JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

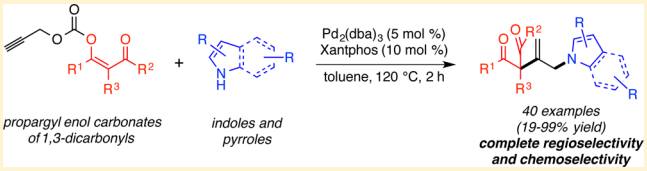
Catalytic Chemo- and Regioselective Coupling of 1,3-Dicarbonyls with *N*-Heterocyclic Nucleophiles

Miles Kenny, Daniel J. Kitson, and Vilius Franckevičius*

Department of Chemistry, Lancaster University, Lancaster LA1 4YB, United Kingdom

Supporting Information

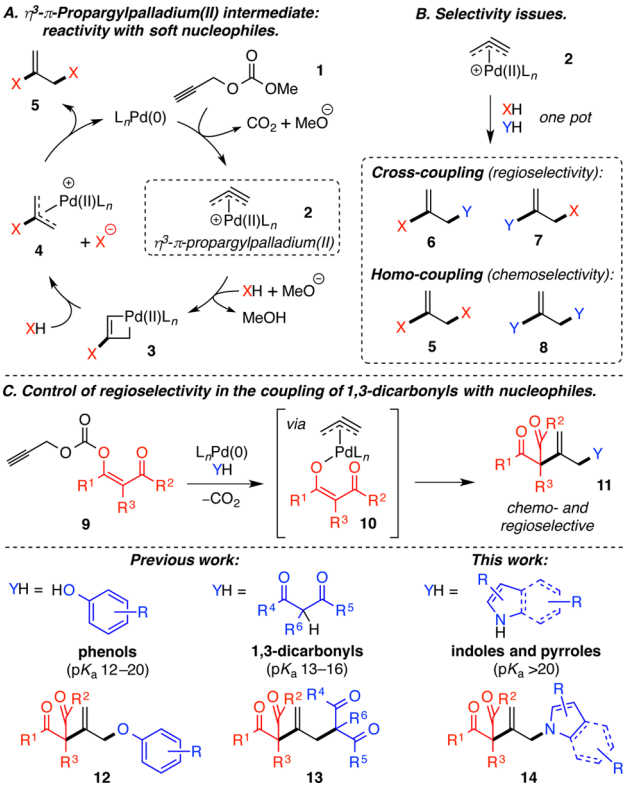
ABSTRACT: The development of a decarboxylative palladium-catalyzed coupling of 1,3-dicarbonyl compounds with indole, pyrrole, imidazole, and pyrazole nucleophiles via an allylic linker under neutral conditions is disclosed. This process enables the installation of an all-carbon quaternary center and new C−C and C−N bonds in a single operation. Despite the weakly acidic nature of *N*-heterocycles, the reactions proceed with good efficiency and complete regio- and chemoselectivity.



INTRODUCTION

Since the seminal report of the palladium-catalyzed allylic alkylation reaction of nucleophiles with allylic electrophiles,[1] this process has undergone revolutionary expansion to a range of new asymmetric C−C and C−heteroatom bond-formation methodologies.[2] The analogous propargylic electrophiles can also be used, but the transformation to products involving nucleophiles and palladium(0) is distinct and more complex.[3] Typically, this process commences with the formation of η^3-π-propargylpalladium(II) intermediate **2** through oxidative addition of palladium(0) to **1** (A, Scheme 1).[4] At this point, hard nucleophiles, such as organometallic reagents, tend to undergo either propargylation or allenylation.[5] However, if the nucleophile HX is relatively acidic and can therefore give rise to a stabilized anion, with enolates of 1,3-dicarbonyl compounds and phenolate anions being examples, then addition of the nucleophile to the *central* carbon atom of the η^3-π-propargylpalladium(II) motif **2** takes place.[6] The resulting putative palladacyclobutene intermediate **3**[7] is then protonated by a second equivalent of the nucleophile HX, generating η^3-π-allylpalladium(II) complex **4**. In the final stage, an allylic alkylation process affords product **5**.[8] The overall transformation is the union of two molecules of the nucleophile via an allylic linker in **5** in a single operation. The utility of this reaction can be greatly enhanced by being able to couple two different nucleophiles selectively (B, Scheme 1). However, for this to be a viable process, the following conditions must be met: the order of addition of the two nucleophiles must be controlled, resulting in the correct regioselectivity of cross-coupling (**6** versus **7**), and the undesired homocoupling of both nucleophiles must be prevented (**5** and **8**). To date, attempts to meet these criteria in the coupling of two different nucleophiles in an intermolecular sense have proven difficult.[9] Instead, control of regio- and chemoselectivity is imparted by tethering at least two of the reacting components in a cyclization process, thus favoring the intramolecular reaction pathway over all others.[10]

Scheme 1. Reactivity of η^3-π-Propargylpalladium(II) Intermediates with Nucleophiles

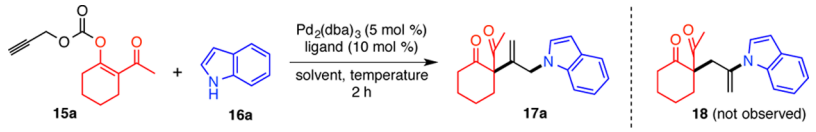


Seeking to control the selectivity of the intermolecular coupling of two nucleophiles, we became inspired by recent developments in the palladium-catalyzed decarboxylative allylic alkylation reaction for the synthesis of congested all-carbon

Received: April 5, 2016
Published: May 22, 2016

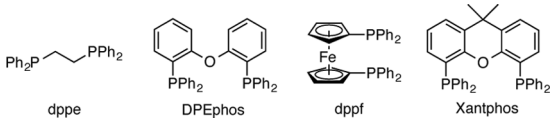
DOI: 10.1021/acs.joc.6b00731
J. Org. Chem. 2016, 81, 5162−5172

Table 1. Optimization of the Reaction Conditions[a]



entry	ligand[f]	solvent	T (°C)	regioselectivity (**17a**:**18**)[b,c]	**17a**:**16a**[b]	yield[d] (%)
1	dppe	1,4-dioxane	80		no reaction	
2	PPh_3[e]	1,4-dioxane	80	>19:1	1:4.7	13
3	DPEphos	1,4-dioxane	80	>19:1	1:2.3	27
4	dppf	1,4-dioxane	80	>19:1	1:2.1	28
5	**Xantphos**	**1,4-dioxane**	**80**	**>19:1**	**1:2.0**	**32**
6	Xantphos	DMF	80		complex mixture	n.d.
7	Xantphos	MeCN	80	>19:1	1:3.5	11
8	Xantphos	THF	80	>19:1	1:1.8	24
9	Xantphos	CH_2Cl_2	80	>19:1	1:1.9	35
10	Xantphos	toluene	80	>19:1	1:0.8	37
11	**Xantphos**	**toluene**	**120**	**>19:1**	**1:0.7**	**55**
12	Xantphos	xylene	150	>19:1	1:0.8	32

[a]All reactions were performed with 0.24 mmol of **15a** and **16a**; concn = 0.16 M. [b]Determined by ^{1}H NMR analysis of the crude product mixtures. [c]In all cases, no homocoupling of **15a** or **16a** (chemoselectivity) was observed. [d]Yield of isolated **17a**. [e]$[Pd(PPh_3)_4]$ was used in place of $[Pd_2(dba)_3]$. n.d. = not determined. [f]Ligands:



quaternary centers.[11] This approach regiospecifically generates a latent enolate from allylic enol carbonates or esters that can be associated with the palladium metal complex after decarboxylation.[12] We postulated that, if the analogous propargyl enol carbonate of type **9** were to undergo similar decarboxylation under palladium catalysis (C, Scheme 1), and if the resulting enolate remained associated with the π-propargylpalladium(II) motif following decarboxylation (**10**), then the addition of the enolate to the central carbon atom of the π-propargyl unit in **10** should take place faster than that of the external nucleophile owing to the intramolecular nature of the reaction. In this way, both regio- and chemoselectivity could be controlled in the formation of product **11**. Indeed, we have found this to be the case in the coupling of 1,3-dicarbonyls with phenols to generate structures of type **12**.[13] Subsequently, we reported the coupling of two different 1,3-dicarbonyl compounds (**13**),[14] the regioselectivity of which can be controlled by judiciously adding one of the nucleophiles as the propargyl enol carbonate.

Because the accepted reaction mechanism involves protonation of palladacyclobutene intermediate **3**, the acidity of the external nucleophile is expected to be important; phenols (pK_a 12−20 in DMSO)[15] and 1,3-dicarbonyl compounds (pK_a 13−16 in DMSO)[16] are relatively acidic and, hence, are readily incorporated without the need for acid or base additives. However, the use of less acidic *N*-heterocyclic nucleophiles, such as pyrroles and indoles (pK_a 23 and 21 in DMSO, respectively),[17] in this coupling reaction is more challenging. In this report, we disclose the development of a regio- and chemoselective palladium-catalyzed decarboxylative coupling reaction of 1,3-dicarbonyl compounds with weakly acidic *N*-heterocyclic nucleophiles under neutral conditions. This one-pot process installs new C−C and C−N bonds and an all-carbon quaternary center in a single step and proceeds with full regiocontrol and chemoselectivity.

RESULTS AND DISCUSSION

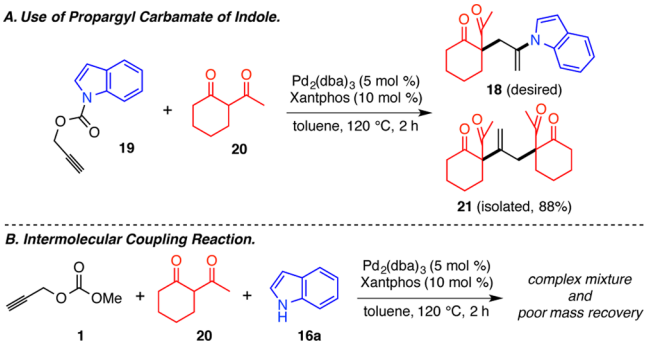
In the first instance, we tested the reactivity of propargylic carbonate **15a** derived from a 1,3-diketone and indole (**16a**) in the presence of a source of palladium(0) and a phosphine ligand in 1,4-dioxane as the solvent at 80 °C (Table 1). With the exception of dppe (entry 1), palladium tetrakis(triphenylphosphine) (entry 2) as well as large-bite-angle bidentate ligands, that is, DPEphos, dppf, and Xantphos (entries 3−5) all afforded desired coupled product **17a**. The reaction with Xantphos as the ligand afforded the highest yield of **17a** (entry 5), but the reaction efficiency was relatively low with significant quantities of unreacted indole (**16a**) being observed in the crude product mixtures. This result was perhaps not surprising given the lower acidity of indole (**16a**) as compared to phenols and 1,3-dicarbonyls. Remarkably, however, no formation of regioisomer **18** nor homocoupled products of **15a** or **16a** was observed. With Xantphos as the chosen ligand, a solvent screen (entries 6−10) led to a small increase in the yield of **17a** when the reaction was run in toluene (entry 10). Pleasingly, the yield of **17a** was improved to 55% by elevating the reaction temperature to 120 °C (entry 11), conditions where smaller quantities of unreacted indole (**16a**) were detected. The reaction at a higher temperature of 150 °C in xylene as the solvent did not result in an improvement of the yield of **17a** (entry 12). It should be noted that only *N*-alkylation of indole (**16a**) took place with no *C*-alkylated products being observed. This result is in contrast to the previously reported *C*-allylation of indoles.[18] Similarly, reactions of indoles with propargylic compounds also follow the *C*-alkylation pathway,[19] albeit most likely due to the intramolecular arrangement of the reacting centers.

Having established that the use of enol carbonate **15a** in the presence of indole (**16a**) affords the predicted regioisomer **17a** with complete selectivity, we sought to investigate whether the opposite regioisomer **18** could be accessed by utilizing a

DOI: 10.1021/acs.joc.6b00731
J. Org. Chem. 2016, 81, 5162−5172

propargyl carbamate of indole (**19**) (A, Scheme 2). Surprisingly, the only process that took place was the

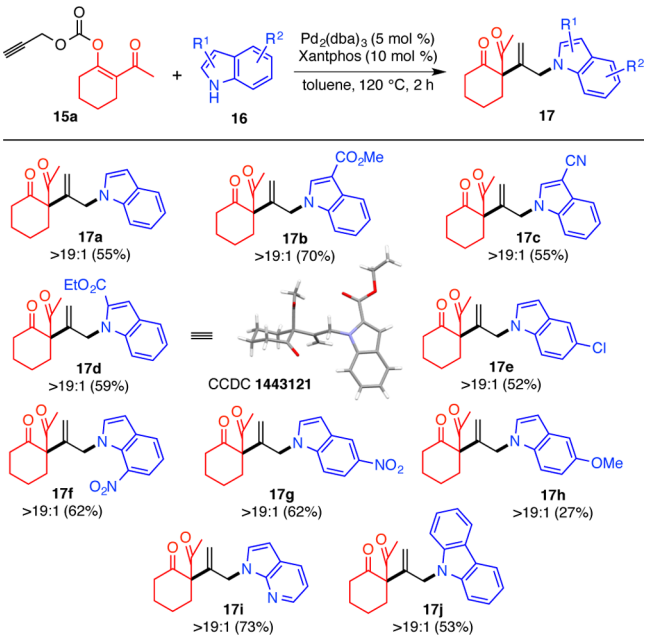
Scheme 2. Control of Regio- and Chemoselectivity



homocoupling of 1,3-diketone **20** to **21**. It is likely that the anion of indole, formed by decarboxylation of **19**, is basic enough to generate a nucleophilic enolate of 1,3-diketone **20**, which then reacts preferentially. A purely intermolecular coupling reaction between carbonate **1**, 1,3-diketone **20**, and indole (**16a**) led to poor mass recovery of a complex mixture of products (B, Scheme 2). These results highlight the requirement for a propargyl enol carbonate as the coupling partner if high levels of selectivity are to be obtained.

