not generate products that retain the electrophilic enone functionality, but instead isomerize to generate triarylmethanes.[8] The bismuth-catalyzed 1,6-addition reactions reported in our study lead to δ-heteroarylated, β,β-disubstituted enones that still possess a key enone functional group handle for further functionization. To demonstrate the synthetic utility of the δ-heteroarylated, β,β-disubstituted enone products, we sought to develop a palladium-catalyzed 1,4-addition of an arylboron nucleophile to enable rapid synthesis of β-arylated, δ-heteroarylated ketones that contain a quaternary carbon center at the β-position.[14] We investigated the reaction of 3-(2-(1*H*-indol-3-yl)ethyl)cyclohex-2-en-1-one **5a** with 4-biphenylboronic acid to show proof-of-concept. The addition of 4-biphenylboronic acid to **5a** forms the corresponding β-arylated, δ-heteroarylated ketone product **6** in 51% yield when the reaction is run in the presence of a catalyst prepared *in situ* from palladium trifluoroacetate and 2,2′-bipyridine (eq 5). Although we have not investigated the scope of additional nucleophiles that could participate in 1,4-additions to our δ-heteroarylated, β,β-disubstituted enone products, this result clearly demonstrates the potential synthetic utility of these compounds.



4. Conclusion

In summary, we have developed a series of 1,4- and 1,6-additions of electron-rich heteroarenes that occur in the presence of bismuth(III) triflate. The 1,4-additions of heteroarenes encompass reactions of indole, pyrrole, thiophene, and furan nucleophiles with a selection of cyclic β,β-disubstituted enones. These 1,4-addition processes enable rapid synthesis of a range of β-heteroarylated cyclic ketones containing a quaternary carbon center in up to 88% yield. Control experiments point to triflic acid derived from bismuth triflate as the active catalyst required for these 1,4-additions of heteroarenes. The sensitivity of these acid-catalyzed 1,4-additions to the identity of the substiuent at the β-position of the enone substrate has also led to the development of bismuth-catalyzed 1,6-additions of heteroarenes to a cyclic β-vinylenone. The 1,6-additions of heteroarenes to 3-vinyl-2-cyclohexenone also encompass indole, pyrrole, thiophene, and furan nucleophiles and lead to the formation of a variety of δ-heteroarylated, β,β-disubstituted enones in up to 93% yield. In contrast to the 1,4-addition processes, control experiments clearly show that the 1,6-addition reactions are bismuth-catalyzed process and that the bismuth catalyst plays a key role in the nearly complete selectivity for 1,6-addition. The δ-heteroarylated, β,β-disubstituted enones generated from our 1,6-addition reactions have significant potential to serve as valuable synthetic building blocks. We have demonstrated one such application through the palladium-catalyzed conjugate addition of an arylboronic acid to form a β-arylated, δ-heteroarylated ketone containing a quaternary carbon center at the β-position.

5. Experimental

5.1 Materials and methods

Indole, 7-methoxyindole, 7-bromoindole, 7-cyanoindole, *N*-methylindole, 2-methylpyrrole were purchased from AK Scientific and used without further purification. 7-Methylindole, 2-methylindole, and bismuth(III) triflate were purchased from Sigma-Aldrich and used without further purification. 6-Methylindole, 5-methylindole, and 4-methylindole were purchased from Combi-Blocks and used without further purification. 2-Phenylindole, 2-methoxythiophene, 3-methyl-2-cyclohexenone were purchased from TCI America and used without further purification. Anhydrous acetonitrile and methanol were purchased from Sigma-Aldrich and used as received. Enone substrates were either purchased from TCI America (3-methyl-2-cyclohexenone) or were prepared according to literature procedure.[15] Flash column chromatography was performed on SiliFlash® P60 silica gel (40-63μm, 60Å) or using a Teledyne Isco Combiflash® R*f* system with Redi*Sep* GoldTM columns using hexanes/ethyl acetate or hexanes/ether. Reaction products were visualized on TLC under UV light or by staining with $KMnO_4$. HRMS (ESI) analysis was performed at the Iowa State University Chemical Instrumentation Facility on an Agilent 6540 QTOF spectrometer. ^1H and ^{13}C NMR spectra were acquired on Varian MR-400 MHz and Bruker Avance III 600 MHz spectrometers at the Iowa State University Chemical Instrumentation Facility. Chemical shifts are reported in ppm relative to a residual solvent peak ($CDCl_3$ = 7.26 ppm for ^1H and 77.16 ppm for ^{13}C). Coupling constants are reported in hertz.

5.2. Representative procedure for the 1,4-addition of electron-rich heteroarenes to β,β-disubstituted enones

To a 1 dram vial was added $Bi(OTf)_3$ (4.2 mg, 0.0063 mmol, 0.025 equiv), 2,3-dimethylfuran (26 μL, 0.25 mmol), 3-methyl-2-cyclohexenone (82.6 mg, 0.75 mmol), and acetonitrile/methanol (10:1) solution (0.5 mL). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction was heated to 60 °C and allowed to stir at this temperature for 1 h. The mixture was cooled and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography on silica gel (5:1 hexane/ether) to yield a clear colorless oil (46.2 mg, 0.220 mmol, 88%).

5.3. Spectroscopic data for β-heteroarylated ketones

*5.3.1. 3-(4,5-dimethylfuran-2-yl)-3-methylcyclhexan-1-one (**3a**).* Synthesized according to the general procedure and purified by flash column chromatography (5:1 hexane/ether) to afford a colorless oil (46.2 mg, 0.220 mmol, 88%). ^1H NMR (600 MHz, $CDCl_3$): δ 5.80 (s, 1H), 2.74 (d, J = 14.4 Hz, 1H), 2.36-2.26 (m, 3H), 2.24-2.20 (m, 1H), 2.18 (s, 3H), 1.90-1.86 (m, 4H), 1.76-1.62 (m, 2H), 1.32 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 210.9, 156.5, 145.9, 114.0, 108.3, 51.9, 40.7, 40.3, 35.9, 27.3, 22.1, 11.2, 9.8. HRMS (ESI) calcd. for $C_{13}H_{19}O_2^+$ $[M+H]^+$ 207.1380, found 207.1381.

*5.3.2. 3-(5-methoxythiophen-2-yl)-3-methylcyclhexan-1-one (**3b**).* Synthesized according to the general procedure and purified by flash column chromatography (5:1 hexane/ether) to yield an orange oil (39.3 mg, 0.175 mmol, 70%). ^1H NMR (600 MHz, $CDCl_3$): δ 6.38 (d, J = 3.6 Hz, 1H), 5.93 (d, J = 3.6 Hz, 1H), 3.83 (s, 3H), 2.77 (d, J = 14.4 Hz, 1H), 2.39 (d, J = 14.4 Hz, 1H), 2.35-2.23 (m, 2H), 2.07-1.99 (m, 1H), 1.92-1.84 (m, 2H), 1.81-1.73 (m, 1H), 1.35 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 210.6, 164.7, 139.0, 120.6, 102.6, 60.2, 53.6, 42.2, 40.7, 39.5, 31.2, 22.1. HRMS (ESI) calcd. for $C_{12}H_{17}O_2S^+$ $[M+H]^+$ 225.0955, found 225.0952.

*5.3.3. 3-(5-methyl-1H-pyrrol-2-yl)-3-methylcyclhexan-1-one (**3c**).* Synthesized according to the general procedure and purified by flash column chromatography (5:1 hexanes/ether) to yield a white solid (33.6 mg, 0.174 mmol, 70%). ^1H NMR (600 MHz, $CDCl_3$): δ 7.64 (br, s, 1H), 5.79 (m, 1H), 5.75 (m, 1H), 2.74 (ddd, *J* = 14.4, 1.6, 1.6 Hz, 1H), 2.36 (d, *J* = 14.4 Hz, 1H), 2.33-2.26 (m, 2H), 2.23 (s, 3H), 2.08-1.98 (m, 1H), 1.92-1.80 (m, 2H), 1.75-1.63 (m, 1H), 1.32 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 211.4, 136.4, 126.9, 105.8, 105.0, 53.1, 40.9, 39.7, 38.0, 29.5, 22.4, 13.2. HRMS (ESI) calcd. for $C_{12}H_{18}NO^+$ $[M+H]^+$ 192.1394, found 192.1390.

*5.3.4. 3-(1H-indol-3-yl)-3-methylcyclohexan-1-one (**3d**).* Synthesized according to the general procedure using (5.00 equiv of 3-methyl-2-cyclohexenone and purified by flash column chromatography (hexanes/ethyl acetate = 95:5 to 85:15) to yield a white solid (48.1 mg, 0.210 mmol, 84%).^1H NMR (600 MHz, $CDCl_3$): δ 8.03 (br, s, 1H), 7.76 (d *J* = 7.8 Hz, 1H), 7.37 (d *J* = 7.8 Hz, 1H), 7.19 (dd, *J* = 8.4, 7.8 Hz, 1H), 7.10 (dd, *J* = 8.4, 7.8 Hz, 1H) , 6.96 (d, *J* = 2.4 Hz, 1H), 2.91 (d, *J* = 14.4 Hz, 1H), 2.62-2.55 (m, 2H), 2.48 (d, *J* = 14.4 Hz, 1H), 2.36-2.24 (m, 2H), 1.96-1.79 (m, 3H), 1.53 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 212.8, 137.4, 125.1, 122.2, 122.0, 121.9, 120.9, 119.1, 111.7, 54.4, 41.1, 40.2, 36.7, 29.4, 22.5. HRMS (ESI) calcd. for $C_{15}H_{18}NO^+$ $[M+H]^+$ 228.1394, found 228.1390.