In the next stage of this study, a range of indoles were screened under the optimized reaction conditions (Table 2). All substrates were found to react with *complete* chemo- and regioselectivity. In addition to unsubstituted indole product **17a**, the presence of electron-withdrawing substituents at the 3-position afforded **17b** in a higher yield, presumably due to the higher acidity of the indole NH proton. However, the yield of **17c**, containing a 3-nitrile substituent, was similar to that of

Table 2. Indole Scope[a]

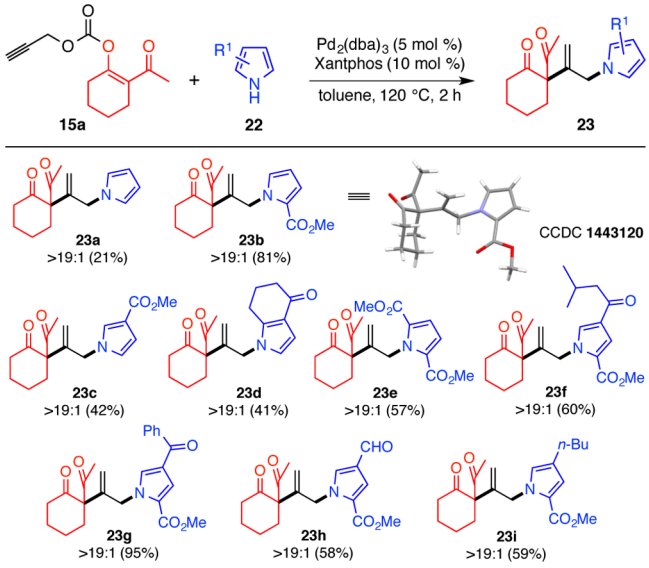


[a]All reactions were performed with 0.24 mmol of **15a** and **16**; concn = 0.16 M. Regioselectivity was determined by ^{1}H NMR analysis of the crude product mixtures. In all cases, no homocoupling of **15a** or **16** (chemoselectivity) was observed. Yields of isolated **17** are shown.

unsubstituted **17a** (55%). An electron-withdrawing ester side-chain in the 2-position gave **17d**, the structure of which was confirmed by X-ray crystallography,[20] thus unequivocally proving the regioselectivity of the reaction. The presence of electron-withdrawing substitution on the benzene ring also gave rise to products **17e–g** in moderate to good yields. These results were in contrast to substitution with an electron-donating methoxy group, whereby a lower yield of product **17h** was obtained and larger quantities of unreacted indole **16h** were observed in the crude product mixture. It is likely that the decreased acidity of indole **16h** is responsible for its reduced reactivity. Finally, analogues of indole, namely, 7-azaindole (**16i**) and carbazole (**16j**), gave rise to products **17i** and **17j** in 73 and 53% yield, respectively.

To the best of our knowledge, there are no reports of palladium-catalyzed reactions of pyrroles with propargylic compounds. Therefore, encouraged by the desired reactivity of indoles in the reaction, the coupling of pyrroles **22** as *N*-heterocyclic nucleophiles with a 1,3-diketone was explored (Table 3). To our surprise, the reaction with unsubstituted

Table 3. Pyrrole Scope[a]



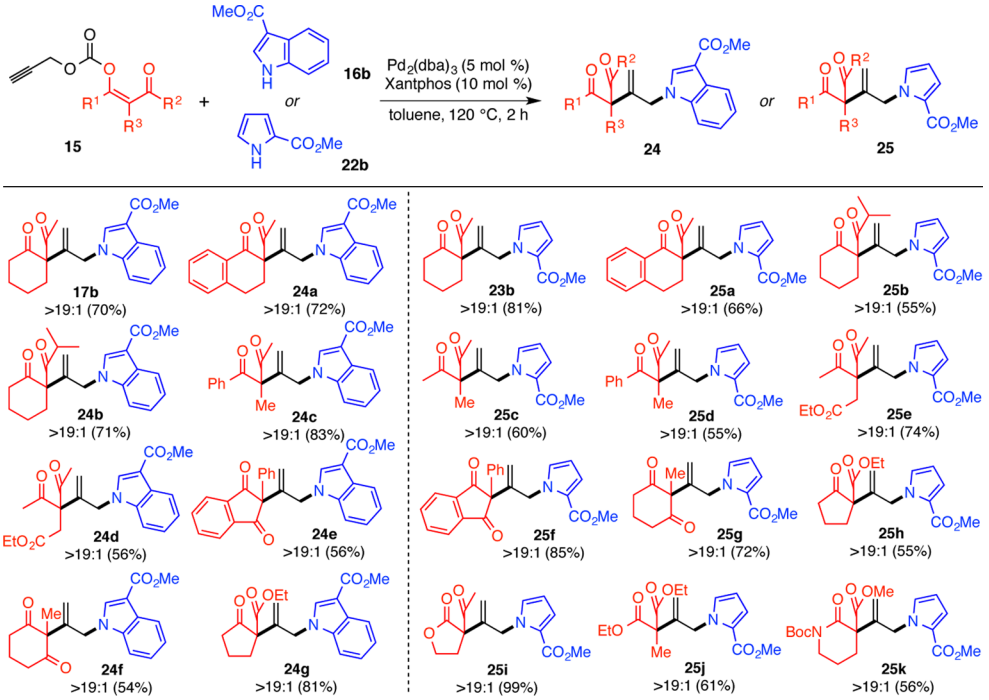
[a]All reactions were performed with 0.24 mmol of **15a** and **22**; concn = 0.16 M. Regioselectivity was determined by ^{1}H NMR analysis of the crude product mixtures. In all cases, no homocoupling of **15a** or **22** (chemoselectivity) was observed. Yields of isolated **23** are shown.

pyrrole (**22a**) was found to be less efficient than that with indole (**16a**), and significant quantities of unreacted pyrrole (**22a**) were present in the crude product mixture. Despite this, **23a** was formed with complete regio- and chemoselectivity, and no *C*-alkylation took place. The introduction of an electron-withdrawing group in the 2-position of pyrrole **22b** significantly enhanced its reactivity, and **23b** was isolated in excellent yield. The sense of the regioselectivity of the reaction was confirmed by the X-ray crystal structure of **23b**.[20] The introduction of electron-withdrawing substituents in the 3-position paved the way to **23c** and **23d** in moderate yields. Further decoration of the pyrrole motif with two carbonyl side chains afforded products **23e–h** in good to excellent yields. A mix of electron-donating and -withdrawing substituents was also effective (**23i**).

Having demonstrated the desired reactivity of a set of indole and pyrrole substrates in the reaction, attention was focused on

DOI: 10.1021/acs.joc.6b00731
J. Org. Chem. 2016, 81, 5162–5172

Table 4. 1,3-Dicarbonyl Scope[a]



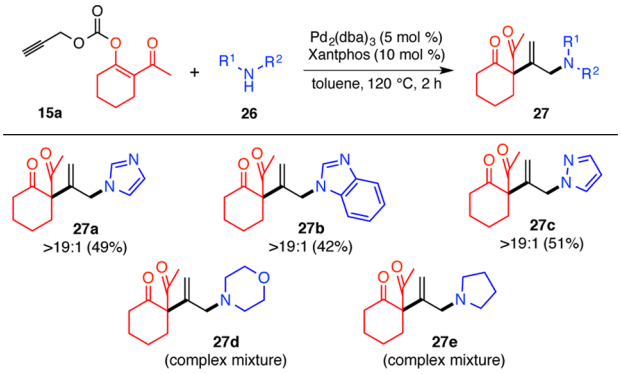
[a]All reactions were performed with 0.24 mmol of **15** and **16b** or **22b**; concn = 0.16 M. Regioselectivity was determined by ^{1}H NMR analysis of the crude product mixtures. In all cases, no homocoupling of **15**, **16b**, or **22b** (chemoselectivity) was observed. Yields of isolated **24** and **25** are shown.

other 1,3-dicarbonyl compounds and the efficiency and selectivity with which they can be coupled with *N*-heterocycles (Table 4). In the case of indole **16b** as the coupling partner, cyclohexanone-based systems provided products **24a** and **24b** in good yields and complete selectivity. Similarly, the use of propargyl enol carbonates derived from linear and cyclic 1,3-diketones readily generated products **24c−f**. We were pleased to discover that a ß-ketoester also underwent the desired coupling to give **24g** in 81% yield. In the coupling reaction of pyrrole **22b** with a set of propargyl enol carbonates **15**, cyclohexanone-based and linear 1,3-diketones provided compounds **25a−e** in moderate to good yields. Similarly, products **25f** and **25g**, containing cyclic 1,3-diketones, were isolated in high yields. ß-Ketoesters were also readily incorporated with **25h** and **25i** being isolated in 55 and 99% yields, respectively, with complete selectivity. Finally, it was encouraging to discover that malonates and ß-amidoesters were successfully transformed into desired products **25j** and **25k** in 61 and 56% yields, respectively.

In addition to indoles and pyrroles, we found that the analogous aromatic *N*-heterocyles containing two nitrogen atoms, such as imidazole (**26a**), benzimidazole (**26b**), and pyrazole (**26c**), all afforded coupled products **27a−c**, respectively, in moderate yields with complete chemo- and regioselectivity. Unfortunately, saturated cyclic amines morpholine (**26d**) and pyrrolidine (**26e**), which are significantly less acidic than their aromatic counterparts, failed to invoke the desired reactivity (**27d** and **27e**), and only complex mixtures of product were obtained.

For a better understanding of the mechanism of the reaction and the origin of regioselectivity to be obtained, an enolate crossover experiment was conducted (A, Scheme 3). Two structurally similar propargyl enol carbonates [D]-**15a** and **15b** were reacted with pyrrole **22b**, and the products were isolated.

Table 5. *N*-Heterocycle Scope[a]

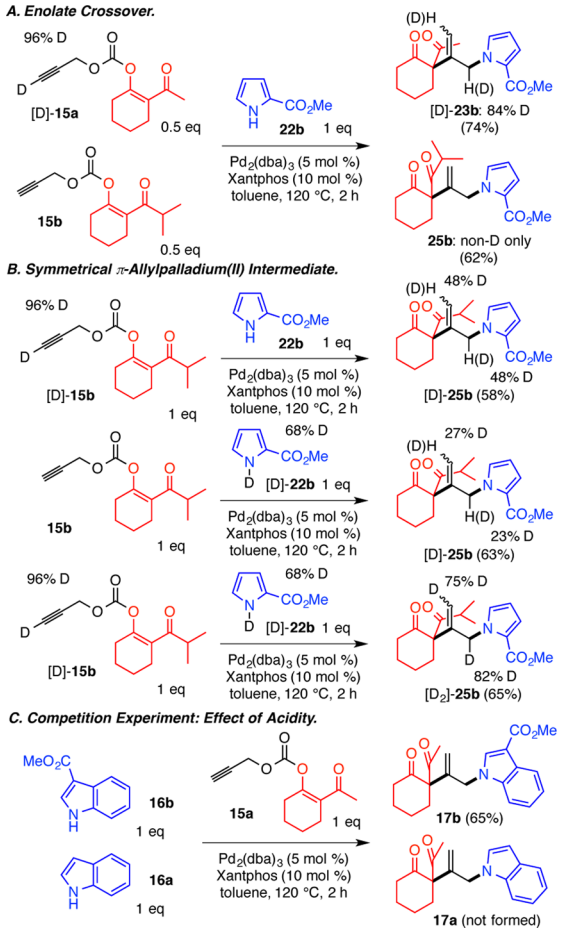


[a]All reactions were performed with 0.24 mmol of **15a** and **26**; concn = 0.16 M. Regioselectivity was determined by ^{1}H NMR analysis of the crude product mixtures. In all cases, no homocoupling of **15a** or **26** (chemoselectivity) was observed. Yields of isolated **27** are shown.

^{1}H NMR spectroscopy indicated 84% deuterium incorporation in [D]-**23b** and no deuteration of **25b**. This observation illustrates that there is no enolate crossover in the reaction, suggesting that the η^3-π-propargylpalladium(II) complex is tightly bound to the enolate following the decarboxylation step. The reaction of [D]-**15b** with pyrrole **22b** resulted in the scrambling of the deuterium label between the vinylic and allylic positions in [D]-**25b** (B, Scheme 3). Deuterium scrambling across the allyl group also took place when nondeuterated carbonate **15b** was coupled with deuterated pyrrole [D]-**22b**. These results were further confirmed by the incorporation of two deuterium labels in near-equal amounts at the vinylic and allylic positions in [D_2]-**25b** when [D]-**15b** was coupled with [D]-**22b**. It is, therefore, feasible to conclude that a deprotonation step of the nitrogen nucleophile and a

DOI: 10.1021/acs.joc.6b00731
J. Org. Chem. 2016, 81, 5162−5172

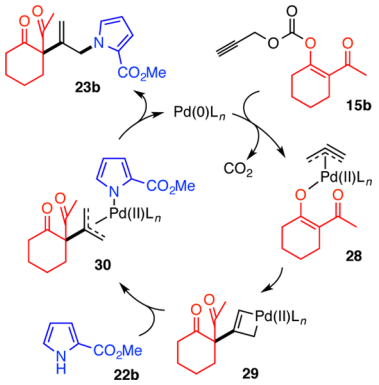
Scheme 3. Mechanistic Study



symmetrical π-allylpalladium(II) intermediate are implicated in the mechanism. Finally, a competition experiment between indole **16b**, containing an ester side-chain in the 3-position, and an unsubstituted indole (**16a**) was performed (C, Scheme 3). Although each of these substrates takes part in individual reactions with carbonate **15a**, the reaction of the mixture of the two resulted solely in the formation of product **17b**, not **17a**. Given that substituted **16b** is more acidic than **16a**, it can be postulated that the rate of deprotonation of **16b** and, therefore, the rate of nucleophilic addition, is faster than that of **16a**. This conclusion is corroborated by the fact that reactions with more acidic indoles and pyrroles generally give rise to higher yields of product.

In light of the above results and the observation that complete regio- and chemoselectivity was observed in the coupling reactions, a feasible mechanism commences with oxidative addition of palladium(0) to propargyl enol carbonate **15b** and decarboxylation (Scheme 4). The resulting η^3-π-propargylpalladium(II) motif is likely to be tightly associated with the intermediate enolate in **28**, preventing enolate crossover from taking place. It is, therefore, likely that an inner-sphere addition mechanism of the enolate to the central carbon atom of the η^3-π-propargylpalladium(II) unit operates, ensuring complete regioselectivity of the reaction. The resulting transient palladacyclobutene intermediate **29**[21] is then protonated by *N*-heterocycle **22b**. The ensuing symmetrical η^3-π-allylpalladium(II) complex **30** finally undergoes *N*-alkylation and affords product **23b** with the concomitant regeneration of the palladium(0) catalyst.

Scheme 4. Proposed Reaction Mechanism



In conclusion, we have developed a decarboxylative palladium-catalyzed coupling reaction of 1,3-dicarbonyl compounds with only weakly acidic *N*-heterocycles under neutral conditions, which generates new C−C and C−N bonds and an all-carbon quaternary center in a single step. The broad scope of this transformation has been demonstrated through the successful coupling of a variety of 1,3-dicarbonyl compounds with a range of indole, pyrrole, imidazole, and pyrazole substrates. In all cases, the reactions proceed with complete chemo- and regioselectivity, which is efficiently controlled by judiciously utilizing a propagyl enol carbonate as one of the coupling partners. Mechanistic studies indicate that the association of the palladium metal with the enolate following decarboxylation is likely to be responsible for the high levels of regiocontrol. Access to enantioenriched products forms the focus of our current work in the area.

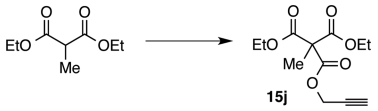
EXPERIMENTAL SECTION

1. General Information. All commercially available starting materials were used as received without further purification. Solvents were of reagent grade and dried prior to use. Petrol refers to the fraction of petroleum ether that boils between 40 and 60 °C. All reactions were performed under an argon atmosphere in oven dry glassware. Reactions were monitored by thin layer chromatography using precoated silica gel plates with a fluorescent indicator (254 nm) and visualized by UV light (254 nm) or by staining with potassium permanganate or aqueous acidic ammonium molybdate(IV) solutions. Flash column chromatography was carried out using Fisher silica gel (60 Å particle size, 230−400 mesh). NMR spectra were recorded on either 400 or 300 MHz instruments (^{1}H NMR at 400 and 300 MHz, respectively, and ^{13}C{^{1}H} NMR at 100 and 75 MHz, respectively) in $CDCl_3$. Residual solvent $CHCl_3$ was referenced at 7.26 ppm for ^{1}H NMR spectra, and the central resonance of $CDCl_3$ was referenced to 77.0 ppm for ^{13}C{^{1}H} NMR spectra. IR spectra were recorded on an FTIR spectrometer as a neat film. High resolution mass spectrometry data were recorded using electron spray ionization on an LCMS-IT-TOF mass spectrometer. Melting points were uncorrected. Structures of **17d** and **23b** were solved by single crystal X-ray diffraction.

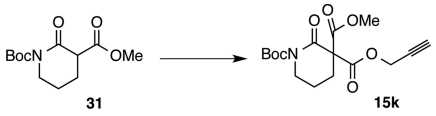
The syntheses of all propargyl enol carbonates **15**, including [D]-**15a**, as well as methyl propargyl carbonate **1**, are reported in the literature,[13,14] with the exception of propargyl esters **15j** and **15k**, the procedures for which are reported below. Indole propargyl carbamate **19** was prepared by a procedure different to that used in the literature.[22] The following pyrroles were synthesized via precedented methods: **22c**,[23] **22e**,[24] **22f**,[25] **22g**,[25] **22h**,[26] and **22i**.[25] All other *N*-heterocycles were obtained from commercial sources.

2. Synthesis of Propargyl Esters and Carbamates. *1,1-Diethyl 1-Prop-2-ynyl Ethane-1,1,1-tricarboxylate (**15j**).* To a solution of diethyl methyl malonate (425 μL, 2.5 mmol) in THF (20 mL) was added potassium *tert*-butoxide (313 mg, 3.13 mmol), and the mixture

DOI: 10.1021/acs.joc.6b00731
J. Org. Chem. 2016, 81, 5162−5172



was stirred at room temperature for 10 min. Propargyl chloroformate (270 μL, 3.12 mmol) was added dropwise, and the solution was stirred at room temperature for 90 min. The reaction was quenched with aq. HCl (1 N, 20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash column chromatography [petrol:EtOAc 9:1] afforded **15j** (300 mg, 47%) as a colorless oil. R_f = 0.66 [petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 3280, 2963, 1731; δ_H (400 MHz, $CDCl_3$) 4.73 (d, J = 2.5 Hz, 2H), 4.22 (q, J = 7.1 Hz, 4H), 2.47 (t, J = 2.5 Hz, 1H), 1.69 (s, 3H), 1.24 (t, J = 7.2 Hz, 6H); δ_C (100 MHz, $CDCl_3$) 167.2, 166.9, 76.5, 75.4, 62.3, 61.7, 53.3, 18.6, 13.7; HRMS (ESI) m/z calcd for $C_{12}H_{16}O_6$ [M + Na]$^+$ 297.0839, found 279.0818.



*1-tert-Butyl 3-Methyl 3-Prop-2-ynyl 2-oxopiperidine-1,3,3-tricarboxylate (**15k**).* A suspension of sodium hydride (60 wt %, 48.5 mg, 1.2 mmol) in THF (10 mL) was cooled to 0 °C. A solution of **31** (300 mg, 1.1 mmol), prepared via a literature procedure,[27] in THF (5 mL) was added dropwise, and the mixture was stirred at 0 °C for 10 min. Propargyl chloroformate (117 μL, 1.2 mmol) was added dropwise, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with aq. HCl (1 N, 20 mL) and extracted with EtOAc (3 × 25 mL). The combined organic fractions were washed with brine (25 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash column chromatography [petrol:EtOAc 9:1] afforded **15k** (211 mg, 57%) as a yellow oil. R_f = 0.17 [petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 3270, 2980, 1716; δ_H (400 MHz, $CDCl_3$) 4.80 (dd, J = 5.7, 2.5 Hz, 2H), 3.83 (s, 3H), 3.65 (t, J = 6.4 Hz, 2H), 2.56−2.51 (m, 2H), 2.48 (t, J = 2.3 Hz, 1H), 1.90−1.80 (m, 2H), 1.52 (s, 9H); δ_C (100 MHz, $CDCl_3$) 167.4, 166.6, 165.1, 152.6, 83.7, 76.5, 75.6, 65.6, 53.7, 53.5, 45.3, 28.1, 27.9, 19.4; HRMS (ESI) m/z calcd for $C_{16}H_{21}NO_7$ [M + Na]$^+$ 362.1210, found 362.1216.

*Prop-2-ynyl 1H-Indole-1-carboxylate (**19**).* A suspension of sodium hydride (60 wt %, 110 mg, 2.75 mmol) in THF (15 mL) was cooled to 0 °C. A solution of indole (296 mg, 2.5 mmol) in THF (5 mL) was added dropwise, and the mixture was stirred at 0 °C for 10 min. Propargyl chloroformate (268 μL, 2.75 mmol) was added dropwise, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with aq. HCl (1 N, 20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash column chromatography [petrol:EtOAc 9:1] afforded **19** (130 mg, 26%) as a red/brown solid. R_f = 0.35 [petrol:EtOAc 4:1]; mp 48−51 °C; ν_{max} (film)/cm^{-1} 3281, 2137, 1712, 1604; δ_H (300 MHz, $CDCl_3$) 8.21 (d, J = 7.9 Hz, 1H), 7.62 (d, J = 3.8 Hz, 1H), 7.57−7.55 (m, 1H), 7.39−7.32 (m, 1H), 7.30−7.22 (m, 1H), 6.62 (dd, J = 3.8, 0.7 Hz, 1H), 5.02 (d, J = 2.5 Hz, 2H), 2.59 (t, J = 2.5 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 150.2, 135.3, 130.5, 125.4, 124.7, 123.3, 121.1, 115.2, 108.7, 76.9, 76.0, 54.3. Data matches literature values.[22]

3. Palladium-Catalyzed Coupling of 1,3-Dicarbonyls with *N*-Heterocycles. *General Procedure.* Carbonate **15** (0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol), and indole **16**, pyrrole **22**, or *N*-heterocycle **26** (0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added, and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 h, then allowed to cool to room temperature and concentrated in vacuo. Purification by flash column chromatography afforded coupled products **17** (Table 2), **23** (Table 3), **24** (Table 4), **25** (Table 4), and **27** (Table 5).

*2,2′-(Prop-2-ene-1,2-diyl)bis(2-acetylcyclohexan-1-one) (**21**).* Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded homocoupled **21** (34 mg, 88%) as a 1.2:1 mixture of diastereoisomers rather than the desired cross-coupled product **18**. R_f = 0.32 [petrol:EtOAc 4:1]; mp 123−126 °C; ν_{max} (film)/cm^{-1} 2931, 2848, 1697; δ_H (400 MHz, $CDCl_3$) 5.03−4.99 (m, 1H), 4.93−4.89 (m, 1H), 2.57−2.48 (m, 3H), 2.44−2.36 (m, 3H), 2.32−2.24 (m, 1H), 2.23 (s), 2.20 (s) and 2.19 (s) (6H), 2.15−2.07 (m, 1H), 2.01−1.84 (m, 2H), 1.83−1.57 (m, 8H); δ_C (75 MHz, $CDCl_3$) 210.0, 209.9, 209.8, 209.6, 209.1, 209.1, 208.3, 207.9, 140.6, 140.3, 117.3, 117.0, 73.9, 73.8, 67.0, 66.9, 41.3, 41.1, 41.0, 41.0, 37.1, 36.6, 36.2, 35.3, 33.3, 33.1, 27.5, 27.4, 27.2, 27.1, 26.7, 26.6, 26.5, 26.3, 21.9, 21.8, 21.8, 21.7; HRMS (ESI) m/z calcd for $C_{19}H_{26}O_4$ [M + H]$^+$ 319.1904, found 319.1906.

*2-(3-(1H-Indol-1-yl)prop-1-en-2-yl)-2-acetylcyclohexanone (**17a**).* Flash column chromatography [petrol:EtOAc 19:1−9:1] afforded **17a** (27 mg, 55%) as a yellow solid. R_f = 0.52 [petrol:EtOAc 4:1]; mp 94−96 °C; ν_{max} (film)/cm^{-1} 3386, 3089, 3056, 2946, 2858, 1709, 1694, 1652, 1610, 1511; δ_H (400 MHz, $CDCl_3$) 7.63 (dt, J = 8.1, 1.1 Hz, 1H), 7.36 (dq, J = 8.1, 0.8 Hz, 1H), 7.23−7.17 (m, 1H), 7.13−7.07 (m, 1H), 7.06 (d, J = 3.2 Hz, 1H), 6.54 (dd, J = 3.1, 0.9 Hz, 1H), 4.99−4.98 (m, 1H), 4.85−4.79 (m, 1H), 4.63−4.57 (m, 2H), 2.55 (dd, J = 8.0, 5.9 Hz, 2H), 2.48−2.41 (m, 1H), 2.22 (s, 3H), 2.12−2.02 (m, 1H), 2.01−1.91 (m, 1H), 1.90−1.75 (m, 2H), 1.73−1.65 (m, 1H); δ_C (100 MHz, $CDCl_3$) 208.8, 206.8, 142.3, 136.3, 128.6, 128.3, 121.8, 120.8, 119.5, 115.8, 109.7, 101.8, 72.2, 48.3, 41.1, 33.3, 27.0, 26.3, 22.0; HRMS (ESI) m/z calcd for $C_{19}H_{21}NO_2$ [M + H]$^+$ 296.1645, found 296.1650.

*Methyl 1-(2-(1-Acetyl-2-oxocyclohexyl)allyl)-1H-indole-3-carboxylate (**17b**).* Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded **17b** (59 mg, 70%) as a pale yellow solid. R_f = 0.20 [petrol:EtOAc 4:1]; mp 108−110 °C; ν_{max} (film)/cm^{-1} 2950, 1692, 1528; δ_H (400 MHz, $CDCl_3$) 8.20−8.15 (m, 1H), 7.78 (s, 1H), 7.46−7.41 (m, 1H), 7.32−7.24 (m, 2H), 5.02 (q, J = 0.6 Hz, 1H), 4.92−4.85 (m, 1H), 4.61−4.54 (m, 2H), 3.91 (s, 3H), 2.63−2.53 (m, 2H), 2.53−2.44 (m, 1H), 2.23 (s, 3H), 2.10−1.95 (m, 2H), 1.93−1.83 (m, 1H), 1.82−1.73 (m, 1H), 1.72−1.64 (m, 1H); δ_C (100 MHz, $CDCl_3$) 208.6, 206.8, 165.3, 141.5, 136.8, 135.0, 126.4, 123.1, 122.0, 121.6, 115.8, 110.5, 107.7, 72.2, 51.0, 48.9, 41.1, 33.6, 27.0, 26.2, 22.1; HRMS (ESI) m/z calcd for $C_{21}H_{23}NO_4$ [M + H]$^+$ 354.1700, found 354.1683.

*1-(2-(1-Acetyl-2-oxocyclohexyl)allyl)-1H-indole-3-carbonitrile (**17c**).* Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded **17c** (43 mg, 55%) as a yellow solid. R_f = 0.20 [petrol:EtOAc 4:1]; mp 96−99 °C; ν_{max} (film)/cm^{-1} 3121, 2942, 2214, 1697, 1645; δ_H (400 MHz, $CDCl_3$) 7.76−7.73 (m, 1H), 7.60 (s, 1H), 7.51−7.47 (m, 1H), 7.36−7.31 (m, 1H), 7.30−7.24 (m, 1H), 5.06 (br s, 1H), 4.94−4.87 (m, 1H), 4.60−4.53 (m, 2H), 2.64−2.46 (m, 3H), 2.22 (s, 3H), 2.07−1.97 (m, 2H), 1.94−1.85 (m, 1H), 1.82−1.72 (m, 1H), 1.71−1.63 (m, 1H); δ_C (100 MHz, $CDCl_3$) 208.5, 206.7, 141.3, 135.7, 135.6, 127.6, 124.2, 122.3, 119.8, 115.9, 115.7, 111.1, 86.4, 72.2, 49.1, 41.1, 33.7, 27.0, 26.2, 22.1; HRMS (ESI) m/z calcd for $C_{20}H_{20}N_2O_2$ [M + H]$^+$ 321.1598, found 321.1591.