*5.3.5. 3-(4,5-dimethylfuran-2-yl)-3-methylcyclopentan-1-one (**3e**).* Synthesized according to the general procedure and purified by flash column chromatography (5:1 hexanes/ethyl acetate) to yield a yellow oil (36.2 mg, 0.188 mmol, 75%). ^1H NMR (600 MHz, $CDCl_3$): δ 5.80 (s, 1H), 2.65 (d, *J* = 18.0 Hz, 1H), 2.39-2.28 (m, 3H), 2.20 (d, *J* = 18.0 Hz, 1H), 2.15 (s, 3H), 1.97-1.90 (m, 1H), 1.88 (s, 3H), 1.41 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 218.7, 157.0, 146.3, 114.2, 107.3, 51.4, 40.7, 37.1, 35.3, 25.9, 11.4, 10.0. HRMS (ESI) calcd. for $C_{12}H_{17}O_2^+$ $[M+H]^+$ 193.1223, found 193.1227.

*5.3.6. 3-(4,5-dimethylfuran-2-yl)-3-methylcycloheptan-1-one **(3f)**.* Synthesized according to the general procedure and purified by flash column chromatography (5:1 hexanes/ether) to yield a colorless oil (43.7 mg, 0.198 mmol, 79%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.75 (s, 1H), 2.98 (d, *J* = 13.8 Hz, 1H), 2.62 (d, *J* = 13.8 Hz, 1H), 2.42 (dd, *J* = 6.0, 6.0 Hz, 2H), 2.22-2.17 (m, 1H), 2.14 (s, 3H), 1.87 (s, 3H), 1.79-1.67 (m, 5H), 1.22 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 213.4, 158.2, 145.7, 114.1, 107.0, 54.1, 44.3, 42.2, 37.6, 28.0, 25.6, 24.1, 11.4, 10.0. HRMS (ESI) calcd. for $C_{14}H_{21}O_2^+$ $[M+H]^+$ 221.1536, found 221.1539.

*5.3.7. 3-(4,5-dimethylfuran-2-yl)-3-ethylcyclhexan-1-one **(3g)**.* Synthesized according to the general procedure and purified by flash column chromatography (hexanes/ethyl acetate = 100:0 to 90:10) to yield a colorless oil (35.2 mg, 0.163 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76 (s, 1H), 2.67 (dd, *J* = 14.4 Hz, 1H), 2.32-2.21 (m, 3H), 2.17-2.12 (m, 4H), 1.85-1.78 (m, 4H), 1.77-1.68 (m, 2H), 1.58-1.50 (m, 2H), 0.70 (dt, *J* = 7.8, 2.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.2, 154.3, 146.1, 114.0, 110.8, 49.4, 44.3, 41.1, 34.4, 33.7, 22.00, 11.4, 10.0, 8.4. HRMS (ESI) calcd. for $C_{14}H_{21}O_2^+$ $[M+H]^+$ 221.1539, found 221.1537.

*5.3.8. 3-benzyl-3-(4,5-dimethylfuran-2-yl)cyclhexan-1-one **(3h)**.* Synthesized according to the general procedure and purified by flash column chromatography (5:1 hexanes/ethyl acetate) to yield a colorless oil (37.4 mg, 0.134 mmol, 53%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.23-7.15 (m, 3H), 6.81 (d, *J* = 6.5 Hz, 2H), 5.62 (s, 1H), 3.02 (d, *J* = 13.2 Hz, 1H), 2.85 (d, *J* = 13.2 Hz, 1H), 2.45 (d, *J* = 14.2 Hz, 1H), 2.33-2.23 (m, 3H), 2.20 (s, 3H), 2.22 (m, 1H), 1.89-1.81 (m, 4H), 1.75 (m, 1H), 1.55-1.43 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 211.0, 153.4, 146.1, 137.0, 130.4, 127.9, 126.5, 114.3, 111.9, 49.0, 47.8, 45.0, 40.9, 34.3, 21.9, ll.4, 10.0. HRMS (ESI) calcd. for $C_{19}H_{23}O_2^+$ $[M+H]^+$ 283.1693, found 283.1697.

5.4. Representative procedure for the 1,6-addition of electron-rich heteroarenes to 3-vinyl-2-cyclohexenone

To a 1 dram vial was added $Bi(OTf)_3$ (6.7 mg, 0.010 mmol, 0.025 equiv), indole (47 mg, 0.40 mmol), 3-vinyl-2-cyclohexenone (97.7 mg, 0.80 mmol), and acetonitrile/methanol (10:1) solution (0.8 mL). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction was heated to 60 °C and allowed to stir at this temperature for 3 h. The mixture was cooled and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography on silica gel (hexanes/ethyl acetate = 80:20 to 70:30) to yield a white solid (82.1 mg, 0.343 mmol, 86%).

5.5. Spectroscopic data for δ-heteroarylated enones

*5.5.1. 3-(2-(1H-indol-3-yl)ethyl)cyclohex-2-en-1-one **(5a)**.* Synthesized according to the general procedure and purified by flash column chromatography (hexanes/ethyl acetate = 80:20 to 70:30) to yield a white solid (82.1 mg, 0.343 mmol, 86%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.98 (br, s, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.21 (dd, *J* = 7.8, 7.2 Hz, 1H), 7.13 (dd, *J* = 7.8, 7.2 Hz, 1H), 6.99 (d, *J* = 1.2 Hz, 1H), 5.97 (s, 1H), 2.99 (t, *J* = 7.8 Hz, 2H), 2.64 (t, *J* = 7.8 Hz, 2H), 2.37 (dd, *J* = 6.6, 6.6 Hz, 2H), 2.33 (dd, *J* = 6.0, 6.0 Hz, 2H), 1.99 (ddd, *J* = 13.2, 6.6, 6.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.1, 166.3, 136.4, 127.3, 126.1, 122.3, 121.4, 119.5, 118.7, 115.3, 111.4, 38.6, 37.5, 30.0, 23.1, 22.9. HRMS (ESI) calcd. for $C_{16}H_{18}NO^+$ $[M+H]^+$ 240.1383, found 240.1395.