*Ethyl 1-(2-(1-Acetyl-2-oxocyclohexyl)allyl)-1H-indole-2-carboxylate (**17d**).* Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded **17d** (52 mg, 59%) as a pale yellow solid. R_f = 0.45 [petrol:EtOAc 4:1]; mp 102−104 °C; ν_{max} (film)/cm^{-1} 2957, 1697, 1649; δ_H (300 MHz, $CDCl_3$) 7.70−7.63 (m, 2H), 7.41−7.33 (m, 2H), 7.16 (ddd, J = 8.1, 7.0, 0.8 Hz, 1H), 5.24−5.08 (m, 2H), 4.88 (t, J = 1.6 Hz, 1H), 4.38−4.28 (m, 2H), 4.20 (t, J = 1.2 Hz, 1H), 2.67−2.59 (m, 2H), 2.52−2.42 (m, 1H), 2.36 (s, 3H), 2.28−2.16 (m, 1H), 2.02−1.90 (m, 2H), 1.90−1.80 (m, 1H), 1.78−1.64 (m, 1H), 1.38 (t, J = 7.1 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 209.3, 207.9, 161.7, 142.2, 139.5, 127.2, 125.7, 125.5, 122.3, 120.9, 113.4, 111.4, 110.8, 72.0, 60.4, 46.7, 41.0, 33.4, 27.3, 26.6, 22.0, 14.3; HRMS (ESI) m/z calcd for $C_{22}H_{25}NO_4$ [M + H]$^+$ 368.1856, found 368.1847.

*2-Acetyl-2-(3-(5-chloro-1H-indol-1-yl)prop-1-en-2-yl)cyclohexan-1-one (**17e**).* Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded **17e** (41 mg, 52%) as a brown solid. R_f = 0.45 [petrol:EtOAc 4:1]; mp 113−115 °C; ν_{max} (film)/cm^{-1} 2948, 1701, 1643; δ_H (300 MHz, $CDCl_3$) 7.57 (d, J = 2.1 Hz, 1H), 7.30 (dt, J = 8.8, 0.8 Hz, 1H), 7.15 (dd, J = 8.7, 2.0 Hz, 1H), 7.06 (d, J = 3.2 Hz, 1H), 6.46 (dd, J =

DOI: 10.1021/acs.joc.6b00731
J. Org. Chem. 2016, 81, 5162−5172

3.2, 0.9 Hz, 1H), 5.00−4.98 (m, 1H), 4.86−4.77 (m, 1H), 4.59−4.49 (m, 2H), 2.59−2.51 (m, 2H), 2.45 (dddd, J = 14.4, 8.3, 5.5, 2.2 Hz, 1H), 2.20 (s, 3H), 2.08−1.93 (m, 2H), 1.91−1.74 (m, 2H), 1.72−1.63 (m, 1H); δ_C (100 MHz, $CDCl_3$) 208.7, 206.8, 142.2, 134.7, 129.9, 129.4, 125.3, 122.1, 120.2, 115.7, 110.9, 101.5, 72.2, 48.7, 41.1, 33.5, 27.0, 26.3, 22.1; HRMS (ESI) m/z calcd for $C_{19}H_{20}NO_2Cl$ $[M + H]^+$ 330.1255, found 330.1257.

*Acetyl-2-(3-(7-nitro-1H-indol-1-yl)prop-1-en-2-yl)cyclohexanone (**17f**).* Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded **17f** (51 mg, 62%) as a brown solid. R_f = 0.63 [petrol:EtOAc 4:1]; mp 125−128 °C; ν_{max} (film)/cm^{-1} 2948, 1714, 1694, 1504; δ_H (400 MHz, $CDCl_3$) 7.88 (dd, J = 7.8, 1.0 Hz, 1H), 7.82 (dd, J = 7.9, 1.1 Hz, 1H), 7.27 (d, J = 3.4 Hz, 1H), 7.14 (t, J = 7.9 Hz, 1H), 6.71 (d, J = 3.4 Hz, 1H), 4.97−4.91 (m, 1H), 4.88−4.81 (m, 2H), 4.31−4.29 (m, 1H), 2.55 (dd, J = 8.0, 5.9 Hz, 2H), 2.50−2.42 (m, 1H), 2.24 (s, 3H), 2.09−2.00 (m, 1H), 1.99−1.84 (m, 2H), 1.82−1.73 (m, 1H), 1.70−1.62 (m, 1H); δ_C (100 MHz, $CDCl_3$) 208.7, 207.3, 142.6, 136.8, 133.8, 133.6, 127.4, 127.0, 120.2, 118.7, 114.7, 103.7, 72.1, 51.8, 41.0, 33.3, 27.1, 26.5, 22.0; HRMS (ESI) m/z calcd for $C_{19}H_{20}N_2O_4$ $[M + H]^+$ 341.1496, found 341.1500.

*Acetyl-2-(3-(5-nitro-1H-indol-1-yl)prop-1-en-2-yl)cyclohexanone (**17g**).* Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded **17g** (51 mg, 62%) as an orange solid. R_f = 0.22 [petrol:EtOAc 4:1]; mp 120−122 °C; ν_{max} (film)/cm^{-1} 2927, 2111, 1709, 1694, 1511; δ_H (400 MHz, $CDCl_3$) 8.57 (d, J = 2.1 Hz, 1H), 8.11 (dd, J = 8.1, 2.1 Hz, 1H), 7.46 (d, J = 9.0 Hz, 1H), 7.21 (d, J = 3.2 Hz, 1H), 6.70 (d, J = 3.2 Hz, 1H), 5.05−5.03 (m, 1H), 4.90 (dt, J = 17.4, 1.5 Hz, 1H), 4.57 (dt, J = 17.5, 1.6 Hz, 1H), 4.54 (s, 1H), 2.65−2.45 (m, 3H), 2.22 (s, 3H), 2.10−1.96 (m, 2H), 1.95−1.85 (m, 1H), 1.83−1.62 (m, 2H); δ_C (100 MHz, $CDCl_3$) 208.6, 206.8, 141.8, 141.8, 139.2, 131.8, 127.6, 118.1, 117.6, 115.6, 110.0, 104.5, 72.2, 48.9, 41.1, 33.6, 27.0, 26.2, 22.1; HRMS (ESI) m/z calcd for $C_{19}H_{20}N_2O_4$ $[M + H]^+$ 341.1496, found 341.1485.

*2-Acetyl-2-(3-(5-methoxy-1H-indol-1-yl)prop-1-en-2-yl)-cyclohexanone (**17h**).* Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded **17h** (21 mg, 27%) as a red oil. R_f = 0.25 [petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 3121, 2942, 2214, 1697, 1645; δ_H (300 MHz, $CDCl_3$) 7.27−7.23 (m, 1H), 7.08 (d, J = 2.4 Hz, 1H), 7.02 (d, J = 3.0 Hz, 1H), 6.87 (dd, J = 8.9, 2.5 Hz, 1H), 6.44 (dd, J = 3.1, 0.8 Hz, 1H), 4.98 (t, J = 1.3 Hz, 1H), 4.78 (dt, J = 17.6, 1.6 Hz, 1H), 4.63 (t, J = 1.6 Hz, 1H), 4.55 (dt, J = 17.6, 1.6 Hz, 1H), 3.85 (s, 3H), 2.56 (t, J = 6.7 Hz, 2H), 2.48−2.39 (m, 1H), 2.20 (s, 3H), 2.11−2.00 (m, 1H), 2.00−1.91 (m, 1H), 1.90−1.77 (m, 2H), 1.73−1.64 (m, 1H); δ_C (75 MHz, $CDCl_3$) 208.8, 206.8, 154.1, 142.5, 131.7, 129.2, 128.9, 115.9, 112.1, 110.6, 102.5, 101.4, 72.3, 55.8, 48.7, 41.1, 33.4, 27.0, 26.4, 22.1; HRMS (ESI) m/z calcd for $C_{20}H_{23}NO_3$ $[M + H]^+$ 326.1751, found 326.1747.

*2-(3-(1H-Pyrrolo[2,3-b]pyridin-1-yl)prop-1-en-2-yl)-2-acetylcyclohexanone (**17i**).* Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded **17i** (52 mg, 73%) as a brown solid. R_f = 0.20 [petrol:EtOAc 4:1]; mp 60−62 °C; ν_{max} (film)/cm^{-1} 2931, 1709, 1695, 1511; δ_H (400 MHz, $CDCl_3$) 8.26 (dd, J = 4.8, 1.6 Hz, 1H), 7.88 (dd, J = 7.9, 1.6 Hz, 1H), 7.27 (d, J = 3.6 Hz, 1H), 7.03 (dd, J = 7.8, 4.6 Hz, 1H), 6.48 (d, J = 3.6 Hz, 1H), 4.97 (t, J = 1.3 Hz, 1H), 4.84 (t, J = 1.4 Hz, 2H), 4.68 (t, J = 1.6 Hz, 1H), 2.65−2.48 (m, 2H), 2.45−2.35 (m, 1H), 2.27 (s, 3H), 2.21−2.11 (m, 1H), 1.95−1.74 (m, 3H), 1.73−1.64 (m, 1H); δ_C (100 MHz, $CDCl_3$) 209.1, 207.2, 147.6, 143.1, 142.9, 128.7, 128.6, 120.2, 116.1, 115.8, 100.0, 72.4, 45.9, 41.0, 32.9, 27.1, 26.8, 21.8; HRMS (ESI) m/z calcd for $C_{18}H_{20}N_2O_2$ $[M + H]^+$ 297.1598, found 297.1588.

*2-(3-(9H-Carbazol-9-yl)prop-1-en-2-yl)-2-acetylcyclohexanone (**17j**).* Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded **17j** (44 mg, 53%) as an orange solid. R_f = 0.30 [petrol:EtOAc 4:1]; mp 105−107 °C; ν_{max} (film)/cm^{-1} 2942, 1701, 1645; δ_H (400 MHz, $CDCl_3$) 8.11 (dt, J = 7.8, 0.8 Hz, 2H), 7.46 (dd, J = 7.0, 1.1 Hz, 2H), 7.40 (dt, J = 8.2, 0.8 Hz, 2H), 7.25 (dd, J = 7.2, 1.2 Hz, 2H), 4.99 (dt, J = 18.3, 1.7 Hz, 1H), 4.92 (t, J = 1.4 Hz, 1H), 4.71 (dt, J = 18.3, 1.9 Hz, 1H), 4.50 (t, J = 1.9 Hz, 1H), 2.68−2.60 (m, 2H), 2.56−2.48 (m, 1H), 2.35 (s, 3H), 2.26−2.16 (m, 1H), 2.07−1.90 (m, 2H), 1.89−1.81 (m, 1H), 1.80−1.69 (m, 1H); δ_C (100 MHz, $CDCl_3$) 208.9, 207.3, 140.6, 140.2, 126.0, 122.9, 120.3, 119.3, 114.9, 108.9, 72.2, 45.1, 41.2, 33.6, 27.2, 26.5, 22.3; HRMS (ESI) m/z calcd for $C_{23}H_{23}NO_2$ $[M + H]^+$ 346.1802, found 346.1795.

*2-(3-(1H-Pyrrol-1-yl)prop-1-en-2-yl)-2-acetylcyclohexanone (**23a**).* Flash column chromatography [petrol:EtOAc 19:1−4:1] afforded **23a** (12.5 mg, 21%) as a black solid. R_f = 0.56 [petrol:EtOAc 4:1]; mp 114−116 °C; ν_{max} (film)/cm^{-1} 3386, 3099, 3056, 2944, 2858, 1695, 1511; δ_H (400 MHz, $CDCl_3$) 6.59 (t, J = 2.1 Hz, 2H), 6.14 (t, J = 2.3 Hz, 2H), 5.07 (t, J = 1.0 Hz, 1H), 4.92 (t, J = 1.5 Hz, 1H), 4.55 (dt, J = 16.5, 1.2 Hz, 1H), 4.36 (dt, J = 16.5, 1.2 Hz, 1H), 2.50 (dd, J = 8.0, 6.2 Hz, 2H), 2.42−2.35 (m, 1H), 2.11 (s, 3H), 2.03−1.88 (m, 2H), 1.83−1.70 (m, 2H), 1.68−1.61 (m, 1H); δ_C (100 MHz, $CDCl_3$) 208.8, 206.8, 144.0, 121.5, 116.9, 108.4, 72.4, 51.7, 41.0, 33.1, 26.9, 26.7, 21.9; HRMS (ESI) m/z calcd for $C_{15}H_{19}NO_2$ $[M + H]^+$ 246.1489, found 246.1491.

*Methyl 1-(2-(1-Acetyl-2-oxocyclohexyl)allyl)-1H-pyrrole-2-carboxylate (**23b**).* Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded **23b** (59 mg, 81%) as a yellow solid. R_f = 0.43 [petrol:EtOAc 4:1]; mp 104−106 °C; ν_{max} (film)/cm^{-1} 2946, 1716, 1692, 1643; δ_H (300 MHz, $CDCl_3$) 6.96 (dd, J = 4.1, 1.9 Hz, 1H), 6.89 (dd, J = 2.5, 1.8 Hz, 1H), 6.18 (dd, J = 3.9, 2.6 Hz, 1H), 5.01−4.91 (m, 2H), 4.86 (dt, J = 16.7, 1.5 Hz, 1H), 4.40 (t, J = 1.7 Hz, 1H), 3.76 (s, 3H), 2.64−2.47 (m, 2H), 2.44−2.35 (m, 1H), 2.26 (s, 3H), 2.17−2.07 (m, 1H), 1.96−1.78 (m, 3H), 1.75−1.62 (m, 1H); δ_C (75 MHz, $CDCl_3$) 209.0, 207.3, 161.2, 143.9, 129.8, 121.9, 118.1, 114.2, 108.6, 72.1, 51.0, 50.2, 41.0, 33.1, 27.2, 26.7, 21.8; HRMS (ESI) m/z calcd for $C_{17}H_{21}NO_4$ $[M + Na]^+$ 326.1363, found 326.1348.

*Methyl 1-(2-(1-Acetyl-2-oxocyclohexyl)allyl)-1H-pyrrole-3-carboxylate (**23c**).* Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded **23c** (30.5 mg, 42%) as a dark yellow solid. R_f = 0.09 [petrol:EtOAc 4:1]; mp 74−76 °C; ν_{max} (film)/cm^{-1} 2952, 1712, 1694; δ_H (400 MHz, $CDCl_3$) 7.23 (t, J = 2.0 Hz, 1H), 6.57−6.52 (m, 2H), 5.11 (br s, 1H), 4.93−4.90 (m, 1H), 4.56 (dt, J = 16.5, 1.3 Hz, 1H), 4.31 (dt, J = 16.3, 1.1 Hz, 1H), 3.77 (s, 3H), 2.55−2.36 (m, 3H), 2.10 (s, 3H), 1.99−1.90 (m, 2H), 1.84−1.76 (m, 1H), 1.75−1.68 (m, 1H), 1.65−1.57 (m, 1H); δ_C (100 MHz, $CDCl_3$) 208.5, 206.7, 165.1, 143.1, 126.7, 122.7, 117.1, 116.1, 110.2, 72.3, 52.0, 50.9, 41.0, 33.3, 26.9, 26.1, 21.9; HRMS (ESI) m/z calcd for $C_{17}H_{21}NO_4$ $[M + Na]^+$ 326.1363, found 326.1348.

*1-(2-(1-Acetyl-2-oxocyclohexyl)allyl)-1,5,6,7-tetrahydro-4H-indol-4-one (**23d**).* Flash column chromatography [petrol:EtOAc 9:1−1:1] afforded **23d** (31 mg, 41%) as a dark orange oil. R_f = 0.10 [petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2939, 1697, 1647; δ_H (400 MHz, $CDCl_3$) 6.57 (d, J = 3.2 Hz, 1H), 6.51 (d, J = 3.2 Hz, 1H), 5.09 (br s, 1H), 4.63−4.60 (m, 1H), 4.53 (dt, J = 17.5, 1.8 Hz, 1H), 4.24 (dt, J = 17.4, 1.5 Hz, 1H), 2.69 (t, J = 6.2 Hz, 2H), 2.55−2.44 (m, 4H), 2.18 (s, 3H), 2.15−2.10 (m, 2H), 2.07−1.98 (m, 2H), 1.93−1.83 (m, 1H), 1.81−1.72 (m, 2H), 1.70−1.62 (m, 1H); δ_C (75 MHz, $CDCl_3$) 208.5, 206.7, 194.4, 144.2, 142.4, 122.9, 120.9, 115.7, 105.9, 72.0, 48.9, 41.0, 37.7, 33.5, 26.9, 26.1, 23.7, 22.0, 21.4; HRMS (ESI) m/z calcd for $C_{19}H_{23}NO_3$ $[M + Na]^+$ 336.1570, found 336.1551.

*Dimethyl 1-(2-(1-Acetyl-2-oxocyclohexyl)allyl)-1H-pyrrole-2,5-dicarboxylate (**23e**).* Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded **23e** (49 mg, 57%) as a dark orange solid. R_f = 0.29 [petrol:EtOAc 4:1]; mp 144−146 °C; ν_{max} (film)/cm^{-1} 2946, 1727, 1699; δ_H (300 MHz, $CDCl_3$) 6.96 (s, 2H), 5.61 (dt, J = 17.0, 2.0 Hz, 1H), 5.43 (dt, J = 16.9, 1.6 Hz, 1H), 4.84 (t, J = 1.8 Hz, 1H), 4.16 (t, J = 1.9 Hz, 1H), 3.82 (s, 6H), 2.81−2.65 (m, 1H), 2.45−2.33 (m, 1H), 2.28 (s, 3H), 2.31−2.26 (m, 2H), 2.09−1.89 (m, 2H), 1.86−1.70 (m, 2H); δ_C (75 MHz, $CDCl_3$) 209.4, 206.6, 160.6, 144.1, 127.6, 117.0, 113.9, 72.2, 51.7, 47.9, 40.9, 32.5, 27.6, 27.1, 21.5; HRMS (ESI) m/z calcd for $C_{19}H_{23}NO_6$ $[M + Na]^+$ 384.1418, found 384.1406.

*Methyl 1-(2-(1-Acetyl-2-oxocyclohexyl)allyl)-4-(3-methylbutanoyl)-1H-pyrrole-2-carboxylate (**23f**).* Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded **23f** (56 mg, 60%) as a light yellow solid. R_f = 0.56 [petrol:EtOAc 4:1]; mp 75−78 °C; ν_{max} (film)/cm^{-1} 3188, 2953, 1697, 1636; δ_H (400 MHz, $CDCl_3$) 7.47 (d, J = 1.8 Hz, 1H), 7.35 (d, J = 1.9 Hz, 1H), 5.00−4.97 (m, 1H), 4.94−4.92 (m, 2H), 4.44−4.41 (m, 1H), 3.78 (s, 3H), 2.60 (d, J = 7.0 Hz, 2H), 2.56 (dd, J = 8.2, 6.3 Hz, 2H), 2.49−2.39 (m, 1H), 2.29−2.19 (m, 4H),

DOI: 10.1021/acs.joc.6b00731
J. Org. Chem. 2016, 81, 5162−5172

2.13−2.04 (m, 1H), 2.00−1.85 (m, 2H), 1.85−1.75 (m, 1H), 1.71−1.61 (m, 1H), 0.96 (d, J = 6.4 Hz, 6H); δ_C (100 MHz, $CDCl_3$) 208.8, 207.2, 195.2, 160.8, 143.2, 132.4, 125.3, 123.2, 117.7, 114.1, 72.0, 51.4, 50.8, 48.5, 41.0, 33.3, 27.1, 26.5, 25.4, 22.7, 22.7, 21.9; HRMS (ESI) m/z calcd for $C_{22}H_{29}NO_5$ $[M + Na]^+$ 410.1938, found 410.1923.

*Methyl 1-(2-(1-Acetyl-2-oxocyclohexyl)allyl)-4-benzoyl-1H-pyrrole-2-carboxylate (**23g**).* Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded **23g** (93 mg, 95%) as a red oil. R_f = 0.22 [petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2950, 1701, 1638; δ_H (400 MHz, $CDCl_3$) 7.84−7.79 (m, 2H), 7.54 (tt, J = 7.3, 2.3 Hz, 1H), 7.51−7.45 (m, 3H), 7.43 (d, J = 2.1 Hz, 1H), 5.01−4.96 (m, 3H), 4.49−4.46 (m, 1H), 3.79 (s, 3H), 2.55 (dd, J = 7.8, 6.3 Hz, 2H), 2.49−2.40 (m, 1H), 2.27 (s, 3H), 2.14−2.04 (m, 1H), 1.99−1.85 (m, 2H), 1.84−1.75 (m, 1H), 1.71−1.63 (m, 1H); δ_C (100 MHz, $CDCl_3$) 208.7, 207.1, 189.0, 160.8, 143.2, 138.9, 134.4, 131.9, 128.9, 128.3, 123.5, 123.2, 119.5, 114.1, 72.0, 51.4, 50.0, 41.0, 33.3, 27.1, 26.5, 21.9; HRMS (ESI) m/z calcd for $C_{24}H_{25}NO_5$ $[M + Na]^+$ 430.1625, found 430.1609.

*Methyl 1-(2-(1-Acetyl-2-oxocyclohexyl)allyl)-4-formyl-1H-pyrrole-2-carboxylate (**23h**).* Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded **23h** (46 mg, 58%) as an orange solid. R_f = 0.19 [petrol:EtOAc 4:1]; mp 96−99 °C; ν_{max} (film)/cm^{-1} 2953, 1720, 1697, 1668, 1518; δ_H (400 MHz, $CDCl_3$) 9.76 (s, 1H), 7.01 (d, J = 4.2 Hz, 1H), 6.97 (d, J = 4.4 Hz, 1H), 5.51 (dt, J = 17.3, 2.2 Hz, 1H), 5.37 (dt, J = 17.3, 2.0 Hz, 1H), 4.89−4.87 (m, 1H), 4.21−4.18 (m, 1H), 3.84 (s, 3H), 2.74−2.66 (m, 1H), 2.47−2.40 (m, 1H), 2.30 (s, 3H), 2.36−2.21 (m, 2H), 2.08−1.97 (m, 1H), 1.95−1.83 (m, 1H), 1.87−1.78 (m, 1H), 1.78−1.68 (m, 1H); δ_C (100 MHz, $CDCl_3$) 209.2, 206.8, 181.0, 160.6, 143.7, 135.3, 129.0, 121.3, 117.5, 113.8, 72.1, 51.9, 48.1, 40.9, 32.7, 27.4, 27.0, 21.5; HRMS (ESI) m/z calcd for $C_{18}H_{21}NO_5$ $[M + K]^+$ 370.1051, found 370.1062.

*Methyl 1-(2-(1-Acetyl-2-oxocyclohexyl)allyl)-4-butyl-1H-pyrrole-2-carboxylate (**23i**).* Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded **23i** (51 mg, 59%) as a yellow oil. R_f = 0.51 [petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2927, 1697; δ_H (400 MHz, $CDCl_3$) 6.79 (d, J = 1.9 Hz, 1H), 6.68 (d, J = 1.9 Hz, 1H), 4.94−4.86 (m, 2H), 4.82−4.75 (m, 1H), 4.43 (t, J = 2.2 Hz, 1H), 3.76 (s, 3H), 2.66−2.48 (m, 2H), 2.42 (t, J = 8.1 Hz, 2H), 2.45−2.34 (m, 1H), 2.27 (s, 3H), 2.17−2.08 (m, 1H), 1.96−1.78 (m, 3H), 1.74−1.59 (m, 1H), 1.52 (quintet, J = 7.7 Hz, 2H), 1.33 (sextet, J = 7.7 Hz, 2H), 0.90 (t, J = 7.2 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 209.2, 207.4, 161.2, 144.1, 127.7, 124.8, 121.3, 117.7, 114.2, 72.1, 50.9, 50.0, 41.0, 33.0, 33.0, 27.2, 26.8, 26.2, 22.7, 21.8, 13.9; HRMS (ESI) m/z calcd for $C_{21}H_{29}NO_4$ $[M + Na]^+$ 382.1989, found 382.1993.

*Methyl 1-(2-(2-Acetyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)allyl)-1H-indole-3-carboxylate (**24a**).* Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded **24a** (69 mg, 72%) as a yellow solid. R_f = 0.24 [petrol:EtOAc 4:1]; mp 149−152 °C; ν_{max} (film)/cm^{-1} 2946, 1697, 1533; δ_H (400 MHz, $CDCl_3$) 8.17−8.12 (m, 1H), 8.04 (dd, J = 8.1, 1.3 Hz, 1H), 7.76 (s, 1H), 7.51 (td, J = 7.5, 1.4 Hz, 1H), 7.42−7.38 (m, 1H), 7.33 (td, J = 8.0, 1.2 Hz, 1H), 7.29−7.22 (m, 3H), 4.97 (q, J = 1.3 Hz, 1H), 4.83 (t, J = 1.5 Hz, 2H), 4.63−4.61 (m, 1H), 3.89 (s, 3H), 3.11−2.96 (m, 2H), 2.70 (ddd, J = 14.3, 7.3, 6.1 Hz, 1H), 2.43 (ddd, J = 14.0, 7.0, 5.1 Hz, 1H), 2.31 (s, 3H); δ_C (100 MHz, $CDCl_3$) 204.7, 195.7, 165.3, 142.8, 140.7, 136.8, 134.9, 134.3, 131.8, 128.8, 128.0, 127.1, 126.4, 123.2, 122.1, 121.6, 116.5, 110.4, 107.8, 68.5, 51.0, 49.2, 29.8, 27.7, 25.9; HRMS (ESI) m/z calcd for $C_{25}H_{23}NO_4$ $[M + H]^+$ 402.1700, found 402.1681.

*Methyl 1-(2-(1-Isobutyryl-2-oxocyclohexyl)allyl)-1H-indole-3-carboxylate (**24b**).* Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded **24b** (65 mg, 71%) as a pale yellow solid. R_f = 0.20 [petrol:EtOAc 4:1]; mp 81−83 °C; ν_{max} (film)/cm^{-1} 2950, 1758, 1723, 1684; δ_H (300 MHz, $CDCl_3$) 8.17−8.10 (m, 1H), 7.74 (s, 1H), 7.49−7.42 (m, 1H), 7.30−7.20 (m, 2H), 4.94 (br s, 1H), 4.75 (dt, J = 17.6, 1.5 Hz, 1H), 4.62 (dt, J = 17.5, 1.6 Hz, 1H), 4.50 (br s, 1H), 3.88 (s, 3H), 3.01 (heptet, J = 6.7 Hz, 1H), 2.51 (t, J = 6.5 Hz, 2H), 2.47−2.38 (m, 1H), 2.12−1.99 (m, 1H), 1.98−1.68 (m, 4H), 1.16 (d, J = 6.5 Hz, 3H), 1.11 (d, J = 6.7 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 213.1, 209.0, 165.4, 141.2, 138.0, 135.0, 126.4, 123.2, 122.1, 121.6, 115.9, 110.7, 107.8, 72.6, 51.0, 49.1, 41.3, 37.2, 32.9, 26.7, 22.1, 21.3, 20.6; HRMS (ESI) m/z calcd for $C_{23}H_{27}NO_4$ $[M + H]^+$ 382.2013, found 382.2007.