*5.5.2. 3-(2-(1-methyl-1H-indol-3-yl)ethyl)cyclohex-2-en-1-one **(5b)**.* Synthesized according to the general procedure and purified by flash column chromatography (hexanes/ethyl acetate = 80:20 to 70:30) to yield a colorless oil (43.0 mg, 0.170 mmol, 42%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.24 (dd, *J* = 7.8, 7.2 Hz, 1H), 7.12 (dd, *J* = 7.8, 7.2 Hz, 1H), 6.84 (s, 1H), 5.98 (s, 1H), 3.75 (s, 3H), 2.98 (t, *J* =7.8 Hz, 2H), 2.63 (t, *J* = 7.8 Hz, 2H), 2.38 (dd, *J* = 6.6, 6.6 Hz, 2H), 2.34 (dd, *J* = 6.0, 6.0 Hz, 2H), 2.00 (ddd, *J* = 13.2, 6.6, 6.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.0, 166.2, 137.1, 127.7, 126.2, 126.0, 121.8, 118.9, 118.8, 113.7, 109.4, 38.8, 37.5, 32.7, 30.0, 23.0, 22.8. HRMS (ESI) calcd. for $C_{17}H_{20}NO^+$ $[M+H]^+$ 254.1539, found 254.1560.

*5.5.3. 3-(2-(2-methyl-1H-indol-3-yl)ethyl)cyclohex-2-en-1-one **(5c)**.* Synthesized according to the general procedure and purified by flash column chromatography (hexanes/ethyl acetate = 80:20 to 70:30) to yield a white solid (60.0 mg, 0.237 mmol, 60%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.91 (br, s, 1H), 7.47 (d, *J* = 7.2 Hz, 1H), 7.27 (d, *J* = 7.2 Hz, 1H), 7.13 (dd, *J* = 7.8, 7.2 Hz, 1H), 7.10 (dd, *J* = 7.8, 7.2 Hz, 1H), 5.95 (s, 1H), 2.91 (t, *J* = 7.8 Hz, 2H), 2.52 (t, *J* = 7.8 Hz, 2H), 3.37 (dd, *J* = 6.6, 6.6 Hz, 2H), 2.53 (s, 3H), 2.31 (dd, *J* = 6.0, 6.0 Hz, 2H), 1.98 (ddd, *J* = 13.2, 6.6, 6.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.1, 166.6, 135.4, 131.0, 128.4, 126.0, 121.2, 119.4, 117.8, 110.6, 110.5, 39.0, 37.5, 30.2, 22.9, 22.5, 11.8. HRMS (ESI) calcd. for $C_{17}H_{20}NO^+$ $[M+H]^+$ 254.1539, found 254.1561.

*5.5.4. 3-(2-(4-methyl-1H-indol-3-yl)ethyl)cyclohex-2-en-1-one **(5d)**.* Synthesized according to the general procedure and purified by flash column chromatography (hexanes/ethyl acetate = 80:20 to 70:30) to yield a white solid (62.0 mg, 0.245 mmol, 61%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.12 (br, s, 1H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.07 (dd, *J* = 7.8, 7.2 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.86 (d, *J* = 7.2 Hz, 1H), 6.01 (s, 1H), 3.15 (t, *J* = 7.8 Hz, 2H), 2.72 (s, 3H), 2.62 (t, *J* = 7.8 Hz, 2H), 2.40 (dd, *J* = 6.6, 6.6 Hz, 2H), 2.36 (dd, *J* = 6.0, 6.0 Hz, 2H), 2.02 (ddd, *J* = 13.2, 6.6, 6.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.1, 166.1, 136.9, 130.8, 126.0, 125.8, 122.4, 121.5, 121.3, 116.3, 109.3, 40.0, 37.5, 30.1, 25.1, 22.9, 20.5. HRMS (ESI) calcd. for $C_{17}H_{20}NO^+$ $[M+H]^+$ 254.1539, found 254.1558.

*5.5.5. 3-(2-(5-methyl-1H-indol-3-yl)ethyl)cyclohex-2-en-1-one **(5e)**.* Synthesized according to the general procedure and purified by flash column chromatography (hexanes/ethyl acetate = 80:20 to 70:30) to yield a white solid (68.9 mg, 0.272 mmol, 68%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.07 (br, s, 1H), 7.37 (s, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.93 (s, 1H), 5.99 (s, 1H), 2.96 (t, *J* = 7.8 Hz, 2H), 2.64 (t, *J* = 7.8 Hz, 2H), 2.48 (s, 3H), 2.38 (dd, *J* = 6.6, 6.6 Hz, 2H), 2.34 (dd, *J* = 6.0, 6.0 Hz, 2H), 2.00 (ddd, *J* = 13.2, 6.6, 6.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.1, 166.4, 134.8, 128.7, 127.5, 126.0, 123.9, 121.5, 118.4, 114.8, 111.0, 38.6, 37.5, 30.0, 23.1, 22.9, 21.7. HRMS (ESI) calcd. for $C_{17}H_{20}NO^+$ $[M+H]^+$ 254.1539, found 254.1554.

*5.5.6. 3-(2-(6-methyl-1H-indol-3-yl)ethyl)cyclohex-2-en-1-one **(5f)**.* Synthesized according to the general procedure and purified by flash column chromatography (hexanes/ethyl acetate = 80:20 to 70:30) to yield a white solid (94.3 mg, 0.372 mmol, 93%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.05 (br, s, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.15 (s, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.89 (s, 1H), 5.99 (s, 1H), 2.97 (t, *J* = 7.8 Hz, 2H), 2.63 (t, *J* = 7.8 Hz, 2H), 2.48 (s, 3H), 2.38 (dd, *J* = 6.6, 6.6 Hz, 2H), 2.33 (dd, *J* = 6.0, 6.0 Hz, 2H), 1.99 (ddd, *J* = 12.6, 6.6, 6.0 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.2, 166.6, 136.9, 131.9, 125.9, 125.1, 121.1, 120.8, 118.3, 114.9, 111.3, 38.6, 37.4, 29.9, 23.1, 22.8, 21.8. HRMS (ESI) calcd. for $C_{17}H_{20}NO^+$ $[M+H]^+$ 254.1539, found 254.1559.

*5.5.7. 3-(2-(7-methyl-1H-indol-3-yl)ethyl)cyclohex-2-en-1-one **(5g)**.* Synthesized according to the general procedure and purified by flash column chromatography (hexanes/ethyl acetate = 80:20 to 70:30) to yield a white solid (72.3 mg, 0.285 mmol, 71%). ^{1}H

NMR (600 MHz, $CDCl_3$): δ 8.07 (br, s, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.07 (dd, *J* = 7.8, 7.2 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.98 (s, 1H), 5.98 (s, 1H), 2.99 (t, *J* = 7.8 Hz, 2H), 2.65 (t, *J* = 7.8 Hz, 2H), 2.49 (s, 3H), 2.38 (dd, *J* = 6.6, 6.6 Hz, 2H), 2.34 (dd, *J* = 6.0, 6.0 Hz, 2H), 2.00 (ddd, *J* = 13.2, 6.6, 6.0 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.2, 166.5, 136.0, 126.8, 126.0, 122.7, 121.1, 120.6, 119.6, 116.4, 115.6, 38.6, 37.5, 30.0, 23.2, 22.8, 16.7. HRMS (ESI) calcd. for $C_{17}H_{20}NO^+$ $[M+H]^+$ 254.1539, found 254.1560.

*5.5.8. 3-(2-(5-cyano-1H-indol-3-yl)ethyl)cyclohex-2-en-1-one (**5h**).* Synthesized according to the general procedure and purified by flash column chromatography (hexanes/ethyl acetate = 60:40 to 50:50) to yield a white solid (42.0 mg, 0.159 mmol, 40%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.41 (br, s, 1H), 7.93 (s, 1H), 7.44-7.41 (m, 2H), 7.11 (d, *J* = 2.4 Hz, 1H), 5.91 (s, 1H), 2.98 (t, *J* = 7.8 Hz, 2H), 2.63 (t, *J* = 7.8 Hz, 2H), 2.37 (dd, *J* = 6.6, 6.6 Hz, 2H), 2.34 (dd, *J* = 6.0, 6.0 Hz, 2H), 2.00 (ddd, *J* = 13.2, 6.6, 6.0 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.0, 165.3, 138.1, 127.2, 126.3, 125.3, 124.5, 123.6, 120.8, 116.2, 112.3, 102.7, 38.3, 37.5, 29.9, 22.8, 22.6. HRMS (ESI) calcd. for $C_{17}H_{17}N_2O^+$ $[M+H]^+$ 265.1335, found 265.1343.

*5.5.9. 3-(2-(7-cyano-1H-indol-3-yl)ethyl)cyclohex-2-en-1-one (**5i**).* Synthesized according to the general procedure and purified by flash column chromatography (hexanes/ethyl acetate = 60:40 to 50:50) to yield a white solid (49.6 mg, 0.188 mmol, 47%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.27 (br, s, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.04 (s, 1H), 7.01 (dd, *J* = 7.8, 7.8 Hz, 1H), 5.96 (s, 1H), 2.96 (t, *J* = 7.8 Hz, 2H), 2.62 (t, *J* = 7.8 Hz, 2H), 2.37 (dd, *J* = 6.6, 6.6 Hz, 2H), 2.31 (dd, *J* = 6.0, 6.0 Hz, 2H), 1.98 (ddd, *J* = 13.2, 6.6, 6.0 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): 200.0, 165.9, 141.2, 135.1, 128.5, 126.1, 124.6, 122.0, 120.6, 118.0, 116.5, 105.0, 38.4, 37.5, 30.0, 23.1, 22.8. HRMS (ESI) calcd. for $C_{17}H_{17}N_2O^+$ $[M+H]^+$ 265.1335, found 265.1355.