*Methyl 1-(3-Benzoyl-3-methyl-2-methylene-4-oxopentyl)-1H-indole-3-carboxylate (**24c**).* Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded **24c** (78 mg, 83%) as an orange oil. R_f = 0.24 [petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2948, 1697, 1677, 1533; δ_H (400 MHz, $CDCl_3$) 8.21−8.13 (m, 1H), 7.92−7.85 (m, 2H), 7.78 (s, 1H), 7.59 (tt, J = 7.6, 1.4 Hz, 1H), 7.50−7.45 (m, 2H), 7.43−7.38 (m, 1H), 7.30−7.23 (m, 2H), 5.12 (q, J = 1.2 Hz, 1H), 4.94 (dt, J = 17.9, 1.8 Hz, 1H), 4.81 (dt, J = 17.4, 1.7 Hz, 1H), 4.58−4.55 (m, 1H), 3.91 (s, 3H), 2.25 (s, 3H), 1.81 (s, 3H); δ_C (100 MHz, $CDCl_3$) 206.1, 199.6, 165.4, 143.7, 136.8, 135.5, 135.1, 133.4, 129.2, 128.7, 126.4, 123.1, 122.0, 121.6, 115.0, 110.5, 107.7, 68.5, 51.0, 49.2, 27.6, 21.2; HRMS (ESI) m/z calcd for $C_{24}H_{23}NO_4$ $[M + H]^+$ 390.1670, found 390.1675.

*Methyl 1-(3,3-Diacetyl-5-ethoxy-2-methylene-5-oxopentyl)-1H-indole-3-carboxylate (**24d**).* Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded **24d** (54 mg, 56%) as an orange solid. R_f = 0.10 [petrol:EtOAc 4:1]; mp 104−107 °C; ν_{max} (film)/cm^{-1} 2935, 1716, 1692, 1531; δ_H (400 MHz, $CDCl_3$) 8.22−8.15 (m, 1H), 7.76 (s, 1H), 7.33−7.23 (m, 3H), 4.97 (q, J = 1.4 Hz, 1H), 4.89 (t, J = 1.7 Hz, 2H), 4.53 (q, J = 1.9 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.92 (s, 3H), 3.22 (s, 2H), 2.29 (s, 6H), 1.30 (t, J = 7.3 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 203.6, 170.8, 165.3, 141.7, 136.6, 134.8, 126.4, 123.2, 122.1, 121.8, 117.0, 110.0, 108.0, 72.3, 61.5, 51.0, 48.7, 39.6, 27.6, 14.0; HRMS (ESI) m/z calcd for $C_{22}H_{25}NO_6$ $[M + Na]^+$ 422.1574, found 422.1580.

*Methyl 1-(2-(1,3-Dioxo-2-phenyl-2,3-dihydro-1H-inden-2-yl)allyl)-1H-indole-3-carboxylate (**24e**).* Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded **24e** (59 mg, 56%) as a dark orange oil. R_f = 0.40 [petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2946, 1697; δ_H (300 MHz, $CDCl_3$) 8.10−8.05 (m, 1H), 8.00−7.95 (m, 2H), 7.87−7.81 (m, 2H), 7.65 (s, 1H), 7.52−7.47 (m, 2H), 7.42−7.34 (m, 3H), 7.24−7.18 (m, 3H), 5.08−5.06 (m, 1H), 4.85 (t, J = 1.6 Hz, 2H), 4.74−4.71 (m, 1H), 3.88 (s, 3H); δ_C (75 MHz, $CDCl_3$) 198.4, 165.2, 141.3, 140.7, 136.6, 136.3, 135.1, 134.4, 129.1, 128.4, 128.2, 126.4, 124.0, 123.0, 122.0, 121.5, 117.9, 110.4, 107.7, 66.6, 50.9, 48.9; HRMS (ESI) m/z calcd for $C_{28}H_{21}NO_4$ $[M + H]^+$ 436.1543, found 436.1534.

*Methyl 1-(2-(1-Methyl-2,6-dioxocyclohexyl)allyl)-1H-indole-3-carboxylate (**24f**).* Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded **24f** (44 mg, 54%) as a yellow oil. R_f = 0.12 [petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2946, 1692, 1533; δ_H (300 MHz, $CDCl_3$) 8.19−8.11 (m, 1H), 7.72 (s, 1H), 7.29−7.21 (m, 3H), 4.97 (q, J = 1.1 Hz, 1H), 4.62 (q, J = 1.9 Hz, 1H), 4.55 (t, J = 1.3 Hz, 2H), 3.88 (s, 3H), 2.69−2.57 (m, 4H), 2.00−1.84 (m, 2H), 1.50 (s, 3H); δ_C (75 MHz, $CDCl_3$) 207.5, 165.2, 142.3, 136.6, 135.0, 126.4, 123.2, 122.2, 121.7, 115.7, 110.2, 108.0, 70.2, 51.0, 48.5, 38.3, 19.9, 17.4; HRMS (ESI) m/z calcd for $C_{20}H_{21}NO_4$ $[M + H]^+$ 340.1543, found 340.1537.

*Methyl 1-(2-(1-(Ethoxycarbonyl)-2-oxocyclopentyl)allyl)-1H-indole-3-carboxylate (**24g**).* Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded **24g** (72 mg, 81%) as a red oil. R_f = 0.19 [petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2940, 1695, 1533; δ_H (400 MHz, $CDCl_3$) 8.20−8.11 (m, 1H), 7.78 (s, 1H), 7.38−7.32 (m, 1H), 7.27−7.21 (m, 2H), 5.09 (br s, 1H), 5.02 (dt, J = 17.4, 1.5 Hz, 1H), 4.86 (dt, J = 17.2, 1.5 Hz, 1H), 4.56−4.54 (m, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.88 (s, 3H), 2.58−2.43 (m, 2H), 2.39−2.27 (m, 2H), 2.05−1.88 (m, 2H), 1.26 (t, J = 6.8 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 211.7, 170.2, 165.4, 139.3, 136.8, 135.1, 126.5, 123.0, 122.0, 121.5, 114.9, 110.5, 107.5, 64.4, 62.2, 50.9, 48.7, 37.9, 33.7, 19.5, 14.0; HRMS (ESI) m/z calcd for $C_{21}H_{23}NO_5$ $[M + H]^+$ 370.1649, found 370.1629.

*Methyl 1-(2-(2-Acetyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)allyl)-1H-pyrrole-2-carboxylate (**25a**).* Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded **25a** (56 mg, 66%) as a pale yellow solid. R_f = 0.60 [petrol:EtOAc 4:1]; mp 92−95 °C; ν_{max} (film)/cm^{-1} 2939, 1694; δ_H (300 MHz, $CDCl_3$) 8.06 (dd, J = 7.9, 1.3 Hz, 1H), 7.48 (td, J = 7.5, 1.5 Hz, 1H), 7.32 (tt, J = 8.0, 0.6 Hz, 1H), 7.24 (d, J = 8.1 Hz, 1H), 6.96 (dd, J = 4.1, 2.0 Hz, 1H), 6.88 (dd, J = 2.5, 1.8 Hz, 1H), 6.18 (dd, J = 4.0, 2.7 Hz, 1H), 5.26 (dt, J = 17.2, 1.8 Hz, 1H), 4.89−4.81 (m, 2H), 4.38−4.36 (m, 1H), 3.76 (s, 3H), 3.14 (ddd, J = 17.0, 9.9, 4.9 Hz, 1H), 3.01 (ddd, J = 17.5, 5.9, 4.7 Hz, 1H), 2.72−2.61 (m, 1H), 2.48 (ddd, J = 14.2, 6.5, 4.6 Hz, 1H), 2.37 (s, 3H); δ_C (75 MHz, $CDCl_3$) 205.8, 195.9, 161.2, 143.5, 143.3, 133.9, 132.1, 129.7, 128.8,

DOI: 10.1021/acs.joc.6b00731
J. Org. Chem. 2016, 81, 5162−5172

127.9, 126.9, 122.0, 118.2, 115.0, 108.8, 68.7, 51.1, 50.3, 29.4, 28.1, 25.7; HRMS (ESI) m/z calcd for $C_{21}H_{21}NO_4$ $[M + K]^+$ 390.1102, found 390.1105.

*Methyl 1-(2-(1-Isobutyryl-2-oxocyclohexyl)allyl)-1H-pyrrole-2-carboxylate (**25b**).* Flash column chromatography [petrol:EtOAc 9:1] afforded **25b** (44 mg, 55%) as an orange oil. R_f = 0.70 [petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2946, 1697; δ_H (300 MHz, $CDCl_3$) 6.97 (dd, J = 4.0, 1.8 Hz, 1H), 6.91 (dd, J = 2.5, 1.9 Hz, 1H), 6.18 (dd, J = 3.9, 2.6 Hz, 1H), 5.12 (dt, J = 17.1, 1.9 Hz, 1H), 4.88–4.85 (m, 1H), 4.69 (d, J = 17.0, 1.5 Hz, 1H), 4.42 (t, J = 1.9 Hz, 1H), 3.77 (s, 3H), 3.02 (heptet, J = 6.3 Hz, 1H), 2.74–2.64 (m, 1H), 2.47–2.39 (m, 1H), 2.36–2.27 (m, 1H), 2.26–2.17 (m, 1H), 2.01–1.89 (m, 2H), 1.86–1.73 (m, 2H), 1.14 (d, J = 6.8 Hz, 3H), 1.10 (d, J = 6.8 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 213.2, 209.8, 161.3, 143.3, 129.7, 122.0, 118.1, 114.8, 108.7, 72.8, 51.0, 50.2, 41.1, 37.4, 32.4, 26.9, 21.5, 20.9; HRMS (ESI) m/z calcd for $C_{19}H_{25}NO_4$ $[M + Na]^+$ 354.1676, found 354.1660.

*Methyl 1-(3-Acetyl-3-methyl-2-methylene-4-oxopentyl)-1H-pyrrole-3-carboxylate (**25c**).* Flash column chromatography [petrol:EtOAc 9:1–4:1] afforded **25c** (40 mg, 60%) as a yellow solid. R_f = 0.22 [petrol:EtOAc 4:1]; mp 58–61 °C; ν_{max} (film)/cm^{-1} 2991, 1716, 1692, 1531; δ_H (400 MHz, $CDCl_3$) 6.96 (dd, J = 4.0, 1.8 Hz, 1H), 6.86 (dd, J = 2.5, 1.8 Hz, 1H), 6.18 (dd, J = 3.9, 2.5 Hz, 1H), 4.95–4.92 (m, 1H), 4.89 (t, J = 1.6 Hz, 2H), 4.38 (td, J = 1.9, 0.6 Hz, 1H), 3.76 (s, 3H), 2.23 (s, 6H), 1.64 (s, 3H); δ_C (100 MHz, $CDCl_3$) 206.9, 161.2, 144.3, 129.7, 121.8, 118.2, 113.9, 108.6, 70.1, 51.0, 50.0, 27.0, 18.4; HRMS (ESI) m/z calcd for $C_{15}H_{19}NO_4$ $[M + Na]^+$ 300.1206, found 300.1192.

*Methyl 1-(3-Benzoyl-3-methyl-2-methylene-4-oxopentyl)-1H-pyrrole-2-carboxylate (**25d**).* Flash column chromatography [petrol:EtOAc 19:1–9:1] afforded **25d** (45 mg, 55%) as a pale yellow solid. R_f = 0.75 [petrol:EtOAc 4:1]; mp 91–93 °C; ν_{max} (film)/cm^{-1} 2948, 1707, 1654; δ_H (300 MHz, $CDCl_3$) 7.97–7.92 (m, 2H), 7.53 (tt, J = 7.5, 2.1 Hz, 1H), 7.46–7.38 (m, 2H), 6.98 (dd, J = 4.1, 1.9 Hz, 1H), 6.86 (dd, J = 2.5, 1.9 Hz, 1H), 6.19 (dd, J = 3.9, 2.6 Hz, 1H), 5.28–5.19 (m, 1H), 4.99–4.90 (m, 2H), 4.38–4.35 (m, 1H), 3.78 (s, 3H), 2.25 (s, 3H), 1.78 (s, 3H); δ_C (75 MHz, $CDCl_3$) 206.0, 200.2, 161.2, 145.5, 135.3, 132.9, 129.8, 129.7, 128.3, 121.9, 118.1, 114.4, 108.6, 68.7, 51.0, 50.2, 27.3, 20.4; HRMS (ESI) m/z calcd for $C_{20}H_{21}NO_4$ $[M + Na]^+$ 362.1363, found 362.1339.

*Methyl 1-(3,3-Diacetyl-5-ethoxy-2-methylene-5-oxopentyl)-1H-pyrrole-2-carboxylate (**25e**).* Flash column chromatography [petrol:EtOAc 9:1–4:1] afforded **25e** (62 mg, 74%) as a red oil. R_f = 0.15 [petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2952, 1733, 1701, 1533; δ_H (400 MHz, $CDCl_3$) 6.97 (dd, J = 4.0, 1.8 Hz, 1H), 6.76 (dd, J = 2.6, 1.8 Hz, 1H), 6.19 (dd, J = 4.0, 2.6 Hz, 1H), 4.99 (q, J = 1.7 Hz, 1H), 4.88 (t, J = 1.9 Hz, 2H), 4.36–4.34 (m, 1H), 4.16 (q, J = 7.3 Hz, 2H), 3.76 (s, 3H), 3.20 (s, 2H), 2.31 (s, 6H), 1.27 (t, J = 7.2 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 204.5, 170.8, 161.1, 142.7, 129.3, 121.7, 118.3, 115.3, 108.8, 71.5, 61.1, 51.0, 50.0, 37.4, 27.8, 14.0; HRMS (ESI) m/z calcd for $C_{18}H_{23}NO_6$ $[M + Na]^+$ 372.1418, found 372.1416.

*Methyl 1-(2-(1,3-Dioxo-2-phenyl-2,3-dihydro-1H-inden-2-yl)-allyl)-1H-pyrrole-2-carboxylate (**25f**).* Flash column chromatography [petrol:EtOAc 9:1–4:1] afforded **25f** (79 mg, 85%) as an orange oil. R_f = 0.40 [petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2948, 1699, 1593; δ_H (300 MHz, $CDCl_3$) 8.06–8.01 (m, 2H), 7.89–7.83 (m, 2H), 7.49–7.44 (m, 2H), 7.40–7.30 (m, 3H), 6.87 (dd, J = 4.0, 1.9 Hz, 1H), 6.67 (dd, J = 2.6, 1.9 Hz, 1H), 6.07 (dd, J = 3.9, 2.6 Hz, 1H), 5.07 (t, J = 1.5 Hz, 2H), 5.02 (t, J = 1.5 Hz, 1H), 4.59 (t, J = 1.8 Hz, 1H), 3.75 (s, 3H); δ_C (75 MHz, $CDCl_3$) 198.4, 161.0, 143.5, 141.0, 136.1, 134.6, 129.3, 128.9, 128.4, 128.2, 124.0, 122.4, 118.1, 116.6, 108.6, 67.1, 51.0, 50.3; HRMS (ESI) m/z calcd for $C_{24}H_{19}NO_4$ $[M + Na]^+$ 408.1206, found 408.1186.