*5.5.10. 3-(2-(5-bromo-1H-indol-3-yl)ethyl)cyclohex-2-en-1one (**5j**).* Synthesized according to the general procedure and purified by flash column chromatography (hexanes/ethyl acetate = 80:20 to 70:30) to yield a white solid (72.0 mg, 0.226 mmol, 57%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.24 (br, s, 1H), 7.69 (s, 1H), 7.26 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 6.97 (s, 1H), 5.93 (s, 1H), 2.92 (t, *J* = 7.8 Hz, 2H), 2.60 (t, *J* = 7.8 Hz, 2H), 2.37 (dd, *J* = 6.6, 6.6, Hz, 2H), 2.32 (dd, *J* = 6.0, 6.0 Hz, 2H), 1.99 (ddd, *J* = 13.2, 6.6, 6.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.1, 165.9, 135.0, 129.1, 126.2, 125.1, 122.7, 121.4, 114.9, 112.83, 112.78, 38.4, 37.5, 30.0, 22.84, 22.83. HRMS (ESI) calcd. for $C_{16}H_{17}BrNO^+$ $[M+H]^+$ 318.0488, found 318.0506.

*5.5.11. 3-(2-(7-bromo-1H-indol-3-yl)ethyl)cyclohex-2-en-1-one (**5k**).* Synthesized according to the general procedure and purified by flash column chromatography (hexanes/ethyl acetate = 80:20 to 70:30) to yield a white solid (61.8 mg, 0.194 mmol, 49%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.35 (br, s, 1H), 7.68 (s, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 6.96 (s, 1H), 5.93 (s, 1H), 2.91 (t, *J* = 7.8 Hz, 2H), 2.59 (t, *J* = 7.8 Hz, 2H), 2.37 (dd, *J* = 6.6, 6.6 Hz, 2H), 2.32 (6.0, 6.0 Hz, 2H), 1.98 (ddd, *J* = 12.6, 6.6, 6.0 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.2, 166.2, 135.0, 129.0, 126.1, 124.9, 122.8, 121.3, 114.7, 112.9, 112.6, 38.4, 37.4, 29.9, 22.8, 22.8. HRMS (ESI) calcd. for $C_{16}H_{17}BrNO^+$ $[M+H]^+$ 318.0488, found 318.0505.

*5.5.12. 3-(2-(5-methoxy-1H-indol-3-yl)ethyl)cyclohex-2-en-1-one (**5l**).* Synthesized according to the general procedure and purified by flash column chromatography (hexanes/ethyl acetate = 80:20 to 70:30) to yield a white solid (68.9 mg, 0.256 mmol, 64%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.13 (br, s, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 1.8 Hz, 1H), 6.95 (s, 1H), 6.87 (dd, *J* = 8.4, 1.8 Hz, 1H), 5.98 (s, 1H), 3.87 (s, 3H), 2.94 (t, *J* = 7.8 Hz, 2H), 2.63 (t, *J* = 7.8 Hz, 2H), 2.37 (dd, *J* = 6.6, 6.6 Hz, 2H), 2.33 (dd, *J* = 6.0, 6.0 Hz, 2H), 1.99 (ddd, *J* = 13.2, 6.6, 6.0 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.2, 166.5, 154.0, 131.6, 127.6, 126.0, 122.2, 114.7, 122.2, 112.1, 100.7, 56.1, 38.3, 37.4, 30.0, 23.0, 22.8. HRMS (ESI) calcd. for $C_{17}H_{20}NO_2^+$ $[M+H]^+$ 270.1589, found 270.1490.

*5.5.13. 3-(2-(7-methoxy-1H-indol-3-yl)ethyl)cyclohex-2-en-1-one (**5m**).* Synthesized according to the general procedure and purified by flash column chromatography (hexanes/ethyl acetate = 80:20 to 70:30) to yield a white solid (65.4 mg, 0.243 mmol, 61%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.30 (br, s, 1H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.05 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.95 (s, 1H), 6.66 (d, *J* = 7.8 Hz, 1H), 5.98 (s, 1H), 3.96 (s, 3H), 2.97 (t, *J* = 7.8 Hz, 2H), 2.63 (t, *J* = 7.8 Hz, 2H), 2.37 (dd, *J* = 6.6, 6.6 Hz, 2H), 2.32 (dd, *J* = 6.0, 6.0 Hz, 2H), 1.98 (ddd, *J* = 12.6, 6.6, 6.0 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.1, 166.4, 146.3, 128.6, 126.9, 126.0, 121.0, 119.8, 115.5, 111.4, 102.0, 55.4, 38.6, 37.4, 29.9, 23.2, 22.8. HRMS (ESI) calcd. for $C_{17}H_{20}NO_2^+$ $[M+H]^+$ 270.1589, found 270.1507.

5.5.14. 3-(2-(5-methyl-1H-pyrrol-2-yl)ethyl)cyclohex-2-en-1-one (**5n**). Synthesized according to the general procedure and purified by flash column chromatography (hexanes/ethyl acetate = 80:20 to 70:30) to yield a yellow solid (54.2 mg, 0.266 mmol, 67%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.78 (br, s, 1H), 5.92 (s, 1H), 5.79-5.78 (m, 1H), 5.76-5.75 (m, 1H), 2.77 (t, *J* = 7.8 Hz, 2H), 2.54 (t, *J* = 7.8 Hz, 2H), 2.37 (dd, *J* = 6.6, 6.6 Hz, 2H), 2.30 (dd, *J* = 6.0, 6.0 Hz, 2H), 2.24 (s, 3H), 2.00 (ddd, *J* = 13.2, 6.6, 6.0 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.0, 165.7, 129.4, 126.7, 125.9, 106.0, 105.5, 38.1, 37.5, 30.0, 25.5, 22.8, 13.1. HRMS (ESI) calcd. for $C_{14}H_{21}O_2^+$ $[M+H]^+$ 221.1536, found 221.1539. HRMS (ESI) calcd. for $C_{13}H_{18}NO^+$ $[M+H]^+$ 204.1383, found 204.1394

*5.5.15. 3-(2-(5-methoxythiophen-2-yl)ethyl)cyclohex-2-en-1-one (**5o**).* Synthesized according to the general procedure and purified by flash column chromatography (hexanes/ethyl acetate = 80:20 to 70:30) to yield a yellow oil (46.3 mg, 0.196 mmol, 49%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.37 (d, *J* = 3.6 Hz, 1H), 5.97 (d, *J* = 3.6 Hz, 1H), 5.89 (s, 1H), 3.84 (s, 3H), 2.88 (t, *J* = 7.8 Hz, 2H), 2.52 (t, *J* = 7.8 Hz, 2H), 2.35 (dd, *J* = 6.6, 6.6 Hz, 2H), 2.29 (dd, *J* = 6.0, 6.0 Hz, 2H), 1.99 (ddd, *J* = 13.2, 6.6, 6.0 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.8, 164.6, 164.5, 129.5, 126.4, 121.7, 103.1, 60.3, 39.8, 37.5, 29.9, 28.1, 22.8. HRMS (ESI) calcd. for $C_{13}H_{17}O_2S^+$ $[M+H]^+$ 237.0944, found 237.0957.

*5.5.16. 3-(2-(4,5-dimethylfuran-2-yl)ethyl)cyclohex-2-en-1-one (**5p**).* Synthesized according to the general procedure and purified by flash column chromatography (hexanes/ethyl acetate = 80:20 to 70:30) to yield a colorless oil (41.9 mg, 0.192 mmol, 48%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.88 (s, 1H), 5.76 (s, 1H), 2.74 (t, *J* = 7.8 Hz, 2H), 2.51 (t, *J* = 7.8 Hz, 2H), 2.35 (dd, *J* = 6.6, 6.6 Hz, 2H), 2.28 (dd, *J* = 6.0, 6.0 Hz, 2H), 2.14 (s, 3H), 1.98 (ddd, *J* = 13.2, 6.6, 6.0 Hz, 2H), 1.87 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.9, 165.2, 151.2, 145.9, 126.1, 114.4, 108.8, 37.5, 36.6, 29.8, 25.7, 22.8, 11.4, 10.0. HRMS (ESI) calcd. for $C_{14}H_{19}O_2^+$ $[M+H]^+$ 219.1380, found 219.1388.

5.6. Experimental procedure for competition experiments

5.6.1. A competition experiment for generating heteroarylated products **3d** and **5a** was carried out by the following procedure. To a 1 dram vial was added $Bi(OTf)_3$ (4.1 mg, 0.0063 mmol, 0.025 equiv) indole (29.3 mg, 0.25 mmol), 3-methyl-2-cyclohexenone (55.1 mg, 0.500 mmol), 3-vinyl-2-cyclohexenone (61.3 mg, 0.500 mmol), and acetonitrile/methanol (10:1) solution

(0.5 mL). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction was heated to 60 °C and allowed to stir at this temperature for 3 h. The mixture was cooled and concentrated under reduced pressure. The crude reaction mixture was concentrated under reduced pressure. The crude mixture was dissolved in $CDCl_3$ with CH_2Br_2 as the internal standard. The ratio of products **5a**:**3d** was determined to be 8.4:1 by ^{1}H NMR spectroscopy. The ^{1}H NMR yields of **5a** and **3d** were determined to be 67% and 8%, respectively.