*Methyl 1-(2-(1-Methyl-2,6-dioxocyclohexyl)allyl)-1H-pyrrole-2-carboxylate (**25g**).* Flash column chromatography [petrol:EtOAc 9:1–4:1] afforded **25g** (50 mg, 72%) as a yellow solid. R_f = 0.41 [petrol:EtOAc 4:1]; mp 84–87 °C; ν_{max} (film)/cm^{-1} 2939, 1725, 1690; δ_H (400 MHz, $CDCl_3$) 6.96 (dd, J = 4.0, 1.8 Hz, 1H), 6.73 (dd, J = 2.6, 1.8 Hz, 1H), 6.17 (dd, J = 4.0, 2.6 Hz, 1H), 4.79 (t, J = 1.8 Hz, 2H), 4.77–4.75 (m, 1H), 4.21 (dt, J = 2.7, 0.8 Hz, 1H), 3.77 (s, 3H), 3.03–2.94 (m, 2H), 2.62–2.53 (m, 2H), 2.28–2.18 (m, 1H), 1.81–1.68 (m, 1H), 1.42 (s, 3H); δ_C (100 MHz, $CDCl_3$) 207.7, 161.1, 145.7, 129.4, 121.9, 118.3, 112.4, 108.8, 71.3, 51.1, 49.7, 38.7, 18.2, 17.6; HRMS (ESI) m/z calcd for $C_{16}H_{19}NO_4$ $[M + Na]^+$ 312.1206, found 312.1204.

*Methyl 1-(2-(1-(Ethoxycarbonyl)-2-oxocyclopentyl)allyl)-1H-pyrrole-2-carboxylate (**25h**).* Flash column chromatography [petrol:EtOAc 9:1–4:1] afforded **25h** (42 mg, 55%) as an orange oil. R_f = 0.35 [petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2978, 1750, 1701; δ_H (400 MHz, $CDCl_3$) 6.95 (dd, J = 4.0, 1.7 Hz, 1H), 6.85 (d, J = 2.8, 2.1 Hz, 1H), 6.16 (dd, J = 4.1, 2.7 Hz, 1H), 5.20 (dt, J = 16.9, 1.4 Hz, 1H), 4.99–4.95 (m, 2H), 4.34 (t, J = 1.6 Hz, 1H), 4.21–4.12 (m, 2H), 3.76 (s, 3H), 2.64–2.54 (m, 1H), 2.46–2.35 (m, 3H), 2.05–1.93 (m, 2H), 1.29 (t, J = 7.3 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 212.1, 170.0, 161.2, 142.0, 129.7, 121.9, 118.1, 113.1, 108.4, 65.1, 61.9, 50.9, 50.1, 37.8, 33.3, 19.4, 14.0; HRMS (ESI) m/z calcd for $C_{17}H_{21}NO_5$ $[M + Na]^+$ 342.1312, found 342.1284.

*Methyl 1-(2-(3-Acetyl-2-oxotetrahydrofuran-3-yl)allyl)-1H-pyrrole-2-carboxylate (**25i**).* Flash column chromatography [petrol:EtOAc 9:1–4:1] afforded **25i** (69 mg, 99%) as a brown oil. R_f = 0.67 [petrol:EtOAc 2:1]; ν_{max} (film)/cm^{-1} 2922, 1761, 1701, 1533; δ_H (400 MHz, $CDCl_3$) 6.98 (dd, J = 4.0, 1.8 Hz, 1H), 6.81 (dd, J = 2.6, 1.9 Hz, 1H), 6.19 (dd, J = 3.9, 2.6 Hz, 1H), 5.23 (dt, J = 2.5, 0.9 Hz, 1H), 5.06 (dt, J = 17.0, 1.8 Hz, 1H), 4.83 (dt, J = 16.9, 1.7 Hz, 1H), 4.48–4.45 (m, 1H), 4.30 (ddd, J = 13.1, 7.9, 5.2 Hz, 1H), 4.25–4.18 (m, 1H), 3.76 (s, 3H), 3.04 (ddd, J = 13.2, 7.2, 5.3 Hz, 1H), 2.53–2.45 (m, 1H), 2.41 (s, 3H); δ_C (100 MHz, $CDCl_3$) 200.6, 173.0, 161.2, 141.5, 129.6, 121.7, 118.5, 114.8, 108.8, 66.1, 65.7, 51.1, 50.1, 30.2, 25.7; HRMS (ESI) m/z calcd for $C_{15}H_{17}NO_5$ $[M + Na]^+$ 314.0999, found 314.0986.

*Diethyl 2-(3-(2-(Methoxycarbonyl)-1H-pyrrol-1-yl)prop-1-en-2-yl)-2-methylmalonate (**25j**).* Flash column chromatography [petrol:EtOAc 19:1–9:1] afforded **25j** (49 mg, 61%) as a colorless oil. R_f = 0.25 [petrol:EtOAc 19:1]; ν_{max} (film)/cm^{-1} 2983, 1727, 1705; δ_H (400 MHz, $CDCl_3$) 6.95 (dd, J = 4.0, 1.8 Hz, 1H), 6.88 (dd, J = 2.6, 2.0 Hz, 1H), 6.17 (dd, J = 3.9, 2.6 Hz, 1H), 5.18 (t, J = 1.6 Hz, 2H), 5.05–5.02 (m, 1H), 4.34 (t, J = 1.9 Hz, 1H), 4.25 (q, J = 7.0 Hz, 4H), 3.77 (s, 3H), 1.69 (s, 3H), 1.30 (t, J = 7.1 Hz, 6H); δ_C (100 MHz, $CDCl_3$) 170.6, 161.2, 144.2, 129.5, 122.2, 117.9, 112.9, 108.5, 61.8, 58.6, 51.0, 50.1, 20.8, 14.0; HRMS (ESI) m/z calcd for $C_{17}H_{23}NO_6$ $[M + Na]^+$ 360.1418, found 360.1407.

*1-tert-Butyl-3-methyl-3-(3-(2-(methoxycarbonyl)-1H-pyrrol-1-yl)-prop-1-en-2-yl)-2-oxopiperidine-1,3-dicarboxylate (**25k**).* Flash column chromatography [petrol:EtOAc 9:1–4:1] afforded **25k** (57 mg, 56%) as a light brown oil. R_f = 0.12 [petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2953, 1701, 1533; δ_H (400 MHz, $CDCl_3$) 6.97 (dd, J = 4.0, 1.8 Hz, 1H), 6.94 (dd, J = 2.6, 1.9 Hz, 1H), 6.18 (dd, J = 3.9, 2.6 Hz, 1H), 5.26 (dt, J = 17.0, 2.0 Hz, 1H), 5.05–5.03 (m, 1H), 4.92 (dt, J = 16.7, 1.4 Hz, 1H), 4.41–4.39 (m, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.72–3.60 (m, 2H), 2.53–2.46 (m, 1H), 2.28 (ddd, J = 13.2, 6.1, 3.9 Hz, 1H), 2.03–1.85 (m, 2H), 1.49 (s, 9H); δ_C (100 MHz, $CDCl_3$) 170.7, 169.1, 161.3, 153.3, 143.2, 130.0, 121.8, 118.1, 114.3, 108.6, 83.3, 62.6, 53.0, 51.0, 49.9, 46.2, 28.6, 27.9, 19.0; HRMS (ESI) m/z calcd for $C_{21}H_{28}N_2O_7$ $[M + Na]^+$ 443.1789, found 443.1771.

*2-(3-(1H-Imidazol-1-yl)prop-1-en-2-yl)-2-acetylcyclohexanone (**27a**).* Flash column chromatography [9:1 petrol:EtOAc + 1% Et_3N – EtOAc + 1% Et_3N] afforded **27a** (31 mg, 49%) as an orange solid. R_f = 0.23 [EtOAc]; mp 92–94 °C; ν_{max} (film)/cm^{-1} 3386, 3117, 2946, 2924, 2873, 1695, 1641, 1507; δ_H (400 MHz, $CDCl_3$) 7.43 (t, J = 1.1 Hz, 1H), 7.03 (t, J = 1.2 Hz, 1H), 6.87 (t, J = 1.3 Hz, 1H), 5.14 (q, J = 0.8 Hz, 1H), 4.92–4.91 (m, 1H), 4.61 (dt, J = 16.6, 1.1 Hz, 1H), 4.36 (dt, J = 16.8, 1.1 Hz, 1H), 2.56–2.40 (m, 3H), 2.10 (s, 3H), 2.00–1.91 (m, 2H), 1.87–1.78 (m, 1H), 1.77–1.66 (m, 1H), 1.64–1.54 (m, 1H); δ_C (100 MHz, $CDCl_3$) 208.5, 207.6, 142.8, 137.9, 129.5, 119.6, 117.1, 72.3, 48.7, 41.0, 33.4, 26.8, 26.0, 21.9; HRMS (ESI) m/z calcd for $C_{14}H_{18}N_2O_2$ $[M + H]^+$ 247.1441, found 247.1441.

*2-(3-(1H-Benzo[d]imidazol-1-yl)prop-1-en-2-yl)-2-acetylcyclohexanone (**27b**).* Flash column chromatography [9:1 petrol:EtOAc + 1% Et_3N – EtOAc + 1% Et_3N] afforded **27b** (32 mg, 42%) as an orange solid. R_f = 0.10 [petrol:EtOAc 1:1]; mp 90–92 °C; ν_{max} (film)/cm^{-1} 3093, 2958, 2942, 2860, 1697, 1645, 1615, 1496; δ_H (400 MHz,

DOI: 10.1021/acs.joc.6b00731
J. Org. Chem. 2016, 81, 5162–5172

$CDCl_3$) 7.89 (s, 1H), 7.82−7.78 (m, 1H), 7.50−7.45 (m, 1H), 7.33−7.26 (m, 2H), 5.07 (q, J = 1.2 Hz, 1H), 4.91 (dt, J = 17.5, 1.5 Hz, 1H), 4.69 (q, J = 0.8 Hz, 1H), 4.60 (dt, J = 17.5, 1.6 Hz, 1H), 2.64−2.48 (m, 3H), 2.23 (s, 3H), 2.09−1.97 (m, 2H), 1.93−1.86 (m, 1H), 1.83−1.73 (m, 1H), 1.73−1.60 (m, 1H); δ_C (100 MHz, $CDCl_3$) 208.5, 206.7, 143.7, 143.5, 141.3, 133.9, 123.3, 122.2, 120.2, 115.9, 110.2, 72.2, 46.7, 41.1, 33.6, 26.9, 26.2, 22.1; HRMS (ESI) m/z calcd for $C_{18}H_{20}N_2O_2$ $[M + H]^+$ 297.1598, found 297.1598.

*2-(3-(1H-Pyrazol-1-yl)prop-1-en-2-yl)-2-acetylcyclohexanone (**27c**).* Flash column chromatography [9:1 petrol:EtOAc + 1% Et_3N − EtOAc + 1% Et_3N] afforded **27c** (30 mg, 51%) as a yellow solid. R_f = 0.14 [petrol:EtOAc 1:1]; mp 61−63 °C; ν_{max} (film)/cm^{-1} 2935, 1699, 1558; δ_H (400 MHz, $CDCl_3$) 7.50 (dd, J = 1.8, 0.5 Hz, 1H), 7.41 (dd, J = 2.5, 0.6 Hz, 1H), 6.25 (t, J = 2.1 Hz, 1H), 5.12 (br s, 1H), 4.97 (t, J = 1.5 Hz, 1H), 4.81 (dt, J = 16.3, 1.2 Hz, 1H), 4.66 (dt, J = 16.3, 1.1 Hz, 1H), 2.51 (dd, J = 7.7, 6.0 Hz, 2H), 2.44−2.36 (m, 1H), 2.12 (s, 3H), 2.07−1.98 (m, 1H), 1.97−1.87 (m, 1H), 1.86−1.68 (m, 2H), 1.67−1.55 (m, 1H); δ_C (100 MHz, $CDCl_3$) 208.9, 207.0, 142.6, 139.6, 130.5, 117.8, 105.9, 72.3, 54.1, 41.0, 33.1, 26.9, 26.3, 21.8; HRMS (ESI) m/z calcd for $C_{14}H_{18}N_2O_2$ $[M + Na]^+$ 269.1261, found 269.1267.

4. Mechanistic Study. The synthesis of [D]-**15a** has been previously reported.[13] Analysis by ^1H NMR spectroscopy indicated 96% deuterium incorporation.

*2-Isobutyrylcyclohex-1-en-1-yl (Prop-2-yn-1-yl-3-D) Carbonate ([D]-**15b**).* According to a literature procedure,[28] to a solution of propargyl enol carbonate **15b** (203 mg, 0.81 mmol) in MeCN (8 mL) was added solid potassium carbonate (167 mg, 1.20 mmol). The suspension was stirred at room temperature for 30 min. Deuterium oxide (1.5 mL) was added via syringe, and the solution was stirred at room temperature for 1 h. The mixture was extracted with CH_2Cl_2 (10 mL), dried ($MgSO_4$), and concentrated in vacuo to afford deuterated alkyne [D]-**15b** (170 mg, 83%) as a pale yellow oil. Analysis by ^1H NMR spectroscopy indicated 96% deuterium incorporation. R_f = 0.54 [petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2935, 2564, 1975 (C−D); δ_H (400 MHz, $CDCl_3$) 4.78 (s, 2H), 2.93 (heptet, J = 7.0 Hz, 1H), 2.41−2.31 (m, 4H), 1.80−1.64 (m, 4H), 1.07 (d, J = 6.9 Hz, 6H); δ_C (100 MHz, $CDCl_3$) 206.6, 151.8, 150.6, 76.2, 76.0, 55.9, 33.1, 27.6, 25.7, 22.2, 21.7, 18.3; HRMS (ESI) m/z calcd for $C_{14}H_{17}DO_4$ $[M + Na]^+$ 274.1160, found 274.1153.