5.6.2. A competition experiment for generating δ-heteroarylated enones **5a** and **5l** was carried out by the following procedure. To a 1 dram vial was added $Bi(OTf)_3$ (16.4 mg, 0.0250 mmol, 0.10 equiv), indole (58.6 mg, 0.50 mmol), 5-methoxyindole (73.6 mg, 0.50 mmol), 3-vinyl-2-cyclohexenone (30.5 mg, 0.25 mmol), and acetonitrile/methanol (10:1) solution (0.5 mL). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction was heated to 60 °C and allowed to stir at this temperature for 3 h. The mixture was cooled and concentrated under reduced pressure. The crude reaction mixture was concentrated under reduced pressure. The crude mixture was dissolved in $CDCl_3$ with CH_2Br_2 as the internal standard. The ratio of products **5l**:**5a** was determined to be 1.9:1 by ^{1}H NMR spectroscopy. The ^{1}H NMR yields of **5l** and **5a** were determined to be 21% and 11%, respectively.

5.6.3. A competition experiment for generating δ-heteroarylated enones **5a** and **5j** was carried out by the following procedure. To a 1 dram vial was added $Bi(OTf)_3$ (16.4 mg, 0.0250 mmol, 0.10 equiv), indole (58.6 mg, 0.50 mmol), 5-bromoindole (98.0 mg, 0.50 mmol), 3-vinyl-2-cyclohexenone (30.5 mg, 0.25 mmol), and acetonitrile/methanol (10:1) solution (0.5 mL). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction was heated to 60 °C and allowed to stir at this temperature for 3 h. The mixture was cooled and concentrated under reduced pressure. The crude reaction mixture was concentrated under reduced pressure. The crude mixture was dissolved in $CDCl_3$ with CH_2Br_2 as the internal standard. The ratio of products **5a**:**5j** was determined to be 3.7:1 by ^{1}H NMR spectroscopy. The ^{1}H NMR yields of **5a** and **5j** were determined to be 11% and 3%, respectively.

5.6.4. A competition experiment for generating δ-heteroarylated enones **5j** and **5l** was carried out by the following procedure. To a 1 dram vial was added $Bi(OTf)_3$ (16.4 mg, 0.0250 mmol, 0.10 equiv), 5-bromoindole (98.0 mg, 0.50 mmol), 5-methoxyindole (73.6 mg, 0.50 mmol), 3-vinyl-2-cyclohexenone (30.5 mg, 0.25 mmol), and acetonitrile/methanol (10:1) solution (0.5 mL). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction was heated to 60 °C and allowed to stir at this temperature for 3 h. The mixture was cooled and concentrated under reduced pressure. The crude reaction mixture was concentrated under reduced pressure. The crude mixture was dissolved in $CDCl_3$ with CH_2Br_2 as the internal standard. The ratio of products **5l**:**5j** was determined to be 10.3:1 by ^{1}H NMR spectroscopy. The ^{1}H NMR yields of **5l** and **5j** were determined to be 41% and 4%, respectively.

5.7. Procedure for the palladium-catalyzed 1,4-addition of 4-biphenylboronic acid to 3-(2-(1*H*-indol-3-yl)ethyl)cyclohex-2-en-1-one 5a

*5.7.1. 3-(2-(1H-indol-3-yl)ethyl)-3-phenylcyclohexan-1-one (**6**).* Prepared according to a modified literature procedure.[10d] To a 1 dram vial was added $Pd(OCOCF_3)_2$ (3.3 mg, 0.0100 mmol), 2,2′-bipyridine (1.9 mg, 0.0120 mmol), 4-$PhC_6H_4B(OH)_2$ (59.7 mg, 0.30 mmol), enone **5a** (23.9 mg, 0.10 mmol, 1.0 equiv) and were dissolved in dichloroethane (0.2 mL). The vial was sealed with a PFTE/silicone-lined septum cap. The reaction was heated to 60 °C and allowed to stir at this temperature for 10 h. The mixture was cooled to room temperature, and passed through a short plug of silica gel (eluting with 20 mL of ethyl acetate). The crude reaction mixture was purified by flash column chromatography on silica gel (hexanes/ethyl acetate = 80:20 to 70:30) to yield a white solid (19.8 mg, 0.0507 mmol, 51%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.88 (br, s, 1H), 7.63-7.61 (m, 4H), 7.47-7.44 (m, 4H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.35 (m, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.16 (ddd, *J* = 7.8, 7.2, 1.2 Hz, 1H), 7.07 (ddd, *J* = 7.8, 7.2, 1.2 Hz, 1H), 6.88 (s, 1H), 3.12 (d, *J* = 14.4 Hz, 1H), 2.62 (d, *J* = 14.4 Hz, 1H), 2.57 (ddd, *J* = 13.2, 13.2, 4.8 Hz, 1H), 2.40-2.35 (m, 3H), 2.31-2.28 (m, 1H), 2.18 (ddd, *J* = 13.2, 13.2, 4.4 Hz, 1H), 2.13-2.04 (m, 2H), 1.93-1.88 (m, 1H), 1.73-1.66 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 211.5, 144.1, 140.8, 139.2, 136.4, 128.9, 127.4, 127.3, 127.13, 127.11, 127.10, 122.1, 121.0, 120.9, 118.8, 116.5, 111.2, 51.1, 46.3, 44.0, 41.2, 36.9, 21.7, 19.5. HRMS (ESI) calcd. for $C_{28}H_{28}NO^+$ $[M+H]^+$ 394.2165, found 394.2169.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at DOI:

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