*Methyl 1H-Pyrrole-2-carboxylate-1-D ([D]-**22b**).* A suspension of sodium hydride (60 wt %, 70 mg, 1.75 mmol) in THF (10 mL) was cooled to 0 °C. A solution of pyrrole **22b** (200 mg, 1.6 mmol) in THF (5 mL) was added dropwise, and the mixture was stirred at 0 °C for 30 min. Deuterium oxide (2 mL) was added dropwise, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with H_2O (10 mL) and extracted with EtOAc (10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to afford [D]-**22b** (152 mg, 76%) as a purple solid. Analysis by ^1H NMR spectroscopy indicated 68% deuterium incorporation. R_f = 0.60 [petrol:EtOAc 4:1]; mp 74−77 °C; ν_{max} (film)/cm^{-1} 3287, 2924, 2458 (N−D), 1668, 1530; δ_H (400 MHz, $CDCl_3$) 9.09 (br s, 0.32H), 6.96 (dd, J = 2.7, 1.5 Hz, 1H), 6.92 (dd, J = 3.7, 1.5 Hz, 1H), 6.27 (dd, J = 3.7, 2.6 Hz, 1H), 3.86 (s, 3H); δ_C (75 MHz, $CDCl_3$) 150.0, 135.1, 130.4, 125.3, 124.6, 123.2, 121.0, 115.1, 108.5, 76.9, 76.0, 54.2.

*D-Methyl 1-(2-(1-Acetyl-2-oxocyclohexyl)allyl)-1H-pyrrole-2-carboxylate ([D]-**23b**) and Methyl 1-(2-(1-Isobutyryl-2-oxocyclohexyl)-allyl)-1H-pyrrole-2-carboxylate (**25b**).* Reaction of deuterated carbonate [D]-**15a** (26.8 mg, 0.12 mmol) and carbonate **15a** (30 mg, 0.12 mmol) with pyrrole **22b** (30 mg, 0.24 mmol) according to the general procedure. Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded [D]-**23b** (27 mg, 74%) and **25b** (24.5 mg, 62%). Analysis by ^1H NMR spectroscopy indicated 84% deuterium incorporation in [D]-**23b**, and no deuterium incorporation in **25b**. HRMS analysis indicated the presence [D]-**23b** and nondeuterated **25a** only.

[D]-**23b**: ν_{max} (film)/cm^{-1} 2946, 1694, 1531; HRMS (ESI) m/z calcd for $C_{17}H_{20}DNO_4$ $[M + Na]^+$ 327.1426, found 327.1425. **25b**: HRMS (ESI) m/z calcd for $C_{19}H_{25}NO_4$ $[M + Na]^+$ 354.1676, found 354.1666.

*D-Methyl 1-(2-(1-Isobutyryl-2-oxocyclohexyl)allyl)-1H-pyrrole-2-carboxylate ([D]-**25b**).* Reaction of deuterated carbonate [D]-**15b** (60 mg, 0.24 mmol) with pyrrole **22b** (30 mg, 0.24 mmol) according to the general procedure. Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded [D]-**25b** (46 mg, 58%). Analysis by ^1H NMR spectroscopy indicated 48% deuterium incorporation at the vinylic position and 48% at the allylic position. HRMS (ESI) m/z calcd for $C_{19}H_{24}DNO_4$ $[M + Na]^+$ 355.1739, found 355.1727.

[D]-**25b** was also obtained by the reaction of carbonate **15b** (60 mg, 0.24 mmol) with deuterated pyrrole [D]-**22b** (30 mg, 0.24 mmol) according to the general procedure. Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded [D]-**25b** (50 mg, 63%). Analysis by ^1H NMR spectroscopy indicated 27% deuterium incorporation at the vinylic position and 23% at the allylic position. HRMS (ESI) m/z calcd for $C_{19}H_{24}DNO_4$ $[M + Na]^+$ 355.1739, found 355.1752.

*D_2-Methyl 1-(2-(1-Isobutyryl-2-oxocyclohexyl)allyl)-1H-pyrrole-2-carboxylate ([D_2]-**25b**).* Reaction of deuterated carbonate [D]-**15b** (60 mg, 0.24 mmol) with deuterated pyrrole **22b** (30 mg, 0.24 mmol) according to the general procedure. Flash column chromatography [petrol:EtOAc 9:1−4:1] afforded [D_2]-**25b** (52 mg, 65%). Analysis by ^1H NMR spectroscopy indicated 75% deuterium incorporation at the vinylic position and 82% at the allylic position. HRMS (ESI) m/z calcd for $C_{19}H_{23}D_2NO_4$ $[M + Na]^+$ 356.1801, found 356.1790.

In the competition experiment between indoles **16a** (28 mg, 0.24 mmol) and **16b** (53 mg, 0.24 mmol) with carbonate **15a** (53 mg, 0.24 mmol) according to the general procedure, flash column chromatography [petrol:EtOAc 9:1−4:1] afforded **17b** (55 mg, 65%) only. For physical characterization data of **17b**, see above.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00731.

^1H and ^{13}C NMR spectra for all novel compounds and mass and ^1H NMR spectra of compounds arising from deuterium-labeling experiments (PDF)

Crystallographic data for **17d** (CIF)

Crystallographic data for **23b** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: v.franckevicius@lancaster.ac.uk.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge Lancaster University (M.K. and V.F.) and the Royal Society of Chemistry (Undergraduate Research Bursary to D.J.K.) for financial support. We also thank Dr. Nathan Halcovitch for X-ray diffraction analysis and Dr. David Rochester for mass spectrometry analysis. Concerning data accessibility, all relevant data are provided in full in the Experimental Section of this paper and the Supporting Information files.

■ REFERENCES

(1) Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, *6*, 4387.

(2) (a) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089. (b) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1. (c) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (d) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813. (e) Trost, B. M.; Fandrick, D. R. *Aldrichimica Acta* **2007**, *40*, 59. (f) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258. (g) Trost, B. M. *Org. Process Res. Dev.* **2012**, *16*, 185. (h) Oliver, S.; Evans, P. A. *Synthesis* **2013**, *45*, 3179. (i) Zhuo, C.-X.; Zheng, C.; You, S.-L. *Acc. Chem. Res.* **2014**, *47*, 2558.

DOI: 10.1021/acs.joc.6b00731
J. Org. Chem. 2016, 81, 5162−5172

(3) (a) Tsuji, J.; Mandai, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2589. (b) Ma, S. M. *Eur. J. Org. Chem.* **2004**, 1175.
(4) (a) Tsutsumi, K.; Ogoshi, S.; Nishiguchi, S.; Kurosawa, H. *J. Am. Chem. Soc.* **1998**, *120*, 1938. (b) Tsutsumi, K.; Kawase, T.; Kakiuchi, K.; Ogoshi, S.; Okada, Y.; Kurosawa, H. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2687.
(5) (a) Tamaru, Y.; Goto, S.; Tanaka, A.; Shimizu, M.; Kimura, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 878. (b) Tsutsumi, K.; Ogoshi, S.; Kakiuchi, K.; Nishiguchi, S.; Kurosawa, H. *Inorg. Chim. Acta* **1999**, *296*, 37. (c) Yoshida, M.; Ueda, H.; Ihara, M. *Tetrahedron Lett.* **2005**, *46*, 6705. (d) Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novak, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist, J. A.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. *Chem. - Eur. J.* **2011**, *17*, 14199. (e) Yang, Y. Z.; Szabó, K. J. *J. Org. Chem.* **2016**, *81*, 250.
(6) (a) Guo, L.-N.; Duan, X.-H.; Liang, Y.-M. *Acc. Chem. Res.* **2011**, *44*, 111. (b) Yoshida, M. *Chem. Pharm. Bull.* **2012**, *60*, 285. (c) Yoshida, M. *Heterocycles* **2013**, *87*, 1835.
(7) Yoshida, M.; Fujita, M.; Ihara, M. *Org. Lett.* **2003**, *5*, 3325.
(8) (a) Tsuji, J.; Watanabe, H.; Minami, I.; Shimizu, I. *J. Am. Chem. Soc.* **1985**, *107*, 2196. (b) Geng, L.; Lu, X. *Tetrahedron Lett.* **1990**, *31*, 111. (c) Labrosse, J. R.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **1999**, *40*, 9025. (d) Labrosse, J. R.; Lhoste, P.; Sinou, D. *Org. Lett.* **2000**, *2*, 527. (e) Labrosse, J. R.; Lhoste, P.; Sinou, D. *J. Org. Chem.* **2001**, *66*, 6634. (f) Zong, K. W.; Abboud, K. A.; Reynolds, J. R. *Tetrahedron Lett.* **2004**, *45*, 4973. (g) Dominczak, N.; Damez, C.; Rhers, B.; Labrosse, J.-R.; Lhoste, P.; Kryczka, B.; Sinou, D. *Tetrahedron* **2005**, *61*, 2589. (h) Cacchi, S.; Fabrizi, G.; Filisti, E.; Goggiamani, A.; Iazzetti, A.; Maurone, L. *Org. Biomol. Chem.* **2012**, *10*, 4699. (i) Montgomery, T. D.; Rawal, V. H. *Org. Lett.* **2016**, *18*, 740.
(9) Nishioka, N.; Koizumi, T. *Tetrahedron Lett.* **2011**, *52*, 3662.
(10) (a) Ambrogio, I.; Cacchi, S.; Fabrizi, G. *Org. Lett.* **2006**, *8*, 2083. (b) Duan, X.-H.; Guo, L.-N.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2006**, *8*, 5777. (c) Yoshida, M.; Higuchi, M.; Shishido, K. *Org. Lett.* **2009**, *11*, 4752.
(11) (a) Tunge, J. A.; Burger, E. C. *Eur. J. Org. Chem.* **2005**, *2005*, 1715. (b) Mohr, J. T.; Stoltz, B. M. *Chem. - Asian J.* **2007**, *2*, 1476. (c) Weaver, J. D.; Recio, A., III; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846. (d) Liu, Y. Y.; Han, S. J.; Liu, W. B.; Stoltz, B. M. *Acc. Chem. Res.* **2015**, *48*, 740. (e) Hong, A. Y.; Stoltz, B. M. *Eur. J. Org. Chem.* **2013**, 2745.
(12) (a) Keith, J. A.; Behenna, D. C.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Oxgaard, J.; Stoltz, B. M.; Goddard, W. A., III *J. Am. Chem. Soc.* **2007**, *129*, 11876. (b) Sherden, N. H.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6840.
(13) Schröder, S. P.; Taylor, N. J.; Jackson, P.; Franckevičius, V. *Org. Lett.* **2013**, *15*, 3778.
(14) Kenny, M.; Christensen, J.; Coles, S. J.; Franckevičius, V. *Org. Lett.* **2015**, *17*, 3926.
(15) Bordwell, F. G.; Branca, J. C.; Hughes, D. L.; Olmstead, W. N. *J. Org. Chem.* **1980**, *45*, 3305.
(16) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.
(17) Bordwell, F. G.; Drucker, G. E.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 632.
(18) (a) Kagawa, N.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2008**, *10*, 2381. (b) Montgomery, T. D.; Zhu, Y.; Kagawa, N.; Rawal, V. H. *Org. Lett.* **2013**, *15*, 1140.
(19) (a) Nemoto, T.; Zhao, Z. D.; Yokosaka, T.; Suzuki, Y.; Wu, R.; Hamada, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 2217. (b) Iwata, A.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *Chem. Commun.* **2014**, *50*, 298. (c) Gao, R.-D.; Liu, C.; Dai, L.-X.; Zhang, W.; You, S.-L. *Org. Lett.* **2014**, *16*, 3919. (d) Montgomery, T. D.; Nibbs, A. E.; Zhu, Y.; Rawal, V. H. *Org. Lett.* **2014**, *16*, 3480. (e) Nibbs, A. E.; Montgomery, T. D.; Zhu, Y.; Rawal, V. H. *J. Org. Chem.* **2015**, *80*, 4928.
(20) Details of the X-ray data for **17d** and **23b** are available in the Supporting Information. These data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1443121 for **17d** and CCDC 1443120 for **23b**), which can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.
(21) (a) Baize, M. W.; Blosser, P. W.; Plantevin, V.; Schimpff, D. G.; Gallucci, J. C.; Wojcicki, A. *Organometallics* **1996**, *15*, 164. (b) Casey, C. P.; Nash, J. R.; Yi, C. S.; Selmeczy, A. D.; Chung, S.; Powell, D. R.; Hayashi, R. K. *J. Am. Chem. Soc.* **1998**, *120*, 722. (c) Labrosse, J. R.; Lhoste, P.; Delbecq, F.; Sinou, D. *Eur. J. Org. Chem.* **2003**, 2813. (d) Horino, Y.; Homura, N.; Inoue, K.; Yoshikawa, S. *Adv. Synth. Catal.* **2012**, *354*, 828.
(22) Heller, S. T.; Schultz, E. E.; Sarpong, R. *Angew. Chem., Int. Ed.* **2012**, *51*, 8304.
(23) Blackaby, W. P.; De Kort, M.; Enthoven, M.; Hinchliffe, P. S.; Paulie, C.; Timmers, C. M.; Verkaik, S. PCT Int. Appl. WO2013041458.
(24) Fabbro, C.; Armani, S.; Carloni, L. E.; De Leo, F.; Wouters, J.; Bonifazi, D. *Eur. J. Org. Chem.* **2014**, 5487.
(25) Pham, C. C.; Park, M. H.; Pham, J. Y.; Martin, S. G.; Schramm, M. P. *Synthesis* **2013**, *45*, 1165.
(26) Madanahalli Ranganath Rao, J.; Gurram Ranga, M.; Pachiyappan, S. PCT Int. Appl. WO2014202580.
(27) Proto, S.; Amat, M.; Pérez, M.; Ballette, R.; Romagnoli, F.; Mancinelli, A.; Bosch, J. *Org. Lett.* **2012**, *14*, 3916.
(28) Bew, S. P.; Hiatt-Gipson, G. D.; Lovell, J. A.; Poullain, C. *Org. Lett.* **2012**, *14*, 456.

DOI: 10.1021/acs.joc.6b00731
J. Org. Chem. 2016, 81, 5162−5172